The Revised Structure of the Cytotoxic Heliangolide Euparhombin

Mariano Martínez-Vázquez, José S. Calderón, and Pedro Joseph-Nathan

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THE REVISED STRUCTURE OF THE CYTOTOXIC HELIANGOLIDE EUPARHOMBIN

MARIANO MARTÍNEZ-VÁZQUEZ, JOSÉ S. CALDERÓN,

Instituto de Química, Universidad Nacional Autónoma de México, Circuito Exterior, Ciudad Universitaria, México, D.F., 04510 México

and PEDRO JOSEPH-NATHAN*

Departamento de Química del Centro de Investigación y de Estudios Avanzados, Instituto Politécnico Nacional, Apartado 14-740, México, D.F., 07000 México

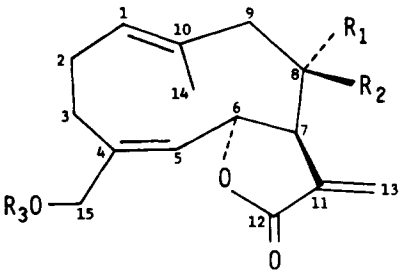
ABSTRACT.—A single crystal X-ray diffraction study of euparhombin establishes the stereostructure of this sesquiterpene lactone isolated from *Ageratina rhomboidea* as 6,8,15-trihydroxyheliang-6-olide 8-*O*-methacrylate [**4**].

The structure of euparhombin, a cytotoxic heliangolide from the aerial parts of *Ageratina rhomboidea* (HBK) King & Rob. (Asteraceae), was established several years ago (1) as **1** based on spectroscopic and chemical evidence. At that time another group of authors isolated two very closely related heliangolides from *Eupatorium mohrii* and *Eupatorium hyssopifolium* (2) and established their structures as **2** and **3**, respectively. Compound **1** differs from the other two heliangolides in the nature and orientation of the ester residue at C-8. Thus, while **1** was described as having a methacrylate in α orientation, compounds **2** and **3** possess a 4-hydroxytiglate in β orientation.

Since the nmr chemical shifts of H-1, H-5, H-6, and H-8 for the three natural products are almost identical and a literature search reveals that up to now all heliangolides isolated from the *Eupatorium* and *Ageratina* genera have β-oriented ester groups at C-8 (3–6), we decided to establish the stereostructure of euparhombin unequivocally.

RESULTS AND DISCUSSION

The stereostructure of euparhombin was established by a single crystal X-ray diffraction study of the natural product. For this purpose, suitable crystals were obtained by slow crystallization from diisopropyl ether. A stereoview of the molecule is shown in Figure 1, and the atomic coordinates for the non-hydrogen atoms are listed in Table 1. Bond distances and bond angles can be considered as being normal. This study thus establishes the stereostructure of the molecule as **4** and demonstrates that the ester group at C-8 is β-oriented in agreement with all heliangolides isolated from the



1 R_1=OOCC(Me)=CH_2, R_2=R_3=H
2 R_1=R_3=H, R_2=OOCC(Me)=$CHCH_2OH$
3 R_1=H, R_2=OOCC(Me)=$CHCH_2OH$, R_3=Ac
4 R_1=R_3=H, R_2=OOCC(Me)=CH_2

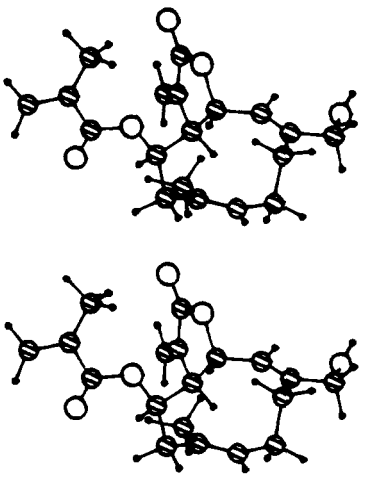


FIGURE 1. Stereoview of the molecular structure of euparhombin [**4**].

Eupatorium and *Ageratina* genera. It also provides the conformation of the ten-membered ring in the solid state, which proved that the C-14 methyl group is oriented above and towards H-6β.

EXPERIMENTAL

CRYSTAL DATA[1].—Euparhombin [**4**], available from a previous study (1): $C_{19}H_{24}O_5$, M = 332.4, tetragonal, space group $P4_12_12$, $a = b = 9.835$ (3), $c = 38.38$ (1) Å, U = 3712.88 Å^3, $D_c = 1.189$ g/cm^3, Z = 8, F(000) 1423.85, μ (CuKα) = 7.39 cm^{-}, Final R = 6.38% (235 parameters), $R_w = 7.38\%$ for 1989 unique reflections with $|I_o| \geq 3\sigma|I_o|$ in the range $3° \leq 2\theta \leq 110°$, residual electron density within ±0.34 e$^-$/Å^3.

DATA COLLECTION AND STRUCTURE REFINEMENT.—The intensity data were collected using a Nicolet R3m four circle automatic diffractometer with graphite monochromatized CuKα radiation (λ = 1.5418 Å) operataed in the θ:2θ scanning mode with variable scan speed (4–29.3 deg/min) at room temperature. The intensity data were corrected for background and Lorentz-polarization effects; crystal decay was negligible and no absorption corrections were applied. The solid state structure was solved by direct methods using software provided by the diffractometer manufacturer and refined by full-matrix least-squares. For the structural refinements the non-hydrogen atoms were treated anisotropically, the hydroxyl hydrogen became evident from a ΔF synthesis, and the hydrogen atoms bonded to carbons, included in the structure factor calculation, were refined isotropically. The least-squares weighting scheme used was: $w = 1/\sigma^2(I_o) + G(I_o)^2$, where σ is the standard deviation of observed amplitudes based on counting statistics and G is a variable adjusted after each cycle to minimize the function $\Sigma w(\Delta I)^2$. The final G value was 0.00429, and a few reflections were excluded from the final refinement calculation to improve the fit.

TABLE 1. Atomic Coordinates (× 10^4) of Euparhombin [**4**].

Atom	*x*	*y*	*z*
C-1 . . .	4086(5)	2979(5)	1015(1)
C-2 . . .	5333(5)	3225(5)	795(1)
C-3 . . .	4959(5)	3888(5)	444(1)
C-4 . . .	4225(4)	5239(4)	480(1)
C-5 . . .	2880(4)	5395(4)	491(1)
C-6 . . .	1830(4)	4287(4)	492(1)
O-6 . . .	820(3)	4571(3)	214(1)
C-7 . . .	990(4)	4270(4)	837(1)
C-8 . . .	644(4)	2881(4)	982(1)
O-8 . . .	67(3)	2111(3)	689(1)
C-9 . . .	1795(5)	2100(5)	1161(1)
C-10 . . .	3114(5)	2037(4)	957(1)
C-11 . . .	−372(4)	5000(5)	349(1)
O-11 . . .	−1311(4)	5304(4)	160(1)
C-12 . . .	−298(4)	5003(5)	729(1)
C-13 . . .	−1212(6)	5587(7)	929(2)
C-14 . . .	3237(7)	910(6)	689(1)
C-15 . . .	5149(4)	6458(5)	510(1)
O-15 . . .	4482(4)	7730(4)	527(1)
C-16 . . .	−898(5)	1172(5)	765(2)
O-16 . . .	−1185(5)	860(5)	1059(1)
C-17 . . .	−1528(5)	563(6)	445(2)
C-18 . . .	−2208(8)	−690(9)	500(3)
C-19 . . .	−1390(9)	1293(9)	119(2)

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