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

THE SYNTHESIS OF CUSCOHYGRINE

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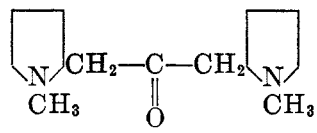
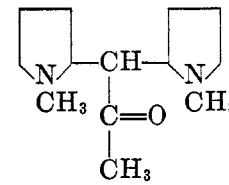
Two structures, I and II, have been proposed for cuscohygrine, one of the minor alkaloids of South American coca leaves. Formula I, advanced by Liebermann in a note to Willstätter (1), appears to best explain the isolation of hendecane and 6-hendecanol from Hofmann degradation of dihydrocuscohygrine; however, a rearrangement of the dihydro compound corresponding to structure II during the degradation has also been suggested to explain the appearance of these products (2).



I



II

The objective of the present investigation was to establish the structure of cuscohygrine by an unequivocal synthesis of 1,3-bis(1′-methyl-2′-pyrrolidyl)-2-propanone (I). At the same time, it was hoped to obtain information on the relative configuration of the two similar asymmetric carbon atoms in this structure. Natural cuscohygrine is optically inactive, could not be resolved into active components (3), and on reduction gave two alcohols (2). These facts are consistent with a *meso* configuration for the natural material but this assumption does not explain the existence of two isomeric hydrazones (4). The suggestion of Sohl and Shriner (5), that the natural material is a mixture of *meso* and racemic forms, would account for the two hydrazones but should lead to three rather than two alcohols.

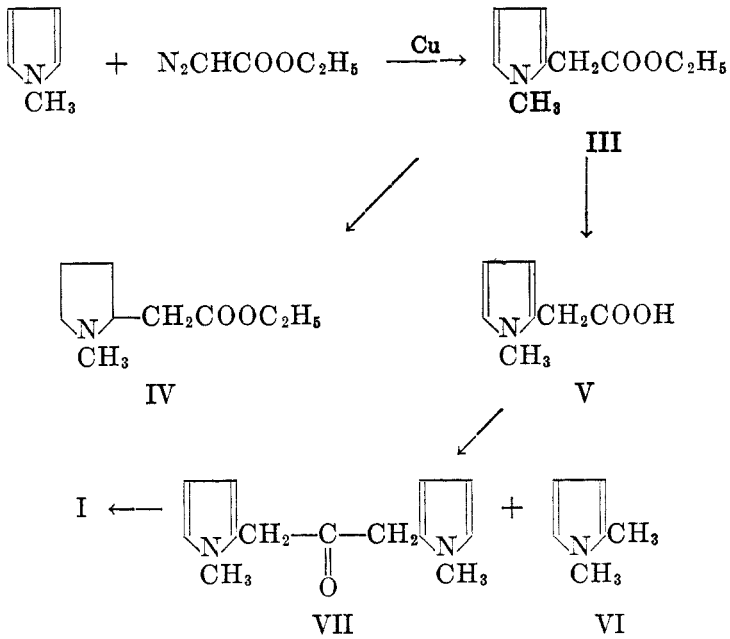
Two syntheses of cuscohygrine have been reported in the recent literature.[1] The first, by Lazurevskii (6), was purportedly accomplished by pyrolysis of the barium salt of 1-methyl-2-pyrrolidineacetic acid; however, no experimental details were given. A successful synthesis by this method seemed surprising since the compound being pyrolyzed was a substituted β-amino acid and might be expected to suffer cleavage of the amino group under the drastic conditions required. In view of this, an attempt was made to repeat the synthesis. Ethyl 1-methyl-2-pyrrolidineacetate (IV), prepared in good yield as outlined below by several modifications of the procedure of Sohl and Shriner (5), was converted to

[1] After this paper had been accepted for publication, a note appeared by Anet, Hughes, and Ritchie, *Nature*, **163**, 289 (1949), in which the synthesis of cuscohygrine was reported from acetone dicarboxylic acid and γ-methylaminobutyraldehyde. However, no experimental details were presented.

the barium salt and the latter dry-distilled. The pyrolysate was then fractionally distilled and four fractions were obtained, all of which appeared to be unsaturated, secondary amines. No evidence could be obtained for the presence of cuscohygrine in any of the various fractions.

The second reported synthesis, by Späth and Tuppy (7), became known to us only after our work had been practically completed. They describe a successful synthesis of cuscohygrine by substantially the same method used in the present work. However, there appear to be sufficient differences, especially in the characterization of the final product, to warrant reporting our results at this time. No mention is made by Späth and Tuppy of the prior claim to synthesis by Lazurevskii, undoubtedly because this information was unavailable to them.

In the present synthesis, 1,3-bis(1′-methyl-2′-pyrryl)-2-propanone (VII) was prepared by pyrolysis of the barium salt of 1-methyl-2-pyrroleacetic acid (V), and the resulting ketone was catalytically hydrogenated to give the final product. When purifying the crude acid (V), obtained by saponification of the ester (III), it was found that a surprisingly facile decarboxylation to 1,2-dimethylpyrrole (VI) took place merely on heating in cyclohexane. Substitution of methylene



chloride–pentane as the crystallization solvent resulted in excellent recoveries of pure acid (V) which was then converted to the barium salt and pyrolyzed under reduced pressure. The pyrolysate was easily separated into crystalline ketone (VII) (12% yield) and 1,2-dimethylpyrrole (49% yield). Späth and Tuppy (7) report a higher yield of crude ketone by pyrolysis of the lead salt on a much smaller (one one-hundredth) scale.

To effect the hydrogenation of the pyrrole rings in VII, platinum oxide in

glacial acetic acid was used. These are the conditions recently employed by Šorm (8) to prepare 1-methyl-2-acetonylpyrrolidine from the corresponding pyrrole compound without reducing the carbonyl group. When applied to VII, hydrogenation ceased after eight hours with the absorption of the theoretical four moles of hydrogen. The crude hydrogenation product was then separated by fractional distillation into four distinct fractions. Späth and Tuppy (7), using a palladium catalyst for the hydrogenation and working on an extremely small scale, observed only two fractions at this point.

Fraction B, which appeared to be most similar to natural cuscohygrine on the basis of boiling point and refractive index, was further examined by salt formation. With alcoholic picric acid, a picrate was obtained which, after three crystallizations from ethanol and one from water, melted at 216–217° and gave no depression on admixture with an authentic sample of cuscohygrine dipicrate[2] melting at the same temperature. The nitrate was prepared using alcoholic nitric acid, and repeated crystallization from absolute ethanol gave material whose melting point (203–204°) was not depressed by addition of cuscohygrine dinitrate (m.p. 204–205°).

In order to secure a pure sample of synthetic cuscohygrine as the free base, the remainder of fraction B was converted to the nitrate and subjected to a systematic fractional crystallization. The free base liberated from the pure nitrate so obtained distilled (bath temperature 110° and 0.1 mm. pressure) as a very pale yellow oil with n_D^{25} 1.4833. This refractive index is in fairly close agreement with that of natural cuscohygrine, variously reported as n_D^{17} 1.4864 (6), $n_D^{18.4}$ 1.4845 (2), and n_D^{20} 1.4832 (5).

The evidence presented above, we believe, demonstrates beyond doubt that a synthetic sample of cuscohygrine has been prepared. Also, the method of synthesis lends strong support to the formulation of its structure as I. However, the appearance of several other products in the final step prevents calling this synthesis an absolute proof of structure until the structures of these accompanying products have been established and the reaction shown to take a normal course. The question of the relative configuration of the two asymmetric carbon atoms also remains unsettled.

EXPERIMENTAL

All melting points are corrected, and all above 200° were taken in evacuated tubes. Microanalyses were performed by C. W. Koch and V. H. Tashinian.

N-Methylpyrrole. N-Methylpyrrole was prepared by pyrolysis of methylammonium mucate using the same procedure as in the preparation of pyrrole (9). With one mole of mucic acid to 2.5 moles of methylamine (as an approximately 10 *N* aqueous solution), 38–39% yields of N-methylpyrrole were obtained; b.p. 112–114°.

Ethyl 1-methyl-2-pyrroleacetate (III). The coupling between N-methylpyrrole and ethyl diazoacetate (10) was carried out according to the method of Sohl and Shriner (5). By extending the addition time of the N-methylpyrrole to three hours and using thoroughly dried reagents, the yield of ethyl 1-methyl-2-pyrroleacetate, allowing for recovered material, was increased to 71%; b.p. 105–110° at 6 mm.

[2] We are indebted to Dr. R. L. Shriner who very kindly supplied us with a sample of natural cuscohygrine dinitrate from which all our derivatives for comparison were prepared.

Ethyl 1-methyl-2-pyrrolidineacetate (*IV*). A solution of 30 g. (0.18 mole) of ethyl 1-methyl-2-pyrroleacetate in 200 ml. of glacial acetic acid was hydrogenated at forty pounds pressure and room temperature using 3.0 g. of platinum oxide as catalyst. Hydrogenation ceased after the theoretical amount of hydrogen had been absorbed in three hours. The catalyst was filtered, the cooled filtrate was partially neutralized with 320 ml. of 12 *N* potassium hydroxide and the reaction mixture was then made basic to litmus with a saturated potassium carbonate solution. After extracting the solution with five 100-ml. portions of ether, the combined ether extracts were dried over potassium carbonate, filtered, and distilled to give 27 g., 88% yield, of ethyl 1-methyl-2-pyrrolidineacetate, b.p. 88–89° at 10 mm., n_D^{25} 1.4443 [reported (5) b.p. 88–89° at 10 mm., n_D^{20} 1.4465].

1-Methyl-2-pyrrolidineacetic acid. The ester (IV) was saponified by heating under reflux for three hours with a slight excess of barium hydroxide in three times its weight of water. Carbon dioxide was then bubbled in, the precipitated barium carbonate filtered, and the filtrate evaporated to dryness in vacuum. Crystallization of the hygroscopic residue from benzene gave 1-methyl-2-pyrrolidineacetic acid, m.p. 122–124° [reported (11) m.p. 124°].

The *picrate* of the *dimethylamide* was prepared as directed by Šorm (11), m.p. 144–145° (reported m.p. 147°).

Pyrolysis of the barium salt of 1-methyl-2-pyrrolidineacetic acid. An aqueous solution of the acid from 30 g. (0.175 mole) of ethyl 1-methyl-2-pyrrolidineacetate was treated with 390 ml. of 0.45 *N* barium hydroxide. The solution was evaporated and the thoroughly dried, finely ground residue was distilled at 260–300° (bath temperature) at 2–6 mm. to give 4 g. of distillate. Fractionation of this material resulted in four fractions, all of which gave positive tests for secondary amines (Hinsberg Test) and rapidly decolorized bromine in carbon tetrachloride and aqueous permanganate. No crystalline picrate could be obtained from any of the fractions.

1-Methyl-2-pyrroleacetic acid (*V*). The ester was saponified by heating under reflux for four hours with potassium hydroxide in 50% aqueous ethanol. After distilling the ethanol, the solution was cooled, acidified with concentrated hydrochloric acid, and the precipitated acid and potassium chloride filtered. The solid was thoroughly dried in a vacuum desiccator and then digested with four 100-ml. portions of ether. Evaporation of the combined and dried ether extracts gave the crude acid as light tan crystals, m.p. 102–105°. Crystallization from cyclohexane gave pure material but in very low recovery due to extensive decarboxylation. Methylene chloride–pentane was a much more satisfactory solvent. The purified acid melted at 110–112° [reported (12) m.p. 112°, 113°].

1,2-Dimethylpyrrole (*VI*). Heating 3 g. of 1-methyl-2-pyrroleacetic acid to 170° gave 2 g., 97% yield, of 1,2-dimethylpyrrole as distillate. On redistillation it boiled at 139–140°, n_D^{25} 1.4913.

Anal. Calc'd for C_6H_9N: C, 75.74; H, 9.54.
Found: C, 75.92; H, 9.43.

The *azobenzenesulfonic acid derivative* was formed by adding an ether solution of 1,2-dimethylpyrrole to an equimolar quantity of diazobenzenesulfonic acid dissolved in water. Vigorous shaking caused an immediate precipitate of the *p*-(1,2-dimethyl-5-pyrrylazo)-benzenesulfonic acid which was purified by dissolving in 0.1 *N* sodium hydroxide and reprecipitating with 0.1 *N* hydrochloric acid. After thorough washing and drying it melted at 273–275° with dec.

Anal. Calc'd for $C_{12}H_{13}N_3O_3S$: C, 51.60; H, 4.69; S, 11.48.
Found: C, 50.97; H, 4.59; S, 11.36.

1,3-Bis(1'-methyl-2'-pyrryl)-2-propanone (*VII*). The barium salt of 1-methyl-2-pyrroleacetic acid was prepared by neutralizing an aqueous solution of the acid with an equivalent amount of 0.37 *N* barium hydroxide, taking the usual precautions for exclusion of carbon dioxide. Evaporation of the solution at reduced pressure and heating the residue at 100° in a vacuum oven gave an anhydrous barium salt which was then well ground and dry-distilled from a 250 ml. Claisen flask in 30–40 g. batches. Distillation was carried out at 3 mm. pressure over the course of an hour as the bath temperature was raised from 270°

to 350°. From 263 g. (0.64 mole) of barium salt, a total of 80.6 g. of distillate was collected in the water-cooled receiver and acetone-Dry Ice trap. This material was dissolved in ether, combined, dried over sodium sulfate, and distilled to give 59 g. (49% yield) of 1,2-dimethylpyrrole, b.p. 139–140°, and 16.7 g. (12% yield) of 1,3-bis(1′-methyl-2′-pyrryl)-2-propanone (VII), b.p. 153–163° at 1–2 mm. The ketone crystallized in the receiver, and for analysis a sample was recrystallized several times from ethanol, m.p. 67–68° [reported (7) m.p. 68–69°].

Anal. Calc'd for $C_{13}H_{16}N_2O$: C, 72.19; H, 7.46.
Found: C, 72.18; H, 7.24.

The *semicarbazone* was prepared by heating under reflux for one hour an ethanolic solution of the ketone, semicarbazide hydrochloride, and pyridine. Crystallization from aqueous ethanol gave material melting at 189–191° with dec. [reported (7) m.p. 194–197° with dec.].

Anal. Calc'd for $C_{14}H_{19}N_5O$: C, 61.51; H, 7.01.
Found: C, 61.71; H, 7.24.

Hydrogenation of 1,3-bis(1′-methyl-2′-pyrryl)-2-propanone (VII). A solution of 6.2 g. (0.029 mole) of ketone (VII) in 50 ml. of glacial acetic acid was hydrogenated at room temperature and thirty pounds pressure using 0.062 g. of platinum oxide catalyst. Hydrogen absorption ceased after four moles had been taken up in eight hours. The catalyst was filtered, the acetic acid evaporated at reduced pressure, and the cooled residue basified with saturated potassium carbonate solution. Extraction with six 50-ml. portions of ether, drying the combined ether extracts over sodium sulfate, and distillation gave 4.06 g. (63% yield) of a light yellow oil, b.p. 110–130° at 1 mm., n_D^{25} 1.5046. A total of 7.11 g. of crude distillate was then distilled through a one-meter Podbielniak column at 2.5 mm. pressure and the following fractions collected:

FRACTION	WT., G.	B.P. (2.5 MM.)	n_D^{25}
A	0.52	106–107°	1.4856
B	1.68	126–127°	1.4878
C	1.63	132–134°	1.4990
D	2.75	144–145°	1.5311

On the basis of physical constants and a preliminary examination of picrate formation, fraction B appeared to be the most similar to natural cuscohygrine and was investigated further.

Examination of fraction B. Picrate formation. A 0.2-g. sample of Fraction B, dissolved in 25 ml. of ethanol, was treated with 10 ml. of saturated alcoholic picric acid. The precipitated picrate was digested with 35 ml. of ethanol, cooled to room temperature, and filtered. After this process was repeated three times, the insoluble material was crystallized from water to give, after drying at 100° in vacuum, 0.14 g. (23% yield) of crystalline *picrate*, m.p. 216–217° with dec. On mixing with a sample of natural cuscohygrine dipicrate (m.p. 216–217°) there was no depression in the melting point.

Nitrate formation. To a solution of 0.2 g. of Fraction B in 5 ml. of commercial absolute ethanol was added a solution of nitric acid in ethanol (1 ml. of conc'd nitric acid in 10 ml. of absolute ethanol) until the mixture was acid to Congo Red. Cooling gave crystals which were recrystallized four times from 15-ml. portions of absolute ethanol and dried at 100° in vacuum; yield, 0.06 g., 19%, m.p. 203–204°. A mixture with natural cuscohygrine dinitrate (m.p. 204–205°) melted at 203–204°.

Free base. A 1.0 g. sample of Fraction B was converted to nitrate as described above and subjected to a systematic fractional crystallization. The 0.28 g. of pure nitrate obtained (m.p. 202–204°) was dissolved in 5 ml. of water, basified with 6 *N* sodium hydroxide, and extracted with four 5-ml. portions of ether. After drying and evaporating the ether, the residue was distilled at bath temperature 110° and 0.1 mm. pressure to give about 0.15 g. of pale yellow oil, n_D^{25} 1.4833.

SUMMARY

Cuscohygrine has been synthesized by a method that strongly supports 1,3-bis(1′-methyl-2′-pyrrolidyl)-2-propanone as its structure.

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