Anal. Calcd. for $C_{11}H_{12}O_6$: C, 55.00; H, 5.04. Found: C, 55.22; H, 5.14.

The substance was insoluble in water but dissolved in aqueous sodium hydroxide with formation of a red color and destruction of the starting material. It was recovered unchanged after 5 minutes of refluxing in a mixture of equal parts of dioxane and 1.0 *N* sulfuric acid.

Diels–Alder Reactions of 2,5-Dicarbomethoxy-5-methylcyclohexene-1,4-dione. A. With 2,3-Dimethylbutadiene.—A suspension of 400 mg. of 2,5-dicarbomethoxy-5-methylcyclohexene-1,4-dione (X) in 1.2 g. of freshly distilled 2,3-dimethylbutadiene was allowed to stand in a stoppered container at room temperature. After 1.5 hours all of the dienophile had dissolved and the solution had become perceptibly paler. After 40 hours the colorless solution was concentrated *in vacuo* giving 525 mg. of viscous residue. The latter could not be induced to crystallize and was therefore chromatographed over acid-washed alumina. After a number of oily eluates had been collected by elution with 9:1 petroleum ether–ether, a crystalline product appeared in the 8:2 petroleum ether–ether eluates. The crystals (50 mg.) were collected and recrystallized from ether–petroleum ether; m.p. 90°.

Anal. Calcd. for $C_{17}H_{22}O_6$: C, 63.34; H, 6.88. Found: C, 63.51; H, 6.77.

B. With 3-Ethoxy-1,3-pentadiene.—A mixture of 500 mg. of the dienophile (X) and 1.5 g. of freshly distilled 3-ethoxy-1,3-pentadiene in a small closed vial reacted spontaneously and with evolution of heat. After an hour the yellow color had completely disappeared and the excess diene was largely removed *in vacuo*. The colorless residue could not be induced to crystallize even after chromatography over acid-washed alumina. A portion of the original adduct was hydrolyzed at room temperature in 0.01 *N* aqueous acetic acid and the hydrolysis product chromatographed, but again no crystalline substance could be obtained.

Acknowledgment.—The authors are indebted to Mr. Richard N. Boos and his associates for the microanalyses reported herein.

RAHWAY, NEW JERSEY RECEIVED AUGUST 6, 1951

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF MERCK & CO., INC.]

Approaches to Total Synthesis of Adrenal Steroids. III. 5-Carbomethoxy-5-methylcyclohexene-1,4-dione as a Dienophile

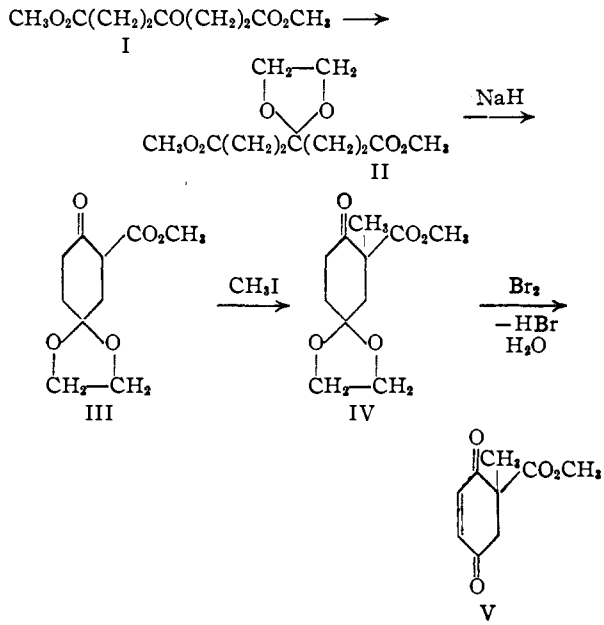
BY ROBERT M. LUKES, GEORGE I. POOS AND LEWIS H. SARETT

5-Carbomethoxy-5-methylcyclohexene-1,4-dione (V) has been prepared in a five-step reaction series from dimethyl γ-ethylenedioxypimelate. It has been found to react with 1,3-dienes at a much slower rate than do 2,5- and 3,5-dicarbomethoxy-5-methylcyclohexene-1,4-dione.

The ease with which 2,5- and 3,5-dicarbomethoxy-5-methylcyclohexene-1,4-dione react with 1,3-dienes[1] made an investigation of a comparable cyclohexene-1,4-dione containing a single carbomethoxy substituent seem attractive. Accordingly the synthesis of 5-carbomethoxy-5-methylcyclohexene-1,4-dione (V) was undertaken. Dimethyl γ-ketopimelate (I) reacted smoothly with ethylene glycol to give dimethyl γ-ethylenedioxypimelate which was cyclized with sodium hydride according to the previously described procedure.[1] When the dimethyl γ-ketopimelate was treated with ethyl orthoformate,[2] however, and the crude reaction product submitted to conditions suitable for the Dieckmann condensation, no 1,4-cyclohexanedione derivatives could be obtained.

Methylation of 2-carbomethoxy-4-ethylenedioxycyclohexanone (III) according to the conditions of Cornubert and Borrel[3] yielded 2-carbomethoxy-2-methyl-4-ethylenedioxycyclohexanone (IV). Support for the formulation of IV was afforded by the stepwise acid hydrolysis, first to 2-carbomethoxy-2-methylcyclohexane-1,4-dione and then under more vigorous conditions to methylcyclohexane-1,4-dione.

Treatment of the methylated ketodioxolane (IV) with one molecular equivalent of bromine gave an unstable monobromo derivative which by dehydrobromination and regeneration of the protected ketonic function afforded the desired 5-carbomethoxy-5-methylcyclohexene-1,4-dione (V). It was found that the order of the last three steps could be altered. Thus the free diketone itself could be monobrominated and then dehydrobrominated, or the bromodioxolane could be hydrolyzed to the bromodiketone and dehydrobrominated. The yield following the first sequence was the best.



An *a priori* appraisal of the activity of V as a dienophile presents difficult points. Lacking an augmentative polarizing group such as is present in the dienophiles 2,5- and 3,5-dicarbomethoxy-5-methylcyclohexene-1,4-dione, it must be appreciably less active than these. Because of the quaternary carbon atom which might be expected

(1) See Part II of this series, THIS JOURNAL, 74, 1397 (1952).
(2) *Cf.* R. Robinson and E. Seijo, *J. Chem. Soc.*, 582 (1941).
(3) R. Cornubert and C. Borrel, *Bull. soc. chim.*, [4] 47, 301 (1930).

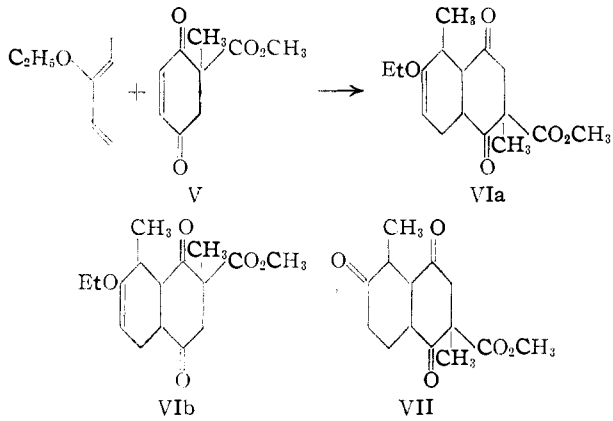
to perturb a biplanar complex, V should react more slowly with a diene than does methoxybenzoquinone or toluquinone, for example. The *rate* of addition of dienophiles like benzoquinone or cyclohexene-1,4-dione is of considerable practical importance because the initial *cis*-addition product isomerizes to a *trans* derivative, or derivatives, at quite an appreciable rate[4] under simple thermal activation. Experimentally, it was found that V added to 2,3-dimethylbutadiene and to 3-ethoxy-1,3-pentadiene so slowly that ample opportunity was afforded the *cis*-adduct to isomerize to the *trans*-form. The reactivity of V may be contrasted with that of 2,5-dicarbomethoxy-5-methylcyclohexene-1,4-dione by noting that the latter is almost completely combined with 2,3-dimethylbutadiene in a few hours at room temperature while the former requires ten days at 40–45° to proceed to the extent of 45%. Similarly the latter combined with 3-ethoxy-1,3-pentadiene in less than two hours at room temperature while the former required several days at 40–45°. An additional opportunity for isomerization occurred during the distillation which was necessary to separate the adduct from unreacted dienophile and by-products.

The adduct of V with 3-ethoxy-1,3-pentadiene could not be crystallized directly and was converted by mild acid hydrolysis into the corresponding triketone. Three crystalline isomers of this material could be obtained. As indicated above, some of the isomers undoubtedly represent *trans* modifications arising during the initial prolonged reaction time and also during the subsequent isolation procedures. Vigorous acid hydrolysis of two of these isomers gave the known 2,5-dimethylperhydronaphthalene-1,4,6-trione.[1] The other isomer was obtained in insufficient quantity to permit acid hydrolysis and decarboxylation.

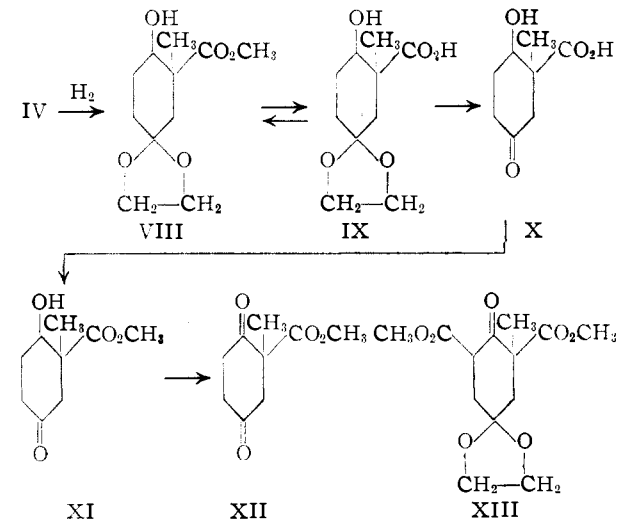
The addition of 3-ethoxy-1,3-pentadiene to V could theoretically give four *dl*-pairs in both the *cis*-2,5-dimethyldecalin and *cis*-1,7-dimethyldecalin series. It is likely, however, that the C_5-methyl group and the two bridgehead hydrogen atoms have the same spatial relationship in all cases.[5] The number of probable *dl*-pairs would then be reduced to two in each series. The four activated complexes leading to these four isomers should differ appreciably in their energies because of (a) a steric factor involving the difference in size of the methyl and the carbomethoxy groups in the dienophile portion and (b) polar effects arising from interaction of the methyl or carbomethoxy group of the dienophile and the ethoxy, group of the diene. It would not be improbable therefore, for a single isomer to predominate in the addition product. It is unfortunate that direct crystallization must be relied on as the sole means of telling whether this is so. Inasmuch as the addition reaction did not yield a crystalline product directly, the question of whether the addition *initially* leads to all four of the most probable isomers, or to fewer, must be left unsettled.

(4) W. Hückel, *Ann.*, **441**, 1 (1925), has shown that *cis*-α-decalone isomerized to the *trans*-form slowly at room temperature. We have found that the *cis*-1,4-diketodecalins are considerably less stable.

(5) *Cf.* addition of benzoquinone and toluquinone to 3-ethoxy-1,3-pentadiene described in Part I of this series. See also K. Alder, *ibid.*, **571**, 157 (1951).



It was felt that the possibility that the optically active adduct VIa or VIb might have a higher degree of crystallinity than the *dl*-form justified exploratory steps toward its preparation. To this end the ketodioxolane (IV) was reduced catalytically. A single isomer of 2-methyl-2-carbomethoxy-4-ethylenedioxycyclohexanol (VIII) was obtained in nearly quantitative yield. Saponification gave the corresponding acid (IX) which hydrolyzed with great ease to 1-methyl-2-hydroxy-5-ketocyclohexanecarboxylic acid (X). A facile resolution of the latter was achieved by crystallization of the brucine salt. Re-esterification of the (+)-acid, oxidation to the diketone (XII) and introduction of the double bond yielded the (+)-form of V. As with the *dl*-form, (+)-V gave no directly crystallizable adduct with 3-ethoxy-1,3-pentadiene.



The ketodioxolane (IV) served as starting material for a new method of synthesis of 2,6-dicarbomethoxy-2-methyl-4-ethylenedioxycyclohexanone (XIII). Although IV was moderately sensitive to sodium alkoxides it could be condensed with dimethyl oxalate in the presence of methanolic sodium methoxide. The crude oxalyl ketone underwent decarbonylation on pyrolysis according to the procedure of Bachmann, Cole and Wilds.[6] The resulting crystalline dicarbomethoxymethylketodioxolane (XIII) was identical with that pre-

(6) W. E. Bachmann, W. Cole and A. L. Wilds, THIS JOURNAL, **62**, 824 (1940).

viously prepared by cyclization of dimethyl α-carbomethoxy-α-methyl-γ-ethylenedioxypimelate.

Experimental[7]

Dimethyl γ-Ketopimelate (I).—This compound was prepared essentially according to the procedure of Marckwald[8] for the preparation of the ethyl ester. In a 2-liter flask fitted with a mineral oil-sealed stirrer, a reflux condenser, and a gas inlet tube were placed 300 g. of furylacrylic acid and 1200 cc. of methanol. Dry hydrogen chloride gas was introduced at a rapid rate with stirring. As soon as the solution reached the boiling point, the flow of gas was diminished to a rate which provided only a small flow from the top of the reflux condenser. During this time the reaction solution was maintained at the boiling point, through application of heat when necessary. At the end of four hours the solution was concentrated to one-fourth volume *in vacuo*. Two liters of benzene was added to the residue, the distillation was continued at atmospheric pressure until the vapor temperature reached 80° and then the remainder of the benzene was removed *in vacuo*. To the residue was added 1 liter of methanol and 1 cc. of 96% sulfuric acid, and the resulting solution was refluxed for 16 hours. At the end of this time 600 cc. of the methanol was distilled *in vacuo*, the residue was dissolved in 2 liters of benzene, and the benzene solution washed with 1 *N* sodium carbonate solution in 200-cc. portions until the aqueous layer remained alkaline, and then with 200 cc. of water. The benzene was removed at aspirator pressure and the residue distilled *in vacuo*. Dimethyl γ-ketopimelate, a white solid of m.p. 49–50°, distilled at 90–93° (0.10 mm.); yield 351 g. (80%).

Attempted Preparation of 2-Carbomethoxycyclohexane-1,4-dione *via* the Diethyl Ketal of Dimethyl γ-Ketopimelate.—A solution of 20 g. of dimethyl γ-ketopimelate, 9.6 g. of absolute ethanol, 1 cc. of 4.8% hydrogen chloride in ethanol and 16 g. of ethyl orthoformate was allowed to stand at room temperature. After 3 days the alcohol and excess ethyl orthoformate were distilled *in vacuo*, and the oily residue taken up in 30 cc. of sodium-dried ether. To this ethereal solution was added 2.4 g. of sodium hydride pellets and 0.2 cc. of absolute methanol, and the resultant mixture was stirred under nitrogen for 2 days. Twenty-five cc. of water was added to the reaction mixture, the aqueous layer was separated and brought to *p*H 2 with 6 *N* hydrochloric acid, and then extracted with ether. The ethereal solution was dried, evaporated, and the oily residue distilled *in vacuo*. The product, a white solid of m.p. 37–38° and b.p. 70–75° (0.25 mm.), gave a strong enol test with alcoholic ferric chloride. This compound, upon hydrolysis in 0.03 *N* sulfuric acid for 16 hours at 100°, gave an amorphous acidic material (positive ferric chloride reaction) but no cyclohexane-1,4-dione. It was obvious from this hydrolysis that the cyclization of the "ketal" of dimethyl γ-ketopimelate did not give the desired 2-carbomethoxy-1,4-cyclohexanedione. Several additional attempted cyclizations gave similar results.

Dimethyl γ-Ethylenedioxypimelate (II).—A mixture of 100 g. of dimethyl γ-ketopimelate, 34.5 g. of redistilled ethylene glycol, 250 cc. of benzene and 200 mg. of *p*-toluenesulfonic acid was heated in a flask fitted with a Bidwell–Sterling receiver with a reflux condenser. After 12 hours 9 cc. of water had been collected. Refluxing was discontinued, another 250 cc. of benzene was added to the reaction mixture, and the resulting solution was washed with 25 cc. of saturated sodium bicarbonate solution and then with 100 cc. of water. The benzene was removed *in vacuo* and the residue distilled. After a small forerun of ethylene glycol and dimethyl γ-ketopimelate, 99 g. of crude dimethyl γ-ethylenedioxypimelate (II) was collected at 94–100° (0.08 mm.). Redistillation gave 75 g. (61.5%) of dimethyl γ-ethylenedioxypimelate, b.p. 96–98° (0.08 mm.), $n^{25}D$ 1.4501.

Anal. Calcd. for $C_{11}H_{18}O_6$: C, 53.65; H, 7.37. Found: C, 53.39; H, 7.14.

2-Carbomethoxy-4-ethylenedioxycyclohexanone (III).—A mixture of 164 g. of dimethyl γ-ethylenedioxypimelate in 1 liter of sodium-dried ether and 16 g. of sodium hydride pellets was stirred together under reflux in a nitrogen atmosphere for five days. At the end of this time the sodium hydride had disappeared and the ether held a large amount of yellow solid in suspension. To this suspension was added with rapid stirring 60 cc. of glacial acetic acid and then 60 cc. of water. The ether solution was washed with aqueous sodium bicarbonate, dried and evaporated. The yellow oily residue was distilled *in vacuo* and the distillate boiling at 90–95° (0.25 mm.) was collected (111 g., 78%). Upon standing overnight it solidified. Recrystallization from methanol gave 92 g. (65%) of 2-carbomethoxy-4-ethylenedioxycyclohexanone, m.p. 60–61°.

Anal. Calcd. for $C_{10}H_{14}O_5$: C, 56.15; H, 6.51. Found: C, 56.00; H, 6.45.

2-Carbomethoxy-2-methyl-4-ethylenedioxycyclohexanone (IV).—To a suspension of 53.3 g. of III in 500 cc. of absolute methanol maintained at −40° was added dropwise, with stirring, a solution of 13.5 g. of sodium methoxide in 200 cc. of absolute methanol. The temperature of the reaction mixture was allowed to rise to −15° and was maintained there, with stirring, for one hour. Then 45 g. of methyl iodide was added, the reaction flask was stoppered, and the mixture allowed to stand at room temperature. After three days the reaction mixture had become neutral to litmus, and the methanol was distilled *in vacuo* at a temperature below 25°. The semi-solid residue was extracted with 500 cc. of ether, the inorganic salts were removed by filtration, and the resulting clear ether solution was washed with 50 cc. of ice-cold 1 *N* potassium hydroxide solution and then with 50 cc. of ice-water. The ether solution was dried over anhydrous sodium sulfate, filtered, and evaporated to a volume of 200 cc. Addition of 200 cc. of petroleum ether and cooling overnight in the refrigerator gave 43 g. (76%) of 2-carbomethoxy-2-methyl-4-ethylenedioxycyclohexanone (IV), m.p. 50–51°.

Anal. Calcd. for $C_{11}H_{16}O_5$: C, 57.88; H, 7.07. Found: C, 58.03; H, 6.82.

Mild acid hydrolysis of IV gave 2-carbomethoxy-2-methylcyclohexane-1,4-dione (see below). A sample of the latter was heated with 6 *N* sulfuric acid for two hours at 100°. Extraction with ether and crystallization of the product gave methylcyclohexane-1,4-dione, m.p. and mixed m.p. 47–48°.

5-Carbomethoxy-5-methylcyclohexene-1,4-dione (V). A. By Bromination, Dehydrobromination and Hydrolysis of IV.—A solution of 3.94 g. (0.0173 mole) of IV in 50 cc. of dry chloroform was cooled to 15–20° and with rapid stirring treated with 2.76 g. (0.0173 mole) of bromine in 7.5 cc. of dry chloroform in one portion. The mixture warmed to room temperature without reaction and then abruptly lost color. Hydrogen bromide and a portion of the solvent was immediately removed *in vacuo*. To the resulting cold solution, 4.2 cc. of pyridine was added without delay. Volatile material was then removed under aspirator vacuum and the concentration completed by heating at 50° for 30 minutes. The residue was neutralized with 10% hydrochloric acid with cooling, dissolved in 30 cc. of methanol, and then treated with 18 cc. of 1 *N* hydrochloric acid. An oil separated from the yellow solution. After being stirred overnight, the hydrolysis mixture was homogeneous. Methanol was distilled *in vacuo* and the oily product was collected in ether, the ether solution was washed twice with water, dried and distilled. The residue amounted to 2.76 g. and upon distillation gave 2.25 g. (71.5%) of crude product, b.p. 101–110° (0.40 mm.), $n^{26.5}D$ 1.4942. This once-distilled material was contaminated with a bromine-containing impurity. Two careful redistillations yielded 1.18 g. (37.2%) of a pale yellow product with constant boiling point and refractive index; b.p. 69.5° (0.5 mm.), $n^{25.0}D$ 1.4951; λ_{max} 222.5 mμ, E_{mol} 10,800; λ_{max} 340 mμ, E_{mol} 180.

Anal. Calcd. for $C_9H_{10}O_4$: C, 59.33; H, 5.53. Found: C, 59.68; H, 5.89.

B. By Hydrolysis, Bromination and Dehydrobromination of IV.—A solution of 16.1 g. of IV in 100 cc. of methanol and 100 cc. of 1 *N* hydrochloric acid was left at room temperature overnight. Methanol was distilled *in vacuo*, the aqueous solution was extracted with ten 50-cc. portions of ether and the ether solution was washed twice with water, dried and distilled. There was obtained 11.9 g. (92.5%) of 2-carbomethoxy-2-methylcyclohexane-1,4-dione as a colorless oil, b.p. 93–94° (0.20 mm.), $n^{25}D$ 1.4755.

Anal. Calcd. for $C_9H_{12}O_4$: C, 58.70; H, 6.57. Found: C, 58.98; H, 6.51.

(7) All melting points were taken on the Kofler micro hotstage.

(8) W. Marckwald, *Ber.*, **20**, 2813 (1887).

Bromination and dehydrobromination of this material was carried out essentially as described in section A. From 5.61 g. of diketoester there was obtained 4.27 g. (77%) of once distilled product; b.p. 97–102° (0.20 mm.); $n^{24.5}D$ 1.4987. Three more distillations were required to obtain pure halogen-free V by this route.

C. By Bromination, Hydrolysis and Dehydrobromination of IV.—A chloroform solution of 1.90 g. of IV was treated with 1.34 g. of bromine as described in section A. All of the solvent was removed *in vacuo* and the residue was hydrolyzed by refluxing one hour in a mixture of 12 cc. of methanol and 12 cc. of 1 *N* sulfuric acid. Methanol was distilled, the organic material was collected in ether and the ether solution was washed with water and dried. Three cubic centimeters of pyridine was added to the ether solution and the ether was distilled with a final brief heating of the residue on the steam-bath. After the addition of water and extraction with ether, the ether solution was washed once with 10% hydrochloric acid, twice with water and was dried and concentrated. The distillable portion of the residue amounted to 1.07 g.; b.p. 90–120° (0.20 mm.), $n^{25}D$ 1.4978. Redistillation and ultraviolet spectra showed this product to be considerably less pure than that obtained by the other routes.

Diels–Alder Reaction of V with 2,3-Dimethylbutadiene.—A mixture of 1.50 g. of 5-carbomethoxy-5-methylcyclohexene-1,4-dione and 2.04 g. (3 molecular equivalents) of 2,3-dimethylbutadiene was sealed in a small bottle and maintained at 40–45° in the dark for ten days. Fractional distillation of the reaction mixture gave 1.30 g. of unchanged diene, 0.63 g. of an intermediate fraction consisting largely of unchanged dienophile and 0.98 g. (45%) of adduct as a viscous oil, b.p. 125° (0.10 mm.), $n^{28.0}D$ 1.5045.

A cold solution of the adduct in ether–petroleum ether (1:1) yielded white prisms melting at 50–65° together with an oily material. After four recrystallizations from petroleum ether the crystalline portion melted at 67–69°.

Anal. Calcd. for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 68.04; H, 7.61.

The oily product on standing in ether–petroleum ether yielded additional adduct melting at 61–66° together with a trace of white needles, m.p. 84–88°, which was not further investigated.

Diels–Alder Reaction of V with 3-Ethoxy-1,3-pentadiene.—A sealed bottle containing 3.63 g. of V and 7.08 g. (3.16 molecular equivalents) of 3-ethoxy-1,3-pentadiene was maintained at 40–45° in the dark for seven days. After distillation of unreacted diene there was obtained 2.43 g. of material boiling at 80–130° (0.10 mm.) (consisting of a small amount of unreacted dienophile and what appeared to be diene dimer) followed by 4.68 g. (79.8%) of product as a viscous yellow oil, b.p. 130–133° (0.10 mm.), $n^{25}D$ 1.5005. The adduct was redistilled once for analysis: b.p. 124° (0.07 mm.), $n^{25}D$ 1.5003.

Anal. Calcd. for $C_{16}H_{22}O_5$: C, 65.28; H, 7.53. Found: C, 65.61; H, 7.55.

Attempts to obtain a crystalline product were largely unsuccessful. The gummy material was chromatographed over basic and acid-washed alumina and calcium sulfate both before and after distillation. In one case a trace of crystalline material melting at 120–132° was obtained.

The adduct was also prepared in 65% yield by heating the reactants at 120° for 20 minutes and in 48% yield at 0° for two weeks.

Hydrolysis to Isomeric Carbomethoxymethylperhydronaphthalenetriones.—A solution of 2.99 g. of the above adduct in 20 cc. of 50% methanol was treated with four drops of 10% hydrochloric acid and left to stand at room temperature for one hour. Methanol was removed from the cool solution *in vacuo* and sodium bicarbonate was added to neutralize the acid. The product was extracted with ether, the ether solution was washed with water, dried and concentrated giving 2.42 g. (91%) of thick oil. Fractional crystallization first from methanol, then ether and finally ether–petroleum ether gave the following compounds: (a) Platelets from methanol, m.p. 148–151°. *Anal.* Calcd. for $C_{14}H_{18}O_5$: C, 63.14; H, 6.81. Found: C, 62.81; H, 7.31.

(b) Prisms from methanol, m.p. 134–134.5°. Found: C, 63.32; H, 6.78.

(c) Prisms from methanol, m.p. 150–153°. Found: C, 63.31; H, 6.60.

The last compound was obtained by chromatography over acid-washed alumina of the oil remaining after the separation of the above material. The three compounds were shown to be different by a series of mixed melting point determinations.

Degradation of Carbomethoxymethylperhydronaphthalenetriones.—Isomer a (83 mg.) was heated at 100° for two hours in 5 cc. of 5 *N* sulfuric acid. The solution was cooled, saturated with sodium sulfate and extracted with benzene. The benzene solution was dried and concentrated to yield 60 mg. of a thick yellow oil which was chromatographed over 2 g. of acid-washed alumina. A crystalline material was eluted with 8:2 petroleum ether–ether. Recrystallization from methylcyclohexane gave a few milligrams of 2,5-dimethylperhydronaphthalene-1,4,6-trione[1] as needles, m.p. 120–123°.

Isomer b was degraded in a similar fashion and gave the same 2,5-dimethylperhydronaphthalene-1,4,6-trione.[1]

Isomer c was not obtained in sufficient quantity for degradation.

Methyl 1-Methyl-2-hydroxy-5-ethylenedioxycyclohexanecarboxylate (VIII).—A solution of 15 g. of IV in 350 cc. of absolute ethanol in which was suspended 2.5 g. of freshly prepared Raney nickel was treated with hydrogen at room temperature. The solution rapidly absorbed one molecular equivalent. After filtration the ethanol was distilled *in vacuo*. The oily residue crystallized from ether–petroleum ether, giving 14 g. (93%) of methyl 1-methyl-2-hydroxy-5-ethylenedioxycyclohexanecarboxylate (VIII), m.p. 56–58°.

Anal. Calcd. for $C_{11}H_{18}O_5$: C, 57.38; H, 7.88. Found: C, 57.46; H, 7.76.

1-Methyl-2-hydroxy-5-ethylenedioxycyclohexanecarboxylic Acid (IX).—A suspension of 325 mg. of VIII in 1.5 cc. of 2 *N* aqueous potassium hydroxide was heated at 100° for five minutes, during which time the mixture became homogeneous. The solution was cooled to 0° and was acidified to *p*H 2 with 6 *N* hydrochloric acid, care being taken to keep the temperature at 0° during the acidification. The resultant acidic solution was immediately extracted with three 10-cc. portions of chloroform. Evaporation of the combined chloroform extracts gave an oily residue which crystallized upon standing several days. Recrystallization from acetone–petroleum ether and from ethyl acetate–petroleum ether gave 100 mg. (33%) of 1-methyl-2-hydroxy-5-ethylenedioxycyclohexanecarboxylic acid (IX), m.p. 114°.

Anal. Calcd. for $C_{10}H_{16}O_5$: C, 55.55; H, 7.45. Found: C, 55.65; H, 7.22.

1-Methyl-2-hydroxy-5-ketocyclohexanecarboxylic Acid (X).—A suspension of 13 g. of VIII in 50 cc. of 3 *N* aqueous potassium hydroxide was heated at 100° for five minutes, during which time the mixture became homogeneous. The solution was acidified to *p*H 1 with 12 *N* hydrochloric acid, and was then extracted continuously with chloroform for 16 hours. Evaporation of the chloroform extract gave a crystalline residue which upon recrystallization from acetone–petroleum ether yielded 7.5 g. (78%) of 1-methyl-2-hydroxy-5-ketocyclohexanecarboxylic acid (X), m.p. 155–157°.

Anal. Calcd. for $C_8H_{12}O_4$: C, 55.80; H, 7.07. Found: C, 55.46; H, 7.21.

Methyl 1-Methyl-2-hydroxy-5-ketocyclohexanecarboxylate (XI).—An ice-cold ethereal solution of diazomethane was prepared from 6 g. of N-nitrosomethylurea and was added to 5 g. of solid X. After evolution of nitrogen had ceased, the ether and excess diazomethane were evaporated. The oily residue upon crystallization from ether–petroleum ether gave 4.9 g. (90%) of methyl 1-methyl-2-hydroxy-5-ketocyclohexanecarboxylate (XI), m.p. 57–58°.

Anal. Calcd. for $C_9H_{14}O_4$: C, 58.05; H, 7.58. Found: C, 57.88; H, 7.33.

Optical Resolution of X.—A dry mixture of 2.2 g. of X and 4.9 g. of anhydrous brucine (m.p. 176–178°) was dissolved in 60 cc. of boiling acetone. Upon standing at room temperature the solution began to deposit the salt of the (−)-acid in rosettes of fine needles. When deposition of the rosettes of needles had ceased, thick prisms of the other diastereomeric salt began to separate. The supernatant liquid was immediately decanted into another vessel, where deposition of the prisms continued. After three recrystallizations from acetone the brucine salts of (+)- and (−)-X

had the following constants: salt of (+)-acid, m.p. 188–190°; $[\alpha]^{25}D$ −16 ± 1° (water, *c* 1.8); salt of (−)-acid, m.p. 146–148°; $[\alpha]^{23}D$ −29 ± 1° (water, *c* 1.7).

(+)- and (−)-1-Methyl-2-hydroxy-5-ketocyclohexanecarboxylic Acid (X).—To a solution of 6.5 g. of the brucine salt of the (+)-acid (X) in 50 cc. of water was added 10 cc. of 25% aqueous potassium hydroxide. This mixture was shaken well, and the liberated brucine was extracted with three 15-cc. portions of chloroform. The resulting homogeneous aqueous solution was brought to *p*H 2 with 96% sulfuric acid, and was extracted continuously with chloroform for 16 hours. The chloroform extract was then evaporated, and the oily residue was crystallized from acetone–petroleum ether, giving 1.8 g. (91%) of (+)-1-methyl-2-hydroxy-5-ketocyclohexanecarboxylic acid (X), m.p. 138–140°, $[\alpha]^{25}D$ +48 ± 1° (water, *c* 1.3). A similar treatment of 6.0 g. of the brucine salt of the (−)-acid gave 1.6 g. (88%) of (−)-1-methyl-2-hydroxy-5-ketocyclohexanecarboxylic acid (X), m.p. 137–139°, $[\alpha]^{25}D$ −48 ± 1° (water, *c* 1.3). A mixture of equal amounts (23 mg.) of the (+)- and (−)-acids upon recrystallization from acetone–petroleum ether gave 35 mg. of the *dl*-acid (X), m.p. and mixed m.p. 155–157°.

(+)-Methyl 1-Methyl-2-hydroxy-5-ketocyclohexanecarboxylate.—An ice-cold ethereal solution (300 cc.) of diazomethane was prepared from 14 g. of N-nitrosomethylurea and was added to 10.7 g. of the solid (+)-acid (X). When evolution of nitrogen had ceased, the ether and excess diazomethane were evaporated. The oily residue crystallized from ether–petroleum ether upon standing in the refrigerator overnight, giving 10.5 g. (91%) of (+)-methyl 1-methyl-2-hydroxy-5-ketocyclohexanecarboxylate, m.p. 48–49°, $[\alpha]^{24}D$ +47 ± 1° (dioxane, *c* 2.0).

(+)-2-Carbomethoxy-2-methyl-1,4-cyclohexanedione.—To an ice-cold solution of 5.0 g. of (+)-XI in 25 cc. of 90% aqueous acetic acid was added portionwise over ten minutes 50 cc. of a 1 *N* solution of chromic acid in 90% aqueous acetic acid. The cooling bath was removed and the solution was stirred for three hours. Then the solution was overlayered with 200 cc. of ether, and a solution of 85 g. of potassium carbonate in 120 cc. of water was added dropwise with rapid stirring. The ether layer was separated, the aqueous solution extracted with 200 cc. of ether, and the combined ether extracts were dried over anhydrous sodium sulfate. Filtration and evaporation yielded a colorless oil which upon distillation gave 3.8 g. (76%) of (+)-2-carbomethoxy-2-methyl-1,4-cyclohexanedione (XII), b.p. 102° (0.15 mm.), $[\alpha]^{24}D$ +56 ± 1° (dioxane, *c* 2.8).

(+)-5-Carbomethoxy-5-methylcyclohexene-1,4-dione.—The bromination–dehydrobromination procedure outlined in section B for the preparation of *dl*-5-carbomethoxy-5-methylcyclohexene-1,4-dione was used to convert 3.46 g. of (+)-2-carbomethoxy-2-methyl-1,4-cyclohexanedione to its unsaturated derivative. After three distillations, there was obtained 1.48 g. (42%) of pale yellow oil, b.p. 67° (0.02 mm.), $n^{24.8}D$ 1.4955, $[\alpha]^{22}D$ +45 ± 1° (dioxane, *c* 2.1).

Diels–Alder Reaction with 3-Ethoxy-1,3-pentadiene.—A mixture of 1.41 g. of (+)-5-carbomethoxy-5-methylcyclohexene-1,4-dione and 4.12 g. (4.75 molecular equivalents) of 3-ethoxy-1,3-pentadiene was maintained at 35–40° for four days. Distillation yielded 1.66 g. (73%) of adduct, b.p. 129–133° (0.07 mm.), $n^{25}D$ 1.4990, $[\alpha]^{23}D$ −26 ± 1° (dioxane, *c* 0.92). A portion of this material was chromatographed over acid-washed alumina in an unsuccessful attempt to obtain crystalline material.

2,6-Dicarbomethoxy-2-methyl-4-ethylenedioxycyclohexanone (XIII) from 2-Carbomethoxy-2-methyl-4-ethylenedioxycyclohexanone (IV).—A solution of 3.0 g. of 2-carbomethoxy-2-methyl-4-ethylenedioxycyclohexanone in 10 cc. of absolute methanol was treated with 4.0 g. of dimethyl oxalate. To the cold solution was added 4.8 cc. of 3.16 *N* methanolic sodium methoxide. The mixture was allowed to stand at 0° for 23 hours, then poured into a separatory funnel containing ice and 1.2 cc. of acetic acid. The mixture was extracted thrice with chloroform, the chloroform extract washed with dilute aqueous sodium bicarbonate, dried and concentrated *in vacuo*. Excess dimethyl oxalate was removed from the residue by distillation at 90° (0.3 mm.). The yellow oily residue (4.0 g.) gave a wine-red color with ferric chloride solution. It could not be induced to crystallize and was therefore treated with 1.5 g. of powdered soft glass and then heated at 160° for five minutes. The mixture was cooled, treated with ether and decanted from the powdered glass. The ether solution was extracted with three 10-cc. portions of cold 1 *N* aqueous potassium hydroxide. The aqueous alkaline solution was acidified with acetic acid and the resulting yellow crystalline precipitate filtered and washed with water. Recrystallization from ether gave 880 mg. of 2,6-dicarbomethoxy-2-methyl-4-ethylenedioxycyclohexanone, m.p. 89–92°. After several recrystallizations from methanol, an analytically pure product, m.p. 93.5–95.0°, was obtained.

Anal. Calcd. for $C_{13}H_{18}O_7$: C, 54.54; H, 6.34. Found: C, 54.78; H, 6.28.

A higher melting form, m.p. 106–108°, was obtained by passage of an ether–petroleum ether solution of this material over alumina. A mixed melting point of the higher melting form with a sample of the 2,6-dicarbomethoxy-2-methyl-4-ethylenedioxycyclohexanone previously described[1] did not show a depression.

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