391. *The Synthesis of Compounds related to the Sterols, Bile Acids, and Oestrus-producing Hormones. Part VII.*

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A serious obstacle to the successful use of derivatives of 1-keto-1 : 2 : 3 : 4-tetrahydrophenanthrene for the synthesis of equilenin, an œstrogenic hormone excreted by pregnant mares, lies in the great tendency for the intermediate dihydrophenanthrene derivatives to become fully aromatic (compare Cook and Hewett, J., 1933, 1105). This is further illustrated by experiments now reported (but completed in 1933) with 2-*methyl*-1-*allyl*-3 : 4-

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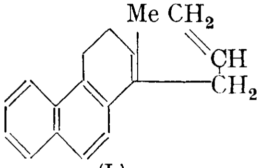
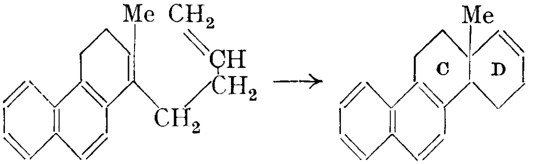
* "Polymerised" oiticica oil was employed in order to avoid the troublesome separation of licanic acid from solid saturated fatty acids.

dihydrophenanthrene (I), obtained from allylmagnesium bromide and 1-keto-2-methyl-1 : 2 : 3 : 4-tetrahydrophenanthrene. This unsaturated hydrocarbon was unaffected by boiling formic acid, but with hydrogen chloride in acetic acid underwent rearrangement to 2-*methyl*-1-n-*propylphenanthrene*, and not the desired cyclisation to a tetracyclic singly-unsaturated hydrocarbon which might have been transformed into deoxyequilenin through an intermediate oxide. The same migration of hydrogen from the nucleus to the side chain took place when the allyl compound (I) was heated with selenium.



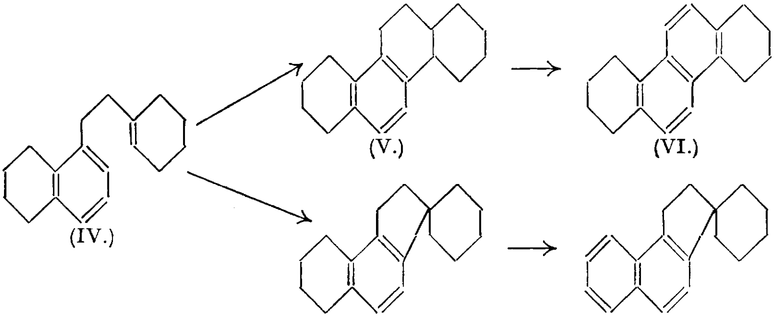
(I.)



(II.) (III.)

On the hypothesis that a six-membered ring might be formed more readily than a five-membered ring by cyclisation of an unsaturated side chain, the behaviour of 2-*methyl*-1-Δ^{γ}-*butenyl*-3 : 4-*dihydrophenanthrene* (II) was then examined. This likewise was resistant to the cyclising action of formic acid, but was converted by sulphuric acid in acetic acid into an *isomeride* (III?), which gave chrysene in moderately good yield when dehydrogenated with selenium. The drastic conditions necessary for cyclisation of (II) may have caused migration of the double bond away from the position (formula III) necessary for degradation to deoxyequilenin, and attempts to isolate a homogeneous product from the cyclised hydrocarbon were hampered by its failure to yield crystalline derivatives. Subsequent to the completion of these experiments (mentioned at a discussion meeting of the Chemical Society on March 21st; see *Chem. and Ind.*, 1935, **54**, 315) the dehydration of 1-methyl-2-Δ^{γ}-butenyl*cyclo*hexanol to a dicyclic hydrocarbon which appeared to have the *cis*-configuration was reported by Linstead (*Chem. and Ind.*, *loc. cit.*).* As we were mainly interested in methods which would lead to *trans*-linkages between rings C and D (formula III), our investigation of the cyclisation product of (II) has not been pursued.

A survey of the synthetic œstrogenic compounds (Cook, Dodds, Hewett, and Lawson, *Proc. Roy. Soc.*, 1934, *B*, **114**, 272) suggests that a high order of œstrogenic activity requires the presence of two polar groups on opposite sides of a suitable hydroaromatic condensed ring system, and the synthesis of a variety of such compounds is being undertaken. It is known that partial dehydrogenation of dodecahydrochrysene (V) gives *s*-octahydrochrysene (VI) (v. Braun and Irmisch, *Ber.*, 1932, **65**, 883), and it seems likely that (VI) could be oxidised to a diketone which would be worthy of examination for œstrogenic properties. In an attempt to render dodecahydrochrysene more accessible for this purpose, β-5-tetralylethylmagnesium chloride was condensed with *cyclo*hexanone, and the resulting *carbinol* dehydrated to 1-(β-5′-*tetralylethyl*)-Δ^1-cyclo*hexene* (IV), which was then cyclised with aluminium chloride at 0°.


(IV.) (V.) (VI.) (VII.) (VIII.)

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* Our projected study of the hydrocarbons resulting from the dehydration of the readily accessible 2-methyl-1-Δ^{γ}-butenyl*cyclo*hexanol was forsaken when Dr. Linstead privately informed one of us, on the occasion of this meeting, that he had already examined this case.

This led to a mixture of saturated hydrocarbons which, on complete dehydrogenation with selenium or platinum-black, gave chrysene and a hydrocarbon, $C_{18}H_{20}$. The latter, in the light of a previous investigation (Cook and Hewett, J., 1934, 365), is undoubtedly the *spiran* (VIII), formed by dehydrogenation of the primary cyclisation product (VII). The amount of chrysene obtained showed that not more than 10% of the original hydrocarbon mixture consisted of dodecahydrochrysene (V), and although octahydrochrysene (VI) was isolated after partial dehydrogenation, the small yield precluded the use of the method for preparative purposes.

The high proportion of spirocyclic hydrocarbon present in the cyclisation mixture is remarkable in view of the fact that cyclisation under the same conditions of β-phenyl-ethyl-Δ^1-*cyclo*hexene gives mainly *as*-octahydrophenanthrene (Cook and Hewett, J., 1933, 1106; Cook and Haslewood, this vol., p. 767). The unexpected influence of the additional ring present in (IV) is a further example of the sensitivity of the course of the cyclisation process to comparatively slight modifications of molecular structure (compare J., 1934, 653, 1727; this vol., p. 667).

EXPERIMENTAL.

Dihydrophenanthrene Derivatives.

1-*Keto*-2-*methyl*-1 : 2 : 3 : 4-*tetrahydrophenanthrene*.—Haworth's method (J., 1932, 1125) was found inconvenient for the preparation of large amounts of this ketone, and the following procedure was adopted: The potassio-compound from ethyl methylmalonate (100 g.) and powdered potassium (19 g.) in toluene (200 c.c.) was heated with β-1-naphthylethyl bromide (85 g.) at 130° for 30 hours. The resulting ester (58 g.), isolated in the usual way, had b. p. 196—197°/1·5 mm., and was hydrolysed by alcoholic potash to the malonic acid, which was decarboxylated by heating at 200°. The resulting γ-1-naphthyl-α-methylbutyric acid (38 g.; b. p. 210°/6 mm.) was dehydrated to 1-keto-2-methyl-1 : 2 : 3 : 4-tetrahydrophenanthrene (29 g.) as described by Haworth.

2-*Methyl*-1-*allyl*-3 : 4-*dihydrophenanthrene*.—A mixture of allyl bromide (9·6 g.), magnesium turnings (2 g.), 1-keto-2-methyl-1 : 2 : 3 : 4-tetrahydrophenanthrene (8 g.), ether (20 c.c.), and anisole (25 c.c.) was boiled for 3 hours, and then decomposed with ice and ammonium chloride. The ethereal extract was washed and dried (sodium sulphate) and the ether and the anisole were removed. The residual oil (10 g.) would not crystallise, and was boiled for ½ hour with 98% formic acid (20 c.c.). After removal of the formic acid the product was twice distilled in a vacuum. The hydrocarbon (I), b. p. 177—179°/0·6 mm. (2·7 g.), was characterised as its *picrate*, which crystallised from methyl alcohol in small crimson needles, m. p. 75—76° (Found : C, 62·2; H, 4·75. $C_{18}H_{18},C_6H_3O_7N_3$ requires C, 62·2; H, 4·6%). The liquid hydrocarbon regenerated from this pure picrate had an iodine value of 192 when titrated with the Rosenmund–Kuhnhenn reagent (calc. for 2 double bonds, 184). The position (formula I) assigned to the new double bond introduced by dehydration of the carbinol is based partly on analogy, and partly on the fact that the unsaturated hydrocarbon did not react with maleic anhydride in boiling xylene.

2-*Methyl*-1-n-*propylphenanthrene*.—(a) A solution of the diene (I) in glacial acetic acid saturated with hydrogen chloride was heated for an hour at 100°. The product gave a *picrate* which crystallised from alcohol in yellow needles, m. p. 121·5—122° (Found : C, 62·9; H, 4·5. $C_{18}H_{18},C_6H_3O_7N_3$ requires C, 62·2; H, 4·6%). 2-*Methyl*-1-n-*propylphenanthrene*, obtained from this picrate by washing an ethereal solution with dilute aqueous sodium carbonate, crystallised from light petroleum in colourless needles, m. p. 65°, and was saturated (Found : C, 92·15; H, 7·9. $C_{18}H_{18}$ requires C, 92·25; H, 7·75%). The s-*trinitrobenzene complex* crystallised from alcohol in pale yellow needles, m. p. 131° (Found : C, 64·45; H, 4·7. $C_{18}H_{18},C_6H_3O_6N_3$ requires C, 64·4; H, 4·7%). (b) The diene (I) was heated with an equal weight of selenium at 320° for 15 hours. The crystalline hydrocarbon thus formed was identical with that prepared as described under (a), identification being completed by comparison of the picrates and *s*-trinitrobenzene complexes.

2-*Methyl*-1-Δ^γ-*butenyl*-3 : 4-*dihydrophenanthrene*.—A cold Grignard solution prepared from Δ^γ-butenyl bromide (14 g.; Juvala, *Ber.*, 1930, 63, 1989; Linstead and Rydon, J., 1934, 1998), magnesium turnings (5 g. = 2 atoms), and anhydrous ether (20 c.c.) was decanted from the excess of magnesium and slowly treated with a solution of 1-keto-2-methyl-1 : 2 : 3 : 4-tetrahydrophenanthrene (15 g.) in ether (60 c.c.). The mixture was kept for an hour at room temperature and then boiled for 1½ hours. After decomposition with ice and ammonium chloride, the ethereal solution was dried, and the solvent removed. The crude resinous carbinol (17·4 g.) was dehydrated by boiling for ½ hour with 98% formic acid (35 c.c.). Vacuum distillation of the product gave 8·1 g., b. p. 140—150°/0·1—0·2 mm., and 4·2 g. of a higher fraction, b. p. 155—160°/0·3 mm. The higher fraction was mainly the desired diene (II) (iodine value, 192; calc. for two double bonds, 205), and was characterised by its *picrate*, which crystallised from alcohol, containing a little picric acid, in dark red needles, m. p. 77—78° (Found: C, 62·6; H, 4·8. $C_{19}H_{20},C_6H_3O_7N_3$ requires C, 62·85; H, 4·9%).

In larger scale preparations of the butenyl compound (II) difficulties were experienced in isolating a homogeneous product, repeated crystallisation of the picrates failing to give a substance of the correct m. p. This was shown to be due to contamination with 2-methyl-3 : 4-dihydrophenanthrene arising from dehydration of a carbinol formed by the reducing action of the Grignard reagent on the original ketone. For, after cyclisation (see below) and dehydrogenation, 2-methylphenanthrene was isolated from the lower-boiling fractions, and was identified by its m. p. (55—56°) and that of its picrate (118°) (Haworth, *loc. cit.*, gives 55—56° and 118—119°, respectively). This 2-methylphenanthrene was further characterised by its s-*trinitrobenzene complex*, which crystallised from alcohol in large, flat, yellow needles, m. p. 155—157° (Found: C, 62·3; H, 3·8. $C_{15}H_{12},C_6H_3O_6N_3$ requires C, 62·2; H, 3·7%).

Cyclisation of 2-*Methyl*-1-Δ^{γ}-*butenyl*-3 : 4-*dihydrophenanthrene* (II).—A solution of the diene (II) (1 g.) in glacial acetic acid (10 c.c.) and concentrated sulphuric acid (0·5 c.c.) was heated at 100° for 2¼ hours (no reaction took place during 20 hours at room temperature). After dilution with water, the product was extracted with ether, washed with dilute sodium carbonate solution, and distilled in a vacuum. About half of the original diene was recovered. A higher-boiling fraction (0·15 g.), b. p. 180°/0·05 mm., gave no picrate, and was shown to consist mainly of methylhexahydrochrysene (compare III) by selenium dehydrogenation to chrysene in 40% yield (16 hours at 310°). The chrysene, m. p. 246—247°, was identified by direct comparison with an authentic specimen, and by conversion into its 2 : 7-dinitroanthraquinone complex, m. p. 295°.

Attempts to oxidise the hexahydrochrysene derivative obtained in larger-scale experiments gave no crystalline acid, possibly on account of the presence of appreciable amounts of 2-methyl-3 : 4-dihydrophenanthrene (see above).

1-(β-5′-*Tetralylethyl*)-Δ^1-cyclo*hexene and its Cyclisation Products.*

1-(β-5′-*Tetralylethyl*)cyclo*hexanol*.—To an ice-cold Grignard solution prepared from β-5-tetralylethyl chloride (J., 1934, 1736) (22 g.), magnesium turnings (2·7 g.), and anhydrous ether (100 c.c.) was slowly added *cyclo*hexanone (10 g.), diluted with ether (10 c.c.). After being kept at room temperature for 2 hours, the product was decomposed with ice and ammonium chloride, and the ethereal solution washed, dried, and distilled. The carbinol fraction (17 g.) had b. p. 175—180°/0·4 mm., and gave a 3 : 5-*dinitrobenzoate*, which crystallised from alcohol in small yellowish needles, m. p. 124—125° (Found: C, 66·5; H, 6·5. $C_{25}H_{28}O_6N_2$ requires C, 66·3; H, 6·2%).

1-(β-5′-*Tetralylethyl*)-Δ^1-cyclo*hexene* (IV).—The aforesaid carbinol (15 g.) was heated for an hour at 160—170° with potassium hydrogen sulphate (25 g.). The unsaturated *hydrocarbon* (IV) (12·5 g.) was redistilled over sodium, forming a colourless viscous liquid, b. p. 140—150°/0·05 mm. (Found: C, 89·3; H, 10·05. $C_{18}H_{24}$ requires C, 89·9; H, 10·1%).

Cyclisation. Finely powdered anhydrous aluminium chloride (12 g.) was added to an ice-cold solution of 1-(β-5′-tetralylethyl)-Δ^1-*cyclo*hexene (11·5 g.) in carbon disulphide (110 c.c.). After being kept at 0° for 7½ hours with occasional shaking, the red solution was decanted from the aluminium chloride sludge, shaken with dilute hydrochloric acid, and distilled at 0·1 mm. Two fractions were collected: I, b. p. 123—130° (1·3 g.), and II, b. p. 130—140° (6·6 g.) (Found: C, 89·5; H, 10·1%). Both fractions were completely saturated, colourless syrups.

s-*Octahydrochrysene* (VI).—Fraction II of the mixture of cyclised hydrocarbons (5·5 g.) was heated with selenium (3 g.) at 300—310° for 14 hours. The alcoholic extract of the product was treated with picric acid (5 g.), and the resulting red needles were recrystallised from alcohol. This picrate (0·3 g.) was decomposed with ammonia, and gave *s*-octahydrochrysene, m. p. 136—138°, the picrate of which formed characteristic scarlet needles, m. p. 139—140° (v. Braun and Irmisch, *loc. cit.*, give 138—140°, and 136—139°, as the m. p.'s of this hydrocarbon and its picrate). Dehydrogenation of the pure hydrocarbon with platinum-black at 300° gave chrysene.

4 : 5-*Benzhydrindene*-1-spirocyclo*hexane* (VIII).—The liquid hydrocarbon mixture (4 g.)

recovered from the liquors after isolation of *s*-octahydrochrysene was heated with platinum-black at 300—320° for 3 hours. The product was extracted with *cyclo*hexane, and the chrysene (0·3 g.) collected and identified in the usual manner. The liquors were evaporated, and the residual syrup was treated with picric acid (4 g.) in alcohol. After recrystallisation from alcohol the *picrate* (4·2 g.) formed orange needles of constant m. p. 125—126° (Found : C, 62·2; H, 5·2. $C_{18}H_{20},C_6H_3O_7N_3$ requires C, 61·9; H, 5·0%). The hydrocarbon regenerated from this picrate was distilled over sodium, and had b. p. 140°/0·1 mm. 4 : 5-*Benzhydrindene*-1-spirocyclo*hexane* (VIII) crystallised on standing, and separated from alcohol in colourless sparkling crystals, m. p. 56—57° (Found : C, 91·2; H, 8·7. $C_{18}H_{20}$ requires C, 91·5; H, 8·5%).

Complete dehydrogenation of fraction I (1·2 g.) of the cyclised hydrocarbons (see above) with platinum-black gave 50 mg. of chrysene, the picrate of the spiran (VIII) being isolated from the liquors. Complete dehydrogenation of fraction II (0·6 g.) with selenium at 300—320° gave 50 mg. of chrysene, in addition to the spiran.

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