Cyclisation Reactions. Part III.[1] Cyclisation of *trans*-2,3-Epoxy-9-*m*-methoxyphenyl-2,6-dimethylnon-6-ene

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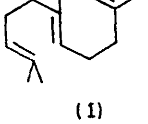
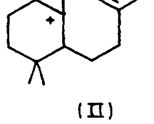
9-*m*-Methoxyphenyl-2,6-dimethylnona-2,6-diene (VI) has been converted into the 2,3-epoxide (VIII) and the latter cyclised to give (±)-13-methoxypodocarpa-8,11,13-trien-3β-ol (IX) (25%) as the major product. An alcohol and a ketone isolated in 12 and 17% yield respectively have been tentatively assigned as the 11-methoxy-isomer (X) and *trans*-3-(2-*m*-methoxyphenylethyl)-2,2,4-trimethylcyclohexanone (XII).

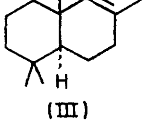
DURING the past few years, we have been studying the cyclisation of 9-aryl-2,6-dimethylnona-2,6-dienes (I; R = H or OMe) and analogues [1,2] to give synthetically useful podocarpa-8,11,13-trienes (III).[3,4] Though the latter is the major product [*ca.* 60% in case of (I; R = H)] (the other products being two isomeric hydrophenalenes and the 5β,10β-podocarpatriene),[2] the reaction is not concerted. This has been demonstrated by isolation of identical products both from the *cis*- and *trans*-dienes, thus indicating a common precursor, presumably the cyclohexyl cation (II) or its equivalent. The alternative possibility of the dienes being equilibrated through protonation of the central double bond prior to cyclisation is ruled out by the observation that 4,8-dimethyl-1-phenylnon-7-en-4-ol, which would generate the same cationic species in acid medium, gave a different product with the hydrophenalenes predominating (*ca.* 80%).[2] Recently, epoxide-initiated



(I)



(II)



(III)

cyclisation of polyolefins has been used in stereoselective syntheses of terpenoid compounds from acyclic precursors,[5] and in this context, we now report the cyclis-

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[1] Part II, D. Nasipuri, S. R. Ray Chaudhuri, A. Mitra, and C. K. Ghosh, *Indian J. Chem.*, 1972, **10**, 136.

[2] D. Nasipuri, R. Bhattacharya, and C. K. Ghosh, *J. Chem. Soc.* (*C*), 1969, 782.

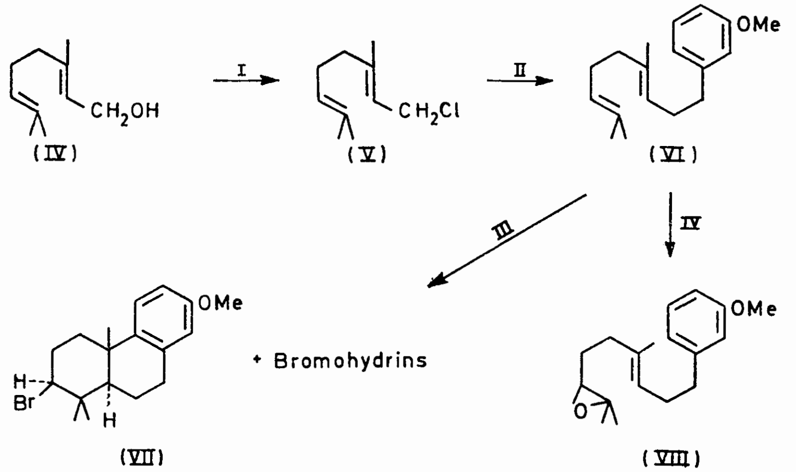
[3] D. Nasipuri and M. Guha, *J. Chem. Soc.*, 1962, 4248.

[4] See also M. Ansell and B. Gadsby, *J. Chem. Soc.*, 1959, 2994.

[5] E. E. van Tamelen, *Accounts Chem. Res.*, 1968, **1**, 111; for a recent review see J. W. ApSimon, 'Elucidation of Organic Structures by Physical and Chemical Methods,' part III, 2nd edn., Wiley-Interscience, 1972, p. 351.

ation of *trans*-2,3-epoxy-9-*m*-methoxyphenyl-2,6-dimethylnon-6-ene (VIII).

trans-9-*m*-Methoxyphenyl-2,6-dimethylnona-2,6-diene (VI) was prepared from geraniol (IV) by the route in the Scheme. The formation of the chloride (V)[6] and its subsequent coupling[7] proceeded in good yield with retention of configuration. G.l.c. analysis showed the product to contain >90% of the *trans*-diene (VI), identical with a specimen previously obtained[1] from a Wittig reaction and separation on preparative g.l.c. Treatment of the diene with *N*-bromosuccinimide[8,9] gave a dibromohydrin as major product along with 10% of a cyclic bromo-compound which was easily separated by column chromatography. From mechanistic consideration and by analogy,[10] structure (VII) is assigned to the bromo-compound, and is supported by its n.m.r. spectrum (three aromatic protons and absence of vinyl proton). Apparently, the bromonium ion initiated a concerted cyclisation. The epoxy-olefin (VIII) was finally obtained in good yield by controlled oxidation of the diene with perbenzoic acid.[11] The spectral characteristics agreed well with its structural and stereochemical assignment.



SCHEME Reagents: i, Ph_3P–CCl_4, CH_3CN; ii, *m*-MeO·$C_6H_4CH_2MgBr$, hexamethylphosphoramide; iii, *N*-bromosuccinimide, aqueous Me_2SO or aqueous tetrahydrofuran; iv, $PhCO_3H$

Treatment of the epoxy-olefin with boron trifluoride–ether complex in methylene dichloride[12] yielded a complex mixture of cyclised products. Chromatography on silica gel afforded four fractions, of which the most polar was a crystalline solid (yield 25%), identical (i.r. and n.m.r.) with the tricyclic alcohol (IX), prepared from the corresponding ketone[13] by reduction with lithium aluminium hydride. A similar product (IX; H in place of OMe) has recently been isolated in a peroxide-initiated thermal cyclisation of the diene (I; R = H).[14]

Two more alcoholic fractions were isolated from the reaction mixture. The second most polar fraction, obtained in 12% yield, was assigned the structure (X) by comparison of its n.m.r. spectrum with that of the alcohol (IX). The differences in the two spectra closely paralleled those recorded[12] for two analogous compounds [(IX) and (X); CH_2OH in place of 4α-Me] in the aromatic region and the position of the angular methyl groups (see Experimental section). Similar isomeric cyclised products have been observed in other reactions.[15] The third alcohol (~10%), which was obtained impure, did not give a C*H*OH signal at τ 6·60, and cannot therefore be the 5β,10α-isomer of (IX); it is tentatively identified as the alcohol (XIII), formed from (VIII) by the route shown.

Finally, a ketonic fraction was isolated in 17% yield from the earlier eluants, and had $\nu_{max.}$ 1705 and 1600 cm^{-1}; τ 2·68—3·20 (4H, m, ArH), 6·20 (3H, s, OMe), 7·10—7·66 (4H, m, 2 × CH_2), 8·00—8·80 (6H, m, 2 × CH_2 and 2 × CH), and 8·90—9·05 (9H, m, 3 × Me). The presence of a ketonic group and four aromatic protons, and the absence of any vinyl proton clearly indicated a monocyclised product, and structure (XII) was assigned. This was presumably formed by an intramolecular hydride transfer in an intermediate cationic species (XI), possibly π-complexed, as suggested by Goldsmith and Phillips[12] for a similar case. No rigid proof for the stereochemistry, however, could be given. The cyclisation of the epoxy-olefin, therefore,

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[6] E. Axelrod, G. M. Milne, and E. E. van Tamelen, *J. Amer. Chem. Soc.*, 1970, **92**, 2139.

[7] G. Stork, P. A. Grieco, and M. Gregson, *Tetrahedron Letters*, 1969, 1393.

[8] D. R. Dalton, V. P. Dutta, and D. C. Jones, *J. Amer. Chem. Soc.*, 1968, **90**, 5498.

[9] E. E. van Tamelen and T. J. Curphey, *Tetrahedron Letters*, 1962, 121.

[10] E. E. van Tamelen and E. J. Hessler, *Chem. Comm.*, 1966, 411.

[11] K. Mori, *Tetrahedron*, 1972, **28**, 3754.

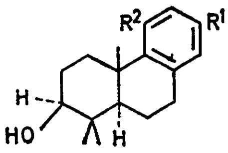
[12] D. J. Goldsmith and C. F. Phillips, *J. Amer. Chem. Soc.*, 1969, **91**, 5862.

[13] G. Stork, A. Meisets, and J. E. Davies, *J. Amer. Chem. Soc.*, 1963, **85**, 3419.

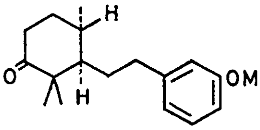
[14] D. Mansury and M. Julia, *Bull. Soc. chim. France*, 1972, 2695.

[15] G. Stork and M. Marx, *J. Amer. Chem. Soc.*, 1969, **91**, 2371; G. Stork and M. Gregson, *ibid.*, p. 2373; G. Stork and P. A. Grieco, *ibid.*, p. 2407.

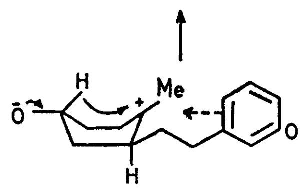
appeared to be more stereospecific than that of the dienes.



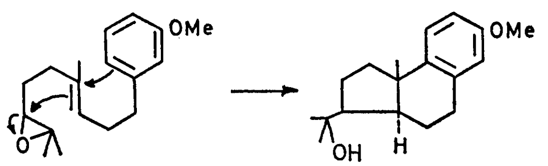
(IX) R^1 = OMe, R^2 = H
(X) R^1 = H, R^2 = OMe



(XII)



(XI)



(VIII) (XIII)

(Only one enantiomer is shown)

EXPERIMENTAL

N.m.r. spectra were measured with a Varian T60 spectrometer for solutions in [^{2}H]chloroform with tetramethylsilane as internal standard. T.l.c. was carried out in 20 × 20 cm plates with 0·1 mm layers of silica gel G. Analytical g.l.c. was carried out on a column (6 ft × $\frac{1}{8}$ in) of 10% poly(diethylene glycol succinate) on Gaschrom-Z (60—80 mesh) with nitrogen as carrier gas. Petroleum refers to the fraction of b.p. 40—60°. All organic extracts were dried over anhydrous sodium sulphate.

Geraniol (IV).—Commercial geraniol * was purified by formation of an adduct with calcium chloride and subsequent decomposition with cold water, repeated twice. The purified alcohol, b.p. 112° at 8 mmHg was homogeneous by t.l.c. and g.l.c.

Geranyl Chloride (V).—Geraniol (10 g, 0·065 mol) in dry acetonitrile (30 ml) was mixed with triphenylphosphine (18·9 g, 0·072 mol) and shaken vigorously at 25°. Dry carbon tetrachloride (11·4 g, 0·074 mol) was added slowly to the mixture, when a clear solution resulted. This was stirred at 25° for 6 h more and left overnight. Solvent was removed under reduced pressure and the precipitate was filtered off with a little petroleum. The oil remaining after removal of solvent was distilled to give geranyl chloride (V) (8 g, 70%), b.p. 55—60° at 0·2 mmHg (lit.,[7] 64—65° at 0·05 mmHg), homogeneous by t.l.c. and g.l.c.

trans-9-m-*Methoxyphenyl*-2,6-*dimethylnona*-2,6-*diene* (VI).—A solution of *m*-methoxybenzylmagnesium bromide [from *m*-methoxybenzyl bromide (25 g, 0·124 mol) and magnesium (3·65 g, 0·152 mol) in dry ether (100 ml)] was added slowly to geranyl chloride (4g, 0·023 mol) in tetrahydrofuran (60 ml) and hexamethylphosphoramide (30 ml). During the addition (4 h), the colour changed from yellow *via* orange and red to pink. The homogeneous solution was left overnight and then refluxed on a steam-bath for 2 h. After removal of ether and tetrahydrofuran, the residue was decomposed with saturated aqueous ammonium chloride solution and the organic matter was worked up in the usual way to furnish the *diene* (VI) (5·7 g) as an oil, b.p. 145—150° at 0·4 mmHg (Found: C, 83·5; H, 10·15. $C_{18}H_{26}O$ requires C, 83·7; H, 10·0%); n_D^{32} 1·5108; $\nu_{max.}$ (neat) 1608, 1590, 1490, 1460, 1440, 1380, 1265, 1155, 1050, 775, and 690 cm^{-1}; τ 2·50—3·30 (4H, m, ArH), 4·80 (2H, m, vinyl H), 6·20 (3H, s, OMe), 7·20—8·00 (8H, m, 4 × CH_2), and 8·30—8·50 (9H, m, 3 × Me).

3β-*Bromo*-13-*methoxypodocarpa*-8,11,13-*triene* (VII).—To a cold solution of the foregoing diene (0·516 g, 2 mmol) in dry dimethyl sulphoxide (10 ml) or in tetrahydrofuran (10 ml) containing a trace of water (0·06 g), *N*-bromosuccinimide (0·45 g, 2·5 mmol) was added in portions in the cold with stirring under nitrogen. The mixture was stirred at room temperature for 1·5 h and then diluted with water. The product was extracted with ether, and the extract was washed with water, dried, and the solvent removed to furnish a red oil (0·64 g). This was chromatographed over silica gel (20 g; 60—100 mesh). Elution with petroleum gave unchanged diene (VI) as an oil (0·110 g). Ether–petroleum (1 : 19) eluted the *bromo-compound* (VII) (0·068 g) which distilled (140° at 0·5 mmHg) as a viscous liquid (Found: C, 64·3; H, 7·5; Br, 23·9. $C_{18}H_{25}BrO$ requires C, 64·1; H, 7·4; Br, 23·7%); $\nu_{max.}$ (Nujol) 1610, 1590, 1460, 1380, 1320, 1260, 1155, 1040, 870, 775, and 690 cm^{-1}; τ 2·50—3·50 (3H, m, ArH), 6·05br (1H, t, 3-H), 6·18 (3H, s, OMe), 7·00—8·50 (9H, m, 4 × CH_2 and CH), and 8·70—9·10 (9H, m, 3 × Me). A third fraction (0·20 g), eluted by ether–petroleum (1 : 3) was a complex mixture possibly of mono- and dibromohydrins with the latter predominating (t.l.c.). Final elution of the column with ether gave an unidentified viscous gum.

2,3-*Epoxy*-9-m-*methoxyphenyl*-2,6-*dimethylnon*-6-*ene* (VIII).—A solution of perbenzoic acid (0·238 g, 1·85 mmol) in chloroform (5·5 ml) was added to the diene (VI) (0·516 g, 2 mmol) in chloroform (1 ml) at 0—5°. The mixture was left overnight in a refrigerator, then diluted with chloroform, and the chloroform solution was washed with aqueous 5% sodium hydrogen carbonate, dried, and evaporated to furnish an oil (0·520 g). The product showed two spots on t.l.c., the upper corresponding to the diene. The mixture was absorbed on activated alumina (20 g) and eluted with petroleum. After an initial fraction of the diene (0·07 g), the *epoxy-olefin* (VIII) (0·35 g, 64%), homogeneous to t.l.c. in different solvent systems, was eluted (Found: C, 78·6; H, 9·4. $C_{18}H_{26}O_2$ requires C, 78·8; H, 9·5%); τ 2·85 and 3·30 (4H, m, ArH), 4·83br (1H, t, 7-H), 6·23 (3H, s, OMe), 7·10—8·20 (9H, m, 4 × CH_2 and 3-H), 8·47 (3H, s, 6-Me), and 8·74 and 8·77 (6H, d, 2 × Me).

Cyclisation of the Epoxy-olefin (VIII).—To an ice-cooled solution of the preceding epoxide (0·3 g, 1·1 mmol) in dry methylene chloride (10 ml), was added boron trifluoride–ether complex (0·03 g). The ice-bath was removed and stirring continued for 20 min. After dilution with water, the mixture was extracted with methylene chloride, and the extract was washed with water and then with aqueous sodium bicarbonate, dried, and evaporated to yield an oily product (0·3 g) showing several spots on t.l.c. This was

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* We thank Dr. J. Verghese, Christian Medical College, Vellore, India, for a gift of geraniol.

chromatographed on silica gel (30 g) to give the following fractions: (i) Elution with petroleum yielded a mixture (0·08 g) of nonpolar compounds. G.l.c. on an SE-30 column (6 ft × ¼ in) showed several peaks, and it was not investigated further. (ii) Further elution with petroleum afforded trans-3-(2-m-*methoxyphenylethyl*)-2,2,4-*trimethylcyclohexanone* (0·05 g) as an oil, homogeneous to t.l.c. (Found: C, 78·6; H, 9·6. $C_{18}H_{26}O_2$ requires C, 78·8; H, 9·5%); the spectral data are discussed above. (iii) Elution with benzene–petroleum (3 : 7) afforded an alcoholic fraction as an impure oil (0·031 g) which was not further purified owing to paucity of material, $\nu_{max.}$ (Nujol) 3380 and 1600 cm^{-1}; τ 2·70—3·40 (3H, m, ArH), 6·20 (3H, s, OMe), 7·10 (2H, t, *J* 7 Hz, $ArCH_2$), 8·00—8·60 (9H, m), and 8·70, 8·90, and 9·10 (9H, m, 3 × Me); this is tentatively identified as 2,3,3a,4,5,9b-hexahydro-3-(1-hydroxy-1-methylethyl)-7-methoxy-1*H*-benz[*e*]indene (XIII). (iv) Further elution with benzene–petroleum (4 : 6) first afforded 11-methoxypodocarpa-8,11,13-trien-3β-ol (X) as an oil (0·036 g, 12%) (Found: C, 78·5; H, 9·8. $C_{18}H_{26}O_2$ requires C, 78·8; H, 9·5%); $\nu_{max.}$ (Nujol) 3300 and 1600 cm^{-1}; τ 2·73, 2·90, 3·04, 3·17, 3·24, 3·27, and 3·40 (3H, m, ArH),[12] 6·20 (3H, s, OMe), 6·60 (1H, t, *J* 7 Hz, 3-H), 7·15 (2H, t, *J* 7 Hz, $ArCH_2$), 8·00—8·60 (8H, m, 3 × CH_2, CH, and OH), 8·67 (3H, s, 10-Me), and 8·90 and 9·07 (6H, d, 2 × Me). This was followed by the 13-*methoxy-isomer* (IX) (0·075 g, 25%), as plates (from petroleum), m.p. 131—132° (Found: C, 78·6; H, 9·6. $C_{18}H_{26}O_2$ requires C, 78·8; H, 9·5%); $\nu_{max.}$ (Nujol) 3400, 1600, 1500, 1450, 1370, 1320, 1260, 1240, 1160, 1095, 1070, 1030, 1005, 970, 930, 890, 850, 825, and 805 cm^{-1}; τ 2·67, 2·84, 3·14, 3·27, and 3·34 (3H, m, ArH), 6·20 (3H, s, OMe), 6·60 (1H, t, *J* 7 Hz, 3-H), 7·07 (2H, t, *J* 7 Hz, $ArCH_2$), 7·70br (1H, t, 5-H), 8·00—8·65 (7H, m, 3 × CH_2 and OH), 8·80 (3H, s, 10-Me), and 8·94 and 9·12 (6H, d, 2 × Me); mixed m.p. undepressed when admixed with the synthetic alcohol (IX) described below.

(±)-13-*Methoxypodocarpa*-8,11,13-*trien*-3β-*ol* (IX).—13-Methoxypodocarpa-8,11,13-trien-3-one, m.p. 73·5—74° (from hexane)[16] (lit.,[13] 56—58°) * (25 mg) was reduced with a solution of lithium aluminium hydride in ether and the product worked up in the usual way. The alcohol (IX) was obtained as a gum which crystallised from petroleum in plates, m.p. 132° (Found: C, 78·9; H, 9·3. Calc. for $C_{18}H_{26}O_2$: C, 78·8; H, 9·5%), $\nu_{max.}$ (Nujol) identical with that of the foregoing alcohol.

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* According to Prestwich,[16] the compound described by Stork *et al.*[13] was a 50 : 50 mixture of the A/B-*cis*- and A/B-*trans*-13-methoxypodocarpatriene (n.m.r. and t.l.c.). We are grateful to Dr. Prestwich for a sample of the ketone.

[16] G. D. Prestwich, personal communication.