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STUDIES IN SESQUITERPENES—XXXIII

HIMACHALOL*†

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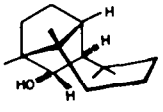
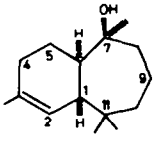
Abstract—Isolation and structure determination of himachalol, a constituent of the essential oil of *Cedrus deodara*, Loud., is described. This alcohol is directly related to the recently described himachalenes.

THE presence of a tertiary alcohol, giving himachalene dihydrochloride on interaction with hydrogen chloride, in the essential oil of Himalayan deodar (*Cedrus deodara*, Loud.) has been reported earlier;[1] these authors named this alcohol himachalol. In extension of our work[2] on this essential oil, we examined, in detail, its alcohol fraction (~15%), which was found to contain, besides (+)-longiborneol (I, 29%) two new sesquiterpene alcohols of m.p. 67–68° (41%) and m.p. 85–86° (30%). The name himachalol has been retained for the alcohol of m.p. 67–68°, because, as will be shown subsequently, this gives himachalene dihydrochloride on treatment with hydrogen chloride;‡ the other alcohol, the structure of which is discussed in the following communication, has been named allohimachalol. In the present paper we describe evidence leading to the absolute stereostructure II for (+)-himachalol.



I



II

Himachalol analyses for $C_{15}H_{26}O$ and is clearly an unsaturated alcohol from its IR spectrum (Fig. 1: OH 3300, 1135, 1030 cm^{-1}; C=C 1650, 867 cm^{-1}). Its PMR spectrum (Fig. 2) shows signals assignable to two quaternary Me's (two 3H sharp s's at 50 and 59 c/s), one vinylic methyl (3H s at 99 c/s), one Me attached to a carbon linked to oxygen (3H sharp s at 72 c/s),[3] and one olefinic proton (1H, essentially a d centred at 330 c/s, J = 3 c/s); the absence of any signal§ for a proton attached to a carbon linked to oxygen shows that the alcohol must be tertiary.

* Communication No. 1128, National Chemical Laboratory, Poona.

† Abstracted from the Ph.D. Thesis (Agra University, 1965) of S. C. Bisarya.

‡ The earlier sample of himachalol,[1] which is liquid, has been found (GLC) to be essentially the total alcohol fraction.

§ Usual range for such protons is δ = 3·5–4·5 ppm.[4]

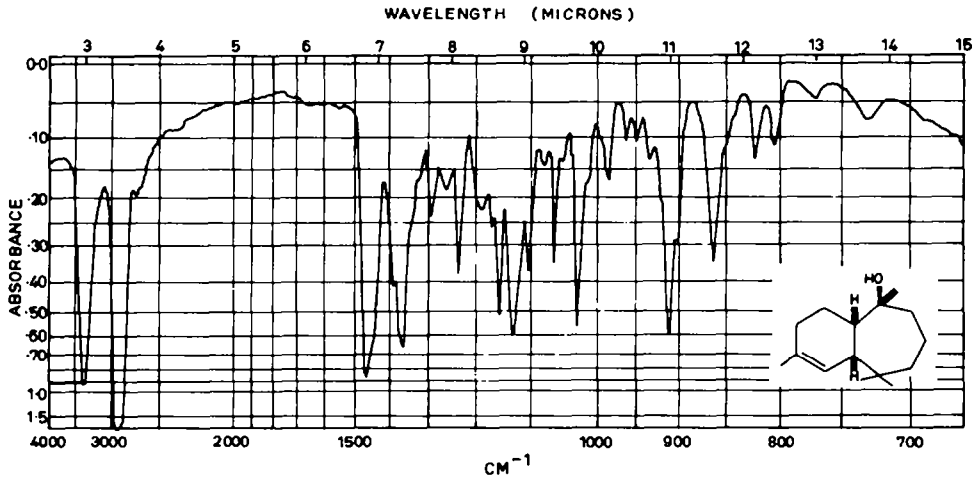


FIG. 1 IR Spectrum of himachalol.

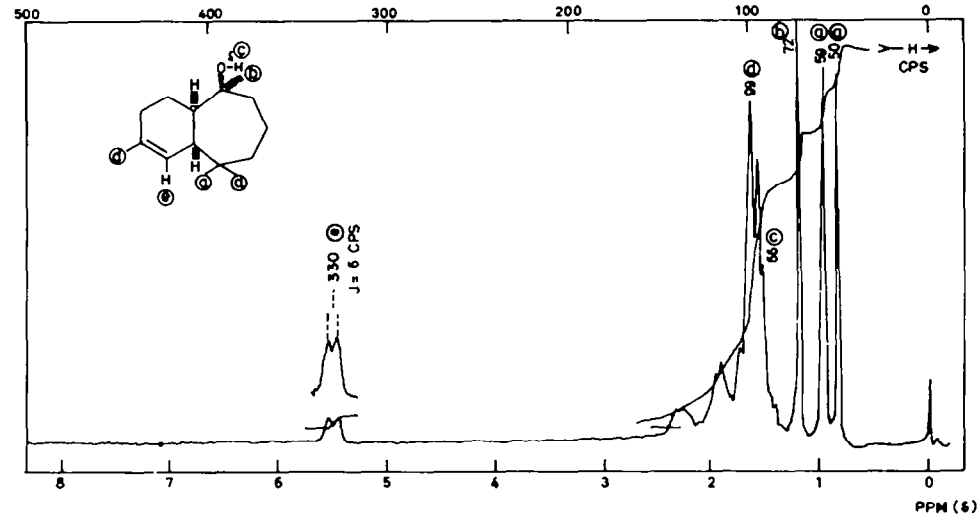
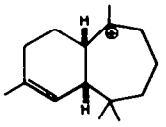
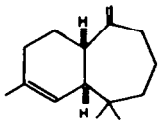


FIG. 2 PMR Spectrum of himachalol.

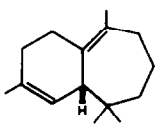
It has been pointed out earlier[5] that the ion III is the most likely biogenetic progenitor of himachalenes (IV, V). As can be seen, the same ion, by substitution, can furnish a tertiary alcohol (VI), which has all the structural requirements deduced above. That this is indeed so, was shown by the following experiments.



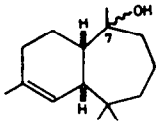
III



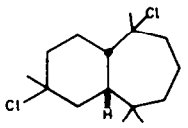
IV



V



VI

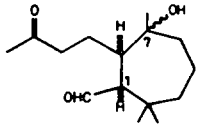


VII

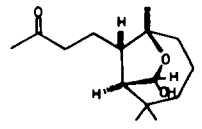
On treatment with dry HCl in AcOH, himachalol readily gave himachalene dihydrochloride (VII).[6] On dehydration with Al_2O_3 at 230°, conditions under which isomerizations are minimal,[7] it furnished, in almost quantitative yield, a hydrocarbon mixture, shown by GLC to consist of two components in the ratio 1:4·5 (increasing retention time). The identity of these hydrocarbons, suspected to be α-himachalene (IV) and β-himachalene (V) respectively from retention times, was established by comparing the IR spectrum and $[\alpha]_D$ of this mixture with those of an authentic mixture of the same composition. The dehydration of himachalol by heating with $KHSO_4$[8] and, by treatment with $POCl_3$–pyridine[9] was also studied. The first reagent gave α- and β-himachalene in the ratio 1:4·5, while under the second set of conditions the ratio of α- to β-himachalene was 1:3. The yields in both cases were almost quantitative. In the case of dehydration with $POCl_3$–pyridine, it was established that the composition of the product is under kinetic control, as under the conditions of reaction α-himachalene remained unchanged.

From the formation of α-himachalene (IV), a compound of established absolute stereochemistry,[10] in the above dehydration reactions, and keeping in view the functional features of himachalol, structure VI follows for this alcohol, in which the only point of ambiguity is the configuration at C_7. This point was clarified as follows:

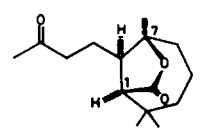
Hydroxylation of himachalol with OsO_4[11] proceeded smoothly to give a crystalline triol. Oxidation with $Pb(OAc)_4$ resulted in a complex mixture. However, $NaIO_4$ in methanol smoothly cleaved the α-glycol linkage to give a product, which was found to be quite labile and hence was studied as such without further purification. That this product is essentially VIII, was clear from its spectral characteristics: CH_3CO (PMR: 3H s at 126 c/s), HC=O (IR: 2800 cm^{-1}; PMR: d centred at 592 c/s, J = 2 c/s), C=O (IR: 1735, 1750 cm^{-1}) and OH (IR: 3520 cm^{-1}). However, in



VIII



IX



X

some samples the aldehyde proton signal integrated for considerably less than a proton, with the appearance of another signal (essentially a d) at ~260 c/s. These results suggest that the aldehyde (VIII) must be slowly cyclizing to give the himiacetal (IX). This in itself requires that the C_7OH and the C_1 aldehyde must be *cis* to each other. In full confirmation of this, chromic acid oxidation of the crude cleavage product (VIII–IX) readily gave in high yield a neutral product, characterized as a γ-lactone (X): C=O (IR: 1740, 1785 cm^{-1}), MeCO (PMR: 3H s at 126 c/s), three quaternary Me's (3H s's at 58·5, 67 and 82 c/s). Since the configuration of H at C_1 has been earlier deduced as α, the C_7 Me must also be α to allow the γ-lactone ring-closure (X). Thus, the C_7OH in himachalol must be β-configurated and the absolute stereostructure II can now be assigned to (+)-himachalol.

EXPERIMENTAL

All m.ps and b.ps are uncorrected. Pet. ether refers to the fraction b.p. 40–60°. All solvent extracts were dried over Na_2SO_4. Optical rotations were measured in $CHCl_3$.

IR spectra were taken on a Perkin-Elmer Infracord model 137E. All PMR spectra were taken in ~10% CCl_4 solution on a Varian Associates A-60 spectrometer with TMS as the internal standard; the signals are recorded in c/s from TMS as zero.

GLC analyses were carried out on "Aerograph" (model A-350-B) using a column (2 meters × 4·5 mm) packed with 20% diethyleneglycol polysuccinate on Chromosorb W and employing H_2 as the carrier gas. Al_2O_3 used for chromatography was made neutral by the HNO_3 method and standardized according to Brockmann. TLC was carried out on 0·5 mm layers of SiO_2-gel containing 15% gypsum.

Isolation of longiborneol, himachalol and allohimachalol

Raw material. The essential oil* (10 litres) was carefully fractionated, under reduced pressure on a Podbielniak column,† at a reflux ratio of 10:1. Thirty-four cuts (being guided mostly by b.p.; if the b.p. remained essentially constant, cuts of not more than 300 ml were collected) were made, which depending on the physical properties (n_D, $[\alpha]_D$), IR spectra and GLC, were pooled into eight groups.‡ Pool No. 6 (Fr. 25–30, b.p. 124–137°/4·5 mm, 1800 ml), consisted of a complex mixture of alcohols and ketones and was used as the raw material for the isolation of himachalol and other components.

Separation into ketonic and non-ketonic portions. GLC (programmed: 100–200°, 5°/min; gas 70 ml/min) of the above material showed it to consist of at least 12 components of which three (GLC components 8, 9, 10, increasing RT) were major. This mixture, which consisted of alcohol and ketones (IR) could not be separated by chromatography on Al_2O_3 and it was found necessary to remove the ketonic material first by treatment with a Girard reagent.[12]

The above material (20 g, λ_{max} 239 mμ, ε 4000), Girard P reagent (20 g; m.p. 199–200°), 95% EtOH (630 ml) and gl. AcOH (50 ml) were mixed, refluxed (6 hr) on a steam-bath, cooled to room temp and poured into ice–water (4·9 l.) containing 40 g of Na_2CO_3, with stirring. This was extracted with pet. ether (150 ml × 6), the extracts washed with water (200 ml × 3), brine (200 ml × 2) and dried. The solvent was flashed off and the residue (15·5 g) distilled to give a non-ketonic portion (15 g), b.p. 99–117°/2 mm, n_D^{30} 1·5057, $[\alpha]_D$ +40·8; λ_{max} 239 mμ, ε 1000. This product was employed for the isolation of alcohols. The aqueous portion and the washings were combined and cautiously acidified with cooling with conc H_2SO_4 (120 ml). The acidified soln, after having been allowed to stand at room temp (23–29°) for 24 hr, was extracted with pet. ether (150 ml × 5), the extracts washed with Na_2CO_3 aq (5%; 120 ml × 3), water and brine and dried. The solvent was removed and the residue (3·8 g) distilled to give the ketonic portion‡ (3·5 g), b.p. 123–124°/1·9 mm, n_D^{30} 1·4971; λ_{max} 239 mμ, ε 12,000.

* Supplied by the R.R. Laboratory, Jammu (India).

† Model No. 3730, Podbielniak, Chicago, USA.

‡ Full details of these will be published subsequently in a paper dealing with the minor constituents of the essential oil.

Himachalol (GLC component 9). The non-ketonic product (40 g) was chromatographed over Al_2O_3/II (1200 g; 24·5 cm × 8 cm), while monitoring various fractions by GLC.

Fraction 1	Pet. ether	6 × 700 ml	3·9 g, himachalenes (GLC)
Fraction 2	Pet. ether–25% C_6H_6	5 × 700 ml	0·6 g
Fraction 3	Pet. ether–50% C_6H_6	19 × 700 ml	3·8 g, essentially GLC components 8, 9 in the ratio 3:7
Fraction 4	C_6H_6	23 × 700 ml	10·0 g, essentially GLC component 9; slowly solidified, m.p. 45–50°
Fraction 5	C_6H_6	5 × 700 ml	1·9 g
Fraction 6	C_6H_6–1% MeOH	6 × 700 ml	2·0 g
Fraction 7	C_6H_6–2% MeOH	15 × 700 ml	16·7 g, GLC component 9, 10 in the ratio 3:2

Fraction 4 (10 g) was rechromatographed over Al_2O_3/II (300 g, 25 cm × 4 cm) when after pet. ether (6 × 200 ml) elution, pet. ether–50% C_6H_6 (15 × 200 ml) eluted with 1·6 g of a mixture of longiborneol and himachalol (GLC peaks 8, 9) and, C_6H_6 (27 × 200 ml) eluted 5·4 g of crude himachalol (m.p. 50–53°). The latter was recrystallized from acetonitrile at −15° to give a solid (4·8 g), m.p. 53–56°. Two crystallizations from the same solvent at ~5° yielded pure himachalol (2·4 g) as white needles, m.p. 67–68°, $[\alpha]_D$ +72·9° (*c*, 1·8%). (Found: C, 80·8; H, 12·0. $C_{15}H_{26}O$ requires: C, 81·0; H, 11·8%).

Longiborneol (GLC component 8). Fraction 3 above (3·8 g) was combined with the mother liquors of himachalol (3 g, see above), as both had similar composition (GLC) and fractionated on a spinning-band column,* under total reflux. The first 7 fractions (1·2 g, b.p. 120–124°/3 mm) contained himachalol and longiborneol (GLC) in ~1:1 ratio. More quantity of material of similar composition was collected from another experiment and the total quantity (4·54 g) fractionated, once again, as above. This fractionation gave some fractions (No. 5–12, 1·88 g) having ~85–90% of GLC component 8. This was chromatographed over Al_2O_3/II (19 cm × 1·8 cm):

Fraction 1	Pet. ether	15 × 30 ml	0·39 g
Fraction 2	Pet. ether–25% C_6H_6	7 × 30 ml	0·27 g
Fraction 3	Pet. ether–50% C_6H_6	2 × 30 ml	0·04 g
Fraction 4	Pet. ether–50% C_6H_6	6 × 30 ml	1·03 g, 97% pure 8 m.p. 88–90°
Fraction 5	Pet. ether–50% C_6H_6	3 × 30 ml	0·26 g, 75% pure 8

Fraction 4 was crystallized thrice from acetonitrile to get white needles (0·5 g) m.p. 103–105°, $[\alpha]_D$ +14·8° (*c*, 3·2%). IR spectrum: OH 3360, 1050 cm^{-1}. PMR spectrum: quaternary Me's 50, 50, 56 c/s; CHOH broad hump centred at 220 c/s. Mixed m.p. with an authentic sample[13] (m.p. 106–107°) of longiborneol was 105–106°. (Found: C, 81·5; H, 12·0. $C_{15}H_{26}O$ requires: C, 81·0; H, 11·8%).

Allohimachalol (GLC component 10). The C_6H_6–2% MeOH eluted fractions (37 g; see under himachalol) were combined and chromatographed over Al_2O_3/II (1100 g, 22 cm × 8 cm), while monitoring by GLC:

Fraction 1	Pet. ether	4 × 1 l.	—
Fraction 2	Pet. ether–50% C_6H_6	5 × 1 l.	6·2 g almost pure himachalol
Fraction 3	Pet. ether–50% C_6H_6	19 × 1 l.	14·5 g of 9 and 10, ratio 2:3
Fraction 4	C_6H_6	23 × 1 l.	6·2 g of 9 and 10, ratio 2:3
Fraction 5	C_6H_6–1% MeOH	5 × 1 l.	0·12 g
Fraction 6	C_6H_6–2% MeOH	5 × 1 l.	6·4 g, viscous, brown product

Fractions 3–4 (20·7 g) were combined and fractionated on a spinning band column, under total reflux. Separation was very inadequate and only towards the end, a few fractions No. 29–30, b.p. 130°/3 mm, 1·5 g; (total fractions 31) containing 80% GLC component 10, partly sodidified. This material was thrice crystallized from aqueous acetonitrile (1:9) to give white shining needles (0·6 g), m.p. 85–86°, $[\alpha]_D$ +37·4° (*c*, 3·3%). (Found: C, 80·9; H, 11·8. $C_{15}H_{26}O$ requires: C, 81·0; H, 11·8%).

* Model No. NF 115 (computed theoretical plates: 23), manufactured by Nester and Faust, Newark, USA.

Action of hydrogen chloride on himachalol

Himachalol (50 mg) in gl. AcOH (0·4 ml) was treated with a slow stream of dry HCl gas at ~0° for 1 hr (anhyd conditions) and the colored product allowed to attain room temp (27°). The solvent was flashed off under suction and the residue on crystallization from C_6H_6–pet. ether (1:4) yielded colorless, fine needles (17 mg), m.p. 117–118° (dec); mixed m.p. with an authentic sample (m.p. 118–119°) was 117·5–118·5°.

Dehydration of himachalol

(i) *With alumina.* Himachalol (52 mg) was mixed with pyridine-treated alumina (200 mg)[7b] and heated (N_2) at 225–230° for 2 hr. The reaction mixture was slurried with pet. ether (20 ml), filtered and the alumina washed with ether (10 ml × 2). From the combined filtrates, solvent was removed to give a mobile liquid (48 mg) which was distilled: b.p. 120–125° (bath)/3 mm, yield 45 mg.

(ii) *With* $KHSO_4$. Himachalol (100 mg) on distillation over $KHSO_4$ (5 mg; freshly fused and powdered) furnished a colorless, mobile liquid, b.p. 128–132° (bath)/3 mm, $[\alpha]_D$ +149·6° (*c*, 2%), yield 90 mg; a synthetic mixture of α-himachalene (1 part) and β-himachalene (4·5 parts) shows $[\alpha]_D$ +150° (calc ~ +150°).

(iii) *With* $POCl_3$–*pyridine.* Himachalol (100 mg), dry pyridine (1·6 ml) and $POCl_3$ (1·0 ml) were mixed and refluxed (oil bath) for 6 hr. The reaction mixture was cooled, poured into ice–water (15 ml) and extracted with pet. ether (6 ml × 3). The extract was washed with water, HCl aq, $NaHCO_3$ aq, water, brine and dried. Solvent was removed and the residue distilled: b.p. 120–125° (bath)/3 mm, yield 82 mg (90%).

GLC of all the samples was carried out at 160°, and gas pressure 15 lb psi; the same two components with RRT of 1, 1·25 were indicated.

Hydroxylation oh himachalol

A soln of OsO_4 (325 mg) in 1:1 ether–pet. ether (15 ml) was slowly added to himachalol (275 mg) dissolved in ether–pet. ether (1:1, 15 ml) containing anhyd pyridine (0·8 ml), and the reaction mixture left aside at room temp (21–30°) for 8 days. The crystalline osmic ester (580 mg, m.p. 145–148°) was collected, dissolved in dry benzene (45 ml) and the solution saturated with dry H_2S with cooling. The brownish-black ppt was filtered off and washed with dry benzene (5 ml). The solvent was removed under suction at ~40° and the solid residue (240 mg, m.p. 112–115°) crystallized from acetonitrile to afford colorless needles (180 mg) m.p. 123–123·5°, $[\alpha]_D$ −55·9° (*c*, 1·5%). IR spectrum: OH 3327, 1025 cm^{-1}; other st. band: 858, 908, 1128 cm^{-1}. (Found: C, 70·7; H, 11·0. $C_{15}H_{28}O_3$ requires: C, 70·3; H, 11·0%).

Action of $NaIO_4$ *on the above triol*

A soln of $NaIO_4$ (0·2 g dissolved in 0·5 ml water and diluted with 5 ml of MeOH) was added with swirling to the triol (100 mg) dissolved in MeOH (5 ml) and, the reaction mixture left aside at room temp (25–29°) in the dark. The course of the reaction was monitored by TLC (solvent: C_6H_6–40% EtOAc) every 6 hr. After 18 hr, all the triol had disappeared, giving essentially a single new spot. At this stage the solvent was removed at room temp under suction, and the residue diluted with water (15 ml) and extracted with ether (3 × 10 ml). The extract was washed with water, dried and the solvent removed, under suction, to give a gum (92 mg; single spot in TLC), which was *immediately* used in the next step. (The material, after standing at room temp for an hr, shows a number of compounds by TLC).

Chromic acid oxidation of crude VIII

The above product (86 mg), dissolved in acetone (1·5 ml; distilled over $KMnO_4$), was treated slowly with a soln (0·4 ml) of CrO_3 (266·7 mg dissolved in 0·4 ml water and 0·2 ml conc H_2SO_4 and diluted with water to 10 ml) at ~20° and the reaction mixture left aside for 30 hr. This was diluted with water (15 ml), extracted with ether (3 × 10 ml) and the extracts worked up in the usual manner to give after solvent removal, a product (77 mg) showing one major spot in TLC (solvent: C_6H_6–40% EtOAc). This was purified by TLC to give after distillation, a colorless liquid (44 mg), b.p. 178–184° (bath)/3 mm. (Found: C, 70·7; H, 9·5. $C_{15}H_{24}O_3$ requires: C, 71·4; H, 9·6%).

REFERENCES

[1] G. S. Krishna Rao, Sukh Dev and P. C. Guha, *J. Indian Chem.* **29**, 721 (1952).

[2] T. C. Joseph and Sukh Dev, *Tetrahedron Letters* 216 (1961); Parts XXIX–XXXII of the present series: Studies in Sesquiterpenes.

[3] L. M. Jackman, *Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry* pp. 51–54. Pergamon Press, London (1959).
[4] J. N. Shoolery and M. T. Rogers, *J. Am. Chem. Soc.* **80**, 5121 (1958).
[5] T. C. Joseph and Sukh Dev, *Tetrahedron* **24**, 3809 (1968).
[6] T. C. Joseph and Sukh Dev, *Tetrahedron* **24**, 3841 (1968).
[7] [a] L. Beranek, M. Kraus, K. Kochloefl and V. Bazant, *Coll. Czech. Chem. Comm.* **25**, 2513 (1960);
[b] E. V. Rudloff, *Canad. J. Chem.* **39**, 1860 (1961);
[c] E. J. Corey and A. G. Hortmann, *J. Am. Chem. Soc.* **85**, 4033 (1963).
[8] H. H. Inhoffen, K. Weissermel and G. Quinkert, *Ber. Dtsch. Chem. Ges.* **88**, 1313 (1955).
[9] J. L. Beton, T. G. Halsall, E. R. H. Jones and P. C. Phillips, *J. Chem. Soc.* 753 (1957); R. R. Sauers, *J. Am. Chem. Soc.* **81**, 4873 (1959).
[10] T. C. Joseph and Sukh Dev, *Tetrahedron* **24**, 3852 (1968).
[11] For a review see: F. D. Gunstone in *Advances in Org. Chem. Methods and results* (Edited by R. A. Raphael, E. C. Taylor and H. Wynberg) Vol. I; pp. 110–117. Interscience, New York (1960).
[12] For a review see: O. H. Wheeler, *Chem. Rev.* **62**, 205 (1962); cf.: C. L. Teitelbaum, *J. Org. Chem.* **23**, 646 (1958).
[13] U. R. Nayak and Sukh Dev, *Tetrahedron* **8**, 42 (1960).