

Structure of 4-(2-Imidazolin-2-ylamino)-2-methylindazole Hydrochloride, Indanidine: SGD-101-75

BY ABDESLAM H'NAÏFI, JEAN-MICHEL LÉGER AND ALAIN CARPY

Laboratoire de Chimie Analytique, ERA 890, CNRS, Faculté de Pharmacie, Université de Bordeaux II, Place de la Victoire, 33076 Bordeaux CEDEX, France

(Received 6 May 1985; accepted 25 October 1985)

Abstract. α_1 -Adrenoceptor agonist. Sympathomimetic. $C_{11}H_{14}N_5^+.Cl^-$, $M_r = 251.76$, monoclinic, $P2_1/n$, $a = 10.472$ (1), $b = 8.840$ (2), $c = 13.509$ (2) Å, $\beta = 107.32$ (1)°, $V = 1193.9$ (3) Å³, $Z = 4$, $D_x = 1.40$ g cm⁻³, $\lambda(Cu K\alpha) = 1.54178$ Å, $\mu = 27.74$ cm⁻¹, $F(000) = 528$, room temperature, $R = 0.060$ for 1257 observed reflections. 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 crystals and in the isolated molecule is biplanar [with an angle of 63 (1)° between the planes]. The three N atoms of the guanidine group are involved in hydrogen bonds responsible for the crystalline cohesion.

Introduction. Most of the imidazolines structurally related to clonidine present an α_2 -adrenergic agonist activity (Timmermans & Van Zwieten, 1984). The title compound was synthesized in an attempt to find a clonidine-like drug (Molnar, Thiele, Geissmann & Jahn, 1982) but its pharmacological profile was unusual. Indanidine can act as an agonist, partial agonist or antagonist on the α -adrenoceptors of isolated tissues (Ismail, Jahn & Weetman, 1981). A detailed study of this compound led to the description of a new subtype of α_1 -adrenoceptors, named α_{1s} (Coates, Jahn & Weetman, 1982).

The X-ray investigation of this compound is part of a drug-modelling of α -adrenergic pharmacophores started a few years ago in our laboratory (Carpy, Léger, Leclerc, Decker, Rouot & Wermuth, 1982).

Experimental. Small white plates (from ethanol), 0.25 × 0.15 × 0.03 mm, Enraf-Nonius CAD-4 diffractometer with graphite monochromator (with calculation of the azimuthal position of minimum absorption, as determined by the flat shape of the crystal and the way the crystal is mounted on the goniometer head); 25 reflections ($8 < \theta < 16^\circ$) used to refine orientation matrix; systematic absences: $h0l$ for $h + l$ odd, $0k0$ for k odd; 1760 ($\pm h, k, l$) independent with $\theta < 60^\circ$, $h - 11$ to $+11$, $k 0$ to 9 , $l 0$ to 15 ; 1257 with $l \geq 3\sigma(l)$; Lp correction, absorption ignored; two check

reflections (221, $\bar{1}\bar{2}1$) every 5400 s showed no unusual variation (all within $\pm 3\sigma$); direct methods, MULTAN80 (Main, Fiske, Hull, Lessinger, Germain, Declercq & Woolfson, 1980); anisotropic block-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; $R = 0.060$, $wR = 0.079$, $S = 1.258$ (1257 reflections, 210 parameters); max. $\Delta\rho$ excursion ± 0.5 e Å⁻³ in final ΔF map; in final cycle mean and max. $\Delta/\sigma = 0.2$ and 0.6 ; H-atom form factor from Stewart, Davidson & Simpson (1965), all other form factors from *International Tables for X-ray Crystallography* (1974); Mini 6–92, CII-Honeywell–Bull (programs CRISTA, CRISAF, CRISEC, UTIL, Laboratory of Crystallography, University of Bordeaux I, Talence).

Discussion. Table 1 gives the atomic coordinates and Table 2 the bond lengths and angles.* A diagram of the molecule with the atom numbering is shown in Fig. 1.

Bond distances and angles within the methylindazole group having the expected values will not be discussed. The imidazoline part of the molecule is protonated; consequently the three N atoms N(10), N(12) and N(15) are chemically equivalent. The three bond lengths C(11)–N [mean value 1.332 (6) Å] are shorter than N(12)–C(13) = 1.467 (6) Å and N(15)–C(14) = 1.478 (6) Å; their values are intermediate between a double bond (1.265 Å) and a single bond (1.470 Å). This result indicates a delocalization of the double bond on the guanidine group and a delocalization of the positive charge on the central C atom of this group C(11) and probably on the H atoms bonded to the three N atoms. In order to verify this assumption, CNDO/2 calculations (Pople & Segal, 1966) were performed on the protonated molecule. Only the results concerning the guanidine group present some interest. The charge

* Lists of structure factors, anisotropic thermal parameters, H-atom coordinates and mean planes of atoms have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 42602 (15 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 1. Atomic coordinates ($\times 10^4$) and equivalent isotropic temperature factors
$$B_{eq} = \frac{1}{3} \sum_i \sum_j \beta_{ij} a_i \cdot a_j$$

	x	y	z	$B_{eq}(\text{\AA}^2)$
C(1)	5304 (5)	1229 (6)	1386 (4)	3.2 (2)
C(2)	4190 (5)	2156 (5)	1229 (4)	3.2 (2)
N(3)	4128 (4)	2977 (5)	379 (3)	3.3 (2)
N(4)	5124 (4)	2699 (5)	-39 (3)	3.4 (2)
C(5)	5874 (5)	1627 (6)	588 (3)	3.1 (2)
C(6)	7020 (5)	888 (6)	479 (4)	3.8 (2)
C(7)	7558 (5)	-243 (6)	1171 (4)	4.0 (2)
C(8)	6991 (5)	-672 (2)	1967 (7)	3.8 (2)
C(9)	5894 (5)	22 (6)	2084 (4)	3.3 (2)
N(10)	5270 (4)	-429 (5)	2843 (3)	3.6 (2)
C(11)	4832 (5)	-1829 (6)	2893 (3)	3.0 (2)
N(12)	4807 (4)	-2928 (4)	2224 (3)	3.3 (2)
C(13)	4139 (5)	-4268 (6)	2477 (4)	3.6 (2)
C(14)	4126 (5)	-3921 (6)	3587 (4)	3.5 (2)
N(15)	4310 (4)	-2262 (5)	3647 (3)	3.4 (2)
C(16)	3060 (6)	4037 (7)	-132 (4)	4.5 (2)
Cl(17)	4238 (1)	2124 (2)	3953 (1)	3.9 (1)

Table 2. Bond distances (\AA) and angles ($^\circ$)

C(1)–C(2)	1.389 (6)	C(7)–C(8)	1.427 (7)
C(1)–C(5)	1.424 (7)	C(8)–C(9)	1.352 (7)
C(1)–C(9)	1.436 (6)	C(9)–N(10)	1.427 (6)
C(2)–N(3)	1.343 (6)	N(10)–C(11)	1.329 (6)
N(3)–N(4)	1.349 (5)	C(11)–N(12)	1.322 (6)
N(3)–C(16)	1.465 (6)	C(11)–N(15)	1.346 (6)
N(4)–C(5)	1.355 (6)	N(12)–C(13)	1.467 (6)
C(5)–C(6)	1.412 (6)	C(13)–C(14)	1.535 (7)
C(6)–C(7)	1.370 (7)	C(14)–N(15)	1.478 (6)
C(2)–C(1)–C(5)	105.1 (4)	C(7)–C(8)–C(9)	121.7 (4)
C(2)–C(1)–C(9)	135.7 (4)	C(1)–C(9)–C(8)	118.4 (4)
C(5)–C(1)–C(9)	119.0 (4)	C(1)–C(9)–N(10)	118.7 (4)
C(1)–C(2)–N(3)	105.9 (4)	C(8)–C(9)–N(10)	122.9 (4)
C(2)–N(3)–N(4)	114.4 (4)	C(9)–N(10)–C(11)	122.4 (4)
C(2)–N(3)–C(16)	125.7 (4)	N(10)–C(11)–N(12)	125.9 (4)
N(4)–N(3)–C(16)	119.7 (4)	N(10)–C(11)–N(15)	121.8 (4)
N(3)–N(4)–C(5)	104.0 (4)	N(12)–C(11)–N(15)	112.2 (4)
C(1)–C(5)–N(4)	110.5 (4)	C(11)–N(12)–C(13)	110.3 (4)
C(1)–C(5)–C(6)	121.7 (4)	N(12)–C(13)–C(14)	102.1 (4)
N(4)–C(5)–C(6)	127.7 (4)	C(13)–C(14)–N(15)	102.3 (4)
C(5)–C(6)–C(7)	117.2 (4)	C(11)–N(15)–C(14)	108.5 (4)
C(6)–C(7)–C(8)	122.0 (4)		

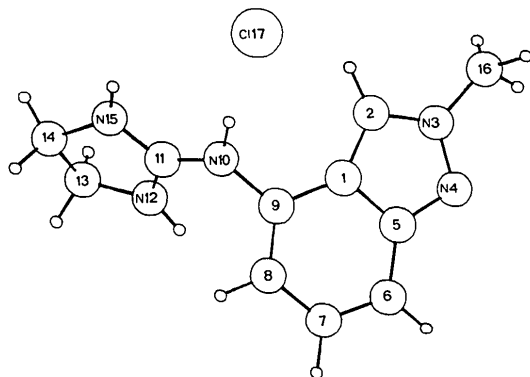


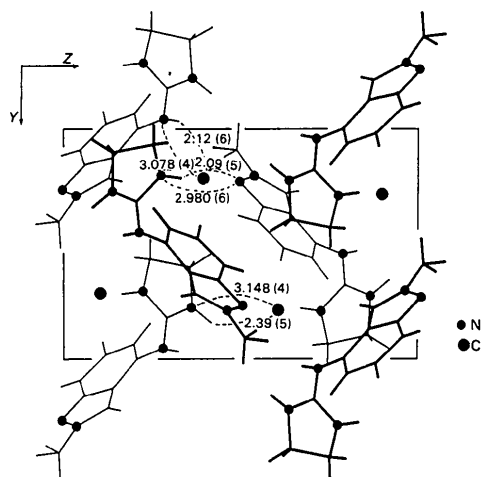
Fig. 1. Perspective view of the molecule showing the numbering of atoms. The bare numbers are for C atoms.

distribution within this particular group is the following: +0.45 on C(11), -0.17 on N(10), -0.18 on N(12), -0.20 on N(15), +0.16 on H(110), +0.18 on H(112) and +0.17 on H(115). One can say that 50% of the positive charge is located on C(11) and the remaining 50% is evenly distributed on the three H atoms of the guanidine function.

The solid-state conformation is defined by the two torsion angles $C(1)–C(9)–N(10)–C(11) = -59 (1)^\circ$ and $C(9)–N(10)–C(11)–N(12) = -6 (1)^\circ$. The guanidine group is planar, the atoms C(13) and C(14) being respectively below $[-0.110 (5) \text{\AA}]$ and above $[0.239 (5) \text{\AA}]$ the plane. The guanidine group subtends an angle of $63 (1)^\circ$ with the plane containing the indazole ring. A similar result was already found in the α_2 -adrenergic agonist tolonidine [2-(2-chloro-4-methylphenylamino)-2-imidazoline nitrate] (Carpy, Hickel & Léger, 1979) in which only the 2-ortho position of the phenyl ring was occupied by a Cl atom.

The crystalline cohesion is ensured by three hydrogen bonds involving the three N atoms of the guanidine function: $N(10) \cdots Cl(17) = 3.078 (4)$, $H(110) \cdots Cl(17) = 2.12 (6) \text{\AA}$, $N(10)–H(110) \cdots Cl(17) = 169 (4)^\circ$; $N(12) \cdots N(4)(1-x, \bar{y}, \bar{z}) = 2.980 (6)$, $H(112) \cdots N(4) = 2.09 (5) \text{\AA}$, $N(12)–H(112) \cdots N(4) = 173 (5)^\circ$; $N(15) \cdots Cl(17) (1-x, \bar{y}, 1-z) = 3.148 (4)$, $H(115) \cdots Cl(17) = 2.39 (5) \text{\AA}$, $N(15)–H(115) \cdots Cl(17) = 152 (4)^\circ$ (Fig. 2).

In our previous model of α_2 -pharmacophore derived from the study of several imidazoline compounds (Carpy *et al.*, 1982) we have found a common biplanar conformation, the two planes being at 60, 75 or 90°. This study was performed by means of X-ray analysis, NMR and theoretical calculations on the isolated molecules using the *PCILO* program (Pullman, 1971). In the present compound, the conformation found in the crystals and confirmed by *PCILO* (it corresponds to an energy minimum) is also biplanar with $63 (1)^\circ$ between

Fig. 2. Packing of molecules projected on (100) (Distances in \AA .)

the two planes. The characteristic distances found, *i.e.* D [distance between N(15) and the middle of C(1)–C(5)] and h [height of N(15) above the indazole ring] are respectively 5.31 (1) and 1.120 (4) Å. These are slightly higher than the corresponding distances found in the α_2 -agonists ($D \approx 5$, $h \approx 1$ Å).

The authors acknowledge the gift of the sample (Siegfried AG, Zofingen, Switzerland).

References

- CARPY, A., HICKEL, D. & LÉGER, J.-M. (1979). *Cryst. Struct. Commun.* **8**, 945–948.
 CARPY, A., LÉGER, J.-M., LECLERC, G., DECKER, N., ROUOT, B. & WERMUTH, C. G. (1982). *Mol. Pharmacol.* **21**, 400–408.
 COATES, J., JAHN, U. & WEETMAN, D. F. (1982). *Br. J. Pharmacol.* **75**, 549–552.

- International Tables for X-ray Crystallography* (1974). Vol. IV. Birmingham: Kynoch Press. (Present distributor D. Reidel, Dordrecht.)
 ISMAIL, S., JAHN, U. & WEETMAN, D. F. (1981). *Br. J. Pharmacol.* **72**, 535P–536P.
 MAIN, P., FISKE, S. J., HULL, S. E., LESSINGER, L., GERMAIN, G., DECLERCQ, J.-P. & WOOLFSON, M. M. (1980). *MULTAN80. A System of Computer Programs for the Automatic Solution of Crystal Structures from X-ray Diffraction Data*. Univs. of York, England, and Louvain, Belgium.
 MOLNAR, I., THIELE, K., GEISSMANN, F. & JAHN, U. (1982). European Patent Application No. 47 328.
 POPLE, J. A. & SEGAL, G. A. (1966). *J. Chem. Phys.* **44**, 3289–3296.
 PULLMAN, B. (1971). *Aspects de la Chimie Quantique Contemporaine*, pp. 271–297. Paris: CNRS.
 STEWART, R. F., DAVIDSON, E. R. & SIMPSON, W. T. (1965). *J. Chem. Phys.* **42**, 3175–3187.
 TIMMERMANS, P. B. M. W. M. & VAN ZWIETEN, P. A. (1984). *Drugs Future*, **9**, 41–51.

Acta Cryst. (1986). **C42**, 341–343

Structure de la Dichloro-1,4 Butanedione-2,3

PAR BERNARD DUCOURANT

Laboratoire des Acides Minéraux UA n° 79, Université des Sciences et Techniques du Languedoc, Place Eugène Bataillon, 34060 Montpellier CEDEX, France

CATHERINE MAURY, JEAN-PIERRE LERE-PORTE ET JEAN PETRISSANS

Laboratoire de Chimie Générale, Université des Sciences et Techniques du Languedoc, Place Eugène Bataillon, 34060 Montpellier CEDEX, France

ET JEAN-LOUIS RIBET

Laboratoire d'Etudes des Phases Condensées LA 233, Université des Sciences et Techniques du Languedoc, Place Eugène Bataillon, 34060 Montpellier CEDEX, France

(Reçu le 1 mars 1985, accepté le 30 octobre 1985)

Abstract. $C_4H_4Cl_2O_2$, $M_r = 154.98$, monoclinic, $P2_1/c$, $a = 8.167$ (3), $b = 6.712$ (3), $c = 5.542$ (2) Å, $\beta = 91.87$ (2)°, $V = 303.6$ (8) Å³, $Z = 2$, $D_m = 1.65$, $D_x = 1.658$ g cm⁻³, Mo $K\alpha$, $\lambda = 0.7107$ Å, $\mu = 9.6$ cm⁻¹, $F(000) = 1000$, $T = 216$ K, $R = 0.0346$ for 535 reflections. The molecule exhibits an antiperiplanar conformation of the carbonyl groups and a synperiplanar orientation of the adjacent C–Cl and C=O bonds. The conjugation between the two C=O groups is not appreciably affected by the two chlorine atoms. The Cl...O distance of 2.93 Å is less than the sum of the van der Waals radii.

Introduction. L'étude de la butanedione-2,3 par spectrométrie de vibration (Noack & Jones, 1960; Durig, Hannum & Brown, 1971), diffraction des électrons (Hagen & Heldberg, 1973; Danielson & Hedberg, 1979) et des RX (Eriks, Hayden, Hsi Yang &

Chan, 1983)* a montré qu'à l'état gazeux, liquide et solide, cette molécule se présente sous une conformation antiperiplanaire, résultat qui est *a priori* inconciliable avec le moment dipolaire mesuré pour le composé à l'état gazeux (Zahn, 1932; Bloom & Sutton, 1941) ou dissous (Bloom & Sutton, 1941).

Tout récemment, des déterminations effectuées par spectrométrie IR et dipolométrie sur les dihalogéno-1,4 butanediones-2,3 (Maury, Lere-Porte & Petrisans, 1986) nous ont conduit à envisager l'éventualité d'une modification de l'angle dièdre formé par les deux carbonyles sous l'influence de la substitution des atomes d'halogène. En vue de vérifier la fiabilité de cette dernière hypothèse, nous avons entrepris l'étude de la dichloro-1,4 butanedione-2,3 par diffraction des RX.

* Mémoire publié durant la réalisation de ce travail.