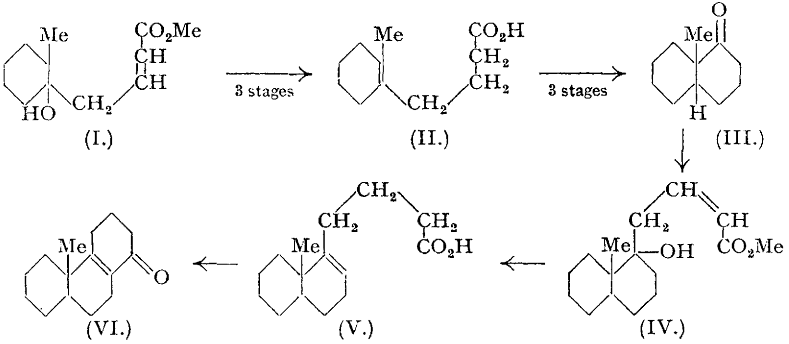
40. *Synthetic Studies in the Steroid Series. Part I. Use of Methyl γ-Bromocrotonate in the Synthesis of Fused-ring Hydroaromatic Ketones.*

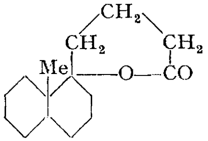
By J. W. Cook and R. Philip.

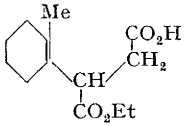
cis-9-Methyl-1-decalone (III), an intermediate suitable for the synthesis of compounds of the aetiocholane series, has been prepared by a new method and converted by a series of reactions similar to that used in its preparation into 1-*keto*-13-*methyl*-$\Delta^{11(12)}$-*dodecahydrophenanthrene* (VI). By Johnson's extension of the Stobbe reaction, 2-methyl*cyclo*hexanone has been transformed into a methyl-1-hydrindanone (probably XII).

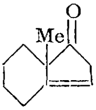
Cook and Schoental (*J.*, 1945, 288) described a simple synthesis of a hydroaromatic ketone, based on Ziegler's elegant method of preparation of methyl γ-bromocrotonate and its use in the Reformatsky reaction (*Annalen*, **1943**, **551**, 80, 120). The extension to other hydroaromatic systems was foreshadowed, and some preliminary work in this field is now recorded in view of the use of very similar methods by Bachmann and Wendler (*J. Amer. Chem. Soc.*, 1946, **68**, 2580). Our work, which has obvious possibilities in the synthesis of fully reduced compounds of the steroid group, is being extended in collaboration with Dr. S. H. Tucker and Mr. G. W. Crosbie.

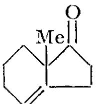
cis-9-Methyl-1-decalone (III) has been prepared by a variety of methods during the past decade; in many of them an intermediate is γ-(2-methyl*cyclo*hex-1-enyl)butyric acid (II), which is cyclised to 9-methyl-1-octalone by a process developed by Cook and Lawrence (*J.*, 1935, 1637; 1937, 817). In the present work this intermediate acid has been prepared by condensing 2-methyl*cyclo*hexanone with methyl γ-bromocrotonate and zinc to give the hydroxy-ester (I); this was hydrogenated and the resulting saturated hydroxy-ester was dehydrated to give the ester of the required acid (II). By this route, *cis*-9-methyl-1-decalone was obtained from 2-methyl*cyclo*hexanone in an overall yield of 20%.

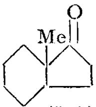


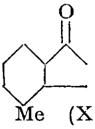

(VII.)


(VIII.)


(IX.)


(X.)


(XI.)


(XII.)

The dicyclic ketone so obtained was submitted to a new Reformatsky reaction with zinc and methyl γ-bromocrotonate, in order to build up a third six-membered ring. The crude hydroxy-ester (IV) which resulted was hydrogenated, and the product dehydrated and then hydrolysed. The resulting acid, which appeared to consist essentially of (V), was not obtained crystalline and the crude material was submitted to an internal Darzens reaction which gave a mixture of 1-*keto*-13-*methyl*-Δ-$^{11(12)}$-*dodecahydrophenanthrene* (VI) and an amorphous material having the character of a lactone. The latter (possibly VII) gave a further amount of the tricyclic ketone (VI) when its solution in acetic acid and acetic anhydride, containing zinc chloride, was boiled for

5 hours. The intermediate products in this series of reactions have not yet been characterised, and the structure of the ketone (VI) requires confirmation in view of the possibility of methyl migration in the dehydration of the hydroxy-ester (IV).

The ketone (VI), if available in sufficient quantity, may conceivably be converted into 1-keto-2 : 13-dimethylperhydrophenanthrene, from which a sterol ring system might be elaborated by building on a five-membered ring. For this last process several possible methods are available, of which a particularly promising one is the modified Stobbe reaction and ring-closure devised by Johnson *et al.* (*J. Amer. Chem. Soc.*, 1945, **67**, 1360, 1366). As a model for this, we have condensed 2-methyl*cyclo*hexanone with ethyl succinate by means of potassium *tert.*-butoxide. This led to the *half-ester* (VIII or an isomeride), which was converted by zinc chloride in acetic acid and acetic anhydride and then hydrochloric acid into an unsaturated ketone which, from the m. p. of its *semicarbazone*, was clearly different from the ketone (IX or X) synthesised by Chuang, Tien, and Ma (*Ber.*, 1936, **69**, 1494). Hydrogenation of our ketone gave a saturated ketone of which the semicarbazone melted at a temperature (210°) slightly lower than the figure given by Chuang, Tien, and Ma for the semicarbazone of their corresponding saturated ketone. This m. p. was, however, much lower than those given by other workers (Kon, Linstead, and Simons, *J.*, 1937, 814; Robinson and Walker, *J.*, 1937, 1160; Bachmann and Kushner, *J. Amer. Chem. Soc.*, 1943, **65**, 1963) for the semicarbazones of the pure *cis*- and *trans*-8-methyl-1-hydrindanones (XI) (*e.g.*, *cis*, 225°; *trans*, 242°). For comparison, therefore, an authentic specimen of *cis*-8-methyl-1-hydrindanone was prepared by degradation of *cis*-9-methyl-1-decalone (III) (cf. Johnson, *J. Amer. Chem. Soc.*, 1943, **65**, 1317; 1944, **66**, 215). Its semicarbazone depressed the m. p. of the semicarbazone of our ketone under examination. This evidence suggests that our ketone is not one of the 8-methyl-1-hydrindanones but a structural isomeride (XII).

EXPERIMENTAL.

New Synthesis of γ-(2-*Methyl*cyclo*hex*-1-*enyl*)*butyric Acid* (II).—Pure zinc filings (10 g.), prepared by milling arsenic-free zinc rods, were placed in a flask with a little mercuric chloride and heated over a free flame until a sublimate formed. The activated zinc was covered with benzene (50 c.c.), which was heated to boiling and then cooled. 2-Methyl*cyclo*hexanone (11 g.) and methyl γ-bromocrotonate (21 g.) were then added. A vigorous reaction set in and the solution boiled spontaneously for 5—7 minutes, water-cooling being used as necessary to moderate the reaction. The whole was then boiled by steam-heating for ½ hour, cooled, and the zinc complex decomposed by the addition of ice-cold dilute hydrochloric acid. The product was extracted with ether, and the extract was dried (Na_2SO_4) and distilled. A solution of the distillate (I ; 11 g.), b. p. 170—175°/15 mm., in ethanol (45 c.c.) was shaken with palladium black (0·1 g.) and hydrogen until absorption was complete (13 hours). The saturated hydroxy-ester (9 g.) had b. p. 144—160°/12 mm. For dehydration, a few crystals of iodine were added to this material (6·1 g.) and the liquid was heated almost at its b. p. for ½ hour. Water was liberated. The resulting unsaturated ester was hydrolysed by aqueous methanolic sodium hydroxide at room temperature (24 hours) and the acidic product isolated in the usual way. The crude solid acid (4·9 g.), when pressed on porous porcelain, had m. p. 39° [Elliott and Linstead, *J.*, 1938, 660, give m. p. 44° for γ-(2-methyl*cyclo*hex-1-enyl)butyric acid]. Dehydration of the hydroxy-ester was also effected by anhydrous sodium hydrogen sulphate at 180° in ½ hour. The unsaturated acid (II) was cyclised in the usual way (cf. Cook and Lawrence, *loc. cit.*), The resulting 9-methyloctalone gave a semicarbazone, m. p. 225—226° (Found : C, 65·4; H, 8·5; N, 18·8. Calc. for $C_{12}H_{19}ON_3$: C, 65·1; H, 8·5; N, 19·0%), and the m. p. was not depressed by admixture with an authentic specimen. The unsaturated ketone (4·5 g.) was hydrogenated to *cis*-9-methyl-1-decalone with a palladium-black catalyst. On a larger scale it was found convenient to work under pressure. A solution of the methyloctalone (50 g.) in ethanol (500 c.c.) was agitated at 50° for 6 hours with palladised strontium carbonate (20 g.) and hydrogen (initial pressure, 115 atmospheres). The crude distilled 9-methyl-1-decalone (44 g.), b. p. 108—112°/12 mm., gave a semicarbazone which crystallised from ethanol in colourless needles, m. p. 221—222°, depressed to 204—207° by admixture with the semicarbazone of the unsaturated ketone (Found : C, 64·7; H, 9·5. Calc. for $C_{12}H_{21}ON_3$: C, 64·4; H, 9·4%).

1-*Keto*-13-*methyl*-$\Delta^{11(12)}$-*dodecahydrophenanthrene* (VI).—*cis*-9-Methyl-1-decalone (10 g.) was added to a suspension of amalgamated zinc (10 g.), prepared as described above, in benzene (50 c.c.). To the warm solution methyl γ-bromocrotonate (20 g.) was added. The vigorous reaction was moderated by water-cooling, and was completed by boiling under reflux for ½ hour. The suspension of zinc complex was then cooled and decomposed by stirring with ice-cold dilute hydrochloric acid. Ether was added, and the ether–benzene layer was collected, washed, and dried (Na_2SO_4), and the solvents were distilled on the water-bath. The residual brown oil (containing IV) (14·8 g.) was dissolved in ethanol (100 c.c.) and shaken with hydrogen and palladium-black (0·2 g.) until absorption ceased (10—12 hours). Further absorption was then brought about by addition of more catalyst, the total uptake of hydrogen being 650 c.c. After removal of the solvent from the filtered solution, the residue was heated to boiling for ½ hour, after addition of a few crystals of iodine. The crude unsaturated ester was hydrolysed at room temperature with aqueous methanolic sodium hydroxide. The neutral material which was then recovered by ether extraction was shown to consist of unreacted 9-methyl-1-decalone (*ca.* 4 g.). Acidification of the aqueous alkaline solution gave a brown viscous gum (5·9 g.) which appeared to be a mixture of the unsaturated acid (V) and the lactone (VII).

The crude mixture was treated with thionyl chloride (2·5 c.c.) in pyridine and pure ether and the crude acid chloride so formed was treated with stannic chloride in carbon disulphide at −15° (compare Cook and Lawrence, *loc. cit.*). After decomposition with ice and hydrochloric acid there separated a brown gum, insoluble in both phases, which solidified when treated with aqueous ethanol. The resulting brown amorphous material (0·8 g.) could not be crystallised. It had the character of a lactone (VII ?), and when its solution in acetic acid (13 c.c.), and acetic anhydride (14 c.c.) containing zinc chloride (60 mg.) was boiled for 4½ hours there was formed a ketonic product, which after distillation at 110—130°/0·3 mm. gave the 2 : 4-dinitrophenylhydrazone, m. p. 225°, described below.

The carbon disulphide solution from which the lactonic material had been separated was distilled, dimethylaniline (2 g.) was added, and the solution then heated at 200° for 3 hours. The neutral material isolated after working up in the usual way was distilled from an air-bath at 105—108°/0·25 mm. and formed a mobile yellow oil (0·7 g.), probably consisting of (VI). The 2 : 4-*dinitrophenylhydrazone* crystallised from acetic acid in red microscopic needles, m. p. 225° (Found: C, 63·7; H, 6·9; N, 14·3. $C_{21}H_{26}O_4N_4$ requires C, 63·3; H, 6·6; N, 14·1%). The *semicarbazone* had m. p. 245—246° (Found: C, 69·7; H, 8·9; N, 15·25. $C_{16}H_{25}ON_3$ requires C, 69·8; H, 9·1, N, 15·3%).

Methyl-1-hydrindanone.—A mixture of 2-methyl*cyclo*hexanone (5·6 g.) and ethyl succinate (13 g.) in *tert.*-butyl alcohol (10 c.c.) was added to an ice-cold solution of potassium *tert.*-butoxide (from 2·15 g. of potassium and 40 c.c. of *tert.*-butyl alcohol). The brownish-red solution was heated under reflux for 40 minutes in an atmosphere of nitrogen and then kept at room temperature for 4 hours. Acidification gave a straw-coloured solution which was concentrated under reduced pressure. Addition of water dissolved the potassium chloride which separated, and sufficient sodium carbonate solution was then added to give an alkaline solution. Undissolved oil was extracted with ether, and the reaction product was precipitated from the aqueous solution by addition of hydrochloric acid. This was extracted with ether and distilled from an air-bath at 0·15 mm. The upper fraction (temperature of bath 130—150°) was a viscous liquid which crystallised after several days. Recrystallisation from ligroin and then hexane gave colourless leaflets, m. p. 99—100°, of *β-carbethoxy-β-(2-methyl*cyclo*hex-1-enyl)propionic acid* (VIII) (Found: C, 65·1; H, 8·2. $C_{13}H_{20}O_4$ requires C, 65·0; H, 8·3%). An attempt to effect a similar condensation of 2-methyl*cyclo*hexanone with ethyl glutarate was unsuccessful (cf. Johnson, Johnson, and Petersen, *J. Amer. Chem. Soc.*, 1946, **68**, 1926).

The distilled, but not recrystallised, half-ester (VIII) (2 g.) was dissolved in a mixture of acetic anhydride (28 c.c.), acetic acid (10 c.c.), and an acetic acid solution of zinc chloride (6 c.c. of solution containing 70 mg. of zinc chloride per c.c.). The solution was boiled for 4 hours, during which a stream of nitrogen was passed. The solution was then evaporated under reduced pressure. The residual oil was decarbethoxylated by boiling its solution in acetic acid (10 c.c.) and concentrated hydrochloric acid (8·5 c.c.) for 40 minutes. The solution was again evaporated under reduced pressure and the residue was warmed on the water-bath for several hours with 5% potassium hydroxide solution (40 c.c.). Finally, the product was extracted with ether and the crude unsaturated ketone recovered from the extract. This (0·3 g.) gave a *semicarbazone* which formed clusters of colourless needles (from ethanol), m. p. 240·5°, after becoming discoloured at 230° (Found: C, 63·4; H, 8·0; N, 20·2. $C_{11}H_{17}ON_3$ requires C, 63·8; H, 8·2; N, 20·3%).

For hydrogenation, a solution of the crude unsaturated ketone (0·6 g.) in ethanol (30 c.c.) was shaken with hydrogen and palladium-black (0·1 g.) until hydrogen was no longer absorbed. The resulting saturated ketone (probably XII) gave a semicarbazone which crystallised from ethanol in colourless needles, m. p. 210—211°. The mixed m. p. with a specimen of the semicarbazone, m. p. 222—223°, of *cis*-8-methyl-1-hydrindanone (XI), prepared by degradation of *cis*-9-methyl-1-decalone, was 200—202°, after previous sintering.

UNIVERSITY OF GLASGOW.

[*Received, March 5th*, 1947.]