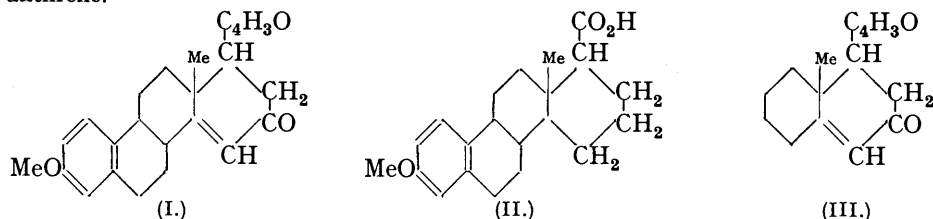


**79.** *Experiments on the Synthesis of Substances related to the Sterols. Part XXXV. Furfurylideneacetone as a Reagent for the Extension of Ring Systems.*

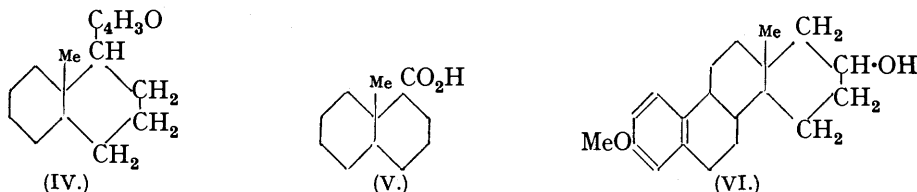
By L. E. KING and SIR ROBERT ROBINSON.

A number of miscellaneous observations have been made in the course of an exploration of the methods available for adding a *substituted* homocyclic ring to an existing nucleus and, although most of the projected lines of investigation failed for reasons which it is hardly necessary to explain in detail, one new process of interest has been brought to light. This is the condensation of the sodio-derivative of a 2-substituted *cyclohexanone* with furfurylideneacetone. For example, the unsaturated *ketone* (I) is so

obtained from 1-keto-7-methoxy-2-methyl-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-octahydrophenanthrene.

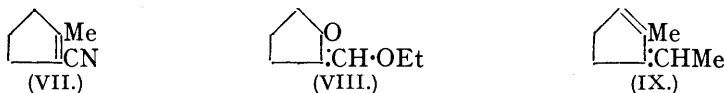


The next contemplated stages are reduction and then oxidation to (II), which could doubtless be degraded to  $\alpha$ -oestrone methyl ether. Experiments in this direction are in progress; meanwhile, (III) has been prepared in the same fashion from 2-methylcyclohexanone and has been reduced to (IV) and oxidised to (V). It remains to transform (V) into *cis*- or *trans*-9-methyl- $\alpha$ -decalone in order to establish its stereochemical configuration.



The *sec.-alcohol* (VI) has been prepared from ketomethoxymethyloctahydrophenanthrene by an application of the "butenyl" method of Hibbit and Linstead (J., 1936, 470; cf. J., 1936, 476; 1937, 1136, 1140; 1938, 666).

2-METHYL- $\Delta^1$ -CYCLOPENTENE-1-ALDEHYDE has been obtained by Wallach (*Annalen*, 1906, 347, 338), but the method gives a very poor yield and is not suitable for preparative purposes. The Stephen reduction of the corresponding *nitrile* (VII) could not be accomplished, but the aldehyde was obtained by heating the barium salt of 2-methylcyclopentene-1-carboxylic acid with barium formate (cf. Davis, Heilbron, Jones, and Lowe, J., 1935, 584).



It was intended to condense this aldehyde with ethyl acetonedicarboxylate in the hope of making a hydrindene derivative, but varied trials with more readily accessible models gave no promise of a successful outcome.

2-Ethoxymethylencyclopentanone (VIII) was brought into reaction with methylmagnesium iodide, but the product was a *hydrocarbon*,  $C_8H_{12}$ , possibly (IX), and not the expected carbinol. No adduct was obtained from this hydrocarbon and maleic anhydride in benzene solution, but it is hard to devise a plausible formula not containing conjugated bonds. Some other avenues were closed at an early stage. Although 2-chlorobutadiene (chloroprene) condenses readily with maleic anhydride and  $\alpha$ -naphthaquinone (Carothers, Williams, Collins, and Kirby, *J. Amer. Chem. Soc.*, 1931, 53, 4204), we have not been able to isolate an adduct with citraconic anhydride.

The preparation of *ethyl 1-methylcyclopentan-2-one-1-acetate* has been carried out (cf. Adamson, McQuillin, Robinson, and Simonsen, J., 1937, 1576; Ruzicka, Koolhaas, and Wind, *Helv. Chim. Acta*, 1931, 14, 1169 for the method of purification of such esters), but no glycide ester could be obtained by reaction with ethyl chloroacetate or ethyl bromoacetate in alcoholic sodium ethoxide solution. Hückel and Goth (*Ber.*, 1934, 67, 2104) reported that the dehydration of 5-hydrindanol gave a mixture of hydrocarbons. The experiment was performed at rather a high temperature, but we find that the action of alcoholic potassium hydroxide on 5-bromohydrindane yields the same mixture.

The *hydrochrysene* derivative (VI) mentioned in the summary (above) was obtained

in such small yield that further work was prohibited by the relative inaccessibility of the intermediate.

Of the several topics touched, we consider the following most worthy of further attention and the extension of the work is in active progress. Rapson and Robinson (J., 1935, 1285) prepared a phenyloctalone by the condensation of styryl methyl ketone and the sodio-derivative of cyclohexanone. 2-Keto-4-furyl-10-methyl- $\Delta^1:9$ -octalin (III) may be similarly obtained and the assumed constitution is supported by many analogies. Catalytic reduction affords the dihydro-ketone, which was fully reduced to (IV) by an application of the Wolff-Kishner method. Oxidation by potassium permanganate (cf. Reichstein, *Helv. Chim. Acta*, 1935, 18, 721) was unsuccessful and the action of bromine water gave no acidic product. The furan ring was first opened by hydrolysis; the product was then amenable to oxidation with permanganate and 9-methyldecalin-1-carboxylic acid (V) was produced. It is hoped to improve this process and to convert (V) into one of the known members of the decalin group. Only when this model has been thoroughly worked through will it be desirable to apply selected processes to the complex substance (I), which is of the most direct interest for the synthesis of  $\alpha$ -oestrone. Naturally we have also in mind a similar series of operations starting from 1-keto-7-methoxy-2-methyl-1:2:3:4-tetrahydrophenanthrene.\*

#### EXPERIMENTAL.

**2-Methylcyclopentanone Cyanohydrin.**—Anhydrous hydrogen cyanide from potassium cyanide (50 g.; cf. Wade and Panting, J., 1898, 73, 256), cooled in a freezing mixture, was mixed with a few drops of aqueous potassium cyanide, and 2-methylcyclopentanone (45 g.) slowly added with shaking. The mixture was kept at 0° overnight and then neutralised with sulphuric acid, and the excess of hydrogen cyanide removed under diminished pressure. The residue was a colourless viscid liquid (49 g.), b. p. 118°/14 mm.

In another preparation the bisulphite compound of methylcyclopentanone was treated with aqueous potassium cyanide; the same cyanohydrin was obtained, b. p. 116°/13 mm., but the yield was inferior.

**2-Methyl- $\Delta^1$ -cyclopentene-1-nitrile (VII).**—Thionyl chloride (48 g.) was slowly added with shaking to an ice-cold mixture of the above cyanohydrin (25 g.) and dry pyridine (32 g.), which was then heated on the steam-bath for 1 hour. The nitrile was isolated in the usual way and had b. p. 68—70°/14 mm. (yield, 80%) (Found: N, 13.0.  $C_7H_9N$  requires N, 12.9%). The odour was benzonitrile.

**2-Methyl- $\Delta^1$ -cyclopentene-1-carboxylic Acid.**—Methylcyclopentenitrile (10 g.) was refluxed for 48 hours with a solution of potassium hydroxide (15 g.) in water (150 c.c.). The acid, obtained in 85% yield, was volatile in steam, and crystallised from hot water in colourless needles, m. p. 125° (Found: C, 66.9; H, 7.8.  $C_7H_{10}O_2$  requires C, 66.7; H, 7.9%).

**2-Methylcyclopentene-1-aldehyde.**—The potassium salt of the above acid (6 g.) in water (25 c.c.) was mixed with a solution of barium chloride (4.9 g.) in water (30 c.c.) with stirring. The precipitated barium salt was washed with water and dried by distilling its suspension in benzene under reduced pressure. An intimate mixture of the barium salt (5.2 g.) and barium formate (3.1 g.), with an equal bulk of silver sand, was heated for 2 hours (oil-bath, 150—200°) under 2 mm. pressure until no more oil distilled. A small quantity of the aldehyde was obtained on redistillation, b. p. 70—75°/14 mm. This was converted into a 2:4-dinitrophenylhydrazone, which crystallised from acetic acid in red needles, m. p. 200° (Found: C, 53.7; H, 5.0; N, 19.0.  $C_{13}H_{14}O_4N_4$  requires C, 53.8; H, 4.8; N, 19.3%). On keeping, the aldehyde polymerised.

**2-Ethoxymethylenecyclopentanone (VIII).**—A mixture of cyclopentanone (21.5 g.) and ethyl orthoformate (37 g.) was slowly added to sodium ethoxide (16.5 g.) suspended in dry ether (200 c.c.), with shaking and cooling. Next day, water and ether were added, and the solution neutralised with acetic acid. On distillation, an oil (12.3 g.), b. p. 115—122°/11 mm., was obtained, and characterised by preparation of a semicarbazone, which crystallised from alcohol in colourless prisms, m. p. 222—223° (Found: N, 20.3.  $C_9H_{16}O_2N_3$  requires N, 20.6%).

**Reaction with methylmagnesium iodide.** The Grignard reagent prepared from methyl iodide (1 mol.) was added slowly to 2-ethoxymethylenecyclopentanone (1 mol.) in ethereal solution, and the reaction was completed by refluxing for 3 hours. The mixture was poured on ice, and

\* Already under way and the condensation with furfurylideneacetone proceeds more smoothly in this case.—R. R.

hydrochloric acid added; the ethereal extract was washed, dried, and evaporated. On distillation, a colourless oil, b. p. 96—98°/11 mm., was obtained (Found: C, 87.7; H, 10.7.  $C_8H_{12}$  requires C, 88.8; H, 11.2%).

*Ethyl 1-Methylcyclopentan-2-one-1-acetate*.—A mixture of 2-methylcyclopentanone (49 g.), sodamide (19.5 g.), and ether (700 c.c.) was refluxed for 10 hours, hydrogen being passed to remove ammonia. After cooling in ice, ethyl chloroacetate (57 g.) was added with vigorous shaking, sodium chloride separating. The reaction was completed by refluxing for 5 hours; ice was then added, and the product collected (ether). Distillation of the oil under 14 mm. gave methylcyclopentanone (18 g.), a fraction (31 g.), b. p. 125—135°, and a higher-boiling fraction.

A mixture of the crude ester (25 g.), ethyl oxalate (22.4 g.), and powdered sodium (3.3 g.) in light petroleum (500 c.c.) was shaken on the machine for 3 days. The product was worked up following Ruzicka, Koolhaas, and Wind (*loc. cit.*). The oil so recovered was heated for 1 hour at 180°/18 mm., carbon monoxide being evolved; it then distilled as a colourless, viscous liquid, b. p. 140—155°/0.5 mm.; redistillation gave *ethyl 3-carbethoxy-1-methylcyclopentan-2-one-1-acetate*, b. p. 142—146°/0.5 mm. (Found: C, 60.3; H, 7.9.  $C_{13}H_{20}O_6$  requires C, 60.9; H, 7.9%).

The ester (10 g.) was hydrolysed by boiling with concentrated hydrochloric acid (100 c.c.) for 20 hours. The crude, oily acid was esterified with boiling alcohol (100 c.c.) and sulphuric acid (18 g.), and *ethyl 1-methylcyclopentan-2-one-1-acetate* was obtained as a colourless oil, b. p. 130—133°/14 mm. (Found: C, 65.2; H, 8.9.  $C_{10}H_{16}O_3$  requires C, 65.2; H, 8.7%).

*Bromination of 8-Methyl-6-hydrindanone*.—*cis*-8-Methyl-6-hydrindanone (3 g.) (Errington and Linstead, J., 1938, 666) was treated with 2 drops of concentrated hydrobromic acid and then with a solution of bromine (1 c.c.) in acetic acid (30 c.c.). The isolated, crude, bromo-ketone (4 g.) was boiled with dry pyridine (70 c.c.) for 12 hours. The product was mixed with water, neutralised with dilute sulphuric acid, and extracted with ether. The oil obtained gave a semicarbazone which, crystallised from methyl alcohol, had m. p. 199° (Found: C, 62.9; H, 9.6. Calc. for  $C_{11}H_{17}ON_3$ : C, 63.8; H, 8.2%. Calc. for  $C_{11}H_{15}ON_3$ : C, 63.1; H, 9.1%).

In another experiment the crude bromo-ketone (4 g.) was boiled for 3 hours with quinoline (70 c.c.), and the product worked up in the usual manner and converted into the semicarbazone, m. p. 199° (Found: C, 64.2; H, 9.3%).

The crude oil obtained in these two experiments exhibited no unsaturated properties. It decolourised permanganate solution in 1—2 minutes, and bromine water was unaffected.

The crude bromo-ketone (4 g.) was then heated in a sealed tube with trimethylamine (9.5 g.) in alcohol (30 g.) at 100° for 6 hours. The contents of the tube were washed out with alcohol and evaporated to dryness under diminished pressure. The residue separated from alcohol in light yellow crystals, m. p. 240°. The quaternary bromide was dissolved in the necessary quantity of 90% alcohol, and shaken for 2 hours with twice the calculated quantity of silver oxide. The solution was filtered, and the dried product after removal of solvent was distilled at <1 mm. pressure, the receiver being well cooled in a freezing mixture. The distillate was dissolved in ether, and any base removed by washing with hydrochloric acid. The ethereal solution was washed with sodium bicarbonate and water and dried; after removal of the solvent, the residue distilled as a faintly yellow oil, b. p. 112—118°/12 mm. This was converted into a semicarbazone, which crystallised from methyl alcohol in large clusters, m. p. 200° (Found: C, 62.2; H, 8.6%). A mixture with a specimen of the semicarbazone of 8-methyl-6-hydrindanone had m. p. 193°. The oil decolourised permanganate immediately and also bromine water.

The ketone (2 g.), alone and also in benzene solution, was heated in a sealed tube at 160° for 6 hours with vinylcyclohexene (1.9 g.), prepared by the method of Cook and Lawrence (*loc. cit.*); there was no evidence of any reaction.

$\Delta^4$ - and  $\Delta^5$ -Tetrahydrohydrindenes.—*cis*-5-Hydrindanol (Linstead and Mead, J., 1934, 946) (3 mols.) was mixed with phosphorus tribromide (1.5 mols.) with vigorous shaking below 0°. After 12 hours ice and ether were added, and the ethereal extract washed with sodium carbonate and water and dried. After removal of the solvent, 5-bromohydrindane distilled as a colourless oil, b. p. 104—105°/15 mm. The bromide was refluxed for 10 hours with an excess of alcoholic potassium hydroxide (20%). The hydrocarbon was isolated in the usual way and was distilled over sodium as a mobile, colourless oil, b. p. 175—177°/750 mm. (Found: C, 88.4; H, 11.6. Calc. for  $C_9H_{14}$ : C, 88.5; H, 11.5%).

The hydrocarbon (5 g.) was oxidised at 40° with potassium permanganate (16.4 g.) and potassium hydroxide (3.9 g.) in water (600 g.), and the acidic products isolated in the known

manner, m. p. 70—118°. On fractional crystallisation from hot water, two acids were obtained, m. p. 173° and m. p. 101° (cf. Linstead and Mead; Hüchel and Goth, *loc. cit.*).

1-Keto-7-methoxy-2-methyl-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-octahydrophenanthrene.—1-Keto-7-methoxy-2-methyl-1 : 2 : 3 : 4 : 9 : 10-hexahydrophenanthrene (5 g.) (Robinson and Walker, J., 1936, 193) was hydrogenated under 3 atms. in methyl alcohol (50 c.c.) with a 2% palladised strontium carbonate catalyst (2.5 g.). Absorption of gas was regular and was complete after 9 hours. The filtered solution was evaporated; the residue distilled as a viscous syrup, b. p. 171—175°/0.25 mm., which set to a stiff glass. A mixture of this hydrophenanthrol (4.5 g.), acetone (100 c.c.), aluminium *tert.*-butoxide (7.6 g.), and benzene (200 c.c.) was refluxed for 48 hours. Dilute sulphuric acid was added, and the benzene solution washed and dried. The residue was converted into the semicarbazones of the stereoisomeric 1-keto-7-methoxy-2-methyl-octahydrophenanthrenes. The mixed semicarbazones were hydrolysed with 20% oxalic acid solution; the resulting ketone was isolated by means of ether and, after the semi-solid product had been washed with methyl alcohol, crystallised from ether, affording the pure ketone, m. p. 118—119° (Found: C, 78.1; H, 8.3. Calc. for  $C_{16}H_{20}O_2$ : C, 78.7; H, 8.2%). No depression of m. p. was observed on admixture with the ketone obtained by the method of Robinson and Walker (J., 1936, 747; 1938, 183).

5-Hydroxy-14-methoxy-3-methyl-1 : 2 : 3 : 4 : 5 : 6 : 7 : 8 : 9 : 10 : 11 : 18-dodecahydrochrysene (VI).—A solution of 1-keto-7-methoxy-2-methyl-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-octahydrophenanthrene (2.1 g.) in ether (70 c.c.) was added to an excess of the well-stirred Grignard reagent made from  $\Delta^7$ -butenyl bromide (3 g.) and magnesium (0.58 g.) in dry ether (40 c.c.). The product, isolated as previously described, was a brownish, viscous oil (some low-boiling components were removed by distillation); it was cyclised with a mixture of acetic acid, sulphuric acid, and acetic anhydride (cf. Linstead *et al.*, *loc. cit.*), and the isolated acetate was hydrolysed with a solution of potassium hydroxide (2.5 g.) in methyl alcohol (25 c.c.). Methyl alcohol was evaporated, and the product collected by means of ether. A solution of the viscous residue in methyl alcohol was kept in the ice-chest for 2 weeks. The solid (0.5 g.) that separated crystallised from methyl alcohol in colourless leaflets, m. p. 161—168° (Found: C, 79.7; H, 9.4.  $C_{20}H_{28}O_2$  requires C, 80.0; H, 9.3%). The *p*-nitrobenzoate (pyridine method) crystallised from alcohol as a pale yellow powder, m. p. 239°.

2-Keto-4-furyl-10-methyl- $\Delta^{1:9}$ -octalin (III).—A sodio-derivative was prepared from 2-methylcyclohexanone (20 g.) and sodamide (7 g.) in dry ether (250 c.c.), the ammonia produced being removed in a stream of dry nitrogen. Furfurylideneacetone (24.3 g.) (*Organic Syntheses*, 7, 42), dissolved in dry ether (100 c.c.), was then added gradually during 2 hours with vigorous stirring and cooling in ice-water. After 12 hours, water and ether were added, and the ethereal layer was shaken quickly with dilute sulphuric acid, washed, and dried. The residue, after removal of the solvent, was distilled and yielded 2-methylcyclohexanone (3 g.), and then a fraction, b. p. 160—170°/0.5 mm., which redistilled (17 g.) as a pale yellow, very viscous oil that could not be induced to crystallise (Found: C, 77.9; H, 7.9.  $C_{18}H_{18}O_2$  requires C, 78.3; H, 7.8%).

2-Keto-4-furyl-10-methyldecalin.—The foregoing compound (15 g.), methyl alcohol (150 c.c.), and palladium–strontium carbonate catalyst (10 g. of 2%) were shaken under hydrogen (1.5 atms.). Absorption of the gas (1 mol.) was complete in  $\frac{1}{2}$  hour. After filtration and removal of solvent, the residue distilled as a pale yellow oil, b. p. 160—161°/0.4 mm. The decalone (14.6 g.) was treated with semicarbazide hydrochloride (9 g.) and sodium acetate (14.6 g.) in aqueous alcoholic solution. The *semicarbazone* crystallised from butyl alcohol in colourless prisms, m. p. 126° (Found: C, 66.6; H, 8.0.  $C_{19}H_{23}O_2N_3$  requires C, 66.4; H, 8.0%), sparingly soluble in methyl and ethyl alcohols.

1-Furyl-9-methyldecalin (IV).—The above semicarbazone (5 g.) was heated in a sealed tube with sodium ethoxide (3 g.) in alcohol (12 c.c.) at 180° for 18 hours. The isolated product distilled over sodium as a colourless, mobile oil (1.9 g.), b. p. 122—124°/0.4 mm. (Found: C, 82.5; H, 10.0.  $C_{18}H_{22}O$  requires C, 82.6; H, 10.1%). A second fraction was a viscous yellow oil (1 g.), b. p. 155—160°/0.4 mm., which did not react with Brady's reagent and did not form a semicarbazone.

9-Methyldecalin-1-carboxylic Acid (V).—A mixture of furylmethyldecalin (8 g.), ethyl alcohol (80 c.c.), and hydrochloric acid (23 g., *d* 1.16) was refluxed for 20 hours, and the alcohol then removed by distillation, finally under diminished pressure. Concentrated hydrochloric acid (36 c.c.), acetic acid (36 c.c.), and water (72 c.c.) were added to the residue, and the whole refluxed (oil-bath) for 8 hours. The aqueous solution was then decanted from the oil (reaction with 2 : 4-dinitrophenylhydrazine), which was oxidised by addition of saturated aqueous

potassium permanganate to an acetone solution until decoloration of the permanganate became slow at the b. p. of the liquid. The red, viscous residue obtained by evaporation of the decolorised and filtered solution was triturated with aqueous sodium carbonate; the *acid* set free on acidification of the extract crystallised from dilute acetic acid (charcoal) in colourless prisms, m. p. 164° (yield, 25%) (Found : C, 73·1; H, 10·1.  $C_{12}H_{20}O_2$  requires C, 73·4; H, 10·2%).

6-Keto-14-methoxy-4-furyl-3-methyl-1 : 2 : 3 : 4 : 5 : 6 : 9 : 10 : 11 : 18-decahydrochrysene (I).—A mixture of ketomethoxymethyloctahydrophenanthrene (3·1 g.), sodamide (0·5 g.), and dry ether (100 c.c.) was refluxed for 10 hours in a stream of dry nitrogen. Furfurylideneacetone (1·7 g.) in ether (25 c.c.) was added dropwise with vigorous stirring and cooling in ice-water during 3 hours. A dark reddish, non-crystalline substance separated from the mixture, which was kept for 12 hours. Water and ether were then added, the ethereal extract washed and dried, and the ether removed. The viscous residue was rubbed with methyl alcohol and the light yellow substance that separated was crystallised from methyl alcohol. It formed almost colourless prisms, m. p. 172° (Found : C, 80·0; H, 6·8.  $C_{24}H_{26}O_3$  requires C, 79·6; H, 7·2%).

Note.—Ethyl  $\beta$ -2-methoxy-6-naphthoylpropionate gave no new products in attempted Reformatzky reactions with ethyl  $\alpha$ -bromopropionate and ethyl  $\alpha$ -bromosuccinate.

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