Oxazepines and Thiazepines

XIII†—Conformational Analysis of 2,3-Dihydrobenzothiazepine Derivatives

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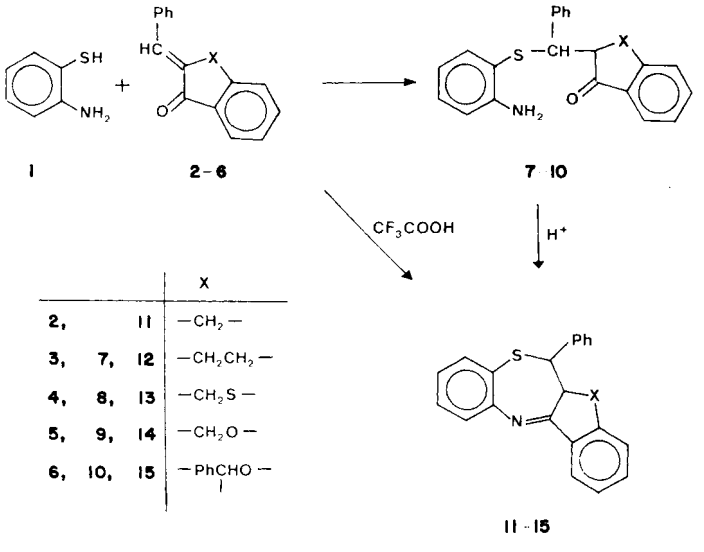
The conformation and relative configuration of various condensed heterocycles possessing a 2,3-dihydro-1,5-benzothiazepine moiety and their synthetic intermediates were determined by ^{1}H and ^{13}C NMR spectroscopy. It was found that epimerization takes place during the ring closure reaction.

INTRODUCTION

The reaction of 2-aminothiophenol with chalcones and related α,β-unsaturated ketones has been investigated by several research groups, and numerous 2,3-dihydro-1,5-benzothiazepines have been synthesized in this manner.[1–9] As a continuation of these studies, we prepared a series of 2,3-dihydro-1,5-benzothiazepines, depicted in Scheme 1, starting from exocyclic α,β-unsaturated ketones.[10–12]



	X
2, 11	$-CH_2-$
3, 7, 12	$-CH_2CH_2-$
4, 8, 13	$-CH_2S-$
5, 9, 14	$-CH_2O-$
6, 10, 15	$-PhCHO-$

Scheme 1.

To our knowledge, benzothiazepines have been synthesized in similar reactions only from 2-arylidene-1-tetralones,[3] but without any discussion concerning the stereochemistry of the compounds obtained.

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† For Part XII, see Ref. 9.

EXPERIMENTAL

Preparation of 2-aminophenyl-α-substituted-benzyl sulphides 7–10

(A) The α,β-unsaturated ketones **3–6** (5.0 mmol) and 2-aminothiophenol (6.0 mmol) were refluxed in dry toluene (35.0 ml) for 3 h; the solvent was then evaporated *in vacuo*. The residue was recrystallized from methanol, giving white crystalline substances, **7–10**. Under these reaction conditions, the 2-benzylidene-1-indanone **2** gave the corresponding benzothiazepine **11**, and compound **3** a mixture of compounds **7** and **12** (yields 30.5% and 38.2%, respectively).

Preparation of 2,3-dihydrobenzothiazepines 11–15

(B) Compounds **7–9** (0.5 g) were refluxed for 1 h in a mixture of anhydrous methanol (30.0 ml) and acetic acid (1.0 ml) on a steam bath. Crystalline materials which precipitated on cooling were filtered off and recrystallized from methanol to afford benzothiazepines **12–14**.

(C) A mixture of starting material (**2–6**) (5.0 mmol), 2-aminothiophenol (6.0 mmol), trifluoroacetic acid (1.0 ml) and dry toluene (35.0 ml) was refluxed for 3 h in an apparatus provided with a water separator. The solvent was removed under reduced pressure and the residue recrystallized from methanol to obtain benzothiazepines **11–15**, respectively, in 75–95% yields.

The mixtures were separated by column chromatography over silica gel. All compounds gave satisfactory microanalyses and IR bands. Melting points and yields (in parentheses) are as follows: **7**, 141–142 °C (30.5%); **8**, 100–101 °C (66.7%); **9**, 124–125 °C (84.2%); **10**, 155–156 °C (68.1%); **11**, 157–158 °C (70.3%); **12**, 178–179 °C (80.8%); **13**, 173–174 °C (86.3%); **14**, 207–208 °C (84.1%); **15**, 148–149 °C

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(63.8%). The melting points are uncorrected and the yields for **12–15** correspond tó method B.

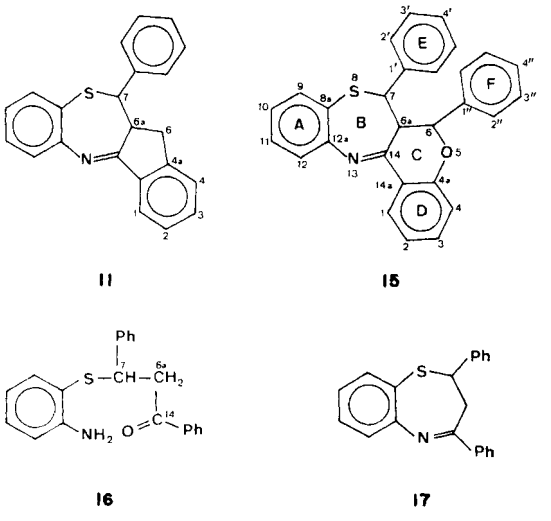
Measurements

The ^{1}H NMR spectra were recorded in $CDCl_3$ in the PFT mode (16K/32 data points for the FID) at 100, 250 and 400 MHz using JEOL FX-100, Bruker WM-250 and WM-400 spectrometers, respectively. The ^{13}C NMR spectra were obtained at 25 MHz using a JEOL FX-100 spectrometer. Typical acquisition parameters were spectral width 6000 Hz, flip angle 30° and pulse delay 2 s. Samples were recorded in 5 mm o.d. tubes. The ^{1}H and ^{13}C chemical shifts were determined relative to internal TMS.

RESULTS AND DISCUSSION

Stereochemistry and ^{1}H NMR investigations

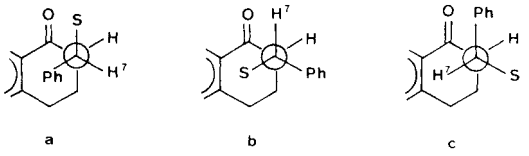
The ^{1}H NMR chemical shifts, multiplicities, coupling constants and intensity data of compounds **7–17** (Scheme 2) are summarized in Table 1. To have a more comprehensive picture of the ^{1}H data we included those of β-phenyl-β-(2-aminophenylmercapto)propiophenone (**16**) and of 2,4-diphenyl-2,3-dihydro-1,5-benzothiazepine (**17**), the syntheses of which were published earlier.[4] The numbering of the hydrogen and carbon atoms applied in the schemes and Tables 1 and 2 is not in accordance with IUPAC nomenclature. This modification, however, facilitates the comparison of spectroscopically analogous atoms in **7–17**.



Scheme 2.

The ABX-type spectrum of the aliphatic protons in **16** suggests that there is rapid rotation around the CH—CH_2 bond, but the 3.5 Hz splitting of the H-7 signal in **7** corresponds to a predominating conformer (a or b), where the H-7 and H-6a protons are in *gauche* positions (Scheme 3).

The splitting of the H-7 signal in **8** is 6.8 Hz, and it is concluded, therefore, that in this case the population



Scheme 3.

of conformers a, b and c are approximately equal. In **10**, however, conformer c predominates.

In contrast to all other compounds investigated, **9** proved to be a 2:1 mixture of diastereomeric pairs, and the overlapping of the signals prohibits the analysis of the H-7 and H-6a signals.

The H-6 signals in compounds **8** and **9** indicate the quasi-equatorial position of the substituent at C-6a in ring C. Since both C-6a and C-6 are substituted in **10**, the possibility of *cis* and *trans* isomers must be considered. The 3.7 Hz splitting of the H-6 signal shows that **10** corresponds to the *cis* isomer, because such a coupling in the *trans* isomer occurs only in the very unfavourable conformation with *trans*-diaxial substituents.

Among the aromatic protons in compounds **7–10** and **16** those of H-1 always appear at lowest field, owing to the anisotropy effect of the *peri*-positioned carbonyl group.[13] The remaining aromatic proton signals overlap strongly in the range $\delta = 6.9$–7.6, and only those of H-12 and H-10 are shifted upfield by the shielding NH_2 group.

Using **3**, **4** and **6** as starting materials only one diastereoisomer (**7**, **8** and **10**, respectively) was isolated together with the final benzothiazepine (**12**, **13** and **15**, respectively) in each case. As shown below, these benzothiazepines were always from the same isomeric series. Since it is highly unlikely that the addition reaction is stereoselective to such a great extent, it is assumed that the one diastereomeric pair of the addition product which has the same configuration as the benzothiazepine undergoes the ring closure step directly. The 'unfavourable' diastereomeric (*R,R*/*S,S*) pair cannot cyclize under these conditions and is isolated. In the presence of catalyst, ring closure is also possible after epimerization of this isomer.

In the reaction of **5** a 2:1 mixture of the two diastereomeric pairs of **9** was found. This can be interpreted by assuming that in this particular case the rate of the ring closure reaction decreases.

These arguments are supported by the finding that a diastereomeric mixture of **9** can be converted to **14**, which proved to be a single diastereomer (*R,S* and *S,R*). Exceptions from this behaviour are observed in the reactions of **2** and **5**. In the former case only the benzothiazepine **11** is also isolated, again as one diastereomeric pair. It is assumed that here the epimerization is accelerated owing to the strain of the five-membered cyclopentanone ring. Compound **10** could only be converted into **15** by using trifluoroacetic acid instead of acetic acid and over a longer reaction period (8 h); this might be a consequence of a slower epimerization process requiring stronger reaction conditions.

Comparing the spectra of compounds possessing ring B (**11–15** and **17**) and those without (**7–10** and **16**), the most pronounced difference is that in the

Table 1. ^{1}H chemical shifts ($\delta_{TMS} = 0$), multiplicities, coupling constants (Hz) and intensity data of compounds 7–17[a]

	H-7	H-6a	H-6	H-5	H-1	H-12	H-10	Ar-H	NH_2
16	4.74dd	3.67 3.76 6.8 Hz 7.6 Hz *J*(*gem*) = 17.8 Hz	—	—	7.88m(2)	6.64dd	6.50dt	6.9–7.6m(11)	4.44
7	5.08d 3.5 Hz	2.7–3.1m	2.1–2.4m(2)	2.7–3.1m(2)	8.11dd	6.64dd	6.41td	6.9–7.6m(10)	4.70
8	4.98d 6.8 Hz	3.3 m	3.40dd 3.69dd 3.5 Hz 10.0 Hz *J*(*gem*) = 13.5 Hz	—	7.95dd	6.60dd	6.45td	6.9–7.6m(10)	4.59
9[b]	4.75	3.0–3.3m	4.05dd 4.58dd 8.5 Hz 4.5 Hz *J*(*gem*) = 12.0 Hz	—	7.82dd 7.80dd	6.55dd	6.42td 6.38td	6.8–7.6m(10)	4.38
10	4.25d 8.9 Hz	3.75dd	5.59d 3.7 Hz	—	8.00dd	6.49dd	6.28td	6.6–7.6m(14)	4.17
17	4.97	3.06 3.31 12.5 Hz 4.9 Hz *J*(*gem*) = 13.0 Hz	— —	—	8.05m(2)	—	—	7.0–7.7m(12)	—
11	4.45 11.7 Hz	3.38dd	2.60 3.00dd 1.5 Hz 7.0 Hz *J*(*gem*) = 17.0 Hz	—	8.10dd	—	—	6.9–7.7m(12)	—
12	4.79d 12.5 Hz	3.38dd 5.0 Hz, 2.5 Hz	1.40ddd 1.88ddd 2.5 Hz 5.0 Hz 2.5 Hz 5.0 Hz 5.0 Hz 12.5 Hz *J*(*gem*) = 14.0 Hz	2.68ddd 3.09ddd 5.0 Hz 12.5 Hz 2.5 Hz 5.0 Hz *J*(*gem*) = 17.5 Hz	8.55dd	—	—	7.0–7.7m(12)	—
13	5.18d 12.0 Hz	3.44ddd	2.22dd 3.23dd 2.8 Hz 3.4 Hz *J*(*gem*) = 13.7 Hz	—	8.67m	—	—	7.0–7.7m(12)	—
14	4.98d 12.3 Hz	3.08ddd	3.77dd 4.03dd 1.2 Hz 2.9 Hz *J*(*gem*) = 11.6 Hz	—	8.37dd	—	—	6.9–7.7m(12)	—
15	4.98d 12.5 Hz	3.66	4.93d — 1.4 Hz	—	8.22dd	—	—	6.9–7.7m(17)	—

[a] All compounds were measured in $CDCl_3$ at 100 MHz, but **15** was also measured at 250 and 400 MHz.
[b] Where two values are given, the upper one refers to the major and the lower to the minor isomer.

Table 2. ^{13}C chemical shifts ($\delta_{TMS} = 0$) of compounds 7–17 (solvent: $CDCl_3$)

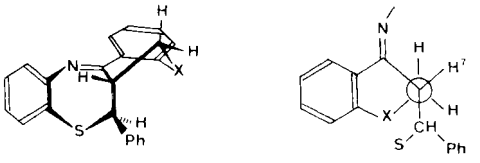
C	16	7	8	9_{major}	9_{minor}	10	17	11	12	13	14	15
1	128.3	126.9	127.1	127.3	127.3	127.3	127.3	123.7	126.8[a]	128.0	126.9	126.6
2	128.0	126.3	124.9	121.3	121.4	121.7	128.6	126.0	127.1[a]	125.1	123.9	121.8
3	133.0	133.4	133.1	135.7	135.9	135.9	130.9	132.3	131.1	131.0	133.2	133.7
4	128.0	128.6	129.8	117.8[a]	117.6	117.7[a]	128.6	127.7	128.8	129.0	119.9	118.0
4a	128.3	143.7	139.9	160.9	161.2	160.2	127.3	148.2	139.7	137.1	157.9	155.5
5	—	28.8	—	—	—	—	—	—	24.3	—	—	—
6	—	24.0	28.8	68.5	68.1	80.9	—	35.0	24.8	29.1	66.6	75.9
6a	44.2	54.4	52.9	48.3	51.4	54.7	37.4	47.8	42.7	42.1	43.7	46.2
7	47.4	51.6	51.1	49.9	49.3	47.0	60.4	65.3	60.4	59.5	59.2	60.6
8a	115.9	115.6	115.1	115.0	114.8	115.2	122.8	123.5	123.1	124.5	123.9	123.5
9	130.5	130.0	130.3	130.4	130.4	130.2	129.6	129.5	129.7	129.8	129.9	130.2
10	117.9	117.4	117.8	117.4[a]	117.6	117.5[a]	125.2	125.6	125.3	125.1	125.4	125.3
11	137.6	136.9	137.0	137.1	137.0	137.3	135.0	135.0	134.9	134.9	135.0	135.1
12	114.8	114.7	114.8	114.7	114.7	114.4	125.1	124.9	124.8	125.1	125.2	124.9
12a	149.5	149.3	149.3	149.1	149.2	149.6	152.3	152.9	152.3	151.7	151.6	151.9
14	197.0	197.2	193.2	192.1	191.4	192.9	168.7	176.4	167.8	164.3	162.8	161.9
14a	136.9	132.5	130.9	120.4	120.8	121.3	137.5	138.1	131.9	131.0	119.1	120.1
1′	141.7	141.2	141.2	139.6	138.4	140.6	144.0	143.9	143.4	142.9	142.7	142.7
2′, 6′	127.6	128.1	128.1	128.2	128.2	128.0	125.9	126.6	126.2	126.5	126.6	126.6
3′, 5′	128.5	128.6	128.4	128.4	128.2	128.2	128.6	128.7	128.8	128.9	128.8	129.0
4′	127.2	127.6	127.3	127.5	127.5	127.8	127.7	127.7	127.7	127.7	129.0	128.2
1″						135.5						138.1
2″, 6″						126.1						126.0
3″, 5″						127.5						128.4
4″						126.5						127.7

[a] May be interchanged pairwise.

former there is no NH_2 signal. Thus, the signals of H-10 and H-12 do not appear at higher field.

The ^{1}H NMR spectrum of **17** was investigated earlier by Hunter and Webb.[14] They established that the seven-membered ring is flexible, the ring inversion needs only a low activation energy and, moreover, among the two conformers of the seven-membered ring the one in which the phenyl group adopts the quasi-equatorial position is preferred.[14] The 12 Hz splittings of the H-7 signals in **11–15** prove that the phenyl groups at C-7 exist in the quasi-equatorial position.

On investigating the multiplicities of the H-6a and H-6 signals, it can be established that in **11–14** ring C is in the half-chair conformation and H-6a adopts the quasi-equatorial position and, thus, is *gauche* to both methylene protons at C-6 (see Scheme 4).

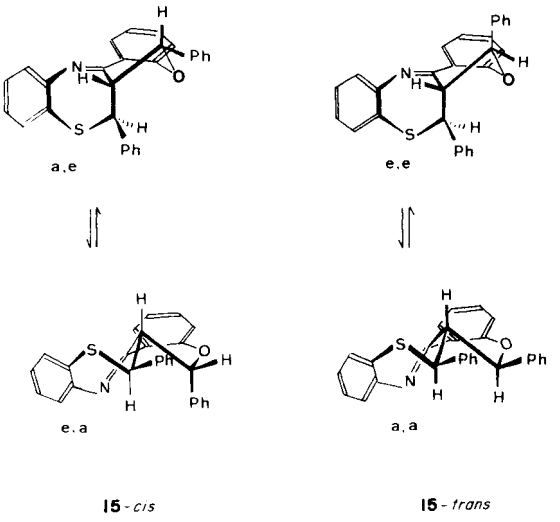


Scheme 4.

In compound **15** there are three chiral centres and, thus, four diastereomeric pairs are conceivable. The analysis of the three aliphatic proton signals is needed in order to establish the structure of the isolated compound, but owing to the strongly coupled spectrum this was not possible at 100 MHz. The three signals appear separately at 250 MHz, but the analysis and the assignment of the signals at $\delta = 4.98$ and $\delta = 4.93$ needed further investigation. Since the assignment of the corresponding C-7 and C-6 ^{13}C signals is straightforward (see below), selective ^{1}H decoupling of the ^{13}C nuclei was attempted, but this gave unambiguous answers at 250 and 400 MHz. Eventually, it was proved that the chemical shift for H-7 is 4.98 and at 4.93 for H-6 by applying the method of selective population inversion (SPI)[15] at 400 MHz. On the basis of the coupling constants J(H-7, H-6a) = 12.5 Hz and J(H-6, H-6a) = 1.4 Hz it can be shown that H-7 and H-6a are *trans*-antiperiplanar, i.e. the phenyl group at C-7 again occupies a quasi-equatorial position. Furthermore, the H-6a and H-6 protons are *gauche*, and the torsional angle is approximately 70°[16].

It was thus concluded that two alternative diastereomeric structures are possible, **15**-*cis* and **15**-*trans* (Scheme 5), where H-6 and H-6a are *cis* in the former and *trans* in the latter. Both isomers can each occur in two different conformations which are inter-converted by ring inversion. Considering the measured coupling constant of 1.4 Hz, **15**-*trans* a, a and **15**-*cis* a, e can be ruled out. In the latter the torsional angle between H-6 and H-6a is roughly 50° (estimated from the Dreiding model), which is not in agreement with the 1.4 Hz coupling.

It cannot be established from the ^{1}H NMR data alone which of the alternative **15**-*cis* e, a and **15**-*trans* e, e structures is correct. The analogous compound **14** exists in a conformation similar to **15**-*trans* e, e, as was proved above. The introduction of a phenyl substituent at C-6 in a quasi-axial position (**14** → **15**-*trans* e, e) does not cause a pronounced unfavourable steric interaction with other parts of the molecule.



Scheme 5.

^{13}C NMR investigations

For the assignment of the signals with the same multiplicities in the off-resonance spectra, known additivity rules[17] and the chemical shift data of appropriate reference compounds were applied. The chemical shifts and assignments for compounds **7–17** are summarized in Table 2.

In **7–17** the phenyl rings E exist in similar steric environments, and so it is expected, and found, that the chemical shifts of these carbon atoms are similar in the different compounds. On comparing the two different types of compounds, the presence of ring B produces a small downfield shift of C-1′ and an upfield shift of the C-2′, 6′ signals (both approximately 2 ppm). In order to assign the signals of the ring D carbon atoms, the chemical shift data of the reference compounds propiophenone,[18] indanone,[10,19,21] tetralone,[19,20] thiochromanone,[22] chromanone[22] and flavanone[23] were used. Substitution of the hetero ring does not involve a change in the chemical shifts of the aromatic carbon atoms of the chromanone moiety. Hence, the data in Table 2 are very near to the data of the reference compounds. The effect of converting the O=C group into N=C can be seen on comparing the appropriate signals of compounds **10** and **15**: only at C-3 and C-4a is there a small upfield signal shift. The assignment of C-1 in **15** was further supported by a selective ^{13}C{^{1}H} experiment, and it emerges that C-1 and C-2′, 6′ are isochronous. To support the assignment of compound **17**, 14 further derivatives which possess different substituents in the *para* position of rings D and F were investigated. The results will be discussed in a separate paper.[24]

The assignment of the carbon atoms of ring C does not require any comment. The only problem was for the C-5 and C-6 signals of **12**, which absorb close together ($\Delta\delta = 0.5$ ppm). Using selective ^{13}C{^{1}H} experiments it was proved that the signal at $\delta = 24.8$ corresponds to C-6.

Owing to the different γ_{anti} effects of the C, S and O atoms[25] in position 6 in compounds **8–10**, clear upfield shifts of the C-7 signal occur in this sequence. In **10** a further 2.9 ppm upfield shift of the C-7 signal is observed compared with **9**. This can be easily explained by a γ_{gauche} effect of the phenyl group at C-6, supporting the previously suggested *cis*-type structure for **10** (see ^{1}H NMR section). In **12–14** the X-6 and C-7 atoms are in γ_{gauche} position, and little upfield shift of the C-7 signals occurs in this sequence.[25] There is no upfield shift at C-7 in **15** compared with **14** (cf. **9** → **10**) but, instead, a small 1.4 ppm downfield shift. From this it is concluded that the C-6 phenyl group and C-7 cannot be in the γ_{gauche} position as in structure **15**-*cis* e, a, but in the γ_{anti} position, i.e. the **15**-*trans* e, e structure is correct for **15** (Scheme 5).

The correct assignment of the C-6a, C-7 and C-6 signals in **15** was very important for interpreting the ^{1}H NMR data. Thus, the proton-coupled spectrum of **15** was also measured. The direct coupling constants [^1J(CH)] are 135, 140 and 151 Hz, respectively. The increase corresponds to the increasing electron-withdrawing ability of the attached substituents.[26]

The substituent effects of the —NH_2[17] and —SCH_2Ph[27] groups were used for the assignment of the carbon atoms in ring A. As expected, conversion of the —NH_2 into an —N=C group produced a pronounced downfield effect at the *ipso*, *ortho* and *para* carbons, but the signals of *meta* carbon atoms C-9 and C-11 did not experience any change.

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