THE SYNTHESIS OF HEMOPYRROLE-DICARBOXYLIC ACID AND OF SOME DIPYRROMETHENES[1]

By S. F. MacDonald and R. J. Stedman[2]

ABSTRACT

The pyrrole II*e* was obtained through the known II*c* and hydrolyzed to III*b*. This last could be partially decarboxylated to hemopyrrole-dicarboxylic acid III*c* or, with formic acid, converted into the dipyrromethene VII*b*. The isomeric dipyrromethene VII*a* was obtained analogously.

Of the two key pyrroles related to the uroporphyrins, cryptopyrrole-dicarboxylic acid I*a* has already been synthesized (10). The synthesis of the second of these, hemopyrrole-dicarboxylic acid III*c*, is now reported.

With ethyl cyanoformate and hydrogen chloride, the pyrrole II*c* (10), for which an improved preparation is given, gave the glyoxylic ester II*d*. Consistently high yields were obtained only when the usual conditions (cf. (6)) were modified to ensure that the intermediate ketimine hydrochloride crystallized. The glyoxylic ester was catalytically reduced in acetic–sulphuric acid over palladium black (cf. (9)) to II*e*, which Treibs and Ott have obtained from II*c* by a different route (13). When this reduction was attempted with W-6 Raney nickel in refluxing ethanol (cf. (12)), with hydrogen (cf. (15)) at 130–150° and 3000 to 4000 lb. per sq. in. in ethanol over copper chromite (1), or with zinc dust in boiling acetic acid, the only product isolated was II*c* identified by melting point and mixed melting point, the positive Ehrlich's reaction in the cold, and, in the first case, by analysis for C, H, and N. The loss of an acyl group on catalytic reduction was unexpected but is not without analogy (cf. (8)).

Alkaline hydrolysis of II*e* resulted in III*a* or in III*b*, differing in their Ehrlich's reactions. These structures were confirmed by decarboxylating the latter to the known hemopyrrole-carboxylic acid IV*a*. With water at 100°, III*b* gave a dicarboxylic acid which could not be directly shown to be III*c* rather than IV*b*, for the latter is known only as a half-ester (7*b*). Under these conditions I*a* had been obtained from I*b* (10) and IV*b* would be expected to lose its α-carboxy group. Further, the dimethyl ester of the dicarboxylic acid gave a strongly positive Ehrlich's reaction in the cold, behavior consistent with III*c* but not with IV*b*. However, the dicarboxylic acid was shown definitely to be hemopyrrole-dicarboxylic acid III*c* by conversion of its dimethyl ester into V*e* (see below) with phosgene and methanol (cf. (7*c*)).

As the preparation of the intermediates might have proved more convenient using the higher-melting methyl esters, methyl α-oximino-β-ketoadipate and benzyl acetoacetate were combined in the Knorr synthesis to give V*a*, which

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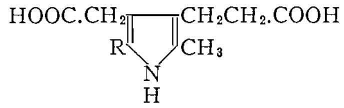
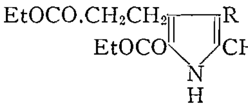
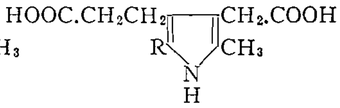
[2] *National Research Council of Canada Postdoctorate Fellow.*



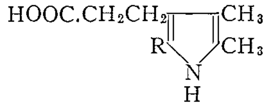
I*a*, R = H
b, R = COOH



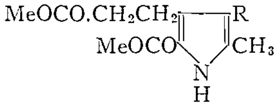
II*a*, R = $COOCH_2.C_6H_5$
b, R = COOH
c, R = H
d, R = CO.COOEt
e, R = $CH_2.COOEt$



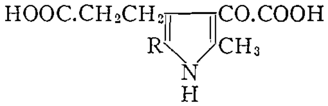
III*a*, R = COOEt
b, R = COOH
c, R = H



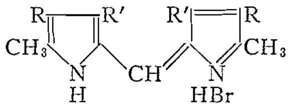
IV*a*, R = H
b, R = COOH



V*a*, R = $COOCH_2.C_6H_5$
b, R = COOH
c, R = H
d, R = CO.COOMe
e, R = $CH_2.COOMe$



VI*a*, R = COOEt
b, R = COOH



VII*a*, R = $CH_2CH_2.COOH$; R′ = $CH_2.COOH$
b, R = $CH_2.COOH$; R′ = $CH_2CH_2.COOH$

was converted into V*b*, V*c*, V*d*, and V*e*. The structures of these were confirmed by relating V*d* and V*e* to the ethyl esters for which there was independent analytical proof. Thus II*d* could be hydrolyzed either to VI*a* or VI*b*, and the latter gave V*d* with diazomethane; similarly II*e* was hydrolyzed to III*b*, which was converted into V*e* with diazomethane.

Two better methods were found for converting ethyl β-keto-α-carbethoxyadipate into ethyl β-ketoadipate (cf. (5, 14)), an intermediate in the preparation of II*a*: the triester was allowed to stand with sulphuric acid, and alcohol added to the mixture, or the triester was boiled with water (cf. (4, 2)). To obtain the methyl β-ketoadipate of Bardhan (3) required in the synthesis of V*a*, β-carbomethoxy-propionyl chloride and the ethoxymagnesium derivative of ethyl malonate gave methyl δ,δ-dicarbethoxylevulinate, which was converted into β-ketoadipic acid with hydrochloric acid (cf. (5)), and the acid esterified.

Both the pyrroles I*b* and III*b* reacted normally with formic acid and hydrogen bromide at 100° (cf. (7*d*)) to give the dipyrromethenes VII*a* and VII*b* respectively. At lower temperatures, the hydrobromides of I*a* and III*c* were the predominant products (16).

EXPERIMENTAL

2-Methyl-5-carboxypyrrole-4-(propionic acid) Diethyl Ester, IIc

Up to 500 gm. of the benzyl ester II*a* have been hydrogenated in 1 liter of ethanol in a 3 liter autoclave as previously described (10). The mixture of crude acid II*b* and catalyst (277 gm.) from 378 gm. of the benzyl ester II*a* was dry distilled in two lots at 230° rising to 260° (air bath temperatures) under the water-pump vacuum (initially and finally 15 mm.). The pyrrole II*c* rapidly solidified in the air condenser. It was recrystallized from pentane by extraction (Soxhlet) giving 155 gm. (63% from the benzyl ester), m.p. 67-67.5° (cf. (10)).

2-Methyl-5-carboxypyrrole-3-(glyoxylic acid)-4-(propionic acid) Triethyl Ester, IId

The pyrrole II*c* (45 gm.) in ethyl cyanoformate (45 ml.), dry ether (150 ml.), and chloroform (50 ml., dry and alcohol free) was stirred in an ice–salt bath and protected from moisture while dry hydrogen chloride was passed in for three hours. Dry air was then passed through without cooling until the mixture was largely crystalline. Ether (100 ml.) was added, the mixture kept at 0° overnight, the ketimine hydrochloride filtered off, washed with ether, dried *in vacuo*, and dissolved in ice-water (3 liters). After several hours, the glyoxylic ester was filtered off and washed with water. It was dissolved in alcohol, filtered with charcoal, and the charcoal washed with alcohol. After the filtrate and washings (110 ml.) were diluted with 85 ml. of water and allowed to stand at 25° then at 0°, 53 gm., m.p. 78–79°, were collected. The mother liquors diluted with 100 ml. of water and allowed to stand as above gave 4.8 gm., m.p. 77–78° (total, 92% as used for reduction). For analysis, the ester was recrystallized twice and dried *in vacuo*, forming colorless needles, m.p. 78.5°–79°. Ehrlich's reaction slowly positive hot. Found: C, 57.64; H, 6.72; N, 4.01%. Calc. for $C_{17}H_{23}O_7N$: C, 57.78; H, 6.56; N, 3.96%.

2-Methyl-5-carboxypyrrole-3-(acetic acid)-4-(propionic acid) Triethyl Ester (Ethyl α-Carbethoxyhemopyrrole-dicarboxylate), IIe

The glyoxylic ester II*d* (24 gm.) in acetic acid (100 ml.) and sulphuric acid (3.75 ml.) was shaken for six hours with palladium black (1.2 gm., freshly prepared (17)) under hydrogen (60 lb. per sq. in.) at 27°. After the theoretical uptake in two hours, absorption nearly ceased. The filtrate and washings from the catalyst were added to ice-water (3 liters) containing sodium bicarbonate (70 gm.), seeded, and left at 0° overnight. The solid was filtered off, washed, and dried. The acidified filtrate was extracted once with ether, and the ether evaporated from the extract.

Three reductions, using 57.8 gm. glyoxylic ester, were worked up together. When the solid was extracted with pentane (Soxhlet) most of the product crystallized from the pentane. More was obtained by combining the partially hydrolyzed pentane-insoluble material with the residue from the ether extract, esterifying it with 5% ethanolic hydrogen chloride at 25° overnight, pouring it into ice water, and extracting the dried solid with pentane (Soxhlet). Yield 44 gm. (79%), long colorless needles, m.p. 63–64°, or prisms, m.p. 64–65°. Ehrlich's reaction negative cold but positive hot. For analysis, it was recrystallized three times from aqueous ethanol and dried *in vacuo*, needles m.p. 63–64°. Found: C, 59.98; H, 7.26; N, 4.26%; mol. wt. (Rast) 333. Calc. for $C_{17}H_{25}O_6N$: C, 60.16; H, 7.43; N, 4.13%; mol. wt. 339.

When less active palladium black was used, the yield fell to about 50%.

This pyrrole and the isomeric ethyl α-carbethoxycryptopyrrole-dicarboxylate (10) were not clearly distinguished by their melting points or by their infrared spectra in carbon disulphide. However, their mixed melting point showed a depression.

α-Carboxyhemopyrrole-dicarboxylic Acid, IIIb

The triethyl ester II*e* (2 gm.) in ethanol (25 ml.) and 10% sodium hydroxide (25 ml.) was heated for two and a half hours on the steam bath in an open flask. The solvent was removed *in vacuo*, the residual gum dissolved in water (25 ml.), warmed, and filtered with charcoal, and the product (1.27 gm., 84%), a yellow powder m.p. 144–145° (decomp.), precipitated with sulphur dioxide at 0° and washed with ice-water. After three recrystallizations from acetone (dried over potassium carbonate) (thimble) it formed small very pale violet needles, m.p. 155–156° (decomp.), Ehrlich's reaction strongly positive cold. Found in material dried *in vacuo*: C, 51.29; H, 5.36; N, 5.54%. Calc. for $C_{11}H_{13}O_6N$: C, 51.76; H, 5.13; N, 5.49%. It is stable when kept under nitrogen, or *in vacuo* over phosphorus pentoxide.

Hemopyrrole-dicarboxylic Acid, IIIc

The crude tricarboxylic acid III*b* (0.802 gm., m.p. 148°) in water (3 ml.) was heated under nitrogen on the steam bath to solution and cessation of effervescence (*ca.* 15 min.). After the solution was cooled to 0°, the product (0.544 gm., 84%) was collected and washed with a little ice-water, as very pale pink prisms, m.p. 150–150.5° (decomp.), Ehrlich's reaction positive cold, no insoluble picrate was formed in wet ether. After three recrystallizations from water (4 ml.) the melting point was unchanged. Found in material dried *in vacuo* and stored over nitrogen: C, 56.78; H, 6.26; N, 6.82%. Calc. for $C_{10}H_{13}O_4N$: C, 56.86; H, 6.20; N, 6.63%.

Dimethyl Hemopyrrole-dicarboxylate[3]

Hemopyrrole-dicarboxylic acid III*c* (3.05 gm.) was allowed to stand overnight with a cooled ethereal solution of diazomethane. After removing the ether *in vacuo*, the crystalline residue was distilled (135°, 5×10^{-5} mm.). The ester (3.33 gm., 96%) formed yellow crystals, m.p. 50–51°, raised to 51°–52.5° by resublimation, Ehrlich's reaction strongly positive cold. Found: C, 60.39; H, 7.35; N, 6.03%. Calc. for $C_{12}H_{17}O_4N$: C, 60.23; H, 7.16; N, 5.86%.

Unless protected from light and stored *in vacuo* or under nitrogen, the product turns red.

Conversion of Dimethyl Hemopyrrole-dicarboxylate to 2-Methyl-5-carboxypyrrole-3-(acetic acid)-4-(propionic acid) Trimethyl Ester, Ve

Dimethyl hemopyrrole-dicarboxylate (2.11 gm., distilled in high vacuum at 110–115°) was dissolved in dry ether (70 ml.), cooled in ice-water, and treated with a rapid stream of phosgene for 15 min. The solution initially became cloudy, but rapidly cleared and darkened. After one and a quarter hours at room temperature the ether and excess phosgene were removed by a stream of dry air, and the crystalline residue was briefly dried *in vacuo* and dissolved in dry methanol (50 ml.). Evaporation under reduced pressure after 60 hr. gave a

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[3] *This preparation is due to Dr. K. H. Michl.*

dark gum which rapidly crystallized and was freed from hydrogen chloride by drying *in vacuo* over potassium hydroxide. Recrystallization from 15 ml. of methanol and 30 ml. of water (charcoal) gave the trimethyl ester (2.30 gm., 87%) as light brown crystals, m.p. 91°–91.5°.

A further crystallization from methanol–water gave light yellow plates, melting point unchanged, undepressed by authentic V*e* (see below), and indistinguishable from it by its infrared spectrum in carbon disulphide. The Ehrlich's reaction was positive hot. Found, in material recrystallized from pentane (thimble) and dried at 60° *in vacuo*: C, 56.77; H, 6.55; N, 4.83%. Calc. for $C_{14}H_{19}O_6N$: C, 56.56; H, 6.44; N, 4.71%.

Hemopyrrole-carboxylic Acid, IVa, from α-Carboxyhemopyrrole-dicarboxylic Acid, IIIb

The tricarboxylic acid III*b* (0.583 gm., m.p. 155°) in glycerol was heated under nitrogen at 200° for 15 min. After the mixture was poured into water (100 ml.) and extracted with ether (4 × 25 ml.), the extract was washed with water (25 ml.), dried over sodium sulphate, and the ether evaporated. The crystalline residue on sublimation (100°, 5×10^{-4} mm.) gave cream colored crystals (0.224 gm., 58%), m.p. 120–125°. After three crystallizations from water it formed cream colored rectangular plates, m.p. 127–128° (lit. 130–131° (7*a*)), Ehrlich's reaction positive cold. Found in material stored under nitrogen: C, 64.60; H, 8.06; N, 8.65%. Calc. for $C_9H_{13}O_2N$: C, 64.65; H, 7.83; N, 8.38%.

Methyl Hemopyrrole-carboxylate

Hemopyrrole-carboxylic acid (77 mgm., m.p. 128–129°, from III*b*) was added to ethereal diazomethane (from 2 gm. nitrosomethylurea) under nitrogen. After one hour the ether solution was washed with dilute hydrochloric acid, the acid neutralized with sodium bicarbonate and washed with ether, the ether washed twice with water and dried over sodium sulphate. The dark crystalline residue left after evaporation of the ether was sublimed (50–60°, 10^{-3} mm.) giving methyl hemopyrrole-carboxylate as colorless prisms (31.5 mgm., 38%), m.p. 48–51°; after recrystallization from aqueous methanol, colorless plates, m.p. 49–51°, were obtained.

The methyl ester picrate, long chocolate-brown prisms, m.p. 118.5–120° (lit. 121–122° (7*a*)) was obtained from the ester with picric acid in wet ether.

The methyl ester, regenerated from the picrate with ether and aqueous sodium bicarbonate, melted at 50–53° (lit. 57° (7*a*)) after sublimation.

α-Carbethoxyhemopyrrole-dicarboxylic Acid, IIIa

The triethyl ester II*e* (1.94 gm.) in 20 ml. of ethanol and 14.2 ml. of 0.889 *N* sodium hydroxide (2.2 equiv.) was heated for two hours in an open flask on the steam bath. After it was taken to dryness *in vacuo*, the residual gum was dissolved in 9 ml. of water and the product precipitated with sulphur dioxide at 0° and washed with ice-water. After it was suspended in 12 ml. of water at 100° for 15 min., filtered at 0° and washed, the cream colored product (1.16 gm., 72%) melted at 232–234° (decomp.). For analysis, it was recrystallized four times from acetone (thimble) giving very light brown elongated prisms, m.p. 237–238° (decomp.), Ehrlich's reaction very weak cold but strongly positive hot. Found in material dried *in vacuo* at 60°: C, 55.49; H, 5.82; N, 5.09%. Eq. wt. 140.6. Calc. for $C_{13}H_{17}O_6N$: C, 55.12; H, 6.05; N, 4.94%. Eq. wt. 141.6.

2-Methyl-3-carbobenzoxy-4-(2-carbomethoxyethyl)-5-carbomethoxypyrrole, Va

Sodium nitrite (45 gm.) in water (75 ml.) was slowly added at $\leqslant 8°$ with stirring to methyl β-ketoadipate (101.3 gm.) in acetic acid (350 ml), and the excess nitrite was destroyed with ammonium sulphamate. This solution and zinc dust (300 gm.) were added slowly with stirring and cooling to benzyl acetoacetate (121 gm.) and ammonium acetate (100 gm.) in acetic acid (250 ml.) at 60–70°. After one hour at 90° the solution was decanted into ice-water (6 liters) and the zinc washed with hot acetic acid (50% then glacial). After the oil which separated had solidified, it was filtered off, well washed with water, and dried *in vacuo*, m.p. 120–126°. Recrystallization from ethanol (400 ml.) gave the product as pale yellow crystals (118 gm., 61%), m.p. 128–130°. For analysis, it was recrystallized three times from ethanol giving nearly colorless rectangular plates, m.p. 130–130.5°, Ehrlich's reaction positive hot. Found in material dried at 60° *in vacuo*: C, 63.71; H, 5.56; N, 3.74%. Calc. for $C_{19}H_{21}O_6N$: C, 63.50; H, 5.89; N, 3.90%.

2-Methyl-3-carboxy-4-(2-carbomethoxyethyl)-5-carbomethoxypyrrole, Vb

The benzyl ester V*a* (112 gm.) in 800 ml. of ethanol was hydrogenated for eight hours at 130° and 1100 lb. per sq. in. over 10 ml. of Raney nickel. When filtered off and washed with ethanol, the product (87 gm., containing nickel) was suitable for decarboxylation. A portion (14 gm.) was ground and filtered with 1 liter of ice-cold *N*/10 sodium carbonate, the product precipitated from the filtrate with carbon dioxide, filtered, and washed, giving 9 gm., m.p. 243–244° (decomp.). After two recrystallizations from ethanol and one from methanol, it formed colorless plates, melting point unchanged, Ehrlich's reaction positive hot. Found in material dried *in vacuo*: C, 53.76; H, 5.87; N, 5.36%. Calc. for $C_{12}H_{15}O_6N$: C, 53.53; H, 5.62; N, 5.20%.

2-Methyl-4-(2-carbomethoxyethyl)-5-carbomethoxypyrrole, Vc

The crude acid V*b* (73 gm., containing nickel) was distilled in two portions under the vacuum of a water pump at 230° rising to 245° (air-bath temperature) into an air condenser. The pale yellow waxy product was recrystallized from pentane (thimble) to give pink prisms (39 gm. 66% from the benzyl ester), m.p. 71–72°. This was suitable for the next stage. Two further recrystallizations gave the pyrrole as cream colored prisms, m.p. 72.5–73.5°. Ehrlich's reaction was slowly positive in the cold. Found in material dried *in vacuo*: C, 58.64; H, 6.86; N, 6.45%. Calc. for $C_{11}H_{15}O_4N$: C, 58.65; H, 6.71; N, 6.22%.

2-Methyl-5-carboxypyrrole-3-(glyoxylic acid)-4-(propionic acid), VIb

The ethyl ester II*d* (5.295 gm.) was heated in an open flask on the steam bath for two and one-half hours with 60 ml. of ethanol and 60 ml. of 10% sodium hydroxide. After removal of the residual solvent *in vacuo*, the gum was dissolved in 50 ml. of water, filtered, and the product precipitated with excess hydrochloric acid at 0°. The tricarboxylic acid VI*b* (2.81 gm., 70%) obtained as a white powder by washing the precipitate with water and drying it *in vacuo* had a melting point of 197–198° (decomp.), which was depressed by admixture of 2-methyl-5-carbethoxypyrrole-3-(glyoxylic acid)-4-(propionic acid) VI*a* (see below). Ehrlich's reaction was slowly positive in the cold.

Precipitation by sulphur dioxide instead of hydrochloric acid gave a product containing sodium.

2-Methyl-5-carboxypyrrole-3-(glyoxylic acid)-4-(propionic acid) Trimethyl Ester, Vd

(*i*) *From the Triethyl Ester IId by Hydrolysis and Re-esterification*

The glyoxylic acid VI*b* (2 gm.) was added in portions to diazomethane (from 14 gm. of nitrosomethylurea) in ether. After it had stood for three hours, the ethereal solution was washed with dilute hydrochloric acid, with aqueous sodium bicarbonate, and with water, dried over sodium sulphate, and evaporated to dryness. The residue, which crystallized slowly at 0°, was recrystallized from methanol (12 ml.) – water (18 ml.), and had the melting point 106–107.5° (1.82 gm., 78%). After three recrystallizations from aqueous methanol, it formed long colorless prisms, m.p. 108–109° or, with slow heating, 114–115°. The Ehrlich's reaction was positive hot. Found in material dried *in vacuo* at 60°: C, 53.63; H, 5.10; N, 4.57%. Calc. for $C_{14}H_{17}O_7N$: C, 54.01; H, 5.51; N, 4.50%.

Subsequent preparations gave only the higher melting form, colorless rectangular plates, m.p. 114.5–115°, and undepressed by admixture of the lower melting form. Ehrlich's reaction was positive hot. Found: C, 54.22; H, 5.48; N, 4.69%.

(*ii*) *From 2-Methyl-4-(2-carbomethoxyethyl)-5-carbomethoxypyrrole, Vc (Preparative Method)*

The pyrrole V*c* (32.6 gm.) was dissolved in 35 ml. of methyl cyanoformate (b.p. 97.5–98.5°), 38 ml. of chloroform (dry and alcohol free), and 120 ml. of dry ether, cooled in ice-salt with the exclusion of moisture, stirred, and treated with a rapid stream of dry hydrogen chloride for three hours. Solid separated during the reaction; the mixture was evaporated to dryness by a stream of dry air passed into the mixture, without cooling, for four hours. Dry ether (120 ml.) was added and, after 12 hr. at 0°, the ketimine hydrochloride was collected as a yellow powder, washed with ether, and dried under water pump vacuum. The hydrochloride was powdered and added portionwise, with stirring, to ice-water (3 liters). The glyoxylic ester was collected, washed with water, and dried *in vacuo* after the initially clear yellow solution had been allowed to stand for four hours at 0°. The crude product was dissolved in methanol (160 ml.), warmed with charcoal, filtered, and recrystallized by the addition of water, giving colorless plates (39.0 gm., 86.5%) m.p. 111°-113°, sufficiently pure for hydrogenation.

2-Methyl-5-carboxypyrrole-3-(acetic acid)-4-(propionic acid) Trimethyl Ester, Ve

(*i*) *By Reduction of the Glyoxylic Ester (Preparative Method)*

The glyoxylic ester V*d* (36.4 gm., m.p. 111–113°, prepared by method (*ii*)) in acetic acid (120 ml.) and sulphuric acid (6.49 ml.) with palladium black (2.3 gm., freshly prepared) was shaken at 28° under hydrogen (60 lb. per sq. in.) for four hours. After the theoretical uptake in two hours, absorption nearly ceased. The filtrate and acetic acid washings from the catalyst were evaporated to dryness under reduced pressure on the steam bath after the addition of anhydrous sodium carbonate (13.5 gm.). The residue was taken up in dry benzene (320 ml.), which was distilled, initially at atmospheric pressure, and finally to dryness under water pump vacuum. The rapidly solidifying gum was dissolved in dry methanolic hydrogen chloride (160 ml. of 10%), warmed to 55° in a water bath, and allowed to cool in the bath overnight. The crystals that rapidly separated when the solution was poured into ice-water (2.5 liters) were collected after one hour at 0°, well washed with water, and dried *in vacuo*. The crude product was recrystallized from methanol (180 ml.) – water (320 ml.) to give the pyrrole (27.0 gm., 78%) as pale pink plates, m.p. 92°.

(*ii*) A sample prepared in the same way by reducing glyoxylic ester (m.p. 114–115°, prepared by method (*i*)) and recrystallized twice from aqueous methanol formed colorless plates, m.p. 92°, giving a positive Ehrlich's reaction (hot). Found in material dried *in vacuo*: C, 56.32; H, 6.41; N, 4.93%. Calc. for $C_{14}H_{19}O_6N$: C, 56.56; H, 6.44; N, 4.71%.

The melting point of this specimen was not depressed by admixture of material prepared by method (*i*).

(*iii*) *From the Ethyl Ester IIe Via the Tricarboxylic Acid IIIb*

The tricarboxylic acid III*b* (0.116 gm., m.p. 144–145°) was esterified with diazomethane (from 2 gm. of nitrosomethylurea). After one hour the ether was washed with dilute hydrochloric acid, with aqueous sodium bicarbonate, and with water, and dried over sodium sulphate. The gum which remained after evaporation of the ether rapidly crystallized. Recrystallization from methanol (2 ml.) – water (9 ml.) gave the product (64 mgm., 47%), m.p. 91–92°. The melting point was unchanged after recrystallizations from aqueous ethanol and aqueous methanol. Found, in material dried *in vacuo*: N, 4.81%. The identity of this product and the analytical sample of (*ii*) above was confirmed by their mixed melting point and by their infrared spectra in carbon disulphide.

2-Methyl-5-carbethoxypyrrole-3-(glyoxylic acid)-4-(propionic acid), VIa

The triethyl ester II*d* (7 gm.) in ethanol (45 ml.) and 0.889 *N* sodium hydroxide (50 ml., 2.23 equiv.) was heated in an open flask on the steam bath for 35 min. The solvent was removed *in vacuo* and the partially crystalline residue dissolved in water (25 ml.) and made strongly acid with hydrochloric acid at 0°. The crude product was filtered off and washed with ice-water. Two recrystallizations from water (20 ml.) gave 2.17 gm. (37%), m.p. 195–196° (decomp.), eq. wt. 148.0 (calc. 148.6). Large pale pink prisms, m.p. 198–199°, Ehrlich's reaction positive hot, were obtained after two further recrystallizations. Found in material dried *in vacuo*: C, 52.20; H, 5.16; N, 5.03%. Calc. for $C_{13}H_{15}O_7N$: C, 52.52; H, 5.09; N, 4.71%.

As in the case of VI*b*, the crude product contained sodium when precipitated by sulphur dioxide.

Diethyl β-Ketoadipate

(*i*) To diethyl β-keto-α-carbethoxyadipate (809.5 gm.) (14) cooled in an ice–salt bath, sulphuric acid (810 ml.) was added at ⩽20° with stirring. After 12 hr. at 27°, absolute ethanol (1500 ml.) was added with stirring, together with solid carbon dioxide to keep the temperature at ⩽10°. After 20 hr. at room temperature, the solution was poured into ice-water (8 liters) and extracted with benzene (3 × 500 ml.). The extracts were washed twice with dilute sulphuric acid, thrice with dilute sodium bicarbonate, twice with water, and dried over sodium sulphate. Distillation through a Vigreux column gave the diester (330 gm. 54%), b.p. (0.4 mm.) 112–120°, η_D^{25} 1.4390.

(*ii*) Three liters of water and 1406 gm. of ethyl β-keto-α-carbethoxyadipate were gently boiled with vigorous stirring under a 12 in. Vigreux column for four and one-half hours. A hydrometer showed 180 gm. (theory 225 gm.) of ethanol in the 1.8 liters of distillate. The undistilled residues from two such runs were combined. The ester was separated and combined with the ether wash (1 liter) of the water layers, washed with saturated sodium bicarbonate, four times with water, and with 4 × 250 cc. of cold saturated sodium carbonate which was then back-washed with ether. The organic layer was clarified with anhydrous sodium sulphate, washed three times with water, three times with dilute sulphuric acid, and four times with water, clarified with an anhydrous sodium sulphate, filtered, the ether removed on the steam bath, and the residue distilled to 150° at 0.2 mm. The fractionation of the distillate at 0.2 mm. with a 12 in. lagged Vigreux column was followed refractometrically; the product (1367 gm., 65%, η_D^{26} 1.4390) consisted of the main fraction (1280 gm., b.p. 108–119°, nearly all 117–119°) together with that obtained by refractionating the 95–108° cut.

Methyl δ,δ-Dicarbethoxylevulinate

The ester (214 gm., 81%) b.p. 140° (0.4 mm.) was obtained according to the method used for the triethyl ester (14) from 145.5 gm. of β-carbomethoxypropionyl chloride, 162 gm. of malonic ester, and 23.4 gm. of magnesium. For analysis, it was slowly distilled through a 3 in. Vigreux column and collected at 115° (0.25 mm.), as a colorless liquid, η_D^{27} 1.4486, giving a violet-brown color with ferric chloride. Found: C, 52.60; H, 6.51%. Calc. for $C_{12}H_{18}O_7$: C, 52.55; H, 6.61%.

Dimethyl β-Ketoadipate

β-Ketoadipic acid (281.5 gm.) from the above ester and hydrochloric acid (cf. (5)) gave the dimethyl ester (3) (126 gm., 38%) b.p. (0.6 mm.) 100–104°, η_D^{27} 1.4416, when esterified with 250 ml. of methanol containing 93 gm. of hydrogen chloride.

5,5′-Dimethylpyrromethene-3,3′-(diacetic acid)-4,4′-(dipropionic acid) Hydrobromide, VIIa

The tricarboxylic acid I*b* (1 gm., crude m.p. 143°) (10) was heated on the steam bath with 98% formic acid (5 ml.) and 30% hydrogen bromide in acetic acid (2.5 ml.) under reflux for 40 min. After two hours at 10° the product was filtered off and washed with cold formic acid. The brown powder, 0.535 gm. (53%), m.p. 200–201° (decomp.), gave orange-yellow micro needles (0.385 gm.), melting point unchanged, on recrystallizing from formic acid (8 ml.). Found in material dried *in vacuo*: C, 49.22; H, 5.08; N, 5.45; Br, 15.39%. Calc. for $C_{21}H_{25}O_8N_2Br$: C, 49.13; H, 4.91; N, 5.46; Br, 15.57%.

It is stable when kept *in vacuo* over phosphorus pentoxide and protected from light.

5,5′-Dimethylpyrromethene-3,3′-(dipropionic acid)-4,4′-(diacetic acid) Hydrobromide, VIIb

The crude tricarboxylic acid III*b* (1.02 gm., m.p. 145°) was heated under reflux on the steam bath with 98% formic acid (5 ml.) and 30% hydrogen bromide in acetic acid (2.5 ml.) for one hour. The reaction mixture was evaporated to dryness under reduced pressure and acetic acid (15 ml.) added to the rapidly crystallizing brown residue. After one hour at 0°, the methene hydrobromide was collected, washed with cold acetic acid, and dried *in vacuo*. The orange-powder (0.641 gm., 62%), m.p. 217°–218° (decomp.), was recrystallized from formic acid (4 ml.) to give small orange elongated prisms (0.405 gm.), m.p. 218–218.5° (decomp.). The melting point was unchanged by further recrystallization. Found in material dried *in vacuo*: C, 49.38; H, 4.95; N, 5.36; Br, 15.55%. Calc. for $C_{21}H_{25}O_8N_2Br$: C, 49.13; H, 4.91; N, 5.46; Br, 15.57%.

The hydrobromide was stored *in vacuo* over phosphorus pentoxide, and protected from light.

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