Structural Investigation of Lac Resin. Part 13.[1] Stereochemistry of Some Derivatives of Shellolic Acid, and of its 2-, 10-, and 2,10-Epimers

By **Gobiehettipalayam B. Venkatasubramanian,* Krishnarajanagar N. Ganesh, Virender S. Chauhan, and Vijay K. Mahajan,** Department of Chemistry, University of Delhi, Delhi-110007, India

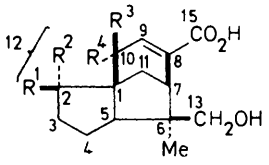
The formation and stereochemistry of 9,10-epoxides and some bromohydrins derived from the title compounds have been studied. The configurations of the bromohydrins have been investigated with reference to their behaviour towards alkali.

DURING elucidation of the structure of shellolic acid (1), Yates *et al.*[2] and Cookson *et al.*[3] obtained a bromo-lactone (2) by the action of bromine on its dimethyl ester. The configurational details of this lactone obtained through its reactions and spectroscopic data were confirmed by an *X*-ray analysis.[4] Yates *et al.*[2] also commented that while the bromo-lactone (2) existed in the chair conformation (9α-bromo-10β-lactone, *trans*-diequatorial) the corresponding bromohydrin appeared to favour a boat-like conformation as indicated by the values of $J_{9,10}$ in the two cases. Since the geometry now consists of the favourable diaxial disposition of the bromide and hydroxy in the bromohydrin, the corresponding epoxide should be formed readily on treatment with alkali. However, a ketone (3) was reported [2,3] from such a reaction, amounting to a *cis*-elimination of hydrogen bromide or else the configuration of the parent bromohydrin happened to be *cis* rather than *trans*.

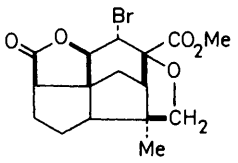
This unexpected stereochemistry of the reaction was

[1] G. B. V. Subramanian, Uma Majumdar, V. S. Chauhan, K. N. Ganesh, and V. K. Mahajan, *J.C.S. Perkin I*, 1977, 1734.
[2] P. Yates, P. M. Burke, and G. F. Field, *Tetrahedron*, 1970, **26**, 3159.
[3] R. C. Cookson, N. Lewin, and A. Morrison, *Tetrahedron*, 1962, **18**, 547; R. C. Cookson, A. Melera, and A. Morrison *ibid.*, p. 1321.
[4] E. J. Gabe, *Acta Cryst.*, 1962, **15**, 759.

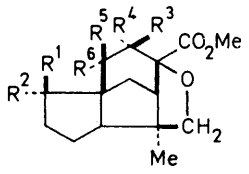
commented upon by both groups of workers. While Cookson *et al.* have invoked involvement of the neighbouring ether oxygen to explain unexpected elimination, Yates *et al.* pointed out that the epoxide was



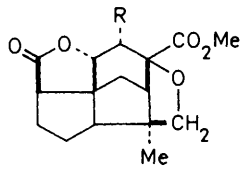
(1) $R^1 = CO_2H$, $R^2 = H$, $R^3 = OH$, $R^4 = H$
(4) $R^1 = CO_2H$, $R^2 = H$, $R^3 = H$, $R^4 = OH$
(5) $R^1 = H$, $R^2 = CO_2H$, $R^3 = H$, $R^4 = OH$
(6) $R^1 = H$, $R^2 = CO_2H$, $R^3 = OH$, $R^4 = H$



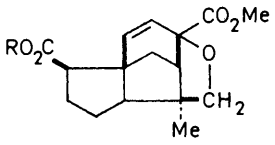
(2)



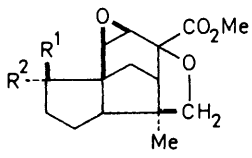
(3) $R^1 = CO_2Me$, $R^2 = R^3 = R^4 = H$, $R^5R^6 = O$
(8) $R^1 = R^3 = R^5 = H$, $R^2 = CO_2Me$, $R^4 = Br$, $R^6 = OH$
(11) $R^1 = CO_2Me$, $R^2 = R^3 = R^5 = H$, $R^4 = R^6 = OH$
(14) $R^1 = R^3 = R^6 = H$, $R^2 = CO_2Me$, $R^4 = Br$, $R^5 = OH$
(16) $R^1 = CO_2Me$, $R^2 = R^4 = R^5 = H$, $R^3 = OH$, $R^6 = Br$
(17) $R^1 = CO_2Me$, $R^2 = R^5 = R^6 = H$, $R^3R^4 = O$



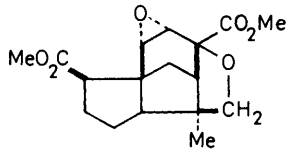
(7) R = Br
(9) R = OH



(10) R = H
(12) R = Me



(13) $R^1 = CO_2Me$, $R^2 = H$
(15) $R^1 = H$, $R^2 = CO_2Me$



(18)

perhaps formed as an intermediate but subsequently underwent ready rearrangement to the ketone during the acid work-up. We have recently found [5] that zinc-promoted debromination of (2) involved the neighbouring lactone function, as well as the ether oxygen, to an extent comparable with that found in previous work [2,3] where only the lactone function was reported to be involved in the elimination process. In fact when zinc–methanol instead of zinc–acetic acid was used, elimination involved entirely the ether function.

We have now obtained [1] 10-*epi*- (4) and 2-*epi*-10-*epi*- (5) shellolic acids from shellolic acid (1) and its 2-epimer (6), respectively, through the intermediate formation of the corresponding 10α-bromo-derivatives and noticed during the course of these reactions that α-side was prone to preferential attack. This observation is similar to those reported by Ourisson *et al.*[6] and Brown *et al.*[7] on α- and β-cedrenes themselves.

The 10-*epi*-derivatives underwent reaction with bromine smoothly, yielding a lactone (7) in the case of dimethyl 10-*epi*-shellolate and a bromohydrin (8) in the case of dimethyl 2-*epi*-10-*epi*-shellolate. The hydrolysis and re-esterification of (7) always gave the corresponding bromohydrin admixed with the lactone, thus indicating the readiness with which lactonisation occurs in this compound. Dreiding models indicated that this *cis*-bromo-lactone (9α-bromo-10α-lactone) might prefer a boat conformation rather than the severely strained chair conformation, in spite of the 1 : 4-interaction involving the bromine atom. A comparable compound is the hydroxy-lactone (9) which was readily prepared from the cyclic ether (10) by *cis*-hydroxylation with osmium tetraoxide. Since the β-face is sterically crowded for complex formation, it was assigned the 9α,10α-configuration. In this case, also, lactone formation was so ready that hydrolysis and re-esterification gave the parent lactone rather than the *cis*-diol (11). This diol was obtained directly by the *cis*-hydroxylation of the cyclic ether (12) and could be lactonised to the hydroxy-lactone (9) by heating under reflux with benzene in the presence of a trace of toluene-*p*-sulphonic acid.

The n.m.r. spectra of the hydroxy-lactone (9) and the bromo-lactone (7) were similar. The low-field 9,10-vicinal two-proton quartets (at δ 4.49, and 4.6, respectively) in both cases showed $J_{9,10}$ 5.0—6.0 Hz, unlike the *trans*-bromo-lactone (2) which had $J_{9,10}$ 11.0 Hz[2,3] indicative of the configurational difference. Zinc-promoted debromination of (7) in methanol gave dimethyl 10-*epi*-shellolate as the only product; while in acetic acid debromination gave three compounds, of which the major compound (10) was isolated pure and characterised. Treatment of (7) with alkali yielded the oxo-ether (3) as the only product. The bromohydrin (8) from 2-*epi*-10-*epi*-shellolate exhibited parallel behaviour.

The action of alkali on the bromo-lactone (2) was re-investigated under different conditions. While aqueous sodium hydroxide (1N) at 25 °C for 3 h gave the corresponding bromohydrin reported earlier,[2,3] treatment with aqueous sodium hydroxide (2N) at 25 °C for 24 h, followed by esterification, gave a bromine-free compound (M^+ 322), m.p. 91 °C. The same compound was obtained when (2) was heated under reflux with aqueous potassium carbonate, the conditions employed by Yates *et al.*[2] The oxo-ether (3) reported earlier from this reaction was absent from the reaction mixture. The compound under consideration is apparently the 9β,10β-epoxide (13). The bromohydrin (14) gave the 2-*epi*-9β,10β-epoxide (15).

[5] G. B. V. Subramanian, K. N. Ganesh, and V. K. Mahajan, *Indian J. Chem.*, in the press.

[6] W. Wojnarowski and G. Ourisson, *Bull. Soc. chim. France*, 1967, 219.

[7] S. P. Acharya and H. C. Brown, *J. Org. Chem.*, 1970, **35**, 196.

The epoxide (13) reacted readily with aqueous hydrobromic acid (48%) [8] to give a bromohydrin (16) which, on reaction with alkali, gave a ketone (17) (M^+ 322) different from (3). The direction of the oxiran ring opening to yield the bromohydrin (16) was also indicated by a zinc–methanol reaction on the 9-*O*-acetate of (16). While the product was a mixture, the major component was identified as the cyclic ether (12). No trace of dimethyl shellolate or its 10-epimer was present in the reaction mixture which would have been the case had the bromine atom and the ether function been vicinal to each other. The bromohydrin (16) itself on prolonged heating under reflux with zinc–methanol gave only (12). Hence this bromohydrin was assigned the configuration 10α-bromo-9β-hydroxy (16).

The 9α,10α-epoxide (18) was prepared from (12) by the action of monoperphthalic acid. The n.m.r. spectrum of this epoxide was comparable to that of (11) (see Experimental section). The acid-catalysed oxiran ring opening of (13) and (18), respectively, did not produce any trace of the corresponding ketones (3) and (17). The nature of the products and other reactions of (13) and (18) are under investigation.

EXPERIMENTAL

T.l.c. of the methyl esters was carried out in chloroform–methanol (98.5 : 1.5) and of the free acids in toluene–ethyl formate–formic acid (5 : 4 : 1) on silica gel plates. Spots were located by spraying with 50% aqueous sulphuric acid followed by charring. Esterifications were carried out in methanolic solution with ethereal diazomethane. Crystallisations were carried out from hot petroleum (b.p. 60—80 °C) unless otherwise stated. All optical rotations were measured for methanol solutions.

Bromo-lactone (7).—Dimethyl 10-*epi*-shellolate (200 mg) was kept in contact with liquid bromine (0.5 ml) at 25 °C for 15 h. The reddish-brown gum was extracted into chloroform (60 ml) and washed with aqueous sodium thiosulphate (10%) till the organic layer became colourless. The extract was dried (anhydrous sodium sulphate) and concentrated, whereupon a sticky residue was obtained. Crystallisation from ether–petroleum gave colourless needles of 9α-*bromo*-8,13-*epoxy*-10α-*hydroxycedrane*-12,15-*dioic acid* 12,10-*lactone* 15-*methyl ester* (7) (150 mg), m.p. 160°, $[\alpha]_D$ −32.5° (*c*, 0.8) (Found: C, 51.3; H, 5.4. $C_{16}H_{19}BrO_5$ requires C, 51.8; H, 5.2%), $\nu_{max.}$ (KBr) 1 780 and 1 740 cm^{-1}, δ 3.63(q, $-CH_2O-$ partially overlapping with signal for CO_2Me), 4.6(q, 2 H, $CHOCO-CHBr$, *J* 6.0 Hz).

Bromohydrin (8).—Dimethyl 2-*epi*-10-*epi*-shellolate (100 mg) on reaction with liquid bromine gave *dimethyl* 9α-*bromo*-8,13-*epoxy*-2βH-10α-*hydroxycedrane*-12,15-*dioate* (8) (80 mg), m.p. 149°, $[\alpha]_D$ −25° (*c*, 0.4) (Found: C, 51.0; H, 6.1. $C_{17}H_{23}BrO_6$ requires C, 50.5; H, 5.7%), $\nu_{max.}$ (KBr) 3 500, 1 724, and 1 695 cm^{-1}, δ 3.55(q, CH_2-O, partially overlapping with signal for CO_2Me), 4.78(d, $-CHBr$, *J* 5.0 Hz).

Action of Alkali.—(a) *On bromo-lactone* (7). The bromo-lactone (7) (50 mg) was dissolved in dioxan (0.5 ml) and was treated with aqueous sodium hydroxide (8%; 1.5 ml) at 25 °C for 15 h. The clear solution was acidified with ice-cold hydrochloric acid, extracted with ethyl acetate, and washed with water and dried. Removal of solvent, esterification of the residue, and crystallisation from ethyl acetate–petroleum afforded dimethyl 8,13-epoxy-10-oxocedrane-12,15-dioate (3) (40 mg), m.p. 123—124° (lit.,[2] 124.5—125.5°) (mixed m.p., i.r., and n.m.r.).

(b) *On bromohydrin* (8). The bromohydrin (8) (50 mg) on similar reaction with aqueous sodium hydroxide (8%; 1.5 ml) at 25 °C for 15 h followed by esterification and crystallisation gave dimethyl 8,13-epoxy-2β*H*-10-oxocedrane-12,15-dioate (35 mg), m.p. 149—150° (lit.,[2] 151°).

Zinc Debrominations.—(a) The bromo-lactone (7) (150 mg) was dissolved in glacial acetic acid (8 ml), zinc dust (AnalaR) (400 mg) was added, and the mixture kept at 60 °C for 2 h. The zinc dust was filtered off and washed twice with hot acetic acid, and the combined filtrate was concentrated under reduced pressure. The residue was acidified with dilute hydrochloric acid (2N, 3 ml) and extracted with ethyl acetate. Removal of solvent followed by crystallisation gave 8,13-epoxycedr-9-ene-12,15-dioic acid 15-methyl ester (10) (90 mg), m.p. 146° (lit.,[3] 147.5—148.5°) (mixed m.p., i.r., and n.m.r.).

(*b*) The bromo-lactone (7) (50 mg) was dissolved in methanol (15 ml) and heated under reflux for 5 h with zinc dust (AnalaR) (100 mg) added in three lots. Work-up gave a gum (t.l.c. pure) identified as dimethyl 10-*epi*-shellolate (i.r. and n.m.r.).

(*c*) The bromohydrin (8) (50 mg) on similar reaction with zinc–methanol gave dimethyl 2-*epi*-10-*epi*-shellolate, m.p. 150° (lit.,[1] 150—151°).

Osmium Tetraoxide Hydroxylations.—*Hydroxy-lactone* (9). The cyclic ether (10) (300 mg) was dissolved in dioxan (25 ml) and treated with osmium tetraoxide (250 mg) at 25 °C for 6 days. The reaction mixture was saturated with hydrogen sulphide gas, the dark brown precipitate was filtered off and washed with dioxan (2 × 5 ml), and the combined filtrate and washings were concentrated under reduced pressure. The gummy residue on crystallisation from ethyl acetate–petroleum gave cubic crystals of 8,13-*epoxy*-9α,10α-*dihydroxycedrane*-12,15-*dioic acid* 12,10-*lactone* 15-*methyl ester* (9), m.p. 186°, $[\alpha]_D$ −24° (*c*, 0.5) (Found: C, 62.7; H, 6.8. $C_{16}H_{20}O_6$ requires C, 62.3; H, 6.5%), $\nu_{max.}$ (KBr) 3 450, 1 754, and 1 730 cm^{-1}. δ 3.7(q, $-CH_2O$, partially overlapping with signal for CO_2Me), 4.49(q, 2 H, $CHOCO-CHOH$, *J* 5.0 Hz).

9α,10α-cis-*Diol* (11).—(*a*) The cyclic ether (12) (150 mg) on reaction with osmium tetraoxide (100 mg) in dioxan (15 ml) at 25 °C for 6 days, work-up, and crystallisation from benzene–hexane gave colourless needles of *dimethyl* 8,13-*epoxy*-9α,10α-*dihydroxycedrane*-12,15-*dioate* (11) (120 mg), m.p. 155°, $[\alpha]_D$ −40° (*c*, 0.2) (Found: C, 59.6; H, 6.9. $C_{17}H_{24}O_7$ requires C, 60.0; H, 7.1%), $\nu_{max.}$ (KBr) 3 450 and 1 724 cm^{-1}, δ 3.71(s, CO_2Me), 3.82(s, CO_2Me), signal for CH_2O merging with signals for CO_2Me, 4.23(s, 2 H, $CHOH-CHOH$).

(*b*) The 2-*epi* cyclic ether of (12) (100 mg) on similar reaction with osmium tetroxide (80 mg) in dioxan (8 ml) gave *dimethyl*-8,13-*epoxy*-2βH-9α,10α-*dihydroxycedrane*-12,-15-*dioate* (75 mg), m.p. 95° (Found: C, 60.3; H, 6.6. $C_{17}H_{24}O_7$ requires C, 60.0; H, 7.1%), $\nu_{max.}$ (KBr) 3 330—3 280 and 1 735 cm^{-1}, δ 3.70(s, CO_2Me), 3.82(s, CO_2Me), signal for CH_2O merging with signals for CO_2Me, 4.21(d, 2 *H*, $CHOH-CHOH$).

Lactonisation of cis-*Diol* (11).—The 9α,10α-*cis*-diol (11) (30 mg) was dissolved in dry benzene (2 ml) containing a trace of toluene-*p*-sulphonic acid and heated under reflux for 1 h. It was diluted with benzene (15 ml), washed with

[8] D. H. R. Barton, D. A. Lewis, and J. F. McGhie, *J. Chem. Soc.*, 1957, 2907.

water, and the dried benzene solution was concentrated. The residue on crystallisation from ethyl acetate–petroleum gave the hydroxy-lactone (9) (25 mg), m.p. 186°.

9β,10β-*Epoxide* (13).—(*a*). The bromo-lactone (2) (500 mg) was dissolved in dioxan (3 ml) and treated with aqueous sodium hydroxide (8%; 10 ml) at 25 °C for 24 h. The clear solution was acidified and extracted into ether (3 × 30 ml). Removal of solvent, esterification, and crystallisation yielded feathery needles of *dimethyl* 8,13-*epoxy*-9β,10β-*epoxycedrane*-12,15-*dioate* (13) (400 mg), m.p. 91°, $[\alpha]_D$ −53.7° (*c*, 0.8) (Found: C, 62.8; H, 6.9. $C_{17}H_{22}O_6$ requires C, 63.3; H, 6.9%), $\nu_{max.}$ (KBr) 1 754 and 1 724 cm^{-1}. δ 3.28(q, CH_2–O), 4.0(q, 2 H, CH–CHO, partially overlapping with signal for CO_2Me, *J* 8.0 Hz).

(*b*) The bromo-lactone (2) (300 mg) was heated under reflux with aqueous potassium carbonate (250 mg in 1.5 ml H_2O) for 5 h. The clear solution was acidified and extracted into ether. The dried extract on concentration and esterification gave the 9β,10β-epoxide (13) (250 mg).

The bromohydrin (14) (50 mg) on similar reaction with aqueous potassium carbonate, followed by esterification gave *dimethyl* 8,13-*epoxy*-9β,10β-*epoxy*-2βH-*cedrane*-12,15-*dioate* (15) (40 mg), m.p. 78° (Found: C, 63.7; H, 6.8. $C_{17}H_{22}O_6$ requires C, 63.3; H, 6.9%), $\nu_{max.}$ (KBr) 1 724 cm^{-1}, δ 3.25(d, CH_2O, *J* 4.0 Hz), 4.0(q, 2 H, CH–CHO, partially overlapping with signal for CO_2Me).

Bromohydrin (16).—The 9β,10β-epoxide (13) (500 mg) was dissolved in chloroform (15 ml) and stirred with aqueous hydrobromic acid (48%; 3 ml) at 25 °C for 4 h. The solution was diluted with chloroform (50 ml), washed with water, aqueous sodium carbonate, and dried (anhydrous sodium sulphate). Concentration of the chloroform solution gave a gum which on crystallisation from ethyl acetate–petroleum gave shining plates of *dimethyl* 10α-*bromo*-8,13-*epoxy*-9β-*hydroxycedrane*-12,15-*dioate* (16) (450 mg), m.p. 179°, $[\alpha]_D$ −104° (*c*, 0.5) (Found: C, 50.1; H, 6.1. $C_{17}H_{23}BrO_6$ requires C, 50.5; H, 5.7%), $\nu_{max.}$ (KBr) 3 505, 1 735, and 1 720 cm^{-1}. δ 4.46(s, 2 H, CHBr–CHOH), quartet for CH_2O merges with signals for CO_2Me.

9-*Acetate of* (16).—The bromohydrin (16) (100 mg) was acetylated with acetic anhydride–pyridine (1:1, 2 ml) at 60 °C for 30 min. The cooled reaction mixture, on dilution with water (3 ml) and stirring, gave a solid, crystallised from benzene–petroleum as needles of *dimethyl* 9β-*acetoxy*-10α-*bromo*-8,13-*epoxycedrane*-12,15-*dioate* (85 mg), m.p. 168°, $[\alpha]_D$ −68° (*c*, 0.5) (Found: C, 51.5; H, 5.3. $C_{19}H_{25}BrO_7$ requires C, 51.2; H, 5.6%), $\nu_{max.}$ (KBr) 1 739 cm^{-1}. δ 2.18(s, $CHOCOCH_3$), signal for CH_2O merges with signals for CO_2Me, 4.61(d, CHBr, *J* 8.0 Hz), 5.73(d, CHOAc, *J* 8.0 Hz).

Zinc Debromination of 10-*Acetate of* (16).—The bromo-compound (50 mg) was dissolved in methanol (15 ml) and heated under reflux with zinc dust (AnalaR) (150 mg) for 7 h. The reaction mixture on work-up and crystallisation gave dimethyl 8,13-epoxycedr-9-ene-12,15-dioate (12) (30 mg), m.p. 63—64° (lit.,[3] 65.5—66.5°).

Oxo-ether (17).—The bromohydrin (16) (500 mg) was dissolved in dioxan (5 ml) and treated with aqueous sodium hydroxide (8%; 15 ml) at 25 °C for 15 h. The clear solution was acidified and extracted into ethyl acetate, and the organic extract was dried (anhydrous sodium sulphate). On concentration, a gummy residue was obtained which was esterified. Crystallisation gave *dimethyl* 8,13-*epoxy*-9-*oxo*-*cedrane*-12,15-*dioate* (17) (415 mg), m.p. 140—141°, $[\alpha]_D$ −38° (*c*, 1.0) (Found: C, 63.2; H, 6.9. $C_{17}H_{22}O_6$ requires C, 63.3; H, 6.9%), $\nu_{max.}$ (KBr) 1 755, 1 740, and 1 725 cm^{-1}. δ 3.7(s, CO_2Me), 3.8(s, CO_2Me), 2.9(q, $-CH_2O$, partially overlapping with signal for CO_2Me).

9α,10α-*Epoxide* (18).—The cyclic ether (12) (500 mg) was dissolved in anhydrous ether (10 ml) and treated with monoperphthalic acid [9] in ether and stirred at 10 °C for 48 h. The reaction mixture was diluted with ether and washed with aqueous sodium hydrogen carbonate, and the ether extract was dried over anhydrous sodium sulphate. Concentration gave a gum which was chromatographed over silica gel (10 g). Elution with benzene (5 × 25 ml) gave the cyclic ether (12) (50 mg), m.p. 63—64°. 2% Ethyl acetate–benzene eluted *dimethyl* 8,13-*epoxy*-9α,10α-*epoxycedrane*-12,15-*dioate* (18) (300 mg), m.p. 125°, $[\alpha]_D$ −15.6° (*c*, 0.6) (Found: C, 63.1; H, 6.8. $C_{17}H_{22}O_6$ requires C, 63.3; H, 6.9%), $\nu_{max.}$ (KBr 1 748 and 1 724 cm^{-1}, δ 3.1(s, CH_2–O), 3.9(s, CH–CHO).

One of us (G. B. V. S.) thanks Lord Todd, F.R.S., for encouragement. Financial assistance from the Council of Scientific and Industrial Research, India (to K. N. G.), and the University Grants Commission (to V. K. M.) is gratefully acknowledged. We are indebted to the Dyson Perrins Laboratory, Oxford, for some mass spectra and elemental analyses.

[7/1146 *Received*, 1*st July*, 1977]

[9] A. I. Vogel, 'A Text Book of Practical Organic Chemistry,' Longmans, London, 1968, p. 810.