[CONTRIBUTION FROM THE MCPHERSON CHEMICAL LABORATORY, THE OHIO STATE UNIVERSITY]

SYNTHESIS AND REACTIONS OF METHYL 2-METHYL-3-OXO-1-CYCLOPENTENECARBOXYLATE

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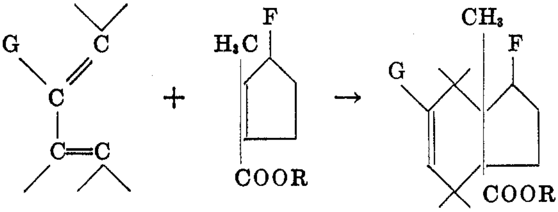
Received March 22, 1954

One possible route to a synthesis of steroid compounds involves a Diels-Alder reaction between a 2-methyl-1-cyclopentenecarboxylate containing some oxygenated function (F) at position 3 (I), and a suitable substituted diene (II) (1). The adduct (III) would be expected to have the methyl and carboxylate functions in the *cis* position but on removal of the carboxylate group it was thought that the correct *trans* position for substituents might be attained. If the group G were oxygenated, *e.g.* a methoxy group, acid hydrolysis would lead to a ketone in the 11 position (steroid nucleus). In this paper are described the synthesis and reactions of 2-methyl-3-oxo-1-cyclopentenecarboxylic acid, IXa and methyl ester, IXb. (See chart.)



II I III

The cyanoester (IV) (2) was converted to V by cyanoethylation (3) in almost quantitative yield. Acid hydrolysis of V followed by decarboxylation and esterification afforded the triester (VI) (4) in 93% over-all yield from IV. Cyclization to VII using sodium hydride followed by hydrolysis, decarboxylation, and esterification yielded the ketoester (VIIIc) in 85% over-all yield (5) from VI. In one experiment, the ester VIIIc was obtained in 92% yield from VII by preferential hydrolysis of the carbethoxy group adjacent to the ketonic function.

Bromination of VIIIb or VIIIc followed by dehydrobromination afforded a difficultly separable mixture. After hydrolysis, the crystalline acid (IXa) was isolated by crystallization but the yield could never be raised above 50% in the case of the ethyl ester or 62% for the methyl ester in spite of many attempts at improvement. Fair amounts (30–22% respectively) of starting acid (VIIIa) were recovered. In the bromination, one equivalent of bromine was readily absorbed, but in the reaction mixture considerable quantities of unbrominated ester could be recovered. Possibly the monobromoketoester formed readily and disproportionated (6) to yield dibromoester plus unbrominated ester but no fraction corresponding to a dibromoester was found. The unsaturated ketoacid (IXa) has been obtained previously from the degradation of picrotoxin and its structure was proved by ozonization (7). On comparison by means of mixture

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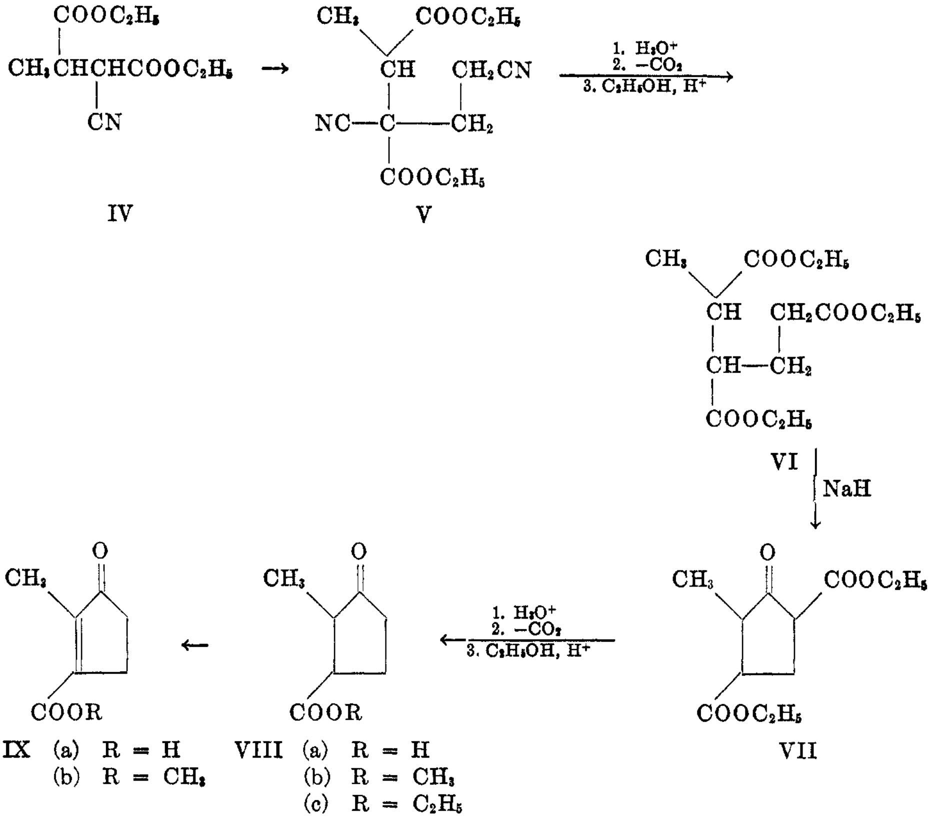
[1] Taken from the Ph.D. thesis of J. L. McPherson, Ohio State University, 1953.

m.p. and infrared absorption spectra, our acid was shown to be identical to that isolated from picrotoxin. We thank Drs. E. Schlittler and M. Sutter for these comparisons.



IX (a) R = H
(b) R = CH_3

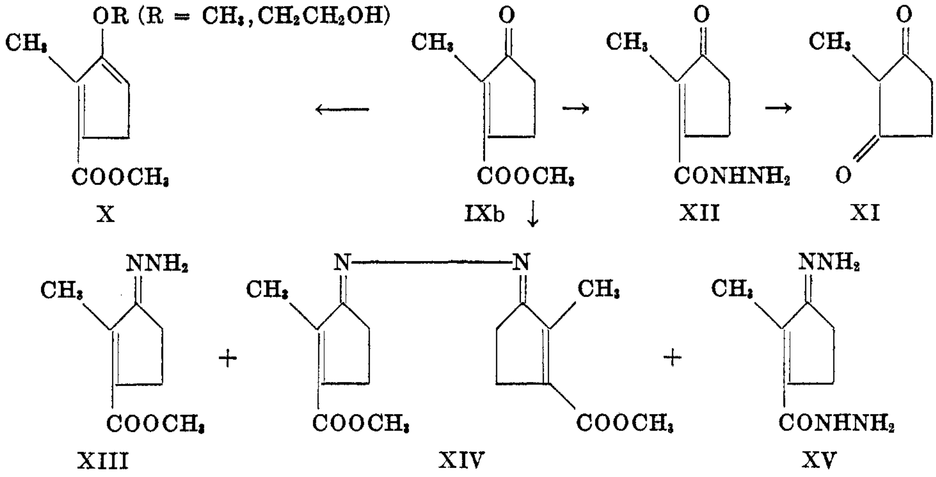
VIII (a) R = H
(b) R = CH_3
(c) R = C_2H_5

In spite of numerous attempts to effect a Diels-Alder condensation between the methyl ester (IXb) and butadiene, 2,3-dimethyl-1,3-butadiene, and 2-methoxy-1,3-butadiene no trace of adduct was found. For this reason we are abandoning this approach to steroid synthesis.

Attempts were made to convert the ketone group in the methyl ester of IXb to a ketal, using methyl and ethyl orthoformates and ethylene glycol. Only enol ethers (X) were formed. The double bond locations in these compounds are assumed but not established. It is noteworthy that while the ester (IXb) yielded only enol ethers (X) on attempted ketalization, the corresponding saturated ester (VIIIb) yielded ketals in high yield.

We were unsuccessful in attempting to prepare ethynyl carbinols from VIIIb or c and IXb.

In the hope of converting IXb into 2-methyl-1,3-cyclopentanedione (8) (XI), needed for other work, IXb was treated with hydrazine under various conditions. However, it was not possible to obtain the desired acid hydrazide (XII). Instead mixtures containing mainly compounds XIII, XIV, and XV were always obtained.



EXPERIMENTAL

Diethyl 2-cyano-3-methylbutanedioate (IV) (2, 5). To a stirred solution of 3 equivalents of sodium ethoxide in 1000 cc. of absolute ethanol was added 341.6 g. (3.02 moles) of ethyl cyanoacetate at a fast drop rate. Cooling was necessary near the end of the addition. With intermittent cooling to keep the temperature just below reflux, 543 g. (2.99 moles) of ethyl α-bromopropionate, b.p. 62–64° at 14 mm., was added at a fast drop rate. The mixture was then refluxed for 1 hour and allowed to stand for 1 hour. There was obtained 466 g. (73%) of IV, b.p. 156° at 17 mm. [This is the average of 6 experiments for which the best yield was 78%.]

Diethyl 2-cyano-2-(2-cyanoethyl)-3-methylbutanedioate (V) (3). To a solution formed by adding a pea-sized piece of sodium to 100 cc. of absolute ethanol was added 42.6 g. (0.2 mole) of IV. This was followed by the portion-wise addition of 12.2 g. (0.2 mole plus 15% excess) of acrylonitrile. The temperature was maintained between 26° and 34° by cooling. After standing for 1.5 hours the sodium ethoxide was neutralized with acetic acid. Distillation afforded 50 g. (94%) of V, b.p. 176–179° at 2–3 mm.

Triethyl 4-methyl-1,3,4-pentanetricarboxylate (VI) (4). In the preparation of VI it was found more convenient to go directly from IV to VI without isolation of the intermediate nitrile V or the tricarboxylic acid corresponding to VI. A solution of 853 g. (4 moles) of IV in 1000 cc. of absolute ethanol containing about 0.5 g. of sodium was treated with 244 g. (4.6 moles, 15% excess) of acrylonitrile at 26–34° as described. Stirring was continued for 2 hours and acetic acid was used to neutralize the sodium ethoxide. After standing overnight 1800 cc. of alcohol was removed by distillation. The flask was cooled in an ice-bath and 2650 cc. of conc'd hydrochloric acid was added in 500-cc. portions over a period of 1 hour. With the bottom of the flask immersed in an ice-bath the temperature rose to 60°. After standing at room temperature for 2 hours the mixture was heated to 70–80°. At this point the heating bath was withdrawn and the reaction proceeded without further heating for 2 to 3 hours. A temperature just below the reflux temperature was maintained till the evolution of carbon dioxide ceased (48–72 hours). Using an oil-bath at 65–75° the mixture was vacuum-distilled nearly to dryness using a water aspirator. After the addition of 1000 cc. of benzene distillation at atmospheric pressure was continued until the temperature of the distillate reached 80°. The previously recovered 1800 cc. of ethanol was added and the mixture was saturated with hydrogen chloride gas. The esterification using the azeotropic method of water removal required 8–10 days for completion. After removal of excess alcohol and benzene and neutralization of the acid, there was obtained by distillation 1072 g. (93% over-all yield) of VI, b.p. 150–153° at 3 mm. (4). [This is an average of 4 experiments for which the best yield was 95%.]

Diethyl 2-methyl-3-oxo-1,4-cyclopentanedicarboxylate (VII). To 97.2 g. (4 moles plus 1.2% excess) of sodium hydride was added 2400 cc. of dry ether containing 5 cc. of absolute ethanol (conduct hydrogen evolved to hood). At ice-bath temperature 1153.3 g. (4 moles) of VI was added with stirring over a period of 20 hours (4). [In experiments in which the ester VI was added at such a rate as to maintain ether reflux the yields were 20–30% lower.] The product was worked up by adding 1000 cc. of 6 *N* hydrochloric acid and separating the ether layer. After washing with 10% sodium carbonate solution followed by distillation there was obtained 892 g. (92.1%) of VII, b.p. 153–156° at 6–7 mm. (5).

Ethyl 2-methyl-3-oxocyclopentanecarboxylate (VIIIc). To 780 g. (3.2 moles) of VII was added 2000 cc. (approximately 4 times the volume of ester) of 10% hydrochloric acid. After refluxing overnight on a steam-bath the mixture was distilled until the temperature of the distillate reached 95°. After cooling, the solution was saturated with ammonium sulfate and ether extracted. Esterification of the material obtained from the ether extract afforded 500 g. (92.5%) of VIIIc, b.p. 124–125° at 16 mm., n_D^{25} 1.4489.

Anal. Calc'd for $C_9H_{14}O_3$: C, 63.5; H, 8.2.

Found:[2] C, 63.5; H, 8.0.

In one experiment in which the alcohol resulting from hydrolysis of the 4-carbethoxy group of VII was allowed to distill during the first part of the reaction, the ester VIIIc was obtained in 92% yield. In other words, with care, the ester group in position 4 can be preferentially hydrolyzed and the acid decarboxylated before the ester group in position 1 is hydrolyzed.

2-Methyl-3-oxo-1-cyclopentenecarboxylic acid (IXa). To a solution of 524 g. (3.08 moles) of VIIIc and 2300 cc. of dry redistilled carbon tetrachloride kept at 0° was added with stirring 491.2 g. (3.07 moles) of bromine in 767 cc. of carbon tetrachloride at a fast drop rate. The bromine color disappeared immediately; however, there was very little noticeable hydrogen bromide evolution until approximately half of the bromine had been added. It was found convenient at this point to connect a water aspirator and remove as much of the hydrogen bromide as possible while keeping the reaction flask cooled in an ice-bath. Then 435 cc. of triethylamine was added without delay (otherwise much polymerization) and after refluxing the mixture for 2 hours the salt formed was filtered. The excess triethylamine and carbon tetrachloride were removed by distillation, and the residue was washed with 10% sodium carbonate and dried over sodium sulfate. The material was distilled first from a Claisen flask at a low pressure and then through a packed column at 16 mm. Each fraction was found to be a mixture of the saturated and unsaturated esters corresponding to the acids VIII and IX, ranging from 30 to 85% unsaturated ester as found by saponification of the esters and separation of the acids by recrystallization.

The combined distillate was treated with 1240 cc. of 10% sodium hydroxide and stirred vigorously. The temperature rose to 65° and after 1 hour of stirring only a very small amount of insoluble top layer remained. After removal of the insoluble material with ether, the liquid was saturated with ammonium sulfate and concentrated hydrochloric acid was added until no further organic precipitate was formed. The precipitated acid was treated with decolorizing carbon (Darco G-60) and recrystallized from hot water to yield 215 g. (50% yield from VIIIc) of IXa, m.p. 175–175.5°, *semicarbazone*, m.p. 251–276° w. decomp., *2,4-dinitrophenylhydrazone*, m.p. *ca.* 205° (9). [When the starting ester was VIIIb, the yield of unsaturated acid (IXa) was 62% and the recovered VIIIa amounted to 22%.]

Anal. Calc'd for $C_7H_8O_3$: C, 60.0; H, 5.8.

Found: C, 59.8; H, 5.7.

The aqueous filtrate was concentrated, saturated with ammonium sulfate, and ether ex-

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[2] All analyses by the Clark Laboratory, Urbana, Illinois.

tracted. This white crystalline acid was recrystallized from petroleum ether (b.p. 65–110°) to give 130 g. (30%) of 2-methyl-3-oxo-cyclopentanecarboxylic acid (VIIIa), m.p. 94° (4).

Anal. Calc'd for $C_7H_{10}O_3$: C, 59.1; H, 7.1.

Found: C, 59.6; H, 7.1.

2-Methyl-3-oxo-1-cyclopentenecarboxylic acid (IXa) (*alternate procedure*). To a solution of 170 g. (1 mole) of VIIIc in 400 cc. of freshly distilled carbon tetrachloride was added with stirring a solution of 135 g. (1 mole) of redistilled sulfuryl chloride, b.p. 69–70°, in 150 cc. of carbon tetrachloride at such a rate as to maintain a pot temperature of 55°. After refluxing for 1.5 hours the mixture was cooled and 101 g. (1 mole) of triethylamine was added. After stirring in the cold for 1 hour the mixture was refluxed for 1 hour. Filtration gave 136 g. (theoretical 137.5 g.) of triethylamine hydrochloride. A rapid distillation from a Claisen flask gave 137 g. of material boiling in the range 76–88° at 1 mm. This was saponified and upon rectification gave 82 g. (59%) of IXa, m.p. 174.5°, and 40 g. (28%) of VIIIa as described above.

Methyl 2-methyl-3-oxo-1-cyclopentenecarboxylate (IXb). This ester, b.p. 84° at 2 mm., 126.5–127.0° at 16 mm., n_D^{26} 1.4954, was prepared in 95% yield by treatment of IXa with an ethereal solution of diazomethane.

Anal. Calc'd for $C_8H_{10}O_3$: C, 62.3; H, 6.4.

Found: C, 62.5; H, 6.4.

Reaction of methyl 2-methyl-3-oxo-1-cyclopentenecarboxylate (IXb) *with butadiene, 2,3-dimethyl-1,3-butadiene* (9), *and 2-methoxy-1,3-butadiene* (10). No adduct was found for the Diels-Alder reaction under a wide variety of conditions. The attempted reactions were run in sealed tubes with variation of temperature from room temperature to 200° for periods of time varying from 10 hours to 55 hours. The ratio of diene to dienophile was varied from 0.1 to 10.0.

Reaction of methyl 2-methyl-3-oxo-1-cyclopentenecarboxylate (IXb), *with methyl orthoformate.* To a solution of 7.7 g. (0.05 mole) of IXb and 10.6 g. (0.10 mole) of freshly distilled trimethyl orthoformate, b.p. 99–100°, was added 8 g. of absolute methanol containing a trace of hydrogen chloride gas (if more than a trace is used the yield suffers). After standing overnight the mixture was poured over sodium carbonate, warmed, and filtered. Distillation afforded 7.5 g (89%) of the enol ether, methyl 3-methoxy-2-methyl-1,3-cyclopentadiene-1-carboxylate (X), b.p. 126° at 16 mm., m.p. 29°, n_D^{25} 1.5026.

Anal. Calc'd for $C_9H_{12}O_3$: C, 64.3; H, 7.2.

Found: C, 63.9; H, 7.3.

Reaction of methyl 2-methyl-3-oxo-1-cyclopentenecarboxylate (IXb) *with ethylene glycol.* To a solution of 7.73 g. (0.05 mole) of IXb and 3.41 g. (0.055 mole) of freshly distilled ethylene glycol was added 100 cc. of thiophene-free benzene and 1 g. of Dowex-50 (sulfonated polystyrene resin). The apparatus used was similar to the standard set up for acid esterification using a column equipped with a phase separating head for continuous removal of water. At the end of about 15 hours 1 cc. of water had been collected, and the ethylene glycol layer in the pot had disappeared. There was very little coloration. (When hydrogen chloride was used as a catalyst a dark brown color resulted and the yield was very low.) After filtration of the catalyst distillation afforded 8.3 g. (83%) of the enol ether, methyl 3-(2-hydroxyethoxy)-2-methyl-1,3-cyclopentadienecarboxylate (X), b.p. 133° at 16 mm., 93.5° at 2 mm., n_D^{25} 1.4895. This enol ether reacted with sodium to form hydrogen as contrasted to the unreactivity of the ethylene glycol cyclic ketal of the saturated ester.

Anal. Calc'd for $C_{10}H_{14}O_4$: C, 60.6; H, 7.1.

Found: C, 60.6; H, 6.8.

Reaction of ethyl 2-methyl-3-oxocyclopentanecarboxylate (VIIIc) *with triethyl orthoformate.* Using the same procedure as for the reaction of IXb except that *p*-toluenesulfonic acid was used in place of Dowex-50 there was obtained (81%) the ethylene acetal of VIIIc, b.p. 141–143° at 16 mm., n_D^{25} 1.4534.

Anal. Calc'd for $C_{11}H_{16}O_4$: C, 61.7; H, 8.4.

Found: C, 61.7; H, 8.4.

Reaction of methyl 2-methyl-3-oxo-1-cyclopentenecarboxylate (IXb) *to form ethynyl car-*

binols. Two methods (with variation of conditions) of ethynylation were tried without success: (a) sodium, liquid ammonia, and acetylene, (b) ethynylmagnesium bromide (11) and acetylene (under 1.5 atm. pressure). We were equally unsuccessful with the saturated ester, VIIIc.

Hydrazone of methyl 2-methyl-3-oxo-cyclopentenecarboxylate (XIII). To 3.85 g. (0.025 mole) of IX at 0° was added 0.88 g. (0.025 mole plus 10% excess) of anhydrous hydrazine and the mixture kept in a refrigerator overnight. The solid was collected and washed with absolute methanol. When this solid, 1 g., was shaken with 3000 cc. of cold benzene 0.4 g., m.p. 217–218° w. decomp., remained undissolved. This compound was the hydrazide-hydrazone, XV (see below). The benzene-soluble portion was chromatographed using a column 4 cm. x 30 cm. filled with 400 cc. of a mixture of pre-treated silicic acid-Celite 1.55: 1 (12), and prewashed with 250 cc. of petroleum ether (b.p. 65–110°) and 250 cc. of benzene. The column was developed with 1000 cc. of a solution containing 500 cc. of ether, 250 cc. of benzene, and 250 cc. of petroleum ether (b.p. 65–110°). The chromatographic column was extruded and streaked with 0.025% $KMnO_4$. Two bands were evident, a narrow 5 mm. band at the top of the column and the main 25 mm. band in the middle of the column. The two bands were eluted separately with ether. Upon evaporation of the ether the extract of the top 5-mm. band gave a very small amount of material which after crystallization from methanol melted at 153°. The material obtained from the main band on recrystallization from methanol yielded 0.4 g. of an ivory-colored material, m.p. 155–156°. Analysis indicated that this compound was XIII.

Anal. Calc'd for $C_8H_{12}N_2O_2$: C, 57.1; H, 7.2; N, 16.7.
Found: C, 57.2; H, 7.2; N, 16.7.

Azine of methyl 2-methyl-3-oxo-1-cyclopentenecarboxylate (XIV). A mixture of 7.7 g. (0.05 mole) of IXb, 1.76 g. (0.05 mole plus 10% excess) of anhydrous hydrazine, and 50 cc. of absolute methanol was refluxed 12 hours. A bright yellow solid weighing 6.6 g. was precipitated. Repeated recrystallizations of a small quantity of this crude material from methanol and Cellosolve[3] failed to give a pure compound.

A benzene solution of 0.5 g. of this material was chromatographed using the same procedure and quantities of wash and developer as were used in the chromatography of the hydrazone XIII. In the development of the column the yellow-colored band containing the main fraction of the material was collected in 6 fractions. Upon removal of the solvent these yielded 0.4 g. of a yellow crystalline material m.p. 193–193.5°, which on analysis indicated the azine (XIV).

Anal. Calc'd for $C_{16}H_{20}N_2O_4$: C, 63.1; H, 6.8; N, 9.2.
Found: C, 63.2; H, 6.8; N, 9.2.

Hydrazine-hydrazone of methyl 2-methyl-3-oxo-cyclopentenecarboxylate (XV). Upon mixing 7.7 g. (0.05 mole) of IXb with 5.28 g. (0.15 mole plus 10% excess) of anhydrous hydrazine there was precipitated 3 g. of a white solid. The filtrate was treated with 10 drops of hydrazine and warmed. Upon cooling a white precipitate weighing 2.9 g. was formed. After four repetitions a total of 8.4 g. of a mixture of crude hydrazide-hydrazone (XV), and hydrazone (XIII) was collected. The mixture was treated with 3000 cc. of benzene and the solid remaining undissolved was recrystallized from pyridine to give 4 g. (47.6%) of XV, m.p. 217–218°.

Anal. Calc'd for $C_7H_{12}N_4O$: C, 50.0; H, 7.2; N, 33.3.
Found: C, 50.2; H, 7.2; N, 33.1.

The benzene-soluble fraction contained 4.2 g. (50%) of the hydrazone (XIII).

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[3] Trade name for 2-ethoxyethanol.

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