861. *Terpene Synthesis. Part III.*[1] *Benzyloxymethylation as a Method of Synthesis of Terpene Carboxylic Acids.*

By C. L. Graham and F. J. McQuillin.

Benzyloxymethylation of ketones of the type (IV; R = H or CH_3O) is shown to be highly stereoselective in favour of production of the α-substituted derivative (V) and is applied to the synthesis of (±)-dehydrodeisopropylabietic acid and of an isomer of (±)-podocarpic acid methyl ether.

Benzyloxymethylation of ketones, as in (I) ⟶ (II), has been described [2] as an alkylation procedure for the introduction of the hydroxymethyl and derived groups in terpene synthesis. We have now examined the value and limitations of this method for the elaboration of acids of the type (III) *via* benzyloxymethylation of the related ketones (IV; R = H or CH_3O).

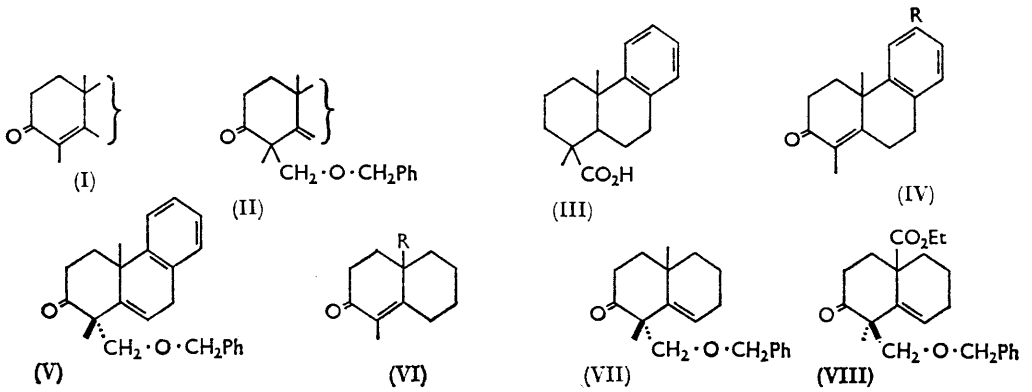
Stereoselectivity of alkylation, depending on the principle of least-hindered approach, has been found, in simpler instances, to be reversed by the presence of a polar substituent, *e.g.*, (VI; R = Me) ⟶ (VII),[2a] and (VI; R = CO_2Et) ⟶ (VIII).[2b] Selectivity is also rather sensitive to relatively minor structural changes.[3] In (IV) the aromatic residue introduces a steric constraint and in comparison with (VI) removes two axial substituents. In fact the compounds (IV; R = H or CH_3O) undergo specific α-alkylation.

[1] Part II, *J.*, **1963**, 4726.

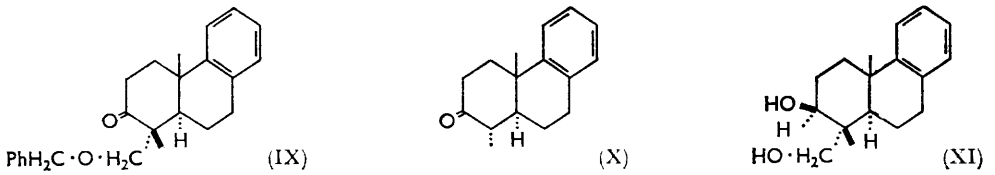
[2] (*a*) Graham and McQuillin, *J.*, **1963**, **3634**; (*b*) McQuillin and Simpson, *J.*, **1963**, **4726**; (*c*) Graham, McQuillin, and Simpson, *Proc. Chem. Soc.*, **1963**, **136**.

[3] (*a*) Johnson and Allen, *J. Amer. Chem. Soc.*, 1957, **79**, 1261; (*b*) Fried, Arth, and Sarrett, *ibid.*, 1960, **82**, **1684**; (*c*) Fried, Nutile, and Arth, *ibid.*, p. 5704.

The ketones (IV; R = H or CH_3O) were obtained by Robinson annelation of the appropriate 1-methyl-2-tetralone, as has already been described.[4] The second ketone (IV; R = CH_3O) is new. The 1-methyl-2-tetralones were conveniently obtained by peracetic-acid oxidation of the appropriate 3,4-dihydro-1-methylnaphthalene combined with acid rearrangement (*e.g.*, refs. 4*a* and 5).



Benzyloxymethylation of the ketone (IV; R = H) as the sodio-enolate in dioxan gave a product which by chromatography was shown to consist of an *O*-benzyloxymethyl ether,



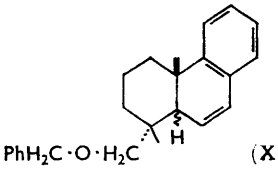
readily hydrolysed by acid, and on acid-stable *C*-benzyloxymethylation product, which behaved as a single isomer. Since the latter was transformed (see below) to give (±)-dehydrodeisopropyl abietic acid it is formulated as the α-benzyloxymethyl derivative (V). Catalytic debenzylation and hydrogenation gave a crystalline hydroxymethyl ketone, the structure of which was established as (IX), since with perchloric acid in aqueous dioxan it was converted by loss of formaldehyde into the ketone (X). The latter was obtained from (IV) as the sole product of Birch reduction, and as the major product of hydrogenation after acid isomerisation of the β-methyl isomer initially present.

On treatment with sodium borohydride followed by catalytic debenzylation, the ketone (V) gave a crystalline diol which is evidently to be formulated as (XI) (cf., ref. 2*a*).

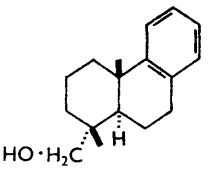
By Wolf–Kishner reduction under the usual conditions,[2] (V) gave a deoxo-derivative in good yield, but with, as expected, concomitant movement of the olefinic bond into conjugation with the aromatic ring. The product showed absorption at $\lambda_{max.}$ 264 mμ (log ε 3·97) characteristic of a styrene. Hydrogenation gave the derived alcohol which was shown by chromatography to consist of two closely similar substances. The deoxo-product is evidently a mixture of the two isomers of (XII) leading to a mixture of (XIII) and (XIV) on reduction and debenzylation. Bond-conjugation with equilibration has been noted [6] in instances structurally similar to (XII). We have not yet examined Wolf–Kishner reduction

[4] (*a*) Howell and Taylor, *J.*, 1958, 1248; (*b*) Kuehne, *J. Amer. Chem. Soc.*, 1961, **83**, 1492.
[5] Ghosh and Robinson, *J.*, 1944, 506; Raman and Rao, *Experimentia*, 1956, **12**, 472; Newhall, Harris, Holly, Johnston, Richter, Walton, Wilson, and Folkers, *J. Amer. Chem. Soc.*, 1955, **77**, 5646.
[6] Wenkert and Stevens, *J. Amer. Chem. Soc.*, 1956, **78**, 2318; Ghatak, Datta, and Ray, *ibid.*, 1960, **82**, 1728.

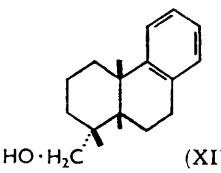
under milder conditions,[7] but the benzyloxymethyl group was found unstable[8] to the sequence of reactions involved in removal of the oxo-group via the ethylenedithioketal.[9]



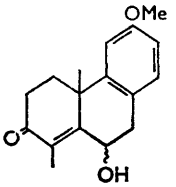
(XII)



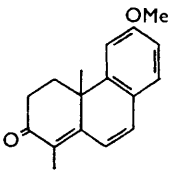
(XIII)



(XIV)



(XV)



(XVI)

The alcohols (XIII) and (XIV) were not separately characterised, but the mixture was oxidised directly to the derived carboxylic acids. Simultaneous benzylic oxidation gave a crude product showing some α-tetralone absorption, $\lambda_{max.}$ 252 mμ (log ε 3·52), which, however, could readily be removed by hydrogenation. The mixture of acids obtained m. p. 122—124°, was resolved by crystallisation to give (±)-dehydrodeisopropyl abietic acid,[10] m. p. 173°, identical with an authentic specimen. The accompanying acid, presumably the known[11] *cis*-isomer of dehydrodeisopropyl abietic acid, m. p. 146°, could not be separated by chromatography. We obtained no evidence, however, for the presence of higher-melting[12] desoxypodocarpic acids. This result, along with the apparent homogeneity of the primary benzyloxymethylation product (V; R = H), indicates that alkylation of (IV; R = H) is highly stereoselective and in the α-sense.

A parallel sequence starting from benzyloxymethylation of (IV; R = CH_3O) led to a Wolf–Kishner reduction-product consisting of a pair of isomers and thence by hydrogenation to an alcohol which melted fairly sharply at 87—89°. This material gave with (+)-podocarpinol methyl ether (m. p. 91°) a melting-point depression and by chromatography could be resolved into isomers (R_F 0·44 and 0·39) both different from (+)-podocarpinol methyl ether (R_F 0·37). Oxidation gave as principal product an acid, m. p. 132—134°, isomeric with (+)-podocarpic acid methyl ether,[13] m. p. 158°, with which it was compared by chromatography.

These examples indicate a stereo-preference in benzyloxymethylation, as in (I) ⟶ (II), for substitution from the less hindered, α-side of the molecule, which is consistent with the closely parallel case described by Stork and Schulenberg,[14] and with the orientation of the benzyloxymethyl group assigned, on other grounds, to the products described in Part I.

The methoxylated series of substances related to (IV; R = CH_3O) gave some trouble in purification. This we ascribe in part to auto-oxidation. The parent substance, 7-methoxy-1-methyl-2-tetralone, rapidly absorbed oxygen in air to give a crystalline peroxide. In converting (IV; R = CH_3O) to its sodio-enolate derivative with sodium hydride some oxidation occurred to give a product showing hydroxyl absorption (ν 3433 $cm.^{-1}$). Since conversion to the 2,4-dinitrophenylhydrazone caused dehydration, this oxidation product

[7] Cf. Cram, Sahyn, and Knox, *J. Amer. Chem. Soc.*, 1962, **84**, 1734.
[8] Cf. Fieser, *J. Amer. Chem. Soc.*, 1954, **76**, 1945.
[9] Cf. Petit and Van Tamelen, *Org. Reactions*, 1962, **12**, 356.
[10] Wenkert and Chamberlin, *J. Amer. Chem. Soc.*, 1959, **81**, 688.
[11] Saha, Ganguly, and Dutta, *J. Amer. Chem. Soc.*, 1959, **81**, 3670.
[12] Haworth and Barker, *J.*, 1939, 1299; Parham, Wheeler, and Dodson, *J. Amer. Chem. Soc.*, 1955, **77**, 1166; Ghatak, Datta, and Ray, *ibid.*, 1960, **82**, 1728; Wenkert and Tahara, *ibid.*, p. 3229.
[13] Campbell and Todd, *J. Amer. Chem. Soc.*, 1942, **64**, 928.
[14] Stork and Schulenberg, *J. Amer. Chem. Soc.*, 1962, **84**, 284.

is formulated as (XV), the derivative corresponding to (XVI). Precedent examples have been described.[15]

Experimental

Unless otherwise specified, chromatography refers to use of Kieselgel G (Merck) as a thin layer. The R_F values have only relative significance. Detection was usually by use of phosphomolybdic acid spray.

1-*Methyl*-2-*tetralone*.—Peracetic acid (0·266 mole) in chloroform (313 c.c.) at 0° was added slowly to 1,2-dihydro-4-methylnaphthalene [16] (38·3 g., 0·266 mole) in chloroform (200 c.c.) cooled in ice–salt. The mixture was kept overnight at the ordinary temperature when 1 mole of peracetic acid had been consumed. The solution was washed with sodium hydroxide solution (10%), and water, and dried and evaporated, after making sure diacetyl peroxide was absent. The residue (44 g.) with 6N-sulphuric acid (300 c.c.) in ethanol (300 c.c.) was warmed on the steam-bath (2 hr.) to give 1-methyl-2-tetralone (29·2 g.), b. p. 110°/4 mm., n_D^{20} 1·5518, ν 1715 (>C:O), 769 and 752 cm.$^{-1}$ (ArH); semicarbazone, m. p. 201° d. Howell and Taylor [4a] give b. p. 128°/14 mm., n_D^{20} 1·5568; semicarbazone, m. p. 202° d.

2,3,4,9,10,12-*Hexahydro*-1,12-*dimethyl*-2-*oxophenanthrene*.—To the methiodide from 1-diethylaminopentan-3-one (23 g.) and methyl iodide (21 g.) 1-methyl-2-tetralone (23·6 g.) in dry benzene (150 c.c.) was added, and at 0° a solution of sodium (5·65 g.) in dry ethanol (150 c.c.) run in during 10 min. After stirring (1½ hr.) and warming (¾ hr.), extraction gave 2,3,4,9,10,12-hexahydro-1,12-dimethyl-2-oxophenanthrene (23 g.), m. p. 86—87°, $\lambda_{max.}$ 248 mμ (log 4·21), ν 1663 (>C:C—C:O), 769 and 751 cm.$^{-1}$ (ArH).

The 2,4-dinitrophenylhydrazone formed lustrous red flakes, m. p. 239°, from ethanol–ethyl acetate. Ghatak, Datta, and Ray [12] give m. p. 88°, $\lambda_{max.}$ 248 mμ (log ε 4·2) and 2,4-dinitrophenylhydrazone, m. p. 238°.

Thin-layer chromatography in benzene–ethyl acetate (9 : 1) showed only one spot (R_F 0·57); gas chromatography showed only traces of impurity.

1,2,3,4,9,10,11α,12-*Octahydro*-1α,12β-*dimethyl*-2-*oxophenanthrene*.—(*a*) *Lithium in liquid ammonia reduction*. 2,3,4,9,10,12-Hexahydro-1,12-dimethyl-2-oxophenanthrene (0·5 g.) in dry ether (10 c.c.) was added to a stirred solution of lithium (0·165 g.) in liquid ammonia (100 c.c.) and after 0·25 hr. ammonium chloride was added and the ammonia allowed to evaporate. The product distilled as an oil, b. p. 115°/0·01 mm., n_D^{20} 1·5655 which crystallised to give 1,2,3,4,9,10,11α,12-octahydro-1α,12β-dimethyl-2-oxophenanthrene as prisms, m. p. 90—91°, from pentane, ν 1703 (>C:O) and 770 cm.$^{-1}$ (ArH) (Found: C, 84·35; H, 8·65. $C_{16}H_{19}O$ requires C, 84·6; H, 8·35%); 2,4-*dinitrophenylhydrazone*, orange-yellow prisms, m. p. 197—198°, from ethanol–ethyl acetate (Found: C, 64·45; H, 6·05. $C_{22}H_{24}N_4O_4$ requires C, 64·7; H, 5·9%).

(*b*) *Catalytic hydrogenation*.—2,3,4,9,10,12-Hexahydro-1,12-dimethyl-2-oxophenanthrene (0·27 g.) in ethanol (25 c.c.) with palladised charcoal (0·1 g.) absorbed one molar equivalent of hydrogen in 70 min. The product formed an oil, b. p. 120°/0·01 mm., n_D^{20} 1·5649, which gave a crude solid, m. p. 71—75°, recrystallisation of which from methanol gave 1,2,3,4,9,10,11α,12-octahydro-1α,12β-dimethyl-2-oxophenanthrene, m. p. 88—89°, identical with the material prepared above. A residue oil (0·14 g.) after treatment under reflux (2 hr.) with sulphuric acid (10%; 0·1 c.c.) in ethanol (5 c.c.), cf. Sondheimer and Mazur,[17] could be seeded to give further 1,2,3,4,9,10,11α,12-octahydro-1α,12β-dimethyl-2-oxophenanthrene, m. p. 88—89°.

1α-*Benzyloxymethyl*-1,2,3,4,9,12-*hexahydro*-1,12-*dimethyl*-2-*oxophenanthrene*.—2,3,4,9,10,12-Hexahydro-1,12-dimethyl-2-oxophenanthrene (10 g., 0·044 mole) in dry dioxan (50 c.c.) was added to sodium hydride (1·25 g.) in dry dioxan (50 c.c.), and the mixture stirred and heated (3 hr.) on the steam-bath in pure nitrogen prepared by passing commercial oxygen-free nitrogen successively through Fieser's solution, saturated lead acetate solution, and concentrated sulphuric acid. Freshly distilled benzyl chloromethyl ether (6·9 g., 0·044 mole) in dry dioxan (70 c.c.) was then added rapidly with stirring at 10°, and stirring continued at the ordinary temperature for 2 hr. Distillation of the product gave a fraction (1·5 g.), b. p. 150—185°/0·05 mm., n_D^{20} 1·5850 from which 2,3,4,9,10,12-hexahydro-1,12-dimethyl-2-oxophenanthrene (0·8 g.) could be recovered, followed by material (11·2 g.), b. p. 190—200°/0·1 mm., n_D^{20} 1·5880, $\lambda_{max.}$ 227 mμ (shoulder, log ε 3·97) and 250—255 mμ (log ε 3·6). Chromatography in benzene–ethyl acetate

[15] Cardwell and McQuillin, *J.*, 1955, 525; Howe and McQuillin, *J.*, 1958, 1513.
[16] English and Cavaglieri, *J. Amer. Chem. Soc.*, 1943, **65**, 1085.
[17] Sondheimer and Mazur, *J. Amer. Chem. Soc.*, 1958, **80**, 5220.

(9 : 1) showed mainly *C*-alkylated material (R_F 0·52) together with *O*-alkylated material (R_F 0·65) characterised by giving yellow and red spots, respectively, with 2,4-dinitrophenylhydrazine in alcoholic hydrochloric acid. The crude alkylation product (7·0 g.), kept 24 hr. with 0·1N-sulphuric acid in aqueous dioxan (90%, 70 c.c.) under nitrogen, gave 1α-*benzyloxymethyl*-1,2,3,4,9,12-*hexahydro*-1β,12β-*dimethyl*-2-*oxophenanthrene* (5·5 g., 78%), b. p. 190—200°/0·1 mm., n_D^{20} 1·5850, $\lambda_{max.}$ 260—270 mμ (log ε 2·74), ν 1715 (>C:O), 1096 (ether), 757, 735, and 969 cm.$^{-1}$ (ArH) (Found: C, 82·9; H, 7·55. $C_{24}H_{26}O_2$ requires C, 83·2; H, 7·5%) which ran as one spot on thin-layer chromatography. *The semicarbazone* formed prisms, m. p. 168—169°, from methanol (Found: C, 74·7; H, 7·6. $C_{25}H_{29}O_3N_3$ requires C, 74·45; H, 7·2%).

1,2,3,4,9,10,11α,12-*Octahydro*-1α-*hydroxymethyl*-1β,12β-*dimethyl*-2-*oxophenanthrene*.—1α-Benzyloxymethyl-1,2,3,4,9,12-hexahydro-1β,12β-dimethyl-2-oxophenanthrene (0·34 g.) in ethyl acetate (30 c.c.) with palladised charcoal (0·16 g.) absorbed two molar equivalents of hydrogen in 36 hr. to give a largely crystalline product, m. p. 139—141° which by recrystallisation from light petroleum–ethanol gave 1,2,3,4,9,10,11α,12-*octahydro*-1α-*hydroxymethyl*-1β,12β-*dimethyl*-2-*oxophenanthrene* as long prisms, m. p. 146—147°, ν 3413 (OH), 1680 (>C:O), and 769 cm.$^{-1}$ (ArH) (Found: C, 78·75; H, 8·6. $C_{17}H_{22}O_2$ requires C, 79·0; H, 8·5%).

Elimination of Formaldehyde from 1,2,3,4,9,10,11α,12-*Octahydro*-1α-*hydroxymethyl*-1,12-*dimethyl*-2-*oxophenanthrene*.—The hydroxymethyl ketone (20 mg.) was warmed (44 hr.) on the steam-bath in aqueous dioxan (60%, 7 c.c.) with 0·1N-perchloric acid, the reaction being followed by chromatography in benzene–ethyl acetate (9 : 1) of samples withdrawn at regular intervals. The solution, neutralised with aqueous sodium carbonate (10%), evaporated to small bulk and diluted with water gave an oil (17 mg.), which mainly crystallised to give 1,2,3,4,9,10,11α,12-octahydro-1α,12β-dimethyl-2-oxophenylanthrene, m. p. 88—89°, identified by mixed m. p., infrared spectrum, and thin-layer chromatography.

1α-*Benzyloxymethyl*-1,2,3,4,9,12-*hexahydro*-2β-*hydroxy*-1β,12β-*dimethylphenanthrene*.—1α-Benzyloxymethyl-1,2,3,4,9,12-hexahydro-1,12-dimethyl-2-oxophenanthrene (0·5 g.) in ethanol (5 c.c.) with sodium borohydride (0·25 g.) gave 1α-*benzyloxymethyl*-1,2,3,4,9,12-*hexahydro*-2β-*hydroxy*-1β,12β-*dimethylphenanthrene* (0·35 g.), b. p. 190°/0·01 mm., n_D^{20} 1·5875, ν 3472 (HO), 1075 (ether), 787, 757, and 696 cm.$^{-1}$ (ArH) (Found: C, 83·1; H, 8·05. $C_{24}H_{28}O_2$ requires C, 82·7; H, 8·05%).

1,2,3,4,9,10,11α,12-*Octahydro*-2β-*hydroxy*-1α-*hydroxymethyl*-1β,12β-*dimethylphenanthrene*.—The benzyl ether (0·21 g.) in ethanol (25 c.c.) with palladised charcoal (0·21 g.) absorbed two molar equivalents of hydrogen in 30 hr. The product on contact with ether solidified (m. p. 150—152°) and gave 1,2,3,4,9,10,11α,12-*octahydro*-2β-*hydroxy*-1α-*hydroxymethyl*-1β,12β-*dimethylphenanthrene*, m. p. 161°, as prisms from light petroleum–benzene, $\lambda_{max.}$ 265 mμ (log ε 2·8) and 272 mμ (log ε 2·82), ν 3300 (HO), 760 and 720 cm.$^{-1}$ (ArH) (Found: C, 78·0; H, 9·4. $C_{17}H_{24}O_2$ requires C, 78·4; H, 9·25%).

1α-*Benzyloxymethyl*-1,2,3,4,11,12-*hexahydro*-1β,12β-*dimethylphenanthrene*.—1α-Benzyloxymethyl-1,2,3,4,9,12-hexahydro-1β,12β-dimethyl-2-oxophenanthrene (2·5 g.) dispersed in hot diethylene glycol (20 c.c.) was added to a solution of sodium (0·78 g.) in freshly distilled diethylene glycol (20 c.c.) containing freshly prepared anhydrous hydrazine (3·2 c.c.) under oxygen-free nitrogen.[18] The mixture was heated at 180° (3 hr.) and hydrazine distilled at 210° (2 hr.). Careful distillation of the reaction product gave 1α-*benzyloxymethyl*-1,2,3,4,11,12-*hexahydro*-1β,12β-*dimethylphenanthrene* (1·5 g.), b. p. 160—170°/0·075 mm., n_D^{20} 1·5800, $\lambda_{max.}$ 219 mμ (log ε 4·39) and 265 mμ (log ε 3·97), ν 1094 (ether), 750, 732, and 694 cm.$^{-1}$ (ArH) (Found: C, 86·15; H, 8·3. $C_{24}H_{28}O_2$ requires C, 86·65; H, 8·45), followed by a slightly higher boiling fraction, b. p. 170—175°/0·15 mm., from which a further quantity of the product was isolated by chromatography on silica gel (15 g.) with light petroleum.

1,2,3,4,9,10,11,12-*Octahydro*-1α-*hydroxymethyl*-1β,12β-*dimethylphenanthrenes*.—1α-Benzyloxymethyl-1,2,3,4,11,12-hexahydro-1β,12β-dimethylphenanthrene (1 g.) in alcohol (30 c.c.) with palladised charcoal (0·52 g.) absorbed 1·9 molar equivalents of hydrogen during 5 days. The product, which did not crystallise, was 1,2,3,4,9,10,11,12-octahydro-1α-hydroxymethyl-1β,12β-dimethylphenanthrenes (0·7 g.), b. p. 130—135°/0·05 mm., n_D^{20} 1·5685, $\lambda_{max.}$ 267 mμ (log ε 2·86) and 274 mμ (log ε 2·88), ν 3340 (HO), 759 and 721 cm.$^{-1}$ (ArH) (Found: C, 83·6; H, 9·8. $C_{17}H_{24}O$ requires C, 83·6; H, 9·85%). Chromatography in benzene–ethyl acetate (9 : 1) revealed two isomers (R_F 0·33 and 0·25).

(±)-*Dehydrodeisopropylabietic Acid*.—Chromic anhydride (0·58 g., 0·0057 mole) in aqueous

[18] Barton, Ives, and Thomas, *J.*, 1955, 2056.

acetic acid (80%, 5 c.c.) was added to the mixed 1,12-dimethyl-1α-hydroxymethyl-octahydrophenanthrenes (0·52 g., 0·002 mole) and kept overnight under nitrogen. The green solution was diluted with a saturated aqueous solution of ammonium sulphate and repeatedly extracted with chloroform. Separation gave a neutral product (0·2 g.), found by chromatography to contain some starting material, two ketonic substances, and an acid (0·25 g.). The last, $\lambda_{max.}$ 250—254 mμ (log ε 3·52) in glacial acetic acid (25 c.c.) with palladised charcoal (0·25 g.) absorbed 14·5 c.c. of hydrogen during 24 hr. when absorption ceased. The reduction product on silica (4·5 g.) by benzene elution gave a mixture of 1,2,3,4,9,10,11,12-octahydro-1β,12β-dimethylphenanthrene-1α-carboxylic acids (80 mg.), m. p. 118—122°, $\lambda_{max.}$ 265 mμ (log ε 2·73) and 272 mμ (log ε 2·74) as a series of fractions. Thin-layer chromatography on silica gel or on alumina in numerous solvent mixtures failed to resolve this mixture, but repeated recrystallisations from light petroleum–ethyl acetate gave an acid, m. p. 172—173°, alone or on admixture with an authentic sample of (±)-dehydrodeisopropylabietic acid kindly supplied by Professor P. C. Dutta.

1,2,3,4-*Tetrahydro*-7-*methoxy*-1-*methylnaphthalene*.—1,2-Dihydro-6-methoxy-4-methylnaphthalene [4a] (0·31 g.) in ethanol (25 c.c.) with palladised charcoal (0·097 g.) absorbed one molar equivalent of hydrogen during 2 hr. to give 1,2,3,4-*tetrahydro*-7-*methoxy*-1-*methylnaphthalene*, b. p. 110—115°/7 mm., n_D^{20} 1·5405, $\lambda_{max.}$ 225 mμ (log ε 4·04), 280 mμ (log ε 3·38), and 287 mμ (log ε 3·34) (Found: C, 81·7; H, 8·7. $C_{12}H_{16}O$ requires C, 81·75; H, 9·1%).

7-*Methoxy*-1-*methyl*-2-*tetralone*.—Treated with peracetic acid (0·207 mole) in chloroform (250 c.c.), 1,2-dihydro-6-methoxy-4-methylnaphthalene (36 g., 0·207 mole) in chloroform (200 c.c.) (cooled in ice–salt), consumed the theoretical quantity of peracid overnight. Washed free of peroxides, the chloroform solution gave a residue (47·2 g.) which in ethanol (300 c.c.) and water (250 c.c.) was then refluxed (2 hr.) with sulphuric acid (50 c.c.). 7-Methoxy-1-methyl-2-tetralone (26·5 g., 68%) was obtained, b. p. 115—120°/0·3 mm., n_D^{20} 1·5520, $\lambda_{max.}$ 221 mμ (shoulder, log ε 3·97), 281 mμ (log ε 3·38), and 287 mμ (shoulder, log ε 3·34), ν 1718 (>C:O), 871 and 813 cm.$^{-1}$ (ArH).

1-*Acetoxy*-1,2,3,4-*tetrahydro*-7-*methoxy*-1-*methylnaphth*-2-*ol*.—Oxidation of 1,2-dihydro-6-methoxy-4-methylnaphthalene (55 g.) on one occasion gave a partially crystallised product from which material (19 g.) was obtained which is regarded as 1-*acetoxy*-1,2,3,4-*tetrahydro*-7-*methoxy*-1-*methylnaphth*-2-*ol*, m. p. 123°, from light petroleum–benzene, ν 3458 (HO), 1712 and 1236 (acetate), 872 and 810 cm.$^{-1}$ (ArH) (Found: C, 67·0; H, 7·05. $C_{14}H_{18}O_4$ requires C, 67·2; H, 7·2%). This glycol monoacetate (16 g.) refluxed (2 hr.) in ethanol (150 c.c.) with water (125 c.c.) and conc. sulphuric acid (25 c.c.) gave 7-methoxy-1-methyl-2-tetralone (11·3 g., 93%), b. p. 119—120°/0·5 mm., n_D^{20} 1·5505, identical with previously prepared samples.

1,2,3,4-*Tetrahydro*-1,2-*dihydroxy*-7-*methoxy*-1-*methylnaphthalene*.—1-Acetoxy-1,2,3,4-tetrahydro-7-methoxy-1-methylnaphth-2-ol (1 g.), kept with potassium hydroxide (0·33 g.) in 90% aqueous methanol (20 c.c.), gave 1,2,3,4-*tetrahydro*-1,2-*dihydroxy*-7-*methoxy*-1-*methylnaphthalene*, m. p. 87—88° (from light petroleum), ν 3279 cm.$^{-1}$ (HO) (Found: C, 69·1; H, 7·55. $C_{12}H_{16}O_3$ requires C, 69·2; H, 7·7%).

7-*Methoxy*-1-*methyl*-2-*tetralone* 1-*hydroperoxide*.—7-Methoxy-2-tetralone kept in air was converted in a few days into a mass of crystals, which from benzene–light petroleum gave 7-*methoxy*-1-*methyl*-2-*tetralone* 1-*hydroperoxide*, m. p. 119—120°, ν 3372 (HO), 1718 (>C:O), 877 and 822 cm.$^{-1}$ (ArH) (Found: C, 64·7; H, 6·4. $C_{12}H_{14}O_4$ requires C, 64·8; H, 6·3%), which liberated iodine from potassium iodide in aqueous acetic acid.

2,3,4,9,10,12-*Hexahydro*-6-*methoxy*-1,12-*dimethyl*-2-*oxophenanthrene*.—The methiodide of diethylaminopentan-3-one (18·4 g., 0·117 mole) and methyl iodide (16·6 g., 0·117 mole) was treated with freshly distilled 7-methoxy-1-methyl-2-tetralone (22·6 g., 0·117 mole) in dry benzene (120 c.c.) and the mixture cooled to 0°. An ice-cold solution of sodium (4·48 g., 0·195 g.-atom) in dry ethanol was then added in 10 min., under oxygen-free nitrogen, and the mixture stirred for 1¼ hr. After warming on the steam-bath (0·75 hr.) the solution was cooled and neutralised (hydrochloric acid, 10%), and the product isolated. Distillation gave an oil, b. p. 160—165°/0·1 mm., n_D^{20} 1·5875 (25·6 g.), which gave crystalline material, m. p. 59—60° (18·7 g., 65%), from which 2,3,4,9,10,12-hexahydro-6-methoxy-1,12-dimethyl-2-oxophenanthrene was obtained, m. p. 61—62°, from light petroleum containing a little acetone; $\lambda_{max.}$ 229 mμ (log ε 4·12) and 247 mμ (log ε 4·23), ν 1653 (>C:C·C:O), 864 and 807 cm.$^{-1}$ (ArH) (Found: C, 79·85; H, 7·9. $C_{17}H_{20}O_2$ requires C, 79·7; H, 7·8%). Thin-layer chromatography, with benzene–ethyl acetate (93 : 7) showed only one spot (R_F 0·35), gas chromatography indicated only traces of impurity.

The *semicarbazone* formed prisms, m. p. 184—185°, from ethanol (Found: C, 69·15; H, 7·75. $C_{18}H_{23}O_3N_3$ requires C, 69·05; H, 7·35%). The *2,4-dinitrophenylhydrazone* separated as red flakes, m. p. 215°, from ethanol–ethyl acetate, $\lambda_{max.}$ ($CHCl_3$) 262 mμ (log ε 4·25), 287 mμ (shoulder, log ε 4·11), and 391 (log ε 4·47) (Found: C, 63·25; H, 5·6. $C_{23}H_{24}O_5N_4$ requires C, 63·3; H, 5·5%).

2,3,4,12-Tetrahydro-1,12-dimethyl-6-methoxy-2-oxophenanthrene.—The above ketone when stirred and heated (3 hr.) on the steam-bath with sodium hydride (33 mg.) in dry dioxan (4 c.c.) in dry but not entirely oxygen-free nitrogen, gave a product which showed $\lambda_{max.}$ 248 (log ε 4·11), ν 3433 cm.$^{-1}$ (HO) and 1653 cm.$^{-1}$ (>C:C·C:O) and failed to seed with 2,3,4,9,10,12-hexahydro-6-methoxy-1,12-dimethyl-2-oxophenanthrene. This product with 2,4-dinitrophenylhydrazine formed a derivative which precipitated first as a red solid which changed rapidly to purple. Recrystallisation from ethyl acetate–ethyl alcohol gave a 2,4-dinitrophenyl hydrazone, m. p. 233—235°, forming deep purple plates $\lambda_{max.}$ ($CHCl_3$) 262 mμ (log ε 4·28) and 293 mμ (log ε 3·38) (Found: C, 63·9; H, 5·25. $C_{23}H_{23}O_5N_4$ requires C, 63·6; H, 5·05%).

1α-Benzyloxymethyl-1,2,3,4,9,12-hexahydro-6-methoxy-1,12-dimethyl-2-oxophenanthrene.—6-Methoxy-2,3,4,9,10,12-hexahydro-1,12-dimethyl-2-oxophenanthrene (3·57 g., 0·14 mole) in dry dioxan (20 c.c.) was added to sodium hydride (0·39 g.) under dry dioxan (20 c.c.) and the mixture stirred and heated (3 hr.) on the steam-bath under oxygen-free nitrogen (prepared as previously described). After cooling to 5—10°, freshly distilled benzylchloromethyl ether (2·18 g., 0·14 mole) in dry dioxan (20 c.c.) was added rapidly, and the mixture stirred for 1 hr. and kept overnight. The product, by chromatography in benzene, was shown to contain *C*-alkylated (R_F 0·1), along with *O*-alkylated material (R_F 0·35) and starting ketone (R_F 0·07), which appeared as a yellow and two red spots with 2,4-dinitrophenyl hydrazine reagent. The product (5 g.), reisolated after warming (20 min.) on the steam-bath with 0·5N-sulphuric acid in aqueous dioxan, gave on distillation a first fraction (0·55 g.), b. p. 160—170°/0·2 mm., n_D^{20} 1·5890, followed by 1α-benzyloxymethyl-1,2,3,4,9,12-hexahydro-6-methoxy-1,12-dimethyl-2-oxophenanthrene (2·4 g.), b. p. 190—200°/0·025 mm., n_D^{20} 1·5832, $\lambda_{max.}$ 232 mμ (log ε 4·23) and 280 mμ (log ε 3·49), ν 1712 (>C:O), 1098 (ether), 737 and 697 cm.$^{-1}$ (benzyl). An analytically pure sample was obtained by chromatography on a series of thick (0·5 mm.) alumina chromatoplates developed in benzene. The spots, located by viewing under ultraviolet light were removed with ether to give *1α-benzyloxymethyl-1,2,3,4,9,12-hexahydro-6-methoxy-1β,12β-dimethyl-2-oxophenanthrene*, b. p. 190—200°/0·025 mm. (Found: C, 80·0; H, 7·15. $C_{15}H_{28}O_3$ requires C, 79·75; H, 7·45%).

1α-Benzyloxymethyl-1,2,3,4,9,12-hexahydro-2β-hydroxy-6-methoxy-1β,12β-dimethylphenanthrene.—1α-Benzyloxymethyl-1,2,3,4,9,12-hexahydro-6-methoxy-1,12-dimethylphenanthrene (2·0 g.) kept overnight under nitrogen in ethanol (20 c.c.) with sodium borohydride (0·75 g.) gave 1α-benzyloxymethyl-1,2,3,4,9,12-hexahydro-2β-hydroxy-6-methoxy-1β,12β-dimethylphenanthrene, as a viscous oil was characterised as the *3,5-dinitrobenzoate*, m. p. 182—184°, from methanol which, however, required chromatography on silica for purification (Found: C, 67·34; H, 5·55. $C_{32}H_{32}O_8N_2$ requires C, 67·1; H, 5·6%).

1α-Benzyloxymethyl-1,2,3,4,11,12-hexahydro-6-methoxy-1β,12β-dimethylphenanthrene.—1α-Benzyloxymethyl-1,2,3,4,9,12-hexahydro-6-methoxy-1,12-dimethyl-2-oxophenanthrene (5·8 g.) dispersed in hot diethylene glycol (20 c.c.) was added, under oxygen-free nitrogen, to a solution of sodium (1·41 g.) in diethylene glycol (60 c.c.) containing freshly prepared anhydrous hydrazine (5·85 c.c.). The mixture was heated to 180° for a time and after distilling out water and hydrazine for 2 hr. at 210° the solution was cooled and the product recovered as an oil (2·9 g.), b. p. 195—220°/0·1 mm., n_D^{20} 1·5990. Chromatographed on silica gel (60 g.), fractions eluted with light petroleum–benzene (13 : 7) gave *1α-benzyloxymethyl-1,2,3,4,11,12-hexahydro-6-methoxy-1β,12β-dimethylphenanthrene*, b. p. 175—180°/0·01 mm., n_D^{20} 1·5818, $\lambda_{max.}$ 274 mμ (log ε 4·1), ν 1098 (ether), 735 and 697 cm.$^{-1}$ (benzyl) (Found: C, 82·95; H, 8·4. $C_{25}H_{30}O_2$ requires C, 82·9; H, 8·3%). Thin-layer chromatography of this substance in benzene partially resolved two spots.

1,2,3,4,9,10,11,12-Octahydro-1α-hydroxymethyl-6-methoxy-1β,12β-dimethylphenanthrenes.—1α-Benzyloxymethyl-1,2,3,4,11,12-hexahydro-1,12-dimethylphenanthrenes (0·53 g.) in ethanol–ethyl acetate (1 : 1) (30 c.c.) with palladised charcoal (0·47 g.) absorbed 1·9 molar equiv. of hydrogen during 5 hr.; the first mole rapidly. The product by filtration, evaporation, and distillation gave an oil (0·32 g.), b. p. 142—147°/0·01 mm., n_D^{20} 1·5680, $\lambda_{max.}$ 232—233 mμ (log ε

4·17), 280 mμ (log ε 3·45), and 286—287 mμ (shoulder, log ε 3·43) (Found: C, 79·1; H, 9·1. $C_{18}H_{22}O_2$ requires C, 78·8; H, 9·5%). Hexane-extraction gave an oil which partially crystallised (130 mg.), m. p. 83—86°, and could be recrystallised to give a mixture of isomeric 1,2,3,4,9,10,11,12-*octahydro*-1α-*hydroxymethyl*-6-*methoxy*-1β,12β-*dimethylphenanthrenes* as prisms, m. p. 87—89°, from pentane, $\lambda_{max.}$ 215—229 mμ (shoulder, log ε 3·85), 280 mμ (log ε 3·40), and 286 mμ (log ε 3·36) (Found: C, 78·65; H, 9·75. $C_{18}H_{26}O_2$ requires C, 78·8; H, 9·5%). The infrared spectrum was very similar to that of podocarpinol methyl ether but different in detail. Mixed with podocarpinol methyl ether (m. p. 90—91°), its melting point was depressed. Thin-layer chromatography of the prisms, m. p. 87—89°, in benzene–ethyl acetate (8 : 2) revealed two components (R_F 0·44 and 0·39) in similar amount; on the same plate podocarpinol methyl ether showed R_F 0·37. The substance (m. p. 87—89°; 45 mg.) on silica (35 g.) eluted with benzene–ether (9 : 1) as described by Duncan [19] gave small amounts of two pure components before and after the bulk of the material which was eluted unresolved. The first eluted fractions recrystallised from pentane as a powdery solid (3 mg.), m. p. 61—63°, but the last eluted fractions, corresponding to the second component, failed to crystallise. Careful comparison of the infrared absorption in CCl_4 of both components with that of podocarpinol methyl ether showed broad similarities but differences in detail.

1,2,3,4,9,10,11,12-*Octahydro*-6-*methoxy*-1β,12β-*dimethylphenanthrene*-1α-*carboxylic Acid*.—The product (0·24 g.) from hydrogenation of 1α-benzyloxymethyl-1,2,3,4,11,12-hexahydro-1,12-dimethylphenanthrene was kept overnight with chromium trioxide (0·24 g.) in acetic acid (4 c.c.). The acidic product, $\lambda_{max.}$ 277 mμ (log ε 3·89), in glacial acetic acid (20 c.c.) with palladised charcoal (0·1 g.) absorbed 12·4 c.c. of hydrogen during 36 hr. The hydrogenation product on silica by elution with benzene–ether (3 : 1) gave crystalline fractions, m. p. 132—134°, from light petroleum (Found: C, 75·3; H, 8·9. $C_{18}H_{24}O_3$ requires C, 75·1; H, 8·4%). Thin-layer chromatography with benzene–ethyl alcohol (4 : 1) as solvent showed the above acid to be mainly one substance and different from podocarpic acid methyl ether.

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[19] Duncan, *J. Chromatog.*, 1962, **8**, 37.