Table 3. *Cone-angle data (°) for 5-phenyldibenzophosphole 5-selenide (I) and triphenylphosphine selenide (II)*

		(I)	(II)
P(1)–Se(1)–H[C(136)]	θ/2	71	92
P(1)–Se(1)–H[C(126)]		73	79
P(1)–Se(1)–H[C(112)]		85	82
	θ	153	168
P(2)–Se(2)–H[C(236)]	θ/2	73	92
P(2)–Se(2)–H[C(226)]		73	78
P(2)–Se(2)–H[C(212)]		85	82
	θ	158	168
	Average θ	155	168

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Structure of Diethyl 2,6-Dimethyl-4-(5-methyl-3-phenylisoxazol-4-yl)-1,4-dihydropyridine-3,5-dicarboxylate, a Calcium Antagonist

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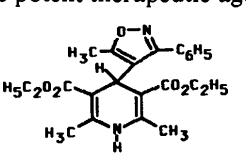
(*Received* 21 *October* 1985; *accepted* 22 *January* 1986)

Abstract. $C_{23}H_{26}N_2O_5$, $M_r = 410{\cdot}48$, orthorhombic, *Pbca*, $a = 8{\cdot}828\ (3)$, $b = 17{\cdot}181\ (5)$, $c = 27{\cdot}896\ (7)$ Å, $V = 4231\ (1)$ Å^3, $Z = 8$, $D_x = 1{\cdot}29$ g cm^{-3}, Mo $K\alpha$, $\lambda = 0{\cdot}71073$ Å, $\mu = 0{\cdot}85$ cm^{-1}, $F(000) = 1744$, $T = 140$ K, $R = 0{\cdot}052$ for 2808 observed reflections. In molecules of the title compound, (I), the 1,4-dihydropyridine ring exhibits a boat conformation. The five-membered isoxazolyl heterocyclic ring is held perpendicular to the dihydropyridine ring by interaction with the ester substituents. Both of these structural factors may be important to the calcium antagonist activity of (I).

Introduction. Some derivatives of 1,4-dihydropyridine, such as nifedipine, are potent calcium antagonists, or 'slow channel blockers'. The previously delineated structural requirements for biological activity for this class of compound (Janis & Triggle, 1983) include: (*a*) integrity of the 1,4-dihydropyridine ring, (*b*) no substitution on the N atom at the 1 position, (*c*) 2,6-dialkyl substituents, (*d*) 3,5-diester substituents, (*e*) an aryl substituent at the 4 position of the dihydropyridine ring.

Compound (I) bears a substituted isoxazolyl five-membered ring at the 4 position, instead of the aryl substituent characteristic of nifedipine and related compounds. Compound (I) was originally synthesized (Natale & Quincy, 1983) to ascertain whether the presence of the five-membered heterocyclic isoxazolyl ring substituent at the 4 position of the 1,4-dihydropyridine ring would preserve calcium antagonist activity. If so, the isoxazolyl ring would allow ready substitution by a variety of groups, in attempts to discover yet more potent therapeutic agents.



(I)

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Compound (I), together with related compounds, possesses biological activity comparable to that of nifedipine (McKenna, 1985) in the slow channel blocker mode. The structure of (I) has been determined in order to discover to what degree (I) possesses the structural characteristics that are associated with the calcium antagonist activity of the nifedipine class of compounds.

Experimental. The synthesis of (I) has been described previously (Natale & Quincy, 1983). Crystal [0·32 mm (100 → $\bar{1}$00) × 0·48 mm (010 → 0$\bar{1}$0) × 0·42 mm (001 → 00$\bar{1}$)] obtained by recrystallization from ethanol and petroleum ether. Nicolet *R*3*m* diffractometer, cell constants from least-squares fitting of setting angles for 22 reflections ($2\theta_{ave} = 21{\cdot}99°$). Data collected for $3{\cdot}5° \le 2\theta \le 50°$, $-11 \le h \le 0$, $0 \le k \le 21$, $0 \le l \le 34$, $\theta/2\theta$ scans. Three control reflections monitored every 200 reflections showed no significant variation. Data corrected for Lorentz and polarization factors, but not for absorption; of 4232 measured reflections, 2808 observed [$F \ge 2\sigma(F)$] and used in further calculations. Structure solved by direct methods, using *SOLV* (Sheldrick, 1983); all non-hydrogen atoms refined anisotropically; carbon-bound hydrogen atoms included in calculated positions; positional parameters and isotropic thermal parameter refined for the hydrogen atom on the dihydropyridine nitrogen atom. Block cascade, weighted $\{w = [\sigma^2(F) + gF^2]^{-1}$, $g = 5{\cdot}5 \times 10^{-4}$ (refined)$\}$ least-squares refinement on F yielded $R = 0{\cdot}052$, $wR = 0{\cdot}069$, and $S = 1{\cdot}51$ at convergence (mean shift/e.s.d. $< 0{\cdot}010$ over last three cycles) with largest peak in final difference Fourier synthesis $+0{\cdot}25$ e Å^{-3} and minimum of $-0{\cdot}28$ e Å^{-3}. Neutral-atom scattering factors used (*International Tables for X-ray Crystallography*, 1974); software for diffractometer provided with Nicolet *R*3*m*; *SHELXTL* programs (Sheldrick, 1983) used for structure solution, refinement, and plotting.*

Discussion. The molecular structure and numbering scheme for (I) are depicted in Fig. 1. Final atomic coordinates and equivalent isotropic thermal parameters for all non-hydrogen atoms are given in Table 1, while bond lengths and angles are listed in Table 2.

Nifedipine [dimethyl 2,6-dimethyl-4-(2-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate] and a series of closely related compounds, all of which possess varying degrees of biological activity, have been structurally characterized (Triggle, Shefter & Triggle, 1980; Fossheim, Svarteng, Mostad, Rømming, Shefter & Triggle, 1982). The structural features of the 1,4-dihydropyridine ring which are associated with calcium antagonist activity in nifedipine are preserved in (I). Thus, the dihydropyridine ring in (I) adopts a shallow boat configuration, with N(1) and C(3) 0·083 (2) and 0·230 (2) Å, respectively, above the four-atom plane (within 0·004 Å) through C(1), C(2), C(4) and C(5). Bond lengths and angles within the 1,4-dihydropyridine ring of (I), as well as for the 2-, 3-, 5- and 6-substituents, are unexceptional.

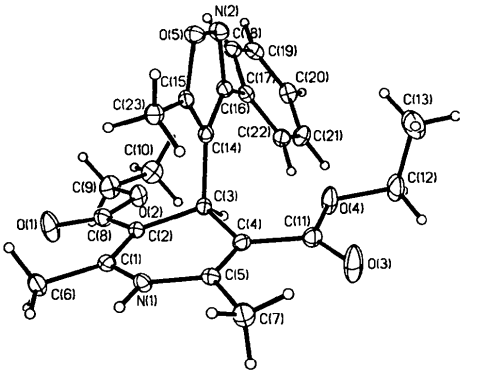

Fig. 1. A thermal-ellipsoid plot (50%) depicting the structure and numbering scheme for (I).

Table 1. *Atomic coordinates* (×10^4) *and thermal parameters* (Å^2 × 10^3)

Estimated standard deviations in the least significant digits are given in parentheses.

	x	*y*	*z*	U_{iso}*
C(1)	9233 (3)	4226 (1)	1699 (1)	23 (1)
C(2)	9847 (3)	3503 (1)	1671 (1)	22 (1)
C(3)	9719 (3)	3013 (1)	1216 (1)	21 (1)
C(4)	9321 (3)	3526 (1)	786 (1)	22 (1)
C(5)	8745 (3)	4249 (1)	844 (1)	24 (1)
C(6)	9177 (3)	4740 (1)	2132 (1)	33 (1)
C(7)	8193 (3)	4794 (2)	461 (1)	33 (1)
C(8)	10634 (3)	3184 (1)	2087 (1)	28 (1)
C(9)	12244 (3)	2193 (2)	2380 (1)	40 (1)
C(10)	13128 (3)	1516 (2)	2201 (1)	42 (1)
C(11)	9494 (3)	3198 (1)	305 (1)	27 (1)
C(12)	10132 (4)	2047 (2)	−129 (1)	44 (1)
C(13)	8859 (5)	1536 (3)	−202 (2)	96 (2)
C(14)	8567 (3)	2364 (1)	1282 (1)	21 (1)
C(15)	7050 (3)	2465 (1)	1340 (1)	23 (1)
C(16)	8759 (3)	1536 (1)	1315 (1)	22 (1)
C(17)	10105 (3)	1023 (1)	1294 (1)	24 (1)
C(18)	10086 (3)	332 (1)	1561 (1)	27 (1)
C(19)	11258 (3)	−194 (1)	1522 (1)	30 (1)
C(20)	12467 (3)	−50 (2)	1223 (1)	32 (1)
C(21)	12518 (3)	643 (2)	968 (1)	33 (1)
C(22)	11354 (3)	1175 (1)	1005 (1)	28 (1)
C(23)	6023 (3)	3146 (1)	1374 (1)	26 (1)
N(1)	8622 (2)	4561 (1)	1296 (1)	24 (1)
N(2)	7457 (2)	1183 (1)	1378 (1)	27 (1)
O(1)	10686 (3)	3462 (1)	2485 (1)	51 (1)
O(2)	11376 (2)	2517 (1)	1984 (1)	32 (1)
O(3)	9265 (3)	3515 (1)	−69 (1)	65 (1)
O(4)	9997 (3)	2465 (1)	318 (1)	42 (1)
O(5)	6354 (2)	1766 (1)	1393 (1)	27 (1)

* The equivalent isotropic U for anisotropic atoms is defined as one third of the trace of the orthogonalized U_{ij} tensor.

* Lists of anisotropic thermal parameters, hydrogen-atom coordinates, and observed and calculated structure factors have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 42785 (22 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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

Estimated standard deviations in the least significant digits are given in parentheses.

C(1)–C(2)	1·358 (3)	C(1)–C(6)	1·494 (3)
C(1)–N(1)	1·375 (3)	C(2)–C(3)	1·529 (3)
C(2)–C(8)	1·458 (3)	C(3)–C(4)	1·529 (3)
C(3)–C(14)	1·520 (3)	C(4)–C(5)	1·353 (3)
C(4)–C(11)	1·465 (3)	C(5)–C(7)	1·502 (3)
C(5)–N(1)	1·371 (3)	C(8)–O(1)	1·211 (3)
C(8)–O(2)	1·351 (3)	C(9)–C(10)	1·487 (4)
C(9)–O(2)	1·455 (3)	C(11)–O(3)	1·192 (3)
C(11)–O(4)	1·335 (3)	C(12)–C(13)	1·441 (6)
C(12)–O(4)	1·445 (3)	C(14)–C(15)	1·360 (3)
C(14)–C(16)	1·435 (3)	C(15)–C(23)	1·484 (3)
C(15)–O(5)	1·357 (3)	C(16)–C(17)	1·481 (3)
C(16)–N(2)	1·313 (3)	C(17)–C(18)	1·401 (3)
C(17)–C(22)	1·391 (3)	C(18)–C(19)	1·378 (3)
C(19)–C(20)	1·378 (4)	C(20)–C(21)	1·387 (4)
C(21)–C(22)	1·379 (4)	N(2)–O(5)	1·397 (3)

C(2)–C(1)–C(6)	126·9 (2)	C(2)–C(1)–N(1)	119·5 (2)
C(6)–C(1)–N(1)	113·6 (2)	C(1)–C(2)–C(3)	121·5 (2)
C(1)–C(2)–C(8)	119·2 (2)	C(3)–C(2)–C(8)	119·3 (2)
C(2)–C(3)–C(4)	110·5 (2)	C(2)–C(3)–C(14)	110·6 (2)
C(4)–C(3)–C(14)	111·4 (2)	C(3)–C(4)–C(5)	121·5 (2)
C(3)–C(4)–C(11)	118·2 (2)	C(5)–C(4)–C(11)	120·2 (2)
C(4)–C(5)–C(7)	127·5 (2)	C(4)–C(5)–N(1)	119·9 (2)
C(7)–C(5)–N(1)	112·6 (2)	C(2)–C(8)–O(1)	126·8 (2)
C(2)–C(8)–O(2)	112·4 (2)	O(1)–C(8)–O(2)	120·8 (2)
C(10)–C(9)–O(2)	108·7 (2)	C(4)–C(11)–O(3)	127·4 (2)
C(4)–C(11)–O(4)	111·8 (2)	O(3)–C(11)–O(4)	120·8 (2)
C(13)–C(12)–O(4)	111·1 (3)	C(3)–C(14)–C(15)	125·4 (2)
C(3)–C(14)–C(16)	131·0 (2)	C(15)–C(14)–C(16)	103·6 (2)
C(14)–C(15)–C(23)	135·2 (2)	C(14)–C(15)–O(5)	110·3 (2)
C(23)–C(15)–O(5)	114·5 (2)	C(14)–C(16)–C(17)	133·1 (2)
C(14)–C(16)–N(2)	111·3 (2)	C(17)–C(16)–N(2)	115·6 (2)
C(16)–C(17)–C(18)	118·3 (2)	C(16)–C(17)–C(22)	123·2 (2)
C(18)–C(17)–C(22)	118·5 (2)	C(17)–C(18)–C(19)	120·4 (2)
C(18)–C(19)–C(20)	120·7 (2)	C(19)–C(20)–C(21)	119·4 (2)
C(20)–C(21)–C(22)	120·4 (2)	C(17)–C(22)–C(21)	120·7 (2)
C(1)–N(1)–C(5)	123·9 (2)	C(16)–N(2)–O(5)	106·4 (2)
C(8)–O(2)–C(9)	114·7 (2)	C(11)–O(4)–C(12)	118·1 (2)
C(15)–O(5)–N(2)	108·4 (2)		

The puckering of the 1,4-dihydropyridine ring of (I) at N(1) and C(3), which is apparently so important to the biological activity of this class of compounds, is reflected in the torsion angles about the ring bonds to these atoms. For C(1)–C(2)–C(3)–C(4), the torsion angle is +18·5 (3)° in (I), compared to +17·9° in nifedipine; for C(2)–C(3)–C(4)–C(5), the torsion angle is −17·6 (3)° in (I), compared to −22·0° in nifedipine. The torsion angles about the bonds to N(1) in (I) are −8·1 (4)° [C(2)–C(1)–N(1)–C(5)] and +9·0 (4)° [C(4)–C(5)–N(1)–C(1)]; the corresponding angles in nifedipine are −11·3 and +7·4°.

The isoxazolyl ring bound to C(3) in (I) takes the place of the 2-nitrophenyl ring at the same position in nifedipine. The isoxazolyl ring is planar, as the average of the absolute values of the deviations from the least-squares plane through the five ring atoms is 0·005 Å. The isoxazolyl ring is also approximately perpendicular to the 1,4-dihydropyridine ring; the dihedral angle between the plane of the five-membered ring and the plane through the four carbon atoms C(1), C(2), C(4) and C(5) is 91·4°. Metric parameters for the isoxazolyl ring are as expected, with the C(14)–C(16) distance [1·435 (3) Å], in particular, indicating a degree of delocalization consistent with the ring's planar structure.

Steric interactions between the 3-phenyl and 5-methyl substituents on the isoxazolyl ring and the ethyl ester groups bound to C(2) and C(4) of the dihydropyridine ring serve to orient the plane of the five-membered heterocyclic ring nearly parallel to the C(3)–N(1) vector. This is shown by the near equality of the magnitudes of the torsion angles C(2)–C(3)–C(14)–C(15) [+66·8 (3)°] and C(4)–C(3)–C(14)–C(15) [−56·6 (3)°]. Such interactions held the 2-nitrophenyl substituent of nifedipine in a similar orientation.

The phenyl substituent on the isoxazolyl ring cannot be coplanar with the isoxazolyl ring, as the steric clash between the *ortho* hydrogen atom on C(22) and the hydrogen atom on C(3) would undoubtedly be severe. To avoid such an interaction in (I), the phenyl ring twists to the side about the C(16)–C(17) bond, resulting in the observed dihedral angle of 33·0° between the planes of these two rings. As a result of this twist, the ethyl ester group containing C(11) cannot remain coplanar with the 1,4-dihydropyridine ring, although coplanarity is still possible for the ethyl ester moiety containing C(8). In particular, the methyl group containing C(13) is forced to occupy a position considerably out of the plane of the dihydropyridine ring and its other substituents.

The Nicolet *R*3*m*/E X-ray diffractometer and crystallographic computing system at Colorado State University were purchased with funds provided by the National Science Foundation (CHE 81-03011). NRN thanks the M. J. Murdock Charitable Trust of the Research Corporation and the National Institutes of Health (Biomedical Research Support Grant No. 2-S07-RR07170-06) for financial support.

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