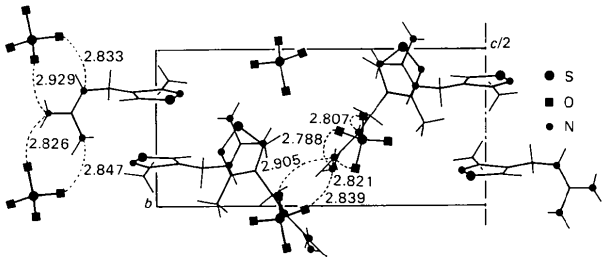

Fig. 2. Packing of the molecules projected along [100] showing the hydrogen bonds (e.s.d.'s 0·006 Å).

values, including N(9) and N(60), are close to but slightly different from those found in dihydroimidazoles and guanidines related to clonidine: $D \simeq 5$ Å, $h \simeq 1$ Å, $\varphi = 90$, 75 or 60° (Carpy *et al.*, 1982). These differences could explain the different pharmacological actions of the present compound compared with drugs related to clonidine.

The crystalline cohesion is ensured by strong hydrogen bonds involving the sulfate ions (Fig. 2).

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Structure of α-Isopropyl-α-[(*N*-methyl-*N*-homoveratryl)-γ-aminopropyl]-3,4-dimethoxyphenylacetonitrile Hydrochloride,* Verapamil, $C_{27}H_{38}N_2O_4.HCl$

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Abstract. Ca^{2+} channel antagonist; major therapeutic indications: angina, hypertension. $M_r = 491{\cdot}08$, triclinic, $P\bar{1}$, $a = 7{\cdot}086$ (3), $b = 10{\cdot}591$ (2), $c = 19{\cdot}196$ (4) Å, $\alpha = 100{\cdot}10$ (1), $\beta = 93{\cdot}73$ (3), $\gamma = 101{\cdot}55$ (3)°, $V = 1382{\cdot}1$ (3) Å^3, $Z = 2$, $D_x = 1{\cdot}18$ g cm^{-3}, Cu $K\bar{\alpha}$, $\lambda = 1{\cdot}54178$ Å, $\mu = 14{\cdot}88$ cm^{-1}, $F(000) = 524$, room temperature, $R = 0{\cdot}048$ for 1182 reflections. The bond lengths and angles have the values expected, with the normal folding of the bridge chain around the N atom. Critical sites for antagonism of α_1- and α_2-adrenoceptors are investigated. The title compound is unusual in having a methyl substituent on the protonated N atom.

* IUPAC name: 5-[*N*-(3,4-dimethoxyphenethyl)-*N*-methylamino]-2-(3,4-dimethoxyphenyl)-2-isopropylvaleronitrile hydrochloride.

Introduction. Verapamil has a number of therapeutic indications. Firstly, it is an antianginal agent but it is also used in supraventricular tachycardia, in ventricular tachyarrhythmia, in atrial flutter and fibrillation and in hypertension (Stone, Antman, Muller & Braunwald, 1980; Flaim & Zelis, 1982). The description of this drug as a Ca^{2+} channel antagonist is due to the investigations of Fleckenstein (1964) who first observed that it mimics the cardiac effect of Ca^{2+} withdrawal.

On the other hand, verapamil and D600 (a methoxy analogue of verapamil) block some Na^+ channels, K^+ channels and a variety of receptor types (adrenergic α_1 and α_2, muscarinic cholinergic and opiate) (Janis & Triggle, 1983). Of particular interest for our purpose are the results of Glossmann & Hornung (1980) showing that these two molecules interact with both α_1- and α_2-adrenoceptors with higher affinity for the α_1

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subtype. Further studies indicate that verapamil blocks α_1-adrenoceptors and muscarinic receptors at concentrations that are similar to those achieved clinically (Karliner, Motulsky, Dunlap, Heller Brown & Insel, 1982). It has been recently used for protection experiments against benextramine blockade of rat vas deferens adrenergic α-receptors (Melchiorre & Galluci, 1983).

This drug was investigated in order to point out the recognition sites for the α-adrenoceptors.

Experimental. Small white prisms (from ethanol), 0·30 × 0·13 × 0·08 mm, Enraf–Nonius CAD-4 diffractometer, 23 reflections ($7 < \theta < 14°$) used to refine orientation matrix, no systematic absences, 4095 independent reflections with $\theta < 60°$, h −7 to +7, k −11 to +11, l 0 to +21, 1182 with $I \geq 3\sigma(I)$, Lp correction, absorption ignored; two check reflections ($1\bar{1}1$, $\bar{1}21$) every 5400 s showed no unusual variation (all within $\pm 3\sigma$); direct methods, *MULTAN*80 (Main, Fiske, Hull, Lessinger, Germain, Declercq & Woolfson, 1980), anisotropic diagonal matrix, refinement on F using observed reflections, $w = 1$ if $|F_o| < P$, $P = (F_o{}^2{}_{max}/10)^{1/2}$, $w = (P/F_o)^2$ if $|F_o| > P$, H from ΔF synthesis – isotropic, $R = 0{\cdot}048$, $wR = 0{\cdot}061$, $S = 0{\cdot}804$ (1182 reflections, 463 parameters), max. peak $\pm 0{\cdot}3$ e Å^{-3} in final ΔF map, $(\Delta/\sigma)_{max} = 0{\cdot}4$, H-atom form factors from Stewart, Davidson & Simpson (1965), all other form factors from *International Tables for X-ray Crystallography* (1974); Mini 6, CII computer.

Discussion. Table 1 gives the atomic coordinates and Table 2 the bond distances and angles.* Fig. 1 shows the molecule with the atom numbering.

The interatomic distances and angles have expected values. The relatively high e.s.d.'s on bond lengths (and on the x and y coordinates) are the consequence of the small size of the crystal (too few intensity data compared with the number of parameters to be varied). The conformation of the bridge chain is defined by the values of the torsional angles (±1°) listed in Table 3. As in most of the long flexible molecules that are selective α_1-adrenoceptor antagonists such as WB-4101 {*N*-[2-(2,6-dimethoxyphenoxy)ethyl]-2,3-dihydro-1,4-benzodioxin-2-methylamine} (Carpy, Colléter & Léger, 1981) the bridge chain is folded in the nitrogen area: C(8)–N(9)–C(10)–C(11) = −56 (1)°. The position of the two dimethoxyphenyl rings *A* and *B* with regard to the chain is different: C(2)–C(1)–C(7)–C(8) = 94 (1) and C(12)–C(13)–C(14)–C(15) = 119 (1)°.

* Lists of structure factors, anisotropic thermal parameters, H-atom coordinates and least-squares planes have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 39969 (29 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 1. *Atomic coordinates* (×10⁴) *and* B_{eq} *values*

$B_{eq} = \frac{4}{3}\sum_i \sum_j \beta_{ij} \mathbf{a}_i . \mathbf{a}_j$.

	x	y	z	B_{eq}(Å²)
C(1)	−3534 (15)	2601 (10)	6936 (5)	4·1 (5)
C(2)	−2246 (16)	3065 (11)	6465 (6)	5·0 (5)
C(3)	−2807 (15)	2779 (11)	5730 (6)	5·0 (5)
C(4)	−4639 (16)	2036 (11)	5473 (5)	4·6 (5)
C(5)	−5955 (14)	1641 (10)	5968 (6)	4·3 (5)
C(6)	−5436 (14)	1913 (10)	6683 (5)	4·2 (4)
C(7)	−2841 (16)	2843 (10)	7734 (5)	4·6 (5)
C(8)	−3407 (14)	4116 (10)	8097 (5)	4·1 (4)
N(9)	−2493 (10)	4486 (8)	8875 (4)	3·5 (3)
C(10)	−3074 (14)	5716 (10)	9263 (5)	4·0 (4)
C(11)	−2601 (14)	6926 (10)	8907 (6)	4·3 (5)
C(12)	−388 (14)	7560 (10)	9013 (5)	3·8 (4)
C(13)	119 (14)	8563 (10)	8524 (5)	3·9 (4)
C(14)	−213 (13)	7879 (9)	7735 (5)	3·3 (4)
C(15)	−1510 (15)	8147 (10)	7242 (5)	4·0 (4)
C(16)	−1685 (14)	7501 (10)	6525 (5)	4·0 (4)
C(17)	−529 (14)	6623 (10)	6319 (5)	3·7 (4)
C(18)	792 (13)	6363 (10)	6824 (5)	3·7 (4)
C(19)	965 (14)	6970 (10)	7531 (5)	3·6 (4)
O(20)	−5295 (10)	1620 (7)	4764 (4)	5·5 (3)
C(21)	−3869 (17)	1834 (14)	4266 (6)	6·9 (6)
O(22)	−7776 (10)	975 (8)	5650 (4)	5·7 (3)
C(23)	−9242 (15)	636 (13)	6111 (6)	6·2 (6)
C(24)	−3099 (17)	3417 (11)	9289 (5)	4·9 (5)
C(25)	2280 (16)	9342 (11)	8709 (5)	5·1 (5)
C(26)	2877 (18)	10263 (12)	8173 (6)	6·9 (6)
C(27)	2652 (17)	10205 (12)	9467 (6)	6·3 (6)
C(28)	−1142 (16)	9519 (11)	8634 (5)	4·8 (5)
N(29)	−2122 (15)	10255 (10)	8740 (5)	6·4 (5)
O(30)	−570 (9)	5946 (7)	5632 (3)	4·5 (3)
C(31)	−2014 (16)	6122 (13)	5111 (5)	5·9 (5)
O(32)	1888 (10)	5489 (7)	6556 (3)	4·6 (3)
C(33)	3434 (16)	5283 (12)	7032 (6)	5·5 (5)
Cl(34)	1798 (4)	4565 (3)	8836 (2)	5·2 (1)

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

C(1)–C(2)	1·406 (13)	C(13)–C(25)	1·573 (12)
C(1)–C(6)	1·408 (12)	C(13)–C(28)	1·476 (12)
C(1)–C(7)	1·538 (12)	C(14)–C(15)	1·381 (12)
C(2)–C(3)	1·403 (13)	C(14)–C(19)	1·417 (11)
C(3)–C(4)	1·386 (13)	C(15)–C(16)	1·412 (12)
C(4)–C(5)	1·430 (12)	C(16)–C(17)	1·381 (12)
C(4)–O(20)	1·374 (11)	C(17)–C(18)	1·404 (12)
C(5)–C(6)	1·363 (12)	C(17)–O(30)	1·382 (10)
C(5)–O(22)	1·385 (11)	C(18)–C(19)	1·382 (12)
C(7)–C(8)	1·545 (12)	C(18)–O(32)	1·377 (10)
C(8)–N(9)	1·539 (11)	O(20)–C(21)	1·447 (12)
N(9)–C(10)	1·528 (11)	O(22)–C(23)	1·440 (12)
N(9)–C(24)	1·505 (11)	C(25)–C(26)	1·559 (14)
C(10)–C(11)	1·545 (12)	C(25)–C(27)	1·553 (13)
C(11)–C(12)	1·562 (12)	C(28)–N(29)	1·145 (12)
C(12)–C(13)	1·543 (12)	O(30)–C(31)	1·446 (11)
C(13)–C(14)	1·541 (12)	O(32)–C(33)	1·455 (11)
C(2)–C(1)–C(6)	120·6 (8)	C(14)–C(13)–C(25)	109·6 (7)
C(2)–C(1)–C(7)	119·3 (8)	C(14)–C(13)–C(28)	108·3 (7)
C(6)–C(1)–C(7)	120·1 (8)	C(25)–C(13)–C(28)	107·9 (7)
C(1)–C(2)–C(3)	120·2 (8)	C(13)–C(14)–C(15)	123·5 (7)
C(2)–C(3)–C(4)	119·5 (8)	C(13)–C(14)–C(19)	115·5 (7)
C(3)–C(4)–C(5)	119·0 (8)	C(15)–C(14)–C(19)	120·9 (7)
C(3)–C(4)–O(20)	124·5 (8)	C(14)–C(15)–C(16)	119·8 (8)
C(5)–C(4)–O(20)	116·5 (8)	C(15)–C(16)–C(17)	119·7 (8)
C(4)–C(5)–C(6)	122·2 (8)	C(16)–C(17)–C(18)	120·0 (8)
C(4)–C(5)–O(22)	113·7 (7)	C(16)–C(17)–O(30)	124·5 (7)
C(6)–C(5)–O(22)	124·1 (8)	C(18)–C(17)–O(30)	115·5 (7)
C(1)–C(6)–C(5)	118·3 (8)	C(17)–C(18)–C(19)	121·2 (8)
C(1)–C(7)–C(8)	107·9 (7)	C(17)–C(18)–O(32)	114·9 (7)
C(7)–C(8)–N(9)	109·1 (7)	C(19)–C(18)–O(32)	123·9 (7)
C(8)–N(9)–C(10)	110·9 (6)	C(14)–C(19)–C(18)	118·3 (7)
C(8)–N(9)–C(24)	112·7 (6)	C(4)–O(20)–C(21)	116·3 (7)
C(10)–N(9)–C(24)	107·2 (6)	C(5)–O(22)–C(23)	117·5 (7)
N(9)–C(10)–C(11)	114·9 (7)	C(13)–C(25)–C(26)	111·6 (7)
C(10)–C(11)–C(12)	111·9 (7)	C(13)–C(25)–C(27)	112·5 (7)
C(11)–C(12)–C(13)	111·1 (7)	C(26)–C(25)–C(27)	107·6 (8)
C(12)–C(13)–C(14)	111·0 (7)	C(13)–C(28)–N(29)	177·9 (10)
C(12)–C(13)–C(25)	110·9 (7)	C(17)–O(30)–C(31)	116·7 (6)
C(12)–C(13)–C(28)	109·0 (7)	C(18)–O(32)–C(33)	117·9 (6)

Contrary to the most potent α-ligands, the nitrogen in verapamil is methyl substituted. This nitrogen is protonated in the hydrochloride. The critical areas for binding of antagonists to the α-adrenoceptors have been based on similarities in the structures of the stereoisomers of yohimbine and WB-4101 (McGrath, 1982). Three sites seem to be important in the pentacyclic alkaloids: two areas rich in electrons (the aromatic ring *A* and the carboxymethyl substituent on ring *E*) at 5·1 Å from an ionizable nitrogen. Since being proposed on theoretical models by McGrath (1982), these similarities have been found between the crystal structures of yohimbine (Ambady & Kartha, 1973) or raubasine (Dubost, Léger, Goursolle, Colléter & Carpy, 1984) and several structures of α_1-adrenoceptor antagonists (Carpy, 1984). In fact the only critical sites for antagonism of α_1 and α_2 should be an aromatic system and an amino group. This is supported by the 'selective' α_1-antagonist thymoxamine (Carpy, Colléter, Léger & Dubost, 1985) and the two 'selective' α_2-antagonists, RS-21361 {2-[(1-ethyl-2-imidazolyl)-methyl]-2,3-dihydro-1,4-benzodioxin} (Carpy, Montagut & Léger, 1984), and RX-781094 [4,5-dihydro-2-(2,3-dihydro-1,4-benzodioxin-2-yl)-1*H*-imidazole) (Carpy & Cattier-Humblet, 1985).

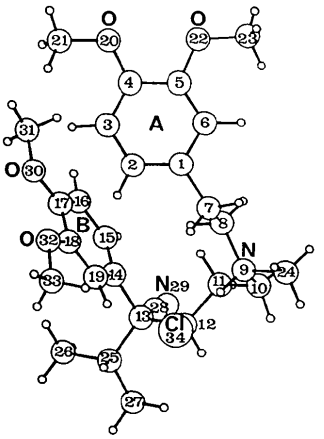

Fig. 1. Perspective view of the molecule showing the numbering of atoms. The bare numbers are for C atoms.

Table 3. *Critical torsional angles* (±1°)

C(2)–C(1)–C(7)–C(8)	94
C(1)–C(7)–C(8)–N(9)	188
C(7)–C(8)–N(9)–C(24)	−58
C(7)–C(8)–N(9)–C(10)	182
C(8)–N(9)–C(10)–C(11)	−56
N(9)–C(10)–C(11)–C(12)	−74
C(10)–C(11)–C(12)–C(13)	168
C(11)–C(12)–C(13)–C(14)	−66
C(11)–C(12)–C(13)–C(25)	172
C(11)–C(12)–C(13)–C(28)	53
C(12)–C(13)–C(25)–C(26)	174
C(12)–C(13)–C(25)–C(27)	−65
C(12)–C(13)–C(28)–N(29)	31
C(12)–C(13)–C(14)–C(15)	119

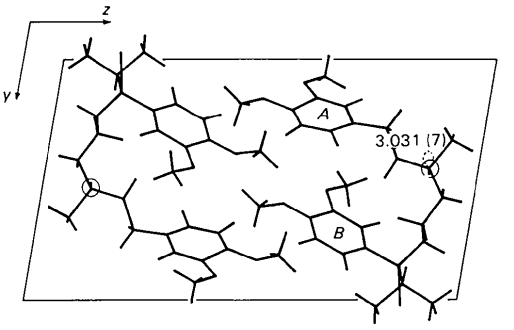

Fig. 2. Packing of molecules projected on (100). (Distance in Å.)

In verapamil hydrochloride we have two aromatic rings *A* and *B* and a protonated nitrogen. The angle between ring *A* and ring *B* is 69 (1)°. The distance between N(9) and φ_1 (centre of ring *A*) is 5·18 (1) Å and the distance between N(9) and φ_2 (centre of ring *B*) is 5·09 (1) Å. These distances are in agreement with McGrath's model but the distance φ_1–φ_2 is completely different [5·25 (1) Å instead of 8–9 Å found in the pentacyclyl alkaloids or in WB-4101]. This would suggest that as a small antagonist molecule verapamil could interact in either position N(9)–φ_1 or N(9)–φ_2. It is however difficult to speculate on a clear relationship between the solid-state conformation of this compound and its selectivity for the α_1-adrenoceptors.

The crystalline cohesion (Fig. 2) is strengthened by the hydrogen bond N(9)···Cl(34) = 3·031 (7), N(9)–H(109) = 0·98 (7) Å, N(9)–H(109)···Cl(34) = 166 (6)°.

The authors wish to thank Knoll (Milan) for the generous gift of the sample.

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Acta Cryst. (1985). C**41**, 627–630

Structures et Configurations Absolues de Trois Isomères du (Chloro-3 phénoxy)-6 Méthyl-2 Oxa-1 Aza-4 Spiro[4,5]décanone-3, $C_{15}H_{18}ClNO_3$

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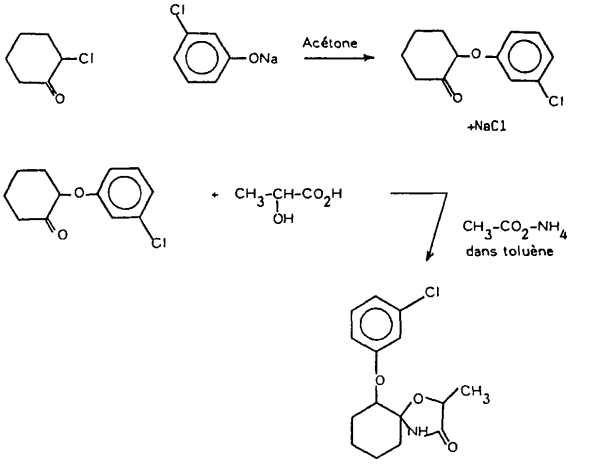
Abstract. CERM 3726®. Isomer (I): $M_r = 295{\cdot}77$, monoclinic, $P2_1$, $a = 11{\cdot}225$ (3), $b = 16{\cdot}861$ (4), $c = 8{\cdot}473$ (2) Å, $\beta = 108{\cdot}88$ (4)°, $V = 1517{\cdot}4$ Å^3, $Z = 4$, $D_x = 1{\cdot}29$ g cm^{-3}, m.p. = 404 K, Cu $K\alpha$, $\lambda = 1{\cdot}5418$ Å, $\mu = 21{\cdot}78$ cm^{-1}, $F(000) = 624$, $T = 298$ K, $R = 0{\cdot}089$ for 2754 observed reflexions. Isomer (II): $M_r = 295{\cdot}77$, orthorhombic, $P2_12_12_1$, $a = 7{\cdot}913$ (2), $b = 28{\cdot}843$ (5), $c = 6{\cdot}285$ (2) Å, $V = 1434{\cdot}4$ Å^3, $Z = 4$, $D_x = 1{\cdot}37$ g cm^{-3}, m.p. = 448 K, Cu $K\alpha$, $\mu = 23{\cdot}03$ cm^{-1}, $F(000) = 624$, $T = 298$ K, $R = 0{\cdot}071$ for 1550 observed reflexions. Isomer (III): $M_r = 295{\cdot}77$, monoclinic, $P2_1$, $a = 11{\cdot}933$ (3), $b = 7{\cdot}883$ (2), $c = 9{\cdot}094$ (2) Å, $\beta = 119{\cdot}02$ (4)°, $V = 748{\cdot}0$ Å^3, $Z = 2$, $D_x = 1{\cdot}31$ g cm^{-3}, m.p. = 424 K, Cu $K\alpha$, $\mu = 23{\cdot}31$ cm^{-1}, $F(000) = 312$, $T = 298$ K, $R = 0{\cdot}076$ for 1474 observed reflexions. Synthesis is from lactic acid L(+) (*S* configuration). (I) (both independent molecules) has 6*S*, 5*S*, 2*S*, (II) has 6*R*, 5*R*, 2*S* and (III) has 6*S*, 5*R*, 2*S*. In each case, the cohesion of the crystals is the result of intermolecular N—H···O hydrogen bonds and van der Waals interactions. The cyclohexyl ring has a chair conformation, with the heterocyclic ring more or less planar.

Introduction. Le CERM 3726* est un composé à activité stimulante dont l'étude clinique est en cours. Le but de ce travail est de déterminer les configurations de trois isomères qui ont été séparés par chromatographie liquide à haute performance. La synthèse a été effectuée en utilisant de l'acide lactique L(+) de configuration *S* suivant le schéma suivant.



Partie expérimentale. Données expérimentales décrites dans Tableau 1.* Composé synthétisé au CERM.

* Brevet CERM, Belg. 833,651 – Ger. Offen. 2,542,154 – Neth. Appl. 7,511,389.

* Les listes des facteurs de structure, des paramètres thermiques et des coordonnées des atomes d'hydrogène ont été déposées à la British Library Lending Division (Supplementary Publication No. SUP 39965: 33 pp.). Des copies peuvent être obtenues en s'adressant à: The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, Angleterre.

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