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

The Synthesis of Some β,β-Dipyrrylpropionic Esters[1,2]

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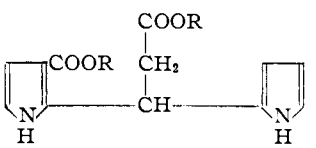
Appropriately substituted β,β-dipyrrylpropionic esters are of potential interest as intermediates in a proposed synthetic approach to porphyrins closely related to chlorophyll *a*. Two condensation methods have proved useful for the preparation of certain β,β-dipyrrylpropionic esters. The structure of the first prepared of these compounds has been confirmed through degradation in order to authenticate both of the condensation methods by which it was synthesized. Three β,β-dipyrrylpropionic esters have been prepared in all. One of these is isomeric with a β,β-dipyrrylpropionic ester which is potentially a synthetic precursor of chloroporphyrin e_5 and other closely related porphyrins.

The total synthesis of pheoporphyrin a_5 by Hans Fischer and co-workers still stands as an unique achievement in its field. The presence in pheoporphyrin a_5 of both the 9-oxo and 10-carbomethoxy groupings renders its isocyclic ring structurally identical with that of chlorophyll *a*. In no other reported instance has the unequivocal total synthesis of a porphyrin or chlorin containing such an isocyclic ring been accomplished. The successful synthetic sequence devised by Fischer consisted in first preparing γ-phylloporphyrin,[3,4] an appropriately substituted γ-methylporphyrin with a free 6-position; then subsequently incorporating the isocyclic ring into this porphyrin through a series of further synthetic transformations.[5-7] Attempts to extend this method to the total synthesis of mesopheophorbide *a*,[8-10a] of pheophorbide *a* and its 2-acetyl and 2-hydroxyethyl analogs[10b] and of 2-desvinylpheophorbide *a*[11] have been reported, but in none of these instances has the achievement of a total synthesis been rigorously demonstrated. Up to the present time the method has thus proved inapplicable to the total synthesis of chlorophyll *a*.

A proposed alternative synthetic route to porphyrins and chlorins of this type is now under investigation in this Laboratory. As a part of the program it has been proposed to explore the possibility of synthesizing porphyrins of the type of pheoporphyrin a_5 or chloroporphyrin e_6 directly from two dipyrryl intermediates, one of which already contains all of the structural features essential for the facile production of the isocyclic ring. A β,β-dipyrrylpropionic ester of the type of I is just such an intermediate and is therefore of potential interest from the synthetic standpoint.



I

Although numerous dipyrrylmethanes with a variety of substituent groupings on the methane bridge have been prepared,[12] in no instance has the synthesis of a β,β-dipyrrylpropionic ester been reported. For this reason the exploration of possible synthetic routes to β,β-dipyrrylpropionic esters was undertaken.

A majority of both bridge-substituted and bridge-unsubstituted dipyrrylmethanes prepared up to the present time have been obtained by the acid-catalyzed condensation of one mole of an aldehyde or ketone with two moles of an α-free or β-free pyrrole. Application of this rather general method to the synthesis of a β,β-dipyrrylpropionic ester would require formylacetic ester as the aldehyde moiety. However, the tendency of this particularly reactive intermediate to undergo self-condensation is reportedly so great[13] that free formylacetic ester itself has not been isolated. It thus seemed advisable to conduct exploratory condensation experiments with a somewhat less labile, though structurally similar, intermediate, and the ethyl hydrogen oxalacetate (II) of Wislicenus[14,15b,16b] was selected for this purpose. Fischer and Gademann[17] had previously investigated the condensation of closely related pyruvic acid with 3-carbethoxy-2,4-dimethylpyrrole (III). The α,α-dipyrrylpropionic acid structure which they assigned to the product is in all probability correct, although no proof of structure was undertaken.

It was anticipated that reaction of ethyl hydrogen oxalacetate(II) with pyrrole III would afford an ethyl hydrogen *gem*-dipyrrylsuccinate which might, it was hoped, be made to undergo subsequent decarboxylation to yield β,β-dipyrrylpropionic ester IV. Actually the condensation of one mole of II with two moles of pyrrole III in refluxing glacial acetic acid has been found to proceed smoothly with attendant decarboxylation to afford IV directly.

The successful preparation of IV from II and III prompted us to examine a closely related alternative synthetic approach to IV. The key intermediate for our investigation was the already known 4,α-dicarbethoxy-3,5-dimethyl-2-pyrroleacrylic acid (VI).[18b] Küster and co-workers had

(1) Studies in the Pyrrole Series. XXV. Paper XXIV, G. G. Kleinspehn and A. H. Corwin, THIS JOURNAL, **75**, 5295 (1953).

(2) This work was carried out under a research grant from the National Science Foundation.

(3) H. Fischer and H. Helberger, *Ann.*, **480**, 255 (1930).

(4) H. Fischer, W. Siedel and L. le T. d'Ennequin, *ibid.*, **500**, 167 (1933).

(5) H. Fischer and H. Kellermann, *ibid.*, **524**, 25 (1936).

(6) H. Fischer and E. Stier, *ibid.*, **542**, 224 (1939).

(7) H. Fischer, E. Stier and W. Kanngiesser, *ibid.*, **543**, 258 (1940).

(8) H. Fischer and F. Gerner, *ibid.*, **553**, 67 (1942).

(9) H. Fischer and M. Strell, *ibid.*, **556**, 224 (1944).

(10) H. Fischer and F. Gerner, *ibid.*, **559**, (a) 77, (b) 84 (1948).

(11) M. Strell and A. Kalojanoff, *ibid.*, **577**, 97 (1952).

(12) H. Fischer and H. Orth, "Die Chemie des Pyrrols," Vol. I, Akademische Verlagsgesellschaft m.b.H., Leipzig, 1934, pp. 351-359.

(13) M. Cogan, *Bull. soc. chim.*, **8**, 125 (1941).

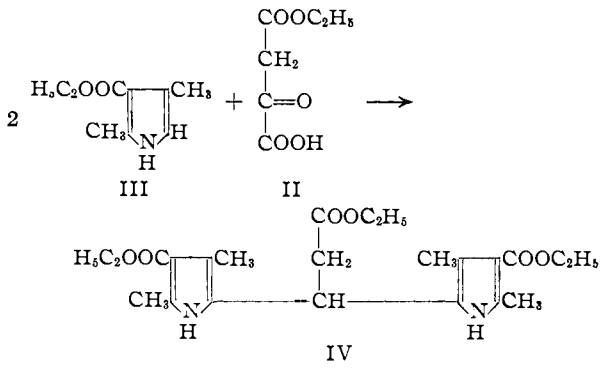
(14) W. Wislicenus, *Ber.*, **19**, 3226 (1886).

(15) W. Wislicenus, *Ann.*, **246** (a) 318; (b) 323 (1888).

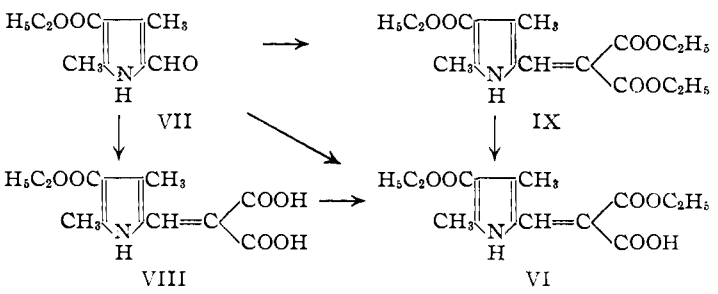
(16) W. Wislicenus and A. Endres, *ibid.*, **321**, (a) 373, (b) 381 (1902).

(17) H. Fischer and H. Gademann, *ibid.*, **550**, 196 (1942).

(18) W. Küster, E. Brudi and G. Koppenhöfer, *Ber.*, **58**, (a) 1018, (b) 1019 (1925).

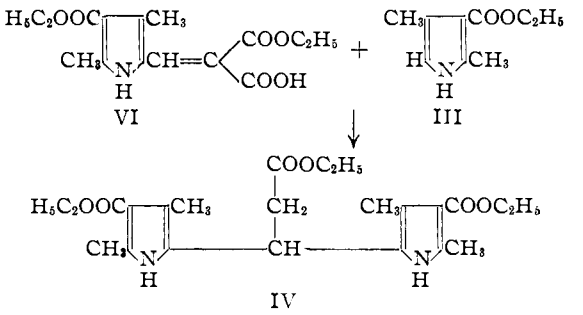


obtained α-carbethoxyacrylic acid VI from the aldehyde VII[19,20] *via* the α-carboxyacrylic acid VIII, whose monosilver salt afforded VI upon reaction with ethyl iodide. We have found that VI may be prepared from the aldehyde by either of two other methods: (A) alkaline monohydrolysis of the known triester IX,[18a,21] which is obtained by condensation of VII with diethyl malonate; (B) condensation of VII with ethyl hydrogen malonate to afford VI directly.

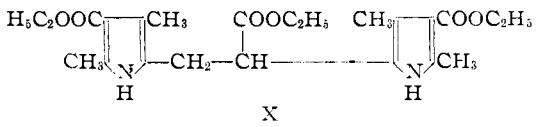


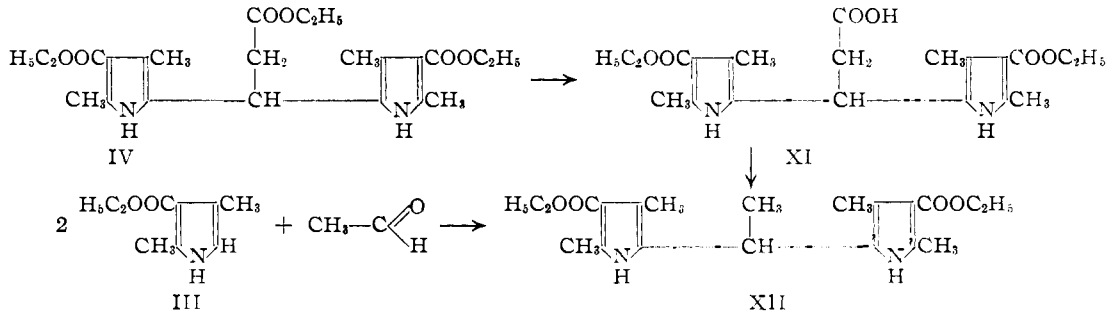
As had been anticipated, condensation of α-carbethoxyacrylic acid (VI) with pyrrole III did provide a product identical with the β,β-dipyrrylpropionic ester (IV) obtained from ethyl hydrogen oxalacetate (II) and pyrrole III. It should be noted that Fischer and Gademann[17] had previously studied the closely analogous reaction of 5-carbethoxy-2,4-dimethyl-3-pyrroleacrylic acid with 2-carbethoxy-3,5-dimethylpyrrole. On the basis of rather meager evidence they assigned to the product a 1,2-dipyrrylethane rather than a 1,1-dipyrrylethane structure.

The preparation of β,β-dipyrrylpropionic ester IV from VI and III is of particular interest because in this instance the potential methane bridge with its substituent grouping is already bonded to one of the pyrrole units prior to the condensation. Thus with respect to the production of β,β-dipyrrylpropionic esters in which the two pyrrole units are different, the method is inherently less ambiguous than the ethyl hydrogen oxalacetate method. Since our projected synthetic approach either to chlorophyll *a* or to closely related porphyrins requires just such unsymmetrical dipyrrylpropionic ester intermediates, this is an important consideration.



In order to establish the structure of IV and thereby definitely preclude the rather unlikely possibility that both condensations might have afforded the isomeric α,β-dipyrrylpropionic ester (X), the degradation of IV to the known 1,1-dipyrrylethane (XII)[22] was undertaken. Saponification of IV with one mole of base effected a selective hydrolysis of the propionic ester grouping to produce the acid XI. When crystallized from 95% ethanol, XI was observed to retain one mole of ethanol of solvation, a rather unusual observation in the pyrrole series.





Acid XI was then thermally decarboxylated to afford a product identical with the 1,1-dipyrrylethane XII[22] obtained from the condensation of pyrrole III with acetaldehyde.

One important structural requirement for a β,β-dipyrrylpropionic ester which is to be used in the synthesis of a chlorophyll-type porphyrin is illustrated by structure I. This is the presence in one pyrrole ring of a β-carbethoxy substituent grouping

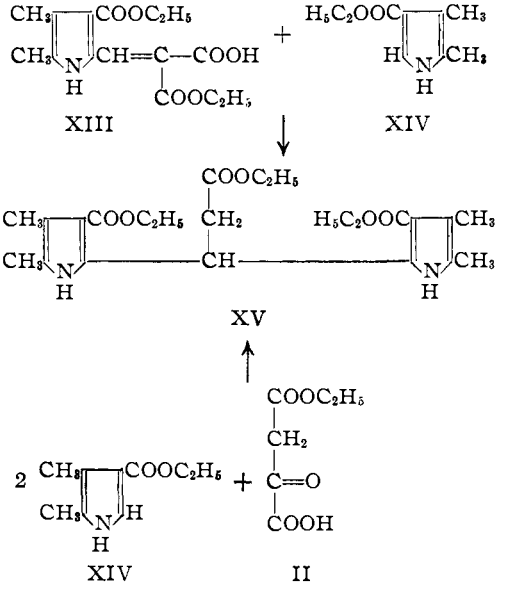
(19) H. Fischer and W. Zerweck, *Ber.*, **55**, 1945 (1922).

(20) A. H. Corwin and J. S. Andrews, THIS JOURNAL, **58**, 1088 (1936).

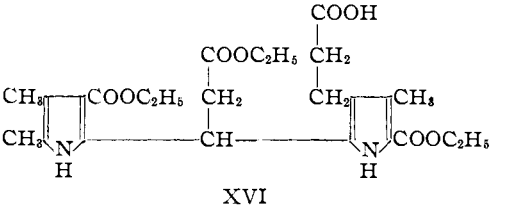
(21) W. Küster and H. Maurer, *Ber.*, **56**, 2479 (1923).

(22) H. Fischer and E. Bartholomäus, *Z. physiol. Chem.*, **87**, 264 (1913).

adjacent to the methane bridge. For this reason application of the two previously successful condensation methods to the synthesis of a simple β,β-dipyrrylpropionic ester of this type was next attempted. Reaction of 3-carbethoxy-2-formyl-4,5-dimethylpyrrole[23] with ethyl hydrogen malonate afforded α,3-dicarbethoxy-4,5-dimethyl-2-pyrroleacrylic acid (XIII), and subsequent condensation of XIII with 3-carbethoxy-4,5-dimethylpyrrole (XIV)[24] gave β,β-dipyrrylpropionic ester (XV). A product identical with XV resulted from condensation of two moles of pyrrole XIV with ethyl hydrogen oxalacetate (II).

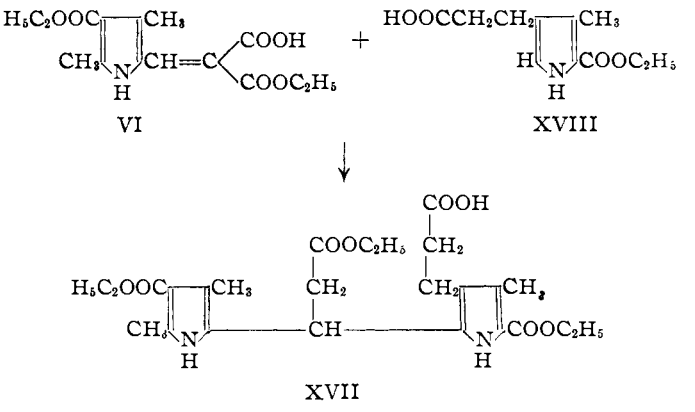


The next objective was the preparation of a β,β-dipyrrylpropionic ester of a type which might prove to be of synthetic utility in obtaining a porphyrin closely similar to chlorophyll *a*. It will be seen that structure XVI represents such an intermediate, for the substituent groups in the β-positions of each pyrrole ring are such that XVI constitutes a potential synthetic unit comprising one half of the chloroporphyrin e_6 diester molecule.

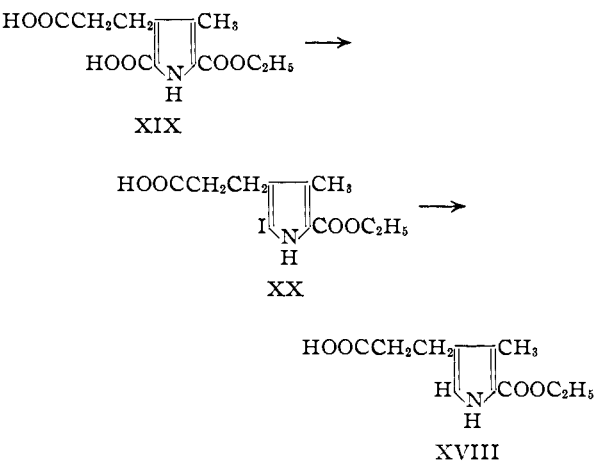


Because of the relative availabilities of the required intermediates at that time, the preparation of the isomeric β,β-dipyrrylpropionic ester (XVII) was first attempted. As outlined in the accompanying figure it was proposed to accomplish the synthesis of XVII from α,4-dicarbethoxy-3,5-dimethyl-2-pyrroleacrylic acid (VI) and α-free pyrrolepropionic acid (XVIII.)

(23) H. Fischer and H. Beller, *Ann.*, **444**, 244 (1925).
(24) O. Piloty and K. Wilke, *Ber.*, **45**, 2587 (1912).



Pyrrole XVIII had been previously reported.[25,26] In the present instance it was prepared from diacid XIX[27] in over-all yield of 71% by the two-step process shown below. Iodinative decarboxylation, previously successful with other pyrrolecarboxylic acids,[28,29] converted XIX to iodopyrrole XX. Subsequent catalytic hydrogenation of XX afforded α-free pyrrolepropionic acid (XVIII). Fischer and coworkers[25] had obtained XVIII in 60% yield by a one-step decarboxylation of XIX.



Condensation of VI and XVIII did in fact produce XVII, though in rather low yield. Dipyrrylpropionic ester (XVII) crystallizes from ethanol–water with the unexpected retention of one mole of water of hydration, which may, however, be readily removed by heating *in vacuo*.

Attempts to prepare the desired isomer XVI through a condensation of α-carbethoxyacrylic acid (XIII) with α-free propionic acid (XVIII) have not thus far met with success. The principal acidic component isolated from the reaction mixture is unchanged XVIII. Consequently, further work directed toward the synthesis of XVI is now in progress in this Laboratory.

(25) H. Fischer, H. Friedrich, W. Lamatsch and K. Morgenroth, *Ann.*, **466**, 171 (1928).
(26) H. Fischer and M. Hussong, *ibid.*, **492**, 153 (1932).
(27) H. Fischer and W. Lamatsch, *ibid.*, **462**, 246 (1928).
(28) J. L. A. Webb and R. R. Threlkeld, *J. Org. Chem.*, **18**, 1409 (1953).
(29) G. G. Kleinspehn and A. H. Corwin, THIS JOURNAL, **75**, 5295 (1953).

Experimental[30,31]

Ethyl Hydrogen Oxalacetate (II).[14,15b,16b]—The procedure described below is a modification of the method of Wislicenus and Endres.[16b] The copper derivative of diethyl oxalacetate was prepared[15a,16a] and recrystallized from boiling 95% ethanol. Twenty-nine and one-tenth grams of the thus purified copper derivative was taken up in 250 ml. of boiling 95% ethanol, and a solution of 8.2 g. of potassium hydroxide in 60 ml. of 95% ethanol was then added a portion at a time with frequent stirring. After being cooled to room temperature, then refrigerated, the dark green precipitate was filtered off by suction and washed with water. It was next decomposed with a solution of 8 ml. of concentrated sulfuric acid in 100 ml. of water, care being taken to break up all large pieces of the copper derivative. Several more milliliters of dilute sulfuric acid and an additional 90 ml. of water were then added with stirring. The somewhat turbid mixture was extracted with six 125-ml. portions of ether and the combined extracts, after drying with anhydrous sodium sulfate, were concentrated on the steam-bath to a small volume. The light tan, crystalline product separated on standing overnight at room temperature, and additional ether was removed *in vacuo*. The crude solid was then recrystallized from about 30 ml. of hot benzene to give 7.65 g. or 37% yield of product melting over the range 87–96°. A second recrystallization from benzene altered the melting range only very slightly. However, the resulting product proved sufficiently pure for synthetic purposes.

The previously reported *p*-nitrophenylhydrazone[32] was prepared. Its decomposition point proved to be largely dependent upon the rate of heating. Thus upon increasing the temperature at a rate of 2° per minute, the substance began to soften at 172°, melting with decomposition at 174–176.5°. Heating at a rate of 10° per minute raised the decomposition point to 181–182° with previous softening at 179°; lit. 181.5–182°.[32]

Anal. Calcd. for $C_{12}H_{13}O_6N_3$: C_2H_5O, 15.26. Found: C_2H_5O, 15.30.

3-Carbethoxy-2,4-dimethylpyrrole (III).—This pyrrole was prepared by thermal decarboxylation of 3-carbethoxy-5-carboxy-2,4-dimethylpyrrole,[33,34] a reaction first carried out by Knorr.[33] The procedure is basically that of Fischer, Berg and Schormüller.[35] It has been found useful in this Laboratory for decarboxylation of pyrrole acids.[36–38]

Ethyl β,β-Bis-(4-carbethoxy-3,5-dimethyl-2-pyrryl)-propionate (IV) from Ethyl Hydrogen Oxalacetate (II) and Pyrrole III.—Thirteen and three-tenths grams of 3-carbethoxy-2,4-dimethylpyrrole, 6.4 g. of ethyl hydrogen oxalacetate and 40 ml. of glacial acetic acid were heated together under reflux for three hours while a slow stream of nitrogen gas was passed through the reaction vessel. When the mixture had cooled to room temperature, trituration of a single drop on a glass slide with a drop of glacial acetic acid produced a crystalline solid which was used for seeding the reaction mixture. After being allowed to stand overnight, the product was filtered off and washed liberally with glacial acetic acid. Slow evaporation of the filtrate *in vacuo* at room temperature afforded a second crop, and a third was obtained in a similar manner. Total yield of crude product, 10.4 g. or 60% based upon III. The analytically pure material was obtained by repeated recrystallization from hot ethanol–water. It is imperative that the ratio of alcohol to water be high. Otherwise a viscous phase separates out and subsequent crystallization is tediously slow; m.p. 152.5–153.5°.

Anal. Calcd. for $C_{23}H_{32}O_6N_2$: C, 63.87; H, 7.46; N, 6.48; C_2H_5O, 31.26. Found: C, 63.77, 63.87; H, 7.46, 7.45; N, 6.38[39]; C_2H_5O, 31.42.

Ethyl α-4-Dicarbethoxy-3,5-dimethyl-2-pyrroleacrylate (IX).[18a,21]—The preparative method employed is essentially that of Küster, *et al.*,[18a] but substituting piperidine for diethylamine. Eight and forty-two hundredths grams of 3-carbethoxy-5-formyl-2,4-dimethylpyrrole,[19,20] 7.3 ml. of diethyl malonate, 65 ml. of absolute ethanol and 3.0 ml. of piperidine were refluxed for four hours. Twenty-seven milliliters of solvent was then distilled off and the product was set aside for about 24 hours while the product crystallized. After a few hours refrigeration, the product was filtered off, washed with a little cold ethanol and dried to constant weight *in vacuo;* yield 8.76 g. or 60% of product melting at 84.5–88°; lit. 86–87°.[18a]

α-4-Dicarbethoxy-3,5-dimethyl-2-pyrroleacrylic Acid (IV).[18b] **(A) From Triester IX.**—Seven and ninety-hundredths grams of pyrrole IX was dissolved in 64 ml. of 95% ethanol by warming. The solution was then cooled to 35–40° and a solution of 1.48 g. of potassium hydroxide in 14 ml. of water was added. The reaction mixture was stoppered and set aside for 10 hours. Upon pouring into 320 ml. of water with stirring, a precipitate separated. To ensure coagulation the mixture was stirred for 45 minutes, then filtered. Acidification of the filtrate to a *p*H of 1 or less produced a voluminous orange precipitate of the desired product. The crude product was then dissolved by stirring with a solution of 5 g. of sodium bicarbonate in 5 ml. of 95% ethanol and 100 ml. of water. After treatment with Norit A the solution was filtered, and the product was reprecipitated from the filtrate as before with hydrochloric acid. This was filtered off, dried and recrystallized from 30 ml. of 95% ethanol and 7 ml. of water to give 4.20 g. or 58% yield of VI, m.p. 113–115°; lit. 114°.[18b] Mixed melting point with VI prepared by method (B) below showed no depression. The substance was recrystallized from 95% ethanol for analysis.

Anal. Calcd. for $C_{15}H_{19}O_6N$: C_2H_5O, 29.14. Found: C_2H_5O, 29.11.

(B) From 3-Carbethoxy-5-formyl-2,4-dimethylpyrrole (VII) and Ethyl Hydrogen Malonate.—Thirty-nine hundredths of a gram of the aldehyde, 0.25 ml. of ethyl hydrogen malonate,[40] 2.5 ml. of absolute ethanol and 0.20 ml. of piperidine were refluxed for two hours. After cooling the reaction mixture it was poured with stirring into a solution of 0.8 g. of potassium bicarbonate in 20 ml. of water and refrigerated overnight. The insoluble material was filtered off and discarded. Acidification of the filtrate with concentrated hydrochloric acid to a *p*H of 1 or less caused precipitation of VI. The product was filtered off and dried; weight 0.26 g. One recrystallization from boiling 95% ethanol afforded 0.21 g. or 34% of product melting at 114.5–115.5°. One additional recrystallization gave the analytically pure substance.

Anal. Calcd. for $C_{15}H_{19}O_6N$: C, 58.24; H, 6.19; C_2H_5O, 29.14. Found: C, 57.91; H, 5.95; C_2H_5O, 29.10.

Ethyl β,β-Bis-(4-carbethoxy-3,5-dimethyl-2-pyrryl)-propionate (IV) from Pyrroles III and VI.—The procedure was essentially that described for the preparation of IV from III and II. Four and twenty-hundredths grams of VI, 2.30 g. of III and 15 ml. of glacial acetic acid were used; total yield (three crops) of crude product 4.09 g. or 70%. Repeated crystallization from ethanol–water afforded the analytically pure material; m.p. 152.5–153.5°; mixed melting points with the product from pyrrole III and ethyl hydrogen oxalacetate (II) showed no depression.

Anal. Calcd. for $C_{23}H_{32}O_6N_2$: C, 63.87; H, 7.46; C_2H_5O, 31.26. Found: C, 63.86, 63.78; H, 7.39, 7.13; C_2H_5O, 31.46.

β,β-Bis-(4-carbethoxy-3,5-dimethyl-2-pyrryl)-propionic Acid (XI).—A solution of 702 mg. of potassium hydroxide in 2 ml. of water was diluted to 10 ml. with 95% ethanol, and 1.85 ml. of the resulting solution was added to 865 mg. of IV. After further addition of 3.5 ml. of 95% ethanol the reactants were refluxed for five hours. Four milliliters of water and 16 drops of glacial acetic acid were then introduced, followed by dropwise addition of water (about 4 ml.) until a few drops of oil separated. At this point a drop of the reaction mixture was placed upon a glass slide and rubbed until crystallization occurred. The resulting solid was used to seed the reaction mixture. As soon as crystallization

(30) All melting points were determined on the Fisher–Johns melting point apparatus.

(31) Carbon and hydrogen microanalyses by Joseph A. Walter.

(32) A. Quilico and L. Panizzi, *Gazz. chim. ital.*, **72**, 469 (1942).

(33) L. Knorr, *Ann.*, **236**, 322 (1886).

(34) W. Küster, W. Weber, H. Maurer, P. Schlack, W. Niemann, E. Willig and R. Schlayerbach, *Z. physiol. Chem.*, **121**, 135 (1922).

(35) H. Fischer, H. Berg and A. Schormüller, *ibid.*, **480**, 114 (1930).

(36) A. H. Corwin and W. M. Quattlebaum, Jr., THIS JOURNAL, **58**, 1083, 1085 (1936).

(37) A. H. Corwin and P. Viohl, *ibid.*, **66**, 1145 (1944).

(38) A. H. Corwin and J. L. Straughn, *ibid.*, **70**, 1420 (1948).

(39) The authors wish to thank Dr. Anna Leone for this Dumas nitrogen analysis.

(40) D. S. Breslow, E. Baumgarten and C. R. Hauser, THIS JOURNAL, **66**, 1287 (1944).

had set in, an additional 21 ml. of water was slowly added and the mixture was then refrigerated. The crude acid was filtered off and dried to constant weight *in vacuo;* yield 872 mg. or 97% assuming the crude acid to be solvated with one mole of ethanol. The crude product was recrystallized from ethanol–water, then from 95% ethanol to give the analytically pure solvated acid melting with decomposition at 180–184°.

Anal. Calcd. for $C_{21}H_{28}O_6N_2 \cdot C_2H_5OH$: C, 61.31; H, 7.61; C_2H_5O, 30.01. Found: C, 61.46; H, 7.55; C_2H_5O, 29.59.

Recrystallization from dioxane–toluene gave the unsolvated acid melting with decomposition at 185.5–187°.

Anal. Calcd. for $C_{21}H_{28}O_6N_2$: C, 62.36; H, 6.98; C_2H_5O, 22.28. Found: C, 62.26; H, 6.96; C_2H_5O, 22.01.

1,1-Bis-(4-carbethoxy-3,5-dimethyl-2-pyrryl)-ethane (XII).[22] **(A) From Pyrrole III and Acetaldehyde.**—It was found advantageous to substitute acetic acid for hydrochloric as the acid catalyst in the method of Fischer and Bartholomäus.[22] In this way a pure product was more easily obtained.

Five and one-hundredth grams of 3-carbethoxy-2,4-dimethylpyrrole was dissolved in 10 ml. of 95% ethanol and 4.0 ml. of acetaldehyde at room temperature. Five milliliters of water and 20 drops of glacial acetic acid were then added, and the mixture was refluxed for 30 minutes using an efficient condenser. A drop of the reaction mixture was withdrawn and rubbed with a stirring rod to produce crystals. These were used to seed the reaction mixture which was cooled to room temperature, then refrigerated. The crude crystalline product was filtered off and washed with a little ethanol–water; yield 4.93 g. or 91% of the 1,1-dipyrrylethane melting at 171.5–172.5°. Recrystallization from 95% ethanol afforded an analytically pure product of unchanged melting point; lit. 171–172°.[22]

Anal. Calcd. for $C_{20}H_{28}O_4N_2$: C, 66.64; H, 7.83; C_2H_5O, 15.00. Found: C, 66.70; H, 7.77; C_2H_5O, 24.76.

(B) From β,β-Bis-(4-carbethoxy-3,5-dimethyl-2-pyrryl)-propionic Acid (XI).—Decarboxylation of 393 mg. of XI, which had been previously recrystallized from 95% ethanol, was carried out by heating for six minutes in an oil-bath at 175–220°. The viscous product was taken up in 2.2 ml. of boiling 95% ethanol. After addition of a little solid sodium bicarbonate, water was added dropwise to turbidity. One drop was then withdrawn and rubbed on a watch glass until crystals formed. These were used to seed reaction mixture, and a little ethanol, then 15 ml. of water were introduced to complete separation of the solid product. After refrigerating the mixture overnight, the product was filtered off, recrystallized once from ethanol–water, then once from 95% ethanol. The product was combined with that from a second run of similar size and then recrystallized once more from ethanol for analysis; m.p. 170.5–172°; mixed melting point with the authentic 1,1-dipyrrylethane from (A) showed no depression.

Anal. Calcd. for $C_{20}H_{28}O_4N_2$: C, 66.64; H, 7.83. Found: C, 66.59; H, 7.73.

3-Carbethoxy-4,5-dimethylpyrrole (XIV).[24]—Thirty-nine and three-tenths grams of crude 3-carbethoxy-2-carboxy-4,5-dimethylpyrrole[24,41,42] prepared by the method of Corwin and Krieble[42] was placed in a one-liter distilling flask and heated in an oil-bath at 210–240° for 70 minutes. While the mixture was cooling, 80 ml. of U.S.P. glycerol was made anhydrous as described in the preparation of III. After addition of the anhydrous glycerol to the reaction mixture, distillation of the pyrrole was carried out by heating as rapidly as possible until the vapor temperature reached 290°. The hot distillate was made homogeneous by addition of ethanol and heating, then was poured into 375 ml. of ice–water mixture. The crude product was filtered off, washed with water and dried *in vacuo;* yield 26.6 g. or 85% of a product melting at 106–110.5°. A single recrystallization from ethanol–water raised the melting point to 111.5–112°; lit. 110–111°.[24]

3-Carbethoxy-2-formyl-4,5-dimethylpyrrole.[25]—This aldehyde was prepared by the Adams modification[43,44] of the Gattermann aldehyde synthesis. The procedure is essentially that of Corwin and Andrews[20] who applied the method to the preparation of the isomeric aldehyde VII.

Twenty grams of crude 2,3-dimethyl-4-carbethoxypyrrole, 28 g. of technical zinc cyanide and 270 ml. of anhydrous ether were used. The yield after two recrystallizations from boiling 95% ethanol was 17.0 g. or 73% of product melting at 131.5–132°; lit. 129°.[23]

α,3-Dicarbethoxy-4,5-dimethyl-2-pyrroleacrylic Acid (XIII).—The (B) procedure described for the preparation of the isomeric α-carbethoxypyrroleacrylic acid (VI) was employed. Three and ninety-hundredths grams of recrystallized 3-carbethoxy-2-formyl-4,5-dimethylpyrrole, 2.5 ml. of ethyl hydrogen malonate,[40] 2.0 ml. of piperidine and 40 ml. of absolute ethanol were refluxed for 2.5 hours. In this instance the crude product was neither redissolved in bicarbonate solution, nor treated with Norit; yield of crude XIII 3.41 g. or 55%. Two recrystallizations from hot 95% ethanol gave the analytically pure product melting at 121.5–122.5°.

Anal. Calcd. for $C_{15}H_{19}O_6N$: C, 58.24; H, 6.19; C_2H_5O, 29.14. Found: C, 58.22; H, 6.13; C_2H_5O, 29.13.

Ethyl β,β-Bis-(3-carbethoxy-4,5-dimethyl-2-pyrryl)-propionate (XV). (A) From Ethyl Hydrogen Oxalacetate and Pyrrole XIV.—This was prepared by the procedure previously described for the preparation of β,β-dipyrrylpropionic ester IV from II and III. Five-tenths of a gram of ethyl hydrogen oxalacetate and 1.0 g. of crude pyrrole XIV and 3 ml. of glacial acetic acid were used. In this instance the product crystallized upon cooling the reaction mixture to room temperature, then refrigerating. After one recrystallization from ethanol–water and three more from 95% ethanol the product melted at 148.5–150°.

Anal. Calcd. for $C_{23}H_{32}O_6N_2$: C, 63.87; H, 7.46; C_2H_5O, 31.26. Found: C, 64.11; H, 7.64; C_2H_5O, 31.06.

(B) From Pyrroles XIII and XIV.—One and five-hundredths gram of XIII and 0.57 g. of crude XIV were refluxed for three hours with 3 ml. of glacial acetic acid. Yield of crude product was 0.94 g. or 64%. One recrystallization from ethanol–acetic acid–water, then two from 95% ethanol gave the pure product melting at 150–151.5°; mixed melting point with product from procedure (A) 149–151°.

Anal. Calcd. for $C_{23}H_{32}O_6N_2$: C, 63.87; H, 7.46; C_2H_5O, 31.26. Found: C, 64.10; H, 7.41; C_2H_5O, 31.13.

5-Carbethoxy-2-carboxy-4-methyl-3-pyrrolepropionic Acid (XIX).[27]—This intermediate was prepared by the method of Fischer and Lamatsch.[27]

5-Carbethoxy-2-iodo-4-methyl-3-pyrrolepropionic Acid (XX).—One and seventy-eight hundredths grams of XIX, which had been once recrystallized from glacial acetic acid, was dissolved in a solution of 2.0 g. of potassium bicarbonate in 13 ml. of water. After heating the solution, a solution of 1.70 g. of iodine in 20 ml. of 95% ethanol was added dropwise during a few minutes. The iodine color was finally discharged by heating to the boiling point and the reaction mixture was poured into 70 ml. of water. The *p*H was then adjusted to 5 by adding 3 ml. of glacial acetic acid. After cooling to room temperature the crude product was filtered off; yield 2.01 g. or 86%. Two recrystallizations from ethanol–water gave the analytically pure material melting at 181.5–183° with subsequent decomposition.

Anal. Calcd. for $C_{11}H_{14}O_4NI$: C, 37.62; H, 4.02; C_2H_5O, 12.83. Found: C, 37.90; H, 3.78; C_2H_5O, 13.16.

5-Carbethoxy-4-methyl-3-pyrrolepropionic Acid (XVIII)[25,26]—One and eighty-hundredths grams of crude XX, 1.8 g. of 5% palladium on carbon, 1.1 g. of anhydrous sodium acetate and 19 ml. of 95% ethanol were placed in a semi-micro hydrogenation vessel and hydrogenation was begun at a hydrogen pressure of 17–18 lb. (2–3 lb. gage). After 24 hours, a little solid sodium bisulfite was added and the catalyst was filtered off and washed with 95% ethanol. The filtrate was evaporated *in vacuo* at room temperature to a sirup; then 13 ml. of water was added slowly to precipitate the pyrrolepropionic acid. The product was filtered off and dried to constant weight *in vacuo;* yield 958 mg. or 83% of product melting at 106–108.5°. A sample was twice recrystallized from benzene, then dried 2.5 hours *in vacuo* at 90–95°; m.p. 107.5–109°; lit. 106°,[25] 103°.[26]

Anal. Calcd. for $C_{11}H_{15}O_4N$: C, 58.65; H, 6.71; C_2H_5O, 20.01. Found: C, 58.79; H, 6.95; C_2H_5O, 19.81.

(41) H. Fischer and W. Kutscher, *Ann.*, **481**, 199 (1930).
(42) A. H. Corwin and R. Krieble, THIS JOURNAL, **63**, 1831 (1941).
(43) R. Adams and I. Levine, *ibid.*, **45**, 2373 (1923).
(44) R. Adams and E. Montgomery, *ibid.*, **46**, 1518 (1924).

Ethyl β-[5-Carbethoxy-3-(2-carboxyethyl)-4-methyl-2-pyrryl]-β-(4-carbethoxy-3,5-dimethyl-2-pyrryl)-propionate (XVII).—An intimate mixture of 306 mg. of α-carbethoxyacrylic acid (VI) and 223 mg. of the pyrrolepropionic acid (XVIII) was heated for 8.5 hours at 119–124°. The viscous melt was then taken up in glacial acetic acid by heating on the water-bath. After addition of water to incipient turbidity, ethanol was gradually added until subsequent cooling caused separation of some solid. The oil which separated simultaneously was brought to crystallization by alternate brief heating and cooling of the mixture. After cooling slowly to room temperature, then refrigerating, the crystalline product A[45] was filtered off and washed with 1:1 ethanol–water. In order to separate acidic from non-acidic substances product A was dissolved in a little warm ethanol–water and potassium bicarbonate was added to the cessation of effervescence. The mixture was then added to about 15 ml. of water to precipitate product B, which was filtered off after standing for a few hours. Acidification of the filtrate to a *p*H of 5 with acetic acid caused separation of product C.

Concentration of the mother liquor from which product A had crystallized, and subsequent separation of the residue into acidic and non-acidic components by the above procedure, but employing centrifugation rather than filtration, yielded a small amount of viscous acidic product. This was combined with product C and recrystallized from minimum hot ethanol–water to give 148 mg. or 29% of XVII monohydrate. The analytically pure monohydrate was obtained by repeated recrystallization from hot ethanol–water. The substance did not melt sharply presumably because of gradual loss of its water of hydration. A 3 to 7° melting range was usually observed somewhere between the limits of 87 and 101°, depending upon the rate of heating and the state of subdivision of the sample. The melt began to resolidify when a temperature a little above the melting point was maintained for several minutes

Anal. Calcd. for $C_{25}H_{34}O_8N_2 \cdot H_2O$: C, 59.04; H, 7.14; C_2H_5O, 26.58. Found: C, 59.30; H, 7.08; C_2H_5O, 26.61, 26.70.

The monohydrate was quantitatively dehydrated to the anhydrous β,β-dipyrrylpropionic ester XVII by heating *in vacuo* at 75–80° for 30 minutes, then at 105–115° for 90 minutes.

Anal. Calcd. for $C_{25}H_{34}O_8N_2 \cdot H_2O$: H_2O (of hydration), 3.54. Found: loss in weight on heating as above, 3.69, 3.72, 3.69.

The thus obtained anhydrous XVII melted at 150–152°.

Anal. Calcd. for $C_{25}H_{34}O_8N_2$: C, 61.21; H, 6.99; C_2H_5O, 27.56; mol. wt., 491. Found: C, 61.34; H, 6.88; C_2H_5O, 27.42; mol. wt., 496 ± 7 (ebullioscopic in chloroform).[46]

(45) Although in the experiment described here most of the β,β-dipyrrylpropionic ester acid XVII was present in product A, such was not the case in other similar runs. Product A frequently consists largely of non-acidic by-product, the XVII remaining in the mother liquor.

(46) The authors wish to thank Mr. James Ogilvie for this determination of the molecular weigbt.

BALTIMORE, MARYLAND

[CONTRIBUTION FROM THE OHIO STATE UNIVERSITY RESEARCH FOUNDATION]

Triazines. IX. 1,3,5-Triazine and its Formation from Hydrocyanic Acid[1,2]

BY CHRISTOPH GRUNDMANN AND ALFRED KREUTZBERGER

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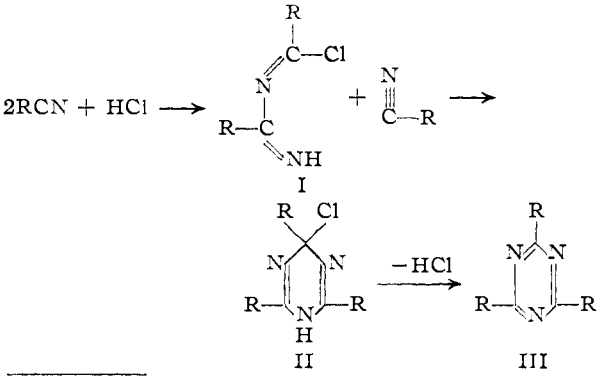
The identity of the long known "dimer of hydrocyanic acid" with *s*-triazine, $C_3H_3N_3$, has been established. New chemical and spectroscopical data for *s*-triazine are presented. The formation of $C_3H_3N_3$ from HCN *via* the "sesquihydrochloride of hydrocyanic acid" and the "chloromethylene–formamidine" is discussed, and new structures for these intermediates are proposed. Other known modes of formation of dimeric HCN are discussed in view of the new structure.

The mechanism of the acid-catalyzed polymerization of nitriles to *s*-triazines has recently been explained as a kind of Diels–Alder reaction in which two molecules of the nitrile and one molecule of hydrochloric acid form at first an intermediate I which then adds another molecule of the nitrile, the resulting product II splitting off hydrochloric acid to give the *s*-triazine (III)[3]



But as already reported our attempts to trimerize hydrocyanic acid to *s*-triazine failed, hydrocyanic and hydrochloric acid forming rapidly the long known so-called "sesqui-hydrochloride of hydrocyanic acid," 2HCN·3HCl, to which formulas IVa[4] and more recently IVb[5] have been assigned. This compound under a variety of conditions readily loses two thirds of its hydrogen chloride content yielding a product formulated as chloromethylene–formamidine (V). As this has the structure expected for the intermediate of hydrocyanic acid in the trimerization (I, R = H), we tried to react this compound with another nitrile or hydrocyanic acid itself. As no condensation to the expected triazine took place, we assumed that the second intermediate (II, R = H) might be more stable in this special case, and we decided to carry out the reaction with addition of a tertiary base as a scavenger of hydrochloric acid in the last step (II → III). We found then that this experiment had already been made by Hinkel, *et al.*, heating either the sesquihydrochloride of hydrocyanic acid or chloromethylene–formamidine with quinoline.[6] Since free hydrocyanic acid is reported always to occur during these reac-

(1) This article is based on work performed under project 116-B of The Ohio State University Research Foundation sponsored by the Mathieson Chemical Corporation, Baltimore, Md.

(2) Preceding communication: Ch. Grundmann and H. Schroeder, *Chem. Ber.*, **87**, 747 (1954).

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(5) (a) L. E. Hinkel and T. 1. Watkins, *J. Chem. Soc.*, 647 (1944); (b) L. E. Hinkel and R. Hullin, *ibid.*, 1033 (1949).

(6) L. E. Hinkel and R. T. Dunn, *ibid.*, 1834 (1930).