ported[3] for the formation of the dimethyl ester except for use of lower temperature of reaction (25–30°) and longer reaction time (8 days). The yield of dimethyl ester was 8%. The process for recovery of the starting hydroxydiacid X gave instead a 70% yield of a monomethyl ester of X. This material had an ultraviolet spectrum in acid–methanol with λ_{max} 305 mμ, log ε 3.87. In base–methanol it had λ_{max} 316 mμ, log ε 3.68, and λ_{max} 270 mμ, log ε 3.45.

Anal. Calcd. for $C_9H_9NO_5$: C, 51.16; H, 4.30; N, 6.63; neut. equiv., 211.2. Found: C, 51.13; H, 4.15; N, 6.40; neut. equiv., 211.

Pyridoxine Hydrochloride (XII). General Hydride Reduction Procedure.—A 1-liter round-bottom flask was equipped with gas inlet (positive pressure of nitrogen maintained throughout the reaction), a gas outlet at the top of a condenser (no water), stirrer, addition funnel and thermometer. Commercial diglyme, 120 ml. (0.07% water by modified Karl Fischer, 0.04–0.05% –OH by acetylation) and 8 g. of sodium borohydride (98% by manufacture's assay) were added to the flask and stirred to dissolve the solid. Powdered 2-methyl-3-hydroxypyridine-4,5-dicarboxylic acid (11.8 g., 0.06 mole) was added portionwise over 20 minutes. The internal temperature rose to 45°[21] and a dark orange solution resulted. There was then added 9.3 g. of aluminum chloride (anhydrous reagent, sublimed, small lump[22]) dissolved in 70 ml. of diglyme. The latter addition required 10 minutes with internal temperature rising to 68°. At one point the bright yellow reaction mixture set up, but thinned out readily on the addition of further aluminum chloride solution. The stirred mixture then was heated to 135° for 15 minutes. By the time 115° was reached, the mixture had changed from bright yellow to white and reaction was undoubtedly nearly complete by this stage.[23] The reaction mixture was cooled and unreacted hydride destroyed by the dropwise addition of 250 ml. of methanolic HCl (saturated at *ca.* 50°). Methyl borate was removed by the fractional distillation through a 1″ × 18″ column packed with $^3/_{16}$″ glass helices. To obtain a negative flame test, 75 ml. of distillate was required. Sodium chloride was removed from the distillation residue by a hot filtration with 2 × 50 ml. of wash with hot methanol. The methanol was distilled out of the filtrate at atmospheric pressure from a steam-bath. By this time the flask contained a crystalline solid and two liquid layers. Cooling and the addition of 15 ml. of methanolic HCl brought the lower and somewhat viscous layer back into solution. After storing in the refrigerator for 2.5 days, the product was filtered off with a minimum of wash with cold methanol. The yield of crude pyridoxine hydrochloride was 10.1 g., m.p. 196–199°, purity determined by the ultraviolet spectrum was 90%. The crude was recrystallized from 95% ethanol to yield 9.0 g. (73% of theoretical), m.p. 204–206° dec., literature[24] m.p. 205–212° dec. This material had an ultraviolet spectrum identical with that of purified commercial pyridoxine hydrochloride; in acid–methanol it has λ_{max} 292 mμ, log ε 3.96, and in base–methanol λ_{max} 307 mμ, log ε 3.84, and λ_{max} 246 mμ, log ε 3.85.

Anal. Calcd. for $C_8H_{12}NO_3Cl$: C, 46.72; H, 5.88; N, 6.81; Cl^-, 17.24. Found: C, 46.67; H, 5.83; N, 6.78; Cl^-, 17.31.

Pyridoxine hydrochloride also was obtained by the reduction of the monomethyl ester[12] of 2-methyl-3-hydroxypyridine-4,5-dicarboxylic acid. The yield (with 3.0 moles of sodium borohydride per mole of substrate) was 71%.

Finally, pyridoxine was prepared by the catalytic dechlorination of 6-chloropyridoxine. A slurry of 2.7 g. of 6-chloropyridoxine, 150 ml. of 95% ethanol and 2 g. of 5% palladium-on-calcium carbonate was shaken in a Parr low pressure hydrogenation apparatus (40 to 30 p.s.i.; temperature, 20–40°). The catalyst was removed by filtration and an excess of concentrated hydrochloric acid was added to the filtrate. Evaporation to dryness and then recrystallization from 95% ethanol gave 1.6 g. (58%) of pyridoxine hydrochloride.

Acknowledgment.—The authors are indebted to Dr. L. H. Conover for preliminary work which demonstrated the successful sodium borohydride–aluminum chloride reduction of the dimethyl ester of 2-methyl-3-hydroxypyridine-4,5-dicarboxylic acid to pyridoxine and for later helpful suggestions. The authors are also indebted to Messrs. E. J. Bianco, R. F. Shannon and A. T. Gilman for the preparation of some of the intermediates in larger quantities, Mr. R. L. Robertson for microanalyses, Mrs. R. M. Reynolds for ultraviolet spectra and to Messrs. J. A. Aimetti and C. F. Schultz for technical assistance.

(21) The temperature should be kept in the range of 30 to 45°. If over-cooled the hydroxydiacid will not react immediately, but will build up in the mixture and suddenly react with much foaming. If over-heated, a sticky complex will fall out of solution and conversion will be cut considerably.

(22) Powdered aluminum chloride will react with the diglyme too vigorously and may even ignite from the heat.

(23) Lower temperatures, *e.g.*, 95° for 1 hour or 45° for 18 hours, are equally satisfactory.

(24) "The Merck Index," 6th edition, Merck and Co., Inc., Rahway, N. J., 1952.

GROTON, CONN.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF KANSAS]

Studies on the Formation and Reactions of 1-Pyrroline[1]

BY DONALD W. FUHLHAGE[2] AND CALVIN A. VANDERWERF

RECEIVED JUNE 23, 1958

1-Pyrroline is formed by partial dehydrogenation of pyrrolidine and by partial hydrogenation of pyrrole. It can be synthesized by dehydrohalogenation of N-chloropyrrolidine, or by periodate degradation of 3-hydroxypiperidine. 1-Pyrroline undergoes condensation with pyrrole and alkylated pyrroles to form a new series of compounds, the pyrrolidylpyrroles. The major isomer formed by condensation of 1-pyrroline with pyrrole is 2-(2-pyrrolidyl)-pyrrole. 1-Piperideine undergoes a similar condensation with pyrrole.

Introduction

Theoretically, partial hydrogenation of pyrrole or partial dehydrogenation of pyrrolidine can result in the formation of any combination of three isomers, 1-pyrroline (I), 2-pyrroline (II) and 3-pyrroline (III).

Catalytic hydrogenation has been reported for pyrrole[3–5] and several substituted pyrroles.[6,7]

(1) This investigation was performed as a part of American Petroleum Institute Research Project 52 on "Nitrogen Constituents of Petroleum," which is conducted at the University of Kansas in Lawrence, Kan., and at the Bureau of Mines Experiment Stations at Laramie, Wyo., and Bartlesville, Okla.

(2) From the dissertation submitted by Donald W. Fuhlhage to the Graduate School of the University of Kansas in partial fulfillment of the requirements for the Degree of Doctor of Philosophy.

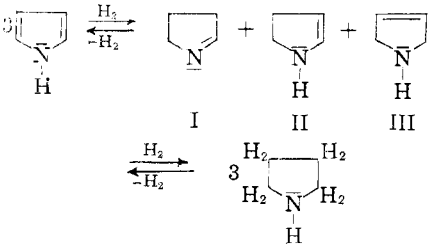
(3) N. D. Zelinsky and Y. K. Yur'ev, *Ber.*, **64B**, 101 (1931).

(4) M. de Jong and J. P. Wibaut, *Rec. trav. chim.*, **49**, 237 (1930).

(5) J. P. Wibaut, *ibid.*, **44**, 1101 (1925).

(6) F. K. Signaigo and H. Adkins, THIS JOURNAL, **58**, 709 (1936).

(7) J. L. Rainey and H. Adkins, *ibid.*, **61**, 1104 (1939).



Catalytic dehydrogenation of pyrrolidine[3-5,8] and a number of substituted pyrrolidines[9,10] has been described. In none of these cases was the formation of pyrrolines demonstrated.

Chemical reduction of pyrrole with zinc and hydrochloric acid affords 3-pyrroline.[11-13]

1-Pyrroline is not well characterized in the literature. Schöpf[14] reported its formation from γ-aminobutyraldehyde diethyl acetal upon hydrolysis at *p*H 5. It was not isolated, but was condensed *in situ* with *o*-aminobenzaldehyde. The condensation product was isolated as the picrate, which was identified by chromic acid oxidation to the known picrate of 2,3-trimethylene-4-quinazolone Enzymatic oxidation of 1,4-diaminobutane dihydrochloride to form 1-pyrroline also has been reported.[15]

2-Pyrroline is not known. It is the enamine tautomer of the aldimine 1-pyrroline, and as such would be expected to be much less stable than 1-pyrroline. Recent work in which 2-substituted pyrrolines formed by the action of Grignard reagents on γ-chlorobutyronitrile were shown to have the 1-pyrroline structure [16-19] supports this view.

The present investigation was undertaken to test the possibility that catalytic dehydrogenation of pyrrolidine and catalytic hydrogenation of pyrrole occur as stepwise processes in which pyrrolines are formed as stable intermediates.

Results

The salient results of the investigation are: (1) Studies on the vapor phase dehydrogenation of pyrrolidine over 5% palladium-on-charcoal revealed that 1-pyrroline is formed during the process, probably as an intermediate in the dehydrogenation to pyrrole.

(2) Investigation of the rapid hydrogenation of pyrrole at low pressure and room temperature under rhodium–alumina catalysis revealed that 1-pyrroline is formed in this process in at least 31% yield. 1-Pyrroline may then be further hydrogenated to pyrrolidine.

(3) A method for the synthesis of 1-pyrroline from pyrrolidine was developed. Treatment of pyrrolidine acetate with sodium hypochlorite gave N-chloropyrrolidine, which, upon careful treatment with alcoholic potassium hydroxide, yielded 1-pyrroline.

(4) 1-Pyrroline was synthesized through the action of sodium periodate on 3-hydroxypiperidine.

(5) It was shown that 1-pyrroline undergoes condensation with pyrrole upon heating to form as the major product the new compound 2-(2-pyrrolidyl)-pyrrole (IV), a white crystalline solid. This reaction serves as a convenient means of derivatizing 1-pyrroline from solutions in pyrrole and pyrrolidine, in which it occurs in product mixtures from hydrogenation of pyrrole and dehydrogenation of pyrrolidine.

(6) The principal isomer formed in the condensation of 1-pyrroline with pyrrole was assigned the structure 2-(2-pyrrolidyl)-pyrrole (IV) on the basis of: (a) presence in dilute chloroform solution of an infrared absorption peak at 3460 cm.$^{-1}$, characteristic of a non-associated pyrrolic N–H group; (b) formation of a diacetylated dipyrrolidine by reduction followed by acetylation; (c) formation, by careful acetylation, of a monoacetylated pyrrolidylpyrrole which showed an infrared absorption peak at 3365 cm.$^{-1}$, characteristic of an associated pyrrolic N–H group. The position and shape of this peak were independent of concentration, indicating intramolecular hydrogen bonding; (d) formation of proline by ozonolysis.

(7) The general reactivity of 1-pyrroline toward pyrroles was shown through condensations with 2-methylpyrrole, 3-methylpyrrole, 2,5-dimethylpyrrole and indole. Attempted condensations with 1-methylpyrrole and carbazole were not successful.

(8) 1-Piperideine was shown to condense with pyrrole upon heating to form a (2-piperidyl)-pyrrole.

Discussion of Results

1-Pyrroline formation by catalytic dehydrogenation of pyrrolidine occurred through the entire temperature range studied, 200–400°. The highest yield of pyrroline was 24% at 400°. At this temperature, pyrrole also was formed in about 50% yield under the conditions employed. It is interesting to note that 1-pyrroline was obtained in 8% yield at 200°, a temperature at which no appreciable amount of pyrrole was formed. 1-Pyrroline was identified by its reaction with pyrrole to form 2-(2-pyrrolidyl)-pyrrole. 3-Pyrroline does not undergo a similar reaction.

The formation of 1-pyrroline by rhodium–alumina-catalyzed hydrogenation of pyrrole was proved by the isolation of 2-(2-pyrrolidyl)-pyrrole from the product mixtures. Reduction for 28 minutes gave a 31% yield of 1-pyrroline based upon the hydrogen absorbed, whereas the yield was only 9.2% when reduction was extended over a 24-hour period. This implies initial formation of 1-pyrroline, followed by further reduction to pyrrolidine.

In summary, the behavior of the pyrrole–pyrrolidine–hydrogen system in the presence of platinum metal catalysts seems to be described by an equilibrium which includes 1-pyrroline as a stable

(8) J. P. Wibaut, C. C. Molster, H. Kauffmann and A. M. Lennssen, *Rec. trav. chim.*, **49**, 1127 (1930).

(9) A. P. Terent'ev and M. A. Volodina, *Doklady Akad. Nauk S.S.S.R.*, **88**, 845 (1953).

(10) H. Adkins and L. G. Lundsted, THIS JOURNAL, **71**, 2964 (1949).

(11) L. Knorr and P. Rabe, *Ber.*, **34**, 3491 (1901).

(12) L. H. Andrews and S. M. McElvain, THIS JOURNAL, **51**, 887 (1929).

(13) A. Treibs and D. Dinelli, *Ann.*, **517**, 170 (1935).

(14) C. Schöpf and F. Oechler, *ibid.*, **523**, 1 (1936).

(15) P. J. G. Mann and W. R. Smithies, *Biochem. J.*, **61**, 89 (1955).

(16) P. M. Maginnity and J. B. Cloke, THIS JOURNAL, **73**, 49 (1951).

(17) P. M. Maginnity and T. Gair, *ibid.*, **74**, 4958 (1952).

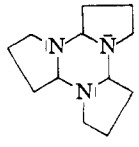
(18) B. Witkop, *ibid.*, **76**, 5597 (1954).

(19) M. C. Kloetzel, J. L. Pinkus and R. W. Washburn, *ibid.*, **79**, 4222 (1957); see, also, G. G. Evans, *ibid.*, **73**, 5230 (1951).

intermediate. Low temperatures favor the formation of pyrrolidine, while high temperatures favor the formation of pyrrole.

1-Pyrroline was prepared by a modification of the method used by Schöpf[20] for the preparation of 1-piperideine. Schöpf prepared 1-piperideine from piperidine by forming first N-chloropiperidine, then submitting this product to dehydrohalogenation through treatment with hot alcoholic potassium hydroxide. The product underwent rapid trimerization, and was isolated as the trimer, α-tripiperideine.

Adaptation of this method to the synthesis of 1-pyrroline required several modifications because of the lower stability of the compounds involved. N-Chloropyrrolidine could not be isolated in pure form, but was kept in concentrated ether solution. The dehydrohalogenation step required careful temperature control in order to prevent polymerization, probably to the trimer, tripyrroline



Similar difficulties were encountered in the isolation of the product. α-Tripiperideine is sufficiently stable to be isolated by evaporation of the solvent under mild vacuum at 60°. Removal of solvent from the 1-pyrroline product mixture was carried out at several combinations of temperature and pressure. In all cases, most of the product was carried over with the solvent. When the solvent was distilled off at room temperature and 1 mm. pressure, a product which apparently was α-tripyrroline was isolated from the residue in 5% yield. However, it could not be made to crystallize. The remainder of the product was carried over with the solvent, presumably as the monomer.

This behavior of 1-pyrroline upon distillation is analogous with the behavior shown by α-tripiperideine under somewhat more extreme conditions. Schöpf found that tripiperideine underwent slow de-polymerization on heating, with distillation of some monomer over a wide temperature range. He reported that distillation occurred over a temperature range of 130–220° under aspirator pressure and of 60–140° at 0.1 mm. The trimer reformed quickly in the distillate.[21]

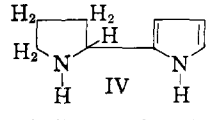
Comparison of the infrared spectrum of the 1-pyrroline isolated from the distillation residue with those of α-tripiperideine and 2-methyl-1-pyrroline, which was prepared by the method of Craig and Hixon,[22] indicates considerable similarity with the α-tripiperideine structure. The 1-pyrroline and α-tripiperideine spectra have in common an unusually large number of peaks in the region between 2500 and 2910 cm.$^{-1}$. α-Tripiperideine shows peaks at 2910, 2840, 2770, 2710, 2570 and 2520 cm.$^{-1}$. 1-Pyrroline shows peaks at 2910, 2840, 2760, 2680, 2630, 2580 and 2500 cm.$^{-1}$. In contrast, 2-methyl-1-pyrroline shows peaks only at 2920, 2875 and 2480 cm.$^{-1}$ in this region. 1-Pyrroline and α-tripiperideine both show many sharp peaks in the region between 1500 and 800 cm.$^{-1}$. 2-Methyl-1-pyrroline shows fewer peaks in this region. The principal difference in the 1-pyrroline and the α-tripiperideine spectra is the presence of a peak at 1620 cm.$^{-1}$ in the spectrum of 1-pyrroline; α-tripiperideine shows no appreciable absorption in this region. 2-Methyl-1-pyrroline shows a peak at 1650 cm.$^{-1}$, which is much more intense than that in the 1-pyrroline spectrum. The —C=N— function is expected to show strong absorption in this region.

On the basis of these spectra, the 1-pyrroline which was isolated appears to be largely trimeric, with a slight amount of dissociated monomer or dimer present. This interpretation is also consistent with the distillation behavior. The 1-pyrroline trimer when heated with an excess of pyrrole formed 2-(2-pyrrolidyl)-pyrrole in 87.5% yield.

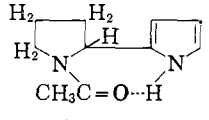
The periodate degradation of 3-hydroxypiperidine (VI) demonstrates a promising method for obtaining 1-pyrrolines from piperidines. This reaction may proceed through the intermediate formation of γ-aminobutyraldehyde, which is known to undergo rapid ring closure.[14]

The reaction is a simple one, requiring merely the heating of the reactants in dilute aqueous solution. However, the nature of the product, 1-pyrroline, presents special difficulties in the isolation of the product from the reaction mixture. Formation of 1-pyrroline was demonstrated by reaction of the product with pyrrole to form 2-(2-pyrrolidyl)-pyrrole, but no suitable method for isolation of 1-pyrroline in pure form was developed.

The assignment of the structure 2-(2-pyrrolidylpyrrole) (IV) to the major product formed in the addition of pyrrole to 1-pyrroline was based on



IV



V

several lines of evidence. Infrared studies and catalytic hydrogenation to a pyrrolidylpyrrolidine which formed a diacetylated derivative indicated that both nitrogen atoms were unsubstituted. Formation of proline upon ozonolysis of the pyrrolidylpyrrole proved that the attachment to the pyrrolidine ring was at the 2-position. In the infrared spectrum of the monoacetyl derivative of the pyrrolidylpyrrole in chloroform solution, the presence of a strong characteristic associated N–H peak at 3365 cm.$^{-1}$, the position and shape of which was independent of concentration, can be explained only on the basis of intramolecular hydrogen bonding. Of the theoretically possible pyrrolidylpyrroles which might be formed by addition of 1-pyrroline to pyrrole, only 2-(2-pyrrolidyl)-pyrrole would form a monoacetylated derivative, 2-[2-(1-acetylpyrrolidyl)]-pyrrole (V) which would be expected to exhibit significant intramolecular hydrogen bonding.

Consideration of the probable mechanism for the addition of pyrrole to 1-pyrroline leads to the pre-

(20) C. Schöpf, A. Komzak, F. Braun, E. Jacobi, M. L. Borgmuth, M. Bullnheimer and I. Hagel, *Ann.*, **559**, 1 (1948).

(21) C. Schöpf, H. Arm and H. Krimm, *Chem. Ber.*, **84**, 690 (1951).

(22) L. C. Craig, H. Bulbrook and R. M. Hixon, THIS JOURNAL, **53**, 1831 (1931).

diction that 2-(2-pyrrolidyl)-pyrrole should be the major product. The reaction is very likely a nucleophilic addition at the 1-pyrroline double bond, particularly if the reactive species are the 1-pyrrolinium ion and the pyrrole anion, which would be expected to exist at least to a slight extent in a mixture of 1-pyrroline and pyrrole.[23] The first step in the addition may then be considered as an electrophilic substitution on pyrrole or pyrrole anion, and the predicted attack would be that of the carbon at the 2-position in 1-pyrroline (or 1-pyrrolinium ion) on the carbon at the 2-position in pyrrole (or pyrrole anion). In all known cases of electrophilic substitution on pyrrole itself reaction is primarily at the 2-position. It has not been generally determined whether such reactions are accompanied by some substitution in the 3-position. It is known, however, that 3-substitution occurs when no 2-position is available, but at a considerably slower rate.[24] A small amount of an isomeric pyrrolidylpyrrole was formed in the addition of pyrrole to 1-pyrroline. This was not isolated in pure form, but infrared studies on the mixture, based on a comparison with the spectrum for 3-methylpyrrole,[25] indicated that it probably was 3-(2-pyrrolidyl)-pyrrole. No evidence was found for the presence of 1-(2-pyrrolidyl)-pyrrole or 1-(3-pyrrolidyl)-pyrrole.

The addition of pyrroles to 1-pyrroline was shown to be a general reaction of N-unsubstituted pyrroles with free 2- or 3-positions by successful reaction of 1-pyrroline with 2-methylpyrrole, 3-methylpyrrole, 2,5-dimethylpyrrole and indole. The isomeric structure of the products was not proved in these cases. Infrared studies showed that the product from 2-methylpyrrole was not substituted at the pyrrole nitrogen and, by analogy with the pyrrole case, it is probable that 2-methyl-5-(2-pyrrolidyl)-pyrrole is the major product. With 3-methylpyrrole the product was definitely a mixture of isomers, probably 3-methyl-2-(2-pyrrolidyl)-pyrrole and 4-methyl-2-(2-pyrrolidyl)-pyrrole. The product in the case of 2,5-dimethylpyrrole showed the characteristic pyrrolic N–H absorption in the infrared and is therefore almost certainly 2,5-dimethyl-3-(2-pyrrolidyl)-pyrrole. With indole, the structure is likely that of 3-(2-pyrrolidyl)-indole, because electrophilic substitution in indole is known to occur preferentially at the 3-position. It was found that 1-piperideine also reacts with pyrrole. The product is a piperidylpyrrole, probably 2-(2-piperidyl)-pyrrole.

In the light of current theories regarding the origin of petroleum, the formation of 1-pyrroline by partial hydrogenation of pyrrole and its ready condensation with pyrroles suggest the strong possibility that pyrrolidylpyrroles may occur in crude oil.

(23) See S. N. Vinogradov and R. H. Linnell, *J. Chem. Phys.*, **23**, 93 (1955), for a study of the system pyridine–pyrrole. H. C. Yuan, in unpublished work from this Laboratory, obtained strong evidence, based on infrared studies, for partial ionization in the system pyrrolidine–pyrrole.

(24) K. W. Doak and A. H. Corwin, THIS JOURNAL, **71**, 159 (1949).

(25) R. E. Lancaster and C. A. VanderWerf, *J. Org. Chem.*, **23**, 1208 (1958).

Experimental[26]

1-Pyrroline.—(A) A modification of the method developed by Schöpf for 1-piperideine[20] was used for the preparation of 1-pyrroline. A sodium hypochlorite solution was prepared as follows: chlorine gas was bubbled into 1000 ml. of a well-stirred solution of 1 *N* sodium hydroxide at 0° until 35.5 g. (0.500 mole) had been absorbed. To this solution there was added slowly, so that the temperature was kept below 5°, a solution of pyrrolidine acetate previously prepared by the slow addition of 41.7 ml. (0.500 mole) of pyrrolidine to a cooled solution of 28.6 ml. (0.500 mole) of glacial acetic acid and 5 ml. of water. After addition was complete the mixture was extracted with 250 ml. of ether in 50-ml. portions. The resulting ether solution of N-chloropyrrolidine, after several hours of drying over sodium sulfate, was subjected to vacuum distillation at room temperature for removal of most of the solvent. The ether could not be removed completely, for pure N-chloropyrrolidine reacts spontaneously with itself at room temperature. For this reason, the product was not distilled or otherwise purified. The concentration of N-chloropyrrolidine in the concentrated solution could be estimated by addition of an aliquot portion to aqueous potassium iodide followed by titration with standard sodium thiosulfate solution. This concentration was, for safety, kept below 80%.

The resulting solution of N-chloropyrrolidine was added slowly with stirring to a solution of 32 g. of potassium hydroxide in 250 ml. of ethanol or 1-butanol while the temperature was maintained below 25°. The mixture then was allowed to stand at room temperature for two hours and was finally filtered to remove potassium chloride.

The resulting solution contained 1-pyrroline, potassium hydroxide and some potassium chloride in alcoholic solution. Attempts to isolate large quantities of the 1-pyrroline from the solvent were unsuccessful. On distillation, either at atmospheric pressure or under vacuum, the pyrroline became distributed throughout the solvent fractions. A small amount of pyrroline was, however, isolated as follows: the alcoholic solution was vacuum distilled at room temperature. The residue from this process was taken up in dilute sodium hydroxide, salted out with potassium carbonate, and extracted with ether. This extract was dried for one hour with sodium sulfate, then dried under a vacuum of 1 mm. pressure at room temperature. This left a residual liquid, light orange in color, weighing 2.1 g. (5% of the theoretical), which, upon refluxing with 28 ml. of pyrrole for 24 hours, formed 3.7 g. of 2-(2-pyrrolidyl)-pyrrole (87.5% of the theoretical), m.p. 77–83°. Vacuum sublimation gave a pure product, m.p. 84.0–86.0°.

Anal. Calcd. for $C_8H_{12}N_2$: C, 70.5; H, 8.9; N, 20.6. Found: C, 70.9; H, 8.8; N, 20.1.

A methanol solution of this compound added to methanolic picric acid gave a picrate, m.p. 164.0–165.5°.

Anal. Calcd. for $C_{14}H_{15}N_5O_7$: C, 46.0; H, 4.1; N, 19.2. Found: C, 46.0; H, 4.3; N, 19.1.

Refluxing of the alcoholic solution from the vacuum drying with 50 ml. of pyrrole for 24 hours gave 16.8 g. (24%) of 2-(2-pyrrolidyl)-pyrrole, m.p. 77–84°. Vacuum sublimation raised the melting point to 83.0–85.5°. Addition of a small amount of pyrrolidine to the solution before refluxing improved the quality of the product.

(B) A mixture of 1200 ml. of water, 5 g. of sodium hydroxide, 10.7 g. of sodium periodate and 5 g. of 3-hydroxypiperidine was heated to distillation temperatures. The first 200 ml. of aqueous distillate was partially saturated with potassium carbonate, then extracted with a mixture of 25 ml. of pyrrole in 100 ml. of ether in three portions. The extract was distilled until the vapor temperature reached 40°, then was refluxed for 48 hours. Vacuum drying of the resulting solution gave a residue which upon one sublimation yielded 1.4 g. (20%) of 2-(2-pyrrolidyl)-pyrrole, m.p. 78–83°. The infrared spectrum was identical with that of 2-(2-pyrrolidyl)-pyrrole as obtained from the dehydrohalogenation product.

Formation of 1-Pyrroline by Dehydrogenation of Pyrrolidine.—The dehydrogenation apparatus consisted of a dropping funnel, a vaporization chamber made from 18-

(26) Boiling points and melting points are uncorrected. Infrared spectra were determined with a Perkin-Elmer model 21 double beam spectrophotometer. Microanalyses by Schwarzkopf Microanalytical Laboratory.

mm. Pyrex tubing, a Pyrex reaction chamber of 100-ml. capacity (18 mm. inside diameter, 46 cm. length) and a product collection system consisting of a condenser followed by a Dry Ice trap. The vaporization chamber, which was heated to 250°, and reaction chamber were wound with number 22 Nichrome resistance wire and wrapped with asbestos. The reaction chamber was packed with 5 g. of 5% palladium-on-charcoal, supported by 3 g. of Pyrex wool. Hydrogen, introduced through a sidearm on the vaporization chamber, was passed through the column at the rate of 30 ml. per minute during each run. The column was flushed with dry nitrogen before being heated to reaction temperature. Temperatures were obtained by previous calibration of the column.

A series of runs was made in order to determine the amount of pyrroline formed at various temperatures. Pyrrolidine in 50-ml. batches was passed through the freshly packed column at a rate of 0.3 ml. per minute. The raw product was distilled at low temperature under 1 mm. pressure up to a temperature of 100°. The residue consisted of a viscous yellow liquid, from which no pyrrolidylpyrrole could be separated. The distillate now was refluxed for 24 hours to bring about reaction between pyrrole and 1-pyrroline, then redistilled (1 mm.). The residue remaining after a pot temperature of 100° had been reached consisted of a white solid, melting typically at 72–78°, picrate, m.p. 163.5–165.5°. Infrared spectra indicated that this compound was identical with the 2-(2-pyrrolidyl)-pyrrole obtained by condensation of pyrrole with an authentic sample of 1-pyrroline. For the runs at higher temperatures, in which formation of pyrrole predominated over that of 1-pyrroline, the amount of 2-(2-pyrrolidyl)-pyrrole formed upon refluxing of the product distillate gave a direct measure of the total 1-pyrroline formed. For the runs at lower temperatures, in which 1-pyrroline formation predominated, the yield of 2-(2-pyrrolidyl)-pyrrole was used as the basis for the calculation of the total pyrrole formed, but an additional step was required for determination of total 1-pyrroline. To the material, presumably containing the excess 1-pyrroline, which distilled from the 2-(2-pyrrolidyl)-pyrrole, an excess of additional pyrrole was added and the resulting mixture was refluxed for 20 hr. The 2-(2-pyrrolidyl)-pyrrole formed was isolated as before, and the total 1-pyrroline then was calculated from the total 2-(2-pyrrolidyl)-pyrrole isolated in the two stages.

Run	Temp., °C.	Yield of pyrrole, %	Yield of pyrroline, %	Yield, %, of 2-(2-pyrrolidyl)-pyrrole
1	200	0	2.0	
2	200		8.0	
3	240	5.5	7.0	11.0
4	320	8.0	12.0	16.0
5	350		15.0	30.0
6	400	(53.0)	24.0	48.0

The pyrrole yield given for run 6 was obtained in another run at the same temperature, in which the pyrrole was isolated directly by distillation at atmospheric pressure.

Formation of 1-Pyrroline in the Hydrogenation of Pyrrole.—(A) In a Parr low-pressure hydrogenation apparatus, 29 ml. (0.40 mole) of pyrrole was shaken with 1 g. of 5% rhodium–alumina until it had taken up 0.20 mole of hydrogen over a period of 24 hours. After removal of the catalyst, 5 ml. of pyrrole was added and the mixture was refluxed for 24 hours. Vacuum distilling followed by vacuum sublimation yielded 2.5 g. (9.2% based on hydrogen absorbed) of 2-(2-pyrrolidyl)-pyrrole, m.p. 77–82°, infrared spectrum identical with that of the compound obtained by condensation of pyrrole with synthetic 1-pyrroline.

(B) Pyrrole (29 ml., 0.40 mole) was hydrogenated in the presence of 2 g. of 5% rhodium–alumina for 28 minutes with absorption of 0.052 mole of hydrogen. The product mixture was filtered, then refluxed for 24 hours. Vacuum drying followed by two vacuum sublimations yielded 2.2 g. (31% based on hydrogen absorbed) of 2-(2-pyrrolidyl)-pyrrole, m.p. 82–86°.

Purification of Crude 2-(2-Pyrrolidyl)-pyrrole.—Three successive fractional distillations under reduced pressure (0.5 mm.) of 66.5 g. of crude 2-(2-pyrrolidyl)-pyrrole accumulated from a series of pyrrolidine dehydrogenation runs afforded a total of 38.7 g. of pure 2-(2-pyrrolidyl)-pyrrole, b.p. 94° (0.5 mm.), m.p. 86.3–87.8°, and 4.5 g. of a material, b.p. 96–130° (0.5 mm.), which appeared, from analysis and infrared spectra, to be a mixture of isomeric monopyrrolidylpyrroles with dipyrrolidylpyrroles. Comparison of the infrared spectrum of the mixture with that of 3-methylpyrrole[24] indicated that the second monopyrrolidylpyrrole present was likely 3-(2-pyrrolidyl)-pyrrole. In addition, a total of 8 g. of a mixture of pyrrole and 2-pyrroline was collected during the distillations, indicating that the condensation is reversible. The remainder of the material was accounted for as tarry distillation residues.

Proof of Structure of 2-(2-Pyrrolidyl)-pyrrole. (A) Hydrogenation.—A 2.6-g. (0.019 mole) sample of the pure pyrrolidylpyrrole, m.p. 86.3–87.8°, in 18 ml. of glacial acetic acid was hydrogenated in a Parr low-pressure apparatus in the presence of 1 g. of rhodium–alumina catalyst with absorption of 0.039 mole of hydrogen. The catalyst was removed by filtration through sintered glass. The solvent was then taken off under reduced pressure (0.5 mm.) and 10 ml. of acetic anhydride was added to the residue. After standing overnight, this solution was heated on the steam-bath for 0.5 hour; then the solvent was removed under reduced pressure. Crystallization from ethyl acetate gave 1.4 g. (33%) of a diacetylated dipyrrolidine, m.p. 173–176°. Recrystallization from ethyl acetate raised the melting point to 174.2–176.6°. Formation of a diacetylated pyrrolidylpyrrolidine indicates that both nitrogen atoms in the original pyrrolidylpyrrole were unsubstituted.

Anal. Calcd. for $C_{12}H_{20}N_2O_2$: C, 64.3; H, 9.0; N, 12.5; mol. wt., 224. Found: C, 64.4; H, 9.1; N, 12.5; mol. wt., 218.

(B) **Acetylation.**—Pyrrolidylpyrrole (3.6 g.), m.p. 86.3–87.8°, was added to 25 ml. of ice-cold acetic anhydride with cooling (ice-bath), and the mixture stored in a refrigerator for three days. It was then dried at 0.5 mm. pressure and room temperature. After most of the acetic anhydride was removed, 10 ml. of absolute ethanol was added to the residue and the mixture was allowed to stand for 30 minutes. It was again dried at 0.5 mm. pressure up to a temperature of 50°. The viscous orange residue (4.8 g.) was transferred to a molecular distillation apparatus and distilled at 25 μ pressure at a bath temperature of 150°. The colorless distillate (3.3 g., 69%) crystallized upon addition of ethyl acetate. Recrystallization from ethyl acetate and petroleum ether gave 2.1 g. of an N-acetylpyrrolidylpyrrole, m.p. 74.2–75.1°. The infrared spectra of the crude residue, the distillate, and the recrystallized solid were identical. All showed a strong peak at 3365 $cm.^{-1}$, characteristic of an associated pyrrolic N–H group, the position and shape of which were independent of concentration.

Anal. Calcd. for $C_{10}H_{14}N_2O$: C, 67.4; H, 7.9; N, 15.7; mol. wt., 178. Found: C, 67.6; H, 8.1; N, 15.9; mol wt., 186.

(C) **Ozonolysis.**—Ozone was passed into a solution of 2 g. of the pure pyrrolidylpyrrole in a mixture of 20 ml. of acetone and 20 ml. of methanol at Dry Ice temperature until absorption ceased. Then 1 g. of 5% palladium-on-charcoal was added to the reaction mixture, and hydrogen was bubbled through for 2 hours, at Dry Ice temperature. The solution was warmed to room temperature and filtered, and 6 ml. of 30% hydrogen peroxide was added to the filtrate. This mixture was allowed to stand overnight after which 20 ml. of water was added. This solution was stored over 6 g. of Dowex 50 ion exchange resin in a closed container for 24 hours. The resin was separated by filtration, and was eluted with dilute ammonia. The resulting solution, after removal of excess ammonia by evaporation, was analyzed by paper chromatography.

The circular filter paper chromatographic technique, with Whatman No. 1 filter paper, was employed. The chromatograms were developed with a 4:1:3 mixture of butanol, acetic acid and water. A solution of 0.4% isatin in butanol, with 4% acetic acid added, was used as indicator.

Chromatograms of the ozonolysis product solution and of a solution of known proline in water were run simultaneously under identical conditions. In chromatograms which were developed for 65 minutes, treatment with isatin gave a blue band at a distance of 28 mm. in both the ozonolysis mixture and the authentic proline.

Formation of proline by means of ozonolysis indicates that the pyrrole nucleus in the original pyrrolidylpyrrole is joined to the pyrrolidine ring at the 2-position.

1-Pyrroline–Pyrrole Condensations.—For the following reactions, 50-ml. aliquots were taken from a 1-pyrroline–

butanol solution, prepared as described previously. Catalytic hydrogenation of one portion showed absorption of 0.039 mole of hydrogen, indicating that each aliquot contained not more than 2.7 g. of 1-pyrroline.

3-Methylpyrrolidylpyrroles.—A mixture of 1.2 g. of 3-methylpyrrole, b.p. 143°, prepared by the method of Lancaster and VanderWerf,[25] and 50 ml. of pyrroline–butanol solution was refluxed for 24 hours. Vacuum distilling and then four vacuum sublimations of the residue gave 0.73 g. (33%) of a mixture of 3-methylpyrrolidylpyrrole, m.p. 85–97°. The picrate formed from methanolic solution was a deep red oil which could not be made to crystallize.

Anal. Calcd. for $C_9H_{14}N_2$: C, 72.0; H, 9.4; N, 18.7; mol. wt., 150. Found: C, 72.0; H, 9.5; N, 18.6; mol. wt., 153.

2-Methylpyrrolidylpyrroles.—A mixture of 6.8 g. of 2-methylpyrrole, b.p. 148°, and 50 ml. of pyrroline–butanol solution was refluxed for 22 hours. The low-boiling materials were boiled off at 0.5 mm. up to a temperature of 100°. This left 4.5 g. (79%) of a viscous yellow oil which could not be made to crystallize. The picrate, formed in methanolic solution, melted at 159.0–161.0°.

Anal. Calcd. for $C_{15}H_{17}N_5O_7$: C, 47.5; H, 4.5; N, 18.5. Found: C, 47.4; H, 4.6; N, 18.4.

2,5-Dimethyl-3-(2-pyrrolidyl)-pyrrole.—A mixture of 17 g. of 2,5-dimethylpyrrole, b.p. 63–65° at 19 mm., and 50 ml. of pyrroline butanol solution was refluxed for 17 hours. Vacuum distilling up to 50° at 0.25 mm. pressure left 3.2 g. of a viscous yellow residue. Vacuum sublimation gave 2.5 g. (40%) of 2,5-dimethyl-3-pyrrolidylpyrrole, a clear waxy solid. Crystallization from ethyl acetate gave 0.5 g. of white crystals, probably 2,5-dimethyl-3-(2-pyrrolidyl)-pyrrole.

Anal. Calcd. for $C_{10}H_{16}N_2$: C, 73.1; H, 9.8; N, 17.1; mol. wt., 164. Found: C, 73.2; H, 9.8; N, 16.9; mol. wt., 154.

3-(2-Pyrrolidyl)-indole.—A mixture of 2 g. of indole, 50 ml. of butanol–pyrrolidine and 5 ml. of pyrrolidine was refluxed for 30 hours. Vacuum drying and then vacuum sublimation of the residue and crystallization from ethyl acetate gave 1.2 g. (32%) of white crystals, probably 3-(2-pyrrolidyl)-indole, m.p. 135–140°. Recrystallization from ethyl acetate raised the melting point to 145.8–146.6°.

Anal. Calcd. for $C_{12}H_{14}N_2$: C, 77.4; H, 7.6; N, 15.0; mol. wt., 186. Found: C, 77.4; H, 7.6; N, 15.3; mol. wt., 183.

Attempted condensations of 1-pyrroline with 1-methylpyrrole and with carbazole gave only recovered starting materials.

Reaction of α-Tripiperideine with Pyrrole.—A mixture of 0.50 g. of pure α-tripiperideine, m.p. 61–63°, prepared by the method of Schöpf and Oechler,[14] and 10 g. of pyrrole was refluxed for 24 hours. Vacuum drying and then vacuum sublimation, gave 0.66 g. (74%) of a piperidylpyrrole, m.p. 87.5–90.5°.

Anal. Calcd. for $C_9H_{14}N_2$: C, 72.0; H, 9.4; N, 18.7; mol. wt., 150. Found: C, 72.0; H, 9.5; N, 18.9; mol. wt., 152.

LAWRENCE, KANSAS

[CONTRIBUTION FROM THE MOORE LABORATORY OF CHEMISTRY, AMHERST COLLEGE]

The Preparation of 1,5-Pyrindine[1]

BY MICHAEL M. ROBISON[2]

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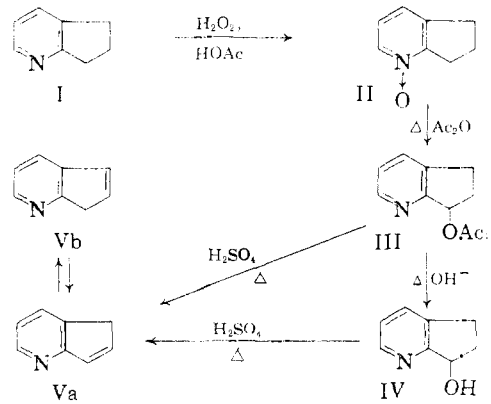
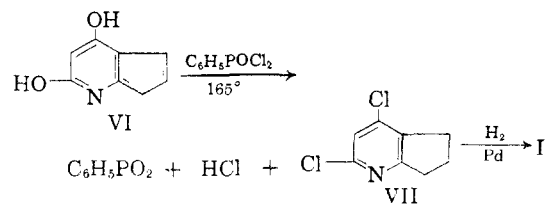
1,5-Pyrindine has been synthesized by treatment of 7-hydroxy-6,7-dihydro-1,5-pyrindine or its acetate ester with hot, concentrated sulfuric acid. The ester was prepared by treatment of 6,7-dihydro-1,5-pyrindine-N-oxide with acetic anhydride. Sodium bisulfite may be added to the rather unstable pyrindine in a manner apparently analogous to its addition to 2-vinylpyridine. Other chemical and physical properties of the unsaturated compound are described.

Although "pyrindane" (6,7-dihydro-1,5-pyrindine, I) and derivatives have been known for some time, no unsubstituted pyrindine has been prepared.[3] Perhaps the most purposeful approach to the synthesis of the unsaturated compound was that of Prelog and Szpilfogel[4] who attempted to dehydrogenate pyrindane. Dehydrogenation could not be effected either with palladium–charcoal at 350° or with selenium at 400°; in both cases starting material was recovered. Since the desired double bond could not be produced by this method, an alternative approach employed in this Laboratory involved the introduction of a functional group in the five-membered ring whose subsequent elimination resulted in unsaturation. This end was attained by rearrangement of pyrindane-N-oxide (II) on treatment with acetic anhydride.[5]



The requisite pyrindane was obtained *via* 2,4-dihydroxy-6,7-dihydro-1,5-pyrindine (VI) and the 2,4-dichloro derivative VII,[4] the former being



(1) This investigation was supported in part by a research grant, number C-2574, from the National Cancer Institute of the National Institutes of Health, Public Health Service.

(2) CIBA Pharmaceutical Products, Inc., Summit, N. J.

(3) R. C. Elderfield and E. T. Losin in Elderfield's "Heterocyclic Compounds," John Wiley and Sons, Inc., New York, N. Y., Vol. 3, 1952, p. 342.

(4) V. Prelog and S. Szpilfogel, *Helv. Chim. Acta*, **28**, 1684 (1945).

(5) *Cf.* G. Kobayashi and S. Furukawa, *Pharm. Bull. Japan*, **1**, 347 (1953); V. Boekelheide and W. J. Linn, THIS JOURNAL, **76**, 1286 (1954), and O. H. Bullitt and J. T. Maynard, *ibid.*, **76**, 1370 (1954), for analogous rearrangements with alkylpyridines.