

An X-Ray Diffraction Study of the Potentially Antidepressant Isomer of 3-(4-Bromophenyl)-*N,N*-dimethyl-3-(3-pyridyl)-allylamine

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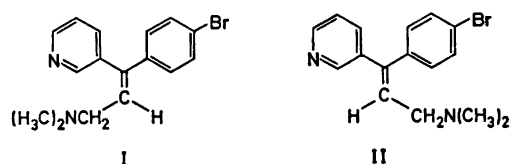
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An X-ray single crystal analysis has been performed on the dihydrochloride of that isomer of 3-(4-bromophenyl)-*N,N*-dimethyl-3-(3-pyridyl)allylamine which selectively inhibits the neuronal uptake of 5-hydroxytryptamine, showing this compound to be the *Z* isomer, formula I.

It is a well-established hypothesis that the tricyclic antidepressants act clinically by inhibiting the neuronal uptake of the transmitter amines noradrenaline (NA) and/or 5-hydroxytryptamine (5-HT), see *e.g.* Iversen.¹ As different types of depressive disorders are known, it is of interest to try to find compounds which normalize the transmitter status in the brain *via* reactions with high selectivity, cf. van Praag.²

Most of the known tricyclic antidepressants do inhibit the NA uptake, some of them rather selectively, but selective inhibitors of the 5-HT

uptake have been lacking. A finding by one of us that some antihistamines of pheniramine type inhibit the neuronal uptake of 5-HT³ initiated a study of structurally related substances. Among the compounds synthesized was a pair of *cis-trans* isomers, I and II.⁴



As seen from Table 1, they are both inhibitors of the amine uptake, and it is noteworthy that there is a clear difference in the selectivities of their action. Compound I acts more selectively on the 5-HT uptake than does chlorimipramine which has been found earlier to block preferentially this uptake.⁵

Table 1. Inhibition *in vitro* of the uptake of noradrenaline (NA) and 5-hydroxytryptamine (5-HT)⁶ by the method of Ross *et al.*⁷

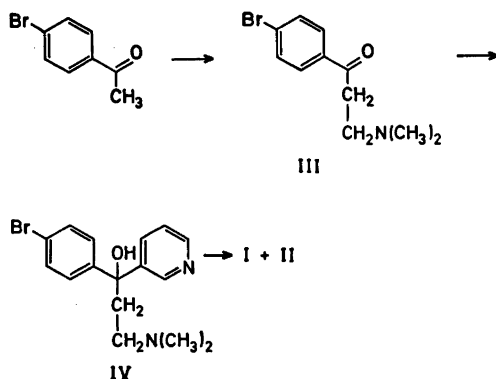
	Astra Reg. No.	EC ₅₀ NA	μM 5-HT	5-HT Selectivity ^a
I. Hydrochloride	A 10124	24.5	1.7	14
II. Oxalate	A 23140	5.5	5.5	1
Chlorimipramine		0.9	0.09	10

^a Defined as EC₅₀ (NA)/EC₅₀ (5-HT).

With these figures in mind we considered it of interest to have unambiguous information on the detailed structures of I and II. Attempted interpretation of UV and NMR spectra gave no conclusive evidence of the sterical relationships. An X-ray single crystal analysis of the 5-HT selective isomer was therefore performed.

EXPERIMENTAL

The amines were prepared using the previously described synthetic procedure⁴ shown in the scheme:



Starting with *p*-bromoacetophenone, a Mannich reaction gives the amino ketone III which reacts with pyridyllithium to the amino alcohol IV. Dehydration with sulfuric acid then gives a mixture of the *cis-trans* isomers I and II. One isomer was isolated by precipitation with concentrated hydrochloric acid from an acetone solution and purified by recrystallization from isopropyl alcohol containing about 2% of water. The pure isomer was obtained as the dihydrochloride with 1 mol water of crystallization. From the mother liquors the other isomer could be isolated as its oxalate, which was recrystallized from ethanol. The pure salt contains oxalic acid and amine in the molar proportions three to two. The salts analyzed correctly and gave spectra in good correlation with the gross structure of I and II.

CRYSTAL DATA

Molecular formula	C ₁₆ H ₂₁ BrCl ₂ N ₂ O
Unit cell monoclinic	<i>a</i> = 16.771(8), <i>b</i> = 9.810(4), <i>c</i> = 11.064(7) Å
	β = 98.23(3)°
<i>V</i>	1801 Å ³
M.W.	408.17
<i>Z</i>	4

<i>D</i> _c	1.505 g cm ⁻³
<i>D</i> _m	1.502 g cm ⁻³
Systematic absences	<i>h</i> 0 <i>l</i> : <i>l</i> = 2 <i>n</i> + 1, 0 <i>k</i> 0: <i>k</i> = 2 <i>n</i> + 1
Space group	<i>P</i> 2 ₁ / <i>c</i>

The intensity data were recorded on a Picker FACS1 diffractometer with the Vanderbilt software system.⁸ 10 steps ($\theta/2\theta$) of 2 s each and a width of 0.2° were used to measure the reflexion intensity with graphite monochromated CuK α radiation. 10 s background counts were taken on each side of the reflexion. In all 2752 reflexions up to $2\theta = 120^\circ$ were recorded of which only 818 were more than 4 standard deviations above background and considered observed. This limit, though, was consistent with counts obtained for systematically absent reflexions. The data were corrected for Lorentz and polarization effects but not for extinction or absorption. Scattering factors for the non-hydrogen atoms were taken from the International Tables for X-Ray Crystallography⁹ and for hydrogen from Stewart *et al.*¹⁰ The scattering curves for bromine and chlorine were corrected for anomalous dispersion (real part). All calculations were performed on a Datsaaba-PDP15 dual computer system, using programs developed at the Department of Structural Chemistry.

STRUCTURE DETERMINATION AND REFINEMENT

The bromine atom was located from a sharpened Patterson series. All other non-hydrogen atoms were then found from successive structure factor/electron density calculations. At an *R*-value of 0.27, it was evident which of the peaks represented the two nitrogen atoms. Cycles of block diagonal least-squares refinement using anisotropic temperature factors for the non-hydrogen atoms reduced the *R*-value to 0.07. At this stage a difference series revealed all hydrogen atoms except those on the water oxygen and that on the quaternary nitrogen atom. All hydrogen atoms except those of the water molecule were now included in the computations at their calculated positions with isotropic temperature factors corresponding to those of their parent atoms. No hydrogen parameters were, however, refined.

Table 2. Fractional atomic coordinates. The standard deviations (in parentheses) are multiplied by 10^5 for the bromine and chlorine atoms and 10^4 for the other non-hydrogen atoms.

	<i>x</i>	<i>y</i>	<i>z</i>	<i>B</i> (Å ²)
Br(1)	0.41137(12)	0.23240(21)	-0.55741(20)	
Cl(1)	0.94230(26)	0.24402(50)	-0.33309(41)	
Cl(2)	0.25080(29)	0.28251(50)	-0.28388(43)	
O(1)	0.9920(8)	0.0369(14)	-0.1319(11)	
N(1)	0.8458(8)	0.0553(13)	-0.0474(13)	
N(2)	0.8386(8)	0.5758(12)	-0.0366(14)	
C(1)	0.4959(9)	0.2516(20)	-0.4229(16)	
C(2)	0.4998(9)	0.3729(18)	-0.3629(16)	
C(3)	0.5620(10)	0.4013(20)	-0.2636(18)	
C(4)	0.6186(11)	0.2990(19)	-0.2269(13)	
C(5)	0.6131(10)	0.1793(19)	-0.2902(14)	
C(6)	0.5513(10)	0.1525(17)	-0.3881(18)	
C(7)	0.6893(11)	0.3203(17)	-0.1367(17)	
C(8)	0.7304(9)	0.1968(14)	-0.0782(14)	
C(9)	0.7003(9)	0.1137(18)	0.0029(18)	
C(10)	0.7429(11)	0.0090(17)	0.0593(17)	
C(11)	0.8153(14)	-0.0191(17)	0.0293(17)	
C(12)	0.8063(10)	0.1629(17)	-0.1056(16)	
C(13)	0.7114(10)	0.4485(18)	-0.1016(16)	
C(14)	0.7735(12)	0.4846(18)	0.0045(18)	
C(15)	0.8845(13)	0.5028(17)	-0.1236(19)	
C(16)	0.8947(12)	0.6266(17)	0.0701(17)	
H(11)	0.896	0.031	-0.071	2.28
H(12)	0.814	0.654	-0.078	1.96
H(21)	0.460	0.439	-0.040	1.81
H(31)	0.571	0.493	-0.230	4.13
H(51)	0.655	0.116	-0.274	2.47
H(61)	0.553	0.065	-0.422	3.20
H(91)	0.646	0.123	0.019	2.57
H(101)	0.723	-0.044	0.120	2.47
H(111)	0.843	-0.094	0.072	2.19
H(121)	0.828	0.217	-0.165	2.68
H(131)	0.684	0.521	-0.145	2.83
H(141)	0.748	0.532	0.067	2.21
H(142)	0.797	0.403	0.044	2.21
H(151)	0.846	0.473	-0.192	3.08
H(152)	0.909	0.425	-0.084	3.08
H(153)	0.922	0.560	-0.151	3.08
H(161)	0.921	0.551	0.113	2.69
H(162)	0.866	0.676	0.124	2.69
H(163)	0.935	0.684	0.044	2.69

The refinement was terminated at an *R*-value of 0.058.

RESULTS AND DISCUSSION

The final structure factor list can be obtained from the Department of Structural Chemistry. The atomic coordinates are given in Tables 2 and 3. Interatomic distances and angles for the heavier atoms are given in Fig. 1 which also shows the atomic numbering. The distances

and angles show no unexpected features when the standard deviations (all about 0.02 Å) are considered. The molecular configuration and conformation are illustrated in Fig. 2. The analysis definitely establishes that the isomer precipitated as the hydrochloride is (*Z*)-3-(4-bromophenyl)-*N,N*-dimethyl-3-(3-pyridyl)allylamine, corresponding to formula I.

There is a slight twist about the double bond. C(4) is thus 0.24 Å and C(8) 0.12 Å on opposite sides of the plane through C(7), C(13)

Table 3. Anisotropic thermal parameters in the form $\exp[-2\pi^2(h^2a^{*2}U_{11} + k^2b^{*2}U_{22} + l^2c^{*2}U_{33} + 2klb^*c^*U_{23} + 2hla^*c^*U_{31} + 2hka^*b^*U_{12})]$. Standard deviations are given in parentheses. All values have been multiplied by 10^4 .

	U_{11}	U_{22}	U_{33}	U_{23}	U_{31}	U_{12}
Br(1)	329(9)	403(11)	483(11)	-44(13)	-125(8)	32(13)
Cl(1)	489(26)	337(27)	409(28)	69(28)	43(21)	50(29)
Cl(2)	560(29)	328(26)	391(29)	-69(25)	-77(22)	21(26)
O(1)	523(94)	435(86)	290(90)	133(70)	95(70)	211(76)
N(1)	299(88)	184(80)	355(104)	-360(77)	-132(77)	153(68)
N(2)	209(85)	-11(67)	508(109)	46(71)	-58(74)	-58(62)
C(1)	333(96)	346(121)	357(102)	-95(113)	90(75)	-229(114)
C(2)	142(97)	348(108)	310(118)	-29(96)	43(82)	203(86)
C(3)	327(118)	303(115)	436(139)	-258(100)	-61(98)	110(91)
C(4)	456(108)	442(123)	1(89)	-92(85)	199(77)	-144(97)
C(5)	379(110)	475(124)	5(95)	-57(85)	-43(77)	226(91)
C(6)	249(105)	93(90)	616(150)	-116(96)	266(99)	52(80)
C(7)	377(109)	138(97)	368(118)	-65(90)	-63(94)	19(88)
C(8)	216(85)	25(79)	163(92)	143(67)	3(70)	16(68)
C(9)	92(96)	233(102)	580(140)	84(96)	-259(87)	-93(79)
C(10)	337(114)	208(101)	366(119)	-58(88)	75(89)	-290(90)
C(11)	939(179)	122(97)	196(120)	79(87)	41(107)	-244(108)
C(12)	249(99)	182(94)	236(108)	-110(81)	-31(81)	-75(77)
C(13)	158(94)	272(103)	363(129)	-31(94)	-6(84)	202(85)
C(14)	595(125)	279(111)	156(117)	-15(95)	158(93)	98(98)
C(15)	645(144)	68(101)	473(146)	-271(97)	-10(113)	-15(97)
C(16)	576(133)	85(90)	324(123)	168(87)	-77(100)	-208(93)

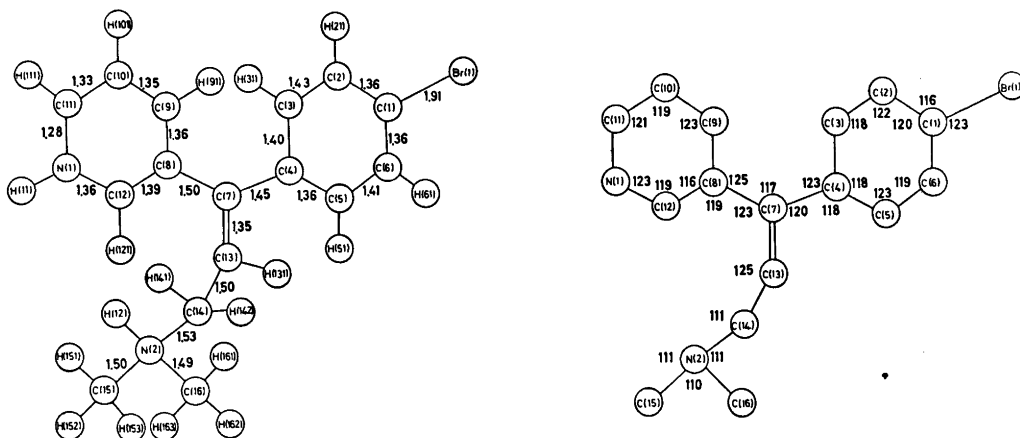


Fig. 1. Bond distances and angles.

and C(14). The benzene ring forms an angle of 23.4° with this double bond plane whereas the angle for the pyridine ring is 78.1° . C(13), C(14), N(2), and C(16) form an extended zig-zag chain which is planar within 0.04 \AA . C(15) is then 1.26 \AA off the plane. The chain plane

is inclined 56.7° to the double bond plane.

The molecules are arranged in double layers with bromobenzene rings in the interior and the polar parts on the outside in contact with chloride ions and water (Fig. 3). The hydrogen atom on N(1) points straight towards the water

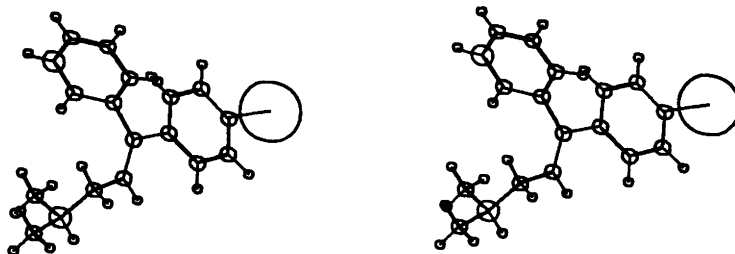


Fig. 2. Stereopair of the molecular ion.

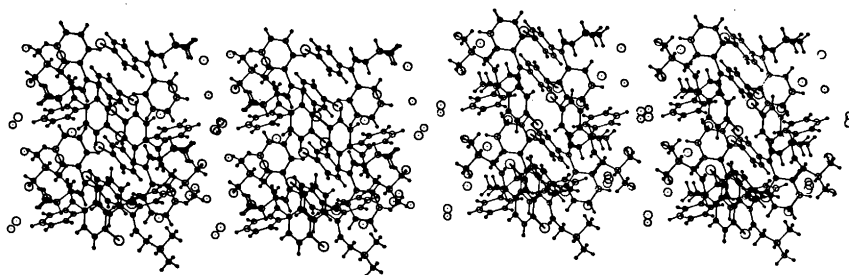


Fig. 3. Molecular packing.

oxygen and the N(1)···O(1) distance of 2.75 Å indicates a fairly strong hydrogen bond. The water oxygen is also close to a symmetry translated oxygen (2.98 Å) and has furthermore two contacts with symmetry related Cl(1)'s (3.04 and 3.12 Å). As the water hydrogens could not be found it is difficult to determine the exact hydrogen bonding scheme around the oxygen. The hydrogen atom on N(2) is involved in a hydrogen bond with the second chloride ion (Cl(2), 3.07 Å) which is thereby forced into a nonpolar neighbourhood. The closest other contacts are Br(1) at 3.41 Å and C(11) at 3.39 Å.

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