TERPENOIDS—XL

THE STRUCTURE AND ABSOLUTE CONFIGURATION OF KHUSOL*

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(Received 26 December 1962)

Abstract—Khusol, a crystalline primary sesquiterpene alcohol, $C_{15}H_{24}O$, isolated from North Indian vetiver oil has been assigned the structure and absolute configuration represented by I. It belongs to the antipodal group of cadinenic alcohols.

THE laevorotatory vetiver oil (*Vetiveria zizaniodes*, linn.) from north India yielded hydrocarbons isobisabolene¹ and γ_2 -cadinene,² and crystalline alcohols khusinol³ and khusol. Khusol, C₁₅H₂₄O, m.p. 101–102°, $[\alpha]_D^{25} - 137°$, earlier isolated⁴ was obtained in a yield of about 3%. A tentative structure of khusol, based on preliminary experiments, was reported by Bhattacharyya *et al.*⁵ In the present investigation, it is conclusively shown that the structure and absolute configuration is represented by I.

The I.R. spectrum of khusol (Fig. 1) shows absorption bands due to a primary hydroxyl group (3340, 1028 cm⁻¹), an end methylenic group (1642, 892 cm⁻¹) and a trisubstituted double bond (798, 840 cm⁻¹). Khusol easily forms a liquid acetate, catalytic hydrogenation confirms the presence of two double bonds and the UV spectrum indicates absence of conjugation.

On ozonolysis it yields formaldehyde as the only volatile product, confirming the presence of an exocyclic methylenic double bond. The non-volatile portion gave positive tests for methyl ketone and aldehyde. On partial hydrogenation in presence of palladium-charcoal in ethanol, khusol absorbs only one mole of hydrogen and furnishes a liquid dihydro-khusol, C_{15} H₂₆O (II) having I.R. bands at 793 and 831 cm⁻¹ due to a trisubstituted double bond. On catalytic hydrogenation in glacial acetic acid in the presence of Adams catalyst, khusol furnishes a liquid tetrahydrokhusol (III) along with a small amount of its acetate. In spite of repeated column chromatography over alumina neither dihydro nor tetrahydrokhusol could be obtained in crystalline form.

On oxidation with pyridine-chromic acid complex,⁶ khusol gives a liquid aldehyde, $C_{15}H_{22}O$ (IV, semicarbazone, $C_{16}H_{25}ON_3$, m.p. 165°), which shows I.R. absorption bands at 2710 and 1724 cm⁻¹. The U.V. absorption spectra of the liquid aldehyde or its semicarbazone did not show any characteristic absorption due to α,β -unsaturated aldehyde function. Khusol can be regenerated on reduction of the aldehyde with lithium aluminium hydride.

* Contribution No. 561 from the National Chemical Laboratory, Poona-8 (India).

¹ P. S. Kalsi, K. K. Chakravarti and S. C. Bhattacharyya, Tetrahedon 18, 1165 (1962).

⁸ A. A. Rao, K. L. Surve, K. K. Chakravarti and S. C. Bhattacharyya, Tetrahedron in press.

- ⁵ S. N. Dhingra, D. R. Dhingra and S. C. Bhattacharyya, Perf. & Ess. Oil Rec. 47, 350 (1956).
- ⁶G. I. Poos, G. E. Arth, R. E. Beyler and L. H. Sarett, J. Amer. Chem. Soc. 75, 422 (1953).

² C. C. Kartha, P. S. Kalsi, A. M. Shaligram, K. K. Chakravarti and S. C. Bhattacharyya, *Tetrahedron* in press.

⁴ N. L. Zutshi and Sadgopal, Perf. & Ess. Oil Rec. 47, 88 (1956).



As the selenium dehydrogenation product of khusol itself was difficult to characterize, it was thought desirable to dehydrogenate the hydrocarbon prepared from khusol. With this object in view, the crystalline tosyl derivative, $C_{22}H_{30}O_3S$, m.p. 114–115° was reduced with lithium aluminium hydride and the product on subsequent chromatography and distillation over sodium gave a hydrocarbon, $C_{15}H_{24}$ (IX, I.R. spectrum, Fig. 1), which on dehydrogenation with selenium gave an excellent yield of cadalene.

The position of the trisubstituted double bond in khusol was fixed by the labelling method of Campbell and Soffer.⁷ The dihydro product obtained on hydrogenation of IX with palladium-charcoal, on treatment with perbenzoic acid furnishes an epoxy compound which is converted to a ketone (V) with borontrifluoride-etherate. The ketone on prolonged treatment with methyl magnesium iodide yielded an alcohol which on dehydrogenation with selenium afforded 1,2,5-trimethylnaphthalene (VI). Introduction of a methyl group at C₅ position eliminated the bulky isopropyl group at C₇ during dehydrogenation.⁸

In order to establish the position of the primary alcohol group in khusol, the aldehyde (IV) was oxidized with silver oxide to the acid (VII), $C_{15}H_{22}O_2$, m.p. 118–119° (methyl ester, $C_{16}H_{24}O_2$). This acid on dehydrogenation with selenium, gave 1,6-dimethyl-4-ethylnaphthalene⁹ (VIII) thus establishing the position of the primary alcohol group as the --CH(CH₂OH)CH₃ moiety shown in I.

⁷ W, P. Campbell and M. D. Soffer, J. Amer. Chem. Soc. 64, 417 (1942).

⁸ M. D. Soffer, M. Brey and J. Fournier, J. Amer. Chem. Soc. 81, 1678 (1959).

⁹ K. V. H. Padmanabhan, J. Indian Inst. Sci. 37A, 160 (1955).

The I.R. spectrum and physico-chemical properties of the hydrocarbon (IX) are identical with those of (+)- γ -cadinene (X), $[\alpha]_D$ +148° isolated¹⁰ from citronella oil. However, the specific rotation, $[\alpha]_D^{26}$ -145°, clearly indicates that the hydrocarbon



(IX) is the optical antipode of $(+)-\gamma$ -cadinene (X). The hydrocarbon (IX) gives a dihydrochloride (XI), m.p. 117°, $[\alpha]_D^{25} + 38^\circ$, identical by mixed melting point determination with a sample of (+)-cadinene dihydrochloride obtained earlier from $(-)-\gamma$ -cadinene via khusinol (XII). This established the absolute configuration of khusol as represented in (I). It also belongs to the antipodal group of cadinenes, such as

* The authors are indebted to Dr. F. A. L. Anet of the University of Ottawa for measurement and discussion of the N.M.R. spectrum of khusol. Help from Drs. A. K. Bose and E. R. Malinowski of the Stevens Institute of Technology, U.S.A. is also gratefully acknowledged.

¹⁰ V. Herout, T. Kolos and J. Pliva, Chem. Listy 47, 440 (1953); Coll. Trav. Chem. Tchecosl. 18, 886 (1953).

 γ_2 -cadinene² and khusinol³ isolated from vetiver oil and γ_1 -cadinene³ from Malabar lemongrass oil. The NMR spectrum* of khusol (Fig. 2) supports this structure.



EXPERIMENTAL

All m.p. are uncorrected. Rotations were measured in chloroform solution. U.V. spectra were determined in alcohol solution on Beckman DK-2 recording spectrophotometer by Miss Prabhu. I.R. spectra were determined with Perkin-Elmer Infracord spectrophotometer by Mr. Gopinath. Microanalyses were carried out by Mr. Pansare and colleagues.

Isolation of khusol (I). Vetiver oil (600 g) (Bharatpur or Biswan variety) was chromatographed on neutral alumina (grade III, 18 kg) and eluted successively with pet. ether (201.), benzene (221.) and ether (121). The product (175 g) obtained by elution with ether deposited crystals of khusol (18 g) on cooling at -10° and were crystallized from pet. ether, m.p. $101-102^{\circ}$, $[\alpha]_{D}^{27} -137^{\circ}$ (c, 2.9) (Found: C, 81.77; H, 11.10. C₁₅H₂₄O requires: C, 81.76; H, 10.98%). I.R. spectrum in nujol (Fig. 1.)

Khusol acetate. Khusol (0.5 g) was treated with pyridine (40 ml) and acetic anhydride (6 ml) at room temp for 14 hr and the mixture poured into cold water. The crude acetate was chromatographed over alumina (grade II, 30 g) and the product on distillation gave khusol acetate, b.p. 155° (bath)/ 0.7 mm, n_{17}^{27} 1.5060; [α]³⁴ -115° (c, 2.0) (Found: C, 77.60; H, 9.50. C₁₇H₂₆O₂ requires: C, 77.82; H, 9.99%). I.R. spectrum bands at: 1748 and 1240 cm⁻¹.

Ozonolysis of khusol (I). A stream of dry ozonized oxygen was passed through a solution of khusol (0.5 g) in dry chloroform (55 m) cooled to 0° , until ozonization was complete. Solvent was removed under red. press. and the ozonide decomposed by heating with water. The volatile portion was characterized as formaldehyde by its dimedone derivative (m.p. and mixed m.p. 189–190°). The non-volatile portion gave a positive iodoform test for methyl ketone group and Fehling's solution test for aldehyde function.

Dihydrokhusol (II). A solution of khusol (0.5 g) in ethanol (15 ml) was hydrogenated in the presence of 10% palladium-charcoal catalyst (200 mg). The hydrogen absorbed (63 ml at 25° and 711 mm in 1 hr) corresponded to one double bond, further absorption being extremely slow. The catalyst was filtered off, the ethanol removed from the filtrate on a steam bath *in vacuo* and the residue in pet. ether chromatographed over alumina (20 g, grade II) to give dihydrokhusol (II), b.p. 155° (bath)/1.5 mm; $[\alpha]_{17}^{27} + 60^{\circ}$ (c, 1.7), n_{D}^{27} 1.5080. (Found: C, 80.80; H, 11.90; C₁₅H₂₆O requires: C, 81.02; H, 11.79%).

Tetrahydrokhusol (III). A solution of khusol (0.266 g) in acetic acid (20 ml) was hydrogenated in presence of 55 mg pre-reduced Adams catalyst (61.9 ml hydrogen at 25° and 711 mm in 11 hr) which corresponded to 2 moles of hydrogen. The product was chromatographed over alumina (grade II, 10 g) to give tetrahydrokhusol (III, 0.221 g), b.p. 140° (bath) 0.5 mm; $[\alpha]_{D}^{27} + 34^{\circ}$ (c, 2.0); n_{D}^{38} 1.4951 (Found: C, 80.00; H, 12.50. C₁₅H₂₈O requires: C, 80.29; H, 12.58%).

Aldehyde (IV) from khusol. Khusol (2 g) in pyridine (20 ml) was oxidized with pyridine-chromic acid complex (40 ml pyridine and 2 g chromic acid) at room temp for 24 hr with shaking. The product after chromatography over alumina (grade II, 30 g) gave the pure aldehyde (0.98 g). An analytical sample had b.p. 135° (bath) 1.5 mm; n_2^{p} 1.5172; $[\alpha]_2^{p}$ -165° (c, 2.5). (Found: C, 82.70; H, 10.1. C₁₈H₂₂O requires: C, 82.51; H, 10.16%). I.R. spectrum (Fig. 1.)

The semicarbazone was obtained as fine needles on crystallization from ethanol, m.p. 165° (Found: N, 14.96; $C_{18}H_{28}N_{3}O$ requires: N, 15.26%).

(--)- γ -Cadinene (IX). A mixture of khusol (5 g) in dry pyridine (20 ml) and freshly crystallized *p*-toluenesulphonyl chloride (6 g) in dry pyridine (40 ml) was kept at room temp for 94 hr. It was poured into crushed ice, taken up in ether and the ether layer washed successively with dil. hydro-chloric acid, sodium-bicarbonate solution and finally with water and dried. After the removal of the solvent the crystalline tosylate (6·2 g) crystallized from pet. ether in white shining needles, m.p. 114-115° (Found: C, 70·6; H, 7·9; S, 8·1. C₂₂H₃₀O₃S requires: C, 70·9; H, 8·0; S, 8·5%). The I.R. spectrum in nujol was devoid of hydroxyl band and showed intense bands due to the tosyl group (1600, 1490, 1190, 1176 and 1100 cm⁻¹). The tosyl derivative (5 g) in dry ether (20 ml) was added dropwise to a slurry of well powdered lithium aluminium hydride (2 g) in dry ether (45 ml) at 0° with stirring ($\frac{1}{2}$ hr). The contents were then refluxed for 7 hr, the mixture decomposed with moistether and worked up to afford (-)- γ -cadinene (2·6 g) which was chromatographed over alumina (grade I, 50 g), and distilled over sodium, b.p. 100° (bath) 0·5 mm; n_{31}^{31} 1·5060; [α]₃₅²⁶-145° (c, 3·8); d_4^{24} 0·9182. (Found: C, 88·10; H, 12·10. C₁₅H₂₄ requires: C, 88·16; H, 11·84%). I.R. spectrum in liquid cell 0·1 mm (Fig. 1).

Cadalene on dehydrogenation. The hydrocarbon (IX, 0.35 g) was mixed with selenium (0.5 g) and heated in nitrogen atm. at 300° for 16 hr. The product, in pet. ether was chromatographed over alumina (grade I) and characterized as cadalene by picrate, m.p. and mixed m.p. with an authentic sample 114–115°.

Dihydro-(-)- γ -cadinene. A solution of (-)- γ -cadinene (IX, 0·473 g) in ethanol (20 ml) was hydrogenated in the presence of 10% palladium charcoal catalyst (300 mg) at 710 mm and 25° (0·94 mole hydrogen absorbed in 1·5 hr), and the product on distillation over sodium yielded dihydro-(-)- γ cadinene, b.p. 90° (bath) 0.8 mm; $n_{\rm P}^{\rm D}$ 1·4900; $[\alpha]_{\rm D}^{\rm 27}$ +70° (c, 0·9). (Found: C, 87·49; H, 12·52 C₁₅H₂₆ requires: C, 87·30; H, 12·70%).

Ketone (V). Dihydro-(-)- γ -cadinene (0.45 g) was reacted with excess perbenzoic acid in chloroform for 16 hr at 0°. The resulting epoxide (0.42 g) was treated in dry benzene (30 ml) with borontrifluoride etherate (0.5 ml) for 15 min at room temp. Working up in the usual manner and chromatography over alumina (grade II, 10 g) yielded the ketone (V), b.p. 130° (bath) 0.5 mm, n_{20}^{20} 1.4880; $[\alpha]_{27}^{27}$ +45° (c, 1.2). (Found: C, 81.20; H, 12.00. C₁₅H₂₆O requires: C, 81.02; H, 11.79%).

I.R. spectrum showed an intense band at: 1715 cm^{-1} due to a carbonyl group on a six membered ring but absorption near 1420 cm⁻¹ due to the presence of a methylene group adjacent to carbonyl function was absent.

1,2,5-Trimethylnaphthalene (VI). The ketone (V, 350 mg) was refluxed with stirring for 48 hr with Grignard's reagent prepared from magnesium (0.8 g) and methyl iodide (3.7 g) in dry ether (45 ml). After decomposition with ice and dil. sulphuric acid, the desired carbinol was isolated in the usual way (0.3 g) and purified through chromatography over alumina (grade II, 6 g). The I.R. spectrum showed absorption at 3445 cm^{-1} ; absorption in the vicinity of 1700 cm^{-1} being absent.

The carbinol (0.25 g) was heated with selenium (0.5 g) at $290-300^{\circ}$ for 16 hr. The product was extracted with pet. ether and filtered through alumina. The oily material thus obtained gave a TNB complex m.p. 159°. The mixed m.p. with an authentic sample of TNB complex of 1,2,5-trimethyl-naphthalene remained undepressed.

Acid (VII) from aldehyde (IV). To a cold solution of aldehyde (IV, 0.8 g) and powdered silver nitrate (1.6 g) in ethanol, was added dropwise a solution of sodium hydroxide (0.9 g) in aqueous ethanol (20 ml) with stirring. After 24 hr at room temp the mixture was diluted with water and acidified with cold dil. sulphuric acid. It was extracted with ether and the ethereal solution washed repeatedly with cold water and dried. After removal of the solvent, the acid (VII, 0.6 g), crystallized from pet. ether, m.p. 118–119°; $[\alpha]_{12}^{n_4} - 123^\circ$ (c, 1.7) (Found: C, 76.42; H, 9.55. C₁₃H₂₂O₂ requires: C, 76.88; H, 9.46%). I.R. spectrum bands at: 3175 and 1710 cm⁻¹.

Acid (VII, 0.2 g) in dry ether was converted to its methyl ester (ethereal solution of diazomethane) and chromatographed over alumina (grade II, 5 g) and eluted with pet. ether: benzene mixture (1:1), and distilled b.p. 135°(bath) 1.7 mm. (Found: C, 77.20; H, 10.00. $C_{16}H_{24}O_2$ requires: C, 77.37; H, 9.74%). I.R. spectrum, bands at: 1740, 1645, 1250, 1200, 1175, 1165, 892, 835 and 790 cm⁻¹.

1,6-Dimethyl 4-ethyl naphthalene (VIII). The acid (VII, 0.3 g) was heated with selenium (0.4 g) in nitrogen atm. at 290-300° for 16 hr. The dehydrogenation product in pet. ether was chromatographed over alumina (grade I) using pet. ether as eluent. Evaporation of the solvent gave 1,6-dimethyl-4-ethylnaphthalene, picrate m.p. 94-95°, TNB derivative, m.p. 134-135° (Found: N, 10.79. $C_{20}H_{19}O_6N_3$ requires: N, 10.58%). (Lit.* picrate m.p. 99-100°; TNB derivative m.p. 134.5-136°).

(+)-Cadinene dihydrochloride (XI). A solution of (-)- γ -cadinene (IX, 1 g) in dry ether (60 ml) was saturated with dry hydrogen chloride, and the solvent removed at 30° under suction. The product deposited on cooling and was crystallized from pet. ether as the dihydrochloride, m.p. 116-117° $[\alpha]_{27}^{B7}$ +38° (c, 1·2). Mixed m.p. with an authentic sample of (+)-cadinene dihydrochloride obtained via khusinol (m.p. 117.5°, $[\alpha]_{27}^{B4}$ +36.27°) remained undepressed.