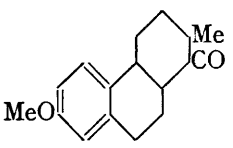
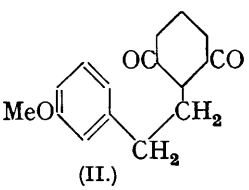
12. *The Synthesis of Compounds related to the Sterols, Bile Acids, and Oestrus-producing Hormones. Part VIII.*

By C. L. Hewett.

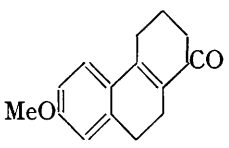
In Part I (Cook and Hewett, J., 1933, 1105) comment was made on the difficulties experienced in synthesising the sterol type of ring system from 1-keto-1 : 2 : 3 : 4-tetrahydrophenanthrene, and the view was expressed that these difficulties would be overcome by the use of analogous derivatives of *as*-octahydrophenanthrene. This view has been accepted by Robinson and Schlittler (J., 1935, 1288), who state "one of the more promising methods for the synthesis of oestrone and related substances depends in principle on the appropriate modification of such an intermediate as the ketomethoxymethyloctahydrophenanthrene" (I).



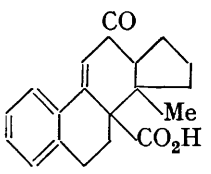
(I.)



(II.)



(III.)



(IV.)

Methods of synthesis of compounds of type (I) are under investigation in this laboratory, and in view of the paper by Robinson and Schlittler, preliminary experiments in connection with one such method (compare Cohen and Cook, J., 1935, 1571) are recorded.

The condensation of dihydroresorcinol with benzyl chloride, β-1-naphthylethyl bromide, and β-m-*methoxyphenylethyl bromide* has been studied, as the formation of the *C*-alkyl compounds (II) would give a simple route to polycyclic ketones of the desired type. With benzyl chloride *C*-alkylation took place to a reasonable extent, but with β-1-naphthylethyl bromide *O*-alkylation occurred almost exclusively. From β-*m*-methoxyphenylethyl bromide the O-*alkyl* compound was mainly formed, but there was also obtained a small yield of β-*m*-methoxyphenylethyl*cyclo*hexane-2 : 6-dione (II), the properties of which agree with those given for this compound by Robinson and Schlittler. By cyclisation of (II) with 80% sulphuric acid at 100°, 1-keto-7-methoxy-1 : 2 : 3 : 4 : 9 : 10-hexahydrophenanthrene (III) was rapidly formed in good yield, this method being preferable to that used by Robinson and Schlittler.

The predominating *O*-alkylation of dihydroresorcinol renders the method unsuitable for preparative purposes. The method of Robinson and Schlittler is lengthy, and a promising simpler method is under investigation.

Preliminary attempts have also been made to utilise the Michael reaction for the synthesis of polycyclic compounds related to oestrone. For example, the condensation of ethyl β-phenylethylmalonate with 2-acetyl-1-methyl-Δ^1-*cyclo*pentene (prepared from methyl-Δ^1-*cyclo*pentene by the method of Darzens, *Compt. rend.*, 1910, **150**, 707) led to the isolation in small yield of an *acid*, the analysis of which suggested that it was represented by (IV). This experiment was made before it was known that the quaternary methyl group of oestrone is at C_{13} and not at C_{14}, and the investigation of (IV) has not been pursued.

Experimental.

m-*Bromoanisole*.—Conversion of *m*-bromoaniline into *m*-bromphenol by the method of Diels and Bunzl (*Ber.*, 1905, **38**, 1495) gave poor yields and the following modification was adopted: To a solution of *m*-bromoaniline (100 g.) in methyl alcohol (500 c.c.) at 0°, concentrated sulphuric acid (65 c.c.) was added very slowly, followed by amyl nitrite (76 g.). After 1 hour the diazonium sulphate was washed with alcohol and ether, dissolved in ice-cold water, and added to boiling *N*-sulphuric acid (1 l.). Ether extracted *m*-bromphenol (60 g.), b. p. 120° (vacuum of the water-pump). This (170 g.) was heated on the water-bath for 3 hours with 10% potassium hydroxide solution (650 c.c.) and methyl *p*-toluenesulphonate (230 g.). The bromoanisole was distilled in steam after the addition of 150 c.c. of 10% potassium hydroxide solution. Yield, 154 g. after vacuum distillation.

β-m-*Methoxyphenylethyl Bromide*.—To an ice-cold Grignard solution prepared from *m*-bromoanisole (90 g.), magnesium (12 g.), and ether (500 c.c.) was added ethylene oxide (25 g.) diluted with ether (50 c.c.) (compare Shoesmith and Connor, J., 1927, 2233). After standing overnight, the ether was distilled off, and the residue heated at 100° for 1 hour. It was then decomposed with ice and hydrochloric acid, and the product was extracted with ether, washed, dried, and fractionated in a vacuum, giving 43 g. of the alcohol, b. p. 150—155°/18 mm. The **3 : 5-*dinitrobenzoate*** separated from alcohol in pale yellow, prismatic needles, m. p. 106·5—107·5° (Found: C, 55·8; H, 4·5. $C_{16}H_{14}O_7N_2$ requires C, 55·5; H, 4·1%). Phosphorus tribromide (25 g.) was rapidly added to the alcohol (37·5 g.), dissolved in carbon tetrachloride (50 c.c.) previously warmed to 60°, and the whole was refluxed for 15 minutes. The solution was then cooled, washed with water and dilute aqueous sodium carbonate (to remove acid phosphite ester), dried, and distilled, giving β-m-*methoxyphenylethyl bromide* (34·5 g.) as an almost colourless liquid, b. p. 138°/12 mm. (Found: C, 50·75; H, 5·3. $C_9H_{11}OBr$ requires C, 50·2; H, 5·2%).

Dihydroresorcinol Condensations.—Dihydroresorcinol and "molecular" potassium in benzene gave a red resinous product and the condensations were therefore effected by sodium ethoxide. Sodium (1 mol.) was dissolved in ethyl alcohol (25 c.c. per g. of sodium), dihydroresorcinol (1 mol.) and the halide (1 mol.) added, and the whole boiled under reflux (3 hours in the case of benzyl chloride; 24 hours in the other two cases). The alcohol was then removed, water added, and the neutral part removed by extraction with ether; this consisted of unchanged halide and the *O*-alkyl compound. The alkaline solution on acidification with dilute sulphuric acid yielded the *C*-alkyl compound.

(i) *Condensation with benzyl chloride*. The precipitate from the alkaline solution crystallised from aqueous alcohol (charcoal) in colourless needles of *benzyl*cyclo*hexane*-**2 : 6-*dione***, m. p. 184—185° (yield, 1·9 g. from 6·3 g. of benzyl chloride) (Found: C, 76·9; H, 7·0. $C_{13}H_{14}O_2$ requires C, 77·1; 7·0%). In an attempt to effect ring closure to a fluorene derivative by concentrated sulphuric acid at — 15° the diketone was converted into a *sulphonic acid*, which crystallised from aqueous acetic acid in pink rhombic tablets, m. p. 193—194° (Found: C, 52·5; H, 5·65. $C_{13}H_{14}O_5S,H_2O$ requires C, 52·0; H, 5·4%). The diketone (0·2 g.) was recovered unchanged after boiling for 1 hour with potassium hydroxide (0·2 g.) in aqueous alcohol.

(ii) *Condensation with* β-1-*naphthylethyl bromide* (28·2 g.). Acidification of the alkaline solution and extraction with ether yielded 1·2 g. of a mixture of oil and crystals which could not be purified. The neutral fraction when washed with ether gave a sparingly soluble, crystalline solid, which was recrystallised from alcohol (yield, 10 g.). 3-*Keto*-Δ^1-cyclo*hexenyl* **β-1-*naphthylethyl ether*** formed colourless silky needles, m. p. 138—139°, insoluble in dilute alkali solution (Found: C, 80·8; H, 6·8. $C_{18}H_{18}O_2$ requires C, 81·15; H, 6·8%).

An attempt to make the oxime of this keto-ether (0·3 g.) with hydroxylamine hydrochloride (0·3 g.) and pyridine (3 c.c.) at 100° resulted in hydrolysis to β-1-naphthylethyl alcohol, which was also obtained when the ether (0·5 g.) was hydrolysed with potassium hydroxide (0·5 g.) in aqueous alcohol on the water-bath for 1 hour.

(iii) *Condensation with* β-m-*methoxyphenylethyl bromide*. Acidification of the alkaline solution gave β-*m*-methoxyphenylethyl*cyclo*hexane-**2 : 6-dione** (II), m. p. 149—150° after crystallisation from alcohol (Robinson and Schlittler, *loc. cit.*, give m. p. *ca.* 150°). Yield, 0·3 g. from 6·3 g. of bromide (Found: C, 73·5; H, 7·7. Calc.: C, 73·2; H, 7·3%).

The neutral fraction from the condensation was distilled and the fraction, b. p. 205—207°/0·5 mm., was collected and redistilled. The β-m-*methoxyphenylethyl* ether of dihydroresorcinol formed a colourless viscous liquid, b. p. 205—207°/0·5 mm. (Found: C, 72·85; H, 7·45. $C_{15}H_{18}O_3$ requires C, 73·2; H, 7·3%).

β-*m*-Methoxyphenylethyl*cyclo*hexane-2 : 6-dione (100 mg.) was heated on the water-bath with 80% sulphuric acid (10 parts) for 5 minutes, the product poured into water and extracted with ether, and the ethereal solution washed with dilute aqueous sodium carbonate, dried, and evaporated. The residual syrup was converted into the 2 : 4-dinitrophenylhydrazone (of III), m. p. 253—255° after recrystallisation from xylene (90 mg.) (Robinson and Schlittler give 256°) (Found : C, 62·2; H, 5·0. Calc. : C, 61·8; H, 4·9%).

Condensation of Ethyl β-*Phenylethylmalonate with* 2-*Acetyl*-1-*methyl*-Δ^1-cyclo*pentene*.—Into a well-cooled solution (— 10°) of anhydrous stannic chloride (6·5 g.) in carbon disulphide (150 c.c.) was slowly dropped a mixture of acetyl chloride (19·6 g.) and Δ^1-methyl*cyclo*pentene (20·5 g.; Skraup and Binder, *Ber.*, 1929, **62**, 1135). After 5 hours at 0°, ice and hydrochloric acid were added and the carbon disulphide layer was washed with dilute hydrochloric acid and water. The solvent was removed (after the addition of 1 mol. of dimethylaniline) and the residue was heated at 180° for 3 hours, cooled, diluted with ether, washed with dilute hydrochloric acid and water, dried, and evaporated. Distillation gave 10·5 g. of a colourless liquid, b. p. 115°/11 mm.

To a solution of sodium (0·8 g.) in alcohol (11·3 c.c.), ethyl β-phenylethylmalonate (Horne and Shriner, *J. Amer. Chem. Soc.*, 1933, **55**, 4653) (9·2 g.) was added, followed by 2-acetyl-1-methyl-Δ^1-*cyclo*pentene (4·3 g.), prepared as described above. The whole was boiled for 24 hours, diluted with water, and washed with ether. The aqueous layer was then acidified and the solid which was precipitated was extracted with a large volume of ether. After evaporation of the ether, the residue was crystallised from methyl alcohol, and then from acetic acid, forming almost colourless plates (0·6 g.), m. p. 242° (Found : C, 76·9; H, 6·7. $C_{19}H_{26}O_3$ requires C, 76·9; H, 6·75%). This *acid* (probably IV) was soluble in boiling dilute sodium carbonate solution, from which the sodium salt separated in needles on cooling.

The Research Institute of the Cancer Hospital (Free),
London, S.W. 3.

[*Received, November 12th*, 1935.]