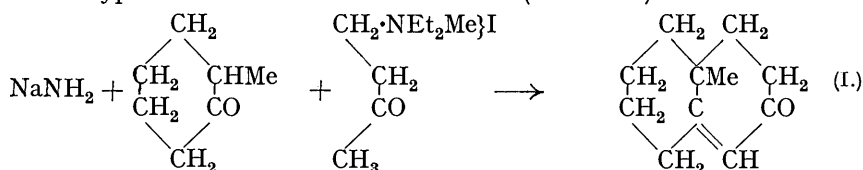


**13. Experiments on the Synthesis of Substances related to the Sterols. Part XIV. A Simple Synthesis of Certain Octalones and Ketotetrahydrohydrindenes which may be of Angle-methyl-substituted Type. A Theory of the Biogenesis of the Sterols.**

By E. C. DU FEU, F. J. MCQUILLIN, and ROBERT ROBINSON.

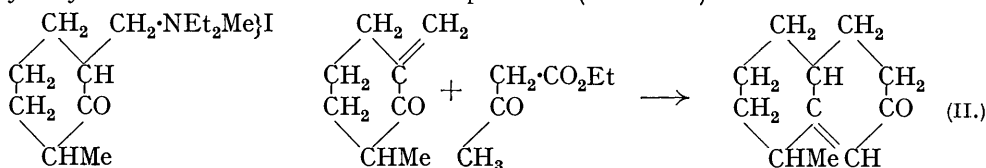
A LARGE number of experiments have been made with the object of extending the scope of the synthesis of cyclohexenones described by Rapson and Robinson (J., 1935, 1285) so as to embrace the condensation of cyclic ketones with the simpler  $\alpha\beta$ -unsaturated ketones such as methyl vinyl ketone. Owing, however, to the ready polymerisation of these substances in the presence of catalysts, no direct condensation could be realised analogous to those which succeed with acetylcyclohexene or acetylcyclopentene. We therefore made trials with substances capable of ready decomposition with formation of the unsaturated ketones, hoping to take advantage in this way of the progressive liberation of the reactant in minimal concentration and at optimal reactivity. No success followed our earlier attempts to employ the  $\beta$ -chloroalkyl methyl ketones, but when most of the present work was completed the condensation of 2-methylcyclohexanone and methyl  $\beta$ -chloroethyl ketone in alcoholic solution in the presence of sodium ethoxide was found to yield (about 15–20%) 2-keto-10-methyl- $\Delta^{1:9}$ -octalin (I). Apart from this case we have employed quaternary ammonium salts as the source of the unsaturated ketones. The crude, uncrystallisable methiodides of bases prepared by the Mannich reaction (condensation of a keto-methylene with diethylamine hydrochloride and formaldehyde,  $\cdot\text{CO}\cdot\text{CH}_2\cdot + \text{CH}_2\text{O} + \text{NHEt}_2 \longrightarrow \cdot\text{CO}\cdot\text{CH}\cdot\text{CH}_2\cdot\text{NEt}_2$ ) were condensed under various conditions with the sodio-derivatives of ketones or with ketones (containing  $\cdot\text{CO}\cdot\text{CH}\cdot$ ) in the presence of sodium ethoxide. A typical case is that illustrated below (method A) :



The yield in this example was 35–40%. The constitution (I) attributed to the product follows from its behaviour on dehydrogenation and from the independent synthesis of the isomeride which might have been obtained if the 6-methylene group of 2-methylcyclohexanone had been implicated in the reaction.

The methyloctalone (I) was not dehydrogenated on heating with palladised charcoal, and when heated with selenium it afforded  $\beta$ -naphthol in poor yield. Catalytic reduction of (I) afforded a crystalline methyldecalone.

For the preparation of 2-keto-8-methyl- $\Delta^{1:9}$ -octalin (II), the "Mannich" base from 2-methylcyclohexanone was converted into a methiodide and then condensed with ethyl acetoacetate in alcoholic sodium ethoxide; the intermediate  $\beta$ -ketonic ester suffered hydrolysis under the conditions of the experiment (method B) :



The methyl octalone (II) is quite different from (I); the respective *semicarbazones* and *2:4-dinitrophenylhydrazones* show depressed melting points on admixture, and when it was heated with palladised charcoal, 7-hydroxy-1-methylnaphthalene was obtained and recognised as its *p*-nitrobenzeneazo- and benzoyl derivatives. Thus, by adopting one or the other of the above devices, we can build on the new *cyclohexane* ring in either of the alternative directions at will. In the case of *cyclohexanone*, method A is not satisfactory because *cyclohexylidenecyclohexanone* is produced and is difficult to separate from the octalone. Accordingly ethyl *cyclohexanone*carboxylate is employed and the product with  $\text{Me}\cdot\text{CO}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{NEt}_2\text{Me}$  is the keto-ester (III). This is hydrolysed with formation of *2-keto- $\Delta^{1:9}$ -octalin* (IV). Naturally method B is also available for the preparation of (IV), and this route is the better of the two; the starting materials are more readily accessible and the yield is superior.

The octalone (IV) is readily dehydrogenated on heating with palladised charcoal, with formation of  $\beta$ -naphthol.



Catalytic reduction of (IV) in neutral solution gives *cis*- $\beta$ -decalone.

Starting with 2-methylcyclopentanone, method A gave *5-keto-8-methyl- $\Delta^{4:9}$ -tetrahydrohydrindene* (V): method B was used for the preparation of *5-keto-6-carbethoxy-3-methyl- $\Delta^{4:9}$ -tetrahydrohydrindene* (VI).



The ketone, isomeric with (V), obtained on hydrolysis was mixed with a substance of lower carbon content, but its derivatives could be isolated in a pure condition and were quite different from those of (V).

The sodio-derivative of *trans*- $\beta$ -decalone condensed with 4-diethylaminobutan-2-one methiodide (method A) with formation of *2-keto- $\Delta^{1:13}$ -dodecahydroanthracene* (VII), the constitution of which follows from its dehydrogenation with formation of anthracene and  $\beta$ -anthranol.

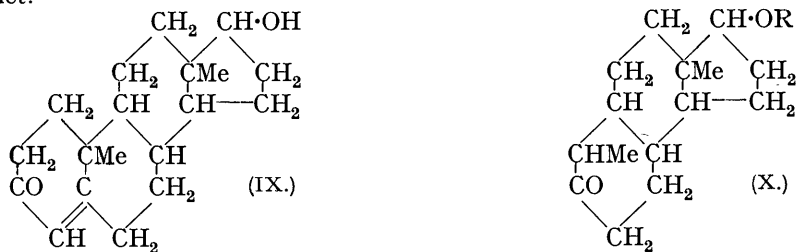


This result is in harmony with the observations of Butenandt and Wolff (*Ber.*, 1935, 68, 2093), who show that cholestanone and coprostanone are brominated in the 2- and the 4-position respectively. Hence we anticipate that *cis*- $\beta$ -decalone will be convertible by method A into a ketododecahydrophenanthrene and experiments with the object of testing this point are in progress.

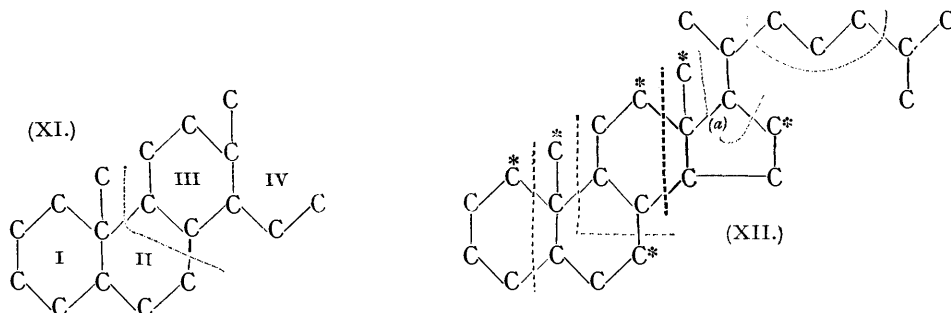
In order to complete the chain of evidence for the constitution of the ketones (I) and (II), it seemed desirable to show that the "Mannich" base from 2-methylcyclohexanone is of the form assumed and not (VIII). It was accordingly successively converted into *2-methyl-6-methylenecyclohexanone*, the known *2:6*-dimethylcyclohexanone, and *2:6*-dimethylphenol.

In connection with the dehydrogenation of *cyclohexanones* we place on record a convenient method for the preparation of 2:6-dibenzylphenol from dibenzylidenecyclohexanone. This transformation has been effected by Weiss and Ebert (*Monatsh.*, 1935, **65**, 399), who heated the unsaturated ketone with a mixture of acetic acid, acetic anhydride and hydrogen bromide at 52—55° for 11 hours and obtained dibenzylphenyl acetate. The isomeric change is brought about under our conditions by successive hydrogenation and dehydrogenation with or without isolation of the intermediate dibenzylcyclohexanone. 2:6-Di-*p-anisylphenol* was readily obtained in a similar fashion from dianisylidenecyclohexanone. The methods herein described have many applications to groups other than the sterols and testicular hormones and they are particularly relevant to the sesquiterpene field; this subject is being pursued in collaboration with Professor J. L. Simonsen.

*Biogenesis of the Sterols.*—It is obvious that testosterone (IX) could be synthesised by an application of method A to the ketone (X) provided that the latter has the correct stereochemical constitution and that the neutral group R can be safely detached from the product.



This is not surprising, because we directed our work into these channels with foreknowledge that the structures obtained would be analogous to those of the sterol group. It seemed, however, more than a mere coincidence that the same method could theoretically be used to build up the rings I, II, and III of the sterol skeleton, each stage of *cyclohexanone* construction being followed by reduction. Starting from a methylcyclopentanone derivative (ring IV), the addition of ring III would require methyl vinyl ketone. Then ring II is added by means of ethyl vinyl ketone, and ring III with methyl vinyl ketone again. Examination of the sterol skeleton in this light shows that it may be split up into acetone residues which may be substituted in one or both of the methyl groups. It is noteworthy that rings I, II, III and part of IV involve doubling of one and the same chain (XI).



The complete dissection of the sterol skeleton into  $\alpha$  or  $\alpha\alpha'$ -substituted acetones is shown in (XII), in which the asterisked carbon atoms represent the  $\alpha$ -substituents. Thus the units are 3—1, 1—3—1, 3—1, 1—3—1, 3, 3, 3 and in ergosterol one of the side chains also is  $\alpha$ -substituted.

The carbon to carbon link denoted (a) is the only one requiring a special hypothesis and it is surely remarkable that by similar reactions, analogous to our method A, the ring skeleton of the sterols can be plausibly elaborated from acetone and formaldehyde or their biological equivalents.

It appears possible that sterinoids are synthesised in the animal organism, and should

this prove to be the case a hypothesis on the lines adumbrated would doubtless be preferred to one based on the condensation of isopentane units. Similarly sterols are characteristic constituents of yeasts and other fungi which do not, so far as we are aware, synthesise typical terpenoid substances with the exception of the lipochromes (cf. Reader, *Biochem. J.*, 1925, 19, 1040).

#### EXPERIMENTAL.

*4-Diethylaminobutan-2-one*.—This substance is mentioned in a patent ("Fortschritte," 10, 1011) and the dimethylamino-analogue was obtained by Mannich (*Arch. Pharm.*, 1917, 255, 261). A mixture of acetone (30 c.c.), diethylamine hydrochloride (21 g.), paraformaldehyde (8.4 g.), and alcohol (5 c.c.) was refluxed for 8 hours. The base, isolated by addition of sodium hydroxide, ether extraction, and distillation, had b. p. 76—78°/15 mm.,  $n_D^{20}$  1.4628 (21 g. or 66%). On treatment with an equal weight of methyl iodide in the cold, the viscous methiodide was obtained; it could not be purified and was employed after washing with ether.

*2-Keto- $\Delta^{1:9}$ -octalin* (IV).—The methiodide of 2-diethylaminomethylcyclohexanone, which could not be crystallised, was prepared by mixing the components below 30°; it is a white, semi-solid mass, readily soluble in alcohol and water and insoluble in ether. (A) A solution of diethylaminomethylcyclohexanone methiodide (35.5 g., 1 mol.) in a little alcohol was added to one of ethyl sodioacetoacetate (from 3.14 g. of sodium and 18 g. of the ester; 1.25 mols.) in absolute alcohol (140 c.c.) and the mixture was refluxed for 3 hours. After dilution with water the neutral product was isolated by means of ether and distilled; b. p. 95—105°/2—3 mm.; redistilled, b. p. 101—102°/2—3 mm. (8 g. or 50%),  $n_D^{18}$  1.5238 (Found: C, 79.8; H, 9.3.  $C_{10}H_{14}O$  requires C, 80.0; H, 9.3%).

(B) A solution of ethyl cyclohexanone-2-carboxylate (17 g.) in alcoholic sodium ethoxide (2 g. of sodium in 150 c.c.) was cooled in ice, and diethylaminobutanone methiodide (20 g.) in alcohol (60 c.c.) gradually added. After 1 hour the solution was refluxed for 3 hours, cooled, and mixed with water and ether. After removal of the solvent from the dried ethereal layer the residue was distilled and afforded 3.2 g. of recovered ethyl cyclohexanonecarboxylate, a small mixed fraction, and then 8.4 g., b. p. 179—180°/15 mm.; redistilled, b. p. 175—176°/10 mm.;  $n_D^{20}$  1.5102 (Found: C, 69.6; H, 8.0.  $C_{13}H_{18}O_3$  requires C, 70.3; H, 8.1%). The substance is slightly impure ethyl 2-keto- $\Delta^{1:9}$ -octalin-10-carboxylate (or, much less probably, ethyl 2-keto- $\Delta^{1:9}$ -octalin-8-carboxylate). This ester (5 g.) was hydrolysed by boiling for 8 hours with potassium hydroxide (5 g.) and water (25 c.c.), after which 0.6 g. of unchanged substance could be recovered on isolation and distillation of the oil. The lower-boiling fraction (1.1 g.), b. p. 104—105°/4 mm.,  $n_D^{17}$  1.5241, was found to be identical with the octalone obtained according to (A).

The semicarbazone, prepared in cold aqueous alcoholic solution in the presence of sodium acetate, crystallised from alcohol in white needles, m. p. 208° (Found: C, 69.3; H, 8.3; N, 20.3.  $C_{10}H_{17}ON_3$  requires C, 63.8; H, 8.2; N, 20.3%). A mixture of specimens prepared from ketones from (A) and (B) had m. p. 208°.

The 2:4-dinitrophenylhydrazone (from A or B) crystallised from aqueous methyl alcohol, or alcohol-ethyl acetate, in scarlet plates, m. p. 168° (Found: C, 58.1; H, 5.7; N, 16.6.  $C_{16}H_{18}O_4N_4$  requires C, 58.2; H, 5.5; N, 17.0%). A mixture of the derivatives prepared from (A) or (B) ketones had m. p. 167—168°.

On hydrogenation at room temperature and atmospheric pressure in the presence of palladised strontium carbonate (2%), a product, b. p. 74—76°/2 mm.,  $n_D^{20}$  1.4888, was obtained. This was found to be a  $\beta$ -decalone, since it gave a 2:4-dinitrophenylhydrazone crystallising from alcohol in orange needles, m. p. 155—156° (Found: C, 57.9; H, 6.2; N, 16.5.  $C_{16}H_{20}O_4N_4$  requires C, 57.8; H, 6.0; N, 16.9%). A mixture with the dinitrophenylhydrazone of *trans*- $\beta$ -decalone had m. p. 137°.

The semicarbazone was prepared and crystallised to constant m. p. 182—183°. Hüchel (*Annalen*, 1925, 441, 1) gives m. p. 182—183° for the semicarbazone of *cis*- $\beta$ -decalone (*trans*- $\beta$ -decalone semicarbazone, m. p. 192—193°). Hence the decalone obtained by reduction of the octalone is probably *cis*- $\beta$ -decalone. It should be noted, however, that crude decalone containing approximately 40% of the *cis*-isomeride affords the semicarbazone, m. p. 182—183°. It is possible, therefore, that the *cis*-decalone we have obtained was mixed with some of the *trans*-isomeride.

*Dehydrogenation of 2-Keto- $\Delta^{1:9}$ -octalin. Formation of  $\beta$ -Naphthol*.—The octalone (0.7 g.) was heated with palladised charcoal\* (0.1 g.) for 4 hours at 330—335°, hydrogen being rapidly

\* Prepared according to Ruzicka from 2 g. of palladous chloride and 11 g. of active charcoal.

evolved. The ether-soluble product was almost entirely pseudo-acidic and, on acidification of the filtered alkaline solution, crude  $\beta$ -naphthol (0.4 g.) was obtained. A portion crystallised from light petroleum had m. p. 120—121°, alone or mixed with authentic  $\beta$ -naphthol.

**2-Methyl-6-diethylaminomethylcyclohexanone.**—The yield in the preparation of this substance varies within wide limits according to the conditions, but, working in the following manner, it should be from 60—65%. A mixture of 2-methylcyclohexanone (40 g., 2 mols.), diethylamine hydrochloride (19.6 g., 1 mol.), paraformaldehyde (6.5 g., 1.2 mols.), and cyclohexanol (100 g.) was heated at 110° during 2 hours. Water and ether were added, the aqueous layer (A) separated, then basified with cooling in ice, and the base isolated by means of ether. The product had b. p. 95—98°/3 mm.,  $n_D^{25}$  1.4642 (Found: C, 73.1; H, 11.7; N, 7.1.  $C_{12}H_{23}ON$  requires C, 73.1; H, 11.7; N, 7.1%). The extremely hygroscopic methiodide was obtained from the components by interaction below 30°.

**2-Methyl-6-methylenecyclohexanone.**—If the aqueous solution (A, above) is concentrated, a crude hydrochloride is obtained; this, heated under diminished pressure, decomposes with formation of the methylene-ketone, which is purified by distillation; b. p. 62°/9 mm.,  $n_D^{18}$  1.476 (Found: C, 76.8; H, 9.7.  $C_8H_{12}O$  requires C, 77.4; H, 9.7%). The condensation product with 2:4-dinitrophenylhydrazine may be a hydrazone or a pyrazoline; it crystallised from alcohol in bright red needles, m. p. 155° (Found: C, 55.5; H, 5.4; N, 18.6.  $C_{14}H_{16}O_4N_4$  requires C, 55.3; H, 5.3; N, 18.4%). The methylene-ketone was hydrogenated under 2 atmospheres pressure, palladised strontium carbonate being used as the catalyst. The product had b. p. 60°/10—11 mm.,  $n_D^{14}$  1.453 (Wallach, *Annalen*, 1913, **397**, 200, gives  $n_D$  1.4476 for 2:6-dimethylcyclohexanone), indicating that reduction was not quite complete. The vapour of this ketone was slowly passed ten times over palladised charcoal at 330—335°; the product then crystallised, m. p. 47° (Found: C, 78.2; H, 8.3. Calc. for  $C_8H_{10}O$ : C, 78.7; H, 8.2%). Bamberger (*Ber.*, 1903, **36**, 2036) stated that 2:6-dimethylphenol had m. p. 49° and our substance had the characteristic odour and other properties of this xlenol.

**2:6-Dibenzylphenol.**—Borsche (*Ber.*, 1912, **45**, 50) has reduced dibenzylidenecyclohexanone in alcoholic solution by means of hydrogen in the presence of colloidal palladium; he gives the m. p. 114°. We worked in dioxan solution with 5% of a nickel-kieselguhr catalyst (20% of nickel) at 100°. Rapid decolorisation occurred and the product had m. p. 119° after crystallisation from light petroleum (yield, quantitative) (Found: C, 86.3; H, 7.9. Calc. for  $C_{20}H_{22}O$ : C, 86.3; H, 7.9%). Dehydrogenation could not be effected by the nickel catalyst, but occurred when palladised charcoal was employed. Eventually a virtually one-stage process was evolved and the yield of dibenzylphenol was raised to 75—80%. Hence this is a preparative method of some importance and the details are the following:

Hydrogen was bubbled through a mixture of dibenzylidenecyclohexanone (100 g.) and palladised charcoal (3 g.) at 200—250°, the colour being quickly discharged. The temperature was then raised to 325—330° and hydrogen was evolved during about 9 hours. The product was distilled; the fraction, b. p. 235—245°/11 mm., crystallised as a waxy mass (Weiss and Ebert, *loc. cit.*, give b. p. 238°/10 mm.; they describe the phenol as a solid but did not recrystallise it. Short, J., 1929, 553, obtained the phenol as an oil, one of the products of interaction of sodium *o*-benzylphenoxide and benzyl chloride). After redistillation it had b. p. 210°/3 mm., m. p. 30° (Found: C, 87.5; H, 6.7. Calc. for  $C_{20}H_{18}O$ : C, 87.6; H, 6.6%). The substance may be crystallised from light petroleum (b. p. < 40°), by chilling the solution, in long colourless needles, m. p. 30°. The acetyl derivative was obtained by the use of acetic anhydride and pyridine; it crystallised from aqueous acetic acid in needles, m. p. 75.2° (Weiss and Ebert, *loc. cit.*, give m. p. 74—77°) (Found: C, 83.6; H, 5.9. Calc. for  $C_{22}H_{20}O_2$ : C, 83.6; H, 6.3%). 2:6-Dibenzylphenol is cryptophenolic, being insoluble in 2*N*-sodium hydroxide, even on warming.

It is interesting to note that according to Huston, Swartout, and Wardwell (*J. Amer. Chem. Soc.*, 1930, **52**, 4484), 4-benzyl-2-methylphenol is easily soluble in 5% sodium hydroxide solution, whereas 6-benzyl-2-methylphenol is not.

**4-Nitro-2:6-dibenzylphenol.**—A mixture of nitric acid (1.2 g., *d* 1.42) and acetic acid (10 c.c.) was added to dibenzylphenol (5 g.) dissolved in acetic acid (100 c.c.) with stirring at room temperature. After 10 minutes sufficient water was added to produce a turbidity; the almost pure derivative crystallised. A less pure product is obtainable from the filtrate by addition of more water. The substance crystallised from 50% acetic acid in very pale yellow needles, m. p. 124° (Found: C, 75.6; H, 5.3; N, 4.2.  $C_{20}H_{17}O_3N$  requires C, 75.2; H, 5.3; N, 4.4%). It is insoluble in cold aqueous sodium carbonate but, on heating, a yellow solution is produced and the undissolved crystals are coloured bright orange-red. On cooling and shaking with ethyl

acetate the whole of the substance passes into the organic solvent. On shaking the ethyl acetate solution with aqueous sodium hydroxide a bright yellow sodium salt is precipitated. This is the form that crystallises in needles from aqueous solutions containing a little sodium hydroxide; on warming, best in presence of excess of sodium hydroxide, it is transformed into the needles of the orange-red modification. The alcoholic solution of the nearly colourless nitrophenol is bright yellow and gives the yellow sodium salt on the addition of sodium hydroxide. On reduction in acid solution the very unstable dibenzyl-*p*-aminophenol was obtained and no satisfactory method for the oxidation of this to *dibenzyl-p-benzoquinone* was discovered. Ferric chloride gave a 5% yield of the quinone (Found: C, 83.3; H, 5.7.  $C_{20}H_{16}O_2$  requires C, 83.3; H, 5.5%). The latter substance, which is readily soluble in most organic solvents, crystallises from aqueous acetic acid in yellow needles, m. p. 76—77°; its alcoholic solution becomes purple on the addition of sodium hydroxide, the colour changing through greenish-brown to reddish-brown. The solution in sulphuric acid becomes deep reddish-brown on heating and a brown solution is obtained on dilution with water; this gives a violet coloration on the addition of sodium carbonate.

The *methyl* ether of the nitrodibenzylphenol was prepared from its potassium salt, suspended in alcohol, and methyl sulphate in excess. The very pale yellow substance was crystallised from aqueous alcohol and had m. p. 70—71° (Found: C, 75.6; H, 5.7.  $C_{21}H_{19}O_3N$  requires C, 75.7; H, 5.7%). After reduction of this derivative, oxidation to the quinone was found to be no easier than in the case of the aminophenol.

**2:6-Di-*p*-anisylphenol.**—This, obtained in 60% yield from dianisylidenecyclohexanone by treatment with palladised charcoal and hydrogen as described for dibenzylphenol, crystallised from light petroleum (b. p. 60—80°) in colourless prismatic needles, m. p. 66—67° (Found: C, 79.2; H, 6.3.  $C_{22}H_{22}O_3$  requires C, 79.0; H, 6.6%). Demethylation of this substance afforded resinous material, which is not surprising because the product should be a possible condensation product of 3PhOH with  $2CH_2O$ .

**2-Keto-8-methyl- $\Delta^{1:9}$ -octalin** (II).—A solution of 2-methyl-6-diethylaminomethylcyclohexanone methiodide (6.9 g., 1 mol.) in a little absolute alcohol was added to one of ethyl sodioacetate (from 0.52 g. of sodium and 2.9 g. of the ester; 1.1 mols.) in alcohol (25 c.c.) and the mixture refluxed for 4 hours. The *product*, worked up as in the case of the lower homologue (above), gave 2 g. (60%), b. p. 97—105°/2—3 mm.; redistilled, b. p. 102°/2—3 mm.,  $n_D^{20}$  1.5148 (Found: C, 80.3; H, 9.8.  $C_{11}H_{16}O$  requires C, 80.4; H, 9.8%). The *semicarbazone* crystallised from alcohol in colourless needles, m. p. 210—211° (Found: C, 65.5; H, 8.5; N, 18.9.  $C_{12}H_{19}ON_3$  requires C, 65.2; H, 8.6; N, 19.0%). The **2:4-dinitrophenylhydrazone** crystallised from alcohol in dark red needles, m. p. 172° (Found: C, 59.0; H, 5.8; N, 16.0.  $C_{17}H_{20}O_4N_4$  requires C, 59.3; H, 5.8; N, 16.3%). Dehydrogenation by means of palladised charcoal, under the conditions already described for the conversion of octalone into  $\beta$ -naphthol, afforded a phenolic product that could not be crystallised. It undoubtedly consisted, however, of 7-hydroxy-1-methylnaphthalene, because it gave a *p*-nitrobenzeneazo-derivative and a benzoyl derivative tallying with the description of Vesely and Stursa (*Coll. Czech. Chem. Comm.*, 1933, 5, 170). The former derivative crystallised from acetic acid and from nitrobenzene in red prismatic needles, m. p. 260° (Vesely and Stursa give m. p. 262°) (Found: C, 66.3; H, 4.4; N, 13.8. Calc. for  $C_{17}H_{13}O_3N_3$ : C, 66.4; H, 4.2; N, 13.8%). The benzoate crystallised from methyl alcohol in large, colourless prisms, m. p. 88—89° (*loc. cit.*, m. p. 88—90°).

**2-Keto-10-methyl- $\Delta^{1:9}$ -octalin** (I).—(A) A mixture of 2-methylcyclohexanone (33 g.), powdered sodamide (6.1 g.), and dry ether (50 c.c.) was stirred for 4 hours in a stream of dry nitrogen at room temperature. A solution of 4-diethylaminobutan-2-one methiodide (43 g.) in absolute alcohol (20 c.c.) was then gradually added and after 4 hours the solution was refluxed for 2 hours. Dilute hydrochloric acid and ether were added and the ethereal solution was separated, dried, and distilled, giving 9.3 g. (38%), b. p. 143—145°/16 mm.; redistilled, b. p. 139°/15 mm.,  $n_D^{20}$  1.5341 (Found: C, 80.0; H, 9.7.  $C_{11}H_{16}O$  requires C, 80.4; H, 9.8%). The *semicarbazone* crystallised from alcohol in colourless prisms, m. p. 203.5—204° (Found: C, 65.1; H, 8.7; N, 18.8.  $C_{12}H_{19}ON_3$  requires C, 65.2; H, 8.6; N, 19.0%). The **2:4-dinitrophenylhydrazone** formed scarlet prisms from alcohol; m. p. 169° (Found: C, 59.3; H, 5.9; N, 16.1.  $C_{17}H_{20}O_4N_4$  requires C, 59.3; H, 5.8; N, 16.3%). Mixtures with the isomeric derivatives of 2-keto-8-methyloctalin (above), m. p.'s 211° and 172—173° respectively, melted at 185—187° (semicarbazones) and 136—140° (dinitrophenylhydrazones).

(B) 2-Methylcyclohexanone (9.5 g., 1 mol.) was added to a solution of sodium isopropoxide (from 2.5 g. of sodium) in isopropyl alcohol (400 c.c.). (Later we found that ethyl alcohol may be employed with almost the same results.) Into the mixture, cooled below 0°, 4-chloro-

butan-2-one (10 g., 1 mol.) was introduced during  $\frac{1}{2}$  hour. After being kept at 0° for 18 hours, the product was worked up in the known manner and afforded 2 g., b. p. 129—133°/12 mm.,  $n_D^{20}$  1.5250. The yield was therefore about 15%, but we are engaged in efforts to develop this potentially useful variant. The semicarbazone, m. p. 204°, and the 2 : 4-dinitrophenylhydrazone, m. p. 169°, when intimately mixed with authentic specimens (prepared as under A) did not depress the respective melting points.

*Dehydrogenation of 2-Keto-10-methyloctalin.*—The ketone (2.9 g.) was kept at 330° for 8 hours with palladised charcoal (0.2 g.): hydrogen was not evolved and 1.1 g. of unchanged methyloctalone could be recovered. The tarry residue was not phenolic. When, however, the ketone (1.5 g.) was heated with selenium (6 g.) at 300—315° for 4 hours and then at 330—340° for 18 hours,  $\beta$ -naphthol (0.2 g.) was produced, m. p. (after crystallisation from light petroleum) 120—121° alone or mixed with an authentic specimen.

*2-Keto-10-methyldecalin.*—2-Keto-10-methyl- $\Delta^{1:9}$ -octalin (3.2 g.) in alcoholic solution absorbed 460 c.c. of hydrogen at atmospheric pressure in the presence of palladised strontium carbonate (0.3 g. of 2%). The reduction product had b. p. 95—96°/3 mm. and crystallised on cooling. It separated from light petroleum in rectangular prisms, m. p. 47° (Found: C, 79.7; H, 10.7.  $C_{11}H_{18}O$  requires C, 79.5; H, 10.8%). The 2 : 4-dinitrophenylhydrazone crystallised from methyl alcohol in pale yellow needles, m. p. 152—152.5° (Found: C, 59.2; H, 6.2; N, 16.2.  $C_{17}H_{22}O_4N_4$  requires C, 58.9; H, 6.3; N, 16.2%).

*2-Methyl-5-diethylaminomethylcyclopentanone.*—A mixture of 2-methylcyclopentanone (9.8 g.), diethylamine hydrochloride (10.8 g.), paraformaldehyde (4 g.), and alcohol (5 c.c.) was heated on the steam-bath for 4 hours. The base (12.3 g.) was isolated in the usual manner, b. p. 112—114°/17 mm.,  $n_D^{19}$  1.4617 (Found: C, 72.1; H, 11.3; N, 7.6.  $C_{11}H_{19}ON$  requires C, 72.1; H, 11.4; N, 7.7%). The methiodide prepared from this base (25.4 g.) and methyl iodide (19.9 g.) by heating on the steam-bath for  $\frac{1}{2}$  hour was a viscous uncrystallisable liquid, freely soluble in alcohol and insoluble in ether.

*5-Keto-6-carbethoxy-3-methyl- $\Delta^{4:9}$ -tetrahydrohydrindene (VI).*—Ethyl acetoacetate (18.3 g.) and 2-methyl-5-diethylaminomethylcyclopentanone (45.2 g.) were added successively to an alcoholic solution (50 c.c.) of sodium ethoxide (3.3 g. of sodium); the mixture was then refluxed for 5 hours. On working up in the known manner there were obtained 10 g. of recovered ethyl acetoacetate and 5.5 g., b. p. 140—160°/20 mm. This fraction redistilled at 120—125°/3 mm.;  $n_D^{20}$  1.4993 (Found: C, 70.1; H, 8.1.  $C_{13}H_{18}O_3$  requires C, 70.3; H, 8.1%).

*Derivatives of 5-Keto-3-methyl- $\Delta^{4:9}$ -tetrahydrohydrindene.*—The hydrolysis of the foregoing ester has been carried out under a variety of conditions including the use of aqueous methyl alcoholic potash, boiling 5% hydrochloric acid, and glycerol (containing 10% of water) at 180—190° for 3 hours. The typical product had b. p. 88—90°/3 mm. and  $n_D^{18}$  1.5045. The analytical results indicated admixture of the expected ketone,  $C_{10}H_{14}O$ , with  $C_{10}H_{16}O_2$ , probably as the result of hydration at the ethylenic linkage and consequent ring-fission. However, derivatives of the ketone  $C_{10}H_{14}O$  were obtained from this material. The semicarbazone crystallised from ethyl alcohol in colourless, nearly rectangular prisms, m. p. 196—197° (Found: C, 63.7; H, 8.2; N, 20.2.  $C_{11}H_{17}ON_3$  requires C, 63.8; H, 8.2; N, 20.3%). The 2 : 4-dinitrophenylhydrazone crystallised from alcohol-ethyl acetate in brick-red prisms, m. p. 159—160° (Found: C, 57.9; H, 5.7; N, 17.0.  $C_{16}H_{18}O_4N_4$  requires C, 58.2; H, 5.4; N, 17.0%).

*5-Keto-8-methyl- $\Delta^{4:9}$ -tetrahydrohydrindene (V).*—A mixture of 2-methylcyclopentanone (49 g.), powdered sodamide (9.8 g.), and dry ether (200 c.c.) was stirred in a stream of dry nitrogen for 3 hours; 4-diethylaminobutan-2-one methiodide (71.6 g.) was then added during 2 hours with vigorous stirring, which was continued for 4 hours. After 12 hours, water was added, the alkali neutralised, and the whole extracted with ether. After removal of the solvent from the dried extract the residue was fractionated, giving some recovered methylcyclopentanone, then 11 g., b. p. 112°/4 mm.,  $n_D^{20}$  1.4984, and 3.1 g., b. p. 150—152°/3 mm. The lower-boiling fraction was the required product (Found: C, 80.3; H, 9.4.  $C_{10}H_{14}O$  requires C, 80.0; H, 9.3%). The semicarbazone crystallised from aqueous methyl alcohol in long prisms, m. p. 205° (Found: C, 63.6; H, 8.3; N, 20.2.  $C_{11}H_{17}ON_3$  requires C, 63.8; H, 8.2; N, 20.3%). A mixture with the semicarbazone of 5-keto-8-methyl- $\Delta^{4:9}$ -tetrahydrohydrindene melted at 182—188°. The 2 : 4-dinitrophenylhydrazone crystallised from alcohol-ethyl acetate in scarlet prisms, m. p. 153° (Found: C, 58.3; H, 5.5; N, 17.0.  $C_{16}H_{18}O_4N_4$  requires C, 58.2; H, 5.4; N, 17.0%). A mixture with the isomeric derivative (above) had m. p. 133—136°.

*2-Keto- $\Delta^{1:13}$ -dodecahydroanthracene (VII).*—A mixture of *trans*- $\beta$ -decalone (44 g.), powdered sodamide (5.9 g.), and ether (200 c.c.) was stirred in a stream of dry nitrogen for 3 hours. 4-Diethylaminobutan-2-one methiodide (42.8 g.) was then introduced during 1 hour with ice-

cooling and vigorous stirring, which was continued for 4 hours. Next day the product was worked up as in the last example and afforded 8.7 g., b. p.  $152^{\circ}/3$  mm.,  $n_D^{25}$  1.5224 (Found : C, 82.1; H, 9.9.  $C_{14}H_{20}O$  requires C, 82.4; H, 9.8%). The 2:4-dinitrophenylhydrazone crystallised from alcohol-ethyl acetate in red prisms, m. p.  $197-198^{\circ}$  (Found : C, 62.2; H, 6.4; N, 14.9.  $C_{20}H_{24}O_4N_4$  requires C, 62.5; H, 6.2; N, 14.6%).

*Dehydrogenation of Ketododecahydroanthracene. Formation of Anthracene and  $\beta$ -Anthranol.*—The unsaturated ketone (1.5 g.) was heated with selenium (6 g.) for 6 hours at  $290-300^{\circ}$  and the cooled product was extracted with ether. The solution was well washed with 10% aqueous sodium hydroxide, dried, and evaporated. The residue was treated in alcoholic solution with charcoal, recovered, crystallised from light petroleum (giving 40 mg., m. p.  $175-180^{\circ}$ ), and then sublimed in a vacuum. This material (20 mg.), m. p.  $194-196^{\circ}$ , was oxidised by means of chromic acid in the usual manner; the product sublimed in a vacuum, forming long, characteristic needles, m. p.  $273^{\circ}$  alone or mixed with authentic anthraquinone (m. p.  $275^{\circ}$ ). The substance exhibited the anthranol reaction.

The aqueous alkaline washings (above) gave on acidification a crude phenolic substance (0.25 g.), which by repeated crystallisation from alcohol was obtained in pale brown needles, m. p.  $197^{\circ}$ , exhibiting the blue fluorescence in solution and other properties of  $\beta$ -anthranol (m. p.  $200^{\circ}$ ).

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