Acta Cryst. (1977). B**33**, 2311–2313

Nialamide NF: *N*-Benzyl-β-(N^2-isonicotinoylhydrazino)propionamide Hydrochloride; Niamid® (Pfizer)

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(*Received* 25 *November* 1976; *accepted* 15 *February* 1977)

Abstract. $C_{16}H_{18}N_4O_2.HCl$, $M_r = 334{\cdot}807$, monoclinic, Cc, $a = 17{\cdot}224\,(2)$, $b = 10{\cdot}094\,(1)$, $c = 11{\cdot}052\,(1)$ Å, $\beta = 119{\cdot}6\,(1)^\circ$, $V = 1669{\cdot}2\,(1)$ Å^3, $Z = 4$, $D_x = 1{\cdot}33$ g cm^{-3}, $\mu = 2{\cdot}983$ cm^{-1}, $F(000) = 704$. Niamid was synthesized by Pfizer Laboratories as an antidepressant monoamine oxidase inhibitor. The structure was refined by least-squares calculations to an R value of 5·0%. There is a strong relation between the intramolecular geometry and the intermolecular contacts; each molecule is involved in seven hydrogen bonds and all the N atoms are proton donors.

Introduction. From this study of the crystal structure of nialamide and studies of other antidepressant drugs presently in progress, we have accumulated information about their conformations and charge distributions from which conclusions may be drawn about the structure–activity relation. It was also of interest to investigate the behaviour of the amide and hydrazide groups in the solid state, and the basicity of the N atoms.

A crystalline sample of Niamid was kindly provided by Pfizer. The sample was recrystallized by slow evaporation at room temperature from an aqueous solution. A single crystal of $\sim 0{\cdot}3 \times 0{\cdot}4 \times 0{\cdot}3$ mm was selected for the X-ray investigation. The lattice constants were obtained from a least-squares analysis of the settings of 30 reflexions measured on a four-circle diffractometer.

The intensity data were recorded with ω–2θ scans on a Philips PW 1100 diffractometer. Monochromated Mo $K\alpha$ radiation was used. Three reflexions were monitored after every 36 measurements and showed good stability. 2215 independent reflexions were collected in the range $2^\circ < \theta < 30^\circ$; of these, 826 were considered as unobserved according to the criterion $I < 2\sigma(I)$, where $I = C_p - C_{b_1} - C_{b_2}$ and $\sigma^2(I) = C_p + C_{b_1} + C_{b_2} + (0{\cdot}04I)^2$, I being the integrated intensity and $\sigma(I)$ its estimated standard deviation. Structure amplitudes were obtained after the usual Lorentz and polarization corrections. No correction for absorption was applied. The extinction effect was not appreciable.

The position of the Cl atom was located by a three-dimensional Patterson map. After refinement of the Cl position by the least-squares method, a three-dimensional Fourier ($F_o - F_c$) synthesis was calculated using the Cl phases, and four non-hydrogen atoms were located. Two more Fourier ($F_o - F_c$) syntheses, alternating with least-squares refinement, were made and the positions of all the remaining non-hydrogen atoms were located. After three cycles of full-matrix least-squares refinement (1382 observed reflexions) with isotropic temperature factors and three more cycles with anisotropic temperature factors, the conventional R value for the observed reflexions was 0·072. All H-atom positions were determined from a difference Fourier map, limiting $\sin\theta/\lambda$ to 0·5. The refinement was continued including these atoms with fixed isotropic temperature factors.

Table 1. *The positional parameters* ($\times 10^4$) *for non-hydrogen atoms*

Standard deviations are given in parentheses.

	x	y	z
Cl	5000 (0)	2524 (2)	5000 (0)
N(1)	711 (2)	2659 (4)	8001 (4)
C(1)	770 (3)	3758 (6)	7395 (5)
C(2)	954 (3)	3701 (5)	6310 (5)
C(3)	1045 (2)	2467 (5)	5844 (4)
C(4)	960 (4)	1334 (6)	6485 (6)
C(5)	811 (4)	1462 (6)	7599 (6)
C(6)	1199 (3)	2255 (5)	4620 (4)
O(1)	992 (3)	1227 (3)	3986 (4)
N(2)	1555 (3)	3296 (4)	4320 (4)
N(3)	1710 (2)	3264 (4)	3163 (3)
C(7)	2476 (3)	2438 (5)	3447 (4)
C(8)	2567 (3)	2363 (5)	2152 (5)
C(9)	2714 (3)	3723 (4)	1679 (4)
O(2)	2126 (2)	4233 (3)	597 (3)
N(4)	3505 (3)	4269 (4)	2476 (4)
C(10)	3775 (4)	5502 (6)	2107 (7)
C(11)	3690 (3)	6724 (6)	2793 (5)
C(12)	3353 (4)	6735 (7)	3704 (6)
C(13)	3322 (4)	7931 (6)	4322 (6)
C(14)	3630 (4)	9083 (7)	4066 (7)
C(15)	3950 (4)	9080 (7)	3144 (7)
C(16)	3969 (4)	7916 (6)	2500 (6)

The R value including all H atoms was 0·052 with unit weights. The $1/\sigma^2(F)$ weighting scheme was tested, but a close correlation was noticed between the $\langle w\Delta^2F \rangle$ values and $|F_o|$. The weighting scheme adopted was $w = 1/(a + b|F_o|)^2$ with $a = 1{\cdot}2468$ and $b = -0{\cdot}1554$ for $0 < F_o < 5{\cdot}73$ and $a = 0{\cdot}3674$, $b = 0{\cdot}0052$ for $5{\cdot}73 < F_o < 100$. After least-squares refinement with these weights, the final unweighted and weighted agreement indices were $R = 0{\cdot}050$ and $R_w = 0{\cdot}049$, where $R_w = (\Sigma\, w\Delta^2F/\Sigma\, w|F_o|^2)^{1/2}$. With these weights, little correlation was noticed between $\langle w\Delta^2 \rangle$ values and $\langle |F_o| \rangle$ or $\langle \sin\theta/\lambda \rangle$. A final difference synthesis showed no electron density greater than 0·1 e Å^{-3}.

Table 2. *The positional and thermal parameters (all* $\times 10^3$*) for hydrogen atoms*

Standard deviations are given in parentheses. Thermal factors are $U = B/8\pi^2$.

	x	y	z	U(Å^2)
H[N(1)]	60 (5)	288 (7)	874 (7)	46 (4)
H[C(1)]	70 (4)	464 (7)	774 (7)	46 (3)
H[C(2)]	97 (4)	455 (7)	585 (7)	40 (3)
H[C(4)]	100 (5)	52 (7)	609 (7)	56 (4)
H[C(5)]	72 (5)	72 (7)	801 (8)	59 (4)
H[N(2)]	176 (4)	393 (6)	488 (6)	33 (2)
H[N(3)]	119 (4)	282 (5)	240 (6)	23 (2)
H[C(7)]	250 (4)	157 (7)	376 (6)	42 (3)
H'[C(7)]	303 (5)	274 (7)	418 (7)	49 (3)
H[C(8)]	193 (4)	187 (7)	122 (7)	41 (3)
H'[C(8)]	304 (4)	163 (7)	229 (7)	41 (3)
H[N(4)]	380 (4)	392 (7)	303 (7)	46 (2)
H[C(10)]	435 (5)	538 (8)	234 (8)	56 (4)
H'[C(10)]	343 (5)	565 (8)	110 (8)	56 (4)
H[C(12)]	322 (5)	584 (8)	399 (8)	61 (4)
H[C(13)]	312 (5)	794 (8)	502 (8)	68 (6)
H[C(14)]	371 (5)	995 (8)	459 (9)	73 (5)
H[C(15)]	416 (5)	1002 (8)	292 (7)	63 (4)
H[C(16)]	425 (4)	797 (6)	182 (7)	43 (4)

Positional and isotropic thermal parameters, with estimated least-squares deviations in parentheses, are given in Tables 1 and 2.*

Discussion. The nialamide hydrochloride structure indicates a strong relation between the intramolecular geometry and the intermolecular contacts. As is shown on the upper left molecule of Fig. 1, each molecule is involved in seven hydrogen bonds [O(2) is shown as an H acceptor in the molecule below]. On the other hand each Cl atom accepts three hydrogen bonds. There are five independent hydrogen bonds, characterized in Table 3. As can be seen, all N atoms of the molecule are proton donors; N(1), N(3) and N(4) donate to three symmetry-related Cl atoms, while N(2) is a proton donor to the carbonyl O(2) of a neighbouring molecule. The fifth hydrogen bond is C(5)—H···O(1). The two carbonyls of the molecule are hydrogen acceptors. Comments on these interactions are made below.

Fig. 2(*b*) shows the bond distances and angles in the molecule. The phenyl and pyridine rings at the ends of the chain possess their usual geometry, and the C—N bond distances are similar to recently reported values (Martinez-Ripoll & Lorenz, 1976). They also agree with the results of CNDO/2 calculations for nitrogen-protonated pyridines (Rodriguez, Alberola & Tomas, 1976). The wide angle C(1)—N(1)—C(5) implies that N(1) is substituted (Singh & Ahmed, 1965), but in fact all the N atoms of the molecule proved to be unsubstituted in the difference electron density map. An interpretation of the singularities of the chain is represented in Fig. 2(*c*), where Linnett's (1966) model has been used to describe the best electron and charge

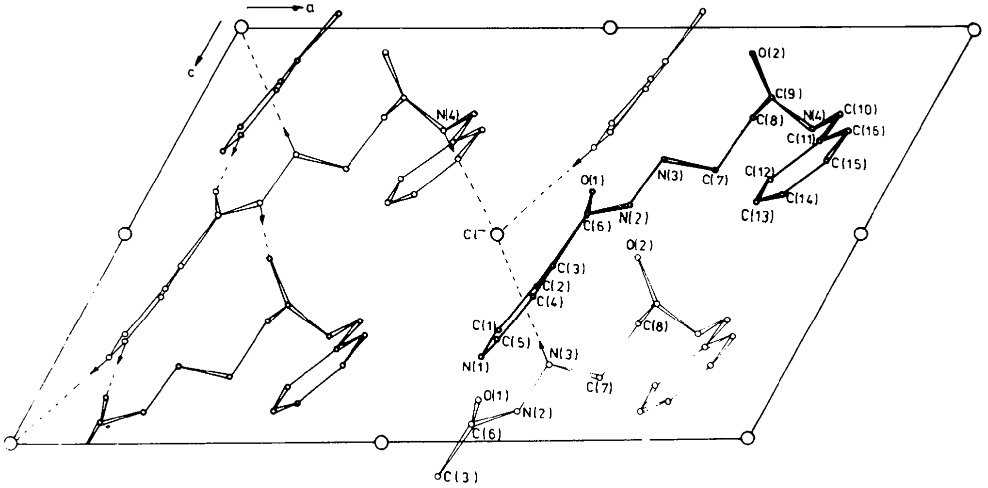

Fig. 1. Molecular packing of nialamide hydrochloride showing the hydrogen bonds.

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* Lists of structure factors and anisotropic thermal parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 32571 (10 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

Table 3. *The geometry of the hydrogen bonds* A–H$\cdots B$

Averaged s.d.'s are 0·08 Å for AH, 0·01 Å for AB and 5° for angle AHB

A–H$\cdots B$	AH	HB	AB	AHB	B in position
N(1)–H[N(1)]$\cdots$Cl	0·95 Å	2·15 Å	3·01 Å	150°	$-\frac{1}{2}+x, \frac{1}{2}-y, \frac{1}{2}+z$
N(4)–H[N(4)]$\cdots$Cl	0·95	2·32	3·24	161	x, y, z
N(3)–H[N(3)]$\cdots$Cl	0·98	2·49	3·37	156	$-\frac{1}{2}+x, \frac{1}{2}-y, -\frac{1}{2}+z$
N(2)–H[N(2)]$\cdots$O(2)	0·84	1·98	2·79	164	$x, 1-y, \frac{1}{2}+z$
C(5)–H[C(5)]$\cdots$O(1)	0·94	2·14	3·06	159	$x, -y, \frac{1}{2}+z$

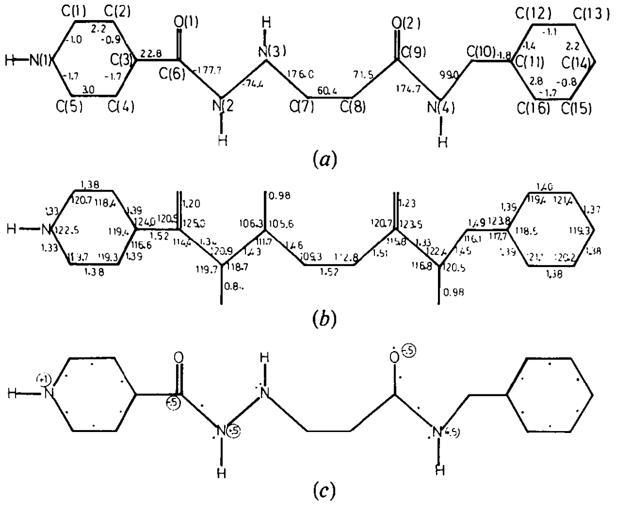

Fig. 2. The nialamide molecule. (*a*) Torsion angles, average s.d. 0·7°. (*b*) Bond distances and angles, average s.d.'s 0·01 Å and 0·7° for non-hydrogen atoms. Angles involving H atoms have a s.d. of 5°. (*c*) An electron distribution model for the molecule. A dot represents one electron.

distributions matching the X-ray model. For example, the short N–C peptide bonds are shown as three-electron bonds ($\dot{-}$) which would repel the C=O bonds, opening the bond angles in between.

The nearly planar nitrogens N(2) and N(4) indicate the presence of a lone electron per nitrogen. On the other hand the tetrahedral angles around N(3) reveal the presence of an electron pair which would strongly repel the three attached bonds. Other features of the bonding are also shown on Fig. 2(*c*).

To return to the hydrogen bonds, there are three different NH$\cdots$Cl bonds corresponding to nitrogen donors of three different basicities. The shortest, N(1)H$\cdots$Cl, is a salt bridge, where the proton from HCl has been transferred to N(1), forming the hydrogen-bonded ion pair $N^+H\cdots Cl^-$.

An interesting feature in this structure is the short hydrogen bond C(5)H$\cdots$O(1), a C(sp^2)–H$\cdots$O=C$<$ bond. This type of bond has been reported by Goldstein (1975), with C$\cdots$O distances between 3·20 and 3·35 Å. Also, Ramachandran (1967) suggests the presence of interpeptide C–H$\cdots$O=C$<$bonds in polyglycine II. For nialamide, the C$\cdots$O distance is significantly shorter (3·06 Å) and could be due to the electron-withdrawing effect of the basic N(1) towards C(5). The shortening of N(2)–N(3) could be due to the electronegativity of N(2).

Fig. 2(*a*) shows the torsion angles of the chain. Note the correspondence between the unusually long C(3)–C(6) bond and the large torsion angle of 23° for C(2)–C(3)–C(6)–N(2).

Most of the computations were performed with the XRAY system of crystallographic programs (Stewart, Kundell & Baldwin, 1970) on the 1108 Univac Computer of the Centro de Proceso de Datos del Ministerio de Educación y Ciencia, Madrid. The authors wish to thank Dr M. Martínez-Ripoll for his help with the calculations.

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