Eregoyazin and Eregoyazidin, Two New Guaianolides from *Eremanthus goyazensis*[1]

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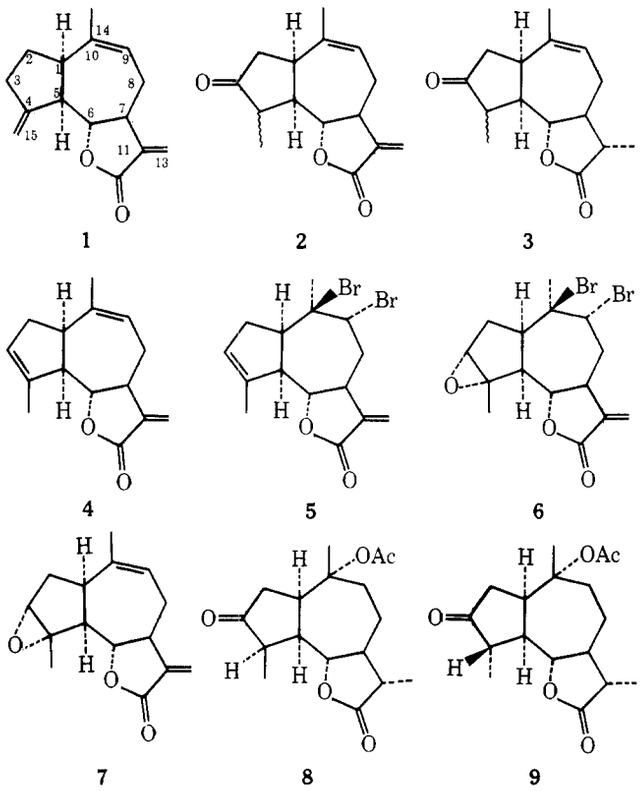
Isolation and structure determination of eregoyazin and eregoyazidin, two new guaianolides from the wood of *Eremanthus goyazensis* Sch.-Bip., by physical methods and by correlation with isoeremanthin are reported. Evidence concerning the stereochemistry of these compounds at C-4 based on methods used customarily for the determination of configuration of 3-oxoguaianolides at this center is contradictory.

Extracts of *Eremanthus* species (Vernonieae, Elephantopodinae) and other Compositae have demonstrated schistosomicidal properties.[3-5] The active component of the wood oil of *E. eleaegnus* Sch.-Bip., also isolated from the schistosomicidal wood oil of *Vanillosmopsis erythropappa* Sch.-Bip., was the guaianolide eremanthin (**1**)[3,5] which was subsequently[6] shown to be identical with a substance named vanillosmin by Italian workers. The herbaceous parts of *E. goyazensis* Sch.-Bip. yielded a schistosomicidal and cytotoxic heliangolide goyazensolide[8] which is closely related to eremantholide A from *E. eleaegnus* (plant part unspecified)[9] and to deoxygoyazensolide[10] from the herbaceous parts of *V. erythropappa*. Investigation of the wood of *E. goyazensis* has now resulted in the isolation, in small amount, of two new guaianolides eregoyazin (**2**) and eregoyazidin (**3**). Structure and stereochemistry (except for the center at C-4) were established by NMR and CD spectroscopy and confirmed by synthesis of **2** and **3** from isoeremanthin (**4**).[11]



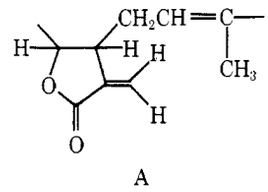
1 **2** **3**

4 **5** **6**

7 **8** **9**

Eregoyazin (**2**), $C_{15}H_{18}O_3$ (high-resolution mass spectrum), mp 178–181 °C, was an α-methylene α,β-unsaturated lactone (IR bands at 1760 and 1665 cm^{-1}; λ_{max} (EtOH) 219 nm (ϵ 18 500), narrowly split doublets at 5.60 and 6.30 ppm in the ^1H NMR spectrum). The existence of another carbonyl function, probably a cyclopentanone, was indicated by an IR band at 1740 cm. The presence of a second, trisubstituted double bond was indicated by a broad one-proton resonance at 5.65 and a somewhat broadened singlet characteristic of a vinyl methyl group at 1.78 ppm. Hence the new substance had a bicyclic carbon skeleton.

Identification of the H-7 resonance (multiplet at 2.97 ppm) was achieved by irradiating the narrowly split doublets of the exocyclic methylene group. Irradiation at the frequency of H-7 not only collapsed these doublets into singlets, but changed a triplet at 4.07 ppm (H-6) into a doublet and affected signals at 2.74 and 2.08 ppm (H-8a and H-8b) which were in turn coupled geminally. Irradiation at the frequency of H-8b affected the vinyl resonance at 5.65 ppm which was in turn coupled to the vinyl methyl signal, thus leading to partial structure A.

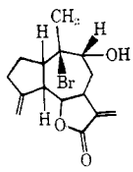
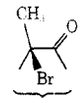
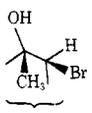


A

Irradiation at the frequency of H-6 affected a multiplet at 2.28 ppm (H-5) as well as the H-7 resonance. Irradiation at the frequency of H-5 simplified a signal at 2.37, a two-proton signal centered at 2.52 ppm, and the resonance of H-6. One of the protons at 2.52 ppm (H-2a) was geminally coupled to a proton (H-2b) whose signal appeared as a multiplet at 3.22 ppm; the other (H-4) was coupled to a methyl group responsible for a doublet at 1.24 ppm. Both H-2a and H-2b were vicinally coupled to the proton responsible for the resonance at 2.37 ppm (H-1); the chemical shifts of H-2a, H-2b, which indicated that they were α to the ketone group, and H-4 and the lack of further coupling established the gross structure of eregoyazin as that shown in **2**.

The stereochemistry of eregoyazin at C-1, C-5, C-6, and C-7 was deduced as follows. The negative Cotton effect at 256 nm

Table I

Compound	δ, ppm ($CDCl_3$)
	4.85
	5.03
	4.02
	4.00
1	3.98
4	4.03

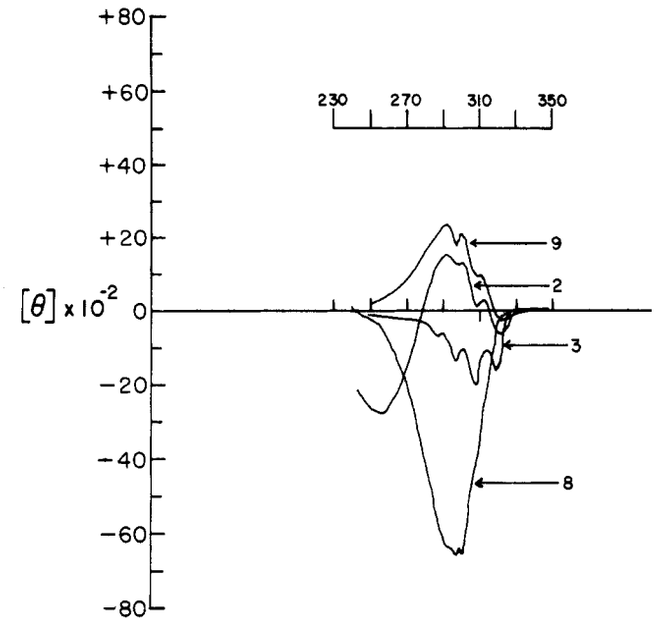


Figure 1. CD curves of eregoyazin (**2**), eregoyazidin (**3**), acetyl-4β-methyl- (**8**) and acetyl-4α-methyl-5α*H*-dihydroisophotosantonic acid lactone (**9**).

(Figure 1) and the magnitude of $J_{7,13}$ (3 Hz)[14] indicate that the lactone ring is trans fused. Since H-7 is α in sesquiterpene lactones from higher plants, H-6 must be β, in agreement with the value of $J_{6,7}$ (11 Hz). The magnitude of $J_{5,6}$ (10 Hz) indicates that H-5 and H-6 are trans; hence H-5 is α in accordance with biogenetic considerations.[15] Lastly, comparison of $J_{1,5}$ (3.5 Hz) with values derived by inspection of models with H-1 α and β leads to the conclusion that H-1 is α, again in accordance with biogenetic considerations. The stereochemistry at C-4 will be discussed subsequently together with that of eregoyazidin.

Eregoyazidin (**3**), $C_{15}H_{20}O_3$ (high-resolution mass spectrum), mp 186–189 °C, had IR bands at 1760 and 1735 cm^{-1}, indicative of a γ-lactone and a cyclopentanone. The UV spectrum showed only end absorption, while the NMR spectrum displayed significant resonances as follows: one vinylic proton at 5.56, a proton under lactone oxygen at 4.03, a vinyl methyl group at 1.80, and two secondary methyl groups at 1.26 and 1.22 ppm. Comparison with the spectral data of eregoyazin thus indicated that eregoyazidin was a 11,13-dihydro derivative of **2**. The above conclusion was substantiated by decoupling experiments which will not be discussed in detail. From the values of $J_{6,7}$ (10 Hz), $J_{5,6}$ and $J_{1,5}$ (3 Hz) and on the assumption that H-7 is α, it could again be deduced that H-6 is β and H-1 and H-5 are α.

The gross structure and stereochemistry so far assigned to eregoyazin and eregoyazidin was confirmed by partial synthesis from isoeremanthin (**4**).[11] Reaction of **4** with 1 mol equiv of Br_2 in ether at −70 °C gave a mixture from which **5** could be isolated in ~53% yield. That addition of Br_2 had taken place at the 9,10 double bond was clearly indicated by the NMR spectrum which retained the broadened C-4 methyl singlet (at 1.95 ppm) and one of the two vinyl resonances of **4** at 5.50 ppm, but exhibited the C-10 methyl resonance as a sharp singlet at 2.00 and a new triplet (H-9) at 4.79 ppm. The stereochemistry assigned to **5** is based on inspection of models (predominant attack of halogen from the less-hindered side), the facile debromination observed subsequently, and chemical shift data[16] (Table I). Peracid oxidation of **5** from the less-hindered side afforded mainly the α-epoxide **6** whose NMR spectrum displayed the H-3 signal at 3.44 and the C-4 methyl resonance as a sharp singlet at 1.63 ppm. Exposure of **6** to methanolic zinc resulted in debromination to **7** whose NMR spectrum exhibited relevant signals at 1.67 (C-4 methyl), 1.79 br (C-10 methyl), 3.33 m (H-3), and 5.59 m (H-9). Finally, treatment of **7** with BF_3·OEt_2 afforded a substance identical in all respects with eregoyazin. Further reduction of **2** with zinc in hot glacial acetic acid yielded eregoyazidin (**3**).

The conversion of **7** to eregoyazin with BF_3·OEt_2 suggested that the C-4 methyl groups of eregoyazin and, because both base- and acid-catalyzed equilibration of acetyl 4β-methyl-5α*H*-dihydroisophotosantonic acid lactone (**8**) leads exclusively to the 4α-methyl epimer **9**[18,20] and the presence of the 9,10 double bond was not expected to affect the stability relationships,[21] eregoyazidin were α oriented. To confirm this supposition the CD curves of eregoyazin and eregoyazidin were compared with those of the model compounds **8** and **9** which exhibit Cotton effects of opposite sign near 300 nm[22,24] (Figure 1). To our great surprise, the two CD curves were roughly enantiomeric, that of eregoyazin being essentially superimposable on that of the more stable **9** if allowance is made for the lactone Cotton effect near 256 nm. On this basis alone one would conclude that the stereochemistries of eregoyazin and eregoyazidin at C-4 are opposite, with eregoyazin, like **9**, having the 4α-methyl configuration and eregoyazidin, like **8**, having the 4β-methyl configuration. However, prolonged treatment of eregoyazidin with Al_2O_3 or K_2CO_3–MeOH at room temperature under conditions which effect isomerization of **8** and **9** had no effect on the CD curve and resulted in recovery of starting material. Hence the C-4 methyl group of eregoyazidin occupies the stable configuration, whatever its orientation, as would indeed be expected from the method of preparation.

We are therefore forced to the conclusion that either the CD curves of **8** and **9** cannot always be used as models for other 3-oxoguaianolides (even though the stereochemistry at C-1, C-5, C-6, and C-7 be the same) or that **8** and **9** cannot be used to anticipate the relative stabilities at C-4 of such compounds as eregoyazin and eregoyazidin due to subtle conformational factors. Similarly, the argument that epoxidation of **5** could have occurred predominantly from what appears to be the more-hindered β face, that BF_3-catalyzed rearrangement of the resulting 3β,4β-epoxide, if concerted, would therefore have produced eregoyazin with a 4β-methyl group, and that Zn–acetic acid reduction to eregoyazidin could have been ac-

companied by isomerization of C-4[25] would require that for some reason the CD curves of eregoyazin and eregoyazidin be enantiomeric with those of **8** and **9**, respectively. Further work is now under way to shed light on this set of contradictions.

Some uncertainty also surrounds the stereochemistry of eregoyazidin at C-11 to which we tentatively assign the α-11-methyl configuration because of the mode of preparation from eregoyazin.[23] Attempts to verify this by NMR spectroscopy failed for the following reasons: (1) The magnitude of $J_{7,11}$ could not be used for this purpose as construction of models with H-11 α and β indicated that the coupling constant would be approximately the same. (2) The solvent shift method, useful for determining the stereochemistry of C-11 methyl group in the case of γ-lactones attached to rigid six-membered rings,[26] could not be extended to the present situation as the values obtained were intermediate between the values reported for quasiequatorial and quasiaxial methyls.[27]

Experimental Section[29]

Isolation of Eregoyazin and Eregoyazidin. *Eremanthus goyazensis* Sch.-Bip. was collected by Dr. Silvio José Sarti in the vicinity of Orlândia, São Paulo State, Brasil in May 1974. The powdered wood (wt, 22 kg) was extracted with hot ethanol. This gave 497 g of crude extract which was chromatographed over 3 kg of silica gel, 600-mL fractions being eluted in the following order: 1–123 (benzene), 124–133 (benzene–$CHCl_3$ 20:1), 134–141 (benzene–$CHCl_3$ 15:1), 142–151 (benzene–$CHCl_3$ 10:1), 152–157 (benzene–$CHCl_3$ 5:1), 158–163 (benzene–$CHCl_3$ 1:1), 164–169 ($CHCl_3$), 170–217 ($CHCl_3$–EtOAc 10:1), 218–222 ($CHCl_3$–EtOAc 5:1), 223–227 ($CHCl_3$–EtOAc 1:1), 228–266 (EtOAc), 267–273 (EtOH). Fractions 130–137 (150 mg) showed one major spot on TLC and were combined and purified by preparative TLC on silica gel (benzene–EtOAc 5:1) to give 60 mg of eregoyazin: mp 178–181 °C; UV λ_{max} 219 nm (ϵ 18 500); IR bands at 1760, 1735, 1660, 1240, 1130, 991, 951, 831, 810, 790, and 720 cm^{-1}; NMR signals ($CDCl_3$) at 2.37 (dd, H-1, $J_{1,5}$ = 3, $J_{1,2a}$ = 6 Hz), 3.22 (dd, H-2a, $J_{2a,2b}$ = 15 Hz), 2.52 (m, H-2b and H-4, $J_{4,5}$ = 10, $J_{4,15}$ = 6 Hz), 2.28 (m, H-5, $J_{5,6}$ = 10.5 Hz), 4.07 (t, H-6, $J_{6,7}$ = 10 Hz), 2.97 (m, H-7, $J_{7,8a}$ = 10, $J_{7,13a}$ = $J_{7,13b}$ = 3 Hz), 2.08 (t, H-8a, $J_{8a,8b}$ = 16 Hz), 2.74 (dd, H-8b, $J_{8b,9}$ = 6 Hz), 5.55 (dbr, H-9, H-13a), 6.24 (d, H-13b), 1.24 (d, C-4 methyl), and 1.78 (br, C-10 methyl); NMR signals (C_6D_6) at 1.98 (m, H-1, H-2a, or H-2b, H-8b), 1.48 (m, H-2a or H-2b, H-5), 2.19 (m, H-4, H-7), 3.03 (t, H-6), 2.41 (dd, H-8a), 4.98 (br, H-9), 4.83 (d, H-13a), 6.09 (d, H-13b), 1.05 (d, C-4 methyl), and 1.34 (br, C-10 methyl); NMR signals (C_5D_5N) at 3.10 (m, H-1), 2.44 (m, H-2a, H-2b, H-4, H-8b), 2.11 (m, H-5), 3.07 (t, H-6), 2.89 (m, H-7), 1.89 (t, H-8a), 5.36 (br, H-9), 5.42 (d, H-13a), 6.23 (d, H-13b), 1.14 (d, C-4 methyl), and 1.62 (br, C-10 methyl); mass spectrum *m/e* (rel intensity) 246 (M^+, 100), 218 (27), 190 (26), 190 (26), 175 (21), 150 (65), 149 (90), 93 (39), 91 (35), 69 (57), 41 (49).

Anal. Calcd for $C_{15}H_{18}O_3$: mol wt, 246.1255. Found: mol wt (MS), 246.1255.

Fractions 164–169 (144 mg) showed one major spot on TLC and were combined and purified by preparative TLC (benzene–EtOAc 5:1) to give 50 mg of eregoyazidin: mp 186–188 °C; UV, end absorption only; IR bands at 1760, 1735, 1180, 985, and 739 cm^{-1}; NMR signals ($CDCl_3$) at 2.54 (m, H-1, H-8b, and H-11), 3.10 (m, H-2a, $J_{2a,2b}$ = 12, $J_{1,2a}$ = 6 Hz), 2.25 (m, H-2b, H-4), 2.13 (m, H-5, $J_{4,5}$ = 8, $J_{1,5}$ = 3 Hz), 4.02 (t, H-6, $J_{5,6}$ = $J_{6,7}$ = 10 Hz), 2.09 (m, H-7), 5.54 (dbr, H-9, $J_{8b,9}$ = 6 Hz), 1.24 (d, C-4 methyl, $J_{4,15}$ = 6 Hz), 1.78 (br, C-10 methyl), and 1.20 (d, C-11 methyl, $J_{11,13}$ = 6 Hz); mass spectrum *m/e* (rel intensity) 248 (M^+, 37), 220 (11), 205 (9), 152 (73), 151 (100), 93 (22), 91 (40), 41 (86), and 39 (61).

Anal. Calcd for $C_{15}H_{20}O_3$: mol wt, 248.1412. Found: mol wt (MS), 248.1410.

A solution of 5 mg of this substance in ethanol was hydrogenated with 1.5 mg of Adams catalyst at 10 psi pressure and room temperature. After 1 h, the solution was filtered and evaporated. After recrystallization from acetone–hexane (2:1), the residual solid melted at 196–199 °C, reminiscent of tetrahydroestafietone (mp 198 °C)[30] which has α-oriented C-4 and C-11 methyl groups. An authentic sample of this substance was not available for comparison.

Reaction of Isoeremanthin with Bromine. To a solution of **4** (1.50 g, 6.50 mmol) in 50 mL of dry ether kept at −70 °C was added dropwise and with stirring a solution of Br_2 (1.029 g, 6.50 mmol). The mixture was allowed to stand for 1 h at −70 °C; subsequently 5% aqueous $NaHCO_3$ (10 mL) was added at once. The mixture was allowed to come to reach room temperature slowly and diluted with $CHCl_3$. The organic phase was washed with water, dried ($MgSO_4$), and concentrated in vacuo. The resulting oil was purified by column chromatography, yield 1.33 g of **5** (53%): mp 94–96 °C dec; IR bands at 1765, 1654, 1235, 1210, and 1115 cm^{-1}; NMR signals at 1.89 (br, C-4 methyl), 2.00 (C-10 methyl), 4.87 (t, J = 9 Hz, H-6), 4.79 (t, J = 3 Hz, H-9), 5.48 (m, H-3), 5.45 (d), and 6.22 (d, J = 3.5 Hz, H-13), mass spectrum *m/e* (rel intensity) 392 (M^+, 12) 390 (M^+, 17), 388 (M, 11), 319 (23), 312 (55), 310 (28), 231 (86), 150 (75), 81 (53), 80 (80), 79 (98), 77 (100).

Anal. Calcd for $C_{15}H_{18}Br_2O_2$: C, 46.27; H, 4.62; Br, 40.87. Found: C, 45.86; H, 4.46; Br, 41.28.

Other fractions from the chromatogram represented a mixture of tetrabromides, a trace of a hexabromide, and starting material (16%).

Epoxidation of 5. To a solution of **5** (1.0 g, 2.57 mmol) in CH_2Cl_2 (30 mL) cooled to 0 °C was added with stirring *m*-chloroperbenzoic acid (0.66 g, 3.85 mmol). After 3 h, the mixture was diluted with $CHCl_3$ (15 mL), washed with $NaHCO_3$ and water, dried, and concentrated to give approximately 1 g of a clear oil which was chromatographed over 20 g of silica gel. Gradient elution with hexane–EtOAc gave after concentration 0.64 g (61%) of **6** as colorless needles: mp 107 °C; IR bands at 1765, 1650, 1145, 955, and 825 cm^{-1}; NMR signals at 1.63 (C-4 methyl), 2.00 (C-10 methyl), 3.44 (m, H-3), 4.80 (m, H-6 and H-9), 5.46 and 6.23 (d, J = 3.5 Hz, H-13); mass spectrum *m/e* (rel intensity) 393 (M^+, 2), 391 (M^+, 5), 389 (M^+, 3), 327 (73), 325 (66), 245 (43), 81 (29), 79 (26), 43 (100).

Anal. Calcd for $C_{15}H_{18}Br_2O_5$: C, 44.44; H, 4.44; Br, 39.25. Found: C, 44.44; H, 4.52; Br, 39.50.

Another substance which was tentatively identified as the β-epoxide was also isolated in ca. 20% yield.

Debromination of 6. To a solution of **6** (0.408, 0.98 mmol) in MeOH (20 mL) was added with vigorous stirring 1 g of zinc powder and 0.15 mL of AcOH. After 1 h of stirring at room temperature, the mixture was filtered and the precipitate washed with ca. 20 mL of $CHCl_3$. The combined filtrate and washings were evaporated in vacuo, the residue was taken up in $CHCl_3$, washed with $NaHCO_3$ and H_2O, dried, and evaporated to give 0.24 g (96%) of **7**: mp 185–188 °C, IR bands at 1760, 1660, 1135, 978, and 813 cm^{-1}; NMR signals at 1.67 (C-4 methyl), 1.79 (br, C-10 methyl), 3 33 (br, H-3), 3.93 (dd, J's = 9.5, 12 Hz, H-6), 5.59 (br, H-9), 5.49 and 6.23 (d, J = 3.5 Hz, H-13); mass spectrum *m/e* (rel intensity) 246 (M^+, 7), 231 (6), 152 (7), 95 (100), 43 (32).

Anal. Calcd for $C_{15}H_{18}O_3$: mol wt, 246.1251. Found: mol wt (MS), 246.1175.

Conversion of 7 to Eregoyazin. To a solution of **7** (0.22 g, 0.89 mmol) in benzene (20 mL) was added with stirring freshly distilled BF_3·OEt_2 (0.12 mL, 0.89 mmol). After 1 h at room temperature, $CHCl_3$ (40 mL) and aqueous $NaHCO_3$ (5%, 20 mL) was added. The organic layer was washed with H_2O, dried, and concentrated. Purification of the residue by column chromatography (13 g of adsorbent, gradient elution with hexane–EtOAc) gave 0.18 g of **2**, mp 178–181 °C, identical in all respects with the substance isolated from *E. goyazensis*.

Zn–Acetic Acid Reduction of Eregoyazin. To a solution of **2** (0.15 g, 0.61 mmol) in glacial AcOH (15 mL) was added with vigorous stirring 3.5 g of zinc powder. The mixture was stirred at 70 °C for 8 h, cooled, and filtered, and the solid was washed with $CHCl_3$. The combined filtrate and washings were evaporated in vacuo; the residue was taken up in $CHCl_3$, washed with $NaHCO_3$ solution and H_2O, dried, and evaporated. A 2:1 mixture of hexane–benzene was added and the mixture was refluxed for 1 min. After cooling, the mixture was filtered. TLC analysis of the precipitate showed that it consisted mainly of material not absorbing strongly in the UV region. Further purification of the residue by column chromatography (2 g of adsorbent, gradient elution with hexane–EtOAc) gave 0.105 (66%) of **3**, mp 186–189 °C, identical in all respects with eregoyazidin from *E. goyazensis*.

Registry No.—**2**, 63569-75-5; **3**, 63599-46-2; **4**, 63569-76-6; **5**, 63569-77-7; **6**, 63569-78-8; **7**, 63569-79-9.

References and Notes

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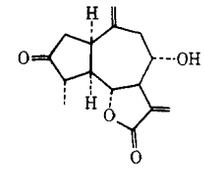
(2) On leave of absence (1975–1976) at Florida State University on a grant from Fundacão de Amparo a Pesquisa do Estado de São Paulo.

(3) P. M. Baker, C. C. Fortes, E. G. Fortes, G. Gazinelli, B. Gilbert, J. N. C. Lopes, J. Pellegrino, T. C. B. Tomassini, and W. Vichnewski, *J. Pharm. Pharmacol.*,

24, 853 (1972).
(4) T. C. B. Tomassini and B. Gilbert, *Phytochemistry*, **11**, 1177 (1972).
(5) W. Vichnewski and B. Gilbert, *Phytochemistry*, **11**, 2563 (1972).
(6) M. Garcia, A. J. R. Silva, P. M. Baker, B. Gilbert, and J. A. Rabi, *Phytochemistry*, **15**, 331 (1976).
(7) A. Corbella, P. Gariboldi, G. Jommi, and G. Ferrari, *Phytochemistry*, **13**, 459 (1974).
(8) W. Vichnewski, S. J. Sarti, B. Gilbert, and W. Herz, *Phytochemistry*, **15**, 191 (1976).
(9) R. Raffauf, P.-K. C. Huang, P. W. LeQuesne, S. B. Levery, and T. F. Brennan, *J. Am. Chem. Soc.*, **97**, 6884 (1975). The source of extract yielding eremantholide A was not specified but we assume that it was prepared from the nonwoody part of the shrub.
(10) W. Vichnewski, J. N. C. Lopes, D. D. S. Filho, and W. Herz, *Phytochemistry*, **15**, 1775 (1976).
(11) L. A. Macaira, M. Garcia, and J. A. Rabi, *J. Org. Chem.*, in press.
(12) W. Stöcklin, T. G. Waddell, and T. G. Geissman, *Tetrahedron*, **26**, 2397 (1970). Although many departures from this generalization have been found and discussed,[13] the rule is applicable to guaianolides of type **2**.
(13) P. Sundararaman, R. S. McEwen, and W. Herz, *Tetrahedron Lett.*, 3809 (1973); P. S. Sundararaman and R. S. McEwen, *J. Chem. Soc., Perkin Trans. 2*, 1975 (1975); W. Herz and S. V. Bhat, *J. Org. Chem.*, **37**, 906 (1972); W. Herz and S. V. Bhat, *Phytochemistry*, **12**, 1737 (1973); W. Herz and R. P. Sharma, *ibid.*, **14**, 1561 (1975); P. J. Cox, G. A. Cox, and W. Herz, *J. Chem. Soc., Perkin Trans. 2*, 459 (1975); W. Herz and R. P. Sharma, *J. Org. Chem.*, **41**, 1015, 1248 (1975).
(14) Z. Samek, *Tetrahedron Lett.*, 671 (1970).
(15) W. Parker, J. S. Roberts, and R. Ramage, *Q. Rev., Chem. Soc.*, **21**, 311 (1967); W. Herz, in "Pharmacognosy and Phytochemistry", H. Wagner and L. Hörhammer, Ed., Springer-Verlag, New York, N.Y., 1971, p 64; W. Herz in "Chemistry in Botanical Classification", Nobel Symposium 25, Nobel Foundation and Academic Press, New York, N.Y., 1973, p 153.
(16) The effect exerted by β-oriented C-10 Br on the chemical shift of H-6 in various derivatives of eremanthin[17] is shown in Table I. The table shows that, while a β-oriented bromine atom of C-9 has little or no effect on the chemical shift of H-9, a β-oriented bromine atom attached to C-10 causes a marked downfield shift (>0.8 ppm). In the NMR spectrum of **5**, the H-6 signal appears at 4.87 ppm, thus strongly supporting the proposed stereochemistry.
(17) L. A. Macaira, M. Garcia, and J. A. Rabi, unpublished results.
(18) D. H. R. Barton, J. E. D. Levisalles, and J. T. Pinhey, *J. Chem. Soc.*, 3472 (1962).
(19) T. Sasaki and S. Eguchi, *Bull. Chem. Soc. Jpn.*, **41**, 2453 (1968).
(20) E. H. White, S. E. Eguchi, and J. N. Marx, *Tetrahedron*, **25**, 2099 (1969).
(21) For example, grossheimin, which has been assigned the 4α-methyl configuration,[22,23] is not epimerized by K_2CO_3 or alumina, reagents which effect the conversion **8** → **9**.



(22) Z. Samek, M. Holub, K. Vokáč, B. Drozdz, G. Jommi, P. Gariboldi, and A. Corbella, *Collect. Czech. Chem. Commun.*, **37**, 2611 (1972).
(23) A. G. Gonzales, J. Bermejo Barrera, J. L. Breton Funes, and M. Rodriguez Rincones, *Anal. Quim. Acta*, **69**, 563 (1973).
(24) ORD curves of **8** and **9** have been recorded previously.[22]
(25) Unfortunately, after the dichotomy was discovered, the amount of eregoyazidin remaining at our disposal was too small to permit assessment of its behavior toward K_2CO_3.
(26) C. R. Narayanan and N. K. Venkatasubramanian, *Tetrahedron Lett.*, 5865 (1966).
(27) While the behavior of 11,13-dihydroguaianolides on boiling with 10% K_2CO_3–MeOH has been used as a criterion for the configuration at C-11, careful examination of recent work[28] suggests that the matter is more complicated than represented ordinarily. Exposure of a few milligrams of eregoyazidin to these conditions[28] resulted in disappearance of the Cotton effect and formation of a mixture of epimeric 3-ketoguaianolides (IR bands at 1760 and 1735 cm^{-1}) which we did not attempt to separate.
(28) A. G. Gonzalez, J. Bermejo, G. M. Massanet, J. M. Amaro, B. Dominguez, and A. Morales, *Phytochemistry*, **15**, 991 (1976).
(29) Melting points were determined on a Köfler hot-stage microscope or in a mel-temp apparatus and are uncorrected. IR spectra were run as KBr pellets on Perkin-Elmer 137-B or 257 spectrophotometers. Proton NMR spectra are given in $CDCl_3$ solution using Me_4Si as internal standard and were recorded on a Varian XL-100 instrument, except for the experiments involving eregoyazin and eregoyazidin which were carried out on a Bruker HX-270 instrument. CD spectra were recorded in $CHCl_3$ solution on a Jasco spectropolarimeter. High-resolution mass spectra were obtained on Varian-Mat CH-5 and MS-902 instruments. Silica gel GF_{254}, PF_{254}, and Kieselgel 60 were used for TLC, preparative TLC, and column chromatography, respectively.
(30) F. Sanchez-Viesca and J. Romo, *Tetrahedron*, **19**, 1285 (1963); A. Romo de Vivar, A. Cabrera, A. Ortega, and J. Romo, *ibid.*, **23**, 3906 (1967).

New *ent*-Clerodane-Type Diterpenoids from *Baccharis trimera*[1a]

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The isolation of three new closely related *trans*-clerodane-type diterpenoids, **1a**, **1b**, and **2a**, from the medicinal plant *Baccharis trimera* (Less.) DC is described. Proof for the proposed structures and definite evidence for the stereochemistry were provided by x-ray analysis of **2a**. The flavone eupatorin was also isolated from *B. trimera* and the dihydroflavone sakuranetin from *B. retusa* DC.

Several members of the large Western hemisphere genus *Baccharis* (Compositae, tribe Astereae) are used as folk medicines by the populations of their respective habitats. In the present communication, we report on constituents of two such species which are native to São Paulo and neighboring states of Brazil.

Ethyl acetate extracts of *Baccharis trimera* (Less.) DC, a well-known medicinal plant of this region,[3,4] afforded protection against infection by cercaria of *Schistosoma mansoni*. Large-scale extraction and extensive chromatography afforded four crystalline compounds in relatively small amounts. One of these was eupatorin (3′,5-dihydroxy-4′,6,7-trimethoxyflavone, **3**)[8]; the others were three new apparently closely related diterpenoids: $C_{20}H_{28}O_4$, mp 151–153 °C (**1a**); $C_{20}H_{28}O_5$, mp 203–205 °C (**1b**); and $C_{20}H_{26}O_5$, mp 195–196 °C (**2a**).

The extra oxygen of **1b** and **2a** was that of a secondary hydroxyl group as evidenced by the IR spectra and the facile oxidation of **1b** and **2a** to the ketones **1c** and **2b** which exhibited new IR bands at 1705 and 1700 cm^{-1}, respectively, and lacked a multiplet near 4.1 ppm found in the NMR spectra of **1b** and **2a** (Table I). A pronounced diamagnetic shift of a doublet near 5.3 ppm (also present in the NMR spectrum of **1a**) to near 4 ppm accompanied these oxidations, the doublet being the downfield half of an AB system where B, near 3.9 ppm, was in turn coupled (J = 3 Hz) to another proton. The chemical shift of the AB system seemed characteristic of the methylene protons in the grouping –(O=)$COCH_2$– (A), with the B proton apparently long-range coupled to another proton.

In the same region of the NMR spectra, **1a–c** also displayed the AB part of an ABX system near 4.45 and 3.95 ppm. The