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[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Quinone Imides. XLV. Structures of Aromatic Amine Adducts of *p*-Benzoquinonedibenzimide*

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The adduct of benzene and *p*-benzoquinonedibenzenesulfonimide has been shown to be 2-phenyl-*p*-phenylenedibenzenesulfonamide by an unequivocal synthesis. 2-Piperidino- and 2-morpholino-*p*-phenylenedibenzamide, formed from *p*-benzoquinonedibenzimide and piperidine and morpholine, respectively, were synthesized by another route. Aniline adds 1,6 to *p*-benzoquinonedibenzimide as shown by the preparation of the benzoyl derivative from 4-amino-4'-nitrodiphenylamine. Methylaniline and dimethylaniline add to *p*-benzoquinonedibenzimide with the carbon atom para to the amine function taking part in the reaction and becoming attached in the 2-position.

The reactions of quinone imides with secondary aliphatic, alicyclic, and aliphatic aromatic amines and with primary aliphatic and aromatic amines follow various pathways, depending on the reaction conditions, the nature of the quinonoid system, and the substituent on the imide nitrogen. Thus *p*-benzoquinonedibenzenesulfonimide and morpholine[2] may lead to any or all of several different products, including 2-morpholino- and 2,5-dimorpholinodibenzenesulfonamide and *p*-benzenesulfonamidophenylmorpholine. The addition of aniline follows a comparably complex course resulting mainly in benzenesulfonamide, N,N'-diphenyl-*p*-phenylenediamine, and 2,5-dianilino-*p*-benzoquinonedianil. Methylaniline and dimethylaniline,[3] however, yield only single products, the 2-substituted diamides, in which addition was postulated to involve the carbon atom of the aromatic ring *para* to the amine function.

In the case of 1,4-naphthoquinonedibenzenesulfonimide,[2-4] on the other hand, morpholine, aniline, and methylaniline all add to form single products which were assumed to have the nitrogen of the reagent attached to the 2-carbon atom of the diamide. The structures were assigned merely on the basis of the non-reactivity of dimethylaniline, the addition of *p*-toluidine, and spectroscopic evidence.

Morpholine was found to react with *p*-benzoquinonedicarbethoxyimide and *p*-benzoquinonedicarbobenzoxyimide,[5] piperidine with *o*-benzoquinonedibenzimide and 4-chloro-*o*-benzoquinonedibenzimide,[6] and aniline, morpholine, and piperidine with *p*-benzoquinonedibenzimide[5] to form adducts, which presumably are diamides with the nitrogen atom of the reagent attached in the 2-position. However, no proofs of structure were included in the investigation.

The addition of aniline to 2,3,5,6-tetrachloro-*p*-benzoquinonedibenzenesulfonimide[7] resulted in a product for which the chemical and spectroscopic evidence indicated formula I to be the correct structure.

* This paper is a contribution in honor of Lyndon F. Small, former Editor of the Journal.

(1) An abstract of a thesis submitted by Leslie M. Werbel to the Graduate College of the University of Illinois in partial fulfillment of the degree of Doctor of Philosophy, 1957; Minnesota Mining & Manufacturing Co. Fellow, 1952; Allied Chemical and Dye Corp. Fellow, 1955–56; Dow Chemical Fellow, 1956–57.

(2) R. Adams and K. A. Schowalter, *J. Am. Chem. Soc.*, **74**, 2597 (1952).

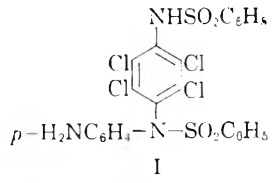
(3) R. Adams, B. H. Braun and S. H. Pomerantz, *J. Am. Chem. Soc.*, **75**, 4642 (1953).

(4) R. Adams and R. A. Wankel, *J. Am. Chem. Soc.*, **73**, 131 (1951).

(5) R. Adams and D. S. Acker, *J. Am. Chem. Soc.*, **74**, 5872 (1952).

(6) R. Adams and J. W. Way, *J. Am. Chem. Soc.*, **76**, 2763 (1954).

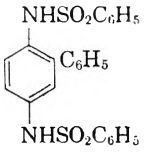
(7) R. Adams and B. H. Braun, *J. Am. Chem. Soc.*, **74**, 5869 (1952).



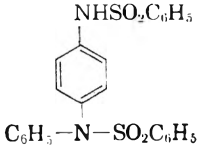
I

This investigation suggested the desirability of a restudy of the structures of the products obtained from addition not only of the aromatic and alicyclic amines but also of aromatic hydrocarbons in the presence of anhydrous aluminum chloride to *p*-benzoquinone diimides.

The product of addition of benzene to *p*-benzoquinonedibenzenesulfonimide was assumed[8] to have structure II in spite of the fact that lead tetraacetate oxidation of the adduct resulted in degradation with formation of *p*-benzoquinonedibenzenesulfonimide.

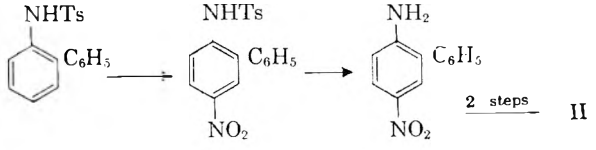


II



III

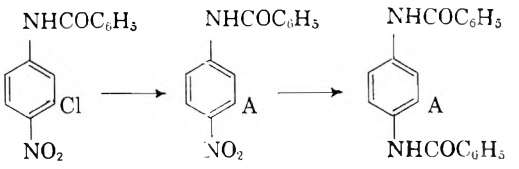
Structure III for the adduct, which involves 1,6-addition, was not considered as a possibility in the initial paper. Therefore, synthesis by an unequivocal method of structure II was undertaken. 2-*p*-Toluenesulfonamidobiphenyl (IV) was nitrated to 5-nitro-2-*p*-toluenesulfonamidobiphenyl (V). Detosylation with hydrobromic acid and phenol (VI), followed by reduction and benzenesulfonation resulted in a product (II) identical with the adduct of benzene to *p*-benzoquinonedibenzenesulfonimide.



IV V VI

The structures of the adducts of amines to *p*-benzoquinonedibenzimide were next considered. Unequivocal syntheses of 2-morpholino-, 2-piperidino-, and 2-anilino-*p*-phenylenedibenzamide in which the nitrogen atoms of the amines were attached to the 2-positions in the rings were successfully completed. 3-Chloro-4-nitroaniline was benzoylated (VII) and then treated with morpholine, piperidine, and aniline, to replace the chlorine atom and provide the three amine derivatives. Subsequent reduction of the products followed by benzoylation gave the desired diamides (IX.)

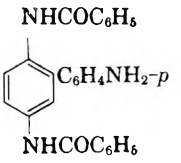
(8) R. Adams and K. R. Eiler, *J. Am. Chem. Soc.*, **73**, 1149 (1951).



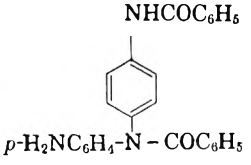
VII VIII IX

A = (a) piperidino
(b) morpholino
(c) anilino

The piperidine and morpholine compounds were identical with the piperidine and morpholine adducts of *p*-benzoquinonedibenzimide, thus establishing the constitutions of the latter. But the aniline compound was different. Therefore, the adduct of aniline to *p*-benzoquinonedibenzimide was assumed to have one of the two structures X or XI.



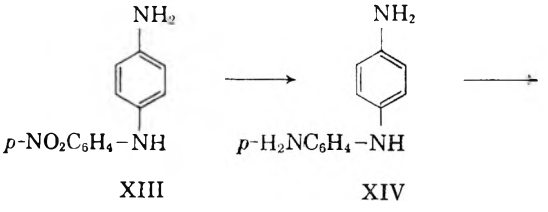
X



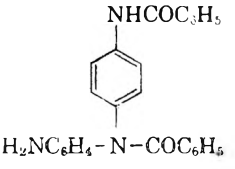
XI

Either structure satisfies the infrared spectrum and accounts for the presence of a primary amino group as shown by diazotization and coupling with β-naphthol and preparation of tosyl and benzoyl derivatives.

Structure XI was shown to be the correct one by comparison of its benzoyl derivative (XII) with a compound synthesized by an unequivocal route. *N*-*p*-Nitrophenyl-*p*-phenylenediamine (XIII) was reduced and the resulting triamine (XIV) benzoylated to give compound XII.



XIII XIV

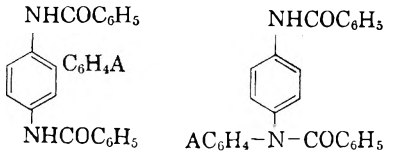


XII

Thus a second example of 1,6-addition to *p*-benzoquinone diimides has been established and for the first time this mode of addition has been conclusively substantiated by chemical evidence.

The adducts of methylaniline and dimethylaniline with *p*-benzoquinonedibenzimide were assumed to have structures similar to those postulated for

the analogous *p*-benzoquinonedibenzenesulfonimide adducts, as indicated by type formula XV. If,



XV XVI

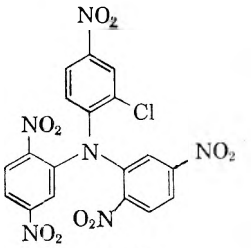
A = (a) *p*-$N(CH_3)_2$
(b) *p*-$NHCH_2$

however, 1,6-addition had occurred the structures would be those shown by type formula XVI. The analogy in structure of the monomethylaniline and dimethylaniline adducts was determined in the dibenzenesulfonamide series by conversion of the former to the latter by methylation with methyl iodide in dimethylformamide.[3] Similar results now have been obtained in the dibenzamide series by effecting methylation with formaldehyde and formic acid. The selection of type formula XV for the adducts was indicated by active hydrogen determinations on the dimethylaniline adducts of the dibenzenesulfonimide and dibenzimide. Both compounds possess two active hydrogens whereas only one should have been found if type structure XVI were correct.

The dimethylaniline adduct of *p*-benzoquinonedibenzimide showed a wide melting range and a mixture was suspected. However, a similar melting point was observed for the same product when prepared by methylation of the sharp-melting monomethylaniline adduct. The wide melting point is apparently a function of the crystallinity of the material.

The yields of the adducts of methylaniline and dimethylaniline to *p*-benzoquinonedibenzenesulfonimide and *p*-benzoquinonedibenzimide were excellent and only single entities were obtained. In contrast, aniline added to give mixtures from which the chief products were sometimes difficult to isolate in pure form. On the other hand, all the amines added to 1,4-naphthoquinonedibenzenesulfonimide in good yield through the nitrogen function and hence no reaction occurred with dimethylaniline.

In attempting to prepare 2-chloro-1,4-dinitrobenzene from 2-chloro-4-nitroaniline by means of oxidation with peroxytrifluoroacetic acid,[9] an interesting red crystalline by-product was obtained which appears to be a triphenylamine derivative (XVII) formed by condensation of one mole of 2-chloro-4-nitroaniline with two moles of the product, 2-chloro-1,4-dinitrobenzene.



XVII

EXPERIMENTAL

All melting points are corrected.

5-Nitro-2-p-toluenesulfonamidobiphenyl (V). A mixture of 2.5 g. of 2-*p*-toluenesulfonamidobiphenyl,[10] 25 ml. of water, and 25 ml. of yellow fuming nitric acid was warmed on a steam bath for 13 hr. On cooling, a deep orange solid mass resulted. This was powdered, filtered, and recrystallized from acetic acid to yield 1.5 g. (53%) of product, m.p. 170–172° (lit.[10] m.p. 169°).

2-Amino-5-nitrobiphenyl (VI). A mixture of 1 g. of 5-nitro-2-*p*-toluenesulfonamidobiphenyl, 2 g. of phenol, and 15 ml. of commercial 48% hydrobromic acid[11] was heated under reflux for 1.5 hr. After cooling and pouring into 100 ml. of water the solution was made basic with 15% aqueous sodium hydroxide. The yellow precipitate which formed was filtered and recrystallized from ethanol, yielding 0.32 g. (56%) of yellow crystals, m.p. 124.0–125.5°.

Anal. Calcd. for $C_{12}H_{10}N_2O_2$: C, 67.28; H, 4.71; N, 13.08. Found: C, 67.07; H, 4.70; N, 13.01.

2,5-Dibenzenesulfonamidobiphenyl (II). In a 100 ml. three-neck round bottom flask equipped with stirrer, dropping funnel, and reflux condenser was placed a solution of 1 g. of 2-amino-5-nitrobiphenyl in 20 ml. of absolute methanol, and approximately 0.5 g. of a water slurry of Raney nickel. The stirrer was started and a solution of 0.3 g. of 100% hydrazine hydrate in 8 ml. of methanol was added dropwise. Gas evolution occurred. After the addition was complete the mixture was heated under reflux on the steam bath for 45 min. The catalyst was removed by filtration, and the pale purple filtrate evaporated to dryness. The resulting dark purple liquid was dissolved in 25 ml. of pyridine and 3.3 g. of benzenesulfonyl chloride added. After the heat generated had dissipated, the solution was poured into iced hydrochloric acid. The resultant pink solid was filtered and dried to yield 1.87 g. of crude diamide, m.p. 189–191° (86.4% based on nitro amine). It was purified by three crystallizations from ethanol; white crystals, m.p. 202–203°.

Anal. Calcd. for $C_{24}H_{20}N_2O_4S_2$: C, 62.05; H, 4.34; N, 6.03. Found: C, 62.29; H, 4.27; N, 6.02.

N-Benzoyl-3-chloro-4-nitroaniline (VII). To a solution of 5.3 g. of 3-chloro-4-nitroaniline[12] in pyridine was added 4.9 g. of benzoyl chloride. The mixture was warmed for 3 hr. on the steam bath, cooled, and poured into iced hydrochloric acid. The resultant precipitate weighed 7.85 g. (91.3%). Crystallization from ethanol yielded yellow needles, m.p. 163–164°.

Anal. Calcd. for $C_{13}H_9ClN_2O_3$: C, 56.43; H, 3.28; N, 10.13. Found: C, 56.74; H, 3.36; N, 10.00.

N-Benzoyl-3-anilino-4-nitroaniline (VIIIc). In a 50 ml. side-arm flask fitted with a reflux condenser and nitrogen inlet tube was placed 1.9 g. of *N*-benzoyl-4-chloro-4-nitroaniline and 25 ml. of aniline that had been distilled over zinc dust. The mixture was heated at 185° for 3 hr. under a nitrogen atmosphere, cooled, and poured into 100 ml. of water and steam-distilled to remove excess aniline. Upon cooling a black-orange solid remained in the container.

(9) W. D. Emmons, *J. Am. Chem. Soc.*, 76, 3470 (1954).

(10) F. Bell, *J. Chem. Soc.*, 2773 (1928).

(11) H. R. Snyder and R. E. Heckert, *J. Am. Chem. Soc.*, 74, 2006 (1952).

(12) H. H. Hodgson and A. Kershaw, *J. Chem. Soc.*, 2919 (1929).

This was filtered and treated with 25 ml. of ethanol, resulting in 1.2 g. of orange solid, m.p. 216.5–218° (52.4%). The melting point was unchanged by recrystallization from ethanol.

Anal. Calcd. for $C_{19}H_{15}N_3O_3$: C, 68.46; H, 4.54; N, 12.61. Found: C, 68.51; H, 4.28; N, 12.61.

2-Anilino-p-phenylenedibenzamide (IX). To a solution of 0.4 g. of *N*-benzoyl-3-anilino-4-nitroaniline in approximately 75 ml. of methanol was added a small scoop of Raney nickel, followed by 0.4 ml. of 100% hydrazine hydrate. An exothermic reaction occurred and bleaching of the original color was noted. The mixture was heated on the steam bath for 1 hr., the catalyst removed by filtration, and the filtrate evaporated to dryness. The resultant brown gum was taken up in pyridine and treated with 0.2 ml. of benzoyl chloride. The solution was heated for 1 hr. on the steam bath, cooled, and poured into a slurry of ice and hydrochloric acid. The precipitated violet solid weighed 0.3 g. (32.4%). It was purified by recrystallization from dilute ethanol; white crystals, m.p. 248–249°.

Anal. Calcd. for $C_{26}H_{21}N_3O_2$: C, 76.64; H, 5.20; N, 10.31. Found: C, 76.52; H, 5.21; N, 10.45.

N-Benzoyl-3-morpholino-4-nitroaniline (VIIIb). A mixture of 0.7 g. of *N*-benzoyl-3-chloro-4-nitroaniline and 2 ml. of morpholine was heated under reflux for 1.5 hr., cooled and poured into ice and water. The oil which formed solidified upon standing to yield 0.83 g. (quant.) of bright yellow solid. Recrystallization from dilute ethanol afforded yellow crystals, m.p. 150–151.5°.

Anal. Calcd. for $C_{17}H_{17}N_3O_4$: C, 62.37; H, 5.24; N, 12.84. Found: C, 62.59; H, 5.57; N, 12.85.

2-Morpholino-p-phenylenedibenzamide (IXb). To a solution of 0.25 g. of *N*-benzoyl-3-morpholino-4-nitroaniline in 15 ml. of methanol was added a small amount of Raney nickel and sufficient 100% hydrazine hydrate (about 1 ml.) to bleach the color. Evolution of heat caused the methanol to boil. The mixture was heated on the steam bath for 25 min., filtered, and evaporated to dryness. The gummy residue was taken up in pyridine and 0.3 ml. of benzoyl chloride added. After heating on the steam bath for 1.5 hr. the mixture was poured into ice and hydrochloric acid. The pinkish solid that resulted weighed 0.2 g. (65.3%). Recrystallization from dilute ethanol gave white crystals, m.p. 213.5–214.5°.

Anal. Calcd. for $C_{24}H_{23}N_3O_3$: C, 71.80; H, 5.77; N, 10.47. Found: C, 72.08; H, 5.90; N, 10.27.

N-Benzoyl-3-piperidino-4-nitroaniline (VIIIa). This material was prepared analogously to the morpholine compound. Yellow crystals were obtained in yield of 78.5% and were purified by recrystallization from a mixture of benzene and cyclohexane, m.p. 117.5–118.5°.

Anal. Calcd. for $C_{18}H_{19}N_3O_3$: C, 66.45, H, 5.89; N, 12.92. Found: C, 66.56; H, 5.91; N, 12.79.

2-Piperidino-p-phenylenedibenzamide (IXa). This material was prepared analogously to the morpholine compound. A quantitative yield of white, feathery solid, m.p. 180–181°, resulted. It was purified by recrystallization from dilute ethanol.

Anal. Calcd. for $C_{25}H_{25}N_3O_2$: C, 75.16; H, 6.31; N, 10.52. Found: C, 75.11; H, 6.37; N, 10.55.

p-Toluenesulfonamide of adduct of aniline and p-benzoquinonedibenzimide: N-benzoyl-4-benzamido-4′-p-toluenesulfonamidodiphenylamine. A solution of 0.1 g. of the adduct of aniline and *p*-benzoquinonedibenzimide in pyridine was treated with 55 mg. of *p*-toluenesulfonyl chloride and heated on the steam bath for 3 hr., cooled, and poured into ice and hydrochloric acid. The white solid weighed 0.15 g. (quant.). Purification was effected by recrystallization from ethanol; white plates, m.p. 260.5–262.5°.

Anal. Calcd. for $C_{33}H_{27}N_3O_4S$: C, 70.57; H, 4.85; N, 7.48. Found: C, 70.20; H, 5.05; N, 7.40.

Addition of benzene to p-benzoquinonedibenzenesulfonimide. Attempted duplication of the preparation of the benzene adduct of *p*-benzoquinonedibenzenesulfonimide according to the original directions[8] disclosed that the reaction did not always proceed with the facility indicated. A crude brown-green solid which was obviously a mixture was sometimes obtained from the reaction. It could not be purified by crystallization so was subjected to chromatographic separation on a column of aluminum oxide. The solid was suspended on top of the column. Elution with 2:1 ethyl acetate–acetone produced 2-phenyl-*p*-phenylenedibenzenesulfonamide, followed by *p*-phenylenedibenzenesulfonamide and 2-chloro-*p*-phenylenedibenzenesulfonamide. Melting points of mixtures of these materials, after recrystallization respectively from ethanol, glacial acetic acid, and benzene, with authentic samples showed no depression.

Addition of aniline to p-benzoquinonedibenzimide. Repetition of this preparation according to the original directions[6] indicated that the reaction was not always a simple one. Although a good yield of amorphous solid was formed, only 8.5% of pure adduct could be isolated by the recommended purification techniques.

Addition of methylaniline to p-benzoquinonedibenzimide; 2-(p-methylaminophenyl)-p-phenylenedibenzamide (XV). A solution of 2 g. of *p*-benzoquinonedibenzimide in 20 ml. of chloroform was treated with 0.69 g. of redistilled methylaniline in 20 ml. of chloroform. The mixture was allowed to stand for 24 hr. and then poured into approximately 300 ml. of petroleum ether (b.p. 80–100°). The product precipitated as a grey solid (quant.). Recrystallization from dilute ethanol afforded white plates, m.p. 209.5–211.5°.

Anal. Calcd. for $C_{27}H_{23}N_3O_2$: C, 76.94; H, 5.50; N, 9.97. Found: C, 76.95; H, 5.43; N, 9.84.

Addition of dimethylaniline to p-benzoquinonedibenzimide; 2-(p-dimethylaminophenyl)-p-phenylenedibenzamide (XV). The reaction was conducted in a manner exactly analogous to the monomethylaniline addition. A quantitative conversion resulted. The product was purified by recrystallization from ethanol, m.p. 230°.

Anal. Calcd. for $C_{28}H_{25}N_3O_2$: C, 77.22; H, 5.79; N, 9.65. Found: C, 77.26; H, 5.83; N, 9.83.

The pure dimethylaniline adduct recrystallized from ethanol melted mainly at 230° but a small portion always remained unmelted up to about 244° (capillary). Similar results were obtained when the material was crystallized from benzene-cyclohexane. However, the melting point on a micro hot stage was sharp, m.p. 226.5–228.5°.

Conversion of monomethylaniline adduct to the dimethylaniline adduct. A solution of 0.5 g. of monomethylaniline adduct in 15 ml. of 90% formic acid and 140 mg. of 35% formaldehyde was heated on the steam bath for 8 hr. After cooling and pouring onto ice it was made basic with 15% aqueous sodium hydroxide. The resulting solid weighed 0.49 g. Recrystallization from dilute ethanol gave white crystals, m.p. 230.5° (except for a small amount which did not melt until 243°).

Anal. Calcd. for $C_{28}H_{25}N_3O_2$: C, 77.22; H, 5.79; N, 9.65. Found: C, 77.45; H, 6.07; N, 9.33.

N,N′,N″-Tribenzoyl-4,4′-diaminodiphenylamine (XII). *A.* To 0.2 g. of the adduct of aniline and *p*-benzoquinonedibenzimide in pyridine was added 0.1 ml. of benzoyl chloride. The mixture was warmed on the steam bath for 1 hr., cooled, and poured into ice and hydrochloric acid. The white solid, weighing 0.24 g. (95%), was recrystallized from ethanol; white plates, m.p. 310–312°.

Anal. Calcd. for $C_{33}H_{25}N_3O_3$: C, 77.48; H, 4.93; N, 8.21. Found: C, 77.54; H, 5.09; N, 8.07.

B. A solution of 0.2 g. of 4-amino-4′-nitrodiphenylamine in methanol was treated with a pinch of Raney nickel and approximately 0.1 ml. of 100% hydrazine hydrate. After the vigorous bubbling had subsided the suspension was warmed on the steam bath for 1 hr. and filtered, yielding a violet solution which darkened quickly. The solution was evaporated rapidly to dryness. The crystalline solid which resulted was taken up in pyridine and heated under reflux for 4 hr. with 0.3 ml. of benzoyl chloride. The solution was then cooled and poured onto a mixture of ice and hydrochloric acid. The resulting solid was formed in quantitative

yield. Recrystallization from ethanol gave white plates, m.p. 309–311°.

Anal. Calcd. for $C_{33}H_{25}N_3O_3$: C, 77.48; H, 4.93; N, 8.21. Found: C, 77.46; H, 5.01; N, 8.13.

The melting point of a mixture of this material with that prepared in *A* by the benzoylation of the aniline adduct was not depressed.

Peroxytrifluoroacetic acid oxidation of 2-chloro-4-nitroaniline. Into a 200-ml. three-neck round bottom flask equipped with stirrer, reflux condenser, and dropping funnel was placed 65 ml. of trifluoroacetic acid. The liquid was heated to boiling (71°), and 5 g. of 2-chloro-4-nitroaniline was dissolved in the hot acid. To the refluxing solution was added 17.3 ml. of 30% hydrogen peroxide dropwise during a 30 min. period. The color of the solution bleached at first and then became deep red. The solution was heated under reflux for 1 hr. after the addition was complete, cooled to room temperature, and poured into ice water. The orange solid removed by filtration weighed 4.0 g. One gram of this material when extracted with petroleum ether (b.p. 80–100°) gave 0.17 g. of deep red insoluble material. The ether soluble material melted at 57–59° and was undoubtedly the desired 2-chloro-1,4-dinitrobenzene. The red insoluble material was recrystallized from benzene, m.p. 280–281°.

Anal. Calcd. for $C_{18}H_9ClN_6O_{10}$: C, 42.83; H, 1.80; N, 16.65. Found: C, 42.88; H, 1.82; N, 16.26.

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URBANA, ILL.

[COMMUNICATION NO. 1785 FROM THE KODAK RESEARCH LABORATORIES, EASTMAN KODAK CO.]

Infrared Absorption and Structure of Certain Derivatives of Cyclopropane*

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The infrared absorptions of twenty derivatives of cyclopropane, mostly with carbonyl or other functional groups adjacent to the ring, have been obtained. Neither the 2.3μ nor the 9.8μ region, previously suggested for characterizing the C_3 ring, affords a clear indication of either the presence or absence of this group.

The infrared spectrum of unsubstituted cyclopropane has been studied in detail and most of the fundamental modes of vibration have been identified.[1–3] In studying the spectra of cyclopropane derivatives which were mostly hydrocarbons, a number of workers[4–6] have reported that a characteristic absorption near 9.8μ (1000–1020 cm.$^{-1}$) is invariably present. Another strong absorption near 11.6μ (866 cm.$^{-1}$) found in some derivatives does not occur consistently.[5] These absorption bands are also found in cyclopropane itself and have been assigned to a ring deformation and to a CH_2 wagging vibration.[3]

In more recent work,[7–9] questions have been raised as to the reliability and usefulness of these bands at longer wave lengths. While Wiberley and Bunce[7] confirmed the 9.8μ band in nine nonhydrocarbon cyclopropyl derivatives, they concluded that absorptions in this region were too common to provide a clear identification of the ring structure and suggested the use of C—H stretching bands at 3.23 and 3.32μ for CH_2 groups in the cyclopropyl system. Two additional ketones containing the cyclopropyl ring also showed[8] this pair of bands, whereas Cole[9] reported only a single band between 3.28 and 3.31μ (3024–3058 cm.$^{-1}$) in isocholestane and two other natural products. No such band was reported for 3-carene, where each of the carbons of the three-membered ring has at least one substituent. In work with dicyclopropyl ketone, -carbinol, and -methane,[10] the two C—H bands were again noted near 3.3μ (3030 cm.$^{-1}$) and 3.23μ (3100 cm.$^{-1}$), as well as several strong bands in the 9.6–10μ region.

In a recent summary of spectral-structure correlations for cyclopropane derivatives,[11] fourteen references are cited to support the use of a band between 9.8 and 10.0μ (1000–1020 cm.$^{-1}$) as indicating a cyclopropyl ring. The presence of a band in this position in the spectra of substances of unknown structure has also been interpreted as sup-

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* This paper is a contribution in honor of Lyndon F. Small, former Editor of the Journal.

(1) G. Herzberg, *Infrared and Raman Spectra of Polyatomic Molecules*, D. Van Nostrand Co., Inc., New York, 1945, pp. 352–353.

(2) A. W. Baker and R. C. Lord, *J. Chem. Phys.*, **23**, 1636 (1955).

(3) Hs. H. Günthard, R. C. Lord, and T. K. McCubbin, Jr., *J. Chem. Phys.*, **25**, 768 (1956).

(4) J. D. Bartleson, R. E. Burk, and H. P. Lankelma, *J. Am. Chem. Soc.*, **68**, 2513 (1946).

(5) J. M. Derfer, E. E. Pickett, and C. E. Boord, *J. Am. Chem. Soc.*, **71**, 2482 (1949).

(6) V. A. Slabey, *J. Am. Chem. Soc.*, **74**, 4928 (1952).

(7) S. E. Wiberley and S. C. Bunce, *Anal. Chem.*, **24**, 623 (1952).

(8) F. J. Piehl and W. G. Brown, *J. Am. Chem. Soc.*, **75**, 5023 (1953).

(9) A. R. H. Cole, *J. Chem. Soc.*, 3807 (1954).

(10) H. Hart and O. E. Curtis, Jr., *J. Am. Chem. Soc.*, **78**, 112 (1956).

(11) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, Methuen and Co., Ltd., London, 1954, pp. 27–28.

porting the presence of a cyclopropane ring in several instances.[12-14]

The availability of twenty cyclopropane derivatives, many of them heavily substituted, has made it possible to contribute additional evidence bearing on the reliability of infrared evidence for the C_3 ring. While those expert in the field may already be aware of the limitations, it is felt that some attempted applications indicate a need for additional information on this point. The substances examined are listed in Table I. For those samples not specifically described in previous papers, the source and criteria of purity used are noted in the Experimental Section.

Infrared absorptions near 10 microns. Infrared spectra were obtained in the 2–16μ region, using pressings in potassium bromide or mineral oil mulls for the solids. No differences have been noted which might be due to interaction with potassium bromide. These spectra have been made available to the National Research Council Committee on Spectral Absorption Data[15] for future publication in the NRC-NBS series of reference spectra.

To illustrate the spectral region of particular concern in this paper, the absorptions between 9 and 11μ are reproduced in Fig. 1. In general, the strongest bands in each complete spectrum show less than 5% transmission. Of the 20 spectra, 3 show no significant absorption maxima between 9.8 and 10.0μ (compounds II, III, and IV), and three others (compounds VIII, XIV, and XIX), show only bands which appear on the sides of stronger absorptions which lie outside the region in question. In order to include an absorption from all of the compounds it would be necessary to widen the region from a lower limit of 9.66μ to an upper limit of 10.05μ.

To obtain an indication of the extent of interference from noncyclopropane structures which absorb in the 9.7–10.05μ region, 200 spectra were selected by the use of a table of random sample numbers[16] from the first 9,400 spectra in the Sadtler file.[17] Examination showed that although none were of cyclopropanes, 50% contained one or more moderate or strong absorptions between 9.7 and 10.05μ. In the more limited range between 9.75 and 9.90μ, similar interference was noted in 31% of the cases. In a separate survey of unpublished spectra of 200 compounds selected at ran-

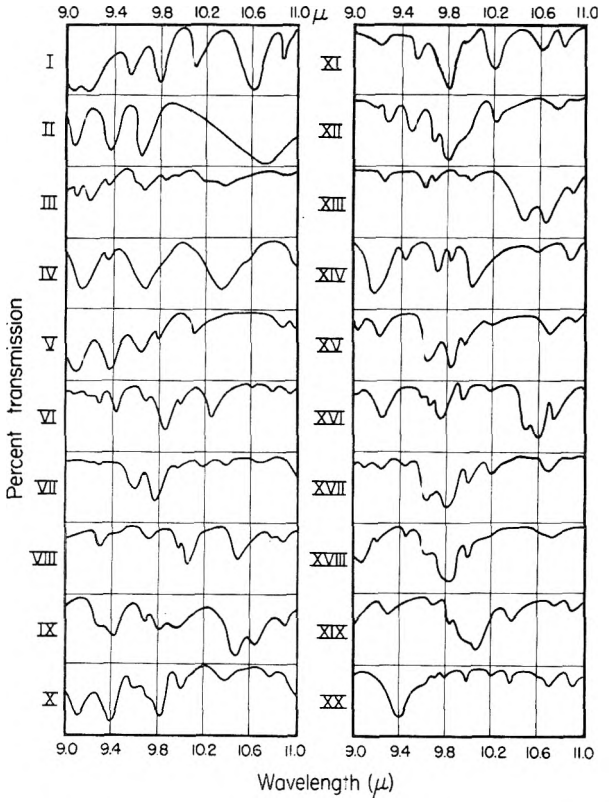


FIG. 1. INFRARED ABSORPTIONS IN THE 9–11μ REGION FOR COMPOUNDS IDENTIFIED IN TABLE I.

TABLE I

CYCLOPROPANES

I	α-Hydroxyethyl-
II	Carboxy-
III	Ethyl chrysanthemumate
IV	Acetyl-
V	Dicyclopropyl ketone
VI	2-Benzoyl-1-nitro-1-phenyl- (isomer, m.p. 131°)[a]
VII	1,2-Dibenzoyl-1-phenyl- (isomer, m.p. 125°)[b]
VIII	1,2-Dibenzoyl-1-phenyl- (isomer, m.p. 129°)[b]
IX	Dioxime of above[b]
X	Monophenylhydrazone of same[b]
XI	1,2-Dibenzoyl-3-phenyl- (isomer, m.p. 119°)[c]
XII	1,2-Dibenzoyl-3-phenyl- (isomer, m.p. 151°)[c]
XIII	Dioxime of XI
XIV	2-(4-Chlorobenzoyl)-1-nitro-3-phenyl- (isomer, m.p. 121°)[d]
XV	2-Benzoyl-1-cyano-1,3-diphenyl- (isomer, m.p. 169.5°)[e]
XVI	2-Benzoyl-1-cyano-1,3-diphenyl- (isomer, m.p. 176.5°)[e]
XVII	2-Benzoyl-1-carboxamido-1,3-diphenyl-[f]
XVIII	2-Benzoyl-1-cyano-1-(4-nitrophenyl)-3-phenyl- (isomer, m.p. 150°)[g]
XIX	2-Benzoyl-1-cyano-1-(4-nitrophenyl)-3-phenyl- (isomer, m.p. 172°)[g]
XX	Methyl 3-phenylcyclopropane-1,1,2,2-tetracarboxylate

[a] C. F. H. Allen and M. P. Bridgess, *J. Am. Chem. Soc.*, **51**, 2151 (1929). [b] C. F. H. Allen and W. E. Barker, *J. Am. Chem. Soc.*, **54**, 736 (1932). [c] E. P. Kohler and W. N. Jones, *J. Am. Chem. Soc.*, **41**, 1249 (1919). [d] E. P. Kohler and L. I. Smith, *J. Am. Chem. Soc.*, **44**, 624 (1922). [e] E. P. Kohler and C. F. H. Allen, *J. Am. Chem. Soc.*, **46**, 1522 (1924). [f] C. F. H. Allen and R. Boyer, *Can. J. Res.*, **9**, 159 (1933). [g] C. F. H. Allen, *J. Am. Chem. Soc.*, **47**, 1733 (1925).

(12) K. Hofmann, *Record Chem. Progr.*, **14**, 14 (1953).

(13) J. P. Verma, B. Nath, and J. S. Aggarwal, *Nature*, **175**, 85 (1955).

(14) K. K. Chakravarti and S. C. Bhattacharyya, *Perfumery Essent. Oil Record*, **46**, 256 (1955).

(15) E. C. Creitz, Sec'y., c/o National Bureau of Standards, Washington 25, D. C.

(16) L. H. C. Tippett, *Random Sampling Numbers*, Cambridge Univ. Press, Cambridge, 1927, Table VII.

(17) Samuel P. Sadtler and Son, Philadelphia, Pa., "Catalog of Infrared Spectrograms."

dom from the list of Eastman Organic Chemicals, 42% showed absorptions between 9.7 and 10.0μ which were at least as strong as the average shown by the compounds in Table I. We thus conclude that between one-third and one-half of all organic compounds might be expected to have one or more bands in this region which has been suggested as characterizing the cyclopropane ring.

Infrared absorptions near 3.3 microns. Examination of the C—H stretching vibrations in the spectral region between 3.2 and 3.5μ requires, for optimum results, resolution greater than can be obtained with a spectrometer having a sodium chloride prism. Such spectra have been obtained on eighteen of the substances in Table I by using a lithium fluoride prism, with the results shown in Fig. 2. Since aromatic and ethylenic C–H's would

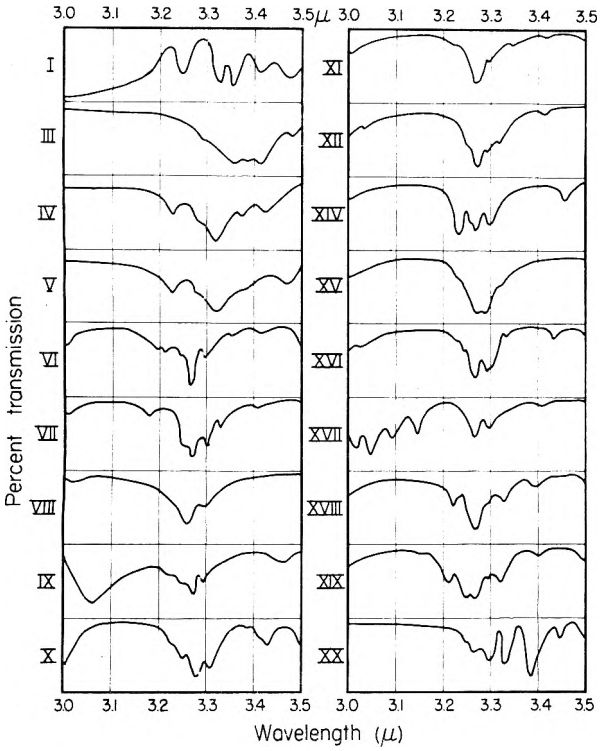


FIG. 2. INFRARED ABSORPTIONS IN THE 3.0–3.5μ REGION. Spectra obtained on potassium bromide pressings, except compounds I, III, IV, V as liquids and VII, VIII and XX as 5% solutions in CCl_4.

also be expected to absorb in the 3.2–3.3μ portion of the range, it is not surprising that, for our highly substituted cyclopropanes, this region, likewise, shows ambiguities at least as serious as those noted for bands near 10μ.

In the work of Wiberley and Bunce,[7] the two bands noted for cyclopropanes containing unsubstituted CH_2 groups at 3.23μ (3096 cm.$^{-1}$) and 3.32μ (3012 cm.$^{-1}$) are so close to the fundamental frequencies ν_6 (3090 cm.$^{-1}$) and ν_8 (3019 cm.$^{-1}$) for liquid cyclopropane[2] that it seems clear that the same parallel and perpendicular modes of vibration of ring CH_2 groups are involved. Since this is the case, it would be unrealistic to expect both bands in compounds containing only CHR or CR_2. In the eighteen compounds examined in this wave length range, ring CH_2's are found in I, IV, V, VII, VIII, and IX, but, in all but the simplest cases, they represent only a minor part of the molecule. In the experimentally determined spectra, only I, IV, and V show clearly the expected two bands. Most of the others show their strongest absorption between 3.26 and 3.28μ, with from one to three other bands in the 3.22–3.3μ region. In VII, VIII, and IX, there is no useful absorption at 3.23μ, even though a ring CH_2 is present in each, whereas in XIV, XVIII, and XIX, a band is observed at 3.22–3.23μ, although no such group is present.

Recent high-resolution work by Tallent and Siewers[18] on vinyl, aromatic, and heterocyclic =CH— absorptions show significant overlap into the region involving the cyclopropyl methylene groups. Tallent and Siewers and also Henbest, Meakins, Nicholls, and Taylor[19] show that there is close correspondence between C—H absorptions in a three-membered carbocylic ring and those in an epoxy system, which adds to the difficulty. One must, therefore, conclude that the general similarity between spectra of all of the phenyl and benzoyl cyclopropanes is attributable to the C–H's in the noncyclopropane parts of the molecule.

The data of Roberts and Chambers[20] indicate that the inherent weakness of C—H stretching absorptions in the cyclopropyl structure (as compared with C—H bonds in larger rings) would also make difficult any identification based on the 3μ region of the infrared spectrum.

To illustrate the difficulties encountered in using the 3.3μ absorptions to distinguish between a cyclopropane derivative and a closely similar compound not containing the C_3 ring, methyl 3-phenylcyclopropane-1,1,2,2-tetracarboxylate (XX) was compared with methyl benzaldimalonate (XXI). The second of these contains two aliphatic hydrogen atoms, which are absent in the ring structure of the first. The spectra obtained from 5% solutions (0.5 mm. cell) in carbon tetrachloride are reproduced in Fig. 3, which is plotted in terms of relative absorption, the base line being that for a carbon tetrachloride blank. When examined as a mull or a potassium bromide pressing, the tetracarboxylate (XX) showed only a single band at 3.308μ, whereas, in solution, separate bands were observed at 3.298 and 3.328μ. No similar effect of crystallinity was noted in any of the other materials which were ex-

(18) W. H. Tallent and I. J. Siewers, *Anal. Chem.*, **28**, 953 (1956).

(19) H. B. Henbest, G. D. Meakins, B. Nicholls and K. J. Taylor, *J. Chem. Soc.*, 1459 (1957).

(20) J. D. Roberts and V. C. Chambers, *J. Am. Chem. Soc.*, **73**, 5030 (1951).

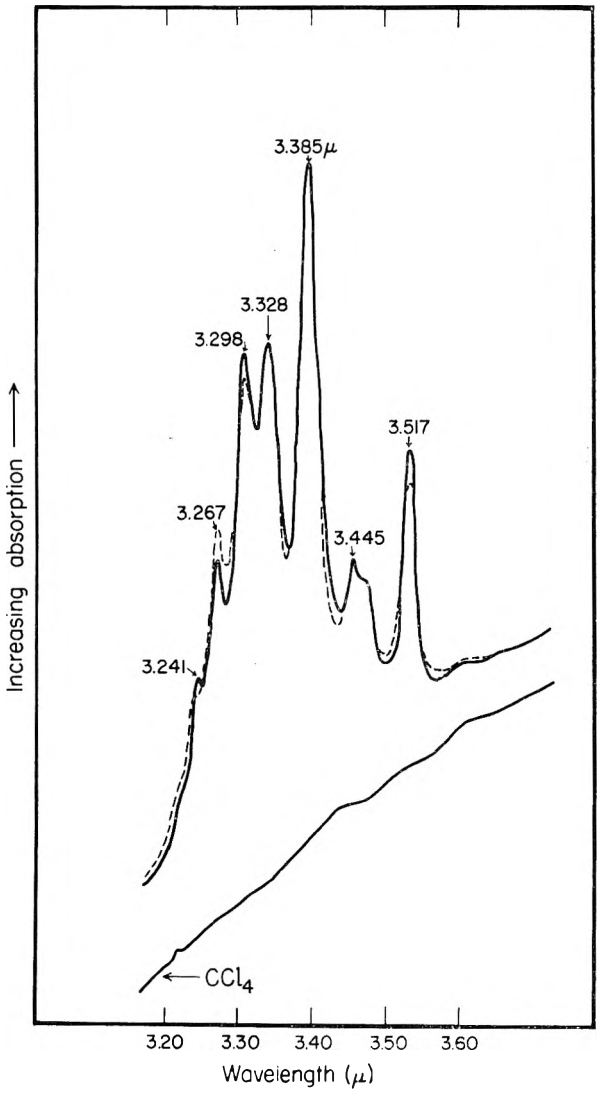


FIG. 3. COMPARISON OF METHYL 3-PHENYLCYCLOPROPANE-1,1,2,2-TETRACARBOXYLATE (- - - -) AND METHYL BENZALDIMALONATE (——) IN THE 3.2–3.6μ REGION.

amined both in solution and as solids. From the results in solution (Fig. 3), we conclude that only slight differences in the relative intensities of minor peaks can be detected, and there is no basis on which one could assign the cyclopropane structure to either of the compounds from the available infrared data.

EXPERIMENTAL

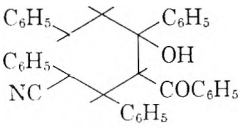
Incidental to the investigation of infrared absorptions characteristic of the cyclopropane ring, the spectra have been most useful in confirming functional group substitutions, in establishing the homogeneity of stereoisomeric forms, and in revealing the components of mixtures of such forms. Thus, in the highly substituted 2-benzoyl-1-carboxamido-1,3-diphenylcyclopropane (XVII), the presence of the carboxamido group could be readily confirmed, although this was difficult to do chemically. Also, as noted in the following section, stereoisomers of two of the compounds which had been reported previously could be eliminated as being mixtures.

Preparation of materials. Acetylcyclopropane,[21] dicyclopropyl ketone,[22] ethyl chrysanthemumate,[22] carboxycyclopropane,[23] and α-hydroxyethylcyclopropane[24] were obtained from commercial sources and redistilled where necessary, by using a 10-inch glass-packed column with a variable take-off head, and taking a fraction with constant boiling point and refractive index. Acetylcyclopropane, b.p. 110°, n_D^{25} 1.4200; ethyl chrysanthemumate, b.p. 218°, n_D^{25} 1.4581; dicyclopropyl ketone, b.p. 162°, n_D^{25} 1.4632; cyclopropanecarboxylic acid, n_D^{25} 1.4353. The infrared spectrum of dicyclopropyl ketone was the same as that recently reported.[25] The two stereoisomeric forms of 1,2-dibenzoyl-3-phenylcyclopropane[26] and its dioxime, m.p. (corr.) 175°, were newly prepared.* Most of the others were the original analytical samples;[27, 28] however, the two higher-melting stereoisomeric forms [m.p. (corr.) 169.5, 176.5] of 2-benzoyl-1-cyano-1,3-diphenylcyclopropane[21, 29] were also freshly prepared, in an unsuccessful attempt to secure more of the low-melting (143°) isomer. The only product in this range was a mixture of the two other forms; this conclusion was confirmed by the infrared absorptions. Since none of the original sample was available, and since its isolation could not be repeated, its existence must now be regarded as doubtful.

Similarly, the present work on 2-benzoyl-1-cyano-1-(4-nitrophenyl)-3-phenylcyclopropanes (XVIII, XIX) has shown that the isomer previously reported as melting at 144°[27] was a mixture of the other two.

2-Benzoyl-1-cyano-1,3-diphenylcyclopropane. The procedure was improved over the original[29] by using a continuous reactor[30] for the first two steps, for preparing the δ-ketonic nitrile and two bromo derivatives. In the general form of the apparatus, at the rate of one mole per hour, the yield of adduct from benzyl cyanide and benzalacetophenone is 87.7%, of which 95% is the higher-melting form and 5% is the "trimolecular product." The former has two polymorphic modifications, m.p. 118.5° and 120.5°, which can be interconverted by suitable manipulation; their infrared spectra are different in Nujol mulls which are different from their solution.

The trimolecular product is now believed to be the cyclohexane (XXII), since infrared assay indicated the presence of tertiary OH, CN, and only 47% of the extinction of the O ‖ —C— that would be expected from the open-chain form (which has two carbonyl groups).



XXII

* All melting points are corrected.

(21) Eastman Kodak Co.

(22) Aldrich Chemical Co.

(23) *Org. Syntheses*, Coll. Vol. 3, 221 (1956).

(24) Tennessee Eastman Co., kindness of E. B. Towne. Methyl cyclopropyl ketone was hydrogenated at 100° and 2000 p.s.i. over barium-promoted copper chromite catalyst. The carbinol, b.p. 120–120.9° (727 mm.), n_D^{20} 1.4312, is known [V. A. Slabey and P. H. Wise, *J. Am. Chem. Soc.*, 71, 3252 (1949)].

(25) H. Hart and O. E. Curtis, Jr., *J. Am. Chem. Soc.*, 78, 112 (1956).

(26) Table I, Ref. c.

(27) Table I, Ref. g.

(28) Table I, Ref. a, b, d (cpd. XIV; kindness of J. B. Shohan), f.

(29) Table I, Ref. e.

(30) C. F. H. Allen, J. R. Byers, W. J. Humphlett, and D. D. Reynolds, *J. Chem. Educ.*, 32, 394 (1955), Fig. 1.

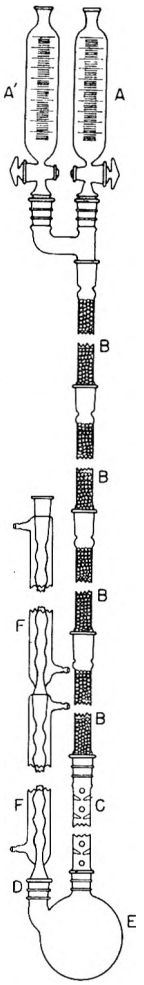


FIG. 4. APPARATUS FOR CONTINUOUS BROMINATION.

Bromination of the adduct by using a form of the continuous reactor[30] modified for bromination (Fig. 4), gives a 95% yield of mixed isomers (m.p. 173°; 131°) in the ratio of 3:2; there is none of the gummy by-product that always appears in a batch procedure. The column is made up of five 20- × 1-inch sections (B-C); the upper four (B) are packed with glass helices and the lower (C) is a Vigreux. Each is wrapped with 0.5-inch heating tape and is covered, in turn, with 0.5-inch asbestos paper tape. Hydrogen bromide escapes at the top of two reflux condensers (F), which are cooled with circulating ice water. A 25% solution of the nitrile in acetic acid, and an equal volume of acetic acid containing the required amount of bromine, were admitted from A, A'. With the Variacs set at 60, the capacity was 165 grams of product per hour. Since this is a very rapid bromination, only two sections (B) suffice.

Methyl 3-phenylcyclopropane-1,1,2,2-tetracarboxylate. The necessary methyl benzalmalonate was prepared in a large (4-inch diameter), continuous reactor (general form).[30] On using 6.1 moles each of benzaldehyde and methyl malonate, 16 min. were required for the addition, with Variacs set at 85 (bottom) and 55 (top). The yield was 952 g. (75%). It was fractionated through an 8-inch Vigreux column and had b.p. 115–116° at 0.4 mm.; n_D^{25} 1.5552 (unchanged on refractionation). The methyl benzaldimalonate[31] melted at 77° (lit. 64–65° uncorr.).

Anal. Calcd. for $C_{17}H_{20}O_8$: C, 57.9; H, 5.7. Found: C, 58.2; H, 5.8.

The new monobromoester, m.p. 103.5°, was obtained in a yield of 93% on bromination in chloroform in the usual fashion.[29, 31]

Anal. Calcd. for $C_{17}H_{19}O_8Br$: C, 47.3; H, 4.4. Found: C, 47.5; H, 4.7.

Methyl cyclopropane-1,1,2,2-tetracarboxylate, m.p. 87°, was obtained from the monobromoester by the usual procedure,[31] and treatment with alcoholic potassium acetate.

Anal. Calcd. for $C_{17}H_{18}O_8$: C, 58.3; H, 5.2. Found: C, 58.2; H, 5.0.

The mixed melting point of a 1:1 mixture of methyl benzaldimalonate and the tetracarboxylic methyl ester was 62.5°–63.5°.

The ethyl ester is known.[32] Both methyl and ethyl esters are hydrolyzed and decarboxylated to the same 3-phenylcyclopropane-1,2-dicarboxylic acid,[32] m.p. 174°; neut. equiv. Calcd., 103. Found, 103.

Acknowledgment. We are pleased to acknowledge the technical assistance of A. L. Geddes, for the infrared spectra obtained by using a lithium fluoride prism and of Messrs. W. Blum, J. R. Byers, Jr., and D. D. Reynolds, all of these Laboratories.

ROCHESTER 4, N. Y.

(31) H. Meerwein, *Ann.*, **360**, 344 (1908).

(32) A. Kötz and P. Spiess, *J. prakt. Chem.*, [2], **68**, 163 (1903).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF PURDUE UNIVERSITY]

Heterogeneous Bimolecular Reduction. I. General Considerations of Mechanism. The Emmert Reaction*,[1]

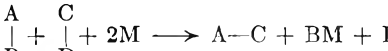
G. BRYANT BACHMAN, M. HAMER,[2a] E. DUNNING,[2b] AND R. M. SCHISLA[2c]

Received May 24, 1957

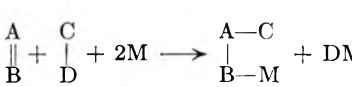
Heterogeneous bimolecular reduction has been defined as a general category of reactions. It has been discussed as to its applications, variations, and limitations in specific cases. The coreduction of carbonyl compounds and pyridine with metals to give pyridyl alcohols has been studied critically as an example of this type of reaction.

The classification of organic reactions into general types serves not only to correlate known reactions, but also to suggest new reactions and to simplify mechanism studies. The purpose of this research has been to investigate the general type of reaction in which two different kinds of molecules are coupled under reductive conditions. We will refer to this as Heterogeneous Bimolecular Reduction (Het BR) to distinguish it from reactions in which like molecules are so coupled, which will be called Homogeneous Bimolecular Reduction (Hom BR).

Het BR reactions may occur in various ways. Three subtypes may be illustrated by the following equations in which A, B, C, and D are atoms of any element, but usually are carbon, oxygen, nitrogen, halogen, or sulfur, and M is a reducing agent.



(1)



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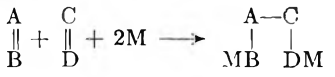


(3)

Familiar examples of these types include:

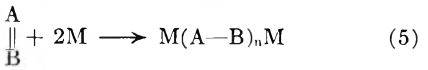
Type (1): the Wurtz,[3] and Wurtz-Fittig[4] and Grignard reactions; with A and C carbon, and B and D halogen.

Type (2): the Reformatskii reaction;[5,6] with A and C carbon, B oxygen, and D halogen.

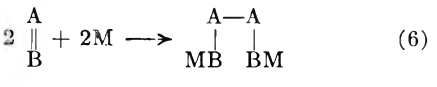
Type (3): the pinacol reduction of unlike ketones,[7,8] with A and C carbon, and B and D oxygen; the oxo or hydroformylation reaction[9] with A, B, and C carbon, and D oxygen; the coreduction of aldehydes and nitro compounds to dialkyl amines,[10] with A carbon, C nitrogen, and B and D oxygen.

Because of its apparently greater applicability in organic chemistry the third of the above types has attracted our attention first. Casual reflection will reveal that this type of reaction is likely to be accompanied by other reactions including: (4) monomolecular reduction, (5) telomerization, and (6) Hom BR.

(4)



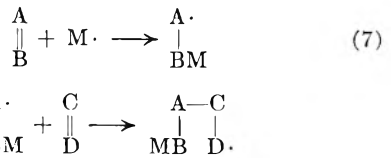
(5)



(6)

All of the factors which influence the relative extent of (3) versus (4), (5), and (6) have not been determined although it would be expected that the natures of A=B, C=D, M, and any solvent employed would be important.

Another less obvious factor would be the mechanism by which the reaction proceeds, *i.e.*, the nature of the intermediates involved. Thus the overall reaction (3) might involve a free radical intermediate (7) or an anionic intermediate (8) depending on whether the reducing agent M supplies one or two electrons at a time.



(7)

* This paper is a contribution in honor of Lyndon F. Small, former Editor of the Journal.

(1) Contains material from the Ph. D. theses of M. Hamer, August, 1953; E. Dunning, August, 1954; and R. M. Schisla, June, 1957; all at Purdue University.

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(c) Indiana Elks Fellow, 1954–55; Allied Chemical Dye Corp. Fellow, 1955–56. Present address: Monsanto Chemical Co., Dayton, Ohio.

(3) C. A. Wurtz, *Ann.*, **96**, 364 (1855).

(4) R. Fittig and B. Tollens, *Ann.*, **131**, 303 (1864).

(5) S. N. Reformatskii, *Ber.*, **20**, 1210 (1887).

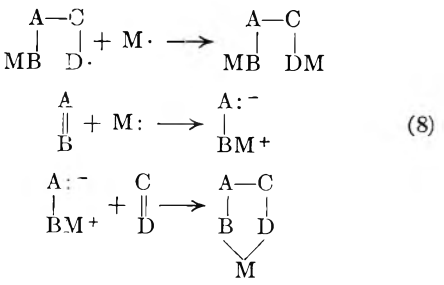
(6) R. L. Schriner, *Org Reactions*, **I**, 1 (1942).

(7) N. V. Elagina and N. D. Zelinskii, *Doklady Akad. Nauk S.S.S.R.*, **71**, 293 (1950).

(8) R. C. Fuson, *Record Chem. Progr.* **12**, 1 (1951).

(9) H. H. Storch, N. Golumbic and R. B. Anderson, *The Fischer-Tropsch and Related Syntheses*, John Wiley and Sons, Inc., New York, 1951, p. 441.

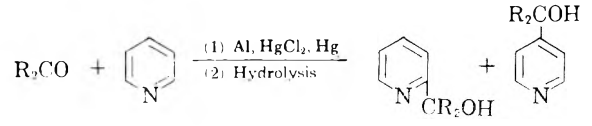
(10) W. S. Emerson and H. W. Mohrmann, *J. Am. Chem. Soc.*, **62**, 69 (1940).



(8)

Since reducing agents possessing two or more electrons do not necessarily supply them in pairs it is not possible to decide *a priori* whether a given M will follow mechanism (7) or (8). If however, a C=D compound could be found which was known to be more readily attacked by anions than by free radicals, then in this case it should be possible to demonstrate a preference for mechanism (8). Such a substance is available in pyridine which resists substitutive attack by cations, is slowly attacked by free radicals, and is readily attacked by anions. Furthermore pyridine is preferentially attacked by anions at the 2- and 4-positions while it is attacked by free radicals at all positions.[11] This latter fact serves to sharpen the differentiation of free radical from anion attack which would otherwise be dependent on rate differences only.

The coreduction of aldehydes or ketones and pyridine with magnesium or aluminum produces pyridyl alcohols.[12] The reaction has been used for



synthetic purposes,[13–17] but it has not been studied extensively otherwise, and no detailed mechanism for it has been proposed. Because it meets so admirably the requirements for our study of Het BR we decided to examine it in some detail and especially to determine the effect on it of variations in the reactants and conditions.

The nature of the reaction. Small amounts of the carbonyl compound and pyridine are heated with the amalgamated metal at reflux until the reaction begins as evidenced by the formation of color (usually green, changing to brown). The remainder of the reactants are added slowly to prevent too rapid reaction, and the mixture is finally heated at reflux until the metal has disappeared, or until no further change is noted. The reaction mixture is then cooled, hydrolyzed with base, the organic products acid extracted, basified, and the nitrogenous products fractionally distilled.

The nature of the reducing agent. The metals magnesium and aluminum seem to be specifically suitable reducing agents and give yields of products up to about 50%.[18] In spite of careful attempts by ourselves and the previous workers to find other isomers, only the 2- and 4-pyridyl alcohols were found. The ratio of the two isomers averages about 4/1 for aluminum while magnesium produces the 2-isomer only. From these facts it would appear that the reaction involves an anion intermediate as in (8).

Numerous attempts were made to produce pyridyl alcohols with reducing agents known to be capable of supplying only one electron at a time. Sodium, lithium, binary mixture ($Mg + MgI_2$),[19] chromous acetate $Cr(OCOCH_3)_2$,[20] vanadous chloride (VCl_2),[20] and hypophosphorous acid[21] gave Hom BR of the carbonyl compound only or at best traces of Het BR. Sunlight converts a mixture of benzophenone and 2-propanol to benzopinacol apparently by a free radical (single electron) process.[22] However we found that a similar mixture containing pyridine gave a 66% yield of benzopinacol and no pyridyl alcohol on illumination. From these unsuccessful attempts we conclude that agents supplying electrons by single-electron processes are incapable of causing the Emmert reaction to occur.

A series of bivalent metals beside magnesium were investigated. Those with low reduction potentials (zinc, 0.76 v.; manganese, 1.1 v.) did not react. One with a high reduction potential but a poor coördinating power[23] (calcium, 2.87 v.) reacted but gave the pinacol and no pyridyl alcohols.

(11) R. C. Elderfield, *Heterocyclic Compounds*, John Wiley and Sons, Inc., New York, N. Y., 1950, Vol. I, pp. 401–410.

(12) B. Emmert and E. Asendorf, *Ber.*, **72**, 1188 (1939); B. Emmert and E. Pirot, *Ber.*, **74**, 714 (1941).

(13) G. B. Bachman and D. D. Micucci, *J. Am. Chem. Soc.*, **70**, 2381 (1948).

(14) C. H. Tilford, R. S. Shelton, and M. G. Van Campen, Jr., *J. Am. Chem. Soc.*, **70**, 4001 (1948).

(15) H. L. Lochte, P. F. Kruse, Jr., and E. N. Wheeler, *J. Am. Chem. Soc.*, **75**, 4477 (1953).

(16) C. H. Tilford and M. G. Van Campen, Jr., *J. Am. Chem. Soc.*, **76**, 2431 (1954).

(17) F. J. McCarty, C. H. Tilford, and M. G. Van Campen, Jr., *J. Am. Chem. Soc.*, **79**, 472 (1957).

(18) Yields on the reaction have been calculated by different authors on different bases, *i.e.*, on the metal or on either of the other reagents. When calculated on the metal the basis may be the total valence of the metal or some fraction thereof depending on the assumed mechanism of the reaction. We have in general used the total reducing-power approach and calculated yields on the basis of one molecule of product resulting from each pair of valence electrons in the metal atom, *i.e.*, % yield = $\frac{\text{moles products} \times 100}{\text{gram atoms metal} \times \text{metal valence}/2}$

(19) M. Gomberg and W. E. Bachmann, *J. Am. Chem. Soc.*, **49**, 236 (1927).

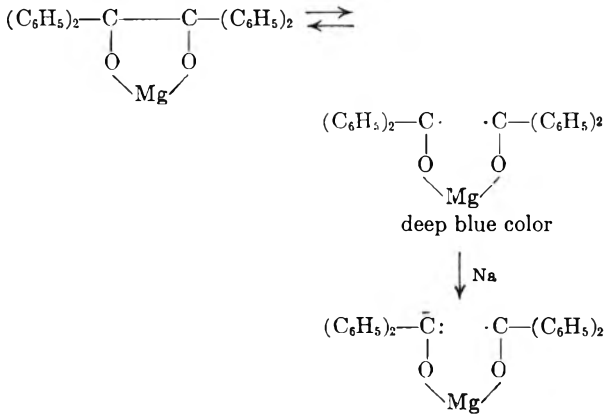
(20) J. B. Conant and H. B. Cutter, *J. Am. Chem. Soc.*, **48**, 1016 (1926).

(21) T. Moeller, *Inorganic Chemistry*, John Wiley and Sons, Inc., New York, N. Y., 1953, p. 641.

(22) W. E. Bachmann, *Org. Syntheses*, **Coll. Vol. II**, 71 (1944).

(23) A. A. Grinberg and K. B. Yatsimirsky, *Bull. acad. sci. U.R.S.S.*, **2**, 239 (1952), on the basis of the heats of formation of chelates between metal ions and bases, arranges the metals in the following order of complexing ability: Be > Cu > Hg > Ni > Zn > Co > Fe > Cr > Mg > Mn > Cd > Ca.

One with a high reduction potential and a high coordinating power (beryllium, 1.69 v.) gave a very low yield (2%) of the 2-pyridyl alcohol and a good yield of pinacol. We conclude that while a minimum reduction potential and coordinating power are important, the essential factor in the reducing agent is an ability to transfer two electrons at a time to the carbonyl compound. Magnesium (2.4 volt) and aluminum (1.7 volt) seem to combine these characteristics better than any other metals although beryllium is apparently able to function this way to a minor extent.[24] A combination of zinc (low reduction potential, high coordinating power) and sodium (high reduction potential, low coordinating power) gave the same results as sodium alone. However, separately prepared magnesium benzopinacolate, which alone did not react with pyridine, did give a pyridyl alcohol when sodium was added. A possible rationalization of this latter result is,

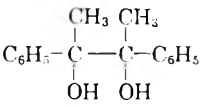


The same reaction would not be expected to occur with magnesium acetone pinacolate because it does not dissociate readily at the central C-C bond.

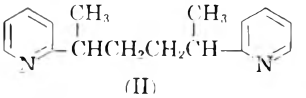
Nature of the pyridine compound. The introduction of a substituent in the 2-position of the pyridine ring might be expected to increase the relative extent of reaction at the 4-position and a compound like 2,6-lutidine might be expected to react at the 4-position only. However steric effects interfere and 2-picoline gives only about 5–15% yields of the 2,6-isomer,[12,14,15] while 2,6-lutidine gives only pinacols and no pyridyl alcohols.[12] We conclude that the product before hydrolysis consists of a cyclic coordination compound with metal attached to nitrogen and that groups in the 2-position interfere with its formation. Very good yields are obtained with 3-picoline[12,15] and 4-picoline[14,15] and fair yields with quinoline.[12]

(24) Investigations by R. Muller, F. Holz, W. Knaus, F. Planiszig, and K. Prett, *Monatsh.*, 44, 205 (1923), on the electrodeposition of metals from pyridine solutions of their salts show that the reduction potentials of the metals are not the same in pyridine as in water. Thus magnesium and sodium are electrodeposited from pyridine, while aluminum is not. Hence, reduction potentials in water cannot be taken as an exact measure of reduction potentials in pyridine, although it is reasonable to suppose that there is a rough correlation between the two.

Vinylogs of pyridine, such as 2-vinylpyridine, 2-isopropenylpyridine, and 2-stilbazole, react with ketones and aluminum to give Hom BR products from both reactants. Thus 2-isopropenylpyridine, acetophenone, and aluminum give I and II as well as about equal amounts of the monomolecularly

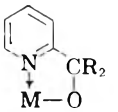


(I)

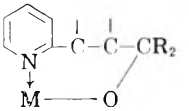


(II)

reduced product 2-isopropylpyridine. Similar results were obtained with the other two vinylogs except that 2-vinylpyridine gave much polymer. We conclude from these experiments that the postulated cyclic coordination compound obtained with pyridine is less probable with pyridine vinylogs because of the increased size of the ring (IV).

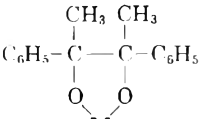


(III)

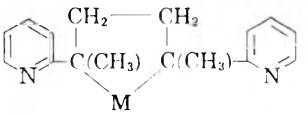


(IV)

Instead a different pair of 5-membered rings, V and VI, form



(V)



(VI)

These lead to the dimeric forms I and II on hydrolysis. α,β-Unsaturated carbonyl compounds also are reported[12] not to react satisfactorily to give pyridyl alcohols probably for a similar reason. Assuming conjugate addition of the pyridine and the metal to the unsaturated ketone a seven-membered ring would again have to form.

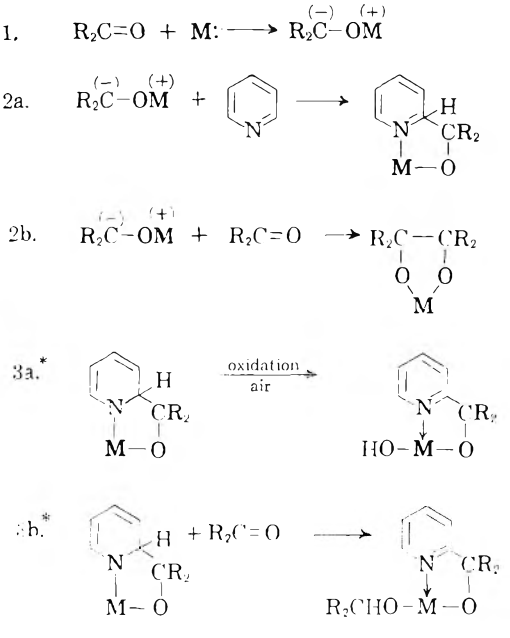
Nature of the carbonyl compound. Simple dialkyl, diaryl, alkyl aryl, and cycloalkyl ketones react satisfactorily with pyridine to give pyridyl alcohols. However ortho substituents sterically inhibit the reaction with aryl compounds.[14] Thus *o*-methylacetophenone gives a moderate yield while *o*-methoxy- and *o*-chloroacetophenone gives zero yields. This hindrance is less apparent in *ortho*-substituted benzaldehydes, since *o*-chloro- and *o*-methoxybenzaldehydes give fair yields of the corresponding pyridyl alcohols.

Groups in the *para*-position of the benzene ring exert electronic influences which may assist or hinder the reaction. Thus methyl and methoxyl groups assist, while the chloro group hinders the reaction. These results suggest that electron-supplying groups assist by increasing the negativity of the intermediate anion and hence by increasing the ease with which it attacks the pyridine ring.

Electron withdrawing groups have the opposite effect. An alkyl group in a ketone similarly reinforces (by hyperconjugation) the negativity of the anion to a greater extent than the hydrogen of an aldehyde group. This may account for the generally better yields obtained with simple ketones than with simple aldehydes.

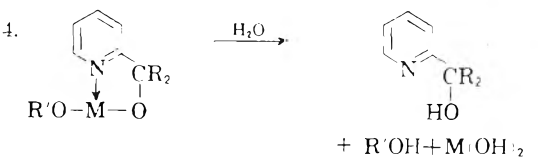
The nature of the medium. Moisture hinders or prevents the Het BR reaction of pyridine and carbonyl compounds. Scrupulous care must be used to dry the reagents thoroughly. Similarly, solvents which can supply protons through ionization cannot be used. This includes carboxylic acids and alcohols. Apparently these solvents either prevent the formation of the carbanion intermediate or neutralize it before it can attack the pyridine nucleus. It is interesting to compare these results with the effects of *p*H changes in the electroreduction of ketones. Using a polarograph it was observed by Pasternak[25] that benzophenone is reduced monomolecularly by a two-electron process at *p*H 4–9 to the alcohol (benzhydrol), while at *p*H 1.3 and below it is reduced bimolecularly by a single-electron process to benzopinacol. Here also the higher proton concentration apparently interferes with the two-electron or anionic process but not with the one-electron or free radical process.

Mechanism of the reaction. The above studies of factors influencing the Het BR reaction of carbonyl compounds and pyridine with metals are summarized in Table I. They suggest the following series as a rational explanation of the overall synthesis:

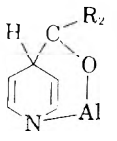


(25) R. Pasternak, *Helv. Chim. Acta.*, **31**, 753 (1948).

* Each of these processes probably involves more than one step.



The adaptation of these equations to a trivalent metal like aluminum would be cumbersome but not complicated. The fact that aluminum gives some of the 4-isomer while magnesium does not may depend on the greater size of the aluminum atom which more readily permits a transannular bridge between the hetero atom and the 4-position.



(Note, however, our remarks concerning the nonformation of IV). Step 3 (a and b) represents oxidations of the assumed dihydropyridine intermediate which results in restoration of the full resonance of the pyridine ring and as such should proceed very readily.[26] To the extent that this step involves unreacted carbonyl compound the potential yields based on this reagent are reduced. However only minor amounts of the corresponding alcohol are found in the products indicating that other oxidizing agents are also involved. The fact that no hydrogenated pyridines are found in the products suggests that air may be the primary oxidizing agent.

Conclusions. For success the Emmert reaction requires: (*a*) a two-electron transferring agent of strong reducing power (> Mn) and strong coordinating power (> Ca), (*b*) a heterocyclic base containing a —N=ring member, an unsubstituted α-position, and freedom from steric interference (by α-substituents) to chelation of the nitrogen atom to a metal atom, (*c*) a carbonyl compound capable of accepting two electrons to form a carbanion and no groups which by resonance stabilization or steric hindrance interfere with its ability to attach itself to the pyridine ring, and (*d*) a reaction medium which is not able to furnish protons in sufficient concentration to hamper the formation of the carbanion or to neutralize it before it can react with the pyridine.

An important implication of this analysis is that metals differ in their relative capacities to react with carbonyl compounds by one-electron and two-electron processes, and that in pyridine there exists a suitable reagent for detecting this difference. It is our intention to pursue this conclusion further and to study other examples of Het BR.

(26) See reference (11), p. 621.

TABLE I. Coreduction of Heterocyclic and Carbonyl Compounds

Expt. No.	Heterocyclic Compound	Carbonyl Compound	Reducing Agent	Procedure Used	Products, % Yield[a] Pyridyl Alcohol	Others
1	Pyridine	Acetone[12, 15]	Al	A	2-, 31–39	
2	Pyridine	Benzaldehyde[14]	Mg	A	2-, 14	
3	Pyridine	Benzaldehyde	VCl_2	C	0	Hydrobenzoins
4	Pyridine	Acetophenone[12, 14]	Al	A	2-, 32 4-, 4	
5	Pyridine	Acetophenone	Mg + MgI_2	A	0	[b]
6	Pyridine	Acetophenone	Li	B	0	[b]
7	Pyridine	Acetophenone	Zn	A	0	[b]
8	Pyridine	Acetophenone	Zn + Na	A	0	Pinacol
9	Pyridine	Acetophenone	Mn	A	0	[b]
10	Pyridine	Acetophenone	Ca	A	0	Pinacol
11	Pyridine	Phenylacetone[14]	Al	A	2-, 29	
12	Pyridine	2,3-Dimethoxyphenylacetone	Al	A	0	Tar
13	Pyridine	4-Hydroxy-3-methoxyphenylacetone	Al	A	0	Tar
14	Pyridine	4-Chlorophenylacetone	Al	A	0	Tar
15	Pyridine	α-Dimethylaminoacetophenone	Al	A	0	[b]
16	Pyridine	Benzophenone[12]	Mg	A	2-, 22	[b]
17	Pyridine	Benzophenone	Na	B	4-, 2[c]	Tar
18	Pyridine	Benzophenone	$(CH_3)_2CHOH$, sunlight	E	0	Pinacol, 66
19	Pyridine	Fluorenone	Al	A	0	Pinacol
20	Pyridine	Magnesium acetone pinacolate	...	F	0	[b]
21	Pyridine	Magnesium benzpinacolate	...	F	0	[b]
22	Pyridine	Magnesium benzpinacolate	Na	F	2-, 10	
23	Pyridine	Benzaldehyde	H_3PO_2,H^+	G	0	[b]
24	Pyridine	Benzaldehyde	H_3PO_2,OH^-	G	0	[b]
25	Pyridine	Benzaldehyde	H_3PO_2, pH 7	G	0	[b]
26	2-Picoline	Benzaldehyde	Mg	A	2, 6-, 5[d]	[b]
27	2-Picoline	Benzaldehyde	Al	A	0	[b]
28	2-Picoline	*p*-Methoxybenzaldehyde	Mg	A	0	
29	2-Picoline	p-Methoxybenzaldehyde	Al	A	0	
30	2-Picoline	Phenylacetone	Al	A	0	[b] Tar
31	4-Picoline	Acetophenone[14]	Al	A	2-, 30	
32	4-Picoline	Acetophenone	Be	A	2-, 2	Pinacol, 54.5
33	4-Picoline	Phenylacetone	Al	A	2-, 56[e]	
34	2,6-Lutidine	Acetophenone	$Cr(OCOCH_3)_2$	D	0	[b]
35	2,6-Lutidine	Acetophenone	Al	A	0	[b]
36	2,6-Lutidine	Acetophenone	Mg	A	0	[b]
37	2,6-Lutidine	Benzophenone	Al	A	0	[b]
38	2,6-Lutidine	Benzophenone	Mg	A	0	[b]
39	Ethyl nicotinate	Acetophenone	Mg	A	0	Tar
40	2-Vinylpyridine	Acetophenone	Al	A	0	2-Ethylpyridine, 10[f], 10[f,g] Pinacol, 20[a]
41	2-Isopropenylpyridine	Acetophenone	Al	A	0	2-isopropylpyridine, 33[h] II, 24[i,j] Pinacol, 13.5[a]
42	2-Stilbazole	Acetone	Al	A	0	[b]
43	2-Stilbazole	Acetone	Mg	A	0	[b]
44	2-Stilbazole	Benzaldehyde	Al	A	0	2-Phenethylpyridine, 19.5[k] Isohydrobenzoin, 5[a], 33[g,i,k]
45	2-Stilbazole	Acetophenone	Al	A	0	2-Phenethylpyridine, 25–34[k] Pinacol, 12[a], 29[g,i,k]
46	2-Stilbazole	Phenylacetone	Al	A	0	2-Phenethylpyridine, 44[k] 33[g,i,k]
47	Quinoline	Acetophenone	Al	A	2-, 14–20	
48	Quinoline	Phenylacetone	Al	A	0	Tar
49	Isoquinoline	Acetophenone	Al	A	0	Tar
50	Quinaldine	Acetophenone	Al	A	0	Tar
51	2-Phenoxyquinoline	Acetophenone	Al	A	0	Tar

[a] Yield based on metal. [b] Recovered starting material. [c] M.p. 234–235°, lit. m.p. 234° and 235°.[29] [d] M.p. 87–88.5°, hydrochloride m.p. 174–175°. *Anal.* Calcd. for $C_{13}H_{13}NO$: N, 7.03. Found: N, 6.97. This material was oxidized with $KMnO_4$ in H_2SO_4 to pyridine-2,6-dicarboxylic acid (m.p. 228–230° d.). [e] M.p. 76–77°. *Anal.* Calcd. for $C_{15}H_{17}NO$: C, 78.64; H, 7.50; N, 6.10. Found: C, 78.96; H, 7.62; N, 6.19. [f] Yield based on 2-vinylpyridine; picrate, m.p. 106–107°, lit. m.p. 107.8–108.3°.[27] [g] Dimer like II. [h] Yield based on 2-isopropenylpyridine; picrate m.p. 116.5°, lit. m.p. 118.1–118.7°.[27] [i] See experimental. [j] Calcd. for $C_{16}H_{20}N_2$: M R_D, 73.73; found M R_D, 73.65. [k] Yield based on 2-stilbazole; methiodide m.p. 190°, lit. m.p. 190–191°.[28]

EXPERIMENTAL

The following experimental details are provided to illustrate the various procedures listed in Table I.

Procedure A. Bimolecular reduction of 4-picoline and acetophenone. Granular (30 mesh) aluminum (27 g., 1 mole), 0.5 g. of mercuric chloride and a few drops of mercury were preheated together for 0.5 hr at 100° in a 1-l. three-necked flask fitted with a dropping funnel, condenser, and mercury sealed stirrer. A mixture of 25 g. each of 4-picoline and acetophenone was added in one portion and stirred until the reaction began. The beginning of the reaction was accompanied by an evolution of heat and a color change to dark green. The remaining picoline (290 g., 3.5 moles total) was added in one portion, and 185 g. acetophenone (1.75 moles total) was added dropwise. The temperature was kept at 130° during the addition with the aid of a heating mantle. The ketone addition required 5.5 hr.; the temperature was kept at 130° for an additional 3.5 hr., rapid stirring being maintained during this time. The reaction mixture was then cooled and decomposed by pouring into 1 l. of 3*N* sodium hydroxide solution. The separating oil was extracted successively with 200 ml. portions of 6*N* hydrochloric acid. The acid extract was made basic with sodium hydroxide. The separating organic layer was dried over calcium sulfate and distilled. The fraction boiling 130–135° (0.8 mm) yielded a total of 85 g. (30% yield) of the pyridyl alcohol. Recrystallization from petroleum ether (b.p. 60–70°) gave a colorless solid, m.p. 69.5–70°. This compound is reported to melt at 70–71°.[14] It should be noted that larger amounts of $HgCl_2$ (0.2 mole per 1 mole of metal) were used with all the other bivalent metals (*i.e.*, Zn, Mn, Mg, Ca, and Be) listed in Table I where procedure A is employed.

Procedure B. Bimolecular reduction of pyridine and benzophenone with sodium. A mixture of pyridine (40 g.), benzophenone (90 g.), and toluene (500 ml.) was placed in a 3-necked flask fitted with a stirrer, dropping funnel, and condenser. The pyridine and toluene used were thoroughly dried over CaH_2. The flask was flushed with dry nitrogen, and a nitrogen atmosphere was maintained throughout the reaction. Sodium dispersion (40 g. National Distillers Co. sample, dispersed in xylene, 50% by weight) was added dropwise under nitrogen. The first drop gave a dark blue color which intensified as more was added. Reaction was slightly exothermic. The reaction mixture was allowed to stand at room temperature under nitrogen for 5.5 days, after which the color was dark brown. The reaction mixture was then oxidized by passing moist air through the flask. The oxidation procedure required 4 hr., and was exothermic but not vigorous. The light-orange solution was then decomposed with 6*N* hydrochloric acid, and the acid extract made basic with 3*N* sodium hydroxide. An ether extract of the basic layer gave no crystals on evaporation. A solid substance which precipitated from the basic solution showed m.p. 227–231° when recrystallized from benzene, and 232.5–234° when recrystallized from ethyl acetate. Literature values are 234° and 235° for 4-pyridyldiphenylcarbinol.[29] The crystals were insoluble in ether and gave a positive phenyl test with $AlCl_3$ and chloroform. The yield of the 4-pyridyl alcohol was less than 2%.

A mixture of benzophenone (61 g.), pyridine (26.3 g.), and toluene (50 ml.) was added slowly to sodium dispersion (30 g.), the temperature being maintained at 75–85° by means of a heating mantle during the addition and for 1 hr. thereafter. The solution was air-oxidized and decomposed with water. After cooling, 0.55 g. (0.75% yield) of the 4-isomer separated. No other condensation product could be isolated. Tar formation was greater than in the previous experiment.

Other variations in the reaction conditions included extended heating, rapid addition of the reactants, and allowing the reaction mixture to stand for two weeks at room temperature, but in no case was a yield better than 2% obtained, and the 2-isomer was never isolated.

Procedure C. Reaction between vanadous ion, pyridine and benzaldehyde. A solution of vanadous chloride prepared from 25 g. V_2O_5, 37.5 g. of zinc metal (amalgamated), 100 cc. water, and 140 cc. concentrated hydrochloric acid according to the procedure of Conant and Cutter,[20] was filtered through glass wool into a three-necked flask previously swept out with CO_2 gas. A solution of benzaldehyde (11 g.), ethanol (40 cc.), pyridine (32 g.), and hydrochloric acid (50 g.) was added dropwise with rapid stirring. After the addition was complete (3 hr.) the solution was stirred for 1 hr. The reaction mixture was then extracted eight times with ether, giving, after drying with Drierite and evaporating the solvent, 11 g. of a non-basic crystalline material, with a wide melting range. Oxidation of this material with permanganate yielded benzoil. These results parallel those which Conant and Cutter[20] obtained in the absence of pyridine.

Procedure D. Reaction of chromous ion with 2,6-lutidine and acetophenone. Chromous acetate (7.8 g.), acetophenone (15 g.), and 50 ml. of benzene were added in one portion to a refluxing mixture of 17 g. of 2,6-lutidine. The mixture was refluxed for 24 hr., during which time it turned from red-brown to green. The solution was cooled to room temperature, filtered, and the inorganic salts removed by extraction with water. Distillation of the residue gave 16 g. of 2,6-lutidine and no condensation product.

A three-necked flask containing a mixture of 17 g. of 2,6-lutidine and 15 g. of acetophenone was flushed out with nitrogen. Chromous acetate (7.8 g.) was added in one portion, and the temperature raised to 140° for 6 hr. The reaction mixture was cooled, filtered, extracted, and distilled. Only unreacted starting material could be isolated.

Procedure E. Irradiation of mixtures of benzophenone, acetophenone, and pyridine. A mixture of pyridine (26 g.), benzophenone (61 g.), and isopropyl alcohol (344 g.) was placed in a flask and a cork stopper was wired in place. The flask was exposed to sunlight for 7 days, after which the crystals which had formed were filtered off and purified. Forty-one grams (66% yield) of benzopinacol were found. Distillation of the liquid filtrate yielded 20 g. of pyridine and a small amount of a non-distillable tar.

Another reaction identical with the above except that acetophenone was used in place of the benzophenone resulted in the recovery of the starting materials.

Procedure F. Reaction of magnesium benzpinacolate with pyridine in the absence and presence of sodium. Benzpinacol[19] (24 g., 0.66 mole) in ether was added to 154 cc. of 0.4*M* Et_2Mg solution[30] in a 3-necked flask under nitrogen, giving first a cherry red color, and then a deep blue. The solution was allowed to stand at room temperature for 1 hr., and then pyridine (21.2 g., 0.25 mole) was added, and the solution was heated at 100° for 8 hr. The reaction mixture was cooled and decomposed with ammonium chloride solution and extracted with toluene. The toluene layer was dried and evaporated, giving 21 g. (89%) recovered benzopinacol. The aqueous layer was made basic and extracted with benzene, and the benzene extracts were evaporated. No bimolecular reduction product could be found.

Another reaction mixture containing magnesium benzopinacolate, which was prepared by adding benzopinacol (18.3 g., 0.05 mole) in ether dropwise to an ethereal solution of Et_2Mg (116 cc., 0.05 mole), was allowed to stand for 2 hr. under nitrogen, and then pyridine (21.2 g., 0.25 mole) was added rapidly to the mixture. Finally sodium (5 g., 0.22 mole) was added in small pieces over a period of 1 hr.

(27) H. C. Brown and W. A. Murphey, *J. Am. Chem. Soc.* **73**, 3308 (1951).

(28) A. P. Phillips, *J. Org. Chem.*, **13**, 622 (1948).

(29) L. C. Anderson and N. V. Seegar, *J. Am. Chem. Soc.*, **71**, 343 (1949).

(30) R. Kullman, *Compt. rend.*, **231**, 866 (1950).

There was no color change, but a metallic luster appeared. The reaction mixture was allowed to stand at room temperature for 73 hr. At the end of this time the metallic luster which was present at the beginning of the reaction had disappeared but the color was still deep blue. The reaction mixture was decomposed by adding 3*N* hydrochloric acid dropwise to the reaction mixture, allowing the slight evolution of gas to subside after each addition. The mixture was then filtered, ether was added, and the layers were separated. The residue from the filtration was a small amount of an orange-red solid, insoluble in acid, base, water, acetone, and ethanol. The aqueous layer was made basic, filtered, and extracted with toluene, and the toluene extracts were dried and allowed to evaporate. The crystals which were left were recrystallized from ethanol, yielding 1.3 g. (10%) of 2-pyridyldiphenylcarbinol, m.p. 102–103°, lit. m.p. 104–105°.[14] Hydrochloride, m.p. 178–179°, mixed m.p. with an authentic sample, 177–179°.

Procedure G. Reaction of hypophosphorous acid with pyridine and benzaldehyde. Three reactions were set up involving H_3PO_2, pyridine, and benzaldehyde, in acidic, basic, and neutral (pyridine) solutions. The mixtures contained:

(*a*)	Pyridine,	10 g. (0.13 mole)
	C_6H_5CHO,	14 g. (0.13 mole)
	H_3PO_2,	32 g. (0.5 mole)
(*b*)	Pyridine,	16 g. (0.2 mole)
	NaOH,	8 g. (0.2 mole)
	C_6H_5CHO,	10.6 g. (0.1 mole)
	Water	20 cc.
	H_3PO_2,	6.6 g. (0.1 mole)
(c)	Pyridine,	32 g. (0.4 mole)
	C_6H_5CHO,	10.6 g. (0.1 mole)
	H_3PO_2,	6.6 g. (0.1 mole)

Each mixture required the addition of a little ethanol to obtain a homogeneous solution. All were refluxed for 11 hr. except for (*b*) which was allowed to stand at room temperature for 24 hr. The (*a*) was extracted with ether, while the (*b*) and (c) were first acidified with HCl and then ether extracted. The ether extracts were extracted with sodium bisulfite and gave, on evaporation, non-basic materials with a very wide melting range. Oxidation of these products with nitric acid gave benzoic acid as the only insoluble product.

The (*a*), (*b*), and (c) were basified with sodium hydroxide. Extraction of these basic solutions with ether followed by evaporation of the ether gave no basic material other than pyridine.

Determination of the structure of the dimer of 2-isopropenylpyridine with the aid of infrared analysis. The structure II was assigned to the dimer obtained from the attempted coreduction of 2-isopropenylpyridine and acetophenone on the basis of the following characteristic absorption peaks: (*a*) 12.73 μ and 13.40 μ-strong bands corresponding to monosubstitution at the 2-position of the pyridine nucleus,[31] and (*b*) a weak band in the region 9.52–9.62 μ corresponding to the linkage $CH_3-\overset{|}{\underset{|}{C}}H$. Bands corresponding to disubstitution on the pyridine nucleus were absent.[32] Bands corresponding to an olefinic linkage were also absent. Dimeric forms containing gem-dimethyl groups were eliminated by the absence of an absorption peak in the range 8.35–8.40 μ—a characteristic peak for this grouping.[33] Finally, any dimeric form containing a cyclobutane ring was eliminated by the absence of absorption bands in the range 10.9–11.52μ—a region which has been reported to exhibit characteristic absorption peaks for mono-alkyl-cyclobutanes (10.9–11.0 μ)[34] and more highly substituted cyclobutanes (11.28–11.52 μ).[35] Of the possible simple dimers of 2-isopropenylpyridine only II meets all of these requirements of spectral analysis. The dimers of 2-stilbazole and 2-vinylpyridine were assumed by analogy to possess structures similar to II.

LAFAYETTE, IND.

(31) W. A. Murphey, Ph. D. Thesis, Purdue University, August, 1950, has shown that 2-isopropylpyridine exhibits characteristic absorption bands at 12.73 μ and 13.38 μ originating in out-of-plane vibrations of the unsubstituted hydrogen atoms of the ring.

(32) H. E. Podall, Ph. D. Thesis, Purdue University, August, 1955.

(33) L. J. Bellamy, *The Infra-Red Spectra of Complex Molecules*, Methuen and Co., Ltd., London, 1956, p. 235.

(34) J. M. Derfer, E. E. Pickett, and C. E. Boord, *J. Am. Chem. Soc.*, **71**, 2482 (1949).

(35) E. B. Reid and M. Sack, *J. Am. Chem. Soc.*, **73**, 1985 (1951).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF PURDUE UNIVERSITY]

Heterogeneous Bimolecular Reduction. II. Direct Acylation of Pyridine and Its Homologs and Analogs*[1]

G. BRYANT BACHMAN AND R. M. SCHISLA[2]

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Heterogeneous bimolecular reduction of pyridine and acid derivatives with metals has been found to yield *C*-acylated pyridines. The general applicability of this reaction has been studied and a series of new heterocyclic ketones has been prepared. Intermediate steps in the synthesis have been postulated.

Pyridine, quinoline, and related heterocyclic bases have never been directly and substitutively acylated.[3] Apparently the ring member =N— is sufficiently electrophylic in nature to deactivate the remainder of the ring to attack by cations. Hence the Friedel-Crafts and related reactions fail.

It occurred to us that acylation of pyridine might be achieved satisfactorily if acyl anions could be

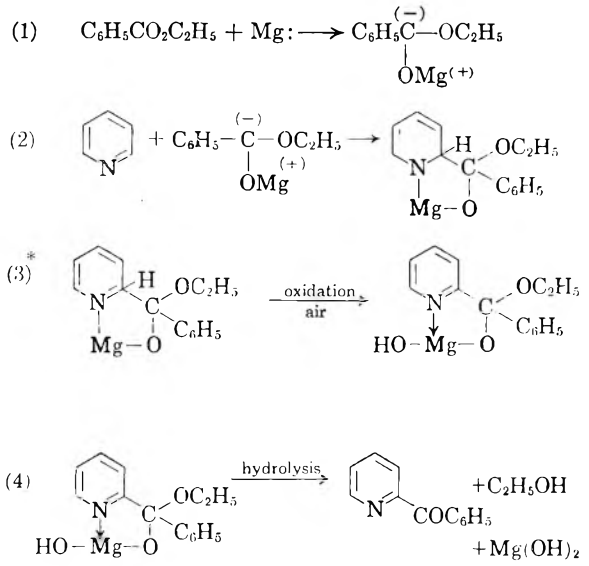
* This paper is a contribution in honor of Lyndon F. Small, former Editor of the Journal.

(1) From the Ph.D. thesis of R. M. Schisla, June 1957, Purdue University.

(2) Indiana Elks Fellow, 1954–55; Allied Chemical & Dye Corp. Fellow, 1955–56. Present address, Monsanto Chemical Co., Dayton, Ohio.

(3) R. C. Elderfield, *Heterocyclic Compounds*, John Wiley and Sons, Inc., New York, N. Y., 1950, Vol. I, p. 403–410.

created in the presence of this heterocyclic base. Anions such as NH_2^-, OH^- and $(alkyl)^-$ have been shown to attack pyridine rather easily and to introduce these groups into the ring in place of hydrogen at the 2- or 4-position. Based on the hypotheses developed in the previous paper in this series,[4] a reasonable approach to the formation of acyl anions would be to treat acid derivatives with metals like magnesium and aluminum. In contrast to metals like zinc and sodium, these metals appear to be able to reduce carbonyl groups by a two-electron transfer process to form carbanions. The expected series of reactions between pyridine, ethyl benzoate, and magnesium would therefore be:



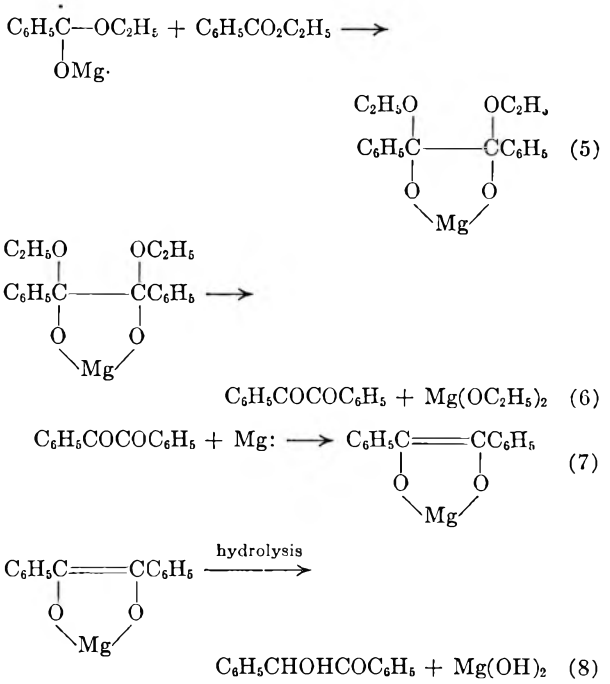
The success of this synthesis was recently announced in a Communication To The Editor of this journal.[5] The present paper describes the application of this method to pyridine homologs and analogs and to other esters. The overall synthesis is another example of heterogeneous bimolecular reduction.

The nature of the reaction. A small amount of the acid derivative and pyridine mixture is heated with amalgamated aluminum until reaction starts which is made evident by the appearance of a brown coloration. The remainder of the pyridine and acid derivative is added slowly, and refluxing is continued until the metal is consumed or until no further change is noted.

The product may be worked up as described in the preceding paper or preferably by isolating the metallic complex in solid form before hydrolyzing by pouring the reaction mixture into four to five volumes of petroleum ether. This method is more convenient, more rapid, and gives a cleaner product than direct hydrolysis, although the yields are slightly (3–5%) lower. This procedure may be applied equally successfully to the preparation of pyridyl alcohols.

The results of a number of such reactions are summarized in Table I.

The effects of various metals. In the order of decreasing yields of desired mixed ketone the metals may be arranged in the series: Al > Mg > Be > other metals. This corresponds exactly to the series observed in the coreduction of pyridine and ketones and suggests that acylation of pyridine is also a two-electron transfer process. A single-electron transfer process probably occurs simultaneously, and leads, by homogeneous bimolecular reduction of the ester, to benzil and benzoin.



The yields of the mixture of benzil and benzoin are generally inversely proportional to the yields of benzoyl pyridine, *i.e.*, they increase as the metal becomes increasingly a single-electron transfer agent. Metals with lower reduction potentials, like zinc, do not react.

The effects of substituents on the pyridine ring. Only a few experiments were performed with pyridine homologs and analogs. It was found that γ-picoline gave good yields of 2-benzoyl-4-methylpyridine and that quinoline gave good yields of 2-benzoylquinoline, but none of the 4-isomer. In general it would be anticipated that pyridines substituted in the 2- and 2,6-positions would give poor yields because of steric hindrance which is also an interfering factor in coreductions of such pyridines with ketones. On the other hand pyridines substituted in the 3- or 4-positions would not be subject to such steric hindrance and yields comparable to those obtained with pyridine should be obtained.

* This process probably involves more than one step.

(4) G. B. Bachman, M. Hamer, E. Dunning, and R. M. Schisla, *J. Org. Chem.*, **22**, 1296 (1957).

(5) G. B. Bachman and R. M. Schisla, *J. Org. Chem.*, **22**, 858 (1957).

TABLE I

COREDUCTION OF HETEROCYCLIC COMPOUNDS AND ACID DERIVATIVES

Expt. No.	Heterocyclic Compound	Acid Derivative	Reducing Agent	Procedure Used	Products, % Yield[a]	
					Pyridyl ketone	Others
1	Pyridine	Acetophenone	Al	B	2-, 31[b] 4-, 3.8[b]	Pinacol, 1
2	Pyridine	Ethyl benzoate	Al	A	2-, 23.9 4-, 6.4	2.8[z] 2.8[z]
3	Pyridine	Ethyl benzoate	Al	B	2-, 32.5 4-, 7.1	12.7[z]
4	Pyridine	Ethyl benzoate	Mg	A	2-, 10	19.1[z]
5	Pyridine	Ethyl benzoate	Be	A	2-, 8.2	46.1[z]
6	Pyridine	Ethyl benzoate	Zn	A	0	0
7	Pyridine	Ethyl *p*-chloro-benzoate	Al	A	2-, 26.4[d]	6.9[e]
8	Pyridine	Ethyl *p*-nitro-benzoate	Al	A	0	4,4′-bis(carbethoxy)a-zobenzene, 2.1[f]
9	Pyridine	Ethyl cinnamate	Al	A	2-, 8.3[g]	tars
10	Pyridine	Ethyl phthalate	Al	A	0	tars
11	Pyridine	Ethyl picolinate	Al	A	2-, 7.3[h]	tars
12	Pyridine	Ethyl formate	Al	A	0	[c]
13	Pyridine	Ethyl formate	Mg	A	0	[c]
14	Pyridine	Ethyl carbonate	Al	A[aa]	0	[c]
15	Pyridine	Ethyl oxalate	Al	A	0	Tars
16	Pyridine	Ethyl oxalate	Al	B	0	Tars
17	Pyridine	Ethyl malonate	Al	A[aa]	0	[c]
18	Pyridine	Ethyl acetoacetate	Al	A[aa]	0	Tars
19	Pyridine	Ethyl acetoacetate	Al	B	0	Tars
20	Pyridine	Ethyl acetate	Al	A	0	[c]
21	Pyridine	Secondary-butyl acetate	Al	A	2- +4-, 5.5[i,j]	[c]
22	Pyridine	*n*-Amyl acetate	Al	A[aa]	2- + 4-, 5.8[i,k]	[c]
23	Pyridine	2-Ethyl-hexyl acetate	Al	A[aa]	2- +4-, 13.0[i,l]	[c]
24	Pyridine	Ethyl propionate	Al	A[aa]	2- +4-, 8.3[i,m,n]	[c]
25	Pyridine	Methyl phenylace-tate	Al	A[aa]	2-, 9.2[o]	tars
26	Pyridine	*N*,*N*-Dimethylfor-mamide	Al	A[aa]	0	[c]
27	Pyridine	*N*,*N*-Dibutylace-tamide	Al	A[aa]	0	[c]
28	Pyridine	*N*,*N*-Dimethyl-benzamide	Al	A	2-, 36 4-, 6	17.4[z]
29	Pyridine	*N*,*N*-Dimethyl-benzamide	Al	B	2-, 32 4-, 5.9	6.4[z]
30	Pyridine	*N*,*N*-Dimethyl-benzamide	Mg	A	2-, 44.5 4-, 4.5	22[z]
31	Pyridine	*N*,*N*-Dimethyl-benzamide	Be	A	2-, 4.2	11.7[z]
32	Pyridine	*N*,*N*-Dimethyl-benzamide	Zn	A	0	[c]
33	Pyridine	*N*,*N*-Dimethyl-benzamide	Na	D	2-, 3.7[p]	11.7[z] 2,2′-dipyridyl, 13 4,4′-dipyridyl, 50.3
34	Pyridine	Acetonitrile	Al	A	0	[c]
35	Pyridine	Benzonitrile	Al	A	2-, 3.4[q]	[c]
36	Pyridine	Acetic anhydride	Al	C	0	Acetamide, 4-ethylpyri-dine[u]
37	Pyridine	Acetic anhydride	Mg	C	0	Acetamide, 4-ethylpyri-dine[u] Acetoin[v] Biacetyl[v,w]
38	Pyridine	Butyric anhydride	Al	C	0	Tars
39	Pyridine	Phthalic anhydride	Al	C	0	Tars
40	4-Picoline	Acetophenone	Al	B	2-, 36[b,r]	Pinacol, 14
41	4-Picoline	Ethyl benzoate	Al	A	2-, 32.9[s]	
42	Quinoline	Ethyl benzoate	Al	A	2-, 29[t]	12.4[z]
43	Quinoline	Ethyl benzoate	Al	B	2-, 19.7[u]	10.2[z]
44	Quinoline	*N*,*N*-dimethyl-benzamide	Al	B	2-, 16.1[z]	13.2[z]

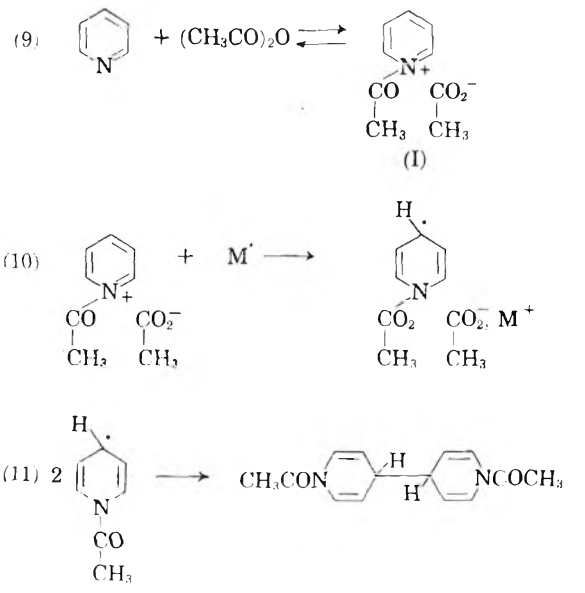
For footnotes, see opposite page →

The effects of different acid derivatives. Acid esters, *N,N*-dialkylamides, and nitriles, in the order listed, gave decreasing yields of acylated pyridines. Numerous factors, however, influence the yields in individual cases, so that variations within a class may be greater than variations between classes. Thus low-boiling acid derivatives may fail to produce good yields because of the difficulty in keeping them in the reaction mixture at the temperatures required (100° or more). Another important factor is the ease of formation or stability of the assumed intermediate carbanion which is strongly influenced by resonance interactions with the groups attached to it. Thus aliphatic esters are less satisfactory than aromatic esters probably because the carbanions produced from the former lack the resonance stabilization provided by the aryl nucleus in those from the latter.* Even esters of phenylacetic acid lack this stabilization and give yields of ketones comparable to those from unsubstituted aliphatic acid esters. Ring substituents in aromatic acid esters have varying effects; a *p*-chlorobenzoate reacted satisfactorily, a *p*-nitrobenzoate[6] and an *o*-carbethoxybenzoate did not. Ethyl picolinate gave low yields of 2,2′-dipyridyl ketone and much tar. Substituents in aliphatic esters with a single exception had a deleterious effect on the reaction. Ethyl cinnamate gave an 8% yield of the expected ketone, but ethyl carbonate, oxalate, malonate, and acetoacetate gave only tars from which the desired products could not be isolated.

Although nitriles are not carbonyl compounds they do resemble them and might be expected to acylate pyridine under reductive conditions. Benzonitrile, but not acetonitrile, gave low yields of the expected ketone.

The coreduction of acid anhydrides with pyridines. No ketones were obtained in attempted heterogeneous bimolecular reductions of acetic, butyric, or phthalic anhydrides and pyridine with metals. A careful study of the reaction with acetic anhydride showed that the products were instead 2,3-butanedione (biacetyl), 3-hydroxy-2-butanone (acetoin), 4-ethylpyridine, and acetamide. The first two of these products probably result from a homogeneous bimolecular reduction of the acetic anhydride. The latter two products indicate that the reaction has taken an entirely different course than it does with esters, amides, and nitriles. A further indication of this change in mechanism is the fact that similar products are obtained with zinc[7] as the reducing agent–a metal which fails to react with mixtures of pyridine and the other acid derivatives studied. Furthermore, the reaction with acid anhydrides is much more vigorous than with esters, amides, and nitriles and yields only a 4-substituted pyridine and none of the 2-isomer.

We believe the above facts can be rationalized by assuming a preliminary rapid acylation of the pyridine heterocyclic base followed by reduction proceeding by a single-electron transfer step, a pinacol-like dimerization, and subsequent changes as shown below.

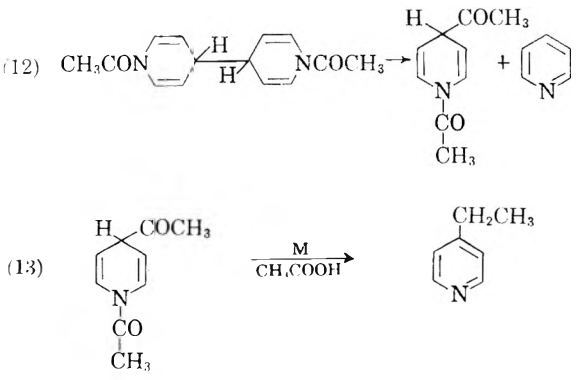


* A substituent group may, through its particular resonance effect, influence yields in opposite directions for esters and ketones, since in the one case a needed increase in reactivity of the anion may result while in the other case a needed increase in stability of the anion may result, *c.f.* the first paper in this series. Further work will be required to unravel these effects.

(6) Ethyl *p*-nitrobenzoate gave no pyridyl ketone but did give a small yield of 4,4′-bis(carbethoxy)azobenzene. This compound was previously prepared by treating the diazonium salt of ethyl *p*-aminobenzoate with an ammoniacal solution of cupric oxide, *cf.* R. Vorlander and F. Meyer, *Ann.*, **320**, 136 (1902).

(7) J. P. Wibaut and J. F. Arens, *Rec. trav. chim.*, **60**, 119 (1941).

[a] Yield based on metal, see reference 4. [b] The pyridyl alcohol was isolated here instead of the pyridyl ketone.[9, 10] [c] Starting material recovered. [d] M.p. 79°, *Anal.* Calcd. for $C_{12}H_8ClNO$: Cl, 16.28; N, 6.43. Found: Cl, 16.00; N, 6.67. [e] 4,4′-Dichlorobenzil, m.p. 196–197°, lit. m.p. 200°.[11] [f] M.p. 144–145°, *Anal.* Calcd. for $C_{18}H_{18}N_2O_4$: C, 66.24; H, 5.55; N, 8.58. Found: C, 66.32; H, 5.61; N, 8.77. [g] 2-Cinammoylpyridine, m.p. 74–75°, lit. m.p. 74–75°.[12] [h] 2,2′-Dipyridyl ketone, m.p. 54–55°, lit. m.p. 51–53°.[13] [i] Mixture of 2- and 4-acetylpyridines (see Experimental). [j] n_D^{25} 1.5182. [k] n_D^{25} 1.5174. [l] n_D^{25} 1.5179. [m] Mixture of 2- and 4-propionylpyridines. [n] $n_D^{20} = 1.5162$, lit, $n_D^{16.3} = 1.5166$.[14] [o] M.p. 106–107°, *Anal.* Calcd. for $C_{13}H_{11}NO$: N, 7.10. Found: N, 7.16. [p] Somewhat contaminated with 4,4′-dipyridyl. [q] Identified as 2-benzoylpyridine after hydrolysis of the imine with 6*N* HCl. [r] Only one isomer is possible in this case. [s] M.p. 89–89.5°, *Anal.* Calcd. for $C_{13}H_{11}NO$: N, 7.10. Found: N, 6.90. [t] 2-Benzoylquinoline, m.p. 111°, lit. m.p. 110–111°.[15] [u] M.p. of picrate derivative 167–168°, lit. m.p. 169.4–169.8°.[16] [v] M.p. of 2,4-dinitrophenylhydrazone derivative 309–312°, lit. m.p. 315°.[17] [w] Biacetyl gives the same 2,4-dinitrophenylhydrazone as acetoin. [x] Mixture of benzil and benzoin. [y] A 16.4% yield of 2-benzoylquinoline was also obtained from the petroleum ether filtrate. [z] A 10% yield of 2-benzoylquinoline was also obtained from the petroleum ether filtrate. [aa] Additional amounts of mercuric chloride used, 15–25 grams per mole of aluminum.



Salt (I)[8] would be expected to be even more easily reduced than pyridine itself since cations are generally better electron acceptors than the corresponding neutral molecules. Hence even zinc will cause the reaction to take place, and in this case at least the process appears likely to proceed by way of a free radical intermediate.* The products of equations (11) and (12) using zinc have been isolated by Wibaut and Arens[7] and shown to react as indicated in equations (12) and (13). The absence of 2-ethylpyridine in the products probably is conditioned by the steric requirements of the *N*-acyl group which hampers dimerization of the corresponding 2-position radical. The acetamide obtained probably arises through hydrolysis or acetolysis of the quinonoid intermediate shown as the products of reactions (10) or (11). The normal pyridine ring is too highly stabilized by resonance for such a cleavage.

Conclusions. The direct, substitutive acylation of pyridine, its homologs, or its analogs may be accomplished by treatment with acid derivatives and metals. From pyridine itself the 2-pyridyl ketones are the primary products, although smaller amounts of the 4-pyridyl ketones are also obtained in some cases. Suitable metals are aluminum, magnesium, and beryllium, in order of decreasing effectiveness. Suitable acid derivatives are esters, *N*,*N*-dialkylamides, and nitriles, also in decreasing order of effectiveness. Acid anhydrides react entirely differently and yield alkylated instead of acylated pyridines. The acylation process appears to involve an anionic intermediate produced by a two-electron transfer step from the metal to the acid derivative and subsequent attack by this anion at the 2- and 4-positions of the pyridine ring.

EXPERIMENTAL

Procedure A. Bimolecular reduction of ethyl benzoate and pyridine with aluminum. Granular aluminum metal (27.0 g., 1.0 mole) was heated with mercuric chloride (5.0 g.) and several drops of mercury for 2 hr. at 100° in a three-necked flask fitted with an addition funnel, condenser, and stirrer. Ethyl benzoate (25 g.) and pyridine (25 g.) were added to the metallic mixture to initiate the reaction. A green color developed immediately and turned to a muddy brown within a few minutes. Pyridine (250 g., 3.5 moles total) was added dropwise over a period of 2 hr. keeping the reaction mixture at total reflux. At the end of this addition the reaction mixture was dark colored. Ethyl benzoate (425 g., 3.0 moles total) was added dropwise to the reaction mixture over a period of 24 hr. at which time all of the aluminum metal had reacted. The partially cooled reaction mixture was poured into a liter of 6*N* sodium hydroxide and the gel that developed was broken up by stirring. The oil layer was separated and extracted several times with 6*N* hydrochloric acid, and then distilled under vacuum through a 30 cm. glass-helix-packed column. The following fractions were isolated:

Fractions	Boiling Range, °C. (Mm.)	Amount (Grams)
I	78–84, (3.5–4.0)	208.5
II	94–101, (3.4–4.0)	3.5
III	140–146, (2.8)	6.5

Fraction I was ethyl benzoate (46% recovery) while fraction II was benzoic acid. Fraction III was identified as a mixture of benzil and benzoin (2.8% yield).

The acid extracts were made basic with an excess of 6*N* sodium hydroxide and the generated oil taken up in ether, dried over potassium hydroxide pellets, and rapidly distilled, eventually under vacuum. The higher boiling distillate was refractionated through a 30 cm. glass-helix-packed column and the fraction boiling at 126–146°, (1.9 mm.) was refrigerated. The solid material which crystallized was deintified as 4-benzoylpyridine after recrystallizations from petroleum ether (90–100°). This material (17.7 g., 6.4% yield) melted at 72.5–73.0°, lit. m.p. 71.5–72.6°.[18] The picrate derivative melted at 160–161°, lit. m.p. 160.[18]

The mother liquor from this refrigeration was refractionated through a small Vigreux column to give a yellow oil, b.p. 124–126° (1.5 mm.), 65.8 g., 23.9% yield; n_D^{20} 1.5940. d_4^{20} 1.1458. It was identified as 2-benzoylpyridine by preparing a variety of derivatives including: (*a*) phenyl-2-pyridylmethanol hydrochloride, m.p. 180–181.5°, lit. m.p. 182–184°,[10] (*b*) phenyl-2-piperidylmethanol hydrochloride, m.p. 199.5–201°, lit. m.p. 200–202°[18] for this enantiomorphic pair, (*c*) 2,4-dinitrophenylhydrazone 196–197.5°, lit.

(8) *cf.* Ref. 3, p. 482.

* Ionic intermediates are also conceivable of course, but the behavior of Zn in other Het BR reactions causes us to prefer the free radical type of intermediate here.

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(16) H. C. Brown and W. A. Murphey, *J. Am. Chem. Soc.*, **73**, 3308 (1951).

(17) R. L. Schriner and R. C. Fuson, *Identification of Organic Compounds*, John Wiley and Sons, Inc., New York, N. Y., 1948, p. 262.

(18) K. E. Crook and S. M. McElvain, *J. Am. Chem. Soc.*, **52**, 4006 (1930).

m.p. 196.5–197.5°,[19] and (*d*) picrate, m.p. 129–130°, lit. m.p. 130°*d*,[20] 122–123°,[18] 124–127°.[13]

Anal. Calcd. for $C_{12}H_9NO$: MR_D, 54.47. Found: MR_D, 54.25.

It should be noted that larger amounts of $HgCl_2$ (0.2 mole per 1 mole of metal) were used with all the other bivalent metals (*i.e.* Zn, Mg, and Be) listed in Table 1 where Procedure A is employed.

Procedure B. Isolation of the intermediate complex. Bimolecular reduction of ethyl benzoate and pyridine with aluminum. The same steps were followed as in Procedure A, and the same amounts of reactants were used. The cooled reaction mixture was stripped of unreacted pyridine using an aspirator and mild heating, and then the remaining viscous oil (about 350–400 ml.) was poured into 1500 ml. of petroleum ether (90–100°). This addition resulted in the precipitation of a brown solid (286 grams) which could be filtered, dried, and allowed to stand in the presence of air without any noticeable decomposition. This complex was hydrolyzed with 6*N* hydrochloric acid and worked up in a manner similar to the techniques previously discussed for obtaining 2- and 4-benzoylpyridine. The following products were isolated and identified:

Compounds from Complex	Grams	Yield, %
2-Benzoylpyridine	87.0	32.5
4-Benzoylpyridine	19.4	7.1
Benzil and benzoin	26.7	12.7

After removal of the excess petroleum ether and unreacted starting material from the filtrate by mild heating under vacuum, the remaining viscous oil was hydrolyzed with 6*N* hydrochloric acid and the resulting mixture worked up using previously described techniques. The following products were found:

Compounds from Filtrate	Grams	Yield, %
2-Benzoylpyridine	6.3	2.3
4-Benzoylpyridine	2.5	0.9
Benzil and benzoin	10	4.8

Since the 4-isomer was found to be present in both the filtrate and the complex, no advantages of separation of the 2- and 4-isomers by isolating the complex could be found. However, the purity of the 2-isomer obtained from the hydrolysis of the complex was high as evidenced by its molecular refractivity (54.27). The presence of benzil and benzoin in the complex eliminated any possibility of studying the true composition of the pyridine component in the complex.

Procedure C. Attempted bimolecular reduction of acetic anhydride and pyridine with aluminum. The same reaction procedure was used as that previously described as procedure A except that the reaction was highly exothermic and only mild heating of the reaction mixture at various intervals was necessary to keep the reaction in progress. The following amounts of reactants were used; aluminum (27 g., 1 mole), mercuric chloride (5 g.), acetic anhydride (306 g., 3.0 moles), pyridine (275 g., 3.5 moles), and several drops of mercury. The cooled reaction mixture was hydrolyzed with a liter of 3*N* sodium hydroxide and the generated oil separated from the aqueous layer, which was discarded. This oil was dried, stripped of pyridine, and the distillate b.p. 30–95° (1.8 mm.), 59.5 g. was redistilled through a 30 cm. glass-helix-packed column under vacuum.

Fractions	Boiling Range, °C. (Mm.)	Amount (Grams)
I	30–42, (2.7)	24.6
II	44–55, (2.7)	5.3
III	73–74, (2.8)	10.9

Fraction I was principally 4-ethylpyridine, picrate m.p. 167–168°, lit. m.p. 169.4–169.8°,[16] mixture m.p. 168°. Fraction II represented forerun, while fraction III gave acetamide, m.p. 81°, upon refrigeration, mixture m.p. 81° with an authentic sample. No fraction corresponding to 2- or 4-acetylpyridine could be isolated.

Procedure D. Attempted bimolecular reduction of N,N-dimethylbenzamide and pyridine with sodium. Sodium metal was made into a fine sand in a three-neck flask fitted with a condenser, Hershberg stirrer, nitrogen inlet, and dropping funnel, by rapidly stirring the molten metal under previously dried toluene. The cooled toluene was decanted and the reaction carried out under a slight positive pressure of nitrogen in the same manner as that previously described as Procedure A. The amounts of reactants used were; sodium (23 g., 1 mole), pyridine (158 g., 2 mole), *N,N*-dimethylbenzamide (137 g., 0.9 moles), and toluene (50–60 ml.) as a diluent. The cooled reaction mixture was filtered through a sintered-glass funnel to remove a small amount of unreacted sodium. The filtrate was decomposed with 1 l. of 6*N* hydrochloric acid and the resulting mixture washed several times with 100 ml. portions of benzene. The benzene washings were combined, dried, and stripped of benzene using an aspirator. The remaining oil was distilled under vacuum.

Fractions	Boiling Range, °C. (Mm.)	Amount (Grams)
I	67–94, (1.5)	7.7
II	100–101, (1.6)	10.7
III	140–151, (2.0)	12.3
IV	b.p. > 160 (2.0)	8.3

Fraction I (n_D^{20} 1.5470) was a mixture of benzaldehyde and N,N-dimethylbenzamide while fraction II was unreacted *N,N*-dimethylbenzamide (n_D^{20} 1.5565; 7.8% recovery). Fraction III crystallized and was identified as a mixture of benzil and benzoin. Fraction IV was a non-distillable tar.

The acid soluble material obtained from the hydrolysis of the reaction mixture was made basic with excess 6*N* sodium hydroxide and the generated oil taken up in ether, dried over potassium hydroxide pellets, and stripped of ether using an aspirator. The remaining oil was distilled under vacuum. Fraction I was unreacted pyridine (29% recovery),

Fractions	Boiling Range, °C. (Mm.)	Amount (Grams)
I	25–30, (4–5)	45.8
II	100–135, (2.0)	61.4
III	135–155, (2.0)	32.1
IV	b.p. > 165, (2.0)	27.8

while fraction IV was a non-distillable tar. Fractions II and III were refractionated separately through a small Vigreux column and then converted to picrates. After many recrystallizations two constant-melting picrate derivatives were obtained. One picrate derivative melted at 143–144° while the other melted at 256–257° *d*. The latter derivative corresponded to the picrate listed for 4,4′-dipyridyl, lit. m.p. 257°.[21] It is possible that the other derivative is a picrate of 2,2′-dipyridyl, (lit. m.p. 155°[22]), contaminated with a less insoluble picrate.

All of the previously mentioned fractions were also treated with 2,4-dinitrophenylhydrazine in order to obtain any evidence for benzoylation of the pyridine nucleus. Only one fraction (b.p. 150–156°, 2.0 mm.) gave a derivative which

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(21) H. Maier-Bode and J. Altpeter, *Das Pyridin und seine Derivate*, Wilhelm Knappe Halle, Saale, 1934, p. 75.

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melted at 196–197° after recrystallizations from 90% acetic acid and finally ethyl acetate. This derivative failed to depress the melting point of an authentic sample of a 2,4-dinitrophenylhydrazone derivative of 2-benzoylpyridine (m.p. 196–197°). However, this represents only a trace identification of 2-benzoylpyridine since the fraction from which it was obtained contained primarily 4,4'-dipyridyl.

Discussion of infrared results. The fractions obtained from the Het BR of *sec*-butyl acetate, *n*-amyl acetate, 2-ethylhexyl acetate, and ethyl propionate with pyridine using aluminum gave picrate and 2,4-dinitrophenylhydrazone derivatives. However the purification of these derivatives failed to yield constant melting solids, and since the yields were low, attempts to separate the isomers proved to be impractical. Therefore infrared spectra of the mixtures presumed to be 2- and 4-acetylpyridine and 2- and 4-propionylpyridine were obtained.

The characteristic absorption peak for the carbonyl band was split in these spectra, more than likely due to the presence of the 2- and 4-isomers. The absorption frequencies observed for a mixture of 2- and 4-acetylpyridine were 1655 cm.$^{-1}$ (6.04 μ) and 1680 cm.$^{-1}$ (5.94 μ), and for a mixture of 2- and 4-propionylpyridine 1660 cm.$^{-1}$ (6.02 μ) and 1685 cm.$^{-1}$ (5.93 μ). These absorption values check with those listed in the literature for carbonyl bands present in aryl alkyl ketones (1700–1680 cm.$^{-1}$).[23]

The characteristic peaks for the pyridine nucleus were also present in these spectra. Thus the mixture of 2- and 4-acetylpyridines showed absorption at 785 cm.$^{-1}$ (12.72 μ) and 746 cm.$^{-1}$ (13.40 μ), while the mixture of 2- and 4-propionylpyridine showed absorption at 835 cm.$^{-1}$ (11.99 μ) and 760 cm.$^{-1}$ (13.18 μ). These strong bands have been shown to originate in the out-of-plane vibrations of the unsubstituted hydrogen atoms of the ring.[24]

Thus we conclude from these spectra that acylation of the pyridine nucleus has occurred yielding mixtures of the 2- and 4-pyridyl substituted ketones.

LAFAYETTE, IND.

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(24) See reference 22, p. 235.

[CONTRIBUTION NO. 1454 FROM THE STERLING CHEMISTRY LABORATORY AND FROM THE BINGHAM OCEANOGRAPHIC LABORATORY, YALE UNIVERSITY]

Contributions to the Study of Marine Products. XLV. Sponge Nucleic Acids*,[1]

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Nucleic acids have been isolated from sixteen different species of sponges, and all have been degraded to the nucleosides. All pentose nucleic acids gave the four usual ribonucleosides, and all deoxypentose nucleic acids gave the four usual deoxyribosides. There were no detectable quantities of arabinosides or other unusual nucleosides among the hydrolysis products. The nucleic acids of *Cryptotethia crypta* were exceptional in their extraordinarily low content of ribonucleic acid. The significance of these observations has been discussed.

It has been shown in previous papers of this series that extended acetone extraction of the Caribbean sponge, *Cryptotethia crypta*, affords a mixture of three unusual nucleosides which have been identified as 3-β-D-arabofuranosylthymine (spongothymidine),[3] 3-β-D-arabofuranosyluracil (spongouridine),[3] and 9-β-D-ribofuranosyl-2-methoxyadenine.[4] Some earlier observations[5] had pointed to the possibility that these new nucleosides are products of the autolysis of more complex units such as nucleic acids.

To investigate this attractive possibility we began several years ago a systematic study of sponge nucleic acids of which previous knowledge was altogether lacking. Suitable methods for the isolation and examination of the nucleic acids were developed on the common sponges of Long Island Sound rather than the more promising but less accessible Caribbean sponge, *Cryptotethia*. This sponge and other species were subsequently collected near the island of Bimini.[6] They were quickly frozen and kept in this state until shortly before their extraction. A third group of sponges was collected in the Bermudas[6] and extracted there while still quite fresh. Altogether sixteen different species were investigated which included representatives of the three well-known groups, the keratineous, siliceous, and calcareous sponges. All of these sponges had previously been investigated in this laboratory for other reasons, but with the exception of *Cryptotethia*, none of them had been observed to afford the unusual nucleosides.

The nucleic acids were isolated and characterized by modifications of procedures well described in the literature. Most of them were patterned after the

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(6) The authors express their sincere gratitude to the directors of the Lerner Marine Laboratory, Bimini, Bahamas, and of the Bermuda Biological Station for their most valuable help.

TABLE I

SPONGE NUCLEIC ACIDS

Order	Species	Origin	Method[a]	Yield[b]	Ultraviolet Absorption		DNA	RNA
					λ_{max}	$E^{1\%}_{1\,cm.}$		
Keratosa	*Ircinia fasciculata*	Bermuda 1956	II	40	257 mμ	134.7	+?[c]	+++
	Dysidia crawshayi	Bermuda 1956	II	150	258 mμ	173.5	++	+++
	Dysidia etheria[d]	Bermuda 1956	I		257 mμ	144.0	+	+++
	Ianthella ardis	Bermuda 1956	II	65	259 mμ	97.0	+	−++
	Verongia fistularis	Bimini 1954	II	130	259 mμ	57.5	+?[c]	−++
Poecilosclerina	*Tedania ignis*	Bermuda 1956	II	120	257 mμ	63.8	−	+++
	Microciona prolifera	Long Island 1953	IVa				+	+++
Halichondrina	*Halichondria panicea*	Long Island 1953	I	105	258 mμ	230.0	−	+++[e]
Hadromerina	*Spheciospongia vesparia*	Bimini 1954	I	40	259 mμ	73.0	+	+++
	Spheciospongia othello	Bermuda 1956	II	45	259 mμ	98.0	+?[c]	+++
	Terpios fugax	Bermuda 1956	II	155	257 mμ	148.0	+?[c]	+++
Epipolasida	*Cryptotethya crypta*	Bimini 1954	I	30	259 mμ	59.6	++	+?
			III	45	259 mμ	60.5	++	+?
			IVb	60	259 mμ	60.0	++	+?
	Tethya actinia	Bermuda 1956	II	40	257 mμ	105.0	+?[c]	+++
Choristida	*Cinachyra cavernosa*	Bermuda 1956	II	40	260 mμ	63.4	+	+++
Carnosa	*Chondrilla nucula*	Bimini 1954	IVa				+	+++
Asconosa	*Leucetta floridana*	Bermuda 1956	II	70	258 mμ	152.0	+	+++

[a] Full details of these extraction methods are given in the experimental section. [b] Milligrams of nucleic acid–polysaccharide per 250 grams of wet sponge. [c] These preparations gave very weak positive reactions in the Dische test for deoxypentose. The amount of DNA was too small to allow its identification by degradative methods. [d] This sponge was investigated by Mr. Joel S. Kovel. [e] This was the purest nucleic acid obtained. Found: P, 7.1%; N, 12.3%; $\epsilon\,(P)_{258}$, 10,000.

method used by Dutta, Jones, and Stacey[7] in the isolation of bacterial nucleic acids, which involves precipitations with cetyltrimethylammonium bromide. In a few cases the nucleic acids were isolated by the older method of the alcohol precipitation of the sodium salts. The deproteinization was accomplished with chloroform,[8] followed on one occasion by phenol.[9]

The acids thus obtained were more or less heavily contaminated with polysaccharides. Only in the case of the abundant Long Island sponge, *Halichondria panicea*, was this impurity largely removed, and a nucleic acid was obtained with a phosphorus and nitrogen content of 7.1% and 12.3% respectively. Otherwise extensive removal of the polysaccharides was not attempted for reasons of economy. At this stage of the investigation we were less concerned with the over-all constitution of the nucleic acids than with the structure of the individual nucleosides to be derived from them. A judicious choice of methods generally avoided the interference by polysaccharide degradation products in the identification of the bases and carbohydrates derived from the nucleic acids.

Table I lists the sponges which are included in the present investigation, their classification, origin, and the nucleic acid material obtained from them. In cases where the total nucleic acids showed a negative or a faint Dische-test for deoxypentose nucleic acids, they were hydrolyzed by both unfractionated snake venom to nucleosides and by acids to the purine bases and pyrimidine nucleotides. The hydrolyzates were chromatographed on paper against authentic markers in the conventional manner. In other cases, where significant amounts of deoxypentose were indicated, the pentose nucleic acids were first hydrolyzed with alkali to the nucleotides and these in turn to nucleosides with prostatic phosphatase. The nucleosides were then chromatographed on paper as before.

The spots on the chromatograms were eluted, and the ultraviolet spectra of the eluted fractions determined. For further identification the electro-

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(8) M. G. Sevag, D. B. Lackman, and J. Smolens, *J. Biol. Chem.*, **124**, 425 (1938).

(9) K. S. Kirby, *Biochem. J.*, **64**, 405 (1956).

TABLE II

ACID DEGRADATION OF SPONGE RIBONUCLEIC ACIDS

Sponge	Adenine	Guanine	Cytidylic Acid	Uridylic Acid	Purines / Pyrimidines
Halichondria panicea	10.0	20.1	11.0	11.3	1.35
Verongia fistularis	10.0	18.5	11.0	8.7	1.45
Spheciospongia othello	10.0	16.1	8.8	8.2	1.53
Tedania ignis	10.0	20.0	10.6	7.5	1.66
Terpios fugax	10.0	16.8	10.0	6.8	1.60
Ircinia fasciculata	10.0	17.8	10.0	9.6	1.42
Tethia actinia	10.0	15.3	8.5	7.2	1.61

phoretic mobilities in a borate buffer (*p*H 9.3) of the sponge nucleosides were compared with those of authentic nucleosides.[10] Such a comparison is most important because on paper chromatograms uridine and spongouridine, for example, show the same R_f value although one is a riboside and the other an arabinoside.[11] In a borate buffer, however, the mobility of the riboside is substantially greater than that of the arabinoside. When tested by this sensitive method none of the nucleosides gave evidence of the presence of arabinosides. For final identification at least one of the nucleosides from every nucleic acid was hydrolyzed, and the liberated carbohydrate identified chromatographically. All sponge pentose nucleic acids afforded only the four familiar ribonucleosides, guanosine, adenosine, uridine, and cytidine, see Table II.

The mixtures of deoxynucleic acids and polysaccharides were hydrolyzed with deoxyribonuclease and snake venom, and the hydrolyzates chromatographed on paper against authentic deoxyribosides. As before, the spots were eluted, and the absorption spectra of the eluted fractions determined. In all cases the usual unity proportions of purines to pyrimidines were observed; see Table III. In separate hydrolyses by formic acid the free bases were prepared and identified. The only carbohydrate obtained from any of the deoxynucleoside mixtures was 2-deoxyribose. The deoxynucleic acids from sponges, like those from other sources therefore afford the 2-deoxyribosides of adenine, guanine, thymine, and cytosine.

5-Methylcytosine has been observed in the hydrolyzates of nucleic acids from several invertebrates. Wyatt[12] obtained it from the locust and sea urchin sperm, and Rosedale[13] has stated that the nucleic acids of termites and the larvae of certain flies give about equal quantities of cytidylic and 5-methylcytidylic acid but no uridylic acid. Conscious of these observations we have looked for 5-methylcytosine in the hydrolyzates of sponge nucleic acids, but have not found any.

The results of the present study therefore show that on the whole the nucleic acids do not differ significantly in their over-all composition from other pentose or deoxypentose nucleic acids. Some rather unusual features, however, were noticed among the nucleic acids from *Cryptotethia crypta*, the only sponge which has so far given the unusual nucleosides. As has been stated before, the sponge nucleic acids appear to be quite intimately associated with polysaccharides. This is particularly evident in the case of *Cryptotethia*, where three different methods of isolation gave products of an almost identical carbohydrate content of 75% as determined by optical density measurements. The two fractions were not separable in the ultracentrifuge at 59,780 r.p.m.[14]

Among the nucleic acids of all other sponges the proportion of ribonucleic acid was always found much greater than that of deoxyribonucleic acid; in fact several samples contained only minute quantities of the latter. This is the commonly encountered quantitative relationship between the two acids. In the case of the nucleic acids from *Cryptotethia crypta*, however, the relationship was found to be quite reversed. Here, the ribonucleic acid represented less than 4% of the total nucleic acid fraction. The amount was so small that it could have been derived not from the sponge itself but from other form of life to be found on it.

It should be mentioned here, however, that for technical reasons the *Cryptotethia* sponges from which the nucleic acids had been isolated had to be kept in cold storage for more than two years before the beginning of the first extraction. The low ribonucleic acid content may thus be attributable to enzymic action over this period. Yet in all other sponges which had been stored similarly for an equal length of time, the ribonucleic acid did not differ significantly from that observed in fresh sponges. It would seem to be more than a coincidence that this very low ribonucleic acid content is found solely in *Crypotothethia*, the only sponge which has so far yielded free nucleosides in such extraordinary amounts and of such unusual struc-

(10) D. C. Burke, *Chemistry & Industry*, 1510 (1954)

(11) D. M. Brown, A. R. Todd, and S. Varadarajan, *J. Chem. Soc.*, 2388 (1956). These authors differentiate uridine and spongouridine on a paper chromatogram by means of the periodate-Schiff spray reaction.

(12) G. R. Wyatt, *Biochem. J.*, 48, 581 (1951).

(13) J. L. Rosedale, *J. Entomol. Soc., S. Africa*, 11, 34 (1948).

(14) The authors are indebted to Prof. S. J. Singer of this department for his help in this matter.

ture. There may exist therefore in this particular sponge a metabolic aberration which diverts most of the normal intermediates of ribonucleic acid synthesis to the formation of free spongothymidine, spongouridine, and spongosine or perhaps to an unstable substance of greater complexity incorporating these nucleosides. Examination of aqueous extracts of *Crypototeithia* has not so far provided any evidence for the presence of the phosphates of the three unusual nucleosides or of larger units, but this important problem will be further pursued as soon as facilities for the speedy extraction of the living sponge have become available.

EXPERIMENTAL

Isolation of nucleic acids. All operations were carried out in a cold room at 3° except in cases involving the use of 1% or stronger cetyltrimethylammonium bromide solutions. At this temperature and concentration the detergent is prone to precipitate, and these operations were therefore carried out as speedily as possible at room temperature. Table I lists the species of sponges examined in the present investigation, their classification according to de Laubenfels[15] and their origin. It also includes the extraction procedures used for each of the various species together with the respective yields, the ultraviolet absorption data of the products, and an indication of their content of deoxyribose nucleic acid.

The methods I and II (Table I) are modifications of the techniques used by Dutta, Jones, and Stacey[7] in the isolation of bacterial nucleic acids. The methods III and IVa and b are based on older and more commonly used procedures.

Method I. The frozen sponge was cut into small pieces and homogenized in a high-speed, rotary blendor for about 3 min. with twice its weight of 0.01*M* sodium arsenate solution. The homogenate was diluted with six volumes of water, allowed to stand for 24 hours at 3°, strained through a cheesecloth, and centrifuged at 1100 r.p.m. Cetyltrimethylammonium bromide[16] was gently stirred into the supernatant solution until precipitation of the cetyltrimethylammonium salts was complete. The suspension was kept at 3° for 15 hr., centrifuged, and the resulting pellet was washed twice with water. The washings were discarded, and the pellet thoroughly extracted with *M* sodium chloride solution, and the extract centrifuged. The liquid was diluted with water to 0.25*M* sodium chloride, and the resulting precipitate redissolved as far as possible in *M* sodium chloride and reprecipitated by diluting the centrifuged solution to 0.25*M*. This procedure was repeated until the precipitated cetyltrimethylammonium salts became completely resoluble in *M* sodium chloride. The clear solution which was eventually obtained was deproteinized according to Sevag's method,[8] and the nucleic acids were precipitated from the protein-free solution by addition of two volumes of 95% ethanol. The precipitated material was collected by centrifugation, washed successively with 75% ethanol, 95% ethanol, and acetone, and finally dried *in vacuo*. For further purification, the material was redissolved in a 1% solution of cetyltrimethylammonium bromide in *M* sodium chloride (1 ml. of this solution per mg. of nucleic acid) and precipitated as the cetyltrimethylammonium salt by dilution of the solution to 0.3*M* sodium chloride. The salt thus obtained was reprecipitated twice more from *M* sodium chloride solution containing 1% cetyltrimethylammonium bromide by dilution with water, and was then reconverted into the sodium nucleate by alcohol precipitation from its solution in *M* sodium chloride. An aqueous solution of the sodium nucleate was then dialyzed against distilled water in the customary manner and lyophilized.

Method II. The frozen sponge was homogenized with 7.5% sodium chloride solution containing 0.01*M* sodium arsenate (100 ml. of solution for every 100 g. of wet sponge), and the homogenate was allowed to stand overnight at 5°. It was then strained through cheesecloth, diluted with four volumes of water, and stirred gently while cetyltrimethylammonium bromide was added in small amounts until the precipitation of the insoluble quaternary salts was complete. The suspension was allowed to stand at 5° for 24 hr., when the precipitate was collected by centrifugation and thoroughly extracted with 10% sodium chloride solution. Centrifugation of the extract afforded a clear solution which was diluted with two volumes of ethanol and centrifuged. The precipitate was washed successively with 80% ethanol, 95% ethanol, and acetone, and dried *in vacuo* and, if necessary, stored at −20°. It was redissolved in a 10% sodium chloride solution, and deproteinized and further purified over the cetyltrimethylammonium salt as described under Method I.

Method III. The frozen sponge was homogenized for about 3 min. with an approximately equal weight of 10% sodium chloride solution, and the homogenate was allowed to stand at 3° for 24 hr. It was then strained through cheesecloth, and the solid material retained by the cloth was re-extracted twice more with 10% sodium chloride solution. The combined extracts were centrifuged to remove suspended matter and then diluted with two volumes of ethanol. The precipitate was collected by centrifugation, suspended in physiological saline solution (100 ml. for every 100 g. of the original sponge), and the suspension stirred with one-tenth of a volume of a 5% solution of sodium dodecylsulfate in 45% ethanol at 3° for 2 days. Sufficient solid sodium chloride was then added to make the solution molar, and stirring was continued at room temperature for a further 3 hr. The protein precipitate was removed by centrifugation, and the clear solution was diluted with two volumes of ethanol. The precipitate was collected by centrifugation and extracted for 24 hr. at 3° with *M* sodium chloride solution (100 ml. for every 100 g. of the original sponge). Further deproteinization according to Sevag[8] and purification over the cetyltrimethylammonium salt was done as described under Method I.

Method IVa. The sponge was extracted with an approximately equal weight of 10% sodium chloride solution as described under Method III. Two volumes of ethanol were added to the extract, and the resulting precipitate collected by centrifugation and deproteinized according to Sevag's method.[8] The nucleic acid-polysaccharide mixture thus obtained was precipitated three times with ethanol from a *M* sodium chloride solution, washed successively with 75% ethanol, 95% ethanol, and acetone, and then dried under diminished pressure.

Method IVb. The nucleic acid preparation obtained by Method IVa was further deproteinized by shaking its aqueous solution with 90% phenol, followed by centrifugation and separation of the aqueous, phenolic, and protein phases. The aqueous phase was twice more treated with phenol in an analogous manner. After the final treatment the aqueous phase was made molar with respect to sodium chloride, and the nucleic acid-polysaccharide mixture was precipitated with ethanol, and then washed and dried as described under Method IVa.

Degradation of the sponge nucleic acids. Chromatographic techniques and solvent systems. The descending chromatographic technique was employed and Whatman No. 1 paper was used. The chromatograms were analyzed under ultraviolet light. The following solvent systems were used:

(15) M. W. de Laubenfels, Carnegie Institution of Washington, Publication No. 467 (1936).

(16) Technical Grade Quality, supplied by Matheson, Coleman and Bell.

A. 1-Butanol, ethanol, and 5*N* hydrochloric acid in volumes of 3:2:2.[17]

B. 1-Butanol saturated with water at about 23° and 15*N* ammonium hydroxide in volumes of 100:1.[18]

C. Isobutyric acid and 0.5*N* ammonium hydroxide in volumes of 10:6.[19]

D. One volume of pyridine added to the upper layer of a mixture of 1-butanol, pyridine, and water in volumes of 3:1:1.5.[20]

E. 1-Butanol saturated with water at about 23°.

F. 1-Butanol, ethanol, and water in volumes of 4:1:5.[20]

G. 2-Propanol (65 ml.), concentrated hydrochloric acid corresponding to 0.2 g. mol. of HCl, and water to give a total of 100 ml.[21]

H. The upper layer of a mixture of 1-butanol, glacial acetic acid, and water in volumes of 4:1:5.

The nucleotides used as marker substances were mixtures of 2′ and 3′ isomers.

Electrophoresis. The buffer solution used in the electrophoresis of the pentose nucleosides was 0.1*M* sodium borate, *p*H 9.3.[22] Whatman No. 3 mm. paper was used and a gradient of 20 volts/cm. was maintained.

Ultraviolet absorption spectra. These were determined with a Cary Recording Spectrophotometer (Model II S).

Degradation of the sponge ribonucleic acids. (A) Acid hydrolysis. Smith and Markham's[23] method was applied to the nucleic acid preparations which gave a negative or only weakly positive Dische test for deoxypentose nucleic acids. The following quantities of crude nucleic acids were hydrolyzed each with 0.2 ml. of *N* hydrochloric acid in a sealed tube for 1 hr. at 100°: *Halichondria panicea*, 5 mg.; *Verongia fistularis*, 8 mg.; *Spheciospongia othello*, 5 mg.; *Tedania ignis*, 8 m.; *Terpios fugax*, 3 mg.; *Ircinia fasciculata* 4 mg.; and *Tethia actinia*, 5 mg. In each case the hydrolyzate was directly applied to a paper strip and chromatographed using the solvent system A against authentic markers of guanine, adenine, cytidylic acid, and uridylic acid. No differences were noted between the R_f values of the sponge products and the markers. The spots derived from the sponge nucleic acids and appropriate blanks of equal size were cut from the chromatogram, and each was eluted with 5 ml. of 0.1*N* hydrochloric acid. The spectra of the eluates at both *p*H 1 and *p*H 12.5 were identical with those recorded for the corresponding marker substances. Table II lists the molar proportions of degradation products calculated from the optical densities of the original acidic eluates at their respective absorption maxima.

B. Enzymatic hydrolysis. The enzymatic hydrolyses were carried out with the crude venom of the rattle snake, *Crotalus adamanteus.*[24] *B1. Ribonucleic acid-polysaccharide mixtures.* The same nucleic acid preparations were used as in the acid hydrolyses (A), but in approximately double the amounts. A solution of the nucleic acid and 2.3 mg. of the crude snake venom in 1.3 ml. of 0.1*M* ammonium acetate buffer (*p*H 8.5) containing 1.3 mg. of magnesium chloride was incubated for 20 hr. at 37°. Two volumes of 95% ethanol were added, and the resulting precipitate of polysaccharide was removed by centrifugation. In the case of the highly purified nucleic acid preparation from *Halichondria*, no precipitate was formed at this stage, but only a slight turbidity due to the separation of the enzyme. In all cases the centrifuged, clear solutions were concentrated *in vacuo* to about 0.2 ml. Aliquots of these solutions were chromatographed in solvent system B for 40 hr. against authentic guanosine, adenosine, cytidine, and uridine markers. No R_f differences were noted between the authentic and the sponge nucleosides. The identity of the sponge nucleosides with the marker substances was confirmed by measurements of the ultraviolet absorption spectra of the eluted spots in acid, neutral, and alkaline media, and by electrophoretic comparison of the sponge nucleosides with the authentic materials in 0.1*M* sodium borate buffer of *p*H 9.3.

B2. Ribonucleic acid-deoxyribonucleic acid-polysaccharide mixtures. The following method was applied to the nucleic acid preparations from the following sponges, and on the quantities indicated in parentheses: *Dysidea crawshayi* (10 mg.), *Cinachyra cavernosa* (30 mg.), *Ianthella ardis* (20 mg.), and *Leucetta floridana* (10 mg.). The nucleic acid preparation was dissolved in 0.5 ml. of 0.3*N* potassium hydroxide, and the solution was incubated at 37° for 20 hr. The *p*H was then adjusted to 2.5 by addition of 3% perchloric acid solution. Unreacted deoxyribonucleic acid and polysaccharides were precipitated by addition of two volumes of 95% ethanol, collected by centrifugation, washed successively with 80% and 90% ethanol, and stored for the analysis of the deoxyribonucleic acid. The acidic supernatant solution remaining after removal of the deoxyribonucleic acid and the polysaccharides was neutralized with dilute potassium hydroxide and concentrated to about 0.1 ml. Precipitated potassium perchlorate was removed by centrifugation, and the supernatant solution was evaporated to dryness at 30°. The residue was dissolved in 0.3 ml. of 0.1*M* ammonium acetate buffer, *p*H 5.3, the solution centrifuged, and the supernatant liquid was incubated at 37° for 3 hr. with 0.003 ml. of a prostatic phosphatase solution,[25] prepared according to the standard procedure of Schmidt.[26] Two volumes of ethanol were added, the mixture clarified by centrifugation, and the supernatant liquid concentrated to about 0.1–0.2 ml. This material was then transferred onto paper and chromatographed in solvent system E for 2–3 days. The nucleoside spots were identified as described under B1. In some cases the guanosine spot streaked from the origin presumably because of the continued presence of potassium perchlorate. No other differences were observed in the chromatographic, electrophoretic, and ultraviolet spectral characteristics of any of the sponge ribonucleosides and the authentic nucleosides, guanosine, cytidine, uridine, and adenosine.

Degradation of Cryptotethia crypta ribonucleic acid. Fifty mg. of the ribonucleic acid–deoxyribonucleic acid–polysaccharide mixture obtained from *Cryptotethia* by extraction method IVb were hydrolyzed in 2 ml. of 0.3*N* potassium hydroxide for 20 hr. at 37°. The nucleotides obtained from the ribonucleic acid were then separated from the deoxyribonucleic acid and the polysaccharides, and hydrolyzed to the nucleosides according to the method described under B2. The total nucleoside solution was transferred to a paper strip and chromatographed in solvent system E for 4 days. The four bands, corresponding in R_f values to guanosine, cytidine, uridine, and adenosine, were each eluted with 5 ml. of water, and the ultraviolet spectra of the eluates were measured. They were identical with those of the authentic ribonucleosides. Their identity was further confirmed by the respective mobilities in a sodium borate buffer, *p*H 9.3, and their ultraviolet absorption spectra in acid and base. The molecular proportions of the sponge ribonucleosides, estimated from the optical densities of the aqueous eluates at their absorption maxima were guanosine, 20.0; adenosine,

(17) G. E. Eastman, *Biochim. et Biophys. Acta*, 9, 258 (1952).

(18) W. S. Macnutt, *Biochem. J.*, 50, 384 (1952).

(19) B. Magasanik, E. Vischer, R. Doniger, D. Elson, and E. Chargaff, *J. Biol. Chem.*, 186, 37 (1950).

(20) E. Chargaff, E. Vischer, R. Doniger, R. Green, and F. Misani, *J. Biol. Chem.*, 177, 405 (1949).

(21) G. R. Wyatt, *Biochem. J.*, 48, 584 (1951).

(22) L. Jaenecke and T. Volbrechthausen, *Naturwiss.*, 39, 86 (1952).

(23) J. D. Smith and R. Markham, *Biochem. J.*, 46, 509 (1950).

(24) Obtained from Ross Allen's Reptile Institute.

(25) We are indebted to Dr. C. E. Carter, Yale University, for this preparation.

(26) G. Schmidt, *Methods in Enzymology*, Academic Press, 1955, Vol. II, p. 529.

TABLE III

SPONGE DEOXYRIBONUCLEOSIDE PROPORTIONS

Sponge	Adenine Deoxyriboside	Thymidine	Guanine Deoxyriboside	Cytosine Deoxyriboside	Purines / Pyrimidine
Cryptotethia crypta	10.0	9.0	8.9	8.9	1.05
Dysidia craushayi	10.0	10.4	7.5	7.0	1.01
Cinachyra cavernosa	10.0	10.0	9.5	9.4	1.01
Ianthella ardis	10.0	10.0	15.3	15.0	1.01
Leucetta floridana	10.0	11.1	5.7	5.6	0.94

10.0; cytidine, 13.1; uridine, 7.0; and purine:pyrimidine, 1.65. The total weight of the nucleosides was approximately 300 μg., corresponding to 0.75% of ribonucleic acid in the original nucleic acid–polysaccharide mixture.

Identification of ribose. Hydrolyses were carried out with *N* hydrochloric acid in the usual manner.[23] The hydrolyzate was neutralized by passage through a column of Dowex-I (OH-form) before application to the paper. The chromatography was carried out in solvent systems D, E, and F, and the spots were detected with aniline hydrogen phthalate spray.[27] Where deoxyribonucleic acid and polysaccharides were present, the ribonucleic acid was first degraded enzymatically to the nucleosides, and adenosine was separated from the mixture by paper chromatography and subsequently eluted and hydrolyzed in the usual manner. The carbohydrate spots obtained from each of the sponge ribonucleic acid preparations by any one of the methods showed no differences in R_f value from authentic D-ribose.

Degradation of sponge deoxyribonucleic acids. A. Deoxyribonucleosides. Deoxyribonucleic acid–polysaccharide mixtures obtained by the method described under B2 were further freed from residual potassium perchlorate by two ethanol precipitations from *M* sodium chloride solution. The dried preparation was then dissolved in 0.3 ml. of 0.1*M* ammonium acetate buffer, *p*H 6.8, containing 300 μg. of magnesium chloride and about 50 μg. of deoxyribonuclease, and the solution was incubated at 37° for 5 hr. About 2 mg. of crude snake venom was then added, and the incubation continued for 15 hr. The mixture was diluted with two volumes of ethanol, and the polysaccharide precipitate removed by centrifugation. The supernatant solution was concentrated to about 0.1 ml., and chromatographed in solvent system E against the authentic deoxyribonucleosides of guanine, adenine, cytosine, and thymine. The four spots given by the sponge nucleosides showed the same R_f values as the authentic markers.

In the case of *Cryptotethia crypta*, the cytosine and thymine nucleosides were eluted from a duplicate chromatogram, and rechromatographed in three additional solvent systems, B, G, and H. In these solvent systems they also gave the same R_f values as authentic cytosine deoxyriboside and thymidine, respectively. Spongothymidine gives an appreciably lower R_f value than thymidine in all four solvent systems.

In all cases the nucleoside spots were cut from the chromatograms together with blanks of equal size, each eluted with 5 ml. of water for 24 hr., and the ultraviolet absorption spectra of the eluates were measured. The spectra in neutral, acidic, and basic solutions did not differ from those of the corresponding authentic nucleosides. Table III lists the molar proportions of the individual deoxyribonucleosides as calculated from the absorption maxima of the original neutral eluates.

Degradation of sponge deoxyribonucleic acids. B. Free bases. Deoxyribonucleic acid–polysaccharide mixtures, such as used in the degradation to the nucleosides, were hydrolyzed with 98% formic acid in sealed tubes for 30 min. at 175°.[21] The formic acid was removed *in vacuo*, and the residues dissolved in 0.1*N* hydrochloric acid and chromatographed in solvent system G against guanine, adenine, cytosine, and thymine markers. The chromatograms were marred in most cases by streaking, fluorescent polysaccharide degradation products, but dark absorbing spots with R_f values equal to those of the markers were readily discernable. In no case were any other spots observed.

Identification of 2-deoxy-D-ribose. Polysaccharide-free solutions of sponge deoxyribonucleosides, prepared as described above (A) were concentrated to about 0.1 ml. and hydrolyzed by bringing the solutions to *p*H 1 with hydrochloric acid, and by heating them in sealed tubes at 100° for 10 min. The hydrolyzates were applied directly to paper and chromatographed in solvent systems D, E, and F against authentic 2-deoxy-D-ribose. Spots were detected with *m*-phenylenediamine spray.[20] No R_f differences between the sugar from the sponge nucleic acid and authentic 2-deoxy-D-ribose could be detected. In the case of *Cryptotethia crypta*, adeninedeoxyriboside and guaninedeoxyriboside, following chromatographic separation and elution, were individually hydrolyzed. They gave 2-deoxy-D-ribose as the only carbohydrate moiety.

(27) S. M. Partridge, *Nature*, 164, 443 (1949).

NEW HAVEN, CONN.

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The Oxymercuration of Δ^1-Terpineol*

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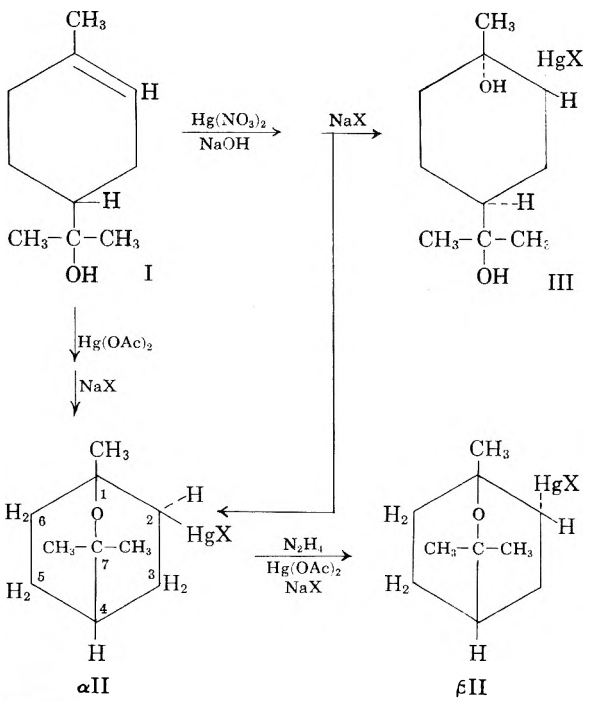
The supposed diastereomers of 2-iodomercuri-*trans*-terpin reported by Sand and Singer have been found to be polymorphs. It has also been shown that the *trans*-terpin mercurial is not an intermediate in the formation of the halogenomercuricineoles, which seem to be formed directly from the salt expected from the alcoholysis of mercuric acetate by Δ^1-terpineol. It has been found that hydrogen sulfide decomposes α-halogenomercuri-*trans*-terpin to give terpineol, whereas comparable treatment of the β-diastereomer yields bis(*trans*-terpinmercuri) sulfide. The β-diastereomers of the halogenomercuricineoles have been prepared by equilibration with the α form by hydrazine hydrate. The unusual stability of these β-diasteromers toward hydrochloric acid lends support to the theory that decomposition of oxymercurials by this acid proceeds through a quasi-cyclic intermediate. There is still doubt whether addition of the elements of mercuric salts to alkenes occurs in the *cis* or *trans* manner despite the fact that this reaction has been known for more than fifty years. This doubt has not been dispelled in the present study of Δ^1-terpineol oxymercuration. However a choice must be made in order to describe the terpins and cineoles which have been prepared. We have chosen to express the stereochemical structures in terms of *cis* addition and elimination because this expression describes best the known facts of oxymercuration, whereas *trans* addition and elimination may at present be applied only by analogy with reactions which are not necessarily related to oxymercuration. If new facts of oxymercuration subsequently favor the *trans* mode then the terpin structures of section I and the cineole structures of section II may easily be revised in accordance with such new discoveries.

I. TERPIN MERCURIALS

It has recently been shown[1] that the two pairs of compounds which Sand and Singer[2,3] reported as the oxymercuration products of 2,6-dimethylhepten-5-ol-2 were in reality one cyclic and one linear oxymercurial. In the same publications Sand and Singer described the oxymercuration of Δ^1-terpineol (I). They reported that one bicyclic and two monocyclic oxymercurials were obtained when the basic reaction mixture was treated with sodium iodide and carbon dioxide.



They specified that the bicyclic compound, to be discussed in Section II, was 2-iodomercuri-1,8-cineole (II, X = I) because they were able to reduce it with sodium amalgam to 1,8-cineole. We have confirmed their opinion, first by reduction with hydrazine hydrate[4] to give cineole, and second by oxidation of II with alkaline permaganate to yield cineolic acid. They also reduced their monocyclic products to *trans*-terpin by means of sodium amalgam, and this designated the mercurials as 2-iodomercuri-*trans*-terpins (III, X = I). Since oxygen was thus shown to be attached to carbon 1 in all three products, the isomeric forms of III seemed not to be position isomers. Sand and Singer then designated III (X = I) in two diastereomeric forms. Since both products, upon reduction, yielded *trans*-terpin, it is evident that their postulated diastereoisomerism must involve the disposition of the hydroxy versus the iodomercuri group.

This designation may be questioned from two aspects. First, no instance is yet known when a single geoisomer (in which category Δ^1-terpineol must be considered) has yielded more than a single diastereomeric mercurial. Second, Sand and Singer reported that the low-melting form of III was converted to the high-melting form simply by treating with cold absolute ethanol or by heating in benzene or ethyl acetate. Such easy conversion is not characteristic of diastereomers. However Sand and Singer also reported that the low-melting form of III was more easily hydrolyzed by aqueous acids than was the other. This property has been found to be characteristic of diastereomeric oxymercurials.[4–6]

* This paper is a contribution in honor of Lyndon F. Small, former Editor of the Journal.

(1) A. G. Brook, A. Rodgman, and G. F Wright, *J. Org. Chem.*, **17**, 988 (1952).

(2) J. Sand and F. Singer, *Ber.*, **35**, 3170 (1902).

(3) J. Sand and F. Singer, *Ann.*, **329**, 166 (1903).

(4) G. F Wright, *Can. J. Chem.*, **30**, 268 (1952).

(5) J. Romeyn and G. F Wright, *J. Am. Chem. Soc.*, **69**, 697 (1947).

(6) A. G. Brook, R. Donovan, and G. F Wright, *Can. J. Chem.*, **31**, 536 (1953).

It thus seemed worthwhile to resolve this discrepancy by repetition of the work of Sand and Singer.

We found at once that the low-melting form of III (X = Iodine) is not so stable as Sand and Singer implied. When first isolated, it is a gummy solid at 25°, although it is hard and brittle at 4°. Its melting point gradually rises from 45–50° to 91° over a period of four days at 25°. When either high-melting (m.p. 143–4° after crystallization from benzene) or the unstable low-melting isomer is dissolved in alkali and reprecipitated by carbon dioxide, it cannot be predicted which isomer will be obtained. However, deliberate inoculation with one of the isomers at the moment before precipitation when the liquor becomes cloudy always promotes precipitation of that isomer. This behavior designates the isomers as simple polymorphs.

The physical and chemical properties of the two isomers of III (X = Iodine) are those usually expected for labile and stable polymorphic modifications. The low-melting (labile) modification dissolves more easily in a variety of solvents than the high-melting form. Each shows a characteristic X-ray diffraction powder pattern, although the pattern of the labile polymorph obviously is less distinctive than that of the stable form, which can be crystallized to high purity. The polymorphism of 2-iodomercuri-*trans*-terpin may extend to the chloromercuri analog (III, X = Cl). But when either of the polymorphs of III (X = Iodine) is treated with silver acetate and then with sodium chloride only one chloromercuri-*trans*-terpin is obtained. This would seem to constitute sufficient proof that III (X = I) exists in polymorphic rather than diastereomeric form. There is, then, not yet an exception to the rule that in oxymercuration the addition to an alkene linkage is diastereomerically unique.

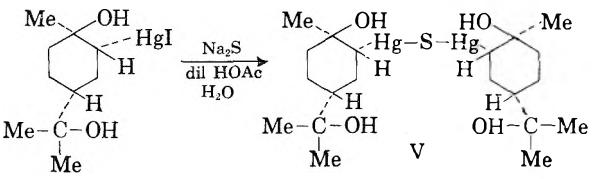
The single diastereomer (III) is evidently 2-halogenomercuri-*trans*-terpin, notwithstanding the fact that the structure proof involving reduction with sodium amalgam is not completely reliable. Such a reducing agent has been known to remove the oxymercurial addend with regeneration of the alkene linkage. However if such a reaction sequence had occurred in the present instance (and water had then added to the double bond), the product would have been *cis*-terpin hydrate. The latter geoisomer is invariably the product when Δ^1-terpineol is hydrated.[7] Since only *trans*-terpin was isolated after reduction with sodium amalgam, the hydroxyl group in III must be situated oppositely from the hydroxypropyl group with respect to the cyclohexane ring. It will be assumed subject to further consideration that the mercuri substituent is oppositely disposed relative to the hydroxypropyl group.

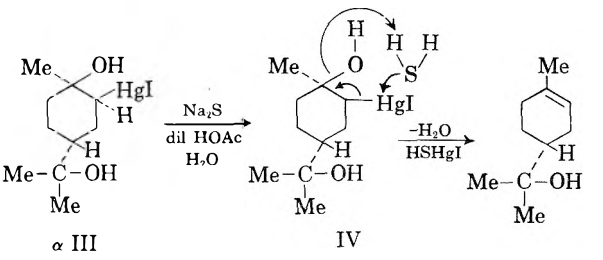
(7) J. L. Simonsen, *The Terpenes*, Cambridge Press, 1947, Vol. 1, p. 302.

Since the 2-iodomercuri-*trans*-terpins of Sand and Singer are polymorphs rather than diastereomers we suggest that their designations, "alpha" and "beta," be abandoned in favor of "labile" and "stable" forms. The Greek letters may then be used according to an earlier suggestion[4] to designate the diastereomer obtained from a *cis*-alkene as "alpha," and from a *trans*-alkene as "beta." Since Δ^1-terpineol resembles cyclohexene in its geometry the pair of polymorphs (III, X = Iodine) may be said to comprise the α-diastereomer of 2-iodomercuri-*trans*-terpin.

The α-diastereomer may be converted to a mixture of itself and the β form of III (X = Iodine) by treatment of a hot alkaline solution of α-III with a small amount of hydrazine hydrate.[4] When this mixture is treated carefully with hydriodic acid, the α part is decomposed to Δ^1-terpineol and mercuric iodide. After the system is made basic and steam-distilled to remove terpineol, the β-diastereomer may be isolated by acidification. Reduction of this more stable isomer by sodium amalgam yields *trans*-terpin, showing that the configuration of the mercuri group, but not the hydroxy group, has been inverted relative to the hydroxypropyl group in the β-diastereomer.

In accordance with previous observations[6] the dipole moment of β-iodomercuri-*trans*-terpin (4.59 D) in dioxane solution at 20° is found to be larger than the comparably-determined moment (4.21 D)





of the α-diastereomer. This difference may be related to the behavior of the two diastereomers towards sodium sulfide. The α-diastereomer (α-III, X = I) reacts quickly in aqueous acetic acid with regeneration of terpineol, I. We suggest that this demercuration occurs *via* a cyclic intermediate (IV) in which molecular hydrogen sulfide partakes. By contrast β-III (X = I) reacts with sodium sulfide to give β-bis(*trans*-terpinmercuri) sulfide (V). The stability of this sulfide, unique among comparable oxymercurials so far investigated, may be attributed to steric reactions not present in the demercuration of the β-diastereomer. Such steric

effects would be operative in the cyclic intermediate which we have postulated.

II. THE CINEOLE MERCURIALS

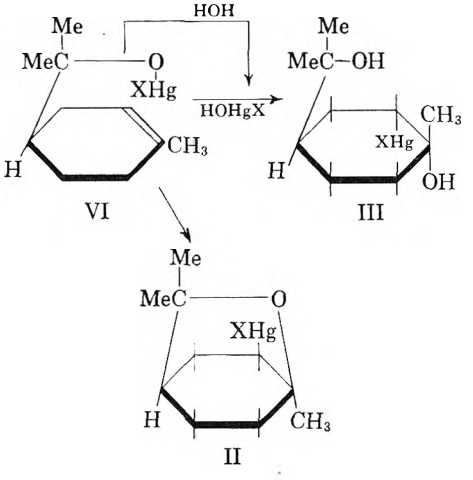
One can not discern from the reaction procedure of Sand and Singer whether the bicyclic cineol-mercurial (II) is formed directly from Δ^1-terpineol or indirectly from a mercurial of *cis*- or *trans*-terpin by spontaneous dehydration. One might postulate that the theoretically-possible nitratomercuri-*cis*-terpin was indeed formed by *cis* oxymercuration but subsequently lost the elements of water to form nitratomercuricineole.[2,3] Alternatively the diastereomeric nitratomercuricineole might have been formed from nitratomercuri-*trans*-terpin *via* replacement of hydroxyl by tertiary alkoxyl at C_1 with inversion.

The effect of *p*H during the hydroxymercuration of α-terpineol has been shown by Mr. Paul Chu to vitiate the first alternative.

The *p*H of the basic mercuric salt as described by Sand and Singer[2,3] lies between 1 and 2. In this system the yields of α-2-iodomercuri-*trans*-terpin and α-2-iodomercuricineole were 62% and 8% respectively. If the *p*H were raised to 3, where some mercuric oxide appeared, the yields were 56% and 25%. When sodium acetate as a buffer raised the *p*H to 4–5 the yields were 40% and 37% respectively while at *p*H 6 they were 24% and 39%. Thus it may be seen that the 2-iodomercuricineole yield is highest under conditions where ether formation by dehydration ought to be least. Actually the yield of the bicyclic product is greatest in circumstances where the *tert*-alkoxymercuric salt (see VI, X = OAc) ought to be most stable.

Indeed it is found that mercurated cineole is formed under conditions where the mercurated terpin cannot be present. By treatment of anhydrous Δ^1-terpineol with mercuric acetate in suspension we have shown that αII (X = OAc) can be formed directly. Some oxidation occurs at the same time since 15% of the mercuric salt is reduced to the mercurous form. The oxidation product (identified by Mr. D. A. Shearer of this laboratory as pinol hydrate, 6% yield) is separable from the mercurial because of its insolubility in alkali. The separated alkaline solution precipitates a 60% yield of α-2-chloromercuricineole when it is treated with sodium chloride and carbon dioxide.

The mechanism by which the cineole mercurial (II) is formed may be illustrated by postulation of the basic mercuric salt (VI, X = OAc) as an intermediate. In absence of water, II can be the only mercurial formed, but when water is present this intermediate may be expected to hydrolyze either before or after hydroxymercuric acetate has been added to the double bond to form the *trans*-terpin mercurial (III, X = OAc). In the latter event the presence of the hydroxypropyl group or its mercuric salt would be expected on steric grounds to prevent formation of the diastereomer alternative to III which could be formed by *cis* addition.



The reduction of an alkaline solution of 2-iodomercuricineole by an excess of hydrazine hydrate was shown in the present report to yield cineole. On the other hand a stoichiometric deficiency of hydrazine hydrate forms a diastereomeric mixture of α- and β-iodomercuricineoles; the same behavior is observed with the α-bromo- and α-chloromercuricineoles. β-Chloromercuricineole may be isolated from the diastereomeric mixture because of its stability (unique among any vicinally-linked oxymercurials that are known) toward mineral acid. This property is undoubtedly related to the rigidity imposed by the bicyclic ring system. The stability of the β-isomer is utilized for its isolation by dissolving the mixture in alkali and then acidifying with hydrochloric acid.[5] The α-diastereomer is immediately decomposed to Δ^1-terpineol and mercuric chloride. The terpineol may be removed by steam distillation of the suspension after it is made basic. The residual liquor is filtered to remove mercuric and mercurous oxides, then acidified with hydrochloric acid to precipitate the β-chloromercuricineole. The β-bromo- and β-iodomercurials are obtained by appropriate modifications.

The β-halogenomercuricineoles differ from their α-diastereomers not only in stability toward mineral acid but also in lower melting points and greater solubility in hydroxylic solvents. On the other hand β-hydroxymercuricineole is much less soluble in hydroxylic solvents than the α-diastereomer, and this property may also be utilized in separation of the two.

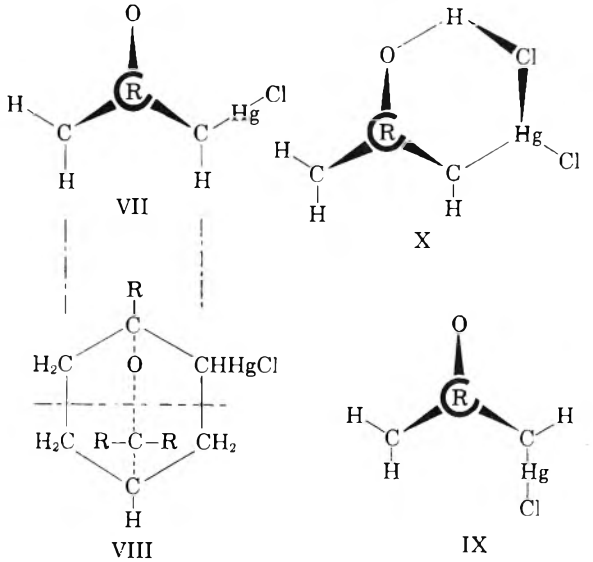
The electrical polarizations of the α and β chloromercuricineoles have been determined in dioxane at 20° as 314.8 and 556.8 cc. respectively by calculation from the dielectric constants and specific volumes of the solutions according to the method of Halverstadt and Kumler.[8] From the di-

(8) I. F. Halverstadt and W. D. Kumler, *J. Am. Chem. Soc.*, 64, 2988 (1942).

electric constants of a series of pellets[9,10] the combined atomic and electronic polarization has been found to be 68.5 cc. for the α- and 66.9 cc. for the β-diastereomer. From these data the dipole moment is calculated as 3.42 D for α-chloromercuricineole and 4.82 D for the β-diastereomer. Thus the cineole mercurials resemble other diastereomeric pairs of oxymercurials since the form having the lowest dipole moment is the one most easily decomposed by mineral acids.[4-6]

The group fixation in these cineoles permits of comparison with the oxy- and mercuri-groups which are fixed analogously in the oxymercuration product of 1,4-↑↑-methylene-Δ^5-cyclohexene-2,3-↓↓-dicarboxylic acid.[11] In both instances the bridge limits the variety of atomic constellations that are otherwise possible in a cyclohexane ring system. Insofar as 5-↓-hydroxy-6-↓-chloromercuri-1,4-↑↑-methylenecyclohexane-2,3-dicarboxylic acid, γ lactone of moment 3.88 D and its inverted diastereomer 5-↓-hydroxy-6-↑-chloromercuri-1,4-↑↑-methylenecyclohexane-2,3-dicarboxylic acid, γ-lactone of moment 7.18 D[12] can be compared with the α- and β-chloromercuricineoles a configurational assignment may be made. According to this criterion the α-diastereomer would be represented by the plan and side elevations shown as structures VII and VIII (R = CH_3) while the β-diastereomer would be represented, in plan elevation, as IX.

Other opinions in respect of the mode of addition in oxymercuration have been expressed.[13] Those favoring "trans" addition would describe the bicyclic oxymercuration product of Δ^1-terpineol as IX. A final decision should not be made on the basis of the evidence now available. However it may be noted that the planar arrangement of O-C-C-HgCl in IX should from conformational considerations be unusually favorable for demercuration if such elimination occurred in the *trans* manner. Actually α-2-chloromercuricineole is not unduly sensitive toward acid-actuated demercuration. Moreover highly dissociated acids are not very effective, and demercuration occurs easily only when hydrogen halides are present in molecular form. This behavior has led us to favor structure VII-VIII as the α-diastereomer because it permits the existence of a quasi-cyclic complex (X) with hydrogen halide. If easy demercuration involves such a complex, it is understandable that β-chloromercuricineole, if it is represented by IX, is very resistant to the action of hydrogen halide.



EXPERIMENTAL[14]

α-2-Chloromercuricineole. A. From mercuric acetate. A suspension of 160 g. (0.5 mole) of mercuric acetate in 375 g. (2.42 mole) of Δ^1-terpineol was stirred at 40–45° for 2 days (although a test for mercuric ion was negative after 12 hr.) and then was filtered by suction to remove 26.4 g. of mercurous salt. From the filtrate was distilled 228 g. of unchanged Δ^1-terpineol at 60–70° under 0.01–0.001 mm. The residue was suspended in 200 ml. of petroleum ether (b.p. 60–70°). This suspension was extracted successively with 400, 300, and 200 ml. of 5% aqueous sodium hydroxide and then with four 200 ml. portions of water. The combined aqueous extract was treated with Darco decolorizing charcoal and filtered. After solution of 100 g. of sodium chloride into this filtrate, it was saturated with carbon dioxide. The vacuum-dried precipitate weighed 122 g., m.p. 151°. This was crystallized from 1400 ml. of hot 95% ethanol with 1 g. of Darco. The purified product weighed 83 g. (43%) and melted at 164°. The X-ray powder diagram gave relative intensities at d spacings of [10] 16.05; [9] 10.71; [7] 5.30; [6] 3.22; [4] 7.96, 2.65; [3] 5.88, 4.39, 3.77, 3.65, 2.86; [2] 5.62, 4.91, 3.96, 3.57, 3.42, 2.45, 2.16; [1] 4.61, 2.77, 2.10.

Anal. Calcd. for $C_{10}H_{17}OHgCl$: C, 30.9; H, 4.37. Found: C, 30.7; H, 4.39.

The petroleum ether extract, when combined with the evaporated mother liquors from crystallization was steam-distilled with 10% alkali to remove residual Δ^1-terpineol. The non-aqueous residue was crystallized from chloroform, which yielded 5.1 g. (6%) of impure pinol hydrate. After crystallization from chloroform and benzene it melted at 133.0–133.5°. A mixed melting point with an authentic specimen was not lowered.

Anal. Calcd. for $C_{10}H_{18}O_2$: C, 70.6; H, 10.6. Found: C, 70.0; H, 10.8.

B. From basic mercuric nitrate in water. A solution of mercuric nitrate was prepared from 21.6 g. (0.1 mole) of mercuric oxide in 80 ml. of 20% nitric acid. A solution of 15.4 g. (0.1 mole) of Δ^1-terpineol (d_4^{28} 0.936, n_D^{20} 1.47902) in 30 ml. of diethyl ether also was prepared. To the first solution in a separatory funnel was added 10% aqueous potassium hydroxide until a white precipitate appeared. A portion of the second solution was added and the mixture was shaken while the ether was allowed to boil away through the stop cock. Alternate addition of alkali to restore the white pre-

(9) C. C. Meredith and G. F Wright, *Can. J. Technology*, **33**, 182 (1955).

(10) C. C. Meredith, L. Westland, and G. F Wright, *J. Am. Chem. Soc.*, **79**, 2385 (1957).

(11) K. H. McNeely, A. Rodgman, and G. F Wright, *J. Org. Chem.*, **20**, 714 (1955).

(12) G. F Wright, *Annals New York Academy of Science*, **65**, 436 (1957).

(13) J. Chatt, *Chem. Revs.*, **48**, 7 (1951).

(14) All melting points have been corrected against reliable standards. X-Ray diffraction patterns were determined with CuK_α radiation (Ni filtered) and are recorded as d spacings in Å at relative intensities $[I/I_0]$.

cipitate and of terpineol to remove it until final addition of alkali (about 250 ml. total) precipitated black mercurous salt. The mixture was filtered and the filtrate treated with 15 g. of potassium hydroxide dissolved in 30 ml. of water. To this slightly cloudy solution was then added 15 g. (0.09 mole) of potassium iodide in 20 ml. of water. The precipitate was filtered off. This 3.80 g. yield (8%) of 2-iodomercuricineole was crystallized from 50 ml. of absolute ethanol, m.p. 151–152°. Its X-ray diffraction pattern was [10] 5.98, 3.45; [8] 12.62; [6] 11.32, 7.49; [5] 3.16, 1.84, 1.57; [4] 5.21, 4.48, 2.96, 2.44, 2.23, 1.99, 1.93; [3] 3.61, 2.56, 2.34, 2.14; [2] 4.72, 4.23, 4.00, 1.68; [1] 2.81, 1.86, 1.79, 1.73, 1.65, 1.60, 1.55, 1.52, 1.48, 1.44, 1.42, 1.39, 1.35, 1.27, 1.18, 1.14, 1.11, 1.08, 1.04, 1.00, 0.97.

This product could be converted to 2-chloromercuricineole in 65% yield by treatment of 0.6 g. (0.00125 mole) and 0.26 g. (0.0016 mole) of silver acetate as a suspension in 7 ml. of ethanol and 8 ml. of water for 12 hr. The silver halide was then filtered off. The filtrate was treated with 15 ml. of potassium hydroxide to remove mercurous salt. The alkaline filtrate was treated with 10 ml. of saturated aqueous sodium chloride and then with gaseous carbon dioxide. The precipitate (0.3 g.) melted at 161–162° after crystallization from 5 ml. of absolute ethanol.

α-2-Bromomercuricineole. When an ethanolic solution of α-chloromercuricineole was treated with aqueous sodium bromide the precipitate melted at 152°. This α-bromomercuricineole was crystallized repeatedly from the hot 95% ethanol (11 ml. per g.), m.p. 152.6°.

Anal. Calcd. for $C_{10}H_{17}OHgBr$: C, 27.7; H, 3.84. Found: C, 27.6; H, 3.86.

The X-ray diffraction pattern was [10] 12.55; [9] 5.94; [6] 4.49, 3.27; [5] 3.88; [4] 4.94, 2.58; [3] 7.34, 6.73; [2] 4.17, 3.57, 3.38, 3.10, 3.02, 2.97; [1] 2.84; [0.5] 5.30, 4.76, 2.66, 2.50, 2.41, 2.34, 2.28, 2.22, 2.11, 2.00, 1.97, 1.92, 1.87, 1.82, 1.76, 1.66, 1.63, 1.59, 1.56.

Polymorphic α-2-iodomercuri-trans-terpins. The solution from which the 2-iodomercuricineole was filtered according to the foregoing procedure *B* was saturated with gaseous carbon dioxide at 0°. This precipitated a gummy solid (31 g., 62%) which was filtered off at the same temperature. It was redissolved in 150 ml. of warm 10% aqueous sodium hydroxide and was reprecipitated by gaseous carbon dioxide at 0°. This compound, evidently Sand and Singer's labile isomer, weighed 27 g. and melted indefinitely at 45–48°. Its X-ray diffraction pattern was determined: [10] 7.52; [7] 5.50; [4] 6.75; [2] 4.53, 4.15; [1] 3.78, 3.46, 3.37. After four days in dry vacuum it melted at 89–94°. Two crystallizations of either the product melting at 45–48° or that melting at 89–94° from hot benzene (15 ml. per g.) raised the melting point to 142–144°. This stable isomer was found to be identical with 3.0 g. (6%) of the precipitate collected 12 hr. after the labile isomer was precipitated by carbon dioxide. Identity was established by mixed melting point and by X-ray diffraction pattern: [10] 9.93; [8] 7.82; [5] 5.68; [3] 6.91, 5.90 (?), 4.07; [2] 11.18, 4.25, 3.69; [1] 12.99, 4.41, 3.85, 3.62; [0.5] 6.51, 5.27, 4.98, 4.72, 3.49, 3.40, 2.98, 2.79, 2.69, 2.59, 2.45. When this polymorph melting at 142–144° was dissolved in 40% aqueous potassium hydroxide (2 g. per 40 ml.) and the ice-cold filtered solution was treated with carbon dioxide a turbidity appeared. If a seed of the identical polymorph was added, only this high-melting form was precipitated. On the other hand a seed of the material melting at 45–48° caused the exclusive crystallization of the low-melting form, identified by its diffraction pattern.

2-Chloromercuri-trans-terpin. To 5.0 g. (0.01 mole) of 2-iodomercuri-*trans*-terpin, m.p. 140–142°, suspended in 25 ml. of water and 25 ml. of ethanol was added 2.0 g. (0.012 mole) of silver acetate. The mixture was stirred vigorously overnight. The yellowish-grey precipitate was removed and the filtrate was treated with 20 ml. of 10% sodium hydroxide solution which precipitated a little black solid. This was filtered off and the filtrate was treated with 25 ml. of saturated sodium chloride solution, and then was carbonated at 0°. A small quantity of grey-white precipitate was removed and the filtrate was extracted several times with chloroform. The combined extracts, after drying, were evaporated to dryness and the resulting gum was treated with a little ether which caused crystallization. This crude 2-chloromercuri-*trans*-terpin, m.p. 135–150°, weighed 2.5 g. (62%). Recrystallization from 3:1 benzene:acetone (15 ml./g.) raised the m.p. to 162–164°.

Anal. Calcd. for $C_{10}H_{19}O_2HgCl$: C, 29.5; H, 4.66. Found: C, 29.9; H, 4.85.

The X-ray diffraction pattern was: [10] 11.04, 6.80; [8] 4.57; [7] 5.90, 3.07; [6] 3.23; [5] 8.58, 2.79; [4] 3.17; [2] 5.53, 3.75, 3.60, 3.48, 2.94, 2.71; [1] 7.99, 4.23, 3.98, 2.42, 2.39, 2.29, 1.89, 1.71; [0.5] 5.06, 2.58, 2.53, 2.21, 2.16. In another experiment, which we cannot yet repeat and which involved a slow deposition out of ethanolic solution, we obtained a product of m.p. 134.5–135.5° of correct elemental composition which gave a different diffraction pattern, in part [10] 9.11; [7] 4.24; [6] 5.14, 3.81; [4] 7.39; [3] 6.21, after crystallization from benzene.

A melting point-composition diagram for α-2-iodomercuri-*trans*-terpin, m.p. 143°, and α-2-chloromercuri-*trans*-terpin, m.p. 164°, showed a continuous solid-solution curve, m.p. 145° at 25%, 148° at 50%, 152° at 75% and 157° at 90% of the chloromercurial.

Effect of pH on the yields of 2-iodomercuri-trans-terpin and 2-iodomercuricineole from mercuric nitrate and Δ^1-terpineol (by Paul Chu). The preparation was modified as follows in order to study the effect of *p*H on the yields of the various products. A mixture of 7.7 g. (0.05 mole) of Δ^1-terpineol in 70 ml. of warm water was placed in a three necked flask provided with a stirrer. Aqueous mercuric nitrate (prepared by dissolving 10.8 g. (0.05 mole) of mercuric oxide in 40 ml. in 20% nitric acid) and 10% potassium hydroxide solutions were added from two separatory funnels over about 15 min. The reaction was worked up as described above.

When the reagents were added so that a small amount of mercuric oxide was always present (about *p*H 3) the yields of 2-iodomercuri-*trans*-terpin and 2-iodomercuricineole were 56% and 25% respectively.

When an equivalent of sodium acetate was included in the mercurating system as a buffer so that the *p*H was about 4–5, the corresponding yields were 40% and 37.5%.

When the *p*H was maintained at about 6, much mercuric oxide was present and the yields were 24% and 39% respectively. Above this *p*H so much mercuric oxide formed that the yields of both products were greatly decreased.

β-2-Chloromercuricineole. To a solution of 19.4 g. (0.05 mole) of α-chloromercuricineole in 200 ml. (0.25 mole) of 5% aqueous sodium hydroxide was added 0.25 ml. (0.004 mole) of 85% hydrazine hydrate and the whole was boiled under reflux for 130 min. The reaction mixture was cooled and extracted with ether; this extract was eventually discarded. The aqueous layer was filtered to remove metallic mercury and was acidified to *p*H 4 with 12% hydrochloric acid. After 10 min. this suspension was made alkaline with 30 ml. of 10% aqueous sodium hydroxide and boiled until the odor of Δ^1-terpineol was no longer apparent. The black suspension was filtered off and the cooled filtrate was acidified to *p*H 5 with 12% hydrochloric acid. Ether was added and then evaporated to coagulate the precipitate. The crude β-chloromercurial which was filtered off weighed 9.95 g., m.p. 86–7°. This was purified by solution in alkali, etherous extraction of the alkaline solution, and then re-acidification to *p*H 5. In this way 6.78 g. (35% of theoretical) of β-2-chloromercuricineole was obtained, m.p. 101.7–102.3°. This was crystallized from 95% ethanol (15 ml. per g.) with addition of Nuchar, m.p. 104.5°. The X-ray diffraction pattern was: [10] 12.80; [9] 5.55; [6] 6.37; [4] 4.74; [3] 3.81, 3.64, 3.50, 3.06; [2] 2.59; [1] 4.25, 3.17, 2.97, 2.93, 2.82, 2.77, 2.63, 2.53, 2.50, 2.33, 2.21, 1.93, 1.89; [0.5] 5.21, 2.27, 2.15, 1.98.

TABLE I

ELECTRIC POLARIZATION DATA IN DIOXANE AT 20°

Substance	α	β	P_T	P_{E+A}	R_D	D_4^{20}	μ, D
α-Chloromercuricineole	4.06	0.458	314.8	68.5		2.099	3.42
β-Chloromercuricineole	7.85	0.442	556.8	66.9		2.197	4.82
α-Iodomercuri-*trans*-terpin	4.80	0.565	447.0		73.2		4.21
β-Iodomercuri-*trans*-terpin	5.60	0.545	516.5		73.2		4.59

Anal. Calcd. for $C_{10}H_{17}OHgCl$: C, 30.9; H, 4.37. Found: C, 31.3; H, 4.56.

When the amount of hydrazine hydrate was doubled, the crude product (5.8 g., 30%) melted at 100–101°. Further increase in amount of hydrazine hydrate caused the formation of cineole. Thus a 20-fold molar excess of the hydrate gave steam-distillable cineole in 10% yield. This product (b.p. 63°/15 mm., n_D^{25} 1.4579) was identified by its crystalline derivative with *o*-cresol.[7]

Diastereomeric chloromercuricineoles with hydrochloric acid. A mixture of 0.1 g. each of α- and β-chloromercuricineole in 2.5 ml. of methanol was treated with 0.05 ml. of concentrated hydrochloric acid for 1 min., then diluted to 4.5 ml. with water, and neutralized to *p*H 4 with alkali. The precipitate, weighing 0.07 g., was filtered and washed with petroleum ether. It was pure β-chloromercuricineole, m.p. 103–104°. The α-chloromercuricineole was converted chiefly to Δ^1-terpineol.

When 3.89 g. (0.01 mole) of the α-diastereomer was treated with 0.1 ml. of concentrated hydrochloric acid and 10 ml. of methanol for 20 min. a 90% yield of dipentene dihydrochloride, m.p. 48° (crystallized from petroleum ether, m.p. 52.8°), could be filtered off. This was identified by mixture melting point with the identical product of Δ^1-terpineol and concentrated hydrochloric acid. Under the same conditions the β-chloromercuricineole was recovered unchanged.

Oxidation of α-chloromercuricineole. A solution of 3.89 g. (0.01 mole) of α-chloromercuricineole in 32 ml. of 3% aqueous sodium hydroxide was treated with 10 g. (0.063 mole) of potassium permanganate in 150 ml. of water over 75 min. The excess was destroyed with methanol and the manganese dioxide was filtered off. The filtrate was saturated with carbon dioxide to demonstrate that no mercurial remained and then was concentrated to a volume of 15 ml. and acidified to *p*H 2.7. The precipitate (cineolic acid) weighed 1.72 g. (80%), m.p. 202–203°. Crystallization from hot water (30 ml. per g.) raised the melting point to 207°.

Anal. Calcd. for $C_{10}H_6O_5$: C, 55.3; H, 7.47. Found: C, 55.5; H, 7.54.

β-Bromomercuricineole. An ethanolic solution of the β-chloromercuricineole was shaken for 12 hr. with one equivalent of silver acetate and the filtrate drowned with sodium bromide. The precipitate was crystallized from hot 95% ethanol (5 ml. per g.) with addition of Nuchar, m.p. 113–114°.

Anal. Calcd. for $C_{10}H_{17}OHgBr$: C, 27.7; H, 3.84. Found: C, 27.6; H, 3.97.

The X-ray diffraction pattern was: [10] 13.18; [9] 5.59, 3.85, 3.70; [8] 6.49, 3.55, 3.20; [6] 2.67; [4] 4.78; [3] 4.34; [2] 1.86; [1] 5.21, 3.32, 3.12, 2.79, 2.59, 2.52, 2.36, 2.32, 2.24, 2.19, 2.09, 1.92, 1.77; [0.5] 3.44, 2.99, 2.15, 2.03, 1.98, 1.95, 1.89, 1.81, 1.73, 1.66, 1.63, 1.59, 1.55, 1.49, 1.43, 1.38, 1.30, 1.28, 1.24.

β-Iodomercuricineole. The ethanolic solution of acetoxymercuricineole (described above) was treated with sodium iodide. The product was crystallized from hot 95% ethanol (5 ml. per g.), m.p. 116–117°.

Anal. Calcd. for $C_{10}H_{17}OHgI$: C, 25.0; H, 3.56. Found: C, 25.8; H, 3.28.

The X-ray diffraction pattern was: [10] 13.38; [9] 3.86; [5] 6.65, 5.67, 3.75, 3.61; [4] 3.02, 2.62; [2] 4.74, 2.53, 1.96; [1] 5.20, 4.45, 4.30, 3.16, 2.73, 2.33, 2.24, 2.17, 2.13, 2.01, 1.92, 1.81, 1.70, 1.63; [0.5] 3.41, 3.27, 2.90, 2.79, 2.37, 2.08, 1.85, 1.76, 1.65, 1.58, 1.52, 1.49, 1.45.

β-Iodomercuri-trans-terpin. A solution of 4.98 g. (0.01 mole) of α-iodomercuri-*trans*-terpin in 32 ml. (0.02 mole) of 2.5% aqueous sodium hydroxide was warmed to 60° and then 0.05 ml. (0.001 mole) of 85% hydrazine hydrate was added. After 12 hr. at room temperature the system was diluted to 200 ml. volume and reheated to dissolve the white precipitate and was then filtered to remove mercury. Addition of gaseous carbon dioxide to the filtrate precipitated 3.35 g. of mercurial mixture melting below 80°. The aqueous phase was extracted with chloroform; this residue from evaporation of the extract was combined with the solid product and dissolved in 25 ml. of methanol. This solution was cooled to 0°, then treated with 1 ml. of concentrated aqueous hydriodic acid for exactly 1 min., and then was diluted with 60 ml. of 2% aqueous sodium hydroxide. This suspension was boiled until the odor of terpineol was no longer apparent. After replacement of the water which had distilled over, the remainder was partially cooled and filtered. The cold filtrate was acidified with hydriodic acid and extracted with five 10-ml. portions of chloroform. The extract was evaporated and the residue crystallized from 30 ml. of hot benzene; 0.6 g., m.p. 158–159°. This 12% yield was thrice crystallized from benzene (42 ml. per g., 85% recovery), m.p. 161.8–162.2°. When the compound was heated for 1 hr. in pyridine at 60–70°, dilution with ether precipitated it unchanged.

Anal. Calcd. for $C_{10}H_{19}O_2HgI$: C, 24.1; H, 3.84. Found: C, 24.4; H, 3.95.

Reduction of 0.3 g. (0.0062 mole) of this β-mercurial with 2 g. (0.0017 atom) of 2% sodium amalgam in 2.5 ml. of water during 9 hr. yielded by exhaustive ether extraction 0.12 g. (50%) of *trans*-terpin, m.p. 155–156°, depressed by admixture with the β-mercurial to 135°.

Dielectric constant determinations. An apparatus described previously[9] was used for these studies. The solvent, dioxane, had a dielectric constant of 2.2210 and a specific volume of 0.9681 at 20°. Extrapolation of the $d\epsilon/d\omega(\alpha)$ and $dV/d\omega(\beta)$ plot to $\omega = 0$ gave intercepts in close agreement with ϵ and V for the pure solvent. Combined electronic and atomic polarizations as well as densities were determined as described previously,[10] while molecular refraction (R_D) was calculated additively. Significant data are recorded in Table I.

β-2-Acetoxymercuri-trans-terpin. A mixture of 2.49 g. (0.005 mole) of β-iodomercuri-*trans*-terpin and 11.5 g. (0.05 mole) of silver oxide in 70 ml. of acetone plus 5 ml. of water was shaken for 12 hr. and then filtered. The filtrate was vacuum-evaporated leaving 1.87 g. of non-crystalline residue which was dissolved in 5.2 ml. (0.05 mole) of acetic anhydride and filtered at once. Within 10 min. crystals began to appear. After 2 hr. filtration yielded 1.53 g., m.p. 129.5–130° (65%) which was crystallized from 7 ml. of toluene, 1.19 g., m.p. 130°. Treatment with aqueous sodium chloride converted this compound to 2-chloromercuri-*trans*-terpin, m.p. 120.5–121°, authenticated by mixture melting point.

Anal. Calcd. for $C_{12}H_{22}O_4Hg$: C, 33.4; H, 5.15. Found: C, 33.8; H, 5.26.

β-2-Chloromercuri-trans-terpin. A solution of 0.6 g. of the acetoxymercuri analog in 6 ml. of chloroform was shaken with saturated aqueous sodium chloride. The crystalline substance (0.48 g.) which precipitated from the non-aqueous layer melted at 120–120.6° and was unchanged in melting point by crystallization (2 ml. per g.) from hot chloroform.

Anal. Calcd. for $C_{10}H_{19}O_2HgCl$: C, 29.5; H, 4.70. Found: C, 29.3; H, 4.51.

Bis-β-2-mercuri-trans-terpin sulfide. A solution of 2.49 g. (0.005 mole) of β-2-iodomercuri-*trans*-terpin in 65 ml. of acetone was treated with 0.4 ml. (0.0066 mole) of acetic acid and then 1.20 g. (0.005 mole) of sodium sulfide nonahydrate in 6 ml. of water was added. After a day the solvent was evaporated leaving a filterable residue, 1.72 g. (88%), m.p. 190°. Solution in dimethylsulfoxide (10 ml. per g.) followed by addition of one-half volume of water raised this melting point to 194–194.5°. After 3 hr. of reflux in methanol 55% was recovered unchanged. Treatment with lead acetate trihydrate in acetic acid precipitated lead acetate at once yielding a complex product, m.p. 134–138°.

Anal. Calcd. for $C_{20}H_{38}Hg_2O_4S$: C, 30.9; H, 4.97; S, 4.13. Found: C, 30.6; H, 4.95; S, 4.30.

By contrast to the preparation of this sulfide the same reaction conditions applied to α-iodomercuri-*trans*-terpin yielded only terpineol.

Acknowledgment. The authors are grateful to Mr. Paul Chu for aid in the experimental work.

TORONTO, CANADA

[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF THE STATE UNIVERSITY OF IOWA]

Model Compounds for Comparison with Lignin.* I. Preparation and Properties of 8-Methoxy-6-methylflavanone and 2′-Hydroxy-3′-methoxy-5′-methylchalcone

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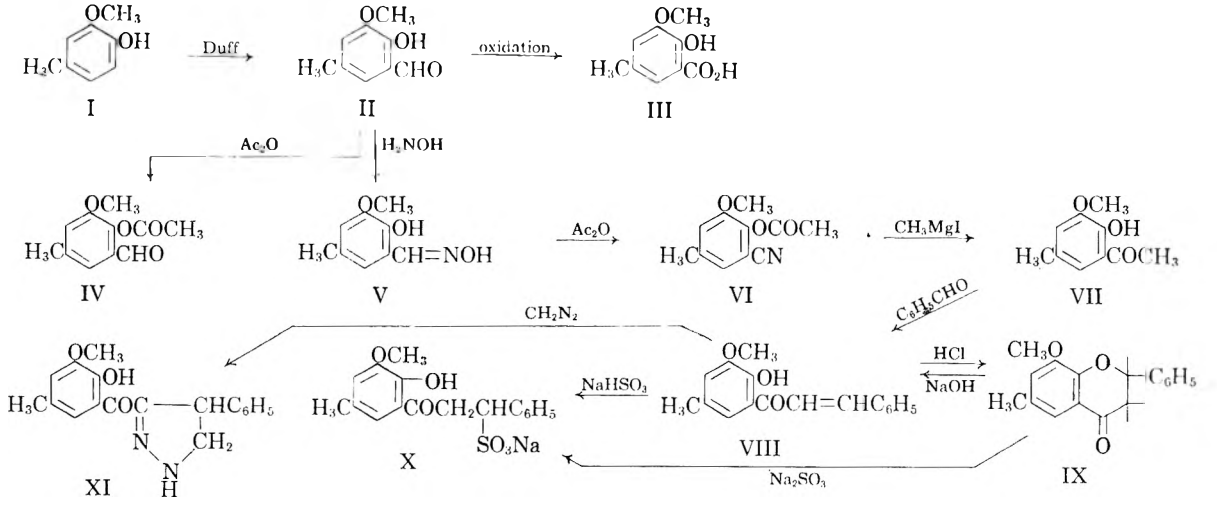
The syntheses of 8-methoxy-6-methylflavanone and 2′-hydroxy-3′-methoxy-5′-methylchalcone are described. These compounds differed from those reported for soft wood lignin with respect to ultraviolet and infrared spectra and also in their chemical properties.

Brauns[2] and Harris[3] have reviewed the various structures proposed for spruce lignin. One of the polymeric structures incorporated a substituted chalcone unit in equilibrium with the flavanone unit.[4,5] For purposes of comparison, two model compounds, 2′-hydroxy-3′-methoxy-5′-methylchalcone (VIII) and 8-methoxy-6-methylflavanone (IX) have been prepared and their properties compared with some of the reactions reported for lignin. Chart I summarizes the reactions and inter-



* A contribution in honor of Lyndon F. Small and a tribute to his services as former Editor of this Journal, as Chairman and member of the Executive Committee of the Division of Organic Chemistry and for his outstanding investigations in organic chemistry.

(1) From the Ph.D. Thesis submitted to the Graduate College of the State University of Iowa.

(2) F. E. Brauns, *The Chemistry of Lignin*, Academic Press, Inc., New York (1952).

(3) E. E. Harris, *Progress in the Chemistry of Lignin*, Report No. 2020, Forest Products Laboratory, Madison, Wis. (1955).

(4) (a) A. Russell, *J. Am. Chem. Soc.*, **70**, 1060 (1948); (b) A. Russell, J. H. Baity, and H. E. Smith, *J. Am. Chem. Soc.*, **71**, 956 (1949); (c) H. E. Smith, C. R. Russell, L. E. Schniepp, *J. Am. Chem. Soc.*, **73**, 793 (1951).

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mediates involved in the syntheses of these two compounds. Each step paralleled reactions previously described in the literature and the procedures are given in the experimental part.

Comparison of the properties of these two model compounds with those reported in the literature[2,3] for soft wood lignin preparations showed marked differences in the following respects:

(*1*) The colorless flavanone (IX) was insoluble in dilute aqueous alkali but dissolved in 24% sodium hydroxide solution in 50% ethanol or dioxane to form a beautiful red solution of the sodium salt of the chalcone (VIII). Careful acidification precipitated the orange-red crystals of the chalcone. Alcoholic hydrochloric acid readily converted the chalcone to the flavanone. Lignin preparations dissolve in alkali to give a yellow to brown color and give no indication of behavior paralleling the above.

(*2*) The ultraviolet absorption spectra of lignin preparations[6] show a rather broad maximum at about 276 mμ to 280 mμ which is not shown by either the chalcone or flavanone. Maxima for the chalcone were found at 325 mμ ($\epsilon = 28 \times 10^3$); 323 mμ ($\epsilon = 17 \times 10^3$) and about 207 mμ ($\epsilon = 33 \times 10^3$). The flavanone had maxima at 218 mμ ($\epsilon = 27 \times 10^3$); 268 mμ ($\epsilon = 18 \times 10^3$) and 242 mμ ($\epsilon = 7 \times 10^3$). The curves for VIII and IX were quite different from those for lignin preparations.

(*3*) The chemistry of the reaction of lignin with bisulfite solutions has been extensively investigated.[2,3] The reaction appears to be a sulfonation accompanied by hydrolysis. The chalcone (VIII) reacted with aqueous alcoholic sodium bisulfite to form the sodium sulfonate, X, but the flavanone (IX) failed to react under the same conditions. With alkaline aqueous-alcoholic sodium sulfite the ring of IX was opened and the same sulfonate (X) was formed.

(*4*) Lignin preparations have been methylated by methyl sulfate and aqueous alkalies. Brauns[7] used a reaction mixture kept slightly alkaline and Russell[4a] used 10% alkali. The chalcone (VIII) did undergo methylation with an excess of methyl sulfate and 17% aqueous sodium hydroxide solution at 60–70° but a pure product with the theoretical methoxyl content could not be isolated. Treatment of the flavanone (IX) with the same methylation procedure resulted in a 93% recovery of the flavanone. This was somewhat surprising in view of the opening of the flavanone ring by alcoholic alkali mentioned above. However, the flavanone was insoluble in aqueous alkali and the reaction between methyl sulfate and alkali formed methanol and sodium methyl sulfate which reduced the alkalinity of the reaction mixture.

(*5*) Spencer and Wright[8] found that diazomethane methylated the phenolic group in lignin and also formed a nitrogen containing methoxylated lignin which had about 1% nitrogen. This may be due to the addition of the diazomethane to a conjugated system. The flavanone (IX) did not react with diazomethane but the chalcone (VIII) reacted rapidly (within 4 min.) to give high yields of a substituted pyrazoline XI. This product gave a greenish tan color with ferric chloride solution and analysis showed that the phenolic hydroxyl of VIII was not methylated.

Because of its high melting point (207–208°), and yellow color, it seems probable that the diazomethane reaction product has the conjugated Δ^2-pyrazoline structure by analogy to the structure assigned by Smith and Pings[9] for the high-melting product obtained from chalcone and diazomethane.

Evidently the diazomethane added rapidly to the conjugated system of the chalcone to precipitate the pyrazoline. The methylation of the phenolic group is hindered by the strong hydrogen bonding of the *ortho*-hydroxyl group with the carbonyl group. Evidence of this chelation was found in the infrared absorption spectrum of the chalcone which does not show a typical hydroxyl peak. The chalcone has a carbonyl band at 1638 cm.$^{-1}$ indicating hydrogen bonding. The flavanone (IX) has a strong carbonyl band at 1691 cm.$^{-1}$ The infrared bands for the two model compounds differ from those reported for lignin.[10]

EXPERIMENTAL

2-Hydroxy-3-methoxy-5-methylbenzaldehyde (II). This aldehyde was made from *o*-creosol (I) by the Duff[11] reaction using the general method of Manske and Ledingham[12] with the modification suggested by Liggett and Diehl.[13] Yields of 40 to 50% were obtained of light yellow needles melting at 76° (Manske and Ledingham[12] reported 77°). A small sample of this aldehyde was oxidized to the acid (III) using alkali and a suspension of silver oxide. The acid melted at 190° which agreed with that previously reported by Wacek and Nittner.[14]

When 2.5 g. of the aldehyde (II) was refluxed with 15 ml. of acetic anhydride for 45 min., then cooled and poured into water, the acetyl derivative (IV) separated. Recrystallization from 50% ethanol-water gave 2.3 g. (74%) of colorless needles melting at 115–117°.

Anal. Calcd. for $C_{11}H_{12}O_4$: C, 63.48; H, 5.81. Found: C, 63.38; H, 5.78.

2-Hydroxy-3-methoxy-5-methylbenzaldoxime (V). A solution of 125 g. of the aldehyde (II) and 65 g. of hydroxyl-

(6) Ref. 3, p. 14.

(7) F. E. Brauns, *J. Am. Chem. Soc.*, 61, 2120 (1939).

(8) E. Y. Spencer and G. F Wright, *J. Am. Chem. Soc.*, 63, 2017 (1941).

(9) L. I. Smith and W. B. Pings, *J. Org. Chem.*, 2, 23 (1937).

(10) Ref. 3, pp. 14, 15.

(11) J. C. Duff, *J. Chem. Soc.*, 1941, 547.

(12) R. H. F. Manske and A. E. Ledingham, *Can. J. Res.*, 22B, 115 (1944).

(13) L. M. Liggett and H. Diehl, *Proc. Iowa Acad. Sci.*, 52, 191 (1945).

(14) A. v. Wacek and E. Nittner, *Cell. Chem.*, 18, 29 (1940).

amine hydrochloride in 500 ml. of pyridine and 500 ml. of absolute ethanol was refluxed for 12 hr. The solvents were removed under reduced pressure in a stream of nitrogen gas. Addition of 300 ml. of water to the residual mass caused the oxime to separate as dark greenish crystals. They were collected on a filter, washed well with ice water, and recrystallized from 25% ethanol. Pale yellow needles of the oxime weighing 117 g. (87%) and melting at 162–164° were obtained (Manske and Ledingham[12] reported m.p. 165°).

Anal. Calcd. for $C_9H_{11}NO_3$: C, 59.70; H, 6.07; N, 7.73. Found: C, 59.56; H, 6.05; N, 7.98.

2-Acetoxy-3-methoxy-5-methylbenzonitrile (VI). A mixture of 117 g. of the oxime (V), 2 g. of anhydrous sodium acetate, and 500 ml. of acetic anhydride was refluxed 3 hr. The mixture was decomposed with 500 g. of ice and 2 l. of water and after standing several hours the oil solidified. The solid was collected on a filter, dried, and recrystallized from ligroin (60–100°). A yield of 117 g. (88%) of white prisms of the nitrile (VI) melting at 76–78° was obtained.

Anal. Calcd. for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.35; H, 5.40; N, 6.90.

2-Hydroxy-3-methoxy-5-methylacetophenone (VII). A solution of 50.0 g. (0.24 mole) of the above nitrile in 750 ml. of benzene was distilled until 600 ml. of benzene had been collected. To the remaining anhydrous solution of the nitrile was added 1.5 l. of absolute ether and then with vigorous stirring was added 800 ml. of ether containing 202 g. (1.22 moles) of methyl magnesium iodide. After refluxing with stirring for 12 hr. 20 ml. of water was cautiously added dropwise and then a solution of 70 g. of ammonium chloride in 400 ml. of water was added. Emulsions which formed in some runs were broken by adding 100 to 600 ml. of ethanol. Concentrated hydrochloric acid was added slowly with vigorous stirring until the mixture was acid to litmus. The ether was removed from a water bath and the aqueous solution concentrated to about 400 ml. and cooled. The tan precipitate was collected on a filter, washed with a little ice water, and dried. The crude product (42 g. 95%) was recrystallized from 80% ethanol to give 32 g. (72%) of pale greenish prisms melting at 82–84°.

Anal. Calcd. for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 66.31; H, 6.65.

In only 0.3 mole of the Grignard reagent to 0.2 mole of the nitrile was used in the above reaction, the acetoxy group was hydrolyzed but the nitrile group was not attacked. The product melted sharply at 123° and analyzed for 2-hydroxy-3-methoxy-5-methylbenzonitrile.

Anal. Calcd. for $C_9H_9NO_2$: C, 66.24; H, 5.56; N, 8.59. Found: C, 65.98; H, 5.51; N, 8.65.

2'-Hydroxy-3'-methoxy-5'-methylchalcone (VIII). While nitrogen gas was bubbled through a solution of 120 g. of sodium hydroxide in one liter of 50% ethanol-water, there was added with stirring, 60 g. (0.33 mole) of 2-hydroxy-3-methoxy-5-methylacetophenone followed by 60 g. (0.56 mole) of freshly distilled benzaldehyde. The solution turned red and set to a thick slurry in about 20 min. It was allowed to stand 12 hr., and 250 ml. of water followed by 250 ml. of concentrated hydrochloric acid were added slowly with stirring. The still basic solution was cooled in an ice bath and saturated with carbon dioxide. Red crystals of the chalcone separated first and were quickly filtered, and washed with water. The chalcone was recrystallized from 95% ethanol. The yield was 10 g. (11%) of red crystals melting at 95–96°.

Anal. Calcd. for $C_{17}H_{16}O_3$: C, 76.10; H, 6.01. Found: C, 76.08; H, 5.97.

The acetyl derivative was prepared by refluxing 1 g. of the chalcone with 15 ml. of acetic anhydride for 3 hr. After pouring into 100 ml. of water, the solid was collected and recrystallized from 95% ethanol to give pale yellow needles melting at 85–86°. This derivative gave no color with ferric chloride solution.

Anal. Calcd. for $C_{19}H_{18}O_4$: C, 73.53; H, 5.85; Acetyl, 13.85. Found: C, 73.34; H, 5.81; Acetyl, 13.53%.

When the filtrate from the chalcone preparation was cooled and allowed to stand, crystals of the flavanone separated. To recover as much flavanone as possible, the above filtrate was mixed with 250 ml. of concentrated hydrochloric acid, refluxed for 3 hrs., and then cooled. The crude flavanone was collected on a filter and recrystallized from ethanol. There was obtained 33 g. of flavanone (IX) melting at 142–143° identical with that obtained below.

8-Methoxy-6-methylflavanone (IX). A solution of 3.5 g. of the chalcone (VIII) in 150 ml. of 95% ethanol and 37 ml. of concentrated hydrochloric acid was refluxed 5.5 hr. The volume was reduced to about 80 ml. by distillation, 50 ml. of water added, and the solution chilled in an ice bath. The flavanone which separated was recrystallized from ethanol and then from petroleum ether. Colorless needles, melting at 142–143° and amounting to 2.5 g. (72%) were obtained. This product gave no color with ferric chloride solution.

Anal. Calcd. for $C_{17}H_{16}O_3$: C, 76.10; H, 6.01. Found: C, 76.11; H, 5.91.

4-Phenyl-3-(2-hydroxy-3-methoxy-5-methylbenzoyl)Δ^2*-pyrazoline* (XI). A 100 ml. ether solution containing 2.8 g. (0.066 mole) of diazomethane was added to 2.7 g. (0.01 mole) of the chalcone in 100 ml. of ether. A light yellow precipitate formed in 4 min. but the mixture was allowed to stand overnight. The precipitate was collected on a filter and recrystallized from 95% ethanol to give 1.5 g. (48%) of golden needles melting with decomposition at 207–208°. In 95% ethanol this pyrazoline gave the same greenish-tan color with a drop of 10% ferric chloride as was observed for the chalcone.

Anal. Calcd. for $C_{18}H_{18}N_2O_3$: C, 69.66; H, 5.85; N, 9.03. Found: C, 69.34; H, 6.00; N, 8.92.

Reaction of the chalcone (VIII) *with sodium bisulfite.* A mixture of 20 ml. of saturated sodium bisulfite solution, 30 ml. of 95% ethanol, 10 ml. of water, and 1 g. of the chalcone was heated on a steam bath until the volume was reduced to 25 ml. When cooled, the solid was collected on a filter and recrystallized from 10 ml. of water. Light yellow needles were obtained which melted at 65° after air drying. When dried in a vacuum pistol they melted at 121° and the weight (2 g.) indicate a hydrate. A sample was dried at 100° over phosphorus pentoxide for 24 hr. to obtain an anhydrous sample of the salt which decomposed over a range of 166–176°. It gave a blue green color with ferric chloride solution.

Anal. Calcd. for $C_{17}H_{17}O_6SNa$: C, 54.83; H, 4.60; Na, 6.18. Found: C, 53.03; H, 4.66; Na, 6.02.

The carbon analyses on this salt were low due to retention by the copper oxide of sodium carbonate along with sodium sulfate. To check the composition, this sodium sulfonate (X) was converted back to the chalcone (VIII) by refluxing a sample with 24% sodium hydroxide solution which gave the typical red solution of the salt of the chalcone. Acidification with acetic acid precipitated the chalcone which melted at 94–95° after recrystallization from 95% ethanol.

The flavanone (IX) was recovered unchanged when subjected to the reaction with sodium bisulfite using the same conditions as above. However, when 1 g. of the flavanone, 30 ml. of water, 20 ml. of saturated sodium sulfite solution, and 30 ml. of 95% ethanol were boiled and concentrated on a steam bath light yellow needles of the hydrate of the sodium sulfonate salt were obtained identical with those obtained above.

IOWA CITY, IOWA

[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

Studies of Imidazoles. VII. Substituted 1-Phenethylimidazoles and Related Compounds*[1]

W. N. CANNON, C. E. POWELL, AND R. G. JONES

Received June 27, 1957

A series of 1-aralkylimidazoles, 2-mercaptoimidazoles, and 2-substituted mercaptoimidazoles is described. 1-Homoveratryl-2-methylmercaptoimidazole was found to possess marked local anesthetic and appreciable bronchodilator activities. The 1-phenethylimidazoles and also 1-benzyl and 1-(3-phenylpropyl)imidazole caused effects on blood pressure and heart rate of experimental animals of about the same kind and magnitude as ephedrine.

1-Benzylimidazole,[2] when tested in anesthetized cats and dogs, was found to have a pharmacological activity closely resembling that of ephedrine. 1-Phenethylimidazole had even greater pressor activity. These observations led us to prepare a series of substituted 1-phenethylimidazoles and related compounds to test as possible broncholdilator agents.

The preparation of the compounds described in the accompanying tables involved methods previously reported.[3] In general the reaction sequence was as follows: An appropriate amine was heated with chloroacetal to form an *N*-substituted aminoacetal (Table I). The aminoacetal was allowed to react with thiocyanic acid to yield a 1-substituted-2-mercaptoimidazole (Table II). This was either desulfurized with Raney nickel to produce a 1-substituted imidazole (Table III) or was allowed to react with methyl iodide to yield a 1-substituted-2-methylmercaptoimidazole (Table IV).

The compounds of Table III generally had appreciable bronchodilator activities, but at the same time they almost all caused marked elevations of the blood pressure of experimental animals. For this reason they were not intensively tested. Some of the 2-methylmercaptoimidazoles of Table IV, and particularly 1-homoveratryl-2-methylmercaptoimidazole, had good bronchodilator activity and little or no effect on blood pressure or heart rate.

1-Homoveratryl-2-methylmercaptoimidazole underwent preliminary testing in the clinic, but the results were disappointing. During the clinical observation the compound was discovered to be a potent local anesthetic, and its apparent bronchodilator activity could probably be ascribed to its local anesthetic effects.

Several additional 1-homoveratryl-2-alkyl and aralkylmercaptoimidazoles were prepared and are presented in Table V. They were pharmacologically less interesting than the methylmercapto compound.

At first impression it may be thought that the effects of the 1-β-phenylethylimidazoles (Table III) on blood pressure and heart rate are due to the β-phenethylamine fragment present in the structures; or that perhaps the imidazole ring is degraded in the animal body with formation of an

* This paper is a contribution in honor of Lyndon F. Small, former Editor of the Journal.

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(2) R. G. Jones, *J. Am. Chem. Soc.*, **71**, 383 (1949).

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TABLE I

N-SUBSTITUTED AMINOACETALS

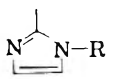
$RNHCH_2CH(OC_2H_5)_2$

R	B.P., °C./mm.	n_D^{25}	Yield, %	Formula	Analyses: Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
$C_5H_{11}CH(CH_3)$[a]	117–121/10	1.4289	64.3	$C_{13}H_{29}NO_2$	67.48	67.05	12.63	12.03	6.05	6.34
$C_5H_{11}CH(CH_3)$[b]	125–129/10	1.4283	53	$C_{13}H_{29}NO_2$	[b]					
$C_6H_5CH_2CH(CH_3)$	154–159/8	1.4839	68.3	$C_{15}H_{25}NO_2$	71.67	71.40	10.03	9.80	5.57	5.75
p-$CH_3OC_6H_4CH_2CH_2$	170/4	1.4923	77	$C_{15}H_{25}NO_3$	67.38	67.11	9.43	9.41	5.24	5.25
3,4-$(CH_3O)_2C_6H_3CH_2CH_2$	190–191/3	1.5015	62	$C_{16}H_{27}NO_4$	64.62	64.37	9.15	9.15	4.71	4.49
o-$ClC_6H_4CH_2CH_2$	130–135/1	1.5020	53	$C_{14}H_{22}ClNO_2$	61.87	61.59	8.15	8.02	5.15	5.17
p-$ClC_6H_4CH_2CH_2$	140–145/1.5	1.4983	61	$C_{14}H_{22}ClNO_2$	61.87	61.60	8.15	8.20	5.15	5.13
2,4-$(Cl)_2C_6H_3CH_2CH_2$	160–165/2	1.5131	46	$C_{14}H_{21}Cl_2NO_2$	54.91	54.97	6.91	7.17	4.57	4.42
3,4-$(Cl)_2C_6H_3CH_2CH_2$	151–152/1	1.5203	41.2	$C_{14}H_{21}Cl_2NO_2$	54.91	54.74	6.91	6.41	4.57	4.88
$C_6H_5CH_2CH_2CH_2$	163/4	1.4849	73.5	$C_{15}H_{25}NO_2$	71.67	71.41	10.03	10.10	5.57	5.61
$(CH_3)_2CHCH_2CH_2$	100–102/10	1.4250	75	$C_{11}H_{25}NO_2$	64.98	65.30	12.39	12.17	6.89	7.05
$CH_3(CH_2)_6CH_2$	97/0.25	1.4311	73	$C_{14}H_{31}NO_2$	68.52	69.05	12.73	12.58	5.71	5.67

[a] 4-Methyl-2-hexyl. [b] 2-Heptyl, see ref. 3.

TABLE II

1-SUBSTITUTED 2-MERCAPTOIMIDAZOLES

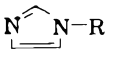


R	M.P., °C.[a]	Yield, %	Formula	Analyses: Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
$C_5H_{11}CH(CH_3)$[b]	82	53	$C_{10}H_{18}N_2S$	60.58	60.45	9.15	9.20	14.13	14.03
$C_5H_{11}CH(CH_3)$[c]	75–76	45	$C_{10}H_{18}N_2S$	[c]					
$C_6H_5CH_2CH(CH_3)$	126–126.5	83.5	$C_{12}H_{14}N_2S$	66.02	66.39	6.46	6.61	12.83	12.91
p-$CH_3OC_6H_4CH_2CH_2$	152	87.2	$C_{12}H_{14}N_2OS$	61.51	61.80	6.02	5.78	11.96	11.99
3,4-$(CH_3O)_2C_6H_3CH_2CH_2$	171	66.4	$C_{13}H_{16}N_2O_2S$	59.06	59.29	6.09	6.08	10.60	10.26
o-$ClC_6H_4CH_2CH_2$	140.5	83	$C_{11}H_{11}ClN_2S$	55.34	55.35	4.65	4.63	11.74	11.50
p-$ClC_6H_4CH_2CH_2$	202–203	79	$C_{11}H_{11}ClN_2S$	55.34	55.60	4.65	4.64	11.74	11.77
2,4-$(Cl)_2C_6H_3CH_2CH_2$	179.5–180	71.5	$C_{11}H_{10}Cl_2N_2S$	48.36	48.35	3.69	3.65	10.26	10.10
3,4-$(Cl)_2C_6H_3CH_2CH_2$	153–154	62	$C_{11}H_{10}Cl_2N_2S$	48.36	48.29	3.69	3.79	10.26	10.24
$C_6H_5CH_2CH_2CH_2$	113–114	81.5	$C_{12}H_{14}N_2S$	66.01	65.74	6.46	6.47	12.83	12.65
$(CH_3)_2CHCH_2CH_2$	95–96	78	$C_8H_{14}N_2S$	56.42	56.04	8.29	8.31	16.45	16.29
$CH_3(CH_2)_6CH_2$	57–57.5	87.5	$C_{11}H_{20}N_2S$	62.21	62.31	9.49	9.57	13.19	12.96

[a] Melting points were taken on a Fisher-Johns apparatus and are uncorrected. [b] 4-Methyl-2-hexyl. [c] 2-Heptyl, see ref. 3.

TABLE III

1-SUBSTITUTED IMIDAZOLES



R	B.P., °C./mm.	n_D^{25}	Yield, %	Formula	Analyses: Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
$C_5H_{11}CH(CH_3)$[a]	91–92/1	1.4731	65	$C_{10}H_{18}N_2$	72.24	72.16	10.91	11.18	16.85	16.65
$C_5H_{11}CH(CH_3)$[b,c]	118–119/3	1.4705	66	$C_{10}H_{18}N_2$	[d]					
$C_6H_5CH_2CH(CH_3)$	133/1	1.5535	65.5	$C_{12}H_{14}N_2$	77.37	77.28	7.58	7.69	15.04	15.12
p-$CH_3OC_6H_4CH_2CH_2$	158/0.5	1.5261	54.5	$C_{12}H_{14}N_2O$	71.26	71.00	6.98	7.08	13.85	13.61
3,4-$(CH_3O)_2C_6H_3CH_2CH_2$	195/1[e]	1.5659	60	$C_{13}H_{16}N_2O_2$	67.22	67.08	6.94	7.05	12.06	11.94
o-$ClC_6H_4CH_2CH_2$	139–140/1	1.5689	58.5	$C_{11}H_{11}ClN_2$	63.92	63.64	5.36	5.22	13.55	13.65
p-$ClC_6H_4CH_2CH_2$	159–161/1	[f]	73.7	$C_{11}H_{11}ClN_2$	63.92	63.95	5.36	5.51	13.55	13.49
2,4-$(Cl)_2C_6H_3CH_2CH_2$	152/0.25	1.5798	63	$C_{11}H_{10}Cl_2N_2$	54.79	54.87	4.18	4.34	11.62	11.70
3,4-$(Cl)_2C_6H_3CH_2CH_2$	221/1.25	1.5800	70	$C_{11}H_{10}Cl_2N_2$	54.79	54.75	4.18	4.03	11.62	11.82
$C_6H_5CH_2CH_2CH_2$	141/1	1.5547	68	$C_{12}H_{14}N_2$	77.37	77.23	7.58	7.52	15.04	15.21
$(CH_3)_2CHCH_2CH_2$	108/8	1.4742	70.3	$C_8H_{14}N_2$	69.52	69.95	10.21	10.27	20.27	20.12
$CH_3(CH_2)_6CH_2$	115–117/0.25	1.4781	35	$C_{11}H_{20}N_2$	73.28	73.52	11.18	11.19	15.54	15.60

[a] 4-Methyl-2-hexyl. [b] 2-Heptyl. [c] In this one case the mercaptoimidazole was desulfurized by treatment with nitric acid–sodium nitrite. [d] Analyzed as the hydrochloride salt. Calcd. for $C_{10}H_{19}ClN_2$: N, 13.82; Found, N, 13.51. [e] The liquid crystallized; m.p. 71–72°. [f] The liquid crystallized; m.p. 72–72.5°.

active β-phenethylamine. That such is not necessarily the case was indicated by the fact that 1-benzylimidazole and 1-(3-phenylpropyl)imidazole (Table III) were highly active in raising the blood pressure and increasing the heart rate of experimental animals. Thus, the pharmacological activities appear to be associated with the 1-substituted imidazole structure, and these compounds may be considered as a new class of potent pressor substances.

EXPERIMENTAL

Substituted phenylethylamines. The majority of the amines used in this investigation were commercially available. Those that appear not to have been described previously were prepared in the usual manner through the substituted benzyl cyanides with subsequent reduction to the amine.

2,4-Dichlorobenzyl cyanide. A mixture of 162 g. (3.3 moles) of sodium cyanide, 586.5 g. (3.0 moles) of 2,4-dichlorobenzyl chloride, 500 ml. of ethanol, and 500 ml. of water was refluxed 8 hr. After removing the ethanol by distillation, the product was extracted with diethyl ether. Removal of the ether yielded a residue which on recrystallization from ethanol provided 368 g. of the nitrile as a tan solid; m.p. 59–60°. An additional 65 g. of the product was recovered from the ethanol filtrate; 78% yield.

Anal. Calcd. for $C_8H_5Cl_2N$: C, 51.64; H, 2.71; N, 7.53. Found: C, 51.81; H, 2.89; N, 7.62.

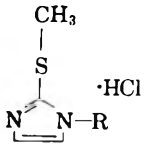
In a like manner, 3,4-dichlorobenzyl cyanide was prepared in 55% yield; m.p. 37–37.5°.

Anal. Calcd. for $C_8H_5Cl_2N$: C, 51.64; H, 2.71; N, 7.53. Found: C, 51.88; H, 2.75; N, 7.61.

β-(3,4-Dichlorophenyl)ethylamine. A solution of 186 g. (1.0 mole) of 3,4-dichlorobenzyl cyanide in 500 ml. of diethyl ether was added slowly to a stirred suspension of 38 g. (1.0 mole) of lithium aluminum hydride in 2 l. of ether at such a rate as to maintain gentle boiling. The mixture was then decomposed by the cautious addition of 25 ml. of

TABLE IV

1-SUBSTITUTED 2-METHYLMERCAPTOIMIDAZOLE HYDROCHLORIDES

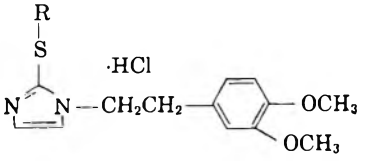


R	M.P., °C.	Yield, %	Formula	Analyses					
				Carbon, %		Hydrogen, %		Nitrogen, %	
				Calcd.	Found	Calcd.	Found	Calcd.	Found
$C_6H_{11}CH(CH_3)$[a]	152–154	49.5	$C_{11}H_{21}ClN_2S$	53.09	52.80	8.50	8.25	11.26	11.02
$C_5H_{11}CH(CH_3)$[b]	142–143	81.5	$C_{11}H_{21}ClN_2S$	53.09	53.39	8.50	8.51	11.26	11.31
$C_6H_5CH_2CH(CH_3)$	164–164.5	86	$C_{13}H_{17}ClN_2S$	58.09	58.39	6.37	6.18	10.42	10.43
p-$CH_3OC_6H_4CH_2CH_2$	158–159	58.5	$C_{13}H_{17}ClN_2OS$	54.82	54.79	6.02	6.03	9.83	9.90
3,4-$(CH_3O)_2C_6H_3CH_2CH_2$	149–150	58	$C_{14}H_{19}ClN_2O_2S$	53.41	53.53	6.08	6.15	8.89	9.12
o-$ClC_6H_4CH_2CH_2$	128–129	64	$C_{12}H_{14}Cl_2N_2S$	49.83	49.91	4.88	5.12	9.68	9.83
p-$ClC_6H_4CH_2CH_2$	171–172	39.5	$C_{12}H_{14}Cl_2N_2S$	49.83	49.93	4.88	4.65	9.68	9.86
2,4-$(Cl)_2C_6H_3CH_2CH_2$	188	56	$C_{12}H_{13}Cl_3N_2S$	44.52	44.70	4.05	4.26	8.65	8.93
3,4-$(Cl)_2C_6H_3CH_2CH_2$	173.5	52	$C_{12}H_{13}Cl_3N_2S$	44.52	44.73	4.05	3.99	8.65	8.68
$C_6H_5CH_2CH_2CH_2$	95–96	76	$C_{13}H_{17}ClN_2S$	58.09	58.35	6.37	6.29	10.42	10.49
$(CH_3)_2CHCH_2CH_2$	130–131	78.5	$C_9H_{17}ClN_2S$	48.96	48.94	7.76	7.51	12.69	12.48
$CH_3(CH_2)_6CH_2$	117–118	69	$C_{12}H_{23}ClN_2S$	54.83	55.08	8.82	8.24	10.66	10.53
C_6H_{11}[c]	166–167	76	$C_{10}H_{17}ClN_2S$	51.59	51.74	7.36	7.14	12.03	12.20
$C_6H_5CH_2$	169–170	82.3	$C_{11}H_{13}ClN_2S$	54.87	55.33	5.44	5.59	11.63	11.71

[a] 4-Methyl-2-hexyl. [b] 2-Heptyl. [c] Cyclohexyl.

TABLE V

1-[β-(3,4-DIMETHOXYPHENYL)ETHYL]-2-SUBSTITUTED MERCAPTOIMIDAZOLE HYDROCHLORIDES



R	M.P., °C.	Yield, %	Formula	Analyses					
				Carbon, %		Hydrogen, %		Nitrogen, %	
				Calcd.	Found	Calcd.	Found	Calcd.	Found
$CH_3CH_2CH_2$	117–118	70	$C_{16}H_{23}ClN_2O_2S$	56.04	56.17	6.76	6.81	8.17	8.13
$CH_3(CH_2)_4CH_2$	108–109	72	$C_{19}H_{29}ClN_2O_2S$	59.27	59.29	7.59	7.32	7.27	7.38
$CH_3CH_2CO_2CH_2CH_2$	107–108	64	$C_{18}H_{25}ClN_2O_4S$	53.92	53.54	6.28	6.40	6.98	7.08
$C_6H_5CH_2$	129–130	82	$C_{20}H_{23}ClN_2O_2S$	61.44	61.40	5.93	6.08	7.16	7.29
$C_6H_5CHCH_2$ | OH	151–152	74	$C_{21}H_{25}ClN_2O_3S$	59.91	59.45	5.98	6.20	6.65	6.41

ethanol, 40 ml. of water, 30 ml. of 20% aqueous sodium hydroxide, and 140 ml. of water. The granular inorganic salts were removed by filtration and washed with more ether. The combined ether solution was dried over anhydrous magnesium sulfate and the ether evaporated. Upon distillation, a small forerun was collected up to 118° (1.5 mm.) followed by a 54% yield of the product boiling at 118–120° (1.5 mm.); n_D^{25} 1.5650. The hydrochloride salt was prepared as a white, non-hygroscopic solid by treating an ether solution of the amine with anhydrous hydrogen chloride. A sample for analysis was recrystallized three times from ethanol-ether; m.p. 169–170°.

Anal. Calcd. for $C_8H_{10}Cl_2N$: C, 42.41; H, 4.45; N, 6.18. Found: C, 42.38; H, 4.46; N, 6.39.

In a similar manner β-(*o*-chlorophenyl)ethylamine was obtained in 63% yield; b.p. 94–95° (4–5 mm.); n_D^{25} 1.5483. The hydrochloride salt melted at 139–140°.

Anal. Calcd. for $C_8H_{11}Cl_2N$: C, 50.02; H, 5.77; N, 7.29. Found: C, 50.41; H, 5.65; N, 7.33.

β-(2,4-Dichlorophenyl)ethylamine, b.p. 114–120° (3 mm.), n_D^{25} 1.5639, was obtained in 67% yield. The hydrochloride salt melted at 164–165°.

Anal. Calcd. for $C_8H_{10}Cl_3N$: C, 42.41; H, 4.45; N, 6.18. Found: C, 42.26; H, 4.66; N, 6.48.

N-Substituted aminoacetals. These compounds, described in Table I, were all prepared by the same general procedure. The preparation of *N*-[β-(3,4-dimethoxyphenyl)ethyl]aminoacetaldehyde diethylacetal is described below:

A mixture of 91.8 g. (0.6 mole) of chloroacetaldehyde diethylacetal and 362 g. (2.0 moles) of homoveratrylamine was heated in a wax bath at 120° for 24 hr. After cooling to room temperature, 180 ml. of 50% aqueous sodium hydroxide was added. The oily organic phase was extracted into chloroform. The chloroform extract was washed with water and dried over anhydrous potassium carbonate. After removing the drying agent the chloroform was evaporated. Distillation of the residue gave 189 g. of unreacted homoveratrylamine and 110 g. of the desired acetal, b.p. 190–195° (3–4 mm.).

1-Substituted-2-mercaptoimidazoles. These compounds, pre-

sented in Table II, were obtained by the reaction of the substituted aminoacetals with thiocyanic acid. The preparation of 1-[β-(*o*-chlorophenyl)ethyl]-2-mercaptoimidazole is illustrative of this procedure:

To a solution of 57 g. (0.135 mole) of *N*-[β-(*o*-chlorophenyl)ethyl]aminoacetaldehyde diethylacetal in 125 ml. of ethanol was added 18.2 g. (0.16 mole) of potassium thiocyanate and 75 ml. (0.15 mole) of 2*N* hydrochloric acid. The mixture was heated on the steam bath for 4 hr., during which time most of the ethanol was allowed to evaporate. The dark, oily organic layer solidified on cooling. This was filtered and washed with water. The damp filter cake was dissolved in a solution of 5.4 g. of sodium hydroxide in 300 ml. of water. This solution was heated to boiling, treated with decolorizing carbon, filtered, and acidified with concentrated hydrochloric acid. The pink colored precipitate was filtered and washed with water. The sample for analysis was recrystallized from ethanol.

1-Substituted imidazoles. These compounds, described in Table III, were, with one exception as noted in the table, prepared by the Raney nickel desulfurization of the mercaptoimidazoles. The preparation of 1-[β-(*p*-methoxyphenyl)ethyl]imidazole serves to illustrate this procedure.

The mercaptoimidazole, 11.7 g. (0.05 mole) was dissolved in 250 ml. of ethanol with gentle warming. To this solution was added an excess of ethanol-wet Raney nickel. Some frothing was noted. The resulting mixture was stirred under reflux for 5 hr. The mixture was filtered, and the filter cake washed with more ethanol. The combined filtrate and washings were concentrated *in vacuo*. The residue was dissolved in diethyl ether, and the ether solution washed with 100 ml. of 10% sodium hydroxide solution, and then with water. The alkaline wash, on acidification with concentrated hydrochloric acid, produced none of the original mercaptoimidazole. The ether solution, after drying over anhydrous magnesium sulfate, was evaporated and the residue distilled under reduced pressure. The product distilled at 158° (0.5 mm.) to give 5.5 g. of a clear, viscous liquid.

1-Substituted-2-methylmercaptoimidazole hydrochlorides. All of the compounds described in Table IV were prepared by the same general method.[4] The preparation of 1-(2-heptyl)-2-methylmercaptoimidazole hydrochloride illustrates this method.

There was added 21.3 g. (0.15 mole) of methyl iodide to a solution of 19.8 g. (0.1 mole) of 1-(2-heptyl)-2-mercaptoimidazole in 100 ml. of ethanol. The mixture became quite warm, and cooling in an ice bath was necessary. After the initial reaction had subsided, the flask was stoppered and kept overnight at room temperature. An excess of diethyl ether was added to complete the precipitation of the hydroiodide salt. This salt was removed by filtration and washed with more ether. The salt was added to a solution containing 4 g. of sodium hydroxide in 500 ml. of water. The organic phase was extracted into diethyl ether and washed twice with water. The ether solution was dried over anhydrous magnesium sulfate, and the drying agent then removed by filtering. The ethereal filtrate upon treatment with anhydrous hydrogen chloride precipitated the product as a white, crystalline solid. This was filtered and washed well with ether. The sample for analysis was recrystallized twice from a mixture of ethanol and ether.

1-[β-(3,4-Dimethoxyphenyl)ethyl]-2-substituted mercaptoimidazole hydrochlorides. These compounds, described in Table V, were prepared in a manner similar to the above, using the appropriate bromo compounds in place of methyl iodide.

Acknowledgment. The authors are grateful to W. L. Brown, G. Beckmann, H. L. Hunter, and G. M. Maciak for the microanalyses.

INDIANAPOLIS 6, IND.

(4) W. Marckwald, *Ber.*, 25, 2360 (1892).

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE UNIVERSITY OF CALIFORNIA]

Reactivity of Organocadmium Reagents toward Halides Other than Acid Chlorides. Improvement of Conditions for the Reformatsky Reaction*,[1]

JAMES CASON AND RALPH J. FESSENDEN

Received June 3, 1957

The organocadmium reagent has been found to be considerably more inert than the Grignard reagent towards coupling with alkyl halides. In boiling ether solution, there was no significant rate of reaction of the cadmium reagent with either 2-iodooctane or allyl bromide. Reaction with a tertiary chloride is vigorous, but the principal products are the alkene resulting from dehydrohalogenation of the tertiary halide and the alkane corresponding to the alkylcadmium reagent. Reaction with α-bromo esters is also rapid, but in this instance the products are the alkyl bromide corresponding to the alkylcadmium reagent and the metal enolate (cadmium reagent) of the bromo ester. The reagent obtained from α-bromo esters in this way gives the same reactions as those observed in the Reformatsky reaction with zinc. An initial impression that the cadmium reagents give better yields in reaction with hindered ketones than are obtained in parallel Reformatsky reactions later proved to be a solvent effect. With hindered ketones, Reformatsky reactions in benzene-ether solvent give significantly better yields than in the conventional benzene or benzene-toluene solvent. Better yields were also realized in β-keto ester synthesis from a nitrile, zinc and α-bromo ester (Blaise reaction) when a benzene-ether solvent was used. Thermal cracking of three of the β-hydroxy-α,β-dialkyl esters prepared during this investigation yielded β,γ-unsaturated esters containing little, if any, of the α,β-unsaturated isomers.

In the initial investigation of the organocadmium reagents by Gilman and Nelson,[2] it was reported that these reagents exhibit a very low order of reactivity towards polar multiple bonds, but are re-

* This paper is a contribution in honor of Lyndon F. Small, former Editor of the Journal.

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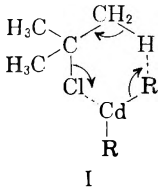
(2) H. Gilman and J. F. Nelson, *Rec. trav. chim.*, 55, 518 (1936).

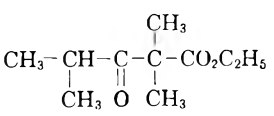
active towards acid chlorides. These characteristics have rendered the organocadmium reagents of considerable utility for synthesis of ketones, especially polyfunctional ketones containing other groups with polar multiple bonds.[3-5] Reaction of organocadmium compounds with other types of halogen derivatives has been reported relatively infrequently. Coupling occurs with α-halogen ethers,[6] including carbohydrate derivatives of this type;[7] and alkylquinolinium iodides[8] have been described as reacting in the 2-position with alkylcadmium reagents. Benzenesulfonyl chloride reacts to give diphenyl sulfone and benzenesulfinic acid,[2] while *tert*-butyl chloride has been reported[2] to yield isobutylene, although no experimental details for the latter reaction were given.

In the present work, no significant quantities of coupling products could be isolated from reactions in which an alkylcadmium reagent had been heated under reflux in ether solution with 2-iodooctane or allyl bromide. Thus, the cadmium reagent is less reactive towards alkyl halides than is the Grignard reagent. It would follow that extraction of halogen by a cadmium reagent from an acid chloride results, not from a high order of reactivity towards the halogen, but rather because the cadmium reagent is so inert towards addition to the carbonyl group that there is sufficient time for the alternative reaction with halogen.

In accord with the report of Gilman and Nelson,[2] both *tert*-butyl chloride and 3-chloro-3-propylheptane were dehydrohalogenated by a cadmium reagent. In the former instance, in which the *n*-octylcadmium reagent was used, a 76% yield of *n*-octane was isolated as the other product of the reaction. Although the dehydrohalogenation may have proceeded by an E_i mechanism, it seems more probable that there is involved a cyclic transition state (I), which is analogous to the intermediate involved in conversion of a ketone to the enolate by a Grignard reagent.

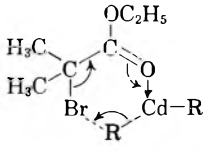


I

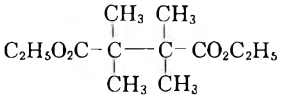


II

When the butylcadmium reagent was allowed to react with ethyl α-bromoisobutyrate there was obtained in rather good yield (72%) a product which was eventually identified as ethyl 2,2,4-trimethyl-3-oxopentanoate (II). When the dodecylcadmium reagent was substituted for the butylcadmium reagent in reaction with ethyl α-bromoisobutyrate, the product was again keto ester II. In this instance, the other product of the reaction was shown to be dodecyl bromide, isolated in 62% yield. The only reasonable fomulation for production of keto ester II appears to be condensation of the enolate of ethyl isobutyrate with ethyl α-bromoisobutyrate, followed by removal of the halogen from the bromo keto ester by the cadmium reagent. Although ethyl isobutyrate is known to give relatively poor yields in the Claisen ester condensation,[9] in the present instance the condensation may be promoted by an increase in the reactivity of the condensing carbonyl on account of electron withdrawal by alpha bromine. It has been reported[10] that similarly good yields of keto ester II may be secured by reaction of ethyl α-bromoisobutyrate with magnesium. In that instance, the enolate is no doubt obtained through reaction of magnesium with halogen in the manner of formation of a Grignard reagent. When the cadmium reagent is used to secure the enolate, it seems probable that reaction proceeds by way of a transition state such as shown in formula III. This transition state is similar to that proposed by Hauser and Walker[11] in formation of the enolate of ethyl isobutyrate by diethylaminomagnesium bromide except that in this instance hydrogen is abstracted. In the case of an α-bromo ester, co-ordination of halogen with cadmium is no doubt discouraged by the relatively positive nature of the halogen. Thus, positive halogen is removed by the alkylcadmium to give the alkyl halide. It seems probable that the metallic enolate, rather than the dissociated enolate ion, reacts with bromo ester to give bromo keto ester, for the sodium enolate reacts in an entirely different manner. When the sodium enolate of ethyl isobutyrate, prepared with sodium triphenylmethyl, is allowed to react[12] with ethyl α-bromoisobutyrate the product proves to be diethyl tetramethylsuccinate (IV).



III



IV

If the intermediate in formation of keto ester II is indeed the enolate of ethyl isobutyrate, then it

(3) J. Cason, *Chem. Revs.*, **40**, 15 (1947).
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(11) C. R. Hauser and H. G. Walker, Jr., *J. Am. Chem. Soc.*, **69**, 295 (1947).
(12) B. E. Hudson, Jr., and C. R. Hauser, *J. Am. Chem. Soc.*, **63**, 3161 (1941).

TABLE I

COMPARISON OF THE REFORMATSKY REACTION WITH CONDENSATIONS PROMOTED BY CADMIUM REAGENTS

Reagents Condensed		Average Yields (%)	
Ketone	α-Bromo ester	Cadmium reagent	Reformatsky reaction
$CH_3—C(=O)—C_6H_{13}$	$CH_3—CH(Br)—CO_2C_2H_5$	75	79
$CH_3—C(=O)—C_6H_{13}$	$CH_3—C(CH_3)(Br)—CO_2C_2H_5$	83	78
$CH_3—CH(CH_3)—CH_2—C(=O)—CH_2—CH(CH_3)—CH_3$	$CH_3—CH(Br)—CO_2C_2H_5$	47	68

would seem probable that reaction could be secured with other carbonyl components. This has proved to be the case; in fact, reaction with 2-octanone gives a rather high yield (83%) of ethyl 2,2,3-trimethyl-3-hydroxynonanoate. It has also been found that ethyl α-bromopropionate yields the enolate of ethyl propionate, which may be similarly condensed with aldehydes or ketones.

When the enolate of ethyl propionate, prepared from the cadmium reagent, was allowed to condense with diisobutyl ketone, there were obtained yields of β-hydroxy ester in the range 40–50%, whereas the Reformatsky reaction carried out in an orthodox manner[13] proved to give yields of this hydroxy ester amounting to only about 25%. This difference was shown to be a solvent effect, rather than any difference in reactivity of the reagent obtained from zinc or the cadmium reagent; in fact, when the Reformatsky reaction was carried out in a 1:1 mixture of benzene and ether, rather than in benzene, the yield was somewhat higher than had been obtained by use of the cadmium reagent. In other examples investigated, as shown in Table I, yields in the Reformatsky reaction and in the reaction utilizing the cadmium reagent were quite similar. Furthermore, as shown in Table II, yields in the Reformatsky reaction are higher when the benzene-ether solvent is used, rather than benzene, in instances where there is significant steric hindrance in the carbonyl component. These findings are in contrast with an earlier report,[14] in which benzene or a benzene-toluene mixture was recommended as the solvent of choice for the Reformatsky reaction. The yield obtained in the present work (52%) with 2-heptadecanone and ethyl α-bromopropionate in the Reformatsky reaction in benzene-ether solvent is of particular interest on account of the poor results obtained previously in this laboratory[15] and the difficulties encountered in securing a 2,3-disubstituted acid by other routes.[16]

TABLE II

SOLVENT EFFECTS IN REFORMATSKY REACTIONS

Reagent Condensed with Ethyl α-Bromopropionate	Average Yields (%)	
	Benzene solvent	Benzene-ether solvent
$CH_3—(CH_2)_5—CHO$	64	73
$CH_3—C(=O)—C_6H_{13}$	79	76
$C_3H_7—C(=O)—C_3H_7$	66	80
$CH_3—CH(CH_3)—CH_2—C(=O)—CH_2—CH(CH_3)—CH_3$	25	68
$CH_3—(CH_2)_6—CN$	44	55

Since the use of ether-benzene solvent seems to be especially favorable with less reactive carbonyl components, it seemed of interest to examine the effect of solvent on the reaction of an ester enolate with a nitrile (sometimes called the Blaise reaction[17]). In this instance also, considerably higher yields were obtained than have been previously reported[17] when benzene was used as solvent. With the ether-benzene solvent, better yields have been obtained with ethyl α-bromopropionate than had been obtained previously with *sec*-butyl α-bromopropionate.[17]

(13) J. Cason and K. L. Rinehart, Jr., *J. Org. Chem.*, **20**, 1591 (1955); K. L. Rinehart, Jr., and E. G. Perkins, *Org. Syntheses*, **37**, 37 (1957).

(14) The use of a benzene-ether mixture as solvent in the Reformatsky reaction has not been uncommon (for example, *cf.* ref. 18, pp. 17 and 18); however, no specific advantage appears to have been recognized for this mixture. A general preference for a benzene or benzene-toluene solvent has been reported by S. Natelson and S. P. Gottfried, *J. Am. Chem. Soc.*, **61**, 970 (1939).

(15) J. Cason, H. J. Wolfhagen, W. Tarpey, and R. E. Adams, *J. Org. Chem.*, **14**, 147 (1949).

(16) Reduction of 2,3-dimethyl-4-oxooctadecanoic acid proved to give very low yields [J. Cason, G. Sumrell, and R. S. Mitchell, *J. Org. Chem.*, **15**, 850 (1950)], and synthesis *via* alkylation of diethyl methylmalonate also proved unsatisfactory on account of the low yield of pure 2-bromoheptadecane obtained in the silver salt and bromine reaction (unpublished work in this laboratory by Bradford H. Walker).

(17) J. Cason, K. L. Rinehart, and S. D. Thornton, Jr., *J. Org. Chem.*, **18**, 1594 (1953); K. L. Rinehart, Jr., *Org. Syntheses*, **35**, 15 (1955).

It has been observed that the tertiary β-hydroxy esters prepared in the present work are cracked only slowly at temperatures below 200°, and dehydration is facilitated little, if any, by addition of iodine. After ethyl 2,3-dimethyl-3-hydroxynonanoate had been heated at 150° in presence of iodine for 3 hours, about one third of the hydroxy ester was recovered. The unsaturated ester obtained in this way consisted almost entirely of the β,γ-isomer (*cf.* Fig. 1), which is a less substituted alkene than

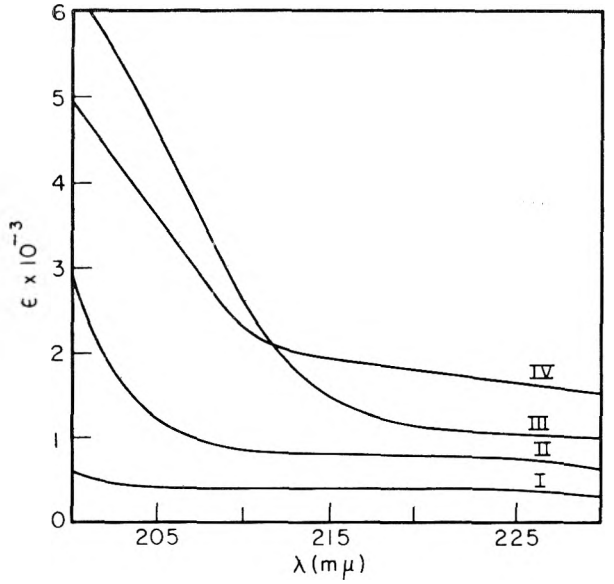

FIG. 1. ULTRAVIOLET ABSORPTION SPECTRA OF UNSATURATED ESTERS. I, reaction product from 2-heptadecanone and ethyl α-bromopropionate, Frac. (c). II, reaction product from 2-heptadecanone and ethyl α-bromopropionate, Frac. (b). III, ethyl 2,5-dimethyl-3-isobutyl-3-hexenoate. IV, ethyl 2,3-dimethyl-3-hexenoate.

the α,β-isomer, in addition to being non-conjugated. Thermal dehydration of ethyl 2,5-dimethyl-3-isobutyl-3-hydroxyhexanoate and of ethyl 2,3-dimethyl-3-hydroxyoctadecanoate yielded the β,γ-unsaturated esters containing such small amounts of the α,β-isomers that none could be detected in the ultraviolet spectra (*cf.* Fig. 1). These results are in contrast with many previous reports[18] of dehydration of β-hydroxy esters by use of various reagents. There has normally been obtained a mixture of the α,β- and β,γ-unsaturated isomers, frequently a predominance of the α,β-unsaturated isomer. The presently observed results may be unique to thermal cracking; however, there are uncontrolled or unknown variables in the present work, and the investigation has not yet been pursued further.

It is of interest that the β-hydroxy esters prepared in the present investigation uniformly showed evidence of infrared absorption at two frequencies in the carbonyl region: a doublet, a shoulder on the main band, or a broad band. It seems reasonable to ascribe this effect to chelation of the β-hydroxyl with the ester carbonyl. This effect was especially striking in the reaction product of ethyl α-bromopropionate with 2-heptadecanone, which consisted of a mixture of the β-hydroxy ester with the unsaturated ester (*cf.* Experimental). In different fractions, the strength of the doublet band in the carbonyl region was proportional to the intensity of absorption in the hydroxyl region.

(18) For a review of products obtained by dehydration of β-hydroxy esters, refer to R. L. Shriner, *Org. Reactions*, 1, 12 (1942).

EXPERIMENTAL[19]

Attempted reaction of 2-iodooctane with di-n-propylcadmium. 2-Iodooctane was prepared by heating 2-bromooctane overnight under reflux with excess of sodium iodide in acetone. Distillation of the product gave, after a considerable forerun of unsaturated material, a 64% yield of product with b.p. 90–92°/15 mm., n_D^{25} 1.4860 [literature,[20] b.p. 101°/22 mm., n_D^{20} 1.489€].

A Grignard reagent was prepared in the usual fashion from 29.5 g. (0.24 mole) of distilled *n*-propyl bromide (n_D^{25} 1.4326) and 6 g. (0.25 mole) of magnesium turnings in 125 ml. of ether. The Grignard reagent was converted to the cadmium reagent by heating under reflux with stirring for 45 min. with 29.3 g. (0.16 mole) of anhydrous cadmium chloride. To the solution of cadmium reagent, cooled to room temperature, there was added in one portion a solution of 50 g. (0.20 mole) of 2-iodooctane in 20 ml. of benzene. There was no evolution of heat or other evidence of reaction after this addition or during a subsequent period of heating for 1 hr. under reflux. Decomposition of the reaction mixture with ice and acid, followed by work-up in the usual fashion and distillation of the product at 17 mm. pressure, yielded 1.1 g. of fore-run, b.p. 80–94°, n_D^{25} 1.4800, and 37.6 g. (75%) of recovered 2-iodooctane, b.p. 94–96°, n_D^{25} 1.4852. No other products were isolated.

In similar experiments with 2-bromobutane, no coupling products were obtained.

Attempted reaction of allyl bromide with di-n-octylcadmium. There was prepared, by the procedure described for preparation of the propylcadmium reagent, a cadmium reagent from 56 g. (0.29 mole) of distilled *n*-octyl bromide. To the stirred solution of cadmium reagent, at room temperature, there was added in one portion a solution of 24.2 g. (0.20 mole) of distilled allyl bromide (n_D^{25} 1.4657) in 50 ml. of ether. There was no evidence of reaction during the addition or a subsequent 5-hour period of heating under reflux with stirring. A usual work-up of the reaction mixture, followed by distillation, yielded the following fractions: (*a*) fore-run, 0.8 g., b.p. 75–120°, n_D^{25} 1.4785–1.4058; (*b*) *n*-octane, 23.3 g. (71%), b.p. 120–124°, n_D^{25} 1.3975–1.3978, probably con-

(19) Melting points are corrected and boiling points are uncorrected. All distillations, unless otherwise specified, were through a 65-cm. column of the simple Podbielniak design with heated jacket and partial reflux head (*cf.* J. Cason and H. Rapoport, *Laboratory Text in Organic Chemistry*, Prentice-Hall, Inc., New York, 1950, p. 237). Infrared spectra were recorded on a Baird recording spectrophotometer, using thin films. Ultraviolet spectra were determined on a Beckman model DU spectrophotometer with fused quartz prism, in optically pure heptane at concentrations such that optical densities were in the range 0.15–1.5. Microanalyses are by the Microanalytical Division, Department of Chemistry, University of California, Berkeley.

(20) A. Audsley and F. R. Goss, *J. Chem. Soc.*, 358 (1942); R. H. Pickard and J. Kenyon, *J. Chem. Soc.*, 99, 45 (1911).

taining a little *n*-octene (literature,[21] for *n*-octane, b.p. 125°, n_D^{20} 1.3988); (*c*) 2.8 g., b.p. 87–89°/32 mm., n_D^{25} 1.4338. The highest boiling fraction, which gives a positive qualitative test for halogen and has d^{25} 0.8927, is believed to be a mixture of *n*-octyl bromide and a hydrocarbon, possibly a very small amount of coupling product. *n*-Octyl bromide has n_D^{25} 1.4501 and is reported[22] to have d^{25} 1.1099, while 1-undecene is reported[23] to have b.p. 188–190°, n_D^{20} 1.4284, d^{20} 0.7630.

Reaction of tert-butyl chloride with di-n-octylcadmium. A cadmium reagent was prepared as described above from 46.4 g. (0.23 mole) of distilled *n*-octyl bromide (b.p. 66–67°/4.8 mm., n_D^{25} 1.4501). The reaction was carried out under nitrogen, as usual, and any gas passing out of the system through the mercury valve was led through two wash tubes maintained at 10–20°, each containing 30 g. of bromine, and finally through a gas trap cooled in Dry Ice and acetone.

The stirred solution of cadmium reagent was cooled in an ice bath as there was added, in two portions, 18.5 g. (0.2 mole) of distilled *tert*-butyl chloride (b.p. 49–52°, n_D^{25} 1.3825). After addition of the first portion, there was a brief induction period, after which a vigorous reaction occurred. When this reaction had subsided, the second portion was added, then the mixture was stirred in the ice bath for 30 min. and finally for 2 hr. under reflux. Since there was no condensate retained in the cold trap, products were obtained by working up the solution in the reaction flask and the bromine in the wash bottles.

The ether solution of the reaction mixture was treated with water and the aqueous phase was extracted with benzene. The ether solution and benzene extract were combined, solvent was removed by distillation through the column, and the residue was distilled to yield: (a) 17.3 g. (76%, based on *tert*-butyl chloride) of *n*-octane, b.p. 123–124°, n_D^{25} 1.3970 (literature[21] b.p. 125°, n_D^{20} 1.3988); (b) 2.0 g. of hexadecane, b.p. 127°/4.5 mm., n_D^{25} 1.4328 (literature[24] b.p. 156–158°/18 mm., n_D^{20} 1.4321).

Excess bromine in the wash bottles was decomposed by shaking with aqueous sodium sulfite, and the oily residual liquid was extracted with ether. Distillation of the dried extracts yielded 9.2 g. (21%) of 1,2-dibromo-2-methylpropane, b.p. 72–73°/60 mm., n_D^{25} 1.5050 (literature[25] b.p. 149°).

Reaction of di-n-butylcadmium with 4-chloro-4-n-propylheptane. 4-*n*-Propyl-4-heptanol was prepared by reaction of *n*-propylmagnesium bromide with 4-heptanone by a procedure similar to that described by Blatt and Stone.[26] The crude undistilled carbinol was then converted to the tertiary chloride by the procedure which has been described for preparation of *tert*-butyl chloride.[27] After a fore-run consisting largely of alkene, the tertiary chloride was obtained in 56% overall yield, b.p. 78–79°/11 mm., n_D^{25} 1.4372 (literature[28] b.p. 80°/12 mm., n_D^{15} 1.4421).

The reaction of 0.20 mole of 4-chloro-4-*n*-propylheptane with the butylcadmium reagent was carried out as described for the reaction with *tert*-butyl chloride except that the organometallic reaction mixture was worked up for alkene. Distillation of the product yielded the following fractions: (*a*) 22.1 g. (79%) of 4-*n*-propyl-3-heptene, b.p. 61–62°/18 mm., n_D^{25} 1.4265 (literature[29] b.p. 160–162°/734 mm., n_D^{20} 1.4386); (*b*) 1.6 g. of 4-chloro-4-*n*-propylheptane, b.p. 83–88°/18 mm., n_D^{25} 1.4360; (*c*) 1.1 g. of b.p. 108–110°/18 mm., n_D^{25} 1.4342. The final fraction probably consists of an impure sample of the coupling product 4,4-di-*n*-propyloctane (literature[30] b.p. 104–105°/18 mm., n_D^{15} 1.4358).

Although the observed index of refraction of 4-*n*-propyl-3-heptene is in disagreement with the literature value it agrees with the value observed by us for the alkene obtained as a by-product in preparation of 4-chloro-4-*n*-propyl heptane; also, it is consistent with the value, n_D^{20} 1.4303, which has been reported[31] for 3-ethyl-2-octene. In addition, this alkene gave an infrared spectrum containing only bands characteristic of alkenes; and on quantitative catalytic hydrogenation, absorption of hydrogen was equal to 105% of theory for one double bond.

Ethyl 2,2,4-trimethyl-3-oxopentanoate. A Grignard reagent was prepared in the usual manner under nitrogen from 3.9 g. (0.16 mole) of magnesium turnings and 20 g. (0.15 mole) of distilled *n*-butyl bromide (b.p. 99–100°, n_D^{25} 1.4376). This reagent was converted to the cadmium reagent by heating under reflux with stirring with 13.7 g. (0.075 mole) of anhydrous cadmium chloride. After a negative Gilman test for Grignard reagent had been obtained, ether was distilled from the mixture until distillation became slow, then 100 ml. of benzene was added.

After the slurry containing the cadmium reagent had been cooled to room temperature, there was added drop-wise with vigorous stirring a benzene solution of 17.9 g. (0.1 mole) of ethyl α-bromoisobutyrate (n_D^{25} 1.4438). A mildly exothermic reaction occurred during the addition. The mixture was finally heated under reflux with stirring for 1 hr. and then decomposed by addition of ice and 6*N* sulfuric acid. The product was extracted with benzene, the extracts were washed with water, solvent was removed by flash distillation, and the residue was distilled at reduced pressure. Except for a small fore-run, the only product was keto ester, 6.7 g. (72%), b.p. 89–90°/17 mm., n_D^{25} 1.4216. The infrared spectrum shows two bands in the carbonyl region, a strong band at 5.85 μ and a weaker band at 5.70 μ. Although this keto ester has previously been reported,[10] b.p. 93–94°/15 mm., it was characterized by analysis, conversion to a solid derivative, and cleavage to diisopropyl ketone.

Anal. Calcd. for $C_{10}H_{18}O_3$: C, 64.52; H, 9.68. Found: C, 65.01; H, 9.73.

The *pyrazolone*, 1-(2,4-dinitrophenyl)-3-isopropyl-4,4-dimethyl-5-pyrazolone, was prepared by the procedure of von Auwers,[32] except that 2,4-dinitrophenylhydrazine was used in place of phenylhydrazine. Crystallized from ethanol until the melting point became constant, the pyrazolone had m.p. 169.5–170°.

Anal. Calcd. for $C_{14}H_{16}N_4O_5$: C, 52.50; H, 5.00; N, 17.50. Found: C, 52.56; H, 4.87; N (Dumas), 17.41.

Basic cleavage of the keto ester was accomplished by heating 5.0 g. under reflux overnight with a solution of 4.5 g. of potassium hydroxide dissolved in 100 ml. of absolute ethanol. Work-up of the reaction mixture for neutral material yielded 2 g. of a volatile oil (infrared band at 5.85 μ) which was converted[33] to the 2,4-dinitrophenylhydrazone. After recrystallization from ethanol, this had m.p. 96.5–97° (literature[34]

(21) K. von Auwers and F. Eisenlohr, *Z. Physik. Chem.*, **83**, 429 (1913).

(22) A. I. Vogel, *J. Chem. Soc.*, **1943**, 636.

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(27) J. F. Norris and A. W. Olmsted, *Org. Syntheses*, Coll. Vol. 1, 144 (1941).

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(29) J. M. Church, F. C. Whitmore, and R. V. McGrew, *J. Am. Chem. Soc.*, **56**, 176 (1934).

(30) A. D. Petrov and E. A Chernyshev, *Doklady Akad. Nauk. S.S.S.R.*, 86. 957 (1952); *Chem. Abstr.*, **47**, 10453 (1953).

(31) F. C. Whitmore and F. E. Williams, *J. Am. Chem. Soc.*, **55**, 406(1933).

(32) K. von Auwers and F. Dersch, *Ann.*, **462**, 115 (1928).

(33) R. L. Shriner and R. C. Fuson, *The Systematic Identification of Organic Compounds*, 3rd ed., John Wiley and Sons, New York, 1948, p. 171.

(34) Ref. 33, p. 262.

for the 2,4-dinitrophenylhydrazone of diisopropyl ketone, m.p. 95°).

Anal. Calcd. for $C_{13}H_{18}N_4O_4$: C, 53.06; H, 6.12. Found: C, 53.28; H, 6.20.

For *identification of the bromide resulting from enolate formation*, a Grignard reagent was prepared from 12.3 g. (0.5 mole) of magnesium turnings and 75 g. (0.3 mole) of distilled *n*-dodecyl bromide (b.p. 126–128°/4.7 mm., n_D^{25} 1.4557). The solution of Grignard reagent was separated from excess magnesium by transferal under nitrogen pressure to another flask, then it was converted to the cadmium reagent and used for preparation of β-keto ester in the manner described above. Distillation of the product at 5.5 mm. pressure yielded: (*a*) 24.9 g. of a mixture of dodecane and β-keto ester, b.p. 66–75°; (*b*) 1.3 g. of intermediate fraction; (*c*) 30.9 g. of *n*-dodecyl bromide, b.p. 120–125°, n_D^{25} 1.4515–1.4555. The major portion (24.3 g.) of fraction (c), which was collected at 123–125°, n_D^{25} 1.4555, exhibited an infrared spectrum and index of refraction identical with those of an authentic sample of *n*-dodecyl bromide. The residue from the distillation, 7.7 g., yielded on crystallization from ethanol the coupling product, tetracosane, m.p. 47–48° (literature[35] m.p. 51°).

Preparation of β-hydroxy esters. Specific directions are given for the preparation of ethyl 2,3-dimethyl-3-hydroxynonanoate according to both the cadmium and Reformatsky condensations. For similar preparations of the other β-hydroxy esters, only pertinent results are reported. In summary, it may be noted that a large excess of cadmium reagent over ketone and α-bromo ester is of no advantage, while an excess of cadmium reagent and α-bromo ester over ketone results in a lower yield based on ketone. In the Reformatsky reaction, excess of α-bromo ester and zinc over ketone appears to be of little or no advantage, even with hindered ketones. This is in contrast to the previously published[13] procedure.

Ethyl 2,3-dimethyl-3-hydroxynonanoate. A. Cadmium condensation. The Grignard reagent was prepared in an atmosphere of nitrogen in the usual manner from 13.3 g. (0.55 mole) of magnesium turnings and 61.5 g. (0.50 mole) of *n*-propyl bromide (n_D^{25} 1.4326). For formation of the cadmium reagent, this reaction mixture was heated under reflux with 55.0 g. (0.30 mole) of finely ground anhydrous cadmium chloride until a negative Gilman test for Grignard reagent was obtained.

The reaction mixture was cooled to room temperature, then there was added with vigorous stirring during 1.5 hr. a solution in 30 ml. of benzene of 43.4 g. (0.35 mole) of 2-octanone (b.p. 172–173°, n_D^{25} 1.4136) and 63.3 g. (0.35 mole) of ethyl α-bromopropionate. After addition had been completed, the reaction mixture was stirred under reflux for an additional 2 hr. The reaction mixture was decomposed with ice and sulfuric acid, then worked up in the usual manner. Distillation of the product yielded, after a small fore-run, 60.4 g. (74%) of β-hydroxy ester, b.p. 120–122°/5.5 mm., n_D^{25} 1.4374. The infrared spectrum showed hydroxyl absorption at 2.85 μ and the doublet carbonyl band at 5.80 μ and 5.85 μ. A center cut, b.p. 122°/5.5 mm., was used for analysis.[36]

Anal. Calcd. for $C_{13}H_{26}O_3$: C, 67.82; H, 11.30. Found: C, 67.73; H, 11.01.

In a run carried out similarly except that the cadmium reagent was made from 0.75 mole of *n*-propyl bromide, the yield was the same. In a third run carried out as the first run, except that the quantity of ketone was reduced to 0.12 mole, the yield based on ketone was only 55%.

B. Reformatsky condensation. The Reformatsky reaction was carried out essentially as has been described in *Organic Syntheses*,[13] using benzene as solvent, except that 0.20 mole of each reactant was used (zinc, ethyl α-bromopropionate, and 2-octanone). Distillation of the product yielded 36.2 g. (79%) of the β-hydroxy ester, b.p. 127–131°/7.0 mm., n_D^{25} 1.4377.

In a similar run in benzene, except that a threefold excess of zinc and α-bromo ester was used, the yield was essentially the same, 82%, of product with n_D^{25} 1.4373. In another similar run using an equimolar ratio of reactants, but with a solvent consisting of 150 ml. of benzene and 150 ml. of ether, the yield was again similar, 76%, of product with n_D^{25} 1.4378.

Dehydration of ethyl 2,3-dimethyl-3-hydroxynonanoate. A 9.4-g. sample of the hydroxy ester was mixed with a few crystals of iodine and heated at 150° for 3 hr. Distillation of the product at 3.7 mm. yielded 0.5 g. of fore-run followed by 2.6 g. of a fraction consisting largely of the unsaturated ester, b.p. 92–100°, n_D^{25} 1.4380–1.4400; and finally there was collected 2.5 g. of a fraction consisting largely of recovered hydroxy ester, b.p. 100–113°, n_D^{25} 1.4390. The infrared spectrum of the unsaturated ester fraction showed a very weak hydroxyl band at 2.85 μ and a single carbonyl band at 5.75 μ. The ultraviolet spectrum of this fraction (Fig. 1) showed presence of only a trace of α,β-unsaturated ester, which has a maximum near 220 mμ. Quantitative hydrogenation of this fraction gave absorption of hydrogen equivalent to 98% of the theoretical amount for one double bond.

Ethyl 2,2,3-trimethyl-3-hydroxynonanoate. A. Cadmium condensation. The cadmium reagent was prepared from 48.0 g. (0.39 mole) of *n*-propyl bromide and allowed to react in benzene-ether solution with 24.8 g. (0.20 mole) of 2-octanone and 53.6 g. (0.26 mole) of ethyl α-bromoisobutyrate (n_D^{25} 1.4430). Distillation of the product yielded a fore-run of 6.1 g., which consisted chiefly of ethyl 2,2,4-trimethyl-3-oxopentanoate, and 40.5 g. (83%) of β-hydroxy ester, b.p. 112–116°/3.3 mm., n_D^{25} 1.4404. The infrared spectrum showed characteristic bands for hydroxyl at 2.79 μ and for carbonyl a doublet at 5.80 μ and 5.85 μ. For analysis, there was used a center cut of b.p. 115°/3.3 mm.

Anal. Calcd. for $C_{14}H_{28}O_3$: C, 68.85; H, 11.47. Found: C, 68.83; H, 11.58.

B. Reformatsky condensation. In benzene solution, condensation was carried out with 0.30 mole of zinc, 0.10 mole of 2-octanone and 0.30 mole of ethyl α-bromoisobutyrate. Distillation of the product yielded 19.1 g. (78.4%) of the β-hydroxy ester, b.p. 118–121°/4.1 mm., n_D^{25} 1.4406.

Ethyl 2,5-dimethyl-3-isobutyl-3-hydroxyhexanoate. A. Cadmium condensation. The cadmium reagent was prepared from 0.43 mole of *n*-propyl bromide and allowed to react with 0.10 mole of distilled diisobutyl ketone (b.p. 166–168°, n_D^{25} 1.4102) and 0.30 mole of ethyl α-bromopropionate. On distillation, there was a fore-run of 16.2 g. which contained β-keto ester, and 12.6 g. (52%) of β-hydroxy ester which was collected in two fractions: (*a*) 1.0 g., b.p. 104–106°/4.5 mm., n_D^{25} 1.4376; (*b*) 11.6 g., b.p. 106–108°/4.5 mm., n_D^{25} 1.4368. The infrared spectrum showed a hydroxyl band at 2.75 μ and a carbonyl band at 5.80 μ, with a shoulder at 5.75 μ.

Anal. Calcd. for $C_{14}H_{28}O_3$: C, 68.85; H, 11.47. Found: C, 68.81; H, 11.61.

In a similar run in which the cadmium reagent from 0.29 mole of *n*-propyl bromide was allowed to react with 0.20 mole each of ketone and α-bromo ester, the yield of β-hydroxy ester was 20.3 g. (41.3%), b.p. 103–105°/3.5 mm., n_D^{25} 1.4377.

B. Reformatsky condensation. In a run carried out in benzene in which there were used 0.20 mole each of zinc, bromo ester, and ketone, the yield of β-hydroxy ester was 12.0 g. (24.6%), b.p. 109–113°/4.5 mm., n_D^{25} 1.4383. In a second run in which there was used a threefold excess of zinc and α-bromo ester, the yield of β-hydroxy ester was 12.8 g. (26%), b.p. 106–109°/4.5 mm., n_D^{25} 1.4379. In both these

(35) F. Kraft, *Ber.*, **15**, 1718 (1882).

(36) In combustion analysis of the β-hydroxy esters and unsaturated esters obtained in this investigation, there was persistent difficulty with low values for carbon. Use of a high furnace temperature and slow burning usually gave results near theory.

runs, substantial amounts of unreacted ketone were recovered.

In a run carried out in benzene-ether solvent, using 0.20 mole each of zinc, α-bromo ester, and ketone, the yield of β-hydroxy ester was 33.5 g. (68.5%), b.p. 105–107°/4.5 mm., n_D^{25} 1.4377.

When the Reformatsky reaction was carried out in purified tetrahydrofuran as solvent the zinc reacted completely, but 74% of starting ketone was recovered, and there could be isolated neither β-hydroxy ester nor unsaturated ester. Similarly, in a mixture of anisole and benzene, the zinc reacted readily; however, neither β-hydroxy ester nor unsaturated ester could be isolated from the reaction. None of the products of either of these reactions were identified.

Ethyl 2,5-dimethyl-3-isobutyl-3-hexenoate. In one run of the Reformatsky reaction with 0.20 mole each of zinc, ethyl α-bromopropionate, and diisobutyl ketone, essentially complete dehydration of the β-hydroxy ester occurred during work-up. This was unexpected since considerable difficulty was usually experienced in deliberate attempts at dehydration of these β-hydroxy esters. Presumably, this behavior should be ascribed to presence of an unidentified impurity acting as catalyst. Distillation of the product yielded, after a small fore-run, 28.9 g. (64%) of unsaturated ester, b.p. 87–91°/4.7 mm., n_D^{25} 1.4351. The infrared spectrum showed no hydroxyl band and a single carbonyl band at 5.75 μ. The ultraviolet spectrum (*cf.* Fig. 1) showed absence of α,β-unsaturated ester. A center cut was used for analysis.

Anal. Calcd. for $C_{14}H_{26}O_2$: C, 74.33; H, 11.50. Found: C, 74.27; H, 11.59.

The ester was saponified by heating under reflux overnight a solution of 10 g. of the ester and 4 g. of sodium hydroxide in a mixture of 100 ml. of ethanol and 100 ml. of water. Work-up of the reaction mixture and distillation yielded 6 g. (70%) of *2,5-dimethyl-3-isobutyl-3-hexenoic acid*, b.p. 127–128°/4.2 mm., n_D^{25} 1.4471. A center cut, having the same index of refraction as the main fraction, was used for analysis.

Anal. Calcd. for $C_{12}H_{22}O_2$: C, 72.73; H, 11.11; Equiv. wt., 198. Found: C, 72.80; H, 10.90; Equiv. wt., 195.

Ethyl 2-methyl-3-n-propyl-3-hydroxyhexanoate. The Reformatsky reaction was carried out in benzene solution with 0.20 mole each of zinc, ethyl α-bromopropionate, and distilled 4-heptanone (b.p. 142–143°, n_D^{25} 1.4040). Distillation yielded, after a small fore-run, 28.6 g. (66.4%) of β-hydroxy ester, b.p. 116–118°/16 mm., n_D^{25} 1.4348.

A similar run in benzene-ether solvent yielded 34.8 g. (80.5%) of β-hydroxy ester, b.p. 107–110°/6.0 mm., n_D^{25} 1.4340–1.4342. The infrared spectrum showed the hydroxyl band at 2.75 μ and the carbonyl band at 5.80 μ, with a shoulder at 5.70 μ. For analysis, there was used a center cut with n_D^{25} 1.4342.

Anal. Calcd. for $C_{12}H_{24}O_3$: C, 66.66; H, 11.11. Found: C, 66.80; H, 10.96.

Ethyl 2-methyl-3-hydroxynonanoate. In the Reformatsky reaction in benzene, using 0.20 mole each of zinc, ethyl α-bromopropionate, and distilled *n*-heptaldehyde (b.p. 149–150°), there was obtained 27.5 g. (64%) of β-hydroxy ester, b.p. 138–140°/14 mm., n_D^{25} 1.4360.

In a similar run in benzene-ether, the yield of β-hydroxy ester was 31.3 g. (73%), b.p. 122–125°/5.0 mm., n_D^{25} 1.4363 (literature[37] b.p. 124–128°/6 mm.). The infrared spectrum showed the hydroxyl band at 2.75 μ and a broad carbonyl band at 5.75 μ.

Reformatsky reaction between 2-heptadecanone and ethyl α-bromopropionate. A reaction carried out in benzene-ether solution utilized 0.03 mole of zinc, 0.03 mole of ethyl α-bromopropionate, and 0.016 mole of 2-heptadecanone (m.p. 45–46°). Distillation of the product yielded: (*a*) 1.09 g. of fore-run; (*b*) 1.38 g., b.p. 185–195°/2.0 mm., n_D^{25} 1.4491; (*c*) 1.53 g., b.p. 195–197°/2.0 mm., n_D^{25} 1.4491. The ultraviolet spectrum (*cf.* Fig. 1) shows that Fraction (*b*) consists largely of β,γ-unsaturated ester containing no more than traces of the α,β-unsaturated ester, while Fraction (*c*) contains a low percentage of unsaturated ester. The infrared spectrum of (*b*) shows a very weak hydroxyl band at 2.75 μ, while (*c*) shows a strong hydroxyl band at 2.75 μ; thus, (*c*) consists largely of the β-hydroxy ester. The infrared spectra of both Fractions (*b*) and (*c*) show a doublet carbonyl band at 5.75 μ and 5.80 μ; however, in (*b*) the band at 5.80 μ is barely detectable on the shoulder of the 5.75 μ band, whereas in (*c*) it is stronger than the band at 5.75 μ. This is consistent with the view that doubling of the carbonyl band in the β-hydroxy esters should be ascribed to chelation of the carbonyl with β-hydroxyl. The principal contributor to the carbonyl band in (*b*) is the carbonyl in the unsaturated ester.

The total yield of unsaturated ester and hydroxy ester is 2.9 g. (52%).

Ethyl 2-methyl-3-oxodecanoate. A Blaise reaction was carried out as has been previously described[17] except that the copper catalyst was not used and the solvent was a 1:1 mixture of benzene and ether. Reactants were 9.7 g. (0.15 mole) of zinc, 27.2 g. (0.15 mole) of ethyl α-bromopropionate, and 12.5 g. (0.10 mole) of distilled octanenitrile (b.p. 93–95°/17 mm.). Distillation of the product at 13 mm. yielded 6.2 g. of fore-run, b.p. 72–105°, n_D^{25} 1.4184; 0.8 g. of intermediate fraction; and 13.0 g. (57%) of β-keto ester, b.p. 143–145°, n_D^{25} 1.4339–1.4344. The infrared spectrum showed carbonyl bands at 5.70 μ and 5.80 μ.

Anal. Calcd. for $C_{13}H_{24}O_3$: C, 68.42; H, 10.53. Found: C, 68.49; H, 10.10.

In a second run using the same conditions as described above, the yield was 53% of β-keto ester with n_D^{25} 1.4338.

In a run using the same conditions except that only benzene was used as solvent, the yield was 44% of β-keto ester of b.p. 145–149°/12 mm., n_D^{25} 1.4341. This yield is slightly higher than that previously reported[17] for a similar preparation when a copper catalyst was employed and benzene alone was used as solvent.

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(37) S. Obata, *J. Pharm. Soc. Japan*, **73**, 1295 (1953); *Chem. Abstr.*, **49**, 175 (1955).

[CONTRIBUTION FROM THE NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES, NATIONAL INSTITUTES OF HEALTH, PUBLIC HEALTH SERVICE, U. S. DEPARTMENT OF HEALTH, EDUCATION AND WELFARE]

Electronic Control of Steric Hindrance in Hindered Phenols[1]

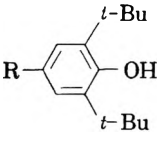
LOUIS A. COHEN

Received July 1, 1957

2,6-Di-*tert*-butylphenols with electronegative substituents in the *para* position have been prepared and found to be readily soluble in aqueous alkali. The phenomenon has been explained in terms of facilitation of charge dispersion. The preparation of the corresponding highly hindered anisoles is described.

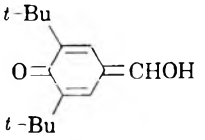
The chemistry of the highly hindered 2,6-di-*tert*-butylphenols has been the subject of a number of investigations in recent years.[2] The noteworthy properties of these compounds include (*a*) the stability of the phenoxy radicals,[2c,e,g] (*b*) the ease of formation and the stability of the corresponding cyclohexadienones,[2b,d,f,h] and (*c*) the failure to exhibit normal phenolic properties.[2a,h]

During the course of synthetic work on some amino acid analogs, 3,5-di-*tert*-butyl-4-hydroxybenzaldehyde (I) was prepared[2b] and was found to be readily soluble in dilute, aqueous alkali.[3] The observation of this one exception to the general behavior of 2,6-di-*tert*-butylphenols prompted an investigation of the phenomenon, a portion of that investigation being the subject of the present report.



I, R = CHO III, R = CN
II, R = CH_3 IV, R = $CO_2C_2H_5$

Two explanations for the behavior of the aldehyde were considered: (1) Solubility in alkali was due to the enolic form V, the result of a facile tautomerism or (2) the inductive and/or resonant properties of the carboxaldehyde function greatly increased the acidity of the phenol. That tautomerism does not offer a rigorous explanation was demonstrable by the following observations: (1) III and IV were also soluble in dilute alkali and could be recovered upon acidification of the alkaline solutions. (2) A comparison of the infrared absorption bands of the phenols and of their sodium salts (Table I) suggests that a somewhat greater fraction of the negative charge may reside on the *para* substituent in the hindered than in the unhindered phenols.[3a] The same conclusion may be drawn from a comparison of the ultraviolet spectra in neutral and alkaline media (Table II), particularly for compounds I and IV. By treatment of the sodium salts of II, III and IV with methyl iodide, the corresponding anisoles, VIII, IX, and X were obtained. Attempts to make VII by the same procedure led only to the isolation of the diphenoquinone VI.

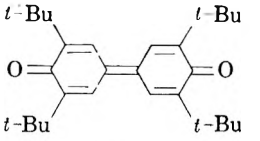


V

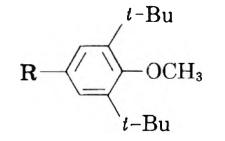
TABLE I

EFFECT OF ALKALI ON INFRARED SPECTRA

	Phenol	Sodium Phenoxide	Di-*tert*-butyl Phenol	Sodium di-*tert*-butyl Phenoxide
p-Formyl	5.92 μ	6.10 μ	5.93 μ	6.16 μ
p-Carbethoxy	5.85	5.95	5.86	6.05
p-Cyano	4.50	4.50	4.51	4.57



VI



VII, R = CHO
VIII, R = CH_3
IX, R = CN
X, R = $CO_2C_2H_5$

I, III, and IV, as well as II, failed to react with diazomethane or with sodium in boiling ligroin, confirming the assumption that the stereochemistry at the phenol has not been modified by a *para* substituent.

(1) This paper is a contribution in honor of Lyndon F. Small, former Editor of the Journal.

(2) For example, *Cf.* (a) G. H. Stillson, D. W. Sawyer, and C. K. Hunt, *J. Am. Chem. Soc.*, **67**, 303 (1945). (b) T. W. Campbell and G. M. Coppinger, *J. Am. Chem. Soc.*, **74**, 1469 (1952). (c) G. M. Coppinger and T. W. Campbell, *J. Am. Chem. Soc.*, **75**, 734 (1953). (d) C. D. Cook, *J. Org. Chem.*, **18**, 261 (1953). (e) C. D. Cook, N. G. Nash, and H. R. Flanagan, *J. Am. Chem. Soc.*, **77**, 1783 (1955). (f) C. D. Cook and B. E. Norcross, *J. Am. Chem. Soc.*, **78**, 3797 (1956). (g) E. Müller, K. Ley, and W. Schmidhuber, *Chem. Ber.*, **89**, 1738 (1956) and earlier papers. (h) T. Fujisaki, *J. Chem. Soc., Japan*, **77**, 733 (1956) and earlier papers.

(3) The same observation has been reported recently from another laboratory: G. R. Yohe, J. E. Dunbar, R. L. Pedrotti, F. M. Scheidt, F. G. H. Lee, and E. C. Smith, *J. Org. Chem.*, **21**, 1289 (1956).

(3a) R. N. Jones and C. Sandorfy, *Chemical Applications of Spectroscopy*, W. West, editor, Interscience Press, Inc., New York, N. Y., 1956, p. 481.

TABLE II

EFFECT OF ALKALI ON ULTRAVIOLET SPECTRA

	Phenol			Di-*tert*-butylphenol		
	Neutral	Alkali[a]	Δλ	Neutral	Alkali[a]	Δλ
p-Formyl	284 mμ (4.2)[b]	350 mμ (3.9)	46	287 mμ (4.1)	370 mμ (4.5)	83
p-Carbethoxy	255 (4.3)	300 (4.4)	45	262 (4.2)	330 (4.5)	68
p-Cyano	247 (4.3)	280 (4.3)	33	252 (4.2)	287 (4.5)	35

[a] Sodium ethoxide solution was added to the ethanol solutions to make a final concentration of 0.01*M*. [b] Figures in parentheses are log ϵ_{max}.

The dissociation constants of I, III, and IV (Table III) show the same order of activation by the *para* substituent as do the nonalkylated phenols. However, the acidity is substantially lower.

If we regard the ability of a phenolate anion to become solvated and to disperse its negative charge through the solvent sphere as a prerequisite to acidic behavior and alkali solubility, it is evident that II cannot meet these requirements. This phenomenon has been termed "steric hindrance to solvation." [4] However, if the negative charge has an opportunity to become dispersed *via* resonance between the phenolate anion and a strong *para* electron-sink, as in I, III, and IV and the corresponding structures Ia, IIIa, and IVa, the ease of anion formation should be greatly increased. Either a much smaller solvent sphere is necessary or the phenolic oxygen for charge dispersion or no solvent participation at all.

On the basis of models, the impairment of resonance should be greater in the methyl ethers than in the phenols.[4a] No significant differences were found in the ultraviolet absorption spectra of the anisoles and of corresponding unhindered compounds (Table IV). However, the 6.25-μ aromatic band in the infrared was markedly reduced in intensity by the bulky *ortho* substituents.

TABLE III

DISSOCIATION CONSTANTS OF PHENOLS

	Phenol pK_a	Di-*tert*-butyl Phenol[a] pK_a
p-Formyl	8.81[b]	11.3
p-Cyano	9.10[b]	11.4
p-Carbethoxy	9.61[b]	11.8
p-Bromo	10.50	[c]

[a] Dissociation constants were measured in 50% ethanol by the procedure of T. V. Parke and W. W. Davis, *Anal. Chem.*, 26, 642 (1954). [b] These values were obtained by adding 1.15 units (to correct for the solvent difference) to the values measured in water as recorded in E. A. Braude and E. C. Nachod, *Determination of Organic Structures by Physical Methods*, Academic Press Inc., New York, 1955, p. 589. [c] The acidity was too weak to measure in this system.

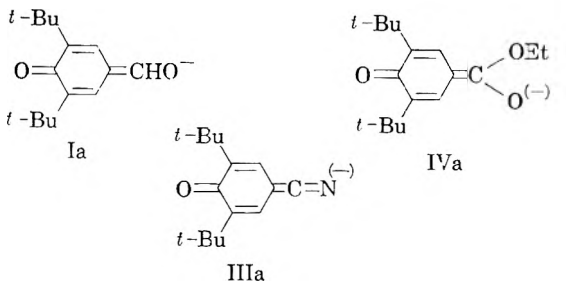


TABLE IV

ULTRAVIOLET SPECTRA OF ANISOLES

	Anisole	Di-*tert*-butyl anisole
p-Methyl	275 mμ (3.2)	275 (3.0)
p-Formyl	277 (4.2)	
p-Carbethoxy	254 (4.3)	250 (4.0)
p-Cyano	255 (4.3)	243 (4.2)

EXPERIMENTAL[5]

3,5-Di-tert-butyl-4-hydroxybenzaldehyde (I). For large-scale preparation, the use of aqueous acetic acid as solvent was found preferable to tertiary butyl alcohol. The method of Coppinger and Campbell[2(c)] was adapted to a larger scale.

A solution of 80 g. (0.36 mole) of 2,6-di-*tert*-butyl-4-methylphenol (II) (commercial grade) in 800 ml. of glacial acetic acid was diluted with 200 ml. of water. Two equivalents of bromine (37 ml.) was added dropwise with mechanical stirring over a period of 2 hr. Toward the end of the addition the product began to separate. Stirring was continued for 1 hr. and the suspension diluted with 500 ml. of ice water. After the mixture had been chilled for several hours at 0°, it was filtered, and the pale yellow product was washed with 50% acetic acid and with water and dried *in vacuo*. In several preparations, yields of 77–85% were obtained, the aldehyde melting at 178–181° (lit.[2(c)] 189–190°). For purification, the compound was recrystallized from ligroin; however, the crude product was satisfactory for further work in most instances.

3,5-Di-tert-butyl-4-hydroxybenzaldoxime. The oxime was prepared from crude aldehyde by the usual procedure, using a 0.1 mole scale. A colorless oil was obtained which was dis-

(4) P. D. Bartlett, M. Roha, and R. M. Stiles, *J. Am. Chem. Soc.*, 76, 2349 (1954). N. D. Coggeshall and A. S. Glessner, Jr., *J. Am. Chem. Soc.*, 72, 2275 (1950). E. E. Betts and L. R. C. Barclay, *Can. J. Chem.*, 33, 1768 (1955). The low acidity observed by Betts and Barclay for 2,4,6-tri-*tert*-butylbenzoic acid may be due to steric hindrance to solvation of the carboxylate anion.

(4a) P. Rumpf and H. Lumbroso, *Bull. soc. chim. France*, 283 (1950); K. B. Everard and L. F. Sutton, *J. Chem. Soc.*, 2312 (1949); M. S. Newman, *Steric Effects in Organic Chemistry*, John Wiley & Sons, Inc., New York, N. Y., 1956, p. 511.

(5) All melting points were taken on a Kofler block and are corrected. Infrared spectra were measured in chloroform solution; spectra of sodium phenolates were run on Nujol mulls. Ultraviolet spectra were run in absolute ethanol. Unless otherwise specified, petroleum ether refers to the 30–40° fraction.

solved in 100 ml. of ligroin (90–100°) and concentrated. The residual syrup deposited 16 g. of thin plates from petroleum ether, m.p. 120–125°. Evaporation of the mother liquor yielded an additional 6 g. The oxime appeared to be solvated whether recrystallized from petroleum ether or dilute alcohol. The combined fractions separated as thin plates from dilute alcohol. After the total product had been dried at 100°/1 mm. for 12 hr. it weighed 20 g. (80%), m.p. 138–139°.

Anal. Calcd. for $C_{15}H_{23}O_2N$: C, 72.25; H, 9.30; N, 5.62. Found: C, 72.39; H, 9.50; N, 5.51.

3,5-Di-tert-butyl-4-hydroxybenzonitrile (III). A solution of 24.9 g. (0.1 mole) of the oxime in 50 ml. of acetic anhydride was heated on a steam bath for 2 hr. The solution was poured into one l. of normal sodium bicarbonate and stirred until hydrolysis of the acetic anhydride was complete. The solid residue was extracted with 2 × 150 ml. of methylene chloride, and the extract was washed with sodium bicarbonate, dried, and concentrated to a yellow solid. The material was best purified by extracting an ether solution with cold normal sodium hydroxide and precipitating with 3*N* hydrochloric acid. The product separated as colorless granules which were dried and recrystallized from petroleum ether as needles, m.p. 147°; 18 g. (78%).

Nitrile absorption in the infrared occurred at 4.51 μ. In the ultraviolet, the nitrile absorbed at 252 mμ (log ϵ_{max} 4.18). When sodium ethoxide solution was added to make the final concentration 0.01 molar in base, the spectrum shifted to 232 mμ (log ϵ_{max} 3.82) and 287 mμ (log ϵ_{max} 4.46).

Anal. Calcd. for $C_{15}H_{21}ON$: C, 77.88; H, 9.15; N, 6.05. Found: C, 77.95; H, 9.05; N, 6.27.

Ethyl 3,5-di-tert-butyl-4-hydroxybenzoate (IV). A solution of 23.1 g. (0.1 mole) of the nitrile (III) in 200 ml. of ethanol was saturated with hydrogen chloride at 0° and stored at 25° for 2 days. The red-violet solution was concentrated to a crystalline residue of the iminoether hydrochloride (m.p. 260°). The material was extracted with 3 × 100 ml. of ether and the almost colorless residue was dissolved in 100 ml. of 50% ethanol. After addition of 100 ml. of normal sodium bicarbonate, the mixture was heated on steam for 1 hr. and concentrated to a small volume. The oily ester was extracted with 2 × 150 ml. of methylene chloride and the extract was dried and concentrated to a colorless sirup. The product separated from petroleum ether as granules, m.p. 107–108°, 21 g. (75%). It was recrystallized from dilute alcohol as plates, m.p. 108–109°.

Ester absorption in the infrared occurred at 5.86 μ. In the ultraviolet, IV absorbed at 262 mμ (log ϵ_{max} 4.15); in 0.01*M* sodium ethoxide, the spectrum shifted to 240 mμ (log ϵ_{max} 3.96) and 330 mμ (log ϵ_{max} 4.47).

Anal. Calcd. for $C_{17}H_{26}O_3$: C, 73.34; H, 9.41. Found: C, 73.21; H, 9.19.

A sample of the ester was saponified by heating with 0.1*N* sodium hydroxide to form 3,5-di-*tert*-butyl-4-hydroxybenzoic acid, m.p. 216–217° (lit.[3] 217–218°).

Alkali solubility test. One-tenth gram samples of I, III, and IV were dissolved in several drops of ethanol and diluted with 20 ml. of normal sodium hydroxide. Solution was complete in each case. After acidification, the phenols could be recovered.

2,6-Di-tert-butyl-4-bromophenol, was prepared by the bromination of commercial 2,6-di-*tert*-butylphenol in carbon tetrachloride solution. Contrary to the experience of Hart and Cassis,[6] bromination proceeded rapidly to give an excellent yield of the bromophenol.

2,6-Di-tert-butyl-4-methylanisole (VIII). *Method A.* The sodium salt of II was prepared in liquid ammonia according to the published procedure[2(a)] using 2.2 g. (0.01 mole) of the cresol. Without isolating the salt, the ammonia was evaporated and replaced with 50 ml. of toluene. After concentration to dryness to remove residual ammonia, 50 ml. of toluene was added and the suspension transferred to a pressure bottle. Ten ml. of methyl iodide was added, the air was replaced by nitrogen, the bottle was sealed and the mixture was heated by steam for 18 hr. It was then cooled and concentrated. The residue was extracted with 2 × 50 ml. of petroleum ether and the extract was concentrated to a pale green oil weighing 1.7 g. Purification could not be achieved by fractional distillation, VIII and II distilling at about the same temperature. The oil was transferred to a column of 25 g. of basic alumina and eluted with petroleum ether. Progress of the elution could be followed by using the phosphomolybdic acid test for phenols on the dried fractions.[2(a)] The methyl ether was the first material to separate from the column, 1.4 g. (60%) of colorless oil being obtained.

The infrared spectrum showed only a weak aromatic band at 6.25 μ. In the ultraviolet, VIII absorbed at 275 mμ.

Anal. Calcd. for $C_{16}H_{26}O$: C, 81.99; H, 11.18. Found: C, 81.97; H, 11.33.

Method B: To a solution of 2.2 g. (0.01 mole) of II in 25 ml. of methanol was added 10 ml. of molar sodium methoxide and the mixture was concentrated to dryness under reduced pressure. Fifty ml. of toluene was added, the mixture concentrated to dryness and the process repeated. The residual material, which had begun to darken, was transferred to a pressure bottle as described above. From this point, Method A was followed and a 10% yield of the anisole was obtained after chromatography.

Attempted preparation of 3,5-di-tert-butyl-4-methoxybenzaldehyde (VII). When Method A was used to prepare the sodium salt of I (purified), the products obtained from the alkylation were 3,5-di-*tert*-butyl-4-hydroxybenzyl alcohol (m.p. 137–138°;[2(c)] and the corresponding methyl benzyl ether (m.p. 102–103°).[2(h)] Apparently, sodium in liquid ammonia preferentially reduced the aldehyde and formed the sodium salt of the newly-formed primary hydroxyl.

Using Method B, a dark red oil was obtained. The only nonphenolic material which could be isolated by chromatography was VI, m.p. 245–246°.[2(h)] Presumably, the diphenoquinone was formed *via* a free-radical dimerization.

3,5-Di-tert-butyl-4-methoxybenzonitrile (IX). The methyl ether was prepared from III using method B. After chromatographic purification, a 65% yield of colorless plates was obtained, m.p. 73–75°. The melting point was unchanged by recrystallization from cold petroleum ether. The infrared spectrum showed a nitrile band at 4.51 μ and a weak aromatic band at 6.29 μ. In the ultraviolet, the compound absorbed at 243 mμ (log ϵ_{max} 4.18).

Anal. Calcd. for $C_{16}H_{23}ON$: C, 78.32; H, 9.45; N, 5.71. Found: C, 78.35; H, 9.64; N, 5.75.

Ethyl 3,5-di-tert-butyl-4-methoxybenzoate (X). The methyl ether was prepared from IV by method B. A 58% yield of colorless oil was obtained after chromatography. The infrared spectrum showed an ester band at 5.83 μ and a weak aromatic band at 6.25 μ. Absorption in the ultraviolet occurred at 250 mμ (log ϵ_{max} 3.98).

Anal. Calcd. for $C_{18}H_{28}O_3$: C, 73.93; H, 9.65. Found: C, 73.82; H, 9.89.

Sodium salts of I, III, and IV and of the corresponding nonalkylated phenols were obtained by Method B but were dried *in vacuo* after two concentrations with toluene.[7] The residues were triturated several times with ether, the solvent was decanted, and the sodium salts again dried *in vacuo*. The compounds were stored under nitrogen at 0°.

Acknowledgment. The author thanks Dr. William C. Alford and his associates, all of this institute, for carrying out the microanalyses, and Wm. M. Jones for measuring the infrared and ultraviolet spectra.

BETHESDA 14, MD.

(6) H. Hart and F. A. Cassis, Jr., *J. Am. Chem. Soc.*, **73**, 3179 (1951).

(7) Rigorous drying was necessary to free the phenolates completely from solvent.

[CONTRIBUTION FROM WAYNE STATE UNIVERSITY AND THE STATE UNIVERSITY OF IOWA]

The Preparation of 3,5-Di-*O*-methyl-D-glucose and 2,3,5-Tri-*O*-methyl-D-glucose*

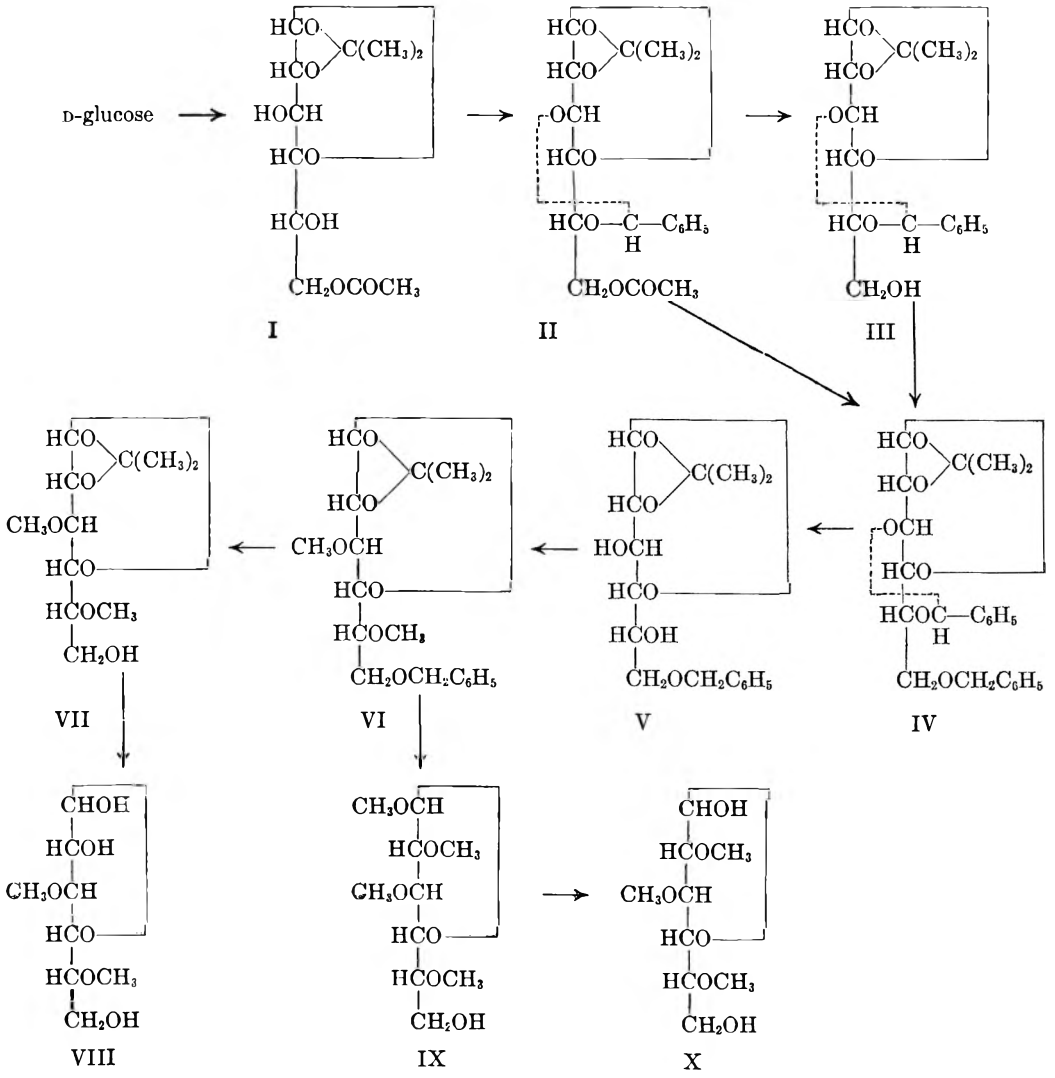
GEORGE H. COLEMAN, STANLEY S. BRANDT,[1] AND CHESTER M. McCLOSKEY[2]

Received July 1, 1957

3,5-Di-*O*-methyl-D-glucose (VIII) has been prepared by the hydrogenolysis and hydrolysis of crystalline 6-*O*-benzyl-1,2-*O*-isopropylidene-3,5-di-*O*-methyl-D-glucose (VI). Methanolysis of the latter compound followed by methylation and hydrogenolysis formed a crystalline methyl 2,3,5-tri-*O*-methyl-D-glucoside, (IX).

Interest in the di-*O*-methyl-D-glucoses as reference compounds and as intermediates has led previously to the preparation of all but two of the normal structural isomers; these are 3,5-di-*O*-methyl-D-glucose and 4,5-di-*O*-methyl-D-glucose.

The synthesis of 3,5-di-*O*-methyl-D-glucose has now been carried out and in connection with the proof of structure of the various compounds involved in the synthesis 2,3,5-tri-*O*-methyl-D-glucose was prepared by a new method and a crystalline methyl 2,3,5-tri-*O*-methyl-D-glucoside obtained.



2,3,5-Tri-*O*-methyl-D-glucose had been prepared previously by two different pathways. Smith[3] in 1944 reported the synthesis of this compound from

* This paper is a contribution in honor of Lyndon F. Small, former Editor of the Journal.

(1) Present address: E. I. du Pont de Nemours and Co., Inc., Louisville, Ky.

(2) Present address: California Institute of Technology, Pasadena 4, Calif.

(3) F. Smith, *J. Chem. Soc.*, 571 (1944).

the methyl furanoside *via* the 6-*O*-trityl derivative. Dimler, Davis, and Hilbert[4] prepared the same compound by methylation and hydrolysis of 1,6-anhydro-β-D-glucofuranose, a new anhydride of glucose which had been isolated from the mixture of products resulting from the vacuum pyrolysis of starch.

The present syntheses were based on 6-*O*-benzyl-1,2-*O*-isopropylidene-D-glucose (V). This compound had previously been prepared by Ohle and Tessmar[5] from 5,6-anhydro-1,2-*O*-isopropylidene-D-glucose. The development of a simplified method for the preparation of 6-*O*-acetyl-1,2-*O*-isopropylidene-D-glucose (I) utilizing 3.5 mole quantities of reactants made possible the ready preparation of V *via* the 3,5-*O*-benzylidene derivatives II and IV. Methylation of V formed the crystalline 6-*O*-benzyl-1,2 - *O* - isopropylidene - 3,5 - di - *O* - methyl - D-glucose (VI). By the hydrogenolysis of (VI) 1,2-*O*-isopropylidene-3,5-di-*O*-methyl-D-glucose (VII) was obtained as a sirup. For additional characterization of this compound a crystalline derivative, the *p*-phenylazobenzoate was prepared. Hydrolysis of VII formed the sirupy 3,5-di-*O*-methyl-D-glucose (VIII). As a further confirmation of structure, as well as an illustration of the versatility of these compounds as intermediates, compound VI, 6-*O*-benzyl-1,2-*O*-isopropylidene-3,5-di-*O*-methyl-D-glucose, was subjected to methanolysis followed by hydrogenolysis with palladium charcoal catalyst, then methylation and final hydrolysis to yield the known compound 2,3,5,6-tetra-*O*-methyl-D-glucose.[6]

Using a different sequence of similar reactions with compound VI, methanolysis was followed by methylation and then hydrogenolysis to remove the benzyl group. The product formed was a crystalline methyl 2,3,5 - tri - *O* - methyl - β - D - glucofuranoside (IX). Hydrolysis of IX formed sirupy 2,3,5-tri-*O*-methyl-D-glucose (X) which was identified by oxidation to the gluconic acid and preparation of the known phenylhydrazide.

EXPERIMENTAL[7]

6-O-Acetyl-1,2-O-isopropylidene-D-glucofuranose[8-10] (I). Anhydrous glucose (640 g.) and 220 g. of boric acid were added to a solution prepared by adding 256 ml. of concentrated sulfuric acid to 8 l. of cold acetone. The mixture was stirred 4–5 hr. until the glucose had gone into solution, then cooled in an ice bath and 790 ml. of pyridine added slowly with stirring. After a few minutes the pyridine sulfate was allowed to settle and the acetone solution decanted from the sirupy residue. The acetone solution was stirred for 3 hr. with 250 g. of anhydrous potassium carbonate, decanted from the salts, and concentrated on a steam bath. Sodium acetate (250 g.) was added to the residue, the mixture cooled in an ice bath and 700 ml. of acetic anhydride added. After stirring a short time the mixture was heated for 20 min. on a steam bath and then 2 kg. of ice was added followed by 3 l. of water. The resulting solution was extracted with 600 ml. of a mixture (3:1) of benzene and ligroin (b.p. 60–70°), followed by a second extraction with 300 ml. of the benzene-ligroin mixture. The aqueous solution was saturated with sodium chloride by stirring with an excess of rock salt. The use of rock salt was found to be desirable as it facilitated separation of the product in the following steps. The crystals that formed were filtered off and dried. The dry material was extracted with 5 l. of hot chloroform from which I separated on cooling. The crystals were filtered off and the filtrate concentrated to one fourth the volume to obtain a second crop. The combined yield was 330 g. (35.2%) m.p. 145–146° (lit.[9] m.p. 145.5°).

6-O-Acetyl-3,5-O-benzylidene-1,2-O-isopropylidene-D-glucose (II) was prepared by the method of Freudenberg and Hüll.[10] From 125 g. of I, 500 ml. of benzaldehyde and 125 g. of powdered anhydrous zinc chloride, after 5 hr. of shaking, dilution with 2 l. of water, and concentration under reduced pressure, there was obtained after recrystallization of the residue from ethanol 125 g. of II, m.p. 125–127° (uncorr.) (lit.[9] 126–127°).

3,5-O-Benzylidene-1,2-O-isopropylidene-D-glucofuranose (III). Compound II was deacetylated by dissolving 100 g. in 150 ml. of dioxane, adding 150 ml. of methanol containing sodium methoxide from 1.5 g. of sodium, heating to reflux, and allowing the reaction mixture to stand overnight. Water was added to the solution and III crystallized out in nearly quantitative yield, m.p. 149–150° (uncorr.) (lit.[10] 148.5–150°).

6-O-Benzyl-3,5-O-benzylidene-1,2-O-isopropylidene-D-glucose (IV). A mixture of 100 g. of III (II was also used) and 125 g. of powdered potassium hydroxide was added in four portions with vigorous stirring to 500 ml. of benzyl chloride heated on a steam bath. Following the first addition, each successive addition was made after the reaction mixture had thinned from the previous addition. After 5 hr. most of the excess benzyl chloride was removed by distillation under reduced pressure and the residual mixture subjected to steam distillation until no more benzyl chloride came over. The aqueous layer was decanted. The residue solidified on standing overnight and was washed to remove salts. A crude yield of 128 g. (99%) was obtained. For analysis, a sample was crystallized from ligroin, b.p. 60–70°, and then from ether by cooling in an ice bath. $[\alpha]_D^{25}$ −1.3° (c 2, U.S.P. $CHCl_3$), m.p. 83.5–84°.

Anal. Calcd. for $C_{23}H_{26}O_6$: C, 69.33; H, 6.58. Found: C, 69.64; H, 6.73.

6-O-Benzyl-1,2-O-isopropylidene-D-glucofuranose (V). A solution of 100 g. of IV in 1 l. of acetone, 40 ml. of water, and 4 ml. of concentrated hydrochloric acid was refluxed for 75 min. The solution was neutralized with silver carbonate, filtered, saturated with hydrogen sulfide, and filtered through a charcoal mat. The filtrate was mixed with 200 ml. of water and evaporated to a sirup. The residue was dried by adding 50 ml. of toluene and reconcentrating to a residue which solidified on standing. It was recrystallized from a mixture of ethyl acetate and ligroin, (b.p. 60–70°) to yield 60 g. (80%), m.p. 78.5–79° (uncorr.) (lit.[5] 78.5–79°), b.p. 172°/0.16 mm.

6-O-Benzyl-1,2-O-isopropylidene-3,5-di-O-methyl-D-glucose (VI). A solution of 100 g. of V in 1 l. of acetone was methylated at 50° by the dropwise addition of 490 ml. of methyl sulfate and 826 ml. of 50% sodium hydroxide solution. After heating at 50° for 30 min., the temperature was raised to 70° until the acetone had distilled, 500 ml. of water was added, and the reaction mixture maintained at 70° for 1 hr. After standing overnight the solution was separated from the salts by decantation and extracted with one 400 ml. and

(4) R. J. Dimler, H. A. Davis, and G. E. Hilbert, *J. Am. Chem. Soc.*, **68**, 1377 (1946).

(5) H. Ohle and K. Tessmar, *Ber.*, **71**, 1843 (1938).

(6) C. G. Anderson, W. Charlton, and W. N. Haworth, *J. Chem. Soc.*, 1329 (1929).

(7) Melting points are corrected unless otherwise indicated. Boiling points are uncorrected.

(8) L. von Vorgha, *Ber.*, **66**, 706 (1933).

(9) D. J. Bell, *J. Chem. Soc.*, 859 (1936).

(10) K. Freudenberg and G. Hüll, *Ber.*, **74**, 237 (1941).

two 300 ml. portions of chloroform. The combined extracts were concentrated to a sirup and distilled, b.p. 127–128°/0.008 mm. The product has recrystallized from ligroin to give 43 g. (40%) of plates, m.p. 80.8–81.3°; $[\alpha]_D^{20}$ −41.65° (c 10, U.S.P. $CHCl_3$).

Anal. Calcd. for $C_{18}H_{26}O_6$: C, 63.88; H, 7.74. Found: C, 64.15; H, 7.80.

*1,2-O-Isopropylidene-3,5-di-O-methyl-*D*-glucofuranose* (VII). A solution of 25 g. of VI in 50 ml. of ethyl acetate was treated with hydrogen in the presence of palladium charcoal catalyst. After filtering off the catalyst, the filtrate was concentrated to a sirup and distilled under reduced pressure, b.p. 89–90°/0.011 mm., to give a nearly quantitative yield of sirup which did not crystallize on standing for several months. It formed a crystalline *p*-phenylazobenzoate which was recrystallized from ligroin, m.p. 93.2–93.5°.

Anal. Calcd. for *p*-phenylazobenzoyl: 45.83. Found: 45.64.

*3,5-Di-O-methyl-*D*-glucofuranose* (VIII). A solution of 6.5 g. of VII in 70 ml. of acetone and 96 ml. of water containing 5 ml. of concentrated hydrochloric acid was refluxed for 2 hr. The solution was neutralized as in the preparation of V and concentrated under reduced pressure to yield 13 g. of a sirup $[\alpha]_D^{20}$ −20.1° (c 1.37, H_2O).

Anal. Calcd. for $C_8H_{16}O_6$: C, 46.15; H, 7.75. Found: C, 46.11; H, 7.74.

*2,3,5,6-Tetra-O-methyl-*D*-glucose.* A solution of 15 g. of VI in 150 ml. of methanol containing 0.5% hydrogen chloride was refluxed for 3 hr. The solution was neutralized with silver carbonate, treated with charcoal, and filtered. The filtrate was shaken for 15 hr. under a hydrogen atmosphere in the presence of a palladium charcoal catalyst. After filtering off the catalyst and concentrating the filtrate to a sirup the residue was methylated with 68 ml. of methyl sulfate and 114 g. of 50% sodium hydroxide. The product was extracted with 400 ml. of chloroform and the chloroform distilled. The residue was refluxed for 5 hr. in a solution of 70 ml. of acetone, 70 ml. of water, and 5 ml. of concentrated hydrochloric acid. The solution was neutralized with sodium bicarbonate, filtered, and evaporated under reduced pressure. The sirupy residue was extracted with ether and the extract concentrated under reduced pressure to a sirup. $[\alpha]_D^{20}$ −30.0° (c 1.06, U.S.P. $CHCl_3$).

The product, *2,3,5,6-tetra-O-methyl-*D*-glucose* was oxidized with bromine to the 2,3,5,6-tetra-*O*-methyl-D-gluconic acid from which the phenylhydrazide was prepared, m.p. 135–135.5° (lit.[7,11,12] 136°).

Anal. Calcd. for $C_{16}H_{28}O_3N_2$: N, 8.18. Found: N, 8.05.

*Methyl 2,3,5-tri-O-methyl-β-*D*-glucofuranoside* (IX). A solution of 30 g. of VI in 300 ml. of methanol containing 0.5% hydrogen chloride was refluxed for 3 hr. The solution was neutralized with silver carbonate, concentrated, and the crude product methylated with 100 ml. of methyl sulfate and 170 ml. of 50% sodium hydroxide as described in the preparation of VI except that the methylation was started at 10° and then raised to 50°. The sirup produced was distilled and the product (25 g.) dissolved in ethyl acetate and shaken in a hydrogen atmosphere with palladium charcoal for 15 hr. After filtration and concentration to a sirup the residue was distilled, b.p. 81–84°/0.01 mm. The product crystallized on standing and was recrystallized from ligroin, b.p. 60–70°, m.p. 74–75°: $[\alpha]_D^{20}$ −69.7° (c 1.8; H_2O).

Anal. Calcd. for $C_{10}H_{20}O_6$: C, 50.87; H, 8.47. Found: C, 50.81; H, 8.48.

*2,3,5-Tri-O-methyl-*D*-glucose* (X). A solution of IX in 60 ml. of water and 5 ml. of hydrochloric acid was refluxed for 5 hr. The solution was neutralized as described in the preparation of V and concentrated to a sirup. The product was a hydroscopic liquid $[\alpha]_D^{20}$ −13.4 (c 2.14, H_2O).

Anal. Calcd. for $C_9H_{18}O_6$: C, 48.67; H, 8.10. Found: C, 48.75; H, 8.04.

Compound X was oxidized as described by Smith[1] and the 2,3,5-tri-*O*-methyl-D-gluconic acid identified by the preparation of its phenylhydrazide, m.p. 156–156.5° (lit.,[1,2] 156°, 156–157°).

Anal. Calcd. for $C_{15}H_{24}O_6N_2$: N, 8.53. Found: N, 8.45.

DETROIT 2, MICH.

(11) W. N. Haworth and S. Peat, *J. Chem. Soc.*, 129, 3094 (1926).

(12) W. N. Haworth and C. W. Long, *J. Chem. Soc.*, 544 (1927).

(CONTRIBUTION FROM THE MERCK SHARP AND DOHME RESEARCH LABORATORIES)

Synthetic Antiviral Agents. I. 4-Arylmethyl-4-aryl-5-oxohexanoic Acids and Certain of Their Derivatives*,[1]

EDWARD J. CRAGOE, JR., AND A. M. PIETRUSZKIEWICZ

Received July 29, 1957

A number of 4-arylmethyl-4-aryl-5-oxohexanoic acids were prepared by the following series of reactions: Various arylacetones were condensed with certain arylmethyl halides to give the corresponding 3,4-diphenyl-2-butanones. Cyanoethylation produced the 4-arylmethyl-4-aryl-5-oxohexanenitriles which upon hydrolysis yielded the corresponding 4-arylmethyl-4-aryl-5-oxohexanoic acids.

Several of the 4-arylmethyl-4-aryl-5-oxohexanoic acids were resolved through the brucine salts. Derivatives of some of the hexanoic acids were prepared. Among the derivatives were esters, amides, and enol-lactones. Many of the compounds described have been found to have antiviral activity against certain influenza viruses.

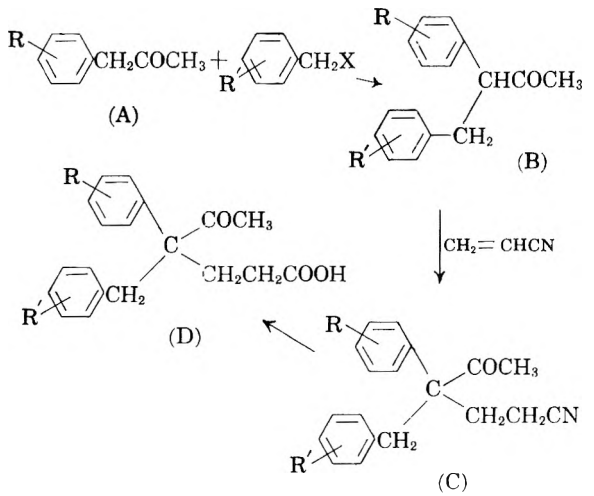
Interest in this group of compounds began with an observation by the virologists associated with this organization that 4,4-diphenyl-5-oxohexanoic acid markedly inhibited the multiplication of PR8 influenza virus in the allantoic cavity of the chicken embryo as measured by hemagglutinin production. This effect was also observed when the mouse served as the host and activity was measured by inhibition of lung lesions or by hemagglutinin formation. In the investigation that followed strong

* This paper is a contribution in honor of Lyndon F. Small, former Editor of the Journal.

(1) A portion of the material contained in this paper was presented by the authors at the First Regional Meeting of the Delaware Valley Sections of the AMERICAN CHEMICAL SOCIETY, Feb. 16, 1956.

antiviral activity was noted in certain 4-arylmethyl-4-aryl-5-oxohexanoic acids. Therefore a number of the members of this series of compounds and their derivatives were prepared for studying as antiviral agents.

The synthetic procedure consisted of the following four steps: Preparation of phenylacetones (A) which, in turn, were alkylated with certain arylmethyl halides to give substituted 3,4-diphenyl-2-butanones (B). Cyanoethylation produced 4-arylmethyl-4-aryl-5-oxohexanenitriles (C) which upon hydrolysis yielded the corresponding 4-arylmethyl-4-aryl-5-oxohexanoic acids (D). In some instances the racemic hexanoic acids were resolved in order to obtain one or both of the two antipodes.



This synthetic method is essentially that employed by Campbell and Fairfull[2] who prepared a few 4-alkyl-4-aryl-5-oxohexanoic acids. Similar methods were used by Schultz[3] of these laboratories to prepare 4,4-diphenyl-5-oxohexanoic acid and 4-benzyl-4-phenyl-5-oxohexanoic acid.

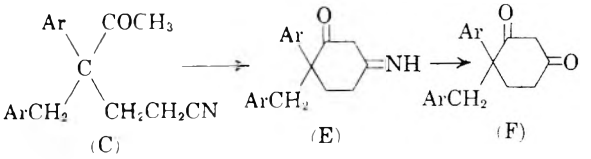
The substituted 3,4-diphenyl-2-butanones (B) were prepared by the reaction of a phenylacetone with an arylmethyl halide. It has been reported[4] that phenylacetone itself can be alkylated with certain alkyl halides using sodium hydroxide as a condensing agent. Corrigan[5] of these laboratories had found that the polymerization of phenylacetone and the hydrolysis of the alkyl halide contributed to a decreased yield when the reaction was carried out by adding the alkyl halide to a mixture of the ketone and sodium hydroxide. He had found that these side reactions could be avoided to a considerable extent by employing elevated temperatures and adding the phenylacetone and alkyl halide simultaneously to the alkali. When this technique was applied to the present study the yields were markedly higher. The yield of 4-(*o*-chlorophenyl)-3-phenyl-2-butanone resulting from phenylacetone and *o*-chlorobenzyl chloride was increased from 51% to 79%.

This alkylation is readily carried out using potassium *tert*-butoxide in *tert*-butyl alcohol as the condensing agent. Although few comparative data are available the yields appear to be a little higher when this agent is employed, especially if either reactant is sterically inhibited. The only specific example where a compound was prepared by both methods was in the synthesis of 4-(*o*-bromophenyl)-3-phenyl-2-butanone which was produced in 79% yield by the sodium hydroxide method and in 84% yield by the potassium *tert*-butoxide method. A summary of the preparations is presented in Table I.

Cyanoethylation of the ketones was carried out by the usual procedures outlined by Bruson.[6] Each of the cyanoethylations presented in Table II was carried out in *tert*-butyl alcohol at temperatures of 25° to 45° except for two reactions. Acetonitrile was employed as a solvent in these two instances. This solvent was used with 4-(2,6-dichlorophenyl)-3-phenyl-2-butanone since it will tolerate the elevated reaction temperature required to obtain the maximum yield. It was used with 4-(*m*-cyanophenyl)-3-phenyl-2-butanone in order to provide better solvent properties. The steric problems presented by 4-phenyl-3-(*o*-chlorophenyl)-2-butanone, 4-(2,6-dichlorophenyl)-3-phenyl-2-butanone, and 3,4-bis-(*o*-chlorophenyl)-2-butanone undoubtedly account for the lower yields obtained with these ketones.

The hydrolysis of the 4,4-disubstituted-5-oxohexanenitriles to the corresponding carboxylic acids was effected by refluxing a short time with a mixture of acetic acid, sulfuric acid, and water. This method appeared to be superior to the use of aqueous alkali which Campbell[2] employed. The yields are generally good as indicated in Table III.

By either hydrolysis method by-products were formed, although smaller quantities of these substances appeared to arise when the acid hydrolysis method was employed. The most troublesome by-products were the 4-arylmethyl-4-aryl-1,3-cyclohexanediones (F) and, in some cases, the intermediate 4-arylmethyl-4-aryl-3-oxocyclohexanimines (E). The strongly acidic nature and the solubility characteristics of the cyclohexanediones made them difficult to separate from the carboxylic acids. These by-products will be discussed in a later paper.



(2) N. Campbell and A. E. S. Fairfull, *J. Chem. Soc.*, 1239 (1949).

(3) E. M. Schultz, unpublished data.

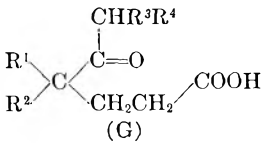
(4) E. M. Schultz, J. B. Bicking, S. Mickey, and F. S. Crossley, *J. Am. Chem. Soc.*, 75, 1072 (1953).

(5) J. R. Corrigan, unpublished data.

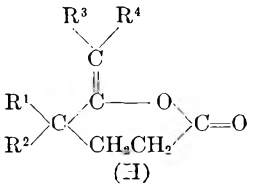
(6) H. A. Bruson, *Org. Reactions*, 5, 79 (1949).

Since each of the carboxylic acids prepared possesses an asymmetric carbon atom, the product that was isolated in each instance was the racemic modification. It was considered possible that the biological activity resided in one of the two antipodes. Therefore, one of the more active racemates, 4-(*o*-chlorobenzyl)-4-phenyl-5-oxohexanoic acid, was resolved so that the two pure antipodes might be studied biologically. The resolution was quite simple since the solubility of the brucine salt of the *levo* acid in methanol was considerably less than that of the *dextro* acid. It was found that the *levo* antipode possessed most, if not all of the antiviral activity as measured by most tests.

Two more resolutions were carried out. In each instance the *levo* form was the more readily isolated since it gave the less soluble brucine salt. Furthermore, this isomer was the more attractive biologically as deduced from the earlier experience. Therefore, only with the *levo* form was an effort made to obtain high optical purity. With one compound no attempt was made to isolate the *dextro* isomer and with the other compound no attempt was made to purify the crude *dextro* isomer. A summary of data concerning the resolutions appears in Table IV.



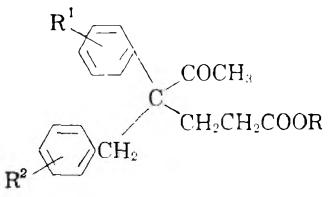
(G)



(H)

Vorlander and Knotzsch[7] reported that 5-oxohexanoic acid (G, where R^1, R^2, R^3, and R^4 = H) was converted to the corresponding enol-lactone (H) by boiling acetic anhydride. However, Campbell and Fairfull[2] found that 4-ethyl-4-phenyl-5-oxohexanoic acid (G, where R^1 = ethyl, R^2 = phenyl, and R^3 = R^4 = H) was unaltered by boiling acetic anhydride. The latter authors also found that 4-phenyl-6-methyl-5-oxoheptanoic acid (G, where R^1 = phenyl, R^2 = H, and R^3 = R^4 = methyl) was unchanged either by boiling acetic anhydride or by heating with a mixture of sirupy phosphoric acid and phosphorus pentoxide.

In the present work it was found that the 4-arylmethyl-4-aryl-5-oxohexanoic acids were also unaltered by the action of boiling acetic anhydride. However, it was found that isopropenyl acetate[8] produced the enol-lactones (H) in good yields. Both the DL and *levo*-4-(*o*-chlorobenzyl)-4-phenyl-5-hydroxy-5-hexenoic acid lactones were prepared by this method. These enol-lactones served as useful intermediates for the preparation of derivatives of the acids. They are particularly advantageous in obtaining the more complex or difficultly accessible esters and amides.



I

Esters of type *I* are readily produced from the corresponding acid (D) when R is derived from a simple alcohol. Refluxing 4-benzyl-4-phenyl-5-oxohexanoic acid or *levo*-4-(*o*-chlorobenzyl)-4-phenyl-5-oxohexanoic acid with methanol and a little concd. sulfuric acid produced the corresponding methyl esters in excellent yields. More complex esters, such as 2-dimethylaminoethyl 4-(*o*-chlorobenzyl)-4-phenyl-5-oxohexanoate or the corresponding *levo* isomer, were prepared by the interaction of the required enol-lactone (H) with 2-dimethylaminoethanol.

levo-4-(*o*-Chlorobenzyl)-4-phenyl-5-oxohexanamide was prepared by the action of ammonia on either *levo*-methyl 4-(*o*-chlorobenzyl)-4-phenyl-5-oxohexanoate or *levo*-4-(*o*-chlorobenzyl)-4-phenyl-5-hydroxy-5-hexenoic acid lactone. Only the synthesis by the former method is described in the Experimental section although the two methods appear to be equally acceptable.

Like many other methyl ketones the 4-arylmethyl-4-aryl-5-oxohexanoic acids will react under the conditions of the Mannich reaction to produce the expected product. Thus 4-(*o*-chlorobenzyl)-4-phenyl-5-oxo-7-dimethylaminoheptanoic acid was prepared from dimethylamine, paraformaldehyde, and the appropriate 5-oxohexanoic acid.

Because of its structural relationship to the series of compounds under study, 4-(*m*-carboxyphenyl)-3-phenyl-2-butanone was prepared for comparison of the biological activity; its preparation is described in the Experimental.

Many of the 4-benzyl-4-phenyl-5-oxohexanoic acids and their derivatives were found to have antiviral activity against the influenza virus. This effect has been noted in several hosts as measured by several criteria. One compound, *levo*-4-(*o*-chlorobenzyl)-4-phenyl-5-oxohexanoic acid has been assigned the generic name caprochlorone. This compound has received a considerable amount of detailed study as an antiviral agent, some of which has already been reported by Liu and his colleagues.[9,10] The nature of the substituents on the

(7) D. Vorlander and A. Knotzsch, *Ann.*, **294**, 317 (1897).

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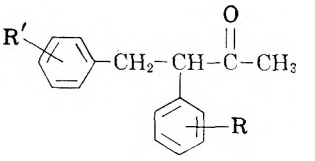
(10) O. C. Liu, R. G. Malsberger, J. L. Carter, A. N. DeSanctis, F. P. Wiener, B. Hampil, *Bacteriological Proceedings of the Society of American Bacteriologists*, Houston, Tex., page 69, M19 (1956).

TABLE I

PREPARATION OF 3,4-DIPHENYL-2-BUTANONES



R	R′	% Yield	Condensing Agent	B.P. °C./Mm. or M.P. (°C.)	Calcd. for	Analysis C Calcd.	C Found	H Calcd.	H Found	Halogen Calcd.	Halogen Found
H	H	62	NaOH	122–124/0.3 25.5–28.5	$C_{16}H_{16}O$[a]						
H	2-F	82[b]	Potassium *tert*-butoxide	145–149/0.25 28–28.5	$C_{16}H_{15}FO$	79.31	79.10	6.24	6.15	...	...
H	2-Cl	79[c]	NaOH	153–159/2.3	$C_{16}H_{15}ClO$	74.27	74.47	5.84	5.72	13.70	13.44
H	3-Cl	75[d]	Potassium *tert*-butoxide	157–160/0.2	$C_{16}H_{15}ClO$	74.27	74.27	5.84	5.99	...	...
H	4-Cl	46	NaOH	160–165/0.2 79–80[e]	$C_{16}H_{15}ClO$	74.27	74.39	5.84	5.71	13.70	13.48
H	2,4-Cl_2	48	NaOH	155–162/0.2 69–70[f]	$C_{16}H_{14}Cl_2O$	65.54	65.41	4.81	4.79	24.19	24.02
H	3,4-Cl_2	65[g]	NaOH	178–182/0.1	$C_{16}H_{14}Cl_2O$	65.54	65.52	4.81	4.88	24.19	23.99
H	2,6-Cl_2	82	Potassium *tert*-butoxide	160–165/0.1 68–70[h]	$C_{16}H_{14}Cl_2O$	65.54	65.50	4.81	4.98	24.19	24.12
H	2-Br	84[i]	Potassium *tert*-butoxide	166–170/0.1	$C_{16}H_{15}BrO$	63.38	63.27	4.99	4.99	26.36	26.39
		79	NaOH								
H	2-CH_3	63	NaOH	142–146/0.15	$C_{17}H_{18}O$	85.67	85.54	7.61	7.64	...	...
H	3-CH_3	59[j]	NaOH	132–136/0.2	$C_{17}H_{18}O$	85.67	85.58	7.61	7.55	...	...
H	2-CH_3O	77[k]	Potassium *tert*-butoxide	150–154/0.2	$C_{17}H_{18}O_2$	80.28	79.92	7.13	7.12	...	...
H	3-CN	82	Potassium *tert*-butoxide	180–186/0.2 67–69[l]	$C_{17}H_{15}NO$	81.90	81.72	6.06	6.05[m]	...	...
2-Cl	H	93[n]	Potassium *tert*-butoxide	150–155/0.3	$C_{16}H_{15}ClO$	74.27	74.10	5.84	6.05	13.70	13.64
2-Cl	2-Cl	78[o]	Potassium *tert*-butoxide	161–165/0.1	$C_{16}H_{14}Cl_2O$	65.54	65.59	4.81	4.98	24.19	24.00

[a] Reported by Schultz *et al.*[3] [b] n_D^{25} 1.5455. [c] n_D^{25} 1.5678. [d] n_D^{25} 1.5679. [e] Recrystallized from hexane then ethanol. [f] Recrystallized from ethanol. [g] n_D^{25} 1.5779. [h] Recrystallized from hexane. [i] n_D^{25} 1.5839. [j] n_D^{25} 1.5555. [k] n_D^{25} 1.5657. [l] Recrystallized from methanol. [m] Calcd. for N: 5.62; found: 5.60. [n] n_D^{25} 1.5682. [o] n_D^{25} 1.5762.

benzyl, phenyl, or carboxyl groups greatly influences the antiviral activity of the compound. A paper dealing with the relationship of the structure to the activity of these compounds is planned for the future.

EXPERIMENTAL[11]

A. Preparation of intermediates: o-Methoxybenzyl alcohol, n_D^{25} 1.5428, was prepared in 59% yield by the catalytic hydrogenation of *o*-methoxybenzaldehyde using Adams catalyst according to a procedure similar to that employed by Carothers[12] for the synthesis of the *p*-isomer. *o-Methoxybenzyl chloride*, b.p. 110–114°/14 mm., was prepared in 57% yield by the action of hydrogen chloride on *o*-methoxybenzyl alcohol.[13] *o-Fluorobenzyl chloride*, b.p. 172–175°/760 mm. n_D^{25} 1.5148, was prepared in 73% yield by the chlorination of *o*-fluorotoluene.[14] *m-Chlorobenzyl chloride*, b.p. 219–222°, n_D^{25} 1.5556, was prepared in 37% yield by chlorination of *m*-chlorotoluene.[15] *m-Cyanobenzyl bromide*, m.p. 92.5–93.5°, was prepared in 35% yield by the bromination of *m*-tolunitrile.[16] *2,6-Dichlorobenzyl chloride*, b.p. 117–119°/14 mm., was prepared in 73% yield by the chlorination of 2,6-dichlorotoluene.[17] *o-Bromobenzyl bromide*, b.p. 129–130°/16 mm., was prepared in 73% yield by the bromination of *o*-bromotoluene.[18] *1-(o-Chlorophenyl)-2-nitro-1-propene*, m.p. 38–41°, was prepared in 62% yield by the method of Schales.[19] *1-(o-Chlorophenyl)-2-propanone*, b.p. 94–97°/2 mm., n_D^{25} 1.5340, was prepared by the iron and hydrochloric acid reduction of 1-(*o*-chlorophenyl)-2-nitro-1-propene. Johns and Burch[20] had previously prepared it by another method. The

(11) All melting and boiling points recorded are uncorrected values unless otherwise specified. Analytical data and specific rotations were supplied by K. B. Streeter and his staff.

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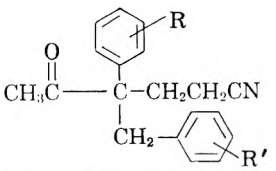
TABLE II

4-ARYLMETHYL-4-ARYL-5-OXOHEXANENITRILES



R	R′	Yield, %	Product B.P. °C./Mm. or M.P., °C.	Recryst. Solvent	Reaction[a] Temp., °C.	Calcd. for	Analysis: Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
H	H	95	127.5–129	Ethyl alcohol	25	$C_{19}H_{19}ON$[b]						
H	2-F	95	123.5–125.5	*n*-Propyl alcohol	40	$C_{19}H_{18}FNO$	77.26	77.28	6.14	6.07	4.74	4.72
H	2-Cl	92	106–108	Isopropyl alcohol	25	$C_{19}H_{18}ClNO$	73.19	73.10	5.82	5.77	4.49	4.47
H	3-Cl	81	220–225/0.4 53.5–55.5[c]	...	40	$C_{19}H_{18}ClNO$	73.19	73.09	5.82	5.70	4.49	4.50
H	4-Cl	80	197–203/0.2 86–88	Isopropyl alcohol	40	$C_{19}H_{18}ClNO$	73.19	73.19	5.82	5.90	4.49	4.47
H	2,4-Cl_2	79	215–220/0.5 89–91	Isopropyl alcohol	25	$C_{19}H_{17}Cl_2NO$	65.90	65.95	4.95	4.91	4.05	4.02
H	3,4-Cl_2	87	105–107	Isopropyl alcohol	40	$C_{19}H_{17}Cl_2NO$	65.90	66.15	4.95	4.77	4.05	4.03
H	2,6-Cl_2	31	205–212/0.4 97.5–99.5	Isopropyl alcohol	82[d]	$C_{19}H_{17}Cl_2NO$	65.90	65.76	4.95	5.09	4.05	4.05
H	2-Br	85	114–115	Isopropyl alcohol	45	$C_{19}H_{18}BrNO$	64.05	64.16	5.09	5.11	3.93	3.92
H	2-CH_3	89	88–90	Isopropyl alcohol	40	$C_{20}H_{21}NO$	82.44	82.39	7.26	7.48	4.81	4.81
H	3-CH_3	87	94.5–96	Isopropyl alcohol	40	$C_{20}H_{21}NO$	82.44	82.42	7.26	7.22	4.81	4.81
H	2-CH_3O	83	110–111	Isopropyl alcohol	42	$C_{20}H_{21}NO_2$	78.14	78.30	6.89	6.90	4.56	4.56
H	3-CN	83	227–235/0.05 86–88	Ethanol	40[d]	$C_{20}H_{18}N_2O$	79.44	79.46	6.00	6.19	9.27	9.23
2-Cl	H	30	200–212/0.2 124–126	Isopropyl alcohol	45	$C_{19}H_{18}ClNO$	73.19	73.15	5.82	5.56	4.49	4.50
2-Cl	2-Cl	16	195–200/0.1	...	45	$C_{19}H_{17}Cl_2NO$	65.90	66.03	4.95	4.82	4.05	4.05

[a] All reactions carried out in *tert*-butyl alcohol unless otherwise specified. [b] Compound reported by Schultz.[3] [c] M.p. of the product which solidified after distillation. No attempt was made to recrystallize it. [d] Acetonitrile was used as a reaction solvent.

remaining intermediates were either made by well described methods or they were commercially available.

B. Preparation of 3,4-diphenyl-2-butanones. These ketones were prepared by condensing an arylacetone with an arylmethyl halide using either sodium hydroxide or potassium *tert*-butoxide as a condensing agent. An example of each method is presented. A summary of each of the syntheses appears in Table I.

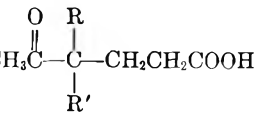
4-(o-Chlorophenyl)-3-phenyl-2-butanone. Flake sodium hydroxide (Bakers purified) (89 g., *ca.* 2 moles) was placed in a 1-liter 4-necked, round-bottomed flask equipped with a mechanical stirrer, dropping funnel, thermometer, and reflux condenser protected from moisture with a drying tube. Phenylacetone (Mathesons' practical grade) (201.5 g., 1.5 moles) and *o*-chlorobenzyl chloride (Eastman Kodak) (282 g., 1.75 moles) were thoroughly mixed and approximately 100 ml. of the mixture added to the reaction vessel with vigorous stirring. The reaction mixture was heated on a steam bath to 70° and the remaining ketone-halide mixture added dropwise at a rapid rate while no heat was applied. The temperature rose to 90–95° and then remained constant for about 15 min. After this time it was necessary to heat the mixture with a steam bath to maintain a temperature of 90–100°. The total addition time was 35 min.

After the addition was complete, the mixture was stirred and heated on the steam bath for a total of 9 hr. The mixture was then cooled and treated with water (200 ml.) and benzene (200 ml.). Concd. hydrochloric acid (50 ml.) was added to acidify the mixture. The mixture was shaken and the layers separated. The aqueous layer was washed with benzene (50 ml.). The combined organic layers were dried over anhydrous sodium sulfate. Fractional distillation gave 308 g. (79%) of material boiling at 145–150° at 1.5 mm. Refractionation gave a 90–93% recovery of material boiling at 155–159° at 2.3 mm.

4-(o-Bromophenyl)-3-phenyl-2-butanone. Potassium (31.6 g., 0.81 mole) was added to sodium-dried *tert*-butyl alcohol (700 ml.) in a 2-liter 4-necked, round-bottomed flask fitted with a mechanically driven Hershberg stirrer, dropping funnel, thermometer, and reflux condenser protected with a soda-lime drying tube. The potassium was dissolved rapidly by heating the solvent until the potassium melted and then violently agitating the mixture. After cooling, phenylacetone (108.8 g., 0.86 mole) was added within a period of a few minutes. *o*-Bromobenzyl bromide (214.5 g., 0.81 mole) was dissolved in dry benzene (100 ml.) and the solution added dropwise with stirring over 40 min. while the temperature was maintained at 35–40° by cooling when necessary. The

TABLE III

4-ARYLMETHYL-4-ARYL-5-OXOHEXANOIC ACIDS



R	R'	Yield, %	M.P., °C.	Calcd. for	Analysis					
					Carbon		Hydrogen		Halogen	
					Calcd.	Found	Calcd.	Found	Calcd.	Found
Phenyl	Benzyl[a]	87[b]	143–144.5	$C_{19}H_{20}O_3$						
Phenyl	*o*-Fluorobenzyl	96[c]	165–167	$C_{19}H_{19}FO_3$	72.59	72.45	6.09	5.80	...	...
Phenyl	*o*-Chlorobenzyl	97[d]	132–134	$C_{19}H_{19}ClO_3$	68.98	69.20	5.79	5.64	10.72	10.23
Phenyl	*m*-Chlorobenzyl	97[c]	119–121	$C_{19}H_{19}ClO_3$	68.98	69.29	5.79	5.51	10.72	10.76
Phenyl	*p*-Chlorobenzyl	96[c]	131–132.5	$C_{19}H_{19}ClO_3$	68.98	69.14	5.79	5.51	10.72	10.48
Phenyl	2,4-Dichlorobenzyl	94[e]	147–148.5	$C_{19}H_{18}Cl_2O_3$	62.48	62.80	4.97	4.87	19.42	19.33
Phenyl	3,4-Dichlorobenzyl	94[f]	117.5–119	$C_{19}H_{18}Cl_2O_3$	62.48	62.72	4.97	4.99	19.42	19.27
Phenyl	2,6-Dichlorobenzyl	91[g]	164.5–166	$C_{19}H_{18}Cl_2O_3$	62.48	62.69	4.97	5.24	19.42	19.43
Phenyl	*o*-Bromobenzyl	96[c]	122–123.5	$C_{19}H_{19}BrO_3$	60.81	60.89	5.10	5.04	21.30	21.15
Phenyl	*o*-Methylbenzyl	77[h]	115–117	$C_{20}H_{22}O_3$	77.39	77.88	7.14	7.05	...	...
Phenyl	*m*-Methylbenzyl	81[i]	122.5–124	$C_{20}H_{22}O_3$	77.39	77.61	7.14	7.26	...	...
Phenyl	*o*-Methoxybenzyl	74[j]	110–113	$C_{20}H_{22}O_4$	73.60	73.91	6.79	6.58	...	...
Phenyl	*m*-Carboxybenzyl[k]	95[l]	239–241	$C_{20}H_{20}O_5$	70.57	70.55	5.92	6.13	...	...
o-Chlorophenyl	Benzyl	69[c]	185–187	$C_{19}H_{19}ClO_3$	68.98	68.92	5.79	5.57	10.72	10.76
o-Chlorophenyl	*o*-Chlorobenzyl	82[c]	179.5–181.5	$C_{19}H_{18}Cl_2O_3$	62.48	62.42	4.97	4.95	19.42	19.33

[a] Prepared by E. M. Schultz[3] by alkaline hydrolysis of the nitrile. [b] Recrystallized from isopropyl alcohol. [c] Recrystallized from acetonitrile. [d] Recrystallized from acetic acid–water then acetonitrile. [e] Recrystallized from acetonitrile then toluene. [f] Recrystallized from cyclohexane then carbon tetrachloride. [g] Recrystallized from toluene, acetic acid, then ethyl acetate. [h] Recrystallized from benzene-hexane then acetic acid–water. [i] Recrystallized from cyclohexane then ethyl acetate–cyclohexane. [j] Recrystallized from benzene-hexane, toluene-heptane, then acetic acid–water. [k] Prepared by the hydrolysis of 4-phenyl-4-(*m*-cyanophenyl)-5-oxohexanenitrile. [l] Recrystallized from acetic acid then *n*-butyl alcohol.

reaction mixture was stirred for an additional 10 min. and then refluxed for 2 hr.

The solvents were distilled off at reduced pressure and the residue treated with benzene (200 ml.) and water (200 ml.). The two layers were separated and the aqueous layer extracted with benzene (50 ml.). The combined organic layers were dried over anhydrous sodium sulfate and the solvent distilled. Fractional distillation of the residue at reduced pressure gave 205 g. (84%) of product, b.p. 164–170° at 0.1 mm. Refractionation gave material b.p. 166–170° at 0.1 mm.

C. Preparation of 4-arylmethyl-4-aryl-5-oxohexanenitriles. The nitriles of this type were prepared by cyanoethylation of the corresponding 3,4-diphenyl-2-butanones. A typical example follows and a summary of all the preparations appears in Table II.

4-(o-Chlorobenzyl)-4-phenyl-5-oxohexanenitrile. 4-(*o*-Chlorophenyl)-3-phenyl-2-butanone (456 g., 1.76 moles) was dissolved in *tert*-butyl alcohol (Eastman Kodak) (1200 ml.) in a flask fitted with a mechanical stirrer and dropping funnel. A solution of 40% aqueous benzyltrimethylammonium hydroxide (Eastman) (20 ml.) was added to the solution and acrylonitrile (Eastman) (112 g., 2.12 moles) added dropwise with stirring. The solution was externally cooled so that the temperature remained below 30°.

After the addition was complete stirring was continued at room temperature for 2 hr. and then for 1 hr. at 38–45°. A check was made at periodic intervals to be sure the solution remained alkaline throughout the reaction. (If a neutral or weakly alkaline reaction was observed, more catalyst was added.) The solution was neutralized with sulfuric acid and the solid which had separated during the reaction was removed by filtration. The dry product weighed 491 g. (90%), m.p. 103–106°. Recrystallization from isopropyl alcohol (1500 ml.) gave 467 g., m.p. 104.5–107°. A second recrystallization gave material melting at 106–108°.

D. Preparation of 4-arylmethyl-4-aryl-5-oxohexanoic acids. These compounds were all prepared by hydrolysis of the corresponding nitriles. Essentially the same procedure was employed in all instances. An example is described in detail and Table III summarizes all of the syntheses which were carried out.

Four of the acids were resolved. Again similar procedures were used in each instance. An example of the resolution procedure is presented along with a summary (Table IV) of all of the preparations.

DL-*4-(o-Chlorobenzyl)-4-phenyl-5-oxohexanoic acid.* 4-(*o*-Chlorobenzyl)-4-phenyl-5-oxohexanenitrile (412.5 g., 1.32 moles) was suspended in a mixture of concd. sulfuric acid (450 ml.), glacial acetic acid (2 liters), and water (600 ml.). Upon heating to boiling the solid dissolved. The mixture was refluxed for 1.25 hr.

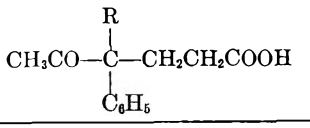
After this time a sample of the reaction mixture was completely soluble when made alkaline with sodium hydroxide. The mixture was poured, with stirring, into cold water (8 l.). An oil separated which solidified upon stirring. The solid was separated by filtration, washed with water, dried, and pulverized. The yield was 415 g. (97%), m. p. 106–125°. Material at this stage may contain as much as 10% 4-(*o*-chlorobenzyl)-4-phenyl-1,3-cyclohexanedione. One recrystallization from acetonitrile (830 ml.) gave 354 g., m.p. 124–130°. Several more recrystallizations from acetic acid–water and/or acetonitrile gave material melting at 132–134°.

levo-4-(o-Chlorobenzyl)-4-phenyl-5-oxohexanoic acid. A mixture of DL-4-(*o*-chlorobenzyl)-4-phenyl-5-oxohexanoic acid (354.4 g., 1.07 moles) and brucine (422.6 g., 1.07 moles) were dissolved in boiling methanol (975 ml.). The solution was cooled and seeded with a few crystals of the product. After 24 hr. at room temperature followed by 24 hr. at 5° the white solid that separated was removed by filtration and dried. The yield was 351 g. (91% of one antipode), m.p. 97–101°. (The mother liquors were saved for recovery of the *dextro* antipode.)

One recrystallization from methanol gave 300 g., m.p. 100–102°. A second recrystallization gave 289 g. (74%), m.p. 100–102°. Analysis of the brucine salt indicated it to be

TABLE IV

RESOLUTION OF 4-ARYLMETHYL-4-ARYL-5-OXOHEXANOIC ACIDS



R	Yield, %[a]	M.P.	Antipode	Specific Rotation[b]	Calcd. for	Analysis: Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
o-Fluorobenzyl[c]	58	121–121.5	levo[d]	−137.6[e]	$C_{19}H_{19}FO_3$	72.59	72.26	6.09	6.05
o-Chlorobenzyl[f]	70	110–111	levo	−143.1	$C_{19}H_{19}ClO_3$	68.98	69.04	5.79	5.75
o-Chlorobenzyl[g]	63	109–110	dextro	+142.0	$C_{19}H_{19}ClO_3$	68.98	69.11	5.79	6.04
o-Bromobenzyl[h]	57	85.5–87.5	levo	−118.5	$C_{19}H_{19}BrO_3$	60.81	60.96	5.10	5.40
o-Bromobenzyl[i]	50	77–84	dextro	+106.6	$C_{19}H_{19}BrO_3$	...	...	..	..

[a] Calculated on the basis that 100% is the theoretical yield for each antipode. [b] Specific rotation of a 2% solution in 95% ethanol at 25°. [c] The brucine salt was recrystallized from an isopropyl alcohol–water mixture and the free acid from cyclohexane. [d] No attempt was made to isolate or purify the dextro antipode. [e] A 3% solution was used in this case. [f] The brucine salt was recrystallized from methanol; the free acid from heptane. [g] Recrystallized from acetonitrile then from heptane. [h] The brucine salt was recrystallized from methanol; the free acid was recrystallized from cyclohexane. [i] No attempt was made to obtain this antipode in pure form.

solvated. Adjusting for solvation by calculation, the specific rotation of the brucine salt is −87.9° for a 2% solution in 95% ethanol at 25°.

The *levo*-acid-brucine salt was treated with dilute hydrochloric acid (1500 ml., 1*N* concn.) and then extracted twice with benzene (500 ml. portions). The combined benzene extracts were dried over sodium sulfate and the solvent removed by distillation at reduced pressure. The yield of dry solid residue was 120 g. (70%), m.p. 106–109°. Recrystallization from heptane gave 118.5 g., m.p. 109–110°. Several more recrystallizations from either acetic acid–water or heptane gave material melting at 110–111°, $[\alpha]_D^{25}$ −143.1° for a 2% solution in 95% ethanol.

dextro-4-(o-Chlorobenzyl)-4-phenyl-5-oxohexanoic acid. The mother liquors from the initial crystallization of the *levo*-acid-brucine salt were evaporated to dryness to give a viscous liquid residue. This crude brucine salt was treated by a procedure similar to that described for the *levo*-acid-brucine salt. The crude *dextro*-acid generated in this manner was dissolved in a small volume of acetonitrile (about 1 ml. per g.) and the solution refrigerated. The material which separated was the racemic acid (*ca.* 15%). Evaporation of the solvent gave the *dextro*-acid (63%), m.p. 97–101°. Recrystallization, first from a small volume of acetonitrile, then several times from heptane gave material melting at 109–110°, $[\alpha]_D^{25}$ +142° for a 2% solution in 95% ethanol.

Preparation of derivatives of 4-arylmethyl-4-aryl-5-oxohexanoic acids. Methyl 4-benzyl-4-phenyl-5-oxohexanoate. A mixture of 4-benzyl-4-phenyl-5-oxohexanoic acid (50 g., 0.169 mole), absolute methanol (200 ml.) and concd. sulfuric acid (14 ml.) was refluxed under anhydrous conditions for 7.5 hr. The mixture was poured into ice water. An oil separated which soon solidified. The solid was dissolved in ether and the solution washed with water, then with aqueous sodium bicarbonate and finally with water. After drying over sodium sulfate the solvent was removed by evaporation. The residue consisted of 52 g. (99%) of white crystalline solid, m.p. 89–90°. The ester obtained by this method is quite pure and does not require further purification.[21]

levo-Methyl 4-(o-chlorobenzyl)-4-phenyl-5-oxohexanoate. levo-4-(*o*-Chlorobenzyl)-4-phenyl-5-oxohexanoic acid (100 g., 0.3 mole) was dissolved in a mixture of absolute methanol (400 ml.) and concd. sulfuric acid (16 ml.) and the mixture refluxed for 7 hr. The mixture was concentrated to 200 ml. at reduced pressure then poured into water (350 ml.) and extracted four times with toluene (350 ml. total).

The combined toluene extracts were washed with water (50 ml.), then with saturated sodium bicarbonate (50 ml.) and finally with water (25 ml.). After drying over sodium sulfate the solvent was removed by distillation and the residue fractionally distilled *in vacuo*. A total of 90.4 g. (87%) was collected, b.p. 187–192°/0.2 mm. Refractionation gave material boiling at 194–199°/0.2 mm., n_D^{25} 1.5621. The $[\alpha]_D^{25}$ of a 4% solution in 95% ethanol was −117.6°.

Anal. Calcd. for $C_{20}H_{21}ClO_3$: C, 69.66; H, 6.14; Cl, 10.28. Found: C, 69.78; H, 6.14; Cl, 10.18.

4-(o-Chlorobenzyl)-4-phenyl-5-hydroxy-5-hexenoic acid lactone. 4-(*o*-Chlorobenzyl)-4-phenyl-5-oxohexanoic acid (82.7 g., 0.25 mole), isopropenyl acetate (75.1 g., 0.75 mole) and concd. sulfuric acid (3 drops) were placed in a flask equipped with an 18 in. fractionating column attached to a downward condenser. The mixture was heated with an electric heating mantle so that a slow distillation occurred. About 40 ml. of material (mostly acetone) boiling at 55–59° was collected in 2.5 hr.

The residue was transferred to a Claisen flask and fractionally distilled *in vacuo*. A total of 66 g. (85% of material, b.p. 196–204° at 0.1 mm., m.p. 126–132°, was obtained. Recrystallization first from toluene, then from cyclohexane gave material melting at 134.5–136°.

Anal. Calcd. for $C_{19}H_{17}ClO_2$: C, 72.96; H, 5.48. Found: C, 72.78; H, 5.47.

levo-4-(o-Chlorobenzyl)-4-phenyl-5-hydroxy-5-hexenoic acid lactone. levo-4-(*o*-Chlorobenzyl)-4-phenyl-5-oxohexanoic acid (125 g., 0.378 mole) was dissolved in isopropenyl acetate (151 g., 1.5 moles) and concd. sulfuric acid (5 drops) was added. The mixture was heated as described for the racemic material for 7 hr. The volatile components were distilled off at reduced pressure and the residue was treated with hexane to give 84 g., of white solid, m.p. 100–106°. Recrystallization from heptane gave 62.2 g., m.p. 112–113°. The combined mother liquors from the two recrystallizations were evaporated to dryness and the residue was fractionally distilled *in vacuo* to give 42.6 g., b.p. 205–215°/0.2 mm. This material was treated with isopropenyl acetate (60 g., 0.6 mole) and concd. sulfuric acid (3 drops). The mixture was heated as before for 4 hr. Fractional distillation of the product gave 40.6 g., b.p. 200–210°/0.2 mm., m.p. 106–110°. Recrystallization from heptane gave 33.5 g., m.p. 111.5–113°.

The total yield was 95.7 g. (81%). A final recrystallization from heptane gave material melting at 113–113.5°. The $[\alpha]_D^{25}$ for a 3% solution in dry toluene was −382.2°.

Anal. Calcd. for $C_{19}H_{17}ClO_2$: C, 72.96; H, 5.48. Found: C, 72.96; H, 5.36.

(21) E. M. Schultz[3] reported a melting point of 88.5–90°.

2-Dimethylaminoethyl 4-(o-chlorobenzyl)-4-phenyl-5-oxohexanoate hydrobromide. 4-(o-Chlorobenzyl)-4-phenyl-5-hydroxy-5-hexenoic acid lactone (36.1 g., 0.115 mole) was dissolved in dry 2-dimethylaminoethanol (89 g., 1 mole) and the mixture was heated at 95° under anhydrous conditions. After a few minutes at this temperature the mixture was refluxed for 2 hr. The excess amine was removed by distillation at reduced pressure and the residue was dissolved in benzene (250 ml.).

The solution was washed with water twice and then dried over sodium sulfate. The benzene was removed by distillation and the residue dissolved in cyclohexane (150 ml.) and dry hydrogen bromide was introduced into the solution until precipitation no longer occurred. Addition of benzene (50 ml.) caused the conversion of the gummy product to a white solid, 48.2 g. (87%), m.p. 144–148°. Two recrystallizations from isopropyl alcohol gave 41.7 g., m.p. 149–151°.

Anal. Calcd. for $C_{23}H_{29}BrClNO_3$: C, 57.20; H, 6.05; N, 2.90; Br, 16.55. Found: C, 56.95; H, 6.35; N, 2.90; Br, 16.59.

levo-2-Dimethylaminoethyl 4-(o-chlorobenzyl)-4-phenyl-5-oxohexanoate hydrobromide. levo-4-(o-Chlorobenzyl)-4-phenyl-5-oxohexanoic acid lactone (37.5 g., 0.12 mole) and freshly distilled dry 2-dimethylaminoethanol (107 g., 1.2 moles) were refluxed for 2 hr. and the product isolated as described for the racemic modification. The free base was dissolved in isopropyl alcohol and treated with hydrogen bromide gas to give 52.6 g. (90%) of the hydrobromide salt. Two recrystallizations from isopropyl alcohol gave 46.5 g. of pure material, m.p. 149.5–151.5°. The $[\alpha]_D^{26}$ of a 1% water solution was −37.7°.

Anal. Calcd. for $C_{23}H_{29}BrClNO_3$: C, 57.20; H, 6.05; N, 2.90; Br, 16.55. Found: C, 57.65; H, 5.98; N, 2.86; Br, 16.49.

4-(o-Chlorobenzyl)-4-phenyl-5-oxo-7-dimethylaminoheptanoic acid hydrochloride. 4-(o-Chlorobenzyl)-4-phenyl-5-oxohexanoic acid (66.2 g., 0.2 mole), dimethylamine hydrochloride (16.3 g., 0.2 mole), and paraformaldehyde (6.6 g., 0.22 mole) were intimately mixed and placed in a one-liter flask fitted with a Claisen head and receiver. The system was evacuated by means of a water aspirator and the mixture heated at 140° using a metal bath.

The solids melted and vigorous bubbling occurred for a few minutes. After heating at 135–145° for 30 min. the mixture was cooled and the resulting sirup was digested with butanone. After cooling the solid that had formed was removed by filtration and dried. The yield was 48.6 g. (57%), m.p. 123–139°. Two recrystallizations from isopropyl alcohol gave 29.2 g. of pure material, m.p. 165–167°.

Anal. Calcd. for $C_{22}H_{27}Cl_2NO_3$: C, 62.26; H, 6.41; N, 3.30; Cl, 16.69. Found: C, 62.73; H, 6.17; N, 3.25; Cl, 16.93.

levo-4-(o-Chlorobenzyl)-4-phenyl-5-oxohexanamide. Ammonia gas (31 g., 1.8 moles) was dissolved in 2-methoxyethanol (200 ml.) at −40°. *levo*-Methyl 4-(o-chlorobenzyl)-4-phenyl-5-oxohexanoate (25 g., 0.073 mole) was dissolved in 2-methoxyethanol (50 ml.) and the solution cooled to −40°. The two solutions were united in an autoclave and heated at 100° for 4 hr. After standing at room temperature for 48 hr. the solvent was removed by distillation at reduced pressure.

The residue was dissolved in benzene (150 ml.) and washed with saturated sodium bicarbonate solution (25 ml.) and then with water (25 ml.). The benzene solution was dried over sodium sulfate and the solvent was removed by distillation. Treatment of the residue with a mixture of benzene and hexane gave a solid. The yield was 14.7 g. (64%), m.p. 58–69°. After one recrystallization from a mixture of benzene and hexane and two recrystallizations from benzene, 8.1 g. remained, m.p. 81–83°.

Anal. Calcd. for $C_{19}H_{20}ClNO_2$: C, 69.19; H, 6.11; N, 4.25; Cl, 10.75. Found: C, 69.97; H, 6.22; N, 4.16; Cl, 10.38.

4-(m-Carboxyphenyl)-3-phenyl-2-butanone. 4-(m-Cyanophenyl-3-phenyl-2-butanone (25 g., 0.1 mole) was suspended in a mixture of glacial acetic acid (150 ml.), water (70 ml.), and concd. sulfuric acid (50 ml.). The mixture was refluxed for 2 hr. and then cooled and poured into water (2 l.). The oil that separated was extracted with ethyl acetate. The ethyl acetate extract was evaporated to dryness and the residue treated with an excess of aqueous potassium hydroxide solution. The solution was extracted with a little benzene to remove a small amount of insoluble material.

The aqueous solution was acidified with hydrochloric acid. The oil which separated initially solidified upon standing. The product was removed by filtration and dried. The yield was 18.6 g. (70%), m.p. 86–90°. Two recrystallizations from cyclohexane gave pure material (15.1 g.), m.p. 87–89°.

Anal. Calcd. for $C_{17}H_{16}O_3$: C, 76.10; H, 6.01. Found: C, 76.35; H, 6.01.

WEST POINT, PA.

[CONTRIBUTION FROM THE ROCKEFELLER INSTITUTE FOR MEDICAL RESEARCH]

Further Studies with the Bacitracin Polypeptides*

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The fractionation of bacitracin by countercurrent distribution has been reinvestigated from the standpoint of obtaining a product with the highest antibiotic activity. Evidence has been given that the decrease in antibiotic activity at lower *p*H may be associated with a change in the optical activity of at least one of the amino acid residues, probably the isoleucine residue forming part of the thiazoline ring. This is a transformation apparently not related to that occurring at higher *p*H which leads to the F type of peptide.

Preliminary data for the characterization of bacitracin B have been given. These include amino acid analyses, ultimate analyses, determination of the amino groups capable of reacting with the Sanger reagent, and antibiotic activity.

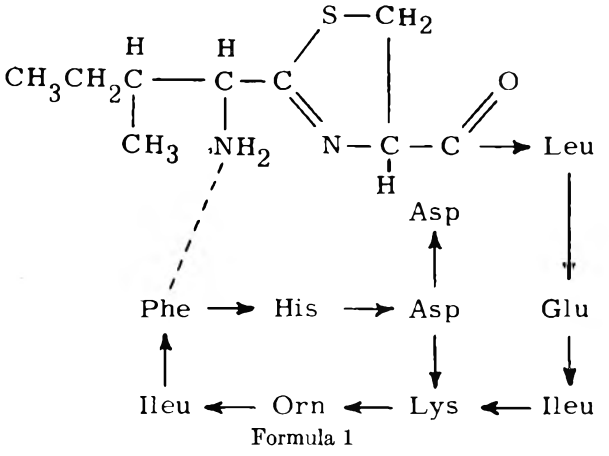
The bacitracin polypeptides[1] comprise an interesting family of naturally occurring antibiotics with unique structures. None of them has been brought to a crystalline state as yet, although the major features of a structural formula for bacitracin A, the most abundant member of the family, appear to have been established. Formula 1 derived in this laboratory[1,2] and independently in England by

* This paper is a contribution in honor of Lyndon F. Small, former Editor of the Journal.

** Fellow of the National Science Foundation.

(1) L. C. Craig, 3rd Congr. Intern. Biochim., Brussels, 1955, 416.

(2) J. R. Weisiger, W. Hausmann, and L. C. Craig, *J. Am. Chem. Soc.*, **77**, 3123 (1955).



Formula 1

Lockhart, Abraham, and Newton[3] rationalizes nearly all the experimental observations thus far made. Although an earlier preliminary communication by Porath[4] suggested an amino acid sequence which bore little relationship to Formula 1, a later paper[5] has stated that the data accumulated in this third laboratory which bears on the structure of bacitracin A, are now in agreement with those from the other two laboratories.

Formula 1, therefore, can be regarded as a provisional working formula but there remains still a number of puzzling observations to be substantiated and explained.

One of the uncertain features involves the quantitative antibiotic activity of bacitracin A. The standard preparation of A prepared in this laboratory by countercurrent distribution (C.C.D.) with the system 2-butanol/3% acetic acid always gave an assay approximating 50 units per mg. This material has been shown to be the acetate[6] and in addition contains 10–15% of solvent which can be removed at 100°. Even correcting for the acetate and the solvent the material appeared to be less active than the commercial product. This discrepancy was made more apparent by the fact that C.C.D. and ultraviolet absorption spectrum measurements always showed the commercial preparation to contain about 20% of the F type of peptide, a transformation product with very low activity. A number of reports in the literature[7,8] have given activities above 70 u/mg. A background such as this clearly suggests that further fractionation work is needed.

Assuming the correctness of the thiazoline ring system in Formula 1, it seemed that this might offer value to the difficulty of obtaining a product with maximum activity, to say nothing of preserving the activity level after it had been achieved. Such a thiazoline offers a very labile structure as is known for other synthetic thiazolines.[9] Thus the double bond might not always keep the position shown in the formula and might be expected to cause racemization of the alpha carbon atom of the isoleucine residue. Racemization of the single center of asymmetry could reduce the antibiotic activity of a preparation to half but would be expected to have very little effect on the physical properties of the molecule such as the partition ratio. A mixture of diastereoisomers of the size of bacitracin could well behave as a pure substance by C.C.D.

With the thought that the *p*H of the solvent might have an influence on the more subtle changes of the type mentioned, the fractionation of commercial bacitracin by C.C.D. has again been taken up. Newton and Abraham[10] used a system buffered with phosphate at *p*H 7, but in our hands their system gave rise to a slow but steady transformation[11] of bacitracin A to F. The low *p*H of the 3% acetic acid system completely inhibited the A to F transformation, but could have accelerated another type of transformation with loss of activity. In order to test this hypothesis several new systems offering a variety of *p*H levels have been developed. It also appeared worthwhile to investigate the effect of other solvents on the stability.

It seemed that this approach could well be combined with a careful study of optical rotation of the fractions. Although earlier measurements of optical activity with bacitracin A had shown very little, if any, rotation, reinvestigation at higher concentration could well be rewarding. DNP amino acids usually show higher rotations than the free amino acids. A study has therefore been made of the optical activity of the various fractions obtained when bacitracin A and B are treated with fluoro-2, 4-dinitro benzene. This study could also serve to confirm or cast doubt on the thesis of purity.

In a family of closely related natural products valuable information is usually derived by the simultaneous study of several members of the family. With the bacitracins very little has been reported thus far concerning the nature of B, C, D, etc., although F has been shown to be a transformation product[2,10] of A. In the course of the fractionation studies presented in this paper a moderate supply of bacitracin B has been accumulated. A number of preliminary observations regarding its relationship to A can now be reported.

(3) I. M. Lockhart, E. P. Abraham, and G. G. F. Newton, *Biochem. J.*, **61**, 534 (1955).
(4) J. Porath, *Nature*, **172**, 871 (1953).
(5) J. Porath, *Acta Chem. Scand.*, **8**, 1813 (1954).
(6) W. Hausmann, J. R. Weisiger, and L. C. Craig, *J. Am. Chem. Soc.*, **77**, 721 (1955).
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(11) L. C. Craig, J. R. Weisiger, W. Hausmann, and E. J. Harfenist, *J. Biol. Chem.*, **199**, 259 (1952).

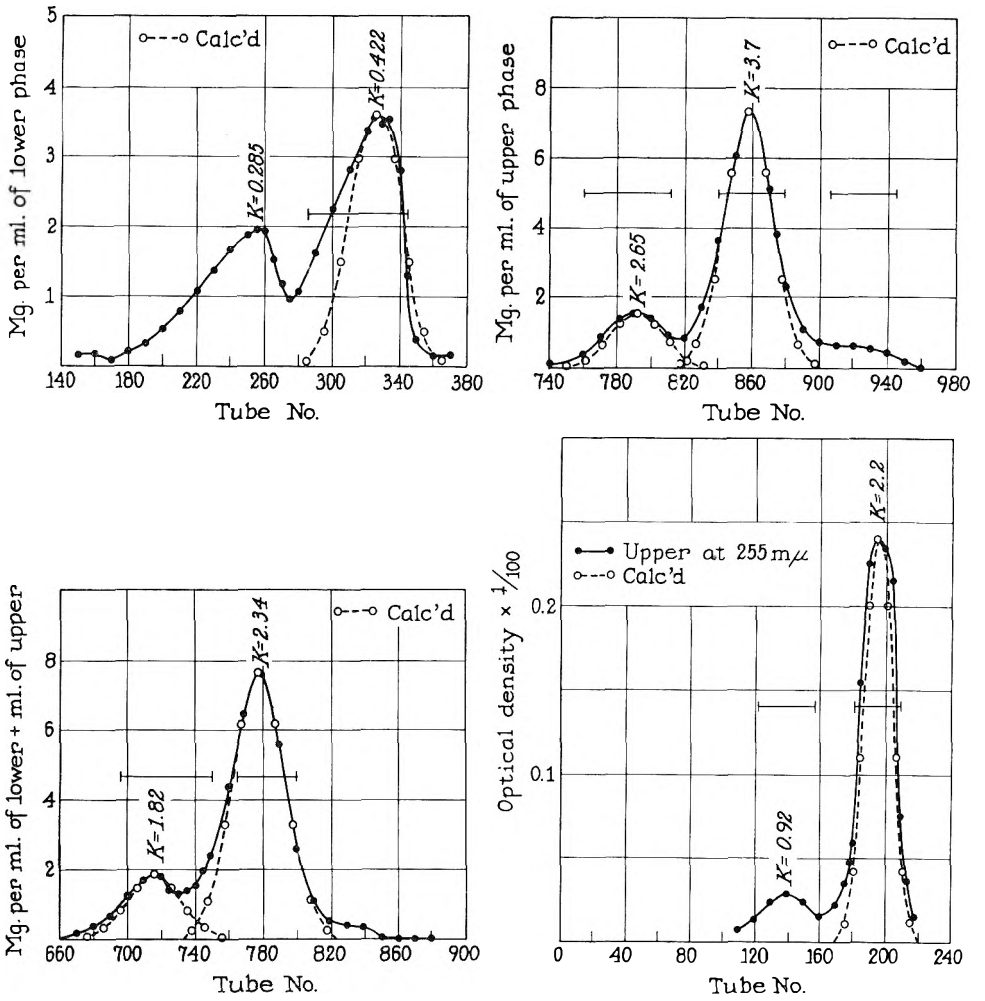


FIG. 1. COUNTERCURRENT DISTRIBUTION PATTERNS OF A AND B COMPONENTS OF BACITRACIN. Upper left; pattern 1. Upper right; pattern 2. Lower left; pattern 3. Lower right; pattern 4.

EXPERIMENTAL

The bacitracin used in the present study was obtained from the Commercial Solvents Corporation. We wish to express our thanks to them for this material and for all the antibiotic assays reported in this paper.

The distributions were made at 25° in an automatic C.C.D. apparatus of the type described earlier.[12] All solvents were distilled prior to use.

Our experience with four systems in fractionating bacitracin will be reported. These systems were the following:

1. 1-butanol, glacial acetic acid, and water in the volume proportions of 75, 15, 100 respectively.
2. 1-butanol, glacial acetic acid, pyridine, and water in the proportions of 20, 5, 5, 30. *p*H of lower phase: 4.59.
3. 1-butanol, pyridine, 0.1% acetic acid in the volume proportions of 15, 9, 33. *p*H of lower phase: 6.7.
4. 1-butanol, 0.5 *M* phosphate buffer at pH 5.4 in equal volumes.

In each system the initial load of peptide was 5 g., scattered in the first 10 tubes of the train. Sufficient amount of the lower phase was added at each transfer during the run to maintain the level of the lower phases. The settling time for the first three systems approximated 1 min., but about 5 min. for the fourth.

Analyses in the first three runs were made by weight, but in the fourth by optical density at 255 mμ since it contained phosphate buffer. For the weight analysis in the first run, 1 ml. of the lower phase was evaporated, dried at 100°, and weighed. In the second, 1 ml. of the upper phase was evaporated, while in the third, 1 ml. of lower phase plus 1 ml. of upper phase were evaporated.

The distribution patterns for the A and B components in each of the four runs is shown in Fig. 1. The C component in each run was removed before the run was completed and is not shown. Thus in run 1 at 220 transfers, effluent was collected in the fraction collector, but at 280 transfers all the F had emerged from the train. It was then arranged for recycling. At 580 transfer the A, B, and C components were apparent with the C component well separated with a maxima at tube 67 (K = 0.132) and amounting to about one third of the B component. This is more of the C component than appeared in the following runs. Run 1 was made on a preparation (Lot B-277B) received a year or more earlier than that (Lot B-55-10) on which the others were made. At 580 transfers the C component was removed and the distribution continued to 1098 transfers to give pattern 1.

In the case of run 2, the F component was removed at 560 transfers. It had a K of 9.5 in this system. The distribution was then continued to 1090 transfers to give pattern 2. Very little of the C component was found, but some of it may be in the left hand side of the B band as an overlap.

With run 3, the F component was removed at 656 transfers. It had a K of 3.8 in this system. At 1110 transfers pattern 3 was obtained.

Since the selectivities of the system were higher in run 4, it was stopped at 292 transfers. The F component which

(12) L. C. Craig, W. Hausmann, E. H. Ahrens, Jr., and E. J. Harfenist, *Anal. Chem.*, 23, 1236 (1951).

had a K of 7 was permitted to emerge from the train as effluent. At the beginning some difficulty was experienced in the separation of the phases, but soon a settling time of 5 min. was possible.

For recovery, cuts were taken as shown in Fig. 1. With the first three systems the organic solvents were removed by evaporation in the rotary evaporator[13] until an aqueous solution remained. This was freeze-dried.

With the fourth run the cuts were treated with 60 ml. of 2*M* K_2HPO_4 and shaken. The butanol phase containing the peptide was set aside and the aqueous phase extracted with fresh 1-butanol. The butanol extracts were treated with water and the butanol removed in the rotary evaporator. The aqueous solutions remaining were freeze-dried. This material contained considerable phosphate. The phosphate was removed by a 30-transfer distribution of each cut in system 3. It had a low K in this system and was easily removed.

When an attempt was made to obtain reproducible analytical results on the recovered bacitracins A and B, difficulty was encountered in choosing conditions for drying the sample. This was also complicated by the fact that the dry sample was hygroscopic and tended to fly out of the boat due to static electricity. Drying in high vacuum to constant weight at 100° was finally chosen. The recovered A from run 1 gave analytical data in agreement with that previously published[6] for the acetate but in the case of the other three systems the final product was recovered by freeze-drying a pyridine acetate solution and gave figures more in agreement with the free peptide.

Anal. Calcd. for $C_{66}H_{103}O_{16}N_{17}S$: C, 55.6; H, 7.3; N, 16.7. Found: C, 55.4; H, 7.3; N, 16.8.

In the case of bacitracin B the material from run 1 should be the acetate.

Anal. Calcd. for $C_{73}H_{116}O_{19}N_{18}S$: C, 55.3; H, 7.4; N, 15.9; S, 2.1. Calcd. for $C_{73}H_{118}O_{20}N_{18}S$: C, 54.8; H, 7.4; N, 15.7; S, 2.0. Found: C, 54.4; H, 7.4; N, 15.5; S, 2.3.

With the other three runs as with A, a higher carbon and nitrogen value was obtained indicating the free peptide.

Anal. Calcd. for $C_{71}H_{112}O_{17}N_{18}S$: C, 56.0; H, 7.4; N, 16.5. Calcd. for $C_{71}H_{114}O_{18}N_{18}S$: C, 55.4; H, 7.5; N, 16.4. Found: C, 55.2; H, 7.4; N, 16.4.

A quantitative amino acid analysis of a sample of B from run 4 by the ion exchange method of Moore and Stein[14] was made. This gave the result shown in Table I. The result previously published[2] for bacitracin A is given for comparison. The fraction to be analyzed was directly weighed for hydrolysis and then the weight corrected to dry weight at 100°. Hydrolysis was accomplished by heating in 6*N* HCl at 108° for 24 hr. in a sealed evacuated tube.

TABLE I

AMINO ACID ANALYSES

Amino Acid	Bacitracin B Corr. μM	Bacitracin B Nearest integer	Bacitracin A Corr. μM
Aspartic acid	1.76	2	1.77
Cystine (half)	.812	1	1.0
Valine	.900	1	none
Allo-isoleucine	.330		0.5
Isoleucine	1.89	2	1.83
Leucine	1.02	1	1.02
Phenylalanine	1.08	1	1.03
Lysine + ornithine	2.24	2	1.69
Histidine	1.22	1	0.80
NH_3	1.21	1	1.3

(13) L. C. Craig, J. D. Gregory, and W. Hausmann, *Anal. Chem.*, 22, 1462 (1950).

(14) S. Moore and W. H. Stein, *J. Biol. Chem.*, 211, 907 (1954).

The antibiotic assays were made by the Commercial Solvents Corporation. All assays reported in this paper are corrected to a dry weight (at 100°) basis. Optical rotations were determined in a 5% solution in glacial acetic acid of the peptide with the Keston polarimetric attachment for the Beckmann U.V. spectrophotometer. The setting of the instrument was standardized against sucrose solutions. The antibiotic activities and rotations are given in Table II.

TABLE II

ANTIBIOTIC ACTIVITIES AND OPTICAL ROTATIONS

System	Units/mg. A	Units/mg. B	Units/mg. (2 yrs. later) A	Units/mg. (2 yrs. later) B	$[\alpha]_D^{25}$ (C = 5.0 in 0.01 HAc) A	$[\alpha]_D^{25}$ (C = 5.0 in 0.01 HAc) B
2-Butanol/3% HAc Run 1	58	..	55	..	−3.6	
1-Butanol/HAc, H_2O Run 2	56	50	..	35	...	
1-Butanol/pyridine acetate pH 4.59 Run 3	60	57	51	42	−3.8	
1-Butanol/pyridine acetate pH 6.7 Run 4	76	80	72	70	−2.4	−2.8
1-Butanol/phosphate pH 5.4	72	69	70	65	−2.4	

Tri-DNP-bacitracin B. Fifty mg. of bacitracin B was converted to the tri-DNP derivative as was described for bacitracin A.[2] It was separated from the other reaction products by a 52-transfer distribution in the benzene-chloroform-acetic acid-.01 HCl (1:1:2:1) used for A but with 5/10 upper/lower volumes. The main peak had a partition ratio of 4 in this system as compared to a value of 2.66 in the case of tri-DNP-bacitracin A. It showed a type of absorption spectrum indistinguishable from A. A solution containing 1.143 mg./ml. in acetic acid of the material recovered from the main band showed an optical density of 5.60 at 350 mμ. From these data and from similar data with DNP-isoleucine and di-DNP-histidine indicating molecular extinctions of 14,500 for each, a molecular weight of 1940 can be calculated. Theoretical: 2037.

Hydrolysis of Tri-DNP-bacitracin B. A sample weighing 50 mg. was hydrolyzed in 10 ml. of 1:1 glacial acetic acid-concentrated hydrochloric acid in an evacuated sealed tube at 108° for 24 hr. The acid was evaporated, the residue taken up in a little water and extracted with ethyl ether. Evaporation of the ether gave a yellow residue weighing 7 mg. This was distributed to 120 transfers in a hand-operated 120-tube machine requiring 2 ml. lower phase volumes. The machine permitted up to 4 ml. of upper phase but 1 ml. was used. The system was the benzene, acetic acid, 0.1 *N* HCl (2:2:1) system[15] previously used with DNP amino acids.

Analysis by optical density at 350 mμ showed two major, partly overlapping bands whose widths were in accord with calculated bands. One had a partition ratio of 2.7 to 2.8 and the other had a partition ratio of 1.5. These correspond to the partition ratios of the DNP derivatives of isoleucine and valine. The yields calculated on the basis of a tri-DNP-derivative were 36% and 33% respectively.

In the distribution of the DNP amino acids from the hydrolysis there was a smaller, well separated band nearer the origin which had a partition ratio suggesting that it could be dinitro aniline with a K in this system of .43.

(15) W. Hausmann, J. R. Weisiger, and L. C. Craig, *J. Am. Chem. Soc.*, 77, 723 (1955).

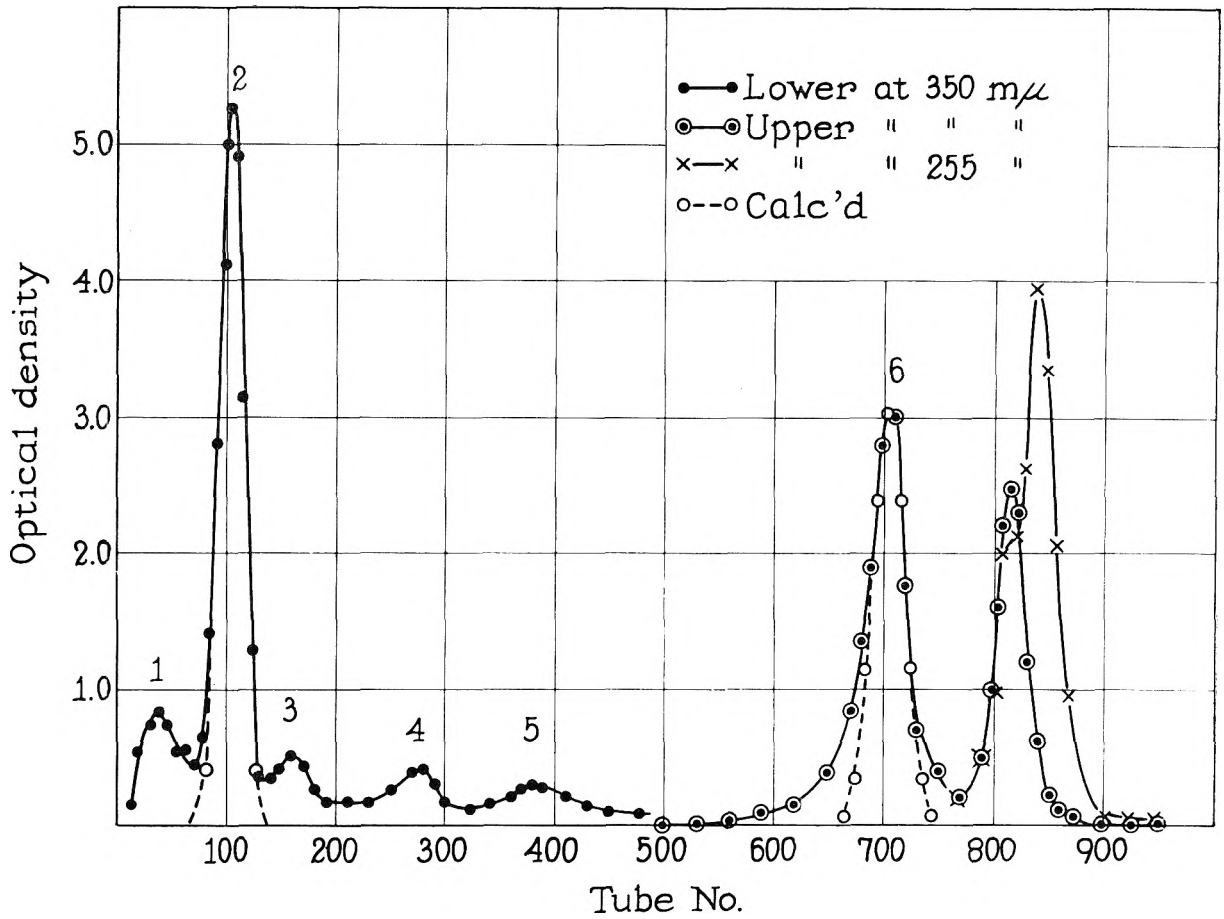


FIG. 2. COUNTERCURRENT DISTRIBUTION PATTERN of the reaction products of bacitracin B with FDNB at *p*H 4.66.

Reaction of fluorodinitrobenzene with the bacitracins at pH 4.66. A sample of the bacitracin weighing 300 mg. was dissolved in 4.5 ml. of 2*M* sodium acetate buffer at *p*H 4.66 and 1.5 ml. of ethanol added. After adding 1.2 ml. of FDNB the mixture was held at 40° for 1 hr. with occasional shaking.

Ethyl ether was added and the ether layer was removed. The suspension remaining was extracted twice more with ethyl ether. Sufficient glacial acetic acid was added to the aqueous suspension to make it a 75% solution with respect to the acetic acid. This solution was dialyzed[16] in 18/32 Visking against 75% acetic acid for 24 hr. This would be expected to remove all the unreacted bacitracin, dinitrophenol, etc.

Sufficient water, ethyl acetate, and chloroform were added to the acetic acid solution so that the solvent composition would approximate that of the system next to be used for the distribution. This system contained chloroform, acetic acid, ethyl acetate, and water in the volume proportions of 2:2:0.2:1. After 1000 transfers analysis by optical density at 350 and 255 mμ gave the pattern shown in Fig. 2 in the case of bacitracin B. This distribution was made in a 1000-tube automatic apparatus with 2 ml. of each phase in every tube.

A cut including the solutes in tubes 775 to 850 was recovered by evaporation of the solvents in a rotary evaporator and redistributed in a more favorable solvent system. This system contained ethyl acetate, glacial acetic acid, water, and 1-butanol in the volume proportions of 3:1:3:0.3 respectively. The apparatus was a hand-operated train of 120 tubes with 2 ml. of each phase per tube. The result after 120 transfers is shown in Fig. 3.

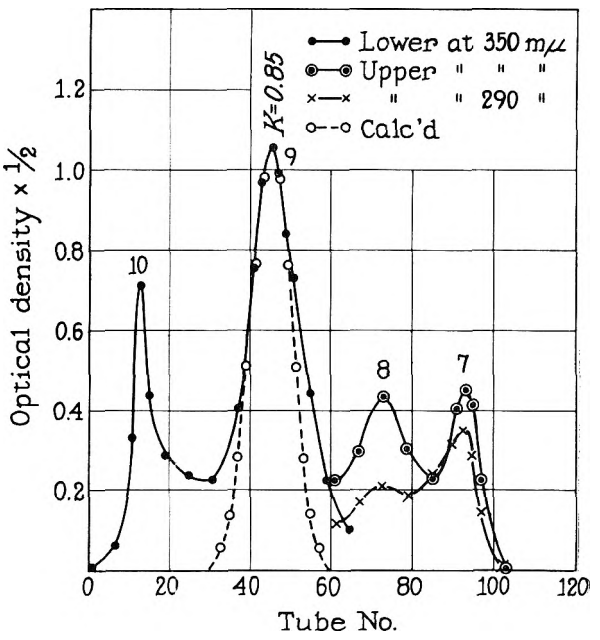


FIG. 3. PATTERN OBTAINED ON REDISTRIBUTING most polar overlapping bands from the distribution shown in Fig. 2.

Conversion of Bacitracin B to the F type. Bacitracin B was found to have an absorption spectrum in the ultraviolet which was almost superimposable on that of A[2] except that its extinction coefficient at 255 mμ was slightly lower.

(16) L. C. Craig and T. P. King, *J. Am. Chem. Soc.*, **77**, 6620 (1955).

One hundred milligrams of the peptide was dissolved in 10 ml. of 0.5 *M* phosphate buffer at *p*H 7.59. It showed the same absorption curve as at a lower *p*H. The solution was kept at 38° for two weeks redetermining the absorption curve from time to time. The shallow maximum at 255 slowly decreased but absorption increased in the 290 mμ range. After two weeks there was not even an inflection at 255 mμ but a definite maximum at 290 mμ where F from A has its maximum.

A control experiment with bacitracin A under the same conditions underwent the same type of spectral shift but not as rapidly as did B. This would indicate A to be somewhat more stable than B. The transformation product with B was purified by C.C.D. as reported[2] for the F from A. It had a similar partition ratio. The purified material had an absorption spectrum not different from the crude reaction product and almost superimposable on the spectrum[2] of F prepared from A.

A sample of the F from B was hydrolyzed in 6 *N* HCl in a sealed tube at 108° for 24 hr. The recovered amino acids were studied by two dimensional paper chromatography[15] in the 2-butanol-ammonia system and in the 2-butanol-formic acid system. All the spots found in F from A were present and in addition there was a strong spot in the position of valine.

DISCUSSION

The data given in this paper and shown in Fig. 1 definitely permit a better fractionation by C.C.D. of the bacitracin polypeptides. The exact choice of a system would depend somewhat on the equipment available. Thus with automatic equipment and a long train, system 3 is perhaps best. About the same resolution can be obtained with system 4 in approximately one fourth the number of transfers. It does not permit weight analysis but does permit analysis by optical density. System 3 does not permit analysis by optical density but does by weight. The two systems thus compliment each other very well. With system 4 recovery of the solute in phosphate-free form required a further short distribution in system 3.

Aside from the question of separation, systems 3 and 4 appeared best from the standpoint of recovery of a product with the highest antibiotic activity. The activities shown in the first two columns of Table II were determined a few weeks after the material was recovered. Since the different fractions are freeze-dried preparations they contain varying amounts of solvent up to 15% which can be removed on drying at 100°. A previous experiment with the acetate indicated that the antibiotic potency was not markedly decreased with this treatment. For comparison all the activities reported in this paper are given on the basis of the dry weight. The C.S.C. sample, Lot B-55-10, from which the fractionations were made assayed 67 u/mg. on a similar basis.

After these results were obtained the samples were set aside to await further work. They were stored part of the time in a cold room at +4° and part of the time in a deep freeze at −10°. After about 6 months the A and B fractions from run 3 together with a sample of the C.S.C. starting preparation for control were again sent for assay. A result corresponding to 73, 69, and 65 u/mg., respectively, was obtained. Approximately 18 months later the fractions in Table II were again sent for assay. This gave the results shown in the third and fourth columns. At the time, the control sample of C.S.C., Lot B-55-10, again gave an assay of 65 units.

It had been known for some time[17] that there was a loss of antibiotic potency on recovery of peak material from a distribution in the 2-butanol/3% HAc system since an assay of the solutions directly gave a higher result than after isolation. At first it was thought that this loss was connected with F formation. However, ultraviolet absorption spectral studies as well as redistribution showed F type to be absent from the recovered product. A more subtle type of transformation was indicated.

Optical rotation measurements as a help in this problem at first did not appear promising because of the low rotations found. Four of the amino acid residues emerge after acid hydrolysis as predominantly dextrorotary aside from the N terminal isoleucine. However, a careful study in 5% solution has now given significant results as shown in Table II. These measurements were made on material stored for two years. The more highly potent preparations were found to have a lower optical activity. This was further confirmed by measuring the optical activity at other *p*H values.

It was hoped that direct evidence might be obtained that the terminal isoleucine is involved in the shift of rotation by a study of the rotations of DNP derivatives since a DNP amino acid usually has a much higher rotation than the free amino acid. Substitution on the δ-amino group of the ornithine or the imidazole of the histidine would not be expected to enhance the rotation. However, the approach proved to be complicated by the fact that bacitracin is transformed in part to the F type under the alkaline conditions of the DNP reactions. For this reason a rapid reaction was chosen in the earlier work[18] but in the present study the possibility of obtaining substitution at an acidic *p*H was explored. A *p*H of 4.66 was finally chosen. It was thought that a reaction time of 1 hr. at 40° would give mainly a mixture of the monoderivatives and the di-DNP derivatives with little substitution on the strongly basic delta amino group of the ornithine.

Three bacitracin preparations were studied in this way: a preparation of A from the 2-butanol/3% acetic acid system (low potency, $\alpha = -3.6°$), a preparation of A from run 3 (high potency, $\alpha = -2.4°$), and a sample of bacitracin B from run 4. After extraction with ether and dialysis to remove the buffer and unreacted bacitracin, the yellow

(17) L. C. Craig, J. D. Gregory and G. T. Barry, *J. Clin. Invest.*, XXVIII, 1014 (1949).

(18) L. C. Craig, W. Hausmann, and J. R. Weisiger, *J. Biol. Chem.*, 200, 765 (1953).

mixture was distributed in a system which gave about equal distribution of the color. All three bacitracin preparations gave remarkably similar patterns. Because of this only the pattern obtained with bacitracin B is shown, Fig. 2, in the interest of saving space.

Analysis of the band on the right at more than one wavelength indicated it to be a mixture and since it has too high a partition ratio to be separated most efficiently, this material was redistributed in a more favorable system as shown in Fig. 3. The different discrete bands from Fig. 2 and 3 are numbered in the order of their decreasing polarity. At least 10 substances are obviously formed by the reaction of FDNB on each bacitracin at *p*H 4.66.

In order to learn the nature of each band a sample was hydrolyzed and the hydrolysate was studied by paper chromatography using a variety of systems much as was done previously.[16]

In the case of the DNP reaction with bacitracin A from system 3 (the most potent preparation), band 2 was obviously the tri-DNP derivative since paper chromatography of the hydrolysate showed δ-DNP-ornithine, DNP-isoleucine, and the characteristic degradation products of im-DNP histidine. Free histidine and ornithine were lacking. The weight-optical density relationship at 350 mμ indicated[16] the molecular weight of the DNP derivative to be 1960 assuming three DNP groups, two of which give the molecular extinction found for di-DNP-histidine (14,500). Calculated: 1920.

A similar study of band 6 indicated the ornithine to be free. Otherwise it was the same as band 2 with no free histidine. The weight-extinction ratio indicated a molecular weight of 1730 again on the basis of the molecular extinction of di-DNP-histidine. Calculated for a di-DNP-derivative: 1754.

A similar study of band 9 showed DNP-isoleucine and all the free amino acids of bacitracin including the ornithine and histidine spots. Weight-optical density relationship at 350 mμ on the basis of 1 DNP permitted a value of 1810 to be derived. Calculated for acetate of mono DNP derivative, 1648.

Band 10 was not yellow and could be the mono-imidazole derivative while band 8 could be the mono-ornithyl derivative. The nature of bands 1, 3, 4, and 5 remain in doubt as yet. In 1 and 3 the ornithine, isoleucine, and histidine imidazole are covered. Bands 4 and 5 appear to be di-DNP derivatives with the ornithine and histidine imidazole being involved. One might expect to find three di-DNP derivatives, one known to be the DNP-Ileu, DNP-im of band 6, a DNP-Orn, DNP-im and a DNP-Orn, DNP-Ileu.

It is interesting to note that in the earlier work[18] on the partial substitution of A with the Sanger reagent at alkaline *pH* a good yield of a di-DNP band was obtained which had the imidazole of the histidine unsubstituted. Apparently this imidazole is more reactive to the Sanger reagent at an acid *p*H than at an alkaline one since there can be little of such a derivative in the mixture prepared here. Hydrolysis of all bands, 1 through 6, of Fig. 2 failed to show free histidine but showed the decomposition products of *im*-DNP-histidine.

When histidine itself was reacted with the Sanger reagent under the above conditions at *p*H 4.66 and the products distributed only one band was obtained. It proved to be the mono-alpha-DNP derivative. No di-DNP derivative was formed and very little, if any, mono-imidazole-DNP derivative. Under the alkaline conditions with $NaHCO_3$ two bands were obtained, one of which was the di-DNP derivative and the other the alpha-DNP derivative.

Sanger[19] found that α-acetyl histidine did not react readily with FDNB under the usual reaction conditions with $NaHCO_3$. Ramachandran and McConnell[20] found that when histidine reacts with insufficient FDNB under the same conditions only the alpha derivative is formed. With more reagent the di-derivative is formed but no mono-DNP-imidazole derivative. The reaction of FDNB with histidine is being further studied with the though that a transfer of the DNP group from the imidazole to the more basic nitrogen may be involved.

When the bacitracin A preparation of lower potency corresponding to the first two preparations of Table II was converted to the DNP derivative at *p*H 4.66 and studied in the same way as the high potency material the only definite difference noted thus far has been concerned with the optical activities of the bands. Table III shows the comparison of the rotations taken in glacial acetic acid although there was not sufficient material to take rotations with the highest precision as given in Table II. Nonetheless, these data strongly support the conclusion already reached from Table II that a loss in antibiotic potency is accompanied by a shift in the optical activity of at least one of the optically active centers. This center could be, and most likely is, in the terminal isoleucine but because this res-

TABLE III

OPTICAL ROTATIONS OF DNP DERIVATIVES $[\alpha]_D^{25}$

Band	DNP from High Potency Bacitracin A	DNP from Low Potency Bacitracin A	DNP from Bacitracin B
1	0	+38	− 4
2	−11	0	− 7
3	−17	0	0
4	−12	+26	−11
5	− 8	+10	..
6	−12	0	− 4
9	−16	..	− 9

(19) F. Sanger, *Biochem. J.*, **39**, 507 (1945).

(20) L. B. Ramachandran and W. B. McConnell, *Nature*, **176**, 931 (1955).

idue[2,3] may also be tied into the carboxyl of the phenylalanine residue in some obscure way, another residue also may be involved.

The behavior of bacitracin B has a bearing on this puzzling problem. Complete amino acid analysis by the Moore-Stein procedure gave the result shown in Table I. B differs from A by having an additional valine residue in it. However, ultimate analysis is in agreement with the formula, $C_{71}H_{112}O_{17}N_{18}S$, obtained by adding a valine residue to the formula of bacitracin A, only when an additional molecule of water is added. This, of course, may be a tightly bound water of hydration.

When bacitracin B was treated with the Sanger reagent under alkaline conditions a derivative was obtained after C.C.D. for which the weight-optical density relationship indicated a tri-DNP derivative. However, on total hydrolysis of this derivative paper chromatography clearly showed δ-DNP ornithine, the breakdown products of *im*-DNP-histidine, DNP-isoleucine, and, in addition, a spot in the position of DNP-valine. Free histidine and ornithine spots were lacking. All the other free amino acid spots expected were found, including valine.

In order to confirm the DNP-valine a distribution was made on the ether soluble fraction as given in the experimental part. DNP-valine was found in an amount corresponding to 33% of a mole as compared to 36% of a mole of isoleucine. The latter is a higher yield of DNP-isoleucine than has thus far been obtained[2] from tri-DNP-bacitracin A.

When bacitracin B was reacted with the Sanger reagent at *p*H 4.66, the results shown in Fig. 2 and 3 were obtained. Band 2 was the tri-DNP derivative already discussed above. M. W. from weight-optical density at 350 mμ, 1840; calculated, 1920. Hydrolysis and paper chromatography of band 6 indicated the ornithine to be free but the histidine to be involved. There was no spot of free histidine but only the spots characteristic of the acid degradation of *im*-DNP-histidine. Yellow spots corresponding to DNP-isoleucine and DNP-valine were found. Yet again the weight-optical density relationship at 350 mμ was consistent only with the presence of 1 DNP group in the intact DNP-peptide aside from the one on the imidazole, 1700; calculated, 1754.

Hydrolysis and paper chromatography of band 9 showed the ornithine and histidine to be free. Yellow spots corresponding to DNP-isoleucine and DNP-valine were found. Again the weight-optical density relationship with the intact DNP-peptide was consistent with only 1 DNP group, 1830; calculated for acetate of mono-DNP derivative, 1765.

Bacitracin B was found to be transformed to an F type even more rapidly than A. The F from B on complete hydrolysis showed a strong valine spot with paper chromatography. Since it is known[2] that F from A is formed by loss of the amino group of the terminal isoleucine,[21] the valine cannot be terminal in bacitracin B unless it is attached in some manner in the vicinity of the isoleucine so that isomerization is possible and either the isoleucine or valine, but not both, could serve as the terminal group. The latter possibility could explain the behavior found with the DNP derivatives.

Even with respect to the DNP derivatives of bacitracin A it could be that the postulated linkage from the so-called terminal isoleucine to the carboxyl of the phenylalanine could make the α-amino group of the histidine reactive to the DNP reagent. Here it would be a case of the DNP group becoming attached to either the isoleucine or the α-amino of the histidine, but not both. Its presence on the α-amino of the histidine could not be detected since the histidine DNP derivatives decompose on hydrolysis. This theory would explain the anomalously low yield of DNP-isoleucine obtained on hydrolysis of tri-DNP-bacitracin A.[2]

Two other explanations for the behavior of the bacitracin polypeptides should not be overlooked. One concerns the possibility that the DNP group can be transferred from one position to another during acid hydrolysis. In this connection the histidine and thiazoline ring could be suspect.

The other could be based on the theory that in spite of all the precise fractionation thus far done on the free peptides and DNP derivatives, the preparations are still mixtures of closely related peptides. The data presented in this paper indeed do seem to indicate that they may not be entirely pure with respect to the optical configurations of all the amino acids. Similarly, the data are not sufficient to exclude mixtures of the type where in one an isoleucine and a valine residue have exchanged places. If so, this could indicate a certain lack of specificity in the enzyme systems which have produced the peptides. In the particular case above this could be investigated by isolation of the ketothiazole[2] from F prepared from bacitracin B to determine if any of it has the isobutyryl side chain. This work is in progress.

The alloisoleucine formed (0.5 mole) on hydrolysis of A comes from the terminal isoleucine since tri-DNP-bacitracin A and F from A do not give a detectable amount.[2] This indicates complete racemization of the alpha carbon atom of the isoleucine during hydrolysis. Bacitracin B gave only 0.330 mole (0.355 mole on a check analysis). Abraham[22] obtained no alloisoleucine when hydrolysis of A was preceded by deamination. Also the isoleucinol formed on hydrogenolysis of A gave 33%

(21) The ketothiazole[2] postulated on hydrolysis of F has been synthesized in this laboratory and will soon be described by Dr. J. R. Weisiger.

(22) E. P. Abraham, 3rd Congr. Intern. Biochem., Brussels, 1955, 423.

allo when oxidized back to isoleucine. A recent analysis of bacitracin A of high potency from system 3 again gave 0.5 mole of alloisoleucine.

Acknowledgment. We wish to thank Mr. James Rigakos for the ultimate analyses reported in this paper. Thanks are also due Miss Gerty Walker and Mrs. Judy O'Brien for technical assistance.

NEW YORK, N. Y.

[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY, UNIVERSITY OF VIRGINIA]

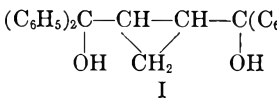
Pinacollike Rearrangement of a Cyclopropane-1,2-dimethylene Glycol*

ROBERT A. DARBY[1] AND ROBERT E. LUTZ

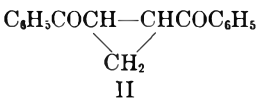
Received May 20, 1957

The cyclopropylog[2] of a 1,2-glycol, namely *trans*-1,2-di(diphenylhydroxymethyl)cyclopropane, was made by addition of phenyllithium to *trans*-1,2-dibenzoylcyclopropane. It underwent facile acid-catalyzed pinacol-type rearrangement with shift of a phenyl group to the adjacent cyclopropane carbon and concomitant cleavage of the ring, to produce the unsaturated ketone, 1,2,5,5-tetraphenyl-4-pentene-1-one. The structure of this product was demonstrated by its properties and by oxidative degradation to β-benzoyl-β-phenylpropionic acid.

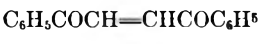
The rearrangement of the cyclopropylog[2] of a 1,2-glycol, namely *trans*-1,2-di(diphenylhydroxymethyl)cyclopropane (I), was discovered in the course of new studies on the preparation and reactions of *trans*-1,2-dibenzoylcyclopropane (II)[3,4] which had been undertaken for the purpose of comparing the conjugated system of this latter compound (II) with that of the olefinic analog, *trans*-1,2-dibenzoylethylene (III).



I

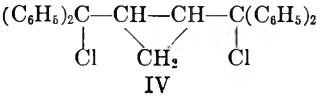


II

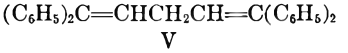


III

The cyclopropane-1,2-dimethylene glycol (I) was made by the action of phenylmagnesium bromide or phenyllithium on 1,2-dibenzoylcyclopropane (II). It had been the authors' intention to subject both this glycol (I) and the corresponding dichloride (IV) to the action of reducing agents. It was believed that possibly the conjugation between the functional groups through the cyclopropane ring might to some extent permit or favor 1,6-reduction with consequent formation of 1,1,5,5-tetraphenyl-1,4-pentadiene (V), reactions for which there are ample olefinic analogies (*cf.* the 1,6-reduction of pseudocodeine[5,6] and the 1,4-reductive-elimination of halogens from 2-butene-1,4-dihalides[7]).

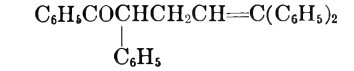


IV



V

In an attempt to prepare the dichloride (IV), the glycol (I) was subjected to the action of thionyl chloride. The crystalline product, however, proved to be halogen-free and analysis and molecular weight established the empirical formula $C_{29}H_{24}O$. The infrared absorption spectrum contained a band corresponding to a benzoyl-type carbonyl group (5.94 μ), and did not have the characteristic strong cyclopropane band in the 9.8–10 μ region. These results led to the conclusion that there had occurred a pinacol-type rearrangement with the glycol (I) functioning in the sense of a cyclopropylog[2] of a tetraphenyl-1,2-glycol, and that the product was the pinacolone partial-analog (VI).



VI

Consistent with the above formulation of the product (VI) the ultraviolet absorption spectrum of the compound showed a strong band at 248.5 mμ, ε, 16,530, which is significantly close to the summation of the expected molar absorptivities of the two independent chromophores, benzoyl and

* This paper is a contribution in honor of Lyndon F. Small, former Editor of the Journal.

(1) Philip Francis du Pont Fellow, 1955–57. Assistance during the summer from an Office of Ordnance Research Contract, U. S. Army, is acknowledged. Present location, Experimental Station, E. I. du Pont de Nemours, Inc., Wilmington, Del.

(2) We use this term in a sense comparable with the terms homolog and vinylog.

(3) R. A. Darby, dissertation, University of Virginia, May 1957. The cyclopropanes I and II were assigned *trans* configurations on the basis of failure of II to isomerize under the action of 1% alcoholic sodium hydroxide, conditions which readily effect rearrangement of the unstable stereoisomer of 3-phenyl-1,2-dibenzoylcyclopropane. (See ref. 15).

(4) J. B. Conant and R. E. Lutz, *J. Am. Chem. Soc.*, **49**, 1083 (1927).

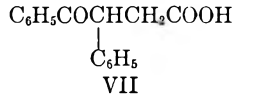
(5) R. E. Lutz, *J. Am. Chem. Soc.*, **56**, 1378 (1934).

(6) R. E. Lutz and L. F. Small, *J. Am. Chem. Soc.*, **56**, 2466 (1934).

(7) J. Thiele, *Ann.*, **308**, 339 (1899).

styryl (these chromophores in the compounds α-methyldesoxybenzoin and 1,1-diphenylpropene-1 give rise to values of *ca.* 12,000 and 12,500 at 233–242 and 248–253 mμ, respectively[8,9]).

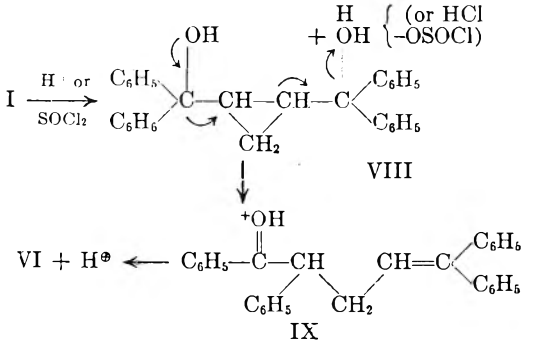
Unequivocal proof of the structure VI was obtained through oxidative degradations. With potassium permanganate in pyridine-water mixture,[10] 1.3 molar equivalents of benzoic acid and 0.32 of benzophenone were obtained, products which conclusively demonstrated the migration of one phenyl group of the glycol (I). Partial oxidation by chromic acid-acetic acid-chloroform mixture[11] gave a small but nevertheless significant yield of β-benzoyl-β-phenylpropionic acid VII which was identified by analysis, and by infrared absorption spectral comparisons and mixture melting point with an authentic synthetic sample.[12]



VII

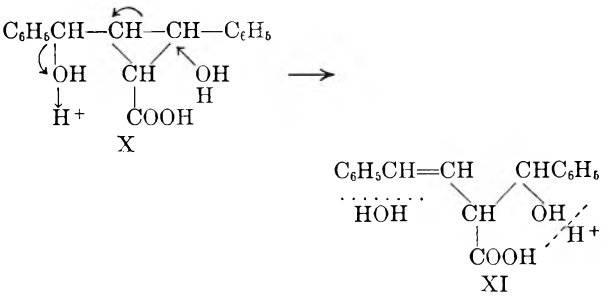
On further study it was found that the glycol (I) could also be rearranged, readily and in 75% yield, by short heating of an acetic acid solution (refluxing for 1 min.). The fact that the glycol was recovered unchanged after fusion for 5 min. at the much higher temperature 200–210° shows that acid catalysis is important as it is in the characteristic rearrangements of simple cyclopropanes which without catalyst require relatively high temperatures.[13]

A logical representation of the mechanism of the rearrangement of the glycol (I) to the unsaturated ketone (VI), in partial analogy both with the pinacol rearrangement and with rearrangements of cyclopropanes to olefins, is as follows:



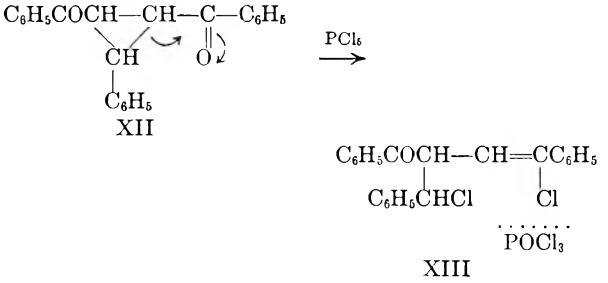
IX

In connection with the above results and discussion three other cyclopropane rearrangements should be cited as related although not fully analogous. One of these is the acid-catalyzed rearrangement of 3-phenyl-2-(phenylhydroxymethyl)-cyclopropane-1-carboxylic acid (X) to the open-chain unsaturated hydroxy acid (XI).[14]



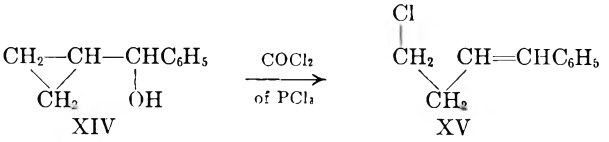
X XI

The second is the reaction and rearrangement of 3-phenyl-1,2-dibenzoylcyclopropane (XII) with phosphorus pentachloride to the open-chain unsaturated dichloro ketone (XIII)[15] (analogous to the Straus reaction of α,β-unsaturated ketones[16]).



XII XIII

The third is the recently reported rearrangement of α-cyclopropylbenzyl alcohol XIV to 4-chloro-1-phenylbutene-1 (XV).[17]



XIV XV

It will be of interest to learn of the results of experiments in progress on the action of acid on the cyclobutane analog of (I) and on 1,1,4,4-tetraphenylbutene-2-diol-1,4 which is a true vinylog of a pinacol.[18]

EXPERIMENTAL[19]

1,2-Di-(diphenylhydroxymethyl)cyclopropane (I). A solu-

(8) P. Preisweik and H. Erlenmeyer, *Helv. Chim. Acta*, **17**, 329 (1934).

(9) R. Lucas and M. J. Hoch, *Bull. soc. chim. France*, (5) **2**, 1376 (1935).

(10) D. A. Shirley, *Preparation of Organic Intermediates*, John Wiley and Sons, Inc., New York, N. Y., 1951, p. 219.

(11) B. Riegel, R. B. Moffett, and A. V. McIntosh, *Org. Syntheses*, **Coll. Vol. III**, 234–236 1955.

(12) A. Ali, *et al.*, *J. Chem. Soc.*, 1013 (1937).

(13) G. E. Egloff, G. Hulla, and V. I. Komarewsky, *Isomerization of Pure Hydrocarbons*, Reinhold Publishing Corp., New York, N. Y., 1952, pp. 95–97.

(14) C. F. H. Allen and R. Boyer, *Can. J. Research*, **9**, 159 (1933).

(15) E. P. Kohler and W. N. Jones, *J. Am. Chem. Soc.*, **41**, 1249 (1919).

(16) C. F. H. Allen and A. H. Blatt, *Organic Chemistry. An Advanced Treatise*, H. Gilman, ed., Vol. I, Second Edition, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 680.

(17) W. J. Close, *J. Am. Chem. Soc.*, **79**, 1455 (1957).

(18) C. F. Dickerson, dissertation, University of Virginia, May 1954; and further experiments which are in progress.

(19) Microanalyses by B. J. Williamson and Mrs. T. C. Jensen. Ultraviolet absorptivities were determined using a Beckman DU quartz spectrophotometer and 2×10^{-5} molar absolute ethanol solution. Infrared determinations were made on a Perkin-Elmer Model 21 double beam spectrophotometer using potassium bromide pellets.

tion of phenyllithium was prepared under nitrogen from 0.9 g. of lithium in 25 ml. of dry ether by dropwise addition of 5.3 ml. (0.05 mole) of distilled, dried bromobenzene in 25 ml. of dry ether over a period of 20 min. with stirring and slight warming to initiate the reaction. After stirring for an additional 1.5 hr. a solution of 5 g. (0.02 mole) of 1,2-dibenzoylcyclopropane (II) in 250 ml. of ether was added under gentle refluxing over a period of 30 min. Hydrolysis, washing with water, drying the ether solution over sodium sulfate, and evaporating under reduced pressure, gave a colorless solid which was recrystallized from benzene-ligroin mixture, m.p. 169.5–171.5°, yield 6.26 g. (77%).

Anal. Calcd for $C_{29}H_{26}O_2$: C, 85.68; H, 6.45. Found: C, 85.37; H, 6.19. Infrared absorption: 2.8, 9.93 μ.

In a similar experiment using phenylmagnesium bromide, except that hydrolysis was with 10% sulfuric acid, the yield of the glycol (I) was 33%.

One gram of the glycol after heating at 200–210° for 5 min. was recovered almost quantitatively.

1,2,5,5-Tetraphenyl-4-pentene-1-one (VI). A suspension of 0.5 g. (0.00123 mole) of the glycol (I) in 10 ml. of acetic acid was brought rapidly to boiling and refluxed for one min. Upon cooling a white precipitate of VI formed and was recrystallized from absolute ethanol, m.p. 130.5–132.5°; yield 0.36 g. (75%).

Anal. Calcd. for $C_{29}H_{24}O$: C, 89.65; H, 6.22; mol. wt. 388.5. Found: C, 89.43; H, 5.91; mol. wt. (Rast), 408. Ultraviolet absorption in absolute ethanol (2.02×10^{-5} *M*): λ_{max}, 248.5; ϵ, 16,530. Infrared absorption: 5.94, 6.23, 6.67, 6.9, very slight peak at 9.95 μ.

In another experiment, 5 g. (0.0123 mole) of the glycol (I) dissolved rapidly in 40 ml. of thionyl chloride with the evolution of gas. The red solution was warmed on a steam bath for 20 min., and the excess thionyl chloride was evaporated under reduced pressure. Ligroin was added and evaporated. The residue was recrystallized from benzene-ligroin mixture or from absolute ethanol; m.p. 131.5–132.5°; yield 3.0 g. (61%).

Numerous *ozonolysis* attempts were unsuccessful.

Potassium permanganate oxidation (cf. Ref. 10). A solution of 4 g. of VI (0.0103 mole) in 100 ml. of pyridine and 30 ml. of water on a steam bath was treated with six 2.1-g. portions of potassium permanganate (a total of 0.08 mole) at 1-hr. intervals. Upon steam distillation 0.69 g. (32%) of benzophenone, m.p. 44–46.5°, was obtained and identified by a mixture melting point determination. Work-up of the residue from steam distillation produced 1.6 g. (64%) of the calculated two equivalents of benzoic acid, m.p. 119–120° (identified by a mixture melting point determination).

Chromic acid oxidation.[11] A solution of 5 g. (0.0128 mole) of VI in 30 ml. of chloroform and 39 ml. of acetic acid at 45–50° was treated dropwise over 10 min. under stirring with a solution of 4.8 g. (0.048 mole) of chromic acid in 4 ml. of water and 26 ml. of acetic acid. After stirring for an additional 20 min. at this temperature and treatment dropwise with methanol to destroy excess reagent, the reaction mixture was concentrated on a steam bath under reduced pressure and evaporated to near dryness at room temperature under reduced pressure. The residue was triturated with ether, filtered, and placed in 150 ml. of water. Extraction of ether, washing with 10% hydrochloric acid, drying over sodium sulfate, evaporation under reduced pressure, and trituration of the viscous residue with ether, gave 0.9 g. of a white crystalline solid, m.p. 153–160°; recrystallized from dilute ethanol, m.p. 163–165°. It was identified as VI by a correct analysis, and by mixture m.p. with, and identity of the infrared absorption spectrum with that of an authentic sample prepared as described below.

β-Benzoyl-β-phenylpropionic acid. This synthesis is based on a procedure outlined briefly by Ali, *et al.*[12] To a solution of 0.5 g. of sodium in 15 ml. of absolute ethanol was added portion-wise 5 g. (0.0254 mole) of desoxybenzoin (m.p. 52–5°). After all of the ketone had been added, the mixture was treated with 2.8 ml. (4.2 g., 0.0252 mole) of distilled ethyl bromoacetate and was refluxed for 5 hr.; the alcohol was then evaporated. A solution of the residue and 1.5 g. of sodium hydroxide in 25 ml. of ethanol was refluxed for 30 min., cooled, diluted with water, and neutralized with concentrated hydrochloric acid. The resulting white precipitate was recrystallized from dilute ethanol; m.p. 163–165°; (A[12], m.p. 163°); yield 3.6 g. (55%).

CHARLOTTESVILLE, VA.

[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY, UNIVERSITY OF VIRGINIA]

Lead Tetraacetate Oxidations of 2,5-Diarylfurans*,[1a]

CHI-KANG DIEN[1b] AND ROBERT E. LUTZ

Received February 4, 1957

Lead tetraacetate in chloroform solution oxidized five 2,5-diarylfurans to the *cis* unsaturated 1,4-diketones and converted three β-acetoxy-2,5-diarylfurans into the corresponding 2-acetoxy-3-furanones. 2,5-Dimesitylfuran and 3,4-dichloro-2,5-diphenylfuran did not react under these conditions.

In refluxing concentrated acetic acid lead tetraacetate, behaving differently, brought about two-stage oxidations of three 2,5-diarylfurans to the 2-acetoxy-3-furanones. In one of these cases the reaction could be stopped at the first stage of oxidation with production of the 3-acetoxyfuran. Four 3-acetoxy-2,5-diarylfurans were oxidized to 2-acetoxy-3-furanones.

These reactions are consistent with expectations based on known behaviors of the reagent, effects of different types of substituents, and present views of mechanism.

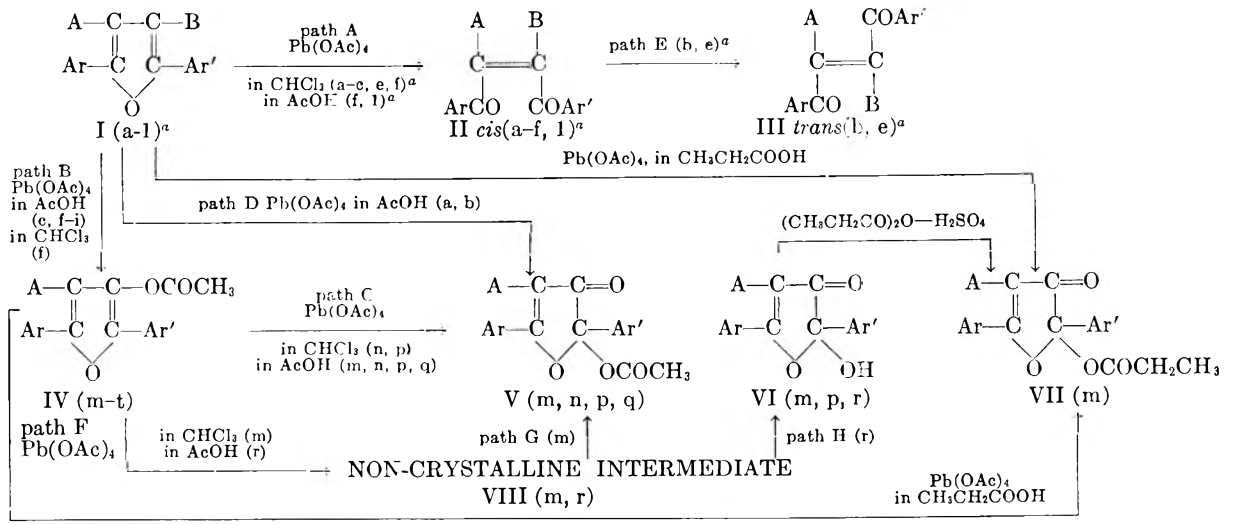
Numerous 2,5-diarylfurans (I), including one carrying a sterically hindering mesityl group at one of the two α-positions, undergo oxidative-cleavage by nitric-acetic acids to *cis* unsaturated 1,4-diketones (II),[2] but 2,5-dimesitylfurans (Ij)[3] resist this

* This paper is a contribution in honor of Lyndon F. Small, former Editor of the Journal.

(1) (a) This investigation was supported in part by a contract with the Office of Ordnance Research, U. S. Army, and in part by a grant-in-aid from the National Science Foundation. (b) Present location, National Aniline Div. Allied Chemical & Dye Corp., Buffalo, N. Y.

(2) (a) A. P. Dunlap and F. N. Peters, *The Furans*, Reinhold Publishing Corp., N. Y., 1953, and references cited therein; see especially p. 50. (b) R. E. Lutz and F. N. Wilder, *J. Am. Chem. Soc.*, 56, 978 (1934); (c) R. E. Lutz and W. P. Boyer, *J. Am. Chem. Soc.*, 63, 3189 (1941).

CHART I



1[a]–	Substituents[b]			Reaction path:	
VIII	Ar, Ar′	A	B	$CHCl_3$[c]	AcOH[a,c]
a	C_6H_5	H	H	A[d]	D[e]
b	BrC_6H_4[b]	H	H	A[d], E	D
c	C_6H_5	Cl	H	A	B
d	C_6H_5	Cl	Cl	N[b]	E
e	C_6H_5	CH_3	CH_3	A, E[d]	E[f]
f	C_6H_5	C_6H_5	H	A, B	A, B
g	C_6H_5	C_6H_5CO	H	N[b]	B
h	C_6H_5	BrC_6H_4CO	H	—	B
i	C_6H_5	$C_9H_{11}CO$	H	—	B
j	C_9H_{11}	H	H	N[b]	R[b]
k	C_9H_{11}, BrC_6H_4	II	H	R[b,e]	R[b]
l	C_6H_5	H	OCH_3	R[b]	A
m	C_6H_5	H	—	F, G	C
n	BrC_6H_4	H	—	C	C
o	C_9H_{11}	H	—	N[b,e]	—
p	C_6H_5	Cl	—	C	C
q	C_6H_5	C_6H_5	—	—	C
r	C_6H_5	C_6H_5CO	—	—	F, H
s	C_6H_5	BrC_6H_4CO	—	—	—
t	C_6H_5	$C_9H_{11}CO$	—	—	—

[a] The first column designates by letters a–t the formulas I–VIII. The letters under the formulas and above the arrows specify those compounds of the list which reacted according to the several paths A–H. [b] Abbreviations: AcOH = CH_3COOH; BrC_6H_4 = *p*-bromophenyl; C_9H_{11} = mesityl; N = no reaction occurred; R = reaction occurred but product did not crystallize. [c] Reaction temperature was refluxing unless otherwise specified: [d] at 30°; [e] at 50°; [f] the reaction undoubtedly proceeded through IIe but IIe was not isolated or detected.

reaction. A mechanism involving attack at one unhindered α-position without completion of a 1,4-addition was suggested to account for the results.[2c] Clausen-Kaas[4] in recent studies on the action of other oxidizing agents such as lead tetraacetate, hydrogen peroxide, and the halogens, on simpler furans, has isolated completed-addition compounds or derivatives of them (*e.g.* 2,5-diacetoxy and 2,5-dimethoxy compounds analogous to XI). The present paper deals with some results of a further examination of the 2,5-diarylfurans in respect to the action of oxidizing agents, specifically lead tetraacetate,[5,6] and the marked effects of the solvents chloroform and acetic acid on the mode of reaction. The results are outlined in formulas I–VIII which show the several oxidation paths involved (A–H).

Lead tetraacetate reactions in chloroform solution at 30° with 2,5-diphenyl- and 2,5-di-(*p*-bromophenyl)-furans (Ia, b), gave chiefly the *cis* unsaturated diketones (IIa, b). In the latter case, IIb, where the *cis* compound is relatively very labile, a small amount of the stable *trans* isomer IIIb was obtained also. 3-Chloro-2,5-diphenylfuran (Ic) reacted but only at refluxing temperature and also gave the *cis* unsaturated diketone IIc. 3,4-Dichloro- and 3-benzoyl-2,5-diphenylfurans (Id and g) failed to react at refluxing temperature. 3,4-Di-

(3) R. E. Lutz and C. J. Kibler, *J. Am. Chem. Soc.*, **62**, 1520 (1940).

(4) (a) N. Clauson-Kass, *Kgl. Danske Videnskab. Selskab, Mat-fys. Medd.*, **24**, 6 (1947). (b) N. Elming and N. Clauson-Kass, *Acta Chem. Scand.*, **6**, 535 (1952). (c) N. Clauson-Kaas, *Acta Chem. Scand.*, **6**, 569 (1952). (d) N. Elming, *Acta Chem. Scand.*, **6**, 578 (1952). See also references cited in reference 2(a).

(5) Empirically the reagent lead tetraacetate is said to react in three ways, by addition of two acetoxyls to a double bond, by substitution of an acetoxyl for an "active" hydrogen, and by abstraction of two suitably located hydrogens of systems such as that in a 1,2-glycol (*cf.* W. A. Waters, *Organic Chemistry*, H. Gilman, 1953, Vol. IV, p. 1185). The 2,5-diarylfurans are capable of only the first two.

(6) For recent studies see: (a) W. A. Mosher and C. L. Kehr, *J. Am. Chem. Soc.*, **75**, 3172 (1953); (b) H. E. Barron, G. W. K. Cavill, E. R. Cole, P. T. Gilham, and D. H. Solomon, *Chemistry & Industry*, 76 (1954); (c) G. W. K. Cavill, E. R. Cole, P. T. Gilham and D. J. McHugh, *J. Chem. Soc.*, 2785 (1954); (d) G. W. K. Cavill and D. H. Solomon, *J. Chem. Soc.*, 1404, 3943 (1954); (e) R. Criegee, *Ann.*, **481**, 263 (1930); (f) R. Criegee and H. Beuker, *Ann.*, **541**, 218 (1939); (g) F. V. Brutcher and F. J. Vara, *J. Am. Chem. Soc.*, **78**, 5695 (1956).

methyl-2,5-diphenylfuran (Ie) reacted smoothly at 30° to give largely the *cis* unsaturated diketone IIe together with a small yield of the stable *trans* isomer IIIe which was doubtless formed by stereoisomerization. It is noteworthy that as would be expected the electron-attracting groups chlorine and benzoyl in the β-position of the furan ring retard the reaction while the electron-repelling methyl group facilitates it.

The reaction with 2,3,5-triphenylfuran (If) deviated from the above pattern; in addition to a sizable yield of *cis* unsaturated diketone IIf there was produced some of the β-acetoxy furan IVq.

2,5-Dimesitylfuran (Ij) was largely recovered after reaction at refluxing temperature but an unidentified product of high oxygen content was produced in small yields. 2-Mesityl-5-*p*-bromophenylfuran (Ik) resisted reaction at room temperature but gave a non-crystalline product at refluxing temperature. Evidently two α-mesityl groups by steric interference with addition at the α-carbons slow down the oxidation reaction in chloroform solution as they do the nitric-acetic acid oxidation.[3]

3-Methoxy-2,5-diphenylfuran (Il) reacted readily, as expected because of the activating β-methoxyl group, but gave an intractable resin.

The reaction between the lead tetraacetate-chloroform reagent and 2,5-diarylfurans carrying the activating β-acetoxyl group, in the main followed a course different from the above, one which was followed also in acetic acid as solvent. Attack was at the adjacent α-position. 3-Acetoxy-2,5-diphenylfuran (IVm), 3-acetoxy-4-chloro-2,5-diphenylfuran (IVp), and 3-acetoxy-2,5-di-(*p*-bromophenyl)furan (IVn) reacted somewhat more slowly than those unsubstituted in the 3,4-positions. In the case of the latter two (IVn and p) the products were the corresponding acetoxyfuranones (Vn,p). In the case of 3-acetoxy-2,5-diphenylfuran (IVm) the product was an oil (VIII) which was believed to contain the completed addition product, the triacetoxydihydrofuran XIV or XV, which under the action of refluxing acetic acid then produced the acetoxyfuranone Vm in significant amounts. 3-Acetoxy-2,5-dimesitylfuran (IVo) constituted an exception to the above generalization; it failed to react with the reagent in chloroform, presumably because of steric hindrance at the α-carbons.[7]

It should be emphasized that in chloroform solution β-acetoxylation did not take place in any of the compounds studied except in the triphenyl series (If → IVq).

The lead tetraacetate reactions in acetic acid in many cases exhibited striking differences from those in chloroform. The 2,5-diarylfurans Ia and b, instead of undergoing the one-step oxidation-cleavage to the *cis* unsaturated diketone II, underwent a two-fold rise in oxidation level and gave the corresponding 2-acetoxy-2,5-diaryl-3-furanones (Vm,n). The best yields (*ca.* 70%) were obtained at refluxing temperature using two molar equivalents of reagent. The possibility that the different course of the reaction in the two solvents was due to a temperature rather than a solvent effect was eliminated by experiments on 2,5-diphenylfuran (Ia) in acetic acid at refluxing temperature and at 40–50°; from these reactions only the 2-acetoxy-3-furanone, Vm could be obtained.

The 3-chloro-, 3-benzoyl-, 3-(*p*-bromobenzoyl)-, and 3-mesitoyl-2,5-diphenylfurans (Ic,g-i) reacted under similar conditions but underwent a rise in oxidation level of only one stage by substitution of acetoxyl for the β-hydrogen to give the corresponding β-acetoxy furans (IVp,r-t).

3-Acetoxy-2,5-diphenyl- and 3-acetoxy-2,5-di-(*p*-bromophenyl)furans (IVm,n), which might be presumed to be the intermediates in the two-stage reactions with the parent 2,5-diarylfurans (Ia,b), actually did react readily in separate experiments to give the corresponding 2-acetoxy-3-furanones (Vm,n). 3-Acetoxy-4-chloro-2,5-diphenylfuran (IVp) reacted similarly but required prolonged heating and an excess of reagent. 3-Acetoxy-4-benzoyl-2,5-diphenylfuran (IVr) reacted still more slowly and gave an oil which presumably consisted largely of a triacetoxyl addition compound of the type XIV or XV because it was converted into the 2-hydroxy-3-furanone VI upon treatment with alcoholic potassium hydroxide.

In these reactions it is seen, again, that an electron-attracting substituent in the β-position retards reaction. On the other hand, a β-acetoxyl group specifically directs attack at the adjacent α-carbon.

The possibility in the above formation of the 3-acetoxyfurans and 2-acetoxy-3-furanones of a reaction path involving initially the oxidative cleavage of the parent diarylfurans to *cis*-diaroylethylenes (II) followed by *cis*-addition-cyclization, was tested and shown to be unlikely by a series of experiments in which both *cis* and *trans*-dibenzoylethylenes (IIa and IIIa) and *cis*-1-chloro-1,2-dibenzoylethylene (IIc) were subjected to the above reaction conditions. In each case unreacted materials were recovered, and it is certain in these cases at least that neither the 3-acetoxyfuran nor the 2-acetoxy-3-furanone, which could easily have been detected, was produced in any significant amount.

In contrast to the above results 3-methoxy-2,5-diphenylfuran (Il) upon treatment with the lead tetraacetate–acetic acid reagent at refluxing temperature gave as the only tractable product *cis*-1-methoxy-1,2-dibenzoylethylene (III) although in only 24% yield. 3,4-Dichloro- and 3,4-dimethyl-2,5-diphenylfurans (Id,e) both of which are incapable of simple β-substitution, reacted with lead

(7) *cf.* Similar resistance to nitric acid oxidative cleavage (ref. 3).

tetraacetate in boiling acetic acid, with some difficulty in the former case and more readily in the latter. In the case of the 3,4-dichlorofuran (Id) the noncrystalline product evidently contained the low-melting *cis*- unsaturated diketone (IId) (or possibly the intermediate diacetoxy compound XII because it gave a sizable yield of the easily crystallizable *trans* unsaturated diketone (IIId) when placed in chloroform solution containing iodine and subjected to the action of sunlight. In the case of the 3,4-dimethylfuran (Ie) the reaction produced the unsaturated diketone in its stable *trans* form (IIIe) in 20% yield.

2,3,5-Triphenylfuran (If) reacted with lead tetraacetate in acetic acid as it did in chloroform to give a mixture of both the *cis* unsaturated triketone (IIf) and the 3-acetoxyfuran (IVq), but in this case the acetoxyfuran was produced in a relatively much greater yield. Thus the solvent effect in this borderline case is operative although it does not dominate as in the other cases studied.

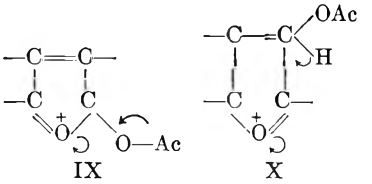
Reactions by lead tetraacetate in acetic acid with 2,5-dimesitylfuran and 2-mesityl-5-(*p*-bromophenyl)furan (Ij and k) took place rapidly but unfortunately gave non-crystalline materials (in the former case a small amount of unidentified high-melting product was obtained).

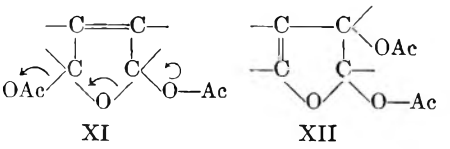
It should be noted that in the oxidation of a 3-acetoxyfuran to a 2-acetoxy-3-furanone, the 3-acetoxy group has been eliminated and a 2-acetoxy group gained. When propionic acid was used as solvent rather than acetic acid in typical oxidations of either 2,5-diphenylfuran (Ia) or 3-acetoxy-2,5-diphenylfuran (IVm), as was to be expected, the product was the 2-propionoxyfuranone-3[8] (VIIm). This product was subsequently synthesized in another way by the action of propionic anhydride and sulfuric acid on the 2-hydroxy-3-furanone (VI). It was shown in an independent experiment that the exchange of propionoxyl for or by acetoxyl does not occur in the furanone (Vm,VIIm) under the reaction conditions. The formation of the propionoxy compound in the above oxidation therefore must have involved either a group exchange in the lead tetraacetate before reaction or pick-up of a solvent molecule at the 2-position during but not after completion of the formation of the furanone system.

Discussion of results. In spite of frequently poor yields and formation of sizable amounts of resinous products, it is possible to draw some limited and tentative conclusions. The reactions of the 2,5-diarylfurans with lead tetraacetate, summarized in formulations I–VIII, involve three one-stage processes, paths A, B, and C. One of these (A) is the oxidative cleavage of the ring to give the *cis*-unsaturated 1,4-diketone (II). This is the favored reaction in chloroform solution, but it has been observed in a few instances in acetic acid as solvent, notably where both β-positions were occupied by substituents other than acetoxyl; and significantly it occurred in the case of the β-phenyl and β-methoxy compounds (If and l).

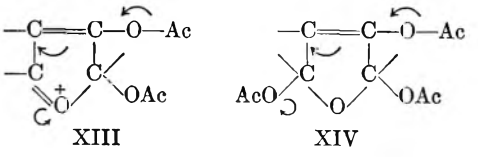
The second mode of attack (B) is substitution of acetoxyl for a β-hydrogen to give 3-actoxyfurans (IV), and is favored in acetic acid. The third process (C) which applies only to the 3-acetoxyfurans (IV), leads to 2-acetoxy-3-furanones (V) and takes place both in chloroform and in acetic acid solution. The two processes B and C often occur as successive steps in one-operation oxidations (D) to 2-acetoxy-3-furanones (V) of furans which have an open β-position. However, it is to be noted that when there is present one β-acetoxyl which would direct the primary attack alpha to that group, a second (β′) acetoxylation has not been observed.

In all of these reactions there is a fundamental similarity expressible in terms of "oxidation" or electrophilic attack at "active" or nucleophilic points on an enol or diene-ol ether system, —C=C—O— or —C=C—C=C—O—, whatever form or direction the completion of the reactions may take.[9] Thus the furan system may be pictured as responsive toward both α- and β-attack by $^{+}OCOCH_3$ or its equivalent, possibly through prior complexing with $Pb(OCOCH_3)_4$.[9] This attack would be followed by break-up of the resulting cation IX[10] or X, or of a completed 1,4- or 1,2-diacetoxyl-addition product XI or XII, and would lead to unsaturated 1,4-diketones of necessarily *cis* configuration, or to 3-acetoxyfurans.





The β-acetoxyl group specifically directs reaction to the adjacent α-position to give the 2-acetoxy-3-furanones (V) and these reactions also can be rationalized, *cf. e.g.*, XIII, XIV, XV.



(8) *cf.* The analogous oxidation of mesitol with lead tetraacetate in propionic acid to 2,4,6-trimesityl-2-propionoxycyclohexadienone (Cavill and co-workers, ref. 6).

(9) For comprehensive review and analysis of organic oxidation reactions see L. S. Levitt, *J. Org. Chem.*, 20, 1257 (1955).

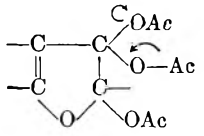
(10) *cf.* Suggested mechanism of nitric acid oxidation of 2-(*p*-bromophenyl)-5-mesitylfuran (2c).

TABLE I

LEAD TETRAACETATE OXIDATIONS

Compound	G.	$Pb(OAc)_4$, G.	Solvent	Ml.	Reaction Temp., C.	Reaction Time, min.	Recovered, %	Product, %
Ia	1	2.2	$CHCl_3$	30	20–30°	300	—	IIa, 59
Ia	*1*	2.2	*$CHCl_3$*	20	Reflux	15	35	IIa, 12
Ia	2	4.5	AcOH	40	40–50°	120	61	Vm, 14[a]
Ia	1	4	AcOH	20	Reflux	5	—	Vm, 69
Ia	1	6	AcOH	20	Reflux	5	—	Vm, 21[b]
Ia	2	4.5	C_2H_5COOH	40	Reflux	5	52	VIIm,[c] 25
IIa	0.85	1.5	AcOH	20	Reflux	5	—	IIIa, 16.5[b]
IIIa	2	4	AcOH	40	Reflux	5	10.5	[b]
VIIm	0.5	1	AcOH	10	Reflux	5	91	—
Vm	0.5	1	C_2H_5COOH	10	Reflux	5	82	—
Ib	1	1.5	$CHCl_3$	20	20–30°	180	—	IIb, 43
					50–60°	20	—	IIIb, 9
Ib	5	7.5	AcOH	80	Reflux	15	28	Vn,[c] 42
Ic	2	5	$CHCl_3$	40	Reflux	40	—	IIc, 60[a]
Ic	2	5	AcOH	30	Reflux	5	—	IVp, 51
IIc	1	2.5	AcOH	20	Reflux	5	48	—
Id	*0.8*	1.6	*$CHCl_3$*	25	Reflux	25	94	—
Id	0.8	1.6	AcOH	20	Reflux	15	60	[b,d]
Ie	1	2	$CHCl_3$	30	20–30°	240	—	IIe, 35; IIIe, 14
Ie	1	2	AcOH	20	Reflux	15	—	IIIe, 20[b]
If	1	2	$CHCl_3$	25	Reflux	20	—	IVq, 26; IIf, 53
If	*1*	2	AcOH	25	Reflux	10	—	IVq, 49· IIf, 36
Ig	1	2	$CHCl_3$	30	Reflux	20	91	—
Ig	1	2	AcOH	20	Reflux	15	—	IVr, 35
Ih	1	1.5	AcOH	20	Reflux	10	—	IVs, 31[e]
Ii	1	2	AcOH	20	Reflux	10	—	IVt, 12[b,e]
Ij	2	4	$CHCl_3$	50	50–60°	60	60	[f]
Ij	2	4	AcOH	40	Reflux	15	—	[b,g]
Ik	2	4	$CHCl_3$	50	20–30°	600	—	[b,h]
Ik	2	5	AcOH	40	Reflux	5	—	[b,i]
Il	0.5	1	$CHCl_3$	15	40–50°	20	—	[b]
Il	*1*	*1*	*AcOH*	20	Reflux	5	—	*III*, 24[b]
IVm	1	2	$CHCl_3$	25	Reflux	10	25	[b,j]
IVm	1	2	AcOH	20	Reflux	5	—	Vm, 65
IVm	1	2	C_2H_5COOH	25	Reflux	5	—	VIIm, 41
IVn	2	2.6	$CHCl_3$	40	Reflux	15	56	Vn, 27
IVn[c]	*1*	1.3	AcOH	30	Reflux	10	—	Vn, 70
IVo	0.6	1.5	$CHCl_3$	20	Reflux	15	83	—
IVo	0.8	2	AcOH	20	Reflux	5	65	[k]
IVp	0.8	1.6	$CHCl_3$	20	Reflux	20	—	Vp,[c] 65
IVp	0.7	1.5	AcOH	30	Reflux	30	—	Vp,[c] 75
IVq	1	2	AcOH	25	Reflux	30	—	Vq, 77
IVr	1	2	AcOH	30	Reflux	60	18	[b,l]

[a] At room temperature. No reaction occurred. [b] The product or major product was noncrystalline. [c] New compound; see Experimental for details. [d] The oil was converted to IIId in 30% yield from Id by exposing a chloroform solution of it containing a trace of iodine to sunlight for 2 hr. [e] C-K. Dien and R. E. Lutz, *J. Org. Chem.*, 21, 1492 (1956). [f] Colorless unknown product (0.12 g.) was isolated; m.p. 180–181°. *Anal.*: C, 54.87; H, 4.61. [g] A small amount (0.04 g.) of yellow unknown product was isolated; m.p. 172–174°. *Anal.*: C, 54.69; H, 4.53. [h] At lower temperatures (0–25°, 2 hr.) starting material was recovered. [i] At lower temperature (40–50°, 30 min.) the product also was an oil; a trace of *p*-bromobenzoic acid was isolated. [j] The oil was converted to Vm in 26% yield after refluxing 10 min. in acetic acid solution. [k] Prolonged heating (30 min.) gave only an oil. [l] The oil was converted to VIr in 28% yield by treatment with alcoholic potassium hydroxide.



XV

In two cases (IVm,r) evidence for the completed additions (XIV or XV) was obtained but unfortunately in neither case was the addition compound actually isolated in pure condition and characterized. Evidently in the series under investigation the 2,5-diaryl groups militate against the stability and isolability of such intermediates.

The above results seem generally consistent with the effect of substituents on diacetoxyl additions to olefins.[11] They are to be compared with lead tetraacetate oxidations in general,[5] and specifically with the oxidations of simple furans[4] where occasionally 1,4-diacetoxy addition compounds have

(11) R. Criegee, *Newer Methods of Preparative Organic Chemistry* (Bergmann), Interscience Publishers, Inc., N. Y., 1949, p. 1.

been isolated, and with the oxidation of anthracene through or accompanied by 1,4-diacetoxyl additions to produce acetoxyanthracene and acetoxyanthrone.[12]

EXPERIMENTAL[13]

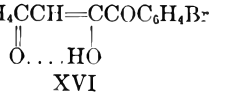
Materials. Lead tetraacetate[14] was recrystallized from acetic acid and dried *in vacuo*. Dry acetic acid was prepared by mixing 100 ml. of concd. acetic acid with 3 ml. of acetic anhydride. Reagent grade chloroform was dried by washing with concd. sulfuric acid.

General oxidation procedure. The furan was treated with lead tetraacetate in dry acetic acid or chloroform solution under the different conditions specified in Table I. The acetic acid solutions were diluted with water and extracted with ether, and the extract was washed, dried, and evaporated. The chloroform solutions were washed with water, dried, and evaporated. The products were crystallized from benzene-ligroin or ethyl acetate-ligroin mixtures. The known compounds were identified by mixture melting point.

3-Acetoxy-2,5-di-(p-bromophenyl)furan (IVn). A mixture of 6 g. of *trans*-di-(*p*-bromobenzoyl)ethylene (IIIb), 40 ml. of acetic anhydride, 20 ml. of acetyl chloride, and 5 drops of concd. sulfuric acid, was allowed to stand at 40–60° for 18 hr. and then on the steam bath for 1 hr. The dark red solution was hydrolyzed with ice water and the resulting product was extracted with ether. Evaporation and crystallization of the residue from ethyl acetate gave 5.6 g. (85%) of nearly colorless product; melting point after repeated recrystallizations from ethyl acetate-methanol mixture, 122–123°.

Anal. Calcd. from $C_{18}H_{12}Br_2O_3$: C, 49.57; H, 2.77. Found: C, 49.54; H, 2.58. λ_{max} 232.5, 332 mμ, ε 17,000, 36,500; shoulders at 250, 349 mμ, ε 12,000, 26,500; λ_{min} 264 mμ, ε 4,400.

2-Acetoxy-2,5-di(p-bromophenyl)furanone-3 (Vn) [prepared from Ib or IVn as described above (see Table I)] was also obtained by treatment of di(*p*-bromobenzoyl)ethanol (XVI)[15] with acetic anhydride and concd. sulfuric acid in the usual way (room temperature, 20 min.); crystallized from benzene-ligroin mixture, m.p. 173–174°.



XVI

Anal. Calcd. for $C_{18}H_{12}Br_2O_4$: C, 47.82; H, 2.68. Found: C, 47.51; H, 2.45. λ_{max} 226, 257, 312 mμ, ε 18,500, 9,200, 24,200. λ_{min} 243, 270 mμ, ε 7,200, 7,400.

Hydrolysis of 1 g. of Vn by refluxing methanolic sodium hydroxide (15 min.) gave 0.42 g. of XVI, m.p. 168–170°.[15]

2-Acetoxy-2,5-diphenylfuranone-3 (Vm). The ultraviolet absorption spectrum of this compound was determined for reference because it is the parent compound of this type. λ_{max} 245, 309 mμ, ε 6,500, 17,600; slight shoulder at 300 mμ, ε 16,500; λ_{min} 235, 260 mμ, ε 6,100, 4,400. This is not far different from the absorption of the corresponding 2-methoxy analog (λ_{max} 247, 314 mμ, ε 8,540, 17,400[16]). Substitution of bromines in the two phenyl *para*-positions has caused a negligible bathochromic shift in the long wave length band and a sizable increase in the absorptivity.

2-Acetoxy-4-chloro-2,5-diphenylfuranone-3 (Vp) was prepared by oxidation of 3-acetoxy-4-chloro-2,5-diphenylfuran (IVp)[17] as described above. It was also obtained by the action of acetic anhydride and concd. sulfuric acid on VIp[18] (which exists chiefly in this cyclic form) at 40–50° for 40 min. It was isolated by crystallizing from ethyl acetate–ligroin mixture; recrystallized from ethyl acetate; m.p. 173–174°.

Anal. Calcd. for $C_{18}H_{13}ClO_4$: C, 65.78; H, 3.99. Found: C, 65.62; H, 3.95. λ_{max} 250, 321 mμ, ε 7,800, 15,400; λ_{min} 240, 274 mμ, ε 6,500, 3,800.

Hydrolysis with refluxing alcoholic sodium hydroxide (5 min.) regenerated VIp in 65% yield.

2-Propionoxy-2,5-diphenylfuranone-3 (VIIm) was prepared: (*a*) by oxidation of either 2,5-diphenylfuran (Ia) or 3-acetoxy-2,5-diphenylfuran (IVm) in propionic acid as described above; crystallized from ethyl acetate-methanol mixture; m.p. 157–158°.

Anal. Calcd. for $C_{19}H_{14}O_4$: C, 74.01; H, 5.23. Found: C, 73.77; H, 4.84. λ_{max} 245, 309 mμ, ε 7,400, 18,500; λ_{min} 235, 261 mμ, ε 6,000, 4,600.

(*b*) By treatment of dibenzoylethenol (VIm) with propionic anhydride and concd. sulfuric acid (room temperature, 10 min.) yield 80%; m.p. and mixture m.p. with (a), 155–158°.

When VIIm was refluxed with lead tetraacetate-acetic acid for 5 min. only unchanged material was recovered in 91% yield. Treatment of Vm with lead tetraacetate–propionic acid (refluxing 5 min.) gave also unchanged material in 82% yield.

Hydrolysis of VIIm (0.3 g.) with methanolic potassium hydroxide (room temperature, 15 min.) gave 0.18 g. (73%) of VIm; identified by mixture melting point.

Dibenzoylacetylene was recovered largely unchanged after treatment for 1 hr. with acetic anhydride and sulfuric acid (2 drops in 20 ml.) at 50–60°. This experiment was carried out in the ill-founded hope that addition and cyclization to the acetoxyfuranone (VIm) would occur.

CHARLOTTESVILLE, VA.

(12) L. F. Fieser and S. T. Putnam, *J. Am. Chem. Soc.*, **69**, 1038 (1947).

(13) (a) Melting points are "corrected"; (b) microanalyses were by Miss Yuen-May Lai.

(14) L. F. Fieser, *Experiments in Organic Chemistry*, 2nd ed., D. C. Heath and Co., N. Y., 1941, p. 436.

(15) R. E. Lutz, F. N. Wilder, and C. I. Parrish, *J. Am. Chem. Soc.*, **56**, 1980 (1934).

(16) R. E. Lutz, T. Amacker, S. M. King, and N. H. Shearer, *J. Org. Chem.*, **15**, 181 (1950).

(17) R. E. Lutz, A. H. Stuart, F. N. Wilder, and W. C. Connor, *J. Am. Chem. Soc.*, **59**, 2314 (1937).

(18) R. E. Lutz and A. H. Stuart, *J. Am. Chem. Soc.*, **59**, 2322 (1937).

[JOINT CONTRIBUTION FROM THE DEPARTMENTS OF CHEMISTRY OF WAYNE STATE UNIVERSITY AND FLORIDA STATE UNIVERSITY]

Optical Rotatory Dispersion Studies. XIII.[1] Assignment of Absolute Configuration to Certain Members of the Guaianolide Series of Sesquiterpenes*[2]

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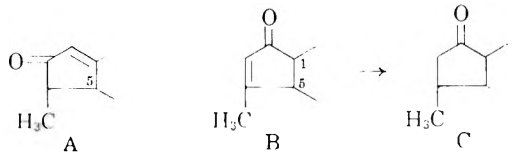
The rotatory dispersion curves of tenulin, helenalin, geigerin, and of many of their derivatives have been measured. These results demonstrate that (*a*) tenulin and helenalin contain the same substitution pattern in the cyclopentenone ring and (*b*) that they belong to the same stereochemical series insofar as the ring juncture is concerned. A tentative assignment of absolute configuration at C-1 and C-5 is made by comparison of their rotatory dispersion curves with those of steroid reference compounds.

The guaianolide series of sesquiterpenes encompasses a group of lactones which is based on the skeleton I and which yields guaiazulene and/or chamazulene upon dehydrogenation. The most extensively studied members are tenulin (IIa)[4,5] and helenalin (VI),[6-9] but a considerable number of additional representatives are being uncovered[10-12] and a striking connection with the large group of eudalenoid sesquiterpenes has been presented.[13] In view of the key role which the guaianolides play in the biogenetic scheme of the sesquiterpenes, it appeared of interest to apply rotatory dispersion measurements[14] to certain outstanding structural and stereochemical problems in this field.

Structure IIa for tenulin, as proposed first by Barton and de Mayo[4] was in substantial agreement with the independent degradation experiments of the Florida group[5] except for certain ambiguities relating to the cyclopentenone ring for which a second alternative (IIb) was suggested.[5,15] This point of difference has now been settled in favor of IIa on the basis of two independent lines of evidence:

(*a*) In the nuclear magnetic resonance spectra of tenulin (IIa) and dihydrotenulin (III), or isotenulin (IV) and dihydroisotenulin (Va), the peak corresponding to the hydrogen atoms in $-\overset{|}{\underset{|}{C}}-CH_3$ remained constant. This is only consistent with partial structure A (=IIa) since hydrogenation of the double bond in the alternative B (=IIb) would lead to C, which possesses three more hydro-



* This paper is a contribution in honor of Lyndon F. Small, former Editor of the Journal.

(1) Paper XII, C. Djerassi and D. Marshall, *Tetrahedron*, **1**, 238 (1957).

(2) The work at Wayne State University was supported by a research grant (No. CY-2919) from the National Cancer Institute, National Institutes of Health. The work at Florida State University was supported by a grant from the Research Corp.

(3a) Wayne State University, Detroit, Mich.; (b) Florida State University, Tallahassee, Fla.

(4) D. H. R. Barton and P. De Mayo, *J. Chem. Soc.*, 1956, 142.

(5) B. H. Braun, W. Herz, and K. Rabindran, *J. Am. Chem. Soc.*, 78, 4423 (1956).

(6) E. P. Clark, *J. Am. Chem. Soc.*, **62**, 597 (1940) and earlier papers.

(7) R. Adams and W. Herz, *J. Am. Chem. Soc.*, **71**, 2546, 2551, 2554 (1949).

(8) G. Büchi and D. Rosenthal, *J. Am. Chem. Soc.*, **78**, 3860 (1956).

(9) V. Herout, M. Romanuk, and F. Sorm, *Collection Czechoslov. Chem. Commun.*, **21**, 1359 (1956).

(10a) Z. Cekan, V. Herout, and F. Sorm, *Collection Czechoslov. Chem. Commun.*, **19**, 798 (1954); Z. Cekan, V. Herout, and F. Sorm, *Chemistry & Industry*, 604 (1954), 1234 (1956); V. Herout and F. Sorm, *Collection Czechoslov. Chem. Commun.*, **18**, 854 (1953), **19**, 792 (1954); F. Sorm, L. Novotny and V. Herout, *Chemistry & Industry*, 569 (1955); V. Herout, L. Novotny and F. Sorm, *Collection Czechoslov. Chem. Commun.*, **21**, 1484 (1956); V. Herout, L. Dolejs and F. Sorm, *Chemistry & Industry*, 1236 (1956).

(10b) A. Meisels and A. Weizmann, *J. Am. Chem. Soc.*, **75**, 3865 (1953); Y. Mazur and A. Meisels, *Chemistry & Industry*, 492 (1956).

(10c) Y. Naves, *Helv. Chim. Acta*, **31**, 1172 (1948); L. Crabalona, *Bull. soc. chim. France*, **15**, 357 (1948); M. Romanuk, V. Herout, and F. Sorm, *Collection Czechoslov. Chem. Commun.*, **21**, 894 (1956).

(10d) T. Kariyone, S. Naito, and J. Chatani, *Pharm. Bull.*, **2**, 339 (1954); T. Kariyone and S. Naito, *J. Pharm. Soc. Japan*, **75**, 39 (1955); S. Naito, *J. Pharm. Soc. Japan*, **75**, 93, 325 (1955).

(11) G. W. Perold, *J. Chem. Soc.*, 47 (1957). The position of the hydroxyl group in geigerin was established by D. H. R. Barton and collaborators (to be published).

(12) W. Herz, unpublished observation.

(13) D. H. R. Barton, P. De Mayo, and M. Shafiq, *J. Chem. Soc.*, 929 (1957).

(14) For general survey see C. Djerassi, *Bull. soc. chim. France*, 741 (1957).

(15) Formula IIb was originally favored by one of us (W.H.) because of a remarkable base-catalyzed cleavage reaction which dehydrodesacetyldihydroisotenulin undergoes.[5] Barton, quoted by P. de Mayo, *Perfumery Essent. Oil Record*, **48**, 68 (1957), has recently suggested a rationalization for this transformation based on IIa. Work to establish more definitely the orientation of the lactone ring of tenulin is still in progress.

gen atoms contributing to the NMR peak under discussion.[16]

(*b*) As pointed out in earlier papers,[14] the characteristic shapes of rotatory dispersion curves of cycloalkanones and cycloalkenones should be governed chiefly by the carbonyl chromophore rather than by additional substituents (*e.g.*, esters, hydroxyl groups, lactones[17]) unless certain conformational factors interfere.[18] Since the structure of helenalin (VI) appears to be settled (cyclopentenone ring as in A),[8] it could serve as an adequate rotatory dispersion standard for differentiating between expressions IIa and IIb for tenulin, provided that the absence of major conformational distortion in the cycloheptane ring due to the different attachment of the butenolide ring could be demonstrated. This assumption was found to be valid as shown in the sequel.

In Fig. 1 are reproduced the rotatory dispersion

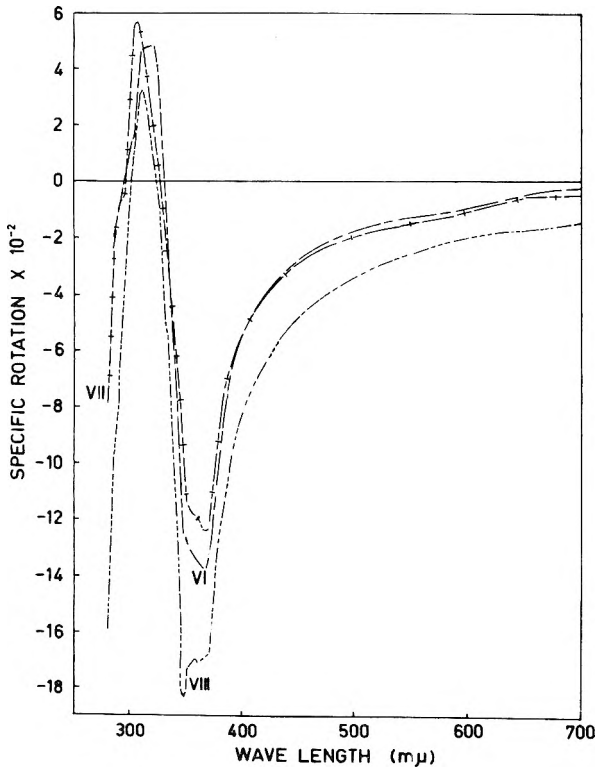


FIG. 1. ROTATORY DISPERSION CURVES OF HELENALIN (VI), DIHYDROHELENALIN (VII), AND ISOHELENALIN (VIII).

curves of helenalin (VI), dihydrohelenalin (VII), and isohelenalin (VIII). These three substances differ only in the lactone ring and it is evident that alterations in that portion of the molecule play only a negligible role, since except for some amplitude[19] changes, the rotatory dispersion curves are very similar and are characterized by a negative Cotton-effect curve[19] with some fine structure in the 350–375 mμ region.

The rotatory dispersion curves of tenulin (IIa) and isotenulin (IV) are given in Fig. 2 and the close correspondence of these two curves—except for some amplitude differences below 325 mμ—demonstrates that the additional ring involving the hemiketal system of tenulin (IIa) as compared to an ordinary acetoxyl substituent in isotenulin (IV) does not affect the rotatory dispersion picture.

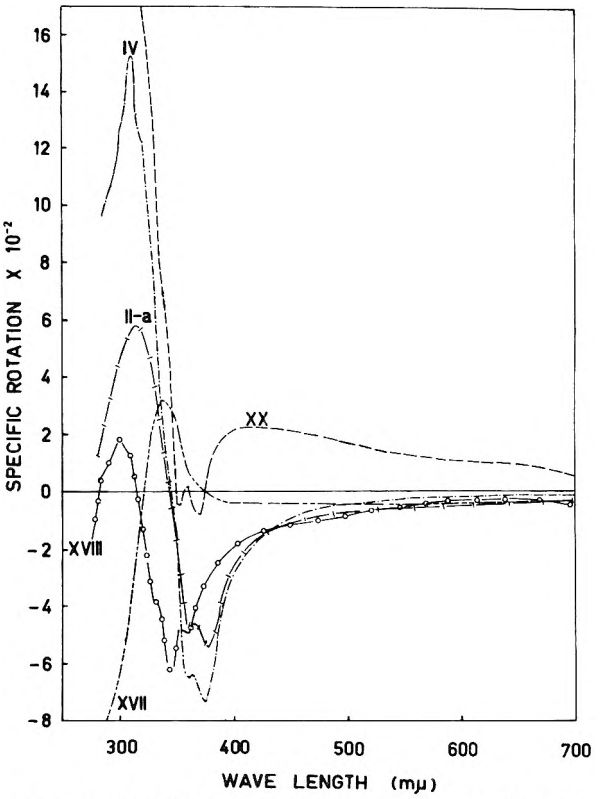


FIG. 2. ROTATORY DISPERSION CURVES OF TENULIN (IIa), ISOTENULIN (IV), DESACETYLNEOTENULIN (XVII), GEIGERIN (XVIII), AND ISOPHOTOSANTONIC LACTONE (XX).

With the above demonstration that alterations in the cycloheptane ring affect the amplitude but not the shape of the dispersion curve, a comparison of the pertinent curves in Figs. 1 and 2 (*e.g.* helenalin (VI) *vs.* tenulin (IIa) appears valid and the striking coincidence of their respective dispersion curves leaves little doubt that both sesquiterpenes must possess the same cyclopentenone chromophore (type A). This in turn implies that the angular hydrogen atom in both tenulin and helenalin must have the same orientation, since otherwise

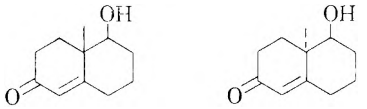
(16) We are indebted to Dr. R. E. Glick, now at Pennsylvania State University, who determined the NMR spectra of these compounds in the chemical laboratories of Harvard University.

(17) The negligible effect of butenolide systems has been demonstrated in a detailed study of the rotatory dispersion of steroidal cardiac aglycones (to be published).

(18) A case in point is the marked difference in the rotatory dispersion curves of α- and β-vetivone (C. Djerassi, R. Riniker, and B. Riniker, *J. Am. Chem. Soc.*, **78**, 6377 (1956).

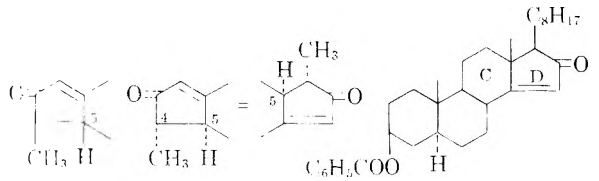
(19) For nomenclature and method of recording rotatory dispersion data in the experimental section, see C. Djerassi and W. Klyne, *Proc. Chem. Soc*, 55 (1957).

the curves in Fig. 1 and in Fig. 2 would have been of mirror image types in spite of the fact that helenalin and tenulin are not antipodes. This statement is best supported by a concrete example illustrated in Fig. 3 with the rotatory dispersion curves of (8S, 9S)-(+)-(XII) and (8S, 9R)-(−)-(XIII) Δ^4-9-methyl-8-hydroxy-3-octalones [prepared by Prelog and Acklin.[20] While these two substances are not antipodes, their dispersion curves are nevertheless of mirror image type since the angular substituents are of opposite orientation[21] and the hydroxyl group plays no role in this instance. The rotatory dispersion curve of XII is essentially identical with that of typical Δ^4-3-keto steroids (ref. 18), thus providing definitive proof for the assignments of absolute configurations made by Prelog and Acklin[18] by the less secure method of molecular rotation differences.



XII XIII

The above rotatory dispersion evidence indicates that tenulin (IIa) and helenalin (VI) possess the same cyclopentenone chromophore and identical stereochemistry at C-5 and it appeared of interest to determine whether this type of approach could be extended to assign actual absolute configurations to these two sesquiterpenes, *i.e.* whether they should be represented by partial formulas D or E (the methyl group at C-4 being assumed to be equatorially oriented).



D E XIV

In an earlier paper,[22] it was shown that substitution of an angular methyl group by a hydrogen atom did not affect the rotatory dispersion curve. Similarly, introduction of equatorial alkyl groups α to the carbonyl system had no important effect,[22,23] and consequently, if one assumed that substitution of a cyclohexane for a cycloheptane ring would not result in drastic alteration of the dispersion picture, then it should be possible to utilize an appropriate steroid ketone as a reference substance of known absolute configuration. The

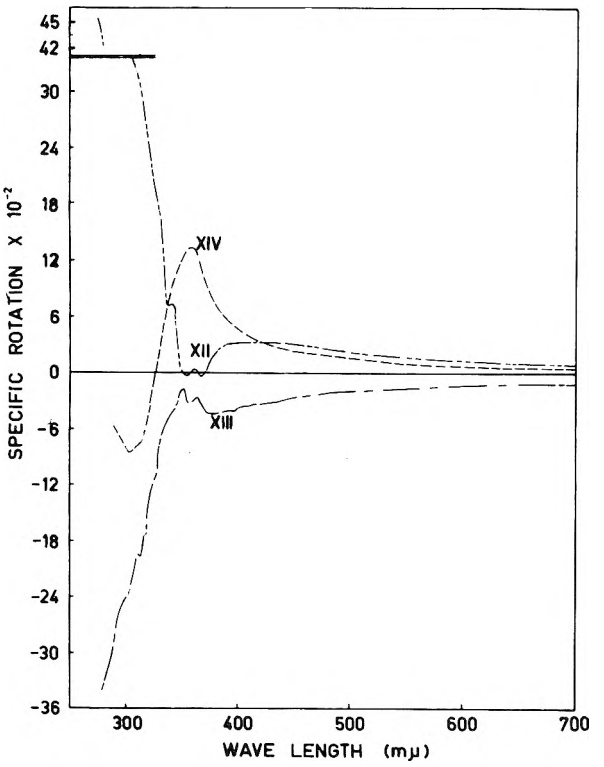


FIG. 3. ROTATORY DISPERSION CURVES OF (8S, 9S)-(+)-Δ^4-9-METHYL-8-HYDROXY-3-OCTALONE (XII), (8S, 9R)-(−)-Δ^4-9-METHYL-8-HYDROXY-3-OCTALONE (XIII) AND Δ^{14}-CHOLESTEN-3β-OL-16-ONE BENZOATE (XIV).

steroid chosen by us for this purpose was Δ^{14}-cholesten-3β-ol-16-one benzoate (XIV)[24,25] and its rotatory dispersion curve (Fig. 3) is characterized by a strongly positive Cotton-effect curve[19] in contrast to the negative Cotton effect exhibited by helenalin (Fig. 1) and tenulin (Fig. 2). With the reservations outlined above, rings C and D of the steroid XIV can be used as a reference system of established absolute configuration, from which it follows that tenulin (IIa) and helenalin (VI) should be assigned the absolute configuration expressed by partial formula E (C-5 hydrogen atom α oriented).

This same approach can also be extended to the reduction products of tenulin and helenalin with a saturated cyclopentanone ring. In Fig. 4 are collected the rotatory dispersion curves of dihydrotenulin (III), dihydroisotenulin (Va), its desacetyl derivative (Vb), and desacetyldihydroalloisotenulin (XI). All of these compounds are identical insofar as the bicyclic ring juncture is concerned and differ only in the nature of the attachment or substitution of the lactone ring. Since the cyclopentanone moiety and its immediate stereochemical environment should govern the shape of the rotatory dispersion curve, it is not surprising that, ex-

(20) V. Prelog and W. Acklin, *Helv. Chim. Acta*, **39**, 748 (1956).

(21) The reason, of course, is that the governing chromophores—in this instance the octalone systems of XII and XIII—are enantiomeric.

(22) C. Djerassi, R. Riniker, and B. Riniker, *J. Am. Chem. Soc.*, **78**, 6362 (1956).

(23) Unpublished observation.

(24) K. Tsuda and R. Hayatsu, *J. Am. Chem. Soc.*, **78**, 4107 (1956).

(25) Esters, such as acetates or benzoates, do not contribute to the shape of the rotatory dispersion curve.

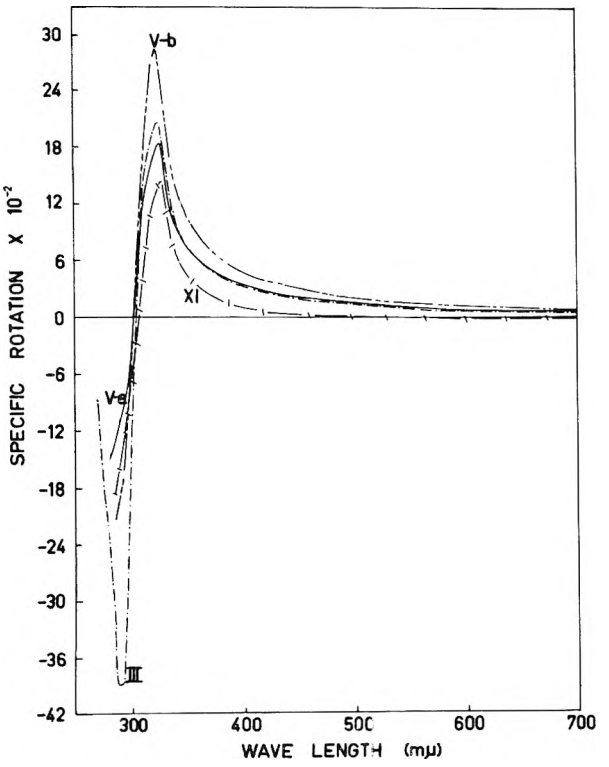


FIG. 4. ROTATORY DISPERSION CURVES OF DIHYDROTENULIN (III), DIHYDROISOTENULIN (Va), DESACETYLDIHYDROISOTENULIN (Vb), AND DESACETYLDIHYDROALLOISOTENULIN (XI).

cept for amplitude differences, all of the curves are similar and characterized by a single, positive Cotton-effect curve.[19] Virtually identical results are noted in Fig. 5 with the appropriate saturated helenalin derivatives, dihydroisohelenalin (IX) and tetrahydrohelenalin (X).[26]

The conclusion can be reached from Figs. 4 and 5 that the ring juncture (C-1 and C-5) in the saturated tenulin and helenalin derivatives is the same and it now remains to be determined whether absolute configurations F or G apply to these hydrogenation products, since either one could be derived from the cyclopentenone precursor E. In the absence of any knowledge of the stereochemistry of the substituents in the cycloheptane ring which could strongly affect the mode of hydrogen addition, no prediction could be made. However, if one again equates a cyclohexane with a cycloheptane ring, then rings A and B of the A-nor steroids XV and XVI could be selected as reference standards. The rotatory dispersion curve[22] of the *trans*-hydrindanone derivative XV is characterized by a powerful, positive, single Cotton effect[27] while the *cis*-ketone XVI exhibits a negative one. On that basis, the rotatory dispersion curves of the sesquiterpene reduction products discussed above are

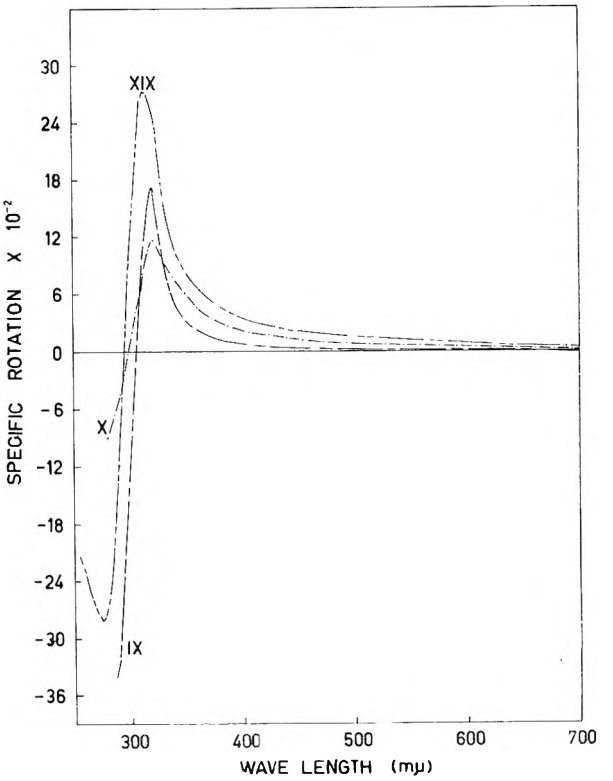
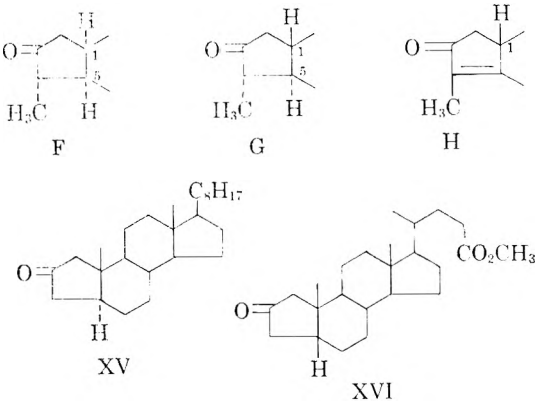


FIG. 5. ROTATORY DISPERSION CURVES OF DIHYDROISOHELENALIN (IX), TETRAHYDROHELENALIN (X), AND DIHYDROGEIGERIN (XIX).

of the same type as that of the steroid XV and we assign tentatively the absolute configuration implicit in partial structure G to them.



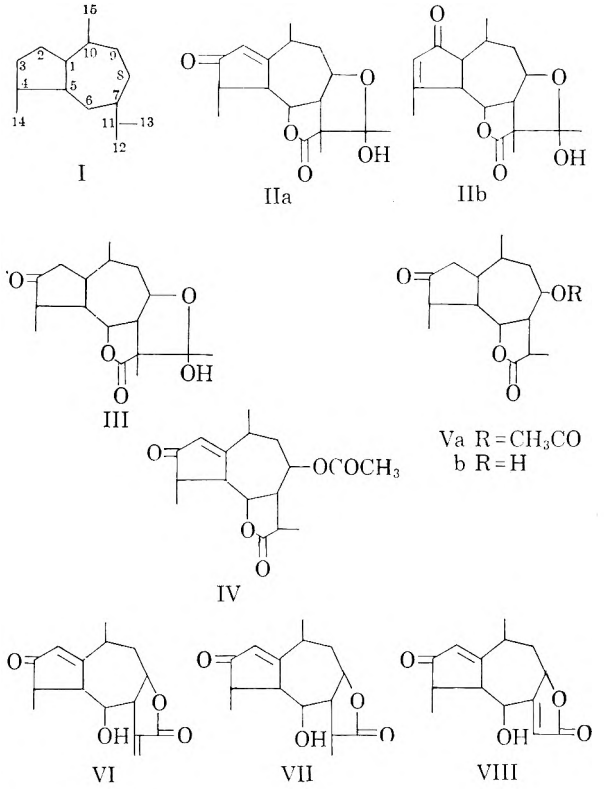
An interesting case is represented by desacetylneotenulin (XVII),[4] geigerin (XVIII),[11] and isophotosantonic lactone (XX)[13] in which the double bond in the cyclopentenone ring occupies the alternate position as compared to tenulin (IIa) and helenalin (VI). The mode of substitution in that ring has been established by ultraviolet spectral measurements as well as by ozonolysis and isolation of acetic acid. The rotatory dispersion curves

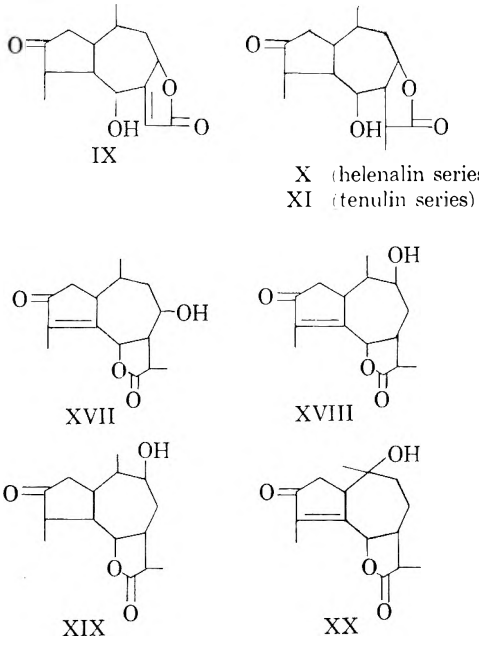
(26) Tetrahydrohelenalin (X) and desacetyldihydroalloisotenulin (XI) are not identical and must differ in the orientation of one or more asymmetric centers in the cycloheptane ring (*excluding* the ring juncture).

(27) This is to be expected since it should be the mirror image of a 16-ketosteroid which is known [C. Djerassi, W. Closson, and A. E. Lippman, *J. Am. Chem. Soc.*, **78**, 3163 (1956)] to show a strong negative Cotton effect.

of geigerin (XVIII) (Fig. 2) and of dihydrogeigerin (XIX) (Fig. 5) are so similar in shape to those of tenulin and dihydrotenulin, that we conclude that geigerin (XVIII) is represented by the partial, absolute structure H and dihydrogeigerin (XIX) by G. Desacetylneotenulin (XVII) on the other hand exhibits a completely different type of dispersion curve (Fig. 2) and while it is not the mirror image of that of geigerin (XVIII), the Cotton effect is nevertheless of opposite sign and barring some unknown conformational effect produced by substituents in the cycloheptane ring, desacetylneotenulin should be represented as the antipode of H (C-1 hydrogen atom α).

Isophotosantonic lactone (XX) exhibits a dispersion curve (Fig. 2) of the tenulin (IIa) type except that the entire curve is moved towards positive rotation and no peak is noticeable in the 300 mμ region. In fact, its curve is strikingly similar to that of Δ^4-3-keto steroids,[22,28] which again suggests that XX should be assigned the absolute configuration H with the C-1 hydrogen atom β-oriented.[29]





(28) It was shown in refs. 18 and 22 that the methyl group on the double bond did not influence the rotatory dispersion curve of Δ^4-3-ketosteroids.

(29) The striking difference in ease of hydrogenation between geigerin and isophotosantonic lactone, on the one hand, and desacetylneotenulin, on the other, may conceivably be rationalized by invoking the above argument concerning the configuration of these three substances. Whereas geigerin and isophotosantonic lactone[13] are reportedly converted to the respective dihydroderivatives on shaking with palladium catalysts in ethanol, desacetylneotenulin remains unaffected under these conditions (unpublished observations by K. Rabindran).

EXPERIMENTAL[30]

Tenulin (IIa). R. D. (Fig. 2) in dioxane (c 0.056), 25°: $[\alpha]_{700}$ −39°, $[\alpha]_{589}$ −50°, $[\alpha]_{375}$ −537°, $[\alpha]_{365-367.5}$ −461°, $[\alpha]_{360}$ −472°, $[\alpha]_{312.5}$ +577°, $[\alpha]_{280}$ +123°.

Dihydrotenulin (III). R. D. (Fig. 4) in dioxane (c 0.106), 25°: $[\alpha]_{700}$ +60°, $[\alpha]_{589}$ +106°, $[\alpha]_{325}$ +2050°, $[\alpha]_{290}$ −3890°, $[\alpha]_{270}$ −901°.

Isotenulin (IV). R. D. (Fig. 2) in dioxane (c 0.10), 26°: $[\alpha]_{700}$ −16°, $[\alpha]_{589}$ −20°, $[\alpha]_{372.5}$ −727°, $[\alpha]_{362.5}$ −638°, $[\alpha]_{360}$ −650°, $[\alpha]_{315}$ +1270° (infl.), $[\alpha]_{310}$ +1520°, $[\alpha]_{285}$ +960°.

Dihydroisotenulin (Va). R. D. (Fig. 4) in dioxane (c 0.10), 24°: $[\alpha]_{700}$ +77°, $[\alpha]_{589}$ +99°, $[\alpha]_{325}$ +1837°, $[\alpha]_{280}$ −1500°.

Desacetyldihydroisotenulin (Vb). R. D. (Fig. 4) in dioxane (c 0.10), 24°: $[\alpha]_{700}$ +80°, $[\alpha]_{589}$ +137°, $[\alpha]_{322.5}$ +2848°, $[\alpha]_{285}$ −2125°.

Helenalin (VI) (G. Büchi). R. D. (Fig. 1) in dioxane (c 0.10), 25°: $[\alpha]_{700}$ −25°, $[\alpha]_{589}$ −102°, $[\alpha]_{365}$ −1369°, $[\alpha]_{350}$ −1274° (infl.), $[\alpha]_{320}$ +485°, $[\alpha]_{300}$ +140° (infl.), $[\alpha]_{285}$ −190°.

Dihydrohelenalin (VII) (G. Büchi). R. D. (Fig. 1) in dioxane (c 0.087), 25°: $[\alpha]_{700}$ −46°, $[\alpha]_{589}$ −122°, $[\alpha]_{367.5}$ −1232°, $[\alpha]_{356}$ −1185° (infl.), $[\alpha]_{305}$ +575°, $[\alpha]_{295}$ −46° (infl.), $[\alpha]_{280}$ −782°.

Isohelenalin (VIII) (G. Büchi). R. D. (Fig. 1) in dioxane (c 0.0825), 25°: $[\alpha]_{700}$ −139°, $[\alpha]_{589}$ −208°, $[\alpha]_{360}$ −1705°, $[\alpha]_{357.5}$ −1695°, $[\alpha]_{347.5}$ −1833°, $[\alpha]_{310}$ +327°, $[\alpha]_{380}$ −1589°.

Dihydroisohelenalin (IX) (G. Büchi). R. D. (Fig. 5) in dioxane (c 0.098), 25°: $[\alpha]_{700}$ −4°, $[\alpha]_{589}$ +5°, $[\alpha]_{320}$ +1720°, $[\alpha]_{285}$ −3420°.

Tetrahydrohelenalin (X) (G. Büchi). R. D. (Fig. 5) in dioxane (c 0.08), 24°: $[\alpha]_{700}$ +23°, $[\alpha]_{589}$ +41°, $[\alpha]_{320-322.5}$ + 1150°, $[\alpha]_{283}$ −925°.

(30) For experimental procedure and errors see footnote 34 in ref. 18. The only difference between the current and earlier measurements was that in the present work a mechanically oscillating polarizer [H. Rudolph, *Proc. Instrum. Soc. Amer.*, Sept. 1956 (paper No. 56-3-1)] was employed which resulted in a saving of time. We are greatly indebted to the various investigators listed in the experimental section for supplying us with samples. Where no source is listed, the specimen came from the collection of W. H. The data are presented in the manner recommended in ref. 19.

Desacetyldihydrocalloisotenulin (XI). R. D. (Fig. 4) in dioxane (c 0.102), 25°: $[\alpha]_{700}$ −7°, $[\alpha]_{589}$ −2°, $[\alpha]_{327.5}$ +1441°, $[\alpha]_{285}$ −1853°.

(8S, 9S)-(+)-Δ⁴-9-methyl-8-hydroxy-3-octalone (XII) (V. Prelog). R. D. (Fig. 3) in dioxane (c, 0.152), 25°: $[\alpha]_{700}$ +111°, $[\alpha]_{589}$ +161°, $[\alpha]_{405}$ +340° (sh.), $[\alpha]_{370}$ −16°, $[\alpha]_{362.5}$ +54°, $[\alpha]_{357.5}$ −14°, $[\alpha]_{342.5}$ −737°, $[\alpha]_{340}$ +692°, $[\alpha]_{275}$ +4550°.

(8S, 9R)-(−)-Δ⁴-9-methyl-8-hydroxy-3-octalone (XIII) (V. Prelog). R. D. (Fig. 3) in dioxane (c 0.104), 25°: $[\alpha]_{700}$ −100°, $[\alpha]_{589}$ −125°, $[\alpha]_{410-412.5}$ −345° (infl.), $[\alpha]_{389}$ −442° (sh.), $[\alpha]_{365}$ −258°, $[\alpha]_{357.5}$ −316°, $[\alpha]_{352.5}$ −160°, $[\alpha]_{315}$ −1980°, $[\alpha]_{312.5}$ −1900°, $[\alpha]_{280}$ −3390°.

Δ¹⁴-Cholesten-3β-ol-16-one benzoate (XIV) (K. Tsuda). R. D. (Fig. 3) in dioxane (c 0.10), 25°: $[\alpha]_{700}$ +77°, $[\alpha]_{589}$ +97°, $[\alpha]_{360}$ +1332°, $[\alpha]_{305}$ −845°, $[\alpha]_{290}$ −555°.

Desacetylneotenulin (XVII) (D. H. R. Barton, W. Herz). R. D. (Fig. 2) in dioxane (c 0.085), 24°: $[\alpha]_{700}$ −41°, $[\alpha]_{589}$ −48°, $[\alpha]_{337.5}$ +318°, $[\alpha]_{290}$ −800°.

Geigerin (XVIII) (G. W. Perold). R. D. (Fig. 2) in dioxane (c 0.10), 24°: $[\alpha]_{700}$ −52°, $[\alpha]_{589}$ −30°, $[\alpha]_{357.5}$ −499°, $[\alpha]_{352.5}$ −481°, $[\alpha]_{346}$ −623°, $[\alpha]_{330}$ −376° (infl.), $[\alpha]_{300}$ +180°, $[\alpha]_{275}$ −175°.

Dihydrogeigerin (XIX) (G. W. Perold). R. D. (Fig. 5) in methanol (c 0.085), 24°: $[\alpha]_{700}$ +46°, $[\alpha]_{589}$ +102°, $[\alpha]_{312.5}$ +2720°, $[\alpha]_{275}$ −2827°, $[\alpha]_{255}$ −2144°.

Isophotosantonic lactone (XX) (D. H. R. Barton). R. D. (Fig. 2) in dioxane (c 0.10), 24°: $[\alpha]_{700}$ +56°, $[\alpha]_{589}$ +117°, $[\alpha]_{405}$ +224°, $[\alpha]_{370}$ −74°, $[\alpha]_{360}$ +26°, $[\alpha]_{352.5}$ −48°, $[\alpha]_{275}$ +2836°.

DETROIT, MICH.
TALLAHASSEE, FLA.

[CONTRIBUTION FROM THE NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES, NATIONAL INSTITUTES OF HEALTH, DEPARTMENT OF HEALTH, EDUCATION AND WELFARE, PUBLIC HEALTH SERVICE]

Structures Related to Morphine. VIII. Further Syntheses in the Benzomorphan Series*[1,2]

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Received June 3, 1957

2,5,9-Trimethyl-6,7-benzomorphan (VIII) has been synthesized from 3,4-lutidine methiodide (V) and benzylmagnesium chloride or from β-tetralone, while the hydroxy derivative (X) results from V and *p*-methoxybenzylmagnesium chloride. Compound VIII has also been converted to X *via* nitration, reduction, and diazotization and has been degraded to 1,2-dimethylnaphthalene.

Compound X, a close chemical relative of the potent analgesic racemorphan (IIIb) is an effective analgesic in mice with relatively low toxicity.

Recent studies in our laboratories have shown that 2,5-dimethyl-6,7-benzomorphan (IVa)[3] and the phenolic congener (IVb)[4] possess lower analgesic activity and lower toxicity than *N*-methylmorphinan (IIIa) and racemorphan (IIIb)[5,6] respectively. Stereochemically, structure IV simulates structure III except at carbon 9 (carbon 14 in III). The introduction of a methyl substituent at position 9 would complete this stereochemical approximation, and might be expected to enhance the analgesic effectiveness of IV. The present report is concerned with such an alteration of IV, the synthesis of 2,5,9-trimethyl 6,7-benzomorphan (VIII) and the hydroxy analog (X), compounds in which the C-methyl groups may be regarded as fragments of ring C of III. Attempts were first made to synthesize VIII by the sequence of reactions employed in the preparation of IVa.[3] However, the Knoevenagel reaction with 5-dimethylamino-3-methyl-3-phenyl-2-pentanone, a key step in this scheme of reactions, failed.[2] We then turned our attention to the synthesis developed by Grewe[5] for the morphinans (III and analogs)[6] which is outlined in Fig. 1. Transposing to our own case would merely involve substituting 3,4-lutidine methiodide (V) for 2-methyl-5,6,7,8-tetrahydrohydroisoquinoline methiodide (I).

In 1909 Freund and Bode[7] reported the formation of unstable dihydropyridines when pyridine methiodides and Grignard reagents were brought to reaction in ether. When we utilized benzylmagnesium chloride and V in this manner, a readily autoxidizable dihydro derivative (VI) was obtained. It was quickly distilled at 0.5 mm. and hydrogenated (palladium–barium sulfate) to the more stable tetrahydro compound (VII) which was cyclized (after distillation) to VIII with 85% phosphoric acid. The overall yield of VIII, based on 3,4-lutidine methiodide, was 20%. No attempt was made to characterize VI and VII. Similarly 2′-hydroxy-2,5,9-trimethyl-6,7-benzomorphan (X) resulted from *p*-methoxybenzylmagnesium chloride

* This paper is a contribution in honor of Lyndon F. Small, former Editor of the Journal.

(1) The benzomorphan nomenclature was proposed by Dr. J. A. Barltrop [*J. Chem. Soc.*, 399 (1947) and private communication (1956).]

(2) Paper VII, E. L. May, *J. Org. Chem.*, **22**, 593 (1957).

(3) E. L. May and J. G. Murphy, *J. Org. Chem.*, **20**, 257 (1955).

(4) N. B Eddy, J. G. Murphy, and E. L. May, *J. Org. Chem.*, **22**, 1370 (1957).

(5) R. Grewe and A. Mondon, *Chem. Ber.*, **81**, 279 (1948); R. Grewe, A. Mondon, and E. Nolte, *Ann.*, **554**, 161 (1949).

(6) O. Schnider and A. Grüssner, *Helv. Chim. Acta*, **32**, 821 (1949).

(7) M. Freund and G. Bode, *Ber.*, **42**, 1746 (1909).

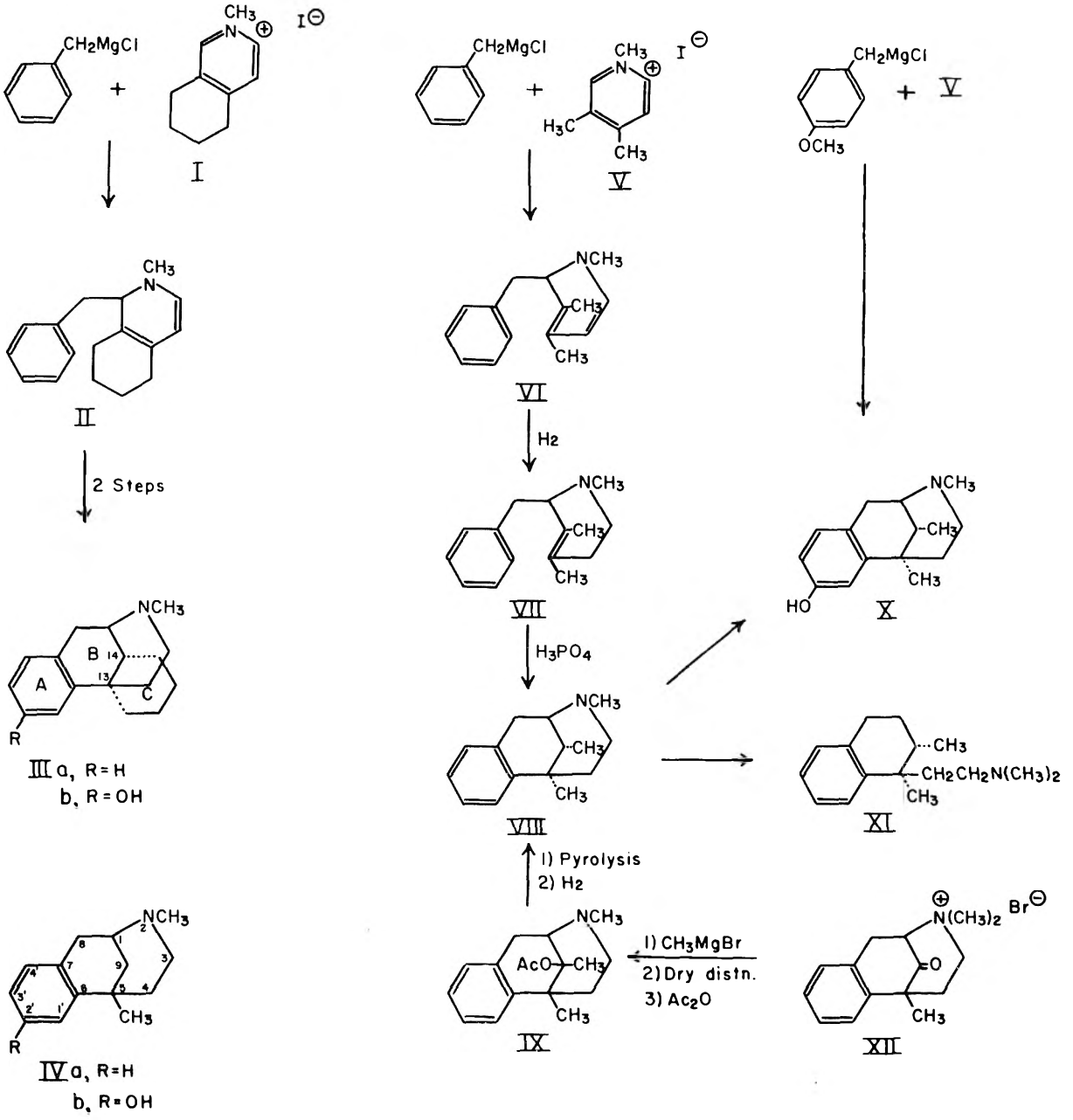


FIGURE 1.

and V. Ring closure in this instance was effected with either phosphoric or hydrobromic acid, methyl ether cleavage taking place simultaneously. Compound X could also be obtained from VIII by nitration, hydrogenation, and diazotization.

The structure of VIII (and thus X) was confirmed by subjecting its methiodide to Hofmann elimination, hydrogenating the resulting methine to 1,2-dimethyl-1-(2-dimethylaminoethyl)-1,2,3,4-tetrahydronaphthalene (XI) and aromatizing XI (palladium-charcoal) to the known 1,2-dimethylnaphthalene. Furthermore, an alternative synthesis was developed for VIII. In this synthesis 2,5-dimethyl-9-oxo-6,7-benzomorphan methiodide (XII)[3] was first brought to reaction with excess methylmagnesium iodide. Dry distillation of the resultant methylcarbinol methiodide in high vacuum followed by acetylation of the distilled base yielded the ester IX. On pyrolysis, IX lost acetic acid; hydrogenation of the methylene derivative resulting afforded VIII. This alternative synthesis is potentially useful for the preparation of homologs of VIII and X.

Regarding the stereochemistry of VIII and X, the iminoethano system is undoubtedly *cis*-fused to the hydroaromatic ring. With less certainty the methyl groups at C-5 and C-9 are assigned as *cis* for the newly formed hydroaromatic ring B in analogy to the morphinans (III)[5] where it has been shown that rings B and C are *cis*-fused. This is

consistent with an expected *trans* addition[8] (on ring closure) to the olefinic double bond of VII or the dihydrogenated II. It is noteworthy that a diastereoisomer[9] of VIII could not be detected in either of the methods employed for its synthesis.

Compounds VIII and X are from one third to two thirds as potent, in mice, as the morphinan analogs IIIa and IIIb respectively. They are also less toxic than IIIa and IIIb. A more detailed account of their pharmacology is presented in the following communication.[4]

EXPERIMENTAL

Microanalyses are from the Institute's service analytical laboratory under the direction of Dr. William C. Alford. Infrared data are from Mr. William Jones of this Institute.

3,4-Lutidine methiodide (V). A mixture of 5 ml. of 3,4-lutidine,[10] 3 ml. of methyl iodide, 15 ml. of benzene, and 15 ml. of acetone, left for 2 hr. (occasional shaking and ice-cooling) and cooled at 0° for 4 hr. gave 11 g. (96%) of V; long prisms from acetone, m.p. 123–124°.

Anal. Calcd. for $C_8H_{12}IN$: C, 38.57; H, 4.85. Found: C, 38.24; H, 4.90.

2,5,9-Trimethyl-6,7-benzomorphan (VIII) *hydrochloride.* To a stirred suspension of 12 g. of V and 100 ml. of dry ether (cooled in ice water) was added during 5 min., 100 ml. of 0.5*M* ethereal benzylmagnesium chloride. The mixture was then stirred without cooling for 1.5 hr., poured into ice water–ammonium chloride, and basified with ammonium hydroxide. The ethereal layer was extracted three times with 10% hydrochloric acid in *ca.* twofold excess. The combined extracts were basified with cold ammonium hydroxide and the liberated base was dried in ether and distilled at 0.5 mm. (air-bath temperature 125°). The resultant 5.8 g. of air-sensitive VI was quickly dissolved in 100 ml. of normal hydrochloric acid and hydrogenated with 2.0 g. of 5% palladium–barium sulfate. During 6 hr. 0.8 molecular equivalent of hydrogen was absorbed; uptake had practically ceased. The mixture was filtered through Super-Cel, basified with ammonium hydroxide, and the liberated VII dried in ether. Distillation as described for VI gave 3.8 g. of VII which, with 38 g. of 85% phosphoric acid, was kept at 145–150° for 2.5 days. The cooled, dark solution was poured into ice and made alkaline with ammonium hydroxide. After drying and distillation, as described before, 3.3 g. of base was obtained. It was dissolved in 50 ml. of ethyl acetate and acidified to Congo Red with gaseous hydrogen chloride. On seeding, 2.5 g. (20% overall yield from V) of VIII hydrochloride, m.p. 167–170°[11] eventually separated. It was at first hygroscopic but quickly changed to a stable powder which appeared to contain about 0.5 mole of solvate water. The solvent-free hydrochloride was obtained by conversion of the above hydrochloride to the base and acidifying this base with ethereal hydrogen chloride; small prisms, m.p. 203–205°, from acetone.

Anal. Calcd. for $C_{16}H_{22}ClN$: C, 71.54; H, 8.80. Found: C, 71.70; H, 8.62.

The *picrate*, prepared from the hydrochloride with alcoholic picric acid, melted at 122–123°. A recrystallization of this picrate from alcohol gave another crystalline modification, large, yellow prisms of m.p. 114–115°.

Anal. Calcd. for $C_{21}H_{24}N_4O_7$: C, 56.75; H, 5.44. Found: C, 56.72; H, 5.26.

The *methiodide* crystallized from acetone in rods; m.p. 227.5–228°.

Anal. Calcd. for $C_{16}H_{24}NI$: C, 53.79; H, 6.77. Found: C, 53.72; H, 6.77.

2'-Hydroxy-2,5,9-trimethyl-6,7-benzomorphan (X). To 12.5 g. (0.05 mole) of V and 100 ml. of dry ether was added during 10 min. (stirring, 25°) 300 ml. (0.075 mole) of 0.25*M* ethereal *p*-methoxybenzylmagnesium chloride.[12] The mixture was stirred for 1.5 hr. and treated as described for the corresponding reaction above. The base obtained from the dried ether solution was distilled evaporatively at 0.5 mm. (air-bath temperature 150–160°). The resultant 6.4 g. of distillate, 2.0 g. of 5% palladium–barium sulfate and 85 ml. of normal hydrochloric acid absorbed 0.8 molecular equivalents of hydrogen during 4 hr. when reaction ceased. The filtered (through Super-Cel) solution was basified with aqueous ammonia and the liberated tetrahydro base was dried in ether and distilled at 150° (air bath/0.5 mm.). The 4.5 g. of distillate and 45 ml. of 48% hydrobromic acid were kept at 135–140° (oil-bath temperature) for 30 hr., cooled, poured into 1–2 volumes of ice water and basified with concentrated ammonium hydroxide. The semisolid was filtered and dissolved in the minimum (8–10 ml.) of boiling methanol. On cooling, finally to −5°, 1.6 g. (14% based on V) of X, m.p. 228–232° was obtained; the analytical sample melted at 232–235°; plates from methanol-water.

Anal. Calcd. for $C_{15}H_{21}NO$: C, 77.88; H, 9.15. Found: C, 78.13; H, 9.10.

The *hydrochloride* crystallized from absolute alcohol-ether as the monohydrate in rods of m.p. 194–196°.

Anal. Calcd. for $C_{15}H_{22}ClNO \cdot H_2O$: C, 63.03; H, 8.46; H_2O, 6.30. Found: C, 63.34; H, 8.28; Loss in wt. (117°), 6.22.

Analysis of the dried sample gave the following values: Calcd.: C, 67.27; H, 8.28. Found: C, 67.00; H, 8.50.

The *tosyl* derivative of X gave a crystalline picrate which crystallized from alcohol-acetone in small yellow prisms, m.p. 191–193°.

Anal. Calcd. for $C_{28}H_{30}N_4O_{10}S$: C, 54.71; H, 4.92. Found: C, 54.57; H, 5.04.

The tosyl derivative did not yield VIII on treatment with Raney nickel W-7 in boiling alcohol; mainly starting material was recovered.

2'-Nitro-2,5,9-trimethyl-6,7-benzomorphan picrate.[13] To a stirred, ice-cooled mixture of 8 ml. of fuming nitric acid (Sp. Gr. 1.49–1.50) and 5 ml. of acetic acid was added during 1.5 hr., 1.5 g. of VIII in 3 ml. of acetic acid. The solution was kept overnight at 25°. Acetic acid was evaporated with water-pump vacuum (bath temperature 55–60°). Addition of ice and aqueous ammonia gave an oil which was dried in ether. Evaporation of the ether left a residue which, in 8 ml. of acetone, was added to a solution of 2.0 g. of picric acid in 40 ml. of acetone. On standing for 2 hr. at room temperature and 3 hr. at 0°, 2.0 g. (60%) of picrate was deposited; m.p. 240–242° (dec.); yellow prisms from acetone, m.p. 248–250° (dec.).

Anal. Calcd. for $C_{21}H_{23}N_5O_9$: C, 51.52; H, 4.74. Found: C, 51.28; H, 4.48.

The *hydrochloride* crystallized from acetone in needles of m.p. 253–254° (dec.).

(8) M. S. Newman, *Steric Effects in Organic Chemistry*, John Wiley & Sons, Inc., N. Y., Chapman Hall Limited, London, 1956, p. 242.

(9) A small yield of *N*-methylisomorphinan (M. Gates, R. B. Woodward, W. F. Newhall, and R. Künzli, *J. Am. Chem. Soc.*, 72, 1141 (1950)) epimeric with IIIa at C_{14} was isolated along with IIIa.[5]

(10) We are indebted to Dr. F. E. Cislak, Director of Research, Reilly Tar and Chemical Corp., for a generous supply of 3,4-lutidine.

(11) Prolonged boiling of the ethyl acetate solution occasionally gave another modification (needles) of the hydrochloride which melted at 204–206°.

(12) M. G. Van Campen, D. F. Meisner, and S. M. Parmerter, *J. Am. Chem. Soc.*, 70, 2296 (1948).

(13) The procedures used in this and the subsequent hydrogenation and diazotization experiments were taken from the paper by Schnider and Grüssner.[6]

Anal. Calcd. for $C_{15}H_{21}ClN_2O_2$: C, 60.67; H, 7.13. Found: C, 60.13; H, 7.06.

Conversion of 2'-nitro-2,5,9-trimethyl-6,7-benzomorphan to X. A mixture of 0.5 g. of 2'-nitro-2,5,9-trimethyl-6:7-benzomorphan hydrochloride, 0.2 g. of 5% palladium-barium sulfate, and 3 ml. of methanol absorbed three molecular equivalents of hydrogen quickly, when reduction stopped. The filtered solution was evaporated to dryness *in vacuo* to give an amorphous hydrochloride which was dissolved in 4 ml. of 3*N* sulfuric acid. To the stirred, ice-cooled solution was added during 25 min. 0.14 g. of sodium nitrite in 1 ml. of water. The yellow solution was then treated dropwise (at 60–70°) with 2.4 ml. of sulfuric acid in 2.4 ml. of water. During the next 30 min. the mixture was warmed to 80°, cooled, poured into ice water, and basified with ammonium hydroxide (total volume 100 ml.). Some intractable solid was filtered and the filtrate was extracted three times with chloroform. The dried chloroform extracts were evaporated to dryness and the residue was triturated with ether to give 180 mg. (46%) of 2'-hydroxy-2,5,9-trimethyl-6,7-benzomorphan (X) which melted at 232–235° after a recrystallization from methanol. It proved to be identical with that prepared as described above.

9-Hydroxy-2,5,9-trimethyl-6,7-benzomorphan methiodide. To 11.2 g. of 2,5-dimethyl-9-oxo-6,7-benzomorphan methobromide (XII)[3] was added 170 ml. (5 molecular equivalents) of 1.0*M* methylmagnesium bromide. Only a portion of the solid reacted at once, the adduct apparently coating unreacted solid. The ether was distilled until the liquid adduct became much more fluid. The magma was then manually manipulated with a stirring rod until all the solid passed into the fluid state. The mixture was decomposed with water and the solids were dissolved in 30 ml. of 6*N* hydrochloric acid. Excess aqueous potassium iodide was added with the formation of the crystalline methiodide. Purified from alcohol, it melted at 247–249°; yield 9.4 g. (70%).

Anal. Calcd. for $C_{16}H_{24}INO$: C, 51.48; H, 6.48. Found: C, 51.25; H, 6.26.

9-Hydroxy-2,5,9-trimethyl-6,7-benzomorphan. A distilling flask containing 5.9 g. of the above methiodide was kept in a salt bath at 275–280° under a pressure of 0.1–0.4 mm. The solid did not melt but decomposed to an oil which distilled. The small amount of solid which sublimed was decomposed with a free flame. The colorless distillate weighed 3.6 g. (98%); b.p. 112–115°/0.5 mm.

Anal. Calcd. for $C_{15}H_{21}NO$: C, 77.88; H, 9.15. Found: C, 78.04; H, 9.03.

9-Acetoxy-2,5,9-trimethyl-6,7-benzomorphan (IX). The above alcohol (3.6 g.), 7 ml. of acetic anhydride, and 0.7 ml. of pyridine were refluxed for 3 hr., excess reagent was removed under reduced pressure, and the product was distilled at *ca.* 122°/0.1 mm.; yield 3.9 g. (93%).

Anal. Calcd. for $C_{17}H_{23}NO_2$: C, 74.69; H, 8.48. Found: C, 74.29; H, 8.46.

The *perchlorate*, made by addition of perchloric acid to an ethereal solution of IX, crystallized from alcohol in high yield; m.p. 265–267° (gas).

Anal. Calcd. for $C_{17}H_{24}ClNO_6$: C, 54.62; H, 6.47. Found: C, 54.60; H, 6.42.

9-Methylene-2,5-dimethyl-6,7-benzomorphan. The acetate IX (2.8 g.), in a distilling flask immersed in a salt bath at 325–340° lost acetic acid during about 30 min. The pressure was then reduced to 0.2 mm. with distillation of the product at 95–110°. Dissolved in ether, it was converted to the crystalline perchlorate by the addition of 60% perchloric acid. The crude salt (1.23 g., 38%) melted at 204–219°. After purification from alcohol the m.p. was 218–220°.

Anal. Calcd. for $C_{15}H_{20}ClNO_4$: C, 57.41; H, 6.42. Found: C, 57.52; H, 6.45.

2,5,9-Trimethyl-6,7-benzomorphan (VIII) *methiodide.* The crude perchlorate of the methylene compound above (0.3 g.) in alcohol with platinum oxide absorbed almost one molecular equivalent of hydrogen. The filtered solution gave 0.2 g. of a perchlorate of m.p. 201–210°. Recrystallization from alcohol did not improve the melting point. It was converted to the base (aqueous alkali-ether) and the latter was converted to the methiodide. The methiodide, after crystallization from alcohol–ethyl acetate, melted at 225–226.5° alone or when mixed with the VIII methiodide prepared from V as described above. Furthermore, infrared spectra diagrams of specimens of the methiodides prepared by the two methods were virtually identical.

1,2-Dimethyl-1-(2-dimethylaminoethyl)-1,2,3,4-tetrahydronaphthalene (XI) *hydrochloride.* The methiodide of VIII (4.0 g.), 4.0 g. of sodium hydroxide and 36 ml. of water were kept on the steam bath for 1.5–2 hr., cooled, and extracted with ether. The dried ether extract was evaporated to dryness leaving a liquid which was dissolved in 10 ml. of methanol and hydrogenated (35 mg. of platinum oxide) to the absorption of one molecular equivalent of hydrogen (1 hr.). The filtered solution was evaporated to dryness at reduced pressure. The residue, in ether, was acidified with dry hydrogen chloride to give 2.9 g. (97%) of XI hydrochloride, m.p. 199–202°; needles from acetone, m.p. 203–204°.

Anal. Calcd. for $C_{16}H_{26}ClN$: C, 71.76; H, 9.78. Found: C, 71.62; H, 9.65.

1,2-Dimethylnaphthalene from XI. A stoppered test tube fitted with a vent and containing an intimate mixture of 0.3 g. of XI (oily base) and 0.2 g. of 5% palladium-charcoal was immersed in an oil bath preheated to 250°. During 10 min. the temperature was raised to 310° and kept at 310–320° for an additional 20 min. The tube was then cooled and extracted three times with benzene. The benzene extracts were evaporated *in vacuo* and the residue was distilled at 0.1 mm. (bath temperature 115°) to give 0.1 g. of distillate which was treated with 2.3 ml. of saturated alcoholic picric acid. The yield of picrate, m.p. 130–131.5°,[14] was 125 mg. (25%), undepressed in melting point by picrate prepared from authentic 1,2-dimethylnaphthalene furnished by The Aldrich Chemical Co., Inc.

Anal. Calcd. for $C_{18}H_{15}N_3O_7$: C, 56.11; H, 3.92. Found: C, 56.39; H, 3.99.

The infrared diagram of the 1,2-dimethylnaphthalene prepared from XI was identical with that of authentic 1,2-dimethylnaphthalene.

BETHESDA 14, MD.

(14) If the temperature rise was very slow the m.p. was 133–134°, indicating dimorphism.

[CONTRIBUTION FROM THE NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES, NATIONAL INSTITUTES OF HEALTH, PUBLIC HEALTH SERVICE, DEPARTMENT OF HEALTH, EDUCATION AND WELFARE]

Structures Related to Morphine. IX.*[1] Extension of the Grewe Morphinan Synthesis in the Benzomorphan Series and Pharmacology of Some Benzomorphans

NATHAN B. EDDY, JAMES G. MURPHY, AND EVERETTE L. MAY

Received June 28, 1957

2,5-Dimethyl-6:7-benzomorphan (IIIa) and the phenolic derivative (IIIb) have been synthesized in a three-step process from γ-picoline methiodide and benzylmagnesium chloride or *p*-methoxybenzylmagnesium chloride respectively. The analgesic activity and acute toxicity, in mice, of these and other closely related compounds are summarized.

The synthesis and analgesic activity of 2,5-dimethyl-6:7-benzomorphan (IIIa) have been reported in an earlier paper.[2] Two different approaches to IIIa were successful, one from β-tetralone and one from hydratroponitrile. To date neither of these approaches has proved applicable to the preparation of the 2′-hydroxy relative (IIIb), a compound one could expect to have greater analgesic potency than IIIa. The Grewe morphinan synthesis,[3] which provided a relatively facile method for obtaining 2,5,9-trimethyl-6:7-benzomorphan and the 2′-hydroxy analog, (from 3,4-lutidine),[1] has now been found to have limited utility in the synthesis of IIIa and IIIb. In this instance γ-picoline served as the starting base.

The reaction of benzylmagnesium chloride or the *p*-methoxy derivative with γ-picoline methiodide gave a good yield of the crude, very unstable dihydro derivative (I) which was distilled with considerable loss, and hydrogenated in dilute hydrochloric acid with palladium–barium sulfate. Because of little hindrance of the 3,4-double bond of the nitrogen-containing moiety, it was impossible to effect a selective reduction of I to the tetrahydro stage in contrast to experience in this laboratory with the corresponding 3,4-lutidine derivative,[1] where hydrogen absorption ceased after the 5,6-double bond was saturated. Best results were obtained with I if the reduction was interrupted after 0.7–1.0 molecular equivalent of hydrogen had been absorbed. Phosphoric or hydrobromic acid treatment of the reduction mixture containing II gave IIIa and IIIb respectively in 5.5% and 4% over-all yields based on γ-picoline methiodide. A by-product was also isolated along with IIIb. The yield of this material was very low, varying directly with the extent of hydrogen absorption of Ib. It is presumed to be 2-(*p*-hydroxybenzyl)-1,4-dimethylpiperidine resulting from complete hydrogenation of the heterocyclic ring of IIb. Compound IIIb was also prepared from IIIa *via* nitration, reduction, and diazotization, a conversion affording sufficient proof of structure of IIIb. The identity of specimens of IIIb prepared by the different methods in addition establishes the position of entry of the nitro group into IIIa.

In Table I are presented the analgesic activities and acute toxicities of the principal benzomorphans prepared to date. Similar data are given also for a few derivatives and degradation products as well as for *N*-methylmorphinan and 3-hydroxy-*N*-methylmorphinan (racemorphan). Compounds 1 and 3 are about half as potent as but less toxic than *N*-methylmorphinan (No. 9) by subcutaneous administration while 2 and 4, analogs of racemorphan, are respectively, from a tenth to a third as effective as racemorphan (No. 10) but again somewhat less toxic than the morphinan derivative. The introduction of a hydroxyl or an acetoxyl group into position 8 of compound 1 or cleavage of the nitrogen ring of 1 and 3 does not markedly alter analgesic effectiveness but does reduce toxicity (*cf.* compounds 5–8). The ratio of subcutaneous to oral dose for these benzomorphans compares favorably with that of *N*-methylmorphinan and racemorphan. Once again it can be observed that appropriate substitution of a phenolic hydroxyl is efficacious. The most interesting compound of the benzmorphan series, racemic 2′-hydroxy-2,5,9-trimethyl-6:7-benzomorphan (No. 4) with a therapeutic ratio of 1:58 is being assessed for addiction liability in the monkey.

EXPERIMENTAL

Microanalyses are by Dr. William C. Alford and staff of this institute, and infrared spectra are from William Jones also of this institute.

2,5-Dimethyl-6:7-benzomorphan (IIIa) *hydrochloride.*[2] To a vigorously stirred mixture of 15.5 g. of γ-picoline methiodide and 40 ml. of dry ether was added at 10–20° during 20–30 min., 100 ml. of 1.3*M* ethereal benzylmagnesium chloride. After 1 hr. of stirring the mixture was poured into ice water-ammonium chloride, basified with ammonium hydroxide and the ethereal layer extracted with two por-

* This paper is a contribution in honor of Lyndon F. Small, former Editor of the Journal.

(1) E. L. May and E. M. Fry, *J. Org. Chem.*, 22, 1366 (1957).

(2) E. L. May and J. G. Murphy, *J. Org. Chem.*, 20, 257 (1955).

(3) R. Grewe, *Angew. Chem.*, 59, 194 (1947).

TABLE I

PHARMACOLOGICAL RESULTS

No.	Compound Name	Toxicity, LD_{50}, Mice		Analgesic Effect, ED_{50}, Mice	
		Orally	Subcutaneously	Orally	Subcutaneously
1	2,5-Dimethyl-6:7-benzomorphan, IIIa		148 (143–153)	42.1 (39.2–45.3)	22.1 (19.3–25.2)
2	2'-Hydroxy derivative, IIIb		175 (164–186)		10.4 (9.0–11.8)
3	2,5,9-Trimethyl-6:7-benzomorphan[1]		155 (147–162)		27.3 (23.6–31.5)
4	2'-Hydroxy derivative[1]		175 (161–190)	23.9 (21.8–26.3)	3.0 (2.6–3.4)
5	8-Hydroxy-2,5-dimethyl-6:7-benzomorphan[2]		323 (307–340)		29.3 (26.5–32.3)
6	O-Acetyl derivative[2]			29.3 (26.5–32.3)	32.2 (29.4–35.2)
7	1-(2-Dimethylaminoethyl)-1-methyl-1,2,3,4-tetrahydronaphthalene[2]		362 (336–391)		24.9 (22.3–27.7)
8	1,2-Dimethyl-1-(2-dimethylaminoethyl)-1,2,3,4-tetrahydronaphthalene[1]		411 (349–483)		41.0 (37.4–44.9)
9	*N*-Methylmorphinan[3,4,6]	267 (243–293)	92 (88–96)	40.9 (38.2–43.8)	11.3 (10.1–12.7)
10	3-Hydroxy-*N*-methylmorphinan (racemorphan)[4,5,6]	276 (253–301)	131 (124–138)	7.0 (5.6–8.9)	0.93 (0.84–1.03)

Compounds 1–8 were tested as hydrochlorides and 9 and 10 were tested as the phosphate and hydrobromide, respectively, by a method described previously.[7] Doses are in mg./kg. and are derived by probit analysis of the data; figures in parentheses are 1 × SE-limits.

tions of excess, cold, 10% hydrochloric acid. The combined extracts were washed with ether, basified with cold ammonium hydroxide, extracted twice with ether, and the ethereal extracts were dried over sodium sulfate in a stoppered flask at 0°. The residue (9 g.) from distillation of the ether *in vacuo* was quickly distilled, evaporatively, through a short path at 0.3 mm. in an air bath preheated to 125°. The 5.1 g. of distillate, 70 ml. of normal hydrochloric acid and 1.5 g. of 5% palladium–barium sulfate absorbed 1.0 molecular equivalent of hydrogen in 1.5 hr. when the rate of hydrogen absorption was constant at 2 ml./min. (original rate 16 ml./min.). The filtered (through Super-Cel) solution was basified with ammonium hydroxide and the liberated IIa was dried in ether and distilled as described for Ia. The 3.5 g. of distillate and 25 ml. of 85% phosphoric acid were kept at 150° for 3 days, poured into ice water, basified, and the liberated base was distilled as described before. This distillate (3.0 g.), in ether, was treated with gaseous hydrogen chloride. After cooling at 5° the ether was decanted from the viscous hydrochlorides which were dissolved in 5 ml. of warm acetone. Seeding and cooling at 5° for 1–2 days 0.85 gave g. (5.5% based on γ-picoline methiodide) of IIIa hydrochloride, m.p. 193.5–195°, indistinguishable (infrared diagram, mixed m.p.) from that described previously.[2] The picrate, m.p. 175–178°, was likewise identical with IIIa picrate reported previously.[2]

2'-Hydroxy-2,5-dimethyl-6:7-benzomorphan (IIIb). To a stirred ice-cooled mixture of 15 g. of γ-picoline methiodide and 90 ml. of dry ether was added during 10 min., 300 ml. of 0.3*M* ethereal *p*-methoxybenzylmagnesium chloride.[8] The suspension was stirred for an hour at *ca.* 25° and treated as described in the preparation of Ia except that the air bath temperature in the distillation was 150°. The 6.2 g. of reddish brown distillate (Ib), 1.5 g. of 5% palladium–barium sulfate, and 100 ml. of normal hydrochloric acid absorbed 70–75% of one molecular equivalent of hydrogen during 1 hr. when hydrogenation was proceeding at 40% of the maximum rate. The 3.6 g. of IIb distillate (distillation bath temperature 150°) obtained as described for IIa and 35 ml. of 48% hydrobromic acid were kept at 135–140° for 20 hr., poured into 300 ml. of ice water and basified with ammonium hydroxide. Insoluble material was filtered. The filtrate was extracted thrice with chloroform. The dried chloroform extracts were evaporated at reduced pressure to give 2.1 g. of amorphous material which was dissolved in 7–10 ml. of acetone to give, after cooling to 0°, 0.55 g. (4% over-all from γ-picoline methiodide) of IIIb, m.p. 206–210°; prisms from methanol, m.p. 217–218.5°.

Anal. Calcd. for $C_{14}H_{19}NO$: C, 77.38; H, 8.81. Found: C, 77.60; H, 8.66.

The hydrochloride crystallized from absolute alcohol–ether in rods, m.p. 240–243° (dec.).

Anal. Calcd. for $C_{14}H_{20}ClNO$: C, 66.26; H, 7.94. Found: C, 66.37; H, 8.02.

The acetone filtrate from the 0.55 g. of IIIb was acidified with dry hydrogen chloride. After a few hours the clear supernatant solution was decanted. On seeding it deposited, after 20 hr., 0.15 g.[9] of hydrochloride which appears to be *1,4-dimethyl-2-(p-hydroxybenzyl) piperidine hydrochloride* of m.p. 216–218.5°, resulting from complete reduction of the *N*-containing ring of Ib; rods from absolute alcohol–ether m.p. 219–220.5°.

(4) O. J. Braenden, N. B. Eddy, and H. Halbach, *Bull. World Health Organization*, **13**, 937 (1955).

(5) R. Grewe, A. Mondon, and E. Nolte, *Ann.*, **564**, 161 (1949).

(6) O. Schnider and A. Grüssner, *Helv. Chim. Acta*, **32**, 821 (1949).

(7) N. B. Eddy and D. Leimbach, *J. Pharmacol. Exptl. Therap.*, **107**, 385 (1953).

(8) M. G. Van Campen, D. F. Meisner, and S. M. Parmerter, *J. Am. Chem. Soc.*, **70**, 2296 (1948).

(9) If, in the hydrogenation of IIb, hydrogenation was allowed to proceed to completion, 5–10% yields of this substance were obtained.

Anal. Calcd. for $C_{14}H_{22}ClNO$: C, 65.73; H, 8.67. Found: C, 65.32; H, 8.77.

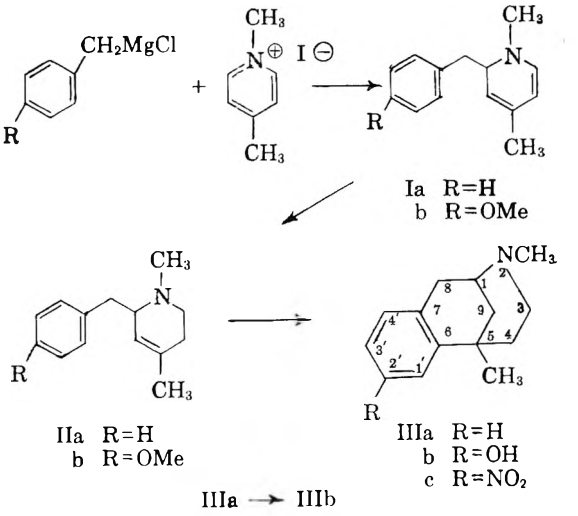
The corresponding *base* crystallized from methanol in prisms, m.p. 196–197.5°. It was dried *in vacuo* at 77° for analysis.

Anal. Calcd. for $C_{14}H_{21}NO$: C, 76.67; H, 9.64. Found: C, 76.46; H, 9.63.

2,5-Dimethyl-2'-nitro-6:7-benzomorphan (IIIc) *picrate.* To 11 ml. of nitric acid (sp. gr. 1.49–1.50) and 6 ml. of acetic acid, stirred and kept at 3–7°, was added during 2 hr. 2.3 g. of IIIa in 5 ml. of acetic acid. The solution was left for 20 hr. at *ca.* 25°, freed of acetic acid *in vacuo* at a bath temperature below 60°, and basified with ice–ammonium hydroxide. The liberated oil was dried in ether. Evaporation of the ether left 2.8 g. of base which, in 10 ml. of acetone, was added to 3.0 g. of picric acid in 30 ml. of acetone. Left at room temperature for 2 hr. and at 0° for 2 hr. the solution deposited 3.9 g. (72%) of IIIc picrate, m.p. 227–229°. The analytical sample (prisms from acetone) melted at 233–234.5° (dec.).

Anal. Calcd. for $C_{20}H_{21}N_5O_9$: C, 50.53; H, 4.45. Found: C, 50.69; H, 4.47.

Conversion of IIIc to IIIb. A mixture of 1.3 g. of IIIc (from 2.9 g. of picrate), 5 ml. of methanol, and 0.5 g. of 5% palladium–barium sulfate absorbed three molecular equivalents of hydrogen during 15 min. The filtered solution was evaporated to dryness. To the residue in 8 ml. of 3*N* sulfuric acid was added (0°, stirring) during 30 min., 0.3 g. of sodium nitrite in 2.5 ml. of water. The solution was then treated at 60–70° with a solution of 6 ml. of water and 6 ml. of water and 6 ml. of sulfuric acid, warmed to 80° during 15–20 min., poured into ice–ammonium hydroxide, and extracted with 40 ml. of chloroform in 4 portions. The dried extract was evaporated to give 0.8 g. of residue which crystallized from 8 ml. of acetone in a yield of 0.3 g. (25% from IIIc) m.p. 210–215°. A recrystallization from methanol (Norit) gave material identical with the IIIb described above. It was converted to the hydrochloride, m.p. 240–243° (dec.) whose infrared spectrum was identical with that of the IIIb hydrochloride prepared from γ-picoline methiodide.



Acknowledgment. We are indebted to Wendy Ness of this institute for statistical analysis of the pharmacological data.

BETHESDA, MD.

[CONTRIBUTION FROM THE DIVISION OF PURE CHEMISTRY, NATIONAL RESEARCH COUNCIL OF CANADA]

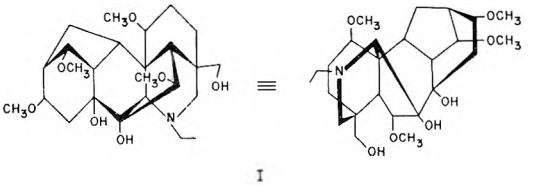
Lycoctonine: The "α-iso" and "Anhydro-α-iso" Compounds*[1]

O. E. EDWARDS, LÉO MARION, AND K. H. PALMER[2]

Received June 27, 1957

The lactam II from the *Delphinium* alkaloid lycoctonine can be oxidized by lead tetraacetate to a diketone III. This underwent internal aldol condensation to a compound IV which on heating with acid gave an isomer V. Further action of acid on V produced a pinacolic dehydration to VII. By hydrolysis of a methoxyl and lead tetraacetate cleavage, VII was converted to the γ-lactone acid IX. The properties and reactions of these compounds lend strong support to the currently accepted structure I for lycoctonine.

Structure I for lycoctonine[3] follows unambiguously[4] from the structure for des(oxymethylene)-lycoctonine determined by x-ray crystallography.[5] Most of the published chemistry of lycoctonine has been interpreted on the basis of this formula.[4]



I

The structures tentatively assigned to the transformation products of the *seco*diketone III derived from lycoctonam (II) seemed capable of chemical

* This paper is a contribution in honor of Lyndon F. Small, former Editor of the Journal.

(1) Issued as N.R.C. No. 4516.

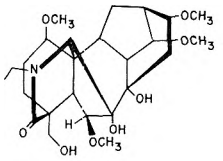
(2) National Research Council of Canada Postdoctoral Fellow.

(3) The representation showing the diterpenoid character of the structure (I) will be used in this communication.

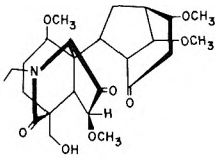
(4) O. E. Edwards, L. Marion, and D. K. R. Stewart, *Can. J. Chem.*, **34**, 1315 (1956).

(5) M. Przybylska and L. Marion, *Can. J. Chem.*, **34**, 185 (1956).

verification. We wish now to report on the results of a study of these products.

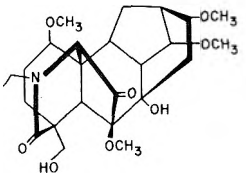


II



III

Treatment of III with bicarbonate or activated alumina[6] converted it to an isomer which was considered to be the internal aldol condensation product IV since the cyclopentanone carbonyl remained.[4,6] The correctness of this assignment of

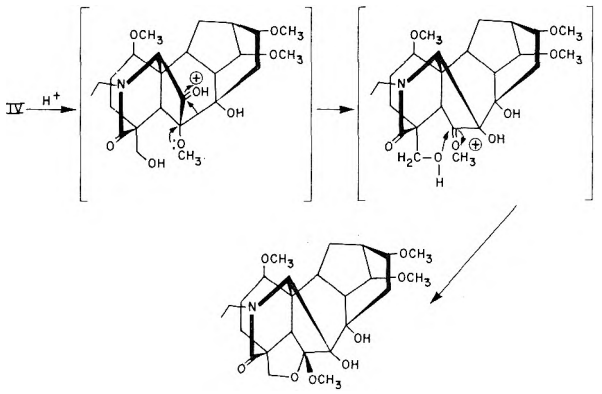


IV

iso COMPOUND

structure to the *iso* compound has now been established by tests of the structures of its acid-catalyzed transformation products, the *α-iso* and *anhydroiso* compounds.[6]

It was suggested[4] that the action of hot mineral acid on the *iso* compound IV brought about an interesting analog of the acid-catalyzed rearrangement of *tert*-α-ketols, giving rise to a second isomer, the *α-iso* compound. The probable mechanism for this transformation is illustrated below:



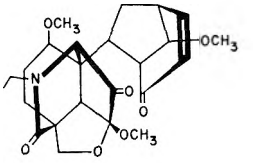
V

α-iso COMPOUND

A fully concerted mechanism is unlikely because of the difficulty of bringing the hydroxyl into bonding distance with the carbon holding the methoxyl, as long as this is tetrahedral (methoxyl interferes). Furthermore, such a mechanism ignores the role of the methoxyl in the reaction. We consider it very unlikely that a retropinacol-type reaction would take place with facility if no methoxyl were present.

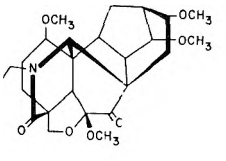
(6) O. E. Edwards and L. Marion, *Can. J. Chem.*, **32**, 195 (1954).

In structure V the original carbon skeleton of lycoctonine has been regenerated, and the vicinal glycol system is present in a very similar environment to that in lycoctonam (II). The obvious way to test this possibility was to try to cleave the molecule to a *seco*diketone, which should have unusual absorption spectra similar to those of III.[6] The *α-iso* compound was indeed cleaved by lead tetraacetate to a diketone having the characteristic carbonyl absorption in the infrared at 1716 and 1759 cm.$^{-1}$, and an ultraviolet spectrum (λ_{max} 3358 Å, log ϵ 2.13) similar to that of *seco*lycoctonam diketone (III). In addition, on treatment with acid the new *seco*diketone lost the elements of methanol under the same conditions[6] as *seco*lycoctonam diketone (III). The product had ultraviolet (λ_{max} 3460 Å, log ϵ 2.18; λ_{max} 2230 Å, log ϵ 3.96) and infrared absorption (max. 1765 cm.$^{-1}$, shoulder at 1670 cm.$^{-1}$) similar to that of desmethanol*seco*lycoctonam diketone,[6] hence can be formulated as VI. Thus strong support is provided for structure V for the *α-iso* compound.

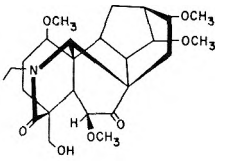


VI

Even more striking evidence for the correctness of the above assignments came however from a consideration of the structure of the *anhydroiso* compound. It was soon demonstrated that this product was not produced directly from IV, as we had originally assumed,[4] but was the product of further action of acid on V. (We shall, therefore, designate this substance as the *anhydro-α-iso* instead of *anhydroiso* compound.) Since the action of mineral acid on the glycol system of lycoctonam produces first a pinacolic dehydration,[7] a very reasonable postulate for the structure of the *anhydro-α-iso* compound was VIIa, the analog of the structure assigned to anhydrolycoctonam VIIb.



VII a



VII b

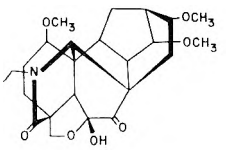
anhydro-α-iso COMPOUND

As would be expected from the fact that the *anhydro-α-iso* compound is the product of reaction in hot aqueous acid, the methoxyl of the postulated masked α-diketone of this compound proved difficult to hydrolyze. However, refluxing 6*N* acid

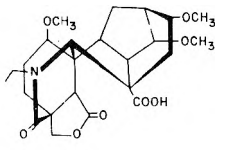
(7) O. E. Edwards and L. Marion, *Can. J. Chem.*, **30**, 627 (1952).

slowly hydrolyzed one methoxyl of the *anhydro-α-iso* compound producing a compound which should be the hemiketal VIII.

The correctness of all the assigned structures was demonstrated by the cleavage of VIII to the acid IX containing a γ-lactone (IR max. 1783 cm.$^{-1}$ in the acid, 1785 cm.$^{-1}$ in the methyl ester).



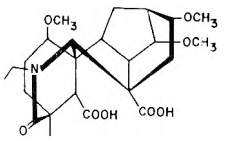
VIII



IX

The above reaction sequences confirm: (*1*) The nature of the *iso*, *α-iso* and *anhydro-α-iso* compounds. (*2*) The correctness of the direction of migration assigned to the pinacolic dehydration.[4] (*3*) The presence of a methoxyl alpha to the vicinal glycol system. A methoxyl had been located in this position earlier on the basis of much weaker chemical evidence.[6]

Finally, the extensive correspondence of the chemistry of lycoctonine with the x-ray crystallographic structure lends strong support to that structure.



X

The lactone acid IX can possibly be converted to the dicarboxylic acid X. This structure has been assigned to a lactam dicarboxylic acid from delpheline.[8] If the two proved identical this would firmly establish the assumed relationship between lycoctonine and delpheline.[9]

EXPERIMENTAL

The physical constants, unless otherwise stated, were determined as follows. Melting points, uncorrected, were made on a Kofler microscope hot stage; optical rotations were measured in absolute ethanol at the cited room temperature; ultraviolet spectra in 95% ethanol using a Carey 11M recording spectrophotometer; the infrared spectra using the nujol mull technique were recorded on the Perkin-Elmer DB 21 instrument. The neutral reaction alumina[10] used for adsorption chromatography was standardized according to Brockman.[11]

Secolycoctonam diketone (III). In a trial experiment lycoctonam hydrate (10.0 mg.) was dissolved in a saturated solution of lead tetraacetate in glacial acetic acid (10 ml.). The molar ratio of the lead tetraacetate consumed after 2 hr. was 1.02; after 20 hr., 1.08.[12]

Lycoctonam hydrate (4.9 g.) was dissolved in acetic acid (100 ml.) and was added to a solution of lead tetraacetate (5.4 g.) in acetic acid (180 ml.). After 2.5 hr. sodium metabisulfite was added followed by a saturated solution of sodium sulfate, and the precipitated lead sulfate was removed by centrifugation. The supernatant liquid together with the precipitate washings were evaporated to a small volume under reduced pressure, neutralized and extracted with chloroform. Evaporation of this extract gave the *seco*diketone III as a white froth (4.8 g.).

Iso Compound (IV). Activity 2 alumina (48 g.) was added to a solution of *seco*lycoctonam diketone (4.8 g.) in benzene (60 ml.). The resultant slurry was shaken for 2.5 hr., then poured on to the top of a column of alumina (96 g.) of activity 2. Elution of the column 24 hr. later with a benzene-chloroform mixture (1:1) gave after two recrystallizations from acetone the "iso" compound (3.09 g.), m.p. 217–218°.

α-Iso and anhydro-α-iso compound. To a solution of the *iso* compound (3.0 g.) in methanol (10 ml.) was added 6*N* sulfuric acid (100 ml.) at 95°C.; the resulting initially opalescent solution was heated on a boiling water bath for 0.5 hr. The neutral product (2.96 g.) extracted by chloroform from the cold reaction mixture was adsorbed from benzene (25 ml.) on to a chromatographic column made with activity 2 alumina (79 g.).

Eluate Fractions (50 Ml.)		Weight Eluted (Mg.)
1–3	Benzene	12.5
4–9	Benzene-chloroform (1:1)	1025
10	Chloroform	199
11–15	Chloroform-ethanol (400:3)	838
16–21	Methanol	616

Fractions 4–9 when crystallized from ether gave transparent square plates (0.98 g.) m.p. 204° alone or in admixture with the *anhydro-α-iso* compound (VIIa). After crystallization from acetone-ether, fractions 10–15 gave colorless prisms (0.99 g.), m.p. 175–176° alone or in admixture with the *α-iso* compound (V).

Seco-diketone from V. A solution of 14.9 mg. of *α-iso* compound V in a saturated solution of lead tetraacetate in acetic acid (10 ml.) showed a molar uptake of reagent of 0.93 mole in 1 hr., and 0.99 in 2 hr.

To a solution of *α-iso* compound (154 mg.) in acetic acid (2.0 ml.) was added a saturated solution of lead tetraacetate in acetic acid (10 ml.). After 4 hr. the oxidation was stopped and the cleavage product extracted as for *seco*-lycoctonam diketone. The resultant white froth (151 mg.) when crystallized twice from acetone-ether gave long colorless needles (110 mg.) which melted at 202–203° $[\alpha]_D^{27}$ +1.9° (c, 1.03), $[M]_D^{27}$ +9°.

Anal. Found: C, 62.77; H, 7.28; OCH_3, 27.34. Calcd. for $C_{25}H_{35}O_8N$: C, 62.87; H, 7.39; $4OCH_3$, 27.77.

Ultraviolet spectrum, λ_{max} 3358 Å., log ε 2.13. Infrared spectrum (nujol mull) 1759 cm.$^{-1}$ and 1716 cm.$^{-1}$ (carbonyls), 1655 cm.$^{-1}$ (lactam).

Desmethanol-seco-diketone (VI). Sulfuric acid (2.5 ml. 6*N*) was added to a solution of *seco*-diketone (from V) (50 mg.) in methanol (0.2 ml.), the turbid solution was heated on a steam bath for 45 min., cooled and extracted with chloroform. The neutral product (47 mg.) from the extraction after two crystallizations from acetone-ether gave colorless prisms (35 mg.), m.p. 230°, $[\alpha]_D^{29}$ −10° (c, 1.04), $[M]_D^{29}$ −43°.

Anal. Found: C, 64.54; H, 6.92; OCH_3, 20.69. Calcd. for $C_{24}H_{31}O_7N$: C, 64.70; H, 7.01; $3OCH_3$, 20.90.

(8) R. C. Cookson and M. E. Trevett, *J. Chem. Soc.*, 3864 (1956).

(9) R. C. Cookson and M. E. Trevett, *J. Chem. Soc.*, 3121 (1956).

(10) "Woelm" brand neutral alumina.

(11) H. Brockman and H. Schodder, *Ber.*, **74**, 73 (1941).

(12) These determinations were kindly made by Dr. D. K. R. Stewart.

Ultraviolet spectrum, λ_{max} 2230 Å., log ϵ 3.96; λ_{max} 3460 Å., log ϵ 2.18. Infrared spectrum (nujol mull) 1765 cm.$^{-1}$, shoulder at 1670 cm.$^{-1}$ (carbonyls), 1660 cm.$^{-1}$ (lactam).

Anhydro-α-iso compound from the α-iso compound. Sulfuric acid (3 ml., 6*N*) was added to a solution of *α-iso* compound (20 mg.) in methanol (0.1 ml.). The initially cloudy solution was heated on a steam bath for 3 hr., cooled and extracted with chloroform. Evaporation of the extract under reduced pressure gave a white froth (20 mg.) which was dissolved in benzene (0.5 ml.) and chromatographed on an activity 2 alumina (1.5 g.) column.

Eluate Fractions (25 Ml.)		Weight in Mg.
1–2	Benzene	1.6
3–5	Benzene-chloroform (1:1)	13.7
6–7	Chloroform-methanol (200:1)	6.0

Fractions 3–5 crystallized from ether in square plates (10 mg.), m.p. 204° alone or in admixture with *anhydro-α-iso* compound. Comparison of the infrared spectra confirmed the identity. Unchanged starting material (5 mg.) was recovered from fractions 6–7.

Des(O-methyl)anhydro-α-iso compound (VIII). *Anhydro-α-iso* compound (1 g.) was dissolved in a small amount of methanol (2 ml.), 6*N* sulfuric acid was added (50 ml.), and the resultant mixture was heated under reflux for 5 hr. The cold solution was extracted with chloroform, and the extract after evaporation under reduced pressure gave a faintly yellow froth (0.962 g.). This was dissolved in benzene (8 ml.) and chromatographed on an activity 2 alumina (20 g.) column.

Eluate Fractions (50 Ml.)		Weight in Mg.
1–3	Benzene	12
4–8	Benzene-chloroform (1:1)	300
9–13	Chloroform	270
14–17	Chloroform-methanol (9:1)	340

Fractions 4–8 when crystallized from ether gave unchanged starting material, m.p. 204°. Depending upon the solvent system used, crystallization of the products from fractions 9–13 and 14–17 gave two distinctly different crystallographic forms, benzene-hexane (1:1) gave colorless needles, m.p. 238–240°, ether gave square plates, m.p. 237–240°, while acetone gave needles m.p. 224–225°. All these forms are interconvertible and their infrared spectra (solution in chloroform) are identical. $[\alpha]_D^{29}$ +57° (c, 1.23), $[M]_D^{29}$ +261°.

Anal. Found: C, 64.57; H, 7.52; N, 3.27; OCH_3, 20.50. Calcd. for $C_{24}H_{33}O_7N$: C, 64.41; H, 7.43; N, 3.13; $3OCH_3$, 20.78.

Ultraviolet spectrum, λ_{max} 2980 Å., log ϵ 1.66. Infrared spectrum (nujol mull) 3500 cm.$^{-1}$ (—OH), 1742 cm.$^{-1}$ (>C=O), 1652 cm.$^{-1}$ (lactam) and 1100 cm.$^{-1}$ (—OCH_3).

Lead tetraacetate oxidation of des(O-methyl) anhydro-α-iso compound (VIII). The compound (34.6 mg.) in 23 ml. of lead tetraacetate solution (a saturated solution in glacial acetic acid diluted with 10% of its volume of water) consumed 0.27 (1 hr.), 0.33 (2 hr.), 0.80 (7 hr.), 1.02 (24 hr.) moles of reagent.

A solution of des(*O*-methyl)anhydro-α-iso compound (203 mg.) in 90% aqueous acetic acid (5 ml.) was added to 25 ml. of the above lead tetraacetate solution. After 28 hr. the excess lead tetraacetate was decomposed with sodium metabisulfite. The solution treated as previously described gave a white froth (204 mg.) from the chloroform extract, which after two recrystallizations from anhydrous methanol yielded colorless needles (83 mg.), m.p. 239–240° (immersion at 200°). $[\alpha]_D^{30}$ +34° (c, 1.01) $[M]_D^{30}$ +156°.

Anal. Found: C, 62.06; H, 7.07; N, 2.92; OCH_3, 19.98. Calcd. for $C_{24}H_{33}O_8N$: C, 62.25; H, 7.18; N, 3.02; 3 OCH_3, 20.04.

Ultraviolet spectrum, featureless. Infrared spectrum (nujol mull) 2580 cm.$^{-1}$ (—OH, acid), 1783 cm.$^{-1}$ (γ-lactone), 1716 cm.$^{-1}$ (>C=O acid), 1615 cm.$^{-1}$ (lactam).

Methyl ester of the γ-lactone acid. A saturated solution of diazomethane in ether (5 ml.) was added to a solution of the γ-lactone acid (35 mg.) in methanol (4 ml.); after 5 min. the solution was evaporated to dryness under reduced pressure. The residue (35 mg.) after two recrystallizations from acetone-ether gave colorless prisms (23 mg.), m.p. 222–224°, $[\alpha]_D^{29.5}$ +42° (c, 1.05) $[M]_D^{29.5}$ +200°.

Anal. Found: C, 62.30; H, 7.33. Calcd. for $C_{25}H_{35}O_8N$: C, 62.87; H, 7.39.

Ultraviolet spectrum, featureless. Infrared spectrum (nujol mull) 1785 cm.$^{-1}$ (γ-lactone), 1736 cm.$^{-1}$ (>C=O, ester), 1645 cm.$^{-1}$ (lactam).

Acknowledgments. We wish to thank Dr. R. N. Jones and Mr. R. Lauzon for obtaining the infrared spectra and Mr. H. Seguin for the microanalysis.

OTTAWA, CANADA

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

Action of Metal Hydrides on β-(3-Indolyl)ethyl-1-pyridinium Salts*[1,2]

ROBERT C. ELDERFIELD, BALTHASAR FISCHER, AND JEANNE M. LAGOWSKI

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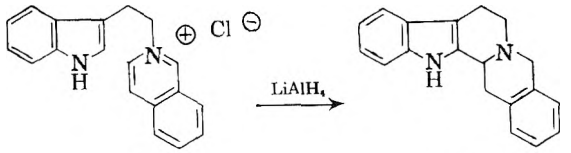
β-(3-Indolyl)ethyl-1-pyridinium bromides are reduced with lithium aluminum hydride or sodium borohydride to give tetrahydropyridine derivatives in good yield. No cyclization to tetracyclic β-carbolines occurred. Stepwise reduction of 4-styrylquinoline has been studied. An improved preparation of tryptophol is described.

In recent years the group of pentacyclic β-carbolines derived from the basic yohimbane skeleton or its stereoisomers has attracted considerable attention largely as a result of the interest in reserpine. In contrast, the chemistry and pharmacology of the analogous tetracyclic β-carbolines has been the subject of comparatively few investigations. In this paper and succeeding ones we wish to present the results of work looking to the synthesis of representative tetracyclic and pentacyclic β-carbolines.

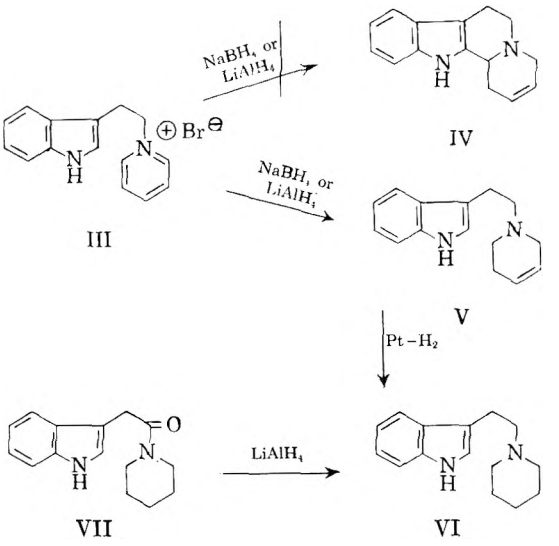
Belleau[3] and Potts and Robinson[4] have shown that reduction of the condensation product of 3-(β-chloroethyl)indole and isoquinoline (I) with lithium aluminum hydride leads to *5,6,7,8,13a,13b*-hexahydrobenz[g]indolo[2.3-*a*]quinolizine (II).



I II

McCurdy[5] suggested that the cyclization might also occur with sodium borohydride as the reagent. Use of sodium borohydride presents obvious advantages, *e.g.* retention of ester groups without reduction by virtue of its reported selectivity of action. Accordingly the action of both hydrides on various condensation products of 3-(β-bromoethyl)indole and selected pyridine derivatives has been investigated as a possible route to tetracyclic β-carbolines.

At the outset, β-(3-indolyl)ethyl-1-pyridinium bromide (III) was reduced with either lithium aluminum hydride or sodium borohydride. The product was the same regardless of the reagent.



III IV V VII VI

It gave analytical data which agreed with $C_{15}H_{18}N_2$ rather than with the hexahydroindolo[2.3-*a*]-quinolizine (IV).[6] On further reduction with hydrogen over platinum oxide, the reduction product absorbed one equivalent of hydrogen to give a substance which was not identical with 1,2,3,4,6,7,12,12*b*-octahydroindolo[2.3-*a*]-quinolizine.[7]

It thus appeared that reduction of two double bonds of the pyridine ring of III without cyclization to yield V might have occurred under the influence of the metal hydrides. This was, indeed, shown to be the case. The structure of the product of catalytic reduction of V was shown to be VI by the preparation of VI by reduction of 1-(3-indoleacetyl)piperidine (VII) with lithium aluminum hydride.

The mechanism of this reductive ring closure is unknown. In view of the fact that it is successful with isoquinolinium compounds but fails with pyridinium compounds, electronic effects associated with the double bonds in the benzene ring of isoquinoline must play a role in the ring closure reaction. Therefore the action of the two metal

* This paper is a contribution in honor of Lyndon F. Small, former Editor of the Journal.

(1) This investigation was supported in part by a research grant, H-1733, from the National Heart Institute, Public Health Service.

(2) Portions of this work are taken from a dissertation submitted by Jeanne M. Lagowski in partial fulfillment of the requirements for the degree of Doctor of Philosophy at the University of Michigan.

(3) B. Belleau, *Chemistry and Industry*, 229 (1955).

(4) K. T. Potts and Sir Robert Robinson, *J. Chem. Soc.*, 2675 (1955).

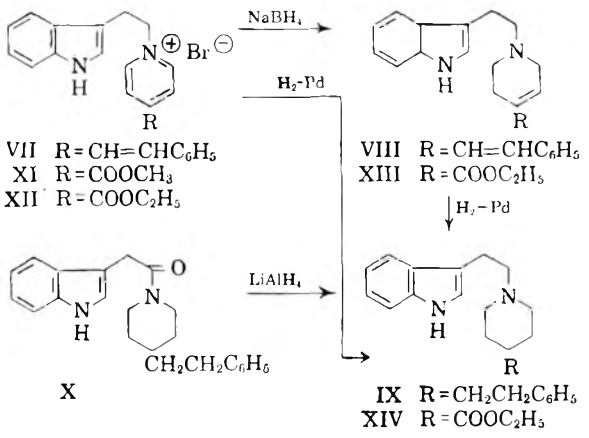
(5) O. L. McCurdy, Ph.D. Dissertation, University of Michigan, 1956.

(6) The position of the double bond in IV and V is assigned on a purely arbitrary basis. No evidence is at hand for placing it in any particular position. See J. J. Panouse [*Bull. soc. chim. France*, D 60 (1953)] for a discussion of the reduction of pyridinium methiodides with metal hydrides.

(7) We are indebted to Dr. D. S. Tarbell of the University of Rochester for an authentic sample of the quinolizine.

hydrides on pyridinium compounds carrying substituents which might be expected to exert a stabilizing effect on the Δ^3 double bond of the pyridine ring was investigated. The two β-(3-indolyl)-ethyl-1-pyridinium salts derived from 4-stilbazole and methyl isonicotinate were selected for this purpose.

The condensation product (VII) of 3-(β-bromoethyl)indole and 4-stilbazole on reduction with sodium borohydride gave excellent yields of a product which absorbed two equivalents of hydrogen on catalytic reduction over palladium in acetic acid to give a substance (IX) which was identical with that formed by the action of lithium aluminum hydride on 1-(3-indoleacetyl)octahydro-4-stilbazole (X). The structure of the product of the reduction of VII is therefore represented by VIII and cyclization to a β-carboline has not occurred in this instance. With lithium aluminum hydride VII gave an unstable base which has resisted all attempts at crystallization, hydrogenation and salt formation. IX also was formed when VII was reduced catalytically over palladium.



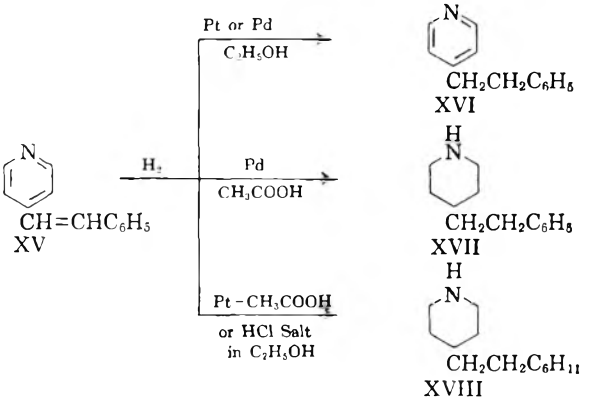
Condensation of 3-(β-bromoethyl)indole with methyl or ethyl isonicotinate readily gave the corresponding pyridinium compounds (XI and XII). Reduction of XI with sodium borohydride in methanol solution gave a waxy product which could not be crystallized and which failed to yield crystalline salts. The infrared spectrum showed a bond at 1715 cm.$^{-1}$ which indicates that the ester had not been reduced. On the other hand, reduction of XII with sodium borohydride in ethanol also gave a waxy base (XIII) from which a picrate could be prepared. The infrared spectrum showed a bond at 1705 cm.$^{-1}$ characteristic of α,β-unsaturated esters. Further reduction of XIII over platinum resulted in the uptake of one equivalent of hydrogen and the formation of a crystalline base (XIV). XIV was also obtained when XII was reduced over palladium.

With lithium aluminum hydride XII gave an unstable base which has resisted all attempts at crystallization, hydrogenation or salt formation.

In order to complete the study, the condensation products of 3-(β-bromoethyl)indole and methyl nicotinate and 6-methylnicotinate were prepared. Reduction of both substances with sodium borohydride gave intractable tars or waxes from which no crystalline product could be isolated.

It therefore appears that the exact limitations of this interesting reductive ring closure remain to be determined. As indicated above, the mechanism of the reaction is obscure. Further work is in progress which it is hoped will clarify the factors governing the course of the reaction. It appears from this work that ring closure to a β-carboline does not occur when β-(3-indolyl)ethyl-1-pyridinium salts are reduced with either lithium aluminum hydride or sodium borohydride.

During this investigation the hydrogenation of 4-stilbazole (XV) was studied. When the free base is reduced in ethanol solution over either platinum or palladium, the ethylenic double bond only was attacked with the formation of dihydro-4-stilbazole [4-(β-phenethyl)pyridine] (XVI). Hydrogenation over palladium in acetic acid solution produced octahydrostilbazole [4-(β-phenethyl)piperidine] (XVII). Complete reduction resulted when platinum was the catalyst in acetic acid solution yielding 4-(β-cyclohexylethyl)piperidine.



Finally, the yield of tryptophol is considerably increased over that previously reported when ethyl indole-3-acetate rather than indole-3-acetic acid is reduced with lithium aluminum hydride.

EXPERIMENTAL[8,9]

Ethyl 3-indoleacetate. To a hot solution of 87 g. of indole-3-acetic acid in 200 ml. of absolute ethanol in which 25 g. of anhydrous sodium sulfate was suspended was added 5 ml. of a saturated solution of anhydrous hydrogen chloride in absolute ethanol. After standing 24 hr. at room temperature, the ethanol was removed under reduced pressure, excess sodium bicarbonate solution was added and the mixture was extracted with ether. Evaporation of the ether left a

(8) All melting points are corrected for stem exposure except as noted. All boiling points are uncorrected.

(9) Microanalysis by Spang Microanalytical Laboratory, Ann Arbor, Mich., or by Mrs. Anna Griffin, of the University of Michigan.

pale yellow oil, b.p. 164–166° (1 mm.). Reported b.p. 180° (2 mm.).[10] The yield was 95 g. (95%).

Tryptophol. To a slurry of 2 g. of lithium aluminum hydride in 100 ml. of absolute ether a solution of 4 g. of ethyl indole-3-acetate in 50 ml. of absolute ether was added dropwise with stirring. The mixture was stirred under reflux for 1.5 hr. After decomposition of excess hydride by cautious addition of a little water, the mixture was filtered through a layer of Celite. After drying the filtrate over anhydrous sodium sulfate, removal of the solvent under reduced pressure left an oil which slowly crystallized, m.p. 57–58°. Reported m.p., 58°.[10] The yield was 2.95 g. (92%).

β-(3-Indolyl)ethyl-1-pyridinium bromide (III). A solution of 1.7 ml. of anhydrous pyridine and 4.06 g. of β-(3-indolyl)-ethyl bromide, prepared by the action of phosphorus tribromide on tryptophol,[11] in 75 ml. of absolute ethanol was allowed to stand at room temperature for 5 days. The red solution was concentrated under reduced pressure on the steam bath. On cooling pale yellow crystals separated which were filtered in a moisture-free atmosphere and recrystallized from absolute ethanol–absolute ether. The yield of broad straw-colored needles, m.p. 235–237° (dec.), was 2.66 g. (48%). The ultraviolet spectrum showed maxima at 261–262 (log ε 3.94), 281 (log ε 3.85) and 290 (log ε 3.77) mμ and minima at 240 (log ε 3.46), 277 (log ε 3.84), and 287 (log ε 3.75) mμ.

Anal. Calcd. for $C_{15}H_{15}BrN$: C, 59.41; H, 4.99; N, 9.24. Found: C, 59.43; H, 4.98; N, 9.51.

Reduction of β-(3-indolyl)ethyl-1-pyridinium bromide. A. With Lithium aluminum hydride. III (3.5 g.) was added in small portions over 40 min. to a suspension of 1.75 g. of lithium aluminum hydride in 350 ml. of anhydrous ether. After stirring at room temperature for 3.5 hr., the excess hydride was decomposed by careful addition of a few drops of water followed by 100 ml. of 10% sodium bicarbonate solution. The ether layer was separated, the aqueous layer was extracted with ether, and the combined ether extracts were dried over anhydrous magnesium sulfate. Removal of the ether left a red brown oil which became semisolid on cooling and rubbing. The semisolid was extracted with *n*-hexane in a Soxhlet apparatus for 24 hr. Concentration and cooling of the hexane extract gave a yellow, crystalline solid, m.p., 140–149° (uncorr.). Repeated recrystallization from hexane gave 1.3 g. (48%) of stout, white needles, m.p. 152–153°.

Anal. Calcd. for $C_{15}H_{16}N_2$: C, 80.32; H, 7.19; N, 12.49. Calcd. for $C_{15}H_{18}N_2$: C, 79.61; H, 8.02; N, 12.37. Found: C, 79.54; H, 8.00; N, 12.19.

The ultraviolet spectrum, taken in ethanol, showed maxima at 283 (log ε 3.74), 291 (log ε 3.68) and a shoulder at 275 (log ε 3.71) mμ. Minima occurred at 244 (log ε 2.95) and 288 (log ε 3.65) mμ.

The compound depressed the melting point of 1,2,3,4,-6,7,12,12*b*-octahydroindolo[2.3-*a*] quinolizine 27° on admixture with the latter. The Ehrlich color test[12] for an indole unsubstituted in the α position, and the modified Adamkiewicz color test[13] for a β-carboline nucleus were inconclusive.

B. With sodium borohydride. To a solution of 1.5 g. of III in 50 ml. of absolute methanol was added slowly with stirring a solution of 4.5 g. of sodium borohydride in 75 ml. of absolute methanol. The yellow color of III was discharged immediately on addition of the borohydride. After stirring at room temperature for 2 hr., the mixture was diluted with 25 ml. of water and the methanol was removed under reduced pressure. The remaining aqueous solution was acidified (litmus) with hydrobromic acid and then made basic with potassium carbonate. The basic solution was extracted with ether. After drying the ether extracts with anhydrous magnesium sulfate, removal of the solvent left 0.24 g. (22%) of V, m.p. and mixture m.p. with the substance obtained by lithium aluminum hydride reduction, 152–153°. The infrared and ultraviolet spectra of V prepared by the two methods were identical.

Hydrogenation of V (VI). Three drops of concentrated ammonium hydroxide solution were added to a solution of 0.2 g. of V in 50 ml. of absolute methanol. *p*-Hydrion paper indicated a *p*H of 7. Adams' platinum oxide catalyst (99 mg.) was suspended in the solution which was then shaken with hydrogen at room temperature and atmospheric pressure. One equivalent of hydrogen was absorbed in about 15 min. and no appreciable additional hydrogen absorption was apparent after 4 hr. After filtration from the catalyst, the filtrate was taken to dryness under reduced pressure. The residual pale green oil crystallized on cooling and was recrystallized from absolute ether-hexane with decolorization with Norite yielding 105 mg. (52%) of white, feathery needles, m.p. 151–152°.

Anal. Calcd. for $C_{15}H_{18}N_2$: C, 79.61; H, 8.02; N, 12.37. Calcd. for $C_{15}H_{20}N_2$: C, 78.90; H, 8.83; N, 12.27. Found: C, 78.82; H, 8.76; N, 11.90.

The ultraviolet spectrum taken in ethanol solution showed maxima at 283 (log ε 3.74), 291 (log ε 3.68), and a shoulder at 275 (log ε 3.71) mμ. Minima occurred at 244 (log ε 2.95) and 288 (log ε 3.65) mμ.

p-Toluenesulfonic acid salt of VI. To a solution of 0.10 g. of VI in 15 ml. of anhydrous ether was added a solution of 0.10 g. of *p*-toluenesulfonic acid monohydrate in 25 ml. of anhydrous ether. After standing overnight at room temperature the precipitate was filtered off. Recrystallization from absolute ethanol-absolute ether gave lustrous, white plates, m.p. 181–182°.

Anal. Calcd. for $C_{22}H_{26}N_2O_3S$: C, 66.30; H, 6.58; N, 7.03. Calcd. for $C_{22}H_{28}N_2O_3S$: C, 65.97; H, 7.05; N, 7.00. Found: C, 65.97; H, 7.16; N, 7.07.

1-(β-[3-Indolyl]ethyl)piperidine. To a solution of 3-indolylacetyl chloride, prepared from 2.0 g. of indole-3-acetic acid[14] in 50 ml. of anhydrous ethyl acetate was added slowly and with cooling a solution of 4 ml. of piperidine in 25 ml. of anhydrous ethyl acetate. After standing for 4 hr. at room temperature the crystalline precipitate was collected. The filtrate was washed successively with three 50 ml. portions of 1*N* hydrochloric acid and three 50 ml. portions of 10% sodium carbonate solution. After drying over anhydrous magnesium sulfate, removal of the solvent left a viscous, red-brown oil which could not be crystallized and which was reduced directly without purification.

To a solution of the crude piperidide in 200 ml. of anhydrous ether a slurry of 1.3 g. of finely powdered lithium aluminum hydride in 200 ml. of anhydrous ether was slowly added. The mixture was stirred at room temperature for 5 hr. after addition of the hydride was complete. Excess hydride was destroyed by careful addition of a few drops of water and 50 ml. of 10% sodium hydroxide solution was then added. The ether layer was separated and the aqueous layer was filtered and extracted exhaustively with ether. After drying the combined ether extracts over anhydrous magnesium sulfate, removal of the solvent left 1.25 g. (39% based on indole-3-acetic acid) of light tan crystals. Recrystallization from *n*-hexane-ether (Norite) gave white, feathery needles, m.p. 151–152°. The melting point was not depressed on admixture with VI obtained as described above and the infrared spectra of the compound obtained by the two routes were superimposible.

Anal. Calcd. for $C_{15}H_{20}N_2$: C, 78.90; H, 8.83; N, 12.27. Found: C, 78.83; H, 8.60; N, 12.21.

The *p*-toluenesulfonic acid salt of VI prepared by reduction of the piperidide melted at 181–182°. The melting

(10) R. W. Jackson, *J. Biol. Chem.*, 88, 659 (1930).

(11) T. Hoskins and K. Shimodaira, *Ann.*, 520, 19 (1935).

(12) F. C. Happold and L. Hoyle, *Biochem. J.*, 28, 1171 (1934).

(13) N. J. Leonard and R. C. Elderfield, *J. Org. Chem.*, 7, 556 (1942).

(14) E. Shaw and D. W. Woolley, *J. Biol. Chem.*, 203, 979 (1953).

point was not depressed on admixture with the salt obtained as above and the infrared spectra of the salts obtained by the two routes were identical.

Anal. Calcd. for $C_{22}H_{28}N_2O_3S$: C, 65.97; H, 7.05; N, 7.00. Found: C, 65.83; H, 6.95; N, 7.06.

Condensation of 4-stilbazole with 3-(β-bromoethyl)indole (VII). A solution of 2.2 g. of 3-(β-bromoethyl)indole and 1.8 g. of 4-stilbazole[15] in 30 ml. of absolute methanol was refluxed for 15 min. After addition of ether to the hot solution a first crop of orange clumps was filtered off. Additional material was obtained from the mother liquor. The total yield was 2.5 g. (63%). Recrystallization from ethanol gave material, m.p. 231° (dec.). The infrared spectrum taken in a Nujol mull showed peaks at 765, 1170, 1615, 2350, 3700, and 3800 cm.$^{-1}$

Anal. Calcd. for $C_{23}H_{21}BrN_2$: C, 68.13; H, 5.23; N, 6.91. Found: C, 68.29; H, 5.23; N, 6.94.

Reduction of VII with sodium borohydride (VIII). To a suspension of 2 g. of VII in 200 ml. of absolute ethanol 6 g. of sodium borohydride was added gradually. The mixture was stirred at room temperature for 2 hr. after addition of the hydride was complete. After addition of 50 ml. of 5% hydrochloric acid the ethanol was removed under reduced pressure. The aqueous solution was made basic to litmus with 0.1*N* sodium hydroxide solution and extracted with ether. After drying over anhydrous sodium sulfate, removal of the ether left a residue which was recrystallized from acetone to give 1.3 g. (80%) of material, m.p. 193°. The Ehrlich color test indicated that the α position of the indole nucleus was unsubstituted. The infrared spectrum taken in a Nujol mull showed peaks at 680, 735, 955, 1105, 1230, 1490, and 1590 cm.$^{-1}$

Anal. Calcd. for $C_{23}H_{22}N_2$: C, 84.52; H, 6.87; N, 8.68. Calcd. for $C_{23}H_{24}N_2$: C, 84.01; H, 7.37; N, 8.53. Found: C, 83.97; H, 7.33; N, 8.71.

Hydrogenation of VIII. *1-[β-(3-indolyl)ethyl]-4-(β-phenethyl) piperidine* (IX). A solution of 325 mg. of VIII in 50 ml. of glacial acetic acid was shaken with 10 mg. of 5% palladium on charcoal catalyst under hydrogen at room temperature and atmospheric pressure. Two equivalents (50 ml.) of hydrogen (calcd. 51 ml.) were absorbed in 12 min. and no further hydrogen uptake was noted. After filtering from the catalyst, removal of the solvent left an oil. This was taken up in water, and, after making the solution alkaline with potassium carbonate, it was extracted with ether. After drying over anhydrous magnesium sulfate, removal of the ether gave 320 mg. (97%) of fine white needles, m.p. 119° (uncorr.), after recrystallization from benzene-ligroin. The Ehrlich test indicated a free α position in the indole nucleus.

Anal. Calcd. for $C_{23}H_{26}N_2$: C, 83.59; H, 7.93; N, 8.48. Calcd. for $C_{23}H_{28}N_2$: C, 83.08; H, 8.49; N, 8.43. Found: C, 83.40; H, 8.44; N, 8.14.

The hydrobromide of IX was prepared in and recrystallized from absolute ethanol. It formed irregular white prisms, m.p. 219–221° (dec.) (uncorr.).

Anal. Calcd. for $C_{23}H_{27}BrN_2$: C, 66.90; H, 6.67; N, 6.86. Calcd. for $C_{23}H_{29}BrN_2$: C, 66.81; N, 7.07; N, 6.78. Found: C, 66.61; H, 6.92; N, 6.78.

1-[β-(3-Indolyl)ethyl]-4-phenethylpiperidine (IX). A solution of 1.5 ml. of 4-phenethylpiperidine and 2 ml. of *N*-ethylmorpholine in 25 ml. of anhydrous ethyl acetate was added slowly with cooling to a solution of 3-indolylacetyl chloride (prepared from 2.0 g. of indole-3-acetic acid) in 25 ml. of anhydrous ethyl acetate. After standing for 4 hr. at room temperature, the orange liquid was decanted and washed successively with dilute aqueous solutions of potassium carbonate, hydrochloric acid, and sodium bicarbonate. After drying over anhydrous sodium sulfate, removal of the ether left the amide as a foamy mass which could not be crystallized and was reduced directly.

To a solution of the crude amide in 20 ml. of anhydrous tetrahydrofuran was added slowly a slurry of 1.1 g. of finely powdered lithium aluminum hydride in 200 ml. of anhydrous ether. The mixture was stirred for 3 hr. after addition of the hydride was complete. After careful addition of a few drops of water the mixture was filtered through Celite. Evaporation of the solvent under reduced pressure gave a white solid which was dried by repeated evaporation with benzene. Recrystallization from ether-petroleum ether gave fine white needles, m.p. and mixture m.p. with the substance obtained by hydrogenation of VIII, 119° (uncorr.). The infrared spectra of the compounds obtained by the two routes were identical.

The hydrobromide of IX prepared by reduction of the amide melted at 219–221° (dec.) (uncorr.) and the infrared spectra of the two hydrobromides were identical.

4-Carbomethoxy-1-(β-[3-indolyl]ethyl)pyridinium bromide. (XI). To a solution of 2.24 g. of β-(3-indolyl)ethyl bromide in 125 ml. of anhydrous ether was added dropwise 1.5 g. of methyl isonicotinate. After standing at room temperature for 4 days the solution was concentrated at reduced pressure. The red-orange residual oil solidified on rubbing with cold anhydrous ether. Recrystallization from absolute methanol-anhydrous ether gave 2.4 g. (67%) of fine orange needles which darkened at 290° and decomposed at 300–301° (uncorr., copper block).

Anal. Calcd. for $C_{17}H_{17}BrN_2O_2$: C, 56.52; H, 4.75; N, 7.76. Found: C, 56.58; H, 4.77; N, 7.76.

4-Carboethoxy-1-(β-[3-indolyl]ethyl)pyridinium bromide. (XII). A hot solution of 2.2 g. of 3-(β-bromoethyl)indole and 1.5 g. of ethyl isonicotinate in 40 ml. of absolute methanol was allowed to cool and stand at room temperature for 48 hr. Removal of the methanol on the steam bath left an oil which furnished long needles from ether after 48 hr. Recrystallization from ethanol gave 2.3 g. (61%) of orange prisms, m.p. 202–203° (dec.) (uncorr.).

Anal. Calcd. for $C_{18}H_{19}BrN_2O_2$: C, 57.60; H, 5.11; N, 7.47. Found: C, 57.65; H, 5.23; N, 7.52.

Reduction of XII *with sodium borohydride* (XIII). To a suspension of 800 mg. of XII in 70 ml. of ethanol 2 g. of sodium borohydride was added in portions during 10 min. The mixture was stirred for 20 hr. during which the color of the solution changed to pale green. After addition of 50 ml. of water, the ethanol was removed under reduced pressure and the excess hydride was decomposed with 10% hydrochloric acid. The aqueous solution was made basic with 0.1*N* sodium hydroxide solution and extracted with ether. After drying over anhydrous sodium sulfate, removal of the ether left a gum which did not crystallize. A picrate, m.p. 168–171° was prepared in ethanol. The yield was 600 mg. The infrared spectrum showed a band at 1705 cm.$^{-1}$ (α,β-unsaturated ester).

Anal. Calcd. for $C_{24}H_{25}N_5O_9$: C, 54.64; H, 4.78; N, 13.28. Found: C, 54.59; H, 4.78; N, 13.22.

Hydrogenation of XIII. A solution of 350 mg. of the crude base, XIII, in 70 ml. of ethanol was shaken with 20 mg. of platinum oxide under hydrogen at room temperature and atmospheric pressure. After 3 hr., 19 ml. of hydrogen was absorbed. Calcd. for one equivalent: 22 ml. After filtering from the catalyst, removal of the solvent left an oil. A picrate, m.p. 185–187°, was prepared in and recrystallized from ethanol. The yield was 130 mg. The infrared spectrum showed a band at 1725 cm.$^{-1}$ characteristic of an ester.

Anal. Calcd. for $C_{24}H_{27}N_5O_9$: C, 54.44; H, 5.14; N, 13.23. Found: C, 54.60; H, 5.13; N, 13.21.

A hydrobromide, m.p. 155–157°, after recrystallization from acetone-ether, was prepared from the picrate in 25% yield. It darkened on exposure to air.

Anal. Calcd. for $C_{18}H_{25}BrN_2O_2$: C, 56.68; H, 6.61; N, 7.35. Found: C, 56.66; H, 6.61; N, 7.31.

Hydrogenation of 4-carbethoxy-1-[β-(3-indolyl)ethyl]pyridinium bromide (XIV). A solution of 376 mg. of XII in 80 ml. of ethanol was shaken with 20 mg. of platinum oxide at room temperature and atmospheric pressure. In 2 hr.

(15) C. E. Kaslow and R. D. Stayner, *J. Am. Chem. Soc.*, 67, 1717 (1945).

64 ml. of hydrogen were absorbed. Calcd. for 3 equivalents: 66 ml. After filtering from the catalyst, removal of the solvent left the free base which could not be crystallized. The picrate, m.p. 184–186°, and the hydrobromide, m.p. 154–155°, did not depress the melting points of the salts prepared above. The infrared spectra of the salts prepared by the two routes were identical.

3-Carbomethoxy-1-[β-(3-indolyl)ethyl]pyridinium bromide. To a solution of 10.6 g. of 3-(β-bromoethyl)indole in 100 ml. of absolute methanol and 75 ml. of anhydrous ether was added 7.1 g. of methyl nicotinate. After standing at room temperature for 3 days, the mixture was concentrated. On cooling it crystallized. The crystalline material was recrystallized from absolute methanol yielding 2.3 g. (21%) of stout yellow needles which darkened at 207° and decomposed at 218–220° (m.p. block) (uncorr.).

Anal. Calcd. for $C_{17}H_{17}BrN_2O_2$: C, 56.52; H, 4.74; N, 7.76. Found: C, 56.48; H, 4.81; N, 7.84.

3-Carboxy-1-[β-(3-indolyl)ethyl]pyridinium bromide. To a solution of 4.85 g. of 3-(β-bromoethyl)indole in 125 ml. of absolute ethanol was added 2.60 g. of nicotinic acid. After warming to effect solution, the mixture was allowed to stand 4 days at room temperature. The yellow solid which deposited after concentration at reduced pressure was recrystallized from 95% ethanol giving 3.16 g. (42%) of yellow needles, m.p. 269–270° (dec.). The ultraviolet spectrum of an ethanolic solution showed absorption maxima at 289 (log ε 3.82) and 270 (log ε 4.00) mμ and a shoulder at 280 mμ (log ε 3.92). Minima occurred at 241 (log ε 3.54) and 287 (log ε 3.80) mμ.

Anal. Calcd. for $C_{16}H_{15}BrN_2O_2$: C, 55.34; H, 4.35; N, 8.07. Found: C, 55.55; H, 4.30; N, 8.09.

5-Carboxy-1-[β-(3-indolyl)ethyl]-2-methylpyridinium bromide. This was prepared from 5.25 g. of 3-(β-bromoethyl)-indole and 3 g. of 6-methylnicotinic acid by the same procedure as was used for the preceding compound. The yield of pale yellow feathery needles from 95% ethanol was 4.84 g. (61%). The substance darkens at about 263° and decomposes at 274–275°. The ultraviolet spectrum of an ethanolic solution showed a maximum at 272 mμ (log ε 3.94), a shoulder at 289 mμ (log ε 3.70), and a minimum at 240–242 mμ (log ε 3.33).

Anal. Calcd. for $C_{17}H_{17}BrN_2O_2$: C, 56.52; H, 4.74; N, 7.76. Found: C, 56.56; H, 4.94; N, 7.69.

Dihydrostilbazole [4-(β-phenethyl)pyridine] (XVI). A solution of 1.83 g. of 4-stilbazole (XV) in 100 ml. of ethanol was shaken under hydrogen at room temperature and atmospheric pressure with 100 mg. of 5% palladium on charcoal catalyst. During 12 hr. 273 ml. of hydrogen was absorbed. Calcd. for 1 equivalent: 255 ml. The resultant dihydrostilbazole crystallized in quantitative yield from benzene-ligroin. It melted at 69–70°. Reported m.p. 69–71°[16] and 65°.[17] The picrate melted at 162–163°. Reported m.p., 162–163°.[16]

The same base was obtained when the reduction was done in ethanol over platinum oxide.

Octahydrostilbazole (4-phenethylpiperidine) (XVII). A solution of 1.83 g. of 4-stilbazole in 100 ml. of glacial acetic acid was shaken under hydrogen at room temperature and atmospheric pressure with 200 mg. of 5% palladium on charcoal. After 6 hr., 4 equivalents of hydrogen (1,121 ml.) had been absorbed. Removal of the solvent from the filtered solution left an oil which was dissolved in water. After making the solution basic with sodium hydroxide solution, it was extracted with ether. The oil remaining after concentration of the dried ether solution was converted directly to the benzenesulfonamide, m.p. 130° (uncorr.), from ethanol. Reported m.p. 130°.[18]

4-(β-Cyclohexylethyl)piperidine (XVIII). A solution of 1.83 g. of 4-stilbazole in 100 ml. of ethanol containing an excess of anhydrous hydrogen chloride was shaken with 350 mg. of Adams' platinum oxide catalyst under hydrogen at room temperature and atmospheric pressure. During the course of 9 hr., 7 equivalents of hydrogen were absorbed. The free base, m.p. 33–35° showed no absorption in the ultraviolet.

For characterization, the base was converted to the 3,5-dinitrobenzamide by treatment with 3,5-dinitrobenzoyl chloride in pyridine for 1 hr. On dilution the amide crystallized. After recrystallization from ethanol, it melted at 154°.

Anal. Calcd. for $C_{20}H_{27}N_3O_5$: C, 61.68; H, 6.99; N, 10.79. Found: C, 61.63; H, 6.97; N, 10.95.

The benzenesulfonamide, prepared as in the preceeding case, melted at 120° after recrystallization from ethanol.

Anal. Calcd. for $C_{19}H_{29}NO_2S$: C, 68.03; H, 8.71; N, 4.18. Found: C, 67.76; H, 8.49; N, 4.14.

ANN ARBOR, MICH.

(16) B. Fels, *Ber.*, **37**, 2147 (1904).
(17) K. Friedländer, *Ber.*, **38**, 2837 (1905).
(18) S. M. McElvain, *J. Am. Chem. Soc.*, **52**, 1637 (1930).

[CONTRIBUTION FROM THE CHEMICAL LABORATORY, HARVARD UNIVERSITY]

Cholesterol and Companions. X.[1] The Diol Fraction

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A technique of inverse chromatography facilitated isolation from various cholesterol samples of 25-hydroxycholesterol, cerebrostenediol (24-OH isomer), 7-ketocholesterol, and an alkane-1,2-diol mixture. 25-Hydroxycholesterol appears not to be a product of animal origin but to result from air-oxidation of crystalline cholesterol.

Oxidation of cholesterol with a variety of reagents has afforded no less than twenty oxidation products in which the original 27 carbon atoms are retained. The structure, and indeed the origin, of one of these products still awaits elucidation. This substance, designated ketone 104,[3] is a somewhat hindered ketone of the formula $C_{27}H_{44}O_3$[3,4] which is formed in 0.5–0.9% yield on oxidation of either commercial cholesterol or

(1) Paper IX: L. F. Fieser and R. Stevenson, *J. Am. Chem. Soc.*, **76**, 1728 (1954).

(2) A friendship with the late Lyndon F. Small which began when we were fellow graduate students was later enlivened by his outstanding work on morphine and on general phenanthrene chemistry. Reviewing his work in books has been a pleasure, both because the experimentation is always meticulously done, and because I have known and admired this keen experimentalist. L.F.F.

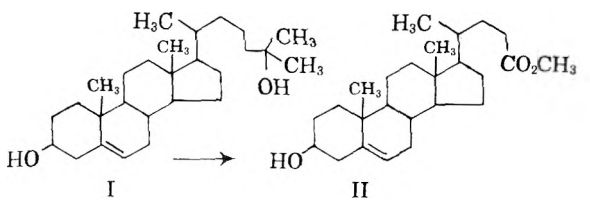
(3) L. F. Fieser, *J. Am. Chem. Soc.*, **75**, 4395 (1953).

(4) L. F. Fieser and B. K. Bhattacharyya, *J. Am. Chem. Soc.*, **75**, 4418 (1953).

cholesterol purified through the dibromide. The previous observations suggested that the substance contains two oxidic bridges and that it probably is a product of oxidation of an oxygen-rich companion substance rather than of cholesterol itself. The present investigation was undertaken in the hope that isolation of a precursor might cast light on the nature of the anomalous oxidation product.

Since an oxygen-rich precursor would be expected to be more hydrophilic than cholesterol and more strongly adsorbed on alumina than this sterol, we designed a technique for isolation based upon these predicted properties. An initial crystallization from ethanol eliminates, in the crystallizate, the bulk of the cholesterol (and the accompanying cholestanol and lathosterol[3]). The material recovered from the mother liquor is then crystallized from acetic acid (quickly, in order to repress acetylation), when an additional crop of cholesterol separates as the acetic acid complex. The residual glassy material recovered from the mother liquor is then processed by a scheme of inverse chromatography: a solution of the material in ether is stirred with two or three successive, relatively small, batches of alumina (Merck acid-washed), and these are collected, washed extensively with benzene, dried, and made into a chromatograph column. Elution with suitable benzene-ether mixtures (or with convenient ether–petroleum ether equivalents) removes residual cholesterol and readies the column for delivery of more strongly adsorbed companions, or for stripping with ether-methanol for recovery of the total diol fraction for chromatography after acetylation. Selective adsorption of this fraction onto alumina seems to effect separation as efficiently as the conventional, far lengthier process of chromatography and greatly facilitated the processing of batches of several hundred grams.

The more strongly adsorbed material is called the diol fraction because diols are indeed the most characteristic components. Thus the first substance isolated was identified as 25-hydroxycholesterol (I) by comparison with synthetic material[5,6]



I II

kindly supplied by Dr. A. I. Ryer. The substance was further characterized by hydrogenation to the stanediol, Oppenauer oxidation to the Δ^4-ene-3-one, and oxidation as the acetate dibromide and conversion to methyl 3β-acetoxy-Δ^5-cholenate,[7] II. Hydroxylation at the tertiary position C_{25} may well be the initial step in the chromic acid oxidation by which the sterol side chain is transformed into the bile acid side chain and acetone.[8]

On checking the history of the cholesterol from which the 25-hydroxy compound was first isolated, we were informed by Dr. David Klein of the Wilson Co. that the material was from a lot produced just four years prior to the isolation experiment. We therefore decided to investigate samples stored in ordinary containers for longer and for shorter periods. Dr. Konrad Bloch, then at Chicago, kindly supplied us with a batch of Wilson Co. cholesterol remaining from a research of F. C. Koch[9] and estimated to be 24 years old. The melting point had dropped off about 30°, and the material afforded a very large diol fraction. The presence of black gums and noncrystalline chromatograph fractions probably obscured the actual content of companions, but even so 25-hydroxycholesterol was isolated in 0.34% yield, as compared to a yield by the same technique of 0.14% from four-year old cholesterol. We then processed 450 g. of a batch of cholesterol two months after it has been produced in the Wilson Laboratories. The glassy residue prior to adsorption on alumina in this case amounted to only 0.9% of the starting material, as compared to 2.4% and 18% for the 4- and 24-year old samples. No 25-hydroxycholesterol was encountered and the only crystalline product found was 7-ketocholesterol, isolated in 0.005% yield. The ketone probably was present in the older samples and obscured isolation of the 3,25-diol.

The results obtained with cholesterol samples manufactured in a standard process and differing only in age indicate that cholesterol undergoes oxidation to the 3,25-diol on storage in the crystalline state in the presence of air.[10] A few exploratory autoxidation experiments were made with the idea that appreciable hydroxylation at any of the tertiary positions 17, 20, or 25 might open a route to production of hormones. After bubbling air through a refluxing solution of cholesterol in benzene for five days the melting point had dropped about 50°. The diol fraction in this case was segregated by extraction from petroleum ether with aqueous methanol. Early extracts afforded cholestane-3β,5α,6β-triol, and later extracts afforded, after acetylation, 7-ketocholesteryl acetate

(5) A. I. Ryer, W. H. Gebert, and N. M. Murrill, *J. Am. Chem. Soc.*, **72**, 4247 (1950).

(6) W. G. Dauben and H. L. Bradlow, *J. Am. Chem. Soc.*, **72**, 4248 (1950).

(7) E. S. Wallis and E. Fernholz, *J. Am. Chem. Soc.*, **57**, 1504 (1935).

(8) A. Windaus and K. Neukirchen, *Ber.*, **52**, 1915 (1919). See comments by J. R. Billeter and K. Miescher, *Helv. Chim. Acta*, **30**, 1409 (1947); L. F. Fieser, *J. Am. Chem. Soc.*, **70**, 3239 (1948).

(9) F. C. Koch, E. M. Koch, and I. K. Ragins, *J. Biol. Chem.*, **85**, 141 (1929).

(10) Compare W. G. Dauben and P. H. Payot, *J. Am. Chem. Soc.*, **78**, 5657 (1956).

in 1.6% yield; 25-hydroxycholesterol was not encountered. Treated in the same way, cholestanol yielded cholestanone as the only identified oxidation product.

Dr. R. T. Rapala of the Armour Laboratories kindly supplied us with material from the mother liquor from a final crystallization of cholesterol from beef spinal cord. The processing of 600 g. of this material by inverse chromatography afforded 60 mg. of material identical with cerebrostenediol, a 24-hydroxycholesterol isolated by Ercoli and de Ruggieri[11] from horse brain cholesterol. Later fractions, when acetylated and rechromatographed, afforded 24 mg. of 7-ketocholesteryl acetate. In confirmation of the Italian work, we isolated cerebrostenediol from a batch of horse brain cholesterol provided by Dr. Ercoli.

Cerebrostenediol was also isolated from a concentrate from wool fat (100 g.) kindly supplied by Dr. Lester I. Conrad of the American Cholesterol Co. The cholesterol derivative was a minor component (10 mg.) of the diol fraction in comparison to another diol (2.2 g.) eluted in later fractions and characterized by being readily soluble in both petroleum ether and in methanol. In a preliminary characterization we had established that the substance is an alkane-1,2-diol by glycol cleavage to formaldehyde and a higher aldehyde, when a paper by Horn and Hougen[12] appeared reporting an extensive investigation of the nonsaponifiable fraction of wool wax. By using amounts of material large enough for fractional distillation of the acetates, these authors isolated five alkane-1,2-diols. Our material undoubtedly is a mixture, but comparison of the constants suggests that a major component is 20-methylheneicosane-1,2-diol, $(CH_3)_2CH(CH_2)_{17}CHOHCH_2OH$.

It is evident that, contrary to our original expectations, this investigation failed to disclose an oxygen-rich precursor of ketone 104. The results indeed confirm the conclusion reached in a subsequent analytical study (to be reported) that ketone 104 is a product of oxidation of cholesterol.

EXPERIMENTAL

Isolation of 25-hydroxycholesterol (L.F.F.). (a) From 4-yr. old cholesterol. Wilson Co. cholesterol (from spinal cord and brain of cattle) lot No. 74708, produced in March, 1949, was processed just four years later. The dibromide from 150 g. of sterol was debrominated in ether-acetic acid[13] and a first crop of nearly pure cholesterol was let crystallize and combined with successive crops (melting in the range 146–150°) obtained by concentration and recrystallization as required. The tail fraction from the mother liquor was a a brown glass (2.4 g.), the next-to-tail fraction a low-melting solid (2.3 g.). Chromatography of the tail fraction afforded 50 mg. of cholesteryl acetate, 200 mg. of crude cholesterol then bromine-containing material (colorless glass; crystals from methanol, m.p. 125–140°; stable to zinc dust in ether–acetic acid[13]), and then, on elution with 1:4 benzene-ether and with ether, a total of 225 mg. of 25-hydroxycholesterol. An eluate fraction containing this diol uncontaminated with companions is recognizable from the fact that on evaporation the diol is left as a white scum on the walls of the flask. Crystallization from acetone gave a microcrystalline powder, m.p. 172–173°, α_D −41.0° Chf (c 0.85), λ^{Chf} 2.8, 6.08 μ.

Anal. Calcd. for $C_{27}H_{46}O_2$: C, 80.54; H, 11.52. Found: C, 80.25; H, 11.29.

Earlier, glassy fractions containing brominated material on digestion with petroleum ether afforded more solid diol, which was readily purified by dissolving it in ether, adding 2–3 volumes of petroleum ether, and concentrating to the point of crystallization. The next-to-tail fraction afforded only 5 mg. of the 3,25-diol, and the total cholesterol removed in the fractional crystallization when reprocessed yielded 58 mg. more of the diol; total yield 288 mg. (0.19%).

Once the diol was identified, purification of the starting material through the dibromide was recognized as not only unnecessary but disadvantageous, because of the formation of troublesome bromine-containing substances. Thus a 600-g. batch of the same cholesterol when processed as described in (b) (crystallization from acetic acid; adsorption of the mother liquor from ether onto two 75-g. portions of alumina) easily afforded 840 mg. (0.14%) of the diol.

(b) *From 24-yr. old cholesterol.* The Wilson Co. cholesterol remaining from a research of F. C. Koch was yellowish, had a strong urine odor, and melted at 116–128°. Crystallization of 199 g. of material from 1 l. of 95% ethanol gave 107 g. of crystals, and the material recovered from the mother liquor on crystallization from 300 ml. of acetic acid gave 9.6 g. of sterol, m.p. 138–140°. An ethereal extract of the diluted acetic acid mother liquor was almost black, but when shaken with alkali the upper layer cleared to a light tan and an oily brown sodium salt separated at the interface above a dirty, milky suspension. The aqueous layer and the oil were drawn off and back extracted with ether, and the dried ethereal solution gave 37 g. of a light yellow, glassy residue. A solution of this material in 200 ml. of ether was stirred for 10 min. with 75 g. of alumina and the solid collected, washed on the Büchner with 400 ml. of benzene, and dried at 80° for 10 min. (A, 78.3 g.). The ethereal mother liquor was stirred with two more 75-g. portions of alumina and the solids (B, C) washed and dried as before. A column was then prepared with a lower layer of 75 g. of fresh alumina overlaid with A, B, and C. Elution with 1:1 ether-methanol removed a series of early fractions to give a diol concentrate amounting to 9.7 g. By chromatography on 300 g. of alumina with solvents in the usual range from benzene to methanol, the material was spread over 100 fractions, but only two homogeneous crystalline products were encountered. The first was cholesterol (from methanol: 0.57 g., m.p. 146–148°). Later fractions eluted by petroleum ether–ether (2:3 and 3:7) afforded 25-hydroxycholesterol contaminated with a petroleum ether–soluble companion. Crystallization from ether–petroleum ether gave a total of 680 mg. (0.34%) of 25-hydroxycholesterol, m.p. 170–171°.

(c) *Examination of freshly extracted cholesterol.* Wilson Co. cholesterol lot No. 86529 was processed two months after production as follows: 450 g. was crystallized from 2.4 l. of 95% ethanol (384 g. of crystals) and the residue left on evaporation of the mother liquor (21 g.) crystallized from acetic acid (170 ml.; 16.3 g. of crystals). The fraction recovered from the mother liquor on crystallization from methanol afforded a few crops of crystals melting in the cholesterol range and afforded 4.0 g. (0.9%) of a residual glass (compare 2.4 and 18.5%, from the 4- and 24-yr. old samples). Selective adsorption from ether onto two 75-g. portions of alumina and elution with methanol gave 1.7

(11) A. Ercoli and P. de Ruggieri, *J. Am. Chem. Soc.*, **75**, 3284 (1953); A. Ercoli, S. di Frisco, and P. de Ruggieri, *Gazz. chim. ital.*, **83**, 78 (1953). For configuration, see W. Klyne and W. M. Stokes, *J. Chem. Soc.*, 1987 (1954).

(12) D. H. S. Horn and F. W. Hougen, *J. Chem. Soc.*, 3533 (1953).

(13) L. F. Fieser, *J. Am. Chem. Soc.*, **75**, 5421 (1953).

g. of a "diol" fraction, which was first chromatographed as acetate. The only identifiable material separated from early petroleum ether eluates as an oil (0.57 g.), which on saponification and crystallization from acetic acid gave crude cholesterol, m.p. 140–142° (0.21 g.). On chromatography of the saponified "diol" fraction, benzene eluted a little cholesterol, and 1:1 benzene-ether afforded, in late fractions, 25 mg. of a solid that crystallized from ether–petroleum ether in clusters of white needles, m.p. 169–170°; very faint color with tetranitromethane. The substance depressed the m.p. of both 25-hydroxycholesterol and of cerebrostenediol but gave no depression in m.p. when mixed with an authentic sample of *7-ketocholesterol*, m.p. 171–172°, α_D −107° Chf (c 24.8), −97° Di (c 23.3).[14]

Characterization of 25-hydroxycholesterol (*W.-Y. H.*). Further crystallization of the diol isolated from commercial cholesterol raised the melting point only to 175–177°, slightly lower than reported values: 181.5–182.5°, α_D −39.3° Chf;[5] 177–179°, α_D −38.6° Chf.[6] Our material may have contained a little cerebrostenediol (see below); it did not depress the melting point of a synthetic sample kindly supplied by Dr. Ryer and the infrared spectra were identical except that our material gave a slightly more intense band at 6.08 μ. The *monoacetate* of the isolated diol when crystallized from aqueous acetone melted at 141–142°, α_D −40.2° Chf (c 1.54), λ^{Chf} 2.8, 2.9, 5.82, 8.0 μ; undepressed on admixture with synthetic material from Dr. Ryer (m.p. 142–142.8°, α_D −40.4° Chf).

Anal. Calcd. for $C_{29}H_{48}O_3$: C, 78.32; H, 10.88. Found: C, 77.92; H, 10.96.

Cholestane-3β,25-diol (*W.-Y. H.*). Hydrogenation of 25-hydroxycholesterol (isolated) in ethanol in the presence of Adams catalyst and a trace of perchloric acid, and crystallization from methanol, gave a product saturated to tetranitromethane, m.p. 194–195°, α_D +24° Chf (c 0.83).

Anal. Calcd. for $C_{27}H_{48}O_2$: C, 80.14; H, 11.96. Found: C, 80.16; H, 11.89.

The *monoacetate*, crystallized from aqueous acetone, melted at 124–125°, α_D +8° Chf (c 0.90).

Anal. Calcd. for $C_{29}H_{50}O_3$: C, 77.97; H, 11.25. Found: C, 77.48; H, 11.20.

Oxidation of 25-hydroxycholesteryl acetate dibromide (*W.-Y. H.*). A solution of 778 mg. of 25-hydroxycholesteryl acetate in 5 ml. of ether was treated with 295 mg. of bromine in 2 ml. of acetic acid and the resulting semisolid mixture let stand overnight in a dry ice bath. The ether was then removed at reduced pressure (25°) and the residue diluted with 25 ml. of acetic acid, treated with 2 g. of chromic anhydride, and the suspension was stirred mechanically for 1.5 hr. and then let stand for 30 min. The oxidized material was then heated with zinc dust and acetic acid for 30 min. on the steam bath to effect debromination, and the product was separated into neutral and acidic fractions by extraction from ether with 4*N* aqueous alkali. The neutral fraction was crystallized from methanol (m.p. 125–135°) and then chromatographed. Early fractions afforded 150 mg. of crystals, m.p. 120–130°, and late fractions gave 257 mg. of starting material, m.p. 140–142°. The acidic fraction, esterified with diazomethane and chromatographed, gave as the main product *methyl 3β-acetoxy-Δ⁵-cholenate*, m.p. (from methanol) 154–156°, α_D −50° Chf (c 0.70). The substance did not depress the melting point of a comparison sample, m.p. 155–157°, −43° Chf (c 1.81), prepared from a sample of 3β-hydroxy-Δ⁵-cholenic acid, m.p. 240–241°, α_D −32.4° Di, supplied by the Research Division of Schering Corp. Both samples showed distinctly stronger levorotation than previously reported[7]: m.p. 156°, α_D −18.7° Chf.

25-Hydroxy-Δ⁴-cholestene-3-one (*B. K. B.*). A mixture of 200 mg. of 25-hydroxycholesterol, 1 ml. of cyclohexanone, 600 mg. of redistilled aluminum isopropoxide, and 7 ml. of toluene was refluxed for 3 hr. and the reaction product isolated in the usual way and chromatographed (m.p. 147–149°). Two crystallizations from ether–petroleum ether and one from petroleum ether–acetone raised the m.p. to 149–150°, α_D +96° Chf (c 0.6), λ^{Chf} 241.5 mμ (16,440); yield 80 mg.

Anal. Calcd. for $C_{27}H_{44}O_2$: C, 80.94; H, 11.07. Found: C, 81.29; H, 11.2..

Cerebrostenediol (*a*). *From beef spinal cord* (*L. F. F.*). The starting material from the Armour Laboratories was material from the ethanol mother liquor of a first crystallization that produced cholesterol of high purity. On digestion of 600 g. of the material with 2.2 l. of 95% ethanol, a little dark solid remained undissolved and the crystals that separated on cooling were dirty, m.p. 141–147°. Evaporation of the mother liquor left a glassy residue that only partially dissolved on digestion with ether. Suction filtration (slow) left a horn-like residue of ether-insoluble material (25.5 g.), and evaporation of the filtrate gave a glassy residue (32 g., contained solvent). When this was rubbed with acetic acid at room temperature it partly dissolved and gave a paste of cholesterol–acetic acid, which was removed (dry weight 9.8 g.). Extraction of the diluted mother liquor gave 12 g. of residue; this was dissolved in ether and the solution stirred with 250 g. of alumina, which was then collected, washed with benzene, dried, and made into a column. Petroleum ether–ether (1:1) eluted mobile yellow oils (fractions 1–4), then solid sterol (5–7), and then a series of fractions (11–17) of material which initially was a glass but which on standing afforded crystalline granules embedded in the glass. On digestion with petroleum ether the granules remained undissolved and could be collected. The total solid (60 mg., m.p. 168–170°) dissolved slowly in acetone, and after the solution had been concentrated to a small volume the product crystallized in tufts of needles, m.p. 173–174°. The substance depressed the melting point of 25-hydroxycholesterol and of 7-ketocholesterol, but a mixture with a sample of cerebrostenediol[11] supplied by Dr. A. Ercoli melted at 173.5–175°.

Anal. Calcd. for $C_{27}H_{46}O_2$: C, 80.54; H, 11.52. Found: C, 80.83; H, 11.57.

Fractions 21–30 (1:4 petroleum ether–ether) afforded glassy material very soluble in petroleum ether; when rechromatographed as the acetate this afforded in terminal fractions (4:1 petroleum ether–ether) a solid that on crystallization from methanol gave 24 mg. of rosettes of blades, m.p. 155–158°, identified as *7-ketocholesteryl acetate* by mixed melting point determination (158–159°).

Further elution with ether removed no more material, and then 1:1 ether-methanol (36–37) eluted a total of 0.8 g. of a substance similar in properties to the lipid diol described below.

(b) *From horse brain.* A 17.4-g. sample of total sterol (m.p. 135–140°) from horse brain kindly supplied by Dr. A. Ercoli was crystallized from methanol (12.6 g., m.p. 147–148°) and the material recovered from the mother liquor was crystallized from acetic acid (1 g., m.p. 145–147°). The glassy residue (1.9 g.) recovered on ether extraction of the acetic acid mother liquor on chromatography afforded, after removal of early sterol fractions (m.p. 141–145°), a series of solid fractions eluted by 1:1 benzene-ether that on crystallization from acetone slowly gave a round cluster of well-formed needles of cerebrostenediol (8 mg.), m.p. 173.5–175°, mixed m.p. 174–175° (also identified by comparison of the infrared spectra).

Cerebrostenediol dibenzoate (*W.-Y. H.*), prepared by benzoylation in pyridine at 25° overnight, was crystallized from ether-acetone and had the constants: m.p. 182–183°, α_D −19° Chf (c 1.20), λ^{Chf} 5.85, 6.2, 6.86, 7.8 μ.

Anal. Calcd. for $C_{41}H_{54}O_4$: C, 80.61; H, 8.91. Found: C, 81.06; H, 8.95.

Cerebrostenediol and a lipid diol from wool fat (*L. F. F.*). The starting material (American Cholesterol Co.) was a commercial concentrate designated Amerchol concentrate

(14) S. Bergstrom and O. Wintersteiner, *J. Biol. Chem.*, **141**, 597 (1941), report m.p. 170–172, α_D −104 Chf.

C-53, a fraction intermediate between cholesterol and lanolin and including material from the ethanolic mother liquor from crystallization of cholesterol. One hundred g. of the light tan, soft resin was dissolved in 500 ml. of methanol and the solution was cooled and scratched until the oil that initially separated had solidified. The solid was removed by filtration, the mother liquor evaporated, and a solution of the residue (24 g.) in ether stirred with two successive 100-g. portions of alumina, each of which was washed liberally with benzene and briefly dried (108, 103.5 g.). A column was then constructed with a lower layer of fresh alumina (50 g.), followed by the second and then the first adsorbate. Elution with 1:1 petroleum ether–ether removed a series of solid fractions (6–8) melting in the range 120–135°. A 1:4 mixture first eluted only mixtures (9–11) and then (12–17), material identified as cerebrostenediol; this appeared as dots of solid that could be triturated with petroleum ether and collected (10 mg.). The substance crystallized from acetone in small blades, m.p. 170–171.5°, mixed m.p. 170–172°.

Fractions 22–32 (1:4 petroleum ether–ether) and 33–34 (ether) afforded small amounts of glassy material which solidified on standing and which when dissolved in a small amount of petroleum ether separated on cooling as a white powder (0.8 g.). More of the same material, designated *lipid diol*, was obtained by terminal elution with ether–methanol (4:1); a solution of the brown eluate in hot petroleum ether was filtered from small amounts of tar and a white solid, evaporated (2.9 g.) and crystallized from acetone, to give 1.45 g. of slightly yellowish solid, m.p. 68–69°. The colorless solid (0.8 g.) from fractions 22–34 on successive crystallizations from acetone melted at 68–70°, 72–74°, 76–77°, 78–79°, 78–79°, α_D^{24} +1.5° Chf (c 2.02), λ^{Chf} 2.8, 2.9, 8.9, 9.4 μ (see below for characterization).

Preliminary characterization of the lipid diol (*W.-Y. H.*). The material from wool fat, m.p. 78–79° (after several crystallizations; a larger sample, rechromatographed and recrystallized, m.p. 79–80°) appeared to be a mixture of average composition corresponding to the formula $C_{22}H_{46}O_2$. Horn and Horgen[12] report for 20-methylheneicosane-1,2-diol the m.p. 84–84.4°.

Anal. Calcd. for $C_{22}H_{46}O_2$: C, 77.12; H, 13.53. Found: C, 77.21, 77.38; H, 13.44; 13.43.

The derivatives briefly investigated are seen from the analyses to differ somewhat from the starting material in homolog composition; the theoretical values cited are those corresponding to the C_{22}-formula for the diol. A mono-*p*-nitrobenzoate (excess reagent in pyridine at 25°) separated from methanol as a granular solid, m.p. 75–76°.

Anal. Calcd. for $C_{29}H_{49}O_5N$: C, 70.84; H, 10.05; N, 2.85. Found: C, 69.92; H, 9.57; N, 3.12.

Periodic acid titrations indicated the substance to be a *vic*-diol of molecular weight 380, 374. Oxidation of 100 mg. of material in ethanol (25 ml.)-water (5 ml.) gave, after chromatography, material which appeared to be a mixture of an aldehyde (medium band at 5.78 μ) and its diethyl acetal (strong band at 8.9 μ). Conversion to the aldehyde 2,5-dinitrophenylhydrazone and chromatography gave a light yellow microcrystalline powder, m.p. 81–82°, λ^{EtOH} (1% Chf) 358 mμ (20,100).

Anal. Calcd. for $C_{27}H_{46}O_4N_4$: C, 66.09; H, 9.45; N, 11.47. Found: C, 65.45; H, 9.17; N, 11.50.

In another experiment the product, after crystallization from ether-ethanol, appeared to consist exclusively of the acetal: m.p. 63–64°, λ^{Chf} 8.9 μ (no carbonyl band). Drying for analysis effected conversion to the free aldehyde.

Anal. Calcd. for $C_{21}H_{42}O$: C, 81.21; H, 13.63. Found: C, 80.95; H, 13.69.

Oxidation of the diol (100 mg.) with lead tetraacetate gave a volatile component isolated and identified as formaldehyde 2,4-dinitrophenylhydrazone. Chromatographed and crystallized from aqueous methanol, this formed orange needles, m.p. 164–165°, λ^{EtOH} (1% Chf) 348 mμ (19,400), identical with an authentic sample in UV and IR spectra and in mixed melting point. The nonvolatile component was extracted with ether and the solution washed with potassium iodide–sodium acetate and then with sodium thiosulfate solution. An acid was obtained as a granular solid, m.p. 60° (characteristic carboxyl IR absorption; no ether band).

Anal. Calcd. for $C_{21}H_{42}O_2$: C, 77.23; H, 12.96. Found: C, 77.73; H, 13.11.

Treatment of the above aldehyde-acetal mixture with sulfuric acid in aqueous dioxane followed by oxidation with dichromate in acetic acid gave a similar acidic product, m.p. 58–59°; direct dichromate oxidation of the diol gave an acid, m.p. 54–56°. The *p*-bromophenacyl ester melted at 80–82°. The amide, obtained from acetone as a granular solid, melted at 97° (IR spectrum almost identical with that of stearamide).

Anal. Calcd. for $C_{21}H_{43}ON$: C, 77.48; H, 13.32. Found: C, 77.12; H, 13.17.

The sample did not depress the melting point of either of the amides:[15] $(CH_3)_2CH(CH_2)_{19}CONH_2$, m.p. 100°; acid, m.p. 62°, $(CH_2)_2CH(CH_2)_{17}CONH_2$ (m.p. 94°; acid, m.p. 55.6°).

Autoxidation experiments (*B. K. B.*). A solution of 200 g. of cholesterol (purified through the dibromide) in 400 ml. of benzene was oxidized by bubbling air through the boiling solution for 120 hr. Melting points observed during this period were as follows: 24 hr., 133–141°; 48 hr., 125–133°; 72 hr., 110–125°; 96 hr., 100–123°. After evaporation of the benzene, 70 g. of the residue was dissolved in 1 l. of petroleum ether and the solution was equilibrated with two 350-ml. portions of 50% methanol-water (by volume). The material recovered from the two extracts (5 g.) on chromatography afforded cholesterol and cholestane-3β,5α,6β-triol, m.p. 235°; no depression in mixed melting point. Further extraction of the petroleum ether solution with two 350-ml. portions of 75% aqueous methanol removed 2 g. of material of which the only component identified was cholesterol. Three extractions with 90% methanol gave 10.8 g. of material which was chromatographed. After removal of cholesterol (2 g.), the column was stripped with methanol and the material eluted was acetylated. Direct crystallization afforded 500 mg. of 7-ketocholesteryl acetate, m.p. 158–160°, α_D +97.5° Chf (c 1.0); no m.p. depression. Chromatography afforded a further 600 mg. of the same product, m.p. 158–160°.

Cholestanol (48 g.) was air-oxidized in the same way and a solution of the residue remaining on evaporation of the solvent dissolved in petroleum ether (500 ml.) and sufficient ether to produce a homogeneous solution. This was extracted three times with 95% methanol and the combined extracts evaporated and diluted with water. Extraction with ether gave 7 g. of yellow solid, which was chromatographed. The only product identified, other than cholestanol, was eluted by 10% ether in benzene and melted at 126–128°. Two crystallizations from methanol gave 400 mg. of cholestanone, m.p. 129.2–129.8°, α_D +43.8° Chf (c 1.03); no depression in melting point.

Anal. Calcd. for $C_{27}H_{46}O$: C, 83.87; H, 11.99. Found: C, 84.22; H, 11.99.

Acknowledgment. This investigation was supported in part by a research grant C 1696 (C 1 Endo) from the National Cancer Institute of the National Institutes of Health, Public Health Service, and in part by research grants from the National Science Foundation, Research Corporation, and the American Cancer Society.

CAMBRIDGE, MASS.

(15) Samples kindly supplied by Dr. A. W. Weitkamp; see *J. Am. Chem. Soc.*, 67, 447 (1945).

[CONTRIBUTION FROM THE NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES, NATIONAL INSTITUTES OF HEALTH, PUBLIC HEALTH SERVICE, U. S. DEPARTMENT OF HEALTH, EDUCATION AND WELFARE]

Concerning 2-Carbomethoxytropinone*

STEPHEN P. FINDLAY†

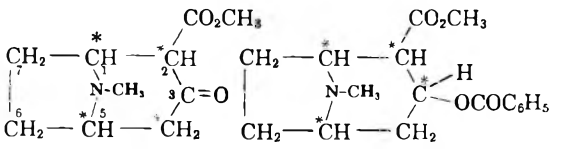
Received June 25, 1957

Racemic 2-carbomethoxytropinone is obtainable by the partial saponification of 2,4-dicarbomethoxytropinone and, more conveniently, by the condensation of monomethyl β-ketoglutarate, got from β-ketoglutaric anhydride, with succindialdehyde and methylamine. 2-Carbomethoxytropinone can conceivably exist in three racemic and six optically active forms. Of these only one has been obtained heretofore. The configurational relation of *d*-(2-carbomethoxytropinone) and its *l* antipode to *l*-cocaine is established by the Kiliani chromic acid oxidation of pseudoecgonine methyl ester to the former. Previous methods of preparing racemic 2-carbomethoxytropinone, the properties of 2,4-dicarbomethoxytropinone, and incidental experimental data are discussed.

In any synthetic scheme for cocaine (II) and its stereoisomers, 2-carbomethoxytropine (I) is an obvious and probably the best key intermediate and has indeed been used to prepare *d*- and *l*-cocaine and racemic pseudococaine.[1,2] In connection with the synthesis of the other two isomers, allococaine and allopseudococaine, unreported until recently,[3] relatively large amounts of this β-keto ester were needed, and it was accordingly desirable to ascertain the most efficient method of its preparation.

Of the four synthetic methods recorded, one (Sequence A) is rather involved, and the cyclization of 1-methyl-2,5-dicarboethoxypyrrolidine (III, R = C_2H_5) to 2-carboethoxytropinone (IV, R = C_2H_5) difficult.[1,4,5] Another (Sequence B), in principle the simplest, is reported to give only a twenty per cent yield of product.[6] Hence, only the remaining two (Sequences C[7] and D[2]), which are relatively simple and claimed to proceed in good yield, came into consideration.

On the basis of the yields reported and the availability of the starting materials Sequence C seemed preferable. Tropinone (V), the components for the Robinson Synthesis of which are now obtainable commercially (see Experimental), can be made in high yield (~ 75%)[8,9] and, according to Preobrashenski,[7] is readily convertible (70–80%) by sodium or potassium and dimethyl carbonate in boiling benzene or xylene to 2-carbomethoxytropinone. It was here found, however, that, although the reported yields of tropinone are not exaggerated, this base is thus transformed to 2-carbomethoxytropinone only in rather low yield (~ 35%). For such a process many side reactions are conceivable, and in fact some or all of them do occur and produce large amounts of resinous by-products.



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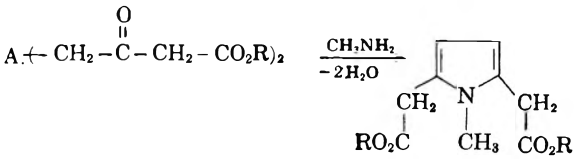

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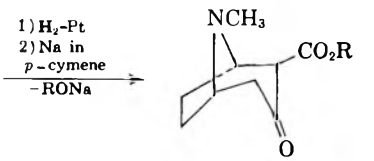

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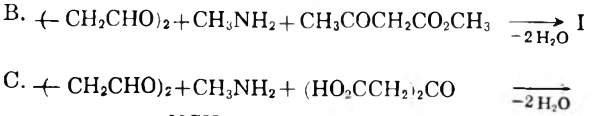

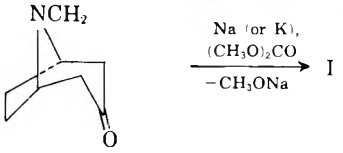

V

Certain variations of the reaction were also tried. Substituting sodium methoxide in toluene did not alter the outcome appreciably. Sodium methoxide in a small volume of methanol gave a somewhat lower yield. By increasing the relative amount of methanol and prolonging the time of reaction correspondingly the product is markedly reduced and

* This paper is a contribution in honor of Lyndon F. Small, former Editor of the Journal.

(1) R. Willstätter and M. Bommer, *Ann.*, **422**, 15 (1921).

(2) R. Willstätter, O. Wolfes, and H. Mäder, *Ann.*, **434**, 111 (1923).

(3) S. P. Findlay, *J. Org. Chem.*, **21**, 711 (1956).

(4) R. Willstätter and A. Pfannenstiehl, *Ann.*, **422**, 1 (1921).

(5) The use of the dimethyl ester (R = CH_3) would presumably not improve the over-all yield of sequence A appreciably.

(6) German Patent **345,759**.

(7) N. A. Preobrashenski, M. N. Schtschukina, and R. A. Lapina, *Ber.*, **69**, 1615 (1936).

(8) C. Schöpf and G. Lehmann, *Ann.*, **518**, 1 (1935).

(9) L. C. Keagle and W. H. Hartung, *J. Am. Chem. Soc.*, **68**, 1608 (1946).

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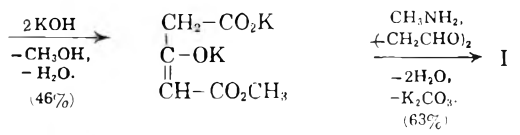
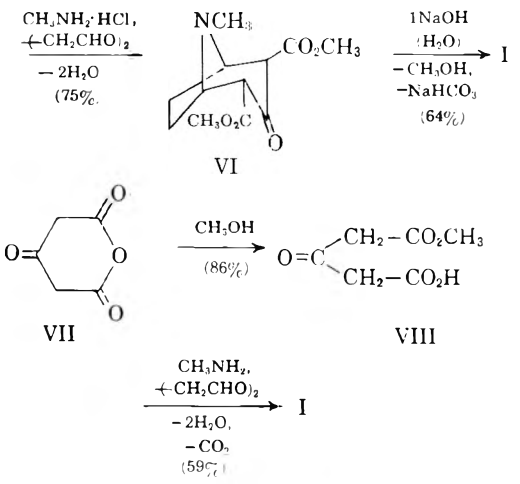
much unreacted tropinone is recoverable, excess solvent reversing the reaction presumably.[10]

D. $(CH_3O_2CCH_2)_2CO$



E. $(CH_3O_2CCH_2)_2CO$



In these circumstances Willstätter's synthesis[2] (Sequence D) or some modification thereof promised to be more satisfactory. The chief difficulty of Willstätter's method lies in preparing the pure dipotassium salt of monomethyl β-ketoglutarate, the yield being less than 50%. Although it was found that treatment of dimethyl β-ketoglutarate with methanolic potassium hydroxide affords a high yield of somewhat impure dipotassium salt, also convertible to 2-carbomethoxytropinone, no essential improvement of Willstätter's over-all yield (~30%) of the keto ester was realized in this manner. The formation of other potassium salts of lesser solubility and the ease with which β-ketoglutarates undergo self-condensation in the presence of basic catalysts[11] are probably the chief factors contributory to the low harvest of pure dipotassium salt.

By a reversal (E) of Willstätter's sequence one might hope to avoid some or all of the foregoing complications. Indeed the Robinson Synthesis of 2,4-dicarbomethoxytropinone (VI) appears to proceed in high yield; and its partial saponification is, moreover, effected more readily than that of the parent compound.

This procedure is, however, tedious, and another variation (F) of Willstätter's synthesis, consisting in the use of monomethyl β-ketoglutarate as its methylammonium salt, was therefore investigated. β-Ketoglutaric anhydride (VII),[4,12] which was obtained in excellent amount by a modification of Kaushall's procedure, is converted to the requisite monomethyl β-ketoglutarate by dissolving it in methanol. Although the optimum conditions for its condensation subsequently with succindialdehyde and methylamine were not determined, racemic 2-carbomethoxytropinone was thus obtained in satisfactory quantity (52–59%). Unlike the condensation, discussed in more detail below, of dimethyl β-ketoglutarate this proceeds with fewer side reactions in alkaline solution. For both simplicity and yield this sequence is very likely superior to all others presently known and probably represents also a convenient means of synthesizing certain derivatives of cycloheptane.

2,4-Dicarbomethoxytropinone (VI) which may be the first isolated dicarboalkoxy derivative of tropinone is a sufficiently unusual compound to merit some description. Its formation in high yield is contingent on the use of methylamine as its hydrochloride or similar salt: the greater the proportion of free amine used, the larger the quantity of dark, polymeric by-products. In his classical article on the synthesis of tropinone, Robinson prepared a solution of the 2,4-dicarboethoxy analog by a similar procedure. His use of free methylamine may account for the apparently low yield of tropinone obtained therefrom by acid hydrolysis.[13] The large number of isomers, both geometric and tautomeric, which are possible for compounds of such structure, should, partly because of the basic nitrogen atom and partly because of their presumably similar stabilities, be readily interconvertible; and the failure of this representative to exhibit either reproducible or sharply defined physical properties is therefore not surprising. Anhydrous 2,4-dicarbomethoxytropinone seems to exist only as a liquid, but two possibly distinct modifications of a solid hemihydrate, $C_{12}H_{17}NO_5 \cdot 1/2H_2O$, one white (m.p. 82.5–84°) and the other tan (m.p. 88–91°), were obtained. These forms, which precipitated slowly and appeared to be only partly crystalline, have nearly indistinguishable infrared spectra in Nujol. The binoxalate salt seems to exist in two modifications also, one being obtainable directly from the hemihydrate and melting about 146°, the other from the newly liberated anhydrous base and melting about

(10) The strength of the indicated bonds, NaO—H and NaO—R, being different, one need not expect sodium alkoxides or enolates to effect acid cleavage of β-keto esters. While no ester of acetoacetic acid itself has seemingly been observed to yield a dialkyl carbonate, malonic ester and sodium ethoxide do give under certain conditions about 10% of diethyl carbonate which may be a decomposition product of the carboethoxyphloroglucinols, the chief products of this reaction. H. Leuchs and A. Geserick, *Ber.*, **41**, 4171 (1908); H. Leuchs and F. Simion, *Ber.*, **44**, 1874 (1911).

According to V. H. Wallingford, A. H. Homeyer, and D. M. Jones [*J. Am. Chem. Soc.*, **63**, 2252 (1941)] excess methanol lowers the yield in such reactions.

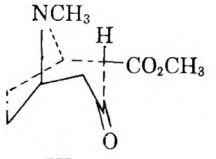
(11) (a) E. Ormerod, *Proc. Chem. Soc. London*, **22**, 205 (1906); (b) H. Cornelius and H. v. Pechmann, *Ber.*, **19**, 1446 (1886); (c) L. F. Fieser and M. M. Pechet, *J. Am. Chem. Soc.*, **68**, 5277 (1946).

(12) R. Kaushall, *J. Indian Chem. Soc.*, **17**, 138 (1940).

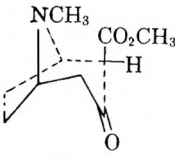
(13) R. Robinson, *J. Chem. Soc.*, **111**, 762 (1917).

155°. In aqueous sodium sulfate or in aqueous acetone equivalent amounts of 2,4-dicarbomethoxytropinone and sodium hydroxide react slowly to give a yellow precipitate which may be the sodium salt of the half ester and which is decomposed by mineral acids to carbon dioxide and racemic 2-carbomethoxytropinone.

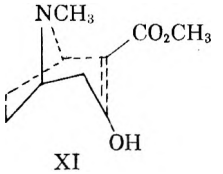
Although 2-carbomethoxytropinone (I) has three asymmetric carbon atoms and hence, theoretically, four racemic forms, the formation of only two of these (IX and X and their antipodes) is, of course, to be expected. Another kind of racemate, that of the enol form (XI and its antipode), is also possible and the benzoyl derivative thereof has indeed been prepared.[2] According to Willstätter,[2] racemic 2-carbomethoxytropinone melts at 111° and its monohydrate at 100°; but whether these two forms have the same molecular constitution has not been established before. Neither he nor Preobrashenski[7] looked for or found more than one racemic form.



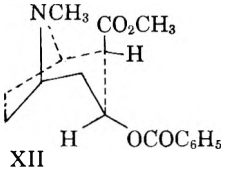
IX



X



XI



XII

None of the numerous batches of anhydrous racemic 2-carbomethoxytropinone prepared in this investigation melted sharply or as high as 111°. An analytically pure sample, generated from the pure picrate and then sublimed, melted at 103.5–104.6°; and chromatography of a somewhat less pure sample furnished material which melted no higher. In one instance needles melting at 104–107.4° were obtained. Furthermore, no monohydrate melting at or near 100° could be isolated. Indeed the only analytically pure hydrated form obtained in this work crystallized from aqueous acetone or from aqueous methyl acetate as colorless needles melting at 93–96° and having the composition of a dihydrate. Another form (m.p. 81.5–86°), which appeared to be largely a monohydrate, was also obtained from aqueous acetone; and from aqueous methanol a granular modification slowly separated which melted at 97.5–98° and had a composition approximating that of a trihydrate. From all of these forms the anhydrous base can be obtained by sublimation or distillation in high vacuum. It is noteworthy that Preobrashenski[7] reported the hydrate to melt at 96–98°.

These indications that racemic 2-carbomethoxytropinone, as usually obtained, is a somewhat variable mixture of easily interconvertible epimers or tautomers were supported by the isolation of two picrate salts. One, which is granular or powdery and melts about 167°, is got from acetone solution; the other, which crystallizes well and melts at 176°, separates from solutions in methyl alcohol. One form may be converted to the other merely by recrystallization from the other solvent. Two binoxalate salts were also found. One crystallizes from water as a sesquihydrate, is readily dehydrated, and melts about 135° with decomposition. The other crystallizes from water as a dihydrate, is less readily dehydrated, and melts at 145° with little or no decomposition. Both binoxalates regenerate one and the same form of racemic 2-carbomethoxytropinone.

The inhomogeneity of anhydrous 2-carbomethoxytropinone was confirmed by infrared measurements. In chloroform solution the base absorbs in regions characteristic of both keto and enol structures. On the other hand the dihydrate in Nujol gives no evidence of the presence of the keto form; and, similarly, 2,4-dicarbomethoxytropinone hemihydrate appears to exist exclusively as the enol. The ultraviolet spectra of the two esters in absolute alcohol demonstrate the predominance of the enol form of such compounds in polar solvents, and a molecular model of 2-carbomethoxytropinone suggests that the bridged-ring structure characteristic of the tropane alkaloids contributes to the stability of this tautomer. One concludes that, although this β-keto ester in the anhydrous state is usually obtained as a mixture of ketone (IX and/or X and their optical antipodes) and enol (XI and its antipode), it exists largely or entirely as the enol when hydrated or dissolved in a hydroxylic solvent. Since Willstätter employed methanol which favors the enol form to recrystallize the base, the high and sharp melting point reported by him may represent that of the pure anhydrous enol.

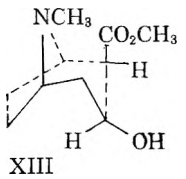
2-Carbomethoxytropinone was readily resolved by recrystallizing its L- and D-bitartrates from water. The L-bitartrate dihydrate has a specific rotation in water of +15.4° ($[M]_D^{20}$ + 5898 ±40). Recovered from the L-bitartrate, *d*-(2-carbomethoxytropinone) has a specific rotation in methanol of +18.3°. Like the racemic modification it crystallizes in the presence of water as a dihydrate and gives, seemingly, two picrate salts. It melts higher and more distinctly at 108.5–109.5° (Table I).

TABLE I

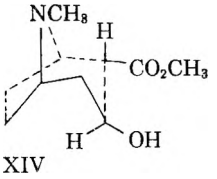
MELTING POINTS OF 2-CARBOMETHOXYTROPINONES AND SOME OF THEIR SALTS

	Racemic	*d*- or *l*-
Anhydrous Base	103.5–104.6° (111°[2])	108.5°–109.5°
Dihydrate	93–96° (100°[2])	98.5–101.5°
Picrate	167–168° and 176° (164°[7])	174 and 176.5°
Binoxalate	137° and 145°	142°

To ascertain its configurational relation to the naturally occurring, parent alkaloid, *l*-cocaine, the oxidation of *l*-ecgonine methyl ester (XIII) and its C_2-epimer,[14] *d*-pseudoecgonine methyl ester (XIV), was undertaken.



XIII



XIV

Although catalytic dehydrogenation, dehydrobromination, and photochemical oxidation experiments were unsuccessful, a small yield of the keto ester as the *d*-antipode was at length obtained by oxidizing either epimer in acetone with Kiliani's chromic acid solution.[15,16] Accordingly, *d*-(2-carbomethoxytropinone) is derived configurationally from *l*-cocaine (XII)[17] and must therefore have the structures, IX-XI, rather than their mirror images.[12] The low yield of the β-keto ester may be owing both to the resistance of equatorial hydroxyl groups[14,18] to oxidation and to the ease with which this product is further oxidized.[2]

Inasmuch as racemic 2-carbomethoxytropinone has been reduced both with sodium amalgam[2] and with catalytic hydrogen[3] to the two possible configurations of the C_3-hydroxyl group, which have been converted in turn to the four possible racemic cocaines,[2,3] the resolution of racemic 2-carbomethoxytropinone just described is tantamount to the direct synthesis of all the optically active cocaine isomers, known and unknown. Indeed, catalytic reduction of the *d* antipode in aqueous acetic acid furnished what is presumably alloecgonine methyl ester[3] which was isolated as the optically active hydroacetate.

The results here set forth are in essential agreement with the long and excellent memoir of Mannich concerning the preparation and properties of the analogous 1,2,6-trialkyl-3,5-dicarboalkoxy-4-piperidones from which were obtained "open" tropine, cocaine, and their derivatives.[19] A few of the similarities of and the differences between these two similar classes of compounds are noteworthy. Mannich likewise obtained better yields of keto diesters by using methylamine as the hydrochloride rather than as the free base, noted the instability of such compounds and their salts in hydroxylic solvents, and resolved 1,2,6-trimethyl-4-keto-3-carbomethoxypiperidine by means of the bitartrate salts. On the other hand, he was unable to obtain this last compound in good yield by partial saponification and found that catalytic hydrogenation of its hydrochloride resulted in the formation of racemic β-hydroxy esters.[20]

Miscellaneous Observations. Tropinone, prepared approximately according to the procedure of Keagle and Hartung,[9] was contaminated by a small quantity of a high-boiling, liquid by-product, which is presumably the other possible form of 2,5-diacetonyl-1-methylpyrrolidine.[8] It was characterized as its picrate and *bis-p*-nitrophenylhydrazone.

Reduced with ethereal lithium aluminum hydride, racemic 2-carbomethoxytropinone gave a mixture which could not be readily purified. One of the products, isolated as the picrate, appeared to be racemic anhydroecgonine methyl ester.

Dimethyl β-ketoglutarate was prepared in 65% yield by adding dry methanol to the mixture resulting from the reaction of anhydrous citric acid and fuming sulfuric acid.[21] Distillation had the expected effect on the keto-enol equilibrium. The action of fuming sulfuric acid on dimethyl citrate produces this ester directly in small yield.

Exploratory experiments to determine whether racemic 2-carbomethoxytropinone can be got from 2,5-diethoxytetrahydrofuran or succindialdehyde, methylamine, and the readily available methyl acetoacetate resulted, according to the conditions, in two seemingly new compounds, $C_{11}H_{18}N_2O_2$ (m.p. 166°) and $C_{15}H_{21}NO_5$ (m.p. 119–124°), which were rather laboriously separated from large quantities of viscous by-products. The former is basic and gives a well-defined binoxalate; the latter is neutral.

EXPERIMENTAL[22]

Materials. Carbide and Carbon 2,5-diethoxytetrahydrofuran (n_D^{20} 1.4208; reported:[23] n_D^{25} 1.4164), Charles Pfizer

(14) S. P. Findlay, *J. Am. Chem. Soc.*, **76**, 2855 (1954).

(15) H. Kiliani, *Ber.*, **46**, 676 (1913), footnote 1. I am indebted to Dr. Walter A. Jacobs of The Rockefeller Institute for supplying this reference.

(16) Dr. Yoshio Sato of this Institute kindly called this method to my attention and conducted the first oxidation experiment.

(17) The structure, XII, also represents the absolute configuration of *l*-cocaine [E. Hardegger and H. Ott, *Helv. Chim. Acta*, **38**, 312 (1955)].

As will be set forth in more detail elsewhere, *l*-cocaine and its derivatives are more dextrorotatory than the corresponding salts. In the seven examples so far examined only one exception to this rule has been found. By using the value of the molecular rotation for ammonium bitartrate [H. Landolt, *Ber.*, **6**, 1073 (1873); J. H. Long, *J. Am. Chem. Soc.*, **23**, 815 (1901)] or that of bitartrate calculated from the rotations of the L- and D-bitartrates of *d*-(2-carbomethoxytropinone) (see Experimental), one finds that the molecular rotation of *d*-(2-carbomethoxytropinone) is more dextrorotatory, *i.e.*, more positive, than the calculated molecular rotation of the corresponding ammonium ion.

(18) W. Klyne, *Progress in Stereochemistry*, Vol. 1, The Academic Press, New York, 1954, pp. 60 and 63.

(19) C. Mannich, *Arch. Pharm.*, **272**, 323 (1934).

(20) 2-Carbomethoxytropinone hydrochloride is under similar conditions nearly inert (unpublished observations of the author).

(21) *Cf.*, B. R. Baker, R. E. Schaub, M. V. Querry, and J. H. Williams, *J. Org. Chem.*, **17**, 97 (1952).

(22) All melting points recorded herein are corrected and were observed in Pyrex glass capillaries.

(23) J. Fakstorp, D. Raleigh, and L. E. Schniepp, *J. Am. Chem. Soc.*, **72**, 869 (1950).

β-ketoglutaric acid (m.p. 133°), Fisher sodium methoxide, and Fisher methylamine hydrochloride (C.P.) were used without further purification. Eastman Kodak dimethyl carbonate was dried over potassium carbonate and distilled from silver carbonate: b.p. 88°/760 mm., n_D^{20} 1.3684 (reported:[24] n_D^{20} 1.3687). L-Tartaric acid (the naturally occurring, dextrorotatory tartaric acid, also known as L-threaric acid) was a Mallinckrodt Chemical Works product; D-tartaric acid was obtained from Aldrich Chemical Company, Milwaukee, Wis.

Tropionone. 2,5-Diethoxytetrahydrofuran (32 g., 0.200 mole) was stirred 15 min. under nitrogen with 0.2*N* sulfuric acid (160 ml.) and kept 4–5 hr. under nitrogen with occasional agitation.[25] The homogeneous solution was then stirred with $BaCO_3$ (8 g.) until nearly neutral and the barium salts collected and washed. The filtrate (~200 ml.) was added to a solution of disodium phosphate (142 g., 1.00 mole), β-ketoglutaric acid (36.5 g., 0.250 mole), and methylamine hydrochloride (16.9 g., 0.250 mole) in water (1800 ml.) at 10° and the whole kept 3 days at room temperature. The initial and final *p*H's were about 6.8. The pale yellowish-green solution was worked up according to the directions of Keagle and Hartung. From two such preparations was obtained after two distillations tropinone (40 g., 72%), m.p. 39–43.8°, b.p. 107–110°/23 mm. The base, initially colorless, acquires a brown coloration in a matter of hours. Inasmuch as the base is scarcely darker after a month than after the first day, the discoloration is no doubt caused by a small quantity of unstable impurity.

Evaporative distillation (80°/1 mm.) of the high-boiling residue from the first distillation (above) gave a small amount (~0.6 g.) of colorless, basic oil which became red on keeping. Prepared in and purified from methanol, its *bis-p*-nitrophenylhydrazone was obtained as small, yellowish-orange, stout prisms having hexagonal faces, m.p. 112–114° (softening at 102°).

Anal. Calcd. for $C_{23}H_{29}N_7O_4 + 2CH_3OH$: C, 56.48; H, 7.02; N, 18.45. Found: C, 56.91; H, 6.59; N, 18.40.

Its picrate, which is extremely soluble in acetone but sparingly so in methanol and alcohol, was purified from the last solvent: slender prisms, m.p. 167.6–168.6°.

Anal. Calcd. for $C_{17}H_{22}N_4O_9$: C, 47.88; H, 5.20; N, 13.14. Found: C, 47.83; H, 4.84; N, 13.02.

The reaction of tropinone with dimethyl carbonate. (*a*) *Using sodium in xylene.*[7] To a warm solution of tropinone (3.6 g.) and dimethyl carbonate (6.1 ml.) in dry xylene (7.0 ml.) was added sodium (0.70 g.) in small pieces; and the reaction mixture, protected against moisture and carbon dioxide, heated quickly to boiling. The initially nearly colorless solution, which gradually darkened during the subsequent heating, was refluxed 20 min., the sodium dissolving with effervescence within about 13 min. After cooling to 0°, the mixture was extracted with cold water (2 × 10 ml.), the aqueous extracts mixed with ammonium chloride (2.0 g.) and extracted with chloroform (5 × 50 ml.), and the dried extracts concentrated *in vacuo* to a brown oil (5.8 g.). Mixed with water (1.5 ml.) at 0° this gave the crude hydrate (3.2 g.) which was collected after several hours and which darkened on keeping overnight. It was recrystallized by dissolving in hot acetone, cooling, adding a little water, and rubbing to induce crystallization. The yellowish-brown crystals were then freed of remaining gummy by-products by sublimation *in vacuo alto:* 1.8 g. (36%) of yellowish deposit, m.p. 97–102° (reported:[2] 111°). Unlike pure 2-carbomethoxytropinone this material soon darkened.

(*b*) *Using sodium methoxide.* Sodium methoxide (1.35 g., 0.025 mole) was added to a solution of tropinone (3.48 g., 0.025 mole) and dimethyl carbonate (4.0 ml.) in dry methanol (5.0 ml.) and the mixture heated at reflux temperature 1 hr. The mixture gradually thickened and became dark red. It was mixed at 0° with water (15 ml.) containing ammonium chloride (2.5 g.) and extracted with chloroform (4 × 50 ml.). The dried extracts were concentrated to an oil which was taken up in ether (100 ml.) and washed twice with a mixture of saturated aqueous potassium carbonate (6 ml.) and 3*N* potassium hydroxide (3.0 ml.). The oil which separated at the interface was taken up in saturated aqueous ammonium chloride, extracted into chloroform, and purified as described above: 0.05 g. of 2-carbomethoxytropinone. From the ether solution was recovered tropinone (3.0 g.).

Another experiment, conducted the same way except by using less methanol (2 ml.) and 10 min. of refluxing, gave 0.7 g. of 2-carbomethoxytropinone. A third experiment, conducted like the first except that toluene (10 ml.) and 30 min. of refluxing were used, gave 1.5 g. of nearly pure 2-carbomethoxytropinone and unreacted tropinone recovered as picrate (2.7 g.), m.p. 200°.

Dimethyl β-ketoglutarate. Powdered, anhydrous citric acid[26] (192 g., 1.00 mole), m.p. 153°, was added in 32-g. portions to fuming sulfuric acid (383 g., 202 ml., 21%) with stirring, the first two cautiously at 0° and the other four at 15–20° during 1.5 hrs. The mixture was stirred 1 hr. at 25°, 3 at 35°, and 17 at 25°.

To the stirred, yellow mixture absolute methanol (500 ml.) was added dropwise at −5 to 0° (3 hrs.). The mixture was kept 13–20 hrs. at 25° and added to a stirred mixture of sodium bicarbonate (700 g.), ice (500 g.), and water (200 g.). The precipitated salts were immediately filtered off and washed with 50% aqueous methanol (150 ml.). The slightly alkaline yellow filtrates were extracted with ether (7 × 400 ml.), the extracts dried (Na_2SO_4), and the solvent removed on the water bath and then *in vacuo*. The residual oil, which contained some water, was distilled *in vacuo:* after two distillations 112 g. (64%, b.p. 85°/1 mm., n_D^{20} 1.4452 (after several days), d_4^{20} 1.202). A small fore-run (5 g.) and a residue of trimethyl citrate (3.5 g.) were obtained from the first distillation. Distillation of nearly pure dimethyl β-ketoglutarate (100 g.) (n_D^{20} 1.4463) afforded two fractions:

Fraction	B.P.	Wt.	n_D^{21} (Immediately After distillation)
1	77–77.7°/0.65–0.60 mm.	50 g.	1.4539
2	77.7–78°/0.65–0.7 mm.	40 g.	1.4538

After a week Fraction 1 had n_D^{20} 1.4466.[27]

When 31% fuming sulfuric acid (265 g.) was substituted in the foregoing procedure, the yield was 10% lower. At 0° the reaction between anhydrous citric acid and fuming sulfuric acid is slow even after half of the citric acid has been added. At the height of the reaction the foaming mixture fills a 2-l. flask. The evolution of carbon monoxide is not complete even after 24 hr. The amount of fuming sulfuric acid employed is that calculated to convert all the water theoretically formed to sulfuric acid.

β-Ketoglutaric acid itself is perhaps obtainable in better yield than reported. The procedure in Organic Syntheses[28] prescribes U.S.P. citric acid, which is a monohydrate;[29] but

(24) P. N. Kogerman and J. Kranig, *Chem. Zentr.*, 1928 II, 2551.

(25) *Cf.*, J. Meinwald, S. L. Emerman, N. C. Yang, and G. Büchi, *J. Am. Chem. Soc.*, **77**, 4401 (1955).

(26) Citric acid, which is efflorescent (*Merck Index*, 6th Ed., p. 252), loses its moisture by exposure to air in dry weather, more readily by heating *in vacuo* at 60°.

(27) The refractive index of the freshly distilled ester changed much more rapidly between the prisms of the refractometer than in the container. That of the equilibrated ester does not change between the prisms.

(28) *Org. Syntheses*, Coll. Vol. I, 10 (1946).

(29) *The Pharmacopeia of the United States of America*, 14th Revision, The Mack Printing Company, Easton, Pa., 1950, p. 143.

the yield reported there (85–90%) is calculated on the assumption that the anhydrous acid was used.

Under similar conditions dimethyl citrate[30,31] and fuming sulfuric acid gave dimethyl β-ketoglutarate directly in about 10% yield.

Monomethyl β-ketoglutarate, dipotassium salt. A solution of potassium hydroxide (33.6 g., 0.600 mole) in absolute methanol (150 ml.) was added dropwise at 0° during 35 min. to a mixture of dimethyl β-ketoglutarate (43.5 ml., 0.300 mole) and methanol (10 ml.). When about one fifth of the alkali had been added a granular precipitate began to separate, and a yellow color appeared when the addition was about half complete.[1] The mixture was kept 3 hours at room temperature during which period it became thicker. After storing overnight in the refrigerator, the salt was collected and washed with cold methanol (15 ml.): 56.5 g.

Anal. Calcd. for $C_5H_6O_5K_2$: K, 33.09. Found: K, 27.41.

Another experiment differing only in that the alkali was admitted at room temperature during 1 hr. afforded the same yield of salt of the same potassium content. Kept in a closed jar the salt slowly turned orange and after a year contained 2% more potassium.

2,4-Dicarbomethoxytropinone (VI). Powdered succindialdoxime[32] (23.2 g., 0.200 mole), m.p. 172–173°, was suspended in 1*N* sulfuric acid (410 ml.), and a solution of sodium nitrite (27.6 g., 0.400 mole) in water (250 ml.) was added dropwise at 2–3° with mechanical stirring during 3–3.5 hr. The stirred, pale yellow mixture, protected from air, was kept 2 hr. at room temperature,[33] stirred with $BaCO_3$ (5.0 g.) and Super-cel, filtered through Super-cel, and diluted to 1.00 l. (By treating an aliquot with a slight excess of aqueous *p*-nitrophenylhydrazine hydrochloride and recovering the *p*-nitrophenylhydrazone,[8,32] the yield of succindialdehyde was estimated to be 96–97%.) The dialdehyde solution was mixed successively with methylamine hydrochloride (15.0 g., 0.222 mole), methanol (100 ml.), and dimethyl β-ketoglutarate (34.8 g., 0.200 mole) in methanol (50 ml.) [a small sample removed at the beginning had a pH of ~4.30 at the beginning, 4.20 after 10 min., 4.12 after 30, 4.09 after 40, 4.06 after 60, 3.90 after 12 hr.; no change occurred on longer keeping], and allowed to warm slowly.

After 20 hr. the solution, which had become yellowish orange, was mixed with potassium bicarbonate (30.0 g., 0.300 mole), and extracted with chloroform (5 × 200 ml.). The combined extracts were dried over sodium sulfate and concentrated *in vacuo* to a reddish orange oil (49.8 g.). This was dissolved in methanol (50 ml.) and mixed at room temperature with powdered oxalic acid dihydrate (24.5 g.). The crystalline binoxalate which slowly separated was stored overnight at 0°, collected, and washed with cold methanol: 52.1 g., m.p. 150.5–151° (dec.). By diluting the mother liquor and washings with an equal volume of ether and storing a day at 0°, a second crop was obtained: 3.1 g., m.p. 150.5–151° (total yield: 55.2 g. or 80%).

The powdered binoxalate (55.2 g., 0.160 mole) was stirred with chloroform (100 ml.) and water (150 ml.), potassium bicarbonate (35.0 g.) added cautiously, and the mixture shaken. The aqueous phase was extracted with more chloroform (3 × 100 ml.), and the base recovered approximately as before: 45.4 g. of light orange oil. It was dissolved in ether (100 ml.), water (2.5 ml.) added, and the mixture seeded and stirred 8 hr. at room temperature. The light tan, voluminous precipitate, which was augmented by storing 2 days at 0°, was collected and washed with ether: 39.6 g. (75%), m.p. 85–88.5°.

In later experiments succindialdehyde generated from 2,5-diethoxytetrahydrofuran as described above and appropriately diluted was employed. The ethanol necessarily present did not seem to contaminate the product appreciably through ester exchange. Conduct of the reaction at room temperature indicated that the condensation is fairly rapid, very mildly exothermic, and not notably favored by low temperatures. The intermediate binoxalate salt usually melted about 152° (sometimes at 155°), acquired a superficial pink coloration during drying, and was probably a mixture of at least two isomeric binoxalates.

Anal. Calcd. for $C_{14}H_{19}NO_9$: C, 48.69; H, 5.55. Found: C, 48.60; H, 5.51.

The base generated as described above melted as low as 85–88° and as high as 88–91° and was obtained in over-all yields of 69–79%.

Anal. Calcd. for $C_{12}H_{17}NO_5 \cdot 1/2H_2O$: C, 54.54; H, 6.87. Found: C, 54.29; H, 6.88.

In the first experiments, methylamine hydrochloride was always neutralized by adding potassium bicarbonate. The yield of 2,4-dicarbomethoxytropinone in these experiments was comparatively low owing to the formation of large quantities of brown, polymeric by-products. By using lower temperatures and greater dilutions in the experiments with free methylamine the tendency to by-product formation was somewhat reduced; but the isolation became correspondingly more laborious, and in alkaline solution at any dilution some ester appeared always to be lost by hydrolysis. In the foregoing procedure, neutralization of only 10% of the methylamine hydrochloride with potassium hydroxide lowered the yield about 10%.

Properties of 2,4-dicarbomethoxytropinone. Anhydrous 2,4-dicarbomethoxytropinone was obtained only as an oil which was at least moderately soluble in all common solvents, polar and non-polar. Isolated as described above the hemihydrate has usually a tan coloration, is relatively high melting, seems to be largely amorphous, and is partially (but not completely) liquefied by storing *in vacuo* over potassium hydroxide. Crystallized by dissolving in the minimum quantity of warm acetone, adding about 10% of water, seeding, and storing in the cold, the anhydrous oil afforded a white product melting at 82.5–84° and giving some extinction under the polarizing microscope.

Anal. Calcd. for $C_{12}H_{17}NO_5 \cdot 1/2H_2O$: C, 54.54; H, 6.87; CH_3O, 23.5. Found: C, 54.50; H, 6.75; CH_3O, 23.2.

A solution composed of equal parts of the hemihydrate and methanol was mixed with the theoretical amount of powdered oxalic acid dihydrate. On cooling the solution and scratching the *binoxalate* crystallized out: aggregates of minute, colorless prisms melting at 143–145° or at 146° and remaining colorless. The higher-melting binoxalate described above could not be thus obtained.

Anal. Calcd. for $C_{14}H_{19}NO_9$: C, 48.69; H, 5.55; CH_3O, 17.96. Found: C, 48.43; H, 5.58; CH_3O, 17.54.

The *nitrate* was prepared from 3*N* nitric acid at 0° and purified from methanol-ether and from acetone: minute, stout prisms, m.p. 146–146.5°.

Anal. Calcd. for $C_{12}H_{17}NO_5 \cdot HNO_3$: C, 45.28; H, 5.70. Found: C, 45.34; H, 5.66.

The *picrate* was prepared in aqueous acetone and purified from acetone: needles, m.p. 167–167.5°.

Anal. Calcd. for $C_{18}H_{20}N_4O_{12} \cdot 1/2H_2O$: C, 43.82; H, 4.29. Found: C, 43.84; H, 4.26.

Racemic 2-carbomethoxytropinone (I). (a) *From 2,4-dicar-*

(30) G. Schroeter and L. Schmitz, *Ber.*, **35**, 2085 (1902).

(31) C. A. Naw, E. B. Brown, and J. R. Bailey, *J. Am. Chem. Soc.*, **47**, 2596 (1925).

(32) S. P. Findlay, *J. Org. Chem.*, **21**, 644 (1956).

(33) The equation for this reaction appears to be as follows:

$$(\text{CH}_2\text{—CH=NOH})_2 + 2\text{NaNO}_2 + \text{H}_2\text{SO}_4 \longrightarrow (\text{CH}_2\text{—CHO})_2 + \text{NaSO}_4 + 2\text{H}_2\text{N}_2\text{O}_2$$

Hyponitrous acid, which is known to result from the reaction of nitrous acid and hydroxylamine, slowly decomposes liberating nitrous oxide; and the evolution of gas for at least 24 hr. from another dialdehyde solution, similarly prepared, indicates its presence in this reaction too. It appears not to interfere appreciably with the subsequent condensation reaction.

bomethoxytropinone. Finely divided 2,4-dicarbomethoxytropinone hemihydrate (21.1 g., 0.0800 mole) was dissolved at room temperature with stirring in a solution (41 ml.) made by diluting sodium hydroxide (8.0 g.) and saturated aqueous sodium sulfate (25 ml.) to 100 ml. of aqueous solution. During the stirring (5 hr.) the light orange mixture became turbid. After keeping 48 hr. at room temperature, this mixture, which had become a yellowish white semi-solid, was suspended in water (50 ml.) and 6*N* aqueous sulfuric acid (~27.5 ml.) added cautiously (effervescence!) to *p*H 4.0. The mixture was made basic with potassium bicarbonate (12 g.) and extracted with chloroform (5 × 50 ml.). After removing about 75% of the solvent from the dried (Na_2SO_4) extracts on the steam bath, the solution was concentrated *in vacuo* to a yellow oil which slowly solidified when seeded: ~16 g. of crude product.

This was purified by dissolving it in hot methyl acetate (30 ml.), adding to the cold solution water (4 ml.) and acetone (4 ml.), and keeping several hours at 0°. The yellowish product was collected and washed with cold methyl acetate: 10.3 g., m.p. 97–101°. From the mother liquors additional material was recovered. By evaporative distillation about 100°/1 mm. a solid, partly yellow and partly white, was obtained: 10.2 g. (64%), m.p. 102.5–105°, of anhydrous base. No tropinone was isolated unless excess base was used in the saponification.

One part of diester dissolved in two parts of acetone and the stoichiometric amount of 4*N* aqueous sodium hydroxide gave a lower yield of the keto ester.

(*b*) *From the dipotassium salt of dimethyl β-ketoglutarate.* The potassium salt and succindialdehyde, prepared as described above, were combined with methylamine approximately according to the directions of Willstätter.[2] Based either on succindialdeyhde or on the dipotassium salt, the yield of 2-carbomethoxytropinone was 45%.

(c) *From β-ketoglutaric anhydride.*[12] β-Ketoglutaric acid (40 g.) was suspended in a mixture of glacial acetic acid (60 ml.) and acetic anhydride (43 ml.) at *ca.* 10° and stirred 3 hrs. at 8–15°. Usually the acid dissolved in about an hour, and almost at once the anhydride began to crystallize. The crude product was collected, washed with benzene, and dried *in vacuo* over potassium hydroxide 2–3 hr.: 30 g. (86%), m.p. 137.5–138.5° (reported:[4] 138–140°).

Crude β-ketoglutaric anhydride (13.5 g., 0.105 mole) was dissolved in cold methanol (50 ml.) and the solution kept 1 hr. at room temperature. It was added to a solution of methylamine hydrochloride (10.0 g., 0.148 mole) and sodium hydroxide (4.0 g., 0.100 mole) in water (850 ml.) and aqueous succindialdehyde (125 ml. of *ca.* 0.8*N*) stirred in. The mixture warmed almost imperceptibly, turned slowly yellow, and evolved carbon dioxide slowly. After keeping 24 hr. at room temperature the yellow solution was brought to *p*H 4.00 with 6*N* mineral acid (effervescence), washed with chloroform (35 ml.) to remove neutral and colored by-products, basified with sodium hydroxide (20 ml. of 4*N*) and potassium bicarbonate (4 g.), and extracted with chloroform (9 × 100 ml.). Recovered as above described racemic 2-carbomethoxytropinone was obtained as a yellowish brown oil which, when seeded, slowly crystallized as yellowish brown warts: 16.9 g. (86%), m.p. 92–93°. This material was recrystallized from acetone-water as described above: 12.1 g., m.p. 96–98.5°, of granular, pale yellow product. By sublimation *in vacuo* this and the material from the mother liquors were freed of water and small amounts of resinous impurities: 11.6 g. (59%), m.p. 93–100°.

When the reactants were combined near 0° and the mixture kept in the refrigerator 24 hr., the yield was somewhat lower: 10.3 g. (52%), m.p. 99.5–104.4°. When no sodium hydroxide was used to generate free methylamine, the yield of the keto ester was much smaller, and a proportionately greater quantity of resinous by-products was obtained.

Properties of racemic 2-carbomethoxytropinone. The analytically pure base was obtained by mixing the picrate (6.1 g., m.p. 167–168°), described below, with potassium carbonate (2.0 g.) in water (50 ml.) at 0°, filtering off the potassium picrate, and isolating the base as described above: 2.4 g. which, after two sublimations, was colorless and melted at 103.5–104.6°.

Anal. Calcd. for $C_{10}H_{15}NO_3$: C, 60.89; H, 7.67. Found: C, 61.15; H, 7.51.

Anhydrous racemic 2-carbomethoxytropinone (3.0 g.) was dissolved in hot acetone (10 ml.) and water (1 ml.) added to the cooled solution. A crust of rosettes of colorless, small prisms slowly formed. After 24 hr. at room temperature the crystals were washed with acetone and dried: 2.3 g., which melted at 93–96° and at 101–104° after cooling and reheating.

Anal. Calcd. for $C_{10}H_{15}NO_3 \cdot 2H_2O$: C, 51.49; H, 8.21. Found: C, 51.56; H, 8.13.

Another sample from aqueous acetone having the same composition melted at 96–98°. From the mother liquors rosettes of needles melting at 81.5–86° separated.

Anal. Calcd. for $C_{10}H_{15}NO_3 \cdot 1H_2O$: C, 55.80; H, 7.96. Found: C, 54.47; H, 8.11.

Similarly recrystallized from methyl acetate the dihydrate was obtained as colorless prisms melting at 93–97°.

Anhydrous racemic 2-carbomethoxytropinone (4.0 g.) was dissolved in hot absolute methanol (4.0 ml.) and the cooled solution poured into water (8.0 ml.). Small mounds or warts separated slowly from the cold solution. After several hours these (~1 g.) were collected. From the filtrate a more finely divided precipitate separated: 3 g., m.p. 97.5–98°.

Anal. Calcd. for $C_{10}H_{16}NO_3 \cdot 3H_2O$: C, 47.80; H, 8.42. Found: C, 48.18; H, 8.52.

The yellow crude product from the partial saponification was chromatographed on alumina. Elution with benzene gave about one third which was colorless and, after sublimation, melted at 90–98°. Further elution afforded approximately the same amount melting, after sublimation, at 101–103°. Secondary butyl alcohol and methanol removed gummy material and a trace of benzene-insoluble substance. The color and about one fifth of the sample were retained by the adsorbent.

The initially obtained crude anhydrous base did not always solidify readily when seeded or scratched. Furthermore, the high-vacuum sublimation of the crude base gave frequently a mixture of solid and liquid, the latter crystallizing only when scratched. The particular phenomena observed appeared to be related to the history of the preparation: whether ammonia or potassium bicarbonate had been used to liberate the base and whether the chloroform extracts had been concentrated *in vacuo* or not.

The anhydrous base dissolves in all the common solvents, polar and non-polar, and is especially soluble in hot methanol, methyl acetate, and acetone. Sublimed about 90°/1 mm. the anhydrous base collects as white flakes and warts which electrify readily. It was also obtained as prisms melting at 104–107.4° from the upper walls of flasks containing the anhydrous base previously generated as noted above from pure salts.

The base gives an intense color with ferric chloride, dissolves in aqueous alkali, and is precipitated therefrom by either carbon dioxide or ammonium chloride. It is unstable in hot water.

The *binoxalate* was prepared in and purified from water in which it is quite soluble even at room temperature. By evaporation of an aqueous solution at room temperature the salt was obtained in two forms: porous mushroom-like growths and colorless prisms. From concentrated aqueous solutions either form could be obtained by seeding, the former separating as a voluminous precipitate. The former melted about 87°. Dried to constant weight *in vacuo* at 40°, the salt lost 8.50% of its weight (theory for $1^1/_2$ H_2O: 8.60%) and melted about 137° (bubbling and discoloration).

Anal. Calcd. for $C_{12}H_{17}NO_7$: C, 50.17; H, 5.97. Found: C, 49.93; H, 6.29.

The prisms melted about 98° and, when partially dehydrated, again at 145° (bubbling, but little or no discoloration). They are not completely dehydrated by heating *in vacuo* first at 57° and then 12 hr. at 80°.

Anal. Calcd. for $C_{12}H_{17}NO_7 \cdot 2H_2O$: C, 44.58; H, 6.55. Found: C, 44.67; H, 5.80.

Regenerated in the customary manner, the base from one salt was indistinguishable from that from the other.

The anhydrous base (0.43 g.) was dissolved in butanone (5 ml.) and a solution of picric acid (0.46 g.) in butanone (5 ml.) added. Rather large polyhedra (0.8 g.) of the *picrate* melting at 175–176° separated overnight. Recrystallized from methanol the salt was obtained either as rhombohedra or as small, transparent, yellow prisms melting at 176–177°.

Anal. Calcd. for $C_{16}H_{18}N_4O_{10}$: C, 45.07; H, 4.25; N, 13.14. Found: C, 45.11; H, 3.95; N, 12.99.

A hydrated form (0.43 g.) was dissolved in methanol (5 ml.) and a solution of picric acid (0.46 g.) in warm methanol (5 ml.) added. Seeded with impure picrate recovered from another experiment, a light yellow granular precipitate was obtained: 0.7 g., m.p. 165–167°. Recrystallized to constant melting point from acetone, the salt was obtained as a yellow powder melting at 167.5–168°.

Anal. Calcd. for $C_{16}H_{18}N_4O_{10}$: C, 45.07; H, 4.25. Found: C, 44.79; H, 4.46.

It was necessary to dry both salts several hours *in vacuo alto* about 125° before analysis. Dried at room temperature both appeared to retain tenaciously a third of a mole of water per mole of salt. The high-melting picrate, which is rather insoluble in hot methanol, gives with this solvent supersaturated solutions from which both varieties of the picrate can be obtained. Recrystallized from acetone in which it dissolves rather easily, it is converted to the low-melting, powdery picrate. A solution of this form (0.5 g.) in methanol (50 ml.), after refluxing 4 hr. and keeping 2 days at 5°, gave the high-melting form (0.4 g.). The lower-melting modification may be the same as that reported by Preobrashenski to melt at 163–164°.[7]

The *hydrochloride* was prepared in methanol and purified from methanol-ether: m.p. 180° (reported:[2] 180°).

Lithium aluminum hydride reduction. To a solution of lithium aluminum hydride (0.6 g.) in dry ether (200 ml.) was added dropwise during 2 hr. a solution of anhydrous racemic 2-carbomethoxytropinone (2.0 g.) in ether (100 ml.). Near the end of the addition a precipitate was obtained. After refluxing the mixture 1 hr., it was kept 2 days, decomposed with ethereal acetone, and extracted with 6*N* sulfuric acid (25 ml.). The aqueous extract was diluted with water (25 ml.), filtered, mixed with Rochelle's salt (10 g.), and basified with sodium hydroxide (6 g.). Continuous extraction with chloroform removed an orange oil (1.8 g.) which could be distilled *in vacuo alto*. It did not give a crystalline hydrochloride, oxalate, or binoxalate. Neutralized with methanolic picric acid it was converted to an orange gum which, after the evaporation of the solvent, slowly and only partially solidified. By repeated recrystallization from methanol the solid portion was obtained as a rather deep yellow substance which dissolved in methanol with difficulty but readily gave supersaturated solutions therein. Under the polarizing microscope it appeared either to be amorphous or to consist of aggregates of minute crystals. It melted at 206–207° and had a composition approximating that of the picrate of racemic *anhydroecgonine methyl ester*.

Anal. Calcd. for $C_{16}H_{18}N_4O_9$: C, 46.83; H, 4.42; N, 13.65. Found: C, 47.14; H, 4.79; N, 13.57.

d-(2-Carbomethoxytropinone). A mixture of anhydrous racemic 2-carbomethoxytropinone (19.7 g., 0.100 mole), m.p. 100–104°, and L-tartaric acid (15.0 g., 0.100 mole) was finely ground and dissolved in warm water (80–100 ml.). On keeping at room temperature or on seeding a large quantity, augmented by cooling to 0°, of feathery needles of the L-bitartrate separated: m.p. 85–91°. These were recrystallized to constant rotation from water: 4.0 g., m.p. 91–94° (bubbling); $[\alpha]_D^{20}$ +15.4° (*c*, 2, water). Dried at 57° in high vacuum to constant weight (5 hr.), the weight loss was 9.89% (theoretical loss for converting the dihydrate to the anhydrous bitartrate: 9.40%). The dried sample was analyzed.

Anal. Calcd. for $C_{10}H_{15}NO_3 \cdot C_4H_6O_6$: C, 48.41; H, 6.10; CH_3O, 8.93. Found: C, 48.29; H, 6.08; CH_3O, 9.00.

Evidence of the transitory existence of a more dextrorotatory L-bitartrate was obtained.

The *d*-base was obtained by mixing the salt with a slight excess of potassium bicarbonate, extracting with chloroform, removing the solvent, and subliming the residue: colorless, minute prisms, m.p. 108.5–109.5°, which electrify readily; $[\alpha]_D^{20}$ +18.3° (*c*, 1, methanol).

The D-*bitartrate* prepared in water from stoichiometric amounts of the *d*-base and D-tartaric acid was obtained as colorless, rather stout prisms by evaporation at room temperature. These were converted to the anhydrous salt by dissolving in methanol and removing the solvent at room temperature. This form was recrystallized from absolute methanol in which it is noticeably less soluble than the hydrate: rosettes of prisms (which were dried over $CaCl_2$), m.p. 145–146° (dec.), $[\alpha]_D^{20}$ −7.0° (*c*, 2.5, water).

Anal. Calcd. for $C_{10}H_{15}NO_3 \cdot C_4H_6O_6$: C, 48.41; H, 6.10. Found: C, 48.32; H, 6.08.

l-(2-Carbomethoxytropinone). The mother liquors from the L-bitartrate were evaporated to dryness, and the base was regenerated in the usual manner. This was combined with an equivalent amount of D-tartaric acid, and the resulting D-bitartrate purified as above noted for the L-bitartrate: white slender prisms; $[\alpha]_D^{20}$ −15.4° (*c*, 2, water). Recrystallized from methanol the pure dihydrate was converted to stout prisms of the anhydrous D-bitartrate: m.p. 159.5° (dec.); $[\alpha]_D^{20}$ −16.9° (*c*, 2, water).

The base was generated in the manner already described: m.p. 108.6–109.6°, $[\alpha]_D^{20}$ −18.3° (*c*, 1, methanol); $[\alpha]_D^{20}$ −36.7° (*c*, 1.7, H_2O).

Anal. Calcd. for $C_{10}H_{15}NO_3$: C, 60.89; H, 7.67. Found: C, 60.98; H, 7.73.

The hydrated form was obtained by mixing with a slight excess of distilled water and drying *in vacuo* over anhydrous sodium sulfate: m.p. 98.5–101.5°.

Anal. Calcd. for $C_{10}H_{15}NO_3 + 2H_2O$: C, 51.49; H, 8.21. Found: C, 51.16, 51.16; H, 7.85, 8.22.

To a solution of the hydrate (0.60 g.) in methanol (~1 ml.) was added picric acid (0.64 g.) dissolved in methanol (1 ml.). The *picrate* of the *l*-base separated suddenly from the supersaturated solution as balls of prisms: m.p. 176–177° (bubbling). These were recrystallized from methanol: minute, slender prisms, m.p. 176–176.5° (bubbling). The sample was dried to constant weight at 125° *in vacuo alto* for analysis (weight loss: 1.49%).

Anal. Calcd. for $C_{16}H_{18}N_4O_{10}$: C, 45.07; H, 4.25. Found: C, 45.16; H, 4.23.

Recrystallized to constant melting point from acetone this form gives another modification melting at 174° (bubbling) which seems, however, to be indistinguishable from the first in crystalline form. It was similarly dried for analysis.

Anal. Calcd. for $C_{16}H_{18}N_4O_{10}$: C, 45.07; H, 4.25. Found: C, 44.95; H, 4.43.

The *binoxalate* was prepared in methanol and crystallized therefrom by adding ether: m.p. 142–143°.

Dehydrogenation experiments. Efforts to dehydrogenate ecgonine, ecgonine methyl ester, and pseudoecgonine methyl ester in alcoholic solution with freshly prepared Raney nickel[34] did not succeed. Silver carbonate in boiling benzene had no effect on either of the foregoing esters. No 2-carbomethoxytropinone was obtained from pseudoecgonine methyl ester by the action of N-bromosuccinimide in chloro-

(34) R. Mozingo, *Org. Syntheses*, 21, 15 (1941).

form, by the action of N-bromoacetamide,[35] or by the Oppenauer oxidation. The irradiation of a fused mixture of pseudoecgonine methyl ester and benzophenone containing a small amount of glacial acetic acid with a G.E. Sunlamp produced no 2-carbomethoxytropinone as indicated by a negative ferric chloride test.

d-(2-Carbomethoxytropinone) from pseudoecgonine methyl ester. Kiliani's chromic acid solution[15] (4.0 ml.) was added dropwise during 1 hr. to a stirred solution of pseudoecgonine methyl ester (1.0 g.) dissolved in Fisher Reagent acetone (250 ml.). The first third of the reagent produced an orange turbidity. The remainder caused a color change to greenish orange and the separation of a granular, greenish deposit. After stirring another hour the acetone solution was filtered, made just alkaline with ammonia, and concentrated *in vacuo* to a brown oil. This was taken up in aqueous potassium carbonate, excess ammonium chloride added, and the mixture extracted with chloroform (3 × 50 ml.). The green salts were mixed with aqueous sodium sulfate, made slightly alkaline with potassium bicarbonate, and extracted with chloroform (3 × 50 ml.), emulsions being broken by centrifuging. The dried (Na_2SO_4) extracts were combined, and the residue recovered in the customary manner: ~0.6 g. of crystalline material consisting mainly of unchanged ester. An ether solution of this mixture was extracted twice with a mixture of saturated aqueous potassium carbonate (3 ml.) and 3*N* potassium hydroxide (1.0 ml.). Crude *d*-(2-carbomethoxytropinone) was thus obtained as a yellow, concentrated aqueous solution of its potassium salt. It was washed with ether (10 ml.), treated with excess saturated ammonium chloride, and extracted with chloroform (3 × 50 ml.). Drying and removal of the solvent in the usual manner afforded crude *d*-(2-carbomethoxytropinone): 0.105 g. It was sublimed *in vacuo alto* for analysis: m.p. 103.5–106.7°, $[\alpha]_D^{20}$ + 17° (c, 1, methanol).

Anal. Calcd. for $C_{10}H_{15}NO_3$: C, 60.89; H, 7.67; N, 7.11. Found: C, 60.80; H, 7.58; N, 6.82.

Like the synthetic base, it gives an intense red color when treated with ferric chloride.[2] From the ether solution 0.5 g. of pseudoecgonine methyl ester was recovered.

Ecgonine methyl ester, similarly oxidized, gave a much lower yield of the keto ester.

Alloecgonine methyl ester. The keto ester (0.125 g.) from natural sources was dissolved in Mallinckrodt A.R. glacial acetic acid (45 ml.), water was added (9.0 ml.), and the mixture was shaken 12 hr. with platinum oxide (0.17 g.) and hydrogen (at approximately atmospheric pressure). The catalyst-free solution was concentrated *in vacuo* to a yellowish gum. The base was recovered by adding aqueous potassium carbonate, extracting with ether (4 × 30 ml.), and concentrating the dried extracts on the water bath and then *in vacuo*. Inasmuch as the base did not crystallize, it was dissolved in ether (1 ml.) and treated with an acetone-ether solution (1 ml.) containing the stoichiometric amount of acetic acid. The hydroacetate which separated was recrystallized from acetone to constant melting point: 0.07 g., m.p. 111.5–1113.5°, $[\alpha]_D^{20}$ −3.6° (c, 2, methanol). The dibenzoyl-L-bitartrate was prepared in methanol and thrice recrystallized therefrom, but not to constant melting point: small crystals having hexagonal faces, m.p. 159.5–160°. This melting point was not depressed by admixture with the dibenzoyl-L-bitartrate (m.p. 160°) similarly obtained from the synthetic *d*-base.

Anal. Calcd. for $C_{28}H_{31}NO_{11}$: C, 60.31; H, 5.60. Found: C, 60.54; H, 5.64.

Experiments with methyl acetoacetate. (a) Methylamine hydrochloride (20.3 g.), potassium acetate (29.4 g.), and water (25 ml.) were warmed and agitated until the mixture was homogeneous. It was diluted with glacial acetic acid (200 ml.), 2,5-diethoxytetrahydrofuran (16.0 g.) added, and then methyl acetoacetate (10.7 ml.). The mixture, initially yellow, had become brown within 24 hr. After 2 weeks it was filtered, concentrated *in vacuo* to a dark syrup, treated with excess aqueous potassium carbonate, and extracted with chloroform (3 × 100 ml.). Removal of the solvent from the dried (Na_2SO_4) extracts on the steam bath and then *in vacuo*, gave a dark thick oil which was leached with hot ligroin (4 × 100 ml.), b.p. 60–70°. Removal of the ligroin afforded an orange brown oil (11 g.) which partially crystallized. The solid material was filtered off and purified from methanol: ~2 g., m.p. 166.5–167°. This material, which retains some methanol, was sublimed for analysis. In chloroform solution it had strong bands at 3.03 μ, 6.09 μ, and 6.27 μ but none for saturated ketone or unconjugated ester groupings. The Rast method indicated the molecular weight of the unsublimed material to be 191. For the same material the methoxyl content was 15.7%.

Anal. Calcd. for $C_{11}H_{18}N_2O_{27}C_2$: C, 62.83; H, 8.63; N, 13.33. Found: C, 63.05; H, 8.59; N, 13.20.

The binoxalate was prepared in and purified from methanol: irregularly shaped crystals, m.p. 193–194°.

Anal. Calcd. for $C_{13}H_{20}N_2O_6$: C, 51.99; H, 6.71; N, 9.33. Found: C, 51.78; H, 6.80; N, 9.22.

(b) Succindialdehyde, prepared from 2,5-diethoxytetrahydrofuran (16 g.) as described under "Tropinone," was diluted to 125 ml., mixed with methylamine hydrochloride (6.75 g.), then with potassium bicarbonate (10.0 g.), and finally with methyl acetoacetate (10.7 ml.) in methanol (350 ml.). The initially pale green solution had become brown within a few hours. During the next two weeks the solution did not become noticeably darker. It was filtered and concentrated *in vacuo* to a mixture of water and oil which partially crystallized on keeping. Purified from methanol it was obtained as minute, stout prisms: 5.9 g. (20%), m.p. 119–124°.

Anal. Calcd. for $C_{16}H_{21}NO_5$: C, 61.00; H, 7.17; N, 4.74. Found: C, 61.09; H, 7.14; N, 4.69.

It is neutral and gives no ferric chloride test. After sublimation it melted at 118–119°. In chloroform solution the sublimed material exhibited pronounced absorption at 5.76 μ, 5.85 μ, 6.02 μ, and 6.45 μ.

Spectral measurements. In chloroform solution racemic 2-carbomethoxytropinone (m.p. ~104°) showed noticeable absorption in the 3.0 μ region and gave two medium bands at 5.74 μ[36] and 5.83 μ and two strong bands at 6.04 μ[36] and 6.18 μ characteristic of unconjugated ester, ketone, conjugated ester, and ethylenic groupings, respectively.

In Nujol the dihydrate gave strong bands at 2.95 μ, and at 6.0 μ. The absence of any bands for unconjugated ester and keto groupings indicates strongly that these two bands are for the hydroxyl and the conjugated ester groups of the enol form.

In Nujol samples of 2,4-dicarbomethoxytropinone hemihydrate melting at 82.5–84° and at 88–91° had strong bands at 2.95 μ, 5.74 μ,[36] and 5.97 μ characteristic of hydroxyl, unconjugated ester, and conjugated ester groupings, respectively. There was little or no evidence of ketone absorption near 5.80 μ.

In absolute alcohol anhydrous racemic 2-carbomethoxytropinone had λ_{max} 255 μ (ε 6190) and 2,4-dicarbomethoxytropinone λ_{max} 255 mμ (ε 7882). In the same solvent methyl acetoacetate had λ_{max} 240 mμ (ε 1513 after 5 min.; 1667 after 1 or more hr.).

The infrared measurements were made with a Perkin-Elmer Recording Spectrophotometer (Model 21) having a sodium chloride prism and the ultraviolet adsorption spectra with a Cary Recording Spectrophotometer (Model 11).

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(36) K. Kuratani, *Rept. Inst. Sci. Technol., Univ. Tokyo*, **5**, 25 (1951); *Chem. Abstr.*, **46**, 1354 (1952).

Charles Pfizer Company, and Merck and Company for generous samples of 2,5-diethoxytetrahydrofuran, β-ketoglutaric acid, and tropinone, respectively. The microanalyses herein reported are principally by Miss Paula M. Parisius, Mrs. Evelyn G. Peake, and Mr. Byron Baer of the Microanalytical Service Laboratory directed by Dr. William C. Alford. Mr. Harold K. Miller made the infrared measurements, and Mrs. Charles I. Wright, determined the ultraviolet absorption spectra. He is indebted to Mr. Miller and Dr. William R. Nes for helpful interpretations of the infrared absorption spectra.

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[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Keto Grignard Reagents. Intramolecular Reduction*[1]

REYNOLD C. FUSON AND NORMAN SHACHAT[2]

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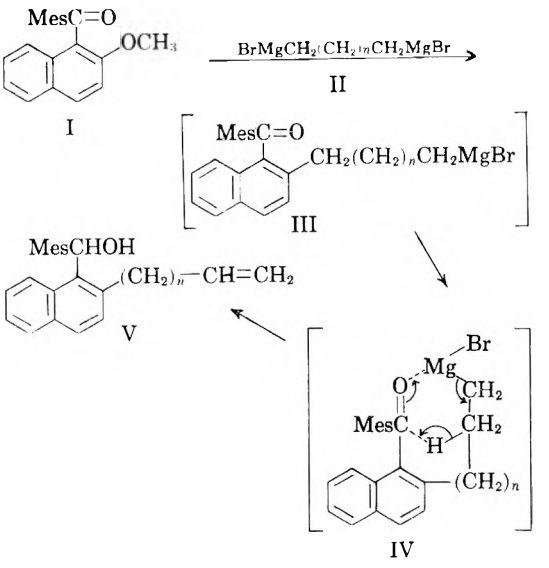
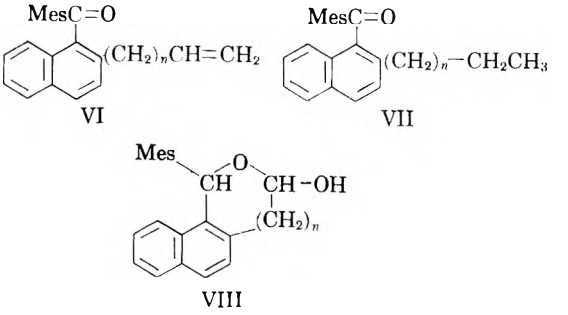
1-Mesitoyl-2-methoxynaphthalene (I) reacts with the dimagnesium derivatives (II) of 1,4-dibromobutane, 1,5-dibromopentane, and 1,6-dibromohexane to yield products that could be derived from intermediate keto Grignard reagents (III). With 1,4-butanedimagnesium dibromide, for example, the principal product is 2-(γ-butenyl)naphthyl-1-mesitylcarbinol (V, $n = 2$). The amount of reduction product decreases progressively as the chain of the Grignard reagent is lengthened. Similarly, duryl 2-methoxyphenyl ketone (X) and the Grignard reagent from 1,4-dibromobutane gave 2-(γ-butenylphenyl)durylcarbinol (XII).

The condensation of esters with certain aliphatic bifunctional Grignard reagents to give cyclic carbinols[3] appears to involve the formation of keto Grignard reagents as transient intermediates. The object of the present study was to determine whether such a keto Grignard reagent could be produced by the action of a dibromomagnesium compound on a hindered *o*-methoxyaryl ketone, a vinylog of an ester.

1-Mesitoyl-2-methoxynaphthalene (I) has been found to react with the Grignard reagent from 1,4-dibromobutane (II, $n = 2$) to give the olefinic carbinol V ($n = 2$) in a yield of 65%. This unexpected product was formed presumably by way of the keto Grignard reagent III ($n = 2$), which may undergo intramolecular reduction by way of a transition state resembling the *quasi*-cyclic system IV ($n = 2$).[4] Since *n*-butylmagnesium bromide displaces the methoxyl group of the methoxy ketone I in 55% yield,[5] the intramolecular reduction of the keto Grignard reagent III ($n = 2$) probably occurs rapidly and quantitatively.



Oxidation with dichromate in glacial acetic acid, by preferential attack of the carbinol function, produced the olefinic ketone VI ($n = 2$), which was hydrogenated catalytically to give 2-*n*-butyl-1-mesitoylnaphthalene (VII, $n = 2$).



The terminal position of the double bond in the side chain of the carbinol was established by ozonization. In addition to formaldehyde, a larger frag-

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(2) Allied Chemical and Dye Corporation Fellow, 1956–1957.

(3) C. D. Nenitzescu and I. Necsoiu, *J. Am. Chem. Soc.*, **72**, 3483 (1950).

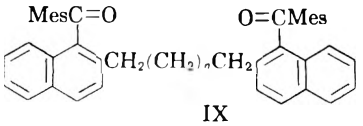
(4) H. S. Mosher and E. La Combe, *J. Am. Chem. Soc.*, **72**, 3994 (1950).

(5) R. C. Fuson and S. B. Speck, *J. Am. Chem. Soc.*, **64**, 2446 (1942).

ment was isolated which had the composition of the expected hydroxy aldehyde; its infrared spectrum corresponds instead to the seven-membered hemiacetal VIII (n = 2). The existence of such a ring is not without precedent.[6] The compound formed a derivative with methone.

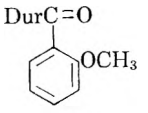
The pentenyl carbinol (V, n = 3), obtained in 36% yield by the use of the *di*-Grignard reagent from 1,5-dibromopentane (II, n = 3), underwent ozonization to yield the interesting eight-membered hemiacetal (VIII, n = 3). In view of the findings of Hurd and Saunders[6c] that simple ω-hydroxy aldehydes capable of forming cyclic hemiacetals of ring size greater than six members exist mainly as the free aldehyde, it is remarkable that in this system (hydroxy aldehyde form of VIII) of much reduced mobility the seven- and eight-membered cyclic hemiacetals are favored. The carbinol was accompanied by the isomeric n-pentyl ketone (VII, n = 3), which would be formed from the keto Grignard reagent (III, n = 3) by hydrolysis.

1,6-Hexanedimagnesium dibromide (II, n = 4) gave none of the hexenyl carbinol (V, n = 4). It is curious that the amount of the original ketone (I) that was recovered rose from zero for the C_4-reagent to 36% for the C_6-reagent. Also, with the C_5- and C_6-reagents small amounts of di-displacement products were isolated. These correspond to formula IX in which n has the values 3 and 4, respectively.

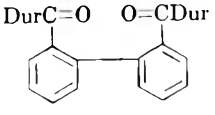


IX

Coupling was the chief reaction when duryl 2-methoxyphenyl ketone (X) was treated with 1,4-butanedimagnesium dibromide; 2,2′-diduroylbiphenyl (XI)[7] was obtained in a yield of 45%. The amount of this diketone remained undiminished even when great care was taken to free the Grignard reagent of magnesium metal. This result is in accord with the observation that reduction of a ketone to the corresponding pinacol may be brought about by a Grignard reagent.[8]

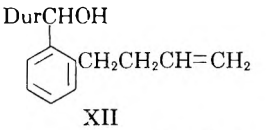


X

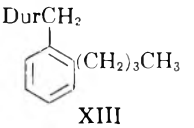


XI

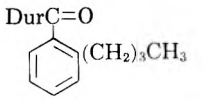
Intramolecular reduction occurred with the duryl ketone (X) also, but the yield of the unsaturated alcohol (XII) was only 8.5%.



XII



XIII



XIV

Hydrogenation of this carbinol gave 2-(n-butylphenyl) durylmethane (XIII) in high yield. Reduction of 2-n-butylphenyl duryl ketone (XIV), effected with sodium in ethanol, gave the same hydrocarbon.

It is to be noted that three of the four types of products of these several reactions—the olefinic carbinols (V), the alkylated ketones (VII), and the diketones (IX)—are those to be expected from the postulated keto Grignard reagents (III).

EXPERIMENTAL[9]

Treatment of 1-mesitoyl-2-methoxynaphthalene (I) *with the di-Grignard reagent from 1,4-dibromobutane.* A solution of the Grignard reagent was prepared from 2.8 g. (0.013 mole) of 1,4-dibromobutane and 1.0 g. (0.041 g. atom) of magnesium in 35 ml. of ether. To it was added, slowly with stirring, a solution of 2.01 g. (0.0067 mole) of the methoxy ketone in a mixture of 15 ml. of benzene and 10 ml. of ether. The red reaction mixture, which contained a precipitate, was heated under gentle reflux for 4 hr., cooled in an ice water bath, and hydrolyzed with 50 ml. of a saturated ammonium chloride solution. The organic layer was washed with 10% sodium bicarbonate solution and water, then dried over anhydrous sodium sulfate. Two recrystallizations from high-boiling petroleum ether yielded 1.2 g. of the colorless product, 2-(γ-butenyl)naphthyl-1-mesitylcarbinol (V, n = 2), m.p. 85.5–88.5°.

Anal.[10] Calcd. for $C_{24}H_{26}O$: C, 87.23; H, 7.93. Found: C, 87.38; H, 8.14.

The infrared spectrum[11] (CS_2) shows absorption bands which can be assigned to a hydroxyl function (3570 and 1038 cm.$^{-1}$), a vinyl group (1641, 915, 1005 cm.$^{-1}$), a mesityl group (857 cm.$^{-1}$), and a 1,2-disubstituted naphthalene ring (821 and 747 cm.$^{-1}$).

The crystallization filtrates were concentrated and the residual 0.9 g. of yellow oil was subjected to chromatography with alumina as the adsorbent and cyclohexane-ether mixtures as the eluting solvents. In this way an additional 0.23 g. of product was isolated; total yield 1.43 g. (65%).

Hydrogenation of 2-(γ-butenyl)naphthyl-1-mesitylcarbinol (V, n = 2). A solution of 0.33 g. (0.001 mole) of the carbinol in 15 ml. of absolute ethanol was hydrogenated over a palladium-charcoal catalyst at atmospheric pressure and room temperature. After 15.5 hr., the theoretical amount of hydrogen (0.002 mole) had been absorbed. The product, a colorless oil, has an infrared spectrum (CS_2) that is consistent

(6) (a) H. Pringsheim and S. Kalodny, *Ber.*, **59**, 1135 (1926); (b) B. Helferich and G. Sparmberg, *Ber.*, **64B**, 104, 1151 (1931); (c) C. D. Hurd and W. H. Saunders, Jr., *J. Am. Chem. Soc.*, **74**, 5324 (1952).

(7) R. C. Fuson and R. O. Kerr, *J. Org. Chem.*, **19**, 373 (1954).

(8) W. Theilacker and M. L Wessel, *Ann.*, **594**, 229 (1955).

(9) All melting points are corrected.

(10) The microanalyses were performed by Mr. Joseph Nemeth, Mrs. R. Benassi, Mr. Rolo Nesset, Miss Claire Higham, Mrs. Ruby Ju, and Mrs. M. Stingl.

(11) The infrared spectra were determined by Mr. James Brader, Mrs. Louise Griffing, Mr. Sy Portnow, and Mr. Brian Cloonan.

with the hydrocarbon structure, 2-(*n*-butyl)naphthyl-1-mesitylmethane; strong absorption bands appear at 2920, 1079, 851, 815, and 749 cm.$^{-1}$. The bands ascribed to the hydroxyl and vinyl groups of the starting material are completely absent.

Transformation of 2-(γ-butenyl)naphthyl-1-mesitylcarbinol (V, *n* = 2) *to 2-n-butyl-1-mesitylnaphthalene* (VII, *n* = 2).

Oxidation. To a solution of 0.5 g. (0.0015 mole) of the carbinol in 20 ml. of benzene and 15 ml. of glacial acetic acid was added dropwise a solution of 1.8 g. of sodium dichromate dihydrate in 3 ml. of concentrated sulfuric acid, 10 ml. of water, and 2 ml. of glacial acetic acid. The dark red reaction mixture was stirred at room temperature for 17 hr. After water and benzene had been added to increase the volume of the layers, the organic solution was washed with water and dried. A yellow oil remained when the solvent was removed. When subjected to chromatography, however, this oil gave only clear colorless oils. An infrared spectrum (CS_2) of this material was consistent with the structure 2-γ-butenyl-1-mesitoylnaphthalene (VI, *n* = 2).

Hydrogenation. A solution of the yellow oil in absolute ethanol was hydrogenated over 30% palladium-on-charcoal at 752 mm. and 32°. The uptake of hydrogen ceased after 2.5 hr.; 23.2 ml. (0.0009 mole) had been absorbed. The product crystallized from ethanol, m.p. 70–72°, yield 0.2 g. (40%). The infrared spectrum (CS_2) of this product is superimposable on that of 2-*n*-butyl-1-mesitoylnaphthalene (VII, *n* = 2).[5]

Ozonolysis of 2-(γ-butenyl)naphthyl-1-mesitylcarbinol (V, *n* = 2). A solution of 0.5 g. (0.0015 mole) of the unsaturated carbinol in 20 ml. of methanol was treated with ozone at −20 to −30° for 12 min. at a flow rate of approximately 0.171 millimole of ozone/min. To the cold solution of ozonide was added 1.0 g. of sodium iodide and 1.0 ml. of glacial acetic acid. The mixture was allowed to warm to room temperature slowly during 1.5 hr. A 10% solution of sodium thiosulfate was added dropwise to reduce the iodine that formed. The colorless solution was distilled under vacuum, and the distillate was collected in an acetone–Dry Ice trap at −80°. Ether and water were added to the solid residue. The organic layer was dried and the solvent removed. Two recrystallizations from ethanol produced 0.3 g. (60%) of colorless product, m.p. 181–182°.

Anal. Calcd. for $C_{23}H_{24}O_2$: C, 83.10; H, 7.28. Found: C, 83.20; H, 7.33.

The infrared spectrum ($CHCl_3$) of this compound exhibits absorption bands at 3605, 3420, 1091, 1057, 1037, and 855 cm.$^{-1}$.

The *methone derivative* of the major fragment, prepared in the usual manner,[12] was recrystallized from a methanol-water mixture, m.p. 195.5–198.5°. Its infrared spectrum ($CHCl_3$) exhibits a weak broad band at 3160 cm.$^{-1}$, a very strong band at 1621 cm.$^{-1}$, and a weak band at 856 cm.$^{-1}$.

To the distillate was added a slight excess of *p*-nitrophenylhydrazine. The red solution was heated on a steam bath for 20 min., cooled, and filtered. The reddish-orange solid product was recrystallized several times from an ethanol-water mixture, m.p. 177.5–180.5° (dec.) (reported m.p. 181°), yield 0.05 g. This product exhibits the same infrared spectrum (Nujol) as an authentic sample of formaldehyde *p*-nitrophenylhydrazone.

Treatment of 1-mesitoyl-2-methoxynaphthalene (I) *with the di-Grignard reagent from 1,5-dibromopentane.* To a solution of 1,5-pentanedimagnesium dibromide prepared from 1.46 g. (0.06 g. atom) of magnesium, 4.6 g. (0.02 mole) of 1,5-dibromopentane, and 50 ml. of ether was added dropwise a solution of 3.04 g. (0.01 mole) of the methoxy ketone in a mixture of 20 ml. of benzene and 10 ml. of ether. The dark red mixture was treated as described for the previous *di*-Grignard reaction. A crystallization from high-boiling petroleum ether gave 0.56 g. of a colorless product, m.p. 95.5–96.5°.

Anal. Calcd. for $C_{25}H_{28}O$: C, 87.16; H, 8.19. Found: C, 87.30; H, 8.39.

The infrared spectrum (CS_2), which is very similar to that of 2-(γ-butenyl)naphthyl-1-mesitylcarbinol, exhibits bands at 3605, 1640, 1034, 1005, 910, 852, 818, and 745 cm.$^{-1}$. These data are consistent with the structure, 2-(δ-pentenyl)-naphthyl-1-mesitylcarbinol (V, *n* = 3).

The solvent was removed from the crystallization filtrates, and the residual oil was chromatographed. A clear colorless oil, 0.4 g. (11.5%), was eluted in the early fractions. Repeated attempts to effect crystallization were unsuccessful. The infrared spectrum (CS_2) of the oil is very similar to that of 2-*n*-butyl-1-mesitoylnaphthalene. A Beilstein test was negative with respect to the presence of halogen. Therefore, it is not unreasonable to assign the structure, 1-mesitoyl-2-*n*-pentylnaphthalene (VII, *n* = 3) to this material. By combination of fractions and recrystallization from high-boiling petroleum ether, 0.26 g. (8.5%) of starting material was recovered, m.p. 125–127°. A new compound was obtained by elution of the column with 1:4 cyclohexane-ether. Two recrystallizations from ethanol afforded 0.23 g. (7.5%) of the colorless di-displacement product (IX, *n* = 3), m.p. 148–149°.

Anal. Calcd. for $C_{45}H_{44}O_2$: C, 87.62; H, 7.19. Found: C, 87.39; H, 7.28.

The infrared spectrum (CS_2) exhibits bands which are assignable to a conjugated hindered ketone group (1657 cm.$^{-1}$), a mesityl group (853 cm.$^{-1}$), and a 1,2-disubstituted naphthalene ring (824 and 749 cm.$^{-1}$).

Finally, elution of the column with alcohol gave an additional 0.68 g. of 2-(δ-pentenyl)naphthyl-1-mesitylcarbinol, m.p. 94.5–96°, total yield 1.24 g. (36%).

Ozonolysis of 2-(δ-pentenyl)naphthyl-1-mesitylcarbinol (V, *n* = 3). A solution of 1.0 g. (0.0029 mole) of the unsaturated carbinol in 20 ml. of methanol was treated with ozone at −20 to −30° for 24 min. at a flow rate of approximately 0.171 millimole of ozone/min. The work-up was similar to that previously described. The major fragment was purified by recrystallization from an ether–low-boiling petrolum ether mixture, m.p. 108–109°, yield 0.6 g. (60%).

Anal. Calcd. for $C_{24}H_{26}O_2$: C, 83.20; H, 7.56. Found: C, 83.17; H, 7.79.

The infrared spectrum (CS_2) of the compound shows absorption bands at 3600, 3410, 1081, 1023, 1002, 855, 820, and 747 cm.$^{-1}$.

The *methone derivative* of the major fragment, prepared in the usual manner,[12] was recrystallized from low-boiling petroleum ether, m.p. 180–181°. Its infrared spectrum ($CHCl_3$) exhibits a weak band at 3610 cm.$^{-1}$, a very broad weak band at about 2650 cm.$^{-1}$, a very strong band at 1597 cm.$^{-1}$, and a weak band at 855 cm.$^{-1}$.[13]

The *p*-nitrophenylhydrazone of formaldehyde was isolated from the distillate and identified by its melting point and infrared spectrum (Nujol).

Treatment of 1-mesitoyl-2-methoxynaphthalene (I) *with the di-Grignard reagent from 1,6-dibromohexane.* A solution of 0.01 mole of the ketone in 50 ml. of benzene was added dropwise during a period of 2.5 hr. to the two-layer Grignard system prepared from 2.2 g. (0.09 g. atom) of magnesium,

(12) E. C. Horning and M. G. Horning, *J. Org. Chem.*, 11, 95 (1946).

(13) It is interesting that the infrared spectra of the methone derivatives of the hemiacetals VIII (*n* = 2 and 3) exhibit only a single absorption in the carbonyl region, a very intense band near 1600 cm.$^{-1}$; whereas strong absorption bands at both 1700 and 1605 cm.$^{-1}$ are found in the infrared spectrum of methone itself. (L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, John Wiley and Sons, Inc., New York, 1954, p. 123.) The methone derivative of butyraldehyde (m.p. 134–135°)[12] was prepared for infrared inspection. Its spectrum ($CHCl_3$) also shows a lone, intense carbonyl band at 1595 cm.$^{-1}$.

7.3 g. (0.03 mole) of 1,6-dibromohexane, and 60 ml. of ether. The red reaction mixture was heated under reflux for 2 hr. and hydrolyzed with a cold, saturated ammonium chloride solution. The cloudy organic layer was washed with water and filtered. The colorless solid which collected on the filter was recrystallized several times from a chloroform-ethanol mixture, m.p. 272–274° (bubbles of gas appear at melting point), yield 0.12 g. (4%).

Anal. Calcd. for $C_{41}H_{40}O_4$: C, 82.52; H, 6.76. Found: C, 82.50; H, 6.99.

The infrared spectrum ($CHCl_3$) of this substance exhibits bands at 1636, 1614, 1569, 1264, and 855 cm.$^{-1}$. These data are consistent with a tetrahydrobinaphthyl structure.

The clear organic layer was dried and concentrated. Ether was added to the residual red oil, and the solution was cooled. Crystals of starting material (0.39 g.) were removed by filtration and recrystallized from high-boiling petroleum ether, m.p. 125–128°. The remaining product mixture was subjected to chromatography. The first fraction (pure cyclohexane) contained a trace of an oily solid which was submitted for infrared analysis. The spectrum (CS_2) almost bare except for one very intense band in the carbon-hydrogen stretching region (2900 cm.$^{-1}$), suggests that the substance is a long-chain hydrocarbon. Next, 0.94 g. (26.3%) of a clear colorless oil was eluted (4:1 cyclohexane-ether). Repeated attempts to effect crystallization were unsuccessful. The infrared spectrum (CS_2) of this material is almost identical with the spectra of 2-*n*-butyl-1-mesitoylnaphthalene (VII, $n = 2$) and 1-mesitoyl-2-*n*-pentylnaphthalene (VII, $n = 3$). A Beilstein test showed that the substance does not contain halogen. Therefore, the structure 2-*n*-hexyl-1-mesitoylnaphthalene (VII, $n = 4$) was assigned to the compound.

Anal. Calcd. for $C_{26}H_{30}O$: C, 87.10; H, 8.44. Found: C, 86.70; H, 8.71.

Elution of the column with 3:2 and 1:1 cyclohexane-ether yielded an additional 0.7 g. of 1-mesitoyl-2-methoxynaphthalene, m.p. 126–128°, total yield 1.09 g. (36%).

The colorless di-displacement compound (IX, $n = 4$) was eluted with 1:4 cyclohexane-ether and recrystallized from ethanol, m.p. 135–137°, yield 0.1 g. (3.2%). It exhibits an infrared spectrum (CS_2) which is almost identical with that of the analogous product of the previous *di*-Grignard reaction (eluted with 1:4 cyclohexane-ether).

Anal. Calcd. for $C_{46}H_{46}O_2$: C, 87.58; H, 7.35. Found: C, 87.68; H, 7.51.

In one experiment, a trace (0.05 g.) of a colorless compound was isolated and recrystallized from a chloroform-ethanol mixture, m.p. 276.5–278°.

Anal. Calcd. for $C_{42}H_{38}O_4$: C, 83.14; H, 6.31. Found: C, 83.93; H, 6.41.

The infrared spectrum ($CHCl_3$) exhibits an intense band at 1654 cm.$^{-1}$ which can be assigned to a conjugated hindered carbonyl function, a band at 876 cm.$^{-1}$ attributable to a lone aromatic hydrogen atom, and a band at 845 cm.$^{-1}$ assignable to a mesityl group. These data suggest a binaphthyl structure.

A dark red oil (0.5 g.) was eluted from the column with methanol and subjected to infrared analysis (CS_2). By comparison with the spectra of the olefinic carbinols V ($n = 2$ and 3), it was concluded that 2-(ϵ-hexenyl)naphthyl-1-mesitylcarbinol (V, $n = 4$) is present, if at all, in only a slight trace. Therefore, this oil was not treated further.

In view of the large amount of recovered starting material, the experiment was repeated several times under different conditions. One variation involved a much longer period of reflux, and another, an increase in the ratio of benzene to ether. Initially, the experiment was carried out under conditions identical with the previous *di*-Grignard reaction. These modifications, however, did not effectively alter the quantities of products; approximately 30% of the starting material was recovered in each instance.

Treatment of duryl 2-methoxyphenyl ketone (X) *with 1,4-butanedimagnesium dibromide.* A solution of 4.36 g. (0.02 mole) of 1,4-dibromobutane in 60 ml. of ether was added slowly to 0.97 g. (0.04 g. atom) of magnesium under nitrogen. The two-layer system of 1,4-butanedimagnesium dibromide was heated under reflux for 1 hr. with stirring. A few pieces of magnesium remained unchanged. During a period of 0.5 hr., a solution of 5.36 g. (0.02 mole) of duryl 2-methoxyphenyl ketone[7] in 50 ml. of dry ether was added. The reaction mixture turned orange, brown, green, blue-green, and finally dark blue. After addition was complete, the solution was allowed to remain at room temperature for 1 hr. Carbonation was effected by dropping the mixture into a slurry of 100 g. of Dry Ice in 100 ml. of ether. When room temperature had been reached, the solution was hydrolyzed with dilute hydrochloric acid. The organic layer was extracted with three 25-ml. portions of 5% sodium hydroxide. Acidification of the basic extract produced a cloudy aqueous solution; even when cooled, however, this solution gave no solid acid. The organic layer was washed, dried, and concentrated to a semi-solid mass. When a hot ethanol solution of the residue was cooled, an egg-shell white powder formed, m.p. 216–235°. Several recrystallizations from a chloroform-ethanol mixture afforded 1.65 g. of colorless crystals, m.p. 247.5–251°. The infrared spectrum (CS_2) of this material is identical with that of 2,2′-diduroylbiphenyl (XI). Furthermore, a mixture melting point with an authentic sample of that diketone was not depressed.

The solvent was removed from the combined crystallization filtrates, and the remaining oil was subjected to chromatography. The first compound that was eluted was a colorless crystalline solid, which was recrystallized several times from a chloroform-ethanol mixture, m.p. 273.5–276.5°, yield 0.10 g.

Anal. Found: C, 89.06; H, 8.04. Calcd. Empirical Formula $C_{38}H_{40}O$.

The infrared spectrum (CS_2) of this compound is similar to that of 9,10-didurylphenanthrene.[7] Prominent absorption bands appear at 736, 761, 872, 1010, 1022, 1387, and 2908 cm.$^{-1}$.

The second material to be eluted was a colorless oil that slowly crystallized from ethanol, m.p. 38–39.5°, yield 0.15 g.

Anal. Calcd. for $C_{25}H_{34}O$: C, 85.66; H, 9.78. Found: C, 85.36; H, 10.08.

The infrared spectrum (CS_2) of this product is almost identical with that of 2-*n*-butylphenyl duryl ketone (XIV)[14] (m.p. 96.5–97°). The band ascribed to the carbon-hydrogen stretching frequency (2900 cm.$^{-1}$), however, is more intense in the spectrum of the product than in that of the butylated ketone (XIV). Thus, the compound was identified as duryl 2-*n*-octylphenyl ketone.

Next, 0.48 g. of 2,2′-diduroylbiphenyl was eluted; total yield 2.13 g. (45%).

The column was flushed with methanol, and the eluted material was dissolved in hot ethanol. From the cooled solution, 0.15 g. of a highly insoluble substance was removed by filtration. The solid was recrystallized from a chloroform-ethanol mixture, m.p. 260–262°. Its infrared spectrum was identical with that of 2-duroyl-2′-(durylbiphenyl)carbinol.[15] The ethanol filtrate was allowed to remain in the refrigerator for about 2 months. A colorless crystalline compound was removed by filtration and recrystallized from ethanol, m.p. 80–82°, yield 0.5 g. (8.5%).

Anal. Calcd. for $C_{21}H_{26}O$: C, 85.66; H, 8.90. Found: C, 85.53; H, 8.77.

The infrared spectrum (CS_2) exhibits bands assignable to a hydroxyl function (3470 and 1020 cm.$^{-1}$), a vinyl group (1639, 1000, and 913 cm.$^{-1}$), and an *ortho*-disubstituted benzene ring (756 cm.$^{-1}$). The data are consistent with the structure, 2-(γ-butenylphenyl)durylcarbinol (XII).

(14) This ketone and its infrared spectrum were kindly supplied by Mr. J. R. Larson.

(15) R. C. Fuson and C. Hornberger, Jr., *J. Org. Chem.*, 16, 637 (1951).

In a subsequent experiment, in which the excess magnesium was removed from the *di*-Grignard reagent by filtration before the duryl 2-methoxyphenyl ketone was added, the coupling products were isolated in undiminished yields.

Hydrogenation of 2-(γ-butenylphenyl)durylcarbinol (XII). A solution of 0.38 g. (0.0013 mole) of the carbinol in 25 ml. of ethanol was hydrogenated over 0.04 g. of 30% palladium-on-charcoal at atmospheric pressure (748 mm.) and room temperature (31°). The theoretical uptake of hydrogen (0.0026 mole) had occurred after about 1 hr.; however, the treatment was continued for an additional 3 hr. The catalyst was removed by filtration and the solvent by distillation. The product, recrystallized from ethanol, formed colorless needles, m.p. 81–83°, yield 0.31 g. (86%). A pure sample melted at 83–84°.

Anal. Calcd. for $C_{21}H_{28}$: C, 89.94; H, 10.06. Found: C, 89.68; H, 10.04.

The infrared spectrum (CS_2) contains bands at 2905, 1600, 1383, 868, and 757 cm.$^{-1}$ which are consistent with the hydrocarbon structure 2-(*n*-butylphenyl)durylmethane (XIII).

Reduction of 2-n-butylphenyl duryl ketone (XIV) *with sodium and ethanol.* To a boiling solution of 0.1 g. (0.00034 mole) of the ketone in 10 ml. of absolute ethanol was added, slowly with stirring, 1.0 g. of sodium in small pieces. After all the sodium had reacted, the hot solution was poured into a mixture of 15 ml. of concentrated hydrochloric acid and 30 g. of ice. The organic material was extracted from the cloudy aqueous solution with benzene. The benzene solution was washed, dried, and concentrated; the residual yellow oil crystallized from an ethanol-water mixture in slightly yellow crystals, yield 0.0264 g. (28%), m.p. 77–80°. A mixture melting point with the product of the previous reaction was 78–81°. In addition, the infrared spectrum (CS_2) is identical with that of the product of the previous reaction.

URBANA, ILL.

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

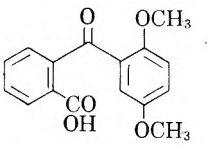
The Synthesis of Some Linear Tetracyclic Substances*[1]

MARSHALL GATES AND CLIFFORD L. DICKINSON, JR.[2]

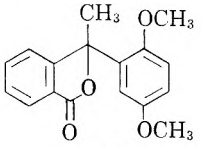
Received July 29, 1957

Several synthetic paths leading to linear tetracyclic substances have been investigated, and a dihydroxydioxomethylhexahydronaphthacene has been prepared.

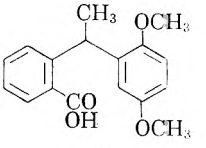
With a view toward assembling large molecules which might have some of the chelating properties associated with the tetracyclines, we have prepared some linear tetracyclic substances bearing several oxygenated functional groups. Our approach has been through *o*-(2,5-dimethoxybenzoyl)benzoic acid (I),[3] readily available by the condensation of *o*-carbomethoxybenzoyl chloride with hydroquinone dimethyl ether.[4] This substance was converted to 3-methyl-3-(2,5-dimethoxyphenyl)phthalide (II) in high yield by the action of methyl magnesium iodide. Reduction of the phthalide II with zinc and ammonia[5] yielded the corresponding acid III which readily cyclized in high yield on treatment with sulfuric acid to give 1,4-dimethoxy-10-methyl-9-anthrone (IV).



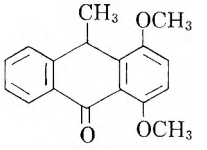
I



II



III



IV

We had hoped to extend the linear annulation of IV by the addition of butadiene or substituted butadienes to the 1,4-quinone corresponding to IV. This approach has the merit of converting the aromatic hydroquinone ring of IV to a hydroaromatic ring corresponding to ring B of the tetracyclines. The deep red quinone VI was readily prepared in high yield from IV by demethylation with aluminum bromide followed by oxidation with ferric chloride, but proved to be too unstable for successful use in the Diels-Alder reaction.

On the assumption that the instability of the quinone was largely the result of the acyl substituent, an attempt to prepare the ethylene thioketal of V prior to its oxidation to the quinone was made, but only unreacted starting material was obtained.

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* This paper is a contribution in honor of Lyndon F. Small, former Editor of the Journal.

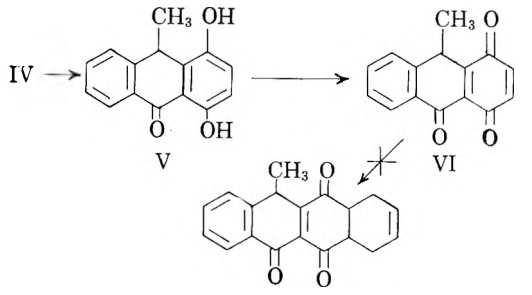
(1) Taken from the Ph.D. dissertation of Clifford L. Dickinson, Jr., the University of Rochester, 1955.

(2) E. I. du Pont de Nemours Fellow, 1954–1955.

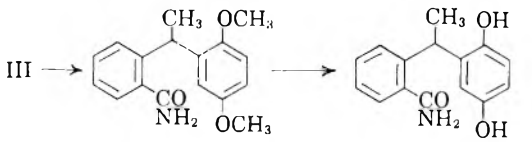
(3) K. Lagodzinski, *Ber.*, **28**, 116 (1895).

(4) C. Dufraisse and A. Allais, *Bull. Soc. Chim.*, [5], **11**, 531 (1944). This method was preferred to the simpler one using phthalic anhydride since it would allow structural specificity with substituted phthalic acid derivatives, *e.g.* the 3-methoxy derivative, whose use was contemplated in extending this synthesis to more highly oxygenated substances.

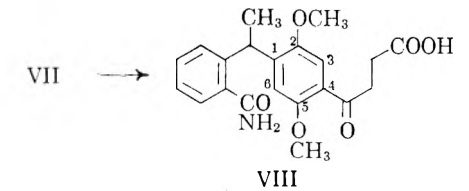
(5) The procedure was based on that of Bergmann for the similar reduction of 3-methyl-3-phenyl phthalide. *cf.* E. Bergmann, *J. Org. Chem.*, **4**, 1 (1939).



An attempt to convert the acid III or one of its derivatives into the corresponding quinone with a view toward carrying out the Diels-Alder reaction before ring closure (This would be the equivalent of establishing ring A before ring C of the tetracyclines.) also failed. Demethylation of III with hydrobromic acid led not to the corresponding hydroquinone but to V, and attempts to convert III into its acid chloride also resulted in cyclization. The corresponding amide VII was successfully prepared by the mixed anhydride method, however, and could easily be demethylated. Successful hydrolysis of the refractory amide



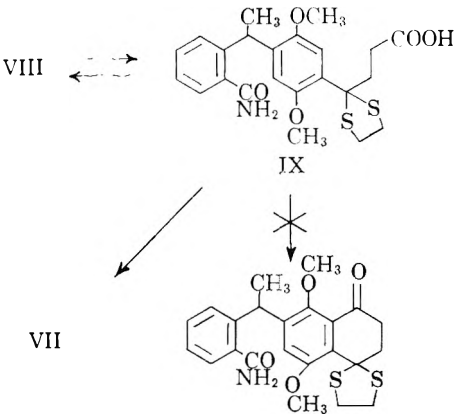
group at a later stage in the presence of reactive groups seemed remote, however, so the amide VII was used in an alternative scheme. Condensation with β-carbomethoxypropionyl chloride in the presence of polyphosphoric acid led to a single substance in 45% yield. This was assumed to have structure VIII on the basis of the following argument: Of the three positions available



for substitution in the substituted dimethoxybenzene ring, the 6 position can be eliminated. It is di-*o*-substituted, and the hindrance produced by the *ortho*-substituted 1-phenylethyl group must be very large. Of the other two positions, both the aliphatic substituent and the steric effect[6] favor position 4. This structural assignment was confirmed by certain characteristics of the completely cyclized compound to be discussed herewith.

We wished, if possible, to retain the carbonyl group of VIII in the final product, but for easy cyclization its deactivating effect on the aromatic ring had to be reduced or eliminated. The action of ethanedithiol and boron fluoride etherate in acetic acid[7] produced the thioketal IX in nearly quantitative yield. Its infrared spectrum shows carbonyl absorption at 5.86 and 6.01 μ. That of VIII shows three bands in this region, at 5.84, 6.01, and 6.05 μ. The common bands at 5.84 and 6.01 μ can be assigned to the carboxyl and carbamide groups, respectively, leaving that at 6.05 μ, somewhat longer than the usual aromatic carbonyl band, assignable to the ketonic group of VIII.

All attempts to cyclize the thioketal IX failed. Hydrogen fluoride gave only starting material, as did concentrated sulfuric acid at room temperature. At higher temperatures complete decomposition took place. Boron fluoride etherate gave either no reaction or resulted in cleavage to VIII[8] depending on conditions. In polyphosphoric acid VIII was again obtained, but in addition to an unidentified sulfur-containing compound containing no aromatic ring, VII was also obtained. This reversal of the Friedel-Crafts reaction, while unexpected, is not abnormal if cleavage of the thioketal takes place first, since Rosenmund and Schurr[9] have reported a number of instances of deacylations of acyl phenols and phenol ethers. These results suggest that an equilibrium is established between VII, a β-carbomethoxypropionylpolyphosphoric acid complex, and VIII, and this suggestion receives support from the observation that in the acylation of VII, some unchanged starting material is invariably recovered.[10]



Although IX could not be cyclized, the corresponding hydroquinone might be expected to be sufficiently active for cyclization with, *e.g.*, hydrogen fluoride. Accordingly, VIII was demethylated to yield the corresponding hydroquinone X, but all

(6) The "buttressing effect" [M. Rieger and F. H. Westheimer, *J. Am. Chem. Soc.*, **72**, 19 (1950)] clearly produces more hindrance at position 3 than at 4.

(7) L. F. Fieser, *J. Am. Chem. Soc.*, **76**, 1945 (1954).

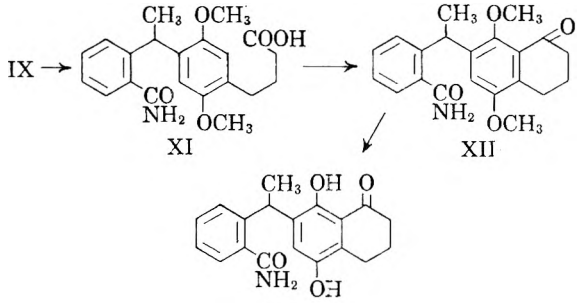
(8) Possibly through an intermediate enol thioether, *cf.* A. Sporzynski, *Arch. Chem. Farm.*, **3**, 59 (1936).

(9) K. W. Rosenmund and W. Schurr, *Ann.*, **460**, 56 (1928).

(10) A possible explanation of the failure of IX to cyclize may be that the sulfur atoms, functioning as Lewis bases, form complexes with the condensing agent which inductively deactivate the ring.

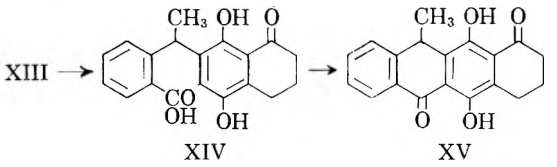
attempts to prepare its thioketal, even under forcing conditions, failed. This failure, coupled with the similar failure of V to form a thioketal strongly suggests that the strong hydrogen bonding present in V and X presents thioketal formation.

At this point we reluctantly abandoned our efforts to retain the carbonyl of VIII and removed it by desulfurization of IX with Raney nickel to give the butyric acid XI, which was easily cyclized with polyphosphoric acid to the tetralone XII.[11]



Demethylation with hydrobromic acid-hydriodic gave the hydroquinone XIII in high yield, and this substance was hydrolyzed to the free acid XIV with oxygen-free sodium hydroxide under nitrogen.[12]

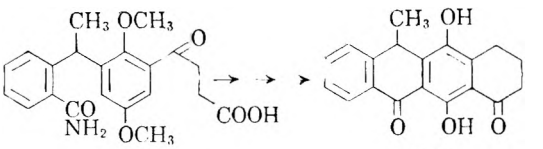
Cyclization of XIV with fresh polyphosphoric acid proceeded satisfactorily to give the dark orange 5,12-dihydroxy-1,6-dioxo-1,2,3,4,6,11-hexahydro-11-methylnaphthacene XV.



Although this substance cannot be extracted from benzene with 10% sodium hydroxide, it is readily extracted with Claisen's alkali to give a deep blue solution. Its infrared spectrum shows bands at 6.08, 6.13, and 6.16 μ, assignable to the hydrogen-bonded tetralone carbonyl, the aromatic ring, and the hydrogen-bonded diarylketo groups, respectively, and no absorption in the 3.0 μ region. The absence of hydroxyl absorption in the latter region confirms the assignment of structure to VIII, since if acylation had taken place in the 3 position the spectrum of the tetracyclic substantance resulting from the further transformations described (XVI) should show hydroxyl absorption in the 3.0 μ region.

(11) The infrared spectrum of XII exhibits only one band in the carbonyl region (6.00 μ) indicating that the ketonic and amide carbonyl bands coincide. The presence of the amide group is confirmed by the characteristic —N—H bands at 2.98 μ and 3.18 μ, that of the ketonic group by the formation of a 2,4-dinitrophenylhydrazone.

(12) Neither XIV nor XIII shows the bathochromic shift in carbonyl stretching frequency expected as a result of strong hydrogen bonding with the adjacent phenolic hydroxyl.



XVI

The oxime of XV, which carries a nitrogen atom in the position occupied by the dimethylamino group of the tetracyclines, was also prepared.

EXPERIMENTAL[13]

o-(2,5-Dimethoxybenzoyl)benzoic acid (I). The procedure of Dufraisse and Allais[4] for the preparation of the methyl ester was modified for large-scale use and the ester was saponified to the acid without purification, yield 64%, m.p. 159.5–161.5° (reported[3] 162°).

3-Methyl-3-(2,5-dimethoxyphenyl)phthalide (II). To a solution of methyl magnesium iodide prepared from 12.1 g. (0.525 mole) of magnesium, 75.0 g. (0.525 mole) of methyl iodide and 250 ml. of ether was added 60.0 g. (0.21 mole) of finely divided *o*-(2,5-dimethoxybenzoyl)benzoic acid in small portions with mechanical stirring during the course of an hour. The resulting mixture was heated under reflux for 1 hr., cooled, and decomposed with 200 ml. of cold 3*N* hydrochloric acid. The aqueous layer was extracted with two 200-ml. portions of ether. The combined ethereal solution was washed successively with 200 ml. of 5% sodium bicarbonate solution, 200 ml. of about 1*N* sodium thiosulfate solution, then water, and dried over anhydrous sodium sulfate. Removal of the solvent left 50.0 g. (85%) of yellow-brown oil.

A small portion of this oil was purified by chromatography on alumina with a 50–50 benzene–petroleum ether mixture as the eluent. The colorless oil that resulted crystallized on long standing and was recrystallized from hexane, m.p. 83.0–84.0°. The crude oil, on seeding, crystallized and melted at 78.0–80.5°.

Anal. Calcd. for $C_{17}H_{16}O_4$: C, 71.82; H, 5.67. Found: C, 71.70; H, 5.70.

o-[1-(2,5-Dimethoxyphenyl)ethyl]benzoic acid (III). To a solution of 50.0 g. (0.170 mole) of 3-methyl-3-(2,5-dimethoxyphenyl)phthalide in 200 ml. of alcohol was added 1 l. of 15% ammonium hydroxide solution, 120 g. of zinc dust, and 50 ml. of normal copper sulfate solution. The mixture was heated under reflux for 20 hr., cooled, and filtered. The filter cake was heated on a steam bath with 250 ml. of 10% sodium hydroxide solution until only the suspended zinc dust was undissolved, cooled, and filtered. The combined aqueous filtrates on acidification yielded 42.0 g. (83%) of solid, m.p. 155–161°. Recrystallization from benzene gave 36.0 g. (71%), m.p. 163.5–165°. Several further recrystallizations from benzene gave material of m.p. 164.0–165.5°.

Anal. Calcd. for $C_{17}H_{18}O_4$: C, 71.31; H, 6.34. Found: C, 71.44; H, 6.28.

Its methyl ester, prepared by the action of an excess of diazomethane, melted after several crystallizations from alcohol, at 109.5–110.5°.

Anal. Calcd. for $C_{18}H_{20}O_4$: C, 71.98; H, 6.71. Found: C, 72.12; H, 6.80.

1,4-Dimethoxy-10-methyl-9-anthrone (IV). A solution of 8.00 g. (0.028 mole) of *o*-[1-(2,5-dimethoxyphenyl)ethyl]-benzoic acid in 50 ml. of concentrated sulfuric acid was allowed to stand for 30 min., then slowly poured into ice and

(13) All melting points are corrected. Analyses were carried out by Miss Annette Smith and by the Micro-Tech Laboratories. Infrared spectra were determined by Mr. Carl Whiteman on a Perkin-Elmer Model 12c Infrared Spectrophotometer equipped with a sodium chloride prism using Nujol mulls.

water. A viscous yellow solid separated and was taken into chloroform. The aqueous solution was extracted with two 100 ml. portions of chloroform, and the combined chloroform solutions were washed with 5% sodium bicarbonate solution and water and dried over anhydrous magnesium sulfate. Removal of solvent left 6.00 g. (80%) of pale yellow solid with a melting point of 135.0–136.5°. Recrystallization from ethyl acetate gave a colorless material, m.p. 138.0–139.0°.

Anal. Calcd. for $C_{17}H_{16}O_3$: C, 76.10; H, 6.01. Found: C, 76.01; H, 6.01.

1,4-Dihydroxy-10-methyl-9-anthrone (V). *A. From 1,4-dimethoxy-10-methyl-9-anthrone.* A solution of 1.08 g. (0.0040 mole) of 1,4-dimethoxy-10-methyl-9-anthrone in 15 ml. of dry benzene was added to a solution of 3.30 g. (0.0123 mole) of anhydrous aluminum bromide in 15 ml. of dry benzene, and the mixture was heated under reflux for 2 hr. Hydrochloric acid (20 ml. of 6*N*) was added and the two phase system was heated under reflux until the insoluble red complex disappeared. The layers were separated and the aqueous layer was extracted with 20 ml. of benzene. The combined benzene solution was washed with water and concentrated to yield 0.90 g. (93%) of bright yellow needles, m.p. 186.0–188.5°. Several further recrystallizations from benzene raised the melting point to 190.0–191.0°. Infrared max. 6.16 μ.

Anal. Calcd. for $C_{15}H_{12}O_3$: C, 74.99; H, 5.03. Found: C, 75.14; H, 5.23.

B. From o-[1-(2,5-dimethoxyphenyl)ethyl]benzoic acid. A solution of 1.00 g. (0.0035 mole) of *o*-[1-(2,5-dimethoxyphenyl)ethyl]benzoic acid in 20 ml. of 48% hydrobromic acid and 10 ml. of glacial acetic acid was heated under reflux for 2 hours, cooled, and diluted with 25 ml. of water. The dark brown precipitate was collected and recrystallized from benzene to give 0.40 g. of yellow needles, m.p. 189.0–191.5°, not depressed by mixture with the sample described above.

1,4-Diacetoxy-10-methyl-9-anthrone was prepared from the dihydroxy compound by acetylation with acetic anhydride and potassium acetate. It was purified by chromatography on alumina and crystallization from benzene-hexane. The colorless product melted at 68.5–70.5° when heated rapidly. When heated slowly from 65–71°, the compound softens but does not melt, and if then heated rapidly above 71° it melts at 112.0–113.5°. However, if heated slowly to 108–114° the final melting point is 127.0–128.5°.

Anal. Calcd. for $C_{19}H_{16}O_5$: C, 70.36; H, 4.98. Found: C, 70.80; H, 5.17.

10-Methyl-1,4,9,10-tetrahydro-1,4,9-triketoanthracene (VI). To a solution of 0.200 g. (0.00084 mole) of 1,4-dihydroxy-10-methyl-9-anthrone in 10 ml. of ethanol was added 1 ml. of 2*N* ferric chloride solution. After 10 min., 30 ml. of water containing 5 drops of concentrated hydrochloric acid was added and the mixture was allowed to stand in the refrigerator overnight. The precipitate was collected to give 0.196 g. (98%) of bright red crystals, m.p. 176.5–179.5°. Although this compound appeared to be stable in the solid state or when suspended in the acid solution, all attempts to recrystallize it resulted in decomposition.

The compound was reduced with sodium hydrosulfite solution to give 1,4-dihydroxy-10-methyl-9-anthrone as shown by melting point and mixed melting point.

Attempted condensation of 10-methyl-1,4,9,10-tetrahydro-1,4,9-triketoanthracene with 1,3-butadiene. A mixture of 0.050 g. (0.00021 mole) of the quinone, 3 ml. of pure dioxane, and a large excess of 1,3-butadiene was heated in a pressure bottle at 50–60° for 15 hours. The cooled contents were removed by solution in acetone, and the acetone was evaporated to give a dark brown tarry residue. This residue was treated with dilute hydrochloric acid, dissolved in benzene, and extracted with 10% sodium hydroxide solution. No material was extracted into the sodium hydroxide solution.

Attempted preparation of the ethylene thioketal of 1,4-dihydroxy-10-methyl-9-anthrone. A solution of 0.100 g. (0.00042 mole) of 1,4-dihydroxy-10-methyl-9-anthrone, 5 drops of ethylene dithioglycol, and 5 drops of boron trifluoride etherate in 2 ml. of glacial acetic acid was allowed to stand at room temperature for 24 hr. Dilution with water gave only starting material as shown by mixed melting point.

When ethylene dithioglycol was used as the solvent as well as the reactant, the result was the same.

o-[1-(2,5-Dimethoxyphenyl)ethyl]benzamide. VII. *A. Attempted preparation through the acid chloride.* A solution of 0.500 g. (0.00175 mole) of *o*-[1-(2,5-dimethoxyphenyl)-ethyl]benzoic acid and 0.380 g. (0.00180 mole) of phosphorus pentachloride in 25 ml. of dry benzene was heated under reflux for 1 hr. Ammonia gas was then bubbled through the solution for 10 min. and 20 ml. of 15% ammonium hydroxide solution was added. The benzene layer was separated, washed with water, and evaporated to dryness. The remaining solid was shown to be 1,4-dimethoxy-10-methyl-9-anthrone by a mixed melting point.

B. By the mixed carbonic anhydride procedure. A solution of 20.00 g. (0.0070 mole) of *o*-[1-(2,5-dimethoxyphenyl)-ethyl]benzoic acid and 14.40 g. (0.137 mole) of triethylamine in 300 ml. of chloroform (Reagent Grade) was cooled to −10° in an ice-salt mixture and 15.10 g. (0.137 mole) of ethyl chlorocarbonate was added slowly with vigorous mechanical stirring so that the temperature did not rise above −5°. The solution was allowed to stand for 30 min. after the addition of the ethyl chlorocarbonate. A stream of gaseous ammonia was then passed in at a rate such that the temperature did not rise above 0°. After 2 hr. 150 ml. of water was added. The layers were separated and the chloroform layer was washed with 100 ml. of water. The combined aqueous layers on acidification gave 1.80 g. of starting material.

The dried chloroform solution was concentrated and the semisolid residue was dissolved in 100 ml. of methanol, 100 ml. of 10% sodium hydroxide solution was added, and the resulting mixture was heated to boiling on a steam bath until colorless crystals began to separate. The solution was diluted with 100 ml. of water and cooled. The crystalline precipitate was collected to give 12.20 g. (61%), m.p. 156–158°. After recrystallization from ethyl acetate the melting point was 158.5–159.0°. The filtrate on acidification gave 4.20 g. of additional starting material. The yield of amide based on unrecovered starting material was 87%.

Anal. Calcd. for $C_{17}H_{19}O_3N$: C, 71.56; H, 6.71. Found: C, 71.76; H, 6.87.

o-[1-(2,5-Dihydroxyphenyl)ethyl]benzamide. A solution of 2.85 g. (0.01 mole) of *o*-[1-(2,5-dimethoxyphenyl)ethyl]-benzamide (VII) in 40 ml. of dry thiophene-free benzene was added to a solution of 8.70 g. (0.031 mole) of aluminum bromide in dry thiophene-free benzene. The resulting mixture was heated under reflux for 1.5 hr., diluted with 50 ml. of 6*N* hydrochloric acid, and again heated for 30 min., the benzene being allowed to boil away. The solution was cooled in ice and the precipitate collected to give 2.50 g., m.p. 193.0–195.0°. After recrystallization from dilute alcohol and treatment with Norite, the yield was 1.90 g., m.p. 209.0–210.0°. Several further recrystallizations raised the melting point to 217.5–218.5°.

Anal. Calcd. for $C_{15}H_{15}O_3N$: C, 70.02; H, 5.88. Found: C, 70.04; H, 5.93.

o-[1-(2,5-Diacetoxyphenyl)ethyl]benzamide. A mixture of 1.00 g. (0.0039 mole) of *o*-[1-(2,5-dihydroxyphenyl)ethyl]-benzamide, 6.0 g. of acetic anhydride, and 0.25 g. of sodium acetate was heated on a steam bath for 30 min. and diluted with water. The precipitate was collected to give 0.80 g. (60%), m.p. 135.0–144°. After several recrystallizations from benzene, the melting point was 149.5–150.0°.

Anal. Calcd. for $C_{19}H_{19}O_5N$: C, 66.85; H, 5.61. Found: C, 66.80; H, 5.72.

β-{2,5-Dimethoxy-4-[1-(o-carboxamidophenyl)ethyl]benzoyl}-propionic acid (VIII). A mixture of 10.00 g. (0.0352 mole) of *o*-[1-(2,5-dimethoxyphenyl)ethyl]benzamide, 7.00 g.

(0.0467 mole) of β-carbomethoxypropionyl chloride,[14] and 150 g. of polyphosphoric acid was heated at 45–50° with mechanical stirring until the brown mixture became orange. The time required varied from 45 min. to 2 hr., depending upon the freshness of the polyphosphoric acid. The reaction mixture was diluted with water and a viscous yellow material separated. The organic material was taken into chloroform (two extractions), and the chloroform solution was washed with water, dried, and concentrated. The oily solid residue was taken into 75 ml. of methanol, treated with 150 ml. of 10% sodium hydroxide solution, and heated on a steam bath (open flask) for 45 min., cooled, diluted with 100 ml. of water, and filtered. The 4.00 g. of material collected was shown to be unreacted starting material by a mixed melting point. Acidification of the filtrate gave 7.50 g., m.p. 194.0–196.0°. Recrystallization from alcohol gave 6.00 g. (45%), m.p. 199.0–200.5°. Infrared maxima 5.84, 6.01, 6.05 μ.

Anal. Calcd. for $C_{21}H_{23}O_6N$: C, 65.44; H, 6.02. Found: C, 65.41; H, 5.91.

Ethylene thioketal of β-{2,5-dimethoxy-4-[1-(o-carboxamidophenyl)ethyl]benzoyl}propionic acid (IX). A solution of 3.80 g. (0.0099 mole) of β-{2,5-dimethoxy-4-[1-(o-carboxamidophenyl)ethyl]benzoyl}propionic acid, 4.00 g. of ethylene dithioglycol in 40 ml. of glacial acetic acid containing 4 ml. of boron fluoride etherate was allowed to stand for 18 hr. at room temperature and then diluted with 150 ml. of water. The colorless precipitate was collected, dissolved in 125 ml. of 5% sodium bicarbonate solution, extracted with three portions of benzene to remove the ethylene dithioglycol, and acidified with dilute hydrochloric acid. The precipitate was collected to give 4.39 g. (98.5%), m.p. 201.5–203.0°. After several recrystallizations from ethyl acetate the melting point was 202.5–203.3°. Infrared maxima 5.86, 6.01 μ.

Anal. Calcd. for $C_{23}H_{27}O_5S_2N$: C, 59.84; H, 5.90. Found: C, 59.62; H, 6.10.

Attempted cyclization of the ethylene thioketal of β-{2,5-dimethoxy-4-[1-(o-carboxamidophenyl)ethyl]benzoyl}propionic acid. A. With anhydrous hydrogen fluoride. A solution of 0.200 g. (0.00043 mole) of the ethylene thioketal in 4.0 g. of anhydrous hydrogen fluoride was allowed to stand until the hydrogen fluoride had evaporated. The residue was completely soluble in 5% sodium bicarbonate solution, and acidification of this solution yielded only starting material (mixed melting point).

B. With sulfuric acid. A solution of 0.100 g. (0.00022 mole) of the ethylene thioketal in 5 ml. of concentrated sulfuric acid was allowed to stand at room temperature for 1 hr. and then diluted. The precipitate was shown to be unchanged starting material by mixed melting point.

C. With boron trifluoride etherate. A solution of the ethylene thioketal in 1 ml. of boron trifluoride etherate was heated at 60° for 1 hr., cooled, and decomposed with 10 ml. of water. A viscous oil separated and the odor of ethylene dithioglycol was pronounced. The oil was taken into benzene and extracted with 5% sodium bicarbonate solution. Acidification of the bicarbonate solution gave a colorless precipitate that was collected and recrystallized from alcohol. This compound was shown to be β-{2,5-dimethoxy-4-[1-(o-carboxamidophenyl)ethyl]benzoyl}propionic acid (VIII) by mixed melting point.

The remaining benzene solution was evaporated to dryness leaving an amorphous tan powder. Attempts to induce this material to crystallize were unsuccessful.

D. With polyphosphoric acid. A mixture of 1.00 g. (0.0022 mole) of the ethylene thioketal and 20 g. of polyphosphoric acid was heated at 45–50° with stirring for 1 hr., diluted with water, and extracted several times with chloroform. The chloroform solution was washed with water, extracted with 50 ml. of 5% sodium bicarbonate solution, and dried. The sodium bicarbonate solution on acidification gave 0.100 g. of tan precipitate which after recrystallization from alcohol melted at 199.0–200.0°. It did not depress the melting point of β-{2,5-dimethoxy-4-[1-(o-carboxamidophenyl)-ethyl]benzoyl}propionic acid (VIII).

The chloroform solution was concentrated under reduced pressure to give 0.650 g. of viscous brown oil which was chromatographed on 40 g. of silica with a 75–25 benzene-ethyl acetate mixture as the eluent. The first fractions yielded 0.114 g. of an unidentified colorless crystalline sulfur-containing material, melting point, after several recrystallizations from benzene, 243.5–244.5°.

The following fractions yielded 0.125 g. of tan solid, m.p. 140–150°. After several recrystallizations from benzene, it melted at 158.5–160.0°, and did not depress the melting point of *o*-[1-(2,5-dimethoxyphenyl)ethyl]benzamide (VII).

Further elution with 50–50 benzene–ethyl acetate yielded a yellow oil that could not be induced to crystallize.

β-{2,5-Dihydroxy-4-[1-(o-carboxamidophenyl)ethyl]benzoyl}-propionic acid (X). A solution of 4.00 g. (0.015 mole) of aluminum bromide in 50 ml. of dry thiophene-free benzene was treated with stirring with 1.06 g. (0.00275 mole) of finely divided β-{2,5-dimethoxy-4-[1-(o-carboxamidophenyl)ethyl]benzoyl}propionic acid (VIII). The mixture was heated under reflux for 1.5 hr., then diluted with 30 ml. of 6*N* hydrochloric acid. Heating was continued for 30 min., during which the benzene boiled away. The mixture was then cooled in an ice bath to yield 0.96 g. (97%) of solid, m.p. 175.0–180.0°. After recrystallization from dilute alcohol and treatment with Norit, it melted at 187.0–187.5°.

Anal. Calcd. for $C_{19}H_{19}O_6N$: C, 63.86; H, 5.36. Found: C, 63.98; H, 5.61.

Attempted preparation of the ethylene thioketal of β-{2,5-dihydroxy-4-[1-(o- carboxamidophenyl)ethyl]benzoyl}propionic acid. A. In acetic acid. A solution of 0.200 g. (0.00056 mole) of the hydroquinone X, 5 drops of boron trifluoride etherate, and 5 drops of ethylene dithioglycol in 10 ml. of glacial acetic acid was allowed to stand 48 hr. at room temperature. The precipitate was collected and shown to be unchanged starting material by a mixed melting point.

B. In ethylene dithioglycol. A solution of 0.200 g. of the hydroquinone X, 5 drops of boron trifluoride etherate was allowed to stand for 24 hr., diluted with chloroform, and extracted with 30 ml. of 5% sodium bicarbonate solution. The bicarbonate solution on acidification gave only starting material (mixed melting point).

γ-{2,5-Dimethoxy-4-[1-(o-carboxamidophenyl)ethyl]phenyl}-butyric acid. (XI). A solution of 9.50 g. (0.0206 mole) of the ethylene thioketal of β-{2,5-dimethoxy-4-[1-(o-carboxamidophenyl)ethyl] benzoyl}propionic acid in 100 ml. of ethyl alcohol was treated with 110 g. of Raney nickel and heated under gentle reflux for 19 hr. The catalyst was removed and extracted with alcohol in a Soxhlet extractor for 48 hr. The combined alcoholic solutions on concentration gave an oily solid which was heated on the steam bath for 15 min. with 100 ml. of 10% sodium hydroxide. The cooled solution was treated with Norit, filtered, and acidified with dilute hydrochloric acid to give 6.50 g. (89%) of a solid, m.p. 174.0–178.0°. After several recrystallizations from ethyl acetate the melting point was 178.5–179.5°.

Anal. Calcd. for $C_{21}H_{25}O_5N$: C, 67.90; H, 6.78. Found: C, 67.66; H, 7.05.

5,8-Dimethoxy-7-[1-(o-carboxamidophenyl)ethyl]-1-tetralone (XII). A mixture of 3.00 g. (0.0081 mole) of the butyric acid XI and 40 g. of polyphosphoric acid was heated at 45–50° with stirring for 1.5 hr. and then diluted with water. The organic material was taken into chloroform (three extractions), washed with 5% sodium bicarbonate solution, water, and dried. Removal of the chloroform left a yellow-brown solid that was treated with Norit and recrystallized from ethyl acetate. The yield was 2.14 g. (75%), m.p. 170.5–173.0°. After several recrystallizations from benzene the melting point was 174.5–175.5°. Infrared maxima 2.98, 3.18, 6.00 μ.

Anal. Calcd. for $C_{21}H_{23}O_4N$: C, 71.37; H, 6.56. Found: C, 71.12; H, 6.88.

(14) J. Cason, *Org. Syn.*, 25, 19 (1945).

Its *2,4-dinitrophenylhydrazone* melted at 254.5–255.5° when crystallized from ethyl acetate.

Anal. Calcd. for $C_{27}H_{27}O_5N_5$: C, 60.78; H, 5.10. Found: C, 60.73; H, 5.23.

5,8-Dihydroxy-7-[1-(o-carboxamidophenyl)ethyl]-1-tetralone (XIII). A solution of 5.25 g. of the tetralone XII in 30 ml. of glacial acetic acid was treated with 30 ml. of 48% hydrobromic acid and 30 ml. of 57% hydroiodic acid and heated under reflux for 2 hr. Dilution with ice and water gave a bright yellow precipitate, 4.20 g. (87%), m.p. 246.5–247.5°. Several recrystallizations from alcohol did not raise the melting point. Infrared maxima 2.96, 3.08, 5.96 μ.

Anal. Calcd. for $C_{19}H_{19}O_4N$: C, 70.14; H, 5.89. Found: C, 70.04; H, 5.99.

5,8-Dihydroxy-7-[1-(o-carboxyphenyl)ethyl]-1-tetralone (XIV). A solution of 0.820 g. (0.0025 mole) of 5,8-dihydroxy-7-1-(*o*-carboxamidophenyl)ethyl-1-tetralone (XIII) in 15 ml. of 10% sodium hydroxide solution through which a stream of nitrogen had been passed to remove the oxygen was heated under nitrogen on a steam bath for 11 hr. The solution was carbonated and filtered rapidly, and the filtrate was immediately acidified with 3*N* hydrochloric acid. The precipitate was collected and washed with ether to give 0.650 g. (79%) of a dark yellow solid that did not melt, but decomposed at 255.0–260°. This was recrystallized from ethanol to give 0.450 g. of bright yellow material that decomposed at 265–267°. Infrared maxima broad, 5.96 to 6.00 μ.

Anal. Calcd. for $C_{19}H_{18}O_5$: C, 69.92; H, 5.56. Found: C, 69.92; H, 6.03.

5,12-Dihydroxy-1,6-dioxo-1,2,3,4,6,11-hexahydro-11-methylnaphthacene (XV). A mixture of 1.00 g. (0.00307 mole) of crude XIV and 25 g. of freshly opened polyphosphoric acid was heated at 55–60° with stirring for 2 hr., diluted with water, and extracted with three 30-ml. portions of benzene. The benzene solution was extracted with 50 ml. of 5% sodium bicarbonate solution, washed with water, dried, and concentrated to yield 0.800 g. (85%) of dark orange crystalline material, m.p. 139.0–142.0°. Recrystallization from alcohol gave 0.600 g. (63%), m.p. 142.0–144.0°. The analytical sample was recrystallized several times from a very small amount of ethyl acetate and melted at 148.5–149.0°. Infrared max. 6.08, 6.13, 6.16 μ. No absorption in the 3.0 μ region.

Anal. Calcd. for $C_{19}H_{16}O_4$: C, 74.01; H, 5.23. Found: C, 73.89; H, 5.23.

5,12-Diacetoxy-1,6-dioxo-1,2,3,4,6,11-hexahydro-11-methylnaphthacene. A mixture of 0.100 g. (0.000325 mole) of 5,12-dihydroxy-1,6-dioxo-1,2,3,4,6,11-hexahydro-11-methylnaphthacene and 0.5 ml. of acetic anhydride was treated with a drop of concentrated sulfuric acid. The mixture was stirred for 10 min., during which a yellow solid separated, and then diluted with water. After several recrystallizations from alcohol, the precipitated material melted at 194.0–195.0°. Infrared max. 6.04, 6.13 μ.

Anal. Calcd. for $C_{23}H_{20}O_6$: C, 70.40; H, 5.14. Found: C, 70.55; H, 5.10.

5,12-Dihydroxy-1,6-dioxo-1,2,3,4,6,11-hexahydro-11-methylnaphthacene-1-oxime (XXX). A solution of 0.100 g. (0.000325 mole) of XV and 0.025 g. (0.00036 mole) of hydroxylamine hydrochloride in 1 ml. of a 50–50 pyridine-alcohol was heated on a steam bath for 2 hr., and the solvent was then removed with a stream of nitrogen. The product was washed with water, collected, and recrystallized from benzene to give a solid of m.p. 196.0–196.5°. Although the melting point was sharp, two crystalline forms, one pale orange and the other dark orange, persisted through several further recrystallizations.

Anal. Calcd. for $C_{19}H_{17}O_4N$: C, 70.57; H, 5.30. Found: C, 70.82; H, 5.45.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

Alkylation and Related Reactions of Dibenzo-*p*-dioxin*

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A number of alkyl derivatives of dibenzo-*p*-dioxin(I) have been prepared. These include the 2-(II), 2,7(8)-di-*t*-butyldibenzo-*p*-dioxin(III); 2-(IV), 2,3-di-(V), 2,3,7,8-tetra-(VI), and a hexaisopropyldibenzo-*p*-dioxin(VII); and 2-benzyldibenzo-*p*-dioxin(VIII). Also obtained in the study were ethyl dibenzo-*p*-dioxin-2-dithiocarboxylate(IX), methyl dibenzo-*p*-dioxin-2-dithiocarboxylate(X), diethyl dibenzo-*p*-dioxin-2,7-bis(dithiocarboxylate)(XI), 2-chloromethyldibenzo-*p*-dioxin (XII), and the dibenzo-*p*-dioxin-2-carboxaldehyde(XIII). A 2,4-dinitrophenylhydrazone was formed from XIII yielding (XIV).

The acylation of dibenzo-*p*-dioxin (I) is known to proceed under normal conditions to a mixture of the 2, the 2,7 and, in one case, the 2,8 substituted compounds.[1,2] It is also fairly easy to obtain exclusively the mono or the di products by employing special conditions.[3]

In an extension of the above work, a study was made of direct alkylation of dibenzo-*p*-dioxin using mainly *t*-butyl chloride and isopropyl chloride since these reagents presented the least possibility of isomerization. Ethyl chloride, ethyl bromide, and methyl iodide were also used, but failed, as has already been reported[4–6] for other compounds, to give the normal alkylation products in carbon disulfide.

A number of solvents were tried before the choice of carbon disulfide was made. *s*-Tetrachloroethane could not be used since it apparently reacted with

* This paper is a contribution in honor of Lyndon F. Small, former Editor of the Journal.

(1) German Patent 668,875 (December 13, 1938) [*Chem. Abstr.*, **33**, 5006 (1939)].

(2) M. Tomita, *J. Pharm. Soc. Japan*, **56**, 906 (1936).

(3) M. Tomita, *J. Pharm. Soc. Japan*, **57**, 131 (1937).

(4) H. Jorg, *Ber.*, **60**, 1466 (1927).

(5) H. Gilman and N. Calloway, *J. Am. Chem. Soc.*, **55**, 4197 (1933).

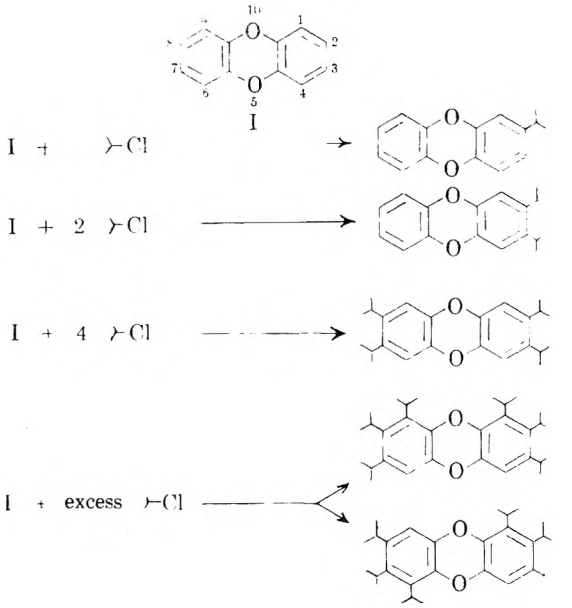
(6) P. George, Abstracts of Papers, 130th AMERICAN CHEMICAL SOCIETY Meeting, Atlantic City, N. J., Sept. 16–21, 1956, p. 54-O.

dibenzo-*p*-dioxin at room temperature in the presence of aluminum chloride to give a glossy brown, polymeric material. Likewise chlorobenzene at 15° participated in the reaction to yield alkylated chlorobenzenes. No attempt was made to alkylate in nitrobenzene although this solvent has been frequently employed by others.[7,8]

Using *t*-butyl chloride, it was possible to make two derivatives that analyzed correctly as a mono and as a di derivative respectively. On the basis of infrared spectral analysis, it was concluded that the mono derivative was the 2-*t*-butyldibenzo-*p*-dioxin (II) and the di derivative either the 2,7- or the 2,8-di-*t*-butyldibenzo-*p*-dioxin(III). The possibility of both groups being in one ring was ruled out by the absence of a 1,2 disubstitution band at 13.3μ and the presence of a strong 1,2,4 trisubstitution band at 12.4μ. The mono derivative had strong bands at 13.3μ and 12.4μ. An attempt was made to increase the yield of the 2-*t*-butyldibenzo-*p*-dioxin by alkylating with *n*-octadecyl bromide since it had been used earlier[9] to produce ethyl 4-*t*-butyl-5-bromo-2-furoate from ethyl 5-bromo-2-furoate in about 20% greater yield than the next best alkyl halide.

Attempts to make poly-*t*-butyl derivatives, *i.e.*, substitution directly into the 1 position after first blocking the 2,3 and the 7,8 positions sterically with two *t*-butyl groups, met only with the formation of glasses and very viscous oils which could not be purified. Only metalation has so far succeeded in attacking this seemingly inert position.[10]

Four derivatives were obtained when isopropyl chloride was used as the alkylating agent. The mono derivative had the customary infrared bands at 12.4μ and 13.3μ. It was therefore presumed to be the 2-isopropyldibenzo-*p*-dioxin(IV). In addition to the bands at 12.4μ and 13.3μ the di derivative had a new, strong band at 12.8μ. This band had previously been noticed in the infrared spectra of 2,3,7,8-tetrabromodibenzo-*p*-dioxin.[11] On this basis, the diisopropyl derivative was designated 2,3(V). No 1,2 disubstitution band was evident in the spectrum of the tetraisopropyl derivative, but the bands at 12.4μ and 12.8μ were present. It was thus assigned the 2,3,7,8(VI) configuration. Forced conditions yielded the final isopropyl derivative which contained six isopropyl groups and is designated only as a hexaisopropyldibenzo-*p*-dioxin(VII). Steric considerations lead to the conclusion that the six groups are divided equally between the two rings. This may lead to two different products although only one was isolated.



Benzyl chloride produced only polymeric material when aluminum chloride was used as a catalyst and failed to react when anhydrous zinc chloride was used. However, a catalytic amount of anhydrous ferric chloride promoted the formation of a mono benzyl derivative which is believed to be the 2-benzyldibenzo-*p*-dioxin(VIII) on the basis of infrared analysis and previous evidence on the position of electrophilic attack.

Ethyl bromide failed to yield the normal alkylated product in carbon disulfide, but produced the ethyl ester of the dithio acid(IX).[4-6] The reaction of this ester with alcoholic potassium hydroxide proceeded directly to the dibenzo-*p*-dioxin-2-carboxylic acid[12] upon acidification. Likewise, methyl iodide under more drastic conditions, refluxing carbon disulfide, yielded the methyl ester of the dithio acid(X). The diethyl ester of the bis-dithio acid(XI) was formed at room temperature by bubbling ethyl chloride into the carbon disulfide mixture. A proof of structure was effected by oxidizing the bis-dithio ester to the acid by means of hydrogen peroxide[5] and conversion of the acid to the dimethyl ester, a known compound,[13] in this case the 2,7 isomer.

From the work done here and that accomplished earlier,[4-6] it is concluded that dithio esters form only when the alkylating species has no possibility of rearranging to a secondary or tertiary carbonium ion. This has been checked[5] and was rechecked in this series by using *n*-propyl chloride, *n*-butyl chloride, and some other *n*-alkyl halides. In all instances, only alkylation products were formed which in some instances could not be identified or even purified.

(7) N. Calloway, *Chem. Revs.*, 17, 327 (1935).
(8) Charles Thomas, *Anhydrous Aluminum Chloride in Organic Chemistry*, Reinhold Publishing Corporation, New York, 1941. See also, C. C. Price, *Org. Reactions*, III, 1 (1946).
(9) H. Gilman and R. Burtner, *J. Am. Chem. Soc.*, 57, 909 (1935).
(10) H. Gilman and C. G. Stuckwisch, *J. Am. Chem. Soc.*, 65, 1461 (1943).
(11) H. Gilman and J. J. Dietrich, *J. Am. Chem. Soc.*, 79, 1439 (1957).
(12) M. Tomita, *J. Pharm. Soc. Japan*, 62, 476 (1942).
(13) M. Tomita, *J. Pharm. Soc. Japan*, 57, 607 (1937).

Chloromethylation proceeds smoothly to give the 2-chloromethyldibenzo-*p*-dioxin (XII) in fair yield. This material tends to polymerize so care must be taken to have very clean equipment during the vacuum distillation. The structure is based on the infrared spectrum and could be easily verified by oxidation to the corresponding acid. Treatment with silver nitrate readily causes the precipitation of silver chloride.

The dibenzo-*p*-dioxin-2-carboxaldehyde(XIII) was formed in very low yield *via* a Gattermann-Koch reaction. Identification was based on the infrared spectrum and the work-up used to obtain the final product. A 2,4-dinitrophenylhydrazone(XIV) derivative was also obtained from XIII and analyzed.

Since the dibenzo-*p*-dioxin nucleus appeared to be easily alkylated, several attempts were made at direct Friedel-Crafts arylations. Chattaway[14] succeeded in condensing α-chloronaphthalene with benzene, and bromobenzene with naphthalene. In a similar manner, *p*-fluorophenol was condensed with benzene.[15] Both of the above reactions employed no solvent. 2-Chloroquinoline, 4,7-dichloroquinoline, and 2-chlorobenzothiazole react with resorcinol and 4-chlororesorcinol in nitrobenzene or dry quinoline, the better solvent, to give the expected Friedel-Crafts products.[16]

Both of these solvents were tried in unsuccessful attempts to condense *p*-chlorophenol, α-bromonaphthalene, and α-fluoronaphthalene with dibenzo-*p*-dioxin. The more promising solvent appeared to be quinoline since the dibenzo-*p*-dioxin nucleus is not destroyed at the temperatures used to effect reaction when this solvent is employed. No dibenzo-*p*-dioxin was recovered from the reactions employing nitrobenzene.

The compounds described at this time were prepared incidental to a study concerned with organic liquid solution scintillators. Evaluation of the compounds for this purpose is being made by Drs. Wright H. Langham, F. Newton Hayes, and Donald G. Ott of the Los Alamos Laboratories who will report the results later.

EXPERIMENTAL[17]

2-t-Butyldibenzo-p-dioxin (II). While a mixture of 9.2 g. (0.05 mole) of dibenzo-*p*-dioxin, 22 g. (0.16 mole) of aluminum chloride, and 100 ml. of carbon disulfide was stirred at room temperature, 4.62 g. (0.05 mole) of *t*-butyl chloride was added over a period of 10 min. Stirring was continued for 1 hr. Hydrolysis was effected with ice–hydrochloric acid and the carbon disulfide layer was then washed with sodium carbonate solution followed by drying over anhydrous sodium sulfate. Evaporation of the carbon disulfide and vacuum distillation of the residue produced 1 g. of a product, b.p. 125–128° (0.25 mm.). This was recrystallized three times from methanol-water to yield 0.3 g. (2.5%) of white needles, m.p. 97–98.5°.

Anal. Calcd. for $C_{16}H_{16}O_2$: C, 80.00; H, 6.66. Found: C, 79.76, 79.74; H, 6.66, 6.58.

2,7(8)-Di-t-butyldibenzo-p-dioxin (III). The residue remaining in the flask after vacuum distillation of the 2-*t*-butyldibenzo-*p*-dioxin was recrystallized three times from ethanol to produce 0.5 g. (3.3%) of white plates, m.p. 226–228°.

Anal. Calcd. for $C_{20}H_{24}O_2$: C, 81.08; H, 8.10. Found: C 81.14, 81.15; H, 8.31, 8.26.

2-Isopropyldibenzo-p-dioxin (IV). To a stirred mixture of 9.2 g. (0.05 mole) of dibenzo-*p*-dioxin, 22 g. (0.16 mole) of aluminum chloride and 100 ml. of carbon disulfide was slowly added 3.9 g. (0.05 mole) of isopropyl chloride at room temperature. The resulting mixture was stirred for 1.5 hr. at room temperature, hydrolyzed with ice–hydrochloric acid, and the resulting carbon disulfide layer washed with sodium carbonate solution before drying over anhydrous sodium sulfate. Evaporation of the carbon disulfide followed by vacuum distillation of the residue produced 1.5 g. of a product, b.p. 126–131° (0.5 mm.). Two recrystallizations of this material from methanol-water produced 1 g. (9%) of white needles, m.p. 87.5–89°.

Anal. Calcd. for $C_{15}H_{14}O_2$: C, 79.64; H, 6.19. Found: C, 79.46, 79.43; H, 6.30, 6.38.

n-Propyl chloride also produced the isopropyl derivative under the same conditions employed above.

2,8-Diisopropyldibenzo-p-dioxin (V). This reaction was conducted in the same manner as that used to obtain 2-isopropyldibenzo-*p*-dioxin except that two equivalents of isopropyl chloride were used. A 0.025 mole run produced 1 g. (8%) of the redistilled, colorless oil, b.p. 128–131° (0.25 mm.), n_D^{20} 1.5670.

Anal. Calcd. for $C_{18}H_{20}O_2$: C, 80.60; H, 7.46. Found: C, 80.47, 80.49; H, 7.61, 7.75.

2,3,7,8-Tetraisopropyldibenzo-p-dioxin (VI). This reaction was run under the same conditions used for the preparation of 2-isopropyldibenzo-*p*-dioxin. A 0.05 mole run was made using a four to one ratio of isopropyl chloride to dibenzo-*p*-dioxin. The crude product obtained by vacuum distillation was redistilled to yield 9.5 g. (54%) of colorless oil, b.p. 158–161° (0.5 mm.), n_D^{20} 1.5475.

Anal. Calcd. for $C_{24}H_{32}O_2$: C, 81.81; H, 9.09. Found: C, 81.74, 81.83; H, 9.06, 9.04.

Hexaisopropyldibenzo-p-dioxin (VII). The stirred mixture of 9.2 g. (0.05 mole) of dibenzo-*p*-dioxin, 11 g. (0.08 mole) of aluminum chloride, and 100 ml. of carbon disulfide was kept at room temperature while 31.4 g. (0.46 mole) of isopropyl chloride was added over a period of 15 min. After addition, a calcium chloride drying tube was attached to the condenser and the mixture refluxed for 1 hr. Work-up produced 1.7 g. of material melting from 93–170°. Three recrystallizations of this material from petroleum ether (b.p. 60–70°) yielded 0.3 g. (1.4%) of white needles, m.p. 251–252°.

Anal. Calcd. for $C_{30}H_{44}O_2$: C, 82.57; H, 10.09. Found: C, 82.68, 82.74; H, 10.18, 10.14.

2-Benzyldibenzo-p-dioxin (VIII). To a stirred mixture of 9.2 g. (0.05 mole) of dibenzo-*p*-dioxin, 1 g. of anhydrous ferric chloride and 100 ml. of carbon disulfide was slowly added 6.2 g. (0.05 mole) of benzyl chloride at room temperature. The resulting reaction mixture was then worked up in the usual manner. After evaporation of the dry carbon disulfide layer, the residue was vacuum-distilled to produce 2 g. of material, b.p. 178–180° (0.25 mm.). This material was recrystallized twice from ethanol to produce 1.2 g. (9%) of white needles, m.p. 106–108°.

Anal. Calcd. for $C_{19}H_{14}O_2$: C, 83.21; H, 5.11. Found: C, 82.96, 83.05; H, 4.95, 5.12.

Ethyl dibenzo-p-dioxin-2-dithiocarboxylate (IX). To a stirred mixture of 9.2 g. (0.05 mole) of dibenzo-*p*-dioxin, 22 g. (0.16 mole) of aluminum chloride and 100 ml. of carbon

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(15) A. Weston and C. Suter, *J. Am. Chem. Soc.*, **61**, 2556 (1939).

(16) G. Illuminati and H. Gilman, *J. Am. Chem. Soc.*, **74**, 2896 (1952).

(17) All melting points are uncorrected.

disulfide at room temperature was added 5.5 g. (0.05 mole) of ethyl bromide. Stirring was continued for 1.5 hr. and then the reaction mixture was worked up. The crude product was dissolved in benzene and chromatographed on alumina. Distillation of the benzene followed by two recrystallizations of the product from absolute ethanol resulted in 2.2 g. (16%) of orange needles, m.p. 104–106°.

Anal. Calcd. for $C_{15}H_{12}O_2S_2$: C, 62.50; H, 4.17; S, 22.22. Found: C, 62.37, 62.50; H, 4.37, 4.21; S, 22.33, 22.22.

Methyl dibenzo-p-dioxin-2-dithiocarboxylate (X). To a stirred mixture of 9.2 g. (0.05 mole) of dibenzo-*p*-dioxin, 22 g. (0.16 mole) of aluminum chloride and 100 ml. of carbon disulfide was added 7.1 g. (0.05 mole) of methyl iodide. The mixture was then refluxed for 6.5 hr. and then worked up in the usual manner. After evaporation of the carbon disulfide, the residue was dissolved in benzene and chromatographed on alumina. This did not effect purification, so the crude material was subjected to vacuum sublimation. The unreacted dibenzo-*p*-dioxin sublimed away from the product which was recrystallized twice from ethanol to yield 0.2 g. (1.4%) of orange needles, m.p. 121–123°.

Anal. Calcd. for $C_{14}H_{10}O_2S_2$: S, 23.36. Found: S, 23.73, 23.51.

Diethyl dibenzo-p-dioxin-bis(dithiocarboxylate) (XI). Ethyl chloride was slowly bubbled into 9.2 g. (0.05 mole) of dibenzo-*p*-dioxin, 22 g. (0.16 mole) of aluminum chloride, and 200 ml. of carbon disulfide over a period of 1.5 hr. at room temperature. The usual work-up produced crude material which was recrystallized three times from benzene-ethanol to form 1.7 g. (7%) of dark orange needles, m.p. 174–176°.

Anal. Calcd. for $C_{18}H_{16}O_2S_4$: S, 32.65. Found: S, 32.65, 32.74.

2-Chloromethyldibenzo-p-dioxin (XII). A mixture of 9.2 g. (0.05 mole) of dibenzo-*p*-dioxin, 4 g. (0.13 mole) of paraformaldehyde, 50 ml. of glacial acetic acid, 40 ml. of concentrated hydrochloric acid, and 15 ml. of 85% phosphoric acid was heated at 80° for 10 hr. with stirring. Dilution of the reaction mixture with water followed by suction filtration produced 12.7 g. of crude material. Vacuum-distillation of the crude product yielded 3 g., b.p. 143–144° (0.15 mm.). This material was recrystallized three times from ethanol to form 1.5 g. (13%) of white needles, m.p. 111–113°.

Anal. Calcd. for $C_{13}H_9O_2Cl$: Cl, 15.28. Found: Cl, 15.41, 15.31.

Dibenzo-p-dioxin-2-carboxaldehyde (XIII). An excess of carbon monoxide and hydrogen chloride, obtained by dropping chlorosulfonic acid into formic acid, was bubbled into a mixture of 9.2 g. (0.05 mole) of dibenzo-*p*-dioxin, 23 g. (0.175 mole) of aluminum chloride, 3 g. of cuprous chloride and 50 ml. of benzene for 8 hr. at 40–50°. After hydrolysis and distillation of the benzene layer, the residue was dissolved in methanol and treated with saturated sodium bisulfite solution. The precipitate which formed was washed with ethanol and ether. Treatment of the precipitate with dilute hydrochloric acid produced the product which melted 87–90°. Two recrystallizations from ethanol-water yielded 0.2 g. (2%) of white crystals, m.p. 91–93°.

Anal. Calcd. for $C_{13}H_8O_3$: C, 73.58; H, 3.77. Found: C, 74.40, 74.31; H, 3.54, 3.62.

The 2,4-dinitrophenylhydrazone recrystallized from pyridine-ethanol melted 300–301°.

Anal. Calcd. for $C_{19}H_{12}O_6N_4$: N, 14.29. Found: N, 13.89, 14.00.

Attempted preparation of 2-(α-naphthyl)dibenzo-p-dioxin. A mixture of 11 g. (0.08 mole) of aluminum chloride, 9.2 g. (0.05 mole) of dibenzo-*p*-dioxin, 10 g. (0.08 mole) of quinoline, and 7.3 g. (0.05 mole) of α-fluoronaphthalene were stirred at 150° for 2 hr. Then 7 g. (0.055 mole) more of aluminum chloride was added and the temperature raised to 180° for 2 hr. The purple-black mixture was allowed to cool and hydrolyzed with ice–hydrochloric acid. This was extracted with ether and dried over anhydrous sodium sulfate. The residue, obtained by evaporation of the ether, was vacuum distilled to yield a small amount of α-fluoronaphthalene. By chromatographing the material remaining in the flask after vacuum distillation, 2.5 g. (28%) of starting material was obtained. No product has been isolated.

The other runs using α-bromonaphthalene and *p*-chlorophenol were very similar to that described above except for variations in the solvent.

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AMES, IOWA

[CONTRIBUTION FROM DEPARTMENT OF CHEMISTRY, ISRAEL INSTITUTE OF TECHNOLOGY]

Alicyclic Studies. XIII.[1] Preparation and Reactions of 1,1′-Dicycloalkenyls*

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The preparation of 1,1′-dicyclopentenyl, 1,1′-dicyclohexenyl, 1,1′-dicycloheptenyl, and 1,1′-dicyclooctenyl has been improved. Diels-Alder reactions of these dienes are described.

Diene reactions of 1,1′-dicylopentenyl[1] (Ia) and 1,1′dicylohexenyl[2,3] (Ib) have been described. However, it is clear that particularly in the former case, the diene has not heretofore been obtained pure. The dienes are prepared by dehydration under acidic conditions of the pinacols resulting from pinacol-reduction of cyclopentanone and cyclohexanone, respectively. It has been shown that acidic dehydration of 1,1′-dihydroxy-1,1′-dicyclopentyl gives primarily 2-spirocyclopentanocyclohexanone (II).[4] The yields of Diels-Alder adducts form

* This paper is a contribution in honor of Lyndon F. Small, former Editor of the Journal.

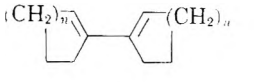
(1) Part XII, Y. Amiel and D. Ginsburg, *Tetrahedron*, 1, 19 (1957).

(2) E. B. Barnett and C. A. Lawrence, *J. Chem. Soc.*, 1104 (1935).

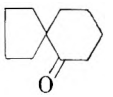
(3) E. E. Gruber and R. Adams, *J. Am. Chem. Soc.*, 57, 2555 (1935).

(4) M. Qudrat-i-Khuda and A. K. Ray, *J. Indian Chem Soc.*, 16, 525 (1939).

1,1′-dicyclopentenyl as described by Barnett and Lawrence[2] show that their diene component could not have contained more than 25 per cent of pure diene even when alum was used to dehydrate the corresponding pinacol. These authors report that they were unable to obtain good analytical results for their diene. When their work was repeated, the infrared spectrum of the product indeed showed that the product of alum dehydration of the pinacol was primarily the spiroketone. The method of choice for this dehydration was found to be through phosphorus oxychloride in pyridine. No rearrangement occurs under these conditions and no carbonyl band is exhibited by the infrared spectrum of the product. The pure diene thus obtained afforded a quantitative yield of adduct with maleic anhydride.



Ia; n = 1
a; n = 2
c; n = 3
d; n = 4



II

Although relatively less of the corresponding spiroketones accompany the dienes Ib, Ic, and Id when they are prepared by acidic dehydration of their pinacols, the phosphorus oxychloride-pyridine method afforded the smoothest means for their preparation.

An alternative method was tried in the case of 1,1′-dicyclooctenyl (Id). 1-Cyclooctylcyclooctene prepared by self-condensation of cyclooctene in the presence of sulfuric acid[5] was brominated with one mole of *N*-bromosuccinimide and the allylic bromide was dehydrobrominated. That the desired symmetrical diene was not thus obtained was shown by the fact that no adduct could be prepared *via* the Diels-Alder reaction with maleic anhydride. Probably a homoannular diene was obtained by bromination-dehydrobromination of 1-cyclooctylcyclooctene. The homoannular product is either 1- or 2-cyclooctylcycloocta-1,3-diene but its structure was not further elucidated.

As stated above, 1,1′-dicyclopentenyl afforded a quantitative yield of adduct with maleic anhydride. All attempts at aromatization of the product gave a central benzenoid ring and no quinonoid arrangement of double bonds throughout the tricyclic (carbocyclic) system could be obtained even from the adduct of the diene with methyl acetylenedicarboxylate. Treatment of the latter substance with excess of *N*-bromosuccinimide followed by dehydrobromination afforded the product with a central benzenoid ring. The same situation obtained in the products of the Diels-Alder reaction of 1,1′-dicycloheptenyl with various dienophiles.

Since the adducts of the dienes with *p*-benzoquinone are cyclohexenediones which can, in principle, readily isomerize to give phenols, the Diels-Alder reaction of 1,1′-dicyclopentenyl with this quinone was carried out under the same conditions as previously reported.[2] It was found from the infrared spectrum of the adduct that it is, indeed, the enedione as formulated. However, when several of the dienes reacted with *p*-benzoquinone in the *absence* of methanol it was clear from the infrared spectrum of one of the products that a phenol had been formed by aromatization of the immediate product of the condensation. The detailed descriptions of these reactions are given in the experimental section.

EXPERIMENTAL

Melting points and boiling points are uncorrected.

1,1′-Dihydroxy-1,1′-dicyclopentyl. This pinacol was prepared by the method of Barnett and Lawrence.[2] The yield was the same as reported and decreased appreciably when magnesium was used instead of aluminum. It had m.p. 109° (from pentane). Lit.[2] m.p. 109°.

1,1′-Dicyclopentenyl (Ia). (*a*) Dehydration of the above pinacol was attempted with oxalic acid in boiling toluene but afforded material which did not react with maleic anhydride. The reported method[2] using anhydrous alum afforded a product, b.p. 205–210°. The condensation of this product with maleic anhydride[2] afforded an adduct in 10–15% yield. The infrared spectrum of the dehydration product exhibited a strong band at 1702 cm.$^{-1}$ (C=O) showing the presence of a large amount of *2-spirocyclopentanocyclohexanone* (II). It gave an orange *2,4-dinitrophenylhydrazone*, m.p. 111–112° (from ethanol).

Anal. Calcd. for $C_{16}H_{20}O_4N_4$: N, 16.86. Found: N, 17.22.

The *spiro*-ketone (7 g.) itself was isolated from the dehydration product (10 g.) through the use of Girard P reagent[6] and the resulting diene from this separation (3 g.) was still slightly contaminated by the spiroketone. The dehydration mixture afforded the above 2,4-dinitrophenylhydrazone in 70–75% yield, again indicating that no more than 25% of diene is present in the mixture.

(b) *By means of phosphorus oxychloride in pyridine.* A mixture of the pinacol (40 g.), phosphorus oxychloride (40 ml.), and dry pyridine (200 ml.) was carefully warmed on the steam bath until a very exothermic reaction occurred, necessitating cooling in an ice bath. When the reaction became moderate, the mixture was warmed on the steam bath for 6 hr. and most of the pyridine was removed at the water pump. Ice cold water was added with cooling to a total volume of *ca.* 250 ml. and the thick mixture was shaken mechanically for 30 min. in order to complete dissolution of the water-soluble compounds. The mixture was extracted with pentane and the pentane extracts were washed with 10% hydrochloric acid, with aqueous sodium bicarbonate, with water, and then dried (sodium sulfate). Removal of the pentane followed by distillation afforded *1,1′-dicyclopentenyl*, b.p. 32°/0.05 mm. (27.5 g.; 84%) as a light yellow mobile liquid. The analytical sample was prepared by dissolving a portion of the diene in dry ether and refluxing the solution over sodium wire until the latter was no longer attacked. The analytical sample had b.p. 34°/0.1 mm., n_D^{19} 1.5251.

Anal. Calcd. for $C_{10}H_{14}$: C, 89.49; H, 10.51. Found: C, 89.39; H, 10.31.

3,4,5,6-Dicyclopentano-1,2,3,6-tetrahydrophthalic anhydride.

(5) W. Reppe, O. Schlichting, K. Klager, and T. Toepel, *Ann.*, **560**, 41 (1948).

(6) A. Girard and G. Sandulesco, *Helv. Chim. Acta*, **19**, 1095 (1936).

A mixture of pure 1,1'-dicyclopentenyl (4 g.), maleic anhydride (2.9 g.), and cyclohexane (4 ml.) was warmed gently until the powder melted. Cooling was necessary to control the strongly exothermic reaction. After 2 hr. the mixture solidified. The *anhydride* was removed by filtration (6.5 g.; 94%) and the crude material had m.p. 101°. The analytical sample had m.p. 104° (from cyclohexane). Lit.[2] m.p. 104°.

Anal. Calcd. for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94; O, 20.67. Found: C, 72.30; H, 7.15; O, 21.00.

Infrared absorption ($CHCl_3$): 1852 cm.$^{-1}$, 1775 cm.$^{-1}$ (C=O bands of anhydride).

3,4,5,6-Dicyclopentanophthalic anhydride. (*a*) A mixture of the above anhydride (1.95 g.), *N*-bromosuccinimide (2.67 g.; 2 equiv.), and carbon tetrachloride (200 ml.) was heated under reflux for 3 hr. At this point all of the NBS had been converted to succinimide. Anhydrous sodium acetate (1.23 g.) and glacial acetic acid (1.5 ml.) were added and refluxing was continued for an additional 18 hr. The mixture was poured into water and the solid which appeared between the aqueous and organic layers was removed by filtration (250 mg.). The solvents were removed from the organic phase and trituration of the residual bromine-containing oil with a small amount of carbon tetrachloride afforded more solid (350 mg.). The residual oil was not further investigated. Recrystallization of the solid gave the pure *aromatic anhydride*, m.p. 265° (from toluene).

Anal. Calcd. for $C_{14}H_{12}O_3$: C, 73.67; H, 5.30; O, 21.03. Found: C, 73.51; H, 5.56; O, 21.12.

Infrared absorption (KBr): 1833 cm.$^{-1}$, 1760 cm.$^{-1}$ (C=O bands of anhydride).

Dimethyl 3,4,5,6-dicyclopentano-3,6-dihydrophthalate. A mixture of 1,1'-dicyclopentenyl (6.7 g.) and dimethyl acetylenedicarboxylate (7.1 g.) was warmed on the steam bath. After 15 min. a vigorous reaction set in. Warming was interrupted for 10 min. and then continued for 8 hr. Trituration of the cold reaction mixture with methanol afforded the *ester* (9.7 g.; 70%), m.p. 127° (from methanol).

Anal. Calcd. for $C_{16}H_{20}O_4$: C, 69.54; H, 7.30; O, 23.16. Found: C, 69.54; H, 6.91; O, 23.63.

A portion of the crude ester was saponified by aqueous methanolic potassium hydroxide. The crude product obtained after removal of the methanol and acidification was recrystallized from acetic acid and from toluene and was identical with the aromatic anhydride described above by mixed m.p. determination.

Aromatization of the diester. A mixture of the above diester (2.76 g.), *N*-bromosuccinimide (2.0 g.) and carbon tetrachloride (50 ml.) was refluxed for 2 hr. After removal of the succinimide and the solvent the crude product was saponified by aqueous methanolic potassium hydroxide. Removal of the methanol, acidification and recrystallization from toluene afforded the aromatic anhydride, identical with that described above by mixed melting point determination.

Reaction of 1,1'-dicyclopentenyl and p-benzoquinone. (*a*) 1,1'-Dicyclopentenyl (7.4 g.; 2 equiv.) and *p*-benzoquinone (3 g.) were mixed at ice-bath temperature and then warmed on the steam bath for 1 hr. The reaction mixture was treated with methyl cyclohexane (100 ml.) and a solid, m.p. 171° (from methylcyclohexane), was obtained. This was *p*-hydroquinone.

The methylcyclohexane solution was concentrated to about one quarter of its original volume and crystals were obtained, m.p. 150° (from methylcyclohexane) (1.9 g.). Infrared absorption (chloroform): broad band 1695–1712 cm.$^{-1}$ (C=O). This must correspond to *1,2,3,4,5,6,7,8-tetracyclopentano-1,4,4a,5,8,8a,9a,10a-octahydro-9,10-anthraquinone* which was also obtained by Barnett and Lawrence,[2] who report m.p. 152° for the product from their mono-adduct of 1,1'-dicyclopentenyl and *p*-benzoquinone with an additional mole of the diene.

Anal. Calcd. for $C_{26}H_{32}O_2$: C, 82.93; H, 8.57; O, 8.50. Found: C, 82.76; H, 8.57; O, 8.68.

After evaporation of the methylcyclohexane from the mother liquor an additional portion (4 g.) of the same diketone was obtained, m.p. 150° (from aqueous ethanol or acetone). The overall yield of products was therefore 57%.

(*b*) The same reaction was carried out repeating the conditions of Barnett and Lawrence,[2] in order to determine the infrared spectrum of their mono-adduct: A mixture of the diene (3.3 g.), *p*-benzoquinone (2 equiv.) and methanol (10 ml.) was heated under reflux. The product was *5,6,7,8-dicyclopentano-1,4,4a,5,8,8a-hexahydronaphthalene-1,4-dione*, m.p. 124° (from methanol) (4 g.). Lit.[2] m.p. 124°. Infrared absorption (chloroform): broad band 1695, 1660 cm.$^{-1}$ (strong band, O=C—C=C—C=O).

Anal. Calcd. for $C_{16}H_{18}O_2$: C, 79.31; H, 7.49; O, 13.21. Found: C, 79.15; H, 7.46; O, 13.56.

1,2,3,4-Dicyclopentano-1,4,4a,9a-tetrahydro-9,10-anthraquinone. A mixture of the diene (2.2 g.) and 1,4-naphthoquinone (2.7 g.) was warmed on the steam bath. A dark homogeneous melt was obtained immediately and solidified after cooling. Recrystallization afforded the *diketone*, m.p. 130° (from 2-propanol) (3.5 g.; 72%).

Anal. Calcd. for $C_{20}H_{20}O_2$: C, 82.15; H, 6.89; O, 10.95. Found: C, 81.86; H, 6.92; O, 11.06.

Infrared absorption ($CHCl_3$): 1682 cm.$^{-1}$ (C=O). Lit.[2] m.p. 134°.

1,1'-Dihydroxy-1,1'-dicycloheptyl. A solution of mercuric chloride (8 g.) in cycloheptanone (100 g.) was added to coarse aluminum powder (16 g.) in dry benzene (150 ml.). After warming on the steam bath for 5–10 min. a strong reaction began and had to be controlled by external cooling. After moderation of the reaction the mixture was refluxed for 12 hr. Benzene was added (150 ml.) and water (60 ml.) was added dropwise during 30 min. The mixture was warmed for an additional 2 hr. with occasional shaking, and filtered. The solid was extracted with benzene (150 ml.) and the combined benzene extracts were distilled at the water pump up to a bath temperature of 150°. Unreacted cycloheptanone (10 g.) was recovered. Pentane was added to the residual oil and the solution was refrigerated overnight. The crystals of pinacol were filtered and washed well with pentane, m.p. 78°.

Anal. Calcd. for $C_{14}H_{26}O_2$: C, 74.28; H, 11.58; O, 14.14. Found: C, 73.62; H, 11.34; O, 14.28.

The mother liquor was distilled and afforded 1,1'-dicycloheptenyl, b.p. 85–86°/0.01 mm. (15.7 g.) and further portion of pinacol, b.p. 117–118°/0.05 mm. (9 g.). The total yield including diene was 77%. The use of magnesium instead of aluminum gave a lower yield of product.

1,1'-Dicycloheptenyl (Ic). The preferred method for dehydration of the pinacol was by means of phosphorus oxychloride in pyridine as described above for the preparation of 1,1'-dicyclopentenyl. The reaction in this case was less vigorous and requires no external cooling. From the pinacol (25 g.) and phosphorus oxychloride (25 ml.) was obtained the *diene* (19 g.; 90%), b.p. 83–84°/0.05 mm. The infrared spectrum showed no hydroxyl or carbonyl absorption; n_D^{19} 1.5223.

Dehydration can be effected in 90% yield by means of oxalic acid or in 82% yield by using the method of Gruber and Adams[3] for the dehydration of 1,1'-dihydroxy-1,1'-dicyclohexyl by means of 10% sulfuric acid. However, both of these products contained *2-spirocycloheptanocyclooctanone*, although in very small amount, and this was characterized as the orange *2,4-dinitrophenylhydrazone*, m.p. 113–114° (from ethanol).

Anal. Calcd. for $C_{20}H_{28}N_4O_4$: N, 14.42. Found: N, 14.70.

For example, 10 g. of pinacol gave 8 g. of product after oxalic acid dehydration and by the use of Girard P reagent, only 100 mg. of *spiro*ketone was isolated.

3,4,5,6-Dicycloheptano-1,2,3,6-tetrahydrophthalic anhydride. A mixture of the diene (5 g.) maleic anhydride (2.6 g.) and methylcyclohexane (5 ml.) was warmed carefully until the powder melted. Slight shaking started a strongly exothermic reaction which was moderated by external cooling. After a few minutes the mixture solidified. After stand-

ing overnight the solid was filtered. It had m.p. 157–158° (from methylcyclohexane) (5.1 g.; 68%).

Anal. Calcd. for $C_{18}H_{24}O_3$: C, 74.97; H, 8.39; O, 16.64. Found: C, 74.39; H, 8.39; O, 16.81.

Infrared absorption ($CHCl_3$): 1855, 1777 cm.$^{-1}$ (anhydride).

3,4,5,6-Dicycloheptanophthalic anhydride. (*a*) The above adduct (2 g.) was heated with sulfur (0.42 g.) at 245° for 20 min. After crystallization from toluene in the presence of activated carbon a nearly colorless product, m.p. 240° was obtained (0.8 g.). Further recrystallization from toluene raised the m.p. to 254°. (*b*) The adduct (0.29 g.) was dissolved in chloroform (50 ml.) and bromine (0.16 g.) in chloroform (5 ml.) was added. No color change was apparent at room temperature. Refluxing for 2 hr. discharged the bromine color and hydrogen bromide was evolved. The solution was washed with 5% sodium bicarbonate solution and dried (sodium sulfate). The solvent was removed and the residue was recrystallized from carbon tetrachloride, m.p. 253° (0.12 g.). Further recrystallization from toluene yielded snow-white crystals, m.p. 254–255°. (c) A mixture of the adduct (1.4 g.), *N*-bromosuccinimide (1.78 g.) and carbon tetrachloride (125 ml.) was refluxed overnight. The mixture was then poured into water and the solid was filtered. The solvent was removed from the organic phase and the residue was triturated with methanol and the solid filtered. The combined solids were recrystallized from toluene and afforded the purest sample of the *aromatic anhydride*, m.p. 256° (0.64 g.) identical with the specimens obtained in (a) and (b) above both by mixed melting point determination.

Anal. Calcd. for $C_{18}H_{20}O_3$: C, 76.03; H, 7.09; O, 16.88. Found: C, 75.55; H, 6.88; O, 16.86.

Infrared absorption (KBr): 1831, 1762 cm.$^{-1}$ (anhydride).

3,4,5,6-Dicycloheptano-3,6-dihydrophthalic acid. A mixture of the diene (11 g.) and dimethyl acetylenedicarboxylate (8.2 g.) was heated on the steam bath for 8 hr. The product was then heated with aqueous (20 ml.) methanolic (200 ml.) potassium hydroxide (20 g.) for 8 hr. The methanol was removed by distillation, water was added, and the mixture was extracted with ether to remove unsaponified material (5 g.). Acidification of the aqueous phase precipitated a colorless solid (10.3 g.). The product after recrystallization from glacial acetic acid had m.p. 102°.

Anal. Calcd. for $C_{18}H_{22}O_3$: C, 75.49; H, 7.74; O, 16.76. Found: C, 75.20; H, 7.68; O, 16.93.

Infrared absorption (chloroform): 1840, 1765 cm.$^{-1}$ (anhydride). This was the *dienic anhydride*. The *acid* could be obtained by aqueous hydrolysis, m.p. 140° (from methylcyclohexane).

Anal. Calcd. for $C_{18}H_{24}O_4$: C, 71.02; H, 7.95; O, 21.03. Found: C, 71.33; H, 8.28; O, 20.30.

When the acid was refluxed in methylcyclohexane for 24 hr. it afforded a small amount of the aromatic anhydride, m.p. 256°, and as the major product the dienic anhydride, m.p. 102°. The dienic acid was aromatized in the usual way by treatment with one mole of *N*-bromosuccinimide, yielding the aromatic anhydride, m.p. 256°.

All attempts to isolate products containing more extended conjugation failed. In all cases the aromatic anhydride described above was the only characterizable product. Alternative attempts to add maleic anhydride to brominated 1,1′-dicycloheptenyl in order to introduce bromine atoms in the seven-membered rings in addition to the double bonds in the central six-membered ring, and thence remove them by dehydrobromination, also led to the aromatic anhydride and to an intractable mixture of oily bromoderivatives which could not be resolved.

5,6,7,8-Dicycloheptano-5,8-dihydronaphthalene-1,4-diol. The reaction between 1,1′-dicycloheptenyl (4.3 g.; 2 equiv.) and *p*-benzoquinone (1.2 g.) was carried out exactly as in the case of 1,1′-dicyclopentenyl. The product (2.7 g.; 82%) had m.p. 181° (from wet benzene) and its infrared spectrum showed bands at 3570, 3350 cm.$^{-1}$ (OH). It was therefore the *diphenol*, in the form of its monohydrate.

Anal. Calcd. for $C_{20}H_{26}O_2 \cdot H_2O$: C, 75.91; H, 8.92. Found: C, 76.41; H, 8.90.

Removal of the solvent and addition of 2-propanol afforded the yellow bis-diketone, *1,2,3,4,5,6,7,8-tetracycloheptano-1,4,4a,5,8,8a,9a,10a-octahydro-9,10-anthraquinone* (0.2 g.), m.p. 315° (from dioxane; in preheated bath). The analysis shows the substance to be the bis-diketone but the carbonyl band in the infrared spectrum appeared at abnormally low frequency (1645 cm.$^{-1}$).

Anal. Calcd. for $C_{34}H_{48}O_2$: C, 83.55; H, 9.90; O, 6.55. Found: C, 83.74; H, 9.34; O, 7.10.

The same product was obtained in 20% yield by heating 2 equiv. of diene with 1 equiv. of *p*-benzoquinone in dioxane for 3 hr.

5,6,7,8-Dicycloheptano-1,4,4a,5,8,8a-hexahydronaphthalene-1,4-dione. 1,1′-Dicycloheptenyl (1.05 g.), *p*-benzoquinone (0.6 g.), and methanol (4 ml.) was heated on the steam bath for 1 hr. Filtration after refrigeration overnight afforded a dark-red solid (0.6 g.). Recrystallization gave the dark-red *diketone*, m.p. 133–134° (from methanol). Infrared absorption ($CHCl_3$): 1660 cm.$^{-1}$ (C=O).

Anal. Calcd. for $C_{20}H_{26}O_2$: C, 80.49; H, 8.78; O, 10.72. Found: C, 80.47; H, 8.19; O, 11.21.

After removal of the solvent the above diphenol, m.p. 181° (0.8 g.) was obtained.

1,2,3,4-Dicycloheptano-1,4,4a,9a-tetrahydro-9,10-anthraquinone. The diene (3.84 g.) and 1,4-naphthoquinone (3.18 g.) afforded the *diketone*, m.p. 105° (from 2-propanol) (6 g.; 86%).

Anal. Calcd. for $C_{24}H_{28}O_2$: C, 82.72; H, 8.10; O, 9.18. Found: C, 82.45; H, 8.18; O, 9.31.

Infrared absorption (chloroform): broad band, 1680–1695 cm.$^{-1}$ (C=O).

1,1′-Dihydroxy-1,1′-dicyclooctyl. The pinacol was prepared in a manner exactly analogous to the preparation of its seven-membered ring homolog except that the reflux period was only 9 hr. Cyclooctanone (12 g.) was recovered and the pinacol was obtained after refrigeration overnight in pentane solution (56 g.). It had m.p. 93–94°. Lit.[7] m.p. 93–94°. Distillation afforded 1,1′-dicyclooctenyl, b.p. 113–114°/0.1 mm. (11 g.) and an additional portion of the pinacol (4 g.) (total yield of products 72%).

1,1′-Dicyclooctenyl (Id). (*a*) A mixture of the pinacol (10 g.), oxalic acid (10 g.), and water (20 ml.) was refluxed for 15 hr. at 140°. Pentane extraction followed by distillation afforded the crude diene (8.2 g.) whose infrared spectrum showed the presence of 2-spirocyclooctanocyclononanone (C=O band at 1684 cm.$^{-1}$). The spiroketone (150 mg.) could be isolated through the use of Girard P reagent. (*b*) A mixture of pinacol (75 g.), phosphorus oxychloride (75 ml.), and pyridine (375 ml.) afforded, in the usual way pure *1,1′-dicyclooctenyl*, b.p. 113–114°/0.1 mm.; 118–120°/0.2 mm. (63 g.; quant. yield). Lit.[7] b.p. 122–123°/0.4 mm. The product crystallized spontaneously, m.p. 43°.

3,4,5,6-Dicyclooctano-1,2,3,6-tetrahydrophthalic anhydride. A mixture of 1,1′-dicyclooctenyl (1.09 g.), maleic anhydride (0.40 g.), and methylcyclohexane (1 ml.) gave the adduct, m.p. 155–160° (1.53 g.). The pure anhydride was obtained by recrystallization, m.p. 179–180° (from methylcyclohexane).

Anal. Calcd. for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92; O, 15.17. Found: C, 75.65; H, 8.97; O, 15.45.

Infrared absorption ($CHCl_3$): 1852, 1775 cm.$^{-1}$ (anhydride).

3,4,5,6-Dicyclooctanophthalic anhydride. The above anhydride (1.05 g.) was aromatized as usual by refluxing with *N*-bromosuccinimide (1.19 g.; 2 equiv.) in carbon tetrachloride (125 ml.) for 2.5 hr. The colorless *aromatic anhydride* (0.65 g.) had m.p. 199–200° (from toluene).

(7) L. Ruzicka and A. A. Boekenoogen, *Helv. Chim. Acta*, **14**, 1319 (1931).

Anal. Calcd. for $C_{20}H_{24}O_3$: C, 76.89; H, 7.74; O, 15.37. Found: C, 77.30; H, 7.88; O, 15.50.

Infrared absorption (KBr): 1833, 1760 cm.$^{-1}$ (anhydride).

1-Cyclooctylcyclooctene. This product was obtained according to the method described by Reppe *et al.*[5] in 66% yield. It had b.p. 135–140°/2 mm. The cyclooctene which was required as starting material was prepared in 70–80% yield by dehydration of cyclooctanol b.p. 120°/37 mm. with 85% phosphoric acid.[6] It had b.p. 142–146°.

1- or 2-Cyclooctylcycloocta-1,3-diene. A mixture of 1-cyclooctylcyclooctene (4.5 g.), *N*-bromosuccinimide (3.65 g.; 1 equiv.), and carbon tetrachloride (50 ml.) was refluxed for 15 min. The reaction was over in 10 min. The succinimide was filtered, the solvent was removed by distillation and collidine (25 ml.) was added. An immediate precipitation of collidine hydrobromide occurred. The mixture was refluxed for 2 hr. to ensure completion of the dehydrobromination. Filtration of the solution after cooling afforded crystalline collidine hydrobromide (3.8 g.; theory 4 g.). The residual collidine was removed in the usual way and the *diene* was distilled, b.p. 105–110°/0.2 mm. (3.5 g.) No adduct could be obtained from the diene with maleic anhydride.

Dimethyl 3,4,5,6-dicyclooctano-3,6-dihydrophthalate. A mixture of 1,1′-dicyclooctenyl (10.9 g.) and dimethyl acetylenedicarboxylate (7.1 g.) was heated on the steam bath for 8 hr. Trituration of an aliquot (1.5 g.) of the cooled reaction mixture with methanol gave the *ester* (1.2 g.; 80%), m.p. 115° (from methanol).

Anal. Calcd. for $C_{22}H_{32}O_4$: C, 73.30; H, 8.95; O, 17.75. Found: C, 72.66; H, 9.04; O, 17.90.

Infrared absorption ($CHCl_3$): broad band, 1710–1735 cm.$^{-1}$ (C=O of ester).

Saponification of the rest of the crude ester afforded the crude acid (15.3 g.), which after recrystallization from glacial acetic acid afforded the *dienic acid*, m.p. 205° (sintering at 200°).

Anal. Calcd. for $C_{20}H_{28}O_4$: C, 72.26; H, 8.49; O, 19.25. Found: C, 71.80; H, 8.07; O, 19.26.

(8) *Cf. Org. Syntheses*, Coll. Vol. II, 152 (1943).

Aromatization with 1 mole of NBS afforded the aromatic anhydride, m.p. 199–200°.

Reaction between 1,1′-dicyclooctenyl and p-benzoquinone. A mixture of the diene (40 g.; 2 equiv.) and *p*-benzoquinone (10 g.) was heated on the steam bath. After 30 min. of heating the liquid mass solidified. After an additional 1 hr. the mixture was again liquid and after one more hour it afforded a yellow crystalline mass. Methylcyclohexane was added and the pink solid (26 g.) was filtered. It formed needles, m.p. 186° (from wet benzene) and was phenolic. (Infrared band at 3330 cm.$^{-1}$). This is therefore *5,6,7,8-dicyclooctano-5,8-dihydronaphthalene-1,4-diol* in the form of its monohydrate.

Anal. Calcd. for $C_{22}H_{30}O_2 \cdot H_2O$: C, 76.70; H, 9.36; O, 13.93. Found: C, 77.11; H, 9.63; O, 13.99.

The solvent was removed from the mother liquor, a small amount of 2-propanol was added, and the solution was refrigerated. The yellow solid was filtered (2 g.) and had m.p. 252° (from dioxane). Infrared absorption ($CHCl_3$): 1710 cm.$^{-1}$ (satd. C=O). This is *1,2,3,4,5,6,7,8-tetracyclooctano-1,4,4a,5,8,8a,9a,10a-octahydro-9,10-anthraquinone.*

Anal. Calcd. for $C_{38}H_{56}O_2$: C, 83.77; H, 10.36. Found: C, 83.09; H, 10.16.

1,2,3,4-Dicyclooctano-1,4,4a,9a-tetrahydro-9,10-anthraquinone. A mixture of the diene (24 g.) and 1,4-naphthoquinone (17.5 g.) was heated on the steam bath for 1 hr. and afforded a brown glassy mass. Trituration with methylcyclohexane afforded a tan solid which was filtered (32 g.; 72%). The dark brown mother liquor deposited a further crop of large transparent rhombs (8 g.). The *diketone* had m.p. 155° (from methylcyclohexane or isopropanol). Infrared absorption (KBr): 1695 cm.$^{-1}$ (C=O adjacent to aromatic ring).

Anal. Calcd. for $C_{26}H_{32}O_2$: C, 82.93; H, 8.57; O, 8.50. Found: C, 82.37; H, 8.57; O, 8.85.

1,1′-Dicyclohexenyl (Ib). (Experiment carried out by M. Berdichev). The pinacol from cyclohexanone was prepared in the usual way.[2] Dehydration with phosphorus oxychloride in pyridine as described for the various pinacol homologs afforded the *diene*, b.p. 70–76°/0.05 mm. (95% yield).

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF TEXAS]

Reactions of Aromatic Sulfonyl Chlorides with Organocadmium Reagents*[1]

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Aromatic sulfonyl chlorides react with diarylcadmium reagents to form simple or mixed aryl sulfones in fair yields; sulfinic acids and aryl halides are by-products. Aromatic sulfonyl chlorides react with dialkylcadmium reagents to yield alkyl chlorides and solid products; the latter react with hydrochloric acid to form arylsulfinic acids, and with nitric acid to give *N,N*-bis(arenesulfonyl)hydroxylamines.

The interaction of organocadmium reagents with acyl chlorides is an accepted method for preparation of ketones.[3] By analogy, the interaction of the cadmium reagents with sulfonyl chlorides might well be expected to yield sulfones. This reaction, if successful, might become the method of choice for production of mixed sulfones, RSO_2R'.

There appears to be but one published reference to the interaction of a sulfonyl chloride with an organocadmium compound, namely, that of Gilman and Nelson.[4] They reported that from 0.3 mole of benzenesulfonyl chloride and diphenylcadmium (prepared from 0.34 mole of phenylmagnesium bromide and 0.17 mole of anhydrous cadmium chloride), and subsequent acidification of the reac-

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(3) (*a*) J. Cason, *Chem. Revs.*, **40**, 15 (1947). (*b*) D. A. Shirley, *Org. Reactions*, VIII, 28 (1954).

(4) H. Gilman and J. F. Nelson, *Rec. trav. chim.*, **55**, 518 (1936).

TABLE I

PRODUCTS OF INTERACTION OF ARYLSULFONYL CHLORIDES AND ARYLCADMIUM REAGENTS

Reactants		Sulfone		Arylsulfinic Acid	
$R—SO_2Cl$	$R_2'Cd$	$R—SO_2—R'$		$R—SO_2H$	
R—	R'—	Yield, %	M.p., °C.	Yield, %	M.p., °C.
$—C_6H_5$	$C_6H_5—$	46	122–123[a]	25[b]	—
$—C_6H_4CH_3$-*p*	$C_6H_5—$	41	124.5–125.0[c]	8.5	88–90[d]
$—C_6H_3(CH_3)_2$-2,5	$C_6H_5—$	42[e]	108.0–110.5	12.7	82–84[f]
$—C_6H_3Cl_2$-2,5	$C_6H_5—$	31	144–146[g]	43	120–123[h]
$—C_6H_3Cl_2$-3,4	$C_6H_5—$	36	121.5–122.5[i]	45	95–97[j]
$C_{10}H_7$-2	$C_6H_5—$	30	114.5–115.5[k]	3.1	101–104[l]
C_6H_5	C_6H_4Cl-4	60.5	90.5–91.5[m]		
$C_6H_5—$	$CH_3OC_6H_4$-4	[n]	(m.p. of *p,p'*-dianisyl)[n]		

[a] H. Berckurtz and R. Otto [*Ber.*, **11**, 2066 (1878)] reported m.p. 124°. [b] Identified as the ferric benzenesulfinate. [c] A. Michael and A. Adair [*Ber.*, **11**, 116 (1878)] reported m.p. 124.5°. [d] E. Knoevenagel and J. Kenner [*Ber.*, **41**, 3318 (1908)]. [e] *Anal.* Calcd. for $C_{14}H_{14}O_2S$: C, 68.26; H, 5.72. Found: C, 67.86; H, 5.61. [f] Ref. (*d*) reported m.p. 84–85°. [g] J. Huismann (Ger. Pat. **701,954**) [*Chem. Abstr.*, **36**, 98 (1942)] reported m.p. 146°. [h] S. Smiles and D. T. Gibson [*J. Chem. Soc.*, **125**, 176 (1924)] reported m.p. 122°. [i] Ref. (*g*) reported m.p. 125°. [j] The *S*-benzylthiuronium derivative of 3,4-dichlorobenzenesulfinic acid was prepared, m.p. 180–182°. *Anal.* Calcd. for $C_{14}H_{14}Cl_2N_2O_2S$: N, 7.42. Found: N, 7.61; this derivative has been reported as melting at 170–171° by F. Kurzer and J. R. Powell, *J. Chem. Soc.*, 3730 (1952). [k] A. Michael and A. Adair [*Ber.*, **10**, 585 (1877)] reported m.p. 115.6°. [l] E. Gessner [*Ber.*, **9**, 1502 (1876)] reported m.p. 105°. [m] H. Meyer [*Ann.*, **433**, 327 (1923)] reported m.p. 93°. [n] A. Gillmeister [*Ber.*, **30**, 2849] reported m.p. 172° for *p,p'*-dianisyl; in this experiment was obtained a 73% yield of *p,p'*-dianisyl of m.p. 172°.

tion mixture, was obtained a 15% yield of diphenylsulfone and some benzenesulfinic acid.[4a]

In the present study, the results of Gilman and Nelson have been confirmed; a slightly better yield of sulfone resulted from "inverse addition" of the diphenylcadmium solution to benzenesulfonyl chloride. The latter procedure, however, is more time consuming, since filtration from the cadmium and magnesium halides is necessary in order to facilitate dropwise addition of the organocadmium reagent. Utilization of a twofold excess of diphenylcadmium results in a slightly higher yield of sulfone, but employment of boiling benzene, in place of ether, as a solvent was detrimental. This study was extended to include interaction of diphenylcadmium with other arylsulfonyl chlorides and to reaction between bis (4-chlorophenyl) cadmium and benzenesulfonyl chloride; in each case, the anticipated sulfone was the chief product formed (see Table I).

In an attempt to prepare 4-methoxyphenyl phenyl sulfone, it was found that, as Grignard[5] had stated, *p*-methoxyphenylmagnesium bromide is only slightly soluble in ether. The corresponding bis-(4-methoxyphenyl)cadmium appeared to be even less soluble than the Grignard reagent; because of the difficulty of filtering and assaying the organocadmium content of the nonhomogeneous mixture, therefore, the benzenesulfonyl chloride was added directly to the latter. After the reaction mixture was processed in the usual manner, the only product which could be isolated was *p-p*-bianisyl, obtained in 73% yield.

In sharp contrast to the successful preparations of diaryl sulfones was the failure to obtain any ethyl phenyl sulfone from interaction of diethylcadmium and benzenesulfonyl chloride under the conditions satisfactory for production of aryl sulfones. Although precipitation of solid material occurred, separation and subsequent hydrolysis of the latter under various conditions yielded no sulfone.

Decomposition of the solid reaction product, from interaction of a dialkylcadmium and an arylsulfonyl chloride, by treatment with hydrochloric acid or sulfuric acid permitted recovery of some of that sulfonic acid, together with some of the corresponding sulfinic acid. In one case, that most thoroughly investigated, much of the alkyl group was recovered as the alkyl chloride (not the bromide initially used). When decomposition of the addition product was accomplished with nitric acid, however, a wholly different product resulted. Thus, for example, the same product was obtained regardless of whether diethylcadmium or dipropylcadmium reacted with the sulfonyl chloride. The reaction product was shown to be *N,N*-bis(benzenesulfonyl) hydroxylamine, $(C_6H_5SO_2)_2NOH$.

The presence of sulfinic acid, in the mixture resulting from acidification of the solid reaction product derived from an arylsulfonyl chloride and a dialkylcadmium, suggests that it reacts with nitrous acid (derived from partial reduction of nitric acid by the organic matter present) to form the

(4a) A Referee has called attention to the fact that the reaction of Grignard reagents with aromatic sulfonyl halides is a well known process for the preparation of certain sulfones in indifferent yields (see M. S. Kharasch and O. Reinmuth, *Grignard Reactions of Nonmetallic Substances*, 1954, Prentice-Hall, Inc., New York, pp. 1290–1294). It appears that use of diarylcadmiums is productive of better yields than is utilization of aryl Grignard reagents; seemingly, in two cases alkylmagnesium halides have produced sulfones, in contrast to the failure of dialkylcadmiums, but in these two cases no statement of yield is given.

(5) V. Grignard, E. Bellet and Ch. Courtot, *Ann. chim.*, (9) **4**, 28 (1915).

disulfonylhydroxylamine derivative in the usual manner. Such a series of events explains why the hydroxylamine derivatives are formed only under certain conditions falling in a narrow range of concentrations and temperatures.

It was instructive to study the interaction of benzenesulfonyl chloride and dihexylcadmium; again, treatment of the addition compound with nitric acid yielded *N,N*-bis(benzenesulfonyl)hydroxylamine, and the major portion of the hexyl group was recovered in the form of hexyl chloride. Decomposition with nitric acid of the reaction product between benzenesulfonyl chloride and diphenylcadmium likewise yielded *N,N*-bis(benzenesulfonyl)hydroxylamine. Finally, interaction of either diethylcadmium or dipropylcadmium with *p*-toluenesulfonyl chloride gave a product which reacted with nitric acid to produce *N,N*-bis(*p*-tolylsulfonyl)hydroxylamine.

EXPERIMENTAL

Preparation of organocadmium reagents. These were prepared in the usual manner[3a] by interaction of an ether solution of a Grignard reagent with anhydrous cadmium chloride. After a Gilman test for the Grignard reagent was found to be negative, the mixture was filtered, as rapidly as possible, through paper on a Buchner funnel and placed, in a well-stoppered container, in a refrigerator. After several hours, the clear amber solution could be decanted, from the grey sludge which had deposited, and was assayed before further use.

Preparation of aryl sulfones. Apparatus typical of use for Grignard reactions was employed. One hundred milliliters of 2*N* diphenylcadmium solution, diluted with anhydrous ether, was slowly dropped into a well-stirred solution of 0.2 mole of arylsulfonyl chloride; a somewhat gummy, white precipitate appeared. The addition of 100 ml. of 5*N* hydrochloric acid caused partial solution of the solid material. The two liquid phases were separated and the ether layer was washed with 10% sodium hydroxide solution; from the alkaline solution, after acidification, sulfinic acid was recoverable. The ether layer was concentrated and subjected to steam distillation; the residue contained most of the sulfone. Additional sulfone was recovered by working up the material which had not been dissolved by the acid. Certain data concerning the products of these reactions are listed in Table I.

Additional experiments were carried out in attempts to improve the yields of sulfones. For example, use of "inverse addition" of the filtered solution of diphenylcadmium reagent to the solution in ether of benzenesulfonyl chloride produced a slightly better (46% *vs.* 36%) yield of sulfone. However, the advantage of the slightly higher yield is offset by the time-consuming sequence of filtration from inorganic salts, subsequent period of standing in a refrigerator, and final decantation or filtration before assay of the cadmium reagent solution. Using a twofold excess of diphenylcadmium resulted in a small enhancement (4%) in yield. No improvement in yield resulted from replacement of the ether by means of benzene or anisole.

Interaction of benzenesulfonyl chloride and dialkylcadmiums. To one molar equivalent of benzenesulfonyl chloride was added 0.5 molar equivalent of filtered diethylcadmium in ether; the mixture formed a thick, white precipitate. The latter stood overnight before it was decomposed by treatment with 10% hydrochloric acid. The resulting slurry was filtered, the layers of the filtrate were separated, and the aqueous layer was extracted with chloroform. Evaporation of the ether and chloroform extracts yielded a very small amount of liquid, presumably benzenesulfonyl chloride. The solid, previously removed by filtration, was dried and triturated successively with dioxane, acetone, and hot benzene. Virtually no extractive material was thus recovered. The residual dry material, which contained carbon, hydrogen, chlorine, sulfur, and cadmium (and presumably oxygen), was set aside as Compound I.

Similar results were noted when other dialkylcadmium reagents reacted with benzenesulfonyl chloride. The solid products, similar to Compound I, represented between 87% and 118% of the sum of the weights of the reactants.

Compound I was insoluble in water, dilute alkali, and common organic solvents, but dissolved slowly in hot, dilute acids. The analytical data for chlorine (14.3%) and sulfur (21.2%) checked well with those calculated for $[(C_6H_5SO_2Cl)_2\cdot(C_2H_5)_2Cd]$. The hydrolysis of this solid material by means of either warm hydrochloric acid or sulfuric acid (2–10%) resulted only in formation of solutions from which no organic matter could be obtained by organic solvent extraction. Concentration of the acidic solutions yielded crystalline material which decolorized potassium permanganate solution, and could be identified as benzenesulfinic acid.

To a solution of 100 ml. of water and 7.5 ml. of concentrated nitric acid, heated to 70–75°, was added 10 g. of Compound I (these concentrations and temperature are critical), followed immediately by 10 ml. of ethyl alcohol. The mixture was stirred vigorously for 5 min., while the temperature was maintained at 70–75°, then was chilled rapidly and placed in a refrigerator for 6–8 hr., when precipitation of crystals was virtually complete; yield, 2.5 g.; m.p. 85–107°. Purification was conveniently accomplished by solution in hot, 5% sodium hydroxide solution, with filtration and subsequent acidification and chilling. Final recrystallization from chloroform yielded material melting at 115–118° (dec.). The same product (Compound II) resulted from interaction of benzenesulfonyl chloride with dipropylcadmium with subsequent decomposition of the reaction product with nitric acid.

Anal. Calcd. for $C_{12}H_{11}NO_2S$: C, 46.00; H, 3.55; N, 4.47; S, 19.64. Found: C, 45.69; H, 3.44; N, 5.32; S, 20.46; analyses by Geller Microchemical Laboratory.

Similarly, a product [Compound III, of m.p. 124–126° (dec.)] was obtained by nitric acid treatment of the solid produced by interaction of *p*-toluenesulfonyl chloride with either diethylcadmium or dipropylcadmium.

Interaction of benzenesulfonyl chloride and dihexylcadmium. To 53 g. (0.3 mole) of benzenesulfonyl chloride, dissolved in 150 ml. of anhydrous ether, was added 250 ml. of 1.2*N* dihexylcadmium solution (0.15 mole of dihexylcadmium). The mixture was stirred for 1 hr., centrifuged, the white, solid material washed with ether and dried in a vacuum oven and dessicator. The ethereal solution was fractionated to give a heart-fraction of b.p. 133–135°; n_D^{20} 1.4215; d_4^{20} 0.884. The material contained chlorine, but not sulfur or bromine. This material was identified as hexyl chloride, despite the fact that hexyl bromide had been used initially. The highest boiling fraction was identified as benzenesulfonic acid by conversion into its amide.

The solid material, obtained by centrifugation, represented 84% of the combined weights of reactants, and, treated with warm nitric acid and alcohol, yielded a white crystalline solid of m.p. 119–121° (dec.); the melting point behavior was unchanged in mixture with Compound II.

Non-aqueous titration of Compound II in benzene with sodium methoxide, using thymol blue as indicator, showed an equivalent weight of 142. The compound was dissolved in excess standard sodium hydroxide solution and back-titrated with hydrochloric acid, using a Beckmann *p*H meter; at *p*H 7.3, the neutral equivalent was found to be 140, very strong buffering action was apparent in the *p*H region 3–4. The molecular weight was determined, ebulliometrically in anhydrous ether, to be 279–302. This com-

pound readily reduced potassium permanganate to manganous ion in sodium hydroxide solution. From the solution resulting from oxidation in acetone solution could be recovered benzenesulfonate as the *S*-benzylthiuronium derivative. Compound II gave no positive test for the presence of a sulfhydryl group.

The physical properties and analytical composition found for Compound II were suggestive of those listed for *N,N*-bis(benzenesulfonyl)hydroxylamine.[6] The latter, therefore, was synthesized, according to the directions of Koenigs,[6] through interaction of sodium benzenesulfinate and sodium nitrate in hydrochloric acid solution; white crystals were obtained, which melted, alone or in mixture with Compound II, at 115–118° (dec.). The infrared absorption spectra of both samples were identical.

Formation of N,N-bis(benzenesulfonyl)hydroxylamine by treatment with nitric acid of the reaction product of diphenylcadmium and benzenesulfonyl chloride. It was of interest to demonstrate that this hydroxylamine derivative can result from use of an arylcadmium reagent as well as from dialkylcadmiums. To a solution of 3.8 g. (0.02 mole) of benzenesulfonyl chloride in anhydrous ether was added 10 ml. of 2.0*N* diphenylcadmium solution (0.01 mole diphenylcadmium). The precipitated solid was removed, washed with ether, and dried before being mixed at 70° with 100 ml. of water, 7.5 ml. of concd. nitric acid, and 10 ml. of ethyl alcohol. The mixture was stirred for 5 min. before being chilled; seemingly, much of the original product had not dissolved. Next day, the mixture was filtered, the solid was triturated with hot 5% sodium hydroxide solution and filtered; the filtrate was acidified and the precipitated material was removed, dried, and recrystallized from chloroform. The melting point of this sample, alone or in admixture with the authentic hydroxylamine derivative, was 115–117°.

Identity of Compound III [*N,N-bis(p-tolylsulfonyl)-hydroxylamine*]. This substance closely resembled Compound II in physical and chemical properties, and in composition.

Anal. Calcd. for $C_{14}H_{15}NO_2S$: C, 49.35; H, 4.41; N, 4.08; O, 23.41; S, 18.76. Found: C, 49.53; H, 4.60; N, 3.61; O, 23.73; S, 18.56, analyses by Huffman Microchemical Laboratory.

The infrared absorption spectrum of this tolyl derivative was quite similar to that of the lower homolog of established structure; the former, therefore, is formulated as *N,N*-bis-(*p*-tolylsulfonyl)hydroxylamine.

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AUSTIN, TEX.

(6) W. Koenigs, *Ber.*, 11, 615 (1878).

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11-Oxygenated Steroids. XVIII. Wagner-Meerwein Rearrangement of Some 17α-Hydroxysteroids*

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The rearrangements of pregnane-3α,11β,17α,20β-tetrol 3,20-diacetate and 5-pregnene-3β,17α,20β-triol 3,20-diacetate by the action of *p*-toluenesulfonic acid in acetic acid–acetic anhydride solution, to 18-nor-17β-methyl-17-iso-12-pregnene-3α,11β,20β-triol 3,11,20-triacetate and 18-nor-17β-methyl-17-iso-5,12-pregnadiene-3β,20β-diol 3,20-diacetate, respectively are described. Under the same conditions, pregnane-3α,17α,20β-triol-11-one 3,20-diacetate affords the unrearranged 3,17,-20-triacetate. The mechanism is discussed.

Subsequent to the discoveries that the tertiary 17α-hydroxyl group[2] and the 11β-hydroxyl group[3] can be acetylated with acetic anhydride in the presence of an acid catalyst, we had occasion to investigate the possibility of acetylating pregnane-3α,-11β, 17α, 20β-tetrol 3,20-diacetate[4] (I) in an acetic anhydride–acetic acid-*p*-toluenesulfonic acid system at room temperature. We found that two products were produced, II and III, yields of the former averaging about 60% and those of the latter about 10%.

The structure of III was readily apparent. Infrared examination revealed the absence of hydroxyl groups and the presence of intense acetate absorptions. The empirical formula derived from carbon-hydrogen analyses was consistent with the presence of four acetate groups. Treatment of III with excess lithium aluminum hydride afforded the parent tetrol IV,[4] identical with an authentic sample, and acetylation of IV with acetic anhydride in pyridine regenerated I.

The structure of II was considerably more complex. From the infrared absorption spectrum it was possible to decide that there was no hydroxyl present, that there were probably three acetate groups, and possibly a trisubstituted unsaturation. Carbon-hydrogen analyses were in reasonable accord with the formula $C_{27}H_{40}O_6$, which corresponded to three

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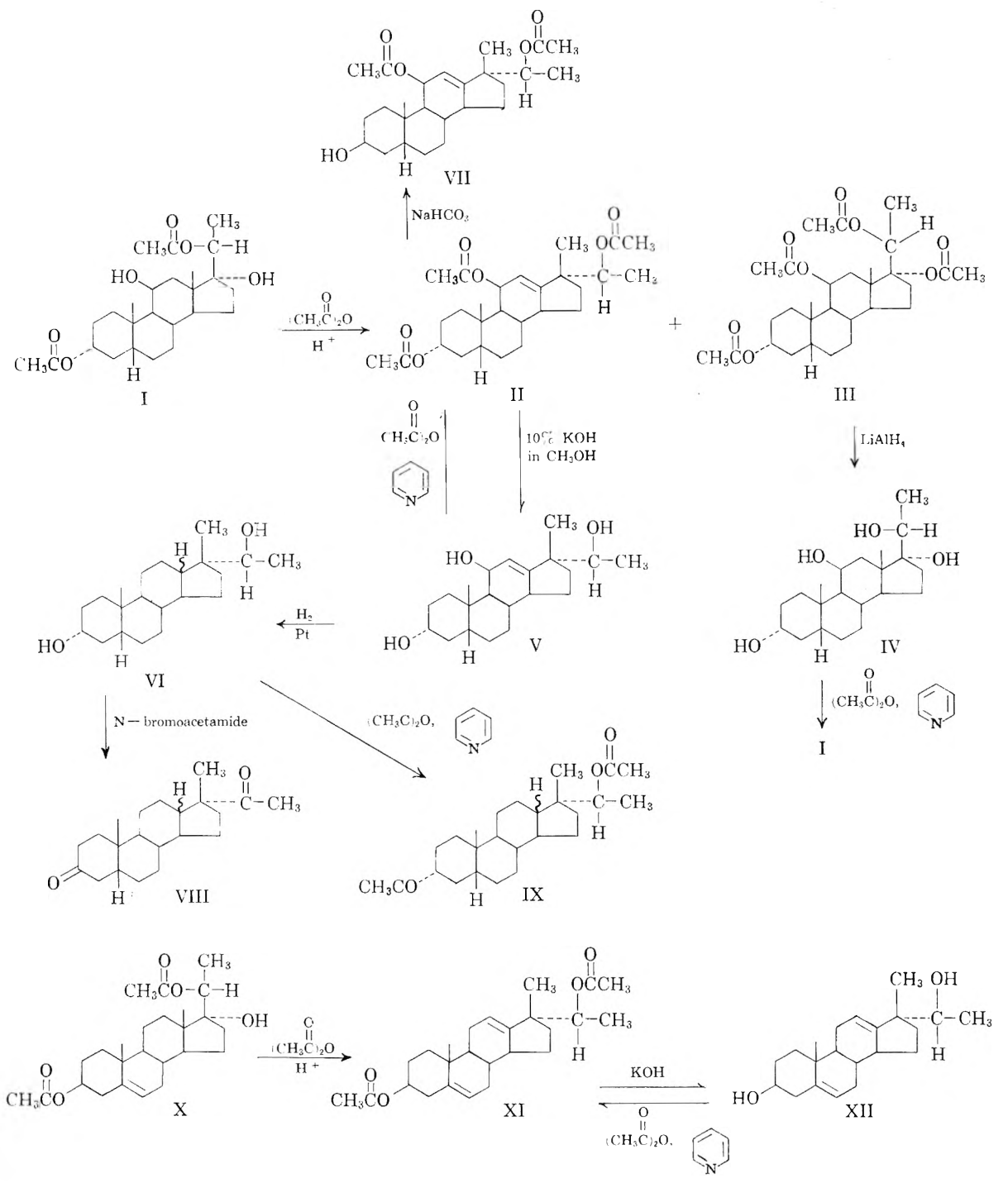

acetate groups being present and to the loss of one hydroxyl (or acetate) with the concomittant formation of a double bond. *All of the acetate groups could be removed by solvolysis with 10% alcoholic potassium hydroxide*, an unsaturated triol (V) resulting thereby. *Acetylation of V with acetic anhydride in pyridine solution at room temperature regenerated II.* From the preceding two observations, it was apparent that disturbances affecting positions 11 and 17 had occurred. This follows from the fact that in I, IV, and all known, similarly hydroxylated pregnanes and pregnenes, the 11β- and 17α-hydroxyl groups resist acetylation in this medium at room temperature, and the 11β- acetate resists hydrolysis by the technique described. Incidentally, it was observed that only one acetate group was removed by hydrolysis of II with sodium bicarbonate, and this was presumed to lead to VII.

Hydrogenation of V in acetic acid solution with Adams' platinum catalyst resulted in the loss of *still another hydroxyl group* as well as saturation of the double bond, the empirical formula of VI corresponding to $C_{21}H_{36}O_2$. The loss of the hydroxyl group was best rationalized by assuming that it was

in a position to be activated toward hydrogenolysis by being allylic to the unsaturation. The presence of only two hydroxyl groups in VI was further illustrated by the formation of an hydroxyl-free diacetate (IX) with acetic anhydride in pyridine and by oxidation to a diketone (VIII) with *N*-bromoacetamide. All of the facts gathered to this point were consistent with the hypothesis that a Wagner-Meerwein type rearrangement, as well as acetylation, occurred when I was treated with the indicated medium. Acid-promoted loss of the 17-hydroxyl group was followed by migration of the methyl group from 13β to 17β and finally by loss of a proton from 12 with resultant formation of a double bond. It was now reasonable to expect that the altered stereochemistry of ring C might reduce hindrance at 11 sufficiently to permit ready hydrolysis of an 11β-acetate and ready reesterification by a mild acetylating medium.[4a] Furthermore, loss of the 11β-hydroxyl group under strong hydrogenating conditions was properly accommodated.

A rearrangement of a similar type has been proposed by Heusler and Wettstein[5] to describe the reaction of 16α, 17α-oxidopregnenolone 3-acetate with formic acid–sulfuric acid. These authors propose that the product which results bears a double bond at 13, but this is not proved. We suggest that the location of this double bond is in doubt, and that 12 is a more likely possibility in the light of our results.

Since migration of a double bond from 13 to 12 might conceivably occur on the platinum employed as a hydrogenation catalyst, it was desirable to test further the assignment of the double bond to 12 in V (and II). It has been reported that nuclear magnetic resonance (NMR) spectra of compounds containing hydrogen atoms attached to carbon bearing a double bond contain a band peculiar to this structure.[6] Since the assignment of the double bond to 12 leads to one such grouping and assignment to 13 affords none, it was hoped that NMR measurement would provide an unequivocal answer. With this end in view we invoked the kind offices of Dr. James N. Shoolery of the Varian Associates, and his measurements of the NMR spectrum of II showed clearly that the double bond is at 12, in accord with the evidence from hydrogenation.

Pregnane-3α, 17α, 20β-triol-11-one 3,20-diacetate had been selected as a substrate for rearrangement in the hope that the reaction would follow the path described for I, and the product, which resulted might then possess a conjugated carbonyl system in ring C, whose presence could be substantiated readily by ultraviolet and infrared measurements. However, no rearrangement was observed under essentially the conditions employed previously with I. Instead, pregnane-3α, 17α, 20β-triol-11-one 3, 17, 20-triacetate was the only product isolated. Its structure was confirmed by hydrolysis with alkali to the triol and reacetylation with acetic anhydride in pyridine solution to the starting material. The failure of the 11-carbonyl compound to rearrange is not peculiar to this series. Beyler and Hoffman[7] observed that 16α, 17α-oxidopregnane-3α-ol-11,20-dione, an analog of the compound studied by Heusler and Wettstein,[5] did not undergo Wagner-Meerwein rearrangement in formic acid–sulfuric acid, but instead gave normal solvolysis of the epoxide.

On the other hand, 5-pregnene-3β, 17α, 20β-triol 3,20-diacetate (X) afforded rearrangement in the anticipated fashion under the conditions described previously. The structure of the resulting product (XI) was inferred from analytical data, the ready solvolysis with alkali of the two acetate groups, reacetylation of XII with acetic anhydride in pyridine to XI, and by analogy with the structure of II.

From the observations reported here, one can propose that stereochemical and/or electronic effects are present which control events occurring at a point two carbon atoms removed from the site of variable substitution.[7a] On the one hand, hydroxyl and hydrogen substituents axial at 11 promote or do not interfere with migration of the axial 13β-methyl group, while 11-carbonyl inhibits or does not promote rearrangement. The forces influencing the reaction might be considered as (*a*) the positive push towards 17 provided by steric repulsion between an axial substituent at 11 and the angular methyl group or (*b*) the inhibiting, electron-withdrawing, inductive effect of the 11-carbonyl which reduces electron availability at the 13-methyl with resultant decreased tendency toward migration to a positive center at 17.

Since the completion of these experiments, preliminary reports have appeared[8,9] which describe a closely related Wagner-Meerwein rearrangement in which 17α, 21-oxido-4-pregnen-11β-ol-3,20-dione rearranges into 13α, 21-oxido-17β-methyl-18-nor-17-iso-4-pregnen-11β-ol-3,20-dione upon acid treatment.

(4a) It is possible that inversion may have occurred at 11 under the strongly acid conditions of the rearrangement and hence it is not permissible to rule out the α-configuration for the 11-acetate.

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EXPERIMENTAL[10]

Pregnane-3α,11β,17α,20β-tetrol 3,20-diacetate (I). A solution of 2.00 g. of pregnane-3α,11β,17α,20β-tetrol[4] in 15 ml. of acetic anhydride and 50 ml. of pyridine was allowed to stand at room temperature overnight. The solution was diluted with water and the precipitate which formed following the completion of hydrolysis of the acetic anhydride was removed by filtration. The dried solid was taken up in xylene, boiled to remove traces of water, and concentrated to dryness *in vacuo*. The resulting oil was crystallized from xylene from which there resulted 2.07 g. of I, m.p. 181–184°. Recrystallization from ether-hexane raised the m.p. to 184–185°, λ_{max}^{Nujol} 2.82 μ (OH), 5.76 μ (acetate carbonyl) and 8.10 μ (C—O—C of acetate), $[\alpha]_D^{25}$ +70° ($CHCl_3$).

Anal. Calcd. for $C_{25}H_{40}O_6$: C, 68.77; H, 9.24. Found: C, 68.58; H, 9.43.

Solvolysis of I with 10% alcoholic potassium hydroxide. A solution of 400 mg. of I in 10 ml. of 10% methanolic potassium hydroxide was refluxed for 3 hr. Crystallization of the product began after 5 min. of reflux. The reaction mixture was cooled to room temperature and diluted with water. Filtration of the resulting precipitate afforded 260 mg. of pregnane-3α,11β,17α,20β-tetrol, m.p. 278–282°, identical in all respects with that from which I was prepared.

Acetylation of I to yield II and III. To a solution of 15.15 g. of I in 134 ml. of glacial acetic acid was added 134 ml. of acetic anhydride and 2.05 g. of *p*-toluenesulfonic acid. The reaction mixture was maintained at 25° overnight and was then diluted with water. Following hydrolysis of the unreacted acetic anhydride, the reaction mixture was extracted with methylene chloride and the extracts were washed to neutrality with water. The dried extracts were concentrated and crystallized from aqueous methanol. There resulted 14.63 g., m.p. 109–122°. Chromatography of this solid on 120 g. of Florisil, prepared with hexane, and elution with mixtures of hexane and ether afforded a series of crystalline fractions. From 1% and 5% ether-in-hexane there resulted 9.60 g. of crystals, m.p. 116–124.5°. Recrystallization of these from aqueous methanol gave 8.63 g. of II, as needles, m.p. 122–124°. Additional recrystallization raised the m.p. to 124–125°, $[\alpha]_D^{25}$ +83° ($CHCl_3$), λ_{max}^{Nujol} 5.79 μ (acetate carbonyl) and 8.00 μ (C—O—C of acetate).

Anal. Calcd. for $C_{27}H_{40}O_6$: C, 70.40; H, 8.74. Found: C, 70.18; H, 9.12.

From 10% and 20% ether-in-hexane and 100% ether, there resulted 2.64 g. of solid melting about 115°, resolidifying, and remelting as high as 165°. Recrystallization from heptane afforded 1.62 g. of III, m.p. 170–179°. A portion of this solid was rechromatographed over Florisil in the way described previously and the 20% ether-in-hexane fractions were combined and crystallized from heptane giving III, m.p. 177–179°, $[\alpha]_D^{25}$ +56° ($CHCl_3$), λ_{max}^{Nujol} 5.76 and 5.79 μ (acetate carbonyls), 8.02 and 8.14 μ (C—O—C of acetate).

Anal. Calcd. for $C_{29}H_{44}O_6$: C, 66.90; H, 8.52. Found: C, 66.70; H, 8.30.

Partial hydrolysis of II. A solution of 460 mg. of II in 17 ml. of methanol to which had been added a solution of 250 mg. of sodium bicarbonate in 3 ml. of water was refluxed for 2 hr. Water was added to the cooled solution and the resulting precipitate was removed by filtration. There was isolated 350 mg. of fine needles of VII, m.p. 81.5–86°. Recrystallization from aqueous methanol afforded VII, m.p. 85–88°, $[\alpha]_D^{25}$ +59° ($CHCl_3$), $\lambda_{max}^{CS_2}$ 2.94 μ (OH), 5.77 μ (acetate carbonyl), 8.06 μ (C—O—C of acetate). Integration of the acetate carbonyl band showed that two acetate groups were present.

Anal. Calcd. for $C_{25}H_{38}O_5.H_2O$: C, 68.77; H, 9.24. Found: C, 68.81; H, 9.75.

Acetylation of VII with acetic anhydride in pyridine regenerated II.

Solvolysis of II. A solution of 5.00 g. of II in 250 ml. of methanol containing 25 g. of potassium hydroxide was refluxed for 3 hr. The reaction mixture was cooled to 5°, and neutralized with 4*N* hydrochloric acid. The precipitated potassium chloride was removed by filtration, and the filtrate was concentrated with gradual addition of water. Long needles of V precipitated and were recovered by filtration. There resulted 3.48 g. of V, m.p. 158–160°, $[\alpha]_D^{25}$ +14° (dioxane), λ_{max}^{Nujol} 3.06 μ (OH).

Anal. Calcd. for $C_{21}H_{34}O_5.H_2O$: C, 71.55; H, 10.30. Found: C, 71.83; H, 10.03.

Acetylation of V to give II. A solution of 200 mg. of V in 4 ml. of pyridine and 2 ml. of acetic anhydride was allowed to stand overnight at room temperature. The solution was diluted with water and extracted with methylene chloride. The extracts were washed with water, dried, and concentrated. The residue was recrystallized from methanol-water. There resulted 190 mg. of II, m.p. 123–124°, which did not depress the melting point of the product (II) of acid catalyzed acetylation of I. Infrared spectra of the two samples were identical.

Reduction of V to VI. A solution of 1.5 g. of V in 100 ml. of glacial acetic acid containing 1.5 g. of Adams platinum oxide catalyst was shaken under 1 atm. of hydrogen at room temperature until hydrogen uptake ceased (usually 24 hr.). The catalyst was removed by filtration and the filtrate *in vacuo* to a residue. A solution of the residue in methylene chloride was washed with water, dried, and concentrated with gradual addition of hexane. There precipitated then a total of 800 mg. of VI, m.p. 177–181°. Further purification by chromatography over Florisil raised the m.p. to 185–187°, $[\alpha]_D^{25}$ +1.3° (dioxane), λ_{max}^{Nujol} 3.10 μ (OH). Quantitative estimation of hydroxyl by integration indicated that two hydroxyl groups were present.

Anal. Calcd. for $C_{21}H_{36}O_2$: C, 78.67; H, 11.32. Found: C, 78.56; H, 11.27.

Acetylation of VI to IX. A solution of 200 mg. of VI in 4 ml. of pyridine was treated with 2 ml. of acetic anhydride overnight at room temperature. The reaction mixture was hydrolyzed and extracted as before, and the total residue was chromatographed on Florisil. Elution with hexane afforded 130 mg. of IX, crystallized from aqueous methanol, m.p. 74–76°. Two additional crystallizations from aqueous acetone gave IX, m.p. 78–80°, $[\alpha]_D^{25}$ +26° (dioxane), λ_{max}^{Nujo} 5.76 μ (acetate carbonyl) and 8.06 μ (C—O—C of acetate). Integration of the carbonyl band indicated that two acetate groups were present.

Anal. Calcd. for $C_{25}H_{40}O_4$: C, 74.21; H, 9.97. Found: C, 74.56; H, 10.06.

Oxidation of VI to VIII. A solution of 340 mg. of VI in 50 ml. of acetone and 10 ml. of water was treated with 840 mg. of N-bromoacetamide at room temperature and the reaction mixture was placed in the icebox. After 3 hr., the reaction mixture was diluted with aqueous sodium sulfite until the red-orange color disappeared. It was then diluted with water and extracted with methylene chloride. The extracts were washed with water, dried, and concentrated, and the residue was crystallized from aqueous methanol. There resulted 250 mg. of VIII, m.p. 80–83° which, on further recrystallization, melted at 82–83°, $[\alpha]_D^{25}$ −4.3° (dioxane), λ_{max}^{Nujol} 5.87 μ (carbonyl).

Anal. Calcd. for $C_{21}H_{32}O_2$: C, 79.70; H, 10.19. Found: C, 79.62; H, 10.21.

Lithium aluminum hydride reduction of III to IV. A solution of 85 mg. of III in 100 ml. of tetrahydrofuran was refluxed overnight with 200 mg. of lithium aluminum hydride. A few drops of acetone were added to destroy the excess reagent and then water was added. The precipitated solids were removed by filtration, washed thoroughly with ether, and the filtrate was extracted with ether. The com-

(10) All melting points are corrected. Analyses and optical data were obtained by the Physical Chemistry Department of Schering Corp. and by Galbraith Laboratories, Knoxville, Tenn. Dr. Jo-Yun Chen, Miss Cecilia Vitiello, and Messrs. Milton Yudis and Edward Townley interpreted the infrared spectra.

bined extracts were washed with water, dried, concentrated, and crystallized from methylene chloride–hexane. There resulted 40 mg. of IV, m.p. 278–282°, with an infrared spectrum identical with that of an authentic sample.[4]

Acetylation of IV with acetic anhydride in pyridine according to the procedure noted earlier gave I.

Preparation of 5-pregnene-3β,17α,20β-triol. A solution of 10 g. of 17α-hydroxypregnenolone 3-acetate in 1500 ml. of methanol was treated with a solution of 10 g. of sodium borohydride in 100 ml. of water. External cooling was applied and the reducing agent was added gradually to reduce the vigor of the reaction. The reaction mixture was allowed to stand overnight at room temperature and was then concentrated to 600 ml. on the steam bath. About 200 ml. of water was added to induce crystallization. The resulting solid weighed 10.4 g. and did not melt below 280°. From the weight and melting point it was surmised that the product was present as a borate ester of some kind. The solid was boiled with 400 ml. of water for 3 hr. and allowed to stand overnight. It was then removed by filtration and recrystallized from methanol-water. There resulted 7.0 g. of 5-pregnene-3β,17α,20β-triol, m.p. 217–223°. A sample recrystallized for analysis, melted at 220–223°, $[\alpha]_D^{25}$ −108° ($CHCl_3$), λ_{max}^{Nujol} 3.2 μ (OH). The analytical sample was dried *in vacuo* at 110°C. for 24 hr.

Anal. Calcd. for $C_{21}H_{34}O_3$: C, 75.40; H, 10.25. Found: C, 75.56; H, 10.29.

5-Pregnene-3β,17α,20β-triol 3,20-diacetate (X). Acetylation of 5-pregnene-3β,17α,20β-triol with acetic anhydride in pyridine solution according to procedures given previously afforded the 3,20-diacetate. Recrystallization from methylene chloride–hexane gave the desired product, m.p. 155–157°, $[\alpha]_D^{25}$ −33° ($CHCl_3$).

Anal. Calcd. for $C_{25}H_{38}O_5$: C, 71.74; H, 9.15. Found: C, 71.73; H, 9.09.

Acid catalyzed acetylation and rearrangement of X to XI. To a solution of 0.84 g. of diacetate in 4 ml. of acetic acid and 4 ml. of acetic anhydride was added 0.12 g. of *p*-toluenesulfonic acid. The reaction mixture was allowed to stand overnight at room temperature, whereupon 50 ml. of ice water was added. The resulting gray solid was removed by filtration, washed with water, dried (yield 0.78 g., m.p. 110–116°), and chromatographed over Florisil (0.68 g. chromatographed on 10 g. of Florisil). The desired product was eluted with 5% ether-in-hexane. A total of 0.40 g., m.p. 123–130° was collected in eight fractions. Recrystallization, effected from acetone-water, gave 0.26 g. of rearranged product XI, m.p. 131–132°, $[\alpha]_D^{25}$ −64° ($CHCl_3$), λ_{max}^{Nujol} 5.75 μ (acerate carbonyl) and 8.10 μ (C—O—C of acetate).

Anal. Calcd. for $C_{25}H_{36}O_4.C_3H_6O$: C, 73.32; H, 9.23. Found: C, 73.61; H, 9.52.

Solvolysis of XI to XII. A solution containing 0.40 g. of rearranged diacetate from the preceding experiment in 10 ml. of 10% methanolic potassium hydroxide was refluxed for 3 hr. The solution was diluted with water and neutralized with 4*N* hydrochloric acid. The resulting precipitate was removed by filtration and recrystallized from methanol-water. There resulted 0.27 g. of XII, m.p. 139–140°. Further recrystallization did not alter the m.p., $[\alpha]_D^{25}$ −213° ($CHCl_3$), λ_{max}^{Nujol} 3.02 μ (OH).

Anal. Calcd. for $C_{21}H_{32}O_2$: C, 79.70; H, 10.19. Found: C, 79.80; H, 10.36.

Acetylation of XII to XI. Acetylation of the product of the previous experiment in the usual way afforded the previously described diacetate XI, m.p. 128–130° in quantitative yield. The infrared spectrum matched that of a sample obtained from acid-catalyzed acetylation of X.

Pregnane-3α,17α,20β-triol-11-one. This compound was prepared according to Oliveto and Hershberg[11] with the exception that the reaction was stopped after 15 min. at room temperature. From 1 g. of pregnane-3α,17α-diol-11,20-dione with 100 ml. of *t*-butyl alcohol, 1 g. of sodium borohydride, and 25 ml. of water there resulted 0.53 g. of triolone, m.p. 219–222°.

Pregnane-3α,17α,20β-triol-11-one 3,20-diacetate. This compound was prepared by acetylation in the usual way with acetic anhydride in pyridine.[11] The constants were in agreement with the published values.

Pregnane-3α,17α,20β-triol-11-one 3,17,20-triacetate. A suspension of 0.15 g. of the 3,20-diacetate, described previously, in 1.4 ml. of acetic acid and 1.4 ml. of acetic anhydride containing 0.02 g. of *p*-toluenesulfonic acid was allowed to stand overnight at room temperature. All the starting material had dissolved in this interval. Twenty-five ml. of ice water was added and the oily precipitate was extracted with methylene chloride. The extracts were washed to neutrality with water, dried, and concentrated. The residue, upon crystallization from ether-hexane, gave 0.08 g. of large, rectangular prisms, m.p. 99–105° dec., $[\alpha]_D^{25}$ +50° (dioxane), λ_{max}^{Nujol} 5.72 and 5.79 μ (acetate carbonyl), 5.85 μ (11-carbonyl) and 8.08 μ (C—O—C of acetate).

Anal. Calcd. for $C_{27}H_{40}O_7$: C, 68.04; H, 8.46. Found: C, 67.65; H, 8.87.

This steroid was the only crystalline product isolated and identified though the quantities of catalyst and solvents were increased separately, and together, as much as fourfold, and crystallization mother liquors were chromatographed.

Alkaline hydrolysis of pregnane-3α,17α,20β-triol-11-one 3,17,20-triacetate. A solution of 0.40 g. of triacetate in 10 ml. of 10% methanolic potassium hydroxide was refluxed for 3 hr. The reaction mixture was diluted with water, neutralized with 4*N* hydrochloric acid and extracted with methylene chloride. The extracts were washed with water, dried, concentrated, and the residue was crystallized from acetone-hexane. There resulted 0.14 g. of pregnane-3α,17α,-20β-triol-11-one, m.p. 213–217°, whose infrared spectrum was identical with that of an authentic sample.[11]

Acetylation of the triolone from this experiment with acetic anhydride in pyridine solution in the usual way afforded pregnane-3α,17α,20β-triol-11-one 3,20-diacetate, identical in infrared spectrum and melting point with an authentic sample.

Acknowledgment. We wish to acknowledge helpful discussions with Drs. A. Nussbaum, D. Gould, and Mr. E. L. Shapiro of these laboratories, and Dr. J. Meinwald of Cornell University.

BLOOMFIELD, N. J.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

Decomposition of Allylanilines in the Presence of Zinc Chloride*

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In the decomposition at elevated temperatures of *N*-allylaniline in the presence of zinc chloride these products were isolated: *o*-allylaniline, *p*-propylaniline, hydrogen, propylene, tar. Comparably, *N*-cinnamylaniline and zinc chloride gave rise to *o*-cinnamylaniline, *p*-cinnamylaniline, 2-phenylquinoline, hydrogen, tar. A mechanism for these reactions and related Hofmann rearrangements is proposed. Several new compounds and new syntheses of old compounds are included.

Hofmann, in his classic study[2] of the pyrolysis of methylaniline hydrochloride, established that rearrangement into *p*-toluidine hydrochloride occurred on heating for a day at 350°. To explain this result he proposed thermal dissociation into aniline and methyl chloride, followed by their reaction to yield toluidine; but he sensed that any free methyl chloride should also give rise to tertiary and quaternary ammonium salts. In 1924, Howard and Derick[3] confirmed the essential accuracy of Hofmann's work. They reported rearrangement to begin at about the same temperature (300°) that quaternary salt formation was noticed.

Reilly and Hickinbottom[4] were engaged in a similar study in 1920, after which (1927–1935) a succession of papers appeared from Hickinbottom's laboratory.[5] In this work it was established that hydrobromides of *N*-alkylanilines may undergo thermal rearrangement to the *para* isomer accompanied by rearrangement of the wandering radical (as *N*-isobutylaniline to *p*-*t*-butylaniline), that olefins may accompany this change (as *N*-*n*-butylaniline to 2-butene), and that *N*-alkylanilines isomerize at elevated temperatures in the presence of metal halides as $ZnBr_2$ or $CoBr_2$ without rearrangement of the wandering radical (as *N*-isobutylaniline to *p*-isobutylaniline).

To gain further insight into this reaction *N*-allylaniline and *N*-cinnamylaniline were selected for study. Carnahan and Hurd[6] investigated the pyrolysis of *N*-allylaniline, finding as products aniline, propylene, and tar, but they used no zinc chloride or other acid during the heating.

In the present work it was found that a refluxing mixture of *N*-allylaniline and zinc chloride in xylene gave rise to *o*-allylaniline in 42% yield. No reaction occurred in refluxing benzene. At temperatures of 200–250° (no solvent) the products identified were aniline (35% yield), *p*-propylaniline (5-6% yield), gas (0.55 mole per mole of amine) which was 95% hydrogen and 3% propylene, and tarry products. Quinoline was not noticed.

N-Cinnamylaniline was treated similarly. Heating a mixture of it with zinc chloride and bromobenzene at 100° caused no change, but heating at 150° for 0.5 hr. yielded aniline, *o*-cinnamylaniline, 2-phenylquinoline, and a residue. It is noteworthy that no inversion of the cinnamyl group occurred in this process. A simple but apparently unreliable explanation for the formation of 2-phenylquinoline is cyclization of the *o*-cinnamylaniline, followed by dehydrogenation. Actually, however, no phenylquinoline was observed in the products from *o*-cinnamylaniline (150°, $ZnCl_2$, C_6H_5Br). Partial isomerization to *p*-cinnamylaniline, however, may have taken place.

When *N*-cinnamylaniline and zinc chloride were heated at 100° in toluene, aniline and 2-phenylquinoline were formed but no *o*-cinnamylaniline. About half of the *N*-cinnamylaniline was unchanged.

The major product from more drastic heating of zinc chloride and *N*-cinnamylaniline up to 250° was a red tar. Gas evolution, chiefly hydrogen, was brisk at 125–180°. Small amounts of aniline and 2-phenylquinoline were separable from the tar, but there was no *p*-(3-phenylpropyl)aniline. The latter would be analogous to *p*-propylaniline from *N*-allylaniline.

It will be noticed that our results resembled Hickinbottom's in that there was no isomerization or inversion of the wandering cinnamyl radical; thus, *o*- and *p*-cinnamylaniline from *N*-cinnamylaniline. This eliminates from consideration the intramolecular mechanism that is analogous to that which applies for the pyrolytic rearrangement of phenyl cinnamyl ether into *o*-(1-phenylallyl)phenol, and such a mechanism also is made unreasonable by two other facts. One fact is that it would not apply to the rearrangement of the saturated, wandering alkyl groups such as isobutyl in *N*-isobutylaniline. Secondly, a concerted mechanism of this type requires activation of the ortho nuclear position. This does obtain in the allyl ethers (I) but it cannot occur in the amine salts (II) because no

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* This paper is a contribution in honor of Lyndon F. Small, former Editor of the Journal.

(1) Standard Oil Company (Ind.) Fellow, 1948–1949.

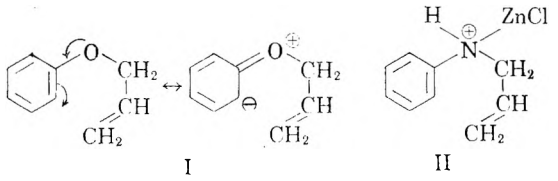
(2) A. W. Hofmann and C. A. Martius, *Ber.*, **4**, 742 (1871); A. W. Hofmann, *Ber.*, **5**, 720 (1872).

(3) J. W. Howard and C. G. Derick, *J. Am. Chem. Soc.*, **46**, 166 (1924).

(4) J. Reilly and W. A. Hickinbottom, *J. Chem. Soc.*, **117**, 128 (1920).

(5) W. A. Hickinbottom and collaborators, *J. Chem. Soc.*, 64 (1927); 1558, 1566 (1930); 1281 (1931); 1700 (1934).

(6) F. L. Carnahan and C. D. Hurd, *J. Am. Chem. Soc.*, **52**, 4586 (1930).



I II

unshared electrons are available on the nitrogen to contribute to the resonance. Also, it is well known that a positive group deactivates the ortho and para positions.

Hickinbottom[5] postulated a carbonium intermediate to explain the rearrangement of *N*-alkylanilines in the presence of metal halides, followed "by reaction of the positive alkyl 'ion' with the aniline nucleus reacting in the quinonoid form." To account for retention of structure of the wandering group he stated that "the expelled 'ion', in general, suffers no internal rearrangement, either on account of the stabilizing effect of the metal salt or because its reaction with the nucleus is catalyzed by the metal salt." This hypothesis would seem adequate to care for the rearrangement of *N*-isobutylaniline hydrobromide into *p*-*t*-butylaniline hydrobromide in view of what is known today of the facile hydrogen transfer found in the change of *i*-butyl carbonium into *t*-butyl carbonium. The latter either could alkylate the aniline nucleus or change into isobutylene by loss of a proton. It seems quite improbable, however, that a metallic salt such as zinc chloride should stabilize *i*-butyl carbonium against rearrangement into *t*-butyl. Hence, some other mechanism than the one proposed by Hickinbottom should be advanced to explain the rearrangements, in the presence of metal salts, which involve no isomerization of the wandering group.

The following mechanism is suggested. All previous workers have recognized that the rearrangement involves the salt and not the free amine, but the evidence shows that it makes a difference if the salt involves a strong acid such as hydrochloric (IIIa) or a mild Lewis acid such as zinc chloride (IIIb). It has been recognized also that the N-R

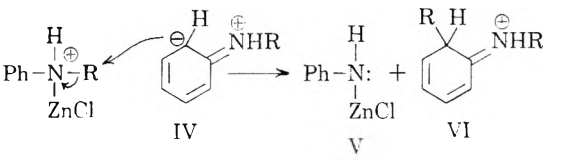
IIIa IIIb

bond in III is weaker than in the parent amine. Hofmann proposed dissociation into alkyl halide and Hickinbottom postulated cleavage into alkyl carbonium ion. In our opinion the bond is indeed weakened but not necessarily broken. We suggest that whereas the N-R bond in IIIa may be broken to yield a carbonium ion at sufficiently elevated temperatures, that in IIIb is not broken. Thus, in IIIa there are two competing dissociation reactions at elevated temperatures: $H^+ + C_6H_5NHR \rightleftarrows$ IIIa $\rightleftarrows R^+ + C_6H_5NH_2$. In IIIb, however, there is but one or, at least, the second is greatly minimized:

$$ClZn^+ + C_6H_5NHR \rightleftarrows \text{IIIb}.$$

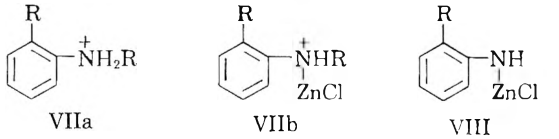
Three features about this last equation stand out: (1) a weakened N-R bond in IIIb. (2) a nucleus in IIIb that is resistant to substitution because of low electron density at ortho and para positions. (3) a high electron density at ortho and para positions in the free amine, C_6H_5NHR (see IV).

Finally, it is proposed that the basis of the rearrangement is attack of the weakened N-R bond of IIIb by the negative charge of IV:



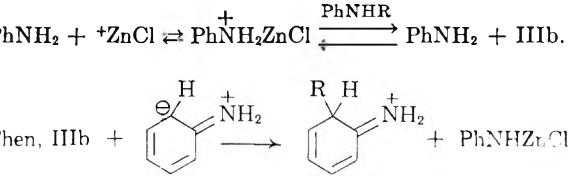
IV V VI

This mechanism calls for no separation of an alkyl carbonium ion, hence R would be attracted to the *ortho* or *para* position without inversion or isomerization. V is the precursor of aniline. VI tautomerizes to the substituted ammonium ion VIIa. Then: VIIa + V → $C_6H_5NH_2$ + VIIb, after which VIIb + IV → VIII (analogous to V) + VI. Eventually, the R groups become transferred from nitrogen to carbon.



VIIa VIIb VIII

This interpretation portrays VIII as coming from the original amine *via* VI and VII but one may also regard it as coming from aniline or V. To this end,



Insufficient facts are at hand to offer a sound explanation for the formation of 2-phenylquinoline, especially in view of its non-formation from *o*-cinnamylaniline.

Another compound requiring explanation is the *p*-propylaniline from *N*-allylaniline at 200–250°. One may make the reasonable assumption that *p*-allylaniline is formed first, and that it becomes reduced to *p*-*n*-propylaniline by hydrogen abstraction from the other products which ultimately appear as tar. The evolution of hydrogen supports this viewpoint. It does not seem likely that propylene would be the precursor since then the product should be *p*-isopropylaniline. Hickinbottom[7] has

(7) W. A. Hickinbottom, *J. Chem. Soc.*, 2396 (1932); 319, 1981 (1934); 1279 (1935).

reported that styrene, butadiene, and other olefins act towards aniline salts in this way.

Several new compounds were made and new syntheses developed in the course of this work. *N*-Allylaniline, formerly made by reaction of sodioformanilide[8] or sodioacetanilide[6] with allyl bromide or iodide, was prepared smoothly by reaction of allyl chloride and two parts of aniline.

An independent synthesis of *p*-propylaniline was developed from allylbenzene by hydrogenation, nitration to *p*-nitropropylbenzene, and reduction of the latter. Its derivative with phenyl isothiocyanate was prepared and found to melt at 119–120°, not 127–128° as was reported by Hickinbottom and Waine.[9] In a personal communication to us from Professor Hickinbottom, he accepts the lower value and believes that the value of 127–128° may have been an error in copying (for 117–118°).

o-Allylaniline and *p*-allylaniline, both new compounds, were made from allylbenzene by nitration to a separable mixture of *o*- and *p*-allylnitrobenzene. Reduction of these compounds to *o*- and *p*-allylaniline was by use of ferrous sulfate, boiling water, and ammonium hydroxide which was added gradually. Several solid derivatives of these amines were prepared. The structure of each allylaniline was proved by changing it to the corresponding, known allylphenol.

The synthesis of *o*-cinnamylaniline has not been previously described. It will be recalled that the synthesis selected for *o*-allylaniline started with nitration of allylbenzene, but a comparable synthesis from cinnamylbenzene would run the risk of nitration in the wrong aromatic nucleus. Hence, hydrocinnamic acid was taken as the starting point. After nitration to *o*-nitrohydrocinnamic acid, it was changed to the acyl chloride and then to ω-(*o*-nitrophenyl)propiophenone. The para isomer was also prepared in an identical manner.

These two ketones were prepared also from ω-phenylpropiophenone, but the separation of isomers was tedious and there was no improvement in the quality of the products.

The two nitro ketones were reduced to the corresponding nitro alcohols by use of aluminum isopropoxide, after which they were dehydrated to the *o*- and *p*-cinnamylnitrobenzenes. Ferrous sulfate again proved to be an efficient reducing agent for the nitro group without disturbing the olefinic group. In this way, *o*- and *p*-cinnamylaniline were prepared. Certain acyl derivatives of these amines were made for purposes of characterization.

EXPERIMENTAL

Preparation of reagents.

N-Allylaniline from allyl chloride. A mixture of 666 ml. of aniline and 296 g. of allyl chloride (some evolution of heat) was kept for 3 days at 25°, 8 hr. at 100°, then was cooled overnight. The solid mass of aniline hydrochloride was broken up, mixed with ether, collected, and rinsed with ether; yield 393 g., m.p. 192–193° dec. Titration with standard sodium hydroxide (phenolphthalein) demonstrated an equivalent weight of 127.5, 128.5 as compared to the calculated 129.6.

The filtrates were combined, washed twice with dilute sodium hydroxide, water, then dried (Na_2SO_4) and distilled. Diminished pressure was employed after the ether was removed, and these fractions were collected: (1) forerun, 202 g. (2) 88–96° (8 mm.), 232.5 g. (3) residue, 73 g. The residue, on distillation, yielded 15 g. of *N,N*-diallylaniline, b.p. 102–103.5° (8 mm.), n_D^{24} 1.5558. Carnahan and Hurd[6] reported b.p. 123° (18 mm.), n_D^{23} 1.5556.

Fraction 2 was redistilled. A 16-g. forerun was discarded, then 170 g. of *N*-allylaniline was collected at 93–95° (7 mm.), n_D^{20} 1.5636.

N-Cinnamylaniline. This compound was prepared by reaction of freshly distilled aniline in ether solution with freshly prepared cinamyl bromide, following the method of von Braun.[10] The fraction taken boiled at 159–160° at 1.2 mm.

N,N-Diallylanilinium picrate. Equivalent amounts of the amine and picric acid were mixed, both in benzene solution. Yellow crystals resulted which were collected and recrystallized from benzene; m.p. 122–122.8°.

Anal. Calcd. for $C_{18}H_{18}N_4O_7$: C, 53.74; H, 4.49. Found: C, 53.80; H, 4.50.

N-Allylaniline, on the other hand, formed no crystalline picrate when either benzene or ethanol were used as solvents.

o- and p-Nitroallylbenzenes. A nitrating solution was prepared of 58.5 ml. of fuming nitric acid (*d.* 1.5), 60 ml. of glacial acetic acid, and 47.5 ml. of acetic anhydride. The cold solution was added dropwise during 135 min. to a stirred solution of 110 g. of allylbenzene in 500 ml. of acetic anhydride. Temperature was maintained at 5–10° by cooling with an ice bath. The mixture then was poured onto 2.5 l. of ice, and after warming to room temperature and saturating with salt, the mixture was extracted with ether. Processing included ether extraction, washing, drying, distilling. After removing unreacted allylbenzene (35 g.), the nitro derivatives were collected at 94–105° (2 to 3 mm.). Redistillation gave a 29.5-g. fraction of *o*-nitroallylbenzene at 82–84° (1 mm.), n_D^{20} 1.5490, d_4^{20} 1.115.

Anal. Calcd. for $C_9H_9NO_2$: N, 8.58. Found: N, 8.55.

The fraction of *p*-nitroallylbenzene boiled at 89–94° at 1 mm. (5.2 g.). A center cut gave these constants: n_D^{20} 1.5532, d_4^{20} 1.112.

Anal. Calcd. for $C_9H_9NO_2$: N, 8.58. Found: N, 8.65.

Further evidence that this was *p*-nitroallylbenzene was its ready decolorization of bromine (in CCl_4), and by its oxidation to *p*-nitrobenzoic acid, m.p. 230–232°, with warm potassium permanganate solution.

o-Allylaniline. A solution of 286 g. of ferrous sulfate heptahydrate in 700 g. of water was brought to the boiling point and 23.7 g. of *o*-nitroallylbenzene was added. Then 200 ml. of concentrated ammonium hydroxide was added in small portions during 4.5 hr. Refluxing was maintained throughout. The mixture was filtered hot, and the precipitate and filtrate, after cooling, were washed thoroughly with ether. The washings were collected and extracted with dilute hydrochloric acid leaving 2.7 g. of original *o*-nitroallylbenzene. The acid extracts were washed once with ether, made alkaline, and extracted with ether. The extracts were combined, washed with water, dried, and the solvent distilled. The residue was fractionated. The *o*-allylaniline (10.6 g.) boiled at 99–100° at 8 mm ; n_D^{20} 1.5661, d_4^{20} 0.982.

Anal. Calcd. for $C_9H_{11}N$: N, 10.51. Found: N, 10.36.

Benzoylation, using benzoyl chloride and pyridine at 100° for 30 min., yielded *o*-allylbenzanilide, m.p. 122–122.5°.

(8) F. B. Dains, R. Brewster, J. Blair, and W. Thompson, *J. Am. Chem. Soc.*, 44, 2637 (1922).

(9) W. Hickinbottom and A. C. Waine, *J. Chem. Soc.*, 1930, 1558.

(10) J. von Braun and L. Tauber, *Ann.*, 458, 102 (1927).

The reported m.p. is 123–124°.[11] The following two new derivatives were prepared also.

o-Allylbenzenesulfonanilide. A mixture of 1.3 g. of *o*-allylaniline, 1.76 g. of benzenesulfonyl chloride, and 20 ml. of 10% sodium hydroxide was shaken vigorously for 10 min. and kept overnight. The mixture was diluted with water and washed with ether. The alkaline layer was acidified, warmed on the steam bath, cooled, and a poor yield of precipitate formed which was collected on the filter. The product was recrystallized from ethanol-water; m.p. 83.5–84°.

Anal. Calcd. for $C_{15}H_{15}NO_2S$: C, 65.90; H, 5.53. Found: C, 65.78; H, 5.64.

N-o-Allylphenyl-N'-phenylthiourea. This compound was prepared in good yield by addition of the amine to phenyl isothiocyanate. It was purified by crystallizations from ethanol, and melted at 115.2–115.4°.

Anol. Calcd. for $C_{16}H_{16}N_2S$: C, 71.60; H, 6.01. Found: C, 71.02; H, 5.89.

o-Allylphenol. A solution of 2.7 g. of *o*-allylaniline in 200 ml. of 4% aqueous sulfuric acid was prepared and chilled to −1°. A solution of 1.4 g. of sodium nitrite in 10 ml. of water was added slowly and with stirring. When addition was complete, a small amount of urea was added and the solution was gradually warmed to 25°. This dark solution was steam-distilled, the 700 ml. of distillate was extracted with ether, and the extract was washed several times with 10% aqueous sodium hydroxide solution. The alkaline extracts were washed once with ether, acidified with mineral acid, and extracted with ether. The ether solution was washed once with water, dried, and freed of solvent, and the residue was distilled *in vacuo*. The main fraction (0.9 g.) boiled at 100–105° at 11–12 mm. A forerun of 1.1 g. of material resembling allylbenzene was collected.

Reaction of this *o*-allylphenol with phenyl isocyanate, followed by several crystallizations from ligroin, yielded a derivative of m.p. 104.5–105°. For *o*-allylphenyl phenylcarbamate, Claisen and Eisleb[12] reported the m.p. of 106–106.5°.

p-Allylaniline. This reduction of *p*-nitroallylbenzene (5.1 g.) with ammoniacal ferrous sulfate followed the general procedure given for the *ortho* isomer, except that a steam distillation step was introduced rather than filtration to separate the product from the iron compounds. The yield of *p*-allylaniline was 1.95 g.; b.p. 98–102° at 15 mm.; n_D^{20} 1.5668, d_4^{2c} 0.975.

Anal. Calcd. for $C_9H_{11}N$: N, 10.53. Found: N, 10.81.

These three new derivatives were prepared from *p*-allylaniline by reaction respectively, with benzoyl chloride and pyridine, with acetic anhydride, and with phenyl isothiocyanate: *p*-allylbenzanilide, m.p. 136–137° after crystallization from alcohol; *p*-allylacetanilide, m.p. 91–92°, frxm alcohol and water; N-*p*-allylphenyl-N'-phenylthiourea, m.p. 115.9–116° from alcohol.

Anal. of *p*-allylbenzanilide. Calcd. for $C_{16}H_{15}NO$: C, 81.00; H, 6.36. Found: C, 81.41; H, 6.46.

Anal. of *p*-allylacetanilide. Calcd. for $C_{11}H_{13}NO$: C, 75.40; H, 7.48. Found: C, 75.39; H, 7.78.

Anal. of N-*p*-allylphenyl-N'-phenylthiourea. Calcd. for $C_{16}H_{16}N_2S$: C, 71.60; H, 6.01. Found: C, 71.53; H, 5.97.

p-Allylphenol. Four grams of *p*-allylaniline was mixed with 150 ml. of 8% aqueous sulfuric acid. The mixture was chilled to −2° and, while stirring, a solution of 2.07 g. of sodium nitrite in 10 g. of water was added slowly. After stirring for 1 hr. and adding a little urea, the mixture was warmed to 20° and steam distilled thereby collecting 500 ml. of distillate. The product was isolated in the same manner as *o*-allylphenol. The forerun (0.7 g.) possessed the odor of allylbenzene. The main product (1.72 g.) boiled at 105–110° at 11 mm.

That this was *p*-allylphenol was confirmed by treating it with 3,5-dinitrobenzoyl chloride[13] to obtain the known *p*-allylphenyl 3,5-dinitrobenzoate, m.p. 103–103.5° (lit., 103.5–104°).

ω-(o-Nitrophenyl)propiophenone. Crude *o*-nitrohydrocinnamic acid, m.p. 107–110°, was prepared according to the method of Konek and Pacsu.[14] Its conversion into ω-(*o*-nitrophenyl)propiophenone, m.p. 68–69°, has been reported by Jaenisch[15] but with no experimental details.

We mixed 3.9 g. of the acid and 16 g. of thionyl chloride, refluxed the mixture for 90 min., removed the excess of thionyl chloride under reduced pressure, and dissolved the residual nitrohydrocinnamoyl chloride in 25 ml. of benzene. This solution was added dropwise during 20 min. into a stirred suspension of 3 g. of anhydrous aluminum chloride in 50 ml. of pure benzene. The mixture was stirred for 45 min. at 20°, 30 min. at 40°, and then was poured into 200 g. of cracked ice and water which contained 10 ml. of concd. hydrochloric acid. After several hours the mixture was extracted with ether and the combined extracts were washed with water, then with saturated sodium bicarbonate solution and dried, and the solvent was distilled. The residue weighed 5 g., m.p. 55–56°. The product was crystallized from 100 ml. of cyclohexane; yield, 3.5 g., m.p. 57–59°.

ω-(p-Nitrophenyl)propiophenone. This isomeric ketone was prepared in exactly the same manner as its *ortho* isomer. From 3.9 g. of crude *p*-nitrohydrocinnamic acid, m.p. 160–163°, there was obtained 6 g. of crude product. After crystallizing it from 50 ml. of methanol and drying, the purified product weighed 4 g. and melted at 99–100°.

Anal. Calcd. for $C_{15}H_{13}NO_3$: N, 5.49. Found: N, 5.40.

Direct nitration of ω-phenylpropiophenone. Cupric nitrate trihydrate (125 g.) was added in small portions during 90 min. to a stirred solution of 85 g. of ω-phenylpropiophenone[16] in 500 ml. of acetic anhydride that was kept at 20° by cooling. Then the mixture was stirred for 0.5 hr. at 20° and was poured into 2 l. of cracked ice and water. After several hours the product was collected on a filter, washed well with sodium bicarbonate solution and water, and air dried. The crude product (105 g.) was washed three times with 100-ml. portions of cold ether. The residue, when dried, weighed 70 g., m.p. 55–59° with softening at 53°.

Sixty grams of this mixture was washed twice with 200- and 100-ml. portions of ether. The residue, 21 g., melted at 94–96° and was crude *para* isomer. Recrystallization from methanol brought the m.p. to 99–100°; mixed m.p. with the *para* isomer prepared above, 99.5–100°. Evaporation of the ether from the filtrate gave about 40 g. of the crude ortho isomer, m.p. 55–58°. A 25-g. sample was crystallized from cyclohexane. The purified material (17.5 g. melted at 57–59° and a mixed m.p. with ω-(*o*-nitrophenyl)propiophenone was 57–59°. The material melting at 57–59° was used as such, but it was considered to be a constant melting mixture of the two isomers, composed chiefly of the ortho isomer.

1-Phenyl-3-o-nitrophenyl-1-propanol. Crude ω-(*o*-nitrophenyl)propiophenone, m.p. 57–59°, was reduced by the method of Meerwein, Ponndorf, and Verley as modified by Lund.[17] From 4 g. of the ketone there was obtained 4 g. of crude alcohol, m.p. 43–45°. One crystallization from benzene (25 ml.)-ligroin (100 ml.) gave 3.4 g. of product of m.p. 44.5–46°.

Anal. Calcd. for $C_{15}H_{15}NO_3$: C, 70.02; H, 5.88; N, 5.45. Found: C, 69.90, 70.00; H, 5.30, 5.88; N, 5.45.

1-Phenyl-3-p-nitrophenyl-1-propanol. This alcohol was prepared in the same manner as its *ortho* isomer. Four grams

(11) J. von Braun and A. Steindorff, *Ber.*, **37**, 4726 (1904).

(12) L. Claisen and O. Eisleb, *Ann.*, **401**, 73 (1913).

(13) M. Phillips and G. Keenan, *J. Am. Chem. Soc.*, **53**, 1924 (1931); S. Palkin and R. Wells, *J. Am. Chem. Soc.*, **55**, 1556 (1933).

(14) F. Konek and E. Pacsu, *Ber.*, **51**, 855 (1918).

(15) A. Jaenisch, *Ber.*, **56**, 2448 (1923).

(16) This ketone was kindly supplied by G. D. Searle and Co., Skokie, Ill.

(17) A. L. Wilds, *Org. Reactions*, **II**, 178–223 (1944).

of ketone gave rise to 4 g. of crude alcohol, m.p. 111–112°. The product, after crystallization from 25 ml. of ethanol and drying, weighed 3 g.; m.p. 112–113°.

Anal. Calcd. for $C_{15}H_{15}NO_3$: C, 70.02; H, 5.88; N, 5.45. Found: C, 69.93; H, 5.92; N, 5.43.

o-Cinnamylnitrobenzene. A solution of 6.3 g. of 1-phenyl-3-*o*-nitrophenyl-1-propanol in 70 ml. of glacial acetic acid and 0.3 ml. of concentrated sulfuric acid was refluxed for 1 hr. and poured into 300 g. of cracked ice and water. After keeping it for 1 day, the product was collected on a filter and dried *in vacuo* over sodium hydroxide; yield, 6 g., m.p. 40–47°. The crude product was extracted with 150 ml. of boiling petroleum pentane, leaving a residue of 1–1.5 g. From the chilled extracts, 4 g. of product crystallized, m.p. 41–42.5°. Recrystallization from pentane brought the m.p. to 42–43°.

Anal. Calcd. for $C_{15}H_{13}NO_2$: C, 75.29; H, 5.48; N, 5.86. Found: C, 75.33; H, 5.52; N, 5.83.

p-Cinnamylnitrobenzene. From 7.7 g. of 1-phenyl-3-*p*-nitrophenyl-1-propanol, treated identically, there was obtained 6.8 g. of crude product, m.p. 60–62°. After one recrystallization from 75 ml. of ligroin (b.p. 85–100°) using Darco, and a second crystallization from 50 ml. of ligroin, the pure product melted at 62–63°; yield, 4.3 g.

Anal. Calcd. for $C_{15}H_{13}NO_2$: C, 75.29; H, 5.48; N, 5.86. Found: C, 75.55; H, 5.59; N, 5.79.

o-Cinnamylaniline. To a boiling suspension of 25.3 g. of crude *o*-cinnamylnitrobenzene, m.p. 37–46°, in 500 g. of water that contained 205.5 g. of ferrous sulfate heptahydrate was added 145 ml. of concd. ammonium hydroxide during a period of 0.5 hr. The mixture was stirred at reflux for 4 hr., then was filtered to remove the iron compounds. The details of processing followed closely those given above for *o*-allylaniline. The product boiled at 158–165° at 1 mm.; yield, 11.3 g. (51%). A crystalline picric salt could not be prepared in ethanol. These derivatives were made.

o-Cinnamylbenzanilide. One gram of *o*-cinnamylaniline was mixed with 0.7 g. of benzoyl chloride and 5 g. of pyridine. After 1 hr. at 100°, the mixture was poured into acidified water. An oil resulted which granulated quickly; yield, 1.3 g. One crystallization from 25 ml. of ethanol, with the filter aids Darco and Dicalite, gave 0.7 g. of product of m.p. 157–160°. A recrystallization gave the pure derivative, m.p. 160–160.5°.

Anal. Calcd. for $C_{22}H_{19}NO$: N, 4.47. Found: N, 4.43.

The filtrate from the crystallization contained 0.1 g. of *p*-cinnamylbenzanilide, m.p. 133–136°. This indicated that some of the *para* isomer had carried through in all the steps starting with *o*-nitrohydrocinnamic acid.

o-Cinnamylbenzenesulfonanilide. One gram of *o*-cinnamylaniline, 1 g. of benzenesulfonyl chloride, and 20 ml. of 10% aqueous sodium hydroxide were mixed and shaken for 5 min. with occasional cooling by tap water. An additional gram of the halide was added and the mixture was shaken and kept for about 1 hr. The alkali soluble material was then isolated in good yield. It was crystallized from ethanol; m.p. 130–131°.

Anal. Calcd. for $C_{21}H_{19}NO_2S$: N, 4.01; S, 9.18. Found: N, 3.98; S, 8.99.

p-Cinnamylaniline. This compound was prepared in the same manner as the *ortho* isomer. From 15 g. of *p*-nitrocinnamylbenzene was obtained 5 g. of the amine, b.p. 172–176° at 2 mm. The distillate solidified and melted at 53–55°. A crystalline picric salt could not be prepared in ethanol.

p-Cinnamylbenzanilide. The derivative was prepared in the same manner as its *ortho* isomer. The crude product formed in good yield but it was crystallized from ethanol with difficulty. The pure product was obtained in a microcrystalline state; m.p. 134–136°. The melting point was not altered by changing crystallizing solvents.

Anal. Calcd. for $C_{22}H_{19}NO$: N, 4.47. Found: N, 4.42.

PROPYLBENZENE, *p*-PROPYLANILINE AND ALLIED COMPOUNDS

Propylbenzene. This compound has been prepared by several methods in the past, but not by hydrogenation of allylbenzene. To this end, 35.4 g. of allylbenzene (b.p. 155–158°) was added to a suspension of 1 g. of 5% palladium-on-charcoal catalyst (Wilkins-Anderson Co.) in 150 ml. of glacial acetic acid. The mixture was hydrogenated in a low-pressure Parr hydrogenation apparatus until a pressure drop of 25.3 lbs. was observed. The catalyst was removed on a filter and the filtrate was chilled, neutralized with 40% aqueous sodium hydroxide, and extracted with ether. The combined extracts were washed with water, dried, and distilled. The desired product (28.1 g.) boiled at 157–158.5°.

Nitration. To a mixture of 37 g. of propylbenzene in 165 ml. of acetic anhydride was added a nitrating solution at 0° to −5° during 80 min. [19.2 ml. of fuming nitric acid (*d.* 1.5), 15.6 ml. of acetic anhydride, 18 ml. of glacial acetic acid]. After treatment with crushed ice, alkaline washes, and drying 25 g. of *o*-nitropropylbenzene was collected at 115–122° (13 mm.) and 6.3 g. of *p*-nitropropylbenzene at 132–140° (13 mm.). Baddeley and Kenner reported[18] 133–140° and 150–160° at 20 mm., respectively. They used a nitric-sulfuric nitrating mixture.

p-Propylaniline. A suspension of 0.15 g. of 5% palladium-on-charcoal catalyst in 75 ml. of ethanol and 6.25 g. of *p*-nitropropylbenzene was hydrogenated in the low pressure Parr machine. Hydrogenation ceased when a pressure drop of 7 lbs. was observed. The catalyst was removed, and after adding 6 ml. of concd. hydrochloric acid to the filtrate the solvent was distilled off under reduced pressure. The solid residue was dissolved in water and the solution was made alkaline and ether extracted. The extracts were washed with water and dried, the solvent was removed, and the residue was distilled. The main fraction (2.35 g.) boiled at 102–105° at 11–12 mm. Baddeley and Kenner's value[18] was 112° (20 mm.). Benzoylation yielded a crystalline product, m.p. 118–119°, comparing with the known[19] benzo-*p*-propylanilide.

Derivatives of p-propylaniline. N-p-Propylphenyl-N'-phenylthiourea. p-Propylaniline, b.p. 103–105° (12 mm.), was treated with phenyl isothiocyanate. The crude product, obtained in high yield, was crystallized three times from ethanol; m.p. 119.1–119.2°. See ref. 9.

Anal. Calcd. for $C_{16}H_{18}N_2S$: C, 71.06; H, 6.70. Found: C, 71.20; H, 6.87.

Reaction of N-allylaniline with zinc chloride. At 140°. N-Allylaniline (13.3 g.), 13.6 g. of powdered, anhydrous zinc chloride and 30 ml. of xylene were mixed and refluxed for 3 hr., then left overnight and cooled in an ice bath while enough 40% sodium hydroxide aqueous sodium hydroxide was added to dissolve the initially precipitated zinc hydroxide. The xylene layer was separated, the alkaline layer extracted three times with ether, and the extracts were combined with the xylene layer. The latter was washed once with water, dried (Na_2SO_4), and distilled. After removing the xylene, there was a forerun of 1.0 g. which boiled up to 119° at 28 mm. The main fraction of 5.2 g. was collected between 119–122.5° at 28 mm. The residue weighed about 3 g. and decomposed on attempted distillation.

The main fraction was *o*-allylaniline, obtained in 42% yield. Its identity was certified by changing it into these derivatives: *o*-allylbenzanilide, m.p. and mixed m.p. 121–122°; *N-o*-allylphenyl-*N'*-phenylthiourea, m.p. and mixed m.p. 115–116°.

At reflux temperature. N-Allylaniline (100 g.) and 50 g. of zinc chloride were mixed in a flask fitted with an air condenser. The mixture was heated to boiling, when a vigorous reaction took place with gas evolution (see below). The mixture was refluxed for 2 hr. and, while still hot, was poured

(18) G. Baddeley and J. Kenner, *J. Chem. Soc.* 303 (1935).

(19) G. Schultz, *Ber.*, 42, 3614 (1909), listed m.p. 115°; ref. 9 listed the m.p. as 116–117°.

into cold water, made alkaline (40% NaOH), and steam distilled. Three liters of distillate was collected during which time the alkaline suspension became purple in color. The material which did not distil was collected by decantation and weighed 40–45 g. when practically dry. This substance was a black tar possessing a fecal or skatole-like odor.

The distillate was saturated with salt, ether-extracted three times, and the extracts were washed with water, dried, and distilled. Fraction I was aniline (25.1 g., b.p. 64–70° at 7 mm., thiocarbanilide, m.p. 149–150°). Fraction II (3.8 g., b.p. 70–90° at 7 mm.) was the forerun to fraction III (9.3 g., b.p. 90–132° at 7 mm.). Fraction III, on redistillation, gave 6.4 g. (5–6% yield) of quite pure *p*-propylaniline, b.p. 102–105° (12 mm.). From it was made *N*-*p*-propylphenyl-*N'*-phenylthiourea, m.p. 119.9–120°; mixed m.p. with an authentic specimen, 119°. Benzo-*p*-propylanilide, m.p. 117–118°, also was prepared from this amine; mixed m.p., 117.5–118.6°.

Gas was collected from a similar, smaller run (*N*-allylaniline 25 g., $ZnCl_2$ 12.5 g) in which the heating up to a final internal temperature of 300° was conducted in an atmosphere of carbon dioxide. Two liters of gas was evolved and was analyzed in a modified Orsat apparatus. The CO_2 content was 0.6 l. Traces of air and carbon monoxide comprised 0.03 l. Of the remaining 1.37 l. the composition was hydrogen 97.2%, olefin 2.8%. The olefin fraction was absorbed by 85% sulfuric acid, thus pointing to propylene[20] and excluding ethylene or acetylene.

In refluxing benzene. No product other than starting material (71% recovery) was found after 2 hr. refluxing of a mixture of 13.3 g. of *N*-allylaniline, 13.6 g. of zinc chloride, and 50 ml. of benzene.

Reaction of N-cinnamylaniline with zinc chloride. At 150° in bromobenzene. A mixture of 52.5 g. of *N*-cinnamylaniline, 34 g. of pulverized, anhydrous zinc chloride, and 150 ml. of bromobenzene was warmed at 147–152° (internal temperature) with stirring for 30 min., then was cooled to 25° and 33% aqueous sodium hydroxide was added until all of the zinc hydroxide dissolved. The mixture was extracted with ether and the combined ether layers were extracted thoroughly with dilute hydrochloric acid. The acidic extract was made alkaline and the base was isolated by ether-extraction. The extract was washed with water, dried, and distilled under diminished pressure. The forerun was aniline (8. g.); it yielded benzanilide as derivative (1.5 g. from 1 g.), m.p. and mixed m.p. 161–162°.

The main fraction weighed 17 g. There was a residue of 14 g. which was not processed. The 17-g. fraction, b.p. 168–184° at 1 mm., yielded 14 g. on redistillation, b.p. 172–174° at 1 mm. As shown below, half of it was *o*-cinnamylaniline and about 35–40% of it was 2-phenylquinoline. The latter was characterized by way of its insoluble picrate,[21] m.p. and mixed m.p. 186–188°, that was obtained by mixing hot alcoholic solutions of the base and picric acid.

A 2-g. portion of the 14-g. fraction was treated with 2 g. of benzenesulfonyl chloride and an excess of dilute sodium hydroxide solution. This yielded 0.70–0.75 g. (35–38%) of insoluble 2-phenylquinoline, and a soluble fraction that contained 0.85 g. of crude *o*-cinnamylbenzenesulfonanilide which precipitated on acidification. After 3 crystallizations from alcohol the latter melted at 128–128.5°; mixed m.p. with authentic sample (130–131°), 128.5–130°.

A 1-g. portion of the 14-g. fraction, treated with benzoyl chloride and pyridine for an hour at 100°, yielded 0.6 g. (40%) of a benzoyl derivative. After two crystallizations from alcohol, it melted at 159.5–160° and analysis showed 4.4% nitrogen, which is correct for $C_{22}H_{19}NO$. A mixed m.p. with authentic *o*-cinnamylbenzanilide (160–160.5°) was 159.5–160°.

At 110° in toluene. The quantities in this run were 24.5 g. of *N*-cinnamylaniline, 15.8 g. of zinc chloride, and 150 ml. of toluene. The mixture was stirred at 110° for 2 hr., then was left 15 hr. before processing essentially as in the above run. The basic products, when distilled, contained aniline (3.9 g.), a main fraction at 168–175° (1 mm.) weighing 12.6 g., and a residue (6. g.). The main fraction was about four-fifths unchanged N-cinnamylaniline (alcohol-soluble picrate) and one-fifth 2-phenylquinoline (alcohol-insoluble picrate), and it was separated by way of the picrates.

That o-cinnamylaniline was absent was shown by testing with cold nitrous acid and then attempting diazo coupling with alkaline 2-naphthol; no azo dye resulted, hence no primary amine was present in significant amounts.

At 250°. No solvent was used, as 72 g. of *N*-cinnamylaniline and 38 g. of zinc chloride were heated in CO_2 atmosphere in a flask equipped for gas collection. At a bath temperature of 100° the mixture began to turn red, at 125° gas evolution commenced, and at 150° gas evolution was brisk. Reaction became exothermic and the internal temperature reached 228° (bath, 190°). The gas volume was about 300 cc. When reaction subsided, heating was continued. At 215° the mixture began to froth with moderate gas evolution, at 231° decomposition seemed to commence, and at 233° frothing was vigorous. The reaction was stopped at 250°. After sweeping the apparatus with carbon dioxide the total volume of gas collected was about 1350 cc. The reaction mixture, while hot, was poured into a liter of water.

That portion of the gas that was insoluble in caustic solution was 405 cc. (STP). This was 97% hydrogen and the rest was chiefly air and a trace of olefin.

From the reaction mixture was isolated 5 g. of aniline, 2.5 g. of 2-phenylquinoline, and a large amount of brilliant red tar that was insoluble in acids, alkali, or ether. No *o*-cinnamylaniline remained, but if the heating was stopped at 150° then some was observed and identified as the benzenesulfonyl derivative, m.p. 130–131°.

Reaction of o-Cinnamylaniline with zinc chloride at 150°. No gas was liberated when a mixture of 4.5 g. of *o*-cinnamylaniline (containing some para isomer), 3.5 g. of anhydrous, powdered zinc chloride, and 20 ml. of bromobenzene was warmed at 150° for 30 min. The mixture was cooled to room temperature and 75 ml. of 33% sodium hydroxide solution was added. The basic material was processed as in other runs. It weighed about 2.8 g., b.p. 152–155° at 0.8 mm. with only about 0.5 g. of residue. The distillate partially solidified and a sample, dried on unglazed porcelain, melted at 52–54°. A mixed m.p. with *p*-cinnamylaniline (m.p. 53–55°) was 52–55°. One gram of distillate formed 1.5 g. of the crude, damp benzoyl derivative which, after two crystallizations from ethanol, melted at 120–131°. A mixed m.p. with a known mixture of *o*- and *p*-cinnamylbenzanilides (m.p. 119–121.5°) was 118–128°. If it is assumed that the material which was lost during the reaction was chiefly *o*-cinnamylaniline then the percentage of *para* isomer in the distillate would be raised since it was an original impurity.

Neither the distillate nor the residue formed a crystalline picrate in ethanol. This is the expected behavior for *o*- and *p*-cinnamylaniline, but not for a mixture containing any appreciable amount of 2-phenylquinoline.

The *ortho* isomer was identified by reaction of 1 g. of the above distillate with 2 g. of benzenesulfonyl chloride and 20 ml. of 10% aqueous sodium hydroxide. The crude yield of *o*-cinnamylbenzenesulfonamilide was 1.1 g. (64%). One crystallization from 4 ml. of ethanol gave the pure amide (0.6 g.), m.p. and mixed m.p. 130–131°.

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EVANSTON, ILL.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF CALIFORNIA, LOS ANGELES]

Arylallenes. II. Synthesis of Diarylallenes. Partial Asymmetric Synthesis of Allenes*[1,2]

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1,3-Diphenylallene and 1-(*p*-biphenyl)-3-phenylallene have been synthesized by prototropic rearrangement of 1,3-diphenylpropyne and 1-(*p*-biphenyl)-3-phenyl-1-propyne by adsorption on basic alumina. The second of these allenes was also prepared by rearrangement in an inert solvent in the presence of solid alkali. These methods appear to be general for the synthesis of such unstable allenes. A partial asymmetric synthesis of these allenes was accomplished by carrying out the rearrangement with brucine or quinine adsorbed on alumina.

The rearrangement of 1-(*p*-bromophenyl)-3-(*β*-naphthyl)-1- and 2-propynes (I and II, R = *p*-BrC_6H_4, R′ = *β*-$C_{10}H_7$) to 1-(*p*-bromophenyl)-3-(*β*-naphthyl) allene (III, R = *p*-BrC_6H_4, R′ = *β*-$C_{10}H_7$) by adsorption on activated alumina was reported earlier.[2] It was of interest to examine the isomerization more closely and to extend it to other diarylallenes because no others have been reported.

$$\underset{\text{I}}{RC{\equiv}CCH_2R'} \longrightarrow \underset{\text{III}}{RCH{=}C{=}CHR'} \longleftarrow \underset{\text{II}}{RCH_2C{\equiv}CR'}$$

This paper describes the synthesis of 1,3-diphenylallene and 1-(*p*-biphenyl)-3-phenylallene; a rearrangement of the corresponding propynes by brucine or quinine adsorbed on alumina has resulted in a partial asymmetric synthesis of these allenes.

It was found that a highly active, basic alumina was required to accomplish the isomerization of 1,3-diarylpropynes to allenes. Harshaw's 80-mesh activated alumina was effective only after heating for some time. This alumina is basic (*p*H∼9); when it was treated with ethyl acetate, which gave a more nearly neutral material, and activated by heat, it would no longer cause isomerization. It was found that the yield of allene was improved if the time of residence on the adsorption column was reduced; thus the yield of 1-(*p*-bromophenyl)-3-(*β*-naphthyl)allene was improved from 50%[2] to 82% by reducing the time on the column from 8 hr. to the minimum time required for elution (∼20 min.). This did not result in recovery of unreacted acetylene, but did reduce the amount of non-crystalline, by-product material, apparently formed by further rearrangement of the allene. The yield of such by-products was also increased by using too long a column. With each new propyne examined, some experimentation was usually necessary to find the correct column length, basicity of adsorbent, and time of residence on the column for optimum yields. With 1,3-diphenylpropyne, which rearranges somewhat slowly, the yield of 1,3-diphenylallene was 52% when ordinary Harshaw alumina was simply activated by heat and used with rapid elution and a short column, but rose to 75% when alumina impregnated with potassium hydroxide was used. The rearrangement of 1-(*p*-biphenyl)-3-phenyl-1-propyne was accomplished in 69% yield on the ordinary, heat-activated alumina.

The nature of the by-products formed from the allenes is under investigation and will be reported in a separate paper.

An easier method of isomerization which permitted the preparation of larger amounts of the allenes was realized by shaking substituted propynes in an inert solvent with pellets of sodium hydroxide or potassium hydroxide at room temperature for a number of hours. This method failed with 1,3-diphenylpropyne, and appeared to give slightly lower yields with other propynes.

Partially asymmetric rearrangements of 1,3-diphenylpropyne and 1-(*p*-biphenyl)-3-phenyl-1-propyne to the corresponding allenes were accomplished by adsorbing the acetylenic compounds on columns of neutral, activated alumina which had been impregnated with brucine or quinine. The products with the brucine-impregnated columns were levorotatory and the maximum specific rotations were −1.24° and −7.0° respectively. With quinine-impregnated columns, dextrorotatory products were obtained with maximum specific rotations of +2.48° and +8.57° respectively. Infrared spectra of the products sometimes indicated a mixture of the starting acetylene with allene, but in other experiments the products appeared to be pure allenes; in every instance however the products had broad melting points. Attempts to isolate a pure enantiomer were unsuccessful although it was possible to increase the specific rotation slightly by fractional crystallization; these allenes are not easy to recrystallize, and during manipulation, dimers and other transformation products form readily.

* This paper is a contribution in honor of Lyndon F. Small, former Editor of the Journal.

(1) Part of this work was carried out under a contract with the Office of Ordnance Research, U. S. Army, and part under a contract with the Office of Naval Research. Reproduction in whole or in part is permitted for any purpose of the United States Government. The material is taken from the Ph.D. thesis of David Dankner. A preliminary report of this work was given at the Minneapolis meeting of the AMERICAN CHEMICAL SOCIETY, September, 1955 (see Abstracts of Papers Presented, page 42-0).

(2) For paper I see T. L. Jacobs and S. Singer, *J. Org. Chem.*, **17**, 475 (1952).

Although the observed rotations are small it appears very unlikely that they result from impurities. The products were carefully washed in ether under nitrogen with aqueous hydrochloric acid to remove any traces of active base. When attempts were made to rearrange the propynes with brucine or quinine by shaking in solution in the absence of alumina, only inactive starting material was isolated; the purification was the same as used to insure the absence of optically active bases from the products of successful rearrangements. Isolation of dimeric material from successful rearrangements gave an inactive, crystalline dimer. Finally it was found that the broad-melting, *levo*-l-(*p*-biphenyl)-3-phenylallene was hydrogenated to an inactive product (no activity in the crude sample) with absorption of two molecular equivalents of hydrogen. Pure 1-(*p*-biphenyl)-3-phenylpropane was isolated without difficulty from the hydrogenation product.

The allenes were characterized by analysis, molecular weight determination, hydrogenation to the propane derivatives (also obtained from the starting propynes), and especially by infrared spectroscopy. Although the aryl groups in both the starting propynes and in the allenes give a series of small bands[3,4] between 1650 cm.$^{-1}$ and 2000 cm.,$^{-1}$ one of which usually has a maximum near 1950 cm.$^{-1}$ where the characteristic strong absorption which results from the antisymmetrical C=C=C stretching vibration is observed,[4,5] the allene absorption is so much stronger that it is easily distinguishable. The starting propynes showed a characteristic C≡C absorption in the 2200–2250 range[4] where the allenes did not absorb. All three of the allenes prepared during this investigation are solids, and it was necessary to observe the spectra in rather concentrated solutions to bring out the characteristic absorptions.

The ultraviolet absorption spectra of the allenes are interesting. Celmer and Solomons[6] pointed out that very little conjugation across the allene system would be expected since the orbitals of the π electrons are at right angles to each other. Each double bond of the allene group conjugates independently with the groups attached to it and the spectrum of each allene should be approximately equivalent to a summation of the spectra of the two corresponding olefins. In general, however, λ_{max} for the most intense absorption of the allenes appears to occur at slightly longer wavelengths. Thus styrene[7] shows λ_{max} 244 while 1,3-diphenylallene has λ_{max} 255. As would be expected the extinction coefficients are higher for the allenic systems.

The starting propynes were prepared by conventional methods[2,8] as detailed in the experimental part. The final step in this synthesis is the reaction of an acetylenic Grignard reagent with benzyl *p*-toluenesulfonate. The *p*-toluenesulfonate is unstable and must be used in double the molecular amount of the acetylenic compound because the first equivalent reacts with the Grignard reagent to give benzyl bromide. An attempt was made therefore to alkylate the Grignard reagent with benzyl bromide in the presence of cuprous chloride.[9] With phenylethynylmagnesium bromide a 35% yield of 1,3-diphenylpropyne was obtained, whereas benzyl *p*-toluenesulfonate gave 72% yield.[8] With *p*-phenylphenylethynylmagnesium bromide no 1-(*p*-biphenyl)-3-phenyl-1-propyne was isolated when benzyl bromide was used, but benzyl *p*-toluenesulfonate gave 33% of the desired propyne.

An investigation of the reactions of the allenes obtained in this work is underway and will be reported in a separate paper.

EXPERIMENTAL

All melting points were taken on a Hershberg[10] immersion apparatus. Infrared spectra were determined on a Model 21 Perkin-Elmer instrument using a sodium chloride prism.

1,3-Diarylpropynes. 1-(*p*-Bromophenyl)-3-(β-naphthyl)-1-propyne was a sample prepared by S. Singer.[2] 1,3-Diphenylpropyne was prepared from benzyl *p*-toluenesulfonate and phenylethynylmagnesium bromide as described earlier,[8] $n_D^{19.8}$ 1.5995. It was also prepared by the method of Gensler and Thomas[9b] for coupling acetylenic Grignard reagents with propargyl bromides. Phenylacetylene (22.6 g.; 0.22 mole), dissolved in dry ether was added dropwise to a stirred, ethereal solution of ethylmagnesium bromide (0.2 mole). The solution was refluxed for 1 hr. and cuprous chloride (0.4 g.) as well as cupric chloride (0.4 g.) were added. The solution was refluxed for another 30 min. Benzyl bromide (34.3 g.; 0.2 mole) dissolved in ether was added dropwise with stirring to the reaction mixture. The stirred reaction mixture was refluxed for 46 hr.; a heavy yellow precipitate formed. The reaction mixture was decomposed with cold aqueous hydrochloric acid solution. The organic layer was washed with cold water, neutralized with cold aqueous sodium bicarbonate solution and finally washed with cold water. It was dried over anhydrous magnesium sulfate. On distillation phenylacetylene (3.83 g.) and benzyl bromide (13.31 g.) were recovered. 1,3-Diphenylpropyne (13.78 g.: 35.6%) distilled at 140–145°C/3 mm.

Ultraviolet absorption spectrum of 1,3-diphenylpropyne, in 95% ethanol: λ_{inf} 232, ϵ = 16,650; λ_{max} 240, ϵ = 25,200; λ_{max} 251, ϵ = 22,900; $\lambda_{shoulder}$ 264, ϵ = 1400; $\lambda_{shoulder}$ 267.5, ϵ = 1100; λ_{max} 272, ϵ = 1050; λ_{max} 279, ϵ = 800; $\lambda_{shoulder}$ 287, ϵ = 480; λ_{max} 305, ϵ = 460; λ_{max} 326, ϵ = 370.

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The infrared spectrum of 1,3-diphenylpropyne shows a medium absorption peak at 2217 cm.$^{-1}$ attributed to the internal acetylenic bond. Likewise it shows several phenyl bands betwen 1650 cm.$^{-1}$ and 2000 cm.$^{-1}$ The principal peaks are at 1665 cm.$^{-1}$, 1743 cm.$^{-1}$, 1795 cm.$^{-1}$, 1868 cm.$^{-1}$, and 1944 cm.$^{-1}$.

p-Biphenylacetylene. To 156 g. (0.75 mole) of phosphorus pentachloride in 200 ml. of dry benzene in a 2-l., round-bottomed, 3-neck flask equipped with stirrer, condenser, and dropping funnel was added dropwise a solution of 98.5 g. (0.5 mole) of methyl-(*p*-biphenyl)-ketone[11] in dry benzene containing a few crystals of 4-*tert*-butylcatechol. The flask was wrapped to exclude light. Evolution of hydrogen chloride began at once. After addition was completed the yellow solution was refluxed for 3.5 hr., stirred overnight at room temperature, and poured into ice water. A white suspension formed and was stirred for 40 min.; it was then left in the hood for several hours until all of the benzene had evaporated. The organic chloride was taken up in ether, which left behind a considerable amount of solid soluble neither in ether nor in chloroform; the ether solution was washed with water and dried over anhydrous magnesium sulfate. The ether was removed and the residue added to 1.5 moles of sodamide in a liter of liquid ammonia. The dark brown solution was stirred for several hours, neutralized with ammonium chloride (80.3 g., 1.5 moles), diluted with ether and concentrated by allowing the ammonia to evaporate. The ether solution was washed with cold, dilute hydrochloric acid, 1*N* aqueous sodium carbonate and water, dried over anhydrous magnesium sulfate, and concentrated to leave a dark brown solid. Recrystallization from ethanol (decolorizing), then from carbon tetrachloride gave white crystals of *p*-biphenylacetylene, m.p. 86–87°. The yield was 38.8 g. (43.4%). In one instance the acetylene was purified by making the silver salt.

Anal. Calcd. for $C_{14}H_{10}$: C, 94.34; H, 5.66. Found: C, 94.29; H, 5.85.

1-(p-Biphenyl)-3-phenyl-1-propyne was synthesized from *p*-phenylphenylethynylmagnesium bromide (0.027 mole) and benzyl *p*-toluenesulfonate (0.06 mole) according to the directions used for 1,3-diphenylpropyne.[5] The product was purified by rapid chromatography on a very short column of activated, undried alumina and recrystallized from petroleum ether (b.p. 20–40°) or methanol to give white crystals, m.p. 75.4–76.6°, yield 2.4 g. (33%).

Anal. Calcd. for $C_{21}H_{16}$: C, 93.99; H, 6.01; mol. wt., 268.3. Found: C, 94.01; H, 6.19. Mol. wt., (Signer method[12]) 302.

Hydrogenation of the acetylene (100 mg.) in 10 ml. of methanol over palladium-on-carbon resulted in absorption of 2 molecular equivalents of hydrogen. The product was recrystallized from methanol to give 32 mg., m.p. 40–41.6°.

The infrared spectrum of 1-(*p*-biphenyl)-3-phenyl-1-propyne was determined in carbon tetrachloride solution (25% by weight) with a cell thickness of 0.4 mm. Even at this concentration the characteristic acetylenic bond (2242 cm.$^{-1}$) shows 64% transmission. The phenyl bonds between 1650 cm.$^{-1}$ and 2000 cm.$^{-1}$ are all stronger; the principal peaks are at 1668 cm.$^{-1}$, 1687 cm.$^{-1}$, 1700 cm.$^{-1}$, 1795 cm.$^{-1}$, 1870 cm.$^{-1}$, 1902 cm.$^{-1}$ and 1942 cm.$^{-1}$

Ultraviolet absorption spectrum, in 95% ethanol: λ_{max} 273, ϵ = 45,060.

Basic activated alumina. Harshaw's 80-mesh alumina of the sort commonly used for chromatography was found to be slightly basic. It was dried for 5 days at 160–170° before use and was then effective for the acetylene-allene rearrangement. It will be referred to as alumina A. With the compounds examined in this work the undried alumina of this grade did not effect the rearrangement, nor would alumina treated with ethyl acetate and then dried as above give successful results.

A more basic alumina was prepared by shaking 1 kg. of Harshaw's 80-mesh activated alumina with 250 g. of potassium hydroxide or sodium hydroxide in 750 ml. of water in a 3 l., round-bottomed flask heated with a heating mantle until most of the water was evaporated. Evaporation was interrupted before the mixture became completely dry in order to prevent cake formation. The alumina was stored under nitrogen; just before use it was dried at 160° at 3 mm. for a period of 14 hr. The dried alumina absorbs carbon dioxide rather rapidly from the air and is then less effective for the rearrangement. No attempt was made to study the effect of varying the quantity of the base on the activity of the alumina for the rearrangement. This alumina will be referred to as alumina B.

To prepare alumina impregnated with an optically active base 650 g. of Harshaw's 80-mesh alumina was heated with an open flame for 1 hr., soaked in 815 ml. of ethyl acetate for 24 hr., washed on a Buchner funnel first with 1630 ml. of water, then with 1630 ml. of methanol and dried in a desiccator under vacuum overnight; it was finally dried at 250° for 4 hr. Fifty grams of this neutral alumina was stirred for 2 hr. with a solution of 5 g. of anhydrous quinine or anhydrous brucine in about 70 ml. of chloroform, filtered, and finally dried at 135° under 5 mm. pressure. This will be referred to as alumina C. When an attempt was made to impregnate with twice the amount of quinine, a column of the alumina became gelatinous during use with pentane, and elution was difficult.

1,3-Diphenylallene. A solution of 0.68 g. of 1,3-diphenylpropyne in 20 ml. of *n*-pentane was placed on a 2.7 × 10 cm. column of alumina A and eluted at once with *n*-pentane. The first 150 ml. of *n*-pentane coming through the column contained neither allene nor starting material; from the next fractions was isolated 0.35 g. (51.5% yield) of 1,3-diphenylallene, m.p. 43–48°C. Some greenish oil, apparently decomposition product, was also collected.

Similarly 1.17 g. of 1,3-diphenylpropyne in 20 ml. of *n*-pentane was placed on a 2 × 9 cm. column of alumina B and eluted at once. A deep red band formed at the top of the column as soon as the propyne was added. The allene came off the column in the first 50 ml. of eluate and was isolated by evaporating the solvent at room temperature under nitrogen with a water aspirator to yield 0.87 g. (74.5%) of white crystals, m.p. 46.4–51.4°C. The product was recrystallized from *n*-pentane by cooling the solution in a Dry Ice–acetone bath to −40°C. The recrystallized product melted at 49–51°C.

Anal. Calcd. for $C_{15}H_{12}$: C, 93.71; H, 6.29; Mol. wt., 192.25. Found: C, 93.55; H, 6.07; Mol. wt., (cryoscopic in benzene), 201.

Ultraviolet absorption spectrum in 95% ethanol: $\lambda_{shoulder}$ 230, ϵ = 14,720; λ_{max} 236.5, ϵ = 20,550; λ_{max} 255, ϵ = 52,200; $\lambda_{shoulder}$ 279, ϵ = 6,870; λ_{max} 289.5, ϵ = 3,900.

The infrared absorption spectrum of 1,3-diphenylallene shows a strong allene absorption at 1947 cm.$^{-1}$ The characteristic phenyl peaks between 1650 cm.$^{-1}$ and 1900 cm.$^{-1}$ are well defined; however, in comparison with the 1947 cm.$^{-1}$ peak they are extremely weak.

1-(p-Biphenyl)-3-phenylallene. A solution of 0.768 g. of 1-(*p*-biphenyl)-3-phenyl-1-propyne in *n*-pentane was placed on a 1.7 × 11 cm. column of alumina A and eluted after 45 min. with *n*-pentane. The solvent was removed at room temperature under an atmosphere of nitrogen. The yield of 1-(*p*-biphenyl)-3-phenylallene was 0.527 g. (68.6% yield) m.p. 84.8–86.4°C.

1-(*p*-Biphenyl)-3-phenylallene was also prepared by shaking a solution of 0.100 g. of 1-(*p*-biphenyl)-3-phenyl-1-propyne, in 50 ml. of petroleum ether (b.p. 20–40°), with 1 g. of sodium hydroxide pellets, for 11 hrs. at room temperature. The solution was filtered and concentrated. When cooled in an ice bath the concentrated solution deposited white crystals of 1-(*p*-biphenyl)-3-phenylallene (58% yield,

(11) L. M. Long and H. R. Henze, *J. Am. Chem. Soc.*, **63**, 1939 (1941).

(12) E. P. Clark, *Semimicro Quantitative Organic Analysis*, Academic Press, New York (1943), p. 47.

m.p. 91–94°C.). Further purification was effected by recrystallizing from petroleum ether (b.p. 20–40°). The melting point was raised to 94.6–95.5°C.

Anal. Calcd. for $C_{21}H_{16}$: C, 93.99; H, 6.01; M.W., 268. Found: C, 93.83; H, 6.09; M.W. (cryoscopic in benzene), 242.

The infrared absorption spectrum of 1-(*p*-biphenyl)-3-phenylallene shows a strong allene absorption at 1944 cm.$^{-1}$ Just as in the case of 1,3-diphenylallene, the phenyl peaks between 1650 cm.$^{-1}$ and 1900 cm.$^{-1}$ are well defined, but they are extremely weak in comparison with the 1944 cm.$^{-1}$ peak.

levo-1,3-Diphenylallene. A solution of 1.18 g. of 1,3-diphenylpropyne in 20 ml. of *n*-pentane was placed on a column of alumina C (alumina-brucine mixture, total weight of mixture, 30 g.) and eluted at once with excess *n*-pentane. The solvent was removed at room temperature under an atmosphere of nitrogen, using a water aspirator. The solid residue was taken up in ether and extracted with cold 0.1*N* hydrochloric acid, washed with cold dilute aqueous sodium bicarbonate solution and finally washed with cold water. After drying over anhydrous magnesium sulfate, the ether was removed. The residue, a white solid, weighed 0.94 g. (80% yield), m.p. 41.8–50.6°C. The infrared spectrum of this solid showed a strong allene absorption band at 1940 cm.$^{-1}$ whereas, no acetylene absorption was observed. Rotation was taken in a carbon tetrachloride solution, using a 1 dcm. polarimeter tube. $[\alpha]_D^{23}$ −1.24° (c 10.58); observed rotation α_D^{23} −0.131° ± 0.009. The specific rotation of the allene was increased to $[\alpha]_D^{22.8}$ −1.82° (carbon tetrachloride, c = 3.19) by fractional recrystallization, using *n*-pentane as solvent and cooling the solution in a Dry Ice–acetone bath.

When 1,3-diphenylpropyne (1 g.) was treated with a solution of anhydrous brucine (6.15 g.) in chloroform (31 ml.) at room temperature, for 11.5 hr., only the starting propyne (0.86 g.) was isolated and it was optically inactive.

dextro-1,3-Diphenylallene was prepared by the method described for the preparation of levo-1,3-diphenylallene, using alumina C (alumina-quinine mixture). The yield of allene was 73.3%. The rotation was taken in carbon tetrachloride solution using a 1 dcm. polarimeter tube. $[\alpha]_D^{23}$ +2.48° (c 10.7); observed rotation α_D^{23} +0.265° ± 0.023. A side-product in this reaction was a white compound m.p. 191.5–194°C. It was found to have twice the molecular weight of 1,3-diphenylpropyne. This compound was optically inactive.

levo-1-(p-Biphenyl)-3-phenylallene was prepared by the method described above for the preparation of levo-1,3-diphenylallene. The yield of allene (m.p. 83–95°C.) was 69.3%. An infrared spectrum of the product was identical with that of racemic 1-(*p*-biphenyl)-3-phenylallene. The rotation was taken in carbon tetrachloride solution using a 1 dcm. polarimeter tube. $[\alpha]_D^{22.8}$ −7.0 (c = 10.35); observed rotation $\alpha_D^{22.8}$ −0.725 ± 0.022°.

Hydrogenation of levo-1-(*p*-biphenyl)-3-phenylallene (m.p. 83–95°C.; $[\alpha]_D^{22.8}$ −7.0°) over platinum oxide catalyst at room temperature and atmospheric pressure, using benzene as solvent, indicated an uptake of 2 moles of hydrogen. The isolated crude product was optically inactive. Recrystallization of the product yielded a solid m.p. 37.5–40°C. A mixture melting point of this solid with the hydrogenation product of 1-(*p*-biphenyl)-3-phenyl-1-propyne (m.p. 40–41.6°C.) maintained a sharp melting point, 39–41°C. Platinum oxide was chosen as the catalyst in this experiment because it has been reported[13] to give very little racemization in the reduction of (−)-3-phenyl-1-butene to (−)-2-phenylbutane. In this olefin the double bond is adjacent to the asymmetric center, and there is also a phenyl group on the asymmetric carbon. The possibility that the observed optical activity of our allene might result from the presence, as an impurity, of a compound bearing an asymmetric center appears very unlikely because all activity is destroyed by the hydrogenation.

dextro-1-(p-Biphenyl)-3-phenylallene. A column, 1.7 × 10 cm., of neutral alumina (20 g.)-quinine (4 g.) mixture, prepared as described for the preparation of alumina C, was covered with *n*-pentane. The rate of migration of *n*-pentane on the column was very slow; it could be increased by using a water aspirator. 1-(*p*-Biphenyl)-3-phenyl-1-propyne (0.5 g.), dissolved in *n*-pentane was placed on the column. After 5 days the column was eluted with *n*-pentane and *n*-heptane. The solution was filtered and the solvent removed at room temperature, under an atmosphere of nitrogen and reduced pressure. The solid residue was taken up in ether, washed with cold 0.1*N* hydrochloric acid, dilute aqueous sodium bicarbonate solution and finally with cold water. It was dried over anhydrous magnesium sulfate. The ether was removed at room temperature under an atmosphere of nitrogen, using a water aspirator. Light yellow crystals (0.171 g., 34% yield, m.p. 67.2–82.8°C.) were obtained. An admixture of product and starting material showed a depression of the melting point (54°–75°C.). An infrared spectrum of the product was identical with that of racemic 1-(*p*-biphenyl)-3-phenylallene. The rotation was taken in carbon tetrachloride solution, using a 1 dcm. polarimeter tube. $[\alpha]_D^{24}$ +8.57°, (c 10.03); observed rotation α_D^{24} +0.860 ± 0.029.

Los Angeles, Cal.

(13) D. J. Cram, *J. Am. Chem. Soc.*, **74**, 5518 (1952).

[CONTRIBUTION FROM THE ROCKEFELLER INSTITUTE]

The Aconite Alkaloids. XXXV. Structural Studies with Delphinine Derivatives*

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The investigations reported do not permit the derivation of a ring structure for delphinine and aconitine. Renewed studies on the exhaustive methylation of delphonine confirm our previous findings. This could not be brought beyond the stage of the first methine base. The formation of the latter with the nitrogen attached to a diterpenoid geminal methyl would require rearrangement of the other methoxyl-bearing geminal group. The oxidation of oxodelphonine, dihydropyrooxodelphonine, and dihydroisopyrooxodelphonine has in each case been intercepted at the stage of a cyclopentanone (infrared data) which can be oxidized further to a keto acid in which the new keto group is in a six-membered or larger ring. The cyclopentanones, in contrast to the original hydroxy compounds, are all readily isomerized to strongly levorotatory stereoisomers. This is apparently due to enolization. On vacuum sublimation the keto acid from dihydroisopyrooxodelphonine readily cyclizes to yield the previously described neutral diketone in contrast to the acids from α-oxodelphonine and dihydropyrooxodelphonine which distil unchanged. A number of these derivatives have been crystallized. Attempts to reconcile all of our data with a lycoctonine or napelline structure have not been successful and our previous proposal for delphinine has been withdrawn.

The aconite alkaloids which have been grouped provisionally into the very poisonous highly oxygenated aconitine type of ester bases and the less toxic atisine type have been long suspected to be chemically related, and recent work has given data from a number of them which strengthen this suspicion. The first clue to the relationship of these substances to the diterpenes was found in the dehydrogenation studies of this laboratory.[2] More recent work has led to the practically complete structural elucidation of veatchine,[3,4] atisine,[4,8] and garryfoline and cuauchichicine.[9] The dehydrogenation procedure unfortunately proved much less satisfactory with the aconitine type of base but the accumulated data made quite certain that a saturated hexacyclic structure is involved in the case of aconitine and delphinine in which a ring nitrogen carries an ethyl or a methyl group. Extensive studies have shown the nature and probable interrelationships of the substituting groups of delphinine.[10,11] The first derivation of the actual skeletal structure of a hexacyclic aconitine base, however, was shown by the outstanding x-ray studies of a lycoctonine derivative by Przybylska and Marion.[12] This was shown to be related in part to a phyllocladene structure in which ring B has been enlarged to a cycloheptane at the expense of ring C and the latter reduced to a cyclopentane with other changes. Such a ring structure has been satisfactorily adopted by Cookson and Trevett[13] for their experimental data with delpheline and by Anet, Clayton and Marion for delcosine.[14] Very recently Wiesner *et al.* have adopted a more normal diterpenoid core to explain their data with napelline and napellonine.[15]

In this laboratory the attempt was once made to correlate the data accumulated for delphinine with the lycoctonine structure, but a number of facts persist which appear inconsistent with this interpretation unless unusual rearrangements are assumed to occur. There is the authors' early and now recently repeated experience in an attempted exhaustive methylation of delphonine.[16,17] At the

* This paper is a contribution in honor of Lyndon F. Small, former Editor of the Journal.

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(3) K. Wiesner *et al.*, *J. Am. Chem. Soc.*, **76**, 6068 (1954).

(4) K. Wiesner and J. A. Edwards, *Experientia*, **11**, 255 (1955).

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(6) S. W. Pelletier and W. A. Jacobs, *J. Am. Chem. Soc.*, **76**, 4496 (1954).

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(9) C. Djerassi, C. R. Smith, A. E. Lippman, S. K. Figdor, and J. Herran, *J. Am. Chem. Soc.*, **77**, 4801, 6633 (1955).

(10) W. A. Jacobs and S. W. Pelletier, *J. Am. Chem. Soc.*, **76**, 161 (1954).

(11) W. A. Jacobs and S. W. Pelletier, *Chemistry and Industry*, 948 (1955).

(12) M. Przybylska and L. Marion, *Can. J. Chem.*, **34**, 185 (1956).

(13) R. C. Cookson and M. E. Trevett, *J. Chem. Soc.*, 3121 (1956).

(14) R. Anet, D. W. Clayton, and L. Marion, *Can. J. Chem.*, **35**, 397 (1957).

(15) K. Wiesner, Z. Valenta, J. F. King, R. K. Mandgal, L. G. Humber, and Shô Iho, *Chemistry and Industry*, 173 (1957).

(16) L. C. Craig, L. Michaelis, S. Granick, and W. A. Jacobs, *J. Biol. Chem.*, **154**, 293 (1944).

(17) In earlier work in this laboratory all attempts to carry such degradation beyond this first stage to nitrogen-free material proved unsuccessful. In view of the recent papers of Schneider [*Arch. d. Pharm.* **283**, 86, 281 (1950)] who reported carrying the procedure to nitrogen-free material which was then oxidized to an acid $C_{20}H_{24}O_{12}$, the authors have repeated this study. After the first step, attempted methylation of the methine base with subsequent distillation of the "ammonium base" always gave negligible amounts of nitrogen-free material. The recovered base gave *N*-methyl analyses incompatible with further methylation. By following the experimental conditions reported

first stage the methyl ammonium base yields without difficulty what appears to be an *N*-dimethyl methine base. Barring rearrangement perhaps involving the methoxyl bearing geminal methyl group such a product would not be expected to arise from a lycoctonine type of skeleton. A second point is the formation from dihydroisopyrooxodelphonine[18] of a keto acid, $C_{24}H_{35}NO_8$[19] which readily cyclizes on vacuum sublimation to give the diketone, $C_{24}H_{33}NO_7$. This was shown more recently to contain both a cyclohexanone and a cyclopentanone ring.[20] An attempt was made in the authors' last communication[20] to reconcile the data at hand with a new structural proposal for delphinine.[21] However, more recent work has now shown such a structure to be untenable, and inconsistencies also persist with a lycotonine or napelline type of skeleton for it.

Unless no change in ring structure can be shown to occur in the steps leading to the formation of isopyrooxodelphonine, the data obtained with the latter could give rise to false conclusions. The authors have therefore studied other delphinine derivatives beginning with delphonine. In a recent study of the latter it has been found that when allowed to stand exposed it gradually becomes contaminated, probably by oxidation, and shows infrared peaks of varying intensity at 1710 and 1653 cm.$^{-1}$. However, when chromatographed through alumina, such contaminating material can be readily removed and the purified delphonine shows no significant band in this region. Schneider[22] has attributed the absorption of crude delphonine at 5.87 μ to an –NCHOH– group which opens to give an amino aldehyde. The authors' experience does not substantiate this conclusion.

On turning to α-oxodelphonine it was recently obtained crystalline for the first time, separating from methanol with one mole of solvent. On oxidation with chromic oxide it passes through the stage of a beautifully crystalline α-oxodelphonone, $C_{24}H_{35}NO_8$, which shows the absorption of a cyclopentanone (1751 cm.$^{-1}$ in Nujol). On further oxidation the amorphous keto acid was obtained showing a band at 1736 cm.$^{-1}$ (Nujol) 1728 (chf.). The position of this absorption does not permit a decision between a cyclopentanone and a larger ring ketone. Because of the infrared data found with the amorphous methyl ester (1706 cm.$^{-1}$, cyclohexanone; 1730 cm.$^{-1}$, methyl ester) it is probable that the keto acid contains a cyclohexanone or larger ring.

A return was then made to the study of the pyro series. Dihydropyro-α-oxodelphonine[19] has recently been obtained crystalline from methanol. On oxidation with chromic acid it yields the previously reported keto acid, $C_{24}H_{35}NO_8$[19]. The latter has been found to crystallize also from methanol but in a solvated form (m.p. 183–190°) different from that previously described. The infrared absorption (1724 cm.$^{-1}$) in Nujol of the latter indicates a cyclohexanone or larger ring. After sublimation this remained the same.

The formation of the ketoacid was intercepted at the stage of the neutral intermediate crystalline ketone, dihydropyro-α-oxodelphonone, $[\alpha]_D+9.4^0$. The infrared absorption (1749 cm.$^{-1}$ in Nujol; 1766 in CCl_4) of the latter again indicates a cyclopentanone. This on further oxidation gave the keto acid. The keto acid yields a crystalline methyl ester with absorption indicating a cyclohexanone (or higher) acid. (1706, 1734 cm.$^{-1}$ in CCl_4; 1711, 1727 in $CHCl_3$). Contrary to the experience with the keto acid from dihydroisopyro-α-oxodelphonine which forms a neutral diketone on sublimation, this keto acid is distilled as such in mercury pump vacuum without loss of water; infrared absorption (1724 cm.$^{-1}$ in Nujol). The fact that the keto acid from dihydropyrooxodelphonine can be distilled unchanged in contrast to the previously recorded behavior of the keto acid from dihydroisopyrooxodelphonine, which yielded a neutral diketone containing a new cyclopentanone ring, suggested the possibility of a change in ring size during the isomerization of pyrooxodelphonine to the isoderivative.[23] To check such a possibility the oxidation of dihydropyroisooxodelphonine was again studied. Under conditions analogous to those used with its isomer, chromic oxide was found to oxidize it through an intermediate neutral ketone to the previously recorded keto acid.[19] Unfortunately, this neutral ketone was not obtained in pure crystalline form. It was found to separate as mixed crystals with its precursor. From the rotation of this mixture, $[\alpha]_D$ −25°, the ketone must be less levorotatory, if not actually dextrorotatory, than its precursor of $[\alpha]_D$ −36°. Preliminary infrared study of such mixtures showed a small fractional peak at 1754 cm.$^{-1}$ ($CHCl_3$) as required by a cyclopentanone and resembling the data from the

by Schneider similar results were obtained. In the available communications of the author, no nitrogen analysis on the "nitrogen-free" material is reported. His statement that the product gave a negative Lassaigne nitrogen test is hardly convincing.

It can be reported in this connection that reaction of the methine base with methyliodide has given in small yield a beautifully crystalline iodide of lower methoxyl content and of no greater *N*-methyl content. This suggests possible loss of the methoxyl-bearing geminal methyl group. This is being studied further.

(18) W. A. Jacobs and C. F. Huebner, *J. Biol. Chem.*, **170**, 209 (1947).

(19) W. A. Jacobs and Y. Sato, *J. Biol. Chem.*, **180**, 479 (1949).

(20) W. A. Jacobs and S. W. Pelletier, *J. Am. Chem. Soc.*, **78**, 3542 (1956).

(21) In several formulas given in this paper an error has come to the authors' attention in which the position at 9,14 assigned to the double bond violates Bredt's rule. However, this can be overcome by placing the double bond at 8,14 or the acetoxyl group at 8 and the former at 7,8.

(22) W. Schneider, *Chem. Ber.*, **89**, 768 (1956).

(23) Such a proposal, but without any experimental data, was also made by K. Wiesner in a personal communication to us.

isomeric dihydropyrooxodelphonone. The attempt to separate this mixture through acid-washed alumina (*p*H 4.5) led to a most unusual result. More than a third of the material was eluted as a ketone before the appearance of the original unoxidized dihydroisopyrooxodelphonine. But the ketonic material was now strongly levorotating, $[\alpha]_D$ −127°. Its infrared absorption showed a strong cyclopentanone peak at 1747 cm.$^{-1}$ (CCl_4) which approximated that of the original mixture. Its analysis confirmed it to be an isomer of the intermediate neutral ketone, $C_{24}H_{35}NO_7$. On further oxidation with chromic acid it yielded an amorphous keto acid, $C_{24}H_{35}NO_8$, $[\alpha]_D$ −3°, isomeric with the crystalline oxidation product from dihydroisopyro-oxodelphonine.

Dihydropyrooxodelphonone was also found to isomerize when passed through acid-washed alumina to yield an amorphous strongly levo rotating isomer, $[\alpha]_D$ −107°.[24] This isomerization was shown to be rather general, since α-oxodelphonone was similarly isomerized by alumina to a strongly levorotating amorphous iso-α-oxodelphonone, $[\alpha]_D$ −80°. Since the preparation of these intermediate ketones was carried out under acid conditions it appeared probable that such alumina-induced (*ca.* *p*H 4 to 5) isomerizations were not due to acid. This was substantiated in the case of α-oxodelphonone by its rapid change with sodium hydroxide to the same substance obtained with alumina. It was not affected in a similar way by acid and was in part recovered unchanged. Since the precursors of the intermediate ketones are obtained by alkali saponification, the isomerizations must involve the carbonyl group of the ketones, and are presumably effected by enolization with a vicinal hydrogen-bearing carbon atom, with change of configuration and formation of the epimeric ketone.

Since attempts to accommodate our data to a specific ring system have not been satisfying as yet, the authors shall not attempt, at the present time, to propose a structure for delphinine or its derivatives. This will be left to a later opportunity when work which is still in progress has been completed. But it can be concluded that the data here reported are inconsistent with the previously proposed structure for delphinine.[20] There are only two positions in ring C in such a structure available for a benzoylated secondary hydroxyl group which after saponification followed by oxidation would yield an intermediate cyclopentanone. Although the latter, on further oxidative ring cleavage could give a ketoacid containing a cyclohexanone or larger ring ketone, in neither case, barring unusual rearrangements, would cyclization occur to give a new cyclopentanone ring such as is present in the neutral diketone obtained from dihydroisopyro-α-oxodelphonine.

(24) Unfortunately infrared data for all of these isomerized substances were not available at the time of the writing of this paper.

EXPERIMENTAL

Delphonine. A solution of 20 g. of delphinine in a mixture of 200 ml. of ethanol and 200 ml. of 10% sodium hydroxide was heated under reflux for 2 hr. After removal of most of the alcohol *in vacuo* the delphonine was extracted with ether. The extract was dried over potassium carbonate. After removal of solvent 15 g. of resin remained. A solution of 11.5 g. of this material in 100 ml. of benzene was chromatographed through 550 g. of Merck alumina and first eluted with benzene (1 l.) then with 0.5% methanol in benzene (1 l.) without result. On changing to 1% methanol no solid emerged until 1800 ml. was used and then elution began in very small fractions of about 30 mg./25 ml. which gradually rose to about 90 mg. After 80 such fractions, the eluted material had diminished to about 60 mg. in 25 ml., and a change to 2% methanol was made. Since this did not quickly affect the result after another 600 ml. was used, a change to 3% methanol was made. The eluted material gradually reached a peak of 0.2 g. per 25 ml. After about 900 ml. was used this quickly diminished to very small amounts of solid. However, only in this final material which totaled only about 0.48 g. was a large peak shown in the infrared at 1652 cm.$^{-1}$ The fractions from the beginning of elution through the greatest part which totaled about 9.2 g. showed no appreciable infrared absorption in the 6-μ region. $[\alpha]_D^{27}$ +36° (c, 0.6 in $CHCl_3$).

Anal. Calcd. for $C_{24}H_{39}NO_7$: C, 63.55; H, 8.67. Found: C, 63.52; H, 8.64.

α-Oxodelphonine. A suspension of 10 g. of α-oxodelphinine in 250 ml. of 95% alcohol was brought to a boil and after addition of 50 ml. of 4% aqueous sodium hydroxide was refluxed for 7 min. during which solution rapidly occurred. Sufficient 50% acetic acid was added to acidify the mixture which was then concentrated *in vacuo* to remove the alcohol. The residue was dissolved in water and treated with sodium bicarbonate solution and the solution was extracted 10 times with chloroform. The cleared extract yielded 8.55 g. of resin. Contrary to earlier experience this was finally crystallized from methanol forming four-sided, pointed platelets which contained 1 mole of solvent and melted at 118–120°; $[\alpha]_D^{29}$ −7.5° (c, 0.80 in chloroform). It is readily soluble in acetone.

Anal. Calcd. for $C_{24}H_{37}NO_8 \cdot CH_3OH$: CH_3OH, 6.22. Found: 6.28.

For analysis it was dried at 100° at 0.2 mm.

Anal. Calcd. for $C_{24}H_{37}NO_8$: C, 61.65; H, 7.98. Found: C, 61.38; H, 7.99.

α-Oxodelphonone and the keto acid $C_{24}H_{35}NO_9$. A solution of 3 g. of α-oxodelphonine in 75 ml. of redistilled acetic acid[25] was stirred at room temperature and treated during 10 min. with 5.6 ml. (4.3 ml. represents about one equivalent of oxygen) of a fresh 10% aqueous chromium trioxide solution. After an hour the mixture was diluted with 100 ml. of water and extracted 10 times with chloroform. At this point and at the following steps of the procedure, the addition of small amounts of NaCl solution to the aqueous phases aided an otherwise somewhat slow phase separation. The extract was washed four times with 20-ml. portions of water and then with water containing sufficient sodium carbonate to remain alkaline to phenolphthalein. This was followed by repeated washings with small portions of water until the washings were no longer alkaline. The chloroform layer, after clearing with sodium sulfate, concentrating *in vacuo* to dryness, and flashing off with benzene yielded 2.28 g. of resin. When dissolved in a small volume of acetone α-oxodelphonone soon crystallized as well-formed hexagonal or rhombic platelets

(25) The acetic acid used in all of the oxidations reported was twice distilled over CrO_3.

of varying width and length. Because of persistent contamination with starting material it was necessary to recrystallize it repeatedly; m.p. 198–208°; $[\alpha]_D^{29}$ +33° (*c*, 0.52 in chloroform) ν^{Nujol} 1751 $cm.^{-1}$ It contained solvent and for analysis was dried at 110° and 0.2 mm. It also crystallized readily from methanol.

Anal. Calcd. for $C_{24}H_{35}NO_8$: C, 61.92; H, 7.58. Found: C, 61.90; H, 7.51.

As described later, this substance is changed on standing with alkali or on attempted chromatographing through alumina.

Following the separation of additional less pure fractions from the acetone mother liquors, a resinous solid remained which crystallized readily from methanol on seeding and proved to be starting material.

The sodium carbonate extract with subsequent aqueous washings was repeatedly extracted with chloroform to remove retained dissolved neutral material, then acidified with sulfuric acid and repeatedly extracted with chloroform. The latter on concentration yielded 277 mg. of the keto acid, $C_{24}H_{35}NO_9$. All attempts to crystallize this acid were unsuccessful and it was therefore analyzed directly after drying at 110° and 0.2 mm. $[\alpha]_D^{29}$ +9.6° (*c*, 0.52 in chloroform). ν^{Nujol} 1736, ν^{CHCl_3} 1728 $cm.^{-1}$

Anal. Calcd. for $C_{24}H_{35}NO_9$: C, 59.86; H, 7.33. Found: C, C, 59.91; H, 7.20.

The same keto acid was obtained by similar oxidation of the previous intermediate ketone. 0.1 g. of the latter gave 47 mg. of the keto acid; $[\alpha]_D^{29}$ +10° (*c*, 0.50 in chloroform). ν^{Nujol} 1736 $cm.^{-1}$

Anal. Found: C, 59.97; H, 7.21.

The methyl ester which was obtained with diazomethane could not be crystallized. $[\alpha]_D^{31}$ −24.5° (*c*, 0.49 in $CHCl_3$) ν^{Nujol} 1706, 1730 $cm.^{-1}$ For analysis it was dried at 100° and 0.2 mm.

Anal. Calcd. for $C_{25}H_{37}NO_9$: C, 60.59; H, 7.53. Found: C, 60.13; C, 7.48.

Dihydropyro-α-oxodelphonine. Two grams of octahydropyro-α-oxodelphinine in 25 ml. of methanol was treated with 25 ml. of 10% sodium hydroxide and allowed to stand at room temperature for 1 hr. The solution was diluted with 20 ml. of saturated sodium chloride solution to aid separation and extracted ten times with chloroform. The latter was washed with sodium chloride solution and the solvent was removed *in vacuo* followed by flashing with benzene. The resin crystallized from methanol as nearly rectangular platelets. When recrystallized from methanol, it contained one mole of solvent and melted at 103–104°. $[\alpha]_D^{29}$ −24°. (*c*, 0.50 in chloroform).

Anal. Calcd. for $C_{24}H_{37}NO_7 \cdot CH_3OH$: CH_3OH, 6.65. Found: CH_3OH, 6.40. For analysis it was dried at 0.2 mm. and 100°.

Anal. Calcd. for $C_{24}H_{37}NO_7$: C, 63.81; H, 8.26. Found: C, 63.74; H, 8.13.

Oxidation of dihydropyro-α-oxodelphonine. Different conditions than previously reported were used in this oxidation. A stirred solution of 1.49 g. of solvent-free dihydropyro-α-oxodelphonine in 50 ml. of acetic acid was carefully treated during 10 min. with 7.0 ml. of a fresh 10% aqueous chromium trioxide solution which was approximately 50% in excess of the amount required for conversion to the keto acid. However, even after an additional 5 min., when the reaction was interrupted, oxidation was found to be incomplete as shown by the isolation of some of the intermediate ketone in the neutral fraction. The diluted solution, after addition of sodium chloride to aid separation, was thoroughly extracted with a good volume of chloroform. The dried extract was concentrated *in vacuo*, finally flashing off the residue with benzene to remove acetic acid. The residue was dissolved in acetone, filtered from a small amount of inorganic material, and concentrated to a small volume. On careful addition of water and seeding, the acid gradually separated as micro leaflets and was collected with 25% acetone. It possessed the properties previously reported and contained water of crystallization; m.p. 132–136° after preliminary sintering. Additional succeeding fractions were gradually obtained by concentration and seeding of the filtrates. The yield of crude keto acid was about 0.64 g. These fractions were found to be contaminated increasingly with neutral material and were therefore purified by extraction of their chloroform solution with dilute sodium carbonate solution followed by washing with water. It was found necessary to rextract these combined aqueous phases repeatedly with chloroform before acidification to remove some neutral material which was carried into the aqueous phase. The reacidified carbonate solution was then further extracted with chloroform to obtain the keto acid. This has been found to crystallize from methanol as well-formed four-sided plates or prisms which contained solvent and gradually melted at 183–190°; $[\alpha]_D^{28}$ −5.7° (*c*, 0.47 in $CHCl_3$); ν^{Nujol} 1724 $cm.^{-1}$ The analysis of this material was found difficult since even when dried at 130° and 0.2 mm. it retained solvent and gave low carbon figures.

Anal. Calcd. for $C_{24}H_{35}NO_8$: C, 61.92; H, 7.58. Found: C, 61.35; H, 7.80.

When such material was dissolved in acetone and the solvent was flashed off *in vacuo* it gave correct figures when dried at 110°.

Anal. Found: C, 61.82; H, 7.68.

Contrary to the isomeric keto acid from dihydroiso-pyro-α-oxodelphonine this keto acid sublimed largely unchanged. It (0.2 g.) was introduced into the sublimation apparatus with acetone and after removal of solvent it was gradually heated in an oil bath under a mercury pump vacuum of 0.01 to 0.001 mm. Condensation occurred especially from 170–190°. After reaching 220° practically all had sublimed during a total of 33 minutes' heating. The condensate was dissolved in chloroform and extracted with dilute sodium carbonate solution. The latter with the washings, after reacidification, was reextracted with chloroform. It yielded 0.15 g. of unchanged keto acid, ν^{Nujol} 1724 $cm.^{-1}$

Anal. Calcd. for $C_{24}H_{35}NO_8$: C, 61.92; H, 7.58. Found: C, 61.85; H, 7.38. It recrystallized readily from methanol; m.p. 183–190°; $[\alpha]_D^{27}$ −4° (*c*, 0.56 in $CHCl_3$).

Dihydropyro-α-oxodelphonone. The filtrate from the keto acid in the previous oxidation was dissolved in chloroform and extracted with sodium carbonate solution followed by several washings with water. The chloroform containing the neutral fraction, after drying and concentration *in vacuo*, yielded 0.43 g. In a small volume of methanol the ketone crystallized gradually as microneedles or four-sided and six-sided, long platelets which contained 1 mole of solvent; m.p. 169–177°; $[\alpha]_D^{29}$ +9.4° (*c*, 0.48 in $CHCl_3$). ν^{Nujol} 1749 $cm.^{-1}$; ν^{CCl_4} 1766 $cm.^{-1}$

Anal. Calcd. for $C_{24}H_{35}NO_7 \cdot CH_3OH$: CH_3OH, 6.65. Found: CH_3OH, 6.80. For analysis it was dried at 0.2 mm. and 125–130°.

Anal. Calcd. for $C_{24}H_{35}NO_7$: C, 64.12; H, 7.85. Found: C, 64.08, H, 8.02.

The solvent-free ketone (36 mg.) was further oxidized in acetic acid with excess chromium trioxide. After dilution and exhaustive extraction with chloroform, the keto acid was extracted with dilute sodium carbonate and aqueous washings. After reacidification and reextraction 22 mg. of the above keto acid was obtained which crystallized readily from methanol on seeding; m.p. 180–185°. $[\alpha]_D^{31}$ −13.5° (*c*, 0.52 in $CHCl_3$). The somewhat different rotation obtained with the material isolated above in the direct oxidation will require further study. The substance as obtained from methanol again showed the difficulty in removing solvent for analysis.

Anal. Found: C, 61.16; H, 7.64.

The methyl ester. The keto acid (45 mg.) in acetone readily yielded the ester with diazomethane. It crystallized without solvent from methanol mostly as four-sided prisms or from methanol-ether as needles; m.p. 177–180°; $[\alpha]_D^{28}$ −25° (*c*, 0.48 in $CHCl_3$). ν^{CHCl_3} 1725, 1712 $cm.^{-1}$; ν^{CCl_4} 1733, 1706 $cm.^{-1}$

Anal. Calcd. for $C_{25}H_{37}NO_8$: C, 62.61; H, 7.78. Found: C, 62.71; H, 7.65.

The oxidation of dihydroisopyrooxodelphonine. A solution of 0.4 g. of dihydroisopyrooxodelphonine [$[\alpha]_D^{30}$ −36° (*c*, 0.5 in $CHCl_3$)] in 13.6 ml. of acetic acid was gradually treated with stirring with 1.2 ml. of fresh 5% aqueous chromium trioxide solution (1 mole). The reagent was used up quite rapidly and after 35 min. the solution was diluted, treated with 1 ml. of saturated sodium chloride solution to aid separation, and extracted 13 times with chloroform. The extract was washed once with 5 ml. of water, cleared with sodium sulfate, and concentrated *in vacuo* to dryness with final flashing off with benzene to remove acetic acid. The solution in chloroform was extracted with a solution of 0.15 g. of sodium carbonate dissolved in 2 ml. of water, followed by three 1-ml. washings with water. After standing about an hour the combined sodium carbonate and water washings were extracted 7 times with chloroform. The latter yielded only 8 mg. of neutral material. The acidified aqueous phase after extraction with chloroform gave 0.112 g. of the previously described keto acid[19] which crystallized readily from acetone-ether as needles, m.p. 169–173°. The melting point varies considerably with the conditions of crystallization but this and the rotation of $[\alpha]_D^{31}$ −13.5° (*c*, 0.52 in $CHCl_3$) are somewhat different from the values obtained with the keto acid previously described.[19] The rotation of the latter has now been found to be $[\alpha]_D^{29}$ −3.6° (*c*, 0.56 in $CHCl_3$). This suggests isomerization at some stage which will require further study.

Anal. Calcd. for $C_{24}H_{35}NO_8$: C, 61.92; H, 7.58. Found: C, 61.66; H, 7.61.

The chloroform solution containing the main neutral fraction yielded 0.295 g. of residue after flashing off with acetone. When dissolved in a small volume of acetone crystallization started, especially after addition of ether and partial concentration; after several hours a first fraction of 0.15 g. was collected, $[\alpha]_D^{28}$ −25°. (*c*, 0.48 in $CHCl_3$); m.p. 166–175°.

The mother liquor when similarly manipulated gave a second crystalline fraction of 55 mg; after sintering at 154° it gradually melted at 162 to 182°; $[\alpha]_D^{28}$ −28° (*c*, 0.54 in $CHCl_3$). Preliminary attempts to resolve this material into its components were not promising although from certain observations which will be left to a later communication it is probable that this can be done by the proper use of solvents. The attempt was made to do this with alumina washed to a *p*H of 4.5.

A solution of 0.21 g. of this mixture was chromatographed in benzene through 8.5 g. of alumina. Following preliminary unsuccessful elution with 100 ml. of benzene, 0.5% methanol in benzene was used. After 50 ml it gradually yielded continuously very small fractions the nature of which was followed by rotations. The rotation of the initial fraction $[\alpha]_D^{30}$ −127° (*c*, 0.7 in $CHCl_3$) and succeeding fractions gave about the same value until elution had become very small. After the use of about 600 cc. solvent about 65 mg. were eluted, ν^{CCl_4} 1747 cm.$^{-1}$

Anal. Calcd. for $C_{24}H_{35}NO_7$: C, 64.12; H, 7.85. Found: C, 64.38; H, 7.87.

The later elution with 1% methanol in benzene gradually yielded a total of 0.124 g. of unoxidized dihydroisopyrooxodelphonine which showed no ketonic band in the infrared.

A solution of 49 mg. of the ketone in 1.7 ml. of acetic acid was treated with 0.3 ml. of 5% chromium trioxide. Reaction quickly occurred. After 40 min. the mixture was diluted and extracted with chloroform. After removal of solvent and acetic acid the chloroform solution was extracted with sodium carbonate solution. The latter, after acidification and reextraction, yielded 35 mg. of amorphous keto acid which could not be crystallized. $[\alpha]_D^{31}$ −3° (*c*, 0.34 in $CHCl_3$).

Anal. Calcd. for $C_{24}H_{35}NO_8$: C, 61.92; H, 7.58. Found: C, 62.12; H, 7.34.

Dihydropyro-α-oxodelphonone and alumina. Dihydropyro-α-oxodelphonone (66 mg.) was chromatographed through 3.5 g. of acid-washed alumina as described in the case of its isomer. The material which was eluted with 0.5 methanol in benzene showed $[\alpha]_D^{28}$ −107° (*c*, 0.67 in $CHCl_3$). It formed a low-melting resin which could not be crystallized.

Anal. Calcd. for $C_{24}H_{35}NO_7$: C, 64.12; H, 7.85. Found: C, 64.20; H, 8.06.

Treatment of α-oxodelphonone with alumina. A solution of 0.24 g. of the ketone was chromatographed through 10 g. of acid-washed alumina. After benzene, 1% methanol in benzene was finally required for elution. Material appeared in successive fractions. The material could not be crystallized and showed a rotation of $[\alpha]_D^{28}$ −80°. (*c*, 0.625 in $CHCl_3$).

Anal. Calcd. for $C_{24}H_{35}NO_8$: C, 61.92; H, 7.58. Found: C, 61.94; H, 7.68.

A suspension of 25 mg. of α-oxodelphonone in 4 ml. of water and 1 ml. of methanol was warmed to effect solution. The cooled solution was treated with 0.5 cc. of 0.1*N* NaOH. The rotation taken within 11 minutes showed $[\alpha]_D$ −66°. No significant change of rotation was found after 24 hr. The diluted solution when extracted with chloroform yielded amorphous material which showed $[\alpha]_D^{30}$ −79.5° (*c*, 0.44 in $CHCl_3$).

Anal. Calcd. for $C_{24}H_{35}NO_8$: C, 61.92; H, 7.58. Found: C, 62.12; H, 7.69.

Acknowledgment. All of the analytical data reported were obtained by Dmitrius Rigakos. Gerhard Bitterlich participated greatly in the laboratory.

Note added in proof: Since sending in this manuscript a paper on delphonine by N. K. Abubakurov and S. Yu. Unusov [*J. Gen. Chem. URSS*, 26, 2011 (1956)] has come to our attention. From data obtained with a substance which they considered to be delphonine and which was obtained from saponified mother liquors of a mixture of alkaloids isolated from *Delphinium rotundifolium* Afan. they concluded that delphonine is not an *N*-methyl base but an *N*-ethyl base and that its formula is $C_{25}H_{41}NO_9$. This and other data which they report are so incompatible with the wealth of analytical data which we have obtained along with our other findings that we cannot accept their conclusions. There is the possibility that their "delphonine" is not identical with the delphonine from *Delphinium staphisagria*.

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[CONTRIBUTION FROM THE CHEMICAL INSTITUTE, UNIVERSITY OF ZÜRICH]

Some *Ind-N*-methyl-3-alkyl-β-carbolines and *Ind-N*-ethyl-3-alkyl-β-carbolines*

P. KARRER AND H. MÜLLER

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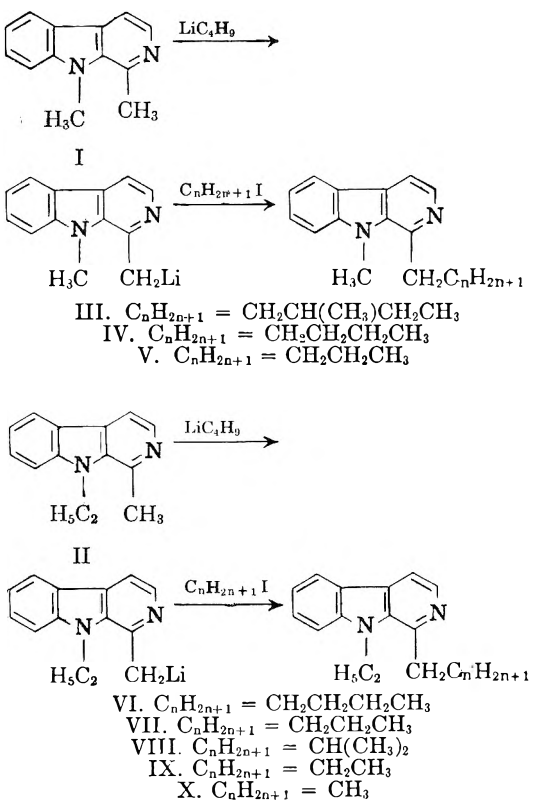
In the course of the experimental investigation of the indole alkaloids, which in the last few years have become of increasing importance, simple β-carboline derivatives were sometimes obtained, the constitution of which could not easily be elucidated on account of the small amounts available. Therefore, some of the compounds which could be expected as degradation (dehydration) products of indole and β-carboline alkaloids, respectively, were synthesized. Knowledge of these compounds may facilitate their identification.

These syntheses were carried out by alkylation of the lithium derivatives of *ind-N*-methylharman and *ind-N*-ethylharman with alkyl halides.

All compounds were characterized as picrates. Furthermore, their quaternary ammonium salts were made by heating them with methyl iodide. Finally the R_f values of the corresponding chlorides were determined on paper chromatograms. These qualities, which are essential contributions to the characterization of the various *ind-N*-methyl-3-alkyl-β-carbolines and *ind-N*-ethyl-3-alkyl-β-carbolines respectively, are listed in Table I.



EXPERIMENTAL

Ind-N-methylharman. Ten mg. of dry liquid ammonia was distilled with exclusion of moisture and oxygen into 220 mg. of potassium and 2 mg. $Fe(NO_3)_3$. After short stirring at room temperature the deep blue colors of the solution disappeared and potassium amide precipitated. To this mixture was added 1 g. harman which dissolved immediately giving a yellow color. Then 10 ml. of dry 1,2-dimethoxyethane was added and the ammonia was removed by warming the solution to 80° in a current of nitrogen. To the yellow solution of the harman potassium salt in 1,2-dimethoxyethane was added dropwise at ordinary temperature within 40 min. a solution of 0.33 ml. of dry methyl iodide in 4 ml. of the same solvent. During the reaction the mixture was stirred; heated shortly to its boiling point, diluted with ether, and the separated potassium iodide was filtered off. The residue was boiled out several times with ether and chloroform. The extracts were combined and evaporated, and the residue was distilled in the "Kugelrohr" under high vacuum, whereupon the substance distilled at 120–150° (temperature of the air bath) as a light yellow oil which crystallized after a short time. After two crystallizations from ether/pentane we obtained 634 mg. *ind-N*-methylharman, m.p. 102–104°.

Alkylation of ind-N-methylharman with 1-bromo-2-methylbutane. A solution of 200 mg. *ind-N*-methylharman in 3 ml. of dry ether was added dropwise at room temperature with stirring and exclusion of moisture to the solution of 1.0 g. *n*-butyllithium. The apparatus was filled with nitrogen. Immediately a dark yellow precipitate appeared. After having stirred the mixture for 15 min. at room temperature the solution of 0.130 ml. of dry 1-bromo-2-methylbutane in 1 ml. ether was added dropwise within 15 min. Then it was boiled for 1 hr. with stirring and exclusion of oxygen. After this time was added again 0.015 ml. of the bromide dissolved in 1 ml. ether and the mixture was boiled again for 2 hours. It was at first green but became finally light yellow. After having reached room temperature it was decomposed by water and the ether layer was separated. The water layer was extracted again with ether, the ether extracts combined, dried, the solvent evaporated, and the residue distilled in high vacuum. It went over at 125–145°/0.03 mm. (temperature of the air bath). The first drops of the distillate were removed. The distilled product was dissolved in methanol and picric acid was added. A mixture of picrates precipitated when the mixture was boiled with methanol, *ind-N*-methyl-3-(3′-methylpentyl)-β-carboline picrate went into solution while some *ind-N*-methylharman picrate remained undissolved. The former was crystallized from methanol several times; m.p. 165–166°.

Anal. Calcd. for $C_{24}H_{25}N_5O_7$: C, 58.17; H, 5.08; N, 14.12. Found: C, 57.97; H, 5.04; N, 14.17.

Alkylation of ind-N-methylharman with various alkyl halides. For the preparation of the following compounds the same method was applied as in the example mentioned above. *Ind-N*-methyl-3-*n*-pentyl-β-carboline picrate, m.p. 191°.

Anal. Calcd. for $C_{23}H_{23}N_5O_7$: C, 57.37; H, 4.82; N, 14.54. Found: C, 56.98; H, 4.91; N, 14.32.

* This paper is a contribution in honor of Lyndon F. Small, former Editor of the Journal.

TABLE I.

PROPERTIES OF *ind-N*-ALKYL-β-CARBOLINES

Compound	*ind-N*-alkyl	C(3)-alkyl	M.P. of Picrate	R_f Values of the Chlorides of the Quaternary Ammonium Bases	
				On washed paper	On unwashed paper
III	CH_3	$-CH_2CH_2CH(CH_3)CH_2CH_3$	165°	0.42	0.38
IV	CH_3	$-CH_2CH_2CH_2CH_2CH_3$	191°	0.37	0.34
V	CH_3	$-CH_2CH_2CH_2CH_3$	195°	0.34	0.30
	CH_3	$-CH_3$		0.18	0.17
VI	C_2H_5	$-CH_2CH_2CH_2CH_2CH_3$	156°	0.44	0.37
VII	C_2H_5	$-CH_2CH_2CH_2CH_3$	181°	0.39	0.33
VIII	C_2H_5	$-CH_2CH(CH_3)CH_3$	186°	0.34	0.29
IX	C_2H_5	$-CH_2CH_2CH_3$	206°	0.30	0.26
X	C_2H_5	$-CH_2CH_3$	236°	0.22	0.20
	C_2H_5	$-CH_3$		0.198	0.19

Ind-N-methyl-3-*n*-butyl-β-carboline picrate, m.p. 195°. Anal. Calcd. for $C_{22}H_{21}N_5O_7$: C, 56.53; H, 4.52; N, 14.96. Found: C, 56.89; H, 4.89; N, 14.67.

Ind-N-ethylharman. This substance was prepared in the same way as described for the synthesis of *ind-N*-methylharman. The substance crystallizes from ether/pentane in colorless leaflets, m.p. 74°; yield 800 mg. from 1 g. harman.

Alkylation of ind-N-ethylharman with n-butyl-bromide. The solution of 200 mg. *ind-N*-ethylharman in 3 ml. ether was added dropwise at room temperature to the solution of 1.0 *g. n*-butyllithium. The liquid was stirred and nitrogen was passed through the apparatus. A deep yellow precipitate appeared. After having stirred the mixture for 15 min. at room temperature, the solution of 0.12 ml. dry *n*-butyl bromide in 1 ml. ether was added. Then it was boiled for an hour with stirring and exclusion of oxygen. After this time we added 0.034 ml. *n*-butyl bromide dissolved in 1 ml. ether and boiled the mixture again for 2 hr. at which time it had become colorless. It was kept for 2 hr. at room temperature and then decomposed by water, and the ether layer was separated. The water layer was extracted again with ether, the ether extracts combined, dried, the solvent removed, and the residue distilled in high vacuum (Kugelrohr, 125–150°/0.04 mm.).

When picric acid was added to the distilled compound dissolved in methanol, a mixture of two picrates precipitated. It was extracted with boiling methanol. The picrate of *ind-N*-ethyl-3-*n*-pentyl-β-carboline went into solution while some *ind-N*-methylharman-picrate remained undissolved. *Ind-N*-ethyl-3-*n*-pentyl-β-carboline-picrate melted at 156° after several crystallizations from methanol.

Anal. Calcd. for $C_{24}H_{25}N_5O_7$: C, 58.17; H, 5.08; N, 14.12. Found: C, 58.21; H, 5.29; N, 14.48.

Other ind-N-ethyl-3-alkyl-β-carbolines. For the syntheses of the following compounds the same method was applied as for the preparation of *ind-N*-ethyl-3-*n*-pentyl-β-carboline.

Ind-N-ethyl-3-*n*-butyl-β-carboline picrate, m.p. 181°. *Anal.* Calcd. for $C_{23}H_{23}N_5O_7$: C, 57.37; H, 4.86; N, 14.56. Found: C, 57.64; H, 5.01; N, 14.71.

Ind-N-ethyl-3-isobutyl-β-carboline-picrate, m.p. 186°. *Anal.* Calcd. for $C_{23}H_{23}N_5O_7$: C, 57.37; H, 4.86; N, 14.56. Found: C, 57.63; H, 4.88; N, 14.74.

Ind-N-ethyl-3-*n*-propyl-β-carboline-picrate, m.p. 206°. *Anal.* Calcd. for $C_{22}H_{21}N_5O_7$: C, 56.6; H, 4.69; N, 15.02. Found: C, 56.73; H, 4.76; N, 15.06.

Ind-N-ethyl-3-ethyl-β-carboline-picrate, m.p. 236°. *Anal.* Calcd. for $C_{21}H_{19}N_5O_7$: C, 55.52; H, 4.19; N, 15.88. Found: C, 55.41; H, 4.31; N, 15.78.

R_f-values of the chlorides of the quaternary ammonium bases. From the picrates (3 mg.) the free bases of the β-carbolines were recovered as lacquers by treating them with 2*N*-NaOH, extracting with ether, and distilling at 110–120° (temperature of the air bath). Then these bases were combined with a few drops of methyl iodide and kept for 12 hr. in a sealed tube at 30°. After having removed the excess of CH_3I with a stream of nitrogen the crude methyl iodides were transformed in acetone–water solution (7:3) into the chlorides with the chloride form of Amberlite IRA 400. These quaternary β-carbolinium salts can be made visible on paper strips by their intensive blue fluorescence in ultraviolet light.

Several test chromatograms served to find a solvent with satisfactory separation activity.

The paper chromatograms were made on Whatman No. 1 paper at 18–20° with the mixture: ethyl acetate–pyridine–water (7.5:2.3:1.6) (descending method). For comparison purposes all the compounds were put side by side on the same paper strip and their chromatograms developed simultaneously.

In the chromatograms of some of the investigated substances there appeared beside the main spot a very small second spot, which was caused by traces of the methochlorides of the starting materials (*ind-N*-methylharman methochloride and *ind-N*-ethylharman methochloride, respectively) which, in spite of the repeated crystallizations of the picrates, were not completely removed.

SUMMARY

With the intention of facilitating the identification of simple β-carboline-derivatives, which are often obtained as degradation products of indole alkaloids, the following substances were synthesized: *ind-N*-methyl-3-(3′-methylpentyl)-β-carboline picrate (III), *ind-N*-methyl-3-*n*-pentyl-β-carboline picrate (IV), *ind-N*-methyl-3-*n*-butyl-β-carboline picrate (V), *ind-N*-ethyl-3-*n*-pentyl-β-carboline picrate (VI), *ind-N*-ethyl-3-*n*-butyl-β-carboline picrate (VII), *ind-N*-ethyl-3-isobutyl-β-carboline picrate (VIII), *ind-N*-ethyl-3-*n*-propyl-β-carboline picrate (IX), and *ind-N*-ethyl-3-ethyl-β-carboline picrate (X).

ZÜRICH, SWITZERLAND

[CONTRIBUTION FROM THE INSTITUTE OF ORGANIC CHEMISTRY, UNIVERSITY OF CHICAGO]

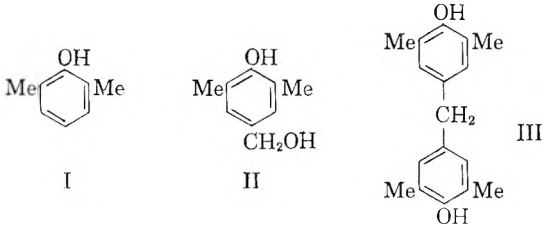
Reactions of Hindered Phenols. I. Reactions of 4,4′-Dihydroxy-3,5,3′,5′,-tetra-*tert*-butyl Diphenylmethane*

M. S. KHARASCH AND B. S. JOSHI[1]

It was found that the base-catalyzed condensation of formaldehyde with 2,6-di-*tert*-butyl phenol gives products VI and V depending on the alcohol used as a solvent. Compound V, when treated with bromine (in various media), undergoes unusual transformations which are here elucidated. The oxidations by ferricyanide of XVI and V are described. The latter compound gives a free radical; one canonical form of this resonance hybrid is indicated by XV. An explanation is offered which accounts for the color of XIII in solution (*i.e.* formation of a stable anion XII).

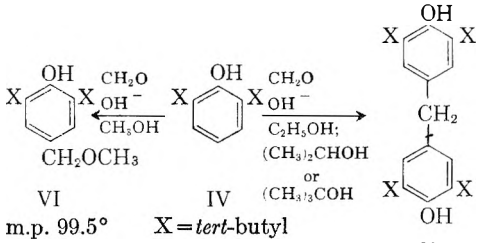
In connection with an investigation of steric effects on the behavior of free radicals, some chemical transformations of highly hindered phenols have been investigated. The first paper on this subject deals with certain chemical reactions of 4,4′-dihydroxy-3,5,3′,5′-tetra(*tert*-butyl)diphenylmethane. The second paper deals with the oxidation products.

It was claimed by Bamberger[2a] that, in the

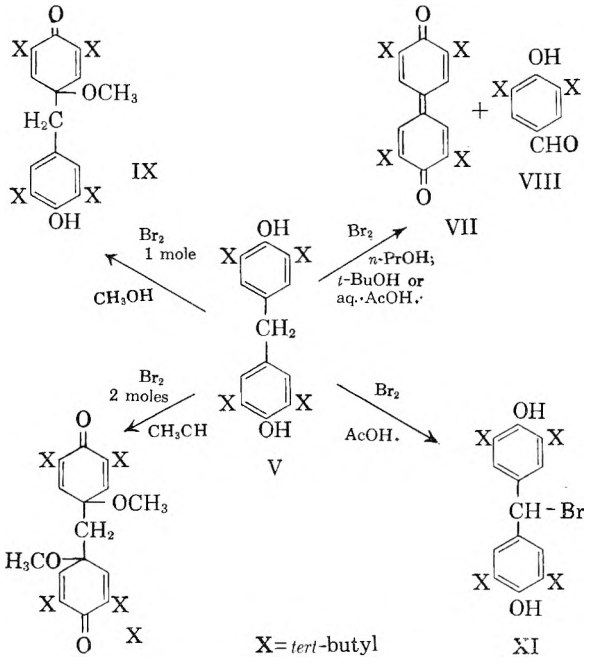


presence of alkali, I reacts with formaldehyde at room temperature to give II. About 30 years later this observation was disputed by Granger.[2b] The latter investigator claimed that, under a variety of experimental conditions, I condenses with formaldehyde to give exclusively III. The authors, however, found no difficulties in preparing II by the Bamberger procedure, nor in preparing III by the procedure used by Auwers.[2c]

The base-catalyzed condensation of formaldehyde with IV is here carefully examined and is shown to give two different products depending upon the alcohol used as a solvent.



On the basis of analyses, as well as determination of the molecular weight and the ultraviolet[3] (λ_{max} 276, 282 mμ; ϵ_{max} 4100 and 4050, respectively) and infrared spectra[4] (hindered OH group, 3640 cm.$^{-1}$), structure V was assigned to the compound melting at 154°. The formation of VI in methanol and not in other alcohols (ethanol, 2-propanol, *t*-butyl alcohol) may be attributed to the higher acidity of methanol.[5] In the literature there is no detailed description of the preparation of V, although this substance was used by Coppinger,[6] in the preparation of XV. It should be emphasized that oxygen must be rigidly excluded in all the base-catalyzed reactions of IV, otherwise there is a rapid condensation of IV to 3,5,3′,5′-tetra-*tert*-butyldiphenoquinone VII. This subject will be discussed in greater detail in the next paper.



* This paper is a contribution in honor of Lyndon F. Small, former Editor of the Journal.

(1) The authors are deeply indebted to Dr. N. C. Yang for many helpful discussions of the spectroscopic data here recorded.

(2) (*a*) E. Bamberger, *Ber.*, **36**, 2036 (1903); (*b*) F. S. Granger, *Ind. Eng. Chem.*, **24**, 442 (1932); (c) K. Auwers, *Ber.*, **40**, 2524(1907).

(3) H. Hart and E. A. Haglund, *J. Org. Chem.*, **15**, 396 (1950); N. D. Coggeshall and A. S. Glessner, *J. Am. Chem. Soc.*, **71**, 3150 (1949).

(4) W. C. Sears and L. J. Kitchen. *J. Am. Chem. Soc.*, **71**, 4110 (1949); N. D. Coggeshall, *J. Am. Chem. Soc.* **69**, 1620 (1947).

(5) J. Hine and M. Hine, *J. Am. Chem. Soc.*, **74**, 5266 (1952).

(6) G. M.Coppinger, *J. Am. Chem. Soc.*, **79**, 501 (1957).

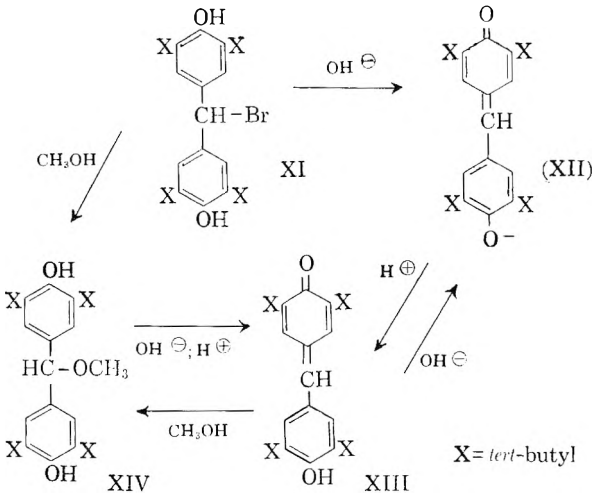
Compound V undergoes many interesting reactions. Bromination in dilute acetic acid, isopropyl alcohol or *tert*-butyl alcohol gives VII (3,5,3′,5′-tetra-*tert*-butyldiphenoquinone) and VIII (4-hydroxy-3,5-di-*tert*-butylbenzaldehyde). Both these compounds were identified by comparison with authentic samples.[7,8] But when the bromination of V was carried out in absolute methanol, other products were obtained. When one mole of bromine was used compound IX was the predominant product, whereas when two moles of bromine were used and the reaction mixture was allowed to stand for about 1.5 hr., compound X was formed.

Structure IX is assigned to the compound on the basis of (*a*) analyses and (*b*) determinations of the ultraviolet and infrared spectra. The ultraviolet spectrum shows absorption due to the dienone[8] ($\lambda_{max}^{iso\text{-}octane}$ 229 mμ; ϵ_{max}16,000) and the phenolic functions ($\lambda_{max}^{iso\text{-}octane}$ 271 mμ; ϵ_{max} 2700). The infrared spectrum (OH stretching frequency at 3640 cm.$^{-1}$; a twin band at 1665 and 1646 cm.$^{-1}$ due to the dienone structure, and a single band at 1070 cm.$^{-1}$ due to the ether linkage) supports the above conclusion.[9]

The structure of compound X is based on considerations similar to those cited above ($\lambda_{max}^{iso\text{-}octane}$ 239 mμ; ϵ_{max} 22,600. No OH bands occur in the infrared spectrum; there is a twin band at 1665 and 1645 cm.$^{-1}$, characteristic of the dienone grouping, and a single ether band at 1070 cm.$^{-1}$). Both compounds IX and X are quite stable in ethanolic alkali even in the presence of oxygen.

An entirely different reaction takes place when V is treated with bromine in glacial acetic acid. Here a good yield of the monobromo compound XI is obtained. The structure XI is assigned to this compound on the basis of (*a*) analyses, (*b*) determination of the infrared spectrum (OH stretching at 3620 cm.$^{-1}$ and no carbonyl bands), and (*c*) determination of the ultraviolet spectrum in iso-octane (λ_{max} 257 mμ; ϵ_{max} 11,000).

Compound XI is quite stable when dry. In hydroxylic solvents it reacts immediately with aqueous silver nitrate to give silver bromide. Solutions of XI in organic solvents give an intense purple upon addition of alkali, due to the formation of the anion XII. Dehydrobromination of XI in ethanolic alkali and subsequent neutralization give XIII. The structure of XIII was deduced from: (*a*) analyses and (*b*) determination of the infrared spectrum [OH stretching at 3620 cm.$^{-1}$, and four intense absorption bands in the carbonyl region (1500–1610 cm.$^{-1}$)].



Compound XIII, dissolved in ethanol, has a weak absorption band at 575 mμ, indicating that there is little ionization (Fig. 1). Upon addition of alkali an intensely purple solution is obtained. At the same time there is a tremendous increase in the intensity of the absorption (λ_{max} 575 mμ; ϵ_{max} 220,000), and the compound is transformed into the anion XII. The very deep color of this anion is probably associated with resonance stabilization.

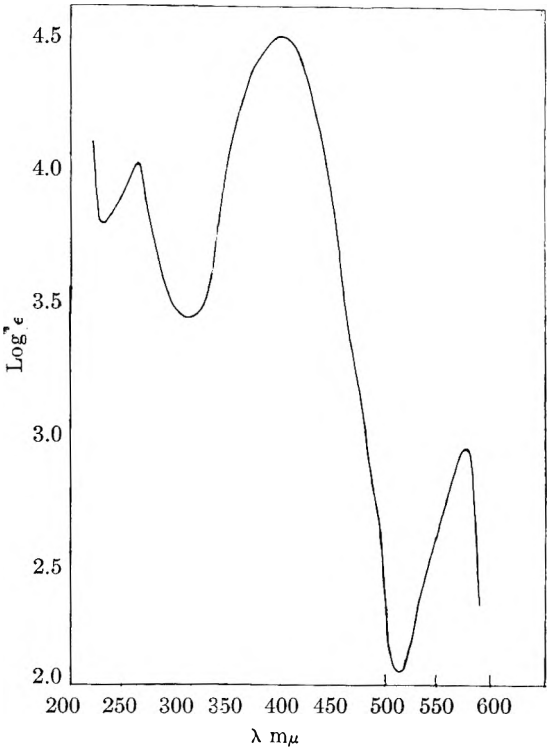


FIG. 1. (XIII) SOLVENT—ABSOLUTE ETHANOL

Compound XIII, dissolved in methanol, is transformed by acid into XIV,[6] the product formed by heating XI in methanol. The structure assigned

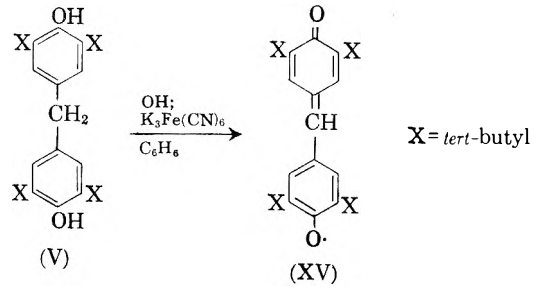
(7) H. Hart and F. A. Cassis, *J. Am. Chem. Soc.*, **73**, 3179 (1951); G. R. Yohe *et. al.*, *J. Org. Chem.*, 21, 1289 (1956).

(8) G. M. Coppinger and Campbell, *J. Am. Chem. Soc.*, **75**, 734 (1953).

(9) Note that the compound IX shows a hypsochromic shift when compared with other dienone structures which absorb around 234–240 mμ; the chemical and infrared evidence, however, leaves no doubt about the structure of this compound.

to XIV was substantiated by: (*a*) analyses; (*b*) determination of the infrared (OH stretching at 3640 cm.$^{-1}$ and ether linkage at 1075 cm.$^{-1}$); and (*c*) determination of the ultraviolet spectrum (phenolic absorption bands at λ_{max} 273 and 281 mμ; ϵ_{max} 3400 and 3300, respectively). Compound XIV when treated with alkali reacts as does XI; it gives first XII, which, when acidified, gives XIII.

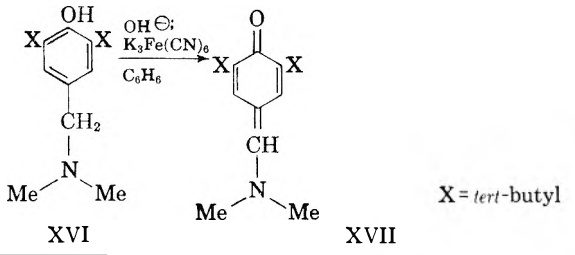
Many papers dealing with one-electron oxidations of hindered phenols have recently appeared.[6,10] Coppinger,[6] in an excellent communication, reports that an ethereal solution of V is readily oxidized by lead dioxide to the free radical XV. This free radical was here obtained by the ferricyanide oxidation of V dissolved in benzene. It crystallizes from ethanol in deep blue needles. Its visible spectrum (iso-octane solution) shows an intense absorption band at λ_{max} 423 mμ; ϵ_{max} 180,000; its infrared spectrum shows a strong band which has been attributed to the oxygen radical[11] in the carbonyl region at 1570 cm.$^{-1}$ Electron magnetic resonance studies of the free radical XV gave "g" = 2.006 ± 0.0005, indicating an unpaired electron.[12]



(V) (XV)

It is of interest that a benzene solution of XV is quite stable toward oxygen, whereas other free radicals formed from hindered phenols react with oxygen.[10] Solutions of XV in hydroxylic solvents tend to decompose when allowed to stand in air in the presence of alkali. The products formed when XV decomposes will be discussed in the next paper.

Compound IV undergoes the Mannich reaction and with dimethylamine gives 2,6-di-*tert*-butyl-4-(*N*,*N*-dimethylaminomethyl)phenol XVI. Oxidation of XVI with potassium ferricyanide gives the methylenequinone XVII, the absorption at λ_{max} 372 mμ; ϵ_{max}31,000 may be attributed to the conjugated system containing the dimethylamino and the carbonyl groups.[13] The infrared spectrum (KBr disk) shows a medium band at 1665 cm.$^{-1}$ (C=O), and two strong bands at 1605 and 1535 cm.$^{-1}$ The methylenequinone hydrolyzes very readily to give 3,5-di-*tert*-butyl-4-hydroxybenzaldehyde VIII.



XVI XVII

EXPERIMENTAL

4-Hydroxy-3,5-di-tert-butylbenzyl methyl ether (VI). 2,6-Di-*tert*-butylphenol (5.2 g.), 36% formaldehyde (5 ml.) and absolute methanol (50 ml.) were dissolved in a three-necked flask and a solution of potassium hydroxide (2 g. in 2 ml. water) was added under an atmosphere of nitrogen. The solution was refluxed for 30 min. under a current of nitrogen. After cooling, the pale yellow crystalline product was collected (5.5 g., 82%) on a filter, and crystallized several times from methanol. Colorless plates were thus obtained which melted at 99.5°.

Anal. Calcd. for $C_{16}H_{26}O_2$: C, 76.8; H, 10.4. Found: C, 76.9; H, 10.4.

4,4'-Dihydroxy-3,5,3',5'-tetra-tert-butyldiphenylmethane (V). 2,6-Di-*tert*-butylphenol (20.6 g.) and 36% formaldehyde (15 ml.) were dissolved in absolute ethanol (50 ml.) and nitrogen gas (Linde) was bubbled in throughout the reaction. A solution of sodium hydroxide (8 g. in 15 ml. water) was gradually added and the solution gently heated for 10–15 min. A vigorous reaction took place and a crystalline mass (20 g., 90%) separated from the mixture. Crystallization of this material from ethanol (100 ml.) gave shining colorless plates which melted at 154°.

Anal. Calcd. for $C_{29}H_{44}O_2$: C, 82.0; H, 10.4; mol. wt. 426. Found: C, 81.9; H, 10.3; mol. wt. 416.

2,6,3',5'-Tetra-tert-butyl-4'-hydroxyphenyl-4,1'-methylene-4-methoxy-2,5-cyclohexadiene-1-one (IX). Compound V (1.06 g.) was dissolved in methanol (20 ml.) and bromine (0.16 ml.) in methanol (6 ml.) was added. The solution was flushed with nitrogen and left at room temperature for 20 min. The crystalline material which separated was collected on a filter. The material (0.8 g.) when crystallized from methanol gave colorless plates of IX which melted at 122–123°.

Anal. Calcd. for $C_{30}H_{46}O_3$: C, 79.3; H, 10.2. Found: C, 79.4; H, 10.4.

2,6,3',5'-Tetra-tert-butyl-4,1'-dimethoxy-4,1'-methylene-2,5,-2',5'-bis cyclohexadiene-1,4'-one (X). Compound V (1.06 g.) was dissolved in absolute methanol (20 ml.) and bromine (0.32 ml. in 5 ml. methanol) was added. The flask was flushed with nitrogen, then stoppered and left at room temperature for 1.5 hr. On scratching the sides of the flask, a crystalline precipitate (0.8 g.) separated. On crystallization from methanol (three times) colorless plates were obtained which melted at 126–127°.

Anal. Calcd. for $C_{31}H_{48}O_4$: C, 76.9; H, 9.9. Found: C, 77.4; H, 10.0.

Oxidation of 4,4'-dihydroxy-3,5,3'5',-tetra-tert-butyl diphenylmethane with bromine. Bromine (0.2 ml.) was added to a solution of the diphenylmethane V (1 g.) in *n*-propyl alcohol (20 ml.). The mixture was allowed to stand at room temperature (22°) for 20 min. The crystalline precipitate which separated was collected on a filter. The material upon crystallization from ethanol melted at 245–246°. The ultraviolet, visible, and infrared spectra of the compound were shown to be identical with an authentic sample of 3,5,3',5' tetra-*tert*-butyldiphenoquinone.

(10) C. D. Cook and coworkers, *J. Am. Chem. Soc.*, 78, 3797 (1956) and earlier papers; E. Müller and coworkers, *Ber.*, 89, 1738 (1956) and earlier papers.

(11) E. Müller and K. Ley, *Ber.*, 87, 922 (1954); 88, 601 (1955).

(12) We are grateful to Professor C. A. Hutchison, Jr. for these measurements.

(13) A. Burawoy, *J. Chem. Soc.*, 1177 (1939).

The filtrate after removal of the quinone gave, on concentration, shining white flakes (0.2 g.) melting at 185° and identical in all respects with 4-hydroxy-3,5-di-*tert*-butylbenzaldehyde.

Similarly, when the bromination was carried out in *tert*-butyl alcohol, or in aqueous acetic acid, the diphenoquinone and the aldehyde were found to be the reaction products.

4,4'-Dihydroxy-3,5,3',5'-tetra-tert-butyldiphenylbromomethane (XI). To a solution of the diphenylmethane V (1.06 g., 0.0025 mole) in glacial acetic acid (25 ml.), bromine (0.2 ml., 0.0036 mole) in glacial acetic acid (2 ml.) was gradually added. The solution was left at room temperature for about 2 hr. The colorless silky needles which separated were collected on a filter stick (nitrogen atmosphere is absolutely necessary) and quickly transferred to a desiccator and dried at reduced pressure. The yield of the bromo compound XI was (1 g., 80%). In the presence of a solvent, the bromo compound readily changes to a yellow product. A small sample of the material when crystallized from acetic acid, and dried at 60°/0.1 mm. melted at 159–160°.

Anal. Calcd. for $C_{29}H_{43}O_2Br$: C, 69.3; H, 8.5; Br, 15.9; Found: C, 69.2; H, 8.1; Br, 15.6.

2,6,3',5'-Tetra-tert-butyl-4'-hydroxyphenyl-4-methylene-2,5-cyclohexadiene-1-one (XIII). To a solution of the bromo compound XI (60 mg.) in ethanol (5 ml.), 5% sodium hydroxide (0.2 ml.) was added. A slow current of nitrogen was passed through the solution. The solution immediately changed to a deep purple. After 20 min. the reaction mixture was poured into crushed ice, neutralized with acetic acid, and extracted with ether. From the ether extract was obtained 45 mg. of a yellow solid which melted at 150–152°. The material was readily soluble in ether, petroleum ether, and benzene. Two crystallizations of the material from aqueous ethanol gave bright yellow needles which melted at 158–159°.

Anal. Calcd. for $C_{29}H_{42}O_2$: C, 82.5; H, 9.9. Found: C, 82.4; H, 9.9.

4,4'-Dihydroxy-3,5,3',5'-tetra-tert-butyldiphenylmethoxymethane (XIV). (*a*) *From the bromo compound* (*XI*). The compound XI (0.2 g.) was refluxed with absolute methanol (10 ml.) for about 10 min. and anhydrous sodium acetate (50 mg.) was added to the solution. It was heated about 5 min. longer and the mixture was filtered when hot. Upon cooling the filtrate a product separated. Upon two crystallizations from methanol, colorless plates of XIV were obtained which melted at 160–161°.

Anal. Calcd. for $C_{30}H_{46}O_3$: C, 79.3; H, 10.1. Found: C, 79.3; H, 10.1.

(*b*) *From the methylenequinone* (XIII): The methylenequinone XIII (50 mg.) was added to methanol (2 ml.) containing a trace of hydrochloric acid, and the whole was heated for about 10 min. and filtered when hot. From the filtrate colorless plates identical with XIV were obtained which melted at 160°. This product was identical with XIV; prepared from the bromo compound (XI).

2,6,3',5'-Tetra-tert-butyl-4'-phenoxy-4-methylene-2,5-cyclohexadiene-1-one radical (XV). A solution of 3,5,3',5'-tetra-*tert*-butyl-4,4'-dihydroxydiphenylmethane V (1.41 g; 0.0033 mole) in benzene (15 ml.) was added within 30 min. to a well-stirred mixture of potassium ferricyanide (3.94 g; 0.012 mole), potassium hydroxide (0.6 g.), water (15 ml.), and benzene (80 ml.). All of the operations were performed in an atmosphere of nitrogen. The reddish yellow mixture was stirred for about one hr. The benzene layer was washed thoroughly with water, dried over sodium sulfate, and the benzene was removed at reduced pressure. The dark blue crystalline powder (1.3 g.) thus obtained melted at 150–151°. It is very soluble in petroleum ether, benzene, and cyclohexane. When crystallized rapidly from absolute ethanol deep blue needles are obtained which melt at 157.5°. The solutions of the free radical in methanol or ethanol decompose upon standing.

Anal. Calcd. for $C_{29}H_{41}O_2$: C, 82.6; H, 9.7. Found: C, 82.6; H, 9.8.

The absorption spectrum (iso-octane) showed λ_{max} 280, 289, 400, and 423 mμ; $\epsilon_{max} \times 10^{-3}$ 9.39, 9.4, 24.3 and 180.0 respectively.

2,6-Di-tert-butyl-4-(N,N-dimethylaminomethyl)phenol (XVI). A mixture of 2,6-di-*tert*-butylphenol (4.1 g.) in ethanol (50 ml.), formaldehyde (36%; 2 ml.), and dimethylamine (25%; 5 ml.) was stirred for 1 hr. The whole was then refluxed for 1 hr. on the water bath, and evaporated to dryness at reduced pressure. The crude product (4.2 g.) was crystallized twice from ethanol. Large colorless plates were thus obtained which melted at 91.5°. The compound has a very pleasant odor.

Anal. Calcd. for $C_{17}H_{29}ON$: C, 77.5; H, 11.1. Found: C, 77.7; H, 10.9.

2,6-Ditert-butyl-4(N,N-dimethylaminomethylene)-2,5-cyclohexadiene-1-one (XVII). A mixture consisting of potassium ferricyanide (6 g.), potassium hydroxide (1 g.), water (25 ml.), and benzene (50 ml.), was stirred in an oxygen-free atmosphere and a solution of compound XVI (1.3 g.) dissolved in benzene (50 ml.) was added during the course of 30 min. The solution was stirred for 1 hr longer and the red-colored benzene layer separated and washed with water. The benzene solution was dried with sodium sulfate and the benzene removed at reduced pressure. The solid thus obtained appeared to be a mixture of two colored products, yellow and red, in which the yellow product predominated. It was washed with hot ligroin (30–60°). The greenish yellow residue (1 g.) which remained was crystallized twice from *n*-hexane. Bright yellow needles which melted at 158–159° were thus obtained.

Anal. Calcd. for $C_{17}H_{27}ON$: C, 78.1; H, 10.4. Found: C, 78.5; H, 10.5.

The absorption spectrum showed $\lambda_{max}^{iso\text{-}octane}$ 268, 372 mμ ϵ_{max} 6300 and 31,000 respectively and an inflexion at 225 mμ having ϵ, 4200.

The petroleum ether washings gave on concentration, red-brown crystals (0.15 g.) m.p. 242–243°. This material was shown to be 3,5,3',5'-tetra-*tert*-butyldiphenoquinone.

The compound XVII (100 mg.) was dissolved in ethanol (20 ml.) and a solution of 2,4-dinitrophenylhydrazine added to it. The yellow-orange precipitate was collected on a filter and crystallized from ethanol. Shining orange-red plates which melted at 236–238° were thus obtained. The material did not depress the melting point of the 2,4-dinitrophenylhydrazone prepared from an authentic sample of 3,5-di-*tert*-butyl-4-hydroxybenzaldehyde.

CHICAGO, ILL.

[CONTRIBUTION FROM THE INSTITUTE OF ORGANIC CHEMISTRY, UNIVERSITY OF CHICAGO]

Reactions of Hindered Phenols. II. Base-Catalyzed Oxidations of Hindered Phenols*

M. S. KHARASCH AND B. S. JOSHI[1]

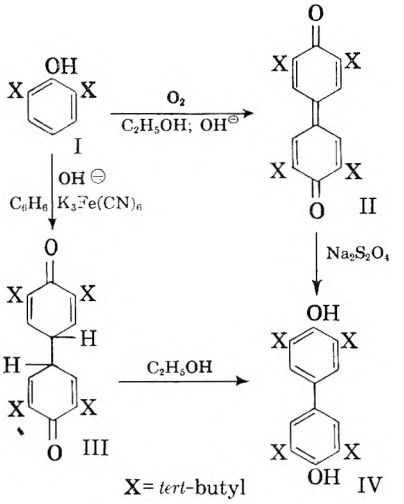
Received June 27, 1957

2,6-Di-*tert*-butylphenol (I) reacts with oxygen in the presence of a base to give 3,5,3′,5′-tetra-*tert*-butyl-4,4′-diphenoquinone. A stable keto tautomer of the phenol (IV) was obtained by oxidation of I with potassium ferricyanide. It has been established that a nearly quantitative yield of the hydroperoxide (XI) is formed upon treatment of V with oxygen in the presence of a base. The hydroperoxide (XI) is readily hydrolyzed to the alcohol (XII). The treatment of XVI with oxygen in the presence of a base gives X and IX along with a small amount of XVII. But a high yield of XVII is obtained when the free radical (XVIII) is allowed to stand for a few hours in the presence of a strong base. Mechanisms are suggested which account for many of the reactions here discussed.

There is an extensive literature dealing with the products formed upon oxidation of hindered phenols. These investigations may be classified as follows: (*a*) oxidations with so-called one electron oxidizing agents (ferricyanide, silver oxide, lead dioxide, etc.,[2–13] (*b*) oxidations with benzoyl peroxide;[14,15] (*c*) oxidations with alkyl hydroperoxides[16,17]; and (d) base-catalyzed oxidations with oxygen at elevated temperatures.[18,19]

The present investigation deals with the base-catalyzed oxidations of some hindered phenols by oxygen. The phenols were dissolved in hydroxylic solvents (ethanol or *tert*-butyl alcohol), the base was added, and the reaction mixture was vigorously agitated in the presence of oxygen. The pressure in the apparatus was only two or three centimeters above atmospheric pressure. The reaction was interrupted when the predetermined amount of oxygen was absorbed.

Oxidation of 2,6-di-tert-butylphenol. Under the experimental conditions previously cited, compound I absorbs one mole of oxygen to give a quantitative yield of 3,5,3′,5′-tetra-*tert*-butyl-4,4′-diphenoquinone (II) and hydrogen peroxide (85% of calculated amount). The diphenoquinone has been prepared previously.[19,20] The product here obtained melted at 246°. The structure of II was confirmed by examination of the ultraviolet and visible ($\lambda_{max}^{iso\text{-}octane}$ 260, 270, and 418 mμ; ϵ_{max} 4300, 4300, and 84,000 respectively) and infrared spectra $\nu_{C=O}$ at 1635 cm.$^{-1}$ (medium) and 1605 cm.$^{-1}$ (strong).[cf. 21]



There are two mechanisms whereby II may be formed from I. The experimental evidence now available does not allow one to make an unequivocal

* This paper is a contribution in honor of Lyndon F. Small, former Editor of the Journal.

(1) The authors are deeply indebted to Dr. N. C. Yang for many helpful discussions of the spectroscopic data here recorded.

(2) C. D. Cook, *J. Org. Chem.*, **18**, 260 (1953).

(3) C. D. Cook and R. C. Woodworth, *J. Am. Chem. Soc.*, **75**, 6242 (1953).

(4) C. D. Cook, N. G. Nash, and H. R.Flanagan, *J. Am. Chem. Soc.*, **77**, 1783 (1955).

(5) C. D. Cook, D. A. Kuhn, and P. Fianu, *J. Am. Chem. Soc.*, **78**, 2002 (1956).

(6) C. D. Cook and B. E. Norcross, *J. Am. Chem. Soc.*, **78**, 3797 (1956).

(7) E. Müller and K. Ley, *Z. Naturforsch.*, **8b**, 694 (1953).

(8) E. Müller and K. Ley, *Chem. Ber.*, **87**, 922 (1954).

(9) E. Müller, K. Ley, and W. Kiedaisch, *Chem. Ber.*, **87**, 1605 (1954).

(10) E. Müller and K. Ley, *Chem. Ber.*, **88**, 601 (1955).

(11) E. Müller, K. Ley, and W. Kiedaisch, *Chem. Ber.*, **88**, 1819 (1955).

(12) E. Müller, K. Ley, and W. Schmidhuber, *Chem. Ber.*, **89**, 1738 (1956).

(13) G. M. Coppinger, *J. Am. Chem. Soc.*, **79**, 501 (1957).

(14) S. L. Cosgrove and W. A. Waters, *J. Chem. Soc.*, 3189 (1949).

(15) S. L. Cosgrove and W. A. Waters, *J. Chem. Soc.*, 388 (1951).

(16) T. W. Campbell and G. M. Coppinger, *J. Am. Chem. Soc.*, **74**, 1469 (1952).

(17) A. F. Bickel and E. C. Kooyman, *J. Chem. Soc.*, 3211 (1953).

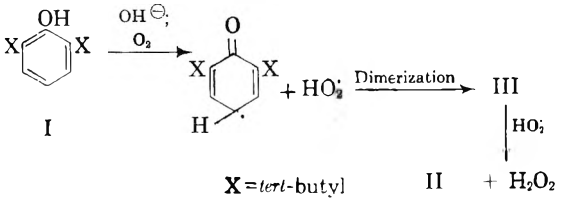
(18) G. R. Yohe, D. R. Hill, J. E. Dunbar, and F. M. Scheidt, *J. Am. Chem. Soc.*, **75**, 2688 (1953).

(19) G. R. Yohe, J. E. Dunbar, R. L. Pedrotti, F. M. Scheidt, F. G. H. Lee, and E. C. Smith, *J. Org. Chem.*, **21**, 1289 (1956).

(20) H. Hart and F. A. Cassis Jr., *J. Am. Chem. Soc.*, **73**, 3179 (1951).

(21) N. Fuson, M. L. Josien, and E. M. Shelton, *J. Am. Chem. Soc.*, **76**, 2526 (1954).

choice between them. However, it appears that II is formed from I by the following sequence of reactions.

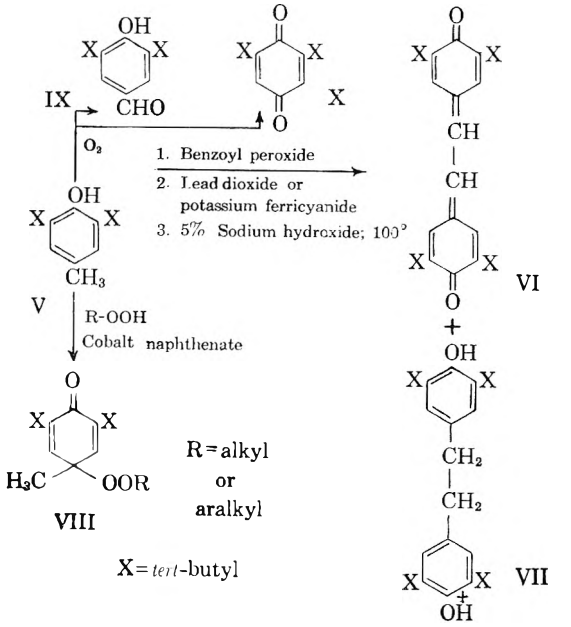


The formation of II from I by an ionic mechanism would involve a condensation reaction; but attempts to synthesize II from certain reasonable intermediates were of no avail.

When a solution of I in benzene was oxidized by alkaline ferricyanide, a different product (III) resulted. The ultraviolet (λ_{max} at 242 mμ; ϵ_{max} 15,000) and infrared spectra (characteristic dienone absorption at 1657 and 1638 cm.$^{-1}$, and no hydroxyl band) are in agreement with the structure assigned to III. Compound III is stable when dry, and in non-polar solvents. However, in polar solvents (ethanol) III is rapidly isomerized to IV (λ_{max} 265 mμ; ϵ_{max} 18,000).

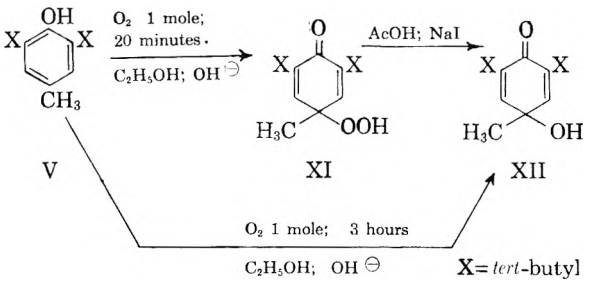
Compound III is unique—it is the keto tautomer of IV. As far as we are aware no such pair of keto-enol tautomers of phenolic compounds has ever been isolated. There is of course abundant evidence that, upon demand of a reagent, certain phenolic substances react as if they existed in equilibrium with the keto form.

Reaction of 2,6-di-tert-butyl-4-methylphenol (V) with oxidants and with oxygen. The oxidation of V by a variety of oxidants has been investigated previously. Thus, small quantities of VI and VII are formed when a solution of V in chloroform is heated with benzoyl peroxide for 70 hr.[15,18] The two compounds (VI) and (VII) have also been prepared by oxidation of V with lead dioxide or alkaline ferricyanide.[2,4] Treatment of V with alkyl or aralkylhydroperoxides and cobalt naphthenate gave 2,6-di-*tert*-butyl-4-methyl-4-alkyl(or aralkyl)peroxy-2,5-cyclohexadiene-1-one (VIII),[16,17]



Very low yields of identifiable products have been obtained from the reaction of V with oxygen in the presence or absence of alkali. Thus it is claimed that when a solution of V in a "petroleum base lubricating oil" is heated with oxygen at 110° in the presence of polished copper foil catalyst some amount of IX is formed.[22] When the temperature was maintained at 95° for 2–3 days and oxygen was bubbled in, (in the presence of a "copper-iron catalyst") about 8 percent of X was isolated.[23] Furthermore it is claimed[18] that small amounts of VI and VII are formed when a suspension of V in 5 percent alkali is heated with oxygen.

It seems fairly obvious, from the work thus far recorded, that the primary reaction product of V with oxygen is unstable and undergoes further changes when heated or upon prolonged standing in the presence of alkali. To overcome this difficulty, a solution of V in ethanolic potassium hydroxide was shaken with oxygen until one molar equivalent of the gas was absorbed and the reaction mixture worked up at once. Under these conditions the hydroperoxide XI was obtained in excellent yield (86%).[24] The oxygen absorption was very rapid – usually about 20 to 25 min.



The structure assigned to XI is based on the following considerations: (*a*) analyses, (*b*) the ultraviolet (characteristic dienone chromophore λ_{max} 234 mμ; ϵ_{max} 10,400) and (*c*) the infrared spectra (doublet at 1665 and 1645 cm.$^{-1}$ due to the conjugated carbonyl group, the hydroxyl stretching frequency at 3538 cm.$^{-1}$ and the peroxide linkage at 845 cm.$^{-1}$). The hydroperoxide XI, dissolved in acetic acid, liberates iodine from an acetic acid solution of sodium iodide and is converted into XII.[25]

(22) J. I. Wasson and W. M. Smith, *Ind. Eng. Chem.*, **45**, 197 (1953).

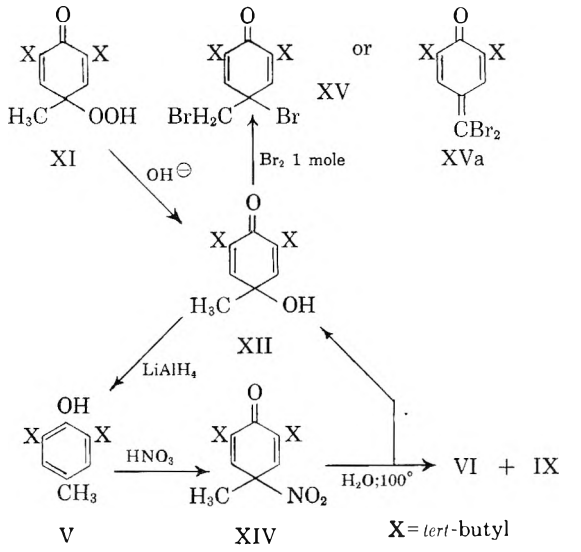
(23) S. J. Metro, *J. Am. Chem. Soc.*, **77**, 2901 (1955).

(24) Coppinger (private communication) prepared XI from V, hydrogen peroxide, and cobaltous, or other metal salts.

(25) Compound (XII) has been prepared by Coppinger (private communication) by reduction of (XI) with hydrogen gas in the presence of a platinum catalyst.

An ethanolic potassium hydroxide solution of XI (m.p. 115–116°) decomposes (complete loss of peroxide titer) within 2–3 hr. About 45 per cent of the hydroperoxide is converted into XII (m.p. 111–112°), about 20 per cent into a substance XIII melting at 159–160°. Compound (XIII) (mol. wt. 416) has the empirical formula $C_{30}H_{46}O_2$. Its ultraviolet (λ_{max} 237, 273 mμ; ϵ_{max} 20,000 and 2600 respectively) and infrared spectra (OH stretching at 3638 cm.$^{-1}$ and a doublet at 1658 and 1638 cm.$^{-1}$) were examined, but did not furnish sufficient information for assignment of a structure to XIII. Further work on this compound is contemplated.

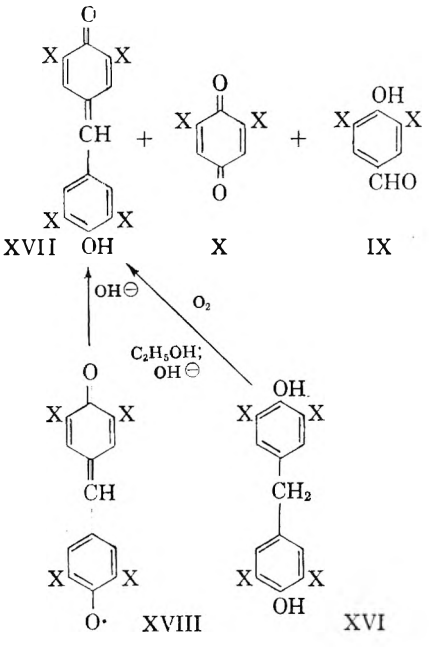
Structure (XII) is based on (*a*) analyses, (*b*) ultraviolet (λ_{max} 234 mμ; ϵ_{max} 10,400), and (*c*) infrared spectra (OH stretching at 3580 cm.$^{-1}$, twin band at 1665 and 1645 cm.$^{-1}$, and tertiary hydroxyl at 1045 cm.$^{-1}$). The alcohol (XII) undergoes a number of interesting transformations. These are in indicated below. Two items are of particular interest. First, the lithium aluminum hydride reduction of XII to V. Second, the transformation by bromine of XII into compound (XV). With one molar equivalent of bromine, a dibromide



is formed which could be either XV or XVa. Structure (XV) is preferred for the dibromide over XVa. This conclusion is based on the ultraviolet spectrum of the compound (λ_{max} 250 mμ; ϵ_{max} 8300), and because compounds structurally similar to XVa have been shown to absorb at λ_{max} 220 mμ; ϵ_{max} 3600.[3]

Reaction of 4,4'-dihydroxy-3,5,3',5'-tetra-tert-butyl diphenylmethane in the presence of base. A solution of XVI in ethanolic potassium hydroxide absorbs one molar equivalent of oxygen very rapidly. The second mole of oxygen is absorbed in about 40 min. During the absorption of oxygen, the reaction mixture acquires a dark purple color.

Examination of the visible spectrum of the alkaline solution indicates that the color is due to the anion of XVII (see previous paper). From the intensity of the color, it is estimated that this product is formed to the extent of about 2–4 per



cent. Neutralization of the reaction mixture gives a yellow oil of average molecular weight 265, indicating that extensive cleavage had taken place. Two products (IX) and (X) were isolated when the oil was chromatographed on alumina.

A solution of the free radical (XVIII) in ethanolic sodium hydroxide absorbs two molar equivalents of oxygen. The second mole of oxygen is absorbed rather slowly. A deep purple colored solution is thus obtained. Examination of the visible spectrum of the alkaline solution indicates that about half of the compound (XVIII) is transformed into the anion of XVII. Oxygen, however is not essential for this transformation, since a solution of XVIII in ethanolic sodium hydroxide (but in the absence of oxygen) gives the same yield of XVII. Examination of the other reaction products was not attempted, because the author of a recent communication[13] indicated that this work was underway in his laboratory.

EXPERIMENTAL

3,5,3',5'-Tetra-tert-butyl-4,4'-diphenoquinone (II). To a well agitated solution of 2,6-di-*tert*-butylphenol (2.06 g; 0.01 mole) in *tert*-butyl alcohol (25 ml.), potassium hydroxide (2 g. in 3 ml. water) was added and the flask was connected to an oxygen buret. It took 25 min. for the absorption of 224 ml. (0.01 mole) of oxygen. The brown colored reaction mixture was diluted with water (25 ml.) and the precipitate (2.0 g; 98%) was collected on a filter. Upon crystallization from ethanol red-brown plates with a purple reflex were obtained which melted at 246°. This material did not depress the melting point of an authentic sample of 3,5,3',5'-tetra-*tert*-butyl 4,4'-diphenoquinone (prepared by nitric acid oxidation of 2,6-di-*tert*-butylphenol[20]).

Anal. Calcd. for $C_{28}H_{40}O_2$: C, 82.4; H, 9.8. Found: C, 82.5; H, 9.8.

The alkaline filtrate after removal of II was acidified with acetic acid and the iodine liberated after addition of sodium iodide was estimated by titration with sodium thiosulfate.

In another experiment, a solution of 2,6-di-*tert*-butylphenol (1 g.) in *tert*-butyl alcohol (15 ml.) and water (1 ml.) was mixed with sodium hydroxide (0.3 g.) in an evacuated tube. The solution changed to a faint bluish green. No dimerized product was formed although the mixture was kept for 6 mo.

4,4'-Dihydroxy-3,5,3',5'-tetra-tert-butyl diphenyl (IV). The diphenoquinone (II; 0.2 g.) was dissolved in ethanol (50 ml.), sodium hydrosulfite added (1 g. in 10 ml. water), and the whole heated for 20 min. The precipitate which separated was collected on a filter and crystallized from ethanol. Pale yellow needles were thus obtained which melted at 185°.

Anal. Calcd. for $C_{28}H_{42}O_2$: C, 81.9; H, 10.3. Found: C, 81.5; H, 10.6.

3,5,3',5'-Tetra-tert-butyl-1,1'-dihydro-2,5,2',5'-bis-cyclohexadiene-4,4'-one (III). A benzene solution of 2,6-di-*tert*-butylphenol (4.12 g. in 50 ml.) was added dropwise under a current of nitrogen to a well stirred mixture of potassium ferricyanide (24 g.), water (100 ml.), benzene (200 ml.), and potassium hydroxide (4 g.). The red colored solution was poured onto crushed ice. The benzene layer was separated, washed with water, and dried over sodium sulfate. The solvent was removed at reduced pressure in a nitrogen atmosphere. The crude product thus obtained was washed with 35 ml. of petroleum ether. A colorless solid (2.6 g.) was thus obtained. Upon crystallization from iso-octane large colorless plates were obtained which melted at 151–152°.

Anal. Calcd. for $C_{28}H_{42}O_2$: C, 81.9; H, 10.3. Found: C, 81.8; H, 10.0.

The petroleum ether washings upon evaporation gave (1 g.) which melted at 245°.

2,6-Di-tert-butyl-4-methyl-4-hydroperoxy-2,5-cyclohexadiene-1-one (XI). 2,6-Di-*tert*-butyl-4-methylphenol (4.4 g; 0.02 mole) was dissolved in ethanol (50 ml.) and a solution of potassium hydroxide (2 g. in 5 ml. water) was added. The flask was quickly connected to an oxygen buret and the solution was vigorously agitated. In about 25 min., 450 ml. (0.02 mole) of oxygen was taken up. The solution which had become pale yellow, was immediately poured into ice water (700 ml.) and neutralized with acetic acid. The precipitate which separated was collected on a filter, washed with water, and dried (4.8 g.). Upon addition of sodium iodide to a solution of the crude hydroperoxide in glacial acetic acid, free iodine was liberated. Titration with sodium thiosulfate showed that the crude material was 90% pure. (Yield of pure XI calculated on the basis of the starting compound was 86%). Upon crystallization from *n*-hexane, colorless needles were obtained which melted at 115–116°.

Anal. Calcd. for $C_{15}H_{24}O_3$: C, 71.4; H, 9.6. Found: C, C, 71.3; H, 9.6.

Dilution of the acetic acid solution, after reaction of the pure hydroperoxide with sodium iodide, gave a solid which melted at 110°. This product was shown to be identical with an authentic sample of XII.

2,6-Di-tert-butyl-4-methyl-4-hydroxy-2,5-cyclohexadiene-1-one (XII). To a solution of 2,6-di-*tert*-butyl-4-methylphenol (22 g.; 0.1 mole) in ethanol (150 ml.), potassium hydroxide (15 g. in 15 ml. water) was added and the apparatus was connected to an oxygen buret. After about 20 min. the solution became dark brown. The temperature of the reaction mixture rose to 55°. At this point it was cooled externally with water. A total of 2250 ml. of oxygen (about 0.1 mole) was absorbed in 1 hr. The oxygen buret was then disconnected and the whole allowed to stand for two hours longer. The brown colored reaction mixture was then poured into ice water (800 ml.). It was neutralized by addition of acetic acid, and the pale yellow precipitate which separated was collected on a filter and thoroughly washed with water and dried over phosphorus pentoxide. The crude material (18.7 g.) (yield, 80% calculated) melted at 78–92°. The product did not liberate iodine when treated with an acetic acid solution of sodium iodide.

A part of the crude material (3 g.) was dissolved in benzene and chromatographed on a column (10 in. long) of alumina (70 g.) using benzene as solvent and eluent. The least adsorbed fraction (100 ml.) gave a solid (0.9 g.) which melted at 150–152°. Upon two crystallizations of this material from ethanol, colorless needles were obtained which melted at 160°.

Anal. Calcd. for $C_{30}H_{46}O_2$: C, 82.1; H, 10.5; mol. wt. 438. Found: C, 82.1, 82.0; H, 10.0, 10.1; mol. wt. 416.

The next fraction (300 ml.) gave a white solid (XII) (1.6 g.) which upon crystallization from *n*-hexane melted at 111–112°.

Anal. Calcd. for $C_{15}H_{24}O_2$: C, 76.2; H, 10.2. Found: C, 76.3; H, 10.1.

Reduction of XII *with lithium aluminum hydride.* A solution of compound (XII) (1 g.) in dry ether (30 ml.) was added to a well stirred suspension of lithium aluminum hydride (3 g.) in ether (50 ml.). The mixture was stirred for 3 hr. and allowed to stand overnight. The whole was then poured into dilute sulfuric acid and extracted with ether, and the layers separated. Upon removal of the ether colorless plates (0.6 g.) were obtained which melted at 66–67°. This product was identical with 2,6-di-*tert*-butyl-4-methylphenol.

2,6-Di-tert-butyl-4-methyl-4-nitro-2,5-cyclohexadiene-1-one (XIV). To a solution of 2,6-di-*tert*-butyl-4-methylphenol (3.3 g.) in glacial acetic acid (20 ml.), 70% nitric acid (2.4 ml.) was added gradually. The temperature of the reaction was maintained at 20° by cooling externally. Upon further cooling of the reaction mixture a crystalline white precipitate separated which was collected (3 g.) on a filter. Upon crystallization from methanol colorless needles were obtained which melted at 97° (dec.).

Anal. Calcd. for $C_{15}H_{23}O_3N$: C, 67.9; H, 8.7. Found: C, 67.9; H, 8.9.

The ultraviolet spectrum showed $\lambda_{max}^{ethanol}$ 233 mμ; ϵ_{max} 10,250.

Hydrolysis of XIV. The nitro compound XIV (1 g.) was dissolved in a small amount of ethanol, water (25 ml.) added, and the whole heated on a low flame for 20 min. The resulting dark-brown oil was extracted with ether, and the ether was removed. Upon standing for 2 days the oily material solidified. The crude product (0.8 g.) was dissolved in benzene, and chromatographed on alumina. The least adsorbed orange colored band gave a red solid (0.3 g.) which was crystallized from acetic acid. Orange-red needles of (VI) were thus obtained which melted at 314°. The light absorption spectrum in ethanol showed λ_{max} 442 mμ; ϵ_{max} 72,000.

On eluting the column with benzene containing 0.5% ethanol, and evaporation of the solvent a colorless compound (0.12 g.) was obtained which melted at 110° This product was shown to be identical with XII. Further elution of the column with benzene containing 2% ethanol gave a small amount of 3,5-di-*tert*-butyl-4-hydroxybenzaldehyde.

2,6-Di-tert-butyl-4-bromo-4-bromomethyl-2,5-cyclohexadiene-1-one (XV). To a solution of the tertiary alcohol (XII; 0.2 g.) in a mixture of acetic acid (2 ml.) and water (0.1 ml.), bromine (0.05 ml.) in acetic acid (1 ml.) was added. After 15 min. shining pale yellow plates (0.2 g.) separated which melted at 118°.

Anal Calcd for $C_{15}H_{22}OBr_2$: C, 47.6; H, 5.8; Br, 42.3. Found: C, 48.3; H, 6.0; Br, 41.7.

Concentration of the mother liquor gave 3,5-di-*tert*-butyl-4-hydroxy benzaldehyde (50 mg.).

Reaction of 4,4'-dihydroxy-3,5,3',5'-tetra-tert-butyl diphenylmethane (XVI) *with oxygen.* To a solution of the diphenylmethane (XVI; 2.1 g.) in ethanol (25 ml.), potassium hydroxide (0.5 g. in 0.5 ml. water) was added, and the flask quickly connected to an oxygen buret. The solution gradually turned deep purple and consumed about 124 ml. of oxy-

gen in 8 min. The purple colored solution was poured into one liter of water and neutralized with acetic acid. The whole was then extracted with ether. Upon evaporation of the ether a yellow oil (2.0 g.) was obtained (mol. wt. 265). On chromatographing the oil (1.5 g.) over a column of alumina using benzene as solvent and eluent, the major fraction gave an orange-yellow crystalline product (0.3 g.) identified as 2,6-di-*tert*-butylbenzoquinone, melting at 67°.[17, 23] The infrared spectrum was identical with that reported by Müller and Ley.[10]

The absorption spectrum in isooctane showed λ_{max} 252, 308, and 380 mμ; ϵ_{max} 15,800, 384, and 261 respectively.

On eluting the column with benzene containing 1% ethanol, a colorless fraction (0.43 g.) was obtained which melted at 187°. The product was shown to be identical with 3,5-di-*tert*-butyl-4-hydroxybenzaldehyde.

Reaction of compound XVIII *with base.* Compound XVIII (0.04 g.) was suspended in a ethanolic (50 ml.) solution of sodium hydroxide (5%; 1 ml.). The air in the apparatus was replaced by nitrogen. The whole was then agitated vigorously. The color of the solution became intense purple in about 10 min. A small sample was withdrawn and its visible absorption measured at 575 mμ at different intervals. The extinction was found to be about ϵ_{max} 120,000 showing approximately half as much of XVII compared to the pure methylenequinone which has ϵ_{max} 220,000.

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[CONTRIBUTION FROM THE INSTITUTE OF ORGANIC CHEMISTRY, THE UNIVERSITY OF CHICAGO]

Bromination of Octene-1 with *N*-Bromosuccinimide*

M. S. KHARASCH, ROBERT MALEC, AND N. C. YANG

Received June 27, 1957

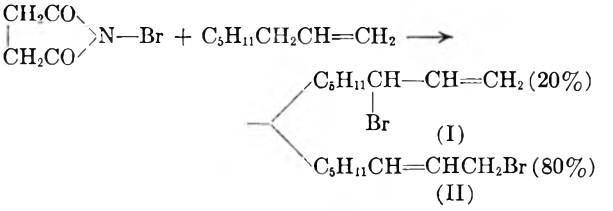
When *N*-bromosuccinimide reacts with octene-1 in light or in the presence of traces of peroxides, there is obtained a mixture consisting of 65% of monobrominated octenes, 15% of dibrominated octenes, and higher bromination products. The monobrominated octenes are *trans*-1-bromooctene-2 (80%; n_D^{20} 1.4760; b.p. 62–63°/6 mm) and 3-bromooctene-1 (20%; n_D^{20} 1.4669; b.p. 69–70°/14 mm). The dibrominated octenes contain one readily replaceable bromine atom per molecule. The reaction in question is retarded by oxygen and completely inhibited by small amounts of nitrosobenzene (0.5 mole %).

It has been claimed[1] that *N*-bromosuccinimide reacts with simple olefins containing a terminal double bond to give mixtures of allylic bromides of unknown composition. The composition of the mixture of the octenyl bromides resulting from the reaction of octene-1 with *N*-bromosuccinimide was investigated as part of an extensive study of the various mechanisms involved when *N*-bromosuccinimide reacts with a variety of organic compounds.

The bromination of octene-1 with *N*-bromosuccinimide was carried out in carbon tetrachloride in the presence of benzoyl peroxide (0.2 mole %) or in light. At 75°, in the absence of oxygen, the reaction is complete in about 1 hr. The reaction mixture was fractionated at low temperature and pressure. Two major fractions were thus obtained: (1) a mixture of monobrominated octenes (65 per cent); (2) a residue consisting of dibrominated octenes and higher bromination products.

Two fractionations of the monobrominated products through a 24-inch tantalum spiral column gave two fractions in the raio of one part to four.

Structures are assigned to these two materials



(I and II) on the basis of their infrared spectra.[2] The lower boiling material (n_D^{20} 1.4670) has bands with maxima at 1635 cm.$^{-1}$, 985 cm.$^{-1}$, and 920 cm.$^{-1}$ (vinyl group) and therefore has structure I (3-bromooctene-1); the higher boiling material (n_D^{20} 1.4760) has bands with maxima at 1658 cm.$^{-1}$ and 962 cm.$^{-1}$ (*trans*-disubstituted double bond) and must therefore be compound II (1-bromooctene-2).

The dibrominated octenes, which form about 15 per cent of the reaction mixture, are extremely unstable; they could be distilled, without decomposition, from the higher bromination products only in a molecular still. Unfortunately, under these conditions small amounts of succinimide (formed in the reaction) are found in each fraction. Analyses, for total bromine and bromine removable by silver nitrate, indicate that only one of the bromine atoms in these dibromides is readily replaceable. Because of the large number of dibromides (each containing only one allylic bromine atom) which would result from bromination of compounds I and II, the dibromides were not examined in detail.

Whether products I and II formed in a ratio of 1 to 4 are primary reaction products, or whether formation of the large amounts of II is due (under

* This paper is a contribution in honor of Lyndon F. Small, former Editor of the Journal.

(1) K. Ziegler, A. Späth, E. Schaaf, W. Schumann, and E. Winkelmann, *Ann.*, **551**, 93 (1942); Two excellent reviews are available (up to 1951) of the reactions of *N*-bromosuccinimide with many types of organic compounds [C. Djerassi, *Chem. Revs.*, **43**, 271 (1948); T. D. Waugh, *N-Bromosuccinimide, Its Reaction and Uses*, Arapahoe Chemicals, Inc., Boulder, Colorado, 1951].

(2) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, John Wiley and Sons, Inc., New York, 1954.

the experimental conditions) to very extensive rearrangement of compound I remains an open question.[3] Examination of the index of refraction and infrared spectrum of the initial mixture of the monobrominated products indicates the same ratio (1 to 4) of the isomers. These data indicate little or no isomerization occurs during the separation (by distillation) of the isomers. On the other hand, it was also noted that compound I when heated to 80° for 1 hr. without solvent in the absence of oxygen rearranges to give a mixture containing about 20 per cent compound II.

It should be noted here (Kharasch and Fono—unpublished work) that the decomposition of benzoyl peroxide in octene-1 gives predominantly a product corresponding to II, in which the ($-OCOC_6H_5$) group occupies the position of the bromine atom. In this connection studies of the rearrangement of type I compounds (in which a benzoyl group occupies the position of the bromine atom) to corresponding type II compounds might provide a partial answer to this interesting and vexing problem.[4]

EXPERIMENTAL

Octene-1. Octene-1 (Phillips Petroleum Co., 99% minimum purity) was refluxed over molten sodium in a nitrogen atmosphere and distilled.

Bromination of octene-1. A mixture of freshly distilled octene-1 (n_D^{20} 1.4088; 50 g.), crystallized *N*-bromosuccinimide (26.7 g.), benzoyl peroxide (0.07 g.), and carbon tetrachloride (113 ml.) was heated under gentle reflux in a nitrogen atmosphere. The reaction was complete in about 1 hr.

The reaction mixture was cooled, and the succinimide which separated was collected on a filter. It was washed several times with small portions of cold carbon tetrachloride and dried. The yield of succinimide was 13.8 g. (93%). The washings were combined with the filtrate, and the solvent and most of the unreacted octene were removed by distillation at reduced pressure (20 mm.). The residue was distilled at 35° (0.06 mm.) and the distillate consisting mostly of monobrominated products was collected in a cold trap (−70°). A non-volatile fraction (Residue I) of 6.6 g. remained. The distillate (23.3 g.) was fractionally distilled at reduced pressure (6 mm.) through a 24-in. tantalum spiral column to give the following fractions:

Fraction	B.P. at 6 Mm.	Weight	n_D^{20}
1	50–57°	2.1 g.	1.4687
2	57–60°	2.1 g.	1.4716
3	61–62°	3.7 g.	1.4746
4	62–63°	10.5 g.	1.4760

Octene-1 (3.3 g., n_D^{20} 1.4093) was recovered from the cold trap and a small amount (0.3 g.) of pot residue remained.

Fraction 4 was essentially pure 1-bromo-2-octene (II) as shown by its infrared spectrum, ν_{max} at 1658 cm.$^{-1}$ and 962 cm.$^{-1}$

Anal. Calcd. for $C_8H_{15}Br$: C, 50.27%; H, 7.91%; Br, 41.81%; mol. wt., 191. Found: C, 50.39%; H, 7.92%; Br, 41.84%; mol. wt. (cryoscopic), 185.

Fraction 1 to 3 were shown by their infrared spectra to contain 3-bromo-1-octene (I), ν_{max} at 1635 cm.$^{-1}$, 985 cm.$^{-1}$, and 920 cm.$^{-1}$ The lower boiling fractions of several runs were combined and fractionated through the same column, and a sample of pure 3-bromo-1-octene was thus obtained [b.p. 61° (9.5 mm.), 69–70° (14 mm.), n_D^{20} 1.4669].

Anal. Calcd. for $C_8H_{15}Br$: C, 50.27%; H, 7.91%; Br, 41.81%; mol. wt., 191. Found: C, 50.62%; H, 8.09%; Br, 41.48%; mol. wt. (cryoscopic), 187.

It was shown that linear relationship existed between the refractive index and the percentage composition of 3-bromo-1-octene and 1-bromo-2-octene mixture. The yield of monobrominated products based on refractive indexes were: 3-bromo-1-octene (I), 3.4 g. (12%); 1-bromo-2-octene, 15.0 g. (53%).

Residue I was placed in a Hickman molecular still and distilled at 10^{-5} mm. and 95° (bath temperature), and the distillate (3.1 g.) collected. A small amount (0.5 g.) of more volatile fraction was recovered from the cold trap. Some crystals of succinimide collected on the wall of the still. A viscous brown tar (2.9 g.) remained in the still. The distillate was shown to contain 49% of bromine by analysis and had an average molecular weight of 230. The infrared spectrum indicated the presence of succinimide. Approximately half of the bromine content could be titrated with aqueous silver titrate.

The bromination proceeded without peroxide under diffused light at a slower rate (8 hr. at 75°), and a similar mixture of products was obtained. The reaction was retarded by molecular oxygen and completely inhibited by a small amount of nitrosobenzene (0.5 mole per cent).

Isomerization of I *and* II. A small amount (100 mg.) of 3-bromo-1-octene (I) was heated in a water bath at 80° (in a nitrogen atmosphere) for 1 hr. The refractive index changed from n_D^{20} 1.4670 to 1.4690. The infrared spectrum of this material was identical with a synthetic mixture of I and II in a ratio of 2:7. The index of refraction of 1-bromo-octene-2 remained unchanged when the material was heated to 80° for 1 hr.

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(3) For rearrangement of allylic bromides (similar to I) to allylic bromides (similar to II) under the action of hydrogen bromide and oxygen, see M. S. Kharasch, E. T. Margolis, and F. R. Mayo, *J. Org. Chem.*, **1**, 393 (1936); see also the excellent and comprehensive review by R. H. DeWolfe and W. G. Young, *Chem. Revs.*, **56**, 775 (1956).

(4) For the bromination of related olefins by *N*-bromosuccinimide see the following papers: Allylbenzene to cinnamyl bromide, and non-1-en-4-yne to 1-bromo-non-2-en-4-yne [E. A. Braude and E. S. Waight, *J. Chem. Soc.*, 1116 (1952)]. Note also that in the case of methyl vinylacetate [E. J. Corey, *J. Am. Chem. Soc.*, **75**, 2251 (1953)] and vinyl acetonitrile [P. Couvreur and A. Bruylants, *Bull. soc. chim. Belg.*, 61, 253 (1952); W. Bailey and J. Bello, *J. Org. Chem.*, **20**, 525 (1955)] no methyl γ-bromocrotonate or γ-bromocrotonitrile were isolated. The reaction of vinyl acetonitrile was repeated in our laboratory. We differ, in a minor point from Bailey and Bello. The index of refraction of the β,γ-dibromobutyronitrile obtained by us was n_D^{20} 1.5485, whereas Bailey and Bello report an index of refraction at 25° of 1.5165.

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Synthesis of 2-Hydroxymethylquinolizidine (*dl*-2-Lupinine)*

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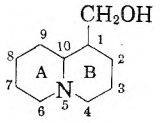
Received July 1, 1957

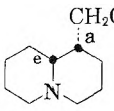
2-Hydroxymethylquinolizidine (*dl*-2-lupinine) has been synthesized by an unequivocal route starting with 2-carbethoxy-1-ketoquinolizidine.

It has been established that the product resulting from the reaction of ethoxymethyl α-picolyl ketone with acetic anhydride is 1-acetyl-3-ethoxypyrrocoline.

1-Hydroxymethylquinolizidine (I) is found in nature as the alkaloids (−)-lupinine (II)[3] and (+)-isolupinine [(+)-epilupinine] (III).[4] In lupinine, the hydrogens at C-1 and C-10 are in the *cis* relation, with the hydroxymethyl group axial to ring B in the chair conformation[5−12] and epimerizable[4,13−16] to the $C_{1,10}$-*trans* isomer with the hydroxymethyl group equatorial. Syntheses of *dl*-lupinine[8,17,13] and *dl*-epilupinine[17,18] have substantiated the structural assignments in these diastereomeric examples. Interest in the position isomers of the alkaloids (I) has led to the synthesis and characterization of the two racemates of 3-hydroxymethylquinolizidine (IV)[11,18−20] *dl*-3-lupinine (CH_2OH axial; CH_2OH α in the enantiomorphic representation where C_{10}-H is β) and *dl*-3-epilupinine (CH_2OH equatorial and β). A synthesis of '*dl*-2-lupinine' (V) has been reported by Winterfeld and Schneider,[21] but, as we have pointed out previously,[22] this synthesis was suspect since the deoxygenated compound related to the supposed "2-hydroxymethylquinolizidine" could not have been 2-methylquinolizidine. We have now devised a straightforward synthetic route to 2-hydroxymethylquinolizidine for the purpose of providing authentic material of structure V.



I



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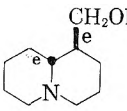
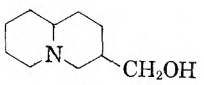
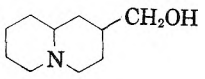


III



IV



V

The reduction of 2-carbethoxy-1-ketoquinolizidine (VI) with 2.2 equivalents of sodium borohydride furnished 2-carbethoxy-1-hydroxyquinolizidine (VII) in 89% yield. Dehydration of VII with sulfuric acid in glacial acetic acid, followed by a reesterification step led to 2-carbethoxy-Δ^1-dehydroquinolizidine, isolated as the hydrochloride (VIII), in 58% yield. Catalytic hydrogenation of VIII was followed by lithium aluminum hydride reduction of the intermediate 2-carbethoxyquinolizidine (hydrochloride) (IX). One racemate of 2-hydroxymethylquinolizidine (V) was obtained having the following properties: m.p. 74–76°; picrate, m.p. 144.5–145°; picrolonate, m.p. 171.5–173°; *p*-nitrobenzoate, m.p. 97–99° (picrate, m.p. 236.5–238°). The synthetic method was checked at the dehydration stage (VII → VIII) where, it might be argued, existed the possibility of rearrangement. Treatment of 2-carbethoxy-1-hydroxyquinolizidine (VII) with phosphorus oxychloride and pyridine,

* This paper is a contribution in honor of Lyndon F. Small, former Editor of the Journal.

(1) Monsanto Chemical Co. Fellow, 1956–57.

(2) National Science Foundation Fellow, 1954–55.

(3) N. J. Leonard, "Lupin Alkaloids," in *The Alkaloids*, edited by R. H. F. Manske and H. L. Holmes, Vol. III, Academic Press, Inc., New York, N. Y., 1953.

(4) E. P. White, *New Zealand J. Sci. Technol.*, **33B**, 50 (1951).

(5) R. C. Cookson, *Chemistry & Industry*, 337 (1953).

(6) P. Karrer, F. Canal, K. Zohner, and R. Widmer, *Helv. Chim. Acta*, **11**, 1062 (1928).

(7) L. Marion, D. A. Ramsay, and R. N. Jones, *J. Am. Chem. Soc.*, **73**, 305 (1951).

(8) V. Boekelheide and J. P. Lodge, Jr., *J. Am. Chem. Soc.*, **73**, 3681 (1951).

(9) N. J. Leonard and B. L. Ryder, *J. Org. Chem.*, **18**, 598 (1953).

(10) F. Galinovsky, O. Vogl, and H. Nesvadba, *Monatsh.*, **85**, 1300 (1954).

(11) J. Ratuský, A. Reiser, and F. Šorm, *Chem. Listy*, **48**, 1794 (1954); *Collection Czechoslov. Chem. Communs.*, **20**, 798 (1955).

(12) If absolute configuration[5] and stereochemical analogy to the steroid conventions[11] are considered, in (−)-lupinine, the C_{10}—H is β and the C_1-CH_2OH is α.

(13) K. Winterfeld and F. W. Holschneider, *Ber.*, **64**, 137 (1931).

(14) C. Schöpf, E. Schmidt, and W. Braun, *Ber.*, **64**, 683 (1931).

(15) K. Krieg, Dissertation, Marburg, 1928.

(16) J. F. Couch, *J. Am. Chem. Soc.*, **56**, 2434 (1934).

(17) G. R. Clemo, W. McG. Morgan, and R. Raper, *J. Chem. Soc.*, 965 (1937); 1574 (1938).

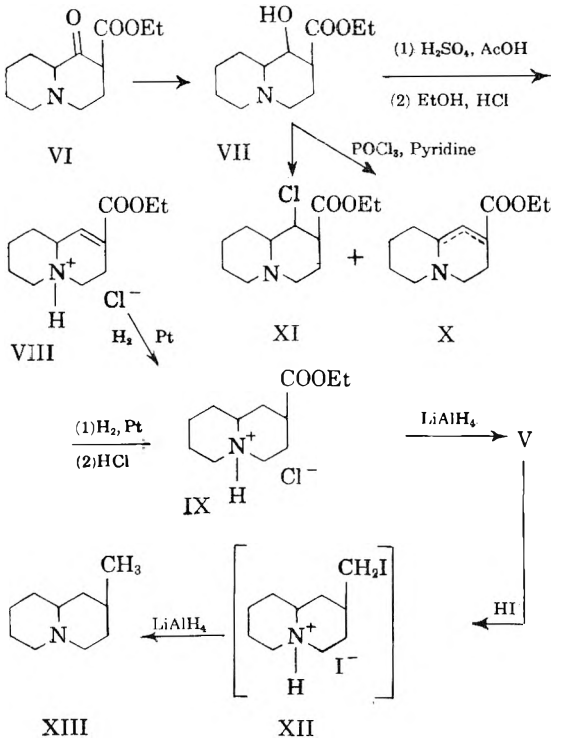
(18) J. Ratuský and F. Šorm, *Chem. Listy*, **47**, 1491 (1953); *Collection Czechoslov. Chem. Communs.*, **19**, 340 (1954).

(19) S. Ohki and K. Yamakawa, *Pharm. Bull. (Japan)*, **1**, 260 (1953).

(20) H. R. Lewis and C. W. Shoppee, *J. Chem. Soc.*, 313 (1956).

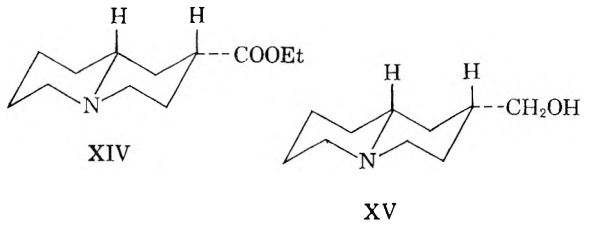
(21) K. Winterfeld and E. Schneider, *Ann.*, **581**, 66 (1953); *Naturwissenschaften*, **40**, 109 (1953).

(22) N. J. Leonard, R. W. Fulmer, and A. S. Hay, *J. Am. Chem. Soc.*, **78**, 3457 (1956).



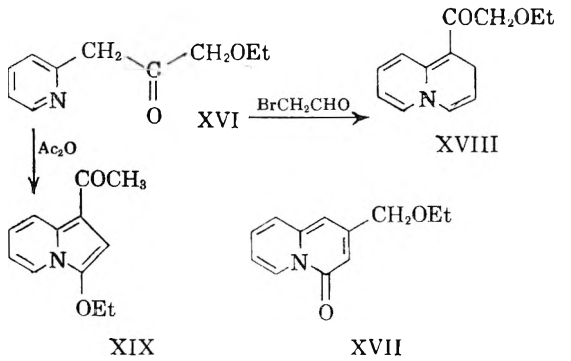
followed by hydrogenation with platinum of the unsaturated ester intermediate (X), produced the same saturated ester (IX) as obtained *via* the acid dehydration route. The chloro ester XI was a by-product.

The structure of our synthetic 2-hydroxymethylquinolizidine (V) was further confirmed by conversion to 2-methylquinolizidine (XIII) and direct comparison with samples of this compound prepared previously in our laboratory.[22] To accomplish this, the 2-hydroxymethylquinolizidine was heated under reflux with fuming hydriodic acid, and the resulting iodide hydriodide (XII) was reduced with lithium aluminum hydride to give an amine, isolated as the picrate (54% over-all yield), m.p. 150–151°, which was identical with the picrate of the predominant synthetic isomer (A)[22] of 2-methylquinolizidine (XIII). In the interest of determining which racemate of 2-hydroxymethylquinolizidine was represented by our synthetic product, we applied isomerizing conditions to the precursor 2-carbethoxyquinolizidine (available from IX). Under both acidic[23] and basic[24] epimerizing conditions (at C-2), over 60% of the original 2-carbethoxyquinolizidine was recovered, and no second racemate could be isolated in pure form. These findings indicate, in the light of parallel experiments in related series,[5,9,23] that the 2-carbethoxyquinolizidine at hand (hydrochloride, m.p. 202–203°) is the thermodynamically more stable isomer, with the C-2 and C-10 hydrogens *cis* and the carbethoxyl group equatorial (XIV, one enantiomorph represented). It follows that the 2-hydroxymethylquinolizidine which is obtained from XIV on lithium aluminum hydride reduction is of similar geometry (XV, one enantiomorph represented) and may be called *dl-2-lupinine* on the basis of nomenclature convention in this series,[11] wherein



the name "x-lupinine" (x = 2, 3, or 4) will be applied to the racemate having the CH_2OH *trans* with respect to the 10-hydrogen, and" x-epilupinine," to the racemate having the CH_2OH *cis* with respect to the 10β-hydrogen.[25]

Since our synthesis led to authentic 2-lupinine, the problem that remained was to determine at which point the synthetic route of Winterfeld and Schneider[21] was diverted from the same goal. The first step in their reaction sequence involved the condensation of ethoxymethyl α-picolyl ketone (XVI) with acetic anhydride in the presence of potassium acetate. The formation of "2-ethoxymethyl-4-quinolizone" ($C_{12}H_{13}NO_2$) (XVII) was postulated, in one rationalization,[21] as a Perkin-type condensation involving the carbonyl of XVI. It seemed more likely to us that XVI would be involved as the active methylene component, and we found that the yellow $C_{12}H_{13}NO_2$ product, m.p. 65.5–66.5°, could be obtained in equivalent yield in the absence of potassium acetate. The acetic anhydride reaction thus becomes reminiscent of pyrrocoline syntheses of Tschitschibabin,[26] and more likely structures (XVIII, XIX), isomeric with XVII, can be postulated for the product of the condensation of ethoxymethyl α-picolyl ketone with acetic anhydride. One of these, 1-ethoxyace-



(23) K. Alder, M. Schumacher, and O. Wolff, *Ann.*, **570**, 230 (1950)

(24) C. Schöpf and O. Thomä, *Ann.*, **465**, 98 (1928).

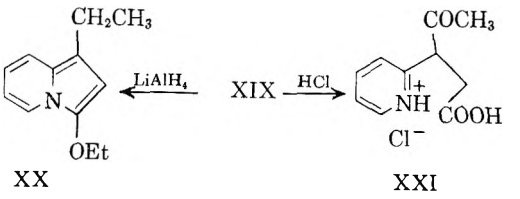
(25) It is perhaps significant that axial CH_2OH at C-1 or C-3 has only *one* 1:3-H interaction (both equatorial and axial isomers have been synthesized), whereas axial CH_2OH at C-2 has *two* 1:3-H interactions (only the equatorial isomer has been obtained thus far by synthesis).

(26) A. E. Tschitschibabin, *Ber.*, **60**, 1607 (1927).

tylpyrrocoline (XVIII), was made by the condensation of XVI with bromoacetaldehyde or, alternatively, with bromopyruvic acid, followed by a decarboxylation step. The yellow solid obtained, $C_{12}H_{13}NO_2$, m.p. 54–55°, was different from the acetic anhydride product.

The second possible pyrrocoline formulation, 1-acetyl-3-ethoxypyrrocoline (XIX), next received favorable consideration. The presence of a carbonyl group attached to a conjugated system was shown by the formation of a greenish black 2,4-dinitrophenylhydrazone. A monobenzylidene derivative was prepared readily under conditions commonly used with acetylpyrrocolines[27] and indicative of the —CH_2—CO— grouping. The fact that the ratio of the benzaldehyde moiety to the nitrogen-containing moiety in this condensation product is 1:1 instead of 1:2 as in the case of pyrrocoline itself[28] further suggested that the reactive 1- and 3-positions on the pyrrocoline nucleus were occupied. The spectral data on the $C_{12}H_{13}NO_2$ product can also be reconciled with structure XIX, but not with formula XVII. The appearance of the carbonyl infrared absorption band at 1645 cm.$^{-1}$ is comparable with the appearance of the C=O stretching maximum at 1635 cm.$^{-1}$ (with a shoulder at 1660 cm.$^{-1}$) in the infrared spectrum of 1,3-diacetylpyrrocoline. Carbonyl absorption in this range appears to be characteristic of a number of variously substituted indole carbonyl compounds as well.[29,30] The ultraviolet spectrum proved particularly useful in eliminating formula XVII, since the spectrum (principal maxima at 233, 332, and 369 mμ) of the $C_{12}H_{13}NO_2$ product was significantly different from that reported for 4-quinolizone.[8]

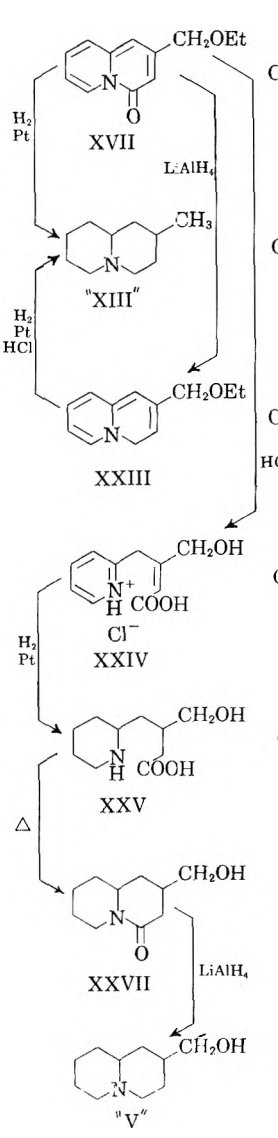
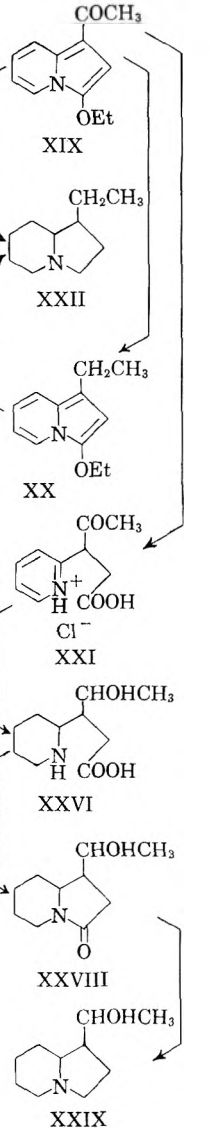
Further evidence strongly in favor of 1-acetyl-3-ethoxypyrrocoline (XIX) was found in the lithium aluminum hydride reduction product, 1-ethyl-3-ethoxypyrrocoline (XX), which had an ultraviolet spectrum closely resembling that reported for 1,3,5,7-tetramethylpyrrocoline.[31] Complete reduction by lithium aluminum hydride of a carbonyl group on the pyrrocoline nucleus to a methylene group has been observed in the case of 2,3-dimethyl-1-formylpyrrocoline,[32] and such reduction has also been observed in closely related compounds (indole-3-aldehyde, 3-acetylindole and 3-acetyl-2,4-dimethylpyrrole).[29,32,33] Cleavage and loss of ethoxyl from XIX was effected by hydrolysis with concentrated hydrochloric acid. The analysis (including the absence of ethoxyl, as determined by



Winterfeld and Schneider[21]) and infrared spectrum are compatible with the presently assigned structure, 3-(2′-pyridyl)-4-ketopentanoic acid hydrochloride (XXI), for the hydrolysis product.

Since the intended synthesis of 2-lupinine by Winterfeld and Schneider[21] departed so early from the designed course, a number of revisions in structural assignments are required, as indicated in the accompanying table. The analyses, where previously supplied, are satisfactory for the new struc-

TABLE I

Structure Previously Assigned[21]	Molecular Formula	Revised Structure
	$C_{12}H_{13}NO_2$	
	$C_{10}H_{19}N$	
	$C_{12}H_{15}NO$	
	$C_{10}H_{12}ClNO_3$	
	$C_{10}H_{19}NO_3$	
	$C_{10}H_{17}NO_2$	
	$C_{10}H_{19}NO$	

(27) E. T. Borrows, D. O. Holland, and J. Kenyon, *J. Chem. Soc.*, 1069 (1946).
(28) M. Scholtz, *Ber.*, **45**, 734, 1718 (1912).
(29) W. P. Samuels, Ph.D. thesis, University of Illinois, 1955.
(30) L. M. Werbel, Ph.D. thesis, University of Illinois, 1957.
(31) J. E. Saxton, *J. Chem. Soc.*, 3239 (1951).
(32) E. D. Rossiter and J. E. Saxton, *J. Chem. Soc.*, 3654 (1953).
(33) A. Treibs and H. Scherer, *Ann.*, **577**, 139 (1952).

tures, since these are isomeric with the old. The "2-lupinane" of Winterfeld and Schneider is now logically represented as 1-ethyloctahydropyrrocoline (XXII) (We have been able to obtain only one racemate.), and the melting points of the picrate (146–147°) and picrolonate (184.5–185.5°) are close to those reported for the corresponding derivatives of "2-lupinane" (141° and 175–179°, respectively).[21] If the reaction sequence is followed formally to the concluding step (Table I), the logical structure to replace Winterfeld and Schneider's "2-lupinine" becomes 1-(1′-hydroxyethyl)-octahydropyrrocoline (XXIX). Furthermore, it is obvious that structural revisions will be necessary for the compounds which Winterfeld and Küllman[34] have reported originating with the reaction of phenyllithium with the compound now known to be XIX.

EXPERIMENTAL[35]

Sodium borohydride reduction of 2-carbethoxy-1-ketoquinolizidine. 2-Carbethoxy-1-hydroxyquinolizidine. To a solution of 10.0 ml. (10.9 g., 0.048 mole) of 2-carbethoxy-1-ketoquinolizidine[22] in 100 ml. of methanol, cooled with stirring in an ice bath, was added 1.0 g. (0.026 mole, 2.2 equiv.) of sodium borohydride in small portions during 10 min. Stirring was continued for 1.5 hr. before the mixture was poured into 200 ml. of ice water and extracted with chloroform. The residue from the combined chloroform extracts was distilled through a Holzman column. The distillation was complicated by the tendency of the material to superheat and also to solidify in the condenser. The yield of *2-carbethoxy-1-hydroxyquinolizidine* was 9.82 g. (89%), b.p. 102–106° (0.11 mm.), n_D^{25} 1.4933–1.4942 (supercooled liquid). The liquid soon solidified to a waxy solid, m.p. *ca.* 70°. The infrared spectrum of a crystal melt exhibited maxima at 3460 (O—H); 2945, 2870, 2810, 2760, 2680 (C—H); and 1735 cm.$^{-1}$ (ester C=O).

Anal. Calcd. for $C_{12}H_{21}NO_3$: C, 63.41; H, 9.31; N, 6.16. Found: C, 63.23; H, 9.24; N, 6.07.

In another reduction in which 4 moles (16 equiv.) of sodium borohydride were used per mole of 2-carbethoxy-1-ketoquinolizidine, the diol, *1-hydroxy-2-hydroxymethylquinolizidine,* was produced. This material was partially separated from the desired reduction product by distillation through a Holzman column. The highest boiling fraction solidified and was recrystallized from cyclohexane, m.p. 104–106°, selected infrared maxima (Nujol) at 3410, 3290, 3140 cm.$^{-1}$ (O—H).

Anal. Calcd. for $C_{10}H_{19}NO_2$: C, 64.82; H, 10.34; N, 7.56. Found: C, 64.83; H, 10.27; N, 7.30.

Sulfuric acid dehydration of 2-carbethoxy-1-hydroxyquinolizidine. 2-Carbethoxy-Δ¹-dehydroquinolizidine hydrochloride. To a solution of 9.67 g. (0.042 mole) of 2-carbethoxy-1-hydroxyquinolizidine in 10 ml. of glacial acetic acid was added 10 ml. of 36*N* sulfuric acid, and the mixture was maintained at 160° for 5 hr. The mixture was cooled and poured into 200 ml. of ice and water. Acetic acid was removed by extraction with ether. The aqueous solution was neutralized with potassium carbonate, and the potassium sulfate which separated was removed by filtration. The filtrate was evaporated to dryness under reduced pressure, absolute ethanol was added, and the mixture was again evaporated. An ethanolic solution of the residue was saturated with anhydrous hydrogen chloride and allowed to stand about 5 hr. After filtration, the filtrate was evaporated to dryness, and the residue eventually crystallized in a desiccator (see below). The solid filter cake was boiled in absolute ethanol, the potassium chloride was removed by filtration, and the filtrate was saturated with anhydrous hydrogen chloride. After standing a day, the same isolation procedure yielded a second crop of crystals. The total yield of 2-carbethoxy-Δ¹-dehydroquinolizidine hydrochloride was 6.02 g. (58%), m.p. 165–184°. Recrystallization from ethanol–ethyl acetate was a wasteful process but served to provide analytically pure material, m.p. 194–195°.

Anal. Calcd. for $C_{12}H_{20}ClNO_2$: C, 58.65; H, 8.20; N, 5.70. Found: C, 58.78; H, 8.45; N, 5.40.

The infrared spectrum (5% solution in chloroform) exhibited maxima at 2960 (C—H), 2300–2400 (amine salt), 1720 (α,β-unsaturated ester C=O) and 1670 cm.$^{-1}$ (C=C).

Hydrogenation of 2-carbethoxy-Δ¹-dehydroquinolizidine. 2-Carbethoxyquinolizidine hydrochloride. A solution of 1.73 g. (7.05 mmoles) of 2-carbethoxy-Δ¹-dehydroquinolizidine hydrochloride (m.p. 165–184°) in 100 ml. of absolute ethanol was hydrogenated at 3 atm. using 0.1 g. of platinum oxide. It was necessary to interrupt the hydrogenation frequently, filter the exhausted catalyst, and add fresh platinum oxide in order to realize the theoretical uptake. Removal of the catalyst and solvent yielded 0.76 g. (43%) of colorless crystals, m.p. 191–195°, which were recrystallized by dissolving in methylene chloride, adding ethyl acetate, and boiling until all the methylene chloride was removed. The analytical sample melted at 202–203°

Anal. Calcd. for $C_{12}H_{22}ClNO_2$: C, 58.17; H, 8.95; N, 5.65. Found: C, 58.53; H, 8.92; N, 5.78.

The infrared spectrum (5% solution in chloroform) showed maxima at 2960 (C—H), 2440 (amine salt), and 1735 cm.$^{-1}$ (ester C=O).

Lithium aluminum hydride reduction of 2-carbethoxyquinolizidine hydrochloride. 2-Hydroxymethylquinolizidine. 2-Carbethoxyquinolizidine hydrochloride (4.19 g., 0.017 mole) was added as a solid during 10 min. to a stirred suspension of 1.93 g. (0.05 mole) of lithium aluminum hydride in 125 ml. of dry tetrahydrofuran. After 1.5 hr., the excess hydride was destroyed, 10 ml. of water was added, and the tetrahydrofuran was removed with a current of steam until the vapor temperature reached 99°. The organic base was extracted from the cooled residue with ether and isolated in the usual manner. Purification by distillation in high vacuum yielded 2.58 g. (90%) of viscous, colorless oil, n_D^{22} 1.5053–1.5066 (supercooled liquid), which could be crystallized from pentane, colorless prisms, m.p. 74–76°.

Anal. Calcd. for $C_{10}H_{19}NO$: C, 70.96; H, 11.31; N, 8.28. Found: C, 71.27; H, 11.16; N, 8.28.

The infrared spectrum (crystal melt) exhibited a band at 3180–3380 (O—H) and maxima at 2809, 2830, 2780, 2740, and 2680 cm.$^{-1}$ (C—H).

The *picrate* of this racemate of 2-hydroxymethylquinolizidine crystallized from methanol as yellow needles, m.p. 144.5–145°.

Anal. Calcd. for $C_{16}H_{22}N_4O_8$: C, 48.24; H, 5.57; N, 14.06. Found: C, 48.07; H, 5.72; N, 13.69.

The *picrolonate* was prepared in methanol and was recrystallized from ethyl acetate containing a trace of methanol, light yellow prisms, m.p. 171.5–173°.

Anal. Calcd. for $C_{20}H_{27}N_5O_6$: C, 55.42; H, 6.28; N, 16.16. Found: C, 55.88; H, 6.03; N, 15.93.

A small sample of the base was boiled with an equivalent of *p*-nitrobenzoyl chloride in benzene for 2.5 hr. Ether and

(34) K. Winterfeld and K. Küllman, *Arch. Pharm.*, 289, 272 (1956).

(35) All melting points are corrected. We are indebted to Mrs. Esther Fett, Mrs. Lucy Chang, Mrs. R. Maria Benassi, Miss Claire Higham and Mr. Jozsef Nemeth for microanalyses, to Mrs. Louise Griffing and Mr. James Brader for determination of the infrared absorption spectra, and to Mr. Mou-shu Chao for determination of the ultraviolet absorption spectra. (Cyclohexane was used as the solvent for the ultraviolet spectra.)

10% aqueous sodium hydroxide solution were added, and the mixture was shaken. The ether layer was divided into 2 portions. The first portion was evaporated to dryness, and the *p-nitrobenzoate* was recrystallized once from aqueous methanol and several times from hexane, colorless leaflets, m.p. 97–99°.

Anal. Calcd. for $C_{17}H_{22}N_2O_4$: C, 64.13; H, 6.97; N, 8.80. Found: C, 64.95; H, 7.01; N, 8.77.

To the second portion of the ethereal solution was added methanolic picric acid. After recrystallization from a large volume of 95% ethanol, the picrate of the *p-nitrobenzoate* was obtained as yellow prisms, m.p. 236.5–238°.

Anal. Calcd. for $C_{23}H_{25}N_5O_{11}$: C, 50.46; H, 4.60; N, 12.79. Found: C, 50.95; H, 4.54; N, 12.61.

Conversion of 2-hydroxymethylquinolizidine to 2-methylquinolizidine. The racemate of 2-hydroxymethylquinolizidine described above (0.52 g., 3.08 mmoles) was heated under reflux overnight with 15 ml. of fuming hydriodic acid. The mixture was evaporated to dryness *in vacuo*, and acetone was used to collect the crystals on a sintered glass funnel, yield 0.99 g. (79%), m.p. 241–250° after darkening at 170°. The infrared spectrum was consistent with the formulation of this material as the hydriodide of 2-iodomethylquinolizidine. The only absorption bands above 1500 cm.$^{-1}$ occurred at 2560, 2710, 2840, and 2910 cm.$^{-1}$

The crude iodide hydriodide was added to a suspension of 0.50 g. of lithium aluminum hydride in 80 ml. of tetrahydrofuran which had been freshly distilled from lithium aluminum hydride. After 2 hr. at reflux temperature the excess hydride was destroyed with ethyl acetate, and water and finally dilute hydrochloric acid were added. The tetrahydrofuran was removed by steam distillation. The mixture was rendered strongly alkaline and extracted with ether. Methanolic picric acid was added to the ethereal solution, and concentration produced yellow needles which were recrystallized from absolute ethanol, yield 0.51 g. (54% over-all yield), m.p. and mixture m.p. with authentic 2-methylquinolizidine (isomer A) picrate,[22] 150–151°.

The infrared spectra (5% solution in acetonitrile) of this picrate of 2-methylquinolizidine and of 2-methylquinolizidine (isomer A) picrate[22] [as well as that of 2-methylquinolizidine (isomer B) picrate[22] in acetonitrile!] were indistinguishable.

Attempted epimerization of 2-carbethoxyquinolizidine. An attempt at isomerization at C-2 of the 2-carbethoxyquinolizidine with sodium ethoxide in refluxing ethanol resulted in recovery of over 60% of the original racemate, as the hydrochloride. A similar result was obtained from an attempted isomerization of 2-carbethoxyquinolizidine with concentrated hydrochloric acid in a sealed tube at 150° for 6 hr.

On the assumption that the mother liquors remaining after isolation of the unique 2-carbethoxyquinolizidine hydrochloride from the attempted isomerizations might contain the epimeric racemate, the following additional reaction sequence was employed. The residue from evaporation of the mother liquors was reduced with lithium aluminum hydride, and the supposed mixture of racemates of 2-hydroxymethylquinolizidine was chromatographed on alumina. A material, the picrate of which was much lower melting than that observed earlier, was obtained, but recrystallization failed to narrow the melting range (107–115°, cloudy melt; clear at 122°).

Anal. Calcd. for $C_{16}H_{22}N_4O_8$: C, 48.24; H, 5.57. Found: C, 48.34; H, 5.54.

The analysis was correct for a picrate of 2-hydroxymethylquinolizidine, so the material was assumed to be a mixture of the two racemates. The mixture was converted to 2-methylquinolizidine *via* the iodide hydriodide as before, but only the familiar isomer A of 2-methylquinolizidine was isolated (12%). Thus, while some of the other racemate of 2-hydroxymethylquinolizidine was probably present in the hydride reduction mixture just described, it was not properly characterized, nor was its presence proved unequivocally.

Phosphorus oxychloride dehydration of 2-carbethoxy-1-hydroxyquinolizidine. A solution of 15.47 g. (0.068 mole) of 2-carbethoxy-1-hydroxyquinolizidine in 93 ml. of pyridine maintained under nitrogen was cooled in ice while 9.3 ml. (*ca.* 0.1 mole) of phosphorus oxychloride was added dropwise with stirring. When the addition was complete, the mixture was stirred at 25° under nitrogen for 48 hr. and then poured into cold 10% aqueous sodium hydroxide solution and extracted with chloroform. The mixture recovered from the chloroform was distilled, b.p. 83–95° (0.06 mm.), n_D^{25} 1.4985–1.4929, weight 9.03 g. The infrared spectrum exhibited maxima at 1715 (α,β-unsaturated ester C=O), 1740 (ester C=O), 1685 (C=C), and a series in the C—H stretching region: 2930, 2850, 2800, and 2755 cm.$^{-1}$

Hydrogenation of the phosphorus oxychloride dehydration product. The distilled dehydration product (11.27 g.) dissolved in 75 ml. of glacial acetic acid was hydrogenated at 3 atm. using platinum oxide. About one third of the theoretical amount of hydrogen was absorbed. Replacing the catalyst with a fresh quantity did not bring about further hydrogen uptake. The mixture was filtered, 12*N* hydrochloric acid was added to the filtrate, and the resulting solution was evaporated to dryness under reduced pressure. The oil was caused to crystallize by the addition of toluene, which was then removed at reduced pressure. The residue was recrystallized from methylene chloride–ethyl acetate as colorless crystals, m.p. 195–198°, yield 5.1 g. (38%), indentified by mixture m.p. and infrared spectrum as the same *2-carbethoxyquinolizidine hydrochloride* which was obtained earlier.

The combined mother liquors would neither crystallize nor absorb additional hydrogen under the conditions described above. Redistillation of the base liberated from these mother liquors followed by chromatography on acid-washed alumina yielded a pure substance which was isolated as the hydrochloride. The structure assigned to this product is *2-carbethoxy-1-chloroquinolizidine hydrochloride*, m.p. 136–137°, weight 1.75 g. The infrared spectrum (5% solution in chloroform) showed maxima at 1739 (ester C=O), 2300–2400 (amine salt), and 2960, 2935 and 2860 cm.$^{-1}$ (C—H).

Anal. Calcd. for $C_{12}H_{21}Cl_2NO_2$: C, 51.07; H, 7.50; N, 4.96. Found: C, 51.02; H, 7.50; N, 4.96.

Reduction of 2-carbethoxy-1-chloroquinolizidine to 2-hydroxymethylquinolizidine. 2-Carbethoxy-1-chloroquinolizidine hydrochloride (1.06 g., 3.75 mmoles) was added as a solid to 0.42 g. of lithium aluminum hydride suspended in 35 ml. of tetrahydrofuran which had just been distilled from lithium aluminum hydride. The mixture was heated under reflux for 14 hr., the hydride was destroyed, and concentrated aqueous sodium hydroxide solution was added. The base was extracted with ether and converted to the picrate, yellow needles from methanol–ethyl acetate, mixture m.p. with 2-hydroxymethylquinolizidine picrate (m.p. 144.5–145°), 147.5–151°, identical infrared spectra in acetonitrile solution.

1-Ethyl-1-hydroxyoctahydropyrrocoline. To the Grignard reagent prepared from 18.7 g. (0.12 mole) of ethyl iodide and 2.9 g. (0.12 g.-atom) of magnesium in 100 ml. of absolute ether was added a solution of 10.3 g. (0.074 mole) of 1-ketooctahydropyrrocoline[36] in 35 ml. of anhydrous ether. The reaction mixture was stirred under reflux for 3 hr. after addition of the ketone was completed. The mixture was treated with aqueous sodium hydroxide solution, and the product was obtained from the ether extracts, b.p. 80–82° (0.9 mm.) [reported[37] 85–87° (1 mm.)], $n_D^{23.5}$ 1.4887, yield 6.16 g. (30%).

Anal. Calcd. for $C_{10}H_{19}NO$: C, 70.94; H, 11.31; N, 8.28. Found: C, 71.06; H, 11.46; N, 8.08.

1-Ethyloctahydropyrrocoline. To a cooled solution of 12 g. of phosphorus pentoxide in 25 ml. of 85% phosphoric acid

(36) G. R. Clemo and G. R. Ramage, *J. Chem. Soc.*, 2969 (1932).

(37) G. R. Clemo and T. P. Metcalfe, *J. Chem. Soc.*, 1518 (1937).

was added 6.0 g. (0.035 mole) of 1-ethyl-1-hydroxyoctahydropyrrocoline. The reaction mixture was gradually raised to 145° and maintained there for 3 hr. The dehydro amine was isolated *via* basification and ether extraction. The crude product of the dehydration was dissolved in 50 ml. of absolute ethanol and hydrogenated at 25° and 3 atm., using Raney nickel catalyst, in 50 min. The solvent was removed by concentration *in vacuo*, and the residue was distilled through a micro spinning band column. Six fractions were collected arbitrarily: the first four had constant refractive index, n_D^{24} 1.4729; the fifth, 1.4740; the sixth, 1.4904. The first four fractions appeared to consist of only one racemate of 1-ethyloctahydropyrrocoline, the sixth fraction was unreacted 1-ethyl-1-hydroxyoctahydropyrrocoline and the fifth fraction appeared to be a mixture of these two compounds. Attempts to isolate a second picrate from the mother liquors of the fractions one through four were unsuccessful. An analytical sample of *1-ethyloctahydropyrrocoline* was prepared by regeneration from the analytically pure picrate of m.p. 146–147°.

Anal. Calcd. for $C_{10}H_{19}N$: C, 78.36; H, 12.50; N, 9.14. Found: C, 78.53; H, 12.73; N, 9.17.

The *picrate* crystallized from ethanol as small yellow needles, m.p. 146–147° (reported[37] 134°).

Anal. Calcd. for $C_{16}H_{22}N_4O_7$: C, 50.25; H, 5.70; N, 14.66. Found: C, 50.54; H, 5.77; N, 14.60.

The *picrolonate* was formed in acetone and recrystallized from ethanol as yellow prisms, m.p. 184.5–185.5° (reported[37] 176°).

Anal. Calcd. for $C_{20}H_{27}N_5O_5$: C, 57.54; H, 6.52; N, 16.78 Found: C, 57.62; H, 6.48; N, 17.02.

1,3-Diacetylpyrrocoline. The procedure was that of Scholtz[28] and Tschitschibabin,[26,38] involving the heating of α-picoline with acetic anhydride in a sealed tube at 220–230°, m.p. 174.5–176°, colorless needles from water. The infrared spectrum (5% solution in chloroform) showed carbonyl absorption at 1630 cm.$^{-1}$ (with a shoulder at 1660) and C—H absorption at 3020 (m) and 3140 cm.$^{-1}$ (w). The ultraviolet spectrum exhibited the following maxima: 226 mμ (log ε 4.11), 254 (4.44), 279 (4.06), 289 (4.23), 335 (4.29), and 345 (4.39). Infection points were observed at 249 (4.35) and 269 (3.77) and minima at 232 (4.06), 263 (3.65), 283 (4.01), 299 (3.71), and 345 (4.18).

Pyrrocoline was obtained from the 1,3-diacetylpyrrocoline by hydrochloric acid hydrolysis with heating,[38] m.p. 72–73°. Attempted reaction of pyrrocoline with ethoxyacetic anhydride in a sealed tube at 230° failed to yield any 1,3-di(ethoxyacetyl)pyrrocoline.

Ethoxymethyl α-picolyl ketone. This compound was prepared by the method of Winterfeld and Schneider[21] from α-picolyllithium and ethyl ethoxyacetate, b.p. 104–106° (0.3 mm.), yield 53%; *picrate*, m.p. 118.5–119° as reported,[21] yellow needles from ethanol.

Anal. Calcd. for $C_{16}H_{16}N_4O_9$: C, 47.06; H, 3.92; N, 13.72. Found: C, 47.40; H, 3.93; N, 14.14.

1-Ethoxyacetylpyrrocoline. The cyclization method of Tschitschibabin[26] was employed, using equimolar quantities of ethoxymethyl α-picolyl ketone and bromoacetylaldehyde,[39,40] but 1-ethoxyacetylpyrrocoline was obtained in only microscopic yield as a pale yellow solid, m.p. 52–53°. The substance showed the usual green fluorescence of a pyrrocoline in solution. It was made more efficiently from bromopyruvic acid. The condensation followed the general conditions of Borrows and Holland.[41]

To a solution of 7.5 g. (0.042 mole) of ethoxymethyl α-picolyl ketone in 200 ml. of absolute ethanol was added 7.0 g. (0.042 mole) of freshly prepared bromopyruvic acid.[42,43] The mixture was warmed on the steam bath for 3 hr. and and then allowed to stand at 25°. The solid that separated was recrystallized from ethanol as light yellow needles, m.p. 175–176° (dec.), yield 4.0 g. (39%) of *1-ethoxyacetylpyrrocoline-2-carboxylic acid.*

Anal. Calcd. for $C_{13}H_{13}NO_4$: C, 63.15; H, 5.30; N, 5.67. Found: C, 63.42; H, 5.34; N, 5.75.

The decarboxylation of this intermediate (0.5 g.) was effected by heating with 0.09 g. of copper bronze catalyst and 4 ml. of freshly distilled quinoline for 30 min. Ether (50 ml.) was then added to the cooled mixture. The ethereal solution was filtered, the ether was evaporated, and the quinoline was distilled. The residue was dissolved in hexane (with a few drops of ethyl acetate) and chromatographed on alumina. From the benzene elution fraction was obtained a brown residue upon removal of the solvent. It was recrystallized, with decolorization, from hexane containing a few drops of ethyl acetate, yielding 200 mg. of *1-ethoxyacetylpyrrocoline*, light yellow prisms, m.p. 54–55°. There was no significant depression of melting point when this product was mixed with that obtained using bromoacetaldehyde.

Anal. Calcd. for $C_{12}H_{13}NO_2$: C, 70.91; H, 6.45; N, 6.89. Found: C, 71.10; H, 6.28; N, 7.12.

Reaction of ethoxymethyl α-picolyl ketone with acetic anhydride. 1-Acetyl-3-ethoxypyrrocoline. The combination of ethoxymethyl α-picolyl ketone, acetic anhydride, and dry potassium acetate followed the directions of Winterfeld and Schneider,[21] and the product was purified by recrystallization from hexane to yield light yellow needles, m.p. 65.5–66.5° (reported[21] 64.5°), yield 34%. In solution the compound exhibited blue fluorescence.

Anal. Calcd. for $C_{12}H_{13}NO_2$: C, 70.91; H, 6.45. Found: C, 70.46; H, 6.54.

The same compound was obtained when potassium acetate was omitted from the reaction mixture. Thus, a mixture of 9.3 g. (0.052 mole) of ethoxymethyl α-picolyl ketone and 20 ml. (0.21 mole) of acetic anhydride was heated under reflux at 140° for 2 hr. Acetic anhydride was removed at aspirator pressure, and the product was collected at 145–160° (0.2–0.3 mm.), yield 4.0 g. (38%). It solidified after distillation and was recrystallized from hexane, light yellow needles, m.p. 65.5–66.5°, identical with the compound obtained following the earlier reaction conditions.

The infrared spectrum (5% solution in carbon tetrachloride) showed a large number of sharp peaks in the fingerprint region. A carbonyl stretching band appeared at 1645 cm.$^{-1}$ and C—H stretching bands at 3005, 2950, and 2900 cm.$^{-1}$ The ultraviolet spectrum exhibited maxima at 233 mμ (log ε 4.42), 256 (3.62), 265 (3.65), 275 (3.52), ~322 (3.93), 332 (3.94), and 369 (3.87). Minima appeared at 253 (3.61), 260 (3.60), 272 (3.47), 283 (3.09), and 345 (3.76). No pure product could be isolated when 1-acetyl-3-ethoxypyrrocoline was heated with ethoxyacetic anhydride in a sealed tube.

The *2,4-dinitrophenylhydrazone* was prepared by dissolving 0.1 g. of 1-acetyl-3-ethoxypyrrocoline in 4 ml. of absolute ethanol and adding a solution containing 0.2 g. of 2,4-dinitrophenylhydrazine. The solid which formed within 3 hr. was collected and recrystallized twice from pyridine and once from a large volume of ethyl acetate to give a mat of black needles with a greenish cast, m.p. 238–239°.

Anal. Calcd. for $C_{18}H_{17}N_6O_5$: C, 56.39; H, 4.47; N, 18.28. Found: C, 56.48; H, 4.31; N, 18.30.

The *benzylidene* derivative was made from 0.1 g. of 1-acetyl-3-ethoxypyrrocoline, 0.2 ml. of benzaldehyde and

(38) A. E. Tschitchibabin and F. N. Stepanow, *Ber.*, **62**, 1068 (1929).

(39) H. Hibbert and H. S. Hill, *J. Am. Chem. Soc.*, **45**, 734 (1923).

(40) E. N. Stepanov, N. Preobrashenski, and M. Schtschukina, *Ber.*, **58**, 1718 (1925); **59**, 2533 (1926).

(41) E. T. Borrows and D. O. Holland, *J. Chem. Soc.*, 673 (1947).

(42) J. Wegman and H. Dahn, *Helv. Chim. Acta*, **29**, 415 (1946).

(43) D. B. Sprinson and E. Chargaff, *J. Biol. Chem.*, **164**, 417 (1946).

one pellet of potassium hydroxide in 5 ml. of absolute ethanol. After 42 hr. at 25°, the mixture was cooled in ice and scratched to induce crystallization of the product. After one recrystallization from aqueous ethanol, the orange prisms melted at 125–126°.

Anal. Calcd. for $C_{17}H_{19}NO_2$: C, 78.33; H, 5.74; N, 4.81. Found: C, 78.56; H, 5.88; N, 4.72.

Lithium aluminum hydride reduction of 1-acetyl-3-ethoxypyrrocoline. 1-Ethyl-3-ethoxypyrrocoline. A solution of 2.8 g. (13 mmoles) of 1-acetyl-3-ethoxypyrrocoline in 70 ml. of anhydrous ether was added to a suspension of 0.57 g. (15 mmoles) of lithium aluminum hydride in 50 ml. of ether. The mixture was heated at the reflux temperature for 2.5 hr., the excess hydride was destroyed cautiously with water, and the mixture was steam distilled. About 800 ml. of distillate was collected before the yellow oil stopped distilling. The layers of the distillate were separated, the aqueous layer was extracted with ether, and the organic extracts were combined, dried, and the ether was removed. The residue was distilled through a Holzman column at 147.5–152° (13 mm.) as an orange mobile liquid, yield 1.80 g. (75%).

Anal. Calcd. for $C_{12}H_{15}NO$: C, 76.15; H, 7.99; N, 7.40. Found: C, 76.46; H, 8.24; N, 8.06.

The infrared spectrum (liquid film) confirmed the complete reduction of the carbonyl function (disappearance of the band at 1645 cm.$^{-1}$ present in the spectrum of 1-acetyl-3-ethoxypyrrocoline); C—H stretching bands appeared at 3100, 2980, 2940, and 2680 cm.$^{-1}$ The ultraviolet spectrum exhibited maxima at 241 mμ (log ε 4.30), 285 (3.50), 296 (3.50), and 382 (3.17) and a well defined minimum at 291 (3.40). The other minima were broad, located approximately at 275 and 315 mμ.

Hydrolysis of 1-acetyl-3-ethoxypyrrocoline. 3-(2′-Pyridyl)-4-ketopentanoic acid hydrochloride. A solution of 0.5 g. of 1-acetyl-3-ethoxypyrrocoline and 1.0 ml. of 12*N* hydrochloric acid was warmed on the steam bath for 2 hr. The mixture was placed in a vacuum desiccator over potassium hydroxide. Crystals soon formed, which were hygroscopic, but washing with boiling chloroform removed this property, m.p. 158–167° [reported[21] 156° (dec.)].

Anal. Calcd. for $C_{10}H_{12}ClNO_3$: C, 52.20; H, 5.27; N, 6.10. Found: C, 52.21; H, 5.33; N, 6.02.

The infrared spectrum (Nujol) indicated the presence of ketone (1710 cm.$^{-1}$) and acid (1725) carbonyls, amine salt (2550), and the pyridinium grouping (1635). Additional bands were present at 1830, 1890, 1955, and 2015 cm.$^{-1}$

URBANA, ILL.

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Preparation of the Pyridalacetones and the Inductive Effect of Nitrogen on the Dehydration of the Intermediate Aldols*[1]

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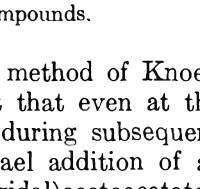
The *trans*-isomers of 2-, 3-, and 4-pyridalacetone have been prepared by two synthetic approaches. The tendency for an olefin-forming elimination by the intermediate ethyl 3-hydroxy-3-pyridyl-2-acetopropionates and the 4-hydroxy-4-pyridyl-2-butanones increases as the position of substitution on the pyridine ring is changed from 2 to 3 to 4, which suggests that the inductive effect of the nitrogen plays an important role in the chemistry of these compounds.

The preparation of the pyridalacetones, which was first attempted by application of the procedures described for benzalacetone[2] and the pyridine analogs of chalcone,[3] was unsuccessful. Acid catalyzed condensations using hydrogen chloride[4] and boron fluoride[5] did not yield the desired products. In order to learn more about the properties of the pyridalacetones so that the more direct synthesis route from the pyridine aldehydes and acetone could be effected, the pyridalacetones were prepared from the ethyl pyridalacetoacetates. The synthesis was first attempted with pyridine-3-aldehyde by the method of Knoevenagel,[6] but it became apparent that even at the low temperature (−20°) or during subsequent steps a large amount of Michael addition of acetoacetic ester to ethyl 2-(3′-pyridal)acetoacetate (VII) was taking place, since distillation after the decarboxylation step yielded a 3-methyl-5-(3′-pyridyl)-Δ^2-cyclohexenone (I). (The position of the double



I

bond has not been definitely fixed in the cyclohexenone ring. It may have migrated to the Δ^5 position.) In order to avoid this side reaction, the condensation was run in an ether solution. In this manner the product crystallized as it was formed, and the ethyl 2-pyridalacetoacetates were obtained relatively free from acetoacetic ester.

* This paper is a contribution in honor of Lyndon F. Small, former Editor of the Journal.

(1) The work discussed herein was performed as a part of the polymer research project sponsored by the National Science Foundation.

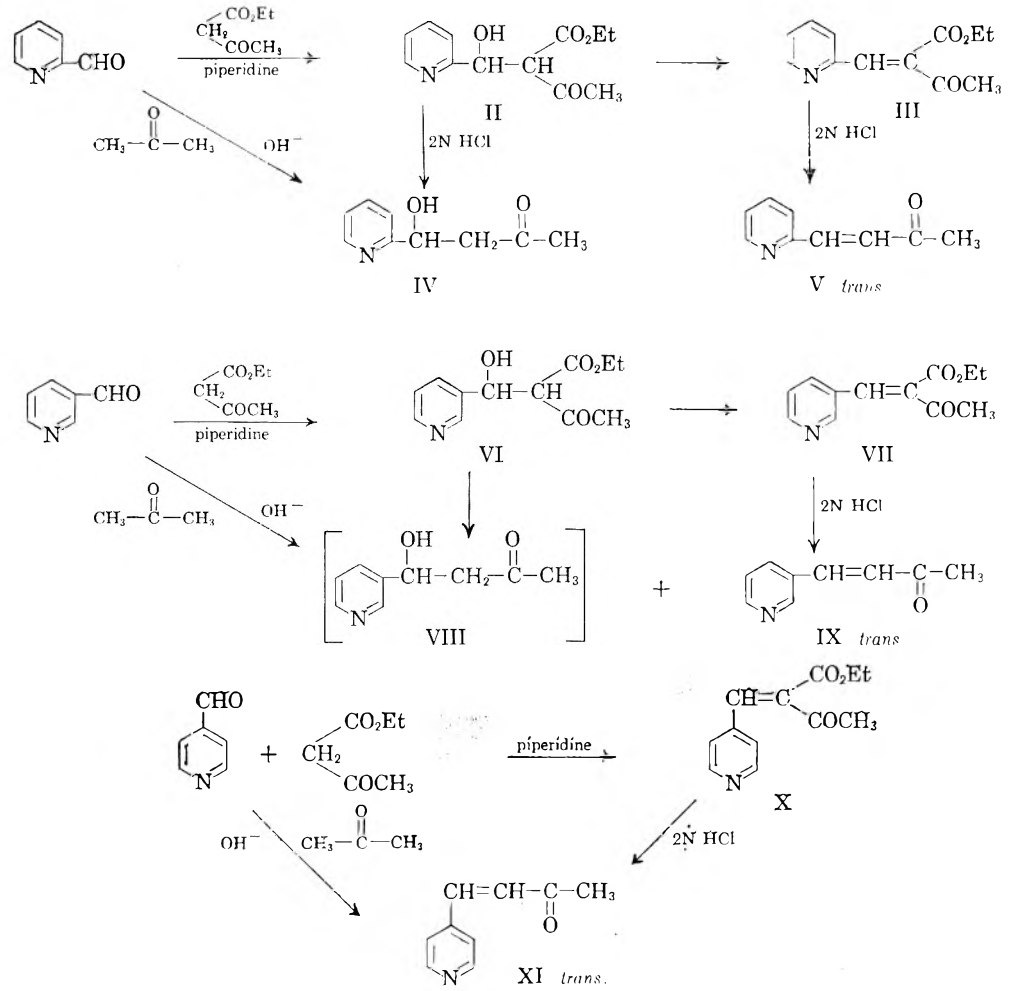
(2) N. L. Drake and P. Allen, Jr., *Org. Syntheses*, Coll. Vol. 1, 77, (1920).

(3) C. S. Marvel, L. E. Coleman, Jr., and G. P. Scott, *J. Org. Chem.*, 20, 1785 (1955).

(4) R. E. Lyle and L. P. Paradis, *J. Am. Chem. Soc.*, 77, 6667 (1955).

(5) C. S. Marvel and J. K. Stille, *J. Org. Chem.*, 21, 1313 (1956).

(6) E. Knoevenagel, *Ber.*, 29, 172 (1896).

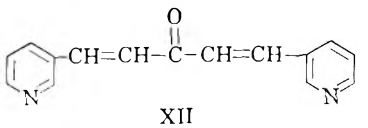


The product isolated in the reaction of pyridine-2-aldehyde was ethyl 3-hydroxy-3-(2′-pyridyl)-2-acetopropionate (II) which was found to be stable when dry and free from impurities, but it underwent an olefin-forming elimination at room temperature when in solution or in the presence of impurities to produce ethyl 2-(2′-pyridal)acetoacetate (III). The elimination is base-catalyzed, since the one step hydrolysis and decarboxylation of a mixture of II and III produced 4-hydroxy-4-(2′-pyridyl)-2-butanone (IV) and 2-pyridalacetone (V). The elimination of water from IV to yield V proved to be even more difficult. Acid catalyzed eliminations were unsuccessful and base catalysis apparently produced V which underwent further reactions to produce a mixture of products similar to the products formed from the base catalyzed condensation of pyridine-2-aldehyde and acetone at room temperature.

The reactions of pyridine-3-aldehyde were similar, yielding ethyl 3-hydroxy-3-(3′-pyridyl)-2-acetopropionate (VI), ethyl 2-(3′-pyridal) acetoacetate (VII), 4-hydroxy-4-(3′-pyridyl)-2-butanone (VIII), and 3-pyridalacetone (IX), but the elimination of water from VI and VIII proceeded with greater ease as the amount of VIII produced was considerably less than with the 2-isomer. None of the corresponding ethyl 3-hydroxy-3-(4′-pyridyl)-2-acetopropionate or 4-hydroxy-4-(4′-pyridyl)-2-butanone could be obtained, and even the infrared spectra of the crude materials failed to show the presence of these products. Apparently the elimination reaction takes place with extreme ease in this case to produce ethyl-2-(4′-pyridal)acetoacetate (X) which decarboxylates to yield 4-pyridalacetone (XI).

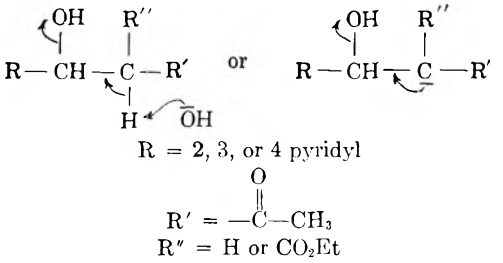
During the course of investigation of these reactions, it was learned that chloroform was the best of the few solvents which would extract the pyridalacetones from an aqueous medium, and that the reactive pyridine aldehydes required low temperatures in their base catalyzed condensation reactions. The reactions of the pyridine aldehydes with acetone were then investigated with various reaction temperatures and orders of addition of reactants and base.[3] Although the reaction of pinacolone with pyridine-2-aldehyde proceeded normally, it was found that the reaction of acetone with the pyridine aldehydes gave the best yields of products at temperatures near −20°. The previously observed elimination trends were also observed in this reaction series. Pyridine-2-aldehyde and acetone produced only IV, while pyridine-3-aldehyde and acetone gave a mixture of VIII and IX and the

4-isomer yielded only XI. Also isolated from the reaction mixture in the case of pyridine-3-aldehyde was a product which is thought to be 3,3′-dipyridalacetone (XII).



XII

The behavior of these three isomers can be conveniently explained if the inductive effect of nitrogen in the pyridine ring is considered. This effect would be that of electron withdrawal from the carbon atom bearing the hydroxyl group, and would increase as the distance from nitrogen to that carbon decreased. This effect is shown to some extent in vinylpyridines where sigma for the vinyl group has been measured.[7] Thus the elimination process becomes more difficult, whether the elimination proceeds by a concerted or an anionic mechanism. This is shown by the fact that in the case of the 4-isomer, all of the product produced is the olefin, and



R = 2, 3, or 4 pyridyl

R′ = —C(=O)—CH₃

R″ = H or CO_2Et

with the 2-isomer the alcohol is a major product in the Knoevenagel condensation and the only product in the aldol condensation. This trend has been observed in the pyridalacetophenone series.[3] It would be expected then that pyridine-2-aldehyde would be the most reactive isomer of the series when the reaction is one which depends upon an electropositive carbonyl carbon. This has been previously shown in the boron fluoride catalyzed reaction of pyridine-2-aldehyde.[5] In all the reactions, the yields of products have decreased in going from the 2-isomer to the 4-isomer. This may be due either to the reactivity of the aldehyde or to the fact that the olefin formed undergoes Michael addition or further condensation with another mole of aldehyde to form a dipyridalacetone thereby reducing the yield of the desired product.

The ultraviolet spectra of the 2-, 3-, and 4-pyridalacetones are as shown in Fig. 1. These spectra are quite different from that of *trans*-benzalacetone[8] in that there is a hypsochromic shift of about 30 mμ and a hypochromic shift of 5,000 in ε from benzalacetone to pyridalacetone. Furthermore, the

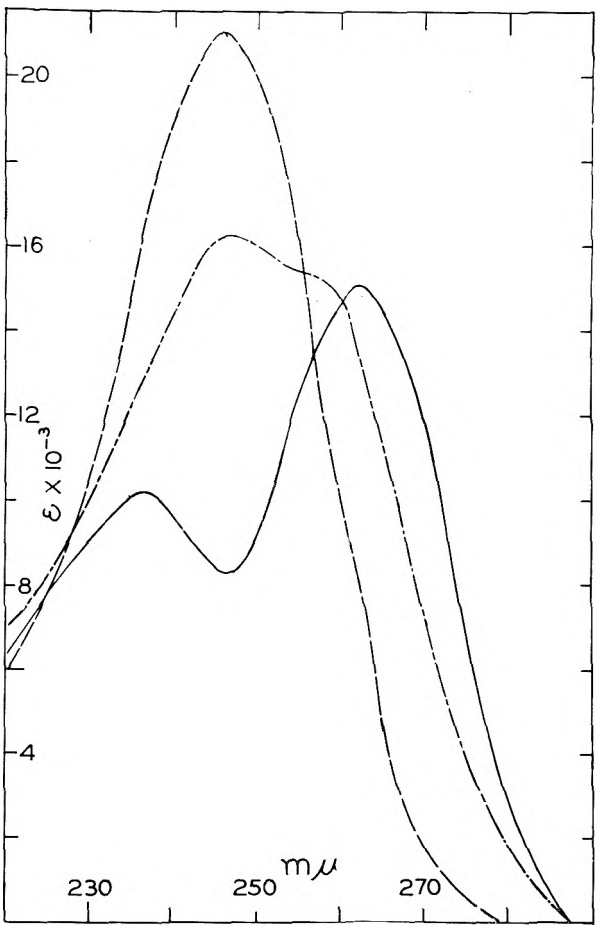


FIG. 1. ULTRAVIOLET SPECTRA OF 2-PYRIDALACETONE (—); 4-PYRIDALACETONE (— — —); AND 3-PYRIDALACETONE (— — — — —).

2- and 3-isomers give a double maximum in the 230–270 mμ region. Two maxima are also present in the ultraviolet spectra of 2-vinylpyridine,[9] 3-vinylpyridine and 3-acetylpyridine.[10] Coleman[11] has reported the ultraviolet spectra of the pyridalacetophenones and the β-pyridalacrylic acids. In these spectra the shapes of the ultraviolet absorption curves are very similar to those of the pyridalacetones. The bathochromic shift of 40 mμ from the pyridalacetones to the pyridalacetophenones might be expected, considering the relative electron-withdrawing effect of the methyl group compared with the phenyl group.[12] When the absorbing system involves the benzene ring instead of the pyridine ring, such as is the case with 2-cinnamoylpyridine, only one maximum is observed.

The absorption curves of the pyridalacetones in the 220–280 mμ region can be easily resolved as

(7) A. Pietrizky, R. Wiley, and D. McDaniel, *J. Org. Chem.*, **22**, 83 (1957).

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(11) L. E. Coleman, Jr., *J. Org. Chem.*, **21**, 1193 (1956) and unpublished data.

(12) H. H. Szmant and H. J. Planmsek, *J. Am. Chem. Soc.*, **76**, 1193 (1954) and earlier papers.

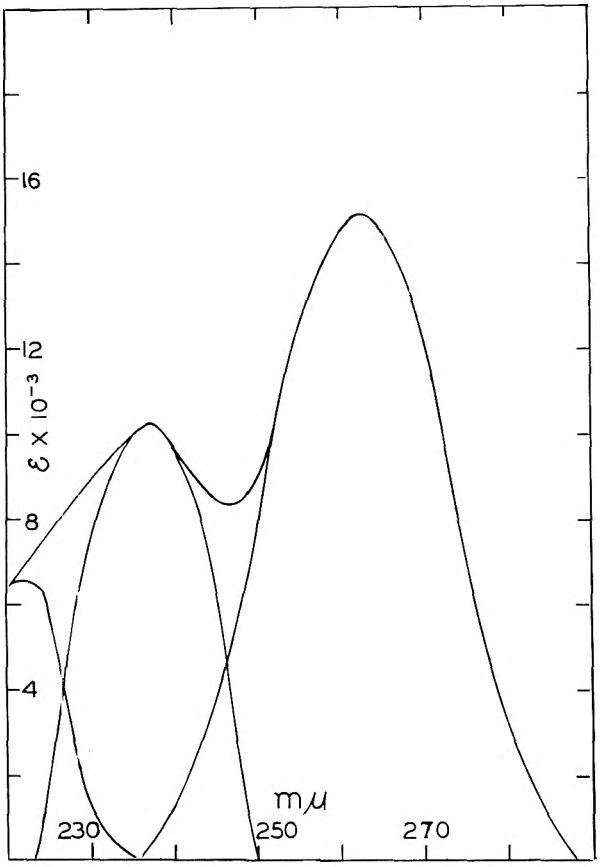

FIG. 2.—ULTRAVIOLET SPECTRUM OF 2-PYRIDALACETONE.

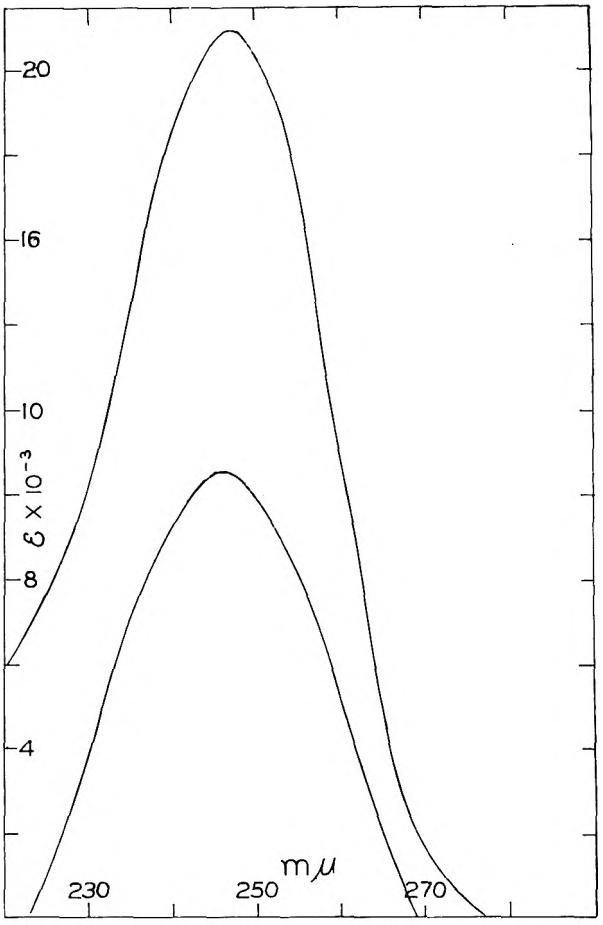

FIG. 4.—ULTRAVIOLET SPECTRUM OF 4-PYRIDALACETONE.

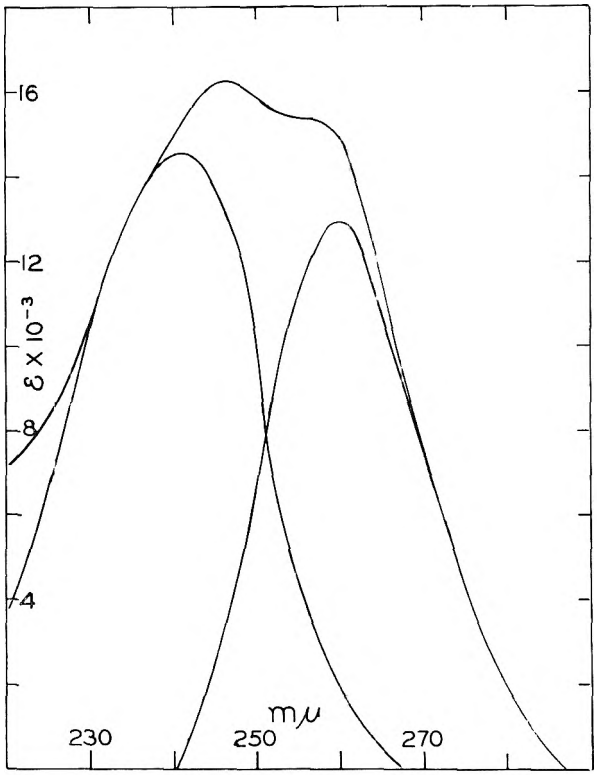

FIG. 3.—ULTRAVIOLET SPECTRUM OF 3-PYRIDALACETONE.

contributions from two absorption peaks (Fig. II–IV). It has been shown[13,14] that λ_{max} is dependent upon the length of the absorbing system, and that it is generally necessary that the excited states shall have ionic wave functions for absorption in the ultraviolet.[15] If the length of the absorbing system in the pyridalacetones can be considered to be from the carbonyl oxygen to nitrogen, it is possible that the position of the two maxima observed are due to the two possible absorption paths around the pyridine ring. Thus when the two paths are equal, as in the case of 4-pyridalacetone, only one maximum is observed. Both bathochromic and hypsochromic shifts from this maximum are noted with the 2- and 3-isomers, the largest shifts being noted with the 2-isomer where the path lengths differ the most.

EXPERIMENTAL

Ethyl 3-hydroxy-3-(2'-pyridyl)-2-acetopropionate (II). This method was developed by modification of the method of Knoevenagel[6] in order to remove the product as it was

(13) G. W. Wheland, *Resonance in Organic Chemistry*, John Wiley and Sons, Inc., New York (1955), p. 676.

(14) A. L. Wilds, L. W. Beck, W. J. Close, C. Djerassi, J. N. Johnson, Jr., T. L. Johnson, and C. H. Shunk, *J. Am. Chem. Soc.*, **69**, 1985 (1947).

(15) R. S. Mulliken, *J. Chem. Phys.*, **7**, 364 (1939).

formed, and obtain a product relatively free from difficultly removable impurities.

To 53.5 g. (0.5 mole) of pyridine-3-aldehyde[16] dissolved in 125 ml. of anhydrous ether was added a solution of 65.1 g. (0.5 mole) of ethylacetoacetate in 125 ml. of anhydrous ether. The resulting solution was cooled to −20°, and a few drops of an ether solution of piperidine were added (25 g. of piperidine in 50 g. of ether). Three such batches were prepared. The reaction mixture was allowed to stand in a deep freeze refrigerator at −20° for at least 24 hr. The white crystals which separated were removed by filtration on a Buchner funnel. A 1-g. portion of this product was removed and recrystallized from absolute ether at −20°, m.p. 54–54.5°.

Anal. Calcd. for $C_{12}H_{15}NO_4$: C, 60.76; H, 6.37; N, 5.91. Found[17]: C, 60.94; H, 6.29; N, 5.93.

The infrared spectrum (Nujol mull) exhibited absorption maxima for —OH (3170 cm.$^{-1}$), ester (1732, 1220 cm.$^{-1}$), ketone (1710 cm.$^{-1}$), and aromatic C=N and C=C (1605, 1581 cm.$^{-1}$ respectively).[18]

Ethyl 2-(2′-pyridal)acetoacetate (III). The remainder of the product was transferred to a large crystallizing dish and placed under reduced pressure (0.05 mm.) at room temperature for 24 hr. A portion of the bright yellow crystals which had formed (284 g., 86.1%) was recrystallized from cyclohexane, m.p. 115–116°.

Anal. Calcd. for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.84; H, 5.91; N, 6.50.

The infrared spectrum (Nujol mull) exhibited absorption maxima for a conjugated β-keto ester (1727 cm.$^{-1}$),[19] β-ester ketone (1667 cm.$^{-1}$), C=C (1630 cm.$^{-1}$), and aromatic C=N and C=C (1582 and 1568 cm.$^{-1}$ respectively). The infrared spectrum of the crude product showed a mixture of II and III.

4-Hydroxy-4-(2′-pyridyl)-2-butanone (IV). To 284 g. of the crude ethyl 2-(2′-pyridal)acetoacetate (III) mixed with hydrated product (II) was added 1200 ml. of 2*N* hydrochloric acid. The solution was transferred to a 2-l. round-bottomed flask fitted with a reflux condenser, at the top of which was fastened a delivery tube. The solution was heated at the reflux temperature for 30 hr., after which time the evolution of carbon dioxide had ceased. The dark solution was neutralized with 10% sodium hydroxide and extracted 12 times with 200-ml. portions of chloroform. The extracts were combined and the chloroform was removed under reduced pressure. The dark oily liquid was distilled into three fractions, the second of which (b.p. 62.5–63°/0.055 mm.) 91.95 g. (41.6%), consisted mainly of 2-pyridalacetone (V) contaminated with the hydrated product (IV). The third fraction (b.p. 78–83°/0.05 mm.) was recrystallized from ether at −20°, m.p. 75.5–76°, 30.11 g. (12.1%).

Anal. Calcd. for $C_8H_{11}NO_2$: C, 65.43; H, 6.71. Found: C, 65.29; H, 6.81.

The infrared absorption spectrum (Nujol mull) exhibited absorption maxima for OH (3110 cm.$^{-1}$), C=O (1721 cm.$^{-1}$), aromatic C=N and C=C (1603 and 1580 cm.$^{-1}$ respectively), and C—O— (1077 cm.$^{-1}$).

trans-2-Pyridalacetone (V). Attempts to separate the hydrated product (IV) from 2-pyridalacetone in the second fraction by distillation or crystallization were incomplete. Analysis of this fraction showed 13% of the material was the hydrated product (IV). In order to effect removal, 20 g. of the mixture was heated overnight on a steam bath with 5.05 g. (0.034 mole) of phthalic anhydride. The reaction flask was protected from moisture by use of a drying tube. The mixture was then neutralized with 10% potassium hydroxide and extracted with chloroform. No potassium salt of the half ester could be isolated from the aqueous layer. The chloroform was removed from the extract under reduced pressure, and the oil residue was distilled, b.p. 59–59.5/10.05 mm., to give 9 g. which represents an overall yield of 18.7%, n_D^{20} 1.5785.

Anal. Calcd. for C_9H_9NO: C, 73.44; H, 6.16. Found: C, 73.62; H, 6.32.

The infrared spectrum exhibited absorption maxima for C=O (1695, 1677 cm.$^{-1}$), C=C (1625 cm.$^{-1}$), aromatic C=N and C=C (1585 and 1568 cm.$^{-1}$ respectively), and *trans* C=C (984 cm.$^{-1}$). The two carbonyl absorption maxima were ascribed one to the carbonyl conjugated with the carbon-carbon double bond and the other to some sort of interaction of the conjugated side chain with the aromatic portion of the molecule.

4-Hydroxy-4-(2′-pyridyl)-2-butanone (IV) *from acetone and pyridine-2-aldehyde.* In order to find a more suitable method for the preparation of 2-pyridalacetone, a method was developed by modification of the method described in *Organic Syntheses*.[2] To 35 g. (0.3 mole) of pyridine-2-aldehyde, 44 g. (0.822 mole) of acetone, and 30 ml. of water mixed and cooled to −20° in a 500-ml. three-necked, round bottomed flask fitted with a motor stirrer, thermometer, and a dropping funnel, was slowly added 25 ml. of 10% sodium hydroxide so that the temperature remained at −20° during the entire course of the reaction. The addition required about 10 min. After a total time of 40 min., the reaction was stopped by neutralization with hydrochloric acid while the mixture was kept at −20°. The product was then extracted with chloroform and the chloroform was removed from the extract under reduced pressure. The paste residue was crystallized from *Skelly C* (b.p. 90–110°) yielding 20.4 g. (41.2%) white crystalline product, m.p. 76–77°. The infrared spectrum was identical to that reported above.

When this reaction was run at 0° or higher temperatures, the product was a yellow powder which could be purified neither by crystallization nor chromatography. The powder is believed to be a mixture of the Michael addition product of acetone to 2-pyridalacetone and 2,2′-dipyridal acetone (infrared). The order of addition of reactants or variations in the concentrations of the reactants did not give better results.

trans-2-Pyridalpinacolone. Since no pyridalacetone could be obtained at reaction temperatures of 0° or higher, the synthesis of 2-pyridalpinacolone was attempted to find out if it proceeded in a normal manner. A solution of 11 g. of sodium hydroxide in 100 ml. of water was cooled to 10° in a three necked 300-ml. flask. To this solution was slowly added 54 g. (0.5 mole) of pyridine-2-aldehyde followed by 25 g. (0.25 mole) of pinacolone. The solution was then allowed to come to room temperature, and was stirred for 4 hr. The bright yellow oil which formed the upper layer was separated from the aqueous layer, washed with water, and dried over magnesium sulfate. Distillation of this oil under reduced pressure yielded 20.3 g. (43.0%) of 2-pyridalpinacolone, b.p. 92°C. (0.1 mm.), n_D^{20} 1.5412.

Anal. Calcd. for $C_{12}H_{15}NO$: N, 7.40. Found: N, 7.23.

The infrared spectrum exhibited absorption maxima for C=O (1687 cm.$^{-1}$), C=C (1622 cm.$^{-1}$), aromatic C=N and C=C (1589 and 1573 cm.$^{-1}$ respectively), and C=C *trans* (995 cm.$^{-1}$).

3-Methyl-5-(3′-pyridyl)-Δ²-cyclohexenone (I). To 53.5 g. (0.5 mole) of pyridine-3-aldehyde and 65 g. (0.5 mole) of ethyl acetoacetate mixed and chilled to −5°C. was added a solution of 0.5 g. of piperidine in 1.0 g. of ethanol. The

(16) The pyridine aldehydes were obtained from Dr. F. Raschig G.M.B.H., Chem. Fabrik, Ludwigshafen, and were freshly distilled before use.

(17) The microanalyses were performed by Mr. Jozsef Nemeth, Mrs. R. Maria Benassi, Mrs. Lucy Chang, Miss Claire Higham and Mrs. Maria Stingl, University of Illinois; Clark Microanalytical Laboratory, Urbana, Ill.; and Micro-Tech. Laboratories, Skokie, Ill.

(18) The infrared spectra were determined by Mr. James Brader, Mrs. Louise Griffith and S. Portnow. The spectra were obtained from a Perkin-Elmer model 21 spectrophotometer.

(19) N. J. Leonard, H. S. Gutowsky, W. J. Middleton, and E. M. Peterson, *J. Am. Chem. Soc.*, **74**, 4070 (1952).

mixture was allowed to remain in the refrigerator at 0° for 24 hr. The reaction mixture, a liquid, was then placed under reduced pressure (0.05 mm.) at room temperature in order to remove any unreacted starting materials. To this crude product (120 g.) was added 360 ml. 2*N* hydrochloric acid and the resulting solution was heated at the reflux temperature for 12 hr., after which time the solution was neutralized with 10% sodium hydroxide. The upper oily layer which formed was distilled under reduced pressure, b.p. 111°/0.01 mm., 15.20 g. (41%), n_D^{25} 1.5632.

Anal. Calcd. for $C_{12}H_{13}NO$: C, 76.99; H, 7.00; N, 7.48. Found: C, 76.99; H, 7.22; N, 7.78.

Infrared spectrum maxima were observed at 1665 and 1637 cm.$^{-1}$

Ethyl 3-hydroxy-3-(3'-pyridyl)-2-acetopropionate (VI). The reaction using pyridine-3-aldehyde was run exactly as described for the 2-isomer, except that a total of 500 ml. of ether and 1.0 molar amounts of reactants were used. It was noted that freshly distilled pyridine-3-aldehyde must be used, and that sometimes it is necessary to seed the reaction mixture. A 5-g. portion of the crude product formed was recrystallized from 25 ml. of ether at −20°, m.p. 74°.

Anal. Calcd. for $C_{12}H_{15}NO_4$: C, 60.76; H, 6.37; N, 5.91. Found: C, 60.74; H, 6.13; N, 5.79.

The infrared spectrum exhibited absorption maxima for OH (3160 cm.$^{-1}$), C=O ester (1738 cm.$^{-1}$), C=O carbonyl (1717 cm.$^{-1}$), aromatic C=N and C=C (1604 and 1589 cm.$^{-1}$ respectively).

Ethyl 2-(3'-pyridal)acetoacetate (VII). The remaining crude product turned yellow and melted on standing. This is due to unsaturation by loss of water as confirmed by infrared analysis of the resulting liquid. The ethyl 3-hydroxy-(3-pyridyl)-2-acetopropionate is reasonably stable at room temperature, however, if it is free from impurities. A 5-g. portion of this product was distilled under reduced pressure, collecting the fraction which boiled at 93° (0.07 mm.), n_D^{25} 1.5442.

Anal. Calcd. for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.96; H, 6.31; N, 6.12.

The infrared spectrum exhibited absorption maxima for C=O conjugated ester (1725 cm.$^{-1}$), C=O conjugated ketone (1670 cm.$^{-1}$), C=C (1630 cm.$^{-1}$), aromatic C=N and C=C (1593 and 1572 cm.$^{-1}$ respectively), and —C—O— (1258 cm.$^{-1}$).

trans-3-Pyridalacetone (IX). The remaining crude product was placed under reduced pressure (0.03 mm.) at room temperature for 24 hr. in order to remove unreacted starting materials. To the 140 g. (68.6%) of crude liquid obtained was added 600 ml. of 2*N* hydrochloric acid, and the resulting solution was heated at the reflux temperature for 25 hr., after which time the evolution of CO_2 had ceased. The solution was cooled and neutralized with 431 ml. of 10% sodium hydroxide. A dark red oil of unknown composition which separated was removed, and the aqueous portion was extracted 20 times with 50-ml. portions of chloroform. The chloroform extracts were treated as described for the 2-isomer. The oil residue was distilled under reduced pressure, and the fraction boiling at 65–72° (0.05 mm.) was collected. This fraction showed mainly the desired product (infrared) contaminated with the hydrated product. The material was redistilled, b.p. 69.5–70° (0.05 mm.), yielding 17.6 g. (12.0%) n_D^{25} 1.5855.

Anal. Calcd. for C_9H_9NO: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.49; H, 6.27; N, 9.27.

The infrared spectrum exhibited absorption maxima for C=O (1695 and 1678 cm.$^{-1}$ also present in the 2-isomer), C=C (1621 cm.$^{-1}$), aromatic C=N and C=C (1596 and 1577 cm.$^{-1}$ respectively), and *trans* C=C (982 cm.$^{-1}$).

trans-3-Pyridalacetone (IX) *from acetone and pyridine-3-aldehyde*. The reaction of pyridine-3-aldehyde with acetone was carried out exactly as described for the 2-isomer. The oil residue left from the chloroform extracts was distilled under reduced pressure, collecting the fraction which boiled at 68.5–70° (0.05 mm.), 12.4 g. (28%), and whose infrared spectrum was as described above. Another fraction which was collected (93°/0.05 mm.) was found to be mainly the hydrated product. In other trials in which pyridine-3-aldehyde was added to a sodium hydroxide solution of acetone, a 50–50 mixture (14% yield each) of 3-pyridal acetone and 4-hydroxy-4-(3-pyridyl)2-butanone was obtained.

TABLE I

ULTRAVIOLET ABSORPTION MAXIMA AND MOLAR EXTINCTION COEFFICIENTS OF THE PYRIDALACETONES

Isomer	Solvent	λ Å	$\epsilon \times 10^{-4}$
2	Water	2365	1.03
		2625	1.51
	Ethanol	2380	1.18
		2610	1.37
3	Water	2460	1.62
		2600	1.48
	Ethanol	2440	1.55
		2610	1.25
4	Water	2460	2.11
	Ethanol	2420	1.93

3,3'-Dipyridalacetone (XII). The residue from the previous distillation was extracted with chloroform, and the chloroform was removed under reduced pressure leaving a light brown powder. The powder was dissolved in hot *Skelly C*, and on cooling a light yellow fluffy precipitate formed. This material was reprecipitated several times yielding 0.5 g. (1.4%), m.p. 144°.

Anal. Calcd. for $C_{15}H_{12}N_2O$: C, 76.25; H, 5.12; N, 11.68. Found: C, 75.75; H, 4.84; N, 11.48.

The infrared spectrum (Nujol mull) exhibited absorption maxima for C=O (1657 cm.$^{-1}$), C=C (1628 cm.$^{-1}$), aromatic C=N and C=C (1605 and 1590 cm.$^{-1}$ respectively), and *trans* C=C (980 cm.$^{-1}$).

Ethyl 2-(4'-pyridal)acetoacetate (X). The preparation of ethyl 2-(4'-pyridal)acetoacetate was carried out as described for the other isomers, except that 3.5 molar amounts were used. The white crystalline product formed could not be identified even after several recrystallizations from ether. Of the 365 g. obtained, 5 g. was distilled (113°/0.03 mm.) yielding a light yellow liquid, n_D^{25} 1.5415.

Anal. Calcd. for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.89; H, 6.05; N, 6.67.

The product showed some anomalous infrared absorption maxima: 3400, 1727, 1710, 1675, 1635, 1600, and 1553 cm.$^{-1}$.

trans-4-Pyridalacetone (XI). The white crystals obtained above were allowed to remain at room temperature for several days, and were then placed under reduced pressure (0.05 mm.) for 48 hr. At the end of this treatment, most of the solid had turned to a yellow oil. The oil was dissolved in 1200 ml. of 2*N* hydrochloric acid, the temperature of the solution was raised to a point just below the reflux temperature (80°) for 24 hr., and finally to the reflux temperature for 12 hr., at the end of which time the evolution of carbon dioxide had ceased. A continuous extraction apparatus was used to extract the neutral solution with chloroform. The extract was worked up as described for the other two isomers, 15.6 g. (3%), b.p. 86–87° (0.05 mm.). This liquid crystallized on standing and was recrystallized from ether at −20°, m.p. 40°.

Anal. Calcd. for C_9H_9NO: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.52; H, 5.92; N, 9.21.

The infrared spectrum (melt) exhibited absorption maxima for C=O (1692, weak, and 1670 cm.$^{-1}$), C=C (1622 cm.$^{-1}$), aromatic C=N and C=C (1599 and 1555 cm.$^{-1}$ respectively), and *trans* C=C (978 cm.$^{-1}$).

trans-4-Pyridalacetone (XI) *from acetone and pyridine-4-aldehyde*. The reaction of pyridine-4-aldehyde with acetone was carried out as described for the 2-isomer. After 5 drops of 10% sodium hydroxide had been added, the temperature

rose rapidly from −20° to 0°, and there was formed a mass of white solid. The reaction mixture was quickly cooled again to −20°, and the rest of the base was added slowly. The mixture turned a red-violet color after 20 min., and at the end of 30 min. the reaction was stopped by the addition of hydrochloric acid. Upon extraction with chloroform, a brown oil which was not identified separated from the aqueous phase, producing three phases. The chloroform extract was worked up in the usual manner, yielding 19.1 g. (20.7%) of a light yellow liquid, b.p. 86–87° (0.07 mm.), which crystallized on standing. This product was recrystallized from ether at −20°, m.p. 40°, with an infrared spectrum identical with that reported above.

Ultraviolet spectra.—The ultraviolet spectra of the pyridalacetones were run in water and ethanol at concentrations from 1.0×10^{-5} to 7.0×10^{-5} molar (Table I).

URBANA, ILL.

[CONTRIBUTION FROM THE NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES, NATIONAL INSTITUTES OF HEALTH, PUBLIC HEALTH SERVICE, U. S. DEPARTMENT OF HEALTH, EDUCATION AND WELFARE]

Influence of a 9(11)-Double Bond on the Course and Mechanism of Alkyl-Oxygen Cleavage Reactions of Unsaturated Steroids*

WILLIAM R. NES AND JOHN A. STEELE

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The rate of the buffered solvolysis of dehydroergosteryl tosylate was found to be slightly slower than the solvolysis rate of ergosteryl tosylate which indicates no homoallylic participation of the 9(11)-double bond in this reaction. The product of solvolysis of ergosteryl tosylate was 3,5-cyclo-7,22-ergostadien-6β-ol (XV) and not the isomeric 3,5-cyclo-6,22-ergostadien-8-ol when prepared in boiling aqueous acetone containing potassium bicarbonate. The same conditions yielded *i*-dehydroergosterol from dehydroergosteryl tosylate and the kinetic data together with the conditions of its preparation prove that the original formulation of this compound as 3,5-cyclo-7,9(11),22-ergostatrien-6β-ol (III) is correct. The failure of the 9(11)-double bond to participate in a typical homoallylic reaction makes it difficult or impossible to account for the acid-catalyzed elimination reaction of dehydroergosterol on the basis of a homoallylic mechanism. In the acid-catalyzed conversion of dehydroergosterol to 5,7,9(11),14,22-ergostapentaene (VI) the hypothesis is offered that the 5-double bond migrates first into the 4-position (I → IV) and that the dehydration proceeds by an allylic mechanism (IV → V).

The acid-catalyzed reactions of 3,5-cyclo-7,22-ergostadien-6β-ol (*i*-ergosterol, XV) and of 3,5-cyclo-7,9(11),22-ergostatrien-6β-ol (*i*-dehydroergosterol, III) in ethanol were also studied quantitatively and qualitatively. The 9(11)-dehydro compound (III) reacted *ca.* 50% faster than XV. This is considered as evidence that the 9(11)-double bond participates in allylic alkyl-oxygen cleavage to but a small extent. *i*-Ergosterol yielded *ca.* 70% of an *i*-hydrocarbon (3,5-cyclo-6,8(14),22-ergostatriene, XVI) and *ca.* 30% of ergosteryl ethyl ether while *i*-dehydroergosterol yielded *ca.* 85% of dehydroergosteryl ethyl ether (X) and *ca.* 15% of an *i*-hydrocarbon [3,5-cyclo-6,8(14),9(11),22-ergostatetraene (VIII)]. The influence of the 9(11)-double bond on the course of this acid-catalyzed reaction is interpreted, *inter alia*, as a conformational effect. Ergosteryl tosylate when submitted to hot pyridine readily underwent elimination to give the *i*-hydrocarbon, but dehydroergosteryl tosylate failed to react analogously and a conformational influence of the 9(11)-double bond is also suggested for this reaction.

Preparative conditions for obtaining 3,5-cyclo-6,8(14),22-ergostatriene and 3,5-cyclo-6,8(14),9(11),22-ergostatetraene are described.

When dehydroergosterol (I) and its derivatives undergo alkyl-oxygen cleavage at C-3, two types of initial product have been shown to arise depending on the conditions of the reaction and the nature of the esterifying group. Thus, solvolysis of the tosylate (II) in aqueous acetone leads to rearrangement and the production of a 3,5-cyclosterol (*i*-dehydroergosterol) for which structure III (3,5-cyclo-7,9(11),22-ergostatrien-6β-ol) has been suggested,[1] while treatment of the free alcohol (I) with hydrogen chloride in chloroform leads to dehydration and the formation of unrearranged hydrocarbons such as 5,7,9(11),14,22-ergostapentaene (VI),[2] which can further undergo a rearrangement to give anthraergostapentaene (VII).[3a,3b] That the anthrasteroid rearrangement[3] proceeds as

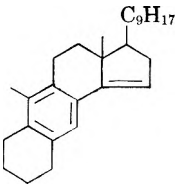
* This paper is a contribution in honor of Lyndon F. Small, former Editor of the Journal.

(1) R. W. Rees and C. W. Shoppee, *J. Chem. Soc.*, 3422 (1954).

(2) W. R. Nes, *J. Am. Chem. Soc.*, **78**, 193 (1956).

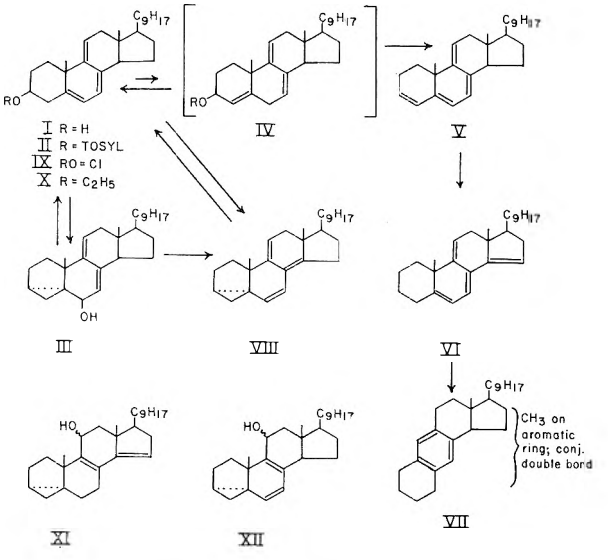
(3a) W. R. Nes and E. Mosettig, *J. Am. Chem. Soc.*, **75**, 2787 (1953); **76**, 3182 (1954).

(3b) Note added in proof: A. W. Burgstahler (Abstracts of papers presented before the New York meeting of the American Chemical Society, September 8–13, 1957, page 25P) has recently achieved hydroxylation of an analog, anthracholestatetraene (W. R. Nes, R. B. Kostic and E. Mosettig, *J. Am. Chem. Soc.*, **78**, 436 (1956)), of VII with osmium tetroxide. The resulting glycol was cleaved with lead tetraacetate yielding a keto-aldehyde which underwent a reverse Michael reaction to give a tricyclic ketone which in turn on reduction with lithium aluminum hydride followed by dehydrogenation furnished 3,9-dimethylanthracene. It has previously been shown in this laboratory that the anthrasteroid rearrangement involves scission of either the C_1–C_{10} bond or the C_9–C_{11} bond.[3] Burgstahler's work establishes that the former is correct. Were the latter true, he would have obtained 2,9-dimethylanthracene. It follows from his degradation that the complete structure of VII is



a subsequent process to the dehydration has been demonstrated experimentally.[2] The present work was undertaken (*a*) to elucidate the mechanism of this acid-catalyzed dehydration and (*b*) to eliminate or confirm an alternate structure[4] [3,5-cyclo-8,14,-22-ergostatrien-11-ol, (XI)] for *i*-dehydroergosterol.

The ease with which these two types of alkyl-oxygen cleavage reaction occur at C-3 suggests that they may be taking place by the same mechanism. Much work,[5,6] has shown that homoallylic participation (1,3-interaction between the π-electrons of a double bond and a reaction center) is responsible for many of the facilitated reactions of sterols unsaturated in ring B, and it is clear that the solvolysis of the tosylate (II) proceeds by this mechanism, because a 3,5-cyclosteroid is produced. It remains only to decide between the alternate structures (III or XI).[4] The ultraviolet spectrum[1,2,4] (λ_{max} 247, ϵ 16,400) of the isolated product leaves only these two possibilities. One of them (III) would arise by the major involvement of the 5-double bond in the reaction; the other (XI) would be a product of bond migration of 3,5-cyclo-6,8,22-ergostatrien-11-ol (XII) which would arise by the complete participation of all three of the double bonds in the reaction. Much less evident is the degree to which homoallylic participation contributes to the mechanism of the acid-catalyzed elimination. A possibility that it might be involved was found in the variation of the rate of disappearance of the 5,7,9(11)-triene system with changes in the substituent at C-3 (20-fold difference between the hydroxy and 3,5-dinitrobenzoxy compounds).[2] On the other hand, a likely intermediate, 3,5-cyclo-6,8(14),9(11),22-ergostatetraene (VIII), has been excluded, because under the conditions of the elimination reaction with less than stoichiometric amounts of HCl as the catalyst the hydrocarbon (VIII) consumed the HCl by addition yielding dehydroergosteryl chloride (IX) in the equivalent amount.[2]



The mechanism of the rearrangement, as first suggested by P. Bladon (*J. Chem. Soc.*, 2176 (1955)), probably follows a course analogous to that of the dienone-phenol rearrangement (R. B. Woodward and T. Singh, *J. Am. Chem. Soc.*, **72**, 494 (1950)).

(4) W. R. Nes and C. W. Shoppee, *J. Chem. Soc.*, **93** (1957).

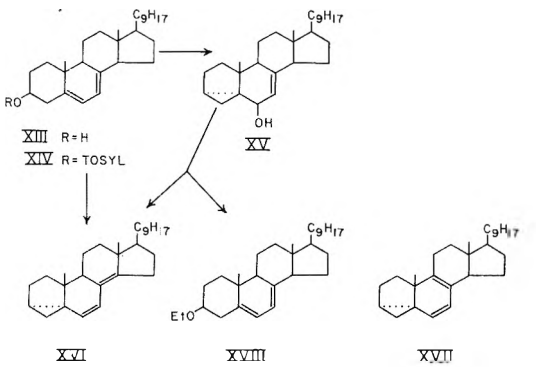
(5) (a) M. Simonetta and S. Winstein, *J. Am. Chem. Soc.*, **76**, 18 (1954); (b) E. M. Kosower and S. Winstein, *J. Am. Chem. Soc.*, **78**, 4347 (1956) and the references cited therein.

(6) (a) C. W. Shoppee and D. F. Williams, *J. Chem. Soc.*, 2488 (1956); (b) C. W. Shoppee and G. H. R. Summers, *J. Chem. Soc.*, 3361 (1952) and the references cited therein.

Dehydroergosterol in the presence of less than stoichiometric amounts of HCl underwent elimination.[2] Another possible intermediate from homoallylic participation is *i*-dehydroergosterol (III), but it has been shown that this likewise undergoes the retro-*i*-steroid rearrangement in acid solution.[4] The reaction was carried out in aqueous acetone and the product was dehydroergosterol (I). We have now extended this to ethanol and have obtained dehydroergosteryl ethyl ether (X) in a high yield. The failure of either III or VIII to be demonstrable intermediates in the acid-catalyzed conversion of I to VI makes it very unlikely that homoallylic participation does in fact contribute significantly to this reaction *unless* this participation occurs without the real formation of a 3,5-cyclosteroid. Shoppee, Summers, and Williams[7] have obtained evidence to show that 1,3-interaction is involved in the reactions of 7-hydroxy-Δ^4-steroids although a cyclopropyl ring does not actually close. It was felt that the question could be settled in the present case by comparing the rate of solvolysis of ergosteryl tosylate (XIV) with that of dehydroergosteryl tosylate (II). There is a great difference in the reactions of ergosterol (XIII) and dehydroergosterol (I) under acid conditions; the latter undergoes dehydration while the former does not.[3] If this increase in the ease of alkyl-oxygen cleavage were due to increased homoallylic participation resulting from an extension of the conjugated system, *i.e.* the change from a 5,7-dienol (XIII) to a 5,7,9(11)-trienol (I), then a similar enhancement in the rate of alkyl-oxygen cleavage would be expected in the solvolysis of the 5,7,9(11)-trienyl tosylate (II) compared to the 5,7-dienyl tosylate (XIV). A comparison of these rates would also indicate whether the *i*-dehydroergosterol resulting from the solvolysis of II could possess an 11-hydroxyl group (XI or XII), because participation of all three double bonds should manifest itself not only in the structure of the product but as well in an enhanced rate of reaction. This expectation rests, among other things, on the

(7) C. W. Shoppee, G. H. R. Summers, and R. J. W. Williams, *J. Chem. Soc.*, 1893 (1956). Solvolysis of ψ-cholesteryl tosylate gave 4-cholesten-7β-ol, *i.e.* the reaction took place with retention of configuration.

findings[8] that the rate of solvolysis of steroidal tosylates rises sharply with the number of double bonds in ring B, *viz.*, a 100-fold and a 3000-fold increase for the introduction, respectively, of a 5-double bond and a 5,7-diene system into a saturated sterol. Extrapolation of these figures suggests a further 10-fold increase on going from a 5,7-dienyl tosylate (XIV) to a 5,7,9(11)-trienyl tosylate (II). The interpretation of these comparative rates to the problem of the structure of *i*-dehydroergosterol rests on the assumption that the isolated product does not result from a secondary isomerization, *e.g.* III to XII. It was necessary first to insure that this assumption was valid, and so the preparation of *i*-dehydroergosterol was carried out under conditions so buffered (potassium bicarbonate in a boiling solution) that the reaction mixture remained alkaline. The original conditions[1,2,4] using the salt (potassium acetate) of a nonvolatile weak acid yielded a solution with a *p*H below 7 when the liberated *p*-toluenesulfonic acid was neutralized. The modified conditions, which constitute by far the best preparative method, gave the same *i*-dehydroergosterol as had been obtained previously. These findings, of course, anticipate the results of our kinetic measurements, for of the two possible structures (III and XI) for *i*-dehydroergosterol one of them (XI) requires that bond migration has taken place (XII → XI) under what almost certainly would have to be acid conditions.



We have prepared ergosteryl and dehydroergosteryl tosylates (XIV and II) essentially according to the procedures reported in the literature[1,9] but with some improvement in the former case. They were submitted to solvolysis in ethanol at 30° in the presence of potassium acetate. The rates of disappearance of the respective polyene systems were followed spectrophotometrically, and it was found that the half-life was 1.64 hr. for ergosteryl tosylate (XIV) and 2.16 hr. for dehydroergosteryl tosylate (II). This is illustrated graphically in Figure 1 in which the logarithm of the intensity of the ultraviolet absorption of the diene and triene systems

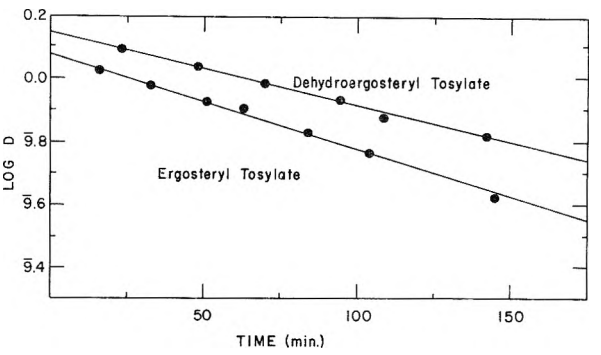


FIG. 1. DISAPPEARANCE OF ERGOSTERYL TOSYLATE (XIV) AND DEHYDROERGOSTERYL TOSYLATE (II) in ethanol buffered with potassium acetate at 30° as observed from the disappearance of absorption at 294 mμ (XIV) and 340 mμ (II). D = optical density.

is plotted as a function of time. It is evident that dehydroergosteryl tosylate actually reacts slightly slower than ergosteryl tosylate rather than several times faster. *One can conclude from this that the 9(11)-double bond does not participate significantly in homoallylic reactions involving C-3.* Furthermore, one can infer (*a*) that homoallylic participation cannot account for the difference in reactivities of ergosterol and dehydroergosterol under acid conditions and, therefore, cannot be involved in the mechanism of the acid-catalyzed elimination (I to VI), and (*b*) that *i*-dehydroergosterol is 3,5-cyclo-7,9(11),22-ergostatrien-6β-ol (III). This structure (III) for *i*-dehydroergosterol was the one originally suggested by Rees and Shoppee[1] and there seems to be no further reason to question it. The assignment of the beta configuration to the 6-hydroxyl group is based on analogy with the configuration of the hydroxyl group in other 3,5-cyclosteroids.[10] The *i*-steroid rearrangement of ergosteryl tosylate (XIV) to an *i*-sterol has not been previously described in the literature, although Fieser, Rosen, and Fieser[11] have shown that the elimination of *p*-toluenesulfonic acid from XIV in the absence of hydroxylic solvents leads to an *i*-hydrocarbon [3,5-cyclo-6,8(14),22-ergostatriene, XVI]. We have submitted ergosteryl tosylate (XIV) to buffered solvolysis in the presence of potassium bicarbonate in aqueous acetone and have isolated in a 90% yield a product which exhibits end-absorption in the ultraviolet with an extinction coefficient at 220 mμ of 2100 and a low intensity maximum (ε 790) at 262 mμ. The latter band corresponds to a 3% content of 3,5-cyclo-6,8(14),22-ergostatriene (XVI). The purified *i*-sterol (λ_{max} 2.76 μ) showed only the end-absorption in the ultraviolet with an extinction coefficient of 1300 at 220 mμ. This absorption is characteristic of Δ^7-steroids and atyp-

(8) See M. Simonetta and S. Winstein[5a] for references and a quotation of unpublished experiments.

(9) P. Karrer and H. Asmis, *Helv. Chim. Acta*, **35**, 1926 (1952).

(10) For a searching analysis of the evidence for the *beta* configuration ref. 5(b) should be consulted together with the paper of D. E. Evans and G. H. R. Summers, *J. Chem. Soc.*, 906 (1957).

(11) M. Fieser, W. E. Rosen, and L. F. Fieser, *J. Am. Chem. Soc.*, **74**, 5397 (1952).

ical of Δ^6-steroids in which the double bond is conjugated with the 3-membered ring. The end-absorption of the former[12] have extinction coefficients of *ca.* 1500 at 220 mμ and the latter[13] have extinction coefficients of *ca.* 8000 at this wave length. This establishes the structure of *i*-ergosterol as 3,5-cyclo-7,22-ergostadien-6β-ol (XV) in which the 6-hydroxyl group is assigned the beta configuration by analogy.[10] The conversion of ergosteryl tosylate predominantly to this compound and not the isomeric 8-hydroxy-Δ^6-derivative is analogous to the reduction of the same starting material to 3,5-cyclo-7,22-ergostadiene with lithium aluminum hydride.[9] It is also analogous to the conversion of dehydroergosteryl tosylate (II) to an *i*-dehydroergosterol with the structure III and the similarity of III and XV is in accord with the kinetic data for the solvolysis reactions. All of these facts are in agreement with the proposition that the major contribution to homoallylic participation is made by the 5-double bond and that the 9(11)-double bond plays little or no electronic role. The contribution which the 7-double bond makes as illustrated by a 30-fold enhancement in the rate of solvolysis of 7-dehydrocholesteryl tosylate compared to cholesteryl tosylate[8] is apparently of the kind which was found[7] for the 7-hydroxy-Δ^4-steroids. The ease with which a 5-double bond can disassociate itself from a 7-double bond is also exemplified in the oxidation of ergosterol (XIII) to ergosterone (4,7,-22-ergostatrien-3-one).[14] The double bond is brought into conjugation with the α,β-unsaturated ketone moiety with HCl in methanol but only as a result of passing through the enol ether (3-methoxy-3,5,7,22-ergostatetraene).[15] The failure of the 9(11)-double bond to give any indication of participating in a homoallylic reaction suggested a study of whether it would produce a marked effect in an allylic reaction. The *i*-sterols (III and XV) presented suitable allylic systems for comparison. They should undergo acid-catalyzed alkyl-oxygen cleavage at rates proportional to the extent of participation of the 9(11)-double bond.[16] We have measured the rates at which *i*-ergosterol (XV) and *i*-dehydroergosterol (III) undergo this reaction in 0.00020*M* ethanolic oxalic acid solution containing 0.4% water. The disappearance of the characteristic maximum at 247 mμ for III could be followed directly (Figure 3). The appearance of the characteristic maximum at 340 mμ for one of the products

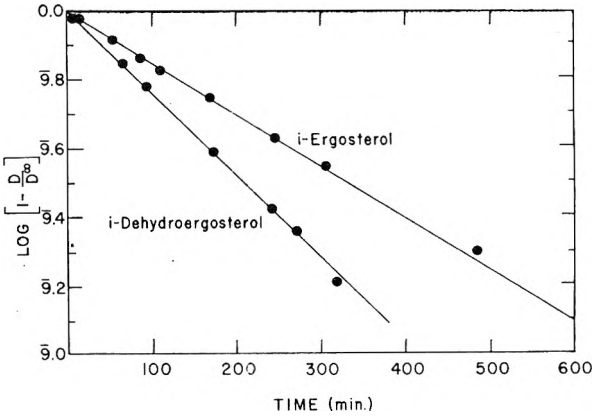


FIG. 2. DISAPPEARANCE OF *i*-ERGOSTEROL (XV) AND *i*-DEHYDROERGOSTEROL (III) in 0.00020*M* ethanolic oxalic acid solution containing 0.4% water at 30° as calculated from the appearance of the absorption at 262 mμ (XVI) for XV and at 340 mμ (X) for III. D = optical density.

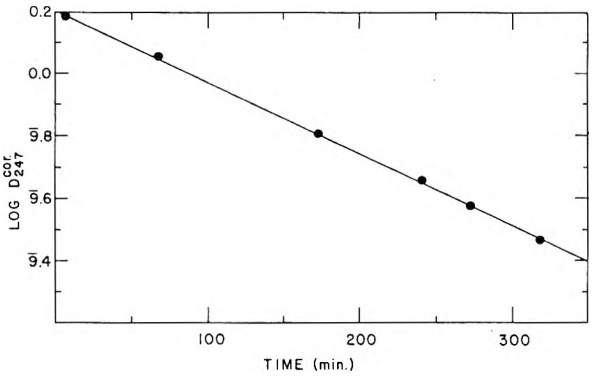


FIG. 3. DISAPPEARANCE OF *i*-DEHYDROERGOSTEROL (III) in 0.00020*M* ethanolic oxalic acid solution containing 0.4% water at 30° as observed from the disappearance of absorption at 247 mμ (III) using a correction for the appearance of absorption at this wave length for VIII and X. D = optical density.

(X) could also be followed (Figure 2) simultaneously and the half-life of *i*-dehydroergosterol (III) as calculated from either measurement was 2.2 hr. The half-life of *i*-ergosterol (XV) could only be calculated from the rate of appearance of the characteristic maxima at 262 and 294 mμ for the products (XVI and XVIII) (Figure 2), because XV has no absorption in the usable region of the ultraviolet which is not greatly interfered with by the absorption of the products. The half-life of *i*-ergosterol was 3.3 hr. It is likely that the corresponding ethyl ethers of III and XV are formed during the course of this reaction. These compounds would have the same absorption as the alcohols and our measurements may actually comprise a comparison of the rates of reaction of the ethers. The increase of less than 100% in the rate of reaction when the 9(11)-double bond was introduced indicates that it does participate in allylic reactions to a small extent. However, its influence is very much smaller than, for instance, the effect of a second double bond (Δ^7) on the solvolysis of cholesteryl tosylate.[8] The presence

(12) P. Bladon, H. B. Henbest, and G. W. Wood, *J. Chem. Soc.*, 2737 (1952).

(13) I. M. Klotz, *J. Am. Chem. Soc.*, **66**, 88 (1944).

(14) R. J. Oppenauer, *Rec. trav. chim.*, **56**, 137 (1937).

(15) D. A. Shepherd, R. A. Donia, J. A. Campbell, B. A. Johnson, R. P. Holysz, G. Slomp, Jr., J. E. Stafford, R. L. Pederson, and A. C. Ott, *J. Am. Chem. Soc.*, **77**, 1212 (1955).

(16) For a discussion of acid-catalyzed alkyl-oxygen cleavage reactions from a kinetic and mechanistic point of view see C. K. Ingold, *Structure and Mechanism in Organic Chemistry*, Cornell University Press, Ithaca, N. Y., 1953, p. 779.

of the 9(11)-double bond manifests itself to a larger extent in a difference in the composition of the products which are obtained from III and XV. *i*-Ergosterol (XV) yielded an approximately 2:1 mixture of 3,5-cyclo-6,8(14),22-ergostatriene (XVI) and ergosteryl ethyl ether (XVIII), but *i*-dehydroergosterol (III) yielded an approximately 1:5 mixture of the corresponding products (VIII and X). There are several possible reasons why introduction of the 9(11)-double bond decreases the extent of elimination relative to retro-*i*-steroid rearrangement. One of these is a greater charge distribution on the intermediate carbonium ion which might decrease the rate at which the proton at C-14 is eliminated, but the kinetic results suggest that this may not be very significant. A factor which may make a larger contribution is that the presence of the 9(11)-double bond reduces by 50% the number of tertiary hydrogen atoms which could be eliminated. *i*-Ergosterol may actually yield, in addition to XVI, 3,5-cyclo-6,8,22-ergostatriene (XVII) which is rapidly isomerized to the more stable isomer (XVI) with a heteroannular diene system. Another possibility is that the conformation of the molecule is changed such that the stereochemical requirements of elimination are satisfied less well in the presence of the 9(11)-double bond than they are in its absence. There is another reason for implicating a conformational influence of the 9(11)-double bond in the reactions of unsaturated steroids. We have submitted ergosteryl and dehydroergosteryl tosylates to treatment with pyridine at 100° and find that ergosteryl tosylate (XIV) is converted to the *i*-hydrocarbon (XVI) in a good yield in *ca.* 17 min. Contrariwise, dehydroergosteryl tosylate undergoes elimination to the extent of only a few percent (yielding VIII) even after 4 hr. Since this elimination reaction to the respective *i*-hydrocarbons is a homoallylic reaction and since the two tosylates solvolyze in ethanol at approximately the same rate, this result is not readily explained on the basis of an electronic influence of the 9(11)-double bond, and a conformational explanation seems more plausible. The small yield of *i*-hydrocarbon from the treatment of dehydroergosteryl tosylate with pyridine is in accord with the small proportion of *i*-hydrocarbon obtained from the acid-catalyzed reaction of *i*-dehydroergosterol and the high yield of *i*-hydrocarbon from ergosteryl tosylate agrees with the high yield from *i*-ergosterol.

The treatment of ergosteryl tosylate with hot pyridine was an easy method for the preparation of 3,5-cyclo-6,8(14),22-ergostatriene (XVI).[17] A slightly purer product, however, was obtained by proceeding through XV. A good method for the preparation of the 9(11)-dehydro analog (VIII)[17] was found in the treatment of *i*-dehydroergosterol (III) with trichloroacetyl chloride in excess pyridine at room temperature. Under these conditions the trichloroacetate underwent elimination. When the reaction was carried out in a benzene solution in the presence of only a slight excess of pyridine and the solution was washed with a cold bicarbonate solution, the product was composed of a large amount of dehydroergosterol resulting from solvolysis of the trichloroacetate with retro-*i*-steroid rearrangement. The benzoate and the *p*-nitrobenzoate[1] of *i*-dehydroergosterol, though not isolated crystalline, were apparently stable, for on alkaline hydrolysis *i*-dehydroergosterol was recovered. 3,5-Dinitrobenzoylation gave the *i*-hydrocarbon (VIII).

Since homoallylic participation does not account for the mechanism of the acid-catalyzed elimination reaction of dehydroergosterol (I), the question is unanswered as to why dehydration should take place more readily with I than with ergosterol (XIII) or, for that matter, why it should take place readily at all. The suggestion is offered, therefore, that the dehydration is an allylic rather than a homoallylic reaction and that it is preceded by migration of the 5-double bond [and less likely the 7- and/or 9(11)-double bonds] into conjugation with the C-O linkage at C-3. A rapid equilibration of dehydroergosterol (I) with a compound such as 4,7,9(11),22-ergostatetraen-3β-ol (IV, R = H) in which the latter existed only in a relatively small amount would account for the observed facts, namely, that facile dehydration takes place and that there is a relationship between the substituent at C-3 and the disappearance of the triene system.[2] The apparent 1,3-interaction would thus be a kinetic consequence of having a two-step process in which the first (I → IV) is rapid equilibration and the second (IV → V) a slow, irreversible and rate-determining step. This sequence of reactions

(17) The presence of smaller amounts of other hydrocarbons in various preparations of VIII and XVI have been considered in previous publications.[4,11] It was found that a hydrocarbon with a maximum at 252 mμ was formed in addition to VIII in the retro-*i*-steroid rearrangement of III.[1,2,4] In the present investigation the sample of VIII which was isolated from the retro-*i*-steroid rearrangement of III in ethanol buffered with potassium bicarbonate displayed a spectrum with an exaggerated intensity of absorption near 244 mμ relative to that at 295 mμ (the second band of VIII) in qualitative though not quantitative agreement with previous work. No explanation for the origin or structure of this material is yet at hand. The hydrocarbon (VIII) was readily obtained pure by the elimination of trichloroacetic acid from the trichloroacetate of III in pyridine. The elimination of *p*-toluenesulfonic acid from II gave only an impure preparation of VIII in 3% yield, but the contaminant was not the same as in the retro-*i*-steroid rearrangement. The hydrocarbon(s) which accompany XVI when it is prepared by dehydration of ergosterol with *p*-toluenesulfonyl chloride has been studied by rotational measurements[11] but no structure was arrived at. We have found that XVI when prepared by the elimination of p-toluenesulfonic acid from pure XIV is accompanied by a hydrocarbon with absorption near 290 mμ. It is possible, although by no means certain, that the contaminant is XVII. The sample of XVI which is obtained by elimination of water from *i*-ergosterol (XV) is obtained readily in at least 97% purity.

would require that an intermediate be 3,5,7,9(11),-22-ergostapentaene (V). We have not as yet isolated this compound, but in the course of the many reactions which have been carried out in connection with the anthrasteroid rearrangement in this laboratory we have often observed the characteristic spectrum (λ_{max} *ca.* 335, 353, and 370 mμ) of this compound (V) in chromatographic eluates. The amount has always been small. Even more significant is that as these reactions were followed spectrophotometrically these long wave-length bands could be discerned early in the reaction. An alternate to an allylic mechanism is one which proceeds directly from dehydroergosterol by production of a carbonium ion with a charge distribution centered around C-3 and the transfer of a hydride ion from C-4 to C-3 followed by elimination of a proton at C-14 and/or C-12. The detection of V in the reaction mixture, however, supports the allylic hypothesis. Furthermore, the mechanism involving a hydride ion shift is really a modification of homoallylic participation which has been rendered untenable. The only difficulty with the allylic mechanism is that the bond migration reaction has not been observed experimentally with 5,7,9(11)-trienols. Nevertheless, there is a precedent for it in the stability of 3,3-(ethane-1,2-dithiyl)-4,7,22-ergostatriene (ethylene thioketal of ergosterone) as opposed to the isomer with a 5,7-diene system. The former is obtained under conditions (zinc chloride) which could cause isomerization.[18] On the other hand, the bond is stable in the 5-position in the corresponding 3,3-dioxy derivative (ethylene ketal of ergosterone).[18] This sensitivity to slight changes in the molecule indicates a small energy difference between the 4- and 5-positions in keeping with the proposal that the $\Delta^{4,7,9(11),22}$-steroid (IV) might exist in equilibrium with dehydroergosterol (I). It is also in accord with the ease with which the 5-double bond can disassociate itself from a 7-double bond as discussed above in connection with the oxidation of ergosterol. The differential in reactivity between ergosterol and dehydroergosterol would then be a consequence of a differential in the rate of the bond migration reaction with the two compounds (I and XIII) and/or in the stability of the isomerized products. The influence of the 9(11)-double bond on this reaction could be a conformational one.

EXPERIMENTAL[19]

Preparation of ergosteryl and dehydroergosteryl tosylates. The sterol (10 g.) was dried by dissolving it in benzene and removing the solvent under reduced pressure. It was then dissolved in pyridine (125 ml. for XIII and 50 ml. for I) and 12 g. of *p*-toluenesulfonyl chloride (freshly recrystallized three times from petroleum ether, b.p. 60–70°) was added. The reaction mixture was allowed to remain at room temperature in the dark overnight and was then poured into a liter of ice cold 4% aqueous potassium bicarbonate solution. The resulting solid tosylate was collected by filtration, washed well with water (and, in the case of II, with a little cold ethanol), and dried in a high vacuum at 37°. The ergosteryl tosylate (XIV) so obtained weighed 13.6 g. but contained some *i*-hydrocarbon (XVI) as shown by ultraviolet assay. It was very sensitive as noted in the literature[9,11] and reproducible results could not be obtained by the reported procedure for its purification.[9] A good product could be obtained consistently, however, by stirring the tosylate (13.6 g.) in 50 ml. of ether at 0° for 1 hr. followed by refrigeration at −20° overnight. This procedure removed the *i*-hydrocarbon without extensive decomposition of the tosylate. The product weighed 8.0 g. and could then be recrystallized from acetone by dissolving it rapidly in a small amount of the hot solvent and immediately cooling to 0° or below. Two such recrystallizations yielded XIV as a colorless mixture of needles and prisms, m.p. 110–112° (lit.[9] m.p. 104–105°), 5.7 g., λ_{max} 223, 262, 272, 282, and 294 mμ (ϵ 14,100, 8500, 11,500, 11,800, and 6,700). It was not necessary to treat dehydroergosteryl tosylate (II) with ether and it (15 g. of dried material from the potassium bicarbonate solution) could be directly recrystallized from acetone. The product from two recrystallizations weighed 11 g. and generally formed in colorless thick prisms but often needles were present. Both forms were separately investigated and found to be the same compound on the basis of their ultraviolet spectra. (See ref. 2 and 4 for the spectrum of II.) The melting point of dehydroergosteryl tosylate has been reported with various values.[1,2] In a previous investigation in this laboratory[2] the melting point of material crystallized from acetone was found to vary in the range of 103 to 113°. We have frequently obtained samples since then by the procedure described above which melted at 112–113° but which possessed ultraviolet spectra qualitatively and quantitatively identical with that reported originally. We have considered the ultraviolet absorption of either tosylate as determined in iso-octane to be the best criterion of purity.

The acetone used for recrystallizations was dried by distillation from anhydrous potassium carbonate.

Preparation of i-ergosterol (3,5-cyclo-7,22-ergostadien-6β-ol, XV). To a well stirred, boiling solution of 1.0 g. of potassium bicarbonate in 125 ml. of water and 500 ml. of acetone was added 2.0 g. of ergosteryl tosylate (XIV) which had been well ground in a mortar to insure rapid solution. The mixture was allowed to reflux for 5 min. during which time a

(18) R. Antonucci, S. Bernstein, R. Littell, K. J. Sax, and J. H. Williams, *J. Org. Chem.*, **17**, 1341 (1952).

(19) All melting points were determined on a Kofler block and are recorded as read. Analyses are by the Microanalytical Service Laboratory of this institute under the direction of Dr. William C. Alford. Rotations were taken in 1% chloroform solutions at 20° by Mrs. E. Peake. The infrared spectra were determined on a Perkin-Elmer double beam spectrophotometer (Model 21) in CS_2 by H. K. Miller with the assistance of F. L. Johnson. Ultraviolet spectra were determined on a Cary recording spectrophotometer (Model 11) with the assistance of Mrs. C. I. Wright. The ultraviolet spectra of isolated compounds were measured in an iso-octane solution unless otherwise noted, and the spectra of samples taken during kinetic experiments were measured directly against ethanol containing, appropriately, potassium acetate or oxalic acid. The ultraviolet absorption from 220 to 400 mμ of every fraction from chromatograms was determined and was the basis for combinations of fractions as well as for the evaluation of the constituents present. The elutions with a given solvent were routinely continued until the material in question no longer was being removed at a significant rate. The alumina used was purchased from M-Woelm-Eschwege, activity grade 1, and was of an acidic or basic nature as indicated. Solvents were purified, distilled, and dried with the help of J. Lyons excepting ethanol and chloroform which were the usual commercial grades of reagent material.

clear, faintly yellow solution was produced. This was distilled at atmospheric pressure until it became cloudy. Approximately 250 ml. of distillate was collected. The oily precipitate crystallized on cooling to 0°, and after being filtered and dried at 80° in a vacuum the product weighed 1.3 g. (90%) and melted at 120–122°. In the ultraviolet it showed end-absorption with ϵ 2100, 1600, and 1300 at 220, 222, and 224 mμ, respectively, as well as a maximum at 262 mμ (ϵ 790) (3% of XVI). In addition, inflections occurred near 294, 312, and 330 mμ (ϵ 50–250). The *i*-sterol was recrystallized twice from acetone and yielded 1.1 g. of colorless needles, m.p. 129–130°, $[\alpha]_D$ −11°, λ_{max} 262 mμ (ϵ 200) (0.8% XVI); end-absorption: ϵ_{220} 1,400. The highest melting point attained was 132–133°, by recrystallization of the compound from ethanol. However, recrystallization from hot ethanol did not always give satisfactory results. On occasion low melting (*ca.* 90°) samples were produced. In one instance the ethyl ether (see below) was obtained. Isooctane, dioxane, and several other solvents were tried, but acetone gave the best and most consistent results. The pure *i*-sterol (XV) (m.p. 132–133°) exhibited only end-absorption in the ultraviolet: ϵ 7400, 4900, 2300, 1300, 650, 320, 140, and 0 at 210, 214, 218, 220, 222, 224, 226 and 230 mμ, respectively, in ethanol. In the infrared it had a sharp hydroxyl band at 2.76 μ and a band of medium intensity at 6.00 μ corresponding to C=C stretching absorption. It is of interest that this double bond absorption is more intense than the absorption of 7,22-ergostadien-3β-ol which has only a weak band at 6.0 μ.

Anal. Calcd. for $C_{28}H_{44}O$ (396.6): C, 84.78; H, 11.18. Found: C, 84.74; H, 11.12.

i-Ergosteryl ethyl ether. A sample of *i*-ergosterol (m.p. 132–133°) was recrystallized from hot ethanol which, though considered to be pure, may have contained traces of acid. The colorless needles which resulted melted at 75–76°. Further recrystallization from the same ethanol or from ethanol-water failed to alter the melting point. The compound showed no O—H stretching absorption in the infrared but did exhibit strong C—O bending absorption at 9.25 μ and a band at 6.0 μ of medium intensity for C=C stretching. In the ultraviolet there was end-absorption with ϵ_{220} 2000, ϵ_{222} 1200, and ϵ_{228} 240.

Anal. Calcd. for $C_{30}H_{48}O$ (424.68): C, 84.84; H, 11.39. Found: C, 84.62; H, 11.24.

Preparation of i-dehydroergosterol (3,5-cyclo-7,9(11),22-ergostatrien-6β-ol, III). *i*-Dehydroergosterol was obtained by following exactly the same procedure as described for *i*-ergosterol except that dehydroergosteryl tosylate (II) was used in place of ergosteryl tosylate. The product which precipitated on cooling the concentrated reaction mixture was recrystallized twice from acetone and afforded III as colorless needles, m.p. 127–128°, λ_{max} 247 mμ (ϵ 16,200), in a 60% yield. The best sample prepared by the older procedure using potassium acetate as the buffer melted at 125–126° (λ_{max} 247 mμ, ϵ 16,400).[2] It is worth noting, however, that the use of potassium bicarbonate gives far superior results from the standpoint of reproducibility and ease of isolation of a pure product. Difficulties with the older procedure have not only been evident in the past but were confirmed during the course of the present work. The acid conditions produced by the potassium acetate technique yield transformation products as contaminants which are not readily separated.

Kinetic experiments. All the kinetic experiments were carried out in a constant temperature bath at 30° using commercial, absolute ethanol. The results recorded in Figures 1, 2, and 3 are typical of a number of experiments in each case.

In the solvolysis experiments 25 mg. of the tosylate (II or XIV) was dissolved in 250 ml. of ethanol containing 18 mg. of fused potassium acetate. At appropriate intervals a sample was removed and the ultraviolet absorption from 220 to 400 mμ was immediately measured directly on the sample. The logarithm of the optical density at 340 mμ for II and at 294 mμ for XIV was plotted against time (Figure 1) and the half-life (98 min. for XIV and 129 min. for II) was obtained graphically. The acid-catalyzed experiments were carried out by dissolving 10 mg. of the *i*-sterols (III or XV) in ethanol, adding 1.0 ml. of a stock solution of 450 mg. of oxalic acid in 100 ml. of water, and diluting the reaction mixture rapidly to 250 ml. with ethanol (initial concentration of steroid = 0.00010*M*). Samples were withdrawn at appropriate intervals and the ultraviolet absorption from 220 to 400 mμ was measured immediately and directly. The intensities of absorption at 247 mμ for III, 247 mμ (λ_{max} 244) for VIII, 340 mμ for X, 262 mμ for XVI, and 294 mμ for XVIII were used in the following calculations.

(A) For the reaction of *i*-dehydroergosterol (III) the extent of conversion to dehydroergosteryl ethyl ether (X) was evaluated as 80–85% by following the reaction spectrophotometrically to many times the half-life period. This agrees well with the percent conversion observed in a boiling solution under preparative conditions for X (see below). It is also in agreement with the previous[4] and present findings (see below) that the retro-*i*-steroid rearrangement of III produces 10–20% of *i*-hydrocarbon(s). The *i*-hydrocarbon (VIII) and the ethyl ether (X) both have some absorption at 247 mμ. A correction for this was made by simultaneously measuring the intensities at 247 mμ and 340 mμ. It was also observed that $\epsilon_{247}/\epsilon_{340}$ = .061 for pure X. Assuming that at any given time (t) the products are composed 18% of VIII which has an extinction coefficient of 14,200 at 247 mμ and that D^{∞}_{340} is the optical density at 340 mμ at complete reaction the following relationship was used to calculate the corrected absorption at 247 mμ for III:

$$D^{\infty}_{247} = D^{t}_{247} - \left[\frac{D^{t}_{340}}{D^{\infty}_{340}}(1.42)(0.18) + D^{t}_{340}(0.061)\right]$$

The half-life found graphically by this method was 131 min. (Figure 3).

(B) Using the same assumptions and notations as above it was possible to calculate the percent of III remaining at any given time from the concentration of the product (X). Thus:

$$\% \text{ of III remaining} = 1 - D^{t}_{340}/D^{\infty}_{340}$$

These are plotted in Figure 2. The half-life found graphically was 129 min.

(C) For the reaction of *i*-ergosterol (XV) by following the reaction spectrophotometrically to many times the half-life period it was found that D_{262}/D_{294} = 10 at all times. It was also observed from the spectrum of pure XVIII that the intensity of absorption at 262 mμ was 1.1 times the intensity at 294 mμ. The extinction coefficient of pure XVI at 262 mμ is 26,800.[11] The extinction coefficient of pure XVIII at 294 mμ is 6,900. Isolation experiments (see below) showed that XVI and XVIII were the only products. Thus, at complete reaction:

$$\frac{D^{\infty}_{262} - D^{\infty}_{294}(1.1)}{2.68} + \frac{D^{\infty}_{294}}{0.69} = 1.00$$

From these relationships it was possible to calculate the final optical density (D^{∞}_{262} = 2.1) which agreed within experimental error with that observed (2.0) and to calculate from this figure the percent conversion to XVI (70%) and to XVIII (30%). Essentially the same figures were found in the isolation experiment. Furthermore, from the final value of the optical density (D^{∞}_{262}) the percent of XV left at any given time (t) could be calculated as follows:

$$\% \text{ of XV remaining} = 1 - D^{t}_{262}/D^{\infty}_{262}$$

The results are plotted in Figure 2 and the half-life found was 198 min.

From a comparison of many experiments the half-life values quoted in this paper are considered to be accurate to within *ca.* 10%. The accuracy of the solvolysis determina-

tions is probably the highest (deviation in $t_{1/2}$ in several experiments less than 5 min.), because no corrections had to be applied and the disappearance of the starting materials could be measured directly. In the text all of the half-life values are quoted in hours so that the figures will not imply a significantly greater accuracy than is inherent in the experiments.

Acid-catalyzed reactions of i-ergosterol (XVI *and* XVIII *from* XV). A solution of 500 mg. of 3,5-cyclo-7,22-ergostadien-6β-ol (*i*-ergosterol, XV) in 50 ml. of ethanol containing 1.0 mg. of oxalic acid was refluxed for 45 min. The solution was evaporated rapidly to dryness under reduced pressure and the residue (489 mg., λ_{max} 262 and 294 mμ) was chromatographed on 15 g. of alumina ("almost neutral"). Elution with petroleum ether yielded 305 mg. (64%) of crystalline 3,5-cyclo-6,8(14)-22-ergostatriene (XVI) which was recrystallized from acetone giving 250 mg. of colorless needles, m.p. 103–104°, $[\alpha]_D$ 95°, λ_{max} 262 mμ (ε 25,900). Lit.[11] m.p. 102–102.5°, $[\alpha]_D$ 92°, λ_{max} 261 mμ (ε 26,800). Elution with chloroform yielded 132 mg. of crystalline 3β-ethoxy-5,7,22-ergostatriene (ergosteryl ethyl ether, XVIII) which was recrystallized from acetone yielding 78 mg of microcrystals, m.p. 120–121°. Further recrystallization from ethanol raised the melting point to 123–124°, λ_{max} 262, 272, 282, and 294 mμ (ε 8000, 11,500, 12,700, and 6900), λ_{max} 9.0–9.1 μ, no OH absorption. Lit.[20] m.p. 123–124°, $[\alpha]_D$ −111°.

Acid-catalyzed reactions of i-dehydroergosterol (III). A. *Preparation of dehydroergosteryl ethyl ether* (X *from* III). A solution of 1.0 g. of 3,5-cyclo-7,9(11),22-ergostatrien-6β-ol (*i*-dehydroergosterol, III) in 100 ml. of absolute ethanol containing 2.0 mg. of oxalic acid was refluxed for 60 min. An aliquot portion was removed and analyzed spectrophotometrically. Based on the intensity of the maxima at 340 mμ and 244 mμ the conversion to dehydroergosteryl ethyl ether (X) was *ca.* 82% and to VIII 10–20%. The solution was evaporated to dryness under reduced pressure in the presence of a small amount of aqueous potassium bicarbonate and the residue was dissolved in a mixture of water and benzene. The benzene extract after being washed with aqueous potassium bicarbonate and then with water was dried and evaporated to dryness under reduced pressure. Chromatography of the residue on 30 g. of alumina ("basic") yielded some hydrocarbon by elution with petroleum ether (b.p. 30–60°). This was followed by elution with ether which yielded X from ethanol as colorless flakes, 0.33 g., m.p. 85–86°. One recrystallization afforded an analytical sample, m.p. 86–87°, $[\alpha]_D$ 197°, λ_{max} 312, 325, and 340 mμ (ε 11,300, 12,500, and 7700).

Anal. Calcd. for $C_{30}H_{46}O$ (422.67): C, 85.24; H, 10.97. Found: C, 85.41; H, 11.02.

In another experiment carried out in a similar manner from 443 mg. of III the total weight of pure X was 208 mg. (65%) obtained from ether eluates, of *i*-hydrocarbon (principally VIII by ultraviolet) 46 mg. (11%) obtained from petroleum ether eluates, and of a mixture (ultraviolet) of these 63 mg. (15%) by stripping the column with chloroform. The ultraviolet spectrum of the 46 mg. of *i*-hydrocarbon differed from pure VIII in that there was a more pronounced inflection at *ca.* 252 mμ, the minimum near 261 mμ was of much higher intensity and the maximum at 295 mμ was only about half the intensity of that at 244 mμ, while normally it is 74% as intense.

B. Rearrangement and retrorearrangement without isolation of i-dehydroergosterol (X *from* II *and* I *from* II). A solution of 200 mg. of dehydroergosteryl tosylate (II) in 20 ml. of ethanol was refluxed for 10 min. in the absence of a buffer. To this was then added 146 mg. of potassium bicarbonate and the ethanol was removed by vacuum distillation. The residue was chromatographed as described in A. The ether (X) was crystallized from ethanol yielding flakes, m.p. 69–72°, λ_{max} 312, 324, and 340 mμ (ε 7900, 9000, and 5600), of 73% purity.

When a similar reaction was carried out for *ca.* 10 min. in aqueous acetone instead of ethanol the product was isolated without chromatography. From 200 mg. of dehydroergosteryl tosylate (II) there was obtained 110 mg. of dehydroergosterol (I), m.p. 101–110°, λ_{max} 244, 312, 324, and 340 mμ (ε 1600, 8000, 9000, 5690), of 77% purity.

The reaction of dehydroergosteryl tosylate in ethanol or aqueous acetone in the absence of a buffer produces a strongly acid reaction mixture. Such conditions are favorable for the product (X or I) to undergo the anthrasteroid rearrangement[3] and probably explains why the chromatographed ether from procedure B was only 73% pure. The reactions of I and X under strongly acid conditions in hydroxylic solvents as well as in chloroform comprise the subject of another investigation which will be reported on shortly. The preparation of dehydroergosteryl ethyl ether (X) from dehydroergosterol is best carried out *via* the pure *i*-sterol (III) as described in A. This appears to be the only method reported for converting dehydroergosterol into its 3-ethers. The preparation of the methyl ether was achieved by Heilbron and Simpson,[20] but these authors first made the methyl ether of ergosterol. This was then dehydrogenated with mercuric acetate.

3,5-Cyclo-6,8(14),22-ergostatriene (XVI) *from ergosteryl tosylate* (XIV) *in pyridine.* A hot solution of ergosteryl tosylate (2.0 g.) in 20 ml. of hot pyridine was maintained at 100° for 17 min. and was then evaporated to dryness under reduced pressure. The residue was extracted with two 100-ml. portions of boiling petroleum ether (b.p. 30–60°) and after filtration the solvent was removed at reduced pressure. The crude product (λ_{max} 262 mμ, ε 15,700; λ_{infl} 290–296 mμ, ε 1500) was crystallized from acetone and yielded 0.77 g. (56%) of XVI, m.p. 94–97°, which was further purified by chromatography on alumina ("almost neutral"). The residue from eluates of petroleum ether (b.p. 30–60°) was crystallized from acetone and yielded 503 mg. of the *i*-hydrocarbon (XVI) as long, colorless prisms, m.p. 102–103°, λ_{max} 262 mμ (ε 24,200), λ_{infl} 290–296 mμ (ε 1300). Lit.[11] m.p. 102–102.5°, $\lambda_{max}^{alc.}$ 261 mμ (ε 26,800). (Cf. XVI from XV.) Fieser, Rosen, and Fieser[11] have reported that dehydration of ergosterol by various procedures yields not only XVI but another hydrocarbon which is isomerized to XVI by heat or acid-washed alumina. Based on the presence of an inflection near 293 mμ in our crude and chromatographed materials it is possible that their second hydrocarbon as well as our contaminant (<10% of our purified product) is the isomer (XVII) with a 6,8-diene system which could originate by elimination of a proton at C-9. Such a homoannular diene system conjugated with a cyclopropyl ring would give rise to a band near 290 mμ, and should isomerize to the more stable heteroannular diene system as in XVI. Still a third contaminant, especially in our crude product, is possible, *viz.*, a compound with an unconjugated diene system as has been reported from dehydrohalogenation of 7-bromocholesterol in pyridine.[21]

Reaction of dehydroergosteryl tosylate with pyridine. A solution of 2.0 g. of dehydroergosteryl tosylate in 20 ml. of hot pyridine was heated at 100° for 30 min. The solution was then evaporated to dryness under reduced pressure and the residue was extracted with four 50-ml. portions of boiling petroleum ether (b.p. 30–60°). A large portion (1.95 g.) of the solid residue failed to dissolve and was not investigated further. The petroleum ether extract was concentrated and adsorbed on a column of alumina ("almost neutral") and elution with the same solvent yielded, after crystallization from acetone, 39 mg. (3%) of slightly impure *i*-hydrocarbon (VIII), m.p. 90–93°, λ_{max} 244 and 295 mμ (ε 14,500 and

(20) I. M. Heilbron and J. C. E. Simpson, *J. Chem. Soc.*, 268 (1932).

(21) K. Tsuda, K. Arima, and R. Hayatsu, *J. Am. Chem. Soc.*, **76**, 2933 (1954); see also W. R. Nes, R. B. Kostic, and E. Mosettig, *J. Am. Chem. Soc.*, **78**, 436 (1956).

10,200). Lit.[2] m.p. 98–100°, λ_{max} 244 and 295 mμ (ε 16,300 and 11,700).

Several similar reactions were carried out for various periods ranging up to 4 hr., but in every case the total extractable (petroleum ether) material amounted to not more than *ca.* 15% of the original weight of starting material.

Preparation of 3,5-cyclo-6,8(14),9(11),22-ergostatetraene (VIII *from* III). A solution of 1.0 g. of *i*-dehydroergosterol (III) (m.p. 126–127°) and 1.0 ml. of trichloroacetyl chloride in 20 ml. of pyridine was allowed to stand overnight at room temperature. The resulting red solution was poured into a mixture of ice and aqueous potassium bicarbonate and the oily product was extracted into chloroform. The chloroform solution was washed, dried, and evaporated to dryness. Chromatography on 30 g. of alumina ("almost neutral") and elution with petroleum ether (b.p. 30–60°) yielded 0.4 g. of the hydrocarbon which after crystallization from acetone-water was still only 92% pure (λ_{max} 244 and 295 mμ, ε 15,000 and 11,000). The pure material was obtained by recrystallizing it twice further from acetone-methanol and gave VIII as colorless, long rods, m.p. 99–101°, λ_{max} 244 and 295 mμ (ε 16,100 and 12,100). Lit.[2] m.p. 98–100°, λ_{max} 244 and 295 mμ (ε 16,300 and 11,700). Elution of the chromatographic column with chloroform gave 88 mg. of dehydroergosterol (I), identified on the basis of its ultraviolet spectrum.

The hydrocarbon (VIII) was also obtained from the reaction of *i*-dehydroergosterol and 3,5-dinitrobenzoyl chloride in pyridine. However, both the reaction of *i*-dehydroergosterol with benzoyl chloride and with *p*-nitrobenzoyl chloride yielded products with ultraviolet spectra consistent with the corresponding 3,5-cyclo steroid ester and hydrolysis of these with hot potassium bicarbonate in aqueous acetone gave back the starting material.

An attempt to prepare and isolate the trichloroacetate of *i*-dehydroergosterol by the reaction (15 min. at room temp.) of *i*-dehydroergosterol in benzene containing 2 equivalents of pyridine and 1 equivalent of trichloroacetyl chloride followed by extraction with a cold aqueous potassium bicarbonate solution yielded an oil exhibiting maxima at 244, 295, 311, 324, and 340 mμ with approximately the same intensities at 244 and 324 mμ. On slow evaporation of the mixture from methanol-water crystals were obtained which showed substantially the same spectrum. The intensities of the maxima indicated a 40% content of I and a 40% content of VIII.

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BETHESDA 14, MD.

[CONTRIBUTION FROM THE NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES, NATIONAL INSTITUTES OF HEALTH PUBLIC HEALTH SERVICE, U. S. DEPARTMENT OF HEALTH, EDUCATION AND WELFARE]

Ribofuranose Derivatives from 3,5-Di-*O*-benzoyl-D-ribosyl Chloride. I. 1,3,5-Tri-*O*-benzoyl-β-D-ribose and 5-*O*-Benzoyl-1,2,3-*O*-benzylidyne-α-D-ribose*[1]

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Received April 16, 1957

Condensation of the crystalline furanosyl halide, 3,5-di-*O*-benzoyl-D-ribosyl chloride (II), in ether solution with silver benzoate gives, in addition to the previously known 1,3,5-tri-*O*-benzoyl-α-D-ribose (I), a new D-ribofuranose tribenzoate which is shown to be 1,3,5-tri-*O*-benzoyl-β-D-ribose (III). Treatment of the same halide (II) in benzene solution with mercuric acetate gives a mono-*O*-benzoyl-*O*-benzylidyne-D-ribose which, by a series of reactions, has been converted to 1,2,3-tri-*O*-benzoyl-5-*O*-methanesulfonyl-β-D-ribose (XII). Synthesis of the latter substance from the known 2,3-*O*-benzylidene-β-D-ribofuranose (XIII) confirmed its structure and led to the conclusion that the orthoester is 5-*O*-benzoyl-1,2,3-*O*-benzylidyne-α-D-ribose (VII).

The nature of the crystalline halide (II) is discussed with particular reference to the question of its anomeric configuration.

In recent communications we have described the preparation of 3,5-di-*O*-benzoyl-D-ribosyl bromide[4] and 3,5-di-*O*-benzoyl-D-ribosyl chloride (II).[5] These two substances are of unusual interest not only because they are the first ribofuranosyl halides to be obtained in crystalline form[6] but also because they are readily accessible from D-ribose[4] or from 2,3,5-tri-*O*-benzoyl-D-ribose[7] and, therefore, are of potential value for the synthesis of ribonucleosides. While both of these halides are relatively labile substances the chloride is, as might be expected, somewhat less reactive than the bromide and is, therefore, a more convenient object of study from the experimental point of view. The present paper will be devoted primarily to a description of the preparation, characterization, and proof of structure

* This paper is a contribution in honor of Lyndon F. Small, former Editor of the Journal.

(1) In earlier papers (refs. 2 and 3) dealing with derivatives of orthobenzoic acid we have used the prefix "orthobenzoyl" to refer to the radical $C_6H_5C{\equiv}$. In the present and following papers we adopt the more accurate prefix "benzylidyne"; *cf. Chem. Abstr.*, **39**, 5963 (1945).

(2) H. G. Fletcher, Jr., and R. K. Ness, *J. Am. Chem. Soc.*, **77**, 5337 (1955).

(3) R. K. Ness and H. G. Fletcher, Jr., *J. Am. Chem. Soc.*, **78**, 1001 (1956).

(4) R. K. Ness and H. G. Fletcher, Jr., *J. Am. Chem. Soc.*, **76**, 1663 (1954).

(5) R. K. Ness and H. G. Fletcher, Jr., *J. Am. Chem. Soc.*, **78**, 4710 (1956).

(6) One more crystalline di-*O*-benzoyl-D-ribofuranosyl halide is reported in the communication immediately following this one.

(7) R. K. Ness, H. W. Diehl, and H. G. Fletcher, Jr., *J. Am. Chem. Soc.*, **76**, 763 (1954).

of the two products derived from 3,5-di-*O*-benzoyl-D-ribosyl chloride which are named in the title.

In an earlier study[5] we described the condensation of 3,5-di-*O*-benzoyl-D-ribosyl chloride (II) in benzene solution with silver benzoate as giving a precipitate from which 1,3,5-tri-*O*-benzoyl-α-D-ribose (I) could be isolated. Subsequent investigation has now shown that the benzene solution contains another D-ribose tribenzoate which is readily isolated in crystalline form. The new ester was not identical with any of the known D-ribose tribenzoates and did not exhibit mutarotation in chloroform solution. Benzoylation afforded the known β-D-ribofuranose tetrabenzoate[7] in good yield; the substance therefore appeared to be a 1,*x*,*x*-tri-*O*-benzoyl-β-D-ribofuranose. Since experiments with β-D-ribofuranose tetrabenzoate showed that its 1-*O*-benzoyl group was readily replaced through the action of boron trifluoride in acetic acid to give 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribose,[8] the new tribenzoate was acetylated and then acetolyzed in this selective manner. The product obtained proved to be the known[4,5] 1,2-di-*O*-acetyl-3,5-di-*O*-benzoyl-β-D-ribose (VI) and the tribenzoate from which it was derived is, therefore, 1,3,5-tri-*O*-benzoyl-β-D-ribose (III), the anomer of the substance (I) obtained earlier. Inspection of the optical rotatory values listed in Table I shows that these figures tend to support this conclusion, the 2*A*-values from the anomeric 1,3,5-tri-*O*-benzoyl-D-riboses agreeing roughly with those from the known anomeric D-ribofuranose tetrabenzoates.

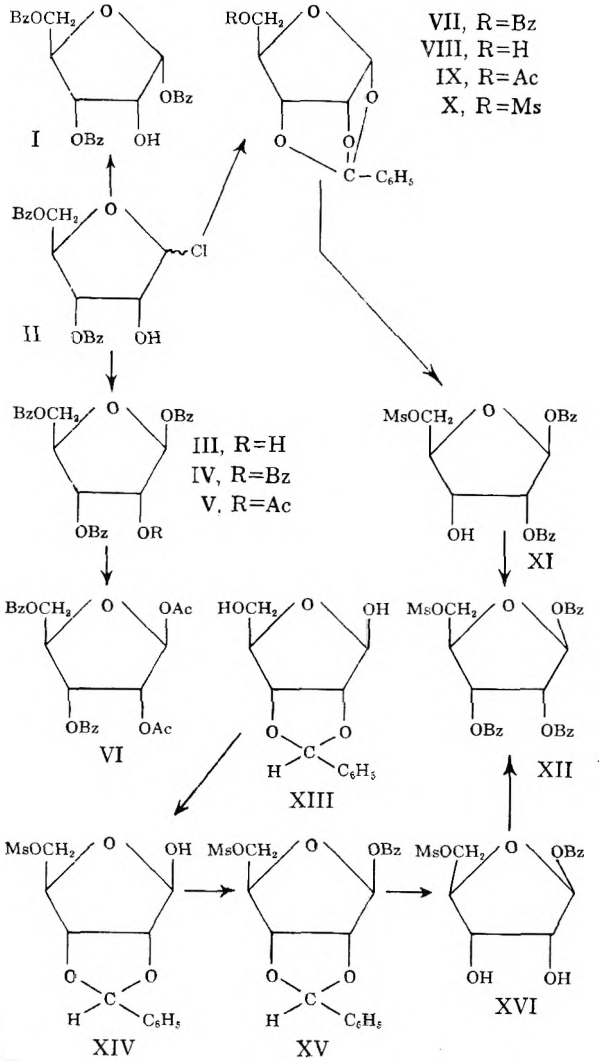


TABLE I
RIBOFURANOSE BENZOATES

	$[\alpha]_D^{20}$ ($CHCl_3$)	$[M]_D^{20}$	Difference 2*A*
α-D-Ribofuranose tetrabenzoate	+90.4°[a]	+51,300	
			41,700
β-D-Ribofuranose tetrabenzoate	+17.0°[b]	+ 9,600	
1,3,5-Tri-*O*-benzoyl-α-D-ribose	+85.3°[c]	+39,400	
			37,700
1,3,5-Tri-*O*-benzoyl-β-D-ribose	+ 3.6°[d]	+ 1,700	

[a] Ref. 5. [b] Ref. 7. [c] Ref. 4. [d] Present work.

When an attempt was made to condense 3,5-di-*O*-benzoyl-D-ribosyl chloride (II) in benzene solution with mercuric acetate a product was obtained which showed no hydroxyl absorption in the infrared and gave analytical values corresponding to a benzoylbenzylidynepentose. Both this substance and the crystalline derivative obtained through barium methoxide-catalyzed debenzoylation showed marked lability, particularly toward acidic reagents, further suggesting a benzylidyne structure. The alkali-debenzoylated product was further characterized through the preparation of its acetate. Mesylation of the orthobenzoate gave a crystalline mesyl ester which was treated in methylene chloride solution at room temperature with benzoic acid to yield a crystalline di-*O*-benzoyl-*O*-methylsulfonylpentose; further benzoylation gave a tri-*O*-benzoyl-*O*-methylsulfonylpentose. The structure of the latter substance was demonstrated unequivocally by the following independent synthesis. 2,3-*O*-Benzylidene-β-D-ribofuranose[9] (XIII) was converted to the 5-*O*-methylsulfonyl derivative (XIV)[10] and thence to 1-*O*-benzoyl-2,3-*O*-benzylidene-5-*O*-methylsulfonyl-β-D-ribose (XV). Mild acid hydrolysis to cleave the cyclic acetal gave 1-*O*-benzoyl-5-*O*-methylsulfonyl-β-D-ribose (XVI) which, on further benzoylation, gave 1,2,3-tri-*O*-benzoyl-5-*O*-

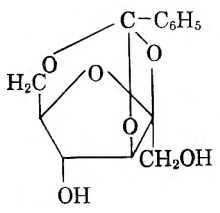
(8) In earlier work (ref. 4) anhydrous zinc chloride, a less convenient reagent, had been used to carry out this transformation.

(9) H. B. Wood, Jr., H. W. Diehl, and H. G. Fletcher, Jr., *J. Am. Chem. Soc.*, 78, 4715 (1956). See also G. R. Barker and J. W. Spoors, *J. Chem. Soc.*, 1192 (1956).

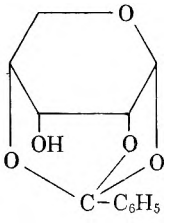
(10) The analogous *p*-tolylsulfonyl derivative has recently been described as an intermediate in the synthesis of 1,5-anhydro-β-D-ribofuranose: E. Vis and H. G. Fletcher, Jr., *J. Am. Chem. Soc.*, 79, 1182 (1957).

methylsulfonyl-β-D-ribose (XII), identical with the substance derived from the orthoester (VIII). Since this sequence of reactions demonstrates that the normal benzoyl group in the benzoylbenzylidynepentose is located at C5,[11] the orthoester may be written as VII, 5-*O*-benzoyl-1,2,3-*O*-benzylidyne-α-D-ribose, the assignment of anomeric configuration appearing to be mandatory on steric grounds.

Several substances closely related to, but probably less strained than, 1,2,3-*O*-benzylidyne-α-D-ribose (VIII) have recently been reported. Helferich and his coworkers,[12,13] for instance, have described a 2,3,6-*O*-benzylidyne-β-D-fructofuranose (XVII) while the present authors[14] have obtained a pyranose analog



XVII



XVIII

of VIII, 1,2,4-*O*-benzylidyne-α-D-ribose (XVIII). It should be noted, however, that both these substances were derived from 1-benzyloxybenzylidene derivatives through the acid catalyzed loss of benzyl alcohol. The formation of 1,2,3-*O*-benzylidyne-α-D-ribose (VII) through dehydrohalogenation of II as described here represents a wholly different approach to this type of compound.

The anomeric configurations of compounds XI, XII and XIV to XVI. These five compounds almost certainly have the same configuration at C1 and have all been assigned the β-configuration on the basis of two different lines of evidence. 2,3-*O*-Benzylidene-β-D-ribofuranose (XIII), $[\alpha]_D^{20}$ −22.4°[9] was earlier shown to be a β-isomer; the rotation of its 5-*O*-mesyl derivative (XIV), $[\alpha]_D^{20}$ −4°, suggests that this also is a β-isomer. The rotation of monobenzoate XV, $[\alpha]_D^{20}$ −47.3°, further supports this view. On the other hand, let us consider the probable mechanism of the scission of the benzylidyne cage by benzoic acid in going from X to XI. This transformation may be rationalized by assuming protonation of X followed by nucleophilic attack with inversion at C1. Obviously, the potential benzoyl group in X may give rise to a normal benzoyl at C2 or C3, retention of configuration being expected at both positions in either case. All question of mechanism aside, we will show in the succeeding paper[15] that benzoic acid alone converts VII to 1,2,5-tri-*O*-benzoyl-β-D-ribose, a transformation which may be construed as supporting the β configurations in the present case and also as favoring by analogy XI rather than its 1,3-di-*O*-benzoyl isomer which *a priori* seems equally plausible.

In passing, attention is drawn to the somewhat unusual circumstance that each of the three benzoyl groups in XII was introduced by a different method when the substance was prepared from 1,2,3-*O*-benzylidyne-α-D-ribose (VIII).

Anomeric configuration of 3,5-di-O-benzoyl-D-ribosyl chloride (II). The anomeric configurations of the fully acylated glycosyl halides are usually indicated quite clearly by their rotations. The aldosyl halides having C2 unsubstituted present a peculiar problem, however, since in contrast to the above class, they often mutarotate in inert solvents. Thus 3,4,6-tri-*O*-acetyl-β-D-glucosyl chloride ($[\alpha]_D$ +28.7°[16]) readily isomerizes to the α-anomer ($[\alpha]_D^{20}$+ 185°) in acetone solution.[16] Matters are further complicated in the case of the 3,5-di-*O*-benzoyl-D-ribosyl halides by the fact that spontaneous loss of halogen acid accompanies mutarotation. Thus, while the bromide shows $[\alpha]_D^{20}$ +96° (3 min.) → +27° (60 min., constant)[4] in absolute chloroform and the chloride shows $[\alpha]_D^{20}$ +1.2° (5 min.) → +50.7° (500 hrs.)[5] in methylene chloride we cannot safely conclude therefore that the bromide is an α-anomer and the chloride a β-anomer. The initial rotations, however, rule out the possibility that both are β-anomers since such a relationship would require the bromide to be more negative than the chloride.[17]

The steric and structural features of replacement products are often a reliable key to the configuration of fully acylated glycosyl halides because the reactions of these substances are dominated by neighboring group effects when an acyloxy group is adjacent and *trans* to the halogen. While C2 bears no acyl group in the present case, it should be pointed out that the conversion of II to I and to VII can easily be rationalized if we assume that the halide is the α-anomer and that the displacement proceeds through participation of the benzoyloxy group at C5.[18] The

(11) Rebenzoylation of VIII afforded VII, showing that catalytic debenzoylation had not affected the orthobenzoate group.

(12) B. Helferich and L. Bottenbruch, *Chem. Ber.*, **86**, 651 (1953).

(13) B. Helferich and W. Schulte-Hürmann, *Chem. Ber.*, **87**, 977 (1954).

(14) Reference 2. The statement made in this paper that "no orthobenzoylribofuranose appeared possible" emphasizes the inadequacy of rigid mechanical models for portraying many of these cage structures.

(15) R. K. Ness and H. G. Fletcher, Jr., *J. Org. Chem.*, **22**, 1470 (1957).

(16) R. U. Lemieux and G. Huber, *Can. J. Chem.*, **31**, 1040 (1953).

(17) C. S. Hudson, *J. Am. Chem. Soc.*, **46**, 462 (1924).

(18) Participation of an acyloxy group at C5 in displacement reactions at C1 in a pentofuranose derivative does not seem wholly unreasonable when one recalls that 2,3-*O*-benzylidene-5-*O*-*p*-toluenesulfonyl-β-D-ribofuranose readily gives 1,5-anhydro-β-D-ribofuranose when treated with alkali (Vis and Fletcher, ref. 10) and that derivatives of 1,5-*O*-benzylidene-β-D-ribofuranose have recently been prepared (Barker and Spoors, ref. 9). Such C5 to C1 interaction has not, to our knowledge, been demonstrated, however.

cyclic intermediate thus formed could react with a benzoate ion to give I or with itself to form a second cyclic intermediate ion involving the benzoyloxy group at C3; the latter could stabilize itself through loss of a proton from the hydroxyl group at C2 with the formation of VII.

EXPERIMENTAL[19]

1,3,5-Tri-O-benzoyl-β-D-ribose (III) *from 3,5-di-O-ribosyl chloride* (II). One gram of 3,5-di-*O*-benzoyl-D-ribosyl chloride[5] was added to an actively stirred suspension of 1.0 g. of silver benzoate in 10 ml. of dry benzene. After 1.5 hr. at room temperature the solid material[20] was removed and washed with benzene. The combined washings and filtrate were concentrated to a sirup; from 10 ml. of ether crystallization was spontaneous: 0.22 g., (18%), m.p. 137–139°. One recrystallization from 2:1 methylene chloride–pentane gave 0.143 g. of pure *1,3,5-tri-O-benzoyl-β-D-ribose* (III), m.p. 144–145°,[21] $[\alpha]_D^{20}$ +3.6° in chloroform (*c* 2.2).

Anal. Calcd. for $C_{26}H_{22}O_8$: C, 67.52; H, 4.80. Found: C, 67.66; H, 4.88.

β-D-Ribofuranose tetrabenzoate (IV) *from 1,3,5-tri-O-benzoyl-β-D-ribose* (III). 1,3,5-Tri-*O*-benzoyl-β-D-ribose (43.6 mg.) was treated with a cold mixture of 0.5 ml. of pyridine and 0.02 ml. of benzoyl chloride for 1 hr. After the usual workup there was obtained from absolute alcohol a total of 41.9 mg. (79%) of crystalline product melting at 120–121°. Mixed with authentic β-D-ribofuranose tetrabenzoate[7] it melted at 120–121°.

1-O-Acetyl-2,3,5-tri-O-benzoyl-β-D-ribose from β-D-ribofuranose tetrabenzoate (IV). A solution of β-D-ribofuranose tetrabenzoate (115.8 mg.) in 4.0 ml. of acetic anhydride was observed to rotate +0.38° in a 1-dm. tube at 20°. The addition of 0.20 ml. of 7.0*M* boron trifluoride in ether caused a rapid mutarotation: +0.89° (45 sec.), +1.05° (85 sec. and 8 min.). Fourteen minutes after the addition of the catalyst the mixture was worked up to yield 47.4 mg. (46%) of crystalline product melting at 129–130°. Mixed with authentic 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribose it melted at 129–131°.

1,2-Di-O-acetyl-3,5-di-O-benzoyl-β-D-ribose (VI) *from 1,3,5-tri-O-benzoyl-β-D-ribose* (III). 1,3,5-Tri-*O*-benzoyl-β-D-ribose (100.9 mg.) was acetylated at −5° with an excess of acetic anhydride in pyridine solution; excess reactants were removed in conventional fashion to give 114.5 mg. of a solvent-free sirup which was treated with 4 ml. of a mixture made from 20 ml. of acetic anhydride and 1 ml. of 7*M* boron trifluoride in ether. After 13 min. the material was worked up to yield 49.8 mg. (51%) of crystalline material melting at 126–127°. Mixed with authentic 1,2-di-*O*-acetyl-3,5-di-*O*-benzoyl-β-D-ribose[4] the product melted at 126–127°.

2-O-Acetyl-1,3,5-tri-O-benzoyl-β-D-ribose (V). 1,3,5-Tri-*O*-benzoyl-β-D-ribose (58.6 mg.) was acetylated at a low temperature with acetic anhydride in pyridine solution following the customary procedure. The addition of water precipitated a sirup which was washed with water and then dissolved in 1 ml. of alcohol. The crystals (36.7 mg., 57%, m.p. 98–100°) which formed were twice recrystallized from absolute ethanol to give a pure product melting at 99–101° and rotating $[\alpha]_D^{20}$ −17° in chloroform (*c* 1.0).

Anal. Calcd. for $C_{28}H_{24}O_9$: C, 66.66; H, 4.80. Found: C, 66.38; H, 4.93.

5-O-Benzoyl-1,2,3-O-benzylidyne-α-D-ribose (VII) *from 3,5-di-O-benzoyl-D-ribosyl chloride* (II). 3,5-Di-*O*-benzoyl-D-ribosyl chloride (1.00 g.) was added over a 6-min. period to a vigorously stirred suspension of 1 g. of mercuric acetate in 10 ml. of dry benzene. After 15 min. from the beginning of the reaction, 30 ml. of saturated sodium chloride solution was added along with methylene chloride. The organic layer was successively washed with water and sodium bicarbonate solution; moisture was removed with sodium sulfate and the solution concentrated *in vacuo* to a crystalline residue. From methylene chloride–ether practically pure 5-*O*-benzoyl-1,2,3-*O*-benzylidyne-α-D-ribose (VII) (0.43 g., 47%) was obtained: m.p. 181–183°. Repetition of the preparation employing 13 g. of the chloride gave the same product in 45% yield. Recrystallization from methylene chloride–pentane afforded a pure product melting at 182–183°, $[\alpha]_D^{20}$ +43.4° in chloroform (*c* 2.62).

Anal. Calcd. for $C_{19}H_{16}O_6$: C, 67.05; H, 4.75; mol. wt., 340. Found: 67.13; H, 4.98; mol. wt., 339 (Rast and cryoscopic in C_6H_6), 350 (signer, CH_2Cl_2).

Infrared absorption measurements in a potassium bromide pellet showed no hydroxyl absorption.

1,2,3-O-Benzylidyne-α-D-ribofuranose (VIII). A solution of 218.4 mg. of 5-*O*-benzoyl-1,2,3-*O*-benzylidyne-α-D-ribose in 5 ml. of methylene chloride was diluted with 5 ml. of methanol and treated with 0.07 ml. of 1.5*N* barium methoxide at room temperature. Part of the starting material precipitated but soon redissolved; polarimetric observations showed the reaction to be complete after a total of 12 min. The mixture was treated with carbon dioxide and then concentrated to a dry mass which was dissolved in methylene chloride and filtered. Concentration of the filtrate followed by dissolution of the residue in *ca.* 1 ml. of ether and *ca.* 1 ml. of pentane gave 0.1194 g. (79%) of crystalline product melting at 102–103°. After two recrystallizations from ether–pentane, one from carbon tetrachloride and another from ether–pentane, pure 1,2,3-*O*-benzylidyne-α-D-ribofuranose, m.p. 106–108°, $[\alpha]_D^{20}$ +41.0° ($CHCl_3$, *c* 1.3, no mutarotation after 3 hr.), was obtained. The substance showed no carbonyl absorption in the infrared (5.6–5.9 μ).

Anal. Calcd. for $C_{12}H_{12}O_5$: C, 61.02; H, 5.12. Found: C, 60.96; H, 5.19.

Rebenzoylation of a sample of the above product with benzoyl chloride in pyridine at 0° for 5 min. gave crystalline 5-*O*-benzoyl-1,2,3-*O*-benzylidyne-α-D-ribose in 96% yield.

5-O-Acetyl-1,2,3-O-benzylidyne-α-D-ribose (IX). 1,2,3-*O*-Benzylidyne-α-D-ribofuranose (103.0 mg.) was added to a cold (0°), stirred mixture of 2.0 ml. of dry pyridine and 0.2 ml. of acetyl chloride. Five minutes later, 10 ml. of saturated aqueous sodium bicarbonate was added and, after cooling, the product was removed by filtration. It was dissolved in ethanol which was then removed *in vacuo:* solution of the residue in 1 ml. of ethanol and addition of 3 ml. of pentane gave 17.9 mg. of crystalline material melting at 114–115°. Two further crops of crude product were recovered from the mother liquor to make a total of 66.0 mg. (54%). Two recrystallizations from hexane gave pure 5-*O*-acetyl-1,2,3-*O*-benzylidyne-α-D-ribose, m.p. 117–118°, $[\alpha]_D^{20}$ +42° in chloroform (*c* 0.67).

Anal. Calcd. for $C_{14}H_{14}O_6$: C, 60.43; H, 5.07. Found: C, 60.59; H, 4.96.

1,2(?)-Di-O-benzoyl-5-O-methylsulfonyl-β-D-ribose (XI) *from 1,2,3-O-Benzylidyne-α-D-ribofuranose* (VIII) *via 5-O-methylsulfonyl-1,2,3-O-benzylidyne-α-D-ribose* (X). 1,2,3-Benzylidyne-α-D-ribofuranose (149 mg.) was added to a cooled mixture of 0.5 ml. of dry pyridine and 0.10 ml. of methanesulfonyl chloride. After 15 min. at room temperature the reaction mixture was cooled and diluted with 5 ml. of saturated aqueous sodium bicarbonate. Five minutes later the crystalline precipitate was filtered off and dissolved in methylene chloride. The solution was dried with sodium

(19) Melting points are corrected.

(20) As described previously (ref. 5), extraction of this solid with methylene chloride afforded 1,3,5-tri-*O*-benzoyl-α-D-ribose. However, our earlier description erred in stating that the extracts were combined with the original filtrate which was not the case. See the correction *J. Am. Chem. Soc.*, 78, 6427 (1956).

(21) As described in the succeeding paper (ref. 15) 1,3,5-tri-*O*-benzoyl-β-D-ribose may exhibit a double melting point.

sulfate, filtered through decolorizing carbon, and concentrated *in vacuo* to give a crystalline mass of crude 5-*O*-methylsulfonyl-1,2,3-*O*-benzylidyne-α-D-ribose: 141.8 mg., m.p. 119–124°. Dissolved in 5 ml. of methylene chloride and observed in a 1.5-dm. tube, this product showed α_D^{20} +1.80° ($[\alpha]_D^{20}$ *ca.* +42°). Benzoic acid (498 mg.) was dissolved in the solution and the rotation observed: +1.65° (3 min.), +1.52° (36 min.), +1.32° (112 min.), −0.24° (26 hr.), −0.44° (42 hr.), and −0.47° (49 hr.). The reaction mixture was then washed with sodium bicarbonate, dried with sodium sulfate and concentrated *in vacuo* at 25° to give a crystalline residue melting at 148–151° (dec.). Recrystallized from ethanol, the 1,2(?)-di-*O*-benzoyl-5-*O*-methylsulfonyl-β-D-ribose was obtained as slightly elongated prisms (96 mg., 35% based on X) melting with decomposition at 170–171° (in bath at 160°; 10°/min.). A second recrystallization failed to change this value. In acetone (*c* 0.94) the substance showed $[\alpha]_D^{20}$ −29.0°.

Anal. Calcd. for $C_{20}H_{20}O_9S$: C, 55.04; H, 4.62. Found: C, 54.99; H, 4.76.

1,2,3-Tri-O-benzoyl-5-O-methylsulfonyl-β-D-ribose (XII) *from 1,2(?)-di-O-benzoyl-5-O-methylsulfonyl-β-D-ribose* (XI). 1,2(?)-Di-*O*-benzoyl-5-*O*-methylsulfonyl-β-D-ribose (20.8 mg.) was treated with a cold mixture of 0.10 ml. of benzoyl chloride and 1.0 ml. of dry pyridine and left at room temperature for 20 min. Aqueous sodium bicarbonate (*ca.* 4 ml.) was then added and the precipitated sirup separated. From 1 ml. of ethanol the product (19.1 mg., 74%) separated as clusters of needles m.p. 103–105°, $[\alpha]_D^{20}$ −1.8° in chloroform (*c* 1.1). A second crystallization from ethanol afforded material melting at 104–105°. Mixed with authentic 1,2,3-tri-*O*-benzoyl-5-*O*-methylsulfonyl-β-D-ribose, prepared as described below, the product melted at 104–106°.

2,3-O-Benzylidene-5-O-methylsulfonyl-β-D-ribose (XIV). 2,3-*O*-Benzylidene-β-D-ribofuranose (XIII, 0.5 g.), prepared as described by Wood, Diehl, and Fletcher,[9] was added to a cold mixture of 1.0 ml. of dry pyridine and 0.19 ml. of methanesulfonyl chloride. After 30 min. saturated aqueous sodium bicarbonate was added and, upon cooling, the solidified mass was removed by filtration. From ethanolic solution this solid gave 0.4683 g. (71%) of crystalline material melting at 139–141° (in bath at 125°, 8°/min.) and decomposing visibly at 150°. Successive recrystallizations from ethanol, from acetone-pentane and from ethanol failed to change this melting point. In chloroform (*c* 0.3) the compound showed $[\alpha]_D^{20}$ −4° (constant over 1 hr.).

Anal. Calcd. for $C_{13}H_{16}O_7S$: C, 49.36; H, 5.10. Found: C, 49.51; H, 5.26.

1-O-Benzoyl-2,3-O-benzylidene-5-O-methylsulfonyl-β-D-ribose (XV). 2,3-*O*-Benzylidene-5-*O*-methylsulfonyl-β-D-ribose (XIV, 381 mg.) was added to a cold (0°) mixture of 1.00 ml. of dry pyridine and 0.20 ml. of benzoyl chloride. After 40 min. at 0° and 80 min. at 25°, 4 drops of aqueous sodium bicarbonate solution was added. Upon the addition of several milliliters of water and cooling, a solid was formed. Crystallization from 5 ml. of ethanol yielded 415.4 mg. (82%) of a product melting at 109–111°; two further crystallizations from ethanol gave pure material melting at 112–114° and rotating $[\alpha]_D^{20}$ −47.3° in chloroform (*c* 2.2).

Anal. Calcd. for $C_{20}H_{20}O_8S$: C, 57.13; H, 4.80; S, 7.63. Found: C, 57.05; H, 5.04; S, 7.54.

1-O-Benzoyl-5-O-methylsulfonyl-β-D-ribose (XVI). 1-*O*-Benzoyl-2,3-*O*-benzylidene-5-*O*-methylsulfonyl-β-D-ribose (XV, 697 mg.) was dissolved in a mixture of 21 ml. of dioxane and 14 ml. of 0.1*N* sulfuric acid and the solution heated at 85° for 3 hr. The cooled reaction mixture was diluted with methylene chloride, washed with saturated aqueous sodium bicarbonate, and dried with magnesium sulfate. Solvent was removed *in vacuo;* the residue, dissolved in methylene chloride–pentane, gave 260 mg. (47%) of product melting at 113–117° (10°/min.). $[\alpha]_D^{20}$ −6.8° in chloroform (*c* 0.4). Two recrystallizations from chloroform afforded material melting at 115–118° (in bath at 108°, 10°/min.),[22] $[\alpha]_D^{20}$ −6.5° in chloroform (*c* 0.6). A third recrystallization from ethanol-pentane failed to change the melting point.

Anal. Calcd. for $C_{13}H_{16}O_8S$: C, 46.98; H, 4.85. Found: C, 46.84; H, 4.98.

1,2,3-Tri-O-benzoyl-5-O-methylsulfonyl-β-D-ribose (XII) *from 1-O-benzoyl-5-O-methylsulfonyl-β-D-ribose* (XVI). 1-*O*-Benzoyl-5-*O*-methylsulfonyl-β-D-ribose (XVI, 76.5 mg.) was added to a mixture of 0.1 ml. of benzoyl chloride and 0.5 ml. of dry pyridine. After 25 min. at 25°, the reaction mixture was diluted with a few drops of aqueous sodium bicarbonate solution and then with 8 ml. of water. The crystalline material thus precipitated was washed and recrystallized from ethanol: 107.8 mg. (87%), m.p. 103–107°. After two more recrystallizations from ethanol the product melted at 104–106° and showed a rotation in chloroform (*c* 1.08) of $[\alpha]_D^{20}$ −7.0°.

Anal. Calcd. for $C_{27}H_{24}O_{10}S$: C, 59.99; H, 4.48; S, 5.93. Found: C, 60.09; H, 4.70; S, 5.90.

Acknowledgments. We wish to thank Mr. William M. Jones for infrared measurements. Combustion analyses were performed in the Institutes' Microanalytical Laboratory under the direction of Dr. William C. Alford.

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(22) The molten material decomposes visibly at 145°. A sample held at 100° and 0.1 mm. was almost completely fused after 20 min., decomposing with the evolution of benzoic acid.

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Ribofuranose Derivatives from 3,5-Di-*O*-benzoyl-D-ribosyl Chloride. II. Further Reactions of 5-*O*-Benzoyl-1,2,3-*O*-benzylidyne-α-D-ribose*

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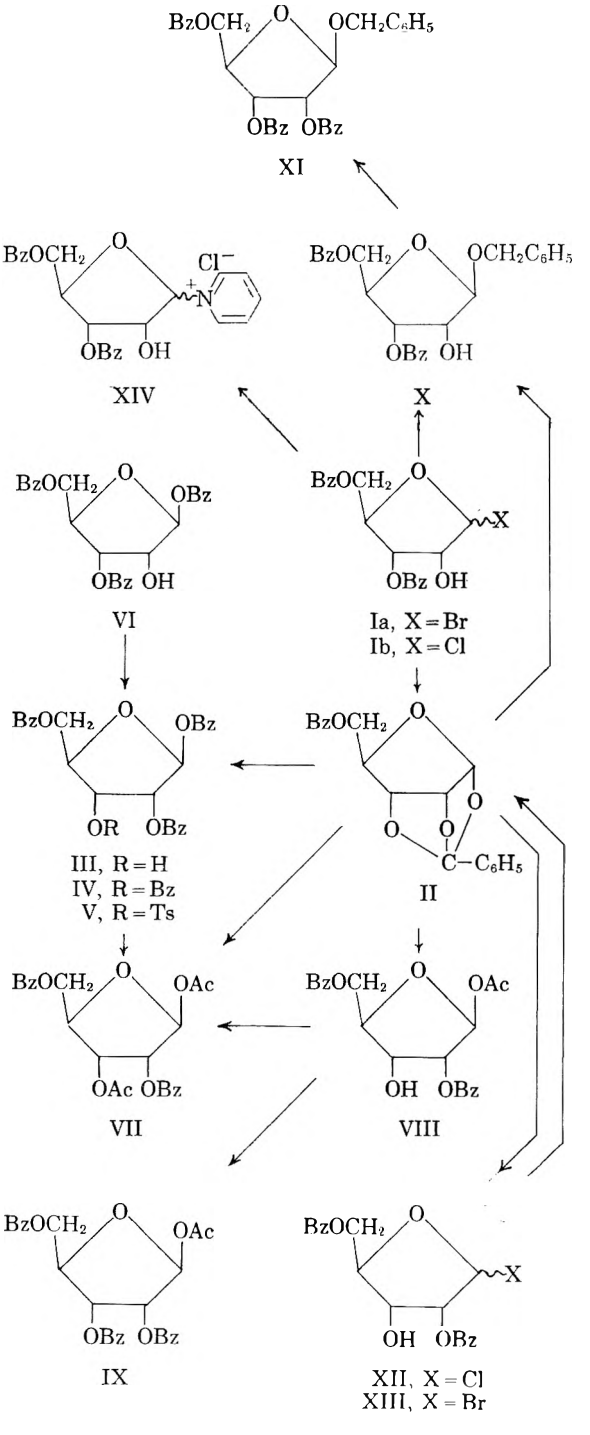
The behavior of 5-*O*-benzoyl-1,2,3-*O*-benzylidyne-α-D-ribose (II) with benzoic acid, acetic acid, acetic anhydride, benzyl alcohol, and hydrogen chloride is described.

In the preceding paper[1] we have described how treatment of 3,5-di-*O*-benzoyl-D-ribosyl chloride[2] (Ib) in benzene solution with mercuric acetate results in dehydrohalogenation with the formation of the somewhat unusual structure 5-*O*-benzoyl-1,2,-3-*O*-benzylidyne-α-D-ribose (II). In the course of investigations designed to throw light on this structure we observed that the orthobenzoate cage in 5-*O*-methylsulfonyl-1,2,3,-*O*-benzylidyne-α-D-ribose was readily cleaved by benzoic acid at room temperature to give a di-*O*-benzoyl-5-*O*-methylsulfonyl-D-ribose. We wish now to report cleavage of the orthobenzoate cage in II by a variety of reagents.

When 5-*O*-benzoyl-1,2,3-*O*-benzylidyne-α-D-ribose (II) was treated in benzene solution with benzoic acid the orthoester grouping was cleaved and a tri-*O*-benzoyl-D-ribose isolated in crystalline form.[3] This ester differed in its physical properties from the anomeric 1,3,5-tri-*O*-benzoyl-D-riboses[1] and other previously known D-ribose tribenzoates. It did not exhibit mutarotation and, on cautious benzoylation, gave β-D-ribofuranose tetrabenzoate (IV). Methylation with Purdie's reagents, followed by debenzoylation, led to a sirup which appeared, on paper partition chromatography, to be a mixture of 2- and 3-*O*-methyl-D-riboses. Although migration of benzoyl groups had obviously occurred during methylation the evidence thus far obtained indicated the substance to be 1,2.5-tri-*O*-benzoyl-β-D-ribose (III). Further evidence tending to favor this structure was obtained as follows. Heating 1,3,5-tri-*O*-benzoyl-β-D-ribose (VI) readily converts it into the new ester. Indeed this conversion can be demonstrated by heating at 135° a potassium bromide plate containing VI whereupon the characteristic infrared spectrum of VI is replaced by that of III. On steric grounds, migration of a benzoyl



* This paper is a contribution in honor of Lyndon F. Small, former Editor of the Journal.

(1) R. K. Ness and H. G. Fletcher, Jr., *J. Org. Chem.*, 22, 1465 (1957).

(2) R. K. Ness and H. G. Fletcher, Jr., *J. Am. Chem. Soc.*, 73, 4710 (1956).

(3) This substance was actually first encountered by us in a mixture resulting from the action of mercuric benzoate on Ib. There it was accompanied by II and, indeed, may have been a secondary product derived from II.

from C_3 to C_2 appears more likely than from C_5 to C_2 and we therefore regard III as the most probable structure for the new D-ribofuranose tribenzoate. It may be noted that the attack on the orthobenzoate cage in II by benzoic acid presumably results first in cleavage of the C1 oxygen linkage with inversion at C1, the potential benzoyl group of II becoming a normal benzoyl at C2 without further inversion.

The behaviour of 5-*O*-benzoyl-1,2,3-*O*-benzylidyne-α-D-ribose (II) with acetic acid was next investigated. Here, a rapid reaction was observed at room temperature in an inert solvent system and an *O*-acetyl-di-*O*-benzoyl-D-ribose isolated in good yield. Benzoylation of this substance to the known 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribose[4] (IX) demonstrated the position of the acetyl group. Acetylation afforded a di-*O*-acetyl-di-*O*-benzoyl-β-D-ribose. The same, fully acylated ribose could also be obtained from 1,2,5-tri-*O*-benzoyl-β-D-ribose (III) through acetylation followed by replacement of the benzoyl group at C1 through the action of acetic anhydride and boron trifluoride.[1] Since this new ester was not identical with the known 1,2-di-*O*-acetyl-3,5-di-*O*-benzoyl-β-D-ribose,[5] the hydroxyl group in the initial product must be at C3 or C5. On mechanistic and steric grounds the latter isomer seems highly unlikely since it would require migration of the benzoyl at C5 in II to C3 or C2.[6] Formula VIII is, therefore, assigned to the product obtained from the orthoester through the action of acetic acid.

Warm acetic anhydride converted the orthoester II into a mixture from which 1,2-di-*O*-acetyl-3,5-di-*O*-benzoyl-β-D-ribose was isolated in 6.8% yield and 1,3-di-*O*-acetyl-2,5-di-*O*-benzoyl-β-D-ribose (VII) isolated in 41% yield.

Benzyl alcohol was found to cleave the orthoester II at an elevated temperature to give a crystalline benzyl D-riboside dibenzoate; the same product was obtained much more rapidly at room temperature when boron trifluoride was used as a catalyst. Further benzoylation converted the dibenzoate into the known benzyl β-D-ribofuranoside tribenzoate[4] (XI). Since the dibenzoate could readily be synthesized from 3,5-di-*O*-benzoyl-D-ribosyl chloride (Ib) we are inclined to assign structure X to it, with the benzoyl group derived from the orthobenzoate cage attached to C3 rather than C2 as in III, VII, and VIII.

When the orthobenzoate II was treated with hydrogen chloride, a crystalline halide was obtained; hydrogen bromide gave an amorphous product. These two substances may be represented by XII and XIII; the chloride was found to revert to II when treated in benzene solution with silver benzoate, otherwise these halides were not further investigated. However, the bromide as formed is more levorotatory ($[\alpha]_D^{20}$ *ca.* −71° in CH_2Cl_2) than the chloride ($[\alpha]_D^{20}$ *ca.* −29° in CH_2Cl_2), suggesting that these halides are β-anomers.

Finally, the halide Ib has been found to give a crystalline quaternary salt with pyridine; the position of the benzoyl groups (possibly XIV) and the anomeric configuration of this substance remain to be investigated.

EXPERIMENTAL[7]

1,2,5-Tri-O-benzoyl-β-D-ribose (III). (*a*) *From 5-O-benzoyl-1,2,3-O-benzylidyne-α-D-ribose* (II). A solution of 1.026 g. of 5-*O*-benzoyl-1,2,3-*O*-benzylidyne-α-D-ribose[1] and 2.5 g. of benzoic acid in 20 ml. of dry benzene was warmed at 40° for 6.5 hr. The reaction mixture was diluted with 10 ml. of pentane and 1.34 g. of material removed by filtration. Washed well with methanol and dried, this product (957 mg., 69%) melted at 184–185° (4°/min.). After two recrystallizations, one from acetone-pentane and another from ethanol, the melting point was essentially unchanged although some variation in melting point was observed depending on the rate of heating. The pure compound showed in chloroform (c 2.42) a rotation of $[\alpha]_D^{20}$ −20.5°.

Anal. Calcd. for $C_{26}H_{22}O_8$: C, 67.52; H, 4.79. Found: C, 67.61; H, 5.07.

(*b*) *From 1,3,5-tri-O-benzoyl-β-D-ribose* (VI). A crude preparation of 1,3,5-tri-*O*-benzoyl-D-ribose (93.4 mg.)[1] which melted at 134°, resolidified and finally melted again at 167°, showed $[\alpha]_D^{20}$ +1.4° in chloroform (*c* 0.93). The solid was heated in a 140° bath for 4 min., during which time it sintered and resolidified. The total reaction mixture then showed $[\alpha]_D^{20}$ −11.5° in chloroform solution; from ether solution it yielded 43.3 mg. (46%) of slightly impure 1,2,5-tri-*O*-benzoyl-β-D-ribose, m.p. 178–180° and $[\alpha]_D^{20}$ −19.8° (c 1.23). The infrared absorption spectrum (potassium bromide plate) showed it to be identical with the product prepared as described in (a) above.

The thermal transformation of the 1,3,5-isomer to the 1,2,5-isomer could be demonstrated readily through infrared measurements. When a potassium bromide plate containing pure 1,3,5-tri-*O*-benzoyl-β-D-ribose was heated at 110° for 50 min. and then 200 min. at 135° the IR absorption spectrum was found to have changed completely from that of the 1,3,5-isomer to that of the 1,2,5-isomer.

β-D-Ribofuranose tetrabenzoate (IV) *from 1,2,5-tri-O-benzoyl-β-D-ribose* (III). 1,2,5-Tri-*O*-benzoyl-β-D-ribose (15.1 mg.) was benzoylated with a cold mixture of benzoyl chloride (0.03 ml.) and pyridine (1 ml.) in the normal fashion. The addition of water afforded 16.7 mg. (89%) of crystalline product melting at 120–121° either alone or in admixture with authentic β-D-ribofuranose tetrabenzoate (m.p. 121–122°).[4]

1,2,5-Tri-O-benzoyl-3-O-p-tolylsulfonyl-β-D-ribose (V). 1,2,5-Tri-*O*-benzoyl-β-D-ribose (104.5 mg.) was added to a solution of 54 mg. of tosyl chloride in 1.0 ml. of dry pyridine

(4) R. K. Ness, H. W. Diehl, and H. G. Fletcher, Jr., *J. Am. Chem. Soc.*, 76, 763 (1954).

(5) R. K. Ness and H. G. Fletcher, Jr., *J. Am. Chem. Soc.*, 76, 1663 (1954).

(6) Normally *O* to *O* migrations of acyl groups proceed from secondary to primary positions; the reverse migration has been observed under forcing conditions. See: R. C. Hockett, H. G. Fletcher, Jr., E. L. Sheffield, and R. M. Goepp, Jr., *J. Am. Chem. Soc.*, 68, 927 (1946); R. C. Hockett, H. G. Fletcher, Jr., E. L. Sheffield, R. M. Goepp, Jr., and S. Soltzberg, *J. Am. Chem. Soc.*, 68, 930 (1946). However, P. E. Verkade and O. E. van Lohuizen [*Koninkl. Ned. Akad. Wetenschap., Proc. Ser. B.*, 56, 324 (1953)] have found that the equilibrium mixture obtained from monoglycerides under acid conditions contains a small but appreciable quantity of the β-monoglyceride.

(7) Melting points are corrected.

which had previously been cooled to 0°. One minute later the reaction mixture was allowed to warm to room temperature. After 25 min., 2 drops of water was added; crystallization was spontaneous. Several milliliters more water was added and the product removed: 132 mg., m.p. 158–175°. Recrystallization from 22 ml. of absolute alcohol gave 111 mg. (80%) of pure material as fine needles melting at 169–170° (in bath at 165°, 4°/min., rapid darkening just above m.p.). A second recrystallization failed to change this value. In chloroform (*c* 1.02) the pure substance showed $[\alpha]_D^{20}$ −4.1°.

Anal. Calcd. for $C_{33}H_{28}O_{10}S$: C, 64.27; H, 4.58. Found: C, 64.47; H, 4.81.

1-O-Acetyl-2,5-di-O-benzoyl-β-D-ribose (VIII) *from 5-O-benzoyl-1,2,3-O-benzylidyne-α-D-ribose* (II). 5-*O*-Benzoyl-1,2,3-*O*-benzylidyne-α-D-ribose (103 mg.), dissolved in 2.0 ml. of methylene chloride, was treated with 2.0 ml. of glacial acetic acid. Within 3 min. the rotation of the solution was constant, and after 8 min. toluene was added and solvent then removed *in vacuo*. Toluene and ether were successively evaporated from the sirup. From ether-pentane the product (94.6 mg., 78%) crystallized as dense clumps of fine needles melting at 99–100°. Two recrystallizations from ether-pentane gave pure 1-*O*-acetyl-2,5-di-*O*-benzoyl-β-D-ribose melting at 101–103° and showing $[\alpha]_D^{20}$ −25.0° in chloroform (c 2.9).

Anal. Calcd. for $C_{21}H_{20}O_8$: C, 62.99; H, 5.04. Found: C, 62.93; H, 5.07.

Benzoylation of 43.9 mg. of the above-described product with benzoyl chloride in pyridine afforded 47.0 mg. (85%) of crystalline material melting at 129–131° either alone or in admixture with authentic 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribose (IX).[4]

1,3-Di-O-acetyl-2,5-di-O-benzoyl-β-D-ribose (VII). (a) *From 5-O-benzoyl-1,2,3-O-benzylidyne-α-D-ribose* (II). A solution of 215.7 mg. of 5-*O*-benzoyl-1,2,3-*O*-benzylidyne-α-D-ribose in 4 ml. of acetic anhydride was heated at 105° for 6 hr. and then poured into ice water. The gummy mass which formed after several hours was dissolved in 1 ml. of absolute alcohol. Seeding with 1,2-di-*O*-acetyl-3,5-di-*O*-benzoyl-β-D-ribose[5] gave 19.2 mg. (6.8%) of this ester in crude form, m.p. 115–124°. Two recrystallizations of this crop yielded a pure product which did not depress the melting point of authentic 1,2-di-*O*-acetyl-3,5-di-*O*-benzoyl-β-D-ribose. The main filtrate, on standing, crystallized; a little pentane was added and 91.1 mg. of practically pure 1,3-di-*O*-acetyl-2,5-di-*O*-benzoyl-β-D-ribose, m.p. 109–110°, obtained. A second crop of less pure material raised the yield to 115 mg. (41%). Recrystallization of the purer fraction from ethanol and from ethanol-pentane gave platelets, m.p. 111–112°, $[\alpha]_D^{20}$ +23.4° in chloroform (c 1.7).

Anal. Calcd. for $C_{23}H_{22}O_9$: C, 62.44; H, 5.01. Found: C, 62.41; H, 5.01.

(*b*) *From 1-O-acetyl-2,5-di-O-benzoyl-β-D-ribose* (VIII). 1-*O*-Acetyl-2,5-di-*O*-benzoyl-β-D-ribose (29 mg.) was acetylated with acetic anhydride and pyridine in the usual manner to yield 14.2 mg. (44%) of 1,3-di-*O*-acetyl-2,5-di-*O*-benzoyl-β-D-ribose melting at 110–111°, $[\alpha]_D^{20}$ +23° in chloroform (*c* 1.0). Mixture with the product obtained in (a) above failed to depress this melting point.

(*c*) *From 1,2,5-tri-O-benzoyl-β-D-ribose* (III). 1,2,5-Tri-*O*-benzoyl-β-D-ribose (103.3 mg.) was acetylated with 2.0 ml. of a 2:1 mixture of pyridine-acetic anhydride at −5°. After 17 hrs. at −5°, the mixture was treated with 0.6 ml. of water and cooled in an ice bath for 35 min. Methylene chloride was added and the organic layer washed successively with water, 3*N* sulfuric acid, and saturated aqueous sodium bicarbonate. Moisture was removed with magnesium sulfate and the solution concentrated *in vacuo* to give 129.6 mg. of sirup which was treated with 4.0 ml. of a mixture made from 20 ml. of acetic anhydride and 1 ml. of 7*M* boron trifluoride in ether. After 13 min. ice was added and the mixture stirred at 0° for 2 hr. Methylene chloride was then added and the organic layer washed successively with water and aqueous sodium bicarbonate. After drying with sodium sulfate and removing the solvent *in vacuo* a residue was obtained; crystallization from ether-pentane afforded 49.8 mg. (50%) of crystalline product, m.p. 109–111°, $[\alpha]_D^{20}$ +26° (*c* 2.2, chloroform). When mixed with 1,3-di-*O*-acetyl-2,5-di-*O*-benzoyl-β-D-ribose, prepared from 5-*O*-benzoyl-1,2,3-*O*-benzylidyne-α-D-ribose, as described above, it melted at 109–111°.

Benzyl 3,5-di-O-benzoyl-β-D-riboside (X). (*a*) *From 3,5-di-O-benzoyl-D-ribosyl bromide* (*Ia*). Benzyl alcohol (2 ml.) was added to 1.05 g. of 3,5-di-*O*-benzoyl-D-ribosyl bromide (m.p. 105–107°). Thirty seconds later silver oxide was added. A slight spontaneous warming of the reaction mixture was noticed and therefore the reaction flask was immediately cooled in an ice bath. Eight minutes later the silver compounds were removed by filtration and washed with methylene chloride. The filtrate was concentrated at 90° (0.03 mm.) and the residue extracted with warm cyclohexane. On cooling the extract deposited 0.06 g. of needles melting at 132–135°. The gum left after the extraction was dissolved in 15 ml. of ether to give 0.11 g. of needles (m.p. 133–136°). The filtrate after concentration and dilution with ethanol-pentane yielded an additional 0.15 g. of crystalline material. These three fractions were combined and recrystallized from ether (methylene chloride used to dissolve fractions being displaced by ether on the steam bath as evaporation occurred). A second recrystallization from ether gave 0.26 g. (23%) of pure material melting at 140–141°. A third recrystallization from 1:1 ethanol-ether did not change this value. The product showed $[\alpha]_D^{20}$ −49.2° (*c* 2.10 in chloroform).

Anal. Calcd. for $C_{26}H_{24}O_7$: C, 69.63; H, 5.39. Found: C, 69.50; H, 5.56.

Benzoylation of the benzyl riboside dibenzoate (21 mg.) in the usual manner afforded 22 mg. of a crude product melting at 63–84°. After one recrystallization from ethanol-hexane and one from ethanol, the melting point of the tribenzoate was 86–88°. When mixed with authentic benzyl β-D-ribofuranoside tribenzoate[4] there was no depression of the melting point. The rotation of the tribenzoate in chloroform was $[\alpha]_D^{20}$ +15° (*c* 0.58); pure benzyl β-D-ribofuranoside tribenzoate had earlier been found[4] to show $[\alpha]_D^{20}$ +14.9° in chloroform.

(*b*) *From 5-O-benzoyl-1,2,3-O-benzylidyne-α-D-ribose* (II). A solution of 220.4 mg. of 5-*O*-benzoyl-1,2,3-*O*-benzylidyne-α-D-ribose in 5 ml. of freshly distilled benzyl alcohol was heated at 140° for 1.5 hr. The mixture was then concentrated *in vacuo* (0.25 mm. and 120° bath) to a sirup which, dissolved in ether-pentane, afforded 96 mg. (33%) of a crystalline product melting at 133–140°. One recrystallization from ethanol and another from ether gave benzyl β-D-ribofuranoside dibenzoate melting at 141–142°; a mixed melting point with the product obtained in (a) above was undepressed. The same transformation could be accomplished catalytically in somewhat higher yield as follows. A suspension of 319.1 mg. of 5-*O*-benzoyl-1,2,3-*O*-benzylidyne-α-D-ribose in 2 ml. of freshly distilled benzyl alcohol was treated with 0.03 ml. of 7*M* boron trifluoride in ether. Within 7 min. solution was complete and 7 min. later *ca.* 3 ml. of ether and *ca.* 10 ml. of pentane were added. The crystalline product (229.8 mg., 55%) which formed melted at 130–136°; successive recrystallizations from carbon tetrachloride, 1:1 ethanol-pentane and ethanol afforded clusters of heavy needles melting at 139–141°, $[\alpha]_D^{20}$ −48.6° in chloroform (*c* 1.4). A mixed melting point with the product obtained in (a) above was undepressed.

2,5-Di-O-benzoyl-D-ribosyl chloride (XII). 5-*O*-Benzoyl-1,2,3-*O*-benzylidyne-α-D-ribose (0.5033 g.) was dissolved in 3.15 ml. (1.00 mole-equivalent) of 0.472*M* hydrogen chloride-methylene chloride. After 75 seconds, 9.5 ml. of pentane was added and crystallization occurred rapidly. Two minutes later, 5.5 ml. more of pentane was added. The product was separated by filtration after cooling to −5°: 0.5099 g. (91%), m.p. (with dec.) 127–128° (in bath at 120°,

10°/min.). One recrystallization from ether-pentane gave the pure halide melting (with dec.) at 128–129° (in bath at 120°, 10°/min.) and exhibiting in methylene chloride (dried over Drierite) (*c* 0.39) $[\alpha]_D^{20}$ −29° (5 min.) → ±0° (97 min.) and in absolute chloroform (*c* 1.79) −20° (4 min.) → +42° (65 hr.).

Anal. Calcd. for $C_{19}H_{17}O_6Cl$: C, 60.56; H, 4.55; Cl, 9.41. Found: C, 60.44; H, 4.42; Cl, 9.34.

5-O-Benzoyl-1,2,3-O-benzylidyne-α-D-ribose (II) *from 2,5-di-O-benzoyl-D-ribosl chloride* (XII). Crystalline 2,5-di-*O*-benzoyl-D-ribosyl chloride (42.3 mg.) was added to a rapidly stirred suspension of 114 mg. of silver benzoate in dry benzene. Ten minutes later the insoluble salts were removed by filtration and washed with methylene chloride. The filtrate and washings were combined and concentrated to a crystalline mass. From 1:1 acetone-ether, crystallization occurred after which an equal volume of pentane was added. The crystalline product was recrystallized from methylene chloride-pentane: 20.7 mg. (55%), m.p. 180–182°, $[\alpha]_D^{20}$ +44° (*c* 1.00, chloroform). When mixed with authentic 5-*O*-benzoyl-1,2,3-*O*-benzylidyne-α-D-ribose,[1] the melting point was not depressed.

N-[3,5-Di-O-benzoyl-D-ribosyl]pyridinium chloride (XIV). Dry pyridine (0.5 ml.) was added to 500 mg. of crystalline 3,5-di-*O*-benzoyl-D-ribosyl chloride. The temperature of the mixture rose slightly and within 10 min. crystallization began. Another ml. of pyridine was added and the reaction mixture was warmed on the steam bath for 1 hr. Methylene chloride (8 ml.) was added to the cooled mixture and the crystalline product, 350 mg. (58%), removed: m.p. 164–166°. Recrystallization from ethanol gave clear prisms, m.p. 171–177° (in bath at 160°, 12°/min.), $[\alpha]_D^{20}$ −64.1° in water (*c* 1.21).

Anal. Calcd. for $C_{24}H_{22}O_6NCl$: C, 63.23; H, 4.87; N, 3.07. Found: C, 63.19; H, 4.95; N, 3.09.

Acknowledgment. Combustion analyses were performed in the Institutes' Microanalytical Laboratory under the direction of Dr. William C. Alford. We are indebted to Mr. William M. Jones for infrared absorption measurements.

BETHESDA 14, MD.

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

Formation of Naphthalenes from Indenes. IV.[1] The Effect of Substitution at the Ethylenic Double Bond*

WILLIAM E. PARHAM[2] AND CHARLES D. WRIGHT[3]

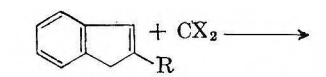
Received April 8, 1957

The yields of 2-halonaphthalenes obtained from eight substituted indenes, in which the substituent has been varied from electron withdrawing to electron donating, indicate that the addition of dihalocarbene to the indene double bond is inhibited by the groups chlorine, bromine, carbethoxy, or phenyl. When the substituent is electron-donating, such as methyl, isopropyl, or ethoxy, the yields of naphthalenes are comparable to those obtained with unsubstituted indene. These data support the view that the two electrons in the dihalocarbene are paired, and that carbenes seek centers of high electron density.

The use of 2-substituted indenes in reactions with haloform and potassium *t*-butoxide results in the formation of 2,3-disubstituted naphthalenes.

2-Chloro-, bromo-, and fluoronaphthalene, and 1-methyl-2-bromonaphthalene have recently been prepared[1,4] by a new method, which involves the reaction of indene, or 3-methylindene, with the appropriate haloform and potassium *t*-butoxide. An investigation of the reaction of eight other monosubstituted indenes with haloform and potassium *t*-butoxide has now been made in order to further define the scope of this synthesis, and to gain additional information concerning the general reaction of carbenes with olefins.

Optimum conditions for the synthesis of 2-halonaphthalenes[1,4] by this method involve the use of excess indene as solvent. In this study a standard procedure was employed using benzene as solvent. The yields of naphthalenes were not optimum (37% compared to 67% for 2-chloronaphthalene); however, the use of this procedure permitted: a direct comparison to be made of the reactivity of the various substituted indenes, the use of indenes which are solid at the reaction temperature, and the use of relatively small amounts of indenes. The indenes studied contained substituents which varied from



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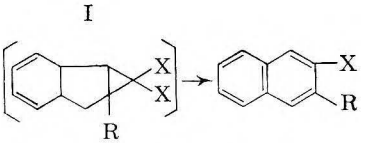


II III

a. R = CH_3, X = Cl
b. R = OC_2H_5, X = Br
c. R = Cl, X = Cl
d. R = Br, X = Cl
e. R = $CO_2C_2H_5$, X = C

* This paper is a contribution in honor of Lyndon F. Small, former Editor of the Journal.

(1) Preceding paper. W. E. Parham and R. R. Twelves, *J. Org. Chem.*, **22**, 730 (1957).

(2) This work was supported in part by a grant (NSF-G2163) from the National Science Foundation.

(3) Visking Corporation Fellow (1954–1955).

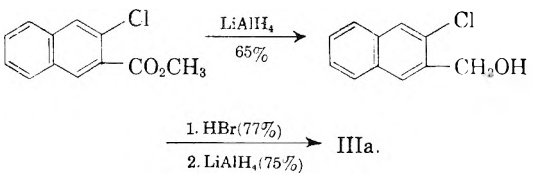
(4) W. E. Parham, H. E. Reiff, and P. Swartzentruber, *J. Am. Chem. Soc.*, **78**, 1437 (1956).

electron withdrawing to electron-donating, and from small to bulky in size.

The 2-substituted indenes Ia-Ie were prepared by modifications of existing procedures, or by new procedures; details are found in the experimental section. The yields of naphthalenes obtained from 2-methylindene (IIIa, 37%), and 2-ethoxyindene (IIIb, 34%) were comparable to the yield of 2-chloronaphthalene obtained from indene (37%); however, only trace amounts of products (<5%) were isolated from reactions in which 2-chloroindene (Ic), 2-bromoindene (Id), or 2-carbethoxyindene (Ie) were employed.

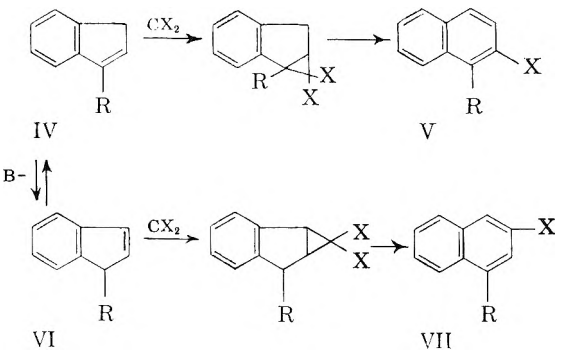
The product (m.p. 82°) obtained from 2-ethoxyindene (Ib) was assigned the structure 2-ethoxy-3-bromonaphthalene (IIIb, reported[5] m.p. 79°). This product was further characterized by its conversion to the corresponding acid (60% yield, m.p. 128–129°, reported[6] m.p. 122°) by carbonation of the intermediate Grignard reagent.

2-Methyl-3-chloronaphthalene (IIIa), obtained in 37% yield from Ia, was unknown. Its structure was confirmed by the independent synthesis shown below.



The structures of the products obtained in very low yield from Ic, Id, and Ie were not established. Two crystalline solids (m.p. 95°, mol. wt. 218–254; m.p. 81°, mol. wt. 300) were obtained by chromatography of the deep blue reaction mixture obtained from 2-carbethoxyindene. These products possessed nearly identical composition (carbon and hydrogen), and infrared spectra (two bands in carbonyl region); however, they were not IIe, IIIe, or the corresponding *t*-butyl derivatives. The naphthalene obtained (2% yield) from 2-bromoindene had the composition calculated for 2-bromo-3-chloronaphthalene (IIId); however, its melting point (130°) was not in agreement with that previously reported[7] for IIId (115°). It was not established whether the previously reported melting point of 2-bromo-3-chloronaphthalene was in error or whether the product obtained from Id was an unexpected isomer of IIId. Only a trace of naphthalenic material was obtained from 2-chloroindene (Ic).

It has been previously shown[4] that steam distillation of the product obtained from 3-methylindene (IVa ⇄ VIa) and dibromocarbene gives only one (Va) of the two possible naphthalenes (Va or VIIa). The initial reaction involved only the most stable isomer IVa, and there was no indication of steric preference for the reaction of the carbene with the least hindered isomer VIa.



a. R = CH_3, X = Br
b. R = $(CH_3)_2CH$, X = Cl
c. R = Cl, X = Cl
d. R = C_6H_5, X = Br

It has now been shown that the reaction of 3-isopropylindene (IVb) with chloroform and potassium *t*-butoxide, with subsequent decomposition of the resulting cyclopropyl intermediate by steam distillation, gives predominantly, if not exclusively, a single naphthalene. Evidence that the product was not a mixture of isomeric naphthalenes was obtained by its conversion, in high yield (< 75%), into a pure solid picrate. The structure of this product was assumed to be 1-isopropyl-2-chloronaphthalene (Vb) by analogy to the results previously obtained with 3-methylindene,[4] and by its infrared spectrum.[8]

The reactions in which 3-chloroindene (IVc) and 3-phenylindene (IVd) were employed resulted in low yields of naphthalenic materials (5% each). These products were assigned the structures 1-phenyl-2-bromonaphthalene (Vd, oil, previously unknown), and 1,2-dichloronaphthalene (Vc, m.p. 35°, reported[9] m.p. 35°). A red hydrocarbon (m.p. 216–217°, $C_{16}H_{10}$) was also obtained in low yield from the reaction with 3-phenylindene; the structure of this product is being examined.

(5) E. Huisgen and G. Sorge, *Ann.*, 566, 179 (1950).

(6) H. Gilman, C. E. Arntzen, and F. Webb, *J. Org. Chem.*, 10, 374 (1945).

(7) H. H. Hodgson and D. E. Hathway, *J. Chem. Soc.*, 842 (1945).

(8) The infrared spectrum of this product was compared with three 1,2-disubstituted naphthalenes (1-methyl-2-bromonaphthalene, 1-methyl-2-aminonaphthalene, and 1-methyl-2-hydroxynaphthalene) which were available in these laboratories, and with the spectra of 1,2-dimethylnaphthalene and 1,3-dimethylnaphthalene (Infrared Spectral Data: American Petroleum Institute, National Bureau of Standards, Spectra Serial Nos. 766, 767). The spectra of all of the 1,2-disubstituted naphthalenes, and of the naphthalene in question, were similar in that three strong bands were present at 739–741, 757–775, and 796–815 cm^{-1}. Only two strong bands were present in this region of the spectrum of 1,3-dimethylnaphthalene. The out-of-plane deformation of aromatic hydrogen atoms gives rise to the bands described. Structure Vb is consistent with the observed spectrum; however, these data cannot be considered as conclusive evidence for the structural assignment in view of the limited number of spectra available.

(9) P. T. Cleve, *Ber.*, 20, 1989 (1887).

Since significant amounts of naphthalenic products were not obtained from any of the three haloindenes studied, the possibility remained that the haloindene reacted with the potassium *t*-butoxide before the haloform had been added. That this was not the case was shown by a high recovery (80%) of 2-bromoindene from a mixture of Id and potassium *t*-butoxide, which had been allowed to react for two and one-half hours. Since dihalocarbenes are known to form under the conditions of the reaction,[4,10–12] it was concluded that a halogen substituent on the ethylenic bond of indene deactivates this bond to attack by the carbene.

The experiments described above show that the addition of dihalocarbenes to the indene double bond is inhibited by substituents which are electron-withdrawing, such as chlorine, bromine, carbethoxy, or phenyl. Such deactivation is not observed when the ethylenic substituent in an electron donating group such as methyl, isopropyl, and ethoxy. These results are in accord with the view that the two electrons of the carbene are paired, and that carbenes seek centers of high electron density.[10,12]

EXPERIMENTAL

Reaction of 2-methylindene, chloroform and potassium t-butoxide. General procedure. A solution of 2-methylindene[13] 15.6 g., 0.12 mole) in dry thiophene-free benzene (15 ml.) was added to dry pulverized potassium *t*-butoxide (maintained under dry oxygen-free nitrogen) prepared from potassium (2.00 g., 0.051 mole) and *t*-butyl alcohol. The orange slurry was stirred vigorously, and cooled in an ice bath, while 4.8 g. (0.040 mole) of freshly distilled chloroform was added over a period of about 15 min. A static nitrogen atmosphere was maintained during the addition, and the mixture was then allowed to stand at room temperature overnight. The entire mixture was steam-distilled from water containing 0.08 mole of sodium carbonate. An undetermined amount of nonvolatile red tar remained in the flask. The distillate was extracted with petroleum ether (b.p. 60–68°), and the condenser was washed with the same solvent. The organic washes and extracts were dried, filtered, and the solvent was removed by distillation. Fractional distillation of the residue afforded 9.6 g. (0.0727 mole) of uureacted 2-methylindene. The light green residue, m.p. 113–120°, was recrystallized once from ethanol, and was obtained as refractive pale green platelets (2.61 g., 37%, m.p. 122.5–123°). This material was further purified (m.p. 123.5–124°) by recrystallization from ethanol using charcoal.

Anal. Calcd. for $C_{11}H_9Cl$: C, 74.79; H, 5.14. Found: C, 74.72; H, 5.34.

The product was identical (m.p., mixture m.p. and infrared spectrum) with authentic 2-methyl-3-chloronaphthalene.

2-Chloro-3-hydroxymethylnaphthalene. A solution of methyl 2-chloro-3-naphthoate[14] (16.3 g., 0.074 mole) in dry ether (40 ml.) was added to lithium aluminum hydride (3.1 g., 0.082 mole) in dry ether (150 ml.) at such a rate as to maintain gentle reflux. The resulting mixture was stirred for 0.5 hr. and then saturated aqueous ammonium chloride (10 ml.) was added. The white solid residue, obtained from the dried ether solution, was recrystallized from a mixture of petroleum ether (500 ml., b.p. 60–68°) and benzene (30 ml.) to give 9.2 g. (65% yield) of 2-chloro-3-(hydroxymethyl)naphthalene (m.p. 110.5–112°, reported[15] 111°).

2-Chloro-3-methylnaphthalene. A solution of 4.0 g. (0.016 mole) of 2-chloro-3-bromomethylnaphthalene (prepared in 77% yield from 2-chloro-3-hydroxymethylnaphthalene by the method reported by Shoesmith and Mackie[15]) in the minimum amount of dry ether was added dropwise to a stirred solution of lithium aluminum hydride (0.50 g., 0.013 moles) in dry ether (60 ml.), and the resulting mixture was heated at the reflux temperature for 3 hr. The mixture was processed as described above, and the product was recrystallized from ethanol. There was obtained 2.1 g. (75% yield) of 2-chloro-3-methylnaphthalene (m.p. 123–123.5°).

2-Ethoxy indene. Dry hydrogen chloride (0.7 g., 0.02 mole) in absolute ethanol (2.5 ml.) was added to a solution of 87.4 g. (0.66 mole) of indanone-2 (prepared[16] from indenebromohydrin[17]), ethyl orthoformate (133 g., 0.90 mole), and absolute ethanol (350 ml.). The resulting solution was allowed to stand at room temperature for 24 hr., and was then made alkaline by the addition of sodium methoxide (4.2 g.). The mixture was processed by distillation, and 76.4 g. (56% yield) of 2,2-diethoxyindane (b.p. 99–101°/3.4 mm., n_D^{25} 1.5303–1.5426, licorice odor), contaminated with 2-ethoxyindene, was obtained.

A mixture of the ketal (45.4 g., 0.220 mole) and *p*-toluenesulfonic acid (0.011 g.) was heated for 1 hr. at 25–60° (25–30 mm.), and the ethanol which was formed was removed by distillation. Distillation of the residue afforded 30.1 g. (86% yield) of 2-ethoxyindene (b.p. 86°/1.6 mm., m.p. (from ethanol-water) 42–45°).

Anal. Calcd. for $C_{11}H_{12}O$: C, 82.46; H, 7.55. Found: C, 82.10; H, 7.24.

2-Ethoxyindene was stored under oxygen-free nitrogen in a tight container The product rapidly turns yellow when exposed to air, and was easily hydrolyzed to indanone-2 (m.p. and mixture m.p. of oxime, 155°).

Reaction of 2-ethoxyindene, bromoform, and potassium t-butoxide. The reaction mixture obtained from potassium *t*-butoxide (from 3.2 g., 0.082 g. atoms, of potassium), 2-ethoxyindene (26.3 g., 0.164 mole), benzene (25 ml.) and bromoform (14.3 g., 0.0565 mole) was processed by the procedure previously described for 2-methylindene. The organic product, obtained from the steam distillate, was distilled to give indanone-2 [12.1 g., 0.0915 moles, b.p. 77°/1.6 mm., m.p. 56–58° (reported m.p. 58°[18]), oxime m.p. 155° (reported 152°[19])], and black tarry residue (7.9 g.). The residue was dissolved in benzene (4 ml.) and chromatographed on acid-washed alumina (200 g.), using petroleum ether (b.p. 60–68°, 1900 ml.) as eluant. The white product (5.4 g., m.p. 76–80°) was recrystallized from methanol to give 4.78 g. (34% yield) of 2-ethoxy-3-bromonaphthalene melting at 79–82.5° (reported m.p. 79°[5]). The melting point of the product was raised to 81.5–82° (A) by

(10) W. von E. Doering and A. K. Hoffman, *J. Am. Chem. Soc.*, **76**, 6162 (1954); W. von E. Doering and P. La Flamme, *J. Am. Chem. Soc.*, **78**, 5447 (1956).

(11) J. Hine, *J. Am. Chem. Soc.*, **72**, 2438 (1950), and other papers by Hine and his coworkers.

(12) P. S. Skell and A. Y. Garner, *J. Am. Chem. Soc.*, **78**, 3409 (1956); P. S. Skell and A. Y. Garner, *J. Am. Chem. Soc.*, **78**, 5430 (1956); P. S. Skell and R. C. Woodworth, *J. Am. Chem. Soc.*, **78**, 4496 (1956).

(13) C. F. Koelsch and P. R. Johnson, *J. Am. Chem. Soc.*, **65**, 567 (1943).

(14) E. Strohbach, *Ber.*, **34**, 4158 (1901).

(15) J. B. Shoesmith and A. Mackie, *J. Chem. Soc.*, 1584 (1930).

(16) P. Pfeiffer and T. Hesse, *J. prakt. Chim.*, **158**, 315 (1941).

(17) C. M. Suter and H. B. Milne, *J. Am. Chem. Soc.*, 62, 3473 (1940).

(18) J. Read and E. Hurst, *J. Chem. Soc.*, **121**, 2554 (1922).

(19) H. D. Porter and C. M. Suter, *J. Am. Chem. Soc.*, **57**, 2022 (1935).

recrystallization from methanol, and 82.2–82.7° (B) by recrystallization from petroleum ether.

Anal. Calcd. for $C_{12}H_{11}BrO$: C, 57.39; H, 4.42. Found: (A): C, 57.80; H, 4.42. (B): C, 57.93; H, 4.66.

2-Ethoxy-3-naphthoic acid. A sample of 2-ethoxy-3-bromonaphthalene (1.5 g.) was converted, by a standard procedure involving the Grignard reagent, into the corresponding acid. The crude product (0.785 g., 60%, m.p. 119–124°) was recrystallized from ethanol and a white acid (m.p. 128.5–129.5°), presumed to be 2-ethoxy-3-naphthoic acid, was obtained. The reported melting point of this acid is 122°.[6]

Anal. Calcd. for $C_{13}H_{12}O_3$: C, 72.21; H, 5.59. Found: C, 72.35; H, 5.83.

3-Isopropylindene. A solution of indanone-1 (50.0 g., 0.378 mole) in ether (100 ml.) was added (under a nitrogen atmosphere) over a 30-min. period to the Grignard reagent prepared from isopropyl bromide (63 g., 0.515 mole), magnesium (12.1 g., 0.50 g. atoms) and ether (200 ml.). The mixture was allowed to stand for 48 hr., and was then decomposed with saturated ammonium chloride solution (88 ml.). The residual oil (60.7 g., 91% yield as 1-isopropyl-1-indanol), obtained from the ether, was added to benzene (250 ml.) containing phosphorus pentoxide (47 g.), and the resulting mixture was heated at the reflux temperature for 12 min. The cooled organic phase was washed with dilute sodium hydroxide, dried (magnesium sulfate), and fractionally distilled. 3-Isopropylindene,[20] contaminated with a small amount of indanone-1 (infrared absorption at 1700 cm^{-1}), was collected at 57.5°/0.55 mm. (25 g., 43% yield, n_D^{25} 1.5472–1.5482).

Anal. Calcd. for $C_{12}H_{14}$: C, 91.08; H, 8.92. Found: C, 90.04; H, 8.99.

Reaction of 3-isopropylindene, chloroform, and potassium t-butoxide. The reaction of 3-isopropylindene (17.3 g., 0.110 mole), potassium *t*-butoxide (from 1.95 g., 0.05 g. atoms, of potassium), chloroform (4.63 g., 0.0388 mole) in benzene (17.3 g.) was carried out as previously described for 2-methylindene. The reddish oil, obtained from the steam distillate, had a strong odor of hydrochloric acid which suggested that the dichlorocyclopropyl intermediate was present; consequently this oil (17.4 g.) was treated with hot ethanol (75 ml.) containing potassium hydroxide (2.05 g., 0.036 mole) for a period of 75 min. Water (75 ml.) was added to the residue after the ethanol had been removed by distillation, and the organic products were extracted with petroleum ether (b.p. 60–68°). The ether solution was dried (magnesium sulfate) and distilled and two fractions were obtained: (*1*) 3-isopropylindene (11.41 g., 0.072 mole), and (*2*) 1-isopropyl-2-chloronaphthalene (3.59 g., b.p. 90°/0.37 mm., n_D^{25} 1.6005–1.6052). The naphthalenic product was redistilled to give 3.04 g. of product (38% yield, b.p. 96–97°/0.6 mm., n_D^{25} 1.6047–1.6059. The product was redistilled (n_D^{25} 1.6055–1.6061) for analysis.

Anal. Calcd. for $C_{13}H_{13}Cl$: C, 76.28; H, 6.40. Found: C, 76.18; H, 6.71.

The picrate (75% yield, orange needles, m.p. 91–92°) was recrystallized from ethanol.

Anal. Calcd. for $C_{19}H_{16}ClN_3O_7$: C, 52.60; H, 3.73; N, 9.69. Found: C, 52.76; H, 4.03; N, 9.86.

The high yield of picrate obtained establishes that one of the two isomeric naphthalenes is formed predominantly. The structure was assigned as 1-isopropyl-2-chloronaphthalene, instead of 1-isopropyl-3-chloronaphthalene, by analogy to the results previously reported employing 3-methylindene,[4] and from infrared spectral data.[8]

The reaction of 2- and 3-haloindenes with potassium t-butoxide and chloroform. The reaction mixture of potassium *t*-butoxide (0.024 mole), *2-chloroindene*[21] (11.4 g., 0.076 mole), chloroform (5.70 g., 0.048 mole) and benzene (10 ml.) was processed by the method described above for 2-methylindene. Unreacted 2-chloroindene (8.76 g., 0.058 mole) was obtained by distillation. The residue from this distillation was chromatographed; however, the small amount of product (yellow semisolid, 200 mg.) was not processed.

Similar results were obtained with *3-chloroindene*[22] (13.5 g., 0.09 mole). The product (0.55 g.) was recrystallized from ethanol to give 0.271 g. (4.7% yield) of 1,2-dichloronaphthalene (m.p. 31–32°). The product melted at 34–35° after recrystallization from petroleum ether (30–60°). The reported melting point of 1,2-dichloronaphthalene is 35°.[9]

Anal. Calcd. for $C_{10}H_6Cl_2$: C, 60.94; H, 3.08. Found: C, 60.91, 60.85; H, 3.85, 3.91.

When *2-bromoindene*[19] (18.0 g., 0.092 mole) was employed, there was obtained: (*1*) unreacted bromoindene (12.0 g., 0.061 mole), and (*2*) a trace of white solid (0.009 g., m.p. 125–129°, by chromatography). In another reaction the steam-distillation step was omitted. The organic products were extracted with petroleum ether (60–68°). Petroleum ether and unchanged 2-bromoindene were removed by distillation at reduced pressure; the residue was chromatographed. There was obtained 0.54 g. of bluish white solid. This product was recrystallized from petroleum ether which afforded 0.184 g. (1.6% yield) of naphthalenic material melting at 126–129°. The melting point was raised to 130° by subsequent recrystallization from petroleum ether.

Anal. Calcd. for $C_{10}H_6BrCl$: C, 49.74; H, 2.50. Found: C, 49.40; H, 2.66.

This product was not identified; however, the expected 2-bromo-3-chloronaphthalene is reported to melt at 115°.[7]

Preparation of 3-phenylindene. A solution of indanone-1 (50.0 g., 0.378 mole) in absolute ether (100 ml.) was added over a period of 50 min. with stirring to the Grignard reagent prepared from magnesium (11.4 g., 0.470 mole) and bromobenzene (75.7 g., 0.48 mole) in absolute ether (390 ml.). The mixture was stirred for 3.5 hr. and was hydrolyzed by the slow addition of saturated ammonium chloride solution (70 ml.). The ether layer was decanted, filtered, dried (magnesium sulphate), and distilled to remove solvent. The yield of crude 1-phenyl-1-indanol was 78.9 g. (99%).

A mixture of crude 1-phenyl-1-indanol (66.9 g., 0.318 mole), phosphorus pentoxide (45.2 g., 0.318 mole), and benzene (300 ml.) was heated at the reflux temperature for 20 min. The benzene solution was cooled, decanted, washed with dilute base, dried (magnesium sulfate), and distilled to remove solvent. Fractional distillation of the orange residue afforded 46.1 g. (76% yield) of 3-phenylindene, b.p. 113–116° (0.40 mm.), n_D^{25} 1.6335–1.6341. The physical constants which are reported in the literature are: b.p. 200–201° (29 mm.),[23] 148–150° (3 mm.),[24] 113–117° (0.05 mm.); n_D^{18} 1.6357,[25] n_D^{24} 1.6313.[24]

Reaction of 3-phenylindene, bromoform, and potassium t-butoxide. The reaction product obtained from potassium *t*-butoxide (0.105 g. atom), 3-phenylindene (45.6 g., 0.237 mole), bromoform (19.85 g., 0.0785 mole), in benzene (45 g.), was steam distilled until 4 liters of distillate were collected. Water was decanted from the product not steam-distilled, and the residual oil was extracted with petroleum ether. The ether extract was dried (magnesium sulfate), and petroleum ether and unchanged 3-phenylindene (b.p. 104–107°/0.10 mm., n_D^{25} 1.6318–1.6338) were removed. The black tarry residue (11.4 g.) was dissolved in benzene and chromatographed on alumina (200 g.), using petroleum ether (b.p. 60–68°) as eluant. Three combined fractions were obtained: (*1*) 3.21 g., blue oil, 185 ml. eluant, (*2*) 1.10 g.,

(20) J. Thiele and K. Merck, *Ann.*, **415**, 257 (1918).

(21) C. M. Suter and G. A. Lutz, *J. Am. Chem. Soc.*, **60**, 360 (1938).

(22) Prepared in 60% yield by the method of J. von Braun and H. Ostermayer, *Ber.*, **70**, 1006 (1937).

(23) J. von Braun, *Ber.*, **50**, 1659 (1917).

(24) C. M. Suter and G. A. Lutz, *J. Am. Chem. Soc.*, **60**, 1365 (1938).

(25) P. A. Plattner, R. Sandrin, and J. Wyss, *Helv. Chim. Acta*, **29**, 1604 (1946).

green-brown oil, 300 ml. eluent, (*3*) 1.36 g., red semi-solid, 650 ml. eluant. Fraction *1* was composed principally of product (1.1 g., 5% as 1-phenyl-2-bromonaphthalene, n_D^{25} 1.6763–1.6768) boiling at 143°/0.45 mm.

Anal. Calcd. for $C_{10}H_{11}Br$: C, 67.86; H, 3.92. Found: C, 68.06; H, 4.22.

Fraction *3* was recrystallized from chloroform-methanol to give 0.154 g. of red needles melting at 197–207°. The melting point of this product, or of one component of the product, was raised to 216–217.3° by subsequent recrystallization.

Anal. Calcd. for $C_{31}H_{22}$: C, 94.38; H, 5.62; mol. wt., 394.5. For $C_{16}H_{10}$: C, 95.01; H, 4.98; mol. wt., 202. Found: C, 94.15, 94.45; H, 5.61, 5.62; mol. wt. (benzene), 199.

2-Carbethoxyindene. Ethyl α-formylhydrocinnamate (41.6 g., 0.202 mole, b.p. 96–98°/0.9 mm., n_D^{25} 1.5142–1.5156, prepared in 22% yield by the method of von Auwers[26]) was added to a warm (70°) solution prepared from phosphorus pentoxide (426 g.) and phosphoric acid (85%, 426 g.). The resulting mixture was stirred vigorously and maintained at 70° for 30 min. The resulting red mixture was poured onto an excess of ice, and the viscous oil was stirred vigorously until the red color disappeared. The hydrolysis mixture was extracted four times with ether and the ether extracts were washed with dilute sodium hydroxide. The basic aqueous wash was extracted once with ether. The combined ether extract was dried, filtered, and distilled to remove solvent. The red oily residue (33.7 g.) was dissolved in the minimum amount of petroleum ether (b.p. 60–68°), absorbed on a column of alumina, and eluted with petroleum ether (b.p. 60–68°). Evaporation of the first eluant fraction (475 ml.) afforded 17.3 g. of product which crystallized from petroleum ether (b.p. 30–60°) as small white needles (16.8 g., 44% yield, m.p. 46.5–49°). Two additional recrystallizations of this product afforded 13.6 g. of 2-carbethoxyindene, m.p. 48.8–50° (reported melting point is 50°).[27]

Anal. Calcd. for $C_{12}H_{12}O_2$: C, 76.57; H, 6.43. Found: C, 76.92; H, 6.73.

Reaction of 2-carbethoxyindene, chloroform and potassium t-butoxide. Benzene was removed (at room temperature) from the brilliant blue mixture obtained from 2-carbethoxyindene (13.60 g., 0.0723 mole), potassium *t*-butoxide (0.031 mole), chloroform (2.87 g., 0.024 mole), and benzene (16 ml.). A portion (16.9 g.) of the bluish black residue (21.1 g.) was dissolved in benzene (7 ml.) and chromatographed on alumina (200 g.), using petroleum ether (60–68°) as developer and eluant. A viscous clear blue oil (6.22 g.) was obtained from the first 600 ml. of eluant. This oil was chromatographed again and the crystalline and oily products were processed by recrystallization from petroleum ether; three white crystalline products were isolated in low yield: (A) unchanged 2-carbethoxyindene (m.p. 48–50°), (B) solid B (less soluble in petroleum ether than C), m.p. 95–96°, (C) solid C, m.p. 80–81°.

Anal. Calcd. for $C_{12}H_{12}O_2$: C, 76.61; H, 6.43; mol. wt., 188. Found: Solid B; C, 76.72; H, 6.43; mol. wt., (benzene) 254, 218. Solid C; C, 77.18; H, 6.30; mol. wt. (benzene) 300.

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[CONTRIBUTION FROM THE NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES, NATIONAL INSTITUTES OF HEALTH, PUBLIC HEALTH SERVICE, U. S. DEPARTMENT OF HEALTH, EDUCATION AND WELFARE]

On the Mechanism of Oxidation of *o*-Quinone by Hydrogen Peroxide[1,2]

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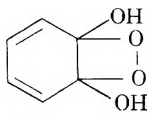
For the hydroperoxide, formed by the action of anhydrous ethereal hydrogen peroxide on *o*-quinone in chloroform solution, structure VIII is suggested which makes it a derivative of *o*-quinone dimer (IV). The latter has been crystallized and its structure proven by rearrangement to the catechol V, which was characterized by its phenazine derivative VI. The products arising from acid- and base-catalyzed rearrangements and by hydrogenation of the hydroperoxide VIII were studied chromatographically (Fig. 1 and 2), electrophoretically (Fig. 3) and chemically (Chart I). A major product, obtained in the base-catalyzed rearrangement of VIII and in the oxidative cleavage of *o*-quinone dimer (IV) by hydrogen peroxide, is also present in the mother liquors of VIII; it is 2,3,6-tricarboxy-4-cyclohexeneacrylic acid X which was converted by partial hydrogenation and oxidation to an epimer (presumably XVa or b) of cyclohexane-1,2,3,4-tetracarboxylic acid. By reduction of the hydroperoxide VIII with Lindlar catalyst a phenolic (or diosphenolic, *cf.* IX) compound $C_{12}H_{12}O_6$ was obtained which could be converted *via* its hexahydro derivative XII to 2,3,6-tricarboxycyclohexanepropionic acid (XI), the hydrogenation product of X.

The mechanism of the enzymatic oxidation of catechol to *cis,cis*-muconic acid (III) by pyrocatechase,[4] has been discussed in terms of an intermediate peroxide II or its cyclic tautomer XVII.[5] The enzymatic intermediate, be it II or XVII, was directly derived from catechol and oxygen, thus rul-



XVII

(1) This paper is a contribution in honor of Lyndon F. Small, former Editor of the Journal.

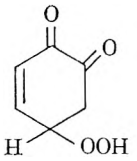
(2) Oxidation Mechanisms. XX. Preceding papers in this series, *cf.* ref. 5 and *J. Am. Chem. Soc.*, **79**, 3191 (1957).

(3) Present address, Research Department, Merck Sharp and Dohme, Rahway, N. J.

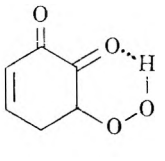
(4) O. Hayaishi, M. Katagiri, and S. Rothberg, *J. Am. Chem. Soc.*, **77**, 5450 (1955).

(5) O. Hayaishi, A. A. Patchett, and B. Witkop, *Ann.*, **608**, 158 (1957). Corrections should be made for some typographical error in the experimental part, p. 166, as follows: line 18: molecular weight of peroxide $(142.1)_2$; lines 20 and 36: Tetracarbonsäure $C_{12}H_{12}O_8$; line 31: Tetracarbonsäure $C_{12}H_{16}O_8$.

ing out an alternate pathway proceeding *via* *o*-quinone (I). Attempting the synthesis of such intermediate peroxides derived from *o*-quinone, we studied the action of hydrogen peroxide on *o*-quinone in the absence of catalytic agents. Peracids oxidize *o*-quinone to *cis,cis*-muconic acid, whose transformation products, rather than precursors, have been observed in this reaction.[6] An intermediate such as the hydroxyhydroperoxyketone II has so far not been noticed. We investigated the action of hydrogen peroxide in dry organic solvents. This reagent is capable of adding to carbonyl groups in ketones and aldehydes to yield a variety of peroxidic substances.[7] Whereas the simplest addition product of H_2O_2 to a ketone, the peroxyhydrate > C(OH)OOH is apparently not observed, a few cases are known where α,β-diketones add ethereal H_2O_2 to give compounds which have been formulated as hydroxyhydroperoxides derived, *e.g.*, from alloxan[8] and dimethyl diketosuccinate.[9] The system *o*-quinone and hydrogen peroxide theoretically might undergo 1,4- or, less likely, 1,6-Michael addition of hydrogen peroxide to give the intermediate hydroperoxides XVIII and XIX, analogous to similar additions in *o*-quinone chemistry.[10] 4,5-Double addition has been reported with ethyleneimine.[11]



XVIII



XIX

Special conditions for the oxidation had to be observed: a 1.5 molar quantity of dry ethereal hydrogen peroxide[7] at 0° was added to a large quantity of chloroform containing one mole of *o*-quinone. Since hydrogen peroxide is not particularly soluble in chloroform a dispersion of what we assume to be fine droplets of concentrated hydrogen peroxide resulted when the ethereal hydrogen peroxide and the chloroform were mixed. The oxidation was allowed to proceed at −5° for about fifteen hours. An insoluble crystalline hydroperoxide (15%) was then collected and the reaction mixture was further worked up, as described previously,[5] to yield *cis,cis*-muconic acid (5–15%) and a tetracarboxylic acid, $C_{12}H_{12}O_8$ (20–25%) with a total balance of isolated products of 40–50%.

When it was discovered that the hydroperoxide could not be converted to *cis,cis*-muconic acid, either by enzymatic or by chemical means, the purely chemical and structural aspects eclipsed the biochemical problem.

Structures XVIII and XIX (expected λ_{max} 255, *cf.* quinone dimer IV), resulting from Michael addition could be ruled out for the hydroperoxide (λ_{max} 230, ϵ 8300). Furthermore, such structures could have gone to the corresponding hydroxyquinones, *e.g.*, to hydroxy-*p*-quinone (from XVIII), a precursor of humic acid,[12] or 3-hydroxy-*o*-quinone (from XIX), a precursor of purpurogallin,[13] neither of which was observed. Various mild hydrolytic and reductive conditions, led to C_{12}-compounds, among them the tetracarboxylic acid, $C_{12}H_{12}O_8$, which is also isolable from the mother liquors of the peroxide. Assuming, in the simplest case, that the hydroperoxide itself was a C_{12}-compound, we suspected dimerization (or polymerization) of *o*-quinone to antecede oxidation by hydrogen peroxide.

In his classical investigations of *o*-quinone, Willstätter[14] had isolated a yellow decomposition product of *o*-quinone which he believed to be dimeric, although no molecular weight was reported. Later workers have occasionally encountered it[15] but gave no proof for its molecular weight and structure. We prepared some of the material in very small yield by refluxing a dry ethereal solution of *o*-quinone and recrystallizing the insoluble precipitate from acetone. The compound formed bright yellow crystals, m.p. 194–196°, and gave a molecular weight of 218 (Rast, calculated 216). In analogy to the structure of a number of dimeric substituted *o*-quinones[16] and *o*-quinonedibenzimides,[17] *o*-quinone dimer may be formulated as IV. The spectral data are in agreement with this structure.

The ultraviolet absorption at 254 mμ (ϵ 7500) compares favorably with a value of 252 (log ϵ 3.95) for the analogous dimer of 4,5-dimethyl-*o*-quinone.[18] In support of the Diels-Alder structure for the *o*-quinone dimer was its mild acid-catalyzed rear-

(6) J. Böeseken, *Proc. Acad. Sci. Amsterdam*, **35**, 750 (1932); J. A. Elvidge, R. P. Linstead, B. A. Orkin, P. Sims, H. Baer, and D. B. Pattison, *J. Chem. Soc.*, 2228 (1950).

(7) A. V. Tobolsky and R. B. Mesrobian, *Organic Peroxides*, Interscience, New York, 1954, p. 44; R. Criegee, in Houben-Weyl, *Methoden der Organischen Chemie*, Georg Thieme Verlag, Stuttgart, Vol. 8, 1952, p. 44.

(8) B. Witkop, S. Goodwin, and T. W. Beiler, *J. Am. Chem. Soc.*, **76**, 5813 (1954).

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(17) R. Adams and J. W. Way, *J. Am. Chem. Soc.*, **76**, 2763 (1954).

(18) L. Horner and K. Sturm, *Ann.*, **597**, 1 (1955).

rangement to a catechol (V) and the preparation of a phenazine (VI) which gave a positive ferric chloride test.

By oxidation of *o*-quinone dimer (IV) with hydrogen peroxide in chloroform at −5° for one week a good yield (~80%) of the tetracarboxylic acid $C_{12}H_{12}O_8$ was obtained. Unfortunately, *o*-quinone dimer (IV) was very insoluble in this mixture, and the reaction had to be continued for a much longer time than for *o*-quinone itself. Hydroxyhydroperoxy intermediates, which hardly could have survived these extended conditions, could not be isolated. The structure which we propose for the hydroperoxide has to rest, therefore, on indirect evidence rather than on a direct synthesis.

The $C_{12}H_{12}O_8$ acid is a tetracarboxylic acid which shows only end absorption in the ultraviolet. It was characterized as its tetrabenzhydryl ester and by conversion to a tetrahydro derivative whose chromatographic behavior is shown in Fig. 1, column 1. The derivation of this acid from *o*-quinone dimer and the available data permit its structural assignment as X.

Fig. 2 summarizes the chromatographic data which we obtained in an attempted conversion of

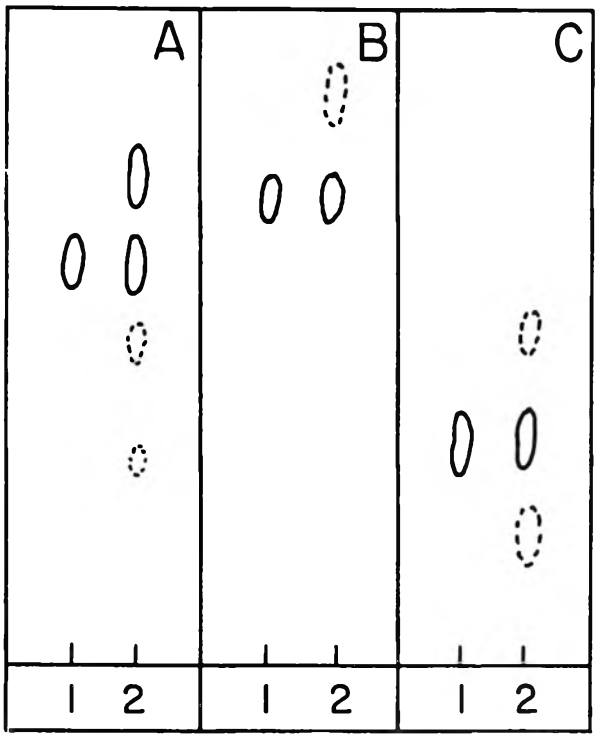


FIG. 1. SOLVENT SYSTEMS: (A) Phenol formic acid-water (120 g: 1.6 cc: 40 cc.), R_F value of 0.6; (B) *sec*-butanol-formic acid-water (75:15:10), R_F 0.7; (C) 99% of a mixture of 2 pts. of methanol, 1 part of benzene, 1 part of *n*-butanol and 1 part of water, and 1% of a 15% aqueous ammonia solution, R_F value 0.3.

1. Analytically pure tetrahydro tetracarboxylic acid XI, m.p. 211–213°; 2. Oxidation mixture from dimethyl ester of XII with periodic and peracetic acid followed by hydrolysis. The spot in solvent system A, in a separate experiment not recorded here, was eluted and rechromatographed in systems B and C to give spots identical with XI.

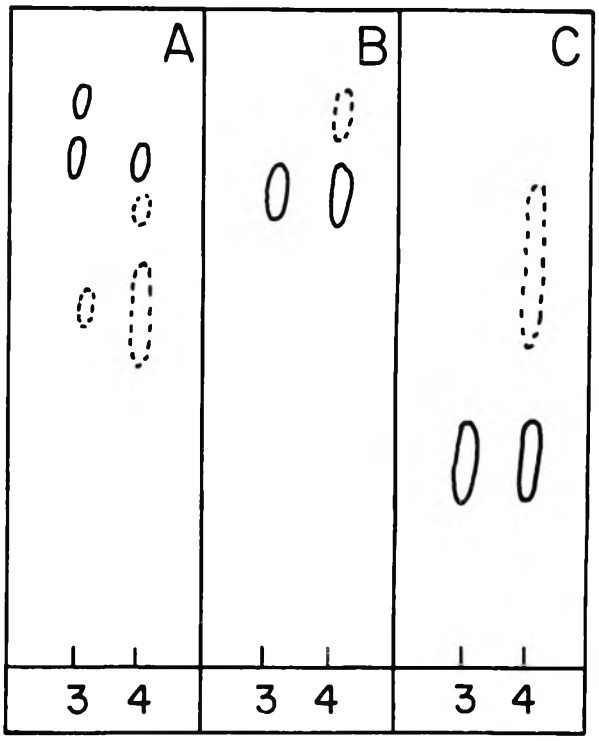
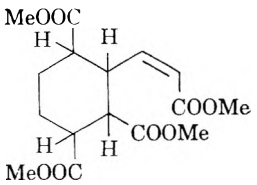


FIG. 2. THE SOLVENT SYSTEMS A, B, C, ARE THE SAME AS IN 1. The products obtained by acid hydrolysis of the tetramethyl ester of XVa are shown under 3, the oxidation products resulting from nitric acid oxidation of the partial hydrogenation product from X are shown under 4.

the acid X to a known cyclohexane-1,2,3,4-tetracarboxylic acid. In order to increase the differential reactivity of the double bonds for the purpose of partial hydrogenation, acid X was converted to its oily tetramethyl ester. The reduction of this ester was stopped after the uptake of one mole of hydrogen. Presumably a considerable quantity of the dihydroester XXI was then in hand. Vigorous oxidation of this ester with refluxing nitric acid, followed by partial purification *via* the (mono) anhydride, led to an acid mixture, one of whose R_f values was identical with one of the two acids derived by acid hydrolysis of authentic tetramethyl *trans-cis-trans*-cyclohexane-1,2,3,4-tetracarboxylate, (XVa, m.p.

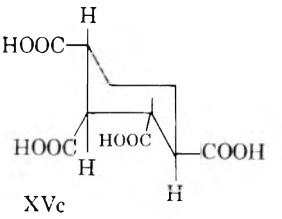


XXI

(19) We are greatly obliged to Professor Kurt Alder for his kind donation of samples of this ester as well as of the all-*cis*-acid XIV, and for information on the epimerization of XVa to the *all-trans*-acid by acid. The acid (XIV) has been described: K. Alder and H. Vagt, *Ann.*, **571**, 153 (1950) and E. H. Farmer and F. L. Warren, *J. Chem. Soc.*, 899 (1929). The acid XVa and its epimers are described in Dipl. Arbeit of R. Reeber, Cologne 1949; Diss. Cologne 1951.

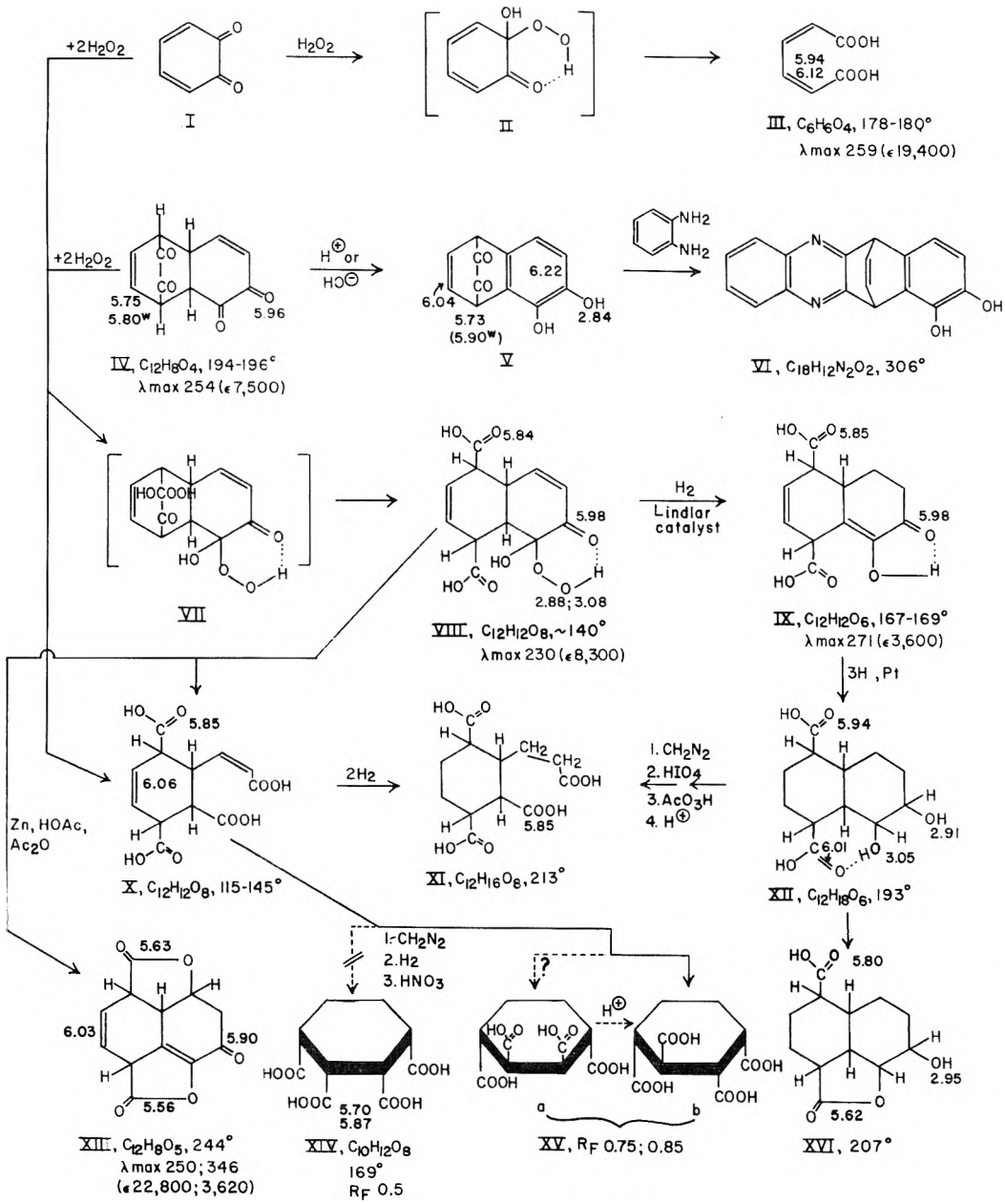
71°).[19] This identity of one of the degradation products with a cyclohexane-1,2,3,4-tetracarboxylic acid is a welcome confirmation for the proposed structure X. No stereochemical assignments for X are made at this point in view of the appearance of *two* spots in the chromatogram of the hydrolyzate of the tetramethylester of XVa.

It was unfortunate that the acid hydrolyzate of authentic tetramethyl *trans-cis-trans*-cyclohexane-1,2,3,4-tetracarboxylate gave two spots. We feel that the conditions were sufficient to effect complete hydrolysis and conclude that epimerizations in this series vitiate steric correlations. The epimerization of the *trans-cis-trans* cyclohexane-1,2,3,-4-carboxylic acid (XVa, preferred constellation 2 equatorial, 2 axial substituents) to the *all-trans-epimer* (XVc, 4 equatorial carboxyls) by the action of strong acid is known.[19] It would be expected to lead through XVb (3e, 1a carboxyl).



XVc

With a knowledge of structure X for the $C_{12}H_{12}O_8$ acid, structure VIII for the hydroperoxide may be envisaged. The spectral data (Chart I) for the hydroperoxide are in agreement with such a structure. Recrystallization of the hydroperoxide was not possible, but the analytical values for the crude



material were close to those calculated for $(C_6H_6O_4)_2$. Titration with base furnished a neutralization equivalent of 136 (theor. 142). The peroxidic nature was evidenced by the liberation of I_2 from acidified KI, by the liberation of oxygen with lead tetraacetate, and by decomposition by mechanical force or by heat. One of the infrared bands coincides with the —OOH band at 2.88.[20] An iodometric determination of the active oxygen content gave a value of 5.7% (theor. 5.6%). An alternative dihydroperoxide formulation VII for the peroxide VIII was also considered. It necessitates the assumption that the hydroperoxide function, derived from the bicyclic diketone system, rearranges rapidly to a diacid in the course of the determination of both neutralization equivalent and active oxygen content. We prefer the simpler explanation that the hydroperoxide as isolated is indeed VIII, and VII its labile nonisolable precursor. The 5.84 μ band in the hydroperoxide, which belongs to the carboxyls, is about twice as intense as the conjugated ketone band at 5.98 μ, as might be expected for structure VIII.

Attempted rearrangement of the hydroxyhydroperoxide VIII under various solvolytic conditions has been briefly studied. Under *acidic conditions* overnight there is little change in the neutralization equivalent and in the active oxygen titer; however, a *new* phenolic substance (m.p. 192–194°), not identical with IX (m.p. 169°), is formed, although the latter gives a major spot on the pherogram (Fig. 3) in an identical position. On the other hand, dilute aqueous *base* at room temperature, led to a pronounced decrease in the neutralization equivalent of such solutions. After twenty-four hours, the active oxygen content had dropped to virtually zero and the increased alkali consumption corresponded very closely to that expected for the formation of two additional carboxyls. Electrophoretic analysis with the Wieland-Pfleiderer pherograph[21] (Fig. 3) showed that the product was the tetracarboxylic acid X unaccompanied by the acid formed under acidic conditions. Acid- and base-catalyzed oxidative cleavages of diketones by hydrogen peroxide are well-known reactions. Anhydride formation has been observed under acid catalysis.[22] Authentic X, as pure as it can be obtained by repeated recrystallization, shows a contaminant, presumably the C2-epimer or the geometric *trans*-isomer of the acrylic acid group.

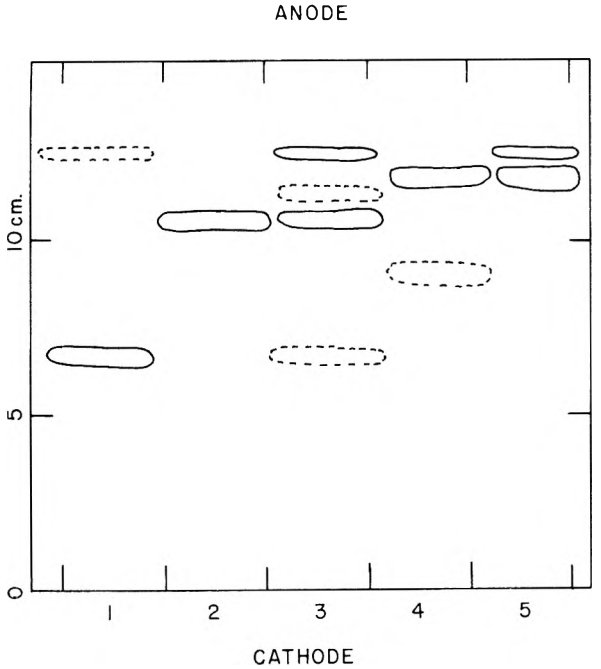
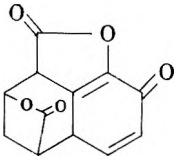


FIG. 3. SEPARATION OF THE HYDROPEROXIDE VIII AND ITS TRANSFORMATION PRODUCTS IN AN ELECTRIC FIELD OF APPROXIMATELY 50 VOLTS PER CM., OVER A PERIOD OF 65 MINUTES IN BUFFER pH 6.5 (PYRIDINE ACETIC ACID WATER 100:10:890) IN A PHEROGRAPH ACCORDING TO WIELAND AND PFLEIDERER. The spraying agent was ammoniacal bromophenol blue. 1. Hydroperoxide VIII in aqueous solution. 2. Hydroperoxide in 5 N hydrochloric acid after twelve hours at 5°. 3. Dicarboxylic acid $C_{12}H_{12}O_6$ (IX). 4. Hydroperoxide, after standing in 1 *N* sodium hydroxide for 12 hours at 5°. 5. Tetracarboxylic acid $C_{12}H_{12}O_8$(X).

Two further substances were obtained in reductions of the hydroperoxide VIII. One is a dilactone formed by the action of zinc in glacial acetic acid on the hydroperoxide. It is isolated in very poor yield by sublimation after the crude reduction product has been treated with acetic anhydride and sodium acetate. On the basis of its composition ($C_{12}H_8O_5$) molecular weight (235, theor. 232), ultraviolet [λ_{max} 259 mμ (ϵ 22,800) and 346 mμ (ϵ 3620)] and infrared bands [at 5.56, 5.63, 5.90, and 6.03 (w) μ] and its neutral character, structures XIII or XXII are considered not unreasonable suggestions.



XXII

A second substance obtained in modest yield in the reduction of the hydroperoxide using Lindlar[23] catalyst has the composition $C_{12}H_{12}O_6$. The material is a dibasic acid with a neutralization equivalent 129 (theor. 126), molecular weight 259 (theor. 252) and major infrared bands at 2.95, 5.86, 5.97, and 6.04 (w) μ (Nujol). There was no absorption in the aromatic region between 6.04 and 6.85 μ. Its ultraviolet spectrum showed λ_{max} 271 mμ (ϵ 3600), shifted by base to 318 mμ (ϵ 2540). This acid on paper responded to several sprays: it reduced ammoniacal silver solution at room temperature,

(20) O. D. Shreve, M. R. Heether, H. B. Knight, and D. Swern, *Anal. Chem.*, **23**, 282 (1951).

(21) Th. Wieland and G. Pfleiderer, *Angew. Chem.*, **67**, 257 (1955).

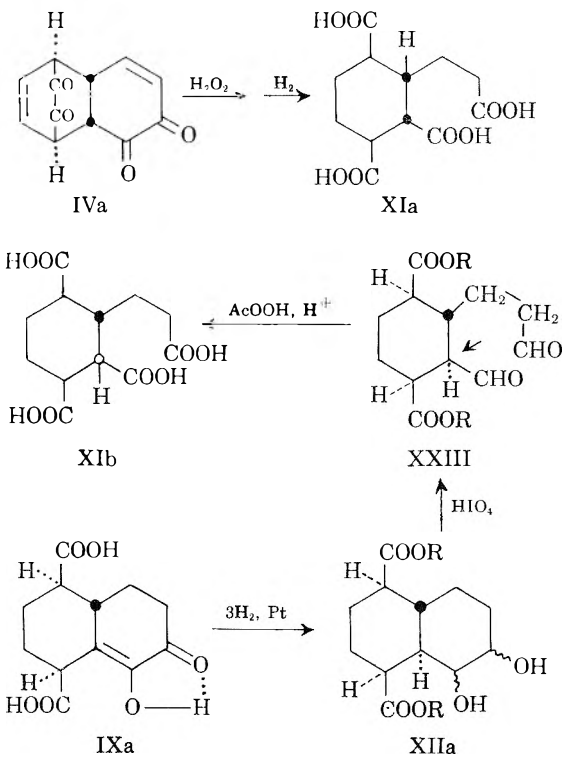
(22) J. E. Leffler, *J. Org. Chem.*, **16**, 1785 (1951).

(23) H. Lindlar, *Helv. Chim. Acta*, **35**, 446 (1952).

gave a weak greyish purple color with 1% $FeCl_3$ in 0.1*N* HCl, showed a greenish-grey color on treatment with phosphomolybdic acid followed by ammonia gas, and yielded an orange spot with diazotized sulfanilic acid. No phenazine could be prepared, but an oily red precipitate resulted after about ten minutes from the reaction (room temperature) with ethanolic 2,4-dinitrophenylhydrazine in the presence of sulfuric acid. The enolic properties of this compound seem to be best explained by the diosphenol structure IX because of the chemical and infrared evidence for carbonyls in the substance other than those belonging to the carboxyls. The shift of the ultraviolet absorption by base to higher wave lengths but lower intensity is also generally taken to be evidence for a diosphenol chromophore.[24,25] However, the low intensity[25] of the 271-mμ band is more like that of a phenol than that of a diosphenol. In addition, we were unable to find precedent for the reduction of the hydroperoxide VIII to yield a diosphenol such as IX. The substance was further characterized by its dibenzhydryl ester which gave a positive $FeCl_3$ test. The infrared bands of this ester were at 2.91, 5.76, 5.95, and 6.01 (w) μ.

A correlation with the tetracarboxylic acid X was achieved by reduction of the $C_{12}H_{12}O_6$ acid to its hexahydro derivative $C_{12}H_{18}O_6$ XII of unspecified configuration. This substance gave no $FeCl_3$ test. On treatment with hydrobromic in glacial acetic acid it formed a lactone XVI. The oily dimethyl ester was oxidized by periodic acid at 80° for ten hours, followed by peracetic acid oxidation at 80° for one hour and hydrolysis of the ester groups with 5*N* hydrochloric acid. Chromatography of the ether-soluble acidic fraction gave material showing R_f values in three different solvent systems (Fig. 1) identical with those of the tetrahydro acid XI obtained from X.

Stereochemical considerations. If one applies the "*endo*-rule"[22] for Diels-Alder reactions of cyclic dienes the configuration of *o*-quinone dimer IV should be expressed by IVa. Accordingly, the tetrahydrotetracarboxylic acid XI would be XIa. On the other hand, acid XI was also identified by paper chromatography to result from XII by a number of steps whose steric course is not certain. For instance, the uptake of hydrogen by IXa from the less hindered side may lead to XIIa. The glycol XIIa, on the other hand, may, at the stage of the dialdehyde (XXIII), epimerize again (arrow). The position of the 2-carboxy group in XIb (open circle) must be left open. The same uncertainty attaches to the conversion of the dehydro precursor of XIa to XVa or XVb.



EXPERIMENTAL[27]

Acid- and base-catalyzed rearrangements of o-quinone-dimer hydroperoxide (VIII). *A. Neutral conditions.* The hydroperoxide VIII[5] (20.3 mg.), containing 5.7% active oxygen (calcd. 5.62%), was dissolved in 10 cc. of water and titrated with 0.0321*N* NaOH to the phenolphthalein end point. The found neutralization equivalent was 127 (other determination on fresher hydroperoxide sampler gave 136, calcd. 142). After standing overnight (17 hr.) there was added to this neutral solution excess potassium iodide and 4 cc. of 3.6*N* H_2SO_4. The iodine was liberated slowly; the reaction mixture was titrated after standing for 10 min. The total volume of 0.0228*N* $Na_2S_2O_3$ solution was 5.6 cc., equivalent to 5.04% active oxygen.

B. Basic conditions. The hydroperoxide VIII (22.6 mg.) was dissolved in 10 cc. of water and neutralized as before (needed 5.64 cc. of 0.321 NaOH). Then was added 1.28 cc. of base (0.0321*N* NaOH) and left standing for 24 hr. Back titration with HCl to a phenolphthalein end point required 9.9 cc. of 0.0207*N* HCl. Considering this and the amount of excess alkali added, it is evident that 0.57 mmole of alkali was consumed after the initial neutralizations. The sample represented 0.079 mmole (22.6/286), hence each mole consumed two additional moles of alkali to form the sodium salt of the tetracarboxylic acid. The pherogram (Fig. 3) of an alkaline solution of the hydroperoxide was made in the same way: after neutralization and evaporation to dryness the rearrangement product was taken up in buffer *p*H 6 (pyridine-water-HOAc) and chromatographed as indicated in Fig. 3. The major product was at the same spot as the tetracarboxylic acid X.

C. Acid catalysis. The hydroperoxide VIII (23.2 mg.) was dissolved in 10 cc. of water and left overnight with 10 cc. of 0.0207*N* HCl. The titration of 0.0227*N* NaOH to the phenolphthalein end point gave a neutralization equivalent of 145. The active oxygen content of this solution amounted to 3.1% of the sample weight. The pherograph showed only one single spot (Fig. 3) at the same place where the di-

(24) D. Lavie, *Chemistry & Industry*, 466 (1956).

(25) D. H. R. Barton and J. F. Eastham, *J. Chem. Soc.*, 424 (1953).

(26) M. C. Kloetzel, *Org. Reactions*, **4**, 10 (1948).

(27) All melting points are corrected.

carboxylic acid IX has a major spot. Since IX could not possibly be formed in this rearrangement, the rearrangement was done on a preparative scale by evaporating the solution of 20 mg. of the hydroperoxide in 4 cc. of 4*N* HCl slowly in a desiccator and isolating the solid residue which could be washed and freed of colored impurities by repeated extraction with cold ether to yield a colorless crystalline powder, m.p. 192–194° (sintering 188°, clear, slightly yellow melt with bubbles at 200°). λ_{max}^{EtOH} 290 mμ (ε 2210); λ_{max}^{Nujol} 5.63, 5.84 μ; no bands between 6.0–6.85 μ. This compound gave a poor ferric chloride test (lactone involving one phenolic hydroxyl?); the ether washings gave a distinct green color with $FeCl_3$.

Dilactone (XIII or XXII) *by the reduction of the hydroperoxide* VIII *with zinc dust.* Glacial acetic acid (15 ml.) was stirred at 60–70° and to this was added in small portions during 5 min. a finely ground mixture of 1.00 g. of the peroxide and 6.00 g. of zinc dust. Fifteen min. after the addition was complete, the solution was filtered and concentrated to dryness. Acetic anhydride (7.5 ml.) and 0.75 g. of fused sodium acetate was added and this acetylating mixture was heated on the steam bath for 3 hr. with the exclusion of moisture. Much of the excess acetic anhydride was removed *in vacuo* and the residue was treated with 0.5*N* HCl and extracted with ethyl acetate. The dried solution left a reddish brown oil which was extracted with 15 ml. of hot benzene. The benzene solution on cooling deposited 0.22 g. of an orange powder. This material sublimed very slowly in high vacuum at 200° to yield a colorless oil and a bright yellow powder. The latter could be recrystallized from methanol to yield 0.018 g. of yellow, cotton-like crystals, m.p. 244°. The major infrared bands were at 5.56, 5.63, 5.90, and 6.03 μ (KBr pellet) and in the ultraviolet λ_{max} 250 mμ (ε 22,800) and 346 mμ (ε 3620) in ethanol, shifted by base to λ_{max} 248 mμ (ε 18,400), 305 mμ (ε 1980) and 345 mμ (ε 2160). A Rast determination in camphor gave a molecular weight of 235, calculated 232.

Anal. Calcd. for $C_{12}H_8O_6$: C, 62.07; H, 3.47. Found: C, 61.79; H, 3.09.

o-Quinone dimer (IV). 1.0 g. *o*-Quinone[28] was refluxed in 400 ml. of dry ether with anhydrous magnesium sulfate for 8 hr. At the end of this time the magnesium sulfate and precipitated material was filtered off and extracted with a total of about 250 ml. of hot acetone. This filtered yellow acetone solution was concentrated until crystals of *o*-quinone dimer appeared. The yield was 0.061 g. of shining yellow plates of m.p. 192–193°. A sample recrystallized from acetone showed m.p. 194–196°. The ultraviolet spectrum was characterized by λ_{max} 254 (7500) and in the infrared bands were at 5.68 (w), 5.75, 5.80 (w), 5.96, and 6.17 (w) μ. Its molecular weight by the Rast method was 218.

Anal. Calcd. for $C_{12}H_8O_4$: C, 66.67; H, 3.73. Found: C, 66.54; H, 4.00.

Rearrangement by acid. When this material was warmed with ethanolic HCl for several minutes on the steam bath and then taken to dryness, the prominent infrared bands were 2.84, 5.73, 5.90 (w), 6.04 (w), and 6.22 (w).

Phenazine derivative VI *of rearranged o-quinone dimer* (V). *o*-Quinone dimer (0.020 g.) was heated on the steam bath with 0.5 ml. of acetic acid and 0.005 g. of anhydrous sodium acetate for 5 min. *o*-Phenylenediamine (0.015 mg.) was then added in 0.5 ml. of methanol. Gentle heating was continued for 30 min. with occasional replenishment of the methanol. Crystallization occurred during this period and was allowed to proceed at room temperature for 3 hr. The crude phenazine weighed 0.019 g. and was of m.p. 304–306° (dec.). With anhydrous $FeCl_3$ in diethylene glycol dimethyl ether (diglyme)[29] it gave a greenish black color changing to deep blue on the addition of a small amount of pyridine. The infrared showed no carbonyl absorption.

Anal. Calcd. for $C_{18}H_{12}O_2N_2$: C, 74.99; H, 4.20; N, 9.72. Found: C, 75.10; H, 4.50; N, 9.31.

Tetracarboxylic acid X *by the oxidation of o-quinone dimer.* *o*-Quinone dimer (IV, 0.100 g.) was added to a suspension of ethereal H_2O_2 (1.5 × theoretical for 2 moles) in 10 ml. of chloroform. The dimer would not dissolve in this mixture and, therefore, the reaction had to be conducted at −5° for 1 week before it had gone to completion. At the end of this time, the chloroform was decanted and evaporated to dryness leaving 0.024 g. of an oil which was shown by paper chromatography to be a mixture of the tetracarboxylic acid X and a second as yet unidentified acid. Left behind in the original flask after the chloroform had been decanted was an oil which dissolved completely in ether. Evaporation of the ether left a foam weighing 0.102 g. and on crystallization from ether and chloroform an acid was obtained in good yield of m.p. 137–148° which was identical with X by infrared comparison. The identity was confirmed by paper chromatography in three solvent systems: phenol:water:formic acid 75:25:1; 1-butanol:formic acid:water 10:2:15; 1-butanol:benzyl alcohol:water:formic acid 45:45:9:1.

Diacid $C_{12}H_{12}O_6$ (IX, *m.p. 167–169°*) *by the reduction of the hydroperoxide* VIII *with Lindlar's catalyst.* One g. of Lindlar catalyst[23] was prereduced in 150 ml. of ethyl acetate. A fine powder of the hydroperoxide (2.00 g.) was added and the reduction was allowed to go to completion. The uptake of hydrogen was 255 ml. (74% of theory for one —OOH group per molecular weight 142). Evaporation of the ethyl acetate left a foam which was submitted to partition chromatography. The supporting phase was 200 g. of silicic acid moistened with 100 ml. of water. The elution mixture consisted of ether and chloroform (1:1) saturated with water; 175-ml. fractions were collected. A dark colored oil came out in the first two fractions. From the 3rd to the 7th fraction an oil appeared which was recrystallized from ether and cyclohexane. This acidic material weighed 0.410 g. (23%) and had m.p. 160–163°. An analytical sample crystallized from the same solvent mixture showed m.p. 167–169°, molecular weight 259 (Rast) and neutralization equivalent 129. The ultraviolet spectrum showed λ_{max} 271 mμ (ε 3600) in ethanol and 318 mμ (ε 2540) in ethanol with base added. The infrared spectrum showed bands at 2.95, 5.86, 5.97, and 6.04 (w). The substance liberated carbon dioxide from $NaHCO_3$ solution, it gave a black-brown color with $FeCl_3$ in diethylene glycol dimethyl ether[29] with added pyridine[29] and it yielded an oily 2,4-dinitrophenylhydrazone after 5 to 10 min. with 2,4-dinitrophenylhydrazine in ethanol with H_2SO_4 as a catalyst. On paper it became visible by spraying with ammoniacal silver nitrate solution which was reduced instantaneously without warming. A 1% solution of $FeCl_3$ in 0.1*N* HCl produced a weak greyish purple color. A greenish grey color with phosphomolybdic acid developed in an atmosphere of ammonia gas. No crystalline phenazine could be prepared when the acid was heated with *o*-phenylenediamine in acetic acid and methanol in the usual manner. Bismuth oxide in hot acetic acid was reduced to a black precipitate.

Anal. Calcd. for $C_{12}H_{12}O_6$: C, 57.14; H, 4.80. Found: C, 57.07; H, 4.75.

Dibenzhydryl ester. Diphenyldiazomethane in slight excess of 2 moles yielded a dibenzhydryl derivative. The reaction was conducted overnight in a small amount of methanol and ether. Two crystallizations of the crude product from ethyl acetate gave the benzhydryl ester m.p. 182–184° with infrared absorption at 2.91, 5.76, 5.95, and 6.01 μ. The substance gave the same $FeCl_3$ color reaction as the parent acid.

Anal. Calcd. for $C_{38}H_{32}O_6$: C, 78.06; H, 5.52. Found: C, 77.88; H, 5.76.

Hexahydrodicarboxylic acid (XII). Platinum oxide (0.1 g.) was prereduced in 95% ethanol and to this was added 0.100 g. of the dicarboxylic acid (IX) which had been prepared by reduction of the hydroperoxide VIII in the pres-

(28) S. Goldschmidt and F. Graef, *Ber.*, 61, 1868 (1928).

(29) S. Soloway and S. H. Wilen, *Ann. Chem.*, 24, 979 (1952).

ence of Lindlar's catalyst. The hydrogenation was allowed to go to completion. The uptake was 24 cc. (2.5 moles) of hydrogen. After completion of the hydrogenation the solution was filtered and evaporated to dryness and the residual oil was dissolved in ethyl acetate. Addition of chloroform precipitated 0.02 g. of amorphous material. The mother liquor was then crystallized from ethyl acetate and petroleum ether (b.p. 65°) to yield 0.047 g. of the hexahydrocarboxylic acid (XII) as colorless prisms of m.p. 168–170°. The substance showed no ferric chloride test. One more crystallization from the same solvent mixture gave the analytical sample, m.p. 192–194°.

Anal. Calcd. for $C_{12}H_{18}O_6$: C, 55.80; H, 7.03. Found: C, 55.51; H, 7.04.

Lactonization (XVI). A solution of XII in glacial acetic acid containing a drop of concentrated hydrobromic acid (48%) left on evaporation in the desiccator at 20° fine feathery crystals, m.p. 205–207°, at 180° sublimation and transformation to stubby cubes. Although the analysis (found: C, 57.89; H, 6.62) indicated incomplete lactonization or retention of ½ mole of water (dried at 100° *in vacuo*), the infrared spectrum (KBr pellet) showed a strong saturated lactone band at 5.62 μ in addition to a band for COOH at 5.80 μ.

Conversion of the hexahydrodicarboxylic acid (XII, *m.p. 194°*) *to the 2,3,6-tricarboxycyclohexanepropionic acid* (XI). A solution of 70 mg. of the hexahydrodicarboxylic acid XII in 5 cc. of absolute ether was reacted at room temperature with 4 cc. of a 0.2*N* ethereal solution of diazomethane. After completion of the reaction and evaporation to dryness the oily dimethyl ester was taken up in 10 cc. of 50% aqueous dioxane. Three equal portions of this solution were mixed with 3 cc. of an aqueous solution of periodic acid containing 6.8 g. of H_5IO_6 in 100 cc. of water. One portion was kept at 80° for 10 hr. Then 0.5 cc. of glacial acetic acid containing 0.5 cc. of 30% H_2O_2 was added and the reaction mixture was kept at 80° for 1 hr. After evaporation to dryness in a vacuum desiccator the residue was taken up in 3 cc. of 50% aqueous dioxane and heated on the steam bath with an equal volume of 5*N* hydrochloric acid. After evaporation to dryness the residual lacquer was extracted with ether. The ether-soluble material was chromatographed in the following three solvent systems: (*A*) phenol-formic acid-water (120 g.:1.6 cc.:40 cc.), R_f value 0.6; (*B*) 2-butanol-formic acid-water (75:15:10), R_f 0.7; (*C*) 99% of a mixture of 2 parts of methanol, 1 part of benzene, 1 part of 1-butanol, and 1 part of water, and 1% of a 15% aqueous ammonia solution. R_f value 0.3. The spraying reagent used was a weakly ammoniacal solution of 0.5 g. of brom phenol blue in 100 cc. of 95% ethanol. The R_f values of authentic XI were identical (see Fig. 1) in every respect.

Conversion of the tetracarboxylic acid X *to one of the hydrolysis products of tetramethyl trans-cis-trans-cyclohexane-1,2,3,4-tetracarboxylate* (XVa). In order to increase the differential reactivity between the conjugated and the unconjugated double bonds in X the tetramethylester (0.586 g.), obtained as a colorless oil by methylation with excess diazomethane in ethereal solution, was hydrogenated in ethyl acetate using 10% palladium-on-carbon as a catalyst. Within 12 min. 39 cc. of hydrogen (1 mole) had been taken up. There was no clear indication of a break in the rate of hydrogen uptake. The hydrogenation was therefore discontinued at this point. The reaction mixture, after evaporation of the solvent, left 0.6 g. of a colorless oil which was heated with 10 cc. of concentrated nitric acid (d = 1.4) at 150° (oil bath) for 2 hr. until the lively evolution of nitrous gases had subsided. After evaporation to dryness the noncrystalline residue was refluxed in 5 cc. of acetyl chloride for 5 hr. and, after evaporation to dryness, separated into a chloroform-soluble part, containing 124 mg. of a light-colored oil, and a chloroform-insoluble part, soluble in ether, consisting of 165 mg. of a brown oil. The infrared spectrum of the chloroform-soluble fraction showed, in chloroform solution, a hydroxyl band at 2.90μ, anhydride bands at 5.36 and 5.58 μ, and a doublet at 5.79–5.82 μ, indicative of free carboxyls. This material, presumably largely the monoanhydride of a tetracarboxylic acid, was reconverted into the free acid by refluxing in water for 2 hr. After evaporation to dryness the brown residue was extracted with ether. This ether extract was used for chromatographic analysis in three different solvent systems (see above and Fig. 2). One of the two spots in the chromatogram of the hydrolyzate of authentic tetramethylester of XVa was identical with that of the major oxidation product from X. Fractionation of the ether-soluble brown residue using chloroform and ethyl acetate gave a small amount of crystalline material showing a characteristic crystalline transformation into colorless long daggers at 160–180°, m.p. 185–186°, depressed to 181° on admixture with a crystalline product (m.p. 195–197°) obtained by hydrolysis of the tetramethyl ester of XVa by refluxing in dioxane 5*N* hydrochloric acid (1:1) for 6 hr.

Acknowledgment. We are greatly indebted to Dr. K. Freter for generous assistance with the preparation and paper chromatographic analysis of compounds, and to Dr. W. A. Alford for titrations and analyses.

BETHESDA 14, MD.

[CONTRIBUTION FROM THE NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES, NATIONAL INSTITUTES OF HEALTH, PUBLIC HEALTH SERVICE, U. S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE]

Quinuclidines. I. 4-Phenylquinuclidines as Potential Analgesics*

T. D. PERRINE

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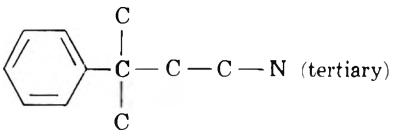
This paper presents the synthesis and structure proof of 4-phenylquinuclidine, the first 4-arylquinuclidine to be reported. The physical and physiological properties are briefly discussed, and several related substances are described.

With few exceptions, substances which are potent analgesics[1] have the common partial structure exemplified in I.

4-Phenylquinuclidine (II) has such a structure. We have been intrigued by the symmetry of II, and felt that examination of it and related compounds might lead to substances of pharmacological interest. Physiological activity in the quinuclidine

* This paper is a contribution in honor of Lyndon F. Small, former Editor of the Journal.



I

series is, of course, not without precedent. The cinchona alkaloids are examples. Of more interest is the recent finding by Sternbach and Kaiser[2] that esters of 3-quinuclidinol show striking physiological action compared with the esters of other amino alcohols.

We have synthesized II as well as its 3-keto (III), 3-hydroxy (IV), 3-acetoxy (Va), and 3-propionoxy (Vb) derivatives. These substances are in the process of being tested for analgesic activity in mice.[3]

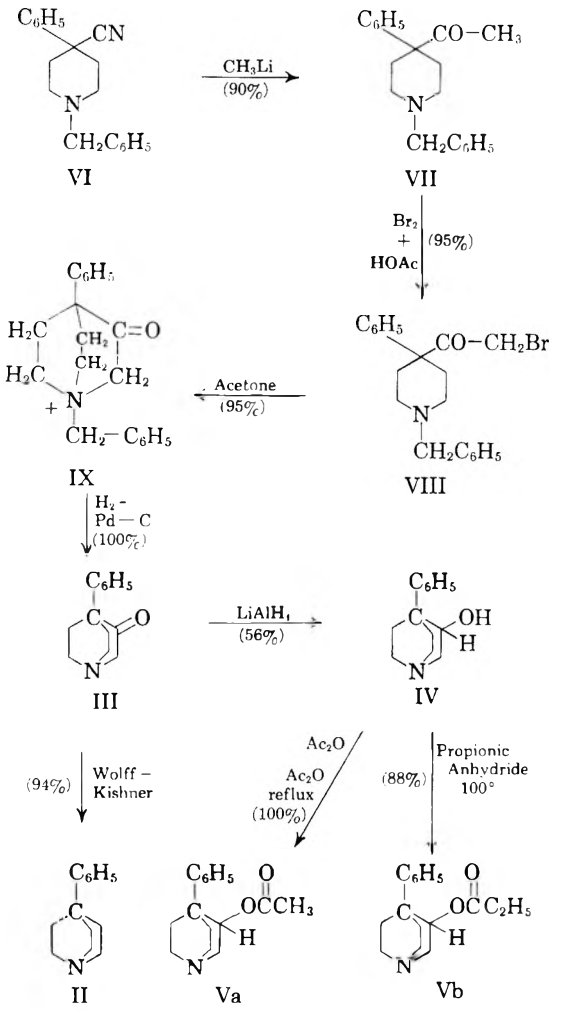


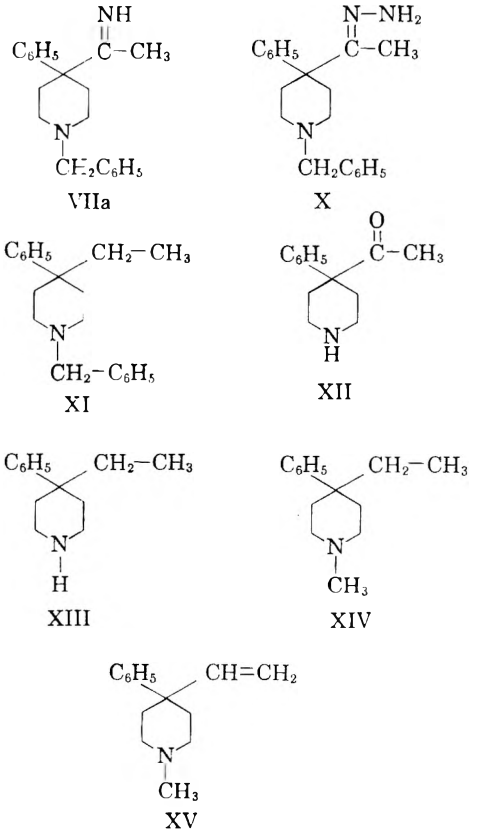
FIGURE 1.

To date we have had only preliminary reports on compounds II and III, both of which show analgesic action. II is apparently quite toxic.

Syntheses were accomplished by the reaction sequence outlined in Fig. 1 (yields being given in parenthesis).

The reaction of 1-benzyl-4-cyano-4-phenylpiperidine (VI)[4] with methyllithium led without complication to the imine of 4-acetyl-1-benzyl-4-phenylpiperidine. Imines of this type seem to be quite stable, and this one was obtained analytically pure by vacuum sublimation followed by recrystallization from ether–petroleum ether. The infrared spectrum shows a strong C=N absorption at 1639 cm.$^{-1}$ Refluxing 5 hr. with 2.5*N* HCl is sufficient to decompose the imine with formation of the expected ketone (VII).[5]

When compound VII was reduced with hydrogen and a palladium-charcoal catalyst in acidic me-



dium, toluene was evolved, and a quantitative yield of 4-acetyl-4-phenylpiperidine was obtained. Attempted bromination of this material in dioxane led to recovered starting material. However, bromination of VII·HCl in glacial acetic acid led to 1-benzyl-4-bromoacetyl-4-phenylpiperidine (VIII)

(1) H. Isbell [*Bulletin on Narcotics*, **VII**, 5 (1956)] discusses the fact that to date it has not been possible to separate analgesic action from addiction liability, and suggests that this may be the consequence of fashioning analgesics after structure I. He proposes that analgesic action be sought in entirely different structures, utilizing new criteria of analgesic action.

(2) L. A. Sternbach and S. Kaiser, *J. Am. Chem. Soc.*, **74**, 2219 (1952).

(3) These tests are being conducted by Dr. N. B. Eddy and associates at this Institute and will be reported in more detail elsewhere.

(4) We are greatly indebted to Dr. C. M. Suter, of the Sterling-Winthrop Research Institute for a very generous supply of compound VI.

(5) Compound VII shows no analgesic activity.

hydrobromide.[6] When this was converted to the base and dissolved in acetone, 1-benzyl-3-keto-4-phenylquinuclidinium (IX) bromide separated almost immediately.

Hydrogenation of the quaternary bromide in aqueous methanol using 10% Pd-charcoal catalyst required 1 hour or less and led to a quantitative yield of 3-keto-4-phenylquinuclidine (III). Compound III was then reduced by the Huang-Minlon modification[7] of the Wolff-Kishner process to II, and by lithium aluminum hydride to carbinol IV. The latter reaction was not as smooth as one might have expected and the yield of pure IV was only 56%. The secondary product, which had in some degree the properties of a quaternary hydroxide or zwitterion (amorphous gum, very soluble in water, difficulty extractable by chloroform) has not been further examined. Acylation of IV was effected by heating with the appropriate acid anhydrides to give esters Va and Vb.

The structures assigned to the compounds herein reported rest largely on the methods used in their synthesis and their further reactions. Both seem fairly straightforward. The method of forming the bridgehead (VIII → IX) has not previously been reported in the quinuclidine series, although it is fairly similar to the 4 β-bromoethylpiperidine ring closure[8] used for quinuclidine itself. The facile ring closure of 1,4-dimethylpiperazine with ethylene bromide to form the quaternary salt[9] is also of interest in this connection. The infrared absorption[10] of the carbonyl function at 5.77 μ in III as compared with 5.85 μ for 4-acetyl-4-phenylpiperidine (XII), 5.87 μ for VII, 5.86 μ for VII·HCl, and 5.82 μ for VIII·HBr indicates a constraint in bond mobility consistent with the assigned structure.

There is no reason to suppose that a rearrangement would occur in the Wolff-Kishner reduction of III[11]. Clemo and Metcalf[12] have reduced 3-keto-quinuclidine to quinuclidine by this process. There is the possibility of acyl cleavage[13] in these reductions, but our anticipation of trouble in this regard was unwarranted: The reduction proceeded smoothly to compound II. Reasonably unequivocal proof of the latter structure was obtained in the Hoffmann exhaustive methylation, when one of the reaction products[14] (XV), after catalytic hydrogenation, proved to be 4-ethyl-1-methyl-4-phenylpiperidine (XIV) identical in all respects with material prepared by the Wolff-Kishner reduction of XII followed by formaldehyde-formic acid methylation. While it may seem to be questionable logic to advance a Wolff-Kishner product as reference material in this case, we find partial vindication in the case of 1,4-dimethyl-4-phenylpiperidine which we have prepared both by the Wolff-Kishner reduction of the 4-aldehyde and by a totally unrelated method starting with β-methylcinnamic ester.[15]

Our work with the 4-phenylquinuclidines has been a delightful experience. Both salts and bases are very stable substances with high non-decomposition melting points[16] and high vapor pressures, subliming readily either at atmospheric pressure or in vacuum. Several of the substances, notably Va and II perchlorate have characteristic, rather pleasant odors.[17] The crystalline forms encountered are especially beautiful, often consisting of large, chunky, perfectly transparent crystals, when the materials are crystallized from solution or sublimed on the hot stage. As we have noted above, the yields are quite satisfactory in almost every instance, and no difficulty has been encountered in bringing the substances to a state of analytical purity.[18]

EXPERIMENTAL[19]

Melting points and elemental analysis of the compounds prepared are given in Table I.

4-Acetyl-1-benzyl-4-phenylpiperidine (VII) *and its imine* (VIIa). A 0.5 molar quantity (156.4 g.) of 1-benzyl-4-cyano-4-phenylpiperidine[4] hydrochloride was converted to the

(6) Formulation of this substance as an α-bromo ketone is supported by the fact that it produces a rather pronounced and long lasting dermatitis, which is accompanied by a marked sensitization of the skin to sunlight. The onset of the dermatitis is quite insidious, and care should be exercised in handling this material.

(7) Ethylene glycol was used as a solvent.

(8) R. Lukes, *et al.*, *Chem. Listy*, **50**, 1624 (1956); *Chem. Abstr.*, **51**, 2779c.

(9) S. M. McElvain and L. W. Bannister, *J. Am. Chem. Soc.*, **76**, 1126 (1954).

(10) Most spectra determinations are by H. K. Miller of this laboratory, who is making an extended survey of these and related compounds which will probably be reported elsewhere, in detail.

(11) D. Todd, *Org. Reactions*, **4**, 378 (1948).

(12) G. R. Clemo and T. P. Metcalf, *J. Chem. Soc.*, 1989 (1937).

(13) E. L. May and E. Mosettig, *J. Org. Chem.*, **13**, 459 (1948).

(14) The other products of the reaction are quinuclidine, identified as its hydrochloride, and a compound which (by analysis) is nearly pure 4-hydroxyethyl-1-methyl-4-phenylpiperidine. The latter exemplifies a rather unusual course for the Hoffmann reaction which is taken by quinuclidine itself.[8] Parenthetically, this alcohol opens up a route to 4-alkyl homologs of pethidine, compounds which are unreported at this time.

(15) Unpublished results obtained in this laboratory.

(16) The physical properties of these compounds lend credence to their formulation as quinuclidines. For example, II melts at 123–125°, III at 157–158°, IV at 199.5°. These high, rather sharp melting points are characteristic of very symmetrical molecules. For example, L. H. Sternback and S. Kaiser [*J. Am. Chem. Soc.*, **74**, 2215 (1952)] report the m.p. 221–223° for 3-quinuclidinol, Clemo and Metcalf[9] give 138° as the m.p. of 3-quinuclidone, while V. Prelog *et al.* [*Ann.*, **32**, 69 (1937)] report 158–159° as the melting point of quinuclidine itself.

(17) When an alcoholic solution of crude III·HBr was concentrated, a rather strong, sweet odor was noted, somewhat reminiscent of vanilla. This has been duplicated to a lesser extent by acidifying dry alcoholic solutions of III with anhydrous acids, and may be due to acetal formation.

(18) An exception to this statement may be found in the case of several of the hydrochlorides, which show considerable tendency to hydrate. Other salts, less soluble in water and other solvents, have given no difficulty in this respect.

TABLE I

DERIVATIVES

Compound	Salt	M.P., °C.	Analysis							
			C		H		N		Halogen	
			Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
II[a]	—	123–125	83.37	83.45	9.15	9.14	7.48	7.34		
	$HClO_4$	271–273	54.26	54.41	6.30	6.23			12.32	12.34
	HCl	>350	69.78	69.68	8.11	8.05			15.85	15.86
	Methiodide	280	51.07	51.12	6.12	6.07			38.55	38.95
III	—	157–158	77.58	77.38	7.51	7.42	6.96	7.15		
	HBr	285–287	55.33	55.07	5.72	5.69			28.32	28.13
	HCl	255–270	65.68	65.83	6.79	6.81				
	Methiodide	189–190	48.99	48.75	5.29	5.14			36.98	37.0
	Semicarbazone	267–268	65.09	65.37	7.02	6.95	21.69	21.92		
IV	—	199.5	76.81	76.52	8.43	8.42	6.89	6.89		
	HCl	339–340	65.12	65.04	7.57	7.38			14.79	14.62
Va	—	92–93	73.44	73.31	7.81	7.74	5.71	5.87		
	$HCl \cdot {}^1/_2H_2O$	275–279	61.95	61.90	7.28	7.34	3.1[b]	2.6[b]	12.20	12.32
Vb	—	60	74.10	74.05	8.16	7.96	5.40	5.23		
	HCl	208–210	64.96	64.73	7.50	7.40	4.74	4.83	11.99	11.61
VII	—	102–103	81.87	82.04	7.90	7.82	4.78	4.97		
	$HCl \cdot 1H_2O$[c]	251–252	69.04	69.13	7.53	7.56	4.03	3.95		
VIIa	—	92–94	82.14	81.89	8.27	8.31	9.58	9.92		
VIII	HBr	Indef.	53.00	52.91	5.11	5.30			35.27	35.45
IX	—	Sublimes								
	Bromide	290–295	64.52	64.48	5.96	6.08			21.47	21.37
	Nitrate	255–256	67.78	67.67	6.26	6.36	7.91	7.91		
X	—	119–121	78.13	78.09	8.20	8.04	13.67	13.63		
XI	HCl	280–287	76.04	75.90	8.30	8.40	4.44	4.66		
XII	HCl	245	65.12	65.14	7.57	7.32	5.84	5.68		
XIII	HCl	210–211	69.16	69.03	8.93	8.80			15.71	15.52
XIV	HCl	228–229	70.12	70.03	9.25	9.21	5.84	5.92	14.79	15.08

[a] Mol. wt. calculated, 187.28; found, 185 (Rast). [b] H_2O, determined *via* $LiAlH_4$. [c] We were unable to obtain VII HCl in its pure anhydrous form. Solvent water is indicated by the hygroscopic nature of the partially dried substance.

base in benzene solution and subsequently dried by azeotropic distillation. To this we added 1 mole of methyllithium in ether. The mixture was let stand 24 hr. and decomposed with ice. The imine (VIIa) of VII precipitated upon the addition of 6*N* HCl to the organic layer and was separated by filtration. A sample of this material was converted to the base and prepared for analysis by sublimation and crystallization from ether-petroleum ether.

The remainder of the VII(a) hydrochloride was hydrolyzed by 5 hr. of refluxing with normal HCl to which enough ethanol had been added to facilitate solution. Upon cooling, VII hydrochloride hydrate separated, and was recovered in 158 g. yield (90%), m.p. *ca.* 250°. We converted this to the base, which was obtained analytically pure upon sublimation (m.p. 101.5–103°). The analytical sample of the hydrochloride was prepared from this base and had the m.p. 251–252°.

4-Acetyl-4-phenylpiperidine (XII). Hydrogenation of 3.5 g. (0.01 mole) of VII HCl hydrate in 40 ml. of methanol, 9 ml. of H_2O and 1 ml. of 2.5*N* HCl, using 2 g. of 10% Pd-C catalyst, yielded 2.4 g. (100%) of XII hydrochloride, which crystallized from ethanol as flat hexagonal plates, m.p. 245°.

Attempted bromination of this substance led only to recovered starting material.

1-Benzyl-4-bromoacetyl-4-phenylpiperidine (VIII).[6] A solution of VII hydrochloride hydrate (26.1 g., 0.075 mole) in 185 ml. of glacial acetic acid was brominated with 100 ml. of an acetic acid solution containing 121 g. of bromine per liter. After standing 3 days, 24.3 g. of chunky crystals had separated, m.p. 190–238° (gas 214°). Fractions *2* and *3* were obtained by the addition of ethyl ether, and weighed 5.4 and 4.5 g., respectively. Fraction *2* melted at 200–225° (gas 214°). Fraction *3* was recrystallized to yield 3.0 g. of material having the same melting point as *2*. Total recovery, 32.6. (95%). This hydrobromide is easily soluble in chloroform, insoluble in water, and was purified for analysis by recrystallization from aqueous ethanol. The melting range is quite indefinite but includes the temperature 200°.

3-Keto-4-phenylquinuclidine (III) *and its quaternary salts* (IX). Conversion of the hydrobromide of VIII to its base was best effected by solution in hot water, rapid chilling, and basification of the solution while it was being vigorously stirred with ether. The base began to cyclize almost immediately upon evaporation of the ether, and in acetone the cyclization appeared to be complete in a few minutes, the product being IX *bromide*. This salt can be recrystallized from ethanol, and sublimes without melting at 290–295°. It is somewhat soluble in water. The yield was 95%.

The *nitrate* of IX was prepared by treating the above bromide in aqueous ethanol with aqueous $AgNO_3$. This salt is soluble to the extent of about 2% in water, from which it crystallizes beautifully in highly refractive chunky crystals which are remarkably transparent and free from imperfections. The m.p. (from ethanol) is 255–256° (gassing).

The *perchlorate* is less soluble in water than the bromide, but was not examined further.

Liberation of III from IX bromide was effected by catalytic hydrogenation of 18.6 g. (50 millimole) batches in 250 ml. of H_2O + 350 ml. of methanol, using 1 g. of 10% Pd-C catalyst. The first hydrogenation required 1 hr., but

(19) All melting point determinations were made on the Köfler hot stage. Those marked "S.T." were taken in evacuated, sealed capillary tubes, whereas the rest were made on microscope slides in the conventional manner. Characteristic changes in crystal structure were often observed to take place below the melting point, and sublimation was a commonplace phenomenon.

we found that subsequent runs (which were made in the same hydrogenation flask without cleaning) required less time for completion—in several instances the reduction was complete in 10 to 15 min.

The resultant III *hydrobromide* was isolated by concentration of the filtered solution *in vacuo*, and the product purified by crystallization from water, m.p. 285–287°. The yield was essentially quantitative.

A rather remarkable phenomenon was observed on concentrating aqueous solutions of this material *in vacuo*. When the concentration was nearly complete, and a heavy crop of crystals had formed, the crystals would assume a brownish coloration and the magma have an odor reminiscent of bromine. The color and odor could be discharged instantly upon the addition of water, and there was apparently no deleterious effect upon the purity of the material.

The base III, m.p. 157–158°, was prepared from the hydrobromide and recrystallized from water.

The *hydrochloride*, prepared from III in ethanolic HCl, and recrystallized from ethanol, melted at 255–270°. The analytical sample, from H_2O-ethanol, was dried 5 hr. at 100° prior to analysis.

The *semicarbazone* was prepared from III hydrobromide and semicarbazide acetate in methanol, followed by conversion to the base and crystallization from ethanol, m.p. 267–268°.

The *methiodide* precipitated almost immediately when a solution of III in acetone was treated with methyl iodide and warmed. After recrystallization from ethanol the melting point was 189–190°.

4-Phenylquinuclidine (II). The Huang-Minlon modification of the Wolff-Kishner reduction was employed, substituting ethylene glycol for the usual diethylene glycol. The reaction of 8 g. of III with 4 g. of 95% hydrazine, 7 g. of 87% KOH pellets and 40 ml. of ethylene glycol led to nitrogen evolution at about 155°. Heating was continued to about 175°, which temperature was maintained until nitrogen evolution ceased (about 2 hr.).

On cooling, II crystallized from the mixture, and was washed with water and recrystallized from aqueous ethanol; m.p. 125°. This was sublimed prior to analysis. The yield was 94%.

The *hydrochloride*, from ethanol-H_2O, did not melt or decompose by 350° (S.T.), but underwent a change in form at 250–255°.

The *perchlorate*, from aqueous ethanol, melted at 271–273°.

The *methoidide*, m.p. 280–281° (from aqueous ethanol), formed with explosive violence when methyl iodide was added to a solution of II in acetone.

3-Hydroxy-4-phenylquinuclidine (IV). To a solution of 26 g. of III in 4 l. of anhydrous ether was added 10 g. of $LiAlH_4$. After standing overnight, the solution gave a positive Michler's ketone color test. Water (60 ml.) was added cautiously and the solid was filtered off and extracted with chloroform. The crude product, which weighed 20.2 g., was recrystallized from ethanol. Fraction 1, 11.2 g., m.p. 198–199°; fraction 2, 3.6 g., m.p. 198–200° (56%). Attempts to recover further quantities of IV led to material which was sparingly soluble in chloroform, and behaved like a quaternary salt. This was not examined further, but it seems possible that reaction with the chloroform may have occurred. Compound IV is nearly insoluble in ether. For analysis, IV was recrystallized from ethanol.

The *hydrochloride*, m.p. 339–340° (without decomposition) was prepared by the action of aqueous HCl on the base in ethanol. This formed a hydrate of undetermined composition, and for analysis was dried 5 hr. at 100°.

3-Acetoxy-4-phenylquinuclidine (Va). The alcohol IV (5.0 g.) was refluxed for 1 hr. with acetic anhydride, poured onto a slurry of ice and 5*N* K_2CO_3 and ether-extracted after 1 hr.; yield, 6.1 g. (100%), m.p. 92–93°. For analysis the product was sublimed.

The *hydrochloride* was prepared by adding 12*N* hydrochloric acid to an ethanol solution of the base; m.p. 275–279° (S.T.). This product formed a very stable hemihydrate which could not be obtained anhydrous by sublimation of the salt in high vacuum. The water content was estimated *via* active hydrogen.

Hydrolysis of this ester with 2.5*N* HCl by refluxing for 1 hr. led to IV hydrochloride, identical in physical properties with authentic IV hydrochloride.

4-Phenyl-3-propionoxyquinuclidine (Vb). This substance was obtained in a procedure parallel to that used for Va, using 4.0 g. of the base and 27 ml. of propionic anhydride (b.p. 76–77°/29 mm.) and heating 1 hr. on the steam bath. The product, 5.3 g., was dissolved in 25 ml. of abs. ethanol, and 1.7 ml. of concd. HCl was added, followed by 150 ml. of dry ether. The Vb *hydrochloride* crystallized at once, and was filtered and washed with ethanol-ether (1:6), ether, and dried *in vacuo* over KOH; yield 5.1 g. (88%); m.p. 208–210°.

The *base*, liberated with NaOH and purified by sublimation, melted at 60°.

4-Acetyl-1-benzyl-4-phenylpiperidine hydrazone (X). Heating a mixture of 3.48 g. (0.01 mole) of VII hydrochloride hydrate, 1 g. of hydrazine, 10 ml. of ethylene glycol and 2 g. of KOH pellets to 205° (internal temperature) for about 15 min. led to no gas evolution. The product was isolated by partitioning between water and chloroform, as a light straw-colored oil which soon crystallized. Recrystallization from ethanol and sublimation yielded pure X, m.p. 119–121°. This showed a strong C=N band in the infrared.

1-Benzyl-4-ethyl-4-phenylpiperidine (XI). When 7.0 g. of VII hydrochloride hydrate was converted to the base, and heated with 4 g. of hydrazine, 8 g. of 87% KOH and 40 ml. of *diethylene glycol* at 200° for 7 hr., N_2 was slowly evolved. The product, XI, was isolated by ether-extraction of the watered reaction mixture, then converted to the *hydrochloride* with 12*N* HCl (5.9 g. yield), which was crystallized from ethanol; yield 4.5 g. This was sublimed, m.p. 280–287° (S.T.).

4-Ethyl-4-phenylpiperidine (XIII). A solution of 4.2 g. of XI hydrochloride in 100 ml. of 70% methanol was hydrogenated in the presence of 1 g. of 10% Pd-C catalyst, a reaction which required 5 hr. The product was crystallized from ethanol-ether as prismatic rods, and further purified by sublimation; m.p. 209°, raised by repeated sublimation to 210–211°. For analysis, the material was recrystallized from alcohol-ether.

4-Ethyl-1-methyl-4-phenylpiperidine (XIV). The methylation of 1.95 g. (10.3 millimoles) of XIII with 2 ml. of 37% formaldehyde and 2 ml. of 90% formic acid by heating 45 min. on the steam bath and then refluxing 5 hr. gave 2.0 g. of a base (mobile oil) which was converted to the *hydrochloride* and recrystallized by dissolution in methanol, adding dioxane and concentrating the mixture to incipient crystallization; m.p. 227.5–229°; yield, 1.9 g.

Hoffmann elimination reaction of II methohydroxide. Vacuum sublimation of II methohydroxide (prepared from the methiodide with Ag_2O) yielded an oil which contained a hydroxyl group (infrared absorption at 2.78 μ) and no vinyl group (absence of absorption at 7 μ, and at 11 μ). When a sample of this material was converted to the hydrochloride and purified by sublimation, the product analyzed for 65.91% carbon and 8.35% hydrogen. The calculated values for $C_{14}H_{22}ClNO$ (mol. wt. 255.79) are: C, 65.73%; H, 8.67%. The product is probably 4-hydroxyethyl-1-methyl-4-phenylpiperidine.[14]

When the methohydroxide was decomposed by heating in a nitrogen atmosphere with 1:1 sodium and potassium hydroxides at 350°, a mobile oil was obtained on ether extraction of the cooled melt. (Stainless steel apparatus was used in this reaction).

On distillation, the product showed all the reactions of a vinyl compound ($KMnO_4$, Br_2, infrared absorption at 10.95,

10.05, and 7.09 μ) and with PtO_2, was completely hydrogenated in 100 sec. to the 4-ethylpiperidine XIV, which was converted to the hydrochloride and found to be identical with authentic material prepared by the Wolff-Kishner reduction of XII followed by formaldehyde–formic acid methylation.

Acknowledgment. Microanalyses were performed by Byron Baer, Paula Parisius, and Evelyn Peake of the Institutes' Microanalytical Laboratory, under the direction of William C. Alford. Some of the infrared determinations[10] were made by William Jones, of the same laboratory.

BETHESDA, MD.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND THE RADIATION LABORATORY, UNIVERSITY OF CALIFORNIA, BERKELEY]

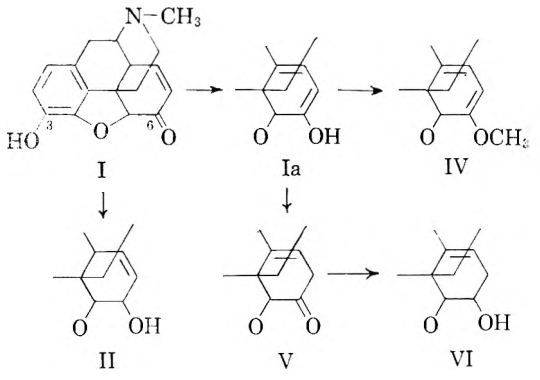
Morphinone*

HENRY RAPOPORT, DON R. BAKER, AND HELEN N. REIST

Received June 17, 1957

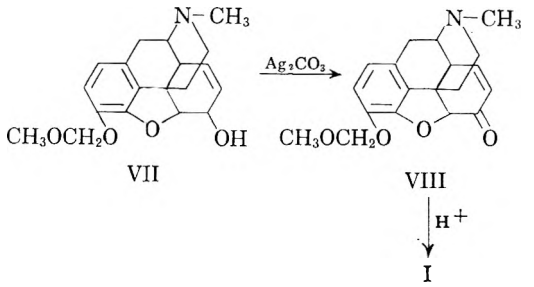
Morphinone, a compound which conceivably might serve as a common precursor for the other morphine alkaloids, has been prepared by silver carbonate oxidation of methoxymethylmorphine to methoxymethylmorphinone, followed by acid hydrolysis. With methyllithium, methoxymethylmorphinone gives the 1,2-adduct which is easily cleaved to 6-methylmorphine. Both monoacetyl derivatives and the diacetyl derivatives of 6-methylmorphine have been prepared. It appears that reactivity at the phenolic hydroxyl group may be influenced by groups at the 6-position.

In recent years there has been considerable interest in morphinone (I) since, as has been pointed out by Schöpf,[1] it (or its enolic form, Ia) conceivably might be the common parent of the other naturally occurring morphine alkaloids. For example, reduction of the carbonyl group would lead to morphine (II), and reduction to the alcohol and methylation of the phenolic hydroxyl would give codeine (III). Conversion to thebaine (IV) might be accomplished by both enol and phenol etherification, while isomerization to the β,γ-unsaturated ketone (IV), either before or after methylation of the phenol, followed by reduction to the alcohol gives neopine (VI).



Further interest in morphinone resides in the fact that it has remained one of the very few ketones still unknown in this series of alkaloids. Codeinone, dihydrocodeinone, and dihydromorphinone are well known compounds.[2] Also neopinone (V, O[3]-methyl ether) recently has been prepared from thebaine.[3] The preparation of morphinone, however, by methods such as employed for the previous ketones, has been precluded by the extreme sensitivity of the molecule. The possibility of overcoming this difficulty was offered by the recent procedure for converting codeine to codeinone[4] in excellent yield by oxidation in benzene with silver carbonate, and it is the application of this method to the preparation of morphinone which is the subject of the present report.

Although the silver carbonate-in-benzene procedure offered the mild, neutral oxidant desired, it was still necessary to protect the phenolic group, and formation of the methoxymethyl ether appeared to be a suitable method, since the protecting group could be removed by mild acid hydrolysis. The oxidation procedure, therefore was applied to the readily prepared methoxymethylmorphine (VII)[5]



* This paper is a contribution in honor of Lyndon F. Small, former Editor of the Journal.

(1) C. Schöpf, *Naturwissenschaften*, **39**, 241 (1952).

(2) L. F. Small, *Chemistry of the Opium Alkaloids*, U. S. Government Printing Office, Washington, D. C., 1932; K. W. Bentley, *The Chemistry of the Morphine Alkaloids*, The Clarendon Press, Oxford, 1954.

(3) H. Conroy, *J. Am. Chem. Soc.*, **77**, 5960 (1955).

(4) H. Rapoport and H. N. Reist, *J. Am. Chem. Soc.*, **77**, 490 (1955).

(5) C. Mannich, *Arch. Pharm.*, **254**, 349 (1916).

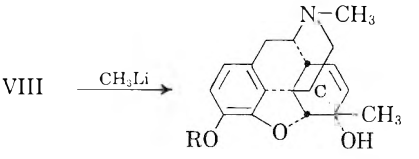
and methoxymethylmorphinone (VIII) was formed in good yield. Acid hydrolysis of the methoxymethyl ether proceeded readily in acid solution or on a sulfonic acid ion-exchange resin, and the morphinone appeared to be reasonably stable to these hydrolytic conditions.

However, attempts to liberate the free base clearly showed that morphinone was extremely sensitive to alkali, and only by keeping contact with alkali to a minimum could pure, crystalline material be isolated. This was achieved by eluting the alkaloid from the column with potassium chloride solution, adding chloroform and cooling before adjusting the *p*H to 8.7, and extracting as rapidly as possible. In this way morphinone exhibiting a strong α,β unsaturated carbonyl absorption at 5.98 μ as the only carbonyl peak could be obtained. If stronger alkali or longer times were used, or if cooling was omitted, a product with a weak additional carbonyl absorption at 5.80 μ resulted, and this impurity could not be removed.

Reduction of morphinone with sodium borohydride gave morphine, and dihydromorphinone was formed on catalytic hydrogenation. Numerous attempts were made to duplicate some of the postulated biogenetic conversions, but these met only with failure. The appearance of a carbonyl absorption at 5.80 μ when morphinone was exposed to alkali looked promising for a possible conversion to the β,γ-unsaturated ketone (V) and thence to neopine (VI). Although longer exposure to alkali increased the intensity of this absorption it also led to polymeric material. The reaction with diazomethane was investigated as a possible route to codeinone and thebaine, but again the reaction was complex and no crystalline product could be isolated.

A reaction of interest was that with methyllithium, since this should lead to a nuclear methylated morphine derivative of possible pharmacological interest. For this purpose, methoxymethylmorphinone (VIII) was the starting material and it was treated with ethereal methyl lithium in the cold. This gave 6-methylmethoxymethylmorphine (IX) which was directly hydrolyzed to 6-methylmorphine (X). The assigned structure as the 1,2-addition product is based on the analogous reaction with codeinone,[6] methylation to 6-methylcodeine,[6] and hydrogenation to 6-methyldihydromorphine.[7]

Both monoacetyl derivatives and the diacetyl derivative of 6-methylmorphine were prepared. The O^3-monoacetyl compound was readily formed on shaking 6-methylmorphine with chloroform, aqueous sodium hydroxide, and acetic anhydride. That it was the phenolic group which was acetylated and not the tertiary hydroxyl was established by its ultraviolet absorption. The compound showed absorption at 282 mμ, typical of morphine alkaloids



IX, R = CH_3OCH_2
X, R = H
XI, R = CH_3

(4)

and due to the guaiacol moiety. However, on addition of alkali, the absorption peak shifted gradually to 300 mμ and the extinction coefficient increased, indicating the progressive hydrolysis of the ester and formation of the phenolate ion. To prepare the O^6-monoacetyl derivative, the methyllithium-methoxymethylmorphinone reaction mixture was treated with acetic anhydride and mild acid hydrolysis removed the O^3-methoxymethyl ether, leaving the O^6-acetyl intact. On addition of alkali to an ethanolic solution of the O^6-acetyl-6-methylmorphine, the shift in absorption maximum from 287 mμ to 300 mμ took place immediately as is characteristic of free phenols.

In order to prepare the O^3, O^6-diacetyl derivative it was necessary to heat the O^6-monoacetyl compound with acetic anhydride and pyridine. The very mild conditions used previously to acetylate the phenolic group of 6-methylmorphine resulted only in unchanged starting material when applied to O^6-acetyl-6-methylmorphine. Apparently the O^6-acetyl group was exerting a slight hindering effect on reactions of the phenol. Considering the stereochemistry of the morphine molecule with the benzene ring on the underside of the piperidine-ring C fused ring system, addition of methyllithium to the carbonyl group of VIII would be expected to occur from above to give the tertiary alcohol with the hydroxyl group on the same side as the benzene ring, as shown in IX. This would allow the O^6-acetyl group to approach fairly close to the phenol and might explain the decreased reactivity.

Another example of this effect was found in a comparison of the rates of hydrolysis of the O^3-acetyl groups of O^3-acetyl-6-methylmorphine and O^3,O^6-diacetyl-6-methylmorphine. Using the appearance of phenolate ion absorption in the ultraviolet to follow the reaction, the half-time for hydrolysis was 40 seconds for the former and 120 seconds for the latter. This result also is consistent with a close approach of the O^6-acetyl group to the phenol.

EXPERIMENTAL[8]

Methoxymethylmorphinone (VIII). Methoxymethylmorphine was prepared by the reaction of sodium morphinate

(6) S. P. Findlay and L. F. Small, *J. Am. Chem. Soc.*, **72**, 3249 (1950).

(7) L. F. Small and H. Rapoport, *J. Org. Chem.*, **12**, 284 (1947).

(8) All melting points are corrected and those above 200° were taken in evacuated capillaries; microanalyses were performed by the Microchemical Laboratory, University of California, Berkeley.

and chloromethyl ether[9] following the procedure of Mannich,[5] m.p. 92–94° (reported[5] m.p. 94–96°). A 16.5 g. (0.05 mole) portion of this methoxymethylmorphine was dissolved in 330 ml. of benzene and 69 g. (0.25 mole) of silver carbonate[4] was added after 30 ml. of benzene had been distilled from the solution. The mixture was heated under reflux in a nitrogen atmosphere with vigorous stirring for 1 hr. during which 20 ml. of benzene was distilled from the reaction mixture. It was then cooled sufficiently to permit the addition of another 69 g. portion of silver carbonate and the process was repeated. The mixture then was filtered, the insoluble material was digested with three 70 ml. portions of benzene, and the combined filtrate and digests were washed with two 100-ml. portions of 1*N* sodium hydroxide. Four 110-ml. portions of *p*H 7 sulfite-bisulfite solution were then used to wash the benzene solution, and these aqueous solutions then were combined, adjusted to *p*H 10 with potassium carbonate, and extracted with benzene. The original benzene solution and the benzene extracts of the *p*H 10 aqueous sulfite solution, on drying and evaporation, yielded 6.1 g. (37%) of recovered methoxymethylmorphine.

To the *p*H 10 sulfite solution was added 15 ml. of 15*N* sodium hydroxide, and this strongly alkaline solution was shaken mechanically with 500 ml. of chloroform for 2 hr. after which the chloroform was removed and a fresh portion added. In all, four such portions were used. Washing with water, drying over magnesium sulfate, and evaporating the chloroform left 6.2 g. (60% yield) of methoxymethylmorphinone, m.p. 121–125°. Crystallization from benzene-hexane gave pure ketone, m.p. 129–130°; $[\alpha]_D^{25}$ −176° (c, 0.98, ethanol).

Anal. Calcd. for $C_{19}H_{21}NO_4$: C, 69.7; H, 6.5. Found: C, 69.7; H, 6.4.

With sodium borohydride in methanol at room temperature, methoxymethylmorphinone was reduced to methoxymethylmorphine, m.p. 94–96°.

Morphinone (I). A solution of 502 mg. (1.5 mmoles) of methoxymethylmorphinone (VIII) in 20 ml. of 0.1*N* hydrochloric acid was added to a Dowex 50 × 1 ion exchange column (50–100 mesh) in the acid form. Distilled water (800 ml.) was washed through the column during 5 hr., after which the morphinone was eluted with four 100-ml. portions of 10% potassium chloride solution. The solutions were cooled, chloroform was added, and the aqueous phase was adjusted to *p*H 8.7 with sodium bicarbonate solution. Separation of the phases and extraction with three additional 50-ml. portions of cold chloroform during three minutes led, after evaporation of the chloroform extracts, to 270 mg. (62% yield) of crude morphinone.

Hydrolysis could also be effected by allowing 1.04 g. (3.2 mmoles) of methoxymethylmorphinone in 20 ml. of 1*N* hydrochloric acid solution to stand at room temperature for 5 hr. Isolation in the same manner as above led to an 85% yield (763 mg.) of crude morphinone. Crystallization of 500 mg. from 5 ml. of absolute ethanol gave 450 mg. of pure morphinone, strongly decomposing at 148° and melting at 230° (evac. cap.); $[\alpha]_D^{25}$ −194° (c, 0.87, methanol); λ_{max} 280 mμ (ε 1420), in ethanol; 297 mμ (ε 2710) in ethanol, 0.01*N* in sodium hydroxide.

Anal. Calcd. for $C_{17}H_{17}NO_3$: C, 72.1; H, 6.1. Found: C, 71.9; H, 6.4.

The *perchlorate* was prepared by dissolving 52 mg. of morphinone in 3 ml. of methanol and adding 1.9 ml. of 0.1*N* ethanolic perchloric acid. Recrystallization from methanol-ether and drying gave hygroscopic material of m.p. 151–155°; $[\alpha]_D^{25}$ −124° (c, 0.75, methanol).

Anal. Calcd. for $C_{17}H_{18}ClNO_7$: C, 53.2; H, 4.7. Found: C, 52.8; H, 5.0.

Reduction of morphinone to morphine was achieved by treating 84 mg. of morphinone in methanol with a solution of 270 mg. of sodium borohydride in 2 ml. of water and 3 ml. of methanol. After standing at room temperature for 1.5 hr., the solution was concentrated to remove methanol, water was added, the *p*H was adjusted to 8.7, and the solution was cooled to allow the crystallization of 60 mg. of *morphine*, identical with authentic material in ultraviolet and infrared spectra and melting point.

Catalytic hydrogenation of morphinone in absolute ethanol using a 5% palladized carbon catalyst proceeded rapidly (30 min.) at room temperature with the absorption of one mole of hydrogen, after which hydrogen uptake ceased. The solution was filtered and concentrated, and cooling gave *dihydromorphinone*, identical with an authentic sample in infrared spectrum and m.p.[10]

6-Methylmorphine (X). To 50 ml. of dry ether was added 20 ml. of 0.93*M* ethereal methyllithium. With cooling (ice-salt bath) and stirring and in a nitrogen atmosphere, 2.5 g. of methoxymethylmorphinone (VIII) was added over a 15-min. period. Stirring and cooling was continued for an additional hour after which 60 ml. of ice water was added. The ether layer was separated, the aqueous phase was washed with four 30 ml. portions of ether, and the combined ether solutions were washed with 1*N* hydrochloric acid (four 40 ml. portions). After being allowed to stand at room temperature for 5 hr., the combined acid solutions were adjusted to *p*H 8.7 and were extracted four times with 80 ml. portions of chloroform. Methanol was added to the combined chloroform solutions to prevent precipitation, they were dried and evaporated, and a 97% yield, 2.22 g., of 6-methylmorphine, m.p. 275–276°, was obtained. A sample crystallized from acetone and then from butanone had m.p. 279–280°; $[\alpha]_D^{25}$ −166° (c, 0.82, methanol).

Anal. Calcd. for $C_{18}H_{21}NO_3$: C, 72.2; H, 7.1; C-CH_3, 5.0. Found: C, 72.0; H, 7.2; C-CH_3, 4.3.

Etherification of 6-methylmorphine in methanol with ethereal diazomethane gave *6-methylcodeine*, identical with an authentic sample.

Hydrogenation of 6-methylmorphine at room temperature in absolute ethanol using a platinum oxide catalyst stopped after 30 min. and the absorption of one mole of hydrogen. *6-Methyldihydromorphine* was isolated by sublimation and was identical with an authentic sample.[7]

O^3-Acetyl-6-methylmorphine was prepared by dissolving 350 mg. (1.2 mmoles) of 6-methylmorphine in 25 ml. of chloroform and 1.8 ml. of 1*N* sodium hydroxide. To this cold mixture was added 150 mg. (1.5 mmoles) of acetic anhydride and, after being shaken vigorously for one min., the phases were separated. The aqueous phase, made alkaline with sodium carbonate, was washed with chloroform, and the combined chloroform solutions were washed with 0.5*M* sodium carbonate. Evaporation of the chloroform and crystallization of the residue from ethyl acetate followed by sublimation at 120°/10 μ gave O^3-acetyl-6-methylmorphine, m.p. 167–168°; $[\alpha]_D^{25}$ −198° (c, 0.78, methanol).

Anal. Calcd. for $C_{20}H_{23}NO_4$: C, 70.4; H, 6.8; CH_3COO—, 12.6. Found: C, 70.1; H, 6.6; CH_3COO—, 12.5.

O^6-Acetyl-6-methylmorphine was prepared by first treating 1.00 g. (3.1 mmoles) of methoxymethylmorphinone (VIII) in 100 ml. of ether with 20 ml. of 0.93*M* ethereal methyllithium in the cold for 1 hr. and then adding 2 ml. of acetic anhydride. This mixture was heated under reflux for 2 hr., after which 100 ml. of 0.1*M* phosphoric acid was added and the ether layer removed. Chloroform was used to wash the aqueous phase (adjusted to *p*H 3), and the water solution then was boiled in a nitrogen atmosphere for 6 hr. After being washed with chloroform, the aqueous layer was adjusted to *p*H 8.7 and was extracted thoroughly with chloroform. Evaporation of the chloroform left 1.0 g. (96% yield) of crude O^6-acetyl-6-methylmorphine which was purified for analysis by crystallization from ethyl acetate

(9) C. S. Marvel and P. K. Porter, *Org. Syntheses*, **Coll. Vol. I**, 377 (1944).

(10) H. Rapoport, R. Naumann, E. R. Bissell, and R. M. Bonner, *J. Org. Chem.*, 15, 1103 (1950).

and sublimation (140°/10 μ); m.p. 244–245°; $[\alpha]_D^{25}$ −212° (c, 0.65, methanol).

Anal. Calcd. for $C_{20}H_{23}NO_4$: C, 70.4; H, 6.8; CH_3COO—, 12.6. Found: C, 70.3; H, 7.1; CH_3COO—, 13.0.

O^3,O^6-Diacetyl-6-methylmorphine resulted when a solution of 96 mg. of O^6-acetyl-6-methylmorphine, one ml. of acetic anhydride and 2 ml. of pyridine was heated under reflux for 1.5 hr. The reaction mixture was concentrated *in vacuo*, the residue was distributed between chloroform and aqueous phosphate buffer (*p*H 3), and the aqueous phase, after adjustment to *p*H 8.7, was extracted thoroughly with chloroform. The residue from evaporation of the dried chloroform extracts was crystallized from ethyl acetate–hexane to give O^3,O^6-diacetyl-6-methylmorphine, m.p. 166–168°; $[\alpha]_D^{25}$ −200° (c, 0.77, methanol).

Anal. Calcd. for $C_{22}H_{25}NO_5$: C, 68.9; H, 6.6; C-CH_3, 12.1. Found: C, 69.3; H, 6.4; C-CH_3, 12.3.

Rates of hydrolysis of the O^3-acetyl derivatives prepared above were determined by dissolving 1 mg. of each compound in 10 ml. of 95% ethanol, 0.01*N* in sodium hydroxide. The ultraviolet absorption at 300 mμ, due to the formation of phenolate ion, was followed as a function of time. With O^6-acetyl-6-methylmorphine, the appearance of this peak was instantaneous and did not change with time. With O^3-acetyl-6-methylmorphine and O^3,O^6-diacetyl-6-methylmorphine, this peak appeared as hydrolysis proceeded and the half-time for hydrolysis was 40 sec. for the former and 120 sec. for the latter. Heroin (O^3,O^6-diacetylmorphine), run for comparison, had a half-time for hydrolysis of 100 sec.

BERKELEY, CALIF.

[CONTRIBUTION FROM THE MERCK SHARP & DOHME RESEARCH LABORATORIES]

Antiparasitic Agents. I. Some New 2,4-Diaminopyrimidines*

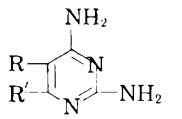
E. F. ROGERS, W. J. LEANZA, AND L. H. SARETT

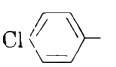
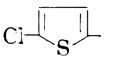
Received July 29, 1957

Six new substituted 2,4-diaminopyrimidines were prepared for chemotherapeutic evaluation. Three of these were found to have activity *vs. S. pyogenes;* one enhances sulfanilamide action *vs. Eimeria spp.*

Various 2,4-diaminopyrimidines and the analogously constituted 2,6-diaminopurines have been found to be folic acid antagonists[1] and, presumably, act in this capacity to inhibit growth of the parasites of malaria[2] and coccidiosis[3] as well as to show antibacterial[4] and antileukemic[5] activity. The most potent of the series in antimalarial activity is pyrimethamine,[2,6] 2,4-diamino-5-*p*-chlorophenyl-6-ethylpyrimidine (I). In addition to its antimalarial activity it also potentiates sulfaquinoxaline and sulfamezathine.[3] These properties prompted us to prepare some new 2,4-diaminopyrimidines related to pyrimethamine.

The new bases which were made are shown in formulas II–VII. In compounds II–IV, fluoroalkyl or alkoxyalkyl groups replace the 6-ethyl substituent in pyrimethamine; in compounds V–VII the 5-*p*-chlorophenyl is replaced by heterocyclic groups. In each case the bases differ in only one ring substituent.



	R	R′
I		$-C_2H_5$
II	"	$-CF_3$
III	"	$-C_2F_5$
IV	"	$-CH(OCH_3)_2$
V		$-C_2H_5$
VI		$-C_2H_5$
VII		$-C_2H_5$

With the exception of compound VII the syntheses presented no special difficulties. The method is illustrated by the synthesis of 2,4-diamino-5-thienyl-6-ethylpyrimidine. These reactions were exploited most successfully by the Wellcome group in their investigations of 5-aryl-2,4-diaminopyrimi-

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* This paper is a contribution in honor of Lyndon F. Small, former Editor of the Journal.

(1) G. H. Hitchings, *Trans. Roy. Soc. Trop. Med. Hyg.*, 46, 467 (1952).

(2) I. M. Rollo, *Trans. Roy. Soc. Trop. Med. Hyg.*, 46, 474 (1952); L. G. Goodwin, *Trans. Roy. Soc. Trop. Med. Hyg.*, 46, 485 (1952); G. R. Coatney and W. C. Cooper, *Trans. Roy. Soc. Trop. Med. Hyg.*, 46, 496 (1952).

(3) R. E. Lux, *Antibiotics and Chemotherapy*, 4, 971 (1954).

(4) E. A. Falco, P. B. Russell, and G. H. Hitchings, *J. Am. Chem. Soc.*, 73, 3753 (1951); E. A. Falco, S. DuBreuil, and G. H. Hitchings, *J. Am. Chem. Soc.*, 73, 3758 (1951).

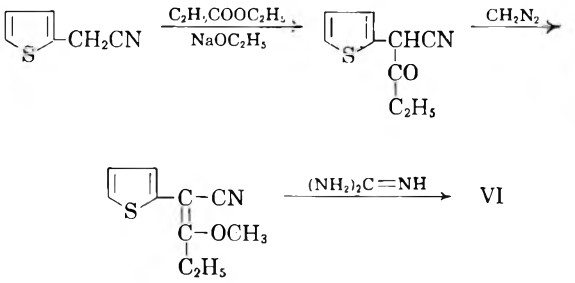
(5) M. L. Murphy, R. R. Ellison, D. A. Karnofsky, and J. H. Burchenal, *J. Clin. Invest.*, 33, 1388 (1954).

(6) P. B. Russell and G. H. Hitchings, *J. Am. Chem. Soc.*, 73, 3763 (1951).

TABLE I

5,6-DISUBSTITUTED 2,4-DIAMINO PYRIMIDINES

	R	R′	M.P., °C.	Formula	Analysis					
					Calcd.			Found		
					C	H	N	C	H	N
II	$C_6H_4Cl(4)$	CF_3	243–245	$C_{11}H_8N_4ClF_3$	45.87	2.79	19.41	46.07	2.83	19.58
III	$C_6H_4Cl(4)$	C_2H_5	200–201	$C_{12}H_8N_4ClF_5$	42.55	2.38	16.54	43.39	2.63	16.81
IV	$C_6H_4Cl(4)$	$CH(OCH_3)_2$	264–267	$C_{13}H_{15}N_4O_2Cl$	52.97	5.13	19.01	52.84	4.92	19.40
V	Furyl	C_2H_5	224–226	$C_{10}H_{12}N_4O$	58.81	5.92	27.44	59.39	5.65	27.71
VI	Thienyl	C_2H_5	247–248	$C_{10}H_{12}N_4S$	54.54	5.49	25.44	54.02	5.26	25.44
VII	5-Chloro-thienyl	C_2H_5	240–242	$C_{10}H_{11}ClN_4S$	47.15	4.35	22.00	47.59	4.20	21.83



dines.[6] The guanidine-β-alkoxyacrylonitrile cyclization apparently originated with Huber and Hoelscher[7] who prepared 5-cyano-2,4-diaminopyrimidine from ethoxymethylenemalononitrile and guanidine.

Satisfactory conditions could not be found for the base-catalyzed condensation of ethyl propionate with 5-chlorothienylacetonitrile; polymerization of the nitrile is competitive with the propionate condensation. Only by working at low temperatures could even a poor yield of β-ketonitrile be obtained.

The uncatalyzed condensation of orthoesters with compounds containing active methylene groups has been investigated by Jones[8] who found, for example, that ethyl orthoformate condenses with ethyl acetoacetate and ethyl cyanoacetate in yields approximating 20% after 2–6 hours at 140–150°. Whittaker[9] reacted ethyl orthopropionate with *p*-chlorophenylacetonitrile under similar conditions and the crude α-*p*-chlorophenyl-β-ethoxyacrylonitrile so obtained was converted to pyrimethamine. This method was utilized to secure sufficient α-(5-chloro-2-thienyl)-β-ethoxyacrylonitrile for guanidine condensation and synthesis of compound VII.

The pyrimethamine analogs have been tested for antibacterial, anticoccidial, and antimalarial activities. Activity against *Streptococcus pyogenes* was noted with compounds V–VII at 4 to 15 γ/ml., approximately the same level at which pyrimethamine shows borderline activity.[10] None of the bases showed prophylactic action in coccidiosis when fed at 0.0125%. One compound, the chlorothienyl analog VII, showed sulfaquinoxaline potentiation when fed in a 1:1 ratio (0.0125% of each). Compounds V–VII were tested as antimalarials. They were ineffective in reducing parasitemia at a daily dose of 0.4 mg./kg. in chickens infected with *P. gallinaceum*.[11] The effective pyrimethamine dose in this test was 0.04 mg./kg.

EXPERIMENTAL

In general the procedures of Russell and Hitchings were followed.

α-Acyl-p-chlorophenylacetonitriles. *p*-Chlorophenylacetonitrile was condensed with the appropriate ethyl ester in the presence of ethanolic sodium ethoxide to give the following derivatives: α-trifluoroacetyl, m.p. 95–97°, yield 54%; α-perfluoropropionyl, m.p. 110–111°, yield 47%; and α-dimethoxyacetyl, m.p. 106–108°, yield 61%.

α-Thienyl and furyl-β-ketovaleronitriles. The base VI intermediate, α(2-thienyl)-β-ketovaleronitrile, was prepared by a standard procedure as above. A 55% yield of crude product melting at 90° was obtained.

Anal. Calcd. for C_9H_9OSN: N, 7.82. Found: N, 7.48.

The corresponding furyl compound, α(2-furyl)-β-ketovaleronitrile, was an oxygen-sensitive oil. The compound was prepared and subsequently condensed with guanidine under nitrogen.

α(5-Chloro-2-thienyl)-β-ketovaleronitrile was formed in very low yields when the Claisen condensation was run at −10 to −20° for 1 hr., then permitted slowly to warm to room temperature during 2 additional hr. A very vigorous reaction occurs if 5-chloro-2-thienylacetonitrile is added to a 10% solution of sodium ethoxide in ethanol; considerable heat is generated and sodium chloride and polymeric material are immediately formed. The product from the low temperature condensation melted at 110° after recrystallization from benzene.

Anal. Calcd. for C_9H_8OClSN: C, 50.59; H, 3.77; N, 6.56. Found: C, 50.63; H, 3.70; N, 6.69.

5,6-Disubstituted-2,4-diaminopyrimidines. The ketonitriles were treated with an excess of diazomethane in ether and kept at 0–5° overnight. After evaporation of the ether and unreacted diazomethane, the residual sirup was dissolved in alcohol and added to a solution of guanidine in alcohol. The mixture was heated for 4 hr., then cooled, and the crystalline product collected and recrystallized from alcohol. The compounds prepared are listed in Table I.

2,4-Diamino-5-(5′-chloro-2′-thienyl)-6-ethylpyrimidine. Fifty-two grams of 5-chloro-2-thienylacetonitrile and 30 g. of ethyl orthopropionate were heated under reflux at 160–165° for 20 hr. An additional 30 g. of orthoester was then

(7) W. Huber and H. A. Hoelscher, *Ber.*, **71**, 87 (1938).
(8) R. G. Jones, *J. Am. Chem. Soc.*, **74**, 4889 (1952).
(9) N. Whittaker, U. S. Patent 2,755,298 (1956).
(10) Personal communication, A. K. Miller, Merck Institute for Therapeutic Research.
(11) Personal communication, A. C. Cuckler and C. Malanga, Merck Institute for Therapeutic Research.

added and the reflux was cut off so that over the next 20 hr. the temperature rose to 185°. The cooled reaction mixture was diluted with 100 ml. of ether and placed in the icebox overnight. The heavy amorphous precipitate was rejected. After ether evaporation the residual oil was pumped out to remove starting materials (2 hr., bath temperature 110–115° at 1–2 mm.). The residual oil, weighing 10.5 g., was carried through the usual guanidine condensation. From the chloroform and 2*N* hydrochloric acid soluble fraction of reaction product 3.2 g. of pyrimidine was obtained. Recrystallization from methanol gave crystals, m.p. 240–242°.

Acknowledgment. The authors are indebted to Drs. Max Tishler and Karl Folkers for their interest and encouragement of this study and to Dr. A. C. Cuckler for helpful advice on biological matters.

RAHWAY, N. J.

[CONTRIBUTION FROM THE NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES, NATIONAL INSTITUTES OF HEALTH, PUBLIC HEALTH SERVICE, DEPARTMENT OF HEALTH, EDUCATION AND WELFARE]

Structure of *x*-Bromoacetyl-*N*-acetyl-9,10-dihydroacridine*[1]

LEWIS J. SARGENT

Received June 27, 1957

The elucidation of the position occupied by the bromoacetyl group in the title compound has been achieved. This, incidentally, represents the first example of a successful Friedel-Crafts acylation in acridine chemistry.

Some years ago in a study of the plasmodicidal properties of diverse acridine derivatives, a series of amino alcohols derived from *x*-bromoacetyl-*N*-acetyl-9,10-dihydroacridine (I) was synthesized.[2]

It was pointed out at the time that the proof of the structure of this key substance depended upon the availability of certain acridine derivatives then unknown. This deficiency was rectified shortly thereafter by the synthesis of the four requisite ethylacridines by unambiguous routes,[3] and the present communication reports the final phase in arriving at the constitution of I.

The reactions involved in degrading I to an ethylacridine of known constitution are shown in the chart. In the presence of sodium acetate the palladium-charcoal catalyzed debromination step occurred smoothly with hydrogen absorption coming to a virtual halt after the uptake of one mole. On the other hand, when sodium acetate was omitted, the hydrogen bromide formed *in situ* not only induced *N*-acyl cleavage–as evidenced by the isolation of a small amount of *x*-acetyl-9,10-dihydroacridine (III) in one instance–but apparently catalyzed reduction at other sites in the molecule as well. The product isolated from the buffered reduction system, *x*-acetyl-*N*-acetyl-9,10-dihydroacridine (II) was a colorless glass that resisted crystallization even after passage through its well-defined semicarbazone. *N*-acyl hydrolysis of II gave *x*-acetyl-9,10-dihydroacridine (III) which was reduced (Wolff-Kishner) to *x*-ethyl-9,10-dihydroacridine (IV). The latter substance proved to be exceedingly air sensitive, more so than the parent 9,10-dihydroacridine. For example, while a pure sample of the latter showed virtually no change in melting point even after one year's keeping in a closed vial, a sublimed specimen of IV exhibited a marked melting point drop after only two days storage in a vial. Potassium dichromate oxidation[4,5] of IV yielded a substance which was identical in all respects with synthetic 3-ethylacridine.[3]

In another approach, *x*-acetyl-9,10-dihydroacridine (III) was oxidized with potassium dichromate to *x*-acetylacridine (VI) which, upon Wolff-Kishner reduction, gave 3-ethylacridine thereby establishing VI as the presently unknown 3-acetylacridine.

After demonstrating that I could be debrominated to *x*-acetyl-*N*-acetyl-9,10-dihydroacridine (II), several attempts (five in all) were made to prepare II through Friedel-Crafts acylation of *N*-acetyl-9,10-dihydroacridine by acetyl chloride or acetyl bromide under the conditions utilized in the synthesis of I.[2] Two experiments with acetyl chloride failed to yield any of the desired product; only starting material was recovered. In one of the two acetyl bromide runs (where the reaction mixture was allowed to stand overnight at 25° before workup) it was possible to isolate *ca.* 1.5% of the desired II (as its semicarbazone) from the mother liquors of recovered (85%) starting material. The infrared spectrum of this semicarbazone was identical with that of the corresponding derivative of II obtained *via* the bromoketone. A final acylation with acetyl bromide in nitrobenzene yielded the following three products: (*a*) starting material, 40%, (*b*) acridine, 20%, and (*c*) dihydroacridine, 10%, along with some tarry material. It is of interest that the latter two substances should turn up in this reaction, and

* This paper is a contribution in honor of Lyndon F. Small, former Editor of the Journal.

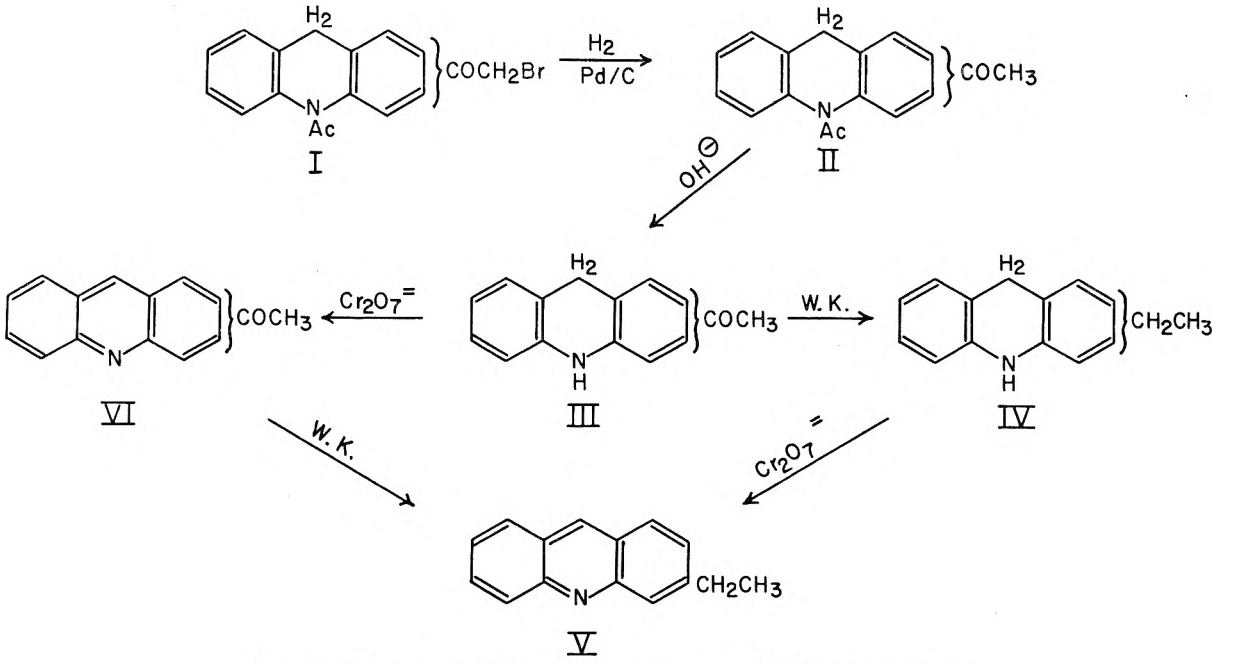
(1) Studies in the Acridine Series X.

(2) L. J. Sargent and L. F. Small, *J. Org. Chem.*, 13, 447 (1948).

(3) L. J. Sargent, *J. Org. Chem.*, 19, 599 (1954).

(4) A. Albert and J. B. Willis, *J. Soc. Chem. Ind. (London)*, 65, 26 (1946).

(5) *Cf.* ref. 3.



THE STRUCTURE OF x-BROMOACETYL-N-ACETYL-9,10-DIHYDROACRIDINE

it is very likely that they were formed during the steam removal of the nitrobenzene by a combination of effects, *viz.* (*a*) hydrolysis of the *N*-acyl group by the hot acid solution and (*b*) oxidation of the sensitive dihydroacridine to acridine by the nitrobenzene.

EXPERIMENTAL[6]

X-Acetyl-N-acetyl-9,10-dihydroacridine (II) *semicarbazone.* A suspension of 1.9 g. of finely powdered I in 90 ml. of 95% ethanol was shaken under hydrogen with 0.63 g. of 5% palladium-on-charcoal and 0.8 g. of powdered, fused sodium acetate. Initial hydrogen uptake was rapid (30 ml./min.) but, after the absorption of 1.15 moles, slowed markedly (*ca.* 0.8 ml./min.). After removal of the catalyst, the colorless filtrate was concentrated (*in vacuo*) and the sirupy residue taken up in 15 ml. of 90% ethanol and heated for 2.5 hr. (reflux) with 0.81 g. of semicarbazide hydrochloride and 0.6 g. of fused sodium acetate. The addition of water precipitated a colorless solid which was collected and recrystallized from methanol to yield colorless prisms (1.25 g.), m.p. 134–136° (foams; apparently solvated). A sample was recrystallized twice again from methanol and dried at 98°/0.1 mm. for 4 hr., m.p. 150–153°.

Anal. Calcd. for $C_{18}H_{18}N_4O_2$: C, 67.1; H, 5.63. Found: C, 66.8; H, 5.95.

Regeneration of the ketone (II). A suspension of 1.12 g. of the above semicarbazone in a solution of 18 ml. of glacial acetic acid, 0.95 ml. of 50% pyruvic acid[7] and 5 ml. of water was boiled under reflux for 15 min. With ice-cooling, 15 ml. of water was added followed by dropwise addition of concd. ammonium hydroxide (in slight excess). The curdy suspension was taken up in ether, the solution washed with saturated sodium bicarbonate and dried. Concentration gave 0.75 g. of a colorless glass.

X-Acetyl-9,10-dihydroacridine (III). A solution of 0.75 g. of II in 15 ml. of 95% ethanol and 9 ml. of 10% ethanolic potassium hydroxide was heated on the steam bath (reflux) for 1 hr. The reaction mixture was diluted with water and the bright-yellow precipitate collected and air-dried—0.63 g. The product was suspended in 50 ml. of methanol at 25°, filtered from a small amount of insoluble material (0.1 g.) and concentrated to a small volume (*in vacuo*) to yield 0.5 g. of pale-yellow leaves, m.p. 169–171°. After sublimation at 165–170°/0.25 mm., the sample melted at 174.5–176°.

Anal. Calcd. for $C_{15}H_{13}NO$: C, 80.7; H, 5.87; N, 6.28. Found: C, 80.3; H, 5.81; N, 6.42.

X-Ethyl-9,10-dihydroacridine (IV). A mixture of III (0.65 g.), potassium hydroxide (0.65 g.) and 0.8 ml. of 85% hydrazine hydrate in 12 ml. of diethylene glycol was heated for 4.5 hr. according to Huang-Minlon.[8] Dilution with cold water precipitated 0.6 g. of a pale-yellow solid which was collected, washed with water and dried under N_2. Although the substance crystallizes in colorless plates from methanol, and may be sublimed at 105°/0.1 mm. in small prisms, m.p. 127–129°, it appears to be even more air-sensitive than 9,10-dihydroacridine and is largely oxidized in a matter of *ca.* 48 hr. (new m.p. 95–105°).

3-Ethylacridine (V). A suspension of 0.6 g. of IV in a hot mixture of 4.5 ml. of 2*N* sulfuric acid and 45 ml. of water was oxidized with 0.3 g. of potassium dichromate in 4 ml. of water, and the product was converted to the dichromate salt with 0.73 g. of potassium dichromate in 8 ml. of water.[4,5] Regeneration of the free base (concd. ammonium hydroxide–ether) gave 0.4 g. of a pale-yellow oil which crystallized when rubbed with petroleum ether. An ice-cooled solution of the base in 2 ml. of absolute ethanol was treated with 0.25 ml. (excess) of 60% perchloric acid; the yellow salt which was collected and washed with a few ml. of absolute ethanol-ether (2:1) weighed 0.49 g. Recrystallization from absolute ethanol (Norit) gave 0.32 g. of slender, yellow prisms, m.p. 179–181° (not depressed when mixed with authentic 3-ethylacridine perchlorate of m.p. 184–185°[3]). A benzene solution of the regenerated base was chromatographed on 6 g. of aluminum oxide, collecting 125 ml. of eluate. Concentration (*in vacuo*) yielded 0.15 g. of a pale-yellow oil which crystallized spontaneously, m.p. 83–85°. After sublimation at 100°/0.1 mm., the m.p. was 87–88.5°, unde-

(6) Analyses are by the Analytical Service Laboratory of this Institute, under the supervision of Dr. W. C. Alford. Melting points are uncorrected.

(7) E. B. Hershberg, *J. Org. Chem.*, **13**, 542 (1948).

(8) Huang-Minlon, *J. Am. Chem. Soc.*, **64**, 2653 (1942).

pressed when mixed with synthetic 3-ethylacridine.[3] Moreover, the infrared spectra were identical.

Anal. Calcd. for $C_{15}H_{13}N$: C, 86.8; H, 6.32. Found: C, 85.8; H, 6.43.

3-Acetylacridine (VI). A hot suspension of 0.33 g. of III in 22 ml. of water (containing 20 drops of acetone) and 2.5 ml. of 2*N* sulfuric acid was oxidized with 0.18 g. of potassium dichromate in 4 ml. of water. The filtered solution was treated with 0.4 g. of potassium dichromate in 4 ml. of water and the precipitated salt converted to the free base (concd. ammonium hydroxide–ether). Concentration of the dried solution gave 0.24 g. of a light-yellow solid which was sublimed at 125–130°/0.1 mm., lemon yellow prisms, m.p. 135–136.5°. The compound possessed a strong carbonyl band at 5.95 μ.

Anal. Calcd. for $C_{15}H_{11}NO$: C, 81.4; H, 5.01. Found: C, 81.2; H, 5.04.

A Wolff-Kishner reduction of 60 mg. of VI in 4 ml. of diethylene glycol with 60 mg. of potassium hydroxide and 0.1 ml. of 85% hydrazine hydrate gave, after the usual work-up, 40 mg. of a tacky yellow solid which was chromatographed on 3 g. of aluminum oxide (benzene). The resulting base was converted to the *perchlorate*, m.p. 176–178° (undepressed when mixed with 3-ethylacridine perchlorate). Regeneration of the base gave a pale yellow oil which crystallized rapidly (scratching), m.p. 75–77°; not depressed when mixed with synthetic 3-ethylacridine. The infrared spectra of the regenerated base and 3-ethylacridine were the same.

BETHESDA 14, MD.

[CONTRIBUTION FROM THE NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES, NATIONAL INSTITUTES OF HEALTH, PUBLIC HEALTH SERVICE, U. S. DEPARTMENT OF HEALTH, EDUCATION AND WELFARE]

Some Reactions of Solasodine*[1]

YOSHIO SATO, H. GEORGE LATHAM, JR., AND ERICH MOSETTIG

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The degradation of the steroidal alkaloid solasodine has led to 5,16-pregnadien-3β-ol-20-one. Solasodine has also been converted into a new isomeric solanidanone and into the diacetate and monoacetate of a "pseudosolasodine." Some reactions of the latter are discussed.

Solasodine (I),[2,3] the aglycone of solasonine[4] obtained from certain solanum species, can be converted to a pregnane derivative by treatment with acetic anhydride and oxidation of the resulting amorphous mass. Thus solasodine (I) yielded the acetate of 5,16-pregnadien-3β-ol-20-one (IV) and 16α-methoxy-5-pregnen-3β-ol-20-one. The latter presumably arose from the addition to the 15,16-double bond of the methanol used in the alkaline hydrolysis[5] of the side chain moiety.

The crude oil obtained from the acetic anhydride treatment of solasodine failed to crystallize, but yielded upon chromatography on alumina a crystalline compound. The analytical values of the latter indicated the structure of the unsaturated *O,N*-diacetyl derivative III. Its principal infrared absorption bands (λ_{max}^{chf} 2.91 and 3.00 μ, NH; 5.98, 6.61 μ, HN—C—CH_3) agreed well with those of the unsaturated *O,N*-diacetyl tomatidine[6] obtained by a similar chromatography on alumina of the so-called unsaturated triacetyltomatidine.[7]

The principal bands of III were also in agreement with those of *N*-acetyldihydrotomatidine and *N*-acetyltetrahydrosolasodine whose structures have been established.[8] The course of the oxidation of compound II, and the analogy of the latter with the unsaturated triacetyl derivative[7,9] of tomatidine obtained in the acetic anhydride treatment indicate strongly structures II and III, tentatively designated as derivatives of pseudosolasodine A. The amorphous material obtained from the acetic anhydride treatment of solasodine, unlike that from tomatidine,[7] was a mixture (indicated by infrared spectra and the isolation of another component as yet unidentified) and the yield of the pregnadienolone acetate (IV) was low (10–20%), while tomatidine had yielded about 60% of 16-allopregnenolone.[7] When 5,6-dihydrosolasodine was employed in this degradation the yield of 16-allopregnenolone again was quite poor showing that it is not the 5,6-double bond that is responsible for the difference in yields.

The exhaustive reduction of solasodine leads to the formation of tetrahydrosolasodine,[10] VIIa, with the uptake of 2 moles of hydrogen. When VIIa was

* This paper is a contribution in honor of Lyndon F. Small, former Editor of the Journal.

(1) A preliminary account of portions of this work was published in the *J. Am. Chem. Soc.*, **73**, 5009 (1951), and in *Chemistry & Industry*, 444 (1955).

(2) L. H. Briggs, W. E. Harvey, R. H. Locker, W. A. McGillivray, and R. N. Seelye, *J. Chem. Soc.*, 3013 (1950).

(3) F. C. Uhle, *J. Am. Chem. Soc.*, **75**, 2280 (1953); *J. Am. Chem. Soc.*, **76**, 4245 (1954).

(4) G. Oddo, *Ber.*, **62**, 267 (1929).

(5) D. K. Fukushima and T. F. Gallagher, *J. Am. Chem. Soc.*, **73**, 196 (1951).

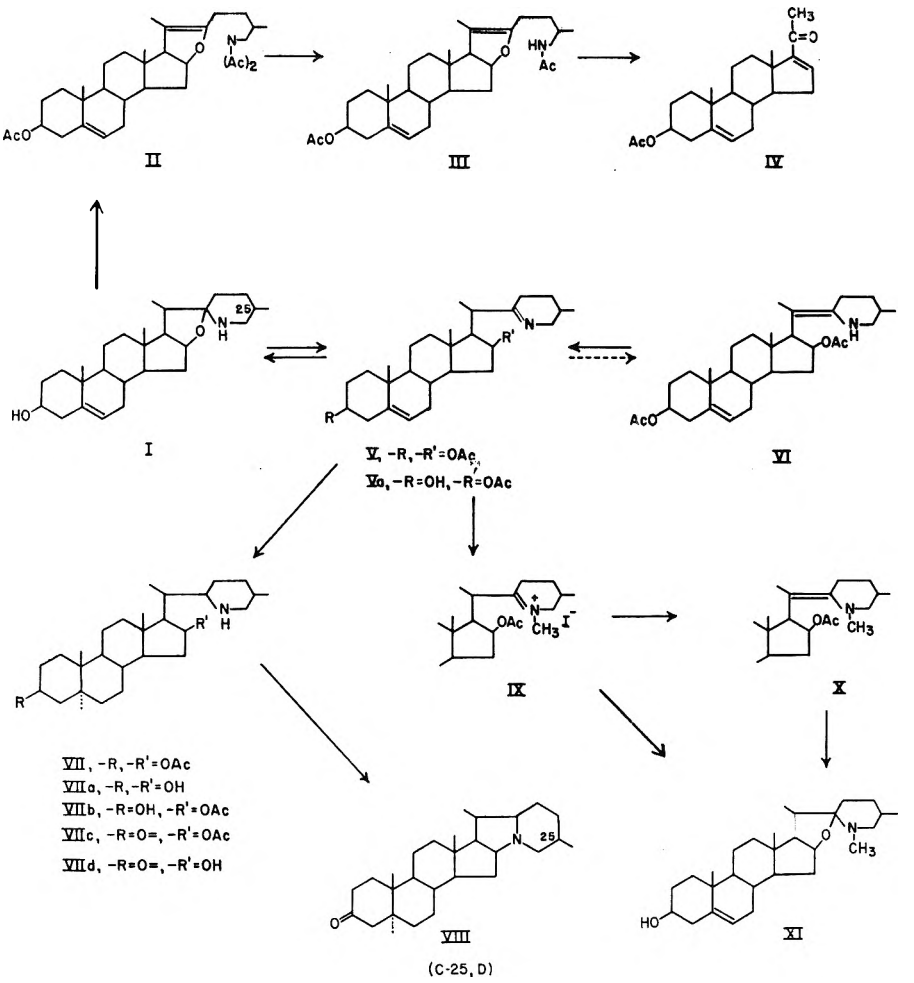
(6) To be published soon.

(7) Y. Sato, A. Katz, and E. Mosettig, *J. Am. Chem. Soc.*, **74**, 538 (1952).

(8) Y. Sato and H. G. Latham, Jr., *J. Am. Chem. Soc.*, **78**, 3150 (1956).

(9) R. Kuhn and I. Löw, *Chem. Ber.*, **85**, 416 (1952).

(10) H. Rochelmeyer, *Arch. Pharm.*, **277**, 329 (1939).



oxidized with Kiliani's reagent[11] in acetone, and the product subsequently reduced on palladium-charcoal, a new isomeric solanidan-3-one (VIII) was obtained.

The structure of compound VIII is based upon the fact that it was formed in a manner entirely analogous to that in which the two C-22 isomeric solanidan-3-ones (C-25, L) were obtained from the C-22 isomeric dihydrotomatidines (ring E opened).[12] Compound VIII being derived from solasodine must have the C-25, D configuration.[13] It remains open to question to which of the two C-22 isomeric solanidanones having the C-25, L configuration[12,14,15] ketone VIII corresponds. During the course of these studies an analogous sequence of reactions was applied to 3-deoxytetrahydrosolasodine[16] which led to a new solanidane with the C-25, D configuration.

When solasodine was treated with a solution of zinc chloride in acetic anhydride and acetic acid, the diacetate (V) of a new unsaturated derivative isomeric with the parent compound was obtained. This compound which we name, for the time being, pseudosolasodine B, probably exists to a large extent in the form of V, and equilibrates only under constraint to its tautomeric form VI. The following spectroscopic data led us to consider the above formulation: Infrared spectra[17] revealed a band of medium intensity at 6.0 μ, (indicative of a >C=N- band) besides a strong acetate band (5.79 μ). In the ultraviolet region of the spectrum there is a modest absorption (ϵ 243) at 242 mμ. The hydrochloride[18] possesses a broad ammonium band at 4.03 μ and an immonium band of medium intensity at 4.93 μ, accompanied by a shift of the 6.0 μ band to 5.88 μ. The appearance of these bands with its concomitant

(11) H. Kiliani, *Ber.*, **46**, 676 (1913). A solution of 53 g. of chromium trioxide and 80 g. of concentrated sulfuric acid in 400 g. of water.

(12) Y. Sato and H. G. Latham, Jr., *J. Am. Chem. Soc.*, **78**, 3146 (1956).

(13) F. C. Uhle and J. A. Moore, *J. Am. Chem. Soc.*, **76**, 6412 (1954).

(14) F. C. Uhle and W. A. Jacobs, *J. Biol. Chem.*, **160**, 243 (1945).

(15) V. Prelog and S. Szpilfogel, *Helv. Chim. Acta*, **27**, 390 (1944).

(16) L. H. Briggs, R. P. Newbold, and N. E. Stace, *J. Chem. Soc.*, 3 (1942).

(17) In normal concentrations (15 mg./ml., 0.5 mm. cell) no >NH stretching band is observed. An extremely weak band (3.03 μ) is observed in a saturated carbon disulfide solution.

(18) The perchlorate of V does not show an ammonium or immonium band but is accompanied by a shift of the 6.0 μ band at 5.91 μ. Some other perchlorates behave similarly.

shifts are in accord with the findings of Witkop[19] for a >C = N— and a possible >C = C — N< system as shown by Leonard and Gash.[20]

Also a number of chemical transformations support the structure of this unsaturated isomerization product. Mild hydrolysis of V with 2% methanolic potassium hydroxide or potassium bicarbonate selectively removed most likely the 3-acetyl group and gave the 16-acetate of pseudosolasodine B (Va) which was converted to the original solasodine (I) by further hydrolysis with 5% methanolic alkali. Vigorous hydrolysis of the 3,16-diacetylpseudosolasodine B (V) with 5% methanolic alkali yielded solasodine directly. Hydrogenation of V proceeded rapidly with the uptake of 2 moles of hydrogen to afford the oily tetrahydrodiacetyl derivative VII, which readily yielded the known tetrahydrosolasodine (VIIa) by alkaline hydrolysis. The lithium aluminum hydride reduction of V followed by catalytic hydrogenation of the 5,6-double bond led also to the same product (VIIa). Hydrogenation of the 16-acetylpseudosolasodine B (Va) afforded the 16-acetate of tetrahydrosolasodine (VIIb) which was oxidized to the 3-oxo derivative VIIc. Hydrolysis of VIIc in methanolic alkali to the keto-alcohol VIId, followed by oxidation and subsequent reduction led to the isomeric solanidan-3-one (VIII) which was prepared above directly from tetrahydrosolasodine (VIIa). Treatment of V with methyl iodide in acetone gave the methiodide of the diacetate (IX), $\lambda_{max}^{chlf.}$ 6.00 μ which when treated with sodium carbonate gave readily the tertiary amine (X) $\lambda_{max}^{chlf.}$ 6.06 μ, $\lambda_{max}^{alc.}$ 230 mμ (ϵ, 4650). The spectrophotometric measurements of X and its salts were in excellent agreement with the findings of Leonard *et al.*[20,21] for an α,β-unsaturated tertiary amine. Finally, the vigorous hydrolysis of IX or X with methanolic alkali produced XI which is very likely *N*-methylsolasodine. Although the elementary analytical values were acceptable, the compound could not be purified sufficiently to give a satisfactory melting range. Several attempts at a direct synthesis of XI from I failed.[22]

EXPERIMENTAL[23]

3β-Acetoxy-5,16-pregnadiene-20-one (IV). A mixture of 1.87 g. of solasodine and 30 ml. of acetic anhydride was refluxed for 1.5 hr. The acetic anhydride was removed *in vacuo* and the crude residue dissolved in 65 ml. of acetic acid. It was oxidized by gradual addition of 1.87 g. of chromium trioxide in 25 ml. of 90% acetic acid. The reaction mixture was allowed to stand for 1.8 hr. and poured into ice water. Methanol was added to destroy excess oxidant and the greenish solution was extracted with ether repeatedly. Some (450 mg.) acidic material soluble in 3% sodium carbonate solution was removed at this stage. The residue obtained by removal of the ether was dissolved in 30 ml. of 2% methanolic potassium hydroxide and refluxed for 20 min. The alkaline mixture was concentrated slightly and water added to it. Extraction with ether yielded 420 mg. of amorphous material. This was chromatographed on alumina, and the crystalline fractions eluted with benzene and ether (160 mg.) were acetylated in the usual manner with pyridine and acetic anhydride. Chromatography on alumina and elution with benzene–Skellysolve B (1:19) yielded the pregnadienolone acetate (IV) m.p. 174–176°, $[\alpha]_D^{20}$ −24.5° ± 4° (ethanol), identical in all respects with an authentic specimen.

Anal. Calcd. for $C_{23}H_{32}O_3$: C, 77.49; H, 9.05. Found: C, 77.38: H, 9.39.

Fractions subsequently eluted with benzene–Skellysolve B were rechromatographed over alumina and the fractions eluted with benzene–Skellysolve B (1:19) were crystallized from petroleum ether to yield needles of m.p. 158–160°, which were identified by direct comparison (m.p., mixture m.p. and infrared spectra) with an authentic specimen of 3β-acetoxy-16α-methoxy-5-pregnen-20-one. The combined yields of the pregnenolone derivatives in general were about 10%.

Unsaturated O,N-diacetylsolasodine (III). Solasodine (300 mg.) was refluxed with 5 ml. of acetic anhydride for 3 hr. After removal of the acetic anhydride *in vacuo*, the residue was triturated with water. The amorphous mass ($\lambda_{max}^{chlf.}$ 5.79, 6.00, and 6.08 μ) was collected, dried, and adsorbed on a neutral alumina column and allowed to stand for 2 hr. before elution. Elution with ether-methanol (99:1) then yielded 104 mg. of plates, $\lambda_{max}^{chlf.}$ 2.90, 2.98 μ (N—H); 5.78 μ (acetoxy); 5.98, 6.60 μ (NH-acetyl), m.p. 134–138° from acetone-hexane. [The first portion of the ether-methanol (99:1) eluates gave an amorphous substance whose structure is still unknown.]

Anal. Calcd. for $C_{31}H_{47}O_4N$: C, 74.81; H, 9.52. Found: C, 74.55; H, 9.51.

Degradation of 5,6-dihydrosolasodine to 16-allopregnen-3β-ol-20-one acetate. Dihydrosolasodine[16] (0.68 g.) was refluxed with 13 ml. of acetic anhydride for 4.5 hr. The crude oil obtained by removal of the acetic anhydride was oxidized with chromic oxide (0.6 g.) and processed as in the preparation of IV. The material recovered after alkaline hydrolysis was chromatographed over alumina. Fractions eluted with benzene–Skellysolve B and benzene were combined and crystallized from aqueous methanol to yield 70 mg. (11.8%) of crystalline allopregnenolone acetate. A sample recrystallized from the same solvent gave hexagonal plates of m.p. 165–166°, identical with an authentic specimen.

Anal. Calcd. for $C_{23}H_{34}O_3$: C, 77.05; H, 9.56. Found: C, 77.30; H, 9.43.

Isomeric solanidan-3-one (VIII) (5α, 25D). To 0.133 g. of tetrahydrosolasodine (VIIa) dissolved in 1 ml. of acetic acid and 25 ml. of acetone was slowly added 0.44 ml. of Kiliani's reagent[11] and the mixture allowed to stand for 15 min. in an ice bath. Several drops of water added to the reaction mixture rendered the turbid mixture clear and simultaneously a greenish oil was deposited. After decanting from

(19) B. Witkop, *Experientia*, **10**, 420 (1954); *J. Am. Chem. Soc.*, **76**, 5597 (1954); *J. Am. Chem. Soc.*, **78**, 2873 (1956).

(20) N. J. Leonard and V. W. Gash, *J. Am. Chem. Soc.*, **76**, 2781 (1954).

(21) N. J. Leonard and D. M. Locke, *J. Am. Chem. Soc.*, **77**, 437 (1955).

(22) Attempted methylation of solasodine by use of methyl iodide failed: *cf.* reference 16. The use of Eschweiler-Clarke modification of the Leuckart reaction seems to lead to an anomalous product. [*Org. Reactions*, **5**, 301 (1949)].

(23) All melting points were taken on the Kofler block and are uncorrected. Infrared spectra were taken on a Perkin-Elmer double beam spectrophotometer by Mr. H. K. Miller of this laboratory. Microanalyses were performed by the Analytical Service Laboratory under the direction of Dr. William C. Alford.

the oil the solution was made alkaline with dilute sodium hydroxide solution and saturated with sodium chloride. When the ethereal extract of the above solution was concentrated *in vacuo* the residue yielded a semi-crystalline mass. Crystallization from methanol yielded plates which melted at 126–129°. The compound is rather unstable and attempts at purification (chromatography) failed. The crude material was dissolved in ethyl acetate and reduced over 10% palladium-charcoal. After the uptake of 1 mol. of hydrogen, the product was chromatographed over alumina. The benzene-hexane, benzene, and benzene-ether eluates yielded plates from aqueous methanol which melted at 146–147°, $[\alpha]_D^{20}$ +49° (chlf.).

Anal. Calcd. for $C_{27}H_{43}ON$: C, 81.55; H, 10.90. Found: C, 81.79; H, 11.02.

Fractions eluted subsequently with 1% methanol in ether yielded small amounts of an alcohol of m.p. 160–167°, crystallizing from aqueous acetone as plates.

Anal. Calcd. for $C_{27}H_{45}ON$: C, 81.14; H, 11.35. Found: C, 81.27; H, 11.46.

Isomeric solanidane. (5α, 25D). 3-Desoxytetrahydrosolasodine[16] was treated in the same manner as described for the preparation of VIII, except that the reduction was carried out with platinum oxide in glacial acetic acid. The product crystallized from aqueous methanol as plates, m.p. 111–113°.

Anal. Calcd. for $C_{27}H_{45}N$: C, 84.52; H, 11.82. Found: C, 84.48; H, 11.56.

3,16-Diacetate of pseudosolasodine B (V). To 2 g. of solasodine was added 70 ml. of a zinc chloride solution (prepared by dissolving 8 g. of zinc chloride in a mixture of 70 ml. of acetic anhydride and 30 ml. of glacial acetic acid), and the solution was allowed to stand at room temperature overnight. The reaction mixture was then poured into ice water. After standing for 0.5 hr. with occasional stirring, concentrated ammonium hydroxide was added until the solution was alkaline and a copious precipitate was obtained. Upon crystallization from aqueous methanol 2.07 g. of plates was obtained. After two crystallizations from aqueous methanol, the compound melted at 188.5–192.5°, $[\alpha]_D^{20}$ +46.6° (chlf) $\lambda_{max}^{chlf.}$ 5.78 μ (acetoxy), 6.00 μ (>C=N—).

Anal. Calcd. for $C_{31}H_{47}O_4N$: C, 74.81; H, 9.52; CH_3—CO, 17.30. Found: C, 74.44; H, 9.47; CH_3—CO, 17.5.

Perchlorate of the 3,16-diacetate of pseudosolasodine B (V). Addition of 65% perchloric acid to an ethanol solution of V gave the salt which crystallized as prisms from aqueous ethanol. The substance melted at 150–155°.

Anal. Calcd. for $C_{31}H_{48}O_8NCl$: C, 62.24; H, 8.09. Found: C, 62.39; H, 8.12.

16-Acetate of pseudosolasodine B (Va). Mild hydrolysis of V with saturated methanolic potassium bicarbonate or 2% methanolic potassium hydroxide yielded the 16-acetyl derivative Va, m.p. 110–113°, $\lambda_{max}^{chlf.}$ 2.75 μ (hydroxyl); 5.75 μ (acetate); 5.97 μ (>C=N—). The elemental analysis was unsatisfactory.

Anal. Calcd. for $C_{29}H_{45}O_3N$: CH_3—CO, 9.45. Found: CH_3—CO, 9.9.

A more vigorous hydrolysis of Va with 5% methanolic potassium hydroxide for several hours yielded solasodine. This can also be obtained directly from the 3,16-diacetate of pseudosolasodine B (V) by hydrolysis with 5% methanolic potassium hydroxide.

The crude solasodine thus obtained was purified by chromatography over alumina and elution with 1% methanol in ether. It melted at 204–206.5° and was identical in every respect with an authentic specimen of solasodine.

Anal. Calcd. for $C_{27}H_{43}O_2N$: C, 78.39; H, 10.49. Found: C, 78.51; H, 10.75.

Conversion of V to tetrahydrosolasodine (VIIa). (*a*) A mixture of 72.5 mg. of V and 35 mg. of PtO_2 absorbed under atmospheric pressure and at room temperature 2 molar equivalents of hydrogen. The reducion product failed to crystallize but the acetyl band of its infrared spectrum indicated the diacetyl tetrahydrosolasodine VII. It was hydrolyzed without further purification with 5% methanolic potassium hydroxide yielding a product melting at 288–290° after crystallization from aqueous methanol, and identical in every respect with an authentic sample of tetrahydrosolasodine.

Anal. Calcd. for $C_{27}H_{47}O_2N$: C, 77.64; H, 11.34. Found: C, 77.36; H, 11.29.

(*b*) To a solution of 226 mg. of V in 50 ml. of dry ether was added gradually 75 ml. of a 1.62*M* ethereal solution of lithium aluminum hydride. After refluxing the mixture for 1.75 hr. the excess reductant was decomposed with ice water. The ethereal phase was washed thoroughly with water, and left after drying and evaporation a product which crystallized from aqueous methanol as heavy granules melting at 258–262°, apparently identical with Briggs' dihydrosolasodenol of m.p. 260–264°.[24] A mixture of the above product (19 mg.) and PtO_2 (18 mg.) in 5 ml. of acetic acid absorbed one molar equivalent of hydrogen. The reduction product after crystallization from aqueous methanol (heavy compact granules), melted at 286–290° and was identical in every respect with an authentic sample of tetrahydrosolasodine.

16-Acetyltetrahydrosolasodine (VIIb). The 16-acetate of pseudosolasodine B (2.3 g., Va) was reduced with 0.25 g. of platinum oxide catalyst in 30 ml. of glacial acetic acid. Two molar equivalents of hydrogen were absorbed. After removal of the catalyst, the filtrate was made alkaline with dilute ammonium hydroxide solution. The precipitate (2.3 g.) was chromatographed over neutral alumina and elution with 0.5% methanol in ether yielded 1.66 g. of 16-acetyltetrahydrosolasodine of m.p. 227–231°, $[\alpha]_D^{20}$ +29.5 ± 0.50 (chlf.).

Anal. Calcd. for $C_{29}H_{49}O_3N$: C, 75.77; H, 10.44. Found: C, 75.80; H, 10.44.

3-Oxo-16-acetyltetrahydrosolasodine (VIIc). 16-Acetyltetrahydrosolasodine (VIIb) (1.66 g.) was oxidized in three portions, each portion being dissolved in 100 ml. of acetone and treated with 1.6 ml. of Kiliani's reagent, at room temperature.[11] The reaction mixture was allowed to stand for 10 min. and a few drops of water was added to bring about solution, and almost simultaneously an oily mass of chromate salts was precipitated. The decantate was made alkaline with 6*N* sodium hydroxide solution with cooling, and after addition of an equal volume of water the resulting cloudy liquid was evaporated *in vacuo* until an amorphous precipitate flocculated. More water was added and the product collected and dried. After it was taken up in hexane-acetone (10:1) some insoluble matter was filtered off, and the solvent removed *in vacuo*. Two recrystallizations from hexane yielded needles (1.4 g.), m.p. 185–190°, $[\alpha]_D^{20}$ +57° (chlf.).

Anal. Calcd. for $C_{29}H_{47}O_3N$: C, 76.10; H, 10.35. Found: C, 76.06; H, 10.26.

3-Oxo-16-hydroxytetrahydrosolasodine (VIId). To 1.40 g. of VIIc was added 100 cc. of 5% potassium hydroxide in methanol, and the mixture refluxed for 1.5 hr. The resulting solution was concentrated and water added to precipitate a white solid which was collected and washed well with water. The yield was 1.18 grams, and the m.p. 197–208°. By chromatography over neutral alumina, and elution with 0.5% methanol in ether 0.677 g. of material was obtained, which gave after recrystallization from acetone-hexane colorless needles of m.p. 224.5–227°, $[\alpha]^{20}$ +4.5° (chlf.).

Anal. Calcd. for $C_{27}H_{45}O_2N$: C, 78.02; H, 10.91. Found: C, 77.86; H, 10.77.

Isomeric solanidan-3-one (VIII). (5β, 25D). VIId (180 mg.) was dissolved in 25 ml. acetone and oxidized with 0.32 ml. of Kiliani's reagent.[11] There was obtained 100 mg. of crude oil which crystallized as plates upon triturating with ether and methanol; m.p. 124–127°. A portion (79 mg.) of this crude crystalline mass was dissolved in 7 ml. of ethyl acetate and reduced over 44 mg. of palladium-charcoal

(24) L. H. Briggs and R. H. Locker, *J. Chem. Soc.*, 3020 (1950).

(10%). One molar equivalent of hydrogen was absorbed. The product crystallized from aqueous ethanol as plates. A thrice crystallized sample melted at 145–147°. It was identical with the substance obtained from the direct oxidation of tetrahydrosolasodine (VIIa), and subsequent catalytic reduction.

Anal. Calcd. for $C_{27}H_{43}ON$: C, 81.55; H, 10.90. Found: C, 81.67; H, 11.01.

Methiodide of 3,16-diacetate of pseudosolasodine B (IX). Compound V (133 mg.) was dissolved in 5 ml. of benzene and 10 ml. of acetone and refluxed with 1 ml. of methyl iodide for 75 min. Excess methyl iodide and solvent were removed *in vacuo* and the residue redissolved in acetone. Upon the addition of *n*-hexane, plates of m.p. 268–270° (dec.), $\lambda_{max}^{chlf.}$ 5.77, 6.00 μ, were obtained in a quantitative yield.

Anal. Calcd. for $C_{32}H_{50}O_4NI$: C, 60.08; H, 7.88; I, 19.85. Found: 60.07; H, 8.02; I, 19.78.

N-Methyl-3,16-diacetate of pseudosolasodine B (X). When IX was treated with a dilute aqueous sodium carbonate solution a compound was obtained which crystallized from aqueous methanol in rods of m.p. 194–197°, $\lambda_{max}^{chlf.}$ 5.77, 6.06 μ.

Anal. Calcd. for $C_{32}H_{49}O_4N$: C, 75.10; H, 9.65; —NCH_3, 2.9. Found: C, 74.91; H, 9.51; —NCH_3, 2.77.

The hydrochloride, $\lambda_{max}^{chlf.}$ 5.77, 5.98 μ, melted at 210–212° (dec.).

N-Methylsolasodine (XI). The methiodide of IX (110 mg.) was dissolved in 20 ml. of 5% methanolic potassium hydroxide and refluxed for 90 min. Although the resulting product was chromatographed over alumina, it appeared to be inhomogeneous, melting partly at 159–162° and partly at 176–180°. Infrared data of the eluates indicated the possible presence of another substance.

Anal. Calcd. for $C_{28}H_{45}O_2N$: C, 78.65; H, 10.60. Found: C, 78.59; H, 10.57.

BETHESDA, MD.

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

A Practical Synthesis of Thieno[3,2-*b*]pyrrole*†

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Pyrrole is converted to 3-thiocyanopyrrole (I) in 50% yield by thiocyanation with methanolic thiocyanogen at −70° or with cupric thiocyanate at 0°. Addition of excess dilute potassium hydroxide to a cold methanolic solution of bromoacetic acid and 3-thiocyanopyrrole leads to (3-pyrrolylthio)acetic acid (II), isolated as the ammonium salt in 90% yield. Under similar conditions, methyl iodide and 3-thiocyanopyrrole yield 3-(methylthio)pyrrole (Vc). Ring closure of the acid II with polyphosphoric acid furnishes 2*H*,3*H*-thieno[3,2-*b*]pyrrol-3-one (III) in 36% yield. The structure of III is proved by desulfurization with Raney nickel catalyst, which yields 2-acetylpyrrole. Reduction of III with sodium borohydride leads to thieno[3,2-*b*]pyrrole (IV) in 62% yield.

Thieno[3,2-*b*]pyrrole (IV) is an isostere of indole, having the fused thiophene ring in place of the benzene nucleus of the latter substance. The development of the chemistry of this simple, unsubstituted heterocycle may be expected to add to the fundamental knowledge of the thiophene and pyrrole systems and of interactions between them. Further, the possibility of preparing isosteres of physiologically active indole compounds from thieno[3,2-*b*]pyrrole makes the problem of devising a useful synthesis of the substance an intriguing one.

Although a synthesis of thieno[3,2-*b*]pyrrole (IV) from thiophene has been completed,[2] a great many steps were required and the final product was not obtained in a state of high purity. These difficulties prompted us to investigate the synthesis of thienopyrroles from pyrrole. Notwithstanding the well known sensitivity of pyrrole and such monosubstitution products as chloropyrrole and alkylpyrroles to air, light, and acids,[3] the readiness with which it undergoes electrophilic substitution reactions[3,4] made pyrrole an attractive raw material for the contemplated syntheses.

Thiocyanation appeared to be the most promising method for affixing a suitably substituted sulfur atom to the pyrrole ring. Numerous examples of thiocyanation of active aromatic systems under mild conditions are known.[5] Thiocyanation of carbethoxydimethylpyrroles has been reported.[6] Thiocyanation of pyrrole itself with ammonium thiocyanate and bromine has been reported to yield a dithiocyano derivative of undetermined structure.[6]

The fact that most reagents attack pyrroles at an unsubstituted α-position in preference to an unsubstituted β-position has been accounted for on the basis of the resonance theory.[4] However, recent molecular orbital calculations[7] indicate that the π-electron density in pyrrole is higher at the β-positions than at the α-positions. If, in the transition state, the pyrrole ring and an electrophilic reagent

* This paper is a contribution in honor of Lyndon F. Small, former Editor of the Journal.

† For a preliminary communication on this subject, see D. S. Matteson and H. R. Snyder, *J. Am. Chem. Soc.*, **79**, 3610 (1957).

(1) National Science Foundation Predoctoral Fellow, 1954–1957.

(2) H. R. Snyder, L. A. Carpino, J. F. Zack, Jr., and J. F. Mills, *J. Am. Chem. Soc.*, **79**, 2556 (1957).

(3) H. Fischer and H. Orth, *Die Chemie des Pyrrols*, Akademische Verlagsgesellschaft m. b. H., Leipzig, 1934, Vol. I, pp. 23–24, 37–38, 79.

(4) R. C. Elderfield, *Heterocyclic Compounds*, John Wiley and Sons, Inc., New York, 1950, Vol. I, pp. 300–301.

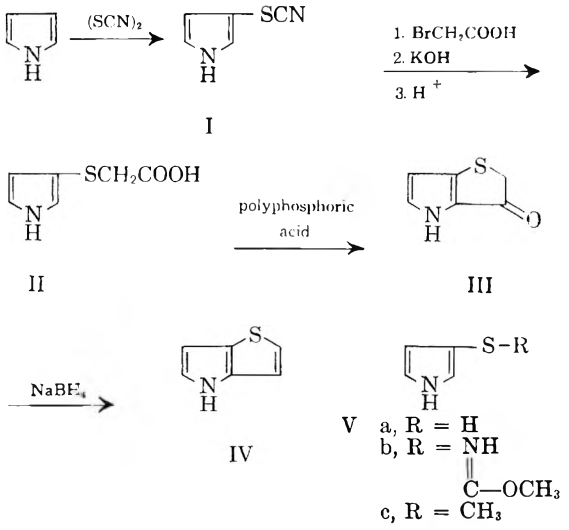
(5) J. L. Wood, *Org. Reactions*, **3**, 240–266 (1946).

(6) P. Pratesi, *Atti reale accad. Lincei*, **16** (6) 9, 443 (1933); *Chem. Zentralblatt* I, 2815 (1933).

(7) R. D. Brown, *Australian J. Chem.*, **8**, 100 (1955).

are far enough apart that little bond-making has occurred, the π-electron density should determine the orientation and the substituent should enter the β-position. On the other hand, if the pyrrole ring and the reagent are near enough in the transition state to form a bond the π-electrons must be localized, and since localization requires less energy at the α-position the substituent should enter at this point. Thus, according to the molecular orbital view, pyrrole could be attacked preferentially at the α-position by certain electrophilic reagents, but at the β-position by others.

When pyrrole was treated with cupric thiocyanate[8] in methanol at 0°, thiocyanation was apparently complete in a few minutes, and a substance shown to be 3-thiocyanopyrrole (I) by conversion to the bicyclic compounds III and IV described below was obtained in moderate yield. Isolation of 3-thiocyanopyrrole presented no difficulty, as the compound crystallized when the reaction mixture was poured onto ice; saturation of the solvent phase with sodium chloride increased the amount of crystalline material recovered. The use of cupric thiocyanate, although convenient for small-scale exploratory experiments, has disadvantages for the preparation of large amounts of an intermediate for synthetic use. At −75° a methanolic solution of thiocyanogen, conveniently prepared from potassium thiocyanate and bromine, reacts rapidly and exothermically with pyrrole; 3-thiocyanopyrrole (I) was obtained in yields equal to those from the cupric thiocyanate procedure.



The most commonly used process for the conversion of thiocyanates to mercaptans is reduction;[5] 2,4-dimethyl-3-mercapto-5-carbethoxypyrrole has been prepared by reduction of the thiocyanate with zinc and acetic acid.[6] Treatment of thiocyanates with sodium hydroxide usually yields disulfides,[5] but thiophenol has been obtained from phenyl thiocyanate upon treatment with sodium ethoxide.[9] Several attempts to isolate 3-mercaptopyrrole (Va) failed. Zinc and acetic acid appeared not to react with 3-thiocyanopyrrole (I) at 20°. Basic reagents, including sodium hydroxide, sodium carbonate, and liquid ammonia, rapidly decomposed 3-thiocyanopyrrole (I) to dark red materials. When 3-thiocyanopyrrole (I) was treated with a limited amount of sodium hydroxide in methanol at 0°, sodium cyanate, characterized by the infrared spectrum and conversion to the silver salt, crystallized in 83% yield. Treatment of 3-thiocyanopyrrole (I) with methanolic magnesium methoxide furnished *S*-3-pyrrolyl *O*-methyl thioimidocarbonate (Vb) in excellent yield. With basic reagents, the thioimidocarbonate Vb decomposed in the same manner as did the thiocyanate I. Although 3-thiocyanopyrrole (I) appeared unaffected by mild treatment with mineral acids, the thioimidocarbonate was attacked by dilute acetic acid; insufficient effort was expended to obtain any single hydrolysis product in good yield. A more promising route to 3-(alkylthio)pyrroles was found and attempts to isolate 3-mercaptopyrrole (Va) were abandoned.

It was found that the anion of 3-mercaptopyrrole (Va), which apparently decomposes almost as rapidly as it is formed, does have a long enough existence to displace halide ion from a moderately active alkyl halide, if the halide is present in the reaction mixture at the time the anion of Va is generated. Treatment of a methanolic solution of 3-thiocyanopyrrole (I) and methyl iodide at 0° with an excess of dilute potassium or sodium hydroxide furnished 3-(methylthio)pyrrole (Vc) in excellent yield.

Treatment of a methanolic solution of 3-thiocyanopyrrole (I) and chloroacetic, bromoacetic, or iodoacetic acid with dilute potassium hydroxide yielded (3-pyrrolylthio)acetic acid (II). Preliminary experiments, in which the calcium salt of the acid II was isolated, indicated that yields from chloroacetic acid were lower than those from bromoacetic or iodoacetic acid. When cooling in an ice-salt bath was used with large-scale preparations, neutralization at 0° of the bromoacetic acid with potassium hydroxide required a longer time than was considered desirable in view of the possible instability of either the bromoacetic acid or its anion in the reaction mixture. Accordingly, the reaction mixture was cooled in a Dry Ice–acetone bath during addition of the alkali. It appeared that potassium bromoacetate precipitated at the low temperatures and further reaction did not take place until the reaction mixture was allowed to warm to about −20°.

Since the liquid (3-pyrrolylthio)acetic acid (II) decomposed on attempted distillation, it was isolated as a salt. The calcium salt was found to be very soluble in water and difficult to purify. The pure crystalline ammonium salt was obtained in ex-

(8) H. P. Kaufmann and K. Kuchler, *Ber.*, **67**, 944 (1934).

(9) J. Ross, *J. Am. Chem. Soc.*, **56**, 727 (1934).

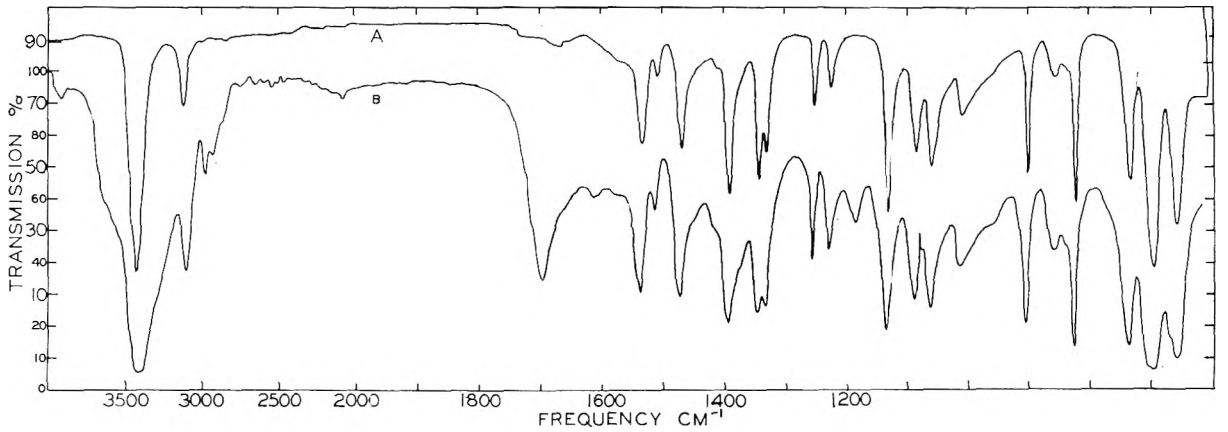


FIG. 1. CURVE A: Thieno[3,2-*b*]pyrrole prepared from 2*H*,3*H*-thieno[3,2-*b*]pyrrol-3-one. CURVE B: Thieno[3,2-*b*] pyrrole prepared from thieno[3,2-*b*]pyrrole-5-carboxylic acid.

cellent yield when a solution of the acid II in methylene chloride was treated with anhydrous ammonia.

Bromoacetal failed to react with 3-thiocyanopyrrole (I) under the conditions used for the reaction of methyl iodide; evidently, the anion of 3-mercaptopyrrole (Va) decomposed faster than it displaced bromide ion from this reagent. Active alkyl halides, such as phenacyl bromide, ethyl bromoacetate and chloropyruvate ion, appeared to be attacked by hydroxide ion more rapidly than was 3-thiocyanopyrrole, with the result that they also failed to give sulfides.

It was found that 2*H*,3*H*-thieno[3,2-*b*]pyrrol-3-one (III) could be prepared in fair yield by the slow addition of a dilute methylene chloride solution of (3-pyrrolylthio)acetic acid (II) to hot, stirred polyphosphoric acid.[10] A few experiments on the effect of varying the temperature were made; the optimum range appeared to be 120–130°.

Several other methods for cyclizing (3-pyrrolylthio)acetic acid (II) were tested. Trituration of the calcium salt of II with polyphosphoric acid at 80–90° for one hour yielded a small amount of the cyclic ketone III. A black tar resulted when a similar reaction mixture was heated to 120°. Triturating the reagents and allowing the mixture to stand overnight at room temperature yielded none of the ketone. Treatment of the acid II with anhydrous hydrogen fluoride for four hours yielded none of the ketone III. Attempts to prepare the acid chloride of II showed no promise. Thionyl chloride reacted vigorously with the acid II, even in ether solution at −70°, or with the calcium salt, to form black polymeric material. Excess phosphorus oxychloride formed red polymeric material from the calcium salt of II.

Desulfurization of 2*H*,3*H*-thieno[3,2-*b*]pyrrol-3-one (III) with Raney nickel catalyst yields 2-acetylpyrrole. The structure of 2-acetylpyrrole, m.p. 90°, has been proved by degradation;[11] furthermore, 3-acetylpyrrole, m.p. 116°, has been synthesized *via* a ring closure.[12] Other structural features of the ketone III are confirmed by the infrared spectrum (Nujol). The presence of an NH group is indicated by a strong band at 3140 cm.$^{-1}$; every sulfur-substituted pyrrole in the present series exhibits a similar band between 3100 and 3500 cm.$^{-1}$. A carbonyl group conjugated with an electron-donating system is indicated by a strong absorption band at 1635 cm.$^{-1}$ in the infrared spectrum of the ketone III. The high melting point of the compound III and its stability to air and to mild acids are consistent with the properties of other acylpyrroles, but not with those expected of the tautomeric enol form. The 2*H*,3*H*-thieno-[3,2-*b*]pyrrol-3-one structure thus appears to be the better representation of the compound.

Sodium borohydride in methanol reduces 2*H*,3*H*-thieno[3,2-*b*]pyrrol-3-one (III) to thieno[3,2-*b*]-pyrrole (IV) in good yield. Liquid IV darkened after a few hours' exposure to air and light, but in a tightly stoppered container in the refrigerator, solid IV appeared to be stable for weeks. The odor of IV was mild and resembled that of indole; with Ehrlich's reagent, IV gave a deep blue color. The infrared spectra of the analytical sample of the above material (IV) (smear) and a less pure sample synthesized from thiophene[2] are shown in Fig. 1. The major impurity in the latter sample is evidently thieno[3,2-*b*]pyrrole-5-carboxylic acid, from which the sample was prepared by decarboxylation.

EXPERIMENTAL[13]

3-Thiocyanopyrrole (I). Even in very dilute solutions, 3-thiocyanopyrrole (I) reacts with human skin to form deep

(10) The polyphosphoric acid was generously supplied by the Victor Chemical Works, 141 W. Jackson Blvd., Chicago 4, Ill.

(11) G. Ciamician and P. Silber, *Ber.*, 20, 2594 (1887).

(12) I. J. Rinkes, *Rec. trav. chim.*, 57, 423 (1938).

(13) All melting points are corrected. Microanalyses were performed by J. Nemeth and his associates. Infrared spectra were determined by James Brader and his associates. Ultraviolet spectra were determined by M. S. Chao.

red stains, and more concentrated solutions cause a burning or itching sensation. For this reason, one should always wear rubber gloves when handling 3-thiocyanopyrrole. If contact with the skin is suspected, the affected area should be washed immediately with soap and water and then treated with 3% hydrogen peroxide. This treatment is usually sufficient to prevent serious staining; however, once the red color has formed, it remains until the stained skin has been replaced.

One hundred twenty-five milliliters of methanol was chilled in a Dry Ice-acetone bath, and 159.8 g. (1 mole) of bromine was added. Two hundred grams (2.06 moles) of potassium thiocyanate (free from large lumps) and 250 ml. of methanol were placed in a flask fitted with a mechanical stirrer and an alcohol thermometer, then chilled in a Dry Ice-acetone bath to below −75°. The mixture was stirred vigorously and kept below −60° while the chilled bromine solution was added from a dropping funnel. The solution of thiocyanogen prepared in this manner was light yellow and contained suspended material, presumably potassium bromide.

A solution of 67.1 g. (1 mole) of redistilled pyrrole in 250 ml. of methanol was chilled to −75°. The thiocyanogen solution described above, also chilled to −75°, was stirred very vigorously while the cold pyrrole solution was added as rapidly as possible through a powder funnel. Within a few seconds after the addition of the pyrrole, the temperature of the reaction mixture rose to between −40° and −30°, then began to fall. The cooling bath was removed and the mixture was stirred until it warmed to −25°. It was then poured onto approximately 2 kg. of crushed ice, and 300 g. of sodium chloride was added. The mixture was agitated occasionally for about 0.5 hr., and the 3-thiocyanopyrrole (I) was collected on a Buchner funnel large enough (5–6 in.) to accommodate the unmelted ice. The solids on the funnel were washed freely with water; most of the remaining ice was removed mechanically and the product was rinsed from it. The crude 3-thiocyanopyrrole (I), which darkened on standing, was dried in a vacuum desiccator. The dry material was recrystallized from 100 ml. of methylene chloride and 500 ml. of methylcyclohexane in the following manner. The solid was dissolved in the methylene chloride, about half the methylcyclohexane was added, and the solution was warmed to about 40°. Magnesium sulfate and Darco were added, the solution was filtered, and the solid residue was washed with methylcyclohexane. Since the solution was still red, the treatment with magnesium sulfate and Darco was repeated. The nearly colorless solution was cooled to just above the temperature at which cloudiness appeared, seeded, and left at 0° overnight. The mixture was finally chilled for a half-hour in an ice-salt bath before the long, colorless needles were collected and dried at room temperature. The yield of 3-thiocyanopyrrole (I), m.p. 40–44°, was 62 g. (50%). By chilling the mother liquor to −70°, additional crude product was obtained that weighed 4 g. after recrystallization, m.p. 40–44°.

The infrared spectrum of a sample of 3-thiocyanopyrrole (I) (in carbon tetrachloride) prepared by the above method was identical to that of a sample prepared from cupric thiocyanate and pyrrole.

Thiocyanation of pyrrole with cupric thiocyanate. A solution of 6.71 g. (0.1 mole) of pyrrole in 75 ml. of methanol was kept at 0–5° with an ice bath and stirred under nitrogen while 0.2 mole (on the basis of a thiocyanogen analysis) of cupric thiocyanate was added in several portions over a period of a few minutes. Stirring at 0–5° was continued 50 min., the cuprous thiocyanate was removed by filtration and washed with 50 ml. of methanol, and the filtrate was poured onto approximately 300 g. of crushed ice. One hundred grams of sodium chloride was added. The solids were collected and the 3-thiocyanopyrrole (I) was washed from the excess sodium chloride with 225 ml. of warm methylcyclohexane. After treatment with Darco, the solution was cooled and seeded, and crystallization was allowed to proceed at 0° overnight. The yield of 3-thiocyanopyrrole (I), m.p. 40–43°, was 5.83 g. (47%). An analytical sample was recrystallized twice from methylcyclohexane, m.p. 41.5–43°.

Anal. Calcd. for $C_5H_4N_2S$: C, 48.36; H, 3.25; N, 22.55. Found: C, 48.72; H, 3.15; N, 22.80.

S-3-Pyrrolyl O-methyl thioimidocarbonate (Vb). Under nitrogen, 1.87 g. (0.075 mole) of magnesium turnings was dissolved in 125 ml. of reagent grade methanol. The solution of magnesium methoxide, which contained a small amount of precipitated magnesium hydroxide, was cooled in an ice-salt bath and 6.2 g. (0.05 mole) of 3-thiocyanopyrrole (IX) was added. After the 3-thiocyanopyrrole was dissolved, the mixture was allowed to stand for 1 hr. in the ice-salt bath. The mixture was poured into 500 ml. of water and 200 ml. of ether, and sufficient solid carbon dioxide was added to dissolve the precipitated magnesium hydroxide. The ether phase was separated and the aqueous phase was extracted with additional portions of ether. The combined ether solutions were dried over magnesium sulfate and the ether was evaporated under reduced pressure. The residue sublimed at 75°, 0.1 mm. The yield of *S*-3-pyrrolyl *O*-methyl thioimidocarbonate (Vb) (m.p. 75–80°, softens at 65°) was 6.8 g. (87%). An analytical sample was recrystallized from toluene, resublimed, recrystallized from aqueous methanol and again resublimed (55–65°/0.1 mm.), m.p. 77–80°.

Anal. Calcd. for $C_6H_8N_2OS$: C, 46.14; H, 5.16; N, 17.94. Found: C, 46.14; H, 5.07; N, 17.78.

3-(Methylthio)pyrrole (Vc). A solution of 6.21 g. (0.05 mole) of 3-thiocyanopyrrole (I) and 8.5 g. (0.06 mole) of methyl iodide in 50 ml. of methanol was cooled below 0° in an ice-salt bath and stirred under nitrogen during the addition of a solution of 7.9 g. (0.12 mole) of 85% potassium hydroxide in 20 ml. of water and 20 ml. of methanol over a period of 10 min. The cooling bath was removed and stirring was continued for 1.5 hr. The excess alkali was neutralized with solid carbon dioxide and the reaction mixture was poured into a solution of 100 g. of sodium chloride in 500 ml. of water. The organic material was extracted with three 50-ml. portions of methylene chloride; the solution was dried over potassium carbonate and the solvent was evaporated under reduced pressure. The residue was distilled; the yield of 3-(methylthio)pyrrole (Vc), b.p. 60–66° at 3.5 mm., was 5.1 g. (90%). An analytical sample was redistilled, b.p. 88–89° at 12 to 13 mm.

Anal. Calcd. for C_5H_7NS: C, 53.06; H, 6.24; N, 12.38. Found: C, 52.22; H, 6.27; N, 12.19.

Ammonium (3-pyrrolylthio)acetate (ammonium salt of II). A solution of 62.1 g. (0.5 mole) of 3-thiocyanopyrrole (I) and 83.5 g. (0.6 mole) of bromoacetic acid in 500 ml. of methanol was cooled below −50° in a Dry Ice-acetone bath and stirred rapidly during the addition of a solution of 123 g. (1.87 moles) of 85% potassium hydroxide in 500 ml. of 50% aqueous methanol over a period of 10 min. The cooling bath was removed and stirring was continued for 2 hr.; at the end of this time the mixture had warmed nearly to room temperature. The excess alkali was neutralized (*p*H 8) with solid carbon dioxide and the solvent was evaporated under reduced pressure in a warm water bath (a steam bath caused excessive bumping) until no visible liquid remained. Five hundred milliliters of methylene chloride was added to the solid residue, and the mixture was stirred while 375 ml. of ice-cold 4*N* hydrochloric acid was added at a rate such that carbon dioxide evolution was kept under control. After separation of the methylene chloride phase, the aqueous phase was extracted with two 250-ml. portions of methylene chloride. The combined methylene chloride solutions were dried over magnesium sulfate, treated with Darco, and filtered. An excess of anhydrous ammonia was bubbled into the solution and ammonium (3-pyrrolylthio)acetate (the ammonium salt of II) crystallized. The yield was 78 g. (90%); m.p. 127–133°, softens at 117°. For preparation of an analytical sample, the ammonium salt was treated with 1*N* hydrochloric acid and the free acid II was extracted with

methylene chloride. The methylene chloride solution was dried over magnesium sulfate and the ammonium salt of II crystallized upon treatment with anhydrous ammonia, m.p. 125–133°.

Anal. Calcd. for $C_6H_{10}N_2O_2S$: C, 41.35; H, 5.78; N, 16.08. Found: C, 41.59; H, 5.73; N, 15.77.

The calcium salt of II was prepared from the acid II and calcium hydroxide. An analytical sample was recrystallized twice, with much loss of material, from a small amount of water; m.p. 112–120° (dec.). The salt apparently contained two moles of water of crystallization.

Anal. Calcd. for $C_{12}H_{16}N_2O_6S_2Ca$: C, 37.1; H, 4.15; N, 7.20. Found: C, 37.25; H, 4.19; N, 6.95.

The methyl ester of II was prepared in 20% yield by refluxing a dilute methanolic solution of the ammonium salt of II with zinc chloride for 20 hr. The ester was purified by extraction followed by distillation in a sublimation apparatus at 0.1 mm., 80°; the liquid so obtained was submitted for analysis.

Anal. Calcd. for $C_7H_9NO_2S$: C, 49.10; H, 5.30; N, 8.18. Found: C, 49.01; H, 5.30; N, 8.31.

2H,3H-Thieno[3,2-b]pyrrol-3-one (III). Two hundred and fifty milliliters of methylene chloride and 17.42 g. (0.1 mole) of ammonium (3-pyrrolylthio)acetate (ammonium salt of II) were shaken with 30 ml. of ice-cold 6*N* hydrochloric acid. After separation, the aqueous phase was further extracted with two 250-ml. portions of methylene chloride. The combined methylene chloride solutions were treated with magnesium sulfate and Darco and filtered; the magnesium sulfate was washed with 150 ml. of methylene chloride, which was then combined with the filtrate. Four hundred grams of polyphosphoric acid[10] was heated to 120–123° and stirred very vigorously while the methylene chloride solution of (3-pyrrolylthio)acetic acid (II) was allowed to drop directly into the most vigorously agitated region of the polyphosphoric acid over a period of 50 min.; the methylene chloride vapor was allowed to escape (into the hood) through an open neck of the flask. When the addition was complete, the reaction mixture was allowed to cool below 100°; 1200 ml. of water and 750 ml. of ethyl acetate were stirred mechanically while the reaction mixture was added slowly, and stirring was continued for 0.5 hr. afterwards. The aqueous layer, the emulsion, and the ethyl acetate layer were separated. The aqueous layer was extracted with 250 ml. of ethyl acetate; 300 g. of sodium chloride was added, and the aqueous solution was further extracted with two 250 ml. portions of ethyl acetate. The emulsion fraction was neutralized with sodium bicarbonate, warmed on the steam bath, and extracted with three 100-ml. portions of ethyl acetate. The combined ethyl acetate solutions were washed with aqueous sodium bicarbonate until free of acid and dried over magnesium sulfate. The ethyl acetate was evaporated under reduced pressure and the residue was sublimed twice at 0.1 mm. at about 120°. The yield of 2*H*,3*H*-thieno[3,2-*b*]-pyrrol-3-one (III) (m.p. 183–188.5°, softens 140°) was 5.0 g. (36%). An analytical sample was resublimed twice, recrystallized twice from aqueous dimethylformamide, again sublimed twice and, after treatment with Darco, recrystallized from methanol; m.p. 187–190°, softens slightly at 165°; ultraviolet spectrum (in 95% ethanol): λ_{max} 330 mμ, ϵ_{max} 7400, λ_{min} 303, ϵ_{min} 3900, λ_{max} 279, ϵ_{max} 16,000, λ_{min} 236, ϵ_{min} 500.

Anal. Calcd. for C_6H_5NOS: C, 51.78; H, 3.62; N, 10.07. Found: C, 52.04; H, 3.82; N, 10.14.

Desulfurization of 2H,3H-thieno[3,2-b]pyrrol-3-one (III). A solution of 0.28 g. (2 millimoles) of 2*H*,3*H*-thieno[3,2-*b*]-pyrrole-3-one (III) in approximately 35 ml. of 95% ethanol was heated under reflux with about 2.5 g. of Raney nickel catalyst (W6) for 1 hr. The solution was filtered; the catalyst was washed freely with ethanol, and the washings were combined with the filtrate. The ethanol was evaporated under reduced pressure and the residue was sublimed. The yield of crude acetylpyrrole was 0.06 g. After recrystallization from water, the yield was 23 mg. (10%); m.p. 89–91°, not depressed upon admixture with an authentic sample.[14] The authentic sample of 2-acetylpyrrole was prepared from pyrrolylmagnesium bromide and acetyl chloride; Oddo[14] used pyrrolylmagnesium iodide. The infrared spectra of the sample of 2-acetylpyrrole prepared by the desulfurization described above and of the authentic sample (in chloroform) were identical.

Thieno[3,2-b]pyrrole (IV). A solution of 1.39 g. (0.01 mole) of 2*H*,3*H*-thieno[3,2-*b*]pyrrol-3-one (III) and 1.5 g. of sodium borohydride in 50 ml. of methanol was refluxed 16 hr. under nitrogen. The reaction mixture was poured into 200 ml. of 15% aqueous sodium chloride solution and the product was extracted with three 50-ml. portions of methylene chloride. The methylene chloride solution was dried over magnesium sulfate, the solvent was evaporated under reduced pressure, and the residue was sublimed.

Thieno[3,2-*b*]pyrrole (IV) sublimed rapidly at 60–70°, 0.1 mm.; after a small amount had condensed on the cold finger as an oil, it was induced to crystallize by rubbing it with a spatula that had been chilled with Dry Ice, and when sublimation was resumed the rest of the material condensed as a solid. The yield was 0.76 g. (62%). A considerable amount of less volatile residue remained; after sublimation at 120°, 0.1 mm., followed by recrystallization from methanol, 0.31 g. of the ketone III, m.p. 184–190°, was obtained. The infrared spectrum of this sample (Nujol) was similar to that of the analytical sample of III; small differences were attributed to impurities. The yield of thieno[3,2-*b*]pyrrole (IV) based on the ketone III consumed was 80%. An analytical sample of IV was recrystallized from ether-pentane at −70° and resublimed three times, m.p. 25–28°; u.v. (in 95% ethanol): λ_{max} 260 mμ, ϵ_{max} 11,800, λ_{min} 233, ϵ_{min} 4900.

Anal. Calcd. for C_6H_5NS: C, 58.50; H, 4.09; N, 11.38. Found: C, 58.60; H, 4.27; N, 11.32.

URBANA, ILL.

(14) B. Oddo, *Ber.*, **43**, 1012 (1910).

Derivatives of Morphine. II.[1] Demethylation of 14-hydroxycodeinone. 14-Hydroxymorphinone and 8,14-Dihydroxydihydromorphinone*

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Demethylation of 14-hydroxycodeinone (III) with aqueous HBr yields 14-hydroxymorphinone (IV) and 8,14-dihydroxydihydromorphinone (V) in varying proportions. V is formed from IV in alkaline medium during isolation, the double bond of the α,β-unsaturated ketone IV being hydrated with unusual ease by alkali. Control of conditions during this step of the isolation procedure permits reproducible preparation of either IV or V.

It has been found[1] that 14-hydroxydihydrocodeinone (I) can be demethylated normally with aqueous HBr to give 14-hydroxydihydromorphinone (II), a compound of considerable analgesic activity. The observation that the tertiary hydroxyl of I survived even the rather drastic conditions of the demethylation reaction[3] suggested a study of the analogous demethylation of 14-hydroxycodeinone (III).[4] Under the conditions used for the preparation and isolation of II, *i.e.*, brief treatment with concentrated HBr at 120°, removal of non-phenolic material by extraction with $CHCl_3$ from alkaline medium, and extraction of the phenolic reaction products with chloroform or chloroform-ethanol at *p*H 8–9, III was found to give varying proportions of two new phenolic substances, IV, $C_{17}H_{17}NO_4$, and V, $C_{17}H_{19}NO_5$, in modest yields. Of those compounds, IV was shown to be 14-hydroxymorphinone, the normal demethylation product of III, while V was identified as 8,14-dihydroxydihydromorphinone, the product of hydration of the double bond of IV. Separation of the two compounds was possible because of the great difference in their solubilities in ethanol and acetone.

14-Hydroxymorphinone, IV, was obtained in two mutually interconvertible forms: recrystallization from ethanol yielded beautiful square platelets of bright yellow color, while recrystallization from a very large volume of benzene gave perfectly colorless needles. The latter crystals darken above 200° and decompose at 255° to a voluminous black mass; the yellow platelets blacken at about 250°, but show no volume increase up to about 300°. Recrystallization from benzene converts the yellow form to the colorless one; the latter, on recrystallization from ethanol, in some cases even on mere contact with it, is changed to the yellow modification. The same change is produced by recrystallization from acetone. Both forms are little soluble in the common organic solvents; neither contains solvent of crystallization. Their infrared spectra in the solid state (KBr pellet) are different, whereby especially the location of the carbonyl stretching band is interesting: colorless form, 1685 cm.$^{-1}$, yellow form, 1660 cm.$^{-1}$.[5]

The structure of IV follows from its composition and physical and chemical properties: solubility in aqueous alkali with bright yellow color, typical of phenolic α,β-unsaturated ketones of the morphine series;[6] blue color with $FeCl_3$ in aqueous medium, no color in ethanolic medium, a behavior characteristic of morphine derivatives with intact oxygen bridge. The location of the carbonyl bands in the infrared spectra is additional evidence for the presence of an α,β-unsaturated ketone.

For final proof of structure, IV was converted to III by brief treatment with diazomethane, and to II by catalytic hydrogenation. Compound V, $C_{17}H_{19}NO_5$, forms fine colorless, silky needles, sparingly soluble in non-polar organic solvents; they decompose at about 222°. The compound is further distinguished from IV by its much greater solubility in ethanol, acetone, and hot water. The reaction with $FeCl_3$ is similar to that of IV. The solution in aqueous alkali is colorless, showing that V is not an α,β-unsaturated ketone; this is further confirmed by the location of the carbonyl band at 1730 cm.$^{-1}$ (Nujol).

Composition and properties suggested identification of V as 8,14-dihydroxydihydromorphinone. This assumption was proven by methylation with diazomethane to the methyl ether, VI. This compound was shown to be identical with authentic 8,14-dihydroxydihydrocodeinone (VI), prepared by the method of Vieböck:[7] reaction of thebaine (VII) with manganic acetate or lead tetraacetate in acetic acid to give VIII, which on brief treatment with hot dilute HCl yields VI. Furthermore, V was converted to IV by hot HCl, in analogy to the reaction VI → III.

The unpredictable appearance of V, sometimes as

* This paper is a contribution in honor of Lyndon F. Small, former Editor of the Journal.

(1) Paper I: *J. Am. Chem. Soc.*, **77**, 5891 (1955).

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(3) *cf.* R. E. Lutz and L. F. Small, *J. Org. Chem.*, **4**, 220 (1939), concerning the unusual stability of this OH group.

(4) M. Freund and E. Speyer, *J. Prakt. Chem.*, (2) 94, 135 (1916).

(5) The two modifications of IV are analogous to the colorless and yellow forms of the related α,β-unsaturated ketone metathebainone (IX), which were observed by L. F. Small and E. Meitzner, *J. Am. Chem. Soc.*, **55**, 4602 (1933).

(6) C. Schöpf and H. Hirsch, *Ann.*, 489, 224 (1931); U. Weiss and N. Weiner, *J. Org. Chem.*, **14**, 194 (1934).

(7) F. Vieböck, *Ber.*, **67**, 197 (1934).

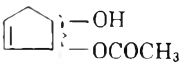
the only isolable phenolic compound from the demethylation of III, sometimes as a minor by-product, was at first tentatively ascribed to some unrecognized variation in the exposure of the alkaloidal material to *acid*, either during the demethylation itself or during subsequent operations. This assumption was based on the finding of Findlay and Small[8] that codeinone (X) undergoes slow conversion into 8-hydroxydihydrocodeinone (XI) in dilute acid; formation of V from IV would be entirely analogous to this reaction. However, experiments where the conditions of the acidic stages of the reaction were varied, failed to show any consistent influence upon the proportion of V obtained.

The explanation for the appearance of V was subsequently found in the exceptional sensitivity of IV to *alkali*. In alkaline medium, IV is converted into V with unexpected ease; the yellow color of a solution of IV in *N* NaOH fades in approximately 30 min. at room temperature, and high yields of V can be isolated from the solution. The formation of V from IV therefore takes place during the removal of the non-phenolic bases by extraction with chloroform from *alkaline* medium; consequently, strict control of the conditions during this step makes it possible to isolate at will either IV or V from the demethylation of III. Alkalinity not exceeding 0.1*N*, low temperature, and short time of exposure lead to IV together with only a small amount of V, while less mild conditions favor the preponderant or exclusive formation of V.

This ready conversion of IV into V suggested the possibility that the analogous reaction of III to give VI might likewise take place, since the reaction mixture contains much unchanged III. Small amounts of VI were actually found in the non-phenolic fractions of the demethylation experiments. The compound was isolated by treatment of the mixed non-phenolic bases with ethanol, which leaves III undissolved on account of its exceptionally low solubility in alcohol; evaporation of the filtrate to dryness, and treatment of the residue with 2*N* HCl gave the hydrochloride of VI, which is very little soluble in dilute HCl.[7] After recrystallization from 2*N* HCl and conversion to the base, pure VI was obtained, m.p. 173°. The total yield of VI obtained in this fashion was very small, indicating that the hydration of the double bond in III proceeds much less readily than that of IV.

The crude reaction mixture from the demethylation of III, after exposure to alkali, therefore contains unchanged III, the product of its demethylation (IV), of its hydration (VI), and of both reactions combined (V).

The hydroxyl groups in C_8 and C_{14} of V and VI are undoubtedly *cis* to each other. This follows not only from the strong hindrance to approach to the back side of C_8 in the morphine series, but also from the fact that Vieböck[7] obtained VIII, the intermediate in the formation of VI, on treatment of VII not only with manganic acetate, but also with lead tetraacetate in acetic acid. The latter reagent should yield a *cis*-monoacetate by analogy with the strong preponderance of *cis*- monoacyl derivatives (XII) in the reaction of cyclopentadiene with lead tetraacetate in acetic acid.[9]



XII

EXPERIMENTAL

14-Hydroxymorphinone (IV). In a round-bottom flask equipped with reflux condenser, stirrer, and thermometer, 300 ml. concentrated aqueous hydrobromic acid was heated to 90–100°; 30 g. 14-hydroxycodeinone (III) was added in one portion, the temperature of the stirred liquid was brought to 115° as fast as possible, and kept between 115 and 120° for 12 min. III dissolved rapidly, and the solution turned dark brown. The flask was next immersed in an ice bath and 600 g. ice was added, followed by dropwise addition, with continued mechanical stirring and ice-cooling, of 10% aqueous NaOH to neutral reaction. Near neutrality, a flocculent precipitate appeared, and the solution became darker. Ten per cent aqueous NaOH was next added rapidly to a final concentration of 0.1*N*, and the dark brown, ice-cold solution was extracted four times with chloroform *as fast as possible*. The extracts contained the non-phenolic bases (see below). The aqueous layer was *at once* acidified with dilute hydrochloric acid and treated with charcoal. The *p*H of the yellow filtrate was adjusted with aqueous ammonia to pink reaction on phenolphthalein paper, and the filtrate was extracted about 10 times with chloroform-ethanol (2:1).[10] The combined extracts were dried with sodium sulfate, filtered, and evaporated under reduced pressure. The solid residue was kept at room temperature for about 24 hr. with 60 ml. acetone, which dissolved the V present. The insoluble residue of IV usually weighed 10–15 g., although the yields were rather variable. Evaporation of the mother liquors and treatment of the residue with a small volume (about 10 ml.) of acetone at room temperature left another small crop of IV undissolved. The crude IV, recrystallized from about 70 volumes of boiling ethanol, yielded bright yellow square platelets, while purification from about 300 volumes of boiling benzene gave colorless needles. Recrystallization of the yellow form from benzene yields the colorless modification; the reverse change takes place on recrystallization from ethanol or acetone.

The *hydrochloride* of IV is crystalline and insoluble in ethanol and dilute HCl (2:1). IV was not precipitated by aqueous perchloric acid or Reinecke-salt, or by alcoholic picric acid; it did not give any color with *m*-dinitrobenzene and alkali.

Anal.[11] Calcd. for $C_{17}H_{17}NO_4$: C, 68.21; H, 5.73. Found: (*a*) Colorless form (dried in vacuo at 120°; no weight loss) C, 68.46; H, 5.97. (*b*) Yellow form (dried in vacuo at 78° to constant weight; no loss in weight, no change in color) C, 68.25; H, 5.68. Microhydrogenation:[11] 8.012 mg. IV (colorless form) took up 0.621 ml. hydrogen; calcd. for one molar equivalent 0.600 ml. (Pd-charcoal as catalyst).

(8) S. P. Findlay and L. F. Small, *J. Am. Chem. Soc.*, **73**, 4001 (1951).

(9) F. V. Brutcher, Jr., and F. J. Vara, *J. Am. Chem. Soc.*, **78**, 5695 (1956).

(10) A. Stoll, J. Renz, and W. Kreis, *Helv. Chim. Acta*, **20**, 1484 (1937).

(11) Microanalyses by Schwarzkopf Microanalytical Laboratory, Woodside 77, N. Y.

Methylation of 14-hydroxymorphinone. Treatment of 30 mg. IV (colorless form) in ice-cold methanol with a slight excess of ethereal diazomethane for 15 min., evaporation of the solvent, and recrystallization of the residue from methanol gave 14-hydroxycodeinone (III), m.p. and mixed m.p. 276–278° (decomp.). The infrared spectrum (KBr pellet) was identical with that of an authentic sample. A part of the material was converted to the perchlorate; m.p. and mixed m.p. with an authentic sample 246–247° (Lutz and Small[3] gave m.p. 241–242°).

Catalytic hydrogenation of 14-hydroxymorphinone. Four hundred mg. IV (yellow form), dissolved in a slight excess of dilute HCl, was reduced with Pd-charcoal as catalyst. After the end of the reaction, the catalyst was filtered off, the filtrate was evaporated *in vacuo*, and the crystalline residue of II hydrochloride was dissolved in water. Addition of a few drops of aqueous ammonia precipitated 14-hydroxydihydromorphinone (II), 250 mg., m.p. 245–247°. Extraction of the filtrate with chloroform gave an additional 64 mg. Recrystallization from ethanol and ethyl acetate gave pure II, m.p. and mixed m.p. 250° (decomp.).

8,14-Dihydroxydihydromorphinone (V). *A. By demethylation of 14-hydroxycodeinone.* The demethylation of III was carried out as described before; however, after cooling and addition of ice, the solution was made strongly alkaline by adding, dropwise and with stirring and ice-cooling, a solution of 120 g. NaOH in 200 ml. water. After removal of the nonphenolic bases from the alkaline liquid by extraction with chloroform, the aqueous layer was acidified with dilute HCl, treated with charcoal, and adjusted to a *p*H of approximately 8 with aqueous ammonia. It was next seeded with V and allowed to stand for 1–2 days at room temperature. Much of the V present crystallized out; the remainder could be obtained from the filtrate by extraction with chloroform-ethanol (2:1). The crude yield was up to about 60%.

The product was purified by dissolving it in a small amount of warm acetone, treating with charcoal, and diluting the filtrate with twice its volume of water; pure V crystallized from the solution in long silky needles. Alternatively, the compound could be purified by recrystallization from hot water. It decomposes at about 220–222° (bath preheated to 200°), the melting point depending somewhat upon the rate of heating. The compound is little soluble in benzene; the solution in aqueous NaOH is colorless.

Anal. Calcd. for $C_{17}H_{19}NO_5$: C, 64.34; H, 5.88. Found (dried *in vacuo* at 100°): C, 64.23; H, 5.87.

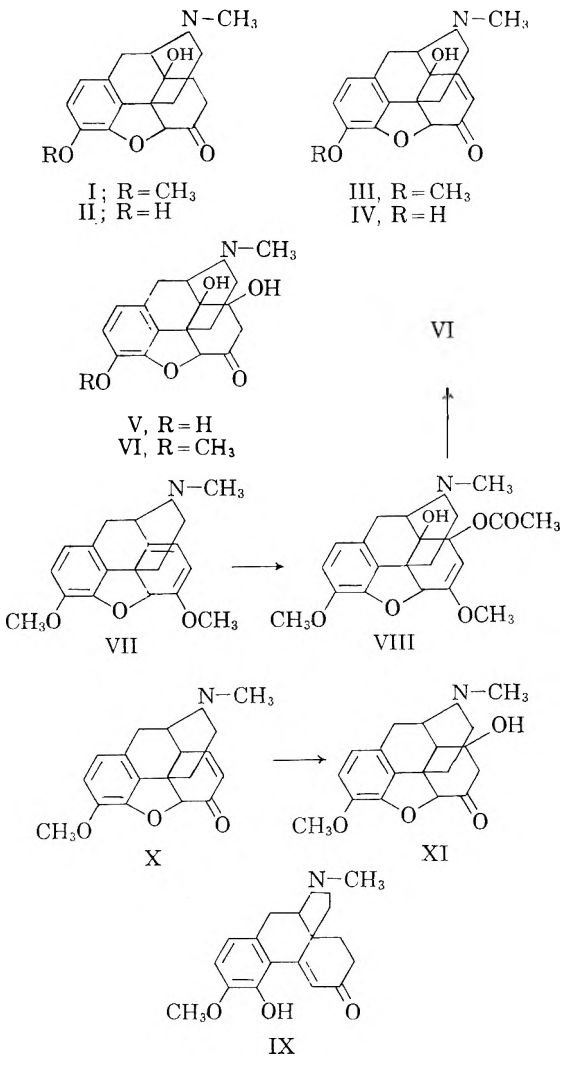
B. By hydration of 14-hydroxymorphinone. Two tenths of a gram of pure IV (yellow form) was dissolved at room temperature in 20 ml. normal NaOH, and the intensely yellow solution was kept at room temperature. The color was much less intense after 10 min., and after about 30 min. it had faded to a pale yellow which did not undergo any further change within another 30 min. The base was isolated as described before. Evaporation of the chloroform-ethanol extracts gave 0.15 g. V, which was purified from ethanol-water to give the pure compound, m.p. and mixed m.p. 222° (decomp.).

Methylation of 8,14-dihydroxydihydromorphinone. Pure V (200 mg.) was dissolved at room temperature in 10 ml. methanol. To the ice-cold solution, a slight excess of ethereal diazomethane was added. After standing at room temperature for 15 min., the solution was evaporated completely under reduced pressure. The foamy residue was treated successively with small quantities of ethanol and benzene, which were distilled off. The solid became crystalline on rubbing with ethyl acetate. Recrystallization from very dilute ethanol gave needles, m.p. about 165° (bath preheated to about 160°), the melting point depending much upon the rate of heating.[12] The compound was therefore identified as 8,14-dihydroxydihydrocodeinone (VI) by establishing identity of the infrared spectrum with that of an authentic sample prepared by the method of Vieböck,[7] rather than by mixed melting point.

Dehydration of 8,14-dihydroxydihydromorphinone to 14-hydroxymorphinone (cf.[7]). V (0.7 g.) was warmed with a mixture of 3.2 ml. concentrated HCl and 4 ml. water in a boiling water bath for 20 min. The solution was cooled and treated with excess 5% aqueous $NaHCO_3$. The orange solution, on standing in the refrigerator for several days, deposited a small amount of unchanged V. Extraction of the filtrate with chloroform gave IV, yellow crystals from ethanol, decomp. about 250°, alone and mixed with authentic IV. The yellow color of the solution in NaOH further confirmed the identification as IV.

Non-phenolic fractions; isolation of 8,14-dihydroxydihydrocodeinone. The chloroform solution containing the nonphenolic fraction from the demethylation of III was dried over Na_2SO_4, filtered, and evaporated. The residue was treated at room temperature for 24 hr. with 30 ml. ethanol. The insoluble residue (3.5 g.) consisted mostly of unchanged III, which was purified *via* the well-crystallized perchlorate. The ethanol filtrate was evaporated to dryness under reduced pressure and the residue was taken up in 2*N* HCl. The base dissolved, and on rubbing and seeding the hydrochloride of 8,14-dihydroxydihydrocodeinone (VI) crystallized out; the salt is little soluble in 2*N* HCl.[7]

It was filtered off, washed cautiously with 2*N* HCl and with acetone, and dried; yield, 0.7 g. This crude salt was



(12) This experiment was carried out before the value of the hydrochloride of VI (see right) for purification had been observed.

purified by rapid recrystallization from hot 2*N* HCl; the white, well-crystallized compound decomposes at about 260°, after partial melting around 220°, followed by resolidification. From its solution in warm water, aqueous Na_2CO_3 precipitated the base (VI), m.p. 173° (bath preheated to 160°), alone and in mixture with authentic material. Heating of a sample of the substance with dilute HCl (1:1) in a boiling water bath for 20 min. converted to III, m.p. and mixed m.p. 275° after purification via the perchlorate.

VI forms a crystalline perchlorate of low water-solubility; decomp. 257°.

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[CONTRIBUTION NO. 368 FROM THE RESEARCH LABORATORIES OF HOFFMANN-LA ROCHE, INC.]

4-Aminomethyl-4′-aminodiphenylsulfone and Related Compounds*

WILHELM WENNER

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4-Aminomethyl-4′-aminodiphenylsulfone and a number of its derivatives carrying substituents in the aliphatic amino group have been prepared starting with 4-methyl-4′-nitrodiphenylsulfone. Several related compounds are described.

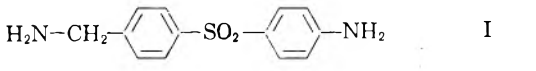
The chemotherapeutic properties of sulfanilamide are changed considerably when the aromatic amino group is replaced by the aminomethyl substituent. Whereas sulfanilamide is more active against aerobic bacteria, 4-aminomethylbenzenesulfonamide[1–4] is superior in its action against anaerobic bacteria.[2,5–8] It appeared worthwhile to prepare compounds containing an aromatic as well as an aliphatic amino group, with the hope of obtaining a sulfa drug exhibiting both types of activity. The simplest compound of this type is 4-aminomethyl-4′-aminodiphenylsulfone I. This sulfone has been described by Klarer[6] and by Dewing,[9] who prepared it from 4-acetylaminomethylbenzenesulfinic acid. In order to obtain in addition to 4-aminomethyl-4′-aminodiphenylsulfone derivatives carrying substituents in the aliphatic amino group, I carried out a different synthesis by which such derivatives are accessible in an unambiguous manner.

The key intermediate in the synthesis is 4-methyl-4′-nitrodiphenylsulfone[10] (II). The compound is prepared in high yields from *p*-thiocresol and *p*-nitrochlorobenzene over 4-methyl-4′-nitrodiphenylsulfide[11] (III), which is oxidized with hydrogen peroxide to II. The alternative procedure of condensing *p*-toluenesulfinic acid with *p*-nitrochlorobenzene gave only low yields.

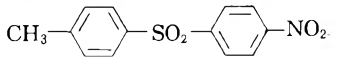
The sulfone II was brominated to the bromomethyl derivative IV. The method of Genvresse,[12] using elementary bromine at 160°, gave poor yields. However, when benzoyl peroxide was added, the bromination in nitrobenzene proceeded well, resulting in yields of 70% and more of IV.

Reaction of the bromosulfone with a number of secondary amines and with benzylamine gave the amino nitro sulfones listed in Table I. Compound V, unsubstituted in the amino group, was obtained according to Mannich and Hahn[13] by the treatment of IV with hexamethylenetetramine followed by acid cleavage.

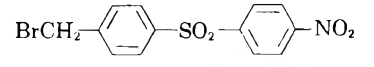
Catalytic hydrogenation of the nitro derivatives yielded the desired 4-aminomethyl-4′-aminodiphenylsulfone (I) and its alkyl derivatives, listed in Table III. The compounds lack outstanding chemo-



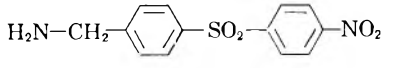
I



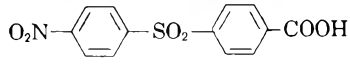
II



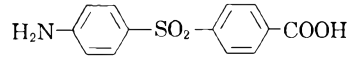
IV



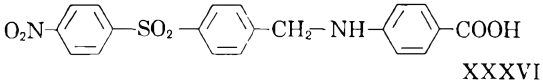
V



XXIX



XXXI



XXXVI

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* This paper is a contribution in honor of Lyndon F. Small, former Editor of the Journal.

(1) Anonymous, *Nature*, **153**, 707 (1944).

(2) Hamre, Walker, Dunham, van Dyke, and Rake, *Proc. Soc. Exp. Biol. Med.*, **55**, 170 (1944).

(3) Klarer, U. S. Patent **2,288,531**; *Chem. Abstr.*, **37**, 888 (1943); Germ. Pat. **726,386**, *Chem. Zentr.*, **114 I**, 978 (1943).

(4) Klarer, *Angew. Chem.*, **56**, 10 (1943).

(5) Klarer, *Klin. Wochschr.*, **20**, 1250 (1941); *Chem. Abstr.*, **37**, 5704 (1943).

(6) Klarer, *Naturforschung und Medizin in Deutschland 1939–1946*, Vol. **43**, Chemotherapie, Wiesbaden, Dietrichsche Verlagsbuchhandlung, 1948, p. 1935.

(7) Lawrence, *J. Bacteriol.*, **49**, 149 (1945).

(8) Mitchell, *Lancet*, **I**, 627, 635 (1944).

(9) Dewing, *J. Chem. Soc.*, 466 (1946).

(10) Louden, *J. Chem. Soc.*, **218**, 220 (1936).

(11) Law and Johnson, *J. Am. Chem. Soc.*, **52**, 3623 (1930).

(12) Genvresse, *Bull. soc. chim. France*, (3) **9**, 707 (1893).

(13) Mannich and Hahn, *Ber.*, **44**, 1542 (1911).

therapeutic properties. Some quaternary derivatives were also prepared. They are listed in Table II.

In addition to these sulfones, two nitro amino sulfides were prepared through the ω-bromo derivative of 4-methyl-4′-nitrodiphenylsulfide (III). The bromination of III in the same manner as described above for the sulfone did not succeed. With *N*-bromosuccinimide and benzoyl peroxide[14] a small amount of the bromomethyl compound XXVI was formed, which was not isolated in pure form. It was allowed to react in the crude state with the appropriate amines to the piperidino (XXVII) and the benzylamino derivative (XXVIII).

The sulfone II was oxidized to the nitro acid XXIX, which was then reduced to the amino acid XXXI. This acid has previously been prepared in a different manner by Roblin and Clapp.[15] Both acids were converted into their methyl esters. The methyl ester of XXXI was converted into the hydrazide XXXIII. None of the acids or their derivatives showed valuable chemotherapeutic properties.

To complete the series of the amino derivatives, the intermediates II and III were catalytically hydrogenated to 4-methyl-4′-aminodiphenylsulfide[11] (XXXIV) and 4-methyl-4′-aminodiphenylsulfone[10] (XXXV). Both compounds showed only moderate antibacterial activity.

When the bromosulfone IV is allowed to react with *p*-aminobenzoic acid, 4-[4-(4-nitrophenylsulfonyl)benzylamino]benzoic acid XXXVI is obtained. Catalytic hydrogenation gave the corresponding amino acid XXXVII.

EXPERIMENTAL

The melting points are uncorrected.

(*1*) *4-Methyl-4′-nitro-diphenylsulfide*[11] (III). To a stirred refluxing solution of 248 g. of *p*-thiocresol and 315 g. of *p*-nitrochlorobenzene in 2000 ml. of abs. ethanol, a solution of 90 g. of sodium hydroxide in 100 ml. of water was slowly added. Heating was continued after complete addition for 3 to 4 hr. After cooling and addition of about 200 ml. of water, 4-methyl-4′-nitrodiphenylsulfide crystallized. Recrystallization from ethanol gave the pure compound which was light yellow and melted at 76–78°. Law and Johnson[11] give m.p. 81.5°. The yield was 450–470 g.

Anal. Calcd. for $C_{13}H_{11}NO_2S$: C, 63.65; H, 4.52; N, 5.71. Found: C, 64.19; H, 4.41; N, 5.65.

(*2*) *4-Methyl-4′-aminodiphenylsulfide*[11] (XXXIV). 4-Methyl-4′-nitrodiphenylsulfide (15 g.) was hydrogenated in 45 ml. of methanol to which 0.1 ml. of acetic acid had been added, with 2 g. of Raney nickel, at 50–60° and 300 lbs. pressure. The filtered solution was distilled to dryness and the residue was crystallized from abs. ethanol, yielding 10 g. of pure 4-methyl-4′-aminodiphenylsulfide of m.p. 178–179°. Law and Johnson[11] report m.p. 183–184°.

Anal. Calcd. for $C_{13}H_{13}NS$: C, 72.52; H, 6.08; N, 6.51. Found: C, 72.38; H, 5.68; N, 6.53.

(*3*) *4-Methyl-4′-nitrodiphenylsulfone* (II). A. From the sulfide. A solution of 400 g. of 4-methyl-4′-nitrodiphenylsulfide in 2000 ml. of glacial acetic acid was stirred and heated to 80–90°. Over a period of about 1 hr., 600 g. of hydrogen peroxide (30%) were added slowly. The originally dark brown solution turned bright yellow and shortly after the beginning of the oxidation, crystals appeared. Heating was continued for 1 hr. after complete addition of the hydrogen peroxide. After cooling for several hours at 0–10°, the sulfone was filtered. It melted at 169°. The yield was 430–440 g.

Anal. Calcd. for $C_{13}H_{11}NO_4S$: C, 56.30; H, 4.00; N, 5.05. Found: C, 56.41; H, 3.83; N, 5.01.

B. *From 4-toluene sulfinic acid* (13). The sodium salt of 4-toluenesulfinic acid[16] (6 g.), 8 g. of 4-nitrochlorobenzene and 20 ml. of abs. ethanol were heated to 170° for 3 hr. in a bomb tube.[17] The resulting dark material was digested with hot water and, after cooling, the undissolved portion was extracted with ether. The remaining crystals were recrystallized from acetic acid, yielding 1.3 g. of 4-methyl-4′-nitrodiphenylsulfone of m.p. 166–168°.

Anal. Calcd. for $C_{13}H_{11}NO_4S$: C, 56.30; H, 4.00; N, 5.05. Found: C, 56.36; H, 3.74; N, 4.95.

The yield could not be improved by adding copper powder, or by using the copper salt of 4-toluenesulfinic acid, or by using other solvents (ethyleneglycol, "carbitol").

(*4*) *4-Methyl-4′-aminodiphenylsulfone*[10] (XXXV). 4-Methyl-4′-nitrodiphenylsulfone (II), (20 g.), was suspended in 30 ml. of methanol. The mixture was hydrogenated with about 2 g. of Raney nickel at 50–60° and 500 lbs. Part of the product had crystallized. It was brought into solution by addition of about 50–70 ml. of methanol and refluxing. The catalyst was removed by filtration of the hot mixture. The filtrate was concentrated to a small volume and was allowed to cool. The crude crystals were recrystallized from 50% acetic acid, yielding 15 g. of pure 4-methyl-4′-aminodiphenylsulfone of m.p. 180–182°.

Anal. Calcd. for $C_{13}H_{13}NO_2S$: C, 63.13; H, 5.30; N, 5.68. Found: N, 5.95.

(*5*) *4-Bromomethyl-4′-nitrodiphenylsulfone* (IV). A mixture of 72 g. of 4-methyl-4′-nitrodiphenylsulfone and 80 ml. of nitrobenzene was stirred and heated to 155–160°. After addition of 1 g. of benzoyl peroxide, 16 ml. of bromine were added through a dropping funnel below the surface of the reaction mixture. The addition was regulated so that no bromine escaped. This required about 4 hr. After cooling, the crystals were filtered and washed thoroughly with benzene. The crude bromo compound weighed about 60–65 g. and melted at 145–150°. It contained some unchanged starting material but was pure enough for further reactions

The pure bromo derivative was obtained by two crystallizations from 4 vol. of dioxane. It melted at 177–178°.

Anal. Calcd. for $C_{13}H_{10}BrNO_4S$: C, 43.83; H, 2.83. Found: C, 44.16; H, 2.80.

Other methods of bromination (without benzoyl peroxide, in other solvents, with *N*-bromosuccinimide) were unsatisfactory.

(*6*) *4-Aminomethyl-4′-nitrodiphenylsulfone* (V). A mixture of 72 g. of crude 4-bromomethyl-4′-nitro-diphenylsulfone and 30 g. of hexamethylene tetramine in 400 ml. of chloroform was refluxed for 8 hr. The crystals were filtered, washed with chloroform, suspended in 400 ml. of methanolic hydrochloric acid (18% HCl) and stirred for 5 hr., with exclusion of moisture. A precipitate appeared slowly and was filtered after standing overnight. The crystals were refluxed with 800 ml. of fresh methanolic hydrochloric acid (18% HCl) for 5 hr. After cooling, the crystals were filtered, washed with abs. ethanol, and dried in a desiccator. The yield was 34 g. Recrystallization from glacial acetic acid yielded pure 4-aminomethyl-4′-nitrodiphenylsulfone monohydrochloride (V) of m.p. 273–274°.

Anal. Calcd. for $C_{13}H_{12}N_2O_4S{\cdot}HCl$: C, 47.49; H, 3.99, N, 8.52. Found: C, 47.19; H, 4.04; N, 8.13.

(14) Karrer and Schmid, *Helv. Chim. Acta*, **29**, 573 (1946).

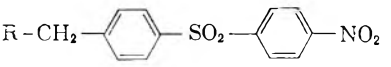
(15) Roblin and Clapp, Brit. Pat. **568,157**; *Chem. Abstr.*, **41**, 3817 (1947).

(16) Whitmore and Hamilton, *Org. Syn.*, **Coll. Vol. I.**, Sec. Ed., 1941, p. 492.

(17) Compare: Ferry, Buck, and Baltzly, *Org. Syn.*, **Coll. Vol. 3**, 1955, p. 239.

TABLE I

4-SUBSTITUTED 4-AMINOMETHYL-4′-NITRO-DIPHENYLSULFONES



Compound	R	Formula	M.P.	Analysis Calcd. / Found C	H	N
V	$-NH_2$	$C_{13}H_{12}N_2O_4S\cdot HCl$		See Exp. 6		
VII	$-N(CH_3)_2$	$C_{15}H_{16}N_2O_4S$		See Exp. 9		
		$C_{15}H_{16}N_2O_4S\cdot HCl$		See Exp. 9		
VIII	$-N(C_2H_5)_2$	$C_{17}H_{20}N_2O_4S$	76°	58.60 58.73	5.79 5.76	8.02 7.88
		$C_{17}H_{20}N_2O_4S\cdot HCl$	206°	53.08 53.23	5.50 5.65	7.08 7.40
IX	$-N(CH_2CH_2CH_3)(CH_2CH_2CH_3)$	$C_{19}H_{24}N_2O_4S$	77–78°	60.61 60.80	6.43 6.16	7.44 7.23
		$C_{19}H_{24}N_2O_4S\cdot HBr$	180–182°	49.87 50.34	5.51 5.45	6.13 6.05
X	$-N(CH_2CH_2CH_2CH_3)(CH_2CH_2CH_2CH_3)$	$C_{21}H_{28}N_2O_4S$	59–60°	62.35 62.13	6.98 6.61	6.93 7.00
		$C_{21}H_{28}N_2O_4S\cdot HBr$	160–161°	51.88 52.01	6.02 6.11	5.77 5.54
XI	$-N(CH_2CH_2)(CH_2CH_2)CH_2$	$C_{18}H_{20}N_2O_4S$	66–68°	59.98 59.87	5.59 5.17	7.77 7.42
		$C_{18}H_{20}N_2O_4S\cdot HCl$	237–238°	54.47 54.56	5.33 5.34	7.06 6.98
XII	$-N(CH_2CH_2)(CH_2CH_2)O$	$C_{17}H_{18}N_2O_5S$	170–171°	56.34 56.52	5.01 5.15	7.73 7.67
		$C_{17}H_{18}N_2O_5S\cdot HBr$	218–220°	46.05 45.81	4.32 4.60	6.23 6.06
XIII	$-NH\cdot CH_2C_6H_5$	$C_{20}H_{18}N_2O_4S\cdot HCl$	259–260°	57.33 57.09	4.41 4.32	6.69 6.59

(7) *4-(4-Nitrophenylsulfonyl)benzylurea* (VI). 4-Aminomethyl-4′-nitrodiphenylsulfone hydrochloride (7 g.), (Exp. 6), was dissolved by warming in 200 ml. of dilute methanol (60%). A solution of 2 g. of potassium cyanate in 25 ml. of water was added and the mixture was heated to 70–80° for 4 hr. Crystals separated slowly. They were purified by two crystallizations from 50% acetic acid and one crystallization from *n*-butanol. The yield of pure 4-(4-nitrophenyl-sulfonyl)benzylurea of m.p. 198–200° was 4 g.

Anal. Calcd. for $C_{14}H_{13}N_3O_5S$: C, 50.15; H, 3.91; N, 12.53. Found: C, 50.08; H, 3.47; N, 12.26.

(8) *Substituted 4-aminomethyl-4′-nitrodiphenylsulfones.* The reactions between 1 mole of 4-bromomethyl-4′-nitrodiphenylsulfone and two moles of secondary amines were carried out by warming the components in benzene, toluene, dioxan, or chloroform. The resulting amino derivatives were isolated over the free bases and converted into salts with mineral acids. As an example, the preparation of one compound is described in detail.

(9) *4-Dimethylaminomethyl-4′-nitrodiphenylsulfone* (VII). Crude 4-bromomethyl-4′-nitrodiphenylsulfone (39 g.) was dissolved in 200 ml. of hot dioxan. The solution was added slowly through a dropping funnel to a stirred solution of 18 g. of dimethylamine in 80 ml. of benzene which was cooled to 20–25°. When the addition was finished, the mixture was warmed for 1 hr. to 40–50°. Dimethylamine hydrobromide crystallized and was filtered off. The filtrate was distilled to dryness *in vacuo*. The residue was boiled with about 600 ml. of 10% hydrochloric acid for 1 hr. This converted the 4-methyl-4′-nitrodiphenylsulfone present as by-product in the starting material into an easy filterable form. The hot mixture was filtered and the filtrate was cooled overnight in the refrigerator. The crude 4-dimethylaminomethyl-4′-nitrodiphenylsulfone hydrochloride was filtered. It was dissolved in water in which it is much more soluble than in dil. hydrochloric acid. The solution was charcoaled and filtered and the filtrate was made strongly acid by addition of concd. hydrochloric acid. The pure 4-dimethylaminomethyl-4′-nitrodiphenylsulfone hydrochloride melted at 243–244°, yield 25–30 g.

Anal. Calcd. for $C_{15}H_{16}N_2O_4S\cdot HCl$: C, 50.49; H, 4.80; N, 7.85. Found: C, 50.75; H, 4.67; N, 7.56.

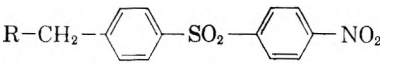
The compound is practically insoluble in acetone and little soluble in alcohol.

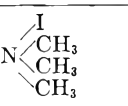
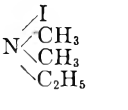
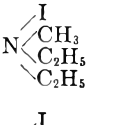
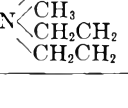
The free base was obtained by dissolving the hydrochloride in water, adding ammonia, and extracting with ether. The ether solution was dried over potassium carbonate and concentrated to a small volume. On cooling, 4-dimethylaminomethyl-4′-nitrodiphenylsulfone of m.p. 106–107° crystallized.

Anal. Calcd. for $C_{15}H_{16}N_2O_4S$: C, 56.23; H, 5.03; N, 8.75. Found: C, 56.33; H, 4.99; N, 8.75.

In Table I are listed the amino derivatives prepared essentially in the above manner. The solubility in water of the

TABLE II



Compounds	R	Formula	M.P.	Analysis Calcd. / Found C	H	N
XIV		$C_{16}H_{19}IN_2O_4S$	226–227°	See Exp. 10A		
XV		$C_{17}H_{21}IN_2O_4S$	215°	42.86 / 42.87	4.44 / 4.32	5.88 / 6.22
XVI		$C_{18}H_{23}IN_2O_4S$	138–139°	44.09 / 44.40	4.73 / 4.55	
XVII		$C_{19}H_{23}IN_2O_4S$	200–201°	45.42 / 45.49	4.61 / 4.48	

salts of these substituted compounds with mineral acids decreases with increasing molecular weight.

(*10*) *Quaternary derivatives of 4-aminomethyl-4′-nitrodiphenylsulfones.* Some of the nitrocompounds were reacted with methyl iodide to the quaternary bases. As an example, the preparation of the methiodide of VII is described.

A. *4-Dimethylaminomethyl-4′-nitrodiphenylsulfone methiodide* (XIV). 4-Dimethylaminomethyl-4′-nitrodiphenyl sulfone (9 g.) was dissolved in 100 ml. of acetone and 5 g. of methyliodide were added. Within 10 min. crystals of the methiodide started to separate. After standing overnight, the dark orange-colored methiodide was filtered and recrystallized from methanol and ether. The yield was 16 g. of m.p. 226–227°.

Anal. Calcd. for $C_{16}H_{19}IN_2O_4S$: C, 41.57; H, 4.14; N, 6.06. Found: C, 41.50; H, 4.34; N, 6.15.

B. *4-Dimethylaminomethyl-4′-nitrodiphenylsulfone methochloride* (XVIII). 4-Dimethylaminomethyl-4′-nitro-diphenylsulfone methiodide (16 g.) was shaken for 24 hr. in 500 ml. of methanol with freshly prepared silver chloride from 10 g. of silver nitrate. The solution was filtered and the silver chloride residue was extracted repeatedly with fresh methanol. The combined methanol solutions were evaporated. The crystalline residue was recrystallized from a little methanol, yielding 8 g. of 4-dimethylaminomethyl-4′-nitrodiphenylsulfone methochloride of m.p. 271°, containing one mole of water of crystallization.

Anal. Calcd. for $C_{16}H_{19}ClN_2O_4S \cdot H_2O$: C, 49.41; H, 5.44; N, 7.21. Found: C, 49.65; H, 5.92; N, 6.94.

C. A few of the other sulfones were also converted into their methiodides. They are listed in Table II.

(*11*) *Reduction of 4-aminomethyl-4′-nitrodiphenylsulfones.* The nitro derivatives described above were reduced catalytically to the corresponding amines. The hydrogenations were carried out mostly by dissolving or suspending the hydrochlorides of the 4-aminomethyl-4′-nitrodiphenylsulfones in water and using Raney nickel as catalyst. The reductions can be carried out also with palladium charcoal in acetic acid.

A. *4-Aminomethyl-4′-aminodiphenylsulfone* (I). 4-Aminomethyl-4′-nitrodiphenylsulfone (10 g.) was suspended in 50 ml. of water and hydrogenated with 2 g. of Raney nickel at 40° and 400 lbs. pressure. When the absorption of hydrogen had stopped, the solution was filtered and distilled to dryness. The crystalline residue was recrystallized from ethanol, yielding 6 g. of pure 4-aminomethyl-4′-aminodiphenylsulfone monohydrochloride of m.p. 195°. The compound contained one mole of water of crystallization. It is very soluble in water.

Anal. Calcd. for $C_{13}H_{14}N_2O_2 \cdot HCl \cdot H_2O$: C, 49.28; H, 5.41; N, 8.84. Found: C, 49.27; H, 5.31; N, 8.87.

The free base may be obtained by neutralizing an aqueous solution of the hydrochloride. It is, however, not very stable and discolors soon in the air, even in the dry state.

B. *Substituted 4-amino-methyl-4′-aminodiphenylsulfones.* The catalytic hydrogenation of the nitro compounds listed in Table I was carried out essentially in the same manner as described in Experiment 11A. The resulting diamines are listed in Table III. In contrast to the compound I the substituted compounds are considerably more stable as free bases. They are best purified by crystallization as free bases. Their salts with mineral acids are generally quite soluble in water.

(*12*) *4-Dimethylaminomethyl-4′-aminodiphenylsulfone methochloride.* 4-Dimethylamino-methyl-4′-nitrodiphenylsulfone methochloride (4 g.) was dissolved in about 50 ml. of water. After addition of 5 ml. of acetic acid the solution was hydrogenated at 25–30° and 50 lbs. pressure. The resulting solution was distilled to dryness. The residue was dissolved in about 5 ml. of water. Acetone was added until a slight turbidity developed. On standing, 2 g. of 4-dimethylaminomethyl-4′-aminodiphenylsulfone methochloride of m.p. 194–195° crystallized. The compound contained one molecule of water of crystallization, which was not lost at 120° *in vacuo*.

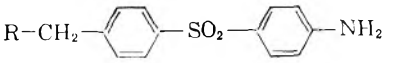
Anal. Calcd for $C_{16}H_{21}ClN_2O_2S \cdot H_2O$: C, 53.54; H, 6.46; N, 7.81. Found: C, 53.61; H, 5.71; N, 7.70.

(*13*) *4-Bromooctoyl-4′-nitrodiphenylsulfide* (XXVI). The bromination of 4-methyl-4′-nitrodiphenylsulfide, according to the procedure described above (Exp. 5) for bromination of the correspondi.g sulfone was not successful, probably because the free bromine oxidizes the sulfur. With bromosuccinimide in the presence of benzoyl peroxide, bromination occurred, but the yields were low. The reaction product, 4-bromomethyl-4′-nitrodiphenylsulfide, is not very stable and is difficult to purify. It was therefore used in the crude state as obtained by simple evaporation of the solution in carbon tetrachloride for the following experiments.

(*14*) *4-(N-Piperidinomethyl)-4′-nitrodiphenylsulfide* (XXVII). 4-Methyl-4′-nitrodiphenylsulfide (25 g.), 18 g. of *N*-bromosuccinimide, and 2 g. of benzoyl peroxide were refluxed in 100 ml. of carbon tetrachloride. Almost immediately after refluxing started, bromine vapors appeared. After 8

TABLE III

4-SUBSTITUTED AMINOMETHYL-4′-AMINO-DIPHENYLSULFONES



Compound	R	Formula	M.P.	Analysis Calcd. / Found C	H	W
I	NH_2	$C_{13}H_{14}N_2O_2S\cdot HCl$	195°	See Exp. 11A		
XIX	$N(CH_3)_2$	$C_{15}H_{18}N_2O_2S$	163–165°	62.04 62.18	6.25 6.52	9.65 9.21
		$C_{15}H_{18}N_2O_2S\cdot HCl\cdot{}^1/_2H_2O$	284–285°	53.64 53.52	6.00 5.72	8.34 8.59
XX	$N(C_2H_5)_2$	$C_{17}H_{22}N_2O_2S$	167–168°	64.12 64.43	6.97 6.15	8.50 8.39
		$C_{17}H_{22}N_2O_2S\cdot HCl\cdot{}^1/_2H_2O$	206°	56.11 56.05	6.65 6.27	7.70 7.47
XII	$N(CH_2CH_2CH_3)_2$	$N_{19}H_{26}N_2O_2S\cdot{}^1/_2H_2O$	108–110°	64.19 63.99	7.66 7.32	7.88 7.56
XXII	$N(CH_2CH_2CH_2CH_3)_2$	$C_{21}H_{30}N_2O_2S$	92–93°	67.34 67.55	8.07 7.66	7.88 7.42
XXIII	$N(CH_2CH_2)_2CH_2$	$C_{18}N_{22}N_2O_2S$	223–224°	65.42 65.41	6.71 5.82	8.48 8.34
		$C_{18}H_{22}N_2O_2S\cdot HCl$	304°	58.92 58.41	6.32 5.88	7.64 7.54
XXIV	$N(CH_2CH_2)_2O$	$C_{17}H_{20}N_2O_3S$	218–220°	61.42 60.88	6.07 5.36	8.43 8.47
		$C_{17}H_{20}H_2O_3S\cdot HCl$	308–310°	55.35 55.05	5.74 5.62	
XXV	$NH—CH_2C_6H_5$	$C_{20}H_{20}N_2O_2S\cdot HCl\cdot{}^1/_2H_2O$	260–261°	60.31 60.15	5.57 5.37	

hr. of refluxing, the solution was filtered and the filtrate was distilled to dryness *in vacuo* at 50°. The crystalline residue was dissolved in 100 ml. of benzene and 20 ml. of piperidine were added. After standing for 2 days, the mixture was filtered. The filtrate was distilled to dryness. The residue was dissolved in abs. ethanol and ethanolic hydrobromic acid was added in excess; on standing, crystals separated slowly. They were filtered after 2 days and were recrystallized repeatedly, first from abs. ethanol, then from water, yielding 6 g. of 4-(*N*-piperidylmethyl)-phenyl-4′-nitrophenyl-sulfide hydrobromide of m.p. 222–223°.

Anal. Calcd. for $C_{18}H_{20}N_2O_2S\cdot HBr$: C, 52.81; H, 5.17; N, 6.84. Found: C, 52.92; H, 5.12; N, 6.61.

(*15*) *4-Benzylaminomethyl-4′-nitrodiphenylsulfide* (XXVIII). Crude 4-bromomethyl-4′-nitrodiphenylsulfide, prepared as described in Experiment 13, was allowed to react with excess benzylamine. After standing for 2 days at room temperature, the solution was filtered. The filtrate was shaken with 10% hydrochloric acid. A crystalline precipitate appeared immediately. It was filtered and recrystallized repeatedly from acetic acid, yielding 3 g. of 4-benzylaminomethyl-4′-nitro-diphenylsulfide hydrochloride of m.p. 241–242°.

Anal. Calcd. for $C_{20}H_{18}N_2O_2S\cdot HCl$: C, 62.09; H, 4.95; N, 7.24. Found: C, 62.18; H, 5.03; N, 7.35.

The remaining benzene solution on evaporation left 24 g. of unchanged 4-methyl-4′-nitro-diphenylsulfide.

(*16*) *4-(4-Nitrophenylsulfonyl)benzoic acid* (XXIX). 4-Methyl-4′-nitrodiphenylsulfone (27 g.) was dissolved in 300 ml. of acetic acid. With stirring and warming to 80°, 30 g. of chromium trioxide were slowly added. After 8 hr. the solution was allowed to cool. After standing overnight, the crude 4-(4-nitrophenylsulfonyl)benzoic acid was filtered off and washed with acetic acid. It was dissolved in boiling 10% sodium hydroxide. The solution was filtered hot from some undissolved starting material. The filtrate was concentrated to a small volume. On cooling, the sodium salt of the acid crystallized. It was filtered and washed with some ice cold water. The yield was 27 g. The sodium salt was dissolved in hot water and the colorless solution was acidified with 10% hydrochloric acid. The free acid separated immediately. It was recrystallized from acetic acid and melted at 305–306°. No melting point is given by Roblin and Clapp.[15]

Anal. Calcd. for $C_{13}H_9NO_6S$: C, 50.82; H, 2.95; N, 4.56. Found: C, 51.18; H, 2.98; N, 4.52.

(*17*) *4-(4-Nitrophenylsulfonyl)benzoic acid methylester* (XXX). 4-(4-Nitrophenylsulfonyl)benzoic acid (16 g.) was stirred and refluxed with a solution of 20 ml. of concd. sulfuric acid in 300 ml. of methanol for 5 hr. After cooling, the crystals

were filtered and washed with a little methanol. They were stirred for 1 hr. with 10% sodium carbonate solution to remove some unreacted acid and were then crystallized from methanol. The yield of pure methylester of m.p. 155–156° was 13 g.

Anal. Calcd. for $C_{14}H_{11}NO_6S$: C, 52.33; H, 3.45; N, 4.36. Found: C, 52.31; H, 3.27; N, 4.52.

(*18*) *4-(4-Aminophenylsulfonyl)benzoic acid* (XXXI). A. *By catalytic reduction.* 4-(4-Nitrophenylsulfonyl)benzoic acid (10 g.) was suspended in 10 ml. of water and sodium hydroxide was added dropwise to dissolve the acid. The solution was hydrogenated with Raney nickel at 50° and 300 lbs. pressure. The catalyst was filtered and the solution was acidified with acetic acid. The crude amino acid was filtered and recrystallized from 80% acetic acid, yielding 6 g. of pure 4-(4-aminophenylsulfonyl)benzoic acid of m.p. 253–254°. Roblin and Clapp[15] do not report the melting point of the acid.

Anal. Calcd. for $C_{13}H_{11}NO_4S$: C, 56.30; H, 4.00; N, 5.05. Found: C, 56.14; H, 4.02; N, 5.00.

B. *By reduction with ferrous sulfate.* A solution of the sodium salt, prepared from 38 g. of 4-(4-nitrophenylsulfonyl)benzoic acid in 500 ml. of water and a small excess of sodium hydroxide, was added with stirring at 25° to a solution of 210 g. of ferrous sulfate ($FeSO_4 \cdot 7H_2O$) in 1000 ml. of water. To this mixture, 400 g. of 25% sodium hydroxide was slowly added. The mixture was stirred for 8 hr. The undissolved material was filtered and the clear filtrate was acidified, yielding 24 g. of 4-(4-aminobenzylsulfonyl)-benzoic acid of m.p. 253–254°.

(*19*) *4-(4-Aminophenylsulfonyl)benzoic acid methylester* (XXXII). A mixture of 5 g. of 4-(4-aminophenylsulfonyl)-benzoic acid, 100 ml. of methanol, and 20 g. of concd. sulfuric acid was refluxed on the steam bath. After about 3 hr., a homogeneous solution had formed. It was filtered and cooled. The crude methyl ester was filtered and recrystallized from about 100 ml. of methanol, yielding 4 g. of pure ester of m.p. 175–176°.

Anal. Calcd. for $C_{14}H_{13}NO_4S$: C, 57.72; H, 4.50; N, 4.87. Found: C, 58.23; H, 4.38; N, 4.92.

(*20*) *4-(4-Aminophenylsulfonyl)benzoic acid hydrazide* (XXXIII). A mixture of 9 g. of the ester (Experiment 19) and 2.5 ml. of hydrazine hydrate in 60 ml. of methanol was refluxed for 3 hr. On cooling in the refrigerator, 8 g. of 4-(4-aminophenylsulfonyl)benzoic acid hydrazide crystallized. Recrystallization from methanol gave the pure compound of m.p. 199–200°.

Anal. Calcd. for $C_{13}H_{13}N_3O_3S$: C, 53.60; H, 4.50; N, 14.42. Found: C, 53.30; H, 4.35; N, 14.63.

(*21*) *4-[4-(4-Nitrophenylsulfonyl)benzylamino]benzoic acid* (XXXVI). 4-Bromomethyl-4′-nitrodiphenylsulfone (18 g.) and 14 g. of p-aminobenzoic acid were refluxed in 125 ml. of dioxane for 4 hr. The hot solution was filtered from undissolved material and distilled to dryness. The residue was dissolved in 3% sodium hydroxide and the solution was again filtered from undissolved crystals. The clear, yellow filtrate was acidified with acetic acid. After 1 hr. the crystals were filtered and recrystallized from dioxane, yielding 12 g. of 4-[4-(4-nitrophenylsulfonyl)benzylamino]benzoic acid of m.p. 256–258°.

Anal. Calcd. for $C_{20}H_{16}N_2O_6S$: C, 58.24; H, 3.91; N, 6.79. Found: C, 58.07; H, 3.80; N, 6.73.

(*22*) *4-[4-(4-Aminophenylsulfonyl)benzylamino]benzoic acid* (XXXVII). The nitro acid (XXXVI) (5 g.) was hydrogenated catalytically with 2 g. palladium charcoal (3% Pd) in 30 ml. of acetic acid at 40° and 500 lbs. pressure. The resulting mixture contained cyrstals. After addition of 40 ml. of acetic acid, it was refluxed and filtered hot from the catalyst. On cooling, the acid crystallized. Recrystallization from acetic acid yielded 2 g. of pure 4-[4-(4-aminophenylsulfonyl)benzylamino]benzoic acid of m.p. 243–244°.

Anal. Calcd. for $C_{20}H_{18}N_2O_4S$: C, 62.81; H, 4.74; N, 7.34. Found: C, 62.60; H, 5.03; N, 7.14

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NUTLEY, N. J.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE OHIO STATE UNIVERSITY]

Glycosidation with Trimethyl Orthoformate and Boron Trifluoride*

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Methanolic trimethyl orthoformate in the presence of boron trifluoride constitutes a convenient system for glycoside synthesis in the sugar field.

Bergmann[3] applied the Claisen[4] acetalation reaction to the preparation of ethyl 4,6-di-*O*-acetyl-α-D-*erythro*-2-*cis*-hexosenide by heating 4,6-di-*O*-acetyl-D-*erythro*-2-*cis*-hexosene under reflux with ethanolic trimethyl orthoformate in the presence of a small amount of ammonium chloride. This reaction has been repeated by Stacey and co-workers[5] and performed, without ammonium chloride catalysis, with the corresponding D-galactose derivative by Lohaus and Widmaier[6] and with the methyl D-glucose analog by Bergmann and Freudenberg.[7] The corresponding reaction[8] with tetramethyl orthosilicate in the presence of hydrogen chloride was applied by Freudenberg and Jakob[9] to the preparation of

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(1) National Science Foundation Research Associate under Grant NSF-G584 to The Ohio State University.

(2) Postdoctoral Fellow of The Foreign Research Scientists Program of the Foreign Operations Administration (Project TAOI-101-3006 EPA 151).

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TABLE I

GLYCOSIDATION WITH TRIMETHYL ORTHOFORMATE AND BORON TRIFLUORIDE[a]

Substance	Product	M.P., °C.	$[\alpha]_D^{20}$ (*c* 1), Water, Degrees	Yield, %
D-Glucurono-3,6-lactone	Methyl α-D-glucofuranosid-urono-6,3-lactone	147–148	+163[b]	41.5
D-Arabinose	Methyl β-D-arabinopyranoside	168–169	−243	28.0
D-Galactose	Methyl β-D-galactopyranoside	177–178	0	28.0
D-Glucose	Methyl α-D-glucopyranoside	165–166	+158	37.5
D-Mannose	Methyl α-D-mannopyranoside	193.5–194.5	+ 78	47.0
D-Xylose	Methyl β-D-xylopyranoside	156–157	− 65	43.0

[a] See experimental section for details. [b] In ethanol.

methyl 2,3,6-tri-*O*-methyl D-glucopyranoside from 2,3,6-tri-*O*-methyl-D-glucose. The latter workers also utilized trimethyl orthoformate, methanol and hydrogen chloride and, without isolating the reaction products, extended their studies to D-glucose, D-galactose and to a series of methylated D-glucose derivatives. By applying hydrolytic rate studies to the reaction mixtures, they noted that pyranoside formation predominated.

According to Freudenberg and Jakob,[9] Schwarz,[10] and Astle and co-workers,[11] orthoformate esters of certain polyhydroxy compounds are formed by their reaction with ethyl orthoformate in the presence of hydrogen chloride or of an acid exchange resin.

In the work herein reported, D-glucurono-6,3-lactone was shaken for three hours at room temperature with trimethyl orthoformate containing a catalytic amount of boron trifluoride. The nonreducing, wine-red solution yielded a crystalline compound which was found to be methyl α-D-glucofuranosid-urono-6,3-lactone. This synthesis represents a convenient and superior method for the preparation of the α-anomer as previously reported methods[12] result in a mixture of anomers from which the α-glycoside can be isolated only with difficulty and in very low yield.

Application of this boron trifluoride-catalyzed reaction to the common aldohexoses and aldopentoses (Table I) led to a mixture from which one pure anomer crystallized in fair yield. The method is convenient and can be considered as the method of choice for methyl β-D-galactopyranoside. The reaction products were investigated by paper chromatography and were found to consist of a glycoside mixture accompanied by small amounts of unchanged sugar and, save for D-glucose, a fast moving component which may have been an orthoester.

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EXPERIMENTAL

Methyl α-D-glucofuranosidurono-6,3-lactone. Two grams of D-glucurono-6,3-lactone, dried at 50° and 0.01 mm., 50 ml. of trimethyl orthoformate, dried over Drierite (anhydrous calcium sulfate), and 0.2 ml. of a 7% solution of boron trifluoride in methanol, were shaken together for 2 hr. The D-glucurono-6,3-lactone slowly dissolved and the mixture turned initially yellow and finally wine-red in color and became nonreducing toward Fehling solution. The solution was poured into 1 l. of carbon tetrachloride and allowed to stand at 10–12° for 48 hr. Crystals formed and were dissolved in methanol, filtered through activated carbon, and the material obtained on solvent removal was recrystallized from ethyl acetate to give methyl α-D-glucofuranosidurono-6,3-lactone (see Table I).

Anal. Calcd. for $C_6H_7O_5(OCH_3)$: C, 44.2; H, 5.26; OCH_3, 16.3. Found: C, 44.44; H, 5.16; OCH_3, 16.28.

Methyl α-D-mannopyranoside. Five grams of D-mannose, dried at 50° and 0.01 mm., 50 ml. of trimethyl orthoformate, dried over Drierite, and 0.5 ml. of a 7% solution of boron trifluoride in methanol, were shaken together for 18 hr. The D-mannose slowly dissolved and the wine-red, nonreducing solution was poured into 1 l. of light petroleum ether (b.p. 30–60°) and allowed to stand at 10–12° for 24 hr. The separated sirup was dissolved in methanol, filtered through activated carbon, and the sirup obtained on solvent removal was crystallized from ethanol to give methyl α-D-mannopyranoside (see Table I).

The above experiment was extended to the other aldoses listed in Table I. In all cases, the initial product was chromatographed on a sheet of Whatman No. 1 filter paper and developed with 1-butanol saturated with water. The spots were detected by spraying with ammoniacal silver nitrate and heating the paper at 100° for a few minutes. There was obtained in all cases evidence for the presence of a small amount of the unreacted sugar, an elongated spot indicating the mixture of glycosides, and a small quantity of a fast-moving unknown component, absent in the case of D-glucose. It is probable that the chromatographic conditions employed would not resolve the glycoside mixture into its components.

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[CONTRIBUTION FROM THE DEPARTMENT OF ORGANIC CHEMISTRY, UNIVERSITY OF ATHENS, GREECE, AND THE LABORATORY OF BIOCHEMISTRY, NATIONAL CANCER INSTITUTE, NATIONAL INSTITUTES OF HEALTH, PUBLIC HEALTH SERVICE, U. S. DEPARTMENT OF HEALTH, EDUCATION AND WELFARE]

Studies on Arginine Peptides. I. Intermediates in the Synthesis of N-Terminal and C-Terminal Arginine Peptides*

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Tricarbobenzoxy-L-arginine, as its sodium salt, was prepared in strongly alkaline medium *via* the carbobenzoxylation of L-arginine. This sodium salt, which was in fact a mixture of at least two different isomeric forms, was converted into a mixture of $N^{\alpha}N,^{\omega}$-dicarbobenzoxy-L-arginine and a single pure isomer of sodium tricarbobenzoxy-L-argininate upon treatment with boiling ethanol. Fractionation of these compounds, followed by acidification of the latter material, yielded pure tricarbobenzoxy-L-arginine wherein the basic properties of the guanido group were completely masked. The utility of this compound in the preparation of *N*-terminal arginine peptides was demonstrated upon its condensation with amino acid benzyl esters, *via* the mixed carbonic-carboxylic acid anhydride procedure, followed by catalytic hydrogenolysis of the condensation product. In addition, the *N*-carboxyanhydride procedure was utilized to effect the transformation of tricarbobenzoxy-L-arginine into N^{ω},N^{ω}-dicarbobenzoxy-L-arginine, and of N^{α},N^{ω}-dicarbobenzoxy-L-arginine into N^{ω}-carbobenzoxy-L-arginine, as well as the benzyl and methyl ester derivatives of the latter. All of these products are of potential value in the synthesis of *C*-terminal arginine peptides. In this connection, the esters of N^{ω}-carbobenzoxy-L-arginine were employed in the synthesis of the benzyl and methyl esters of tricarbobenzoxy-L-arginyl-N^{ω}-carbobenzoxy-L-arginine.

INTRODUCTION

By virtue of the complex nature of the guanido group, the incorporation of the highly basic arginine molecule into synthetic peptides has posed more formidable problems than have been encountered with any of the other protein-derived amino acids. In this connection, the development of an unequivocal synthetic route to arginylarginine affords a particularly tempting challenge, not only in consequence of the natural occurrence of this same residue sequence in polypeptides of biological interest, *e.g.*, adrenocorticotropic hormone, protamines, etc., but also because of the role played by many outstanding investigators in its ill-fated chemical history. Thus, although "arginylarginine," which was characterized as the picrate and nitrate derivatives, was presumed by Fischer and Suzuki[1] in 1905 to have arisen from the autocondensation of L-arginine methyl ester, such presumption was nevertheless qualified by certain reservations. Not only did a Dumas nitrogen analysis of the substance reveal values which were too high, but prolonged treatment of the material with hot concentrated hydrochloric acid resulted in no regeneration of free arginine, a fact which cast some doubt upon its alleged peptide nature. Despite these observations, Edlbacher and Bonem,[2] some twenty years later, reported that the "arginylarginine" of Fischer and Suzuki was completely hydrolyzed upon heating with 25% sulfuric acid for fourteen hours, and that the free amino acid could be recovered from the hydrolyzate in nearly quantitative yield as its picrolonate derivative. In addition, the "arginylarginine" exhibited formol-titratable nitrogen values which were in good agreement with those theoretically expected for this compound, while the action of arginase upon this substance resulted in the liberation of some 20–21% of the total nitrogen as urea. The major arguments barring definite assignment of the arginylarginine structure, tentatively proposed by Fischer and Suzuki, were thereby seemingly removed. However, a disturbing element crept into the picture in 1927 with the announcement by Kossel and Staudt[3] that, in contradistinction to the results of Edlbacher and Bonem, not only did they fail to observe any arginine formation upon prolonged treatment of "arginylarginine" with hot sulfuric acid, but that the picrolonate derivative of arginine described by these latter investigators was, in actuality, the corresponding derivative of unhydrolyzed "arginylarginine." Just one year later, Waldschmidt-Leitz, Schäffner, Schlatter, and Klein[4] reported that an original preparation of Fischer and Suzuki was completely resistant to the hydrolytic action of either trypsin-kinase or intestinal erepsin and thus supported the previous doubt as to the peptide nature of this substance. Such doubt was resolved during the same year with the demonstration by Zervas and Bergmann[5] that the autocondensation of arginine methyl ester to the corresponding dipeptide ester is rapidly succeeded by a disproportionate cleavage of this latter compound into ornithine methyl ester and an anhydride of α,δ-diguanidinovaleric acid. It was the latter product which constituted the controversial "arginylarginine" of Fischer and Suzuki. A somewhat ironical note is presented by the fact

* This paper is a contribution in honor of Lyndon F. Small, former Editor of the Journal.

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that although reference to this peptide as an arginase-susceptible substrate has persisted to the present day in published investigations and reviews, and although a number of synthetic procedures are currently available for incorporating arginine into the peptide chain,[6-11] no authentic or well-defined sample of arginylarginine[12] has yet been described.

The present series of studies was conceived both with an eye toward clarifying the past confusion which surrounded the synthesis and biological properties of this most intriguing compound, as well as with the goal of developing more facile techniques for "joining" an arginine residue at the *C*-terminal or *N*-terminal end of a peptide chain. The first of these studies, presented herein, is concerned primarily with the preparation of suitably substituted arginine derivatives which may serve as starting materials toward the fulfillment of this aim.

RESULTS AND DISCUSSION

Intermediates in the preparation of N-terminal arginine peptides. An earlier communication[13] has alluded to the successful employment of tricarbobenzoxy-L-arginine in the preparation of peptides which incorporate an *N*-terminal arginine residue. Synthesis of this intermediate was inadvertently achieved during an attempt to synthesize the N^{α}, N^{ω}-dicarbobenzoxy derivative of L-arginine, by treatment of a strongly alkaline solution of L-arginine with 2–4 equivalents of carbobenzoxy chloride, in a manner reminiscent of that previously utilized to prepare the corresponding dibenzoyl derivative.[5,14] During the reaction an insoluble material precipitated, which was filtered in the cold and washed with cold sodium carbonate solution, and the wet cake was taken up in alcohol-free chloroform, dried, and concentrated *in vacuo*; on treatment with ether, the residue solidified. Elemental analyses of the material, so derived, unexpectedly conformed to the composition possessed by sodium tricarbobenzoxy-L-argininate (I). Such preparation of a triacylated arginine derivative brings to mind the early observation of Bergmann and Köster[15] that the action of excess acetic anhydride upon L-arginine proceeds with the formation of triacetyl anhydro-DL-arginine. In any event, the ready accessibility of an N^{α}, N^{ω}, N^{ω}-tricarbobenzoxylated arginine, wherein the reactivity of the strongly basic guanido moiety is completely suppressed by a selectively removable acyl substituent,[16] unveiled a compound which qualified as a practical intermediate in the synthesis of N-terminal arginine peptides.[13]

That the sodium salt of tricarbobenzoxy-L-argininate (I) described above was, in reality, a mixture of at least two isomeric forms was suggested by the fact that a 12% solution of the material in ethanol, upon boiling for several minutes, followed by chilling, led to the deposition and ultimate recovery of some 50% of a crystalline material (II) which, although now only sparingly soluble in ethanol, revealed analyses identical with that of the parent mixture, and which, upon neutralization, was converted to the corresponding crystalline free acid (III); m.p. 138–139°; $[\alpha]_D^{25}$ +15.5° (1% in alcohol-free chloroform). Upon concentration of the ethanolic mother liquors, an exceedingly alcohol-soluble material was secured which, subsequent to acidification with acetic acid and crystallization from methanol, analyzed for the hitherto unreported N^{α},N^{ω}-dicarbobenzoxylated amino acid (IV);[17] m.p. 150°; $[\alpha]_D^{25}$ −10.0° (1% in pyridine). That the precursor of N^{α},N^{ω}-dicarbobenzoxy-L-arginine (IV) was, in fact, a highly *alcohol-susceptible* isomer of II, was indicated, aside from elemental analyses, by the following: (*a*) the *alcohol-stable* sodium salt of tricarbobenzoxy-L-arginine (II), after prolonged treatment with boiling ethanol, could be recovered in nearly quantitative yield without having suffered any detectable change in its constitution; (*b*) conversion of the crystalline sodium salt (II), or its parent isomeric mixture (I), to the N^{α},N^{ω}-dicarbobenzoxylated derivative (IV), could be readily achieved upon reaction with one equivalent of alkali in cold ethanol; and (*c*) carbobenzoxylation of IV, under Schotten-Baumann conditions, proceeded with the remark-

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(14) K. Felix and K. Dirr, *Z. physiol. Chem.*, **176**, 29 (1928).

(15) M. Bergmann and H. Köster, *Z. physiol. Chem.*, **159**, 179 (1926).

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(17) Other N^{α},N^{ω}-diacylated arginines which have been previously described include the dibenzoyl,[14] dibenzenesulfonyl [H. T. Clarke and H. B. Gillespie, *J. Am. Chem. Soc.*, **54**, 1964 (1932)], di-*p*-nitrocarbobenzoxy [D. T. Gish and F. H. Carpenter, *J. Am. Chem. Soc.*, **75**, 5872 (1953)], and dibenzylsulfonyl [H. B. Milne and C-H. Peng, *J. Am. Chem. Soc.*, **79**, 642 (1957)] derivatives.

ably facile production of sodium tricarbobenzoxy-L-argininate which, upon fractionation with ethanol, again yielded II and IV.

Although the basicity of N^{α},N^{ω}-diacyl arginines was established as early as 1928 both by Felix and Dirr[14] and by Zervas and Bergmann,[5] who described the hydrochloric salt of N^{α},N^{ω}-dibenzoylarginine, and was more recently reaffirmed by Gish and Carpenter,[17] who determined the apparent dissociation constants of N^{α},N^{ω}-di-*p*-nitrocarbobenzoxyarginine, the carbobenzoxylation of N^{α},N^{ω}-dicarbobenzoxy-L-arginine described herein represents the first reported instance whereby compounds of this general class have been acylated. In this connection, it is of interest to point out that like attempt to carbobenzoxylate N^{α}-carbobenzoxy-L-arginine, under strongly alkaline Schotten-Baumann conditions, resulted in the recovery only of unchanged starting material. No reason for the apparent resistance of this latter compound to acylation can be offered at the present time. As the N^{α}-carbobenzoxy-L-arginine here employed was prepared by the carbobenzoxylation of L-arginine in sodium bicarbonate solution, which is only slightly alakline, possible acylation of the highly basic guanido group was circumvented.

That tricarbobenzoxy-L-arginine may serve as a valuable intermediate in the synthesis of arginyl peptides was attested to by its ready condensation with amino acid esters *via* the mixed carboxylic–carbonic anhydride procedure.[18–20] This intermediate could be equally well utilized either as the free acid, m.p. 138–139°, or as the sodium salt (II) precursor. Where the latter was employed, best results were obtained by preliminary treatment of its chloroform solution with one equivalent of triethylamine hydrochloride in order to effect its conversion to the corresponding triethylamine salt; concomitant deposition of sodium chloride occurred. Coupling was effected with one equivalent of dibenzyl L-glutamate *p*-toluenesulfonate (or hydrochloride) in a chloroform solution containing one equivalent of triethylamine. The corresponding tricarbobenzoxydipeptide ester was secured in some 75% over-all yield and subsequently converted, *via* catalytic hydrogenolysis,[16] to L-arginyl-L-glutamic acid with an $[\alpha]_D$ value of +21.4° as a 1% solution in water. Chromatographic analysis of the compound in several solvent systems revealed its association with only a single ninhydrin positive spot.

Reported $[\alpha]_D$ values for the aforementioned L-arginyl-L-glutamic acid (as anhydrous material), in water, are as follows: +22°,[7] + 24.8°,[9] + 25.1°,[11] and +27.2°.[10] The differences revealed by these values are too large to be accounted for on the basis of experimental deviations in the measurements alone. In this connection, it should be recalled that the magnitude of the optical rotation of analytically pure peptides or peptide derivatives which contain a single center of asymmetry bears an inverse relationship to the amount of optical contamination by its enantiomorph, *i.e.*, the higher the optical rotation value, the greater the degree of optical purity. Polarimetric measurements thereby provide a means whereby the relative degrees of optical purity of a given mono-asymmetric compound, secured through different synthetic procedures, might be roughly estimated. In sharp contrast, however, the magnitude of the rotation of derivatives with two or more asymmetric centers may be expected to provide practically no information with respect to the degree of contamination by the various stereoisomers. This may be vividly demonstrated with the stereoisomers of alanylalanine, the D-D and L-D diastereomeric forms of which possess specific rotation values in water of +21.3° and +72.2°, respectively.[21] Thus, an increasing degree of contamination by L-alanyl-D-alanine in D-alanyl-D-alanine will lead to an increase in the magnitude of the observed rotation, with a 20% contamination, for example, leading to a specific rotation of +31.4°, a value some 50% higher than that possessed by the pure D-D form. No reliable information with regard to the optical integrity of the aforementioned L-arginyl-L-glutamic acids should therefore be expected from a comparison of the relative magnitudes of their respective optical rotation values alone.

The amino acid benzyl ester *p*-toluenesulfonate employed in the above synthesis was conveniently synthesized following a modification[22] of the method of Cipera and Nicholls.[23] Constants for this, as well as several other amino acid benzyl ester *p*-toluenesulfonates, prepared through this same route, are recorded in Table I.

Intermediates in the preparation of C-terminal arginine peptides. The tricarbobenzoxy- and N^{α},N^{ω}-dicarbobenzoxyarginines, described above, may serve as useful intermediates in the synthesis of *C*-terminal arginine peptides after removal of the N^{α}-carbobenzoxy substituent by an appropriate method.[7,24] Thus, conversion of the former compound to N^{ω},N^{ω}-dicarbobenzoxy-L-arginine *N*-carboxyanhydride by the action of thionyl chloride, followed by hydrolysis, led to the formation of N^{ω},N^{ω}-dicarbobenzoxy-L-arginine. Similar treatment of N^{α},N^{ω}-dicarbobenzoxy-L-arginine with thionyl chloride, followed by the action of aqueous

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(23) J. D. Cipera and R. V. V. Nicholls, *Chemistry & Industry*, 16 (1955).

(24) M. Bergmann, L. Zervas, and W. F. Ross, *J. Biol. Chem.*, **111**, 245 (1935).

acetic acid, methanol, or benzyl alcohol upon the N^{ω}-carbobenzoxy-L-arginine *N*-carboxyanhydride, so derived, led to the ultimate isolation, respectively of the free acid, the methyl ester, and the benzyl ester of N^{ω}-carbobenzoxy-L-arginine. Condensation of each of the latter two ester derivatives with tricarbobenzoxy-L-arginine, *via* the mixed carbonic-carboxylic acid anhydride procedures, resulted in the production of the methyl and benzyl esters of tricarbobenzoxy-L-arginyl-N^{ω}-carbobenzoxy-L-arginine. Conversion of these two latter compounds to L-arginyl-L-arginine, as well as exploitation of the aforementioned intermediates for the synthesis of various *C*-terminal and *N*-terminal arginine peptides,[25] will be the subject of a later communication.

EXPERIMENTAL

I. *Preparation of carbobenzoxylated arginines*

Sodium tricarbobenzoxy-L-argininate (I). To a solution of 42.2 g. of L-arginine·HCl[26] in 400 ml. of normal NaOH, chilled to about 2–5°, was added a total of 500 ml. of 2*N* NaOH and 136 ml. of freshly prepared carbobenzoxy chloride, in five equal and alternate portions. The addition, which required some 30 min., was accompanied by vigorous shaking and cooling in an ice bath. During this time, a precipitate of the sodium salt of tricarbobenzoxy-L-arginine formed which, after an additional 30 min. of stirring, was filtered over suction *in the cold* and washed with 200 ml. of *cold*, 5% sodium carbonate solution. The wet precipitate was dissolved in 1 l. of cold, alcohol-free chloroform, the aqueous layer separated, and the chloroform fraction washed with 100 ml. of cold, 5% sodium carbonate solution. Subsequent to filtration, the chloroform layer was dried over anhydrous sodium sulfate and then concentrated to an oily residue under reduced pressure and a bath temperature of 25°. Treatment of the residue with about 1 l. of dry ether, followed by storage for some 12 hr. in the cold, caused it to solidify. This material was filtered, washed with dry ether, and finally dried *in vacuo* over phosphorus pentoxide. Yields of the crude sodium salt ranged from 78 to 85 g.[27]

Anal. Calcd. for $C_{30}H_{31}O_8N_4Na$: N, 9.4; Na, 3.8. Found: N, 9.4; Na, 3.8.

The aforementioned material constitutes a mixture of at least two isomeric forms of sodium tricarbobenzoxy-L-argininate which, upon treatment by the methods given immediately below, may yield one of the component isomers in extremely pure form.

Sodium tricarbobenzoxy-L-argininate (II). *Method A.* Twelve grams of the crude sodium salt (I), described above, was suspended in 100 ml. of absolute ethanol, and solution effected upon boiling for several minutes. The hot solution was filtered and stored at 4° for several hours. A crystalline sodium salt (II) deposited which was filtered over suction and washed first with cold ethanol, then with ether; the combined filtrate and washings were saved for the recovery of α,ω-dicarbobenzoxy-L-arginine (Method A), described below. The yield of crystalline sodium salt, which amounted to 5.8 g., remained unchanged even in those instances where the aforementioned treatment with boiling ethanol was extended to 1 hr. Recrystallization was effected from hot absolute ethanol.

Anal. Calcd. for $C_{30}H_{31}O_8N_4Na$: N, 9.4; Na, 3.8. Found: N, 9.4; Na, 3.8.

Method B. The carbobenzoxylation of 42.2 g. of L-arginine hydrochloride was achieved as described for the preparation of the crude sodium salt of tricarbobenzoxy-L-arginine (I), above. The precipitate was filtered over suction, washed with 100 ml. of cold 5% sodium carbonate, dissolved in about 1 l. of ethanol-free chloroform, and the aqueous layer which formed discarded while the chloroform extract was washed successively with two 100 ml. portions of 5% sodium carbonate, two 100 ml. portions of 2*N* sulfuric acid, and several times with water. All of the above operations were effected at 1–5°C. After drying over anhydrous sodium sulfate, the chloroform fraction was concentrated to dryness under reduced pressure at 35–40°, with complete removal of final traces of chloroform being ensured by the addition of absolute ethanol, followed by reconcentration *in vacuo*. To the residual sirup was added 200–220 ml. of a hot ethanolic solution of 27 g. of sodium acetate trihydrate, and the mixture first boiled for 2 min., with stirring, then permitted to stand at room temperature for some 12–20 hr., during which time the desired crystalline sodium salt (needles) separated. This was filtered off, washed with 30 ml. of absolute ethanol, and filtered with suction, and the wet cake was extracted into 100 ml. of boiling ethyl acetate. Upon chilling the solution at 4°, a solid deposited which was filtered off, washed with 20 ml. of cold ethyl acetate, and then redissolved, while yet moist, in the requisite amount of hot absolute ethanol. A highly pure sodium salt of tricarbobenzoxy-L-arginine precipitated which, after some 24 hr. at 4°, was filtered over suction and washed first with a little cold absolute ethanol, then ether; yield, 21–24 g.

The sodium tricarbobenzoxy-L-argininate, so derived, is extremely pure and yields the free acid, m.p. 138–139°, upon acidification (see procedure below).

Tricarbobenzoxy-L-arginine (III). Two and a half grams of the above-described crystalline sodium salt (II) was suspended in 100 ml. of ethyl acetate and slowly brought into solution by vigorously shaking with 25 ml. of 2% sulfuric acid. The ethyl acetate layer was separated and washed, first with 25 ml. of 2% sulfuric acid, then three times with water, dried over anhydrous sodium sulfate, and then concentrated to dryness *in vacuo*. A crystalline residue was secured which was triturated with petroleum ether and then recovered by filtration over suction; yield, 1.9 g.; m.p. 135°. Two recrystallizations from ethyl acetate raised the melting point to 138–139°; $[\alpha]_D^{25}$ +15.5° (1% in alcohol-free chloroform).

Anal. Calcd. for $C_{30}H_{32}O_8N_4$: C, 62.5; H, 5.6; N, 9.7. Found: C, 62.2; H, 5.7; N, 9.8.

N^{α},N^{ω}-Dicarbobenzoxy-L-arginine (IV). *Method A.* The combined filtrate and washings saved during the preparation of sodium tricarbobenzoxy-L-argininate II (Method A) were concentrated, under reduced pressure, to a residual sirup. This was dissolved in water, the solution acidified with acetic acid, and the tacky precipitate which resulted dissolved in hot methanol. Subsequent cooling proceeded with the deposition of crystalline N^{α},N^{ω}-dicarbobenzoxy-L-arginine; yield, 3.2 g.; m.p. 150°; $[\alpha]_D^{25}$ −10.0° (1% in pyridine).

Anal. Calcd. for $C_{22}H_{26}O_6N_4$: C, 59.7; H, 5.9; N, 12.6. Found: C, 59.3; H, 6.0; N, 12.5.

Method B. To a solution of 8 g. of NaOH in 200 ml. of methanol was added 60 g. of crude sodium tricarbobenzoxy-L-argininate, with cooling in an ice bath. The reaction mixture, after storage at room temperature for 1 hr., was concentrated to approximately 100 ml. at 20–25° under re-

(25) We have recently observed that N^{α},N^{ω}-dicarbobenzoxy-L-arginine will serve as an excellent intermediate in the preparation of *N*-terminal arginine peptides if its condensation with an amino acid ester is effected in anhydrous dioxane according to the dicyclohexyl carbodiimide method [*cf.* J. C. Sheehan and G. P. Hess, *J. Am. Chem. Soc.*, **77**, 1067 (1955) and later papers]. Full details will appear in a subsequent communication.

(26) An equivalent quantity of the free base of L-arginine has also been employed, with somewhat higher yields.

(27) Although the use of 68 ml. (2 equivalents) of carbobenzoxy chloride also led to the separation of sodium tricarbobenzoxy-L-argininate, the yields were necessarily lower than when more of the reagent had been employed.

duced pressure, and 500 ml. of water, then 20 ml. of acetic acid added thereto. A gummy material deposited which was separated from the aqueous layer and repeatedly washed with water by decantation. The residue was finally dissolved in hot methanol; this solution, upon standing first at room temperature for several hours, then at 4°, deposited 38–40 g. of the desired dicarbobenzoxy derivative: m.p. 148°. Purification was effected by solution of the substance in dilute potassium carbonate, acidification, and subsequent crystallization of the precipitated gum from hot methanol. The material exhibited a melting point of 150°, which remained unaltered upon mixture with a sample secured by method A, above. Pure N^{α},N^{ω}-dicarbobenzoxy-L-arginine shows a sparing solubility in methanol and ethanol, and is insoluble in ether, chloroform, ethyl acetate, and benzene.

Carbobenzoxylation of N^{α},N^{ω}-dicarbobenzoxy-L-arginine. To a solution of 22.1 g. of N^{α},N^{ω}-dicarbobenzoxy-L-arginine in 50 ml. of normal NaOH, chilled to about 2–3°, was added a total of 8.5 ml. of carbobenzoxy chloride and 25 ml. of 2*N* NaOH, in three equal and alternate portions. The addition, which required some 10 min., was accompanied by vigorous shaking and cooling in an ice bath. A precipitate appeared during this time which, after an additional 30 min. was filtered over suction. The moist filter cake was dissolved in cold alcohol-free chloroform, the aqueous layer separated, and the chloroform layer washed with 10 ml. of 5% sodium carbonate and dried over anhydrous sodium sulfate. At no time was any of the above operations effected at a temperature greater than 4°. Evaporation of the chloroform solution to dryness at 20–25° *in vacuo*, followed by treatment of the oily residue with absolute ether, resulted in the formation of crystals. These were recovered by filtration, after some 12 hr. at 4°; yield, 20 g. Elemental analyses of the material identified it as sodium tricarbobenzoxy-L-argininate.

Anal. Calcd. for $C_{30}H_{31}O_8N_4Na$: N, 9.4; Na, 3.8. Found: N, 9.4; Na, 3.8.

That the aforementioned substance was a mixture of at least two isomeric forms of sodium tricarbobenzoxy-L-argininate was shown by the fact that 6 g. of the substance, when treated with 50 ml. of boiling absolute ethanol, ultimately yielded 0.7 g. of the crystalline alkali-stable form of sodium tricarbobenzoxy-L-argininate (II) upon standing for 2 days at 4°. The parent material therefore presumably consisted, in the main, of the alcohol-susceptible form.

N^{ω},N^{ω}-Dicarbobenzoxy-L-arginine (V). A solution of 2.9 g. of pure tricarbobenzoxy-L-arginine in 20 ml. of purified thionyl chloride was stored at room temperature for 5 hr. Petroleum ether was then added and the sirup which deposited was washed repeatedly with petroleum ether. The sirup was then dissolved in 20 ml. of acetone and, subsequent to the addition of 0.5 ml. of concentrated hydrochloric acid, was stored at room temperature for 6 hr., after which time it was concentrated to dryness *in vacuo* at 40°. The residue was taken up in water, a small amount of insoluble material was removed by filtration, and the filtrate was adjusted to a faintly alkaline *p*H by the addition of potassium bicarbonate. A precipitate deposited which was filtered over suction; the moist filter cake was crystallized from methanol. Yield, 50% of theory; m.p. 160°.

Anal. Calcd. for $C_{22}H_{26}O_6N_4$: C, 59.7; H, 6.0; N, 12.7. Found: C, 59.6; H, 6.0; N, 12.7.

N^{ω}-Carbobenzoxy-L-arginine (VI). *Method A.* A solution of 4.4 g. of N^{α},N^{ω}-dicarbobenzoxy-L-arginine (IV) in 30 ml. of pure thionyl chloride was stored at room temperature for 1 hr., then concentrated to dryness *in vacuo* at 40–45°. The residual sirupy N^{ω}-carbobenzoxy-L-arginine N-carboxyanhydride hydrochloride was washed repeatedly with petroleum ether in order to remove the benzyl chloride formed during the reaction, and then dissolved in 50 ml. of 10% acetic acid. After 4 hr. at room temperature, the reaction mixture was concentrated to dryness under reduced pressure, the resulting residue dissolved in 50 ml. of water, filtered, and the filtrate, after adjustment to *p*H 9 by the addition of concentrated aqueous ammonia, stored at room temperature in an open vessel in order to permit the excess ammonia to escape. Some 24 hr. later, the precipitate was filtered over suction and washed with cold water; yield 2.6 g. (84%). Recrystallization was effected by the dropwise addition of water to a suspension of the material in boiling ethanol until solution was achieved, followed by the further addition of alcohol and storage at 4°; the crystalline product, recovered by filtration, was ninhydrin positive. M.p. 190°; $[\alpha]_D^{25}$ +9.5° (6.12% in 1 equivalent of aqueous HCl).

Anal. Calcd. for $C_{14}H_{20}N_4O_4$: C, 54.5; H, 6.5; N, 18.2. Found: C, 54.5; H, 6.6; N, 18.2.

Method B. To an ice-cold suspension of 4.4 g. of N^{α},N^{ω}-dicarbobenzoxy-L-arginine, in 30 ml. of dry chloroform, was added 2.1 g. of phosphorus pentachloride. Upon shaking for several minutes at 0°, a homogeneous solution was secured without evident evolution of hydrogen chloride gas (presumably due to the formation of the hydrochloride salt of the acid chloride). The reaction mixture, which became turbid upon storage at room temperature for 1 hr. (formation of the *N*-carboxyanhydride), was concentrated to dryness *in vacuo* at 40–45°, and the residue washed repeatedly with petroleum ether, then treated with 50 ml. of 10% acetic acid. The solution so derived was permitted to stand at room temperature for 4 hr., washed twice with ethyl acetate, and subsequently concentrated to dryness at 40–45° *in vacuo*. An oily residue was secured which was dissolved in 50 ml. of water. Treatment with aqueous ammonia, as described in method A above, led to the desired product in some 65% yield; m.p. 190°.

N^{α}-Carbobenzoxy-L-arginine (VII). To a suspension of 63 g. of sodium bicarbonate in 250 ml. of water, in a 1-l. beaker, was added 42.2 g. of L-arginine·HCl, and the mixture stirred vigorously at room temperature. To the mixture was added 37.4 g. of carbobenzoxy chloride, in about 5 equal portions, over a period of 30 min. The stirring was continued for 1 hr. after the addition was complete, and the reaction mixture then adjusted to *p*H 8.5 with concentrated aqueous ammonia and subsequently stored for 2 hr. at 4°. A crystalline precipitate of the desired product which deposited was filtered off, washed with cold water, and finally recrystallized from boiling water to which a few drops of ammonia had been added; yield, 58.6 g.; m.p. 175°. A melting point of 175° was previously reported[16] for this compound.

II. *Preparation of some amino acid ester derivatives*

N^{ω}-Carbobenzoxy-L-arginine methyl ester (VIII). A solution of 4.4 g. of N^{α},N^{ω}-dicarbobenzoxy-L-arginine in 30 ml. of pure thionyl chloride was stored at room temperature for 1 hr., petroleum ether added thereto, and the resulting sirupy *N*-carboxyanhydride washed repeatedly with petroleum ether. The sirup was then dissolved in 30 ml. of absolute methanol containing about 0.7 g. of hydrogen chloride, and the reaction mixture permitted to stand at room temperature for 3 hr. After this time the solution was evaporated to dryness *in vacuo* at 30–35°, methanol was added, and the evaporation was repeated. The residual sirup was taken up in 7–8 ml. of methanol and 60 ml. of methyl ethyl ketone was added thereto. Upon storage at room temperature in an open vessel, the methanol slowly escaped, and a crystalline substance (prisms) was deposited. After some 24 hr., this was filtered over suction and washed first with methyl ethyl ketone, then with ether; yield, 3.3 g. The substance softened at about 100° and decomposed at 110°; repeated recrystallization of the material from methanol–methyl ethyl ketone did not alter this value. Analytical values indicated the substance to be the dihydrochloride monohydrate.

Anal. Calcd. for $C_{15}H_{22}N_4O_4 \cdot 2HCl \cdot H_2O$: C, 43.6; H, 6.5; N, 13.6; Cl, 17.2. Found: C, 43.5; H, 6.5; N, 13.6; Cl, 17.2.

N^{ω}-Carbobenzoxy-L-arginine benzyl ester (IX). A solution of 4.4 g. of N^{α},N^{ω}-dicarbobenzoxy-L-arginine in 30 ml. of pure thionyl chloride was stored at room temperature for 1 hr. Addition of petroleum ether led to the deposition of a

TABLE I

PHYSICAL CONSTANTS AND ANALYTICAL VALUES OF SOME AMINO ACID BENZYL ESTER *p*-TOLUENESULFONATES

p-Toluenesulfonate Salt	M.P., °C. (Corr.)	$[\alpha]_D^{25}$[a]	Calculated C	Calculated H	Calculated N	Found C	Found H	Found N
D-Alloisoleucine benzyl ester	162–164	− 0.2°	61.0	6.9	3.56	61.1	7.0	3.56
L-Aspartic acid dibenzyl ester	158–160[b]	+ 1.0°	61.8	5.6	2.89	61.7	5.7	2.86
L-*S*-Benzylcysteine benzyl ester	162–163[c]	−20.9°	60.9	5.8	2.96	61.1	5.8	2.90
L-Glutamic acid dibenzyl ester	144–145	+ 7.6°	62.6	5.9	2.80	62.4	5.9	2.80
Glycine benzyl ester	132–134	—	57.0	5.7	4.15	56.7	5.7	4.18
L-Isoleucine benzyl ester	153–154	− 0.1°	61.0	6.9	3.56	61.1	7.0	3.55
L-Leucine benzyl ester	158.5–160	− 1.7°	61.0	6.9	3.56	61.0	6.8	3.49
L-Phenylalanine benzyl ester	170.5–171.5	− 7.2°	64.6	5.9	3.28	64.6	5.8	3.23
L-Tyrosine benzyl ester	179–180.5	−12.2°	62.3	5.7	3.16	62.4	5.8	3.09
L-Valine benzyl ester	158–160	+ 1.2°	60.1	6.6	3.69	59.5	6.6	3.75

[a] Rotations were measured in a photoelectric polarimeter; solutions were 1–2% in methanol. [b] L. Velluz, G. Amiard, J. Bartos, B. Goffinet, and R. Heymes, *Bull. soc. chim. France*, 1464 (1950), reported a m.p. of 155° and an $[\alpha]_D^{20}$ +6.0° (2% in chloroform). [c] K. C. Hooper, H. N. Rydon, J. A. Schofield, and G. S. Heaton, *J. Chem. Soc.*, 3148 (1956), reported a m.p. of 155°.

sirup, which was washed repeatedly with petroleum ether and subsequently dissolved in 20 ml. of benzyl alcohol containing approximately 0.7 g. of hydrogen chloride. The reaction mixture was permitted to stand at room temperature for 3 hr., after which time treatment with dry ether led to the precipitation of the benzyl ester hydrochloride as a sirup. This was dissolved in a small amount of water, the solution was treated with an excess of anhydrous potassium carbonate, and the liberated free ester was extracted into ethyl acetate. Concentration of the ethyl acetate extracts *in vacuo*, followed by the addition of petroleum ether, resulted in the deposition of N^{ω}-carbobenzoxy-L-arginine benzyl ester in the form of prisms. The product was recrystallized from ethyl acetate; yield, 82% of theory; m.p. 121°.

Anal. Calcd. for $C_{21}H_{26}N_4O_4$: C, 63.3; H, 6.6; N, 14.1. Found: C, 63.4; H, 6.5; N, 14.0.

Preparation of the α-acetyl derivative of the above compound was effected upon treatment of a solution of 2 g. of N^{ω}-carbobenzoxy-L-arginine benzyl ester, in 20 ml. of dry chloroform, with 2 ml. of anhydrous pyridine, and 0.6 ml. of acetic anhydride. After some 2 hr., the reaction mixture was washed copiously, first with 10% acetic acid, then with potassium bicarbonate solution, and subsequently evaporated to dryness. The residue was first triturated with cold water, then crystallized from ethyl acetate. A 70% yield of N^{α}-acetyl-N^{ω}-carbobenzoxy-L-arginine benzyl ester m.p. 82° was thereupon secured. Hydrogenolysis of this compound, in the presence of palladium catalyst, resulted in the formation of N^{α}-acetyl-L-arginine monohydrate in nearly quantitative yield; m.p. 270°; $[\alpha]_D$ +7.8° (in water as the anhydrous material).

Glycine benzyl ester p-toluenesulfonate. Into a 500-ml. round-bottom flask were placed 18.8 g. (0.25 mole) of glycine, 48.5 g. (0.255 mole) of *p*-toluenesulfonic acid monohydrate, 100 ml. of benzyl alcohol, and 50 ml. of benzene. The mixture was then heated under reflux, with the liberated water being removed azeotropically and trapped with the aid of a Stark and Dean distilling receiver. A clear solution was obtained soon after reflux began. When water (about 9 ml.) was no longer distilled off (about 2–5 hr.), the reaction mixture was permitted to cool to room temperature and 250 ml. of benzene plus 400 ml. of dry ether added thereto. After standing for about 2 hr. at 4°, the crystalline benzyl glycinate *p*-toluenesulfonate was filtered, washed with anhydrous ether, and recrystallized from methanol-ether. Yield, 84% of theory. Melting point and analytical values are given in Table I.

Other amino acid benzyl esters. The benzyl ester *p*-toluenesulfonate derivatives of L-isoleucine, L-valine, L-leucine, L-aspartic acid (di-ester), L-glutamic acid (di-ester), L-phenylalanine, L-tyrosine, L-S-benzylcysteine, and D-alloisoleucine were prepared by essentially the same procedure as described above for the corresponding glycine derivative. Analytical and optical rotation values for each of these compound are revealed in Table I. The over-all yields, in most instances, ranged from 80–90% of theory.

III. *Preparation of arginine peptides*

Tricarbobenzoxy-L-arginyl-N^{ω}-carbobenzoxy-L-arginine benzyl ester. A solution of 2.85 g. (0.005 mole) of tricarbobenzoxy-L-arginine (III) and 0.7 ml. of anhydrous triethylamine in 15 ml. of dry chloroform was cooled to 0°, and 0.47 ml. of ethyl chloroformate was added. After 15 minutes at 0°, this solution was added to a chloroform solution of 2.0 g. of ω-carbobenzoxy-L-arginine benzyl ester, and the condensation permitted to proceed at room temperature for 1 hr. The chloroform solution was then washed first with dilute acetic acid, then with water, dried over anhydrous sodium sulfate, and concentrated to dryness *in vacuo*. Complete removal of the final traces of chloroform was ensured by the addition of a little methanol, followed again by evaporation to dryness. The crystalline residue obtained was dissolved in hot methanol, 0.3 ml. of triethylamine[28] was added, the solution was cooled for 12 hr. at 4°, and the precipitate which formed was filtered over suction and washed with a little cold methanol, then with ether; yield, 3.5 g.; m.p. 135°. The material, after two recrystallizations from hot methanol, exhibited a constant melting point at 147–148°.

Anal. Calcd. for $C_{51}H_{57}N_8O_{11}$: C, 64.0; H, 6.0; N, 11.7. Found: C, 63.8; H, 6.0; N, 11.6.

Tricarbobenzoxy-L-arginyl-N^{ω}-carbobenzoxy-L-arginine methyl ester. The condensation of 2.85 g. of tricarbobenzoxy-L-arginine (III) and 1.8 g. of ω-carbobenzoxy-L-arginine methyl ester·2HCl·H_2O was effected in essentially the same manner as described above for the corresponding benzyl ester derivative. A 2.3 g. yield of crude product, which melted at 128°, was obtained. After recrystallization from hot ethyl acetate, the substance revealed a m.p. of 135°.

Anal. Calcd. for $C_{45}H_{52}N_8O_{11}$: C, 61.4; H, 5.8; N, 12.7. Found: C, 61.0; H, 6.2; N, 12.4.

(28) Addition of triethylamine was necessary in order to prevent contamination with an unreacted tricarbobenzoxy-L-arginine. Employment of the conventional procedure, which would involve preliminary washing with carbonate or bicarbonate solution in order to remove unchanged acylamino acid, is useless here by virtue of the high solubility of the sodium and potassium salts of tricarbobenzoxy-L-arginine in chloroform solution, and their relatively low solubility in water.

The melting point of a mixture of the above product and tricarbobenzoxy-L-arginine was depressed to 110–115°.

Tricarbobenzoxy-L-arginyl-L-glutamic acid dibenzyl ester. The condensation of tricarbobenzoxy-L-arginine with the hydrochloride or *p*-toluenesulfonate salt of L-glutamic acid dibenzyl ester was carried out in chloroform solution as above. Isolation of the condensation product was achieved in comparable manner, with the exception that the crystalline residue, obtained upon evaporation of the reaction mixture, was first triturated with *cold* methanol containing triethylamine, then filtered over suction and recrystallized twice from ethyl acetate; yield, 75%; m.p. 120–121°.

Anal. Calcd. for $C_{49}H_{51}O_{11}N_5$: C, 66.4; H, 5.8; N, 7.9. Found: C, 66.1; H, 6.0; N, 7.8.

L-Arginyl-L-glutamic acid. Hydrogenolysis of tricarbobenzoxy-L-arginyl-L-glutamic acid dibenzyl ester in 95% acetic acid was effected in the presence of palladium black catalyst.[16] Upon completion of the reaction, the catalyst was filtered off, washed first with methanol, then with water, and the combined filtrates finally evaporated to dryness. The residue was dissolved in a small amount of hot water and crystallized as plates upon the addition of hot ethanol; yield, 90% of theory. Recrystallization from water yielded the crystalline tetrahydrate with a recovery of 90%.

Anal. Calcd. for $C_{11}H_{21}O_5N_5 \cdot 4H_2O$: C, 35.2; H, 7.8; N, 18.7. Found: C, 35.2; H, 7.9; N, 18.4.

The dipeptide tetrahydrate lost 19.1% of its weight upon drying for 2 hr. *in vacuo* at 78° (calcd. for $4H_2O$, 19.2%) and melted at 210–214° prior to, and after its conversion to the anhydrous material; $[\alpha]_D^{24}$ +21.4° for a 1% solution in water, calculated as the anhydrous material.[29]

Anal. Calcd. for $C_{11}H_{21}O_5N_5$: C, 43.6; H, 7.0; N, 23.1. Found: C, 43.5; H, 7.1; N, 23.2.

A sample of the above dipeptide was hydrolyzed with acid to the corresponding free amino acids with 5*N* HCl and the excess acid was removed *in vacuo*. The hydrolysate was taken up in water and the aqueous solution "spotted," together with a sample of the parent dipeptide and reference standards of glutamic acid and arginine·HCl, on Whatman No. 1 paper. Prior to chromatography, the paper was briefly exposed to ammonia vapors. Four different solvent systems were employed, with the dipeptide revealing only a single ninhydrin positive spot with R_f values as follows: formic acid–water-*tert*-butyl alcohol (3:3:14), 0.26; methanol-water-pyridine (20:5:1), 0.28; 70% aqueous ethanol, 0.29; 88% phenol with 10% sodium acetate, 0.53. The hydrolyzate, on the other hand, revealed only two spots which corresponded to glutamic acid and arginine, respectively.

Acknowledgment. We wish to express our appreciation to Dr. T. Otani for skillful technical assistance rendered during a portion of this study, and to Mr. R. J. Koegel and his staff for performing the elemental analyses. Aid from the Anna Fuller Fund for a travel grant to one of us (L. Z.) is gratefully acknowledged.

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(29) These values are in agreement with those reported by Gish and Carpenter[7]; m.p. 205–210° for the dihydrate; $[\alpha]_D$ +22°, calcd. for the anhydrous material in water. Berse and Piche[11] and Hofmann, Peckham, and Rheiner[9] reported melting point values for the anhydrous material as 202–205° and 251–252° dec., respectively, but made no mention of the possibility of hydrate formation. In our experience, the free dipeptide invariably deposits as the tetrahydrate upon crystallization from hot water. However, when precipitation is achieved by the addition of methanol or ethanol to the aqueous solution, a mixture of hydrates is obtained with values found which approach those of either the dihydrate or the tetrahydrate, depending upon the temperature employed. Isolation of the material as the monohydrate has been reported.[17]

[CONTRIBUTION NO. 464 FROM THE RESEARCH LABORATORIES OF HOFFMANN-LA ROCHE INC.]

Piperidine Derivatives. IV. 1,3-Disubstituted-4-aryl-4-acyloxy Piperidines*[1]

A. ZIERING, ALEX MOTCHANE, AND JOHN LEE

Received May 31, 1957

On the basis of the infrared spectra of α-1,3-dimethyl-4-phenyl-4-hydroxypiperidine and β-1,3-dimethyl-4-phenyl-4-hydroxypiperidine, the α-form was tentatively designated *cis* and the β-form *trans* with respect to H and OH. It was also shown that the α and β forms of 1-methyl-3-R-4-phenyl-4-propionoxypiperidine (R = ethyl, allyl, crotyl) can be distinguished by several bands in the infrared. Other esters have been prepared where R is butyl, propyl, hexyl, and benzyl. All of the esters have been examined for their analgesic activity.

In a previous paper,[2] we have described the diastereomeric forms of the low melting (β) [Fig. 1 (1b), R=CH_3] and the high melting (α) [Fig. 1 (1a), R=CH_3] forms of 1,3-dimethyl-4-phenyl-4-propionoxypiperidine hydrochloride.[3] The infrared spectra of the two forms are shown in Fig. 2.

We have now prepared homologous compounds

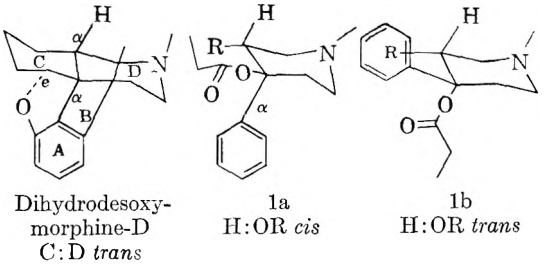


FIGURE 1.

where R is allyl, crotyl, ethyl, propyl, butyl, hexyl, and benzyl. In the case of the first three mentioned, diastereomeric pairs, α and β forms were encoun-

*This paper is a contribution in honor of Lyndon F. Small, former Editor of the Journal.

(1) Presented in part before the Meeting-in-Miniature of the North Jersey Section of the A.C.S., January 28, 1957.

(2) A. Ziering and J. Lee, *J. Org. Chem.*, 12, 911 (1947).

(3) The higher melting isomer is also known as alphaprodine [Nisentil®] and the lower melting form as betaprodine (World Health Organization designations).

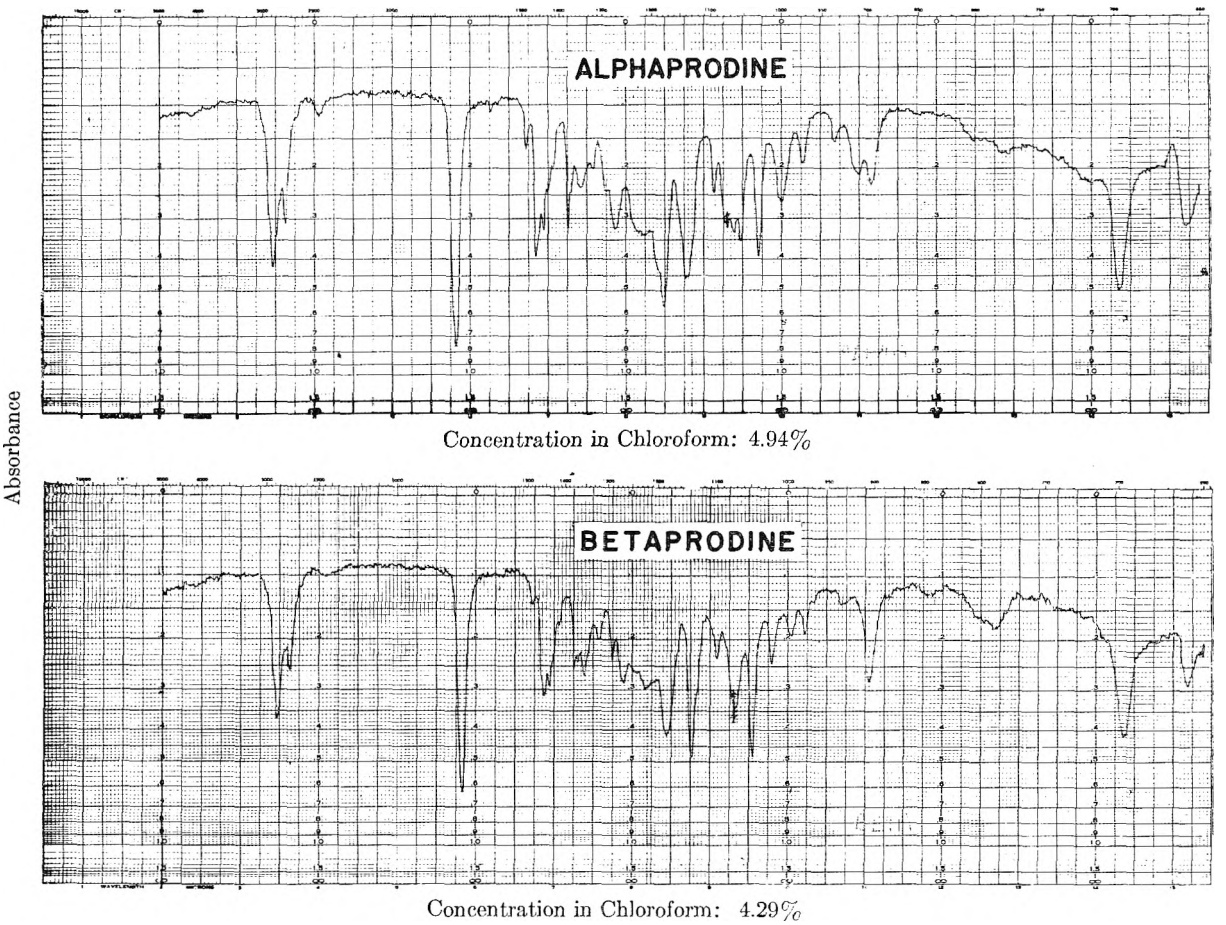


FIG. 2. INFRARED SPECTRA OF DIASTEREOMERIC FORMS OF 1,3-DIMETHYL-4-PHENYL-4-PROPIONOXYPIPERIDINE.

tered but with the last three no attempt was made to isolate the small amounts of the β form that were probably present. Since the compounds are of some pharmacological importance,[4,5] it seemed of interest to assign the diastereomers to the α and β series and to establish, if possible, the absolute configurations.

In the previous paper, we had assigned the structure 1b (*cis* CH_3:OR) to the more active β-diastereomer (betaprodine) since that structure simulated the decahydroisoquinoline ring of dihydrodesoxymorphine-D which, at that time, was assumed to have rings C and D in *cis* conformation. Since then, however, it has been established that rings C and D have a *trans* conformation.[6] Thus, one would expect that the more active isomer (betaprodine) probably would have structure 1a Fig. 1 (*trans* CH_3:OR) on the basis of its similarity to rings C and D of dihydrodesoxymorphine-D and on the basis of the similarity of the analgesic activity of the more active isomer to that of dihydrodesoxymorphine-D in rats.

Beckett and co-workers,[7] on the basis of conformational analysis and hydrolysis rates of 1a and 1b, have arrived at the same conclusion; that betaprodine should be represented by 1a and alphaprodine by 1b.

However, examination of the infrared spectra of the alcohols derived from 1a and 1b permits the tentative deduction that the structure assignments remain as originally postulated, *i.e.*, alphaprodine is 1a and betaprodine is 1b.

The relative position of the phenyl, hydroxyl, and methyl groups was determined using the spectra of the α and β forms of 1,3-dimethyl-4-phenyl-4-hydroxypiperidine, in particular in the region of OH absorption near 3600 cm.$^{-1}$. It is well known that a free OH group will have an absorption band near 3600 cm.$^{-1}$; when association by H-bonding occurs, this absorption band becomes weaker and an absorption band appears at lower frequencies, its intensity depending on the degree of association. Intermolecular H-bonding, which would account for the low OH absorption in both com-

(4) W. M. Benson, D. V. Cunningham, D. L. Hane, and S. VanWinkle, *Arch. intern. pharmacodynamie*, **109**, 171 (1957).

(5) J. Lee, W. M. Benson, and F. F. Foldes, *Can. Anaes. Soc. J.*, **3**, 363 (1956).

(6) H. L. Holmes and R. H. F. Manske, *The Alkaloids*, Academic Press, New York, 1952, Vol. 2, 162, 175; Ajay K. Bose, *Chemistry & Industry*, 130 (1954).

(7) A. H. Beckett and J. Walker, *J. Pharm. and Pharmacol.* **7**, 1039 (1955); A. H. Beckett and A. F. Casy, *J. Pharm. and Pharmacol.*, **6**, 986 (1954).

pounds, depends on the free access to the hydroxyl from the outside. This, in turn, depends on the arrangement of groups surrounding OH within the molecule.

In the case of a *cis* configuration of OH and CH_3, corresponding to the form 1b (Fig. 1), the Courtauld scale model shows that the CH_3 is close to the OH to the extent of causing steric interference which restricts the free rotation around the CO bond. This is not the case for the form 1a.

It has been shown by Smith and Creitz[8] in a study of the OH absorption at 3600–3200 cm^{-1}, that the substitution of a single methyl in the 2-position of 3-pentanol, where free rotation is still possible, restricts notably the intermolecular H-bond formation. A similar effect can be expected in the present case.

A distinct difference between the two substances, α and β, is seen in Fig. 3. The molecular extinction

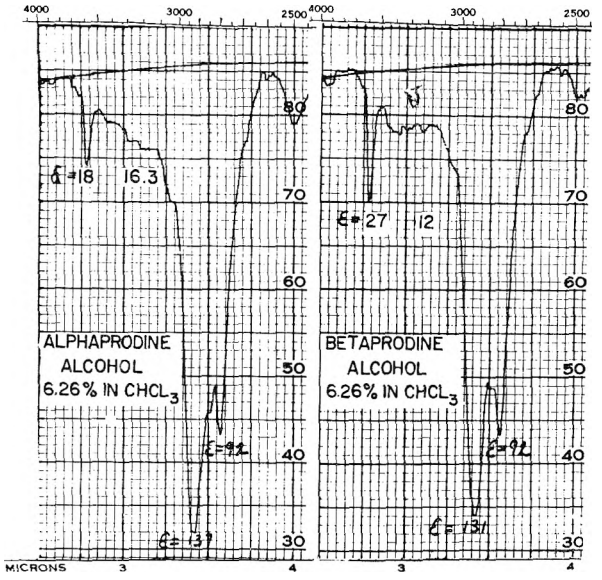


FIG. 3. INFRARED ABSORPTION BANDS (OH AND CH STRETCHING) OF DIASTEREOMERS OF 1,3-DIMETHYL-4-PHENYL-4-HYDROXYPIPERIDINE.

coefficient of the OH stretching band at 3600 cm^{-1} is 18 for the α form and 27 for the β form. These values are about in the same proportion as the values of the area under the free OH peak (between 3700 and 3510 cm^{-1}), which are respectively, 15 and 21 percent of the total area under the curve measured from 3700 to 3070 cm^{-1}. This total area, representing roughly the total OH absorption (free and bonded), agrees, in the two curves, within 10 percent.

That the difference between the free OH peaks is real and significant follows from the comparison of the OH with the CH absorption at 2900 to 2800 cm^{-1} used as an internal standard; this absorption should be equal in the α and β forms. Actually, at 2800 cm^{-1}, the absorption is exactly the same in both forms (ϵ = 92). At 2930 cm^{-1}, where it is nearly the same, the discrepancy is even in the opposite direction from the OH band difference. This is seen to be due to the additional absorption in the region of 3200–3300 cm^{-1} in the α compound (ϵ = 16 for α as against 12 for β), which obviously reaches also to lower frequencies and points to the presence of a bonded OH precisely where the absorption of the free OH, at 3600 cm^{-1}, is lower.

The conclusion appears justified that in the α form the OH is more easily accessible from the outside and consequently less crowded by neighboring groups: the CH_3 group would then be trans to OH, *i.e.*, the α compound would have the structure 1a (Fig. 1), or the corresponding inverted structure. The β form would be 1b, or again the corresponding inverted form (*cis* CH_3:OH) and the higher absorption of the free OH the consequence of a *cis* configuration with respect to the methyl. The absorption in the condensed phase (mull) was essentially in the agreement with this assignment: there was no free OH absorption, but the broad band corresponding to variously bonded OH was displaced farther to lower frequencies in the α compound than in the β, *i.e.*, there was more bonding in α than in β.

A more detailed assignment of frequencies is not certain in the absence of data on dilution effects, which are being explored. Nevertheless, it might be justified to mention here the weak doublet 1323 cm^{-1}, 1337 cm^{-1} in the β form which is absent in α, whereas the α form shows an indication of a band at 1428 cm^{-1}, which is absent in β (Fig. 4). This relationship corresponds rather closely to the one observed by Smith and Creitz[8] with CH_3OH: 1330 cm^{-1}, 1337 cm^{-1} (free), vs. 1420 cm^{-1} (associated) for the (OH) bending motion, and would agree with the above assignment based on the behavior of the (OH) stretching band. The excess absorption obtained by subtracting one curve from another around 1330 cm^{-1} and 1420 cm^{-1}, shown in the figure as shaded areas, corresponds closely to the bands in question.

An attempt has been made to explore the possibility of assigning an absolute configuration. Use could be made of the known difference in the position of the C(3)-OH band in steroids, where the equatorial OH band is shifted by about 30 cm^{-1} with respect to the band of an axial OH.[9]

No such shift appears to be present in any of the bands in the region of 1050 cm^{-1}, which may suggest that there is no difference in the conformation of the OH in the α and β compounds.

Such displacement is considered to be the result of interaction between a substituent group and the ring, and a similar effect should be possible with groups other than OH, as well. The absorption of

(8) F. A. Smith and E. C. Creitz, *J. Research Nat. Bur. Standards*, **46**, 145 (1951).

(9) A. R. H. Cole, R. N. Jones, and K. Dobriner, *J. Am. Chem. Soc.*, **74**, 5571 (1952).

the methyl group near 1380 cm^{-1} showed a characteristic asymmetry of the band in opposite directions in the case of alpha and beta compounds, the band having an inflection on opposite sides (Fig. 4):

	Alpha		Beta	
Position (cm^{-1})	1383	1374	1383	1374
Absorption (cm^2/mol)	94	(25)	(20)	73

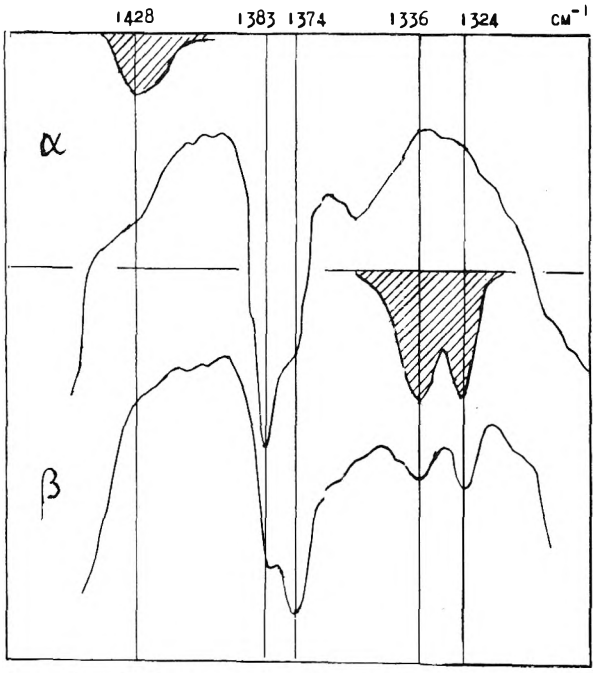


FIG. 4. 1,3-DIMETHYL-4-PHENYL-4-HYDROXYPIPERIDINES. The shaded bands represent differences between the two spectra: $(\beta - \alpha)$ at 1330 cm^{-1} and $(\alpha - \beta)$ at 1428 cm^{-1}.

When compared to the one found with the steroid OH, the observed shift of only 9 cm^{-1} seems small. On the other hand, a similar shift between tropine and pseudotropine,[10] involving again an OH group, was only 17 cm^{-1}, *i.e.*, considerably smaller than in the case of steroid OH. With different bonds involved here the interaction could be expected to produce an effect of different magnitude.

It seems reasonable to conclude that the interaction with the ring results in an increase in the force constant of the bending (CH) symmetric vibration of the CH_3 group. The observed direction of the shift would make the CH_3 equatorial in the α form, and consequently, following our previous demonstration, the hydroxyl equatorial also, and the phenyl axial, *i.e.*, the α compounds would have the form 1a (Fig. 1) and the β-form would be the structure 1b inverted.

The different 3-alkyl derivatives can be distinguished, in the esters, by the frequencies at 950–1050 cm^{-1} (Fig. 5).

The 3-methyl compounds showed a sequence of three bands of decreasing intensity:

(10) S. Archer and T. R. Lewis, *Chemistry & Industry*, 853 (1954).

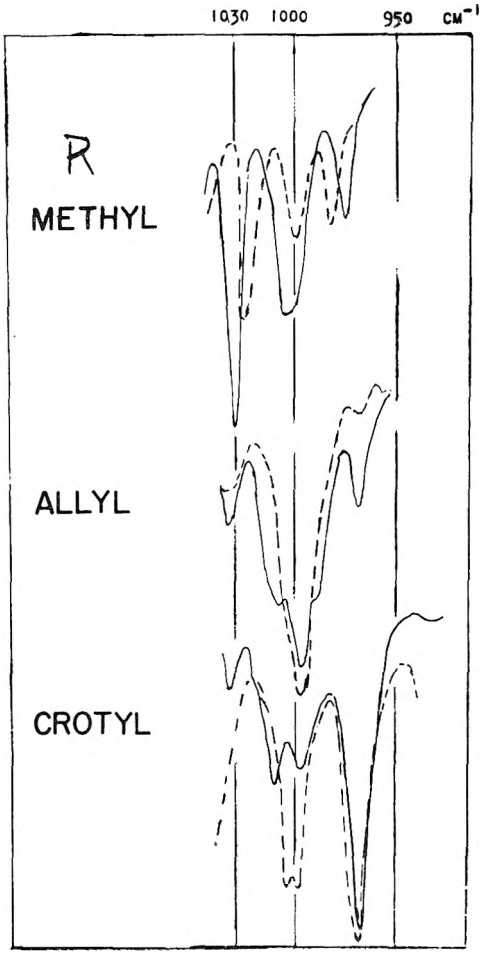


FIG. 5. INFRARED SPECTRA OF THE DIASTEREOMERIC FORMS OF 1-METHYL-3-R-4-PHENYL-4-PROPIONOXYPIPERIDINE.

	cm^{-1}			ϵ		
α	1033	1004	975	182	84	48
β	1024	997	981	84	58	26

The 3-allyl compounds had one prominent complex band and two satellites:

	cm^{-1}			ϵ		
α	1034	997	968	56	113	50
β	(1034)	998	970	(41)	118	13

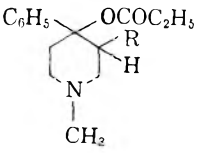
The 3-crotyl compounds had the sequence of intensity reversed with respect to the 3-methyl and the middle band was a doublet.

	cm^{-1}			ϵ		
α	1033	1009,997	967	55	85	188
β	(1035)	1004,997	969	(85)	128	150

The α and β forms, in the esters, can be distinguished by several bands. Two are shown as examples:

	Band 1350 cm^{-1}		Band 1060 cm^{-1}	
	α	β	α	β
3-Methyl	1350	1359	1057	1050
3-Allyl	1349	1357	1063	1051
3-Crotyl	1348	1358	1062	1063
			(1052)	1047

TABLE I



Found	R=	R_f Values pH 6.3	pH 4.9	pH 3.6	pH 2.2	Analgesic Activity (Morphine = 1)
α	CH_3	0.65	0.58	0.46	0.27	1.0
β	CH_3	0.64	0.48	0.37	0.19	7.0
α	C_2H_5	0.73	0.70	0.52	0.33	1.1
β	C_2H_5	0.64	0.57	0.45	0.28	1.25
α	$-CH_2CH=CH_2$	0.79	0.77	0.56	0.39	11.0
β	$-CH_2CH=CH_2$	0.82	0.75	0.51	0.31	3.0
α	$CH_2CH=CH-CH_3$	0.83	0.84	0.61	0 46	0.03
β	$CH_2CH=CH-CH_3$	0.85	0.80	0.58	0.37	0.04

The band near 1060 cm^{-1} shows that the 3-crotyl compounds were not pure, particularly the β form which contained a large amount of the α form.

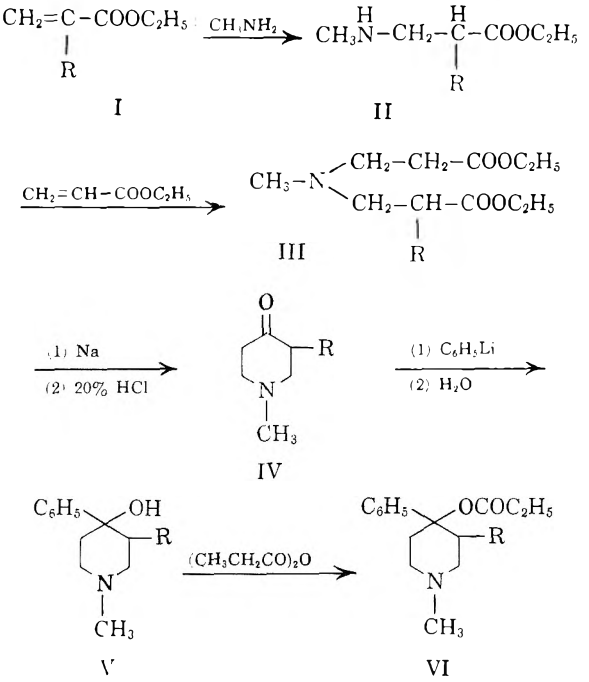
The assignment of equatorial acyloxy groups to both α and β isomers would explain the findings of the relative ease of hydrolysis of alphaprodine and betaprodine found by Beckett[7] and indeed account for the not too great difference of the hydrolytic rate.

The assignment of the 3-substituted compounds to the α or β series by this method is also supported by the behavior of the compounds when chromatographed on buffered paper. The solvent used was a mixture of *t*-amyl alcohol, 80 parts; di-*n*-butyl ether, 7 parts; and water, 13 parts, and the results are shown in Table I.

Separations at *p*H 6.3 and higher were less satisfactory than at the lower *p*H values. The results given show that at *p*H 4.9 and below, the α form has invariably a higher R_f value than the β form and the series align with the infrared data.

A further observation also places the compounds in either the α or β series. The α compound invariably forms in the higher yield under the standardized conditions of the organo-metallic reactions used. In fact, with the higher 3-substituents, *e.g.*, butyl, hexyl, benzyl, the β form was not isolated and was probably formed in very small amounts if at all.

The synthesis of the 1-methyl-3-alkyl-4-phenyl-4-propionoxypiperidines was carried out according to the accompanying scheme.



Pharmacological results. In Table I are also given approximate activities of the compounds with respect to morphine. It would appear that there is little relationship between steric configuration and analgesic activity. When there are one or two carbon atoms in the 3-substituent, the β-series (*cis* 3-R: 4-OR) shows the highest activity. However, when the 3-substituent is allyl, the activity is greatest in the α-series and moreover is greater than that of any of the β-compounds. Hence, it might be assumed that close simulation of the decahydroisoquinoline ring of dihydrodesoxymorphine-D in these structures is not a necessary condition for high activity.

EXPERIMENTAL[11]

α-1,3-Dimethyl-4-phenyl-4-hydroxypiperidine (V, R=CH_3). This compound was prepared according to the procedure of Ziering and Lee.[12] It can also be prepared in a very pure state by hydrolyzing 2.97 g. of α-1,3-dimethyl-4-phenyl-4-propionoxypiperidine hydrochloride, m.p. 220–221° with 1.4 g. of 85% potassium hydroxide in 50 ml. of ethyl alcohol.

(11) All melting points are corrected; boiling points are uncorrected. The infrared spectra were made with a Perkin-Elmer Model 21 spectrophotometer. The cells were 0.1 mm. Molecular weights were determined by titration with perchloric acid in glacial acetic acid.

(12) A. Ziering and J. Lee, *J. Org. Chem.*, 12, 911 (1947).

After the mixture had refluxed for 15 hr., it was filtered and the alcohol distilled off in vacuum. The residue was treated with 30 ml. of water and the oil extracted with ether. The ether extract was dried over anhydrous potassium carbonate and the residue remaining after filtering and distilling off the ether was crystallized from Skellysolve B. The yield of α-1,3-dimethyl-4-phenyl-4-hydroxypiperidine was 1 g., m.p. 100–101°.

α-1,3-Dimethyl-4-phenyl-4-propionoxypiperidine hydrochloride (VI, R=CH_3). To 6 g. of α-1,3-dimethyl-4-phenyl-4-hydroxypiperidine, m.p. 100–101°, was added 20 ml. of propionic anhydride. After the solution was heated on a steam bath for 12 hr., the excess reagent was distilled off in vacuum. The residue was made alkaline with 10% sodium carbonate solution and the oil extracted with ether. The ether solution, after drying over anhydrous potassium carbonate, was filtered and hydrogen chloride bubbled in to precipitate the hydrochloride. The yield of α-1,3-dimethyl-4-phenyl-4-propionoxypiperidine hydrochloride,[12] after crystallizing from acetone-methanol, was 4.7 g., m.p. 220–221°.

β-1,3-Dimethyl-4-phenyl-4-hydroxypiperidine (V, R=CH_3). After separation of the bulk of the α-1,3-dimethyl-4-phenyl-4-propionoxypiperidine hydrochloride from the diastereoisomeric mixture, the residue containing a diastereoisomeric mixture of the α and β forms was converted to the free bases. This mixture(88 g.) was added to a solution of 45 g. of *dl*-malic acid in 200 ml. of acetone, and after standing overnight, 71 g. of crude α-1,3-dimethyl-4-phenyl-4-propionoxypiperidine *dl*-malate, m.p. 139–143° was filtered off. The filtrate was distilled to dryness and the residue crystallized from a mixture of ethyl acetate and methyl ethyl ketone to yield the β-1,3-dimethyl-4-phenyl-4-propionoxypiperidine *dl*-malate, m.p. 118–121°; yield 40 g. This salt was converted to the free base with 10% sodium carbonate solution. Twenty-eight grams of this base was dissolved in 150 ml. of ethyl alcohol containing 7 g. of 85% potassium hydroxide and the solution was refluxed for 20 hr. The alcohol was distilled off in vacuum and 100 ml. of water added. The separated oil was extracted with ether and dried over anhydrous potassium carbonate. The ether was distilled off and the residue crystallized from hot Skellysolve B. The β-1,3-dimethyl-4-phenyl-4-hydroxypiperidine melts at 116–118°; yield 13 g.

β-1,3-Dimethyl-4-phenyl-4-propionoxypiperidine hydrochloride. The β-1,3-dimethyl-4-phenyl-4-hydroxypiperidine (2 g.) was dissolved in 10 ml. of propionic anhydride. After heating 10 hr. on the steam bath, the excess reagent was distilled off in vacuum and the residue made alkaline with 10% sodium carbonate solution. The oil was extracted with ether and the solution dried over anhydrous potassium carbonate. The ether solution was filtered and treated with hydrogen chloride gas. The precipitated β-1,3-dimethyl-4-phenyl-4-propionoxypiperidine hydrochloride was filtered off and crystallized from acetone-methanol, m.p. 199–200°; yield 1.7 g.

Ethyl 2-ethyl-3-methylaminopropionate (II, R=C_2H_5). Ethyl α-ethylacrylate[13] (85 g.) was added to a solution of 20 g. of methylamine in 180 ml. of ethyl alcohol. The solution was kept at room temperature for 7 days. The alcohol was distilled off and the product, ethyl 2-ethyl-3-methylaminopropionate (II, R=C_2H_5) distilled at 97°/29 mm.; yield 78 g.

Anal. Calcd. for $C_8H_{17}NO_2$: Mol. wt., 159. Found: Mol. wt., 157.

Diethyl α-ethyl-β,3′-(methylimino)dipropionate (III, R=C_2H_5). Ethyl acrylate (100 g.) was added to 78 g. of II, (R=C_2H_5) and the solution kept at room temperature for 4 days. The yield of product III, (R=C_2H_5) boiling at 126°/2 mm. was 115 g.

Anal. Calcd. for $C_{13}H_{25}NO_4$: C, 60.23; H, 9.65. Found: C, 59.59; H, 9.57.

(13) C. Mannich and K. Ritsert, *Ber.*, **57**, 1118 (1924).

1-Methyl-3-ethyl-4-piperidone (IV, R=C_2H_5). III, R=C_2H_5 (115 g.) was cyclized according to the procedure described by Lee and coworkers.[11] The yield of 1-methyl-3-ethyl-4-piperidone was 38 g., b.p. 102°/33 mm.

Anal. Calcd. for $C_8H_{15}NO$: Mol. wt., 141. Found: mol. wt., 140.

1-Methyl-3-ethyl-4-phenyl-4-hydroxypiperidine (V, R=C_2H_5). 1-Methyl-3-ethyl-4-piperidone (10.6 g.) was reacted in the usual way[12] with phenyl lithium prepared from 15.7 g. of bromobenzene and 1.5 g. of lithium wire. The yield of α-1-methyl-3-ethyl-4-phenyl-4-hydroxypiperidine (V, R=C_2H_5) after crystallization from Skellysolve B was 10 g., m.p. 96–97°.

Anal. Calcd. for $C_{14}H_{21}NO$: mol. wt., 219. Found: mol. wt., 218. The filtrate on concentration yielded 2 g. of the diastereoisomeric mixture (α and β forms), m.p. 72–82°.

α-1-Methyl-3-ethyl-4-phenyl-4-propionoxypiperidine hydrochloride (VI, R=C_2H_5). The α-1-methyl-3-ethyl-4-phenyl-4-hydroxypiperidine (10 g.) was reacted with 35 ml. of propionic anhydride on a steam bath for 10 hr. The product, α-1-methyl-3-ethyl-4-phenyl-4-propionoxypiperidine (VI, R=C_2H_5) was isolated in the usual way. It was converted to the hydrochloride and crystallized from acetone-methanol; yield 8 g., m.p. 229–230°.

Anal. Calcd. for $C_{17}H_{25}NO_2.HCl$: C, 65.48; H, 8.34. Found: C, 65.44; H, 8.28.

In a similar manner, the diastereoisomeric mixture of alcohols yielded a mixture of propionates from which was isolated the β-1-methyl-3-ethyl-4-phenyl-4-propionoxypiperidine hydrochloride, m.p. 201–203°.

Anal. Calcd. for $C_{17}H_{25}NO_2.HCl$: C, 65.48; H, 8.34. Found: C, 65.01; H, 8.24.

Ethyl 1-allyl-2-methylaminopropionate (II, R=allyl). Ethyl α-allylacrylate[13] (397 g.) was added to a solution of 95 g. of methylamine in 1 l. of ethyl alcohol and the resulting solution heated in an autoclave at 105° for 5 hr. under nitrogen at a pressure of 600 lbs./sq. in. The product (II, R=allyl) distilled at 105–110°/30 mm. and the yield obtained was 315 g.

Anal. Calcd. for $C_9H_{17}NO_2$: Mol. wt., 171. Found: Mol. wt., 168.

Diethyl α-allyl-β,β′-(methylimino)dipropionate (III, R=allyl). Ethyl acrylate (555 g.) was added to 838 g. of II, (R=allyl) and the solution heated in an autoclave at 100° for 6 hr. under 600 lbs. of nitrogen. The product III, (R=allyl) was distilled at 141–144°/4 mm. and the yield obtained was 1009 g.

Anal. Calcd. for $C_{14}H_{25}NO_4$: Mol. wt., 271. Found: Mol. wt., 274.

1-Methyl-3-allyl-4-piperidone (IV, R=allyl). The diester III, (R=allyl) 1009 g. was cyclized in the usual way[14] to 1-methyl-3-allyl-4-piperidone. The yield of product distilling at 117–122°/31 mm. was 242 g.

Anal. Calcd. for $C_9H_{15}NO$: Mol. wt., 153. Found: Mol. wt., 150.

1-Methyl-3-allyl-4-phenyl-4-hydroxypiperidine (V, R=allyl). 1-Methyl-3-allyl-4-piperidone (242 g.) was reacted in the usual way with phenyl lithium prepared from 29.4 g. of lithium wire and 331 g. of bromobenzene. The yield of the main product, α-1-methyl-3-allyl-4-phenyl-4-hydroxypiperidine (V, R=allyl) was 230 g. after crystallization from Skellysolve B, m.p. 110–111°.

Anal. Calcd. for $C_{15}H_{21}NO$. Mol. wt., 231. Found: Mol. wt., 230. The filtrate, on concentration yielded 20 g. of a diastereoisomeric mixture of the α and β forms, m.p. 70–85°.

α-1-Methyl-3-allyl-4-phenyl-4-propionoxypiperidine hydrochloride (VI, R=allyl). The α-1-methyl-3-allyl-4-phenyl-4-hydroxypiperidine (162 g.) was reacted with 500 ml. of propionic anhydride on a steam bath for 10 hr. The product, α-1-methyl-3-allyl-4-phenyl-4-propionoxypiperidine was iso-

(14) A. Ziering, L. Berger, S. D. Heineman, and J. Lee, *J. Org. Chem.*, **12**, 894 (1947).

lated in the usual way. It was converted to the hydrochloride and crystallized from acetone, m.p. 185–186°; yield 180 g.

Anal. Calcd. for $C_{18}H_{25}NO_2.HCl$: C, 66.77; H, 8.04. Found: C, 66.91; H, 8.29.

In a similar manner, the diastereoisomeric mixture of alcohols on treatment with propionic anhydride yielded a mixture of the α and β forms of VI, (R = allyl), which was converted to the hydrochlorides. After repeated crystallizations from acetone, the β-1-methyl-3-allyl-4-phenyl-4-propionoxypiperidine hydrochloride was isolated, m.p. 205–206°. To check the purity of the β ester, it was hydrolyzed back to the β-1-methyl-3-allyl-4-phenyl-4-hydroxypiperidine, m.p. 85–86° (hexane).

Anal. Calcd. for $C_{15}H_{21}NO$. C, 77.91; H, 9.10. Found: C, 78.21; H, 8.72.

Treatment of this β-alcohol with propionic anhydride yielded again the β-1-methyl-3-allyl-4-phenyl-4-propionoxypiperidine which was converted to the hydrochloride (VI, R = allyl), m.p. 205–206°, after crystallization from acetone.

Anal. Calcd. for $C_{18}H_{25}NO_2.HCl$: C, 66.77; H, 8.04. Found: C, 66.83; H, 8.18.

α-1-Methyl-3-propyl-4-phenyl-4-propionoxypiperidine hydrochloride. The α-1-methyl-3-allyl-4-phenyl-4-hydroxypiperidine (3 g.) was catalytically reduced in 150 ml. of ethyl alcohol with Raney nickel at 50 lbs. hydrogen pressure and room temperature. The catalyst was filtered off and the filtrate distilled to dryness. The residue was heated on a steam bath for 8 hr. with 20 ml. of propionic anhydride. By working up in the usual way, α-1-methyl-3-propyl-4-phenyl-4-propionoxypiperidine hydrochloride was isolated. It was crystallized from ethyl acetate–methanol and had a m.p. of 203–205°.

Anal. Calcd. for $C_{18}H_{27}NO_2.HCl$: Mol. wt. 325.5. Found: Mol. wt. 325.

Ethyl α-crotylacrylate (I, R = allyl). Diethyl crotylmalonate[15] (738 g.) was dissolved in 600 ml. of ethyl alcohol and added to a solution of 214 g. of 90% potassium hydroxide in 1300 ml. of ethyl alcohol in the cold. After the solution had stood overnight at room temperature, the monopotassium salt was filtered off and the filtrate distilled down in vacuum. The residue and the monopotassium salt were dissolved in water and the solution acidified with 18% hydrochloric acid. The oil was extracted with ether and the solution dried over anhydrous magnesium sulfate. The ether was distilled off and the crude residue, ethyl hydrogen crotylmalonate (642 g.) was converted according to Mannich's procedure[13] to the ethyl α-crotylacrylate in a yield of 70%, b.p. 104–106°/45 mm., n_D^{23} 1.4434.

Ethyl 1-crotyl-2-methylaminopropionate (II, R = crotyl). Ethyl α-crotylacrylate (370 g.) was added to a solution of 80 g. of methyl amine in 500 ml. of ethyl alcohol and the solution heated at 100° for 4 hr. under 600 lbs. of nitrogen. II, (R = crotyl) distilled at 128–133°/34 mm.; yield 73%.

Diethyl α-crotyl-β,β′-(methylimino)dipropionate (III, R = crotyl). Ethyl acrylate (212 g.) was added to 323 g. of II, (R = crotyl) and the solution heated for 4 hr. at 100° under 600 lbs. of nitrogen. The product, III, (R = crotyl), distilled at 150–153°/2 mm.; yield 224 g.

Anal. Calcd. for $C_{15}H_{27}NO_4$: Mol. wt., 285. Found: Mol. wt., 284.

1-Methyl-3-crotyl-4-piperidone. The diester III, (R = crotyl) 459 g. was cyclized in the usual way[14] to the 1-methyl-3-crotyl-4-piperidone, b.p. 123–124°/23 mm., n_D^{25} 1.4747; yield 116 g.

1-Methyl-3-crotyl-4-phenyl-4-hydroxypiperidine (V, R = crotyl). 1-Methyl-3-crotyl-4-piperidone (33.4 g.) was reacted in the usual way with phenyllithium. The yield of the main product, α-1-methyl-3-crotyl-4-hydroxypiperidine (V, R = crotyl), b.p. 180°/7 mm., after crystallization from Skellysolve B was 30 g., m.p. 98–100°.

(15) D. Barnard and L. Bateman, *J. Chem. Soc.*, 926 (1950).

Anal. Calcd. for $C_{16}H_{23}NO$: Mol. wt., 245. Found: Mol. wt., 246. The filtrate contained the diastereoisomeric mixture of the α and β-alcohols.

α-1-Methyl-3-crotyl-4-phenyl-4-propionoxypiperidine d-tartrate (VI, R = crotyl). α-1-Methyl-3-crotyl-4-phenyl-4-hydroxypiperidine (10 g.) was reacted with propionic anhydride (50 ml.) in the usual way. The ester distilled in vacuo at 152°/1 mm.; yield 9 g.

Anal. Calcd. for $C_{19}H_{27}NO_2$: Mol. wt., 301. Found: Mol. wt. 302. The α-ester (3 g.) was converted to the tartrate salt by adding it to a solution of 1.5 g. of *d*-tartaric acid in 20 ml. of acetone and concentrating to dryness. The residue was dissolved in ethyl acetate to which two drops of water were added. The tartrate salt was filtered off and crystallized from methyl ethyl ketone, m.p. 95–97° after drying overnight in an oven at 63°.

Anal. Calcd. for $C_{19}H_{27}NO_2.C_4H_6O_6.1.5H_2O$: Mol. wt., 478. Found: Mol. wt., 478.

The diastereoisomeric mixture of α and β-alcohols (V, R = crotyl) was converted to the esters in a similar manner. By repeated crystallization of the maleate salt from ethyl acetate, the β-1-methyl-3-crotyl-4-phenyl-4-propionoxypiperidine maleate was obtained, m.p. 126–130°. Infrared spectra showed, however, that this salt was contaminated with the α form.

Anal. Calcd. for $C_{19}H_{27}NO_2.C_4H_4O_4$: Mol. wt., 417. Found: Mol. wt., ≤18.

Ethyl α-butylacrylate (I, R = C_4H_9). By Mannich's procedure,[13] ethyl hydrogen butylmalonate was converted to ethyl α-butylacrylate in 60% yield; b.p. 88°/31 mm.

Ethyl 1-butyl-2-methylaminopropionate (II, R = C_4H_9). To a solution of 51 g. of methylamine in 250 ml. of ethyl alcohol was added 259 g. of ethyl α-butylacrylate. After standing overnight at room temperature, the solution was refluxed for 1 hr. The alcohol was distilled off and the residue distilled in vacuum. The first fraction (105 g.) b.p. 80–84°/30 mm. was ethyl α-butylacrylate. The product (II, R = C_4H_9) distilled at 118–120°/30 mm.; yield 133 g. The recovered starting material (105 g.) was added to a solution of 21 g. of methylamine in 125 ml. of ethyl alcohol and the solution heated in an autoclave under 600 lbs. of nitrogen at 75° for 4 hr. The yield of product (II, R = C_4H_9) was 98 g. The total yield was 231 g. (75% yield).

Anal. Calcd. for $C_{10}H_{21}NO_2$: Mol. wt., 187. Found: Mol. wt., 191.

Diethyl α-butyl-β,β′-(methylimino)dipropionate (III, R = C_4H_9). Ethyl acrylate (143 g.) was added to 231 g. of ethyl 1-butyl-2-methylaminopropionate and the solution heated overnight on a steam bath. The product (III, R = C_4H_9) distilled at 130–135°/1 mm., n_D^{23} 1.4400; yield, 268 g. The fore-run was treated again with ethyl acrylate in a similar manner and an additional 34 g. of product was obtained. The total yield was 302 g. (85% yield).

1-Methyl-3-butyl-4-piperidone (IV, R = C_4H_9). The above diester (III, R = C_4H_9) 302 g. was cyclized in the usual way[14] to yield 114 g. of 1-methyl-3-butyl-4-piperidone (65% yield); n_D^{23} 1.4595; b.p. 130–131°/32 mm.

1-Methyl-3-butyl-4-phenyl-4-hydroxypiperidine (V, R = C_4H_9). The reaction of phenyllithium prepared from 3.7 g. of lithium wire and 42 g. of bromobenzene with 33.8 g. of 1-methyl-3-butyl-4-piperidone yielded 33 g. of 1-methyl-3-butyl-4-phenyl-4-hydroxypiperidine, b.p. 166–168°/5 mm. The product is mainly the α form contaminated perhaps with some of the β form.

Anal. Calcd. for $C_{16}H_{25}NO$: Mol. wt., 247. Found: Mol. wt., 247.

α-1-Methyl-3-butyl-4-phenyl-4-propionoxypiperidine d-tartrate (VI, R = C_4H_9). The 1-methyl-3-butyl-4-phenyl-4-hydroxypiperidine was converted to the propionoxy derivative in the usual way. This base (7.3 g.) was then added to a solution of 3.6 g. of *d*-tartaric acid in 50 ml. of acetone containing 2 drops of water. The solution was distilled to dryness and the residue crystallized from acetone, m.p. 140–143°.

Anal. Calcd. for $C_{19}H_{29}NO_2.C_4H_6O_6.1.5H_2O$: Mol. wt., 480. Found: Mol. wt., 480.

Ethyl α-hexylacrylate (I, R = C_6H_{13}). Ethyl hydrogen hexylmalonate (490 g.) by Mannich's procedure[13] was converted to ethyl α-hexylacrylate in 76% yield; b.p. 100–102°/15 mm.

Ethyl 2-hexyl-3-methylaminopropionate (II, R = C_6H_{13}). Ethyl α-hexylacrylate (316 g.) was added to a solution of 60 g. of methylamine in 250 ml. of ethyl alcohol and the solution heated at 100° for 4 hr. under 600 lbs. of nitrogen. The product distilled at 130–135°/15 mm.; yield 314 g.

Diethyl α-hexyl-3,β'-(methylimino)dipropionate (III, R = C_6H_{13}). Ethyl 2-hexyl-3-methylaminopropionate (315 g.) was added to 150 g. of ethyl acrylate and the solution heated for 4 hr. at 100° in an autoclave under 600 lbs. of nitrogen. The product distilled at 152–158°/1 mm.; yield 345 g. (77%).

Anal. Calcd. for $C_{17}H_{33}NO_4$: Mol. wt., 315. Found: Mol. wt., 316.

1-Methyl-3-hexyl-4-piperidone (IV, R = C_6H_{13}). The above diester (III, R = C_6H_{13}), 345 g. was cyclized in the usual way[14] to 1-methyl-3-hexyl-4-piperidone. The product distilled at 153–155°/25 mm.; yield 153 g. (71%).

1-Methyl-3-hexyl-4-phenyl-4-hydroxypiperidine (V, R = C_6H_{13}). In the usual manner, 40 g. of the ketone (IV, R = C_6H_{13}) was reacted with phenyllithium prepared from 43 g. of bromobenzene and 3.8 g. of lithium wire. The product (V, R = C_6H_{13}) distilled at 170–173°/2 mm.; yield 47 g. (86%). The product is mainly the α form contaminated perhaps with some of the β form.

Anal. Calcd. for $C_{18}H_{29}NO$: Mol. wt., 275. Found: Mol. wt., 275.

α-1-Methyl-3-hexyl-4-phenyl-4-propionoxypiperidine dl-malate (VI, R = C_6H_{13}). 1-Methyl-3-hexyl-4-phenyl-4-hydroxypiperidine was converted to the 4-propionoxy derivative in the usual way; b.p. 191–193°/4 mm. The *dl*-malate was prepared by adding 1.1 g. of the 1-methyl-3-hexyl-4-phenyl-4-propionoxypiperidine to a solution of 0.45 g. of *dl*-malic acid in 10 ml. of acetone. The solution was distilled to dryness and the residue crystallized from ethyl acetate, m.p. 98–100°.

Anal. Calcd. for $C_{21}H_{33}NO_2.C_4H_6O_5$: Mol. wt., 465. Found: Mol. wt., 463.

The citrate was prepared in a similar manner, m.p. 125–127°.

Ethyl α-benzylacrylate. By Mannich's procedure[13], ethyl hydrogen benzylmalonate was converted to ethyl α-benzylacrylate, b.p. 106–107°/3 mm.; yield 78%.

Ethyl 1-benzyl-2-methylaminopropionate (II, R = $CH_2C_6H_5$). Ethyl α-benzylacrylate (170 g.) was added to a solution of 30 g. of methylamine in 200 ml. of ethyl alcohol and the solution heated in an autoclave at 100° for 4 hr. under 600 lbs. of nitrogen. The product distilled at 115–117°/3 mm.; yield 158 g. (80%).

Diethyl α-benzyl-β,β'-(methylimino)dipropionate (III, R = $CH_2C_6H_5$). Ethyl acrylate (140 g.) was added to 158 g. of ethyl 1-benzyl-2-methylaminopropionate and the solution heated in an autoclave at 110° for 4 hr. The product distilled at 160–162°/1 mm.; yield 210 g. (92%).

1-Methyl-3-benzyl-4-piperidone (IV, R = $CH_2C_6H_5$). The diester (III, R = $CH_2C_6H_5$) 210 g. was cyclized in the usual manner[14] to yield the 1-methyl-3-benzyl-4-piperidone,[16] b.p. 142–143°/4 mm.; yield 97 g. (73%).

Anal. Calcd. for $C_{13}H_{17}NO$: Mol. wt., 203. Found: Mol. wt., 203.

1-Methyl-3-benzyl-4-phenyl-4-hydroxypiperidine (V, R = $CH_2C_6H_5$). In the usual way, 1-methyl-3-benzyl-4-piperidone (40.6 g.) was reacted with phenyllithium prepared from 47.1 g. of bromobenzene and 4.2 g. of lithium in ether. Water (100 ml.) was added to decompose the complex, the ether separated and dried over anhydrous potassium carbonate. The ether was distilled off and the α-1-methyl-3-benzyl-4-phenyl-4-hydroxypiperidine crystallized from Skellysolve B, m.p. 126–127°; yield 38 g. The filtrate was examined for the presence of the β form but none could be isolated.

α-1-Methyl-3-benzyl-4-phenyl-4-propionoxypiperidine hydrochloride (VI, R = $CH_2C_6H_5$). Five g. of V, (R = $CH_2C_6H_5$) was added to 15 ml. of propionic anhydride and the solution heated for 4 hr. on a steam bath. The excess propionic anhydride was distilled off in vacuum and the residue made alkaline with 10% sodium carbonate solution. The oil was extracted with ether and the solution dried, filtered and treated with hydrogen chloride gas. The salt formed was filtered off and crystallized from ethyl acetate–methanol, m.p. 207–208°; yield 4 g.

Anal. Calcd. for $C_{22}H_{27}NO_2.HCl$: Mol. wt., 373.5. Found: Mol. wt., 368.

For pharmacological testing, the free base was converted to the *dl*-malate (light yellow sirup) which is more soluble in water than the hydrochloride.

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NUTLEY, N. J.

(16) S. M. McElvain and Gilbert Stork, *J. Am. Chem. Soc.*, **68**, 1049 (1946).

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The Structure of Tri-*O*-methylenevolemitol*

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From the condensation of volemitol with formaldehyde we have obtained a 43% yield of a crystalline tri-*O*-methylene derivative that was converted by acetolysis to a di-*O*-methylene derivative. By combining with our experimental results the well-established empirical rule that in the methylenation of polyhydric alcohols the first preference is for a βC-ring we have established that the tri-*O*-methylenevolemitol is 1,3:2,5:4,6-tri-*O*-methylene-D-*glycero*-D-*manno*-heptitol. Some conformational aspects of this acetal and of the alternative 1,3:4,6:5,7-triacetal are discussed.

In a series of papers from this laboratory, Dr. Raymond M. Hann and Dr. C. S. Hudson, with their collaborators, attempted to correlate the configurations of certain polyhydric alcohols (alditols) with the structures of the cyclic methylene acetals derived from them. They were successful in

* To Lyndon F. Small, colleague and friend for thirty-five years. N.K.R.

devising a set of empirical rules[1] that permitted them to account for all the known cyclic methylene acetals and to predict the probable structures of other cyclic methylene acetals that they were able to prepare later. As additional information on the various cyclic acetals of the polyhydric alcohols became available, Barker and Bourne[2] published an extended statement of the original Hann-Hudson rules.[3] At about the same time Barker, Bourne, and Whiffen[4] suggested that the marked tendency for a carbon chain to adopt the planar zigzag form is sufficient to explain the main features of these empirical rules, since it appears that the most-favored rings involve the least energy for distortion of the planar chain.

Mills,[5] two years later, felt that a study of the end-products of reaction was a safer approach to the problem of acetal formation. He examined the structures of the acetals themselves and found that nearly all known stable cyclic acetals of sugars and sugar alcohols conformed to patterns predictable by methods of conformational analysis already familiar in the alicyclic field. His conformational analyses were of particular interest to us for through them he was able to predict that methylenation of D-arabinitol would afford 1,3:2,4-di-*O*-methylene-D-arabinitol whereas the empirical rules permitted no decision among the four possible di-*O*-methylene derivatives of D-arabinitol.[6] Our experimental results were disclosed almost simultaneously[7] with his prediction and verified it completely.

Mills stated also[5a] that, on the basis of conformational analyses, methylenation of volemitol (I) would probably afford 1,3:2,5:4,6-tri-*O*-methylene-D-*glycero*-D-*manno*-heptitol (IV), which is analogous to the known 1,3:2,5:4,6-tri-*O*-methylene-D-mannitol.[1b] Subsequently, however, he wrote[5b,8] that the alternative 1,3:4,6:5,7-tri-*O*-methylene-D-*glycero*-D-*manno*-heptitol (VIII) could not be ruled out as it might be formed more rapidly than IV and be rather slow to undergo rearrangement. With the encouragement of Dr. Mills we then decided to study the methylenation of volemitol (= D-*glycero*-D-*talo*-heptitol = D-*glycero*-D-*manno*-heptitol, I).

The condensation of volemitol with aqueous formaldehyde, with concentrated hydrochloric acid as catalyst, yielded 43% of a crystalline tri-*O*-methylenevolemitol. From a consideration of the empirical rules, its structure should be either IV or VIII, as already suggested by Mills. Thus, as has been established conclusively, the first preference in the methylenation of a polyhydric alcohol is the formation of a βC-ring[9]; the expected monoacetal, therefore, is the 4,6-acetal, II. The second preference is for a β-ring, and so we should expect the next methylene group to engage either the 1,3- or the 5,7-positions as shown in formulas III and VII, respectively; the empirical rules do not distinguish between these alternatives.[10] If the di-*O*-methylene acetal is III, it should be capable of adding a second β-ring between C5 and C7, whereas if the di-*O*-methylene acetal is VII it should be capable of adding a second β-ring between C1 and C3. The product, in either case, would be the 1,3:4,6:5,7-tri-*O*-methylene-D-*glycero*-D-*manno*-heptitol (VIII) suggested as an alternative possibility by Mills. This cannot be the correct structure, however, for upon acetolysis of our tri-*O*-methylenevolemitol we obtained a substituted di-*O*-methylene derivative, whereas if both terminal hydroxyl groups had been engaged in acetal formation, as in VIII, we should have expected a substituted mono-*O*-methylenevolemitol.

If the intermediate di-*O*-methylenevolemitol is III and it does not proceed to the tri-*O*-methylene acetal VIII, then the only other reaction to be expected with formaldehyde is the closing of a γT-ring between C2 and C5 and the generation of 1,3:2,5:4,6-tri-*O*-methylene-D-*glycero*-D-*manno*-heptitol (IV), the structure suggested originally by Mills on the basis of conformational analysis. The acetolysis of this compound would be expected to form 3-*O*-acetoxymethyl-1,7-di-*O*-acetyl-2,5:4,6-di-*O*-methylene-D-*glycero*-D-*manno*-heptitol (V) whose subsequent deacetylation would yield 2,5:4,6-di-*O*-methylene-D-*glycero*-D-*manno*-heptitol (VI). The last-named compound should be resistant to oxidation with periodate and its tri-*O*-tosyl derivative should exchange two tosyloxy groups

(1) (a) R. M. Hann and C. S. Hudson, *J. Am. Chem. Soc.*, **66**, 1909 (1944); (b) see also A. T. Ness, R. M. Hann, and C. S. Hudson, *J. Am. Chem. Soc.*, **70**, 765 (1948) for an extension of these rules.

(2) S. A. Barker and E. J. Bourne, (a) *J. Chem. Soc.*, 905 (1952); (b) *Advances in Carbohydrate Chem.*, **7**, 137 (1952).

(3) For a still later, minor extension of these rules, see E. Zissis and N. K. Richtmyer, *J. Am. Chem. Soc.*, **76**, 5515 (1954).

(4) S. A. Barker, E. J. Bourne, and D. H. Whiffen, *J. Chem. Soc.*, 3865 (1952).

(5) J. A. Mills, (a) *Chemistry & Industry*, 633 (1954); (b) *Advances in Carbohydrate Chem.*, **10**, 1 (1955).

(6) Mills predicted (ref. 5a) that the 1,3:2,4-acetal would be formed in preference to the 2,4:3,5-structure. According to the empirical rules (ref. 2b, p. 182), the 1,3:4,5- and 1,2:3,5-acetals also would be possible. Mills' reasons for excluding these last two were based presumably on the principle that a fused bicyclic system is formed in preference to two isolated acetal rings.

(7) Ref. 3, footnote 1.

(8) J. A. Mills, personal communication to one of us, December 16, 1954.

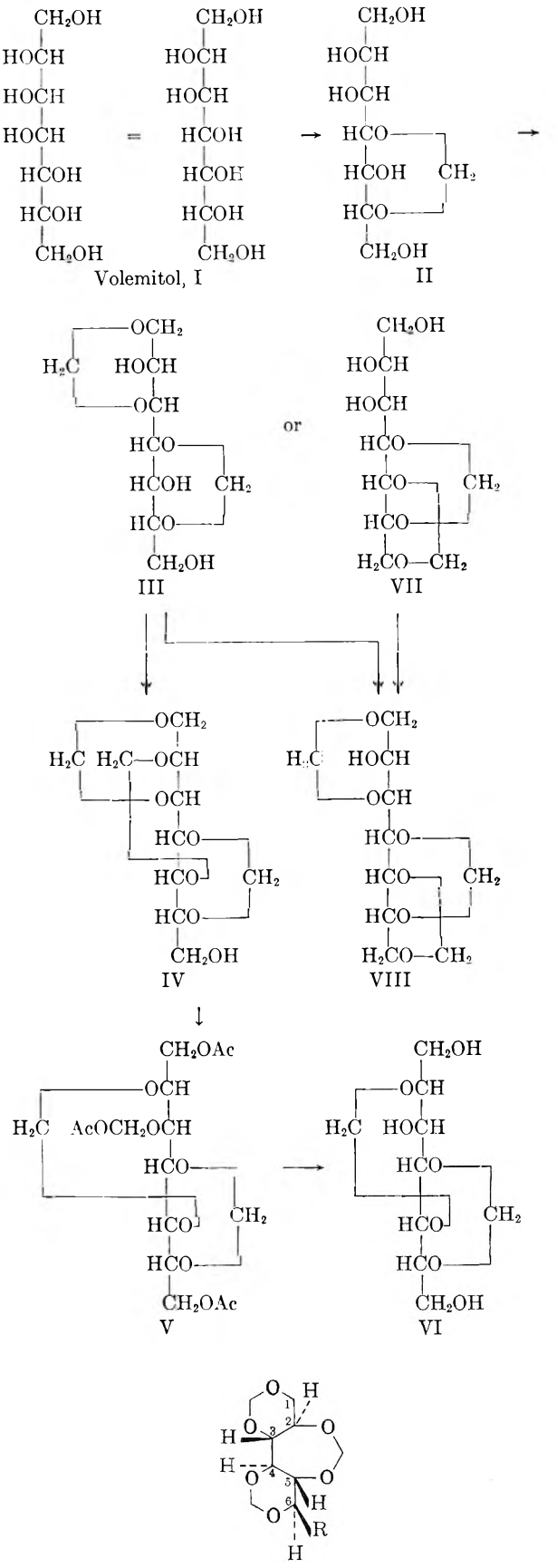
(9) In the notation of Barker and Bourne, the Greek letters signify the relative positions of the two hydroxyl groups engaged in the cyclization, and C and T indicate whether these groups are disposed *cis* or *trans* in the usual Fischer projection formula; C and T are required only when both hydroxyl groups are secondary.

(10) See especially ref. 4, page 3868, on the influence of preformed rings.

for iodine atoms when it is heated with sodium iodide. The experimental results are in agreement with these expectations and we conclude, therefore, that tri-*O*-methylenevolemitol is 1,3:2,5:4,6-tri-*O*-methylene-D-*glycero*-D-*manno*-heptitol (IV).[11]

We have thus demonstrated, through a combination of the best-established empirical rules and our own experiments, that the principal product of the methylenation of volemitol under our conditions must be the 1,3:2,5:4,6- rather than the 1,3:4,6:-5,7-tri-*O*-methylene-D-*glycero*-D-*manno*-heptitol. As Mills has pointed out, the favored structure (X), like that of the analogous tri-*O*-methylene-D-mannitol (IX), consists of two six-membered acetal rings fused to a seven-membered acetal ring, with the three acetals having a *trans-anti-trans* configuration. The free CH_2OH group in X is equatorial and should confer even greater stability to the structure. The unfavored arrangement, as depicted in XI, consists of two six-membered acetal rings fused with a *trans* junction and resembles *trans*-decalin. It is substituted at the original C4 by an isolated six-membered acetal ring and the two components are then mutually equatorial.

The final formula (XII) represents the 1,3:4,6-di-*O*-methylene acetal (with all ring-substituent groups equatorial) that may be an intermediate compound in the production of tri-*O*-methylenevolemitol just as 1,3:4,6-tri-*O*-methylene-D-mannitol appeared to be an intermediate in the preparation of the analogous tri-*O*-methylene-D-mannitol (IX). Although we succeeded in crystallizing only the tri-*O*-methylenevolemitol, we might expect to find this di-*O*-methylene derivative in the mother liquor[11a] or to obtain it by partial hydrolysis of the triacetal as Fletcher and Diehl[12] were able to do in the D-mannitol series.

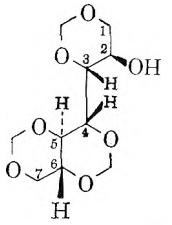


IX (R = H) = 1,3:2,5:4,6-Tri-*O*-methylene-D-mannitol
X (R = CH_2OH) = 1,3:2,5:4,6-Tri-*O*-methylene-D-*glycero*-D-*manno*-heptitol (IV)

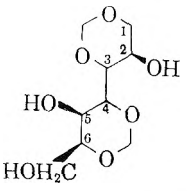
(11) We have considered also three other possibilities: (*a*) the formation from III of a 1,3:2,7:4,6-triacetal, but introduction of the 2,7-acetal ring would be highly improbable, and the compound, if formed, would give only a mono-*O*-methylene derivative on acetolysis; (*b*) the formation from VII of a 1,2:4,6:5,7-triacetal; and (*c*) of a 2,3:4,6:5,7-triacetal. However, the introduction of an α- or an αC-ring would seem to be extremely unlikely while it is still possible to establish an isolated β-acetal linkage between C1 and C3. Furthermore, the 1,2:4,6:5,7-tri-*O*-methylenevolemitol, if formed, would yield only a mono-*O*-methylene derivative on acetolysis.

(11a). *Note added August 2, 1957.* After submitting this paper for publication we succeeded in isolating from the mother liquor 1.2 g. (2%) of a crystalline di-*O*-methylenevolemitol. Because the compound is not oxidized by periodate it cannot be the 4,6:5,7-di-*O*-methylene-D-*glycero*-D-*manno*-heptitol (VII) but must be the expected intermediate 1,3:4,6-di-*O*-methylene-D-*glycero*-D-*manno*-heptitol (III = XII). Its crystalline triacetate is different from that of the isomeric 2,5:4,6-di-*O*-methylene-D-*glycero*-D-*manno*-heptitol (VI). On further methylenation it was converted to the tri-*O*-methylenevolemitol (IV).

(12) H. G. Fletcher, Jr., and H. W. Diehl, *J. Am. Chem. Soc.*, **74**, 3797 (1952).



XI = 1,3:4,6:5,7-Tri-*O*-methylene-D-*glycero*-D-*manno*-heptitol (VIII)



XII = 1,3:4,6-Di-*O*-methylene-D-*glycero*-D-*manno*-heptitol (III)

EXPERIMENTAL

1,3:2,5:4,6-Tri-O-methylene-D-glycero-D-manno-*heptitol* (IV) (=*Tri*-O-*methylenevolemitol*). A solution of 48 g. of volemitol (I)[13] in a mixture of 100 ml. of concentrated hydrochloric acid and 200 ml. of 37% aqueous formaldehyde was heated overnight in an oven at 70°, left at room temperature for a day, and then allowed to evaporate in a crystallizing dish in an evacuated desiccator over concentrated sulfuric acid and solid potassium hydroxide. After 3 weeks the waxy residue was extracted three times by boiling with 75 ml. of water. The cooled extracts deposited 15.3 g., and the concentrated mother liquors an additional 8.7 g., making a total of 24.0 g. (42.7%) of tri-*O*-methylenevolemitol (IV). In spite of repeated recrystallizations from water, the analytical data were not satisfactory until the compound had been converted to its acetate and the latter deacetylated catalytically with sodium methoxide in methanol. Two recrystallizations from water then afforded a pure product as clusters of needles, with m.p. 181–182° and $[\alpha]_D^{20}$ −60.8° in water (*c*, 0.7).

Anal. Calcd. for $C_{10}H_{16}O_7$: C, 48.38; H, 6.50. Found: C, 48.23; H, 6.44.

7-O-*Acetyl-1,3:2,5:4,6-tri*-O-*methylene*-D-glycero-D-manno-*heptitol*. When a mixture of 8.5 g. of the tri-*O*-methylenevolemitol (IV), 1.7 g. of fused sodium acetate, and 51 ml. of acetic anhydride was heated for 2 hr. on the steam bath, the acetal dissolved and then the acetate began to crystallize. After dilution of the solution with ice water, the product was isolated by filtration; wt. 7.5 g. (75.5%). The acetyl derivative was recrystallized from 500 parts of acetone, then from 100 parts of ethanol, and finally from acetone again; the needles melted at 200–201° and showed $[\alpha]_D^{20}$ −60.6° in chloroform (*c*, 1).

Anal. Calcd. for $C_{12}H_{18}O_8$: C, 49.65; H, 6.25; CH_3CO, 14.83. Found: C, 49.63; H, 6.43; CH_3CO, 14.75.

1,3:2,5:4,6-Tri-O-*methylene*-7-O-p-*tolylsulfonyl*-D-glycero-D-manno-*heptitol*. A solution of 0.38 g. of the tri-*O*-methylenevolemitol (IV) and 0.6 g. of *p*-toluenesulfonyl chloride in 5 ml. of pyridine was left at room temperature for 10 days and then poured onto cracked ice. The crystalline product (0.27 g.; 44%) was recovered by filtration. The tosylate was recrystallized once from hot 95% ethanol and then twice from chloroform-pentane. The clusters of prisms melted at 139–140° and showed $[\alpha]_D^{20}$ −40.1° in chloroform (*c*, 0.6).

Anal. Calcd. for $C_{17}H_{22}O_9S$: C, 50.74; H, 5.51; S, 7.97. Found: C, 50.71; H, 5.53; S, 7.70.

3-O-*Acetoxymethyl-1,7-di*-O-*acetyl-2,5:4,6-di*-O-*methylene*-D-glycero-D-manno-*heptitol* (V). To a mixture of 35 ml. of acetic anhydride, 15 ml. of glacial acetic acid, and 0.5 ml of concentrated sulfuric acid, chilled in ice, was added 5 g of the tri-*O*-methylenevolemitol (IV). After 45 min. in the ice bath the solution was poured onto cracked ice. The product began to crystallize immediately. It was left overnight in the refrigerator and then filtered and washed with cold water; the dry product weighed 6.4 g. (81%). It was recrystallized three times from 8 parts of 95% ethanol, forming silky needles melting at 124–126° and showing $[\alpha]_D^{20}$ +19.2° in chloroform (*c*, 0.8).

Anal. Calcd. for $C_{16}H_{24}O_{11}$: C, 48.98; H, 6.16; CH_3CO, 32.91. Found: C, 48.87; H, 6.18; CH_3CO, 32.81.

1,3,7-Tri-O-*acetyl-2,5:4,6-di*-O-*methylene*-D-glycero-D-manno-*heptitol*. Deacetylation of 4.5 g. of the acetoxymethyldiacetyl derivative (V) with sodium methoxide in methanol, followed by deionization and concentration of the solution, left 2.9 g. of amorphous, powdery 2,5:4,6-di-*O*-methylene-D-*glycero*-D-*manno*-heptitol (VI); it was not oxidizable by periodate. Acetylation of 0.75 g. of this material with acetic anhydride and fused sodium acetate yielded 0.8 g. (70%) of the triacetate. It was recrystallized from 5 parts of 95% ethanol and then from chloroform-pentane, separating as needles with m.p. 130–131° and $[\alpha]_D^{20}$ −38.8° in chloroform (*c*, 1).

Anal. Calcd. for $C_{15}H_{22}O_{10}$: C, 49.72; H, 6.12; CH_3CO, 35.64. Found: C, 49.72; H, 6.11; CH_3CO, 35.53.

1,3,7-Tri-C-*benzoyl-2,5:4,6-di*-O-*methylene*-D-glycero-D-manno-*heptitol*. The benzoylation of 1 g. of the amorphous di-*O*-methylene derivative (VI) with excess benzoyl chloride in pyridine for 15 min. on the steam bath produced a gum that was apparently not completely benzoylated. However, by repeated recrystallizations, twice from 95% ethanol, twice from chloroform-pentane, and then four times from 95% ethanol, we were able to isolate 0.1 g. of prismatic needles of the pure tribenzoate. It melted at 147–148° and showed $[\alpha]_D^{20}$ +15.3° in chloroform (*c*, 1.1).

Anal. Calcd. for $C_{30}H_{28}O_{10}$: C, 65.69; H, 5.15. Found: C, 65.73; H, 5.05.

2,5:4,6-Di-C-*methylene-1,3,7-tri*-O-p-*tolylsulfonyl*-D-glycero-D-manno-*heptitol*. The reaction between 1.5 g. of amorphous di-*O*-methylenevolemitol (VI) and 13 g. of *p*-toluenesulfonyl chloride (10.7 molar equivalents) in 25 ml. of dry pyridine for 4 days at room temperature yielded 3.3 g. of a sirup whose sulfur content (12.03%) indicated incomplete tosylation. However, when a solution of this sirup in chloroform-pentane was kept at −5° it deposited slowly a mixture of sirup and crystals. The solid material was separated successfully by 3 recrystallizations from chloroform-pentane and 2 from ethanol, and 0.44 g. of the pure tri-*O*-tosyl derivative was finally obtained. The needles melted at 136–138° and showed $[\alpha]_D^{20}$ −18.5° in chloroform (*c*, 1.5).

Anal. Calcd. for $C_{30}H_{34}O_{13}S_3$: C, 51.56; H, 4.90; S, 13.76. Found: C, 51.64; H, 4.95; S, 13.64.

1,7-Dideoxy-1,7-diiodo-2,5:4,6-di-O-*methylene-3*-O-p-*tolylsulfonyl*-D-glycero-D-manno-*heptitol*. A mixture of 369 mg. of the tri-*O*-tosyl derivative just described and 700 mg. of sodium iodide in 35 ml. of 2-butanone was refluxed for 7 hr. The precipitated sodium *p*-toluenesulfonate weighed 207 mg. (calcd. for 2 replaceable tosyloxy groups: 205 mg.) and not more than a trace of additional precipitate was obtained on heating for another 5 hr. Water was added to the filtrate, the 2-butanone was allowed to evaporate overnight, and the oily product was extracted with chloroform. The extract, washed with water, dried with sodium sulfate, and concentrated *in vacuo*, left a sirup that crystallized spontaneously when warmed with aqueous ethanol. The product weighed 262 mg. (81%); upon recrystallization from ethanol and then from chloroform-pentane the diiodo compound separated as needles that melted at 141–142° and showed $[\alpha]_D^{20}$ +6.6° in chloroform (*c*, 1.1).

Anal. Calcd. for $C_{16}H_{20}I_2O_7S$: C, 31.49; H, 3.30; I, 41.59; S, 5.25. Found: C, 31.65; H, 3.48; I, 41.74; S, 5.37.

(13) L. C. Stewart, N. K. Richtmyer, and C. S. Hudson, *J. Am. Chem. Soc.*, **74**, 2206 (1952).

Added August 2, 1957. 1,3:4,6-Di-O-methylene-D-glycero-D-manno-heptitol (III, XII). By fractional crystallization from aqueous ethanol of the material remaining after separation of the 24 g. of tri-*O*-methylenevolemitol (IV), we have isolated 1.2 g. (2%) of a new di-*O*-methylenevolemitol. This compound, like the tri-*O*-methylene derivative, was purified through its acetate; the deacetylated product was then recrystallized twice from methanol, once from 95% ethanol (as prismatic needles), and finally from aqueous acetone (as long rectangular plates). It melted at 203–212° and showed $[\alpha]_D^{20}$ −45.2° in water (*c*, 1.1). It was not oxidized by periodate.

Anal. Calcd. for $C_9H_{16}O_7$: C, 45.76; H, 6.83. Found: C, 45.87, 45.87; H, 6.87, 6.77.

Proof that this compound was a derivative of volemitol was established by heating 0.50 g. of it with concentrated hydrochloric acid and 37% aqueous formaldehyde for 5 hr. on the steam bath. From this reaction mixture we obtained 0.06 g. (11%) of once-recrystallized tri-*O*-methylenevolemitol (IV), identified by melting point and mixed melting point.

2,5,7-Tri-O-acetyl-1,3:4,6-di-O-methylene-D-glycero-D-manno-heptitol. The 1.2 g. of crude di-*O*-methylenevolemitol (III) was acetylated with acetic anhydride and fused sodium acetate to yield 1.6 g. (87%) of the triacetate, which was recrystallized from 95% ethanol (as plates) and then from chloroform-pentane (as prismatic needles). It melted at 171–173° and showed $[\alpha]_D^{25}$ −9.6° in chloroform (*c*, 1.0).

Anal. Calcd. for $C_{15}H_{22}O_{10}$: C, 49.72; H, 6.12; CH_2CO, 35.6. Found: C, 50.06, 50.05; H, 6.15, 6.13; CH_3CO, 35.9.

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