Tetrahedron. Vol. 24, pp. 3775 to 3786. Pergamon Press 1968. Printed in Great Britain

STUDIES IN SESQUITERPENES—XXVIII*†

BF_3-INDUCED REARRANGEMENT OF EUDESMANE- AND 7-EPIEUDESMANE-BASED 1,2-EPOXIDES

G. MEHTA, G. L. CHETTY, U. R. NAYAK and SUKH DEV

National Chemical Laboratory, Poona, India

(*Received in the UK* 12 *September* 1967; *accepted for publication* 5 *December* 1967)

Abstract—Rearrangement of 4,5-epoxyeudesmane and 4,5-epoxy-7-epi-eudesmane with BF_3-etherate is reported.

AN IMPORTANT aspect of current terpene biogenetic considerations[1,2] is that rearrangements originating at an electron-deficient carbon, constitute a significant pathway leading to the formation of compounds, which otherwise cannot be derived (in theory) from the usual immediate terpenoid precursors (farnesol pyrophosphate, geranylgeraniol pyrophosphate etc). This was first emphasized clearly by Robinson,[3] in explaining the possible genesis of eremophilone (I) and its congeners in nature. At present a variety of sesqui-, di- and tri-terpenoids are known, where carbonium ion rearrangements play an important role in their biogenesis. The present work describes some experiments in the sesquiterpene series, which were expected to simulate some of the rearrangements leading to eudesmane-based rearranged sesquiterpenoids.

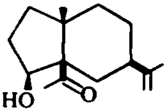
Eremophilone (I)[1,4] and agarospirol (II)[5] can be derived, in principle, from a suitably constituted eudesmane derivative,‡ while valeranone (III)[8] can formally arise from a 7-epi-eudesmane precursor. Given favourable stereoelectronic factors species IV can, in principle, rearrange to I and/or II type skeletons, while V can lead to valerane type. Of the several methods feasible for generating an electron-deficit centre at C_5, the behaviour of 4α,5α-epoxy-eudesmane (VI), 4β,5β-epoxy-eudesmane (VII) and 4β,5β-epoxy-7-epieudesmane (VIII) towards boron BF_3-etherate has been investigated in the first instance.§

---

* Communication No. 1123, National Chemical Laboratory, Poona.

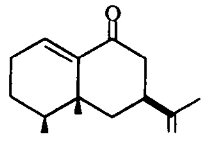
† Abstracted in part from the Ph.D. Thesis (Poona University, 1966) of G. Mehta.

‡ Since the completion of this work, another rearranged eudesmane—cyperolone (a)—has been reported.[6,7] As will be clear from a perusal of the present paper, this work has special significance for cyperolone.

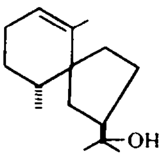


a

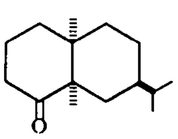
§ cf. e.g. The transformation of (+)-hibaene into (−)-kaurene *via* hibaene epoxide.[9]



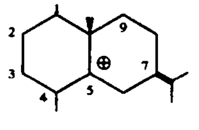
I



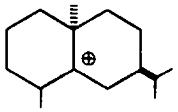
II



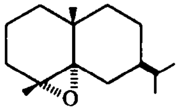
III



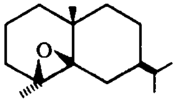
IV



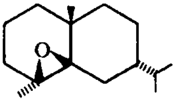
V



VI

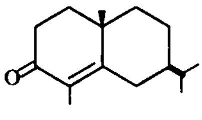


VII

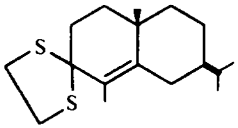


VIII

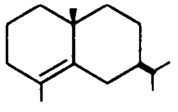
Synthesis of 4,5-epoxides (VI, VII, VIII). (+)-Dihydro-α-cyperone (IX), readily prepared* by the selective hydrogenation of (+)-α-cyperone over Pd–$CaCO_3$ in ethanol, reacted with ethanedithiol in presence of BF_3–Et_2O[11] to give the thioketal (X). Desulphurization of X furnished the required olefin XI, shown to be homogenous by GLC and TLC over $AgNO_3$–SiO_2 gel.[12] Its PRM spectrum is in accord with the structure XI: $(CH_3)_2CH$† (an unsymmetrical 6H d centred at 54 c/s, $J = 6$ c/s), one quaternary Me (3H s, 60 c/s), one vinylic Me (3H s, 94 c/s) and, no olefinic protons.



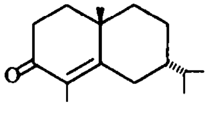
IX



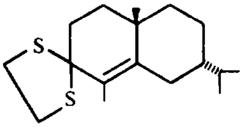
X



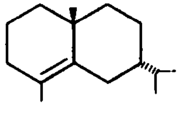
XI



XII



XIII



XIV

The same olefin XI was also prepared by the action of LAH–$AlCl_3$[13] on IX, followed by purification of the product by chromatography over $AgNO_3$–SiO_2 gel.

Epoxidation of the olefin with perbenzoic or percamphoric acids yielded ~1:1 mixture of 4,5-epoxides, which could be separated, after considerable experimentation,‡ on deactivated silica gel by preparative layer chromatography (PLC). The

---

* Dihydro-α-cyperone prepared by this method was always contaminated by 10% of the βγ-unsaturated isomer. Equilibration of the product over t-BuOK in t-BuOH at reflux gave a 2:1 ratio of the αβ- and βγ-isomers.[10]

† s = singlet; d = doublet; m = multiplet.

‡ Both epoxides were found to be unusually labile in contact with activated adsorbents and mutiliated fast on SiO_2-gel to give chiefly olefin mixtures and on Al_2O_3 to furnish essentially alcohols.[14]

fast moving epoxide (solvent: C_6H_6) is assigned the stereostructure VI, while the other epoxide is represented by VII. Their assignment of stereochemistry is discussed later.

Robinson annelation[15] of (−)-tetrahydrocarvone with 1-diethylamino-pentan-3-one methiodide in presence of NaOMe, furnished a mixture of (−)-dihydro-α-cyperone (antipodal IX) and (+)-dihydro-α-7-epi-cyperone (XII),* in which the latter predominated (60%), in agreement with a similar earlier work.[16] The ketones mixture could not be separated either by GLC or TLC and the percentage composition was computed for PMR as well as $[\alpha]_D$ data. It was found unnecessary to separate the mixture as, in the next step of thioketalization the required thioketal XIII crystallized directly from the reaction mixture. The thioketal on desulphurization with Raney Ni gave a single olefin (GLC, TLC) characterized as the required hydrocarbon XIV: PMR spectrum: $(CH_3)_2CH$ (an unsymmetrical 6H doublet centred at 52 c/s, $J = 6$ c/s), one quaternary Me (3H s, 64 c/s), one vinylic Me (3H s, 95 c/s) and, no olefinic protons. This olefin on interaction with perbenzoic acid yielded a single epoxide, which as discussed below is assigned the configuration shown in VIII.

The assignment of configuration to the two epoxides derived from XI is based on their molecular rotation data (Table 1). In the steroid series, it is known that ΔM_D for 4α,5α- minus 4β,5β-epoxycholestane is strongly positive[17,18] and a 4-Me substituent does not alter this trend[18] (Table 1). On this basis the more strongly dextrorotatory of the two isomers has been assigned the 4α,5α-epoxy configuration (steroidal notations). This criterion could not be employed in the 7-epi series, as only one isomer was available. A study of molecular models (Dreiding) shows that whereas in the case of the olefin XI from the normal series, the attack by the peracid can be from either face, for the corresponding olefin in the 7-epi series XIV, the peracid approach would be preferentially directed to the β-face, as the rear attack is well-screened by the isopropyl group.† On this basis, the oxide derived from XIV is considered to have the 4β,5β-configuration (VIII).

TABLE 1. MOLECULAR ROTATIONAL DIFFERENCES

Parent compound	M_D^*			ΔM_D		
	Parent (c)	4α,5α-epoxy (α)	4β,5β-epoxy (β)	(α-c)	(β-c)	(α-β)
Cholest-4-ene[17]	+281·2°	+310°	+ 14°	+ 28·8°	−267·2°	+296°
4-Methylcholest-4-ene[18]	+ 49·9°	+288°	+108°	+238·1°	+ 58·1°	+180°
Eudesm-4-ene (XI)	+128·4°	+238·6°	+ 23·7°	+110·2°	−104·7°	+214·9°

---

* This compound has been prepared earlier[16] by the dehydration of (−)-5β-hydroxy-4β,7β(H)-eudesman-3-one.

† In the quasi-chair-chair conformation of this olefin (XIV), the isopropyl group is axially oriented and, the flipping of this ring to the antipodal chair is precluded by the $\Delta^{4,5}$-olefinic linkage. In an alternate conformation, in which ring B (containing the i-Pr group) becomes a skewed boat, though the 1,3-diaxial interactions on the α-face are reduced and the isopropyl group is now quasi-equatorial, the shape of the molecule is such that the α-face is still considerably screened.

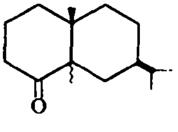
Rearrangement of 4,5-*epoxides* (VI, VII, VIII) *with* BF_3–Et_2O. Though the action of BF_3 on 1,2-epoxides is a well-studied reaction[19] very few examples of this involving tetra-substituted oxiranes had been reported till recently.[*] In principle, the latter reactions can furnish dienes, olefinic tertiary alcohol and/or ketones, a skeletal rearrangement being obligatory for the last product. Table 2 shows the product analysis, functionality-wise, of the reaction of epoxides VI, VII and VIII with BF_3–Et_2O; all the three rearrangements were carried out in toluene solution at −15° for 30 min. As can be seen, the ketonic products have predominated and, furthermore, though a ketone could, in principle, arise by migration of either of the four alkyl residues, essentially only one ketone was produced.

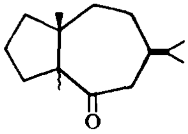
TABLE 2. FUNCTION-WISE PRODUCT ANALYSIS OF EPOXIDE-BF_3 REACTION

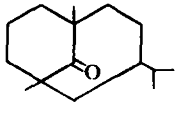
Epoxide	% Composition[*]		
	Ketones	Alcohols	Hydrocarbons
VI	90[†]	7	trace
VII	85[†]	—	15
VIII	80[‡]	trace	15

[*] Based on column chromatography and GLC.
[†] Essentially a single component.
[‡] Mixture of two ketones (7 : 1).

Rearrangement of 4α,5α-*epoxy-eudesmane* (VI). Action of BF_3–Et_2O on VI resulted in essentially a single product, readily obtained pure by PLC. The product, $C_{15}H_{26}O$ ($\nu^{C=O}$ 1701 cm^{-1}; semicarbazone, m.p. 184–185°) exhibits in its PMR spectrum signals for two quaternary Me groups (two 3H s at 65 and 69 c/s) besides those (two d's centred at 53 and 55 c/s, respectively, each with $J = 7$ c/s), assignable to the isopropyl methyls. These spectral characteristics limit its structure to XV, XVI and XVII. Of these, structure XVII is ruled out, as the ketone, under conditions of exhaustive bromination,[25] reacted with ca. 1·75 mole equiv of bromine; valeranone (III) was used as a reference sample, which under the same conditions consumed 2·0 mole equiv of bromine. This is further supported by the occurrence in the PMR spectrum of the ketone, a 2H multiplet centred at 145 c/s, which is assignable to —CH_2—CO, a feature absent in XVII. This multiplet (poorly resolved) has a shape


XV


XVI


XVII

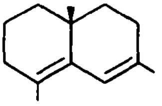
---

[*] At the time this work was started only a few examples (from the steroid field) had been described.[20–22] However, during the course of present work a systematic investigation of BF_3-catalyzed rearrangements of tetrasubstituted steroidal epoxides appeared,[23] as well as the transformation of β-patchoulene epoxide (a tetrasubstituted oxirane) to an isopatchoulene derivative.[24]

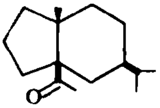
and span (135–155 c/s) quite distinct from the $C\underline{H}_2CO$ signal (2H m located between 128–165 c/s, essentially the AB part of an ABX_2 system) in valeranone (III), suggesting that of the remaining two possibilities, XV and XVI, the former is unlikely, as it should display its CH_2CO signal essentially as in valeranone.* Furthermore, in valeranone and several eudesmane sesquiterpenoids (with no substitution in ring B) the isopropyl group occurs as a doublet, since because of free rotation any differential shielding of the isopropyl Me's gets averaged out. The occurrence of iso-propyl Me's as two doublets,† whose centres are separated by 2 c/s in our ketone, suggests the possibility of restricted rotation and hence a preferred conformation with respect to the carbonyl. An inspection of models suggests that such a situation can arise only in XVI. As a result of these considerations, the ketone is assigned the structure XVI.

Rearrangement of 4β,5β-*epoxy-eudesmane* (VII). Treatment of the epoxide VII with BF_3–Et_2O yielded essentially two products readily separated by PLC into a hydrocarbon (15%) and a ketone (85%).

The hydrocarbon is a conjugated diene (λ_{max} 241 mμ, ε 20,600) and shows in its PMR spectrum the presence of a quaternary Me (3H s at 74 c/s), an isopropyl group (two d's centred at 52·5 and 54·5 c/s, $J = 6{\cdot}5$ c/s), a vinylic Me (3H, somewhat broad s at 102 c/s) and a vinylic proton (1H broadened s at 320 c/s) and hence was readily recognised as (+)-δ-selinene (XVIII).[28] A comparison of its IR spectrum with that of an authentic sample[28] confirmed this.



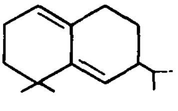
XVIII



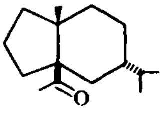
XIX

The ketone ($\nu^{C=O}$ 1724 cm^{-1}; semicarbazone, m.p. 101–102°) showed the following structural features in its PMR spectrum: an isopropyl group (two overlapping unsymmetrical d's centred at 55 c/s, $J = 6$ c/s), one quaternary Me (s, 93 c/s) and a $C\underline{H}_3CO$ group (3H s at 121 c/s). These features can be accommodated in XIX, the genesis of which is discussed below. The unusually large down-field shift of the angular Me resonance is possible only, if the Me and the Ac groups are *cis* to each other and the former essentially co-planar with the CO group. This dictates a *cis*-fusion of the rings in XIX.

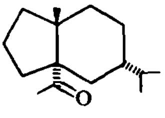
Rearrangement of 4β,5β-7-*epi-epoxide* (VIII). A similar treatment of this epoxide furnished a hydrocarbon (15%) and two ketones (80%). The hydrocarbon from its UV absorption (λ_{max} 240 mμ, ε 19,300) and PMR spectrum (i-Pr group: two overlapping doublets centred at 52 and 55 c/s, $J = 6$ c/s; two quaternary Me's: 3H s's at 55 and 57·5 c/s; olefinic protons: 2H, overlapping signals between 312 and 333 c/s) is provisionally considered to be XX.



XX



XXI



XXII

---

* In either *cis*- or *trans*-XV, the relative disposition of C_2—CH_2, C_3—CH_2 and C_4—CO remains the same as in valeranone.

† Similar situation occurs, for example, in podototarin.[26] Also see Roberts *et al.*[27]

The major ketone ($\nu^{C=O}$ 1728 cm^{-1}) on the basis of its PMR data (i-Pr group: an unsymmetrical, 6H d centred at 53 c/s, $J = 6$ c/s; quaternary Me, 94 c/s, $W_H = 3.8$ c/s; $C\underline{H}_3CO$, 3H s at 122 c/s) is assigned the structure XXI, the *cis*-junction being based on the arguments advanced earlier for XIX.

The minor ketone is represented by XXII, in view of its spectral characteristics ($\nu^{C=O}$ 1715 cm^{-1}, PMR spectrum: i-Pr d centred at 50·5 c/s, $J = 6$ c/s; quaternary Me, 3H sharp s at 54 c/s; $C\underline{H}_3CO$, 3H s at 119 c/s). In this ketone the quaternary Me signal occurs in its "normal" frequency range, consistent with its *trans*-ring junction.

DISCUSSION

Axial nucleophilic attack on an epoxy-cyclohexane, such that the O atom remains attached to the axial position (*trans*-diaxial cleavage), is well established[29] and, the extension of this rule to the fission of tetrasubstituted steroidal 1,2-epoxides by BF_3-etherate has been recently demonstrated.[23d] Our own results with three epoxides from the eudesmane series also fall in line.

The isomerization of VI to XVI is readily visualized as proceeding through XXIII–XXIV to furnish *cis*-XVI (≡ XXV); the conformation (XXV) shown will explain the deshielding of *both* the angular Me's, as actually observed in its PMR spectrum. It must be noted that in the transition state (XXIV)* the 5,10-bond, rather than the 5,6-bond, is better oriented for *trans*-attack at C_4 (cf. XXVI) and hence, the exclusive formation of XXV.

In the case of 4β,5β-epoxy-eudesmane (VII), two extreme conformations XXVII and XXVIII may be written for the C_5-carbonium ion, resulting from axial attack at the epoxy oxygen. In XXVII, the C_4-Me is better oriented for *trans*-migration and should result in the formation of a 5α-methyl-4-ketone, as indeed happens in the case of 4β,5β-epoxy-4-methylcholestane.[23d] On the other hand in XXVIII, the 3,4-bond is better placed for migration (cf. XXIX) and should lead to 5β-acetyl-A-nor product (XIX ≡ XXX). The almost exclusive formation of XIX from VII highlights the importance of XXVIII. Since, energetically the two conformations, XXVII and XXVIII, must be very similar,† the preferred formation of XIX, indicates a kinetically favoured process in going from the epoxide VII‡ to the ion XXVIII. An examination of models shows that in going from the epoxide VII (≡ XXXI) to the ion XXVII, it must pass through XXVIII, which is all set for the migration of the 3,4-bond in a concerted fashion.

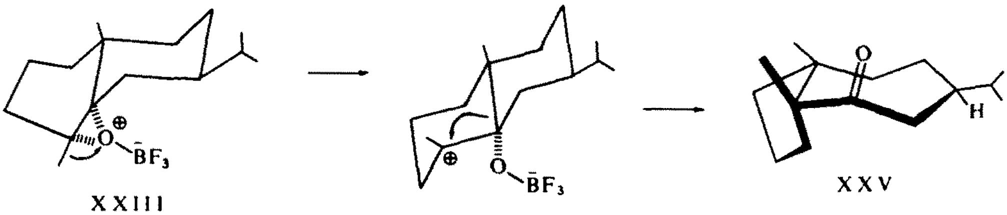
Likewise, the formation of the major ketone XXXIII (≡ XXI) from 4β,5β-epoxy-7-epi-eudesmane (VIII) is readily understood in terms of XXXII (ring B, preferably a twist boat to avoid axial i-Pr). The genesis of the minor ketone (XXII), in terms of the above concepts, remains obscure at present.

---

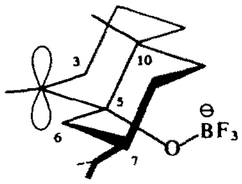
* The structures XXIII and XIV are shown for clarity and do not imply a two-step process in preference to the concerted mechanism which, on energy considerations, should be preferable. These remarks also apply to the other cases of rearrangement discussed below.

† In the case of the ion derived from 4β,5β-epoxy-4-methyl cholestane, Hartshorn[23d] and Kirk conclude that the ion corresponding to XXVII is to be preferred.

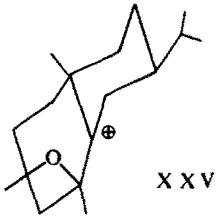
‡ As the epoxy—oxygen—C_5 bond lengthens with the C_4—O bond becoming more and more "upright" (axial), ring A becomes a chair, while B gets slightly deformed, as in XXVIII. Further bending back pushes C_4 slightly below the plane containing C_5, with simultaneous rising of C_6 slightly above this plane; this process converts XXVIII into XXVII.



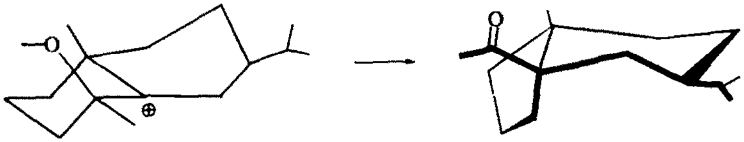
XXIII XXIV XXV



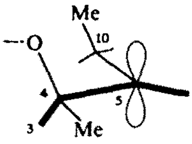
XXVI



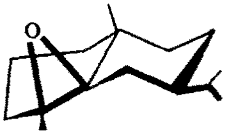
XXVII



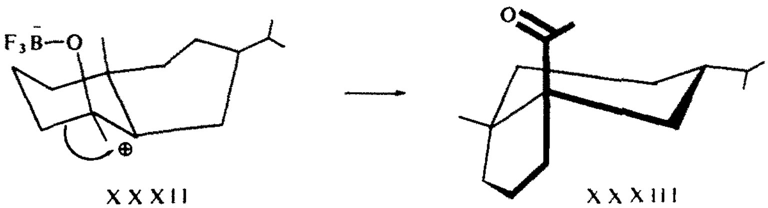
XXVIII XXX



XXIX



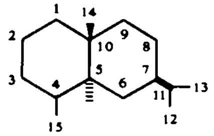
XXXI



XXXII XXXIII

The formation of the hydrocarbons XVIII and XX from the corresponding oxides, can be readily rationalized and will not be discussed here.

Quaternary methyl resonance in the eudesmane series. During the course of this and related investigations, a number of PMR spectra in the series became available. Table 3 shows the angular methyl chemical shifts in variously substituted eudesmanes and 7-*epi*-eudesmanes. Since, the additivity of chemical shifts is well-established[30, 31] for steroids, the chemical shift differences shown in Table 3 may prove useful in



XXXIV

TABLE 3. THE EFFECT OF SUBSTITUENTS ON THE CHEMICAL SHIFT OF THE ANGULAR METHYL IN THE EUDESMANE SERIES AT 60 Mc (CCl_4 soln)

No.	Series	Substituent	Chemical shift (c/s)	Difference (c/s)
1	*Eudesmane* (XXXIV)	—	52	0·0
2		Δ^4	60	8·0
3		$\Delta^{2,11}$	51	−1·0
4		$\Delta^{3,7}$	46	−6·0
5		$\Delta^{3,11}$	48	−4·0
6		$\Delta^{4(15),11}$	44	−8·0
7		Δ^{11}-3β-OH	53	1·0
8		Δ^{11}-3β-OAc	54	2·0
9		Δ^4-3-oxo	71	19·0
10		$\Delta^{4,11}$-3-oxo	74	22·0
11		4α,5α-oxido	61	9·0
12		4β,5β-oxido	61	9·0
13		Δ^4-3-thioketal	64	12·0
14	7-*epi*-Eudesmane	—	—	—
15		Δ^4	64	—
16		Δ^4-3-oxo	71	—
17		4β,5β-oxido	61·5	—
18		Δ^4-3-thioketal	68	—

evaluating the structure of a new eudesmane derivative. Initially it was argued that since an eudesmane may be considered, as a first approximation, as corresponding to similarly functionalized A and B rings of steroids the substitution parameters established by Zürcher[30] for 5α-steroids may be applicable to the eudesmane series in determining the chemical shift of the angular Me. However, a comparison of the data given in Table 3 and Zürcher's tables shows that there are significant departures.

EXPERIMENTAL

All m.ps and b.ps are uncorrected. Pet. ether refers to the fraction of b.p. 40–60°. All solvent extracts were dried over anhyd Na_2SO_4. Optical rotations were measured in $CHCl_3$ on a Perkin–Elmer (model 141) automatic polarimeter.

IR spectra were taken on a Perkin–Elmer Infracord model 137-E. UV spectra were measured on a Perkin–Elmer spectrophotometer model 350. All PMR spectra were taken in 10% CCl_4 soln with TMS as internal standard, on a Varian Associates A-60 spectrophotometer, peaks are reported in c/s from tetramethylsilane as zero.

GLC analyses were carried out on a Wilkens Aerograph A-350-B model on a column (2 meters × 4·5 mm) packed with 20% silicone SE-30 on Chromosorb W (60–80 mesh) and employing H_2 (50 ml/min) as the carrier gas; temp conditions were 160° (for olefins and epoxides) and 200° (for ketones). TLC was performed on silica gel (200 mesh) containing 15% gypsum, unless otherwise indicated.

(+)-*Dihydro-α cyperone* IX

(+)-α*Cyperone*[32] (4·71 g) in abs EtOH (90 ml) was hydrogenated in the presence of 5% Pd–$CaCO_3$ catalyst (1·134 g) at 30°/715 mm. Uptake of H_2 ceased after the consumption of nearly 1 mole of gas and the product was worked up in the usual manner. Chromatography of the residue over neutral Al_2O_3 (gr. II, 120 g, 32 × 2·8 cm) and elution with benzene furnished GLC-pure (IX)* (4·16 g) as a colourless oil: b.p. 148–149°/3·5 mm, n_D^{30} 1·5164, $(\alpha)_D^{30}$ +162·3° (*c*, 1·75%). TNM test +ve. UV spectrum: λ_{max}^{EtOH} 250 mμ (ε = 12,880). IR spectrum (liq.): conj. C═O 1672 cm^{-1}; conj. C═C 1621 cm^{-1}. PMR spectrum: $(CH_3)_2CH$, 6H doublet centred at 56 c/s (*J* = 6 c/s); quaternary CH_3 71 c/s; vinylic CH_3 102 c/s; no olefinic H. (Found: C, 81·8; H, 10·9. $C_{15}H_{24}O$ requires: C, 81·87; H, 10·89%).

Its *semicarbazone* was prepared (pyridine method) and recrystallized from MeOH–pyridine in colourless microprisms, m.p. 210–212°. (Found: C, 69·26; H, 9·98; N, 15·44. $C_{16}H_{27}ON_3$ requires: C, 69·27; H, 9·81; N, 15·15%).

Equilibration of IX. Compound IX (45 mg) was refluxed with t-BuOH (177 mg of K in 5 ml of t-BuOH) for 3 hr under N_2. Usual work-up of the reaction mixture yielded a product, b.p. 160° (bath)/4 mm; GLC: αβ-isomer (66%; conj. C═O 1672 cm^{-1}) and βγ-isomer (33%; C═O 1712 cm^{-1}).

(+)-*Dihydro-α-cyperone thioketal* X

A mixture of IX (4·34 g) ethane dithiol (3·54 g) and abs MeOH (50 ml) was treated with freshly-distilled BF_3–Et_2O (3·5 ml) and left overnight (17 hr) at 4°. After removal of MeOH under reduced press the yellow syrup was taken up in ether (50 ml), washed with sat Na_2CO_3aq followed by brine and dried. Solvent removal and distillation gave X as a colourless viscous liquid (5·44 g, 93%): b.p. 167–168°/1·5 mm, n_D^{30} 1·5671, $[\alpha]_D^{27}$ +126° (*c*, 0·9%), TNM test +ve. Ir spectrum (liq.): C═O absent; strong bands at 1282 and 770 cm^{-1}. PMR spectrum: $(CH_3)_2CH$, d centred at 55 c/s (*J* = 6 c/s); quaternary Me, 64 c/s; vinylic Me, 100 c/s; $(CH_2\text{-}S)_2$, m centred at 196 c/s. (Found: C, 69·07; H, 9·37; S, 20·35. $C_{17}H_{28}S_2$ requires: C, 68·90; H, 9·50; S, 21·60%).

(+)-*Eudesm-4-ene* XI

(a) *By desulphurization of* X. Compound X (5·44 g) 95% EtOH (500 ml) and Raney Ni (W-2, 100 g) were refluxed together on a water bath (16 hr). The catalyst was filtered off and washed with hot EtOH (50 ml × 3). The combined filtrates were concentrated to a small volume, diluted with ether (200 ml), dried, evaporated and the residue distilled to furnish XI as a colourless liquid (2·31 g, 61%): b.p. 123–124°/10 mm, n_D^{30} 1·4917, $[\alpha]_D^{28}$ +62·34° (*c*, 1·27%), TNM test +ve. UV spectrum (end absorption): ε_{210} = 3197, ε_{215} = 2046, ε_{220} = 1165 and ε_{225} = 622. IR spectrum (liq.): no characteristic bands. (Found: C, 87·36; H, 12·86. $C_{15}H_{26}$ requires: C, 87·3; H, 12·7%).

(b) *By the action of* LAH–$AlCl_3$ *on* IX. A slurry of powdered anhyd $AlCl_3$ (4·5 g) in dry Et_2O (75 ml), cooled in ice, was treated with LAH (0·665 g) and shaken well (anhyd conditions). To this was added IX (1·10 g) in dry ether (25 ml) with shaking and cooling. After allowing the reaction mixture to warm up to room temp it was further refluxed gently (30 min). The product was worked up by adding ice–water (50 ml) and then 10% Na–K tartrateaq followed by extraction with pet. ether (75 ml × 4). After washing with sat $NaHCO_3$aq and then brine the extract was dried, evaporated and the residue chromatographed over neutral Al_2O_3 (gr. I, 30 g). The pet. ether eluate (0·82 g) was further purified by $AgNO_3$–SiO_2 gel (15%, 40 g, gr. IIA) chromatography. Elution with light petroleum furnished an olefin (0·51 g) (95% pure by GLC) identified as XI† (mixed GLC, superimposable IR spectra).

4α,5α- *and* 4β,5β-*Epoxy eudesmanes*

(a) *By perbenzoic acid oxidation.* Compound XI (2·018 g) was treated with perbenzoic acid (1·44 g) in benzene (30 ml) at 4° and allowed to react for 45 hr at the same temp. The reaction mixture was diluted with ether (50 ml), washed with sat Na_2CO_3aq followed by brine, dried and evaporated to a colourless oil (2·07 g) which was chromatographed over neutral Al_2O_3 (gr. II, 76 g, 24·5 × 2·45 cm). Elution with pet. ether gave a hydrocarbon fraction (0·23 g) while benzene eluted the epoxides mixture (1·1 g) as a colourless sweet-smelling liquid: b.p. 123°/5 mm, n_D^{30} 1·4782, $[\alpha]_D^{28}$ +30·64 (*c*, 1·09%), TNM test −ve.

(b) *By percamphoric acid oxidation.* Compound XI (0·252 g) in benzene (5 ml) was allowed to react with

---

* This compound has been prepared from (+)-β-cyperone by partial reduction with Zn–AcOH.[33]

† This olefin has recently been prepared by the dehydration of dihydro-neo-internedeol.[34]

percamphoric acid (0·152 g) in benzene (14 ml) at 4° for 96 hr. The precipitated camphoric acid was filtered off and the filtrate worked up as described in (a). The crude product (0·241 g) was adsorbed on neutral Al_2O_3 (gr. II, 7 g; 15 × 0·7 cm). After rejecting the pet. ether eluate (20 ml) benzene eluate (160 ml) furnished the oxides mixture: b.p. 130° (bath)/5 mm; n_D^{30} 1·4788; $[\alpha]_D^{26}$ +47·64° (*c*, 0·83%).

(+)-*4α,5α-Epoxy-eudesmane* VI. The oxides mixture (293 mg) was subjected to PLC on 6 plates (20 × 20 cm) coated with silica gel (1 mm thick) and air-dried for 16 hr. After multiple spotting (ca. 50 mg on each plate) the plates were allowed to develop in benzene (solvent ascent 15 cm); the process was repeated after the plates had been taken out of the chamber and air-dried for 15 min. For visualization of zones thin strips on either side of a plate were sprayed with conc. H_2SO_4 and warmed with a free flame. Then the top, middle and bottom portions of all the plates were respectively pooled together and eluted separately on a column with ether. The fast-moving oxide VI (104 mg) was obtained as a colourless liquid b.p. 117–118°/4 mm, n_D^{30} 1·4793, $[\alpha]_D^{27}$ +107·5° (*c*, 0·68%), 95% pure by GLC. IR spectrum: strong band at 912 cm^{-1}. PMR spectrum: $(CH_3)^2CH$, d centred at 54 c/s (*J* = 6 c/s), quaternary Me, 61 c/s, oxirane-*geminal* Me, 71·5 c/s. (Found: C, 81·16; H, 11·59. $C_{15}H_{26}O$ requires: C, 81·02; H, 11·79%).

(+)-*4β,5β-Epoxy-eudesmane* VII. The slow-moving VII (111 mg) from above was distilled: b.p. 124–125°/5 mm, n_D^{30} 1·4797, $[\alpha]_D^{27}$ +10·7° (*c*, 0·65%). IR spectrum: strong bands at 870, 888 and 916 cm^{-1}. PMR spectrum: $(CH_3)_2CH$, centred at 54 c/s (*J* = 6 c/s), quaternary Me, 60·5 c/s; oxirane-*geminal* Me, 74·5 c/s. (Found: C, 81·16; H, 11·85. $C_{15}H_{26}O$ requires: C, 81·02; H· 11·79%).

7-Epi-eudesm-4-ene XIV

(−)-*Tetrahydrocarvone*. (+)-Carvone ($[\alpha]_D^{27}$ +61·04°, neat; 30 g) was hydrogenated[35] over 5% Pd–$CaCO_3$ catalyst (5·412 g) in EtOH (150 ml). Uptake of H_2 ceased after the absorption of nearly 7 l. at 26°/715 mm in ca. 4 hr. The catalyst was filtered off and the filtrate evaporated. The residue was taken up in ether (250 ml), washed with 10% NaOH aq (50 ml × 4) followed by brine and freed of solvent. Distillation gave tetrahydrocarvone (18·7 g; 63%): b.p. 115–117°/45 mm, n_D^{30} 1·4548, $[\alpha]_D^{26}$ −31·6° (*c*, 1·4%), TNM test −ve. IR spectrum (liq.): C=O 1724 cm^{-1}. Acidification of the aq alkaline extract and usual work up furnished a liquid (11·1 g) which was identified as carvacrol.

Dihydrocyperones (*antipodal* IX *and* XII). 1-Deithylaminopentan-3-one methiodide was prepared[16] from 1-diethylaminopentan-3-one (13·91 g) by slow addition of MeI (12·05 g) with stirring and cooling (0°) during 15 min. A soln of tetrahydrocarvone (12·4 g) in dry benzene (50 ml) was added to the reaction flask followed by dropwise addition of NaOMe* in MeOH (prepared from 2·41 g of Na and 50 ml of anhyd MeOH) with vigorous stirring at 0° during 30 min (anhyd conditions). After allowing the reaction mixture to warm up to room temp (27°) overnight (16 hr) it was further refluxed on the water-bath with stirring (2 hr). After cooling, dry ether (50 ml) and gl. AcOH (6 ml) were added while stirring and then most of the solvent was removed at 40° under reduced press. Dilution with water (200 ml), extraction with ether, washing with sat Na_2CO_3aq followed by brine, drying and removal of solvent yielded a yellow residue (14·7 g). On distillation through a short vigreux column (10 cm) a forerun of tetrahydrocarvone (4·3 g) b.p. 81–83°/3 mm, followed by the epimeric mixture of dihydrocyperones (9·17 g; 78% based on recovered tetrahydrocarvone), b.p. 144–153°/3 mm, was obtained as a pale yellow oil.

(+)-*Dihydro-7-epi-α-cyperone thioketal* XIII. The mixture of dihydrocyperones (8·1 g), ethane dithiol (8 ml) and freshly distilled BF_3–Et_2O (8 ml) were mixed at room temp (25°) and the reaction allowed to proceed for 30 min with frequent swirling. Addition of cold MeOH (200 ml) to the cooled reaction mixture furnished a crystalline solid (6·6 g) of m.p. 81–84°. Recrystallization from MeOH gave the pure thioketal XIII† as colourless microprisms m.p. 92·5–93·5°, $[\alpha]_D^{28}$ +105·5° (*c*, 0·71%). IR spectrum (Nujol): C=O absent; strong bands at 1284 and 769 cm^{-1}. PMR spectrum: $(\underline{CH}_3)_2CH$, a "quartet" centred at 54 c/s (*J* = 6 c/s); quaternary Me 68 c/s; vinylic Me, 113 c/s; $(CH_2\text{-}S)_2$, unresolved s at 196 c/s. (Found: C, 68·48; H, 9·53. $C_{17}H_{28}S_2$ requires: C, 68·9; H, 9·5%).

(+)-*7-Epi-eudesm-4-ene* XIV. Thioketal XIII (6·5 g), 95% EtOH (500 ml) and Raney Ni (W-2, 100 g) were refluxed together on a water bath for 16 hr. The product was isolated as described earlier to furnish XIV as a colourless oil (2·973 g, 71%): b.p. 117–118°/8 mm, n_D^{30} 1·4942, $[\alpha]_D^{25}$ +48° (*c*, 1·3%), TNM test + ve; UV end absorption: ε_{210} = 4054, ε_{215} = 2659, ε_{220} = 1528, ε_{225} = 797; IR spectrum: C=O absent. (Found: C, 87·22; H, 12·75. $C_{15}H_{26}$ requires: C, 87·3; H, 12·7%).

---

* NaH in ether–pyridine[16] gave the epimeric dihydrocyperones in a considerably attenuated yield (27%).

† This thioketal has been prepared recently,[36] m.p. 93–94°, $[\alpha]_D$ +90° (*c*, 5·0% in $CHCl_3$).

(+)-4β,5β-*Epoxy-7-epi-eudesmane* VIII

The epi-olefin XIV (1·001 g) was treated with perbenzoic acid (0·874 g) in benzene (26 ml) at 5° and kept in the refrigerator for 46 hr (ca. 5°). The product was isolated as described earlier and purified by chromatography over neutral Al_2O_3 (gr. II, 40 g; 14 × 2·5 cm). Pet. ether eluted a hydrocarbon fraction (147 mg) followed by the required oxide (747 mg) which came with benzene. Distillation furnished pure VIII as a colourless sweet-smelling liquid: b.p. 120–121°/5 mm, n_D^{30} 1·4818, $[\alpha]_D^{25}$ +26·2° (*c*, 0·5%), TNM test –ve. IR spectrum: characteristic bands at 930, 890 and 870 cm^{-1}. PMR spectrum: $(CH_3)_2CH$, poorly resolved "quartet" centred at 53 c/s (J = 6 c/s); quaternary Me, 61·5 c/s; oxirane-geminal Me, 74 c/s. (Found: C, 81·72; H, 12·27. $C_{15}H_{26}O$ requires: C, 81·02; H, 11·79%).

Rearrangement of 4,5-*epoxides* (VI, VII, VIII) *with* BF_3–Et_2O

(a) *Rearrangement of* 4α,5α-*epoxy-eudesmane* (VI). The epoxide VI (61 mg) in dry toluene (3 ml) was cooled to ca –15° (freezing mixture) and treated with freshly distilled BF_3–Et_2O (0·12 ml). After 30 min at the same temp the light brown reaction mixture was poured into sat Na_2CO_3aq (5 ml); extraction with pet. ether (15 ml × 2), washing with brine, drying and removal of solvent yielded a pale yellow oil (56 mg) which indicated only a slight impurity (TLC). PLC on SiO_2–gel (20 × 20 cm) using toluene–EtOAc (95:5) as solvent system gave the pure XVI (41 mg) after distillation: b.p. 145–146° (bath)/2 mm, n_D^{30} 1·4843, $[\alpha]_D^{28}$ +39·5° (*c*, 1·2%). (Found: C, 81·23; H, 11·64. $C_{15}H_{26}O$ requires: C, 81·02; H, 11·79%).

The *semicarbazone* (pyridine method) was obtained as colourless silky needles m.p. 184–185° on recrystallization from EtOH–pyridine. (Found: N, 14·6. $C_{16}H_{29}ON_3$ requires: N, 15·04%).

(b) *Rearrangement of* 4β,5β-*epoxy-eudesmane* VII. Epoxide VII (48 mg) in dry toluene (2·5 ml) was cooled as before and treated with BF_3 etherate (0·1 ml). The product (44 mg) was isolated exactly as in (a) and TLC revealed it to be a two-component mixture. PLC (same solvent system as before) gave a clean separation: hydrocarbon XVIII (7 mg) and ketone XIX (29 mg). The latter had: b.p. 150° (bath)/3 mm, n_D^{30} 1·4722, $[\alpha]_D^{28}$ +22·8° (*c*, 0·38%).

(c) Once the products from each epoxide were ascertained, BF_3-rearrangement was carried out with the mixture of epoxides for convenience. The epoxides mixture (295 mg) in dry toluene (8 ml) was reacted with BF_3–Et_2O (0·8 ml) and worked up as described above. The crude product (293 mg) was chromatographed on SiO_2–gel (gr. I, 14 g; 24·5 × 1·1 cm) and the separation was monitored by TLC (solvent system: C_6H_6 + EtOAc 5%). Elution with pet. ether (10 ml × 3) gave δ–selinene XVIII (34 mg) which was distilled: b.p. 90° (bath)/2 mm, n_D^{30} 1·5121, $[\alpha]_D^{27}$ + 197° (*c*, 0·86%), GLC, $AgNO_3$–SiO_2 gel TLC: single compound, TNM test: dark brown colour.

Elution with benzene gave XVI obtained by rearrangement of 4α,5α-epoxide. Further elution with the same solvent yielded XIX resulting from 5β,5β-epoxide.

Rearrangement of 4β,5β-*epoxy-7-epi-eudesmane* VIII.

Epoxide VIII (447 mg) in dry toluene (10 ml) was cooled in a freezing mixture and allowed to react with BF_3–Et_2O (1 ml) for 30 min. The usual work up (described above) furnished a pale yellow liquid (421 mg) b.p. 90–135° (bath)/3 mm. GLC analysis of the product revealed the presence of a hydrocarbon (14%) and two ketones (12% and 68%); in conformity with this anslysis, TLC on silica gel also showed 3 spots (solvent: benzene). The components of the mixture (367 mg) were separated by chromatography on SiO_2 gel (gr. IIA, 20 g; 30 × 1·2 cm). Elution with pet. ether (10 ml × 3) furnished the hydrocarbon XX: b.p. 125° (bath)/ 6 mm; n_D^{30} 1·5103, $[\alpha]_D^{27}$ –68·7° (*c*, 1·0%), TNM test: dark brown colour; GLC: ~90% pure.

Elution with pet. ether–benzene (9:1, 10 ml × 2) gave the minor ketone XXII (0·0565 g) further purified by PLC using benzene as developer. It had b.p. 125° (bath)/ 1·5 mm, n_D^{30} 1·4779, $[\alpha]_D^{33}$ –55·7° (*c*, 0·88%). (Found: C, 81·74; H, 11·82. $C_{15}H_{26}O$ requires: C, 81·02; H, 11·79%).

Elution with benzene (10 ml × 6) furnished the major ketone XXI (0·146 g) which was distilled: b.p. 150° (bath)/2 mm, n_D^{30} 1·4759, $[\alpha]_D^{27}$ –56·1° (*c*, 0·54%). (Found: C, 80·8; H, 11·56. $C_{15}H_{26}O$ requires: C, 81·02; H, 11·79%).

The *semicarbazone* prepared by the pyridine method and recrystallized from EtOH–pyridine gave colourless microprisms m.p. 100–102°. (Found: N, 14·96. $C_{16}H_{29}ON_3$ requires: N, 15·04%).

REFERENCES

[1] L. Ruzicka, *Experientia* **9**, 357 (1953); *Proc. Chem. Soc.* 341 (1959).

[2] For a recent review see: J. H. Richards and J. B. Hendrickson, *The Biosynthesis of Steroids, Terpenes and Acetogenins* pp. 173–288. Benjamin, New York (1964).

[3] Cited in: A. R. Penfold and J. L. Simonsen, *J. Chem. Soc.* 87 (1939).

[4] L. H. Zalkow, F. X. Markley and C. Djerassi, *J. Am. Chem. Soc.* **82**, 6354 (1960); L. H. Zalkow, A. M. Shaligram, Shih-en Hu and C. Djerassi, *Tetrahedron* **22**, 337 (1966).

[5] K. R. Varma, M. L. Maheshwari and S. C. Bhattacharyya, *Ibid.* **21**, 115 (1965).

[6] H. Hikino, K. Aota, Y. Maebayashi and T. Takemoto, *Chem. Pharm. Bull.* **14**, 1439 (1966); H. Hikino, N. Suzuki and T. Takemoto, *Ibid.* **14**, 1441.

[7] V. H. Kapadia, V. G. Naik, M. S. Wadia and Sukh Dev, *Tetrahedron Letters* 4661 (1967).

[8] J. Krepinsky, M. Romanuk, V. Herout and F. Šorm, *Coll. Czech, Chem. Comm.* **27**, 2638 (1962) and Refs cited therein; J. A. Marshall, W. I. Fanta and G. L. Bundy, *Tetrahedron Letters* 4807 (1965); E. Wenkert and D. A. Berges, *J. Am. Chem. Soc.* **89**, 2507 (1967).

[9] A. H. Kapadi and Sukh Dev, *Tetrahedron Letters* 1255 (1965).

[10] For similar cases of isomerization see: H. J. Ringold and S. K. Malhotra, *Tetrahedron Letters* 669 (1962).

[11] L. F. Fieser, *J. Am. Chem. Soc.* **76**, 1728 (1954).

[12] A. S. Gupta and Sukh Dev, *J. Chromatog.* **12**, 189 (1963).

[13] cf. J. Broome and B. R. Brown, *Chem. & Ind.* 1307 (1956); J. Broome, B. R. Brown and A. M. S. White, *J. Chem. Soc.* 1406 (1960).

[14] cf. N. P. Damodaran and Sukh Dev, *Tetrahedron Letters* 1941 (1963).

[15] For a review see: E. D. Bergmann, D. Ginsburg and R. Pappo, *Organic Reactions* **10**, 179 (1959).

[16] F. J. McQuillin, *J. Chem. Soc.* 528 (1955); R. Howe and F. J. McQuillin, *Ibid.* 2423 (1955); 2670 (1956).

[17] P. A. Plattner, T. Petrzilka and W. Lang, *Helv. Chim. Acta* **27**, 513 (1944); C. W. Shoppee, M. E. H. Howden, R. W. Killick and G. H. R. Summers, *J. Chem. Soc.* 630 (1959).

[18] H. P. Hartshorn and D. N. Kirk, *Tetrahedron* **20**, 2943 (1964).

[19] For a brief summary see: A. Rosowsky, *Heterocyclic Compounds* (Edited by A. Weissberger) Vol. 19 (Part 1); pp. 251–260. Interscience, New York (1964); D. J. Goldsmith, *J. Am. Chem. Soc.* **84**, 3913 (1962).

[20] H. B. Henbest and T. I. Wrigley, *J. Chem. Soc.* 4596 (1957).

[21] D. N. Kirk and V. Petrow, *Ibid.* 4657 (1960).

[22] W. J. Wechter and G. Slomp, *J. Org. Chem.* **27**, 2549 (1962).

[23] [a] J. M. Coxon, M. P. Hartshorn and D. N. Kirk, *Tetrahedron* **20**, 2531 (1964);
[b] M. P. Hartshorn and D. N. Kirk, *Ibid.* **20**, 2943 (1964);
[c] J. W. Blunt, M. P. Hartshorn and D. N. Kirk, *Ibid.* **21**, 559 (1965);
[d] M. P. Hartshorn and D. N. Kirk, *Ibid.* **21**, 1547.

[24] G. Büchi, W. D. MacLeod and J. Padilla, *J. Am. Chem. Soc.* **86**, 4438 (1964).

[25] C. S. Barnes, D. H. R. Barton, A. R. H. Cole, J. S. Fawcett and B. R. Thomas, *J. Chem. Soc.* 571 (1953).

[26] R. C. Cambie, W. R. J. Simpson and L. D. Colebrook, *Tetrahedron* **19**, 209 (1963); S. M. Bocks, R. C. Cambie and T. Takahashi, *Ibid.* **19**, 1109 (1963).

[27] G. M. Whitesides, D. Holtz and J. D. Roberts, *J. Am. Chem. Soc.* **86**, 2628 (1964).

[28] M. L. Maheshwari, T. C. Jain, R. B. Bates and S. C. Bhattacharyya, *Tetrahedron* **19**, 1079 (1963).

[29] For a summary of evidence see: E. L. Eliel in *Steric Effects in Organic Chemistry* (Edited by M. S. Newman) pp. 130–134. Wiley, New York (1956). Some apparent exceptions have been adequately rationalized: D. H. R. Barton and G. A. Morrison in *Progress in the Chemistry of Natural Products* (Edited by L. Zechmeister) 19; pp. 202–205. Springer-Verlag, Wien (1961).

[30] R. F. Zürcher, *Helv. Chim. Acta* **44**, 1380 (1961); **46**, 2054 (1963).

[31] A. I. Cohen and S. Rock, *Steroids* **3**, 243 (1964).

[32] G. L. Chetty, G. S. Krishna Rao, Sukh Dev and D. K. Banerjee, *Tetrahedron* **22**, 2311 (1966).

[33] R. Howe and F. J. McQuillin, *J. Chem. Soc.* 2670 (1956).

[34] V. B. Zalkow, A. M. Shaligram and L. H. Zalkow, *Chem. & Ind.* 194 (1964).

[35] T. M. Jacob and Sukh Dev, *J. Indian Soc.* **34**, 327 (1957).

[36] D. W. Thoebald, *Tetrahedron* **20**, 2593 (1964).