its complexes with L-aspartic acid and L-glutamic acid (Salunke & Vijayan, 1982; Bhat & Vijayan, 1977). The difference is most striking in the case of the complexes with glutamic acid. A schematic representation of the complexes of L-arginine with L- and D-glutamic acid is given in Fig. 3. The unlike molecules aggregate into separate alternating layers in the LL complex, held together in head-to-tail sequences by hydrogen bonds. The molecules, however, form double layers in the LD complex, with each layer containing both types of molecules in LL and DL types of head-to-tail sequences. Similar differences are found between L-arginine L-aspartate and L-arginine D-aspartate. As indicated earlier, each LL complex and the corresponding LD complex were crystallized under identical conditions. Therefore, the differences between the LL and LD crystal structures are unlikely to have resulted from environmental effects. They must represent the different packing requirements arising out of the reversal in the chirality of one of the components.

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The α_2-Adrenoceptor Agonists B-HT 920, B-HT 922 and B-HT 958,* a Comparative X-ray and Molecular-Mechanics Study

BY PETER LUGER

Institut für Kristallographie, Fachbereich Chemie der Freien Universität Berlin, Takustrasse 6, 1000 *Berlin* 33, *Federal Republic of Germany*

AND GERHART GRISS,† RUDOLF HURNAUS AND GÜNTER TRUMMLITZ

Chemical Research Department, Dr Karl Thomae GmbH, Birkendorfer Strasse 65, 7950 *Biberach* 1, *Federal Republic of Germany*

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Abstract

The crystal structures of the α_2-adrenoceptor agonists B-HT 920, B-HT 922 and B-HT 958 were determined by X-ray analysis. In addition, molecular-mechanics calculations were performed for B-HT 920 and B-HT 922 to reveal any conformational differences tentatively being responsible for the additional dopaminergic effects observed with B-HT 920. The X-ray studies showed that B-HT 920 and B-HT 922 prefer a chair conformation in the crystalline state,

* Compound codes, used particularly in the medicinal-chemistry and pharmacological literature instead of the full chemical names.
† Deceased 10 December 1983.

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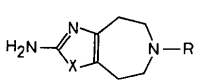
whereas B-HT 958 exists in a twist conformation. Additional differences can be detected with respect to the position of the azepine N atom [N(5)] relative to the hetero-aromatic ring, the torsional angles of the azepine ring and the extent of hybridization of the amino group on the hetero-aromatic ring [N(11)] leading to different spatial orientations of the attached H atoms. Within the crystal strong intermolecular hydrogen bonding is observed. The results of the molecular-mechanics calculations are in good agreement with the findings of the X-ray analysis and suggest that the twist conformation of the thiazoloazepines is equienergetic to the chair conformation. In addition, a third local minimum conformation, a distorted boat, was found. The substituent on the azepine N can adopt several conformational positions. Finally, a hypothesis is presented to account for the observed additional dopaminergic effects in the thiazole compounds B-HT 920 and B-HT 958.

Introduction

Pharmacological investigations by Kobinger & Pichler (1977, 1980) and by Timmermans & van Zwieten (1984) characterize B-HT 920 (I) (6-allyl-2-amino-5,6,7,8-tetrahydro-4*H*-thiazolo[4,5-*d*]azepine), B-HT 922 (II) (6-allyl-2-amino-5,6,7,8-tetrahydro-4*H*-oxazolo[4,5-*d*]azepine) and B-HT 933 (IV) (2-amino-6-ethyl-5,6,7,8-tetrahydro-4*H*-oxazolo[4,5-*d*]azepine) (Griss, Kleemann, Grell & Ballhause, 1972) as highly selective α_2-adrenergic agonists, which, like clonidin, cause a depression of blood pressure by stimulation of peripheral and predominantly central α_2-adrenoceptors.

The structurally related B-HT 958 (III) {2-amino-6-(4-chlorophenyl)methyl-5,6,7,8-tetrahydro-4*H*-thiazolo[4,5-*d*]azepine} is described as a mixed agonist-antagonist at peripheral α_2-adrenoceptors (Pichler, Hörtnagl & Kobinger, 1982; Kobinger & Pichler, 1984), the biological effect being again a decrease of blood pressure.



No.	Code	R	X
I	B - HT 920	$-CH_2-CH=CH_2$	S
II	B - HT 922	$-CH_2-CH=CH_2$	O
III	B - HT 958	$-CH_2-C_6H_4-Cl$	S
IV	B - HT 933	$-C_2H_5$	O

Recently presented results by Andén, Golembiowska-Nikitin & Thornström (1982, 1983), Andén-Grabowska & Andén (1984) and by Hörtnagl, Petsche & Hornykiewicz (1983) and Hörtnagl, Pichler, Holzer-Petsche, Hornykiewicz & Kobinger (1985) showed that the thiazole derivatives B-HT 920 and B-HT 958 have strong and selective dopamine agonist (DA) activity at central DA receptors, whereas the oxazole derivatives (II and IV) are devoid of DA-agonistic effects. Considering the close structure relationship of these two groups of compounds, the observed pharmacological differences seem rather unexpected.

Since physicochemical parameters, *e.g.* pK_a values, partition coefficients, or charge distribution did not yield any clues for the observed biologically different profiles, X-ray studies and molecular-mechanics calculations were performed in order to elucidate structural differences.

In the X-ray studies the monohydrochloride salts of B-HT 920 and B-HT 958, (I*a*) and (III*a*) respectively, were used, since it can be assumed that under physiological conditions the applied drugs are present in the protonated form in the organism. B-HT 922 (II) was used as the free base, since suitable crystals of the hydrochloride could not be obtained. For the purpose of comparison crystals of the free base B-HT 920 (I) were also provided. The results of the already known X-ray structure of B-HT 933 (IV, free base, Carpy, Léger, Colleter, 1982) were used for comparison.

Molecular-mechanics calculations are presented only for the protonated forms of B-HT 920 and B-HT 922. The results for B-HT 958 and 933 are not discussed in this paper because the influence of the side chains on the conformations of the thiazolo- and oxazolo-azepine systems is small in the calculations. Using B-HT 920 and B-HT 922 a comparison is possible of the two most similar structures with different biological activities.

Experiments and calculations (general)

(*a*) *X-ray experiments*

The monohydrochloride salts of B-HT 920 (I*a*) and B-HT 958 (III*a*) were crystallized from ethanol and acetonitrile/water respectively. Crystals of the free bases of B-HT 922 and B-HT 920 were obtained from acetone.

The same procedures were applied in all four X-ray experiments. In a preliminary stage space groups and estimates of lattice constants were obtained from rotation and Weissenberg photographs. Precise lattice constants and three-dimensional intensity data were measured on a Stoe four-circle diffractometer with Ni-filtered Cu $K\alpha$ radiation. Details of the experimental conditions and a summary of the crystal data are given in Table 1.

The phase problems were solved routinely with direct methods (*MULTAN*, Main, Lessinger, Woolfson, Germain & Declercq, 1977). Least-squares refinements were executed with anisotropic temperature factors for the non-hydrogen atoms. For all

Table 1. *Summary of crystallographic data*

	B-HT 920 (I)	B-HT 920Cl (I*a*)	B-HT 922 (II)	B-HT 958Cl (III*a*)
Chemical formula	$C_{10}H_{15}N_3S$	$C_{10}H_{15}N_3S.HCl$	$C_{10}H_{15}N_3O$	$C_{14}H_{16}N_3SCl.HCl.H_2O$
Formula weight	209·32	245·78	193·25	330·28
Lattice parameters (Å, °)	a = 9·767 (2)	a = 14·647 (8)	a = 12·687 (3)	a = 13·067 (1)
	b = 7·114 (2)	b = 16·519 (7)	b = 6·726 (2)	b = 17·767 (1)
	c = 15·914 (2)	c = 10·196 (9)	c = 13·436 (3)	c = 6·913 (1)
	β = 94·99 (3)		β = 110·01 (3)	β = 91·36 (2)
Cell volume (Å^3)	1101·6	2466·9	1077·3	1604·5
Z	4	8	4	4
$F(000)$	448	1040	416	728
D_m (g cm^{-3})	1·250	1·322	1·189	1·426
D_x (g cm^{-3})	1·262	1·323	1·191	1·441
Space group	$P2_1/c$	$Pbca$	$P2_1/c$	$P2_1/n$
Crystal size (mm)	0·20×0·25×0·45	0·30×0·18×0·10	0·30×0·30×0·07	0·50×0·25×0·05
$(\sin\theta/\lambda)_{max}$ (Å^{-1})	0·59	0·56	0·59	0·59
Number of unique reflections	1863	1835	1810	2686
Unobserved [$I<2\sigma(I)$]	133	441	309	335
Linear absorption coefficient (cm^{-1}, Cu K_α, λ = 1·5418 Å)	22·49	40·22	6·53	47·32
Absorption correction	No	Yes*	No	Yes*
wR†‡	0·067	0·068	0·058	0·054
a†	0·65	0·45	0·60	0·60
b†	1·00	20·00	5·00	7·50
$(\Delta/\sigma)_{max}$	0·44	0·24	0·71	0·21
$(\Delta/\sigma)_{av}$	0·12	0·06	0·03	0·12
Final ρ_{max} (e Å^{-3})	0·58	0·41	0·28	0·48
Final ρ_{min} (e Å^{-3})	−0·55	−0·40	−0·26	−0·43
R value	0·055	0·063	0·049	0·041

* Absorption correction with the *ABSCOR* program of Burnham (1966).
† The function minimized was $\sum w(|F_o|-|F_c|)^2$ with $w = x.y$ and $x = 1$ for $\sin\theta > a$, $x = \sin\theta/a$ otherwise; $y = 1$ for $|F_o| < b$, $y = b/|F_o|$ otherwise.
‡ $wR = [\sum w(|F_o|-|F_c|)^2/\sum wF_o^2]^{1/2}$.

structures the H atoms were located from difference syntheses unambiguously and included with isotropic thermal parameters (*XRAY*76 system, Stewart, Machin, Ammon, Dickinson, Heck & Flack, 1976). The quantity minimized was $\sum w(F_o-F_c)^2$, with various weighting schemes applied (see Table 1). Atomic scattering factors were taken from the corresponding standard routine of the *XRAY*76 system (Cromer & Mann, 1968; Stewart, Davidson & Simpson, 1965). After convergence of the refinements the e.s.d.'s of geometric data were in the ranges 0·002–0·009 Å and 0·1–0·7°, respectively. Final atomic parameters are listed in Table 2.

All crystallographic calculations were executed on a CDC Cyber 175 computer (Wissenschaftliches Rechenzentrum, WRB, Berlin).*

(*b*) *Empirical and semi-empirical calculations*

The molecular-mechanics calculations were performed with a modified version of the program *MMPI* (Allinger, 1976). All atoms of the delocalized π system [S(1) or O(1), C(2), C(8), N(9), C(10) and N(11)] were included in the *VESCF* part. One atomic parameter in the subroutine *VALUES* was changed for atom type 9 [atom N(11)]. For the atoms N(9) and S(1) new parameters were chosen, which had been tested for model molecules, such as imidazole, oxazole, thiophene, thiazole, isoxazole, isothiazole. The calculated π-bond orders fitted well with results obtained by the standard CNDO/2 method (Dobosch, 1969).

Because of a lack of many torsional constants, stretching parameters, bond dipole moments, bending and out-of-plane bending constants in the molecular-mechanics part a consistent parameter set for substituted five-membered heteroaromatic ring systems was developed. Using these new parameters a good agreement was obtained between the calculated and the experimentally determined conformational data (bond lengths, bond and torsional angles) and dipole moments of the model compounds (Sheridan, 1974). We also compared the results of our calculations with the published data from other molecular-mechanics programs (Warshel & Lappicirella, 1981) and with the results of our calculations using the semi-empirical quantum-chemical MNDO method (Thiel, 1978), which also allows geometry optimizations. The final parameter set has been deposited.* The atom-numbering scheme (see Fig. 2) used in the calculations and in the X-ray investigations was kept the same in order to facilitate comparison.

* Lists of structure factors, complete atom lists with anisotropic thermal parameters and H atoms included, and the molecular-mechanics parameter set have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 42872 (63 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

* See deposition footnote.

Table 2. *Atomic parameters, U_{eq} (calculated after Hamilton, 1959) and U* ($Å^2 \times 10^2$)

	x	y	z	U_{eq} or U
(*a*) B-HT 920 (I)				
S(1)	0·29501 (5)	0·10064 (7)	0·09829 (3)	4·73 (2)
C(2)	0·2914 (2)	0·2477 (3)	0·1857 (1)	4·10 (5)
C(3)	0·2287 (2)	0·1849 (3)	0·2636 (1)	4·64 (6)
C(4)	0·1416 (2)	0·3319 (3)	0·3031 (1)	4·86 (6)
N(5)	0·2173 (2)	0·4928 (2)	0·3419 (1)	4·28 (5)
C(6)	0·2608 (2)	0·6248 (3)	0·2785 (1)	4·96 (6)
C(7)	0·3861 (2)	0·5633 (3)	0·2347 (1)	5·03 (6)
C(8)	0·3633 (2)	0·4051 (3)	0·1726 (1)	4·06 (5)
N(9)	0·4215 (2)	0·4177 (2)	0·0961 (1)	4·63 (5)
C(10)	0·3938 (2)	0·2675 (3)	0·0507 (1)	4·62 (6)
N(11)	0·4374 (2)	0·2380 (3)	−0·0271 (1)	5·78 (6)
C(12)	0·1254 (2)	0·5891 (3)	0·3967 (1)	5·08 (6)
C(13)	0·1908 (3)	0·7522 (3)	0·4436 (1)	5·61 (7)
C(14)	0·1307 (4)	0·9171 (4)	0·4491 (2)	7·6 (1)
H(31)	0·303 (3)	0·140 (4)	0·307 (2)	5·5 (6)
H(32)	0·172 (3)	0·081 (4)	0·250 (2)	6·2 (7)
H(41)	0·072 (3)	0·380 (4)	0·260 (2)	6·7 (8)
H(42)	0·091 (3)	0·266 (4)	0·347 (2)	5·4 (6)
H(61)	0·287 (3)	0·739 (4)	0·310 (2)	5·0 (6)
H(62)	0·183 (3)	0·650 (4)	0·236 (2)	6·2 (7)
H(71)	0·468 (3)	0·530 (4)	0·280 (2)	6·3 (7)
H(72)	0·416 (3)	0·661 (5)	0·204 (2)	6·0 (7)
H(111)	0·478 (3)	0·334 (5)	−0·047 (2)	6·1 (7)
H(112)	0·387 (4)	0·156 (6)	−0·058 (2)	8·3 (9)
H(121)	0·095 (3)	0·494 (5)	0·439 (2)	7·0 (8)
H(122)	0·040 (3)	0·641 (4)	0·364 (2)	6·2 (7)
H(13)	0·285 (3)	0·737 (4)	0·467 (2)	7·1 (8)
H(141)	0·033 (5)	0·941 (6)	0·422 (3)	10 (1)
H(142)	0·168 (4)	1·027 (7)	0·485 (3)	11 (1)
(*b*) B-HT 920 monohydrochloride (Ia)				
$Cl(1)^-$	0·6330 (1)	0·39149 (9)	0·5989 (1)	7·78 (5)
S(1)	0·98353 (8)	0·22489 (8)	0·6189 (1)	6·80 (5)
C(2)	0·8905 (3)	0·2711 (3)	0·6946 (5)	5·5 (2)
C(3)	0·8789 (4)	0·3606 (3)	0·6859 (7)	7·0 (2)
C(4)	0·8480 (4)	0·4011 (4)	0·8106 (7)	6·6 (2)
N(5)	0·7516 (3)	0·3815 (2)	0·8505 (5)	5·3 (1)
C(6)	0·7424 (4)	0·2985 (3)	0·9067 (5)	5·8 (2)
C(7)	0·7437 (3)	0·2299 (3)	0·8092 (5)	5·3 (2)
C(8)	0·8337 (3)	0·2146 (3)	0·7433 (5)	5·2 (1)
N(9)	0·8599 (3)	0·1329 (2)	0·7268 (4)	5·5 (1)
C(10)	0·9381 (3)	0·1312 (3)	0·6612 (5)	5·2 (2)
N(11)	0·9835 (4)	0·0623 (3)	0·6308 (5)	6·6 (2)
C(12)	0·7176 (4)	0·4452 (4)	0·9459 (7)	7·2 (2)
C(13)	0·6173 (4)	0·4390 (4)	0·9674 (7)	7·7 (2)
C(14)	0·5789 (7)	0·4151 (5)	1·0759 (9)	10·3 (3)
H(31)	0·838 (5)	0·377 (4)	0·612 (6)	8 (2)
H(32)	0·931 (5)	0·383 (4)	0·671 (7)	9 (2)
H(41)	0·883 (4)	0·391 (3)	0·887 (6)	6 (2)
H(42)	0·850 (3)	0·456 (3)	0·798 (4)	5 (1)
H(5)	0·720 (3)	0·388 (3)	0·782 (5)	6 (1)
H(61)	0·690 (4)	0·296 (3)	0·951 (5)	5 (1)
H(62)	0·791 (4)	0·294 (3)	0·979 (6)	7 (1)
H(71)	0·694 (3)	0·237 (3)	0·742 (5)	5 (1)
H(72)	0·722 (4)	0·181 (4)	0·854 (6)	8 (2)
H(111)	1·028 (4)	0·063 (4)	0·563 (6)	8 (2)
H(112)	0·953 (4)	0·020 (4)	0·623 (6)	7 (2)
H(121)	0·750 (4)	0·441 (4)	1·038 (7)	9 (2)
H(122)	0·732 (4)	0·499 (4)	0·902 (5)	8 (2)
H(13)	0·581 (6)	0·458 (5)	0·891 (8)	13 (3)
H(141)	0·510 (9)	0·411 (8)	1·09 (1)	21 (5)
H(142)	0·625 (5)	0·409 (4)	1·152 (8)	10 (2)

Table 2 (*cont.*)

	x	y	z	U_{eq} or U
(*c*) B-HT 922 (II)				
O(1)	0·8094 (1)	−0·2312 (2)	0·8065 (1)	6·66 (5)
C(2)	0·7960 (2)	−0·3523 (3)	0·7181 (2)	6·05 (6)
C(3)	0·7190 (2)	−0·2804 (3)	0·6145 (2)	7·16 (7)
C(4)	0·6672 (2)	−0·4469 (4)	0·5372 (2)	7·25 (7)
N(5)	0·7487 (1)	−0·5742 (2)	0·5115 (1)	6·38 (5)
C(6)	0·7934 (2)	−0·7331 (3)	0·5895 (2)	7·17 (7)
C(7)	0·8892 (2)	−0·6713 (4)	0·6872 (2)	7·40 (8)
C(8)	0·8645 (2)	−0·5073 (3)	0·7508 (2)	5·94 (6)
N(9)	0·9228 (1)	−0·4925 (2)	0·8602 (1)	6·35 (5)
C(10)	0·8868 (2)	−0·3278 (3)	0·8874 (2)	6·25 (6)
N(11)	0·9179 (2)	−0·2421 (3)	0·9828 (2)	8·44 (8)
C(12)	0·7005 (2)	−0·6569 (4)	0·4031 (2)	7·76 (8)
C(13)	0·6003 (2)	−0·7877 (4)	0·3849 (2)	9·3 (1)
C(14)	0·5875 (4)	−0·9644 (5)	0·3486 (3)	11·6 (1)
H(31)	0·659 (2)	−0·206 (4)	0·628 (2)	9·0 (8)
H(32)	0·760 (2)	−0·185 (4)	0·579 (2)	8·5 (7)
H(41)	0·617 (2)	−0·389 (4)	0·472 (2)	8·5 (7)
H(42)	0·624 (2)	−0·534 (4)	0·567 (2)	7·3 (6)
H(61)	0·824 (2)	−0·835 (4)	0·555 (2)	8·3 (7)
H(62)	0·732 (2)	−0·790 (4)	0·611 (2)	8·6 (7)
H(71)	0·958 (2)	−0·637 (4)	0·668 (2)	9·9 (8)
H(72)	0·912 (2)	−0·779 (5)	0·732 (2)	9·4 (8)
H(111)	0·879 (2)	−0·141 (5)	0·992 (2)	8·8 (8)
H(112)	0·967 (2)	−0·310 (4)	1·039 (2)	8·6 (8)
H(121)	0·759 (2)	−0·732 (4)	0·390 (2)	7·2 (6)
H(122)	0·672 (2)	−0·540 (4)	0·354 (2)	9·1 (8)
H(13)	0·527 (5)	−0·727 (8)	0·399 (4)	20 (2)
H(141)	0·653 (7)	−1·03 (1)	0·346 (6)	27 (3)
H(142)	0·516 (3)	−1·043 (6)	0·334 (3)	13 (1)
(*d*) B-HT 958 monohydrochloride (IIIa)				
O(1*W*)	0·1504 (3)	0·3968 (2)	0·1141 (4)	9·0 (1)
$Cl(1)^-$	0·17650 (5)	0·25703 (4)	0·4116 (1)	5·28 (2)
S(1)	0·36346 (6)	0·05021 (4)	−0·30662 (9)	5·13 (2)
C(2)	0·3811 (2)	0·1180 (1)	−0·1285 (3)	3·83 (7)
C(3)	0·3801 (2)	0·2005 (1)	−0·1783 (4)	4·45 (8)
C(4)	0·3159 (2)	0·2457 (1)	−0·0400 (4)	4·29 (8)
N(5)	0·3680 (2)	0·2637 (1)	0·1519 (3)	3·64 (6)
C(6)	0·4402 (2)	0·2042 (1)	0·2266 (4)	3·90 (7)
C(7)	0·3936 (2)	0·1259 (1)	0·2377 (3)	4·04 (8)
C(8)	0·3831 (2)	0·0854 (1)	0·0475 (3)	3·62 (7)
N (9)	0·3697 (1)	0·0054 (1)	0·0539 (3)	3·64 (6)
C(10)	0·3592 (2)	−0·0178 (1)	−0·1293 (4)	4·06 (7)
N(11)	0·3433 (2)	−0·0904 (1)	−0·1816 (5)	5·53 (9)
C(12)	0·4203 (2)	0·3394 (1)	0·1394 (4)	4·36 (8)
C(13)	0·4679 (2)	0·3656 (1)	0·3280 (4)	3·98 (7)
C(14)	0·5725 (2)	0·3721 (1)	0·3478 (4)	4·54 (8)
C(15)	0·6164 (2)	0·4011 (2)	0·5141 (4)	4·69 (8)
C(16)	0·5546 (2)	0·4223 (1)	0·6645 (4)	4·13 (7)
Cl(16)	0·61229 (6)	0·45719 (4)	0·8749 (1)	5·91 (3)
C(17)	0·4504 (2)	−0·4165 (2)	0·6479 (4)	4·66 (8)
C(18)	0·4065 (2)	0·3889 (2)	0·4789 (4)	4·63 (8)
H(1*W*)	0·142 (4)	0·354(3)	0·180 (8)	12 (1)
H(2*W*)	0·132 (4)	0·432 (3)	0·176 (8)	12 (1)
H(31)	0·348 (3)	0·205 (2)	−0·304 (5)	6·0 (9)
H(32)	0·451 (2)	0·220 (2)	−0·185 (4)	4·9 (8)
H(41)	0·300 (2)	0·295 (2)	−0·095 (4)	4·7 (7)
H(42)	0·253 (2)	0·219 (2)	−0·011 (4)	4·5 (7)
H(5)	0·318 (3)	0·268 (2)	0·233 (5)	4·6 (8)
H(61)	0·459 (2)	0·219 (1)	0·359 (4)	3·3 (6)
H(62)	0·498 (2)	0·201 (2)	0·142 (4)	3·8 (6)
H(71)	0·439 (2)	0·094 (2)	0·316 (4)	4·1 (7)
H(72)	0·327 (3)	0·129 (2)	0·297 (5)	5·4 (8)
H(111)	0·345 (2)	−0·099 (2)	−0·309 (5)	4·5 (8)
H(112)	0·351 (3)	−0·121 (3)	−0·101 (7)	9 (1)
H(121)	0·473 (2)	0·334 (2)	0·048 (4)	4·0 (7)
H(122)	0·373 (2)	0·373 (2)	0·097 (4)	3·3 (6)
H(14)	0·613 (3)	0·358 (2)	0·244 (5)	6·1 (9)
H(15)	0·686 (3)	0·409 (2)	0·513 (5)	5·9 (9)
H(17)	0·412 (2)	0·434 (2)	0·747 (5)	5·4 (8)
H(18)	0·336 (3)	0·385 (2)	0·473 (5)	6·2 (9)

The calculations were performed with the protonated forms of B-HT 920 and 922. For the chair conformation of B-HT 920 the X-ray coordinates of B-HT 920 were taken as input geometry. For the twist conformation of B-HT 920 we used the X-ray coordinates of B-HT 958 for S(1) - H(14); H(131) and H(142) were added using standard geometry. For the two conformations of the protonated forms of B-HT 922 the same input coordinates as for B-HT 920 were used, only atom type 30 (sulfur) was replaced by atom type 6 (oxygen). All other conformations were generated by using the dihedral driver option of the program *MMPI* followed by subsequent full-geometry optimization of the new local-minimum conformations.

The *MMPI*, MNDO and CNDO/2 calculations were executed on an IBM 370/4341-2 computer (Dr K. Thomae GmbH, Biberach an der Riss).

Results and discussion

(*a*) *Crystal structures*

The results of the X-ray investigations are illustrated in Figs. 1 to 6; a summary of geometrical data is given in Tables 3 to 5.

For B-HT 920, two structures, the free base (I) and the monohydrochloride (I*a*), were investigated. Since the X-ray results proved the molecular geometry to be equal in both cases [except for some bond-length deviations around the protonated N atom N(5)], only one model is shown in Fig. 1. The overall molecular shape can be described by a planar thiazole ring and a chair-shaped seven-membered ring.

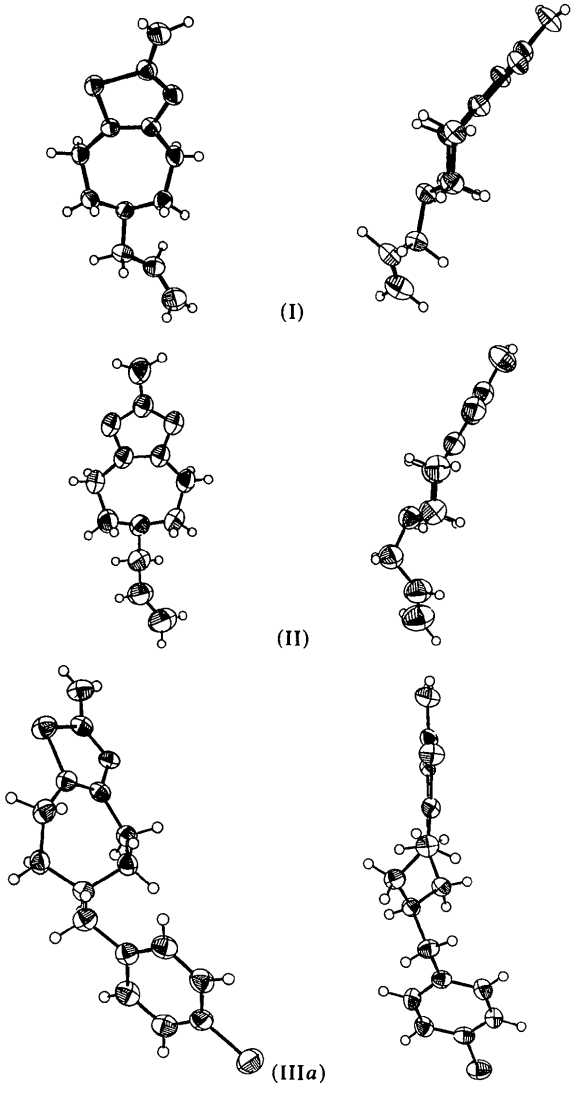


Fig. 1. *ORTEP* representations (Johnson, 1970) of the molecular structures of (I), (II) and (III*a*). On the left a view direction was chosen with three seven-membered-ring atoms [C(3), C(4), C(6)] in the plane of the paper; the view direction on the right is perpendicular to that of the left. Thermal ellipsoids plotted at a 50% probability level.

The average deviation of contributing atoms from a least-squares plane through the thiazolo five-membered ring is 0·002 Å for (I) and 0·005 Å for (I*a*). The exocyclic N atom N(11) of the amino group is in the thiazole-ring plane [distance 0·003 (3) Å for (I) and 0·030 (7) Å for (I*a*)].

The deviations of the amino H atoms from the five-membered-ring plane are 0·08 (6) Å (I)

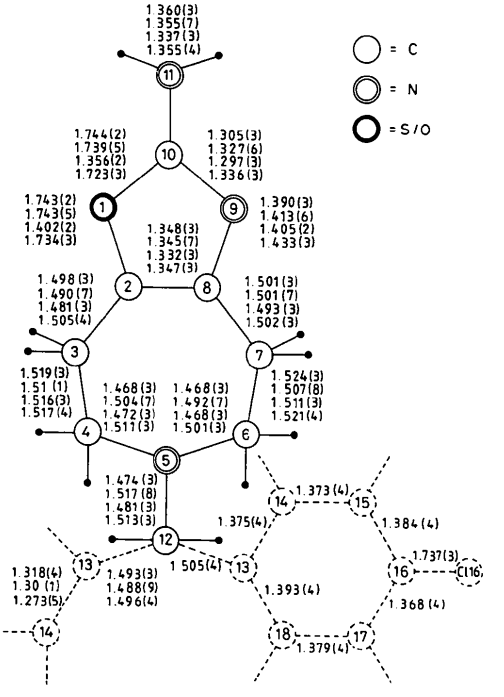


Fig. 2. Atom-numbering scheme and bond lengths obtained from X-ray analyses (Å, e.s.d.'s in parentheses). The order (from the upper value) is (I), (I*a*), (II), (III*a*).

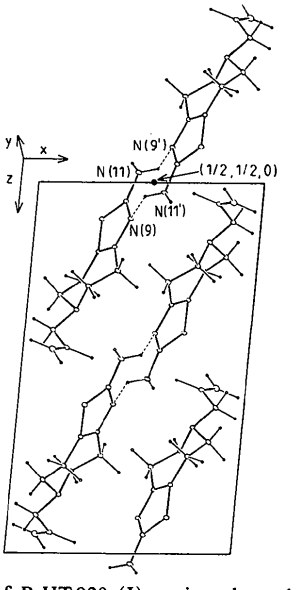


Fig. 3. Unit cell of B-HT 920 (I) projected on the *xz* plane. A 'head-to-head' dimer formed by hydrogen bonds (dashed lines) is shown at the inversion center ($\frac{1}{2}, \frac{1}{2}, 0$).

Table 3. *Bond angles* (°) (*e.s.d.'s in parentheses*)

	(I)	(I*a*)	(II)*	(III*a*)
C(2)–S(1)–C(10)	89·3 (1)	88·9 (2)	104·2 (1)	89·3 (1)
S(1)–C(2)–C(3)	121·3 (1)	119·8 (4)	117·1 (2)	120·9 (2)
S(1)–C(2)–C(8)	109·2 (1)	110·0 (3)	107·4 (2)	110·0 (2)
C(3)–C(2)–C(8)	129·2 (2)	129·8 (5)	135·4 (2)	128·7 (2)
C(2)–C(3)–C(4)	114·9 (2)	115·1 (6)	113·2 (2)	111·9 (2)
C(3)–C(4)–N(5)	115·5 (2)	114·5 (5)	114·6 (2)	114·9 (2)
C(4)–N(5)–C(6)	112·1 (2)	112·7 (4)	112·7 (2)	114·8 (2)
C(4)–N(5)–C(12)	107·5 (2)	109·4 (4)	111·2 (2)	109·4 (2)
C(6)–N(5)–C(12)	109·7 (2)	111·1 (4)	110·9 (2)	111·4 (2)
N(5)–C(6)–C(7)	115·0 (2)	115·9 (4)	114·8 (2)	114·4 (2)
C(6)–C(7)–C(8)	115·9 (2)	115·7 (4)	115·9 (2)	115·0 (2)
C(2)–C(8)–C(7)	124·8 (2)	126·2 (4)	129·1 (2)	125·7 (2)
C(2)–C(8)–N(9)	116·5 (2)	116·8 (4)	109·9 (2)	117·0 (2)
C(7)–C(8)–N(9)	118·7 (2)	116·9 (4)	120·8 (2)	117·2 (2)
C(8)–N(9)–C(10)	110·6 (2)	108·4 (4)	104·2 (1)	106·7 (2)
S(1)–C(10)–N(9)	114·4 (2)	115·9 (4)	114·3 (2)	117·0 (2)
S(1)–C(10)–N(11)	121·3 (2)	120·2 (4)	117·2 (2)	119·0 (2)
N(9)–C(10)–N(11)	124·4 (2)	123·9 (5)	128·4 (2)	124·0 (2)
N(5)–C(12)–C(13)	113·7 (2)	111·8 (5)	115·1 (2)	113·8 (2)
C(12)–C(13)–C(14)	123·5 (2)	124·9 (7)	126·9 (3)	120·1 (2)
C(12)–C(13)–C(18)				120·5 (2)
C(14)–C(13)–C(18)				119·3 (2)
C(13)–C(14)–C(15)				120·6 (3)
C(14)–C(15)–C(16)				119·4 (2)
C(15)–C(16)–Cl(16)				118·5 (2)
C(15)–C(16)–C(17)				121·0 (2)
Cl(16)–C(16)–C(17)				120·6 (2)
C(16)–C(17)–C(18)				119·4 (3)
C(13)–C(18)–C(17)				120·3 (2)

* Replace S by O in bond sequence.

Table 4. *Torsion angles* (°) (*e.s.d.'s in parentheses*)

	(I)	(I*a*)	(II)*	(III*a*)
S(1)–C(2)–C(3)–C(4)	−138·0 (1)	−138·9 (5)	−152·9 (2)	134·5 (2)
N(9)–C(8)–C(7)–C(6)	137·1 (2)	138·7 (5)	152·3 (2)	161·6 (2)
S(1)–C(2)–C(8)–N(9)	0·4 (2)	1·1 (6)	0·6 (2)	−0·7 (3)
C(2)–C(8)–N(9)–C(10)	−0·2 (2)	−1·2 (6)	−0·6 (2)	0·8 (3)
C(8)–N(9)–C(10)–S(1)	−0·1 (2)	0·7 (5)	0·3 (2)	−0·5 (2)
N(9)–C(10)–S(1)–C(2)	0·3 (2)	−0·1 (3)	0·0 (2)	0·1 (2)
C(10)–S(1)–C(2)–C(8)	−0·4 (1)	−0·5 (4)	−0·4 (2)	0·4 (2)
N(11)–C(10)–N(9)–C(8)	−179·5 (2)	178·6 (5)	−178·2 (2)	−179·0 (2)
N(11)–C(10)–S(1)–C(2)	179·7 (2)	−178·1 (4)	178·7 (2)	178·6 (2)
H(111)–N(11)–C(10)–N(9)	−6 (2)	162 (4)	−170 (2)	−173 (2)
H(111)–N(11)–C(10)–S(1)	174 (2)	−21 (4)	11 (2)	8 (2)
H(112)–N(11)–C(10)–N(9)	−157 (3)	27 (5)	−5 (2)	−12 (4)
H(112)–N(11)–C(10)–S(1)	23 (3)	−155 (5)	176 (2)	170 (4)
C(2)–C(3)–C(4)–N(5)	−68·9 (2)	−68·8 (7)	−59·6 (3)	79·5 (3)
C(3)–C(4)–N(5)–C(6)	75·3 (2)	75·0 (6)	84·3 (2)	−33·6 (3)
C(4)–N(5)–C(6)–C(7)	−77·7 (2)	−76·2 (6)	−82·8 (3)	−53·2 (3)
N(5)–C(6)–C(7)–C(8)	72·3 (2)	69·3 (6)	59·2 (3)	77·3 (3)
C(6)–C(7)–C(8)–C(2)	−44·0 (3)	−43·6 (7)	−32·7 (4)	−21·2 (3)
C(7)–C(8)–C(2)–C(3)	−5·3 (3)	−3·5 (9)	1·2 (4)	−5·4 (4)
C(8)–C(2)–C(3)–C(4)	49·4 (3)	48·6 (8)	31·3 (4)	−37·3 (4)
C(12)–N(5)–C(6)–C(7)	163·1 (2)	160·5 (5)	151·7 (2)	−178·3 (2)
C(13)–C(12)–N(5)–C(4)	177·5 (2)	168·2 (5)	−61·8 (3)	175·5 (2)
C(13)–C(12)–N(5)–C(6)	−60·5 (2)	−66·6 (6)	64·6 (3)	−56·4 (3)
C(14)–C(13)–C(12)–N(5)	133·8 (3)	110·4 (8)	−126·2 (3)	113·5 (3)

* Replace S by O in bond sequence.

Table 5. *Summary of hydrogen-bonding data* (*distances in* Å, *e.s.d.'s in parentheses*)

X–H···*Y*	*X*···*Y*	*X*–H	H···*Y*	Symmetry operations for *Y*
Compound (I)				
N(11)–H(111)···N(9)	3·061 (3)	0·86 (3)	2·20 (3)	$1-x, 1-y, -z$
Compound (I*a*)				
N(5)–H(5)···Cl⁻	3·102 (5)	0·84 (5)	2·26 (5)	x, y, z
N(11)–H(111)···Cl⁻	3·296 (5)	0·95 (6)	2·37 (6)	x, y, z
N(11)–H(112)···Cl⁻	3·314 (6)	0·83 (6)	2·49 (6)	x, y, z
Compound (II)				
N(11)–H(112)···N(9)	2·967 (3)	0·92 (3)	2·06 (3)	$2-x, -1-y, 2-z$
N(11)–H(111)···N(5)	3·138 (3)	0·87 (3)	2·28 (3)	$x, -\frac{1}{2}-y, \frac{1}{2}+z$
Compound (III*a*)				
O(1*W*)–H(1*W*)···Cl⁻	3·236 (3)	0·90 (6)	2·38 (5)	x, y, z
N(5)–H(5)···Cl⁻	3·116 (2)	0·87 (3)	2·26 (3)	x, y, z
O(1*W*)–H(2*W*)···N(9)	3·016 (4)	0·79 (5)	2·28 (5)	$\frac{1}{2}-x, \frac{1}{2}+y, \frac{1}{2}-z$
N(11)–H(112)···Cl⁻	3·305 (3)	0·78 (5)	2·56 (5)	$\frac{1}{2}-x, -\frac{1}{2}+y, \frac{1}{2}-z$
N(11)–H(111)···O(1*W*)	3·002 (4)	0·89 (4)	2·11 (4)	$\frac{1}{2}-x, \frac{1}{2}+y, -\frac{1}{2}-z$

[0·24 (8) Å (I*a*)] for H(111) and 0·31 (5) Å (I) [0·28 (9) Å (I*a*)] for H(112). This is supported by the torsion angles H(111)–N(11)–C(10)–S(1) = 174 (2)° (I) [−21 (4)° (I*a*)] and H(112)–N(11)–C(10)–S(1) = 23(3)° (I) [−155 (5)° (I*a*)]. In particular the latter deviates remarkably from the expected zero value. The deviation of the amino N atom from a plane through its substituents H(111), H(112) and C(10) is 0·16 (6) Å (I) and 0·23 (8) Å (I*a*).

The chair form of the seven-membered ring for both B-HT 920 structures can be seen from the ring torsion angles (Table 4) compared with the theoretical ones given by Ermer & Lifson (1973) for cycloheptene (Fig. 9). The seven-membered ring of (I*a*) has a relatively ideal chair conformation [torsion angle along C(2)–C(8) close to zero; other ring torsion angles agree with C_s symmetry]. For (I) some non-negligible deviations from an ideal chair geometry do exist, as the sequence of torsion angles shows.

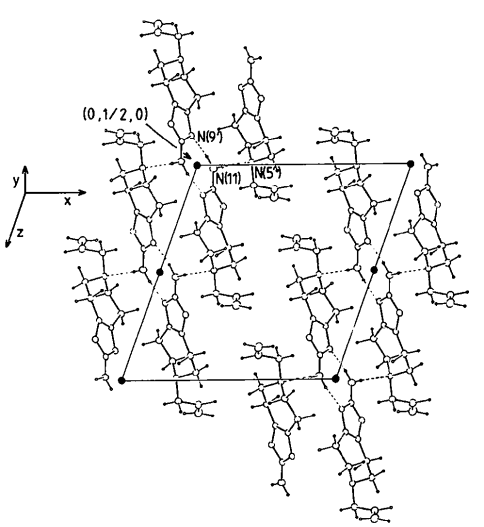


Fig. 4. Illustration of the hydrogen-bonding scheme in B-HT 922 (II), projected on the *xz* plane. Hydrogen bonds (dashed lines) form 'head-to-head' dimers at $(0, \frac{1}{2}, 0)$ and related inversion centers. Additional hydrogen bonds stabilize the lattice in the *x* direction.

For the description of the general folding of the bicyclic ring systems we used three planes: (*A*) all five-membered-ring atoms plus N(11), C(3), C(7), (*B*) C(3), C(4), C(6), C(7), (*C*) C(4), N(5), C(6).

These planes have angles $A/B = 140{\cdot}5\ (3)°$ for (I) and 141·5 (4)° for (I*a*), $B/C = 109{\cdot}3\ (2)°$ for (I) and 115·7 (2)° for (I*a*). This shows that the folding of the ring system is almost the same for (I) and (I*a*). The N atom N(5) is not situated within plane *A*; its distance from this plane is 0·56 (1) Å for (I) and 0·52 (3) Å for (I*a*).

The side chains C(12) to C(14) have the same arrangements for (I) and (I*a*). In both cases C(13) is *trans* with respect to C(4) and *gauche* to C(6) (see torsion angles in Table 4). Overall it can be stated that except for the C–N bonds at N(5) which are longer for the protonated N atom, both molecular structures are very similar.

Although the general molecular conformation of the oxazole analogue B-HT 922 (II) is very similar to those of (I) and (I*a*) some pronounced differences exist upon detailed examination. The oxazole ring is planar (average deviation of contributing atoms from a least-squares plane is $\sigma = 0{\cdot}003$ Å), the amino N atom N(11) is within the plane of this ring [deviation 0·032 (3) Å] and H(111) and H(112) are out of the plane by only 0·10 (6) and 0·02 (6) Å. The deviation of N(11) from a plane through its substituents is only 0·08 (6) Å, so that a pure sp^2 hybridization of the amino group in this structure can be assumed.

In B-HT 922 (II) the seven-membered ring also adopts a chair conformation; however, a comparison of the ring torsion angles shows that there are differences in the ring shape when compared to (I). This is supported when the same folding planes *A*, *B* and *C* are calculated as for (I) and (I*a*). The interplanar angles are $A/B = 153{\cdot}3(3)°$ and $B/C = 115{\cdot}2(2)°$. It follows that - compared to (I) - the oxazolo part of the bicyclic ring system is more flattened with respect to the middle-ring plane *B* of the seven-membered ring, whereas plane *C* is more inclined; in contrast to (I) and (I*a*) the azepine N atom N(5) is within 0·05 (1) Å in plane *A*. The side chain C(12) to C(14) has a *gauche-gauche* conformation of C(13) with respect to C(4) and C(6) in contrast to (I) and (I*a*) where a *trans-gauche* arrangement was found for this group.

The bicyclic ring system of the protonated form (III*a*) of B-HT 958 is chemically equivalent to that of (I*a*); however, the spatial structure is totally different. As can be seen from Fig. 1 and from the ring torsion angles, the seven-membered ring no longer has a chair form but now adopts a twist conformation. Although for the comparable cycloheptene ring the chair form was calculated by Ermer & Lifson to be energetically most favored, they found the twist form less stable by only 1·76 kJ mol^{-1}.

The thiazole ring is planar ($\sigma = 0{\cdot}003$ Å) as in the other structures (I), (II), (IV). The amino H atoms H(111) and H(112) are both out of the thiazole ring plane by 0·31 (6) and 0·10 (7) Å on the same side, so that a slightly pyramidal conformation of the amino group results.

The proton H(5) and the C atom C(12) are both bound bisectionally to N(5). The phenyl ring C(13)–C(18) is in a *trans-gauche* position with respect to C(4) and C(6) as were the side groups in (I) and (I*a*).

Owing to the existence of a twisted seven-membered ring this molecular structure is geometrically totally different from the others. Whereas for

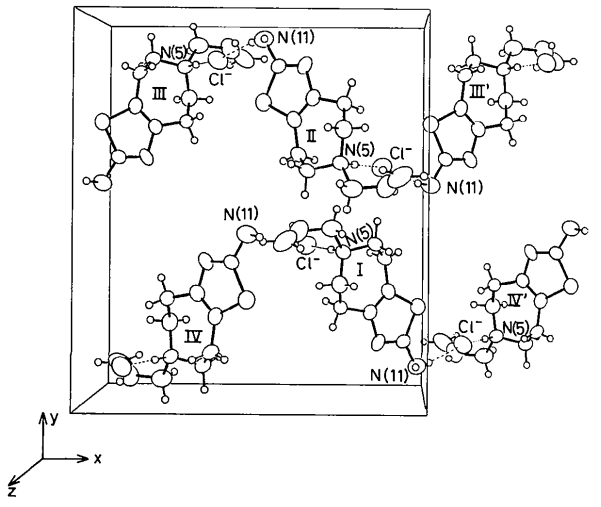


Fig. 5. Illustration of the infinite chains formed by hydrogen bonding (dashed lines) in the hydrochloride of B-HT 920 (I*a*). The projection is on the *xy* plane. For clarity only the following four molecules of the unit cell are plotted: (I) x, y, z; (II) $\frac{3}{2}-x, 1-y, \frac{1}{2}+z$; (III) $1-x, \frac{1}{2}+y, \frac{3}{2}-z$; (IV) $-\frac{1}{2}+x, \frac{1}{2}-y, 2-z$. In addition two molecules of a neighboring cell are drawn, obtained from (III) and (IV) by the translation $1+x$.

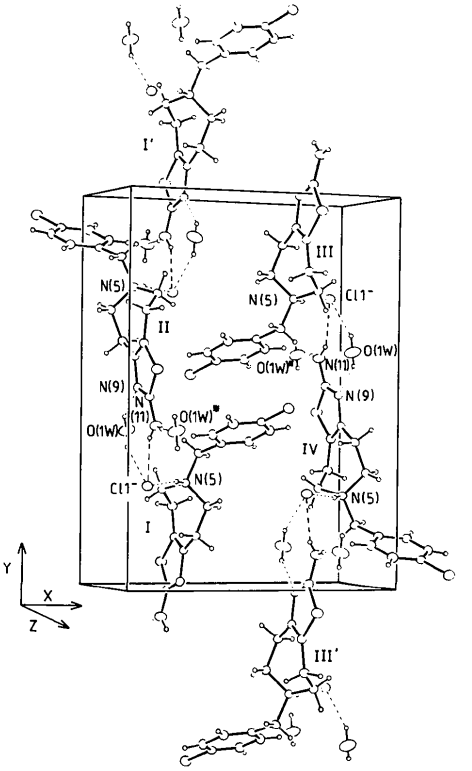
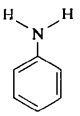
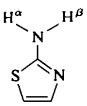
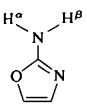
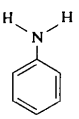
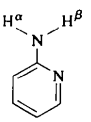
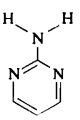


Fig. 6. Illustration of head-to-tail chains in the *z* direction formed by hydrogen bonds (dashed lines) in the crystal lattice of the hydrochloride of B-HT 958. Symmetry operations are: (I) x, y, z; (II) $\frac{1}{2}-x, \frac{1}{2}+y, \frac{1}{2}-z$; (III) $1-x, 1-y, 1-z$; (IV) $\frac{1}{2}+x, \frac{1}{2}-y, \frac{1}{2}+z$. (I') and (II') are translations of (I) and (II) in *y*. O(1*W*)* is obtained from O(1*W*) by translation in *z*.

Table 6. *Energy-minimized* C-N^{amine} *bond lengths and torsion angles of aniline, 2-aminothiazole and 2-aminooxazole calculated with the programs MNDO and MMPI in comparison to the literature values of aniline, 2-aminopyridine and 2-aminopyrimidine*

Two values of the torsion angle are given for nonequivalent H atoms; first value: $\tau(X\text{-C-N-H}^{\alpha})$, second value: $\tau(\text{N-C-N-H}^{\beta})$. Torsion angles in square brackets are calculated from the literature values of the out-of-plane angles φ (amine N) or from the z coordinates of the H atoms. The experimental barriers to inversion of aniline as well as calculated values for all the compounds are included.

	Method, reference	C-N^{amine} (Å)	X-C-N-H (°)	$E(N^{inv})$ (kJ mol^{-1})
	MNDO	1·427	30	17·2
	ab initio (STO-3G), (8)	1·400†	27	11·3
	MMPI	1·402	20	6·7
	MNDO	1·397	42/−14	8·8
	MNDO/X-ray*	1·360*	35/−15	7·5
	MMPI	1·366	12/−5	1·4
	MNDO	1·403	38/−21	13·4
	MNDO/X-ray*	1·337*	33/−16	6·3
	MMPI	1·338	7/−3	0·5
	Microwave, (1)	1·402 (2)	[22]	5·4 [exp., ref. (2)]
	Microwave, (3)	Not determined	[19/−14]	8·8
	X-ray, (4)	1·351 (2)	[6/−8]	[calc., ref. (7)]
	Microwave, (5)	Not determined	[11]	3·6
	X-ray, (6)	1·342 (2)	[13]	[calc., ref. (5)]

References: (1) Lister, Tyler, Høg & Larsen (1974). (2) Quack & Stockburger (1972). (3) Kydd & Mills (1972). (4) Chao, Schempp & Rosenstein (1975). (5) Lister, Lowe & Palmieri (1976). (6) Scheinbeim & Schempp (1976). (7) Christen, Norburg, Lister & Palmieri (1975). (8) Hehre, Radom & Pople (1972).

* MNDO/X-ray values are obtained by a MNDO calculation using X-ray bond lengths and bond angles of the aminothiazole and aminooxazole part of B-HT 920 BS and B-HT 922 BS.

† Studied bond lengths used.

(I), (I*a*) and (II) local mirror symmetry exists involving the bicyclic ring system, local twofold symmetry is present for (III*a*) with the twofold axis passing through N(11), C(10) and N(5).

If the crystal structures for the four structures are compared (Figs. 3 to 6 and Table 5) differences can clearly be observed between the protonated structures (I*a*) and (III*a*) on the one hand and the nonprotonated compounds (I) and (II). For the latter compounds two molecules related by a crystallographic inversion center are connected by a hydrogen-bond pair between one H of the amino group and the N atom of the oxazole/thiazole ring. Thus 'head-to-head' dimers are formed if we regard the amino and five-membered-ring part as the molecular head. In the case of B-HT922 an additional intermolecular hydrogen bond from the second amino H to the nitrogen N(5) of the seven-membered ring stabilizes the structure in the x direction (Fig. 4).

In the case of (I*a*) and (III*a*), the proton H(5) at N(5) acts as an additional donor for a hydrogen bond, and the Cl^- ion as an additional acceptor. For both structures the hydrogen-bond sequence N(5)-H(5)···Cl^-···H(amino)-N(11′) exists causing a chain-like connection of molecular heads and tails *via* the Cl^- anion. Thus in contrast to the free bases infinite 'head-to-tail' chains exist in the crystal lattices. An additional water molecule stabilizes these chains by further hydrogen bonds in the structure of (III*a*).

(*b*) *MM calculations on model compounds*

In addition to the X-ray determinations of the molecular conformations we were interested to obtain information about the global and local minimum-energy conformations and their inversion barriers in the thiazolo- and oxazolo-azepines (I) and (II) from

semi-empirical quantum-chemical and molecular-mechanics calculations.

The results of our earlier MNDO calculations on oxazole and thiazole in comparison to the molecular-mechanics calculations and to experimentally derived microwave structures are shown in Fig. 7. The experimental gas-phase structures were taken from Kumar, Sheridan & Stiefvater (1978) for oxazole ('best' structure derived as average between the r_s structure and the least-squares-fit results) and from Nygard, Asmussen, Høg, Mahashwari, Nielsen, Petersen, Rastrup-Anderson & Sørensen (1971) for thiazole (r_{av} structure). For these model compounds only the *MMPI* geometry fitted well. The situation is the same for the calculation of amino-substituted or condensed oxazoles and thiazoles. Table 6 gives a survey of the exocyclic C–N bond lengths and of the hybridization of the exocyclic amino N atom in aniline and in the heteroaromatic analogues 2-aminopyridine and 2-aminopyrimidine, which have been collected from the literature (see references in Table 6) and which are compared with quantum-chemical (MNDO) and molecular-mechanics (*MMPI*) calculations. The failure of the MNDO method to reproduce the hybridization of N atoms is clearly shown. Even *ab initio* calculations using the STO-3G basis set cannot reproduce the hybridization of the N in aniline (Wolf, Vogts & Schmidtke, 1980). The results obtained with the program *MMPI* encouraged us to use this molecular-mechanics program for the series of B-HT compounds.

(c) *MM calculations on the B-HT compounds* (I) *and* (II)

The conformation and the geometrical structure data for two selected conformations of B-HT 920 and B-HT 922 in their protonated states are shown in Figs. 8, 9, 10 and in Tables 7 and 8 respectively. For comparison the allyl group was fixed in a *trans–gauche* position in both cases as found in the crystal structure of (I). In the case of the thiazolo-azepine B-HT 920 the chair conformation (63·6 kJ mol^{-1}) and the twist form (63·0 kJ mol^{-1}) are nearly equiener-

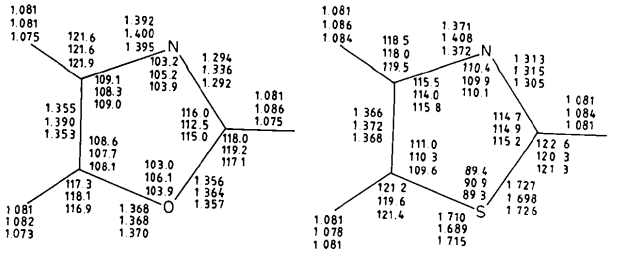


Fig. 7. Molecular structure of oxazole and thiazole as results of optimization by *MMPI* (first value) and MNDO (second value) calculations in comparison to the experimental gas-phase structures (third value) (Kumar, Sheridan & Stiefvater, 1978; Nygard, Asmussen, Høg, Malashwari, Nielsen, Petersen, Rastrup-Anderson & Sørensen, 1971).

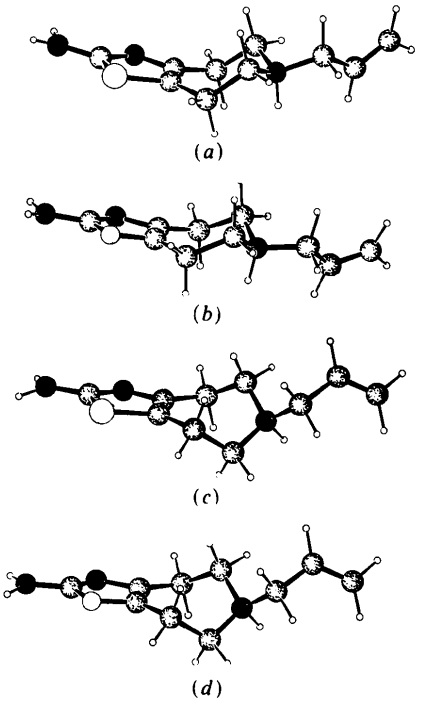


Fig. 8. Illustration of the chair [(*a*), (*b*)] and twist [(*c*), (*d*)] conformations of B-HT 920 and B-HT 922 in their N(5)-protonated forms optimized by *MMPI* calculations (plotted with *SCHAKAL*, Keller, 1980). The allyl chain is always in the same position [C(13) *trans* to C(4)].

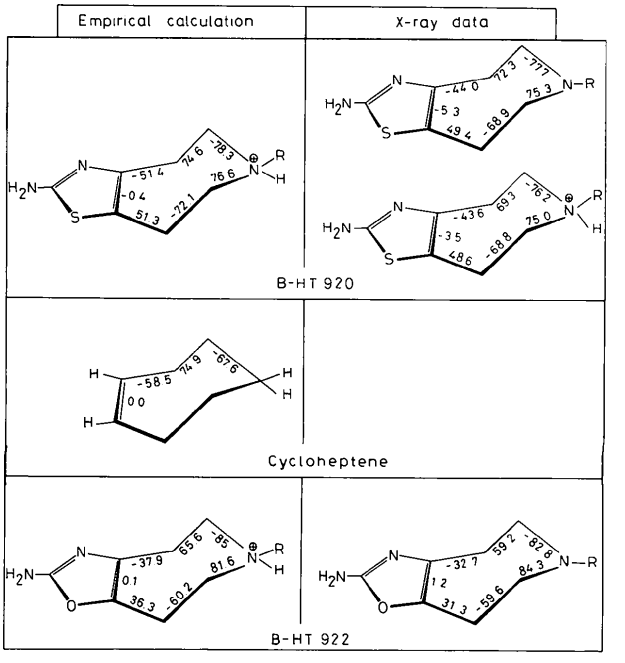


Fig. 9. Energy-minimized torsion angles (°) of the azepine ring in the *chair* conformation for B-HT 920 and B-HT 922 calculated with the program *MMPI* in comparison to the values of the X-ray analysis and to the *EFF* calculations for cycloheptene (Ermer & Lifson, 1973).

Table 7. *Energy-minimized bond lengths* (Å) *of the chair* (*first value*) *and of the twist* (*second value, when different from the first value*) *conformations of B-HT* 920 *and B-HT* 922 *calculated with the program MMPI as illustrated in Fig.* 8

	B-HT 920 chair/twist	B-HT 922 chair/twist
S/O(1)–C(2)	1·740	1·369
C(2)–C(8)	1·360	1·349
C(8)–N(9)	1·380	1·397
N(9)–C(10)	1·321	1·305
C(10)–S/O(1)	1·712	1·357
C(10)–N(11)	1·367	1·337
C(2)–C(3)	1·499 1·504	1·486 1·491
C(3)–C(4)	1·533 1·536	1·532 1·537
C(4)–N(5)	1·501 1·496	1·505 1·500
N(5)–C(6)	1·501 1·492	1·505 1·497
C(6)–C(7)	1·533 1·536	1·533 1·538
C(7)–C(8)	1·501 1·506	1·495 1·500
N(5)–C(12)	1·501 1·496	1·501 1·497
C(12)–C(13)	1·511	1·511
C(13)–C(14)	1·339	1·339

Table 8. *Energy-minimized bond angles* (°) *of the chair* (*first value*) *and of the twist* (*second value, when different from the chair*) *conformations of B-HT* 920 *and B-HT* 922 *calculated with the program MMPI as illustrated in Fig.* 8

	B-HT 920 chair/twist	B-HT 922 chair/twist
C(2)–S/O(1)–C(10)	88·8	103·0
S/O(1)–C(2)–C(3)	121·5 121·1	115·9 119·2
S/O(1)–C(2)–C(8)	110·1	108·7
C(3)–C(2)–C(8)	128·4 128·8	135·2 132·0
C(2)–C(3)–C(4)	112·8 109·9	113·5 108·1
C(3)–C(4)–N(5)	113·7 115·2	113·8 115·5
C(4)–N(5)–C(6)	112·5 113·6	112·3 114·2
C(4)–N(5)–C(12)	110·3 111·6	110·1 111·4
C(6)–N(5)–C(12)	109·9 111·4	109·8 111·2
N(5)–C(6)–C(7)	113·7 114·3	114·0 114·9
C(6)–C(7)–C(8)	112·4 110·8	113·1 109·5
C(2)–C(8)–C(7)	126·4 127·2	129·1 127·2
C(2)–C(8)–N(9)	115·4	109·7
C(7)–C(8)–N(9)	118·2 117·6	121·0 122·9
C(8)–N(9)–C(10)	110·0	102·5
S/O(1)–C(10)–N(9)	115·8	116·1
S/O(1)–C(10)–N(11)	122·6	117·8
N(9)–C(10)–N(11)	121·6	126·1
N(5)–C(12)–C(13)	112·0 112·5	112·1 112·5
C(12)–C(13)–C(14)	123·2 123·7	123·2 123·8

getic. The influence of the allyl-group position and the sign of the H torsion angle of the exocyclic amino group are discussed below. The oxazolo-azepine B-HT 922 shows a preference for the chair (54·8 kJ mol^{-1}) *versus* the twist conformation (57·95 kJ mol^{-1}). It is of interest to note that in the case of B-HT 920 the weak preference for the twist conformation is due to the dipole (and ion-dipole) interactions.

In the second part we studied the conformational interconversion behavior of the azepine ring. Controversies exist in the literature about the third energy minimum in addition to the chair and the twist conformations in the case of cycloheptene. Allinger & Sprague (1972), using *MMI*, proposed the boat conformation as a minimum and Ermer & Lifson (1973) using *CFF* found the boat as a transition state and a 'very distorted' boat as the energy minimum.

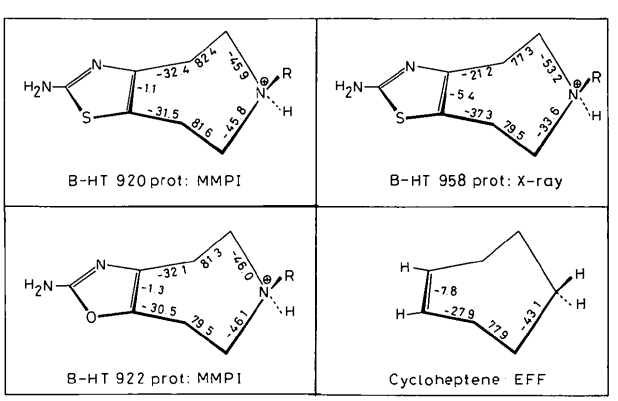


Fig. 10. Energy-minimized torsion angles (°) of the azepine ring in the *twist* conformation of B-HT 920 and B-HT 922 in the protonated form calculated with the program *MMPI* in comparison to the values of the B-HT 958 Cl X-ray structure and to the *EFF* values calculated for cycloheptene.

Our molecular-mechanics calculations using *MMPI* (with additional parametrization for heterocyclic compounds) show the following picture (Fig. 11 and Table 9). Starting from the chair conformation (R^{eq}) and using the dihedral driver for the angle S(1)–C(2)–C(3)–C(4) [passing through the coplanar position of C(7)–C(8)–C(2)–C(3)–C(4), transition state *A*] we reached a distorted boat conformation [the atoms C(4) and N(5) forming a half-boat: C(4)–N(5) boat, R^{eq}]. The torsion angles of this distorted boat conformation are shown in Fig. 12 in comparison to the values of cycloheptene from Ermer & Lifson (1973). The energy of this local minimum is 7·9 kJ mol^{-1} above the chair conformation (in cycloheptene Ermer found 10·9 kJ mol^{-1}). On the other hand, it is possible to reach this half boat starting from the twist [S(1)–R^{cis}] conformation. Here the transition state is the coplanar position of C(3)–C(2)–C(8)–C(7)–C(6) (*B*) but the transition energy is higher (17·6 kJ mol^{-1}). Searching for the boat conformation we applied the dihedral driver for C(6)–C(7)–C(8)–N(9) to the C(4)–N(5) boat, R^{eq}. The boat conformation is found as a transition state (*C*) being 15·1 kJ mol^{-1} above the half boat whereas the energy minimum is a new half boat [N(5)–C(6) boat, R^{eq}] which is nearly equienergetic to the former half boat. It is also possible to go directly from the chair to the boat by passing the coplanar C(3)–C(4)–N(5)–C(6)–C(7) position, but this is energetically less favorable (in the cycloheptene series Allinger found 43·1 kJ mol^{-1}). A second twist form can also be found [twist, S(1)–R^{trans}] but the energy and geometry values are not very different. All the conformations with an axial allyl group (R^{ax}) have not yet been included in driver calculations. Because in the seven-membered rings the steric interactions of the axial

Table 9. *Energies* (kJ mol^{-1}) *of the different local minimum-energy conformations and of some transition states of B-HT* 920 *and B-HT* 922 *with equatorial allyl positions*

Azepine conformation	Allyl-group conformation	E^{ster} (kJ mol^{-1}) B-HT 920	B-HT 922
Chair, R^{eq}	tg	63·6	54·8
	gg	65·3	55·6
	gt	63·6	54·8
C(4)–N(5) boat, R^{eq}	tg	71·5	61·1
N(5)–C(6) boat, R^{eq}	tg	71·1	62·8
Twist, S(1)–R^{cis}	tg	63·0	57·9
	gg	64·0	59·0
	gt	63·0	57·9
Twist, S(1)–R^{trans}	tg	63·2	58·2
(*A*) C(7)–C(8)–C(2)–C(3)–C(4)/pl	tg	74·1	64·0
(*B*) C(6)–C(7)–C(8)–C(2)–C(3)/pl	tg	81·2	72·4
(*C*) Boat, R^{eq}	tg	86·6	79·9

substituents are less pronounced than in the six-membered-ring compounds the axial conformations are expected to have small geometric and energetic differences and should not be different in the oxazolo- and thiazolo-azepines.

The differences within the thiazole and oxazole series are small. The above discussion holds for both series.

We also calculated the energy for the isomers with the opposite orientation of the exocyclic amino group. In all four cases the energies of the inverse forms were not different (<0·4 kJ mol^{-1}).

In Table 9 the influence of the allyl-group position on the steric energy is summarized. The principal orientations of this group are a *trans-gauche* (tg) arrangement of C(13) with respect to C(14) and C(6) [C(13) *trans* to C(4)], a *gauche-trans* (gt) arrangement [C(13) *trans* to C(6)] and a *gauche-gauche* (gg) arrangement [C(13) *gauche* to both C(4) and C(6)]. In the chair conformation the gg form, which is found in the X-ray structure of B-HT 922 and 933, is energetically possible especially in the oxazole series. The gt orientation is not found in any X-ray structure, but there is no energy difference to the tg form. In the twist form gt is equienergetic to tg, but gg because of steric interactions is not preferred. The X-ray conformations found are mainly influenced by crystal-packing forces which play a dominant role in determining the actual conformations in cases where equienergetic conformational varieties exist.

Comparison and conclusions

Comparing the geometry data obtained from X-ray analysis and molecular-mechanics calculations it can be seen that there is generally a good agreement. The molecular shape of the B-HT compounds (I)–(IV) is mainly influenced by the conformation of the azepine ring, being expressed numerically by its endocyclic torsion angles. This can be seen from Figs. 9 and 10. For comparison we include the X-ray values of B-HT 920 free base, and hydrochloride, B-HT 922 and

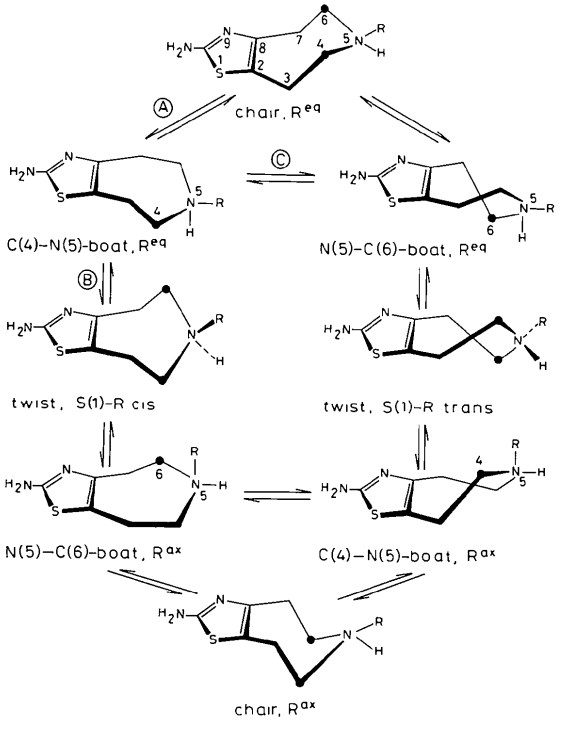


Fig. 11. Conformation of the seven-membered ring: local energy minima and transition states. The energies of the conformations with equatorial allyl groups and of the transition states *A*, *B* and *C* are shown in Table 9.

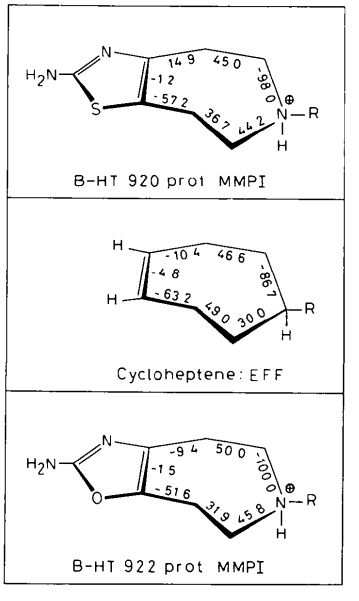


Fig. 12. Energy-minimized torsion angles (°) of the azepine ring in the distorted boat conformation of B-HT 920 and B-HT 922 (protonated form) calculated with the program *MMPI* in comparison to the *EFF* values of cycloheptene.

B-HT 958. The values of B-HT 933 (Carpy *et al.*) are very similar to those of B-HT 922.

The largest difference between the experimental and the calculated structures is found in the bond lengths of the five-membered rings. An explanation for this difference might be the use of molecular-mechanics parameters based on corrected microwave values and electron diffraction data and possibly to an even larger extent the influence of the hydrogen bonds, which are formed in all X-ray structures by the N(9) and H(111) and/or H(112) atoms. We expect that these intermolecular hydrogen bridges influence the bond lengths as follows: The aromatic π system which includes the atoms S/O(1), C(2), C(8), N(9), C(10) and N(11) is to some extent disturbed in the crystals. It can be assumed that under the influence of the hydrogen bonds a quasi-amidine system is formed in the thiazoles by the N(9), C(10) and N(11) atoms and a quasi-isourea system by the atoms N(9), C(10), N(11) and O(1) in the oxazoles. This results in a shortening of the C(2)–C(8) bond and a lengthening of the bonds C(8)–N(9), S(1)–C(10) and O(1)–C(2) respectively.

It is also interesting that in the oxazole derivatives the atoms at the amino group N(11) are more or less in the plane of the heteroaromatic ring, whereas in the thiazoles the H atoms of the amino group seem to be more out of the plane. The good ability of the *MMPI* method to reproduce this critical hybridization correctly (see also Table 6 for similar structures) is due to the good estimation of the π bond orders in the *VESCF* part. For the thiazole derivatives (I), (I*a*) and (III) the average torsion angles of both H atoms H(111) and H(112) are 16°. The *MMPI* results show 15° for H(112) and 5° for H(111). The values for the oxazole compound B-HT 922 (II) and B-HT 933 (IV) are 11 and 10° for H(111), and −5 and −7° for H(112) respectively in the X-ray structures and 7° for H(112) and −3° for H(111) in the *MM* calculations.

Planarization of the amino group in the oxazole series is brought about by the increased conjugation of the two N π electrons with the oxazole ring [sp^2 hybridization, X-ray C(10)–N(11) bond length 1·337 Å for B-HT 922 and 1·335 Å for B-HT 933, *MM* value: 1·337 Å]. Because of less conjugation longer C(10)–N(11) bonds are observed (mixed sp^2–sp^3 hybridization, average X-ray bond length 1·357 Å, *MM* value: 1·367 Å) for the thiazoles.

Another conformational difference between the oxazole- and thiazole-azepines which is revealed by the X-ray and computational studies and which might also account for the observed different biological profile is the position of the azepine N atom N(5) with respect to the heteroaromatic ring. In the thiazole compounds with a chair conformation of the azepine ring (B-HT 920 free base and hydrochloride) the nitrogen N(5) is 0·56 and 0·52 Å respectively above plane *A*. The calculated distance for the protonated form of the B-HT 920 chair is 0·47 Å.

This is not the case for oxazolo-azepines. For B-HT 922 and B-HT 333 these distances are 0·05 and 0·02 Å respectively. The *MMPI* calculations also confirm this value (0·06 Å). The influence of the torsion angles of the azepine ring on these different conformations in comparison to cycloheptene can be seen in Fig. 9.

For the compound B-HT 933 Humblet, Marshall & Wermuth (1981) obtained different results. Using the *MMS-X* molecular modeling system (the predecessor of the *SYBYL* program) the oxazole compound B-HT 933 was optimized starting from the planar X-ray geometry to a conformation where the N position is about 1·0 Å above the five-membered-ring plane. According to our findings this conformation is only typical for the thiazolo-azepines but not for the oxazolo-azepines. The apparent discrepancy between the experimentally determined and the calculated conformation of B-HT 933 might, however, be due to a lack of parameterization in their molecular-modeling system.

The energy requirement for the oxazolo-azepines to adopt the chair conformation of the thiazolo-azepines is about 1·7 kJ mol^{-1} (*MMPI*) and the same value is necessary for the conformational change of the thiazolo-azepines to the oxazolo-azepines.

The different position of the N(5) atom in the chair conformations of B-HT 920 and B-HT 922 also causes a slight difference in the position of the side chains (see Fig. 8). In addition, especially in the oxazolo-azepines, the gg position of the allyl group seems to be energetically possible (in analogy to the X-ray position) whereas this position in B-HT 920 is less preferred by 1·7 kJ mol^{-1}. In all three X-ray structures of the thiazolo-azepine compounds the gt position was not found, but the preference of the tg over the gt position could not be shown by the *MM* calculations (Table 9).

Rather peculiar is, however, the fact, that within the thiazole series a twist form of the azepine ring is found in the X-ray studies. The ability of the thiazolo-azepines to adopt this unique conformation is also confirmed by the molecular-mechanics calculations. In contrast to the oxazole compounds the chair and the twist conformations are nearly equi-energetic.

The position of the allyl group in this conformation does not influence the steric energy (Table 9). By analogy with B-HT 920 it can be assumed that the protonated molecules of B-HT 922 and 933 would also prefer the chair conformation as could be demonstrated by the computational work. However, because of lack of experimental evidence this question is still unsolved.

Based upon these studies a rather hypothetical explanation can be presented for the additional

dopaminergic effect, observed with the thiazole compounds B-HT 920 and B-HT 958 respectively.

If a threefold interaction with the dopamine receptor is assumed, only the simultaneous stimulation of corresponding receptor parts by the thiazole ring, the azepine N^+ and the allyl group should lead to the dopaminergic effect, whereas in the oxazole series because of the different azepine conformations and a somewhat restricted conformational flexibility the receptor can accommodate the oxazoles less. For the interaction with α-adrenergic receptors these conformational differences appear to be less critical.

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