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SPECTROSCOPIC AND MASS SPECTRAL INVESTIGATION OF SOME DIHYDRO- AND TETRAHYDRO-1,5-BENZODIAZEPINES AND THIAZEPINES

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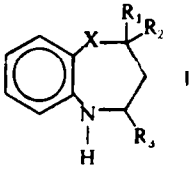
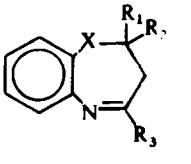
Abstract—Some methyl- and phenyl-substituted 2,3-dihydro- and 2,3.4.5-tetrahydro-1H-1,5-benzodiazepines and 1,5-benzothiazepines are described; new examples are reported and some preparative routes revised. The compounds are characterized by their vibrational and electronic spectra and mass spectral fragmentation paths are assigned.

INTRODUCTION

ALTHOUGH several examples of dihydro- and tetrahydro-1,5-benzodiazepines and benzothiazepines are now known,[1–7] little spectroscopic data has been reported and little is known concerning the structure of the heterocyclic rings. In this paper the compounds in Fig 1 are described; the methyl-substituted tetrahydro-derivatives have been chosen to determine the effect of increasing methyl-substitution upon the conformation of the heterocyclic ring. Benzodiazepines and thiazepines have been extensively studied for medicinal activities[8,9] since the success of chlordiazepoxide and similar drugs, and recently their reaction with metal salts has been described.[10–12]



I



II

	X	R_1	R_2	R_3	Abbreviation
I	NH	H	H	H	NHNH
	NH	Me	H	H	2MeNHNH
	NH	Me	Me	H	22diMeNHNH
	NH	Me	H	Me	24diMeNHNH
	NH	Me	Me	Me	224triMeNHNH
	S	H	H	H	SNH
	S	Me	H	H	2MeSNH
	S	Me	Me	H	22diMeSNH
	S	Me	Me	Me	224triMeSNH
II	NH	Me	Me	Me	224triMeNHN
	NH	Ph	H	Ph	24diPhNHN
	S	Me	Me	Me	224triMeSN
	S	Ph	H	pH	24diPhSN

FIG 1. Structures and Abbreviations for the 1,5-benzodiazepines and 1,5-benzothiazepines studied.

RESULTS AND DISCUSSION

Dihydro-heterocycles

Of the four dihydro-heterocycles in Fig 1 only the 2,4-diphenyl diazepine has not been previously prepared. The vibrational and electronic spectra of the 2,2,4-trimethyl derivatives have been discussed.[13] The electronic spectra of the two diphenyl derivatives closely resemble that of benzylideneaniline indicating the presence of a similar planar conjugated Ph—N=C(—)—Ph system (24diPhSN: λ_{max} 261·5 nm log ε 4·28; 24diPhNHN: λ_{max} 260·0 nm log ε 4·44). Except for a sharp NH stretching vibration at 3345 cm^{-1} in the spectrum of the diazepine, the vibrational spectra of both diphenyl derivatives are very similar.

The NMR spectra of the heterocycles are discussed in detail elsewhere.[14] However it is interesting to note that whereas the symmetrically substituted trimethyl derivatives give rise to simple spectra through ring inversion which is rapid on a NMR time scale, the asymmetrically substituted diphenyl derivatives exist in fixed conformations at room temperature.

The mass spectra of the compounds exhibit simple breakdown patterns. In none of the spectra is the molecular ion the most abundant; all the spectra exhibit strong metastable peaks corresponding to the breakdown of the molecular ions to the related 2-methyl or 2-phenyl benzimidazole or thiazole ions. Except in the spectrum of 224triMeNHN, these latter ions give rise to the base peaks of the spectra. The spectrum of 224triMeNHN is shown in Fig 2. In addition to the breakdown described above it illustrates an alternative degradation route for the diazepines—in this case loss of a methyl radical occurs to give the base peak (*m/e* 173) which in turn yields the ion *m/e* 133 assigned a 2-methyl benzimidazole structure (Fig 3). The thiazepine 224triMeSN does not exhibit this type of fragmentation (the relative abundance of the M—$\dot{C}H_3$ peak is $\simeq$ zero %). As in the case of the tetrahydrothiazepines discussed later the formation of the stable amidinium ion M—$\dot{C}H_3$ is impossible if the initial electron loss occurs at sulphur.

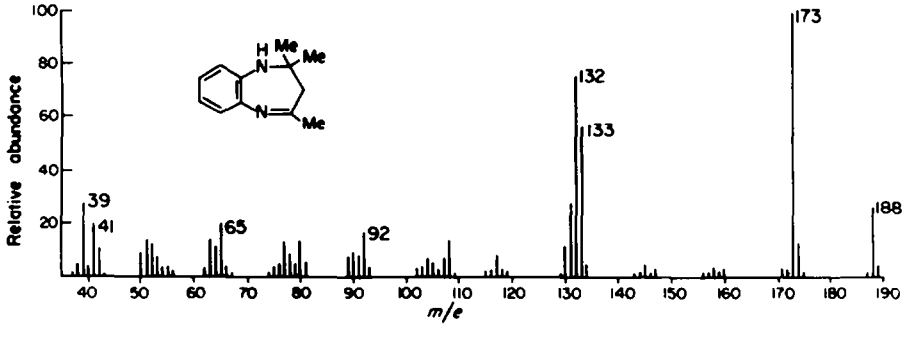
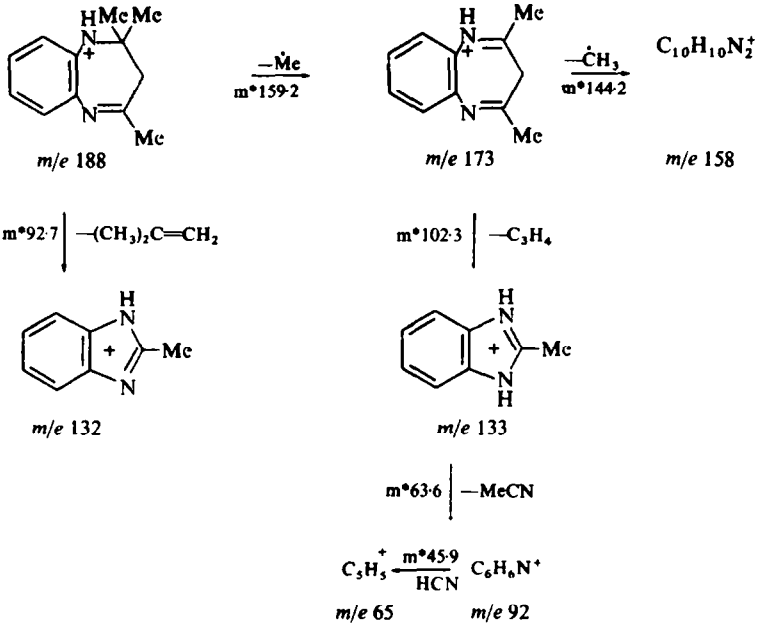


FIG 2. Mass spectrum of 2.2.4-trimethyl-2,3-dihydro-1H-1,5-benzodiazepine.



m* indicates that the step is confirmed by the appropriate metastable peak

FIG 3. Fragmentation of 2,2,4-trimethyl-2,3-dihydro-1H-1,5-benzodiazepine.

Tetrahydro-heterocycles

The vibrational spectra of the diazepines are all very similar and show a characteristic sharp band at $\simeq 3315\ cm^{-1}$ due to a NH stretching vibration. This band occurs at $\simeq 3340\ cm^{-1}$ in the spectra of the thiazepines. The spectra are also characterized by strong absorption at $\simeq 1592\ cm^{-1}$ (diazepines) and $\simeq 1578\ cm^{-1}$ (thiazepines) assigned to both aromatic skeletal vibrations and NH bending vibrations. The bending vibrations of secondary amines are usually masked by the aromatic skeletal vibrations but in this case must contribute considerably to the absorption in this region since the bands diminish greatly in intensity upon formation of transition metal chelates.[12,15] It is interesting that the NH stretching bands of the diazepines and thiazepines decrease in frequency by up to $\simeq 170\ cm^{-1}$ upon metal complex formation.

Electronic spectra data of some of the heterocycles are in Table 1. The spectra of the compounds not listed are very similar although accurate extinction coefficients have not been obtained. The spectra provide useful confirmation of the results obtained by NMR spectroscopy concerning the conformation of the heterocyclic rings.[14]

The use of electronic spectra in conformational analysis has been applied to several systems.[16] It has been shown that conjugation between the heteroatoms and the benzene ring is affected by the steric requirements of the saturated heterocyclic ring. Thus for example a study of 3,4-dihydro-2H-1,5-benzodioxepines has illustrated that the chair is the most stable conformation and that only substitution at the 3-position increases the relative stability of the alternative twist-boat conformation.[17]

TABLE 1. ELECTRONIC ABSORPTION SPECTRA OF SOME TETRAHYDRO-BENZOTHIAZEPINES AND BENZODIAZEPINES IN CYCLOHEXANE SOLUTION

Diazepines	λ(nm)*	(log ε)*	λ(nm)	(log ε)	λ(nm)	(log ε)		
NHNH	224	(4·48)	~250†	(3·76)	304·1	(3·53)		
2MeNHNH	224·1	(4·51)	~250†	(3·79)	303·8	(3·58)		
24diMeNHNH	223·9	(4·53)	~250†	(3·85)	301·2	(3·59)		
224triMeNHNH	224·6	(4·54)	254·6	(3·85)	304·0	(3·61)		
Thiazepines	**λ(nm)***	**(log ε)***	**λ(nm)**	**(log ε)**	**λ(nm)**	**(log ε)**	**λ(nm)**	**(log ε)**
2MeSN	~216	—	240·9	(4·21)	272·0	(3·62)	~305†	(3·39)
22diMeSN	~216	—	244·3	(4·12)	271·2	(3·71)	~300†	(3·47)
224triMeSN	~216	—	243·2	(4·15)	272·6	(3·67)	~300†	(3·31)

* obscured by solvent absorption
† shoulder

If, as suggested by a comparison with the spectra of aniline and *o*-phenylenediamine, the band in the diazepine spectra at ≃250 nm is largely due to the transfer of an electron from the amino group to the benzene ring, then its intensity would be expected to change with a change in conformation. As shown in Table 1, the extinction coefficients increase only slightly with progressive methyl substitution. This corresponds to a small increase in the planarity of the system, i.e. a flattening of the $C_6H_4(NHCH_2)_2$— part of the diazepine structure.

The spectra of the thiazepines exhibit an additional band compared to the diazepines and the two bands at ≃243 and ≃272 nm are assigned to transitions which effectively involve charge transfer from the two different heteroatoms to the benzene ring. The intensities of the bands again indicate that the thiazepines all exist in the same conformation, shown by NMR spectroscopy to be a pseudo-chair structure.[14]

The mass spectra of four benzodiazepines are in Fig 4. Progressive methyl substitution greatly aids peak assignments and the construction of possible fragmentation patterns. Most of the pathways are supported by the appropriate metastable peaks. It is clear from the spectra that two main intermediate species occur, at *m/e* 119 and *m/e* 133. As methyl substitution increases the abundance of the *m/e* 133 peak relative to the *m/e* 119 peak increases and the ions are therefore assigned the benzimidazole structures shown in Fig 5. The base peak in the spectra of some 3-hydroxy-2,3,4,5-tetrahydro-1,5-benzoxazepines[18] may be assigned to an analogous benzoxazole ion.

Initial breakdown of the diazepines is predicted to occur by removal of an electron from a nitrogen atom and emission of a methyl radical (Fig 5). Olefin molecules can then break away to yield the stable benzimidazole ions. Only one alkyl radical is emitted before loss of the alkene, i.e. although the M—CH_3 peak is abundant in each case, the M—2$\dot{C}H_3$ peak is always very weak. The base peak in the spectrum of NHNH is also the benzimidazole ion (*m/e* 119) which in this case must arise through emission of a hydrogen ion. Subsequent loss of MeCN or HCN yields the relatively abundant *m/e* 92 ion. Further loss of HCN gives the cyclopentadienyl ion *m/e* 65 and progressive loss of CH yields in turn $C_4H_4^+$ and $C_3H_3^+$ as usual.[19] The peak at *m/e* 41 which becomes more abundant as methyl substitution increases corresponds to the

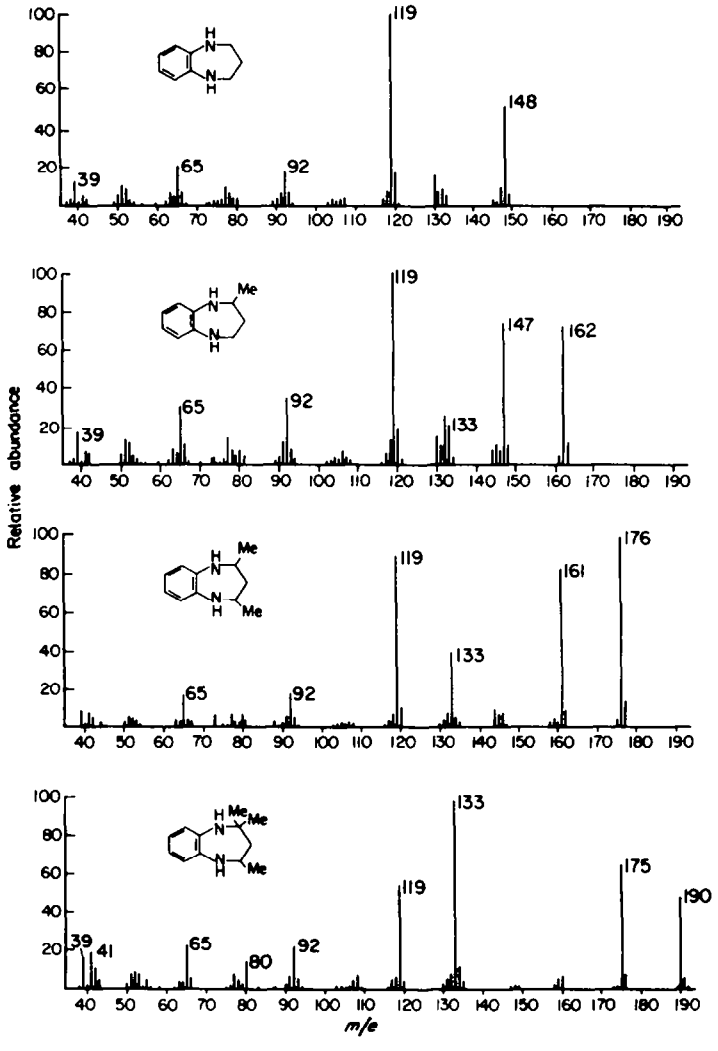
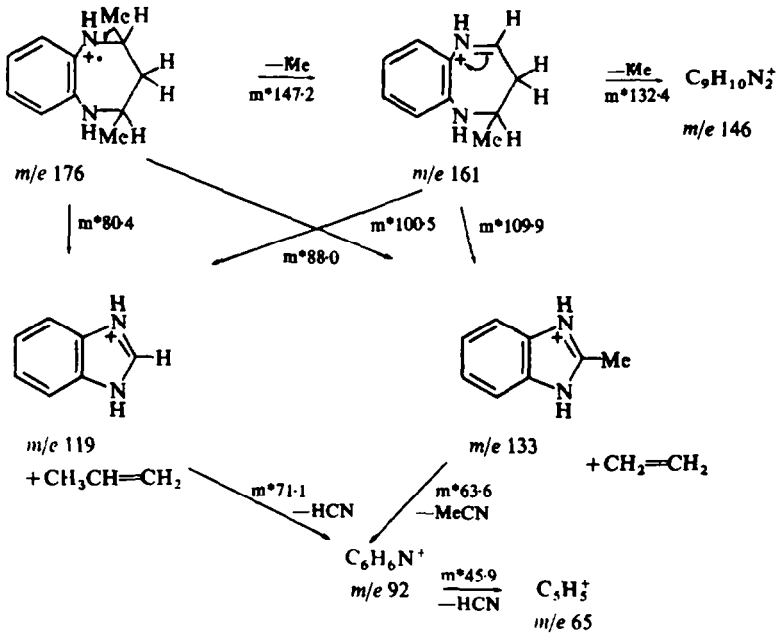


FIG 4. Mass spectra of four 2.3.4.5-tetrahydro-1.5-benzodiazepines.

allylic carbonium ion $CH_2 = CH - CH_2^+$ from propene which in turn arises in the formation of the benzimidazole ions.

To some extent the breakdown patterns of the thiazepines are analogous. The spectrum of 224triMeSNH is illustrated as an example in Fig 6. As expected, the $C_6H_5S^+$ ion at *m/e* 109 occurs to the exclusion of the $C_6H_6N^+$ ion at *m/e* 92 in all of the thiazepine spectra. This ion arises by the loss of HCN from the thiazole ion (base peak *m/e* 136). This thiazole ion (*m/e* 136) represents the base peak in the spectra of all the thiazepines examined. Unlike in the spectra of the diazepine derivatives the $M—\dot{C}H_3$ ion is largely absent in all the thiazepine spectra; if the initial electron loss occurs at the sulphur atom then the formation of the stable amidinium ion $M—\dot{C}H_3$ by expulsion of $\dot{C}H_3$ is impossible, instead the molecular ion may lose an olefin



m* indicates that the step is confirmed by the appropriate metastable peak

FIG 5. Fragmentation of 2,4-dimethyl-2,3,4.5-tetrahydro-1H-1,5-benzodiazepine.

directly to give the ion *m/e* 151 which could then break down to *m/e* 150 or *m/e* 136 (Fig 7).

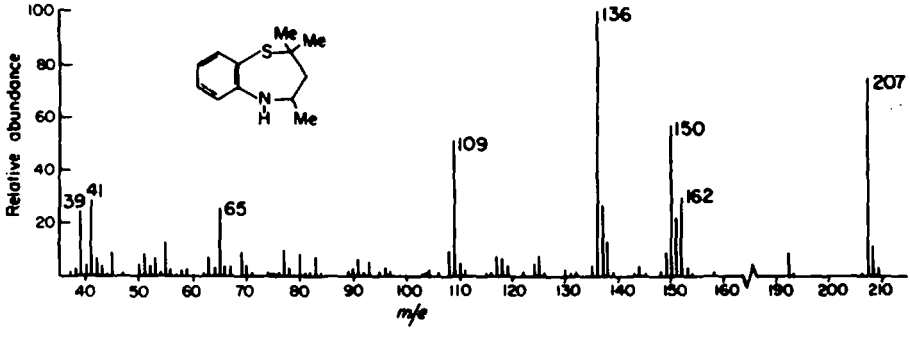
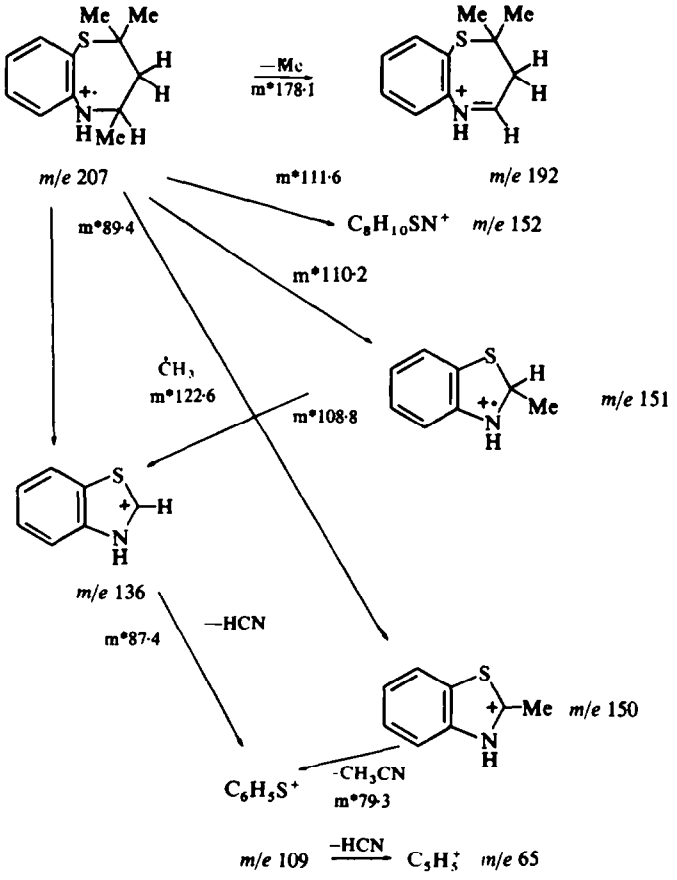


FIG 6. Mass spectrum of 2.2,4-trimethyl-2,3.4.5-tetrahydro-1,5-benzothiazepine.



m* indicates that the step is confirmed by the appropriate metastable peak

FIG 7. Fragmentation of 2,2,4-trimethyl-2,3,4,5-tetrahydro-1,5-benzothiazepine.

EXPERIMENTAL

Methods of preparation of the dihydro- and tetrahydro- benzodiazepines and thiazepines are discussed below. In some cases new and more convenient syntheses are outlined. Analytical data are given only for previously unreported compounds.

Dihydro-heterocycles. Trimethyl diazepine, 224triMeNHN, was prepared as described[4] and recrystallized from petroleum ether. The trimethyl thiazepine 224triMeSN, was prepared as follows: *o*-aminothiophenol (25 g), mesityloxide (19·6 g), conc HCl (18 ml) and EtOH (200 ml) were refluxed for 2·5 hr and stood overnight. EtOH was removed under reduced pressure and 2N NaOH poured into the remaining solution with stirring to precipitate a brown granular solid. This was recrystallized from petroleum ether (80–100°) to yield pale yellow crystals of the thiazepine (33·3 g m.p. 67°). The crystals darken slowly over several weeks.

The diphenyl thiazepine, 24diPhSN, was prepared from *o*-aminothiophenol and benzylideneacetophenone as published.[20] The diphenyl diazepine, 24diPhNHN, was prepared by the partial reduction of 2,4-diphenyl-3H-1,5-benzodiazepine using $NaBH_4$ in EtOH. (Pale yellow crystals, m.p. 114°, (Found: C, 85·02: H, 9·60: N, 5·63. Calc.: C, 84·53; H, 9·39; N, 6·08%).

Tetrahydro-heterocycles. The established route[1,2] to the diazepine NHNH was not employed: considerable difficulty was experienced in the hydrolysis of the N,N'-ditosyldiazepine—only small yields

(~18%) being obtained. NHNH was prepared in high yield more easily by the LAH reduction of either the diazepin-2-one[22] or diazepin-2,4-dione[23].

The preparation of 4-methyl-1,7,3,4,5-tetrahydro-2H-1,5-benzodiazepin-2-one has already been reported;[24] this compound was reduced to 2MeNHNH in high yield by LAH in THF.[1] The diazepine 22diMeNHNH, pale yellow oil, (Found: C, 72·12; H, 9·31; N, 15·22. Calc.: C, 71·96; H, 9·15; N, 15·89%) was prepared in an analogous manner by LAH reduction of the corresponding diazepin-2-one (colourless crystals, m.p. 255°, (Found: C, 68·92; H, 7·40; N, 14·33. Calc.: C, 69·45; H, 7·42; N, 14·73%) derived from 3-methyl-crotonic acid and *o*-phenylenediamine.

The diazepine 24diMeNHNH has been prepared previously in small quantities by the catalytic hydrogenation of either 2,4-dimethyl-3H-1,5-benzodiazepine[3] or its hydrochloride salt.[1] The alternative method reported here is as follows. 2,4-Dimethyl-3H-1,5-benzodiazepine (28 g) was dissolved in abs EtOH (250 ml). A suspension of $NaBH_4$ (12·5 g) in abs EtOH (50 ml) was added and the mixture warmed sufficiently to maintain a very gentle effervescence. After 2 hr the mixture was refluxed for 1 hr. The alcohol was distilled off under reduced pressure and the diazepine extracted from the residue with boiling petroleum ether (120–160°). Reduction in volume led to crystallization of the diazepine which was recrystallized from ether (12·5 g m.p. 57° picrate m.p. 186°). Yield is low, the *trans* isomer is probably formed in addition to the *cis* isomer which preferentially crystallises. The diazepine 224triMeNHNH was prepared similarly in high yield by $NaBH_4$ reduction of 224triMeNHN. This diazepine has been prepared previously by hydrogenation over Raney-nickel.[4]

The thiazepines SNH[5] and 224triMeSNH[6] were prepared as previously reported. The 2MeSNH and 22diMeSNH derivatives were prepared by LAH reduction of the corresponding thiazepin-2-ones[25] as in the case of the diazepines (2MeSNH: pale yellow crystals m.p. 45%; (Found: C, 67·00; H, 7·36; N, 7·58; Calc.: C, 66·99; H, 7·31; N, 7·81%). The thiazepine 22diMeSNH, for example, was prepared as follows: 3-Methylcrotonic acid (30 g) and *o*-aminothiophenol (36 g) were refluxed in a CO_2 atmosphere for 20 min. On cooling, 2,2-dimethyl-2,3,4,5-tetrahydro-1,5-benzothiazepin-2-one crystallized. The thiazepinone was recrystallized from EtOH and dried *in vacuo* (colourless crystals m.p. 220°, (Found: C, 64·14; H, 6·34; N, 6·72; Calc.: C, 63·74; H, 6·32; N, 6·76%. Yield 17·1 g)). LAH (~10 g) was added to freshly-distilled dry THF (300 ml). The thiazepinone was extracted from a sintered glass Soxhlet thimble and reflux continued for 3 hr after the extraction was complete. Excess LAH was decomposed by EtOAc and the suspension made alkaline with 2N NaOH. The organic layer was decanted and the residue washed twice with ether. The organic portions were combined and the solvents removed. The residue was extracted with boiling n-hexane and subsequent evaporation of the hexane yielded a pale yellow oil. Addition of cold water caused crystallization of the thiazepine (pale yellow crystals m.p. 31°. (Found: C, 68·82; H, 7·98; N, 7·30; Calc.: C, 68·35; H, 7·82; N, 7·25%. Yield 12·3 g).

Instrumental. IR spectra were taken on a Perkin–Elmer 457 grating spectrophotometer. Electronic spectra were recorded in spectrosol cyclohexane on a Perkin–Elmer 137 UV double beam spectrophotometer. Mass spectra were measured on an AE1 MS12 machine.

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