284. Crystal Structure and Molecular Conformation in Solution of 6-Phenyl- and 11-Phenyl-3,4,6,11-tetrahydro-2*H*-pyrimido[2,1-*c*][2,4]benzothiazepine

26th Communication on Seven-Membered Heterocycles[1])

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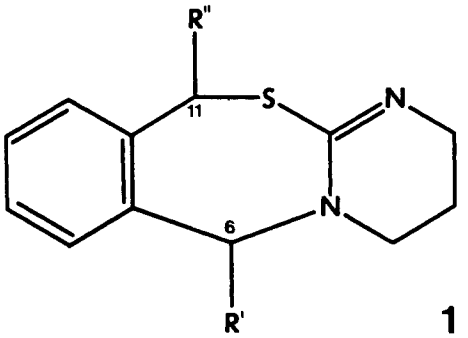
Die Kristallstruktur und die molekulare Konformation in Lösung von 6-Phenyl- und 11-Phenyl-3,4,6,11-tetrahydro-2*H*-pyrimido-[2,1-*c*][2,4]benzothiazepin

Zusammenfassung

Die Röntgenstrukturanalysen der beiden Titelverbindungen ergaben, dass die Konformation der Thiazepinringe zwar voneinander verschieden sind, dass aber in beiden Verbindungen der Phenylsubstituent in axialer Stellung steht. Interpretationen der ^{1}H-NMR.-Daten legen die Vermutung nahe, dass die bevorzugten Konformationen des siebengliedrigen Ringes in Lösung in beiden Molekeln mit den im Kristall beobachteten Konformationen identisch sind.

In the course of the synthesis of tricyclic benzo-2,4-thiazepines of type **1** [1], ^{1}H-NMR. data suggested that in solution the seven-membered thiazepine ring of the unsubstituted compound (**1c**) undergoes rapid *pseudo*-rotation, but that substitution of a phenyl in position 6 or 11 stabilizes the ring in a particular conformation with the aromatic substituent in an *axial* position. In order to study the conformation of the substituted thiazepine rings the crystal structures of the two compounds (**1a**) (hereafter called "*6-phenyl* compound") and of the hydrobromide of (**1b**) (hereafter called "*11-phenyl* compound") were determined by X-ray analysis.



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1a $R' = C_6H_5$, $R'' = H$
1b $R' = H$, $R'' = C_6H_5$
1c $R' = H$, $R'' = H$

[1]) 25th Communication [1].

Crystal Data. – *6-phenyl*-3,4,6,11-tetrahydro-2 *H*-pyrimido[2,1-*c*][2,4]benzothiazepine, $C_{18}H_{18}N_2S$, $M=294$, colourless prismatic crystals, grown from a solution in toluene, m.p. 169–171°, monoclinic, space group $P2_1/c$, $a=6.871$, $b=17.410$, $c=12.670(4)$ Å, $\beta=99.70(2)°$, $V=1494$ Å^3, $d_{calc}=1.31$ g cm^{-3}, $\mu(CuK\alpha)=18.1$ cm^{-1}.

11-Phenyl-3,4,6,11-tetrahydro-2 *H*-pyrimido[2,1-*c*][2,4]-benzothiazepine-hydrobromide, $C_{18}H_{18}N_2S \times HBr$, $M=375$, colourless, needle shaped crystals, grown from a solution in methanol, m.p. 213–216°, monoclinic, space group $P2_1/n$, $a=20.553(5)$, $b=10.263(2)$, $c=8.292(2)$ Å, $\beta=95.38(2)°$, $V=1741$ Å^3, $d_{calc}=1.46$ g cm^{-1}, $Z=4$, $\mu(CuK\alpha)=46.9$ cm^{-1}.

Intensity Data. – For both crystals intensity profiles were measured on a four circle diffractometer (normal-beam equatorial method, crystal in bisecting position) with graphite monochromatized Cu*K*α-radiation, ($\lambda=1.542$ Å, ($\omega/2\theta$)-scan mode, variable scan width $\Delta\omega=1.0°+0.5$ tan (θ) (*11-phenyl* compound), $\Delta\omega=1.0°+0.3$ tan (θ) (*6-phenyl* compound), scan time adjusted so as to accumulate 6000 counts per reflexion (max. scan time 120 s). The net intensity, I, was evaluated by profile analysis [2], and the variance defined as $\sigma^2(I)=\langle I\rangle+c^2I^2$, where $\langle I\rangle$ is the variance based on a *Poisson* distribution of the measured counts, and c^2I^2 an intensity dependent term with $c=0.02$ (both crystals).

The stability and orientation of the crystals were monitored throughout data collection by frequent measurements of check reflexions. 2217 unique reflexions in the range $1.5<\theta<60°$ for the *11-phenyl* compound, and 2186 unique reflexions in the range $1.5<\theta<55°$ for the *6-phenyl* compound, were measured, of which 1846 (*11-phenyl* compound) and 1994 (*6-phenyl* compound) were judged to have significant intensity, *i.e.* $I\geq 3.0\sigma(I)$. Both sets of data were corrected for *Lorentz* and polarisation effects and scaled to absolute structure amplitudes $|F_o|$ by the *Wilson* method [3]. The variance of $|F_o|$ was defined as $\sigma^2(F)=k\cdot Lp\cdot\sigma^2(I)/4I$, where k is the scale factor relating I and $|F_o|^2$, Lp the *Lorentz*-polarization factor. The calculation of normalised structure amplitude, $|E|$, yielded the averages $\langle|E|\rangle=0.789$, $\langle|E^2-1|\rangle=0.975$, $\langle|E|^2\rangle=0.992$ for the *11-phenyl* compound (overall temperature factor $\bar{B}=5.0$ Å^2), and $\langle|E|\rangle=0.804$, $\langle|E^2-1|\rangle=0.945$, $\langle|E|^2\rangle=1.000$ for the *6-phenyl* compound ($\bar{B}=3.4$ Å^2).

Structure Solution and Refinement. – The structure of the *11-phenyl* compound, which was crystallized as the hydrobromide, was solved by the heavy atom method. The quantity $\sum w(|F_o|-k\,g'|F_c|)^2$ was minimised by least squares by use of a block-diagonal approximation. Weights were assigned as $w=1/\sigma^2(F)$ for significant reflexions and $w=0$ for insignificant ones. The LS-procedure was started by refining a scale factor (k), positional parameters for the atoms other than hydrogen, and isotropic temperature factors, and continued by replacement of the isotropic by anisotropic temperature factors. At this stage a difference map revealed the presence of a disordered molecule of methanol with one atom on a center of symmetry. The peak in a general position could be assigned to the oxygen atom, because the distance of 3.30 Å to a bromine atom indicated a hydrogen bond O–H···Br$^-$. The positions of the hydrogen atoms were then calculated and included in the refinement with isotropic temperature factors. In the final stages an isotropic extinction coefficient g' [4] was included into the parameter set, and the least-squares process converged to $R=0.088$ for 1994 significant reflexions, and 281 variables. The average positional error for *C*- and *N*-atoms is around 0.006 to 0.008 Å, for S and Br around 0.001 Å, for H around 0.08 Å. The isotropic extinction factor g' reached a value of 5.0(9), assuming a mean path length of 0.02 cm.

The structure of the *6-phenyl* compound was solved by direct methods. The signs of 513 normalized structure factors with $|E|\geq 1.2$ were determined by an automated symbolic addition procedure [5] using some 8000 triple sign relations. All atoms other than hydrogen were clearly indicated in the E-map. The refinement process followed the same lines as that of the *11-phenyl* compound and converged to $R=0.045$ for 1846 significant structure factors and 267 variables. (*C*-, *N*-, and *S*-atoms anisotropic, *H*-atoms isotropic, scale factor and isotropic extinction factor.) A difference map calculated at the conclusion of the refinement showed no significant residual density. The average positional error for *C*- and *N*-atoms is 0.003 to 0.004 Å, for the sulfur atom 0.001 Å, and for the H-atoms 0.03 to 0.05 Å. The isotropic extinction coefficient refined to 1.6(2), assuming a mean path of 0.02 cm.

Fractional coordinates with e.s.d.'s for both molecules are given in *Table 1*, the atomic numbering is shown in *Figs. 1* and *2*. The scattering factors were taken from "International Tables of Crystallography" (1962). A list of structure factors and vibrational parameters can be obtained from the authors.

Table 1. *Fractional coordinates with e.s.d.'s for the* 11-phenyl *and the* 6-phenyl *compounds.* The coordinates of the heavier atoms are multiplied by 10^5, the values for hydrogen atoms by 10^4

	11-phenyl compound			*6-phenyl compound*		
	x/a	*y/b*	*z/c*	*x/a*	*y/b*	*z/c*
N(1)	35813 (30)	39401 (57)	21905 (70)	46336 (39)	11181 (14)	60860 (24)
C(2)	29979 (58)	37162 (96)	11237 (95)	63128 (57)	6189 (20)	64528 (37)
C(3)	28193 (55)	24852 (92)	8787 (98)	75508 (71)	8920 (24)	74323 (46)
C(4)	30745 (30)	14340 (68)	19433 (82)	80706 (51)	17143 (19)	73884 (29)
N(5)	37069 (20)	17563 (45)	28216 (55)	64818 (32)	21902 (12)	68169 (18)
C(6)	41270 (27)	6678 (55)	35126 (71)	69271 (37)	30159 (15)	68145 (20)
C(6a)	41327 (23)	4621 (52)	52988 (68)	55760 (39)	34894 (14)	73891 (20)
C(7)	40605 (26)	– 8381 (55)	58286 (79)	62952 (43)	37603 (16)	84173 (21)
C(8)	41274 (26)	– 11383 (61)	74283 (81)	50910 (51)	41703 (17)	89832 (23)
C(9)	42712 (26)	– 2049 (66)	85866 (76)	31677 (52)	43234 (18)	85335 (25)
C(10)	43411 (25)	10560 (60)	80976 (70)	24363 (46)	40564 (17)	75121 (24)
C(10a)	42792 (23)	14151 (52)	64798 (64)	36096 (39)	36376 (14)	69336 (21)
C(11)	43195 (24)	28750 (50)	61472 (67)	28077 (40)	33348 (16)	58468 (21)
S(12)	46161 (6)	33610 (14)	41981 (18)	25670 (11)	23008 (4)	57763 (6)
C(12a)	39009 (25)	29757 (55)	29390 (69)	48462 (40)	18355 (15)	62679 (22)
C(13)	36888 (24)	35913 (52)	63873 (64)	72144 (36)	33189 (15)	57168 (21)
C(14)	37188 (29)	48591 (71)	69563 (91)	75369 (41)	28263 (17)	49032 (23)
C(15)	31518 (33)	55073 (70)	72383 (96)	78836 (46)	31227 (21)	39349 (24)
C(16)	25572 (28)	49527 (63)	68823 (79)	78921 (48)	38973 (21)	37618 (26)
C(17)	25116 (25)	36941 (60)	62742 (65)	75996 (49)	43933 (20)	45703 (28
C(18)	30767 (24)	30323 (52)	60515 (66)	72677 (44)	41039 (17)	55447 (24)
Br	38180 (4)	70744 (7)	18940 (10)			
C(Me)	5000 (0)	5000 (0)	0 (0)			
O(Me)	4978 (4)	6173 (9)	– 357 (12)			
H(1)	3722 (34)	4739 (87)	2638 (92)			
H(2X)	3082 (51)	4143 (91)	25 (92)	5977 (62)	87 (24)	6383 (31)
H(2Y)	2628 (49)	4220 (90)	1631 (97)	7428 (66)	676 (28)	5770 (36)
H(3X)	2314 (56)	2535 (85)	888 (89)	6688 (48)	804 (18)	8130 (25)
H(3Y)	2935 (43)	2305 (95)	– 294 (95)	8964 (60)	498 (24)	7629 (31)
H(4X)	3209 (34)	848 (71)	1085 (92)	8611 (60)	1989 (23)	8045 (32)
H(4Y)	2836 (26)	1076 (58)	2797 (68)	9300 (72)	1799 (29)	7021 (38)
H(6X)	4574 (24)	832 (51)	3108 (59)	8239 (37)	3046 (14)	7265 (19)
H(6Y)	4079 (41)	– 4 (91)	3117 (96)			
H(7)	3846 (30)	– 1628 (76)	4831 (82)	7670 (41)	3662 (15)	8773 (22)
H(8)	4082 (21)	– 1768 (48)	7900 (57)	5615 (50)	4341 (18)	9696 (26)
H(9)	4354 (37)	– 105 (84)	9784 (94)	2291 (49)	4629 (19)	8894 (25)
H(10)	4331 (39)	1468 (87)	8970 (95)	1080 (45)	4128 (17)	7188 (24)
H(11X)				1477 (43)	3504 (16)	5625 (23)
H(11Y)	4703 (25)	3395 (60)	6992 (68)	3597 (47)	3503 (18)	5321 (25)
H(14)	4203 (41)	5141 (94)	7456 (92)	7466 (44)	2251 (16)	4999 (23)
H(15)	3134 (29)	6256 (63)	7790 (74)	8183 (54)	2741 (19)	3370 (28)
H(16)	2188 (28)	5426 (64)	7102 (73)	8019 (54)	4098 (19)	3086 (28)
H(17)	2100 (24)	3363 (55)	5942 (62)	7600 (48)	4984 (19)	4467 (24)
H(18)	3133 (23)	2120 (47)	5586 (63)	7107 (43)	4453 (17)	6092 (23)

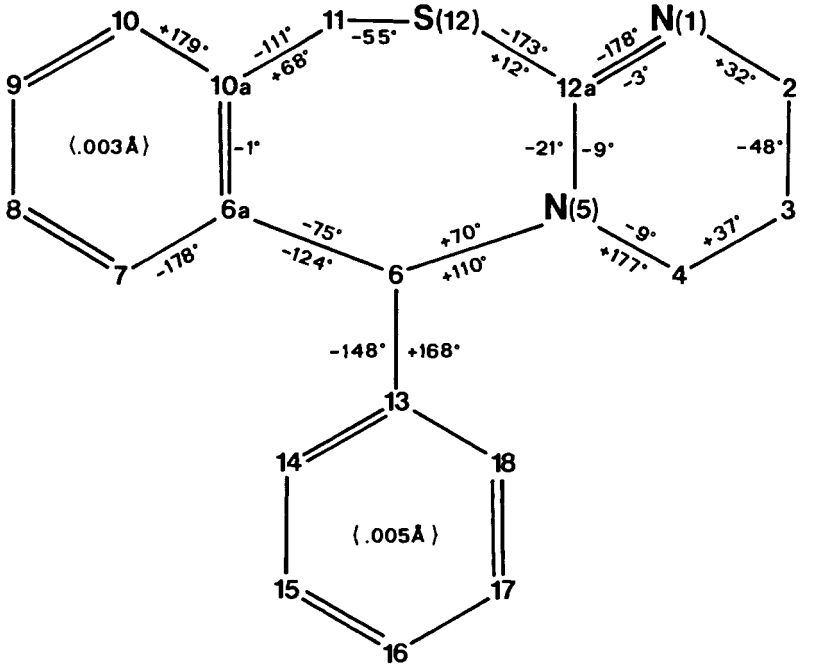

Fig. 1. *Atomic numbering and some torsion angles* (e.s.d. around 1.5°) *of the* 11-phenyl-*compound*

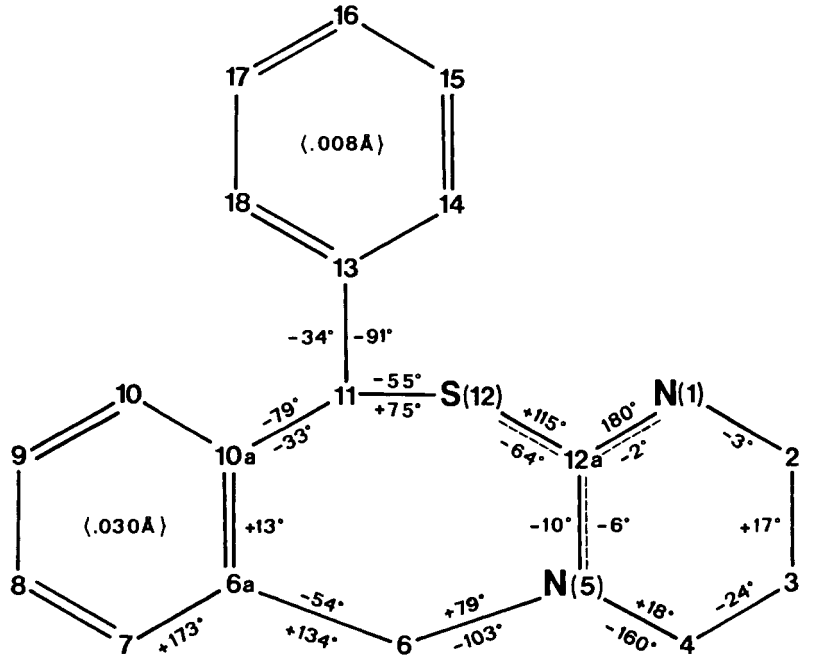

Fig. 2. *Atomic numbering and some torsion angles* (e.s.d. around 1°) *of the* 6-phenyl *compound*

Discussion. – The molecular conformations of the *6-phenyl* and the *11-phenyl* compounds as found in the crystal structure are shown in stereoscopic projections in *Figs. 3* and *4*. Bond lengths and bond angles are given in *Tables 2* and *3*, and some torsion angles are given in *Figs. 1* and *2*.

The thiourea fragment in the *6-phenyl* compound has a distinct C–N double bond, C(12a)–N(1) = 1.274(6) Å, and a partial double bond, C(12a)–N(5) = 1.366(4) Å. The atoms C(12a) and N(5) are slightly pyramidal with out-of-plane deviations of 0.033 Å, and 0.044 Å, respectively, and there is an appreciable torsion around the partial double bond C(12a)–N(5). In the *11-phenyl* compound the thiouronium fragment has two equal C–N partial double bonds of length 1.31(1) Å.

Table 2. *Bond lengths with e.s.d.'s for the* 6-phenyl *and the* 11-phenyl *compounds*

	6-Phenyl compound	*11-Phenyl compound*		*6-Phenyl compound*	*11-Phenyl compound*
N-(1)-C(2)	1.457 (5)	1.440 (13)	C(9)-C(10)	1.387 (5)	1.368 (8)
N(1)-C(12a)	1.274 (4)	1.311 (8)	C(10)-C(10a)	1.385 (4)	1.386 (8)
C(2)-C(3)	1.461 (6)	1.326 (17)	C(10a)-C(11)	1.491 (4)	1.527 (7)
C(3)-C(4)	1.479 (6)	1.460 (15)	C(11)-S(12)	1.809 (3)	1.849 (5)
C(4)-N(5)	1.461 (4)	1.467 (8)	C(11)-C(13)		1.519 (7)
N(5)-C(6)	1.470 (3)	1.493 (7)	S(12)-C(12a)	1.780 (3)	1.766 (6)
N(5)-C(12a)	1.366 (4)	1.314 (7)	C(13)-C(14)	1.387 (4)	1.383 (9)
C(6)-C(6a)	1.516 (4)	1.495 (8)	C(13)-C(18)	1.385 (4)	1.387 (8)
C(6)-C(13)	1.531 (4)		C(14)-C(15)	1.388 (4)	1.381 (10)
C(6a)-C(7)	1.395 (4)	1.417 (8)	C(15)-C(16)	1.367 (5)	1.355 (10)
C(6a)-C(10a)	1.401 (4)	1.397 (7)	C(16)-C(17)	1.380 (5)	1.387 (8)
C(7)-C(8)	1.381 (4)	1.356 (9)	C(17)-C(18)	1.387 (5)	1.373 (8)
C(8)-C(9)	1.374 (5)	1.369 (9)			

Table 3. *Bond angles with e.s.d.'s for the* 6-phenyl *and the* 11-phenyl *compounds*

	6-Phenyl compound	*11-Phenyl compound*		*6-Phenyl compound*	*11-Phenyl compou*
C(2)-N(1)-C(12a)	117.8 (3)	121.4 (7)	C(6a)-C(10a)-C(10)	119.1 (3)	119.1 (5)
N(1)-C(2)-C(3)	113.2 (4)	116.7 (1.1)	C(6a)-C(10a)-C(11)	119.7 (3)	124.9 (5)
C(2)-C(3)-C(4)	113.1 (4)	122.2 (1.2)	C(10)-C(10a)-C(11)	121.2 (3)	115.7 (5)
C(3)-C(4)-N(5)	113.7 (3)	112.6 (7)	C(10a)-C(11)-S(12)	114.5 (2)	116.8 (5)
C(4)-N(5)-C(6)	114.7 (2)	118.4 (5)	C(10a)-C(11)-C(13)		112.9 (5)
C(4)-N(5)-C(12a)	118.5 (3)	120.0 (5)	S(12)-C(11)-C(13)		109.8 (4)
C(6)-N(5)-C(12a)	126.5 (2)	121.6 (5)	C(11)-S(12)-C(12a)	111.6 (1)	97.6 (3)
N(5)-C(6)-C(6a)	112.7 (2)	115.9 (5)	N(1)-C(12a)-N(5)	126.5 (3)	123.3 (6)
N(5)-C(6)-C(13)	113.4 (2)		N(1)-C(12a)-S(12)	108.4 (2)	117.6 (5)
C(6a)-C(6)-C(13)	115.6 (2)		N(5)-C(12a)-S(12)	124.9 (3)	119.1 (5)
C(6)-C(6a)-C(7)	118.9 (3)	116.7 (5)	C(6)-C(13)-C(14)	121.6 (3)	119.2 (5)
C(6)-C(6a)-C(10a)	121.9 (3)	125.2 (5)	C(6)-C(13)-C(18)	119.6 (3)	122.9 (5)
C(7)-C(6a)-C(10a)	119.2 (3)	117.6 (5)	C(14)-C(13)-C(18)	118.8 (3)	117.9 (6)
C(6a)-C(7)-C(8)	120.7 (3)	120.9 (6)	C(13)-C(14)-C(15)	120.0 (3)	120.0 (7)
C(7)-C(8)-C(9)	120.2 (3)	121.5 (6)	C(14)-C(15)-C(16)	121.0 (3)	121.3 (8)
C(8)-C(9)-C(10)	119.6 (3)	118.4 (6)	C(15)-C(16)-C(17)	119.6 (4)	120.0 (7)
C(9)-C(10)-C(10a)	121.2 (3)	122.4 (6)	C(16)-C(17)-C(18)	120.0 (3)	118.7 (6)
			C(13)-C(18)-C(17)	120.7 (3)	122.1 (5)

In comparison to the thiourea fragment in the *6-phenyl* compound the thiouronium is less distorted around C(12a)–N(5), and the two atoms are less pyramidal (out-of-plane deviations 0.011, and 0.016 Å, respectively).

In both molecules the tetrahydropyrimidine ring has an approximate envelope conformation with C(3) as flap. The pronounced thermal anisotropy of the flap atom (see *Figs. 3* and *4*) indicates a certain degree of positional disorder similar to that observed in another tetrahydro-pyrimidine derivative (see preceding paper [6]).

The conformation of the seven-membered thiazepine ring in the two compounds is different (see torsion angles in *Figs. 1* and *2*). In the *11-phenyl* compound the sulfur atom is slightly above, and the nitrogen atom N(5) is below the plane of the aromatic ring, which corresponds to conformation **A**, as shown schematically in *Fig. 5*. In the *6-phenyl* compound, however, both the *S*- and the *N*-atoms are below the aromatic ring plane, which corresponds to conformation **B** of *Fig. 5*. Unexpected is the fact that in both structures the phenyl substituent is in *axial* rather than in *equatorial* position on the thiazepine ring. However, a discussion of the ^{1}H-NMR. spectra given below shows that these conformations observed in the crystal appear to persist also in solution.

In *Figs. 6* and *7* the packing of molecules in the crystal is shown in stereoscopic projection. There are no unusual *inter*molecular distances in the *6-phenyl* com-

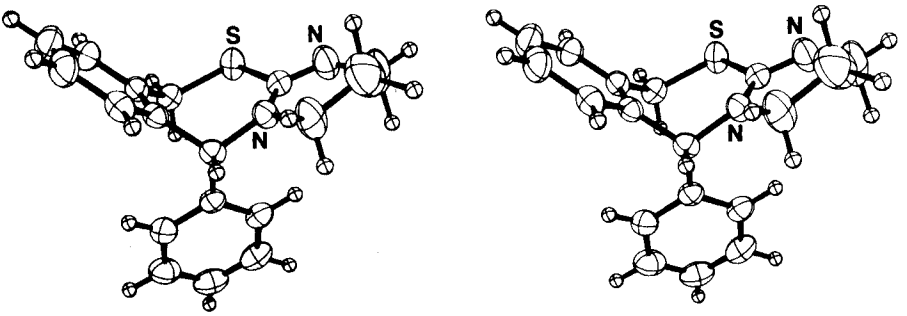

Fig. 3. *Stereoscopic projection of the* 6-phenyl *compound with the 50%-probability ellipsoids of atomic vibrations.* The hydrogen atoms are uniformly drawn with a sphere corresponding to B = 1 Å^2.

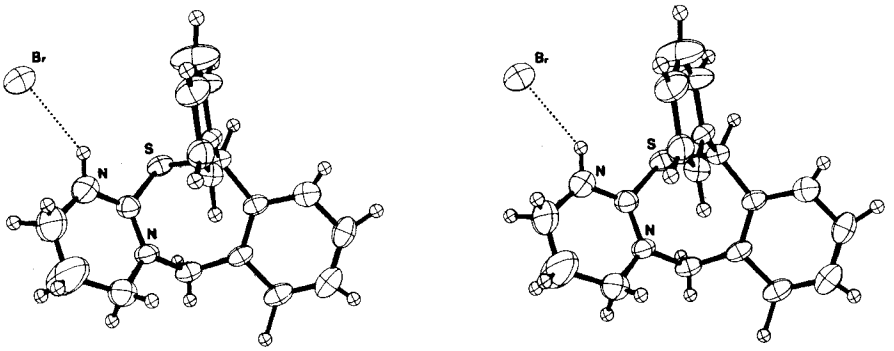

Fig. 4. *Stereoscopic projection of the* 11-phenyl *compound* (same specifications as *Fig. 3*)

pound. In the crystal structure of the *11-phenyl* compound there is a hydrogen bond from the methanol hydroxyl to the bromine, O–H · · · Br^- 3.30(1) Å, and another from the protonated $N^+(1)$ to the bromine, $N^+ - H \cdots Br^- = 3.27(1)$ Å.

^{1}H-NMR. Spectra and the Conformation in Solution. – In the *6-phenyl* and *11-phenyl* derivatives, the geminal protons on C(11), and C(6), respectively, are

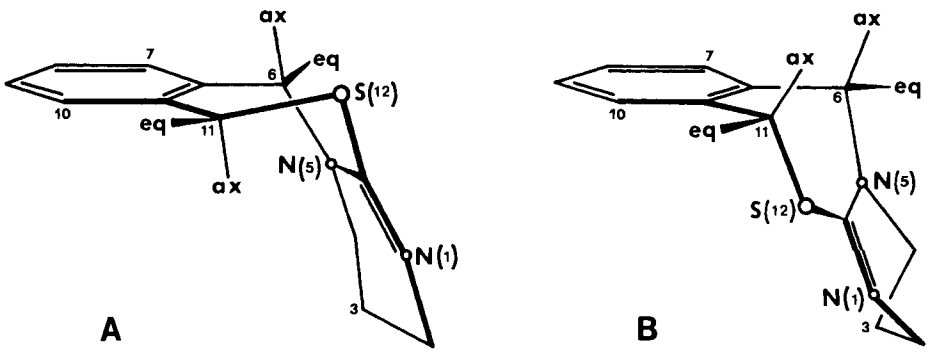

Fig. 5. *Principal conformations of tetrahydropyrimido[2,1-c][2,4]benzothiazepine as obtained from molecular models*

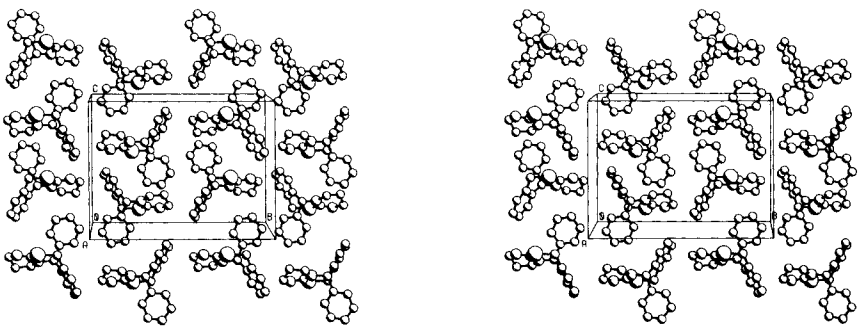

Fig. 6. *Packing diagram of the* 6-phenyl *compound viewed along* a (stereoscopic projection)

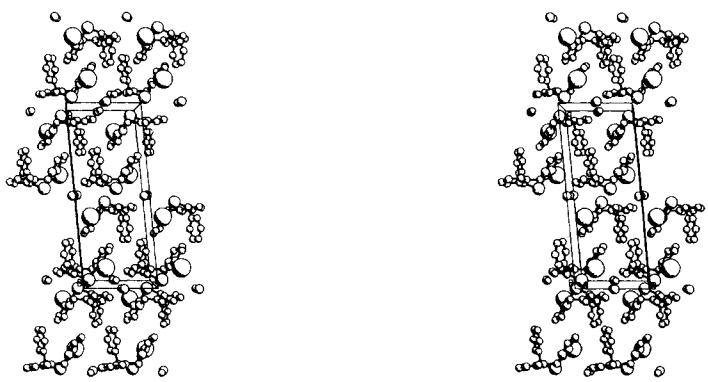

Fig. 7. *Packing diagram of the* 11-phenyl *compound viewed along* b (stereoscopic projection)

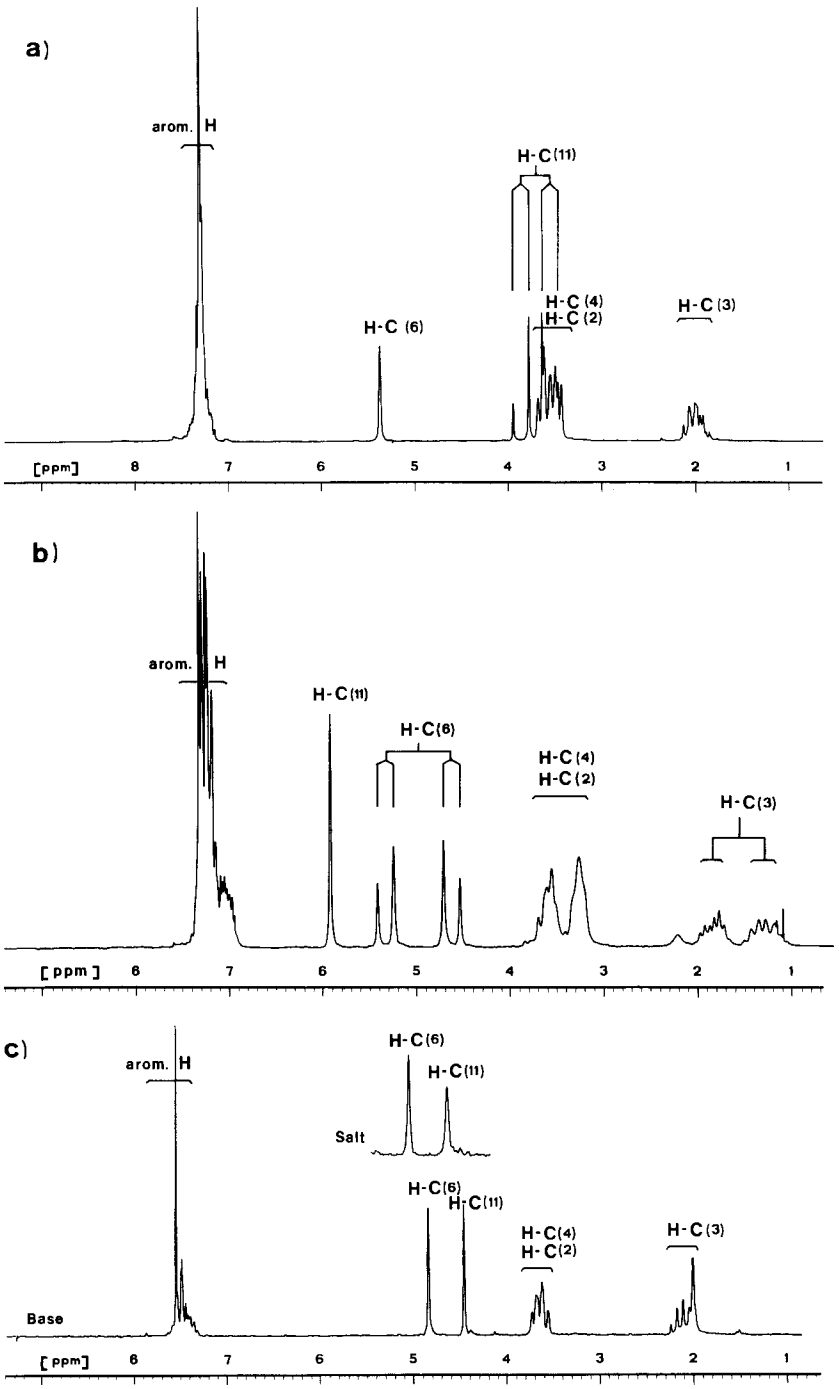

Fig. 8. *90 MHz ^{1}H-NMR. Spectra of* **1a** (a), **1b**-hydrochloride (b), *and* **1c** (c). The spectra were taken on a *Bruker* instrument HX-90-E, $CDCl_3$, TMS = 0 ppm

Table 4. *Hydrogen atoms expected to show high field shifts due to shielding by the phenyl substituent, depending on the conformation of the thiazepine ring, and the position of the substituent*

Conformation of tricyclic frame[a])	Position of phenyl	6	11
A	axial	a) none	e) H_{ax}–C(3)
	equatorial	b) H–C(7)	f) H–C(10)
B	axial	c) H–C(11)	g) H–C(6)
	equatorial	d) H–C(7)	h) H–C(10)

[a]) See *Fig. 5.*

diastereotope [7]. For each of the four possible conformations, *i.e.* the *axially-* or *equatorially*-substituted compounds having conformations **A** or **B**[2]), specific changes in chemical shifts would result due to different shielding effects of the phenyl substituents *(Table 4).*

Thus for the equatorial position of the phenyl substituents on C(6) or C(11) a high field shift of about 0.4 ppm for H–C(7) (cases b and d), or H–C(10) (cases f and h) would be observed for both types of conformation, **A** and **B**. Such shifts have been reported [8] for a similar geometrical situation. Since the spectra *(Fig. 8a, b)* show no signals in the region of about 6.8 ppm, an *equatorial* position of the phenyl is improbable for both compounds.

In the spectrum of the *11-phenyl* compound *(Fig. 8b)*, H_{ax}-C(3) shows a high field shift of about 0.8 ppm relative to the unsubstituted compound (**1c**, *Fig. 8c*). From *Table 4* (case e), the most probable conformation in $CDCl_3$ solution is the same (**A**) as found in the crystal structure.

In the spectrum of the *6-phenyl* compound *(Fig. 8a)* the *AB* pattern of H–C(11) is centered at 3.7 ppm, which corresponds to a high-field shift of about 0.8 ppm relative to the unsubstituted compound (**1c**, *Fig. 8c*). According to case c, *Table 4*, the most probable conformation in $CDCl_3$ solution is again the same (**B**) as found in the crystal structure.

The spectrum of the unsubstituted compound (**1c**, *Fig. 8c*), taken at room temperature or at $-70\,°C$, shows singlets for the geminal protons on both C(6) and C(11), which indicates that the thiazepine ring is in fast *pseudo*-rotation between conformations **A** and **B**, and its mirror images. It appears that substitution of a phenyl ring on C(6), or C(11), impedes *pseudo*-rotation and fixes the seven-membered ring in a conformation corresponding to **B**, or **A**, respectively.

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[2]) The enantiomer conformations need not to be considered separately for this purpose.