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SESQUITERPENE LACTONES OF ARTEMISIA SPECIES. IV. DOUGLANINE FROM ARTEMISIA DOUGLASIANA BESS.

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Artemisia douglasiana Bess. (fam. Compositae, Sec. Abrotanum) contains, in addition to arglanine (I),[2] a second sesquiterpene lactone, douglanine (II). Douglanine, m.p. 115-117°, $[\alpha]_D^{24}$ + 133°, obtained in 0.06% yield from the dried aerial parts of the spring plant,[2] has the composition $C_{15}H_{20}O_3$. Its infrared and ultraviolet spectra show the characteristic features associated with the presence of the α-methylene-γ-lactone grouping, a structural unit commonly found in the lactones of the Compositae. The n.m.r. spectrum confirms this: it shows the highly characteristic pair of one-proton doublets (δ 5.4 and 6.1, J = 3 cps) for the exocyclic methylene group, and, in addition, shows signals at 5.3 (1 H, $=$CH); 1.9 (3 H, singlet, $=\overset{|}{C}-CH_3$); 0.83 (3 H, singlet, $-\overset{|}{\underset{|}{C}}-CH_3$); 3.9 (J = 11 cps) (1 H, triplet, lactone $-\overset{|}{\underset{|}{C}}H-O$), and 3.4 (1 H, multiplet, $-\overset{|}{\underline{C}}HOH$). Douglanine yields an acetate (III), m.p. 146-147°, showing that the third oxygen is in a secondary hydroxyl group, a conclusion substantiated by the smooth oxidation of douglanine to a ketone (IV), m.p. 119-120°, $C_{15}H_{18}O_3$. The ketone shows absorption in the infrared at 1712 cm^{-1} and only end absorption in the ultraviolet (λ_{max} below 220 mμ, ε 11700). The n.m.r. spectrum of the ketone shows the vinyl hydrogen (at 5.4 ppm in II) displaced only slightly downfield. These data indicate that douglanine is not the 2-hydroxy-3-ene and are in accord with the structure II. Further evidence that the 1-hydroxy-3-ene system is present in douglanine is that the C-1 proton (of CHOH) is found at δ = 3.4 ppm (and at 4.68 in the acetate) rather than at the lower field that would be expected for the

2-hydroxy-3-ene structure.

Reduction of the ketone (IV) with sodium borohydride (at 0° for 20 minutes gave two products which showed nearly the same R_f on thin-layer chromatograms and which could be separated by chromatography. One of these, obtained in minor amount, was douglanine; the major product was identical with santamarine (V)[3,4] by mixed melting point and the complete correspondence of their IR spectra. This observation is in accord with the fact that the structure of douglanine, as deduced from spectral and chemical information, is the same in its gross features as santamarine, and shows that the two compounds differ only in the configuration of the C-1 hydroxyl group. The stereochemistry of santamarine has been established by its conversion into santanolide C[3] and by the fact that the ketone formed by oxidation of tetrahydrosantamarine is reduced catalytically to regenerate the alcohol (thus presumably 1-βOH, equatorial) from which it was obtained. If santamarine is indeed the 1-βOH compound, douglanine has the 1-αOH configuration. This conclusion, while probably correct,* is not rigorous and needs final substantiation. Experiments are in progress to prepare a derivative of douglanine suitable for X-ray analysis.

The stereochemistry of douglanine at all of the other centers of asymmetry was confirmed as follows. Catalytic hydrogenation of douglanine yielded two tetrahydro compounds, VI and VII, epimeric at C-4.[5] One of these, m.p. 109-110°, $[\alpha]_D^{28}$ + 72°, upon oxidation with chromic acid gave a compound, (VIII) m.p. 196-198°, $[\alpha]_D^{28}$ + 69°, which was identical (mixed m.p., t.l.c.) with dihydrodeoxyvulgarin, reported[6] m.p. 198-200°, $[\alpha]_D^{27}$ + 74° (also reported[3] m.p. 194-196°, $[\alpha]_D$ + 72°, and m.p. 198°.[8])

Other transformation products of douglanine prepared in this study are XI, m.p. 133.5-134.5°, $[\alpha]_D^{28}$ + 70°, and its 1-epimer, X, m.p. 130-132.5°, $[\alpha]_D^{28}$ + 139°. Compound XI has been prepared from balchanin, with a reported[8] m.p. 132°. A compound to which structure XI was assigned has also been prepared by Romo de Vivar and Jimenez,[3] who report its m.p. as 124-125°.

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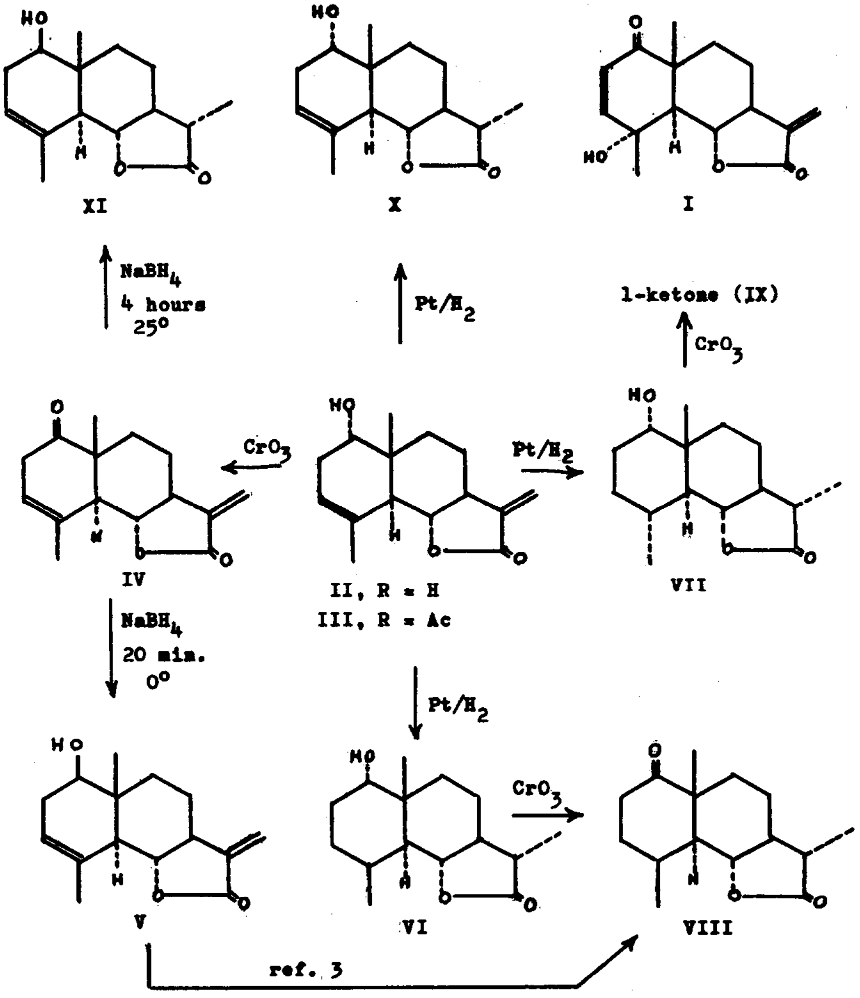
*Experiments in this Laboratory (with J. O. Knight) have shown that the catalytic reduction of pseudosantonin and of several 1-keto steroid and triterpenoid compounds gave principally the 1-βOH isomer; and Suchy[7] found that reduction of 1-ketosantan-5,12-olide (derived from balchanin) with Li $(tBuO)_3AlH$ gave the 1-βOH compound.


HO
HO
O
HO
H
H
H
XI
X
I
NaBH$_4$
4 hours
25°
Pt/H$_2$
1-ketone (IX)
CrO$_3$
O
HO
HO
CrO$_3$
Pt/H$_2$
H
H
H
IV
II, R = H
III, R = Ac
VII
NaBH$_4$
20 min.
0°
Pt/H$_2$
HO
HO
O
CrO$_3$
H
H
H
V
VI
VIII
ref. 3

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References

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4. We are grateful to Dr. Romo de Vivar for a comparison specimen of santamarine.
5. The values of $\delta_{CDCl_3} - \delta_{benzene}$ for the C-11 methyl groups of the 11,13-dihydro compounds prepared by catalytic hydrogenation show that all of these possess the C-11 (α-CH_3) configuration. See. C. R. Narayanan and N. K. Venkatasubramanian, Tetrahedron Letters, No. 47, 5865 (1966).
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Note: Acceptable analytical values and n.m.r. spectra consistent with all of the structural assignments were obtained for the compounds described. Optical rotations were measured in chloroform.