397. *Experiments on the Synthesis of Substances related to the Sterols. Part XLIX. The A ⟶ BCD Route to Androstenedione. Part II.*

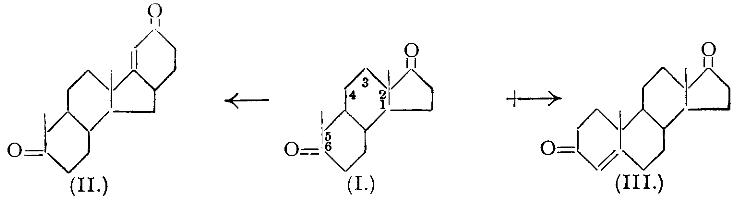
By R. H. Martin and Sir Robert Robinson.

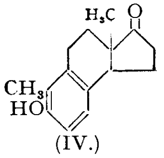
Further examination of the condensation of 4-diethylaminobutan-2-one methiodide and 3′ : 6-diketo-2 : 5-dimethyldecahydro-1 : 2-*cyclo*pentenonaphthalene-x-α (I) in the presence of sodium ethoxide, has shown that the main product at least is a derivative (II) of 1 : 2-benzfluorene and not, as was hoped, of 1 : 2-*cyclo*pentenophenanthrene (cf. III). This follows from a comparison of ultra-violet absorption of substances obtained from the condensation product on the one hand, and a mixture of *cis*- and *trans*-androstenediols on the other, by successive reduction, dehydration, and dehydrogenation.

In order to render the continuation of the synthesis by this route feasible, it will be necessary to prepare a keto-alcohol related to (I) and in which the keto-group is in position 6 of the reduced naphthalene nucleus. Some observations of a miscellaneous character are included, partly bearing on this problem, and partly relating to matters encountered at various stages of the synthesis of (I).

In Part XLI (*J.*, 1943, 491) the present authors described the synthesis of two inactive stereoisomerides of the phenolic ketone (IV), and the diketone (I) was obtained from the more abundant α-isomeride by catalytic reduction followed by oxidation.

An individual compound (I) was isolated but in order to determine the course of the condensation with the Mannich-base methiodide, a mixture of stereoisomerides resulting at the hydrogenation stage was employed. The product was a viscous oil showing the absorption spectrum of an αβ-unsaturated ketone. We had good reason to expect the formation of (III) from analogy with the behaviour of 1-methyl-2-decalone (Robinson and Weygand, *J.*, 1941, 386). It was clearly stated, however, that we had not been able to establish the constitution of the product; we considered the position that would confront us if the condensation had taken the course to (II) (or another undesired direction not indicated above), and in the experimental section we discussed only the ketones, $C_{19}H_{26}O_2$, without naming them.





In the event we have found the mixture of ketones, $C_{19}H_{26}O_2$, to consist chiefly of substances of the structure (II) though we cannot exclude the formation of a small proportion of stereoisomerides (III) (or of the third type resulting from attack of position 7 of the decalone nucleus).

The only possible method of investigation was clearly by degradation to a recognisable aromatic hydrocarbon and we first practised with androstenedione.

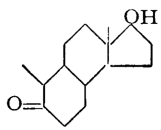
We are very grateful to Messrs. Organon Laboratories and in particular to Dr. C. L. Hewett for gifts of androstenedione and androstenediol.

Androstenedione was reduced by means of sodium and *n*-propanol and the resulting diol was dehydrated by heating with potassium hydrogen sulphate. After dehydrogenation with selenium at 320—340°, the product was chromatographically purified and then crystallised. Its ultra-violet absorption spectrum showed that it was a derivative of 1 : 2-*cyclo*pentenophenanthrene and it was probably essentially the 3′-methyl derivative of this hydrocarbon.

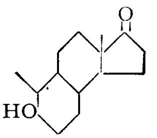
The unsaturated ketones, $C_{19}H_{26}O_2$, gave, by the same treatment, a hydrocarbon of much higher m. p. and contrasting ultra-violet spectrum. The latter resembles the spectrum of 4′-methyl-1 : 2-benzfluorene as described by Mayneord and Roe (*Proc. Roy. Soc.*, 1937, *A*, **158**, 634). Although the first attempt to exploit this A ⟶ BCD route has thus broken down, our resources are far from exhausted thereby, and the obvious programme for further work is to attempt the synthesis of a keto-alcohol corresponding to (I) (6-keto-, 3′-hydroxy-).

In this connexion it is of interest that the pressure-hydrogenation of the phenolic ketone (IV) in ethyl acetate solution in the presence of palladised strontium carbonate has afforded a keto-acetate which, on hydrolysis, is changed to a keto-alcohol. The orientation of the carbonyl and the hydroxyl group in this substance or mixture of substances (V, or VI, or both) has not yet been determined.

The experimental section contains some additional details relating to the intermediates, including the identification of certain by-products.



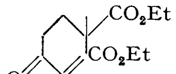
(V.)



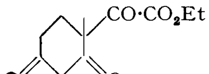
(VI.)

Two matters not so closely connected with the main series of substances are the following.

The condensation of diethylaminobutanone methiodide with ethyl α-ethoxalylpropionate in the presence of sodium ethoxide might have yielded (VII) which would have been of interest to us. However, the second phase of the process involved loss of the elements of alcohol and the product had the properties of a derivative of dihydroresorcinol (VIII).



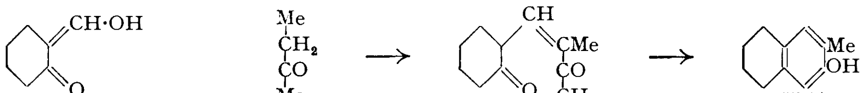
(VII.)



(VIII.)

In Part XLI (*loc. cit.*, p. 493) we described 6-hydroxy-5-methyltetralin, m. p. 113·5—114·5°. It was prepared from 2-methoxy-1-naphthaldehyde by successive hydrogenation and demethylation and therefore the orientation of the substituents seems established.

Parajape, Phalnikar, Bhide, and Nargund (*Rasâyanam*, **1943**, **1**, 273) considered that they had obtained the same hydroxymethyltetralin by condensation of 2-hydroxymethylene*cyclo*hexanone with methyl ethyl ketone, followed by treatment of the product with hydrochloric acid. As their methyltetralol had m. p. 78° it must be an isomeride, and it is almost certainly 6-hydroxy-7-methyltetralin (IX). This is the expected product if the primary condensation involves the methylene group of methyl ethyl ketone.



(IX.)

EXPERIMENTAL.

Degradation of Androstenediols.—Conditions for the reduction of androstenedione, dehydration of the resulting mixture of androstenediols, and finally for dehydrogenation of the product were first established for these substances and used without any modification for the unsaturated ketones $C_{19}H_{26}O_2$. The description given below for the synthetic ketones is therefore applicable.

The main blue-fluorescent band of the chromatogram was separated into 7 fractions by elution with light petroleum (b. p. 60—80°). The middle five fractions crystallised on removal of the solvent and were united and crystallised from methanol. The white, shiny plates had m. p. 115—120° raised to 124—125° (with slight previous sintering) by recrystallisation. The ultra-violet absorption in methanol was found by Dr. F. B. Strauss (Fig. 1) to be almost identical with that of 1 : 2-*cyclo*pentenophenanthrene (cf. Mayneord and Roe, *Proc. Roy. Soc.*, 1935, *A*, **152**, 299). It was probably slightly impure 3′-methyl-1 : 2-*cyclo*pentenophenanthrene.

Some Notes on the Preparation of (IV).—(1) Specimens of methyl oxalate often contain oxalic acid and this has a very deleterious effect on the yield in the methoxalylation stage. (2) The elimination of carbon monoxide from the methoxalyl ketone works best on a relatively small scale and a reduction in the proportion of powdered glass (25—50% of that specified) is advisable. (3) The Reformatzky reaction (*loc. cit.*, p. 494) can be carried out, without diminished yield, with 50 g. of the keto-ester. (4) Arndt–Eistert homologation failed in a series of experiments. This was traced to the use of impure benzene, and the original results (or somewhat better) were obtained when anhydrous "AnalaR" benzene was employed.

Hydrogenation of 6-*Hydroxy*-3′-*keto*-2 : 5-*dimethyl*-1 : 2 : 3 : 4-*tetrahydro*-1 : 2-cyclo*pentenonaphthalene*-a.—The phenolic ketone (*a*) (10 g.) was hydrogenated in ethyl acetate (120 c.c.) in the presence of palladised strontium carbonate (6 g. of 2%). The conditions were: initially, 18°/105 atms.; after 1¼ hours, 215°/156 atms.; after 2¼ hours, 220°/146 atms.; after 6¼ hours, 228°/131 atms.; after 10 hours, 228°/116 atms. The distilled reaction product was oxidised directly with chromic anhydride (cf. Part XLI, *loc. cit.*). A dark gum, precipitated on the addition of the chromic solution in the cold, had completely disappeared after 5 days at room temperature. The resulting product was isolated in the known manner and distilled. After a very small fraction of lower b. p. three fractions were collected: (*a*) air-bath, 130°/0·1 mm., n_D^{19} 1·4360 (Found: C, 79·9; H, 11·1%); (*b*) air-bath, 135°/0·1 mm., n_D^{19} 1·4530 (Found: C, 74·3; H, 9·6%); (*c*) air-bath, 140°/0·1 mm., n_D^{19} 1·4560 (Found: C, 74·3; H, 9·6; Ac, 17·0. $C_{17}H_{26}O_3$, *keto-acetate*, requires C, 73·3; H, 9·4; Ac, 15·5%). The acetate (fractions *b* and *c*) was hydrolysed by means of methanolic potassium hydroxide and the product distilled. The middle fraction (*ca.* 50%), air-bath, 145—150°/0·15 mm., had n_D^{20} 1·5200 (Found : C, 76·3; H, 10·1. $C_{15}H_{24}O_2$ requires C, 76·3; H, 10·2%). All fractions gave sparingly soluble, yellow 2 : 4-dinitrophenylhydrazones.

The condensation of this *keto-alcohol* (V or VI) with 4-diethylaminobutan-2-one methiodide in the presence of alcoholic sodium ethoxide gave, amongst other products, a fraction (separated by repeated chromatographic adsorption and distillation) which on analysis, appeared to be the open-chain *diketone-alcohol* that could be formed (Found : C, 74·4; H, 9·9. $C_{19}H_{30}O_3$ requires C, 74·5; H, 9·9%).

Even on treatment with anhydrous sodium methoxide in boiling benzene under nitrogen this substance did not lose one molecule of water (Found : C, 75·7; H, 10·2%). It is hoped that this material may be further investigated.

Hydrogenation of 3′-*keto*-6-*hydroxy*-2 : 5-*dimethyl*-1 : 2 : 3 : 4-*tetrahydro*-1 : 2-cyclo*pentenonaphthalene*-α. The tricyclic ketone (7·5 g.) was hydrogenated in ethanol (125 c.c.) in the presence of Raney nickel (2—3 g.). The conditions were: initially, 20°/115 atms.; after 50 minutes, 180°/160 atms.; after 1¼ hours, 204°/162 atms.; after 1¾ hours, 216°/149 atms.; after 2 hours, 2147/138 atms.; after 3 hours, 211°/137 atms. The solvent was removed and an ethereal solution of the product washed with aqueous sodium hydroxide (1·2 g. of alkaline-soluble material, see below). The yield of reduced material was 6·3 g. Despite the use of higher temperatures and longer periods of heating, the hydrogenation could never be brought to completion. The di-*sec.*-alcohol was oxidised with chromic anhydride and the diketone (α) isolated in the known manner (Found : C, 76·9; H, 9·8. Calc. for $C_{15}H_{22}O_2$: C, 76·9; H, 9·4%). A Zerewitinoff determination showed that active hydrogen was absent.

FIG. 1.

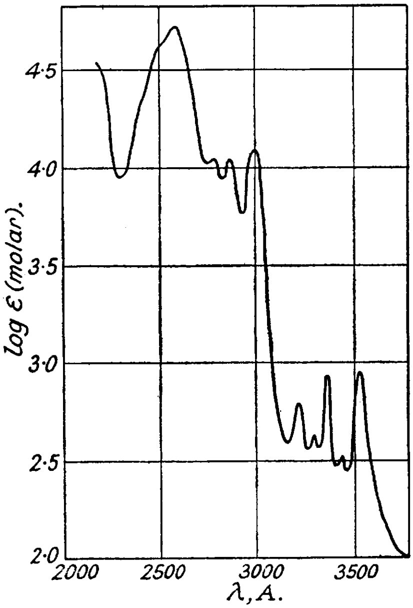
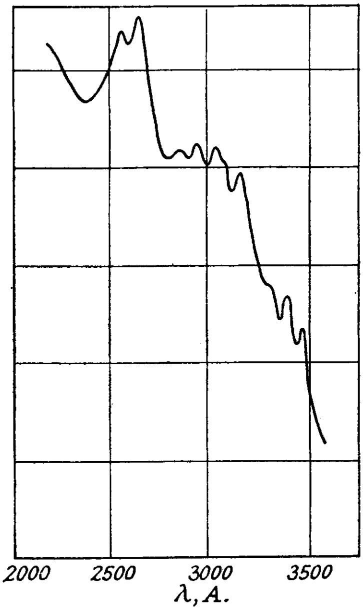


FIG. 2.



3′ : 6-*Dihydroxy*-2 : 5-*dimethyl*-1 : 2 : 3 : 4-*tetrahydro*-1 : 2-cyclo*pentenonaphthalene*-α.—The alkali-soluble material recovered from the above hydrogenation was distilled from an air-bath at 150—160°/0·1 mm. giving a colourless glass (Found : C, 77·6; H, 8·7. $C_{15}H_{20}O_2$ requires C, 77·5; H, 8·7%). This *compound* couples with *p*-nitrobenzenediazonium chloride to an azo-compound which gives a dark violet alkaline solution.

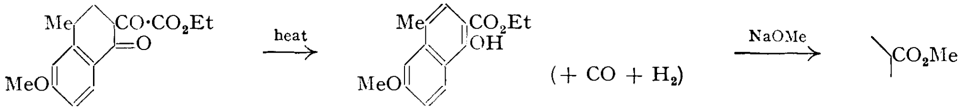
Hydrogenolysis of Methyl 1-*Hydroxy*-2-*carbomethoxy*-6-*methoxy*-2 : 5-*dimethyltetralin*-1-*acetate*.—The hydroxy-dimethyl ester (5 g.) in methanol (120 c.c.) was heated with hydrogen under pressure in the presence of Raney nickel (stirring). The initial conditions were 20°/97 atms. and after 2½ hours at 140—150° the products were isolated by known methods. The α-dimethyl ester of 2-carboxy-6-methoxy-2 : 5-dimethyltetralin-1-acetic acid (2·0 g.) was isolated; it had m. p. 110—112° and was identified by comparison with an authentic specimen (cf. Part XLI, *loc. cit.*). The reaction was accordingly simple replacement of hydroxyl by hydrogen.

Treatment of methyl 3′-keto-6-methoxy-2 : 5-dimethyl-1 : 2 : 3 : 4-tetrahydro-1 : 2-*cyclo*pentenonaphthalene-2-carboxylate-β with hydriodic acid in hot acetic acid solution afforded, in one experiment, 3′-*keto*-6-*methoxy*-2 : 5-*dimethyl*-1 : 2 : 3 : 4-*tetrahydro*-1 : 2-cyclo*pentenonaphthalene*-β. This separated from methanol in stout, white prisms, m. p. 117—118° (Found : C, 78·8; H, 8·4. $C_{16}H_{20}O_2$ requires C, 78·6; H, 8·3%).

Ethyl 6-*Methoxy*-2 : 5-*dimethyl*-1-*tetralone*-2-*carboxylate*.—A mixture of methyl 6-methoxy-2 : 5-dimethyl-1-tetralone-2-carboxylate and ethyl β-chloropropionate in benzene–ether was treated with lithium (cf. Nenitzescu and Przematzky, *Ber.*, 1941, **74**, 674). The reaction product was distilled (*ca.* 160°/0·4 mm.). For analysis it was chromatographed on alumina (B.D.H.) from benzene–light petroleum

(b. p. 40—60°). The non-fluorescent (ultra-violet light) material, eluted with benzene, crystallised from benzene–light petroleum (b. p. 40—60°) in colourless prisms, m. p. 58—59° (Found : C, 69·3; H, 7·3. $C_{16}H_{20}O_4$ requires C, 69·5; H, 7·3%). This *ethyl* ester is insoluble in aqueous sodium carbonate and is saturated towards hydrogen (in the presence of a palladium catalyst), potassium permanganate, and bromine. On boiling with a 30% aqueous solution of sodium hydroxide it gave 6-methoxy-2 : 5-dimethyl-1-tetralone (cf. Part XLI). It is therefore probably the ethyl ester corresponding to the starting material. No organo-metallic type of synthesis occurred.

Methyl 1-*Hydroxy*-6-*methoxy*-5-*methyl*-2-*naphthoate*.—The product of methylation of methyl methoxymethyltetralonecarboxylate (cf. Part XLV) was adsorbed after distillation on a column of charcoal from benzene–light petroleum (b. p. 40—60°), and the column washed with pure benzene. The non-fluorescent fraction consisted of pure methylated material and did not give a ferric reaction. The fluorescent material (ultra-violet light) was eluted with ether. It crystallised from methanol in colourless prisms, m. p. 160·5—161·5° (Found : C, 68·2; H, 5·6. $C_{14}H_{14}O_4$ requires C, 68·2; H, 5·7%). The *ester* is insoluble in aqueous sodium carbonate, couples with *p*-nitrobenzenediazonium chloride and diazobenzenesulphonic acid to azo-compounds, and gives a green coloration with ferric chloride in alcoholic solution. On hydrolysis with hot aqueous sodium hydroxide it gave a substance which was soluble in aqueous sodium carbonate. The most likely constitution is that given above and it is considered to owe its formation to dehydrogenation during the thermal decomposition of the ethoxalylketone :



The Mixed Unsaturated Ketones, $C_{19}H_{26}O_2$.—The penultimate stage was carried out as described in Part XLI (*loc. cit.*, p. 497) and led to stereoisomerides of 3′ : 6-diketo-2 : 5-dimethyldecahydro-1 : 2-*cyclo*pentenonaphthalene-*a*. The following modification was used for the last stage. A mixture of the diketones (2 g., not crystallised), powdered sodamide (2 g.) and ether (50 c.c.) was refluxed for 6 hours under nitrogen, then cooled in ice while a solution of 4-diethylaminobutan-2-one methiodide (from 2 g. of the base) in alcohol (25 c.c.) was slowly introduced (1½ hours). After another 1½ hours in ice, the mixture was kept at room temperature for 14 hours and finally refluxed for 45 minutes. The ethereal extract was distilled. The fraction boiling above 180°/0·1 mm. (air-bath) was redistilled, and the fraction of b. p. 180—190°/0·1 mm. (air-bath) chromatographed from benzene–light petroleum (b. p. 40—60°) (1 : 2). The main bluish-green fluorescent band (ultra-violet light) was eluted with pure benzene and distilled (air-bath) at 190—200°/0·1 mm. (Found : C, 79·8; H, 9·1. Calc. for $C_{19}H_{26}O_2$: C, 79·7; H, 9·2%). The absorption in alcoholic solution (*c*, 1·297 $\times 10^{-4}$) examined by Dr. F. B. Strauss showed $\lambda_{max.}$, 2420 A.; $\varepsilon_{max.}$, 11,780; log $\varepsilon_{max.}$, 4·071; $\varepsilon_{max.}$, 1·528 (cf. Part XLV).

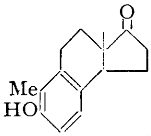
Degradation.—Sodium (10 g.) was added in small portions to a boiling solution of the ketones (0·9 g.), the combined product from a number of condensations (Found : C, 79·3; H, 9·1%) in *n*-propyl alcohol (175 c.c.). When all the sodium had disappeared, water was added and the solution neutralised with acetic acid. The alcohol was removed and the residue extracted with ethyl acetate. The organic layer was washed with aqueous sodium carbonate and water, and dried. The reduction product (0·9 g.) did not react with Brady's reagent.

It was dehydrated by heating for an hour at 180° with fused potassium hydrogen sulphate (2·5 g.). The product (0·65 g.) was then dehydrogenated by selenium (1·5 g.) during 26 hours at 320—340°. A benzene solution of the reaction product was passed through a very short column of charcoal. The solvent was removed, the residue adsorbed on alumina (B.D.H.) from light petroleum (b. p. 60—80°), and the column washed with pure light petroleum (b. p. 60—80°). The main blue-fluorescent band (ultra-violet light) was thus separated into three fractions (A, B, C) and by washing with pure benzene another fraction was obtained (D). These four fractions were rechromatographed separately and yielded 8—10 fractions each. No crystalline fractions were obtained from (A). The two middle fractions from (B) crystallised on removal of the solvent. One of the middle fractions from (C) also crystallised. None of the fractions from (D) could be induced to crystallise. The crystalline fractions from (B) and (C) were sublimed separately at 120°/0·1 mm. and shown to be identical by their absorption spectrum. They were therefore combined and crystallised from methanol. The substance separated in glistening, white plates, m. p. 175—180° raised to 190—198° after recrystallisation. Insufficient material was available for further purification. The absorption in ether of this substance (m. p. 190—198°) was examined by Dr. F. B. Strauss and shows clearly that it is a derivative of 1 : 2-benzfluorene (probably 4′-methyl-1 : 2-benzfluorene) (cf. Fig. 2 and Mayneord and Roe, *loc. cit.*). A thorough search for other crystalline hydrocarbons in the dehydrogenation product failed.

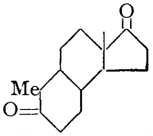
Ethyl 2 : 4-*Diketo*-1-*methyl*cyclo*hexane*-1-*glyoxylate* (VIII).—A solution of sodium ethoxide (2·5 g. of sodium) in anhydrous alcohol (50 c.c.) and benzene (25 c.c.) was added dropwise in an atmosphere of nitrogen to a well-stirred solution of ethyl ethoxalylpropionate (20·2 g.; *Org. Synth.*, 1937, **17**, 54) in benzene (30 c.c.). 4-Diethylaminobutan-2-one methiodide (from 15 g. of the base) in absolute alcohol (50 c.c.) was added gradually to the above ice-cooled solution. The mixture was kept in ice for 2 hours and at room temperature overnight. A further solution of sodium ethoxide (2 g. of sodium) in alcohol (25 c.c.) was added, and the mixture kept for two days at the room temperature. The solution was poured on ice and hydrochloric acid and extracted with ether. The ethereal solution was washed with aqueous sodium hydrogen sulphite, aqueous sodium carbonate, and water. Distillation of the product gave : (i) b. p. 105—109°/9 mm.; (ii) b. p. 150°/0·6 mm. The second fraction on redistillation gave a very pale yellow oil, b. p. 138—140°/0·5 mm. (Found : C, 58·4; H, 6·5. $C_{11}H_{14}O_5$ requires C, 58·4; H, 6·2%).

With ferric chloride in methanol this *diketo*-ester gave a dark brown-red coloration. On treatment of an alcoholic solution with semicarbazide acetate an intense red colour developed and a yellow solid soon separated, m. p. 195—198° (decomp.). It crystallised from methanol in almost colourless crystals, m. p. 198—201° (decomp.) to a red liquid (Found : C, 50·9; H, 6·0. $C_{12}H_{17}O_5N_3$ requires C, 50·9; H, 6·0%). This *semicarbazone* gave a violet coloration with ferric chloride in methanol.

Biological Tests.—



(β) Not œstrogenic.



(α) Not androgenic.

Unsaturated ketones, $C_{19}H_{26}O_2$ (α). Not androgenic.

We wish to thank Mr. F. Hastings for help in the preparation of some of the starting materials, and Imperial Chemical Industries Ltd. for financial assistance. We are also indebted to Prof. E. C. Dodds, F.R.S., for biological tests.

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