Acta Cryst. (1989). C45, 1746–1748

Room-Temperature Structure of (±)-Methyltrachelogenin

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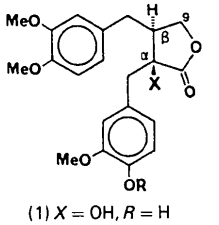
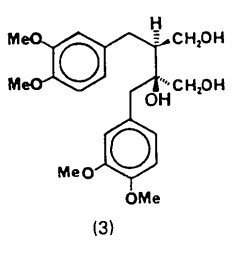
(*Received* 5 *December* 1988; *accepted* 4 *April* 1989)

Abstract. 3,4-Bis[(3,4-dimethoxyphenyl)methyl]-3-hydroxydihydro-2(3*H*)-furanone, $C_{22}H_{26}O_7$, M_r = 402·45, monoclinic, $P2_1/c$, a = 7·257 (3), b = 14·474 (6), c = 19·88 (1) Å, β = 103·38 (4)°, V = 2032 (3) Å^3, Z = 4, D_x = 1·31 Mg m^{-3}, Mo $K\alpha$, λ = 0·71069 Å, μ = 0·06 mm^{-1}, $F(000)$ = 856, room temperature, final R = 0·051, for 956 unique reflections, crystal growth by slow evaporation from a methanolic solution under an ether atmosphere. The title compound was synthetized in racemic form together with its α-epimer. The present X-ray studies confirm that in the title compound and in natural lignans of similar structure, both benzyl groups have *trans* stereochemistry relative to the lactone ring.

Introduction. Many naturally occurring lignans belong to the *trans*-α,β-dibenzyl-γ-butyrolactone series. A few representatives of these compounds, such as (−)-trachelogenin (1), typically have a hydroxyl group in the α position.



(1) X = OH, R = H
(2) X = OH, R = Me
(4) X = H, R = Me



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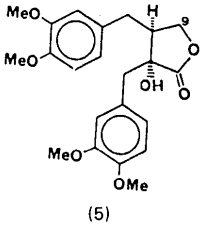

(5)

The structure of (−)-trachelogenin (1) was established by $LiAlH_4$ reduction of its methyl ether (2) to give (−)-tetrahydrogmelinol (3) of known configuration (Inagaki, Hisada & Nishibe, 1972; Nishibe, Hisada & Inagaki, 1973).

Treatment of the lithium enolate of (±)-dimethylmataresinol (4) with oxygen, followed by aqueous sodium sulfite solution, gave an approximately equimolecular mixture of two epimeric α-hydroxylated compounds, (*a*) m.p. 419–420 K and (*b*) m.p. 418·5–420·5 K (Brown, Khamlach & Dhal, 1989), one of them being (±)-methyltrachelogenin (2). The structures of (*a*) and (*b*) could not be elucidated by a mere comparison of their IR and 300 MHz proton NMR spectra. The 90 MHz proton NMR data of both (*a*) and (*b*) are nearly all very close to the values reported for (−)-methyltrachelogenin (2) (Inagaki, Hisada & Nishibe, 1972). The most significant difference is observed for the H(9) protons which produce a doublet at δ 4·07 for (*a*) and δ 4·32 for (*b*). The same protons appear at δ 4·08 in the case of (−)-methyltrachelogenin (2). The ^{13}C NMR spectra of (*a*) and (*b*) are quite similar. The ^{13}C NMR data of (*a*) are identical with those reported for the dextrorotatory enantiomer of (−)-methyltrachelogenin (2) (Kato, Hashimoto & Kidokoro, 1979). All these facts tend to show that (*a*) is racemic methyltrachelogenin (2). However, in order to ascertain the relative configuration of (*a*), we decided to carry out an X-ray study of this compound.

Experimental. Prismatic crystal, 0·08 × 0·09 × 0·13 mm. Data collected on a Siemens AED-2 four-circle diffractometer; ω–2θ step-scan mode in N steps of 0·022°, $37 \le N \le 42$, time per step: 2 s. Aperture D = 3·5 mm. Lattice constants based on 29 reflections ($\theta \simeq 15{\cdot}0°$); no absorption correction. Intensity measurement to $2\theta \le 40°$ within range $-6 \le h \le 6$, $0 \le k \le 13$, $0 \le l \le 18$. Standard reflections $0\bar{3}3$, 113, 042, intensity variation 0·4%; 1995 independent reflections measured and 956 unique reflections used for refinements [$|F| > 4\sigma(|F|)$]. Structure solved by direct methods with the *EEES* option of the *SHELX*76 program (Sheldrick, 1976). F magnitudes used in least-squares refinements: 310 parameters refined; mean Δ/σ = 0·003, max. Δ/σ = 0·056;

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Table 1. *Atomic coordinates and equivalent isotropic temperature factors* (Å^2) *with e.s.d.'s in parentheses*

$B_{eq} = \frac{4}{3}\sum_i\sum_j b_{ij}(\mathbf{a}_i.\mathbf{a}_j)$ (Hamilton, 1959).

	x	y	z	B_{eq}
O(1)	0·9272 (8)	0·2136 (4)	0·1014 (3)	5·7 (4)
C(2)	0·8925 (14)	0·1531 (6)	0·1488 (5)	4·8 (7)
C(3)	0·6790 (12)	0·1359 (6)	0·1363 (4)	3·9 (6)
C(4)	0·5945 (11)	0·2195 (6)	0·0936 (4)	3·6 (6)
C(5)	0·7494 (12)	0·2430 (6)	0·0546 (4)	5·0 (6)
C(6)	0·6113 (12)	0·1192 (5)	0·2026 (4)	4·6 (6)
C(7)	0·6357 (14)	0·2010 (6)	0·2514 (4)	4·2 (6)
C(8)	0·4797 (13)	0·2587 (6)	0·2504 (4)	3·7 (6)
C(9)	0·4922 (12)	0·3318 (6)	0·2945 (4)	3·4 (6)
C(10)	0·6657 (13)	0·3521 (7)	0·3424 (5)	4·3 (7)
C(11)	0·8193 (13)	0·2959 (7)	0·3445 (4)	4·7 (6)
C(12)	0·8029 (12)	0·2213 (7)	0·2995 (5)	4·4 (6)
C(13)	0·3993 (11)	0·2074 (6)	0·0456 (4)	4·4 (6)
C(14)	0·3431 (10)	0·2923 (7)	−0·0004 (5)	4·0 (6)
C(15)	0·2997 (10)	0·3766 (6)	0·0253 (4)	3·7 (5)
C(16)	0·2678 (10)	0·4527 (6)	−0·0172 (5)	3·4 (6)
C(17)	0·2760 (10)	0·4458 (7)	−0·0871 (4)	3·6 (6)
C(18)	0·3128 (11)	0·3611 (8)	−0·1129 (4)	4·5 (6)
C(19)	0·3462 (11)	0·2839 (6)	−0·0696 (5)	4·2 (7)
O(20)	1·0198 (9)	0·1189 (5)	0·1908 (3)	7·2 (5)
O(21)	0·6486 (11)	0·0546 (5)	0·0935 (3)	5·8 (5)
O(22)	0·3507 (8)	0·3934 (4)	0·2987 (3)	5·0 (4)
C(23)	0·1748 (11)	0·3798 (6)	0·2516 (5)	6·0 (7)
O(24)	0·6630 (8)	0·4264 (4)	0·3847 (3)	5·3 (4)
C(25)	0·8403 (12)	0·4557 (7)	0·4274 (4)	6·5 (7)
O(26)	0·2228 (7)	0·5383 (4)	0·0042 (3)	4·5 (4)
C(27)	0·2063 (11)	0·5482 (6)	0·0745 (4)	4·6 (6)
O(28)	0·2433 (7)	0·5280 (4)	−0·1231 (3)	4·9 (5)
C(29)	0·2818 (12)	0·5275 (6)	−0·1900 (4)	5·3 (7)

secondary-extinction factor $x = 9 \times 10^{-8}$; atomic scattering factors for H, C, O from *International Tables for X-ray Crystallography* (1974); calculations with *SHELX*76 program (Sheldrick, 1976).

The automatic 'black-box' procedure of *SHELX*76 (Sheldrick, 1976) gives a solution with 15 non-H atoms. Then, refinements of the atomic coordinates and isotropic thermal motion, followed by Fourier or difference Fourier maps located 29 O and C atoms. Weak thermal motion allowed O and C atoms to be distinguished. H atoms were then found from a difference Fourier map. In order to reduce the number of refined parameters, geometrical constraints were applied to CH_3, CH_2 or CH groups ($d_{C-H} = 1{\cdot}08$ Å) and a unique thermal parameter was refined for all C-bonded H atoms ($R = 0{\cdot}051$, $wR = 0{\cdot}041$). Max. and min. heights in final difference map: 0·14 and −0·14 e Å^{-3}.

Discussion. The final atomic coordinates and equivalent isotropic temperature factors are listed in Table 1.* Selected bond lengths and angles are listed in Table 2.

* Lists of structure factors, anisotropic thermal parameters and H-atom coordinates have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 52049 (9 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 2. *Selected bond lengths* (Å) *and angles* (°) *with e.s.d.'s in parentheses*

C(2)—O(1)	1·353 (9)	C(5)—O(1)	1·468 (9)
C(3)—C(2)	1·531 (11)	O(20)—C(2)	1·200 (9)
C(4)—C(3)	1·523 (10)	C(6)—C(3)	1·529 (9)
O(21)—C(3)	1·439 (9)	C(5)—C(4)	1·544 (10)
C(13)—C(4)	1·525 (10)	C(7)—C(6)	1·515 (10)
C(8)—C(7)	1·403 (10)	C(12)—C(7)	1·391 (10)
C(9)—C(8)	1·365 (9)	C(10)—C(9)	1·423 (10)
O(22)—C(9)	1·377 (8)	C(11)—C(10)	1·372 (10)
O(24)—C(10)	1·368 (9)	C(12)—C(11)	1·390 (10)
C(14)—C(13)	1·529 (10)	C(15)—C(14)	1·386 (10)
C(19)—C(14)	1·386 (10)	C(16)—C(15)	1·375 (10)
C(17)—C(16)	1·408 (9)	O(26)—C(16)	1·373 (8)
C(18)—C(17)	1·378 (10)	O(28)—C(17)	1·380 (9)
C(19)—C(18)	1·398 (10)	C(23)—O(22)	1·412 (8)
C(25)—O(24)	1·433 (8)	C(27)—O(26)	1·437 (7)
C(29)—O(28)	1·421 (7)		

C(5)—O(1)—C(2)	110·6 (7)	C(3)—C(2)—O(1)	109·7 (8)
O(20)—C(2)—O(1)	121·0 (9)	O(20)—C(2)—C(3)	129·3 (9)
C(4)—C(3)—C(2)	102·9 (7)	C(6)—C(3)—C(2)	113·6 (7)
C(6)—C(3)—C(4)	115·9 (7)	O(21)—C(3)—C(2)	103·9 (7)
O(21)—C(3)—C(4)	109·4 (7)	O(21)—C(3)—C(6)	110·2 (7)
C(5)—C(4)—C(3)	102·1 (6)	C(13)—C(4)—C(3)	117·0 (7)
C(13)—C(4)—C(5)	112·9 (7)	C(4)—C(5)—O(1)	104·7 (7)
C(7)—C(6)—C(3)	114·6 (7)	C(8)—C(7)—C(6)	118·8 (8)
C(12)—C(7)—C(6)	124·0 (9)	C(12)—C(7)—C(8)	117·2 (8)
C(9)—C(8)—C(7)	121·3 (8)	C(10)—C(9)—C(8)	120·4 (8)
O(22)—C(9)—C(8)	127·1 (8)	O(22)—C(9)—C(10)	112·5 (8)
C(11)—C(10)—C(9)	119·1 (9)	O(24)—C(10)—C(9)	115·9 (9)
O(24)—C(10)—C(11)	125·0 (9)	C(12)—C(11)—C(10)	119·5 (9)
C(11)—C(12)—C(7)	122·5 (9)	C(14)—C(13)—C(4)	111·3 (7)
C(15)—C(14)—C(13)	122·6 (9)	C(19)—C(14)—C(13)	117·3 (9)
C(19)—C(14)—C(15)	120·0 (9)	C(16)—C(15)—C(14)	120·0 (8)
C(17)—C(16)—C(15)	120·6 (9)	O(26)—C(16)—C(15)	123·4 (8)
O(26)—C(16)—C(17)	116·0 (9)	C(18)—C(17)—C(16)	119·1 (9)
O(28)—C(17)—C(16)	114·1 (9)	O(28)—C(17)—C(18)	126·8 (9)
C(19)—C(18)—C(17)	120·3 (8)	C(18)—C(19)—C(14)	120·0 (9)
C(23)—O(22)—C(9)	116·2 (7)	C(25)—O(24)—C(10)	117·3 (7)
C(27)—O(26)—C(16)	118·1 (7)	C(29)—O(28)—C(17)	115·7 (7)

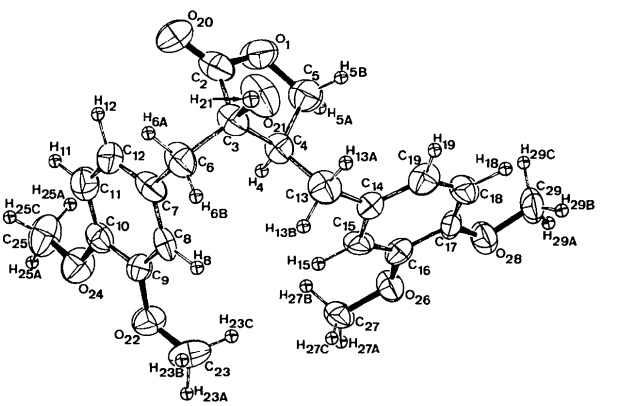

Fig. 1. *ORTEP* (Johnson, 1965) plot of the molecule of methyltrachelogenin. For the sake of clarity, the isotropic thermal parameters of the H atoms were divided by ten.

An *ORTEP* plot (Johnson, 1965) of the molecule of (*a*) is represented in Fig. 1. This perspective view clearly shows that the H(4) proton and the O(21)—H(21) hydroxyl group are *trans* with respect to the lactone ring: the dihedral angle H(4)—C(4)—C(3)—O(21) is equal to 175 (2)°, thus minimizing the steric interaction between the

hydroxyl group and the neighbouring *cis* benzyl group carried by C(4). The dihedral angle C(2)—C(3)—C(4)—C(5) in the lactone ring is 30(2)°, while the dihedral angle C(6)—C(3)—C(4)—C(13) is 82(2)°. The benzyl groups are nearly flat; the maximum distances from the mean planes are 0·02 and 0·07 Å for C(6), C(7), C(8), C(9), C(10), C(11), C(12), O(22), O(24) and C(13), C(14), C(15), C(16), C(17), C(18), C(19), O(26), O(28), respectively.

In short, this study shows that the relative stereochemistry of both benzyl groups of (*a*) is *trans*, and that (*a*) is indeed racemic methyltrachelogenin (2). Since the racemic compound (*b*) is the α-epimer of (*a*), the former has the relative structure (5).

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Acta Cryst. (1989). C**45**, 1748–1751

Structure of the Calcium Channel Antagonist, Nimodipine

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(*Received* 12 *April* 1988; *accepted* 9 *March* 1989)

Abstract. Isopropyl 2-methoxyethyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydro-3,5-pyridinedicarboxylate, $C_{21}H_{26}N_2O_7$, $M_r = 418{\cdot}45$, orthorhombic, $P2_12_12_1$, $a = 12{\cdot}5897\ (6)$, $b = 14{\cdot}6410\ (9)$, $c = 11{\cdot}636\ (1)$ Å, $V = 2144{\cdot}8\ (2)$ Å^3, $Z = 4$, $D_m = 1{\cdot}29$, $D_x = 1{\cdot}30$ g cm^{-3}, λ(Cu $K\alpha$) = 1·54178 Å, $\mu = 7{\cdot}77$ cm^{-1}, $F(000) = 888$, $T = 298$ K, $R = 0{\cdot}047$ for 1629 observed reflections. The structure of the title compound is similar to that of related analogs, the nitrophenyl ring being roughly normal to the dihydropyridine ring, which is in a boat conformation (N1 is 10·75° out of the C2—C3—C5—C6 plane; C4 is 19·55° out of plane). The 3,5 substituents are in an extended conformation, away from the 2,6 methyl groups. The nitro group is distal to N1. Structure/activity relationships of 1,4-dihydropyridines are discussed in light of this structure.

Introduction. Many derivatives of 1,4-dihydropyridine structures exhibit high affinity for calcium channel receptors and may act as agonists or antagonists, depending on the nature of the derivative, the physiological state of the channel and, in some cases, the side of the membrane containing the channel receptor to which the compound is added (Kokubun & Reuter, 1984). D. J. Triggle and colleagues (Triggle, Shefter & Triggle, 1980; Fossheim, Svarteng, Mostad, Rommiing, Schefter & Triggle, 1982) have determined crystal structures of some 1,4-dihydropyridines and have identified some key features of these structures which are apparently correlated with pharmacological activity.

Nimodipine is a highly active antagonist (K_d = 0·1 n*M*) being used in a wide variety of experimental investigations. This compound (Fig. 1) is a typical 1,4-dihydropyridine, with a nitrophenyl substituent at C4, alkyl esters on C3 and C5, and methyl groups on C2 and C6. The structure is very similar to that of the root compound, nifedipine [dimethyl 2,6-dimethyl-4-(2-nitrophenyl)-1,4-dihydro-3,5-pyridinedicarboxylate]. Because the binding affinity of nimodipine is about five times that of nifedipine, the structure of nimodipine was determined to evaluate structural differences or similarities between these compounds and to attempt to relate these differences to functional properties.

Experimental. Material was obtained from Miles Laboratories, New Haven, CT, USA. Crystals, grown from ethanol in reduced light at 296 K, were rectangular. The selected crystal was 0·5 × 0·2 × 0·1 mm. Density measured by flotation. Diffraction data were collected using a *TEXRAY*/Rigaku system with an RU-200 generator, AFC-5 diffractometer and *TEXRAY* control software, all obtained from Molecular Structure Corporation, College Station,

0108-2701/89/111748-04$03.00