pyridine methiodide in 30 ml. of methanol was reduced with 1.0 g. of sodium borohydride by rapid addition of the solution. The methanol was removed in an air stream, 30 ml. of 2% aqueous potassium hydroxide was added, and the mixture was then extracted with benzene. Upon drying of the combined benzene extracts and removal of solvent under vacuum, a white solid remained which sublimed at 100° (1 mm.), yield 0.1 g. (16%).

Anal. Calcd. for $C_{14}H_{16}N_2$: C, 79.21; H, 7.60; N, 13.20. Found: C, 79.38; H, 7.64; N, 13.20.

1-Phenylpyrrolo(3,2-c)pyridine.—A mixture consisting of 15 ml. of anhydrous toluene, 0.3 g. of 5% palladium-on-charcoal and 190 mg. of 1-phenyl-3,4-dihydropyrrolopyridine was refluxed for 7 hours. Upon filtration of the hot toluene solution and washing the catalyst with absolute ethanol, the combined toluene–ethanol phase on removal of solvent under reduced pressure gave a white residue. Recrystallization was carried out from benzene to yield 161 mg. (86%) of product, m.p. 201°. A mixed melting point with the starting material showed an 11° depression.

Anal. Calcd. for $C_{13}H_{10}N_2$: C, 80.38; H, 5.19; N, 14.42. Found: C, 80.42; H, 5.33; N, 14.20.

1-Phenyl-1,2,3,4-tetrahydropyrrolo(3,2-c)pyridine.—A solution of 270 mg. of 1-phenyl-3,4-dihydropyrrolo(3,2-c) pyridine in 30 ml. of anhydrous ether was added dropwise to a solution of 1.0 g. of lithium aluminum hydride in 25 ml. of anhydrous ether. The product was isolated in the usual manner using chloroform for extracting the inorganic residue to yield 240 mg. of a white crystalline material which sublimed at 140° (1 mm.), m.p. 159° after recrystallizing twice from anhydrous benzene.

Anal. Calcd. for $C_{13}H_{14}N_2$: C, 78.75; H, 7.12; N, 14.13. Found: C, 78.97; H, 7.18; N, 13.9.

Catalytic hydrogenation of 100 mg. of the dihydro compound in 35 ml. of methanol using 0.1 g. of platinum oxide gave 58 mg. of the tetrahydro derivative after removal of methanol and recrystallization from benzene.

1-Methyl-3,4-dihydropyrrolo(3,2-c)pyridine.—Cyclization of 1.83 g. of N-acetyl-2-(2-pyrrole)-ethylamine gave 0.29 g. (18%) of product. The analytical sample, m.p. 189°, was prepared by sublimation at 120° (1 mm.) and recrystallization from benzene and acetonitrile.

Anal. Calcd. for $C_8H_{10}N_2$: C, 71.61; H, 7.51; N, 20.86. Found: C, 71.68; H, 7.63; N, 21.2.

The methiodide melted at 203° after two recrystallizations from absolute ethanol.

Anal. Calcd. for $C_9H_{13}N_2I$: N, 10.15. Found: N, 10.10.

The infrared spectrum of the base has a 1620 cm.$^{-1}$ band which is in the C=N absorption region. The ultraviolet spectrum in 95% ethanol shows a minimum at 241 mμ (log ε 3.6) and maxima at 222 and 260 mμ (log ε's 4.88, 3.80).

1,2-Dimethyl-1,2,3,4-tetrahydropyrrolo(3,2-c)pyridine.—One-half of a gram of 1-methyl-3,4-dihydropyrrolo(3,2-c)-pyridine methiodide in 20 ml. of methanol was reduced with 1.0 g. of sodium borohydride and the product isolated in the manner described above for the phenyl homolog. The base did not sublime but boiled at a bath temperature of 135° (1 mm.) to give 0.14 g. of a colorless mass which crystallized on standing. It could not be recrystallized satisfactorily and was therefore identified through the brilliant white crystalline methiodide, yield 0.3 g., m.p. 182° after recrystallization from absolute ethanol.

Anal. Calcd. for $C_{10}H_{17}N_2I$: C, 41.11; H, 5.86; N, 9.59. Found: C, 41.61; H, 6.13; N, 9.25.

1-Methylpyrrolo(3,2-c)pyridine.—A solution of 179 mg. of 1-methyl-3,4-dihydropyrrolo(3,2-c)pyridine in 20 ml. of anhydrous toluene was treated with 0.39 g. of 10% palladium-on-charcoal and refluxed for 7 hours. Upon isolation in the same manner as described above for the phenyl homolog and recrystallization from toluene, 148 mg. (84%) of white crystals was obtained, m.p. 168–168.5°.

Anal. Calcd. for $C_8H_8N_2$: C, 72.70; H, 6.10; N, 21.2. Found: C, 72.33; H, 6.30; N, 21.05.

The ultraviolet spectrum in 95% ethanol has a minimum at 236 mμ (log ε 3.65); maxima at 220 and 272 mμ (log ε's 4.90, 4.05).

1-Methyl-1,2,3,4-tetrahydropyrrolo(3,2-c)pyridine.—1-Methyl-3,4-dihydropyrrolo(3,2-c)pyridine (105 mg.) in a Soxhlet apparatus was reduced with 1.0 g. of lithium aluminum hydride in 50 ml. of ether. Upon destroying excess hydride with 2% aqueous potassium hydroxide, decantation of the ethereal phase and extraction of the residue with chloroform, 101 mg. of the relatively pure base was obtained from the combined organic solutions. This base sublimed at 115–118° (1 mm.) and recrystallized from benzene to a constant m.p. of 142°, yield 89 mg. (83%).

Anal. Calcd. for $C_8H_{12}N_2$: C, 70.55; H, 8.88; N, 20.57. Found: C, 70.71; H, 8.88; N, 20.4.

The infrared spectrum shows no absorption band in the C=N 1600–1650 cm.$^{-1}$ region.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE FLORIDA STATE UNIVERSITY]

The Pomeranz–Fritsch Reaction in the Pyrrole Series. The Synthesis of Apoharmine[1]

BY WERNER HERZ AND STANLEY TOCKER

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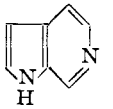
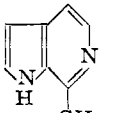
Cyclization of the amino acetals of 2-pyrrolealdehyde and 2-acetylpyrrole results in two types of products, pyrrolo[2,3-c]-pyridines and pyrrolo[1,2-a]pyrazines, the latter being formed in larger amounts. The first direct synthesis of apoharmine is reported.

The occurrence of the pyrrolo[2,3-c]pyridine or 6-azaindole nucleus (I) in the skeletal structure of many alkaloids suggests that a facile route to this ring system might provide compounds of synthetic and pharmacological interest. However the literature dealing with this subject is scanty. The preparation of 6-methylpyrrolo[2,3-c]pyridine in 23% yield by a Madelung cyclization of N-acetyl-3-amino-4-picoline has been described.[2] 2,6-Dimethyl-5-carbethoxy-1,2,3,4-tetrahydropyrrolopyridine has been synthesized[3] by condensing 3-hydroximino-1-methyl-4-piperidone with acetoacetic ester in the presence of zinc dust.



I



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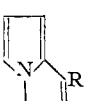

III

Perhaps the best-known representative of this group of compounds is apoharmine (II). The value of II in establishing the structure of the harmala alkaloids is discussed in several reviews.[4] Lawson,

(1) Supported in part by Grant RC-3097 from the United States Public Health Service, Department of Health, Education and Welfare. A preliminary account of this work was published in *Chemistry and Industry*, 603 (1954).

(2) E. Koenigs and A. Fulde, *Ber.*, **60**, 2106 (1927).

(3) G. H. Cookson, *J. Chem. Soc.*, 2789 (1953).

(4) L. Marion, "The Indole Alkaloids," in R. H. F. Manske and H. L. Holmes, ed., "The Alkaloids," Academic Pres, Inc., New York, N. Y., Vol. II, 1952, p. 369.

Perkin and Robinson[5] reported the isolation of a minute amount of II by oxidative and pyrolytic degradation of synthetic methyldiveratroharmyrine. On the other hand, Clemo and Holt[6] state that their efforts to prepare II by Fischer indole closure of the 2-methyl-3-pyridylhydrazone of ethyl pyruvate have so far been unsuccessful.

Although many indole derivatives have been cyclized to β-carbolines[7] there thus exists no example of the direct synthesis of a pyrrolo[2,3-c]pyridine from a pyrrole, presumably because of the poor prospects of applying successfully standard isoquinoline synthesis to simple pyrroles.[8] The success accomplished with other acid-sensitive compounds[9] led us to investigate the applicability of the Pomeranz–Fritsch reaction in the pyrrole series.

2-Pyrrolealdehyde, 2-acetylpyrrole and N-methyl-2-pyrrolealdehyde were condensed with aminoacetal by azeotropic distillation from toluene solution.[10] Cyclization of 2-pyrrolealdehyde aminoacetal with phosphorus oxychloride in refluxing toluene gave an oil which was assumed to be pyrrolo(2,3-c)pyridine (I) on the basis of its elemental analysis. However, cyclization of 2-acetylpyrrole aminoacetal gave rise to two basic fractions, an oil A and a crystalline solid B. The crystalline material was identified as apoharmine by elemental analysis, melting point, melting point of its picrate and ultraviolet absorption spectrum[11] (λ_{max} 224, 260 and 290 mμ, λ_{min} at 237 and 272 mμ; log ϵ_{max} 4.54, 3.86, 4.00, log ϵ_{min} 3.48, 3.76).

This prompted reinvestigation of the first cyclization. Use of a mixture of phosphorus oxychloride and polyphosphoric acid demonstrated that cyclization of 2-pyrrolealdehyde aminoacetal also gave two distinct basic products. The spectrum of the solid fraction (λ_{max} 218, 263 and 296 mμ, λ_{min} 238 and 277 mμ; log ϵ_{max} 4.78, 2.92 and 4.02, log ϵ_{min} 3.34 and 3.78) closely resembled that of apoharmine and the compound is therefore the sought-after pyrrolo(2,3-c)pyridine (6-azaindole). Elemental analysis of the oils indicated that they were isomers of the solids. The absence of strong NH frequencies from the 3200–3800 cm.$^{-1}$ regions of the infrared spectra suggested that ring closure had occurred on the pyrrole nitrogen giving rise to pyrrolo(1,2-a)pyrazines (III, R = H and CH_3). The ultraviolet spectra of the two substances were very similar (III, R = H, λ_{max} 230, 280, 330 and 372 mμ, λ_{min} 248, 300 and 365 mμ; log ϵ_{max} 3.50, 2.70, 2.52 and 2.02, log ϵ_{min} 2.08, 2.15, and 1.95; III, R = CH_3, λ_{max} 230, 280, 330 and 360 mμ, λ_{min} 247, 298 and 357 mμ; log ϵ_{max} 3.45, 3.58, 3.30, and 1.95, log ϵ_{min} 2.15, 2.05 and 1.75). The position of the peaks indicates the presence of an extended conjugated system as might be expected in structures of type III.

To prove this point more conclusively, the cyclization of N-methyl-2-pyrrolealdehyde aminoacetal was studied. As expected, blocking of the pyrrole nitrogen atom resulted in the formation of a single product whose spectrum was very similar to that of apoharmine (λ_{max} 223, 262 and 307 mμ, λ_{min} 246 and 278 mμ; log ϵ_{max} 4.58, 3.72 and 4.06, log ϵ_{min} 3.52 and 3.48). It is therefore 7-methylpyrrolo(2,3-c)pyridine (IV).

These observations find a parallel in reports describing the acid-induced ring closure of 2-substituted indoles. Thus, acylaminoacetals of 2-indolecarboxylic acid may furnish pyrazino(1,2-a)indolones, 2,9-pyrid(3,4-b)indolones or mixtures of the two.[12] We hope to study this situation in the pyrrole series.

In the competitive ring closures the yields of compounds of type III were considerably greater than those of the pyrrolo(2,3-c)pyridines and indicate a pronounced preference for attack on nitrogen. The yields of apoharmine by the phosphorus oxychloride–polyphosphoric acid method were therefore quite low (5.1%) but reproducible. Several early experiments in which 2-acetylpyrrole aminoacetal was added slowly to a solution of phosphorus oxychloride in toluene furnished considerably more apoharmine (25–35%), but repeated efforts to duplicate these yields failed.

Attempts to prepare the aminoacetal of 2-homoveratroylpyrrole, which was intended to serve as a precursor of 1-(3,4-dimethoxybenzyl)-pyrrolo(2,3-c)pyridine, a pyrrole analog of papaverine, gave only starting material or tars, even in the presence of zinc chloride.[13] An alternative method called for the condensation of glyoxal semiacetal[14] with 1-(2-pyrrole)-2-(3,4-dimethoxyphenyl)-ethylamine. However, the yield of the oxime of 2-homoveratroylpyrrole was very poor even after prolonged refluxing, probably due to steric hindrance and a competitive ring-opening reaction.[15] Reduction of the oxime by various methods gave substances which decomposed too rapidly to permit identification.

Acknowledgment.—We are grateful to E. I. du Pont de Nemours and Co., Inc., and to the Monsanto Chemical Co. for the gift of chemicals.

Experimental[16]

2-Pyrrolealdehyde Aminoacetal.—A mixture of 8.0 g. of 2-pyrrolealdehyde, 13.0 g. of aminoacetaldehyde diethyl-

(5) W. Lawson, W. H. Perkin and R. Robinson, *J. Chem. Soc.*, 626 (1924).

(6) G. R. Clemo and R. J. W. Holt, *ibid.*, 1313 (1953).

(7) For references see the reviews by W. M. Whaley and T. R. Govindachari in "Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., Vol. VI, 1951, p. 74, and by W. J. Gensler in R. C. Elderfield, ed., "Heterocyclic Compounds," John Wiley and Sons, Inc., New York, N. Y., Vol. IV, 1952.

(8) A possible exception is the cyclization of porphobilinogen to a substance believed to be 5-(2-carboxyethyl)-3-keto-1,2,3,4-tetrahydropyrrolo(2,3-c)pyridine which has been reported recently by G. H. Cookson, *Nature*, **172**, 457 (1953).

(9) (a) W. Herz, THIS JOURNAL, **73**, 351 (1951); W. Herz and Lin Tsai, *ibid.*, **75**, 5122 (1953); **77**, 3529 (1955); (b) W. Herz and S. Tocker, *ibid.*, **77**, 3554 (1955).

(10) These conditions were suggested by the relative lack of reactivity which is ascribed to 2-pyrrolealdehyde by H. Fischer and H. Orth, "Die Chemie des Pyrrols," Akademische Verlagsgesellschaft, Leipzig, Vol. I, 1951. The yields, 58% from pyrrolealdehyde, 91% from N-methyl-2-pyrrolealdehyde, 92% from furfural,[9b] support the statements of the German authors.

(11) H. Schwarz and E. Schlittler, *Helv. Chim. Acta*, **34**, 629 (1951).

(12) W. O. Kermack, W. H. Perkin and R. Robinson, *J. Chem. Soc.*, **121**, 1872 (1922); J. R. Johnson, A. A. Larson, A. D. Holley and K. Gerzon, THIS JOURNAL, **69**, 2364 (1947).

(13) G. Reddelien, *Ann.*, **388**, 165 (1921); *Ber.*, **43**, 2476 (1910).

(14) E. Schlittler and J. Müller, *Helv. Chim. Acta*, **31**, 914 (1948).

(15) G. Ciamician, *Ber.*, **37**, 4200 (1904).

(16) Melting points and boiling points are uncorrected. Analyses by Drs. Weiler and Strauss, Oxford. Ultraviolet spectra were determined by Mrs. Shirley Ann Pinner with a Beckman model DK automatic recording spectrophotometer. Infrared spectra were run by Mr. Dean S. Keeley on a Perkin–Elmer model 21 recording spectrophotometer.

acetal (aminoacetal) and 35 ml. of toluene was refluxed in a flask fitted with a Dean–Stark trap of 20-ml. capacity until there was no increase in the volume of the water phase formed (about 20 minutes). Solvent and excess aminoacetal were removed at 2 mm. pressure, and the residue was distilled at the lowest possible bath temperature, b.p. 119–125° (2 mm.), n_D^{21} 1.4731, yield 10.3 g. (58%). The reaction conditions are quite critical. Because of the instability of the product, it was analyzed as the picrate, m.p. 173°.

Anal. Calcd. for $C_{17}H_{21}N_5O_9$: N, 15.99. Found: N, 16.00.

2-Acetylpyrrole Aminoacetal.—A mixture of 5.0 g. of 2-acetylpyrrole, 10 g. of aminoacetal and 35 ml. of toluene was refluxed as outlined in the previous section. The yellow condensation product boiled at 126–130° (2 mm.), n_D^{20} 1.5125, yield 7.8 g. (81%), and was converted to the picrate, m.p. 118°, for analysis.

Anal. Calcd. for $C_{18}H_{23}N_5O_9$: N, 15.45. Found: N, 15.80.

N-Methyl-2-pyrrolealdehyde Aminoacetal.—Condensation of 7.0 g. of N-methyl-2-pyrrolealdehyde, prepared by adapting the method of Smith[17] to N-methylpyrrole, with 15.0 g. of aminoacetal afforded 13.1 g. (91%) of a colorless oil which darkened rapidly, b.p. 94° (0.5 mm.), $n^{20}D$ 1.5988.

Anal. Calcd. for $C_{12}H_{20}N_2O_2$: C, 64.25; H, 8.99. Found: C, 63.77; H, 9.44.

Cyclization of 2-Pyrrolealdehyde Aminoacetal.—To polyphosphoric acid (15 g.) heated to 100° was added 2.0 ml. of phosphorus oxychloride with manual stirring. The heating was discontinued and 2.1 g. of the aminoacetal derivative was added dropwise immediately to this mixture with vigorous stirring over a 10-minute period. The temperature was then raised to 120° as soon as addition was completed and held at this level until no additional hydrogen chloride was evolved. After allowing the mixture to cool, it was dissolved in 150 ml. of water. The aqueous solution was extracted with benzene, basified and again extracted with sufficient benzene to remove all soluble organic material. The combined benzene extracts of the basified solution were dried over anhydrous sodium sulfate, evaporated and distilled. The colorless oil distilling at 71° (2 mm.), n_D^{20} 1.6176, yield 0.25 g. (21%), was found to be pyrrolo(1,2-a)pyrazine. Since this base darkened rapidly, it was analyzed as the picrate, m.p. 212°.

Anal. Calcd. for $C_{13}H_9N_5O_7$: C, 44.96; H, 2.61; N, 20.17. Found: C, 44.94; H, 2.74; N, 20.2.

The ultraviolet spectrum of pyrrolo(1,2-a)pyrazine, determined in isoöctane solution, was discussed earlier.

The solid pyrrolo(2,3-c)pyridine remaining in the microstill sublimed in the delivery tube. Resublimation of this material was effected at 130° (1 mm.), and recrystallization was carried out from benzene to a constant melting point of 129.5°, yield 22 mg. (2.2%).

Anal. Calcd. for $C_7H_6N_2$: C, 71.16; H, 5.12; N, 23.71. Found: C, 70.87; H, 5.21; N, 24.0.

The ultraviolet spectrum of this substance was determined in 95% ethanol, because of its limited solubility in isoöctane.

Many other experiments in which time, temperature, solvent and order of addition were varied gave irreproducible results. Frequently starting material accompanied the basic products and could not be separated satisfactorily. This suggests that the aminoacetal is capable of forming a toluene-insoluble quaternary salt which precipitates and is therefore prevented from undergoing cyclization.

Cyclization of 2-Acetylpyrrole Aminoacetal.—The aminoacetal derivative (1.2 g.), cyclized in the same manner as for 2-pyrrolealdehyde aminoacetal, gave 0.23 g. (23%) of 1-methylpyrrolo(1,2-a)pyrazine, b.p. 82° (1.5 mm.) n_D^{20} 1.6910. The unstable oil was analyzed through its picrate, m.p. 230°.

Anal. Calcd. for $C_{14}H_{11}N_5O_7$: N, 19.39. Found: N, 19.20.

The solid material remaining in the distilling flask sublimed at 168° (1 mm.). Recrystallization from benzene to a constant m.p. of 183° (lit.[5,8] 183°) gave 36 mg. (5.1%) of apoharmine.

Anal. Calcd. for $C_8H_8N_2$: C, 72.69; H, 6.10; N, 21.20. Found: C, 73.09; H, 6.09; N, 21.28.

Cyclization of N-Methyl-2-pyrrolealdehyde Aminoacetal.—Cyclization of 2.0 g. of this substance in the manner described previously gave 0.32 g. (27%) of a yellow oil, b.p. 140–141° (11 mm.), $n^{20}D$ 1.6932, whose spectrum identified it as N-methylpyrrolo(2,3-c)pyridine.

Anal. Calcd. for $C_8H_8N_2$: C, 72.70; H, 6.10; N, 21.2. Found: C, 72.39; H, 6.50; N, 20.8.

The picrate melted at 194–195°.

Anal. Calcd. for $C_{14}H_{11}N_5O_7$: C, 46.54; H, 3.07; N, 19.4. Found: C, 46.46; H, 3.31; N, 19.1.

2-Homoveratroylpyrrole.—Under anhydrous conditions a solution of 16.0 g. (0.103 mole) of ethyl iodide in 40 ml. of anhydrous ether was added dropwise to a stirred mixture of 8.0 g. (0.33 mole) of magnesium turnings and 40 ml. of ether in a flask surrounded by an ice-bath. The resultant mixture was then stirred for 45 minutes at room temperature and 6.8 g. (0.101 mole) of pyrrole in 50 ml. of ether was added dropwise to the cooled solution at 5–10°. After stirring the reactants for 30 minutes at room temperature, 20.0 g. (0.093 mole) of freshly distilled homoveratroyl chloride in 100 ml. of ether was added slowly under vigorous stirring, the reactor being surrounded by an ice–salt-bath. Stirring was continued overnight while the bath was permitted to melt, and then 250 ml. of aqueous concentrated ammonium chloride solution was added under vigorous stirring. Benzene (100 ml.) was added and the mixture was vigorously stirred for 10 minutes. The separated benzene–ether phase was washed with 20 ml. of an aqueous concentrated ammonium chloride solution, dried over anhydrous sodium sulfate and stripped of solvent at reduced pressure. Upon dissolving the oily residue in 50 ml. of anhydrous benzene and adding sufficient ligroin to produce incipient turbidity, a brown tar and white solid separated consecutively. Fractional precipitation yielded 1.8 g. (7.2%) of the white solid which was purified further by recrystallization from benzene and ligroin, m.p. 99°.

Anal. Calcd. for $C_{14}H_{15}NO_3$: C, 68.52; H, 6.16; N, 5.71. Found: C, 68.63; H, 6.24; N, 5.45.

Attempts to prepare the oxime of this ketone by treatment with hydroxylamine hydrochloride in the presence of base gave only starting material and tar. On refluxing 1.48 g. of the ketone with 4.0 g. of hydroxylamine hydrochloride in 10 ml. of pyridine for 24 hours, 0.13 g. of an oxime, m.p. 170–171° after recrystallization from absolute ethanol, could be isolated. Shorter periods gave only starting material and traces of oxime.

Anal. Calcd. for $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.20; N, 10.76. Found: C, 64.50; H, 6.13; N, 10.6.

Catalytic hydrogenation of 0.2 g. of oxime in 80 ml. of ethanol with 0.1 g. of platinum oxide at about two atmospheres pressure gave upon removal of solvent a white solid residue which resinified too quickly to permit identification. Lithium aluminum hydride reduction by the Soxhlet method also failed to give a stable product.

An attempt to reduce 2-homoveratroyl pyrrole in ammoniacal solution[18] gave only a brown intractable tar.

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(17) G. F. Smith, *J. Chem. Soc.*, 3842 (1954).

(18) E. R. Alexander and A. L. Misegades, THIS JOURNAL, **70**, 1315 (1948).