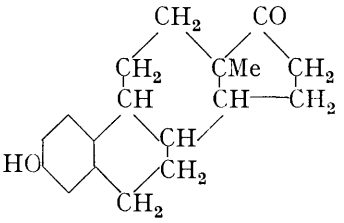
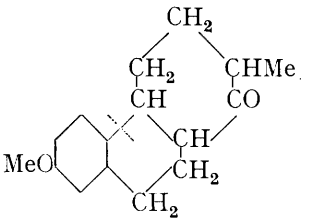
308. *Experiments on the Synthesis of Substances related to the Sterols. Part III. A New Synthesis of Certain Ketohydrophenanthrene Derivatives.*

By Robert Robinson and E. Schlittler.

One of the more promising methods for the synthesis of œstrone (I) and related substances depends in principle on the appropriate modification * of such an intermediate as the keto-methoxymethyloctahydrophenanthrene (II). On account of the favourable orientation of the methoxyl group in (II) we sought a method of ring closure at the point indicated by the

(I.)





(II.)

dotted line: that ultimately devised differs from known processes in that the carbon atoms necessary for the construction of two of the aromatic nuclei are attached in a straight chain to a benzene derivative; two unambiguous cyclisations complete the synthesis.

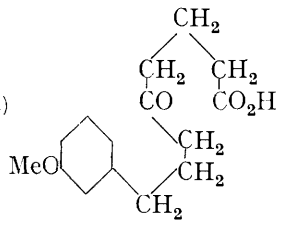
* Feasible final stages are indicated by Hibbit and Linstead's important work on the formation of 9-methyloctalins from butenylmethyl*cyclo*hexanols, and in this laboratory Mr. E. J. Vickers and one of us have independently obtained what is apparently a bicyclic *hydrocarbon*, $C_{10}H_{16}$, by dehydration of 1-allyl-2-methyl*cyclo*hexanol by means of phosphoric oxide. This hydrocarbon has b. p. 169—170° (Found: C, 87·9; H, 12·1. $C_{10}H_{16}$ requires C, 88·1; H, 11·9%) and absorbs 1 mol. of bromine in cold dilute chloroform solution.

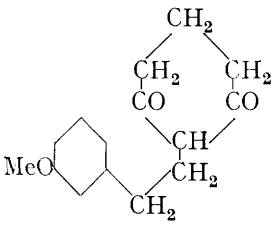
An improved method of preparation of γ-*m*-methoxyphenylbutyric acid (III) (Thompson, J., 1932, 2310) has been worked out in accordance with the scheme :

$$(m)\text{MeO}\cdot C_6H_4\cdot CHO \longrightarrow \text{MeO}\cdot C_6H_4\cdot CH_2\cdot CH_2\cdot CO_2Et \longrightarrow \text{MeO}\cdot C_6H_4\cdot CH_2\cdot CH_2\cdot CH_2\cdot OH\ *$$
$$\longrightarrow \text{MeO}\cdot C_6H_4\cdot CH_2\cdot CH_2\cdot CH_2Cl \longrightarrow \text{MeO}\cdot C_6H_4\cdot CH_2\cdot CH_2\cdot CH_2I \longrightarrow$$
$$\text{MeO}\cdot C_6H_4\cdot CH_2\cdot CH_2\cdot CH_2\cdot CN \longrightarrow \text{MeO}\cdot C_6H_4\cdot CH_2\cdot CH_2\cdot CH_2\cdot CO_2H \quad \text{(III.)}$$

Although the stages are numerous, the overall yield is such as to render the acid a relatively readily accessible substance and considerable quantities of it have been made in connexion with a development of the present investigation.† The necessary extension of the chain of (III) was made by an application of Mrs. G. M. Robinson's keto-acid synthesis (J., 1930, 745), γ-*m*-methoxyphenylbutyryl chloride being brought into reaction with ethyl sodio-α-acetylglutarate and the product hydrolysed in stages to 5-*keto*-8-m-*methoxyphenyloctoic acid* (IV).

(IV.)





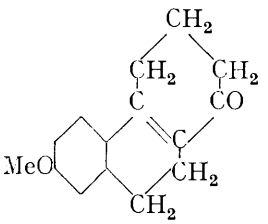
(V.)

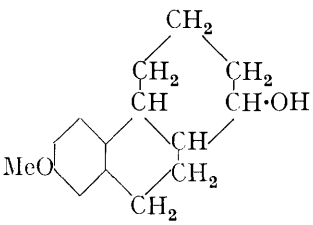
The *methyl* ester of this acid, obtained by means of diazomethane, furnished a dihydroresorcinol derivative (V) when it was treated with sodium ethoxide in an anhydrous ethereal medium.

The dehydration of (V) with the formation of 1-*keto*-7-*methoxy*-1 : 2 : 3 : 4 : 9 : 10-*hexahydrophenanthrene* (VI) was effected by means of phosphoric oxide. Finally the reduction of (VI) by means of sodium and alcohol yielded the secondary alcohol (VII), characterised as the p-*nitrobenzoate*.

Methylation of the dehydrogenation product of (VI) affords 1 : 7-dimethoxyphenanthrene, which will be described in a subsequent communication dealing with its synthesis.

(VI.)





(VII.)

Experimental.

γ-m-*Methoxyphenylpropyl Alcohol.*—A mixture of β-*m*-methoxyphenylpropionic acid (187 g., prepared by catalytic reduction of *m*-methoxycinnamic acid), absolute alcohol (491 c.c.), toluene (700 c.c.), and concentrated sulphuric acid (33 c.c.) was refluxed for 6 hours, and 650 c.c. then removed by distillation. Two layers separated on cooling; the upper one was worked up in the known manner and afforded ethyl methoxyphenylpropionate, b. p. 145—146°/10·5 mm. (170 g.). The reduction of this ester (41 g.) by Bouveault and Blanc's method required sodium (28 g.) and *anhydrous* ethyl alcohol (200 c.c. + 50 c.c. + 50 c.c.) (oil-bath at 160—170°) and a 78% yield of γ-*m*-methoxyphenylpropyl alcohol, b. p. 147°/10·5 mm., was obtained (Found : C, 72·0; H, 8·4. Calc. for $C_{10}H_{14}O_2$: C, 72·0; H, 8·4%). The yield was diminished when the operation was conducted on a larger scale.

The chloride was prepared from the alcohol (126 g.), thionyl chloride (81·4 c.c.), and dimethylaniline (145 c.c.) in chloroform (205 c.c.); b. p. 133°/13 mm. (yield, 92%) (Found : C, 65·4; H, 7·0. Calc. for $C_{10}H_{13}OCl$: C, 65·2; H, 7·1%).

* The work now recorded was completed in 1934. γ-*m*-Methoxyphenylpropyl alcohol and the corresponding chloride have since been described by Cohen (this vol., p. 435).

† See also the preceding paper.

γ-m-*Methoxyphenylbutyric Acid* (III).—*γ*-*m*-Methoxyphenylpropyl chloride (43 g.) was converted into the corresponding iodide by refluxing an alcoholic solution (430 c.c.) containing sodium iodide (86 g.) for 12 hours, with filtration from sodium chloride after 3 and 6 hours. By working up the product, one-seventh of the initial substance was recovered and the fraction, b. p. 152—162°/11 mm., was collected (yield, 144 g. from 126 g. of the chloride).

A mixture of this iodide (71·1 g.), potassium cyanide (37 g.), alcohol (847 c.c.), and water (84 c.c.) was refluxed for 15 hours, and the resulting *nitrile* isolated (77 g. of b. p. 164—170°/11 mm. from 144 g. of the iodide) (Found: C, 75·4; H, 7·5. $C_{11}H_{13}ON$ requires C, 75·4; H, 7·4%). The residue from the distillation of the nitrile crystallised (2—3 g.) and was recrystallised from aqueous alcohol and from benzene, from which it separated in slender colourless needles, m. p. 96—97° (Found: C, 68·0; H, 7·5; N, 7·2. $C_{11}H_{15}O_2N$ requires C, 68·3; H, 7·7; N, 7·3%). The substance is therefore *γ*-m-*methoxyphenylbutyramide*; we are obliged to Mr. J. Resuggan for its isolation and identification.

The nitrile (77·2 g.) was refluxed with a mixture of 25% methyl-alcoholic potassium hydroxide (216 c.c.) and water (65 c.c.) for 64 hours. The yield of the crude acid was practically quantitative. This substance was not crystallised by Thompson (*loc. cit.*); it separated from light petroleum (b. p. 40—60°) in glistening white leaflets, m. p. 49—50° (Found: C, 68·0; H, 7·1. Calc. for $C_{11}H_{14}O_3$: C, 68·0; H, 7·2%).

5-*Keto*-8-m-*methoxyphenyloctoic Acid* (IV).—A mixture of *γ*-*m*-methoxyphenylbutyric acid (21·9 g.), chloroform (100 c.c.), and thionyl chloride (22 c.c., purified by means of sulphur and aluminium chloride) was refluxed for 1 hour and the solvent and excess of thionyl chloride were then removed as far as possible by distillation under diminished pressure. A little dry benzene was added, and the distillation continued; if necessary, the process was repeated, as complete removal of thionyl chloride is essential. The residual chloride, dissolved in dry ether (60 c.c.), was added to an ethereal solution and suspension of ethyl sodio-α-acetylglutarate (from 25·9 g. of the ester and 2·63 g. of finely granulated sodium under 200 c.c. of ether) cooled in a freezing mixture and well shaken. After 2 hours, the mixture was allowed to reach room temperature, then kept for 12 hours, shaken on the machine for 2 hours, and finally refluxed for 1 hour. Water and ether were added and the separated aqueous layer was twice extracted with ether; the combined ethereal solutions were washed with aqueous sodium carbonate and water, dried, and evaporated. The residual oil (42 g.) was shaken on the machine with aqueous potassium hydroxide (1000 c.c. of 2·5%) for 12 hours; the alkali concentration was then raised to 3%, and shaking continued 4 hours longer. The aqueous solution, freed from traces of oil by means of ether, was acidified, and the acidic product isolated by means of ether (dried by sodium sulphate). The yellow oil was cautiously heated on the steam-bath (evolution of carbon dioxide) and occasionally the product solidified (20·1 g.). In any case it was heated on the steam-bath with 2*N*-sodium hydroxide (180 c.c.) for 2 hours, and isolated as before, after the alkaline solution had been washed with ether. The oily acid solidified and was collected and dried (19·5 g.). This crude product (34·6 g.) was methylated by means of diazomethane (34 g. of nitrosomethylurethane) in cold ethereal solution and the esters (freed from unchanged acids) were distilled; methyl *m*-methoxyphenylbutyrate, b. p. 120°/0·22 mm. (oil-bath at 155—175°), was collected, and the residue hydrolysed by means of methyl-alcoholic potassium hydroxide on the steam-bath. After addition of water and removal of the methyl alcohol the keto-acid was regenerated and isolated by means of ether (yield, 15·2 g.). It was crystallised by cautious addition of petroleum (b. p. 100—120°) to its concentrated solution in chloroform and it separated in long prisms (11·0 g.), often sharply pointed, m. p. 69—70° (Found: C, 68·3; H, 7·6. $C_{15}H_{20}O_4$ requires C, 68·2; H, 7·7%).

β-m-*Methoxyphenylethyl*cyclo*hexane*-2 : 6-*dione* (V).—Methyl ketomethoxyphenyloctoate (4·03 g.), prepared from the acid by means of ethereal diazomethane, was dissolved in anhydrous ether (30 c.c.), and granulated alcohol-free sodium ethoxide (1·97 g., Houben-Weyl, III, 701; preferably not powdered) introduced. Reaction proceeded in the cold and after some hours a solid separated; after 12 hours this was broken up, and the mixture shaken; after 20 hours the whole was refluxed for 30 minutes, then cooled, and ice and water added. The alkaline solution was washed with fresh ether, separated, and gradually acidified with dilute sulphuric acid. After each addition of 2 or 3 drops of the acid the liquid was shaken with ether, because, although the dihydroresorcinol derivative is very sparingly soluble in ether, it can be extracted by this procedure. If the substance separated in a crystalline form, it was redissolved in alkali and the process repeated. The ethereal solution deposited crystals on keeping in the ice-chest, and a further quantity separated after the solution had been concentrated (yield, 7·5 g. from 10·9 g. of the keto-acid). The *diketone* crystallised from chloroform–petroleum (b. p. 80—100°) in

colourless, compact, twinning prisms, m. p. *ca.* 150° (Found : C, 72·7, 72·9; H, 7·3, 7·3. $C_{15}H_{18}O_3$ requires C, 73·2; H, 7·3%). The substance has pseudo-acidic character, but its ferric reaction in alcoholic solution is negative.

1-*Keto*-7-*methoxy*-1 : 2 : 3 : 4 : 9 : 10-*hexahydrophenanthrene* (VI).—Phosphoric oxide (10 g.) was added in the course of 1·5 hours to a boiling solution of methoxyphenylethyl*cyclo*hexanedione (1 g.) in benzene (125 c.c., previously shaken with a little water), the semi-solid complex being occasionally stirred with a glass rod. After cooling in a freezing mixture, small pieces of ice were added; the solution was then rendered strongly alkaline, the layers separated, and the aqueous solution extracted with ether. The combined ether–benzene solutions were washed, dried, and evaporated. The residual oil (0·52 g.) distilled at 165—169°/0·23 mm. and then crystallised after some months. The substance could be crystallised from a concentrated solution in methyl alcohol at 0° and occurred in colourless prismatic needles, m. p. 75—76°, readily soluble in most organic solvents (Found : C, 78·8; H, 7·0; MeO, 13·8. $C_{15}H_{16}O_2$ requires C, 78·9; H, 7·0; 1MeO, 13·6%).

The 2 : 4-*dinitrophenylhydrazone* separated when warm alcoholic solutions of the components were mixed, and the highly characteristic blackish-purple derivative crystallised from toluene in needles, m. p. 256° (decomp.) after sintering at 253—254° (Found : C, 61·5; H, 4·9. $C_{21}H_{20}O_5N_4$ requires C, 61·8; H, 4·9%).

Professor E. C. Dodds has kindly examined the ketone for œstrogenic properties; the results were negative, but the concentrations employed were comparable with those usual in experiments with naturally occurring hormones.

Reduction.—Professor I. M. Heilbron and Mr. H. Jackson have kindly studied the hydrogenation of the ketone on the micro-scale and with a very active platinum catalyst. Almost exactly six molecules of hydrogen (5·9; 6·1) were required, so the product must be a hydroxy- or methoxy-tetradecahydrophenanthrene. With a palladium-black–barium sulphate catalyst, 2·07 molecular proportions of hydrogen were taken up in 4 hours, corresponding to the reduction of the ethylene linkage and the carbonyl group.

The ketone (VI) (0·55 g.) was reduced in boiling alcoholic solution (10 c.c. + 10 c.c.) by means of sodium (1·12 g.) and the product (0·49 g.) was isolated as a pale yellow oil which could not be crystallised. The substance is doubtless the saturated alcohol (VII), because a crystalline p-*nitrobenzoate* could be isolated. The oil (0·44 g.), pyridine (1·72 c.c.), and *p*-nitrobenzoyl chloride (0·59 g.) were heated together on the steam-bath for 2 hours, and the derivative isolated after removal of basic and acidic substances. It was crystallised from alcohol and from chloroform–light petroleum (b. p. 40—60°), being obtained as colourless needles, m. p. 140° after sintering at 125° (Found : C, 68·9; H, 6·2. $C_{22}H_{23}O_5N$ requires C, 69·2; H, 6·0%).

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