Stereostructure of Condensed-Skeleton *cis*- and *trans*-Dihydro-1,3-thiazines and 1-Thia-3-azaspiroalkenes†

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The stereostructures of some condensed-skeleton *cis*- and *trans*-dihydro-1,3-thiazines and 1-thia-2-phenyl-3-azaspiro[4*n*+1]alk-2-enes (*n*=3–6) were established by ^{1}H and ^{13}C NMR spectroscopy. A comparative study indicated that the *cis*-thiazines have greater conformational mobility than the corresponding oxazines, although the preferred conformer of the two types of *cis* compounds is the same, with the sulphur axial and the 4-methylene group equatorial relative to the rings.

Many saturated or partly saturated fused-skeleton sulphur and nitrogen heterocycles have been shown to possess bactericidal and fungicidal activity.[1–5] Thia-aza spiro derivatives can counteract phototoxic effects.[5–6] It therefore appeared promising to extend our earlier work on di- and per-hydro oxygen derivatives[7–11] to the sulphur isosteric analogues. From the theoretical point of view, interesting conclusions could be expected from a comparison of the stereochemical, spectroscopic, chemical and physical properties of the oxygen and sulphur analogues; the biological activity of the new compounds seemed to be of practical interest. With these considerations in mind, the syntheses of *cis*- and *trans*-2-phenyl-5,6-tri-, tetra-, penta- and hexa-methylene-5,6-dihydro-4*H*-1,3-thiazines were achieved,[12] making use of methods reported in the literature.[13–15]

cis-5,6-Cycloalkylene-5,6-dihydro-2-phenyl-4*H*-1,3-oxazines (**4a–d**, *n* = 3–6) can be converted into *trans*-5,6-cycloalkylene-5,6-dihydro-2-phenyl-4*H*-1,3-thiazines (**1a–d**, *n* = 3–6) by treatment with phosphorus pentasulphide (P_4S_{10}) at 130 °C, by analogy with Meyer's procedure[13] for related compounds. The analogous conversion of the *trans* isomers **5a–d** could not be effected, however, even at higher temperatures and with longer reaction times; in addition to various amounts of decomposition products, the starting materials were recovered.

The *cis*-5,6-cycloalkylene-5,6-dihydro-2-phenyl-4*H*-1,3-thiazine isomers (**2a–d**, *n* = 3–6) were successfully prepared by heating the *trans*-2-benzoylaminomethyl-1-cycloalkanols **6a–d** with phosphorus pentasulphide. When *cis*-2-benzoylaminomethyl-1-cycloalkanols **7a–d** were treated in the same way, the products of cyclization were partly 1-thia-2-phenyl-3-azaspiro[4*n*+1]alk-2-enes (**3a–d**, *n* = 3–6) and partly the thiazines **2a–d**. The mixtures were separated by chromatography and the structures of the components established by spectroscopy.

The spectroscopic investigations were conducted with three objectives:

1. It was hoped to elucidate whether the expected 5,6-dihydro-4*H*-1,3-thiazines fused with the alicyclic ring had been formed, and whether the binary mixtures consisted of the *cis* and *trans* isomers, or whether compounds with other structures were present.
2. The ring anellation had to be determined in the compounds having the expected structures, since the method of preparation could lead to a configurational change.
3. In the flexible *cis*-anellated compounds the question of the conformations had to be clarified.

The formation of the unexpected spiro compounds **3a–d** was inferred from the following features of the ^{1}H and ^{13}C NMR spectra (see Tables 1–3):

1. The ^{1}H NMR spectra do not show the signals of the protons adjacent to the heteroatom (H-4a,e and H-6) in the region 2.5–4.5 ppm, shifted paramagnetically compared with H-5 and the methylene protons of the alicyclic ring.
2. Instead, in the given range, there is a singlet between 4.1 and 4.3 ppm due to two equivalent methylene protons.
3. The molecules of these compounds contain as many hydrogen atoms as the thiazine derivatives **1a–d** and **2a–d**; the elemental compositions of compounds **1–3** are also identical. In agreement with this, the overlapping multiplets between 1.3 and 2.2 ppm due to the alicyclic methylene groups have a total intensity corresponding to 2(*n*+1)*H* compared with the aromatic and the isolated methylene protons, i.e. the values are 8, 10, 12 and 14. If the multiplets are split into

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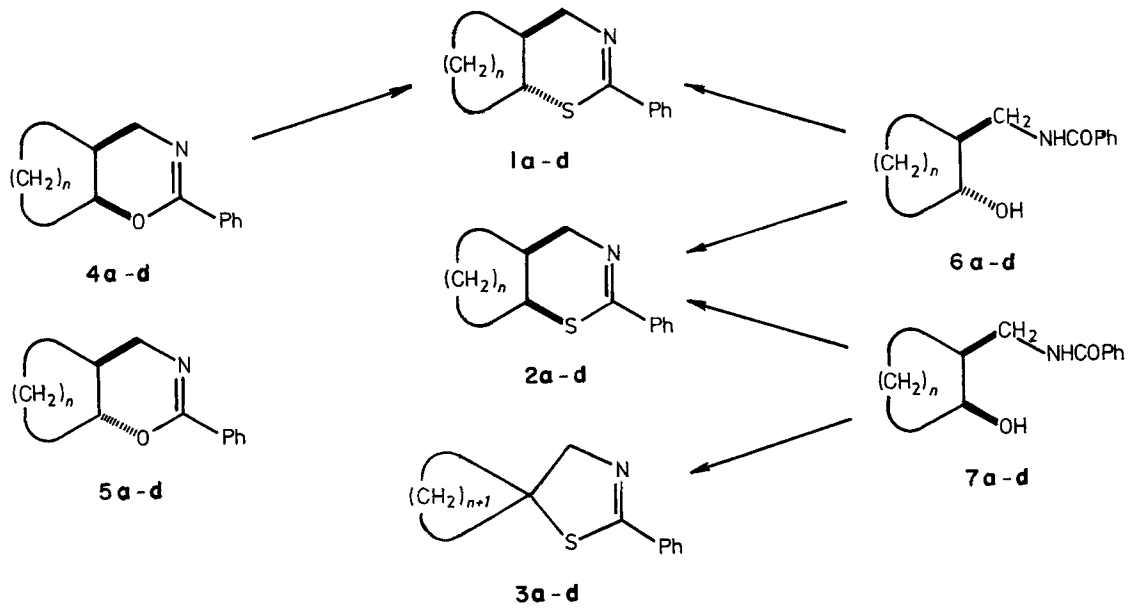

Scheme 1

Table 1. ^{1}H NMR chemical shifts ($\delta_{TMS} = 0$ ppm) of compounds 1a–d to 3a–d in $CDCl_3$ solution at 250.13 MHz

Compound	H-4a dd(1H)	H-4e dd(1H)	H-6 dt(1H)	H-5, 7–12[a] (1–3 m)	ArH(m, p) m(3H)	ArH(o) dd(2H)
1a	3.55	4.40	2.83	~1.2 (1H) ~1.4–1.9 (4H) ~2.1 (2H)	~7.4	7.82
1b	3.30	4.05	3.10	~1.0 (1H) ~1.3–1.55 (4H) ~1.85 (4H)	~7.4	7.75
1c	3.38	4.09	3.11	~1.25 (1H) ~1.6 (6H) ~1.8 (4H)	7.38	7.80
1d	3.48	4.04	3.30[c]	~1.55 (12H) ~1.95 (1H)	7.38	7.84
2a	3.40	3.98	3.50	~1.55 (2H) ~1.65–1.95 (3H) ~2.18 (2H)	~7.4	7.90
2b	~3.68[b]	4.00	~3.65[b]	~1.2–1.9 (9H)	~7.35	7.80
2c	~3.58[b]	3.80	~3.58[b]	~1.35 (2H) ~1.65 (5H) ~1.95 (4H)	~7.4	7.85
2d	3.66	3.92	3.57	~1.5 (10H) ~1.8 (2H) ~2.1 (1H)	~7.35	7.85
3a	4.25[d]		—	~1.65–2.2 (8H)	~7.4	7.80
3b	4.13[d]		—	~1.3–1.8 (8H) ~2.0 (2H)	7.35–7.5	7.82
3c	4.15[d]		—	~1.65 (8H) ~1.9 (2H) ~2.15 (2H)	7.35–7.45	7.80
3d	4.11[d]		—	~1.6 (10H) ~2.05 (4H)	~7.4	7.80

[a] Some partly overlapping multiplets of H-5, 7–9 (**1a, 2a**), H-6–9 (**3a**), H-5, 7–10 (**1b, 2b**), H-6–10 (**3b**), H-5, 7–11 (**1c, 2c**), H-6–11 (**3c**), H-5, 7–12 (**1d, 2d**) or H-6–12 (**3d**) atoms.
[b] Overlapping multiplets.
[c] Lines are coalesced in the multiplet.
[d] s (2H).

several signals, e.g. as in the spectrum of **3c**, the intensities of the separate signals correspond to even numbers of hydrogens, indicating the presence of methylene groups only.

Table 2. Proton–proton coupling constants (Hz) of compounds 1a–d and 2a–d

Compound	J(4a4e)	J(4a5)	J(4e5)	J(56)	J(67a)	J(67e)	$\Delta\nu$H-6[a]
1a	17.4	11.4	4.1	11.1	11.1	6.9	29
1b	16.9	11.0	3.4	11.1	11.1	3.6	26
1c	16.7	11.2	3.3	11	11	3	25
1d	16	11	3				20
2a	13.6	8.2	4.0	7.0	7.0	7.0	21
2b	15	6	4.0				
2c	15.0	7.5	2.8				
2d	16.3	6.3	3.4	7.3	7.3	4.3	19

[a] Approximate half signal width in Hz.

4. As decisive proof of the spiro structure, the number of saturated carbon signals in the ^{13}C spectrum is lower than for **1a–d** and **2a–d**, owing to the presence in **3a–d** of two, two, three and three equivalent carbon atom pairs, respectively. Instead of the 5–8 lines for the alicyclic carbons, only 3, 4, 4 and 5 lines, respectively, are found.

5. In addition to the 2, 3, 3 or 4 methylene carbon signals of the alicyclic ring, there are only two other lines in the range characteristic of saturated carbon atoms. One (C-4) is the paramagnetically shifted signal of the methylene group adjacent to the nitrogen atom, whose assignment is beyond doubt, on the basis of its chemical shift, intensity and the triplet splitting in the proton-coupled spectrum; the other (C-5) is the signal of a more shielded carbon which is not split in the proton-coupled spectrum, showing that it is due to a quaternary, i.e. the spiro, carbon atom.

Table 3. ^{13}C NMR chemical shifts ($\delta_{TMS} = 0$ ppm) of compounds 1a–d to 3a–d in $CDCl_3$ solution at 20.14 MHz

Compound	C-2	C-4	C-5	C-6	C-7	C-8	C-9	C-10	C-11	C-12	C-1′	C-2′,6′	C-3′,5′	C-4′
1a	156.5	54.8	39.4	43.2	31.8	20.5	27.7	—	—	—	139.4	126.5	128.1	130.0
1b	157.5	55.9	35.5	44.2	33.2	25.6	26.1	30.0	—	—	139.2	126.1	127.8	129.7
1c	159.3	58.6	38.8	46.8	35.5	25.7[b]	25.5[b]	27.2	31.8	—	139.1	126.5	128.1	130.0
1d	160.5	59.0	35.5	46.5	33.2	26.9[b]	24.4	25.8[b]	26.1[b]	31.1	139.2	126.6	128.2	130.1
2a	163.1[a]	53.4	36.4	44.0	35.2	23.1	28.6	—	—	—	139.3	127.0	128.3	130.4
2b	157.4	53.4	31.1	40.7	30.1	21.3	24.1	25.9	—	—	139.3	126.0	127.8	129.7
2c	160.3	55.1	34.9	44.5	33.8	25.9	25.7	29.2[b]	29.4[b]	—	138.8	126.1	127.8	129.8
2d	158.3	55.3	31.6	43.4	30.9	26.9[b,c]	24.7	25.6[b]	26.5[b]	26.9[b,c]	138.9	125.8	127.6	129.5
3a	168.2	75.6	68.4	40.2[d]	24.3[e]	24.3[e]	40.2[d]	—	—	—	133.9	127.9	128.2	130.7
3b	166.5	75.8	64.9	38.0[e]	24.7[d]	25.0	24.7[d]	38.0[e]	—	—	133.6	127.5[b]	127.7[b]	130.1
3c	167.6	77.2	68.2	40.9[d]	27.9[e]	24.9[f]	24.9[f]	27.9[e]	40.9[d]	—	133.9	127.7[b]	128.0[b]	130.5
3d	167.5	75.7	68.3	36.1[d]	27.8[e]	24.6[f]	24.4	24.6[f]	27.8[e]	36.1[d]	133.8	127.7[b]	127.9[b]	130.4

[a] Very weak signal, the shift is uncertain.
[b] Reversed assignment is possible.
[c] Overlapping lines of chemically different carbons.
[d,e,f] Common lines of chemically equivalent atom pairs.

6. The signals of C-4 and C-5, and that of C-2 situated between the heteroatoms, experience considerable paramagnetic shifts (in general, 20, 32 and 8 ppm, respectively), relative to the thiazines, showing evidence for a hetero ring of smaller size. The deshielding of C-2 is due to the coplanar structure, where stronger conjugation reduces the electron density at this atom; the deshielding observed for C-5 is explained by the increase in the order of the carbon atom,[16a] and for C-4 by the presence of the neighbouring quaternary carbon.[16b,17]

7. There is no significant change in the shift of the C-6 signal, since the paramagnetic shift caused by the neighbouring heteroatom, observable in compounds **1a–d** and **2a–d**, is largely substituted in the spiro compounds by the deshielding effect of the neighbouring quaternary carbon. However, the other C-ω neighbour of the spiro carbon atom in the alicyclic ring which is C-9, -10, -11 and -12 in **3a–d**, respectively) gives a considerably less shielded signal than in the thiazines, because the net effect of the neighbouring spiro carbon can come fully into play here.

In the determination of the ring anellation of the thiazines, the configuration and conformation should be considered together. These spectroscopic principles have been discussed in detail previously for 2-oxo-[8] and 2-aryl-substituted oxazines;[11] accordingly, only the essentials are given here.

The replacement of oxygen by sulphur may cause fundamental changes, due to the different radii of the heteroatoms and the different C-2—S-1—C-6 bond angles, which result in different distances between the S atom and the other atoms of the molecule as compared with the data for the *O*-analogue. As a consequence of the presence of sulphur and the C=N double bond, the thiazine ring is expected to be more flexible than the hetero rings of the dihydro- or perhydro-2-oxo-[8] and, particularly, the perhydro-2-aryl oxazine derivatives.[11]

The *cis*-tetramethyleneoxazines studied earlier were found to be conformationally homogeneous systems, in spite of the fact that, in contrast to the rigid *trans* isomers containing both rings in the chair conformation (Fig. 1), the *cis* isomers are flexible. We have shown that when an O atom or NH group is attached to the anellated carbon, of the two possible chair–chair conformers of the *cis* isomers (Fig. 1), the 'C-in' conformer, containing the oxygen or NH group in the axial position relative to the cyclohexane ring, will be stable. On the other hand, in the *N*-substituted (NMe, NBzl) derivatives the 'C-out' conformation is predominant, in which the NR group is equatorial.[8,10,11]

In the determination of the steric structure, the data of decisive importance are the chemical shift δX, the line width $\Delta\nu X$ and the coupling constants $J(MX)$ and $J(BM)$ (see Fig. 1). As the empirical rule $\delta H\text{-e} > \delta H\text{-a}$ generally holds for cyclohexane derivatives,[16c] the X proton is more shielded in the 'T' isomer and in the 'C-out' conformation of the *cis* isomers; hence, in the latter case, the chemical shifts δX in the *cis* and *trans*

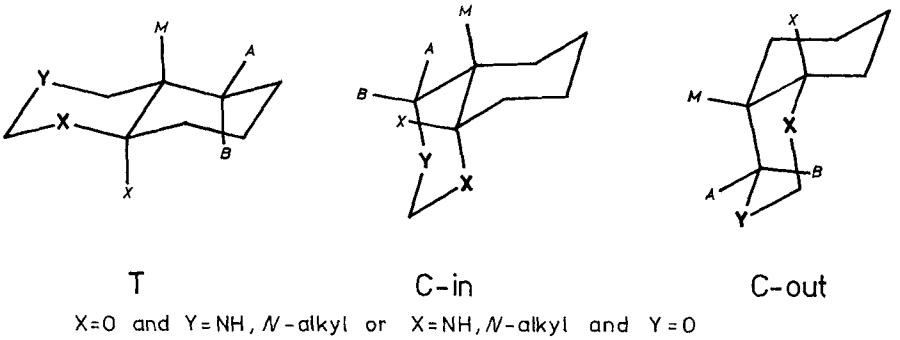

Figure 1. Stable conformations of *trans*- and *cis*-perhydrobenzoxazines.

isomer pairs will not differ significantly, but a considerable difference is to be expected if the 'C-in' conformation is predominant.

Similar conditions apply to the BM coupling constant. According to the Karplus relationship,[18] the diaxial–vicinal coupling is greater than the coupling constants of diequatorial and equatorial–axial interactions and, therefore, J(BM)aa(T) ≈ J(BM)aa (C-out) > J(BM)ae (C-in). On the other hand, the MX couplings, independent of the conformation of the *cis* isomer, are different for the isomer pairs: J(MX)aa(T) > J(MX)ae (C-in) ≈ J(MX)ea (C-out). Finally, as the X atom is axial to the cyclohexane ring, the width of the X signal is much greater for the 'T' and 'C-out' forms, because the diaxial interaction also involves the other neighbouring C-7 axial methylene proton, in addition to the M atom.

The above considerations can be strictly applied only to cyclohexane derivatives, since the empirical rules on the relative magnitudes of the chemical shifts and couplings hold good for these compounds and their hetero analogues. However, as shown by our investigations, an increase in the ring size gives rise only to minor changes in the conformational relationships; the preferred conformer remains the same, only its statistical weight in the conformational equilibrium being altered. This is explained by the relative independence of the dihedral angles about C-4 and C-5 from the conformational motion of the alicyclic ring; this part of the skeleton is rigid, owing to the anellation. This does not mean that the appearance of other bond directions (e.g. isoclinal in pentamethyleneoxazines and thiazines) is excluded in the carbocycles of heterocycles fused with alicycles containing a larger number of ring atoms, as shown by our x-ray diffraction studies.[19,20] In the trimethylene derivative **2a**, the conformational relationships differ considerably, as has been reported for the oxazine analogues.[10]

A study of the spectral parameters of the thiazine isomers **1a–d** and **2a–d** led to the following conclusions.

In the spectra of the *trans* isomers **1b–d** the signal of H-6 is found in the region 3.1–3.3 ppm, whereas the range 3.57–3.65 ppm is characteristic of the *cis* isomers. The shift differences measured for the **b–d** pairs (**1** and **2**) 0.55, 0.47 and 0.27 ppm, respectively. It follows that in the preferred conformation of the *cis* isomers the sulphur atom is axial, similar to the oxygen isosteric compounds. The considerably different shifts found for the *trans* and *cis* isomers **1a** and **2a**, containing a cyclopentane ring, indicate that the *cis*-trimethylene derivative **2a** exists in a conformation different from that of the other *cis* isomers, as in the case of oxazines.[10]

The BM coupling, i.e. the J(4a5) interaction, is smaller in the *cis* isomers, its value being between 6 and 8.2 Hz; the analogous a, a coupling of the *trans* isomers is 11–11.5 Hz (Table 2).

The two relatively high values lead to the conclusion that the dominant conformation of the thiazine ring is a boat form in which the H-4e, H-5 and H-4a, H-5 dihedral angles are approximately 140° and 20°, respectively (Fig. 2).

By assuming this conformation the molecule can

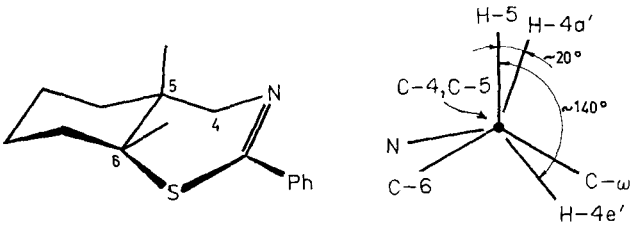

Figure 2. Preferred conformation of compound **2b** with the dihedral angles about the C-4—C-5 bond.

avoid steric hindrance between the H-ω(a) and C-2 atoms, or the former and the phenyl ring, which is present in another stable (twist) conformation of the thiazine ring (Fig. 3).

The MX interaction, i.e. the magnitude of the J(56) coupling constant, cannot be determined by routine measurements in **2b** and **2c** owing to the overlapping of the signals, or in **1d** because of the coalescence of the H-6 multiplet lines. Direct comparison can be made only in the case of the cyclopentane derivatives **1a** and **2a**, where the coupling constants of the isomers differ characteristically (7.0 and 11.1 Hz). However, the unambiguous determination of the anellation is adversely affected by the fact that the differences between the *cis* and *trans* vicinal coupling constants for five-membered rings are smaller, and just the reverse,[16d] $J(cis) > J(trans)$, than those in cyclohexanes. In the vicinity of the sulphur atom, e.g. in di- and per-hydrothiophene derivatives, the usual relationship $J(cis) < J(trans)$[21] is restored, but the literature lists very few such examples and it remains questionable whether this observation can be applied to the thiazines discussed.

The other data (7.3 Hz for the *cis* isomer **2d** and 11.1 Hz for the *trans* anellated **1b** and **1c**) also strongly suggest that the 'C-in' conformation is preferred, together with the axial position of the sulphur in the *cis* isomers. Nevertheless, the difference is smaller than in the oxygen and nitrogen analogues, and the same applies to the width of the H-6 (X) signal. This can be due to several reasons, which probably contribute together in producing the observed effects:

1. Vicinal couplings are greater in the vicinity of the sulphur atom, and there is less difference between the coupling constants of the a, a and a, e interactions.[16e]

2. The coupling constants determined on assuming first-order interactions for the ABMX spin system are not accurate. Owing to the rather large chemical shift difference relative to the coupling constants, the first-order approach is correct in the case of the oxygen and nitrogen analogues. For thiazines, however, the

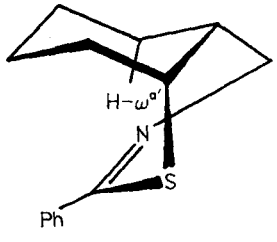

Figure 3. Unstable conformation of compound **2b** with a twisted thiazine ring.

$\Delta\delta$ AB values for compounds **2a–d** are smaller (0.58, 0.32, 0.22 and 0.26 ppm, respectively), and thus the ratio $J/\Delta\nu$ is approximately 0.2; the first-order approach is allowed only if this ratio is smaller than 0.1.[16f]

3. It follows from the above that the thiazine ring is more flexible than the hetero ring of oxazines; hence the molecule is also not rigid in the case of the cyclohexane derivatives. The *cis*-tetramethylene derivatives also form systems with a non-homogeneous conformation, and in the preferred conformer the cyclohexane ring occurs as a boat or twisted boat instead of the classical chair form. The ^{13}C NMR data on the compounds also indicate that, in the conformational equilibrium of the *cis* isomers, preference is given to a form which is similar to 'C-in' but distorted.

Independently, the *cis* and *trans* isomers can also be differentiated with certainty on the basis of the ^{13}C NMR chemical shifts, since steric hindrance gives rise to considerably increased shielding of the ring carbon atoms in *cis*-anellated cyclic systems compared with the *trans* isomers.

The effect is the greatest for the anellated carbon atoms, and decreases gradually with the distance from these carbons. This is seen, for instance, in *cis*- and *trans*-decalin,[22] but it also holds good for the hetero analogues, independently of the variations in the size of fused rings.

This phenomenon is the field effect (steric compression shift[23]), which is manifested in the increased shielding of the carbon atoms bearing sterically hindered groups. A comparison of the data in Table 3 shows that the anellated C-5 and C-6 in the *cis* isomers are more shielded by 3.0, 4.4, 3.9, 3.9, and by (−0.8), 3.5, 2.3 and 3.1 ppm, respectively. The only exception is the anomalous shift of C-6 in the cyclopentane derivative **2a**. This can be explained by the flexible structure of both fused rings in **2a**, with the consequence that the C-7 methylene group and the sulphur atom can easily evade mutual steric hindrance (see below). The *cis* structure of **2a**, however, is beyond doubt, as it is supported by coupling constants analogous to those of **2b–d**, and also by the *trans* structure of its isomeric counterpart **1a**, based on x-ray diffraction analysis.[24]

The field effect can also be observed for C-4 and C-ω, adjacent to the anellated carbon atom. In compound **2b** a very large increase of the shielding of C-8 is seen; as this atom is in the 1,3-diaxial position to the sulphur, it is also sterically hindered. The greater field effect than that measured for C-7 can be regarded as additional evidence for the preference of the 'C-in' conformation.

In the trimethylene derivative **2a** no field effect is found for the methylene carbon atoms of the cyclopentane ring. This suggests that the molecule is present mainly in the sterically most favoured butterfly-wing conformation (Fig. 4), where there are no appreciable steric hindrances compared with the *trans* isomer. This also explains the unusual chemical shift of C-6.

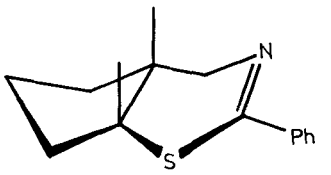

Figure 4. Preferred butterfly-wing conformation of compound **2a**.

To summarize, it can be stated that the conformational relationships of fused-skeleton thiazine derivatives are far more complicated than those of the related oxazines, but the preferred conformation of the *cis* isomers is analogous to the predominant form of the oxygen isosteric compounds.

EXPERIMENTAL

The synthesis and chemical properties of the compounds will be reported elsewhere.[12] The elemental analyses are consistent with the calculated values to within ±0.1%. Melting points are uncorrected. M.p.s (°C): **1a**, 99–101; **1b**, 100–102; **1c**, 55–57; **1d** (perchlorate), 180–182; **2a** (perchlorate), 164–165; **2b** (perchlorate), 205–207; **2c** (perchlorate), 126–128; **2d** (base and perchlorate), 63–65 and 150–152°, respectively; **3a** (perchlorate), 165–158; **3b** (perchlorate), 169–171; **3c** (perchlorate), 133–135. The salts of compound **3d** could not be crystallized; b.p. 155–160 °C/5 mmHg.

Compounds **2a–d** and **3a–d** were separated by preparative chromatography on silica gel; the developing solvent mixture was butanol–diethyl ether–glacial acetic acid (10 : 10 : 1).

The ^1H and ^{13}C NMR spectra were recorded in 5 mm tubes at room temperature in $CDCl_3$ solution on a Bruker WM-250 or WP 80SY FT spectrometer at 250.13 and 20.14 MHz, respectively, using the ^2H signal of the solvent as the lock and TMS as internal standard. The most important measuring parameters for the ^1H and ^{13}C NMR spectra are as follows: sweep width 5 kHz, pulse width 1 and 3.5 μs (*ca* 20° and *ca* 30° flip angle), acquisition time 1.64 s, number of scans 8 and 1–4K, computer memory 16K. Complete proton noise decoupling (*ca* 1.5W) for the ^{13}C spectra and Lorentzian exponential multiplication for signal-to-noise enhancement were used (line width 0.7 and 1.0 Hz).

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