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TERPENOIDS—LV*

CYCLOCOSTUNOLIDES

G. H. KULKARNI, G. R. KELKAR and S. C. BHATTACHARYYA
National Chemical Laboratory, Poona, India

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Abstract—α-Cyclocostunolide (IV), a product of transannular crystalization of costunolide, gives, on treatment with methanol in presence of alkali, (1) α-cyclo-12-methoxydihydrocostunolide (VII) and (2) the corresponding hydroxy acid (VIII). On treatment with ammonia, α-cyclocostunolide is converted to the amide of the hydroxy acid (IX), saponification of which yields VIII. The hydroxy acid (VIII) on catalytic hydrogenation gives the saturated acid (X) which lactonizes to santanolide 'c' on treatment with acid.

THE acid catalysed transannular cyclization of dihydrocostunolide (II) and 12-methoxy dihydrocostunolide (III), leading to α- and β- cyclodihydrocostunolides[1] and cyclo-12-methoxydihydrocostunolides[2] have been described. In this communication, the acid catalysed cyclization of costunolide (I) is reported. Costunolide on treatment with acetic acid and perchloric acid at 0°, affords a mixture of α- and β- cyclocostunolides which can be separated by chromatography. One of the compounds, α-cyclocostunolide (IV) was obtained in the pure form by repeated crystallization from methanol.

The β-isomer has not so far been obtained in the pure form as it is largely held in the column during chromatography. The IR spectrum of α-cyclocostunolide (Fig. 1) shows characteristic peaks at 1760 (γ-lactone), 1660 (trisubstituted double bond), 810[3] and 1400[4] (conjugated α-methylene γ-lactone) cm^{-1}. This is further supported by the UV spectrum of IV which like costunolide (I), shows the characteristic high end absorption (ε 210, 10,000). The MNR spectrum of α-cyclocostunolide (Fig. 3) shows signals at 0·9 δ (3H) due to a quarternary CH_3 group at C.10, 1·8 δ (3H) due to a CH_3 group on a double bond at C.4, 5·25, 5·31, 5·84, 5·89 δ (3H) due to one proton on a trisubstituted double bond at C.3 and two protons on the conjugated exocyclic double bond at C.11. A triplet at 3·6, 3·78, 3·96 δ (1H) is also observed, which is due to the proton at C.6. The NMR spectrum is thus in complete agreement with the structure IV. Catalytic hydrogenation of IV gives santanolide 'c' (V), the formation of which establishes the stereochemistry of the lactone (IV) at all the asymmetric centres. The NMR spectrum of impure β-cyclocostunolide (VI), though in agreement with the structure VI indicates the presence of some α-cyclocostunolide as an impurity. Catalytic hydrogenation of β-cyclocostunolide (VI) gives a mixture of saturated lactones from which V probably arising from α-cyclocostunolide present as an impurity, has been isolated and characterized.

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[1] A. M. Shaligram, A. S. Rao and S. C. Bhattacharyya, *Tetrahedron* **18**, 969 (1962).

[2] G. H. Kulkarni, G. R. Kelkar and S. C. Bhattacharyya, *Tetrahedron* **20**, 1301 (1964).

[3] H. Gopinath, S. K. Paknikar and S. C. Bhattacharyya, IR spectra of conjugated α-methylene-γ-lactones—presented in the Symposium on *Physical Methods in Organic Structure Determination* held in Poona, Dec. 1963 (Abstract of papers, p. 3).

[4] Horak and Pliva, *Chem. & Ind.* 102 (1960).

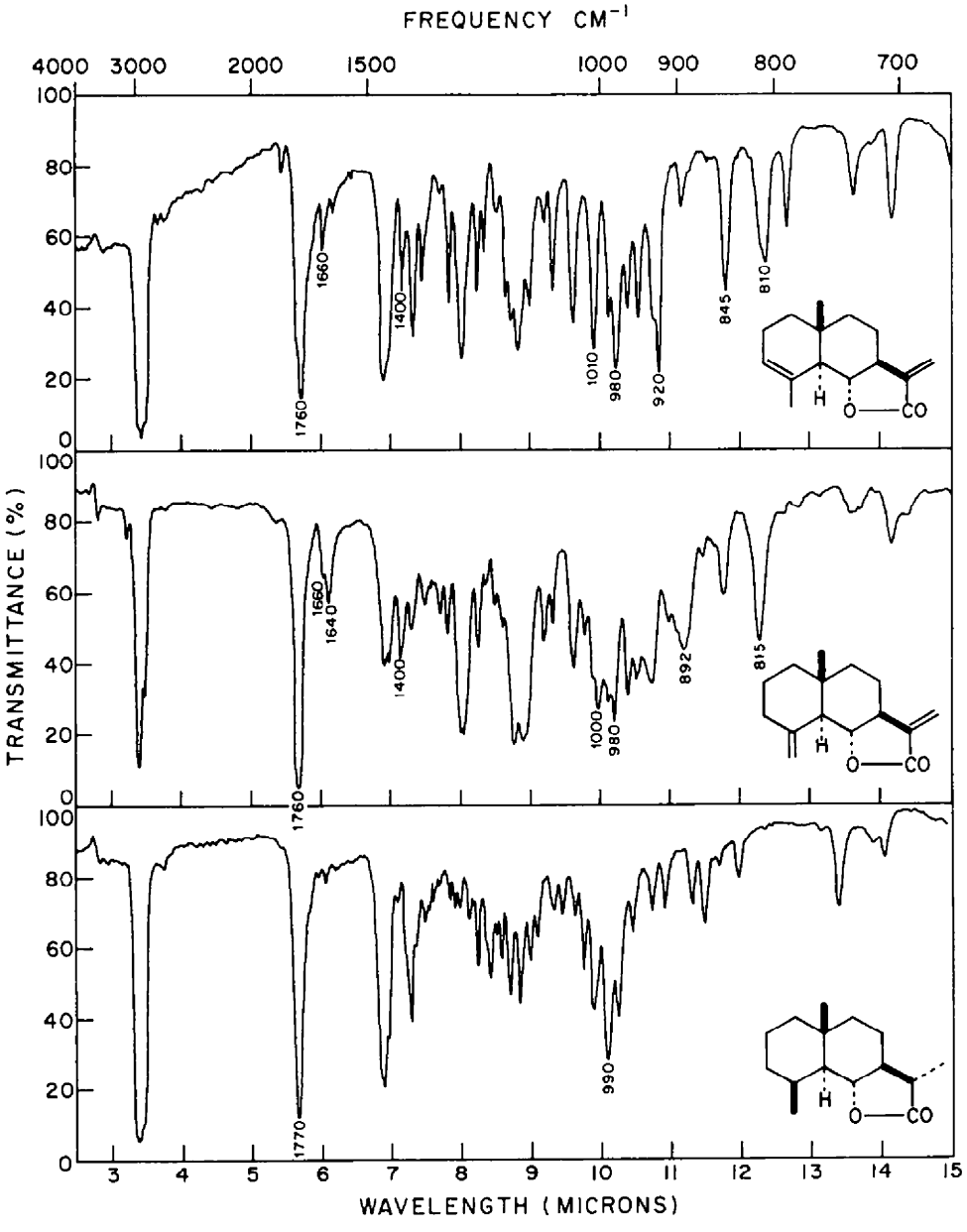


Fig. 1

With a view to further characterize the α-cyclocostunolide (IV) through its 12-methoxy derivative, it was reacted with methanol in presence of base,[5,6] yielding the corresponding 12-methoxy derivative (VII) and the hydroxy acid (VIII), the latter being obtained in high yield (70%). The crude hydroxy acid (mixture of VIII and VIIa, m.p. 154–155°) crystallizes from chloroform to give the pure acid (VIII),

[5] D. K. Fukushima and T. F. Gallagher, *J. Amer. Chem. Soc.* **73**, 196 (1951).
[6] C. F. Koelsch, *J. Amer. Chem. Soc.* **65**, 437 (1943).

m.p. 162–163° (IR spectrum, Fig. 2) but, on treatment with dilute hydrochloric acid, a portion is converted to a lactonic product. The 12-methoxy derivative (VII) can also be obtained by the chromatography of the mother liquors of VIII and crystallization from methanol. The 12-methoxy derivative of α-cyclocostunolide (VII) is identical with α-cyclo-12-methoxydihydrocostunolide, previously obtained as one of the products during acid catalysed transannular cyclization of 12-methoxydihydrocostunolide (VIII). Thus the stereochemistry of α-cyclo-12-methoxydihydrocostunolide is established at C.5 and C.10, since the stereochemistry of IV at these centres is known.

With alcoholic ammonia, IV gives a solid, m.p. 157°, analysing for $C_{15}H_{23}NO_2 \cdot H_2O$. The IR spectrum (Fig. 2) indicates it to be an amide of a hydroxy acid. The compound was saponified with alcoholic potassium hydroxide solution and the acid isolated was identified as VIII by m.p. and mixed m.p. with an authentic sample and superimposable IR spectra. From this it is obvious that the compound obtained from IV was ammonia should be represented by IX.

Although a number of reasonably stable hydroxy acids from dihydro and tetrahydrosantonins have been described in the literature,[7] the somewhat unusual behaviour of α-cyclocostunolide, namely the ease with which the opening of lactone ring takes place by methanolic potassium hydroxide and ammonia at ordinary temperature (and at 0° and −18°), and the stability of the hydroxy acid formed, raises some doubt as regards the configuration of OH group at C.6 in VIII and the amide (IX). Since the original acid being conjugated is not considered convenient for ring closure to a lactone for fear of possible polymerization on heating with acid, its tetrahydro product was prepared and subjected to the reaction.

The hydroxy acid (VIII) was hydrogenated in acetic acid, using platinum catalyst. The resulting product, found by IR spectrum to be a mixture of lactone and acid, was separated into the acidic and neutral components by treatment with sodium bicarbonate. The neutral part gave a solid m.p.155–56°, identified as santanolide 'c' V by IR spectrum (Fig. 1), rotation, m.p. and mixed m.p. with an authentic sample. The formation of V from VIII indicates that no change takes place in the stereochemistry of OH group at C.6 in VIII and it also establishes the stereochemistry of VIII and IX at all the centres.

Catalytic hydrogenation of VIII in alcohol medium using platinum catalyst gives exclusively the tetrahydrohydroxy acid (X). On warming with acetic acid, it lactonizes to V from which its stereochemistry follows.

It thus appears that the stability of VIII is not due to any alteration in the configuration of asymmetric centres at C.6 or C.7 during the opening of the lactone ring of IV.

The compounds VIII and IX are both sparingly soluble in carbon-tetrachloride, chloroform and carbon disulphide and hence were not suitable for NMR spectroscopic studies.

A portion of the hydroxy acid was esterified with diazomethane to the methyl ester (VIIIa) which is soluble in carbon tetrachloride. The IR and NMR spectra which are in agreement with the structure (VIIIa) are shown in Figs. 2 and 3. The

[7] H. Ogura, *J. Org. Chem.* **25**, 679 (1960); see also M. Yanagita and H. Ogura, *J. Org. Chem.* **23**, 1268 (1958).

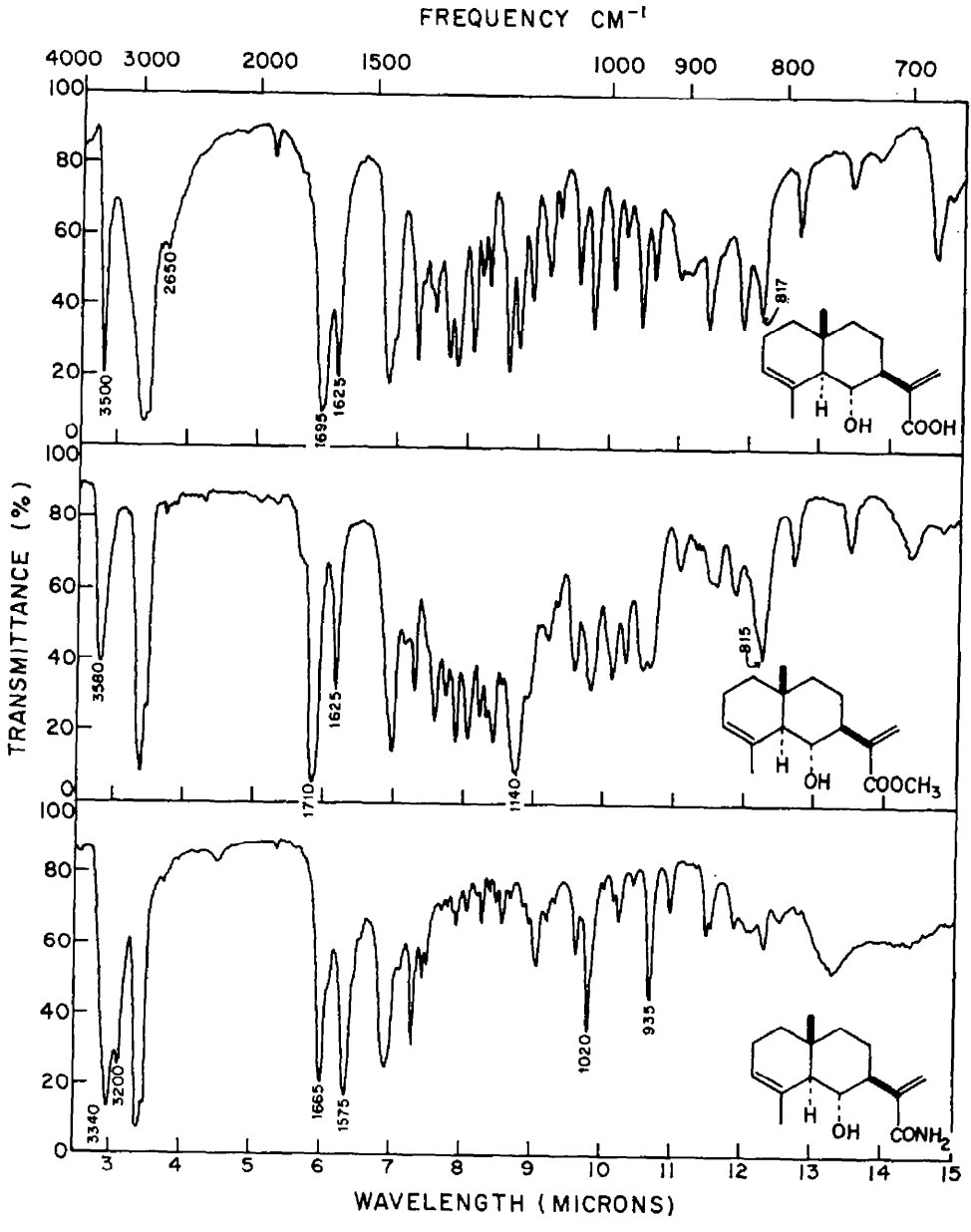

FREQUENCY CM⁻¹
4000 3000 2000 1500 1000 900 800 700
TRANSMITTANCE (%)
3500
2650
1695
1625
817
H
OH
COOH
3580
1625
1710
1140
815
H
OH
COOCH3
3340
3200
1685
1575
1020
935
H
OH
CONH2
3 4 5 6 7 8 9 10 11 12 13 14 15
WAVELENGTH (MICRONS)

Fig. 2

NMR spectrum of VIIIa shows signals at 0·92 δ (3H) due to a quarternary CH_3 at C.10, 1·8 δ (3H) due to a CH_3 on a double bond at C.4, 3·75 δ (3H) due to the CH_3 of the conjugated methyl ester at C.13, 5·3 δ (1H) due to a proton on a trisubstituted double bond on C.3, 5·68 and 6·22 δ (2H), due to two protons on the conjugated unsymmetrical disubstituted double bond.

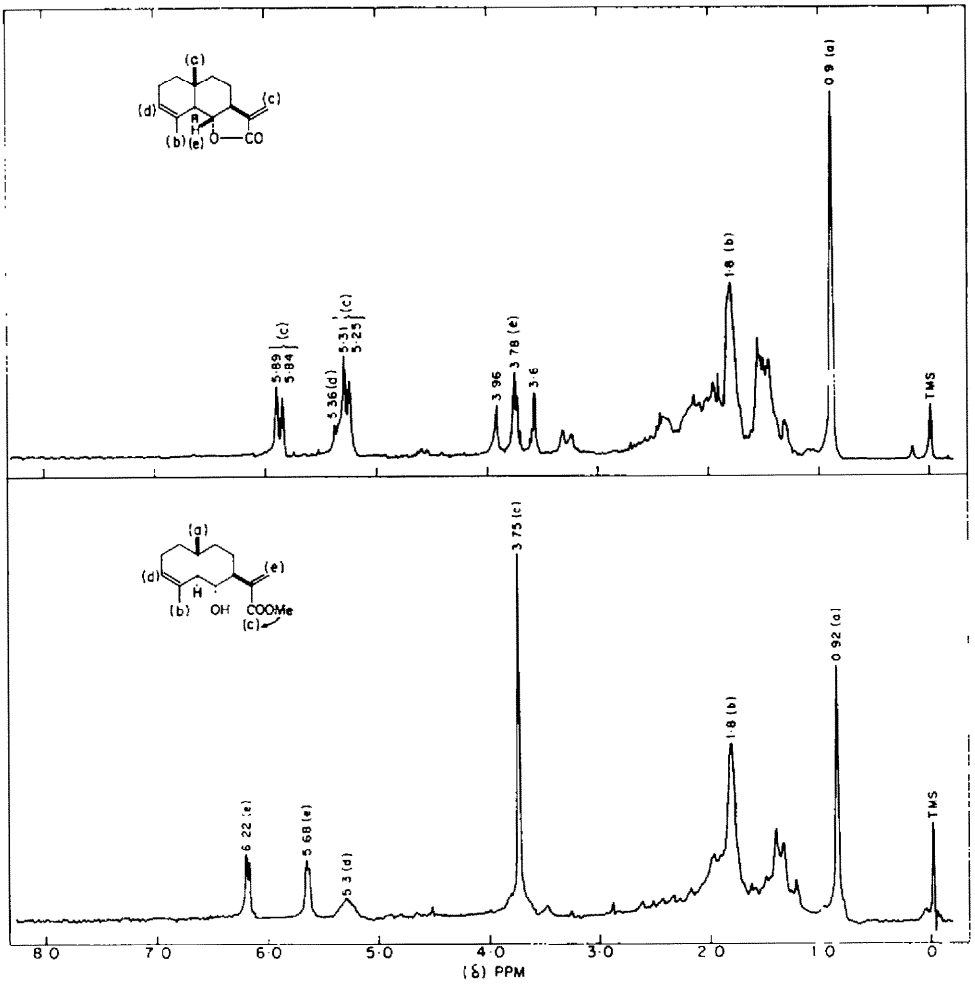


Fig. 3

EXPERIMENTAL

All m.ps and b.ps are uncorrected. Rotations were taken in $CHCl_3$ solution. The UV spectra were taken in ethanol solution on a Beckman DK-II ratio-recording spectrophotometer by Mr. H. Gopinath. The IR spectra were taken on an infracord spectrophotometer model 137B with NaCl optics by Mr. K. G. Deshpande. The IR spectra of solids were taken in nujol and those of liquids as liquid films. The NMR spectra were taken in CCl_4 solution on a 60 m.c. Varian Instrument by Dr. P. M. Nair and colleagues, and the chemical shifts were measured in δ-units. Microanalysis were carried out by Mr. Pansare and colleagues.

Acid catalysed cyclization of costunolide (I). Costunolide (50 g), m.p. 106–107°, $[\alpha]_D$ +126°, was dissolved in glacial acetic acid (250 ml) to which perchloric acid (5 ml) and ether (300 ml) were added. The solution was allowed to stand at 0° for 72 hr, diluted with water (3 l.) and extracted with ether.

The ether layer was washed with Na_2CO_3aq and water, dried (Na_2SO_4) and the ether removed to furnish a liquid (47 g) which was chromatographed on alumina (gr. III, 700 g) and eluted as follows:

Fr. no.	Solvent	Vol. (ml)	Wt. (g)
1	Pet. ether	1500	20
2	Pet. ether–benzene (1:1)	1000	8
3	Ether	500	4
4	Methanol	500	—
5	Acetic acid	500	2 (resinified)

The fraction 1, on cooling at −18° gave a solid (13 g), m.p. 76–77°, which was crystallized twice from methanol to give IV (5 g), m.p. 83–84°, $[\alpha]_D$ +118°; UV end absorption: ε 210, 10,000. IR spectrum (Fig. 1) and NMR spectrum (Fig. 3) were in agreement with structure IV. (Found: C, 77·88; H, 8·71. $C_{16}H_{20}O_2$ requires: C, 77·55; H, 8·68%).

The fraction 3 (4 g) was rechromatographed on alumina (gr. III, 60 g) and eluted with ether to give a liquid (2 g) which showed the following properties, $[\alpha]_D$ +59°, n^{27} 1·5232; UV end absorption, ϵ 210, 9600. The IR spectrum (Fig. 1) indicated it to be an α,β-unsaturated α-methylene-γ-lactone containing an additional exocyclic double bond; bands at 1640, 893 cm^{-1}, due to $\rangle C{=}CH_2$, and at 815 and 1400 cm^{-1}, due to α,β-unsaturated α-methylene-γ-lactone. NMR spectrum also gave similar indications (Found: C, 76·8; H, 8·4. $C_{16}H_{20}O_2$ requires: C, 77·55; H, 8·68%). The sample for analysis was purified by chromatography alone and not distilled.

Hydrogenation of α- and β- cyclocostunolides (IV *and* VI). Pure IV (0·5114 g) was hydrogenated in acetic acid medium using Pt catalyst. The volume of H_2 absorbed (100 ml at NTP) corresponded to two double bonds. The product was worked up and purified by crystallization from pet. ether and methanol to give santanolide 'c' (V), m.p. and mixed m.p. with an authentic sample 153–54°; $[\alpha]_D$ +56° (Found: C, 76·14; H, 10·21. $C_{15}H_{24}O_2$ requires: C, 76·22; H, 10·24%).

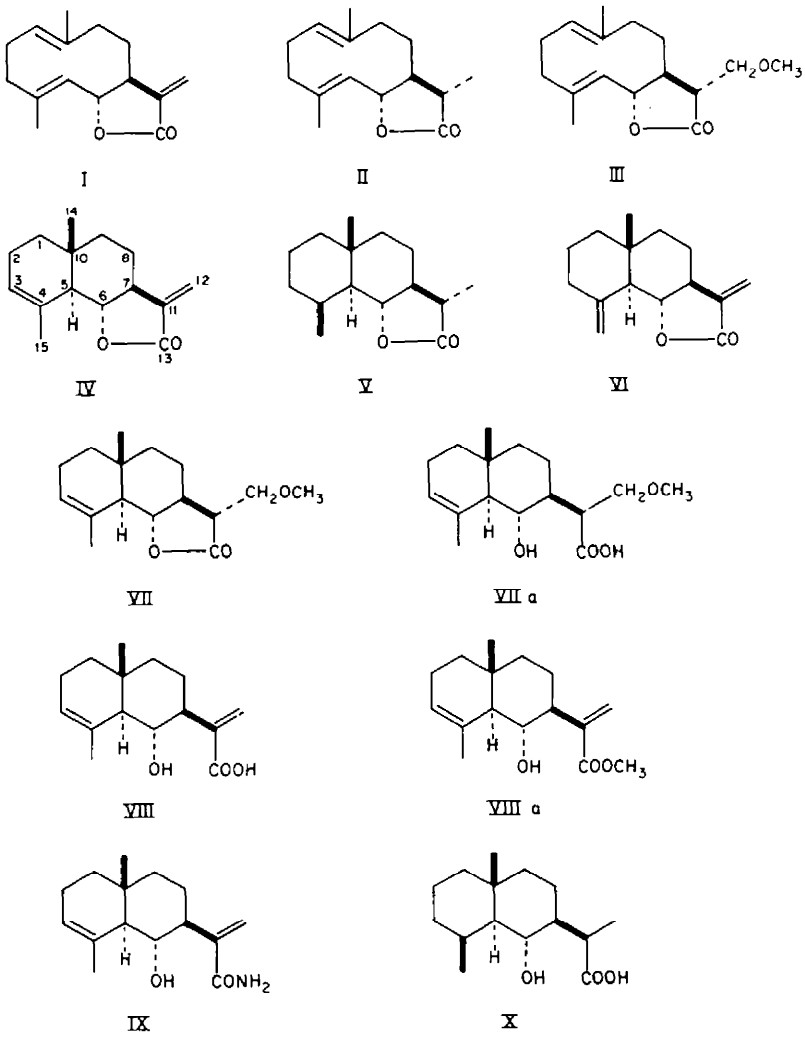
β-Cyclocostunolide fraction (VI) (0·9246 g, liquid, containing some α-cyclocostunolide as impurity) was hydrogenated in acetic acid medium using Pt catalyst. The volume of H_2 absorbed (182 ml at NTP) corresponded to two double bonds. The product was worked up and distilled: b.p. 170–180° (bath)/0·5 mm. The distillate on cooling in pet. ether solution at −18° gave a solid (0·3 g) which was crystallized twice from methanol to give V, m.p. and mixed m.p. with an authentic sample 153–54°; $[\alpha]_D$ +55° (Found: C, 76·4; H, 10·32. $C_{15}H_{24}O_2$ requires: C, 76·22; H, 10·24%).

Hydroxy acid (VIII) *from α-cyclocostunolide* (IV). α-Cyclocostunolide (2 g) dissolved in methanol (50 ml) was added to a solution of methanolic KOH (2 g in 3 ml water and 15 ml methanol) and kept at room temp for 72 hr. It was then diluted with water and extracted with ether. The ether extract, after removal of solvent, did not furnish any material. The aqueous layer was filtered and the filtrate acidified with dil. H_2SO_4 and extracted with ether. Removal of ether gave a solid, m.p. 153–54° (mixture of VIIa and VIII) which was crystallized from $CHCl_3$ to give pure VIII $[\alpha]_D$ +90° (Found: (C, 71·44; H, 8·65, Eq. wt. 245·5. $C_{15}H_{22}O_3$ requires: C, 71·97; H, 8·86%. Eq. wt. 250·33). The mother liquors (0·5 g) of VIII, after removal of $CHCl_3$ were chromatographed on alumina (gr. III, 20 g) and eluted with pet. ether and cooled at −18° to give a solid which was crystallized from methanol to give VII, m.p. and mixed m.p. with an authentic sample 57–58°, $[\alpha]_D$ +82° (Found: C, 72·74; H, 9·18. $C_{16}H_{24}O_3$ requires: C, 72·69; H, 9·15%).

Hydroxy acid amide (IX) *from α-cyclocostunolide* (IV). To a solution of IV (2 g) in ethyl alcohol (75 ml), liquor ammonia (25 ml) was added and the solution kept at 0° for 72 hr. A solid separated which was crystallized from methanol to give IX, m.p. 157° $[\alpha]_D$ +100° (Found: C, 67·28; H, 9·3; N, 5·16. $C_{16}H_{23}NO_3,H_2O$ requires: C, 67·38; H, 9·43; N, 5·25%). The IR spectrum (Fig. 2) indicated it to be an amide of a hydroxy acid.

Saponification of the amide (IX) *to hydroxy acid* (VIII). The amide (0·5 g) was saponified by refluxing with 10% alcoholic KOH (50 ml) for 4 hr. It was diluted with water and extracted with ether to remove the unreacted amide. The aqueous layer was acidified with dil. H_2SO_4 and extracted with ether. Removal of ether and crystallization of residue from $CHCl_3$ furnished VIII, m.p. and mixed m.p. with an authentic sample 162–63°. The IR spectra of both the samples were identical.

The hydroxy acid VIII (0·2 g) was esterified with diazomethane to give the methyl ester VIIIa,



I II III IV V VI VII VII a VIII VIII a IX X

which was purified by distillation, b.p. 190–210° (bath)/0·5 mm., $[\alpha]_D$ +35° (Found: C, 72·63; H, 9·06. $C_{16}H_{24}O_3$ requires: C, 72·69; H, 9·15%). This ester was used for IR and NMR spectra measurements (cf. Figs. 2 and 3).

Hydrogenation of the hydroxy acid (VIII). The hydroxy acid (0·6842 g) was hydrogenated in acetic acid medium using Pt catalyst. The volume of H_2 absorbed (124 ml at NTP) corresponded to two double bonds. The product was worked up and separated into acidic and neutral parts by $NaHCO_3$ aq. The neutral part was purified by crystallization from methanol to give a lactone m.p. and mixed m.p. with an authentic sample of santanolide 'c' 155°, $[\alpha]_D$ +58° (Found: C, 75·63; H, 10·3. $C_{15}H_{24}O_2$ requires: C, 76·22; H, 10·24%). The acidic part was purified by crystallization from $CHCl_3$ (or methanol) to give X, m.p. 141–42°, $[\alpha]_D$ +9° (Found: C, 71·25; H, 10·27. $C_{16}H_{26}O_3$ requires: C, 70·83; H, 10·30%). When VIII is hydrogenated in alcohol the tetrahydrohydroxy acid (X) is exclusively formed which gave santanolide 'c' on warming with acetic acid.