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SHORT COMMUNICATION

SCHISTOSOMICIDAL SESQUITERPENE LACTONE FROM *EREMANTHUS ELAEAGNUS*

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Key Word Index—*Eremanthus elaeagnus;* Compositae; sesquiterpene lactone; eremanthine; schistosomicide.

Abstract—Eremanthine, a new guaianolide isolated from the heartwood oil of *Eremanthus elaeagnus* Sch. Bip., has the structure (I). It is the principal active constituent responsible for the prophylactic action of the oil against the human parasite *Schistosoma mansoni.*

INTRODUCTION

A NUMBER of oils derived from plants of the Compositae, when applied to the skin of experimental animals, protect these against infection by cercariae of the parasite *Schistosoma mansoni.*[1] Among these are the heartwood oils of the related arboreal species *Eremanthus elaeagnus* Sch.-Bip.,[2] *Vanillosmopsis erythropappa* Sch.-Bip., and *Moquinea velutina* Bong. All of these species have been shown to contain α,β-unsaturated γ-lactones which are largely responsible for the reported biological activity.[3]

In the case of *Eremanthus elaeagnus*, the guaianolide eremanthine (I), m.p. 73–74°,[4] forms 13% of the hexane soluble trunk extract. The IR and UV spectra showed the presence of an α,β-unsaturated γ-lactone, ν1665 and 1770 cm^{-1}, λ207 (ϵ 15 100), and both terminal (ν890 cm^{-1}) and trisubstituted (ν820 cm^{-1}) double bonds. The MS determined molecular formula of eremanthine (I), $C_{15}H_{18}O_2$, indicated the sesquiterpenoid nature of the lactone and excluded further oxygen functions. The NMR spectrum showed that there were in fact two terminal methylene groups, one (5·16δ and 4·98δ, J = 0 Hz) evidently close to an oxygen function which deshields one proton, the other (5·45δ and 6·15δ, J = 3·5 Hz) conjugated to the lactone carbonyl function. No angular methyl groups were present but one uncoupled allylic methyl group (1·82δ) was possibly located on the trisubstituted double bond, whose sole proton absorbed as a broad doublet at 5·55δ. This location was confirmed by selective epoxidation of this double bond to give II, the methyl absorption moving to 1·36δ and the new epoxy-linked proton to 2·98δ, doublet, J = 5·5 Hz. The terminal vinyl proton absorptions in II remain unchanged. Hydrogenation of eremanthine (I) resulted in the uptake of three moles of hydrogen with production of the hexahydro-derivative (probably a mixture of isomers, III), $C_{15}H_{24}O_2$, MW 236, which retains the γ-lactone functio

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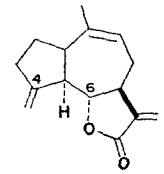
[1] B. GILBERT, J. P. DE SOUZA, M. FASCIO, M. KITAGAWA, S. S. C. NASCIMENTO, C. C. FORTES, A. DO PRADO SEABRA and J. PELLEGRINO, *Anais Acad. Bras. Ciências* 42 supl. 397 (1970).

[2] Collected in the Serra de Ouro Prêto, Minas Gerais, Brazil.

[3] T. C. B. TOMASSINI and B. GILBERT, *Phytochem.* **11**, 1177 (1972).

[4] First isolated from *E. elaeagnus* by E. G. FORTES and C. C. FORTES, Univ. Nac. de Brasília.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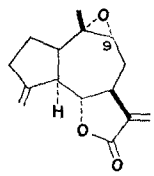
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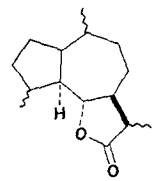
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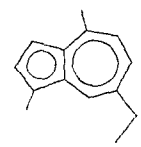
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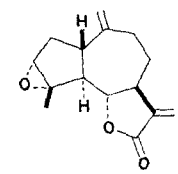
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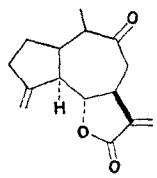
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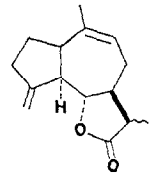
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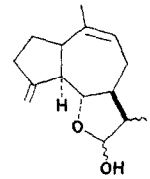
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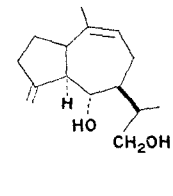
(IX)

(ν1780 cm^{-1}). Eremanthine is thus tricyclic and the production of chamazulene (IV) on Pd dehydrogenation suggested that it was a guaianolide. In fact the IR speetrum of the perhydro-derivative (III) was superimposable on that of III derived from dehydrocostus lactone.[5]

On the basis of the guaianolide skeleton, the lactonic oxygen atom must be located at C-6, since the C-6 proton showed only two *trans* diaxial couplings (with C-5, and C-7 protons). The partly deshielded terminal methylene group could thus be placed at C-4. Further evidence for this location was obtained by comparison of the epoxide (II) with the isomeric epoxide estafiatin (V).[6] In estafiatin the methyl group attached to the epoxide ring absorbs at 1·6δ (deshielded by two oxygen atoms, compare 1·36δ for II, deshielded by only one oxygen atom), while the terminal methylene protons both absorb at 4·91δ in contrast to the downfield shift shown by one similar proton (5·16δ) in II.[5] The trisubstituted double bond in II must, therefore, be located in the seven-membered ring and this was confirmed by rearrangement of the epoxide to the ketone (VI), whose ketonic carbonyl absorption at 1718 cm^{-1} was consistent with location in a seven- but not a five-membered ring.

Reduction of eremanthine with $NaBH_4$ results firstly in saturation of the lactone methylene group to give 11,13-dihydroeremanthine (VII) ν_{CO} 1870 cm^{-1}. Reduction of the lactone function follows to give firstly the lactol (VIII), ν_{OH} 3450 cm^{-1}, and finally the diol (IX). This series of products still shows the IR and NMR absorptions characteristic of the two isolated double bonds and allylic methyl group, while in IX the absorption due to the primary alcoholic protons appears as an ABX pattern between 3 and 4δ and that of the C-13 methyl group as a doublet at 0·98δ.

MS molecular ions and breakdown patterns were consistent with all the structures shown. The *trans*-diaxial coupling observed for the C-6 proton in eremanthine and several derivatives is consistent with the relative stereochemistry illustrated for positions 5, 6, and 7. The fact that the C-9 proton in II absorbs as a doublet indicates that it is perpendicularly disposed relative to one of the C-8 protons and this is only possible when the epoxide ring is attached *cis* to the lactonic oxygen atom. Finally, the negative Cotton effect at 256 nm is in accord with the absolute stereochemistry indicated.[7]

[5] S. B. MATHUR, S. V. HIREMATH, G. H. KULKARNI, G. R. KELKAR, S. C. BHATTACHARYYA, D. SIMONOVIC and A. S. RAO, *Tetrahedron* **21**, 3575 (1965).
[6] J. ROMO and F. SANCHES-VIESCA, *Tetrahedron* **19**, 1285 (1963).
[7] T. G. WADDELL, W. STÖKLIN and T. A. GEISSMAN, *Tetrahedron Letters* 1313 (1969).

The biological activity of eremanthine is under investigation. The presence of the unsaturated lactone function in I appears to provide the plant with a defence mechanism against predatory attack.

EXPERIMENTAL

M.ps are uncorrected. NMR and MS were measured by Drs. Paul M. Baker, Lois J. Durham, and Alan M. Duffield.

Eremanthine (I). Pulverized trunk wood of mature trees of *Eremanthus elaeagnus* (12 k) was extracted at room temp. with hexane (18 l.) giving, after removal of the solvent, a clear brown oil (192 g) from which crude eremanthine (26 g) separated on standing. Recrystallization from hexane gave eremanthine (I) as colourless needles, m.p. 73–74° $[\alpha]_D^{29}$ −59° (*c*, 1·0 in $CHCl_3$), λ_{max}^{EtOH} 207 nm (ϵ 15 100), ν_{max}^{KBr} 1770 (s), 1665 (s), 890 (s), 820 (m) cm^{-1}, NMR (100 MHz, $CDCl_3$) 1·82 (3H, singlet with fine structure, allylic C$\underline{H}_3$), 3·92 (1H, triplet, J = 10 Hz, C-6 H), 4·98 and 5·16 (two 1H singlets, C-4 =C$\underline{H}_2$), 5·45 and 6·15 (two 1H doublets, J = 3·5 Hz, C-11 =C$\underline{H}_2$), and 5·55 δ (1H, broad doublet, with much fine structure, principal J = 7 Hz). The mass spectrum (MS 9 ion source inlet, 70 eV) showed principal peaks at *m/e:* 230·13089 (M^+, calc. for $C_{15}H_{18}O_2$: 230·13067, 27%), 215 (5%), 187 (12%), 172 (41%), 150 (100%), 122 (36%).

Eremanthine-9,10-epoxide (II). A mixture of eremanthine (I, 60 mg) and *m*-chloroperbenzoic acid (60 mg) in $CHCl_3$ was heated under reflux during 30 min, cooled, washed with aq. $NaHCO_3$, H_2O, dried, and evaporated. The residual solid, recrystallized from hexane–benzene gave eremanthine-9,10-epoxide (II, 50 mg) m.p. 153·5–154°, ν_{max}^{KBr} 1760 (s), 1670 (m), 1157 (s), 899 (s) cm^{-1}, NMR (60 MHz, CCl_4) 1·36 (3H, singlet, C-10 C$\underline{H}_3$), 2·98 (1H, doublet, J = 5·5 Hz, epoxide C–H), 3·57 (1H, double doublet, J = 9·0 and 9·5 Hz, C-6 H), 4·98 and 5·16 (two 1H broad singlets, C-4 =C$\underline{H}_2$), 5·45 and 6·15 δ (two 1H doublets, J = 3·5 Hz, C-11 =C$\underline{H}_2$). The MS (MS 9, ion source inlet, 70 eV) showed principal peaks at *m/e*: 246 (M^+, 10%), 203 (73%), 185 (21%), 157 (41%), 131 (30%), 108 (100%), 107 (81%).

9,10-*Dihydroeremanthin-9-one* (VI). The epoxide (II, 30 mg) in benzene (3 ml) was treated with BF_3-etherate (0·25 ml) during 2·5 hr at room temp., then the solution diluted with EtOAc, washed with aq. $NaHCO_3$, H_2O, dried (Na_2SO_4) and evaporated. The residue, chromatographed over silica gel (900 mg) gave, after recrystallization from benzene, 9,10-dihydroeremanthine-9-one (VI, 23 mg), m.p. 103–104°, ν_{max}^{KBr} 1770 (s), 1718 (s), 1005 (s) cm^{-1}. The MS (Atlas CH4, ion source inlet, 70 eV) showed principal peaks at *m/e*: 246 (M^+, 10%), 228 (3%), 217 (8%), 200 (6%), 176 (7%), 109 (22%), 107 (22%), 83 (47%), and 80 (100%).

Hydrogenation of eremanthine. Eremanthine (I, 700 mg) was shaken with hydrogen and platinum black in EtOH (50 ml) at room temp. during 10 hr. The crude hydrogenation product distilled at 120–130°/0·5 mm to give hexahydroeremanthine as a colourless viscous oil, ν_{max}^{film} 1780 (s), 1184 (s), 987 (s) cm^{-1}, no vinyl proton absorption in the NMR spectrum, MS (Atlas CH4, ion source inlet, 70 eV), 236 (M^+ 0·9%), 218 (1·1%), 207 (0·7%), 192 (7%), 163 (54%), 124 (49%), 81 (100%).

Borohydride reduction of eremanthine. To eremanthine (80 mg) in MeOH (5 ml) at room temp. was added slowly $NaBH_4$ (7 mg). Excess reagent was destroyed with ice and dil. HCl and the product extracted with ether. The ethereal solution was washed, dried, evaporated and the residue (74 mg) chromatographed over silica gel (2·5 g) in hexane-EtOAc to give three products. The first, eluted with 10% EtOAc, gave 11,13-dihydroeremanthine (VII, 5 mg), m.p. 64–66°, ν_{max}^{KBr} 1780 (s), 1660 (m), 1184 (s), 995 (s), 885 (s) cm^{-1}, MS (Atlas CH4, ion source inlet, 70 eV): 232 (M^+ 7%), 214 (4%), 152 (100%), 124 (16%), 107 (17%). The second product, eluted with 20% EtOAc, gave the lactol (VIII, 11 mg), m.p. 108–109°, ν_{max}^{KBr} 3450 (m), 1645 (w), and 897 (m) cm^{-1}, MS (MS 9, ion source inlet, 70 eV): 234 (M^+, 16%), 216 (36%), 201 (31%), 154 (100%), 136 (46%), 119 (48%), 107 (56%), 105 (57%). The third product, eluted with 30% EtOAc, yielded the diol (IX, 46 mg), m.p. 78–79°, ν_{max}^{KBr} 3450 (s), 1645 (m), 1031 (s), 910 (s) cm^{-1}, NMR (60 MHz, $CDCl_3$) 0·98 (3H, doublet, J = 6 Hz, C-11 C$\underline{H}_3$), 1·67 (3H, singlet, allylic C$\underline{H}_3$), 3·25–3·82 (2H, ABX pattern after D_2O exchange, J_{AB} = 10 Hz, J_{AZ} = 4 Hz, C$\underline{H}_2$OD), 5·08 (2H, broad singlet, C-4 =C$\underline{H}_2$), 5·38 (1H, broad triplet, C-9 vinyl H). MS (Atlas CH4, ion-source inlet, 70 eV) showed principal peaks at *m/e*: 236 (M^+, 4%), 218 (7%), 187 (9%), 159 (19%), 156 (21%), 134 (65%), 121 (44%), 119 (51%), 107 (43%), 81 (100%).

Dehydrogenation of eremanthine. A mixture of eremanthine (520 mg) and 10% Pd-C (800 mg) in nujol (6 ml) was held at 280–300° during 15 min, cooled, diluted with hexane and filtered. The deep blue filtrate was concentrated, extracted with 85% H_3PO_4 (2 ml) and the lower acidic layer separated, diluted with ice and water (5 ml) and re-extracted with hexane. The hexane extract was dried, concentrated and passed over neutral alumina (50 g) to give a blue eluate (trinitrobenzene adduct, m.p. 123–126° from EtOH; chamazulene trinitrobenzene adduct, lit. m.p. 130–131°). This was taken up into 85% H_3PO_4, washed (CCl_4), and the acid layer diluted and re-extracted with CCl_4. The organic layer, dried ($MgSO_4$) and evaporated gave chamazulene, whose IR spectrum was in full accord with the published spectra.[8] The UV spectrum [λ_{max} 242, 285, 303

[8] L. Manzoni and G. Bandiera, *Gazz. Chim. Ital.* **90,** 947 (1960).

(infl.), 335 (infl.), 348, 366, 612, 664 (sh) nm] also corresponded with lit. values,[9] and NMR absorption ($CDCl_3$, 60 MHz) was observed at 1·32 (3H triplet, $J = 7$ Hz, CH_2 $C\underline{H}_3$); 2·58 (2H, singlet, Ar–$C\underline{H}_3$); 2·72 (2H, singlet, Ar–CH_3), these last absorptions superimposed on a 2 proton quartet due to Ar $C\underline{H}_2$ CH_3; 6·5–8·15 (5H, Ar-H). MS showed the principal peaks at *m/e*: 198 (18%, M^+ of homologous 1,4-dimethyl-7-isopropylazulene), 184 (97%, M^+, chamazulene), 169 (100%, M-CH_3).

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[9] E. STAHL, *Chem. Ber.* **87,** 202 (1954).