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Structural Studies of a New Dihydropyridine Calcium Channel Antagonist, Nilvadipine

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The crystal and molecular structure of nilvadipine, 5-isopropyl-3-methyl-2-cyano-6-methyl-4-(3-nitrophenyl)-1,4-dihydro-3,5-pyridinedicarboxylate, was elucidated by X-ray structural analysis. The dihydropyridine ring adopted a boat-type conformation with the phenyl ring attached to the pseudo-axial position. Each carbonyl double bond in the ester side chains was conjugated with a neighboring double bond of the dihydropyridine ring to form a plane involving the ester group. Nonbonding interaction between the two rings was reduced by puckering of the dihydropyridine ring, lengthening of the exocyclic bond at the pseudo-axial position and twisting of the phenyl ring, keeping the *meta*-nitro group away from the bulky isopropyl ester group. The nuclear Overhauser effects observed in chloroform solution suggest free rotation of the phenyl ring at the pseudo-axial position about the exocyclic bond.

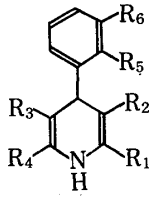
Keywords——nilvadipine; calcium channel antagonist; X-ray analysis; molecular conformation; crystal structure; nuclear Overhauser effect

Introduction

Nifedipine (I) and its analogs, 2,6-dimethyl-3,5-dicarboalkoxy-4-(aryl-substituted)-1,4-dihydropyridines, are calcium channel antagonists characterized by having identical ester groups at both C(3) and C(5) of the dihydropyridine ring. Quantitative structure–activity relationships have been established for these compounds by Rodenkirchen *et al.*,[1] and the crystal structures as well as pharmacological actions have been studied by Triggle *et al.*[2]

Recently, however, 1,4-dihydropyridines with different ester groups at C(3) and C(5) have been gaining clinical prominence, since these asymmetrically substituted derivatives often have superior pharmacological activities as compared to the corresponding symmetrical derivatives.[3] Several of these asymmetric analogs are calcium channel agonists,[4] and the crystal structure of BAY K 8644 (II), one of these agonists, has been determined by X-ray diffraction studies.[5]

Nilvadipine (III), a very potent calcium channel antagonist with greater stability to light than nifedipine, was developed by our research laboratories.[6] It is characterized by having four dissimilar substituents at C(2), C(3), C(5) and C(6) of the dihydropyridine ring. We carried out X-ray crystallographic studies to investigate the conformational features of



nifedipine (I): $R_1=R_4=CH_3$, $R_2=R_3=COOCH_3$, $R_5=NO_2$, $R_6=H$
BAY K 8644 (II): $R_1=R_4=CH_3$, $R_2=NO_2$, $R_3=COOCH_3$, $R_5=CF_3$, $R_6=H$
nilvadipine (III): $R_1=CN$, $R_2=COOCH_3$, $R_3=COOCH(CH_3)_2$, $R_4=CH_3$, $R_5=H$, $R_6=NO_2$

Chart 1

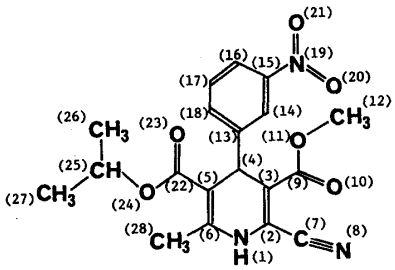


Fig. 1. Nilvadipine Molecule and Atomic Numbering

TABLE I. Crystal Data

Chemical formula	:	$C_{19}H_{19}N_3O_6$
Formula weight	:	385.38
Crystal system	:	Orthorhombic
Space group	:	*Pbca*
Z	=	8
a	=	15.378 (2) Å
b	=	17.469 (5) Å
c	=	14.191 (2) Å
V	=	3812 (1) Å^3
μ (CuK_α)	=	0.812 mm^{-1}
λ	=	1.5418 Å
D_m	=	1.343 (1) Mgm^{-3}
D_x	=	1.343 Mgm^{-3}

nilvadipine. In addition to the solid state structure, we also examined the degree of free rotation of the phenyl ring about the C(4)–C(13) bond in $CDCl_3$ solution by observing the nuclear Overhauser effects (NOEs).

The chemical structure of the nilvadipine molecule is shown in Fig. 1 along with the atomic numbering used in this structure analysis.

Experimental

X-Ray Analysis——Nilvadipine crystallized from ethanol solution as transparent yellow prisms. The crystals belong to an orthorhombic system with space group *Pbca*. The unit cell contains each of four optical *d*- and *l*-isomers. Crystal data are shown in Table I. The crystal density was determined by the flotation method.

The intensities of 3220 independent reflections up to $2\theta=130°$ were collected on a Rigaku AFC-5 diffractometer with graphite-monochromated CuK_α radiation. Corrections were applied for Lorentz and polarization factors, but not for absorption and extinction.

Structure Determination and Refinement——The structure was solved by a direct method using the MULTAN 74 program,[7] and the positions of all the non-hydrogen atoms in the molecule were successfully assigned.

The structure was refined by a block-diagonal matrix least-squares method.[8] The positions of all hydrogen atoms were determined from a difference Fourier synthesis. Positional and isotropic thermal parameters of hydrogen atoms were refined together with the positional and anisotropic thermal parameters of non-hydrogen atoms. The final R value was 0.069 for 2930 non-zero reflections. Throughout the refinements, a unit weight was given to the intensity of each reflection. The atomic scattering factors cited in International Tables for X-Ray Crystallography Vol. IV[9] were used.

NOE Study——Proton nuclear magnetic resonance (^{1}H-NMR) spectra were obtained with a JEOL FX-270 spectrometer (270 MHz). An oxygen-free $CDCl_3$ solution of nilvadipine (35 mg/0.7 ml) at 25 °C was used with tetramethylsilane (TMS) as an internal standard. Signals at δ 5.18 (singlet), δ 7.63 (multiplet) and δ 8.12 (multiplet) were assigned to the H(4), H(18) and H(14) protons, respectively. The NOE was determined from the integrated intensity increments on gated homodecoupling irradiation of corresponding protons.

Results and Discussion

The final atomic coordinates and isotropic thermal parameters are given in Table II. The bond lengths (Å), bond angles (°) and selected torsion angles (°) are listed in Table III. The stereoview of the molecular conformation of nilvadipine drawn by use of the ORTEP II

TABLE II. Final Atomic Coordinates and Isotropic Thermal Parameters (Å^2) with the Estimated Standard Deviations in Parentheses

Atom	x	y	z	B
N(1)	0.1661 (2)	0.4696 (1)	−0.0788 (2)	3.2
C(2)	0.0992 (2)	0.4341 (2)	−0.0321 (2)	3.2
C(3)	0.1015 (2)	0.4212 (2)	0.0612 (2)	2.9
C(4)	0.1860 (2)	0.4347 (2)	0.1138 (2)	2.8
C(5)	0.2414 (2)	0.4938 (2)	0.0626 (2)	2.8
C(6)	0.2318 (2)	0.5067 (2)	−0.0307 (2)	3.1
C(7)	0.0274 (2)	0.4161 (2)	−0.0923 (3)	4.3
N(8)	−0.0253 (2)	0.4062 (2)	−0.1483 (3)	6.8
C(9)	0.0241 (2)	0.3915 (2)	0.1097 (2)	3.5
O(10)	−0.0442 (2)	0.3759 (2)	0.0719 (2)	5.2
O(11)	0.0371 (1)	0.3840 (1)	0.2025 (2)	4.5
C(12)	−0.0347 (3)	0.3530 (3)	0.2569 (3)	6.1
C(13)	0.2334 (2)	0.3579 (2)	0.1259 (2)	2.8
C(14)	0.2189 (2)	0.3147 (2)	0.2068 (2)	3.1
C(15)	0.2599 (2)	0.2441 (2)	0.2143 (2)	3.6
C(16)	0.3132 (2)	0.2140 (2)	0.1458 (3)	4.3
C(17)	0.3265 (2)	0.2572 (2)	0.0648 (3)	4.4
C(18)	0.2867 (2)	0.3292 (2)	0.0554 (2)	3.7
N(19)	0.2448 (2)	0.1990 (2)	0.3009 (2)	4.9
O(20)	0.1826 (2)	0.2151 (2)	0.3502 (2)	7.1
O(21)	0.2950 (2)	0.1466 (2)	0.3178 (2)	7.1
C(22)	0.3087 (2)	0.5300 (2)	0.1221 (2)	3.1
O(23)	0.3170 (2)	0.5154 (1)	0.2057 (2)	4.5
O(24)	0.3593 (1)	0.5791 (1)	0.0765 (2)	4.3
C(25)	0.4325 (2)	0.6142 (2)	0.1259 (3)	4.7
C(26)	0.4469 (3)	0.6894 (2)	0.0744 (4)	6.9
C(27)	0.5085 (3)	0.5611 (3)	0.1216 (3)	6.6
C(28)	0.2831 (2)	0.5594 (2)	−0.0944 (2)	4.4
H(1)	0.159 (2)	0.474 (2)	−0.142 (3)	3.3
H(4)	0.165 (2)	0.451 (2)	0.184 (2)	2.1
H(12a)	−0.051 (3)	0.303 (2)	0.230 (3)	5.1
H(12b)	−0.016 (3)	0.351 (2)	0.318 (3)	5.1
H(12c)	−0.090 (3)	0.388 (2)	0.243 (3)	6.0
H(14)	0.177 (2)	0.333 (2)	0.259 (2)	2.6
H(16)	0.346 (2)	0.159 (2)	0.160 (3)	3.9
H(17)	0.362 (2)	0.237 (2)	0.010 (3)	3.4
H(18)	0.298 (2)	0.358 (2)	−0.008 (2)	2.9
H(25)	0.409 (2)	0.624 (2)	0.198 (3)	3.5
H(26a)	0.393 (3)	0.722 (2)	0.072 (3)	5.4
H(26b)	0.457 (3)	0.638 (2)	0.003 (3)	5.2
H(26c)	0.492 (3)	0.718 (3)	0.104 (3)	6.5
H(27a)	0.493 (3)	0.511 (2)	0.159 (3)	4.3
H(27b)	0.529 (2)	0.554 (2)	0.053 (3)	3.6
H(27c)	0.565 (3)	0.583 (3)	0.159 (3)	6.3
H(28a)	0.264 (2)	0.608 (2)	−0.083 (3)	3.6
H(28b)	0.346 (2)	0.550 (2)	−0.086 (3)	3.8
H(28c)	0.273 (3)	0.553 (2)	−0.163 (3)	5.4

$B_{eq}=\frac{4}{3}\left(\frac{B_{11}}{a^{*2}}+\frac{B_{22}}{b^{*2}}+\frac{B_{33}}{c^{*2}}\right)$ for non-hydrogen atoms.

program[10] is shown in Fig. 2.

As with all previously reported nifedipine analogs,[2] the dihydropyridine ring adopted a boat-type conformation with apexes at N(1) and C(4). Deviations of the apex atoms from the

TABLE III. Bond Lengths (Å), Bond Angles (°) and Selected Torsion Angles (°) with the Estimated Standard Deviations in Parentheses

a) Bond lengths (Å)

N(1)–C(2)	1.371 (4)	C(22)–O(23)	1.221 (4)
N(1)–C(6)	1.381 (4)	C(22)–O(24)	1.327 (4)
C(2)–C(3)	1.343 (4)	O(24)–C(25)	1.461 (5)
C(2)–C(7)	1.432 (5)	C(25)–C(26)	1.520 (7)
C(3)–C(4)	1.517 (4)	C(25)–C(27)	1.494 (6)
C(3)–C(9)	1.469 (5)	N(1)–H(1)	0.91 (4)
C(4)–C(5)	1.524 (4)	C(4)–H(4)	1.09 (3)
C(4)–C(13)	1.536 (4)	C(12)–H(12a)	0.98 (4)
C(5)–C(6)	1.352 (4)	C(12)–H(12b)	0.92 (4)
C(5)–C(22)	1.477 (4)	C(12)–H(12c)	1.07 (5)
C(6)–C(28)	1.512 (5)	C(14)–H(14)	1.03 (3)
C(7)–N(8)	1.147 (6)	C(16)–H(16)	1.10 (4)
C(9)–O(10)	1.211 (4)	C(17)–H(17)	1.01 (4)
C(9)–O(11)	1.337 (4)	C(18)–H(18)	1.05 (3)
O(11)–C(12)	1.452 (5)	C(25)–H(25)	1.10 (4)
C(13)–C(14)	1.393 (4)	C(26)–H(26a)	1.01 (4)
C(13)–C(18)	1.387 (4)	C(26)–H(26b)	1.04 (4)
C(14)–C(15)	1.389 (4)	C(26)–H(26c)	0.96 (5)
C(15)–C(16)	1.375 (5)	C(27)–H(27a)	1.05 (4)
C(15)–N(19)	1.478 (5)	C(27)–H(27b)	1.03 (4)
C(16)–C(17)	1.390 (5)	C(27)–H(27c)	1.09 (4)
C(17)–C(18)	1.405 (5)	C(28)–H(28a)	0.91 (4)
N(19)–O(20)	1.218 (5)	C(28)–H(28b)	0.99 (4)
N(19)–O(21)	1.220 (5)	C(28)–H(28c)	0.99 (4)

b) Bond angles (°)

C(2)–N(1)–C(6)	121.5 (3)	C(2)–N(1)–H(1)	115 (2)
N(1)–C(2)–C(3)	122.2 (3)	C(6)–N(1)–H(1)	122 (2)
N(1)–C(2)–C(7)	112.9 (3)	C(3)–C(4)–H(4)	104 (2)
C(3)–C(2)–C(7)	124.8 (3)	C(5)–C(4)–H(4)	115 (2)
C(2)–C(3)–C(4)	118.8 (3)	C(13)–C(4)–H(4)	106 (2)
C(2)–C(3)–C(9)	120.1 (3)	O(11)–C(12)–H(12a)	108 (2)
C(4)–C(3)–C(9)	121.1 (3)	O(11)–C(12)–H(12b)	106 (3)
C(3)–C(4)–C(5)	110.5 (2)	O(11)–C(12)–H(12c)	107 (2)
C(3)–C(4)–C(13)	109.1 (2)	H(12a)–C(12)–H(12b)	115 (4)
C(5)–C(4)–C(13)	112.3 (2)	H(12a)–C(12)–H(12c)	103 (3)
C(4)–C(5)–C(6)	121.2 (3)	H(12b)–C(12)–H(12c)	117 (4)
C(4)–C(5)–C(22)	114.2 (3)	C(13)–C(14)–H(14)	121 (2)
C(6)–C(5)–C(22)	124.4 (3)	C(15)–C(14)–H(14)	121 (2)
N(1)–C(6)–C(5)	119.1 (3)	C(15)–C(16)–H(16)	119 (2)
N(1)–C(6)–C(28)	111.9 (3)	C(17)–C(16)–H(16)	124 (2)
C(5)–C(6)–C(28)	129.0 (3)	C(16)–C(17)–H(17)	122 (2)
C(2)–C(7)–N(8)	172.3 (4)	C(18)–C(17)–H(17)	118 (2)
C(3)–C(9)–O(10)	125.0 (3)	C(13)–C(18)–H(18)	123 (2)
C(3)–C(9)–O(11)	112.1 (3)	C(17)–C(18)–H(18)	117 (2)
O(10)–C(9)–O(11)	122.9 (3)	O(24)–C(25)–H(25)	105 (2)
C(9)–O(11)–C(12)	116.6 (3)	C(26)–C(25)–H(25)	111 (2)
C(4)–C(13)–C(14)	119.3 (3)	C(27)–C(25)–H(25)	113 (2)
C(4)–C(13)–C(18)	121.0 (3)	C(25)–C(26)–H(26a)	113 (2)
C(14)–C(13)–C(18)	119.5 (3)	C(25)–C(26)–H(26b)	113 (2)
C(13)–C(14)–C(15)	118.2 (3)	C(25)–C(26)–H(26c)	110 (3)
C(14)–C(15)–C(16)	123.7 (3)	H(26a)–C(26)–H(26b)	99 (3)

TABLE III. (continued)

b) Bond angles (°)

C(14)–C(14)–N(19)	117.8 (3)	H(26a)–C(26)–H(26c)	108 (4)
C(16)–C(15)–N(19)	118.5 (3)	H(26b)–C(26)–H(26c)	113 (4)
C(15)–C(16)–C(17)	117.7 (3)	C(25)–C(27)–H(27a)	109 (2)
C(16)–C(17)–C(18)	120.0 (3)	C(25)–C(27)–H(27b)	111 (2)
C(13)–C(18)–C(17)	120.8 (3)	C(25)–C(27)–H(27c)	113 (2)
C(15)–N(19)–O(20)	118.5 (3)	H(27a)–C(27)–H(27b)	116 (3)
C(15)–N(19)–O(21)	117.6 (3)	H(27a)–C(27)–H(27c)	102 (3)
O(20)–N(19)–O(21)	123.8 (3)	H(27b)–C(27)–H(27c)	106 (3)
C(5)–C(22)–O(23)	122.6 (3)	C(6)–C(28)–H(28a)	107 (2)
C(5)–C(22)–O(24)	114.2 (3)	C(6)–C(28)–H(28b)	110 (2)
O(23)–C(22)–O(24)	123.2 (3)	C(6)–C(28)–H(28c)	116 (2)
C(22)–O(24)–C(25)	119.3 (3)	H(28a)–C(28)–H(28b)	116 (3)
O(24)–C(25)–C(26)	104.1 (3)	H(28a)–C(28)–H(28c)	103 (3)
O(24)–C(25)–C(27)	108.8 (3)	H(28b)–C(28)–H(28c)	104 (3)
C(26)–C(25)–C(27)	113.8 (4)		

c) Selected torsion angles (°)

C(6)–N(1)–C(2)=C(3)	−12.3	C(3)–C(9)–O(11)–C(12)	−178.3
N(1)–C(2)=C(3)–C(4)	−10.0	C(6)=C(5)–C(22)=O(23)	−177.8
C(2)=C(3)–C(4)–C(5)	26.1	C(6)=C(5)–C(22)–O(24)	1.6
C(3)–C(4)–C(5)=C(6)	−24.0	C(5)–C(22)–O(24)–C(25)	−175.3
C(4)–C(5)=C(6)–N(1)	4.9	C(22)–O(24)–C(25)–C(26)	−153.6
C(5)=C(6)–N(1)–C(2)	14.8	C(22)–O(24)–C(25)–C(27)	84.4
C(7)–C(2)–C(3)–C(9)	−4.6	C(3)–C(4)–C(13)–C(14)	−91.7
C(28)–C(6)–C(5)–C(22)	−1.2	C(3)–C(4)–C(13)–C(18)	84.8
C(2)=C(3)–C(9)=O(10)	1.1	C(5)–C(4)–C(13)–C(14)	145.5
C(2)=C(3)–C(9)–O(11)	−178.3	C(5)–C(4)–C(13)–C(18)	−38.0

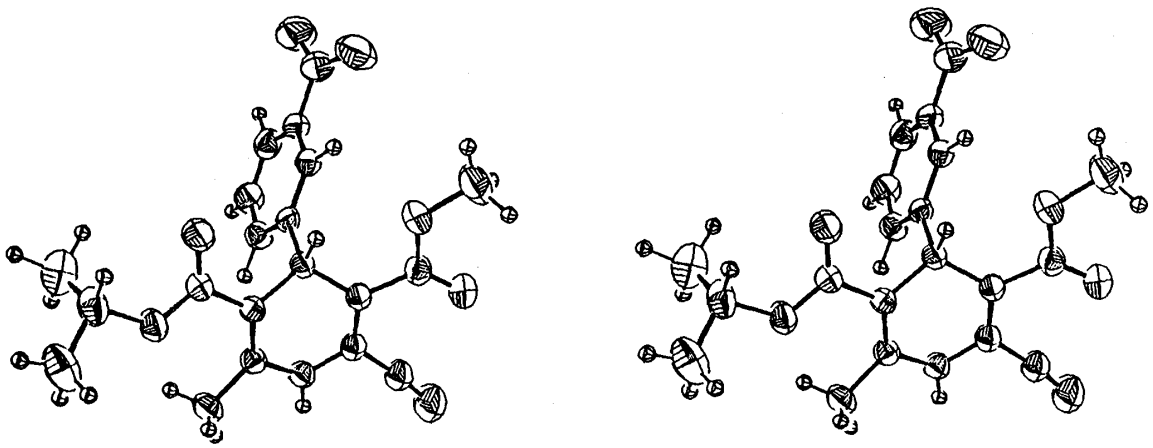


Fig. 2. Stereographic Molecular Conformation of Nilvadipine (ORTEP II)

least-squares plane through C(2), C(3), C(5) and C(6) atoms were 0.136 Å for N(1) and 0.318 Å for C(4), respectively (Table IV).

Triggle and co-workers have suggested a correlation between the degree of dihydropyridine ring flatness and the activity of *ortho*- and *meta*-phenyl-substituted nifedipine antagonists, noting that the more active compounds exhibit smaller degrees of ring distortion from

TABLE IV. Deviations (Å) of Atoms from Least-Squares Planes

I) 1,4-Dihydropyridine ring					
C(2)[a]	0.015	N(1)	0.136	C(13)	1.788
C(3)[a]	−0.014	C(4)	0.318	C(22)	−0.142
C(5)[a]	0.014	C(7)	−0.132	C(28)	−0.226
C(6)[a]	−0.015	C(9)	−0.307	H(1)	0.174
				H(4)	−0.265
II) Methyl-ester side chain at the C(3) position					
N(1)[a]	−0.048	C(4)	0.085	O(11)	−0.093
C(2)[a]	0.060	C(5)	−0.450	C(12)	−0.104
C(3)[a]	0.021	C(6)	−0.448	H(1)	0.018
C(9)[a]	−0.023	C(7)	0.155		
O(10)[a]	−0.009				
III) Isopropyl-ester side chain at the C(5) position					
N(1)[a]	0.001	C(2)	−0.324	C(26)	−0.608
C(5)[a]	−0.010	C(3)	−0.414	C(27)	1.523
C(6)[a]	0.009	C(4)	0.071	H(1)	0.063
C(22)[a]	−0.010	O(24)	−0.023	H(25)	−0.487
O(23)[a]	0.011	C(25)	0.079		

Equations for least-squares planes.
I) $0.510x-0.841y-0.179z+5.535=0.0$.
II) $0.328x-0.924y-0.195z+6.482=0.0$.
III) $0.630x-0.747y-0.212z+4.284=0.0$.
x, y and z refer to the orthogonal coordinate system (Å). *a*) Denote atoms included in the calculations of the least-squares planes.

planarity.[2] Nilvadipine, despite its more potent pharmacological activity (5—16 times greater activity than nifedipine),[11] had greater ring puckering than nifedipine. Though the different ester side chains of the dihydropyridine moiety between nilvadipine and nifedipine analogs may influence the pharmaceutical activity, this inconsistency suggests that a re-evaluation of structure–activity relationships is needed for the dihydropyridine calcium channel antagonists.

The carbonyl group of the C(3) methyl ester is *synperiplanar* to the C(3)–C(2) ring double bond, and that of the C(5) isopropyl ester is *antiperiplanar* to the C(5)–C(6) ring double bond with torsion angles of 1.1° for C(2)–C(3)–C(9)–O(10) and −177.8° for C(6)–C(5)–C(22)–O(23). Therefore these two carbonyl groups face diametrically away from one another. The carbonyl double bonds of the C(3) and C(5) ester side chains are conjugated with the neighboring endocyclic double bonds, contributing to the planar conformation involving the ester groups. This was also clear from the equations of these planes (Table IV).

The phenyl ring attached to the C(4) atom occupies a pseudo-axial position. This conformation is sterically preferred to an equatorial position because of the proximity of the C(3) and C(5) ester side chains of the dihydropyridine ring. As seen in all nifedipine analogs,[2] however, a small degree of strain in the molecule remains as a result of the nonbonding interaction involving the *ortho* hydrogen atoms of the phenyl ring and the ester side chains of the dihydropyridine ring. This strain is relieved in the following three ways: first, puckering of the dihydropyridine ring such that the two conjugated planes consisting of the ester side chains and neighboring endocyclic double bonds are inclined away from the phenyl ring; second, a slight lengthening of the exocyclic C(4)–C(13) bond (1.536 Å), as in other nifedipine analogs[2]; last, a fairly distorted torsion angle (−38°) of C(5)–C(4)–C(13)–C(18) showing that the phenyl ring twists from a *gauche* conformation to avoid steric repulsion between the nitro-group of the phenyl ring and the bulky isopropyl ester group at C(5).

The degree of free rotation of the phenyl ring about the C(4)–C(13) bond in $CDCl_3$

TABLE V. Nuclear Overhauser Effects of Nilvadipine in $CDCl_3$

Irradiated	Observed	NOE (%)
H(14)	H(4)	
δ 8.12	δ 5.18	9.2
H(4)	H(14)	
δ 5.18	δ 8.12	11.8
H(4)	H(18)	
δ 5.18	δ 7.63	9.3

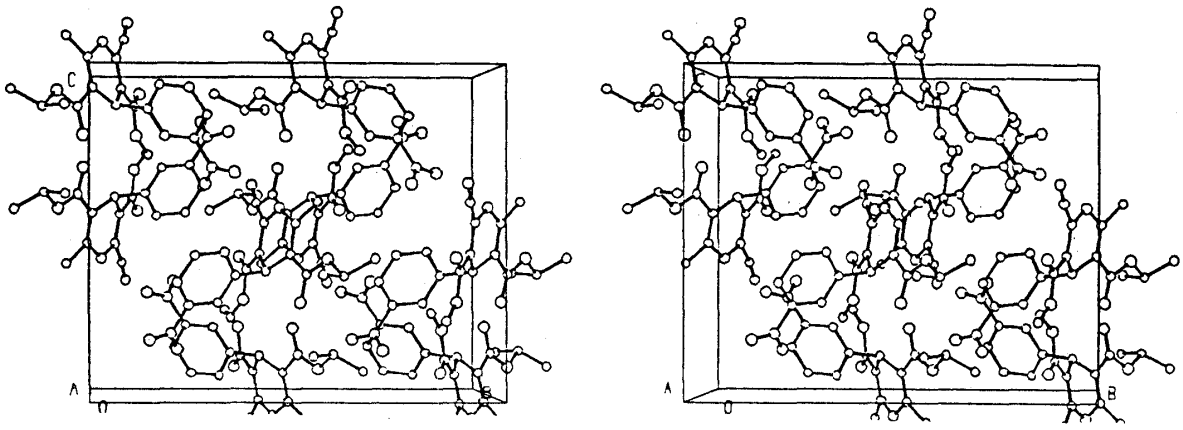


Fig. 3. Molecular Packing Diagram of Nilvadipine (PLUTO)

solution was investigated by means of an NOE study. As shown in Table V, irradiation at the H(14) signal position resulted in an integrated intensity increment of 9.3% for the H(4) signal. Similarly, irradiation at the H(4) signal position resulted in increments of 11.8% for the H(14) signal and 9.2% for the H(18) signal. Nearly equal NOEs between the H(4) atom and the two *ortho* hydrogen atoms, H(14) and H(18), suggested three possibilities for the C(4) phenyl ring conformation: i) free rotation about the C(4)–C(13) bond, ii) a rigid conformation holding H(4) nearly equidistant from the two *ortho* hydrogen atoms, H(14) and H(18), iii) rapid equilibrium between two minimally energetic conformations.

In the crystalline state, the distances between H(4) and the two *ortho* hydrogen atoms, H(14) and H(18), differ somewhat, *i.e.* H(4)$\cdots$H(14)=2.32 Å and H(4)$\cdots$H(18)=3.50 Å.

In nifedipine analogs, various torsion angles (−29.3 °—−90.1 °) for C(5)–C(4)–C(13)–C(18) have been found in the crystalline state,[2] suggesting ready adaptation of the torsion angles about the C(4)–C(13) bond to relieve the strain caused by substituents on the phenyl ring. It has also been reported that the 4-aryl-1,4-dihydropyridines in solution have a considerably lower rotation barrier about the exocyclic C(4)–C(13) bond.[12]

In addition to the results of the NOE study, the above findings suggest that, in chloroform solution, the C(4) phenyl ring of nilvadipine is rotating freely about the exocyclic C(4)–C(13) bond. Moreover, it may be assumed that even in the crystalline state, steric hindrance of C(4) phenyl ring rotation is minimal.

Figure 3 shows a packing diagram drawn using the PLUTO program.[13] In the crystal structures of nifedipine analogs, N(1)–H(1)$\cdots$O=C type bondings were observed.[2] However, because there are neither inter- nor intra-molecular hydrogen bonds in the nilvadipine crystal, the packing force should be due to van der Waals forces only.

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