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CONSTITUENTS OF ZALUZANIA SPECIES—II
STRUCTURES OF ZALUZANIN C AND ZALUZANIN D

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Abstract· Zaluzanin C a constituent of *Zaluzania augusta* (Lag.) Schultz, Bip. and *Z. triloba* Pers has been shown to be a guaianolide with structure Ia. Zaluzanin D another constituent of *Z. triloba* was identified as acetylzaluzanin C (Ib). The eudesmanolide ivalin (XI) was also isolated from *Z. triloba*.

IN OUR previous paper[2] we described the isolation and structure proofs of zaluzanins A (IIa) and B (IIb), constituents of *Zaluzania augusta* (Lag.) Schultz, Bip. We now wish to report the results which led to the structures of two new guaianolides, zaluzanin C and zaluzanin D.

Zaluzanin C (Ia) was isolated from *Z. augusta* and is also a consituent of *Z. triloba* Pers a bitter herb widely distributed in the high plateau of Mexico.

Zaluzanin C (Ia) ($C_{15}H_{18}O_3$) m.p. 95–96°, $[\alpha]_D$ +37° contains a free OH group (IR bands at 3665 and 3595 cm^{-1}) and is readily acetylated and oxidized to a ketone III. The OH group of zaluzanin C (Ia) is therefore secondary. The remaining oxygens are present as part of a 5-membered lactone (IR band at 1760 cm^{-1}). Zaluzanin C (Ia) possesses three exocyclic methylene groups, one of them conjugated with the γ-lactone carbonyl as shown by the following facts. Ia exhibits a UV maximum at 207 mμ (ε, 12400) and has IR bands at 1658, 1635, 1595, 938 and 900 cm^{-1} (C=C double bonds).

Reduction of Zaluzanin C (Ia) with aluminium amalgam yielded a dihydroderivative (IVa) which does not show high absorption at 207 mμ in the UV spectrum. Its IR spectrum has bands at 3675 and 3590 cm^{-1} (OH group), at 1765 cm^{-1} (γ-lactone), at 1640 and 900 cm^{-1} (C=C double bonds). Pyridine–acetic anhydride acetylation of IVa afforded dihydrozaluzanin acetate (IVb).

The NMR spectrum[3] of zaluzanin C (Ia) has the characteristic two low field doublets (J = 3 c/s) at 6·21 and 5·52 corresponding to the hydrogens of an exocyclic methylene conjugated with the γ-lactone. Two singlets at 5·02 and 4·96 are attributed to the hydrogens of the exocyclic methylene group attached to C-10. The signals of the exocyclic methylene bonded at C-4 indicate allylic coupling since they are observed as a pair of triplets (J = 1 c/s) partially superimposed at 5·42 and 5·34. The hydrogen on the carbon bearing the ethereal oxygen of the lactone is responsible for a triplet (J = 9 c/s) centered at 4·14 which remains stationary in the NMR spectra of Ib,

[1] Contribution No. 241 from the Instituto de Química de la Universidad Nacional Autónoma de México.
[2] Previous paper, J. Romo, A. Romo de Vivar and P. Joseph-Nathan, *Tetrahedron* **22**, 29 (1966).
[3] The NMR spectra were determined by Mr. Eduardo Díaz on a Varian A-60A spectrometer, in $CDCl_3$ soln using TMS as internal reference. All chemical shifts are reported in ppm as δ values (c s 60).

III, and the dihydroderivatives IVa, IVb and V. The NMR spectrum of dihydrozaluzanin C (IVa) does not show the low field doublets of the exocyclic methylene protons of Ia, a doublet (J = 7 c/s) centered at 1·22 corresponds to a secondary Me group.

The fact that the NMR spectrum of Ia does not show Me peaks and the similarity of the IR spectrum of dihydrozaluzanin C (IVa) with that of 11-dihydrodehydrocostus lactone[4] suggests that zaluzanin C(Ia) belongs to the guaianolide series. Furthermore the chemical shift and the multiplicity of the signal corresponding to the hydrogen on the carbon bearing the lactone closure in the NMR spectrum of Ia, indicates that the lactone ring is closed toward C-6.[5] As is well known a lactone closure at C-8 produces a more complex signal.[6,7] The above assumptions were confirmed when LAH reduction of the mother liquors of IVa followed by Pd-C dehydrogenation furnished in relatively good yield chamazulene (VI) and artemazulene (VII) characterized as their TNB adducts.

Position at C-3 for the OH group of Ia can be selected on the following basis. The NMR signal of the proton on the carbon bearing the OH group of Ia is spin coupled to two hydrogens and appears as a triplet (J = 7 c/s) centered at 4·58 with smaller doubling, indicating allylic coupling with the protons of the exocyclic methylene group attached to C-4. It is observed at lower field in the NMR spectrum of the acetate Ib. The UV spectrum of dehydrozaluzanin C(III) (λ_{max} 217 mμ, ε 14,600) corresponds to two chromophores, the α,β-unsaturated lactone and an exocyclic methylene group conjugated with a ketone. In dehydrodihydrozaluzanin C (V) obtained by chromium trioxide oxidation of IVa which only possesses the α,β-unsaturated ketone chromophore, the UV maximum appears at 226 mμ (ε 8200). The IR spectra of the ketones III and V indicate that the ketonic groups are found as substituents in 5-membered rings. Dehydrozaluzanin C (III) has a band at 1720 cm^{-1} and dehydrodihydrozaluzanin C (V) at 1725 cm^{-1}. In the NMR spectrum of III, the exocyclic methylene group conjugated with the lactone is responsible for a pair of low field doublets centered at 6·27 and 5·60. The exocyclic methylene group attached at C-4 exhibits doublets (J = 1 c/s) at 6·22 and 5·83. Two singlets at 4·94 and 4·59 correspond to the exocyclic methylene linked at C-10. Two doublets (J = 1 c/s) at 6·23 and 5·78 and two singlets at 4·95 and 4·59 observed in the NMR spectrum of the ketone V correspond to four vinylic protons. A doublet centered at 1·30 is assigned to a secondary Me group.

As a preliminary approach to correlate zaluzanin C (Ia) with estafiatin (VIII)[8] the latter was treated with acetic acid. Attempts to dehydrate the resulting monoacetate (IX) were unsatisfactory. However, PtO_2 catalyzed hydrogenation of V under acid conditions afforded tetrahydroestafiatone (X)[8] of known structure and stereochemistry at C-1, C-4, C-5, C-6, C-7 and C-11.[8] Treatment of dehydrozaluzanin C (III) with toluenethiol in the presence of piperidine and desulfurization of the inter-

[4] S. B. Mathur, S. V. Hiremath, G. H. Kulkarni, G. R. Kelkar and S. C. Bhatacharyya and in part by D. Simonovic and A. S. Rao, *Tetrahedron* **21**, 3575 (1965).

[5] In estafiatin VIII correlated with isophoto-α-santonic lactone (Ref. 8) the signal of the proton at C-6 appears as a pair of doblets (J = 8 c s) centered at 4·17 and 4·00 (see below).

[6] W. Herz, A. Rohde, K. Rabindran and N. Viswanathan, *J. Am. Chem. Soc.* **84**, 3857 (1962).

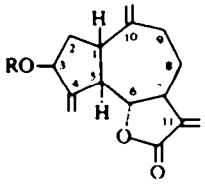
[7] E. Diaz, P. Joseph-Nathan, A. Romo de Vivar y J. Romo, *Bol. Inst. Quim. Univ. Nal. Auton. Mex.* XVII, 122 (1965).

[8] F. Sánchez-Viesca and J. Romo, *Tetrahedron* **19**, 1285 (1963).

mediary adduct followed by hydrogenation also afforded the ketolactone X. Therefore zaluzanin C possesses structure Ia with the asymmetric centers 1, 5, 6 and 7 as in estafiatin (VIII).

Zaluzanin D ($C_{17}H_{20}O_4$) m.p. 103–104°, $[\alpha]_D$ ±0° (λ_{max} 202 mμ 10,200) is a minor constituent of *Z. triloba*. It has IR bands at 1760 cm^{-1} (γ-lactone), at 1730 cm^{-1} (acetyl group), weak bands at 1660, 1640, 1600, 940 and 900 cm^{-1} (C=C double bonds). Zaluzanin D was identified with acetylzaluzanin C (Ib).

A lactone m.p. 133–134°, isolated also from *Z. triloba* was identified with the eudesmanolide ivalin (XI)[9,10] previously found as a constituent of *Iva imbricata* Walt and *I. microcephala* Nutt. The isolation of ivalin (XI) from *Zaluzania* species suggest a close relationship between genera *zaluzania* and *Iva*. Recently Herz *et al.*[11] isolated from *Iva axillaris* Pursh var. robustior three guaianolides whose structures are very similar to those of zaluzanin A (IIa) and zaluzanin B (IIIb)[2]. These findings are also in accord with the above suggestion.



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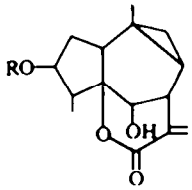
b, R = Ac



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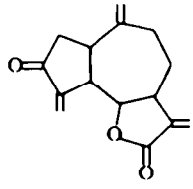

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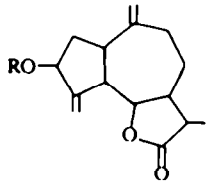

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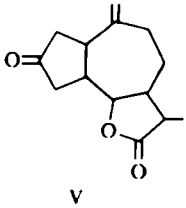
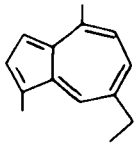
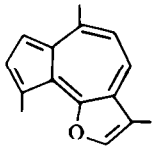
b, R = Ac



V



VI



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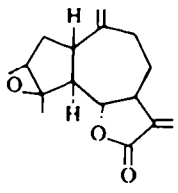
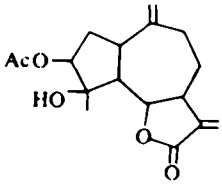
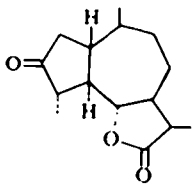


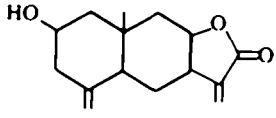
VIII



IX



X



XI

[9] W. Herz and G. Högenauer, *J. Org. Chem.* **27**, 905 (1962).
[10] We are indebted to Dr. Werner Herz for a sample of ivalin.
[11] W. Herz, V. Sudarsanam and J. J. Schmid, *J. Org. Chem.* **31**, 3232 (1966).

EXPERIMENTAL[12]

Isolation of the lactones. Zaluzania triloba Pers was collected in October (1965) in the Valley of Mezquital (Estado de Hidalgo).[13] The dried plant (6k) was extracted with EtOH (18 l.) for 20 hr under reflux. The extract was filtered and concentrated to 3 l. and treated with a soln of lead acetate (60 g) in water (3 l.), left at room temp overnight, filtered, diluted with water (3 l.) and extracted twice with $CHCl_3$. The extract was evaporated to dryness and the residue (55 g) dissolved in benzene was chromatographed on alumina (1·5 k). Some fractions eluted with benzene crystallized. They were combined and recrystallized from AcOEt isopropyl ether yielding 205 mg of zaluzanin D (Ib), m.p. 103 104°, $[\alpha]_D \pm 0°$; λ_{max} 202 mμ; ε 10,200; IR bands at 1760 cm^{-1} (γ-lactone), at 1730 cm^{-1} (acetyl group), at 1660, 1640, 1600, 940 and 900 cm^{-1} (C=C double bonds). (Found: C, 70·97; H, 6·90; O, 22·14. Calc. for $C_{17}H_{20}O_4$: C, 70·81; H, 6·99; O, 22·20%.)

The crystalline fractions eluted with benzene – 5% AcOEt were crystallized from acetone–isopropyl ether. This yielded ivalin (XI) (2·315 g) m.p. 133–134°; $[\alpha]_D$ +144°. Mixed m.p. determination with an authentic specimen showed no depression and the IR spectra are identical.

The crystalline fractions eluted with AcOEt afforded 1·325 g of zaluzanin C (Ia), m.p. 95 96° (small prisms from acetone–isopropyl ether), $[\alpha]_D$ +37°; λ_{max} 207 mμ; ε 12,400; IR bands at 3665 and 3595 cm^{-1} (hydroxyl group), at 1760 cm^{-1} (γ-lactone), at 1658, 1635, 1595, 938 and 900 cm^{-1} (C=C double bonds). (Found: C, 72·87; H, 7·33; O, 19·42. Calc. for $C_{15}H_{18}O_3$: C, 73·15; H, 7·37; O, 19·48%.)

From the less polar fractions of the chromatogram of the extract of *Zaluzania augusta*[2], 2·25 g of zaluzanin C (Ia), m.p. 94 95° were obtained.

Zaluzanin C acetate (Ib). Acetylation of Ia with Ac_2O–pyridine for 1 hr on a steam bath furnished Ib, m.p. 103–104°. Mixed m.p. determination with Ib showed no depression and the IR spectra are identical.

Dehydrozaluzanin C (III). A soln of Ia (300 mg) in acetone (25 ml) was oxidized with 8N CrO_3 at 5° (Ref. 2) until the persistence of an orange colour, after 3 min the soln was diluted with AcOEt, washed with water, $NaHCO_3$ aq, dried over Na_2SO_4 and evaporated to dryness. Crystallization of the residue from acetone–hexane afforded 175 mg of III, m.p. 134 135°; $[\alpha]_D$ +160°; λ_{max} 217 mμ; ε 14,600. IR bands at 1760 cm^{-1} (γ-lactone), at 1720 cm^{-1} (α,β-unsaturated cyclopentanone), at 1658, 1634, 900 and 887 cm^{-1} (C=C double bonds). (Found: C, 73·66; H, 6·69; O, 19·72. Calc. for $C_{15}H_{16}O_3$: C, 73·75; H, 6·60; O, 19·65%.)

Dihydrozaluzanin C (IVa). To a soln of Ia (1·5 g) in EtOH (120 ml) aluminium amalgam (freshly prepared, 4 g) was added. The mixture was refluxed for 8 hr, filtered and evaporated to dryness. Crystallization from ether–hexane yielded 610 mg of IV a, m.p. 99 100°. Further crystallizations from acetone–isopropyl ether raised the m.p. to 107–108°, $[\alpha]_D$ +45·3°; IR bands at 3675 and 3590 cm^{-1} (OH group), at 1765 cm^{-1} (γ-lactone), at 1639 and 900 cm^{-1} (C=C double bonds). (Found: C, 72·28; H, 8·20; O, 19·51. Calc. for $C_{15}H_{20}O_3$: C, 72·55; H, 8·12; O, 19·33%.)

Further reduction of the mother liquors with aluminium amalgam afforded 340 mg of IVa, m.p. 100–103°.

Dihydrozaluzanin C acetate (IV b). Acetylation of IV a with Ac_2O–pyridine for 1 hr on a steam bath furnished IV b, m.p. 132° (prisms from ether–hexane), $[\alpha]_D$ +8°; IR bands at 1775 cm^{-1} (γ-lactone), at 1740 cm^{-1} (acetyl group), at 1650 and 910 cm^{-1} (C=C double bonds). (Found: C, 70·12; H, 7·55; O, 22·31. Calc. for $C_{17}H_{22}O_4$: C, 70·32; H, 7·64; O, 22·04%.)

Dehydrodihydrozaluzanin C (V). Oxidation of IVa (350 mg) with CrO_3 as described for III, yielded 105 mg of V, m.p. 107° (small needles from acetone–isopropyl ether), $[\alpha]_D$ +162·7°; λ_{max} 226 mμ; ε 8200; IR bands at 1772 cm^{-1} (γ-lactone) at 1728 cm^{-1} (α,β-unsaturated cyclopentanone), at 1640 and 910 cm^{-1} (C=C double bonds). (Found: C, 72·95; H, 7·24; O, 19·43. Calc. for $C_{15}H_{18}O_3$: C, 73·15; H, 7·37; O, 19·48%.)

Aromatization of dihydrozaluzanin C (IVa). The mother liquors of IVa (1·3 g) were reduced with LAH (2 g) in the THF (80 ml). The mixture was refluxed for 6 hr and the excess of THF was decomposed with AcOEt and water (5 ml). The soln was filtered, washed with AcOEt and evaporated to dryness. The residue with Nujol (10 ml) and 5% Pd–C (1·5 g) was heated at 300° for 30 min. The mixture was diluted with hexane, filtered and chromatographed on alumina (100 g). The Nujol eluted in the less polar fractions was discarded. Chamazulene was obtained in the next fractions eluted with hexane. Its TNB adduct was prepared. Several

[12] M.ps are uncorrected. Analyses by Dr. Franz Pascher, Bonn, Germany. IR spectra and rotations were run in $CHCl_3$, UV spectra in 95% EtOH. The alumina used in the chromatograms was Alcoa F-20 (washed with AcOEt). We are grateful to Syntex, S.A. for the determination of the rotations.

[13] We are grateful to Dr. Arturo Gómez-Pompa of the Instituto de Biología (U.N.A.M.) for the identification of *Z. triloba*. Voucher Number AR No. 7 Herbario Nacional de la U.N.A.M. (MEXU).

crystallizations from MeOH afforded brownish-black needles (5 mg), m.p. 130° undepressed in m.p. with an authentic specimen.

From the polar fractions eluted with benzene–hexane 1:3, 1:2 and 1:1 artemazulene was obtained. Its TNB adduct (25 mg) showed m.p. 176–180°. Further crystallizations from MeOH raised the m.p. to 189°. It was identified with an authentic sample by the standard methods.

Treatment of estafiatin (VIII *with* AcOH. A soln of VIII (100 mg) in AcOH (5 ml) was refluxed for 2 hr, diluted with water and extracted with AcOEt. The organic layer was washed with water, $NaHCO_3$ aq, dried over Na_2SO_4 and evaporated to dryness. Crystallization from ether–hexane afforded IX as needles (60 mg), m.p. 137–139°; $[\alpha]_D$ −16·77°; λ_{max} 214 mμ; ε, 9500; IR bands at 3560 cm^{-1} (OH group), at 1770 cm^{-1} (γ-lactone), at 1725 cm^{-1} (acetyl group) and weak bands at 1670, 1645, 897 and 870 cm^{-1} (C=C double bonds). (Found: C, 66·65; H, 7·21; O, 25·93. Calc. for $C_{17}H_{22}O_5$: C, 66·65; H, 7·24; O, 26·11%.)

Dehydrohexahydrozaluzanin C (X) *from* V. A soln of V (200 mg) in AcOH (20 ml) was hydrogenated with PtO_2 (80 mg) until no more H_2 was absorbed. The soln was filtered and evaporated to dryness *in vacuo*. Crystallizations from acetone–hexane and acetone–ether yielded prisms (60 mg), m.p. 195–197°. It showed no depression in mixed m.p. determination with X.[9] The IR spectra are identical.

Dehydrohexahydrozaluzanin C (X) *from* III. To a soln of III (200 mg) in benzene (30 ml) toluenethiol (2 ml) and piperidine (2 ml) was added. The mixture was refluxed for 6 hr, washed with dil HCl, water and evaporated to dryness. The oily residue was dissolved in EtOH (100 ml), treated with Raney Ni (8 g), heated under reflux for 20 hr, filtered and evaporated to dryness. The gummy residue was hydrogenated in AcOH (20 ml) with PtO_2 (40 mg) until the uptake of H_2 ceased. Crystallization from acetone–hexane furnished VIII (20 mg), m.p. 192–195°. Identified with tetrahydroestafiatone by the standard methods.