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TERPENOIDS—CIV

COSTOL FRACTION OF COSTUS ROOT OIL*

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Abstract—The 'costol' fraction of costus root oil is an intimate mixture of several alcohols. The presence of "true" costol (I) has been proved by conversion to crystalline costic acid (Ib), the methyl ester of which on reduction with LAH-$AlCl_3$ gives pure costol of high rotation. The tertiary alcohol, elemol (IV) has been identified as another constituent of the mixture.

COSTUS oil from the roots of *Saussurea lappa*, Clarke, contains several sesquiterpene alcohols.[1] Sorm *et al.* isolated an alcohol, costol, from this mixture and assigned to it the stereostructure I on the basis of spectral and chemical evidence.[2]

We have re-examined the alcohol fraction of costus root oil and obtained material with comparable properties to Sorm's costol and found it to be a mixture of at least three major components (two in equal proportion). In spite of rigorous purification (Experimental) we have been unable to separate this intimate mixture of alcohols (henceforth referred to as "costol") into pure substances.

'Costol' does not form any of the conventional solid derivatives. The aldehyde 'costal' obtainable in good yield by oxidation of 'costol' shows two peaks in GLC. Its semicarbazone (m.p. 218°) on decomposition[3] under mild conditions also yields a product containing two components.

The structure and stereochemistry of costic acid[4] (Ib), which we elucidated at the same time, suggested a structural relationship between 'costol' and this acid.

A primary alcohol (GLC pure) which was true costol (I) was prepared from methyl costate (Ic) by reduction with LAH-$AlCl_3$ and compared with 'costol' by GLC analysis. It was found that 'costol' contains one component corresponding to this alcohol. The aldehyde, costal (Ia), derived from this alcohol gives a semicarbazone (m.p. 223°). A mixed m.p. with the semicarbazone of the aldehyde 'costal' (m.p. 218°) from 'costol' showed a slight depression (215°) suggesting that the aldehyde from 'costol' may be a mixture of closely related compounds.

The aldehydes and semicarbazones from both the series show α,β-unsaturation (UV) and hence the present alcohols should be allylic.

True costal (Ia) from methyl costate (Ic) furnishes selinane (II) due to hydrogenolysis during hydrogenation. 'Costol' under similar conditions, however, gives a similar hydrocarbon but somewhat different from selinane in properties.

These observations show that 'costol' is a mixture of alcohols, one of which (40%, GLC) is true costol (I).

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[2] V. Benesova, V. Herout and F. Sorm, *Coll. Czech. Chem. Commun.* **24**, 2365 (1959); cf. S. Katsura, *J. Chem. Soc. Japan* **63**, 1460 (1942); *Chem. Abstr.* **41**, 3447 (1947).

[3] C. H. DePuy and B. W. Ponder, *J. Am. Chem. Soc.* **81**, 4629 (1959).

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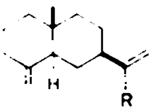
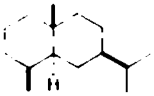
This conclusion is confirmed by the fact that 'costol' on further oxidation with silver oxide[5] furnishes crystalline costic acid (Ib) together with another acid which is not yet identified.

Further, during oxidation by Jones' reagent a substantial quantity of 'costol' remained unoxidized. This fraction, (3 components at least by GLC and TLC), on further processing has yielded elemol[6] (IV) as one of the components. The other alcohols have not been identified.



I, R = CH$_2$OH
Ia, R = CHO
Ib, R = COOH
Ic, R = COOCH$_3$



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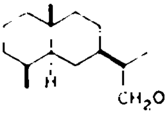
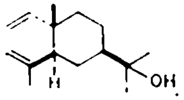


III



IV

EXPERIMENTAL

All m.ps and b.ps are uncorrected. Specific rotations were determined in chf soln unless otherwise stated. UV spectra were measured in EtOH (95%) soln with a Beckman Model DK-2 ratio recording spectrophotometer. IR spectra were taken with the Perkin–Elmer (Model 137b), Infracord spectrophotometer. GLC analyses were carried out using at least two stationary phases employing a Griffin MK-II model and Perkin-Elmer analyser. NMR spectra were measured with a Varian A-60 spectrometer operating at 60 mc with TMS as internal reference.

Isolation of 'costol'

Partially delactonized acid-free costus root oil (355 g) was fractionated under reduced press using an 8' Vigreaux column. Fraction, b.p. 100–130°/0·2 mm (130 g) was saponified by refluxing with alcoholic KOH (200 ml; 10%) for 8 hr. The neutral (95 g) and lactonic constituents were isolated in the usual way. The neutral product (350 g) from several experiments was chromatographed on neutral alumina (grade II; 5·0 kg) and bulk fractions were collected, using different eluents: pet. ether (185 g); benzene (20 g); ether (115 g) and MeOH (20 g). Ether and MeOH eluted fractions were combined (135 g) and fractionated: Fraction 1, b.p. 85–110°/0·3 mm (17 g) and Fraction 2, b.p. 110–25°/0·3 mm (80 g). The higher boiling residue (33 g) was preserved. Fraction 2 (25 g) was chromatographed on neutral alumina (grade II; 500 g) and eluted with pet. ether, pet. ether–benzene, benzene, ether and MeOH. The fractions eluted with ether and MeOH were composed only of alcohols (IR). Alcohol-rich fractions (22 g) were rechromatographed on neutral alumina (grade II; 2·2 kg) and eluted with pet. ether, pet. ether–benzene (1:1), benzene, benzene–ether (1:1), ether, ether–MeOH (1:1) and MeOH. Fifty fractions of 50 ml each were collected. Fractions 1, 8, 15, 24, 38 and 50 were examined by GLC and each fraction had a similar pattern, showing two prominent peaks and two minor ones. Fractions, 24–50 were mixed together and distilled under reduced press, b.p. 140°/(bath)/0·5 mm (10·5 g); n_D^{28} 1·5132; $[\alpha]_D$ +6·7° (*c*, 4·2). IR bands at 3350, 1020, 1640 and 887 cm^{-1}. (Found: C, 81·8; H, 11·4. $C_{15}H_{24}O$ requires: C, 81·76; H, 11·98%.) This product corresponded to Sorm's 'costol'.

Oxidation of 'costol'

(a) *With activated* MnO_2. A mixture of 'costol' (2 g) dissolved in chf (200 ml) and freshly prepared, activated MnO_2 (20 g) was mechanically shaken at the room temp for 24 hr. MnO_2 was filtered off and the filtrate evaporated, when an oil (1·9 g) was obtained, b.p. 180° (bath)/5 mm; n_D^{27} 1·4990.

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[6] S. K. Paknikar and S. C. Bhattacharyya, *Tetrahedron* 18, 1509 (1962); T. G. Halsall, D. W. Theobald and K. B. Walshaw, *J. Chem. Soc.* 1029 (1964).

(b) *With Jones' chromic acid reagent.* 'Costol' (2 g), dissolved in acetone (15 ml) was oxidized with the requisite quantity of Jones' chromic acid reagent at 0°. The reaction mixture was diluted with water and extracted with ether. The ether extract was processed to remove any organic acid formed during oxidation. The ether soln was dried and evaporated to give 'costal' (1·7 g), b.p. 185° (bath)/5 mm n_D^{26} 1·4989. The $NaHCO_3$ soln, on acidification, gave an acid (0·2 g). 'Costal' obtained by the two methods (a) and (b) above, were found to be identical, with IR bands at 2703, 1686, 1633, 890 cm⁻¹; λ_{max} 218 mμ; ε 10,430. GLC analysis revealed two peaks of almost equal intensity and a small hump accounting for about 10% of the product. (Found: C, 81·83; H, 9·9. $C_{15}H_{22}O$ requires: C, 82·51; H, 10·16%.)

Semicarbazone of 'costal'

To 'costal' (1·0 g) in alcohol (10 ml) was added an aqueous soln of semicarbazide hydrochloride (0·5 g) and AcONa (0·8 g). The semicarbazone formed was crystallized 3 times from EtOH, m.p. 218°; $[\alpha]_D$ +35·37° (AcOH; *c*, 0·8); λ_{max} 263 mμ; ε 25,680. (Found: C, 70·04; H, 9·19; N, 15·31. $C_{16}H_{25}N_3O$ requires: C, 69·78; H, 9·15; N, 15·26%.)

Regeneration of 'costal' from the semicarbazone

(a) *With oxalic acid.* A mixture of the semicarbazone (1·0 g), alcohol (15 ml), oxalic acid (2·0 g), dissolved in water (50 ml), aqueous formaldehyde (40%; 8 ml) and pet. ether (40–60°; 100 ml) was refluxed for 6 hr. The organic layer was separated and washed with water and dried. Evaporation of solvent gave 'costal' (0·4 g); b.p. 175° (bath)/4 mm; n_D^{27} 1·4990. It yielded a semicarbazone which was identical with the starting compound.

(b) *With levulinic acid.* A mixture of semicarbazone (1·0 g), levulinic acid (50 ml) and 1N HCl (10 ml) was shaken mechanically at the room temp for 24 hr. The clear soln thus obtained was diluted with water and neutralized with Na_2CO_3. The soln. was extracted thoroughly with ether, washed with water and dried and solvent removed to yield 'costal' (0·7 g), b.p. 160–165° (bath)/3 mm, n_D^{27} 1·4988. (Found: C, 82·32; H, 10·0. $C_{15}H_{22}O$ requires: C, 82·51; H, 10·16%.)

Hydrogenation of 'Costol'

'Costol' (2·0 g) in MeOH (25 ml) was hydrogenated in the presence of Adams' PtO_2 (0·05 g). It absorbed 468 ml of H_2 at NTP corresponding to 2·3 double bonds. The reaction product was isolated as usual (1·9 g).

Isolation of 'selinane' and 'tetrahydrocostol'

The hydrogenated product (1·9 g) was chromatographed on neutral alumina (grade II; 38 g) and eluted with pet. ether and ether.

The pet. ether eluate (100 ml) afforded "selinane" as a mobile liquid (0·5 g). It was distilled over Na; b.p. 130° (bath)/7 mm; n_D^{23} 1·4731; d_{24}^{24} 0·8654; $[\alpha]_D$ +9·65° (*c*, 4·3). (Found: C, 86·4; H, 13·8. $C_{15}H_{28}$ requires: C, 86·45; H, 13·55%.)

The properties of this 'selinane' were somewhat different from those of selinane (II) obtained from crystalline costic acid, as shown below:

	From costic acid	From 'costal'	Sorm's product[8]
Density	0·8871	0·8654	0·8732
Refractive index	1·4793	1·4731	1·4721
Specific rotation	+8·32°	+9·65°	+11·9°

'Selinane', obtained above, was found to be a mixture of at least two components (GLC). Its IR spectrum showed bands at 1466, 1449, 1377, 1369, 1170, 1009, 1001, 982, 932, 916, 853 and 790 cm⁻¹.

The ether eluate yielded 'tetrahydrocostol' (1·1 g), b.p. 145° (bath)/0·7 mm; n_D^{26} 1·4923; $[\alpha]_D$ +11·28° (*c*, 2·3); IR bands at 3340, 1467, 1381, 1037 cm⁻¹. (Found: C, 79·90; H, 12·69. $C_{15}H_{28}O$ requires: C, 80·29; H, 12·58%.) It also consisted of at least two products (GLC).

Oxidation of 'costal' with silver oxide

A mixture of freshly distilled 'costal' (5 g distilled 'costal' dissolved in alcohol 25 ml) and $AgNO_3$ (8 g dissolved in distilled water 20 ml) was cooled to −10°. A soln of KOH (8 g in water 20 ml) was added under stirring at −10°. The total mixture was stirred at the same temp for 30 min and then allowed to come to the room temp. Alcohol (50 ml) was added and the reaction mixture stirred at the room temp for 48 hr. It was filtered, the Ag_2O slurry was washed thoroughly with alcohol and the combined filtrate was evaporated under reduced press. The residue was diluted with water and extracted with ether. The aqueous alkaline soln was acidified and the liberated acid was isolated as usual (4·1 g).

A small quantity of the acid was converted into its methyl ester. It was distilled, b.p. 130° (bath)/0·2 mm. It revealed two peaks on GLC analysis.

The acid (4·0 g) was converted into its cyclohexylamine salt, m.p. 182–184°. The cyclohexylamine salt (4·5 g) was suspended in ether and treated with 5% NaOH aq until all the solid dissolved. The aqueous alkaline layer was acidified and the liberated acid (2·2 g) was isolated. It was then converted into its dicyclohexyalmine salt, m.p. 90–91°. The acid, regenerated from the dicyclohexylamine salt, as described above, was obtained as a solid (1·2 g) and was crystallized from aqueous EtOH to yield pure Ib m.p. 87–88°; $[\alpha]_D$ +21·2° (*c*, 1·8). Mixed m.p. with an authentic sample of natural costic acid was undepressed; λ_{max} 210 mμ; ε 5280; IR bands at 3077, 1681, 1634, 1613, 885 cm^{-1} and was superimposable on that of costic acid. (Found: C, 76·61; H, 9·70; Eq. wt. 232·6. $C_{15}H_{22}O_2$ requires: C, 76·88; H, 9·46% and Eq. wt. 234·33.)

Methyl costate Ic

The acid (m.p. 87–88°) was converted into its methyl ester (diazomethane), b.p. 140° (bath)/0·4 mm: n_D^{27} 1·5055; $[\alpha]_D$ +29·63° (*c*, 2·2); λ_{max} 210 mμ; ε 5700; IR bands at 1706, 1629, 1613, 1245, 885 and 814 cm^{-1}. GLC analysis revealed the presence of a single component. (Found: C, 77·10; H, 9·69. $C_{16}H_{24}O_2$ requires: C, 77·37; H, 9·74%.)

Pure costol (I) *from methyl costate* (Ic)

Methyl costate (1·0 g) dissolved in dry ether (25 ml) was added drop-wise to a stirred slurry of AlH_3 (prepared from 0·42 g anhydrous $AlCl_3$ and 0·46 g LAH), in dry ether at the room temp. Stirring was continued for 45 min. The product was isolated in the customary manner. The alcohol, pure costol (I; 0·8 g) was distilled, b.p. 145° (bath)/0·5 mm; n_D^{26} 1·5177; $[\alpha]_D$ +32·8° (*c*, 4·3); GLC analysis showed a single peak. IR bands at 3356, 1639, 889 cm^{-1}. (Found: C, 81·62; H, 11·51. $C_{15}H_{24}O$ requires: C, 81·76; H, 11·98%.)

Isolation of elemol (IV)

The mother liquor, from the semicarbazone of 'costal' (prepared by Jones' reagent oxidation of 10 g 'costol') was concentrated *in vacuo* and the residue diluted with water and extracted with ether. The ether soln was washed with water and dried. Evaporation of ether gave a thick liquid (3·8 g). This was dissolved in abs alcohol (30 ml) and AcOH (5 ml) was added. To this, Girards' reagent T (2·1 g) was added and the soln refluxed on a water bath for 4 hr. The reaction mixture was diluted with water containing $NaHCO_3$ (3·5 g) and thoroughly extracted with ether. The ether extract was washed with water and dried. On evaporation of ether the non-carbonyl fraction was obtained as a thick liquid (3·1 g). It showed a strong OH band at 3509 cm^{-1} in the IR spectrum, b.p. 140° (bath)/0·4 mm. GLC analysis revealed the presence of at least 3 components.

The distilled alcohol mixture (2·8 g) was chromatographed on neutral alumina (grade II; 84 g) and eluted with pet. ether, pet. ether–benzene (1:1), benzene and ether. The pet. ether-benzene (1:1) eluate, on concentration, afforded a viscous liquid (1·0 g), which was crystallized from pet. ether to yield elemol, m.p. and mixed m.p. 51–52°; $[\alpha]_D$ −4·13° (*c*, 2·8). IR bands at 3425, 1634, 1119, 1008, 909, 889, 813 cm^{-1}; identical with that of an authentic sample of elemol. (Found: C, 80·91; H, 11·60. $C_{15}H_{26}O$ requires: C, 81·02; H, 11·79%.)

Other fractions of the chromatography were not examined.