Phytochemistry, 1976, Vol. 15, pp. 191–193. Pergamon Press. Printed in England.

GOYAZENSOLIDE, A SCHISTOSOMICIDAL HELIANGOLIDE FROM *EREMANTHUS GOYAZENSIS*[*]

WALTER VICHNEWSKI[†], SILVIO JOSÉ SARTI[‡], BENJAMIN GILBERT[§] and WERNER HERZ[||]

Department of Chemistry, The Florida State University, Tallahassee, Florida 32306, U.S.A. and Núcleo de Pesquisas de Productos Naturais da Faculdade de Farmácia e Odontologica, 14.100 Riberão Preto, São Paulo, Brasil

(*Received* 8 *July* 1975)

Key Word Index—*Eremanthus goyazensis*; Compositae; heliangolide; sesquiterpene lactone; schistosomicide.

Abstract—Isolation and structure determination of goyazensolide, a new heliangolide responsible for the schistosomicidal properties of *Eremanthus goyazensis* Sch.-Bip., is reported.

INTRODUCTION

Extracts of several Compositae have demonstrated protection against cercariae of *Schistosoma mansoni* [1–3]. One of these is the wood oil of *Eremanthus elaeagnus* Sch.-Bip., the active ingredient of which was the new guaianolide eremanthine [1,3,4]. In the present Communication, we report isolation and structure determination of a new heliangolide guayazensolide which is responsible for the schistosomicidal properties of another *Eremanthus* species, *E. goyazensis* Sch.-Bip.[¶] (Vernonieae, Elephantopodinae).

RESULTS

Goyazensolide (**1**), $C_{19}H_{20}O_7$ (high resolution mass spectrum and elemental analysis), mp 175–177°, $[\alpha]_D^{22}$ $-22{\cdot}5°$, was a γ-lactone with a conjugated exocyclic methylene group (IR bands at 1765 and 1660 cm^{-1}; UV λ_{max} 205 nm, $\epsilon = 19200$; sharp doublets at 6·22 and 5·47 ppm in the NMR spectrum—see Table 1), a primary hydroxyl group (IR band at 3480 cm^{-1}, 2 proton singlet at 4·38 ppm) and a methacrylic ester function (broad vinyl methyl signal at 1·83 ppm coupled to multiplets at 6·02 and 5·56 ppm, significant high resolution mass spectral peaks at *m/e* M-C_4H_5O and M-C_4H_5O–H_2O).

The sequence H-5 through H-9 and the relationship of H-5 to H-15 was established by double resonance. H-7 at 3·80 ppm was first located by irradiation at the frequencies of H-13; subsequently irradiation at the frequency of H-7 located H-6 at 5·33 and H-8 at 4·53 ppm, the signal at higher field being, as usual, assigned to hydrogen under the lactone oxygen. Irradiation at the frequency of H-6 collapsed a multiplet at 6·27 ppm (H-5) to a narrowly-split triplet; that this signal was that of a vinyl proton could be shown by single frequency off-resonance decoupling of the ^{13}C-NMR spectrum which resulted in collapse of a doublet at 134·6 ppm to a singlet. It could also be demonstrated that broadening of the 6·27 ppm signal was the result of allylic coupling between H-5 and the protons under the carbon carrying the primary hydroxyl group, i.e. H-15, and that the latter were also homoallylically coupled to H-6. Lastly, H-8 was coupled to 2 vicinally coupled resonances at 2·50 and 2·30 ppm (H-9a and H-9b) which were apparently adjacent to a quaternary center.

Table 1. 270 MHz ^{1}H-NMR Spectra of **1** and **2**[*]

	H-2	H-5	H-6	H-7	H-8	H-9	H-13	H-14	H-15	H-3'	H-4'	Misc.
1	5·83	6·27*td* (~1·5, ~1·5)	5·33*td* (~1·3, ~2·5)	3·80*m* (2·5, 2·5, 3·3, 3·0)	4·53*td* (2·5,13)	2·50*dd* (13, 15)	6·22*d* (3·3)	1·52†	4·38*br*‡ (~1·5, ~1·3)	6·02*br* (1)	1·83*m*†	
						2·30*dd* (2·5, 15)	5·49*d* (3·0)			5·56*m* (1·5)		
2	5·86	5·93*br* (~0·8)	4·97*dbr* (5, ~0·8)	4·17*m* (2 5, 5 3·3, 3·0)	4·31*td* (2·5, 12)	2·53*dd* (12, 15)	6·23*d* (3·3)	1·53†	6·17	6·01*m* (1·5)	1·81*m*†	2·07 (*Ac*)
						2·35*dd* (2·5, 15)	5·53*d* (3·0)		6·07	5·54*m* (1·5)		

[*] Run in $CDCl_3$ on a Bruker HFX-270 instrument with TMS as internal standard. Values are in ppm; *d* doublet; *t* triplet; *br* broadened singlet; *m* multiplet. Unmarked signals are singlets. Figures in parentheses are coupling constants in Hz. † Intensity 3 protons. ‡ Intensity 2 protons.

---

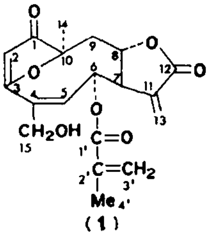
[*] Work at Florida State University supported in part by a grant (CA-13121) from the U.S. Public Health Service through the National Cancer Institute.

[†] Faculdade de Farmácia e Odontologia, Riberão Preto. On leave of absence 1975–1976 at Florida State University.

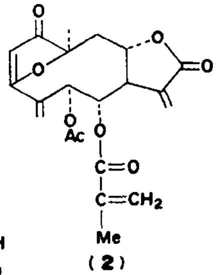
[‡] Riberão Preto; [§] CPPN, Universidade Federal do Rio de Janeiro; [||] Florida State University.

[¶] This bushy species occurs in the altiplano regions of Minas Gerais, Goiás and São Paolo, Brazil.

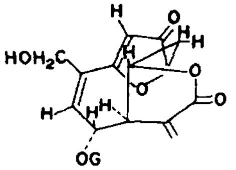
Since the NMR spectrum also exhibited a sharp methyl singlet at 1·52 ppm (methyl on carbon carrying oxygen), the remaining elements of the empirical formula, 2 carbons, 3 oxygens and 1 proton, could only be accommodated by assuming that a dihydrofuran-3-one group was incorporated in formula **1** as shown. The presence of this heterocyclic ring system was supported (cf. calaxin and ciliarin [6]) by the IR (bands at 1690, 1640 and 1590 cm^{-1}), UV (λ_{max} 267·5 nm, ϵ 8520 due to extended conjugation with 4,5 double bond) and the ^{1}H-NMR spectrum (H-2 singlet at 5·83 ppm) and was fully consonant with the ^{13}C-NMR spectrum (Table 2) which displayed the expected signals for C-1, C-2 (again identified by single frequency off-resonance spin decoupling), C-3 and C-10 as well as those of the other carbons whose nature had been established previously.



(**1**)



(**2**)



(**3**)

Acetylation of goyazensolide was accompanied by a shift of the UV maximum to 285 nm and by several significant changes in the ^{1}H-NMR spectrum. The broad 2-proton signal of H-15 was converted to 2 one-proton singlets at 6·17 and 6·07 ppm and the H-5 and H-6 signals had moved upfield (Table 1). The simplest explanation for these observations was to assume that acetylation had resulted in allylic rearrangement to **2**; this was confirmed by examination of the ^{13}C-NMR spectrum (Table 2). The C-15 triplet was now found at 130·6 instead of at 62·9 ppm and the C-5 doublet at 75·0 instead of at 134·6 ppm; assignments were again confirmed by single frequency off-resonance decoupling. The upfield shift of the H-6 resonance can be ascribed to the change from an allylic to a non-allylic situation; comparison of the H-6 and H-8 frequencies in **2** removed any remaining doubt about the orientation of the lactone ring.*

Table 2. ^{13}C-NMR Spectra of **1** and **2***

	1	**2**
C-1	204·6	204·0
C-2	106·4*d*	107·0*d*
C-3	184·6	185·1
C-4	135·6	134·0
C-5	134·6*d*	75·0*d*
C-6	81·7*d*	83·8*d*
C-7	51·0*d*	46·2*d*
C-8	73·5*d*	72·1*d*
C-9	43·3*t*	44·7*t*
C-10	89·7	90·4
C-11	135·6	134·0
C-12	166·8†	166·9†
C-13	126·2*t*	126·5*t*
C-14	20·6*q*	21·1*q*†
C-15	62·9*t*	130·6*t*
C-1′	168·7†	168·2†
C-2′	133·6	133·5
C-3′	124·5*t*	124·0*t*
C-4′	17·8*q*	18·0*q*
C-1″	-	169·5
C-2″	—	21·4*q*†

* Run in $CDCl_3$ on Bruker HFX-270 MHz instrument with TMS as internal standard. † Assignments may be interchanged.

In the NMR spectra of **1** and **2**, the signal corresponding to H-7 has an abnormally low chemical shift which indicates, as has been pointed out previously in similar instances [8,9], that H-7 is close to the oxygen of the furan-ring, that C-3 must have the absolute stereochemistry indicated in the formulas if the C-7 side chain is β-oriented and equatorial as in all sesquiterpene lactones of authenticated stereochemistry, and that the C-4, C-5 double bond must be cisoid. The existence of an appreciable NOE between H-5 and H-15 verified the last deduction. On this basis, using Dreiding models, the stereochemistry presented in the formulas and in scheme 1 best satisfies the values for $J_{5,6}$, $J_{6,7}$, $J_{7,8}$ and $J_{8,9}$ given in Table 1.

EXPERIMENTAL

Experimental details have been specified previously [10].

Extraction of Eremanthus goyazensis. Since the schistosomicidal activity of *E. goyazensis* Sch.-Bip. was exhibited by all above-ground parts of the bush, stem, branches, leaves and flower heads, wt. 3 kg, collected by S. J. Sarti in May 1974 in the vicinity of Orlândia, São Paulo State, Brazil, were extracted with $CHCl_3$ and worked up in the usual manner [11]. The crude gum, wt. 23·5 g, crystallized on standing; recrystallization from C_6H_6 furnished goyazensolide, mp 175–177°, $[\alpha]^{2}_{D}$ $-22·5°$ ($CHCl_3$), CD curve (MeOH) $[\theta_{318}] + 17100$, $[\theta_{267}] - 8200$; UV λ_{max} 267·5, 205 nm (ϵ 8500, 19200); IR bands at 3480, 1765, 1705, 1690, 1660, 1640 and 1590 cm^{-1}; high resolution mass spectrum *m/e* (composition, %), 360 (M, $C_{19}H_{20}O_7$, 15), 342 ($C_{19}H_{18}O_6$, 26·8), 291 ($C_{15}H_{15}O_6$, 8·2), 273 ($C_{15}H_{13}O_5$, 1·3), 248 ($C_{13}H_{12}O_5$, 100), 228 ($C_{14}H_{12}O_3$, 27·7), 203 ($C_{12}H_{11}O_3$, 42·9). *Anal.* Calcd. for $C_{19}H_{20}O_7$: C, 63·3; H, 5·59; O, 31·08; MW, 360·1208. Found: C, 62·45; H, 5·43; O, 31·55; MW (MS), 360·1207. Acetylation of 0·30 g of goyazensolide in 3 ml of C_5H_5N with 4 ml Ac_2O at room temp. overnight followed by the usual work-up afforded 0·22 g of solid **2** which was recrystallized from EtOAc and then had mp 288–290°, $[\alpha]^{27}_{D}$-26·3° ($CHCl_3$), CD curve (MeOH) $[\theta]_{328}$ $+9950$, $[\theta]_{275} - 5720$; λ_{max} 285 (ϵ 7800), UV end absorption ϵ_{205} 20800; IR bands at 1765, 1740, 1710, 1690, 1665, 1635 and 1590 cm^{-1}; high resolution mass spectrum *m/e* (composition, %), 402 (M, $C_{21}H_{22}O_8$, 7·9), 361 ($C_{19}H_{21}O_7$, 6·4), 360 ($C_{19}H_{20}O_7$, 41·4), 342 ($C_{19}H_{18}O_6$, 70·9), 316 ($C_{17}H_{16}O_6$, 8·6), 291 ($C_{15}H_{15}O_6$, 14·5), 274 ($C_{15}H_{14}O_5$, 40), 246 ($C_{14}H_{14}O_4$, 30·2), 228 ($C_{14}H_{12}O_3$, 23·1), 152 ($C_8H_8O_3$, 100). *Anal.* Calcd. for $C_{21}H_{22}O_8$: C, 62·68; H, 5·51; O, 31·81; MW, 402·1313. Found: C, 61·90; H, 5·24; O, 32·18; MW (MS), 402·1314.

Acknowledgement—W.V. thanks Fundação de Amparo a Pesquisa do Estado de São Paulo for a grant which permitted postdoctoral study at Florida State University. Work at Riberão Preto supported in part by Conselho Nacional de Desenvolvimento Cientificoe Tecnologico (formerly CNPq).

REFERENCES

1. Baker, P. M., Fortes, C. C., Fortes, E. G., Gazzinelli, G., Gilbert, B., Lopes, J. N. C., Pellegrino, J., Tomassini, T.

---

* It might have been argued that in **1**, the normal situation (i.e. that hydrogen under carbon carrying lactone oxygen resonates at higher field than hydrogen under carbon carrying ester oxygen) is reversed due to the H-6 being allylic. Such an argument can usually be disposed of by epoxidation of the 4,5-double bond (cf. [7]); however, an attempted epoxidation of guayazensolide was unsuccessful.

C. B. and Vichnewski, W. (1972) *J. Pharm. Pharmacol.* **24**, 853.
2. Tomassini, T. C. B. and Gilbert, B. (1972). *Phytochemistry* **11**, 1177.
3. Vichnewski, W. and Gilbert, B. (1972) *Phytochemistry* **11**, 2563.
4. Eremanthine, mp 73–74°, [3] was also isolated [1] from the schistosomicidal wood oil of *Vanillosmopsis erythropappa* Sch.-Bip. Somewhat later, Italian workers [5] isolated a guianolide vanillosmin, mp 62–62·5°, from the same species which appears to be identical with eremanthin.
5. Corbella, A., Gariboldi, P., Jommi, G. and Ferrari, G. (1974) *Phytochemistry* **13**, 459.
6. Romo de Vivar, A., Guerrero, C., Diaz, E. and Ortega, A. (1970) *Tetrahedron* **20**, 1657.
7. Herz, W. and Bhat, S. V. (1970) *J. Org. Chem.* **35**, 2605.
8. Herz, W. and Bhat, S. V. (1972) *J. Org. Chem.* **37**, 906.
9. Herz, W. and Kalyanaraman, P. S. *J. Org. Chem.* in press.
10. Herz, W., Srinivasan, A. and Kalyanaraman (1975) *Phytochemistry* **14**, 233.
11. Herz, W. and Högenauer, G. (1962) *J. Org. Chem.* **27**, 905.