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TERPENOIDS—LIV

STRUCTURE AND ABSOLUTE CONFIGURATION OF KHUSITONE*

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Abstract—North Indian vetiver oil (*Vetiveria zizanioides*, Linn.) has yielded a new laevorotatory ketone containing only 14 carbon atoms. Structure I has been assigned to it on the basis of chemical and physical evidence. Its absolute configuration II followed from its synthesis from khusol (III) of known absolute stereochemistry.

RECENTLY, from the carbonyl fraction of the North Indian vetiver oil, a novel aldehyde khusilal,[1] $C_{14}H_{18}O$, has been isolated as the major constituent. On the basis of chemical and spectroscopic data structure IV has been assigned to khusilal. Further processing of the carbonyl fraction has led to the isolation of small amounts of a new C_{14}-methyl ketone, $C_{14}H_{20}O$, in a pure form (VPC and TLC). We propose to name it as khusitone. The evidence presented in this paper suggests that its gross structure should be represented by I and its absolute configuration by the structure II. It thus represents yet another member of the rare class of C_{14}-terpenoids[1] and possesses a C_{14}-skeleton similar to that of khusilal.

Khusitone, $[\alpha]_D$ $-134{\cdot}8°$, analyses correctly for molecular formula $C_{14}H_{20}O$. The presence of a methyl ketonic group is indicated by the positive iodoform test. Khusitone yields a crystalline semicarbazone, $C_{15}H_{23}ON_3$, m.p. 183–184°.

The IR spectrum of khusitone (Fig. 1) shows bands at 1706 due to a ketonic group; 3115, 1642 and 891 due to a methylenic double bond ($>C{=}CH_2$) and 826 and 793 cm^{-1} due to a trisubstituted ethylenic linkage ($—CH{=}C\ R_1R_2$). NMR spectrum of hkusitone (Fig. 2) confirms the presence of both types of double bonds: signals at 5·3 and 5·4 τ (2 H) (doublet, $>C{=}CH_2$); 4·9 τ (1 H) (singlet, $—CH{=}C\ R_1R_2$). A signal at 8·35 τ (3 H) is assigned to the methyl group on a double bond and at 7·9 τ (3 H) is due to the methyl group attached to the carbon of the carbonyl group. Catalytic hydrogenation confirms the presence of two double bonds and the UV spectrum indicates absence of conjugation.

Khusitone on reduction in presence of palladium–charcoal in ethanol readily absorbs one mole of hydrogen and furnishes liquid dihydrokhusitone, $C_{14}H_{22}O$ (V), with IR bands showing the presence of trisubstituted double bond and the carbonyl group. On catalytic reduction in acetic acid medium using Adams catalyst, it gives tetrahydrokhusitone (VI). Khusitone on Wolff–Kishner reduction gives the parent hydrocarbon (XIX), $C_{14}H_{22}$ (IR spectrum, Fig. 1).

Reduction of khusitone with lithium aluminium hydride gives the corresponding alcohol khusitol (VII), $C_{14}H_{22}O$, $[\alpha]_D^{27}$ $-100°$ (IR spectrum, Fig. 1), which on dehydrogenation with selenium gives two main dehydrogenation products 1,6-dimethyl-4-ethylnaphthalene (VIII, 60%) and 1,6-dimethylnaphthalene (IX, 40%) (on the

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[1] P. S. Kalsi, K. K. Chakravarti and S. C. Bhattacharyya, *Tetrahedron* **20**, 2617 (1964).

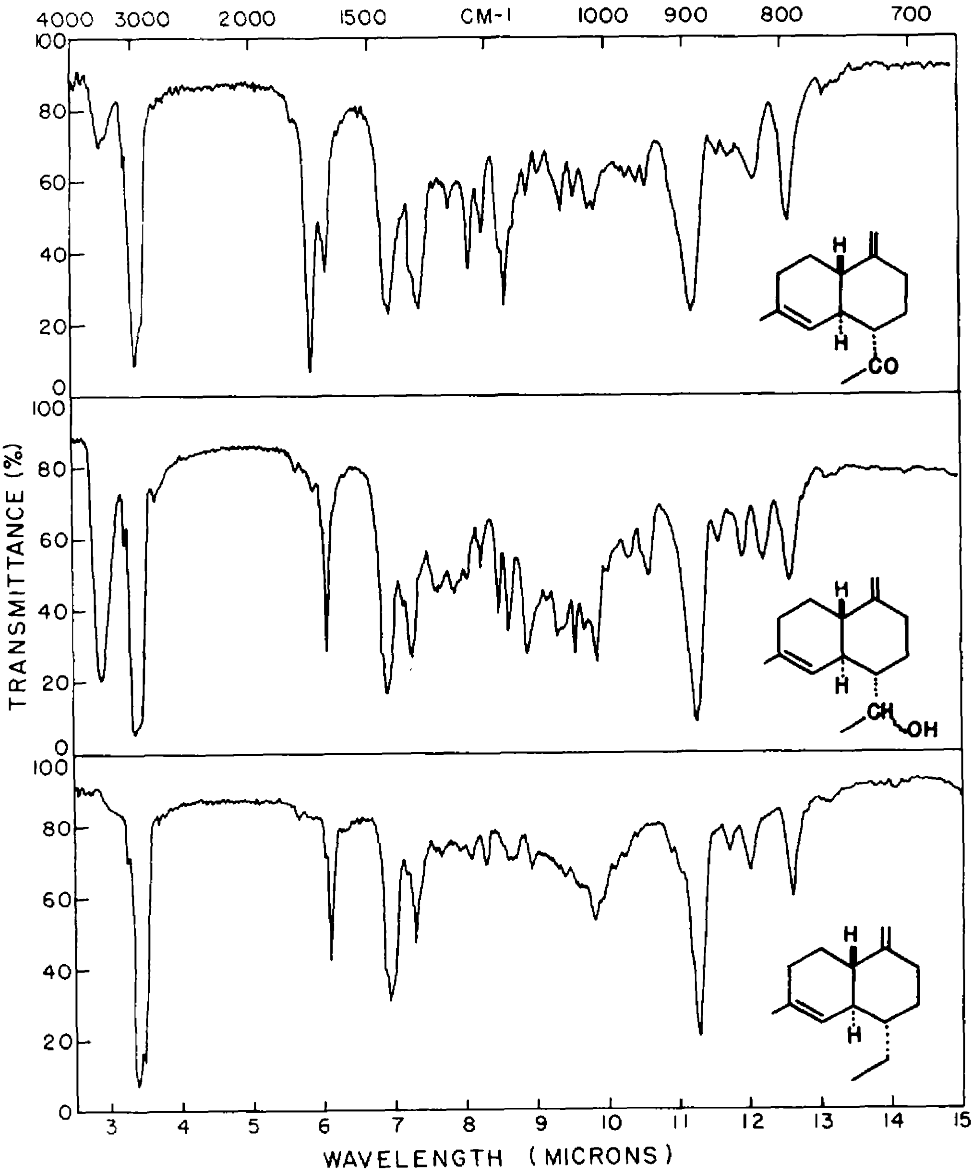

4000
3000
2000
1500
CM-1
1000
900
800
700
100
80
60
40
20
0
TRANSMITTANCE (%)
3
4
5
6
7
8
9
10
11
12
13
14
15
WAVELENGTH (MICRONS)
H
H
CO
CH
OH

Fig. 1

basis of VPC with authentic samples). Formation of 1,6-dimethyl-4-ethylnaphthalene accounts for all the 14 carbon atoms of khusitone and consequently its basic skeleton containing the methyl ketonic function should be represented by X. In conformity with this, khusitone on treatment with methyl lithium[2] gives a crystalline tertiary alcohol (XI), $C_{15}H_{24}O$, m.p. 109–110°; $[\alpha]_D^{27}$ −152°(IR spectrum, Fig. 3). The benzoate (XII) of this alcohol on pyrolysis under standard conditions[3] furnished a

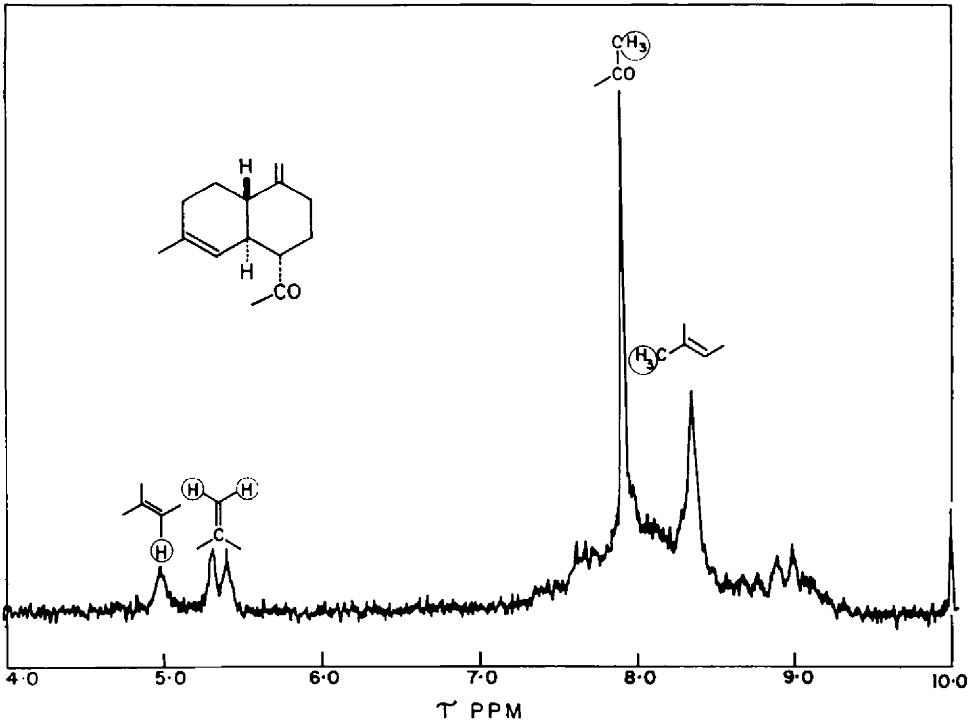


Fig. 2

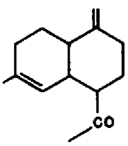
hydrocarbon (XIII), $C_{15}H_{22}$, $[\alpha]_D$ −33° (IR spectrum, Fig. 3). This hydrocarbon on dehydrogenation with selenium gives cadalene in high yields identifiable via its picrate, m.p. and mixed m.p. with an authentic sample 114°. On the basis of this data three possible structures (I, XV or XVI) follow for khusitone, depending on the relative disposition of the double bonds. This was decided from the following experiments. The hydrocarbon (XIII) on treatment with one mole of perbenzoic acid furnishes a monoepoxide (XVII). This on treatment with methyl magnesium iodide yields an alcohol which on dehydrogenation with selenium affords 1,2,5-trimethylnaphthalene (XVIII). Introduction of a methyl group at C.5 position eliminates the bulky isopropyl group[4] at C.7 during dehydrogenation. These reactions conclusively prove the structure I for khusitone.

With a view to elucidating the absolute configuration of asymmetric centres of khusitone it was thought desirable to correlate it with khusol[4] (III) of known absolute

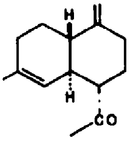
[2] G. Stork and F. H. Clarke, Jr., *J. Amer. Chem. Soc.* **83**, 3114 (1961).

[3] S. K. Paknikar and S. C. Bhattacharyya, *Tetrahedron* **18**, 1509 (1962).

[4] P. S. Kalsi, K. K. Chakravarti and S. C. Bhattacharyya, *Tetrahedron* **19**, 1073 (1963).



I



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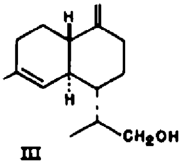
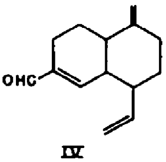
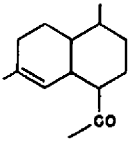


III



IV



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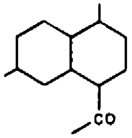

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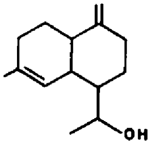
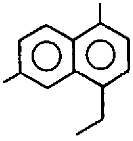
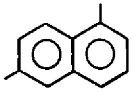


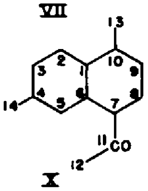
VII



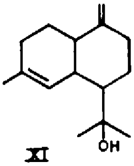
VIII



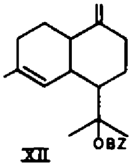
IX



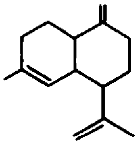
X



XI



XII



XIII

configuration. Khusol on oxidation with pyridine–chromic acid complex[4] gives the corresponding aldehyde (XX), $C_{15}H_{22}O$, which on treatment with piperidine yields the enamine[5] derivative (XXI). This derivative on oxidation with sodium dichromate[5] under controlled conditions gives the desired product khusitone (II), identical with the natural product as shown by the optical rotation, superimposable IR spectrum and other properties. This was further confirmed by preparing the semicarbazone from the synthetic product and establishing the identity of the same with that from the natural product by optical rotation, spectral properties and mixed m.p. These facts establish the absolute configuration of khusitone as represented by II.

EXPERIMENTAL

All m.ps are uncorrected. Rotations were measured in $CHCl_3$ solution. The alumina used for chromatography was acid-washed and activated and graded according to the Brockmann scale of activity. The pet. ether refers to the fraction boiling between 60–80°. The IR spectra were recorded as liquid film or in nujol suspension on a Perkin–Elmer infracord spectrophotometer, Model 137 B. The NMR spectrum was measured with a Varian A–60 spectrometer operating at 60 mc, tetramethyl

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[5] G. Slomp, Jr., Y. F. Shealy, J. L. Johnson, R. A. Donia, B. A. Johnson, R. P. Holysz, R. L. Pederson A. O. Jensen and A. C. Ott, *J. Amer. Chem. Soc.* 77, 1216 (1955).

silane was added as an internal indicator. Microanalysis were carried out in the microanalytical section of the laboratory.

Isolation of khusitone. Vetiver oil (1 kg) obtained from Bharatpur in North India was chromatographed on alumina (grade III, 20 kg) and eluted successively with pet. ether (40 l.), benzene (45 l.) and ether (30 l.). The product (450 g) obtained by elution with pet. ether was further chromatographed on alumina (grade II, 30 kg) in the same manner. From the carbonyl fraction (150 g) obtained by elution with benzene, khusilal (IV) was removed as its crystalline semicarbazone at 0°.

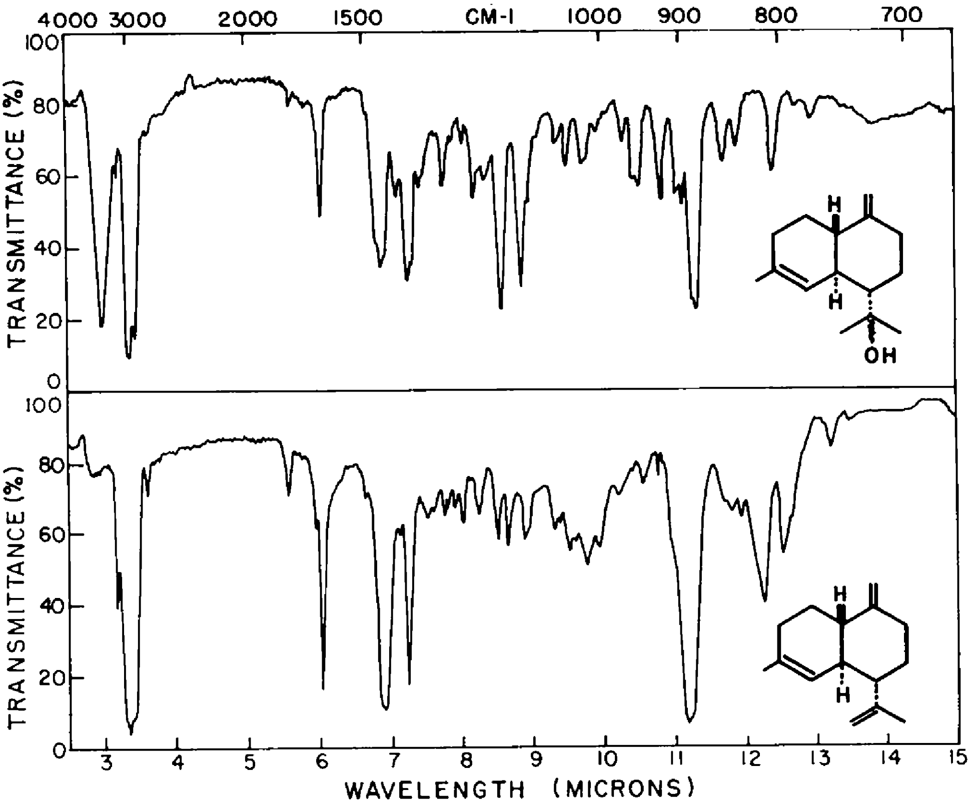
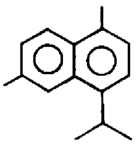


Fig. 3

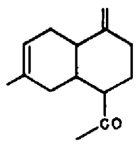
The nonsemicarbazone forming residue, left after the removal of khusilal semicarbazone, was taken in pet. ether and chromatographed over alumina (grade II, 6 kg). On eluting the column with pet. ether–benzene mixture (1:1) khusitone (3 g) was obtained in the tail fractions as a pure (VPC and TLC)., pale yellow liquid, b.p. 118° (bath/0·35 mm., n_D^{29} 1·5060; $[\alpha]_D^{20}$ −134·8° (*c*, 0·59) (Found: C, 82·43; H, 10·2; mol. wt 205. $C_{14}H_{20}O$ requires: C, 82·30; H, 9·87%; mol. wt 204·3). IR spectrum (Fig. 1) bands at: 3115, 1706, 1642, 1372, 1355, 1235, 1208, 1176, 1163, 1149, 1136, 1119, 1101, 1064, 1012, 891, 826 and 791 cm^{-1}.

Semicarbazone of khusitone. It was obtained by refluxing for 15 min a mixture of kusitone (0·2 g) in ethanol (5 ml), semicarbazide hydrochloride (0·2 g) and sodium acetate (0·25 g) in water. The product was collected after 2 days at room temp and recrystallized from ethanol, m.p. 183–184°, $[\alpha]_D$ −65·4° (*c*, 1·22) (Found: N, 15·78. $C_{15}H_{23}ON_3$ requires: N, 16·08%).

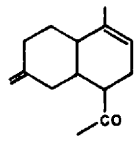
Dihydrokhusitone (V). A solution of khusitone (0·1004 g) in ethanol (15 ml) was hydrogenated in the presence of 10% Pd–C catalyst (40 mg). The H_2 absorbed (13·5 ml, at 27° and 706·2 mm in 30 min) corresponded to one double bond. The hydrogenation was stopped at this stage and the product was chromatographed over alumina (grade II, 20 g) to give dihydrokhusitone, b.p. 101° (bath)/0·6 mm., $[\alpha]_D^{26}$ +44·3° (c. 0·88) n_D^{26} 1·4930 (Found: C, 81·04; H, 11·02. $C_{14}H_{22}O$ requires: C. 81·50; H, 10·75%).



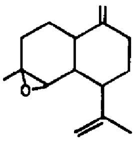
XIV



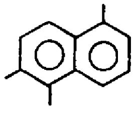
XV



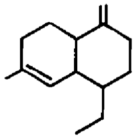
XVI



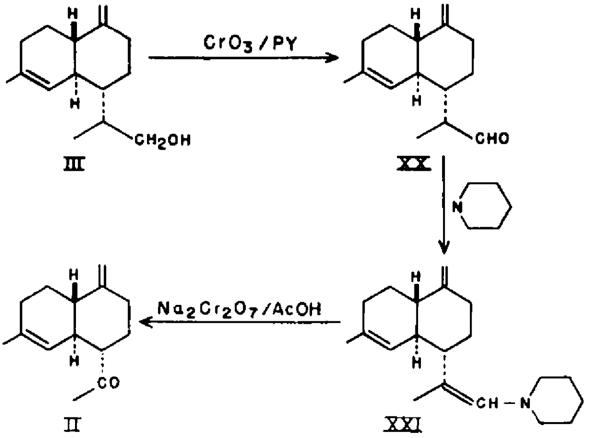
XVII



XVIII



XIX



Tetrahydrokhusitone (VI). A solution of khusitone (0·2004 g) in acetic acid (40 ml) was hydrogenated in presence of pre-reduced Adams catalyst (55 mg). The H_2 absorbed (57·5 ml at 27° and 706 mm, 10 hr) corresponded to 2·1 moles. The product was purified by chromatography over alumina (grade II, 15 g), an analytical sample had b.p. 98° (bath)/0·25 mm., n_D^{21} 1·4800 (Found: C, 80·46; H, 11·59. $C_{14}H_{24}O$ requires: C, 80·71; H, 11·61%).

Khusitol (VII). Khusitone (0·494 g) in dry ether (20 ml) was added to a slurry of $LiAlH_4$ (0·50 g) in dry ether (25 ml) at 0° with stirring (1/2 hr). The contents were then refluxed for 8 hr and worked up to afford khusitol (0·4 g), b.p. 113° (bath)/0·75 mm., n_D^{30} 1·5105; $[\alpha]_D^{27}$ −100° (*c*, 1·8) (Found: C, 80·87; H, 10·73. $C_{14}H_{22}O$ requires: C, 81·50; H, 10·75%); IR spectrum (Fig. 1) bands at: 3425, 3096, 1639, 1407, 1379, 1307, 1267, 1236, 1208, 1176, 1156, 1120, 1087, 1071, 1042, 1030, 1010, 966, 941, 885, 862, 847, 814 and 793 cm^{-1}.

Dehydrogenation of khusitol (VII). Khusitol (0·2 g) was mixed with Se (0·4 g) and heated in N_2 atm at 290° for 16 hr. The reaction mixture in pet. ether was filtered through alumina (grade I, 25 g). The product (0·15 g) on VPC analysis essentially showed the presence of two products, 1,6-dimethyl-4-ethylnaphthalene (VIII, 60%) and 1,6-dimethylnaphthalene (IX, 40%).

Alcohol XI *from khusitone*. CH_3Li was prepared by adding CH_3I (6 ml) to Li (1·8 g, in four pieces) in dry ether (40 ml) with stirring and cooling in ice. When the vigorous reaction had subsided, the mixture was refluxed with stirring for 4 hr. It was then cooled and the unreacted Li was removed. A solution of khusitone (0·4 g) in dry ether (20 ml) was added to it and the mixture refluxed with stirring for 20 hr. Excess CH_3Li was decomposed by adding Na_2SO_4 aq containing some $Na_2S_2O_3$ to the stirred ice-cooled mixture. The product was isolated with ether and crystallized from pet. ether to afford XI (0·2 g), m.p. 109–110°; $[\alpha]_D^{27}$ −152·9° (*c*, 0·34) (Found: C, 80·89; H, 10·64. $C_{15}H_{24}O$ requires: C, 81·76; H, 10·98%). IR spectrum in nujol (Fig. 3) bands at: 3333, 3106, 1650, 1401, 1374, 1362, 1342, 1282, 1240, 1217, 1193, 1163, 1126, 1116, 1066, 1050, 1026, 971, 955, 949, 924, 903, 897, 887, 853, 840 and 803 cm^{-1}.

Hydrocarbon (XIII) *from alcohol* (XI). A solution of XI (0·5 g) in pyridine (5 ml) was mixed with benzoyl chloride (1 ml) and kept at room temp for 60 hr. It was warmed on a water bath for 2 hr and worked up as usual to give the crude benzoate (0·408 g), which was heated in a distillation flask at 210–230° (bath temp) *in vacuo* (100 mm). The distillate was taken up in ether and freed from benzoic acid by washing with $NaHCO_3$ aq. The hydrocarbon (0·24 g) was further purified by chromatography over alumina (grade I, 20 g) and then distilled over Na, b.p. 124° (bath)/3·5 mm., n_D^{26} 1·5130; $[\alpha]_D^{26}$ −33·8° (*c*, 1·62) (Found: C, 88·24; H, 10·73. $C_{15}H_{22}$ requires: C, 89·04; H, 10·96%). IR spectrum (Fig. 3) bands at: 3105, 2778, 1799, 1640, 1383, 1330, 1285, 1248, 1215, 1176, 1157, 1124, 1075, 1053, 1042, 1026, 1007, 980, 949, 896, 816 and 798 cm^{-1}.

Dehydrogenation of the hydrocarbon (XIII). The hydrocarbon (0·2 g) was mixed with Se (0·5 g) and heated in N_2 atm at 290–300° for 18 hr. The product, in pet. ether, was chromatographed over alumina (grade I, 39g) and characterized as cadalene by picrate, m.p. and mixed m.p. with an authentic sample 114–115°.

1,2,5-*Trimethylnaphthalene* (XVIII). Hydrocarbon XIII (0·40 g) was reacted with perbenzoic acid (1 mole) in $CHCl_3$ for 18 hr at 0°. The resulting epoxide (XVII) was isolated according to standard procedure and was refluxed with stirring for 50 hr with Grignard reagents prepared from Mg (0·78 g) and CH_3I (3·9 g) in dry ether (50 ml). After working up in the customary manner the desired carbinol was purified through chromatography over alumina (grade II, 20 g). The IR spectrum showed a strong band at 3439 cm^{-1}. The carbinol (0·25 g) was mixed with Se (0·4 g) and heated at 290–300° for 20 hr in N_2 atm. The product was filtered through alumina (grade I, 20 g). The oily material thus obtained gave a TNB complex, m.p. and mixed m.p. with an authentic sample of TNB complex of 1,2,5-trimethylnaphthalene 159°.

Hydrocarbon (XIX) *by Wolff–Kishner reduction of khusitone*. A mixture of khusitone (0·5 g) in ethanol (1 ml), diethylene glycol (6 ml) and hydrazine hydrate (0·8 ml) was heated at 170–175° for 4 hr in N_2 atm. After cooling KOH pellets (0·7 g) were added to the reaction mixture. Water was removed from the mixture by raising the temp gradually to 200° and then heating at 200° for 8 hr. The product was diluted with water (50 ml), neutralized with cold dil. HCl and extracted with ether. The extract washed in the usual way, dried and evaporated. It was chromatographed over alumina (grade I, 15 g) to give XIX (0·25 g), b.p. 110° (bath)/2 mm, $[\alpha]_D^{27}$ −118° (*c*, 1·4) Found: C, 88·12; H, 11·92. $C_{14}H_{22}$ requires: C, 88·35; H, 11·65%). IR spectrum (Fig. 1) bands at: 3086, 1639, 1391, 1370, 1332, 1302, 1264, 1235, 1206, 1163, 1119, 1064,1018, 990, 917, 885, 852, 833 and 793 cm^{-1}.

Enamine (XXI) *of aldehyde* (XX). The aldehyde (XX), (2·1 g) was prepared from khusol (4 g) by oxidation with pyridine–chromic acid complex as reported in an earlier communication.[4] To a solution of the aldehyde (2 g) in dry benzene (45 ml) was added piperidine (1·02 g) and *p*-toluenesulphonic acid (7 mg). The mixture was heated under brisk reflux in N_2 atm for 10 hr using a water separator to remove the water formed during the reaction. Benzene was removed *in vacuo* to afford the crude enamine (2·3 g), b.p. 160° (bath)/0·3 mm.

Khusitone (II) *from enamine* (XXI). A solution of the enamine (1·98 g) in dry benzene (20 ml) was added dropwise during 1 hr to a stirring solution of $Na_2Cr_2O_7{\cdot}2H_2O$ (2·98 g) in dry benzene (20 ml) and acetic acid (10 ml) at 0°. Stirring was further continued for another 2 hr at 0°. The mixture was diluted with water and extracted with benzene. It was washed successively with NaOH aq (10%), dil. HCl, water and dried. The product (1·18 g) was chromatographed over alumina (grade II, 60 g) to give pure (VPC) khusitone (0·8 g), b.p. 128° (bath)/0·55 mm, n_D^{26} 1·5072; $[\alpha]_D^{26}$ −125·5° (*c*, 2) (Found: C, 82·35; H, 10·3. $C_{14}H_{20}O$ requires: C, 82·51; H, 10·16%). IR spectrum was identical with that of natural khusitone (Fig. 1). Semicarbazone was crystallized from ethanol as sharp needles, m.p. 182–183° $[\alpha]_D^{26}$ −59·1° (*c*, 1·1) (Found: N, 15·67. $C_{15}H_{23}ON_3$ requires: N, 16·08%). Mixed m.p. with the semicarbazone of natural khusitone remained undepressed. The IR spectra were also identical.