The N(1), O(21), O(31) and C(11) substituents are equatorial, while the C(5)—O(51) bond is axial. Packing of the molecules in the unit cell is governed by van der Waals contacts and one H bond [N(1)···O(13)(x, y, $z+1$) = 2·881 (6) Å].

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Acta Cryst. (1986). C**42**, 1068–1071

Structure of 1-Acetonyl-2-[(2,4-dichlorophenyl)imino]imidazolidine Hydrochloride: a New Analgesic Compound

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(*Received* 10 *October* 1985; *accepted* 21 *February* 1986)

Abstract. $C_{12}H_{14}Cl_2N_3O^+.Cl^-$, $M_r = 322·5$, monoclinic, $P2_1/n$, $a = 17·930$ (1), $b = 9·427$ (3), $c = 18·008$ (3) Å, $\beta = 90·38$ (4)°, $V = 3043·2$ (3) Å^3, $Z = 8$ (two independent molecules), $D_x = 1·41$ g cm^{-3}, λ(Cu $K\alpha$) = 1·54178 Å, $\mu = 54·1$ cm^{-1}, $F(000) = 1328$, room temperature, $R = 0·051$ for 3088 independent observed reflections. The title compound is structurally related to clonidine; however, its prevailing activity is one of producing analgesia (Boehringer Ingelheim, 1983). It is synthesized from 2-[(2,4-dichlorophenyl)imino]imidazolidine in two steps. The guanidine function is involved in the protonation process. The delocalization of the positive charge was evidenced by CNDO/2 calculations. The overall conformation in the crystal and in vacuum (PCILO calculations) is biplanar [with an angle of ~70 (1)° between the planes]. The two non-substituted N atoms of the guanidine group are involved in hydrogen bonds responsible for the crystalline cohesion.

Introduction. The title compound, named ESR 1276-CL, is structurally an analogue of clonidine (Catapressan®). The dominant property of clonidine is its hypotensive activity; however, the production of analgesia could also be established clinically (Tamsen & Gordh, 1984). Xylazine, another α-agonist, is in use as an analgesic compound in veterinary medicine (Kroneberg & Schlossman, 1971). The objective of the X-ray study at hand was to investigate whether the difference in activity profile between ESR 1276-CL and clonidine is paralleled by a difference in structure.

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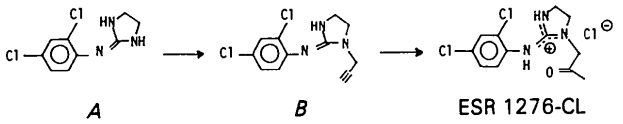
Experimental. *Synthesis of ESR 1276-CL.* The synthesis is outlined below. In the first step, the imidazolidine *A* is deprotonated by means of NaH in THF, then treated with 2-propynyl bromide, which results in selective alkylation at the imidazolidine N, yielding *B*. Hydration of *B* in the second step, by heating it in dilute H_2SO_4 containing $HgSO_4$, affords the ketone, which is transformed by addition of HCl/ether into the hydrochloride, ESR 1276-CL.



A *B* ESR 1276-CL

X-ray analysis. White crystal 0·85 × 0·32 × 0·25 mm (from acetonitrile). Density not determined. Unit-cell parameters and intensity data obtained on an Enraf–Nonius CAD-4 diffractometer with graphite-monochromated Cu $K\alpha$ radiation in ω/θ scan mode ($0 < \theta < 60°$). Cell dimensions refined by least-squares fitting of θ values of 25 reflections. No appreciable drop in intensity of two standard reflections (224 and $2\bar{2}4$) checked every 5400 s. 3161 independent reflections collected in $\pm h,k,l$ range $\bar{2}0,0,0$ to 20,10,20; 3088 with $I \geq 3\sigma(I)$ used in subsequent calculations. Intensities corrected for Lorentz and polarization effects but not for absorption. Scattering factors for non-H atoms from *International Tables for X-ray Crystallography* (1974) and for H from Stewart, Davidson & Simpson (1965). The Wilson statistical test showed a centric intensity distribution. Structure solved with *MULTAN*80 (Main, Fiske, Hull, Lessinger, Germain, Declercq & Woolfson, 1980) and standard Fourier techniques. H atoms located by ΔF synthesis. Block-diagonal-matrix least-squares refinement on F of observed reflections; $w = 1$ if $|F_o| < P$, $P = [F_o^2(\text{max.})/10]^{1/2}$, $w = (P/F_o)^2$ if $|F_o| > P$; anisotropic thermal parameters for all non-H atoms and isotropic ones for H. Final $R = 0{\cdot}051$, $wR = 0{\cdot}064$, $S = 1{\cdot}014$ (3088 reflections, 455 parameters). In final cycle Δ/σ mean and max. 0·1 and 0·5. Residual electron density within $\pm 0{\cdot}3$ e Å^{-3}. Calculations carried out on a Mini 6-92, CII-Honeywell–Bull computer (programs *CRISTA, CRISAF, CRISEC, UTIL,* Laboratory of Crystallography, University of Bordeaux I, Talence).

Discussion. The atomic parameters are given in Table 1* with the numbering scheme shown in Fig. 1.

* Lists of structure amplitudes, anisotropic thermal parameters, H-atom coordinates and least-squares-planes' data have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 42878 (32 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

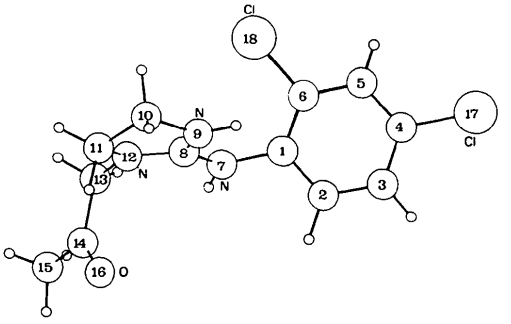


Fig. 1. Perspective view of molecule (I) showing the numbering of atoms. Molecule (II), being very similar to molecule (I), has not been represented.

Table 1. *Atomic coordinates* ($\times 10^4$) *and equivalent isotropic temperature factors*

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

	Molecule (I)				Molecule (II)			
	x	y	z	B_{eq}(Å^2)	x	y	z	B_{eq}(Å^2)
C(1)	−2317 (2)	4311 (4)	2959 (2)	4·2 (2)	2129 (2)	4363 (4)	2368 (2)	4·1 (2)
C(2)	−2617 (2)	4921 (5)	3579 (2)	4·8 (2)	1503 (2)	5029 (5)	2637 (2)	4·5 (2)
C(3)	−2263 (2)	5016 (5)	4248 (2)	5·0 (2)	858 (2)	5138 (5)	2212 (3)	5·0 (2)
C(4)	−1551 (2)	4500 (5)	4292 (2)	4·8 (2)	853 (2)	4565 (5)	1516 (2)	4·5 (2)
C(5)	−1216 (2)	3876 (5)	3696 (3)	5·1 (2)	1457 (2)	3857 (5)	1234 (2)	4·6 (2)
C(6)	−1603 (2)	3776 (4)	3036 (2)	4·6 (2)	2093 (2)	3762 (4)	1665 (2)	4·4 (2)
N(7)	−2738 (2)	4159 (4)	2298 (2)	4·3 (2)	2770 (2)	4213 (4)	2825 (2)	4·9 (2)
C(8)	−2561 (2)	4797 (4)	1666 (2)	3·9 (2)	3407 (2)	4918 (4)	2680 (2)	4·2 (2)
N(9)	−2045 (2)	5805 (4)	1595 (2)	4·7 (2)	3475 (2)	5917 (4)	2172 (2)	4·9 (2)
C(10)	−1927 (2)	6134 (5)	812 (2)	5·2 (2)	4255 (2)	6350 (5)	2115 (3)	5·6 (2)
C(11)	−2636 (2)	5550 (5)	453 (2)	4·8 (2)	4611 (2)	5693 (5)	2798 (3)	5·4 (2)
N(12)	−2878 (2)	4512 (4)	1018 (2)	4·3 (2)	4043 (2)	4669 (4)	3034 (2)	4·5 (2)
C(13)	−3491 (2)	3549 (4)	874 (2)	4·5 (2)	4165 (2)	3703 (5)	3645 (2)	4·8 (2)
C(14)	−4241 (2)	4242 (5)	906 (3)	5·3 (2)	4054 (3)	4364 (5)	4396 (3)	5·7 (2)
C(15)	−4890 (3)	3308 (7)	731 (3)	7·9 (3)	4200 (3)	3422 (7)	5049 (3)	8·1 (3)
O(16)	−4311 (2)	5477 (4)	1063 (2)	7·1 (2)	3856 (2)	5573 (4)	4468 (2)	8·0 (2)
Cl(17)	−1063 (1)	4630 (2)	5125 (1)	7·0 (1)	65 (1)	4726 (2)	961 (1)	7·1 (1)
Cl(18)	−1185 (1)	2934 (2)	2295 (1)	7·5 (1)	2854 (1)	2892 (2)	1301 (1)	6·8 (1)
Cl(19)	−806 (1)	7496 (1)	2411 (1)	5·4 (1)	2424 (1)	2286 (1)	4142 (1)	5·0 (1)

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

	Molecule (I)	Molecule (II)		Molecule (I)	Molecule (II)		Molecule (I)	Molecule (II)
C(1)–C(2)	1·383 (6)	1·376 (6)	C(5)–C(6)	1·374 (6)	1·377 (6)	C(10)–C(11)	1·525 (6)	1·515 (6)
C(1)–C(6)	1·383 (6)	1·388 (6)	C(6)–Cl(18)	1·729 (4)	1·725 (4)	C(11)–N(12)	1·478 (5)	1·468 (6)
C(1)–N(7)	1·412 (5)	1·417 (5)	N(7)–C(8)	1·327 (5)	1·349 (5)	N(12)–C(13)	1·448 (5)	1·443 (5)
C(2)–C(3)	1·378 (6)	1·385 (6)	C(8)–N(9)	1·333 (5)	1·319 (5)	C(13)–C(14)	1·497 (6)	1·504 (6)
C(3)–C(4)	1·369 (6)	1·364 (6)	C(8)–N(12)	1·323 (5)	1·323 (5)	C(14)–C(15)	1·492 (8)	1·495 (8)
C(4)–C(5)	1·366 (6)	1·372 (6)	N(9)–C(10)	1·460 (6)	1·461 (6)	C(14)–O(16)	1·204 (6)	1·201 (6)
C(4)–Cl(17)	1·735 (4)	1·733 (4)						
C(2)–C(1)–C(6)	117·3 (3)	118·3 (3)	C(1)–C(6)–C(5)	121·5 (4)	121·3 (3)	C(10)–C(11)–N(12)	101·2 (3)	102·4 (3)
C(2)–C(1)–N(7)	120·0 (3)	120·1 (3)	C(1)–C(6)–Cl(18)	119·7 (3)	120·6 (3)	C(8)–N(12)–C(11)	110·3 (3)	109·9 (3)
C(6)–C(1)–N(7)	122·5 (4)	121·4 (3)	C(5)–C(6)–Cl(18)	118·7 (3)	118·1 (3)	C(8)–N(12)–C(13)	127·3 (3)	127·2 (3)
C(1)–C(2)–C(3)	122·1 (4)	121·3 (4)	C(1)–N(7)–C(8)	123·2 (3)	121·6 (3)	C(11)–N(12)–C(13)	121·2 (3)	122·3 (3)
C(2)–C(3)–C(4)	118·4 (4)	118·5 (4)	N(7)–C(8)–N(9)	125·1 (3)	124·6 (4)	N(12)–C(13)–C(14)	113·6 (3)	113·8 (3)
C(3)–C(4)–C(5)	121·4 (4)	122·1 (4)	N(7)–C(8)–N(12)	124·1 (3)	123·2 (3)	C(13)–C(14)–C(15)	115·7 (4)	116·0 (4)
C(3)–C(4)–Cl(17)	119·3 (3)	119·7 (3)	N(9)–C(8)–N(12)	110·7 (3)	112·2 (3)	C(13)–C(14)–O(16)	121·7 (4)	122·0 (4)
C(5)–C(4)–Cl(17)	119·2 (3)	118·1 (3)	C(8)–N(9)–C(10)	110·5 (3)	109·9 (3)	C(15)–C(14)–O(16)	122·5 (4)	122·0 (5)
C(4)–C(5)–C(6)	119·2 (4)	118·4 (4)	N(9)–C(10)–C(11)	101·9 (3)	103·1 (3)			

All interatomic distances and angles (Table 2) are normal for this type of compound {see, for example, clonidine hydrochloride: 2-[(2,6-dichlorophenyl)-imino]imidazolidine hydrochloride; Byre, Mostad & Rømming, 1974; Cody & De Titta, 1979}.

The dichlorophenyl and imidazolidine rings are planar within experimental limits. The bond distances and angles within the imidazolidine ring are similar to those observed in ureido rings with the short C(8)–N distances indicative of double-bond character. The geometry about the C(8) atom is planar and almost trigonal: the C(8)–N distances are very similar [mean value 1·327 (5) Å for molecule (I) and 1·330 (5) Å for molecule (II)]; however, the differences are more pronounced for molecule (II) than for molecule (I). In both molecules the sum of the bond angles about C(8) is 360°.

The geometry of the NH linking group is defined by the bond angle C(1)–N(7)–C(8), 123·2 (3)° in molecule (I) and 121·6 (3)° in molecule (II), and the torsion angles C(1)–N(7)–C(8)–N(9) and C(6)–C(1)–N(7)–C(8), −10 (1), −68 (1)° in molecule (I) and 8 (1), 73 (1)° in molecule (II). Such a conformation is also observed in clonidine hydrochloride (0/76°) in which the di-*ortho*-phenyl substitution stabilizes the arrangement of the rings. In fact when both *ortho* positions of the phenyl ring are substituted a nearly perpendicular arrangement of the rings is favoured (Carpy, Léger, Leclerc, Decker, Rouot & Wermuth, 1982). In contrast, a 2,4 occupancy of the phenyl ring favours a dihedral angle between the two rings of close to 60° (Carpy *et al.*, 1982).

The position of the chain borne by N(12) is defined by the torsion angles C(8)–N(12)–C(13)–C(14), 91 (1) and −90 (1)°, and N(12)–C(13)–C(14)–O(16), −2 (1) and 3 (1)°.

The crystal structure is held together by four hydrogen bonds (two for each independent molecule) involving N(7) and N(9) and the Cl(19) anions:

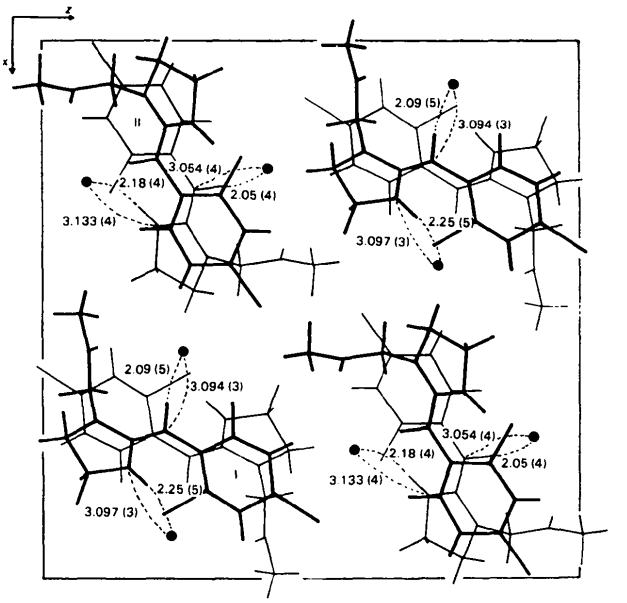


Fig. 2. Projection of the structure on (010) showing the hydrogen bonds (Å).

N(9)···Cl(19) = 3·097 (4), H(109)···Cl(19) = 2·25 (5) Å, N(9)–H(109)···Cl(19) = 153 (3)°, N(7)···Cl(19)($-\frac{1}{2}-x$, $-\frac{1}{2}+y$, $\frac{1}{2}-z$) = 3·094 (3), H(107)···Cl(19) = 2·09 (5) Å, N(7)–H(107)···Cl(19) = 171 (4)° for molecule (I); N(7)···Cl(19) = 3·054 (3), H(107)···Cl(19) = 2·05 (3) Å, N(7)–H(107)···Cl(19) = 166 (2)°, N(9)···Cl(19)($\frac{1}{2}-x$, $\frac{1}{2}+y$, $\frac{1}{2}-z$) = 3·133 (3), H(109)···Cl(19) = 2·18 (4) Å, N(9)–H(109)···Cl(19) = 158 (3)° for molecule (II). The N(12) atom is not involved in the hydrogen bonding (Fig. 2).

In order to determine the net charges on the atoms, CNDO/2 calculations (Pople & Beveridge, 1970) were

performed for the free organic ion. The results are similar to those obtained for the protonated clonidine (Byre *et al.*, 1976), the main part of the positive charge (+0·44) being situated on the central C atom of the guanidine function and on the two H atoms of the N—H groups (+0·17). The net charge on C(14) is +0·26 and on O(16) −0·25. Identical results were found for both molecules.

In order to see if the crystalline conformation is also found in vacuum, PCILO calculations (Pullman, 1971) were performed for the free-base state. The two possible tautomeric forms were considered: imino form (with the C=N double bond exocyclic) and amino form (with the C=N double bond endocyclic). The study consisted of constructing the conformational-energy curve (i) by varying the torsion angle C(6)–C(1)–N(7)–C(8) and (ii) by varying at the same time the torsion angles C(6)–C(1)–N(7)–C(8) and C(1)–N(7)–C(8)–C(9). In the first case, two energy minima were found. The first one corresponds to a conformation close to the crystal conformation (angle variation $\simeq -20°$) and the energy was taken as zero; the second one corresponds to an angle variation of $-300°$ with $E = 3{\cdot}3$ kJ mol^{-1}, the related arrangement of the rings being nearly planar: C(6)–C(1)–N(7)–C(8) = −8 (1)°. In the second case, a strong barrier of energy impedes the rotation of the two torsion angles at the same time.

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Acta Cryst. (1986). C**42**, 1071–1073

Structure of *cis*-*N*-(1-Benzyl-2-methyl-3-pyrrolidinyl)-5-chloro-2-methoxybenzamide*

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(*Received* 8 *January* 1986; *accepted* 28 *February* 1986)

Abstract. $C_{20}H_{23}ClN_2O_2$, $M_r = 358{\cdot}87$, monoclinic, $P2_1/n$, $a = 16{\cdot}68$ (1), $b = 11{\cdot}94$ (2), $c = 9{\cdot}324$ (5) Å, $\beta = 92{\cdot}82$ (5)°, $V = 1855$ (3) Å^3, $Z = 4$, $D_x = 1{\cdot}285$ g cm^{-3}, λ(Mo $K\alpha$) = 0·71073 Å, $\mu = 3{\cdot}35$ cm^{-1}, $F(000) = 760$, $T = 298$ K, $R = 0{\cdot}055$ for 3042 observed reflections with $|F_o| > 3\sigma(|F_o|)$. An intramolecular H bond between the amide N and the methoxy O is observed. The torsion angles of the title compound, a weak dopamine antagonist, are almost identical to those of its potent analogue, YM-09151-2, except for the angle around the N(amide) and C(pyrrolidine) bonds. Furthermore, two geometrical parameters relevant to the estimation of the neuroleptic activity are almost the same as those of YM-09151-2. The significant structural difference is the lack of contribution from the quinonoidal resonance form, owing to the absence of the amino group in the benzamide moiety.

Introduction. The crystal-structure determination of the title compound (1) was undertaken as part of serial studies for finding new potent neuroleptic drugs in

* New Potent Neuroleptic Drugs of Benzamide Derivatives. Part IV.

0108-2701/86/081071-03$01.50