logically similar materials may owe much of their growth-promoting properties to certain nitrogen-free substances not hitherto recognized as being active in this manner. Bioassays carried out in this Laboratory have also disclosed activity in certain other substances, both natural and synthetic. The recent isolation and identification of "kinetin" as 6-furfurylaminopurine by Miller, *et al.*,[15] adds a compound of a still different structural type to the growing list of such active substances. Detailed data on the biological responses to all of the above-mentioned substances, which bear no obvious chemical relationship to one another, will be presented elsewhere. However, their effects on the growth of various plant tissue cultures and their obvious interactions with casein hydrolysate, natural hormones such as indoleacetic acid, and synthetic growth regulators of the general type of 2,4-D, all emphasize that no single substance is the sole answer to the chemical induction of growth by cell division in plants.

ITHACA, N.Y.

(15) C. O. Miller, F. Skoog, F. S. Okumura, M. H. Von Saltza and F. M. Strong, THIS JOURNAL, **77**, 2662 (1955).

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

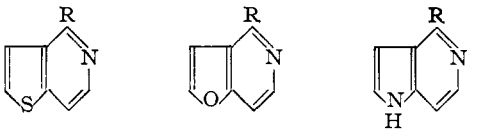
Pyrrolo[3,2-c]pyridines[1]

BY WERNER HERZ AND STANLEY TOCKER

RECEIVED MAY 31, 1955

The Bischler–Napieralski reaction has been applied successfully to derivatives of 2-(2-pyrrole)-ethylamine. The resulting dihydropyrrolo[3,2-c]pyridines were aromatized and their reduction to tetrahydro derivatives was accomplished. N-Formyl- and N-homoveratroyl-2-(2-pyrrole)-ethylamine could not be cyclized.

Earlier papers[2,3] of this series showed that sulfur (I) and oxygen (II) analogs of isoquinolines could be prepared by suitable modifications of the Bischler–Napieralski reaction from derivatives of thiophene and furan. In this paper we report the synthesis of the corresponding nitrogen analogs (III), pyrrolo[3,2-c]pyridines or 5-azaindoles.

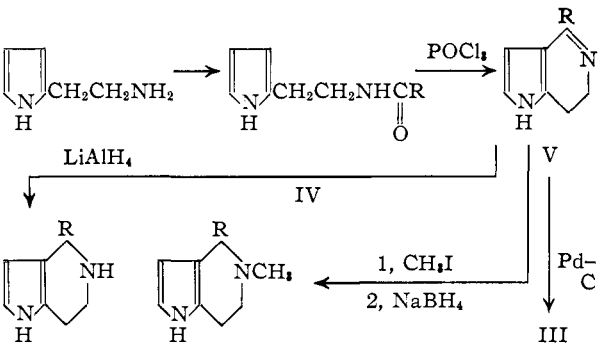


I II III

The only previously reported representative of this class of compounds, 6-methylpyrrolo[3,2-c]pyridine (2-methyl-5-azaindole), was prepared by Clemo and Swan[4] in 1% yield through the Madelung cyclization of 4-acetamido-3-picoline. Their efforts to synthesize 5-azaindole itself were unsuccessful. Our experience with N-acyl-2-(2-furyl)-ethylamines[3] and the availability of 2-(2-pyrrole)-ethylamines[5] suggested the possibility of synthesizing pyrrolo[3,2-c]pyridines by the Bischler–Napieralski method.

The sequence of reactions leading to pyrrolo[3,2-c]pyridines (III) is illustrated in the chart.

Cyclizations with phosphorus oxychloride in toluene were carried out in the mannner described for furan derivatives.[3] N-Benzoyl-2-(2-pyrrole)-ethylamine and the N-acetyl homolog were cyclized to 1-phenyl- and 1-methyl-3,4-dihydropyrrolo[3,2-c]-pyridines (V, R = phenyl, CH_3) in 24 and 18% yield while the N-homoveratroyl- and N-formyl-amides gave only amorphous solids which could not be purified sufficiently for elemental analysis. These yields are somewhat lower than the ones obtained in the thiophene and furan series.



R = H, CH_3, phenyl, 3,4-dimethoxybenzyl

Dehydrogenation of V (R = CH_3 and phenyl) to the completely aromatic 1-substituted pyrrolo[3,2-c]pyridines (III, R = CH_3 and phenyl) was accomplished in good yield by refluxing with palladium-on-charcoal in toluene solution. Spectroscopic evidence for successful aromatization is the observation that the second absorption band of III (R = CH_3) occurs at somewhat longer wave lengths (λ_{max} 220 and 272 mμ, λ_{min} 236 mμ; log ϵ_{max} 4.90 and 4.05, log ϵ_{min} 3.65) than the second band of V (R = CH_3) (λ_{max} at 222 and 260 mμ, λ_{min} 241 mμ; log ϵ_{max} 4.88 and 3.80, log ϵ_{min} 3.6).[6] Furthermore there is a pronounced similarity in the spectra of III, indole[7] and 7-azaindole[8] which supports the postulated structures.

1-Phenyl- and 1-methyl-3,4-dihydropyrrolo(3,2-c)pyridine were reduced by lithium aluminum hy-

(1) Supported in part by Grant RC-3097 from the United States Public Health Service, Department of Health, Education and Welfare.

(2) W. Herz, THIS JOURNAL, **73**, 351 (1951); W. Herz and Lin Tsai, *ibid.*, **77**, 3529 (1955).

(3) W. Herz and S. Tocker, *ibid.*, **77**, 3554 (1955).

(4) G. R. Clemo and G. A. Swan, *J. Chem. Soc.*, 198 (1948).

(5) W. Herz, THIS JOURNAL, **75**, 483 (1953).

(6) The spectra were determined in 95% ethanol and are very similar to those of the corresponding thieno[2,3]- and furano(3,2-c)pyridines.

(7) R. A. Friedel and M. Orchin, "Ultraviolet Spectra of Aromatic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1951.

(8) M. E. Robison and B. L. Robison, THIS JOURNAL, **77**, 457 (1955).

dride or more conveniently by catalytic hydrogenation at low pressure to the corresponding 1-substituted-1,2,3,4-tetrahydropyrrolo(3,2-c)pyridines (VI). A band occurring at 1620 cm.$^{-1}$ in the infrared spectra of V can be ascribed to the C=N function because it disappears on reduction. Reduction of the methiodides of V by the method of Whaley and Robinson[9] furnished low yields of 1-substituted-2-methyl-1,2,3,4-tetrahydropyrrolo-(3,2-c)pyridines (VII).

All of the compounds described in this paper gave a positive Ehrlich test[10] which is characteristic of pyrroles containing at least one unsubstituted α-position. Some of them are being tested pharmacologically.

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[11]

2-(2-Pyrrole)-ethylamine.—In the preparation of 2-pyrroleacetonitrile, repetition of the earlier work[5] on a larger scale gave poor yields of the nitrile and much intractable residue. A number of experiments carried out at different concentrations, in which the heating period was varied, showed that the displacement reaction on a large scale could be carried out successfully by using more concentrated solutions. Possibly, the more rapid formation of the nitrile under these conditions reduced side reactions such as hydrolysis and resinification. Thus, a solution of 90 g. of dimethylaminomethylpyrrole methiodide in 100 ml. of water when added to a solution of 45 g. of sodium cyanide in 125 ml. of water and refluxing for one hour furnished 22.8 g. (63.5%) of the nitrile, b.p. 110–115° (2 mm.).

In an attempt to improve the yield of the amine, customarily prepared by lithium aluminum hydride reduction,[5] a solution of 3.4 g. of the nitrile in 35 ml. of methanol saturated with ammonia was hydrogenated at a pressure of 2 atmospheres with platinum oxide as catalyst. The theoretical amount of hydrogen was absorbed in 2.5 hours. Distillation gave 0.7 g. of 2-(2-pyrrole)-ethylamine, b.p. 91–92° (1.7 mm.), and 1.1 g. of a viscous oil, b.p. 190° (2 mm.). Its analysis showed that it was di-(2-(pyrrole)-ethyl)-amine.

Anal. Calcd. for $C_{11}H_{15}N_3$: C, 70.21; H, 8.55. Found: C, 69.81; H, 7.99.

N-Benzoyl-2-(2-pyrrole)-ethylamine.—To 1.0 g. of 2-(2-pyrrole)-ethylamine in 25 ml. of water was added dropwise with shaking 2.0 g. of benzoyl chloride. Immediately after addition was completed, sufficient aqueous 10% sodium hydroxide was added dropwise with vigorous shaking to make the mixture slightly basic. The reactants were extracted with chloroform, dried over anhydrous sodium sulfate, stripped of solvent and sublimed at 83° (0.5 mm.). Recrystallization from benzene to a constant m.p. of 110° gave 1.6 g. (83.5) of product.

Anal. Calcd. for $C_{13}H_{14}N_2O$: C, 72.87; H, 6.59; N, 13.08. Found: C, 72.67; H, 6.66; N, 12.9.

N-Formyl-2-(2-pyrrole)-ethylamine.—A mixture of 0.50 g. of 2-(2-pyrrole)-ethylamine and 10.0 g. of ethyl formate was refluxed on a steam-bath for seven hours. Excess ethyl formate was removed at reduced pressure and the residue was distilled at 165° (1 mm.), $n^{20}D$ 1.5418, yield 0.46 g. (73%).

Anal. Calcd. for $C_7H_{10}N_2O$: C, 60.87; H, 7.30. Found: C, 60.89; H, 7.51.

(9) W. M. Whaley and C. N. Robinson, THIS JOURNAL, **75**, 2008 (1953).

(10) H. Fischer and H. Orth, "Die Chemie des Pyrrols," Vol. 1, Akademische Verlagsgesellschaft, Leipzig, 1934, p. 66.

(11) 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.

Attempts to cyclize this material by methods successful for derivatives of 2-(2-furyl)-ethylamine and 2-acetylpyrrole aminoacetal gave only traces of a solid basic material which could not be satisfactorily purified for analysis by chromatography, sublimation or recrystallization.

N-Acetyl-2-(2-pyrrole)-ethylamine.—Ten grams of the amine in 60 ml. of water was treated portionwise with 40 ml. of acetic anhydride with vigorous stirring or shaking of the reactor. The mixture was made slightly basic with concentrated aqueous potassium hydroxide solution and was then saturated with potassium carbonate. Isolation of the amide was conveniently carried out by 4 extractions with 10-ml. portions of acetone, removal of acetone on a steam-bath from the combined extracts and distillation of the residue to give 11.9 g. (86%) of colorless oil, b.p. 163° (1 mm.), $n^{20}D$ 1.5293.

Anal. Calcd. for $C_8H_{12}N_2O$: C, 63.13; H, 7.95. Found: C, 63.09; H, 7.90.

N-Homoveratroyl-2-(2-pyrrole)-ethylamine.—Two grams of the amine in 25 ml. of water was treated portionwise with 4.0 g. of freshly distilled homoveratroyl chloride with vigorous shaking of the reactor, and the resultant mixture was made basic with concentrated aqueous potassium hydroxide. A yellow oil separated out which solidified gradually. Recrystallization was carried out from benzene to a constant melting of 105°, yielding 2.5 g. (48%) of white crystals.

Anal. Calcd. for $C_{16}H_{20}N_2O_3$: C, 66.64; H, 6.99; N, 9.72. Found: C, 66.78; H, 7.09; N, 9.9.

Attempts to cyclize this amide by phosphorus oxychloride in refluxing toluene as described below or in combination with polyphosphoric acid failed to give a purifiable basic constituent. A granular brown base was obtained which could not be purified or decolorized through chromatography, recrystallization, treatment with activated charcoal or sublimation. Trial cyclizations with phosphorus oxychloride in toluene behaved differently from successful cyclizations in that there was no discernible induction period before material began to deposit on the reactor surface. Attempts to aromatize the brown base by refluxing with palladium-on-charcoal in toluene solution failed.

General Method of Cyclization for Amides of 2-(2-Pyrrole)-ethylamine.—The cyclization of pyrrole derivatives proceeded at about the same rate as that of furans and hydrogen chloride was evolved continuously as the quaternary salt of the dihydropyrrolo(3,2-c)pyridine precipitated from solution. The amide (0.5–0.6 g.) in 250 ml. of refluxing toluene under anhydrous conditions was treated dropwise with 75 ml. of toluene solution containing a molar quantity of phosphorus oxychloride. Addition was carried out over a period of approximately 20 minutes, and an additional refluxing period of 3 hours was employed to ensure complete conversion. Since the desired salt seemed to be entrained in resin formed in a competitive reaction, it was necessary to wash the reactor contents several times with hot water for complete hydrolysis and solution of the desired basic salt. The aqueous solution (100–250 ml.) was allowed to cool, permitting a fibrous material to be observed in suspension. It was found to be expedient to filter off this apparently inert material in order to preclude emulsions in subsequent extractions. The aqueous phase was extracted twice with 20-ml. portions of chloroform and then made basic with concentrated aqueous potassium hydroxide, liberating the dihydropyrrolopyridine. Repeated extraction with 30-ml. portions of benzene, drying of the combined benzene phases over anhydrous sodium sulfate and azeotropic distillation of water gave an orange or yellow solution. Removal of benzene at reduced pressure left a relatively pure basic residue.

1-Phenyl-3,4-dihydropyrrolo(3,2-c)pyridine.—Two grams of N-benzoyl-2-(2-pyrrole)-ethylamine gave 0.89 g. (24%) of base which sublimed at 163° (1 mm.), m.p. 212° upon recrystallization from benzene and acetonitrile.

Anal. Calcd. for $C_{13}H_{12}N_2$: C, 79.51; H, 6.12; N, 14.28. Found: C, 78.80; H, 5.96; N, 14.30.

The methiodide recrystallized from absolute ethanol melted at 214°.

Anal. Calcd. for $C_{14}H_{15}N_2I$: C, 49.71; H, 4.47; N, 8.29. Found: C, 50.00; H, 4.68; N, 8.05.

2-Methyl-1-phenyl-1,2,3,4-tetrahydropyrrolo(3,2-c)pyridine.—One gram of 1-phenyl-3,4-dihydropyrrolo(3,2-c)-

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.

TALLAHASSEE, FLORIDA

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

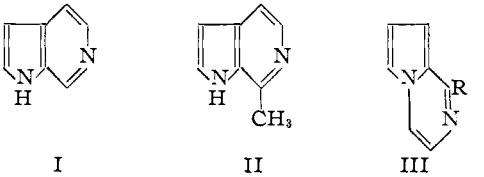
The Pomeranz–Fritsch Reaction in the Pyrrole Series. The Synthesis of Apoharmine[1]

BY WERNER HERZ AND STANLEY TOCKER

RECEIVED MAY 31, 1955

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 II 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.