[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING, UNIVERSITY OF CALIFORNIA]

THE SYNTHESIS OF SOME COMPOUNDS RELATED TO CUSCOHYGRINE

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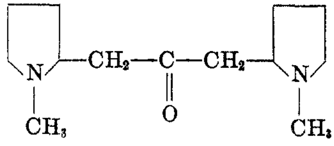
Recently, there have been reported several syntheses of cuscohygrine (I), one of the minor alkaloids of South American coca leaves. Two of these syntheses (1, 2) were under so-called physiological conditions employing the condensation of γ-methylaminobutyraldehyde and acetone dicarboxylic acid. The other two involved pyrolysis[1] of the lead (3) and barium (4) salts of 1-methyl-2-pyrroleacetic acid to give 1,3-bis(1′-methyl-2′-pyrryl)-2-propanone (V) which was then catalytically hydrogenated to I. Both of the latter syntheses gave other products as well as cuscohygrine, and in the case of the barium salt, fractionation of the hydrogenation reaction product gave four distinct fractions. In order to elucidate the structure of some of these unidentified fractions, we are attempting to prepare by direct methods some of the more reasonable possibilities, and this report presents the synthesis of 1,3-bis(1′-methyl-2′-pyrrolidyl)propane (VII, dihydrodesoxycuscohygrine).



I

In order to carry out the preparation on a scale sufficient to allow for accurate purification by fractional distillation of the final liquid products, it was necessary to improve the synthesis of 1,3-bis(1′-methyl-2′-pyrryl)-2-propanone (V) which had been obtained in only 12% yield by barium salt pyrolysis. Since the yield reported from the lead salt pyrolysis is much higher (49%, albeit on a very small scale) this alternative was examined. On a large scale (0.2 mole) the best yield attainable was 16%, and although the lead salt does offer manipulative advantages over the barium salt in that it melts and thus facilitates stirring and heat transfer, the yield is still poor.

Various Claisen ester type condensations were then considered. The condensation of ethyl 1-methyl-2-pyrrolidineacetate might be useful in that the product already would contain pyrrolidine rather than pyrrole rings. However, this reaction has been reported to fail using sodium ethoxide (5) and sodium (6), the product in the latter case possibly being the β-keto ester which resisted hydrolysis. With ethyl 1-methyl-2-pyrroleacetate (II), we have found that con-

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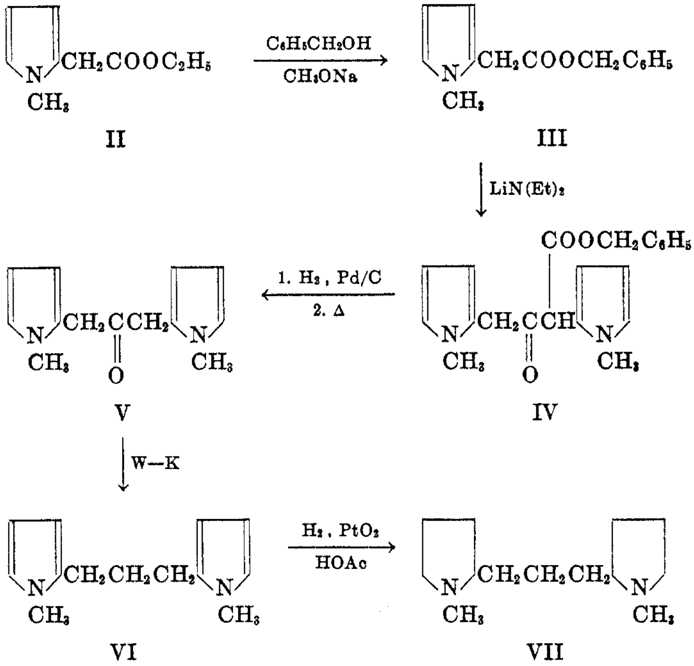
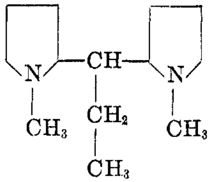
[1] A synthesis of cuscohygrine also has been reported by pyrolysis of barium 1-methyl-2-pyrrolidineacetate [Lazurevskii, *Sbornik Rabot Khim.*, **15**, 43 (1939)]. However, in attempting to repeat this work, we have found no cuscohygrine among the mixture of products.

densation apparently takes place quite readily and the product exhibits the typical β-keto ester properties. Hydrolysis to the ketone, however, reversed the condensation and the only product was 1-methyl-2-pyrroleacetic acid and its decarboxylation product, 1,2-dimethylpyrrole. Since the difficulty was in the hydrolysis and not in the formation of β-keto ester, the method of Bowman (7) which employs the benzyl ester and thus substitutes hydrogenolysis for hydrolysis in the ketone cleavage, offered a promising alternative.



The benzyl ester (III) was prepared in 93% yield from the ethyl ester (II) by trans-esterification, and was then converted to β-keto ester (IV) using lithium diethylamide as the condensing agent according to the procedure of Hammell and Levine (8) for ethyl phenylacetate. Hydrogenolysis with a palladized carbon catalyst and decarboxylation gave 1,3-bis(1′-methyl-2′-pyrryl)-2-propanone (V) in 44% over-all yield from the ethyl ester (II).

To convert the dipyrrylpropanone (V) to the dipyrrolidylpropane (VII), Wolff-Kishner reduction was employed first, in order to avoid any β-aminoketone type intermediates, and the dipyrrylpropane (VI) thus obtained was hydrogenated to 1, 3-bis(1′-methyl-2′-pyrrolidyl)propane (VII). This latter compound appears to be identical with the dihydrodesoxycuscohygrine of Hess and Fink (9), prepared in 10% yield from the α-hydrazone of cuscohygrine and sodium ethoxide. Unfortunately, we could not obtain sufficient natural material to prepare an authentic sample of dihydrodesoxycuscohygrine, but the physical properties are in close agreement. Dihydrodesoxycuscohygrine is reported to boil at 125°/16 mm. and form a dipicrate, m.p. 185–186°, while VII boils at 89–90°/6 mm., and forms a dipicrate, m.p. 185–186°.[2] If these compounds are identical, as appears highly likely, then dihydrodesoxycuscohygrine has the structure VII and not VIII as postulated by Hess and Fink.



VIII

EXPERIMENTAL

All melting points are corrected; microanalyses were performed by the Microchemical Laboratory, University of California.

Ethyl 1-methyl-2-pyrroleacetate. This ester was prepared from 1-methylpyrrole and ethyl diazoacetate as previously described (4); b.p. 105–108°/4 mm., n_D^{25} 1.4871.

Fractionation of the higher-boiling residues gave an appreciable fraction with b.p. 164–167°/4 mm. and n_D^{25} 1.4900. This material was apparently *diethyl 1-methyl-2,5-pyrrolediacetate*[3] on the basis of its saponification equivalent (Calc'd, 127; found, 128) and the formation of a bis-benzylamide derivative, following the general directions of Dermer and King (10). After crystallization from methanol, the bis-benzylamide melted at 214–215°.

Anal. Calc'd. for $C_{23}H_{25}N_3O_2$: C, 73.6; H, 6.7; N, 11.2.

Found: C, 73.5; H, 6.8; N, 10.8.

Pyrolysis of lead 1-methyl-2-pyrroleacetate. The lead salt was prepared by hydrolyzing ethyl 1-methyl-2-pyrroleacetate with 6 *N* potassium hydroxide in 65% ethanol (by weight) using 2.5 moles of alkali per mole of ester and heating under reflux for 3.5 hours. The alcohol was removed by distillation under reduced pressure and sufficient water was added to bring everything into solution after which the solution was adjusted to *p*H 7.5 by adding glacial acetic acid. Addition of a 70% aqueous solution of lead acetate monohydrate (0.6 mole per mole of ester) and cooling to 0° caused precipitation of the lead salt which was dried *in vacuo* to constant weight; yield, 80%, m.p. 123–126°.

Pyrolyses were carried out on 0.2-mole (48.5 g.) batches by adding the dry, powdered salt to a flask arranged for vacuum distillation and stirring with an induction motor (11). With stirring, the lead salt was melted at 160° (bath temperature), the system was evacuated to 3–4 mm., the bath was rapidly heated to 220° with the flask removed, and the flask was then re-immersed in the bath. Distillation commenced immediately and continued over a 1.5 hour period as the bath temperature was increased slowly to 290°. The total distillate (9.5 g.) was dissolved in 75 ml. of chloroform, washed with 10 ml. of 1 *N* sulfuric acid, 15 ml. of 0.5 *N* sodium carbonate, and 10 ml. of saturated sodium chloride solution, after which the dried chloroform solution was evaporated and the residue was fractionated at reduced pressure. A low-boiling fraction of 5.6 g. consisting mostly of 1,2-dimethylpyrrole was collected followed by 3.5 g. (16% yield) of crude 1,3-bis(1′-methyl-2′-pyrryl)-2-propanone, b.p. 168–175°/3–4 mm. Crystallization from ethanol gave 1.7 g. (8% yield) of pure ketone, m.p. 66–67° [reported (4) m.p. 67–68°].

Benzyl 1-methyl-2-pyrroleacetate. A mixture of 100 g. (0.6 mole) of ethyl 1-methyl-2-pyr-

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[2] Späth and Tuppy (3) reported as one of their side-products 7 mg. of an oil, b.p. 120–130°/11 mm.; dipicrate, m.p. 180–182°, which may have been an impure sample of VII.

[3] Diethyl 1-methyl-2,5-pyrrolediacetate has been reported previously by Willstätter and Pfannenstiel [*Ann.*, **422**, 1 (1920)] as melting at 163–164° and by Nenitzescu and Solomonica [*Ber.*, **64**, 1924 (1931)] who obtained it as an oil.

roleacetate, 260 g. (2.4 moles) of pure benzyl alcohol, and 2.4 g. (0.04 mole) of sodium methoxide was heated at a bath temperature of 170° with stirring during the course of two hours as 29 ml. of ethanol was stripped from the solution. Increasing the temperature to 190° resulted in an additional 5 ml. of ethanol (total, 34 ml., 27 g., 98% of theory) and the solution was then cooled, acidified with 25 ml. of glacial acetic acid, and washed with three 75-ml. portions of water. After washing the aqueous portions with benzene, the combined benzene and benzyl alcohol solutions were fractionated and gave 127 g. (93% yield) of benzyl 1-methyl-2-pyrroleacetate; b.p. 160–163°/2 mm., n_D^{25} 1.5469.

Anal. Calc'd. for $C_{14}H_{15}NO_2$: C, 73.3; H, 6.6; Sapn. equiv., 229.
Found: C, 73.0; H, 6.7; Sapn. equiv., 229.

Benzyl α,γ-bis(1-methyl-2-pyrryl)-β-ketobutyrate. Following closely the general procedure of Hamell and Levine (8), a solution of 30 g. (0.13 mole) of benzyl 1-methyl-2-pyrroleacetate in 35 ml. of absolute ether was added dropwise over a two-hour period with stirring to a solution of 0.12 mole of lithium diethylamide (12) in 150 ml. of absolute ether. After the addition was completed, the gently refluxing solution was stirred an additional 1.5 hours at room temperature, and then was added to 300 ml. of 0.6 *N* sodium bicarbonate. The ether layer was washed with three additional portions (50 ml.) of water, dried, and distilled. After removal of ether and benzyl alcohol (0.08 mole), 22 g. (96% yield) of crude β-keto ester remained. Attempts to purify the product by distillation resulted in extensive decomposition; therefore it was subjected directly to hydrogenolysis.

1,3-Bis(1′-methyl-2′-pyrryl)-2-propanone by hydrogenolysis of benzyl α,γ-bis(1′-methyl-2′-pyrryl)-β-ketobutyrate. Using 12.4 g. of 5% palladium on carbon as catalyst, a solution of 105 g. (0.3 mole) of crude β-keto benzyl ester in 140 ml. of butanone was hydrogenated at room temperature and 30 pounds pressure. Approximately one mole of hydrogen was absorbed, after which absorption ceased and the solution was filtered using filter aid. Distillation of the filtrate gave 31.7 g. (49% yield) of crude ketone, b.p. 154–162°/1–2 mm.

Attempted conversion of 1,3-bis(1′-methyl-2′-pyrryl)-2-propanone to a ketal. Several attempts were made to prepare a ketal both with ethylene glycol and triethylorthoformate. With weak acid catalysts such as ammonium chloride, the ketone was recovered unchanged, whereas catalytic amounts of sulfuric acid or *p*-toluenesulfonic acid caused immediate polymerization to pyrrole reds.

1,3-Bis(1′-methyl-2′-pyrryl)propane. Crude ketone (31.7 g., 0.147 mole) was subjected to the Huang-Minlon modification (13) of the Wolff-Kishner reduction using 1200 ml. of ethylene glycol, 36.8 g. of 85% hydrazine hydrate, and 40 g. of potassium hydroxide. After pouring the reaction mixture into a liter of water, it was extracted thoroughly with five 200-ml. portions of ether, the combined ether extracts were washed with water, dried, and evaporated, and the residue was fractionated. 1,3-Bis(1′-methyl-2′-pyrryl)propane was obtained as a very pale yellow oil; yield, 9.1 g., 31%; b.p. 138–139°/2 mm.; n_D^{25} 1.5488.

Anal. Calc'd for $C_{13}H_{18}N_2$: C, 77.2; H, 9.0; N, 13.9.
Found: C, 77.4; H, 8.8; N, 13.8.

1,3-Bis(1′-methyl-2′-pyrrolidyl)propane. A solution of 9.1 g. (0.045 mole) of the dipyrrylpropane in 90 ml. of glacial acetic acid was hydrogenated at 30 pounds pressure and room temperature using 0.91 g. of platinum oxide as catalyst. When hydrogen absorption ceased after about five hours (4 moles absorbed), the solution was filtered, the filtrate concentrated at reduced pressure to about 15 ml., and the residue dissolved in 50 ml. of water. The aqueous solution was washed with ether, basified with solid potassium carbonate (·1½ H_2O), and extracted thoroughly with ether. Evaporation of the dried ether solution and fractionation of the residue gave 7.3 g. (77% yield) of 1,3-bis(1′-methyl-2′-pyrrolidyl)propane as a colorless oil, b.p. 89–90°/6 mm., n_D^{25} 1.4775.

Anal. Calc'd for $C_{13}H_{26}N_2$: C, 74.2; H, 12.5; N, 13.3.
Found: C, 74.5; H, 12.1; N, 13.2.

The *dipicrate* was prepared with ethanolic picric acid and was recrystallized from absolute ethanol; m.p. 185–186°.

Anal. Calc'd for $C_{25}H_{32}N_8O_{14}$: C, 44.9; H, 4.8; N, 16.8.

Found: C, 45.3; H, 4.9; N, 16.6.

The *dimethiodide* was prepared by heating the dipyrrolidylpropane with methyl iodide in methanol, evaporating the methanol, and crystallizing the residue from absolute ethanol-acetone (3:1), m.p. 306–307° (evac. cap.).

Anal. Calc'd for $C_{15}H_{32}I_2N_2$: C, 36.4; H, 6.5; I, 51.4.

Found: C, 36.1; H, 6.3; I, 51.7.

SUMMARY

An improved method has been found for the preparation of 1,3-bis(1′-methyl-2′-pyrryl)-2-propanone which consists in Claisen ester condensation of benzyl 1-methyl-2-pyrroleacetate followed by hydrogenolysis of the benzyl ester and decarboxylation. The dipyrrylpropanone thus prepared has been converted to 1,3-bis(1′-methyl-2′-pyrrolidyl)propane, apparently identical with dihydrodesoxycuscohygrine.

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