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MERIDINOL, A LIGNAN FROM *ZANTHOXYLUM FAGARA*

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Key Word Index—*Zanthoxylum fagara*; Rutaceae; lignan; meridinol; structure elucidation; X-ray; crystal structure.

Abstract—The structure of a novel lignan, meridinol, isolated from *Zanthoxylum fagara* was determined by the evidence of its spectroscopic data and X-ray single crystal structure as (1*S*,2*R*)-1,2-bis (3,4-methylenedioxy benzyl)-1-hydroxy butyrolactone.

INTRODUCTION

Zanthoxylum fagara is a shrub widely distributed over Central and South America. Leaves, fruits and stems extracts are used in indigenous systems of medicine for their sudorific properties and as a sedative [1]. Previous chemical investigations [1–4] have shown the presence of four alkaloids and two coumarins. In this paper we report the isolation, identification and crystal structure determination of a novel dibenzylbutyrolactone lignan from the leaves and stems. This compound, which we have named meridinol (**1**), is the first lignan reported from *Z. fagara*.

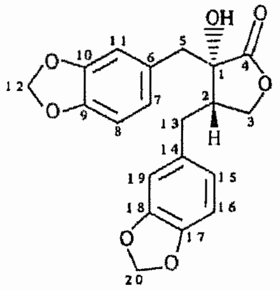
RESULTS AND DISCUSSION

Chromatographic separation of the ethanolic extract resulted in the isolation of compound **1**, as white needles, mp 122–123°, $[\alpha]_D^{25} -30°$. Elemental analysis gave a molecular formula of $C_{20}H_{18}O_7$. Its IR spectrum revealed the presence of a hydroxyl group (3440 cm^{-1}), a lactone ring (1740 cm^{-1}), an aromatic nucleus (1600, 1470 cm^{-1}) and methylenedioxy groups (920 cm^{-1}). It showed UV absorption bands at λ_{max}^{EtOH} (log ε): 287 (3.869), 236 (3.880) and 209 (4.104).

The ^1H NMR of **1** (Table 1) showed singlets, 2H each, at δ5.94 and 5.95, characteristic of two aromatic methylenedioxy groups. A group of signals, six protons, appeared between δ6.55 and 6.80, attributable to six benzenic protons. Detailed assignments of these signals indicated the presence of two 1,3,4-trisubstituted aromatic rings and the aliphatic nature of the hydroxyl group. An unresolved 2H signal centred at δ = 4.02 was assigned to a lactonic methylene. At δ3.05 and 2.92 appeared two 1H doublets with coupling constants of 13.7 Hz, attributable to an isolated benzylic methylene. These data, and the fact that the mass spectrum of **1** exhibited a base peak at *m/z* 135, arising from the fragment ion $[(OCH_2O)C_5H_3CH_2]^+$, evidenced that meridinol (**1**) was a dibenzylbutyrolactone lignan.

Table 1. ^1H and ^{13}CNMR data of meridinol (**1**)

Proton	δ(ppm)	(J, Hz)	Carbon	δ(ppm)
13 (2H)			4	178.19
	2.45–2.52 *m*			
R-OH			17, 18	147.86
2	2.90 *m*		9, 10	146.99
5a	2.92 *d*	($J_{5a,5b}$ = 13.7)	6	132.10
5b	3.05 *d*		14	127.74
3 (2H)	4.02 *m*		7	123.39
12 (2H)	5.94 *s*		15	121.83
20 (2H)	5.95 *s*		11	110.55
15	6.58 *dd*	($J_{15,16}$ = 7.6,	19	109.16
		$J_{15,19}$ = 1.6)	8	108.42
19	6.61 *d*		16	108.36
7	6.62 *dd*	($J_{7,8}$ = 7.6, $J_{7,11}$ = 1.5)	12	101.10
11	6.68 *d*		20	100.98
16	6.74 *d*		1	76.27
8	6.75 *d*		3	69.91
			13	43.97
			5	42.24
			2	31.74



1

A complex ^{1}H NMR signal, 3H, was observed at δ2.45–2.52. One of these protons disappeared after D_2O addition, thus indicating the presence of a hydroxyl function. The absence in the spectrum of any characteristic signal due to a proton geminal to a hydroxyl group [5–7], revealed its tertiary nature. Hence, it had to be located at either C-1 or at C-2 of the butyrolactone ring. Consequently the other two protons at δ2.45–2.52 were assigned to a benzylic methylene. The rest of the spectrum consisted of an 1H multiplet centred at δ2.90. This signal was assigned to the proton attached to the lactone position next to the hydroxyl group. The ^{1}H NMR spectrum, except for signals due to aromatic substituents was closely similar to those found for dibenzylbutyrolactone lignans having a hydroxyl group attached to C-1 of the lactone ring [8–11]. Therefore we proposed for our compound a structure having the hydroxyl group on this position. The 2D ^{1}H/^{1}H homonuclear correlation experiments (COSY) confirmed the connectivities between neighbouring protons in compound **1**. It has been reported that a *cis* or a *trans* relationship between the two benzylic groups in 1,2-dibenzylbutyrolactones can be established from the ^{1}H NMR spectrum: the equivalence of both H-3 protons corresponds to the *cis* configuration, while the opposite corresponds to the *trans* configuration [12, 13]. This criterion cannot be used with certainty in compound 1 because of the presence of a hydroxyl group at C-1. In Table 1 the ^{13}C NMR data are listed. These are in agreement with the proposed structure. Assignments have been elucidated using a direct 2D ^{1}H/^{13}C heteronuclear correlation spectrum.

As none of the above spectroscopic data determined unequivocally the position and configuration of the hydroxyl group on C-1 or C-2, the compound was subjected to X-ray crystallographic analysis from which its structure was determined as (1*S*,2*R*)-1,2-bis(3,4-methylenedioxybenzyl)-1-hydroxybutyrolactone. Spacial arrangement of the atoms is represented in Fig. 1. Coordinates and bond angles are listed in Tables 2 and 3, respectively.

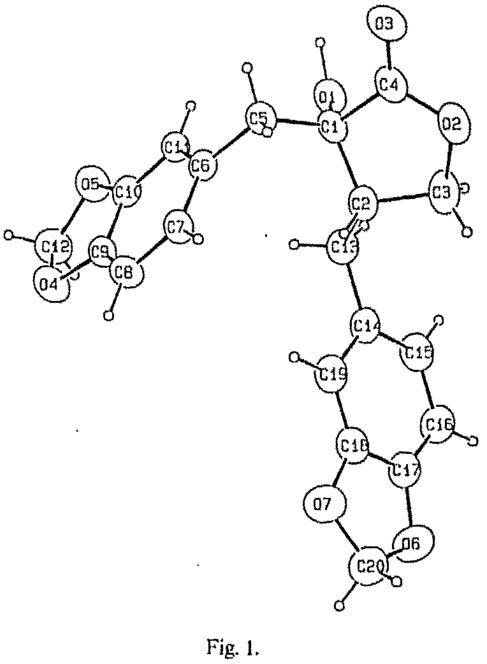


Fig. 1.

EXPERIMENTAL

^{1}H NMR, ^{13}C NMR, COSY and 2D ^{1}H/^{13}C spectra were recorded in $CDCl_3$, chemical shifts on the δ(ppm) scale with TMS as int. std; IR in KBr disks; UV in EtOH. Specific rotations were measured in $CHCl_3$. mps: uncorr.

Plant material. *Z. fagara* (L.) Sarg. was collected in Lagunillas, District of Sucre, Mérida, Venezuela, in July 1982. A voucher specimen is deposited in the Herbarium MERF J. M. Amaro No 14; Universidad de los Andes, Mérida, Venezuela.

Isolation of meridinol (**1**). Dried leaves and stems (5.6 kg) were extracted with EtOH. The extract was chromatographed on a silica gel (Kiesegel 60, 0.2–0.063 mm, Merck) column, and petrol (32.3 g), $CHCl_3$ (75.2 g), EtOAc (9.6 g), Me_2CO (158.6 g) fractions were collected. The $CHCl_3$ eluate (25 g) was rechromatographed on a silica gel (0.2–0.063 mm) column and eluted with petrol–EtOAc mixts; 50 fractions were collected. These were analysed by TLC and combined into four fractions: A, B, C, D. Repeated CC of fraction B on silica gel (Kiesegel 60, under 0.063 mm) with N_2 overpressure, using petrol–EtOAc and $CHCl_3$–MeOH mixts as eluents, yielded meridinol (1) purified by crystallization from petrol–EtOAc, mp 122–123°; $[\alpha]_D^{25} = -30°$ ($CHCl_3$, *c* 0.1); elemental analysis: found C (64.84 %), H (4.76 %); required for $C_{20}H_{18}O_7$ C (64.86%), H (4.90%). MS *m/z* (rel. int.): 370.23 $[M]^+$ (36), 135.15 (100), 105.14 (6), 77.11 (17).

Table 2. Coordinates for lignan 1

Atom	*x*	*y*	*z*	B (A^2)
O-1	0.0558 (2)	0.8383 (1)	0.08748 (5)	4.00 (2)
O-2	0.4578 (2)	0.6691 (1)	0.07795 (5)	4.87 (3)
O-3	0.2865 (2)	0.6826 (1)	0.00356 (5)	4.94 (3)
O-4	0.0663 (2)	1.4710 (1)	0.10061 (5)	4.73 (3)
O-5	−0.1973 (2)	1.3183 (1)	0.09647 (5)	4.64 (3)
O-6	0.9587 (3)	1.1132 (2)	0.29334 (5)	6.47 (4)
O-7	0.9416 (3)	1.2133 (2)	0.21376 (6)	6.44 (4)
C-1	0.2573 (3)	0.8613 (2)	0.06698 (6)	3.33 (3)
C-2	0.4074 (3)	0.8845 (2)	0.11136 (6)	3.57 (3)
C-3	0.4809 (4)	0.7463 (2)	0.12495 (8)	5.27 (5)
C-4	0.3325 (3)	0.7298 (2)	0.04472 (7)	3.95 (3)
C-5	0.2588 (3)	0.9677 (2)	0.02502 (6)	3.55 (3)
C-6	0.2131 (3)	1.1044 (1)	0.04489 (5)	3.20 (3)
C-7	0.3705 (3)	1.1965 (2)	0.04739 (6)	3.58 (3)
C-8	0.3359 (3)	1.3245 (2)	0.06613 (7)	3.86 (3)
C-9	0.1418 (3)	1.3529 (2)	0.08219 (6)	3.44 (3)
C-10	−0.0157 (3)	1.2619 (2)	0.08000 (6)	3.39 (3)
C-11	0.0126 (3)	1.1371 (2)	0.06123 (6)	3.41 (3)
C-12	−0.1386 (4)	1.4439 (2)	0.11630 (8)	4.77 (4)
C-13	0.3226 (3)	0.9596 (2)	0.15826 (6)	4.04 (4)
C-14	0.4908 (3)	0.9952 (2)	0.19638 (6)	3.75 (3)
C-15	0.5019 (4)	0.9365 (2)	0.24462 (7)	4.41 (4)
C-16	0.6553 (4)	0.9692 (2)	0.28023 (7)	5.09 (4)
C-17	0.7972 (4)	1.0615 (2)	0.26553 (6)	4.34 (4)
C-18	0.7870 (3)	1.1207 (2)	0.21787 (7)	4.33 (4)
C-19	0.6364 (4)	1.0913 (2)	0.18280 (6)	4.44 (4)
C-20	1.0620 (4)	1.2003 (2)	0.25960 (8)	5.48 (5)

The equivalent isotropic thermal parameter, for atoms refined anisotropically, is defined by the equation: $4/3[a^2B_{11}+b^2B_{22}+c^2B_{33}+abB_{12}\cos\gamma+acB_{13}\cos\beta+bcB_{23}\cos\alpha]$.

Table 3. Bond angles in degrees for lignan **1**

Atom 1	Atom 2	Atom 3	Angle	Atom 1	Atom 2	Atom 3	Angle
C-3	O-2	C-4	110.6(1)	O-2	C-3	C-2	105.8(1)
C-9	O-4	C-12	105.2(1)	O-2	C-4	O-3	122.4(1)
C-10	O-5	C-12	104.9(1)	O-2	C-4	C-1	110.7(1)
C-17	O-6	C-20	106.1(1)	O-3	C-4	C-1	126.8(1)
C-18	O-7	C-20	105.6(1)	C-1	C-5	C-6	114.0(1)
O-1	C-1	C-2	109.2(1)	C-5	C-6	C-7	119.5(1)
O-1	C-1	C-4	106.6(1)	C-5	C-6	C-11	120.1(1)
O-1	C-1	C-5	112.6(1)	C-7	C-6	C-11	120.4(1)
C-2	C-1	C-4	102.5(1)	C-6	C-7	C-8	121.6(1)
C-2	C-1	C-5	114.9(1)	C-7	C-8	C-9	116.8(1)
C-4	C-1	C-5	110.3(1)	O-4	C-9	C-8	128.3(1)
C-1	C-2	C-3	103.3(1)	O-4	C-9	C-10	109.6(1)
C-1	C-2	C-13	116.5(1)	C-8	C-9	C-10	122.1(1)
C-3	C-2	C-13	112.8(1)	O-5	C-10	C-9	109.9(1)
O-5	C-10	C-11	127.5(1)	C-15	C-16	C-17	117.3(1)
C-9	C-10	C-11	122.5(1)	O-6	C-17	C-16	128.9(1)
C-6	C-11	C-10	116.7(1)	O-6	C-17	C-18	109.8(1)
O-4	C-12	O-5	108.7(1)	C-16	C-17	C-18	121.2(1)
C-2	C-13	C-14	112.2(1)	O-7	C-18	C-17	109.5(1)
C-13	C-14	C-15	121.5(1)	O-7	C-18	C-19	128.1(1)
C-13	C-14	C-19	119.1(1)	C-17	C-18	C-19	122.4(1)
C-15	C-14	C-19	119.4(1)	C-14	C-19	C-18	117.7(1)
C-14	C-15	C-16	122.0(2)	O-6	C-20	O-7	108.3(1)

X-ray structure of meridinol (**1**). A crystal of dimensions 0.20 × 0.42 × 0.44 mm was used for data collection on an Enraf-Nonius CAD4 diffractometer equipped with CuK radiation ($\lambda = 1.54184$ Å) and a graphite monochromator. Crystal data are: $C_{20}H_{18}O_7$, $M_r = 370.4$, orthorombic space group $P2_12_12_1$, $a = 6.4782$ (7), $b = 10.1748$ (4), $c = 25.902$ (2) Å, $V = 1707.4$ (4) Å^3, $Z = 4$, $dc = 1.441$ g/cm^3, μ (CuK$_\alpha$) = 8.8 cm^{-1}. Data were collected by ω-2θ scans of variable speed, designed to yield $I = 50\ \sigma(I)$ for all significant reflections. One octant of data having $2° < \theta < 75°$ was collected at 25°, yielding 2050 unique reflections, of which 1881 had $I > 3\sigma$-(I) and were used in the refinement. Data reduction included corrections for background, Lorentz, polarization, and absorption effects by Ψ scans. The minimum relative transmission coefficient was 83.8%. The structure was solved by direct methods and refined by full-matrix least squares based on F with weiths $\omega = \sigma^{-2}(F_0)$. Non-H atoms were refined anisotropically; H atoms were located from difference maps and refined isotropically. Convergence was achieved with $R = 0.030$ and $R_w = 0.037$ and a maximum residual electron density of 0.12 eÅ^{-3}. Corrdinates for this model are listed in Table 2, and the molecule is illustrated in Fig. 1. Coordinates for H atoms, bond distances and bond angles are deposited with the Cambridge Crystallographic Data Centre. This absolute configuration is considered to be most likely, because the enantiomorphous structure, refined under identical conditions, yielded $R = 0.031$ and $R_w = 0.038$.

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REFERENCES

1. Dominguez, X. A., Benavides, L. and Butruille, D. (1974) *Phytochemistry* **13**, 680.
2. Dreyer, D. L. and Brenner, R. C. (1980) *Phytochemistry* **19**, 935.
3. Stermitz, F. R., Caolo, M. A. and Swinehart, J. A. (1980) *Phytochemistry* **19**, 1469.
4. Snyder, J. and Nakanishi, K. (1981) *Tetrahedron Letters* 5015.
5. Agulló Martinez, E., Bretón Funes, J. L., González A. and Rodríguez Luis, F. (1969) *An. Quím.* **65**, 809.
6. Kamil, W. M. and Dewick, P. M. (1986) *Phytochemistry* **25**, 2093.
7. Miller, R. W., McLaulin, J. L., Powell, R. G., Plattner, R. D., Weislecher, D. Smith Jr., C. R. (1982) *J. Nat. Prod.* **45**, 78.
8. Burden, R. S., Crombie, L. and Whiting, D. A. (1969) *J. Chem. Soc.* (*C*) **5**, 693.
9. Tandon, S. and Rastogi, R. P. (1976) *Phytochemistry* **15**, 1789.
10. Inagaki, I., Hisada, S. and Nishibe, S. (1971) *Phytochemistry* **10**, 211.
11. Nishibe, S., Hisada, S. and Inagaki, I. (1971) *Phytochemistry* **10**, 2231.
12. Corrie, J. E. T., Green, G. H., Ritchie, E. and Taylor, W. C. (1970) *Aust. J. Chem.* **23**, 133.
13. Lopes Lucia, M. X., Yoshida, M. and Gottlieb, O. R. (1983) *Phytochemistry* **22**, 1516.