

TERPENOIDS—LXV

TRANSFORMATION IN THE SANTALENE—LONGIFOLENE SERIES*

P. RANI BAI, S. Y. KAMAT, B. B. GHATGE, K. K. CHAKRAVARTI
and S. C. BHATTACHARYYA
National Chemical Laboratory, Poona, India

(Received 29 September 1964)

Abstract—The crystalline bicyclo-ekasantalic acid of Semmler, obtained by alkaline dehydrohalogenation of hydrochloro-bicyclo-ekasantalate (IV), is shown not to be homogeneous but a mixture of true bicyclo-ekasantalic acid (V) and isobicyclo-ekasantalic acid (VII), together with traces of tricyclo-ekasantalic acid (III). A synthesis of the acid (VII) from the lactone (X) has been developed. In the same context dehydrohalogenation of isobornyl chloride with sodium acetate and acetic acid gives mainly isobornyl acetate and camphene, together with traces of tricyclene and longibornyl chloride (XVII) which results mainly in longifolene (XVIII), together with small amounts of XXI, isolongifolene (XX) and the tetracyclic sesquiterpene longicyclene (XIX).

α -SANTALENE (I), β -santalene (II) and the corresponding alcohols α - and β -santalols (Ia and IIa) are the main sesquiterpenoids occurring in the Indian sandalwood oil.¹

On oxidation with permanganate, α -santalene and α -santalol are converted to the dextrorotatory, $(\alpha)_D +19^\circ$, crystalline (m.p. 76°) tricyclo-ekasantalic acid (III), containing a tricyclene ring system.¹ The crystalline (m.p. 64°), laevorotatory, $(\alpha)_D -44^\circ$, bicyclo-ekasantalic acid (V), is obtained from III via alkaline saponification of the corresponding hydrochloromethyl ester (IV) according to the procedure of Semmler.^{1,6}

The acid (V) has been used by Ruzicka *et al.*² for the elucidation of the structure of β -santalene and β -santalol (II and IIa). The same acid has also been employed by Bhattacharyya *et al.* in this Laboratory³ and earlier⁴ for the synthesis of β -santalene (II) and allied compounds by using simple unambiguous reactions. However, the β -santalene, thus obtained, for no apparent reason, has a low specific rotation ($\sim -45^\circ$) as against a much higher rotation (-92.5° ; -74°) recorded in the literature.^{3,5} This suggests that the 'pure' crystalline, bicyclo-ekasantalic acid of Semmler, may not be homogeneous and this was found to be the case.

By the judicious application of spectroscopy, gas and thin layer chromatography and using Semmler's bicyclo-ekasantalic acid, its methyl ester, and the corresponding

* Communication No. 727 from the National Chemical Laboratory, Poona-8, India.

¹ F. W. Semmler and K. Bode, *Ber. Dtsch. Chem. Ges.* **40**, 1124, 1139 (1907).

² L. Ruzicka and G. Thomann, *Helv. Chim. Acta* **18**, 355 (1935).

³ Mrs. S. K. Ramaswami, *Santalene and Allied Compounds* Ph.D. thesis, Poona University (1962).

⁴ S. C. Bhattacharyya, *Sci. Cult.* **13**, 158 (1947).

⁵ V. Herout, V. Jarolin and J. Pliva, *Coll. Czech. Chem. Comm.* **22**, 773 (1957).

⁶ Suryakumari Ramaswamy, S. K. Ramaswamy and S. C. Bhattacharyya, *J. Org. Chem.* **27**, 2791 (1962).

alcohol (VI) obtained by reduction with LAH, and the corresponding hydrocarbon (VIa), prepared via the reduction of the tosylate of the above alcohol with LAH, it can now be concluded that Semmler's bicyclo-ekasantalic acid is essentially a mixture of true bicyclo-ekasantalic acid (V) and isobicyclo-ekasantalic acid (VII) in which V predominates. The proportion of the components depends on the reagent used for dehydrohalogenation. After trying various reagents, heating with fused sodium acetate and glacial acetic acid was found most convenient, though none of the reagents gives exclusively pure bicyclo-ekasantalic acid (V).

The presence of isobicyclo-ekasantalic acid (VII) in Semmler's bicyclo-ekasantalic acid is proved chemically by ozonizing the mixture and isolating camphenilone (VIII) as the volatile constituent. The product of ozonization resulting from true bicyclo-ekasantalic acid (V) in Semmler's bicyclo acid is the keto carboxylic acid (IX).

The formation of isobicyclo-ekasantalic acid (VII) during dehydrohalogenation of IV involves a methyl migration. Another product, involving the same methyl migration, is the crystalline lactone (X), obtained by hydration of III, V and also VII the structure of which has been established by synthesis⁷ and other operations.⁸ The lactone (X) on reduction with LAH affords the crystalline diol (XI), which may be converted to the corresponding unsaturated alcohol isobicyclo-ekasantalol (XII) by treatment with acetic anhydride, followed by saponification of the resultant acetate (XIIa).⁶ The alcohol (XII) corresponds to the isobicyclo-ekasantalic acid (VII), m.p. 104°, obtained by chromic acid oxidation of XII.

All the three members of the isobicyclo series, the lactone (X), the alcohol (XII) and the acid (VII) have low optical rotations. Conversion of the keto carboxylic acid (IX) via the hydroxy acid (XIII) to optically pure bicyclo-ekasantalic acid (V) with high laevorotation and finally to pure β -santalene, β -santalol and allied products will form the subject matter of a separate communication.

The dehydrohalogenation of methyl hydrochlorobicyclo-ekasantalate (IV) prompted a re-examination of the dehydrohalogenation of isobornyl chloride (XIV),⁸ which can be obtained by hydrochlorination of pinene, camphene, or tricyclene. The reaction with sodium acetate and glacial acetic acid yields isobornyl acetate (80%), together with camphene (XV; 18%) and tricyclene (XVI; 2%), both of which were characterized and estimated by GLC and also by chemical methods.

Longibornyl chloride (XVII)⁹ on heating with sodium acetate and acetic acid is converted almost quantitatively to a mixture of hydrocarbons, which when subjected to GLC analysis (polyester stationary phase) shows only two peaks, one corresponding to longifolene (XVIII; 80%) and the other to the interesting tetracyclic hydrocarbon longicyclene (XIX; 20%) which recently has been isolated and the structure of which has been determined by Nayak and Sukh Dev.¹⁰ The presence of longifolene was confirmed by ozonization and isolation of longifolic acids¹¹ and longicamphenilone (m.p. 49–50°; IR band at 1754 cm⁻¹).⁹

⁷ A. Bhati, *Perf. & Ess. Oil Rec.* 53, 15 (1962); *J. Org. Chem.* 27, 2135 (1962).

⁸ J. L. Simonsen, *The Terpenes* (2nd Edition) Vol. II, p. 342 (1949).

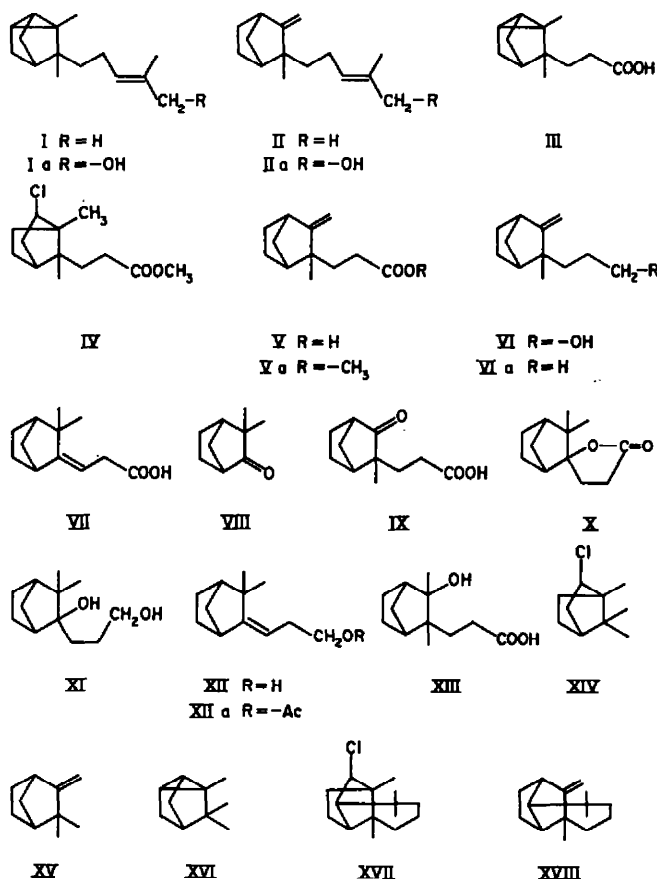
⁹ J. L. Simonsen, *J. Chem. Soc.* 578 (1920); G. Ourisson and P. Naffa, *Chem. & Ind.* 917 (1953).

¹⁰ U. R. Nayak and Sukh Dev, *Tetrahedron Letters* No. 4, 243 (1963). These authors have also observed (personal communication) that longibornyl bromide under certain conditions gives longicyclene in a yield of up to ~30%.

¹¹ U. R. Nayak and Sukh Dev, *Tetrahedron* 19, 2293 (1963).

Exhaustive ozonization or peracid treatment of the hydrocarbon mixture followed by careful chromatography led to the isolation of pure longicyclene (XIX). It has the characteristic IR spectrum (typical bands at 840 and 3049 cm^{-1}). The NMR spectrum shows four characteristic unsplit peaks at 49, 53, 58 and 60 c/s and another peak at 45.8 c/s, identical with the values given in the literature.¹⁰

A quantitative estimation of longicyclene in the hydrocarbon mixture amounted to



$\pm 8\%$. The remaining 12% shown under the peak of longicyclene during gas liquid chromatography in our system, is presumably due to an unsaturated constituent which, like longifolene, is eliminated during ozonization-oxidation and chromatography. Examination of the IR spectrum of the hydrocarbon mixture shows the presence of a product containing a trisubstituted double bond (820, 840 cm^{-1}) which is also supported by the NMR spectrum. This, could be isolongifolene (XX) which has been obtained by treatment of longifolene with acetic acid-sulphuric acid.¹²

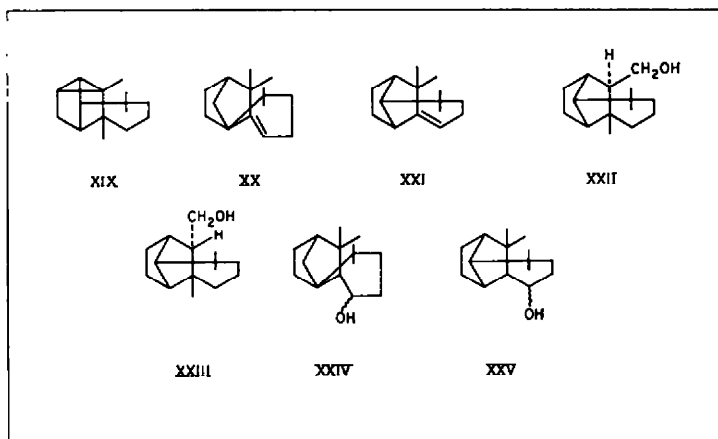
To confirm this, pure longifolene, pure isolongifolene and the hydrocarbon

¹⁰ U. R. Nayak and Sukh Dev, *Tetrahedron*, **8**, 42 (1960); J. R. Prahlad, R. Ranganathan, U. R. Nayak, T. S. Santhanakrishnan and Sukh Dev, *Tetrahedron Letters* No. 8, 417 (1964).

mixture, as obtained by us, were subjected separately to hydroboration-oxidation. Longifolene under these conditions gives a crystalline primary alcohol which from its rotation appears to be a mixture of XXII and XXIII.¹³ Isolongifolene gives the corresponding secondary alcohol (XXIV), m.p. 122°, (α)_D -26.6°. The hydrocarbon mixture gives as expected, a mixture of several products, which on chromatography furnishes (i) longicyclene, (ii) a mixture of primary alcohols (XXII and XXIII) together with a mixture of two crystalline secondary alcohols which melt at about 88°.

On careful GCL analysis one of the components of the mixture was found to be identical with XXIV. The other product which has been obtained in nearly pure form by repeated chromatography has m.p. 115°, (α)_D -15.6°. We presume it to be XXV formed from XXI occurring in the hydrocarbon mixture.

Due to paucity of material, further critical examination of these alcohols was not possible.



EXPERIMENTAL

M.ps and b.ps are uncorrected. Rotations unless, otherwise mentioned, were taken in CHCl_3 solution. IR spectra were determined on a Perkin-Elmer Infracord spectrophotometer by H. Gopinath and K. G. Deshpande. The NMR spectra were taken in CCl_4 solution using tetramethylsilane as internal standard on a Varian A-60 spectrometer by P. M. Nair and colleagues. Microanalyses were carried out by Pansare and colleagues and GLC by Bapat and Sankpal.

Tricyclo-ekasantalic acid (III). The acid was prepared according to the known procedure^{1,6} and crystallized twice from pet. ether; m.p. 76°, (α)_D +19.4° (c, 6.84).

Semmler's bicyclo-ekasantalic acid. Methyl hydrochlorobicyclo-ekasantalate (IV) was prepared by hydrochlorination of tricyclo-ekasantalic acid in methanolic solution. The distilled or undistilled product (10 g) was dehydrochlorinated using different reagents, but refluxing with fused sodium acetate (10 g) glacial acetic acid (60 ml) in an oil bath for 3 hr was found the most convenient.⁶ The properties of methyl bicyclo-ekasantalate depend on the proportion of the constituents and were approximately as follows: b.p. 90°/0.25 mm, n_D^{20} 1.4826; α_D -32° to -48°. (Found: C, 74.46; H, 10.23. $\text{C}_{12}\text{H}_{10}\text{O}_2$ requires: C, 74.96; H, 9.68%).

GLC analysis showed mainly two peaks (2:3 approximately). Saponification with alcoholic potash (10%) followed by usual processing and distillation gave the bicyclo-acid which was crystallized from pet. ether and had approximately the following properties; m.p. 64°, (α)_D -40° to -55°; characteristic IR peaks at: 1653, 880 cm^{-1} ($\text{C}=\text{CH}_2$).

¹³ H. H. Zeiss and M. Arakawa, *J. Amer. Chem. Soc.* **76**, 1653 (1954).

An unsuccessful attempt was made to separate the two acids (V & VII) from this mixture by crystallization of cyclohexylamine, dicyclohexylamine, strychnine and brucine salts.

Reduction of the above ester to the corresponding alcohol. Following standard conditions, the ester (32 g) in ether (230 ml) was reduced by adding to a slurry of LiAlH_4 (6.25 g) in anhydrous ether (800 ml) under stirring and external cooling with ice. The stirring was continued at room temp for 3 hr and then at 40° for another 3 hr. The reaction product was decomposed with moist ether and water, and the ether extract worked up to yield bicyclo-ekasantalol (24.2 g), b.p. $90\text{--}97^\circ/0.84$ mm, n_D^{25} 1.4960; $\alpha_D -40^\circ$ to -55° (neat); GLC showed two peaks (2:3). IR peaks at 3380, 1055, ($-\text{CH}_2\text{OH}$), 880, 1653 ($\text{>C}=\text{CH}_2$) cm^{-1} . (Found: C, 79.27; H, 11.53. $\text{C}_{18}\text{H}_{28}\text{O}$ requires: C, 79.94; H, 11.18%).

The reduction of alcohol to the hydrocarbon. Bicyclo-ekasantalol (5 g) as obtained above was converted to the tosyl derivative by treating in pyridine (50 ml) solution with tosyl chloride (5 g). The tosyl derivative (6 g) was reduced with LiAlH_4 (1.5 g) following the procedure described above for the alcohol. The hydrocarbon (4 g) was passed through neutral alumina (grade I, 100 g) and distilled, b.p. $100\text{--}110^\circ$ (bath)/11 mm, n_D^{27} 1.4730; ($\alpha_D -43\text{--}89^\circ$ (c, 4.89); IR peaks at: 1667 881 ($\text{>C}=\text{CH}_2$). GLC showed two peaks (2:3). (Found: C, 87.72; H, 12.32. $\text{C}_{18}\text{H}_{26}$ requires: C, 87.73; H, 12.27%).

Oxidation of Semmler's bicyclo-ekasantalic acid. The acid (10 g) in acetone (300 ml) was oxidized by gradual addition of powdered KMnO_4 (20 g) during 2 hr under stirring. The mixture was then refluxed for 3 hr. Acetone was distilled off and the residue after addition of water (100 ml) was clarified by passing SO_2 . The product was extracted with ether, washed with water and then separated into acidic and neutral fractions by treatment with NaHCO_3 .

The neutral portion after chromatography and distillation was identified as camphenilone (VIII) by analysis, mixed GLC and superimposable IR spectra with an authentic sample, b.p. 130° (bath)/40 mm, ($\alpha_D -37\text{--}2^\circ$ (c, 5.01). (Found: C, 78.77; H, 10.41. $\text{C}_9\text{H}_{14}\text{O}$ requires: C, 78.21; H, 10.21%).

The acidic portion was preliminarily distilled. The fraction boiling at 180° (bath)/0.5 mm was collected. It (IX) was a thick viscous liquid; characteristic IR peaks at 1748, 1718 cm^{-1} . (Found: C, 67.28; H, 8.83. $\text{C}_{11}\text{H}_{18}\text{O}_2$ requires: C, 67.32; H, 8.22%).

Isobicyclo-ekasantalol (XII). The alcohol was prepared according to the known procedure. The lactone (X, m.p. 103° , ($\alpha_D +2\text{--}8^\circ$) was reduced with LiAlH_4 to the diol (XI, m.p. 112° , ($\alpha_D +1\text{--}94^\circ$). The latter on treatment with fused sodium acetate and acetic anhydride afforded the acetate (XIIa, b.p. $105\text{--}110^\circ/0.5$ mm, n_D^{25} 1.4749; ($\alpha_D -8\text{--}9^\circ$), converted via alkaline hydrolysis to the alcohol (XII), b.p. $96\text{--}98^\circ/2$ mm, n_D^{25} 1.4963; ($\alpha_D -9\text{--}5^\circ$ (c, 9.30); IR peaks at: 1666, 842, ($\text{>C}=\text{CH}-$), doublet at 1382, 1366 (*gem*-dimethyl); 3300, 1050, cm^{-1} ($-\text{CH}_2\text{OH}$).

Oxidation of the alcohol (XII) to isobicyclo-ekasantalic acid (VII). To the alcohol (XII, 2.8 g), dissolved in acetone (200 ml), Jones' reagent (6 ml; 8N CrO_3 in H_2SO_4) was gradually added with ice-cooling and occasional shaking during 5 min. After keeping in the ice-bath for further 5 min, the product was decomposed with methanol and extracted with ether, washed thoroughly with water and then separated into neutral and acidic fractions. The former on spectral evidence was found to consist of aldehyde and alcohol. The acidic portion which was isobicyclo-ekasantalic acid solidified on cooling and was crystallized twice from pet. ether, m.p. 104° , ($\alpha_D -7\text{--}1^\circ$ (c, 10); IR peaks at: 816 ($\text{>C}=\text{CH}-$) doublet at 1391, 1372 cm^{-1} (*gem*-dimethyl). (Found: C, 74.16; H, 9.75. $\text{C}_{18}\text{H}_{26}\text{O}_2$ requires: C, 74.19; H, 9.34%).

On refluxing with dil H_2SO_4 (15%, 40 min) it was converted to the lactone (X) identified by m.p. and mixed m.p. with an authentic sample.

Dehydrohalogenation of isobornyl chloride (XIV). A mixture of isobornyl chloride (5 g) (prepared by hydrochlorination of camphene, m.p. 126° ; ($\alpha_D -6\text{--}6^\circ$), freshly fused sodium acetate (5 g) and glacial acetic acid (30 ml) was refluxed in an oil bath for 8 hr. The reaction mixture was cooled, poured into cold water, extracted with pet. ether ($40\text{--}60^\circ$), the extract was washed thoroughly with NaHCO_3 aq, water, dried and the solvent removed. The residue (3.3 g; ($\alpha_D +5\text{--}8^\circ$) from comparative and quantitative GLC analysis was found to contain isobornyl acetate (79.8%) and a hydrocarbon fraction (20.2%) comparable to camphene.

The above mixture (3 g) was hydrolysed by refluxing (3 hr) with alcoholic KOH (30 ml, 20%) and the neutral product, extracted with ether, chromatographed on neutral alumina (grade I, 60 g) and eluted with pet. ether and ether. The pet. ether portion containing the hydrocarbon, on quantitative GLC analysis, showed the presence of camphene (95%) and tricyclene (5%), which was also supported by IR peaks at: 1642, 877 (camphene); 1034, 1471, 3058 (tricyclene) cm^{-1} . Ether eluate contained isoborneol, crystallized from methyl alcohol, m.p. and mixed m.p. with an authentic sample 214°.

Dehydrohalogenation of longibornyl chloride (XVII). A mixture of longibornyl chloride (10 g; m.p. 59°, $(\alpha)_D + 8.4^\circ$, obtained by hydrochlorination of longifolene), freshly fused sodium acetate (5 g) and glacial acetic acid (30 ml) was refluxed for 8 hr and the reaction product (8.16 g) isolated by following the procedure described earlier for isobornyl chloride. It consisted almost entirely of hydrocarbon, as shown by spectral characteristics and analysis. It was totally distilled over Na and had the following properties; b.p. 82°/2 mm, $\alpha_D + 35.8^\circ$ (neat); IR bands at: 820, 840, 877, 1026, 3080 cm^{-1} . (Found: C, 87.86; H, 11.79. $\text{C}_{18}\text{H}_{14}$ requires: C, 88.16; H, 11.84%). GLC analysis showed two peaks, one corresponding to longifolene (80%) and the other to isolongifolene-longicyclene (20%).

Isolation of longicyclene (XIX). The hydrocarbon mixture (5 g) from the above reaction in CCl_4 (75 ml) was ozonized exhaustively for 8 hr; the solvent was removed and the ozonide decomposed with water and extracted with ether. After treatment with Na_2CO_3 aq, it was separated into a neutral fraction (1 g) and an acidic fraction (3 g).

The neutral fraction was chromatographed on neutral alumina grade I (20 g) and eluted with pet. ether (0.47 g) and ether (0.5 g). The pet. ether fraction on GLC gave a nonresolvable peak and was identified as longicyclene. It was distilled over Na and showed the following constants: b.p. 82°/2 mm, $n_D^{20} 1.4888$; $(\alpha)_D + 30.04^\circ$ (c, 10.3); typical IR bands at: 840 and 3048 cm^{-1} . NMR analysis showed among others 4 unsplit peaks at 49, 53, 58 and 60 c/s and another at 45.8 c/s, fully agreeing with those reported in the literature for longicyclene. (Found: C, 88.26; H, 11.80. $\text{C}_{18}\text{H}_{14}$ requires: C, 88.16; H, 11.84%).

The ether eluate was a solid and was rechromatographed on neutral alumina grade II (13 g) and identified as longicamphenilone by m.p. and mixed m.p. 49°, with an authentic sample and superimposable IR spectra.

The acidic fraction after ozonization was a mixture of longifolic and isolongifolic acids, m.p. 130°, $(\alpha)_D - 24.74^\circ$ (c, 9.9, ethanol). (Found: C, 76.15; H, 10.17. $\text{C}_{18}\text{H}_{14}\text{O}_2$ requires: C, 76.22; H, 10.24%). No attempt was made to separate the isomers.

Hydroboration-oxidation of the hydrocarbon mixture. The mixture of hydrocarbons (5.02 g) obtained by dehydrohalogenation of longibornyl chloride was dissolved in anhydrous tetrahydrofuran (125 ml). A slow stream of N_2 carrying diborane [generated by adding a solution of NaBH_4 (1.6 g) in diglyme (40 ml) to a solution of BF_3 -etherate (40 ml)] was passed through the ice-cold solution of the hydrocarbon during 2½ hr, after which the dissolved diborane gas was also released by heating the generation flask. The reaction mixture was then left overnight at room temp, cooled in ice, and made alkaline by dropwise addition of cold, 15% KOH aq. After addition of a few pieces of ice, excess of H_2O_2 (50 ml, 30%) was added and the mixture left overnight, extracted with ether, washed thoroughly with water and the solvent removed. The product was chromatographed on neutral alumina grade II (110 g) and eluted with pet. ether (40–60°), followed by ether. The pet. ether fraction (0.5 g) was chromatographed on neutral alumina grade II (20 g) and then distilled over Na to yield (0.4 g) pure longicyclene, characterized as previously. The ether eluate (4 g, m.p. 74°; $(\alpha)_D - 25.62^\circ$; GLC 5% secondary alcohols and 95% primary alcohols) was chromatographed on neutral alumina grade II (180 g), the elution being carried out with benzene–pet. ether mixture (75:25). The earlier fractions (0.396 g) showed (GLC) a considerable enrichment of the secondary alcohols (XXIV and XXV). This fraction was rechromatographed twice on neutral alumina grade II and eluted with benzene–pet. ether (80:20) to give in the earlier fractions (0.035 g) crystalline alcohol (95%, GLC), further purified by sublimation *in vacuo* to the alcohol (XXV), m.p. 115°, $(\alpha)_D - 15.6^\circ$ (c, 1.9, ethanol). (Found: C, 81.60; H, 12.25. $\text{C}_{18}\text{H}_{18}\text{O}$ requires: C, 81.02; H, 11.79%). IR peaks at: 3400, 1047 and 1011 cm^{-1} . This was not identical with the alcohol obtained from isolongifolene by m.p. and mixed m.p., comparative GLC and IR spectra.

Hydroboration-oxidation of isolongifolene. The procedure was as in the above case. Isolongifolene (1.45 g), dry tetrahydrofuran (40 ml), BF_3 -etherate (10 ml), 1M NaBH_4 in diglyme (10 ml), H_2O_2 ,

(20 ml, 30%). The solid alcohol obtained was chromatographed on neutral alumina grade II (30 g) and eluted with pet. ether (40–60°) followed by ether. The first ether fraction (0.87 g), m.p. 102°, was sublimed and rechromatographed to yield the pure alcohol (XXIV), GLC (100%), m.p. 122°, $(\alpha)_D -26.6^\circ$, $(c, 4.12, \text{ethanol})$ IR peaks at: 3430, 1035 and 1016 cm^{-1} . (Found: C, 80.60; H, 11.58. $\text{C}_{18}\text{H}_{28}\text{O}$ requires: C, 81.02; H, 11.79%).

Hydroboration-oxidation of longifolene. The procedure followed was the same as in the case of the hydrocarbon mixture, using the same quantity of reagents. The solid alcohol was chromatographed on neutral alumina grade II (110 g) and eluted with pet. ether (40–60°) followed by ether. The ether eluate (4.3 g), solid m.p. 70°, was purified by sublimation *in vacuo* to yield a solid (GLC one peak), m.p. 72°, $(\alpha)_D -22.04^\circ$ ($c, 14.7, \text{ethanol}$). IR peaks at 3340, 1049, 1020 and 1003 cm^{-1} . (Found: C, 80.58; H, 11.34. $\text{C}_{18}\text{H}_{28}\text{O}$ requires: C, 81.02; H, 11.79%).