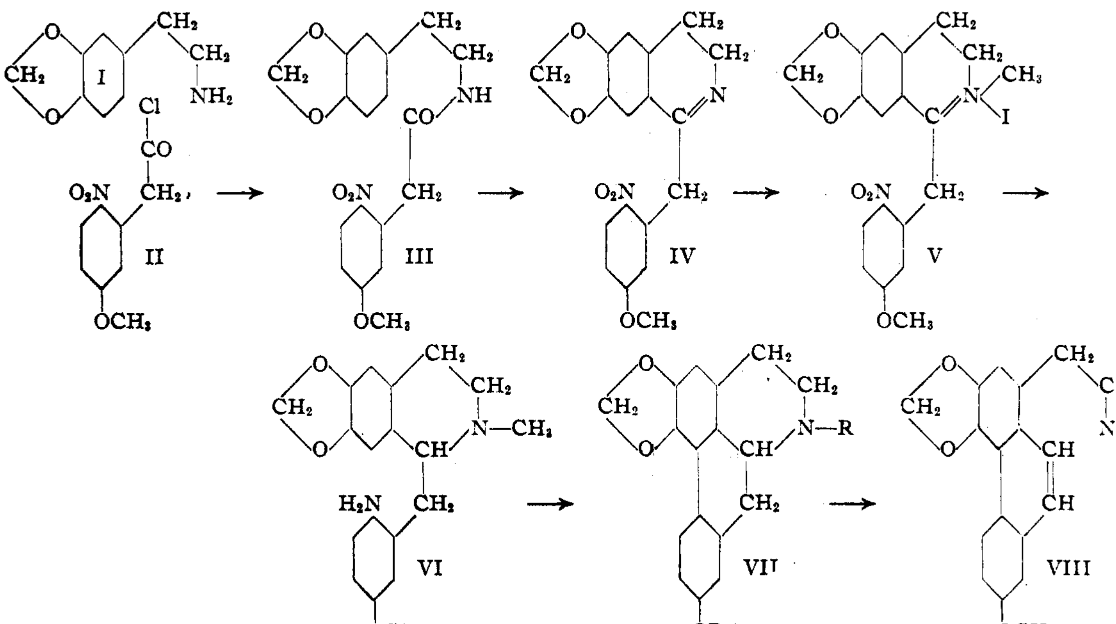
[CONTRIBUTION FROM THE DIVISION OF CHEMISTRY OF THE NATIONAL RESEARCH COUNCIL]

# The Synthesis of O,N-Dimethylanolobine[1]

BY LÉO MARION

The alkaloid anolobine has been isolated from *Asimina triloba* Dunal by Manske,[2] who assigned to it the structure of a phenolic aporphine base VII (R = H). His demonstration, however, is based on an assumption as well as on experimental evidence and it was considered desirable to attempt the synthesis of the base.

Since anolobine is a phenolic secondary base, it was more expedient to try to synthesize O,N-dimethylanolobine and to prepare the corresponding methine base. The identity of this compound with the methine obtained by Manske[2] from anolobine O-methyl ether should afford conclusive proof of the structure of the alkaloid.



The synthesis was achieved from 3,4-methylenedioxyphenylethylamine and 2-nitro-5-methoxyphenylacetyl chloride as starting materials.

The amine I and the acid chloride II were combined to form 6′-nitro-3′-methoxyphenylaceto-$\beta$-3,4-methylenedioxyphenylethyl amide III which, by a modified Bischler–Napieralsky reaction was converted to 6′-nitro-3′-methoxy-6,7-methylenedioxy-1-benzyl-3,4-dihydroisoquinoline IV. The methiodide V of this base was reduced with zinc and hydrochloric acid to 6′-amino-3′-methoxy-6,7-methylenedioxy-1-benzyl-2-methyl-1,2,3,4-tetrahydroisoquinoline VI isolated as the dihydrochloride. Application of the Pschorr ring closure reaction converted the dihydrochloride into *dl*-O,N-dimethylanolobine VII (R = $CH_3$) which could not be induced to crystallize and was characterized by its hydrochloride, picrate and methiodide. The methiodide was decomposed to the methine base VIII which by analysis and mixed melting point was found to be identical with the methine obtained from anolobine. A small quantity of the latter was made available by Dr. R. H. F. Manske to whom the author acknowledges his indebtedness. The picrate of the synthetic methine base was also prepared.

This synthesis, therefore, affords conclusive proof of the correctness of the structure assigned by Manske to anolobine which is represented by VII (R = H).

## Experimental

In order to carry out the synthesis it was necessary first to prepare homopiperonylamine and the 2-nitro-5-methoxy-phenylacetic acid required as starting materials.

### A. Preparation of the Starting Materials

**3,4-Methylenedioxyphenylethylamine.**—Piperonal was condensed with malonic acid as described by Haworth, Perkin and Rankin[3] and the 3,4-methylenedioxy-cinnamic acid produced (75% yield, m. p. 243°[4]) was reduced electrolytically to the corresponding dihydrocinnamic acid (65.2% yield, m. p. 87°). 3,4-Methylenedioxyphenylpropionamide was prepared according to Decker[5] by adding the acid chloride to concentrated ammonium hydroxide (90% yield, m. p. 123°). Incidentally, it may be mentioned that the preparation of the amide proceeds smoothly when phosphorus trichloride is used to make the acid

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(1) Published as N. R. C. No. 1200.

(2) R. H. F. Manske, *Can. J. Research*, **B16**, 76 (1938).

(3) R. D. Haworth, W. H. Perkin and J. Rankin, *J. Chem. Soc.*, **125**, 1693 (1924).

(4) All melting points are corrected.

(5) H. Decker, *Ann.*, **395**, 289 (1913).

chloride. An attempt to use thionyl chloride resulted in the substitution of a second atom of chlorine in the molecule. When the product of the action of thionyl chloride on the acid was poured into 25% ammonium hydroxide there was formed a substance which, after three recrystallizations from chloroform, consisted of colorless crystals melting at 146°. Found: C, 53.63; H, 4.35; N, 6.14. Calcd. for $C_{10}H_{10}O_3NCl$: C, 52.75; H, 4.39; N, 6.14.

The amide was converted into 3,4-methylenedioxyphenylethylamine by the Hofmann reaction as described by Decker.[5] The redistilled amine (b. p. 100–110° (< 1 mm.)) was obtained in 51.3% yield calculated on the weight of the amide. A small quantity of the amine was converted to the picrate in methanol solution. When recrystallized from methanol, it separated as yellow prisms melting at 180.5°. (Rosenmund[6] gives m. p. 174° uncor.). Calcd. for $C_{15}H_{14}O_9N_4$: C, 45.68; H, 3.55. Found: C, 45.51, 45.81; H, 3.41, 3.70.

**2-Nitro-5-methoxyphenylacetic Acid.**—*m*-Cresol was nitrated, the product steam-distilled to remove the 4-nitro-3-hydroxytoluene, the undistilled residue methylated with dimethyl sulfate and sodium hydroxide and again steam-distilled. The 2-nitro-5-methoxytoluene thus produced was distilled twice *in vacuo* and crystallized from petroleum ether. It separated as pale yellow needles melting at 54°; yield, 18%.

2-Nitro-5-methoxytoluene was converted to 2-nitro-5-methoxyphenylpyruvic acid by treatment with potassium ethylate and ethyl oxalate as described by Burton and Stoves[7] (yield, 78%). A small quantity of the acid was recrystallized from benzene–methanol, from which it separated as yellow needles melting at 137°.

The substituted pyruvic acid (26 g.) was dissolved in 2 *N* sodium hydroxide (500 cc.) and 30% hydrogen peroxide added dropwise with stirring until a test no longer gave a red coloration with sodium hydroxide. The solution was then kept in a water-bath at 50° for thirty minutes, cooled and saturated with sulfur dioxide. After standing overnight at room temperature, the crystalline 2-nitro-5-methoxyphenylacetic acid which had separated was filtered off, washed with water and air-dried; wt. 17 g. After two recrystallizations from methanol–benzene, the acid melted at 178.5°. Calcd. for $C_9H_9O_5N$: $OCH_3$, 14.69. Found: $OCH_3$, 15.16.

## B. Synthesis of O,N-Dimethylanolobine

**6′-Nitro-3′-methoxyphenylaceto-β-3,4-methylenedioxyphenylethylamide (III).**—The procedure followed was that of Douglas and Gulland.[8] When a suspension of 2-nitro-5-methoxyphenylacetic acid (17.1 g.) and phosphorus pentachloride (37.5 g.) in chloroform (105 cc.) was agitated for *ca.* thirty minutes, the acid passed into solution in the form of the acid chloride. This solution was added dropwise in the course of thirty minutes to a vigorously stirred and well-cooled mixture of 3,4-methylenedioxyphenylethylamine (16.5 g.), chloroform (90 cc.), 2 *N* sodium hydroxide (480 cc.) and water (750 cc.). After the addition was complete, the stirring was continued for twenty minutes and the contents of the flask poured onto a Büchner funnel to remove the amide which had crystallized. The amide was washed with water, chloroform and dried in air; wt. 17.2 g. The combined filtrate and washings was placed in a separatory funnel, the water layer discarded and the chloroform solution washed with dilute acid, with aqueous sodium carbonate and with water. This chloroform solution yielded a further 3 g. of amide. The combined product was recrystallized from chloroform–methanol from which it separated as aggregates of colorless needles melting at 188°. Calcd. for $C_{18}H_{18}O_6N_2$: C, 60.34; H, 5.03; N, 7.82. Found: C, 60.45, 60.27; H, 5.04, 5.12; N, 7.68, 7.72.

**6′-Nitro-3′-methoxy-6,7-methylenedioxy-1-benzyl-3,4-dihydroisoquinoline (IV).**—The isoquinoline ring closure was carried out by the Bischler–Napieralsky reaction as modified by Gulland and Haworth.[9] The amide III (2 g.) was added to a well-cooled suspension of phosphorus pentachloride (2 g.) in chloroform (12 cc.) and the mixture shaken for *ca.* fifteen minutes. After the amide had all dissolved, the flask was closed with a stopper carrying a calcium chloride tube and allowed to stand at room temperature for one week. Ice was then added and the mixture evaporated to dryness under reduced pressure at 40°. The residual gum was repeatedly extracted with small portions of hot dilute (1:1) hydrochloric acid and the combined extract filtered and poured into a strong solution of potassium hydroxide. The precipitated base was collected in chloroform, the chloroformic solution washed with water and distilled on the steam-bath. The crystalline residue was recrystallized from boiling methanol from which the base separated as small colorless prisms melting at 168° (wt. 1.2 g.). Calcd. for $C_{18}H_{16}O_5N_2$: C, 63.53; H, 4.70. Found: C, 63.24, 63.52; H, 4.64, 4.68. A total of 36 g. of amide was thus converted to the base in 18 runs.

**6′-Nitro-3′-methoxy-6,7-methylenedioxy-1-benzyl-3,4-dihydroisoquinoline Methiodide (V).**—The substituted dihydroisoquinoline IV (2.3 g.) was refluxed with methyl iodide (15 cc.) for six hours. The crystalline methiodide began to separate after a few minutes. After cooling, it was filtered and washed with ether; wt. 3.1 g. When recrystallized from boiling methanol, it was obtained as clusters of small prisms melting at 205°. Calcd. for $C_{19}H_{19}O_5N_2I$: C, 47.30; H, 3.94; N, 5.81. Found: C, 47.29; H, 4.06; N, 5.64.

**6′-Amino-3′-methoxy-6,7-methylenedioxy-1-benzyl-2-methyl-1,2,3,4-tetrahydroisoquinoline (VI).**—The methiodide V (3 g.) was dissolved in water (30 cc.) and concentrated hydrochloric acid (60 cc.) with the aid of heat. In the course of thirty minutes, zinc dust (9 g.) was added to the hot solution with vigorous stirring. During the reduction, the color gradually changed from a yellowish brown to a weak olive green and the hydrochloride crystallized out. The product from several runs was basified with strong ammonia and the base extracted with ether (3 portions). The combined extract was dried over potassium hydroxide pellets and distilled on the steam-bath. This yielded an oily base which was dissolved in a mixture of ether and methanol and the solution saturated with dry hydrogen chloride. After cooling and standing, the base dihydrochloride separated as small stout colorless prisms melting at 268°; yield, 65–74%. Calcd. for $C_{19}H_{24}O_3N_2Cl_2$: C, 57.14; H, 6.02; Cl, 17.79. Found: C, 56.36, 56.30; H, 6.04, 5.80; Cl, 18.28, 20.61.

***dl*-O,N-Dimethylanolobine (VII, R = $CH_3$).**—The dihydrochloride of VI (2 g.) was dissolved in 2 *N* sulfuric acid (20 cc.) and methanol (20 cc.), the solution cooled and diazotized with a solution of sodium nitrite (0.4 g.) in water (4 cc.). The diazotized solution was allowed to stand in the cold for fifteen minutes and kept on the steam-bath for thirty minutes, during which a strong evolution of nitrogen took place. Concentrated hydrochloric acid (2.8 cc.) and zinc dust (1.08 g.) were then added and the mixture kept on the steam-bath a further twenty minutes to complete the reaction and remove most of the methanol. The hot solution was decanted from the unused zinc which was washed by decantation with a little hot water. On cooling, the combined decantate deposited a crystalline hydrochloride which was filtered and recrystallized from boiling water containing a little hydrochloric acid. The base hydrochloride consisted of short colorless needles melting at 266° (dec.); wt. 0.33 g. Calcd. for $C_{19}H_{20}O_3NCl$: Cl, 10.28. Found: Cl, 10.07, 10.17. Some of the oily free base obtained from the hydrochloride was converted to the picrate which separated from acetone–methanol solution as small yellow prisms melting at 226°. Calcd. for $C_{25}H_{22}O_{10}N_4$: N, 10.41. Found: N, 10.29.

**O,N-Dimethylanolobine Methiodide.**—When the oily base (0.68 g.) obtained from O,N-dimethylanolobine hydrochloride was dissolved in methanol containing a little ether and an excess of methyl iodide added to the solution, a sparingly soluble methiodide soon crystallized out; wt. 0.93 g. Redissolved in boiling methanol, it separated on cooling as colorless prisms melting at 241°.

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(6) K. W. Rosenmund, *Ber.*, **43**, 3414 (1910).

(7) H. Burton and J. L. Stoves, *J. Chem. Soc.*, 402 (1937).

(8) R. L. Douglas and J. M. Gulland, *ibid.*, 2893 (1931).

(9) J. M. Gulland and R. D. Haworth, *ibid.*, 581 (1928).

Calcd. for $C_{20}H_{22}O_3NI$: C, 53.21; H, 4.88. Found: C, 53.72; H, 4.90.

**O,N-Dimethylanolobinemethine (VIII).**—O,N-Dimethylanolobine methiodide was decomposed by heating for twenty-four hours on the steam-bath in strongly alkaline solution. The liberated methine base was extracted from the cooled solution with ether. The methine base, which crystallized when its ether solution was evaporated, was recrystallized from dry ether from which it separated as colorless needles melting at 100°. Admixture with the methine obtained from naturally occurring anolobine (m. p. 99°) failed to depress the melting point. Calcd. for $C_{20}H_{21}O_3N$: C, 74.30; H, 6.50; N, 4.33. Found: C, 74.47; H, 6.35; N, 4.29. A small quantity of the methine base was converted to the picrate which was found to be only very sparingly soluble in boiling methanol or acetone. When recrystallized from a large volume of boiling acetone it separated in two forms: long yellow needles and stout orange needles. After standing several hours in contact with the mother liquor the yellow needles had disappeared and the orange needles alone were present; melting point, 258°. Calcd. for $C_{26}H_{24}O_{10}N_4$: C, 56.53; H, 4.35. Found: C, 56.77, 56.67; H, 4.37, 4.38.

## Summary

1. The structure of anolobine has been confirmed by synthesis of the methine base of O-methylanolobine.

2. The synthesis has been effected from methylenedioxyphenylethylamine and 2-nitro-5-methoxyphenylacetyl chloride which was condensed to give an amide and this was converted to the corresponding dihydroisoquinoline by an improved Bischler–Napieralsky reaction. The methiodide of the dihydroisoquinoline was reduced and the product transformed by the Pschorr reaction to *dl*-O,N-dimethylanolobine. The methiodide of the synthetic base was decomposed to the corresponding methine base, identical with that obtained from naturally occurring anolobine.

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[Contribution from the Research and Biological Laboratories of Parke, Davis and Company]

# Arylaminoheterocyclic Compounds. I. Synthetic Method

By C. Kenneth Banks

The literature of arylaminoheterocycles is exceedingly scant, considering the innumerable variations possible. Much of the work that has been done is in the patent literature and identification of the compounds, as pure substances, is frequently lacking. The methods used for such preparations indicate that no generally applicable synthetic method exists and frequently the procedure given will work only for the simplest of arylamines. The general approach has been to regard the synthesis as an Ullmann[1] reaction, although a few variations have been tried. In general, a haloheterocycle, in which the halogen occupies a so-called "active" position, reacts with an excess of the aromatic amine under pressure at high temperatures, with or without copper as a catalyst. With the seemingly more "active" halogen compounds, high boiling organic solvents and potassium carbonate have been used[2,3,4,5] and where extreme "activity" was encountered (cyanuric chloride), conditions characteristic of the Schotten–Baumann reaction have been employed.[6,7]

In every case it is apparent that two assumptions have been made. First, the reaction apparently has been regarded as being reversible since the principles of inorganic chemistry have been applied to prevent reversal. Second, the use of copper as a catalyst is indicative of an association with halobenzenoid compounds. Although it has long been recognized that the positions in heterocyclic nuclei, particularly in nitrogen-containing rings, vary greatly in conferring activity upon substituents, it has been common to classify the positions as "aromatic" or "aliphatic" in character. The possible variation of the electronic configuration due to external agents apparently has not been considered.

Recently we had the problem of condensing arsanilic acid with a halotriazine. Because of the physical nature of the reactants, high pressures and temperatures had to be avoided. In this reaction, it was noted that aqueous condensation was effective and that alkali had a definite inhibitory effect, so much so that the haloheterocycle was frequently hydrolyzed before any reaction was noted. Further experimentation indicated that the addition of acid did not inhibit the reaction but actually speeded it to completion. It was possible to follow the course of the reaction by measurement of the diazotizable amine present and it was found that the reaction could be considered irreversible for all practical purposes, $K^c$ for the reaction being greater than $10^{12}$. In addition to the increased rate of reaction, the rate of hydrolysis of the haloheterocycle was decreased by acid.

With this information it was evident that the nature of the reaction could not be easily explained on the basis of existing information. After some preliminary syntheses, the reaction rates of several amines and haloheterocycles were studied, using varying concentrations of acid and alkali. The haloheterocycles chosen for the study were

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(1) Ullmann, *Ann.*, **355**, 312 (1907).

(2) Bremer, *ibid.*, **514**, 279 (1934).

(3) Mangini and Frenguelli, *Gazz. chim. ital.*, **69**, 86, 97 (1939).

(4) Phillips, *J. Chem. Soc.*, 9 (1941).

(5) Hatlelid, Ph.D. Thesis, University of Nebraska, 1942.

(6) British Patent 309,102 (1929).

(7) U. S. Patent 2,295,574 (1942).