598. *Reduced Cyclic Compounds. Part VIII.* The Synthesis of (±)-6-Methoxypodocarpa-5,7,13(14)-triene and (±)-Abieta-5,7,13(14)-triene.†*

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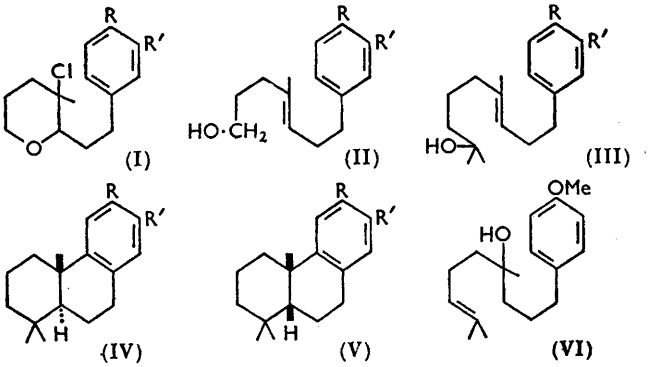
The action of polyphosphoric acid on 9-*m*-isopropylphenyl- and 9-*p*-methoxyphenyl-2,6-dimethylnon-*trans*-6-en-2-ol, whose preparations are described, is shown to yield respectively mixtures of (±)-11α- and -11β-abieta-5,7,13(14)-triene, and (±)-6-methoxy-11α- and -11β-podocarpa-5,7,13(14)-triene. The latter mixture has been separated.

The availability of 5,6-dihydro-3-methyl-4*H*-pyran [1] enables Ansell and Selleck's synthesis [2] of 1,2,3,4,9,10,11,12-octahydrophenanthrenes to be extended to the 12-methyl derivatives. To this end 9-*m*-isopropylphenyl- (III; R = H, R′ = Pr^i) and 9-*p*-methoxyphenyl-2,6-dimethylnon-*trans*-6-en-2-ol (III; R = OMe, R′ = H) were prepared. These nuclear substituents were chosen so that the cyclisation products would be the known abieta-5,7,13(14)-triene (IV; R = H, R′ = Pr^i) and 6-methoxypodocarpa-5,7,13(14)-triene (IV; R = MeO, R′ = H) or stereoisomeric with them.



The alcohols (III) were prepared as follows: the Grignard reagents of the appropriately substituted phenethyl chloride were coupled with 2,3-dichlorotetrahydro-3-methylpyran to yield the compounds (I) which on ring scission with sodium gave the alcohols (II). These were converted into the required tertiary alcohols (III) by treatment of the Grignard

* Part VII, *J.*, 1959, 329. † The nomenclature used is that of Klyne, *J.*, 1953, 3072.

[1] Ansell and Gadsby, *J.*, 1958, 3388.
[2] Ansell and Selleck, *J.*, 1956, 1238.

reagent of the derived chloride (prepared *via* the toluene-*p*-sulphonate) with acetone. The alcohols prepared in this way are considered to have a *trans*-configuration (cf. ref. 1).

Treatment of the methoxy-alcohol (III; R = OMe, R′ = H) with polyphosphoric acid yielded a mixture of (±)-6-methoxy-11α- and -11β-podocarpa-5,7,13(14)-triene, as shown by analysis and dehydrogenation to 6-methoxy-1-methylphenanthrene. The pure crystalline (±)-11β-isomer (V; R = MeO, R′ = H) was obtained from this mixture and was identical with that obtained by Fétizon and Delobelle [3] (following the work of Nasipuri [4]) by cyclisation of the alcohol (VI) with polyphosphoric acid. After removal of the (±)-11β-isomer the residual liquid product had an infrared spectrum which differed from that of the (±)-11β-isomer but was essentially the same as that of the 11α-isomer, which is considered to be the major component of the liquid fraction.

The *m*-isopropyl alcohol (III; R = H, R′ = Pr^{i}) with polyphosphoric acid yielded an essentially (97·8%) saturated product, which with 2,4-dinitrobenzenesulphenyl chloride gave, after chromatography, a product containing not more than 1·5% of diolefinic material. The infrared spectrum revealed no absorption at 750—810 cm.$^{-1}$ (characteristic of 1,2,3-aromatic trisubstitution) but absorption at 820 and 876 cm.$^{-1}$ attributable to a 1,2,4-trisubstituted benzene ring and at 1361, 1370, and 1380 cm.$^{-1}$ indicating the presence of a methyl and *gem*-dimethyl group.[5] These results are consistent with the product's being a mixture of (±)-11α- and -11β-abieta-5,7,13(14)-triene (IV and V; R = H, R′ = Pr^{i}). This conclusion was confirmed by comparison of the infrared spectrum of the cyclisation product with that of authentic abieta-5,7,13(14)-triene.[6]

Conversion of 6-methoxypodocarpa-5,7,13(14)-triene-16-oic acid (6-methoxypodocarpic acid) and abieta-5,7,13(14)-trien-15-oic acid (dehydroabietic acid) into the parent hydrocarbons has been [6,7] effected by Rosenmund reduction of the acid chloride followed by Kishner–Wolff reduction of the aldehyde. An attempt was made to employ an alternative procedure, namely, reduction of the acid to the alcohol followed by reduction of the derived toluene-*p*-sulphonate with lithium aluminium hydride, which has been successful [8] in the 9-methyldecalin series. Although the toluene-*p*-sulphonates were readily obtained the final reduction was not satisfactory. In the methoxy-series the product could not be obtained free from sulphur, and in the isopropyl series a saturated hydrocarbon product was obtained whose properties were not those of abieta-5,7,13(14)-triene. If the final reduction occurs through an S_N1 mechanism,[9] then a neopentyl-type rearrangement is possible to yield 1-ethyl-1,2,3,4,9,10,11,12-octahydro-7-isopropylphenanthrene. Our results are consistent with the product's being a mixture of the latter and abieta-5,7,13(14)-triene.

Experimental

4-Methoxy- and 3-Isopropyl-phenethyl Chloride.—Thionyl chloride (130 g.) was added slowly to a stirred, boiling solution of the substituted phenethyl alcohol (4-methoxy,[10] 3-isopropyl [11]) (0·9 mole) in benzene (150 ml.). The solution was boiled and stirred until evolution of hydrogen chloride ceased, then cooled, and washed successively with 50 ml. portions of 10% aqueous sodium chloride, and distilled. In this way were prepared 4-methoxyphenethyl chloride (144 g., 91%), b. p. 136—139°/24 mm., n_D^{20} 1·5372 (lit.,[10] b. p. 129·5—131°/10 mm.) and *3-isopropylphenethyl chloride* (140 g., 85%), b. p. 120°/11 mm., n_D^{20} 1·5165 (Found: C, 72·1; H, 8·3; Cl, 19·8. $C_{11}H_{15}Cl$ requires C, 72·4; H, 8·2; Cl, 19·5%).

3-Chlorotetrahydro-3-methyl-2-phenethylpyran Derivatives.—A solution of 2,3-dichlorotetrahydro-3-methylpyran [1] [from 5,6-dihydro-3-methyl-4*H*-pyran (40 g., 0·41 mole)] in ether

[3] Fétizon and Delobelle, *Compt. rend.*, 1958, **246**, 2774.
[4] Nasipuri, *Chem. and Ind.*, 1957, 425.
[5] Bellamy, "Infra-red Spectra of Complex Molecules," Methuen, London, 1954.
[6] Jeger, Durst, and Buchi, *Helv. Chim. Acta*, 1947, **30**, 1853.
[7] Campbell and Todd, *J. Amer. Chem. Soc.*, 1942, **64**, 928.
[8] Hussey, Liao, and Baker, *ibid.*, 1953, **75**, 4727; Dauben, Tweit, and MacLean, *ibid.*, 1955, **77**, 48.
[9] Cf. Corey, Howell, Boston, and Young, and Sneen, *ibid.*, 1956, **78**, 5036.
[10] Plimmer, Short, and Hill, *J.*, 1938, 694.
[11] Haworth and Barker, *J.*, 1939, 1299.

(100 ml.) was added dropwise to a stirred solution of the Grignard reagent prepared from the substituted phenethyl chloride (0·55 mole) and magnesium (13·4 g.) at such a rate that gentle refluxing was maintained. The stirred mixture was boiled for 1 hr., then poured on ice and ammonium chloride. The aqueous layer was extracted with ether, and the dried (K_2CO_3) combined ethereal solutions were distilled. In this way were prepared: 3-*chlorotetrahydro*-2-4′-*methoxyphenethyl*-3-*methylpyran* (64·5 g., 59%), b. p. 148—152°/0·1 mm., n_D^{17} 1·5300 (Found: C, 67·5; H, 7·85; Cl, 12·8. $C_{15}H_{21}O_2Cl$ requires C, 67·1; H, 7·8; Cl, 13·2%) [1,4-bis-*p*-methoxyphenylbutane, b. p. 177—182°/0·5 mm., m. p. 75—77° (Found: C, 80·0; H, 8·15. Calc. for $C_{18}H_{22}O_2$: C, 79·8; H, 8·15%), was also obtained (lit.,[12] m. p. 78—79°)], and 3-*chlorotetrahydro*-2-3-*isopropylphenethyl*-3-*methylpyran* (61·4 g., 53·5%) b. p. 126—127°/0·01 mm., n_D^{20} 1·5170 (Found: C, 71·8; H, 8·75; Cl, 13·3. $C_{17}H_{25}OCl$ requires C, 71·1; H, 9·25; Cl, 13·1%).

7-p-*Methoxyphenyl*-4-*methyl*- *and* 7-m-*Isopropylphenyl*-4-*methyl*-*hept*-trans-4-*en*-1-*ol*.—A solution of one of the above 3-chlorotetrahydropyrans (0·24 mole) in ether (100 ml.) was added to a stirred suspension of sodium sand (12 g.) in ether (50 ml.) at such a rate that steady refluxing of the solvent was maintained, and the mixture then stirred for a further hour. Water was then added (caution) to yield two phases, which were separated, and the aqueous phase was extracted with ether. The dried ($MgSO_4$) combined extracts were distilled. In this way were prepared: 7-p-*methoxyphenyl*-4-*methylhept*-trans-4-*en*-1-*ol* (46 g., 81%), b. p. 160—164°/0·1 mm., n_D^{20} 1·5286 (Found: C, 77·2; H, 9·4. $C_{15}H_{22}O_2$ requires C, 76·9; H, 9·4%), and 7-m-*isopropylphenyl*-4-*methylhept*-trans-4-*en*-1-*ol* (46 g., 78%), b. p. 135°/0·02 mm., n_D^{20} 1·5168 (Found: C, 83·1; H, 10·5. $C_{17}H_{26}O$ requires C, 83·0; H, 10·6%).

7-*Chloro*-4-*methyl*-1-*phenylhept*-trans-3-*ene Derivatives*.—One of the above alcohols (0·25 mole) was added slowly to a stirred slurry of toluene-*p*-sulphonyl chloride (57 g.) in " AnalaR " pyridine (30 g.) at 20° ± 2°. After being left overnight the mixture was diluted with water and extracted with ether. The extract was washed with 50 ml. portions of 25% sulphuric acid, water, saturated aqueous sodium hydrogen carbonate, and water. Evaporation of the dried ($MgSO_4$) extract gave the crude toluene-*p*-sulphonate (*ca.* 80%) as a viscous oil. The latter was added to a warm (50°) solution of anhydrous lithium chloride in 2-ethoxyethanol (100 ml.), the resulting mixture stirred at 110° for 4 hr., and the solvent then removed under reduced pressure. Water was added to the residue which was extracted with ether (2 × 100 ml.), and the dried ($MgSO_4$) extract was distilled (from K_2CO_3). In this way were prepared: 7-*chloro*-1-p-*methoxyphenyl*-4-*methylhept*-trans-3-*ene* (40 g., 80%) b. p. 143—148°/0·2 mm., n_D^{20} 15248 (Found: C, 71·1; H, 8·2; Cl, 13·9. $C_{15}H_{21}OCl$ requires C, 71·3; H, 8·3; Cl, 14·05%), and 7-*chloro*-1-m-*isopropylphenyl*-4-*methylhept*-trans-3-*ene* (48 g., 72%), b. p. 178—181°/7 mm., n_D^{20} 1·5144 (Found: C, 77·0; H, 9·3; Cl, 13·35. $C_{17}H_{25}Cl$ requires C, 77·1; H, 9·5; Cl, 13·4%).

2,6-*Dimethyl*-9-*phenylnon*-trans-6-*en*-2-*ol Derivatives*.—Dry acetone (10 g.) was added to a stirred solution of the Grignard reagent derived from one of the above chlorides (0·087 mole) and magnesium (0·22 g.) in ether (40 ml.) at such a rate that steady refluxing was maintained. The mixture was stirred and boiled for 15 min., then left overnight. Excess of 10% sulphuric acid was added, the ethereal layer separated, the aqueous layer extracted with ether, and the dried (K_2CO_3) combined extracts were distilled. In this way were prepared: 9-p-*methoxyphenyl*-2,6-*dimethylnon*-trans-6-*en*-2-*ol* (12 g., 50%), b. p. 135—138°/0·01 mm., n_D^{20} 1·5161 (Found: C, 77·8; H, 9·9. $C_{18}H_{22}O_2$ requires C, 78·3; H, 10·1%), and 9-m-*isopropylphenyl*-2,6-*dimethylnon*-trans-6-*en*-2-*ol* (15·5 g., 62%), b. p. 157—159°/0·1 mm., n_D^{20} 1·5073 (Found: C, 82·9; H, 11·1. $C_{20}H_{32}O$ requires C, 83·3; H, 11·1%).

Cyclisation of 9-p-*Methoxyphenyl*-2,6-*dimethylnon*-trans-6-*en*-2-*ol*.—This alcohol (5 g.) was added to stirred warm (40°) polyphosphoric acid (50 g.), and the mixture vigorously stirred at 80° for 45 min., then cooled, poured on ice, and extracted with ether (2 × 100 ml.); the extract was dried ($MgSO_4$) and distilled, to give 1,2,3,4,9,10,11,12-octahydro-6-methoxy-1,1,12-trimethylphenanthrene (4·2 g., 90%), b. p. 130—136°/0·1 mm. Microhydrogenation indicated 1·1% of diolefinic material and dehydrogenation with selenium, at 300—350° for 50 hr., gave 6-methoxy-1-methylphenanthrene, isolated as the picrate, m. p. 139—141° (lit.,[13] m. p. 140—141·5°). The product was eluted from a column of alumina with pentane, and on removal of the solvent the residue slowly deposited (±)-6-methoxy-11β-podacarpa-5,7,13(14)-triene (0·36 g.) as prisms, m. p. and mixed m. p. with an authentic [3] sample 50—51·5° (Found: C, 84·0; H, 9·9. Calc. for $C_{18}H_{26}O$: C, 83·7; H, 10·1%). A further quantity (0·5 g.; m. p. 50—51·5°) of

[12] Haworth and Moore, *J.*, 1946, 633.
[13] Sherwood and Short, *J.*, 1938, 1006.

this compound was obtained by cooling a pentane solution of the mother-liquors to −60°. The liquid portion of the product, n_D^{20} 1·5489 (Found: C, 83·3; H, 9·6%), was accepted as (±)-6-methoxy-11α-podocarpane (Raman and Rao [14] record b. p. 145—147°/0·8 mm., n_D^{26} 1·5465; Fétizon and Delobelle [3] record b. p. 120—123°/5 × 10^{-3} mm., n_D^{19} 1·5447).

Cyclisation of 9-m-*Isopropylphenyl*-2,6-*dimethylnon*-trans-6-*en*-2-*ol*.—This alcohol (15 g.) was treated with polyphosphoric acid (150 g.) at 80—100° for 45 min., the subsequent procedure being as for the methoxy-analogue. Distillation gave a mixture of predominantly 11α- and 11β-abieta-5,7,13(14)-triene (10·5 g., 75%), b. p. 130—141°/0·1 mm., n_D^{20} 1·5336—1·5364 (microhydrogenation showed 2·2% of diolefinic material). This material, together with 2,4-dinitrobenzenesulphenyl chloride (0·375 g.) in glacial acetic acid (20 ml.), was heated on a steam-bath for 15 min., then cooled and poured into water. The mixture was continuously ether extracted overnight. The extract was washed with 10% aqueous sodium carbonate, dried ($MgSO_4$), and evaporated, and the residue was eluted from a column of alumina, with pentane, to yield 7·3 g. of material (microhydrogenation showed 1·5% of diolefinic material). Fractional distillation (micro-spinning band column, E. Haage, Mulheim) gave material of b. p. 186·5—189°/14 mm., n_D^{20} 1·5360—1·5369 (Found: C, 88·2; H, 11·4. Calc. for $C_{20}H_{30}$: C, 88·9; H, 11·1%) (lit.,[15] for 1,2,3,4,9,10,11,12-octahydro-7-isopropyl-1,1,12-trimethylphenanthrene, b. p. 107—114°/0·1 mm., n_D^{20} 1·5270).

Toluene-p-*sulphonates of* 6-*Methoxypodocarpa*-5,7,13(14)-*trien*-16-*ol and Abieta*-5,7,13(14)-*trien*-15-*ol*.—The appropriate alcohol (0·015 mole) [obtained by reduction (for 18 hr.) of the corresponding acids with lithium aluminium hydride in boiling di-n-butyl ether [16]] was treated in pyridine (40 ml.) with toluene-*p*-sulphonyl chloride (3·05 g., 0·016 mole) in pyridine (20 ml.) and boiled for 12 hr., then cooled and poured into water (150 ml.). The mixture was made alkaline with 2N-ammonia and extracted with ether (2 × 50 ml.). The residue obtained on evaporation of the dried ($MgSO_4$) ether extract was crystallised from ether–pentane and then ethanol. In this way were prepared the *toluene*-p-*sulphonate* (2·25 g., 35%), m. p. 81—82°, of 6-methoxypodocarpa-5,7,13(14)-trien-16-ol (Found: C, 70·0; H, 7·7. $C_{25}H_{32}O_4S$ requires C, 70·1; H, 7·5%), and the *toluene*-p-*sulphonate* (3·04 g., 46%), m. p. 86°, of abieta-5,7,13(14)-trien-15-ol (Found: C, 73·35; H, 8·3. $C_{27}H_{36}O_3S$ requires C, 73·6; H, 8·3%).

Reduction of toluene-p-*sulphonates*. A solution of abieta-5,7,13(14)-trien-15-yl toluene-*p*-sulphonate (24 mmoles) in di-n-butyl ether (50 ml.) was added to a suspension of lithium aluminium hydride (2·3 g., 60 mmoles) in dibutyl ether (50 ml.), and the mixture boiled for 5 hr. Water and 2N-hydrochloric acid were added to the cool mixture, which was then continuously extracted with ether for 14 hr. The residue obtained on evaporation of the dried ($MgSO_4$) extracts was dissolved in pentane and passed through a column of alumina, and the eluant was distilled. The product (3·0 g., 44%), b. p. 154—156°/0·1 mm., n_D^{20} 1·5452, $[\alpha]_D$ +128° in chloroform (Found: C, 88·9; H, 10·8. Calc. for $C_{20}H_{30}$: C, 88·8; H, 11·1%), was saturated to hydrogen in the presence of Adams catalyst and did not form a crystalline dinitro-derivative. Jeger *et al.*[6] record for abieta-5,7,13(14)-triene b. p. 135°/0·05 mm., $[\alpha]_D$ +5: (dinitro-derivative, m. p. 187—188°). Dupont [17] records m. p. 46° for 1-ethyl-1,2,3,4,9,10,11,12-octahydro-7-isopropyl-phenanthrene.

The reduction product of 6-methoxypodocarpa-5,7,13(14)-trien-16-yl toluene-*p*-sulphonate was insoluble in pentane and could not be purified.

The authors are indebted to the D.S.I.R. for an award (to B. G.), to the University of London Central Research Fund for financial assistance, to the Hercules Powder Company for a gift of dehydroabietonitrile, to Dr. F. J. T. Grigg (D.S.I.R., New Zealand) for a gift of podocarpic acid, to Dr. S. S. Brown for a gift of *m*-bromocumene, and to Professor Fétizon for copies of the infrared spectra of (±)-6-methoxy-11α- and -11β-podocarpa-5,7,13(14)-triene and a sample of the 11β-isomer.

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[14] Rao and Raman, *Tetrahedron*, 1958, **4**, 294.
[15] Caliezi and Schinz, *Helv. Chim. Acta*, 1952, **35**, 1649.
[16] Cf. Zeiss, Slimowicz, and Pasternak, *J. Amer. Chem. Soc.*, 1948, **70**, 1981.
[17] Dupont, *Bull. Soc. chim. France*, 1958, **25**, 17.