washed with 4 *N* sodium hydroxide and then water. Solvent was removed and the crude oily product distilled to give 210 mg. (23%) of crude 1,7-dimethylnaphthalene, $n^{24.5}D$ 1.5923.

For identification 200 mg. of the hydrocarbon was oxidized with 0.77 g. of chromium trioxide in 3.8 cc. of 80% acetic acid at 60° for one hour. The reaction mixture was diluted with water and extracted with ether. After removal of the solvent, there was obtained 48 mg. of 2,8-dimethyl-1,4-naphthoquinone (XII) as yellow needles. The analytical sample melted at 133.5–135.5°, after three crystallizations from methanol (lit.[23] m.p. 135–135.5°) and did not lower on admixture with an authentic sample.[22]

Anal. Calcd. for $C_{12}H_{10}O_2$: C, 77.40; N, 5.41. Found: C, 77.50; H, 5.33.

5-Methyl-6-ethoxy-1,2,3,4,4aα,5,8,8aα-octahydronaphthalene-1,4-dione (XIII).—Raney nickel (1.5 tsp. of the benzene-washed preparation, which had been allowed to stand under ethyl acetate for six days) was added to a solution of 72.0 g. of 5-methyl-6-ethoxy-1,4,4aα,5,8,8aα-hexahydronaphthalene-1,4-dione in 550 cc. of benzene. The solution was shaken under 40 p.s.i. of hydrogen for one hour, at which time the addition of hydrogen had reached 98% of theory and the reaction had nearly stopped. The catalyst was removed by filtration, the benzene solution concentrated to 150 cc. and the crystalline product filtered and washed with 9:1 petroleum ether–ether. The mother liquors were concentrated nearly to dryness *in vacuo* and additional product was separated by crystallization from cold ether; total yield, 67.0 g., m.p. 118–122°. For analysis a sample was recrystallized from ether; m.p. 120–122°.

Anal. Calcd. for $C_{13}H_{18}O_3$: C, 70.22; H, 8.17. Found: C, 70.04; H, 8.41.

5-Methylperhydro-(4aα,8aα)-phenanthrene-1,4,6-trione.—A sample (100 mg.) of 5-methyl-6-ethoxy-1,2,3,4,4aα,5,-8,8aα-octahydronaphthalene-1,4-dione was dissolved in 1.0 cc. of 50% aqueous acetic acid. The solvents were immediately removed *in vacuo* at room temperature and the residue crystallized from ethyl acetate; m.p. 146–148°.

Anal. Calcd. for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 68.29; H, 7.51.

5-Methyl-6-ethoxy-1,2,3,4,4a,5,8,8a-octahydronaphthalene-1,4-dione. (trans-isomers).—A solution of 215 mg. of 5-methyl-6-ethoxy-1,2,3,4,4aα,5,8,8aα-octahydronaphthalene-1,4-dione (m.p. 118–122°) in 15 cc. of benzene was passed through a column of 25 g. of (alkaline) alumina. An additional 200 cc. of benzene was passed through the column, the eluates collected and evaporated to dryness *in vacuo*. The crude crystalline residue (201 mg.) was separated by fractional crystallization from Skellysolve C and from ethanol into two major components, m.p. 138–139° and m.p. 74.5–76°.

Anal. Found (isomer of m.p. 138–139°): C, 70.13; H, 8.01. (Isomer of m.p. 74.5–76°): C, 69.91; H, 7.75.

5-Methyl-6-ethoxy-1,2,3,4,4aα,5,8,8aα-octahydronaphthalene-1β,4β-diol (XIV).—To a solution of 2.5 g. of lithium aluminum hydride in 100 cc. of absolute tetrahydrofuran was added 4.8 g. of 5-methyl-6-ethoxy-1,2,3,4,4aα,5,8,8aα-octahydronaphthalene-1,4-dione in 50 cc. of the same solvent. The suspension was stirred at room temperature overnight, excess lithium aluminum hydride destroyed by dropwise addition of 5 cc. of water with stirring, and inorganic salts then separated by filtration through Super-cel.

The filtrate was concentrated *in vacuo* at a maximum temperature of 20° and the residue crystallized from absolute ether; yield: 3.9 g.; m.p. 115–120°. The dihydroxy enol ether was extremely sensitive to acids and to moisture. Recrystallization from solvents not completely free of either lowered the melting point to *ca.* 105°.

For analysis a sample was recrystallized from acetonitrile; m.p. 115–120°.

Anal. Calcd. for $C_{13}H_{22}O_3$: C, 68.98; H, 9.81. Found: C, 68.98; H, 9.98.

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

Approaches to Total Synthesis of Adrenal Steroids. II. 2,5- and 3,5-Dicarbomethoxy-5-methylcyclohexene-1,4-dione as Dienophiles

BY ROGER E. BEYLER AND LEWIS H. SARETT

2,6-Dicarbomethoxy-2-methylcyclohexane-1,4-dione (VI) was synthesized from dimethyl 2-furfurylidenemalonate (I) *via* dimethyl α-carbomethoxy-α-methyl-γ-ethylenedioxypimelate (IV). 2,5-Dicarbomethoxy-2-methylcyclohexane-1,4-dione (IX) was obtained by partial methylation of dimethyl succinosuccinate. Both dicarbomethoxymethylcyclohexanedione isomers yielded the corresponding cyclohexenediones (VII) and (X) by bromination and dehydrobromination and these reacted readily with 3-ethoxy-1,3-pentadiene.

Cyclic 1,4-diketones containing an intercurrent double bond arise from addition of dienes to 1,4-benzoquinones and like the latter may themselves function as dienophiles, though more weakly.[1] The potential usefulness of the substituted monocyclic cyclohexene-1,4-diones in a synthetic approach such as that sketched in the introduction to this series of papers is evident. Particular members of this class which appeared to hold both a practical and a didactic interest are the isomeric esters, 2,5- (X) and 3,5-dicarbomethoxy-5-methylcyclohexene-1,4-dione (VII). Each of these compounds has been synthesized and its reactions with certain 1,3-dienes, particularly 3-ethoxy-1,3-pentadiene,[2] investigated.

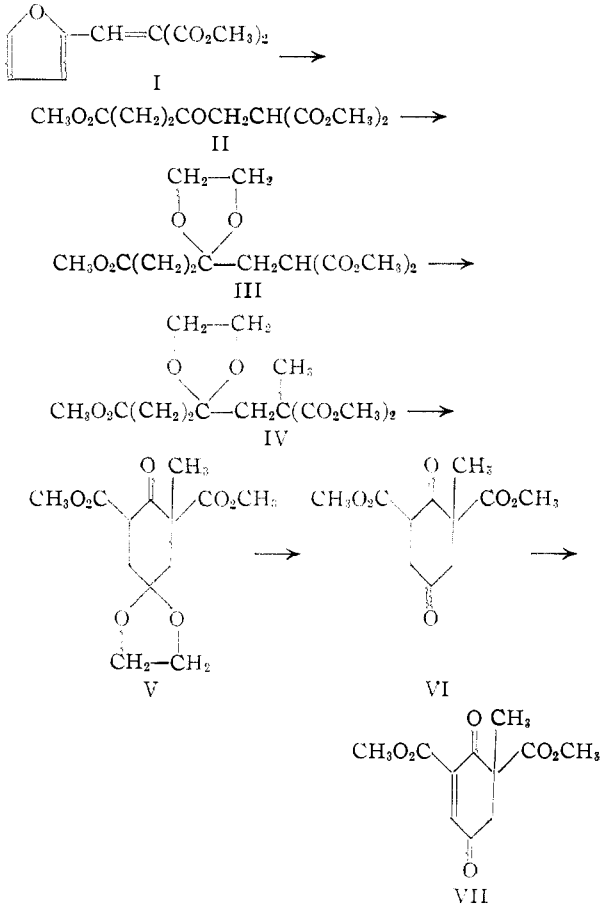
A procedure based upon the furacrylic acid rearrangement[3] was employed for the synthesis of 2,6-dicarbomethoxy-2-methylcyclohexane-1,4-dione (VI). Dimethyl 2-furfurylidenemalonate (I) with methanolic hydrogen chloride yielded 50% of dimethyl α-carbomethoxy-γ-ketopimelate (II) as a

(1) See, for example, K. Alder and G. Stein, *Ann.*, **501**, 247 (1933).

(2) See Part I, THIS JOURNAL, **74**, 1393 (1952).

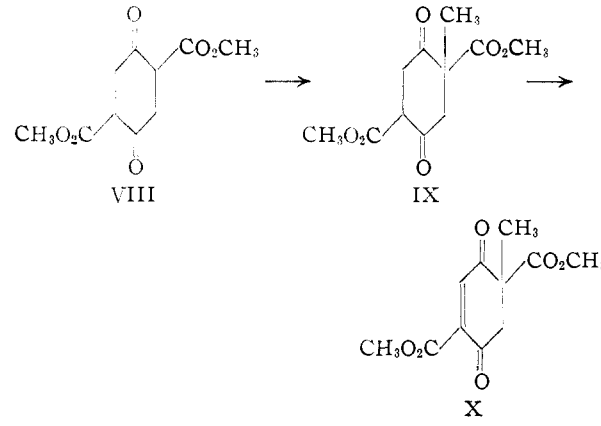
(3) W. Marckwald, *Ber.*, **20**, 2811 (1887).

viscous oil which crystallized after distillation. Reaction of this γ-keto ester with ethylene glycol afforded dimethyl α-carbomethoxy-γ-ethylenedioxypimelate (III), which could be methylated with methyl iodide in the presence of sodium methoxide. Cyclization of the resulting dimethyl α-carbomethoxy-α-methyl-γ-ethylenedioxypimelate (IV) with sodium hydride in ether yielded a single crystalline isomer of 2,6-dicarbomethoxy-2-methyl-4-ethylenedioxycyclohexanone (V). Regeneration of the protected ketonic function by treatment with dilute sulfuric acid gave the corresponding 2,6-dicarbomethoxy-2-methylcyclohexane-1,4-dione (VI). Dehydrogenation to the desired 3,5-dicarbomethoxy-5-methylcyclohexene-1,4-dione (VII) was accomplished by bromination in pyridine solution, the reaction being accompanied by spontaneous loss of hydrogen bromide from the monobrominated intermediate.

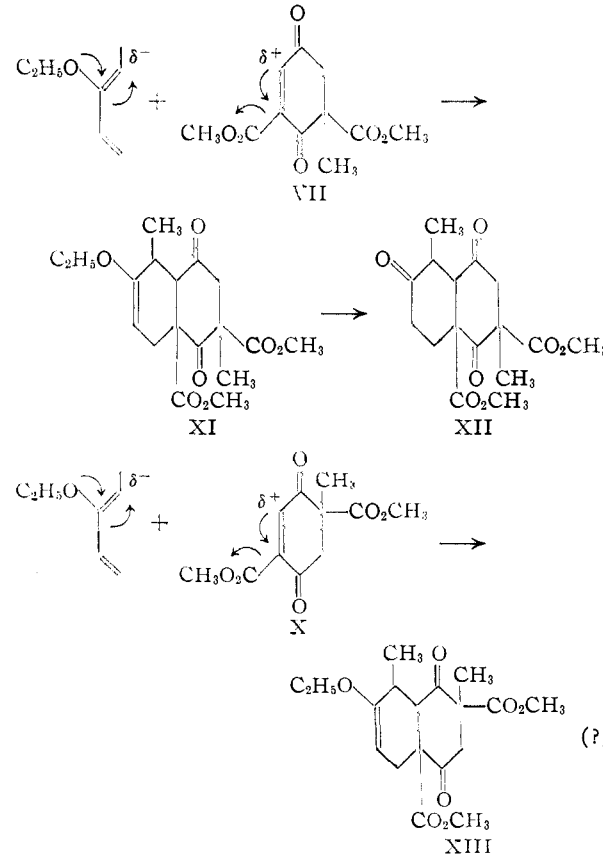


A suitable starting material for the preparation of the isomeric 2,5-dicarbomethoxy-5-methylcyclohexene-1,4-dione (X) was 2,5-dicarbomethoxycyclohexane-1,4-dione (dimethyl succinosuccinate) (VIII),[4] the partial alkylation of which (as the ethyl ester) has been mentioned in the older literature.[5]

The monomethylation of VIII was by no means a selective reaction, owing largely to the extreme insolubility of its sodium or potassium salts in solvents suitable for methylations. The separation of 2,5-dicarbomethoxy-2-methylcyclohexane-1,4-dione (IX) from dimethylated material and from starting material was easily accomplished, however, by fractional crystallization of the enolic portion of the crude methylation product. Bromination and dehydrobromination served satisfactorily to introduce the double bond.



Both VII and X gave brightly colored decomposition products on acid-washed alumina and showed an anticipated instability toward aqueous alkali. They were relatively stable toward dilute mineral acids and could be stored for an indefinite period at 0° without decomposition. Their reactivity as dienophiles was of the same order of magnitude as that of benzoquinone. The 3,5-dicarbomethoxy isomer (VII) yielded crystalline adducts[6] with cyclopentadiene and with 3-ethoxy-1,3-pentadiene. Mild hydrolysis of the latter



(4) H. Ebert, *Ann.*, **229**, 45 (1885).
(5) A. Baeyer, *Ber.*, **26**, 232 (1893).

adduct (XI) gave a 2,8a-dicarbomethoxy-2,5-dimethylperhydronaphthalene-1,4,6-trione (XII).[6] The addition of X to 2,3-dimethylbutadiene proceeded smoothly at room temperature to give a crystalline adduct.[6] With 3-ethoxy-1,3-pentadiene addition occurred rapidly but the product could not be obtained crystalline.

Consideration of the polar effects which are operative in the Diels–Alder reaction between unsymmetrical components leads to the prediction that the addition of 3-ethoxy-1,3-pentadiene to VII and X should proceed predominantly in the directions shown.[7] This prediction was verified for the first case with the crystalline adduct XII, which could be hydrolyzed and decarboxylated with hot 5 *N* sulfuric acid to the known 2,5-dimethylperhydronaphthalene-1,4,6-trione. In the case of X, the failure to obtain a crystalline adduct XIII (or isomer) or crystalline hydrolysis products from the oily adduct leaves the structure of the latter in doubt.

Experimental[8]

Dimethyl 2-Furfurylidenemalonate (I).—A mixture of 165 g. of dimethyl malonate, 130 g. of freshly distilled furfural, 5.6 cc. of piperidine, 5.7 cc. of acetic acid[9] and 100 cc. of benzene was refluxed with continuous water collection in a Bidwell–Sterling apparatus[10] for 16 hours; total water: 25 cc. (theoretical, 22.5 cc.). The resulting dark brown reaction mixture was washed with 200 cc. of 5% aqueous sodium bicarbonate, which was back-extracted with two portions of benzene. The combined and dried benzene extracts were concentrated and the residue fractionally distilled. The product (245 g.), b.p. 103–115° (0.3 mm.), was crystallized from cold ether–petroleum ether giving 237 g. (90%) of dimethyl 2-furfurylidenemalonate (I) in two crops, m.p. 43–44° and 42–43°. An analytical sample was prepared by recrystallization from cold methanol, m.p. 43.5–44°.

Anal. Calcd. for $C_{10}H_{10}O_5$: C, 57.14; H, 4.80. Found: C, 57.06; H, 4.76.

In one experiment in which the dimethyl malonate was used in excess, a *bis*-condensation product, m.p. 69°, was isolated.

Anal. Calcd. for $C_{15}H_{18}O_9$: C, 52.63; H, 5.30. Found: C, 52.76; H, 5.57.

Dimethyl α-Carbomethoxy-γ-ketopimelate (II).—A solution of 83 g. of dimethyl 2-furfurylidenemalonate in 300 cc. of methanol was saturated with dry hydrogen chloride. After standing at room temperature for 11 days the methanol and hydrogen chloride were largely removed *in vacuo*, and the dark brown residue was dissolved in 200 cc. of chloroform. The chloroform solution was washed with concentrated aqueous sodium chloride and aqueous sodium bicarbonate, and the solvent was distilled, leaving 81.7 g. of residue. Upon fractional distillation of this residue a major fraction, 66.8 g., was collected, boiling at 124–136° (0.25 mm.). Crystallization of this fraction from ether–petroleum ether afforded 54.7 g. (53%) of dimethyl α-carbomethoxy-γ-ketopimelate (II) in two crops. After several recrystallizations from ether–petroleum ether a sample melted at 34.5–35.0°.

Anal. Calcd. for $C_{11}H_{16}O_7$: C, 50.76; H, 6.20. Found: C, 51.11; H, 6.41.

(6) Configurations at C_{4a} and C_5 in these compounds are uncertain, since chromatographic purification was required in their isolation.

(7) For examples in which polar effects have influenced the course of Diels–Alder additions, see Kloetzel (Chapt. 1) and Holmes (Chapt. 2) of "Organic Reactions," Vol. IV, John Wiley and Sons, Inc., New York, N. Y., 1948.

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

(9) A. C. Cope, C. M. Hofmann, C. Wyckoff and E. Hardenbergh, THIS JOURNAL, **63**, 3452 (1941).

(10) G. L. Bidwell and W. F. Sterling, *Ind. Eng. Chem.*, **17** [2], 147 (1925).

The forerun from the distillation and the non-crystalline residue from the mother liquors could be recycled in subsequent runs and represented a recovery of 16.5% of starting material.

Dimethyl α-Carbomethoxy-γ-ethylenedioxypimelate (III).—A solution of 52.0 g. of the ketopimelate (II), 13.6 g. of ethylene glycol, and 100 mg. of *p*-toluenesulfonic acid in 100 cc. of benzene was refluxed with continuous separation of water in the Bidwell–Sterling apparatus. After 40 hours, during which 250 mg. of additional *p*-toluenesulfonic acid was added, the final volume of the aqueous layer amounted to 140%. The cooled benzene reaction mixture now was washed with aqueous sodium carbonate and water. After drying and solvent removal 56.7 g. (93%) of dimethyl α-carbomethoxy-γ-ethylenedioxypimelate (III) was obtained as a colorless oil. This oil could not be distilled without partial decomposition, and was used without further purification for the subsequent methylation step. A small sample was distilled in a molecular still at 0.1 mm.; $n^{25}D$ 1.4513.

Anal. Calcd. for $C_{13}H_{20}O_8$: C, 51.31; H, 6.63. Found: C, 51.32; H, 6.41.

Dimethyl α-Carbomethoxy-α-methyl-γ-ethylenedioxypimelate (IV).—A solution of sodium methoxide was prepared in a baked flask from 2.3 g. of sodium and 30 cc. of dry methanol. To this solution, cooled in an ice-bath, 27.5 g. of the above triester (III) in 70 cc. of dry methanol was added dropwise during 40 minutes with stirring. The amber solution of sodium salt was stirred for an additional two hours at 0–5°. Then 14.2 g. of methyl iodide was added and the reaction mixture was allowed to warm to room temperature. After standing for three and a half days, the solution was concentrated *in vacuo* at room temperature, the residue treated with water and ether, and the aqueous layer re-extracted several times with ether. The combined ether extracts were dried and distilled; fractionation of the residue, 25.3 g., gave 20.7 g. (75%) of dimethyl α-carbomethoxy-α-methyl-γ-ethylenedioxypimelate (IV), b.p 126–129° (0.1 mm.). An analytical sample was prepared by distillation; $n^{24}D$ 1.4543.

Anal. Calcd. for $C_{14}H_{22}O_8$: C, 52.83; H, 6.97. Found: C, 53.05; H, 6.70.

2,6-Dicarbomethoxy-2-methyl-4-ethylenedioxycyclohexanone (V).—A solution of 9.50 g. of dimethyl α-carbomethoxy-α-methyl-γ-ethylenedioxypimelate (IV) in 60 cc. of ether was added dropwise during 20 minutes to a suspension of 1.44 g. of sodium hydride in 50 cc. of ether with mechanical stirring. A few ceramic chips were added and the mixture was stirred at room temperature under nitrogen for 18 hours. The resulting suspension of yellow sodium salt was poured into a mixture of 25 cc. of 2.5 *N* hydrochloric acid and 75 cc. of ice-water. After separation, the aqueous layer was further extracted with ether. The combined ethereal solution was extracted portion-wise with 75 cc. of cold 5% aqueous potassium hydroxide, which was immediately acidified with ice-cold dilute hydrochloric acid. From the ethereal solution 1.7 g. of neutral fraction was obtained and could be recycled after distillation. The suspension of solid resulting from acidification of the alkaline solution was extracted into ether. The ether was washed with aqueous sodium bicarbonate, dried, and distilled, giving 4.1 g. (48%) of crystalline 2,6-dicarbomethoxy-2-methyl-4-ethylenedioxycyclohexanone (V). A sample after recrystallization from methanol melted at 104–106° and gave a violet color with ferric chloride solution.

Anal. Calcd. for $C_{13}H_{18}O_7$: C, 54.54; H, 6.34. Found: C, 54.26; H, 6.09.

One hundred milligrams of 2,6-dicarbomethoxy-2-methyl-4-ethyleuedioxycyclohexanone (V) in 1.0 cc. of 5 *N* sulfuric acid was heated for 5 hours on the steam-bath. The suspension of crystalline V changed to an oil which dissolved after about 2.5 hours. Saturation of the cooled solution with sodium sulfate and extraction with ether gave methylcyclohexane-1,4-dione, m.p. 46–47°. A mixed melting point with an authentic sample (*vide infra*) was not depressed.

2,6-Dicarbomethoxy-2-methylcyclohexane-1,4-dione (VI).—A solution of 11.25 g. of 2,6-dicarbomethoxy-2-methyl-4-ethylenedioxycyclohexanone (V), m.p. 100–106°, in 50 cc. of methanol and 50 cc. of 1 *N* sulfuric acid was refluxed for 65 minutes on the steam-bath. The methanol was re-

moved *in vacuo* (bath not over 40°) and the resulting oily product extracted with ether. The washed and dried ethereal extract was concentrated to give 9.40 g. of crude crystalline product. Recrystallization from Skellysolve C–benzene yielded 7.75 g. (81%) of 2,6-dicarbomethoxy-2-methylcyclohexane-1,4-dione (VI), m.p. 75–80°. Recrystallization from benzene–petroleum ether gave bipyramidal crystals, m.p. 81–83°.

Anal. Calcd. for $C_{11}H_{14}O_6$: C, 54.54; H, 5.83. Found: C, 54.36; H, 5.66.

3,5-Dicarbomethoxy-5-methylcyclohexene-1,4-dione (VII).—A solution of 6.09 g. of 2,6-dicarbomethoxy-2-methylcyclohexane-1,4-dione (VI), dissolved in 100 cc. of a 0.5 molar solution of pyridine in chloroform, was cooled in an ice-bath. To this solution was added 50 cc. of ice cold 0.5 molar bromine in chloroform, and the resulting light yellow solution was allowed to stand at room temperature for 50 minutes. An additional 100 cc. of 0.5 molar pyridine in chloroform was added and the reaction kept 20 minutes longer at room temperature. The reaction mixture was washed with dilute hydrochloric acid, dried and concentrated, giving 6.08 g. of crude crystalline residue which after recrystallization from ether yielded 4.09 g. of light yellow prisms, m.p. 75–77°. Several recrystallizations from methanol gave pale yellow prisms, m.p. 75.0–75.5°, suitable for analysis.

Anal. Calcd. for $C_{11}H_{12}O_6$: C, 55.00; H, 5.04. Found: C, 54.77; H, 4.89.

This material sublimed very readily *in vacuo*. It showed an absorption maximum at 225 mμ, E_{mol} 10,800. A solution of the compound in aqueous ethanolic sodium hydroxide darkened very rapidly.

Diels–Alder Reactions of 3,5-Dicarbomethoxy-5-methylcyclohexene-1,4-dione (VII). A. With Cyclopentadiene.—Equal weights, 130 mg., of VII and freshly prepared cyclopentadiene were mixed and placed in the ice-chest at 5°. After 5 hours all of the crystalline dienophile had dissolved in the diene. The mixture was kept at 5° an additional 17 hours, then most of the excess diene was removed *in vacuo*. After attempts to crystallize the residue, 156 mg., from petroleum ether and methanol failed, it was chromatographed over acid-washed alumina. Most of the material was eluted between 9:1 and 6:4 petroleum ether–ether. All the fractions were covered with petroleum ether (sparingly soluble) and allowed to evaporate slowly in the ice-chest. In this way 18 mg. of crystals was obtained in the 8:2 and 6:4 petroleum ether–ether fractions. After methanol recrystallization the prisms obtained melted at 110–111°.

Anal. Calcd. for $C_{16}H_{18}O_6$: C, 62.73; H, 5.93. Found: C, 62.59; H, 6.02.

B. With 3-Ethoxy-1,3-pentadiene.—A mixture of 240 mg. of the dienophile (VII) and 340 mg. of 3-ethoxy-1,3-pentadiene was placed in an ice-chest at 5°. At intervals the mixture was stirred until the dienophile had dissolved completely (6 hours required). The yellow color of the reaction mixture had disappeared after storage at 5° overnight and reaction was approximately complete. However, the mixture was kept in the ice-chest an additional three days. The entire reaction mixture was chromatographed over alkaline alumina (acid-washed alumina gave similar results). After the excess diene had been eluted with petroleum ether the adduct (285 mg. total) was eluted between 8:2 and 6:4 petroleum ether–ether. A number of small fractions were collected, and upon slow evaporation from cold petroleum ether crude crystals, totalling 131 mg., formed in three of the early 8:2 fractions. One recrystallization from petroleum ether gave 82 mg. of crystalline adduct (XI), m.p. 95–108°. After several recrystallizations from methanol, rosettes of prisms, m.p. 111–112°, were obtained.

Anal. Calcd. for $C_{18}H_{24}O_7$: C, 61.35; H, 6.86. Found: C, 61.34; H, 6.85.

In subsequent Diels–Alder experiments, seeding the crude reaction mixture (after removal of excess diene) with the crystalline adduct, failed to induce crystallization. Crystals could always be obtained after chromatography and were also isolated in low yield after a brief treatment with sodium methoxide. It seems probable that the direct adduct which should have a *cis*-ring fusion was partially converted to the *trans*-system by contact with alumina.

2,8a-Dicarbomethoxy-2,5-dimethylperhydronaphthalene-1,4,6-trione (XII).—To 25 mg. of the adduct (XI) were added 1.0 cc. of methanol and 1.0 cc. of 1 *N* hydrochloric acid. After standing at room temperature for 30 minutes the methanol was distilled *in vacuo* and the resulting aqueous solution extracted with ether. The residue obtained after ether evaporation yielded 23 mg. of crystals upon standing under petroleum ether. Several recrystallizations from methanol gave the trione (XII) as needles, m.p. 122–123°.

Anal. Calcd. for $C_{16}H_{20}O_7$: C, 59.25; H, 6.22. Found: C, 59.31; H, 6.48.

2,5-Dimethylperhydronaphthalene-1,4,6-trione.—One hundred milligrams of adduct (XI) was refluxed in 1.0 cc. of 5 *N* sulfuric acid for 20 hours. The reaction mixture was saturated with sodium sulfate and extracted with chloroform. The solvent was dried and distilled, giving 77 mg. of an amber oil. Chromatography yielded 49 mg. of crystals in the fractions from petroleum ether to petroleum ether–ether (7:3). After recrystallization from ether and methylcyclohexane needles, m.p. 122–126°, were obtained. A mixed melting point with an authentic sample of 2,5-dimethylperhydronaphthalene-1,4,6-trione[2] of the same melting point did not show a depression.

2,5-Dicarbomethoxy-2-methylcyclohexane-1,4-dione (IX).—A solution of potassium methoxide was prepared by gradual addition of 96.0 g. (3.0 moles) of methanol to 33.0 g. (0.83 mole) of potassium suspended in 700 cc. of refluxing benzene. The mixture was rendered homogenous by the addition of 250 cc. of absolute tetrahydrofuran after the potassium had been consumed. The resulting solution was cooled to room temperature and added to 188.5 g. (0.83 mole) of dimethyl succinosuccinate dissolved in 1500 cc. of warm benzene The mixture was stirred and heated under reflux for eight hours, then filtered from the bulky precipitate of potassium salts. Concentration of the benzene filtrate gave 63 g. of unreacted ester. The precipitate of potassium salts was transferred, still damp with benzene, to a flask containing 500 cc. of acetone and 100 cc. of methyl iodide. After stirring and refluxing for two hours the potassium salts had largely dissolved and the excess solvents were removed *in vacuo*. The residue was treated with water and extracted with a mixture of ether and benzene. The organic layer was washed again with water, cooled to 0° and extracted with four 50-cc. portions of cold 1 *N* aqueous potassium hydroxide. The aqueous alkaline extracts were immediately acidified with dilute hydrochloric acid and extracted with ether–benzene. The washed extract was evaporated to dryness (residue 54.0 g.) and, after separation of an additional 8.0 g. of starting ester by crystallization from ether, was distilled at 118–122° (0.5 mm.). The distillate (37.6 g.) deposited an additional 1.5 g. of starting material from a cold ethereal solution. The mother liquors were concentrated to dryness and crystallized from cold petroleum ether, giving 28.0 g. of colorless prisms. Recrystallization from cold methanol yielded pure 2,5-dicarbomethoxy-2-methylcyclohexane-1,4-dione (IX), m.p. 66–67°.

Anal. Calcd. for $C_{11}H_{14}O_6$: C, 54.54; H, 5.83. Found: C, 54.72; H, 5.72.

A sample of IX upon refluxing overnight with 0.03 *N* aqueous sulfuric acid, concentration of the solution to a small volume *in vacuo*, and chromatographic purification of the ethereal extract yielded 40% of methylcyclohexane-1,4-dione, m.p. 47.5–48.5°.

Anal. Calcd. for $C_7H_{10}O_2$: C, 66.54; H, 7.98. Found: C, 66.47; H, 8.05.

2,5-Dicarbomethoxy-5-methylcyclohexene-1,4-dione (X).—A solution of 1.0 g. of 2,5-dicarbomethoxy-2-methylcyclohexane-1,4-dione (IX) in 10 cc. of chloroform was cooled to 0° and treated with a solution of 660 mg. of bromine in 10 cc. of cold chloroform. The mixture was then warmed to room temperature over a two-minute period during which the bromine was rapidly consumed. The chloroform solution was quickly washed with dilute sodium bicarbonate solution and concentrated *in vacuo* at 10°. The residue was dissolved in a mixture of 5 cc. of benzene and 3 cc. of pyridine. After standing at room temperature for 10 minutes, the mixture was diluted with more benzene, washed with dilute sulfuric acid and with water, then concentrated to dryness *in vacuo*. The residue crystallized from cold methanol giving 600 mg. of 2,5-dicarbomethoxy-5-methylcyclohexene-1,4-dione (X), as pale yellow plates, m.p. 42.5–43.0°; λ_{max} 227 mμ, E_{mol} 7,900.

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.

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

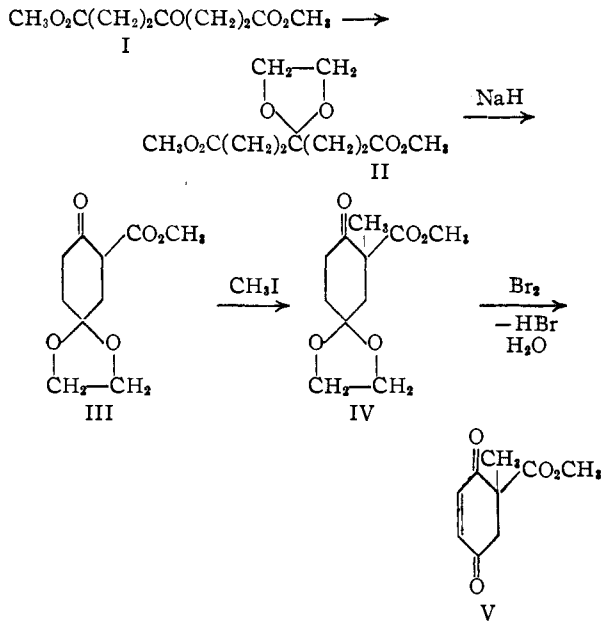
BY ROBERT M. LUKES, GEORGE I. POOS AND LEWIS H. SARETT

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).