

was triturated with petroleum ether and chromatographed on a short column of Fluorasil giving 174 mg. of crystalline material (5.95μ and $\lambda_{max}^{96\% \text{ C}_2\text{H}_5\text{OH}}$ 272 $m\mu$). The n.m.r. was identical with that of the strenuous base-isomerized mixture containing III, IV, and VII. Esterification with ethereal diazomethane followed by irradiation and analysis by

VPC showed the presence of 70% of IV and 30% of a mixture of III and VII.

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Terpenoids. XXXIII. Transformations in the Santalene Series

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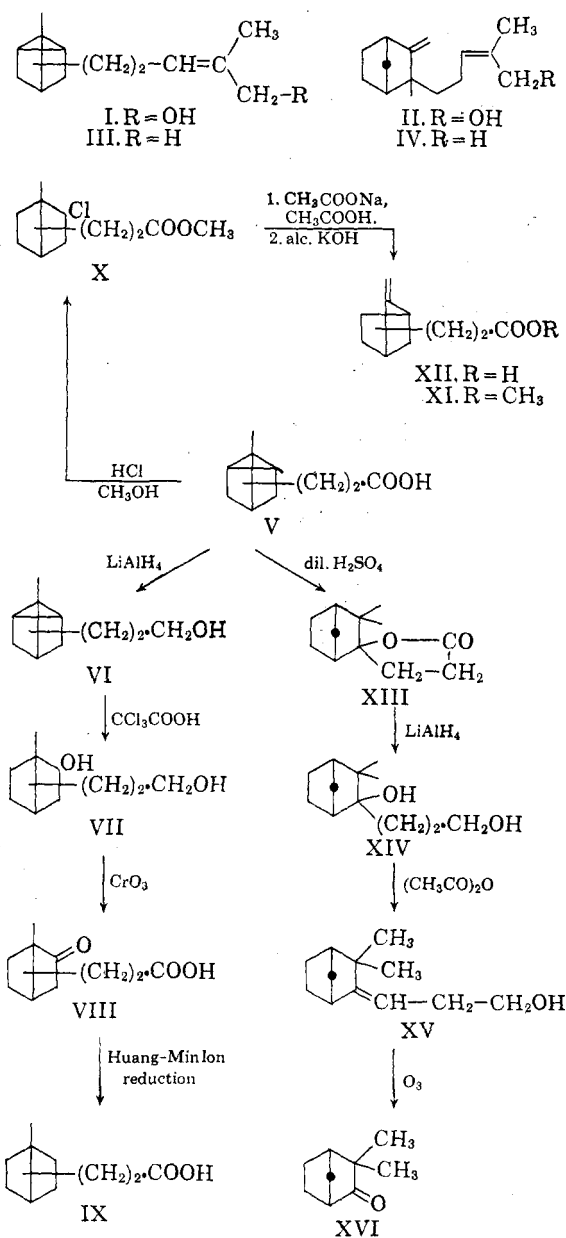
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Starting from the crystalline tricyclic derivative tricycloekasantalic acid, several compounds having different bicyclic ring systems have been obtained. Some of these are of use in the synthesis of compounds of the bornane and camphene series.

α -Santalol (I), β -santalol (II), and the corresponding hydrocarbons, α -santalene (III) and β -santalene (IV), are the main constituents of East Indian sandalwood oil. The chemistry of these interesting compounds and allied products has been investigated by several workers.¹ Some of the earlier investigations² have been extended by us with a view to having a better understanding of the nature of the molecular rearrangements in this series and the results are presented in this communication. We were specially prompted to put our results on record because of a very recent publication.³

α -Santalene gives, on ozonization or permanganate oxidation, the crystalline tricycloekasantalic acid (V), which can be conveniently reduced with lithium aluminum hydride to tricycloekasantalol (VI), previously prepared⁴ by reduction of the corresponding ester with sodium and alcohol. Hydration of VI with trichloroacetic acid and subsequent hydrolysis gave the crystalline diol (VII). Formic acid, dilute sulfuric acid, and trifluoroacetic acid⁵ were found to be less convenient for this purpose. The secondary nature of the ring hydroxyl group was confirmed by chromic acid oxidation of the diol to a crystalline ketocarboxylic acid (VIII) which on Huang-Minlon reduction gave dihydroekasantalic acid (IX).

On treatment with gaseous hydrogen chloride in methanolic solution, tricycloekasantalic acid was converted to the methyl ester (X). Somewhat contrary to the findings of Semmler,⁴ this chloro ester



(1) J. L. Simonsen and D. H. R. Barton, "The Terpenes," Vol. 3, 2nd ed., The University Press, Cambridge, 1952, p. 98; E. J. Corey, S. W. Chow, and R. A. Scherrer, *J. Am. Chem. Soc.*, **79**, 5773 (1957); V. Herout, V. Jarolim, and J. Pliva, *Collection Czech. Chem. Commun.*, **22**, 773 (1957).

(2) P. C. Guha and S. C. Bhattacharyya, *J. Indian Chem. Soc.*, **21**, 281, 271, 281, 333, 341, 377 (1944); S. C. Bhattacharyya, *J. Indian Chem. Soc.*, **21**, 339 (1944); *Sci. and Culture*, **13**, 158 (1947).

(3) A. Bhati, *Perfumery Essent. Oil Record*, **53**, 15 (1962); *J. Org. Chem.*, **27**, 2135 (1962).

(4) F. W. Semmler and K. Bode, *Chem. Ber.*, **40**, 1124 (1907).

(5) E. J. Corey, M. Ohno, S. W. Chow, and R. A. Scherrer, *J. Am. Chem. Soc.*, **81**, 6305 (1959).

on treatment with alcoholic potash gave a mixture of bicycloekasantalic acid (XII) and the starting material (V). However, when the chloro ester (X) was refluxed with sodium acetate and acetic acid, dehydrohalogenation took place very smoothly with the formation of the pure methyl ester of bicycloekasantalic acid (XI) in nearly quantitative yield. This conversion is of considerable importance as bicycloekasantalic acid is a suitable starting material for the synthesis of compounds of the β -santalol series.

One of the most stable compounds in the santalene series is the lactone (XIII), m.p. 103°, obtained by hydration of tricycloekasantalic acid with mineral acid. The structure of this lactone has been elucidated recently.^{3,6} The diol (XIV) obtained by lithium aluminum hydride reduction of the lactone, previously described as a liquid,⁶ has been obtained by us as a highly crystalline solid, m.p. 112°. The tertiary nature of one of the hydroxyl groups in the diol was confirmed by chromic acid oxidation since the original lactone was regenerated. The diol was readily dehydrated to an unsaturated primary alcohol. The infrared spectrum of this alcohol showed the presence of a hydroxyl group (3300 and 1050 cm^{-1}), a *gem*-dimethyl group (doublet at 1382 and 1366 cm^{-1}) and a trisubstituted double bond (1666, 842 cm^{-1}). Catalytic hydrogenation showed the presence of one double bond. Ozonolysis of the alcohol gave as the main product camphenilone (XVI), characterized by its infrared spectrum and semicarbazone.^{4,7} Permanganate oxidation of the unsaturated alcohol gave a dihydroxy acid which on further oxidation, preferably with periodate, gave camphenilone. The alcohol may therefore be represented as XV.

Experimental⁸

Tricycloekasantalic Acid (V).—The higher boiling fraction of East Indian sandalwood oil was oxidized with potassium permanganate according to the method of Semmler⁴ and purified by crystallizing two times from petroleum ether, m.p. 76°, $[\alpha]^{25D} +19.37^\circ$ (*c*, 6.84). The infrared spectrum showed absorption at 2640, 1700 ($-\text{COOH}$), 854, 820 cm^{-1} (tricyclene).

Anal. Calcd. for $\text{C}_{12}\text{H}_{18}\text{O}_2$: C, 74.19; H, 9.34. Found: C, 74.00; H, 9.50.

Tricycloekasantalol (VI).—Tricycloekasantalic acid (V 25 g.) in dry ether (50 ml.) was added to a slurry of lithium aluminum hydride (6 g.) in dry ether (300 ml.). The reaction mixture was refluxed for 2 hr. and worked up in the usual manner to give tricycloekasantalol (19 g.), b.p. 90°/0.5 mm., n^{20D} 1.4869, $[\alpha]^{25D} +14.18^\circ$ (*c*, 8.50), d^{20}_0 0.9804.

(6) A. Bhati, "Essential Oils and Aromatic Chemicals, A Symposium," Council of Scientific and Industrial Research, India, 1958 p. 138.

(7) P. S. Bailey, *Chem. Ber.*, **88**, 795 (1955).

(8) Melting points and boiling points are uncorrected. Microanalyses were carried out by Mr. Pansare and colleagues. Infrared spectra were taken using a Grubb Parson double-beam spectrophotometer and a Perkin-Elmer Infracord spectrophotometer (solid samples using Nujol mulls and liquids as liquid film). Optical rotations were determined in chloroform solution. Petroleum ether refers to the fraction boiling at 60–80°, unless otherwise stated.

The product showed characteristic absorption bands at 3240, 1059 ($-\text{OH}$), 3050, 853, 820 cm^{-1} (tricyclene).

Anal. Calcd. for $\text{C}_{12}\text{H}_{20}\text{O}$: C, 79.94; H, 11.18. Found: C, 80.23; H, 11.10.

2-Hydroxyborn-8-yl Ethanol (VII).—A mixture of tricycloekasantalol (VI, 16 g.) and trichloroacetic acid (35 g.) was stirred for 16 hr. at 80°. The reaction product was poured into water, extracted with ether, the extract washed with sodium bicarbonate solution and finally with water. The crude ester (26 g.) was saponified by refluxing with alcoholic potash (100 ml., 10%) for 3 hr. Work-up of the product yielded a viscous liquid which on fractional distillation using an efficient column gave unchanged VI along with a higher boiling residue (6.5 g.). This was chromatographed over neutral alumina (grade III, 120 g.). The ether-eluted fraction (0.82 g.) was crystallized from ether-petroleum ether mixture to yield the crystalline diol, m.p. 144°, $[\alpha]^{25D} +4.35^\circ$ (*c*, 2.07). Infrared absorption occurred at 3355, 1068, 1054 cm^{-1} ($-\text{OH}$); there was no absorption at 854 and 822 cm^{-1} characteristic of tricyclene.

Anal. Calcd. for $\text{C}_{12}\text{H}_{22}\text{O}_2$: C, 72.68; H, 11.18. Found: C, 72.61; H, 11.11.

2-Ketoborn-8-ylacetic Acid (VIII).—To the diol (VII, 0.50 g.) dissolved in glacial acetic acid (15 ml.), a solution of chromic anhydride (0.70 g.) in glacial acetic acid (14 ml.), and water (1 ml.) was added under cooling and stirring during 10 min. The reaction mixture was then heated on the water bath for 2 hr. Acetic acid was distilled under reduced pressure and any residual chromic acid was decomposed by addition of a few drops of ethanol. The product was extracted with ether and washed with water. The acid was separated by extraction with bicarbonate followed by acidification. On purification by sublimation, 0.18 g. of the acid was obtained, m.p. 126°, $[\alpha]^{25D} -1.65^\circ$ (*c*, 3.34). Infrared absorption (CaF_2 prism) occurred at 1732 (five-membered ring ketone) and 1710 cm^{-1} ($-\text{COOH}$).

Anal. Calcd. for $\text{C}_{12}\text{H}_{18}\text{O}_3$: C, 68.54; H, 8.63. Found: C, 68.52; H, 8.83.

Oxime, m.p. 146° (ethanol). *Anal.* Calcd. for $\text{C}_{12}\text{H}_{18}\text{NO}_3$: N, 6.22. Found: N, 5.81.

8-Bornylacetic Acid (IX).—2-Ketoborn-8-ylacetic acid (VIII, 0.502 g.) was reduced according to the procedure of Huang-Minlon using potassium hydroxide (0.49 g.), hydrazine hydrate (0.30 ml., 100%), and diethylene glycol (2.60 ml.). The reduction product (0.14 g.) after isolation was crystallized two times from ether-petroleum ether mixture, m.p. 120°, $[\alpha]^{25D} -2.81^\circ$ (*c* 4.80). Infrared peaks (CaF_2 prism) occurred at 1702 cm^{-1} ($-\text{COOH}$).

Anal. Calcd. for $\text{C}_{12}\text{H}_{20}\text{O}_2$: C, 73.43; H, 10.27. Found: C, 73.80; H, 10.60.

2-Chloroborn-8-ylacetic Acid Methyl Ester (X).—Tricycloekasantalic acid (V, 10 g.) in dry methanol (150 g.) was cooled in an ice-salt mixture, saturated with dry hydrogen chloride gas and set aside for 12 hr. The mixture was poured into water and extracted with ether. The ether layer was washed free of acid and dried (sodium sulfate). Removal of solvent yielded the ester (12.8 g.), b.p. 100–102°/0.2 mm., n^{20D} 1.4910, $[\alpha]^{25D} +29.27^\circ$, d^{25}_0 1.1110. The product showed infrared absorption at 1740, 1276, 1256, 1190, and 1174 cm^{-1} ($-\text{COOCH}_3$).

Anal. Calcd. for $\text{C}_{13}\text{H}_{21}\text{ClO}_2$: C, 63.77; H, 8.65; Cl, 14.48. Found: C, 66.12; H, 9.50; Cl, 13.80.

Bicycloekasantalic Acid Methyl Ester (XI).—A mixture of the hydrochloro ester (X, 10 g.), fused sodium acetate (10 g.), and glacial acetic acid (60 ml.) was refluxed at 140° for 3 hr. Water was added and the mixture was extracted with ether. The ethereal extract was washed with water, saturated sodium bicarbonate, solution, and finally with water, dried, and distilled to give 8.44 g. of the ester, b.p. 90°/0.25 mm., n^{25D} 1.4826, $[\alpha]^{25D} -32.18^\circ$, d^{25}_0 1.0280. Infrared peaks occurred at 1740, 1276, 1256, and 1190 cm^{-1} ($-\text{COOCH}_3$), 1660, 877 cm^{-1} ($>\text{C}=\text{CH}_2$).

Anal. Calcd. for $\text{C}_{13}\text{H}_{20}\text{O}_2$: C, 74.96; H, 9.68. Found: C, 75.10; H, 9.25.

Bicycloekasantalic Acid (XII).—The ester (XI, 7.74 g.) was saponified by refluxing with alcoholic potash (60 ml., 10%) for 2 hr. After working up, bicycloekasantalic acid (6.3 g.), b.p. 145–155°/0.8 mm. was crystallized from petroleum ether, m.p. 68°, $[\alpha]_D^{25}$ -42.69° (c, 4.68). Characteristic peaks occurred at 2685, 1703 (—COOH), 1658, 880 cm^{-1} ($>\text{C}=\text{CH}_2$) in the infrared region.

Anal. Calcd. for $\text{C}_{12}\text{H}_{18}\text{O}_2$: C, 74.19; H, 9.34. Found: C, 74.01; H, 9.52.

Lactone (XIII).—Tricycloekasantalic acid (V, 25 g.) was stirred under reflux with sulfuric acid (650 ml., 15%) according to the method of Semmler.⁴ The product was taken up in ether and washed free of acid with alkali. Removal of solvent and crystallization (ether–petroleum ether) yielded the lactone (20 g.), m.p. 103°, $[\alpha]_D^{25}$ +2.8° (c, 5.0). Infrared peaks in (CS_2) at 1770 cm^{-1} (γ -lactone), doublet at 1381 and 1361 cm^{-1} (*gem*-dimethyl group).

Anal. Calcd. for $\text{C}_{12}\text{H}_{18}\text{O}_2$: C, 74.19; H, 9.34. Found: C, 74.00; H, 9.50.

Diol (XIV).—The lactone (XIII, 13 g.) was reduced with lithium aluminum hydride (4.09 g.) in ethereal solution. The reaction product crystallized from ether–benzene as white glistening plates, m.p. 112°, $[\alpha]_D^{25}$ +1.94° (c, 5.00). Infrared peaks occurred at 3180, 1066, 1037, 979 cm^{-1} (—OH).

Anal. Calcd. for $\text{C}_{12}\text{H}_{22}\text{O}_2$: C, 72.68; H, 11.18. Found: C, 72.54; H, 11.20.

8-Camphenyl Ethanol (XV).—A mixture of the diol (XIV, 5.0 g.), fused sodium acetate (5.50 g.), and acetic anhydride (25 ml.) was refluxed for 4 hr. at 140°. The acetic anhydride was distilled, the residue diluted with water and warmed on the water bath for 15 min. After cooling, it was extracted with ether and washed with 5% sodium carbonate solution. Removal of solvent yielded the acetate (5.26 g.), b.p. 105–110°/0.5 mm., n_D^{25} 1.4749, α_D^{25} -8.94°. Infrared peaks occurred at 1726, 1240 (— OCOCH_3), 842 cm^{-1} ($>\text{C}=\text{CH}$ —).

Anal. Calcd. for $\text{C}_{14}\text{H}_{22}\text{O}_2$: C, 75.63; H, 9.97. Found: C, 75.13; H, 9.83.

Saponification of the above acetate (5.26 g.) with alcoholic potash (35 ml., 10%) yielded the alcohol (3.5 g.), b.p. 96–98°/2 mm., n_D^{25} 1.4963, $[\alpha]_D^{25}$ -9.49° (c, 9.30). Infrared spectrum showed absorption at 1666, 842 ($>\text{C}=\text{CH}$ —), doublet at 1382 and 1366 (*gem*-dimethyl) 3300, 1050 cm^{-1} (—OH).

Anal. Calcd. for $\text{C}_{12}\text{H}_{20}\text{O}$: C, 79.94; H, 11.18. Found: C, 79.56; H, 11.20.

Hydrogenation of XV.—The alcohol (XV, 0.2706 g.)

was hydrogenated in acetic acid (20 ml.) solution in the presence of Adams catalyst (40 mg.) at 20° and 708.2 mm. The amount of hydrogen taken up (39.50 ml.) corresponded to one double bond.

Ozonolysis of XV.—The alcohol (XV, 3.40 g.) in chloroform (75 ml.) was ozonized to completion. The solvent was removed *in vacuo* and the residual ozonide decomposed with water (10 ml.) on a water bath for 3 hr. The volatile portion showed a negative test for formaldehyde and acetone. The nonvolatile portion (1.80 g.) was extracted with ether and the ether extract washed with sodium bicarbonate solution. The neutral portion (1.50 g.) was chromatographed over alumina (27 g., neutral, grade III). The fraction (0.21 g.) eluted with petroleum ether (b.p. 40–60°) had a strong camphoraceous odor, b.p. 108° (bath)/20 mm., n_D^{25} 1.4702. The infrared spectrum showed strong absorption at 1726 (five-membered ring ketone), a doublet at 1382 and 1366 cm^{-1} (*gem*-dimethyl).

Anal. Calcd. for $\text{C}_9\text{H}_{14}\text{O}$: C, 78.21; H, 10.21. Found: C, 79.29; H, 10.73.

Semicarbazone, melted at 208° (ethanol); mixed melting point was not lowered when admixed with the semicarbazone of an authentic sample of camphenilone.

Anal. Calcd. for $\text{C}_{10}\text{H}_{17}\text{N}_3\text{O}$: C, 61.51; H, 8.78; N, 21.52. Found: C, 61.70; H, 9.10; N, 21.40.

Permanganate Oxidation of (XV).—The alcohol (XV, 2.0 g.) was stirred with water (60 ml.) at room temperature and potassium permanganate (8.04 g.) was added to this in several portions during 4 hr. The filtrate was freed from neutral material and concentrated to about 15 ml. It was acidified, extracted with ether, and dried (sodium sulfate). Removal of solvent yielded 0.872 g. of the acid which was esterified with diazomethane. The methyl ester, b.p. 160° (bath)/0.7 mm. showed infrared peaks at 3445 (—OH) and 1725 cm^{-1} (— COOCH_3).

Anal. Calcd. for $\text{C}_{13}\text{H}_{22}\text{O}_4$: C, 64.44; H, 9.15. Found: C, 63.80; H, 8.60.

Periodate Oxidation.—The dihydroxy ester from the above experiment (0.38 g.) was dissolved in ethanol (6 ml.). Sodium metaperiodate solution (9%, 6 ml.) was added to this dropwise at room temperature during 30 min. with stirring. After addition the contents of the flask were stirred for another 30 min. The solution was filtered and extracted with ether. After removal of solvent, the residue was chromatographed over alumina (10 g., neutral, grade III). The fraction (50 mg.) eluted with petroleum ether (b.p. 40–60°) was identified as camphenilone by its infrared spectrum and semicarbazone, m.p. 208°.

Degradation Products of Hygromycin B¹

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The isolation of D-talose and hyosamine (N-methyl-2-deoxystreptamine) from the antibiotic, hygromycin B, and the structure of hyosamine are reported. A tentative structure is suggested for hygromycin B₂.

The isolation and some of the physical and chemical properties of the antibiotic, hygromycin B, have been reported.³ It is an amorphous, poly-

hydroxy, dibasic compound having pK_a' values of 7.1 and 8.8 and is soluble in water, methanol, and ethanol but insoluble in most less polar solvents. There is one N-methyl group present, but O-methyl and C-methyl groups are absent. A molecular formula of $\text{C}_{15}\text{H}_{28}\text{N}_2\text{O}_8$ -10 was sug-

(1) A preliminary report of a portion of this work has been published. See P. F. Wiley and M. V. Sigal, Jr., *J. Am. Chem. Soc.*, **80**, 1010 (1958).

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(3) R. L. Mann and W. W. Bromer, *J. Am. Chem. Soc.*, **80**, 2714 (1958).