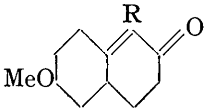
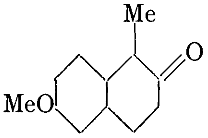
74. *Experiments on the Synthesis of Substances related to the Sterols. Part XXXI.*

By J. G. Cook and Sir Robert Robinson.

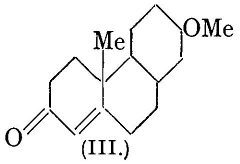
Earlier work (cf. the preceding communication) has shown how rings *A*, *B*, and *C* of testosterone may be constructed and further progress along two lines sought. In the first place the synthesis of the hormone itself is not quite out of reach, but, secondly, ring *C* might be provided with reactive groups which would make the synthesis of close analogues of the androgenic hormones possible. For the reasons mentioned in Part XXX, nuclear synthesis of the appropriate intermediates holds out the best hope of success and the present communication deals with some experiments in this direction.



(I.)

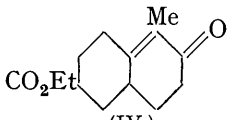


(II.)

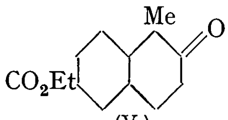


(III.)

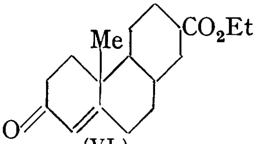
Starting with 4-methoxy*cyclo*hexanone, the *ketones* (I, R = H or Me), (II), and (III) have been obtained, and starting with ethyl *cyclo*hexanone-4-carboxylate, the *ketones* (IV), (V), and (VI) were similarly synthesised.



(IV.)



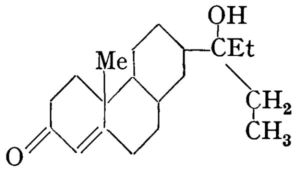
(V.)

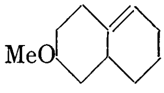


(VI.)

A preliminary attempt to convert (VI) into (VII), which is a close analogue of testosterone, was made and it is hoped that further work on these lines may be pursued.

(VII.)





(VIII.)

4-Methoxy*cyclo*hexanone was converted into a " Mannich base " by reaction with paraformaldehyde and diethylamine hydrochloride, but this decomposed on distillation and was accordingly converted into a methiodide without purification.

This salt condensed with ethyl acetoacetate in alcoholic sodium ethoxide and on hydrolysis the *ketone* (I, R = H) was obtained (cf. Du Feu, McQuillin, and Robinson, J., 1937, 53). This unsaturated ketone could not be converted into an oxide. Reduction by the Wolff or the Clemmensen method afforded 6-*methoxy*-$\Delta^{1:9}$-*octalin* (VIII), the chlorohydrin of which could not be obtained. Catalytic reduction of the ketone gave 6-*methoxy*-2-*decalone*. Ethyl β-ketovalerate being used instead of ethyl acetoacetate, the corresponding 1-*methyl* derivatives (I, R = Me) and (II) were obtained. (II), condensed with diethylaminobutanone methiodide in ethereal solution in the presence of sodamide, furnished (III), which may prove a useful intermediate.

The synthesis of (VI) has been effected by an analogous process and this substance also is well adapted to serve as a basis for attempts to make compounds related to the androgens.

EXPERIMENTAL.

6-*Methoxy*-$\Delta^{1:9}$-2-*octalone* (I, R = H).—A mixture of 4-methoxy*cyclo*hexanone (12 g.), diethylamine hydrochloride (12 g.), paraformaldehyde (3 g.), and alcohol (5 c.c.) was refluxed for 4 hours. Water was added, and the non-basic material removed by means of ether. The aqueous solution was then saturated with potassium carbonate and extracted with ether, and the extract dried and distilled. The colourless oil (6·2 g.) had b. p. 175°/20 mm. and was free from nitrogen (Found : C, 68·6; H, 8·6%).

A better result was obtained when the alcohol in this experiment was replaced by water and the crude oil (10 g.) obtained was not distilled but converted into the methiodide by mixing the components at 0°. Crude methiodide (100 g.) so obtained was washed with ether, dissolved in the minimum quantity of alcohol, and added to ethyl sodioacetoacetate (from 10 g. of sodium and 54 g. of the ester) dissolved in alcohol (200 c.c.). The solution was refluxed for 4 hours, the alcohol evaporated, and the product isolated by addition of water and extraction with ether. On distillation a pale yellow oil (19 g.), b. p. 170—175°/20 mm., was obtained.

For the purpose of analysis, it was found necessary to remove a small quantity of monocyclic diketone by treatment with either sodium ethoxide in ether or 50% sulphuric acid at 50°, followed by distillation (Found : C, 73·1; H, 8·9. $C_{11}H_{16}O_2$ requires C, 73·3; H, 8·9%). This unsaturated *ketone* did not yield an oxide on treatment with hydrogen peroxide and sodium hydroxide or with perbenzoic acid in chloroform solution.

By reaction with methylmagnesium iodide a product, b. p. 125—130°/15 mm., was obtained (Found : C, 82·5; H, 10·2. $C_{12}H_{18}O$ requires C, 81·0; H, 10·1%). This is probably essentially a 6-methoxy-2-methylhexalin, but the high value for carbon suggests contamination with an impurity derived by elimination of the methoxyl group.

6-*Methoxy*-$\Delta^{1:9}$-*octalin* (VIII).—(*a*) Methoxy-2-octalone (1 g.) was refluxed for 12 hours with an excess of hydrazine hydrate, the product extracted with ether, and the solution dried and evaporated. The residue was dissolved in alcohol (5 c.c.) and heated with sodium ethoxide (5 g.) at 180° in a sealed tube for 18 hours. The alcohol was removed, water added, and the product isolated by means of ether; it distilled as a colourless, sweet-smelling oil (5 g.), b. p. 105°/13 mm.

(*b*) Methoxyoctalone (3·7 g.) was dissolved in a little toluene and added to zinc amalgam (6 g.) and concentrated hydrochloric acid (30 c.c.). The mixture was refluxed for 12 hours, cooled, and extracted with ether. On distillation a colourless oil (2·5 g.), b. p. 110°/15 mm., was obtained (Found : C, 79·7; H, 10·9. $C_{11}H_{18}O$ requires C, 79·5; H, 10·8%). There was also obtained a fraction (1·0 g.), b. p. 240°/15 mm.

An attempt to prepare the chlorohydrin of this *methoxyoctalin* was unsuccessful. The analytical results indicated clearly that the action of hypochlorous acid on the unsaturated substance afforded a monochloro-derivative (b. p. 170°/15 mm.).

6-*Methoxy*-2-*decalone*.—A solution of methoxyoctalone (2 g.) in methyl alcohol (20 c.c.) was shaken for 18 hours with a palladium–strontium carbonate catalyst (5 g. of 2%) under hydrogen at 3 atms. The alcohol was removed; the residue distilled as a colourless oil (1·6 g.), b. p. 150°/15 mm. (Found : C, 72·5; H, 10·0. $C_{11}H_{18}O_2$ requires C, 72·5; H, 9·9%).

6-*Methoxy*-1-*methyl*-2-*decalone* (II).—The crude methiodide of 4-methoxy-2-diethylaminomethyl*cyclo*hexanone (20 g.) was dissolved in a little alcohol and added to a solution of ethyl sodio-β-ketovalerate (1·6 g. of sodium and 10 g. of the ester) in alcohol (70 c.c.). The mixture was refluxed for 4 hours, the alcohol evaporated, and water added. 6-Methoxy-1-methyl-$\Delta^{1:9}$-2-octalone was isolated in the usual way; it distilled as a light yellow oil (4 g.), b. p. 145°/15 mm. Analysis indicated admixture with a monocyclic diketone. The crude substance (2·3 g.), dissolved in methyl alcohol (20 c.c.), was shaken for 24 hours with hydrogen at 3 atms. in the presence of a palladium–strontium carbonate catalyst (5 g. of 2%). On working up in the known manner, 6-*methoxy*-1-*methyl*-2-*decalone* was obtained as a colourless, sweet-smelling oil (2 g.), b. p. 140°/10 mm. (Found : C, 73·4; H, 10·3. $C_{12}H_{20}O_2$ requires C, 73·5; H, 10·2%).

2-*Keto*-7-*methoxy*-12-*methyl*-$\Delta^{1:11}$-*dodecahydrophenanthrene* (III).—A mixture of the above saturated ketone (2 g.), sodamide (0·5 g.), and dry ether was refluxed for 8 hours in an atmosphere of nitrogen. A solution of diethylaminobutanone methiodide (from 1·6 g. of the base) in alcohol (7 c.c.) was added, and refluxing continued for 12 hours. Water was then added, and the products isolated by means of ether and distilled, giving unchanged ketone (1 g.), b. p. 140°/10 mm., and a thick yellow oil (0·7 g.), b. p. 170°/1 mm. (Found : C, 72·5; H, 9·2. $C_{16}H_{26}O_3$ requires C, 72·2; H, 9·8%).

Ethyl 1-*Methyl*-2-*decalone*-6-*carboxylate* (V).—An alcoholic solution of ethyl *cyclo*hexanone-4-carboxylate (18 g.), diethylamine hydrochloride (12 g.), and paraformaldehyde (3·5 g.) was refluxed for 5 hours. Water was then added, and the neutral substances extracted with ether. The aqueous solution was basified (potassium carbonate), and the oil collected by means of ether. The residual oil (ethyl 2-diethylaminomethyl*cyclo*hexanone-4-carboxylate) was converted into the methiodide by mixing with methyl iodide at 0°.

The crude methiodide (30 g.), dissolved in a little alcohol, was added to ethyl sodio-β-keto-valerate (from 2·3 g. of sodium and 14 g. of ester) in alcohol (70 c.c.), and the mixture refluxed for 10 hours. On working up in the usual way, ethyl 1-methyl-$\Delta^{1:9}$-2-octalone-6-carboxylate (IV) was obtained as a yellow oil (4 g.), b. p. 197°/10 mm. This keto-ester (3·5 g.), dissolved in methyl alcohol (10 c.c.), was shaken for 24 hours with hydrogen in the presence of a mixture of palladised strontium carbonate and norit. *Ethyl* 1-*methyl*-2-*decalone*-6-*carboxylate* was isolated in the usual way as a colourless oil (3·2 g.), b. p. 180—190°/10 mm. (Found : C, 70·6; H, 9·2. $C_{14}H_{22}O_3$ requires C, 70·4; H, 9·3%).

Ethyl 2-*Keto*-12-*methyl*-$\Delta^{1:11}$-*dodecahydrophenanthrene*-7-*carboxylate* (VI).—A mixture of the above saturated ester (2·5 g.), sodamide (5 g.), and dry ether (25 c.c.) was refluxed for 8 hours under nitrogen. A solution of the methiodide of diethylaminobutanone (1·5 g. of base) in alcohol was added, and the mixture refluxed for a further 14 hours. After addition of water and collection by means of ether, distillation afforded unchanged ester (1 g.), b. p. 140°/1 mm., and a thick yellow oil (5 g.), b. p. 180°/1 mm. (Found : C, 74·2; H, 8·7. $C_{18}H_{26}O_3$ requires C, 74·5; H, 8·3%). This substance was reduced by the Pondorff method (production of acetone noted), and the product isolated and treated with ethylmagnesium bromide. The final product was isolated and oxidised by the Oppenauer method, giving a thick yellowish oil, which was distilled under 1 mm. The substance might, and indeed should, have the structure (VII), but the work had to be abandoned before we could satisfy ourselves on this point. Professor J. H. Burn found it to be non-androgenic (capon test) in doses of 0·27 g. The *tert.*-alcohol group may have undergone dehydration.

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