was recrystallized from benzene to give an additional 11.5 g. of colorless crystals. Total yield was 35.5 g. (80%).

Anal. Calcd. for $C_{14}H_{12}N_2O_4$: C, 61.8; H, 4.42; N, 10.30. Found: C, 61.93; H, 4.60; N, 10.37.

2,2'-*p*-Phenylenebis-[4-isobutyl-5(4H)-oxazolone].—Fifty grams of N,N'-terephthaloylbis-(*dl*-leucine) (0.128 mole) was treated with 250 ml. of acetic anhydride as above to yield 30 g. (65% yield) of large white crystalline flakes after recrystallization from benzene, m.p. 167°.

Anal. Calcd. for $C_{20}H_{24}N_2O_4$: C, 67.4; H, 6.7; N, 7.87. Found: C, 67.6; H, 6.92; N, 8.00.

2,2'-*p*-Phenylenebis-[4,4-dimethyl-5(4H)-oxazolone].—Fifty grams of N,N'-terephthaloylbis-(α-aminoisobutyric acid) (0.149 mole) was heated in 500 ml. of acetic anhydride at 120° for one-half hour. During this time, the solid failed to dissolve but became more crystalline in appearance. After recrystallization from chloroform, there was obtained 32 g. (72% yield) of small white crystals, m.p. 260° (sublimes).

Anal. Calcd. for $C_{16}H_{16}N_2O_4$: N, 9.34. Found: N, 9.12.

2,2'-*p*-Phenylenebis-[5(4H)-oxazolone].—Two grams of N,N'-terephthaloylbis-(glycine) (0.071 mole) was heated in 40 ml. of refluxing acetic anhydride for 15 minutes. The solid failed to dissolve but became more crystalline in appearance. After recrystallization from a large volume of dioxane, there was obtained essentially a quantitative yield of white crystals, m.p. 245° dec.

Anal. Calcd. for $C_{12}H_8N_2O_4$: C, 59.0; H, 3.28; N, 11.49. Found: C, 58.9; H, 3.43; N, 11.53.

2,2'-Tetramethylenebis-[4,4-dimethyl-5(4H)-oxazolone].—Ten grams of N,N'-adipoylbis-(α-aminoisobutyric acid) (0.0316 mole) was warmed with 25 ml. of acetic anhydride on a steam-bath for 20 minutes. After cooling and recrystallization from benzene, there was obtained 8 g. (82% yield) of crystals, m.p. 108–109°.

Anal. Calcd. for $C_{14}H_{20}N_2O_4$: C, 60.00; H, 7.15; N, 10.00. Found: C, 59.29; H, 7.07; N, 10.04.

2,2'-Dimethylenebis-[4,4-dimethyl-5(4H)-oxazolone].—Two grams of N,N'-succinoylbis-(α-aminoisobutyric acid) (0.07 mole) was treated as above with 20 ml. of acetic anhydride and the product recrystallized from a benzene–petroleum ether mixture to yield about 0.5 g. of white crystals (*ca.* 25% yield), m.p. 102–103°.

Anal. Calcd. for $C_{12}H_{16}N_2O_4$: C, 57.2; H, 6.35; N, 11.10. Found: C, 57.3; H, 6.40; N, 11.5.

2,2'-Tetramethylenebis-(spiro-[cyclohexane-1,4'-oxazol]-5'(4'H)-one).—Five grams of N,N'-adipoylbis-(1-aminocyclohexanecarboxylic acid) (0.013 mole) was treated as above with 20 ml. of acetic anhydride and the product recrystallized from a benzene–petroleum ether mixture to yield *ca.* 2.5 g. of white crystals (*ca.* 60% yield), m.p. 109–111°.

Anal. Calcd. for $C_{20}H_{28}N_2O_4$: C, 66.66; H, 7.78; N, 7.78. Found: C, 66.76; H, 7.88; N, 7.85.

Evidence was also obtained for the synthesis of 2,2'-tetramethylenebis-[4-isobutyl-5(4H)-oxazolone] and 2,2'-tetramethylenebis-[5(4H)-oxazolone]. These products were liquids which decomposed during distillation, and complete purification was not effected.

Acknowledgment.—The authors wish to thank Dr. W. A. Gregory of the Grasselli Chemicals Department for suggesting this route to diazlactones.

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

A Novel Route to Certain 2-Pyrrolecarboxylic Esters and Nitriles[1,2]

BY GEORGE G. KLEINSPEHN

RECEIVED SEPTEMBER 7, 1954

Diethyl oximinomalonate undergoes reduction and condensation with certain β-diketones and a β-ketoaldehyde to give 2-pyrrolecarboxylic esters. Similarly, ethyl oximinocyanoacetate and certain β-diketones afford 2-pyrrolecarbonitriles. The method has been applied to the synthesis of five previously known pyrroles: 2-carbethoxy-3,5-dimethylpyrrole, 2-carbethoxy-4-ethyl-3,5-dimethylpyrrole, 5-carbethoxy-2,4-dimethyl-3-pyrrolepropionic acid, 2-carbethoxy-3,4-dimethylpyrrole and 4-ethyl-3,5-dimethyl-2-pyrrolecarbonitrile. This synthetic approach constitutes the most direct route to four of these five pyrroles. A sixth and previously unreported pyrrole, 3,5-dimethyl-2-pyrrolecarbonitrile, also has been prepared by this method.

A little more than a decade ago Fischer and Fink,[3] while attempting a Knorr-type reductive condensation[4] of ethyl α-oximinoacetoacetate with the diethyl acetal of 3-oxobutyraldehyde, observed the unexpected formation of 2-carbethoxy-5-methylpyrrole. Thus it became apparent that in this instance a new type of pyrrole ring-synthesis involving the cleavage of the acetyl group of ethyl α-oximinoacetoacetate was occurring in preference to the anticipated Knorr condensation. Reinvestigation of the reductive condensation of ethyl α-oximinoacetoacetate with 2,4-pentanedione (II) by these same workers[3] revealed that in the case of this β-diketone the new condensation does in fact compete, though very unsuccessfully, with the Knorr cyclization. As has long been known, this reaction affords the Knorr product, 4-acetyl-3,5-dimethyl-2-carbethoxypyrrole, in good yield. From the mother liquor, however, Fischer and Fink[3] were able to isolate 2-carbethoxy-3,5-dimethylpyrrole (V), the product arising from the new-type condensation, in a yield amounting to a few tenths of 1%. A subsequent publication[5] by these investigators reports that two more β-ketoaldehydes have been found to undergo the new-type condensation, and Cookson[6] recently has elucidated a further example of a cyclization of this same general type.

In the interest of achieving a more direct synthetic route to certain 2-pyrrolecarboxylic esters which are important intermediates in the preparation of porphyrins and other polypyrryl compounds, it was decided to attempt a series of condensations closely related to those reported by Fischer and Fink,[3,5] but employing diethyl oximinomalonate (I) rather than ethyl α-oximinoacetoacetate. It was anticipated that the use of I by precluding the possibility of competing Knorr-type cyclizations would both widen the scope of the con-

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[1] Studies in the Pyrrole Series, XXVII. Paper XXVI, A. H. Corwin and K. W. Doak, THIS JOURNAL, **77**, 464 (1955).

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

[3] H. Fischer and E. Fink, *Z. physiol. Chem.*, **280**, 123 (1944).

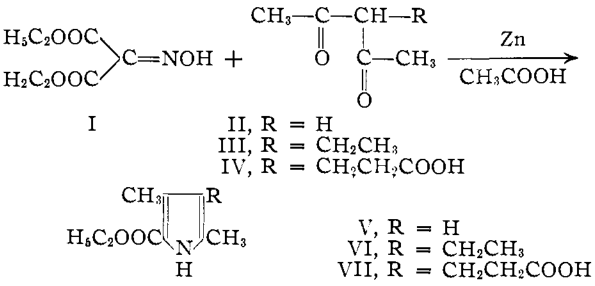
[4] H. Fischer and H. Orth, "Die Chemie des Pyrrols," Vol. I, Akademische Verlagsgesellschaft m. b. H., Leipzig, 1934, pp. 3–5.

[5] H. Fischer and E. Fink, *Z. physiol. Chem.*, **283**, 152 (1948).

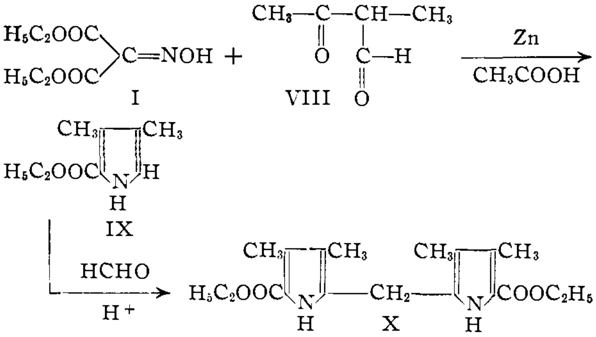
[6] G. H. Cookson, *J. Chem. Soc.*, 2789 (1953).

densation and afford more satisfactory yields of the desired products.

A reductive condensation of diethyl oximinomalonate (I) with 2,4-pentanedione (II) was first carried out, and 2-carbethoxy-3,5-dimethylpyrrole (V) was obtained in a yield of 60%. Some 3-substituted 2,4-pentanediones were next employed in the reaction. Thus, as is shown below, I underwent reductive cyclization with 3-ethyl-2,4-pentanedione (III) and with γ-acetyl-δ-oxohexanoic acid (IV)[7] to afford 2-carbethoxy-4-ethyl-3,5-dimethylpyrrole (VI) and 5-carbethoxy-2,4-dimethyl-3-pyrrolepropionic acid (VII), respectively, in good yield. Each of the pyrroles V, VI and VII was identified by analysis and by mixed melting point with the authentic material. The novel synthesis of VII is of particular interest, for since the acid IV may be prepared from commercially available β-propiolactone and 2,4-pentanedione by a one-step process,[7] pyrrolepropionic acid VII now becomes for the first time a rather directly accessible intermediate.

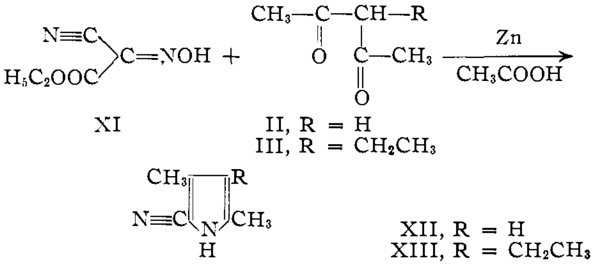


In order to investigate further the applicability of the cyclization reaction, a reductive condensation of diethyl oximinomalonate (I) with the β-ketoaldehyde, 2-methyl-3-oxobutyraldehyde (VIII), was next carried out. Curiously enough, melting point data indicated the product to be 2-carbethoxy-3,4-dimethylpyrrole (IX)[8,9] rather than the isomeric 2-carbethoxy-4,5-dimethylpyrrole which Fischer and Fink[5] had obtained previously from the analogous reductive cyclization of ethyl α-oximinoacetoacetate with VIII.



It has been demonstrated recently by Royals and Brannock[10] that VIII, as usually prepared, contains some isomeric 3-oxovaleraldehyde. Since this impurity could give rise to either or both of two additional pyrroles, it was necessary to establish the structure of our condensation product by converting it to a derivative, an authentic sample of which was available for mixed melting point determinations. Thus our pyrrole was condensed with formaldehyde to give the corresponding pyrromethane, and this pyrromethane indeed proved identical with 5,5′-methylenebis-(2-carbethoxy-3,4-dimethylpyrrole) (X).[11]

The encouraging results obtained with diethyloximinomalonate prompted us to examine the possibility of preparing 2-pyrrolecarbonitriles by reductive condensation of ethyl oximinocyanoacetate (XI) with β-diketones. While attempting such a condensation of 2,4-pentanedione (II) with XI, it was observed that the order of addition of the reactants affects the course of the reaction. Thus when a solution of ethyl oximinocyanoacetate is added slowly to a stirred suspension of zinc dust in a hot solution of 2,4-pentanedione, there results a mixture of 2-carbethoxy-3,5-dimethylpyrrole (V) with what is probably the corresponding nitrile XII. From this mixture ester V may be isolated readily. If, however, zinc dust is slowly introduced with stirring into a hot solution of both XI and the β-diketone II, 3,5-dimethyl-2-pyrrolecarbonitrile (XII) is formed in about 35% yield. Under the latter reaction conditions, ethyl oximinocyanoacetate and 3-ethyl-2,4-pentanedione (III) afford a 45% yield of 4-ethyl-3,5-dimethyl-2-pyrrolecarbonitrile (XIII).[12,13]



Acknowledgment.—The author wishes to acknowledge the helpful consultation and continuing interest of Dr. Alsoph H. Corwin.

Experimental[14,15]

2-Carbethoxy-3,5-dimethylpyrrole (V).—The diethyl oximinomalonate employed in this and subsequent preparations was obtained by the procedure of Cerchez.[16] The crude product was not purified by distillation, but was heated on the steam-bath at 1–2 mm. for 1.5 hr. in order to remove some of the unchanged diethyl malonate.

The following condensation procedure is based upon that described by Corwin and Quattlebaum[17] for the preparation of 2,4-dicarbethoxy-3,5-dimethylpyrrole. A solution of 5.00 g. of 2,4-pentanedione (Carbide and Carbon) in 26 ml. of glacial acetic acid was placed in a 100-ml. three-neck flask equipped with a mechanical stirrer, dropping funnel, thermometer and gas exit. The solution was heated, and

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[7] T. L. Gresham, J. E. Jansen, F. W. Shaver, M. R. Frederick and W. L. Beears, This Journal, **73**, 2346 (1951).

[8] H. Fischer and H. Höfelmann, *Ann.*, **533**, 223 (1938).

[9] W. Siedel, *ibid.*, **554**, 158 (1943).

[10] E. E. Royals and K. C. Brannock, This Journal, **76**, 1180 (1954).

[11] H. Fischer and B. Walach, *Ann.*, **450**, 127 (1926).

[12] H. Fischer, P. Halbig and B. Walach, *ibid.*, **452**, 296 (1927).

[13] H. Fischer and Z. Csukas, *ibid.*, **508**, 183 (1933).

[14] All melting points were determined on the Fisher-Johns melting point block.

[15] Carbon and hydrogen microanalyses were performed by Mr. Joseph A. Walter.

[16] V. Cerchez, *Bull. soc. chim. France*, [4] **47**, 1280 (1930).

[17] A. H. Corwin and W. M. Quattlebaum, Jr., This Journal, **58**, 1083 (1936).

at 80° a mixture of 13 g. of anhydrous sodium acetate and 11 g. of zinc dust was added with vigorous stirring. At 95° the dropwise addition of a solution of 9.47 g. of diethyl oximinomalonate in 12 ml. of acetic acid and 5 ml. of water was begun. The addition was completed in 30 to 40 min. between 95 and 105°, vigorous stirring being maintained constantly throughout. After heating to 100–105° for an additional 20 min., the reaction mixture was poured with stirring into 170 ml. of ice–water mixture, then refrigerated. The crude product was filtered off, washed with water, pressed on the filter then taken up in 50 ml. of boiling 95% ethanol. After filtration of the hot mixture to remove the zinc dust, the filtrate was concentrated to 30 ml., poured into 85 ml. of ice–water mixture and refrigerated. Filtration then afforded a product which after drying *in vacuo* weighed 5.03 g. (60% yield), m.p. 120–124°. Two recrystallizations from 95% ethanol afforded the analytically pure material of m.p. 124–124.5°; mixed melting points with authentic V (m.p. 124.5–125°) prepared by the method of Fischer and Walach[18] showed no depression.

Anal. Calcd. for $C_9H_{13}O_2N$: C, 64.65; H, 7.84; C_2H_5O, 26.95. Found: C, 64.46; H, 7.86; C_2H_5O, 26.95.

2-Carbethoxy-4-ethyl-3,5-dimethylpyrrole (VI).[19]—Fifty millimoles each of I and of 3-ethyl-2,4-pentanedione[20,21] (b.p. 79–83.5° at 23–23.5 mm.) were used. The procedure was that employed for the preparation of V except that the crude product containing zinc dust was taken up in only 30 ml. of boiling 95% ethanol. A 65% yield or 6.36 g. of crude product (m.p. 81–89°) was obtained. Two recrystallizations from 95% ethanol afforded the analytically pure product of m.p. 90–91°. Authentic VI prepared by hydrogenation[22] of the corresponding 4-acetylpyrrole in the presence of a palladium catalyst melted at 89.5–92°; admixture of these two products caused no melting point depression.

Anal. Calcd. for $C_{11}H_{17}O_2N$: C, 67.66; H, 8.78; C_2H_5O, 23.08. Found: C, 67.60; H, 8.76; C_2H_5O, 23.19.

5-Carbethoxy-2,4-dimethyl-3-pyrrolepropionic Acid (VII).[19]—γ-Acetyl-δ-oxohexanoic acid prepared by the method of Gresham, *et al.*,[7] was employed in this instance. However, because the crystallization of this diketo acid IV from the rather viscous distillates proved slow and tedious, purification was achieved instead by repeated fractional distillation of the product, and the appropriate liquid fraction boiling at 155–165° at 1.5 mm. was utilized directly in the synthesis of VII.

Fifty millimoles each of I and IV were employed in the condensation. The procedure was that described for the preparation of V except for the following alteration. In order to effect complete solution of the pyrrole prior to removal of the zinc dust by filtration it was necessary to add 5 ml. of concentrated hydrochloric acid to the 35 ml. of boiling ethanol. The hydrochloric acid presumably converts some salt of the pyrrole acid which is present to free VII. The crude product (7.08 g. or 59% yield) melted over a wide range, but was readily purified by recrystallization from boiling benzene. An analytical sample was obtained after three recrystallizations from benzene and subsequent drying *in vacuo* at 80–90° for one hour; m.p. 154–156°. Mixed melting points with authentic VII of m.p. 155–156° showed no depression. The authentic VII was prepared by hydrogenation[23] of the corresponding 3-pyrroleacrylic acid in glacial acetic acid in the presence of 5% palladium-on-carbon.

Anal. Calcd. for $C_{12}H_{17}O_4N$: C, 60.24; H, 7.16; C_2H_5O: 18.83. Found: C, 59.96; H, 7.30; C_2H_5O, 18.66.

2-Carbethoxy-3,4-dimethylpyrrole (IX).[24]—Twenty-nine milliliters of glacial acetic acid was heated to 85° in a 100-ml. three-neck flask and 7.9 g. of anhydrous sodium acetate was then added with stirring. Next 7.00 g. of the sodium salt[25] of 2-methyl-3-oxobutyraldehyde, 9.48 g. of diethyl oximinomalonate and a solution of 12 ml. of glacial acetic acid in 5 ml. of water were consecutively introduced, and the mixture was heated to 95°. Eleven grams of zinc dust was then added during several minutes between the limits of 95 and 105°, after which the reaction mixture was heated and stirred for an additional 20 minutes. Pouring into 170 ml. of ice–water mixture caused the separation of a pale yellow oil which soon solidified. After refrigeration of the mixture, the product was filtered off, taken up in 10 ml. of boiling ethanol and filtered to remove the zinc dust. The pyrrole was then precipitated by pouring the filtrate into 20 ml. of ice–water mixture; yield 2.49 g. or 30% yield of crude product melting over a wide range. After one recrystallization from 95% ethanol followed by two more from isoöctane the analytically pure product of m.p. 94–95° was obtained; lit.[8,9] m.p. 95–96°.

Anal. Calcd. for $C_9H_{13}O_2N$: C, 64.65; H, 7.84; C_2H_5O, 26.95. Found: C, 64.54; H, 7.85; C_2H_5O, 26.80.

5,5′-Methylenebis-(2-carbethoxy-3,4-dimethylpyrrole) (X).[11]—This methane was prepared from pyrrole IX by heating briefly in ethanolic solution with excess 40% formaldehyde and a few drops of concentrated hydrochloric acid. The product melted at 202–203° and did not depress the melting point of a sample of the authentic methane X[11] which melted at 200–202.5°; lit.[11] m.p. 198°.

Anal. Calcd. for $C_{19}H_{26}O_4N_2$: C_2H_5O, 26.01. Found: C_2H_5O, 26.01.

2-Carbethoxy-3,5-dimethylpyrrole (V) from XI and II.—The procedure was that employed for preparation of V from I and II. Fifty millimoles each of XI and II were used, and the crude product containing zinc dust was taken up in 25 ml. of boiling 95% ethanol. The filtrate was then poured into 75 ml. of ice–water mixture to precipitate the product, yield 2.48 g. of product melting in the range 63–110°. Three crystallizations from ethanol and subsequent sublimation *in vacuo* afforded analytically pure V melting at 124–125°. No depression of the melting point was observed upon admixture with authentic V.

Anal. Calcd. for $C_9H_{13}O_2N$: C_2H_5O, 26.95. Found: C_2H_5O, 27.01.

3,5-Dimethyl-2-pyrrolecarbonitrile (XII) from XI and II.—The preparative procedure for obtaining XII is as follows. Twenty-six milliliters of glacial acetic acid and 5.00 g. of 2,4-pentanedione were heated to 80°. Thirteen grams of anhydrous sodium acetate, 7.11 g. of ethyl oximinocyanoacetate[26] and a solution of 12 ml. of acetic acid in 5 ml. of water were then consecutively introduced, and the mixture was heated to 95°. Zinc dust (11 g.) was then added during 20–25 min. between the limits of 95 and 105°, and the mixture was heated and stirred for an additional 20 min. Pouring the reaction mixture into 170 ml. of ice–water mixture caused the separation of an oil which solidified upon refrigeration. The product was filtered off, taken up in 15 ml. of boiling ethanol and filtered to remove the zinc dust. The nitrile was precipitated by stirring the filtrate into 30 ml. of ice–water mixture and refrigerating. The crude nitrile weighed 2.10 g. (35% yield) and melted at 60–73°. Two recrystallizations from isoöctane with centrifugation of the dark-colored, tarry impurities afforded the analytically pure material of m.p. 75–76.5°.

Anal. Calcd. for $C_7H_8N_2$: C, 69.97; H, 6.71. Found: C, 69.82; H, 6.86.

4-Ethyl-3,5-dimethyl-2-pyrrolecarbonitrile (XIII).—The immediately preceding procedure was utilized in the preparation of XIII, 3-ethyl-2,4-pentanedione[20,21] (b.p. 79–83.5° at 23–23.5 mm.) being substituted for 2,4-pentanedione; yield 3.35 g. of crude product or 45%. A single recrystallization from ethanol–water afforded a product melting at 135–136°. A subsequent recrystallization from benzene–isoöctane gave the analytically pure substance with unchanged melting point; lit.[12,13] m.p. 134°.

Anal. Calcd. for $C_9H_{12}N_2$: C, 72.94; H, 8.16. Found: C, 72.91; H, 8.31.

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(18) H. Fischer and B. Walach, *Ber.*, **58**, 2821 (1925).

(19) The author wishes to acknowledge the collaboration of Dr. Anna Leone who first carried out this condensation employing an electrolytic rather than a zinc dust reduction.

(20) N. P. Buu-Hoï and D. Guettier, *Rec. trav. chim.*, **65**, 505 (1946).

(21) The author wishes to thank Mr. Peter Wei for the preparation of this intermediate.

(22) S. R. Buc, Dissertation, The Johns Hopkins University, 1938, pp. 56–58.

(23) C. S. Vestling, *J. Biol. Chem.*, **135**, 624 (1940).

(24) The author wishes to thank Mr. George T. McGrew who first carried out this preparation.

(25) A. H. Tracy and R. C. Elderfield, *J. Org. Chem.*, **6**, 66 (1941).

(26) M. Fields, D. E. Walz and S. Rothschild, THIS JOURNAL, **73**, 1001 (1951).