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AN NMR STUDY OF SOME SUBSTITUTED 1,5-BENZODIAZEPINES AND 1,5-BENZOTHIAZEPINES

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Abstract—The ^1H NMR spectra of a series of substituted 1,5-benzodiazepines and thiazepines are analysed by the LAOCN3 fitting program. The saturated molecules appear to exist in puckered chair conformations. The effect of increasing methyl substitution is a reduction in the amount of puckering with a flattening of the chair. Symmetrical substitution of the heterocyclic rings allows a ready inversion at room temperature whereas asymmetrical substitution stabilises the least hindered conformation. Variable temperature measurements are reported.

INTRODUCTION

A systematic study by ^1H NMR of the effects of methyl- and phenyl-substitution in the heterocyclic rings of a series of 1,5-benzodiazepines and some analogous 1,5-benzothiazepines is reported. The preparation and characterisation of these molecules are reported elsewhere.[1] The molecules studied are illustrated in Fig 1 together with the abbreviations used to identify them. Although extensive NMR studies on the unsaturated benzodiazepines and other related 1,3-diimine systems have been published,[2–6] of the 2,3-dihydro-benzodiazepine series only the spectrum of 224triMeNHN has been reported previously.[7–8] The tetrahydro-derivatives have also received little attention: the spectrum of the unsubstituted benzodiazepine NHNH[9] and the methyl resonance frequencies of the two isomeric N,N-dibenzoyl-2,4-dimethyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepines have been reported, the latter at 29·92 MHz.[10]

The spectra reported in the present work have been analysed with the help of the LAOCN3 fitting program; the average errors in the chemical shifts and coupling constants are estimated to be $< 0{\cdot}0003$ p.p.m. and $< 0{\cdot}05$ Hz respectively.

RESULTS AND DISCUSSION

The chemical shift and coupling constant data found from the analyses of the 100 MHz NMR spectra of the 15 molecules studied are listed in Table 1.

3H-1,5-*Benzodiazepines*

The chemical shift data found for 24diMeNN and 24diPhNN are in good agreement with previously published values[2–4] and are not discussed further here.

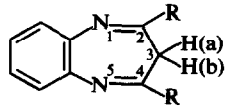
2,3-*Dihydro*-1H-1,5-*benzodiazepines and* 2,3-*dihydro*-1,5-*benzothiazepines*

In contrast to the corresponding tetrahydro-derivative the spectra of both the dihydro-benzodiazepine and benzothiazepine, 224triMeNHN and 224triMeSN, show a single line for the averaged H(a) and H(b) protons and a single sharp peak for the gem-dimethyl groups CH_3(d) indicating that a change in ring conformation occurs at room temperature at a rate which is rapid on the NMR time scale. The spectrum of 224triMeNHN was measured over a range of temperatures between 180 and 300 K. By means of the fast exchange approximation,[11] the free energy of activation for the conformational change, $\Delta G\ddagger$, is estimated to be approximately 38 kJ mol^{-1} from the broadening of the methyl resonance peak CH_3(d). The resonance peak of the internal reference TMS was used to determine the extent of broadening by factors other than exchange.

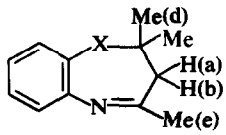
The dihydro-diphenyl-derivatives 24diPhNHN and 24diPhSN both show room temperature spectra indicative of a fixed conformation. The spectra of the heterocyclic ring protons were analysed initially on the basis of an ABX pattern; iteration then yields the parameters listed in Table 1. The spectrum of 24diPhNHN was measured at a series of temperatures up to 140°C, and although some line broadening occurred, no changes were observed consistent with inversion of the heterocyclic ring.

2,3,4,5-*Tetrahydro*-1H-1,5-*benzodiazepines and* 2,3,4,5-*tetrahydro*-1,5-*benzothiazepines*

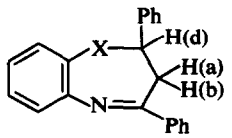
The signal of the methyl protons (c) in the molecule 24diMeNHNH appears as a doublet centred at $\delta = 1{\cdot}215$ due to the coupling of the geminal proton H(d); this has been verified by spin decoupling



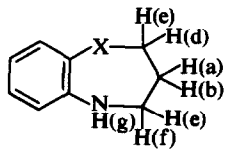
	ABBREVIATION
R = Me (c)	24diMeNN
R = Ph	24diPhNN



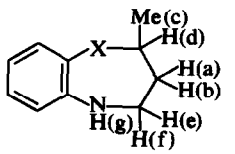
X = NH (g)	224triMeNHN
X = S	224triMeSN



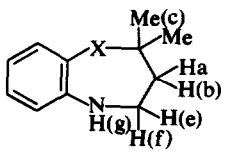
X = NH (g)	24diPhNHN
X = S	24diPhSN



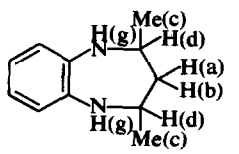
X = NH(g)	NHNH
X = S	SNH



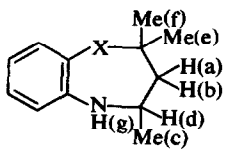
X = NH (g)	2MeNHNH
X = S	2MeSNH



X = NH (g)	22diMeNHNH
X = S	22diMeSNH



24diMeNHNH



X = NH (g)	224triMeNHNH
X = S	224triMeSNH

Fig 1. Structures and abbreviations for the 1,5-benzodiazepines and 1,5-benzothiazepines studied.

measurements. By assuming that the methyl protons (c) and the protons H(d) exhibit pure first-order coupling, and ignoring the quadrupole-broadened signal due to the NH protons, the remaining protons on the heterocyclic ring are analysed as an ABX_2 spin system. The observed magnetic equivalence of the methyl groups (c) on the one hand and the chemical inequivalence of

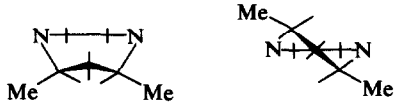
Table 1. NMR data for the heterocyclic ring protons

Compound	Chemical shifts on δ scale (p.p.m.)							Coupling constants (Hz)							
	H(a)	H(b)	H(c)	H(d)	H(e)	H(f)	H(g)	J_{ab}	J_{ad}	J_{ae}	J_{af}	J_{bd}	J_{be}	J_{bf}	J_{cd}	J_{ef}
24diMeNN	— 2·76 —		2·31													
24diPhNN	— 3·62 —															
224triMeNHN	— 2·24 —		2·37	1·34			~3·12									
224triMeSN	— 2·20 —		2·37	1·46												
24diPhNHN	2·996	3·175		5·110			~3·30	13·67	8·78			3·54				
24diPhSN[a]	3·005	3·226		4·918				13·02	12·48			4·60				
NHNH[a]	— 1·721 —		—	— 2·948 —		—	~3·70									
SNH	— 1·885 —		— 3·179 —		— 2·777 —		~3·75									
2MeNHNH	1·512	1·743	1·233	3·072	3·343	2·737	~3·25	12·81	10·06	3·50	9·17	2·85	6·58	3·18	6·52	12·67
2MeSNH	1·695	2·089	1·291	3·259	3·671	2·924	~3·60	13·44	10·36	3·34	6·59	3·74	8·42	3·88	6·94	13·80
22diMeNHNH	— 1·619 —		1·09		— 2·912 —		~3·35	15·6[b]		2·73	8·34		8·34	2·73		
22diMeSNH	— 1·883 —		1·29		— 3·171 —		~3·71	13·7[b]		2·57	8·22		8·22	2·57		
24diMeNHNH	1·381	1·579	1·215	2·757			~3·20	12·87	10·35			2·03			6·42	
224triMeNHNH	1·627	1·464	1·142	3·290	1·244 or 1·049		~3·04	13·20	10·82			2·11			6·28	
224triMeSNH	1·843	1·653	1·206	3·513	1·389 or 1·190		~3·22	13·69	10·55			2·09			6·58	

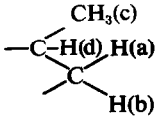
[a]Most room temperature spectra were run in $CDCl_3$ or CCl_4; those with superscript *a* were run in CD_2Cl_2. HCBD was used as solvent for high temperature spectra and CH_2Cl_2 or a mixture of halohydrocarbons for low temperature spectra. TMS was used as internal standard in all cases.

[b]$J_{ab} \approx J_{ef}$, these values are estimates only.

the H(a) and H(b) protons on the other indicates a pseudo-chair conformation rather than the alternative twist-boat conformation. The spectra of 224triMeNHNH and 224triMeSNH are analysed initially as ABX systems. This does not permit an unambiguous assignment for the two sets of



methyl protons (e) and (f) which do not couple with the ring protons. Some justification for analysing the ring protons as ABX systems is obtained from a consideration of the 6-spin system:

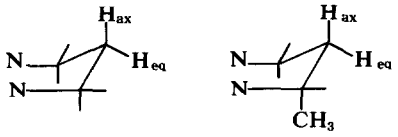


The expected H(d) multiplet pattern has been calculated for the two cases in which the chemical shift between the methyl group (c) and the proton H(d) is finite and in which it is infinite.

The two theoretical spectra are very similar; the difference in the chemical shifts being H(a), H(b) < 0·00002 p.p.m., H(d) < 0·0015 p.p.m. and H(c) < 0·0005 p.p.m., the differences in the coupling constants are negligible. Therefore analysis of the heterocyclic protons as an ABX system appears to be reasonable. The similarity of the H(d) multiplets in the spectra of both 24diMeNHNH and 224triMeNHNH suggests similar conformations for the two molecules.

The spectra of the trimethyl derivatives 224triMeNHNH and 224triMeSNH indicate that the axial proton H(a) resonates at a lower field strength than the equatorial proton H(b); this is the reverse order to that observed in the spectrum of 24diMeNHNH. The alternative assignment of the AB transition of the ABX pattern gives $J_{ad} \approx \pm 11{\cdot}3$ Hz and $J_{bd} \approx \mp 4{\cdot}7$ Hz, incompatible with the observed structure of the H(d) multiplet.

Axial protons most often resonate at higher fields than the geminal equatorial protons. This is usually ascribed to the magnetic anisotropy of the parallel 1,2 and 4,5 bonds.[12] The reverse situation found for



224triMeNHNH and 224triMeSNH could arise from the magnetic anisotropy of the parallel axial >CH—CH_3 bond, resulting in H_{axial} becoming less shielded than $H_{equatorial}$. In order to study the change in the ring conformations of the trimethyl derivatives with variation in temperature, their spectra were recorded at 15° intervals up to ~ 140°C when decomposition occurs. No coalescence of peaks was observed. The NH peaks were observed to broaden slightly and the methyl resonance (c) to move very slightly to higher field.

The NMR spectra of 2MeNHNH and 2MeSNH are analysed by comparison with the spectra already discussed. From the doublet observed for the methyl protons (c) it is assumed that first-order coupling occurs between them and H(d). Consequently the five heterocyclic ring protons are analysed as an ABCDE spin system. The experimental and calculated spectra of 2MeSNH are compared for example in Fig 2 where good agreement is observed. The spectra of 2MeNHNH and 2MeSNH have been taken at a series of temperatures up to about 135°C but no indication of a change in the conformation of the heterocyclic ring was observed. In contrast to the tetrahydro-heterocycles so far discussed, the molecules NHNH, 22diMeNHNH and the corresponding thiazepines all undergo rapid inversion at room temperature giving rise to

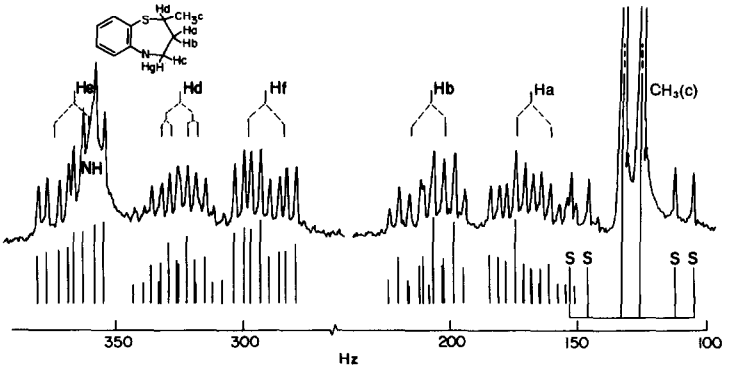


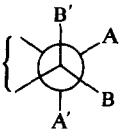
Fig 2. Comparison of the experimental and calculated ^{1}H NMR spectra of 2-methyl-2,3,4,5-tetrahydro-1,5-benzothiazepine. The lines marked S are spinning side-bands.

simplified NMR spectra. These heterocycles are substituted in such a way as to cause both possible chair conformations to be of equal energy. When the methyl substitution is asymmetrical from a conformational point of view, as for example in 24diMeNHNH or 224triMeNHNH, one chair form always involves more synaxial interference than the other, inhibiting inversion between the two conformations.

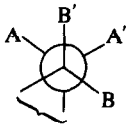
The spectrum of 22diMeSNH is shown in Fig. 3. The splitting of the multiplets at $\delta \approx 1{\cdot}9$ and $3{\cdot}2$ is not simple indicating that some restriction is placed upon the structures of the conformers involved in the inversion. Inspection of the 60 and 100 MHz spectra suggests that the heterocyclic ring protons may be considered as an AA'BB' spin-system.

Bearing in mind that the endocyclic bonds must remain *gauche*, an examination of a Dreiding model shows that throughout the series of probable inversions between chair, boat and twist-boat conformers only two conformations exist in which the two protons in each of the methylene groups are likely to be magnetically inequivalent. These two

B' *gauche* to A and *trans* to A'



B' *gauche* to A and *gauche* to A'



conformations are of equal energy and occur with equal frequency along the inversion path. Consequently $J_{AB'}$ is expected to be approximately the same as J_{gauche} and $J_{A'B'}$ to be approximately equal to the average of J_{trans} and J_{gauche}. By comparison with the spectra of the molecules already discussed these should be about 2Hz and 7Hz respectively. Similarly $J_{AA'}$ and $J_{BB'}$ should be approximately the same as J_{gem}, i.e. about 13 Hz. These values are in good agreement with those obtained by an AA'BB' analysis of the line patterns at $\delta \approx 1{\cdot}9$ and $3{\cdot}2$ (Table 1). The values of J_{gem} reported are not calculated by the LAOCN3 program because transitions 5 and 8 of the AA'BB' spin system[13] are not determined with sufficient accuracy and transitions 6 and 7 are degenerate.

In an attempt to obtain a freezing out of a molecular conformation the NMR spectrum of 22diMeSNH was measured at a series of temperatures down to $-90°C$. Although freezing out was not achieved the collapse of the fine structure of the multiplet at $\delta = 3{\cdot}2$ before that of the multiplet at $\delta = 1{\cdot}9$ was observed.

The unsubstituted diazepine, NHNH, and the corresponding thiazepine SNH are similar to the substituted derivatives, 22diMeNHNH and 22diMeSNH in giving room temperature NMR spectra which arise from inversion averaging. The diazepine spectrum shows two sets of multiplets centered at $\delta \approx 1{\cdot}7$ and $2{\cdot}9$. Although less well resolved the multiplet at $\delta = 2{\cdot}9$ resembles that of the 22diMeNHNH molecule, but the other multiplet is more complicated showing nine peaks. As confirmed by integration, the multiplet at $\delta = 1{\cdot}7$ arises from the H(a) and H(b) protons and that at $\delta = 2{\cdot}9$ from the H(c), H(d), and H(e) and H(f) protons. The effect of the sulphur atom in SNH renders the pairs of protons H(c), H(d) and H(e), H(f) inequivalent. By comparison with the previously analyzed spectra the lower field multiplet is assigned to the methylene group adjacent to the nitrogen atom. This is consistent with the electronegativity difference between sulphur and nitrogen.

Spectra of NHNH were taken at temperatures down to $-85°C$ but again it was not possible to freeze out a particular conformation.

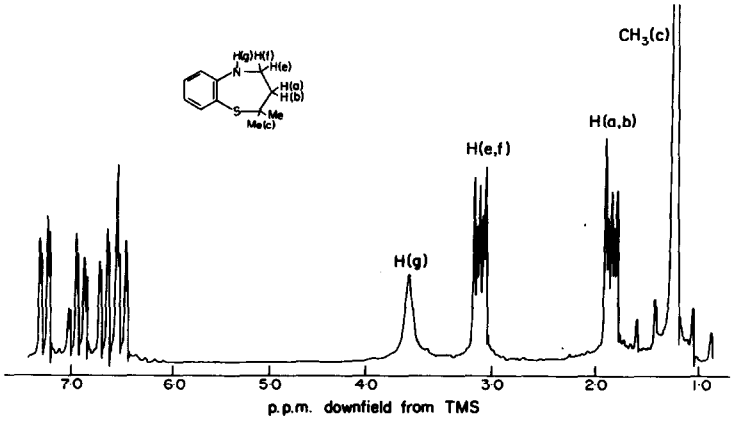


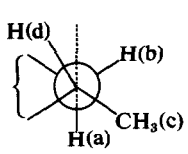
Fig 3. 100 MHz ^{1}H NMR spectrum of 2,2-dimethyl-2,3,4,5-tetrahydro-1,5-benzothiazepine.

The hydrocarbon cycloheptene freezes out into the chair conformation at −80°C[14] and it is apparent that the diazepines and thiazepines have lower activation energies to conformational changes, presumably due to facile inversion at the nitrogen atoms.

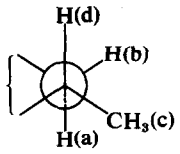
By comparing the chemical shift data in Table 1 for the protons H(a) and H(b) on carbon-3, it is apparent that they exhibit downfield shifts in the spectra of the thiazepines when compared to the spectra of the corresponding diazepines. This is most noticeable for the equatorial protons and may be attributed to the differing magnetic anisotropy of the C–S and C–N bonds. If only the inductive effects of the sulphur and nitrogen atoms were considered the opposite order of shifts would be expected.

Spin-Spin coupling extending beyond three bonds has not been observed in any of the spectra studied. The vicinal coupling constants reported in Table 1 can provide some qualitative information on the heterocyclic ring structures when considered together with arguments based upon a modified version of the Karplus equation.[15]

The values of the coupling constants J_{ad} and J_{bd} for the diazepine 24diMeNHNH fit a typical Karplus curve, giving dihedral angles corresponding to an approximate chair conformation. It is probable that the conformations of 224triMeNHNH and 224triMeSNH are similar to that of 24diMeNHNH. Support is provided by the similarity in the values of J_{ab}, J_{ad} and J_{bd} for the three molecules. Further, it is unlikely that the interchange observed in the order of the chemical shifts of H(a) and H(b) for the trimethyl derivatives, compared to 24diMeNHNH, would occur in the alternative twist-boat conformation. Additionally, at least one methyl group would experience some steric hindrance in the twist-boat form. Finally, no change is observed in the high temperature spectra of 224triMeNHNH and 224triMeSNH, whereas changes would reasonably be expected for the more flexible twist-boat conformer. Since at least one of the methyl groups in the trimethyl derivatives must be in an axial position, a slight flattening of the chair conformation might be expected to alleviate the 2,4-diaxial interference. This ring flattening, relative to the dimethyl derivatives, should result in a decrease in J_{ad} and an increase in J_{bd}. This is not observed. It is suggested therefore that the dimethyl derivative is itself more puckered than the ideal chair structure. This is supported by an examination of Dreiding models. The additional methyl substituent in the axial position now acts to distort the ring into, or slightly beyond, the ideal chair conformation. Since the average C–S bond length (~ 1·82 Å) is greater than the average value for a C–N bond (~ 1·42 Å), and the CŜC angle is usually smaller than CNC, asymmetry is expected in the thiazepine molecules.[16] The sulphur side of the molecule becomes

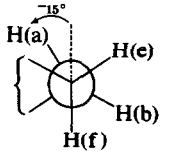


24diMeNHNH

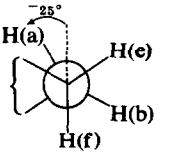


224triMeNHNH

flattened, compared to the nitrogen side, which leads to a C-2 axial methyl substituent causing less synaxial steric hindrance in a thiazepine than in the corresponding diazepine. Consequently, additional distortion due to axial methyl substitution should not be as noticeable in the thiazepine and the consequent changes in the values of J_{ad} and J_{bd}, compared with their values in the dimethyl derivative, should be smaller than in the corresponding diazepine. The observed changes in J_{ad} and J_{bd} tend to support this. For the monomethyl derivatives, 2MeNHNH and 2MeSNH, the values of J_{ab}, J_{ef}, J_{ad}, J_{bd} and J_{cd} are approximately those expected in comparison with the values found for the other molecules examined. However, the values of J_{ae}, J_{af}, J_{be} and J_{bf} differ in the two molecules and are not those expected of a regular chair conformation. They are consistent with structures which are more puckered than an ideal chair, the thiazepine being more puckered than the diazepine. A comparison



2MeNHNH



2MeSNH

of the coupling constant data for 2MeNHNH and 24diMeNHNH suggests that the latter is less puckered than the former. This is consistent with the additional methyl group being equatorial and the angle between the C-2 and C-3 methylene groups becoming more *gauche*. Consequently, in considering the series 2MeNHNH, 24diMeNHNH and 224triMeNHNH the effect of increasing methyl substitution appears to be a decrease in the puckering of the chair conformation with both additional equatorial and axial methyl groups. In the latter case this is due to synaxial interference.

EXPERIMENTAL

The 100 MHz spectra were taken on a Varian HA-100D spectrometer and the 60 MHz on a Perkin Elmer R 10 spectrometer. The LAOCN3 program was originally obtained from QCPE and adapted for use on the ICL 1905F computer.

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