[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY,
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DECARBOXYLATION AND FORMYLATION OF CERTAIN PYRROLE DERIVATIVES*[1]

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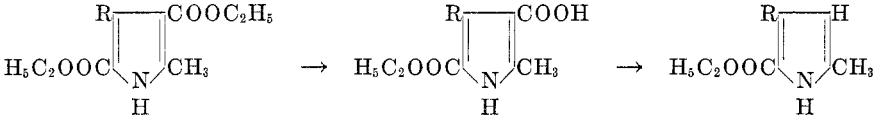
Synthetic samples of coproporphyrin I and III are needed for a further study of the paper chromatography of their dimethyl esters (1). The work reported here is concerned with improved procedures for the preparation of 2,4-dimethyl-5-carbethoxypyrrole and its 3-formyl derivative which are the intermediates needed for the synthesis of coproporphyrin I according to the method of Fischer, *et al.* (2). Similar procedures were used to prepare the related 2-methyl-4-phenyl derivatives.

For the preparation of 2,4-dimethyl-5-carbethoxypyrrole (III), the authors used the method of Fischer and Walach (3) in preference to several other methods described in the literature (4–7). It was prepared from 2,4-dimethyl-3,5-dicarbethoxypyrrole (I) (8–11) by the partial hydrolysis to and subsequent decarboxylation of 2,4-dimethyl-3-carboxy-5-carbethoxypyrrole (II).



I R = CH_3 II R = CH_3 III R = CH_3
IV R = C_6H_5 V R = C_6H_5 VI R = C_6H_5

For decarboxylation the modified procedure of Fischer, *et al.* (12) with glycerol as the heating medium was first tried. However, the evolution of carbon dioxide from the reaction mixture resulted in bad foaming and was very inconvenient. Although this can be controlled by dehydrating the glycerol immediately prior to its use,[2] a more satisfactory solvent was found. Furthermore, the partial decomposition of glycerol at the high temperature necessary for the decarboxylation increased impurities in the product and necessitated purification by distillation, thus lowering the yield. In looking for a suitable solvent capable of absorbing carbon dioxide, 2-aminoethanol was found to be excellent and at its boiling point 2,4-dimethyl-3-carboxy-5-carbethoxypyrrole was smoothly decarboxylated, the carbon dioxide forming 2-aminoethanol bicarbonate (13).

Searching the literature revealed only one example in which 2-aminoethanol was employed as the solvent in a decarboxylation, with 15-carboxy-14,15-dehydroequilenin methyl ether (14); the authors, however, did not report the yield of decarboxylated product, 14,15-dehydroequilenin. On the other hand it has been reported that several aliphatic and aromatic carboxylic acids react with 2-aminoethanol to form ethanolamides (15) without decarboxylation.

* Dedicated to the late Professor W. E. Bachmann.

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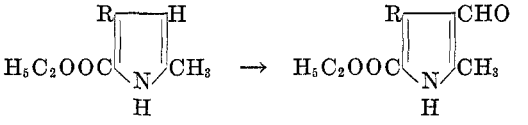
[2] We wish to thank the referee for this information.

In order to test further the applicability of the method, 2-methyl-4-phenyl-3-carboxy-5-carbethoxypyrrole (V) was prepared by partial hydrolysis of 2-methyl-4-phenyl-3,5-dicarbethoxypyrrole (IV). Decarboxylation of this acid (V) also proceeded smoothly in boiling 2-aminoethanol, giving the new 2-methyl-4-phenyl-5-carbethoxypyrrole (VI) in 84% yield.

It appears that the use of 2-aminoethanol in decarboxylation is quite favorable for substituted carboxypyrroles and should find a wide application in the synthesis of pyrrole derivatives.

An improved procedure was also developed for the introduction of a 3-formyl group into these pyrrole derivatives using N,N-dimethylformamide.[3] This reagent has been reported by others to be a good formylation agent for aromatic tertiary amines (16), indole (17), thiophenes (18), and other aromatic compounds (19).



III R = CH_3 VII R = CH_3
VI R = C_6H_5 VIII R = C_6H_5

With 2,4-dimethyl-5-carbethoxypyrrole (III) the yield of the 3-aldehyde derivative was 95% by this method. 2-Methyl-4-phenyl-3-formyl-5-carbethoxypyrrole (VIII) was prepared in a similar manner in excellent yield (97%). An isomer of this compound, 2-methyl-4-phenyl-5-formyl-3-carbethoxypyrrole, was prepared by Cook and Majer (20) with the less available formylating agent, N-methylformanilide and phosphorus oxychloride (21).

EXPERIMENTAL[4]

Preparation of 2,4-dimethyl-3,5-dicarbethoxypyrrole (I) *and 2-methyl-4-phenyl-3,5-dicarbethoxypyrrole* (IV). 2,4-Dimethyl-3,5-dicarbethoxypyrrole was prepared by the Knorr synthesis (8, 9) according to the procedure of Fischer (10). Recrystallization from 95% alcohol yielded colorless needles, 63%, m.p. 135–136°.

A similar procedure was employed to prepare 2-methyl-4-phenyl-3,5-dicarbethoxypyrrole (IV). To the dilute acetic acid solution of ethyl α-nitroso-α-benzoylacetate prepared from 38.5 g. of ethyl benzoylacetate, 28.5 g. of ethyl acetoacetate was added at once. Then 28.5 g. of zinc dust was gradually added, the temperature being controlled so that the reaction mixture was gently boiling during the addition. It was refluxed for two hours and poured into cold water. The crude product was filtered, washed, and recrystallized from 95% alcohol to yield 38 g. (63%) of colorless prisms, m.p. 124–125°.

Anal. Calc'd for $C_{17}H_{19}NO_4$: C, 67.76; H, 6.36; N, 4.65.
Found: C, 67.64; H, 6.37; N, 4.66.

Partial hydrolysis of 2,4-dimethyl-3,5-dicarbethoxypyrrole (I) *and 2-methyl-4-phenyl-3,5-dicarbethoxypyrrole* (IV). The diesters were respectively hydrolyzed by treatment with concentrated sulfuric acid at 40–50° according to the procedure of Fischer (10). For purification they were dissolved in 20% sodium hydroxide solution and reprecipitated by acetic acid. Recrystallization of 2,4-dimethyl-3-carboxy-5-carbethoxypyrrole (II) from acetone

[3] A gift from E. I. du Pont de Nemours and Co., Wilmington, Delaware.

[4] Analyses were done by Dr. A. Elek, Los Angeles, California. All melting points are uncorrected.

yielded 85% of fine prisms. It starts to sublime above 190° and melts with decomposition at 272°.

Recrystallization of 2-methyl-4-phenyl-3-carboxy-5-carbethoxypyrrole (V) from 95% alcohol yielded 78% of colorless platelets, m.p. 220° with decomposition.

Anal. Calc'd for $C_{15}H_{15}NO_4$: C, 65.92; H, 5.53; N, 5.13.
Found: C, 65.98; H, 5.59; N, 5.18.

Decarboxylation of 2,4-dimethyl-3-carboxy-5-carbethoxypyrrole (II) *and 2-methyl-4-phenyl-3-carboxy-5-carbethoxypyrrole* (V). A mixture of 21.1 g. of II and 12.2 g. of 2-aminoethanol was refluxed on a sand-bath for one hour and poured into cold water. The crude 2,4-dimethyl-5-carbethoxypyrrole (III) was filtered, washed, and recrystallized from 95% alcohol to yield 15.3 g. (90%) of colorless prisms, m.p. 124.5–125°.

2-Methyl-4-phenyl-3-carboxy-5-carbethoxypyrrole was likewise decarboxylated to 2-methyl-4-phenyl-5-carbethoxypyrrole (VI). Recrystallization from 95% alcohol gave an 84% yield of colorless needles, m.p. 134.5–135°.

Anal. Calc'd for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11.
Found: C, 73.15; H, 6.72; N, 6.03.

Formylation of 2,4-dimethyl-5-carbethoxypyrrole (III) *and 2-methyl-4-phenyl-5-carbethoxypyrrole* (VI). To a cold mixture of 13.4 g. of III and 7.3 g. of N,N-dimethylformamide,[3] there was gradually added 15.4 g. of phosphorus oxychloride through a condenser, which was then connected to a calcium chloride tube. After the vigorous reaction was over, the reaction mixture was refluxed on a steam-bath for two hours. The brown mass was then stirred with ice-water and neutralized to Congo Red with a saturated solution of sodium acetate. The crude 2,4-dimethyl-3-formyl-5-carbethoxypyrrole (VII) was filtered, washed with a small amount of cold water, and recrystallized from 50% alcohol. A yield of 14.8 g. (95%) of colorless needles resulted, m.p. 145–145.5°. Fischer, *et al.* (4) prepared the same compound in 85% yield by the Gattermann formylation with hydrogen cyanide and hydrogen chloride.

Its *oxime* and *semicarbazone* were also prepared. The oxime melts at 199–200° and semicarbazone decomposes at about 275° with sublimation and without a definite m.p. Fischer, *et al.* (4) reported 196–197° for oxime and 285° for the semicarbazone.

2-Methyl-4-phenyl-3-formyl-5-carbethoxypyrrole (VIII) was similarly prepared from 11.5 g. of VI by treatment with 4.6 g. of N,N-dimethylformamide and 9.6 g. of phosphorus oxychloride. Recrystallization from 95% alcohol yielded 12.4 g. (97%) of colorless prisms, m.p. 144.5–145°.

Anal. Calc'd for $C_{15}H_{15}NO_3$: C, 70.02; H, 5.88; N, 5.44.
Found: C, 69.53; H, 5.90; N, 5.49.

The *oxime* was prepared in a yield of 96% of colorless plates from 95% alcohol, m.p. 210–211°.

Anal. Calc'd for $C_{15}H_{16}N_2O_3$: C, 66.16; H, 5.92; N, 10.29.
Found: C, 66.07; H, 6.02; N, 10.28.

The *semicarbazone* was also prepared in a yield of 66%, fine needles from pyridine. It decomposes at about 280° with sublimation but without a definite m.p.

Anal. Calc'd for $C_{16}H_{18}N_4O_3$: C, 61.13; H, 5.77; N, 17.83.
Found: C, 61.84; H, 5.61; N, 17.41.

SUMMARY

Boiling 2-aminoethanol was found to be an excellent decarboxylation agent for substituted carboxypyrroles. 2,4-Dimethyl-3-carboxy-5-carbethoxypyrrole and 2-methyl-4-phenyl-3-carboxy-5-carbethoxypyrrole were smoothly decarboxylated to 2,4-dimethyl-5-carbethoxypyrrole and 2-methyl-4-phenyl-5-carbethoxypyrrole.

N,N-dimethylformamide and phosphorus oxychloride were found to be superior reagents for formylation of these pyrrole derivatives, giving nearly quantitative yields of the 2,4-dimethyl- and 2-methyl-4-phenyl-5-carbethoxy-3-formyl pyrroles.

The 4-phenyl pyrrole derivatives had not been previously reported.

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