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LASERINE OXIDE, AN EPOXIDE FROM *GUILLONEA SCABRA**†

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Key Word Index—*Guillonea scabra*; Umbelliferae; new laserine derivative; laserine oxide.

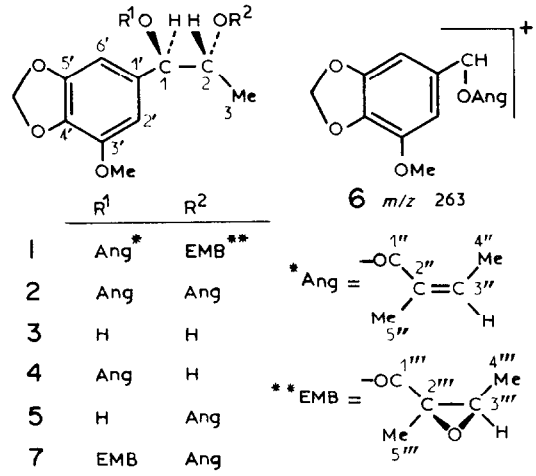
Abstract—From the roots of *Guillonea scabra* several previously known compounds were isolated. In addition, a new epoxy derivative of laserine was obtained and its structure was established by chemical and spectroscopic means.

INTRODUCTION

In our search for new natural products in plants endemic in the Iberian Peninsula [1, 2], we have examined the root of *Guillonea scabra* (Cav.) Cosson (= *Laserpitium scabrum* Cav.), a pubescent perennial umbelliferous species. We have isolated from this source the previously known substances myristicin [3], latifolone [4], scoparone [5, 6], sitosterol, guaiol, malaphilinin [7] and badkysin [8], as well as a new natural product (**1**), the structure of which was established by chemical and spectroscopic means.

RESULTS AND DISCUSSION

Laserine oxide (**1**) has a molecular formula of $C_{21}H_{26}O_8$ and its IR spectrum shows typical absorptions for an aromatic ring (3080, 1635, 1615, 1517, 850 cm^{-1}) and an ester group (1740, 1720 cm^{-1}). The ^1H NMR and ^{13}C NMR spectra of **1** showed characteristic signals for an angelic ester [δ 6.15 (1H, *qq*, $J_{vic} = 7$ Hz, $J_{homoallylic} \simeq 1$ Hz, H-3″), 1.99 (3H, *dq*, $J_{vic} = 7$ Hz, $J_{homoallylic} \simeq 1$ Hz, 3H-4″), 1.96 (3H, *d*, $J_{homoallylic} \simeq 1$ Hz, 3H-5″), and 166.2 (*s*, C-1″), 139.1 (*d*, C-3″), 127.2 (*s*, C-2″), 20.5 (*q*, C-4″) and 15.9 (*q*, C-5″)] [9], and for a 2,3 - epoxy - 2 - methylbutanoate group [δ 3.00 (1H, *q*, $J = 5.5$ Hz, H-3‴), 1.53 (3H, *s*, 3H-5‴), 1.22 (3H, *d*, $J = 5.5$ Hz, 3H-4‴), and 169.0 (*s*, C-1‴), 59.8 (*d*, C-3‴), 59.5 (*s*, C-2‴), 19.1 (*q*, C-4‴) and 16.8 (*q*, C-5‴)] [10–12]. The presence of a 2,3 - epoxy - 2 - methylbutanoate ester was further confirmed by the mass spectrum of compound **1**, which showed a base peak at *m/z* 290, by loss of $C_5H_8O_3$ [10, 11]. The two ester groups must be attached to the vicinal 1,2 positions of a propyl moiety [δ 5.76 (1H, *d*, $J = 7$ Hz, H-1), 5.35 (1H, five lines, $J = 7$ Hz, H-2), 1.17 (3H, *d*, $J = 7$ Hz, 3H-3), and 76.7 (*d*, C-1), 72.3 (*d*, C-2) and 13.5 (*q*, C-3)]. The angeloxy - [2,3 - epoxy - 2 - methyl] - butyriloxy - propyl group was bound to an aromatic ring [δ 6.60 (2H, *s*, H-6′ and H-2′) and 148.8 (*s*, C-3′), 143.4 (*s*, C-5′), 135.2 (*s*, C-4′), 131.2 (*s*, C-1′), 107.3 (*d*, C-6′) and 101.5 (*d*, C-2′)] which had a methoxyl group [δ 3.90 (3H, *s*) and 56.6 (*q*)] and a methylendioxy group [δ 5.97 (2H, *s*) and 101.5 (*t*)] as substituents. All the ^1H NMR spectral assignments have been confirmed by double resonance experiments (see Experimental).



	R^1	R^2
1	Ang*	EMB**
2	Ang	Ang
3	H	H
4	Ang	H
5	H	Ang
7	EMB	Ang

By analogy with laserine (**2**) [4], all the above data of laserine oxide may be accommodated on structure **1**, which was established as follows.

Alkaline hydrolysis of compound **1** under strong conditions yielded the diol **3**, identical in all respects with the compound obtained from laserine (**2**) by identical treatment [4], thus confirming the presence of this structural part in the molecule of compound **1**, and establishing a *threo* configuration for the glycol system (see also Experimental).

On the other hand, mild alkaline treatment of compound **1** produced two isomeric monoangelates (**4** and **5**), one of which (**5**) originated from the other by a transesterification reaction. Comparison of the

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Table 1. ^{1}H NMR chemical shifts of compounds **1**, **4** and **5** (solvent $CDCl_3$)

	1	4	5	δ(1)–δ(4)	δ(1)–δ(5)
Aromatic (2H)	6.60	6.56	6.52	0.04	0.08
Methylen-dioxy (2H)	5.97	5.96	5.90	0.01	0.07
Methoxy (3H)	3.90	3.90	3.84	0.00	0.06
Angeloyl group					
H-3″	6.15	6.11	6.03	0.04	0.12
3H-4″	1.99	1.99	1.90	0.00	0.09
3H-5″	1.96	1.96	1.87	0.00	0.09

^{1}H NMR chemical shifts of the aromatic, methoxyl, methylendioxy and angeloyl protons in compounds **1**, **4** and **5** (Table 1) favours the alternative in which the angelic ester in laserine oxide (**1**) is attached to the C-1 position of the glycol system. Chemical shift differences between compounds **1** and **5** are much larger than those found between **1** and **4**, the latter values being within the limits of experimental error.

The attachment of the angelic ester at the C-1 position is also confirmed by the presence of a prominent peak at *m/z* 263 (ion **6**) in the mass spectrum of compound **1**, in which the peak at *m/z* 279 corresponding to the alternative structure **7** was virtually absent. This favoured fission of the C-1, C-2 bond was also revealed by the mass spectra of compounds **3** and **5** which showed the same base peak at *m/z* 181, by loss of C_2H_5O and $C_7H_{11}O_2$ fragments, respectively, from the molecular ion.

Finally, from the acidic fraction obtained in the mild alkaline hydrolysis of laserine oxide (**1**) we have isolated angelic acid, whereas in the strong alkaline treatment tiglic acid (arising from an isomerization of angelic acid) was obtained. In both cases, another acidic component was isolated as a 7:3 mixture of *threo* and *erythro* - 2,3 - dihydroxy - 2 - methylbutyric acids [13], arising from alkaline opening of the oxirane ring of the 2,3 - epoxy - 2 - methylbutanoate group of the molecule of laserine oxide (**1**). As the opening mechanism in basic medium of α-epoxy acids is known [14], we conclude that the configuration of the oxirane ring in **1** is *Z*, because its alkaline opened product was predominantly the *threo* - 2,3 - dihydroxy - 2 - methylbutyric acid.

Laserine oxide (**1**) is thus a simple derivative of laserine (**2**), and may be formed by a regioselective epoxidation of it.

EXPERIMENTAL

Mps were determined in a Kofler apparatus and are uncorr. ^{1}H NMR and ^{13}C NMR spectra were measured at 90 and 25.2 MHz, respectively, in $CDCl_3$ soln with TMS as internal standard. Assignments of ^{13}C NMR chemical shifts were made with the aid of off-resonance and noise-decoupled ^{13}C NMR spectra. Plant materials were collected in Oct. 1977, at the Sierra de Alcaraz, near Albacete, Spain, and voucher specimens were deposited in the Herbarium of the Faculty of Pharmacy (Madrid, Complutense University).

Extraction and isolation of the components. Dried and finely powdered *G. scabra* roots (1.5 kg) were extracted as previously described [15]. The extract (200 g) was repeatedly chromatographed on Si gel and Si gel plus 6% $AgNO_3$ columns with petrol and petrol–EtOAc mixtures as eluents, yielding the following compounds in order of elution: myristicin (300 mg) [3], latifolone (1.5 g) [4], guaiol (500 mg), sitosterol (200 mg), malaphilinin (300 mg) [7], laserine oxide (**1**, 200 mg), badkysin (150 mg) [8] and scoparone (700 mg) [5, 6]. The previously known products were identified by their physical (mp, $[\alpha]_D$) and spectroscopic (IR, ^{1}H NMR, MS) data and by comparison with authentic samples.

Laserine oxide (**1**). A syrup; $[\alpha]_D^{20} - 21°$ ($CHCl_3$; *c*0.57). IR ν_{max}^{film} cm^{-1}: see Results and Discussion. ^{1}H NMR and ^{13}C NMR: see Results and Discussion. ^{1}H NMR double resonance experiments: irradiation at δ 5.76 (H-1) transformed the signal at 5.35 (H-2) into a quartet; on irradiation at 5.35 (H-2), the H-1 (5.76) and 3H-3 (1.17) signals appeared as two singlets; irradiation at 3.00 (H-3‴) transformed the doublet at 1.22 (3H-4‴) into a singlet and finally irradiation at the signal at 1.99 (3H-4″) transformed the quartet at 6.15 (H-3″) into a singlet with residual allylic coupling. EIMS (direct inlet) 75 eV, *m/z* (rel. int.): 406 $[M]^+$ (52), 307 (5), 290 (100), 275 (9), 263 (33), 247 (6), 235 (8), 234 (8), 208 (23), 192 (44), 179 (75), 165 (18), 135 (15), 91 (45), 83 (85), 84 (80), 71 (32). $C_{21}H_{26}O_8$, MW 406.

Alkaline hydrolysis of **1**. (a) *Strong conditions.* A soln of compound **1** (25 mg) in 0.5 M ethanolic KOH (5 ml) was refluxed for 4 hr. The soln was then extracted with Et_2O yielding compound **3** (10 mg). The aq. residual soln was then acidified and extracted with Et_2O yielding a mixture of acids. This mixture was chromatographed on a Si gel column; elution with *n*-hexane yielded tiglic acid (characterized by their physical and spectroscopic data and by comparison with an authentic sample) and elution with *n*-hexane–EtOAc (2:1) gave a 7:3 mixture of *threo* and *erythro* - 2,3 - dihydroxy - 2 - methylbutyric acids: ^{1}H NMR [90 MHz, $(CD_3)_2CO$]: δ 1.17 (2.1H, *d*, *J* = 7 Hz, H-4 of the *threo* isomer), 1.33 (0.9H, *d*, *J* = 7 Hz, H-4 of the *erythro* isomer) and 1.55 (3H, *s*, H-5 of the two isomers) [13].

(b) *Mild conditions.* To a stirred soln of compound **1** (100 mg) in MeOH (15 ml), a satd aq. soln of K_2CO_3 (3 ml) was added and the mixture left for 24 hr at room temp. Work-up in the usual manner yielded angelic acid (characterized by their physical and spectroscopic data and by comparison with an authentic sample), the 7:3 mixture of *threo* and *erythro* - 2,3 - dihydroxy - 2 - methylbutyric acids and a mixture of compounds **3**–**5**, easily separated on prep. TLC (Si gel) eluted with *n*-hexane–EtOAc (10:1) (yield: 20, 5 and 18 mg, respectively).

Compound **3**. Mp 50–51° (Et_2O–pentane); $[\alpha]_D^{20} - 27°$ ($CHCl_3$; *c*0.50). IR ν_{max}^{film} cm^{-1}: 3380, 2980, 2940, 2900, 1635, 1615, 1517. ^{1}H NMR (90 MHz, $CDCl_3$): δ 6.46 (2H, *s*, H-2′ and H-6′), 5.89 (2H, *s*, $-O-CH_2-O-$), 4.19 (1H, *d*, *J* = 7.5 Hz, H-1), 3.86 (3H, *s*, –OMe), 3.73 (1H, five lines, *J* = 7.5 Hz, H-2) and 1.03 (3H, *d*, *J* = 7.5 Hz, H-3). EIMS (direct inlet) 75 eV, *m/z* (rel. int.): 226 $[M]^+$ (28), 181 (100), 123 (66), 95 (60), 83 (25), 55 (30). $C_{11}H_{14}O_5$, MW 226. Identical in all respect with the product previously described [4] and with an authentic sample of the *threo* isomer; *erythro* isomer: ^{1}H NMR: δ 4.53 (1H, *d*, *J* = 4.4 Hz, H-1) (Grande, M. and Pascual T. J., personal communication).

Compound **4**. A syrup; $[\alpha]_D^{20} - 39°$ ($CHCl_3$; *c*0.25). IR ν_{max}^{film} cm^{-1}: 3460, 2980, 2940, 2900, 2800, 1710, 1635, 1615, 1518. ^{1}H NMR (90 MHz, $CDCl_3$): see Table 1 and δ 5.51 (1H, *d*, *J* = 7 Hz, H-1), 4.05 (1H, five lines, *J* = 7 Hz, H-2) and 1.10 (3H, *d*, *J* = 7 Hz, H-3). EIMS (direct inlet) 75 eV, *m/z* (rel. int.): 308 $[M]^+$ (4), 290 (1), 264 (10), 208 (5), 181 (17), 165 (12), 153 (4), 137 (3), 123 (5), 95 (3), 83 (10), 55 (100). $C_{16}H_{20}O_6$, MW 308.

Compound **5**. Oil; $[\alpha]_D^{20} - 35°$ ($CHCl_3$; *c*0.50). IR ν_{max}^{film} cm^{-1}: 3470, 2990, 2950, 2900, 2790, 1710, 1640, 1615, 1515. ^1H NMR (90 MHz, $CDCl_3$): see Table 1 and δ 4.52 (1H, *d*, $J = 7$ Hz, H-1), 5.07 (1H, five lines, $J \approx 7$ Hz, H-2) and 1.05 (3H, *d*, $J = 7$ Hz, H-3). EIMS (direct inlet) 75 eV, *m/z* (rel. int.): 308 $[M]^+$ (5), 264 (1), 181 (100), 165 (4), 153 (19), 123 (34), 95 (20), 83 (48), 55 (40). $C_{16}H_{20}O_6$, MW 308.

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REFERENCES

1. Rodríguez, B. and Pinar, M. (1979) *Phytochemistry* **18**, 891.
2. Rodríguez, B. and Pinar, M. (1979) *An Quím.* **75**, 936.
3. González, A. G., Estévez, R., Báez, J., Pérez, J. and Ruano, T. (1974) *An Quím.* **70**, 286.
4. Holub, M., de Groote, R., Herout, V. and Sörm, F. (1968) *Collect. Czech. Chem. Commun.* **33**, 2911.
5. Dean, F. M. (1952) *Fortschr. Chem. Org. Naturst.* **9**, 225.
6. Johns, S. R., Lamberton, J. A., Price, J. R. and Sioumis, A. A. (1968) *Aust. J. Chem.* **21**, 3079.
7. Bagirov, V. Y., Sheichenko, V. I., Casanova, R. Y. and Pimenov, M. G. (1978) *Khim. Prir. Soedin.* 811.
8. Serkerov, S. and Sheichenko, V. I. (1970) *Khim. Prir. Soedin.* 425.
9. Pinar, M., Rodríguez, B. and Alemany, A. (1978) *Phytochemistry* **17**, 1736.
10. Seaman, F. C., Juneau, G. P., Di Feo, D. R., Jungk, S. and Fischer, N. H. (1979) *J. Org. Chem.* **44**, 3400.
11. Fischer, N. H., Wiley, R. and Wander, J. D., (1972) *J. Chem. Soc. Chem. Commun.* 137.
12. Walkins, S. F., Fischer, N. H. and Bernal, I. (1973) *Proc. Natl Acad. Sci. U.S.A.* **70**, 2434.
13. Layole, J. (1967) *C. R. Acad. Sci. Ser. C* **265**, 1277.
14. House, H. O. (1972) *Modern Synthetic Reactions*, 2nd edn, pp. 300–302. W. A. Benjamin, Menlo Park.
15. Pinar, M. and Rodríguez, B. (1977) *Phytochemistry* **16**, 1987.