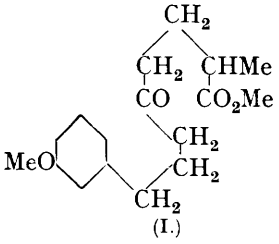
40. *Experiments on the Synthesis of Substances related to the Sterols. Part VIII. A Ketomethoxymethylhexahydrophenanthrene.*

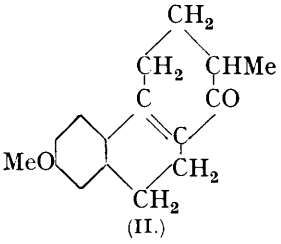
By Robert Robinson and James Walker.

The new hydrophenanthrene synthesis recorded in Part III (Robinson and Schlittler, J., 1935, 1288) involves a double ring-closure and in the final stage a β-arylethyldihydroresorcinol is dehydrated. In the example described in Part III, the course of the reaction was unambiguous, but the presence of a substituent in position 3 of the *cyclo*hexane ring allows of alternative courses.

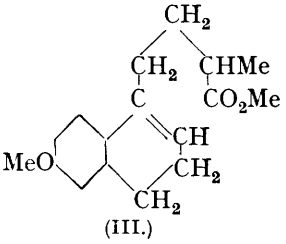
Employing methods similar to those of Part III, we obtained *methyl* 5-*keto*-8-m-*methoxyphenyloctane*-2-*carboxylate* (I), which was converted into a dihydroresorcinol derivative and then into 1-*keto*-7-*methoxy*-2-*methyl*-1 : 2 : 3 : 4 : 9 : 10-*hexahydrophenanthrene* (II); this was, however, contaminated with a small proportion of a substance containing a CH_2·CO group, almost certainly the isomeric ketomethoxy-4-methylhexahydrophenanthrene.



(I.)



(II.)



(III.)

In order to be quite sure of the constitution of the ketone, we carried out the ring closures in a different sequence and obtained a dihydronaphthalene derivative (III) by the action of sulphuric acid on (I) at − 15°. The acid chloride related to (III) was then cyclised to (II) by an adaptation of Darzens' reaction. The ketone thus obtained was readily purified by crystallisation from methyl alcohol and, a seed having been acquired, the product of the first process mentioned above could also be crystallised; it proved to be identical with (II) and it was completely freed from the 4-methyl isomeride. The Darzens–Kipping reaction having served its turn, the method by way of the dihydroresorcinol is to be preferred for the preparation of (II).

Further work on (II) and its lower homologue, and especially on their dihydroderivatives, is being actively prosecuted; the present record is necessitated by a publication of Cook and Lawrence (J., 1935, 1637), who also have employed the Darzens reaction in order to effect ring closure. At the time of writing their paper had been in our hands for a week, and we are thus taking the earliest opportunity to disclose our independent work in a similar direction.

Experimental.

Ethyl m-*Methoxycinnamate.*—*m*-Methoxybenzaldehyde (100 g.) was condensed with methyl acetate (Kindler and Peschke, *Arch. Pharm.*, 1932, **270**, 345). The crude product, containing some *m*-methoxycinnamic acid, was converted into the ethyl ester by refluxing in toluene or benzene with ethyl-alcoholic sulphuric acid; b. p. 172°/14 mm. (135 g.).

m-Methoxycinnamic acid is obtainable in high yield (> 90%) by condensation of *m*-methoxybenzaldehyde with malonic acid at 100° in the presence of pyridine with or without the addition of piperidine. Our experience in this case confirms the observations of Kurien and Pandya (*J. Indian Chem. Soc.*, 1934, **11**, 825) and Vahidy and Pandya (*Proc. Indian Acad. Sci.*, 1935, **2**, 402) that no excess of malonic acid is requisite and the pyridine employed may be restricted to 0·15 molar proportion.

Ethyl β-m-*Methoxyphenylpropionate.*—Ethyl *m*-methoxycinnamate (70 g.) in methyl alcohol (180 c.c.) along with 2% palladised strontium carbonate (12 g.) was shaken in hydrogen under an excess pressure of 2—3 atms. The requisite absorption of hydrogen took place in 12—20 minutes; the filtered solution was evaporated, and ethyl β-*m*-methoxyphenylpropionate isolated, b. p. 145—146°/10·5 mm. (68 g.).

An improvement in the preparation of γ-*m*-methoxyphenylbutyric acid consisted in the direct preparation of its nitrile from γ-*m*-methoxyphenylpropyl chloride with sodium iodide as catalyst.

Ethyl α-*Acetyl*-α′-*methylglutarate.*—Methyl α-methylacrylate and ethyl acetoacetate were condensed as described by Ruzicka (*Helv. Chim. Acta*, 1919, **2**, 153). The reaction mixture was added to much water, rendered just acid with acetic acid, and extracted with ether after saturation of the aqueous layer with sodium chloride. Replacement of methyl by ethyl occurred (Found: C, 58·6; H, 8·2. Calc. for $C_{12}H_{20}O_5$: C, 59·0; H, 8·2%). The ester, b. p. 147—150°/10 mm., was obtained in 25% yield, as found by Ruzicka.

Methyl γ-*Acetyl*-α-*methylbutyrate.*—Ethyl α-acetyl-α′-methylglutarate (46 g.) was hydrolysed as described by Bentley and Perkin (J., 1896, **69**, 1511) for the lower homologue and the crude acid was esterified with an ethereal solution of diazomethane (from 40 g. of nitrosomethylurea). The *ester* (27·2 g.; overall yield, 91%) distilled at 110—112°/24 mm. as a colourless mobile oil, $n_D^{18°}$ 1·4297 (Found: C, 60·8; H, 9·0. $C_8H_{14}O_3$ requires C, 60·8; H, 8·9%).

Methyl 5-*Keto*-8-m-*methoxyphenyloctane*-2-*carboxylate* (I).—A solution of γ-*m*-methoxyphenylbutyryl chloride (from 22 g. of the acid; cf. Robinson and Schlittler, *loc. cit.*) in dry benzene (80 c.c.) was added to one of methyl sodio-α-acetyl-α′-methylglutarate (from 27·5 g. of the ester and 2·6 g. of finely powdered sodium) in dry benzene (250 c.c.). The initially formed gel redissolved on standing and, after 15 hours at room temperature and 2 hours at the boiling point, the mixture was added to water and separated. The benzene solution was washed with sodium carbonate solution, dried (sodium sulphate), and evaporated. On acidification of the aqueous washings a small amount (*ca.* 2 g.) of *m*-methoxyphenylbutyric acid was recovered. The residual syrup (43 g.) was hydrolysed in the manner described by Robinson and Schlittler (*loc. cit.*). The crude hydrolysate (30 g.) from two experiments was esterified with an ethereal solution of diazomethane (from 30 g. of nitrosomethylurea) and fractionated. There were obtained: (i) 18·6 g., b. p. 130—170°/0·3 mm., which consisted of methyl γ-*m*-methoxyphenylbutyrate distilling mainly at 130—145°/0·3 mm., and (ii) 9·1 g., b. p. 170—200°/0·3 mm., a limpid, pale yellow oil (b. p. mainly 190—200°/0·3 mm.). The trace of halogen in

this material (Found : C, 67·5; H, 8·0%) was removed as follows : The *ester* (18·4 g.) in methyl alcohol (150 c.c.) was shaken with 2% palladised strontium carbonate (7 g.) for 2 hours in hydrogen under 1 atm. excess pressure. The solution was filtered from catalyst and concentrated, and the residue distilled; a halogen-free product (17·9 g.) was then obtained, b. p. 210°/1 mm., $n_D^{14.5°}$ 1·5082 (Found : C, 69·3; H, 8·1. $C_{17}H_{24}O_4$ requires C, 69·8; H, 8·2%).

1-*Keto*-7-*methoxy*-2-*methyl*-1 : 2 : 3 : 4 : 9 : 10-*hexahydrophenanthrene* (II).—(A) The above ester (I) (4·5 g.) in dry ether (25 c.c.) was treated at room temperature with alcohol-free sodium ethoxide (2 g.), a quick rise in temperature occurring; after 20 hours at room temperature the mixture was refluxed for an hour and added to ice-cold water. The alkaline aqueous solution was thrice extracted with small amounts of ether, acidified with sulphuric acid, and extracted with chloroform. On drying (sodium sulphate) and evaporation, the chloroform extract yielded a pale yellow syrup (3·9 g.), which turned into a white solid; this became sticky when kept over sulphuric acid in a vacuum and could not be satisfactorily crystallised. This dihydroresorcinol derivative was treated directly in the manner described by Robinson and Schlittler (*loc. cit.*) with phosphoric oxide in pure benzene which had just previously been shaken with water. On distillation of the crude product (2·6 g.) a pale yellow, viscous syrup (2·0 g.) was obtained, b. p. 175—180°/0·2 mm. This solidified in the ice-chest after a few days, but it contained, in addition to the desired product (II), a small amount of the 4-methyl isomeride, as was shown by the following experiment : A solution of the product (50 mg.) and β-resorcylaldehyde (35 mg.) in pure ethyl acetate (1 c.c.) was saturated with dry hydrogen chloride and kept for a few hours; a dark reddish-brown pyrylium salt separated. The salt dissolved in water to an orange solution with a bright orange fluorescence; it dissolved in concentrated sulphuric acid, giving a reddish-orange solution with an intense green fluorescence, and the anhydronium base dissolved in benzene to a deep bluish-red solution. A control experiment with resorcylaldehyde alone under the same conditions afforded no such pyrylium salt.

The product was pressed on porous porcelain and washed with chilled low-boiling light petroleum; it then had m. p. 63—65° (Found : C, 79·4; H, 7·6. $C_{16}H_{18}O_2$ requires C, 79·3; H, 7·4%). Recrystallisation was not effected until nucleation with the homogeneous material from the method B (see below) was practicable, and then the substance was readily separated from the trace of the 4-methyl isomeride by crystallisation from methyl alcohol; it was so obtained as hexagonal flat prisms, m. p. 67—68° alone or in admixture with the ketone derived from the experiment (B). The pure product gave a negative result in the β-resorcylaldehyde test described above.

(B) The ester (III) described below (4·0 g.) was refluxed with 10% methyl-alcoholic potassium hydroxide for 4 hours, and the acid isolated in the usual way and converted into the chloride by the action of thionyl chloride (1·06 c.c.; 1 mol.) in ether (20 c.c.) in the presence of pyridine (1·2 c.c.; 1 mol.) (cf. Carré and Libermann, *Compt. rend.*, 1934, **199**, 1422). The acid chloride, dissolved in carbon disulphide (12 c.c.), was added gradually to a solution of stannic chloride (1·7 c.c.; 1 mol.) in carbon disulphide (20 c.c.) cooled to — 10°. A blackish-brown granular complex was formed which later became reddish-brown and resinous. After 18 hours at room temperature, the complex was decomposed with ice-water, an emulsion being formed which was effectively separated after the addition of ether. The ether–carbon disulphide extract was dried and evaporated and the crude product was heated at 180° for 2 hours with a slight excess of dimethylaniline (3·5 c.c.), cooled, and treated with ether and dilute sulphuric acid. The ethereal solution was washed thrice with dilute sulphuric acid, twice with sodium carbonate solution, dried, and evaporated. The crude product (1·8 g.) was distilled, affording a pale yellow, viscous oil (1·5 g.), b. p. 175—183°/0·26 mm., which rapidly solidified (Found : C, 79·2; H, 7·5. $C_{16}H_{18}O_2$ requires C, 79·3; H, 7·4%). The substance separated from methyl alcohol in hexagonal flat prisms, m. p. 67—68°.

Crude acid (1 g.) (corresponding to III) was recovered from the sodium carbonate washings and by dissolving the pyridine hydrochloride in water and extracting the solution with ether.

The 2 : 4-*dinitrophenylhydrazone* separated when a hot concentrated solution of 2 : 4-dinitrophenylhydrazine and a concentrated solution of the ketone were mixed and cooled. It crystallised from ethyl acetate in bright red, felted needles, m. p. 221° (Found : N, 13·3. $C_{22}H_{22}O_5N_4$ requires N, 13·3%).

Methyl γ-6-*Methoxy*-3 : 4-*dihydro*-1-*naphthyl*-α-*methylbutyrate* (III).—Methyl 5-keto-8-*m*-methoxyphenyloctane-2-carboxylate (I) (15 g.) was dissolved in concentrated sulphuric acid (70 c.c.) at — 15°. The deep reddish-brown solution was kept in the freezing mixture for 3 hours and then poured on ice and extracted with ether. The extract was washed with sodium carbonate solution, dried (sodium sulphate), and evaporated. The product (11·2 g.) distilled

as a practically colourless, viscid oil (10·8 g.) at 181—183°/0·5 mm., $n_D^{16°}$ 1·5480 (Found : C, 74·3; H, 8·1. $C_{17}H_{22}O_3$ requires C, 74·4; H, 8·0%).

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