[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CALIFORNIA, BERKELEY]

Synthesis of Pyrrole-3-carboxylic Acids

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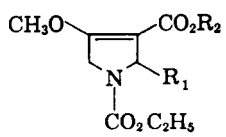
When 3-carbethoxy-4-methoxy-Δ^3-pyrrolines are heated under reflux with alkali, elimination of the methoxyl group occurs and pyrrole-3-carboxylic acids are formed. Since a variety of the requisite pyrrolines are readily available, this procedure is a convenient one for the synthesis of such acids.

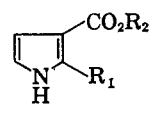
While engaged in the preparation of some 3-methoxypyrroles, we unexpectedly discovered a new synthesis of pyrrole 3-carboxylic acid (I), which proceeded in good yield from readily available starting materials. Since the present method is considerably more convenient for the preparation of I than those given in the literature,[2-4] we pursued several instances of the same reaction in order to gain some insight into its mechanism and generality.

In an effort to convert the pyrroline diester (III) to the pyrroline amino acid (II) without shifting the double bond, mild hydrolytic conditions were employed (60°, *p*H 11). The double bond was indeed stable under these conditions, as shown by the ultraviolet spectra of aliquots as the hydrolysis proceeded. The original maximum absorption of II was at 248 mμ. At the conclusion of the hydrolysis, this β-methoxyacrylic ester absorption of II had been shifted to the β-methoxyacrylic acid anion absorption at 237 mμ. Acidification of the aliquot returned the absorption to 248 mμ, a further indication that the -methoxyacrylic acid chromophore had been preserved.

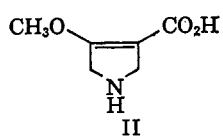
However, only 100 mole % of alkali was consumed over a nine-hour period, and no more was taken up during an additional twelve hours at 60° and pH 11. Furthermore, after diazomethane esterification of the reaction products, the pyrroline diester (IV) was isolated in good yield, showing conclusively that the hydrolysis has been completely selective, leaving the carbamate ester group untouched.



	R_1	R_2
III	H	C_2H_5
IV	H	CH_3
VI	CH_3	C_2H_5
IX	$CO_2C_2H_5$	C_2H_5



	R_1	R_2
I	H	H
V	H	CH_3
VII	CH_3	H
VIII	CH_3	CH_3
X	CO_2H	H
XI	CO_2CH_3	H

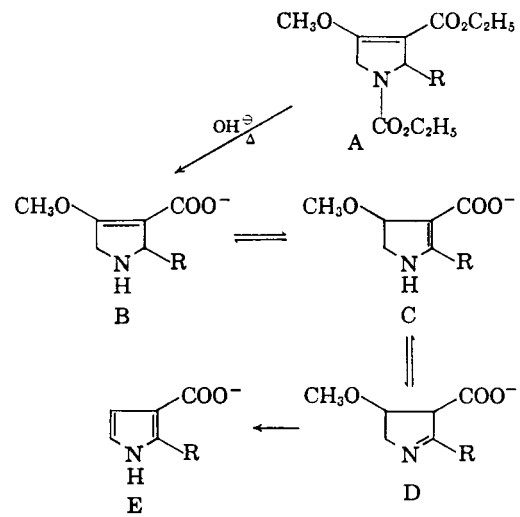


II

We therefore turned to a more vigorous hydrolysis, boiling the pyrroline diester (III) with aqueous barium hydroxide. The only product obtained under these conditions was an acid (I), isolated in 60% yield. This acid (I) could be converted to its methyl ester (V) with diazomethane; I and V were identified as pyrrole-3-carboxylic acid and methyl pyrrole-3-carboxylate, respectively.

The same vigorous hydrolytic conditions, when applied to the pyrrole VI, resulted in a similarly good yield of the corresponding pyrrole acid VII, but when applied to the pyrroline triester IX, gave only a poor yield of the pyrrole diacid X.

A reasonable path by which the β-methoxy-Δ^3-pyrrolines may be converted to the pyrrole-3-carboxylic acids is shown in the following scheme:



Strong alkaline hydrolysis of the ester removes the *N*-carbethoxyl group as well, and the resulting pyrroline may equilibrate among the Δ^3, Δ^2, and Δ^1 forms, B, C, and D. Elimination of the β-methoxyl group from isomer D now takes place readily because of the increased acidity of the hydrogen[5] alpha to the carboxyl.

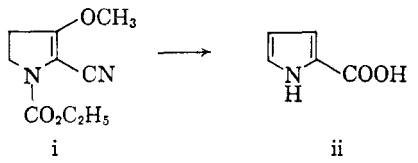
(1) Public Health Service Predoctoral Research Fellow of the National Institute of Mental Health.

(2) I. J. Rinkes, *Rec. trav. chim.*, **56**, 1224 (1937).

(3) I. J. Rinkes, *Rec. trav. chim.*, **57**, 426 (1938).

(4) R. A. Nicolaus and L. Mangoni, *Gazz. chim. ital.*, **86**, 358 (1956).

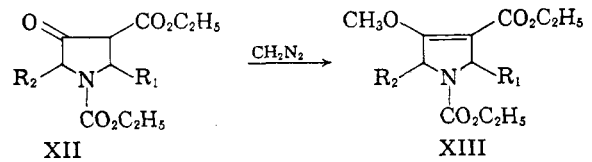
(5) A similar reaction which appears to proceed by the same type of mechanism is the conversion of the pyrroline (i) to the pyrrole acid (ii) by a vigorous alkaline hydrolysis. This reaction will be described in a forthcoming publication.



i ii

In the case where R is carboxyl, isomer C would be the most stable, hence the poor yield of pyrrole-2,3-carboxylic acid on hydrolysis of the triester IX.

By the nature of the reaction, this new synthesis may be employed only in the preparation of pyrrole-3-carboxylic acids unsubstituted at the 1- and 4-positions, since these are the positions from which the carbethoxyl and methoxyl groups, respectively, are eliminated. Otherwise, its application appears to be quite broad. The starting materials are the corresponding 3-pyrrolidones (XII) which are available in variety and in excellent yield by condensation of an *N*-carbethoxy-α-amino acid ester and an α,β-unsaturated ester.[6] Treatment with diazomethane then gives the enol methyl ether XIII.



XII XIII

EXPERIMENTAL[7]

1,3-Dicarbethoxy-4-methoxy-Δ^3-pyrroline (III). To an ethereal solution of 1,3-dicarbethoxy-4-pyrrolidone[6] (69.0 g., 0.3 mole) was added a large excess of ethereal diazomethane. The reaction was carried out at 0°, the diazomethane being added over a period of 15 min. After standing for 3 hr. at room temperature, the reaction mixture was evaporated to a residue which was dissolved in fresh ether and shaken once with 1*N* sodium hydroxide. The ether phase was distilled through a 1-meter Podbielniak column to yield, after a forerun at 104–140°/2.3 mm., 60 g. (83%) of 1,3-dicarbethoxy-4-methoxy-Δ^3-pyrroline (III), m.p. 65–66°; ultraviolet absorption: $\lambda_{max}^{C_2H_5OH}$ 248 mμ (ϵ 7400); infrared absorption: $\lambda_{max}^{CHCl_3}$ 5.85–5.95 μ (s), 6.08 (s).

Anal. Calcd. for $C_{11}H_{17}O_5N$: C, 54.3; H, 7.0; N, 5.8; OR, 3.00/243. Found: C, 54.0; H, 7.2; N, 5.9; OR, 3.02/243.

1,3-Dicarbethoxy-2-methyl-4-methoxy-Δ^3-pyrroline (VI). Treatment of 1,3-dicarbethoxy-2-methyl-4-pyrrolidone[6] (9.7 g., 0.04 mole) with diazomethane was carried out exactly as described above. Distillation of the ether phase at 123–125°/1.0 mm. gave 9.8 g. (94%) of a clear liquid, 1,3-dicarbethoxy-2-methyl-4-methoxy-3-pyrroline (VI); ultraviolet absorption: $\lambda_{max}^{C_2H_5OH}$ 248 mμ (ϵ 4100); infrared absorption: $\lambda_{max}^{CHCl_3}$ 5.85–5.95 μ (s), 6.07 (s).

Anal. Calcd. for $C_{12}H_{19}O_5N$: C, 56.0; H, 7.4; OR, 3.00/257. Found: C, 55.8; H, 7.5; OR, 2.95/257.

1,2,3-Tricarbethoxy-4-methoxy-Δ^3-pyrroline (IX). This was prepared from 1,2,3-tricarbethoxy-4-pyrrolidone by the procedure of Kuhn and Osswald;[6] ultraviolet absorption: $\lambda_{max}^{C_2H_5OH}$ 248 mμ (ϵ 7010); infrared absorption: $\lambda_{max}^{CHCl_3}$ 5.80–6.00 μ (s), 6.07 (m).

1-Carbethoxy-3-carbomethoxy-4-methoxy-Δ^3-pyrroline (IV). A solution of 1,3-dicarbethoxy-4-methoxy-Δ^3-pyrroline (III) (5.0 g., 0.0205 mole) in 60% aqueous methanol was stirred at 60°, while a sodium hydroxide solution was added to bring the *p*H to 11. As the *p*H dropped to *p*H 10 or less, more sodium hydroxide was added to return the *p*H to 11. After 9 hr., 100 mole % of alkali had been consumed, and the *p*H remained constant under these conditions for an additional 12 hrs. In contrast to the starting material, which has ultraviolet absorption at 248 mμ, this solution now absorbed at 237 mμ, but on acidification, the λ_{max} returned to 248 mμ. This dark brown alkaline solution was acidified to *p*H 5 with phosphoric acid and extracted with 1-butanol (6 × 50 ml.). The combined butanol extracts were evaporated *in vacuo*, and the residue was dissolved in ether and treated with a large excess of ethereal diazomethane. After standing for 3 hr. at room temperature, the reaction mixture was evaporated to a residue which was dissolved in fresh ether and washed once with aqueous sodium carbonate, and the ether phase was evaporated to a crystalline residue. Crystallization from hexane and resublimation at 85°/0.1 mm. gave 3.1 g. (66%) of 1-carbethoxy-3-carbomethoxy-4-methoxy-Δ^3-pyrroline (IV), m.p. 90–93°; ultraviolet absorption: $\lambda_{max}^{C_2H_5OH}$ 248 mμ (ϵ 7450); infrared absorption: $\lambda_{max}^{CHCl_3}$ 5.85–5.95 μ (s); 6.08 (s).

Anal. Calcd. for $C_{10}H_{15}O_5N$: C, 52.4; H, 6.6; N, 6.1; OR, 3.00/229. Found: C, 52.8; H, 6.3; N, 6.0; OR, 2.95/229.

The alkyl iodides resulting from the alkoxyl determination were trapped in toluene and examined by gas phase chromatography, giving a ratio of ethyl iodide to methyl iodide of 1:2.

Pyrrole-3-carboxylic acid (I). A heterogeneous mixture of 12.2 g. (0.05 mole) of 1,3-dicarbethoxy-4-methoxy-Δ^3-pyrroline (III) and 50 g. (0.11 mole) of barium hydroxide octahydrate in 250 ml. of water was boiled for 4 hr. The light yellow suspension was filtered, the filtrate was extracted with ether (2 × 100 ml.), and the aqueous phase was acidified to *p*H 1 with 12*N* sulfuric acid. The precipitated barium sulfate was removed, the filtrate was extracted with chloroform (5 × 50 ml.), and the combined chloroform extracts were evaporated to a crystalline residue, which was sublimed at 100°/0.1 mm. to yield 3.0 g. (60%) of pyrrole-3-carboxylic acid (I), m.p. 150–150.5° (reported m.p. 148°,[2] and 146–147°[8]); ultraviolet absorption: $\lambda_{max}^{C_2H_5OH}$ 222.5 mμ (ϵ 7,725), 245 (5,165); infrared absorption: $\lambda_{max}^{CHCl_3}$ 2.92 μ (m), 5.97 (s); pK_a' 5.07 (reported pK_a 4.95[9]).

Methyl pyrrole-3-carboxylate (V). To an ethereal solution of pyrrole-3-carboxylic acid (I) was added a large excess of ethereal diazomethane at room temperature over a period of 5 min. After standing at room temperature for 3 hr., the solution was evaporated, and the residue was dissolved in fresh ether which was washed with 1*N* sodium hydroxide. Evaporation of the ether phase left a crystalline residue, which was sublimed at 60°/1.0 mm. to yield 90% of methyl pyrrole-3-carboxylate (V), m.p. 86–87° (reported m.p. 87°,[2] 88–89°[8]); ultraviolet absorption: $\lambda_{max}^{C_2H_5OH}$ 224 mμ (ϵ 7966), 247 (5310); infrared absorption: $\lambda_{max}^{CHCl_3}$ 2.82 μ (s), 3.55 (w), 5.82 sh (m), 5.90 (s).

2-Methylpyrrole-3-carboxylic acid (VII). A mixture of 1.0 g. (3.9 mmoles) of 1,3-dicarbethoxy-2-methyl-4-methoxy-Δ^3-pyrroline (VI) and 5.0 g. (11.0 mmoles) of barium hydroxide octahydrate in 100 ml. of water was boiled for 4 hr. The suspension was filtered, the filtrate was extracted with ether (2 × 50 ml.), the aqueous phase was acidified to *p*H 1 with 12*N* sulfuric acid, and the precipitated barium sulfate was removed by filtration. The filtrate was extracted with ether (5 × 50 ml.), and the combined ether extracts were evaporated to a crystalline residue which was sublimed at 100°/0.1 mm. to yield 310 mg. (60%) of 2-methylpyrrole-3-

(6) R. Kuhn and G. Osswald, *Ber.*, 89, 1423 (1956).

(7) All melting points are corrected; boiling points are not corrected. Microanalyses were performed by V. Tashinian, Microchemical Laboratory, University of California, Berkeley.

(8) M. Scrocco and R. A. Nicolaus, *Atti accad. naz. Lincei. Rend. Classe sci. fis. mat. e nat.*, 20, 795 (1956).

(9) M. Scrocco and R. A. Nicolaus, *Atti accad. naz. Lincei. Rend. Classe sci. fis. mat. e nat.*, 22, 311 (1957).

carboxylic acid (VII), decomposing sharply at 178–179° (reported[10] m.p. 168° dec.); ultraviolet absorption: $\lambda_{max}^{C_2H_5OH}$ 222 mμ (ε 7297), 254 (6014); infrared absorption: $\lambda_{max}^{CHCl_3}$ 2.91 μ (w), 3.07 (m), 6.02 (s); pK_a' 5.75 (reported pK_a 5.80[9]).

Methyl 2-methylpyrrole-3-carboxylate (VIII). To an ethereal solution of 2-methylpyrrole-3-carboxylic acid (VII) was added a large excess of ethereal diazomethane at room temperature, over a period of 5 min. After standing at room temperature for 3 hr., the solution was evaporated to a residue, which was dissolved in fresh ether, and washed once with 1*N* sodium hydroxide. The ether phase was evaporated to a crystalline residue, which was sublimed at 40°/0.1 mm. to yield 95% of methyl 2-methylpyrrole-3-carboxylate (VIII), m.p. 67–68°; ultraviolet absorption: $\lambda_{max}^{C_2H_5OH}$ 223 mμ (ε 7398); 255 (6341); infrared absorption: $\lambda_{max}^{CHCl_3}$ 2.92 μ (m), 3.07 (w), 5.88 sh (m), 5.93 (s).

Pyrrole-2,3-dicarboxylic acid (X). A mixture of 7.0 g. (0.022 mole) of 1,2,3-tricarbethoxy-4-methoxy-Δ^3-pyrroline (IX) and 30 g. (0.066 mole) of barium hydroxide octahydrate in 100 ml. of water was boiled for 4 hr. The acidic fraction was isolated as above, and the combined ether extracts were evaporated to a solid residue which was sublimed at 180°/0.1 mm.; yield, 170 mg. (5%) of pyrrole-2,3-dicarboxylic acid (X), m.p. 220° dec., sintering at 150° (reported[8] m.p. 225° dec.); ultraviolet absorption: $\lambda_{max}^{C_2H_5OH}$ 241 mμ (ε 2,450), 276 (4,200).

Dimethyl pyrrole-2,3-dicarboxylate (XI). An ethereal solution of pyrrole-2,3-dicarboxylic acid (X) was treated with a large excess of ethereal diazomethane, and the neutral fraction was isolated as above, yielding, after sublimation at 50°/0.1 mm., 36 mg. of dimethyl pyrrole-2,3-dicarboxylate (XI), m.p. 69–71° (reported[11] m.p. 72–73°); ultraviolet absorption: $\lambda_{max}^{C_2H_5OH}$ 242 mμ (ε 2580), 278 (4422); infrared absorption: $\lambda_{max}^{CHCl_3}$ 3.00 μ (m), 5.84 (s), 5.94 (s).

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(10) E. Benary, *Ber.*, **44**, 495 (1911).

(11) M. Scrocco and R. A. Nicolaus, *Atti accad. naz. Lincei. Rend. Classe sci. fis. mat. e nat.*, **22**, 500 (1957).

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

Synthesis of Angularly Substituted Octa- and Decahydroquinolines[1]

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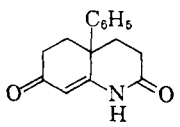
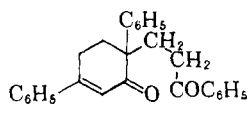
4a-Phenyl-Δ^8-octahydro-2,7-quinolinedione (I) and its *N*-methyl derivative have been reduced with hydrogen and palladium, hydrogen and nickel, and with lithium aluminum hydride. The ultimate reduction product is 4a-phenyldecahydroquinoline or its *N*-methyl derivative, but selection of an appropriate reducing agent enables one to obtain various intermediates in good yield.

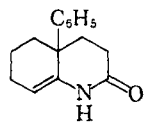
Some time ago it was found that 4a-phenyl-Δ^8-octahydro-2,7-quinoline-dione could be obtained in quantity from readily available materials.[3] The presence of a quaternary carbon in I made it desirable to convert the substance into basic derivatives, for these might have interesting pharmacological properties. Results of experiments in this direction are now reported.



I



II

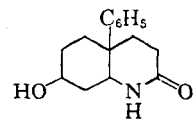


III

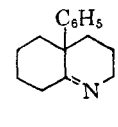
With Grignard reagents, I formed insoluble complexes whose hydrolysis gave back I unchanged. The *N*-methyl derivative of I reacted with phenylmagnesium bromide at both carbonyl groups, but the product lost nitrogen when it was treated with water, and only II was isolated. The structure of this substance was established by synthesis through base-catalyzed reaction of phenylacetone with two equivalents of acrylophenone.

With hydrogen in presence of palladium-charcoal, I lost the ketonic oxygen, forming III. The *N*-methyl derivative of I behaved similarly, forming the *N*-methyl derivative of III. Both of these substances gave the same hydrolysis product, 2-phenylcyclohexanone-2-propionic acid.

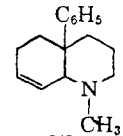
With hydrogen in presence of Raney nickel, I gave a mixture, m.p. 170–205°, in contrast to the previously claimed[3] quantitative formation of IV, erroneously reported to have m.p. 117–119°. The mixture furnished only 48% of IV, m.p. 227–229°, together with 6% of III, and no other pure product could be isolated.



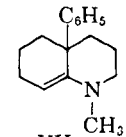
IV



V



VI



VII

With lithium aluminum hydride, I gave V, a deoxidation similar to those discussed by Gaylord.[4] The product (V) was further reduced, using Raney nickel, to known 4a-phenyldecahydroquinoline,

(1) From the Ph.D. Thesis of D. L. Ostercamp, September 1959.

(2) National Science Fellow, 1958–59.

(3) C. F. Koelsch and H. M. Walker, *J. Am. Chem. Soc.*, **72**, 346 (1950).

(4) N. G. Gaylord, Experientia, **10**, 166 (1954). In agreement with structural deductions based on Gaylord's mechanism, the compound showed no NH absorption, and a strong band at 1650 cm.$^{-1}$, corresponding to the 1658 cm.$^{-1}$ C=N band of $\Delta^{1,8a}$-octahydroquinoline assigned by Witkop, *J. Am. Chem. Soc.*, **78**, 2873 (1956).