Phytochemistry, Vol. 26, No. 9, pp. 2577–2579, 1987.
Printed in Great Britain.

0031–9422/87 $3.00 + 0.00

THYMOL DERIVATIVES FROM *CALEA NELSONII*

MARIANO MARTÍNEZ, V., ANTONIO SÁNCHEZ, F. and PEDRO JOSEPH-NATHAN*

Instituto de Química, Universidad Nacional Autónoma de México, Circuito Exterior, Ciudad Universitaria, Coyoacán 04510, México, D.F; * Departamento de Química del Centro de Investigación y de Estudios Avanzados, Instituto Politécnico Nacional, Apartado 14-740 México, D.F., 07000 México

(*Revised received* 10 *February* 1987)

Key Word Index—*Calea nelsonii*; *C. zacatechichi*; Asteraceae; Heliantheae; thymol derivatives; sesquiterpene lactone; flavone.

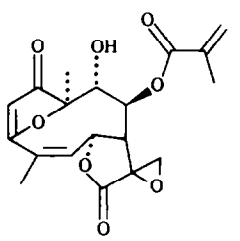
Abstract—*Calea nelsonii* yielded, besides the two known thymol derivatives 8,9-epoxy-7-isobutyryloxythymol isobutyrate and 10-acetoxy-8,9-epoxythymol isobutyrate, the five new thymol derivatives 10-acetoxy-8,9-epoxy-7-isobutyryloxythymol isobutyrate, 10-acetoxy-8,9-epoxy-7-hydroxythymol isobutyrate, 8-hydroxy-9-acetoxy-10-isobutyryloxythymol, 7-acetoxy-8-hydroxy-9,10-diisobutyryloxythymol and 7-isobutyryloxy-8,9-dihydroxythymol, while *C. zacatechichi* provided the known flavones 5-hydroxy-7,4′-dimethoxyflavone and 5,7-dihydroxy-4′-methoxyflavone and a known epoxysesquiterpene lactone. The structures of the new compounds were established by spectral methods. Some chemotaxonomic aspects are discussed.

INTRODUCTION

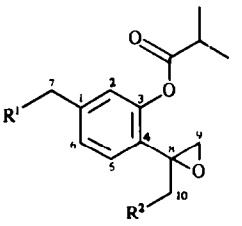
The large genus *Calea* [1] has been revised recently [2] and according to a new classification the name *C. ternifolia*, long thought to correspond to a Colombian species [2], is the correct name for the '*C. zacatechichi*' complex. However, the new botanical situation of the genus *Calea* is in disagreement with chemical findings. According to the new classification, *C. zacatechichi* Schldl and *C. nelsonii* Robinson and Greenman are both synonymns of *C. ternifolia* Kunth var. *ternifolia* [2]. However, our chemical studies of these two species show that their compositions are very different. Thus, from *C. zacatechichi* a known sesquiterpene lactone and two known flavones were isolated, while from two populations of *C. nelsonii* collected at different locations, thymol derivatives were isolated.

RESULTS AND DISCUSSION

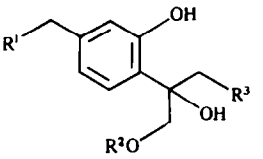
From the aerial parts of *C. zacatechichi* Schldl collected near Yucunduchi, Oaxaca, México, we isolated the known compounds 5-hydroxy-7,4′-dimethoxyflavone [3], 5,7-dihydroxy-4′-methoxy-flavone [4] and the furanoheliangolide type sesquiterpene lactone **1**, previously isolated from *C. pilosa* [5]. These results are in general chemotaxonomic agreement with those previously reported for other populations of *C. zacatechichi* [6, 7] which also afforded furanoheliangolide lactones. Two different collections of *C. nelsonii* Robinson and Greenman provided new (**2–6**) and known (**7**, **8**) thymol derivatives. A collection from Tepanatepec, Oaxaca, México afforded the new thymol derivatives **2–6** and 2-hydroxy-4-methylenehydroxy acetophenone previously reported as a degradation product of thymol derivatives [8]. In addition, the known compounds **7** and **8** were also isolated, their characterization being made by comparison of spectral data with those reported [8, 9]. A collection from Arriaga, Chiapas, México afforded the new thymol derivatives **2–4**.



1



	R^1	R^2
2	O*i*Bu	OAc
3	OH	OAc
7	O*i*Bu	H
8	H	OAc



	R^1	R^2	R^3
4	H	Ac	O*i*Bu
5	OAc	O*i*Bu	O*i*Bu
6	O*i*Bu	H	H

The structure of **2** became evident from the NMR data given in the Experimental section. The ^{13}C spectrum shows six signals due to a benzene ring, two $-CH_2O-$ groups, an epoxide on quaternary and secondary carbons, two isobutyrates and one acetate [10, 11], while the ^1H spectrum shows that one isobutyrate group is at C-3 [8, 9, 12, 13] and the acetate is at C-10 [9, 10, 14, 15].

Table 1. ^{1}H NMR data for the thymol derivatives **4–6** (80 MHz, $CDCl_3$, TMS as int. standard)

H	4	5	6
2	6.65 *br s*	6.80 *br s*	6.82 *br*
5	6.82 *d* (8)*	6.75 *d* (8)	7.00 *d* (8)
6	6.60 *dd* (8, 2)	6.95 *dd* (8, 2)	6.82 *br*
7	2.25 *s*	5.05 *s*	5.01 *s*
9	4.42 *s*	4.42 *s*	3.55 *d* (6)
9′	4.42 *s*	4.42 *s*	3.90 *d* (6)
10	4.42 *s*	4.42 *s*	1.54 *s*
10′	4.42 *s*	4.42 *s*	
AC	2.05 *s*	2.07 *s*	
R^3-CH	2.54 *m*	2.52 *m*	
R^3-C(Me)$_2$	1.12 *d* (7)	1.20 *d* (7)	
R^2-CH		2.52 *m*	R^1 2.54 *m*
R^3-C(Me)$_2$		1.20 *d* (7)	R^1 1.12 *d* (7)

*Values in parentheses are coupling constants in Hz.

Comparison of the ^{1}H NMR data of **2** and **3** revealed the structure of the latter, since the methylene group at C-7 now has an hydroxyl group.

The ^{1}H NMR data of **4**, **5** and **6** are compared in Table 1. In the case of **5**, the signals of the two isobutyrate groups are equivalent, thus indicating that they are linked to C-9 and C-10, and from the chemical shift of the benzylic methylene hydrogens it follows that the acetate is at C-7. Compound **4** has an aromatic methyl group and therefore the ester residues are at C-9 and C-10, while in **6** the only ester group is located at C-7. Further structural evidence for **4** was provided by demonstration that **4** was formed on treatment of **8** with boron trifluoride–etherate.

EXPERIMENTAL

The air-dried powdered plant materials were extracted with EtOAc at room temp. The extracts were fractionated by CC (silica gel) and eventually rechromatographed, the purity of the compounds being verified by TLC (silica gel, 60 mesh F254, thickness 0.25 mm) using hexane–EtOAc (7:3).

The residue (13 g) extracted from the aerial parts (53 g) of *Calea zacatechichi* Schldl (collected near Yucunduchi, Oaxaca, México, July 1985, voucher MEXU 32095 deposited at the Instituto de Biología Herbarium, UNAM) gave 203 mg **1** [5] (hexane–EtOAc 3:2) followed by 397 mg 5-hydroxy-7,4′-dimethoxyflavone [3] (hexane–EtOAc 3:2) and 521 mg 5,7-dihydroxy-4′-methoxyflavone [4] (hexane–EtOAc 1:4).

The residue (105 g) extracted from the aerial parts (441 g) of *Calea nelsonii* Robinson and Greenman (collected near Tepanatepec, Oaxaca, México, July 1985, voucher MEXU 321973 AM104 deposited at the same place as above) when chromatographed using hexane with increasing proportions of EtOAc, successively gave (4:1) 1587 mg **7** [8] (R_f 0.83) and 904 mg **8** [9] (R_f 0.62), then (2:1) 1312 mg **2** (R_f 0.57), followed successively (1:1) by 22 mg **4** (R_f 0.44), 50 mg **5** (R_f 0.37), 26 mg 2-hydroxy-4-methylene-hydroxyacetophenone [8] (R_f 0.30), 196 mg **3** (R_f 0.21) and 103 mg **6** (R_f 0.14).

The extracts (24 g) of the aerial parts (103 g) of *C. nelsonii* (collected near Arriaga, Chiapas, México, voucher MEXU 321973 AM 104) afforded 274 mg **2**, 57 mg **3** and 6 mg **4** when treated as above.

10-*Acetoxy*-8,9-*epoxy*-7-*isobutyryloxythymol isobutyrate* (**2**). Oil, IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1735 (ester), 1610, 1570, 1460 (aromatic ring); MS *m/z* (70 eV) (rel. int.): 319 [M59]$^+$ (5), 291 [M − 87]$^+$ (10), 235 [M − 142]$^+$ (7.1), 71 (36), 43 (100); ^{1}H NMR (90 MHz, $CDCl_3$, TMS): δ 7.49 (1H, *d*, $J_{5,6}$ = 8 Hz, H-5), 7.22 (1H, *dd*, $J_{5,6}$ = 8, $J_{2,6}$ = 2 z, H-6), 7.11(1H, *d*, $J_{2,6}$ = 2 Hz, H-2), 5.10 (2H, *s*, 2H-7), 4.55 (1H, *d*, $J_{10,10'}$ = 12 Hz, H-10), 4.21 (1H, *d*, $J_{10,10'}$ = 12 Hz, H-10′), 3.05 (1H, *d*, $J_{9,9'}$ = 5 Hz, H-9), 2.84 (1H, *m*, Ar-OOCCH), 2.76 (1H, *d*, $J_{9,9'}$ = 5 Hz, H-9′), 2.60 (1H, *m*, OOCCH at C-7), 1.99 (3H, *s*, Ac), 1.32 (6H, *d*, *J* = 7 Hz, Ar–OOCCHMe$_2$) and 1.17 (6H, *d*, *J* = 7 Hz, OOCCHMe$_2$ at C-7); ^{13}C NMR (25.2 MHz, $CDCl_3$, TMS): δ 176.4 (*s*, 7-OOC), 174.8 (*s*, 3-OOC), 170.1 (*s*), 148.7 (*s*, C-3), 138.1 (*s*, C-1), 129.2 (*d*, C-5), 128.7 (*s*, C-4), 125.1 (*d*, C-6), 121.8 (*d*, C-2), 65.2 (*t*, C-10), 64.9 (*t*, C-7), 56.6 (*s*, C-8), 50.8 (*t*, C-9), 34.1 (*d*, CHMe$_2$), 33.9 (*d*, CHMe$_2$), 20.5 (*q*, COMe) and 18.9 (4*q*, 2 CHMe$_2$).

10-*Acetoxy*-8,9-*epoxy*-7-*hydroxythymol isobutyrate* (**3**). Oil, IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3450 (alcohol), 1730 (ester), 1610, 1580, 1460 (aromatic ring); MS *m/z* (70 eV) (rel. int.): 308 (1.2) [M]$^+$ $C_{16}H_{20}O_6$, 183 (31.4), 165 (23), 71 (4), 43 (100); ^{1}H NMR (90 MHz, $CDCl_3$, TMS): δ 7.46 (1H, *d*, $J_{5,6}$ = 8 Hz, H-5), 7.21 (1H, *dd*, $J_{5,6}$ = 8, $J_{2,6}$ = 2 Hz, H-6), 7.09 (1H, *d*, $J_{2,6}$ = 2 Hz, H-2), 4.67 (2H, *s*, 2H-7), 4.52 (1H, *d*, $J_{10,10}$ = 12 Hz, H-10), 4.17 (1H, *d*, $J_{10,10'}$ = 12 Hz, H-10′), 3.04 (1H, *d*, $J_{9,9'}$ = 5 Hz, H-9), 2.80 (1H, *d*, $J_{9,9'}$ = 5 Hz, H-9′), 2.77 (1H, *m*, CH), 2.01 (3H, *s*, Ac) and 1.28 (6H, *d*, *J* = 7 Hz, 2 Me).

8-*Hydroxy*-9-*acetoxy*-10-*isobutyryloxythymol* (**4**). Oil, IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400 (alcohol), 1725 (ester), 1610, 1500, 1465 (aromatic ring); MS *m/z* (70 eV) (rel. int.) 310 (10) [M]$^+$ 237 (20), 167 (80), 149 (40), 71 (84), 43 (100); ^{1}H NMR: see Table 1.

7-*Acetoxy*-8-*hydroxy*-9,10-*diisobutyryloxythymol* (**5**). Oil, IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3450 (alcohol), 1725 (ester), 1610, 1500, 1465 (aromatic ring); ^{1}H NMR: see Table 1.

7-*Isobutyryloxy*-8,9-*dihydroxythymol* (**6**). Oil, IR ν_{max} cm^{-1}: 3595 (alcohol), 1738 (ester), 1628, 1577, 1458 (aromatic ring); ^{1}H NMR: see Table 1.

8,9-*Epoxy*-7-*isobutyryloxythymol isobutyrate* (**7**) [8, 9]. ^{13}C NMR (25.2 MHz, $CDCl_3$, TMS): δ 176.0 (*s*, 7-OOC), 174.4 (*s*, 3-OOC), 148.0 (*s*, C-3), 137.0 (*s*, C-1), 133.1 (*s*, C-4), 127.6 (*d*, C-5), 125.0 (*d*, C-6), 121.6 (*d*, C-2), 64.7 (*t*, C-7), 55.6 (*s*, C-8), 53.9 (*t*, C-9), 33.9 (*d*, CHMe$_2$), 33.6 (*d*, CHMe$_2$) and 18.7 (5*q*, C-10 and 2 CHMe$_2$).

Acknowledgements—We wish to thank Dr A. Ortega (UNAM) for providing plant material and some samples, and to CoNaCyT (México) for partial financial support.

REFERENCES

1. Stuessy, T. F. (1977) in *The Biology and Chemistry of the Compositae* (Heywood, V. H., Harborne, J. B. and Turner, B. L. eds) p. 638. Academic Press, London.
2. Wussow, J. R., Urbatsch, L. E. and Sullivan, G. A. (1985) *Systematic Botany* **10**, 241.
3. Silva, M., Mundaca, J. M. and Sammes, P. G. (1971) *Phytochemistry* **10**, 1942.
4. Guerrero, C., Silva, M., Maldonado, E. and Martínez, M. (1978) *Rev. Lationoam. Quim.* **9**, 71.
5. Bohlmann, F., Fritz, U., King, R. M. and Robinson, H. (1981) *Phytochemistry* **20**, 743.
6. Quijano, L., Romo de Vivar, A. and Ríos, T. (1979) *Phytochemistry* **18**, 1745.
7. Herz, W. and Kumar, N. (1980) *Phytochemistry* **19**, 593.
8. Bohlmann, F., Niebdalla, U. and Schulz, J. (1969) *Chem. Ber.* **102**, 864.
9. Bohlmann, F. and Zdero, C. (1976) *Chem. Ber.* **109**, 791.
10. Hernández, J. D., Román, L. U., Rodríguez, M. J., Espiñeira, J. and Joseph-Nathan, P. (1986) *Phytochemistry* **25**, 1743.

11. González, A. G., Barrera, J. B., Rosas, F. E., Hernández, A. C. Y., Espiñeira, J. and Joseph-Nathan, P. (1986) *Phytochemistry* **25**, 2889.
12. González, A. G., Barrera, J. B., Rosas, F. E., Hernández, A. C. Y. and Joseph-Nathan, P. (1986) *Rev. Latinoam. Quim.* **17**, 54.
13. Bohlmann, F., Mahanta, P. K., Suwita, A., Suwita, A., Natu, A. A., Zdero, C., Dorner, W., Ehlers, D. and Grenz, M. (1977) *Phytochemistry* **16**, 1973.
14. Bohlmann, F. and Zdero, C. (1977) *Phytochemistry* **16**, 1773.
15. Bohlmann, F., Jakupovic, J. and Lonitz, M. (1977) *Chem. Ber.* **110**, 301.