The Crystal and Molecular Structure of 4-Amino-3-(2,6-dichlorobenzylidenehydrazono)-2-methyl-1,2,4-triazoline Hydrochloride Dihydrate

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The crystal structure of the title compound has been determined by three-dimensional single crystal X-ray diffraction methods.

The crystals are triclinic, space group $P\bar{1}$, with unit cell dimensions $a = 11.722(4)$ Å, $b = 10.453(4)$ Å, $c = 7.167(2)$ Å, $\alpha = 89.55(3)°$, $\beta = 110.60(2)°$ and $\gamma = 107.66(4)°$. The structure was solved by direct methods and refined to an R-value of 0.066 for 1574 observed independent reflexions.

The cation is essentially planar. The dihedral angle between the five- and six-membered rings is 1.5°. The C−N bonds in the triazoline ring and the methylene-hydrazino chain indicate a conjugated system.

The analysis of the crystal structure of 4-amino-3-(2,6-dichlorobenzylidenehydrazono)-2-methyl-1,2,4-triazoline (A) hydrochloride dihydrate is part of a program to study the structure-activity relationships in a number of 4-amino-3-benzylidenehydrazino-1,2,4-triazole hydrochlorides.[1] Among them, 4-amino-3-(2,6-dichlorobenzylidenehydrazino)-1,2,4-triazole (B) hydrochloride was found to possess a potent antihypertensive effect.[2] A complementary series of compounds has been prepared by Eriksson and Florvall[2] in order to study the effect of structural variations in the phenyl and triazole part, the amino group and the intermediate methylene-hydrazino chain of the active compound, B-hydrochloride. The monomethylation of compound B was effected with dimethyl sulfate. Since there is a potential hydrazino-hydrazono tautomerism of B, three possible monomethylation products had to be considered.

Chemical evidence of the existence of an amino group in the methylation product was
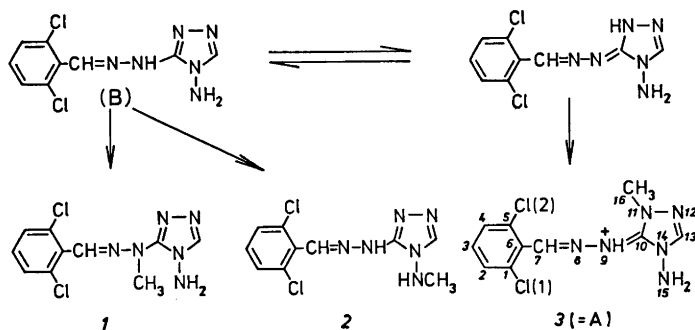

Fig. 1. Potential hydrazino-hydrazono tautomerism of 4-amino-3-(2,6-dichlorobenzylidenehydrazino)-1,2,4-triazole with possible monomethylation products.

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given by Florvall and Eriksson;[2] thereby structure 2 was excluded. It did not prove possible, however, to distinguish unambiguously between the two structural possibilities 1 and 3 by spectroscopic techniques. The present crystallographic analysis has shown that the monomethylation product of B is 3 (=A) (cf. Fig. 1); i.e. the triazole ring is methylated — not the intermediate chain.

EXPERIMENTAL

A sample of A-hydrochloride was kindly provided by Dr. L. Florvall, Astra Läkemedel AB, Södertälje. The substance was recrystallized from an ethanol — water solution of hydrogen chloride to colourless, prismatic crystals of A-hydrochloride dihydrate, $C_{10}H_{10}Cl_2N_6$·HCl.2H$_2$O. A crystal with the approximate dimensions $0.04 \times 0.07 \times 0.54$ mm^3 was mounted on an automatic diffractometer, Philips PW 1100, equipped with a graphite monochromator to reflect Cu$K\alpha$ radiation. The least-squares refined unit cell parameters given in Table 1 were derived from an X-ray powder diffraction photograph taken with strictly monochromatized Cu$K\alpha_1$ radiation in a Guinier-Hägg focussing camera using potassium chloride ($a = 6.2930$ Å) as an internal standard. The photograph was measured by an automatic film scanner system described by Malmros and Werner.[3]

Integrated intensities were obtained by the diffractometer using the $\theta - 2\theta$ scan technique. The scan speed was 1.2° min^{-1}. Backgrounds were estimated by stationary counting at $\pm 1°$ from the position of the peak maximum. Three standard reflexions were measured at regular intervals to monitor crystal stability and crystal orientation. Their intensities remained essentially constant throughout the runs. Significant counts, larger than $3\sigma_{count}$, were recorded for 1574 independent reflexions out of the 2512 accessible for $2\theta \leq 60°$. σ_{count} is the Poisson statistical counting error. Corrections were made for Lorentz and polarisation factors, but not for absorption.

Table 1. Crystal data. 4-Amino-3-(2,6-dichlorobenzylidenehydrazono)-2-methyl-1,2,4-triazoline hydrochloride dihydrate, $C_{10}H_{10}Cl_2N_5$·HCl.2H$_2$O, triclinic.

$a = 11.722(4)$ Å,	$b = 10.453(4)$ Å,	$c = 7.167(2)$ Å,
$\alpha = 89.55(3)°$	$\beta = 110.60(2)°$	$\gamma = 107.66(4)°$
$V = 778.4$ Å^3,	FW = 357.6,	$Z = 2$.
$D_{calc} = 1.526$ g cm^{-3}. Space group $P\bar{1}$.		

STRUCTURE DETERMINATION AND REFINEMENT

The structure was determined by use of the program system MULTAN,[4] starting with 300 reflexions with $|E| \geq 1.24$. An E map calculated from the set of phases with the highest combined figure of merit revealed the positions of all non-hydrogen atoms. Full-matrix least-squares refinements were performed using a modified version of the program LALS.[5] Weights were assigned as $1/\sigma(F)^2$, where $\sigma(F)$ was determined from the value σ_{cs} (F) yielded by counting statistics with a 2.5 % addition for instrumental instability according to the formula:

$$\frac{\sigma(F)}{F} = \left[\left(\frac{\sigma_{cs}(F)}{F} \right)^2 + \left(\frac{2.5}{100} \right)^2 \right]^{1/2}$$

The atomic scattering factors for oxygen, nitrogen and carbon were taken from Freeman,[6] for chlorine from International Tables for X-Ray Crystallography,[7] and for hydrogen from Stewart, Davidson and Simpson.[8]

The positions of all hydrogen atoms except those from the water molecules were derived partly from chemical and geometrical considerations and partly from difference synthesis maps. The hydrogen atom parameters were not refined but included in the structure factor calculations using an isotropic temperature factor of 4 Å^2. The four crystal water hydrogen atoms were not included in the calculations. For all non-hydrogen atoms anisotropic temperature factors were used. The positional and thermal parameters of these atoms were refined to an R value of 0.066. The final atomic parameters are listed in Table 2. A list of the observed and calculated structure factors may be obtained from the author on request.

RESULTS AND DISCUSSION

The molecular structure revealed by this analysis is the triazoline 3 shown in Fig. 1. The atomic numbering is given in the figure, and a perspective view of the cation and the chloride ion is shown in Fig. 2. The bond lengths and bond angles, uncorrected for thermal motion, are listed in Table 3.

The average C—Cl distance, 1.736Å, is in agreement with the distance 1.737 Å reported

Table 2. Atomic coordinates and thermal parameters with their standard deviations. The anisotropic temperature factor is of the form $\exp - (\beta_{11}h^2 + \beta_{22}k^2 + \beta_{33}l^2 + \beta_{12}hk + \beta_{13}hl + \beta_{23}kl)$.

Atom	x/a	y/b	z/c	β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
(a) Non-hydrogen atoms ($\times 10^4$)									
Cl(1)	8630(2)	6981(2)	8263(4)	64(2)	52(2)	332(9)	10(4)	159(7)	−6(7)
Cl(2)	4163(2)	2833(2)	7049(5)	64(2)	43(2)	367(9)	11(2)	125(7)	26(7)
Cl(3)	2971(3)	512(2)	1090(5)	106(3)	65(13)	429(11)	49(4)	221(9)	25(8)
C(1)	7706(7)	5281(7)	7875(12)	59(8)	37(8)	138(24)	−1(12)	40(23)	27(21)
C(2)	8363(8)	4377(8)	7886(15)	79(9)	72(9)	248(30)	78(15)	148(28)	34(27)
C(3)	7684(9)	2999(8)	7650(15)	95(10)	77(11)	260(31)	102(16)	140(29)	72(27)
C(4)	6424(8)	2561(7)	7428(14)	93(10)	39(8)	224(28)	61(14)	89(27)	43(23)
C(5)	5776(8)	3494(7)	7404(13)	61(8)	54(8)	151(25)	16(13)	52(24)	17(22)
C(6)	6418(8)	4910(7)	7674(13)	64(8)	48(7)	137(22)	42(12)	82(21)	21(19)
C(7)	5850(7)	5963(7)	7705(13)	52(8)	52(8)	174(25)	35(12)	51(23)	28(22)
N(8)	4694(6)	5782(6)	7540(11)	54(7)	47(6)	195(22)	46(11)	83(20)	33(18)
N(9)	4395(6)	6961(6)	7616(11)	54(7)	43(7)	231(23)	38(11)	75(20)	15(19)
C(10)	3213(7)	6901(7)	7433(12)	53(8)	58(8)	132(23)	63(13)	72(22)	23(21)
N(11)	2157(6)	5885(6)	7181(11)	55(7)	44(6)	186(21)	32(11)	69(19)	32(18)
N(12)	1139(6)	6312(7)	7022(12)	60(7)	84(9)	248(25)	52(12)	116(22)	32(22)
C(13)	1609(8)	7618(8)	7201(15)	76(10)	74(9)	258(31)	59(15)	106(28)	35(27)
N(14)	2858(6)	8027(6)	7429(11)	48(7)	60(7)	236(23)	37(11)	97(20)	13(20)
N(15)	3736(7)	9349(6)	7632(13)	77(7)	38(7)	364(28)	34(11)	152(24)	41(21)
C(16)	1934(9)	4411(8)	6100(15)	84(9)	46(8)	233(29)	15(14)	120(27)	0(24)
O(1)	8500(6)	171(6)	6038(11)	118(8)	100(7)	289(22)	86(12)	156(21)	81(20)
O(2)	1202(8)	1259(7)	7084(13)	159(10)	130(9)	436(29)	44(15)	240(29)	−29(26)

(b) Hydrogen atoms ($\times 10^4$)

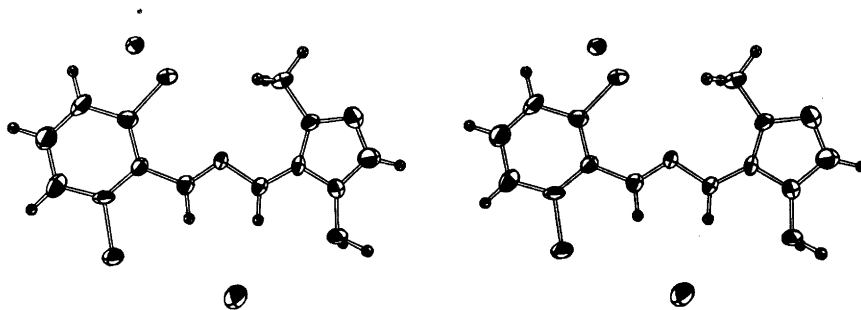| Atom	x/a	y/b	z/c
H(2)	9319	4719	8080
H(3)	8153	2329	7626
H(4)	5954	1560	7294
H(7)	6427	6932	7877
H(9)	5077	7865	7811
H(13)	1091	8245	7203
H(151)	3750	9860	9000
H(152)	3500	9860	6600
H(161)	2705	4104	8037
H(162)	1826	4090	5608
H(163)	1128	3915	7248

Fig. 2. Stereoscopic view of the cation and the chloride ions in the crystal structure. The non-hydrogen atoms are represented by thermal ellipsoids scaled to include 50 % probability.

Table 3. Bond lengths and bond angles with their standard deviations.

(a) Bond distances (Å)

Cl(1)	−C(1)	1.742(7)
Cl(2)	−C(5)	1.729(8)
C(1)	−C(2)	1.387(10)
C(1)	−C(6)	1.394(10)
C(2)	−C(3)	1.397(11)
C(3)	−C(4)	1.358(12)
C(4)	−C(5)	1.403(10)
C(5)	−C(6)	1.422(10)
C(6)	−C(7)	1.453(10)
C(7)	−N(8)	1.272(9)
N(8)	−N(9)	1.386(8)
N(9)	−C(10)	1.327(9)
C(10)	−N(11)	1.319(9)
C(10)	−N(14)	1.361(9)
N(11)	−N(12)	1.365(8)
N(11)	−C(16)	1.481(9)
N(12)	−C(13)	1.296(10)
C(13)	−N(14)	1.344(10)
N(14)	−N(15)	1.423(8)

(b) Bond angles (deg)

Cl(1)	−C(1)	−C(2)	115.2(6)
Cl(1)	−C(1)	−C(6)	120.2(6)
C(2)	−C(1)	−C(6)	124.5(7)
C(1)	−C(2)	−C(3)	117.8(8)
C(2)	−C(3)	−C(4)	121.0(8)
C(3)	−C(4)	−C(5)	120.2(7)
Cl(2)	−C(5)	−C(4)	116.6(6)
Cl(2)	−C(5)	−C(6)	121.8(6)
C(4)	−C(5)	−C(6)	121.6(7)
C(1)	−C(6)	−C(5)	114.9(7)
C(1)	−C(6)	−C(7)	118.9(7)
C(5)	−C(6)	−C(7)	126.2(7)
C(6)	−C(7)	−N(8)	126.0(7)
C(7)	−N(8)	−N(9)	114.5(6)
N(8)	−N(9)	−C(10)	120.1(6)
N(9)	−C(10)	−N(11)	132.9(7)
N(9)	−C(10)	−N(14)	122.4(6)
N(11)	−C(10)	−N(14)	105.0(7)
C(10)	−N(11)	−N(12)	112.2(6)
C(10)	−N(11)	−C(16)	129.8(6)
N(12)	−N(11)	−C(16)	118.0(6)
N(11)	−N(12)	−C(13)	104.2(6)
N(12)	−C(13)	−N(14)	111.4(7)
C(10)	−N(14)	−C(13)	107.5(6)
C(10)	−N(14)	−N(15)	122.0(6)
C(13)	−N(14)	−N(15)	130.5(6)

by Rudman [9] for aromatic C−Cl bonds, which are not adjacent to other C−Cl bonds. The bond angle C(1)−C(6)−C(7) (118.9°) is 7.3° less than the angle C(5)−C(6)−C(7), 126.2°. This fact may be attributed to a repulsion between Cl(2) and N(8). The three N−N bonds

are all in resonance between a double bond, 1.26 Å, and a single bond 1.46 Å[10]. C(7)−N(8), 1.272 Å, is a pure double bond. Also N(12)−C(13), 1.296 Å, is within the limits of error a double bond. The remaining C−N bonds in the five-membered ring and in the intermediate chain all show some degree of double bond character, thus indicating a conjugated system.

The cation is essentially planar. The dihedral angle between the benzylidene and the tri-

Table 4. Least-squares planes. The planes are described in terms of an orthogonal vector basis. $\mathfrak{p} \| \mathfrak{c}$ and $\mathfrak{n}$ in the $\mathfrak{bc}$-plane.

Plane A: $0.2600\mathfrak{m} - 0.0743\mathfrak{n} + 0.9627\mathfrak{p} = 4.2950$
Plane B: $0.2623\mathfrak{m} - 0.0777\mathfrak{n} + 0.9619\mathfrak{p} = 4.3111$
Plane C: $0.2506\mathfrak{m} - 0.0497\mathfrak{n} + 0.9668\mathfrak{p} = 4.4553$

Perpendicular distances of atoms (in Å) from the least-squares planes

Plane A		Plane B		Plane C	
C(1)	−0.005	C(6)	−0.002	C(10)	0.003
C(2)	−0.001	C(7)	−0.003	N(11)	0.001
C(3)	0.001	N(8)	0.008	N(12)	−0.005
C(4)	0.005	N(9)	0.003	C(13)	0.007
C(5)	−0.011	C(10)	−0.004	N(14)	−0.006
C(6)	0.011	N(11)	−0.001	N(15)[a]	−0.030
C(7)[a]	0.016			C(16)[a]	−0.033
Cl(1)[a]	0.051				
Cl(2)[a]	−0.048				

[a] These atoms are not included in the least-squares planes.

Table 5. Hydrogen-bond distances and code for superscripts.

Hydrogen-bond distances (Å)

O(1)	.. O(2[i])	2.835(10)
O(1)	.. O(2[ii])	2.877(10)
Cl(3)	.. O(1[ii])	3.074(7)
Cl(3)	.. O(2[iii])	3.148(8)
Cl(3)	.. N(9[iv])	3.232(6)
Cl(3)	.. N(15[v])	3.270(8)

Code for superscripts:

i		$1+x,y,z$
ii		$1-x,-y,1-z$
iii		$x,y,z-1$
iv		$1-x,1-y,1-z$
v		$x,y-1,z-1$

azoline ring is 1.5°. Details of least-squares planes calculated for various portions of the molecular frameworks are given in Table 4.

The protonated N(9) and N(15) are hydrogen bonded to the chloride ions (*cf.* Table 5). Chains of crystal water, also hydrogen bonded to the chloride ions, are present in the structure. The hydrogen bonds are summarized in Table 5.

A discussion of the structure-activity relations and a comparison with three other closely related compounds is given by Werner, Florvall and Stjernström.[1]

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