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STUDIES IN SESQUITERPENES—XXXI

THE ABSOLUTE STEREOCHEMISTRY OF HIMACHALENES*

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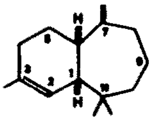
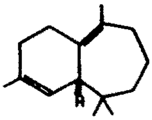
Abstract—The absolute stereochemistry of α- and β-himachalene has been deduced.

In a previous publication[1] we describe evidence leading to the establishment of the gross structures of himachalenes. The work, being reported in this communication, enables us to assign the absolute stereo-structures I and II to α- and β-himachalene respectively.



I

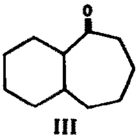


II

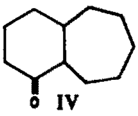
α-Himachalene

Nature of ring junction. A worthwhile approach to the solution of this problem appeared to be the preparation of 2- or 7-oxohimachalane and a study of its equilibration. This, of course, is based on the presumption that the relative stabilities of the himachalanes with *cis*- and *trans*-ring-fusion are deducible, as discussed below, from the principles of conformational analysis.

It has been experimentally established that in both αβ-tetramethylenecycloheptanone (III)[2] and αβ-pentamethylenecyclohexanone (IV),[3] the *trans*-isomers are favoured by a large factor at equilibration.† Unlike decalins, *cis*- and *trans*-perhydrobenzosuberane can assume a large number of conformations. A study of models (Drieding) and an estimation of the interaction energy difference between



III



IV

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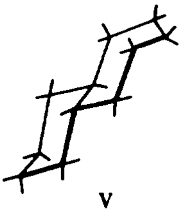
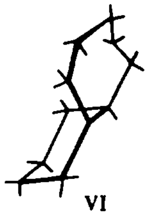
* Communication No. 1126, National Chemical Laboratory, Poona.

† For III: 100% *trans*-ketone after base-equilibration of *cis*-ketone with NaOMe for 0·5 hr.
IV: 87 ± 2·5% *trans*-ketone after equilibration of *cis*-ketone using NaOMe for 20 hr.

the various conformers, according to the method of Turner,[4,*] showed that a reasonable estimate of energy barrier between the energetically more favourable conformer (V) of *trans*-perhydrobenzosuberane and the corresponding conformer (VI) of the *cis*-isomer, would be of the order of 2–3 kcal/mole, a value which would ensure[10] almost complete epimerization of the *cis*- to the *trans*-ketones at equilibrium, as has actually been observed experimentally. A similar analysis of the himachalanes (*cis*- and *trans*-ring junction) reveals that the presence of the *gem*-dimethyl grouping at C_{11} (himachalene numbering) accentuates the energy difference (estimated to be ~4 kcal/mole) between the *cis*- and *trans*-isomers, such that the *trans*-ketones (2 or 7-oxohimachalanes) would be favoured at equilibrium.


V


VI

Ozonolysis of α-himachalene under carefully controlled conditions (in EtOAc containing 1% pyridine and, 1 molar equiv of ozone at −70°) was investigated with the expectation that the vinylidene linkage would be attacked preferentially to furnish the required ketone (VII) suitable for equilibration studies. However, surprisingly, the trisubstituted olefinic linkage was attacked preferentially. Though, this result could not have been predicted *a priori* for a *cis*- ring-fusion of the rings of α-himachalene, a study of models indicates that only if the ring-junction is *cis*, a preferential attack on the trisubstituted double bond could possibly be rationalized.

The only alternative[†] available was to study the equilibration of ketone VIII, described in the preceding communication, though this ketone is not ideally suited for equilibration studies as results could be complicated because of an additional site of epimerization (C_3). However, clear-cut evidence in favour of *cis*-junction in α-himachalene could be obtained from this study.

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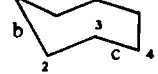
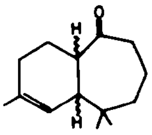
[*] It is agreed that the stable conformation of cycloheptane is a somewhat deformed chair.[5-8,‡] Cyclohexane chair can be fused onto a cycloheptane chair at any one of the four bonds marked a, b, c, d, without deforming the original conformations. Thus, we have a total of four conformers possible for *trans*-fusion and eight for *cis*-fusion, ignoring, of course, the mirror-images and considering only chair-chair conformations. The interaction energies of these structures were calculated by examining the models for extra butane interactions, resulting on fusion of the two chairs, and evaluating their energy-content from the potential energy curve[9] and the dihedral angle (accuracy of measurement, ±5°) of interaction.



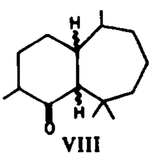
It may also be pointed out that structures resulting from fusion of the cyclohexane chair at a or b are readily interconvertible by a slight manipulation of the carbon 4; the other two structures are quite rigid. Thus entropy factor (like the interaction energy) favours structures with fusion at a or b.[8]

[†] In connection with the structure of himachalene monohydrochloride, the *trans*-ketone corresponding to VII has been prepared and found to be stable to epimerizing conditions (Part XXXII of this series).

[‡] Detailed calculations[7,8] give a value of 2·75–2·49 kcals as the energy difference between the boat and the chair conformation of cycloheptane, a value close to that (2·8 kcals) obtained[5] by the method of Turner.[4]



VII



VIII

The ketone VIII obtained by BF_3-induced isomerization of dihydro-α-himachalene epoxide (henceforth referred to as ketone-1) was found to be quite labile. By mere adsorption (from its pet. ether solution) on a column of Al_2O_3 (II/neutral), it underwent epimerization to an isomer (ketone-II) to the extent of ~10%. When pure ketone-I or ketone-II or their mixtures were equilibrated with t-BuOK in refluxing t-BuOH, the product consisted of four components (GLC), in which the major component (55%) was a new ketone (ketone-IV), while ketone-II and ketone-I were formed to the extent of 30% and 5% respectively. It has been possible to separate these components with the exception of the other minor ketone III. Table 1 summarizes the properties of these isomeric ketones.

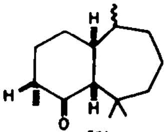
TABLE 1. PROPERTIES OF ISOMERIC C_2-KETONES

	Ketone-I	Ketone-II	Ketone-IV*
M.p.	42–43°	—	—
B.p.	—	128° (bath)/1·5 mm	128–130° (bath)/2 mm
n_D^{30}	—	1·4885	1·4888
$[\alpha]_D$	−93·56°	−10·6°	+79·6°
$\nu^{C=O}$ (cm^{-1})	1697	1705	1700
RRT†	1	0·7	1·1

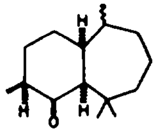
* Only 88% pure by GLC, the contaminant being ketone-I (7%) and ketone-II (5%).

† RRT = relative retention time in terms of ketone-I; diethyleneglycol polysuccinate, 160°, 50 ml (H_2)/min. RRT of ketone-III: 0·8.

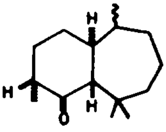
Four stereo-structures (IX–XII) are possible for the ketone VIII.[11] Since ketone-I is present to the least extent at equilibrium, this must represent the thermodynamically least stable isomer (IX, *cis*-fusion, C_3-Me axial) while ketone-IV which is greatly favoured at equilibration should be XI, configurationally the most stable structure. Since ketone-I is directly related to α-himachalene, it follows that *in α-himachalene the rings must be* cis-*fused*. On the basis of this formulation for α-himachalene, a closer look at the results of equilibration of the ketones can be had.



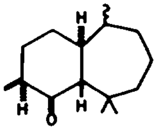
IX



X



XI



XII

The epoxidation of dihydro-α-himachalene should quite reasonably occur from the less-hindered convex-face of the molecule, when dihydro-α-himachalene epoxide* can be written as XIII. The BF_3-induced isomerization of the epoxide is visualised as a one-step concerted process[12] leading to the stereostructure IX for the ketone-I. Of the several conformers possible for IX, the conformation XIV appears to be most likely from a study of its PMR spectrum (Fig. 1). Ketone-I displays its quaternary Me's at 45 and 73 c/s while the other two Me's occur as doublets centred at 58 and 59 c/s. It is clearly seen that one of the quaternary Me's has suffered considerable paramagnetic shift which could be explained only due to the anisotropy of C=O

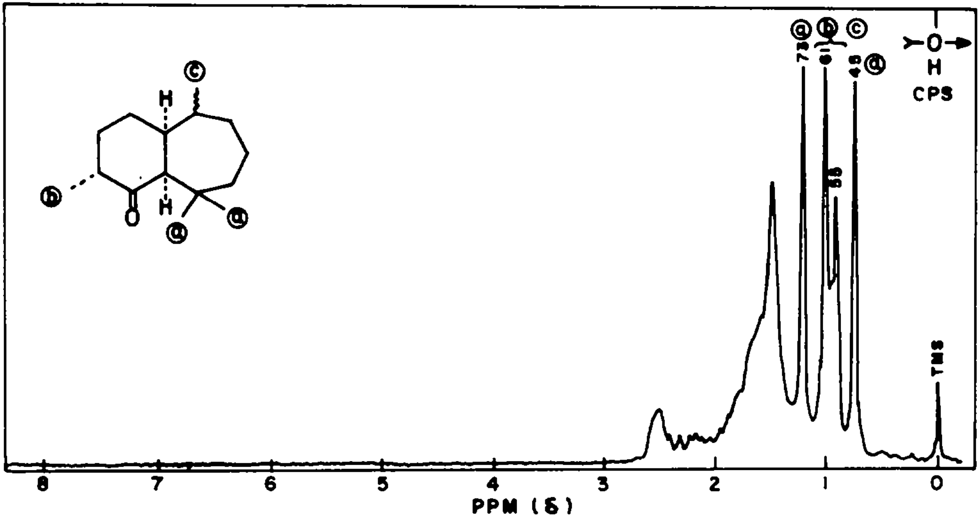
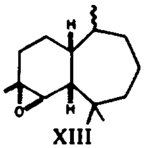
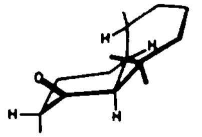


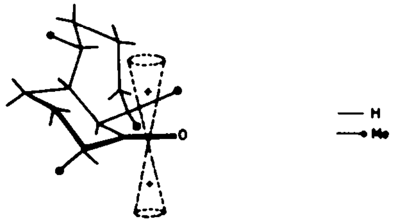
Fig. 1 PMR Spectrum of ketone-(IX).



XIII



XIV



XV

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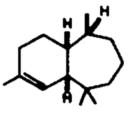
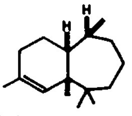
* An examination of models shows that in the hydrogenation of α-himachalene, the attack on the semi-cyclic olefinic linkage could occur so as to give (i) or (ii) depending on the conformation of the 7-membered

i



ii



ring in α-himachalene. However, in dihydro-α-himachalene it is only the convex face which is less hindered for attack by the peracid on the trisubstituted olefinic linkage.

linkage, and for this to be effective only conformation XIV is tenable as is clear from XV. Similar cases of deshielding have been recorded in literature.[13] It must be pointed out that one consequence of this preferred conformation* for ketone-I would be that the configuration of the Me at C_7 should be as shown in XIV, as in the alternative configuration the interaction energy between the C_7-Me and the β-Me at C_{11} would be prohibitive.

The preferred conformation for ketone-IV would appear to be XVI, as this is also in accord with its PMR spectrum (Fig. 2): quaternary Me signals at 55 and 58 c/s.

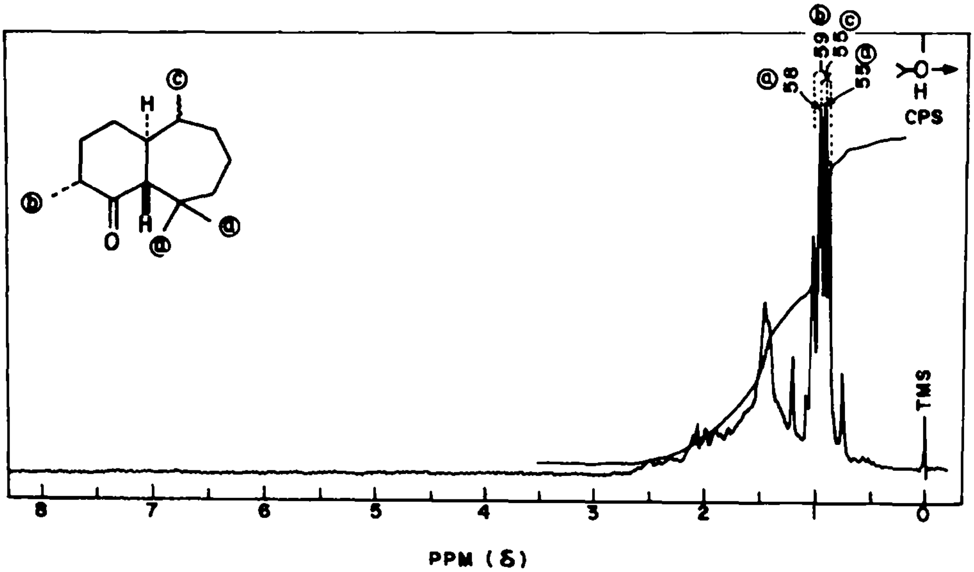


Fig. 2 PMR Spectrum of ketone-(XI).

One of the two alternative stereostructures X, XII must be assigned to the ketone-II. A decision in favour of X can be arrived at on the basis of the fact that epimerization at C_1 in ketone-I (XIV) would necessarily take place through the "flip-over" conformation as the *trans*-locking of the rings is possible only through the diequatorial bonds. This would mean that epimerization at C_1 would directly result in the most stable structure (ketone-IV). However, since, during partial equilibration of ketone-I (IX) over alumina, only ketone-II results, this must involve epimerization at C_3 and consequently ketone-II must be represented by X. The preferred conformation for this would appear to be XVII, which is consistent with its PMR spectrum (Fig. 3).

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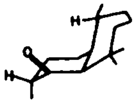
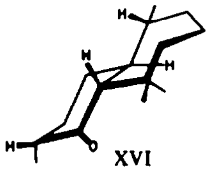
* From a consideration of interaction energy it is hard to see why this conformation should be preferred over iii. However, the "flip-over" conformation of XIV, in which the C_3-Me and the C_6—C_7 bond would

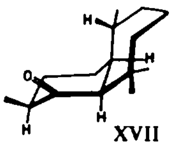


iii

become equatorial, would appear to be less likely as in these the C_1—C_{11} becomes axial and this carries a *gem*-dimethyl group, thus greatly increasing the interaction energy.



XVI



XVII

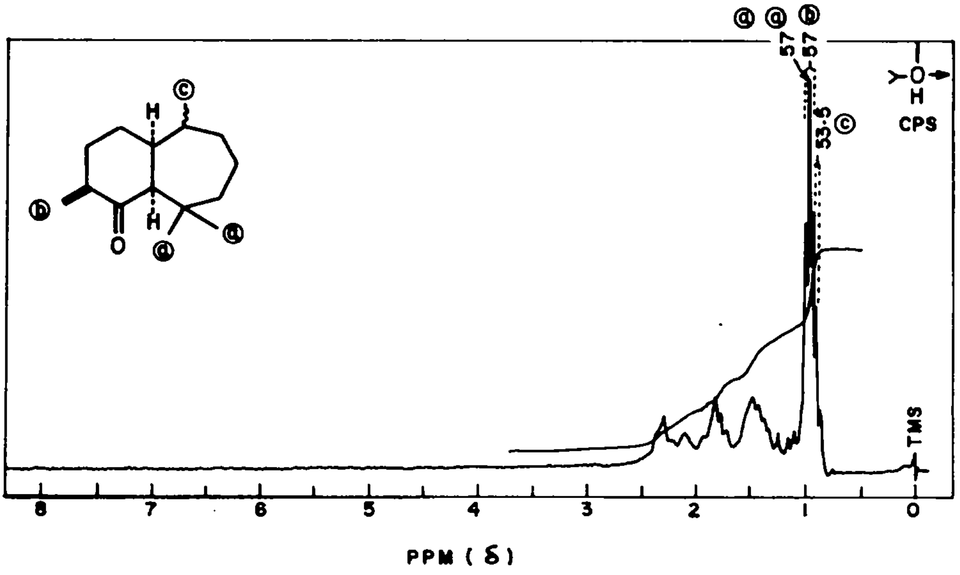


FIG. 3 PMR Spectrum of ketone-(X).

Absolute stereochemistry. The circular dichroism (CD) of the three isomeric ketones (IX, XI and X) is shown in Fig. 4. The signs of Cotton effect, predicted on the basis of octant rule,[14] for their preferred conformations (XIV, XVI and XVII respectively) are indicated in Fig. 5. As can be seen there is excellent agreement between the observed and the predicted nature of the Cotton effects and this requires that these structures (conformations) and not their mirror-images represent the absolute stereochemistry. This leads to the absolute stereostructure I for α-himachalene.

The above conclusion has been further checked by a direct chemical correlation of α-himachalene with a compound of known absolute stereochemistry.

Dihydro-α-himachalene (XVIII) was converted to ketone XXI by following the procedure outlined in Fig. 6. It was anticipated that the product from the pyrolysis of the dicarboxylic acid (XX) would be thermodynamically equilibrated.[15] The product was purified through its semicarbazone and the IR spectrum of the regenerated ketone was found to be almost superimposable on that of the crude product from the pyrolysis reaction, showing that essentially a single ketone was produced in the pyrolytic reaction. The ketone is expected to have the stable *trans*-ring-fusion in view of the known behaviour of the bicyclo-[5.3.0]-decane.[16] In attempted equilibration over $KOBu^t$, it was recovered unchanged.

Munavalli and Ourisson[17] have degraded longifolene (XXII), a compound of well-established absolute stereochemistry,[18] to ketone XXIII by an unambiguous

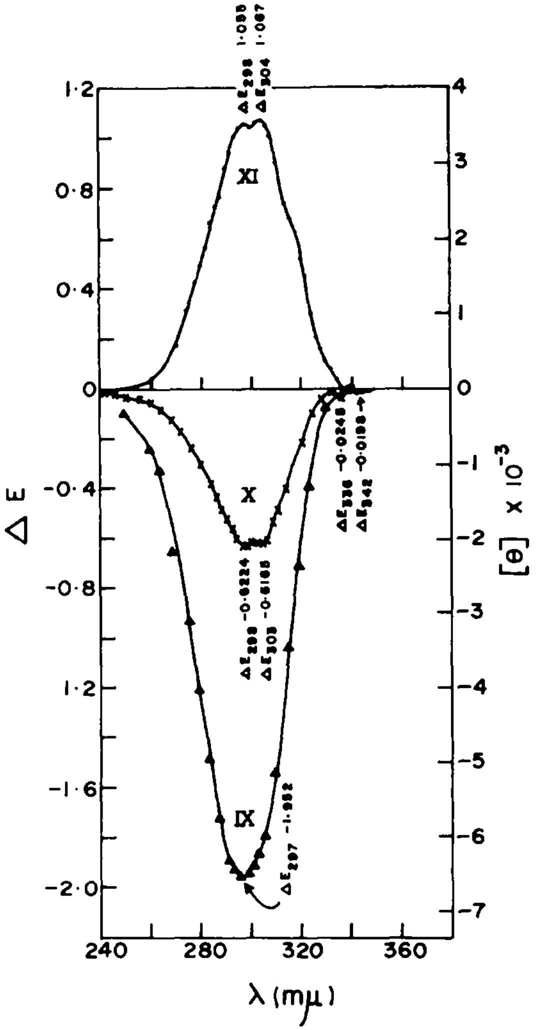
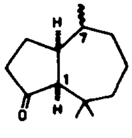


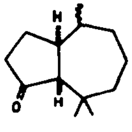
FIG. 4 CD Curves of ketones IX, X and XI.

route. A direct comparison of the IR spectrum of this ketone with that of our material, described above showed the two to be clearly different. However, when these authors passed their ketone (XXIII) through a column of alumina, equilibration took place

XXII



XXIII



XXIV

to produce a material having its IR spectrum almost identical with that of our ketone. Since by the alumina treatment epimerization only at C_1 is possible, the epimer must be represented by XXIV. Figure 7 depicts the CD curves for these three

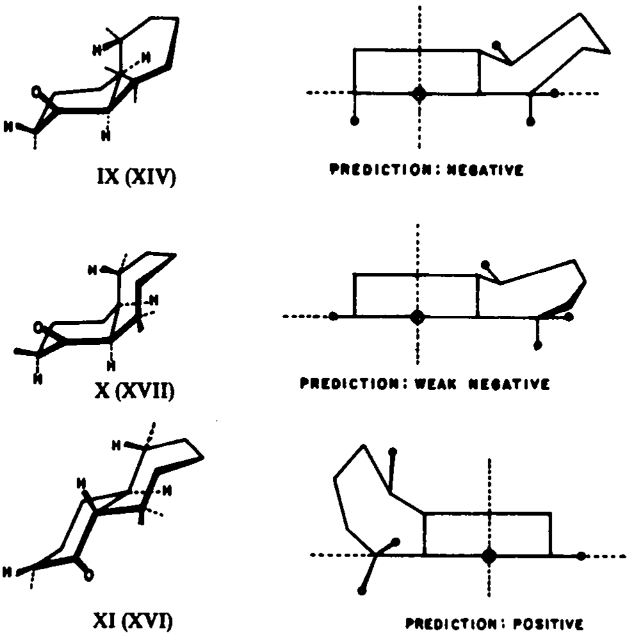
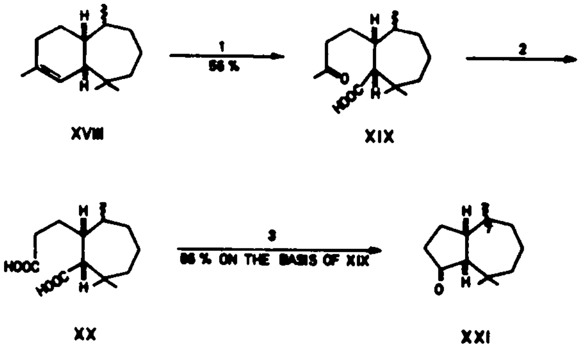


FIG. 5 Octant diagrams of ketones IX, X and XI.



REAGENTS:

1 O_3, $CHCl_3$; H_2O_2
2 NaOBr
3 Ba SALT PYROLYSIS

FIG. 6 Degradation of dihydro-α-himachalene.

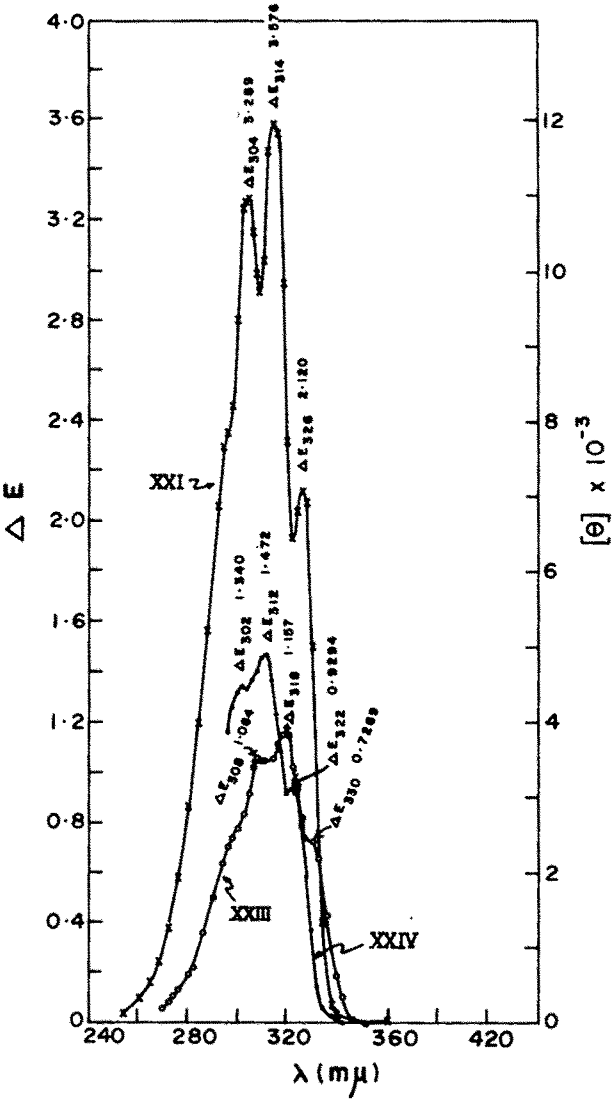


FIG. 7 CD Curves of ketones XXI, XXIII and XXIV.

ketones. It is at once evident that ketones XXI and XXIV have the same sign and position of the CD maxima and consequently must have identical absolute stereochemistry at the ring-junctions.* Thus, α-himachalene must have the same absolute stereochemistry at the common reference points (C_2, C_6) as longifolene and the absolute stereostructure I, thus, follows for α-himachalene.

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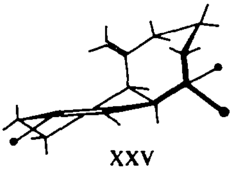
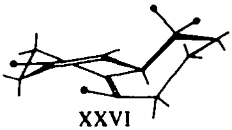
* Since, the amplitudes are different, ketones XXI and XXIV must differ in the stereochemistry at C_7. As pointed out earlier, because of the PMR spectral features of ketone-I (IX) the C_7—Me in IX is considered to be α-oriented (XIV) and hence, it should also be α-configurated in all other compounds derived from dihydro-α-himachalene. However, Munavalli and Ourisson[17] also prefer α-configuration at C_7 for their ketone XXIV. No clear cut decision is possible at present.

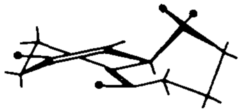
Several conformations for α-himachelene are possible assuming that both the rings occur in quasi-chair conformation. The conformation XXV[*] would appear to account best for the PMR spectrum, wherein both the quaternary Me's have similar chemical shifts (58, 60 c/s) and the vinylic proton on the trisubstituted olefinic bond must make a dihedral angle of ~90° with the adjacent proton at the ring-junction to account for its non-coupling.

β-*Himachalene*

Since α- and β-himachalenes are related through the crystalline dihydrochloride during the formation of which the asymmetric centre at C_1 remains unaffected, α- and β-himachalenes must have the same absolute stereochemistry at C_1 and consequently β-himachalene, must be represented by II. Conformations XXVI–XXVII would appear to fit best for β-himachalene, which account for the observed shielding of one of the quaternary Me's and in these conformations, the mutual orientation of the olefinic linkage (C_6—C_7) and one of the Me's at C_{11} is such as to meet this requirement. The dihedral angle between the olefinic proton and the tert. hydrogen at the ring-junction is also in accord with the type of signal observed for the vinylic proton.


XXV


XXVI


XXVII

EXPERIMENTAL

For general remarks see Part XXIX of this series.

GLC was carried out on 'Aerograph' model A-350-B, using H_2 as the carrier gas and a 2-meter column (outside diam 6 mm) packed with 20% diethyleneglycol polysuccinate on Chromosorb W.

Chromatographic alumina was made neutral by the HNO_3 method and standardized according to Brockmann.

Ozonolysis of α-himachalene

A soln of α-himachalene (1·2 g) in EtOAc (30 ml) containing 1% pyridine, was ozonized at −70° by bubbling ozonized O_2 (160 mg/hr for 100 min, i.e. 1 mole equiv). The solvent was flashed off at room temp under suction and the ozonide reductively decomposed[19] by stirring with LAH (0·4 g) in ether (60 ml) for 2 hr under cooling. The reaction mixture was treated with a sat sod potassium tartarate aq (10 ml) with cooling, and the product extracted with ether (25 ml × 4), washed and dried. After solvent removal, a gummy product (1·2 g) was obtained, which was chromatographed over Al_2O_3 (II: 18 cm × 1·6 cm).

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[*] This conformation should lead to dihydro-α-himachalene wherein the Me at C_7 would be *trans* to the bridgehead proton; this is opposite to what has been deduced earlier in connection with the conformation of ketone-I. This could be rationalized on the reasonable assumption that the conformation in which the molecule gets adsorbed on the catalyst surface is different from this.

Pet. ether (50 ml × 4) eluted 700 mg of a gum, which was evaporatively distilled: b.p. 157° (bath)/1 mm, yield 0·6 g; IR spectrum: OH 3333 cm^{-1}, $>C{=}CH_2$ 893 cm^{-1}. (Found: C, 75·6; H, 12·1. $C_{15}H_{24}O_2$ requires: C, 75·0; H, 11·8%).

Epimerization of ketone-I

(i) *Epimerization over* Al_2O_3. Ketone-I (m.p. 42–43°, 103 mg) in 0·5 ml pet. ether was adsorbed on a column (27 cm × 0·7 cm) of alumina (neutral/II) and eluted, after 40 hr, with pet. ether (50 ml × 2). The product (95 mg) had: b.p. 125–128° (bath)/1 mm, $[\alpha]_D$ −87·2° (*c*, 3·2%). Its GLC (temp 160°, gas flow: 50 ml/min) showed ~10% of ketone-II.

(ii) *Equilibration with* KOBu^t. To a soln of 0·2 g K in t-BuOH (5 ml), ketone-I (102 mg) was added and the mixture refluxed for 9 hr under N_2. The reaction mixture was diluted with HClaq and the product extracted with ether. Usual work-up gave 75 mg of a product of b.p. 140–145° (bath)/3 mm, n_D^{30} 1·4905, $[\alpha]_D$ +19·9° (*c*, 2·5%).

Likewise, when ketone-II (42 mg, see below) was equilibrated, as above, a product with $[\alpha]_D$ +21·8° (*c*, 1·1%) was obtained.

Both the products showed similar patterns in GLC (same conditions as under i).

Isolation of ketone-II *and ketone*-IV

A mixture of ketone-I and ketone-II (5:1, 0·72 g) was refluxed with KOBu^t in t-BuOH (1·5 g K in 38 ml t-BuOH) for 3 hr (N_2) and then worked up as above to give a product (0·63 g), b.p. 117–118°/2 mm. The product (0·46 g) was chromatographed over Al_2O_3 (II; 24 cm × 1·7 cm):

Fraction 1	Pet. ether	20 ml × 5	42 mg
Fraction 2	Pet. ether	20 ml × 3	72 mg of ketone-II.
Fraction 3	Pet. ether	20 ml × 8	86 mg of a mixture.
Fraction 4	Pet. ether	40 ml × 12	185 mg of 75% pure ketone-IV
	10% Bz. in P.E.	40 ml × 4	
	Benzene	30 ml × 2	
Fraction 5	Benzene	30 ml × 8	5 mg

Distillation of fraction 2 gave pure ketone-II having characteristics recorded in Table 1. (Found: C, 81·37; H, 11·72. $C_{15}H_{26}O$ requires: C, 81·01; H, 11·79%).

Fraction 4 (160 mg), rich in ketone-IV, was rechromatographed over Al_2O_3 (II; 27 cm × 1 cm). The major portion (70 mg) which was eluted with pet. ether (40 ml × 10) was 88% pure by GLC (see Table 1). (Found: C, 81·08; H, 12·12. $C_{15}H_{26}O$ requires: C, 81·01; H, 11·79%).

Ozonolysis of dihydro-α-himachalene

A soln of dihydro-α-himachalene (5·3 g) in $CHCl_3$ (60 ml) containing pyridine (1%) was ozonized at −10° by bubbling ozonized O_2 (~180 mg/hr) till it was no longer absorbed (6 hr; KI test). The solvent was removed under water pump suction (50 mm) at room temp and the ozonide decomposed by warming gently with H_2O_2 (30%, 15 ml), water (25 ml) and Na_2CO_3 (2·5 g), first at 60° (1 hr) and finally at 100° (2 hr). The product was cooled and extracted with ether (20 ml × 3) to yield a gum (1·5 g) which was not examined further. The aqueous alkaline layer was acidified (H_3PO_4) and extracted with ether (25 ml × 4) after saturating with $(NH_4)SO_4$. The extract was washed, dried and ether removed to yield the crude acid (3·7 g).

A portion of the acid (0·310 g) was esterified (diazomethane) to give the methyl ester: b.p. 105–107°/2 mm, n_D^{30} 1·4765. The ester readily formed a *semicarbazone* (pyridine method) which after crystallization was obtained in white crystals m.p. 193–195°.

The above acid (2·77 g) was treated with semicarbazide hydrochloride (1·6 g) dissolved in water (2 ml) and pyridine (1·6 ml), followed by EtOH (10 ml) to make the soln homogeneous. After 48 hr, the separated *semicarbazone* (3 g, m.p. 182–183°) was collected and crystallized from EtOH twice to yield white shining flakes, m.p. 195–196°. (Found: N, 13·60. $C_{16}H_{29}O_3N_3$ requires: N, 13·49%).

The semicarbazone (1·2 g), oxalic acid (2·4 g in 17 ml water) and toluene (20 ml) were mixed and refluxed under stirring till a clear soln was obtained (2 hr). The organic layer was separated and the aqueous layer extracted with ether (15 ml × 3), and the combined organic layers washed with brine and dried. After solvent removal, the product (0·850 g) was used for the hypobromite oxidation. An analytical sample was obtained by distilling a small portion of the purified keto-acid: b.p. 165° (bath)/1·3 mm. (Found: C, 71·27; H, 10·69. $C_{15}H_{26}O_3$ requires: C, 70·83; H, 10·30%).

Sodium hypobromite oxidation of XIX

The purified keto-acid (1·25 g) in dioxan (21 ml) was treated with sodium hypobromite [1·2 ml Br_2 and 2·7 g NaOH in 21 ml water] in the course of 55 min at 0° and with stirring. The product was stirred for 3 more hr and left overnight. To the above soln, $NaHSO_3$ (1·5 g) was added to destroy the excess of hypobromite and acidified with conc HCl. It was extracted with ether (20 ml × 5) after saturating with $(NH_4)_2SO_4$, washed, dried and solvent removed: yield 1·273 g.

Pyrolysis to the ketone XXI

The above oxidation product (1·273 g) was mixed with freshly reduced Fe powder (1·2 g) and $Ba(OH)_2$ (0·3 g) and dry distilled at 250 mm. To the cooled residue, water (1·5 ml) was added, which was then distilled off. This aqueous distillate was mixed with the original distillate and the total extracted with ether (5 ml × 4) and dried. After solvent removal, the product was distilled: b.p. 92–94°/1·5 mm, n_D^{30} 1·4847, yield 0·62 g. An analytical sample was obtained by its regeneration (oxalic acid method) from its semicarbazone (see below): b.p. 89·5–90°/1·5 mm, n_D^{30} 1·4820, $[\alpha]_D$ +189·1° (*c*, 2·6%). PMR spectrum: quaternary Me's 45, 70 c/s; CH—$\underline{C}H_3$, doublet centred at 57 c/s, J = 6 c/s. (Found: C, 80·54; H, 11·60. $C_{13}H_{22}O$ requires: C, 80·35; H, 11·41%).

The *semicarbazone* (pyridine method) was crystallized from benzene–MeOH: m.p. 202–202·5°. (Found: C, 67·30; H, 10·14. $C_{14}H_{25}ON_3$ requires: C, 66·89; H, 10·03%).

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REFERENCES

[1] T. C. Joseph and Sukh Dev, *Tetrahedron* **24**, 3809 (1968).

[2] D. Ginsburg and W. J. Rosenfelder, *Tetrahedron* **1**, 3 (1957).

[3] D. Kimchi and S. Bien, *J. Chem. Soc.* 5344 (1961).

[4] R. B. Turner, *J. Am. Chem. Soc.* **74**, 2118 (1952); E. L. Eliel, *Stereochemistry of Carbon compounds* p. 279. McGraw-Hill, New York (1962).

[5] Sukh Dev, *J. Indian Chem. Soc.* **33**, 769 (1956).

[6] N. L. Allinger, *J. Am. Chem. Soc.* **81**, 5727 (1959).

[7] R. Pauncz and D. Ginsburg, *Tetrahedron* **9**, 40 (1960).

[8] J. B. Hendrickson, *J. Am. Chem. Soc.* **83**, 4537 (1961).

[9] E. L. Eliel, *Stereochemistry of Carbon Compounds* p. 126. McGraw-Hill, New York (1962).

[10] Ref. 9, p. 207.

[11] Ref. 1, p. 3819.

[12] H. B. Henbest and T. I. Wrigley, *J. Chem. Soc.* 4596 (1957); also see: D. N. Kirk and V. Petrow, *Ibid.* 4657 (1960); J. P. Dusza, J. P. Joseph and S. Bernstein, *J. Org. Chem.* **28**, 92 (1963).

[13] D. H. Williams, N. S. Bhacca and C. Djerassi, *J. Am. Chem. Soc.* **85**, 2810 (1963); R. Beugelmans, R. H. Shapiro, L. H. Durham, D. H. Williams, H. Budzikiewicz and C. Djerassi, *Ibid.* **86**, 2832 (1964).

[14] W. Moffitt, R. B. Woodward, A. Moscowitz, W. Klyne and C. Djerassi, *J. Am. Chem. Soc.* **83**, 4013 (1961). For a review of its applications see: P. Crabbe, *Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry* pp. 72–157. Holden-Day, San Francisco (1965).

[15] e.g. see: A. H. Cook and R. P. Linstead, *J. Chem. Soc.* 946 (1934).

[16] N. L. Allinger and V. B. Zalkow, *J. Am. Chem. Soc.* **83**, 1144 (1961).

[17] S. Munavalli and G. Ourisson, *Bull. Soc. Chim. Fr.* 2825 (1964). We are grateful to Prof. G. Ourisson for communicating their results to us, prior to their publication.

[18] R. H. Moffett and D. Rogers, *Chem. & Ind.* 916 (1953); G. Ourisson, *Bull. Soc. Chim. Fr.* 895 (1955).

[19] F. L. Greenwood, *J. Org. Chem.* **20**, 803 (1955).