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CHEMICAL STUDIES ON MEXICAN PLANTS USED IN TRADITIONAL MEDICINE, XXI.[1] RATIBINOLIDE II, A NEW SESQUITERPENE LACTONE FROM *RATIBIDA LATIPALEARIS*

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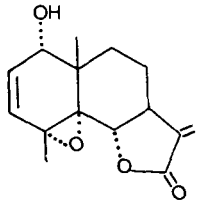
ABSTRACT.—Ratibinolide II [**1**], a new eudesmanolide, and the known flavanone hispidulin have been isolated from *Ratibida latipalearis*. The structure elucidation of the new compound was unequivocally established by spectral and X-ray crystallographic analyses.

The roots and leaves of *Ratibida latipalearis* Richards (Asteraceae) are used by the Tarahumara Indians for treatment of skin wounds, inflammations, and headaches. Recently, we reported the isolation of a novel bioactive geigeranolide, ratibinolide [**2**], from the MeOH/$CHCl_3$ extract of this plant, by guiding the fractionation with brine shrimp lethality (1). Continuning our search for other biologically active metabolites from this species, a new eudesmanolide, ratibinolide II [**1**], and the known flavone hispidulin were isolated. The present communication describes the structural elucidation of compound **1**.

Compound **1** was obtained as a white crystalline solid, and the molecular formula $C_{15}H_{18}O_4$ was indicated by eims. Nmr data were similar to those previously described for several eudesmanolides (2–4). In particular, the spectra demonstrated the trans disposition of the C-6/C-7 lactone (H-6 at δ 4.36, d, $J = 11.6$ Hz, which correlated in the 2D spectrum with H-7 at δ 2.94, ddd, $J = 11.6$, 3 Hz), and the presence of a C-4/C-5 epoxide (δ 71.63, s, C-4 and 61.99, s, C-5 in the ^{13}C-nmr), a disubstituted double bond (δ 6.28 and 5.98 in the ^{1}H nmr; δ 134.24, d, C-2 and 132.28, d, C-3 in the ^{13}C nmr) and a secondary hydroxyl group α-oriented at C-1 (δ 3.48, dd, $J = 11$, 5.8 Hz, H-1 and 2.4, d, $J = 11$ Hz, 1-OH, in the ^{1}H nmr; δ 72.63, d, C-1 in the ^{13}C nmr).

Consistent with the placement of the hydroxyl functionality at C-1 with an α disposition were the chemical shift exhibited by C-14 (δ 18.65) and the diamagnetic shift observed for C-9 (δ 29.80), the latter attributable to the γ gauche effect exerted by any



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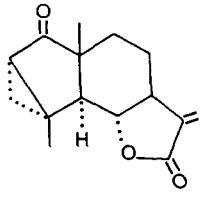

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[1]For Part XX, see R. Mata, V. Rodriguez, R. Pereda-Miranda, R. Bye, and E. Linares, *Phytochemistry* (in press).

substituent at C-1. This γ gauche effect is well documented in other related eudesmanolides (2–4). Finally, the similarity of the chemical shifts of H-7 and H-6 with those of 4,5-epoxydihydroarbusculin B was in good agreement with the α orientation of the epoxy moiety (5).

The structure and the relative stereochemistry of **1** were confirmed unequivocally by X-ray analysis of a crystal. A computer-generated perspective drawing of ratibinolide II is given in Figure 1. The B ring adopts a chair conformation with the C-14 methyl group in the axial position; the five-membered ring and the A ring exhibit a half chair conformation.

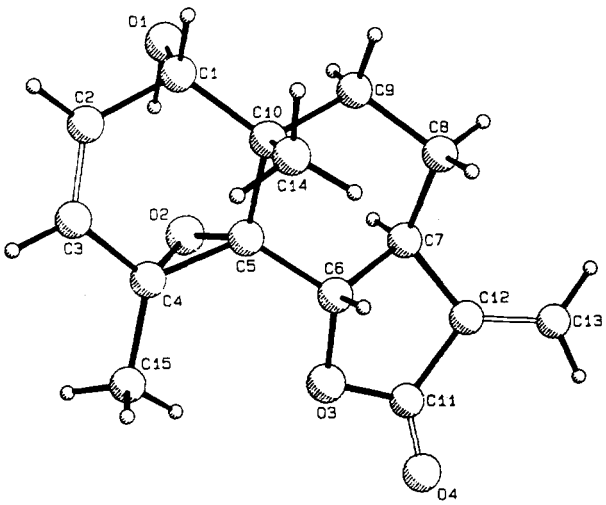


FIGURE 1. Stereoscopic view of ratibinolide II [**1**].

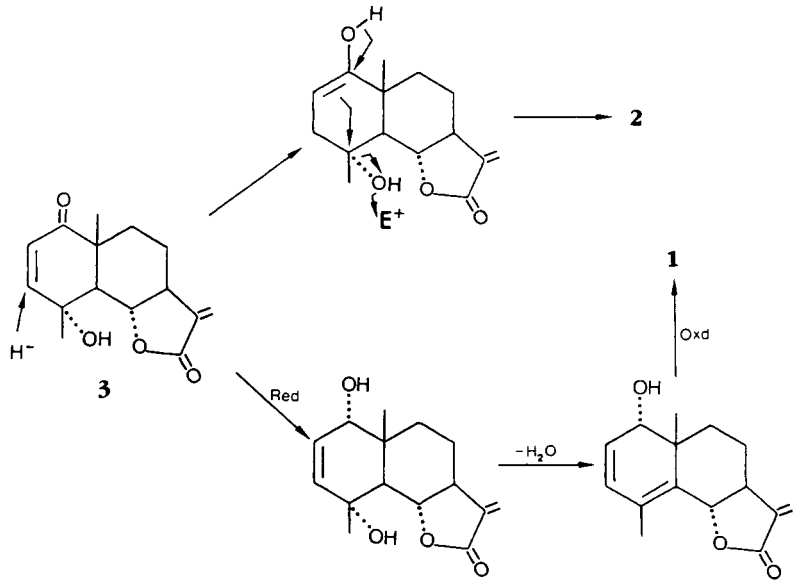
Properties of the flavanone isolated were in good agreement with those previously reported for hispidulin (6). Compound **1** showed moderate activity in the brine shrimp lethality test (7) (BS LC_{50} = 69.53 μg/ml). The coexistence of **1** and **2** suggests that the biogenesis of both compounds may proceed via a common intermediate such as arglanine [**3**] (2,8), as outlined in Scheme 1.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Ir spectra were obtained in KBr on a Perkin Elmer 599 B spectrophotometer; nmr spectra were recorded in a Varian VXR-300S apparatus in $CDCl_3$ solutions, using TMS as internal standard; optical rotations were measured with a JASCO DIP 360 digital polarimeter; eims were registered on a Hitachi-Perkin Elmer RMU-GD. Si gel 60 (70–230 mesh) Merck was used for cc; tlc was done on Si gel 60 GF 254 plates (Merck). X-ray data were collected on a Nicolet R 3m diffractometer with Ni filtered Cu-Kα radiation (λ = 1.54178 A).

EXTRACTION AND ISOLATION.—The plant material, extraction, and initial cc fractionation have been previously described (1). Active combined fractions 48–64 (300 mg) from the original column (1) (BS LC_{50} = 137.12 μg/ml), eluted with hexane-$CHCl_3$ (8:2), were rechromatographed on a Si gel (30 g) column [solvent hexane-Me_2CO (9:1)] to give ratibinolide II (5 mg). Inactive fractions 166–173 of the initial column, eluted with $CHCl_3$, were further column chromatographed on Si gel (350 g); elution was accomplished with $CHCl_3$ with increasing amounts of MeOH; from fractions eluted with $CHCl_3$-MeOH (97:3) crystallized hispidulin (80 mg).

RATIBINOLIDE II [**1**].—Mp 276–278°; $[\alpha]_D$ +155° (c = 1, $CHCl_3$); ir (KBr) 3500, 3040, 2925, 2850, 1770, 1630, 1230 cm^{-1}; ^1H nmr (δ) 6.28 (dd, J = 8.7, 5.8 Hz, H-2), 6.20 (d, J = 3 Hz, H-13), 5.98 (d, J = 8.7 Hz, H-3), 5.56 (d, J = 3 Hz, H-13′), 4.36 (d, J = 11.6 Hz, H-6), 3.48 (dd, J = 11, 5.8, H-1), 2.94 (ddd, J = 11.6, 4, H-7), 2.64 (m, H-9β), 2.40 (d, J = 11, OH-1), 2.28 (m, H-9α), 1.7 (ddd,



SCHEME 1. Biogenesis of ratibinolide [**2**] and ratibinolide II [**1**].

J = 14, 11.6 Hz, H-8β), 1.5 (m, H-8α), 1.76 (s, H-15), 0.96 (s, H-14); ^{13}C nmr (δ) 169.57 s, C-12), 137.81 (s, C-1), 134.24 (d, C-2), 132.28 (d, C-3), 118.93 (t, C-13), 77.28 (d, C-6), 72.63 (d, C-1), 71.63 (s, C-4), 61.99 (s, C-5), 45.87 (d, C-7), 39.67 (s, C-10), 29.80 (t, C-9), 22.03 (t, C-8), 21.54 (q, C-15), 18.65 (q, C-14); eims *m/z* (rel. int.) $[M]^+$ 262 (10).

HISPIDULIN.—Mp 291° [lit. (9) mp 291–292°]. Spectral data were identical to those previously described (6).

SINGLE CRYSTAL X-RAY ANALYSIS OF RATIBINOLIDE II[2].—Crystal data $C_{15}H_{18}O_4$, MW = 262.30, monoclinic, space group $P2_1$, β = 97.17 (3), a = 11.621 (3), b = 7.004 (2), c = 8.060 (3) Å, V = 650.8 (6) Å^3, Z = 2, D_c = 1.34 g/cm^3, Cu radiation, λ = 1.54178 A, μ(Cuα) = 7.52 cm^{-1}, F (000) = 280. The crystal had dimensions 0.20 × 0.50 × 0.30 mm and was mounted on a glass fiber. All reflections in the *hkl* 2 octant according to 3<2θ<110° with index range *h* − 12/12, *k* 0/7, *l* 0/8 were collected. The total number of the data collected was 984 of which 908 reflections have I>3σ (I), and these formed the basis of the structural solution and refinement. The crystal structure was solved by direct methods using the TEXSAN (10) structure analysis package and refined by full matrix least-squares techniques with anisotropic temperature factor for non-hydrogen atoms and with fixed isotropic temperature factor, 1.2 times B eq, for the hydrogen atoms bonded to carbon atoms. The final R value is 0.032 (Rw = 0.048). Final atomic coordinates are listed in Table 1.

BIOASSAY.—The test for lethality to brine shrimp larvae was performed as previously reported (7).

TABLE 1. Positional Parameters and B (eq) for Ratibinolide II.

Atom	*x*	*y*	*z*	B (eq)
O-1	0.1260 (2)	0.9190	0.9409 (3)	6.0 (1)
O-2	0.1967 (2)	0.8801 (5)	0.6234 (2)	4.09 (8)
O-3	0.3766 (1)	0.6772 (5)	0.4602 (2)	4.07 (9)
O-4	0.5402 (2)	0.6961 (5)	0.3429 (3)	5.0 (1)
C-1	0.1110 (3)	0.7201 (7)	0.9042 (4)	4.9 (1)
C-2	0.0064 (2)	0.6914 (7)	0.7762 (4)	4.9 (1)
C-3	0.0150 (2)	0.6913 (7)	0.6154 (4)	4.6 (1)

[2]Atomic coordinates for this structure have been deposited with the Cambridge Crystallographic Data Centre and can be obtained on request from Dr. Olga Kennard, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, UK.

TABLE 1. Continued

Atom	x	y	z	B(eq)
C-4	0.1267(2)	0.7159(6)	0.5487(3)	3.7(1)
C-5	0.2329(2)	0.6884(6)	0.6695(3)	3.5(1)
C-6	0.3479(2)	0.6247(5)	0.6243(3)	3.4(1)
C-7	0.4467(2)	0.7076(6)	0.7450(4)	3.8(1)
C-8	0.4429(2)	0.6209(6)	0.9167(3)	4.2(1)
C-9	0.3271(3)	0.6756(6)	0.9720(3)	4.6(1)
C-10	0.2194(2)	0.6238(6)	0.8487(3)	3.9(1)
C-11	0.4936(2)	0.6840(6)	0.4676(3)	3.9(1)
C-12	0.5461(2)	0.6778(6)	0.6461(3)	4.1(1)
C-13	0.6563(2)	0.6404(7)	0.6895(4)	5.7(2)
C-14	0.2011(3)	0.4068(6)	0.8476(4)	4.7(1)
C-15	0.1251(2)	0.6937(7)	0.3636(4)	4.6(1)
H-15	0.1995	0.7233	0.336	5.5
H-14	0.1388	0.3729	0.7626	5.6
H-16	0.0955	0.6581	1.0036	5.9
H-17	−0.0671	0.6720	0.8126	5.9
H-18	−0.0532	0.6729	0.5386	5.4
H-19	0.3512	0.4880	0.6332	4.0
H-20	0.4338	0.8398	0.7535	4.6
H-21	0.5050	0.6692	0.9926	5.0
H-22	0.4497	0.4851	0.9105	5.0
H-23	0.3270	0.8084	0.9901	5.4
H-24	0.3210	0.6107	1.0754	5.4
H-25	0.7074	0.6248	0.6061	6.8
H-26	0.6868	0.6263	0.8044	6.8
H-27	0.1802	0.3659	0.9531	5.6
H-28	0.2692	0.3430	0.8260	5.6
H-29	0.0689	0.7768	0.3077	5.5
H-30	0.1060	0.5650	0.3326	5.5
H	0.1438	0.9887	0.8206	7.2

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