drolyzed 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.

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

INDIANAPOLIS, INDIANA

[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

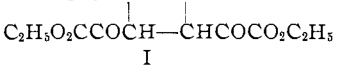
Preparation and Cyclization of Diethyl α,α-Diethoxy-α′-ethoxalylglutarate and Diethyl α,α-Diethoxy-α′-formylglutarate

BY REUBEN G. JONES

RECEIVED MARCH 19, 1955

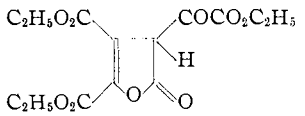
Diethyl α,α-diethoxyglutarate has been prepared and allowed to condense, under Claisen conditions, with ethyl oxalate to give diethyl α,α-diethoxy-α′-ethoxalylglutarate and with ethyl formate to give diethyl α,α-diethoxy-α′-formylglutarate. Treatment of diethyl α,α-diethoxy-α′-ethoxalylglutarate with 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.

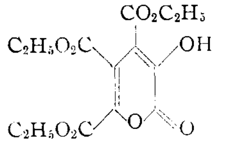


$$\begin{array}{c} C_2H_5O_2C \quad CO_2C_2H_5 \\ | \qquad\quad | \\ C_2H_5O_2CCOCH{-}CHCOCO_2C_2H_5 \end{array}$$

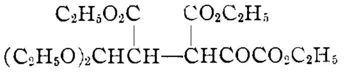
I



II

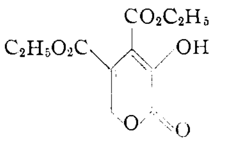


III

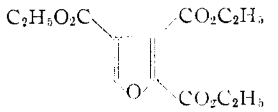


$$\begin{array}{c} C_2H_5O_2C \quad CO_2C_2H_5 \\ | \qquad\quad | \\ (C_2H_5O)_2CHCH{-}CHCOCO_2C_2H_5 \end{array}$$

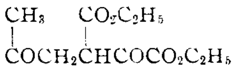
IV



V



VI

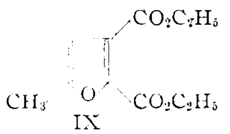


$$\begin{array}{l} CH_3 \quad\;\; CO_2C_2H_5 \\ | \qquad\quad\;\; | \\ COCH_2CHCOCO_2C_2H_5 \end{array}$$

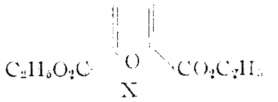
VII

$C_2H_5O_2CCOCH_2CH_2COCO_2C_2H$

VIII



IX



X

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[1] W. Wislicenus and A. Boeckler, *Ann.*, **285**, 11 (1895).

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

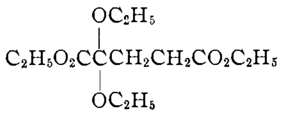
[3] E. C. Kornfeld and R. G. Jones, *J. Org. Chem.*, **19**, 1671 (1954).

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

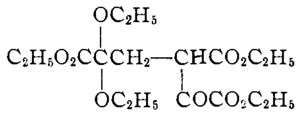
[5] R. Kuhn and K. Dury, U. S. Patent 2,673,860 (March 30, 1954).

In the interest of synthesizing some compounds for biological testing, another α-keto-δ-(potential) carbonyl ester, diethyl α,α-diethoxy-α′-ethoxyalylglutarate (XI), isomeric with IV, has been prepared, and its cyclization with sulfuric acid examined. Compound XI was obtained in good yield by reaction of the diethyl ketal XII of diethyl α-ketoglutarate with ethyl oxalate and sodium. When XI was treated with concentrated sulfuric acid followed by pouring the mixture onto ice, two products were isolated. The one obtained in largest yield (71%) was a crystalline solid, $C_{11}H_{12}O_7$, soluble in dilute base and reprecipitated with acid. It is formulated as 4,6-dicarbethoxy-3-hydroxy-2-pyrone (XIII). The second product, isolated in 7% yield, was triethyl 2,3,5-furantricarboxylate (XIV), a liquid, that was hydrolyzed to give the known 2,3,5-furantricarboxylic acid.[6]

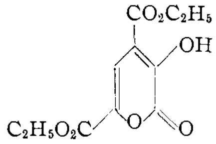
The condensation of XII with ethyl formate in place of ethyl oxalate gave diethyl α,α-diethoxy-α′-formylglutarate (XV). When XV was treated with sulfuric acid, no pyrone corresponding to XVI was obtained. The only product was diethyl 2,4-furandicarboxylate (XVII). Incidentally, 2,4-thiophenedicarboxylic acid (XVIII) and 2,4-pyrroledicarboxylic acid (XIX) were prepared from XV in 45 and 32% yields by methods previously described.[4]


$C_2H_5O_2C\overset{OC_2H_5}{\underset{OC_2H_5}{C}}CH_2CH_2CO_2C_2H_5$

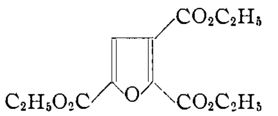
XII


$C_2H_5O_2C\overset{OC_2H_5}{\underset{OC_2H_5}{C}}CH_2{-}\underset{COCO_2C_2H_5}{C}HCO_2C_2H_5$

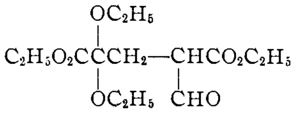
XI



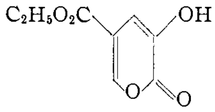
XIII



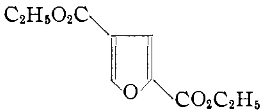
XIV


$C_2H_5O_2C\overset{OC_2H_5}{\underset{OC_2H_5}{C}}CH_2{-}\underset{CHO}{C}HCO_2C_2H_5$

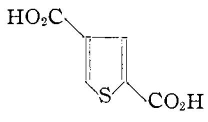
XV



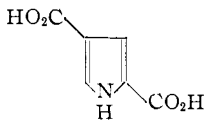
XVI



XVII



XVIII



XIX

The tendency of the esters I, IV and XI to cyclize to 3-hydroxy-2-pyrone compounds III, V and XIII appears to be associated with the presence of at least three carboxyl groups. The esters like XV having only two carboxyl groups, when cyclized with sulfuric acid, have yielded exclusively furan compounds and none of the theoretically possible 3-hydroxy-2-pyrones.

Acknowledgment.—The author is grateful to W. L. Brown, H. L. Hunter, G. M. Maciak and G. Beckmann for the microanalyses.

Experimental

Diethyl α,α-Diethoxyglutarate.—A mixture of 370 g. (1.83 moles) of diethyl α-ketoglutarate,[7] 295 g. (2 moles) of ethyl orthoformate and 70 g. (1.5 moles) of absolute ethanol was treated with 5 ml. of concentrated sulfuric acid. After standing overnight at room temperature, the mixture was heated on the steam-bath for four hours during which time ethyl formate and ethanol were allowed to evaporate. The liquid was cooled, washed with 200 ml. of cold saturated sodium carbonate solution, dried with magnesium sulfate and distilled under reduced pressure. The yield of ketal was 445 g. (88%), b.p. 140–145° (7 mm.), 133–135° (5 mm.); n^{25}_{D} 1.4310; d^{25}_{25} 1.055.

Anal. Calcd. for $C_{13}H_{24}O_6$: C, 56.50; H, 8.76. Found: C, 56.35; H, 8.50.

Diethyl α,α-Diethoxy-α′-ethoxalylglutarate.—In a 3-l. three-necked flask provided with a stirrer, dropping funnel and reflux condenser was placed 1 l. of dry ether and 23 g. of sodium shot. Ten ml. of absolute ethanol was added, and then from the dropping funnel was added with stirring during three or four hours a mixture of 276 g. (1 mole) of diethyl α,α-diethoxyglutarate and 160 g. (1.1 moles) of ethyl oxalate. The mixture was allowed to stand at room temperature for two days. Ice-water, 1500 ml., was added, and the ether layer was separated. The aqueous layer was washed with another 200 ml. of ether and the combined ether solution was dried and evaporated. Distillation of the residue gave 60 g. (22%) of unreacted diethyl α,α-diethoxyglutarate.

The brown aqueous solution was acidified quickly with cold dilute sulfuric acid. The brown oil that separated was collected by extraction with ether. After drying, the ether solution was evaporated on the steam-bath, finally under reduced pressure, leaving 265 g. (70% yield) of crude diethyl α,α-diethoxy-α′-ethoxalylglutarate. No attempt was made to purify the product.

Cyclization of Diethyl α,α-Diethoxy-α′-ethoxalylglutarate with Sulfuric Acid.—The crude ester, 205 g. (0.55 mole), was added during ten minutes with stirring to 400 ml. of concentrated sulfuric acid in a beaker cooled in an ice-bath. The temperature was kept below 50°. After ten minutes the solution was poured slowly with stirring onto 1500 g. of chipped ice. A rose-colored crystalline precipitate separated. This was collected on a large funnel and washed successively with 500 ml. of water, four 200-ml. portions of ether, and finally with 600 ml. of hot water. The yield after drying in the air was 95 g. The aqueous acid solution was extracted with two 300-ml. portions of ether. This was combined with that used to wash the solid and the whole was extracted with 500 ml. of 10% sodium carbonate solution. The sodium carbonate extract was acidified, and a dark oil separated. This partially crystallized. The solid was collected, washed with a little ether and air-dried giving another 5 g. of pink solid and making the total yield 100 g. (71%) of 3-hydroxy-4,6-dicarbethoxy-2-pyrone. The compound was purified by recrystallization from ethyl acetate–petroleum ether mixture or from aqueous acetic acid and finally from a large volume of water. It was obtained as white needles; m.p. 124.5–125°; soluble in sodium bicarbonate solution.

Anal. Calcd. for $C_{11}H_{12}O_7$: C, 51.56; H, 4.69. Found: C, 51.65; H, 4.59.

The above ether solution was dried and evaporated, and the residual oil was fractionally distilled under reduced pressure giving 11 g. (7% yield) of triethyl 2,3,5-furantricarboxylate as a colorless liquid, b.p. 180–183° (6 mm.), n^{25}_{D} 1.4865, d^{25}_{25} 1.190.

Anal. Calcd. for $C_{13}H_{16}O_7$: C, 54.93; H, 5.67. Found: C, 54.38; H, 5.42.

A 3-g. sample of the triethyl ester was hydrolyzed by heating 48 hours with 50 ml. of 6 *N* hydrochloric acid. The resulting light brown solution was decolorized with carbon and evaporated to dryness leaving 2 g. (95% yield) of 2,3,5-furantricarboxylic acid. It was readily soluble in water. A sample was purified by recrystallization from ethyl

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[6] T. Reichstein and A. Grussner, *Helv. Chim. Acta*, **16**, 555 (1933).

[7] W. Wislicenus and M. Waldmüller, *Ber.*, **44**, 1571 (1911).

acetate–petroleum ether mixture and obtained as a white powder, m.p. 258–259°.

Anal. Calcd. for $C_7H_4O_7$: C, 42.01; H, 2.01. Found: C, 42.38; H, 2.31.

The trimethyl ester, obtained in 80% yield by esterification of the acid with methanol and sulfuric acid, was recrystallized from ether–petroleum ether mixture; m.p. 79.5–80° (lit.[6] 76°).

Anal. Calcd. for $C_{10}H_{10}O_7$: C, 49.59; H, 4.16. Found: C, 49.56; H, 4.22.

Diethyl α,α-Diethoxy-α'-formylglutarate.—This was obtained in 60% yield as a crude light brown oil from the reaction of 1 mole of diethyl α,α-diethoxyglutarate and 1.3 moles of ethyl formate with 1 g. atom of sodium shot in dry ether. The reaction was carried out and worked up as described above for the preparation of diethyl α,α-diethoxy-α'-ethoxalylglutarate. Unreacted diethyl α,α-diethoxy-glutarate, 30%, was recovered.

Diethyl 2,4-Furandicarboxylate.—To 50 ml. of concentrated sulfuric acid was added with stirring and cooling 18 g. (0.06 mole) of crude diethyl α,α-diethoxy-α'-formylglutarate. The temperature was kept at 45–50°. After five minutes, the solution was cooled to 20° and poured slowly and with stirring onto 500 g. of ice. The resulting mixture was extracted with two 300-ml. portions of ether. The ether solution was washed with aqueous sodium bicarbonate, dried and evaporated leaving a pale yellow oil that crystallized. The yield was 6.9 g. (55%). A sample recrystallized from petroleum ether was obtained as a white powder, m.p. 43–44°.

Anal. Calcd. for $C_{10}H_{12}O_5$: C, 56.60; H, 5.70. Found: C, 56.70; H, 5.89.

A sample of the ester was saponified by heating with sodium hydroxide solution. Acidification of the solution caused precipitation of 2,4-furandicarboxylic acid, m.p. 274–275° (lit.[8] 266°).

2,4-Thiophenedicarboxylic Acid.—A mixture of 18 g. of crude diethyl α,α-diethoxy-α'-formylglutarate, 13 g. of phosphorus pentasulfide and 80 ml. of toluene was stirred and heated under reflux for 1.5 hours. The toluene solution was washed with two 50-ml. portions of cold 1 *N* sodium hydroxide solution, dried and evaporated. The residue was distilled under reduced pressure to give 11 g. of liquid, b.p. 120–160° (0.5 mm.). This was heated on the steam-bath for two hours with a solution of 5 g. of sodium hydroxide in 10 ml. of water and 25 ml. of ethanol. The solution was evaporated to dryness under reduced pressure. Water, 50 ml., was added, and the resulting solution was acidified with hydrochloric acid causing the precipitation of 4.5 g. (45% yield) of the dicarboxylic acid as a light yellow powder. It was readily recrystallized from water. On the hot stage it remained unmelted up to 300° (lit.[9] m.p. 280° dec.). Above 200° it began to sublime and above 250° it appeared to slowly undergo decarboxylation without melting.

Anal. Calcd. for $C_6H_4O_4S$: C, 41.86; H, 2.34. Found: C, 41.54; H, 2.59.

The dimethyl ester was prepared in excellent yield by esterification with methanol and sulfuric acid. It was recrystallized from petroleum ether; m.p. 123° (lit.[9] 120–121°).

Anal. Calcd. for $C_8H_8O_4S$: S, 16.00. Found: S, 15.92.

2,4-Pyrroledicarboxylic Acid.—A solution of 18 g. (0.06 mole) of crude diethyl α,α-diethoxy-α'-formylglutarate in 100 ml. of dry ether was treated with 12 g. of cold 14% absolute ethanolic ammonia. After the exothermic reaction had subsided, the solution was allowed to stand for about ten minutes and then the solvents were removed by gently warming under reduced pressure. The residual sirup was cooled in an ice-bath, and 50 ml. of concentrated sulfuric acid was added. After about ten minutes at 50° this solution was cooled to 10° and poured slowly into 75 ml. of ice-cold, absolute ethanol. To the resulting solution was added 200 ml. of ethyl acetate followed by 500 ml. of ice-water. The ethyl acetate layer was separated, and the aqueous layer extracted with three additional 100-ml. portions of ethyl acetate. The combined extract was washed with sodium bicarbonate solution, dried and evaporated leaving about 8 g. of brown oil. Since this did not crystallize, it was saponified with aqueous sodium hydroxide. Acidification of the solution (50 ml.) caused precipitation of a brown crystalline solid, which, after two days, was collected and air-dried. The yield was 3.0 g. (42%). A sample recrystallized from water was obtained as a tan powder. It melted and decomposed in a capillary at about 295°, but on a hot stage it remained unmelted up to 300°.

Anal. Calcd. for $C_6H_5NO_4$: C, 46.46; H, 3.25; N, 9.06. Found: C, 46.65; H, 3.58; N, 8.66.

INDIANAPOLIS 6, INDIANA

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(8) F. Feist, *Ber.*, **34**, 1994 (1901).

(9) N. Zelinsky, *ibid.*, **20**, 2017 (1887).

[CONTRIBUTION FROM THE COLLEGE OF PHARMACY OF THE UNIVERSITY OF CALIFORNIA]

The Identity of Some 5-Substituted 1,2,4-Triazolones[1]

BY HENRY G. MAUTNER[2] AND W. D. KUMLER

RECEIVED FEBRUARY 11, 1955

The identity of "N$^\beta$-cyano acid hydrazides" was investigated by means of infrared and ultraviolet spectroscopy, and by the measurement of dissociation constants. These compounds were found to be 5-substituted 1,2,4-Δ^4-triazolones. An acidic isomer of these substances was identified as a 5-substituted 1,2,4-Δ^5-triazolone.

Some time ago it was discovered by Bougault[3,4] that the treatment of the semicarbazones of α-keto acids with iodine and sodium hydroxide resulted in the formation of crystalline products, which will hereafter be referred to as I. These substances sublime easily, form addition products with acid and react with ammoniacal silver nitrate to form mono-silver salts. Acetylation and benzoylation yielded mono-substituted products, which retain the ability to form mono-silver salts. Bougault and Popovici[5] identified I as 5-substituted 1,2,4-triazolones (A).

Girard[6,7] found that treatment of I with boiling alkali resulted in the formation of crystalline weak acids, isomeric with I, which will be referred to as II. These compounds, which have very high melting points and sublime easily, form di-silver salts, and react with acetic anhydride to form monoacetyl derivatives. Girard showed that this group of substances was identical with the hydroxytriazoles obtained by Young and Witham[8] by oxidizing aldehyde semicarbazones with ferric

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(1) The material reported here represents part of a thesis presented by Henry G. Mautner in partial fulfillment of the requirements for the Ph.D. degree in pharmaceutical chemistry.

(2) Fellow of the American Foundation for Pharmaceutical Education 1954–1955.

(3) J. Bougault, *Bull. soc. chim.*, **21**, 183 (1917); **25**, 385 (1919).

(4) J. Bougault, *Compt. rend.*, **163**, 237 (1916).

(5) J. Bougault and L. Popovici, *ibid.*, **189**, 188 (1929).

(6) M. Girard, *Ann. chim. phys.*, [11], **16**, 326 (1941).

(7) M. Girard, *Compt. rend.*, **212**, 547 (1941).

(8) G. Young and E. Witham, *J. Chem. Soc.*, **77**, 228 (1900).