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Structure and Conformation of an Antidepressant Drug, Nitroxazepine Hydrochloride Monohydrate*†

BY R. USHA, M. M. BHADBHADE AND K. VENKATESAN‡

Department of Organic Chemistry, Indian Institute of Science, Bangalore-560 012, *India*

AND K. NAGARAJAN AND J. DAVID

CIBA–GEIGY Research Centre, Bombay-400 063, *India*

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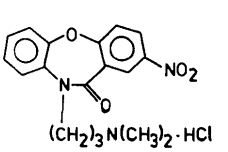
Abstract. $C_{18}H_{20}N_3O_4^+.Cl^-.H_2O$, $M_r = 395$, orthorhombic, $Pn2_1a$, $a = 7{\cdot}710\ (4)$, $b = 11{\cdot}455\ (3)$, $c = 21{\cdot}199\ (3)$ Å, $Z = 4$, $V = 1872{\cdot}4$ Å^3, $D_m = 1{\cdot}38$, $D_c = 1{\cdot}403$ g cm^{-3}, $F(000) = 832$, μ(Cu $K\alpha$) $= 20{\cdot}94$ cm^{-1}. Intensities for 1641 reflections were measured on a Nonius CAD-4 diffractometer; of these, 1470 were significant. The structure was solved by direct methods and refined to an R index of 0·045 using a block-diagonal least-squares procedure. The angle between the least-squares planes through the benzene rings is 125·0 (5)° and the side chain is folded similarly to one of the independent molecules of imipramine hydrochloride.

Introduction. Nitroxazepine, a dibenzoxazepine derivative, is an antidepressant (Nagarajan, Kulkarni & Venkateswarlu, 1968; Nagarajan, Venkateswarlu, Kulkarni, Nagana Goud & Shah, 1974; Nagarajan, David, Grewal & Govindachari, 1974; David & Grewal, 1974) belonging to the group containing imipramine, clomipramine, amitryptiline and doxepin (Maj, 1981). As the hydrochloride salt (Sintamil®) (I) has been found to be a safe and effective drug in the clinic (Nagarajan, David, Kaul, Maller, Rao & Grewal, 1975; Gupta & Marthak, 1981) with distinct advantages over imipramine (Gupta & Mankodi, 1972; Gordon, 1976; Kaiser, 1981). In attempts to relate the conformation of tricyclic antidepressants to their activity and their influence on the uptake of the biogenic amines norepinephrine and serotonin, the three-dimensional structure of (I) has been determined by X-ray studies and the results are presented here.



(I)

The space group and preliminary unit-cell parameters were determined from precession photographs. Systematic absences indicated that the space group could be either $Pn2_1a$ or $Pnma$. The measured density indicated the presence of four water molecules in the unit cell. A crystal of dimensions 0·17 × 0·32 × 0·40 mm was used for data collection. A total of 1641

* IUPAC name: 10-(3-dimethylaminopropyl)-2-nitro-10,11-dihydrodibenz[*b*,*f*][1,4]oxazepin-11-one hydrochloride monohydrate. Registered name: Sintamil®.

† Contribution No. 626 from CIBA–GEIGY Research Centre.

‡ To whom correspondence should be addressed.

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independent reflections were measured on a Nonius CAD-4 diffractometer in the $\omega/2\theta$ scan mode using monochromated Cu $K\alpha$ ($\lambda = 1{\cdot}5418$ Å) radiation. No correction was made for absorption. Out of 1641 reflections, 1470 were considered as significant [$|F_{obs}| \geq 2\sigma(|F_{obs}|)$]. Since the distribution of the normalized structure factors was acentric and the molecule does not have a plane of symmetry, the space group $Pn2_1a$ was chosen for the structure solution.

Initial attempts to solve the structure *via* the direct-methods program *MULTAN* (Germain, Main & Woolfson, 1971) failed. However, a fragment consisting of 19 atoms could be identified in the best E map computed using the direct-methods strategy in the program *SHELX* 76 (Sheldrick, 1976). The isotropic block-diagonal refinement of this fragment gave a conventional R value of 0·33. Successive difference Fourier maps revealed the remaining seven non-hydrogen atoms. The difference Fourier synthesis to locate the H atoms contained a prominent peak, which was identified as the water molecule. Final cycles of least-squares refinement for anisotropic Cl^-, O, N and C atoms and isotropic H atoms using the individual weighting scheme [$w = 1/\sigma(|F_{obs}|)^2$] gave a final R of 0·045.* Final positional and thermal parameters are given in Table 1.

Table 1. *Final positional parameters* ($\times 10^5$, *for* H $\times 10^4$) *and isotropic thermal parameters with e.s.d.'s in parentheses*

For non-H atoms $B_{eq} = \frac{4}{3}\sum_i \sum_j \beta_{ij}\, \mathbf{a}_i \cdot \mathbf{a}_j$.

	x	y	z	B_{eq} or B (Å^2)
Cl	2896 (15)	82402	50839 (5)	4·17 (0·03)
C(1)	10203 (62)	773 (37)	24688 (22)	2·58 (0·09)
C(2)	13226 (58)	−4979 (40)	30303 (22)	2·90 (0·10)
C(3)	6650 (70)	−1038 (42)	35979 (22)	3·11 (0·11)
C(4)	−3008 (61)	9288 (47)	35964 (21)	3·05 (0·12)
C(5)	−5769 (52)	15199 (38)	30385 (20)	2·34 (0·09)
O(6)	−15772 (40)	24972 (28)	30550 (15)	2·97 (0·07)
C(7)	−7081 (57)	34951 (38)	28250 (21)	2·66 (0·10)
C(8)	−2693 (62)	43384 (43)	32594 (24)	3·13 (0·12)
C(9)	4480 (77)	53633 (45)	30671 (30)	4·07 (0·14)
C(10)	7518 (85)	55403 (43)	24258 (29)	3·99 (0·14)
C(11)	3330 (64)	46766 (44)	19987 (25)	3·34 (0·12)
C(12)	−3757 (52)	36196 (38)	21874 (22)	2·53 (0·10)
N(13)	−7582 (45)	27288 (32)	17438 (17)	2·48 (0·08)
C(14)	−4364 (52)	15718 (41)	18279 (21)	2·61 (0·10)
C(15)	656 (55)	10965 (38)	24577 (21)	2·36 (0·09)
O(16)	−5420 (48)	8745 (33)	13889 (15)	3·42 (0·09)
N(17)	23985 (55)	−15562 (33)	30217 (21)	3·47 (0·10)
O(18)	30137 (57)	−18712 (37)	25305 (20)	4·99 (0·11)
O(19)	26074 (72)	−20732 (37)	35271 (21)	5·63 (0·13)
C(20)	−12689 (55)	30660 (42)	10923 (18)	2·81 (0·10)
C(21)	2390 (56)	30095 (44)	6323 (21)	3·01 (0·11)
C(22)	−2259 (65)	33605 (50)	−380 (22)	3·24 (0·11)
N(23)	−16282 (51)	26371 (37)	−3341 (17)	3·22 (0·10)
C(24)	−13417 (93)	13628 (54)	−2734 (32)	5·16 (0·18)
C(25)	−18761 (83)	29936 (85)	−10063 (26)	6·02 (0·21)
W	30200 (64)	6703 (47)	97372 (27)	6·70 (0·16)
H(1)	1428 (51)	−180 (36)	2092 (18)	1·28 (0·74)
H(3)	1004 (80)	−465 (47)	3945 (25)	2·79 (1·06)
H(4)	−615 (66)	1264 (37)	3931 (23)	3·32 (0·96)
H(8)	−623 (91)	4377 (56)	3594 (27)	4·29 (1·35)
H(9)	620 (92)	5949 (60)	3327 (31)	6·93 (1·33)
H(10)	1105 (88)	6219 (49)	2340 (26)	3·10 (1·33)
H(11)	302 (73)	4770 (53)	1664 (33)	4·60 (1·34)
H(201)	−1788 (49)	3814 (36)	1127 (18)	1·27 (0·73)
H(202)	−2371 (70)	2549 (49)	933 (30)	4·12 (1·22)
H(211)	818 (89)	2286 (47)	626 (25)	4·73 (1·18)
H(212)	826 (88)	3535 (45)	793 (27)	3·47 (1·32)
H(221)	921 (95)	3285 (55)	−375 (31)	3·89 (1·49)
H(222)	−995 (114)	4112 (50)	−54 (32)	6·18 (1·71)
H(241)	−1188 (342)	1157 (157)	354 (95)	8·34 (7·21)
H(242)	−2268 (80)	999 (55)	−493 (30)	6·03 (1·45)
H(243)	−388 (87)	946 (66)	−489 (35)	5·74 (1·57)
H(251)	−933 (128)	2773 (71)	−1177 (41)	6·62 (2·18)
H(252)	−2891 (87)	2627 (69)	−1143 (38)	7·88 (1·82)
H(253)	−1890 (93)	3614 (70)	−1056 (37)	5·52 (1·96)
H(*W*1)	3380 (98)	1358 (54)	9812 (31)	7·48 (1·68)
H(*W*2)	3854 (166)	44 (63)	9723 (48)	12·41 (2·53)
H(23)	−2638 (76)	2803 (46)	−125 (26)	2·76 (1·06)

Discussion. A perspective view and the numbering scheme of the molecule are shown in Fig. 1. The tricyclic ring system in (I) is folded about the plane formed by atoms O(6), N(13) and C(14). Least-squares planes through rings A and B make angles of 143·5 (5) and 21·9 (5)° with this plane. The central seven-membered ring is approximately in a boat conformation (Table 2). The angle between the least-squares planes through rings A and B is 125·0 (5)°. The antidepressant imipramine hydrochloride (II) (Post, Kennard & Horn, 1975) is known to exist in two solid-state conformations a and b, the former having a fully extended side chain and the latter a folded one. Conformation a is associated with predominant inhibition of uptake of norepinephrine with the clinical consequence of psychomotor activation, and conformation b, of serotonin correlated with improvement of mood (Martin, Paradkar, Peng, Speth, Yamamura & Horn, 1980). The side chain of (I) is folded at τ_3 similarly to molecule b of imipramine (Table 3). Another important parameter is the distance of the

* Lists of structure factors and anisotropic thermal parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 36690 (12 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

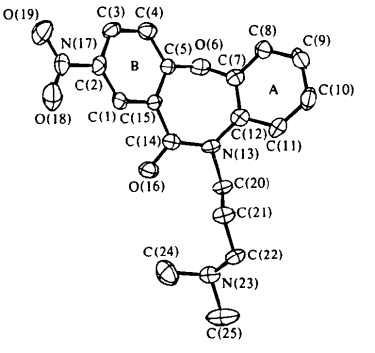

Fig. 1. Perspective view of molecule (I) down **a**.

Table 2. *Torsion angles* (°) *for the seven-membered ring, with e.s.d.'s in parentheses*

C(5)–O(6)–C(7)–C(12)	72·2 (5)
O(6)–C(7)–C(12)–N(13)	−5·0 (6)
C(7)–C(12)–N(13)–C(14)	−43·2 (6)
C(12)–N(13)–C(14)–C(15)	11·6 (6)
N(13)–C(14)–C(15)–C(5)	35·2 (6)
C(14)–C(15)–C(5)–O(6)	−7·3 (6)
C(15)–C(5)–O(6)–C(7)	−61·1 (5)

Table 3. *Side-chain torsion angles* (°) *for* (I) *and* (II) (*e.s.d.'s* ~0·5°)

	(I)	(II) Molecule *a*	(II) Molecule *b*
C(14)–N(13)–C(20)–C(21) τ_1	−71·9	137·2	58·8
N(13)–C(20)–C(21)–C(22) τ_2	−179·4	180·0	160·5
C(20)–C(21)–C(22)–N(23) τ_3	−58·9	173·5	60·5
C(21)–C(22)–N(23)–C(24) τ_4	−49·3	−66·7	64·2
C(21)–C(22)–N(23)–C(25) τ_5	−175·4	164·4	−172·4

terminal nitrogen N(23) from the geometric centres of the benzene rings, which is associated with the norepinephrine receptor binding. In the molecule under discussion, these distances are 7·697 (4) and 6·755 (4) Å.

Bond lengths for (I) are given in Fig. 2 and bond angles in Table 4. The aromatic rings have undergone significant deformation because of the nitro substitution at C(2) in ring *B* and the fusion of these rings to the central seven-membered ring. Bond lengths in ring *B* vary from 1·379 (6) to 1·413 (6) Å [average 1·388 (4) Å], and in ring *A* from 1·360 (7) to 1·394 (8) Å [average 1·379 (4) Å]. Bond angles in ring *B* range from 117·5 (4) to 122·2 (4)° [average 119·9 (3)°], and in ring *A* from 116·4 (4) to 122·3 (4)° [average 119·9 (3)°]. In the central seven-membered ring C(5)–O(6) [1·359 (5) Å] is significantly shorter than the chemically equivalent C(7)–O(6) [1·411 (5) Å], which can be attributed to the delocalization effects involving the nitro-substituted ring *B*.

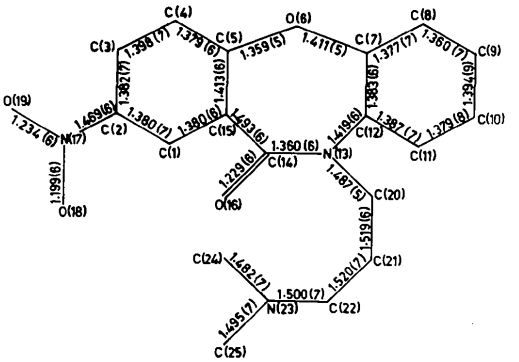

Fig. 2. Bond lengths for (I) with e.s.d.'s in parentheses (Å).

Table 4. *Bond angles* (°) *involving non-hydrogen atoms, with e.s.d.'s in parentheses*

C(2)–C(1)–C(15)	120·6 (4)	C(11)–C(12)–N(13)	121·2 (4)
C(1)–C(2)–C(3)	122·2 (4)	C(12)–N(13)–C(14)	125·2 (4)
C(1)–C(2)–N(17)	118·6 (4)	C(12)–N(13)–C(20)	118·9 (3)
C(3)–C(2)–N(17)	119·2 (4)	C(14)–N(13)–C(20)	115·0 (3)
C(2)–C(3)–C(4)	118·0 (4)	N(13)–C(14)–C(15)	121·3 (4)
C(3)–C(4)–C(5)	120·0 (4)	N(13)–C(14)–O(16)	121·5 (4)
C(4)–C(5)–O(6)	118·0 (4)	C(15)–C(14)–O(16)	117·2 (4)
C(4)–C(5)–C(15)	121·6 (4)	C(1)–C(15)–C(5)	117·5 (4)
O(6)–C(5)–C(15)	120·3 (4)	C(1)–C(15)–C(14)	117·5 (4)
C(5)–O(6)–C(7)	112·9 (3)	C(5)–C(15)–C(14)	124·3 (4)
O(6)–C(7)–C(8)	117·0 (4)	C(2)–N(17)–O(18)	118·8 (4)
O(6)–C(7)–C(12)	120·6 (4)	C(2)–N(17)–O(19)	117·3 (4)
C(8)–C(7)–C(12)	122·4 (4)	O(18)–N(17)–O(19)	123·9 (5)
C(7)–C(8)–C(9)	120·3 (6)	N(13)–C(20)–C(21)	112·5 (3)
C(8)–C(9)–C(10)	119·1 (5)	C(20)–C(21)–C(22)	114·1 (4)
C(9)–C(10)–C(11)	119·8 (5)	C(21)–C(22)–N(23)	114·5 (4)
C(10)–C(11)–C(12)	121·9 (5)	C(22)–N(23)–C(24)	113·6 (4)
C(7)–C(12)–C(11)	116·4 (4)	C(22)–N(23)–C(25)	109·9 (4)
C(7)–C(12)–N(13)	122·4 (4)	C(24)–N(23)–C(25)	111·8 (5)

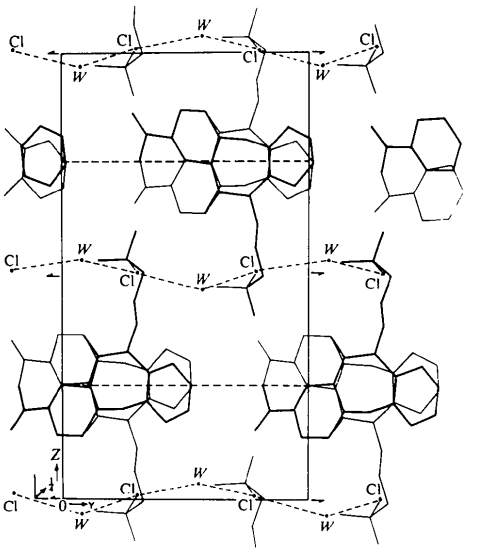

Fig. 3. Packing of the molecules in (I) viewed down **a**.

Table 5. *Hydrogen-bonding parameters*

D–H	*A*	*D* at	*D*···*A* (Å)	*D*–H···*A* (°)	H–*D*···*A* (°)
N(23)–H(23)	Cl⁻	(1)	3·038 (4)	162·9 (5·7)	12·0 (3·5)
W–H(*W*1)	Cl⁻	(2)	3·302 (5)	173·4 (7·0)	4·9 (4·6)
W–H(*W*2)	Cl	(3)	3·309 (5)	162·1 (9·8)	12·8 (6·1)

Symmetry code: (1) $-0·5-x$, $0·5+y$, $0·5+z$; (2) $0·5-x$, $0·5+y$, $z-0·5$; (3) $x-0·5$, $1+y$, $1·5-z$.

The packing of the molecules projected along the *a* axis is shown in Fig. 3. The structure is stabilized by intermolecular hydrogen bonds of the type N–H···Cl⁻ and *W*–H···Cl⁻. Hydrogen-bonding parameters are given in Table 5. Molecules lie in the unit cell in such a way that the tricyclic ring system is roughly parallel to the *b* axis and partially overlaps down the *a* axis,

resulting in three intermolecular contacts $<3\cdot2$ Å involving C and O atoms [O(6)···C(14) = 3·168 (5), C(2)···O(16) = 3·136 (5) and C(3)···O(16) = 3·132 (5) Å].

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Structure of 1-(4-Chlorophenoxy)-3,3-dimethyl-1-(1,2,4-triazol-1-yl)-2-butanone

BY I. W. NOWELL* AND P. E. WALKER

Department of Chemistry, Sheffield City Polytechnic, Pond Street, Sheffield S1 1WB, England

AND N. H. ANDERSON†

Imperial Chemical Industries Limited, Plant Protection Division, Jealott's Hill Research Station, Bracknell, Berkshire RG12 6EY, England

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Abstract. $C_{14}H_{16}ClN_3O_2$, $M_r = 293\cdot8$, $P2_1/n$, $a = 8\cdot076$ (3), $b = 20\cdot317$ (8), $c = 9\cdot307$ (3) Å, $\beta = 97\cdot43$ (5)°, $U = 1514\cdot2$ Å^3, Mo $K\alpha$, $\lambda = 0\cdot71069$ Å, $Z = 4$, $D_m = 1\cdot31$ (2), $D_c = 1\cdot29$ Mg m^{-3}, $\mu = 0\cdot21$ mm^{-1}, $F(000) = 616$. The structure was solved by direct methods and refined to $R = 0\cdot058$ for 1023 counter reflections classed as observed. The triazolyl ring, which shows significant delocalization, is planar and inclined at angles of 73·1 (9) and 61·8 (9)° to the *p*-chlorophenyl ring and to the C–C(O)–C grouping respectively. The exocyclic angles at N(1) of the triazolyl ring are very asymmetric with C–N–N 119·5 (6) and C–N–C 130·7 (6)°.

Introduction. 1-(4-Chlorophenoxy)-3,3-dimethyl-1-(1,2,4-triazol-1-yl)-2-butanone, triadimefon, is well established as an effective systemic fungicide (Martin & Morris, 1979). While the exact mode of action of the fungicide has not been established, treatment of fungi with the compound results in the inhibition of ergosterol biosynthesis (Buchenauer, 1976). From the study of structure–activity relationships in related compounds, it was believed that the triazolyl group and the overall conformation of the molecule played important roles. It is to establish the conformation, albeit in the solid state, that we have determined the crystal structure of the title compound.

A crystal 0·20 × 0·24 × 0·35 mm was mounted about the crystallographic *a* axis and data were collected on a Stoe Stadi-2 two-circle diffractometer in layers of constant *h* up to *h* = 9. The data were

* Author to whom correspondence should be addressed.

† Present address: Long Ashton Research Station, University of Bristol, Long Ashton, Bristol BS18 9AF, England.

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