

F1—C2—C7	117.8 (5)	N14—C15—C16	111.8 (4)
F1—C2—C3	117.3 (5)	C11—C16—C15	111.2 (4)
C3—C2—C7	124.9 (5)	N14—C17—C18	113.2 (4)
C2—C3—C4	119.3 (5)	C17—C18—C19	112.2 (4)
C3—C4—C5	118.3 (5)	C18—C19—C24	123.1 (4)
C4—C5—C10	136.8 (4)	C18—C19—C20	118.0 (4)
C4—C5—C6	119.1 (4)	C20—C19—C24	118.9 (4)
C6—C5—C10	104.1 (4)	C19—C20—O26	124.9 (4)
C5—C6—O8	110.2 (4)	C19—C20—N21	115.8 (4)
C5—C6—C7	124.7 (5)	N21—C20—O26	119.3 (4)
C7—C6—O8	125.0 (4)	C20—N21—C27	116.1 (4)
C2—C7—C6	113.6 (5)	C20—N21—C22	121.3 (4)
C6—O8—N9	107.3 (4)	C22—N21—C27	122.5 (4)
O8—N9—C10	107.0 (4)	N21—C22—C30	119.9 (4)
C5—C10—N9	111.4 (4)	N21—C22—N23	122.7 (4)
N9—C10—C11	120.2 (4)	N23—C22—C30	117.3 (5)
C5—C10—C11	128.4 (4)	C22—N23—C24	118.5 (4)
C10—C11—C16	111.6 (4)	C19—C24—N23	122.7 (4)
C10—C11—C12	113.2 (4)	N23—C24—C25	113.6 (4)
C12—C11—C16	108.8 (4)	C19—C24—C25	123.7 (4)
C11—C12—C13	110.8 (4)	N21—C27—C28	112.5 (4)
C12—C13—N14	111.2 (4)	C27—C28—C29	114.7 (5)
C13—N14—C17	110.7 (4)	C28—C29—C30	109.8 (5)
C13—N14—C15	109.8 (4)	C22—C30—C29	114.8 (6)
C15—N14—C17	111.8 (4)		
N9—C10—C11—C12	-4.8 (6)	C17—C18—C19—C24	-89.7 (6)
C5—C10—C11—C12	176.4 (5)	C20—N21—C27—C28	168.7 (4)
N9—C10—C11—C16	118.4 (5)	C22—N21—C27—C28	-14.2 (7)
C5—C10—C11—C16	-60.3 (6)	C27—N21—C22—C30	5.3 (7)
C13—N14—C17—C18	161.0 (4)	N21—C22—C30—C29	-22.4 (8)
C15—N14—C17—C18	-76.2 (5)	N23—C22—C30—C29	159.6 (5)
C17—N14—C15—C16	178.0 (4)	N21—C27—C28—C29	41.3 (7)
N14—C17—C18—C19	173.8 (4)	C27—C28—C29—C30	-58.4 (7)
C17—C18—C19—C20	87.8 (5)	C28—C29—C30—C22	47.5 (7)

Intensity data were collected using an ω scan with variable scan speed $0.6\text{--}2.4^\circ\text{min}^{-1}$. The scan width was $(60 + N)$ steps of 0.02° with N the number of extra steps to take the $\alpha_1 - \alpha_2$ splitting into account. The number of steps for background counts was 10 on each side of the scan.

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Lists of structure factors, anisotropic thermal parameters, H-atom coordinates and complete geometry have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 71224 (26 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England. [CIF reference: NA1034]

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Structure of a 4-Phenyl-1,4-dihydropyridine Derivative Containing a Nitroxyalkyl Ester at the 3-Position

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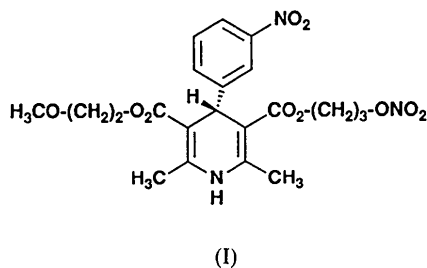
Abstract

In the title compound, (*R*)-(+)-3-nitrooxypropyl 2-methoxyethyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3,5-pyridinedicarboxylate, $[\alpha]_D^{20\text{C}} = +21.4^\circ$ (*c.* 0.5, MeOH), the phenyl ring linked to C4 is perpendicular to the dihydropyridine ring. The orientations of the carbonyl groups at C3 and C5 are antiperiplanar to the C2=C3 double bond and synperiplanar to the C5=C6 double bond.

Comment

In the last decade, synthetic studies on Hantzsch-type 1,4-dihydropyridines (Bossert, Meyer & Wehinger, 1981; Jolly, Hardman & Gross, 1981; Meyer, Bossert, Wehinger, Stoepel & Vater, 1981) have been carried out in many research institutes all over the world because of their vasodilator properties as calcium antagonists. When this work was initiated, nifedipine was the only known compound used clinically for the treatment of *angina pectoris* (Ellrodt, Chew & Singh, 1980; Leonard & Talbert, 1982; Spivack, Ocken & Frishman, 1983; Theroux, Taeymans & Waters, 1983; Vater *et al.*, 1972), and it was also known that nicardipine had been developed in preclinical studies for the treatment of hypertension (Iwanami *et al.*, 1979; Seki & Takenaka, 1977; Takenaka, Miyazaki, Asano, Higuchi & Maeno, 1982; Takenaka, Usuda, Nomura, Maeno & Sado, 1976). The aim of our work was to produce a drug with improved duration of activity. We were interested in the phenomenon that some organic nitro compounds, including nitroglycerine and nicorandil, increase the level of cyclic guanosine 5'-monophosphate (cyclic GMP) produced in various vascular smooth muscle tissues and promote relaxation (Holzmann, 1983; Waldman & Murad, 1988). So the combination of nitro-like and calcium-blocking active sites in a single molecule was expected to realize a vasodilating activity. Therefore, we synthesized novel dihydropyridine derivatives having a nitrate moiety in one of the ester chains.

The activity of the title compound (I) was found to be equal to or greater than that of nifedipine in terms of both potency and duration (Hatayama, Nakazato, Ogawa, Ito & Sawada, 1983; Ogawa, Nakazato, Sato & Hatayama, 1990; Ogawa, Nakazato, Tsuchida & Hatayama, 1993; Ogawa, Matsumoto, Yokoo, Hatayama & Kitamura, 1993).



As can be seen in Fig. 1, the phenyl ring is perpendicular to the dihydropyridine ring owing to the steric hindrance of methoxyethyl and nitrooxypropyl ester groups in the molecule. The endocyclic torsion angles around the N1—C2, C2—C3, C3—C4, C4—C5, C5—C6 and C6—N1 bonds are -16.8 (3), -7.0 (2), 27.1 (2), -27.1 (2), 7.3 (1) and 16.7 (1) $^\circ$, respectively. A large ring distortion is seen at C4 and N1. This feature is observed in other dihydropyridine derivatives (Fossheim *et al.*, 1982; Tamazawa *et al.*, 1986).

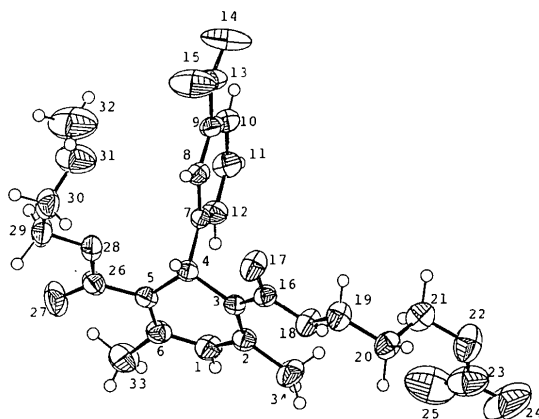


Fig. 1. ORTEP (Johnson, 1976) drawing of the title compound showing the numbering of atoms and thermal ellipsoids at the 50% probability level. H atoms are drawn as spheres of arbitrary radii.

Experimental

Crystal data

$C_{21}H_{25}N_3O_{10}$
 $M_r = 479.44$
 Monoclinic
 $P2_1$

Cu $K\alpha$ radiation
 $\lambda = 1.54178 \text{ \AA}$
 $\mu = 0.87 \text{ mm}^{-1}$
 $T = 288 \text{ K}$

$a = 13.216$ (2) \AA
 $b = 7.980$ (2) \AA
 $c = 10.970$ (2) \AA
 $\beta = 102.39$ (1) $^\circ$
 $V = 1130.0$ (3) \AA^3
 $Z = 2$
 $D_x = 1.41 \text{ Mg m}^{-3}$

Cell parameters from 20 reflections
 $\theta = 27.5\text{--}30^\circ$
 Plate
 $0.60 \times 0.40 \times 0.20 \text{ mm}$
 Light yellow

Data collection

Mac-Science MXC18 diffractometer
 $\omega/2\theta$ scans
 Absorption correction: analytical
 2215 measured reflections
 2032 independent reflections
 2015 observed reflections
 $R_{\text{int}} = 0.01$

$\theta_{\text{max}} = 65^\circ$
 $h = -15 \rightarrow 15$
 $k = 0 \rightarrow 9$
 $l = 0 \rightarrow 12$
 3 standard reflections monitored every 100 reflections
 intensity variation: $<2\%$

Refinement

Refinement on F
 Final $R = 0.035$
 $wR = 0.045$
 $S = 4.70$
 2015 reflections
 390 parameters

Only coordinates of H atoms refined
 $w = 1/[\sigma^2(F_o) + (0.010F_o)^2]$
 $(\Delta/\sigma)_{\text{max}} = 0.37$
 $\Delta\rho_{\text{max}} = 0.22 \text{ e \AA}^{-3}$
 $\Delta\rho_{\text{min}} = -0.17 \text{ e \AA}^{-3}$

Table 1. Positional and equivalent isotropic thermal parameters (\AA^2)

$$B_{\text{eq}} = (8\pi^2/3) \sum_i \sum_j U_{ij} a_i^* a_j^* \mathbf{a}_i \cdot \mathbf{a}_j$$

	x	y	z	B_{eq}
N1	-0.3304 (2)	0.0019 (1)	0.0489 (2)	3.61 (7)
C2	-0.2535 (2)	0.1029 (5)	0.1163 (2)	3.22 (7)
C3	-0.2147 (2)	0.0650 (5)	0.2379 (2)	2.72 (6)
C4	-0.2642 (2)	-0.0735 (5)	0.3013 (2)	2.64 (6)
C5	-0.3164 (2)	-0.2020 (5)	0.2068 (2)	2.97 (7)
C6	-0.3523 (2)	-0.1557 (6)	0.0863 (2)	3.43 (7)
C7	-0.3405 (2)	-0.0006 (5)	0.3741 (2)	2.56 (6)
C8	-0.3194 (2)	-0.0066 (5)	0.5038 (2)	2.93 (7)
C9	-0.3889 (2)	0.0662 (5)	0.5664 (2)	3.26 (7)
C10	-0.4797 (2)	0.1412 (6)	0.5059 (3)	3.93 (8)
C11	-0.5015 (2)	0.1416 (6)	0.3777 (3)	4.03 (8)
C12	-0.4329 (2)	0.0733 (5)	0.3125 (2)	3.39 (7)
N13	-0.3648 (2)	0.0613 (6)	0.7036 (2)	4.88 (8)
O14	-0.4198 (2)	0.1369 (7)	0.7594 (2)	8.4 (1)
O15	-0.2898 (2)	-0.0187 (7)	0.7568 (2)	7.6 (1)
C16	-0.1254 (2)	0.1452 (5)	0.3192 (2)	2.89 (6)
O17	-0.0913 (2)	0.1010 (5)	0.4252 (2)	4.32 (6)
O18	-0.0842 (2)	0.2735 (4)	0.2684 (2)	3.78 (6)
C19	0.0068 (2)	0.3520 (6)	0.3460 (3)	3.96 (8)
C20	0.0312 (2)	0.5043 (6)	0.2762 (3)	3.89 (8)
C21	-0.0461 (3)	0.6399 (6)	0.2793 (4)	4.9 (1)
O22	-0.0231 (2)	0.7889 (5)	0.2141 (3)	6.03 (8)
N23	-0.0643 (3)	0.7957 (8)	0.0881 (4)	7.2 (1)
O24	-0.0405 (4)	0.9195 (8)	0.0408 (4)	11.7 (2)
O25	-0.1234 (3)	0.6838 (9)	0.0441 (3)	9.9 (2)
C26	-0.3286 (2)	-0.3726 (5)	0.2499 (3)	3.45 (7)
O27	-0.3682 (2)	-0.4910 (5)	0.1897 (2)	5.61 (8)
O28	-0.2858 (2)	-0.3862 (4)	0.3728 (2)	3.69 (6)
C29	-0.2871 (3)	-0.5511 (6)	0.4278 (3)	4.38 (9)
C30	-0.2148 (3)	-0.5471 (6)	0.5527 (3)	4.66 (9)
O31	-0.2502 (2)	-0.4337 (6)	0.6314 (2)	6.79 (9)
C32	-0.2038 (6)	-0.452 (1)	0.7578 (4)	9.3 (2)
C33	-0.4155 (3)	-0.2599 (7)	-0.0166 (3)	5.0 (1)
C34	-0.2229 (3)	0.2437 (6)	0.0408 (3)	4.47 (9)

Table 2. Bond lengths (Å) and angles (°)

N1—C6	1.373 (4)	C11—C12	1.382 (5)
N1—C2	1.381 (4)	N13—O14	1.208 (5)
C2—C3	1.356 (3)	N13—O15	1.217 (5)
C2—C34	1.502 (6)	C16—O17	1.206 (3)
C3—C16	1.465 (4)	C16—O18	1.335 (5)
C3—C4	1.526 (5)	O18—C19	1.457 (4)
C4—H4	0.94 (3)	C19—C20	1.507 (6)
C4—C5	1.515 (4)	C20—C21	1.493 (6)
C4—C7	1.529 (4)	C21—O22	1.453 (6)
C5—C6	1.356 (4)	O22—N23	1.374 (4)
C5—C26	1.461 (6)	N23—O24	1.189 (8)
C6—C33	1.503 (5)	N23—O25	1.216 (8)
C7—C8	1.391 (3)	C26—O27	1.205 (5)
C7—C12	1.393 (4)	C26—O28	1.350 (3)
C8—H8	0.97 (4)	O28—C29	1.449 (5)
C8—C9	1.387 (4)	C29—C30	1.493 (5)
C9—C10	1.377 (4)	C30—O31	1.398 (6)
C9—N13	1.470 (3)	O31—C32	1.398 (5)
C10—C11	1.374 (4)		
C6—N1—C2	123.5 (2)	C10—C11—C12	120.8 (3)
C3—C2—N1	118.4 (3)	C11—C12—C7	121.4 (2)
C3—C2—C34	128.3 (3)	O14—N13—O15	122.3 (3)
N1—C2—C34	113.3 (2)	O14—N13—C9	118.9 (3)
C2—C3—C16	125.9 (3)	O15—N13—C9	118.7 (3)
C2—C3—C4	120.1 (2)	O17—C16—O18	121.6 (3)
C16—C3—C4	114.0 (2)	O17—C16—C3	123.0 (3)
C5—C4—C3	110.8 (2)	O18—C16—C3	115.3 (2)
C5—C4—C7	111.2 (2)	C16—O18—C19	116.4 (2)
C3—C4—C7	110.9 (3)	O18—C19—C20	106.8 (2)
C6—C5—C26	122.0 (3)	C21—C20—C19	110.6 (3)
C6—C5—C4	119.6 (3)	O22—C21—C20	111.5 (3)
C26—C5—C4	118.4 (2)	N23—O22—C21	116.6 (4)
C5—C6—N1	119.3 (3)	O24—N23—O25	130.2 (4)
C5—C6—C33	127.0 (4)	O24—N23—O22	112.7 (4)
N1—C6—C33	113.7 (3)	O25—N23—O22	116.9 (5)
C8—C7—C12	118.2 (3)	O27—C26—O28	121.6 (4)
C8—C7—C4	120.8 (2)	O27—C26—C5	128.2 (3)
C12—C7—C4	121.0 (2)	O28—C26—C5	110.2 (3)
C9—C8—C7	118.9 (2)	C26—O28—C29	116.7 (3)
C10—C9—C8	123.0 (2)	O28—C29—C30	107.5 (3)
C10—C9—N13	118.7 (3)	O31—C30—C29	110.3 (3)
C8—C9—N13	118.3 (2)	C30—O31—C32	114.2 (5)
C11—C10—C9	117.7 (3)		

Lorentz and polarization corrections were applied to the data. An absorption correction was applied using an analytical function (Katayama, 1986). The structure was solved by direct methods using *SHELXS86* (Sheldrick, 1986). All H atoms were located by difference Fourier synthesis. Anisotropic least-squares refinement was performed for non-H atoms, isotropic for H atoms (Katayama, 1986). Scattering factors were from *International Tables for X-ray Crystallography* (1974, Vol. IV), with corrections for anomalous dispersion.

Lists of structure factors, anisotropic thermal parameters, H-atom coordinates and complete geometry have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 71165 (16 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England. [CIF reference: OH1015]

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