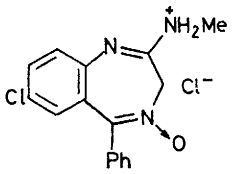
Protonation Sites of Organic Bases with Several Nitrogen Functions: Crystal Structures of Salts of Chlordiazepoxide, Dihydralazine, and Phenformin †

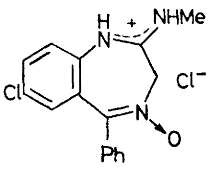
By **Cornelia Herrnstadt, Dietrich Mootz,** * and **Hartmut Wunderlich**, Institut für Anorganische Chemie und Strukturchemie, Universität Dusseldorf, 4000 Düsseldorf, Germany
Hans Möhrle, Institut für Pharmazeutische Chemie, Universität Düsseldorf, 4000 Düsseldorf, Germany

The crystal structures of 7-chloro-2-methylamino-5-phenyl-3*H*-1,4-benzodiazepine 4-oxide (chlordiazepoxide) hydrochloride (1), 1,4-dihydrazinophthalazine (dihydralazine) hydrosulphate trihydrate (2), and 1-(2-phenylethyl)biguanide (phenformin) hydrochloride (3) have been determined by *X*-ray diffraction. All have space group $P2_1/c$, and for (1): a = 13.120(5), b = 8.439(3), c = 15.070(6) Å, β = 107.81(3)°, Z = 4; for (2) a = 6.966(3), b = 11.099(4), c = 19.005(5) Å, β = 104.72(3)°, Z = 4; and for (3) a = 14.947(5), b = 9.396(3), c = 20.345(7) Å, β = 116.73(3), Z = 8. In (1) and (2) protonation occurs at a ring nitrogen atom, leading to amidinium systems. The second proton in (2) is attached to a terminal hydrazine nitrogen. The two independent cations in (3) have the same tautomeric form $RHN{\cdot}C(NH_2)NC(NH_2)_2$. The structure of (1) was determined by direct methods, those of (2) and (3) by the heavy-atom method. The structures were refined to R 0.059, 0.076, and 0.082 for 2 967, 2 015, and 4 672 observed intensities.

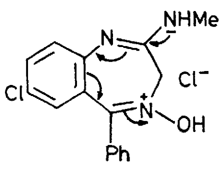
Of the 1,4-benzodiazepines, which are an important group of tranquilizers,[1] chlordiazepoxide (7-chloro-2-methylamino-5-phenyl-3*H*-1,4-benzodiazepine 4-oxide) was the first of medicinal relevance, introduced into therapy as its hydrochloride, Librium (1). Protonation of the base was first believed to occur at the methyl-amino-nitrogen [2] (1a). This view was retained in the description of the drug [3] although on the basis of an n.m.r. study [4] structure (1a) had been rejected and the resonance-stabilized amidinium salt (1b) prepared. A determination of pK_a values of 1,4-benzodiazepines by u.v. spectroscopy [5] had led to the assumption of still another structure (1c) with the proton at the nitrone oxygen.



(1a)



(1b)

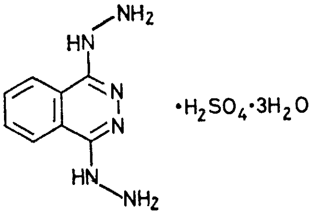


(1c)

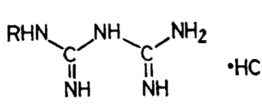
Since (1c) could not be ruled out completely by the results of the n.m.r. study [4] nor by ESCA measurements, final confirmation was sought by crystal-structure analysis. The structures of dihydralazine (1,4-dihydrazinophthalazine) (Nepresol), as its hydrosulphate trihydrate (2), and phenformin [1-(2-phenylethyl)biguanide] (Dipar), as its hydrochloride (3), were also determined in order to establish their tautomeric form.

As a member of the hydrazinonaphthalazine group of antihypertensives,[6] dihydralazine is recorded in several pharmacopoeias.[7] Protonation is formulated at the two terminal amino-groups. Obviously, this is in keeping with an assumed substituted hydrazine character of the base. The alternative amide hydrazone model would require a different mode of protonation, since amide hydrazones, like amidines, are known to form resonance-stabilized cations.

Phenformin and buformin (3; R = Bu^n) as oral hypoglycemic agents, have recently been strongly suspected of the side effect of a lactacidosis,[8] which is fatal in about 50% of all cases, and consequently have been withdrawn from the market in the U.S.A.[9] and W. Germany.[10] Both biguanides are recorded with the tautomeric form of the base as in (3) and the extra proton with phenformin at the terminal imino-group [11] and with buformin at the terminal amino-group.[12] These forms appear unlikely since they are not optimally stabilized by resonance.[13]



(2)



(3) R = $PhCH_2{\cdot}CH_2$

EXPERIMENTAL

Samples of the compounds were obtained from Hoffmann–La Roche, Grenzach/Baden, (1), Ciba–Geigy, Wehr/Baden, (2), and Hoechst, Frankfurt/Main, (3).

Librium (1) and Dipar (3) were crystallized from methanol, and Nepresol (2) from water. Densities were measured by displacement (cyclohexane) and flotation (cyclohexane–chloroform). For the *X*-ray experiments crystals were mounted on quartz fibres. Space groups were

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† Trade names Librium®, Nepresol®, and Dipar®, respectively.

TABLE 1

Crystal data and details of the structure refinements

		(1)	(2)	(3)
Formula		$C_{16}H_{14}N_3OCl{\cdot}HCl$	$C_8H_{10}N_6{\cdot}H_2SO_4{\cdot}3H_2O$	$C_{10}H_{15}N_5{\cdot}HCl$
M		336.2	342.3	241.7
Space group		$P2_1/c$	$P2_1/c$	$P2_1/c$
Z		4	4	8
a/Å		13.120(5)	6.966(3)	14.947(5)
b/Å		8.439(3)	11.099(4)	9.396(3)
c/Å		15.070(6)	19.005(5)	20.345(7)
β/°		107.81(3)	104.72(3)	116.73(3)
U/Å^3		1 589(1)	1 421(1)	2 552(2)
D_m/g cm^{-3}		1.39	1.57	1.25
D_c/g cm^{-3}		1.41	1.60	1.26
μ(Mo-K_α)[cm^{-1}]		4.2	2.8	2.9
2 $\theta_{max.}$/° (Mo-K_α)		60	55	60
Reflectns. (total)		4 761	3 503	7 679
Reflectns. (obs.) *		2 967	2 015	4 672
K †		0.02	0.00	0.00
Variables (last run)		259	259	289
Obs. data:	R	0.059	0.076	0.082
	R'	0.065	0.059	0.144
All data:	R	0.109	0.135	0.128
	R'	0.078	0.063	0.145

* Having $I > 1.96\sigma(I)$. † In $1/w = \sigma_F^2 + (K{\cdot}F)^2$.

determined by film methods, and unit-cell dimensions from positioning of fifteen strong high-order reflections on a Syntex P2$_1$ diffractometer with Mo-K_α radiation.

TABLE 2

Atom co-ordinates (non-hydrogen atoms ×10^4, hydrogen atoms ×10^3) for chlordiazepoxide hydrochloride (1), as fractions of the unit-cell edges

Atom	x	y	z
Cl(1)	8 934(1)	138(1)	501(1)
Cl(2)	6 169(1)	6 614(1)	−2 683(1)
O(1)	6 603(2)	−307(3)	−4 627(1)
N(1)	6 104(2)	2 991(3)	−2 967(2)
N(2)	4 646(2)	2 654(3)	−4 296(2)
N(4)	6 684(2)	102(3)	−3 773(2)
C(2)	5 441(2)	2 104(3)	−3 615(2)
C(3)	5 653(2)	361(3)	−3 585(2)
C(4)	4 215(4)	4 257(5)	−4 343(3)
C(5)	7 588(2)	412(3)	−3 117(2)
C(6)	8 186(2)	386(4)	−1 383(2)
C(7)	8 191(2)	1 037(4)	−537(2)
C(8)	7 595(2)	2 367(4)	−491(2)
C(9)	6 933(2)	3 005(4)	−1 301(2)
C(10)	6 859(2)	2 324(3)	−2 163(2)
C(11)	7 518(2)	1 045(3)	−2 216(2)
C(12)	8 633(2)	239(3)	−3 283(2)
C(13)	8 825(3)	−862(4)	−3 906(2)
C(14)	9 819(3)	−929(5)	−4 046(2)
C(15)	10 636(2)	66(4)	−3 566(2)
C(16)	10 467(3)	1 144(4)	−2 939(3)
C(17)	9 473(2)	1 235(4)	−2 797(2)
H(1)	602(3)	397(4)	−292(2)
H(2)	421(3)	193(4)	−468(3)
H(31)	567(2)	−5(3)	−298(2)
H(32)	512(2)	−19(3)	−406(2)
H(41)	378(3)	443(4)	−499(3)
H(42)	477(4)	504(5)	−412(3)
H(43)	383(4)	440(6)	−391(4)
H(6)	862(2)	−50(3)	−143(2)
H(8)	765(3)	283(4)	7(2)
H(9)	648(3)	397(4)	−124(3)
H(13)	824(3)	−156(4)	−422(2)
H(14)	992(3)	−175(5)	−442(3)
H(15)	1 132(3)	1(4)	−369(2)
H(16)	1 109(4)	196(6)	−253(3)
H(17)	935(3)	203(4)	−231(2)

The same instrument and radiation (graphite monochromatized) served for data collection by the ω-scan technique. During data collection the intensities of three reference reflections remained constant indicating crystal stability. Data processing was carried out in the usual way without correction for absorption. Table 1 gives basic crystallographic information as well as some experimental values and computational figures.

TABLE 3

Atom co-ordinates (non-hydrogen atoms ×10^4, hydrogen atoms ×10^3) for dihydralazine hydrosulphate trihydrate (2), as fractions of the unit-cell edges

Atom	x	y	z
S	5 139(2)	5 534(1)	3 261(1)
O(1)	5 180(6)	6 565(3)	2 773(2)
O(2)	4 730(6)	5 984(4)	3 935(2)
O(3)	7 093(6)	4 937(3)	3 434(2)
O(4)	3 588(7)	4 713(4)	2 893(2)
O(5)	1 758(6)	−2 059(4)	2 229(2)
O(6)	6 876(12)	−698(6)	322(3)
O(7)	9 490(13)	3 862(6)	4 609(3)
N(1)	1 498(7)	−889(4)	3 535(2)
N(2)	1 872(6)	296(4)	3 393(2)
N(3)	1 056(7)	−2 503(4)	4 220(3)
N(4)	417(9)	−3 157(8)	3 561(3)
N(5)	2 903(7)	2 166(4)	3 820(2)
N(6)	2 433(8)	2 493(4)	3 061(2)
C(1)	1 544(7)	−1 356(5)	4 177(3)
C(2)	2 387(7)	989(5)	3 952(3)
C(3)	3 266(8)	1 383(5)	5 301(3)
C(4)	3 406(9)	972(6)	5 981(3)
C(5)	2 906(8)	−224(5)	6 114(3)
C(6)	2 299(8)	−1 000(5)	5 526(3)
C(7)	2 142(7)	−594(5)	4 812(2)
C(8)	2 624(7)	632(4)	4 695(3)
H(1)	361(5)	215(3)	523(2)
H(2)	392(7)	136(4)	633(2)
H(3)	289(6)	− 52(4)	664(2)
H(4)	178(8)	−183(5)	560(3)
H(5)	74(9)	−278(5)	461(3)
H(6)	141(8)	−366(4)	354(3)
H(7)	−65(8)	−361(4)	362(3)
H(8)	275(9)	280(5)	409(3)
H(9)	83(11)	249(6)	288(3)
H(10)	281(11)	338(8)	293(4)
H(11)	333(9)	206(5)	276(3)
H(12)	99(6)	−132(4)	317(2)
H(13)	286(10)	−256(6)	231(3)
H(14)	230(9)	−155(6)	205(3)
H(15)	1 045(11)	405(7)	454(4)
H(16)	871(10)	403(6)	422(3)

The structure of (1) was solved by direct methods, those of (2) and (3) by the heavy-atom method. The unsuspected presence of three water molecules in (2) was established during the structure determination and their presence was later confirmed by chemical analysis.

TABLE 4

Atom co-ordinates (non-hydrogen atoms $\times 10^4$, hydrogen atoms $\times 10^3$) for phenformin hydrochloride (3), as fractions of the unit-cell edges. The first digit (1 or 2) of the atom number denotes the respective independent formula unit

Atom	x	y	z
Cl(1)	8 783(2)	1 256(2)	573(1)
Cl(2)	1 363(2)	1 068(2)	3 041(1)
N(11)	8 844(6)	4 846(7)	524(3)
N(12)	8 527(6)	3 834(7)	−570(4)
N(13)	8 657(5)	6 262(6)	−496(3)
N(14)	9 225(5)	8 555(7)	−272(5)
N(15)	8 102(5)	7 877(6)	152(4)
C(10)	8 671(6)	5 014(8)	−168(4)
C(11)	8 662(6)	7 528(7)	−194(4)
C(12)	7 130(6)	7 268(8)	9(5)
C(13)	6 301(6)	7 916(11)	−652(5)
C(14)	5 274(6)	7 564(8)	−722(4)
C(15)	4 925(6)	6 159(9)	−796(5)
C(16)	3 977(6)	5 854(10)	−857(5)
C(17)	3 372(6)	6 942(12)	−837(5)
C(18)	3 677(7)	8 301(11)	−775(6)
C(19)	4 623(8)	8 627(9)	−720(5)
N(21)	8 652(5)	5 332(6)	−2 985(4)
N(22)	8 809(5)	6 342(6)	−1 922(3)
N(23)	8 483(5)	3 966(6)	−2 059(3)
N(24)	9 201(5)	2 314(6)	−2 568(4)
N(25)	7 907(5)	1 658(6)	−2 303(4)
C(20)	8 666(5)	5 166(7)	−2 319(4)
C(21)	8 531(5)	2 663(7)	−2 323(4)
C(22)	6 975(5)	1 954(8)	−2 253(4)
C(23)	6 717(7)	763(9)	−1 877(5)
C(24)	5 752(6)	1 128(9)	−1 842(5)
C(25)	5 765(7)	1 934(9)	−1 267(5)
C(26)	4 843(8)	2 320(9)	−1 271(6)
C(27)	3 928(8)	1 920(11)	−1 851(7)
C(28)	3 897(8)	1 095(13)	−2 418(6)
C(29)	4 821(8)	697(11)	−2 403(6)

Atom	$n = 1$			$n = 2$		
H(n01)	901	551	82	869	469	−319
H(n02)	911	386	78	894	714	−208
H(n03)	844	383	−87	887	628	−157
H(n04)	975	840	−45	893	289	−243
H(n05)	943	944	6	930	143	−259
H(n06)	817	867	17	791	74	−250
H(n07)	700	633	−17	646	195	−279
H(n08)	699	757	49	706	283	−199
H(n09)	653	891	−66	660	−6	−219
H(n10)	640	777	−112	718	80	−140
H(n11)	533	533	−83	653	220	−84
H(n12)	367	478	−88	483	300	−83
H(n13)	290	666	−77	323	224	−183
H(n14)	322	928	−84	318	76	−295
H(n15)	467	967	−83	485	0	−283

During refinement by the method of full-matrix least-squares all hydrogen atoms of (1) and all but two each of (2) and (3) were located in difference electron-density maps. Refinement was completed with anisotropic thermal parameters for the non-hydrogen atoms and isotropic ones for the hydrogen atoms. Thermal parameters of four hydrogen atoms of (2) and all hydrogen atom parameters of (3) were not refined.

All computations were done on an Eclipse computer (Data General) using the program system EXTL (Syntex) with atomic scattering factors as incorporated. The weighting scheme is detailed in Table 1. Final atomic co-ordinates for the three structures are listed in Tables 2—4. Thermal parameters, observed and calculated structure factors, and bonds and angles involving hydrogen atoms (see later) are listed in Supplementary Publication No. SUP 22426 (57 pp., 1 microfiche).*

RESULTS AND DISCUSSION

Figure 1 [14] shows two formula units of Librium (1) with interatomic distances and angles, linked across the inversion centre at 1/2, 0, 1/2 into a centrosymmetric dimer by NH · · · O and NH · · · Cl hydrogen bonds [N · · · O 2.760(3), N · · · Cl 3.085(3) Å]. The organic base is protonated at the ring nitrogen atom N(1). Thus the result of the low-temperature n.m.r. study of (1) in solution [4] is substantiated for the solid state. The seven-membered ring is in a boat form with carbon atom C(3) at the bow and C(10) and C(11) at the stern. Similar conformations have been observed in the crystal structures of three other 1,4-benzodiazepines with related substitution patterns, diazepam,[15] lorazepam,[16] and nitrazepam.[17]

TABLE 5

Hydrogen bonding distances (Å) and angles (°) in dihydralazine hydrosulphate trihydrate (2); D = proton donor, A = proton acceptor

D–H · · · A	D–H	H · · · A	D · · · A	D–H · · · A
N(1)–H(12) · · · O(5)	0.84(4)	2.16(4)	2.847(6)	139(4)
N(3)–H(5) · · · O(7^{I})	0.88(6)	1.95(6)	2.793(8)	160(6)
N(4)–H(6) · · · O(2^{II})	0.91(5)	2.27(5)	3.059(8)	145(4)
N(4)–H(7) · · · O(3^{III})	0.93(5)	2.22(5)	3.100(7)	159(4)
N(5)–H(8) · · · O(6^{IV})	0.89(6)	1.99(6)	2.859(8)	165(6)
N(6)–H(9) · · · O(5^{V})	1.08(8)	1.83(8)	2.873(7)	160(6)
N(6)–H(10) · · · O(4^{VI})	1.06(9)	1.59(9)	2.636(7)	170(7)
N(6)–H(11) · · · O(1^{VI})	1.06(6)	1.72(6)	2.772(6)	171(5)
O(5)–H(13) · · · O(1^{II})	0.93(7)	1.90(7)	2.799(6)	162(6)
O(5)–H(14) · · · O(3^{VI})	0.80(7)	1.99(7)	2.765(6)	164(7)
O(6) * · · · O(2^{VI})			2.745(8)	
O(6) * · · · O(2^{VII})			2.698(7)	
O(7)–H(15) · · · O(6^{IV})	0.74(8)	1.84(8)	2.549(12)	160(6)
O(7)–H(16) · · · O(3)	0.82(6)	1.92(6)	2.703(8)	161(6)

Roman numeral superscripts denote atoms A in the following equivalent positions relative to the reference molecule at x, y, z:

I	$1 - x, -y, 1 - z$	V	$-x, \frac{1}{2} + y, \frac{1}{2} - z$
II	$x, -1 + y, z$	VI	$1 - x, -\frac{1}{2} + y, \frac{1}{2} - z$
III	$-1 + x, -1 + y, z$	VII	$x, \frac{1}{2} - y, -\frac{1}{2} + z$
IV	$1 - x, \frac{1}{2} + y, \frac{1}{2} - z$		

* Involving probable positions of the two hydrogen atoms not located by the structure analysis, since atom O(2) can only serve as proton acceptor and atom O(6) already is an acceptor in two other hydrogen bonds

Figure 2 [14] shows the doubly protonated base molecule of Nepresol (2) with interatomic distances and angles. Protonation is at the ring nitrogen atom N(1), leading, as in (1), to a resonance-stabilized amidinium system, and at the terminal nitrogen atom N(6) of the opposite hydrazine group. The S–O bond lengths and O–S–O bond angles in the sulphate anion have values between 1.451(5) and 1.478(4) Å and between 108.3(3) and

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* See Notice to Authors No. 7 in *J.C.S. Perkin II*, 1978, Index issue.

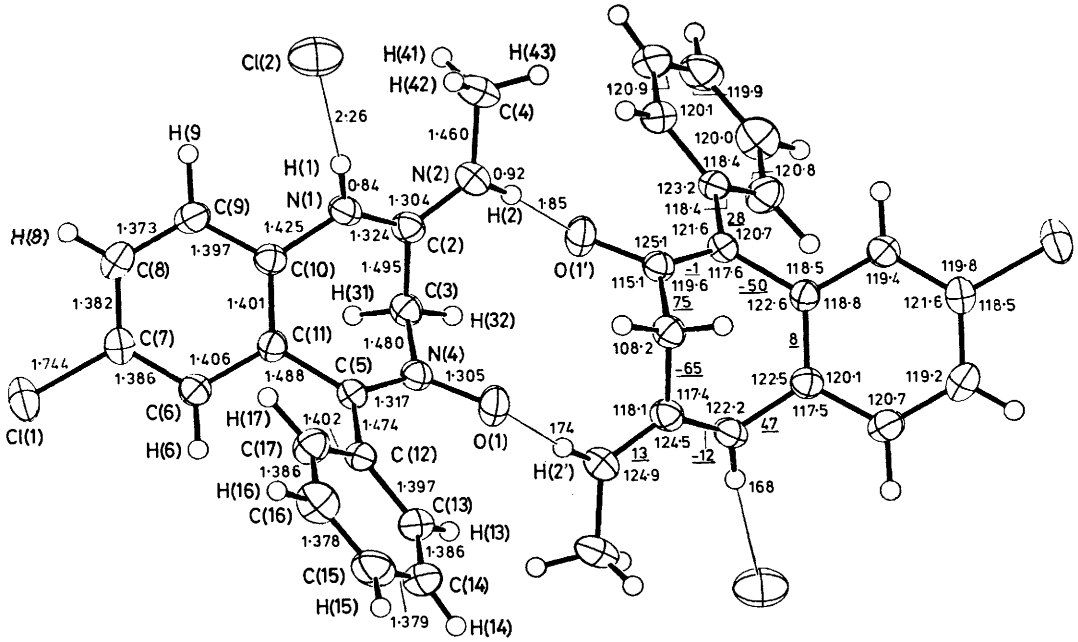
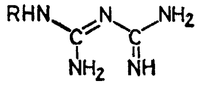


FIGURE 1 Two formula units of chlordiazepoxide hydrochloride (1), hydrogen-bonded across a centre of symmetry. Standard deviations of bond lengths (Å) and angles (°) between non-hydrogen atoms are 0.003—0.005 Å and 0.2—0.3°. Underlined numbers are torsion angles (°)

111.0(3)°. The organic cation with its various proton donating functions, the water molecules as proton donors and acceptors, and the sulphate ion as a multiple acceptor generate a three-dimensional hydrogen-bonded network (Table 5).

The two independent protonated base molecules of Dipar (3) with interatomic distances and angles are shown in Figure 3.[14] They form a hydrogen-bonded dimer through two NH • • • N hydrogen bonds. Protonation sites are not directly evident, since two of the hydrogen atoms, one for each molecule, did not show up in the difference electron-density map and consequently are missing in Table 4 and Figure 3. The hydrogen atoms located probably describe the preferred tautomeric form of the free base (4) and protonation of each of the



$$RHN{-}C(NH_2){=}N{-}C(NH_2){=}NH$$

(4)

two independent molecules occurs at the terminal imino-group. This would allow maximum delocalization of C–N double bonds and positive charge and would correspond to the crystal structures of unsubstituted biguanide[18] and its hydrochloride.[19] The correctness of this model is corroborated by the hydrogen-

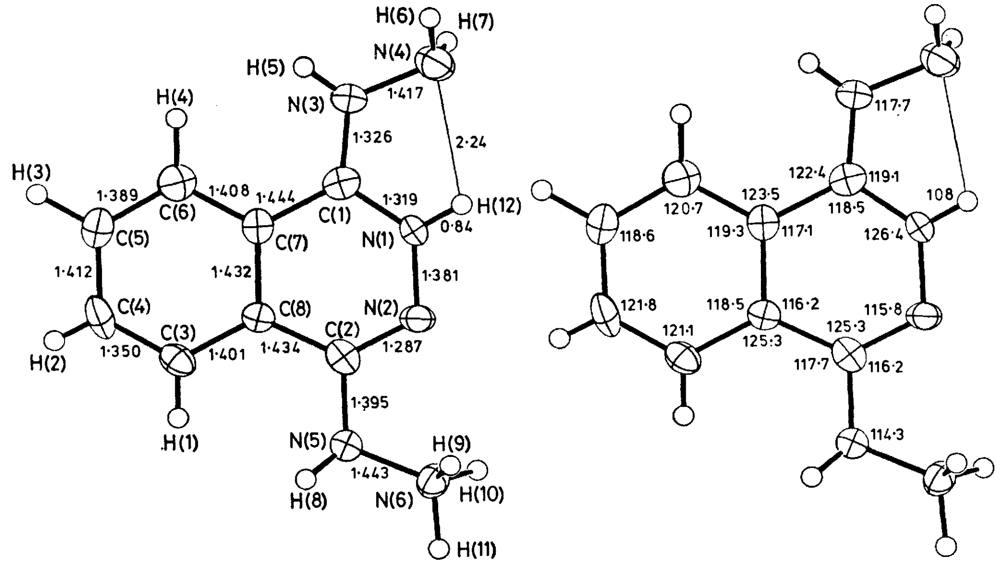


FIGURE 2 The doubly protonated base molecule of dihydralazine (2). Standard deviations of bond lengths (Å) and angles (°) between non-hydrogen atoms are 0.006—0.008 Å and 0.4—0.6°

bonding scheme (see later) and by the observation that bond lengths involving C(n0)and C(n1) are all similar and intermediate between single- and double-bond values. Note, however, that in (3) and in biguanide hydrochloride,[19] as in other related compounds,[20] the protonated biguanide moiety does not achieve an overall planar conformation (see Figure 3, which gives relevant torsion angles).

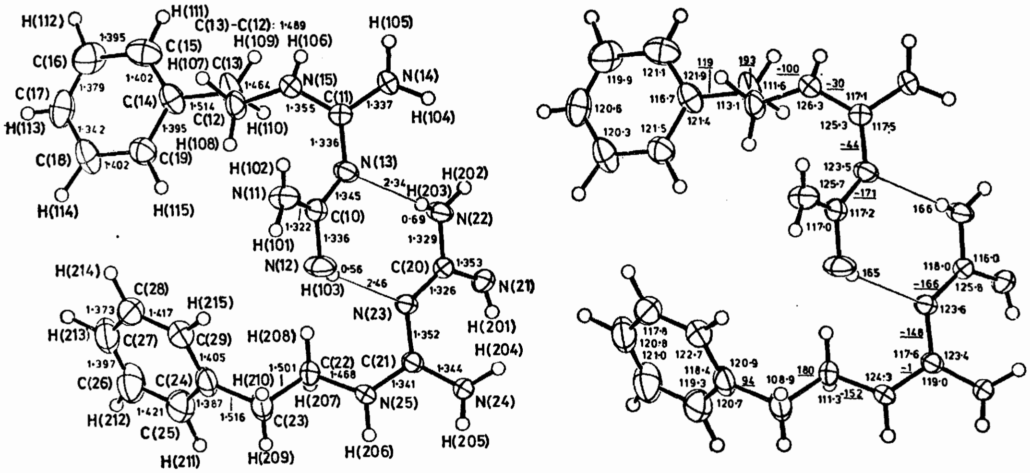


FIGURE 3 The two independent cations of phenformin hydrochloride (3) linked into a hydrogen-bonded dimer. Two protons, one at N(12) and one at N(21) are not shown since they were not directly located from the X-ray data. Standard deviations of bond lengths (Å) and bond angles (°) between non-hydrogen atoms are 0.009—0.018 Å and 0.7—1.1°. Underlined numbers are torsional angles (°)

Figure 4 [14] shows the packing mode of the dimers of (3) in the crystal structure, which is composed of alternating parallel layers (100) of hydrophobic (phenethyl groups, van der Waals bonding) and hydrophilic (protonated biguanide moieties and chloride anions, hydrogen bonded NH • • • N and NH • • • Cl) structural elements and interactions. The hydrogen bonding is analysed in Table 6. The resulting network is unlimited along the b and c axis directions with the phenethyl groups sticking out into the third dimension along a and $-a$ and interleaving with those of neighbouring systems.

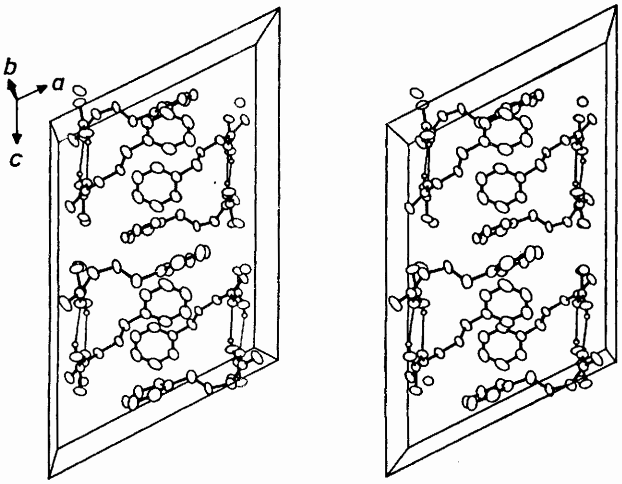


FIGURE 4 Stereoscopic drawing of the arrangement of eight formula units of phenformin hydrochloride (3) in the unit cell viewed along the b axis direction. Hydrogen bonds N–H · · · Cl and all hydrogen atoms except those involved in N–H . . . N hydrogen bonds are omitted for clarity

For all three crystal structures bond lengths and bond angles involving hydrogen atoms, except where these involve hydrogen bonds, are listed in the Supplementary Publication.

TABLE 6

Hydrogen bonding distances (Å) and angles (°) in phenformin hydrochloride (3); D = proton donor, A = proton acceptor

D–H · · · A	D–H	H · · · A	D · · · A	D–H · · · A
N(12)–H(103) · · · N(23)	0.56	2.46	3.002(10)	165
N(22)–H(203) · · · N(13)	0.69	2.34	3.012(9)	166
N(11)–H(101) · · · Cl(2^{I})	0.83	2.67	3.279(7)	132
N(11)–H(102) · · · Cl(1)	1.05	2.50	3.377(7)	141
N(12) * · · · Cl(1)			3.259(7)	
N(14)–H(104) · · · Cl(1^{II})	1.01	2.34	3.304(9)	159
N(14)–H(105) · · · Cl(1^{III})	1.03	2.42	3.296(8)	143
N(15)–H(106) · · · Cl(1^{III})	0.75	2.60	3.326(6)	164
N(21)–H(201) · · · Cl(1^{V})	0.75	2.72	3.375(7)	166
N(21) * · · ·Cl(2^{IV})			3.384(6)	
N(22)–H(202) · · · Cl(2^{IV})	0.88	2.46	3.262(6)	153
N(24)–H(204) · · · Cl(2^{VI})	1.01	2.27	3.268(7)	170
N(24)–H(205) · · · Cl(2^{VII})	0.85	2.55	3.317(6)	150
N(25)–H(206) . . . Cl(2^{VII})	0.96	2.51	3.388(7)	152

Roman numeral superscripts denote the following equivalent positions:

I	$1 - x, \frac{1}{2} + y, \frac{1}{2} - z$	V	$x, \frac{1}{2} - y, -\frac{1}{2} + z$
II	$2 - x, 1 - y, -z$	VI	$1 + x, \frac{1}{2} - y, -\frac{1}{2} + z$
III	$x, 1 + y, z$	VII	$1 - x, -y, -z$
IV	$1 - x, 1 - y, -z$		

* Involve probable positions of the two hydrogen atoms not directly located by the structure analysis.

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Note added in proof: A recent crystal structure analysis of 1-hydrazinophthalazine hydrochloride (hydralazine, Apresoline®), also shows a resonance-stabilized amidinium cation by protonation of the proper ring nitrogen atom (K. Stadnicka and L. Lebioda, *Acta Cryst.*, 1978, **B34**, 1747).