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ANALOGUES OF MALE SEX HORMONES

R. H. JAEGER
The Dyson Perrins Laboratory, Oxford

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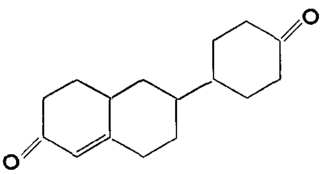
Abstract—The synthesis of *cis*- and *trans*-6-(4′-*oxo*cyclo*hexenyl*)-9-methyldecal-1-ol, which may be regarded as analogues of D-homo-testosterone, is described.

THE spectacular success of stilboestrol and hexoestrol[1] as oestrogenic hormone substitutes immediately led to an intensive search for equally simple active analogues of other sex hormones. Early approaches chiefly consisted in attaching the characteristic C_{17}-side chains of various steroidal hormones to suitable derivatives of diphenylhexane,[2] diethylstilbene,[3,4] dibenzyl[5] and even benzene;[4] a number of analogues of androgens based on perhydrohexoestrol has been described in the patent literature.[6] Some of these compounds were alleged to possess the activity aimed at,[2,4] while others were found to be totally inactive.[3]

It became gradually apparent, however, that biological activity was closely linked with the structure of the natural hormones, except in the case of the oestrogens. Although the limits within which biological activity remains unaffected by structural alterations have not yet been completely defined, they are undoubtedly very restricted;[7] and rogenic activity in particular appears to be extremely structure-specific.

Nevertheless the hope of finding hormone substitutes amongst compounds



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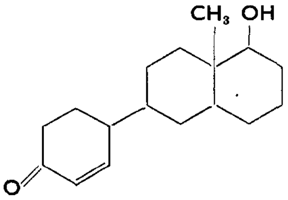

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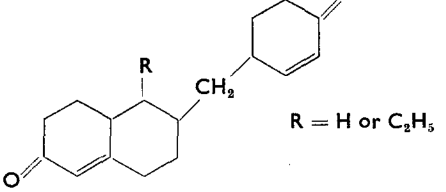

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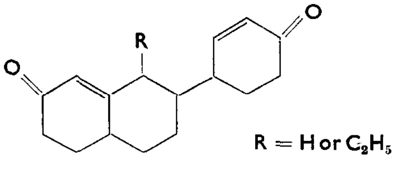

IV

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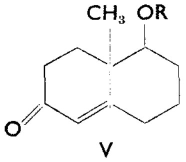
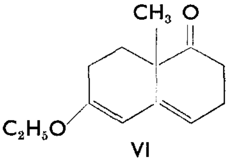
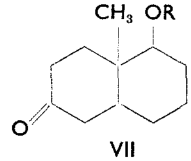
[1] E. C. Dodds, L. Golberg, W. Lawson and R. Robinson *Proc. Roy. Soc.* B **127**, 140 (1939).
[2] The Wellcome Foundation Ltd., G. Brownlee and W. M. Duffin Brit. Pat. 550,262 (1942).
[3] R. H. Jaeger and R. Robinson *J. Chem. Soc.* 744 (1941).
[4] W. H. Linnell and I. M. Roushdi *J. Pharmacol.* **14**, 240 (1941); *Nature, Lond.* **148**, 595 (1941).
[5] W. C. J. Ross *J. Chem. Soc.* 536, 538 (1945).
[6] A. L. Wilds, C. H. Hoffman and T. H. Pearson *J. Amer. Chem. Soc.* **77**, 647 (1955).
[7] A. J. Birch and H. Smith *J. Chem. Soc.* 4909 (1956) and previous papers.

incorporating only part of the steroid molecule has not been entirely abandoned. Encouraged by the claim[8] that the diketone (I) was slightly androgenic it was at that time considered desirable to prepare an analogue of D-homo-testosterone without ring B (II). Since then several compounds bearing rather scantier likeness to the steroids than either (I) or (II)—for instance (III)[9] and (IV)[10]—have been reported as devoid of androgenic activity.

As starting material for the synthesis of the hydroxy-ketone (II) served 1-hydroxy-9-methyl-6-oxo-1:2:3:4:6:7:8:9-octahydronaphthalene (V, R = H) which was readily prepared from the enol ether (VI)[11,12] by reduction with lithium aluminium hydride and subsequent acid hydrolysis (cf.[13]). Condensation of the keto-alcohol (V, R = H) with


V


VI


VII

dihydropyran[14] gave the corresponding tetrahydropyranyl ether (V, R = $\overline{\mathrm{CH{-}O{-}CH_2{-}CH_2{-}CH_2{-}CH_2}}$) from which 9-methyl-6-oxodecal-1-ol (VII, R = $\overline{\mathrm{CH{-}O{-}CH_2{-}CH_2{-}CH_2{-}CH_2}}$) in its *cis*-form was obtained by catalytic hydrogenation, and in the *trans*-form by chemical reduction with lithium in liquid ammonia.[15] The configurations were assigned not only on the basis of the means employed for the elimination of the double bond[16] but also by hydrolysing both saturated ketones to give two hydroxy-ketones (VII, R = H) and establishing the identity of one of them (the product from catalytic hydrogenation) by comparison with a sample previously prepared by a different route for which *cis*-fusion of the rings had been rigidly proved.[17] The infra-red spectra of the two isomers (VII, R = H) differed materially in the region 8–15 μ.

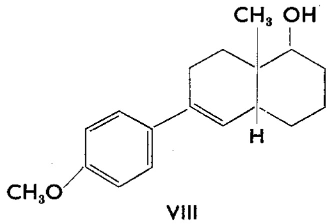
Condensation of the *cis*- and *trans*-isomers

$$(\mathrm{VII},\ R = \overline{\mathrm{CH{-}O{-}CH_2{-}CH_2{-}CH_2{-}CH_2}})$$

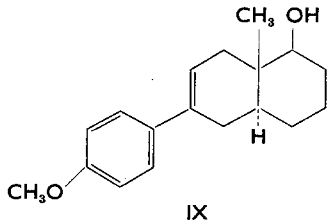
with anisyl magnesium bromide, followed by acid treatment gave the octalin derivatives (VIII) and (IX) respectively. Birch reduction with sodium—alcohol—liquid ammonia of (VIII) gave after acid hydrolysis the β:γ-unsaturated ketone (X) which could not be induced to crystallise. The infra-red spectrum with a single strong band at 5·85 μ and the absence of any appreciable light absorption in the region 200–250 mμ confirmed this structure. Reduction of the *trans*-compound (IX) with lithium and ethanol in liquid ammonia,[18] followed by carefully controlled acid hydrolysis[19] yielded the β:γ-unsaturated ketone (XI) as a gum, which on examination

[8] A. L. Wilds, C. H. Shunk and C. H. Hoffman *J. Amer. Chem. Soc.* **71**, 3266 (1949).
[9] K. W. Bentley and W. C. Firth *J. Chem. Soc.* 2403 (1955).
[10] V. S. Gaind, R. P. Gandhi and S. M. Mukherji *Chem. & Ind.* (*Rev.*) 1593 (1955).
[11] S. Swaminathan and M. S. Newman *Tetrahedron* **2**, 88 (1958).
[12] R. Robinson *et al.* *Tetrahedron* In press.
[13] A. J. Birch, K. A. J. Quartey and H. Smith *J. Chem. Soc.* 1768 (1952).
[14] G. F. Woods and D. N. Kramer *J. Amer. Chem. Soc.* **69**, 2246 (1947).
[15] F. Sondheimer, O. Mancera, G. Rosenkranz and C. Djerassi *Ibid.* **75**, 1282 (1953).
[16] E. E. van Tamelen and W. C. Proost *Ibid.* **76**, 3632 (1954).
[17] R. H. Jaeger, R. Robinson and H. Smith Unpublished work.
[18] A. L. Wilds and N. A. Nelson *J. Amer. Chem. Soc.* **75**, 5360 (1953).
[19] J. C. Sheehan and G. D. Laubach *Ibid.* **72**, 2478 (1950).

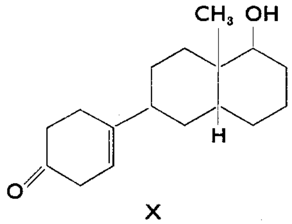
of the carbonyl region by ultra-violet and infra-red spectroscopy gave the same results as the corresponding *cis*-compound (X); furthermore, a yellow 2:4-dinitrophenylhydrazone was obtained with Brady's reagent.



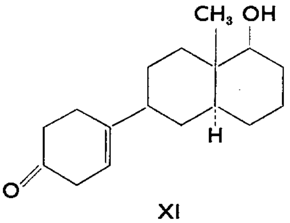
VIII



IX

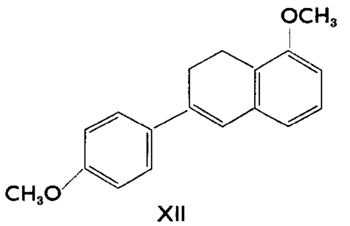


X

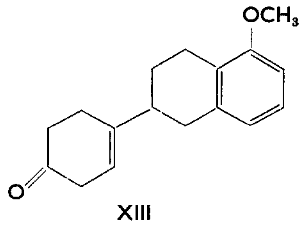


XI

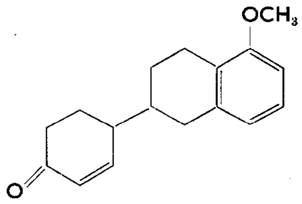
Conversion of the compounds (X) and (XI) to the isomeric α:β-unsaturated ketones (II) was only partly accomplished, treatment with sodium methoxide in methanol in each case resulting in an inseparable mixture of conjugated and unconjugated unsaturated ketones in a ratio of approximately 1:1. This estimate was supported by the light absorption at 220–225 mμ ($\varepsilon = 7000$) and by comparison of the intensity of the carbonyl bands at 5·85 and 5·99 μ. Although not entirely unexpected in view of other worker's failure to isomerise certain substituted *cyclo*hexenones,[20,21] these results were nevertheless disappointing since model experiments carried out in the early stages of this work had been completely successful in this respect.



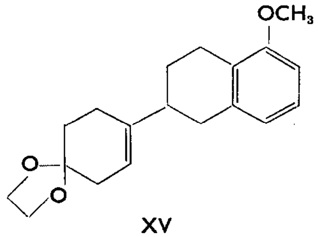
XII



XIII



XIV



XV

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[20] A. J. Birch and S. M. Mukherji *J. Chem. Soc.* 2531 (1949).

[21] A. L. Wilds and N. A. Nelson *J. Amer. Chem. Soc.* **75**, 5366 (1953).

Birch reduction of the compound (XII) obtained from a reaction of 1-methoxy-6-oxo-5:6:7:8-tetrahydronaphthalene with anisyl magnesium bromide yielded after acid hydrolysis the unconjugated ketone (XIII) which gave a yellow 2:4-dinitrophenylhydrazone and did not absorb in the 200–250 mμ region. This was isomerised smoothly by means of sodium methoxide in methanol to the crystalline α:β-unsaturated ketone (XIV) with an absorption maximum at 225 mμ ($\varepsilon = 15{,}000$); with Brady's reagent a red 2:4-dinitrophenylhydrazone was formed. With the intention of reducing the remaining aromatic nucleus by the Birch–Wilds method,[18] the keto-group of (XIII) was protected by forming the cyclic ketal (XV). Other commitments, however, prevented completion of this aspect of the work.

The partially isomerised hydroxy-ketones obtained from (X) and (XI) had no androgenic activity.

EXPERIMENTAL

Light petroleum without further specification means the fraction boiling at 60–80°. Ultra-violet light absorptions were determined in methanolic solutions; Nujol mulls were used for the infra-red spectra of solids.

6-*Ethoxy*-1:2:3:7:8:9-*hexahydro*-1-*hydroxy*-9-*methylnaphthalene*

Powdered lithium aluminium hydride (4 g) was added to a solution of 6-ethoxy-1:2:3:7:8:9-hexahydro-9-methyl-1-oxonaphthalene (VI)[11,12] (15 g) in anhydrous ether (150 cm^3). After 12 hr at room temperature the mixture was refluxed for one hour and the reaction product isolated, omitting the use of mineral acid. The crude product crystallised in contact with traces of moist ether; recrystallisation from either aqueous methanol or a concentrated ethereal solution gave fine long transparent needles, m.p. 105°. (This material liquefied in the vacuum desiccator and evidently contained solvent of crystallisation in its solid state.) (Found: C, 73·8; H, 9·4. $C_{13}H_{20}O_2 \cdot \frac{1}{4}H_2O$ requires C, 73·5; H, 9·2 per cent). The anhydrous material distilled as a yellow oil, b.p. 125–128°/0·1 mm (Found: C, 75·2; H, 9·5. $C_{13}H_{20}O_2$ requires C, 75·0; H, 9·6 per cent). Light absorption: Max. 242·5 mμ ($\varepsilon = 22{,}000$).

9-*Methyl*-1:2:3:4:6:7:8:9-*octahydro*-6-*oxo*-1-(2′-*tetrahydropyranyloxy*)-*naphthalene*

The above enol-ether (12 g), ethanol (155 cm^3), water (40 cm^3) and concentrated sulphuric acid (3·4 cm^3) were refluxed under nitrogen for 1 hr. The solution was poured into brine, the product collected in ether and washed and dried. 1-Hydroxy-9-methyl-1:2:3:4:6:7:8:9-octahydro-6-oxonaphthalene (cf.[13]) distilled as a yellow oil (7·3 g), b.p. 135–137°/0·2 mm (Found: C, 73·2; H, 9·0. $C_{11}H_{16}O_2$ requires C, 73·3; H, 8·9 per cent). Light absorption: Max. 240 mμ ($\varepsilon = 14{,}400$). The 2:4-*dinitrophenylhydrazone* crystallised from ethanol as scarlet prisms, m.p. 172° (Found: C, 56·2; H, 5·6; N, 15·3. $C_{17}H_{20}O_5N_4$ requires C, 56·7; H, 5·6; N, 15·6 per cent).

A solution of the hydroxy ketone (7·2 g) in freshly distilled dihydropyran (20 cm^3) containing a few drops of concentrated hydrochloric acid was kept at room temperature for 12 hr. After addition of ether the solution was washed with aqueous sodium carbonate and a lot of water and was dried. The crude oily product solidified on trituration with light petroleum (b.p. 40–60°) and was recrystallised from this solvent or aqueous methanol; 9-*methyl*-1:2:3:4:6:7:8;9-*octahydro*-6-*oxo*-1-(2′-*tetrahydropyranyloxy*)-*naphthalene* (5·1 g) formed colourless prisms, m.p. 62° (Found: C, 72·4;

H, 9·3. $C_{16}H_{24}O_3$requires C, 72·7; H, 9·1 per cent). Light absorption: Max. 240 mμ (ε = 16·000).

9-*Methyl*-6-*oxo*-1-(2′-*tetrahydropyranyloxy*)-cis-*decalin*

The above unsaturated ketone (5 g) dissolved in absolute ethanol (50 cm^3) was hydrogenated at room temperature and ordinary pressure in the presence of 2 per cent palladised strontium carbonate (0·5 g). The product was isolated in the usual manner and distilled as a colourless oil (5 g), b.p. 135°/0·05 mm (Found: C, 71·9; H, 9·8. $C_{16}H_{26}O_3$ requires C, 72·2; H, 9·8 per cent). A small sample of this material was converted by acid hydrolysis into 9-methyl-6-oxo-*cis*-decal-1-ol, m.p. 91° which had been previously prepared and for which the *cis*-configuration had been established.[17]

9-*Methyl*-6-*oxo*-1-(2′-*tetrahydropyranyloxy*)-trans-*decalin*

To a solution of lithium (0·1 g) in liquid ammonia (110 cm^3) was added dropwise one of 9-methyl-1:2:3:4:6:7:8:9-octahydro-6-oxo-(2′-tetrahydropyranyloxy)-naphthalene (1·16 g) in tetrahydrofuran (40 cm^3). Ten minutes after completed addition the blue solution was decomposed with a few crystals of ammonium chloride followed by water and ether. From the ethereal extract a golden yellow oil (1·04 g) was obtained which was absorbed from light petroleum on activated alumina (30 g). Elution with mixtures of benzene—light petroleum and finally benzene alone yielded crystalline 9-*methyl*-6-*oxo*-1-(2′-*tetrahydropyranyloxy*)-trans-*decalin* (0·90 g) which was recrystallised from very little light petroleum (b.p. 40–60°) to give colourless prisms, m.p. 98–99° (Found: C, 71·9; H, 9·9. $C_{16}H_{26}O_3$ requires C, 72·2; H, 9·8 per cent).

9-*Methyl*-6-*oxo*-trans-*decal*-1-*ol*

The above tetrahydropyranyl ether (110 mg) was refluxed under nitrogen for 30 min with methanol (5 cm^3) and a few drops of dilute hydrochloric acid. The reaction mixture was poured into brine, the product extracted with ether and the extract washed and dried. The crude material solidified on trituration with light petroleum and, after chromatography on a short column of activated alumina, 9-*methyl*-6-*oxo*-trans-*decal*-1-*ol* crystallised from light petroleum (b.p. 40–60°) as colourless prisms, m.p. 69° (Found: C, 72·8; H, 10·1. $C_{11}H_{18}O_2$ requires C, 72·5; H, 9·9 per cent). The 2:4-*dinitrophenylhydrazone*, prepared with Brady's reagent, crystallised from ethanol in orange yellow prisms, m.p. 159° (Found: C, 56·5; H, 6·3; N, 15·7. $C_{17}H_{22}O_5N_4$ requires C, 56·4; H, 6·1; N, 15·5 per cent).

6-*Anisyl*-6-*hydroxy*-9-*methyl*-1-(2′-*tetrahydropyranyloxy*)-cis-*decalin*

A solution of 9-methyl-6-oxo-1-(2′-tetrahydropyranyloxy)-*cis*-decalin (0·75 g) in anhydrous ether (15 cm^3) was added slowly in an atmosphere of nitrogen to ice-cold, well-stirred anisyl magnesium bromide (prepared from 320 mg of magnesium and 1·75 cm^3 of 4-bromoanisole in 25 cm^3 of ether). The mixture was kept at 0° for 30 min, then refluxed for 2 hr and finally stood at room temperature for 4 hr; decomposition at 0° with 10 per cent sulphuric acid, washing and drying of the ether layer isolated an oil, which on fractionation gave a fore-run from which 4:4′-dianisol, m.p. 174° was isolated, and as the main fraction the *carbinol* (0·8 g), pale yellow glass, b.p. 205–210°/0·03 mm (Found: C, 73·5; H, 8·8; OMe, 8·2. $C_{23}H_{34}O_4$ requires C, 73·8; H, 9·1; OMe, 8·3 per cent).

6-*Anisyl*-1-*hydroxy*-9-*methyl*-1:2:3:4:7:8:9-cis-*octahydronaphthalene* (VIII)

The foregoing carbinol (0·55 g) was refluxed for one hour with ethanol (25 cm^3) and three drops of concentrated hydrochloric acid; the mixture was then poured into water and the product isolated by means of ether. After evaporation of the solvent the residue crystallised from light petroleum as colourless, blunt needles, m.p. 147° (0·4 g) (Found: C, 79·7; H, 8·7. $C_{18}H_{24}O_2$ requires C, 79·5; H, 8·8 per cent).

Reduction. Sodium (5·75 g) in small slices was added rapidly with stirring to a solution of the above ether (600 mg) in tetrahydrofuran (15 cm^3), ethanol (30 cm^3) and liquid ammonia (300 cm^3). After disappearance of the blue colour, water (200 cm^3) was added, followed by ether (200 cm^3); the organic layer was washed and the solvent evaporated. The residue (600 mg) was stirred and boiled for 20 min with 3 per cent sulphuric acid under nitrogen. The washed and dried ether extract from this yielded a thick yellow oil (0·53 g) which was absorbed on neutral alumina (15 g) in light petroleum; benzene and benzene-ether (9:1) eluted 6-(4′-*oxo*cyclo*hexenyl*)-9-*methyl*-cis-*decal*-1-*ol* which failed to crystallise and was evaporatively distilled as an almost colourless oil (400 mg), bath temperature 195° at 0·08 mm. The infra-red spectrum had strong bands at 2·95 and 5·85 μ (Found: C, 78·1; H, 10·1. $C_{17}H_{26}O_2$ requires C, 77·9; H, 9·9 per cent). By warming the β:γ-unsaturated ketone at 50° for 25 min with a 5 per cent solution of sodium in methanol only partial isomerisation to the α:β-unsaturated ketone was achieved. The infra-red spectrum indicated a mixture of approximately equal parts of the two isomers, with bands at 2·95, 5·85 and 5·99 μ. This was also supported by the light absorption at 225 mμ (ε = 7·200). (Found: C, 77·7; H, 10·1 per cent).

6-*Anisyl*-1-*hydroxy*-9-*methyl*-1:2:3:4:5:8:9:10-trans-*octahydronaphthalene* (IX)

9-Methyl-6-oxo-1-(2′-tetrahydropyranyloxy)-*trans*-decalin (1·2 g) and anisyl magnesium bromide (prepared from 540 mg magnesium and 4·2 g 4-bromoanisol in 25 cm^3 anhydrous ether) were allowed to react as described previously for the corresponding *cis*-compound. The fraction of b.p. 200–210°/0·05 mm was warmed with aqueous ethanolic hydrogen chloride and the product isolated as usual. Crystallisation from ether—light petroleum gave colourless prisms (650 mg), m.p. 115° (Found: C, 79·6; H, 8·9. $C_{18}H_{24}O_2$ requires C, 79·5; H, 8·8 per cent).

Reduction. Lithium (2·5 g) was added to a stirred solution of this ether (550 mg) in tetrahydrofuran (50 cm^3) and liquid ammonia (500 cm^3); 10 min later ethanol (25 cm^3) was dropped in slowly and after further 10 min the reaction mixture was decomposed with water and worked up as usual. The crude product (530 mg) was stirred under nitrogen at 0° with benzene (35 cm^3) and 25 per cent sulphuric acid (50 cm^3) for 10 min; the mixture was then warmed to 60°, kept at this temperature for 1 hr, and finally at room temperature for 12 hr. The sticky oil (500 mg) thus obtained was absorbed from light petroleum on neutral alumina (15 g); the fraction eluted with benzene—ether (9:1) gave an infra-red spectrum consistent with the structure of the β:γ-unsaturated ketone 6-(4′-*oxo*cyclo*hexenyl*)-9-*methyl*-trans-*decal*-1-*ol* (one intense band in the carbonyl region at 5·86 μ). The pale yellow oil was evaporatively distilled at a bath temperature of 220° at 0·2 mm (Found: C, 77·3, H; 10·2.

$C_{17}H_{26}O_2$ requires C, 77·9; H, 9·9 per cent). The 2:4-*dinitrophenylhydrazone* crystallised from ethanol as yellow prisms, m.p. 108° (Found: C, 62·3; H, 6·8; N, 12·1. $C_{23}H_{30}O_5N_4$ requires C, 62·5; H, 6·8; N, 12·7 per cent). Treatment with warm sodium methoxide in methanol as described before for the corresponding *cis*-compound gave a mixture consisting of α:β- and β:γ-unsaturated ketones. The infra-red spectrum had two bands in the carbonyl region at 5·86 and 5·99 μ. Light absorption: Max. 220 (ε = 7000).

6-*Anisyl*-1-*methoxy*-7:8-*dihydronaphthalene* (XII)

To an ice-cold ethereal suspension of anisyl magnesium bromide (prepared from 1·1 g magnesium and 9·5 g 4-bromoanisol in 50 cm^3 ether) under nitrogen a solution of 1-methoxy-6-oxo-5:6:7:8-tetrahydronaphthalene (4 g) was added slowly with vigorous stirring. After 4 hr at room temperature and 4 hr refluxing ice and dilute sulphuric acid were added and the product isolated in the usual manner. Fractionation yielded an almost colourless oil (3·2 g), b.p. 175–185/0·2 mm which solidified and separated from ethanol in glistening, colourless platelets, m.p. 92–93° (Found: C, 81·1; H, 6·6. $C_{18}H_{18}O_2$ requires C, 81·2; H, 6·8 per cent).

6-(4′-*Oxo*cyclo*hexenyl*)-1-*methoxy*-5:6:7:8-*tetrahydronaphthalene* (XIII)

A fine white precipitate separated on addition of a solution of the above ether (1 g) in tetrahydrofuran (20 cm^3) to liquid ammonia (300 cm^3) and ethanol (60 cm^3) but disappeared when sodium (6·8 g) in small pieces was added with vigorous stirring. The reaction mixture was decomposed and worked up as usual and the crude product stirred and boiled with 3 per cent sulphuric acid under nitrogen for 15 min. Ether extraction isolated an oil which crystallised from light petroleum as clusters of stout prisms (400 mg), m.p. 118–119° (Found: C, 79·7; H, 8·1. $C_{17}H_{20}O_2$ requires C, 79·7; H, 7·8 per cent). Light absorption: Max. 270 mμ (ε = 1480). The 2:4-*dinitrophenylhydrazone* formed with Brady's reagent and crystallised from ethyl acetate—ethanol as yellow prisms, m.p. 162° (Found: C, 63·5; H, 5·8; N, 13·1. $C_{23}H_{24}O_5N_4$ requires C, 63·2; H, 5·5; N, 12·8 per cent).

6-(4′-*Oxo*cyclo*hex*-2-*enyl*)-1-*methoxy*-5:6:7:8-*tetrahydronaphthalene* (XIV)

After warming the β:γ-unsaturated ketone (200 mg) from above for 25 min at 50° with a 3 per cent solution of sodium in methanol (20 cm^3) a pale yellow oil was isolated by ether extraction which solidified on trituration with light petroleum; recrystallisation from ether—light petroleum gave colourless prisms, m.p. 112–114° (Found: C, 79·4; H, 8·2. $C_{17}H_{20}O_2$ requires C, 79·7; H, 7·8 per cent). Light absorption: Max. 225 mμ (ε = 15,000) and 270 mμ (ε = 1560). The 2:4-*dinitrophenylhydrazone* crystallised from ethyl acetate—ethanol as red needles, m.p. 178° (Found: C, 62·9; H, 5·4; N, 12·8. $C_{23}H_{24}O_5N_4$ requires C, 63·3; H, 5·5; N, 12·8 per cent).

6-(4′-*Ethylenedioxy*cyclo*hexenyl*)-1-*methoxy*-5:6:7:8-*tetrahydronaphthalene* (XV)

The ketone (XIII) (500 mg) was refluxed in benzene (50 cm^3) with ethylene glycol (0·5 cm^3) and a few crystals of toluene-*p*-sulphonic acid for 5 hr, using a Dean–Stark head. The cold solution was washed free of acid and dried. After evaporation of the solvent the residue (430 mg) distilled as a pale yellow thick oil, b.p. 165°/0·1 mm (Found: C, 76·6; H, 8·1. $C_{19}H_{24}O_3$ requires C, 76·0; H, 8·0 per cent).