propylene in the presence of catalysts other than those mentioned in Table II. These catalysts were zinc chloride, antimony trichloride, titanium tetrachloride, tin tetrachloride, zirconium tetrachloride, boron trifluoride etherate, 75% sulfuric acid, 85% phosphoric acid and 92% phosphoric acid. Reaction conditions were similar to those reported for successful alkylations of thiophene or benzene, or were similar to methods A and B of the present paper. In each experiment, either the starting product was largely recovered or the reaction mixture was a tar.

It is possible that *only one* of the two observed monoisopropylation products, I and II, is a primary alkylation product and that the observed mixtures are due to partial isomerization of this one isomer under the reaction conditions of isopropylation. Several experiments were carried out to test this possibility. In one, pure I was substituted for the usual mixture of isopropyl chloride and methyl 2-thienyl ketone in a reaction with aluminum chloride otherwise identical with the second experiment of Table I. The recovery of isopropyl-2-thienyl methyl ketone was 65% and no II could be detected in this recovered substance by infrared analysis. In another experiment, a portion of the reaction product from the second experiment of Table I was mixed with 0.02 times an equimolar amount of isopropyl chloride and was allowed to react with twice an equimolar amount of aluminum chloride otherwise exactly as for the previous experiment. The recovery of the starting product was 56% and its composition was 8% I and 92% II. The differences between this composition and that of the starting product (Table I) probably are not significant. In a third experiment, a portion of the reaction product from the second experiment of Table I was mixed with an equimolar amount of methyl 2-thienyl ketone and four times an equimolar amount of aluminum chloride and was allowed to react otherwise exactly as for the previous experiment. The recovery of methyl 2-thienyl ketone was 80%, the recovery of isopropyl-2-thienyl methyl ketone was 67%, and the composition of the latter was 10% I and 91% II. These three experiments seem to indicate that intra- or intermolecular migration of the isopropyl group of a primary monoisopropylation product is not important in determining the composition of an alkylation product.

Acknowledgment.—The authors gratefully acknowledge the helpful assistance of Drs. E. R. Lippincott, M. C. Tobin and E. J. Slowinski in the portion of this work concerned with infrared measurements, a valuable discussion with H. D. Hartough, and a Frederick Gardner Cottrell grant from the Research Corporation.

Storrs, Connecticut

[Contribution from the Lilly Research Laboratories]

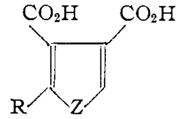
2,3-Furan, Pyrrole and Thiophenedicarboxylic Acids

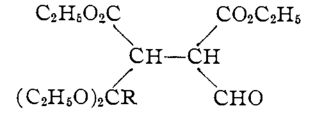
By Reuben G. Jones

Received January 31, 1955

Ethyl 2-formyl-4-ketovalerate, ethyl-2-ethoxalyl-4-ketovalerate and ethyl 2-ethoxalyl-4-ethoxy-3-butenonitrile have been prepared and characterized. From these intermediates the following acids and some of their esters and other derivatives have been prepared: 5-methyl-3-furancarboxylic acid, 5-methyl-2,3-furandicarboxylic acid, 2,3-furandicarboxylic acid, 5-methyl-3-pyrrolecarboxylic acid, 5-methyl-2,3-pyrroledicarboxylic acid, 5-methyl-2,3-thiophenedicarboxylic acid and 2,3-thiophenedicarboxylic acid.

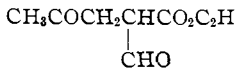
In connection with one of the projects in this Laboratory a number of 2,3- and 3,4-dicarboxylic acids of furan, pyrrole and thiophene were desired. Although several of the dicarboxylic acids of this group are known, the methods of preparation are generally difficult and unsatisfactory. Recently a convenient synthesis of the 3,4-dicarboxylic acids like I was described involving as intermediates the potential 1,4-dicarbonyl esters II.[1]





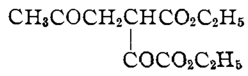
I Z = O, NH, S; R = H, CH$_3$ II

A similar approach now has been investigated for the synthesis of 2,3-dicarboxylic acids of furan, pyrrole and thiophene. This paper reports the preparation of ethyl 2-formyl-4-ketovalerate (III), ethyl 2-ethoxalyl-4-ketovalerate (IV) and ethyl 2-ethoxalyl-4-ethoxy-3-butenonitrile (V) and the cyclizations of these intermediates to form furan, thiophene and pyrrole derivatives.



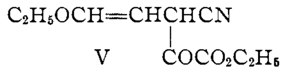
$CH_3COCH_2CH(CHO)CO_2C_2H_5$

III



$CH_3COCH_2CH(COCO_2C_2H_5)CO_2C_2H_5$

IV



$C_2H_5OCH{=}CHCH(COCO_2C_2H_5)CN$

V

When the readily available levulinic acid esters like VI are formylated under Claisen conditions intractable mixtures are obtained. Formylation apparently takes place at each of the three reactive centers. Oxalation of ethyl levulinate also gives a mixture of products, but in this case about a 30% yield of diethyl α,γ-diketopimelate (the product resulting from condensation at the δ-position of VI) can be isolated.[2] In order to direct formylation and oxalation exclusively to the α-position of VI it would be necessary to neutralize the reactive β- and δ-centers. This has been done by converting VI to

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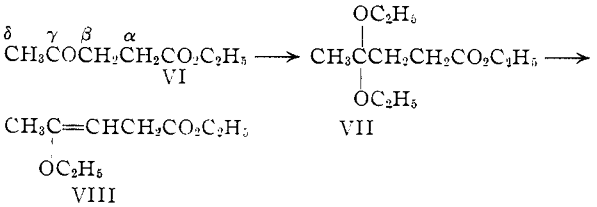
[1] E. C. Kornfeld and R. G. Jones, *J. Org. Chem.*, **19**, 1671 (1954).

[2] W. Wislicenus, *Ber.*, **21**, 2583 (188).

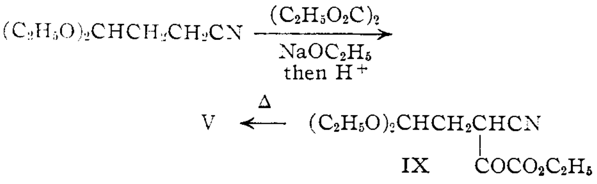
the diethyl ketal (VII). Excellent yields of VII were obtained by the use of ethyl orthoformate and ethanol catalyzed with acid. Unexpectedly, VII easily lost a molecule of ethanol when heated with a trace of acid to give ethyl 4-ethoxy-3-pentenoate (VIII).



$$\overset{\delta}{C}H_3\overset{\gamma}{C}OCH_2\overset{\beta}{C}H_2\overset{\alpha}{C}O_2C_2H_5 \longrightarrow CH_3C(OC_2H_5)_2CH_2CH_2CO_2C_2H_5 \longrightarrow CH_3C(OC_2H_5){=}CHCH_2CO_2C_2H_5$$

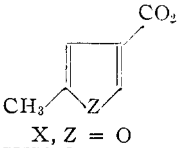
Both VII and VIII underwent condensation with ethyl formate and sodium to give III and with ethyl oxalate and sodium to give IV. Actually, the vinyl ether (VIII), which was more readily prepared in a pure state than VII gave the best yields of III and IV (50–80% crude). During the isolation of III and IV the vinyl ether group was hydrolyzed back to ketone.

Condensation of 4,4-diethoxybutyronitrile[3] with ethyl oxalate and sodium ethoxide formed what appeared to be 2-ethoxalyl 4,4-diethoxybutyronitrile (IX). When this was distilled under reduced pressure, it lost ethanol and gave the vinyl ether (V). Formylation of 4,4-diethoxybutyronitrile was not attempted although there is no reason to believe that 2-formyl-4,4-diethoxybutyronitrile could not readily be prepared.

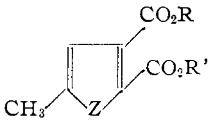


$$(C_2H_5O)_2CHCH_2CH_2CN \xrightarrow[\text{NaOC}_2\text{H}_5 \text{ then H}^+]{(C_2H_5O_2C)_2} (C_2H_5O)_2CHCH_2CH(CN)COCO_2C_2H_5 \xrightarrow{\Delta} V$$

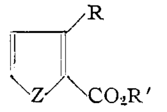
Furans.—Cyclization of crude III by treatment with concentrated sulfuric acid gave a modest yield (38%) of ethyl 5-methyl-3-furancarboxylate (X). Better yields (about 75%) of diethyl 5-methyl 2,3-furandicarboxylate (XI) were obtained by treatment of IV with sulfuric acid. The cyclization of V or IX with sulfuric acid gave moderate to good yields (55–80%) of ethyl 3-carbamyl-2-furancarboxylate (XII). This was hydrolyzed readily to the known acid XIII.[4] No products resembling the hydroxypyrones like XIV were obtained from IV and V or IX, although such might have been expected.[1]



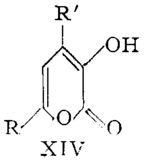
$X, Z = O$
$XIX, Z = NH$



$XI, Z = O, R = R' = C_2H_5$
$XX, Z = NH, R = R' = C_2H_5$
$XXI, Z = NH, R = C_2H_5, R' = H$
$XXIII, Z = NH, R = H, R' = C_2H_5$
$XXIV, Z = NH, R = R' = H$
$XXV, Z = S, R = R' = H$

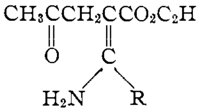


$XII, Z = O, R = CONH_2, R' = C_2H_5$
$XIII, Z = O, R = CO_2H, R' = H$

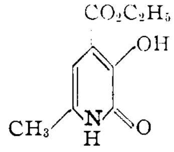


XIV

Pyrroles.—The conversions of III and IV to pyrrole compounds were carried out by a procedure previously described,[1] *i.e.*, by treatment first with ammonia followed by sulfuric acid. Apparently, the eneamines XVII and XVIII are the intermediate products formed by reaction of ammonia with III and IV.



$XVII, R = H$
$XVIII, R = CO_2C_2H_5$



XXII

Ethyl 5-methyl-3-pyrrolecarboxylate (XIX) was obtained in 14% yield from III. When XVIII was treated with sulfuric acid and the mixture poured into absolute ethanol, diethyl 5-methyl-2,3-pyrroledicarboxylate (XX)[5] was isolated in 24% yield. If, however, the mixture was poured into ice-water, only a very small quantity of XX was obtained. From the aqueous solution a crystalline product was slowly deposited. It was a monocarboxylic acid and tentatively was assigned either structure XXI or XXIII. An alternative structure XXII was at first considered but was ruled out when an authentic sample of XXII was prepared according to Feist[6] and found not to have the properties of the new compound. The product, XXI or XXIII, appeared either to exist in two crystalline modifications, or to be a mixture of the two isomers. The crude material melted over the range 160–180°. By recrystallization from absolute ethanol a fraction was obtained melting sharply at 214°; however, this fraction had the same analysis as material melting at 165°. Furthermore, either the high melting or the low melting material upon hydrolysis gave a quantitative yield of practically pure 5-methyl-2,3-pyrroledicarboxylic acid XXIV.

The acid ester (XXI or XXIII) was remarkably stable to heating. It was distilled under reduced pressure and at a temperature above 200° without decomposition. When, however, esterification of either the acid ester or XXIV was attempted by warming in ethanol solution containing sulfuric acid, decarboxylation took place, and the only product obtained (90% yield) was ethyl 5-methyl-3-pyrrolecarboxylate (XIX).

Compound (XXI or XXIII) was also obtained without the use of sulfuric acid, simply by treating IV with ammonia in alcohol.

Thiophenes—5-Methyl-2,3-thiophenedicarboxylic acid (XXV) was prepared in 24% yield from IV by treatment with phosphorus pentasulfide in boiling toluene followed by hydrolysis of the resulting crude diethyl 5-methyl-2,3-thiophenedi-

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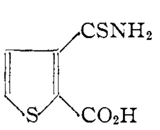
(3) A. Wohl, *Ber.*, **39**, 1952 (1906).

(4) Y. Asahina, J. Murayama, B. Shibata, T. Kariyone, S. Kuwada and M. Asano, *Acta Phytochim.*, **2**, 1 (1924) [*C. A.*, **21**, 2896 (1927)].

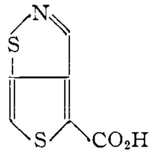
(5) G. H. Cookson, *J. Chem. Soc.*, 2789 (1953); H. Kondo and S. Ono, *J. Pharm. Soc. Japan*, **54**, 683 (1934) [*C. A.*, **31**, 103 (1937)].

(6) F. Feist, *Ber.*, **35**, 1545 (1902); K. Aso, *J. Agr. Chem. Soc. Japan*, **16**, 253 (1940) [*C. A.*, **34**, 6940 (1940)].

carboxylate. The reaction of IX with phosphorus pentasulfide under the same conditions gave only a very small quantity of 2,3-thiophenedicarboxylic acid, isolated in impure form as the dimethyl ester. The main product from this reaction was a monocarboxylic acid containing one nitrogen and two sulfur atoms. At first this product was assumed to be the thioamide XXVI. Analyses, however, indicated a formula $C_6H_3NO_2S_2$, whereas the formula for XXVI is $C_6H_5NO_2S_2$. The compound formed a methyl ester, $C_7H_5NO_2S_2$. Further evidence that this product was not the thioamide was found when attempts were made to hydrolyze it. The acid was recovered unchanged after heating for eight hours at 100° in a mixture of acetic and concentrated hydrochloric acids or after heating for five hours at 120° in 25% aqueous sodium hydroxide solution. On the basis of analysis, method of preparation and properties, the most probable structure for the acid appears to be XXVII.



XXVI



XXVII

The 1,2-benzisothiazoles analogous to XXVII are well known,[7] and they appear not to be hydrolyzed by acid or base. Additional evidence for structure XXVII was provided by the infrared spectrum. There were no NH or OH absorption bands below 3.2 μ which would be expected of structure XXVI. In a mineral oil mull the four most intense infrared absorption bands were at 5.82, 7.73, 8.01 and 13.45 μ. The first was assigned to carbonyl and the last to aromatic CH. Medium intensity bands appeared at 8.80, 9.23, 11.12, 12.28, 12.85 and 14.65 μ.

Acknowledgment.—The author is grateful to Dr. H. E. Boaz for the infrared measurements and interpretations and to W. L. Brown, H. L. Hunter, G. M. Maciak and G. Beckmann for the microanalyses.

Experimental

Ethyl Levulinate Diethyl Ketal (VII).—To a mixture of 144 g. (1.0 mole) of ethyl levulinate, 50 g. (1.1 moles) of absolute ethanol and 165 g. (1.1 moles) of ethyl orthoformate was added ten drops of concentrated sulfuric acid. After a few minutes the mixture became warm. It was allowed to stand overnight. Triethanolamine, 3 ml., was added, and the liquid was heated on the steam-bath to remove ethyl formate and ethanol. The residual liquid was distilled under reduced pressure and, after a very small forerun, 206 g. (94.5% yield) of colorless liquid was obtained, b.p. 98–100° (7 mm.); $n^{25}D$ 1.4219; $d^{25}{}_{25}$ 0.9600.

Anal. Calcd. for $C_{11}H_{22}O_4$: C, 60.50; H, 10.16. Found: C, 60.27; H, 10.21.

When the acid catalyst was not neutralized, or when the distillation was carried out at pressures above 10 mm., partial decomposition took place with the formation of ethyl 4-ethoxy-3-pentenoate (see below).

Ethyl 4-Ethoxy-3-pentenoate (VIII).—A mixture of 144 g. of ethyl levulinate, 50 g. of absolute ethanol, 165 g. of ethyl orthoformate and ten drops of sulfuric acid was allowed to stand for three hours and then heated on the steam-bath for 16 hours. The liquid was distilled under atmospheric pressure until the temperature of the distillate reached 100°. Distillation was continued under reduced pressure through a Vigreux column. A large flask was used because of a tendency of the liquid to foam. After a small forerun, 120 g. of liquid was collected from 79–82° (7 mm.) and 42 g. from 82–100°. The latter fraction was treated with three drops of concentrated sulfuric acid, heated three hours on the steam-bath and again distilled to give 30 g., b.p. 79–83° (7 mm.) making the total yield 150 g. (87%). The product was redistilled and a mid-fraction, b.p. 74° (5 mm.), was taken for analysis; $n^{25}D$ 1.4316; $d^{25}{}_{25}$ 0.9612.

Anal. Calcd. for $C_9H_{16}O_3$: C, 62.76; H, 9.36. Found: C, 62.45; H, 9.36.

Ethyl 2-Formyl-4-Ketovalerate (III).—In a dry 1-l. three-necked flask fitted with a stirrer, dropping funnel and reflux condenser was placed 500 ml. of dry ether, 13 g. (0.56 g. atom) of sodium cut into small pieces, and 5 ml. of absolute ethanol. From the dropping funnel was added with stirring a mixture of 86 g. (0.5 mole) of ethyl 4-ethoxy-3-pentenoate and 45 g. (0.6 mole) of ethyl formate. At first about 20 ml. of the mixture was added. After the reaction had well started, the remainder was dropped in over a period of one hour. The resulting brown solution was allowed to stand overnight, after which it was cooled in an ice-bath and 200 ml. of ice-water was added cautiously from the dropping funnel with stirring. The ether layer was separated, and the aqueous layer was washed with another 100 ml. of ether. The combined ether solution was dried, evaporated, and the residual liquid distilled to give 30 g. (35% yield) of starting ethyl 4-ethoxy-3-pentenoate, b.p. 75–80° (6 mm.).

Immediately after separation from the ether, the aqueous layer was acidified with 50 ml. of concentrated hydrochloric acid. After standing for a few minutes, the mixture was extracted with four 100-ml. portions of ether. The extract was dried with magnesium sulfate and evaporated leaving about 45 g. of brown oil. Distillation of the oil gave 34 g. of liquid, b.p. 100–120° (1 mm.). This was redistilled to yield 30 g. (35%) of colorless liquid, b.p. 83–86° (0.1 mm.); $n^{25}D$ 1.4525; $d^{25}{}_{25}$ 1.156.

Anal. Calcd. for $C_8H_{12}O_4$: C, 55.80; H, 7.03. Found: C, 55.93; H, 6.78.

The above experiment was repeated using 109 g. (0.5 mole) of ethyl levulinate diethyl ketal in place of the ethyl 4-ethoxy-3-pentenoate. Unchanged ketal, 48 g. (44%) was recovered, and the yield of ethyl 2-formyl-4-ketovalerate was 25 g. (29%); b.p. 84–87° (0.2 mm.).

Ethyl 2-Ethoxalyl-4-ketovalerate (IV).—A reaction between 86 g. (0.5 mole) of ethyl 4-ethoxy-3-pentenoate and 75 g. (0.5 mole) of ethyl oxalate using 13 g. (0.56 g. atom) of sodium and 5 ml. of absolute ethanol in 500 ml. of anhydrous ether was carried out and worked up as described above for the preparation of ethyl 2-formyl-4-ketovalerate. The only exception was that 1 l. of water was used instead of 200 ml. to bring the sodium salt into solution. Of the starting ethyl 4-ethoxy-3-pentenoate, 15 g. (13%) was recovered. The yield of ethyl 2-ethoxalyl-4-ketovalerate after two distillations was 50 g. (41%), b.p. 130–135° (0.5 mm.). A mid-fraction was taken for analysis; $n^{25}D$ 1.4540; $d^{26}{}_{25}$ 1.145.

Anal. Calcd. for $C_{11}H_{16}O_6$: C, 54.09; H, 6.60. Found: C, 54.21; H, 6.68.

When the reaction was carried out using ethyl levulinate diethyl ketal in place of ethyl 4-ethoxy-3-pentenoate 19% of the starting ester was recovered and the yield of ethyl 2-ethoxalyl-4-ketovalerate was 30%.

2-Ethoxalyl-4,4-diethoxybutyronitrile (IX) and 2-Ethoxalyl-4-ethoxy-3-butenonitrile (V).—Sodium ethoxide was prepared by adding 25 g. of absolute ethanol in small portions to 12 g. (0.52 g. atom) of sodium shot in 400 ml. of dry ether. After most of the sodium had reacted, 75 g. (0.51 mole) of ethyl oxalate was added dropwise. To the resulting solution was added in one portion 79 g. (0.5 mole) of 4,4-diethoxybutyronitrile,[8] and the flask was stoppered and set aside at room temperature for three days. The brown solution was poured with stirring into 1 l. of ice-water. The water layer was washed with another 200 ml. of ether and, after drying, the combined ether solution was evaporated. Fractionation of the residual liquid gave 27 g. (34%) of unreacted 4,4-diethoxybutyronitrile; b.p. 90–100° (7 mm.).

The brown aqueous solution was acidified with 100 ml.

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(7) L. L. Bambas, "The Chemistry of Heterocyclic Compounds," Vol. 4, Interscience Publishers, Inc., New York, N. Y., 1952, p. 227.

of ice-cold 6 *N* sulfuric acid and immediately extracted with three 200-ml. portions of ether. After the combined ether solution was dried, it was evaporated on the steam-bath, finally under reduced pressure, leaving 70 g. (54% yield) of crude 2-ethoxalyl-4,4-diethoxybutyronitrile (IX) as a brown oil.

A 20-g. portion of the oil was distilled under reduced pressure. At first some decomposition took place, and then a colorless liquid came over at 140–145° (1 mm.). This was redistilled giving 14 g. (70% yield) of 2-ethoxalyl-4-ethoxy-3-butenonitrile (V); b.p. 123–124° (0.5 mm.); n^{25}D 1.4770; d^{25}_{25} 1.131.

Anal. Calcd. for $C_{10}H_{13}NO_4$: C, 56.86; H, 6.20; N, 6.63. Found: C, 56.80; H, 6.44; N, 6.91.

The structure was confirmed by conversion to ethyl 3-carbamyl-2-furancarboxylate (see below).

Ethyl 5-Methyl-3-furancarboxylate (X).—Crude ethyl 2-formyl-4-ketovalerate (III), prepared as described above but not distilled, 40 g., was added with stirring during three minutes to 75 ml. of concentrated sulfuric acid. The temperature of the mixture was allowed to raise to 50° where it was held by brief cooling. After about five to eight minutes at 50°, the mixture was cooled rapidly to 20° and poured with stirring onto 500 g. of chipped ice. The resulting mixture was extracted with three 100-ml. portions of ether. After washing with sodium bicarbonate solution and drying with magnesium sulfate, the ether was evaporated and the residual liquid distilled under reduced pressure to give 13.5 g. (38% yield) of colorless liquid, b.p. 69–71° (6 mm.); n^{25}D 1.4590; d^{25}_{25} 1.066.

Anal. Calcd. for $C_8H_{10}O_3$: C, 62.32; H, 6.54. Found: C, 61.92; H, 6.61.

5-Methyl-3-furancarboxylic Acid.[8]—A 1-g. portion of the above ester was saponified by heating with 1 g. of potassium hydroxide dissolved in 10 ml. of 50-50 alcohol–water. The solution was evaporated to dryness, the residue taken up in water, the solution acidified with hydrochloric acid, and the crystalline precipitate that soon separated was collected on a filter and recrystallized from water. It melted at 114–115° and after sublimation under reduced pressure at 115–116° (lit.[8] 119°).

Anal. Calcd. for $C_6H_6O_3$: C, 57.14; H, 4.80. Found: C, 57.28; H, 5.11.

Diethyl 5-Methyl-2,3-furandicarboxylate (XI).—Crude ethyl 2-ethoxalyl-4-ketovalerate, 57 g., prepared as described above but not distilled, was added with stirring during three minutes to 100 ml. of concentrated sulfuric acid. After ten minutes at 45–50° the mixture was cooled to 20° and poured slowly with stirring onto 700 g. of chipped ice. The mixture was extracted with three 150-ml. portions of ether. After the combined ether extracts had been washed with sodium bicarbonate solution and dried with magnesium sulfate, they were evaporated. The residual liquid was distilled under reduced pressure, and 35 g. (31% yield based on ethyl 4-ethoxy-3-pentenoate) of pale yellow liquid was obtained, b.p. 157–158° (10 mm.); n^{25}D 1.4825; d^{25}_{25} 1.137.

Anal. Calcd. for $C_{11}H_{14}O_5$: C, 58.40; H, 6.24. Found: C, 58.60; H, 5.96.

When distilled ethyl 2-ethoxalyl-4-ketovalerate was used in the above reaction, the yield of diethyl 5-methyl-2,3-furandicarboxylate was 75%.

5-Methyl-2,3-furandicarboxylic Acid.—A sample of the above ester was saponified with sodium hydroxide in aqueous alcohol. The acid separated when the aqueous solution of the sodium salt was acidified. It was recrystallized from water in which it appeared to be appreciably soluble; m.p. 197° (sublimed above 175°).

Anal. Calcd. for $C_7H_6O_5$: C, 49.42; H, 3.56. Found: C, 49.77; H, 3.70.

Ethyl 3-Carbamyl-2-furancarboxylate (XII).—To 150 ml. of concentrated sulfuric acid was added slowly and with stirring 50 g. of crude 2-ethoxalyl-4,4-diethoxybutyronitrile. The temperature was kept at about 50°. After standing for one-half hour, the solution was cooled to 20° and poured onto 750 g. of chipped ice. A finely divided, brown, crystalline precipitate separated. This was collected on a filter and washed with a little water. The filtrate was extracted with three 300-ml. portions of ethyl acetate. The combined ethyl acetate extract was heated to boiling and in it was dissolved the solid that had been collected by filtration. The hot solution was filtered by suction through a pad of anhydrous magnesium sulfate, and then evaporated to dryness under reduced pressure leaving 19 g. (54% yield) of XII. The compound was fairly soluble in ethyl acetate or alcohol, somewhat soluble in ether, and slightly soluble in water. A sample was recrystallized from a large volume of water; m.p. 171–172°.

Anal. Calcd. for $C_8H_9NO_4$: C, 52.46; H, 4.95; N, 7.65. Found: C, 52.44; H, 4.99; N, 7.75.

Ethyl 3-carbamyl-2-furancarboxylate (XII) was obtained in 80% yield when 2-ethoxalyl-4-ethoxy-3-butenonitrile (V) was cyclized with sulfuric acid.

2,3-Furandicarboxylic Acid (XIII).[4]—The ester amide XII was hydrolyzed by heating in 20% aqueous sodium hydroxide on the steam-bath for four hours or by heating with hydrochloric acid on the steam-bath for several hours. It was obtained in 76% yield. A sample was recrystallized from water in which it was appreciably soluble, and obtained as hair-like needles; m.p. 223–224° (lit.[9] 226°).

Anal. Calcd. for $C_6H_4O_5$: C, 46.17; H, 2.58. Found: C, 46.01; H, 2.69.

Ethyl 5-Methyl-3-pyrrolecarboxylate (XIX).—A solution of 25 g. (0.145 mole) of ethyl α-formyllevulinate in 200 ml. of dry ether was treated with 20 g. of 14% absolute ethanolic ammonia (0.165 mole). The solution was evaporated under reduced pressure, and the residue treated with 75 ml. of concentrated sulfuric acid, keeping the temperature below 50° by ice cooling. After five minutes this solution was cooled to 20° and poured onto 500 g. of ice. The mixture was extracted with three 100-ml. portions of ethyl acetate. After washing the combined ethyl acetate extract with sodium bicarbonate solution, it was dried and evaporated. The residual dark oil, 9 g., was distilled under reduced pressure to give 3 g. (14% yield) of crude ethyl 5-methyl-3-pyrrolecarboxylate, b.p. 135–150° (0.5 mm.). This crystallized after standing. It was recrystallized twice from petroleum ether; m.p. 70–71°.

Anal. Calcd. for $C_8H_{11}NO_2$: C, 62.72; H, 7.24; N, 9.14. Found: C, 62.68; H, 7.27; N, 9.14.

3-Carbethoxy-5-methyl-2-pyrrolecarboxylic Acid (XXI).—To a solution of 95 g. (0.39 mole) of crude (undistilled) ethyl 2-ethoxalyl-4-ketovalerate in 200 ml. of dry ether was added slowly 50 g. of 15% ammonia solution in absolute ethanol (0.44 mole of NH_3). A vigorous reaction took place causing the ether to boil. The mixture was immediately evaporated by gently warming on the steam-bath under reduced pressure to remove the ether and alcohol. The dark residual sirup was well-cooled and 250 ml. of cold, concentrated sulfuric acid was added. After thorough mixing, the solution was allowed to stand for ten minutes, the temperature being kept at about 50°. The solution was then cooled to 20° and poured slowly with stirring onto 1500 g. of chipped ice. The resulting solution was extracted with four 300-ml. portions of ethyl acetate. The combined ethyl acetate solution was washed with 200 ml. of saturated aqueous sodium bicarbonate, and these washings were added back to the sulfuric acid solution. After evaporation of the ethyl acetate a brown oil remained. This was distilled and two fractions were obtained. The first, b.p. 110–130° (0.5 mm.), weighed 10 g. and was identified as impure diethyl 5-methyl-2,3-furandicarboxylate (XI). The second fraction, 7 g., b.p. 160–170° (0.5 mm.), partially crystallized on standing. It was diethyl 5-methyl-2,3-pyrroledicarboxylate (see below).

The aqueous acid solution slowly deposited a crystalline precipitate. After 60 hours this was collected on a filter, washed by suspension in three 300-ml. portions of water and air-dried. The yield was 36 g. (47%). A sample, recrystallized from absolute ethanol, melted at 211–212°. It sublimed unchanged at 200° (0.1 mm.); m.p. 212–214°.

Anal. Calcd. for $C_9H_{11}NO_4$: C, 54.82; H, 5.62; N, 7.10. Found: C, 54.84; H, 5.76; N, 7.03.

The crude product melted over the range 160–180°, and recrystallization from aqueous ethanol did not appreciably alter the melting range. When the crude material was heated under 6 mm. pressure it distilled unchanged; b.p.

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(8) H. Gilman, R. R. Burtner and E. W. Smith, This Journal, **55**, 403 (1933).

(9) H. S. Jois and B. L. Manjunath, *Ber*, **69**, 964 (1936).

215–225°; m.p. 165–175°. After recrystallization from ethanol–water this distilled product melted over the range 165–190°.

Anal. Calcd. for $C_9H_{11}NO_4$: C, 54.82; H, 5.62; N, 7.10. Found: C, 54.82; H, 5.68; N, 7.10.

By two recrystallizations of this material from absolute ethanol it was possible to get a small quantity of product melting at 210°.

A sample from another preparation was recrystallized five times from absolute ethanol, and it finally melted sharply at 186–187°.

To a solution of 25 g. (0.1 mole) of crude ethyl 2-ethoxalyl-4-ketovalerate in 50 ml. of dry ether was added 37 g. of 14% absolute ethanolic ammonia (0.3 mole of NH_3). The resulting dark brown solution was allowed to stand in an open flask for four days during which time the solvent partially evaporated, and a crystalline precipitate was deposited. To the mixture was added 150 ml. of water which dissolved all solids. The solution was acidified with 25 ml. of concentrated hydrochloric acid. After several hours a mass of crystalline precipitate separated. The product was collected on a filter, washed well with water and air dried. It weighed 7.2 g. (37% yield). It was soluble in sodium bicarbonate solution, and was precipitated upon acidification. After recrystallization from aqueous ethanol it melted over the range 160–180°, but after recrystallization from absolute ethanol it melted at 210–211° and was shown by comparison of infrared spectra to be identical with the 3-carboethoxy-5-methyl-2-pyrrolecarboxylic acid described above.

5-Methyl-2,3-pyrroledicarboxylic Acid (XXIV).—A solution of 5.0 g. of crude 3-carbethoxy-5-methyl-2-pyrrolecarboxylic acid, melting over the range 160–180°, in 25 ml. of 10% aqueous sodium hydroxide was allowed to stand overnight. The brown solution was filtered and acidified with 10 ml. of concentrated hydrochloric acid. A brown, finely divided crystalline precipitate separated. This was collected, washed with water and air-dried. The yield was 4.0 g. (93%). It melted with decomposition sharply at 225–226°. A sample recrystallized twice from large volumes of water using carbon to remove color was obtained as fine colorless plates; m.p. 225–226° dec.

Anal. Calcd. for $C_7H_7NO_4$: C, 49.71; H, 4.17; N, 8.28. Found: C, 49.57; H, 4.24; N, 8.25.

Esterification of 5-Methyl-2,3-pyrroledicarboxylic Acid.—A solution of 3 g. of crude dicarboxylic acid (XXIV) in 50 ml. of absolute ethanol containing 1.5 ml. of concentrated sulfuric acid was heated under reflux for 14 hours. The solution was evaporated under reduced pressure to small volume, and the residue was taken up in 50 ml. of ethyl acetate. This solution was washed with water followed by aqueous sodium bicarbonate, dried and evaporated leaving 2.5 g. (92% yield) of brown crystalline solid. The product was recrystallized from 50 ml. of petroleum ether (b.p. 60–68°) using decolorizing carbon, and 1.9 g. (70% yield) of colorless prisms was obtained, m.p. 70–71°. The compound was identified as ethyl 5-methyl-3-pyrrolecarboxylate (XIX) (see above) by mixed melting point.

Anal. Calcd. for $C_8H_{11}NO_2$: C, 62.72; H, 7.24; N, 9.14. Found: C, 62.80; H, 7.29; N, 9.33.

A reaction was carried out just as described above except that 3 g. of crude 3-carbethoxy-5-methyl-2-pyrrolecarboxylic acid (XXI) was used in place of the 5-methyl-2,3-pyrroledicarboxylic acid. There was obtained 2.3 g. of crude product that, after recrystallization from petroleum ether, melted at 70–71° and was shown to be ethyl 5-methyl-3-pyrrolecarboxylate.

Diethyl 5-Methyl-2,3-pyrroledicarboxylate (XX).[5]—A solution of 25 g. (0.1 mole) of crude ethyl 2-ethoxalyl-4-ketovalerate in 100 ml. of dry ether was treated with 18 g. of 14% absolute alcoholic ammonia (0.15 mole). After ten minutes the brown solution was evaporated under reduced pressure with gentle warming. The residual sirup was cooled in an ice-bath, and 75 ml. of concentrated sulfuric acid was added. Heat was evolved, but the temperature was kept below 50° by cooling in the ice-bath. After 20 minutes at room temperature, the solution was poured into 150 ml. of ice-cold absolute ethanol. The resulting solution was cooled in an ice-bath and 500 ml. of ethyl acetate was added followed by one liter of ice-water. After thorough shaking the ethyl acetate layer was separated, and the aqueous layer was extracted with two additional 250-ml. portions of ethyl acetate. The combined ethyl acetate solution was washed with water, with sodium bicarbonate solution, dried with magnesium sulfate and evaporated. About 15 ml. of dark brown oil remained. This was fractionally distilled under reduced pressure, and 5.4 g. (24% yield) of diethyl 5-methyl-2,3-pyrroledicarboxylate was obtained as a colorless liquid, b.p. 150–160° (0.5 mm.). It quickly crystallized. A sample recrystallized twice from petroleum ether (b.p. 60–68°) was obtained as colorless needles, m.p. 60.5–61° (lit.[5] 61°).

Anal. Calcd. for $C_{11}H_{15}NO_4$: C, 58.65; H, 6.71; N, 6.22. Found: C, 58.47; H, 6.66; N, 6.14.

Diethyl 1-Phenyl-5-methyl-2,3-pyrroledicarboxylate.—To a solution of 39 g. (0.16 mole) of ethyl 2-ethoxalyl-4-ketovalerate in 50 ml. of dry ether was added 16 g. (0.17 mole) of aniline. Heat was evolved. After 15 minutes the ether was removed by evaporation under reduced pressure on the steam-bath. The residual sirup was added with stirring to 125 ml. of concentrated sulfuric acid. The mixture was kept at about 50° for five minutes, then cooled and poured with stirring onto 750 g. of chipped ice. The mixture was extracted with two 200-ml. portions of ether, and the extract was washed with sodium bicarbonate solution, dried and evaporated. Distillation of the residual liquid under reduced pressure gave 16 g. of product; b.p. 170–210° (1 mm.). This was redistilled and 14 g. (29% yield) of pale yellow oil was obtained, b.p. 170–172° (0.3 mm.). After long standing this crystallized. It was recrystallized from petroleum ether; m.p. 56–57°.

Anal. Calcd. for $C_{17}H_{19}NO_4$: C, 67.76; H, 6.36. Found: C, 67.79; H, 6.17.

1-Phenyl-5-methyl-2,3-pyrroledicarboxylic Acid.—A sample of the above ester was saponified with sodium hydroxide in aqueous ethanol. The precipitate obtained by acidification of the basic solution was collected on a filter and recrystallized from acetic acid–water mixture; m.p. 135–136°.

Anal. Calcd. for $C_{13}H_{11}NO_4$: C, 63.68; H, 4.50; N, 5.72. Found: C, 63.65; H, 4.81; N, 5.84.

5-Methyl-2,3-thiophenedicarboxylic Acid (XXV).—To a solution of 62 g. (0.25 mole) of crude ethyl 2-ethoxalyl-4-ketovalerate in 350 ml. of dry toluene was added 55 g. (0.25 mole) of phosphorus pentasulfide. The mixture was stirred and heated under reflux for four hours. The dark toluene solution was decanted from the black resinous mass in the bottom of the flask. After washing with water and twice with 200-ml. portions of saturated sodium carbonate solution, the toluene solution was dried and evaporated. The dark residual oil was distilled under 6 mm. pressure until nothing more came over. Redistillation of the product gave 27 g. of liquid boiling over the range 100–160° (6 mm.). This was saponified by heating for three hours with a solution of 20 g. of sodium hydroxide in 100 ml. of water and 50 ml. of ethanol. The solution was evaporated under reduced pressure. The residue was taken up in 200 ml. of water, and the solution was acidified with 60 ml. of concentrated hydrochloric acid. An oil separated that soon crystallized. After thorough cooling the solid was collected on a filter. It was dissolved in 300 ml. of hot water. The solution was treated with decolorizing carbon, filtered and 50 ml. of concentrated hydrochloric acid was added. The acid separated as an almost colorless crystalline precipitate which, after cooling, was collected on a filter and air-dried. The yield was 11 g. (24%). It was quite readily soluble in water but much less so in dilute hydrochloric acid. A sample, recrystallized from dilute hydrochloric acid and again from glacial acetic acid, melted at 218°.

Anal. Calcd. for $C_7H_6O_4S$: C, 45.16; H, 3.25; S, 17.20. Found: C, 45.08; H, 3.27; S, 16.88.

The dimethyl ester, obtained with methanol and sulfuric acid, was a liquid, b.p. 124–128° (2 mm.).

Reaction of Phosphorus Pentasulfide with 2-Ethoxalyl-4,4-diethoxybutyronitrile.—A mixture of 40 g. (0.15 mole) of crude 2-ethoxalyl-4,4-diethoxybutyronitrile (IX), 34 g. (0.15 mole) of phosphorus pentasulfide and 250 ml. of toluene was heated under reflux for 1.5 hours. The toluene solution was decanted, washed with two 300-ml. portions of ice-cold 2 *N* sodium hydroxide solution, dried and evaporated. Distillation of the residual sirup gave 15 g. of red-brown liquid boiling at 110 to 160° (1 mm.). This was hydrolyzed by heating with aqueous alcoholic sodium hydroxide. The crystalline solid obtained when the basic solution was acidified was washed well with water and air dried. It weighed 9 g. A sample recrystallized from water melted at 215–216° dec. (compound XXVII).

Anal. Calcd. for $C_6H_3NO_2S_2$: C, 38.93; H, 1.63; N, 7.57. Found: C, 38.63, 38.85; H, 1.59, 1.97; N, 7.53.

The crude acid, 8.5 g., was esterified with methanol and sulfuric acid and worked up in the usual way to give 8 g. of crystalline ester contaminated with an oily impurity. The product was recrystallized from petroleum ether to give 4.5 g. of stout needles. Evaporation of the petroleum ether filtrate left an oil containing a little crystalline material. It was triturated with 4 ml. of cold methanol and filtered giving an additional 0.5 g. of crystalline ester making the total yield 5.0 g. After one more recrystallization from petroleum ether, this methyl ester of XXVII melted at 95.5–96°.

Anal. Calcd. for $C_7H_5NO_2S_2$: C, 42.22; H, 2.53; S, 32.14. Found: C, 42.15; H, 2.75; S, 31.83.

A sample of the ester, 0.5 g., was heated in a mixture of 5 ml. of concentrated hydrochloric acid and 5 ml. of acetic acid on the steam-bath for eight hours. After cooling the solution, the crystalline product was collected and air-dried; yield 0.4 g. (86%). It was identified as the acid XXVII by melting point, mixed melting point and infrared spectrum. The acid XXVII, 0.4 g., in 3 ml. of 25% sodium hydroxide solution was heated at 120° for five hours. The solution was diluted to 10 ml. with water, acidified while hot with hydrochloric acid and, after cooling, the precipitated acid was collected and air-dried. It weighed 0.35 g. and was identified as unchanged XXVII by melting point and infrared spectrum.

4,7-Dihydroxy-5,6-diaza-1-thiaindene.—The 4 ml. of methanol filtrate from the purification of the methyl ester of XXVII mentioned above was evaporated leaving about 1.5 g. of oil. This crystallized when cooled in ice. The product melted at about 30–32° and was believed to be dimethyl 2,3-thiaphenedicarboxylate (lit.[10] m.p. 32–33°). A 0.7-g. portion of this ester in 2 ml. of methanol was treated with 0.5 ml. of hydrazine hydrate. Heat was evolved, and after several minutes a crystalline precipitate separated. This completely dissolved when 10 ml. of water was added, and acidification of the solution caused precipitation of 0.5 g. of another crystalline solid. A sample was sublimed at 250° (0.1 mm.) for analysis.

Anal. Calcd. for $C_6H_4N_2O_2S$: C, 42.86; H, 2.40; N, 16.67. Found: C, 42.78; H, 2.56; N, 16.79.

This compound did not melt below 300°. It was soluble in base, insoluble in acid, and together with its analysis it has all the properties expected of 4,7-dihydroxy-5,6-diaza-1-thiaindene which would be formed by reaction of hydrazine with dimethyl 2,3-thiophenedicarboxylate. Other related diazathiaindenes have been studied in this Laboratory and will be discussed in a subsequent communication.

INDIANAPOLIS, INDIANA

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(10) J. Sice, *J. Org. Chem.*, **19**, 70 (1954).

[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

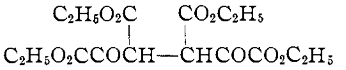
Preparation and Cyclization of Diethyl α,α-Diethoxy-α′-ethoxalylglutarate and Diethyl α,α-Diethoxy-α′-formylglutarate

BY REUBEN G. JONES

RECEIVED MARCH 19, 1955

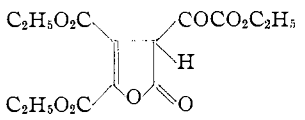
Diethyl α,α-diethoxyglutarate has been prepared and allowed to condense, under Claisen conditions, with ethyl oxalate to give diethyl α,α-diethoxy-α′-ethoxalylglutarate and with ethyl formate to give diethyl α,α-diethoxy-α′-formylglutarate. Treatment of diethyl α,α-diethoxy-α′-ethoxalylglutarate with concentrated sulfuric acid gave a 70% yield of 4,6-dicarbethoxy-3-hydroxy-2-pyrone and only a 7% yield of triethyl 2,3,5-furantricarboxylate. Treatment of diethyl α,α-diethoxy-α′-formylglutarate with concentrated sulfuric acid gave exclusively diethyl 2,4-furandicarboxylate. 2,4-Thiophenedicarboxylic acid and 2,4-pyrroledicarboxylic acid were prepared from diethyl α,α-diethoxy-α′-formylglutarate.

Certain α-keto-δ-carbonyl (or potential carbonyl) esters may undergo cyclization to form either furan or pyrone derivatives. Thus diethyl α,α′-diethoxalylsuccinate (I) appears to lose a molecule of ethanol under a variety of conditions to form an unsaturated lactone. At first this lactone was thought to be the five-membered ring compound II,[1] but more probably it is the 3-hydroxy-2-pyrone (III).[2] Diethyl α-diethoxymethyl-α′-ethoxalylsuccinate (IV) when treated with sulfuric acid gave the pyrone (V), as the main product together with a small yield of the furantricarboxylic ester VI.[3] On the other hand, ethyl α-ethoxalyllevulinate (VII) and diethyl α,α′-diketoadipate (VIII), which are structurally closely related to I and IV, when treated with sulfuric acid gave exclusively the furandicarboxylic esters IX[4] and X[5], respectively.



$$C_2H_5O_2CCO\overset{C_2H_5O_2C}{\overset{|}{C}}H-\overset{CO_2C_2H_5}{\overset{|}{C}}HCOCO_2C_2H_5$$

I



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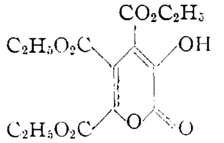

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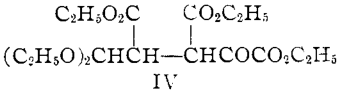
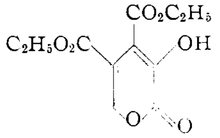
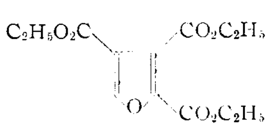


$$(C_2H_5O)_2CH\overset{C_2H_5O_2C}{\overset{|}{C}}H-\overset{CO_2C_2H_5}{\overset{|}{C}}HCOCO_2C_2H_5$$

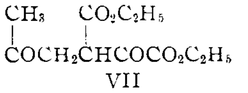
IV



V



VI

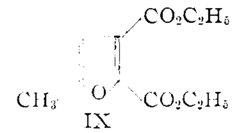


$$\overset{CH_3}{\overset{|}{C}}OCH_2\overset{CO_2C_2H_5}{\overset{|}{C}}HCOCO_2C_2H_5$$

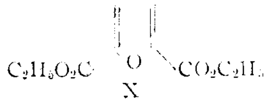
VII

$C_2H_5O_2CCOCH_2CH_2COCO_2C_2H$

VIII



IX



X

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(2) E. E. Blaise and H. Gault, *Compt. rend.*, **148**, 178 (1909).

(3) E. C. Kornfeld and R. G. Jones, *J. Org. Chem.*, **19**, 1671 (1954).

(4) R. G. Jones, THIS JOURNAL, **77**, 4069 (1955).

(5) R. Kuhn and K. Dury, U. S. Patent 2,673,860 (March 30, 1954).