MAGNETIC RESONANCE IN CHEMISTRY, VOL. 29, 687–692 (1991)

Synthesis and Steric Structure of Alicycle-Fused 1,3-Thiazine-β-lactams*

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2 + 2-Cycloaddition reactions of *cis*- and *trans*-cyclopenta-, -cyclohexa- and -cycloheptа- and *trans*-cycloocta[*e*]-2-phenyl-4H-1,3-thiazines gave new types of hydrated tricyclic 1,3-thiazino-β-lactam derivatives having the 2-phenyl substituent and H-9 in *cis* positions. The configurations and conformations of the new compounds were determined by ^{1}H and ^{13}C NMR spectroscopy, including double resonance, DNOE and 2D HSC measurements.

KEY WORDS Alicycle-fused 1,3-thiazino-β-lactams Synthesis ^{1}H and ^{13}C NMR spectra Double resonance DNOE 2D-HSC Conformational analysis

SYNTHESIS

We have previously reported the syntheses and elucidation of the structures of linearly and angularly fused 1,3-benzothiazino-β-lactams.[2,3] As a continuation of this work, we have now prepared derivatives of a new type in which *cis*- and *trans*-cyclopenta-, -cyclohexa- and -cycloheptа- and *trans*-cycloocta[*e*]-2-phenyl-4*H*-1,3-thiazines[4] are fused with a β-lactam ring.

The reactions of *cis*- and *trans*-4a,5,6,7,8,8a-hexahydro-2-phenyl-4*H*-1,3-benzothiazine (**1b**, **3b**) with phenylacetyl chloride in benzene solution in the presence of triethylamine (TEA) gave 6α,7α-diphenyl-2,3-(*cis*- and *trans*-4a,5,6,7,8,8a-hexahydrobenzo)-1-thiaoctames (**2d** and **4e**) (the nomenclature follows that reported in Ref. 5). Under similar conditions, the *cis*- and *trans*-1,3-thiazine derivatives **1a–c** and **3a–d** reacted with chloroacetyl chloride to furnish the chloro-β-lactam derivatives **2a–c** and **4a–d** (Scheme 1).

STRUCTURE

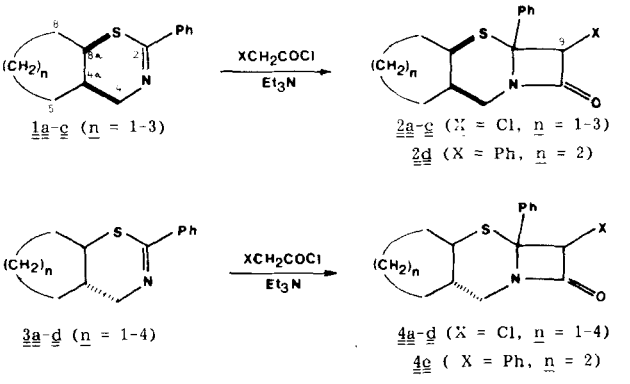
Steric structures of *trans*-annelated compounds 4b and e

From the aspect of determining the steric structure, the simplest cases are the *trans*-annelated compounds containing a cyclohexane ring, since the chair conformation of this ring is evidently preferred and the mobility of the hetero rings is limited; hence these molecules are expected to be conformationally homogeneous.

As *trans*-annelation of the β-lactam ring is impossible for steric reasons, there are four isomeric structures to be considered: by pairs, they differ in the positions of the alicycle and the four-membered ring relative to the thiazine ring (i.e. in the *cis* or *trans* steric positions of the 2-phenyl group and H-4a), and, in the two pairs of these isomers with identical skeletons, the 2-phenyl group and the 9-chloro (**4b**) or phenyl substituent (**4e**) can be *cis* or *trans*.

The unchanged *trans*-annelation of the six-membered rings unequivocally follows[6] from the 10.9-Hz coupling constant *J*(H-4a, H-8a), which gives evidence of the diaxial position of the two interacting protons. This is supported by the high values of the coupling constants *J*(H-4ax, H-4a) and *J*(H-8ax, H-8a); the former is 9.7 and 9.4 Hz for the two compounds and the latter is 10.9 Hz for both compounds (cf. Table 1.)

With the exception of the differently substituted C-9 atoms, the ^{13}C NMR chemical shifts of the saturated skeletal carbon atoms of **4b** and **4e** differ by less than 0.6 ppm (cf. Table 2); these compounds therefore certainly have analogous steric structures. Consequently, our observation that the hydrogens in the 2-phenyl ring are more shielded in **4e** (in the spectrum of **4b** the multiplets between 7.25 and 7.45 ppm are shifted to the range



1a–c (n = 1-3)
2a–c (X = Cl, n = 1-3)
2d (X = Ph, n = 2)
3a–d (n = 1-4)
4a–d (X = Cl, n = 1-4)
4e (X = Ph, n = 2)

Scheme 1

* Saturated Heterocycles, Part 191. For Part 190, see Ref. 1.

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0749-1581/91/070687-06 $05.00
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Received 26 November 1990
Accepted (revised) 29 March 1991

Table 1. Characteristic IR frequencies (cm^{-1}) in KBr discs and ^1H NMR data (chemical shifts, δ; $\delta_{TMS} = 0$ ppm; coupling constants in Hz) in $CDCl_3$ solution at 250 MHz for compounds 2a–d and 4a–e[a]

Compound	νC=O band	$(CH_2)_n$ m's (6–12H)[b]	H-4a m (1H)[c]	4-CH_2 2 × dd	4-CH_2 (2 × 1H)[d]	H-8a m (1H)[e]	H-9 s (1H)	ArH (2-phenyl) m or ~s (5H)[f]
2a	1762	~1.35,[g] 1.5–2.0[h]	2.45	2.81	4.01	3.29	5.22	7.3–7.5
2b	1778	1.3–1.65,[h] 1.7–1.9[h]	2.35	3.26	3.90	3.00	5.08	7.35–7.55
2c	1765	1.0–1.45,[i] 1.55–1.85[i]	2.40	2.93	3.96	3.15	5.11	7.3–7.5
2d	1755	1.1 – 1.4,[h] ~1.55,[g] ~1.68[g]	2.40	3.29	4.00	3.00	4.90	6.7–7.15,[j] 7.28[k]
4a	1791	1.24,[l] 1.48,[m] ~1.75,[n] ~1.95[o]	2.05[p]	3.70	3.77	2.95	5.25	7.25–7.45
4b	1781	~1.1,[m] 1.2–1.4,[q] ~1.75,[r] ~1.9[a]		3.43	3.54	2.90	5.26	7.25–7.4
4c	1770	1.2–1.8,[v] ~1.92[t]		3.39	3.60	3.00	5.30	7.25–7.45
4d	1779	1.2–1.5,[i] ~1.65,[u] ~2.05[t]		3.39	3.63	3.10	5.30	7.25–7.45
4e	1766	1.1–1.4,[h] 1.65–1.85,[h] 1.92[t]		3.50	3.69	2.97	5.07	6.90,[k] 6.95–7.1[j]

[a] Further IR signals: $\gamma C_{Ar}H$ and $\gamma C_{Ar}C_{Ar}$: 750–765 and 690–705 cm^{-1} (split bands for **2d** and **4e**). Assignments were supported by DR (**2a**, **c** and **4a**), DNOE (**2a** and **4a**, **b**, **e**) and 2D HSC measurements (**4a**, **b**).
[b] Intensity 6H for **2a** and **4a**, 8H for **2b**, **d** and **4b**, **e**, 10H for **2c** and **4c** and 12H for **4d**.
[c] Unresolved multiplet. For **2a–d** the half-band width is *ca* 25 Hz.
[d] AB part of an ABX spin system ($\delta A > \delta B$). ^2J(A, B): 14:1 ± 0.1 (**2a–d**), 12.5 (**4a**), 13.4 (**4b**, **e**) and 13.0 (**4c**, **d**); ^3J(A, X): 7.3 (**2a**), 5.5 ± 0.1 (**2b–d**), 10.7 (**4a**), 9.6 (**4b**, **e**), 11.6 (**4c**, **d**); ^3J(B, X): 11.1 (**2a**), 12.2 (**2b**, **d**), 11.5 (**2c**), 6.8 ± 0.2 (**4a–e**).
[e] Approx. q for **2a** ($J \approx 7.6$); dt, J = 12.0, 3.8 and 3.8 (**2b**, **d**), 10.8, 10.8 and 7.1 (**4a**), 10.9, 10.9 and 4.0 (**4b**, **e**); unresolved m, half-band width *ca* 20 (**2c**) and *ca* 25 (**4c**, **d**) Hz.
[f] Total intensity 10 H for **2d** and **4e**.
[g,h,i,j,t,u,v] Intensity $2H^{(g)}$, $4H^{(h)}$, $5H^{(i)}$, $8H^{(j)}$, $1H^{(t)}$, $7H^{(u)}$, $10H^{(v)}$.
[k] dd(2H).
[l] H-5ax.
[m] H-8ax.
[n] H-6ax, eq.
[o] H-5eq + H-4a.
[p] H-8eq.
[q] H-5ax, 6ax, 7ax.
[r] H-6eq, 7eq, 8eq + H-4a.
[s] H-5eq.

6.95–7.1 ppm; cf. Table 1) obviously indicates the parallel *cis* positions of the two phenyl rings in **4e**. The upfield shift of the aromatic multiplet can be explained by the mutual anisotropic effect[7a] of the benzene rings.

The configuration at C-9 therefore being established, the next task is the determination of the steric position of the 2-phenyl group relative to H-8a and H-4a.

From the aspect of H-8a and the 2-phenyl ring, the *cis* isomer is rigid; the six-membered hetero ring is in a half-chair conformation, in which C-4 and C-4a project in opposite directions out of the plane formed by C-2, 8a and the N and S atoms; the four-membered ring is quasi-axial and its plane is parallel with the C-4a—H bond. The H-4a, H-9 distance is about 2.8 Å, and H-9 and H-8a are on opposite sides of the skeleton [Fig. 1(a)].

According to the molecular model, the isomer containing H-8a and the 2-phenyl ring in the *trans* position can have two relatively stable conformations. In these molecules the thiazine ring is nearly in a twist form. The skeleton of one of the conformers [Fig. 1(b)] is flat and the β-lactam ring is attached equatorially to the thiazine ring; H-9 is situated well away from H-8a and from H-4a, which is on the opposite side of the skeleton; the

Table 2. ^{13}C NMR chemical shifts ($\delta_{TMS} = 0$ ppm) of compounds 2a–d and 4a–e in $CDCl_3$ solution at 20.14 MHz[a]

Compound	C-2	C-4	C-4a	C-5	$(CH_2)_n$ (n = 1, 2, 3)	C-8	C-8a	C-9	C=O	2-Phenyl group C-1′	C-2, 6	C-3, 5	C-4′
2a	68.5	40.4	35.8	28.3	22.5	29.7	42.7	69.5	162.8	137.5	126.4	128.3	128.5
2b	66.9	43.4	32.5	29.7[b]	19.9, 26.6	29.9[b]	38.1	70.3	162.0	138.3	128.1[c]	128.4[c]	127.2
2c	68.3	45.0	36.1	30.6	24.0, 27.4, 29.5	32.5	41.4	70.0	162.4	137.8	127.0	128.2	128.5
2d	66.7	43.3	32.8	29.6[b]	20.0, 26.6	30.1[b]	37.8	73.5	166.3	139.9	126.7[c]	128.7[c]	127.0[d]
4a	69.9	44.8	40.5	28.9	22.2	30.9	44.7	71.1	163.5	139.8	126.1	128.2[d]	128.2[d]
4b	69.7	44.0	37.5	32.3[b]	25.2, 25.5	32.2[b]	43.3	71.3	163.3	139.1	125.8	128.1[d]	128.1[d]
4c	70.2	45.5	40.7	31.2[b]	25.3, 25.6, 28.6	31.4[b]	46.3	71.4	163.6	139.2	125.8	128.1[d]	128.1[d]
4d	70.4	45.5	38.9	29.2[b]	25.6, 25.8, 26.1	29.7[b]	45.9	71.6	164.0	139.5	126.1	128.4[d]	128.4[d]
4e	69.9	44.0	38.1	32.4[b]	25.5, 25.8	32.8[b]	43.4	75.3	168.0	140.9	125.4[c]	128.8[c]	127.0[c]

[a] Signals of the 9-phenyl group in **2d** and **4e**: C-1′, 131.9 and 132.5; C-2, 3, 5, 6, 127.7[c], 127.5[c] and 127.7[c], 127.8[c]; C-4′, 127.0[d] and 127.1[c], respectively. The assignments were proved by DEPT measurements for **2a** and **4a–e** and by the 2D HSC spectrum for **4a** and **b**.
[b,c] Interchangeable assignments.
[d] Two coalesced lines.

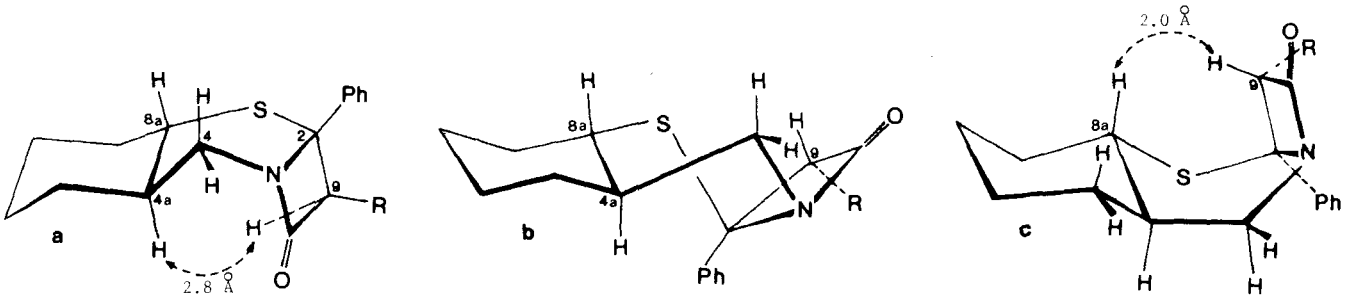

Figure 1. Stable conformations of cyclohexane-condensed homologues of 1,3-thiazine-β-lactams containing *trans*-annelated six-membered rings. (a) Rigid stereostructure of the isomer having H-8a and the 2-phenyl ring in *cis* positions; (b, c) the two possible structures of the corresponding *trans* isomer.

C—H-4a bond is parallel with the plane of the 2-phenyl ring. In the other conformer [Fig. 1(c)], the four-membered ring is attached quasi-axially to the thiazine ring and its plane is parallel with the C-8a—H bond. The H-8a, H-9 distance is *ca* 2.0 Å, and there is strong steric hindrance between these two atoms. The dihedral angles of the CH bonds in the H-4ax—C—C—H-4a and H-4eq—C—C—H-4a chains are about 30° and 90°, respectively. This structure is unlikely (sterically unfavourable), and can be rejected on the basis of the values of the 4,4a coupling constants.

An attempt to decide between the structures shown in Figs 1(a) and (b) was made by means of DNOE (differential nuclear Overhauser effect) measurements. Saturation of H-9 or H-8a caused a mutual weak increase in the intensity of the other signal; therefore, the 'flat-skeleton' structure shown in Fig. 1(b) (4a*R**, 8a*R**, 2*S**, 9*S** relative configuration of **4b**) is probable, where H-9 and H-8a are on the same side of the skeleton. If the structure depicted in Fig. 1(a) were present, a mutual intensity increase for the H-9 and H-4a signals would be expected.

In the assumed steric structure, it is likely that the 2-phenyl group exerts a shielding effect on H-4a. This can be detected by comparing the H-4a chemical shifts of the *cis–trans* pairs. For this purpose it is necessary to assign the H-4a signal unambiguously; this was achieved by 2D HSC (two-dimensional heteronuclear shift correlation) measurements. It was found that H-4a ≈ 1.75 ppm, and the most shielded atom in **4b** is H-8ax; this gives rise to the multiplet at *ca* 1.1 ppm.

Steric structures of *cis*-annelated isomers 2b and d

The conformational relationships are more complicated for the isomers **2b** and **d**, which contain *cis*-annelated six-membered rings, since the cyclohexane ring may adopt the chair form in two ways. The difference is that in one of the conformers the S atom is attached axially, with the 4-methylene group equatorial to the cyclohexane ring, whereas in the other conformer these steric positions are reversed. Our earlier systematic investigations with six-membered 1,3-*N*,*O*-heterocycles fused with various cycloalkanes have shown that, of the two conformers, those containing an axial O atom or NH group are the more stable.[8–10] In the *S*, *N*-analogues there is an equilibrium,[11] and in the *N*-substituted derivatives the form with an equatorial NR group is preferred.[9,10]

In this connection, decisive evidence can be obtained by means of the *J*(H-8ax, H-8a) value, which is smaller for the compounds with an axial S atom, corresponding to an H-8ax—C—C—H-8a, eq dihedral angle of *ca* 60°; if on the other hand the S atom is equatorial, i.e. H-8a is axial to the cyclohexane ring, the coupling constant in question is larger. Since the double triplet of H-8a at 3.00 ppm indicates a coupling of 12.0 Hz in both **2b** and **2d**, it is evident that the conformation with an equatorial *S* atom is preferred; therefore, only these conformations need be considered.

Similarly, the *J*(H-4ax, H-4a) value of 12.1 Hz allows only those conformations of the thiazine ring in which the corresponding dihedral angle is about 180°, i.e. H-4a is axial to the thiazine ring.

In the same way as for isomers **4b** and **4e**, identical steric structures for **2b** and **2d** follow from the barely different chemical shifts of the saturated skeletal carbon atoms, while the *cis* position of the phenyl rings (or, in **2b** of the 2-phenyl ring and Cl-9 follows from the mutual shielding effect of the aromatic rings on the ^{1}H NMR signals of the aromatic hydrogens in **2d**.

In view of the facts described above, the steric structure shown in Fig. 2(a) can be considered in the event of a *cis* position for H-8a and the 2-phenyl group. In this form the C-4a—H bond and the 2-phenyl group are parallel, and H-4ax and H-8ax are near one another (2.1 Å). The corresponding H-8a, 2-Ph-*trans* isomer can also have only one structure that satisfies the above conditions [Fig. 2(b)]. In this case there is strong steric hindrance between H-4ax and H-8ax, the distance between them being *ca* 1.5 Å.

In the spectrum of **2b**, the H-4a signal is shifted downfield by 0.6 ppm as compared with its counterpart **4b**; this corresponds to the value expected[7b] as a consequence of the axial → equatorial change in the position of this hydrogen. It follows that the shielding effect of the 2-phenyl group should appear in both compounds or in neither of them. Hence, for the pair of isomers **2b–4b**, the structures shown in Fig. 2(a) and Fig. 1(b) or those in Fig. 2(b) and Fig. 1(a) can be considered to be probable. As the structure in Fig. 2(b) is sterically unfavourable, and the steric arrangement shown in Fig. 1(a) is improbable according to the

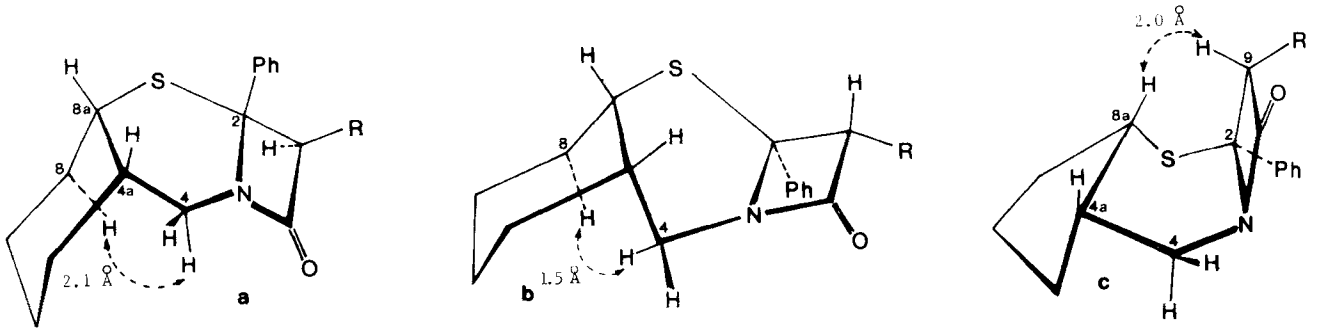

Figure 2. Stable conformations of (a, b) cyclohexane- and (c) cyclopentane-condensed 1,3-thiazine-β-lactams with *cis*-annelated six-membered rings. (a) Conformation of the isomer containing the H-8a atom and the 2-phenyl ring in *cis* position; (b, c) stereostructures of the *trans* homologues.

DNOE spectrum of **4b**, a decision can be made in favour of the structure depicted in Figs 2(a) and 1(b).

Structures of the homologues 2a and c and 4a, c and d

To facilitate the comparison of spectroscopically analogous data the numbering of the cyclohexane derivatives **2b** and **d** and **4b** and **e** has been retained for the homologues **2a** and **c** and the analogous **4a**, **c** and **d** in the text and tables. In the chemical names given in the Experimental section, however, a different numbering, according to the IUPAC nomenclature, has been used.

As shown by assignments based on DR (double resonance) and 2D HSC measurements, the homologues **4a**, **c** and **d** are spectroscopically closely related to the analogues **4b** and **e** discussed above; therefore, the similarity of their steric structures is evident. The DNOE measurements on **4a** confirm that H-8a and H-9 are situated on the same side of the molecular skeleton and that the 2-phenyl and Cl-9 substituents are *cis* to the azetidinone ring (there is no NOE between H-8a and the ArH_{ortho}).

In contrast, the homologues **2a** and **c** of the *cis*-annelated cyclohexane-fused compounds **2b** and **d** have essentially different spectra.

The DR spectra of **2a** and **2c** gave unambiguous evidence of the correct assignments of the H-4ax, 4eq, 4a, 8a signals; at the same time, it was possible to determine exactly all the coupling constants of these protons, which because of the coalescence of the lines was impossible from the multiplets for H-4a and H-8a in the routine spectra. In **2a** and **2c** the H-4ax signal is shifted upfield by 0.47 and 0.35 ppm, respectively, compared with the homologues **2b** and **d**. The vicinal coupling constants of the 4-Hs are also changed: whereas the couplings were very different for **2b** and **d** (12.2 and 5.4 Hz), they are now closer in value, being 11.5 and 7.3 Hz for **2a** and 11.5 and 5.6 Hz for **2c**. On the other hand, the H-8a multiplet is shifted downfield by 0.3 and 0.15 ppm, respectively, and the coupling constants of H-8a are also changed: the triple doublets observed for **2b** and **2d** (J = 12,4 and 4 Hz) are now replaced by a quartet-like signal ($J \approx 7.5$ Hz). All these observations point to simultaneous differences in both the configuration and conformation in **2a** and **2c** as compared with the homologues **2b** and **2d**. The almost identical magnitudes of the three vicinal couplings of H-8a correspond to the value expected on the basis of the dihedral angles (*ca* 30°, 20° and 140°), indicating quasi-axial attachment of the S atom to the alicyclic ring. The downfield shifts of the H-8a signal as compared with those in **2b** and **d** is in accordance with this structure; in **2b** and **d** H-8a is axial, whereas in **2a** and **c** it is quasi-equatorial.

Since saturation of the H-9 signal in a DNOE measurement does not influence the signal intensity of the *ortho* hydrogens in the 2-phenyl ring, the Cl and phenyl substituents are also in the *cis* position in **2a** and **c**. The vicinal coupling constants of the 4-methylene hydrogens are indicative of a boat-like conformation of the six-membered hetero ring, in which C-4 and the S atom lie out of the plane made by C-2, 4a, 8a and the N atom, and the dihedral angles corresponding to the H-4ax, H-4a and H-4eq, H-4a couplings are about 140° and 20°, respectively. In the other, relatively stable, twist conformation, these angles would be about 90° and 30°, and this would give rise to a very low value of one of the coupling constants. Further, this conformation is also less favourable because of steric hindrance between H-5ax and the 2-phenyl group. Consequently, the probable preferred structure of **2a** and **c** is the one in which H-8a and the 2-phenyl group are *trans* to the six-membered heterocycle, while this phenyl group and the Cl substituent are *cis* to the azetidinone ring [Fig. 2(c)]. In this structure, the distance between H-8a and H-9 is *ca* 2.0 Å, which is in accordance with the results of the DNOE measurements.

It must be emphasized that, owing to the presence of the *cis*-annelated five-membered alicyclic ring, this structure is much more flexible than those discussed previously; hence, as compared with the almost conformationally homogeneous molecules shown in Figs 1(a)–(c) and 2(a) and (b), in the case of **2a** the steric structure depicted in Fig. 2(c) represents only the preferred form of the conformational equilibrium.

The conformations with an equatorial S atom are not favoured because of steric hindrance between H-8ax and the 2-phenyl ring, or between H-8ax and H-4ax.

If the *cis* position of H-8a and the phenyl group were assumed, not only would the DNOE results be uninterpretable, but also the conformations allowed by the coupling constants would be improbable, as a consequence of strong steric hindrance in each case.

The similar structure of **2c**, the homologue with a seven membered saturated ring, is obviously a consequence of the greater flexibility of the cycloheptane ring.

The higher flexibility of the molecular skeleton is likewise shown by the downfield shift of the ^{13}C NMR lines of C-2, 4a, 8a in **2a** and **c** (cf. Table 2), which is due to the lack or decrease of the field effects[12] causing upfield shifts in the homologues **2b** and **d**. On the other hand, C-9 is more shielded due to steric interaction between H-8a and H-9.

EXPERIMENTAL

IR spectra were recorded as KBr discs on a Bruker IFS-113v Fourier transform spectrometer equipped with an Aspect 2000 computer and a vacuum optical system.

The NMR spectra were recorded in $CDCl_3$ solution in 5- or 10-mm tubes on Bruker WM-250 or WP-80-SY Fourier transform spectrometers controlled by an Aspect 2000 computer at 250.13 (^1H) and 20.14 (^{13}C) 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: spectrum width, 5 kHz; pulse width, 1 (^1H) and 3.5 (^{13}C) μs (*ca* 20° and *ca* 30° flip angles); acquisition time, 1.64 s; number of scans, 16 (^1H) and 1–12K (^{13}C); and computer memory, 16K. Complete proton noise decoupling (*ca* 1.5 W, ^{13}C) and Lorentzian exponential multiplication for signal-to-noise enhancement were used, line width 0.7 (^1H) and 1.0 Hz (^{13}C).

Conventional cw irradiation of *ca* 0.15 W was used for the DR experiments.

The standard Bruker microprogram DNOE-MULT.AU to generate NOE was used with a selective pre-irradiation time of 5 s and a decoupling power (cw mode) of *ca* 30–40 mW; number of scans, 64–256; dummy scans, 4–8; pulse width, 5.0 μs (90°); and 16K data points for a *ca* 2-kHz spectrum width. A line broadening of 1.0 Hz was applied to diminish residual dispersion signals in the difference spectra.

DEPT[13] spectra were run in a standard way,[14] using only the $\theta = 135°$ pulse to separate CH/CH_3 and CH_2 lines phased 'up and down,' respectively. Typical acquisition data were: number of scans, 128–12K; relaxation delay for protons, 3 s; and 90° pulse widths, 10.8 and 22.8 s for ^{13}C and ^1H, respectively. The estimated value for $J(CH)$ resulted in a 3.7-ms delay for polarization.

The 2D HSC spectra were obtained by using the standard Bruker pulse program XHCORRD.AU. The number of data points was 4K in the ^{13}C domain, and 64–256 increments were used to give a better than 5 Hz per point digital resolution in the ^1H domain; 256 transients were obtained with a relaxation delay of 3 s. All C–H correlations were found by using a value of $J(CH) = 135$ Hz for calculation of the delay.

Melting points are uncorrected.

General procedure for synthesis

2-Chloro-2a-phenyl-2r,2a*c*,3a*t*,4,5,6,6a*t*,7-octahydro-1*H*-azeto[2,1-*b*]cyclopenta[*e*]-1,3-thiazin-1-one (**2a**), 2-chloro-2a-phenyl-2r,2a*c*,3a*c*,4,5,6,7,7a*c*-octahydro-1*H*,8*H*-azeto[2,1-*b*][1,3]-benzthiazin-1-one (**2b**), 2-chloro-2a-phenyl-2r,2a*c*,3a*t*,4,5,6,7,8,8a*t*,9-decahydro-1*H*-azeto[2,1-*b*]cyclohepta[*e*]-1,3-thiazin-1-one (**2c**), 2,2a-diphenyl-2r,2a*c*,3a*c*,4,5,6,7,7a*c*-octahydro-1*H*,8*H*-azeto[2,1-*b*][1,3]benzthiazin-1-one (**2d**), 2-chloro-2a-phenyl-2r,2a*c*,3a*t*,4,5,6,6a*c*,7-octahydro-1*H*-azeto[2,1-*b*]cyclopenta[*e*]-1,3-thiazin-1-one (**4a**), 2-chloro-2a-phenyl-2r,2a*c*,3a*t*,4,5,6,7,7a*c*-octahydro-1*H*,8*H*-azeto[2,1-*b*][1,3]benzthiazin-1-one (**4b**), 2-chloro-2a phenyl-2r,2a*c*,3a*t*,4,5,6,7,8,8a*c*,9-decahydro-1*H*-azeto[2,1-*b*]-cyclohepta[*e*]-1,3-thiazin-1-one (**4c**), 2-chloro-2a-phenyl-2r,2a*c*,3a*t*,4,5,6,7,8,9,9a*c*-decahydro-1*H*,10*H*-azeto[2,1-*b*]cycloocta[*e*]-1,3-thiazin-1-one (**4d**) and 2,2a-diphenyl-2r,2a*c*,3a*t*,4,5,6,7,7a*c*-octahydro-1*H*,8*H*-azeto[2,1-*b*][1, 3]benzthiazin-1-one (**4e**) were synthesized as follows. The 1,3-thiazine derivative (**1a–c** or **3a–d**) (5 mmol) was dissolved in benzene (20 ml) and TEA (5 mmol) was added to the solution. The mixture was stirred and refluxed while a benzene solution (20 ml) of the appropriately substituted acetyl chloride derivative (5 mmol) was added dropwise over a period of 15 min. Refluxing was continued for 1 h. The reaction mixture was then washed with dilute hydrochloric acid and water. The benzene solution was dried (Na_2SO_4) and concentrated, and the product was crystallized (cf. Table 3).

Acknowledgements

Our thanks are due to Ms M. Halász, Mrs B. Csákvári and Mr A. Fürjes for skilled technical assistance.

Table 3. Physical and analytical data for compounds 2a–d and 4a–e

Compound	Yield[a] (%)	Melting point (°C)	Molecular formula	Mol. wt	Analysis (%) (calculated/found) C	H	N	Cl
2a	54.0	97–98	$C_{15}H_{16}ClNOS$	293.81	61.32/61.60	5.49/5.75	4.76/4.89	12.07/12.08
2b	54.0	105–107	$C_{16}H_{18}ClNOS$	307.83	62.42/62.12	5.89/6.05	4.55/4.75	11.52/11.61
2c	37.4	105–107	$C_{17}H_{20}ClNOS$	321.86	63.43/63.60	6.26/6.42	4.35/4.45	11.02/11.23
2d	43.1	165–166	$C_{22}H_{23}NOS$	349.47	75.60/75.62	6.63/6.76	4.01/4.09	—
4a	38.5	117–118	$C_{15}H_{16}ClNOS$	293.81	62.31/62.18	5.49/5.41	4.77/5.01	12.07/12.20
4b	64.0	138–139	$C_{16}H_{18}ClNOS$	307.83	62.42/62.29	5.89/6.06	4.55/4.70	11.52/11.41
4c	45.5	132–133	$C_{17}H_{20}ClNOS$	321.86	63.43/63.68	6.26/6.14	4.35/4.70	11.02/11.26
4d	36.2	91–92	$C_{18}H_{22}ClNOS$	335.86	64.36/64.37	6.60/6.42	4.17/4.12	10.56/10.50
4e	37.5	159–160	$C_{22}H_{23}NOS$	349.47	75.60/75.90	6.63/6.41	4.01/4.16	—

[a] Recrystallized from methanol (**2a, c**), light petroleum (**2b**) or ethanol (**2d, 4a–e**).

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