[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

THE SYNTHESIS OF FURAN, THIOPHENE, AND PYRROLE-3,4-DICARBOXYLIC ESTERS

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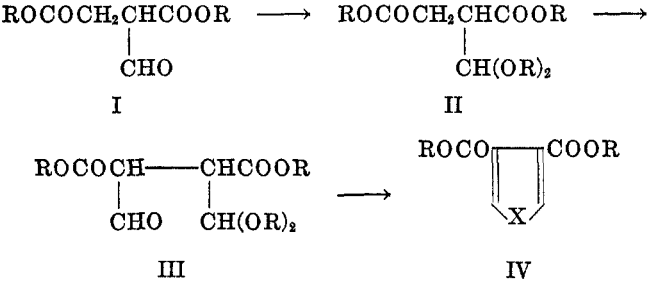
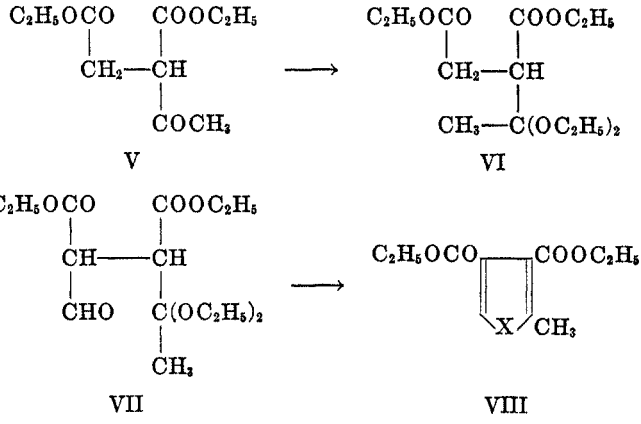
Although the preparation of furans (1), thiophenes (2), and pyrroles (3) by cyclization of 1,4-dicarbonyl compounds is fairly commonplace, the synthesis of such heterocyclic derivatives unsubstituted in the 2 and 5 positions has been limited by the relative inaccessibility of 1,4-dialdehydes. Work underway in these laboratories on the synthesis of heterocycles related to pyridoxine and biotin required as intermediates the 3,4-dicarboxylic esters of furan, thiophene, and pyrrole. The purpose of this communication is to describe a general method of synthesizing these esters by cyclization of appropriate succindialdehyde derivatives, which are also described here for the first time.

The requisite intermediate for these cyclizations was prepared by first converting formyl succinic ester (I) to its acetal (II) and then formylating the acetal to yield 1-formyl-2-dialkoxymethylsuccinic ester (III). These reactions proceeded in good yield when the R group (formulas I–IV) was either methyl or ethyl.

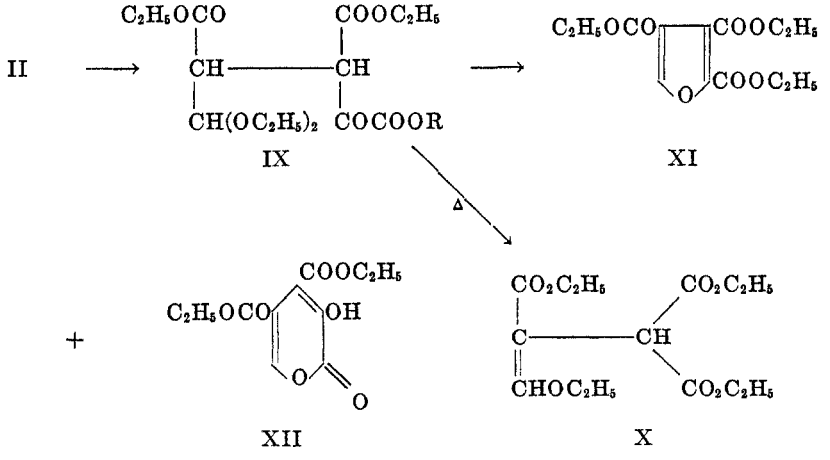


Treatment of the diester (III) with concentrated sulfuric acid caused a smooth cyclization to 3,4-furandicarboxylic ester (IV, X = O) in 66–68% yield. Other acidic condensing agents were also effective, but lower yields resulted. The 3,4-furandicarboxylic ester had been prepared previously by pyrolysis of the partially reduced Diels-Alder adduct of furan and acetylenedicarboxylic ester (4), and the corresponding 3,4-furandicarboxylic acid had been obtained previously by decarboxylation of furan-2,3,4-tricarboxylic acid (5). Reaction of the diester (III) with phosphorus pentasulfide afforded the related 3,4-thiophenedicarboxylic ester (IV, X = S), and finally the generality of the cyclization was confirmed when treatment of the formyl acetal (III) with ammonium acetate and ammonium chloride in acetic acid yielded 3,4-pyrroledicarboxylic ester (IV, X = NH). An improved yield of the pyrrole compound was obtained when the acetal (III) was treated with ammonia followed by concentrated sulfuric acid. When methylamine or aniline were substituted for ammonia, N-methyl-3,4-pyrroledicarboxylic ester (IV, X = NCH_3) and N-phenyl-3,4-pyrroledicarboxylic ester (IV, X = NC_6H_5) respectively were obtained.

The synthetic method was extended to the 2-methyl substituted heterocyclic

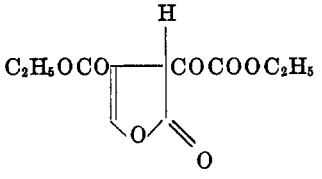


compounds starting from acetylsuccinic ester (V). This was converted to the corresponding ketal (VI) by reaction with ethyl orthoformate, and the ketal in turn was formylated to give the formyl ketal (VII). 2-Methyl-3,4-furandicarboxylic ester (VIII, X = O) and 2-methyl-3,4-pyrroledicarboxylic ester (VIII, X = NH) were obtained from VII by cyclization. A further variation of the method was made in an attempt to develop an independent synthesis for 2,3,4-furantricarboxylic ester. The intermediate compound (IX, R = C_2H_5) needed for this study was obtained in good yield by base-catalyzed condensation of the acetal of formylsuccinic ester (II) with ethyl oxalate. Attempts to distill the resulting diethyl 1-diethoxymethyl-2-ethoxalylsuccinate (IX, R = C_2H_5) under reduced pressure led to decarbonylation and also loss of a molecule of ethanol to yield diethyl 1-carbethoxy-2-ethoxymethylenesuccinate (X).

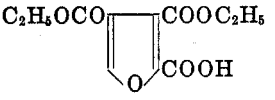


Treatment of IX (R = C_2H_5) with sulfuric acid gave a mixture containing only a small quantity of the desired 2,3,4-furantricarboxylic ester (XI). The principal product was 3-hydroxy-4,5-dicarbethoxy-2-pyrone (XII). When

tert-butyl oxalate was substituted for ethyl oxalate in the above sequence, the resulting *tert*-butoxalylacetal (IX, R = *tert*-C_4H_9) on cyclization again gave a good yield of the α-pyronediester (XII). The structures of the two products, (XI and XII), of these reactions deserve further comment. First of all, the α-pyrone (XII) could be formulated alternatively as the isomeric unsaturated lactone (XIII) or as the furan diester monoacid (XIV). Formation of the same prod-



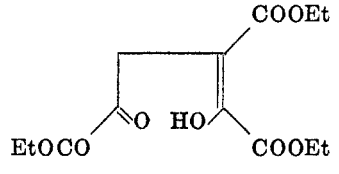
XIII



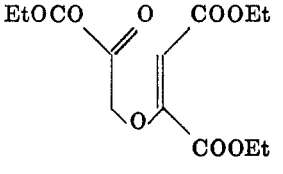
XIV

uct (XII) from *both* the ethoxalyl ester (IX, R = Et), and the *tert*-butoxalyl ester (IX, R = *tert*-C_4H_9) proved that the oxalyl ester grouping was involved in the cyclization, and this fact eliminated structure XIII from further consideration. Structure XIV was excluded when it was found that the product had an acid dissociation constant pK'_a of 6.5 characteristic of a phenol rather than a furoic acid (6). The compound also gave a positive ferric chloride test and was inert to thionyl chloride, thus leaving only the 3-hydroxy-2-pyrone diester (XII) as a reasonable formulation.

Triethyl 2,3,4-furantricarboxylate (XI), the structure of which is reasonably well established by its formation in the reactions described above, was first prepared by Sutter (7) by acid dehydration of the reaction product of bromopyruvic ester and oxaloacetic ester. Sutter incorrectly formulated the furan triester as the 2,3,*5* isomer because he thought the carbon alkylated structure XV to be the correct one for the alkylation product of bromopyruvic ester and



XV



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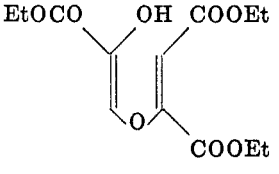

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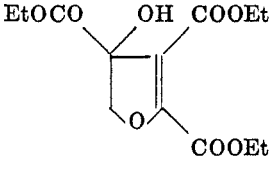
XVI



XVII

the sodium salt of oxaloacetic ester. Reichstein and co-workers (5) later showed by an independent synthesis that Sutter's furan triester was the 2,3,*4* isomer

(XI) and proposed for its precursor the oxygen alkylated structure XVIa. More recently Dunlop and Hurd (8) rejected both XV and XVIa and proposed the hydroxydihydrofuran formulation XVII, for which was suggested a reasonable mechanism of formation. A fourth possibility is the enolic form XVIb of XVIa; however, the compound was found to give no ferric chloride test, thus indicating that this structure was unlikely. Finally, as a means of definitively deciding among the various possibilities, the infrared absorbtion of the alkylation product was studied. The curve showed a strong alcoholic hydroxyl band at 2.83 μ, thus eliminating XVIa which contains no hydroxyl group. Bands at 5.71, 5.86, and 6.06 characteristic respectively of unconjugated ester, conjugated ester, and vinyl ether groupings, make the evidence favoring the Dunlop and Hurd formula (XVII) conclusive.

Triethyl 2,3,4-furantricarboxylate was prepared in quantity and in good yield by a modification of the procedures of Sutter (7) and Reichstein and co-workers (5).

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EXPERIMENTAL[1]

Diethyl α-diethoxymethylsuccinate (II, R = C_2H_5). Diethyl succinate was formylated in the usual fashion (9) using sodium as a condensing agent to yield formylsuccinic ester in about 65% yield. Sodium methoxide was less desirable because of ester interchange during the formylation. Diethyl α-formylsuccinate, 252.5 g., was mixed with 210 g. of ethyl orthoformate, 75 ml. of absolute ethanol, and three drops of concentrated sulfuric acid. The solution was warmed on the steam-bath for 17 hours and was then fractionated *in vacuo*. A colorless liquid was obtained; b.p. 135–145° (7 mm.); yield, 283 g. (82%); n_D^{24} 1.4283; d_{25}^{25} 1.044.

Anal. Calc'd for $C_{13}H_{24}O_6$: C, 56.50; H, 8.75.
Found: C, 56.59; H, 9.07.

The acetal was also obtained by reaction of the aldehyde with a solution of dry hydrogen chloride in ethanol. The yield was 59%.

Diethyl 1-formyl-2-diethoxymethylsuccinate (III, R = C_2H_5). Finely divided sodium (40 g.) was suspended in 1000 ml. of absolute ether contained in a 3 l. three-necked flask fitted with a stirrer, dropping-funnel, and reflux condenser. Absolute ethanol (15 ml.) was added slowly with stirring, after which a mixture of 400 g. of diethyl α-diethoxymethylsuccinate and 214 g. of ethyl formate was added dropwise during 70 minutes. Stirring was continued for 90 minutes, and the mixture then was allowed to stand overnight. Ice and water were added, and the layers were separated. The ether layer was dried and distilled *in vacuo* to yield 55 g. (14%) of starting acetal. The aqueous layer was acidified with dilute sulfuric acid at 0° or lower. The formyl acetal was extracted with 1500 ml. of ether in two portions. The extracts were dried over magnesium sulfate, and the ether was removed by distillation under reduced pressure, finally at 120°. The yield was 332 g. (87%). The crude product was sufficiently pure for cyclization but could be further purified by distillation under reduced pressure; b.p. 124° (0.8 mm.); n_D^{25} 1.4682; d_{25}^{25} 1.117.

Anal. Calc'd for $C_{14}H_{24}O_7$: C, 55.25; H, 7.95.
Found: C, 54.82; H, 7.48.

Dimethyl α-dimethoxymethylsuccinate (II, R = CH_3). Dimethyl succinate was formylated in 50–55% yield using sodium methoxide as catalyst. Dimethyl α-formylsuccinate, 265 g.,

[1] Melting points are uncorrected.

was added to a solution containing 100 g. of dry hydrogen chloride in 1000 ml. of dry methanol. The mixture was allowed to stand at room temperature for about 18 hours after which the solvent was removed completely *in vacuo*. The residual acetal was dissolved in 600 ml. of ether, and the solution was washed first with aqueous sodium bicarbonate and then with about 300 ml. of ice-cold 2 *N* sodium hydroxide solution to remove any unreacted dimethyl α-formylsuccinate. The washed ether solution was dried over magnesium sulfate, the ether was removed under reduced pressure, and the residue was fractionally distilled under reduced pressure; b.p. 125–130° (6 mm.); n_D^{25} 1.4315; yield, 207 g. (62%).

Anal. Calc'd for $C_9H_{16}O_6$: C, 49.08; H, 7.32.

Found: C, 49.08; H, 7.33.

Dimethyl 1-formyl-2-dimethoxymethylsuccinate (III, R = CH_3). To a suspension of 60 g. of sodium methoxide in 1000 ml. of absolute ether, contained in a flask equipped with a stirrer and reflux condenser, was added dropwise during one hour a mixture of 206 g. of dimethyl α-dimethoxymethylsuccinate and 150 g. of methyl formate. Stirring was continued for three hours, after which the reaction mixture was permitted to stand at room temperature for three days. Ice-water (400 ml.) then was added; the mixture was well stirred, and the aqueous layer was separated and acidified with cold dilute sulfuric acid. The product was extracted with two 300-ml. portions of ether, and the extracts were dried over magnesium sulfate. The ether was removed by evaporation *in vacuo*, leaving 113 g. (48%) of dimethyl 1-formyl-2-dimethoxymethylsuccinate sufficiently pure for cyclization. A sample was fractionated under reduced pressure; b.p. 125–130° (0.5 mm.); n_D^{25} 1.4752.

Anal. Calc'd for $C_{10}H_{16}O_7$: C, 48.48; H, 6.50.

Found: C, 48.07; H, 5.60.

Unreacted acetal (74 g.) was recovered from the non-acidic ether fraction above, making the yield of formyl acetal 75% based on acetal consumed in the reaction.

Diethyl 3,4-furandicarboxylate (IV, R = C_2H_5, X = 0). Diethyl 1-formyl-2-diethoxymethylsuccinate, 165 g., was added with stirring over a five-minute period to 330 ml. of concentrated sulfuric acid. The reaction mixture was maintained at 48–52° by periodic cooling. The mixture was kept at 50° for an additional 5 minutes, after which it was cooled rapidly to 0° and then poured onto an excess of crushed ice. The cold solution was extracted with six 250-ml. portions of ether. The extracts were washed with 300 ml. of ice-cold 3 *N* sodium hydroxide solution, dried over magnesium sulfate, and fractionally distilled. The diester had b.p. 125–127° (6 mm.); yield, 78 g. (68%); n_D^{25} 1.860; d_{25}^{25} 1.165.

Anal. Calc'd for $C_{10}H_{12}O_5$: C, 56.60; H, 5.70.

Found: C, 56.16; H, 6.17.

A study of other methods of cyclization to the furan diethyl ester is summarized in Table I. None of these alternatives has any advantage over the sulfuric acid method outlined above.

Dimethyl 3,4-furandicarboxylate (IV, R = CH_3, X = 0). The cyclization of dimethyl 1-formyl-2-dimethoxymethylsuccinate was carried out in sulfuric acid exactly as with the diethyl ester above. The acid solution was poured onto an excess of ice, and in this case the crystalline ester which separated was filtered and washed well with water and then with

TABLE I

CYCLIZATION OF DIETHYL 1-FORMYL-2-DIETHOXYMETHYLSUCCINATE

Condensing Agent	Temp., °C.	Time, min.	Yield, %
$POCl_3$	100	30	30
HF	25	60	40
$ZnCl_2$ in benzene	80	60	43
H_3PO_4	55–85	10	21
BF_3 in benzene	30	120	14

dilute sodium bicarbonate solution, and again with water; yield 66%. After recrystallization from ether-petroleum ether the product had m.p. 49–50°.

Anal. Calc'd for $C_8H_8O_5$: C, 52.18; H, 4.38.
Found: C, 52.15; H, 4.87.

The dimethyl 3,4-furandicarboxylate was also made from diethyl 3,4-furandicarboxylate by first hydrolyzing the diethyl ester with alkali to form 3,4-furandicarboxylic acid, which was then esterified using dry hydrogen chloride in methanol. The over-all yield was 87%.

3,4-Thiophenedicarboxylic acid (IV, R = H, X = S). In a flask provided with a stirrer and reflux condenser was placed 650 ml. of dry toluene, 155 g. of crude, undistilled diethyl 1-formyl-2-diethoxymethylsuccinate, and 110 g. of phosphorus pentasulfide. The mixture was rapidly stirred and heated to the reflux temperature at which it was kept for two hours. After cooling, the toluene solution was decanted from the dark resin. The solution was washed with 500 ml. of water and two 500-ml. portions of ice-cold 2 *N* sodium hydroxide solution. After drying and evaporation of the toluene, the residual dark liquid was distilled at 5–10 mm. pressure until nothing more came over. The distillate was redistilled and the fraction boiling from 100 to 160° (5 mm.) was collected. This weighed 60 g. It could not be purified by fractional distillation; therefore, it was hydrolyzed by heating with a solution of 20 g. of sodium hydroxide in 50 ml. of water and 50 ml. of ethanol. The red solution was evaporated to dryness by heating on the steam-bath under reduced pressure. Warm water, 150 ml., was added to the solid residue, and the resulting solution was acidified with concentrated hydrochloric acid and chilled. A crystalline precipitate separated. This was collected on a filter, washed with two 50-ml. portions of cold ether, and recrystallized from 100 ml. of water to yield 30 g. (35%) of 3,4-thiophenedicarboxylic acid; m.p. 225–226°.

Anal. Calc'd for $C_6H_4O_4S$: C, 41.86; H, 2.34; S, 18.62; Neut. equiv., 86.1.
Found: C, 41.80; H, 2.44; S, 18.82; Neut. equiv., 82.2.

The acid was esterified with methanol and sulfuric acid in the usual way to give the dimethyl ester in 87% yield and a 7.7% recovery of unchanged acid. This ester was a white crystalline solid; m.p. 60–61° (from ether-petroleum ether mixture).

Anal. Calc'd for $C_8H_8O_4S$: C, 47.99; H, 4.03.
Found: C, 48.26; H, 4.03.

The diethyl ester obtained also in 87% yield from the acid and ethanol with sulfuric acid was a liquid; b.p. 156–157° (8 mm.).

Anal. Calc'd for $C_{10}H_{12}O_4S$: C, 52.63; H, 5.26.
Found: C, 52.76; H, 5.45.

Diethyl 3,4-pyrroledicarboxylate (IV, R = C_2H_5, X = NH). Diethyl 1-formyl-2-diethoxymethylsuccinate, 55.5 g., was dissolved in 75 ml. of ether, and a solution of 4 g. of ammonia in 25 ml. of ethanol was added. The solvents were then removed completely *in vacuo*, and the syrupy residue was added gradually and with stirring during three minutes to 110 ml. of concentrated sulfuric acid. The temperature of the reaction mixture during this addition was kept at 45° and then at the same temperature for an additional five minutes. The mixture was then poured onto an excess of ice and the product was filtered and washed with water; yield, 18.9 g. (49%). The diester was purified by recrystallization from aqueous ethanol; m.p. 153–155°.

Anal. Calc'd for $C_{10}H_{13}NO_4$: C, 56.86; H, 6.20; N, 6.63.
Found: C, 56.88; H, 6.27; N, 6.60.

The diethyl 3,4-pyrroledicarboxylate was also obtained, however in only 9% yield, by heating diethyl 1-formyl-2-diethoxymethylsuccinate with a mixture of ammonium acetate, ammonium chloride, and acetic acid.

3,4-Pyrroledicarboxylic acid (IV, R = H, X = NH). The diethyl ester above, 1.5 g., was hydrolyzed in a mixture of 20 ml. of water and 20 ml. of ethanol containing 3 g. of sodium hydroxide by refluxing the solution for 20 hours. The ethanol was distilled, and the aqueous solution was acidified with 7 ml. of concentrated hydrochloric acid. The acid that separated was collected on a filter and washed with water; m.p. 290–292° (dec.); yield, 0.6 g. (55%).

Anal. Calc'd for $C_6H_5NO_4$: C, 46.46; H, 3.25; N, 9.03.
Found: C, 46.73; H, 3.30; N, 9.11.

Diethyl N-methyl-3,4-pyrroledicarboxylate (IV, R = C_2H_5, X = NH). Crude diethyl 1-formyl-2-diethoxymethylsuccinate in dry ether was treated with one equivalent of methylamine in ethanol, and the resulting product was cyclized with sulfuric acid as described above for the preparation of diethyl 3,4-pyrroledicarboxylate. The sulfuric acid-ice mixture was extracted with chloroform. After drying, the chloroform solution was evaporated and the residual liquid was distilled under reduced pressure to give a 45.5% yield of liquid; b.p. 163–167° (0.5 mm.). The ester crystallized after standing, and a sample was recrystallized from an ether-petroleum ether mixture; m.p. 47.5–48°.

Anal. Calc'd for $C_{11}H_{15}NO_4$: N, 6.22. Found: N, 5.93.

A sample of the ester was saponified with aqueous sodium hydroxide. The acid precipitated when the solution was acidified. It was recrystallized from glacial acetic acid and obtained as colorless plates; m.p. 275–276° (dec.).

Anal. Calc'd for $C_7H_7NO_4$: C, 49.70; H, 4.14.
Found: C, 49.89; H, 4.45.

Diethyl 1-phenyl-3,4-pyrroledicarboxylate (IV, R = C_2H_5, X = NC_6H_5). This ester was obtained in 49% yield from the reaction of crude diethyl 1-formyl-2-diethoxymethylsuccinate with aniline followed by cyclization with sulfuric acid. It was extracted from the aqueous acid mixture with ether. The boiling point was 210–215° (1 mm.), 200° (0.5 mm.). It slowly crystallized after standing; m.p. 48° (from petroleum ether).

Anal. Calc'd for $C_{16}H_{17}NO_4$: C, 66.88; H, 5.96.
Found: C, 66.28; H, 6.00.

1-Phenyl-3,4-pyrroledicarboxylic acid, obtained from the ester by hydrolysis, was recrystallized from glacial acetic acid; m.p. 278–280° (dec.).

Anal. Calc'd for $C_{12}H_9NO_4$: N, 6.06. Found: N, 5.84.

Diethyl acetylsuccinate diethyl ketal (VI). To a mixture of 90 g. (0.42 mole) of diethyl acetylsuccinate (10) (freshly distilled), 74 g. (0.5 mole) of ethyl orthoformate, and 23 g. (0.5 mole) of absolute ethanol was added 10 drops of concentrated sulfuric acid. No heat was evolved. After standing in a stoppered flask at room temperature for 64 hours, the solution was heated for one-half hour on the steam-bath to remove the ethyl formate. Triethanolamine, 2 ml., was added, and the liquid was distilled under reduced pressure. The fraction boiling at 110–115° (0.5 mm.) weighed 110 g. (90% yield). A portion was redistilled; b.p. 95° (0.1 mm.); n_D^{25} 1.4405; d_{25}^{25} 1.041.

Anal. Calc'd for $C_{14}H_{26}O_6$: C, 57.91; H, 9.03.
Found: C, 58.16; H, 8.75.

Diethyl 1-formyl-2-α-diethoxyethylsuccinate (VII). A reaction of 82 g. (0.28 mole) of diethyl acetylsuccinate diethyl ketal with 30 g. (0.4 mole) of ethyl formate and 8 g. (0.35 g.-atom) of sodium in 300 ml. of dry ether was carried out and worked up as described above for the preparation of diethyl 1-formyl-2-diethoxymethylsuccinate. The crude product was a dark brown oil. No attempt was made to distill it. The yield was 45 g. (50%), and 38% of the starting ketal ester was recovered unchanged.

Diethyl 2-methyl-3,4-furandicarboxylate (VIII, X = O). Crude diethyl 1-formyl-2-α-diethoxyethylsuccinate, 45 g., was cyclized with sulfuric acid as described above for the preparation of diethyl 3,4-furandicarboxylate. The yield of pale yellow oil was 18 g. (57%); b.p. 133–136° (9 mm.), 127–129° (6 mm.); n_D^{25} 1.4683; d_{25}^{25} 1.139.

Anal. Calc'd for $C_{11}H_{14}O_5$: C, 58.40; H, 6.24.
Found: C, 58.55; H, 6.53.

A sample of the ester was saponified with aqueous-alcoholic potassium hydroxide. The acid that precipitated after acidification was recrystallized from ethyl acetate. It melted at 236–237° corr. [lit. 230–231° (4)].

Diethyl 2-methyl-3,4-pyrroledicarboxylate (VIII, X = NH). A solution of 79 g. (0.25 mole) of crude diethyl 1-formyl-2-α-diethoxyethylsuccinate in 200 ml. of dry ether was treated with 45 g. of 19% absolute alcoholic ammonia (0.5 mole). After the vigorous reaction, the mixture was evaporated under reduced pressure to remove ether and alcohol. The residual product was mixed with 175 ml. of concentrated sulfuric acid keeping the temperature below 55°. After five minutes the sulfuric acid solution was cooled to 20° and poured with

stirring onto 700 g. of ice. The mixture was extracted with two 400-ml. portions of ethyl acetate. This extract was washed with sodium bicarbonate solution, dried, and evaporated. The residual partially crystalline material was taken up in 750 ml. of dry ether, and the solution was filtered and evaporated. The residue was mixed with 100 ml. of petroleum ether (b.p. 60–68°), the mixture was chilled, and the crystalline product was collected and air-dried. It weighed 12 g. (21% yield). A sample recrystallized twice from water was obtained as white, very fine granules; m.p. 124–125°.

Anal. Calc'd for $C_{11}H_{15}NO_4$: C, 58.65; H, 6.71; N, 6.22.
Found: C, 58.37; H, 6.65; N, 6.44.

The petroleum ether filtrate was evaporated, and the remaining dark oil was distilled to yield 19 g. (30%) of diethyl 2-methyl-3,4-furandicarboxylate; b.p. 123–126° (6 mm.); n_D^{25} 1.4677.

Diethyl 1-ethoxalyl-2-diethoxymethylsuccinate (IX, R = C_2H_5). A condensation between 0.5 mole of diethyl formylsuccinate diethyl acetal and 0.5 mole of diethyl oxalate using 0.56 g.-atom of sodium in 250 ml. of dry ether was carried out and worked up as described above for the preparation of diethyl 1-formyl-2-diethoxymethylsuccinate. There was obtained 16 g. (11.5%) of unchanged diethyl formylsuccinate diethyl acetal and 140 g. (75% yield) of crude diethyl 1-ethoxalyl-2-diethoxymethylsuccinate. The latter was heated on the steam-bath under 8 mm. pressure for one hour. Attempts to purify this product by distillation, even under 0.5 mm. pressure resulted in decomposition.

Diethyl 1-carbethoxy-2-ethoxymethylenesuccinate (X). A 100-g. portion of the crude diethyl 1-ethoxalyl-2-diethoxymethylsuccinate was distilled under reduced pressure. Much decomposition with gas evolution took place at first; finally a pale yellow liquid distilled at 186–190° (8 mm.), leaving only a very little dark residue in the flask. The product was redistilled and 84 g. (91% yield) of slightly yellow liquid was obtained; b.p. 162–165° (1 mm.); n_D^{25} 1.4618; d_{25}^{25} 1.112.

Anal. Calc'd for $C_{14}H_{22}O_7$: C, 55.62; H, 7.34.
Found: C, 55.84, 55.81; H, 7.20, 7.44.

The ultraviolet absorption spectrum had an intense band at 237 mμ (ϵ = 14,300) indicating an alkoxy substituted α,β-unsaturated ester grouping, and the infrared curve had a band at 6.12 μ indicating a vinyl ether grouping.

Cyclization of diethyl 1-ethoxalyl-2-diethoxymethylsuccinate. Triethyl 2,3,4-furantricarboxylate (XI), *and 3-hydroxy-4,5-dicarbethoxy-2-pyrone* (XII). Crude diethyl 1-ethoxalyl-2-diethoxymethylsuccinate, 140 g. (0.37 mole), was added with rapid stirring during three minutes to 300 ml. of concentrated sulfuric acid. A little heat was evolved. The temperature was held at about 50° for ten minutes, then was brought to 10° by cooling, and the solution was poured slowly and with stirring onto 1500 g. of chipped ice. The mixture was extracted with two 350-ml. portions of ether, and the combined ether extract was shaken, cautiously at first with 400 ml. of saturated sodium bicarbonate solution. A large quantity of carbon dioxide was evolved. The ether layer was separated, dried, evaporated, and the residual liquid was fractionally distilled under reduced pressure to give 13 g. (12% yield) of triethyl 2,3,4-furantricarboxylate; b.p. 152–153° (0.4 mm.). It was identified by hydrolysis to the acid and then conversion to the *trimethyl ester*; m.p. 108–109° [lit. 107.5–108.5° (5)]. When mixed with a sample of trimethyl 2,3,4-furantricarboxylate prepared by another method (7) (see below), the melting point was unchanged.

The dark brown aqueous sodium bicarbonate solution described above, was added slowly with stirring to the original aqueous sulfuric acid solution. An oil separated. This was extracted with two 200-ml. portions of ether and the extract was dried and evaporated. 3-Hydroxy-4,5-dicarbethoxy-2-pyrone remained as an amber sirup that soon solidified to a hard crystalline cake. The yield was 80 g. (84%). After recrystallization from an absolute ethanol-ethyl acetate-petroleum mixture or better still from aqueous acetic acid it was obtained as white needles; m.p. 93–94°. Potentiometric titration showed a pK'_a of 6.5 in 66% dimethylformamide solution.

Anal. Calc'd for $C_{11}H_{12}O_7$: C, 51.56; H, 4.72.
Found: C, 51.27, 51.40; H, 3.85, 3.92.

3-Hydroxy-4,5-dicarbethoxy-2-pyrone (XII). To a suspension of sodium powder, 6.0 g., in 150 ml. of dry ether was added with stirring during about one-half hour a solution of 49 g. of di-*tert*-butyl oxalate (11) and 67 g. of diethyl α-diethoxymethylsuccinate in 150 ml. of absolute ether. The orange-colored solution was stirred for two hours and then was allowed to stand overnight. A few hundred grams of ice and water were added to the mixture, and the aqueous layer was separated and acidified with cold dilute sulfuric acid. The product was extracted with ether, and the ether solution was dried over magnesium sulfate and the solvent was distilled *in vacuo*. The crude diethyl 1-diethoxymethyl-2-*tert*-butoxalylsuccinate remained as an orange oil; yield, 57 g. (58%). This was added slowly during about three minutes to 120 ml. of concentrated sulfuric acid, keeping the temperature at 45° by periodic cooling. The solution was stirred at 45–47° for 5 minutes, and it then was poured onto ice. The product was extracted with 400 ml. of ether in three portions, and the extracts were washed with water. The acidic fraction was extracted from the ether by washing with an aqueous solution containing 15 g. of sodium bicarbonate. The bicarbonate solution was acidified with dilute sulfuric acid and extracted with 200 ml. of ether. The extract was dried over magnesium sulfate, and the ether was removed *in vacuo*, leaving the crude α-pyrone derivative; yield, 29 g. (81%). After recrystallization from ether-petroleum ether it had m.p. 92–94°. The melting point was not depressed when mixed with the sample prepared as described above using ethyl oxalate. It gave a positive ferric chloride test and did not react with thionyl chloride.

Anal. Calc'd for $C_{11}H_{12}O_7$: C, 51.56; H, 4.72; Neut. equiv., 256.2.
Found: C, 51.26; H, 4.43; Neut. equiv., 249.1.

Triethyl 2,3,4-furantricarboxylate (XI). Ethyl bromopyruvate (12), 510 g. (2.6 moles), was added in a thin stream during one-half hour to a stirred suspension of 560 g. (2.67 moles) of the sodium salt of ethyl oxalacetate in one liter of dry ether. Heat was evolved causing the ether to boil. The mixture was allowed to stand overnight, and then 1500 ml. of water was added. The ether was removed by evaporation under reduced pressure, and a white crystalline precipitate was left in the water. The solid was collected on a filter, washed well with water, then with 200 ml. of ice-cold ether followed by 500 ml. of petroleum ether. The yield of air-dried product, 2,3,4-tricarbethoxy-3-hydroxy-3,4-dihydrofuran (XVII), was 550 g. (70%); m.p. 79°.

Anal. Calc'd for $C_{13}H_{18}O_8$: C, 51.65; H, 6.00.
Found: C, 51.01; H, 5.94.

This crude material, 540 g. (1.79 mole) was added in portions with stirring to one liter of concentrated sulfuric acid cooled in an ice-bath so that the temperature did not go above 50°. After standing for ten minutes at about 50°, the sulfuric acid solution was cooled to 20° and poured slowly with stirring onto 3 kg. of cracked ice. The mixture was extracted with two 700-ml. portions of ether. After it had been washed with sodium bicarbonate solution and dried, the ether solution was evaporated. The residual oil was divided into four equal parts and each was distilled separately under reduced pressure. The combined distillate weighed 403 g. which is an 80% yield of triethyl 2,3,4-furantricarboxylate; b.p. 175–180° (3 mm.); m.p. 45°.

A sample of the triethyl ester was converted *via* the acid to the *trimethyl ester*. This melted at 108–109° (lit. 107.5–108.5°).

SUMMARY

A general method of preparing furan-, thiophene-, and pyrrole-3,4-dicarboxylic esters by cyclization of appropriate 1,4-dicarbonyl derivatives is described.

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