α,β-Di-(*p*-methoxyphenyl)-valeric Acid (V).—A mixture of 12.1 g. of the solid nitrile, 4 g. of sodium hydroxide, 8 ml. of water and 75 ml. of ethylene glycol was refluxed for thirty-six hours.[15,16] An equal volume of water was added and the solution filtered while hot. Acidification of the cooled solution with dilute hydrochloric acid yielded a mixture of isomeric acids. Recrystallization from 95% ethyl alcohol gave 4.65 g. of white product (A), m. p. 177.5–179°.

Anal. Calcd. for $C_{19}H_{22}O_4$: C, 72.58; H, 7.05. Found: C, 72.53; H, 6.90.

Hydrolysis of the liquid nitrile likewise yielded an acid which showed no melting point depression on admixture with A above.

The crude residue (6.0 g.) after removal of alcohol was dissolved in ether and esterified with diazomethane. After standing for two hours, the ether was removed and the residue, which solidified immediately, was recrystallized three times from 95% ethanol. There was obtained 4.92 g. of crystalline methyl ester of the isomeric α,β-di-(*p*-methoxyphenyl)-valeric acid, m. p. 93–94.5°.

Anal. Calcd. for $C_{20}H_{24}O_4$: C, 73.14; H, 7.37. Found: C, 73.12; H, 7.33.

Seven hundred milligrams of the above ester was allowed to stand at room temperature for four hours and then heated on the steam-bath for one hour with 15 ml. of 15% methanolic potassium hydroxide. Water was added and the alcohol removed in a current of air on the steam-bath. Acidification of the cooled solution with hydrochloric acid gave 610 mg. of crude product. Recrystallization from benzene–petroleum ether gave 400 mg. of the isomeric acid (B), m. p. 163–164.5°.

Anal. Calcd. for $C_{19}H_{22}O_4$: C, 72.58; H, 7.05. Found: C, 72.28; H, 7.20.

Two grams of the higher melting isomer (A, m. p. 177.5–179°), on treatment with diazomethane and recrystallization from 95% ethanol, gave 1.36 g. of the solid methyl ester, m. p. 128.5–130°.

Anal. Calcd. for $C_{20}H_{24}O_4$: C, 73.14; H, 7.37. Found: C, 72.83; H, 7.15.

α-Methyl-α,β-di-(*p*-methoxyphenyl)-valeric Acid (VI).—A solution of 5.0 g. of the methyl ester (m. p. 128.5–130°) in 50 ml. of dry ether was treated with 110 ml. of an ethereal solution of triphenylmethyl sodium[17] (0.000162 mole/ml.) in a stoppered Erlenmeyer flask under nitrogen. After standing for three hours at room temperature, 10 ml. of methyl iodide was added and the stoppered flask allowed to stand overnight. Water and a few drops of glacial acetic acid was added and the ether layer separated. After removal of the solvent in a current of air, the crude residue was refluxed for twenty-two hours with a solution of 10 g. of potassium hydroxide in 150 ml. of 95% ethyl alcohol. The solid obtained on acidification amounted to 4.09 g., m. p. 165–175°.

Recrystallization from *n*-butyl alcohol gave a first crop of 2.24 g., m. p. 181–182.5° (A), and a second crop of 0.07 g. of material melting at 154–156° (B). Because of the small amount of the product (B), demethylation and bioassay was carried out only with the higher melting compound.

Anal. Calcd. for $C_{20}H_{24}O_4$: (A) C, 73.14; H, 7.37. Found: C, 72.95; H, 7.15. (B) C, 73.14; H, 7.37. Found: C, 73.13; H, 7.34.

α-Methyl-α,β-di-(*p*-hydroxyphenyl)-valeric Acid (VII).—A mixture of 1.0 g. of the acid, m. p. 181–182.5°, and 25 g. of pyridine hydrochloride was heated at 185–195° for three hours. After cooling, the melt was dissolved in water and extracted repeatedly with ether. The ethereal layer was washed with dilute hydrochloric acid, water, and dried. Removal of solvent gave 0.8 g. of solid material which melted with decomposition at approximately 225°.

Anal. Calcd. for $C_{18}H_{20}O_4$: C, 71.31; H, 6.71. Found: C, 71.00; H, 7.36.

The **diacetate** after recrystallization from dilute ethyl alcohol melted at 210–212.5°.

Anal. Calcd. for $C_{22}H_{24}O_6$: C, 68.73; H, 6.29. Found: C, 68.57; H, 6.28.

Summary

α-Methyl-α,β-di-(*p*-hydroxyphenyl)-valeric acid, an active estrogen possessing certain of the salient structural features of both hexestrol and bis-dehydrodoisynolic acid, has been synthesized.

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[15] We have found the use of sodium hydroxide in ethylene glycol very satisfactory for the preparation of acids from other difficultly hydrolyzed nitriles and esters.

[16] Original procedure of Snyder and McIntosh, This Journal, **63**, 3280 (1941).

[17] "Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., Vol. I, p. 286.

KALAMAZOO, MICHIGAN RECEIVED JUNE 1, 1948

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF BROOKLYN COLLEGE]

The Structure of Meldrum's Supposed β-Lactonic Acid

BY DAVID DAVIDSON AND SIDNEY A. BERNHARD

Meldrum[1] observed that malonic acid and acetone react in the cold in acetic anhydride–sulfuric acid medium, eliminating the elements of water to form a crystalline product, $C_6H_8O_4$. Since this proved to be a monobasic acid which could be titrated in aqueous solution, Meldrum concluded that one of the carboxyl groups of the malonic acid molecule remained intact and proposed that the structure of the new compound was β,β-dimethyl-β-propiolactone-α-carboxylic acid (I).

This view is still current[2] although none of the reactions of Meldrum's product or of its homologs studied by Meldrum and by later workers[3,4,5,6] furnished evidence for the new C:C bond found in I. Instead, all its reactions indicated a notable tendency of the substance to regenerate acetone. Thus, **alkaline hydrolysis**[1] yielded acetone and sodium malonate; **acid alcoholysis**,[3,6] acetone and diethyl malonate; **anilinolysis**,[1] acetone, carbon dioxide and acetanilide; **pyrolysis**,[1,3] acetone, carbon dioxide, acetic acid and carbon suboxide.

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[1] Meldrum, *J. Chem. Soc.*, **93**, 598 (1908).

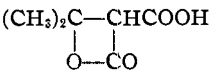
[2] Roger Adams, Editor in Chief, "Organic Reactions," Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1946, p. 124.

[3] Ott, *Ann.*, **401**, 159 (1913).

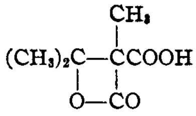
[4] Kandiah, *J. Chem. Soc.*, 1215 (1932).

[5] Michael and Ross, This Journal, **55**, 3684 (1933).

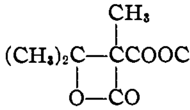
[6] Michael and Weiner, *ibid.*, **58**, 680, 999 (1936).



I



II

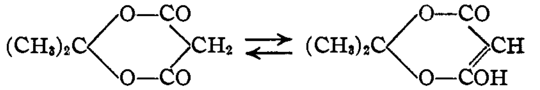


III

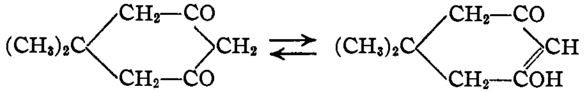
Furthermore, no evidence was adduced for the presence of a carboxyl group. As indicated above, treatment with alcohol and an acid catalyst resulted in scission to acetone and diethyl malonate. Attempts[3,6] to form the nitrile or ethyl ester corresponding to structure I by condensing acetone with cyanoacetic acid or with monoethyl malonate were fruitless. Treatment of the silver salt of Meldrum's acid with methyl iodide also failed to yield the desired ester[3] but gave instead a mixture containing unchanged I, the monomethylated acid, II (obtainable from acetone and monomethylmalonic acid), and a dimethyl derivative which was represented by structure III. No evidence was presented for the ester character of III, the only reaction reported being its pyrolysis to acetone, carbon dioxide and **dimethylketene.**

The occurrence of dimethylketene among the products of pyrolysis of the dimethyl derivative suggested that the substance is actually related to dimethylmalonic acid and, therefore, that the methylene group contained in malonic acid is still present in Meldrum's acid. This idea is supported by the fact[6] that cinnamalmalonic acid (which has no methylene group available for the aldol type of condensation) forms a condensation product with cinnamic aldehyde. Apparently, Meldrum's reaction does not involve the methylene group and one carboxyl group of the malonic acid molecule as he thought but, rather, both its carboxyl groups.

All of this led to the conclusion that Meldrum's acid is **isopropylidene malonate** (2,2-dimethyl-4,6-diketo-1,3-dioxane) (IV). Such a cyclic, bifunctional ester structure accounts for the ease with which acetone is produced from Meldrum's product by hydrolysis, alcoholysis, anilinolysis and pyrolysis. It does not fail to account for acidity of the compound (pK_a 5.1),[7] since the occurrence of the $-COCH_2CO-$ group (or its tautomer) in a cyclic structure is known to be responsible for acidity of intermediate strength (such as is also found in its most carboxylic acids).[8] Thus, for example, methone (V) has a pK_a of 5.2.[9]



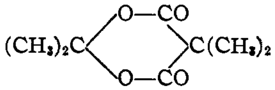
IV



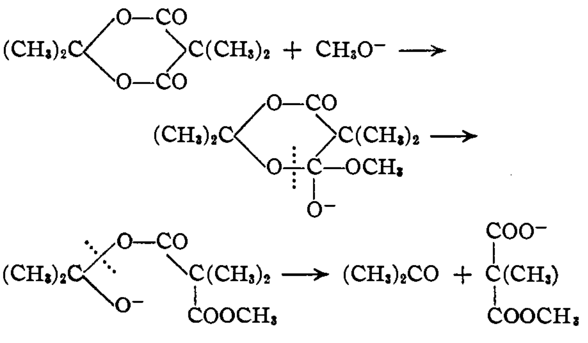
V

The structural similarity of isopropylidene malonate to methone is reflected in its behavior in certain tests. Just as methone reacts with aqueous sodium nitrite to give the violet sodium salt of the nitroso derivative,[10] so also isopropylidene malonate gives a purple product, presumably sodium isopropylidene isonitrosomalonate. Like methone,[9] isopropylidene malonate reacts with *two* moles of bromine when titrated in acetic acid containing three equivalents of potassium acetate to avoid the occurrence of hydrobromic acid. Like methone,[11] isopropylidene malonate, in aqueous or methanolic solution, gives precipitates with aldehydes in the cold.

In order to confirm the proposed structure for Meldrum's acid it remained to demonstrate that its dimethyl derivative[3] formerly represented by III actually has the structure, VI. This was readily accomplished by hydrolysis with dilute hydrochloric acid which gave high yields of both acetone and dimethylmalonic acid. (A substance having the structure III should yield monomethylmalonic acid). The behavior of the substance toward aqueous and methyl alcoholic alkali resembles that of a cyclic anhydride. With aqueous sodium hydroxide it can be titrated (provided the solution is gently heated toward the end) and reacts with two equivalents of the base. Titration with methyl alcoholic potassium hydroxide involves only one equivalent of the base. The latter reaction may be explained by the following mechanism.



VI



The poor conversion and rather cumbersome process involved in the method of methylating Meldrum's acid previously reported[3] made it desirable to attempt improvement. Application of

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[7] Determined by electrometric titration.

[8] For a discussion of varieties of organic acids see Davidson, *J. Chem. Education*, **19**, 154 (1942).

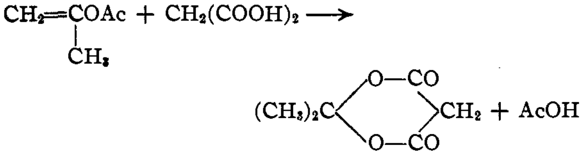
[9] Schwarzenbach and Felder, *Helv. Chim. Acta*, **27**, 1701 (1944).

[10] Barbituric acid gives the purple sodium violurate in this test (Clarke, "Handbook of Organic Analysis," 4th ed., Arnold and Co., London, 1931, p. 215).

[11] Vorländer, *Z. anal. Chem.*, **77**, 241 (1929).

the method employing methyl iodide and silver oxide[12] failed when ethanol or diethyl ether was used as solvent. Acetonitrile, which, in common with other nitriles, is a remarkable solvent for silver salts, proved very useful. Thus, while a suspension of silver oxide in acetonitrile does not react in the cold with methyl iodide, the further addition of a solution of Meldrum's acid in acetonitrile causes an immediate exothermal reaction with the formation of silver iodide and a good yield of the desired product.

Finally, it was found possible to synthesize isopropylidene dimethylmalonate (VI) from dimethylmalonic acid, if only in low yield. In this connection a new approach to Meldrum's acid was developed which involves the reaction of malonic acid with isopropenyl acetate, catalyzed by sulfuric acid. The product obtained by applying



this method to dimethylmalonic acid proved to be identical with that obtained by methylating Meldrum's acid.

Experimental

Preparation of Meldrum's Acid. (1) Modified Meldrum Method.—To a suspension of 52 g. (0.5 mole) of powdered malonic acid in 60 ml. (0.6 mole) of acetic anhydride was added, while stirring, 1.5 ml. of concd. sulfuric acid. Most of the malonic acid dissolved with spontaneous cooling. To the resulting solution, 40 ml. (0.55 mole) of acetone was added while cooling to maintain the temperature at 20–25°. The reaction mixture was allowed to stand overnight in the refrigerator and the resulting crystals filtered by suction and washed three times with sufficient ice water to cover the cake; yield of air-dried product, 35 g. (49%). Recrystallization is conveniently effected without heating by dissolving 10 g. of the product in 20 ml. of acetone, filtering and adding 40 ml. of water. The recovery is about 70%, m.p. 94–95° (dec.).

(2) **Isopropenyl Acetate Method.**—To a suspension of 52 g. (0.5 mole) of powdered malonic acid in 55 g. (62 ml., 0.55 mole) of redistilled isopropenyl acetate (Carbide and Carbon Chemicals Corp.) was added drop by drop, while stirring, 0.5 ml. of concd. sulfuric acid. The temperature rose spontaneously from 23 to 31° in forty-five minutes and all the malonic acid went into solution within an hour. Treatment of the reaction mixture as indicated above gave 37 g. of crude product (50%).

Methylation of Meldrum's Acid.—To a suspension of 26 g. (0.11 mole) of silver oxide in a mixture of 50 ml. of acetonitrile and 20 ml. (0.33 mole) of methyl iodide was dropped in during one hour, while stirring at 10°, a solution of 14.4 g. (0.10 mole) of Meldrum's acid in 50 ml. of acetonitrile. After stirring four hours longer and allowing to stand overnight the silver oxide–silver iodide was filtered by suction and washed with acetonitrile. The solvent was removed from the combined filtrates by distillation below 60° in the vacuum of a water pump. The residual oil was treated with water and after a few minutes the product solidified. The suspension was transferred to a mortar and the solid broken up to facilitate washing. After filtration by suction, washing with water and air-drying the product, which was tan-colored, weighed 12.6 g. (73%). It gave no sign of reaction with sodium bicarbonate (indicating the absence of Meldrum's acid and its monomethyl derivative). Distillation in vacuum (b.p. 127–129° at 33 mm.) gave 11.8 g. of a colorless solid, m.p., 62° (Ott[3] reported a b.p. of 213° at atmospheric pressure and a m.p. of 59.5°). The m.p. was not changed by recrystallization, which was effected by dissolving the substance in a small amount of benzene and then adding petroleum ether. The silver oxide–silver iodide precipitate, after drying at 100°, weighed 50.4 g. (theory, 49.8 g.).

Hydrolysis of the Dimethyl Derivative of Meldrum's Acid.—In a 25-ml. distilling flask connected to a short condenser and ice-cooled receiver were placed 3.44 g. of the dimethyl derivative of Meldrum's acid, 5 ml. of 2*M* hydrochloric acid and an ebulliator tube. The flask was surrounded by a boiling water-bath. The organic compound first melted, then gradually dissolved within a few minutes. Simultaneously, distillation began. When the reaction mixture ceased to boil, the bath was removed and the contents of the flask were allowed to cool, whereupon crystallization occurred. Filtration and air drying yielded 2.1 g. of product (calcd. for dimethylmalonic acid, 2.6 g.). This melted at 192–193° (dec.) (monomethylmalonic acid melts at 135° (dec.)) and showed no depression when mixed with dimethylmalonic acid prepared by methylating diethyl malonate and saponifying. The acetone in the distillate was determined by precipitating the 2,4-dinitrophenylhydrazone; yield, 91% of a product, m. p. 125°.

Synthesis of Isopropylidene Dimethylmalonate from Dimethylmalonic Acid.—To a suspension of 13.2 g. (0.10 mole) of dimethylmalonic acid in 11 g. (0.11 mole) of isopropenyl acetate was added drop by drop, while stirring and cooling, 0.5 ml. of concd. sulfuric acid. The mixture was then stirred for four hours at room temperature, after which the undissolved material was filtered off and the filtrate evaporated to dryness in vacuum at room temperature. To the residue was added 100 ml. of *M* sodium bicarbonate. The undissolved solid was filtered off and air dried; yield of brownish solid, 1.5 g. (8.7%). Vacuum distillation (b.p. 111° at 18 mm.) gave 1.3 g. of a straw-colored solid which when recrystallized from benzene–petroleum ether appeared as colorless crystals, m. p. 62°. A mixture of this product with that obtained by methylating Meldrum's acid showed no change in m.p.

Summary

The condensation product of malonic acid and acetone which Meldrum[1] considered to be β,β-dimethyl-β-propiolactone-α-carboxylic acid has been found to be the cyclic, bifunctional ester, isopropylidene malonate (2,2-dimethyl-4,6-diketo-1,3-dioxane). In some of its chemical properties, including its intermediate acidity, it resembles methone (5,5-dimethyldihydroresorcinol).

BROOKLYN 10, N. Y. RECEIVED JUNE 8, 1948

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[12] Lander, *J. Chem. Soc.*, **77**, 743 (1900).