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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Structure of the Calcium Channel Antagonist, Nimodipine

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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,

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TX, USA. Intensity data were collected to $(\sin\theta)/\lambda = 0{\cdot}561$ Å^{-1} by measuring counts at peak positions, background corrected using counts collected at $\Delta\omega \simeq \pm 0{\cdot}4°$. Cell constants were determined by fitting 20 data points, $20 \le 2\theta \le 34°$. Data were collected for $0 < h < 14$, $0 < k < 16$ and $0 < l < 13$ and corrected for Lorentz and polarization factors but not for absorption. Three standard reflections were monitored every 150 data points, and were found to vary by < 1%. Of 1839 measured reflections, 1629 reflections satisfied the criterion $I > 3{\cdot}00\sigma(I)$ and were used to solve the structure with direct methods. H-atom positions were defined by idealized geometry calculation. Least-squares refinement using F fitting of atomic coordinates and temperature factors (anisotropic for non-H atoms and isotropic thermal parameters for H atoms) resulted in $R = 0{\cdot}047$ and $wR = 0{\cdot}057$ with $w = 1/\sigma(F)$ and $S = 1{\cdot}68$. Maximum shift/e.s.d. in the final cycle was 0·12 and the largest peak in the final difference map was 0·45 e Å^{-3}. Some of the largest F_o (> 1000), such as 002 and 022, showed some evidence of secondary extinction. All crystallographic calculations used the *TEXSAN* package of programs (Molecular Structure Corporation, College Station, TX, USA), including *MITHRIL*. Some graphics and geometric calculations used *CHEM-X*, developed and distributed by Chemical Design Ltd, Oxford, England. Atomic scattering factors from *International Tables for X-ray Crystallography* (1974).

Discussion. The conformation determined for the nimodipine crystal structure is illustrated [*ORTEP* form (Johnson, 1976)] in Fig. 2 and the unit cell is shown in Fig. 3. Non-H coordinates and equivalent isotropic thermal parameters are listed in Table 1.* Torsion angles associated with the 1,4-dihydropyridine ring and bond lengths for all non-H connections are listed in Table 2.

D. J. Triggle *et al.* have published data which suggest that the puckering of the dihydropyridine ring is related to the activity of the derivative in question (Triggle *et al.*, 1980; Fossheim *et al.*, 1982). In this derivative, N1 is 11° out of plane (see Table 3 text) and C4 is 22° out of plane. For the four compounds investigated by D. J. Triggle *et al.*, the authors noted an apparent correlation between activity (as measured by IC_{50} for tonic CD response in guinea pig ileal longitudinal smooth muscle)* and

* Lists of structure factors, anisotropic thermal parameters, bond angles and torsion angles have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 52022 (16 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

* That is, the concentration of drug required to inhibit the tonic response to the agonist *cis*-4-[(dimethylamino)methyl]-2-methyl-1,3-dioxolane methiodide by 50%.

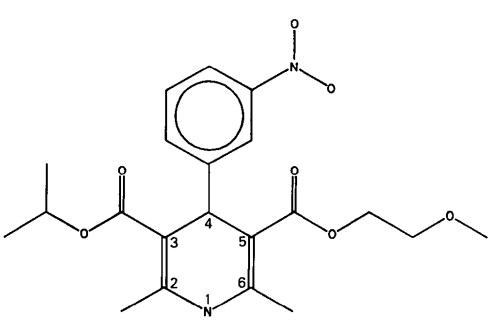

Fig. 1. Nimodipine. The substitutions at C3 and C5 distinguish this compound from the parent compound, nifedipine.

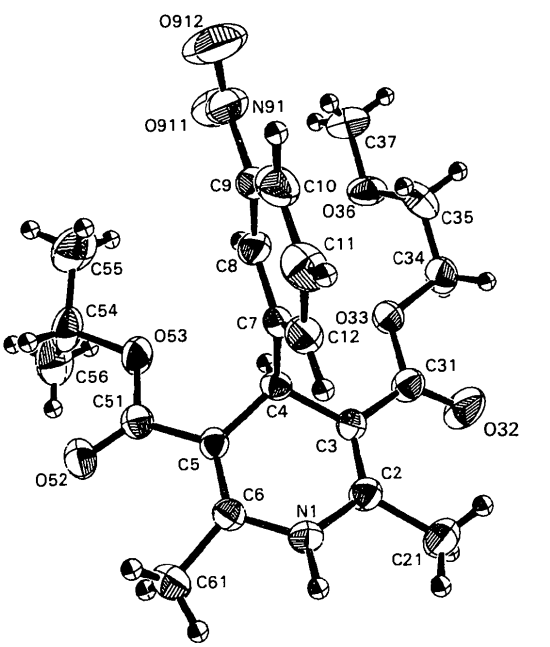

Fig. 2. *ORTEP* drawing of the crystal structure of nimodipine. The structure is generally similar to those of other dihydropyridines.

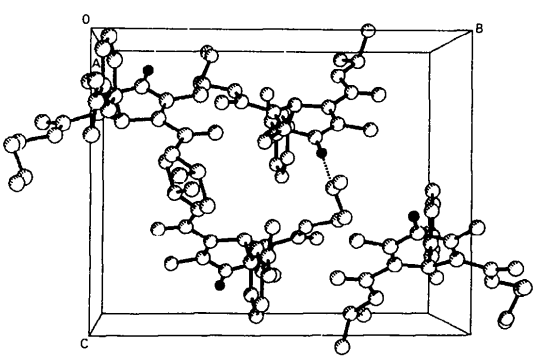

Fig. 3. Unit cell of the nimodipine crystal. H atoms have been omitted for clarity, except for the one involved in the hydrogen bonding between N1 and O36.

Table 1. *Positional parameters and B_{eq} for nimodipine*

$B_{eq} = \frac{8}{3}\pi^2 \sum_i \sum_j U_{ij} a_i^* a_j^* \mathbf{a}_i . \mathbf{a}_j$.

	x	y	z	B_{eq}(Å^2)
N1	0·6318 (2)	0·6269 (2)	0·3325 (3)	3·2 (1)
C2	0·6424 (3)	0·5364 (2)	0·3033 (3)	2·9 (1)
C21	0·5554 (3)	0·4774 (3)	0·3522 (4)	4·3 (2)
C3	0·7252 (3)	0·5097 (2)	0·2377 (3)	2·7 (1)
C31	0·7353 (3)	0·4147 (2)	0·2014 (3)	3·2 (2)
O32	0·6692 (2)	0·3556 (2)	0·2079 (3)	5·9 (2)
O33	0·8327 (2)	0·3979 (2)	0·1578 (2)	3·6 (1)
C34	0·8557 (3)	0·3033 (3)	0·1337 (4)	4·1 (2)
C35	0·9738 (4)	0·2943 (3)	0·1219 (3)	4·1 (2)
O36	1·0072 (2)	0·3299 (2)	0·0163 (2)	4·3 (1)
C37	1·1167 (3)	0·3180 (4)	−0·0035 (5)	6·0 (3)
C4	0·8151 (2)	0·5763 (2)	0·2084 (3)	2·4 (1)
C5	0·7761 (3)	0·6750 (2)	0·2174 (3)	2·4 (1)
C51	0·8374 (3)	0·7476 (2)	0·1601 (3)	2·9 (1)
O52	0·8219 (2)	0·8285 (2)	0·1692 (3)	4·5 (1)
O53	0·9158 (2)	0·7129 (2)	0·0943 (2)	3·9 (1)
C54	0·9848 (4)	0·7794 (3)	0·0360 (4)	4·4 (2)
C55	1·0908 (4)	0·7324 (4)	0·0228 (5)	6·1 (3)
C56	0·9347 (5)	0·8063 (4)	−0·0762 (4)	5·9 (3)
C6	0·6903 (3)	0·6961 (2)	0·2825 (3)	2·6 (1)
C61	0·6450 (3)	0·7892 (2)	0·3049 (3)	3·5 (2)
C7	0·9118 (3)	0·5603 (2)	0·2866 (3)	2·6 (1)
C8	1·0121 (3)	0·5468 (2)	0·2370 (3)	3·1 (2)
C9	1·0982 (3)	0·5347 (2)	0·3093 (4)	3·5 (2)
N91	1·2041 (3)	0·5221 (3)	0·2547 (4)	4·9 (2)
O911	1·2077 (3)	0·5101 (3)	0·1506 (4)	6·9 (2)
O912	1·2817 (2)	0·5229 (3)	0·3155 (4)	7·8 (2)
C10	1·0905 (3)	0·5345 (3)	0·4264 (4)	4·2 (2)
C11	0·9916 (4)	0·5468 (3)	0·4740 (3)	4·1 (2)
C12	0·9026 (3)	0·5591 (2)	0·4046 (3)	3·3 (2)

Table 2. *Bond lengths* (Å) *and selected torsion angles* (°)

E.s.d.'s in the least significant figure are given in parentheses.

N1	C2	1·376 (5)	O52	C51	1·205 (4)		
N1	C6	1·381 (4)	O53	C51	1·348 (4)		
C2	C21	1·506 (5)	O53	C54	1·471 (5)		
C2	C3	1·350 (5)	C54	C55	1·509 (7)		
C3	C31	1·459 (5)	C54	C56	1·503 (7)		
C3	C4	1·533 (5)	C6	C61	1·501 (5)		
O32	C31	1·202 (4)	C7	C12	1·379 (5)		
O33	C31	1·350 (4)	C7	C8	1·402 (5)		
O33	C34	1·442 (4)	C8	C9	1·384 (5)		
C34	C35	1·499 (6)	C9	C10	1·366 (6)		
O36	C35	1·400 (5)	N91	C9	1·489 (5)		
O36	C37	1·409 (5)	O911	N91	1·224 (5)		
C4	C5	1·530 (4)	O912	N91	1·206 (5)		
C4	C7	1·537 (5)	C10	C11	1·375 (6)		
C5	C51	1·474 (5)	C11	C12	1·392 (5)		
C5	C6	1·354 (5)					

1	2	3	4		1	2	3	4	
N1	C2	C3	C4	8·0 (5)	O32	C31	C3	C2	12·2 (7)
N1	C6	C5	C4	−6·0 (5)	O33	C31	C3	C4	7·7 (5)
C2	N1	C6	C5	−12·9 (5)	C5	C4	C7	C12	70·1 (4)
C2	C3	C4	C5	−23·5 (4)	C5	C4	C7	C8	−109·7 (3)
C2	C3	C4	C7	99·9 (4)	C51	C5	C6	C61	0·8 (6)
C21	C2	C3	C31	3·1 (6)	C51	O53	C54	C55	151·4 (4)
C3	C2	N1	C6	11·9 (5)	O52	C51	C5	C6	3·8 (5)
C3	C4	C5	C6	22·4 (4)	O52	C51	O53	C54	1·9 (5)
C3	C4	C7	C12	−53·0 (4)	O53	C51	C5	C4	7·4 (4)
C3	C4	C7	C8	127·2 (3)	C6	C5	C4	C7	−100·9 (3)

The sign of the torsion angle is positive if when looking from atom 2 to atom 3 a clockwise motion of atom 1 would superimpose it on atom 4.

the planarity of the dihydropyridine ring (as indicated by θ_{av}, the average of the absolute value of the torsion angles C2—C3—C4—C5 and C3—C4—C5—C6). The present compound does not fit this trend. Whereas one would expect a planar dihydropyridine ring ($\theta_{av} < 15°$) based on IC_{50} or other measures of activity, θ_{av} is over 20°, in the range of the least active compounds studied by D. J. Triggle's group.

Langs & Triggle (1985) have observed that the majority of 1,4-dihydropyridine analogs have one of the ester groups at positions 3 and 5 in the *cis* conformation and the other in the *trans* conformation. A small number of very active antagonists, however, are found to have *cis,cis* geometry. The present compound is also *cis,cis* and is very active. Because the ester orientation requirement is not fully understood, it is uncertain whether this feature of the crystal structure explains the deviation of this compound from the normal IC_{50}/θ_{av} correlation. It is possible that the two large *cis* subtituents help to constrain the nitrophenyl ring perpendicular to the 1,4-dihydropyridine ring or that this conformation is related to stereochemical constraints near the active site. It is also possible that the conformation of the 3 substituent in the crystal is affected by the presence of the hydrogen bond between O36 and N1 (Fig. 3), and that the conformation in solution is significantly different from that in the crystal.

The deviation of the present compound from the ring planarity structure/activity relationship proposed by Triggle *et al.* (1980) does not refute the general trend for this class of calcium channel antagonists. In fact, inspection of activity data available for the derivatives studied by D. J. Triggle's group suggests that the structure/activity relationship holds well for derivatives (T-I–T-IV) in which the phenyl ring has been modified and the 3 and 5 substituents remain equivalent to those of nifedipine (Bolger, Gengo, Klockowski, Luchowski, Siegel, Janis, Triggle & Triggle, 1983). In light of the proposed membrane bilayer approach hypothesis for 1,4-dihydropyridine binding (Rhodes, Sarmiento & Herbette, 1985), the deviation is probably a reflection of the fact that the activity is dependent on a wide variety of drug characteristics, including the membrane-partition coefficient, the equilibrium position of the drug in the membrane bilayer and the orientation of the drug in the bilayer. Any of these parameters can affect the *effective* concentration of the drug at the active site on the receptor, thus altering the apparent IC_{50} or K_d. These parameters would also be affected by differences in the conformation due to the solvent environment from which the drug reaches the active site (aqueous solution, membrane interior, membrane headgroup region *etc.*). Further, although all of these characteristics are dependent on the drug structure, none would necessarily be reflected in a crystallographic assess-

Table 3. *Planarity of pyridine rings*

A plane was constructed by least-squares fitting of coordinates for C2, C3, C5 and C6. θ_1 is the angle between this plane and a vector from the C3/C5 midpoint to C4. θ_2 is the angle between the plane and a vector from the C1/C6 midpoint to N1. θ_{av} is, as defined by Triggle *et al.* (1980), the average of torsion angles C2—C3—C4—C5 and C3—C4—C5—C6. T and F refer to compounds in Triggle *et al.* (1980) and Fossheim *et al.* (1982), respectively.

Compound	θ_1 (°)	θ_2 (°)	IC_{50}(n*M*)*	θ_{av}(°)
Nimodipine	19·55	10·75	0·8	22·95
F-II	20·72	12·32	4	24·33
T-I	14·56	5·31	4·4	17·03
T-III	15·55	9·80	5·1	19·98
T-IV	25·90	15·17	35	30·16
F-VI	21·74	12·43	110	25·58
F-I	24·70	13·91	200	28·49
F-III	20·28	10·16	3200	23·72
T-II	23·92	14·56	50000	28·06

*IC_{50} is for the tonic methylfurmethide response in guinea pig ileal longitudinal smooth muscle (Triggle & Janis, 1984) except for T-III, which is for CD in the same system (Triggle *et al.*, 1980). The IC_{50} for either agonist is the same for T-III.

ment of structure/activity relationships. What is required is a comparison of the crystal structure of nimodipine with its structure in a membrane bilayer. The latter might be obtained by carrying out neutron scattering experiments with a series of selectively deuterated analogs of the parent compound.

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Structure of *N*-(2,2-Dinitro-1-methylethenyl)-2-bromo-1,1,2-trimethylpropanamine

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Abstract. $C_9H_{16}BrN_3O_4$, $M_r = 310·1$, triclinic, $P\bar{1}$, $a = 7·013$ (1), $b = 9·768$ (3), $c = 9·969$ (2) Å, $\alpha = 73·43$ (2), $\beta = 76·79$ (2), $\gamma = 76·07$ (2)°, $V = 625·8$ (3) Å^3, $Z = 2$, $D_x = 1·646$ g cm^{-3}, λ(Mo $K\alpha$) = 0·71073 Å, $\mu = 32·5$ cm^{-1}, $F(000) = 316$, $T = 100$ (2) K, $R = 0·040$ for 3038 unique observed reflections. An intramolecular N—H···O hydrogen bond [2·00 (3) Å] is formed with an oxygen of one of the nitro groups resulting in a relatively planar conformation of the molecule. A long C—C double bond and short adjacent C—N bonds indicate delocalization of double-bond character in the molecular plane. The second nitro group is twisted by 58·5 (3)° with respect to the molecular plane.

Introduction. Reaction of dibromodinitromethane with tetramethylethylene in acetonitrile yielded a complex mixture from which an unknown yellow solid was isolated as the major product (Boyer, Manimaran & Patterson, 1989). Since no one structure could be unequivocally assigned using conventional spectroscopic methods, the identity of the unknown has been determined by X-ray structure analysis.

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