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# TERPENOIDS—CIII

# SYNTHESIS OF SANTANOLIDE 'C', TETRAHYDROALANTALACTONE, LACTONE OF β-HYDROXY EUDESMAN-15-OIC ACID AND (+) DIHYDROJUNENONE FROM EUDESMOL*

G. D. JOSHI, M. V. KADIVAL, S. N. KULKARNI and S. C. BHATTACHARYYA
National Chemical Laboratory, Poona, India

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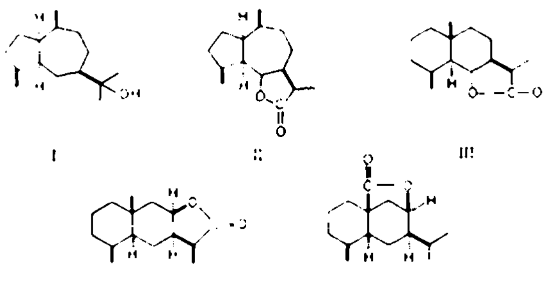
**Abstract**—Dihydroselinene (VII), obtained by the pyrolysis of dihydroeudesmol benzoate (VI) on hydroboration-oxidation yields tetrahydrocostol (VIII, R = $CH_2OH$). The lead tetraacetate oxidation of VIII gives an oxide (IX) which on purification and oxidation with chromic acid in acetic acid affords santanolide 'C'. By a similar series of reactions 8-β-hydroxyeudesmol (XIV) prepared by LAH reduction of eudesman-8-one (XIII) gives tetrahydroalantalactone (IV) and the lactone of 8-β-hydroxyeudesman-15-oic acid (V), in which the lactone V predominates. The dihydrojunenone mixture (XVI), obtained in our earlier work,[10] on equilibration with alkali followed by extensive chromatography, affords pure dihydrojunenone (XVII). The stereochemistry of the various products has been discussed.

OXIDATION of aliphatic alcohols with lead tetraacetate has been investigated[1] and its use in the bicyclic system[2] as well as in the steroid series[3] investigated. The application of this oxidation to terpene and nonterpene alcohols,[4] has led to the conversion of elemol to tetrahydrosaussurea lactone,[5] 1-α-5-α-dihydroguaiol (I) to 1α-5α-hexahydrodehydrocostus lactone[6] (II) and to some novel longifolane derivatives.[7] In the present paper, the method is used for the synthesis of santanolide 'C' (III), tetrahydroalantalactone (IV) and the unusual lactone of 8-β-hydroxyeudesman-15-oic acid (V), starting from eudesmol.

CHART 1



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* Communication No. 960 from the National Chemical Laboratory, Poona-8, India.

[1] V. M. Micovic, R. I. Mamuzic, D. Jeremic and M. Mihailovic, *Tetrahedron* **20**, 2279 (1964).

[2] K. Kitahanaki and A. Matsuura, *Tetrahedron Letters* No. 33, 2263 (1964).

[3] K. Heusler, J. Kalvoda, G. Anner and A. Wettstein, *Helv. Chim. Acta* **46**, 352 (1963) and subsequent papers.

[4] S. G. Patnekar, H. H. Mathur and S. C. Bhattacharyya, *Ind. J. Chem.* **4**, 67 (1966).

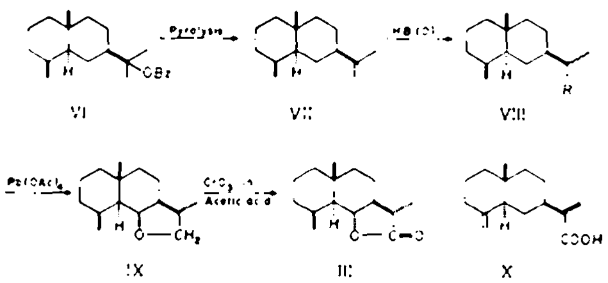
[5] A. D. Wagh, S. K. Paknikar and S. C. Bhattacharyya, *Tetrahedron* **20**, 2647 (1964).

[6] M. V. Kadival, M. S. R. Nair and S. C. Bhattacharyya, *Tetrahedron* **23**, 1241 (1967).

[7] S. G. Patnekar and S. C. Bhattacharyya, *Tetrahedron* **23**, 919 (1967).

Dihydroeudesmol benzoate (VI) on pyrolysis furnishes dihydroselinene (VII), which was found to be 98% pure by GLC analysis. On hydroboration–oxidation VII gives tetrahydrocostol (VIII, R = $CH_2OH$) with identical IR spectrum and rotation with that given in the literature.[8] The identity of this compound is further proved by converting it by Jones' reagent to tetrahydrocostal[8c] (VIII, R = CHO) and tetrahydrocostic acid[8b] (VIII, R = COOH) respectively. This conversion further supports the structure and stereochemistry of costic acid (X), a natural product isolated from costus root oil.[8b] Lead tetraacetate oxidation of VIII (R = $CH_2OH$) gives a mixture of oxides in which IX predominates, as shown by TLC and GLC analysis. This oxide is obtained in the pure form by chromatography over grade I alumina and further purified by distillation. It has b.p. 110–120° (bath)/3 mm, $[\alpha]_D^{26\cdot5}$ $+25\cdot9°$. On oxidation with chromic acid in acetic acid the oxide IX gives santanolide 'C' (III), identical in all respects with an authentic sample.[9]

CHART II



During the synthesis of selinane-8-one[10] (8-keto eudesman) (XIII), we obtained in the hydroboration–oxidation reaction of the hydrocarbon XI an alcohol 8-α-hydroxyeudesman (XII), m.p. 107–108°. The NMR spectrum of this compound shows a proton on the carbon bearing the OH function at 6·4 $\tau$, thus suggesting the axial nature of this proton,[11] and consequently the α-equatorial nature of the secondary OH group. This is also in agreement with the mechanism of hydroboration–oxidation reaction of such a compound, where one should expect the introduction of the OH group from the less hindered α-side. However, when the ketone XIII, obtained either by the oxidation of the alcohol XII or through epoxidation etc. of the hydrocarbon XI,[10] is reduced with LAH, it gives the crystalline alcohol 8-β-hydroxyeudesman (XIV), m.p. 57–58°. The NMR spectrum of this compound shows a proton on the $C_8$ carbon bearing the OH at 5·9 $\tau$, thus showing the equatorial nature of the proton and consequently β-axial nature of the OH group. The stereochemistry of XIV was confirmed chemically[12] by synthesizing the same by an unambiguous method from tetrahydroalantalactone (IV) of known stereochemistry[13] as shown in Chart III. The

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[8a] V. Benesova, V. Sykora, V. Herout and F. Sorm, *Chem. & Ind.* 363 (1958); *Coll. Czeck. Chem. Comm.* **24**, 2365 (1959); [b] A. S. Bawdekar and G. R. Kelkar, *Tetrahedron* **21**, 1521 (1965); [c] K. R. Varma and S. C. Bhattacharyya, *Ibid.* **20**, 2927 (1964).

[9] A. S. Rao, G. R. Kelkar and S. C. Bhattacharyya, *Tetrahedron* **9**, 275, (1960)

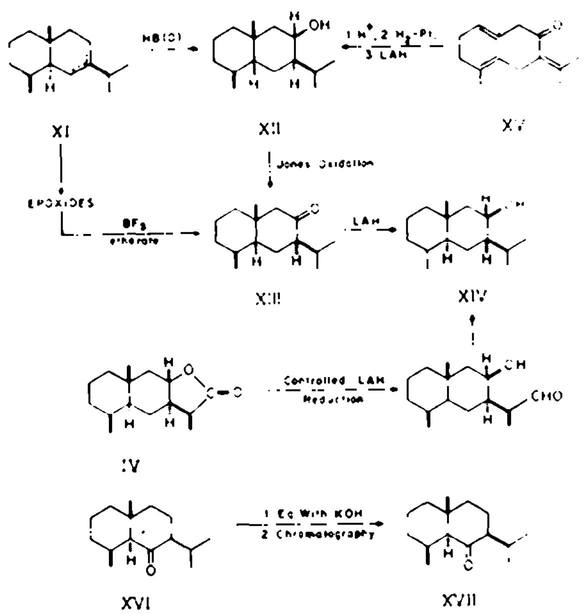
[10] G. D. Joshi, S. K. Paknikar, S. N. Kulkarni and S. C. Bhattacharyya, *Tetrahedron* **22**, 1641 (1966).

[11] N. S. Bhacca and D. H. Williams, *Application of NMR Spectroscopy in Organic Chemistry* p. 77–84. Holden-Day, (1964).

[12] M. M. Mehra, K. G. Deshpande, B. B. Ghatge and S. C. Bhattacharyya, private communication.

[13] J. A. Marshall and N. Cohen, *J. Org. Chem.* **29**, 3727 (1964)

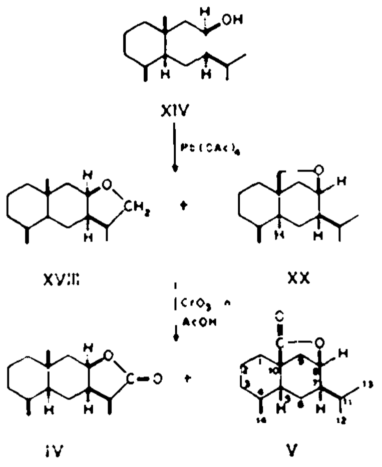
CHART III



(±) compound XII has also been described by Ognjanov,[14] who prepared it by acid-catalyzed cyclization of germacrone* (XV), followed by hydrogenation and reduction with LAH. The m.p. of (±) XII showed no depression when mixed with the optically active compound prepared by the method described above. This proves the stereochemistry of OH as well as the *trans* nature of the ring juncture of (±) XII of Ognjanov. The IR and the NMR spectra of the relevant products are also identical.

The alcohol XIV has been converted to tetrahydroalantalactone (IV) and the lactone of 8-β-hydroxyeudesman-15-oic acid (V), as shown in Chart IV.

CHART IV



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* We thank Dr. I. Ognjanov for a very generous supply of germacrone.

[14] I. Ognjanov, *C.R. Acad. Sci., Bulgr.* 13, 51 (1960).

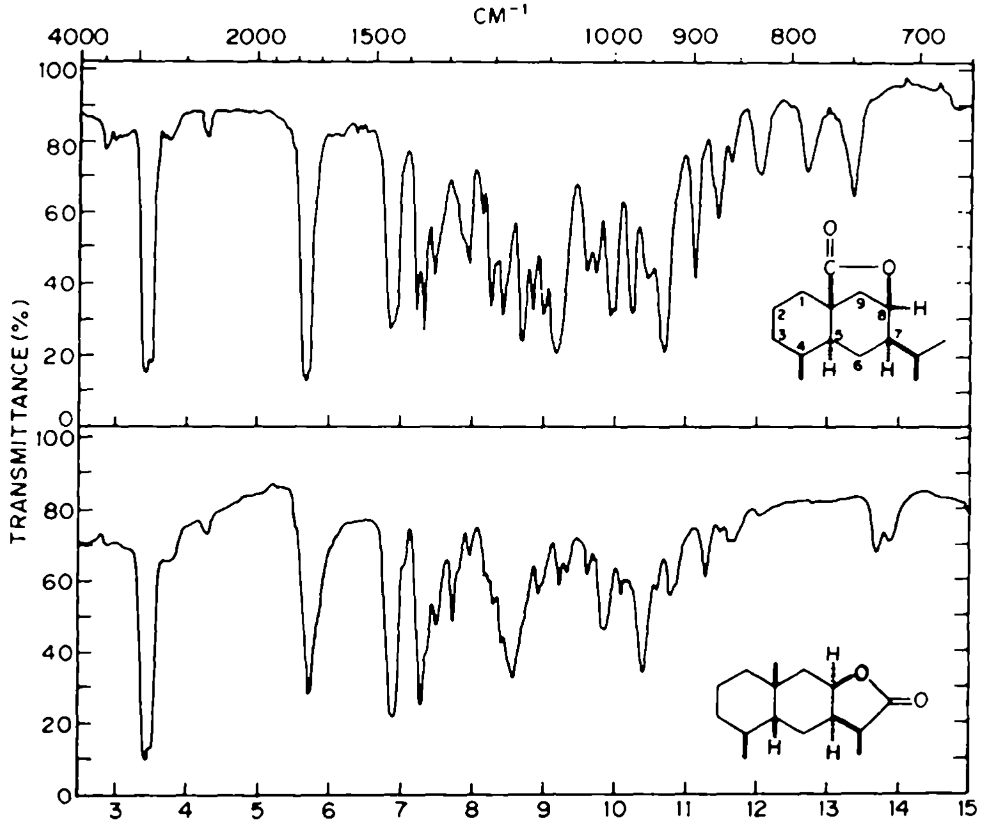

Fig. 1

The β-alcohol XIV on treatment with lead tetraacetate in benzene gives a mixture of two oxides XVIII and XIX in 30% yield. These on oxidation with chromic acid in acetic acid afford a mixture of two lactones IV and V, which were separated by chromatography. The major component was found to be the lactone of 8β-hydroxy-eudesman-15-oic acid (V), which is quite different in its IR and NMR spectrum when compared with the minor component tetrahydroalantalactone (IV). It has b.p. 140°/0·05 mm, $[\alpha]_D^{27}$ −69° (chf). Its IR spectrum (Fig. 1) shows a doublet at 1360 cm$^{-1}$ and 1375 cm$^{-1}$ due to i–Pr grouping, and a lactone at 1757 cm$^{-1}$.

The NMR spectrum (Fig. 2) shows a doublet at 5·41 τ due to the proton at $C_8$ with J, 6·5 c/s. The $C_9$ proton shows a quartet at 7·79 τ with $J_{9\alpha-9\beta}$, 12 c/s, $J_{8\alpha-9\beta}$ 6·5 c/s. This is rather unexpected since the $C_8$ proton forms the X-proton of the ABRX system in which the AB protons are at $C_9$ and the R proton is at $C_7$. Accordingly one would expect the $C_8$ proton to consist of 8 lines and the AB portion also should show 8 lines. The NMR spectrum indicates that $J_{AX}$ (or $J_{BX}$) $\triangleq 0$ and $J_{RX} \triangleq 0$. This indeed seems to be the case because the molecular models indicate that the $C_8$ proton makes an angle of approximately 80° with both $C_9$ α-proton and $C_7$ α-proton. Accordingly $J_{8\alpha-9\alpha}$ and $J_{8\alpha-7\alpha}$ would be very small.

The minor component has m.p. 144° and is found to be identical with tetrahydroalantalactone as judged by mixed m.p. and identical IR spectrum (Fig. 1). We have

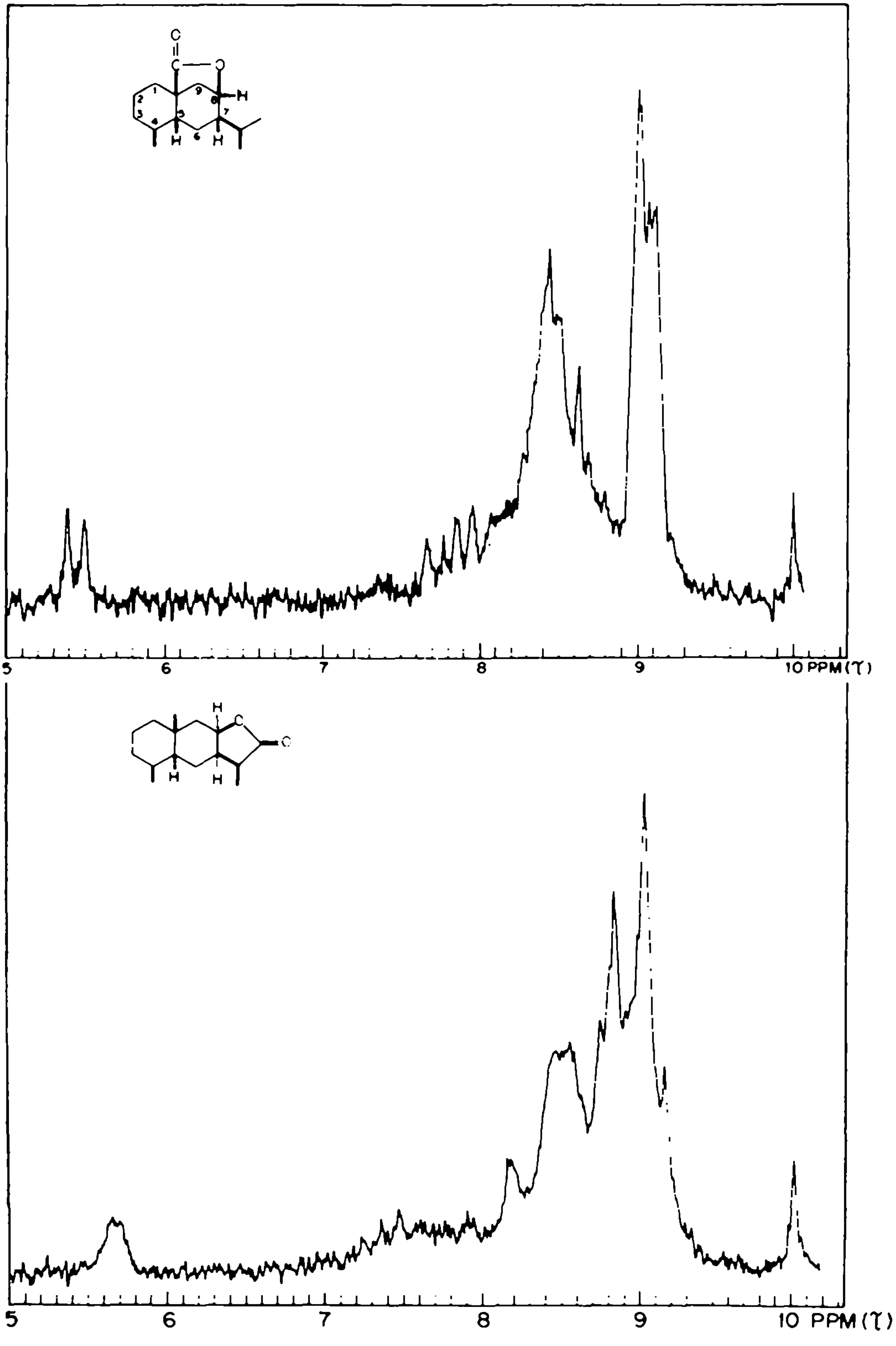

Fig. 2

been unable to isolate any epimer of tetrahydroisoalantalactone in which $C_{11}$ Me group is α-oriented, though the formation of such a product may also be anticipated.

In our earlier paper[10] we prepared the epoxide of hydrocarbon XI and subjected it to $BF_3$-ethereate treatment (chart III). From the reaction mixture we could separate selinane-8-one (XIII) through semicarbazone formation. The nonsemicarbazone forming ketone XVI was structurally identical with dihydrojunenone (XVII) but epimerically not homogeneous, as it gave four peaks on GLC analysis, the major one constituting about 40% of dihydrojunenone as shown by comparative GLC analysis. Now this mixture on equilibration with alkali followed by intensive chromatography[15] gives pure (+) dihydrojunenone (XVII), $[\alpha]_D^{27}$ +5·85° (chf). Its purity is further tested by GLC and TLC analysis and its IR spectrum is identical with an authentic sample of the same. This, therefore, constitutes a simple synthesis of dihydrojunenone.

## EXPERIMENTAL

M.p.s are uncorrected. Rotations were determined in chf soln. Light petroleum refers to fraction b.p. 60–80°. IR spectra were measured with Perkin-Elmer (Model 137-b) infracord spectrophotometer. GLC was done on polyester column.

*Dihydroselinene* VII was prepared according to the method of Varma and Bhattacharyya.[6a]

*Hydroboration of dihydro-selinene to tetrahydrocostol* (VIII, R = $CH_2OH$). Diborane gas was prepared by adding slowly $NaBH_4$ (5 g) in pure diglyme (25 ml) to freshly distilled $BF_3$-etherate (30 ml) in diglyme (30 ml). $N_2$ was used as the carrier gas. The diborane gas was bubbled through a soln of dihydroselinene (6 g) in dry THF (50 ml) at 0° for 1 hr and then 1 hr at room temp. The reaction mixture was kept overnight. The excess of diborane was decomposed by adding small pieces of ice. To this mixture was added 3N KOH (25 ml) followed by a slow addition of $H_2O_2$ (25 ml; 30%) and the mixture kept at room temp for 6 hr. The upper layer was separated and the aqueous layer extracted with ether. The combined ethereal extract was washed thoroughly with water, dried and solvent removed. The residue was chromatographed and distilled to obtain pure tetrahydrocostol (4·5 g), bp. 140–150° (bath)/0·1 mm; $n_D^{29}$ 1·4950; $[\alpha]_D^{27}$ +13·78° (*c*, 3·12). GLC and TLC analysis showed it to be a single component. IR spectrum indicated the presence of —OH grouping. The above values agree with the literature values[6a]. (Found: C, 80·04; H, 12·82: $C_{15}H_{28}O$ requires: C, 80·29; H, 12·58%.)

*Oxidation of tetrahydrocostol by Jones' reagent.* Tetrahydrocostol was oxidized with Jones' reagent in the usual manner. The oxidation product was extracted with ether, and washed with $Na_2CO_3$aq and then with water till neutral. The neutral part after removing the ether gave VIII (R = CHO), which was purified through semicarbazone m.p. 205°(EtOH), undepressed with an authentic sample.[6a] The aldehyde regenerated from the semicarbazone had b.p. 125–130° (bath)/0·1 mm; $n_D^{27}$ 1·4925; $[\alpha]_D^{30}$ +13·22° (*c*, 1·65). The bicarbonate soln on acidification gave VIII (R = COOH), which was converted to its methyl ester[6a] and purified by chromatography and distillation, b.p. 135–140° (bath)/0·1 mm; $n_D^{27}$ 1·4850; $[\alpha]_D^{30}$ +22·54° (*c*, 2·5). GLC and TLC indicated it to be single component. (Found: C, 76·65: H, 11·61. $C_{16}H_{28}O_2$ required: C, 76·14; H, 11·18%.)

*Lead tetraacetate oxidation of tetrahydrocostol.* To a soln of tetrahydrocostol (3 g) in benzene (50 ml), freshly prepared lead-tetraacetate (6 g) was added and the mixture was refluxed on a water bath with mechanical stirring for 2 hr in $N_2$ atm. The reaction flask was cooled, contents filtered and washed with benzene. The filtrate was extracted with ether. The ethereal extract was washed with $Na_2CO_3$aq and finally with water till neutral and then dried. The solvent was removed and the residue was saponified with alcoholic KOH (10%, 25 ml). The product obtained was chromatographed on alumina (gr. II, 78 g). The light petroleum eluate furnished the oxide (1 g). GLC analysis indicated two peaks in the ratio of 25:75. This mixture was rechromatographed on neutral alumina (gr. I, 50 g) and 25 × 5 ml fractions were collected. On the basis of GLC and TLC analysis, similar fractions were mixed and distilled to furnish a pure IX (0·6 g), b.p. 110–120° (bath)/3 m; $n_D^{30}$

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[15] D. W. Theobald, *Tetrahedron* **20**, 2593 (1964).

1·4940; $[\alpha]_D^{26\cdot6}$ − 25·96° (*c*, 4·28). IR spectrum showed band at 1020 cm$^{-1}$ for an oxide. (Found: C, 81·70; H, 11·96. $C_{15}H_{26}O$ requires: C, 81·02; H, 11·79%.)

*Chromic acid oxidation of the oxide* IX. The oxide (0·45 g) in AcOH (15 ml) was treated with chromic acid (0·55 g) in water (3 ml) at 0° during 10 min with occasional shaking and kept at that temp for 2 hr; then at the room temp for 48 hr. The reaction mixture was poured into cold water, extracted with ether, washed successively with water, 10% $Na_2CO_3$aq, again with water and dried. On removing the solvent the residue was saponified with alcoholic KOH (12 ml), refluxed for 1 hr, diluted with water and extracted with ether. The aqueous layer was acidified with HClaq, and heated on water bath for 10 min, cooled and extracted with ether. The ethereal layer was thoroughly washed with $Na_2CO_3$aq, water; dried and solvent evaporated. The santanolide 'C' was obtained by preparative TLC and on crystallization gave the pure III m.p. 152–153°, mixed m.p. with an authentic sample was undepressed. IR spectrum was superimposable with an authentic spectrum. (Found: C, 76·63; H, 10·54, $C_{15}H_{24}O_2$ requires: C, 76·22; H, 10·24%.)

*Preparation of selinane-8-one (Eudesman-8-one)* (XIII). This ketone was isoated as per our previous paper.[10]

*LAH reduction of eudesman-8-one to 8-β-hydroxyeudesman* (XIV). To the stirring mixture of LAH (0·75 g) in dry ether (100 ml) was added dropwise XIII (5 g) in dry ether (50 ml) at 0° during 1½ hr. The mixture was refluxed for 5 hrs then decomposed carefully with moist ether and filtered. The filtrate was extracted with ether, washed thoroughly with $Na_2CO_3$aq, water and dried. Evaporation of solvent gave a residue (4 g). This was chromatographed over alumina (gr. III, 120 g). Light petroleum–benzene (1 : 2) eluate gave XIV (3·2 g). Purity of the product was tested by TLC analysis. IR spectrum indicated the presence of —OH grouping, m.p. 58–59°; $[\alpha]_D^{27}$ ±0°. (Found: C, 80·95; H, 12·61. $C_{15}H_{28}O$ requires: C, 80·29; H, 12·58%.)

8-*α-hydroxy-eudesman* (XII). This was prepared by the hydroboration–oxidation of the hydrocarbon XI as given in our previous paper.[10]

*Isomerization of germacrone with sulphuric acid.*[14] Germacrone (5·5 g) was added to a soln of conc $H_2SO_4$ (2·5 ml, *d.* 1·84) in EtOH (10 ml) and the reaction mixture heated at 60° for ½ hr. The warm soln was poured into water (50 ml), the product extracted with ether, washed with $Na_2CO_3$aq and water till neutral, then the solvent was concentrated and a residue (4·9 g, yellow liquid) was fractionated into 3 main fractions. The middle fraction (2·1 g) b.p. 130–133°/3 mm; $n_D^{30}$ 1·5275, was used.

*Hydrogenation of the middle fraction.* A soln of the above fraction (2·1 g) in AcOH (15 ml) was hydrogenated with Adams catalyst (50 mg) for 17 hr when 500 ml $H_2$ gas was absorbed. The reaction mixture was filtered and the filtrate diluted with water and extracted with ether. After washing the ethereal layer with $Na_2CO_3$aq and water, it was dried over $Na_2SO_4$. The residue (2 g) obtained on removal of solvent indicated by IR spectrum absorption bands due to OH and CO groups. GLC and TLC analysis indicated 2 compounds.

*LAH reduction of the above product to* (+) *8-α-hyrdoxyeudesman* (XIV). To the stirring mixture of LAH (0·3 g) in dry ether (100 ml) was added the above hydrogenated compound (2 g) in dry ether (50 ml) dropwise at 0° in 1½ hr. The stirred mixture was refluxed for 5 hr and worked up in the usual manner. The crude product (1·5 g) was crystallized from EtOH to give XIV, m.p. 105–106°. The mixed m.p. with 8-α-hydroxyeudesman (from eudesmol) was undepressed.

*Lead tetraacetate oxidation of 8-β-hydroxyeudesman* (XIV). A mixture of 8-β-hydroxyeudesman (2·5 g) and freshly prepared lead tetraacetate (7 g) in anhydrous benzene (100 ml) was stirred and refluxed on a water bath for 24 hr in the atm of $N_2$. It was worked up as described for IX. The mixture of oxides (1·22 g) was passed over alumina (gr. I, 50 g) and eluted with light petroleum to yield the mixture of oxides (0·6 g). TLC and GLC analysis showed 2 compounds. IR spectrum showed a band at 1020 cm$^{-1}$ for the oxide.

*Chromic acid oxidation of the oxides to lactones* IV *and* V. This oxide mixture (0·67 g) was oxidized by chromic acid (0·66 g) dissolved in water (2 ml) and ACOH (20 ml). The mixture was stirred and heated on a water bath for 24 hr; cooled and MeOH (3 ml) added. After dilution with water (100 ml) the mixture was extracted with ether and the ethereal extract was washed with $Na_2CO_3$aq and water. The residue obtained after removal of solvent was saponified by refluxing with alcoholic KOH (15 ml, 10%, 3 hr). The alcohol was removed and the residue diluted with water (20 ml) and extracted with ether. The aqueous soln on acidification gave a viscous material (0·5 g). TLC of the above mixture indicated 4 spots; two of which corresponded to the two oxides (less polar) and two lactones IV and V. One of the lactone spots corresponded to tetrahydroalantalactone. The mixture was chromatographed over silica gel (1:30) and eluted first with light petroleum to remove unreacted oxides. Light petroleum–benzene (1:1) elution gave a pure lactone V$[\alpha]_D^{27}$ $-69°$ (*c*, 2·84). (Found: C, 76·21, H, 10·37; $C_{15}H_{24}O_2$ requires: C, 76·20; H, 10·24%.) Further elution with benzene–ether (2:1 gave tetrahydroalantalactone, m.p. 144° (MeOH); mixed m.p. with authentic sample showed no depression; IR spectrum is superimposable with that of the authentic sample.

*Purification of dihydrojunenone mixture*[18] (XVI). The ketone mixture (XVI) which did not form a semicarbazone was purified by the procedure described by Theobald.[18]

A solution of the ketone (2·7 g), KOH (18 g) in EtOH (180 ml) and water (36 ml) was kept under $N_2$ in the dark at 20° for 48 hr. Dilution with water and extraction with ether gave the product (2 g) which was chromatographed over alumina (gr. II, 550 g). Elution with light petroleum–benzene (2:1; 250 ml) gave a nearly pure fraction. This was further purified by rechromatography over alumina (gr. II, 80 g). Elution with light petroleum-benzene (6:1, 20 × 25 ml) yielded a ketone, 11 to 16 fractions of which were found to be pure by GLC and TLC analysis. The IR spectrum indicated bands at 1709 $cm^{-1}$ for CO. $[\alpha]_D^{8·63}$ $+5·85°$ (*c*, 1·88).