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Crystal Structure of the Calcium Channel Antagonist: 3,5-Bis(methoxycarbonyl)-2,6-dimethyl-4-(2-trifluoromethylphenyl)-1,4-dihydropyridine

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The crystal structure of the calcium channel antagonist 3,5-bis(methoxycarbonyl)-2,6-dimethyl-4-(2-trifluoromethylphenyl)-1,4-dihydropyridine has been determined by X-ray crystallographic methods. The crystals are monoclinic, space group $P2_1/a$, with cell parameters a=7.775(4) Å, b=13.919(11) Å, c=15.394(8) Å and β=100.84(4)°. The crystal structure was refined to a conventional R-factor of 0.045. Estimated standard deviations do not exceed 0.003 Å and 0.2° in bond distances and bond angles not involving hydrogen atoms. The crystal structure and antagonist activity of the title compound is discussed in relation to a previously proposed structure-activity model for this class of calcium channel antagonists.

Derivatives of 1,4-dihydropyridine (Fig. 1) comprise one class of a diverse group of organic compounds that are termed "calcium channel antagonists".[1] These compounds inhibit the influx of calcium ions through specific membrane channels, thereby causing negative inotropic effect in heart muscle and relaxation of smooth muscle.[2,3] Recently, dihydropyridines that are very similar in structure to the antagonists have been found to promote Ca^{2+}-influx, thereby producing opposite pharmacological effects.[4] One such agonist is BAY K 8644, where an ester group in the title compound is replaced by a nitro group.

The crystal structures of several antagonists with the general formula shown in Fig. 1 have previously been published.[5,6] In these compounds a correlation was observed between the ability to inhibit the Ca^{2+}-dependent contractile response in smooth muscle preparations and the puckering of the dihydropyridine ring; deviations from planarity being smallest in the most active compounds. This correlation excludes compounds with large para substituents in the phenyl ring. The crystal structure of the title compound has been determined as part of a further study of such structure-activity relationships.

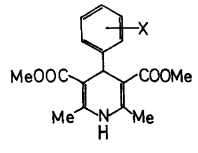

Fig. 1. Structure of 3,5-Bis(methoxycarbonyl)-2,6-dimethyl-4-aryl-1,4-dihydropyridines. Title compound: X=2−CF_3.

0302-4369/85 $2.50

Table 1. Fractional atomic coordinates. Estimated standard deviations in parenthesis.

Atom	X	Y	Z
F122	0.5686(1)	0.5953(1)	0.9804(0)
F123	0.4541(1)	0.7209(1)	0.9133(1)
F124	0.5318(1)	0.6354(0)	0.8569(0)
O32	0.6510(1)	0.4215(1)	0.8618(0)
O33	0.6637(1)	0.2778(1)	0.7975(0)
O52	0.3018(2)	0.6996(1)	0.5492(0)
O53	0.4472(2)	0.6973(1)	0.6887(0)
N1	0.3442(2)	0.3908(1)	0.5677(1)
C2	0.4437(2)	0.3488(1)	0.6429(1)
C3	0.5033(2)	0.4043(1)	0.7140(1)
C4	0.4547(2)	0.5107(1)	0.7169(1)
C5	0.3814(2)	0.5490(1)	0.6244(1)
C6	0.3219(2)	0.4885(1)	0.5562(1)
C7	0.3187(2)	0.5235(1)	0.7769(1)
C8	0.1568(2)	0.4784(1)	0.7476(1)
C9	0.0242(2)	0.4798(1)	0.7956(1)
C10	0.0490(3)	0.5263(1)	0.8764(1)
C11	0.2062(2)	0.5723(1)	0.9069(1)
C12	0.3408(2)	0.5724(1)	0.8576(1)
C21	0.4698(3)	0.2429(1)	0.6324(1)
C31	0.6110(2)	0.3700(1)	0.7975(1)
C34	0.7678(3)	0.2444(1)	0.8803(1)
C51	0.3692(2)	0.6537(1)	0.6135(1)
C54	0.4444(4)	0.8008(1)	0.6899(1)
C61	0.2291(3)	0.5168(1)	0.4651(1)
C121	0.4999(2)	0.6295(1)	0.9005(1)
H11	0.310(2)	0.353(1)	0.525(1)
H22	0.430(4)	0.227(2)	0.575(2)
H23	0.587(4)	0.229(2)	0.638(2)
H24	0.426(4)	0.206(2)	0.675(2)
H35	0.800(3)	0.179(1)	0.870(1)
H36	0.879(3)	0.286(3)	0.895(1)
H37	0.698(3)	0.249(1)	0.928(1)
H41	0.560(2)	0.545(1)	0.741(1)
H55	0.520(3)	0.818(1)	0.742(1)
H56	0.492(3)	0.826(1)	0.639(1)
H57	0.323(3)	0.822(1)	0.686(1)
H62	0.201(3)	0.465(2)	0.429(1)
H63	0.119(4)	0.548(2)	0.465(1)
H64	0.290(3)	0.565(2)	0.436(1)
H81	0.142(2)	0.444(1)	0.694(1)
H91	−0.083(2)	0.450(1)	0.770(1)
H101	−0.037(3)	0.527(1)	0.911(1)
H111	0.224(2)	0.604(1)	0.962(1)

EXPERIMENTAL AND STRUCTURE SOLUTION

Yellowish platy-like crystals were grown by slow evaporation from a methanol solution of the title compound. Data concerning the experimental conditions are given in EXPERIMENTAL CONDITIONS.

Cell parameters were obtained from a least squares fit of the diffractometer settings for 15 general reflections. The measured intensities were corrected for Lorentz and polarisation

effects, but not for absorption. Three reflections that were affected by the beamstop were discarded. The structure was solved by MULTAN[7] and refined by least squares techniques. The weights in least squares were calculated from the standard deviations in intensities $\sigma(I)$, taken as $\sigma(I)=(C_T+(0.02C_N)^2)^{\frac{1}{2}}$, where C_T is the total number of counts and C_N the net peak count. Hydrogen atoms were introduced by stereochemical considerations. Non-hydrogen atoms were refined anisotropically and hydrogen atoms isotropically, using a common thermal parameter for H atoms in methyl groups. The final R value was 0.045 (R_w=0.044) with a goodness-of-fit $S=(w\Delta^2/m-n)^{\frac{1}{2}}=2.19$. The computer programs used are described by Groth.[8] Final positional parameters are given in Table 1. Thermal parameters and tables of observed and calculated structure factors are available from the author.

EXPERIMENTAL CONDITIONS

Instrument	NICOLET P3/F
Radiation	Graphite-monochromatized Mo$K\alpha$, λ=0.71069 Å
Crystal dimensions/mm^3	0.50×0.30×0.10
Scanning mode	$\theta/2\theta$
Scan speed/°min^{-1}	3.0
Scan range/°	$2\theta_{\alpha1}-1.0$ to $2\theta_{\alpha2}+1.0$
Background counts	for 0.35 of scan time at scan limits
Temperature/°C	approximately −150
2θ range/°	2.5–55.0
Number of reflections	3949
Number of observed reflections $I>2.5\sigma(I)$	2731

CRYSTAL DATA

3,5-Bis(methoxycarbonyl)-2,6-dimethyl-4-(2-trifluoromethylphenyl)-1,4-dihydropyridine, $C_{18}H_{18}NO_4F_3$, monoclinic, a=7.775(4) Å, b=13.919(11) Å, c=15.394(8) Å, β=100.84(4)°, V=1636 Å^3, M=369.34, Z=4, $F(000)$=768, space group $P2_1/a$ (No. 14).

RESULTS AND DISCUSSION

Fig. 2 shows a schematic drawing of the molecule with the adopted atomic labeling scheme. Bond distances, bond angles and selected torsion angles may be found in Tables 2,3 and 4.

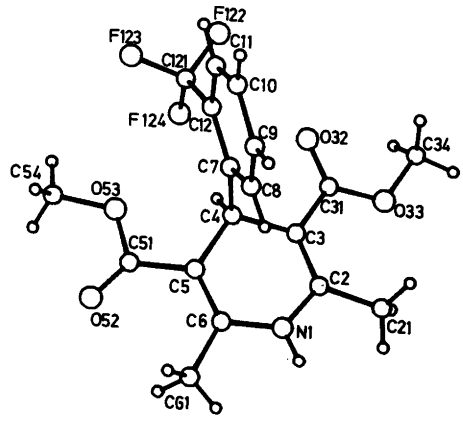

Fig. 2. A PLUTO drawing of the molecule with the adopted atomic labeling scheme.

Table 2. Bond lengths involving non-hydrogen atoms. Estimated standard deviations in parenthesis.

Distance	(Å)	Distance	(Å)
F122–C121	1.333(2)	F123–C121	1.346(2)
F124–C121	1.330(3)	O32–C31	1.214(2)
O33–C31	1.347(2)	O33–C34	1.452(3)
O52–C51	1.212(2)	O53–C51	1.345(2)
O53–C54	1.441(3)	N1–C2	1.394(2)
N1–C6	1.379(3)	C2–C3	1.348(3)
C2–C21	1.500(3)	C3–C4	1.531(3)
C3–C31	1.476(3)	C4–C5	1.526(3)
C4–C7	1.540(3)	C5–C6	1.357(3)
C5–C51	1.469(3)	C6–C61	1.504(3)
C7–C8	1.402(3)	C7–C12	1.398(3)
C8–C9	1.378(3)	C9–C10	1.384(3)
C10–C11	1.382(3)	C11–C12	1.404(3)
C12–C121	1.513(3)		

Table 3. Bond angles involving non-hydrogen atoms. Estimated standard deviations in parenthesis.

Angle	(°)	Angle	(°)
C31–O33–C34	115.1(2)	C51–O53–C54	117.2(2)
C2–N1–C6	123.9(2)	N1–C2–C3	119.1(2)
N1–C2–C21	112.8(2)	C3–C2–C21	128.1(2)
C2–C3–C4	121.9(2)	C2–C3–C31	125.0(2)
C4–C3–C31	113.0(2)	C3–C4–C5	111.2(2)
C3–C4–C7	109.3(2)	C5–C4–C7	109.9(2)
C4–C5–C6	121.2(2)	C4–C5–C51	117.2(2)
C6–C5–C51	121.5(2)	N1–C6–C5	119.7(2)
N1–C6–C61	113.9(2)	C5–C6–C61	126.4(2)
C4–C7–C8	115.5(2)	C4–C7–C12	127.2(2)
C8–C7–C12	117.2(2)	C7–C8–C9	122.6(2)
C8–C9–C10	119.8(2)	C9–C10–C11	119.1(2)
C10–C11–C12	121.3(2)	C7–C12–C11	120.0(2)
C7–C12–C121	126.7(2)	C11–C12–C121	113.3(2)
O32–C31–O33	122.1(2)	O32–C31–C3	122.4(2)
O33–C31–C3	115.5(2)	O52–C51–O53	121.4(2)
O52–C51–C5	128.6(2)	O53–C51–C5	109.9(2)
F122–C121–F123	105.9(2)	F122–C121–F124	105.9(2)
F122–C121–C12	111.6(2)	F123–C121–F124	105.4(2)
F123–C121–C12	110.1(2)	F124–C121–C12	117.1(2)

C(sp^2)–H and C(sp^3)–H bond lengths are within the ranges 0.93–0.95 and 0.91–1.03 Å respectively. The corresponding standard deviations from the mean values are 0.01 and 0.04 Å, as compared to the mean e.s.d. values 0.02 and 0.03 Å.

Steric strain imposed mainly by the short non-bonding distance between F124 and the C4 hydrogen is reflected in relatively large deviations in the bond angles C4–C7–C12, C7–C12–C121 and C12–C121–F124 from ideal sp^2 and sp^3 values. Bond lengths do not

Table 4. Selected torsion angles. Estimated standard deviations in parenthesis.

Dihedral angle	(°)
C6–N1–C2–C3	9.3(3)
N1–C2–C3–C4	4.2(3)
C2–C3–C4–C5	−16.5(3)
C3–C4–C5–C6	17.8(3)
C4–C5–C6–N1	−6.9(3)
C5–C6–N1–C2	−8.0(3)
C21–C2–C3–C31	0.7(5)
C51–C5–C6–C61	−3.8(3)
C2–C3–C31–O32	−174.7(2)
C6–C5–C51–O52	4.0(4)
C3–C31–O33–C34	−179.3(3)
C5–C51–O53–C54	−179.0(2)
C3–C4–C7–C8	−64.0(2)
C3–C4–C7–C12	114.1(2)
C7–C12–C121–F124	1.1(3)

differ significantly from values found in analogous dihydropyridine structures.

As in the previously determined crystal structures in this series, the dihydropyridine ring adopts a flat-boat conformation. This ring is approximately bisected by the plane of the pseudo-axial phenyl ring, as shown by the magnitude of the torsion angle C3–C4–C7–C8. The adopted orientation of the phenyl ring, where the ortho substituent points away from the dihydropyridine ring, is found in all investigated ortho phenyl substituted compounds.[5,6] The same phenyl ring orientation is preferred in solution, as shown by NMR investigations.[9,10] Two different orientations of the phenyl ring are also possible for meta substituted compounds, corresponding to the substituent being on C9 or C11. Both conformers are observed in the solid state; in the 3-CN derivative the substituent is on C9 whereas in the 3-NO_2 and 3-Me derivatives they are on C11. This suggests that the energy difference between the two conformers is smaller in the case of meta than of ortho substitution, because of less steric strain. It would also be expected that rotation round the interring bond (C4–C7) is less hindered in compounds with only ortho hydrogen

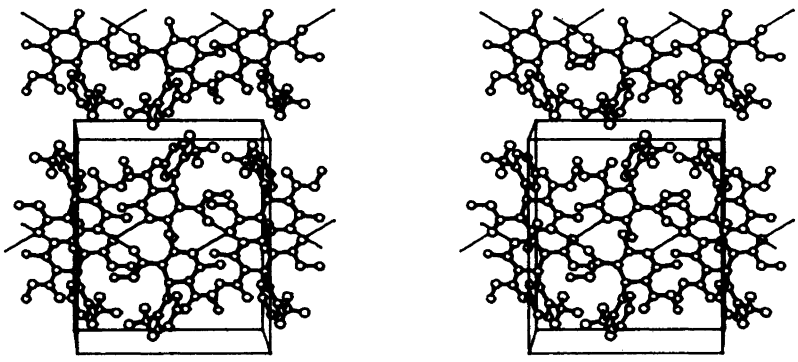

Fig. 3. A stereoscopic drawing of the molecular packing arrangement as seen down the *a*-axis. Hydrogen atoms are omitted for clarity.

substituents. In accordance with this, a greater dispersion of interring torsion angles is found in these compounds.[6] Because of the influence of crystal packing forces, it is an open question whether the conformational difference observed in meta substituted compounds has any relevance to their pharmalogical activity.

A stereoscopic drawing of the molecular packing arrangement is given in Fig. 3. Apparently the molecular packing is determined mainly by forces of van der Waals type. A weak intermolecular hydrogen bond is formed between N1 (donor) and O52 ($\frac{1}{2}$-x, y-$\frac{1}{2}$, 1-z). Hydrogen bonded molecules thus form a pattern of zig-zag chains running parallel to the b-axis. The N···O distance 3.293 Å is longer than in other crystal structures of this series (range: 2.943–3.014 Å). The N–H···O angle is 157°.

The pharmacological activity of this series of calcium channel antagonists is defined as the concentration that produces 50 % inhibition of the tonic (slow) contractile response in smooth muscle prepartions from the guinea pig ileum (ID_{50}).[11] The relative activity of the title compound is 340 (ID_{50}=1.5 nM),[12] measured on a scale where the activity of the well known antagonist nifedipine (X=2-NO_2) is set equal 100. It is thus among the most potent antagonists known. The activity expected from the previously reported linear regression line relating log ID_{50} to the magnitude of ring puckering[6] is in good agreement with the measured value. From the value of this parameter, defined as the sum of the numeric values of the six intraring torsion angles (62.7°), an activity of 320 is inferred.

The marked difference in pharmacological activity observed in these compounds is obviously a result of many composite factors. This is illustrated by the fact that antagonists like the title compound and the agonist BAY K 8644 apparently bind to the same dihydropyridine binding site, yet evoke opposite pharmacological effects.[4] However, the good agreement between measured and predicted activity for the title compound, supports the claim that the puckering of the dihydropyridine ring is a highly significant structural parameter in describing the variance in the pharmacological data within the series of antagonists.

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REFERENCES

1. Rosenberger, L.P. and Triggle, D.J. In Weiss, G.P., Ed., *Calcium and Drug Action,* Plenum, New York 1978.
2. Fleckenstein, A. *Ann. Rev. Pharmacol. Toxicol. 17* (1977) 149.
3. Reuter, H. *Nature 301* (1983) 459.
4. Schramm, M., Thomas, G., Towart, R. and Franckowiak, G. *Nature 303* (1983) 535.
5. Triggle, A.M., Shefter, E. and Triggle, D.J. *J. Med. Chem. 23* (1980) 1442.
6. Fossheim, R., Svarteng, K., Mostad, A., Rømming, C., Shefter, E. and Triggle, D.J. *J. Med. Chem. 25* (1982) 126.
7. Germain, G., Main, P. and Woolfson, M.M. *Acta Crystallogr. A 27* (1971) 368.
8. Groth, P. *Acta Chem. Scand. 27* (1973) 1837.
9. Berntsson, P. and Carter, R.E. *Acta Pharm. Suec. 18* (1981) 221.
10. Goldmann, S. and Geiger, W. *Angew. Chem. 96* (1984) 302.
11. Rosenberger, L.P., Ticku, M.K. and Triggle, D.J. *Can. J. Physiol. Pharmacol. 57* (1979) 333.
12. Triggle, D.J. *Personal communication.*

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