

A mixed melting point of the nitrosamine with dicyclohexylammonium nitrite showed the normal depression and wide range. N-Nitroso di-cyclohexylamine failed to give nitric oxide fumes on treatment with cold hydrochloric acid.

Summary

1. A new method is described for the preparation of alkyl ammonium nitrites from amines, employing sodium nitrite, carbon dioxide and metha-

nol. The nitrites of isopropylamine, diisopropylamine, diisobutylamine and triethylamine have been prepared.

2. Alkyl ammonium nitrite salts of primary amines of low molecular weight and the salts of tertiary amines are in general hygroscopic while the salts of secondary amines are not hygroscopic.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE JOHNS HOPKINS UNIVERSITY]

The Selective Degradation of Certain Pyrrol Polycarboxylic Esters^{1,2}

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Publication of a method for the conversion of Knorr's pyrrole (2,4-dimethyl-3,5-dicarbethoxy-pyrrole) into 2-carboxyl-3,5-dicarbethoxy-4-methylpyrrole⁴ opened the way for the preparation of many new pyrrole derivatives from this substance, providing that methods for selective degradations of the new acid could be found. The present paper describes these selective degradations. Knorr's pyrrole is already one of the most readily available substitution products of pyrrole. The numerous additional substances that can be prepared from it by transformations recorded below make it the most versatile of all pyrrole derivatives in the number and variety of chemical individuals which can be prepared from it.

Mechanism of Formation of 2-Carboxyl-3,5-dicarbethoxy-4-methylpyrrole.—When Knorr's pyrrole is chlorinated with sulfuryl chloride in glacial acetic acid, best yields of the desired acid are obtained if the reaction is performed at as low a temperature as possible. The use of 5% acetic anhydride lowers both the freezing point of the solution and its water content and increases the yield of acid by 5–10%. Increasing the temperature of the reaction, on the other hand, lowers the yield of acid and increases the yield of aldehyde. This observation suggests that the aldehyde represents a by-product of the reaction and not an intermediate in the formation of the acid. This conclusion was confirmed by attempting to halogenate the aldehyde under the conditions of the reaction. No acid could be obtained and the aldehyde was recovered unchanged. When the same reaction was tried using 2-dichloromethyl-3,5-dicarbethoxy-4-methylpyrrole, however, 45% of acid and 36% of aldehyde could be obtained. These results show that the dichloromethylpyrrole can be an intermediate in the reaction and that any of it which is converted to aldehyde in the course of the reaction will not yield acid.

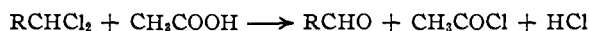
(1) Studies in the Pyrrole Series, XX; Paper XIX, Erdman and Corwin, *THIS JOURNAL*, **69**, 750 (1947).

(2) This paper is taken from the doctoral dissertation of John Lloyd Straughn, The Johns Hopkins University.

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(4) Corwin, Bailey and Vioht, *THIS JOURNAL*, **64**, 1267 (1942).

It is possible to convert benzal chloride and acetic acid to benzaldehyde and acetyl chloride.⁵ The analogous reaction in the pyrrole series can be represented schematically as



It is easily demonstrated that this reaction proceeds at 50° but not rapidly at 17°. At the higher temperature hydrogen chloride is given off and the distillate contains acetyl chloride, as shown by its reaction with aniline to form acetanilide. The dichloromethylpyrrole is best prepared by chlorination in chloroform, to avoid the possibility of aldehyde formation.

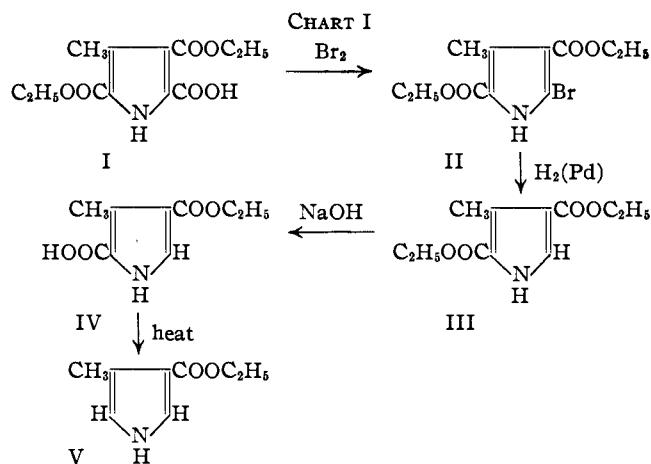
It follows from the observations recorded above that the aldehyde is not an intermediate in the formation of the acid, that the dichloro- and trichloro-pyrroles are intermediates and that reaction conditions should be directed toward the stabilization of the dichloromethylpyrrole.

The Stability of Pyrrol-carboxylic Acids.—By methods outlined below several pyrrol-carboxylic acids were prepared which had one methyl group and various combinations of three electron attracting groups, either carboxyl or carboxylic ester groups. None of these acids could be decarboxylated smoothly by the usual methods. When combinations were tried which contained only two electron attracting groups, however, decarboxylation took place smoothly. This behavior is analogous to that found in the benzene series in which electron releasing groups, such as phenolic hydroxyl groups, facilitate decarboxylation and the addition of electron attracting groups, such as carboxyl, to phenolic compounds hinders decarboxylation.⁶ Because of this situation, further reactions were directed toward preparation and degradation of derivatives of methyl-dicarboxyl pyrroles.

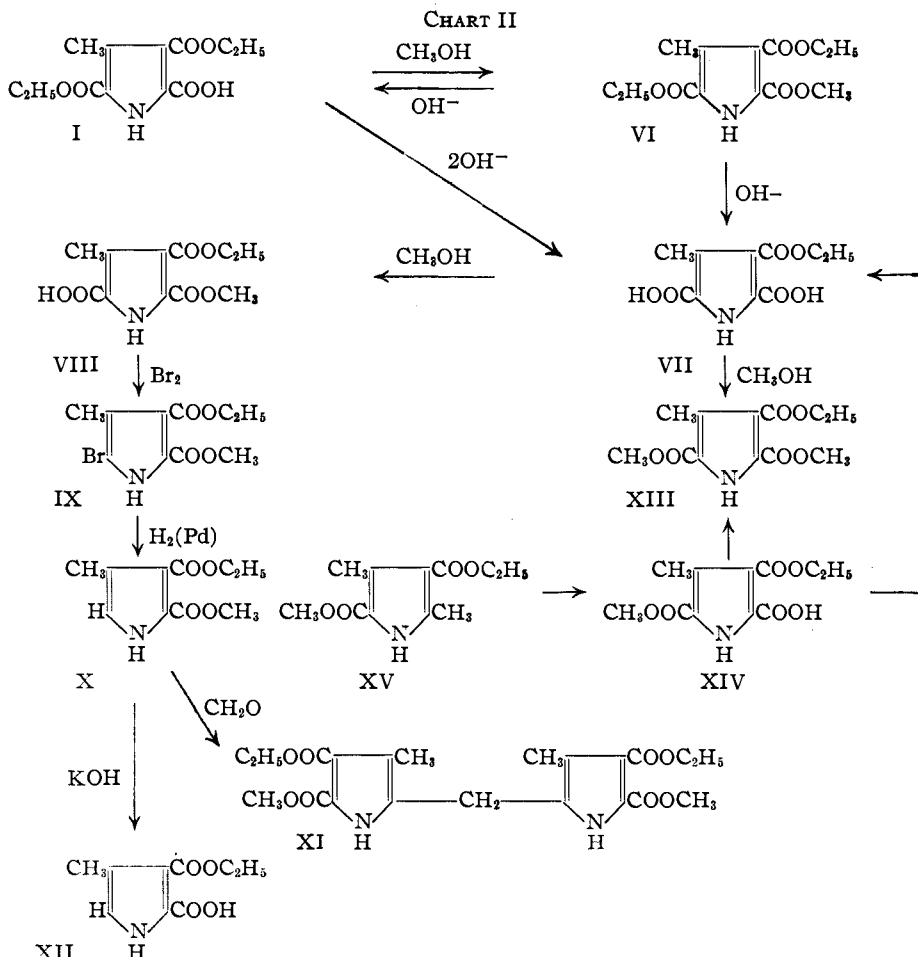
(5) Jacobsen, German Patent 11494 (1879), See *Frdl.*, **1**, 24 (1888).

(6) A close analogy is afforded in the resorcylic acids. 2,6-Dihydroxybenzoic acid decomposes in the range of 150–170° while the addition of a carboxyl group in the 3 position increases the stability so that the material melts at 312° without marked decomposition. See Senhofer and Brunner, *Wien. Akad. Ber.*, **80**, 504 (1879), and Brunner, *Ann.*, **351**, 320 (1907).

The flow sheet for the reactions to free the 2 and 5 positions is given in Chart I.^{4,7}



The flow sheet for the reactions to free the 5 position is given in Chart II.



Compound XIII was prepared from compound XV by reactions analogous to those discussed in

(7) See Corwin and Viohl, *THIS JOURNAL*, **66**, 1145 (1944), for the preparation of compounds IV and V.

the first section of this paper. These reactions prove that compound XIII has a methyl ester group in the 5 position. Compound X had been prepared previously by Fischer and Wiedemann by esterification of XII.⁸ This esterification proves the structure of compound X.

The flow sheet for the freeing of the 3 position is given in Chart III.

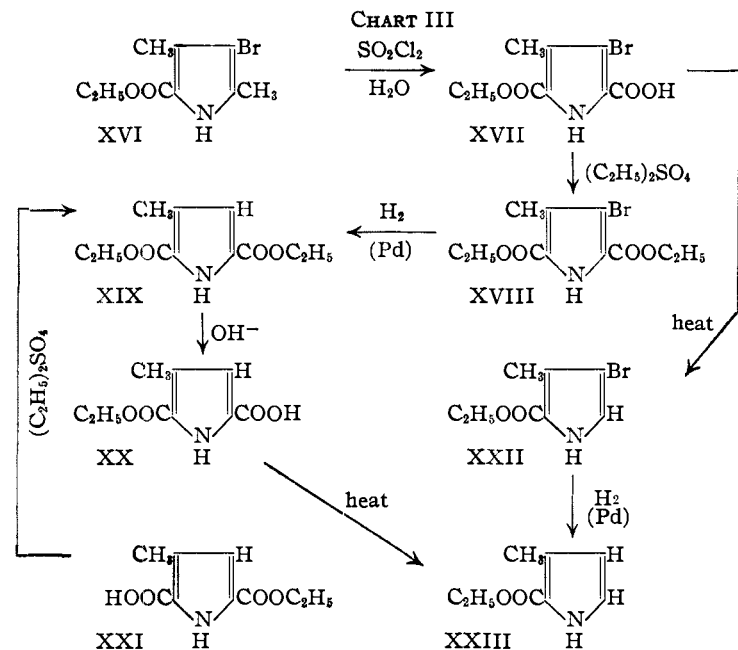
Compounds XXI and XIX were prepared by Kordo, Ono and Sato⁹ by a method which establishes the structure of XIX.

In addition to the reactions outlined above, certain other derivatives of compound I were made as sketched in Chart IV. Interrelationships with substances with previously tagged ester groups are also shown.

The lack of identity of XXV and XXVII makes possible the location of the free carboxyl group in XXV, since it is known from XXXI that the carbomethoxy group in the 3

position is intact. The analysis of XXXI makes

(8) Fischer and Wiedemann, *Z. physiol. Chem.*, **155**, 58 (1926).
 (9) Kordo, Ono and Sato, *J. Pharm. Soc. Japan*, **57**, 1 (1937). See *C. A.*, **31**, 7055 (1937).



it possible to deduce the position of the group in compound XXX which has been hydrolyzed by alkali.

Compounds XXXIII, XXXIV and XXXV were all prepared from compound I. The ester interchange observed in preparing compound XXXIV is not unusual when α -esters are treated with strong base.^{10a} A corresponding change when esterification takes place under the influence of an acid catalyst is rare. The melting point of the triethyl ester, XXXV, is so low, 45–46°, as to render the substance undesirable for preparational purposes. This is the reason for choosing to make derivatives from the monomethyl ester, VIII, which melts at 75°.

The experiments summarized above add five new cases, compounds I, III, VI, X and XXX to the generalization that attack by an alkaline catalyst upon an ester group is oriented α in preference to β whenever there is a choice.

One of us, J. L. S., wishes to acknowledge a grant-in-aid from the Hynson, Westcott and Dunning Research Fund.

Experimental Section

2-Carboxy-3,5-dicarbethoxy-4-methylpyrrole (I).—The directions given by Corwin, Bailey and Viohl⁴ were modified in an effort to find optimum conditions for the reaction. The use of 10% of anhydrous formic acid in glacial acetic acid gave a slight increase in yield, due to the lower freezing point. A 5% solution of acetic anhydride in glacial acetic acid gave a lower freezing point and a consistently higher yield. At 50°, no acid was obtained but a good yield of aldehyde was formed.

2-Formyl-3,5-dicarbethoxy-4-methylpyrrole was treated with bromine and sulfuryl chloride in acetic acid under the conditions used for the halogenation of 2,4-dimethyl-3,5-dicarbethoxypyrrrole. The acetic acid was removed

by distillation under reduced pressure and the residue extracted with ether and then with toluene. The ether solution was concentrated by evaporation and the red oil remaining was allowed to crystallize. These crystals give a positive Beilstein test but on treating with alcohol and water the precipitate formed was the starting aldehyde. After partial evaporation of the toluene solution crystals of the aldehyde were also obtained. In still another experiment the halogenation was completed and the hydrolysis with water carried out in a manner identical to that used for the preparation of the acid. No acid was obtained.

When the same reaction was repeated on 2-dichloromethyl-3,5-dicarbethoxy-4-methylpyrrole (see below) a yield of 45% of the acid and 36% of the aldehyde was obtained.

2-Dichloromethyl-3,5-dicarbethoxy-4-methylpyrrole.—Fifty grams of 2,4-dimethyl-3,5-dicarbethoxypyrrrole was dissolved in 200 cc. of dry, freshly redistilled C. P. chloroform (U. S. P. chloroform is unsuitable because it contains alcohol); 34 cc. of sulfuryl chloride was added at about 40°. The solution was boiled to remove hydrogen chloride and the chloroform was then removed under vacuum.

The crystals which formed were washed with hexane and crystallized from toluene. The use of alcohol for the crystallization, as suggested by Fischer, Sturm and Friedrich,¹¹ causes decomposition of the substance and is probably responsible for the failure of these investigators to obtain the compound; m. p. 124–125°.

Anal. Calcd. for $\text{C}_{12}\text{H}_{16}\text{O}_4\text{NCl}_2$: C, 46.77; H, 4.91. Found: C, 46.83; H, 4.88.

Reaction with Glacial Acetic Acid. (a) Cold.—A solution of 3 g. of the dichloromethylpyrrole in 25 ml. of glacial acetic acid at 17° in a flask was closed with a rubber stopper and placed in an ice-box for eight hours with occasional shaking. The semi-solid mass was then filtered with suction. The filtrate gave no test for acetyl chloride with aniline; 2.3 g. of the starting material was recovered. We conclude that these substances do not react appreciably under the conditions of the trichlorination reaction.

(b) Warm.—A solution of 4 g. of the dichloromethylpyrrole and 25 ml. of glacial acetic acid was placed in a 50-ml. round flask fitted with a small fractionating column with a condenser attached to the side arm. The solution was heated on a water-bath for one hour at 50°, then distilled. The fraction below 60° gave a crystalline precipitate with aniline, identified as acetanilide by its melting point. The solid remaining in the flask was crystallized from dry toluene. A mixed m. p. with 2-formyl-3,5-dicarbethoxy-4-methylpyrrole gave no depression.

2-Carbomethoxy-3,5-dicarbethoxy-4-methylpyrrole (VI). **First method.**—Five grams of (I) was dissolved in a cold solution of 1.1 g. of potassium hydroxide in 25 ml. of methanol and 2.3 ml. of dimethyl sulfate added dropwise while stirring. After standing half an hour, it was poured into aqueous sodium bicarbonate, filtered and the precipitate crystallized from methanol-water. The methyl ester can be purified by distillation at 235–240° at 20 mm. or by crystallization from hexane, in which it is slightly soluble; m. p. 75°.

Second Method.—This is the method of choice. To a mixture of 25 g. of (I) in 125 ml. of anhydrous methanol in a 250 ml. standard taper Erlenmeyer flask 1.5 g. of dry hydrogen chloride was added and the solution then refluxed for an hour. The solution was stirred into five times its volume of ice water containing 6 g. of sodium

(10) Corwin and Ellingson, *THIS JOURNAL*, **66**, (a) 1146, (b) 1150, (c) 1149 (1944).

(11) Fischer, Sturm and Friedrich, *Ann.*, **461**, 267 (1928).

bicarbonate to dissolve any starting material. The ester separated after two hours of standing and was purified by distillation under reduced pressure and by crystallization from purified hexane; yields, 85–95%; m. p. 75°. This ester is insoluble in bicarbonate but is soluble in sodium hydroxide solutions, due to the acidity of the NH group under the influence of the three electron-attracting groups present.

Anal. Calcd. for $C_{13}H_{17}O_6N$: C, 55.09; H, 6.05. Found: C, 55.17; H, 5.92.

2,5-Dicarboxy-3-carbethoxy-4-methylpyrrole (VII).—This substance is best prepared from (I). Fifteen grams of (I), 4.5 g. of sodium hydroxide and 150 ml. of water were refluxed two and one-half hours in a 500-ml. Erlenmeyer flask. The solution was poured into an equal volume of water and acidified to the congo red endpoint with hydrochloric acid. The precipitate was filtered off, washed well with distilled water and pressed dry. The pyrrole acid was then resuspended in water to remove the hydrochloric acid. After filtering and washing, it was dried to constant weight at 70°. A small amount of the di-acid was obtained from the filtrates by allowing them to stand. The material was crystallized from ethanol and from 60% acetone in water; yield (crude), 85–95%; m. p. 236–237° (dec.).

Anal. Calcd. for $C_{10}H_{11}O_6N$: C, 49.79; H, 4.60. Found: C, 49.71; H, 4.56.

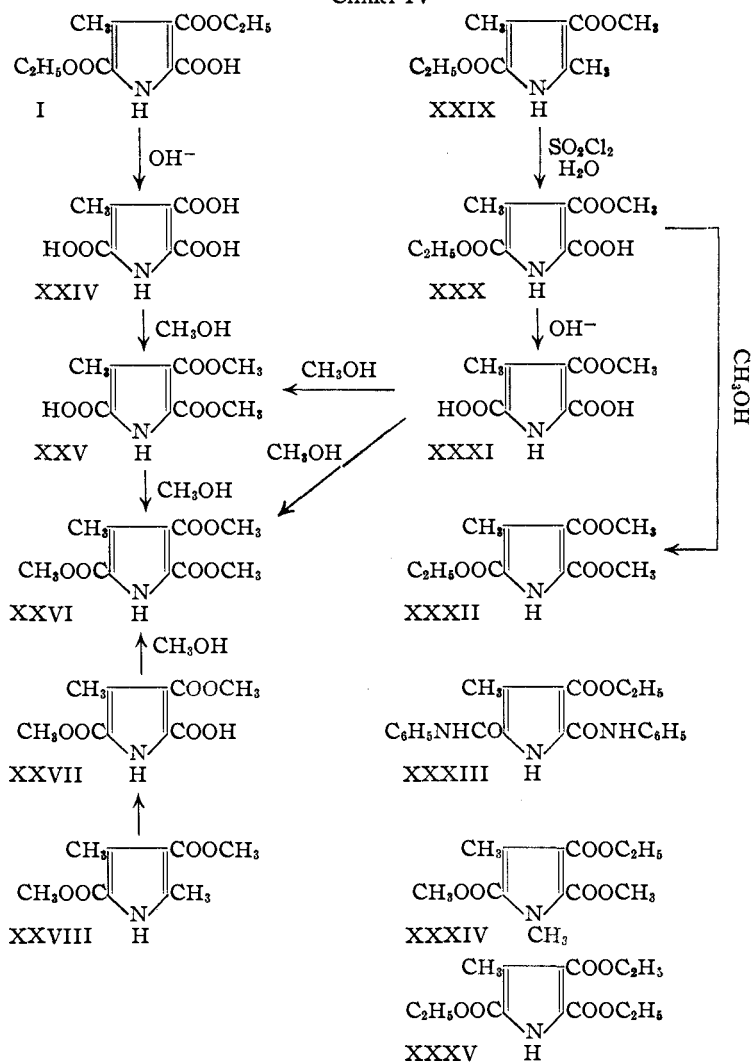
The crude material is sufficiently pure for subsequent reactions if prepared from starting material which has been recrystallized several times from ethanol.

The same substance is obtained by the alkaline hydrolysis of (VI) and of (XXXV). The acidity of the pyrrole nitrogen is sufficient in each case to dissolve the pyrrole esters in aqueous alkali.

2-Carbomethoxy-3-carbethoxy-4-methyl-5-carboxypyrrole (VIII).—Seven and three-tenths grams of (VII) previously crystallized from acetone-water, and 75 ml. of methanol containing 0.5 g. of dry hydrogen chloride were refluxed in a 250-ml. Erlenmeyer flask for one hour, the solution cooled to room temperature and then poured into 300 ml. of ice water containing sufficient sodium bicarbonate to dissolve the half esterified pyrrole. After standing in the ice-box for one hour, the by-product (XIII) was filtered off (dry yield 0.7 g.) and the 5-carboxypyrrole was isolated by acidification of the filtrate. It was washed with water and dried in the oven at 70°; yield, 6.2 g. or 88%. The pyrrole was crystallized from acetone-water or alternatively from acetone-hexane; m. p. 204–205°.

2-Carbomethoxy-3-carbethoxy-4-methyl-5-bromopyrrole (IX).—To a solution of 2.7 g. of (VIII) in 30 ml. of glacial acetic acid at 45°, 1.8 g. of bromine in 8 ml. of glacial acetic acid was added in ten minutes. The solution became clear. After ten minutes of standing 20 ml. of water was added in twenty minutes. After standing for forty-five minutes it was poured into 200 ml. of ice water and placed in the ice-box for one hour. The precipitate was filtered off, washed with water, dissolved in 50 ml. of methanol and sodium bicarbonate added until no more carbon dioxide was evolved. The bromopyrrole was reprecipitated by pouring the methanol solution into 200 ml. of ice water. After standing for one hour, the precipitate was filtered, washed with water and dried at 50°. It can be recrystallized from methanol-water.

CHART IV



A small amount (0.2 g.) of the starting acid was recovered on acidification of the filtrate obtained after the bicarbonate treatment; yield, 1.8 g. or 60%; m. p. 116–117°.

Anal. Calcd. for $C_{10}H_{11}O_4NBr$: C, 41.40; H, 4.17. Found: C, 41.32; H, 4.24. This substance was also obtained by the bromination of compound X (see below).

2-Carbomethoxy-3-carbethoxy-4-methylpyrrole (X).—For the dehalogenation of 2 g. of (IX), it was dissolved in 50 ml. of methanol and 500 mg. of magnesium oxide, 500 mg. of Norite and ten drops of 10% palladium chloride solution were added. The reduction required two hours under a pressure of two atmospheres of hydrogen. The catalyst was filtered off and washed with a few milliliters of hot methanol. The filtrate and washings were combined and dried under reduced pressure below 45°. The solid was dissolved in ether, transferred to a small beaker and the ether evaporated. It was then dissolved in the minimum quantity of ethanol at room temperature and cooled in an ice-bath. Ice water was added, drop by drop, while scratching the sides of the beaker, until the pyrrole crystallized; yield, 1.2 g. or 83%; m. p. 62°.

This pyrrole has also been prepared by the esterification of (XII) with diazomethane⁶; m. p. reported, 59°.

For further identification the pyrrole was brominated in glacial acetic acid. Fine needles of (IX) were obtained, m. p. 116°, mixed m. p., no depression.

2-Carboxy-3-carbomethoxy-4-methylpyrrole (XII).¹²—Two hundred milligrams of (X) was hydrolyzed with 70 mg. of potassium hydroxide and 10 ml. of 80% ethanol. After precipitation and separation from unchanged ester the pyrrole was filtered off, washed, and crystallized from ethanol-water; colorless crystals, m. p. 197–197.5° with loss of carbon dioxide. Piloty and Hirsch¹² report 196°.

3,3'-Dimethyl-4,4'-dicarbomethoxy-5,5'-dicarbomethoxy-dipyrrolylmethane (XI).—Two hundred milligrams of (X), 3 ml. of 70% acetic acid and 0.3 ml. of 40% formaldehyde were refluxed for five minutes and 0.1 ml. more of formaldehyde was added through the condenser. After refluxing for ten minutes longer, 2 ml. of water was added and the solution was placed in an ice box until crystallization was complete. The product was recrystallized from methanol-water; m. p. 158–159°.

Anal. Calcd. for $C_{21}H_{26}O_8N_2$: C, 58.06; H, 6.03. Found: C, 57.79; H, 6.01.

2-Carboxy-3-carbomethoxy-4-methyl-5-carbomethoxy-pyrrole (XIV).—Twenty-five grams of (XV)^{10b} was treated with sulfur chloride and bromine by the procedure given for compound I; yields: aldehyde, 36%; acid 38%; m. p. 187°.

Anal. Calcd. for $C_{11}H_{13}O_8N$: C, 51.76; H, 5.13. Found: C, 51.69; H, 5.17.

2,5-Dicarbomethoxy-3-carbomethoxy-4-methylpyrrole (XIII).—This was prepared from (XIV) by esterification with dimethyl sulfate and with methanol and acid, in each case following the procedure used for compound VI. The latter method gave better yields. The product crystallizes from methanol in colorless crystals; m. p. 131–132°.

Anal. Calcd. for $C_{12}H_{15}O_8N$: C, 53.52; H, 5.62. Found: C, 53.61; H, 5.59.

2-Carboxy-3-bromo-4-methyl-5-carbomethoxypyrrole (XVII).—This was prepared from (XVI)¹³ by a procedure essentially the same as for (I), given above; m. p. 254° with decomposition.

Anal. Calcd. for $C_9H_{10}O_4NBr$: C, 39.13; H, 3.65. Found: C, 39.12, 38.98; H, 4.31, 4.29.

2-Formyl-3-bromo-4-methyl-5-carbomethoxypyrrole.—This was obtained as a by-product in the preceding preparation. If desired in quantity it can be prepared in a manner exactly analogous to that used for 2-formyl-3,5-dicarbomethoxy-4-methylpyrrole.^{4b} It was prepared by Fischer, Berg and Schormüller^{14a} using ether as a solvent. The use of glacial acetic acid is preferable.

2,5-Dicarbomethoxy-3-bromo-4-methylpyrrole (XVIII).¹⁵—This pyrrole was prepared by the esterification of (XVII) with diethyl sulfate in alcoholic potassium hydroxide by the first procedure under compound VI. The product crystallizes from ethanol-water in colorless needles melting at 85°.

Anal. Calcd. for $C_{11}H_{14}O_4NBr$: C, 43.44; H, 4.64. Found: C, 43.43; H, 4.73.

2,5-Dicarbomethoxy-4-methylpyrrole (XIX).—The procedure for the dehalogenation of (XVIII) was the same as that used in the preparation of (X), given above; yield, 62%. Recrystallized from hexane or alcohol-water; m. p. 62°. This pyrrole has also been prepared from (XXI) which in turn was prepared by the condensation of the ethyl ester of glycine hydrochloride with acetylacetoacetic ester in alkaline solution.⁹ Kordo, Ono and Sato report m. p. 61°.

2-Carboxy-4-methyl-5-carbomethoxypyrrole (XX).—One and five-tenths grams of (XIX) was placed in a solution of 0.25 g. of sodium hydroxide in 25 ml. of 80% ethanol and the mixture refluxed for two hours. An equal volume of water was then added, the solution filtered and the

filtrate acidified with hydrochloric acid. The acid was filtered off, washed with water and crystallized from ethanol-water; m. p. 210–215° with decomposition.

Anal. Calcd. for $C_9H_{11}O_4N$: C, 54.82; H, 5.62. Found: C, 54.88; H, 5.58.

2-Carbomethoxy-3-methyl-4-bromopyrrole (XXII).—The decarboxylation of (XVII) was carried out by the method of Fischer, Berg and Schormüller.^{14b} This method could be used only with quantities less than 2.5 g. The decarboxylation must be performed within five to ten seconds, for the bromopyrrole reacts with hot glycerol to form acrolein; m. p. 179–183°; yield, 40%.

Anal. Calcd. for $C_9H_{10}O_2NBr$: C, 41.38; H, 4.31. Found: C, 41.34; H, 4.38.

2-Carbomethoxy-3-methylpyrrole (XXIII).—One and a half grams of (XX) was heated with 6 g. of anhydrous glycerol and the distillate collected in a distilling flask cooled with running water. The new pyrrole distilled between 270 and 290°. Five cc. of ethanol was added to it cautiously and the solution was poured into 25 cc. of ice water. After scratching, the pyrrole precipitated as fine crystals which were filtered off and air-dried; m. p. 56°. Fischer and Wiedemann report 56°.⁸

This substance was also prepared by the dehalogenation by (XXII) by the method used in the preparation of (X) above; m. p. 56°; mixed m. p. with material from the decarboxylation of compound XX, 56°.

2,3,4-Tricarboxyl-4-methylpyrrole (XXIV).—A solution of 25 g. of (I) and 12 g. of sodium hydroxide in 100 ml. of water was placed in a 200-ml. round flask connected to a fractionating column filled with glass helices and fitted with a reflux finger. The side arm of the column was connected to a condenser with a graduated cylinder as the receiver. The flask was heated on a water-bath for two hours. During this time 5 ml. of alcohol was collected below 80°. The flask was then heated with a free flame for four hours longer until the calculated amount, 12 ml., was obtained. The mixture was transferred to a 250-ml. beaker, cooled in an ice-bath and hydrochloric acid added to the congo red end-point. A thick white precipitate was formed which was filtered off with suction and the filtrate used to wash out the beaker. The product was crystallized from boiling water using Norite. It contained some sodium chloride which could be removed by several recrystallizations. The pyrrole is too soluble in cold water to permit washing to remove the salt. The product is insoluble in most organic solvents. It chars slightly when heated to 360°; yield, 15 g. or 76%.

Anal. Calcd. for $C_9H_7O_6N$: C, 45.08; H, 3.31. Found: C, 44.97; H, 3.37.

2,3-Dicarbomethoxy-4-methyl-5-carboxypyrrole (XXV).
First Method.—A solution of 400 mg. of (XXIV) in 7 ml. of methanol previously saturated with dry hydrogen chloride was refluxed for five hours and then poured into 40 ml. of ice-cold sodium bicarbonate solution. After standing overnight in the ice box, the precipitate (XXVI) was removed by filtration and the filtrate acidified with hydrochloric acid. It was necessary to add a small amount of salt and to cool the solution before the product (XXV) precipitated. It was filtered off and crystallized from acetone-water; m. p. 211–211.5° with slight decomposition.

Anal. Calcd. for $C_{10}H_{11}O_6N$: C, 49.79; H, 4.60. Found: C, 49.92; H, 4.71.

Second Method.—Five hundred milligrams of (XXXI) and 10 ml. of methanol containing dry hydrogen chloride were allowed to react in the manner described for the preparation of (VII) above. The pyrrole obtained crystallized from acetone-water and melted at 211–212°; mixed m. p. with XXV prepared from the tricarboxyl-pyrrole, no depression.

2,3,5-Tricarbomethoxy-4-methylpyrrole (XXVI).—This was prepared from (XXVII) with dimethyl sulfate and with methanol and hydrochloric acid by the procedures described above for (VI). The triester crystallizes from methanol; m. p. 142–143°.

(12) Piloty and Hirsch, *Ann.*, **296**, 70 (1913).

(13) Fischer and Ernst, *ibid.*, **447**, 147 (1926).

(14) Fischer, Berg and Schormüller, *ibid.*, **480**, (a) 155, (b) 114 (1930).

(15) Performed by S. R. Buc.

The same substance was also obtained in small amounts in the esterification of XXIV (see XXV above) and of (XXXI). It was also prepared by the esterification of (XXV). Melting points and mixed melting points of all these preparations are identical.

Anal. Calcd. for $C_{11}H_{13}O_6N$: C, 51.76; H, 5.13. Found: C, 51.67; H, 5.10.

2-Carboxy-3,5-dicarbomethoxy-4-methylpyrrole (XXVII).—Seven grams of (XXVIII)¹⁶ was treated with sulfuryl chloride and bromine by the method given for (I); yield of acid, 4.5 g. or 59%; colorless needles from methanol; m. p. 205–206°.

Anal. Calcd. for $C_{10}H_{11}O_6N$: C, 49.79; H, 4.60. Found: C, 49.69; H, 4.58.

2-Carboxy-3-carbomethoxy-4-methyl-5-carbomethoxy-pyrrole (XXX).—Twenty-one grams of (XXIX)^{10a} was treated with sulfuryl chloride and bromine in the manner described for the preparation of (I); yield of acid, 17.3 g., or 73%. This pyrrole crystallizes from ethanol in fine needles; m. p. 157–158°.

Anal. Calcd. for $C_{11}H_{12}O_6N$: C, 51.76; H, 5.13. Found: C, 51.87; H, 5.16.

2,5-Dicarboxy-3-carbomethoxy-4-methylpyrrole (XXXI).—One gram of (XXX) was dissolved in 15 ml. of water containing 0.55 g. of potassium hydroxide and the same procedure followed as for the preparation of (VII). The product obtained was crystallized twice from acetone-water, the first time using Norite; m. p. 243° with decomposition.

Anal. Calcd. for $C_9H_9O_6N$: C, 47.58; H, 3.99. Found: C, 47.59; H, 4.02.

2,3-Dicarbomethoxy-4-methyl-5-carbomethoxypyrrole (XXXII).—The same procedure was followed as for the preparation of (VI) using potassium hydroxide and dimethyl sulfate. The product crystallizes from methanol in colorless needles melting at 111°.

Anal. Calcd. for $C_{12}H_{15}O_6N$: C, 53.52; H, 5.62. Found: C, 53.45; H, 5.57.

2,5-Dicarbonylido-3-carbomethoxy-4-methylpyrrole (XXXIII).—A solution of 10 g. of (I) and 20 cc. of aniline was refluxed for three and a half hours and poured into a mixture of 100 ml. of hydrochloric acid and 500 ml. of water. The precipitate was filtered off, dissolved in hot alcohol and reprecipitated in an ice-hydrochloric acid mixture. The precipitate was then crystallized from methanol; m. p. 196° after sintering at 192°.

Anal. Calcd. for $C_{22}H_{21}O_4N_3$: C, 67.48; H, 5.41. Found: C, 67.34; H, 5.86.

The position of the second anilide group has not been established. It seems probable that it is in the *alpha* position because of the numerous analogies in the pyrrole series.

1,4-Dimethyl-2,5-dicarbomethoxy-3-carbomethoxypyrrole (XXXIV).—A solution of 25 g. of (VI) in 250 ml. of dry toluene was treated with 3 g. of metallic sodium, added in small portions between 95 and 100°. When all of the sodium had reacted, 11 ml. of dimethyl sulfate was added slowly to the solution. The solution was refluxed for one hour, filtered while hot and the toluene distilled off with steam. The residue was dissolved in cold methanol and the pyrrole precipitated by pouring into five times its volume of water. After standing for two hours the

pyrrole was filtered off and crystallized from methanol-water; m. p. 60°.

Anal. Calcd. for $C_{14}H_{19}O_6N$: C, 57.33; H, 6.33. For $C_{18}H_{17}O_6N$: C, 55.05; H, 6.04. Found: C, 55.19, 55.18; H, 6.11, 6.02.

1,4-Dimethyl-2-carboxyl-3-carbomethoxy-5-carbomethoxypyrrole.—A solution of 1 g. of potassium hydroxide in 25 ml. of methanol was added to 5 g. of (XXXIV). A precipitate formed immediately and dissolved on the addition of water. The solution was filtered and the filtrate acidified with hydrochloric acid to precipitate the pyrrole acid. The procedure used for the purification of (VII) was then followed. The product was crystallized from methanol-water; m. p. 88°.

Anal. Calcd. for $C_{12}H_{16}O_6N$: N, 5.21. Found: N, 5.19.

2,3,5-Tricarbomethoxy-4-methylpyrrole (XXXV).¹⁷—This must be prepared from acid (I) which has been recrystallized several times. The preparation is the same as for (VI) except that anhydrous ethanol is used. The alcoholic solution was poured into water containing an excess of sodium bicarbonate. An oil separated and was extracted with ether. The extract was evaporated on a steam-bath. Portions of the residue were purified by distilling three times at 195° and 1 mm. pressure in the Craig microdistillation apparatus.¹⁸ A yellowish oil is obtained that solidifies slowly to give a white, waxy solid; m. p. 45–46°.

*Anal.*¹⁹ Calcd. for $C_{14}H_{19}O_6N$: C, 56.56; H, 6.44. Found: C, 56.33, 56.15; H, 6.54, 6.63.

Summary

1. It is shown that 2-dichloromethyl-3,5-dicarbomethoxy-4-methylpyrrole reacts with glacial acetic acid to form the pyrrol aldehyde and acetyl chloride.

2. This pyrrol aldehyde is not an intermediate in the formation of 2-carboxyl-3,5-dicarbomethoxy-4-methylpyrrole.

3. Carboxylic ester groups hinder decarboxylation in the pyrrole series.

4. Selective freeing of ring positions on tricarbomethoxypyrrole derivatives may be secured by replacing the first carboxyl group with bromine followed by selective degradations of the resulting dicarbomethoxy derivatives.

5. Flow sheets are given for the freeing of the 2,3 and 5 positions in derivatives of 2,3,5-tricarbomethoxy-4-methylpyrrole.

6. Five new cases have been added to the generalization that attack by an alkaline catalyst upon pyrrol-carboxylic ester groups is oriented α instead of β whenever there is a choice.

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(18) Craig, *Ind. Eng. Chem., Anal. Ed.*, **8**, 223 (1936).

(19) Performed by C. Karr.

(16) Küster, Weber, Maurer, Schlack, Niemann, Willig and Schlayerbach, *Z. physiol. Chem.*, **121**, 135 (1922).