Terpenoids. IL. A Study of the Prins Reaction on the Isopropylidene-Type Double Bonds

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Contribution No. 645 from the National Chemical Laboratory, Poona, India

Received December 26, 1963

The addition of formaldehyde to isopropylidene-type trisubstituted olefinic linkages (Prins reaction) present in α- and β-santalenes and some simpler compounds has been studied, and the structures of the resulting primary alcohols have been elucidated. The tricyclene system undergoes rearrangement to the camphene system during the Prins reaction.

The Prins reaction has been applied to the preparation of useful oxygenated products from several monoterpenes and acyclic olefins.[1-3] With the ultimate object of applying the Prins reaction to the synthesis of oxygenated derivatives of possible perfumery value from α- and β-santalenes (XIV and XVIII), obtained as by-products during the distillation of Indian sandalwood oil, the Prins reaction was initially applied to model compounds, tricyclene (I) and camphene (II) representing the skeletal part of santalenes, and 2,6-dimethyloctene-2 (V) and 2-methylheptene-2 (X) representing the isopropylidene side chain. The reaction was studied under two different conditions: (i) by stirring the mixture of olefin and paraformaldehyde in equimolecular proportions in dry chloroform in the presence of anhydrous stannic chloride at room temperature, and (ii) by refluxing the olefin with equimolecular proportions of paraformaldehyde in acetic acid followed by saponification of the resulting acetate to the corresponding alcohol.

Both tricyclene (I) and camphene (II) when condensed with paraformaldehyde in refluxing acetic acid yielded an identical unsaturated acetate which on saponification gave the corresponding monoethynoid alcohol, 8-camphenylcarbinol ($C_{11}H_{18}O$) of known structure[4] (III), the product from tricyclene being formed by an initial rearrangement of the tricyclene to the camphene system. The identity of the alcohols obtained was proved by elemental analysis, hydrogenation, superimposable infrared spectra, and formation of camphenilone (IV) on oxidation. However, as expected, the alcohol obtained from camphene was optically active and that from tricyclene inactive. The cleavage of the cyclopropane ring in tricyclene during the Prins reaction is interesting. Δ^3-Carene[5] under identical conditions gives a product in which the cyclopropane ring remains intact.

2,6-Dimethyloctene-2 (V) was obtained as a single product by the Huang-Minlon reduction of citronellal.[6] Infrared spectrum and ozonolysis showed that the isopropenyl-type isomer was absent. On condensation with formaldehyde at room temperature or under thermal conditions, this hydrocarbon gives mainly an unsaturated alcohol ($C_{11}H_{22}O$) represented by the structure VI. Consistent with its structure it shows characteristic infrared bands at 3366 and 1038 ($-CH_2OH$), and 3086, 1639, and 891 ($>C{=}CH_2$) cm.$^{-1}$, and absorbs 1 mole of hydrogen on hydrogenation. On ozonolysis it yielded formaldehyde and the keto alcohol (VII) which gave the hydroxy acid (VIII) on hypobromite oxidation. The keto alcohol (VII) on oxidation with sodium dichromate and sulfuric acid in aqueous medium gave acetic acid and 4-methylcaproic acid (IX), the latter being obtained also by oxidation of the keto alcohol (VII) by chromic anhydride in acetic acid. The odor of the alcohol (VI) is reminiscent of that of lavandulol (XIIIa) to which it is closely related structurally.

In the same way 2-methylheptene-2 (X), obtained by the Huang-Minlon reduction of methylheptenone, on condensation with formaldehyde yielded 2-isopropenylhexanol (XI) with infrared bands at 1631 and 889 ($>C{=}CH_2$), and 3311 and 1042 ($-CH_2OH$). Ozonolysis yielded formaldehyde and the keto alcohol (XII) which on oxidation with sodium dichromate–sulfuric acid in aqueous medium yielded *n*-valeric acid (XIII) and acetic acid.

In conformity with the model compounds, α-santalene (XIV) on condensation with formaldehyde at room temperature in the presence of stannic chloride catalyst yielded mainly a dextrorotatory unsaturated alcohol ($C_{16}H_{26}O$), along with small amounts of oxides. The structure of the alcohol was established as 2-isopropenyl-3-(π)-tricyclylpropanol (XV) from infrared spectra and degradative studies. It showed infrared bands at 3000, 1639, and 888 ($>C{=}CH_2$ in an aliphatic chain); 877, 852, and 822 (π-substituted tricyclene system)[7]; and 3350 and 1044 ($-CH_2OH$) cm.$^{-1}$. Perbenzoic acid titration as well as catalytic hydrogenation under mild conditions indicated the presence of one double bond. The dihydro product showed infrared absorption at 3067, 877, 854, and 820 (π-substituted tricyclene system), and a doublet at 1383 and 1366 [$-CH(CH_3)_2$] cm.$^{-1}$. On ozonolysis it yielded formaldehyde and the keto alcohol (XVI) in which the keto group is present as methyl ketone as indicated by the bands at 1727 and 1361 cm.$^{-1}$ and a positive iodoform reaction. On oxidation by sodium dichromate–sulfuric acid in aqueous medium, the keto alcohol, consistent with its structure, yielded acetic acid and some products of skeletal rearrangement. It gave tricycloekasantalic acid (XVII) and acetic acid on oxidation by aqueous permanganate. The oxidation appears to proceed *via* a β-keto aldehyde–acid which enolizes and then is cleaved and further degraded to tricycloekasantalic acid and acetic acid. The alcohol (XV) on direct oxidation by permanganate also yields the acid (XVII). Owing to the presence of

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[1] E. Arundale and L. A. Mikeska, *Chem. Rev.*, **51**, 505 (1952).

[2] H. Grutter and H. Schinz, *Helv. Chim. Acta*, **35**, 505 (1952).

[3] N. C. Yang, D. D. H. Yang, and C. B. Ross, *J. Am. Chem. Soc.*, **81**, 133 (1959).

[4] G. Langlois, *Ann. chim.* (Paris), **12**, 256 (1919).

[5] G. Ohloff, H. Farnow, and W. Philip, *Ann. Chem.*, **61B**, 43 (1958).

[6] H. E. Eschinazi, *J. Org. Chem.*, **26**, 3072 (1961); Huang-Minlon, *J. Am. Chem. Soc.*, **68**, 2487 (1946).

[7] S. Ramaswami, S. K. Ramaswami, and S. C. Bhattacharyya, unpublished results.

the cyclopropane ring system, compounds of the α-santalene series, though stable towards alkali, undergo molecular rearrangements in the presence of acids.

On condensation with formaldehyde in refluxing acetic acid, α-santalene (XIV) yields mainly an unsaturated acetate, which on saponification affords the corresponding alcohol (XIX). This was separated from small amounts of oxides and diols by fractionation followed by chromatography. The hydrocarbon recovered from the reaction was found to be similar to β-santalene except in its rotation. The alcohol ($C_{16}H_{26}O$) showed infrared bands at 3390 and 1053 ($-CH_2OH$); 3096, 1656, 889, and 879 ($>C{=}CH_2$); and no characteristic absorption for π-substituted tricyclene system. The levorotation of the alcohol also suggested the absence of the tricyclene skeleton. Catalytic hydrogenation revealed the presence of two double bonds. Ozonolysis gave formaldehyde, thus confirming the presence of the methylenic double bond. This showed that a rearrangement of the tricyclene skeleton to the camphene system has occurred under the conditions of the reaction.

β-Santalene (XVIII) under similar conditions yielded the same alcohol (XIX) as the major product. Catalytic hydrogenation of the alcohol showed two double bonds. Ozonolysis yielded formaldehyde and the keto alcohol (XX) which showed infrared bands at 1724 ($>C{=}O$), 1364 (CH_3CO-), and 3521 and 1045 ($-CH_2OH$) cm.$^{-1}$. The keto alcohol (XX) gave a positive iodoform test. On oxidation with sodium dichromate and sulfuric acid in aqueous medium, acetic acid and camphenilonylacetic acid (XXI),[8] together with traces of dimethylnorcampholidylacetic acid (XXII), were obtained and identified by paper chromatography. Oxidation by chromic acid in acetic acid also afforded camphenilonylacetic acid.

Thus, on thermal condensation, both α- and β-santalenes yield mainly the same alcohol (XIX). Under the conditions of the reaction, the tricyclic α-santalene rearranges to the bicyclic β-santalene system. One molecule of formaldehyde may add either to the trisubstituted double bond in the side chain to give the alcohol XIX or to the exocyclic double bond in the β-santalene ring to give alcohol XXIV. The product contained two methylenic double bonds as indicated by the infrared bands at 899 ($>C{=}CH_2$ in the side chain) and 879 cm.$^{-1}$ ($>C{=}CH_2$ in the five-membered ring). Structure XXIV does not contain any methylenic double bond, whereas XIX accommodates two such bonds, one originally present in β-santalene, and the other formed by migration of the trisubstituted double bond in the side chain to the adjacent position. Results of ozonolysis also confirm this. This evidence is consistent with structure XIX for the alcohol.

Experimental

Melting points and boiling points are uncorrected. Rotations were determined in chloroform solution. Petroleum ether refers to the fraction boiling at 60–80°. Infrared spectra were measured on a Perkin-Elmer Model 137B Infracord spectrophotometer, liquid compounds as liquid film, and solid compounds as Nujol mulls. V.p.c. analyses were carried out on a Perkin-Elmer vapor fractometer 154D, using a 'P' column (succinic acid polyester of diethylene glycol) and hydrogen as carrier gas at 15 lb./sq. in. The solvent system butanol–ethanol–water (40:10:50) upper phase and ammonia (1 ml.) was used for paper chromatography.

Tricyclene (I) was prepared from *d*-camphor[9] and purified by chromatography on neutral alumina (grade I) and sublimation as a white solid, m.p. 68°; infrared bands at 3069, doublet at 1377 and 1359, 873, 856, and 818 cm.$^{-1}$.

8-Camphenylcarbinol (III) from Tricyclene.—Tricyclene (15 g., 0.11 mole) was refluxed with paraformaldehyde (3.6 g., 0.12 mole) and acetic acid (200 ml.) for 24 hr. in a flask fitted with a fractionating column. Removal of the solvent under vacuum and work-up according to the conventional procedure gave the acetate ester (7.9 g.) which was saponified by alcoholic potash (140 ml., 0.5 *N*) to yield 8-camphenylcarbinol (5.62 g.) as a colorless liquid, b.p. 80–85° (0.15 mm.), $n^{27}D$ 1.4977; infrared bands at 3333, 1669, doublet at 1375 and 1355, 1031, 843, and 812 cm.$^{-1}$. It absorbed 1 mole of hydrogen in acetic acid solution in the presence of Adams catalyst.

Anal. Calcd. for $C_{11}H_{18}O$: C, 79.46; H, 10.92. Found: C, 79.27; H, 10.54.

Camphenilone (IV).—The alcohol (III, 2.06 g.) was oxidized by potassium permanganate (10.18 g.) in aqueous medium. Work-up yielded, in the neutral portion, camphenilone (0.61 g.) as a liquid, b.p. 104–108° (bath) at 20 mm.; infrared bands at 1726, doublet at 1382, and 1366 cm.$^{-1}$; semicarbazone, white needles (ethanol), m.p. and m.m.p. (with an authentic sample) 208°.

8-Camphenylcarbinol (III) from camphene (II) was prepared according to the procedure described in the literature,[4] b.p. 97–100° (7 mm.), $[\alpha]^{28}D$ +22.8°, $n^{26}D$ 1.5016. The infrared spectrum was superimposable with that of the alcohol obtained from tricyclene. Analysis, hydrogenation, and oxidation gave similar results.

2,6-Dimethyloctene-2 (V).—Citronellal was purified by the bisulfite method (100% by oximation), b.p. 73–75° (7 mm.), $[\alpha]^{28}D$ +14.81° (*c* 8.17), $n^{24}D$ 1.4474; infrared bands at 2717, 1724, 1400, and 828 cm.$^{-1}$. V was made by reducing citronellal (46.47 g.) according to the Huang-Minlon method by treating with hydrazine hydrate (30 ml., 85%), diethylene glycol (300 ml.), and potassium hydroxide (52 g.). The hydrocarbon (34.90 g.) was purified by fractionation and chromatography followed by distillation over sodium, b.p. 163° (710 mm.), $n^{24}D$ 1.4310, $[\alpha]^{24}D$ +9.2° (*c* 11.2). V.p.c. analysis showed essentially one peak; infrared bands at 1661 and 833 cm.$^{-1}$.

Anal. Calcd. for $C_{10}H_{20}$: C, 85.63; H, 14.37. Found: C, 85.70; H, 14.77.

The Prins Reaction on 2,6-Dimethyloctene-2 (V).—A mixture of the hydrocarbon (V, 14.06 g., 0.10 mole), paraformaldehyde (3.56 g., 0.12 mole), and glacial acetic acid (230 ml.) was refluxed for 24 hr. in a flask fitted with a column. Work-up yielded the acetate ester (25 g.) which was saponified by alcoholic potash (100 ml., 2 *N*) to yield 2-isopropenyl-5-methylheptanol (VI, 19 g.). Chromatography on neutral alumina (500 g., grade II) yielded small quantities of oxides in the fractions eluted with petroleum ether. Pure alcohol (7.6 g.) was eluted in the benzene fractions as a colorless liquid with a pleasant odor, b.p. 123–136° (19 mm.), $[\alpha]^{24}D$ +6.82° (*c* 7.04), $n^{24}D$ 1.4540. V.p.c. analysis showed essentially a single peak; infrared bands at 3366, 3086, 1639, 1038, and 891 cm.$^{-1}$.

Anal. Calcd. for $C_{11}H_{22}O$: C, 77.58; H, 13.02. Found: C, 77.36; H, 13.00.

Catalytic Hydrogenation of the Alcohol (VI).—The alcohol (0.22 g.) was hydrogenated in acetic acid (15 ml.) in the presence of Adams catalyst (38 mg.). The volume of hydrogen absorbed (129 ml. at 17° and 712 mm.) corresponded to 0.91 mole or one double bond.

Ozonolysis of the Alcohol (VI).—The alcohol (4.89 g.) was ozonized in chloroform (100 ml.) at 0° to completion (9 hr.). The ozonide, after removal of solvent *in vacuo* was decomposed with water (60 ml.). The volatile portion gave the dimedone derivative of formaldehyde, m.p. and m.m.p. 189°. The nonvolatile portion was extracted with ether, washed with sodium bicarbonate solution, and dried (Na_2SO_4). Removal of solvent yielded the keto alcohol (VII, 4.66 g.), b.p. 135–140° (bath) at 11 mm., $n^{30}D$ 1.4433, $[\alpha]^{30}D$ +5.7° (*c* 4.04); infrared bands at 3570, 1718, 1355, and 1036 cm.$^{-1}$.

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[8] L. Ruzicka and A. Roethlisberger, *Helv. Chim. Acta*, **18**, 439 (1935).

[9] H. Meerwein and K. van Emster, *Ber.*, **53**, 1815 (1920).

Anal. Calcd. for $C_{10}H_{20}O_2$: C, 69.72; H, 11.70. Found: C, 69.98; H, 11.87.

It gave iodoform (m.p. and m.m.p. 120°) when treated with iodine and sodium hydroxide in dioxane solution.

Oxidation of the Keto Alcohol (VII) by Hypobromite.—The keto alcohol (1 g.) in dioxane (50 ml.) was treated with sodium hypobromite prepared from bromine (1.80 ml.) and sodium hydroxide (4.25 g.) in water (50 ml.) under cooling. The excess hypobromite was decomposed with sodium bisulfite. Work-up yielded the hydroxy acid (VIII, 0.74 g.), b.p. 175–190° (bath) at 3 mm.; infrared bands at 3448, 2632, 1709, 1031, and 938, cm.$^{-1}$.

Anal. Calcd. for $C_9H_{18}O_3$: C, 62.04; H, 10.41. Found: C, 61.25; H, 9.28.

A better analysis was not obtained.

Oxidation of the Keto Alcohol (VII) by Dichromate–Sulfuric Acid.—The keto alcohol (1 g.) was stirred with water (25 ml.) and powdered sodium dichromate (2.12 g.) under cooling, and sulfuric acid (2 ml.) was added dropwise. The mixture was stirred at room temperature for 8 hr. and at 80° for 2 hr. In one experiment, the reaction mixture was subjected to steam distillation at this stage, and the distillate was found to contain acetic acid by paper chromatography. In another experiment, the reaction mixture was diluted and extracted with ether. The acid portion (0.20 g.), obtained by bicarbonate extraction, was identified as 4-methylcaproic acid (IX), b.p. 180–190° (bath) at 23 mm., $n^{30}\mathrm{D}$ 1.4230, $[\alpha]^{30}\mathrm{D}$ +7.91° (*c* 3.16), equivalent weight 129 (theoretical, 130), R_f 0.75 (compared against an authentic sample prepared by ozonization of 2,6-dimethyloctene-2 in chloroform); infrared bands at 2632, 1695, 1403, and 934 cm.$^{-1}$. The infrared spectrum was superimposable with that of an authentic sample.

Anal. Calcd. for $C_7H_{14}O_2$: C, 64.58; H, 10.84. Found: C, 64.39; H, 10.72.

The amide, white plates (ethanol), had m.p. and m.m.p. (with an authentic sample) 92°.

Anal. Calcd. for $C_7H_{15}NO$: N, 10.84. Found: N, 10.84.

The oxidation of the keto alcohol (VII, 1.09 g.) by chromic anhydride (1.11 g.) in acetic acid medium (10 ml.) also led to 4-methylcaproic acid (0.30 g.).

The Prins Reaction on 2,6-Dimethyloctene-2 (V) at Room Temperature.—A mixture of 2,6-dimethyloctene-2 (14.20 g., 0.10 mole), paraformaldehyde (3.02 g., 0.10 mole), dry chloroform (30 ml.), and anhydrous stannic chloride (0.50 ml.) was stirred at room temperature for 40 hr. Work-up, as described subsequently in the case of santalenes, yielded the crude product (13.45 g.) which was chromatographed on neutral alumina (280 g., grade II). The fractions eluted with petroleum ether consisted of oxides (5.42 g.); the alcohol (VI, 3.96 g.) was eluted in the benzene fractions.

2-Methylheptene-2 (X).—Methylheptenone (75 g., b.p. 99–100° at 65 mm., $n^{27}\mathrm{D}$ 1.4440) was reduced according to the Huang-Minlon procedure by treatment with hydrazine hydrate (65 ml., 85%), diethylene glycol (600 ml.), and potassium hydroxide (110 g.). 2-Methylheptene-2 (50 g.) was purified by chromatography on neutral alumina (1000 g., grade I) as a colorless liquid, b.p. 100–120° (710 mm.), $n^{29}\mathrm{D}$ 1.4153; infrared bands at 1667, 843, and 830 (>C=CH–) cm.$^{-1}$.

Anal. Calcd. for C_8H_{16}: C, 85.63; H, 14.37. Found: C, 86.20; H, 14.50.

2-Isopropenylhexanol (XI).—A mixture of 2-methylheptene-2 (X, 33.4 g., 0.30 mole), paraformaldehyde (1.50 g., 0.35 mole), and acetic acid (500 ml.) was refluxed for 26 hr. to yield the acetate ester (50 g.) which on saponification with alcoholic potassium hydroxide (300 ml., 2 *N*) followed by chromatography on neutral alumina (510 g., grade II) yielded the pure alcohol (XI, 15.10 g.) in the benzene fractions, b.p. 133–143° (bath) at 102 mm., $n^{26}\mathrm{D}$ 1.4500; infrared bands at 3311, 3030, 1631, 1042, and 889 cm.$^{-1}$.

Anal. Calcd. for $C_9H_{18}O$: C, 75.99; H, 12.76. Found: C, 75.97; H, 12.80.

Ozonolysis of the Alcohol (XI).—The alcohol (3.03 g.) was ozonized in chloroform (75 ml.) at 0° to completion (8 hr.). Decomposition with water (60 ml.) yielded formaldehyde (dimedone derivative, m.p. and m.m.p. 189°) and the keto alcohol (XII, 2.88 g.), b.p. 169–175° (bath) at 25 mm.; infrared bands at 3500, 1724, 1364, and 1042 cm.$^{-1}$.

Anal. Calcd. for $C_8H_{16}O_2$: C, 66.63; H, 11.18. Found: C, 66.48; H, 11.46.

It gave iodoform with iodine and alkali in dioxane solution.

Oxidation of the Keto Alcohol (XII).—The keto alcohol (1.13 g.) was oxidized with sodium dichromate (2.61 g.) and sulfuric acid (2.50 ml.) in aqueous medium. The reaction mixture was steam distilled and the distillate contained *n*-valeric acid (XIII, R_f 0.58) and acetic acid (R_f 0.23) by paper chromatography.

α- and β-Santalenes (XIV and XVIII).—α- and β-santalenes were obtained by repeated batch-strip fractionation[10] using a packed column followed by elaborate column chromatography on alumina (500-fold, grade I) of "sandalwood oil terpenes" supplied by the Government Sandalwood Oil Factory, Mysore. The purest hydrocarbons[11] showed the following properties: α-santalene, b.p. 112° (7 mm.), $[\alpha]^{29}\mathrm{D}$ +10.84° (*c* 10.72), $n^{29}\mathrm{D}$ 1.4833; β-santalene, b.p. 109° (3 mm.), $[\alpha]^{26}\mathrm{D}$ −73.94° (*c* 11.67), $n^{26}\mathrm{D}$ 1.4940.

2-Isopropenyl-3-(π)-tricyclylpropanol (XV).—A mixture of α-santalene (XIV, 100 g., 0.48 mole), paraformaldehyde (18 g., 0.60 mole), freshly distilled anhydrous stannic chloride (2.4 ml.), and dry chloroform (200 ml.) was stirred at room temperature for 40 hr. Chloroform was removed under reduced pressure, and the residue was diluted with water and warmed with ammonia. The product was repeatedly extracted with ether, washed with water, and dried (Na_2SO_4). Removal of solvent yielded the crude product (109 g.) which was fractionated to remove the low-boiling fractions consisting of α-santalene (19.3 g., b.p. 75–80° at 0.8 mm.). The residue in petroleum ether yielded a mixture of oxides (13.5 g.). The fractions eluted with ether gave after fractionation, 2-isopropenyl-3-(π)-tricyclylpropanol (XV, 18.8 g.) as a colorless, viscous liquid having a sandalwood odor, b.p. 122–125° (0.7 mm.), $[\alpha]^{23}\mathrm{D}$ +2.66° (*c* 21.31), $n^{22}\mathrm{D}$ 1.5018; infrared bands at 3484, 3096, 1655, 1047, 895, 882, 858, and 824 cm.$^{-1}$.

Anal. Calcd. for $C_{16}H_{26}O$: C, 81.99; H, 11.18. Found: C, 81.65; H, 11.00.

Catalytic Hydrogenation of the Alcohol (XV).—The alcohol (0.11 g.) was hydrogenated in ethanol (25 ml.) in the presence of Adams catalyst (56 mg.). The amount of hydrogen absorbed (14.90 ml. at 20° and 709 mm.) corresponded to 0.90 mole or one double bond. The dihydro product showed infrared bands at 3356, 3067, doublet at 1383, 1366, 1049, 877, 854, and 820 cm.$^{-1}$.

2-Homo-π-tricyclyl-3-ketobutanol (XVI).—The alcohol (XV, 5.02 g.) was ozonized in chloroform (100 ml.) to completion (8 hr.) at 0°. After removal of solvent under reduced pressure, the ozonide was heated with water (60 ml.) on a water bath for 4 hr. The volatile portion trapped in ice-cold water gave a copious amount of dimedone derivative of formaldehyde, m.p. and m.m.p 189°. The nonvolatile portion, after being treated with sodium bicarbonate, yielded the keto alcohol (XVI, 4.32 g.), b.p. 160–170° (bath) at 1.5 mm., $n^{26}\mathrm{D}$ 1.4920. It gave iodoform (m.p. and m.m.p. with an authentic sample 120°) with iodine and alkali in dioxane solution; infrared bands at 3521, 3096, 1727, 1351, 1043, 878, 856, and 823 cm.$^{-1}$.

Anal. Calcd. for $C_{15}H_{24}O_2$: C, 76.22; H, 10.24. Found: C, 75.61; H, 10.23.

Oxidation of the Keto Alcohol (XVI). A. By Sodium Dichromate–Sulfuric Acid.—The keto alcohol (1 g.) was stirred with water (20 ml.) and finely powdered sodium dichromate (1.49 g.) under cooling. Concentrated sulfuric acid (2 ml.) was added to this dropwise, and the mixture was stirred at room temperature for 6 hr. and at 80° for 2 hr. The mixture was distilled and the earlier portions of the distillate were trapped in ice-cold liquid ammonia (3 ml.), the solution was extracted with ether, and the aqueous layer was concentrated. It was shown to contain acetic acid (R_f 0.19) by paper chromatography.

B. By Permanganate.—The keto alcohol (XVI, 1.02 g.) was stirred with water (30 ml.), and powdered potassium permanganate (2.05 g.) was added to this in five portions during 1 hr., and the stirring was continued at room temperature for 16 hr. The manganese dioxide sludge was filtered and washed with hot water. The filtrate was extracted with ether; the aqueous layer was concentrated and acidified with hydrochloric acid (1:1). The organic acid was extracted with ether, washed free of mineral acid, and dried (Na_2SO_4). Removal of solvent yielded a mixture of acids which contained mainly tricycloekasantalic acid (R_f 0.76) and small amounts of acetic acid (R_f 0.20) and another acid

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(10) B. B. Ghatge and S. C. Bhattacharyya, *Perfumery Essent. Oil Record*, **47**, 353 (1956).

(11) V. Herout and collaborators [*Collection Czech. Chem. Commun.*, **22**, 773 (1957)] have recorded higher rotations for α- and β-santalenes isolated in milligram quantities. Such high rotations, however, could not be achieved in our case.

(R_f 0.51, probably a keto acid). The ketonic impurities were removed by treatment with Girard's reagent and the product was crystallized from petroleum ether to yield tricycloekasantalic acid, m.p. and m.m.p. 76°; infrared bands at 3058, 2667, 1704, 1408, 946, 878, 855, and 821 cm.$^{-1}$.

Anal. Calcd. for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.00; H, 9.50.

The alcohol (XV) also yielded tricycloekasantalic acid (XVII), when oxidized with permanganate as described.

The Prins Reaction on α-Santalene (XIV) under Thermal Conditions.—α-Santalene (22.4 g., 0.11 mole) was refluxed with paraformaldehyde (3.49 g., 0.11 mole) and glacial acetic acid (350 ml.) for 26 hr. Acetic acid was distilled, the residue was diluted and repeatedly extracted with ether, washed with sodium carbonate and water, and dried (Na_2SO_4). Removal of solvent yielded the unsaturated acetate (22.81 g.), which was saponified by refluxing with alcoholic potassium hydroxide (300 ml., 0.5 *N*) for 2 hr. to yield the crude product (20.56 g.). On fractionation using a spinning band column, the earlier fractions (4.17 g.) were found to consist of a β-santalene-type hydrocarbon from physical properties, elemental analysis, and infrared spectrum. The intermediate fractions (10.54 g.) consisted of the alcohol XIX. The last fractions contained mostly diols.

The alcohol XIX is a colorless liquid having a sandalwood odor, b.p. 150–155° (bath) at 1 mm., $[\alpha]^{27}\text{D}$ −11.92° (*c* 11.11), $n^{28}\text{D}$ 1.5036; infrared bands at 3333, 3050, 1631, 1037, 885, and 877 cm.$^{-1}$.

Anal. Calcd. for $C_{16}H_{26}O$: C, 81.99; H, 11.18. Found: C, 81.56; H, 11.10.

A sample of the alcohol purified by phthalization had identical properties.

It absorbed 1.93 moles of hydrogen on catalytic hydrogenation in presence of Adams catalyst in glacial acetic acid.

The Prins Reaction on β-Santalene (XVIII) under Thermal Conditions.—β-Santalene (10.7 g., 0.05 mole) was refluxed with paraformaldehyde (1.84 g., 0.06 mole) and glacial acetic acid (100 ml.) for 24 hr., and the product was worked up as in the case of α-santalene to yield the acetate ester (11 g.). This was saponified by alcoholic potassium hydroxide (140 ml., 0.5 *N*), and the product was fractionated using a spinning band column to remove unchanged β-santalene (2.74 g.) and higher boiling diols (1.52 g., b.p. 140–156° at 3 mm.). The alcohol (XIX, 4.07 g.) was further purified by chromatography on neutral alumina (100 g., grade II) when a colorless, viscous liquid having a sandalwood odor was obtained, b.p. 140–150° (bath) at 2 mm., $[\alpha]^{28}\text{D}$ −17.58° (*c* 9.98), $n^{30}\text{D}$ 1.5045. Its infrared spectrum was identical with that of the alcohol obtained from α-santalene by thermal reaction.

Anal. Calcd. for $C_{16}H_{26}O$: C, 81.99; H, 11.18. Found: C, 81.62; H, 11.14.

Quantitative hydrogenation showed the presence of two double bonds.

Ozonolysis of Alcohol XIX.—The alcohol (2.70 g.) was ozonized in chloroform (25 ml.) at 0° to completion (6 hr.). After removal of solvent, the ozonide was decomposed with water (35 ml.). The volatile portion gave the dimedone derivative of formaldehyde, m.p. and m.m.p. 189°. The nonvolatile portion (XX, 1.56 g.), after being extracted with sodium bicarbonate, distilled at 170–190° (bath) at 0.4 mm.; infrared bands at 3521, 1724, and 1045 (NaCl prism), and 1732 and 1709 cm.$^{-1}$ (CaF_2 prism).

Anal. Calcd. for $C_{14}H_{22}O_3$: C, 70.55; H, 9.31. Found: C, 72.60; H, 10.34.

A better analysis could not be obtained.

Oxidation of the Keto Alcohol (XX) by Sodium Dichromate–Sulfuric Acid.—The keto alcohol (1 g.) was oxidized with sodium dichromate (1.53 g.) and sulfuric acid (1.11 ml.) in aqueous medium as described before. The reaction mixture was steam distilled; the distillate contained acetic acid (R_f 0.19), identified by paper chromatography. Work-up of the residue yielded an acid mixture which contained mainly camphenilonylacetic acid (R_f 0.51), small proportions of norcampholidylacetic acid (XXII, R_f 0.41), and acetic acid (R_f 0.19). Genuine samples of acids XXI and XXII for comparison were obtained by ozonizing bicycloekasantalic acid in acetic acid.[6]

Oxidation of the Keto Alcohol (XX) by Chromic Acid.—The keto alcohol (1 g.), when oxidized with acetic acid (10 ml.), chromic anhydride (0.98 g.) in water (1 ml.), and glacial acetic acid (10 ml.) according to the procedure described earlier, yielded the acid XXI (0.25 g.) identified by paper chromatography; methyl ester (diazomethane), b.p. 130–140° (bath) at 0.6 mm., infrared bands at 1748 cm.$^{-1}$.

Anal. Calcd. for $C_{12}H_{18}O_3$: C, 68.54; H, 8.63. Found: C, 68.62; H, 9.13.

Acknowledgment.—The authors are grateful to Mr. H. Gopinath for the infrared spectra, Mr. V. S. Pansare and colleagues for the microanalyses, Dr. S. Kanthamani and Dr. G. Lakshmi Kumari for paper chromatography, and Dr. V. G. Naik for the v.p.c. analysis. One of the authors (S. R.) gratefully acknowledges a Junior Research Fellowship awarded to her by the Council of Scientific and Industrial Research, Government of India, during the period of this work.

Azabicyclic Alcohols. I. Stereochemistry of the Hydroxyquinolizidines[1]

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Received January 2, 1964

Each of the 1-, 2-, and 3-hydroxyquinolizidine racemates has been synthesized and characterized. Configurational and conformational assignments have been made on the basis of infrared and n.m.r. spectra, gas–liquid chromatographic retention data, and chemical evidence. In all cases a *trans*-quinolizidine ring fusion is shown to exist. In the case of the 1- and 3-hydroxyquinolizidines, intramolecular hydrogen bonding occurs between the bridgehead nitrogen and an axial β-hydroxyl group.

Although the quinolizidine ring system (I) occurs in many natural products,[2] the simple hydroxyquinolizidines are not known to exist in nature. In the 1-, 2-, and 3-hydroxyquinolizidines, two epimeric racemates are possible, depending upon the configuration of the hydroxyl group relative to that of the bridgehead (C-10) hydrogen. For each epimer both a *cis* and a *trans* ring fusion are possible, and interconversion between the two forms can occur by inversion of the electron pair on the bridgehead nitrogen. Previous studies of these compounds have been reviewed.[3,4] Only recently, however, have the two epimers of the 1- and 2-hydroxyquinolizidines been characterized and configurational assignments given.[5,6] Complete

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