The basic resonance integrals were taken in the ratio given by Kopineck's Tables.[32] For the repulsion integrals, both a point charge approximation[33] and the Kopineck values were tried.

(32) V. H. J. Kopineck, *Z. Naturforsch., A*, 5, 420 (1950).
(33) We find that the atomic positions are too close for the point charge approximation to give optimum results for repulsion integrals.

Acknowledgment. Support of this research by the National Science Foundation, National Institutes of Health Grant GM07487, Army Research Office, Durham, and partial support by the Petroleum Research Fund of the American Chemical Society and the Wisconsin Alumni Research Foundation is gratefully acknowledged.

Pyrroles from Azaindoles. A Synthesis of Porphobilinogen and Related Pyrroles[1,2]

Benjamin Frydman, Santiago Reil, Maria E. Despuy,[3] and Henry Rapoport

Contribution from the Facultad de Farmacia y Bioquimica, Universidad de Buenos Aires, Buenos Aires, Argentina, and the Department of Chemistry, University of California, Berkeley, California. *Received November 8, 1968*

Abstract: A new method for the synthesis of 2-aminomethyl-3-pyrroleacetic acids is described. The condensation of 2-methoxy- and 2-benzyloxy-4-methyl-5-nitropyridine with diethyl oxalate afforded the corresponding ethyl *o*-nitropyridinepyruvates, which on hydrogenation were transformed into the substituted ethyl 6-azaindole-2-carboxylates. Cleavage of the ethers and hydrogenation of the resulting pyrrolopyridones yielded the corresponding carboxypyrrole lactams which on decarboxylation and hydrolysis gave the 2-aminomethyl-3-pyrroleacetic acids. Substitution at the C-3 position of the 6-azaindole with a propionic acid and acetic acid side chain and repetition of the above sequence gave porphobilinogen and 2-aminomethyl-3,4-pyrrolediacetic acid.

In 1952, Westall[4] isolated from the urine of a porphyric patient a pyrrole which he called porphobilinogen and whose structure (XXVIII) was established by Cookson and Rimington.[5] This pyrrole proved to be the only direct biosynthetic precursor of uroporphyrinogen III in the common biosynthetic pathway to heme and chlorophylls. Its transformation into uroporphyrinogen III is an enzymic reaction whose mechanism is still not understood; its acid-catalyzed chemical polymerization results in a mixture of all four possible uroporphyrins[6] after oxidation. Important structural features of porphobilinogen are the 2-aminomethyl group which provides the *meso* carbons of the resulting porphyrinogens and the 3-acetic acid group which can influence the reactivity of the 2-aminomethyl group. The work now being reported was undertaken in order to develop a facile and practical synthesis of pyrroles containing these structural features.

Porphobilinogen (XXVIII) has been the subject of several syntheses in the past both to prove its structure[7,8] and to obtain it in preparative amounts.[9,10] All these syntheses made use of the classical Knorr synthesis of pyrroles and resulted in very poor over-all yields, the best of them[10] being around 1%. We sought a new synthetic procedure for this type of pyrrole and based our approach on the observation that porphobilinogen is easily and reversibly transformed into its lactam (XXV). The lactam may be considered as the α-piperidone form of a suitably substituted pyrrolo[2,3-*c*]pyridine (6-azaindole). The problem was to develop a good general synthesis for 5-substituted 6-azaindoles, which could then be transformed into α-pyridones and reduced to the corresponding α-piperidones.

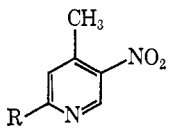
Azaindoles form a relatively little studied heterocyclic system for which the best ring syntheses require such drastic reaction conditions that the synthesis of substituted azaindoles with sensitive groups cannot be achieved.[11] In the specific case of the synthesis of 6-azaindoles the literature presents very few examples. 2-Methyl-6-azaindole was prepared[11a,12] by a Madelung-type cyclization of acetyl- and diacetyl-3-amino-4-picoline which included an alkaline fusion at 300°. 6-Azaindole and 7-methyl-6-azaindole have been prepared[13] by a Pomerantz–Fritsch-type reaction on

(1) A preliminary account of this work has been published: B. Frydman, M. E. Despuy, and H. Rapoport, *J. Am. Chem. Soc.*, 87, 3530 (1965).
(2) This research was supported in part by the Consejo Nacional de Investigaciones de la República Argentina and by the National Institutes of Health (Grants GM-11973 and AI-04888).
(3) Fellow of the Consejo Nacional de Investigaciones de la República Argentina, 1964–1966.
(4) R. G. Westall, *Nature*, 170, 614 (1952).
(5) G. H. Cookson and C. Rimington, *Biochem. J.*, 57, 476 (1954).
(6) D. Mauzerall, *J. Am. Chem. Soc.*, 82, 2601 (1960).
(7) J. J. Scott, *Biochem. J.*, 62, 6P (1956).
(8) C. Rimington and S. Krol, *Nature*, 175, 630 (1955).
(9) A. H. Jackson and S. F. MacDonald, *Can. J. Chem.*, 35, 715 (1957).
(10) G. P. Arsenault and S. F. MacDonald, *ibid.*, 39, 2043 (1961).
(11) For a brief evaluation of various syntheses of azaindoles prior to 1960 see T. K. Adler and A. Albert, *J. Chem. Soc.*, 1794 (1960). Recent azaindole ring syntheses are (a) Madelung type: W. Hertz and D. R. K. Murty, *J. Org. Chem.*, 25, 2242 (1960); J. Reisch, *Ber.*, 97, 2717 (1964); A. Albert and R. E. Willette, *J. Chem. Soc.*, 4063 (1964); R. R. Lorenz, B. F. Tullar, C. F. Koelsch, and S. Archer, *J. Org. Chem.*, 30, 2531 (1965); (b) *via* hydrazones: G. E. Ficken and J. D. Kendall, *J. Chem. Soc.*, 3202 (1959); 584 (1961); A. H. Kelly, D. H. MacLeod, and J. Parrick, *Can. J. Chem.*, 43, 296 (1965); A. H. Kelly and J. Parrick, *ibid.*, 44, 2455 (1966); G. Tacconi and A. Perotti, *Ann. Chim.* (Rome), 55, 810, 1223 (1965); (c) *via* haloalkylpyridines: L. N. Yakhontov, M. Ya. Uritskaya, and M. V. Rubstov, *Zh. Obshch. Khim.*, 34, 1449, 1456 (1964); *Khim. Geterotsikl. Soedin., Akad. Nauk Latv. SSR*, 918 (1965); L. N. Yakhantov and M. V. Rubstov, *Zh. Obshch. Khim.*, 32, 432 (1962).
(12) E. Koenigs and A. Fulde, *Ber.*, 60, 2106 (1927).
(13) W. Herz and S. Tocker, *J. Am. Chem. Soc.*, 77, 6355 (1955).

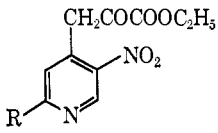
the Schiff bases of 2-pyrrolealdehyde and 2-acetylpyrrole and aminoacetal but the yields were very low (2%). The photochemical decomposition of 3-diazo-1,7-naphthyridin-4(3H)-one and the subsequent decomposition of the resulting pyrrolo[2,3-*c*]pyridine-3-carboxylic acid has given[14] 6-azaindole but this clearly is a very restrictive preparative method.

As a general approach to the synthesis of 6-azaindoles, we examined the reductive cyclization of the ethyl *o*-nitropyridinepyruvates IV and V. Although previous failures in the condensation of *o*-nitromethylpyridines with diethyl oxalate have been reported[15] we found that the 2-methoxy (III) and the 2-benzyloxy-4-methyl-5-nitropyridines (II) condensed easily and at room temperature with diethyl oxalate in the presence of potassium ethoxide to give the 2-substituted ethyl *o*-nitropyridinepyruvates. The two nitropyridines II and III were prepared from 2-chloro-4-methyl-5-nitropyridine (I), itself prepared by an improvement of the original synthesis.[16]

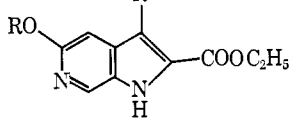
The nmr and ir data showed that the pyruvates existed mainly as the enols; nevertheless, when they were hydrogenated in ethanol the corresponding azaindoles VI and VII were obtained in good yields. The ethyl 2-methoxy-5-nitro-4-pyridinepyruvate (V) was reduced over palladium on carbon and the 2-benzyloxy derivative (IV) was reduced over platinum oxide. When the purified ethyl 5-benzyloxy-6-azaindole-2-carboxylate (VII) was hydrogenated using palladium on charcoal as catalyst, it was directly transformed into the 2-ethoxycarbonylpyrrole lactam XX and no intermediate α-pyridone formation could be detected.

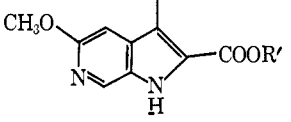


I, R = Cl
II, R = $C_6H_5CH_2O$
III, R = CH_3O



IV, R = $C_6H_5CH_2O$
V, R = CH_3O





	R	R′
VI	CH_3	H
VII	$C_6H_5CH_2$	H
VIII	CH_3	$CH_2N(CH_3)_2$
IX	CH_3	$CH_2CH(COOC_2H_5)_2$
X	$C_6H_5CH_2$	$CH_2N(CH_3)_2$
XI	$C_6H_5CH_2$	$CH_2CH(COOC_2H_5)_2$

	R	R′
XII	CH_2CN	H
XIII	CH_2CN	CH_3
XIV	CH_2COOH	H
XV	CH_2CH_2COOH	H

Since the ethyl 5-methoxy-6-azaindole-2-carboxylate (VI) was obtained in better yields than the 5-benzyloxy derivatives (VII), we investigated its transformation into an α-pyridone (XVI) structure. Although the 2-alkoxypyridines are known to be labile to acids, the 5-methoxy-6-azaindole resisted cleavage with hydrochloric and sulfuric acids, but was cleaved with concentrated hydrobromic acid. The product existed predominantly in the α-pyridone structure XVI as can be deduced from the amide II band. This azaindole acid XVI was smoothly hydrogenated to the carboxy lactam XIX in aqueous solution over palladium on carbon. By boiling the carboxy lactam in water it was easily decarboxylated to the pyrrole lactam XXIV. On the other hand, 2-aminomethyl-5-carboxy-3-pyrroleacetic acid (XXIII) resisted all attempts at thermal decarboxylation, confirming the previous observations made on 2-aminomethylpyrrolecarboxylic acids.[9] The lactam XXIV was hydrolyzed to the aminomethylpyrrole XXVII, which, due to its solubility in water, was isolated as its mercuric salt from which it was liberated as the free acid by hydrogen sulfide.

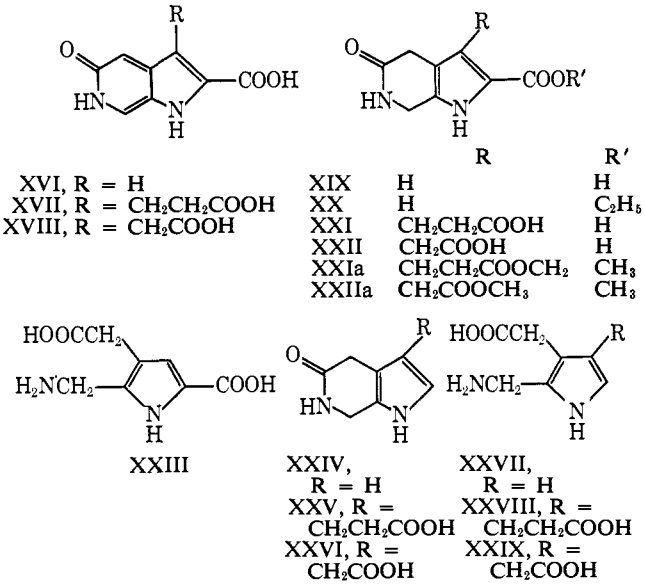
In this manner a synthetic method for 2-aminomethyl-3-pyrroleacetic acids was established. We planned now that by introducing different substituents at C-3 of the azaindoles VI and VII, a number of pyrroles with the aforementioned structure would be obtained. However, the introduction of electrophilic substituents at C-3 was strongly hindered by the electron-withdrawing effect of the 2-carbethoxy group and the pyridine nucleus of the azaindole, and several reactions of this type failed (Vilsmeier reaction, Gatterman reaction, oxalyl chloride attack). Nevertheless, the Mannich bases could be obtained in good yields by the reaction of both azaindoles with dimethylamine hydrochloride and paraformaldehyde, and they were isolated as VIII and X dihydrochlorides. By the reaction of these Mannich bases with diethyl sodiomalonates, the corresponding 6-azaindolylmethylmalonates IX and XI were obtained.

When the 5-benzyloxy-6-azaindolylmethylmalonate XI was treated with concentrated hydrochloric acid, the simultaneous cleavage of the 5-benzyloxy group and the hydrolysis and decarboxylation of the malonate group afforded the 2-carboxy-5-oxo-5,6-dihydro-1H-pyrrolo[2,3-*c*]pyridine-3-propionic acid (XVII), whose α-pyridone structure was again revealed by its ir spectrum. On the other hand, when the 5-methoxy-6-azaindolylmethylmalonate IX was treated in the same way, the azaindolepropionic acid XV was obtained and its transformation into the pyridone acid XVII required cleavage with hydrobromic acid.

No reaction took place when the Mannich base VIII was treated with sodium or potassium cyanide. The corresponding 2-carboxy-5-methoxy-6-azaindole-3-acetonitrile (XII) was obtained when the quaternary salt of the Mannich base was used, and during the reaction the 2-carbethoxy group was hydrolyzed to the acid. The acid acetonitrile XII was then purified through its methyl ester XIII and hydrolyzed to the acetic acid XIV. By treatment of the acid with hydrobromic acid the 2-carboxy-5-oxo-5,6-dihydro-1H-pyrrolo[2,3-*c*]pyridine-3-acetic acid (XVIII) was obtained and again the ir amide band indicated its α-pyridone structure.

The pyridone acids XVII and XVIII were easily hydrogenated in aqueous solution at pH 7 to the corresponding carboxy lactams XXI and XXII and following the previous procedure[9] these were decarboxylated to the lactams XXV and XXVI in boiling water. Ring opening of the lactams[9] was improved by complete hydrolysis to the corresponding pyrroles at room temperature in aqueous potassium hydroxide solution over several days. Porphobilinogen (XXVIII) was isolated at pH 4 in 83% yield and proved to be

(14) O. Süs and K. Möller, *Ann.*, **599**, 233 (1956).
(15) W. Herz and D. R. K. Murty, *J. Org. Chem.*, **26**, 122 (1961); G. M. Badger and R. P. Rao, *Australian J. Chem.*, 17, 1399 (1964).
(16) D. M. Besly and A. A. Goldberg, *J. Chem. Soc.*, 2448 (1954).



XVI, R = H
XVII, R = CH_2CH_2COOH
XVIII, R = CH_2COOH

	R	R′
XIX	H	H
XX	H	C_2H_5
XXI	CH_2CH_2COOH	H
XXII	CH_2COOH	H
XXIa	$CH_2CH_2COOCH_3$	CH_3
XXIIa	CH_2COOCH_3	CH_3

XXIII

XXIV, R = H
XXV, R = CH_2CH_2COOH
XXVI, R = CH_2COOH

XXVII, R = H
XXVIII, R = CH_2CH_2COOH
XXIX, R = CH_2COOH

identical with an authentic sample of porphobilinogen from urine. The 2-aminomethylpyrrole-3,4-diacetic acid (**XXIX**) was very soluble in water and was best isolated as its mercuric salt from the hydrolysis mixture. When the synthetic porphobilinogen was incubated with different enzyme preparations from spinach and wheat germ[17] followed by oxidation it was quantitatively transformed into uroporphyrins.

The yield of porphobilinogen (**XXVIII**) starting from 2-methoxy-4-methyl-5-nitropyridine (III) was 19%. The latter was prepared from the commercially available 2-amino-4-methylpyridine in 42% yield by a series of four known, elementary reactions[16] giving an over-all yield of 8%. This synthetic approach is applicable to the synthesis of a variety of analogous pyrroles of the porphobilinogen type which will be described in future publications. The pyrroles in which the propionic acid residue of porphobilinogen has been replaced by hydrogen and acetic acid (**XXVII** and **XXIX**, respectively) were not substrates for the enzymic system which transformed porphobilinogen into uroporphyrinogens, but they had a very specific inhibitory activity on the enzymes involved. While pyrrole **XXVII** inhibited the formation of uroporphyrinogen I and increased the formation of uroporphyrinogen III, the pyrrole **XXIX** had just the opposite effect on isomer formation. Those results are discussed in detail elsewhere.[18]

Experimental Section[19]

2-Chloro-4-methyl-5-nitropyridine (I). Fifty grams of 2-hydroxy-4-methyl-5-nitropyridine[16] was added to a mixture of 25 g of phosphorus pentachloride and 125 ml of phosphorus oxychloride. The solution was heated at 120° during 3 hr, cooled, and poured over 1 kg of crushed ice with continuous stirring. After being cooled at 5° for several hours, the mixture was filtered and the brown residue was steam distilled. The 4 l. of steam distillate was cooled at 5° and filtered, whereupon 39 g (70% yield) of white crystals were obtained, mp 40–43° (lit.[16] mp 40–44°).

2-Benzyloxy-4-methyl-5-nitropyridine (II). Sixty grams (0.34 mole) of I was added to a solution of 8.5 g (0.37 g-atom) of sodium in 1200 ml of benzyl alcohol. The mixture was left at room temperature for 12 hr, then the benzyl alcohol was evaporated at reduced pressure (90° (10 mm)), and the crystalline residue was washed with water (two 250-ml portions) and recrystallized from ethanol. Slightly colored prisms (85 g, 90% yield) were obtained, mp 82–84°. *Anal.* Calcd for $C_{13}H_{12}O_3N_2$: C, 63.9; H, 4.9; N, 11.5. Found: C, 64.1; H, 5.0; N, 11.2.

2-Methoxy-4-methyl-5-nitropyridine (III) was obtained by the action of methanolic sodium methoxide on I as described;[16] mp 81° (lit.[16] mp 82–84°), λ_{max} 289 mμ (ε 6800).

Ethyl 2-Benzyloxy-5-nitro-4-pyridinepyruvate (IV). To a solution of 620 ml of ether and 50 ml of absolute ethanol was added 8.6 g (0.23 g-atom) of potassium and the mixture was stirred under anhydrous conditions until all the potassium dissolved. Diethyl oxalate (32 ml, 0.23 mole) was then added, followed after 5 min by 54 g (0.22 mole) of II, and the red mixture was stirred for 36 hr. The red potassium enolate was removed by filtration, washed thoroughly with ether, dried, suspended in 1000 ml of water, and decomposed by adjusting the solution to pH 4 with acetic acid, precipitating the pyruvate which was crystallized from ethanol; 44 g, 82% yield allowing for 23 g of starting material recovered from the ether phase, mp 124–126°, λ_{max} 288 mμ (ε 11,700). *Anal.* Calcd for $C_{17}H_{16}O_6N_2$: C, 59.3; H, 4.7; N, 8.1; OEt, 13.1. Found: C, 59.5; H, 4.6; N, 8.2; OEt, 12.7.

Ethyl 2-methoxy-5-nitro-4-pyridinepyruvate (V) was prepared following the same procedure used for the synthesis of the 2-benzyloxy derivative IV. From 50 g of III was obtained 45 g of V. From the ether washings, 20.6 g of III was recovered. Based on the weight of unrecovered III, the over-all yield of V was 93%; mp 97–98° (from ethanol); λ_{max} 287 mμ (ε 10,100); ir, ν_{max} 3350 (enolic OH), 1710 cm^{-1}; nmr, δ 7.8 (H-3), 9.1 (H-6), 7.2 [C*H*=C(OH)]. *Anal.* Calcd for $C_{11}H_{12}N_2O_6$: C, 49.2; H, 4.5; N, 10.4. Found: C, 49.0; H, 4.5; N, 10.4.

Ethyl 5-Methoxy-6-azaindole-2-carboxylate (VI). Seven grams of V was dissolved in 100 ml of ethanol and reduced at atmospheric pressure with hydrogen over 2.5 g of 10% palladium on charcoal. When the hydrogen uptake was completed (45 min), the catalyst was removed and washed with ethanol, the combined filtrate and washings were concentrated *in vacuo* to 10 ml, 20 ml of water was added, and the suspension was cooled at 5° for several hours. The resulting precipitate was filtered, dried, and sublimed (90° and 0.1 mm) giving 4.9 g (85%) of VI: mp 103–106°; λ_{max} 278 mμ (ε 15,000), 287 (17,000), 344 (3600); δ 7.1, 7.2 (H-3, H-4), and 8.7 (H-7). *Anal.* Calcd for $C_{11}H_{12}N_2O_3$: C, 60.0; H, 5.5; N, 12.7. Found: C, 59.9; H, 5.6; N, 13.0.

Ethyl 5-Benzyloxy-6-azaindole-2-carboxylate (VII). Ten grams of IV was dissolved in 200 ml of ethanol and reduced with hydrogen at atmospheric pressure over 1 g of platinum oxide until the theoretical amount of hydrogen was consumed (50 min). The catalyst was removed, the ethanol was evaporated to dryness, and the oily residue was dissolved in a small amount of chloroform and adsorbed on a neutral alumina column (30 × 3 cm) prewashed with chloroform. The azaindole was eluted with chloroform (500 ml), the chloroform was evaporated *in vacuo*, and the crystalline residue was recrystallized from ethanol–water and sublimed at 130° and 0.01 mm, giving 3.1 g (35% yield) of VII: mp 150–152°; λ_{max} 278 mμ (ε 13,000), 287 (15,000). *Anal.* Calcd for $C_{17}H_{16}O_3N_2$: C, 68.9; H, 5.4; N, 9.4. Found: C, 68.7; H, 5.4; N, 9.4.

Ethyl 3-Dimethylaminomethyl-5-methoxy-6-azaindole-2-carboxylate (VIII). Six grams of VI was dissolved in 540 ml of 1-butanol, 8.6 g of dimethylamine hydrochloride and 3 g of paraformaldehyde were added, and the mixture was heated at reflux for 30 min and evaporated thoroughly to dryness *in vacuo*. The residue was dissolved in 250 ml of 4 *N* hydrochloric acid, washed twice with 50 ml of ether, alkalized with solid potassium carbonate, and extracted several times with ether. The ether extracts were dried (Na_2SO_4), filtered, and evaporated, the residue was dissolved in 100 ml of acetone, and hydrogen chloride was passed through the solution until no more precipitate formed. The cooled solution was filtered giving 6.9 g (72% yield) of VIII as the dihydrochloride: mp 162°; λ_{max} 283 mμ (ε 13,800), 292 (13,800), 347 (3700); δ (D_2O) 8.2 (H-7). *Anal.* Calcd for $C_{14}H_{21}N_3O_3Cl_2$: C, 48.1; H, 6.1; N, 12.0. Found: C, 47.9; H, 6.3; N, 11.8.

(17) L. Bogorad, *J. Biol. Chem.*, **233**, 501, 510 (1958).
(18) R. B. Frydman, E. Stevens, and B. Frydman, *Anales Asoc. Quim. Arg.*, in press.
(19) All melting points were taken on the Köfler block, ultraviolet absorptions were measured in ethanol, infrared spectra were obtained on potassium bromide wafers, and nuclear magnetic resonance spectra were taken in deuteriochloroform, unless otherwise noted, with internal TMS (δ 0). Paper chromatography was run on Whatman No. 1 paper with the upper layer of a butanol–acetic acid–water (4:1:5) mixture. Microanalyses were performed by the Microchemical Laboratory, University of California, Berkeley. Several of the nmr spectra were determined at the Department of Organic Chemistry Faculty of Sciences, University of Buenos Aires, Buenos Aires, Argentina.

Ethyl 3-Dimethylaminomethyl-5-benzyloxy-6-azaindole-2-carboxylate (X). Six grams of VII was treated with 5 g of dimethylamine hydrochloride and 1.8 g of paraformaldehyde in 200 ml of 1-butanol as described for the methoxy analog above. The residue after evaporation of the butanol was dissolved in 500 ml of 4 *N* hydrochloride acid and the dihydrochloride of X was isolated in the manner described above; 4 g, 60% yield; mp 178° (from ethanol–ether); δ (D_2O) 8.2 (H-7), 5.5 ($C_6H_5CH_2$), 7.4 (C_6H_5), 6.7 (H-4), 4.7 ($CH_2N(CH_3)_2$), 2.9 ($N(CH_3)_2$). *Anal.* Calcd for $C_{20}H_{25}O_3N_3Cl_2$: C, 56.3; H, 5.9; N, 9.8. Found: C, 56.0; H, 5.6; N, 9.8.

Ethyl 5-Benzyloxy-2-ethoxycarbonyl-6-azaindole-3-(α-ethoxycarbonyl)propionate (XI). Six grams of the dihydrochloride of X was added to a solution of 1.5 g of sodium in 60 ml of diethyl malonate and the mixture was heated at 120° for 6 hr. The reaction mixture was cooled, thoroughly mixed with 90 ml of ether and 90 ml of 5% hydrochloric acid, and filtered after several hours of further cooling. The hydrochloride of XI was collected, dried, and recrystallized from ethanol–ether; 6.6 g (80% yield); mp 158°; λ_{max} 284 mμ (ε 18,100), 292 (21,300), 350 (4500). *Anal.* Calcd for $C_{25}H_{29}O_7N_2Cl$: C, 59.5; H, 5.7; N, 5.5. Found: C, 59.3; H, 5.7; N, 5.5.

Ethyl 2-Ethoxycarbonyl-5-methoxy-6-azaindole-3-(α-ethoxycarbonyl)propionate (IX). The dihydrochloride of VIII was treated with diethyl sodiomalonate and the hydrochloride of IX was isolated in the same manner as for the benzyloxy analog above; yield 80%; mp 188°; λ_{max} 284 mμ (ε 18,600), 294 (20,400), 350 (4600). *Anal.* Calcd for $C_{19}H_{25}O_7N_2Cl \cdot H_2O$: C, 51.1; H, 6.0; N, 6.3. Found: C, 50.8; H, 5.8; N, 6.3.

2-Carboxy-5-methoxy-6-azaindole-3-acetonitrile (XII). Methyl iodide (2 ml) was added to a solution of 3.6 g of the Mannich base VIII in 200 ml of ether, and the mixture was heated under reflux for 15 min. The solvent was evaporated, and the residue was washed with 50 ml of cold acetone, centrifuged, dissolved in 75 ml of 50% aqueous ethanol, and heated under reflux with 1.5 g of potassium cyanide for 3 hr. The solution was then cooled, the ethanol was evaporated *in vacuo*, and the aqueous residue was acidified to pH 4 with acetic acid, giving a precipitate which was removed, dissolved in 1 *N* ammonium hydroxide solution, and filtered through an alumina column (20 × 2 cm) prewashed with the same solution. The eluate was acidified to pH 4 with acetic acid and the precipitate was removed and dried; 1.6 g (90% yield) of the 6-azaindole acid XII was obtained, mp 240° dec. *Anal.* Calcd for $C_{11}H_9O_3N_3$: C, 57.1; H, 3.9; N, 18.2. Found: C, 57.0; H, 4.1; N, 17.8.

Methyl 3-Cyanomethyl-5-methoxy-6-azaindole-2-carboxylate (XIII). Five grams of the cyanomethyl acid XII was suspended in 250 ml of methanol and an ethereal solution of diazomethane was slowly added at 5° with continuous stirring until the yellow color persisted. The solution was then filtered, the filtrate was evaporated to dryness, and the residue was crystallized from methanol giving 3.2 g (61% yield) of the methyl ester XIII: mp 162–164° after sublimation (170° and 0.001 mm); λ_{max} 282 mμ (ε 14,639), 290 (16,900); δ 4.2 (CH_2CN). *Anal.* Calcd for $C_{12}H_{11}O_3N_3$: C, 58.8; H, 4.5; N, 17.1. Found: C, 59.0; H, 4.6; N, 17.5.

2-Carboxy-5-methoxy-6-azaindole-3-acetic Acid (XIV). Two grams of the cyanomethyl methyl ester XIII was heated under reflux with 100 ml of concentrated hydrochloric acid for 6 hr after which the solution was evaporated to dryness and the residue was dissolved in 1 *N* ammonium hydroxide solution and precipitated at pH 4 with acetic acid. The diacid XIV (1.34 g, 70% yield, mp 260° dec) was further purified by dissolution in dilute ammonium hydroxide and precipitation with acetic acid; λ_{max} 282 mμ (ε 12,300), 291 (13,800). *Anal.* Calcd for $C_{11}H_{10}O_5N_2$: C, 52.8; H, 4.0; N, 11.2. Found: C, 52.5; H, 3.8; N, 11.1.

2-Carboxy-5-methoxy-6-azaindole-3-propionic Acid (XV). Compound IX (3.6 g) was dissolved in 40 ml of concentrated hydrochloric acid and the solution was heated under reflux for 6 hr. Evaporation *in vacuo* left a residue which was dissolved in 6 ml of dilute sodium carbonate solution and the solution was adjusted to pH 4 with acetic acid. After cooling, the mixture was filtered and the precipitate was recrystallized by dissolving in dilute ammonium hydroxide solution and precipitating with dilute acetic acid; 2.2 g (100% yield) of the diacid XV was obtained: mp 210–215°; λ_{max} 283 mμ (ε 13,000), 292 (15,700), 350 (4400). *Anal.* Calcd for $C_{12}H_{12}O_5N_2 \cdot 0.5H_2O$: C, 52.7; H, 4.7; N, 10.3. Found: C, 52.7; H, 4.3; N, 10.3.

5-Oxo-5,6-dihydro-1H-pyrrolo[2,3-*c*]pyridine-2-carboxylic Acid (XVI). Five grams of XI was dissolved in 150 ml of 48% hydrobromic acid and the mixture was heated under reflux for 2.5 hr. It was then evaporated to dryness, the residue was dissolved in 5 ml of 1 *N* ammonium hydroxide and filtered through a neutral alumina column (20 × 2 cm) prewashed with the same ammonium hydroxide solution, and the eluates were acidified to pH 4 with acetic acid, cooled, and filtered. The acid XVI was washed with boiling methanol (five 20-ml portions), centrifuged, dried, and recrystallized several times from aqueous acetic acid; 1.6 g (41% yield), mp 260° dec. *Anal.* Calcd for $C_8H_6O_3N_2$: C, 53.9; H, 3.4; N, 15.7. Found: C, 53.6; H, 3.5; N, 15.7.

2-Carboxy-5-oxo-5,6-dihydro-1H-pyrrolo[2,3-*c*]pyridine-3-propionic Acid (XVII). A. From the Methoxyazaindole XV. Five grams of the propionic acid XV was treated with 48% hydrobromic acid solution as described above. The acid obtained was washed with boiling methanol (six 20-ml portions), filtered through alumina as described, and precipitated at pH 4 by adding acetic acid to its ammonium hydroxide solution; 3.2 g (67% yield); mp 280° dec; λ_{max} 292 mμ (ε 4200), 302 (4400); ν_{max} 3250, 1630, and 1600 cm^{-1}. *Anal.* Calcd for $C_{11}H_{10}O_5N_2 \cdot 0.5H_2O$: C, 51.0; H, 4.3; N, 10.8. Found: C, 51.0; H, 4.5; N, 10.7.

B. From the Benzyloxyazaindole XI. Five grams of XI was suspended in 60 ml of concentrated hydrochloric acid and heated under reflux for 6 hr. The solution was evaporated to dryness, the residue was dissolved in 25 ml of a 10% sodium carbonate solution, and the acid was precipitated at pH 4 by adding acetic acid; mp 280° dec, 3.4 g, 91% yield.

2-Carboxy-5-oxo-5,6-dihydro-1H-pyrrolo[2,3-*c*]pyridine-3-acetic Acid (XVIII). Two grams of the acetic acid XIV was treated with 120 ml of 48% hydrobromic acid as described previously, then washed with boiling methanol, filtered through alumina, and crystallized in the usual manner; 900 mg (47% yield); mp 250° dec; λ_{max} 292 mμ (ε 8100), 300 (7100). *Anal.* Calcd for $C_{10}H_8O_5N_2 \cdot 0.5H_2O$: C, 49.0; H, 3.7; N, 11.4. Found: C, 48.8; H, 3.7; N, 11.3.

2-Carboxy-5-oxo-4,5,6,7-tetrahydro-1H-pyrrolo[2,3-*c*]pyridine-3-acetic Acid (XXII). One gram of the 5,6-dihydropyrrolopyridine XVIII was dissolved at pH 7 in 30 ml of sodium carbonate solution, 500 mg of 10% palladium on charcoal was added, and the mixture was shaken with hydrogen at 50 psi for 2 hr. The catalyst was removed, the solution was acidified to pH 4 with acetic acid, and the white crystals were dissolved several times in 1 *N* potassium hydroxide solution and precipitated by adding hydrochloric acid solution to pH 3; 650 mg, 64% yield, mp 270° dec, λ_{max} 270 mμ (ε 16,000). *Anal.* Calcd for $C_8H_8O_3N_2$: C, 53.3; H, 4.5; N, 15.6. Found: C, 52.9; H, 4.2; N, 15.3.

The **dimethyl ester XXIIa** was prepared by treating a methanolic suspension of XXII with ethereal diazomethane; mp 247–250° from ethanol. *Anal.* Calcd for $C_{12}H_{14}O_5N_2$: C, 54.1; H, 5.3; N, 10.5. Found: C, 54.1; H, 5.2; N, 10.7.

5-Oxo-4,5,6,7-tetrahydro-1H-pyrrolo[2,3-*c*]pyridine (XXIV). One gram of the acid XIX was suspended in 100 ml of water, the mixture was heated under reflux for 8 hr, the water was then evaporated, and the residue was sublimed at 180° (0.02 mm). The sublimate [530 mg (71% yield)] had mp 295° dec, R_f 0.78. *Anal.* Calcd for $C_7H_8ON_2$: C, 61.7; H, 5.9; N, 20.6. Found: C, 61.7; H, 5.9; N, 20.5.

Ethyl 5-Oxo-4,5,6,7-tetrahydro-1H-pyrrolo[2,3-*c*]pyridine-2-carboxylate (XX). One gram of VII was dissolved in 50 ml of 25% aqueous ethanol and the solution was shaken with hydrogen at 50 psi over 500 mg of 10% palladium on carbon. The reduction stopped after 2 hr, the catalyst was removed, and the solution was concentrated *in vacuo* to 5 ml and cooled. The lactam crystallized and was recrystallized from ethanol; 600 mg (86% yield), mp 272–274°; λ_{max} 276 mμ (ε 18,500). *Anal.* Calcd for $C_{10}H_{12}O_3N_2$: C, 57.7; H, 5.8; N, 13.5. Found: C, 57.7; H, 5.9; N, 13.1.

2-Aminomethyl-5-carboxy-3-pyrroleacetic Acid (XXIII). 5-Carbethoxypyrrole lactam XX (500 mg) was suspended in 1.5 ml of 2 *N* sodium hydroxide, 1.5 ml of 95% ethanol was added, and the mixture was heated under reflux for 30 min. Cooling and adjusting to pH 4 with acetic acid gave a precipitate which was reprecipitated several times by dissolving it in warm 1 *N* ammonium hydroxide solution and adding acetic acid; 406 mg (85% yield), mp 210° dec. *Anal.* Calcd for $C_8H_{10}O_4N_2 \cdot H_2O$: C, 44.4; H, 5.6; N, 13.0. Found: C, 44.8; H, 5.5; N, 12.8.

2-Carboxy-5-oxo-4,5,6,7-tetrahydro-1H-pyrrolo[2,3-*c*]pyridine-3-propionic Acid (XXI). Five grams of XVII was dissolved in 100 ml of dilute sodium carbonate solution at pH 7 and reduced with hydrogen at 50 psi over 2.5 g of 10% palladium on carbon for 2 hr. The catalyst was removed and the solution was adjusted to pH 4 with acetic acid, cooled at 5°, and centrifuged. The collected solid was dissolved in a small volume of 1 *N* ammonium hydroxide

solution and filtered through an alumina column using the same ammonium hydroxide solution for elution. The eluate was acidified to pH 4 with acetic acid and the precipitated acid was dried; 4.5 g (87% yield), mp 295° (lit.[9] mp 325°), λ_{max} 276 mμ (ε 12,600). *Anal.* Calcd for $C_{11}H_{12}O_5N_2 \cdot H_2O$: C, 48.9; H, 5.2; N, 10.4. Found: C, 48.8; H, 4.8; N, 10.5.

The **dimethyl ester XXIa** was prepared by treating a methanolic suspension of XXI with ethereal diazomethane; mp 207–211° from ethanol. *Anal.* Calcd for $C_{13}H_{16}N_2O_5$: C, 55.7; H, 5.7; N, 10.0. Found: C, 55.8; H, 5.6; N, 10.3.

5-Oxo-4,5,6,7-tetrahydro-1H-pyrrolo[2,3-*c*]pyridine-3-propionic Acid (Porphobilinogen Lactam) (XXV). Four grams of XXI was heated under reflux in 250 ml of water for 4 hr. The solution was evaporated to dryness and the residue was recrystallized from water; 2.67 g (87% yield); mp 295° (lit.[9] mp 280–283°; R_f 0.72; ν_{max} 3200, 1690, 1630 cm^{-1}. *Anal.* Calcd for $C_{10}H_{12}O_3N_2$: C, 57.7; H, 5.8; N, 13.4. Found: C, 57.5; H, 5.7; N, 13.3.

5-Oxo-4,5,6,7-tetrahydro-1H-pyrrolo[2,3-*c*]pyridine-3-acetic Acid (XXVI). One gram of XXII was decarboxylated by boiling in water as described above. The product was further purified by dissolving it in a dilute ammonium hydroxide solution and precipitating with acetic acid; 515 mg (68% yield), mp 255–260° dec, R_f 0.64. *Anal.* Calcd for $C_9H_{10}O_3N_2$: C, 55.7; H, 5.2; N, 14.4. Found: C, 55.8; H, 5.4; N, 14.6.

2-Aminomethyl-3-pyrroleacetic Acid (XXVII). The sublimed lactam XXIV (300 mg) was suspended in 2 ml of 4 *N* sodium hydroxide, 2 ml of ethanol was added, and the mixture was heated under reflux for 1 hr. The solution was then adjusted to pH 5 with acetic acid and 15% aqueous mercuric acetate was added until no more precipitate formed. The solid was centrifuged, the precipitate was suspended in water, and hydrogen sulfide was passed through the suspension until all of the mercuric salt was decomposed. The HgS was centrifuged and washed with water, and the pooled supernatant and wash were evaporated to dryness at 50° *in vacuo*. The crystalline residue was recrystallized by dissolving it in water and adding acetone; 190 mg (56% yield); mp 140° dec; δ (D_2O) 6.9 (d, H-5), 6.1 (d, H-4), 4.2 (CH_2CO_2H), 3.4 (CH_2NH_2). *Anal.* Calcd for $C_7H_{10}O_2N_2$: C, 54.5; H, 6.5; N, 18.2. Found: C, 54.3; H, 6.5; N, 18.0.

2-Aminomethyl-3,4-pyrrolediacetic Acid (XXIX). The lactam XXVI (200 mg) was dissolved in 2 ml of 2 *N* potassium hydroxide and the mixture was left at room temperature for 1 week. The solution was then adjusted to pH 4 with acetic acid and the pyrrolediacetic acid was isolated through its mercury salt as described above. It was recrystallized by dissolving it in water and adding methanol; mp 145° dec, R_f 0.42. *Anal.* Calcd for $C_9H_{12}O_4N_2 \cdot H_2O$: C, 47.0; H, 5.6; N, 12.2. Found: C, 46.8; H, 5.6; N, 12.1.

2-Aminomethyl-3-carboxymethyl-4-pyrrolepropionic Acid (Porphobilinogen, XXVIII). Two grams of porphobilinogen lactam XXV was dissolved in 6 ml of 2 *N* potassium hydroxide and the mixture was left at room temperature for 72 hr. The solution was then adjusted to pH 7 with 7 *N* acetic acid and cooled at 0° for 3 hr. The solid was further purified by dissolution in dilute ammonium hydroxide and precipitation with acetic acid; 1.94 g (83% yield) of porphobilinogen was obtained, mp 167° (lit.[9] mp 170–174°), R_f 0.50. *Anal.* Calcd for $C_{10}H_{14}O_4N_2 \cdot H_2O$: C, 49.2; H, 6.6; N, 11.5. Found: C, 49.4; H, 6.7; N, 11.5.

When ^{14}C-labeled porphobilinogen lactam XXV was used (0.93 mCi/mmole; the label was at C-2 of the propionic acid side chain) and the resulting porphobilinogen (0.95 mCi/mmole) was examined by paper chromatography no other radioactive spot could be detected. The porphobilinogen (XXVIII) had identical ir, R_f, and electrophoretic mobility as an authentic sample.

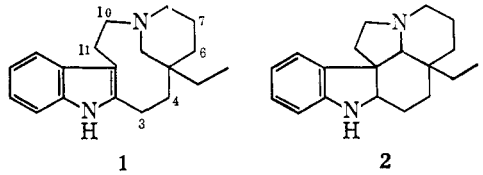
A Synthesis of Quebrachamine and 3,4-Dehydroquebrachamine[1]

Frederick E. Ziegler, James A. Kloek, and Phillip A. Zoretic

Contribution from the Sterling Chemistry Laboratory of Yale University, New Haven, Connecticut 06520. *Received December 13, 1968*

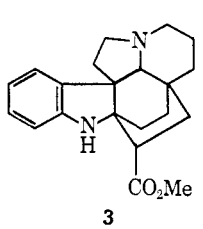
Abstract: A synthesis of quebrachamine (**1**) and 3,4-dehydroquebrachamine (**17**) has been achieved. The approach employs the alkylation of 1-benzyl-3-ethyl-1,4,5,6-tetrahydropyridine (**10**) with methyl haloacetates and subsequent cyclization to a nine-membered ring in high yield with polyphosphoric acid.

Quebrachamine (**1**) can be considered the parent base of that group of indole alkaloids having the aspidosperma[2] skeleton, whose other structural members are represented by aspidospermidine (**2**), kopsinine (**3**), and tuboxenine (**4**).

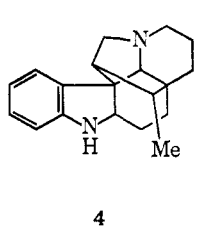


1

2



3



4

Synthetic efforts in this area to date have culminated in syntheses of quebrachamine,[3] aspidospermine,[3] and aspidospermidine.[4] The conversion **1** → **2** has been achieved,[5] while the reverse process[6] (**2** → **1**) serves as the route to all but one of the reported syntheses of quebrachamine.[3d]

The most salient feature of the aspidosperma alkaloids is the presence of geminal diethyl substitution of the piperidine ring at C-5 which, along with the β-indolylethyl chain and varying degrees of oxidation level and substitution, *e.g.*, C-3 carbomethoxyl group, comprises the skeletal framework of these bases. Consequently it was anticipated that 1-benzyl-3-ethyl-1,4,5,6-tetrahydropyridine (**10**) would serve as a

(1) For a preliminary report see F. E. Ziegler and P. A. Zoretic, *Tetrahedron Lett.*, 2639 (1968).

(2) See (a) B. Gilbert, *Alkaloids*, **8**, 335 (1965); and (b) M. Hesse, "Indolalkaloide in Tabellen," Springer-Verlag, Berlin, 1964.

(3) (a) G. Stork and J. E. Dolfini, *J. Am. Chem. Soc.*, **85**, 2872 (1963); (b) Y. Ban, Y. Sato, I. Inoue, M. Nagai, T. Oishi, M. Terashima, O. Yonenitsu, and Y. Kanoaka, *Tetrahedron Lett.*, 2261 (1965); (c) M. E. Kuehne and C. Bayha, *ibid.*, 1311 (1966); (d) J. P. Kutney, N. Abdurahman, P. Le Quesne, E. Piers, and I. Vlattas, *J. Am. Chem. Soc.*, **88**, 3656 (1966); J. P. Kutney, K. K. Chan, A. Failli, J. M. Fromson, C. Gletsos, and V. R. Nelson, *ibid.*, **90**, 3891 (1968).

(4) J. Harley-Mason and M. Kaplan, *Chem. Commun.*, 915 (1967).

(5) A. Camerman, N. Camerman, J. P. Kutney, E. Piers, and J. Trotter, *Tetrahedron Lett.*, 637 (1965).

(6) K. Biemann and G. Spiteller, *ibid.*, 299 (1961).