A SPECTROSCOPIC STUDY OF 1,5-BENZO- DIAZEPINES,
THIAZEPINES AND THEIR TRANSITION METAL COMPLEXES.

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A Thesis submitted in partial fulfilment of the
requirements for the Degree of Doctor of Philosophy.

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ABSTRACT

A spectroscopic study of 1,5-benzodiazepines, their 2,3-dihydro- and 2,3,4,5-tetrahydro- derivatives, and the analogous 2,3-dihydro- and 2,3,4,5-tetrahydro-1,5-benzothiazepines is reported. New examples of the dihydro- and tetrahydro- derivatives have been synthesized. The least known tetrahydro- diazepines and thiazepines have been examined in most detail - vibrational, electronic and NMR spectroscopy, and mass spectrometry, have been employed to determine the effect of progressive methyl substitution upon the conformation of the seven-membered ring. When the ring is symmetrically substituted, inversion that is rapid on a NMR time scale takes place at room temperature. When asymmetrically substituted, the heterocycles exist in fixed chair conformations - a progressive flattening of the chair occurs with increase in methyl substitution.

Compounds derived from the reaction of transition metal salts with 2,4-disubstituted-1,5-benzodiazepines and their monocations have been examined and the possibility of coordination of the diazepinium cation discussed. The compounds prepared are formulated as simple tetrahalometallates and metal sulphate salts of the diazepinium cation - a previously assigned structure for the latter salts is corrected. The structure of the anion in some diazepinium chlorocuprates has been found to depend upon the substitution of the diazepine ring. When 1,5-benzodiazepine bases are treated with metal salts, the base tends to revert to the delocalized cationic structure rather than coordinate to the metal. The possibility of a copper-promoted bromination of the delocalized diazepinium cation has been investigated.

Nickel(II) and copper(II) complexes of the tetrahydrobenzodiazepines have been prepared. Progressive methyl substitution of the diazepine ring increases the ease of preparation and the stability of the complexes; with the 2,2,4-trimethyl- derivative, for example, square-planar complexes are obtained. A decrease in methyl substitution allows the approach of further coordinating molecules or ions and the formation of 5-coordinate species.
I am indebted to my supervisor, Dr. G.A. Webb, for his help and encouragement.

I wish to thank Dr. L.P. Larkworthy and Dr. G.J. Buist of the Chemistry Department for the use of a variable temperature magnetic susceptibility apparatus and a diffuse reflectance spectrophotometer respectively, and Mr. J. Delderfield, Mr. J.P. Bloxsidge and Mr. E. Hopwood of the same department for some of the spectroscopic and analytical data.

I am grateful to Arthur R. Farminer for a thoroughly tested copy of the LA0CN3 NMR program.

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## CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abstract</td>
</tr>
<tr>
<td>Acknowledgements</td>
</tr>
</tbody>
</table>

### INTRODUCTION

<table>
<thead>
<tr>
<th>Section</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1 Nomenclature</td>
</tr>
<tr>
<td>0.2 Synthesis</td>
</tr>
<tr>
<td>0.3 Structure</td>
</tr>
<tr>
<td>0.4 Chemical properties</td>
</tr>
<tr>
<td>0.5 Pharmaceutical properties</td>
</tr>
<tr>
<td>0.6 Metal complexes</td>
</tr>
</tbody>
</table>

### CHAPTER 1 1,5-Benzodiazepines

<table>
<thead>
<tr>
<th>Section</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1 Introduction</td>
</tr>
<tr>
<td>1.2 Tetrahalometallates of the 2,4-dimethyl-1H-1,5-benzodiazepinium cation</td>
</tr>
<tr>
<td>1.3 The reaction of copper(II) chloride with three other 1,5-benzodiazepines</td>
</tr>
<tr>
<td>1.4 Metal sulphate salts of the 2,4-dimethyl-1H-1,5-benzodiazepinium cation</td>
</tr>
<tr>
<td>1.5 The reaction of metal salts with the 2,4-dimethyl-1H-1,5-benzodiazepine base</td>
</tr>
<tr>
<td>1.6 The reaction of copper(II) bromide and chloride with 1,5-benzodiazepines</td>
</tr>
</tbody>
</table>

### CHAPTER 2 2,3-Dihydro-1,5-benzodiazepines and thiazepines

<table>
<thead>
<tr>
<th>Section</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.1 Introduction</td>
</tr>
<tr>
<td>2.2 Vibrational, electronic, NMR and mass spectra</td>
</tr>
<tr>
<td>2.3 Experimental</td>
</tr>
</tbody>
</table>
### CHAPTER 3  2,3,4,5-Tetrahydro-1,5-benzodiazepines and thiazepines

<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.1</td>
<td>Introduction</td>
<td>75</td>
</tr>
<tr>
<td>3.2</td>
<td>Preparation</td>
<td>76</td>
</tr>
<tr>
<td>3.3</td>
<td>Reaction with aldehydes</td>
<td>79</td>
</tr>
<tr>
<td>3.4</td>
<td>3-Amino-2,3,4,5-tetrahydro-1H-1,5-benzodiazepines</td>
<td>80</td>
</tr>
<tr>
<td>3.5</td>
<td>Vibrational spectra</td>
<td>82</td>
</tr>
<tr>
<td>3.6</td>
<td>Mass spectra</td>
<td>84</td>
</tr>
<tr>
<td>3.7</td>
<td>Nuclear magnetic resonance spectra</td>
<td>89</td>
</tr>
<tr>
<td>3.8</td>
<td>Optical activity</td>
<td>123</td>
</tr>
<tr>
<td>3.9</td>
<td>Electronic spectra</td>
<td>123</td>
</tr>
<tr>
<td>3.10</td>
<td>Metal complexes of some saturated heterocyclic molecules</td>
<td>127</td>
</tr>
<tr>
<td>3.11</td>
<td>Transition metal complexes of the 2,3,4,5-tetrahydro-1H-1,5-benzodiazepines</td>
<td>132</td>
</tr>
<tr>
<td>3.12</td>
<td>Copper(II) chloride complexes of the 2,3,4,5-tetrahydro-1,5-benzothiazepines</td>
<td>154</td>
</tr>
<tr>
<td>3.13</td>
<td>Conclusions</td>
<td>155</td>
</tr>
<tr>
<td>3.14</td>
<td>Experimental</td>
<td>156</td>
</tr>
</tbody>
</table>

**REFERENCES** 161
INTRODUCTION

1,5-Benzodiazepines and 1,5-benzothiazepines
The work described in this thesis arose from an initial investigation into the template formation of macrocyclic complexes by the reaction of coordinated amines with $\beta$-diketones, and coordinated ketones with diamines. A study of the literature has shown that under certain conditions both 1,3-diketones and $\alpha,\beta$-unsaturated ketones readily condense with diamines to form the seven-membered heterocyclic diazepines. It was subsequently decided to investigate the metal complexes of these diazepines themselves. Successive chapters deal with unsaturated benzodiazepines; dihydrobenzodiazepines and thiazepines; and tetrahydrobenzodiazepines and thiazepines.

Apart from the following brief introduction to seven-membered heterocyclic rings, reference to the literature will be made where appropriate in each chapter.

0.1 NOMENCLATURE

Benzodiazepines are bicyclic heterocyclic compounds having a benzene ring attached to a seven-membered ring containing two nitrogen atoms. The seven-membered ring of the analogous thiazepines contains one nitrogen atom and one sulphur atom. 1,5-Benzodiazepine and 1,5-benzothiazepine (fig.1) are the parent compounds of extensive series, with various substituted and reduced derivatives.

---

Figure 1

1.1 $3H$-1,5-Benzodiazepine

1.2 1,5-Benzothiazepine
The positions of the double bonds in benzodiazepines are described by denoting the position of the odd hydrogen atom (fig.1.1). Since this type of isomerism is impossible in benzothiazepines the prefix is unnecessary. The reduced derivatives are described by the prefixes dihydro- and tetrahydro- and the odd hydrogen atom is given the lowest possible number (fig.2). Exceptions to this latter rule are those compounds having a substituent described by a suffix. In this case the odd hydrogen atom is given the same number as the suffix (fig.2.3).

Figure 2

2.1 2,3-dihydro-1,5-benzothiazepine

2.2 2,3,4,5-tetrahydro-1H-1,5-benzodiazepine

2.3 4-methyl-1,3,4,5-tetrahydro-2H-1,5-benzodiazepin-2-one

Substituted tetrahydro-derivatives may exist as various isomers in various conformations. In this work substituents on the seven-membered ring are denoted where necessary by a- (axial) and e- (equatorial), in order to avoid the possible ambiguity of the cis-trans nomenclature (fig.3).

Figure 3

2e,4e-dimethyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine
0.2 SYNTHESIS

Comprehensive reviews have dealt recently with both the preparation and properties of benzodiazepines and benzothiazepines [1-4]. References relevant to the preparation of the 1,5-heterocycles, with more recent papers, are summarized below. Particular preparative methods employed in this work are described in greater detail later.

The great majority of synthetic methods involve the condensation of o-phenylenediamine or o-aminothiophenol with 1,3-difunctional molecules. Thus, for example, 1,3-dialdehydes [5-9], 1,3-diketones [10-16], 2-hydroxymethylene- and 3-halovinylcarbonyl compounds [17-21] readily condense with o-phenylenediamine to yield the unsaturated 1,5-benzodiazepines. Dihydrobenzodiazepines have been prepared similarly using 3-halo, 3-hydroxy, 3-amino or α,β-unsaturated carbonyl compounds [22-26]. α,β-unsaturated acids [27-30], 1,3-dicarboxylic acids [31] and their esters [32], 3-keto acids and their esters [33-35] have been used to prepare the intermediate diazepinones which are conveniently reduced to tetrahydrodiazepines [36]. Alternatively the latter have been prepared by the reaction with 1,3-dihalo compounds [37-41].

The reactions of o-aminothiophenol with α,β-unsaturated acids [42-45], esters [46], 3-haloacids [47], 3-keto acids and esters [48,49], α,β-unsaturated carbonyl compounds [50-53], 3-aminoketones [54] and 1,3-dibromo compounds [55,56] are analogous.

Ring enlargement of six-membered cyclic ketones and their oximes by the Schmidt and Beckmann rearrangements respectively provides the other main preparative route to seven-membered 1,5-heterocyclic compounds [57-61].
0.3 STRUCTURE

The structures of the unsaturated and dihydro-heterocycles are now reasonably well established [5,11,13,15,16,62,63]. This has been predominantly due to their investigation by NMR [24,62,64-67]. Details of the NMR spectra of diazepines and thiazepines at the three oxidation levels (-unsaturated, dihydro and tetrahydro) are discussed further in chapter 3. Much of the work described in this chapter concerns the stereochemistry of the less well known tetrahydridiazepines and thiazepines.

0.4 CHEMICAL PROPERTIES

Little has been reported concerning the properties of the tetrahydro-heterocycles, apart from the preparation of simple N-nitroso, N-tosyl [40], N-benzoyle [62], N-sulphonyl [38] and N-carbamoyl [68] derivatives.

Most reactions of the dihydro-derivatives depend upon the C=N group; two examples are reduction [52] and hydrogen cyanide addition [69]. Reaction of the 2,2,4-trimethyltrihydridiazepine (fig.4) with nitrous acid gives a dinitroso-derivative originally formulated as structure (4.2) [23]. This led to the structure (4.1) being assigned to the diazepine. Later however, the more probable structure (4.3) was found to be correct by NMR studies [24,66] implying a prototropic shift during nitrosation [22]. This postulation was recently made unnecessary when the dinitroso-derivative was found to have the 1-nitroso-3-oximino structure (4.4) [69]. The analogous thiazepine forms the 3-oximino compound (4.6).

Figure 4

![Diagram](https://example.com/diagram.png)
Of the three oxidation states, the unsaturated diazepines have received the most attention due to interest in the possible 'aromaticity' of the seven-membered ring. Some properties, particularly electrophilic substitution [70-77], due to the delocalized but non-cyclic sextet of electrons of the analogous 2,3-dihydrodiazepinium cation (fig.5.1) have led to such descriptions as 'quasi aromatic' and 'meneidic' [78,79].
Only to some extent has the benzodiazepinium cation (Fig. 5.2) similar properties [7,80]. The stabilization of the delocalized cation over the benzodiazepine base (Fig. 5.4) is not as great as in the case of its aliphatic analogue (Fig. 5.1 and 5.3). The benzo-derivative is therefore more susceptible to hydrolysis and oxidation; an attempted nitration, for example, caused oxidation [5] and bromination occurred on the benzene ring rather than on the diazepine ring [5]. This difference in behaviour has been attributed to the relative stabilization of the dianil form of the base in the benzodiazepine (Fig. 5.4), due to the interaction with the benzene ring [5].

The benzodiazepine base undergoes several reactions characteristic of a compound containing an active methylene group, for example: C-alkylation [11]. Other reactions of the base include reduction [36,62], nitrosation [11], hydrogen cyanide addition [69] and condensation with aldehydes [11]. The base readily decomposes in atmospheric, aqueous and alkaline conditions to five- or six- membered heterocycles [5,11].

Several attempts have been made to prepare 1,4-diazatropone and 1,4-diazatropylium systems (Fig. 6). Both hydride abstraction [80] and peracidic oxidation [11] of the diazepine have failed, neither can 3-hydroxyiminobenzodiazepine be hydrolysed without ring contraction [11]. A tropone has been prepared recently in small yield by photooxidation of 2,4-diphenyl-3H-1,5-benzodiazepine [81].

Figure 6

![Diagram of tropylium cation and tropone](image-url)
0.5 PHARMACEUTICAL PROPERTIES

Diazepines and thiazepines have been extensively studied for medicinal activity [82-84] since the success of the sedative drug chlordiazepoxide (fig.7), marketed as 'Librium'. The majority of references to diazepines in Chemical Abstracts are to such studies.

Figure 7

![Diazepine Structure](image)

Although 1,4-benzodiazepines have received the most attention, 2,4-dimethyl- and 2,4-diphenyl- 3H-1,5-benzodiazepines (see Chapter 1), for example, have recently been reported as having slight carcinostatic activity [85].

0.6 METAL COMPLEXES

Very little work has been published on the transition metal complexes of either diazepines or thiazepines.

In 1933 Emmert and Gsottschneider [86] reported the accidental preparation of 2,4-dimethyl-1H-1,5-benzodiazepinium hexaaquoiron(II) sulphate † (fig.8.1) by the reaction of acetylacetone and o-phenyl-enediamine in the presence of ferrous sulphate. More recently, detailed studies of the nickel(II) and copper(II) complexes of homopiperazine [87] (fig.8.2) and its N,N'-bis(2-aminoethyl)-derivative [88] have been published. Nickel(II) complexes of 1,4-dithiepane (fig.8.3) have also been reported [89] and are either low-spin square-planar or high-spin six-coordinate complexes,

† although the compound was incorrectly formulated (see section 1.4)
depending upon the anion present. These complexes will be discussed further in Chapter 3.

Since a large proportion of the work described in sections 1.2 and 1.4 was submitted for publication [90], less detailed but parallel work has been reported [91]. Although unfortunate, it is perhaps also encouraging that these authors obtained similar results and arrived at similar conclusions concerning the structures of the compounds described.
CHAPTER 1

1,5-Benzodiazepines
1.1 INTRODUCTION

There has been considerable interest recently in the metal complexes of cyclic amines [87,92-94], particularly when these amines have been positively charged [95-100]. In this chapter the results of an investigation into the reaction of 3H-1,5-benzodiazepines with metal salts are reported.

Vibrational [11,13], electronic [11,15] and NMR [62,64,65,67] spectroscopic data support the structures of the 2,4-dimethyl-3H-1,5-benzodiazepine base and its cations shown in figure 9. The infrared spectrum of the base (fig.12) shows no NH stretching vibrations in the region 3100-3500 cm⁻¹, confirming the 3H- or dianil- structure. The NMR spectrum of the cation indicates that both methyl groups are equivalent and the planar structure involving six delocalized π-electrons in conjunction with the benzene ring is responsible for the characteristic deep-purple colour of all the benzodiazepinium monocations. The mass spectra of the 2,4-dimethyl-benzodiazepine base and cation are discussed later in section 1.6.

Figure 9

9.1 colourless 9.2 deep-purple 9.3 colourless

The base has a pKa of 8.99 and the monocation a pKa of approximately -1 [5]. These can be compared with values of 10.9 and 10.1 for 1,8-diaminoctane, 9.97 and 6.97 for 1,2-diaminoethane and 8.60 and 2.90 for 1,4-diazabicyclo[2.2.2]octane [95]. The differences in the two pKa's reflect the extent of electronic interaction between the two nitrogen atoms, and indicate strong interaction in the benzodiazepinium cation (fig.9.2).
The possible ways in which N-coordination might occur in benzodiazepine complexes are shown in figure 10. Figure 10.1 represents the base as a bridging unit as occurs in some complexes of pyrazine and its derivatives [101,102] and in complexes of 1,4-diazabicyclo[2.2.2]octane [94]. Figure 10.2 depicts coordination following tautomerisation to the less stable 1H-tautomer. Structures 10.3 and 10.4 clearly indicate that coordination from the monoprotonated species is stereochemically possible only if the π-electrons of structure 9.2 are localized. Back-donation is impossible in 10.3 and since the cation has a very low basicity this form of coordination is considered unlikely. Conversely coordination by 10.4 is more probable.

Estimation of the energies required to convert the delocalized planar cation (9.2) into the non-planar structure (10.3) (~53kJmol\(^{-1}\)) and the non-planar structure (10.4) (~21kJmol\(^{-1}\)) may be made from figure 11. These values again suggest that coordination by (10.4) would be more probable than by (10.3), although the coordination of the cation in either form is considered unlikely. The resonance energy of the analogous 2,3-dihydro-1,4-diazepinium cation (fig.5.1) has recently been estimated [79] to be ~92kJmol\(^{-1}\), close to the value estimated previously for the benzo- derivative [15].
Figure 11 Estimated heats of reaction for interconversion between hypothetical diazepine structures.*
(constructed from data given in reference [15])

\[ \Delta H = -34 + T \Delta S^\dagger \text{kJmol}^{-1} \]
\[ \Delta H = 32 \text{kJmol}^{-1} \]
\[ \Delta H = -13 + T \Delta S^\dagger \text{kJmol}^{-1} \]
\[ \Delta H = 36 \text{kJmol}^{-1} \]

†the entropy terms of both protonations are assumed equal.
*methyl groups are omitted from the figures.

The benzodiazepines are comparatively unstable systems [10]. Both the salts and free bases hydrolyse readily in warm aqueous solution to give benzimidazoles [5,11]. The presence of mineral acid inhibits this ring contraction and alcoholic solutions are more stable than aqueous solutions.

For this reason alcoholic solutions of the benzodiazepinium salts at room temperature were used to prepare the metal derivatives described in the following section.
1.2 TETRAHALOMETALLATES OF THE 2,4-DIMETHYL-1H-1,5-BENZODIAZEPINUM CATION

1.2.1 Results and Discussion

The halides listed in table 1 are non-hygroscopic, stable in air and insoluble in most common organic solvents. With the exception of the copper(I) bromide salt they do dissolve in water, ethanol and to a limited extent in dimethylsulphoxide to give the characteristic colour of the diazepinium cation. Examination of the electronic absorption spectra of these solutions indicates the probable decomposition of the metal complexes and the following investigation is therefore limited to the solid state.

The stoichiometry of the compounds indicates the presence of the diazepine as the monoprotonated cation rather than as the base.

The infrared spectra of the metal salts are very similar to one another and to those of the corresponding diazepinium halides. Representative spectra are illustrated in figures 14,15. Apart from the 250-400 cm\(^{-1}\) region, the spectra of analogous tetrahalometallates are superimposable. The diazepinium bromide has three bands in the region 2800-3400 cm\(^{-1}\) which may be assigned to N-H vibrations: a broad band centred at 2960 cm\(^{-1}\) and two sharp bands at 3200 and 3265 cm\(^{-1}\). In the spectrum of the perchlorate salt the broad absorption at \(\sim 2960\) cm\(^{-1}\) is replaced by a weaker band at 3130 cm\(^{-1}\) and the two sharper bands are shifted to 3235 and 3295 cm\(^{-1}\). This indicates weak hydrogen bonding in the diazepinium halides. Deuteration of the diazepinium halides eliminates all three bands. In the spectrum of the deuterated bromide, for example, a strong N-D stretching band appears at 2285 cm\(^{-1}\) \((\nu_{\text{H}}/\nu_{\text{D}} \approx 1.30)\).

The vibrational spectra of the metal salts closely resemble those of the diazepinium halides; a significant difference is the movement of the broad N-H stretching band to higher frequencies. In this respect the spectra of the metal salts show a strong resemblance to the spectra of the diazepinium perchlorate and tetrafluoroborate, indicating the absence of N-H...X (or N-H...O).
<table>
<thead>
<tr>
<th>Complex</th>
<th>Colour</th>
<th>m.pt(°C)</th>
<th>µ(B.M.)</th>
<th>C</th>
<th>H</th>
<th>N</th>
<th>Halogen</th>
<th>C</th>
<th>H</th>
<th>N</th>
<th>Halogen</th>
</tr>
</thead>
<tbody>
<tr>
<td>$D_2\text{MnCl}_4$</td>
<td>violet</td>
<td>240</td>
<td>5.89</td>
<td>48.78</td>
<td>4.77</td>
<td>10.16</td>
<td>-</td>
<td>48.64</td>
<td>4.82</td>
<td>10.31</td>
<td>-</td>
</tr>
<tr>
<td>$D_2\text{CoCl}_4$</td>
<td>blue</td>
<td>245</td>
<td>4.59   *</td>
<td>48.42</td>
<td>4.93</td>
<td>10.37</td>
<td>25.78</td>
<td>48.29</td>
<td>4.79</td>
<td>10.24</td>
<td>25.91</td>
</tr>
<tr>
<td>$D_2\text{CuCl}_4$</td>
<td>brown</td>
<td>200</td>
<td>1.89</td>
<td>47.88</td>
<td>4.79</td>
<td>10.17</td>
<td>25.74</td>
<td>47.88</td>
<td>4.75</td>
<td>10.15</td>
<td>25.70</td>
</tr>
<tr>
<td>$D_2\text{ZnCl}_4$</td>
<td>violet</td>
<td>235</td>
<td>diamagnetic</td>
<td>47.76</td>
<td>4.88</td>
<td>10.04</td>
<td>-</td>
<td>47.73</td>
<td>4.73</td>
<td>10.12</td>
<td>-</td>
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<tr>
<td>$D_2\text{MnBr}_4$</td>
<td>violet</td>
<td>254</td>
<td>5.94</td>
<td>36.81</td>
<td>3.71</td>
<td>7.83</td>
<td>-</td>
<td>36.65</td>
<td>3.63</td>
<td>7.77</td>
<td>-</td>
</tr>
<tr>
<td>$D_2\text{CoBr}_4$</td>
<td>blue</td>
<td>261</td>
<td>4.75   *</td>
<td>36.65</td>
<td>3.45</td>
<td>7.76</td>
<td>43.95</td>
<td>36.45</td>
<td>3.61</td>
<td>7.73</td>
<td>44.03</td>
</tr>
<tr>
<td>$D\text{CuBr}_2$</td>
<td>green-brown</td>
<td>223</td>
<td>$\chi_A \approx 25 \times 10^{-6}$</td>
<td>33.27</td>
<td>3.30</td>
<td>6.94</td>
<td>40.27</td>
<td>33.31</td>
<td>3.30</td>
<td>7.06</td>
<td>40.30</td>
</tr>
<tr>
<td>$D_2\text{ZnBr}_4$</td>
<td>violet</td>
<td>252</td>
<td>diamagnetic</td>
<td>36.12</td>
<td>3.62</td>
<td>7.60</td>
<td>43.58</td>
<td>36.12</td>
<td>3.58</td>
<td>7.66</td>
<td>43.70</td>
</tr>
</tbody>
</table>

* corrected for TIP

† molar susceptibility corrected for diazepine and bromine diamagnetism (cgs units)

D = 2,4-dimethyl-1,5-benzodiazepinium cation
hydrogen bonding in the metal salts. Nitrogen coordination as suggested by the structure (10.3) does not appear to occur since the N-H stretching frequency would be expected to be lowered in such a case [103] [see also section 3.11]. No new halogen-independent band is observed in the region \(450-250\text{cm}^{-1}\) which could be attributed to \(\text{N-N}\) stretching, although in a structure such as (10.4) this may well occur below \(250\text{cm}^{-1}\) [104,105]. The \(\text{N-N}\) absorption frequencies of metal halide complexes of pyridine derivatives, for example, generally lie within the region \(210-270\text{cm}^{-1}\) [106].

Since coordination of the diazepinium cation necessitates the interruption of the delocalized system (fig.10) and a buckling of the planar ring, a considerable change would be expected in the vibrational spectrum. Since such a change is not observed (fig.14,15), then coordination of the cation is almost certainly ruled out.

In a simultaneous investigation of these compounds [91], bands in the region \(1350-1650\text{cm}^{-1}\), assigned to \(\nu(\text{C=O})\), \(\nu(\text{C=Cl})\) or a mixture of these vibrations [7], were reported in some detail. A red shift of \(10-20\text{cm}^{-1}\) in the \(1639\text{cm}^{-1}\) band was noted upon formation of the tetrachlorometallate and was ascribed to interference between the cation and tetrachlorometallate anion. Such a shift is not observed in the case of the bromides (fig.13,14). The apparent shift in the chlorides described above may be caused by the removal of water, and the \(\delta(\text{OH})\) band at \(\sim1630\text{cm}^{-1}\), upon metallate formation. Interference of the diazepinium cation by the tetrahalometallate anion appears to be no greater than by, for example, the halide or perchlorate anion in the simple diazepinium salts. Figures 13-15 illustrate the differences that are observed between the spectra of the bromides and chlorides.

The spectrum of the anomalous cuprous bromide salt (fig.30) differs in some respects from the other three bromide salts and is discussed in a subsequent section (1.6).
Halogen-dependent bands in the spectra of the metal chloride salts are shown in table 2 and figure 16. The bands are broad and show signs of splitting; the Mn-Cl band for example has a half-width of 40 cm\(^{-1}\). This splitting is more pronounced in the cobalt salt although the total band width is no greater.

For a tetrahedrally symmetric \([MCl_4]^{2-}\) ion only one infrared-active band \(\nu_3\) is expected in the region examined. This band is split into two bands when the symmetry is reduced to \(D_{2d}\) and additional splitting may arise if the site-symmetry is still further reduced. The splitting of the \(\nu_3\) band in spectrum of the \([CoCl_4]^{2-}\) clearly indicates a site symmetry lower than \(T_d\). The frequencies of the \([MnCl_4]^{2-}\), \([ZnCl_4]^{2-}\) and the mean position of the \([CoCl_4]^{2-}\) bands correspond well with published data on tetrahalometallate anions [107-110].

Attempts to obtain Laser-Raman spectra [111] were unsuccessful owing to the deep colour of the complexes.

The copper chloride salt exhibits two bands at 305 and 260 cm\(^{-1}\), although the band at 305 cm\(^{-1}\) was not reported previously [91]. This band is more intense than the diazepine band occurring at about the same frequency and is not present in the spectra of the other salts.

Table 2 Vibrations assigned to metal-chlorine stretching in the region 250-500 cm\(^{-1}\)

<table>
<thead>
<tr>
<th></th>
<th>Frequency (cm(^{-1}))</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mn - Cl</td>
<td>282 cm(^{-1})</td>
<td>(shoulders at 269, 295 cm(^{-1}))</td>
</tr>
<tr>
<td>Co - Cl</td>
<td>284, 307 cm(^{-1})</td>
<td>(weak shoulder at 265 cm(^{-1}))</td>
</tr>
<tr>
<td>Cu - Cl</td>
<td>260, 305 cm(^{-1})</td>
<td></td>
</tr>
<tr>
<td>Zn - Cl</td>
<td>269 cm(^{-1})</td>
<td>(shoulders at 285, 293 cm(^{-1}))</td>
</tr>
</tbody>
</table>
Copper-halogen stretching frequencies have been extensively investigated [112-114]. It is, however, difficult to assign a structure solely on the basis of the bands in the region 250-500 cm\(^{-1}\). The two bands in the spectrum of the diazepinium copper salt could, for example, be assigned to the terminal and bridging vibrations of a polymeric \(-\text{Cu-Cl}-\) chain, or perhaps to the \(\nu(\text{Cu-Cl})\) and \(\delta(\text{O-Cu-O})\) frequencies of the tetragonal \([\text{CuCl}_4(\text{H}_2\text{O})_2]^{2-}\) ion [115]. However, taken in conjunction with the stoichiometry and electronic spectrum, the two bands are assigned to the split \(\nu_z\) vibration of the \(D_{2d}\) \([\text{CuCl}_4]^{2-}\) ion [116] although the splitting of \(45\text{ cm}^{-1}\) is larger than is normally observed (20-40 cm\(^{-1}\) [114]).

The spectra of the \(C_3v\) \(M^+(L)LCl_3\) complexes, where \(L^+\) = the coordinated N-methyl-1,4-diazabicyclo[2.2.2]octonium cation, include a strong band between \(300-310\text{ cm}^{-1}\) and a medium band between \(260-280\text{ cm}^{-1}\) due to the IR-active symmetric and antisymmetric \(M-\text{Cl}\) stretching vibrations [95]. Again however, the additional evidence is not compatible with the assignment of a similar coordinated diazepinium structure to the complexes described here.

The solution electronic spectrum of the benzodiazepinium chloride is illustrated in figure 17. The broad band at approximately 19.6 eV is responsible for the intense purple colour of the salts.

Figure 17 Electronic spectrum of 2,4-dimethyl-1H-1,5-benzodiazepinium chloride, Ethanol solution.
The diffuse reflectance spectra of the bromide, chloride and
tetrahalomanganates are illustrated in figure 18. The diazepine base is included for comparison. The spectra clearly show the presence of the diazepine as the cation. Comparison of these spectra, and that of the diazepinium perchlorate, indicates that the tetrahalometallate anions have little perturbing effect on the electronic transitions of the diazepine although in some cases the spectra do exhibit strong charge transfer interaction between the anion and cation (e.g., fig. 21). No bands corresponding to the spin-forbidden transitions of the $\text{MnCl}_4^-$ and $\text{MnBr}_4^-$ ions could be detected due to the strong diazepine absorption in the region 21-30kK [117,118].

The copper chloride salt is characterized by strong bands at 5.1 and 8.3kK absent in the bromide salt (fig. 21). The absorption at 24kK is more intense than in the spectrum of the benzodiazepinium chloride indicating the presence of an additional band. There is also broad absorption in the 32kK region. The lower frequency bands at 5.1 and 8.3kK are assigned
to the $^2B_2\rightarrow^2E$ and $^2B_2\rightarrow^2B_1,^2A_1$ transitions of the $D_{2d}$ $[CuCl_4]^-$ anion (fig.19) [119,120]. The relatively intense higher energy bands are assigned to charge transfer transitions.

Figure 19 Energy levels for Cu(II) $a^9$ ion in Td and $D_{2d}$ environments

![Energy levels diagram]

The spectrum of the copper chloride complex clearly confirms the structure as the tetrachlorocuprate anion with non-coordination of the diazepinium cation. If one or more cations were coordinated, the d-d bands would be expected at higher energies. This movement of the bands may be caused by substitution of Cl$^-$ with a ligand higher in the spectrochemical series [95] or by a flattening or increase in distortion of the $D_{2d}$ ion [120,121]. In figure 20 the spectrum of the diazepinium salt is compared with complexes of known stereochemistry and this illustrates the effect of a decrease in the symmetry from $D_{2d}$.

Figure 20 Near IR spectra of 4-coordinate copper complexes

![Near IR spectra diagram]

A - $D_2$ CuCl$_4$  
B - Cs$_2$ CuCl$_4$  
C - CH$_3$-N\(\equiv\)N-CuCl$_3$  
D - [Pt(NH$_3$)$_4$][CuCl$_4$]  
E - (1,2-dimethylimidazole)$_2$ CuCl$_2$  

symmetry: $D_{2d}$, $D_{2d}$, $C_3v$, $D_{4h}$, $C_2v$  
reference: [this work], [119,122], [95], [122], [123]
The electronic spectra of the copper and cobalt salts are illustrated in figures 21 and 22 on the preceding page. Also included are spectra to be discussed in a subsequent section (1.5).

The spectra of the cobalt salts exhibit d-d bands typical of tetrahalocobaltate anions [124,125]. The bands at ~5 and ~15kK can be assigned to the $^4A_2 \rightarrow ^4T_1(G)$ and $^4A_2 \rightarrow ^4T_1(P)$ transitions of a $d^7$ ion in a tetrahedral environment (fig.23). The transition $^4A_2 \rightarrow ^4T_2$ should occur between 3000-3500 cm$^{-1}$ [126]. It is obscured however by vibrational transitions in the same region and is not observed (fig.15).

**Figure 23** Quartet states of a $d^7$ ion in a tetrahedral environment

![Diagram of quartet states](image)

Parameters calculated from the spectra [125,127] are tabulated below. Experimentally the bands are broad with considerable fine structure; the $v_3$ bands are partially obscured by diazepine absorption. In addition, spin-orbit coupling and any distortion from Td symmetry - as suggested

**Table 3** Diazepinium tetrahalocobaltates

<table>
<thead>
<tr>
<th></th>
<th>$\nu_2$cm$^{-1}$</th>
<th>$\nu_3$cm$^{-1}$</th>
<th>Dq cm$^{-1}$</th>
<th>B$'$ cm$^{-1}$</th>
<th>$\beta^+$</th>
<th>$10^6\chi_{TP}$ (cgs)$^*$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$D_2$ CoCl$_4$</td>
<td>5.41</td>
<td>15.0</td>
<td>310</td>
<td>740</td>
<td>.77</td>
<td>617</td>
</tr>
<tr>
<td>$D_2$ CoBr$_4$</td>
<td>4.94</td>
<td>14.43</td>
<td>282</td>
<td>727</td>
<td>.75</td>
<td>678</td>
</tr>
</tbody>
</table>

$^+$ $\beta$ = nephelauxetic parameter $B'/B$ where $B$ = interelectronic repulsion parameter.

* calculated from $\frac{8k^2\beta^2}{10Dq}$ where $\beta$ = Bohr magneton, $k \approx .96$. 

---

* This document uses traditional chemical nomenclature, including diazepine and diazepinium, which are not widely used today. The current standard is to use simpler names like cobalt(II) or cobalt(III) for these compounds.
by the vibrational data — has been neglected in the calculation. The results shown in table 3 must therefore be regarded as only approximate. The 10Dq values lie within the range expected although the B' values are both slightly larger than in other tetrahalocobaltates [124].

The arguments concerning possible diazepine coordination discussed in the case of the tetrachlorocuprate ion apply also to the tetrahalocobaltates. Again, the formation of complexes of either C2v or C3v symmetry will cause a shift and splitting in the d-d bands [128] relative to the tetrahalocobaltates.

The electronic spectra of ethanol solutions of all the tetrahalometallates are identical to the spectra of the corresponding halide salt. No d-d bands could be detected, due both to the poor solubility and probable decomposition in solution.

The room-temperature magnetic moments of the metal salts are listed in table 1. They agree reasonably well with those of other tetrahalometallates [122,124,125,129-131]. The temperature variation in the susceptibilities of the tetrachlorocuprate and cobaltate are illustrated in figure 24; numerical details are given in tables 4 and 5. The copper chloride salt follows Curie-Weiss behaviour down to 89°K with $\theta = +6^\circ$. The uncorrected susceptibilities of the cobalt salt also exhibit Curie-Weiss behaviour with $\theta = +5^\circ$, although when corrected for temperature independent paramagnetism (TIP), $\theta \approx 0^\circ$.

Figure 24. Temperature variation in the magnetic susceptibilities of the diazepinium tetrachlorocuprate and cobaltate.
The magnetic moments of the tetrahalocobaltates exceed the
spin-only value of 3.88 B.M. due to mixing of the ground state
with the first (and second) excited state under spin-orbit
coupling. As expected [130], the CoBr$_4$ has the higher susceptibility
of the two due to a greater orbital contribution to the moment.
Since the energy difference between the excited and ground states
is less in the CoBr$_4$, the extent of mixing is greater (10Dq: Cl,
3.1; Br, 2.8kK).

An approximate value of the electron delocalization parameter
k can be obtained from the expression for the observed susceptibility
in terms of the spin-only value, spin-orbit coupling constant and
TIP [127].
\[ \chi_A = \chi_{so} \left( 1 - \frac{8k^2\lambda_o}{|10Dq|} \right) + \frac{8k^2\beta^2}{|10Dq|} \]

\( \lambda_o = \) free ion spin-orbit coupling constant = \(-172\text{ cm}^{-1}\)

\( \chi_{so} = \) spin-only susceptibility = \( \frac{\mu^2}{3kT}(n(n+2)) \) \( n = \) no. unpr. spins

= 6250 \( \text{(cgs)} \) at 300\(^\circ\)K

\( 10Dq = 3100 \text{ cm}^{-1} \)

\( \chi_A = 9407 \) at 300\(^\circ\)K by extrapolation

\( k = .96, \) indicating a small degree of delocalization (4%).

1.2.2 Experimental

The 2,4-dimethyl-1H-1,5-benzodiazepinium chloride, bromide, perchlorate and tetrafluoroborate were prepared by methods analogous to those already published \([5,10,11]\) (fig. 25). The free diazepine base was prepared by treating an aqueous solution of the chloride with COLD concentrated sodium hydroxide. The insoluble colourless base was recrystallized from ethanol. The diazepine and its salts were characterized by m.pt., vibrational, electronic and NMR spectroscopy and by mass spectrometry. Analytical data are given in table 6.

Figure 25

The tetrahalometallates included in table 1 were prepared by mixing stoichiometric quantities of the appropriate metal halide and the diazepinium halide in either ethanol or aqueous ethanol at room temperature. After approximately one hour the precipitates were filtered off, washed with small amounts of ethanol, then ether, and dried in vacuo.
Nickel(II) and iron(II) complexes could not be isolated by this method and attempts in anhydrous media were also unsuccessful. Generally, concentration of the reaction mixtures led to precipitation of the diazepinium halides. Similarly, in attempts to prepare metal perchlorate derivatives, concentration of the solutions led to crystallization of the diazepinium perchlorate. Anhydrous solutions were prepared by reaction with 2,2-dimethoxypropane [132] and were filtered before use.

Table 6  2,4-dimethyl-3H-1,5-benzodiazepine and its salts

<table>
<thead>
<tr>
<th></th>
<th>m.pt.</th>
<th>Found</th>
<th>Elemental Analysis</th>
<th>Calculated</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>C</td>
<td>H</td>
<td>N</td>
</tr>
<tr>
<td>Diazepine base*</td>
<td>132°C</td>
<td>76.76</td>
<td>7.11</td>
<td>16.30</td>
</tr>
<tr>
<td>D Cl .2H2O</td>
<td>202°C</td>
<td>53.81</td>
<td>6.76</td>
<td>11.59</td>
</tr>
<tr>
<td>D Br .2H2O</td>
<td>216°C</td>
<td>45.62</td>
<td>6.05</td>
<td>9.65</td>
</tr>
</tbody>
</table>

*picrate 236°C

1.2.3 Conclusions

The data presented in this section are consistent with the diazepine being present in the compounds as the planar delocalized cation, in which neither nitrogen atom is available for coordination. The comparative stability of the delocalized structure, with strong electronic interaction between the two nitrogen atoms, prevents the formation of positively-charged ligand complexes. The electronic spectra and magnetic data indicate a tetrahedral environment, although probably distorted, for the metal ions and the compounds are formulated as diazepinium tetrahalometallates. This formulation in part explains why nickel(II) and iron(II) complexes were not isolated - it is known [129] that tetrahedral halide complexes of these ions are the most unstable, particularly in the presence of water. The inability to obtain metal perchlorate complexes further confirms the assignment as a non-coordinated diazepinium salt.
1.3.1 Results and Discussion

In this section the reaction of copper(II) chloride with the three diazepines illustrated in figure 26 is compared to the reaction with the 2,4-dimethyl- derivative. Although the trimethyl- and tetramethyl- diazepines give apparent analogues of the previously described diazepinium tetrachlorocuprate, the 2-methyl-4-phenyl diazepine gives a compound of stoichiometry $\text{H}_2\text{CuCl}_3$. Analytical data are given in table 7.

As previously, the stoichiometries confirm that the diazepinium cations and not the bases are present in the compounds. The relationship between the infrared spectra of the diazepinium chloride and the diazepinium metallate is, in all three cases, as close as illustrated in the preceding section. Again, since the involvement of the diazepinium cation in coordination necessitates a complete change in the ring structure, and hence in the vibrational spectrum, such coordination is not thought to take place in any of the compounds described here - despite the stoichiometry of the $\text{H}_2\text{CuCl}_3$ salt.

The infrared and visible spectra however show apparent disparity. The low frequency vibrational spectra of the diazepinium salts are illustrated in figure 27. The bands assigned to Cu-Cl stretching clearly differ and indicate an inconsistency in the structures of the halometallate anions. The assignment of structures by examination of the metal-halogen vibrations has been mentioned in the preceding section. The similarity in the spectra of $\text{D}_2\text{CuCl}_4$ and $\text{G}_2\text{CuCl}_4$ suggests the assignment of a similar $D_{2d}$ structure for both chlorocuprate ions. The splitting of the bands ($\sim 45-50\text{cm}^{-1}$) is again larger than usual ($\sim 20-40\text{cm}^{-1}$). The spectrum of $\text{F}_2\text{CuCl}_4$ exhibits a single intense band at $281\text{cm}^{-1}$, a frequency midway between the two bands in the spectra of the other tetrachlorocuprates.
Figure 26

Table 7  Magnetic and Analytical data of the Benzodiazepinium cuprates

<table>
<thead>
<tr>
<th>Complex</th>
<th>Colour</th>
<th>m.pt(°C)</th>
<th>μ(B.M.)</th>
<th>Found</th>
<th>Elemental Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>C</td>
<td>H</td>
</tr>
<tr>
<td>$\text{F}_2\text{CuCl}_4$</td>
<td>purple-brown</td>
<td>162</td>
<td>2.04</td>
<td>49.00</td>
<td>5.10</td>
</tr>
<tr>
<td>$\text{C}_2\text{CuCl}_4$</td>
<td>dark violet</td>
<td>222</td>
<td>1.99</td>
<td>49.28</td>
<td>5.22</td>
</tr>
<tr>
<td>$\text{HCuCl}_3$</td>
<td>green</td>
<td>173</td>
<td>1.98</td>
<td>47.42</td>
<td>3.82</td>
</tr>
</tbody>
</table>
Figure 27  Vibrational spectra of the chlorocuprate salts in the region 250-400 cm$^{-1}$.

The single band suggests a more symmetrical structure - towards either square-planar or tetrahedral symmetry; the latter seems more likely. $\left[3\text{MeAs}\right]_3\left[\text{CuCl}_4\right]_2$, in which the anion is assumed to be tetrahedral, exhibits only one band in this region at 283 cm$^{-1}$ [107]. The anionic part of the $\text{HCuCl}_3$ complex must involve a polymeric structure - $[\text{CuCl}_3]^{2-}$ is normally described as a planar chain with chloride bridges, each Cu$^{2+}$ ion surrounded by 4Cl$^-$ ions in the plane and two further Cl$^-$ ions above and below the plane. CsCuCl$_3$ for example has such a structure [133] and exhibits both terminal (293 and 287 cm$^{-1}$) and bridging (263 cm$^{-1}$) bands [112]. Individual $[\text{Cu}_2\text{Cl}_6]^{2-}$ ions also exhibit terminal and bridging Cu-Cl stretching vibrations at ~305 and ~280 cm$^{-1}$ respectively - in this case again, long bonds above and below the planar dimer complete a 6-coordinate tetragonal species.

It seems probable that the anion of the HCuCl$_3$ salt has a dimeric bridged structure $[\text{Cu}_2\text{Cl}_6]^{2-}$; it is possible that in this case the ion consists of two bridged distorted tetrahedra.
with $\nu(Cu-Cl)_{\text{terminal}} = 309 \text{cm}^{-1}$ and $\nu(Cu-Cl-Cu) = 258 \text{cm}^{-1}$.

The magnetic susceptibility of the HCuCl$_3$ salt was measured down to 89°K to test for antiferromagnetism which might be expected in a polynuclear copper(II) species [134-136]. The results are tabulated below. Although the susceptibilities are field-independent (see table 8) and obey the Curie-Weiss law with $\Theta = -8^\circ$, the magnetic moment exhibits an increase with decrease in temperature. Both the analytical data and field-independence suggest the absence of ferromagnetic impurities.

Table 8 Magnetic susceptibilities of HCuCl$_3$, $10^6 \chi_L = 228$

<table>
<thead>
<tr>
<th>T(°K)</th>
<th>$\chi_A$ (cgs)</th>
<th>$\mu$(B.M.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>295.3</td>
<td>1661</td>
<td>1658</td>
</tr>
<tr>
<td>262.7</td>
<td>1870</td>
<td>1862</td>
</tr>
<tr>
<td>230.3</td>
<td>2137</td>
<td>2125</td>
</tr>
<tr>
<td>198.2</td>
<td>2496</td>
<td>2490</td>
</tr>
<tr>
<td>166.1</td>
<td>3009</td>
<td>3008</td>
</tr>
<tr>
<td>135.2</td>
<td>3783</td>
<td>3766</td>
</tr>
<tr>
<td>103.1</td>
<td>4975</td>
<td>4992</td>
</tr>
<tr>
<td>89.4</td>
<td>5800</td>
<td>5788</td>
</tr>
</tbody>
</table>

*a current of 15amp. corresponds to a field strength ~6700 gauss, and a current of 10amp. to ~5750 gauss.

On the basis of similar behaviour, the complex [(dipy)Cu(OH)$_2$Cu(dipy)]$_2$S$_2$O$_4\cdot 5$H$_2$O has been assigned a triplet ground state, with the singlet state considerably higher in energy [$\mu_{298.5^\circ K} = 1.94$, $\mu_{84^\circ K} = 2.04$ B.M.; $\Theta = -11^\circ K$] [146]. The complex has a dimeric hydroxo-bridged square-pyramidal structure. Recent susceptibility measurements down to 4.2°K [147] have confirmed the ferromagnetism in this and analogous complexes. Although at temperatures above 84°K Curie-Weiss behaviour is followed, at lower temperatures the susceptibilities are field-dependent and deviate from the Curie-Weiss law ($J$ positive). It seems possible that the magnetic behaviour of HCuCl$_3$ may be explained in terms of ferromagnetic interaction between two copper(II) ions in a dimeric [Cu$_2$Cl$_6$]$_2^-$ anion. If so, it is

**dipy = 2,2'-dipyridyl**
possible that the anion is not a bridged tetragonal dimer; this is confirmed to some extent by the electronic spectrum. Further susceptibility measurements at temperatures down to ~4°C are desirable.

The reflectance electronic spectra of the three salts are compared to the D$_2$CuCl$_4$ spectrum in figure 28. Again, disparity in the spectra is noted. The spectrum of F$_2$CuCl$_4$ exhibits bands at slightly lower energies than does the D$_2$CuCl$_4$ spectrum, indicating a more tetrahedral environment i.e. a decreased distortion to D$_{2d}$. It is surprising however that such an apparently small change is sufficient to cause the observed change in the metal-chlorine stretching vibrations. The two other salts show poorly resolved absorption at higher frequencies suggesting further distortion towards a square-planar structure. The absorption of HCuCl$_3$ is not consistent with the assignment of a planar polymeric CuCl$_2$ chain with long bonds completing
a tetragonal environment \([122]\) and the ion is tentatively assigned a binuclear dimeric distorted tetrahedral \((D_{2d})\) structure. The close similarity between the spectra of the diazepinium chlorides and the spectra of the corresponding chlorocuprates clearly indicates the retention of the delocalized structure.

The mass spectrum of the H\(\text{CuCl}_3\) salt shows no evidence of diazepinium coordination but does however exhibit four groups of peaks above the diazepine parent peak at approximate* intervals of 34 m/e units. Analysis of the chlorine isotopic abundances in these groups reveals that they represent ions containing progressively one to four chlorine atoms (table 9). An extensive substitution in the diazepine by chlorine must occur in the mass spectrometer.

Table 9: Peaks higher than the diazepinium parent peak in the mass spectrum of H\(\text{CuCl}_3\)

<table>
<thead>
<tr>
<th>Peak</th>
<th>Relative abundance</th>
<th>Isotopic abundance</th>
<th>Theoretical</th>
</tr>
</thead>
<tbody>
<tr>
<td>(233,234 \ (M^+))</td>
<td>100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(~M^+ + 34^*)</td>
<td>29</td>
<td>(P) 100</td>
<td>Cl ({100})</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(P+2) 32</td>
<td>{32.6}</td>
</tr>
<tr>
<td>(~M^+ + 68)</td>
<td>16</td>
<td>(P) 100</td>
<td>Cl(_2) ({100})</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(P+2) 64</td>
<td>{65.3}</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(P+4) 11</td>
<td>{10.6}</td>
</tr>
<tr>
<td>(~M^+ + 102)</td>
<td>13</td>
<td>(P) 100</td>
<td>Cl(_3) ({100})</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(P+2) 97</td>
<td>{99.8}</td>
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<td></td>
<td></td>
<td>(P+4) 33</td>
<td>{31.9}</td>
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<tr>
<td></td>
<td></td>
<td>(P+6) 4</td>
<td>{3.5}</td>
</tr>
<tr>
<td>(~M^+ + 136)</td>
<td>0.9</td>
<td>(P) 100</td>
<td>Cl(_4) ({100})</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(P+2) 128</td>
<td>{131.0}</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(P+4) 76</td>
<td>{63.9}</td>
</tr>
</tbody>
</table>

*based only on Chlorine natural isotopes.

the precise mass number of these peaks were impossible to measure.
1.3.2 Experimental

The 2,4,7-trimethyl- and 2,4,7,8-tetramethyl-1H-1,5-benzodiazepinium chlorides were prepared in a manner analogous to that used for the 2,4-dimethyl- derivative, using the appropriately substituted o-phenylenediamine. The 2-methyl-4-phenyl-1H-1,5-benzodiazepinium chloride was prepared as previously described [11].

The two tetrachlorocuprates were prepared by mixing 1:1 molar quantities of the diazepinium chloride and copper(II) chloride in IMS solution at room temperature. The precipitates, which quickly formed, were filtered off, washed with ethanol and ether and dried in vacuo.

Addition of a 2-methyl-4-phenyl diazepinium solution to a solution of copper(II) chloride (in IMS, 1:1 molar ratio) caused no precipitation. Rotary evaporation of the solvent under vacuum led to a brownish precipitate, which when washed with ethanol and ether yielded a fine green powder. A similar procedure using cobalt(II) chloride led only to precipitation of the diazepinium chloride.

1.3.3 Conclusions

Other substituted 1,5-benzodiazepines also give diazepinium chlorocuprates. The spectroscopic data indicates however that an alteration in the substitution on the diazepinium cation results in a change in the structure of the halometallate anion. This is most apparent in a comparison of the 2,4-dimethyl- and 2-methyl-4-phenyl- diazepinium chlorocuprates: D$_2$CuCl$_4$ and HCuCl$_3$. 
1.4 METAL SULPHATE SALTS OF THE 2,4-DIMETHYL-1H-1,5-BENZO-
DIAZEPINIMIUM CATION

1.4.1 Introduction

In 1933, during an investigation of the reaction of
1,3-diketones and amines in the presence of ferrous sulphate
to give compounds of the type (29.1), Emmert and Gsottschneider
reported [86] that the reaction of acetylacetone and o-phenylene-
diamine was anomalous in producing a new compound, recognized
as a diazepine. The product was formulated as a ferrous complex
of the diazepine base (fig. 29.2) on the basis of analytical
data. In this section a spectroscopic investigation of the
products of this reaction is reported; they are shown to be
salts of the diazepinium cation (fig. 29.3).

1.4.2 Results and Discussion

The compounds listed in table 10 were prepared both by the
above method (except the copper salt) and by the direct reaction
of the diazepinium hydrogen sulphate and metal sulphate. The
compounds are stable in air and are insoluble in most common
solvents except water.

The vibrational spectra of the sulphates are very similar
both to one another and to that of the diazepinium cation; the
differences are due to the presence of water molecules and
sulphate anions. In the vibrational spectrum of the ferrous
salt, shown in figure 31, the strong bands at 1084 and 615 cm\(^{-1}\)
are assigned to the \(\nu_3\) and \(\nu_4\) vibrations of a tetrahedral
sulphate anion [138]. When the sulphate anion is coordinated,
the symmetry of the ion is lowered to \(C_{3v}\) or \(C_{2v}\) and the
\(\nu_3\) and \(\nu_4\) bands are split (see later section 3.11 when the
analogous perchlorate ion is discussed). In the spectra of
the diazepinium salts the bands at \(\sim 615\) and \(\sim 1084\) cm\(^{-1}\)
are not split indicating clearly that the sulphate anions are not
coordinated. The broad band at 3100–3500 cm\(^{-1}\), and others at
1630, 805 and 349 cm\(^{-1}\) can be assigned to water vibrations [139].
Figure 29

29.1

29.2

29.3

Table 10 Magnetic and Analytical data of the Benzodiazepinium metal sulphates

<table>
<thead>
<tr>
<th>Complex</th>
<th>Colour</th>
<th>m.pt. (°C)</th>
<th>μ(B.M.)</th>
<th>Found C</th>
<th>H</th>
<th>N</th>
<th>H₂O</th>
<th>C</th>
<th>H</th>
<th>N</th>
<th>H₂O</th>
</tr>
</thead>
<tbody>
<tr>
<td>D₂<a href="SO%E2%82%84">Mn(H₂O)₆</a>₂</td>
<td>blue</td>
<td>&gt;310*</td>
<td>5.96</td>
<td>37.64</td>
<td>5.40</td>
<td>8.00</td>
<td>15.25</td>
<td>37.66</td>
<td>5.46</td>
<td>7.99</td>
<td>15.41</td>
</tr>
<tr>
<td>D₂<a href="SO%E2%82%84">Fe(H₂O)₆</a>₂</td>
<td>blue</td>
<td>&gt;310*</td>
<td>5.22</td>
<td>38.01</td>
<td>5.61</td>
<td>7.85</td>
<td>-</td>
<td>37.61</td>
<td>5.45</td>
<td>7.98</td>
<td>-</td>
</tr>
<tr>
<td>D₂<a href="SO%E2%82%84">Co(H₂O)₆</a>₂</td>
<td>violet</td>
<td>303</td>
<td>4.91</td>
<td>37.48</td>
<td>5.55</td>
<td>8.27</td>
<td>-</td>
<td>37.45</td>
<td>5.43</td>
<td>7.94</td>
<td>-</td>
</tr>
<tr>
<td>D₂<a href="SO%E2%82%84">Ni(H₂O)₆</a>₂</td>
<td>blue</td>
<td>169</td>
<td>3.24</td>
<td>37.33</td>
<td>5.44</td>
<td>8.11</td>
<td>-</td>
<td>37.46</td>
<td>5.43</td>
<td>7.94</td>
<td>-</td>
</tr>
<tr>
<td>D₂[Cu(H₂O)₆]_3(SO₄)₂·4H₂O</td>
<td>blue</td>
<td>191</td>
<td>1.97</td>
<td>33.59</td>
<td>5.14</td>
<td>6.76</td>
<td>22.37</td>
<td>33.76</td>
<td>5.93</td>
<td>7.16</td>
<td>23.01</td>
</tr>
<tr>
<td>D₂<a href="SO%E2%82%84">Zn(H₂O)₆</a>₂·H₂O</td>
<td>blue</td>
<td>279</td>
<td>diamag.</td>
<td>36.20</td>
<td>5.34</td>
<td>7.42</td>
<td>17.26</td>
<td>36.18</td>
<td>5.52</td>
<td>7.67</td>
<td>17.23</td>
</tr>
</tbody>
</table>

*decompose below this temperature
The 3100-3500 cm\(^{-1}\) band and the 1630 cm\(^{-1}\) band are assigned to antisymmetric and symmetric O-H stretching and H-O-H bending respectively. The two lower frequency bands strongly suggest coordination of water and are assigned to M-OH\(_2\) rocking and M-OH\(_2\) stretching respectively. The latter is metal-dependent and the individual frequencies are shown below in table 11.

<table>
<thead>
<tr>
<th>M (\text{O}-\text{H}_2)</th>
<th>Mn</th>
<th>Fe</th>
<th>Co</th>
<th>Ni</th>
<th>Cu</th>
<th>Zn</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\nu(M-OH_2))</td>
<td>338</td>
<td>349</td>
<td>347</td>
<td>367</td>
<td>332</td>
<td>332</td>
</tr>
</tbody>
</table>

The frequencies of the \(\nu(M-OH_2)\) bands should reflect the stability of the hexa-aquo ions and the values given in table 11 lie more or less in the Irving-Williams order. The fact that the copper compound does not fit might be expected if the 6-coordinate ion is tetragonally distorted.

On heating the metal sulphate salts at 120°C for 24 hours, all the bands attributed above to water vibrations diminish or disappear. The losses in weight are tabulated (table 10).

The Mössbauer spectrum [140] of the ferrous salt is entirely consistent with the formulation of the salt as a hexa-aquo ion; the quadrupole splitting \(\Delta E_q = 3.38\) mmsec\(^{-1}\) and the isomer shift \(\delta = 1.67\) mmsec\(^{-1}\) relative to sodium nitroprusside [141,142].

The room-temperature magnetic moments of the metal sulphates are given in table 10 and lie within the range normally expected for approximately octahedral symmetry about the metal ion.

The diffuse reflectance electronic spectra of the salts are illustrated in figure 32. No d-d bands can be observed in the spectrum of the manganese salt; the spectrum is effectively that of the diazepinium cation. In the spectrum of the copper
salt there is a weak band centred between 9-10kK. A weak band at ~9-10kK can be observed in the spectrum of the iron salt and corresponds to the $^5T_{2g} \rightarrow ^5E_g$ transition for 6-coordinate iron(II). The spectrum of the cobalt salt shows a weak band at 8.2kK assigned to the $^4T_{1g} \rightarrow ^4T_{2g}$ transition of the $[\text{Co(H}_2\text{O)}_6]^{2+}$ ion. The spectrum of the nickel complex is again very similar: in the near infrared region there is a weak band at 8.3kK assigned to the $^3A_{2g} \rightarrow ^3T_{2g}$ transition of 6-coordinate nickel.

The salts precipitate slowly from solution in large well-defined crystals and preliminary results from a single crystal X-ray diffraction study [143] indicate that the manganese compound is monoclinic (C2/c) with 4 molecules per unit cell [Density = 1.46 g/cc, unit cell volume = 3146.7 Å³, cell dimensions a = 23.3 Å, b = 7.0 Å, c = 19.2 Å, β = 91°52' (±10°)]. In addition, powder patterns indicate that the manganese, iron, copper and nickel salts are isomorphous.

1.4.3 Experimental

The metal sulphate salts listed in table 10 were prepared in aqueous ethanol by mixing stoichiometric quantities of the metal sulphate and diazepinium hydrogen sulphate at room temperature. The latter was prepared by a method described previously [11]. Apart from the copper salt the compounds were also prepared by the method of Emmert and Gsottschneider [86]. Infrared spectra, mixed m.pt.s., magnetic susceptibility and analytical data indicate that the compounds prepared by each method are identical; the manganese(II) salts prepared by each method are isomorphous [143]. Treatment of the complex salts with COLD concentrated sodium hydroxide solution generated the diazepine base, which was extracted by ether and characterized by its m.pt. and infrared spectrum.
1.4.4 Conclusions

The visible colour of these compounds immediately indicates the presence of the diazepinium cation and not the base (fig. 29). It is coincidental that the analytical figures for C, H, N and \( \text{SO}_4^{2-} \) are identical for both formulations in figure 29. The magnetic susceptibilities confirm the molecular weight per metal atom. The infrared spectra strongly indicate the coordination of water and the absence of sulphate coordination. The compounds are assigned the general structure \( D_2 \left[ \text{M(H}_2\text{O)}_6 \right] \left( \text{SO}_4 \right)_2 \cdot x\text{H}_2\text{O} \).
1.5 THE REACTION OF METAL SALTS WITH THE 2,4-DIMETHYL-3H-1,5-BENZODIAZEPINE BASE

1.5.1 Introduction

In many cases the reaction of metal salts with the diazepine base gives inconsistent non-stoichiometric results. The reaction of most metals invariably causes the slow crystallization of the diazepinium salt - analysis shows that such salts contain little, if any, metal ion. For example, iron(II) and nickel(II) bromides, manganese(II) and chromium(III) perchlorates and copper(II) tetrafluoroborate, amongst others, all give relatively pure crystalline precipitates of the corresponding diazepinium salt. In some cases when the salts are visibly contaminated by metal oxides or hydroxides, these finely powdered impurities can be readily separated from the crystalline diazepinium salts and identified.

The dependence of the results described above upon the involvement of water prompted an investigation of such reactions in strictly anhydrous conditions. In no case however were better results obtained - sometimes no precipitation occurred and at other times the diazepinium salt again slowly crystallized. The compounds described below can be obtained in either apparently anhydrous or non-anhydrous conditions.

Although the diazepine base is relatively stable to water alone, when in solution in the presence of metal salts, its tendency is to add a proton in a reversion to the delocalized cation rather than coordinate to the metal ion. The formation of the delocalized cation necessitates the formation of the appropriate metal hydroxide; the precipitation of this hydroxide with its removal from the solution equilibrium presumably helps in the formation of the diazepinium salt.

The work described below concerns the reaction of the base with cobalt chloride and bromide. These cobalt halides were chosen because the initial investigation indicated that the
compounds obtained with these salts contained coordinated diazepine molecules. A description of the reactions involving copper halides is deferred until the following section (1.6).

1.5.2 Results and Discussion

The reaction of 2,4-dimethyl-3H-1,5-benzodiazepine with both cobalt chloride and bromide in a 2:1 molar ratio yields grey-blue compounds of apparent stoichiometry DCoX (by Co, C,H,N and X analysis (table 13)). Magnetic susceptibility measurements confirm the magnetic moment of the cobalt as ~4.8 B.M. and it seems, at first sight, that these compounds are probably polymeric chains containing either diazepine or halide bridges. Such polymeric structures are typical of complexes of diamines from which chelation is impossible [101,102,144].

It became apparent however with a progressive investigation of the compounds that coordination of the diazepine does not occur. Although the stoichiometry indicates the presence of the diazepine base, the infrared spectra clearly indicate the opposite - the spectra of both complexes and their respective tetrahalocobaltates are exactly superimposable - except for two small differences: a band at 3540 cm^{-1} and broad weak absorption in the region 250-450 cm^{-1}. The complexes therefore probably contain the non-coordinated cation. Examination of the electronic spectra (fig.21,22) reveals a close similarity between the two sets of compounds, suggesting the presence of the tetrahalocobaltate in both.

A delocalized diazepine structure and a tetrahalocobaltate structure may be reconciled in a complex such as that illustrated in figure 33. The coordination sphere of the cobalt could be considered to attain completion through halide-bridging with the anions in the formation of a 4- and 6- coordinate polymeric chain. The absence of any other intense absorption in the visible
Figure 33

\[
\begin{align*}
\text{CH}_3 & \quad \text{CH}_3 \\
\left( \begin{array}{c}
\text{N} \\
\text{N}
\end{array} \right)_{2} & \quad \text{Co}^{2+} \\
\text{CoX}_4 & \quad \text{2}^-
\end{align*}
\]

spectra of the compounds suggests that the environment of any other cobalt ion must be 6-coordinate.

This structure is however incorrect. The exact correspondence of the vibrational spectra of these compounds and the tetrahalometallates must be due to the presence of the non-coordinated cation in both cases. In addition, the presence of identical \(\nu(\text{Co-Cl})\) stretching bands in both chloro-complexes makes the assignment of a polymeric chain, with few terminal Co-Cl bonds, very unlikely. Although little difference between the spectra of a coordinated base and a non-coordinated cation might be expected, small differences due to a change in symmetry and distortions arising from crystal lattice alterations should be observable. N-H absorption should also change. The additional vibrational bands, noted previously, are assigned to hydroxide ions (the free OH\(^{-}\) ion absorbs \(~3500\) to \(~3700\)cm\(^{-1}\)). If the diazepine is present as the cation, the compounds may now be formulated as \(\text{D}[\text{CoCl}_2(\text{OH})]\). The hydroxide may be involved in bridging as illustrated in figure 34, although a double salt structure including tetrachlorocobaltate anions is perhaps more likely.

Figure 34

\[
\begin{align*}
\left[ \begin{array}{c}
\text{N} \\
\text{N}
\end{array} \right]_{2} & \quad \left[ \begin{array}{c}
\text{X} \\
\text{X}
\end{array} \right]_{2} \\
\text{Co} & \quad \text{Co}^{2-}
\end{align*}
\]
The magnetic susceptibilities of the chloride were measured at temperatures down to ~89°K. The results are tabulated below. The susceptibilities are field-independent and the compound obeys the Curie-Weiss law with θ = +1°. There is no curvature that would suggest antiferromagnetic exchange. The room-temperature magnetic moment of the bromide = 4.93 B.M. The magnetic moments provide additional evidence for the salt structure – they are similar to those of the tetrahalometallates (section 1.2) and not as high as might be expected if the structure involved both 4- and 6-coordinate cobalt.

Table 12 Magnetic susceptibilities of $\text{D}[\text{CoCl}_2(\text{OH})] 10^5x_L = 144$

<table>
<thead>
<tr>
<th>T(°K)</th>
<th>$10^5x_A$</th>
<th>$\mu$(B.M.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>295.1</td>
<td>10094</td>
<td>4.88</td>
</tr>
<tr>
<td>262.5</td>
<td>11240</td>
<td>4.86</td>
</tr>
<tr>
<td>230.0</td>
<td>12847</td>
<td>4.86</td>
</tr>
<tr>
<td>198.3</td>
<td>14861</td>
<td>4.86</td>
</tr>
<tr>
<td>166.1</td>
<td>17794</td>
<td>4.86</td>
</tr>
<tr>
<td>135.2</td>
<td>21964</td>
<td>4.87</td>
</tr>
<tr>
<td>103.1</td>
<td>28735</td>
<td>4.87</td>
</tr>
<tr>
<td>89.4</td>
<td>32977</td>
<td>4.86</td>
</tr>
</tbody>
</table>

In order to investigate the reaction of the diazepinium base towards Lewis acids and to test the donor-ability of the nitrogen atoms, the base was treated with both boron trifluoride and p-tosyl chloride. The reaction of 2,4-dimethyl-3H-1,5-benzodiazepine with p-toluenesulphonyl chloride has been reported to give an N-tosyl derivative [39]. A repetition of this reaction however gave a typical purple salt - N-tosylation is not believed to occur, rather the formation of a diazepinium tosylate.

The reaction of 1,5-benzodiazepinium bases with boron trifluoride diethyletherate is possibly more surprising. Both the 2,4-dimethyl- and 2,4-diphenyl derivatives were treated in dry ethereal-ethanol solution with the boron trifluoride. Although the diphenyl diazepine gives a white precipitate which immediately turns orange then purple, the dimethyl derivative gives an immediate purple colour and precipitate.
It appears that even if coordination is temporarily achieved, immediate tautomerization and hydrolysis leads to salt formation (fig. 35). Analytical data are given in the experimental section. The infrared spectra of the purple salts clearly confirm the delocalized structure of the diazepine and the presence of the tetrahedral BF$_4^-$ anions. The same compounds are obtained by treatment of the base with fluoroboric acid (as shown by mixed m.p.t. and infrared spectra). The mass spectra of the compounds show no evidence for coordination of the boron trifluoride.

Figure 35

The mass spectrum of DCoCl$_2$OH is very similar to the spectra of both D$_2$CoCl$_4$ and DCl, and shows no evidence for diazepine coordination.

1.5.3 Experimental

The 2,4-dimethyl-3H-1,5-benzodiazepine base was prepared as described in section 1.2 and the preparation of the 2,4-diphenyl derivative has been described previously [11]. The fluoroborate salts were prepared by the dropwise addition of an ethereal solution of boron trifluoride diethyletherate to a stirred dry ether-ethanol solution of the diazepine base. The two cobalt salts were prepared by mixing 2:1 molar quantities
of the diazepine base and cobalt halide in ethanol solution.

When dry conditions were employed, the metal salts were heated at ~130°C, cooled in vacuo, and then shaken with 2,2-dimethoxypropane overnight, diluted with dry ethanol and filtered. Diazepine solutions were also dried by shaking with 2,2-dimethoxypropane.

Table 13 Analytical data

<table>
<thead>
<tr>
<th>Compound</th>
<th>Elements</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C</td>
</tr>
<tr>
<td>DBF₄</td>
<td>Found</td>
</tr>
<tr>
<td>Dimethyl-diazepinium tetrafluoroborate</td>
<td>Calc.</td>
</tr>
<tr>
<td>EBF₄</td>
<td>Found</td>
</tr>
<tr>
<td>Diphenyl-diazepinium tetrafluoroborate</td>
<td>Calc.</td>
</tr>
<tr>
<td>D[CoCl₂(OH)]</td>
<td>Found</td>
</tr>
<tr>
<td></td>
<td>Calc.</td>
</tr>
<tr>
<td>D[CoBr₂(OH)]</td>
<td>Found</td>
</tr>
<tr>
<td></td>
<td>Calc.</td>
</tr>
</tbody>
</table>

1.5.4 Conclusions

The salts of approximate stoichiometry DCoX₂ contain the uncoordinated diazepinium cation. Their electronic spectra indicate the inclusion of the tetrahalocobaltate anion although a hydroxo-bridged structure is possible. The complexes are assigned the general structure D[CoX₂(OH)] and the presence of OH⁻ is confirmed by the vibrational spectra. The reaction of metal salts with the base illustrates the overriding tendency of the diazepine molecule to revert if possible to the delocalized cationic structure. The presence of water is essential to this process but all attempts to obtain alternative
coordinated structures by the exclusion of water failed.

It is interesting in this respect to note that the diamine 'dabco' (fig. 94.1, p. 129) reacts with an ethanol solution of nickel chloride to form a complex of the protonated ligand, \( \text{Ni}(\text{Hdabco})\text{Cl}_3 \) [95]. It is well established that one of the chief difficulties experienced in the use of highly basic amines is the formation of hydroxo-complexes, even when considerable effort is made to exclude water [145].
1.6 THE REACTION OF COPPER(II) BROMIDE AND CHLORIDE WITH 1,5-BENZODIAZEPINES

1.6.1 Introduction

The reaction of copper(II) bromide with the 1,5-benzodiazepines is probably the most interesting of those studied. It has already been noted in section 1.2 (p.19) that the reaction of copper(II) bromide with the 2,4-dimethyl-benzodiazepinium cation is anomalous in giving a compound of apparent stoichiometry DCuBr₂ with complete reduction of copper(II) to copper(I). In a subsequent experiment it was discovered that the reaction of the 2,4-dimethyl-diazepine base with copper(II) bromide results in the same compound, again with reduction of copper(II). As explained in the previous section (p.47) the reaction of the base to give a complex of the cation must presumably involve the formation of a metal hydroxide or hydroxo-complex. Analytical and infrared spectroscopic data shows that in this case the precipitate is not contaminated by copper hydroxide.

Since benzodiazepines having electronegative substituents on the seven-membered ring are more likely to coordinate, because of their decreased basicity, the three 3-bromo-diazepinium bromides illustrated below were prepared.

The reaction of the 3-bromo-2,4-dimethyl-benzodiazepine (36.1) with copper(II) bromide gives again the cuprous salt described above. The compounds derived from all three preparative routes have identical infrared spectra (fig.30), mixed m.pts., and analytical data (table 16); all three compounds are diamagnetic.

Figure 36

![Figure 36](image-url)
This series of reactions was repeated using 2,4-diphenylbenzodiazepines and in each case an identical product is obtained from the reaction with copper(I1) bromide. Reduction of the copper(I1) occurs to give a compound of apparent stoichiometry \( \text{ECu}_2\text{Br}_3 \). In this section these reactions and the compounds obtained are discussed.

1.6.2 Results and Discussion

Although the compounds readily decompose when treated with alkali, the 2,4-dimethyl diazepinium copper salt has been successfully recrystallized from an ethanolic-conc. HBr solution. The crystal structure is at present being determined. The compounds are much less soluble than the tetrahalometallates described in section 1.2, indicating a polymeric structure; they are insufficiently soluble for both conductivity and NMR measurements.

The reduction of the copper(I1) to copper(I) has already been explained \([91]\) in terms of the relative instability of \([\text{CuBr}_4]^-\), compared to \([\text{CuCl}_4]^- \) \([136]\). Reaction of the cation with copper(I1) bromide may therefore be represented simply as:

\[
\begin{align*}
2\text{Cu(I1)Br}_2 & \rightarrow 2\text{Cu(I)Br} + \text{Br}_2 \\
\text{Cu(I)Br} + \text{DBr} & \rightarrow \text{D[CuBr}_2\text{]} 
\end{align*}
\]

As mentioned in section 1.2 (p.19), the spectroscopic evidence is in favour of a delocalized non-coordinated diazepinium salt structure. The product of the reaction of the diphenyl derivative may similarly be assigned an ionic structure \( \text{E[Cu}_2\text{Br}_3 \). The anion of this salt occurs for example as a polymeric ion in the diazonium salt \( \Phi\text{N}_2^+\text{Cu}_2\text{Br}_3^-\), an intermediate in the Sandmeyer reaction. A determination of the crystal structure of this salt has shown that no direct bonding occurs between the diazonium
cation and the polymeric anion [148].

If these structures are correct however, it is difficult to explain the remaining two preparative routes to the compounds.

Comparison of the solid and solution electronic spectra of the 3-bromo-2,4-dimethyl-1H-1,5-benzodiazepinium bromide indicates that no decomposition of the brominated compound occurs in ethanol solution; both spectra exhibit absorption at slightly lower energies than does the spectrum of the non-brominated diazepine. The electronic spectra indicate that the brominated molecules exist in the usual delocalized form (fig.36) and not as shown in figure 37, originally suggested on the basis of the vibrational spectrum [7]. It is interesting to note here that the analogous 6-bromo-2,3-dihydro-1,4-diazepines* readily undergo nucleophilic replacement of the bromine in acidic (HBr) or basic conditions [73].

Figure 37

![Diagram of a molecular structure](image)

The reaction of copper(II) bromide with the 3-bromo-diazepinium bromide to give a salt of the parent diazepinium bromide requires the concurrence of two reductions (fig.38). It seems unlikely that nucleophilic attack on the 3-bromo-derivatives, with removal of bromine, would occur at the same time as the reduction of copper(II) bromide, again with liberation of bromine.

Figure 38

![Diagram of the reaction](image)

\[ \text{Cu(II)Br}_2 \rightarrow \text{Cu(I)Br} + \frac{1}{2}\text{Br}_2 \]
The reverse reaction appears more probable ie. the bromination of the parent diazepine upon reaction with copper(II) bromide:

Figure 39

![Reaction diagram]

Although the reaction of bromine with the benzodiazepinium cation in glacial acetic acid [5] causes multiple bromination of the benzene ring (unlike the analogous 2,3-dihydro-diazepines which brominate at the 6-position [73,76,77]), both Hückel and SCF-VBO molecular orbital calculations suggest that the 3-position is very susceptible to electrophilic attack (table 14) [149,150]. It has been reported [80] that 1,5-benzodiazepines undergo electrophilic substitution with bromine. Fukui's superdelocalizabilities [151] have been calculated for the 2,4-dimethyl-benzodiazepinium cation - results obtained confirm this susceptibility to electrophilic attack [149].

Table 14 Charge densities on the diazepine bridge

<table>
<thead>
<tr>
<th>Position</th>
<th>Hückel</th>
<th>SCF-VBO</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,5</td>
<td>1.649</td>
<td>1.566</td>
</tr>
<tr>
<td>2,4</td>
<td>0.692</td>
<td>0.830</td>
</tr>
<tr>
<td>3</td>
<td>1.204</td>
<td>1.210</td>
</tr>
</tbody>
</table>

The substitution of bromine at the 3-position of the base to give the 3-bromo-benzodiazepinium bromide might explain the derivation of the same compound from both diazepines (fig.40).

Figure 40

![Reaction diagram]
In this case it is possible to postulate intermediate coordination of the copper (fig. 41). It has already been mentioned (section 1.5) that attempts to prepare BF$_3$ adducts failed due to the ready hydrolysis of the products. In a copper(I) complex, back-donation to the diazepine $\pi$ system will stabilize the coordination, although hydrobromic acid produced during the bromination might cause decomposition.

**Figure 41**

Examples of copper-promoted bromination reactions are common [152]; perhaps the most extensively studied bromination has been that of metal acetylacetonates [153-156]. In this and many other examples molecular bromine is added to a metal complex. In some cases however, bromination occurs with cupric bromide alone and involves the reduction of copper(II) to copper(I) eg. the bromination of anthracene [157], isophorone [158] and norbornadiene [159]. Reaction can take place at room-temperature in aqueous methanol but it has been emphasized that the following factors clearly influence the rate of reaction: i) the removal of Cu(I) in coordination to the substrate, ii) the removal of HBr, if necessary by the use of a basic solvent and iii) sufficient electron density at the brominating site. It is possible that these criteria are fulfilled in the case under discussion.

It is clear from the preceding discussion that a satisfactory explanation of the production of identical compounds from three different starting materials is a copper-promoted bromination in two cases. In the bromination of the cation, MO calculations show the 3-position to be susceptible to electrophilic attack. In the bromination of the base, the reducing power of the diazepine, possible complex formation and the liberation of
hydrobromic acid which is then absorbed in the generation of the stable delocalized cation, all favour the reaction. The reducing power of the diazepine base is illustrated later in this section when the reduction of copper(II) chloride is reported.

The determination of possible structures from the spectroscopic and analytical data is however less satisfactory. Analytical data (table 16) confirm the empirical formulae as DCuBr$_2$ and ECu$_2$Br$_3$ and successful recrystallisation further indicates either an ionic or coordinated structure - not merely a stoichiometric mixture.

The vibrational spectra of both compounds confirm the retention of the delocalized diazepinium structure, although comparison of the spectra illustrated in figures 14 and 30 reveals several differences, in particular: an additional strong band at 810 cm$^{-1}$; the movement of $\nu$(N-H) bands to lower frequencies by ~20 cm$^{-1}$ (as in the spectrum of the 3-bromo-2,4-dimethyl-benzodiazepinium cation); the absence of bands at 1639 and 1325 cm$^{-1}$; and a lowering in intensity of the band at 1477 cm$^{-1}$. In some respects the spectrum of the DCuBr$_2$ compound resembles the spectra of the tetrachlorometallates (fig. 15) and changes might be attributable to an alteration in the anion. The spectra of the compounds do not resemble the spectra of the 3-bromo-diazepinium bromides any more than the spectra of the non-brominated diazepinium salts. No bands present in the 3-bromoderivatives can be assigned specifically to C-Br vibrations. The spectra do not exhibit O-H stretching bands which might be expected (~3500 cm$^{-1}$) in hydroxo-complexes - the only absorption present in the region 3000-4000 cm$^{-1}$ has already been assigned to N-H and C-H vibrations.

The diffuse reflectance electronic spectrum of the 2,4-dimethyl-diazepinium copper bromide compound is shown in figure 22 (p.28) and exhibits diazepine bands at frequencies very similar to those of the 2,4-dimethyl-diazepinium cation.
An intense band at ~24kK is assigned to a charge transfer transition. Spectra of the 2,4-diphenyl- derivatives are illustrated in figure 42; the spectrum of the copper(I) bromide salt resembles to some extent that of the 3-bromo-diazepinium cation.

Figure 42 Electronic spectra of 2,4-diphenyl-1,5-benzodiazepine derivatives

The mass spectra of the 2,4-dimethyl-1,5-benzodiazepine, the bromide salt, the 3-bromo derivative and the copper(1) bromide complex are illustrated in figure 43. Although the 3-bromo-2,4-dimethyl-diazepinium cation does show reasonably abundant molecular ion peaks (the isotopic abundances confirm the presence of one bromine atom per ion), the 3-bromo-2,4-diphenyl diazepinium cation exhibits very weak (2%) molecular ion peaks. There are however two strong metastable peaks corresponding to the loss of $^{79}\text{Br}$ and $^{81}\text{Br}$ from the m/e 374.
Table 15

<table>
<thead>
<tr>
<th>Metastable peaks</th>
<th>observed</th>
<th>calculated</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{12}C_{21}^{14}H_{15}^{14}N_{2}^{79}Br$ $\rightarrow$ $^{12}C_{21}^{14}H_{15}^{14}N_{2}$</td>
<td>232.8</td>
<td>232.68</td>
</tr>
<tr>
<td>$^{12}C_{21}^{14}H_{15}^{14}N_{2}^{81}Br$ $\rightarrow$ $^{12}C_{21}^{14}H_{15}^{14}N_{2}$</td>
<td>231.5</td>
<td>231.45</td>
</tr>
</tbody>
</table>

and 376 ions (table 15). It should be noted that the source temperature and pressure used in taking the mass spectra has a considerable effect on the stability of the 3-bromo-diazepinium cations. In five different spectra of the 3-bromo-2,4-dimethylbenzodiazepinium bromide the abundance of the molecular ion relative to the m/e 172 ion varied from 15 to 60%. This facile loss of halogen from the '3-position' is also exhibited by 2-chloro- and 2-bromo-malonaldehydedianilium salts (fig.44)[160].

It is interesting to note the close similarity between the mass spectra of the diazepine base and its bromide salt - the ion m/e 172 is the parent peak in both spectra (fig.43). Additional peaks at m/e 79, 80, 81 and 82 in the spectrum of the bromide salt are assigned to Br$^+$ and HBr$^+$. The similarity between the spectra suggests instability of the cation with ready loss of HBr in the mass spectrometer.

The mass spectra of the copper(1) bromide compounds do not confirm the presence of 3-bromo-diazepines. The ECu$_2$Br$_3$ salt exhibits no metastable peaks as described above for the 3-bromo-diazepinium bromide and the spectrum of the DCuBr$_2$ salt exhibits only a weak peak (3%) corresponding to the 3-bromo-derivative. This peak may be due to bromination within the mass spectrometer (see section 1.3 for a similar chlorination).
Table 16 Analytical data

<table>
<thead>
<tr>
<th>Compound</th>
<th>m.p. (°C)</th>
<th>C</th>
<th>H</th>
<th>N</th>
<th>Br£</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-bromodiazepinium bromides</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2,4-dimethyl-</td>
<td>225</td>
<td>Found 40.86</td>
<td>3.77</td>
<td>8.50</td>
<td>45.42</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Calc. 39.79</td>
<td>3.64</td>
<td>8.44</td>
<td>45.65</td>
</tr>
<tr>
<td>2-methyl-4-phenyl-</td>
<td>228</td>
<td>Found 46.34</td>
<td>3.50</td>
<td>6.81</td>
<td>-</td>
</tr>
<tr>
<td>(H2O)</td>
<td></td>
<td>Calc. 46.62</td>
<td>3.91</td>
<td>6.80</td>
<td>-</td>
</tr>
<tr>
<td>2,4-diphenyl-</td>
<td>234</td>
<td>Found 54.33</td>
<td>3.77</td>
<td>5.94</td>
<td>-</td>
</tr>
<tr>
<td>(H2O)</td>
<td></td>
<td>Calc. 54.22</td>
<td>3.68</td>
<td>6.02</td>
<td>-</td>
</tr>
<tr>
<td>2,4-diphenyl-1H-1,5-benzodiazepinium copper(1) bromides b</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A&lt;sup&gt;d&lt;/sup&gt;</td>
<td>271°</td>
<td>Found 37.83</td>
<td>2.54</td>
<td>4.16</td>
<td>36.01</td>
</tr>
<tr>
<td>B</td>
<td>271°</td>
<td>Found 37.83</td>
<td>2.51</td>
<td>4.14</td>
<td>-</td>
</tr>
<tr>
<td>C</td>
<td>271°</td>
<td>Found 37.72</td>
<td>2.48</td>
<td>4.15</td>
<td>-</td>
</tr>
<tr>
<td>ECU2Br3</td>
<td></td>
<td>Calc. 37.97</td>
<td>2.58</td>
<td>4.22</td>
<td>36.10</td>
</tr>
<tr>
<td>2,4-dimethyl-1H-1,5-benzodiazepinium copper(1) bromides b</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A&lt;sup&gt;d&lt;/sup&gt;</td>
<td>223</td>
<td>Found 33.27</td>
<td>3.30</td>
<td>6.94</td>
<td>40.27</td>
</tr>
<tr>
<td>B</td>
<td>223</td>
<td>Found 33.51</td>
<td>3.40</td>
<td>6.76</td>
<td>-</td>
</tr>
<tr>
<td>C</td>
<td>223</td>
<td>Found 32.45</td>
<td>3.12</td>
<td>6.87</td>
<td>-</td>
</tr>
<tr>
<td>D CuBr2</td>
<td></td>
<td>Found&lt;sup&gt;e&lt;/sup&gt; 33.31</td>
<td>3.30</td>
<td>7.06</td>
<td>40.30</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Calc. 33.31</td>
<td>3.30</td>
<td>7.06</td>
<td>40.30</td>
</tr>
</tbody>
</table>

a: see section 3.14.3 (I).
b: all 6 products are diamagnetic.
c: decomposed.
e: after recrystallisation.

1.6.3 Experimental

3-Bromo-2,4-dimethyl-1H-1,5-benzodiazepinium bromide was prepared by the addition of bromine to the diazepine base in nitromethane as described previously [7]. The 2-methyl-4-phenyl- and 2,4-diphenyl- derivatives were prepared by the same method. Analytical data are listed above (table 16).
Three methods were used to prepare the copper bromide complexes: A, from the diazepinium bromide as described in section 1.2.2 (p.32); B, by mixing dry ethanol solutions of the base and copper(II) bromide at room temperature; and C, as A but using the 3-bromodiazepinium bromide.

1.6.4 Conclusions

Spectroscopic and analytical data do not support the suggestion that bromination of the diazepine ring occurs during the reaction of 2,4-dimethyl- and 2,4-diphenyl- benzodiazepines with copper(II) bromide.

Although bromination of the diazepines explains quite well the production of an identical product by all three routes, there are some discrepancies. For example: although bromination would clearly encourage the reduction of copper(II) (by the removal of bromine), this same reduction upon reaction with the already brominated diazepine is unexplained. Similarly, the stoichiometries of the 3-bromo-diazepinium copper(I) salts might be expected to be $(3\text{Br-D})\text{CuBr}_2$ and $(3\text{Br-E})\text{Cu}_2\text{Br}_3$ and not those observed, unless some form of coordination takes place in the compounds, either from the nitrogen atoms or from the benzene or diazepine ring π systems.

There is no evidence to suggest the formation of complexes such as $(3\text{Br-D})[\text{CuBr(OH)}]$, analogous to the cobalt complexes discussed in the previous section (1.5). Moreover, there is no reason for the formation of such a compound from the diazepinium bromide and copper(II) bromide and it is inconceivable that the hydroxide would be stable towards hydrobromic acid.

Formulating the compounds as salts of the non-brominated diazepines leaves two features unexplained: the removal of bromine from the 3-bromo-diazepines and the absence of hydroxide contamination of the precipitates obtained from the reactions of the bases.
The reaction of copper(II) chloride with the diazepine base in ethanol solution gives non-stoichiometric compounds with incomplete reduction of copper(II) to copper(I). The reaction of the base and copper(II) chloride in 2:1 and 1:1 molar ratios, for example, gives compounds of very approximate stoichiometries 
$'D_2CuCl_2'$ and $'DCuCl_2'$

The magnetic susceptibilities of these two compounds were measured at temperatures down to $89^\circ K$ and found to be field-independent. Three values are given below in table 17.

Although the vibrational spectra are similar in general appearance to the spectrum of the tetrachlorocuprate(II), broad absorption in the region $\sim 3500 \text{ cm}^{-1}$ suggests the presence of water or hydroxide ions and the disappearance of the two bands assigned to Cu - Cl vibrations of the tetrachlorocuprate(II) ion (a new band appears at $318 \text{ cm}^{-1}$) illustrates a change in the anionic metallate. The electronic spectra confirm the absence of a tetrachlorocuprate structure: bands in the near-infrared region are completely absent and broad charge-transfer absorption exists down to $\sim 9 \text{ kK}$.

### Table 17 Magnetic and Analytical data for two diazepinium copper chloride salts

<table>
<thead>
<tr>
<th>Analytical data</th>
<th>$'D_2CuCl_2'$</th>
<th>$'DCuCl_2'$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Found:</td>
<td>C 51.11 H 4.72 N 10.22 Cl 13.88</td>
<td>C 38.56 H 3.55 N 8.07 Cl 22.53</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Magnetic data</th>
<th>$10^6 x_L \approx 241$</th>
<th>$10^6 x_L \approx 144$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$T(\text{°K})$</td>
<td>$10^6 x_A (\text{cgs})$</td>
<td>$\mu (\text{B.M.})$</td>
</tr>
<tr>
<td>295.2</td>
<td>424</td>
<td>$\sim 1.00$</td>
</tr>
<tr>
<td>198.2</td>
<td>600</td>
<td>$\sim 0.98$</td>
</tr>
<tr>
<td>89.5</td>
<td>1173</td>
<td>$\sim 0.92$</td>
</tr>
</tbody>
</table>
CHAPTER 2

2,3-Dihydro-1,5-benzodiazepines and -1,5-benzothiazepines
2.1 INTRODUCTION

The structures of the dihydro- benzodiazepines and benzothiazepines examined in this chapter are illustrated below in figure 45. All four derivatives were prepared primarily as intermediates in the syntheses of the corresponding tetrahydroheterocycles and no work is reported concerning their transition metal complexes. This chapter is devoted to a brief description of some spectroscopic properties of the molecules themselves. As mentioned in the introduction (p.10), the properties of some dihydro- diazepines and thiazepines have been reported previously and their structures are now generally established.

Figure 45

\[
\begin{align*}
X = \text{NH, S} & & X = \text{NH, S}
\end{align*}
\]

2.2 VIBRATIONAL, ELECTRONIC, NMR AND MASS SPECTRA

The infrared spectra of both trimethyl- heterocycles are illustrated in figures 46 and 47. The most obvious difference between the two spectra is the sharp N-H stretching vibration at 3287 cm\(^{-1}\) in the spectrum of the diazepine (the vibration occurs at 3345 cm\(^{-1}\) in the spectrum of the diphenyl diazepine). The strong bands at \(\sim 1630\) cm\(^{-1}\) in both spectra are assigned to \(\nu(\text{C=}=\text{N})\). The weaker bands at 1590 and 1579 cm\(^{-1}\) in the spectra of the diazepine and thiazepine respectively are assigned to aromatic C=C stretching vibrations (stronger bands appear at the same frequencies in the spectra of the tetrahydro- derivatives - see section 3.5). Since the thiazepine contains no N-H group, the bands cannot be due to \(\delta(\text{N-H})\).
The vibrational and electronic spectra of the 2,2,4-trimethyl-2,3-dihydro-1H-1,5-benzodiazepine have been described previously [24].

The electronic spectra of the diphenyl derivatives are illustrated in figure 48. As expected, the spectra of both compounds closely resemble that of benzylideneaniline [161]. Details of the spectra of both the diphenyl- and trimethylheterocycles are included in table 18.

Figure 48  Electronic spectra of 2,4-Diphenyl-2,3-dihydro-1H-1,5-benzodiazepine and -1,5-benzothiazepine
<table>
<thead>
<tr>
<th>Compound</th>
<th>λ_max (nm)</th>
<th>ε</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzylideneaniline</td>
<td>262</td>
<td>17,000</td>
</tr>
<tr>
<td>(ref.[161])</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diphenyldihydrodiazepine</td>
<td>260.0</td>
<td>28,000</td>
</tr>
<tr>
<td>Diphenyldihydrothiazepine</td>
<td>261.5</td>
<td>19,100</td>
</tr>
<tr>
<td>Trimethyldihydrodiazepine (~215)</td>
<td>243</td>
<td>7,700</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>weak shoulders at ~280 and ~320 nm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trimethyldihydrothiazepine</td>
<td>218.5</td>
<td>15,600</td>
</tr>
<tr>
<td></td>
<td>267.5</td>
<td>6,100</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>weak shoulder at ~295 nm</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*obscured by solvent cut-off

The NMR spectra of the four compounds are discussed in section 3.7 where they are compared to the analogous unsaturated and tetrahydro- derivatives. It is interesting to note here however that whereas the symmetrically substituted trimethyl- heterocycles give rise to simple spectra through ring inversion which is rapid on an NMR time scale, the asymmetrically substituted diphenyl-derivatives exist in fixed conformations at room temperature (see sections 3.7.8 and 3.7.9).

The mass spectra of the heterocycles exhibit simple breakdown patterns. An example, the spectrum of 2,2,4-trimethyl-2,3-dihydro-1H-1,5-benzodiazepine is illustrated in figure 49. In none of the

Figure 49

![Mass Spectrum of 2,2,4-trimethyl-2,3-dihydro-1H-1,5-benzodiazepine](image-url)
spectra is the molecular ion the most abundant - ready formation of the corresponding 2-methyl or 2-phenyl benzimidazole or thiazole occurs in each case. All the spectra exhibit strong metastable peaks corresponding to the breakdown of the molecular ions to the related imidazole or thiazole ions and these latter ions are usually the base peaks. The spectrum of the trimethyl diazepine is illustrated (fig.49) in particular because in addition to the breakdown described above, it exhibits an alternative degradation route - loss of a methyl group occurs to give the base peak at m/e 173 which in turn yields the ion m/e 133 (probably a 2-methylbenzimidazolidinium ion - see also section 3.6). All
these paths are supported by the appropriate metastable peak (table 19). The 2,2,4-trimethyl-2,3-dihydro-1,5-benzothiazepine does not show this type of fragmentation (the abundance of the M-CH$_3$ ion is ~zero) which indicates a mechanism such as that shown in figure 50.

The high abundance of the m/e 173 ion and its breakdown to give the imidazolidinium ion suggests stabilization through the formation of the delocalized benzodiazepinium structure (fig. 50) - rearrangements involving migration of hydrogen atoms in molecules containing heteroatoms are common. A similar stabilization of the analogous thiazepine ion is impossible.

It is interesting in this case that the 2,4-dimethyl-1H-1,5-benzodiazepinium bromide breaks down in the same way as the diazepine base, with apparent loss of HBr (see section 1.6, fig. 43.2, p. 61) and shows no evidence for the stability of the delocalized structure. This apparent instability may well depend upon the presence of halogen.

Table 19 Metastable peaks in the mass spectrum of 2,2,4-trimethyl-2,3-dihydro-1H-1,5-benzodiazepine - supporting the breakdown paths illustrated in figure 50

<table>
<thead>
<tr>
<th>Breakdown</th>
<th>Observed metastable peak</th>
</tr>
</thead>
<tbody>
<tr>
<td>188 → 173</td>
<td>159.2</td>
</tr>
<tr>
<td>188 → 132</td>
<td>92.7</td>
</tr>
<tr>
<td>173 → 133</td>
<td>102.3</td>
</tr>
<tr>
<td>133 → 92</td>
<td>63.6</td>
</tr>
<tr>
<td>92 → 65</td>
<td>45.9</td>
</tr>
</tbody>
</table>
2.3 EXPERIMENTAL

The trimethyl diazepine was prepared as described elsewhere [23] and recrystallized from petroleum ether. The trimethyl diazepine was prepared as follows: o-aminothiophenol (25g), mesityl oxide (19.6g), conc. HCl (18ml) and ethanol (200ml) were refluxed together for 2.5hr. and then stood overnight. The ethanol was largely removed under reduced pressure and 2N NaOH poured into the remaining solution with stirring to precipitate a brown granular compound. This was recrystallized from petroleum ether (80-100) to yield pale yellow crystals of the thiazepine (yield 33.3g m.pt.67°C). The crystals darken slowly over several weeks.

The diphenyl thiazepine was prepared from o-aminothiophenol and chalcone (benzylideneacetophenone) by a published method [51]. The diphenyl diazepine was prepared by the partial reduction of 2,4-diphenyl-1H-1,5-benzodiazepine using sodium borohydride in warm ethanol solution. Both the dihydrodiphenyl diazepine and thiazepine could not be reduced further (ie. to the tetrahydro-derivatives) using sodium borohydride. Analytical data are given in table 20.

Table 20 Analytical data

<table>
<thead>
<tr>
<th>Compound</th>
<th>m.pt.(°C)</th>
<th>C</th>
<th>H</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trimethyl diazepine*</td>
<td>127</td>
<td>Found</td>
<td>76.11</td>
<td>8.51</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Calc.</td>
<td>76.55</td>
<td>8.57</td>
</tr>
<tr>
<td>Trimethyl thiazepine</td>
<td>67</td>
<td>Found</td>
<td>70.46</td>
<td>7.58</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Calc.</td>
<td>70.20</td>
<td>7.36</td>
</tr>
<tr>
<td>Diphenyl diazepine</td>
<td>114</td>
<td>Found</td>
<td>85.02</td>
<td>9.60</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Calc.</td>
<td>84.53</td>
<td>9.39</td>
</tr>
<tr>
<td>Diphenyl thiazepine</td>
<td>116</td>
<td>Found</td>
<td>80.00</td>
<td>5.40</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Calc.</td>
<td>79.96</td>
<td>5.43</td>
</tr>
</tbody>
</table>

*picrate 169°C
CHAPTER 3

2,3,4,5-Tetrahydro-1,5-benzodiazepines and -1,5-benzothiazepine
3.1 INTRODUCTION

In comparison to their unsaturated analogues, the tetrahydrobenzodiazepines and thiazepines are less well known. Although many of the organic compounds described in this chapter have been prepared previously, the preparative methods employed have sometimes been laborious, the yields have been variable and seldom has any spectroscopic data been reported.

In the first part of this chapter therefore, an investigation of the structures of these saturated heterocycles by vibrational and electronic spectroscopy, mass spectrometry and detailed NMR spectroscopy is reported. In the latter part of the chapter the preparation and properties of some metal complexes are described.

The diazepines and thiazepines studied are illustrated in figure 51. These compounds were chosen to determine the effect of a gradual increase in methyl substitution both on the structure of the seven-membered ring and on the stereochemistry of the transition metal complexes derived from them. The abbreviations shown are used subsequently in some figures and tables.

Figure 51

<table>
<thead>
<tr>
<th>R₁</th>
<th>R₂</th>
<th>R₃</th>
<th>Abbreviation</th>
<th>R₁</th>
<th>R₂</th>
<th>R₃</th>
<th>Abbreviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>H</td>
<td>H</td>
<td>NN</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>SN</td>
</tr>
<tr>
<td>Me</td>
<td>H</td>
<td>H</td>
<td>2MeNN</td>
<td>Me</td>
<td>H</td>
<td>H</td>
<td>2MeSN</td>
</tr>
<tr>
<td>Me</td>
<td>Me</td>
<td>H</td>
<td>22diMeNN</td>
<td>Me</td>
<td>Me</td>
<td>H</td>
<td>22diMeSN</td>
</tr>
<tr>
<td>Me</td>
<td>H</td>
<td>Me</td>
<td>24diMeNN</td>
<td>Me</td>
<td>Me</td>
<td>Me</td>
<td>224triMeSN</td>
</tr>
<tr>
<td>Me</td>
<td>Me</td>
<td>Me</td>
<td>224triMeSN</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
3.2 PREPARATION

The preparations of those compounds previously reported are not described in detail. The syntheses of three compounds are reported as examples in the experimental section (3.14). In most cases established techniques have been employed. Analytical data of the heterocycles are listed in table 21.

The established route [36,37] to the parent diazepine NN illustrated in figure 52 was not employed. Despite repeated attempts, considerable difficulty was experienced in the final hydrolysis of the tosyl derivative; only small yields being obtained. The diazepine is prepared in high yield more easily by LiAlH₄ reduction of either the diazepinone [27] or diazepindione [31] (fig.52). A similar method was employed for the 2-methyl derivative, from crotonic acid [29], and for the new 2,2-dimethyl derivative, from 3-methylcrotonic acid although the latter derivative was an oil at room temperature and could not be crystallized.

Figure 52
Table 21 Analytical data of the tetrahydrobenzodiazepines, thiazepines and their derivatives

<table>
<thead>
<tr>
<th>Compound</th>
<th>Colour</th>
<th>m.p.t. (°C)</th>
<th>ref.</th>
<th>Found C</th>
<th>Found H</th>
<th>Found N</th>
<th>Calculated C</th>
<th>Calculated H</th>
<th>Calculated N</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>lit.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24diketo-NN</td>
<td>silvery grey</td>
<td>350</td>
<td>360</td>
<td>[31]</td>
<td>61.31</td>
<td>4.65</td>
<td>15.99</td>
<td>61.36</td>
<td>4.53</td>
</tr>
<tr>
<td>NN</td>
<td>white crystals</td>
<td>100</td>
<td>102/3[38/37]</td>
<td>72.77</td>
<td>8.13</td>
<td>18.71</td>
<td>72.94</td>
<td>8.16</td>
<td>18.90</td>
</tr>
<tr>
<td></td>
<td>picrate</td>
<td>185</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4keto-2MeNN</td>
<td>colourless crystals</td>
<td>189</td>
<td>184/8[29/162]</td>
<td>70.29</td>
<td>7.25</td>
<td>16.68</td>
<td>68.16</td>
<td>6.86</td>
<td>15.90</td>
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<tr>
<td>2MeNN</td>
<td>off-white</td>
<td>100</td>
<td>97/102[34/36]</td>
<td>73.92</td>
<td>8.83</td>
<td>17.14</td>
<td>74.03</td>
<td>8.70</td>
<td>17.27</td>
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<tr>
<td>24diMeNN</td>
<td>off-white crystals†</td>
<td>57</td>
<td>57</td>
<td>[62]</td>
<td>71.24</td>
<td>9.19</td>
<td>15.26</td>
<td>71.96</td>
<td>9.15</td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>4keto-22diMeNN</td>
<td>white crystals‡</td>
<td>255</td>
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<tr>
<td>224triMeNN</td>
<td>pale yellow crystals†</td>
<td>67</td>
<td>69</td>
<td>[23]</td>
<td>74.52</td>
<td>9.53</td>
<td>14.94</td>
<td>75.74</td>
<td>9.53</td>
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<td>220</td>
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<tr>
<td>SN</td>
<td>pale yellow oil</td>
<td>-</td>
<td>190</td>
<td>190</td>
<td>[55]</td>
<td></td>
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<tr>
<td>4keto-2MeSN</td>
<td>white</td>
<td>210</td>
<td>205/6[45]</td>
<td>62.18</td>
<td>5.79</td>
<td>7.09</td>
<td>62.15</td>
<td>5.74</td>
<td>7.25</td>
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<tr>
<td>2MeSN</td>
<td>pale yellow crystals†</td>
<td>45</td>
<td></td>
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<tr>
<td>4keto-22diMeSN</td>
<td>colourless crystals†</td>
<td>220</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>22diMeSN</td>
<td>pale yellow‡</td>
<td>31</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>224triMeSN</td>
<td>pale yellow crystals</td>
<td>84</td>
<td>86</td>
<td>[52]</td>
<td>69.46</td>
<td>8.31</td>
<td>6.43</td>
<td>69.52</td>
<td>8.26</td>
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<tr>
<td></td>
<td>picrate</td>
<td>169</td>
<td>170/2[52]</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

*new compound  †new preparative method
The 2,4-dimethyl diazepine (2,4diMeNN) has been prepared previously in small quantities by the catalytic hydrogenation of either the 2,4-dimethyl-3H-1,5-benzodiazepine base (5%Pd/C, 1 atmos.H₂, 30hr.[62]) or its hydrochloride (Pt oxide, 4 atmos.H₂ [36]). In the first method the product was separated into two stereoisomers by column chromatography. Reported attempts to reduce the unsaturated diazepine with LiAlH₄ and with sodium in ethanol were not successful [5]. The new method reported here employs sodium borohydride in warm absolute ethanol, a method prompted by work described in reference [25]. Only the cis (2e,4e) isomer has been isolated although it is probable that the trans (2e,4a) isomer is also produced in the reaction. It should be noted that analogous treatment of 2,4-diphenyl-3H-1,5-benzodiazepine gives only the dihydrobenzodiazepine (cf.section 2.3). The trimethyl diazepine (2,2triMeNN) is similarly produced by sodium borohydride reduction in good yield (fig.53). This diazepine has previously been prepared by hydrogenation over Raney-nickel [23].

![Figure 53](image)

Unlike the analogous diazepine, the parent thiazepine (SN) is prepared directly from o-aminothiophenol and 1,3-dibromopropane without fear of polymerisation (fig.54)[55]. The 2-methyl and 2,2-dimethyl derivatives are prepared by LiAlH₄ reduction of the corresponding thiazepinones, as in the case of the diazepines. The synthesis of the new 2,2diMeSN is described in detail in the experimental section (3.14). The trimethyl thiazepine (2,2triMeSN) is prepared by sodium borohydride reduction of the dihydrothiazepine (cf.chapter 2)[52].
3.3 REACTION WITH ALDEHYDES

The reaction of aldehydes with secondary diamines has been well examined \[163,164\]. If sterically possible the aldehyde will readily form an intramolecular bridge between the two nitrogen atoms. Otherwise dimers or polymers may be formed. Thus N,N'-disubstituted-1,2-diaminoethanes and -1,3-diaminopropanes give imidazolidines and hexahydropyrimidines respectively \[165-168\]. The cyclic diamine piperazine remains in the chair conformation to yield polymers \[169\], whereas in diazacyclooctanes the nitrogen atoms are well-placed sterically for a bridging reaction and bicyclic structures result \[170,171\]. Many of these reactions occur exothermically at room temperature.
A brief investigation has been made into the reaction of the tetrahydrodiazepines with several aldehydes - formaldehyde, acetaldehyde, benzaldehyde and its derivatives. In no case does reaction occur spontaneously at room temperature. Generally, on warming or upon reflux, some reaction does occur but no pure product has been isolated. It is possible that the reactants polymerize to some extent. The nitrogen atoms in tetrahydro-1,5-benzodiazepines are conveniently placed for a bridging reaction, and although this brief attempt to obtain bicyclic structures met with no success, there is little doubt that given the correct conditions, such compounds could be made.

3.4 3-AMINO-2,3,4,5-TETRAHYDRO-1H-1,5-BENZODIAZEPINES

Interest has been shown recently [172-175] in the trigonally distorted 6-coordinate complexes of cis,cis-1,3,5-triaminocyclohexane and its derivatives [176,177]. An attempt was made therefore to prepare a 3-aminotetrahydrobenzodiazepine (fig.55), since similar trigonal-prismatic complexes might result from the use of this compound as a tridentate ligand. It is possible that the amino-group might assume the sterically unfavourable 'axial' position due to intramolecular hydrogen bonding to the ring nitrogen atoms - the so-called 'anomeric effect' [178].

Figure 55

Acetylacetone is treated with nitrous acid to yield the 3-isonitrosos derivative [179]. This diketone is then condensed with o-phenylenediamine to give the corresponding 3-hydroxyimino-diazepine [11]. However, reduction at room temperature by sodium
borylhydride fails to give the expected 3-amino-2,4-dimethyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine. After several attempts, a pale yellow solid (m.pt.~95°C) was isolated from the reaction mixture. Elemental analysis gives poor results and the NMR spectrum indicates two inequivalent methyl groups. The mass spectrum gives a molecular weight of 172 and the compound is considered to be a substituted quinoxaline. 3-Hydroxyimino-2,4-dimethyl-3H-1,5-benzodiazepine is known [180] to be very unstable, decomposing readily to quinoxalines and imidazoles. The preparation of this amino derivative has not been pursued further but it is suggested that a successful route might go via succiniminoacetylacetone [181].
3.5 VIBRATIONAL SPECTRA

The vibrational spectra of the diazepines are very similar to one another. The spectrum of the 2-methyl- derivative is illustrated as an example on the following page (fig. 56), with the analogous thiazepine spectrum (fig. 57) for comparison. The spectra of the two dimethyl and the trimethyl diazepines include absorption bands characteristic of hydrogen-bonded water molecules — there is broad absorption in the region of 3350 cm$^{-1}$ and broad bands at 1660-70 cm$^{-1}$ and 795-805 cm$^{-1}$.

All the diazepines show two characteristic strong sharp bands at ~3315 and ~1592 cm$^{-1}$. The former is due to the N-H stretching of the secondary amine group, while the latter occurs, although weaker, at the same frequency in the dihydrodiazepine and is assigned to an aromatic skeletal vibration. The bending vibration of secondary amines is usually masked by the aromatic skeletal vibrations and may be present under the band at ~1592 cm$^{-1}$.

The compounds exhibit sharp bands just below 3000 cm$^{-1}$ due to the C-H stretching of the methylene and methyl groups of the seven-membered ring. The very weak bands at 1758, 1787, 1830, 1860 and 1891 cm$^{-1}$ are characteristic of o-disubstituted benzene rings, as is the strong band at 750 cm$^{-1}$. The spectra include many sharp bands between 800-1200 cm$^{-1}$ due to the skeletal vibrations of the heterocyclic ring; these bands vary with methyl substitution at various sites.

The difference between the vibrational spectra of a diazepine and thiazepine is illustrated on the following page. The increase in $\nu$(N-H) to ~3340 cm$^{-1}$ and the decrease in frequency of the 1592 cm$^{-1}$ band is general throughout the series examined (a similar change is observed in the dihydroderivatives). As might be expected the bands in the region 800-1200 cm$^{-1}$ are slightly different in the two spectra but the overall appearance remains the same.
The mass spectra of four benzodiazepines are illustrated on the following page (fig. 59). The progressive methyl substitution makes assignment of the peaks and the construction of possible fragmentation patterns relatively easy. 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 133. As the methyl substitution is increased the abundance of the m/e 133 peak relative to the m/e 119 peak increases (table 22) and the ions are therefore assigned the benzimidazolidine structures shown in figures 58 and 60. The base peak in the spectra of some 3-hydroxy-2,3,4,5-tetrahydro-1,5-benzoxazepines [182] may be assigned to an analogous benzoxazolidine ion.

Table 22

<table>
<thead>
<tr>
<th>Diazepine</th>
<th>m/e 119 %</th>
<th>m/e 133 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>NN</td>
<td>96</td>
<td>4</td>
</tr>
<tr>
<td>2MeNN</td>
<td>83</td>
<td>17</td>
</tr>
<tr>
<td>24dimeNN</td>
<td>69</td>
<td>31</td>
</tr>
<tr>
<td>224trimeNN</td>
<td>35</td>
<td>65</td>
</tr>
</tbody>
</table>

Figure 58 Initial breakdown of the methyl-benzodiazepines e.g. 24dimeNN

\[
\text{Initial breakdown of the methyl-benzodiazepines e.g. 24dimeNN}
\]

\[
\text{m/e 119}
\]

\[
\text{m/e 133}
\]

\[
\text{CH}_3
\]

\[
\text{CH}_3
\]

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\text{CH}_3
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\text{CH}_3
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Figure 60  Fragmentation of 24diMeNN

m: indicates that a metastable ion is observed at m/e given.
? : indicates a possible route, no metastable ion observed.
The initial breakdown of the diazepines is predicted to occur by removal of an electron from a nitrogen atom and emission of a methyl radical. Olefin molecules can then break away to give the stable benzimidazolidinium ions. Only one alkyl radical is emitted before loss of the alkene, i.e. although the \( \text{M} - 2\text{CH}_3 \) peak is abundant in each case, the \( \text{M} - 2\text{CH}_3 \) is always very weak. Subsequent loss of acetonitrile or hydrogen cyanide yields the relatively abundant m/e 92 ion. This ion may be formulated either as in figure 60, or as an azatropylium ion. Further loss of hydrogen cyanide gives the cyclopentadienyl ion m/e 65 and progressive loss of CH yields in turn \( \text{C}_4\text{H}_4^+ \) and \( \text{C}_3\text{H}_3^+ \) as usual [183]. The peak at m/e 41 which becomes more abundant as methyl substitution increases corresponds to the allylic carbonium ion \( \text{CH}_2=\text{CH}-\text{CH}_2^+ \) from propene which in turn arises in the formation of the benzimidazolidinium ions (fig. 58).

Figure 61

To some extent, the breakdown patterns of the thiazepines are analogous. An example is shown in figure 62 and the corresponding spectrum is illustrated above in figure 61. As expected, the \( \text{C}_6\text{H}_5\text{S}^+ \) ion at m/e 109 occurs to the exclusion of the \( \text{C}_6\text{H}_5\text{NH}^+ \) ion at m/e 92 in all the thiazepine spectra. This ion arises by the loss of
hydrogen cyanide from the thiazolidinium ion (base peak m/e 136).
It is interesting that the 2-methylthiazolidinium ion (m/e 150) is
less abundant than its imidazolidinium analogue. Unlike in the
diazipine spectra, the unsubstituted 5-membered heterocycle (m/e 136)
remains the base peak throughout the series of thiazepines
examined. For example, in the 2-methyl-thiazepine spectrum, the
peak at m/e 150 is only 6% of the base peak at m/e 136. In this
latter compound there is an anomalous peak at m/e 146 which most
probably occurs through loss of SH⁻. The M-CH₃ peak 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-CH₃ by expulsion of ßH₃ is impossible, instead the
molecular ion may lose an olefin molecule directly to give the
ion m/e 151 which could then breakdown to either m/e 150 or m/e 136.
Most of the degradation routes illustrated above (fig.62), in
which neutral fragments break away, are supported by metastable peaks.
3.7 NUCLEAR MAGNETIC RESONANCE SPECTRA

3.7.1 Introduction

The NMR spectra of the compounds are considered in some detail. After a brief description of the method of operation of the LAOCN3 program [184] used in most of the analyses, the spectrum of each compound is described in turn. The evaluation of chemical shifts and coupling constants, and some variable temperature studies, provide interesting information concerning the structures of the heterocycles. Correlation of the data is discussed at the end of the section. All the compounds are conveniently soluble in solvents such as CCl₄, CDCl₃, CD₂Cl₂ and hexachlorobutadiene.

The spectra of the unsaturated diazepines are included in this section for convenience and the three oxidation states are illustrated in figure 64 on the following page. Although an increase in saturation is normally associated with an increase in geometrical flexibility of a given series of molecules, these spectra illustrate to some extent a reverse situation – both the 2,4-dimethyl- and 2,2,4'-trimethyl-2,3-dihydro-diazepines invert rapidly at room temperature whereas the tetrahydro-diazepine (24diMeNN) exists in a fixed conformation. In the first two compounds the methyl groups are held apart and are equivalent in both conformations but in the tetrahydro-diazepine one conformation involves serious axial-axial interference, preventing inversion. This is illustrated in figure 63.

Figure 63

![Diagram of diazepines showing conformational changes](image-url)
This program has two functions, of which the second is necessarily dependent upon the first. From a given set of chemical shifts and coupling constants for up to seven nuclei \((I = \frac{3}{2})\), the program will generate the line frequencies and intensities of a theoretical spectrum. If this spectrum is similar to the experimental spectrum and the individual lines can be matched, the program will then calculate by iteration the set of chemical shifts and coupling constants which give the best least-squares fit to the experimental line frequencies. Intensities are not considered in the iterative calculations but provide a final check on the validity of the assignments made. Not all lines need be matched, neither need every parameter be varied in the iteration. A different 'isotopic' number (arbitrary integer) can be assigned to protons between which the chemical shift is large, i.e. the program will generate a first-order spectrum if required.

Although degenerate lines are probably best omitted from the iterative calculation, and reliance is placed on those peaks which represent a single transition, sometimes this is not possible. In analysing the spectrum of 2,4-dimethyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine, for example, some degenerate lines could be omitted from the final iteration. However, the 47 observed lines in the \(H_a,b,d,e,f\) part of the spectrum of 2-methyl-2,3,4,5-tetrahydro-1,5-benzothiazepine (fig. 72) represent 128 transitions (119 are experimentally degenerate) and omission is obviously impossible. In this particular case, all transitions under a given peak are assigned the same frequency (although one transition is omitted).

Probable errors in the parameters are calculated by the program - on average these errors are no more than 0.0003\(\delta\) in the chemical shifts and 0.045 Hz in the coupling constants.
Examination of the spectrum (fig. 64) immediately suggests the assignment indicated. Integration confirms this assignment; from 10 to 08 the peaks have areas 4,2,2,2 and 6 respectively. The integration further suggests that little, if any, of the $H_{a,b}$ multiplet is obscured by the methyl resonance. Spinning side bands of the methyl resonance complicate the spectrum and coincide with two lines of the $H_{a,b}$ multiplet – the positions of the side bands are determined by a series of measurements at different spinning rates. Parts of the spectrum are shown expanded, with the theoretical spectrum, below in figure 65.

Before undertaking precise analysis, some information concerning the structure may be derived from the appearance of the spectrum. The methyl resonance suggests magnetic equivalence of

Figure 65
of the methyl groups, indicating a chair or boat conformation and ruling out a twist-boat form. The implied symmetry means magnetic equivalence of the Hd protons and this is confirmed by the shape of the Hd multiplet. Neglecting the methyl groups, the spectrum is essentially of the type $\text{ABX}_2$ [185].

Assuming the Hd multiplet to be first-order (justified by analysis since the 60kHz spectrum is very similar) and knowing $J_{cd} \approx 6.4\text{Hz}$ from the methyl resonance, yields $|J_{ad} + J_{bd}| \approx 12.7\text{Hz}$. Assuming the same relative sign, manual iteration gives $J_{ad} \approx 10.5$ and $J_{bd} \approx 2.2\text{Hz}$. Assignment of the AB quartet (illustrated) in the Hab multiplet yields $J_{ab} \approx 13\text{Hz}$ and $\Delta \nu_{ab} \approx 19\text{Hz}$. Substitution of these parameters into LACCN3 gives a reasonable fit but incorrect line assignments. Adjustment of $\delta a$ and $\delta b$ gives the correct assignments. It should be noted that the second part of the program cannot be used unless the correct assignments have been made. In the final analysis some of the degenerate lines are omitted from the iteration; the parameter set found to give best agreement is tabulated below (table 23).

Table 23

<table>
<thead>
<tr>
<th>Chemical shifts (\delta ppm)</th>
<th>Coupling constants (Hz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ha 1.3813</td>
<td>Jab (-)12.87</td>
</tr>
<tr>
<td>Hb 1.5786</td>
<td>Jad 10.35</td>
</tr>
<tr>
<td>Hc 1.2150</td>
<td>Jbd 2.03</td>
</tr>
<tr>
<td>Hd 2.7572</td>
<td>Jcd 6.42^*</td>
</tr>
<tr>
<td>He \sim 3.20</td>
<td>all others assumed zero</td>
</tr>
</tbody>
</table>

*assuming first-order c-d coupling

*spin-decoupling confirms the coupling of Hc and Hd
3.7.4 2,2,4-Trimethyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine and -1,5-benzothiazepine

The two trimethyl heterocycles give recognisable ABX type spectra [186]; part of the thiazepine spectrum is illustrated below in figure 66.

Neglecting the methyl groups, analysis of the spectra show the chemical shifts of the Ha,b protons to be reversed with respect to the dimethyl derivative. In both spectra the axial proton is at lower field than the equatorial proton. The initial assignment of the two overlapping quartets characteristic of ABX spectra is shown in figure 66. The alternative assignment of the AB transitions gives unrealistic values for Jad and Jbd, which would then be of opposite sign and incompatible with the structure of the Hd multiplet (Jad $\pm 11.3$, Jbd $\mp 4.7$Hz). Substitution of the parameters obtained in the LAOCN3 program gives excellent fits.

Figure 66
Chemical shifts (δppm)   Coupling constants (Hz)

| Chemical  |   | Coupling constants (Hz) |
|-----------|-----------------------------|
| Ha        | 1.8434                      | Jab (-) 13.69 |
| Hb        | 1.6528                      | Jad 10.55 |
| Hc        | 1.2060*                     | Jbd 2.09 |
| Hd        | 3.5125*                     | Jcd 6.58* |
| He       | 1.3890*                     | all others assumed zero |
| Hf       | 1.1895                      | |
| Hg        | ~3.22                       | |

Table 25

Chemical shifts (δppm)   Coupling constants (Hz)

| Chemical  |   | Coupling constants (Hz) |
|-----------|-----------------------------|
| Ha        | 1.6274                      | Jab (-) 13.20 |
| Hb        | 1.4643                      | Jad 10.82 |
| Hc        | 1.1420*                     | Jbd 2.11 |
| Hd        | 3.2903*                     | Jcd 6.28* |
| He       | 1.2440*                     | all others assumed zero |
| Hf       | 1.0485                      | |
| Hg        | ~3.04                       | |

*assuming first-order coupling between Hc and Hd.

To check the assignment of the Hd multiplet the 6-spin system \(-\text{CH(CH}_3\text{)}_{2}\text{CH}_2\) was considered, both assuming an infinite chemical shift between Hc and Hd and allowing for a finite shift. The two theoretical spectra are very similar (the errors involved in the chemical shifts are: Ha,b <0.002Hz; Hd +0.147Hz; and
He -0.05Hz; the errors in the coupling constants are negligible. The first-order assumption is therefore justified. The similarity of the Hδ multiplets in the spectra of the dimethyl and trimethyl diazepines justifies the first-order assumption in the former and indicates a similar structure for both molecules.

The spectrum of the thiazepine was observed at intervals of 15°C up to a temperature of 140°C, when decomposition occurs. No coalescence of peaks occurs, although the Hα methyl resonance peaks shift slightly to higher field and the NH peak broadens.

### 3.7.5 2,2-Dimethyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine and 1,5-benzothiazepine

Both spectra show only one methyl resonance and exhibit symmetrical multiplets at approximately 1.8 and 2.16 (eg. thiazepine spectrum figure 70) indicating that some form of ring inversion is taking place. The splitting of the multiplets in the spectra of both diazepine and thiazepine is not simple however and suggests some restriction on the structures of the conformers involved. If complete rotation of the \(-\text{CH}_2-\text{CH}_2\)- group occurs, a simple \(A_2X_2\) (or \(A_2B_2\)) spectrum is expected (fig. 67).

**Figure 67**

\[
\begin{array}{c}
\text{H}_{12}^{11} & \text{H}_{11}^{11} & \text{H}_{11}^{11} & \text{H}_{11}^{11} \\
910 & 617 & 314 & \text{41}
\end{array}
\]

- **Observed at 60MHz**
  - thiazepine Hz: 5.30, 5.46, 5.70, 77.97
  - diazepine Hz: 5.31, 5.70, 78.50

\[
\begin{array}{c}
\text{310} & \text{261} & \text{322} & \text{244}
\end{array}
\]
The presence of additional lines indicates that although the protons of each methylene group show chemical equivalence, they are magnetically inequivalent. The same pattern is observed at both 60 and 100 kHz. The situation may then be represented by the spin system AA'XX' (strictly AA'BB') and 10 (or 12) transitions should be observed in each multiplet [187]. That so many lines are not present suggests that some coupling constants are either equal, or zero.

Examination of a Dreiding molecular model shows clearly that throughout a series of various inversions through chair, boat and twist-boat conformers only two possible configurations exist in which the relation between the two methylene groups is different. These are illustrated in figure 68. The various inversion mechanisms are discussed at a later stage (section 3.7.11).

Figure 68 View along the C-C bond connecting the two methylene groups

![Diagram of molecule with labels](image)

<table>
<thead>
<tr>
<th>Configuration</th>
<th>Expected coupling constants</th>
</tr>
</thead>
<tbody>
<tr>
<td>X' gauche to A</td>
<td>( J_{AX'} = J_{A'X} \approx J_{\text{gauche}} \approx 2 \text{Hz} )</td>
</tr>
<tr>
<td>trans to A'</td>
<td>( J_{AX} = J_{A'X'} \approx \frac{1}{2} (J_{\text{gauche}} + J_{\text{trans}}) \approx 7 \text{Hz} )</td>
</tr>
<tr>
<td>X' gauche to A'</td>
<td>( J_{AA'} = J_{XX'} \approx J_{\text{gem}} \approx (-)13 \text{Hz} )</td>
</tr>
<tr>
<td>X' never trans to A</td>
<td></td>
</tr>
<tr>
<td>X never trans to A'</td>
<td></td>
</tr>
</tbody>
</table>
This limit on possible configurations becomes clearer when it is realised that the endocyclic bonds must always remain gauche. The conformations are of equal energy and occur with equal frequency along the inversion path. Thus $J_{AX}'$ is expected to have a value approximately equal to the average of $J_{\text{trans}}$ and $J_{\text{gauche}}$, whereas $J_{AX}$ is expected to have a value $\sim J_{\text{gauche}}$. Typical values taken from the spectra already analysed are summarized in table 26. Use of these parameters generates a theoretical spectrum which shows a satisfying similarity to the observed spectrum. Values of the parameters obtained from AA'BB' analyses by LAOCN3 are included in tables 27 and 28. $J_{ab}$ and $J_{ef}$ cannot be calculated since transitions 5 and 8 [187] are not determined accurately and transitions 6 and 7 are degenerate. Only estimates of these parameters are given in the tables below.

Table 27

<table>
<thead>
<tr>
<th>Chemical shifts (δ ppm)</th>
<th>Coupling constants (Hz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$H_a, H_b$</td>
<td>1.8828</td>
</tr>
<tr>
<td>$H_e, H_f$</td>
<td>3.1708</td>
</tr>
<tr>
<td>$H_c$</td>
<td>1.29</td>
</tr>
<tr>
<td>$H_g$</td>
<td>3.71</td>
</tr>
<tr>
<td>$J_{ab}, J_{ef}$</td>
<td>$\sim(-)13.71$</td>
</tr>
<tr>
<td>$J_{ae}, J_{bf}$</td>
<td>8.22</td>
</tr>
<tr>
<td>$J_{af}, J_{be}$</td>
<td>2.57</td>
</tr>
<tr>
<td>all others assumed zero</td>
<td></td>
</tr>
</tbody>
</table>

Table 28

<table>
<thead>
<tr>
<th>Chemical shifts (δ ppm)</th>
<th>Coupling constants (Hz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$H_a, H_b$</td>
<td>1.6186</td>
</tr>
<tr>
<td>$H_e, H_f$</td>
<td>2.9117</td>
</tr>
<tr>
<td>$H_c$</td>
<td>1.09</td>
</tr>
<tr>
<td>$H_g$</td>
<td>3.35</td>
</tr>
<tr>
<td>$J_{ab}, J_{ef}$</td>
<td>$\sim(-)15.63$</td>
</tr>
<tr>
<td>$J_{ae}, J_{bf}$</td>
<td>8.34</td>
</tr>
<tr>
<td>$J_{af}, J_{be}$</td>
<td>2.73</td>
</tr>
<tr>
<td>all others assumed zero</td>
<td></td>
</tr>
</tbody>
</table>
The results of a low temperature study of the thiazepine spectrum are illustrated on the left (fig. 69). It was hoped that the 'freezing out' of a molecular conformation would occur within the temperature range studied. Despite this, the spectra indicate that the barrier to 'C2 wagging' is higher than the barrier to 'C3 wagging' and an estimate of the energy barrier to inversion may be made from the broadening of the methyl resonance. This is discussed further in section 3.7.11.
3.7.6 2-Methyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine and 1,5-benzothiazepine

Both spectra are shown on the preceding page (fig. 70 - inset is a 60KHz spectrum for comparison). Although apparently complicated, the 100KHz spectra are treated initially by a first-order analysis. The Ha,b part of the diazepine spectrum has proved to be the most difficult to analyse due to extensive overlapping of the multiplets, degeneracy of many of the observed transitions and the complication of spinning side bands. This part of the spectrum is shown expanded below (fig. 71).

In the spectrum of the thiazepine (fig. 70 and 72), the 11-line multiplet, known to be characteristic of the Hd proton, is quickly recognized and yields $|J_{ad} + J_{bd}| \approx 14.07$Hz. The two remaining peaks at low field derive from an AB system split further into well-defined multiplets of eight lines. To a first-order approximation,

Figure 71
the lower involves coupling constants of 13.72, 8.24 and 3.61 Hz, and the higher involves coupling constants of 13.84, 6.46 and 3.81 Hz. These two multiplets are assigned to the C2 methylene group. On the basis of previous spectra, the high field multiplets are assigned to the C3 methylene group. Analysis gives the coupling constants 13.40, 10.07, 3.50 and 6.53 for the higher multiplet of the C3 group and 13.20, 4.04, 8.28 and 3.83 Hz for the lower. Since J_{ad} is expected to be ~10 Hz (Ha trans to Hd), the higher multiplet is assigned to Ha and thus: J_{ab} \approx (-)13.30, J_{ad} \approx 10.07, J_{ae} \approx 3.55, J_{af} \approx 6.49, J_{bd} \approx 4.04, J_{be} \approx 8.28, J_{bf} \approx 3.83, J_{ef} \approx (-)13.78. Substitution of these parameters into LA0CN3, with subsequent iteration, gives the set of values listed in table 29. The observed and calculated spectra are compared in figure 72.

Analysis of the diazepine spectrum follows the same lines as described for the thiazepine spectrum. The chosen parameters are decided upon by a trial and error construction of the theoretical Ha,b AB multiplet assuming that the first-order values of Jae, Jaf, Jbe and Jbf are sufficiently accurate and assuming that Ha is at higher field than Hb. The coupling constants have been used in LA0CN3 to calculate the second-order spectrum (type ABCDE). Although in the incorrect order*, the lines are matched and the parameter set obtained after iteration is given in table 30. The spectrum of the diazepine at 135°C indicates that the conformation is still fixed at this temperature.

*(When a spectrum approximates to first-order, comparison of the line frequencies and intensities of the observed and calculated spectra enables the correct assignment of individual lines even though the multiplets may overlap to a different extent in each - giving rise to an incorrect order in the line frequencies)
### Table 29

<table>
<thead>
<tr>
<th>Chemical shifts (δppm)</th>
<th>Coupling constants (Hz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hα 1.6947</td>
<td>Jab (-)13.44</td>
</tr>
<tr>
<td>Hβ 2.0891</td>
<td>Jad 10.36</td>
</tr>
<tr>
<td>Hε 1.2911*</td>
<td>Jae 3.34</td>
</tr>
<tr>
<td>Hδ 3.2589*</td>
<td>Jaf 6.59</td>
</tr>
<tr>
<td>Hε 3.6705</td>
<td>Jbd 3.74</td>
</tr>
<tr>
<td>Hf 2.9238</td>
<td>Jbe 8.42</td>
</tr>
<tr>
<td>Hg ~3.60</td>
<td>Jbf 3.88</td>
</tr>
<tr>
<td></td>
<td>Jcd 6.94*</td>
</tr>
<tr>
<td></td>
<td>Jef (-)13.80</td>
</tr>
<tr>
<td></td>
<td>all others assumed zero</td>
</tr>
</tbody>
</table>

### Table 30

<table>
<thead>
<tr>
<th>Chemical shifts (δppm)</th>
<th>Coupling constants (Hz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hα 1.5122</td>
<td>Jab (-)12.81</td>
</tr>
<tr>
<td>Hβ 1.7434</td>
<td>Jad 10.06</td>
</tr>
<tr>
<td>Hε 1.2332*</td>
<td>Jae 3.50</td>
</tr>
<tr>
<td>Hδ 3.0724*</td>
<td>Jaf 9.17</td>
</tr>
<tr>
<td>Hε 3.3434</td>
<td>Jbd 2.85</td>
</tr>
<tr>
<td>Hf 2.7373</td>
<td>Jbe 6.58</td>
</tr>
<tr>
<td>Hg ~3.25</td>
<td>Jbf 3.18</td>
</tr>
<tr>
<td></td>
<td>Jcd 6.52*</td>
</tr>
<tr>
<td></td>
<td>Jef (-)12.67</td>
</tr>
<tr>
<td></td>
<td>all others assumed zero</td>
</tr>
</tbody>
</table>

*assuming first-order Hε-Hδ coupling
3.7.7 2,3,4,5-Tetrahydro-1H-1,5-benzodiazepine and -1,5-benzo- 
thiazepine

As in the case of the symmetrically substituted 2,2-dimethyl- 
derivatives, these molecules invert rapidly at room temperature 
and time-averaged spectra are obtained. The diazepine spectrum 
shows two multiplets (eg.fig.74). Although less well resolved, 
the lower resembles the multiplets of the 2,2-dimethyl derivatives 
but the higher is more complicated, showing nine peaks. As 
previously, the higher-field multiplet is assigned to Ha,b and 
the lower-field multiplet to 2Hc,d; this is confirmed by 
integration.

Figure 73

<table>
<thead>
<tr>
<th>Chemical shifts</th>
<th>Hc,d</th>
<th>Hf.e</th>
<th>Hb,a</th>
</tr>
</thead>
<tbody>
<tr>
<td>(CH₂Cl₂ solution)</td>
<td>2.948</td>
<td>2.777</td>
<td>1.721</td>
</tr>
<tr>
<td>(CCl₄ solution)</td>
<td>3.179</td>
<td>2.777</td>
<td>1.885</td>
</tr>
</tbody>
</table>

The thiazepine spectrum illustrates the inequivalence of 
Hc,d and Hf.e. Comparison of the spectrum with the previous 
spectra indicates that the lower-field multiplet is due to the 
methylene group adjacent to the nitrogen atom. The inductive 
effect of the less electronegative sulphur atom tends to shield 
the Hc,d group, causing it to resonate at a higher field strength. 
The electronegativities of sulphur and carbon are approximately 
equal (~2.5 [188]) and the protons of the C2 methylene group 
should resonate at approximately the same frequency as they 
do in benzocycloheptenes (ie. δ≈2.60 ppm [189]). Again the 
lower-field multiplets consist of five peaks; the structure 
of the Ha,b multiplet is very similar for both diazepine and 
thiazepine.
Some low temperature spectra of the diazepine are shown in figure 74. This experiment was completed before the 2,2-dimethyl-tetrahydrobenzodiazepine had been prepared and it is not surprising in view of the failure of the 2,2-dimethyl- derivative to 'freeze out' in a particular molecular conformation, that this unsubstituted diazepine also failed to cease ring inversion (compare figure 69).

The possible structures for the inverting rings have been examined by Dreiding models. Although in the twist-boat conformation the two Hc (or Hd) protons of the diazepine are magnetically inequivalent, since their environment is averaged they are effectively equivalent. The population of the twist-boat conformation is immaterial to this argument because both twist-boat forms are of equal energy and must be equally populated. Thus each proton of the pairs Hc, Hc (and Hd, Hd) is involved to the same extent. Figure 75 illustrates the coupling constants involved in the diazepine.
Figure 75  View along the C-C bonds i) connecting C2 and C3 and ii) connecting C4 and C3

i)  

\[
\begin{array}{c}
A \quad X' \\
A' \\
X
\end{array}
\]

\[
\begin{array}{c}
A \quad X' \\
A' \\
X
\end{array}
\]

chair or boat conformation

ii)  

\[
\begin{array}{c}
A \quad X' \\
A' \\
X
\end{array}
\]

boat or chair conformation

\[
\begin{array}{c}
A \quad X' \\
A' \\
X
\end{array}
\]

twist-boat conformation

A equally trans or gauche to X
A always gauche to X'
A' always gauche to X
A' equally trans or gauche to X'

3.7.8 2,2,4-Trimethyl-2,3-dihydro-1,5-benzothiazepine and 1H-1,5-benzodiazepine

The spectrum of the diazepine is shown in figure 64 - the spectrum of the thiazepine is very similar although of course the NH peak is absent. Details are given below.

Figure 76

<table>
<thead>
<tr>
<th></th>
<th>Thiazepine</th>
<th>Diazepine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ha,b</td>
<td>2.20</td>
<td>Ha,b</td>
</tr>
<tr>
<td>Ha</td>
<td>2.37</td>
<td>Ha</td>
</tr>
<tr>
<td>Hb</td>
<td>1.46</td>
<td>Hd</td>
</tr>
<tr>
<td>NH</td>
<td>3.12</td>
<td></td>
</tr>
</tbody>
</table>
As mentioned in section 3.7.1, both molecules invert rapidly at room temperature owing to their symmetrical substitution. The spectrum of the diazepine has been studied at temperatures down to -90°C and the effect on the spectrum is illustrated in figure 77. The broadening of the lines may be used in an estimation of the energies of inversion; this is discussed at a later stage (section 3.7.11).
3.7.9 2,4-Diphenyl-2,3-dihydro-1,5-benzothiazepine and 1H-1,5-benzodiazepine

These compounds, unlike those just discussed, exist in a fixed conformation at room temperature owing to their unsymmetrical substitution. Both spectra include a simple ABX pattern due to the ring protons (fig. 78). Analysis gives the values for the fitting parameters listed in table 31. The assignment of the lines is shown in the figure — unrealistic coupling constants are obtained from the possible alternative assignment. The spectrum of the diazepine has been measured at temperatures up to 140°C; although the lines broaden slightly, no change was observed that could be attributed to ring inversion.

Figure 78

![Figure 78](image-url)
### Table 31

![Chemical structure diagram](image)

<table>
<thead>
<tr>
<th>Chemical shifts (δppm)</th>
<th>Coupling constants (Hz)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diphenyldihydrothiazepine</strong></td>
<td></td>
</tr>
<tr>
<td>Ha 3.0050</td>
<td>Jab (-)13.02</td>
</tr>
<tr>
<td>Hb 3.2256</td>
<td>Jac 12.48</td>
</tr>
<tr>
<td>He 4.9183</td>
<td>Jbc 4.60</td>
</tr>
<tr>
<td><strong>Diphenyldihydrobenzodiazepine</strong></td>
<td></td>
</tr>
<tr>
<td>Ha 2.9963</td>
<td>Jab (-)13.67</td>
</tr>
<tr>
<td>Hb 3.1746</td>
<td>Jac 8.78</td>
</tr>
<tr>
<td>He 5.1097</td>
<td>Jbc 3.54</td>
</tr>
</tbody>
</table>

### 3.7.10 Published Data

Extensive studies of 1,3-diimine systems, including the unsaturated benzodiazepines, have been made [64, 67, 190-192]. The results of some variable temperature studies on 2,4-disubstituted-1,5-benzodiazepines have been used [65] to calculate their free energies of inversion $\Delta G^\ddagger$ (table 32, cf. fig. 63). Similar studies have been made on 4H-1,2-diazepines [193].

### Table 32

<table>
<thead>
<tr>
<th>Diazepine</th>
<th>$T_0^\circ C$</th>
<th>$\Delta G^\ddagger$ kJmol$^{-1}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>2,4-dimethyl</td>
<td>0 + 10°C</td>
<td>52.7 + 2</td>
</tr>
<tr>
<td>2-methyl-4-phenyl</td>
<td>-12 + 7°C</td>
<td>51.1 + 2</td>
</tr>
<tr>
<td>2,4-diphenyl</td>
<td>-26 + 8°C</td>
<td>49.0 + 2</td>
</tr>
</tbody>
</table>
Of the 2,3-dihydro- heterocycles, only the spectrum of the 2,2,4-trimethyl- benzodiazepine has been reported previously [24,66].

Little work has been published concerning the tetrahydro-derivatives although the spectrum of the unsubstituted diazepine, 1N, has been reported [60] and the methyl resonances of the two isomeric N,N'-dibenzoyl-2,4-dimethyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepines have been examined at 29.92 MHz [62]. Generally the diazepinones have received greater attention [30,60,65].

The analogous 6-membered pyrimidine (fig. 79.1) has been shown to oscillate only at the 2-position [167]. The molecule therefore exists as an equilibrium between chair and boat conformations. The spectrum of cis-5,7-dimethyl-hexahydro-1,4-diazepin-2-one (fig. 79.2) has been analysed assuming first-order coupling [194]. The parameters derived agree reasonably well with the values obtained from the spectrum of 2,4-dimethyl-tetrahydro-1H-1,5-benzodiazepine. Thus \( J_{\text{gem}} \approx 14.2 \text{ Hz} \), \( J_{\text{trans}} \approx 10.5 \text{ Hz} \), \( J_{\text{gauche}} \approx 3.0 \text{ Hz} \) and \( J_{\text{CHCH}_3} \approx 6.5 \text{ Hz} \).

Figure 79
3.7.11 Discussion

When a molecule undergoes a conformational change, the magnetic and chemical environment of individual protons may also change. The rate at which the conformational change takes place can in some cases be calculated from the NMR spectrum of the molecule [195-197]. If the exchange rate is slow, or if no exchange occurs, then the spectrum consists of a superposition of the spectra of the conformers present. If the exchange rate is fast then the signals observed depend upon the weighted-mean magnetic environment of the nuclei. At an intermediate exchange rate, the inverse of which is comparable to the 'NMR time scale' [198], the shape of the resonance peaks is affected; broadening and coalescence may occur. The appearance of the spectrum of two exchanging nuclei depends upon the rate of exchange, $K$, and the chemical shift difference of the two nuclei in the absence of exchange, $\Delta \nu$. In this work only the two extremes are encountered: molecules which invert rapidly at temperatures down to -90°C, and molecules which remain in fixed conformations up to temperatures ~140°C, when they generally decomposed. For neither type has a coalescence temperature been reached.

In one instance, 2,2,4-trimethyl-2,3-dihydro-1H-1,5-benzodiazepine (section 3.7.8, fig.77, p.108), an attempt has been made to obtain an estimate of the free energy of inversion $\Delta G^+$ by use of the fast-exchange approximation [199]:

\[
\text{Rate Constant } K = \frac{\pi \Delta \nu^2}{2 \omega}
\]

where $\omega$ is the corrected width at half-height of the exchanging proton resonance peak. The internal reference peak of TMS has been used to determine the extent of broadening by factors other than exchange (e.g. viscosity, field inhomogeneity), and the value for $\Delta \nu$ taken from the data on the saturated diazepine ($\approx 11.7 \text{Hz}$ at 60MHz). The 4-methyl group appears to exchange between two equilibrium positions and is not used as the reference peak.
In transition state theory, the rate of conformational change depends upon the rate at which the molecules pass over the potential barrier separating the two conformers:

$$\text{Rate constant } K = \kappa \left( \frac{k_B}{h} \right) K^*$$

where $K^*$ = an equilibrium constant describing the relative concentration of activated molecules at $T^\circ K$, and $\kappa$ = a transmission coefficient - this depends upon the exchange pathway: if there is no intermediate metastable state, then the value is taken as unity, whereas if the molecule passes through a metastable state then $\kappa = 0.5$. This represents the fact that even though the molecule may cross the first potential barrier there is only a 50% probability of it crossing the second, since it may equally well return over the first.

Free energy change $\Delta G^* = -RT\ln K^*$

Calculation of $\Delta G^*$ from the broadening of the 2,2-dimethyl resonance gives a value of 38.5 kJmol$^{-1}$ at 90°C. A plot of $\ln \left( \frac{K}{T} \right)$ vs. $\frac{1}{T}$ shows a slight curve instead of the expected straight line and indicates some inaccuracy in the measurements. The value obtained is of the order expected although probably too high.

Calculations on other low temperature spectra are not considered to be worthwhile. Qualitatively, the appearance of the low temperature spectra of the symmetrically substituted 2,2-dimethyl diazepine and thiazepine (fig.69, p.99) clearly indicates that the inversion at C4 slows down before inversion at C3, although in the unsubstituted diazepine the rates appear to be approximately equal (fig.74, p.106).

Several similar molecules have been studied previously by variable temperature NMR. Usually estimates of the free energy of inversion $\Delta G^*$ have been calculated from the coalescence temperature when:

$$\text{Rate constant } K = \frac{\pi \Delta \nu}{V^2} \quad [199]$$
It is now understood that in benzocycloheptene and its heterocyclic derivatives there are three possible conformations (fig. 80) [198].

Figure 80®

Chair  Boat  Twist-boat

°the double bond represents the position of the benzene ring which is omitted for convenience.

In most cases the chair conformation is the most stable. Figure 81 illustrates some pertinent molecules which have been previously studied [200-205] (excluding asymmetric molecules). The stability of the chair form of 1,5-heterocycles, relative to the analogous hydrocarbon - benzocycloheptene, is generally increased due to the absence of 1,5- substituents.

Figure 81
Like the unsubstituted benzodiazepine, both cycloheptene and 1,5-benzodioxepane invert rapidly at room temperature. The peaks of the cycloheptene however coalesce at -80°C and the chair form is the stable conformer at low temperatures [203].

The chair form is not always the only stable conformer; for example, 3,3-dimethyl-benzodithiepane exists as a mixture of chair and twist conformers at -80°C [200] and the chair and boat forms are approximately equal in energy in the 3,3,6,6-tetramethylcycloheptene (fig. 81) [205]. Generally the oxygen heterocycles have lower activation energies than the benzocycloheptenes and the sulphur derivatives and it is apparent from the work reported here that the analogous diazepines and thiazepines also have low activation energies, presumably due to facile nitrogen inversion.

It is clear from the molecules illustrated in figure 81 that it is largely the extent and position of methyl substitution that governs which conformer is the most stable. For example, in a boat form of the 3,3-dimethyl derivatives there would be serious interference between a methyl group and the benzene ring; the seven-membered ring would tend to twist to avoid this and in both the gem-dimethyl cycloheptene and dithiepane the twist conformer is more stable than the boat conformer. The opposite is the case in the tetramethyl-benzocycloheptenes: the boat form is more stable than the twist form due to serious interaction of the methyl groups in the latter. In all these gem-disubstituted molecules one of the most stable conformers is always the chair.

The relative stabilities of the individual conformers governs the ease of inversion since the chair conformers can only invert through either the twist or boat forms. A diagram representing the various inversion mechanisms is shown in figure 82. 'XX inversion' represents inversion at both heteroatoms. 'Rotation' represents the sequential rotation of the individual X1-C2, C2-C3, C3-C4, and C4-X5 bonds and generally requires a low activation energy. For example, two equilibria have been distinguished [200] for the 3,3-dimethyl-1,5-benzodithiepane: \( \Delta G^\ddagger_{\text{chair}} = \text{twist} \approx 53 \text{ kJmol}^{-1} \) and \( \Delta G^\ddagger_{\text{rotation}} \approx 35 \text{ kJmol}^{-1} \).
The inversion path is generally accepted to be chair = boat* =
twist or twist* = boat = chair* [198] but in nitrogen heterocycles
the conversion of a chair form to a twist form directly, through a
facile nitrogen inversion, cannot be neglected. It is clear that
the nitrogen atoms do lower the inversion barrier between the two
chair conformers. The descriptions of the mechanisms in figure 82
are to some extent artificial. For example, a C4 wag may be more
accurately described as a single N-inversion with a slight rotation
of the N5-C4 bond. Again, what is described as N-inversion is not
a complete nitrogen inversion but a N 'wag'.
The asymmetrically substituted heterocycles exist in fixed conformations at room temperature. In each case analysis of the spectrum yields values for the coupling constants and chemical shifts which may be useful as standards in the conformational studies of related molecules.

The chemical shifts are generally as expected, with the 'axial' protons usually at higher field than the 'equatorial' protons. The reason for this has been ascribed to the magnetic anisotropy of the parallel 1,2 and 5,4 bonds (fig. 83.1) [206,207]. Only in one case is the situation reversed: in both 2,2,4-trimethyl-tetrahydroheterocycles the 'axial' proton is less shielded than the 'equatorial' proton and resonates at lower field. This may be due to the magnetic anisotropy of the parallel CH-CH$_3$ bond (fig. 83.2).

Figure 83

Another general feature is the shift downfield of the C3 protons, particularly the 'equatorial' proton, in the thiazepine spectra compared to the diazepine spectra. This may be attributed to the differing anisotropy of the C-S bond *(see footnote, next page)*. The reverse effect would be expected if only the inductive effect of the less electronegative sulphur atom were considered (see eg. section 3.7.7, p.105). The greater separation of the Ha,b protons in the spectra of the thiazepines makes their analysis considerably easier than the spectra of the corresponding diazepines.

The coupling between two protons depends essentially upon the hyperfine interactions between the spins of the nuclei and the electrons in the intermediate bonds [208]. In this work the vicinal coupling constants are considered in most detail. In none of the heterocycles is there evidence of coupling extending beyond three
bonds, although such coupling may lead to the broadening of some lines. Karplus, in a valence-bond treatment [209], has derived an expression relating the dihedral angle between two vicinal protons with their spin-spin coupling constant (eqn.1). The solution of the 6-valence-electron system (fig.84.1) involves an exchange integral for the central C-C bond which depends in part on the dihedral angle between the two planes H_1C_1C_2 and C_1C_2H_2 (fig.84.2). The relation of the exchange integral with the dihedral angle determines the angular dependence of the vicinal coupling constant. The original Karplus equation has been slightly modified (eqn.2) [210-212] and it has been emphasized [210-213] that the equation is applicable only in the absence of variation in the C-C bond length, deviation from the tetrahedral angle H\_1\_C\_C\_2\_1\_\_2, θ, and alternative substitution (particularly with substituents of different electronegativity) since these also affect the integrals involved and hence the coupling constants.

Figure 84

* Certain groups, eg. the N-C and S-C single bonds in this case, allow the circulation of electrons only in certain preferred directions. In an applied field these electron currents give rise to zones of unequal magnetic field strength which either diminish or reinforce the applied field in a particular region. In rigid cyclic structures of fixed conformations, anisotropic shielding is important because a proton having a fixed geometrical relationship to a magnetically anisotropic group experiences a constant shielding or deshielding effect. Since the magnetic anisotropy of a group depends on the electron distribution within the group, it is not surprising that the effect of the N-C and S-C bonds differ.
Although a too-literal calculation of angles from the equation is dangerous [210], the relationship is very useful for a comparative study within a given series.

\[
\begin{align*}
J_1 &= k_1 \cos^2 \varphi + c \quad (0 \leq \varphi \leq 90^\circ) \\
J_2 &= k_2 \cos^2 \varphi + c \quad (90^\circ \leq \varphi \leq 180^\circ) \\
\end{align*}
\]

where \( k_1, k_2 \) and \( c \) are empirical constants

\[
J = a (\cos^2 \varphi + n \cos \varphi) \quad (0 \leq \varphi \leq 180^\circ)
\]

where \( a \) and \( n \) are empirical constants

In the majority of the NMR spectra recorded in the present work there are insufficient coupling constants available to solve the Karplus equation (2) rigorously. Some relationships may however be derived by a qualitative treatment.

Since there is only one methyl resonance in the spectrum of the 2,4-dimethyl diazepine, this molecule must exist in a chair conformation with diequatorial methyl groups (fig.85.1). The only other feasible conformation is the twist-boat form of the 2a,4e-isomer (fig.85.2) but in which the Ha,b protons would be chemically equivalent. The coupling constants of this diazepine are typical of large saturated rings and fit typical Karplus curves (fig.86,87).

Figure 85

There is no direct evidence for assuming a similar structure in the trimethyl derivatives but several reasons corroborate such an assumption. Firstly, the coupling constants are very similar to those of the dimethyl diazepine: Jad = 10.35, 10.55 and 10.82 Hz; Jbd = 2.03, 2.09 and 2.11 Hz. Secondly, the interchange of \( \delta \)Ha and
δHb would probably not occur in the alternative twist-boat conformation. Thirdly, at least one methyl group would experience steric hindrance in the twist-boat form, despite the absence of 1,5-sustituents. Fourthly, no change is observed in the high temperature NMR spectra - changes would be expected for the more flexible twist conformer.

Since at least one of the methyl groups in the trimethyl derivatives must be 'axial', a slight flattening of the chair conformation to alleviate the 2,4-diaxial interference might be expected. This flattening of the ring relative to the dimethyl derivative should cause a decrease in Jad and an increase in Jbd (fig.86) - the latter, on a steep section of the Karplus curve, should be more noticeable.

Figure 86

In fact such a change in the coupling constants is not observed. To account for this it is suggested that the dimethyl derivative is itself more puckered than the ideal chair structure - this is confirmed by examination of Dreiding molecular models. The additional substituent in the 'axial' position now distorts the ring into, or slightly past the ideal chair conformation. This effect is illustrated in figure 87.

Figure 87.  View from C2 to C3 (exaggerated)

<table>
<thead>
<tr>
<th></th>
<th>Dimethyl</th>
<th></th>
<th>Trimethyl</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jad</td>
<td>10.35</td>
<td>Jad</td>
<td>10.82</td>
</tr>
<tr>
<td>Jbd</td>
<td>2.03</td>
<td>Jbd</td>
<td>2.11</td>
</tr>
</tbody>
</table>
Whereas substitution of C for N in saturated rings causes little distortion because of the similarity in bond lengths and bond angles, since the C=S bond length (~1.82 Å) is greater than the C=N bond length (~1.42 Å), and a typical C=S (~100°) is smaller than the more tetrahedral C=N [178], asymmetry occurs in the thiazepine ring - molecular models indicate that the sulphur side of the molecule is slightly flattened in comparison to the nitrogen side. This asymmetry means that a C2 axial methyl substituent causes less synaxial steric hindrance in a thiazepine than in the corresponding diazepine. Therefore additional distortion caused by axial methyl substitution should not be so great in the thiazepine and the consequent change in $J_{ad}$ (~10.55 Hz) and $J_{bd}$ (~2.09 Hz) should be smaller than in the diazepine.

The coupling constants involved in the 2-methyl derivatives are listed in tables 29 and 30 (p.104). For both the values of $J_{ab}$, $J_{ef}$, $J_{ad}$, $J_{bd}$ and $J_{cd}$ are approximately those expected on the basis of the other molecules examined. However, the remaining coupling constants, $J_{ae}$, $J_{af}$, $J_{be}$ and $J_{bf}$, differ in the two derivatives and are not those expected of regular chair conformations. The coupling constants which best fit the spectra are included in figure 88. The values obtained suggest the conformations illustrated - both represent structures more puckered than an ideal chair.

Figure 88 View from C4 to C3

<table>
<thead>
<tr>
<th>Diazepine</th>
<th>Thiazepine</th>
</tr>
</thead>
<tbody>
<tr>
<td>$J_{ae}$</td>
<td>3.50</td>
</tr>
<tr>
<td>$J_{af}$</td>
<td>9.17</td>
</tr>
<tr>
<td>$J_{be}$</td>
<td>6.58</td>
</tr>
<tr>
<td>$J_{bf}$</td>
<td>3.18</td>
</tr>
</tbody>
</table>

In a comparison of the two diazepines, 2MeNN and 24DiMeNN, the additional 'equatorial' methyl group of the latter is expected to cause the relationship between the C3 and C4 methylene groups to become more gauche (ie. to approach the ideal chair conformation).
The series of methyl substituted 1,5-benzodiazepines is illustrated in figure 89. It is suggested that the C2-C3-C4 part of the seven-membered ring is more puckered than an ideal chair structure. Substitution of 'equatorial' methyl groups causes a decrease in the puckering through a twisting of the C2-C3 and C4-C3 bonds towards a more gauche conformation. Substitution of 'axial' methyl groups also causes a decrease in the puckering due to synaxial interference.

Figure 89  View from C4 to C3

![Molecular structures](image-url)
3.8 OPTICAL ACTIVITY

It is clear that the unsymmetrically substituted heterocycles may exist in the chair conformation as one of two optical isomers. Such isomers are indistinguishable by NMR spectroscopy. The 2-methyl and 2,2,4-trimethyl diazepines were tested for optical activity and were found to be racemic mixtures—no rotation of plane polarized light occurred. No attempt has been made to separate the isomers.

3.9 ELECTRONIC SPECTRA

The electronic spectra of two heterocycles are illustrated in figure 90; data on the remainder are listed in table 33. These spectra provide a useful confirmation of the results obtained by NMR spectroscopy. The use of electronic spectroscopy in conformational analysis has been applied to several systems [202,214–220].

Figure 90   Electronic spectra  — cyclohexane solution
Table 33  Absorption spectra of benzodiazepines and benzothiazepines in the visible and ultraviolet region - cyclohexane soln.

<table>
<thead>
<tr>
<th>Diazepines</th>
<th>λ(nm)*</th>
<th>log ε*</th>
<th>λ(nm)</th>
<th>log ε</th>
<th>λ(nm)</th>
<th>log ε</th>
</tr>
</thead>
<tbody>
<tr>
<td>D2NN</td>
<td>224</td>
<td>(4.48)</td>
<td>~250†</td>
<td>(3.76)</td>
<td>304.1</td>
<td>(3.53)</td>
</tr>
<tr>
<td>2KKoNN</td>
<td>224.1</td>
<td>(4.51)</td>
<td>~250†</td>
<td>(3.79)</td>
<td>303.8</td>
<td>(3.58)</td>
</tr>
<tr>
<td>22dimeNN</td>
<td>223.9</td>
<td>(4.53)</td>
<td>~250†</td>
<td>(3.85)</td>
<td>301.2</td>
<td>(3.59)</td>
</tr>
<tr>
<td>22trimeNN</td>
<td>224.6</td>
<td>(4.54)</td>
<td>254.6</td>
<td>(3.85)</td>
<td>304.0</td>
<td>(3.61)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Thiazepines</th>
<th>λ(nm)</th>
<th>λ(nm)</th>
<th>log ε</th>
<th>λ(nm)</th>
<th>log ε</th>
<th>λ(nm)</th>
<th>log ε</th>
</tr>
</thead>
<tbody>
<tr>
<td>2MeSN</td>
<td>~216</td>
<td>240.9</td>
<td>(4.21)</td>
<td>272.0</td>
<td>(3.62)</td>
<td>~305†</td>
<td>(3.39)</td>
</tr>
<tr>
<td>22dimeSN</td>
<td>~216</td>
<td>244.3</td>
<td>(4.12)</td>
<td>271.2</td>
<td>(3.71)</td>
<td>~300†</td>
<td>(3.47)</td>
</tr>
<tr>
<td>22trimeSN</td>
<td>~216</td>
<td>243.2</td>
<td>(4.15)</td>
<td>272.6</td>
<td>(3.67)</td>
<td>~300†</td>
<td>(3.31)</td>
</tr>
</tbody>
</table>

*cut-off by solvent
†shoulder

The bands in the diazepine spectra may be assigned by comparison with the spectrum of aniline. Aniline exhibits three bands in the ultraviolet region at ~287nm (log ε 3.2), ~235 (3.9) and ~196 (4.3) [o-phenylenediamine also exhibits bands at 289nm (log ε 3.54) and 235 (3.82) [221]]; these correspond to the diazepine bands at ~300, 250 and ~224nm. The last band is obscured by solvent cut-off. Analysis of the aniline spectrum by the composite-molecule method [215] has indicated that the second band is largely due to the transfer of an electron from the amino group to the benzene ring. This can be represented in a simple valence bond approach as:

\[ R - \text{NH}_2 \quad \longrightarrow \quad \text{R} = \text{NH}_2 \]

In aniline and its N-alkyl derivatives the N-H or N-alkyl groups are almost coplanar with the benzene ring - in this configuration the nitrogen lone pair (in sp² hybridization the lone pair is in a 2pπ orbital) has maximum interaction with the benzene π system. If steric factors in the molecule force some degree of twisting (θ°) or noncoplanarity then the extent of this interaction decreases.
A qualitative relationship between the intensity of the charge transfer transition from the amino group to the benzene ring and the degree of planarity in the system has been based on the Franck-Condon principle [214,216]. If the excited molecule is assumed to be planar (or at least more planar than the ground state molecule) then only that fraction of ground state molecules having $\theta \sim 0^\circ$ should be able to undergo transition to the lowest vibrational level of the excited state (fig.91). The greater the angle of twist in the ground state, the lower the fraction of molecules having a suitable angle $\theta$, and therefore the lower the intensity. In the case of the symmetrically substituted diazepines the ground state potential energy curve must be more complicated than the simple case illustrated in figure 91, with several minima for all conformations involved - the principle however remains the same.

Figure 91

This decrease in intensity (and change in frequency) with increasing angle of twist has been borne out in experiments on $\alpha$-substituted N-alkylanilines [215], N-methylinidoline and its higher cyclic analogues [218], dihydro-1,5-benzodioxepines [202] and cyclic ethers and thioethers [219,220]. A detailed study of benzodioxepines [202] has shown that only when there is substitution in the 3-position is the twist conformation favoured, in agreement with NMR studies [cf. section 3.7.11].

The electronic spectra of all five diazepines are very similar although the extinction coefficients listed in table 33 show a slight increase with progressive methyl substitution. This
corresponds to an increase in the planarity of the system i.e. a flattening of the $O_6H_4(NHCH_2^-)_2$ part of the diazepine. The spectra clearly confirm that for all the diazepines examined the lowest energy conformation is the chair. In the twist-boat conformation the angle of twist $\theta^\circ$ is much smaller than in the chair conformation - therefore if any of the diazepines were to exist in the twist conformation the extinction coefficient of the 250nm band in particular should be greater than is observed.

The spectra of the thiazepines exhibit an additional $n\rightarrow\pi^*$ band compared to the diazepines and the two bands at ~243 and 272nm are assigned to transitions which effectively involve charge transfer from the two different heteroatoms to the benzene ring. The extinction coefficients again indicate that all the thiazepines exist in a chair conformation.
The remainder of this chapter concerns the preparation and properties of some transition metal complexes of the saturated benzodiazepines and benzothiazepines. This particular section consists of a brief introduction to some complexes of saturated diamines and related molecules, especially those with which comparison will be made in the subsequent sections.

Platinum(II) and palladium(II) complexes of N,N'-dimethylpiperazine [222,223] have been shown [224] to involve the piperazine as a chelate in the boat conformation (fig. 92.2).

Figure 92

With first-row transition metals however, piperazine [222,225], and other 1,4-diheterocyclohexanes - 1,4-dioxane [225,226], 1,4-dithiane [225,227], morpholine [103], 1,4-oxathiane [225,228] and thiomorpholine [229], usually form complexes in which the ligand is either monodentate or acts as a bridging group. In these complexes the ligands are generally in the chair conformation and very rarely
are boat-chelate complexes formed [230]. For example, a recent investigation of the nickel(II) chloride complexes of the N-2-aminoethyl derivatives of piperazine and morpholine has shown that the ligands are only bidentate [231], (but see reference [281]).

The strain involved in the boat conformation of piperazine, necessary for chelation, results in less stable complexes than those formed from the corresponding acyclic diamines [222, 232]. Several papers have dealt with both the acid dissociation constants of N- and C- alkylated aliphatic diamines and the stability constants of their transition metal complexes [233-235]. Invariably progressive N-substitution is found to lead to a decrease in the complex stability, attributed to steric hindrance. Thus an examination of the \( \nu_1 \left( ^3_{A_{2g}} \rightarrow ^3_{T_{2g}} \right) \) band for a series of 6-coordinate nickel complexes has demonstrated a decrease in 10Dq with increasing N-alkylation [236]. Heavy N-substitution tends to stabilize a tetrahedral structure relative to a square-planar one and binuclear hydroxy- or halide-bridged complexes may be formed preferentially [145, 233, 237-242] (fig. 92.6). Factors that must be considered are, for example: the size of the transition metal ion [238] [eg. the biscomplex structure 92.5 is formed only with larger metal ions ie. Pd vs. Ni]; the solvent used and the degree of solvation [145]; whether or not the anion is coordinating [238, 242] [eg. for Pd, structure 92.3 when \( X = \text{Cl}^- \) but structure 92.5 when \( X = \text{ClO}_4^- \)]; and the size of the anion if it is coordinating [239] [eg. \( \text{Cl}^- \) vs. \( \text{Br}^- \)]. It is interesting to note that the diazapropellane (fig. 92.1) is specific to palladium [243]. Similarly, the o-phenylenediamine derivative (fig. 92.4) forms stable palladium complexes [244] (\( X = \text{Cl}^-, \text{Br}^-, \text{I}^- \)).

Figure 93.

[Diagram of a complex structure]

Yellow Lifschitz complex

C-substitution has a smaller effect but has been shown to stabilize square-planar rather than tetrahedral stereochemistry [234, 240, 245, 246]. For example, stilbenediamine (fig. 93) [247, 248] and 2,3-dimethyl-2,3-diaminobutane [245] both yield square-planar nickel complexes.
Generally chelates of 1,2-diamines have been found to be more stable than those of 1,3-diamines and higher homologues [249].

Other diamines which are of interest for comparison are those from which chelation is sterically impossible. Thus for example, the bicyclic diamine, 1,4-diazabicyclo[2.2.2]octane* (fig. 94.1), forms polymeric complexes with coordination from both donor sites [93,94,144].

Figure 94

![Diamines](image)

1 'dabco' 2 'dach' 3 'daco' 4 'dtch' 5 'dtco'

The nickel(II) and copper(II) complexes of some seven and eight membered cyclic diamines have been investigated with the explicit purpose of minimizing the steric effects of N-alkylated diamines whilst retaining their advantage of increased basicity. It was reasoned that the strain involved in a conformation suitable for chelation would be less than in the six membered heterocycles. Homopiperazine (fig. 94.2) chelates readily in a pseudo-boat conformation to give 4-coordinate square-planar nickel(II) and copper(II) complexes [87,88,250] and 5-coordinate copper(II) complexes [251-253] (fig. 95.1). Other square-planar complexes (fig. 95.2) have been prepared recently [88] with the associated ligand N,N'-bis(2-aminoethyl)homopiperazine, 'baeda'.

Figure 95

![Complexes](image)

*Abbreviations for ligands are those employed in the original papers, although it should be noted that in some cases more than one abbrev. has been used, for example: 'dabco'[95] = 'TEDA'[93,94] = 'tred'[97].
1,5-Diazacyclooctane (fig. 94.3) forms very stable square-planar copper(II) and nickel(II) chelates in which the ligand is believed to be in the chair-boat conformation (fig. 96.1) [92]. In this conformation, shielding by the axial protons effectively prevents further coordination—the square-planar complex is stable in coordinating solvents. This can be contrasted to the behaviour of the square-planar copper(II) dach complex when further coordination occurs in coordinating solvents to form a square-pyramidal structure [251]. The structure of bis(dach) copper(II) nitrate hemihydrate has been shown to involve either nitrate ions or water molecules in the apical position (fig. 95.1) [253].

The associated ligand 1,5-diazacyclooctane-\(N,N'\)-diacetate ('dacoDA') yields square-pyramidal nickel complexes (fig. 96.2) [Ni(dacoDA)(\(H_2O\))\(\cdot\)2\(H_2O\) [254]. Again the occupation of the sixth position by an axial hydrogen atom results in the stabilization of a 5-coordinate complex.

Finally, amongst amine ligands, comparison may be made with the complexes of the saturated macrocyclic ligands shown in figure 97 [255-260]. Nickel(II) complexes of 'CTH' may exist in three possible isomeric forms (excluding folded 'cis' conformations such as are obtained with 'cyclen' [255]) [258,261]. Both Ni(cyclam)\(Cl_2\) and Ni(meso-CTH)\(Cl_2\) have the structure 98.1 [262]. The complexes Ni(\(\alpha\)-rac-CTH)\(^{2+}\) and Ni(\(\beta\)-rac-CTH)\(^{2+}\) have been assigned.
The electronic spectra of 6-coordinate nickel(II) dithiocyanato complexes of the three isomers exhibit a decrease in the axial ligand field strength in the order meso-CTH > β-rac-CTH > α-rac-CTH, corresponding to an increase in the steric interaction of the axially coordinated ligands and the methyl groups of the macrocycle [261].

Thioethers do not coordinate very strongly to transition metals, apart from Pt(II), Pd(II), Hg(II) etc. [263] - typical class 'b' or 'soft' metals [264, 265]. Chelation however increases the stability of the complexes with first-row transition metals; for example, 4-methylthioveratrole forms unstable nickel(II) complexes [266] and the macrocyclic ligand 'TTP' (fig. 97) forms stable low-spin nickel(II) complexes [267]. Nickel(II) complexes have also been prepared with the bidentate ligands 1,4-dithiepane and 1,5-dithiocane (fig. 94.4 and 94.5): low-spin complexes are obtained with the anions BF$_4^-$ and ClO$_4^-$ but high spin complexes are formed when halide ions are present (except [Ni(dtoo)$_2$I$_2$ which is diamagnetic) [89]. When thioethers are supplemented by amino- groups the multidentate ligand shows a much greater affinity to first-row transition metals than the thioether alone [268].
3.11 TRANSITION METAL COMPLEXES OF THE 2,3,4,5-TETRAHYDRO-1H-1,5-
BENZODIAZEPINES

3.11.1 Introduction

The compounds prepared in this work are listed in table 34 (p.133) together with their analytical and magnetic data. The primary effort was concentrated upon nickel(I1) and copper(I1) compounds since these usually have the most interesting stereochemistry. Also, in order to reduce the number of possible structures, only those ligands which exist in fixed chair forms at room temperature were used initially (it was found later that complexes of the unsubstituted diazepine could not be isolated - oils being generally formed). The preparation of the complexes was always easiest with the most extensively methylated benzo-
diazepines. Great care had to be taken with the 2-methyl derivative (see experimental section 3.14.2) and it is evident that methyl substitution protects the complexes from solvent action. After initial attempts in non-anhydrous conditions, all subsequent preparations were carried out in strictly anhydrous media. 2,2-Dimethoxypropane [132] was used as the dehydrating agent. The complexes are discussed individually in the following sections.

3.11.2 Nickel Perchlorate complexes

The three nickel perchlorate complexes are yellow-orange diamagnetic solids - typical square-planar nickel complexes. They explode violently at ~260°C and care must be taken during m.pt. determinations.

The electronic spectra of the complexes are illustrated in figure 99 (p.134). The strong absorption band at 21.3kK, as well as the broad band at 29-30kK, is typical of analogous complexes [269] - nickel perchlorate complexes of 'dach' and 'daco' (fig.94) exhibit bands at 23.4 and 22.45 kK respectively and the cyclic
Table 34 Analytical and Magnetic data of the complexes of some tetrahydro-1,5-benzodiazepines

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Complex</th>
<th>Colour</th>
<th>m.pt. °C</th>
<th>µ (B.M.)</th>
<th>Found C</th>
<th>H</th>
<th>N</th>
<th>Calculated C</th>
<th>H</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>2KeNN</td>
<td><a href="ClO%E2%82%84">NiL₄</a>₂</td>
<td>orange</td>
<td>260°</td>
<td>d</td>
<td>41.03</td>
<td>4.72</td>
<td>9.72</td>
<td>41.27</td>
<td>4.85</td>
<td>9.63</td>
</tr>
<tr>
<td></td>
<td><a href="ClO%E2%82%84">CuL₄·MeOH</a>₂</td>
<td>grey green</td>
<td>204°</td>
<td>1.78</td>
<td>41.30</td>
<td>5.04</td>
<td>9.23</td>
<td>40.75</td>
<td>5.21</td>
<td>9.05</td>
</tr>
<tr>
<td></td>
<td>[NiL₄Cl]Cl</td>
<td>pale green</td>
<td>211°</td>
<td>3.23</td>
<td>52.71</td>
<td>6.31</td>
<td>12.26</td>
<td>52.90</td>
<td>6.22</td>
<td>12.34</td>
</tr>
<tr>
<td></td>
<td>[CuLCl₂]</td>
<td>dark brown green</td>
<td>135°</td>
<td>~1.72°</td>
<td>41.75</td>
<td>3.73</td>
<td>9.57</td>
<td>40.48</td>
<td>4.76</td>
<td>9.44</td>
</tr>
<tr>
<td>24diKeNN</td>
<td><a href="ClO%E2%82%84">NiL₄</a>₂</td>
<td>yellow pink</td>
<td>268°</td>
<td>d</td>
<td>43.82</td>
<td>5.73</td>
<td>8.81</td>
<td>43.31</td>
<td>5.29</td>
<td>9.18</td>
</tr>
<tr>
<td></td>
<td><a href="ClO%E2%82%84">CuL₄·MeOH</a>₂</td>
<td>grey green</td>
<td>202°</td>
<td>1.92</td>
<td>42.84</td>
<td>5.74</td>
<td>8.60</td>
<td>42.39</td>
<td>5.61</td>
<td>8.66</td>
</tr>
<tr>
<td></td>
<td>[NiL₄Cl]Cl</td>
<td>pale green</td>
<td>248°</td>
<td>3.20</td>
<td>53.23</td>
<td>6.60</td>
<td>11.30</td>
<td>54.81</td>
<td>6.69</td>
<td>11.62</td>
</tr>
<tr>
<td></td>
<td>[CuLCl₂]</td>
<td>green</td>
<td>124°</td>
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<td>41.94</td>
<td>5.18</td>
<td>8.67</td>
<td>42.52</td>
<td>5.19</td>
<td>9.02</td>
</tr>
<tr>
<td>224triKeNN</td>
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<td>orange pink</td>
<td>269°</td>
<td>d</td>
<td>45.35</td>
<td>5.70</td>
<td>8.87</td>
<td>45.17</td>
<td>5.69</td>
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<tr>
<td></td>
<td><a href="ClO%E2%82%84">CuL₄</a>₂</td>
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<td>203°</td>
<td>1.84</td>
<td>44.62</td>
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<td>5.64</td>
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</tr>
<tr>
<td></td>
<td><a href="ClO%E2%82%84">CoL₄</a>₂</td>
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<td>&gt;345°</td>
<td>~4.87°</td>
<td>44.20</td>
<td>5.52</td>
<td>8.95</td>
<td>45.15</td>
<td>5.68</td>
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<tr>
<td></td>
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<td>light yellow</td>
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<td>3.10</td>
<td>46.52</td>
<td>6.02</td>
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<tr>
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<td>124°</td>
<td>4.86</td>
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<td>5.83</td>
<td>7.90</td>
<td>40.47</td>
<td>6.21</td>
<td>7.87</td>
</tr>
</tbody>
</table>

a: explodes violently, b: small amount of material available, c: decomposes, d: diamagnetic
Figure 9. Reflectance spectra of nickel diazepine complexes.
tetramine nickel complex \([\text{Ni}(\text{cyclam})](\text{ClO}_4)_2\) exhibits a strong band at \(\sim 21.3\text{K}\) \([259]\).

The vibrational spectrum of the nickel 224triMeNN complex is illustrated in figure 100 (p. 136). Notable changes in the spectrum compared to that of the ligand are the disappearance of the band at \(\sim 1596\text{cm}^{-1}\) and the movement of the N-H stretching band to a lower frequency (by \(\sim 150\text{cm}^{-1}\)). The positions of these two bands in the spectrum of the diazepine 224triMeNN are shown as dashed lines in figure 100. The disappearance of the band at \(\sim 1596\text{cm}^{-1}\) suggests that it is due in some part to a N-H bending vibration although its complete disappearance is difficult to explain. The decrease in frequency of the N-H stretching vibration has been attributed to the electron-withdrawing influence of the metal ion when it is coordinated to the nitrogen atom \([103]\). It is difficult to determine from the infrared spectrum whether any change in conformation has occurred. The small changes observed in the spectra of the complexes are probably caused by the chelation of the ligand and consequent increased rigidity of the structure. From the NMR studies (cf. section 3.7), the possibility of a conformational change upon complex formation seems very unlikely.

<table>
<thead>
<tr>
<th>(v)</th>
<th>(\text{IR inactive, v. weak})</th>
<th>(\sim 930\text{cm}^{-1}) 1 band</th>
<th>(\sim 930\text{cm}^{-1}) 1 band</th>
</tr>
</thead>
<tbody>
<tr>
<td>(v_1)</td>
<td>(\text{IR inactive})</td>
<td>(\sim 480\text{cm}^{-1}) 1 band</td>
<td>2 bands but 1. IR inactive</td>
</tr>
<tr>
<td>(v_2)</td>
<td>(\sim 1110\text{cm}^{-1}) 1 band</td>
<td>2 components splitting (\sim 100\text{cm}^{-1})</td>
<td>3 components</td>
</tr>
<tr>
<td>(v_3)</td>
<td>(\sim 625\text{cm}^{-1}) 1 band</td>
<td>2 components splitting (\sim 15\text{cm}^{-1})</td>
<td>3 components</td>
</tr>
</tbody>
</table>

Table 35 Vibrations of the perchlorate anion as a function of symmetry \([270]\)

The study of perchlorate anion coordination is now well established \([241,242,270]\) (table 35). In the noncoordinating
tetrahedral perchlorate ion only two vibrations are infrared active (although the \( \nu_1 \) vibration is sometimes observed as a very weak band). When monocoordinate the symmetry is reduced to \( C_{3v} \) and the \( \nu_3 \) and \( \nu_4 \) vibrations are both split. The splitting of \( \nu_4 \) is usually \( \approx 15 \text{ cm}^{-1} \) but the splitting of \( \nu_3 \) may be as much as \( 100 \text{ cm}^{-1} \). Combination bands of \( \nu_1 \) and components of \( \nu_3 \) are sometimes observed. When the perchlorate ion is bidentate then the symmetry is reduced further to \( C_{2v} \) and additional splitting occurs [270].

In the diamagnetic nickel perchlorate complexes it is difficult to detect any splitting of the broad \( 1110 \text{ cm}^{-1} \) band due to the extensive diazepine absorption in this region. The slight splitting of the \( 620 \text{ cm}^{-1} \) band is not thought to be indicative of perchlorate coordination. The splitting occurs only in the spectrum of the 224triMeMNN derivative and may be due to either a ligand vibration or an effect of the crystal packing (a similar apparent splitting is observed in the square-planar \( [\text{Ni(en)}_2](\text{CIO}_4)_2 \) - the lower of the two components in this case has been assigned to a ligand vibration [241]). There is no obvious peak at \( \approx 930 \text{ cm}^{-1} \) which can be assigned to \( \nu_1 \) and it is reasonably certain that the perchlorate ions are not coordinated. Moreover, it is difficult to believe that in a square-planar complex of two potentially bidentate diamines perchlorate coordination is likely. Ionic conductivity measurements have not been obtained due to the insolubility of the complexes.

The band at \( 660 \text{ cm}^{-1} \), an obvious difference between the two infrared spectra on page 136, is difficult to account for. It occurs in the vibrational spectra of the other diamagnetic nickel complexes, \( [\text{Ni}(224\text{triMeNN})_2]X_2 \), \( X=\text{Br}^- \) or \( I^- \), and is therefore not due to the perchlorate. Since it is not present in the copper(II) complexes it almost certainly is derived from a nickel-ligand vibration. Another less noticeable difference is in the low-frequency region where bands at \( 283 \) and \( 310 \text{ cm}^{-1} \) in the nickel and copper 224triMeNN perchlorates respectively may arise from metal-nitrogen vibrations.
Examination of molecular models of possible structures for these square-planar nickel complexes indicates that the structure shown in figure 102 is the most probable one. Since inversion to the boat conformation is virtually impossible the ligands must assume a trans position relative to the nickel ion (ie. centrosymmetric) - the H3a-H3a' interaction is severe in the alternative cis configuration. It is difficult to place four diazepine molecules around the nickel ion without invoking severe steric hindrance - this is the only alternative Ni-N₄ arrangement.

In the trans configuration illustrated in figure 102 the two '3a' hydrogen atoms of the diazepine ligands shield the z axis of the complex. This shielding is sterically very similar to that observed in the nickel complexes of daco and dacoDA (see section 3.10 fig.96 [92,254]). It is seen later however that this shielding is apparently not so effective in the complexes of some diazepines.
3.11.3 Copper Perchlorate complexes

Of the three copper perchlorate complexes the 224triMeM derivative is the most straightforward and is discussed first. Variable temperature magnetic data are listed in table 36; the compound follows Curie - Weiss behaviour down to ~89°K with $\Theta \approx 1°$, consistent with square-planar stereochemistry.

Table 36 Magnetic susceptibilities of $[\text{Cu(224triMeM)}_2](\text{ClO}_4)_2$

<table>
<thead>
<tr>
<th>$T(°\text{K})$</th>
<th>$10^6\chi_A (\text{cgs})$</th>
<th>$\mu(\text{B.M.})$</th>
</tr>
</thead>
<tbody>
<tr>
<td>295.2</td>
<td>1439</td>
<td>1.84</td>
</tr>
<tr>
<td>262.6</td>
<td>1599</td>
<td>1.83</td>
</tr>
<tr>
<td>230.0</td>
<td>1618</td>
<td>1.83</td>
</tr>
<tr>
<td>198.4</td>
<td>2088</td>
<td>1.82</td>
</tr>
<tr>
<td>166.2</td>
<td>2503</td>
<td>1.82</td>
</tr>
<tr>
<td>135.4</td>
<td>3070</td>
<td>1.82</td>
</tr>
<tr>
<td>103.3</td>
<td>3951</td>
<td>1.81</td>
</tr>
<tr>
<td>89.5</td>
<td>4627</td>
<td>1.82</td>
</tr>
</tbody>
</table>

The vibrational spectrum of the complex is illustrated in figure 101 (p.136). The great similarity between the spectra of the corresponding copper and nickel complexes strongly suggests that the structure of the copper complex is square-planar.

The electronic spectrum is included in figure 103. The d-d absorption is present as a shoulder at 20-21kK on what must be a charge transfer band (the intensity of this band is too great for it to arise from a d-d transition). In the same figure the band maxima of some corresponding complexes are shown for comparison. The red-brown colour of the complex is similar to the colour of the dach and daco square-planar copper complexes \[87\]. The position of the band in these complexes is a little higher in energy than normally expected for square-planar Cu-N$_4$ complexes; this has been attributed to the very effective shielding of the 5th and 6th coordination positions by the carbon chains \[cf.fig.96,101]\[92,136\]. As mentioned in section 3.10, substitution on the carbon bridges between coordinating atoms generally stabilizes a square-planar complex due to axial-shielding \[245\].
The copper perchlorate complexes of 2MeNN and 24diMeNN differ from the 224triMeNN complex - this is evident from their visible spectra (fig.103). The colour of the two complexes is a greyish-green in comparison to the red-brown of the square-planar [Cu(224triMeNN)₂](ClO₄)₂.
Whereas the infrared spectrum of \([\text{Cu(224triMeNN)\textsubscript{2}}](\text{C104})\textsubscript{2}\) bears an exact correspondence to its nickel analogue - apart from the differences mentioned earlier the spectra are superimposable (fig.100,101) - the spectra of the copper and nickel complexes of the 2MeNN and 24diMeNN diazepines, although similar, do not correspond so well. In addition there is a broad band at \(\sim 3500\text{cm}^{-1}\) indicating the presence of '-OH' (illustrated by a dashed line in figure 101). It is interesting to compare the decrease in the N-H stretching frequency in the various perchlorate complexes with reference to the free diazepine ligand, since this may well provide a measure of the strength of the diazepine coordination \((\Delta\nu_{\text{NH}} = \nu_{\text{NH ligand}} - \nu_{\text{NH complex}})\). In the three nickel perchlorate complexes, on average, \(\Delta\nu_{\text{NH}} = 137 \pm 12\text{cm}^{-1}\) and in the square planar copper 224triMeNN perchlorate complex, \(\Delta\nu_{\text{NH}} = 135\text{cm}^{-1}\). In the other two copper perchlorate complexes however, \(\Delta\nu_{\text{NH}} = 75\) and \(85\text{cm}^{-1}\). This indicates a weakening of the in-plane field in these complexes. There is a concomitant decrease in the band attributed to \(\nu(\text{Cu-N})\) from \(310\text{cm}^{-1}\) to 299 and 297\(\text{cm}^{-1}\).

In the electronic spectra illustrated in figure 103 both the copper 2MeNN and 24diMeNN complexes exhibit d-d absorption bands at \(\sim 17\text{kk}\). This absorption is at a much lower frequency than is observed for either the square-planar 224triMeNN complex or any of the other square-planar complexes illustrated for comparison in the same figure. Such a lowering in frequency is generally associated with axial (out-of-plane) interaction and the formation of square-pyramidal 5-coordinate or tetragonal 6-coordinate complexes. This is illustrated by the behaviour of the square-planar \([\text{Cu(dach)}\textsubscript{2}](\text{C104})\textsubscript{2}\) for which there is a decrease from 20.3 to 18.45\text{kk} upon addition of water (fig.103) - this complex adds a water molecule in an apical position to form a square-pyramidal complex [cf. section 3.10, fig.95.1][251].

The position of the band at \(\sim 17\text{kk}\) and the absence of further absorption at lower frequencies clearly indicates that the structure of the complex is not a distorted tetrahedron [271]. The intensity of the band suggests a 5-coordinate structure (in which there is no centre of symmetry).
The lowering of the d-d absorption frequency upon addition of a fifth, apical ligand may be understood qualitatively by an examination of figure 104 [272]. When a planar complex adds a fifth, axial ligand the energy of the $d_z^2$ orbital is increased - eventually this increase is sufficient to raise the $d_z^2$ orbital above the $d_{xy}$ orbital in energy. Therefore, as the axial ligand field strength increases, the d-d band, represented by an arrow, undergoes a decrease in frequency. A distortion of a square-pyramidal structure towards trigonal-bipyramidal symmetry also leads to a decrease in the d-d transition energy.

The spectroscopic evidence indicates therefore an increase in the strength of the axial field and a decrease in the strength of the in-plane field. As stated previously, it is difficult for a fifth or sixth ligand to approach the central metal ion in these complexes due to the steric hindrance by axial hydrogen atoms on the ligands. It is however apparent that the decrease in methyl substitution from 224triMeNN to 24diMeNN and 2MeNN allows such an approach to be made in the copper perchlorate complexes of the last two ligands. A similar difference in behaviour between the 224triMeNN and the other diazepine ligands is observed in their nickel halide complexes discussed in the next section.
Figure 105 - showing the twist from square-planar towards trigonal-bipyramidal and the possible approach of a fifth ligand in a copper perchlorate complex of 2MeNN or 24diMeNN - compare figure 102.

The two diazepine ligands in the 2MeNN and 24diMeNN copper perchlorate complexes are probably twisted out of parallel to some extent, towards trigonal-bipyramidal symmetry, to facilitate the approach of a fifth ligand, believed to be methanol in this case. The frequency of the bands in the electronic spectra indicate that the perturbation from a planar $\mathcal{N}_4$ system is small (the d-d bands of copper(II) complexes of approximate trigonal-bipyramidal symmetry are normally observed at $\sim10-15\text{kJ} / \text{mol}$ [272-275], at lower frequencies than in square-pyramidal complexes $\sim16-19\text{kJ} / \text{mol}$ [87]).

The energies of 3d orbitals in $C_{4v}$ and $D_{3h}$ fields are illustrated below in figure 106.

Figure 106 Splitting of the 3d orbitals in $C_{4v}$ and $D_{3h}$ fields [276]
3.11.4 Nickel Halide complexes

The electronic spectra of the nickel(II) halide complexes are illustrated in figure 99 (p.134) and it is evident from these spectra that three different species are involved. The nickel(II) bromide and iodide complexes of 224triMeNN are low spin and appear to be analogous to the nickel(II) perchlorate complex. All three chlorides are paramagnetic but are of two types: NiL₂Cl₂ for 2MeNN and 24diMeNN, and NiLCl₂ for the more extensively substituted 224triMeNN.

The dependence of the spin multiplicity of nickel(II) amine complexes upon the anion is now well known [239,256,259,260]. In many tetragonal nickel(II) diamine and tetramine complexes there is a change in the ground state from ³A₂₃ to ¹A₅₆ (from paramagnetic to diamagnetic behaviour) on going from Ni(N₄)Cl₂ through Ni(N₄)Br₂ to Ni(N₄)I₂. The change may occur between bromide and iodide as in cyclam [259] and N,N-dimethyl-en [239] derivatives or between chloride and bromide as in N,N-diethyl-en derivatives [239]. The effect has been generally attributed to an increase in the axial (tetragonal) distortion of the 6-coordinate complex. It is sometimes difficult to distinguish from the electronic spectrum when such a distorted complex actually becomes square-planar. Some diamagnetic nickel(II) complexes of N₄ macrocycles for example have been shown by X-ray analysis to be 5-coordinate, not square-planar, in the solid state [276,277].

It is apparent from the electronic spectra and magnetic data of the nickel halide complexes that approach by chloride ions, smaller and higher in the spectrochemical series than bromide or iodide ions, is successful in the 2MeNN and 24diMeNN complexes in yielding paramagnetic species. It is suggested that in the 224triMeNN complex the screening of the metal ion is again too great for a similar approach to be made.

Apart from a broader NH absorption (~3040 cm⁻¹) the vibrational spectra of the nickel(II) bromide and iodide complexes of 224triMeNN
show a close similarity to the spectrum of the nickel perchlorate complex. Additional absorption at \(\sim 3410\text{cm}^{-1}\) indicates the presence of water. The nickel chloride complexes of 2MeNN and 24diMeNN exhibit NH vibrations at \(\sim 3140\) and \(\sim 3150\text{cm}^{-1}\) respectively suggesting possible hydrogen bonding of the amine hydrogen atoms to the chloride ions. Strong bands at 311 and 305\text{cm}^{-1} and weaker bands at 260 and 263\text{cm}^{-1} respectively may be due to Ni-N and Ni-Cl stretching. The vibrational spectrum of the nickel chloride complex of 224triMeNN is quite different from the spectra of the 2MeNN and 24diMeNN derivatives; it shows an interesting resemblance to the spectrum of the complex Co(224triMeNN)Cl₂ (section 3.11.6).

It is difficult to reconcile the electronic spectra of the two NiL₂Cl₂ complexes with 6-coordinate tetragonal stereochemistry. If the bands at \(\sim 26.5\) and \(\sim 13.7\text{K}K\) are assigned to the \(\nu_3 (^{3}A_{2g} \rightarrow ^{3}T_{1g}(F))\) and \(\nu_2 (^{3}A_{2g} \rightarrow ^{3}T_{1g}(F))\) transitions (Oh notation), the \(\nu_1\) transition \((^{3}A_{2g} \rightarrow ^{3}T_{2g})\) should be observed at \(\sim 8\text{K}K\). This transition is susceptible to tetragonal distortion and is frequently split into two components \((^{3}B_{1g} \rightarrow ^{3}T_{2g}, ^{3}B_{2g})\) (eg. Ni(neso-CTH)₂Cl₂ \(\nu_1 : 8.1\) and 14.3\text{K}K and Ni(N,N-diethyl-en)₂Cl₂.2H₂O \(\nu_1 : 7.52\) and 10.45\text{K}K [239,278,279]). If the band at 5.7\text{K}K is assumed to be a d-d transition and not totally derived from vibrational overtones, it may be one component; another component may be responsible for the weak shoulder at \(\sim 11\text{K}K\). However this represents a larger splitting, with bands at lower frequencies, than is normally observed [278]. The band at \(\sim 13.7\text{K}K\) is also lower in energy than is generally observed in the spectra of nickel(II) amine complexes [279].

The low energy of the '\(\nu_2\)' band', the apparent absence of a \(\nu_1\) transition, the pronounced shoulder at \(\sim 23\text{K}K\) and the high intensity of the bands in general, all indicate that the axial approach of the chloride ion occurs only at one side of the Ni-\(N_4\) plane, giving rise to a 5-coordinate complex.

An energy level diagram for Ni\(^{2+}\) in square-pyramidal fields is shown in figure 107 [273,280]. It is apparent from the diagram that a relative decrease in axial field strength, compared to the
Figure 107  Triplet energy levels for Ni$^{2+}$ in square-pyramidal fields [273].

in-plane field strength, leads to a decrease in frequency of the $3B_1 \rightarrow 3E$ transition. This decrease in the axial field is related to the distance of the apical ligand from the nickel ion. Thus, for example, in the 5-coordinate complex [Ni(bapz)Cl]Cl$^+$, the distance of the apical chloride ion from the nickel ion is 2.33Å and d-d transitions are observed at 5.5 ($3B_1 \rightarrow 3E$), 10.5 ($3B_1 \rightarrow 3A_2$), 12.8 ($3B_1 \rightarrow 3B_2$) and 15.9 ($3B_1 \rightarrow 3E$) [276,281]. It is interesting to note that a further increase in the nickel-apical ligand distance (to ~2.8Å) may lead to spin pairing and a diamagnetic complex (eg. [Ni(CR)Br]$^+$ [276, 277$^*$]). The assignments of the bands observed in the spectrum of [Ni(2MeNN)Cl]Cl are shown in figure 108.

The electronic spectrum of Ni(224triMeNN)Cl$_2$ strongly suggests a 5-coordinate stereochemistry. The spectrum is compared to that of [Ni(Me$_2$dien)Cl$_2$]$^*$, of known 5-coordinate structure [275]; in figure 109. Comparison of the spectra of the 2MeNN and 224triMeNN complexes (fig.99,108,109) illustrates a general decrease in the transition

*ligand abbreviations:

bapz : N,N'-bis(3-aminopropyl)piperazine.

CR : 2,12-dimethyl-3,7,11,17-tetraazabicyclo[11.3.1]heptadeca-1(17),
     2,11,13,15-pentene.

Me$_2$dien : bis(2-dimethylaminoethyl)methylamine.
energies of the latter. Such a displacement towards lower energy is concomitant with a change in the donor atom set from \(N_4\)Cl to, for example, \(N_2\)Cl\(_3\) [275]. The nickel chloride complexes of 2MeNN and 24diMeNN are assigned 5-coordinate structures of approximate square-pyramidal stereochemistry. The base of the pyramid probably
consists of two bidentate diazepine molecules slightly twisted out of parallel (cf. fig. 105). The apical ligand is thought to be a chloride ion which approaches sufficiently close to stabilize a spin-free configuration.

A similar axial approach is prevented in the 224triMeNN complex by the increased methylation of the diazepine bridge. In this case pentacoordination is thought to occur through chloride-bridging. Figure 110 represents an ideal structure in which both nickel ions are assumed to have a square-pyramidal environment. The similarity of the two spectra illustrated in figure 109 suggests however that the structure is more likely to be intermediate between square-pyramidal and trigonal-bipyramidal.

The electronic spectra of the 224triMeNN nickel(II) bromide and iodide complexes (fig. 99) closely resemble the spectrum of the perchlorate complex - indicating a similar square-planar structure. The anomalous shoulder at ~26kK in the spectrum of the iodide is assigned to a charge transfer transition.

Figure 110 A possible dimeric structure for [Ni(224triMeNN)Cl₂]
3.11.5 Copper Chloride complexes

The reaction of copper(II) chloride with the three diazepines 2MeNN, 24MeNN and 224triMeNN yields in each case a dark green compound of stoichiometry CuLCl₂. The electronic spectra of the compounds are illustrated below in figure 111. Although d-d absorption is obscured in the spectrum of Cu(2MeNN)Cl₂ by an intense charge transfer band, the complexes of the other two diazepines exhibit broad d-d bands at 13.6 and 14.0kK.

The electronic spectra of the complexes resemble the spectra of the copper(II) bromide complexes of some N,N'-polysubstituted ethylenediamines CuLBr₂ - in this series a similar shift to lower frequencies with increasing substitution has been observed [145]. On the basis of their electronic spectra these complexes have been assigned tetragonal structures - achieved through halide bridging [145]. Subsequent studies have shown however that the complexes are monomeric in solution and most probably have pseudo-tetrahedral structures [240]. It appears difficult to determine between 4-, 5- and 6-coordinate copper complexes on the basis of their electronic spectra alone [240,272,275].

![Figure 111](image-url)
Magnetic data are given in table 34 and the low temperature magnetic susceptibilities of the \([\text{Cu}(224\text{triMeNN})\text{Cl}_2]\) complex are tabulated below. The compound obeys the Curie-Weiss law with \(\theta = 7^\circ\).

**Table 37 Low temperature magnetic data for \([\text{Cu}(224\text{triMeNN})\text{Cl}_2]\)**

<table>
<thead>
<tr>
<th>(T(°K))</th>
<th>(10^5\chi_A(\text{cgs}))</th>
<th>(\mu(\text{B.M.}))</th>
</tr>
</thead>
<tbody>
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<td>295.1</td>
<td>1281</td>
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<tr>
<td>103.2</td>
<td>3541</td>
<td>1.71</td>
</tr>
<tr>
<td>89.4</td>
<td>3964</td>
<td>1.69</td>
</tr>
</tbody>
</table>

Although the magnetic moments appear lower than is usual, the susceptibilities are field independent \((5750 \text{ and } 6700\text{gauss})\) and the variation with temperature shows no indication of magnetic exchange. It might be expected that in a halide bridged structure, such as that illustrated in figure 110 for example, magnetic interaction between the copper atoms would occur - although polynuclear halide bridged copper complexes are known which do not exhibit antiferromagnetic behaviour at temperatures down to \(~89°K\) \([135,136]\).

The infrared spectra of the diazepine copper chloride complexes are similar in some respects to the spectra of the \(\text{NiL}_2\text{Cl}_2\) complexes; the spectrum of \([\text{Cu}(224\text{diMeNN})\text{Cl}_2]\) is illustrated as an example in figure 112 \((p.151)\). It is interesting that the vibrational spectrum of the copper complex \([\text{Cu}(224\text{triMeNN})\text{Cl}_2]\) is unlike the spectra of the nickel and cobalt complexes of the same stoichiometry - suggesting a pseudo-tetrahedral rather than polymeric tetragonal structure. Bands at 271 and 307\(\text{cm}^{-1}\) \((\text{fig.112})\) may be assigned to \(\text{Cu-Cl}\) stretching vibrations.

In the absence of conductivity measurements it is difficult to decide the structure of the copper complexes. On the basis of the vibrational spectra and magnetic data the compounds are tentatively assigned a flattened tetrahedral structure.
3.11.6 Cobalt complexes

A brief investigation has been made into the reaction of cobalt salts with 224triMeNN. Although the cobalt chloride and cobalt perchlorate complexes were prepared in anhydrous conditions it is apparent from their vibrational spectra that both contain water; broad absorption bands are present at \(\sim 2800 - 3500\) cm\(^{-1}\) and 1600 cm\(^{-1}\).

The band at 624 cm\(^{-1}\) in the infrared spectrum of the perchlorate complex shows no sign of splitting indicating that the anion is not coordinated. The electronic spectrum (fig.114) exhibits no d-d absorption due to a broad and intense charge transfer band which extends down to \(\sim 8\) kK. The complex has a magnetic moment \(\sim 4.87\) B.M. indicating a 5 or 6-coordinate structure involving water in the axial positions.

The electronic spectrum of the light blue chloride complex (fig.114) shows absorption typical of tetrahedral cobalt compounds, with additional weaker absorption. The strong bands at \(\sim 15kK\) and \(\sim 5kK\) coincide exactly with those of the tetrachlorocobaltate anion (cf. chapter 1). The spectrum does not exhibit the changes expected

Figure 114. Electronic reflectance spectra of the cobalt complexes

![Absorption edge of perchlorate salt](Image)
in the positions and splitting of these bands on a decrease in symmetry to $C_{2v}$ - the symmetry of a monomeric CoLCl$_2$ molecule. The vibrational spectrum shows multiple absorption in the region 3000 - 4000 cm$^{-1}$ and in many respects resembles the spectrum of [Ni(224triMeNN)Cl$_2$]. The complex is assigned an ionic structure involving tetrachlorocobaltate anions. The structure of the cation is uncertain but involves high-spin cobalt(II) in a 5 or 6-coordinate environment containing two diazepine molecules, with water molecules occupying the axial positions.
3.12 COPPER(II) CHLORIDE COMPLEXES OF THE 2,3,4,5-TETRAHYDRO-
1,5-BENZOTHIAZEPINES

Whilst thioethers are known to be poor ligands in comparison
to mercaptide ions, when present in conjunction with an amino-
group, the thioether-amine chelate usually forms stable complexes
[263]. Although this study was limited to preparations at room
temperature, it is surprising that the only complexes isolated
are those shown in table 38. Nickel(II) salts do not give
precipitates. Nickel(II) exhibits borderline class a - class b
behaviour and thioether-nickel complexes are generally unstable
towards water, which readily replaces the sulphur ligand. For this
reason all preparations were attempted in dry conditions, but
without success.

Table 38 Analytical and magnetic data for the copper(II) chloride
complexes of tetrahydrobenzothiazepines.

<table>
<thead>
<tr>
<th>Complex</th>
<th>μ(B.M.)</th>
<th>C</th>
<th>H</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>[Cu(2MeSN)Cl₂]</td>
<td>Found</td>
<td>38.12</td>
<td>4.14</td>
<td>4.31</td>
</tr>
<tr>
<td>m.pt. 121°C, green colour, 1.82</td>
<td>Calc.</td>
<td>38.28</td>
<td>4.18</td>
<td>4.46</td>
</tr>
<tr>
<td>[Cu(224triMeSN)Cl₂]</td>
<td>Found</td>
<td>42.23</td>
<td>5.03</td>
<td>3.99</td>
</tr>
<tr>
<td>m.pt. 165°C, green colour, 1.92</td>
<td>Calc.</td>
<td>42.17</td>
<td>5.01</td>
<td>4.10</td>
</tr>
</tbody>
</table>

The two bright green copper thiazepine complexes appear very
similar to their diazepine analogues; an example of their vibrational
spectra is illustrated in figure 113 (p.151). The electronic spectra
of the two complexes are compared to the analogous diazepine
complexes in figure 111 (p.149); both spectra exhibit asymmetric
absorption centred at ~12.8kK. Again the complexes are tentatively
assigned pseudo-tetrahedral structures.
3.13 CONCLUSIONS

It has been shown by the studies described in the two preceding sections that tetrahydrobenzodiazepines give transition metal complexes of interesting stereochemistries. In general, progressive methyl substitution of the diazepine ring increases the ease of preparation and the stability of the complexes. A decrease in methyl substitution allows the axial approach of further coordinating molecules or ions and the formation of 5-coordinate species. For example, the greater methyl substitution of 224triMeNN prevents the approach of an apical ligand in both the copper perchlorate and nickel chloride complexes: in the former the planar complex is stabilized but in the latter a dimeric chloride bridged structure is formed preferentially. 5-Coordinate nickel complexes of bidentate diamines are not common.

A further investigation of these complexes is desirable, in particular the measurement of ionic conductivities and solution electronic spectra - if a suitable solvent can be found. It would be interesting for example to determine the effect of halide ions upon the square-planar perchlorate salts.

Complexes of other transition metals, in particular second-row metals such as palladium, might prove interesting. A further examination of the thiazepine ligands is required and this might be extended to analogous dithiepines, oxazepines and their eight-membered homologues. N,N'-bis(2-aminoethyl-, and propyl) and N,N'-diacetate derivatives of the diazepines should yield 4- and 5-coordinate complexes. Variation of the ring substitution would probably be worthwhile: for example 3,3-disubstitution would guard against axial approach more effectively than any ligand examined in this work - interligand repulsion in square-planar complexes should not prove prohibitive. Symmetrically substituted diazepines need not chelate in a chair conformation and may give rise to more variable stereochemistries. More extensive substitution and the use of bulkier groups than methyl should slow down the inversion rates of the symmetrically substituted diazepines and it might be possible to study the inversion mechanisms by NMR.
3.14 EXPERIMENTAL

3.14.1 Synthesis of Ligands

The preparations of two diazepines and one thiazepine are described as typical examples:

2,3,4,5-tetrahydro-1H-1,5-benzodiazepine.

O-phenylenediamine (97.2g 0.9m) and malonic acid (46.8g 0.45m) in 400 ml 4N HCl were refluxed for 3 hours. After the reaction mixture had cooled, the product was filtered off and washed with cold water, hot ethanol and then ether. The benzodiazepin-2,4-dione was dried in an oven at 120°C and cooled in vacuo over P₂O₅. Yield 53g 33.4%m.pt.350°C(decomp.), silvery-grey crystalline solid.

The dry diazepindione (24g) was added in small quantities with care to a gently refluxing suspension of lithium aluminium hydride (10g) in 350 ml freshly-distilled sodium-dried tetrahydrofuran. When the addition was complete the mixture was refluxed for 3 hours. After cooling, excess LiAlH₄ was decomposed by the careful addition of ethylacetate. The mixture was made strongly alkaline by addition of 10%NaOH and the THF removed under vacuum. The remaining solid was repeatedly extracted with hot 80-100°C petroleum ether. Rotary evaporation gave brown crystals. Recrystallization from cold petroleum ether (80-100°C fraction) yielded colourless crystals (13.5g) m.pt.100°C.

An alternative method involved the reaction of o-phenylenediamine with o-toluenesulphonyl chloride in pyridine to give the N,N'-ditosyl- derivative. This was reacted with 1,3-dibromopropane in sodium and butanol to yield the N,N'-ditosyl diazepine [36,37]. Several attempts were then made to hydrolyse this derivative to the parent diazepine: i) 70%H₂SO₄/SO₃ with reflux [36,37] gave only an 18% yield. ii) conc.HCl with reflux [38] gave no desired product, the tosyl derivative was recovered. iii) 90%H₂SO₄ for 7 days at room temperature [40] gave a very small yield. One method
not attempted was treatment by \( \text{LiAlH}_4 \) in tetrahydrofuran \([171]\).

\( \text{2e,4e-Dimethyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine.} \)

\( \text{2,4-Dimethyl-3H-1,5-benzodiazepine was prepared as described previously \([cf.\ chapter \ 1]\).} \)

The diazepine base (28g) was dissolved in absolute ethanol (250ml). A suspension of sodium borohydride (12.5g) in absolute ethanol (50ml) was added. The mixture was warmed slightly until effervescence started - if at any time the effervescence died down, the flask was again warmed. After two hours, when the colour had changed from brown to a greenish colour, the mixture was refluxed for one hour. The alcohol was distilled off under reduced pressure and the tetrahydrodiazepine extracted from the residue by boiling with petroleum ether \((120-160)\). Reduction in volume of the ether solution caused crystallization of the diazepine. The diazepine was then recrystallized twice from diethylether and dried in vacuo \((17.1g. \ m.pt. 57°C)\). The yield is low and the alternative trans-isomer is probably formed in addition to the cis-isomer which preferentially crystallized - no attempt has been made to isolate the trans-isomer.

\( \text{2,2-Dimethyl-2,3,4,5-tetrahydro-1,5-benzothiazepine.} \)

\( \text{3-Methylcrotonic acid (30g.) and } \text{o-aminothiophenol (36g.) were refluxed in an atmosphere of carbon dioxide for 20 minutes. On cooling, } \text{2,2-dimethyl-2,3,4,5-tetrahydro-1,5-benzothiazepin-4-one crystallized. The thiazepinone was recrystallized from ethanol and dried in vacuo (17.1g. m.pt. 220°C).} \)

\( \text{Lithium aluminium hydride (10g. an excess but the minimum convenient amount available) was added cautiously to freshly-distilled and sodium-dried tetrahydrofuran (300ml) in a 1 litre flask. The thiazepinone (-16.5g.) was placed in a sintered-glass soxhlet extraction thimble and the THF refluxed until all the thiazepinone} \)
had been removed (precautions should be taken in case of a too-vigorous initial effervescence). Reflux of the suspension was continued for 3 hr. After cooling, the mixture was transferred to a widenecked vessel and excess LiAlH$_4$ decomposed by addition of ethyl acetate. 2N Sodium hydroxide was then added until the mixture became alkaline and turned to a pale yellow colour. The organic layer was decanted and the remainder washed twice with diethylether. All the organic portions were combined and the solvents removed by rotary evaporation under reduced pressure. The residue was extracted with boiling n-hexane and subsequent evaporation of the hexane yielded an oil. Trituration with cold water gave pale yellow plates of the tetrahydrothiazepine (m.pt. 31°C, yield 12.3g.)

3.14.2 Preparation of Metal Complexes

The metal perchlorate hexahydrate or metal halide hydrate was shaken with 2,2-dimethoxypropane (~5ml per gram metal salt) for at least 1 hr. and then left overnight. The solution, or suspension, was diluted by an equal quantity of dry ethanol and after standing for a short time, filtered. The filtrate was added dropwise with vigorous stirring to a dry ethanol solution of the heterocycle. Stirring was continued until precipitation occurred. This usually occurred quickly but in some cases ether was added to promote crystallization. Sometimes it was found best to use dry ethanol-ether solutions of the heterocycles. With the lightly substituted diazepines care must be taken to avoid adding an excess of ether, or oils will result. Oils may also be caused by too rapid addition of the reactants. The precipitates were filtered, washed with dry ethanol and ether, and then 'dried' in vacuo over P$_2$O$_5$. 
3.14.3 Instrumental

A  Infrared spectra: Infrared spectra were taken on a Perkin-Elmer 457 grating infrared spectrophotometer. KBr plates were used in the region 4000-400 cm\(^{-1}\) and polythene plates in the region 500-250 cm\(^{-1}\). Solid samples were prepared as nujol or HCB mulls. Spectra reproduced in the text have been reduced by ~0.5.

B  Ultraviolet-Visible spectra: Solution spectra were measured on a Perkin-Elmer 137 UV spectrophotometer in the region 200-750 nm. 1 cm silica cells were used and samples were weighed on a Cahn electrobalance. Near infrared spectra were recorded on a Zeiss RPQ20A spectrophotometer, 200-2500 nm.

C  Diffuse Reflectance spectra: Diffuse reflectance spectra were measured at room temperature using a Unicam SP700 with LiF as the reference sample.

D  Mass spectra: The mass spectra of all the samples were determined on an AEI MS12 mass spectrometer (Mr. J. Delderfield).

E  Mössbauer spectra: The Mössbauer spectrum of D\(_2\)Fe(H\(_2\)O)\(_6\)(SO\(_4\))\(_2\) was obtained from the P.C.M.U. Harwell (Dr. B. W. Dale). The spectrum was measured at 300°K using a Pd\(^{57}\) source.

F  Magnetic measurements: Magnetic susceptibility data at room temperature were determined by the Gouy method at two field strengths. Hg[Co(NCS)\(_4\)] was used as the calibrant. In general the moments of the copper salts are of lower accuracy than those of the other metal complexes - the paramagnetism of the copper complexes usually just balanced the diamagnetism of the tube and ligand leading to a larger percentage error in these measurements. Low temperature measurements were also made by the Gouy method - at 3 field strengths whenever possible (~3750, ~5750, and ~6700 gauss).

G  Proton Magnetic Resonance spectra: Room temperature spectra were taken at 100 KHz on a Varian HA100 spectrometer,
generally on field sweep. TMS was used as an internal reference. Slow scans (~0.5Hz/sec) were made for the expanded spectra - usually in both directions although this made little difference. Although the peak positions were determined from the chart paper and not determined individually, the paper was calibrated for each spectrum from which measurements were made. The compounds were generally soluble in chloroform-D or carbon tetrachloride. The spin-decoupled spectrum was also run on the HA100 (Mr. D.C. Povey). Variable temperature spectra were run at 60MHz on a Perkin-Elmer R10 (Mr. J. Bloxsidge). For high temperature spectra HCB was used as solvent and for low temperature spectra dichloromethane or a mixture of halohydrocarbons was used. Several of the 100MHz spectra were obtained also at 60MHz.

H Laser-Raman spectra: Attempts to obtain Raman spectra were made using a Spex 1401 double spectrometer, (Mr. A. Saied).

I Elemental Analysis: The halogen analyses and some CHN analyses were carried out at the Bernhardt Microanalytical Laboratory in West Germany. Most CHN analyses however were done in the Microanalytical laboratory of the Chemistry department (Mr. E. Hopwood).
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