¹H AND ¹³C NMR AND X-RAY STUDIES OF 2- AND 4-PHENYL-6,7-DIMETHOXY-3-METHYL-3,4-DIHYDRO-2*H*-1,3-BENZOTHIAZINES [1]

A. KÁLMÁN and GY. ARGAY

Central Research Institute of Chemistry, Hungarian Academy of Sciences, P.O.B. 17, H-1525 Budapest (Hungary)

P. SOHÁR

EGIS Pharmaceuticals, Spectroscopic Department, P.O.B. 100, H-1475 Budapest (Hungary)

J. SZABÓ, L. FODOR and G. BERNÁTH

Institute of Pharmaceutical Chemistry, University Medical School, P.O.B. 121, H-6701 Szeged (Hungary)

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ABSTRACT

The stereochemistry of 2- and 4-phenyl-6,7-dimethoxy-3-methyl-3,4-dihydro-2H-1,3benzothiazine (2, 6) has been studied by ¹H, ¹³C NMR spectroscopy and X-ray diffraction. Crystals of compound 2 ($C_{12}H_{19}NO_2S$) are monoclinic, space group P2₁/n, with a = 11.428(1), b = 10.048(1), c = 14.161(2) Å, β = 100.00(1)°, Z = 4, D_c = 1.247 g cm⁻³. Crystals of 6 are orthorhombic, space group P2₁2₁2₁ with a = 7.068(1), b = 10.857(1), c = 20.343(1) Å, Z = 4, D_c = 1.247 g cm⁻³. The structures are refined to R = 0.041 for 2728 reflections of 2 and R = 0.039 for 1671 reflections of 6. The results unequivocally show that the 3-N-methyl group, and the 4-phenyl group are axial, while the 2-phenyl moiety is equatorial. Comparison are made between conformations of the title compounds and those of the following 1-phenyltetrahydroisoquinolines: unnatural cryptostyline II [2, 3], cryptostyline I [4] and 2-benzyl-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-1phenyl-isoquinolinium iodide [5].

INTRODUCTION

In the course of earlier studies by the authors' working group [6-12] of 1,3-benzothiazines, numerous highly fused benzothiazine derivatives were synthesized and studied by ¹H and ¹³C NMR spectroscopy [9-12]. Although the exact structures of many tetrahydroisoquinolines (7-9) are known from X-ray diffraction studies, the stereochemistry of 3,4-dihydrobenzothiazines has not been investigated as yet.

As one of our present research topics is a synthesis and stereochemical study of the 4-thia analogues of 1-aryl-tetrahydroisoquinoline alkaloids, a comparative X-ray study of the 4-phenyl-3,4-dihydro-2H-1,3-benzothiazine derivative, 6, and the related tetrahydroisoquinoline derivatives, 7–9, [2–5]

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seemed reasonable. We have investigated the effects on the conformation of the hetero ring due to replacement of the 4-methylene group by a sulphur atom. To establish the relationship between the position and possible configurations of the substituents, 6 was compared with the 2-phenyl isomer 2. At the same time, study of these compounds may provide information about whether the structure in the bases 2 and 6 is altered relative to that in the tertiary 7 and quaternary ammonium salts 8, 9.

EXPERIMENTAL

Materials

Compound 2 was synthesized (a) by Zn/acid reduction of the quaternary salt 1 [13, 14] and (b) by condensation of 3 [14] with benzaldehyde [15]. The isomer 6 was prepared in an analogous manner by reduction of the quaternary salt 5 [13] which was obtained from compound 4 [16] (cf. Table 1).

TABLE 1

Com- pound	Method	Yield (%)	M.p. (°C)	Molecular formula	Analysis Caled./H	s Found %	
				(M.w.)	C	Н	N
2	a	67.5	103-104	C ₁₇ H ₁ ,NO ₂ S	67.74	6.35	4.65
2	b	66.6	103 - 104	(301.4)	67.96	6.45	4.90
5	_	65.8	157-159	$C_{17}H_{18}INO_2S$ (437.3)	$47.78 \\ 48.10$	$\begin{array}{c} 4.35\\ 4.34\end{array}$	$3.28 \\ 3.48$
6	а	66.4	155—156	$C_{1,7}H_{1,9}NO_2S$ (301.4)	$\begin{array}{c} 67.75\\ 68.05 \end{array}$	$\begin{array}{c} 6.36 \\ 6.47 \end{array}$	$\begin{array}{c} 4.65\\ 4.55\end{array}$

Physical and analytical data for compounds 2, 5, 6





Scheme 1



¹H and ¹³C NMR studies

¹H and ¹³C NMR spectra were recorded at room temperature in CDCl₃ solution in 5 and 10 mm tubes, on Bruker WM-250 (¹H) and WP-80 SY (¹³C) FT spectrometers at 250.13 (¹H) and 20.14 (¹³C) MHz, respectively, using the deuterium signal of the solvent as the lock and TMS as internal standard. The most important measurement parameters were as follows: sweep width 5 kHz; pulse width 1 (¹H) and 3.5 (¹³C) μ s (~20° and ~30° flip angle); acquisition time 1.64 s; number of scans 16 (¹H) and 1K-4K (¹³C); computer memory 16K. Complete proton noise decoupling (~3W) for the ¹³C spectra, and Lorentzian exponential multiplication for signal-to-noise enhancement, were used (line width 0.7 and 1.0 Hz).

DEPT experiments [17, 18] were performed by running three spectra with 45, 90 and 135° theta-pulses respectively, and then editing the subspectra using a linear combination of the spectra already obtained. The 90° pulse lengths were 10.8 and 22.5 μ s for ¹³C and ¹H nuclei respectively, in the 10 mm probehead. After every scan, a 3 s delay was allowed in order for the protons to relax.

Crystal structure determinations

The intensities of both compounds, 2 and 6, were collected on an Enraf-Nonius CAD-4 diffractometer equipped with a graphite monochromator. In each case the lattice parameters were determined by least-squares refinement of the setting angles of 25 reflections. Data for 2 were obtained using MoK_{α} $(\lambda = 0.71073 \text{ Å})$ radiation in the range $1.5 < \Theta < 27.0^{\circ}$ and for 6 using CuK_{α} radiation ($\lambda = 1.54184 \text{ Å}$) in the range $1.5 < \Theta < 75.0^{\circ}$. The phase problems were solved by direct methods, using the MULTAN program [19]. Full matrix least-squares refinement of the fractional atomic coordinates, with vibrational parameters that were anisotropic for nonhydrogen atoms and isotropic for hydrogen atoms, led to the final conventional *R* values given in Table 2. The hydrogen atoms were placed in calculated positions since they are all bonded to carbon atoms of well-defined geometry. Scattering factors were taken from standard tables [20]. All calculations were performed on a PDP 11/34 minicomputer with an Enraf—Nonius SDP system.

Lists of structure factors and anisotropic temperature parameters are available from the authors on request.

RESULTS AND DISCUSSION

NMR spectroscopic studies

The chemical structures of the new compounds 2 and 6 and their precursors 1 and 5 were established by means of ¹H and ¹³C NMR spectroscopy (Tables 3 and 4).

In the ¹H NMR spectra of 1 and 5 the methylene signal is a singlet due to chemical equivalence of the methylene protons in the planar hetero-ring. In 5, conjugation with the fused dimethoxybenzene ring causes the electron-deficit of the quaternary group to be decreased as the result of electron

TABLE 2

Crystal and relevant X-ray data

	2	6
Formula	C ₁₇ H	NO ₂ S
M.w.	3	01.4
Crystal size (mm ³)	0.6 imes 0.6 imes 0.3	0.6 imes 0.2 imes 0.4
a (A)	11.428(1)	7.068(1)
b(A)	10.048(1)	10.857(1)
c (Å)	14.164(2)	20.343(1)
β(°)	108.00(1)	
$V(A^3)$	1546.8	1553.4
F (000)	6	40
$D_c (\text{gcm}^{-3})$	1.247	1.247
Z	4	4
$\mu (\rm cm^{-1})$	2.0	18.3
Space group	$P2_1/n$	$P2_{1}2_{1}2_{1}$
N _{tot}	2847	1700
Nobs	2728(5o)	$1671(3\sigma)$
R	0.041	0.039
R _w	0.055	0.041

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Compound	NCH ₃ s (3H)	OCH_3 (ϵ 2 × s (2	3, 7) × 3H)	CH ₂ (4 0 s or m ^a (r 2) 2H)	CH (2 or 4) s (1H)	H5 s (1H)	H8 s (1H)	H2', 6' d (2H)	H3', 5' t (2H)	H4' t (1H)
1	3.93	4.00	4.09	5.7	0		6.98	7.53	8.10	7.63	7.74
2	2.38	3.80	3.83	3.80	4.05	5.76	6.63	6.51	7.54	7.3-7	.4 ^b
5	3.58	3.95	4.05	3.6	3	ł	7.12	6.43	7.79	-q9.7	7.75 ^b
9	2.64	3.74	3.87	3.86°	4.50	4.76 ^c	6.65	6.48	7.14	7.2–7	.35 ^b

¹H NMR chemical shifts for compounds 1, 2, 5 and 6 in CDCl₃ at 250 MHz ($6_{TMS} = 0$ ppm)

 ^{3}AB spectrum in cases of 2 and 6, J(A, B) = 16.5 (2) and 12.1 (6) Hz. ^bOverlapping multiplets. ^cLong-range coupling of 1.1 Hz between H4 and the upfield 2-methylene protons.

TABLE 4

¹³C NMR chemical shifts for compounds 1, 2, 5 and 6 in CDCl₃ at 20 MHz (δ_{TMS} = 0 ppm)

Compound	$\begin{array}{c} I CH_{2} \\ (4 \text{ or } 2)^{a} \end{array}$	$\frac{CH/C}{(sp^2)}$	NCH3	0CH3	, (6, 7)	C4a	C5	C6	C7	C8	C8a	C1′	C2′, 6′	C4', 5'	C4
1 ^b	60.3	181.5	48.5	56.7	57.2	120.4	111.8	151.7°	150.5 ^c	108.1	116.1	129.1	131.0	129.8	135.0
2	54.7	71.1	37.4	55.7	55.8	123.6	112.1 ^c	146.5	148.1	110.4 ^c	119.3	139.2	127.7 ^d	127.9 ^d	127.6
5	46.5	170.8	54.0	55.5	56.9	132.3	120.7	147.1	156.3	109.4	117.0	129.6	129.8	128.4	135.3
9	51.4	66.3	41.1	55.8	56.0	124.3	114.3	146.4	148.6	110.3	119.7	142.6	128.1 ^c	128.9 ^c	127.2

⁴In 1 and 2 the methylene group is in pos. 4, and the methine group or the quaternary *sp^{*}* carbon of the imme group is in pos. 2; in 5 and 6 the situation is reversed. ^bThe orders of the carbon atoms corresponding to the individual lines are proved by DEPT experiments [17, 18]. ^{c,d}Reversed assignments may be possible, too.

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displacement from the dimethoxyphenyl moiety. This gives rise to an upfield shift of the NCH₃ singlet and a downfield shift of the H5 signal relative to those for 1. In 1 the electron-attracting quaternary group gives rise to a significant (1.1 ppm) deshielding of H8. The conjugated C=N bond causes deshielding of the *ortho* protons (H2', 6').

Analogously, in the ¹³C NMR spectrum of 5 the lines of C5 and NCH₃ group undergo significant (8.9 and 5.5 ppm, respectively) downfield shifts. The electron displacement from the fused benzene ring towards the positive nitrogen atom is also indicated by the very large shifts — of the same sign — (11.9 and 5.8 ppm, respectively) in the C4a and C7 signals. In addition the characteristically different electron densities of the quaternary group in 1 and 5 strongly influence the shielding of C2 and C4: the greater electron density in 5 is manifested by the upfield shift of these signals (10.7 ppm for the sp² carbon atom and 13.8 ppm for the methylene carbon).

The hetero-ring in 2 and 6 is not planar as indicated by the chemical nonequivalence of the methylene protons (the methylene signal is an AB quartet). The additive I-effects of the sulphur and nitrogen atoms, in agreement with our earlier observations [6], are accounted for by the much smaller *geminal* coupling (12.1 Hz) in 6 relative to that in the structural isomer 2 (16.5 Hz).

From the aspect of structural isomerism, the most important feature is the chemical shift difference between the methine protons. The methine signal undergoes a 1.0 ppm downfield shift in 2.

Owing to the non-planar hetero-ring, problems of configuration (*cis* or *trans* position of the phenyl and methyl groups) and conformation (*equatorial* or *axial* position of these substituents) arise. Because of the relatively low activation energy required for nitrogen inversion, the formation of a conformationally homogeneous system is to be strongly anticipated.

In 2, the *equatorial* position of the bulky phenyl ring seems logical. In 6, however, due to steric hindrance of the fused skeleton, the *quasi-axial* position of the phenyl group has also to be considered; from the results of X-ray diffraction analysis [3, 4] of analogous compounds, we would expect this structure to be favoured. Similarly, the sterically preferred *equatorial* position of the methyl group in both isomers can be compensated for by the unfavoured 1,3-diaxial interaction of the lone pairs of the heteroatoms.

In the ¹H NMR spectrum of **6**, a readily observable long-range coupling can be seen between the 4-methine and the upfield methylene protons (the splitting is 1.1 Hz). This observation can serve as a starting point for the conformational analysis of the hetero-ring.

Long-range interactions occur for dihedral angles of 180° (W-pattern) [21] which suggests strongly the *quasi*-equatorial position of H4 in 6 and hence the *quasi-axial* position of the 4-phenyl group. This is indicated by the fact that the chemical shifts of H5 are nearly equal in the isomers. In contrast, the anisotropic effect of the *quasi-equatorial* phenyl group should affect the H5 signal in 6. The long-range splitting indicates that, in contrast to the general rule valid for the cyclohexanes [22a], the *equatorial* position is more

shielded for the methylene protons. This can be explained by the anisotropic effect of the *equatorial* lone pairs of the adjacent heteroatoms and is characteristic of the six-membered sulphur heterocycles [22b]. The great shift difference (0.66 ppm) renders probable the additivity of the effects of the two heteroatoms: i.e. the lone pair of the nitrogen atom is *equatorial*, and hence the methyl group is *trans-axial*.

Since no long-range interaction occurs in 2, in harmony with energetic considerations, an *equatorial* phenyl group seems likely. This is supported by the downfield shift of signals of the phenyl *ortho*-protons, which can be explained by the anisotropic effect of the nearly-coplanar lone pairs of the heteroatoms. The 0.3 ppm value of this downfield shift relative to 6 also indicates the additive character of the effects of the two heteroatoms, which in turn points to an *axial* N-methyl group in 2. However, the 0.26 ppm upfield shift for the N-methyl singlet relative to that in 6 might be due to the anisotropy of the phenyl ring which would imply the proximity of the substituents, i.e. they occupy *diequatorial* positions. This also implies that, from the aspect of rotation around the C_2-C_1 axis, the rotamer in which the methyl group is "above" the plane of the phenyl ring is favoured (the phenyl group is perpendicular to the plane of the fused skeleton).

The large shift differences observed for the isomer pair 1 and 5 in their ¹³C NMR spectra, contrast with those for 2 and 6 in which these differences are nearly equal. Notable differences can be observed only in the shieldings of the methine, methylene and N-methyl groups and the C1' atom of the phenyl ring. However even these differences are not particularly large (4.8, 3.3, 3.7 and 3.4 ppm, respectively). The other 13 C chemical shift differences between the isomers are less than 1 ppm, except for the C5 signal, which has a shielding 2.2 ppm larger than that in 2. This latter observation is in agreement with a quasi-axial phenyl ring in 6, for in the quasi equatorial position the steric hindrance with H5 would result in increased shielding (steric compression shift [23]) and thus an opposite difference would be expected between the isomers. This field effect is also likely to affect the shielding of the N-methyl carbon in 6 (owing to the 1,3-diaxial interaction of the lone pair of the sulphur atom and the N-methyl group) and, in addition, as this line reveals an upfield shift in 2, it is unlikely that the N-methyl group is equatorial. The further increase in shielding is presumably due to the nearly ideal axial situation of the participants in the 1,3-interaction in 2. The quasiaxial phenyl group gives rise to a greater distortion of the hetero-ring in 6.

In 6, the upfield shift of the methine and methylene resonances, compared to those for 2, is due to the field effect (1,3-diaxial interaction) of the quasiaxial phenyl and the axial methylene proton; the expected effects of the adjacent S-aryl and aryl substitutions are identical [22c]. Thus, these shifts yield further evidence of the different configurations of the phenyl ring in 6 and 2.

Finally, the NMR data unequivocally show that the phenyl group in 2 is *equatorial*, whereas in 6 it is *quasi-axial*, and also that it is likely the *N*-methyl group is *axial* in both isomers.

To confirm the stereostructures deduced from the NMR data, X-ray diffraction analysis was carried out.

X-ray analysis of 2 and 6

A list of fractional atomic coordinates and vibrational parameters with LScomputed standard deviations is given in Tables 5–8. Selected bond angles and torsional angles are listed in Table 9. Perspective views of the molecules 2 and 6 are depicted in Figs. 1 and 2.

Apart from the S1–C2 single bond, the corresponding bond distances in 2 and 6 agree well within experimental error (3σ) . The longer S(II)–C(sp^3) distance (1.862(1) Å) in 2 may be attributed to the effect of the 2-phenyl substituent. However, the shorter bond (1.840(3) Å) in 6 is significantly longer than those found in several 1,3-thiazine derivatives, e.g. a mean value of 1.803(5) Å for four of the structures reported earlier [24]. No such phenomenon was observed for the S(II)–C(sp^2) bonds. The practically identical S1–C8A distances in 2 and 6 (1.768(1) and 1.767(3) Å) agree well with the mean value of 1.766(3) Å for the S(II)–C(sp^2) distances observed in the above structures [24]. The equatorial phenyl substituent at C2 in 2 closes the internal bond angle somewhat more than the pseudoaxial phenyl group

TABLE 5

Atom	x/a	y/b	z/c	B _{eq}
S 1	0.44580(3)	-0.23225(4)	0.56880(2)	3.33(1)
O 6	0.3214(1)	-0.1177(1)	0.1399(1)	3.62(3)
07	0.4672(1)	-0.3111(1)	0.2174(1)	3.16(3)
N3	0.2587(1)	-0.0488(1)	0.5516(1)	2.85(3)
C2	0.3759(1)	-0.0916(1)	0.6180(1)	2.67(3)
C 4	0.2750(1)	-0.0125(1)	0.4630(1)	3.10(4)
C4A	0.3288(1)	-0.0792(1)	0.4020(1)	2.65(3)
C5	0.3009(1)	-0.0552(1)	0.3002(1)	2.88(4)
C6	0.3461(1)	-0.1334(1)	0.2402(1)	2.69(3)
C7	0.4255(1)	-0.2394(1)	0.2823(1)	2.48(3)
C8	0.4555(1)	-0.2627(1)	0.3823(1)	2.59(3)
C8A	0.4065(1)	-0.1842(1)	0.4428(1)	2.55(3)
C9	0.3718(1)	-0.1249(1)	0.7211(1)	2.59(3)
C10	0.3464(1)	-0.2506(1)	0.7495(1)	3.10(4)
C11	0.3441(1)	-0.2742(1)	0.8453(1)	3.43(4)
C12	0.3667(1)	-0.1721(2)	0.9133(1)	3.67(4)
C13	0.3899(1)	-0.0466(1)	0.8850(1)	3.68(4)
C14	0.3926(1)	-0.0227(1)	0.7899(1)	3.08(4)
C15	0.1614(1)	-0.1482(2)	0.5281(1)	3.89(5)
C16	0.2440(2)	-0.0101(2)	0.0957(1)	4.97(6)
C17	0.5429(1)	-0.4231(1)	0.2550(1)	3.60(4)

Fractional coordinates and B_{eq} (A²) for non-hydrogen atoms of **2**. E.s.d.'s are given in parentheses, $B_{eq} = 4/3^*$ trace (B*G), where G is the direct metric tensor

TABLE 6

Atom	x/a	y/b	z/c	B _{eq}
S1	0.0729(1)	-0.09734(8)	0.71779(4)	4.88(3)
O6	0.6959(3)	-0.2043(2)	0.9039(1)	5.2(1)
07	0.3995(3)	-0.0827(2)	0.9423(1)	5.6(1)
N3	0.2688(3)	-0.2712(2)	0.6440(1)	4.2(1)
C2	0.1476(4)	-0.1661(3)	0.6389(1)	4.3(1)
C4	0.4502(4)	-0.2411(2)	0.6754(1)	3.3(1)
C4A	0.4298(4)	-0.1966(2)	0.7461(1)	3.1(1)
C5	0.5713(4)	-0.2209(2)	0.7916(1)	3.4(1)
C6	0.5616(4)	-0.1825(2)	0.8564(1)	3.6(1)
C7	0.4021(4)	-0.1171(2)	0.8773(1)	3.8(1)
C8	0.2596(4)	-0.0932(2)	0.8329(1)	3.8(1)
C8A	0.2726(4)	-0.1312(2)	0.7671(1)	3.4(1)
C9	0.5583(4)	-0.1534(2)	0.6306(1)	3.4(1)
C10	0.6053(5)	-0.1905(3)	0.5673(1)	4.6(1)
C11	0.7002(5)	-0.1125(4)	0.5243(1)	5.6(1)
C12	0.7462(5)	0.0063(3)	0.5450(1)	5.6(1)
C13	0.7024(5)	0.0429(3)	0.6066(1)	5.1(1)
C14	0.6088(4)	-0.0354(2)	0.6503(1)	3.9(1)
C15	0.1755(6)	-0.3777(3)	0.6746(2)	6.2(1)
C16	0.8489(5)	-0.2803(3)	0.8866(1)	5.7(1)
C17	0.2282(7)	-0.0322(3)	0.9671(1)	6.7(1)

Fractional coordinates and B_{eq} (A²) for non-hydrogen atoms of 6. E.s.d.'s are given in parentheses, $B_{eq} = 4/3^*$ trace (B*G), where G is the direct metric tensor

TABLE 7

Fractional coordinates and B_i (Å²) for H atoms of **2**

Atom	<i>x/a</i>	y/b	z/c	B _i
H2	0.428(1)	-0.020(2)	0.624(1)	3,3(3)
H5	0.249(2)	0.018(2)	0.272(1)	4.8(4)
H8	0.509(2)	-0.331(2)	0.413(1)	4.3(3)
H10	0.327(1)	-0.321(2)	0.699(1)	4.7(4)
H11	0.325(2)	-0.362(2)	0.863(1)	4.4(3)
H12	0.365(2)	-0.185(2)	0.980(1)	5.0(4)
H13	0.404(1)	0.028(2)	0.932(1)	4.3(4)
H14	0.412(1)	0.068(2)	0.772(1)	3.8(3)
H41	0.198(2)	0.043(2)	0.422(1)	4.7(4)
H42	0.331(1)	0.094(2)	0.484(1)	4.5(3)
H151	0.087(2)	-0.110(2)	0.489(1)	6.6(5)
H152	0.151(2)	-0.185(2)	0.590(1)	5.3(4)
H153	0.179(2)	-0.225(2)	0.488(1)	5.7(5)
H161	0.239(2)	-0.008(2)	0.025(1)	6.2(5)
H162	0.285(2)	0.074(2)	0.128(1)	5.8(4)
H163	0.160(2)	-0.020(2)	0.107(2)	6.7(5)
H171	0.564(2)	-0.464(2)	0.199(1)	6.0(4)
H172	0.501(2)	-0.488(2)	0.286(1)	5.5(4)
H173	0.616(2)	-0.394(2)	0.305(1)	4.7(4)

TABLE 8

Atom	x/a	y/b	z/c	B ₁
H4	0.520(5)	-0.318(3)	0.678(1)	6.7(8)
H5	0.673(4)	-0.259(3)	0.777(1)	4.7(6)
H8	0.147(4)	-0.061(2)	0.848(1)	4.2(6)
H10	0.558(5)	-0.270(3)	0.554(1)	6.4(8)
H11	0.736(5)	-0.138(3)	0.480(2)	6.5(9)
H12	0.813(5)	0.054(3)	0.510(2)	6.7(9)
H13	0.725(5)	0.120(3)	0.623(2)	7.7(9)
H14	0.570(4)	-0.010(3)	0.691(1)	4.0(6)
H21	0.209(4)	-0.110(3)	0.613(1)	4.9(7)
H22	0.018(4)	-0.191(3)	0.614(1)	5.4(7)
H151	0.049(5)	-0.395(3)	0.651(2)	7.0(1)
H152	0.150(5)	-0.359(3)	0.724(2)	7.3(9)
H153	0.262(7)	-0.454(4)	0.671(2)	7.0(1)
H161	0.927(6)	-0.286(3)	0.928(2)	8.0(9)
H162	0.918(5)	-0.234(3)	0.847(2)	8.2(9)
H163	0.813(6)	-0.357(3)	0.871(2)	8.0(1)
H171	0.251(7)	-0.019(4)	1.017(2)	10.0(1)
H172	0.108(6)	-0.084(4)	0.960(2)	10.0(1)
H173	0.182(6)	0.050(4)	0.943(2)	10.0(1)

Fractional coordinates and B_i (A²) for H atoms of 6

TABLE 9

Selected bond angles and torsion angles of 2 and 6

	2	6		2	6
S1-C2-N3	113.6(2)	115.6(4)	S1C2N3C4	-67.8(2)	-63.1(3)
C2-N3-C4	110.3(2)	112.1(4)	C2-N3-C4-C4A	61.2(2)	62.6(4)
N3-C4-C4A	114.6(2)	113.3(4)	N3-C4-C4A-C8A	-28.4(2)	-31.7(5)
C4–C4A–C8A	123.0(2)	121.9(4)	C4-C4A-C8A-S1	4.1(2)	3.3(3)
C4A-C8A-S1	124.0(2)	125.1(4)	C4A-C8A-S1-C2	-8.2(2)	-2.1(4)
C8A-S1-C2	99.6(1)	100.1(2)	C8A-S1-C2-N3	39.1(1)	31.0(3)
C2-N3-C15	115.7(2)	113.0(5)	C15-N3-C2-S1	61.5(2)	65.5(4)
C4-N3-C15	112.6(2)	112.7(4)	C15-N3-C4-C4A	-69.8(2)	-66.2(5)
C9-C2-S1	109.7(2)	-	C9-C2-S1-C8A	167.2(2)	—
C9-C2-N3	113.4(2)	_	C9-C2-N3-C4	166.0(2)	_
C9-C4-N3	_ ``	108.7(4)	C9-C4-N3-C2	_	-65.6(4)
C9-C4-C4A	—	114.3(4)	C9–C4–C4A–C8A		93.5(4)
			C9-C2-N3-C15	-64.7(2)	_
			C9–C4–N3–C15	_	165.6(5)

at C4 in 6. These differences in the bond angles at C2 and C4 are accompanied by slight alterations in the bond angles at the other ring atoms (Table 9). The greatest change is observed for N3, which has an axial methyl substituent in both compounds. However, these changes have only a slight



Fig. 1. Perspective view of the structures of 2 showing atomic numbering. The bare numbers are for carbon atoms unless indicated otherwise. The numbering of phenyl carbons (9-14) corresponds to the numbering (1'-6') for the NMR discussion. The H positions are shown but not labelled.



Fig. 2. Perspective view of the structure of **6** showing atomic numbering. The bare numbers are for carbon atoms unless indicated otherwise. The H positions are shown but not labelled. The N-methyl and 4-phenyl groups are *diaxial*.

overall impact upon the envelope (sofa) shape of the 1,3-thiazine ring. In both cases there is a mirror (C_s) symmetry of the torsional angles crossing the ring in the vicinity of N3, sitting on the flap. The only difference is that in 2 the envelope is less perfect than in 6 (see the puckering parameters [25] together with the asymmetry parameters [26] and the asymmetry factors [27] in Table 10). In 2, the geometry is shifted somewhat towards a halfchair form. If the geometry of 6 is compared with those of 7, 8 and 9, it TABLE 10

Puckering parameters (Q, ϕ, Θ) , lowest asymmetry parameters $(\Delta C_s \text{ or } \Delta C_s)$ and lowest asymmetry factors $(fC_s \text{ or } fC_2)$ for each hetero-ring in 2, 6, 7, 8, and 9

	Q(pm)	φ (°)	Θ(°)	ΔC_s (°)	$\Delta C_2 (^{\circ})$	fC_s (pm)	fC_2 (pm)	Shape
2	51.5	284.6	132.3	7.6		10.1		E
6	48.9	298.3	129.0	0.9		1.1		E
7	52.5	333.9	130.5		4.0	_	2.2	Н
8	47.6	303.6	135.3	1.2		2.1		\mathbf{E}
9	50.6	305.1	126.7	5.9		3.6		Ε
9	50.6	305.1	126.7	5.9		3.6	5	3



Fig. 3. Perspective view of the structure of 7 (unnatural cryptostyline II) as computed from the atomic coordinates reported in [2, 3]. The *N*-methyl and 1-(3,4-dimethoxy-phenyl) groups are orientated *equatorially*.

becomes apparent that the shape of the hetero-ring and the orientation of the 4-phenyl substituent resembles those in the quaternary salts 8 and 9 depicted in Figs. 4 and 5. In these structures, the hetero-ring also assumes an envelope shape with the N atom on the flap (the corresponding puckering parameters, etc. are listed in Table 10). In contrast to this, in the tertiary salt 7 the hetero-ring possesses an almost percect half-chair shape with a twofold axis (C_2) bisecting the C4A—C8A bond, and the substituents at C1 and N2 are linked *pseudoequatorially* (Fig. 3).



Fig. 4. Perspective view of the molecular skeleton of 8 (cryptostyline I [4]) as computed from the atomic (non-hydrogen) coordinates.



Fig. 5. Perspective view of the molecular skeleton of 9 (2-benzyl-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-1-phenylisoquinolinium iodide [5]) as computed from the atomic coordinates. Both the 1-phenyl and 2-benzyl groups assume *axial* orientation.

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