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TERPENOIDS—CXIII

SYNTHESIS OF α-SANTALENE, α-SANTALOL, α-SANTALIC ACID AND ALLIED PRODUCTS*

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Abstract—Earlier findings in the santalene–santalol series have been re-examined and extended. Tricycloekasantalic acid VI, the corresponding alcohol VIII, the aldehyde XIII and homotricycloekasantalic acid XI have been synthesized starting from V. The reaction of the methyl ester of XI with methyl magnesium iodide yields the crystalline tertiary alcohol, 13-hydroxy-α-santalene (X) dehydration of which affords a mixture of α-santalene (III) and the isomeric hydrocarbon XII, from which pure III is separated (TLC). The Wittig reagent prepared from ethyl-α-bromopropionate reacts with the aldehyde XIII to yield pure, crystalline α-santalic acid (XVI) the ethyl ester of which on reduction with LAH is converted to α-santalol (I), IR, UV and NMR spectral data are consistent with the structures.

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.[1] The synthesis of α-santalene and the allied compounds has been reported,[2-4] and recently, the stereochemistry of the santalols and the santalenes has been studied.[5] Some of the earlier findings[2,6] have now been re-examined and extended, leading to the synthesis of α-santalol, α-santalene, α-santalic acid and other related products. The results are presented in this communication. π-Bromotricyclene (V)[3] on condensation with ethyl potassium malonate, followed by hydrolysis and partial decarboxylation yields tricycloekasantalic acid[6] (VI) identical with an authentic sample[7] by comparison of the IR spectra and mixed m.p.

Methyl tricyclo-ekasantalate (VII) on reduction with LAH gives the corresponding primary alcohol–tricyclo ekasantalol (VIII). Bromination of VIII by phosphorous tribromide–pyridine or bromine in acetic acid gives the bromide IX in poor yields. A procedure based on the method of Meinwald *et al.*,[8] (treating the tosyl derivative

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of the alcohol with lithium bromide in acetone solution), furnishes tricyclo-ekasantalyl bromide IX in an excellent yield. The Grignard reagent formed from IX, combines with a mole of acetone to yield a tertiary alcohol 13-hydroxy-α-santalene (X). This tertiary alcohol was reported to be a liquid[1,2] but we obtained it as a crystalline solid, m.p. 60°.

The alcohol X can also be obtained by another method. Treatment of tricyclo-ekasantalyl bromide (IX) with potassium cyanide followed by hydrolysis gives homotricycloekasantalic acid (XI), a higher homologue of tricyclo-ekasantalic acid which was previously obtained[9] by degradative oxidation of α-santalyl acetic acid as a viscous liquid, but our compound is a crystalline solid, m.p. 55°. The methyl ester of homotricyclo-ekasantalic acid reacts with methyl magnesium iodide to yield X. The identity of the compounds obtained by the two different methods was confirmed by mixed m.p. and GLC and TLC analysis. Dehydration of X with thionyl chloride and pyridine yields a mixture of α-santalene (III) and an isomeric hydrocarbon (possibly XII). From the mixture pure α-santalene was separated by preparative TLC.[10]

In another route, the Wittig reaction was used for the syntheses in the α-santalene series. Tricyclo-ekasantalol (VIII) on oxidation with chromic acid in pyridine[11] gives tricyclo-ekasantalal (XIII, semicarbazone, m.p. 155°). The aldehyde XIII on reaction with carboethoxy isopropyl triphenyl phosphorane[12] (XIV) affords ethyl α-santalate (XV). Saponification of XV gives crystalline α-santalic acid (XVI), m.p. 70°, a compound previously described as a liquid.[2,13] The methyl ester of α-santalic acid on reduction with LAH gives α-santalol (I), recently prepared from α-santalene via selenium dioxide oxidation.[14] Attempts to prepare α-santalene from the aldehyde XIII and Wittig reagent[15] XVII were not successful.

The product obtained in the Wittig reaction (i.e. ethyl α-santalate, α-santalic acid etc.) has the desired *trans* configuration as evident from the UV[16,17], IR[18] and NMR[19] spectra. Cason[16] has shown that for *trans* methyl alkene acids the UV absorption has the ε value of 12,700, whereas the corresponding value for the *cis* isomers is around 9000. Jackman[19] has observed differences between the vinyl and allylic proton resonances in the NMR spectra of methyl tiglate (3·2) and methyl angelate (3·95). The α-santalic acid obtained has the ε value of 12,760 and its methyl ester presents vinylic proton absorption at 3·22 τ. These reasons conclusively show that *trans* isomer is exclusively formed in the Wittig reaction. α-Santalol obtained by the LAH reduction of methyl α-santalate showed NMR signals at 9·15, 8·97, 8·45, 8·37 and 6·12 τ and a multiplet centred at 4·63 τ. The NMR data rules out the possibility of the trisubstituted double bond being reduced in the LAH reduction.

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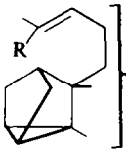
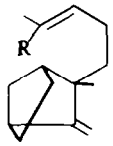
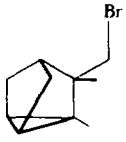
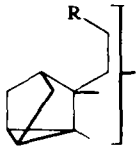


I, R = CH_2OH
III, R = Me
XV, R = COOEt
XVI, R = COOH

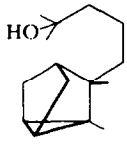


II, R = CH_2OH
IV, R = Me

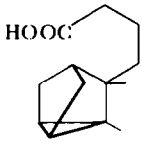




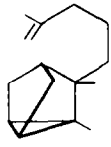
VI, R = COOH
VII, R = COOMe
VIII, R = CH_2OH
IX, R = CH_2Br
XIII, R = CHO



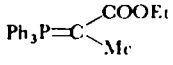
X



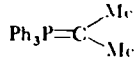
XI



XII



XIV



XVII

EXPERIMENTAL

M.ps and b.ps are uncorrected. Rotations unless otherwise mentioned were taken in $CHCl_3$ soln. IR spectra were determined on a Perkin–Elmer Infracord Spectrophotometer. The NMR spectra were taken in CCl_4 soln using TMS as internal standard on a Varian A-60 spectrometer. Compounds were tested for purity by GLC and TLC. *Tricycloekasantalic acid (VI)*[6]: Clean K (0·78 g) was dissolved in abs EtOH (20 ml) in a 3-necked flask fitted with a reflux condenser and a $CaCl_2$ guard tube. Malonic ester (3·2 g) was added and the mixture heated on the water bath for ½ hr. The EtOH was removed under reduced press and Na-dried xylene (18 ml) containing V (1·81 g) was added. The mixture was heated at 170–190° for 3 hr. From the filtered soln xylene was removed by distillation under diminished press. The crude teresantalyl malonic ester was hydrolysed with 10% alcoholic KOH and then just acidified with dil. HCl and extracted with ether. The impure oily liquid obtained from the etheral extract was decarboxylated by heating in an oil bath at 180–200°/100 mm. After the evolution of CO_2 had ceased, the reaction product was distilled *in vacuo*; crystallization of the crude distillate from light pet ether gave pure tricycloekasantalic acid m.p. 75–76°; $[\alpha]_D$ +18·5° (*c*, 4·63); IR bands at 3058, 878, 855, 821 (tricyclene system); 2667, 1704 cm^{-1} (lit.[7] m.p. 76°). $[\alpha]_D$ +19·37°. (Found: C, 74·42; H, 9·10. Calc. for $C_{12}H_{18}O_2$: C, 74·19; H, 9·34%.)

Methyl ester of tricyclo-ekasantalic acid (VII). Compound VI was esterified with diazomethane to give the methyl ester, b.p. 90°/0·5 mm; $[\alpha]_D$ +17·56° (*c*, 5·24); IR bands at 3058, 1745, 877, 854, 821 cm^{-1}; NMR signals at 9·18, 8·95 and 6·42 τ. (Found: C, 74·85; H, 9·72. Calc. for $C_{13}H_{20}O_2$: C, 74·96; H, 9·72%.)

Tricycloekasantalol VIII. Compound VII (10 g) in ether (80 ml) was reduced by adding to a slurry of LAH (2 g) in anhyd ether (200 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 VIII (8·5 g); b.p. 95°/0·6 mm, n_D^{29} 1·4855, $[\alpha_D^{27}]$

+13·85° (*c*, 6·31). IR bands at 3400, 3050, 1050, 850 cm^{-1}, NMR signals at 9·15, 8·93 τ and a triplet at 6·65 τ (lit.[7] b.p. 90°/0·5 mm, $[\alpha]_D$ +14·18°). (Found: C, 79·75, H, 11·00. Calc. for $C_{12}H_{20}O$: C, 79·94; H, 11·18%.)

Acetylation of VIII gives the acetate derivative b.p. 105° (bath)/0·7 mm. IR bands at 3058, 1748, 1246, 868, 850, 822 cm^{-1}. $[\alpha]_D$ (neat) +10·92° NMR signals at 9·15, 8·93 τ and a triplet centred at 6·65 τ. (Found: C, 75·9; H, 10·15. $C_{14}H_{22}O_2$ requires: C, 75·63; H, 9·97%.)

Tricyclo-ekasantalyl bromide (IX). The alcohol VIII (10 g) was dissolved in pyridine (50 ml). *p*-Toluenesulphonyl chloride (11·2 g) was added during 20 min to the cooled soln (−8°) and the reaction mixture stirred for 5 hr at −8° to −2°, poured into ice-cold water, and acidified with 3N HCl. The aqueous soln was extracted with ether, washed with 3N HCl, water, dil Na_2CO_3 aq and water. The ethereal soln was dried and then evaporated leaving a viscous oil, exhibiting typical tosylate absorption at 1351, 1190 cm^{-1} in the IR spectrum.

The crude tosylate was dissolved in anhyd acetone (15 ml), LiBr (10 g) was added, and the mixture stirred and refluxed for 90 min. The acetone was evaporated and the residue diluted with water and extracted with pet ether. The organic layer was dried over $MgSO_4$. Removal of the solvent yielded IX (80%), b.p. 81°/1 mm, $[\alpha]_D$ (neat) +5·53°; IR bands at 3050, 872, 852, 820 cm^{-1}. (Found: Br, 32·63. Calc. for $C_{12}H_{19}Br$: Br, 32·91%.)

13-*Hydroxy-α-santalene* X—Tricyclo-ekasantalyl bromide (5 g) in abs ether (100 ml) was added to Mg (5 g) in ether (20 ml) during 5 hr. The mixture was heated at reflux for an additional 2 hr. The Grignard reagent was filtered through a glass wool plug into dry acetone (1·5 ml) in ether (10 ml). The mixture was stirred for 2 hr and afterwards allowed to stand at room temp for 96 hr. The Grignard complex was decomposed with sat NH_4Cl aq. The ether soln was washed with water and dried over anhyd Na_2SO_4. The crude product after evaporation of the solvent was chromatographed over neutral alumina (Gr. III). Compound X was found in the late pet ether fractions. Removal of the solvent gave the solid alcohol, which was purified by crystallization from pet ether and finally by sublimation, m.p. 60°; $[\alpha]_D^{27}$ +5·01° (*c*, 10·01); IR bands at 3400, 3050, 1085, 852, 821 cm^{-1}. NMR signals at 9·18, 9·0 and 8·87 τ (lit.[2] b.p. 150–155°/5 mm). (Found: C, 81·23; H, 11·79. Calc. for $C_{15}H_{26}O$: C, 81·23; H, 11·91%.)

Homotricycloekasantalic acid XI. The bromide IX (5 g) was refluxed with KCN (2 g) in rectified spirit (50 ml) for 10 hr. The solvent was removed and the crude cyanide hydrolysed by refluxing with 10% alcoholic KOH (50 ml) for 12 hr. The reaction mixture was poured in ice-cold water and the aqueous layer acidified. The separated solid was filtered off, washed with water, dried and crystallized from pet ether, m.p. 55°; $[\alpha]_D$ +10·15° (*c*, 7·03). IR bands at 3058, 2667, 1724, 856, 821 cm^{-1}. (Found: C, 75·73; H, 9·92. $C_{13}H_{20}O_2$ requires: C, 75·01; H, 9·63%.)

Methyl homo-tricylcoekasantalate has b.p. 120° (bath)/1 mm; $[\alpha]_D$ +9·25° (*c*, 8·93), IR bands at 3058, 1760, 862 cm^{-1}. NMR signals at 9·18, 9·0 and 6·4 τ (lit.[9] b.p. 140–145°/15 mm). (Found: C, 75·68; H, 10·05. $C_{14}H_{22}O_2$ requires: C, 75·63; H, 9·97%.)

Conversion of methyl homo-tricycloekasantalate to X. The Grignard reagent was prepared by adding a soln of MeI (2 g) in dry ether (10 ml) to a stirred suspension of Mg (0·3 g) in dry ether (10 ml). The mixture was refluxed till most of the Mg dissolved and then cooled externally. A soln of methyl homotricycloekasantalate (3 g) in dry ether (15 ml) was added dropwise and the reaction mixture refluxed for 4 hr. The complex was decomposed by the addition of sat NH_4Cl aq. The organic layer was washed with water and dried. The crude product on evaporation of the solvent, was purified by chromatography, m.p. 60°, underpressed with the sample prepared from IX by Grignard reaction.

Dehydration of X *to* III. 13-Hydroxy α-santalene (1 g) was dissolved in dry pyridine (10 ml) and cooled in ice-salt mixture. Freshly distilled $SOCl_2$ (1·8 ml) was added dropwise in the course of 20 min. After stirring for 90 min, the reaction mixture was poured into water and extracted with pet ether (40–60°). The organic layer was washed with water, tartaric acid soln and finally with water and dried. The hydrocarbon mixture was chromatographed over neutral alumina (Gr. I). The TLC of the fraction eluted with pet ether showed 2 spots. From the hydrocarbon mixture pure α-santalene (GLC, TLC) was separated by preparative TLC on $AgNO_3$ impregnated silica gel, b.p. 115°/7 mm. IR bands at 3050, 1670, 858, 840 cm^{-1}, $[\alpha]_D$ +16·15° (*c*, 5·35); lit. b.p. 117°/7 mm, $[\alpha]_D$ +12·5° (natural)[20]; b.p. 116–120°/8 ± 2 mm; $[\alpha]_D$ +18·4° (synthetic)[3]. (Found: C, 87·91; H, 11·65. Calc. for $C_{15}H_{24}$: C, 88·15; H, 11·84%.)

Oxidation of VIII *to* XIII. A soln of VIII (3 g) in pyridine (30 ml) was combined with CrO_3 (3·1 g) in pyridine (30 ml). The flask was stoppered; the contents were mixed thoroughly and allowed to stand at

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

room temp overnight. The reaction mixture was poured into water and extracted with 3 portion of benzene–ether (1 : 1) using filtration through supercel to break the emulsion. The combined organic soln was washed with water, dil acid and again with water, dried over anhyd $MgSO_4$. Removal of the solvent yielded XIII, b.p. 110–115° (bath)/1 mm; n_D 1·4856; $[\alpha]_D$ +12·85° (*c*, 5·0). IR bands at 3060, 2740, 1742, 858, 825 cm^{-1}. (lit. b.p. 109–110°/10 mm, $[\alpha]_D$ + 13·30). (Found: C, 80·04; H, 10·28. Calc for $C_{12}H_{18}O$: C, 80·85; H, 10·18%.) Semicarbazone, m.p. 155°. (Found: N, 17·86. Calc. for $C_{13}H_{21}ON_3$: N, 18·29%.)

Preparation of Wittig reagent XIV.[12] The reaction of triphenyl phosphine (6 g) and ethyl α-bromo propionate (4·1 g) in dry benzene (30 ml), followed by treatment of the crude phosphonium salt with KOH aq yielded the crude XIV (3 g). Recrystallization from AcOEt–pet ether gave pure phosphorane, m.p. 156°.

Ethyl α-santalate XV. To a soln of XIV (2 g) in dry benzene (15 ml), XIII (1 g) was added dropwise and with stirring and the resulting mixture refluxed for 20–25 hr. The soln was concentrated and the residual soln diluted with pet ether (100 ml), filtered to remove the triphenyl phosphine oxide, and the ppt washed with pet ether (25 ml). The combined organic solns were concentrated and distillation of the residue afforded ethyl α-santalate (0·6 g), b.p. 125°/0·5 mm; $[\alpha]_D$ +18·83° (*c*, 2·3). IR bands at 3058, 1725, 1660, 860, 828 cm^{-1} (Found: C, 77·89; H, 9·86. $C_{17}H_{26}O_2$ requires: C, 77·82; H, 9·99%.)

α-Santalic acid XVI. Saponification of ethyl α-santalate with 10% alcoholic KOH afforded α-santalic acid as a viscous oil. Crystallization from pet ether gave crystalline α-santalic acid, m.p. 70°, IR bands at 3058, 2665, 1700, 1660, 860, 829 cm^{-1}. λ_{max}^{EtOH} 211 mμ; ε value 12,760; $[\alpha]_D$ +17·95° (*c*, 6·73) (lit. b.p.[13] 193°/9 mm, n_D^{20} 1·5055. b.p.[2] 171–173°/1 mm). (Found: C, 76·65; H, 9·50. Calc for $C_{15}H_{22}O_2$: C, 76·88; H, 9·46%.)

Reduction of α-santalic acid over Pd/C gave dihydro α-santalic acid, b.p. 180° (bath)/0·1 mm; $[\alpha]_D$ +6·21° (*c*, 11·23); IR bands at 3060, 2665, 1725, 860, 829 cm^{-1}. (Found: C, 76·10; H, 10·14. $C_{15}H_{24}O_2$ requires: C, 76·22; H, 10·24%.)

Esterification of α-santalic acid with diazomethane gave methyl α-santalate, b.p. 120°/2 mm; $[\alpha]_D$ +18·57° (*c*, 2·33); IR bands at 3058, 1725, 1660, 860, 828 cm^{-1}. NMR signals at 9·15, 9·0, 8·2, 6·34 τ and a multiplet centred at 3·22 (lit.[13] b.p. 146°/9 mm, n_D^{20} 1·4910). (Found: C, 77·69; H, 9·84. Calc for $C_{16}H_{24}O_2$: C, 77·37; H, 9·74%.)

α-Santalol (I). Methyl α-santalate (0·5 g) in ether (5 ml) was reduced by adding to a slurry of LAH (0·1 g). Working up of the reaction product yielded α-santalol, b.p. 140° (bath)/0·2 mm; $[\alpha]_D$ +13·5° (*c*, 2·80) IR bands at 3380, 3100, 860, 827 cm^{-1}. (lit.[20] natural b.p. 145°/4 mm, $[\alpha]_D$ +17°). (Found: C, 81·27; H, 11·29. Calc for $C_{15}H_{24}O$: C, 81·76; H, 10·98%.)