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STRUCTURE AND STEREOCHEMISTRY OF MEXICANIN G, AN INTERMEDIATE IN THE BIOGENESIS OF HELENANOLIDES*

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Key Word Index—*Helenium mexicanum*; Asteraceae; guaianolide; biogenesis; X-ray crystallography.

Abstract—The structure of mexicanin G, a guaianolide isolated from *Helenium mexicanum*, is established by means of an X-ray crystallographic analysis. Probably mexicanin G plays an important rôle in the biogenesis of helenanolides.

INTRODUCTION

In earlier articles [1, 2], the physical constants of the lactonic constituents of *Helenium mexicanum* H.B.K. were reported, and over the years this species has been the subject of several studies. The mexicanins A (**1**) [3], C (**2**) [4], D (**3**) [3, 5], E (**4**) [6, 7], H (**5**) [8] and I (**6**) [9] as well as helenalin (**7**) [10] were isolated from this plant and their structures were established by different analytical methods, but the structures of some mexicanins long remained undefined. Just recently, the structure of mexicanin F was determined as **8**, which is a Diels–Alder adduct between the 11,13-double bond of mexicanin E (**4**) and the kinetic enol of the same nor-pseudoguaianolide [11]. All the mexicanins of authenticated structure possess a pseudoguaiane parent skeleton, a cyclopentanone, a C-12/C-8 γ-lactone moiety (*cis*- or *trans*-) and belong to the helenanolide series (Me-C-10α). Here we report the structure and stereochemistry of mexicanin G (**9**), which lacked the general structural features of the mexicanins isolated from the same natural source since it is a guaianolide and therefore may be regarded as a key intermediate in the biogenesis of helenanolides.

RESULTS AND DISCUSSION

The molecular formula of mexicanin G (**9**) ($C_{17}H_{22}O_5$), mp 214–216°, $[\alpha]_D^{25} = 40°$ (*c* 0.1), was determined by elemental analysis and mass spectrometry. The α-methylene-γ-lactone and acetate functionalities were established by their characteristic absorptions in the IR and ^1H NMR spectra (see Experimental). The two-proton complex signal centred at δ4.78 in the ^1H NMR spectrum indicates the presence of the secondary protons geminal to acetate and lactone groups. This spectrum also exhibits, in addition to the C-10 methyl doublet (δ1.18, 3H, *d*, *J* = 7 Hz), a low field singlet at δ1.52 (3H, *s*) of a methyl group, which indicates the presence of a C-3/C-4 tetrasubstituted epoxide ring in a guaiane skeleton, in agreement with the molecular formula. The low chemical shift of the lactonic methine (δ4.78) and biogenetic considerations suggest lactone closure to C-8. Irradiation experiments indicated that the acetate could not be attached to C-6. Of the remaining three possible positions for the acetate (C-2, C-3 and C-9), C-2 is favoured on biogenetic grounds, and therefore **9** is the most probable structure of mexicanin G, regardless of stereochemistry. Due to the uncertain configuration of C-1, C-2, C-3, C-4, C-8 and C-10, and the unavailability of material for chemical transformations, an X-ray analysis of mexicanin G was undertaken. Details of this analysis are given in the Experimental section and listings of pertinent crystallographic data are deposited at the Cambridge Crystallographic Data Centre. Figure 1 is a computer-generated drawing of the 1*S*,2*S*,4*R*,5*S*,7*R*,8*R*,10*R*-enantiomer and probably also represents the absolute stereochemistry on the basis that H-7 in sesquiterpene lactones from higher plants is α [12]. As can be seen from the drawings, the ring junctions of the guaianolide nucleus are *cis* at C-1–C-5 and at C-8–C-7, the acetate is at C-2 and α, the C-3/C-4 epoxide is α as well as the C-10 methyl group.

The co-occurrence of the guaianolide mexicanin G (**9**) and the pseudoguaianolides mexicanins A (**1**), C (**2**), E (**4**), H (**5**), I (**6**), F (**8**) and helenalin (**7**) is in agreement with the generally accepted biogenetic scheme of helenanolides which states that these compounds are formed from a *trans*-guaianolide cation **A** of Scheme 1, (which results from an intramolecular cyclization of a 4(5)-epoxygermacrolide [13] or a 4(5)-epoxy-melampolide [14, 15]). **A** would give the helenanolide skeleton **B** *via* a series of 1,2-migrations (due to antiperiplanar orientation of migrating groups). Mexicanin G (**9**) could be considered an intermediate of this multistep sequential rearrangement, since the eventual carbocation at C-5 **C** (formed *via* two consecutive 1,2-H shifts, from C-1 to C-10 and from C-5 to C-1, see arrows, Scheme 1) could stabilize itself by C-4/C-5 epoxide formation to give **9** (R = Ac). Alternatively, **9** could undergo an epoxide rearrangement and 1,2-methyl shift to a helenanolide [16]. In addition, mexicanin G may be the biogenetic precursor of the sesquiterpene lactones similar to 2α-tigloyloxy-dougaldiolide (**10**), isolated from the closely related genus *Dougaldia*, via the 11β,13-epoxy-derivative of **9**, as previously suggested [17].

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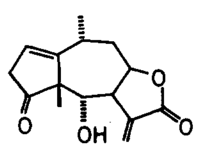

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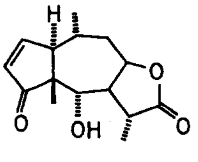

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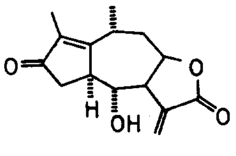

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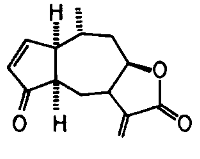

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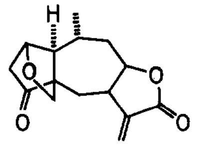

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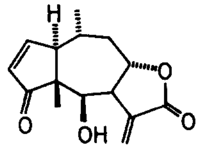

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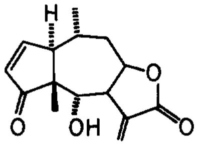

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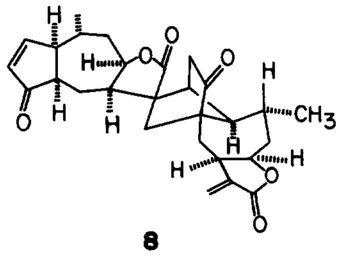

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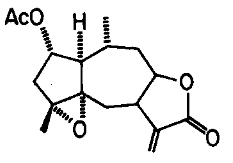

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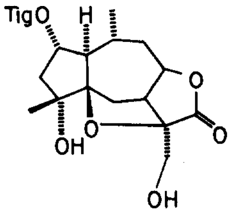

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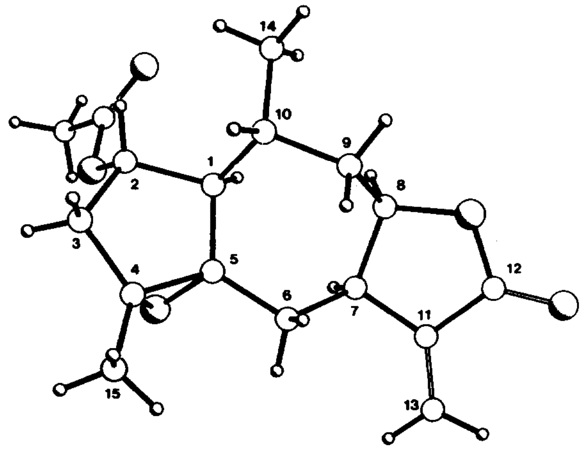
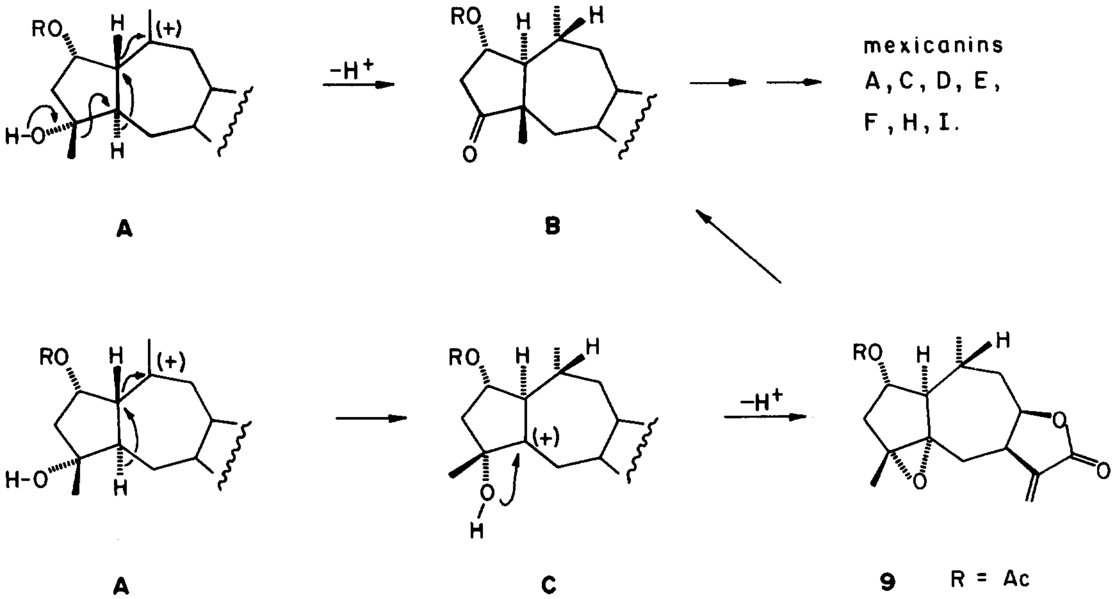


Fig. 1.

EXPERIMENTAL

Slow crystallization from EtOAc–hexane of the extensively purified sample of mexicanin G remaining from the earlier work [2] gave *ca* 5 mg of single crystals which melted somewhat higher than reported previously (mp 214–216°); IR $\nu_{\max}^{CHCl_3}$ cm^{-1}: 3039, 2964, 2929, 1755, 1725, 1659, 1602, 1453, 1383, 1237, 1088, 992; ^{1}H NMR (CDCl$_3$, 80 MHz): δ6.28 (*d*, $J = 3.1$ Hz, H-13a), 5.60 (*d*, $J = 3.0$ Hz, H-13b), 4.98–4.58 (complex, 2H, H-8 and H-1), 3.50 (complex, H-7), 2.05 (3H, *s*, AcO), 1.52 (3H, *s*, 15-Me), 1.18 (3H, *d*, $J = 7$ Hz, 14-Me); EIMS 70 eV, *m/z* (rel. int.): 306 $[M]^+$ (< 1), 291 (3), 263 (10), 246 (12), 155 (9), 154 (11), 152 (10), 151 (12), 60 (83), 43 (100). Found: C, 66.80; H, 7.17; O, 26.26%. $C_{17}H_{22}O_5$ requires: C, 66.65; H, 7.24; O, 26.11%.

The crystals of mexicanin G (**9**) were monoclinic, space group $P2_1$, with $a = 9.3385$ (3) Å, $b = 8.9208$ (3) Å, $c = 9.4978$ (3) Å, $\beta = 92.305$ (3) Å and $z = 2$ ($C_{17}H_{22}O_5$). The intensity data were measured on a Nicolet R3m diffractometer (monochromated CuK$_\alpha$ radiation, ω scans, pulse-high discrimination). The size of



Scheme 1.

the crystal used for data collection was approximately 0.28 × 0.38 × 0.40 mm. A total of 1104 accessible reflections were measured for $2\theta < 45$ of which 1018 were considered to be observed [$I > 2\sigma$ (I)]. The structure was solved by direct methods [18] and was refined by blocked cascade matrix least square methods. In the final refinement, anisotropic thermal parameters were used for the non-hydrogen atoms and fixed isotropic temperature factor $U = 0.045\ A^2$ for the hydrogen atoms. The hydrogen atoms were included in the structure factor calculations. The final discrepancy indices are $R = 0.0345$ and $R_\omega = 0.0378$ for the 1018 observed reflections.

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