Tetrahedron. Vol. 24, pp. 5847 to 5859 Pergamon Press 1968 Printed in Great Britain

STUDIES ON EPOXIDES—V[1]

REACTIONS WITH 5,6-EPOXY-EUDESMAN-8β,12-OLIDES

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(*Received in the UK* 27 *March* 1968; *accepted for publication* 25 *April* 1968)

Abstract—The acid catalysed opening of the epoxide ring in several 5,6-epoxy-eudesman-8β,12-olides has been analysed. Treatment of the α-oriented epoxides XI and XIVb with HBr results in the formation of the diols XIX and XXI, whereas the β-epoxide XIII yields the expected *trans* diequatorial bromohydrin XXVId. The above and some other related reactions of eudesm-5-en-8β,12-olides with osmium tetroxide are described. An internal displacement of the epoxide ring in the epoxy-lactone XVI to yield the hydroxy-lactone XXVII takes place under mild alkaline conditions.

IN PREVIOUS work,[2] the steric course of the acid catalysed opening of the epoxide ring in 4-acetoxy-5,6-epoxycholestanes has been studied. It was shown that the presence of an axial, β-oriented 4-acetoxy group does not affect the direction of the cleavage of the vicinal epoxide if α-oriented, but reverses this direction when the epoxide is β. Indeed, the product obtained by exposing 4β-acetoxy-5β,6β-epoxy-cholestane to hydrobromic acid is the *trans* diequatorial 5β-hydroxy-6α-bromo derivative and not the expected *trans* diaxial bromohydrin.

In the case of the α-oriented epoxide, the formation of the diaxial bromohydrin implies free access of the attacking species (Br^-) at C-6 from the top side of the molecule, a condition which is fulfilled when the reaction substrate has the cholestane skeleton. The behaviour of epoxides under acidic conditions when the accessibility at both C atoms of the oxirane ring is hindered has now been investigated. Appropriate models were found among some derivatives of the sesquiterpene alantolactone (I),[3] in which the possibility of an attack from the top of the molecule at C-5 would be unfavourable owing to hindrance of the β-axial substituents at C-4 and C-10, whereas the bulky β-*cis* lactone ring would prevent free access at C-6.

The compounds which were prepared were the α-oriented epoxides XI, XIV and XVI, and the β-epoxide XIII. The α-oriented epoxide XI was obtained from iso-alantolactone (II) in a nine step sequence. Catalytic hydrogenation of II afforded the known dihydroisoalantolactone (III).† When this hydrogenation was carried out in presence of Pd–C as catalyst, mixtures in variable ratios of III and the isomeric Δ^3-compound were obtained. The required dihydro-isoalantolactone (III) could be prepared in pure form by preventing the slightly acidic medium, inherent to commercial batches of Pd–C, either by adding a few drops of a sodium bicarbonate solution or preferably by using Pd–$CaCO_3$ as catalyst. Ozonolysis of III followed by reductive work-up produced the 4-oxo-derivative (IV) as shown in the IR by a new band at 1710 cm^{-1} indicative of a 6-membered ring ketone. Reduction of the

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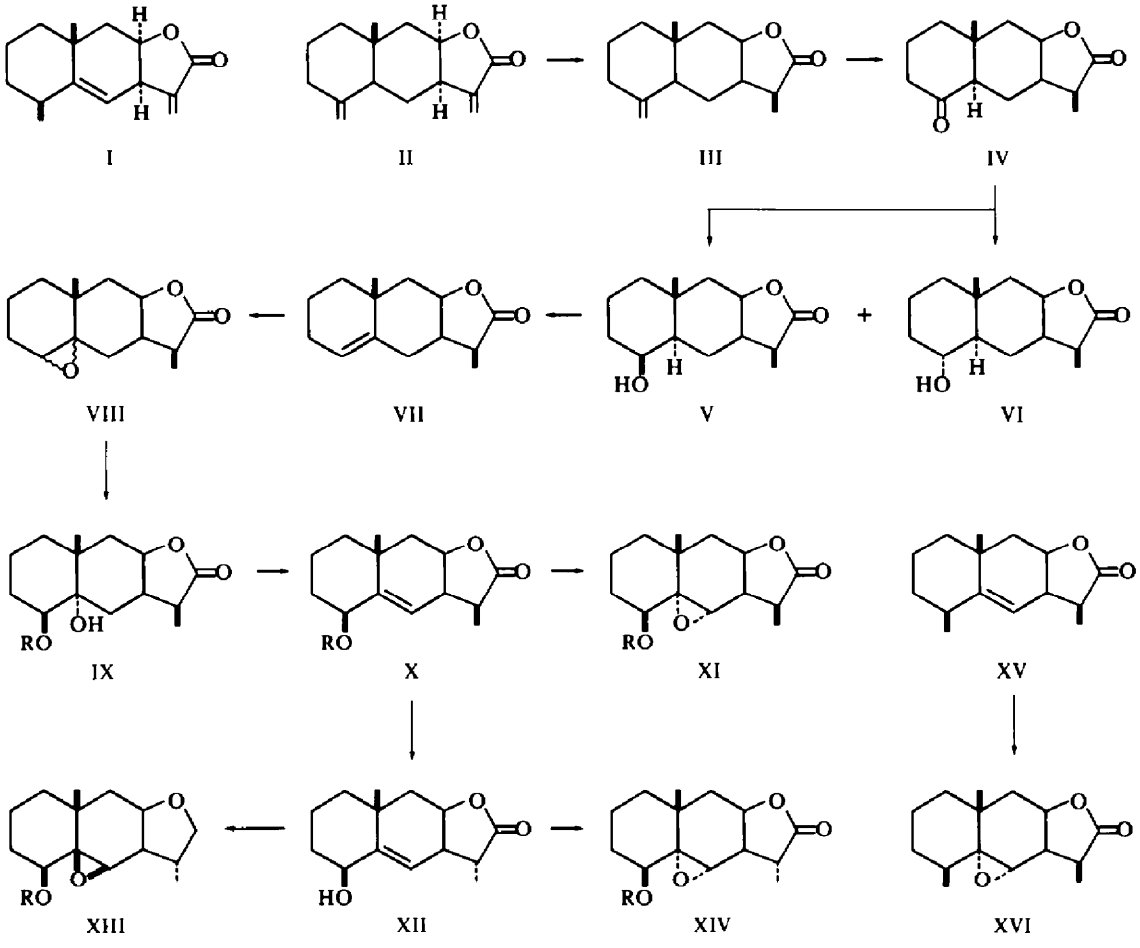
† This compound was also prepared by $NaBH_4$ reduction of isoalantolactone.[4]

ketone IV with sodium borohydride afforded a chromatographically separable mixture of the two epimeric alcohols Va and VI in a ratio of 4:1; the reduction proceeded, stereoselectively over platinum in acetic acid solution to yield only the required axial 4β-hydroxy isomer Va.

Elimination of water in order to produce the unsaturated derivative VII could be performed with thionyl chloride in pyridine, or by heating in benzene with a catalytic amount of toluene-*p*-sulphonic acid; the best results were, however, obtained by decomposing the 4β-mesyloxy derivative Vc in pyridine solution. Following chromatography, the pure 15-noreudesm-4-en-8β,12-olide (VII), was obtained, showing a characteristic triplet at δ 5·51 due to the vinylic 4-H.



Treatment of VII with perbenzoic acid afforded the 4,5-epoxide VIII which owing to the crowding on the β face of the molecule, has to be α-oriented. Upon treatment with perchloric acid in acetone, followed by acetylation of the diol IXa, the required 4β-acetoxy-5α-hydroxy-15-noreudesman-8β,12-olide (IXb) was obtained.

The β-axial orientation of the 4-acetoxyl in IXb was substantiated by the signal displayed in the NMR spectrum by the 4α-H (triplet at δ 4·75). Dehydration of IXb with thionyl chloride in pyridine yielded the 4β-acetoxy-Δ^5-derivative (Xb) which, in addition to the signal of the 4α-H, now at δ 5·28 due to the deshielding effect of the neighbouring double bond, showed a new signal at δ 5·62 (doublet J = 2 c/s) for the vinylic 6-H split by the neighbouring 7α-H. Epoxidation of the latter proceeded stereoselectively to give the corresponding 5α,6α-epoxide XI.

For the preparation of the isomeric 5β,6β-epoxide, advantage was taken of the known[5] directing effect of the hydroxy group in the epoxidation of allylic alcohols, leading to the preferential formation of *cis* epoxy alcohols. Since LAH could not be used for the reduction of the 4-acetate to the corresponding 4-alcohol in view of the concomitant reductive opening of the lactone ring, the fission of the acyl-oxygen bond in the acetate Xb was performed with a strong base, thus ensuring that the allylic system would remain unchanged.[6] However, lactones are known[7] to epimerize under alkaline conditions and indeed, the reaction of the acetate Xb with sodium methoxide resulted in mixtures of the allylic alcohols Xa and XIIa, the latter possessing the 11-Me group α oriented. Prolonged reaction times led to complete epimerization of X into XII.

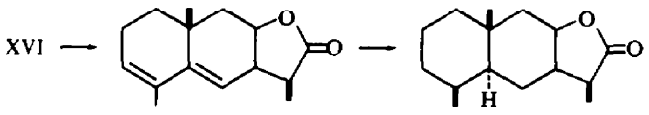
As expected, the signal of the 11-Me group in XIIa is deshielded (δ 1·33) as compared to the signal of the β-axial 11-Me in Xa (δ 1·23). The signals of the 4α-H (tr, δ 4·20) and of the vinylic proton (d, J = 3 c/s, at δ 5·38) indicated that indeed no allylic rearrangement had taken place during the transformation of Xa into XIIa. Upon acetylation of XIIa the corresponding acetate XIIb was obtained which was different from the starting acetate Xb.

Treatment of XIIa with perbenzoic acid yielded the 5β,6β-epoxide (XIIIa) along with an equal amount of the 5α,6α-epoxide (XIVa). The mixture could be resolved only by chromatography of the corresponding acetates XIIIb and XIVb. The stereochemical assignments for the three epoxy derivatives XI, XIII and XIV are based on their mode of formation, and they are substantiated by the signals exhibited by the C-6 epoxidic protons in each of the compounds. Inspection of Dreiding models of the two α-oriented epoxides XI and XIVb shows that the dihedral angle formed by 6β-H and 7α-H is about 85° and accordingly the coupling constant between these two protons should be almost nil; indeed, the 6β-H in compound XI displays a singlet at δ 3·28, whereas in the epoxide XIVb it exhibits a very narrow doublet (J < 1 c/s) at δ 3·30. The problem is more complex in the case of the 5β,6β-epoxide XIIIb which owing to the *cis* A/B ring junction can exist in two conformations: in the steroid like conformer, the dihedral angle between 6α-H and 7α-H is about 60° and consequently the expected coupling constant should be of ~1·5 c/s, and in the nonsteroid like conformer the corresponding angle is of ~30° requiring a J value of ~4 c/s. The signal of the 6α-H in this compound was found to be a doublet (J = 4 c/s) at δ 3·20, thus confirming the β orientation of the epoxide ring, and suggesting on the other hand the non steroid like conformation of XIII.

The fourth epoxide XVI was prepared by epoxidation of dihydroalantolactone (XV); the reaction proceeded stereoselectively to yield the 5α,6α-epoxide, showing in the NMR spectrum a very narrow doublet (J = 1 c/s) at δ 2·90.

Next, the acid catalysed opening of the epoxide ring in compounds XI, XIIIb, XIVb and XVI was examined. Treatment of XVI with hydrobromic acid in acetic

acid solution produced two compounds, none having bromine in the molecule. The major component, which was isolated from the reaction mixture, shows an UV absorption spectrum (λ_{max} 232, 239, 247 mμ) characteristic for a heteroannular diene. Of the two signals due to the secondary Me groups in the NMR spectrum of the starting epoxide XVI (centered at δ 1·12 and 1·38), one disappeared giving place to a new doublet (J = 2 c/s) at δ 1·78, indicating the presence of a vinylic Me group; the small splitting was attributed to coupling with an allylic proton. Replacing the signal of the epoxidic proton in XVI, two low field signals appeared at δ 5·33 (doublet, J = 4 c/s) related to the C-6 vinylic proton, in view of a similar pattern for the same proton in dihydroalantolactone (XV), and at δ 5·61 (tr) for the C-3 vinylic proton.



XVII XVIII

In accordance with the above spectral evidence, structure XVII was assigned to this compound, which upon catalytic hydrogenation was converted into the known tetrahydroalantolactone (XVIII), thus confirming the proposed structure.

It is noteworthy that the same reaction mixture was obtained when compound XVI was treated with a dilute solution of sulphuric acid in acetic acid.

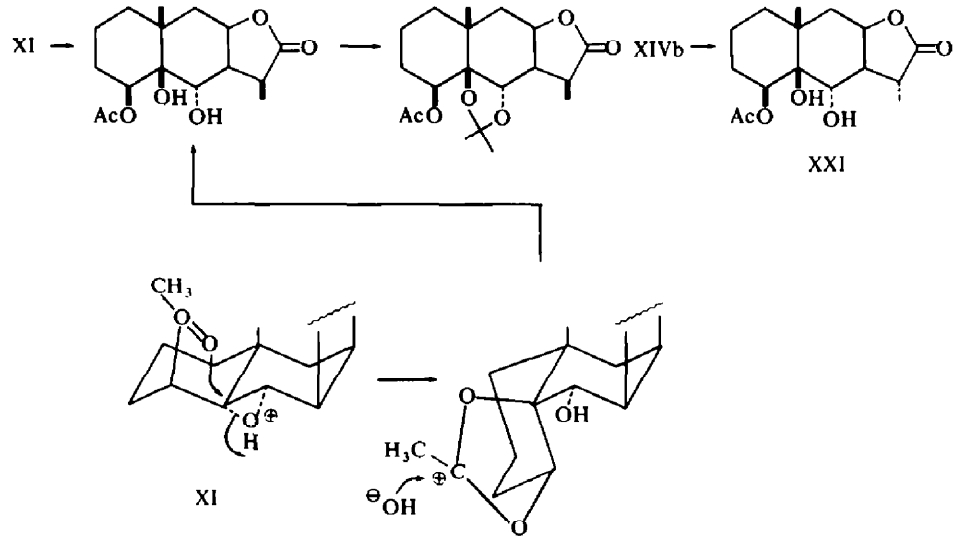
The second compound which was studied was the epoxy-acetate XI which, following a similar treatment with hydrobromic acid in acetic acid solution afforded primarily a Br-free product XIX possessing, however, OH groups as disclosed in the IR spectrum. Again, the reaction followed the same course when sulphuric acid was used instead of the hydrobromic acid.* The molecular ion peak in the mass spectrum of this compound (M^+ 312) corresponded to the addition of the elements of one molecule of water to the starting epoxide XI. The NMR spectrum of XIX was most informative: it indicated that the starting epoxidic proton had disappeared while the multiplet (δ 4·63) due to the 8α-H remained unchanged. A double doublet (J = 10·5 and 5 c/s) at δ 3·95 appeared now with the intensity of one proton, whereas the triplet at δ 4·31 related to the equatorial 4α-H in XI was replaced by a multiplet at δ 5·30, pointing to an axial orientation of this proton. The change in pattern of the 4α-H paralleled the behaviour of the corresponding proton in steroids[2] following the conversion of the junction of rings A/B from *trans* to *cis*. Upon exchange with deuterium oxide, the double doublet at δ 3·95 collapsed to a one proton doublet (J = 10·5 c/s); this is suggestive for a proton next to an OH group in which spin coupling takes place with a proton on a neighbouring C atom (the large coupling), and with the hydroxylic proton (the small coupling). The only assignment for such a H atom is at C-6, the proton inducing the large splitting being at C-7. Indeed, irradiation at the frequency of the latter induced further collapse of the signal to a singlet, thus confirming unequivocally that the δ 3·95 double doublet is due to the proton at C-6, adjacent to an OH group.

* Under these conditions it was expected that a *trans* hydroxy-acetate should be formed.

The presence of a vicinal diol system in XIX was proven by periodic acid titration (consumption of 0·9 moles of reagent) and by formation of an acetonide (XX). A *trans* diaxial diol would resist both periodic acid cleavage and acetonide formation; however, the NMR spectrum of XIX indicates a *cis* A/B ring junction implying a β-orientation of the tertiary OH group at C-5, which is thus equatorial towards ring B. Considering the *trans* opening of epoxide rings, one may assume that the compound which was obtained is the diequatorial 5β,6α-diol. One should emphasise the hindrance of the 6α-OH in this compound, which resisted usual acetylating conditions (acetic anhydride–pyridine).

The failure of hydrobromic acid to produce a bromohydrin by reacting with the epoxide XI, raised the problem of the groups responsible for such a hindrance. Since the attack of the Br anion could come only from the top side of the molecule, in order to leave the OH group α-oriented, it could be assumed that the axial C-11 β-Me group exerts the main hindrance to such an approach at C-6. The availability of the epoxide XIVb in which the C-11-Me is α oriented could provide an answer; the reaction with hydrobromic acid produced again a diol (XXI) epimeric at C-11 with XIX. It can be concluded therefore, that the lactone ring alone can prevent the free access of the Br anion at C-6.

The formation of the 5,6-*trans* diequatorial diol can be eventually interpreted by a neighbouring group participation mechanism involving the 4β-acetate, through a 5-membered ring intermediate as shown in the scheme:

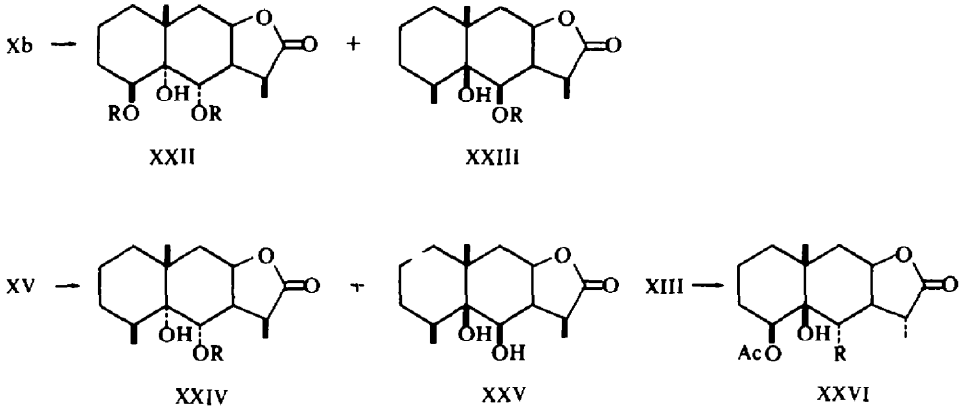


A similar mechanism has been proposed[8] for the opening of the epoxide ring in 3β-acetoxy-4α,5α-epoxycholestane proceeding by assistance of the neighbouring group; in the present case however, opening of the cyclic intermediate leaves the acetate function in its previous position.

In view of the unusual opening reaction of the epoxide ring in compounds XI and XIV, and to obtain further support for the configuration of the diols XIX and XXI,

it was decided to prepare the two possible 5,6-*cis* diols by direct hydroxylation with osmium tetroxide of the double bond in Xb. Since, the β-orientation of the angular 5-OH was clearly established by the NMR data presented above, it was anticipated that by preparing the *cis* diols it would be possible by exclusion, to determine unequivocally the *trans* diequatorial relationship between the two OH groups in XIX.

Upon exposure to osmium tetroxide followed by decomposition of the osmate esters, compound Xb afforded a mixture of two isomeric triols XXIIa and XXIIIa, both showing the same molecular ion peak, M^+ 270. The decomposition of the osmate esters was accompanied by the hydrolysis of the C-4-acetate, a process which was strongly accelerated by the vicinal 5-OH group.[9] The separation of these triols could be achieved by chromatography of the corresponding acetates which were found to be a mixture of a diacetate and a monoacetate. Simple steric considerations indicate that the triol which was converted into the diacetate must be the *cis* α isomer—4β, 5α, 6α-triol XXIIa. Examination of the NMR spectrum of the monoacetate which was presumably obtained from the isomeric β *cis* compound—the 4β, 5β, 6β-triol XXIIIa—led to the conclusion that of the two secondary OH groups available for acetylation, the 6β-OH was converted into the corresponding acetate, the 6α-H exhibiting a one proton doublet at δ 5·65 (J = 9 c/s). The equatorial 4α-H which is adjacent to the remaining free OH group displayed a triplet at δ 3·90, suggesting an axial orientation for the 4β-OH, and consequently a non-steroid type conformation for rings A and B in this compound. Provided that ring B remains in a chair conformation, the 6β-OH should then be equatorial, hence easily acetylated.



a: R = H; b: R = Ac; d: R = Br

The same sequence of reactions was repeated with dihydroalantolactone (XV) and resulted in an inseparable mixture of the *cis* diols XXIVa, and XXV. Upon acetylation the *cis* α-diol XXIVa was converted into the corresponding monoacetate XXIVb (doublet for the 6β-H at δ 5·55, J = 8·5 c/s), whereas the β-*cis* diol XXV remained unchanged (6α-H signal at δ 4·10, doublet, J = 9 c/s). The reactivity of the 6β-OH rather than of the 4β-OH in XXIII is in obvious contrast with the inertness of the 6β-OH in XXV when subjected to similar acetylating conditions. Any explana-

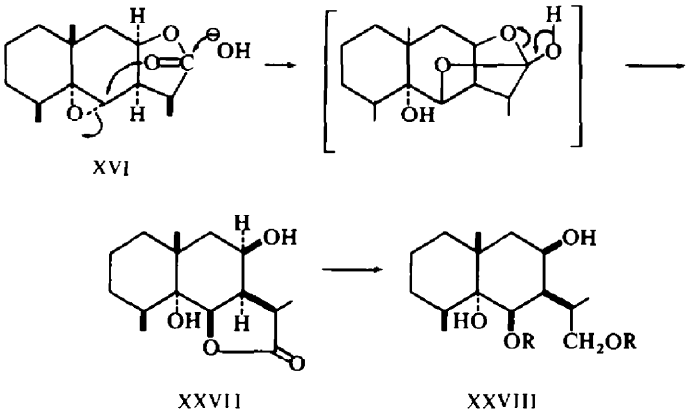
tion for the different behaviour of these compounds (XXIII and XXV) should take into consideration their possible conformational differences. In a steroid type conformation as assumed for XXV, the 6β-OH should be *axial* and the C-4 substituent equatorial, whereas the situation would be reversed in a non-steroid type conformation.

The preparation of the two pairs of *cis* diols while interesting *per se* in view of the conformational problems discussed above, did not, however, contribute in the configurational elucidation of the diol XIX. The *trans* diequatorial orientation of the OH groups at positions 5 and 6 in the latter rests upon the considerations treated earlier.

The last epoxide to be investigated was the 4β-acetoxy-5β,6β-epoxy derivative XIII. The only product obtained by treatment with hydrobromic acid in acetic acid solution was the bromohydrin XXVId. The signal at δ 4·45 $J = 12$ c/s is in agreement with an axial 6β-H coupling its spin with the axial 7α-H. The stereochemistry of the A/B rings junction could be determined from the pattern of the 4α-H signal which was converted from a narrow triplet in the starting epoxide XIII to a double doublet ($J = 10$ and 5 c/s) in the bromohydrin XXVId. The steric implications of such a change in the pattern of this signal have already been discussed[2] in connection with 4β-acetoxy-5β,6β-epoxy-cholestane. Confirmation of the assignment of the doublet at δ 4·45 in the spectrum of XXVId to a hydrogen adjacent to the Br atom at C-6 was obtained by Raney nickel debromination of this compound to yield the hydroxy-acetate XXVIa.

A reaction along different lines which was observed with this series of compounds occurred during the mild alkaline treatment (methanolic potassium bicarbonate) of the epoxy-lactone XVI. The major product was a hydroxy-lactone, the mol wt of which, determined by mass spectrometry, M^+ 268 indicated the addition of the elements of a molecule of water to the starting compound. The NMR spectrum of this compound (pyridine solution), which was assigned structure XXVII, showed, *inter alia*, a one proton multiplet at δ 4·90, a doublet at δ 4·23 ($J = 5$ c/s) and two other signals—singlet at δ 4·93 and doublet at δ 4·03 ($J = 5$ c/s) both disappearing upon addition of D_2O. The signal of the epoxidic 6-H of XVI was not present in XXVII. The compound did not undergo acetylation in the usual mild conditions but was reduced by LAH to a tetrol XXVIIIa yielding a diacetate XXVIIIb. According to the information obtained from the NMR spectrum of the latter, the two OH groups which did not acetylate in the hydroxy-lactone XXVII remained also unacetylated in the product XXVIIIb, whereas the primary and the secondary hydroxyls formed by the reductive opening of the lactone ring did undergo acetylation; this was shown by a two proton doublet at δ 4·23 ($J = 4$ c/s) for the 12-methylene split by the 11-H, and a one proton doublet at δ 4·10 ($J = 5$ c/s) for the 6-H coupling its spin with the 7α-H. The assignment of the δ 4·23 doublet in XXVII and of the δ 4·10 doublet in XXVII to the 6-H of each, was confirmed by decoupling experiments done with the former: irradiation at the frequency of the 7-H (δ 2·9 region) resulted in the collapse of the 4·23 doublet to a singlet.

Opening of the epoxide ring under the mild alkaline conditions employed with XVI can be rationalized by assuming an internal nucleophilic displacement of the epoxide, possibly through an ortho-ester intermediate[10] formed by an attack of the base on the lactonic carbonyl, as shown by the arrows in the following scheme:



XVI

XXVII XXVIII

a: R = H; b: R = Ac

Of the two possible sites at which the epoxide can be opened, the C-6 is favored. The nonacetylability of the 8β-axial OH in XXVII is probably due to the hindrance exerted on this group by the 6β,12-lactone and the C-10 Me group. Had the epoxide ring been displaced at C-5, a hydroxy-lactone characterized by the presence of a 6-membered ring lactone and of two secondary OH groups (8β-OH and 6α-OH), would have been formed; there seems to be no special reason for such a 6α-OH to resist acetylation.

An alternative assumption of a displacement of the epoxide in XVI effected by an attack of the C-8 oxanion* formed upon opening of the lactone ring is not acceptable, since the 8β-OH is not properly disposed from a steric point of view to induce such a displacement; further, the product which was formed was neither an acid nor an oxido-lactone, the mol wt of XXVII not fitting to the latter.

EXPERIMENTAL

M.ps were taken on a Fisher–Johns apparatus and are uncorrected. Optical rotations were recorded with an automatic Perkin–Elmer 141 polarimeter and refer to $CHCl_3$ solns unless otherwise specified. IR spectra were recorded on a Perkin–Elmer Infracord model 137 spectrophotometer equipped with a NaCl prism and were determined in 5–10% $CHCl_3$ soln or in KBr pellets. NMR spectra were recorded on a Varian A-60 spectrometer, for 5–10% solns in $CDCl_3$, or pyridine containing TMS as internal standard. The mol wts, whenever given, were determined by Mrs. A. Jacob on an Atlas CH4 mass spectrometer. Analyses were performed in the microanalytical laboratory of our Institute, under the direction of Mr. R. Heller.

Isolation of alantolactone (I) *and isoalantolactone* (II)

The present procedure is slightly different from that described in the literature. Dried chopped roots of *Inula helenium* were extracted during ~48hr with benzene, the solvent was removed and the oily dark residue dissolved in hot EtOH, then an equal amount of water was added. After cooling, the crystalline material in the upper phase was collected and recrystallized from EtOH to yield a mixture of II (~80%) and IV (~20%). Separation was achieved by chromatography on acid washed alumina (Merck); elution

* An example for such a case is the attack of the C-3-OH op the epoxide ring in the base induced conversion of picrotoxinin into picrotoxic acid.[11]

with hexane–ether (4:6) yielded II, recrystallized from EtOH, m.p. 111–113°[3]. Further elution with the same solvent mixed afforded IV, recrystallized from EtOH, m.p. 172–173°[3].

The lower layer from the crude extract was concentrated to a dark syrup which was redissolved in $CHCl_3$, dried (Na_2SO_4) and the solvent removed. The residue was chromatographed through acid washed alumina. Elution with hexane containing 3–5% ether yielded non crystalline material which was discarded. Further elution with hexane–ether (1:1) yielded a crystalline mixture of lactones which was combined and rechromatographed on acid washed alumina impregnated with 8% of $AgNO_3$ aq (30 ml for 500 g alumina). Elution with hexane–ether (98:2) yielded I, crystallized from EtOH, m.p. 78–79°[3]. Identification of the products in the different phases of the separation was done by TLC on plates of silicagel G (Merck) impregnated with 5% $AgNO_3$.

Dihydroisoalantolactone (III)

An ethanolic soln (600 ml) of isoalantolactone (11 g) was hydrogenated over 5% $Pd/CaCO_3$. After the rapid absorption of one mole H_2, the soln was filtered and evaporated. The product (9·5 g) crystallized from EtOH, m.p. 172–173°.

15-*Noreudesman*-4-*on*-8β,12-*olide* (IV)[12]

Compound III (5·3 g) in $CHCl_3$ (400 ml) was ozonized at 0°, until ca. 1·3 equiv of O_3 had been introduced. Most of the solvent was then removed in vacuum and the crude ozonide was dissolved in AcOH (50 ml) and stirred for several hr with Zn powder (3 g). Following filtration the product was extracted with $CHCl_3$ and the soln washed with $NaHCO_3$ aq, water and dried (Na_2SO_4). Evaporation of the solvent left the product which crystallized from EtOH (4·2 g); m.p. 197–199°, $[\alpha]_D$ +17° (*c* 1·1); ν_{max} 1767 and 1710 cm^{-1}. NMR: C-10 Me, δ 0·88 s; C-11 Me, δ 1·22 (d, 7 c/s).

4β-*Hydroxy*-15-*noreudesman*-8β,12-*olide* (Va) *and* 4α-*hydroxy*-15-*noreudesman*-8β,12-*olide* (VI)

(a) Sodium borohydride (300 mg) was added to a soln of IV (1·0 g) in MeOH (30 ml) and stirred for 2 hr. Excess reagent was destroyed with AcOH and most of the solvent was then removed under vacuum. The product was extracted with $CHCl_3$, the soln washed with water, dried and the solvent removed. The residue (950 mg) which showed two spots on a chromatoplate was chromatographed on acid washed alumina (50 g). Elution with $CHCl_3$–ether (98:2) gave Va (750 mg) which crystallized from acetone–hexane, m.p. 140°, $[\alpha]_D$ +15° (*c*, 1·0). NMR: C-10 Me, δ 1·12 s; C-11 Me, δ 1·17 d; C-4 H, δ 3·83 d. tr.; (Found: C, 70·75; H, 9·44; $C_{14}H_{22}O_3$ requires: C, 70·55; H, 9·31%). Further elution with $CHCl_3$–ether 95:5 afforded VI (100 mg) which crystallized from acetone–hexane, m.p. 60°; NMR: C-10 Me, δ 0·89; C-11 Me, δ 1·17 d; C-4 H, δ 3·45 m. (Found: C, 70·54; H, 9·57; $C_{14}H_{22}O_3$ requires: C, 70·55; H, 9·31%).

(b) The ketone IV (1 g) in AcOH (50 ml) was hydrogenated over Adams catalyst until absorption ceased. The soln was filtered, water was added and the product extracted with ether, washed with $NaHCO_3$ aq and the solvent removed. Crystallization from acetone hexane, afforded Va, m.p. 140° identical with that prepared above.

15-*Noreudesm*-4-*en*-8β,12-*olide* (VII)

(a) To a pyridine soln of Va (1·8 g) mesyl chloride (5·4 ml) was added and the mixture left overnight. Ice was then added and the product extracted with $CHCl_3$ which was washed with dil HCl, $NaHCO_3$ aq and water. Evaporation of the solvent left Vc (2·1 g) it was dissolved in pyridine and heated to reflux for 2 hr. Extraction with $CHCl_3$ yielded crude VII (1·45 g) which was chromatographed on silicagel; elution with hexane–$CHCl_3$ 3:1 afforded the pure compound (1·3 g) which could not be crystallized, although homogeneous on TLC; NMR: C-10 Me δ 1·12 s; C-11 Me, δ 1·18 d; C-4 H, δ 5·51 tr. (Found: M^+, 220; $C_{14}H_{20}O_2$ requires: M. wt. 220·3).

(b) To a soln of Va (500 mg) in dry pyridine (5 ml) a soln of $SOCl_2$ (4 ml) in pyridine (5 ml) was added at 10°. After 1 hr, the soln was poured onto ice, the produce extracted with ether, washed with dil HCl and water and dried (Na_2SO_4). Purification of the crude product (350 mg) could be achieved only by chromatography on neutral alumina (Woelm) impregnated with a 5% $AgNO_3$ aq. Elution with hexane $CHCl_3$ (98:2) yielded almost pure VII (180 mg).

(c) A soln of Va (200 mg) in toluene (50 ml) was heated to reflux for 15 hr in the presence of toluene-*p*-sulphonic acid (30 mg) under azeotropic removal of water. The soln was then washed with $NaHCO_3$ aq, dried and the solvent removed. The residue (180 mg) was chromatographed on alumina impregnated with $AgNO_3$ as above. Elution with hexane–$CHCl_3$ 98:2 yielded VII (140 mg).

4,5-*Epoxy*-15-*noreudesman*-8β,12-*olide* (VIII)

To a soln of VII (1·5 g) in benzene (50 ml) *m*-chloroperbenzoic acid (1·3 g) was added. After 3 hr the soln was washed with $NaHCO_3$ aq and water, then dried and evaporated to leave a crystalline residue (1·4 g); recrystallized from EtOH, m.p. 91°, $[\alpha]_D$ +94° (*c* 0·2). NMR: C-10 Me δ 1·18; C-11 Me δ 1·12 d; C-4 H, δ 3·03 (d. 2·5 c/s). (Found: C, 70·96; H, 8·41; $C_{14}H_{20}O_3$ requires: C, 71·16; H, 8·53%).

4β,5α-*Dihydroxy*-15-*noreudesman*-8β,12-*olide* (IXa)

To a soln of VIII (1·3 g) in acetone (50 ml) a 7% aqueous soln of perchloric acid (1 ml) was added. After ~20 hr at room temp, the soln was neutralized with $NaHCO_3$ aq, then most of the solvent was removed and the ppt filtered off and crystallized from acetone, m.p. 198–199°, $[\alpha]_D$ −16° (pyr. *c* 0·5). (Found: C, 66·32; H, 8·77; $C_{14}H_{22}O_4$ requires: C, 66·11; H, 8·72%).

Acetylation with Ac_2O in pyridine, overnight at room temp followed by the usual work-up yielded IXb, m.p. 149–150° (ether–hexane); $[\alpha]_D$ +28·9° (*c* 0·9). NMR: C-10. Me, δ 1·19; C-11 Me, δ 1·10 d; C-4 H., δ 4·68 tr. (Found: C, 64·96; H, 8·28; $C_{16}H_{24}O_5$ requires: C, 64·84; H, 8·16%).

4β-*Acetoxy*-15-*noreudesm*-5-*en*-8β,12-*olide* (Xb)

A soln of freshly distilled $SOCl_2$ (0·8 ml) in dry pyridine (3 ml) was added dropwise at 0° to a soln of IXb (260 mg) in dry pyridine (4 ml). After 2 hr the mixture was poured onto ice, extracted with ether and the ethereal soln washed with dil HCl, and with $NaHCO_3$ aq. Evaporation of the solvent left an oily residue (220 mg) which crystallized from acetone-hexane, m.p. 84–86°. NMR: C-10 Me, δ 1·28; C-11 Me, δ 1·25 d; C-4 H, δ 5·28 tr.; C-6 H, δ 5·62 (d 2c/s). (Found: C, 69·15; H, 7·80; M^+ 278; $C_{16}H_{22}O_4$ requires: C, 69·04; H, 7·97%; M. wt. 278·3).

4β-*Acetoxy*-5α,6α-*epoxy*-15-*noreudesman*-8β,12-*olide* (XI)

A soln of XIb (250 mg) and *m*-chloroperbenzoic acid (250 mg) in benzene (25 ml) was left overnight at room temp. The reaction mixture was then worked up as described above to yield an oil which crystallized from hexane, m.p. 85–87°, $[\alpha]_D$ −72·9° (pyr. *c* 1·3). NMR: C-10 Me, δ 1·21; C-11 Me, δ 1·28 d; C-4 H, δ 4·28 tr.; C-6 H, δ 3·28 s.; (Found: C, 65·40; H, 7·45; M^+ 294; $C_{16}H_{22}O_5$ requires: C, 65·79; H, 7·53%; M. wt. 294·3).

4β-*Hydroxy*-13-*epi*-15-*noreudesm*-5-*en*-8β,12-*olide* (XIIa)

Compound Xb (400 mg) was dissolved in 10% methanolic MeONa (40 ml) and heated to reflux for 30 min. The soln was then neutralized, most of the MeOH removed and the product extracted with $CHCl_3$ leaving, after evaporation of the solvent, a residue containing mainly XIIa. The crude product was chromatographed over neutral alumina (activity III). Elution with hexane–$CHCl_3$ (4:1) yielded pure XIIa, crystallized from acetone–hexane, m.p. 84–86°; $[\alpha]_D$ −22·7° (*c* 0·66). NMR C-10 Me, δ 1·35; C-11 Me, δ 1·33 d; C-4 H, δ 4·20 tr.; C-6 H, δ 5·38 (d 3 c/s); (Found: M^+ 236; $C_{14}H_{20}O_3$ requires: M. wt. 236·3).

4β-*Acetoxy*-5β,6β-*epoxy*-13-*epi*-15-*noreudesman*-8β,12-*olide* (XIIIb) *and* 4β-*acetoxy*-5α,6α-*epoxy*-13-*epi*-15-*noreudesman*-8β,12-*olide* (XIVb)

To a soln of XIIa (290 mg) in benzene (50 ml) *m*-chloroperbenzoic acid (290 mg) was added and left overnight, then worked-up as usual. The crude product, although showing one spot on a chromatoplate was, according to its NMR spectrum, a mixture of the two epoxides XIIIa and XIVa. Column chromatography on neutral alumina did not lead to a separation.

The mixture was then acetylated with Ac_2O and pyridine overnight at room temp. The mixture of epoxy-acetates which was obtained showed two distinct spots on a chromatoplate and was separated by column chromatography over neutral alumina (grade III).

Elution with hexane–$CHCl_3$ (9:1) yielded XIVb (100 mg) followed by XIIIb (100 mg). Crystallization of the latter from hexane–EtOAc gave pure XIIIb, m.p. 106–107°; $[\alpha]_D$ +60·3° (*c* 0·68). NMR: C-10 Me, δ 1·28; C-11 Me, δ 1·33 d; C-4 H, δ 4·65 tr.; C-6 H, δ 3·20 (d. 4 c/s). (Found: C, 65·20; H, 7·60; M^+ 294; $C_{16}H_{22}O_5$ requires: C, 65·29; H, 7·53%; M. wt. 294·3).

Compound XIVb, although pure according to TLC performed with different solvent mixtures as well as by its NMR spectrum, could not be induced to crystallize. NMR: C-10 Me, δ 1·21; C-11 Me, δ 1·40 d; C-4 H, δ 4·28 tr.; C-6 H, δ 3·30 (d. $J < 1$ c/s); (Found: M^+ 294, $C_{16}H_{22}O_5$ requires: M. wt. 294·3).

5α,6α-*Epoxy-eudesman*-8β,12-*olide* (XVI)

Compound XV, m.p. 132–133°[3] was prepared by catalytic hydrogenation of I (500 mg) over Pd–C in EtOH soln; it was epoxidized with *m*-chloroperbenzoic acid (500 mg) in benzene soln (50 ml). Usual work up performed after keeping the reaction mixture for 3 hr at room temp yielded an oil (450 mg) which crystallized from EtOH, m.p. 192–194°. $[\alpha]_D$ −36·4° (pyr. *c* 1·0), NMR: C-4 Me, δ 1·38 d; C-10 Me, δ 1·10; C-11 Me, δ 1·12 d; C-6 H, δ 2·90 (d. 1 c/s). (Found: C, 72·22; H, 8·78; $C_{15}H_{22}O_3$ requires: C, 71·97; H, 8·86%).

Eudesma-3,5-*dien*-8β,12-*olide* (XVII)

(a) To a soln of XVI (150 mg) in AcOH (10 ml) 48% HBr in AcOH (0·5 ml) was added with stirring at 15°. After 2 hr at this temp, ice water was added, the product extracted with ether, the ethereal soln washed with water and $NaHCO_3$ aq, dried (Na_2SO_4) and the solvent removed leaving an oily product (150 mg) which was chromatographed through silicagel. Elution with hexane–$CHCl_3$ (1:1) yielded XVII (90 mg) which could not be crystallized; ν_{max} 1767 cm^{-1}; λ_{max} 232, 239, 247 mμ (ε 7600, 8500, 6000). NMR: C-4 Me, δ 1·78 (d. 2 c/s); C-10 Me, δ 1·08; C-11 Me, δ 1·27 d.; C-3 H, δ 5·61 tr.; C-6 H, δ 5·33 (d. 4 c/s).

Further elution with hexane–$CHCl_3$ (1:9) yielded fractions of an impure product, which according to the NMR spectrum seem to contain the allylic alcohol, 6-hydroxy-eudesm-4-en-8β,12-olide. This product was not however further investigated.

(b) *By treatment with* H_2SO_4. To a soln of XVI (100 mg) in AcOH (10 ml) 3% H_2SO_4 in AcOH (2 ml) was added and the mixture was kept overnight at room temp. Following the same work-up as above the crude product was chromatographed through silicagel. The same noncrystalline diene (XVII) was obtained (55 mg).

Hydrogenation of XVII *to tetrahydroalantolactone* (XVIII)

Compound XVII (50 mg) in EtOH soln (10 ml) was hydrogenated over 10% Pd–C. The absorption lasted ~6 hr and after filtration and evaporation of the solvent the product crystallized from EtOH, m.p. 144°. Identified by direct comparison with an authentic sample prepared by the hydrogenation of alantolactone.

4β-*Acetoxy*-5β,6α-*dihydroxy*-15-*noreudesman*-8β,12-*olide* (XIX)

(a) *By treatment of* XI *with* HBr. A soln of XI (160 mg) in AcOH (10 ml) was treated with an AcOH soln of HBr (0·5 ml) for 2 hr at 15°. Work-up was then performed as described above. The crude product (150 mg) was chromatographed on acid washed alumina. Elution with hexane–$CHCl_3$ (7:3) yielded homogeneous fractions which were combined and the product (50 mg) crystallized from acetone–hexane, m.p. 173–175°, $[\alpha]_D$ −94° (pyridine, *c* 0·35), ν_{max} 1765 and 1730 cm^{-1}. NMR: C-10 Me, δ 1·28; C-11 Me, δ 1·33 d; C-4 H, δ 5·30 m; C-6 H, δ 3·95 (d.d. 10·5 and 5 c/s). (Found: C, 61·50; H, 7·67; M^+ 312; $C_{16}H_{24}O_6$ requires: C, 61·52; H, 7·75%; M. wt. 312·3).

(b) *By treatment of* XI *with* H_2SO_4. A soln of XI (150 mg) in 3% in AcOH (3 ml) was left overnight at room temp. Ice water was then added, the product extracted with ether, the extract washed with water, $NaHCO_3$ aq, dried and the solvent removed. The product was purified by chromatography and crystallization as described to yield the same XIX (105 mg).

Formation of the acetonide XX.

Two drops of 70% perchloric acid were added to a soln of XIX (40 mg) in acetone (3 ml). After ~20 hr at room temp the soln was neutralized by addition of a few drops of $NaHCO_3$ aq, the solvent removed and the residue chromatographed on neutral alumina (grade III). Elution with hexane–$CHCl_3$ (1:3) yielded pure XX (12 mg), crystallized from acetone–hexane, m.p. 138–140°, $[\alpha]_D$ −23° (*c* 0·1); (Found: M^+ 352; $C_{19}H_{28}O_6$ requires: M. wt. 352·4). Further elution with hexane–$CHCl_3$ (4:1) yielded unreacted XIX (18 mg).

4β-*Acetoxy*-5β,6α-*dihydroxy*-13-*epi*-15-*noreudesman*-8β,12-*olide* (XXI)

Compound XIVb (70 mg) was treated with HBr as described for the formation of XIX. Following chromatography on acid washed alumina, XXI crystallized from acetone–hexane, m.p. 192–194°, $[\alpha]_D$ −24·2° (*c* 0·62). NMR: C-10 Me, δ 1·08; C-11 Me, δ 1·33 d; C-4 H, δ 5·30 m; C-6 H, δ 3·60; (Found: M^+ 312; $C_{16}H_{24}O_6$ requires: M. wt. 312·3).

Osmylation of Xb *to* XXIIa *and* XXIIIa *and acetylation to* 4β,6α-*diacetoxy*-5α-*hydroxy*-15-*noreudesman*-8β,12-*olide* (XXIIb) *and* 6β-*acetoxy*-4β,5β-*dihydroxy*-15-*noreudesman*-8β,12-*olide* (XXIIIb)

To a soln of Xb (560 mg) in pyridine (10 ml) OsO_4 (500 mg) was added. After one week the pyridine was evaporated under vacuum and a soln of Na_2SO_3 (2·2 g) in water (15 ml) and EtOH (25 ml) was added and the mixture boiled for 3 hr. The warm soln was filtered and the salts washed with acetone. Following concentration in vacuum, the residue was acidified and extracted thoroughly with EtOAc. Evaporation of the solvent left a crude mixture of triols (440 mg) which was acetylated with Ac_2O in pyridine, overnight at room temp. Following the usual work-up the acetylated material (490 mg) was chromatographed on Kieselgel H (Merck). Elution with $CHCl_3$ yielded XXIIb (65 mg) crystallized from acetone–hexane, m.p. 262–264°, $[\alpha]_D$ −104° (pyridine *c* 0·7). NMR (pyridine soln): C-10 Me, δ 1·43; C-11 Me, δ 1·30 d; C-4 and C-6 acetates, δ 1·88 and 2·10; C-4 H, δ 5·25 tr.; C-6 H, δ 5·70 (d. 9 c/s). (Found: C, 60·85; H, 7·33; M^+ 354; $C_{18}H_{26}O_7$ requires: C, 61·00; H, 7·40%; M. wt. 354·3).

Further elution yielded XXIIIb (100 mg), m.p. 270–272° (acetone–hexane), $[\alpha]_D$ −116·4° (pyridine *c* 0·9) ν_{max} 1745 and 1721 for lactone and acetate. NMR (pyridine soln): C-10 Me, δ 1·53; C-11 Me, δ 1·27; C-6 acetate, δ 1·92; C-4 H, δ 3·90; C-6 H, δ 5·65 (d. 9 c/s). (Found: M^+ 312; $C_{16}H_{24}O_6$ requires: M. wt. 312·3).

Osmylation of dihydroalantolactone (XV): *preparation of* 6α-*acetoxy*-5α-*hydroxy*-*eudesman*-8β,12-*olide* (XXIVb) *and* 5β,6β-*dihydroxy*-*eudesman*-8β,12-*olide* (XXV)

To a soln of XV (1 g) in pyridine (40 ml) OsO_4 (1·2 g) was added. After 10 days the pyridine was evaporated under vacuum and the osmate esters decomposed with Na_2SO_3 as described above. The residue consisted of a mixture of XXIVa and XXV (1·5 g), M^+ 268. Separation could be achieved after acetylation with Ac_2O and pyridine overnight, at room temp. Following the usual work-up, the mixture was resolved by chromatography on neutral alumina (grade III). Elution with $CHCl_3$–hexane (1:1) afforded XXIVb (220 mg), m.p. 234–235° (acetone–hexane), $[\alpha]_D$ −122° (pyridine *c* 1·1). NMR (pyridine soln): C-4 Me, δ 1·10 d.; C-10 Me, δ 1·17; C-11 Me, δ 1·33 d.; C-6 acetate, δ 1·92; C-6 H, δ 5·55 (d. 8·5 c/s). (Found: C, 65·40; H, 8·54; M^+ 310; $C_{17}H_{26}O_5$ requires: C, 65·78; H, 8·44%; M. wt. 310·3).

Further elution yielded XXV (780 mg), m.p. 212–215°, $[\alpha]_D$ −58° (pyridine *c* 1·0); ν_{max}^{KBr} 1751 cm^{-1}. NMR (pyridine soln): C-4 Me, δ 1·10 d.; C-10 Me, δ 1·20, C-11 Me, δ 1·63 d.; C-6 H, δ 4·10 (d. 9 c/s). (Found: C, 67·20; H, 8·90; major peak *m/e* 250; $C_{15}H_{24}O_4$ requires: C, 67·13; H, 9·02%; M. wt. 268·3; the molecular ion was not recorded).

4β-*Acetoxy*-5β-*hydroxy*-13-*epi*-15-*noreudesman*-8β,12-*olide* (XXVIa)

(a) *Treatment of* XIIIb *with* HBr. The reaction was performed on 80 mg product as described for III. The crude product (XXVId) although homogeneous on TLC, could not be crystallized. NMR: C-10 Me, δ 1·12; C-11 Me, δ 1·32 d.; C-4 H, δ 5·37 d.d; C-6 H, δ 4·45 (d. 12 c/s).

(b) Crude XXVId (70 mg) in dioxan (30 ml) was heated to reflux during 6 hr with Raney Ni (~1 g). After filtration and evaporation of the solvent the residual product was chromatographed through acid washed alumina. Crystallization from acetone–hexane afforded the pure XXVIa, m.p. 184°. NMR: C-10 Me, δ 1·10; C-11 Me, δ 1·26 d; C-4 H, δ 5·00 dd. (Found: C, 65·0; H, 8·05; M^+ 296; $C_{16}H_{24}O_5$ requires: C, 64·84; H, 8·16%; M. wt. 296·3).

5α,8β-*Dihydroxy*-*eudesman*-6β,12-*olide* (XXVII)

Compound XVI (300 mg) was dissolved in a soln of $KHCO_3$ in MeOH (about 280 mg in 10 ml) and left at room temp for 10 days. Most of the solvent was then evaporated under vacuum, water was added, the soln neutralized with a few drops of AcOH, and the product extracted with $CHCl_3$. Crystallization from EtOH yielded XXVII (170 mg), m.p. 247–250°, $[\alpha]_D$ −105° (pyridine soln *c* 0·8) ν_{max} 1739 cm^{-1}. NMR (pyridine soln): C-4 Me, δ 1·25 d.; C-10 Me, δ 1·76; C-11 Me, δ 1·66 d; C-6 H, δ 4·23 (doublet after addition of D_2O, 5 c/s); C-8 H, δ 4·90 m. (Found: C, 67·30; H, 8·95; M^+ 268; $C_{15}H_{24}O_4$ requires: C, 67·13; H, 9·02%; M. wt. 268·2).

This compound XXVII (100 mg) in dry THF (30 ml) was added dropwise to a slurry of LAH (200 mg) in the same solvent (10 ml). After heating 6 hr at reflux, the excess reagent was destroyed with EtOAc; the product obtained following evaporation of the solvent did not show absorption in the IR (CO region). The crude product (110 mg) was acetylated in the usual manner; upon chromatography on neutral alumina and elution with hexane–$CHCl_3$ 7:3, XXVIIIb (50 mg) was obtained. It could not be crystallized;

ν_{max} 1735 cm^{-1}. NMR: C-4 Me, δ 1·45 d; C-10 Me, δ 1·51; C-11 Me, δ 1·27 d; C-6 and C-12 acetates, δ 2·07 (intensity of 6 protons); C-12 methylene, δ 4·23 (d. 4 c/s); C-6 H, δ 4·10 (d. 5 c/s); C-8 H, δ 3·66 m.

Acknowledgement—One of us (P.V.F.) thanks the Consiglio Nazionale delle Ricerche, Italy, for a Research Fellowship. We are indebted to "Plantex" Ltd., Nathania for a generous supply of *Inula helenium* extracts used as starting material.

REFERENCES

[1] Part IV. D. Lavie and E. C. Levy, *Tetrahedron Letters* 2097 (1968).
[2] D. Lavie, Y. Kashman and E. Glotter, *Tetrahedron* **22**, 1103 (1966).
[3] J. A. Marshall and N. Cohen, *J. Org. Chem.* **29**, 3727 (1964); for earlier works, see for instance: L. Ruzicka and J. A. van Melsen, *Helv. Chim. Acta* **14**, 397 (1931); K. Tsuda, K. Tanabe, I. Iwai and K. Funakoshi, *J. Am. Chem. Soc.* **79**, 5721 (1957); C. Asselineau and S. Bory, *C.R. Acad. Sci., Paris* **246**, 1874 (1958). For a general discussion on the stereochemical relationships in the eudesmane group, see W. Cocker and T. B. H. McMurry, *Tetrahedron* **8**, 181 (1960).
[4] M. M. Mehra, K. G. Deshpande, B. B. Ghatge and S. C. Bhattacharyya, *Tetrahedron* **23**, 2469 (1967).
[5] H. B. Henbest and R. A. L. Wilson, *J. Chem. Soc.* 1958 (1957).
[6] P. B. D. de la Mare, *Molecular Rearrangements*, (Edited by P. de Mayo) Vol. I; p. 69. Interscience, New York (1963).
[7] R. B. Woodward and P. Yates, *Chem. & Ind.*, 1391 (1954); N. M. Chopra, W. Cocker and J. T. Edward, *Ibid.* 41 (1955); C. Assellineau, S. Bory and E. Lederer, *Bull. Soc. Chim. Fr.* 1524 (1955); W. Cocker, T. B. H. McMurry and L. O. Hopkins, *J. Chem. Soc.* 1998 (1959).
[8] S. Julia and J. P. Lavaux, *Bull. Soc. Chim. Fr.* 1238 (1963).
[9] See for instance, S. M. Kupchan, P. Slade, R. J. Young and G. W. A. Milne, *Tetrahedron* **18**, 499 (1962).
[10] cf. H. Conroy, *J. Am. Chem. Soc.* **79**, 1726 (1957).
[11] P. I. Burkhill, J. S. E. Holker, A. Robertson and J. H. Taylor, *J. Chem. Soc.* 4945 (1957).
[12] L. Ruzicka and P. Pieth, *Helv. Chim. Acta* **14**, 1090 (1931).