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SHORT COMMUNICATION

SESQUITERPENE LACTONES AND FLAVONES OF *IVA FRUTESCENS**

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Abstract—Extraction of *Iva frutescens* L. ssp. *frutescens* gave a new germacranolide frutescin, whose structure was established, and the flavone centaureidin (5,7,3′-trihydroxy-3,6,4′-trimethoxy-flavone). *Iva frutescens* L. ssp. *oraria* (Bartlett) Jackson furnished pectolinarigenin (5,7-dihydroxy-6,4′-dimethoxyflavone) and hispidulin (6-methoxy-5,7,4′-trihydroxyflavone).

TWO DISTINCT subspecies of *Iva frutescens* L., a shrubby perennial endemic to the East and Gulf coast of the U.S., have been recognized by Jackson.[1] In the present communication we report our work on their constituents.

Collections of subspecies *frutescens* found in the coastal area, generally in salt marshes, from Virginia to Florida and Texas yielded centaureidin (5,7,3′-trihydroxy-3,6,4′-trimethoxy-flavone) and a new sesquiterpene lactone frutescin, whose structure was shown to be IVa.

TABLE 1. NMR SIGNALS OF FRUTESCIN (IVa) AND FRUTESCIN EPOXIDE (V)*

Compound	H-1	H-5	H-7	H-8	H-13a	H-13b	H-14	H-15	Misc.
IV ($CDCl_3$)	6·66 tbr (8·0)	5·05 ddbr (10·0, 6·0)	†	3·93 ddd (4·0, 7·0, 7·5)	5·52 d (2·8)	6·18 d (3·0)	9·47 d (0·8)	1·69 d (1·0)	
IV (C_6D_6)	5·75 tbr (8·0)	4·46 ddbr (10·5, 6·0)	2·1 m	3·51 ddd (3·5, 6·5, 8·0)	4·88 d (3·0)	6·01 d (3·2)	9·21 d (1·0)	1·19 d (1·0)	2·68 ddbr (14·7, 3·5, H-9a)
V ($CDCl_3$)	6·69 tbr (8·0)	†	†	4·42 ddd (4·5, 7·5, 9·5)	5·64 d (2·5)	6·32 d (2·7)	9·49	1·35	2·05 ddbr (14·7, 6·5, H-9b)

* Run at 90 mHz on a Bruker NMR spectrometer, using TMS as internal standard. Unmarked signals are singlets, others are d, doublet; t, triplet; m, multiplet; br, slightly broadened singlet. Figures in parentheses are line separations or coupling constants in Hz.

† Obscured signal.

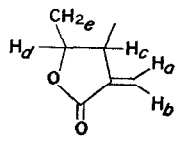
Frutescin, $C_{15}H_{18}O_3$ (mass spectrum), m.p. 158–160°, was a conjugated γ-lactone (IR band at 1770 cm^{-1}). The NMR spectrum (Table 1) exhibited the typical doublets of H_a and H_b of partial structure I at 6·18 and 5·52 and the multiplet of H_d (coupling indicative of an adjoining methylene group) at 3·93 ppm.[2] The presence of the α,β-unsaturated aldehyde structure II was evident from the IR (bands at 1685 and 1640 cm^{-1}) and the NMR spectrum. The latter exhibited H_f as a narrowly split doublet at 9·47 ppm and H_g as a somewhat broadened triplet at 6·66 ppm. The environment of H_d and H_g was confirmed by spin decoupling experiments (*vide infra*). Partial structure III was revealed by a three proton narrowly split doublet at 1·69 ppm (H_i) which was coupled to a narrowly split doublet of

* Part XII in the series "Constituents of Iva Species". For Part XI see W. HERZ and V. SUDARSANAM, *Phytochem.* **9**, 895 (1970).

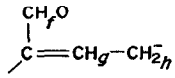
[1] R. C. JACKSON, *Univ. Kansas Sci. Bull.* **41**, 793 (1960).

[2] The H_c resonance was obscured, but could be detected by spin decoupling (*vide infra*).

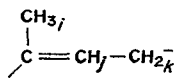
doublets (H_j) at 5·05 ppm. Epoxidation of frutescin converted the signal of H_i to a singlet at higher field (1·35 ppm) and caused disappearance of the H_j resonance.[3]



(I)

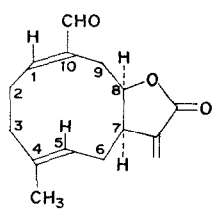


(II)

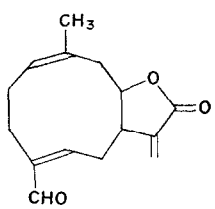


(III)

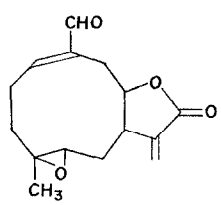
The empirical formula, the NMR spectrum and biogenetic considerations permitted the conclusion that frutescin could be represented by formula IVa or IVb. A decision in favor of IVa (aside from the stereochemistry) was reached by spin decoupling experiments in C_6D_6. Irradiation at the frequency corresponding to H-5 collapsed the vinyl methyl signal to a sharp singlet; conversely irradiation at the frequency of the vinyl methyl sharpened the doublet of doublets of H-5. Hence H-5 was adjacent to a methylene group. Irradiation at the frequency of H-8 collapsed two broadened doublets of doublets at 2·68 and 2·05 ppm (H-9a and H-9b) to doublets whose appearance (AB system, $|J| = 14{\cdot}7$) indicated that the protons responsible for them were gem-coupled.[4] Irradiation at the frequency of H-1 sharpened the broadened doublet of doublets of H-9a, but not that of H-9b; conversely, irradiation of H-9a sharpened the broadened triplet of H-1 (allylic coupling) and simplified H-8 to a doublet of doublets, but did not affect the signal of H-5. Irradiation at the frequency of H-9b collapsed the signal of the aldehyde proton, but did not affect H-1 or H-5. Since the methylene groups of A, B and C were thus shown to be different, and since H_{e1} of A was allyllically coupled to H_g of B and H_{e2} was coupled (W coupling?) to the aldehyde proton H_f, formula IVb was ruled out as a possibility for frutescin.



(IVa)



(IVb)



(V)

If the assumption be made that the absolute configuration of the C-7 side chain is as shown as in all sesquiterpene lactones of authenticated stereochemistry, the positive Cotton effect of the lactone n,π^* transition shows that the lactone fusion is *cis*.[5] This conclusion was supported by the magnitude of $J_{7,8}$ (8 Hz) and by the existence of a pronounced nuclear Overhauser effect (13%) between H-8 and the aldehydic proton (H-14) as required by the model. Irradiation of H-14 also produced a 15% enhancement in the signal strength of H-1, thus demonstrating that the C(10):C(1) double bond is *cis*. Irradiation at the frequency of the vinylic methyl group had no effect on the integrated intensity of H-5; hence the C(4):C(5) double bond is *trans*. This indicates that frutescin belongs to the new melampolide

[3] In the NMR spectrum of V, the resonance of the new epoxidic H_h proton was obscured by a multiplicity of other signals.

[4] Changes in the H-7 signal could not be followed since it was buried under the H-9a resonance.

[5] W. STÖCKLIN, T. G. WADDELL and T. A. GEISSMAN, *Tetrahedron* **26**, 2397 (1970).

subgroup[6] of germacradienolides (Δ^4 *trans*, $\Delta^{1(10)}$*cis*). It is also interesting to note that all sesquiterpene lactones previously isolated from *Iva* species were eudesmanolides, guaianolides or modified guaianolides.[7]

Chloroform extraction of a collection of *I. frutescens* subspecies *oraria* (Bartlett) Jackson which occurs in coastal areas north of Virginia gave as the only crystallizable components the flavones pectolinarigenin (5,7-dihydroxy-6,4′-dimethoxyflavone) and hispidulin (6-methoxy-5,7,4′-trihydroxyflavone). Since this collection was examined several years prior to the isolation of frutescin from ssp. *frutescens*, the absence of frutescin from ssp. *oraria* cannot be regarded as certain.

EXPERIMENTAL

M.ps were determined in capillaries and are uncorrected. IR spectra were run as KBr pellets; UV spectra in 95% EtOH; CD curves in MeOH on a Jasco ORD/UV-5 recording spectrophotometer, mass spectra on an MS-902 high resolution or a Nuclide 12-in medium resolution mass spectrometer at 70 meV. Analyses were by Dr. F. Pascher, Bonn, Germany.

Extraction of Iva frutescens *ssp.* frutescens. A collection of 9 kg of leaves, flowerheads and small stems, collected by Mr. R. Lazor in Franklin County, Florida on 20 September, 1969 (Lazor voucher 3844 on deposit in herbarium of Florida State University) was extracted with $CHCl_3$ in the usual manner.[8] The crude gum, wt. 35 g, was chromatographed over 600 g of silicic acid (Mallinckrodt, 100 mesh) 500 ml fractions being collected in the following order: benzene–$CHCl_3$ mixtures; 9:1 (fr. 1–15), 3:1 (fr. 16–30), 1:1 (fr. 31–45), 1:3 (fr. 46–60), and pure $CHCl_3$ (fr. 61–75), $CHCl_3$–MeOH mixtures; 97:3 (fr. 76–85), 19:1 (fr. 86–100), and 9:1 (fr. 101–110). Fractions 20–26 contained a major spot, were combined and allowed to crystallize. The solid was separated and repeatedly recrystallized from EtOAc-hexane, yield of frutescin 0·4 g, (MeOH, C, 0·22) m.p. 158–160°, IR bands at 1760, 1685 and 1640 cm^{-1}, γ_{max} 221 nm (ϵ 12 000), CD curve γ_{max} 313 and 247 nm (θ −1951 and −7900). (Found: C, 72·97; H, 7·40; O, 19·69; MW (mass spectrum) 246·1256. Calcd. for $C_{15}H_{18}O_3$: C, 73·15; H, 7·37; O, 19·49%; MW, 246·1255.)

Fractions 62–65 gave a flavone which was repeatedly recrystallized from MeOH. The yellow crystals, yield 0·20 g, m.p. 202–204°, were identified as centaureidin (m.p., m.m.p., IR, NMR, TLC) by comparison with an authentic sample.[9]

Frutescin epoxide (V). A solution of 95 mg of frutescin and 77 mg of *m*-chloroperbenzoic acid in 5 ml of $CHCl_3$ was left overnight at 0°. The mixture was diluted with $CHCl_3$, washed with $NaHCO_3$ and H_2O, dried and concentrated *in vacuo*. The residue was recrystallized from EtOAc–hexane, yield 60 mg, m.p. 188–191° (dec), IR bands at 1762, 1685 and 1640 cm^{-1}. (Found: C, 68·86; H, 6·8; O, 25·18; MW (low resolution mass spectrum) 262. Calcd. for $C_{15}H_{18}O_4$: C, 68·69; H, 6·92; O, 24·42%; MW 262).

Extraction of ssp. oraria. Extraction of 3·1 kg of dried leaves, flowerheads and small stems, collected by Dr. B. H. Braun on 6 October 1963 along U.S. 40 in the vicinity of Atlantic City, New Jersey, with $CHCl_3$ in the usual manner yielded 22 g of gum which was chromatographed over 210 g of silicic acid (400 ml fractions). Fractions 1–10 (benzene) eluted a small amount of oil, fractions 11–18 (benzene–$CHCl_3$, 3:1) eluted gums which showed several spots on TLC, fractions 19–24 (benzene–$CHCl_3$, 2:1) eluted a gum which partially solidified on trituration with Et_2O. Recrystallization from benzene gave 80 mg of a flavone, initial m.p. 206–208°, subsequently raised to 216–218° which was identified as pectolinarigenin (m.p., m.m.p., IR, NMR, TLC) by comparison with an authentic sample.[10]

[6] S. NEIDLE and D. ROGERS, *Chem. Commun.* in press (1971).
[7] W. HERZ, in *Pharmacognosy and Phytochemistry* (edited by H. WAGNER and L. HÖRHAMMER), pp. 64–92, Springer-Verlag, Berlin (1970).
[8] W. HERZ and G. HÖGENAUER, *J. Org. Chem.* **27**, 905 (1962).
[9] T. SAITOH, T. A. GEISSMAN, W. HERZ and S. V. BHAT, *Rev. Latinoamer. Quim.* **2**, 68 (1971).
[10] L. FARKAS, M. NOGRADI, V. SUDARSANAM and W. HERZ, *J. Org. Chem.* **31**, 3228 (1966).

Fractions 25–33 (benzene–$CHCl_3$ 1:1) and subsequent fractions (benzene–$CHCl_3$ 1:2, 1:3 and 1:4) gave gums which showed several spots on TLC, $CHCl_3$ eluted material which solidified on trituration with Et_2O. Recrystallization from MeOH–acetonitrile and MeOH furnished 0·12 g of a flavone, m.p. 290°, which was identified as hispidulin (m.p., m.m.p., IR, NMR and TLC) by comparison with an authentic sample.[11] $CHCl_3$–MeOH eluted gums.

[11] W. HERZ and Y. SUMI, *J. Org. Chem.* **29**, 3438 (1964).

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Key Word Index—Iva frutescens; Compositae; sesquiterpenoid lactones; germacranolides; 6-methoxy flavonoids; chemovars.