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TERPENOIDS—C

SYNTHESIS OF TAUREMISIN (VULGARIN), AND SAUSSUREA LACTONE[1,2]

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Abstract—Tauremisin has been synthesized by two different routes starting from santonin. Saussurea lactone has been synthesized starting from santonin.

TAUREMISIN, the crystalline sesquiterpene lactone has been isolated from *Artemisia taurica* Willid[6] and *Artemisia vulgaris L.*[7] On the basis of its spectral properties, elimination reactions, conversion to santanolide—C and other transformations it has been assigned the structure I. In the synthesis of tauremisin we have taken advantage of interesting observations made in connection with the structure elucidation of tauremisin and santamarin.[8]

Treatment of tauremisin with zinc and acetic acid furnishes the β,γ-unsaturated ketone II, which on hydroxylation with OsO_4 gives the β-hydroxy ketone IIa. The latter readily dehydrated in alkaline medium to yield tauremisin.[6] The β,γ-unsaturated ketone II has also been prepared from santamarine which has been converted to tauremisin (I) via the epoxidel II.[9] Appreciable amount of the β,γ-unsaturated ketone II exists in equilibrium with the α,β-unsaturated ketone XI.[7]

The starting point of the present investigations was α-tetrahydrosantonin (XII),[10] one of the hydrogenation products of santonin. Its conversion to a suitable intermediate for the synthesis of tauremisin, involves (i) removal of oxygen function from C_3 (ii) introduction of oxygen function at C_1 and (iii) introduction of a double bond at C_2—C_3 or C_3—C_4. Comparable transformations have been effected in the preparation of Δ^2-cholesten-1α-ol.[11] α-Tetrahydrosantonin was converted to the keto-oxide XV,[12] which on bromination and subsequent dehydrobromination furnished the

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[2] Part of this work has been published as a preliminary communication.[5]
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[6] K. S. Rybalko and L. Dolejs, *Coll. Czech. Chem. Commun.* **26**, 2909 (1961).
[7] T. A. Geissman and G. A. Ellestad, *J. Org. Chem.* **27**, 1855 (1962).
[8] R. D. Vivar and H. Jimenez, *Tetrahedron* **21**, 1741 (1965).
[9] The Mexican workers[8] were apparently unaware of the investigations on tauremisin as no mention has been made of the work reported in Refs. 6 and 7. Though the γ-hydroxyketo lactone prepared by them from the ketone III has not been compared with authentic tauremisin, there can be no doubt about the identity of the product in view of the physical constants quoted and the reactions involved in its preparation. Further support for the identity of hydroxy lactone prepared by Vivar *et al.*, follows from our investigations reported in this paper.
[10] W. Cocker and T. B. H. McMurry, *J. Chem. Soc.* 4549 (1956).
[11] C. Djerassi, D. H. Williams and B. Berkoz, *J. Org. Chem.* **27**, 2205 (1962).
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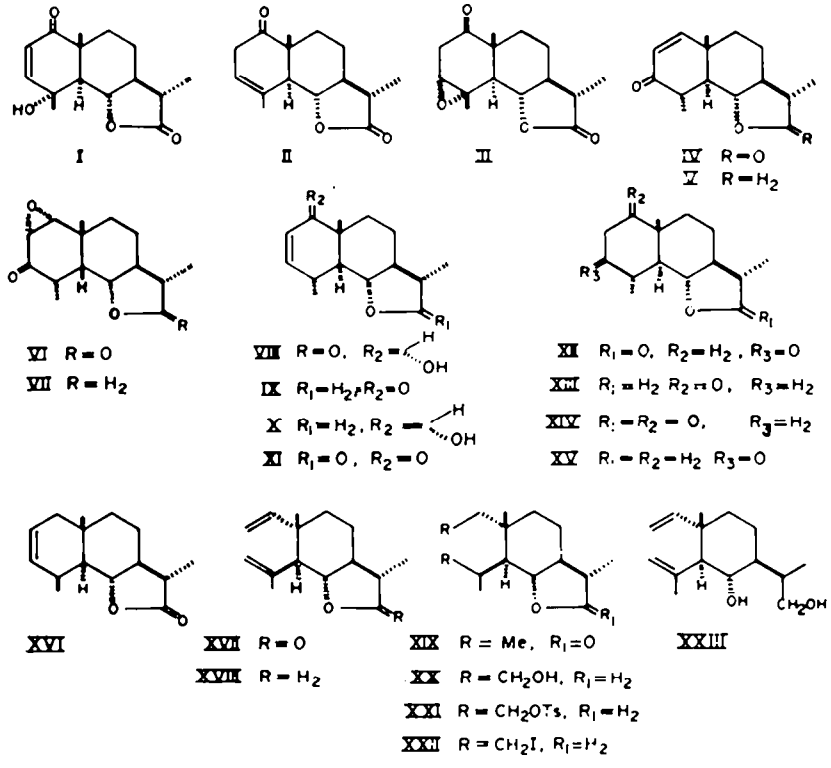
α,β-unsaturated ketone V. The structure assigned to V is consistent with its IR, UV and NMR spectra. (Experimental) Epoxidation of V furnished the α,β-epoxyketone VII which was reduced with hydrazine to the allylic alcohol X. The structure assigned to X is in agreement with its spectral data and is further supported by its oxidation with Jones reagent, to the conjugated ketone IX, having characteristic IR, UV and NMR spectra (Experimental). Further oxidation of the conjugated ketone IX with chromic acid in acetic acid furnished a mixture of ketones XI and II.[7] (ν_{max} 1770,



1701 and 1667 cm^{-1}). This mixture XI and II was treated with perbenzoic acid to convert the latter component to the epoxide III.[8] The epoxidation product on treatment with alkali furnished tauremisin (I) identified by direct comparison with an authentic sample.[13]

In a different approach, the mixture (XI and II), was obtained by the oxidation of the santenolide (XVI)[10] with sodium dichromate in acetic acid solution. Hydrogenation of the mixture (XI and II), followed by chromatography and repeated crystallizations furnished 1-oxo- santanolide-a (XIV), identical with an authentic sample prepared by the oxidation of the keto oxide XIII. The latter was prepared by hydrogenation of the α,β-unsaturated ketone IX.

Examination of the roots of the plant *Saussurea lappa* C. B. Clarke at the Forest Research Institute, Dehra Dun led to the isolation of saussurea lactone[13] (XVII), a

[13] The authors thank Dr. K. S. Rybalko (Moscow) and Dr. L. Dolejs (Prague) for supplying the authentic sample of tauremisin.

crystalline sesquiterpene lactone, identical with the product of pyrolysis of dihydrocostunolide. Tetrahydro-saussurea lactone (XIX) has been synthesized starting from santonin. The oxido-diol XX[12], an intermediate in the synthesis of tetrahydrosaussurea lactone has now been converted to saussurea lactone.

The tosylate XXI, prepared from oxido-diol XX, furnished the iodo compound XXII on treatment with sodium iodide in boiling acetone solution. The elimination reaction of XXII proceeded smoothly, in the presence of potassium-t-butoxide in DMSO to furnish the oxide XVIII. The latter was identical with an authentic sample prepared by LAH reduction of saussurea lactone to the diol XXIII, followed by acid catalysed dehydration of XXIII. The structure assigned to the oxide XVIII is in agreement with its IR spectrum which showed the presence of two distinct methylene groups, $>C-CH_2$ and $-CH=CH_2$ (bands at: 1626, 990, 909 and 885 cm^{-1}). Chromic acid oxidation of the oxide XVIII furnished saussurea lactone (XVII).

EXPERIMENTAL

M.p.s and B.ps are uncorrected. Elemental analysis are due to Mr. Pansare and colleagues of the Microanalytical section of our laboratory. UV spectra are taken in alcohol with Beckman DK-2 ratio recording spectrophotometer and IR spectra in Perkin-Elmer infrared. NMR spectra were determined in CCl_4 soln using TMS as internal standard with Varian A-60 spectrometer. Optical rotations were determined at room temp (25–30°) in chf soln.

3-*Oxo*-5,7α(H),4,6,11β(H)-*eudesm*-1-*en*-6:13 *oxide* (V)

The keto oxide XV[13] (1·44 g) was dissolved in ACOH (12 ml) at room temp and 30% HBr in ACOH (0·1 ml) was added dropwise and then Br_2 (1·88 g) in ACOH (3 ml) with stirring. The reaction mixture was stirred at 40° for 15 min and excess of Br_2 was destroyed by adding EtOH (5 ml). Reaction mixture was poured in ice water (50 ml) and extracted with ether (25 × 2 ml). Ether extract was washed with water, dried and ether evaporated. The crude bromo compound (2·2 g) was refluxed overnight with dry collidine (20 ml) in N_2 atm and the collidine soln poured in cold water and extracted with ether. The ether extract was washed with water, dil. HCl, water, dried and evaporated. The residue on distillation *in vacuo* furnished V (1·2 g) b.p. 160–170° bath/0·5 mm. Recrystallization from pet ether (b.p. 60–80°) furnished 640 mg of crystals, m.p. 88–90°, $[\alpha]_D$ −49° (*c*, 14·8; chf). (Found: C, 77·02; H, 9·61. $C_{15}H_{22}O_2$ requires: C, 76·88; H, 9·46%.)

IR spectrum (Nujol). Prominent band at 1687 cm^{-1} (six membered $>C=O$ in conjugation), other bands were observed at: 2941, 1471, 1385, 1247, 1203, 1163, 1136, 1075, 1054, 1031, 1015, 980, 962, 944, 862, 833 and 775 cm^{-1}

UV spectrum. λ_{max} 227 mμ (ε 9400).

NMR spectrum. Doublet centred at 8·96τ (3H, CH_3 at C_{11}), singlet at 8·91 τ (3H, CH_3 at C_{10}), doublet centred at 8·77 τ (3H, CH_3 at C_4), multiplet centred at 6·64 τ (2H, $O-CH_2$), triplet at 6·02 τ (1H, H attached to C_6) and doublets at 4·26 and 3·39 τ (2H, H attached to C_1 and C_2 respectively; $J_{1,2}$ = 10 c/s).

1α,2α-*Oxido*-3-*oxo* 5,7α(H), 1,2,4,6,11β(H)-*eudesman*-6:13 *oxide* (VII)

Compound V (500 mg) was dissolved in dioxan (50 ml) and then 30% H_2O_2 (10 ml) was added. The mixture was cooled to 0° and 2·5N NaOH (5 ml) was added slowly with constant shaking. It was allowed to stand overnight at 10–15°, diluted with water (200 ml) and extracted with ether (50 × 3 ml). Ether extract on working up furnished the VII (480 mg) $[\alpha]_D$ +40° (*c*, 4·56; chf). (Found: C, 72·64; H, 9·07. $C_{15}H_{22}O_3$ requires: C, 71·97; H, 8·86%.)

IR spectrum (liquid film). Prominent bands were observed at: 2941, 1720 ($>C=O$), 1471, 1389, 1282, 1258, 1163, 1136, 1053, 1029, 980, 962, 885, 848 and 787 cm^{-1}.

UV spectrum. There was no strong absorption around 230 mμ.

NMR spectrum. Singlet at 9·1 τ (3H, CH_3 at C_{10}), doublet centred at 8·98 τ (3H, CH_3 at C_{11}),

doublet centred at 8·78 τ (3H, CH_3 at C_4), signal at 6·88 τ (2H, $\overset{O}{\diagup\diagdown}$ CH—CH—) and multiplet centred at 6·52 τ (2H, —O—CH_2—) and triplet centred at 6·05 τ (1H, H attached to C_6).

Optical rotatory dispersion• $[\phi]^{MeOH}_{322\ m\mu}$ +2340 (first extremum), $[\phi]^{MeOH}_{278\ m\mu}$ −3960 (second extremum).

1α-*Hydroxy*-5,7α(H),1,4,6,11β(H)-*eudesm*-1-*en*-6:13 *oxide* (X)

Epoxide VII (400 mg) was refluxed with 80% hydrazine hydrate (5 ml) for 30 min in N atm, cooled, diluted with water (25 ml) and extracted with ether (15 × 2 ml). Ether extract on working up furnished a residue (260 mg) which was chromatographed over alumina (grade II; 4 g) and the benzene eluted fraction furnished X (210 mg), $[\alpha]_D$ +66° (*c*, 4·4; chf).

IR spectrum (liquid film). The bands were observed at: 3390 (OH), 1667, 1471, 1376, 1258, 1163, 1136, 1079, 1031, 980, 971, 952, 934, 893, 840 and 758 cm^{-1}.

1-*Oxo*-5,7α(H),4,6,11β(H)-*eudesm*-1-*en*-6:13 *oxide* (IX)

Jones reagent was added dropwise at room temp to a solution of X in acetone till the chromic acid colour persisted. The mixture was kept for 30 min at room temp, diluted with water (50 ml) and extracted with ether. Ether extract on working up furnished IX (107 mg), b.p. 140–150° bath/0·1 mm, $[\alpha_D]$ −50° (*c*, 8·71; chf). (Found: C, 76·47; H, 9·44. $C_{15}H_{22}O_2$ requires: C, 76·88; H, 9·46%.)

IR spectrum (liquid film). Prominent band at 1689 cm^{-1} ($\diagup$C—O in conjugation). Other bands were observed at: 2941, 1462, 1384, 1285, 1263, 1199, 1176, 1160, 1139, 1094, 1029, 1010, 980, 961, 925, 885, 869, 840, 819 and 735 cm^{-1}.

UV spectrum. λ_{max} 227 mμ (ϵ 9100).

NMR spectrum. Doublet at 8·98 τ (3H, CH_3 at C_{11}), singlet at 8·96 τ (3H, CH_3 at C_{10}), doublet at 8·72 τ (3H, CH_3 attached to C_4), multiplet centred at 6·65 τ (2H, —O—CH_2), triplet at 6·02 τ (1H, H attached to C_6) and quadruplets centred at 4·27 and 3·53 τ (2H, H attached to C_3 and C_5 respectively).

Tauremisin (I). Ketone IX (473 mg) in glacial AcOH (10 ml) was heated on water bath with chromic acid (453 mg) for 10 min cooled, diluted with water (50 ml) and extracted with ether. Ether layer was washed with water, dried and evaporated. Residue obtained was heated on water bath with 10% alcoholic KOH (15 ml) for 3 hr cooled, diluted with water, and extracted with ether to remove the neutral components. Alkaline layer was acidified with dil HCl and extracted with ether. Ether extract furnished a mixture of XI and II (52 mg). This mixture was dissolved in chf (5 ml) and subjected for epoxidation with perbenzoic acid (1·2N, 1 ml). The chf soln was allowed to stand overnight at 10–15°, washed with 5% Na_2CO_3aq, water, dried and evaporated. The residue was dissolved in t-butanol (2 ml) and was refluxed for 1 hr with 10% Na_2CO_3aq (6 ml) in N atm cooled, diluted with water and extracted with ether. The ether extract furnished a residue (25 mg). Preparative TLC of this material, with AcOEt–benzene (1:3) as eluent furnished I (2·5 mg) m.p. 164–167°. A mixed m.p. with an authentic sample was 165–167°. IR spectrum (chf, 0·05 mm) was identical with the authentic sample.

1-*Oxo*-5,7α(H),4,6,11β(H)-*eudesman*-6:13 *oxide* (XIII)

Compound IX (70 mg) was hydrogenated with 10% Pd–C (15 mg) in EtOH (5 ml) till the H absorption ceased. The reaction product after working up furnished XIII (56 mg) b.p. 140–145° bath/0·5 mm, $[\alpha]_D$ −6° (*c*, 5; chf). (Found: C, 76·25; H, 10·68. $C_{15}H_{24}O_2$ requires: C, 76·22; H, 10·24%.)

IR spectrum (liquid film). IR bands were observed at: 1720 ($\diagup$C—O), 1480, 1390, 1330, 1266, 1165, 1140, 1036, 1015, 980, 965, 990, 840 and 760 cm^{-1}.

1-*Oxo*-5,7α(H),4,6,11β(H)-*eudesman*-6:13 *olide* (XIV)

Method (a). Ketone XIII (600 mg) in glacial AcOH (20 ml) was oxidized with chromic acid (700 mg) following the procedure for IX. The product (150 mg) was chromatographed over alumina (grade III, 5 g) and the fraction eluted with pet. ether–benzene (1 : 1; 50 ml) and furnished XIV

• The authors thank Prof. W. Klyne for supplying the O.R.D. data.

(90 mg), which on recrystallization from dil EtOH had m.p. 117–119°, $[\alpha]_D$ +31° (*c*, 2·6; chf). (Found: C, 71·85; H, 8·95. $C_{15}H_{22}O_3$ requires: C, 71·97; H, 8·86%.)

IR spectrum (Nujol). IR bands were observed at: 1785 (lactone), 1720 (>C=O) 1480, 1390, 1266, 1200, 1170, 1130, 1100, 1020, 1000 and 900 cm^{-1}.

Method (b). A soln of XVI[10,4] (216 mg) and $Na_2Cr_2O_7$ (470 mg) in AcOH (7 ml) was heated at 100° for 6 hr. Excess of $Na_2Cr_2O_7$ was decomposed by adding EtOH (0·25 ml) to the hot soln which was then diluted with hot water. The mixture was cooled, extracted with ether and the extract furnished mixture of XI and II (72 mg).

The above mixture of ketones (65 mg) was subjected to hydrogenation with Pd-C catalyst and acetone as solvent, till the absorption of H ceased. After evaporation of the acetone, the residue was chromatographed over alumina (grade I 4 g). The fraction eluted with pet. ether–benzene (1:1; 30 ml) furnished XIV (9 mg), which on recrystallization from EtOH and sublimation *in vacuo* had m.p. 113–115°. (Found: C, 71·60; H, 8·84. $C_{15}H_{22}O_3$ requires: C, 71·97, H, 8·86%.) The IR spectrum of the ketolactone prepared by method (b) was identical with that of the sample prepared by the method (a).

1α,2α-*Oxido*-3-*oxo*-5,7α(H),1,2,4,6,11β(H)-*eudesman*-6:13 *olide* (VI)

Compound IV[15] (660 mg) was dissolved in dioxan (35 ml) and H_2O_2 (2·5 ml) and 1N NaOH (7 ml) was added one after the other at room temp. The mixture was left overnight at room temp, diluted with water and extracted with ether. Ether extract on working up furnished VI (490 mg) m.p. 112–118°. After recrystallization from EtOH and sublimation *in vacuo* it had m.p. 124–127°. (Found: C, 68·19; H, 7·70. $C_{15}H_{20}O_4$ requires: C, 68·16; H, 7·63%), $[\alpha]_D$ +120° (*c*, 1·5).

IR spectrum (Nujol). Bands at: 1780 (γ-lactone), 1720 (>C=O), 1480, 1420, 1390, 1338, 1290, 1280, 1225, 1218, 1210, 1165, 1125, 1110, 1070, 1033, 1013, 998, 968, 950, 934, 887, 877, 860, 840, 823, 802, 738 and 690 cm^{-1}.

NMR spectrum. Singlet at 9·02 τ (CH_3 at C_{10}), doublet at 8·81 τ (CH_3 at C_{11}), doublet at 8·70 τ (CH_3 at C_4) and signal at 6·77 τ (C_1 and C_5—H).

Optical rotatory dispersion. $[\phi]^{MeOH}_{333m\mu}$ +3140 (first extremum), $[\phi]^{MeOH}_{310}$ −3280 (second extremum).

Oxide (XVIII)

Method (a) *from saussurea lactone* (XVII). Saussurea lactone,[13] m.p. 139–141°, $[\alpha]_D$ +60° (700 mg), was reduced with LAH (300 mg), following the standard procedure. The diol XXIII (650 mg), b.p. 160–170 (bath)/2 mm, $[\alpha]_D$ −13° (*c*, 17; chf), was refluxed with dry benzene (50 ml) and *p*-toluenesulfonic acid (100 mg) for ½ hr on a water bath. The reaction product was chromatographed over alumina (gr. II; 30 g); pet. ether (150 ml) eluted a fraction (340 mg) which on distillation over Na furnished XVIII, b.p. 130–140° (bath)/1·5 mm, n_D 1·4852; $[\alpha]_D$ −17° (*c*, 1·7; chf). (Found: C, 81·2; H, 11·2. $C_{15}H_{24}O$ requires: C, 81·76; H, 10·98%.)

IR spectrum (liquid film); showed prominent bands at: 3030, 1626, 1449, 1399, 1361, 1205, 1163, 1075, 1026, 990, 960, 909, 885 and 833 cm^{-1}.

Method (b) *from ditosylate* (XXI). To the soln of XXI[13] (890 mg) in dry acetone (30 ml) NaI (3 g), was added and the reaction mixture refluxed on a steam bath in the absence of light, for 5 hr. After removal of the acetone on a steam bath, it was cooled, diluted with water (75 ml) and extracted with ether (15 × 3 ml). The ether layer was washed with water, dried and evaporated. The residue was chromatographed over alumina (gr. II; 30 g) and a fraction eluted with pet. ether–benzene (1:1; 150 ml), which on evaporation furnished XXII (540 mg), which was used without further purification.

The compound XXII (540 mg) was added to KtBD[14] soln (50 ml; ca. 0·7N), under a N atm. The reaction mixture was kept at room temp overnight, poured in ice cold water, and extracted with ether. The ether extract was washed with water, dilute acid, water, dried and the solvent evaporated. The residue was distilled twice over Na to furnish the reaction product (120 mg), b.p. 130–140° (bath)/1·5 mm which on the basis of VPC and IR spectrum was predominantly XVIII. Further purification was by preparative TLC on silica gel with benzene as the eluent. The IR spectrum and VPC analysis of XVIII were in good agreement with those of an authentic sample obtained by method (a).

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Chromic acid oxidation of the oxide (XVIII)

The oxide XVIII (86mg) in glacial AcOH (3 ml) was oxidized with chromic acid (80mg), dissolved in water (0·2 ml) and AcOH (3 ml). The mixture was heated on water bath for 10 min with occasional shaking, cooled and diluted with water (20 ml). Extraction with ether (10 × 3 ml) followed by washing with water, 10% Na_2CO_3aq, drying and evaporation of the solvent furnished the oxidation product, which was heated under reflux with alcoholic KOH (10 ml; 5%) for 3 hr. After removing the alcohol the residue was diluted with water (25 ml). The aqueous alkaline soln was extracted with ether to remove the neutral components and the aqueous soln was acidified to congo red. The acidified soln was extracted with ether (10 × 2 ml). Ether layer was washed with water, dried and evaporated. The residue was purified by sublimation to give XVII (13 mg), m.p. 143°, mixed m.p. with authentic sample 145°. IR spectrum was superimposable upon the IR spectrum of an authentic sample.