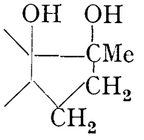
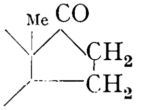
307. *Experiments on the Synthesis of Substances related to the Sterols. Part II. A New General Method for the Synthesis of Substituted* cyclo*Hexenones.*

By William Sage Rapson and Robert Robinson.

The methods for the synthesis of 1 : 5-diketones have been explored in this laboratory for two reasons : (i) it was thought that pinacols such as (I) might furnish the characteristic angle-methyl ketone group (II) of œstrone by intramolecular change ; (ii) the diketones


(I.)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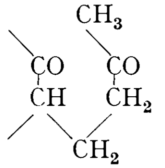
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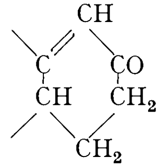
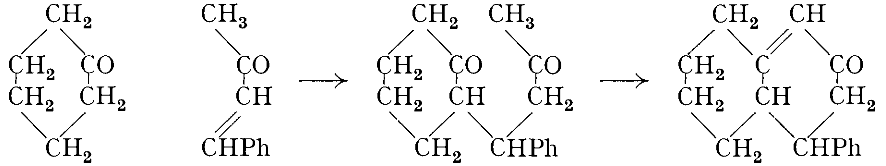

(IV.)

themselves (III) might be dehydrated with the formation of *cyclo*hexenones (IV). The present communication is concerned with the latter scheme, which has not hitherto been realised in the form developed below.

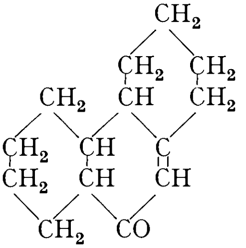
Somewhat analogous *cyclo*hexenone syntheses have been described (Knoevenagel, *Annalen*, 1894, **281**, 25; 1895, **288**, 321; Harries, *Ber.*, 1914, **47**, 784), but in these cases (*e.g.*, the condensation of ethyl sodioacetoacetate and unsaturated ketones) the reactive methylene group is not derived from the unsaturated ketone component.

An approach to the contemplated synthetical method was sought in the study of the condensation of the alkali-metal derivatives of phenols with αβ-unsaturated ketones, a typical case being the coupling of β-naphthol with methyl vinyl ketone (Miller and Robinson, J., 1934, 1535). This succeeded, but the obvious extension implied by the replacement of sodium naphthoxide by sodio*cyclo*hexanone or sodio-β-decalone could not be realised. We now believe the failure to be due to unsuitable conditions of reaction, coupled with the tendency of methyl vinyl ketone to undergo auto-condensation.

Again, the work of Stobbe and his collaborators (*J. pr. Chem.*, 1912, **86**, 209) on the condensation of *cyclo*hexanone and unsaturated ketones in the presence of alkalis or piperidine was not extended to αβ-unsaturated methyl ketones, and we found in a favourable case (styryl methyl ketone and *cyclo*hexanone) that Stobbe's conditions were inapplicable.


(V.)

Interaction, however, between sodio*cyclo*hexanone and styryl methyl ketone in cold ethereal solution afforded 2-*keto*-4-*phenyl*-$\Delta^{1:9}$-*octalin* (V) in 43% yield. On catalytic reduction (palladised strontium carbonate) of (V), 2-*keto*-4-*phenyldecalin* was obtained.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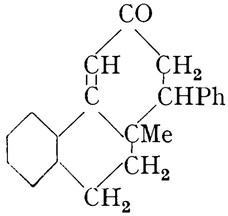
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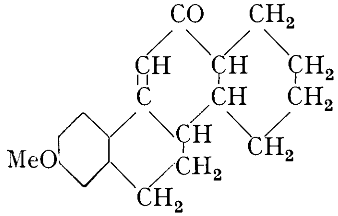
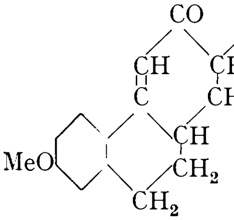

(VIII.)

The general nature of the reaction has been established by the analogous syntheses of (VI), (VII), (VIII), and (IX) from the appropriate components. The yield of (IX) from 1-keto-6-methoxy-1 : 2 : 3 : 4-tetrahydronaphthalene (Thompson, J., 1932, 2314) (preparation improved) is 55%, and unchanged components are recoverable.

The pairing of 2-methyltetralone and acetyl*cyclo*hexene did not proceed normally, but a dimeride of the latter was produced. This affords 1 mol. of acetic acid on oxidation by the Kuhn–Roth micro-method (chromic anhydride) and hence would appear to be (X) rather than (XI). Presumably the failure to form a *cyclo*hexenone from (X) is due to the enfeeblement of the carbonyl reactivity by its union with an unsaturated group. The catalytic reduction of (VIII) and (IX) afforded saturated secondary alcohols, and it is of interest that pure products were obtained in this way. The stereochemical configuration of the ring-systems will, it is hoped, be established by physical methods. It is also proposed to prepare phenols corresponding to the methyl ethers, (VIII) and (IX), and to the related alcohols obtained by reduction or by interaction with the Grignard reagents. The œstrogenic properties of these substances will be examined in view of their close constitutional relationship to the natural hormones.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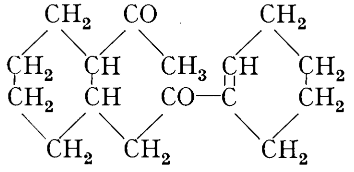
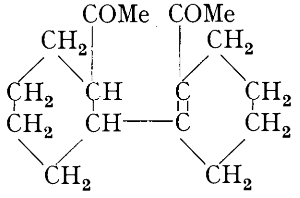

(X.)


(XI.)

*cyclo*Hexenones have also been obtained by the condensation of ethyl sodio*cyclo*hexanonecarboxylate with unsaturated methyl ketones such as styryl methyl ketone. In this case the use of sodamide is, of course, unnecessary, and an account of this aspect of the investigation will shortly be submitted by one of us (W. S. R.). The importance of the method now disclosed lies in its special aptitude for the synthesis of substances containing the characteristic carbon skeletons of the sterols and sex-hormones, and the investigation is being actively pursued.

EXPERIMENTAL.

2-*Keto*-4-*phenyl*-$\Delta^{1:9}$-*octalin* (V).—Sodio*cyclo*hexanone was prepared from *cyclo*hexanone (15 g.) and sodamide (6 g.) in dry ether (200 c.c.), the ammonia being removed in a stream of dry hydrogen. Styryl methyl ketone (22·5 g.) dissolved in ether (20 c.c.) was then added drop-wise with shaking and cooling in ice-water. After 12 hrs., water was added, and the ethereal layer was shaken with dilute sulphuric acid, washed with water, and dried. The residue after removal of the solvent was distilled, b. p. 175—185°/1 mm. (nearly all at 185°) (15 g.). This fraction crystallised in contact with light petroleum and separated from this solvent or from methyl alcohol in colourless prisms, m. p. 91—92° (Found : C, 85·0; H, 7·9. $C_{16}H_{18}O$ requires C, 85·0; H, 7·9%)

2-*Keto*-4-*phenyldecalin*.—A 2% palladium–strontium carbonate catalyst (3 g.) was added to a solution of the foregoing compound (5 g.) in methyl alcohol (50 c.c.), and the mixture was shaken with hydrogen under 1·5 atm. Absorption of hydrogen (1 mol.) was complete in ½ hr., and after evaporation of the filtered solution the residue solidified on rubbing, and was recrystallised from aqueous ethyl alcohol, separating as colourless needles, m. p. 82—83° (Found : C, 84·2; H, 8·7. $C_{16}H_{20}O$ requires C, 84·2; H, 8·8%), readily soluble in most organic solvents. The 2 : 4-dinitrophenylhydrazone was very sparingly soluble in alcohol but dissolved readily in benzene, and crystallised as orange needles, m. p. 180°, on addition of light petroleum to the hot solution.

9-*Keto*-$\Delta^{10:11}$-*dodecahydrophenanthrene* (VI).—Sodio*cyclo*hexanone was prepared from sodamide (2 g.) and *cyclo*hexanone (5 g.) in ether (200 c.c.) and condensed under conditions similar to those already mentioned with acetyl*cyclo*hexene (6·2 g.; *Helv. Chim. Acta*, 1931, **14**, 1157). After the mixture had been finally heated on the steam-bath for 1 hr., the product was isolated, eventually by distillation, b. p. 150—155°/1 mm. (3·5 g.). The distilled substance crystallised from aqueous methyl alcohol in the form of rectangular prisms, m. p. 89° (Found : C, 82·4; H, 9·9. $C_{14}H_{20}O$ requires C, 82·4; H, 9·8%).

Attempt to condense 1-*Keto*-2-*methyl*-1 : 2 : 3 : 4-*tetrahydronaphthalene with Acetyl*cyclo*hexene*.—The sodio-derivative of the methyltetralone (8 g.; Schroeter, Lichtenstadt, and Irineu, *Ber.*, 1918, **51**, 1600) was prepared by refluxing it with sodamide (2 g.) in benzene (100 c.c.) in a current of dry hydrogen for 5—6 hrs. Acetyl*cyclo*hexene was then added (6·4 g.), and the heating continued for 3 hrs.; alternatively, the reaction mixture was kept for 12 hrs. In either case, the methyltetralone was ultimately recovered unchanged, but a fraction, b. p. 180—185°/1 mm. (3·3 g.), was obtained which crystallised in contact with light petroleum. From this product there could be separated a small amount of a substance rather sparingly soluble in light petroleum, but recrystallising from petroleum (b. p. 100—120°) as fine, matted needles, m. p. 205—206° (Found : C, 77·6; H, 10·1. $C_{16}H_{24}O_2$ requires C, 77·4; H, 9·8%). The main bulk of the material, however, was moderately readily soluble in hot light petroleum, and it crystallised in the form of prisms, m. p. 126—127° (Found : C, 77·7; H, 10·0. $C_{16}H_{24}O_2$ requires C, 77·4; H, 9·8%). On oxidation with chromic acid, Dr. H. Roth found the yields of acetic acid to be 89·7 and 93·5% on the assumption that 1 mol. is theoretically obtainable. These substances are considered to be cis- and trans-*forms* of (X).

3-*Keto*-1-*phenyl*-11-*methyl*-2 : 3 : 4 : 9 : 10 : 11-*hexahydrophenanthrene* (VII).—The sodio-derivative of 1-keto-2-methyl-1 : 2 : 3 : 4-tetrahydronaphthalene (6 g.) was prepared by means of sodamide (1·5 g.) in benzene (100 c.c.), in a current of dry hydrogen during 5—6 hrs. After cooling in ice, a solution of styryl methyl ketone (6 g.) in benzene (25 c.c.) was added gradually with shaking, and next day water was added and the product isolated in the usual manner as a very viscous fraction, b. p. 235—240°/1 mm. (5 g.). This was contaminated with polymerised styryl methyl ketone, so it was dissolved in alcohol and after 5 days a hard crystalline mass separated from the solution. The substance then crystallised from light petroleum in irregular, flat prisms, m. p. 135° (Found : C, 87·4; H, 7·1. $C_{21}H_{20}O$ requires C, 87·5; H, 7·0%).

1-*Keto*-6-*methoxy*-1 : 2 : 3 : 4-*tetrahydronaphthalene*.—A mixture of γ-*m*-methoxyphenyl-*n*-butyric acid (14 g.), sulphuric acid (140 c.c.), and water (50 c.c.) was heated in a boiling water-bath for ½ hr. The clear, straw-coloured liquid was then poured on crushed ice, the solid collected, and crystallised from aqueous ethyl alcohol; plates, m. p. 81° (yield, 10 g.); Thompson (*loc. cit.*) gives m. p. 82°.

2-*Keto*-10-*methoxy*-2 : 3 : 4 : 5 : 6 : 7 : 8 : 14 : 15 : 16-*decahydrochrysene* (VIII).—A mixture of 6-methoxytetralone (4·4 g.), finely powdered sodamide (1 g.), and dry ether (100 c.c.) was refluxed in a current of hydrogen for 6 hrs. After cooling, acetyl*cyclo*hexene (3·1 g.) was slowly added, and after 12 hrs. a crystalline mass had separated. After the addition of dilute sulphuric acid, this was collected, washed with water and with alcohol, and crystallised from benzene or *iso*amyl alcohol. The product separated in the form of colourless needles, m. p. 228—229° (yield, 3 g.; and 1·5 g. of methoxytetralone recovered from the ethereal solution) (Found : C, 81·1; H, 7·8. $C_{19}H_{22}O_2$ requires C, 80·8; H, 7·8%). The substance is sparingly soluble in alcohol and many light organic solvents.

Hydrogenation of Ketomethoxydecahydrochrysene.—The substance (1 g.) was suspended in alcohol (200 c.c.), a 2% palladium–strontium carbonate catalyst (2 g.) added, and the mixture shaken with hydrogen under 1·5 atm. for 6 hrs. The residue from evaporation of the solvent was taken up in hot light petroleum (b. p. 100—120°), and on cooling, separated initially in needle-shaped crystals, which rapidly changed to prisms as the solution cooled. From alcohol, however, it crystallised in long needles, m. p. 151°, which could be converted into the prismatic form by solution in petroleum and inoculation with this form (Found : C, 79·6; H, 9·3. $C_{19}H_{26}O_2$ requires C, 79·7; H, 9·1%). The substance is evidently a saturated alcohol, and derivatives are in course of preparation.

1-*Acetyl*cyclo*pentene*.—A mixture of anhydrous stannic chloride (83 g.) and carbon disulphide (200 c.c.) was cooled to — 10°. *cyclo*Pentene (22 g.), prepared from *cyclo*pentanol (Noller and Adams, *J. Amer. Chem. Soc.*, 1926, **48**, 1084) by the method of Harries and Tank (*Ber.*, 1908, **41**, 1703), along with acetyl chloride (27 g.) were then introduced drop-wise with stirring, so that the temperature did not rise above — 10°. After the addition was complete, stirring was continued for 1 hr., and the flask was then kept in the ice-chest for 4 hrs. The reaction mixture was poured on crushed ice, and stirred until the complex was decomposed; the mass was filtered in order to break the emulsion, and the carbon disulphide layer was separated, washed, and dried. The residue left on evaporation of the solvent was mixed with dimethylaniline (40 g.) and heated at 180° for 3 hours. Ether was added, and the dimethylaniline removed by means of dilute hydrochloric acid. Finally, the ethereal layer was washed with dilute alkali, dried, and the ether evaporated. On distillation of the dark residue, there were obtained **13** g. of material, b. p. 75—78°/22 mm. This contained some chlorine and could not be completely purified by distillation. It is, however, essentially acetyl*cyclo*pentene and can be employed in the condensations with the sodio-derivatives of ketones. The *semicarbazone*, which crystallised from alcohol in the form of colourless prisms, m. p. 210—211°, was chlorine-free (Found : N, 25·4. $C_8H_{13}ON_3$ requires N, 25·2%).

3-*Keto*-7-*methoxy*-1 : 2 : 3 : 9 : 10 : 11-*hexahydro*-1 : 2-cyclo*pentenophenanthrene* (IX).—The sodio-derivative of the methoxytetralone (6·6 g.) was prepared as already described (sodamide, 1·8 g.; ether, 120 c.c.). Acetyl*cyclo*pentene (4·5 g.) was added in the cold; heat was evolved, the ether boiled, and the product gradually crystallised from the solution. After the addition of dilute sulphuric acid, it was collected (5·5 g.) and crystallised from light petroleum (b. p. 100—120°) or *iso*amyl alcohol. The substance occurs as colourless needles, m. p. 196—197° (Found : C, 80·8; H, 7·7. $C_{18}H_{20}O_2$ requires C, 80·6; H, 7·5%). Methoxytetralone (2 g.) was recovered from the ethereal filtrate.

Hydrogenation.—A mixture of the last-described substance (1 g.), methyl alcohol (100 c.c.), and a 2% palladium–strontium carbonate catalyst (2 g.) was shaken with hydrogen under 1·5 atm. during 4 hrs.; the product crystallised from aqueous ethyl alcohol in the form of glistening needles, m. p. 167—168° (Found : C, 79·4; H, 8·9. $C_{18}H_{24}O_2$ requires C, 79·4; H, 8·8%). Again, it appears that a tetrahydro-derivative was isolated.

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