400. *Synthetic Studies in the Diterpene Series. Part VI.*[1] *Synthesis of Some Hydrophenalene Derivatives.*

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Two hydrophenalenes (III; R = R″ = H, R′ = OMe; and R = H, R′ = Me, R″ = OMe) have been synthesised and shown to be identical with the cyclisation products of two unsaturated alcohols (I; R = R″ = H, R′ = OMe; and R = H, R′ = Me, R″ = OMe). Some related reactions are described.

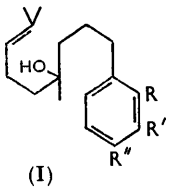
In Part IV of this series [2] it was shown that the ω-arylalkanols (I; R = H or Pr^i, R′ = OMe, R″ = H), on cyclodehydration, do not afford the usual [3] podocarpa-8,11,13-trienes (II) but, instead, the hydrophenalenes (III; R = H or Pr^i, R′ = OMe, R″ = H). The structures of the products were revealed by nuclear magnetic resonance (n.m.r.) and other spectral data, and by oxidation to 4-hydroxycyclohexadienones (IV). Two hydrophenalenes (III; R = R″ = H, R′ = OMe; and R = H, R′ = Me, R″ = OMe) have now been synthesised, confirming the above structures. The synthesis of the latter also validates an earlier suggestion,[2,4] that the major cyclised product of the unsaturated alcohol (I; R = H, R′ = Me, R″ = OMe) is a hydrophenalene derivative.

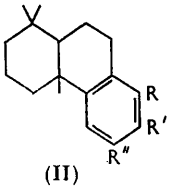
Methyl (or ethyl) 5-hydroxy-8-*m*-methoxyphenyl-5-methyloctanoate (V; R = Me or Et, R′ = OMe, R″ = H), prepared either by the action of methylmagnesium iodide on methyl 8-*m*-methoxyphenyl-5-oxo-octanoate [5] or more conveniently by the condensation of γ-*m*-methoxyphenylpropylmangesium chloride with ethyl 5-oxohexanoate, was cyclodehydrated by means of sulphuric acid to the tetralin (VI; R′ = OMe, R″ = H). This, with an excess of methylmagnesium iodide, afforded the tertiary alcohol (VII; R′ = OMe, R″ = H) which was further cyclodehydrated with polyphosphoric acid to give the hexahydrophenalene (III; R = R″ = H, R′ = OMe) shown, by conversion into the hydroxycyclohexadienone (IV; R = H) and by ultraviolet spectroscopy, to be identical with the product obtained by cyclodehydration of the alcohol (I; R = R″ = H, R′ = OMe).

Methyl 8-(4-methoxy-3-methylphenyl)-5-oxo-octanoate [4] similarly afforded the hexahydrophenalene (III; R = H, R′ = Me, R″ = OMe). The tetralinbutyric acid (VI; R = H, R′ = Me, R″ = OMe) was a solid, and its structure was confirmed by n.m.r. spectroscopy. The above hydrophenalene (III; R = H, R′ = Me, R″ = OMe) was

[1] Part V, Pyne, *J. Indian Chem. Soc.*, 1963, **40**, 905.
[2] Nasipuri and Pyne, *J.*, 1963, 4720.
[3] Nasipuri, *Chem. and Ind.*, 1957, 425; Nasipuri and Guha, *J.*, 1962, 4248.
[4] Nasipuri and Roy, *J. Indian Chem. Soc.*, 1963, **40**, 327.
[5] Nasipuri and Chaudhuri, *J.*, 1958, 2579; Robinson and Thompson, *J.*, 1939, 1739.

oxidised by chromic acid to the aromatic ketone (VIII), which was identical with isonimbiol methyl ether. The latter was obtained [4] along with traces of (±)-nimbiol methyl


(I)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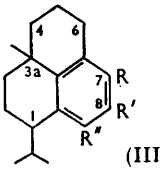
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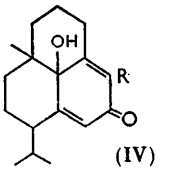
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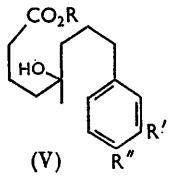
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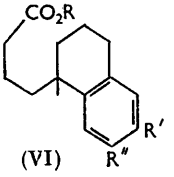
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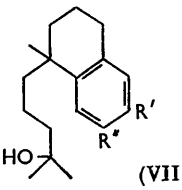
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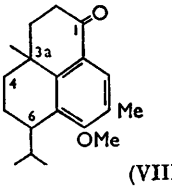
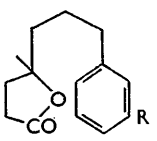
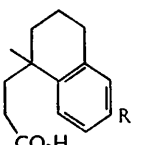

(VIII)

ether,[6] when the unsaturated alcohol (I; R = H, R′ = Me, R″ = OMe) was cyclodehydrated and the product oxidised. Structure (VIII), which was assigned to it provisionally, is thus confirmed.

In view of the possibility of the ring-closure of the tertiary alcohol (VII) in the above synthesis, leading to a seven-membered ring, an alternative and more unambiguous synthetic approach was made as follows. The lactones (IX; R = H or OMe) were prepared by condensation of the appropriate γ-phenylpropylmagnesium chlorides with ethyl


(IX)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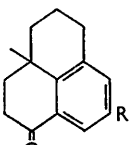
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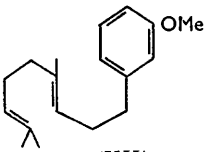
(XII)

lævulinate, and were cyclised, either directly or through the intermediate tetralins (X), to the hydrophenalenones (XI). However, attempts to introduce an isopropyl group by the action of isopropylmagnesium bromide on the ketones failed completely, the original ketones being recovered unchanged. Evidently, extensive enolisation took place during the Grignard reaction. The possibility of the seven-membered ring structure for the above-mentioned product was, however, definitely ruled out by n.m.r. data (cf. Experimental section).

Following an earlier suggestion [2] that the diene (XII), on cyclisation, might conceivably give rise to the desired podocarpa-8,11,13-triene (II; R = R″ = H, R′ = OMe) to an appreciable extent, the triphenylphosphorane [7] prepared from γ-*m*-methoxyphenylpropyl bromide was condensed with 6-methylhept-5-en-2-one, and the resultant di-olefin (XII) cyclised under the usual conditions. (±)-13-Methoxy-5α-podocarpa-8,11,13-triene [8] (II; R = R″ = H, R′ = OMe), m. p. 86—88°, was isolated in approximately 25% yield, along with the hydrophenalene (III; R = R″ = H, R′ = OMe) which was identified by chromic acid oxidation to the ketone (IV; R = H). Some (±)-13-methoxy-5β-podocarpa-8,11,13-triene may also have been formed, but could not be properly characterised.

[6] Sengupta, Chaudhuri, and Khastgir, *Tetrahedron*, 1960, **10**, 45.
[7] Wittig and Schöllkopf, *Ber.*, 1954, **87**, 1318.
[8] Church, Ireland, and Marshall, *Tetrahedron Letters*, 1960, No. 17, 1.

Experimental

N.m.r. spectra were obtained on a 60 Mc. Varian (A-60) instrument, for deuteriochloroform solutions with tetramethylsilane as internal standard (δ 0·00). Light petroleum refers to the fraction of b. p. 40—60°.

Methyl 5-*Hydroxy*-8-m-*methoxyphenyl*-5-*methyloctanoate* (V; R = Me, R′ = OMe, R″ = H).—(*a*) The Grignard reagent prepared from methyl iodide (1·5 ml.), magnesium (0·6 g.), and dry ether (20 ml.) was slowly added with stirring to a cooled solution of methyl 8-*m*-methoxyphenyl-5-oxo-octanoate [5] (4·5 g.) in ether (25 ml.) and benzene (12 ml.). The mixture was stirred for 30 min., left overnight, refluxed on a water-bath for 1 hr., cooled, and decomposed with 2N-sulphuric acid. The product was worked up in the usual way,[3] and hydrolysed with 5% ethanolic potassium hydroxide, to afford the hydroxy-acid (V; R = R″ = H, R′ = OMe) (4 g.) as a gum. This was re-esterified with diazomethane and the crude methyl ester was directly used in the next operation.

(*b*) To a cooled solution of ethyl 5-oxohexanoate (10 g.) in ether (20 ml.) and benzene (20 ml.), was slowly added an ethereal solution of 3-*m*-methoxyphenylpropylmagnesium chloride [from 3-*m*-methoxyphenylpropyl chloride (8·2 g.), magnesium (1·8 g.), and ether (40 ml.)]. The mixture was stirred at room temperature for 30 min. and refluxed for 2 hr. The product was worked up in the usual way and purified through the hydroxy-acid (V; R = R″ = H, R′ = OMe) (yield 8 g.) as in (*a*).

γ-(1,2,3,4-*Tetrahydro*-6-*methoxy*-1-*methyl*-1-*naphthyl*)*butyric Acid* (VI; R = R″ = H, R′ = OMe).—The preceding hydroxy-ester (4 g.) was added to concentrated sulphuric acid (18 g.) and water (2 ml.), and stirred at 0° for 20 min. The red solution was decomposed with ice and the organic matter extracted with ether. The residue, after evaporation of the ether, was hydrolysed with 5% ethanolic potassium hydroxide (40 ml.), to give the acid (VI; R = R″ = H, R′ = OMe) as a gum. This was esterified by refluxing with 3% methanolic hydrogen chloride (40 ml.). The *methyl ester* (VI; R = Me, R′ = OMe, R″ = H) (3·5 g.) had b. p. 175°/2 mm. (Found: C, 73·7; H, 8·8. $C_{17}H_{24}O_3$ requires C, 73·9; H, 8·7%).

2,3,3a,4,5,6-*Hexahydro*-1-*isopropyl*-8-*methoxy*-3a-*methyl*-1H-*phenalene* (III; R = R″ = H, R′ = OMe). The above ester (3 g.) in benzene (40 ml.) was treated with an ethereal solution of methylmagnesium iodide [from methyl iodide (3 ml.), magnesium (1 g.), and ether (40 ml.)]. The tertiary alcohol (VII; R′ = OMe, R″ = H) (3·1 g.) thus obtained was treated with polyphosphoric acid [from phosphorus pentoxide (37 g.) and 89% phosphoric acid (24 ml.)] at 90° for 1 hr. The brown mixture was decomposed with ice and the product worked up in the usual way, to furnish the hydromethoxyphenalene (III; R = R″ = H, R′ = OMe) (2 g.), b. p. 150°/0·2 mm., n_D^{36} 1·5398 (Found: C, 83·6; H, 10·3. Calc. for $C_{18}H_{26}O$: C, 83·7; H, 10·1%), $\lambda_{max.}$ (in EtOH) 280 mμ (log ε 3·38) [lit.,[2] b. p. 150—155°/0·2 mm., n_D^{36} 1·5420, $\lambda_{max.}$ 281 mμ (log ε 3·37)].

1,2,3,3a,4,5,6,9b-*Octahydro*-9b-*hydroxy*-1-*isopropyl*-3a-*methylphenalen*-8-*one* (IV; R = H).—The foregoing hydromethoxyphenalene (1 g.) in acetic acid (13 ml.) was oxidised with a solution of chromic acid (1·3 g.) in 80% acetic acid (18 ml.) in the usual way.[2] The hydroxycyclohexadienone (IV; R = H) (0·8 g.) was isolated from the reaction mixture in nearly 80% yield, m. p. and mixed [2] m. p. 158° (Found: C, 78·4; H, 9·2. Calc. for $C_{17}H_{24}O_2$: C, 78·5; H, 9·2%). The dinitrophenylhydrazone had m. p. and mixed [2] m. p. 124°.

Methyl 5-*Hydroxy*-8-(4-*methoxy*-3-*methylphenyl*)-5-*methyloctanoate* (V; R = R′ = Me, R″ = OMe).—A solution of methyl 8-(4-methoxy-3-methylphenyl)-5-oxo-octanoate [4] (4 g.) in dry benzene (20 ml.) on treatment with methylmagnesium iodide [from magnesium (0·5 g.), methyl iodide 1·2 ml.), and ether (15 ml.)] afforded the hydroxy-ester (V; R = R′ = Me, R″ = OMe) (3·5 g.) which was purified as usual by hydrolysis and re-esterification. The crude ester was used in the next operation.

γ-(1,2,3,4-*Tetrahydro*-7-*methoxy*-1,6-*dimethyl*-1-*naphthyl*)*butyric Acid* (VI; R = H, R′ = Me, R″ = OMe).—The above ester (3 g.) was slowly added to well-stirred 90% sulphuric acid (10 ml.) at 0°. After 30 min. at this temperature, the product was decomposed, and the organic matter was extracted and hydrolysed, to furnish the *product* (2 g.) as white needles, m. p. 114—115° (after several crystallisations from ether–light petroleum) (Found: C, 73·7; H, 8·8. $C_{17}H_{24}O_3$ requires C, 73·9; H, 8·7%). The n.m.r. data (relative areas, splitting patterns, and assignments in parentheses) were as follows: τ −1·21 (1, acidic hydrogen), τ 3·13, 3·26 (2, singlets, aromatic hydrogens), τ 6·20 (3, sharp singlet, methoxyl group), τ 7·85 (3, singlet,

aromatic methyl group), and τ 8·73 (3, sharp singlet, quaternary methyl group), other protons appearing at τ 7·34, 7·68, and ~8·4. The *methyl ester* had b. p. 150—155°/0·2 mm. (Found: C, 74·3; H, 8·8. $C_{18}H_{26}O_3$ requires C, 74·5; H, 8·9%).

2,3,3a,4,5,6-*Hexahydro*-1-*isopropyl*-9-*methoxy*-3a,8-*dimethyl*-1H-*phenalene* (III; R = H, R′ = Me, R″ = OMe).—The foregoing ester (1·5 g.) reacted with an excess of methylmagnesium iodide, and the crude alcohol (VII; R′ = Me, R″ = OMe) cyclodehydrated as before with polyphosphoric acid [from phosphorus pentoxide (18 g.) and 89% phosphoric acid (12 ml.)] at 80° for 45 min. The product was chromatographed on activated alumina (80 g.) and eluted by light petroleum. The *hydrophenalene* was obtained as a colourless oil (1·2 g.), b. p. 150°/0·2 mm., $n_D^{31·5}$ 1·5310 (Found: C, 83·4; H, 10·3. $C_{19}H_{28}O$ requires C, 83·8; H, 10·3%), $\lambda_{max.}$ (in EtOH) 280 mμ (log ε 3·06), $\lambda_{min.}$ 250 mμ (log ε 2·36), τ 3·28 (1, singlet, aromatic hydrogen), τ 6·24 and 6·35 (3, singlets, methoxyl group), τ 7·80 (3, singlet, aromatic methyl group), τ 8·92, 9·00, 9·14, 9·20, and 9·30 (9, one isopropyl and one quaternary methyl group), other peaks at τ 7·20, 8·11, 8·35, and 8·72.

2,3,3a,4,5,6-*Hexahydro*-6-*isopropyl*-7-*methoxy*-3a,8-*dimethylphenalen*-1-*one*(*Isonimbiol Methyl Ether*) (VIII).—The hydrophenalene (III; R = H, R′ = Me, R″ = OMe) (750 mg.), in acetic acid (9 ml.), was oxidised with a solution of chromic acid (930 mg.) in acetic acid (9 ml.) and water (3 ml.) at room temperature for 24 hr. The product was worked up as usual and absorbed on a column of activated alumina (100 g.). Elution with light petroleum afforded a non-ketonic fraction (130 mg.) which was rejected. Elution with benzene yielded the desired *ketone* (VIII) (550 mg.) as a viscous liquid which was sublimed at 155—160°/0·2 mm. (Found: C, 79·6; H, 8·9. $C_{19}H_{26}O_2$ requires C, 79·7; H, 9·1%). The ultraviolet spectrum, having $\lambda_{max.}$ (in EtOH) 275 mμ (log ε 4·08) and $\lambda_{min.}$ 242 mμ (log ε 3·23), was identical with that of isonimbiol methyl ether.[4] It formed a deep red dinitrophenylhydrazone, m. p. and mixed [4] m. p. 271° (from benzene–methanol) (Found: C, 64·3; H, 6·4; N, 12·2. Calc. for $C_{25}H_{30}N_4O_5$: C, 64·4; H, 6·4; N, 12·0%).

Lactone (IX; R = OMe) *of* 4-*Hydroxy*-7-m-*methoxyphenyl*-4-*methylheptanoic Acid*.—The Grignard reagent prepared from 3-*m*-methoxyphenylpropyl bromide (15 g.), magnesium (1·9 g.), and ether (60 ml.) was added slowly to a stirred solution of ethyl lævulinate (13·5 g.) in ether (50 ml.) and benzene (50 ml.). Ether was partly removed by distillation, and the residue refluxed on a water-bath for 3 hr., cooled, and decomposed with cold dilute sulphuric acid. The organic layer was separated and the residue after evaporation of solvent was warmed with 10% aqueous sodium hydroxide (100 ml.), neutral matter was removed with ether, and the solution acidified. The *lactone* thus liberated was extracted with ether, washed with aqueous sodium hydrogen carbonate solution and water, dried (Na_2SO_4), and the solvent evaporated. The residue (7·5 g.) was used in subsequent experiments.

The *lactone* (IX; R = H) (16 g.) of 4-hydroxy-4-methyl-7-phenylheptanoic acid was similarly prepared from 3-phenylpropyl bromide (26 g.), magnesium (3·5 g.), and ethyl lævulinate (27 g.), b. p. 170—180°/4 mm. (Found: C, 76·7; H, 8·2. $C_{14}H_{18}O_2$ requires C, 77·1; H, 8·3%).

2,3,3a,4,5,6-*Hexahydro*-8-*methoxy*-3a-*methylphenalen*-1-*one* (XI; R = OMe).—(*a*) A mixture of the lactone (IX; R = OMe) (3 g.), chlorobenzene (5·3 ml.), and anhydrous aluminium chloride (2 g.) was shaken at room temperature for ½ hr. and warmed on a steam-bath for 5 min. The deep red solution was decomposed with ice and concentrated hydrochloric acid, chlorobenzene removed by steam distillation, and the residue extracted with ether and separated into two fractions: (i) a neutral part (0·1 g.) insoluble in alkali, identified as 2,3,3a,4,5,6-hexahydro-8-methoxy-3a-methylphenalen-1-one (dinitrophenylhydrazone, m. p. 245°), and (ii) β-(1,2,3,4-tetrahydro-6-methoxy-1-methyl-1-naphthyl)propionic acid (X; R = OMe) (1·8 g.). The latter was dissolved in benzene (6 ml.) and treated first with phosphorus pentachloride (1·8 g.), and then with a solution of stannic chloride (1·6 ml.) in benzene (1·6 ml.) in the cold for 15 min. The mixture was decomposed with ice and concentrated hydrochloric acid and the product was worked up in the usual way to afford 2,3,3a,4,5,6-*hexahydro*-8-*methoxy*-3a-*methylphenalen*-1-*one* (1·6 g.), b. p. 160—165°/4 mm. (Found: C, 78·0; H, 8·1. $C_{15}H_{18}O_2$ requires C, 78·3; H, 7·8%). It formed a *dinitrophenylhydrazone*, red needles, m. p. 245° (from chloroform) (Found: C, 61·8; H, 5·3; N, 13·9. $C_{21}H_{22}N_4O_5$ requires C, 61·6; H, 5·4; N, 13·7%).

(*b*) The lactone (IX; R = OMe) (0·5 g.) was mixed with polyphosphoric acid [from phosphorus pentoxide (6·2 g.) and 89% phosphoric acid (4 ml.)] and heated at 100° for 15 min. The product was worked up in the usual way to yield 2,3,3a,4,5,6-hexahydro-8-methoxy-3a-methylphenalen-1-one (0·3 g.), identified by its dinitrophenylhydrazone, m. p. and mixed m. p. 245°.

2,3,3a,4,5,6-*Hexahydro*-3a-*methylphenalen*-1-*one* (XI; R = H).—The lactone (IX; R = H) (1·5 g.) was treated with polyphosphoric acid [from phosphorus pentoxide (18·8 g.) and 89% phosphoric acid (12 ml.)] at 135° for 20 min. The product was worked up in the usual way, to afford the *phenalen*-1-*one* (1 g.), b. p. 140°/3 mm. (Found: C, 83·7; H, 8·1. $C_{14}H_{16}O$ requires C, 84·0; H, 8·0%). The *dinitrophenylhydrazone* formed readily as a red powder, m. p. 253° (from chloroform) (Found: C, 62·8; H, 5·3; N, 14·4. $C_{20}H_{20}N_4O_4$ requires C, 63·2; H, 5·3; N, 14·7%).

The ketones (XI; R = H or OMe) failed to react with an ethereal solution of isopropylmagnesium bromide either in the cold or at reflux temperature.

3-m-*Methoxyphenylpropyltriphenylphosphonium Bromide*.—A mixture of triphenylphosphine (10·5 g.), 3-*m*-methoxyphenylpropyl bromide (9·2 g.), and chlorobenzene (12·5 ml.) was refluxed for 24 hr. The chlorobenzene was decanted off as far as possible from the thick heavy phosphonium compound, and the latter was treated with ether, and filtered, and the residue dried *in vacuo*, to give a white solid (18 g.), m. p. 135—140°.

9-m-*Methoxyphenyl*-2,6-*dimethylnona*-2,6-*diene* (XII).—The above phosphonium compound (6 g.) was suspended in dry ether (60 ml.) and treated with an ethereal solution of butyl-lithium (1·3N, 12·5 ml.) under oxygen-free nitrogen. A red solution was formed which was left overnight at room temperature. 6-Methylhept-5-en-2-one (3 g.) in ether (10 ml.) was added and the mixture stirred for 2 hr. Ether was removed by distillation, tetrahydrofuran (50 ml.) was added, and the whole refluxed for 2 hr. on a water-bath. The solvent was then completely evaporated under reduced pressure and the residue extracted with ether. The ethereal extract was washed with water, dried, and evaporated. Distillation of the residue afforded the *product* (XII) (1·5 g.), b. p. 120—125°/·05 mm., n_D^{32} 1·5105 (Found: C, 82·6; H, 10·2. $C_{18}H_{26}O$ requires C, 83·7; H, 10·1%).

Cyclisation of **9-m-*Methoxyphenyl*-2,6-*dimethylnona*-2,6-*diene*** (XII).—The diene (XII) (2·5 g.) was cyclised with polyphosphoric acid under the usual conditions, and the product (1·8 g.), b. p. 138—140°/0·2 mm., was chromatographed on activated alumina (70 g.). (±)-13-Methoxy-5α-podocarpa-8,11,13-triene (600 mg.) was obtained in the last few fractions and gave white crystals (300 mg.), m. p. and mixed m. p. 86—88° (from ether–light petroleum). The earlier liquid fractions of the chromatogram were combined and oxidised with chromic acid under the usual conditions, to afford the ketone (IV; R = H) (0·35 g.), m. p. 158°, and a liquid fraction (0·6 g.) which was not further investigated.

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