

STUDIES TOWARD THE SYNTHESIS OF  
ANALOGUES OF THE MARINE NEUROTOXINS,  
TETRODOTOXIN AND SAXITOXIN

The work described in this Thesis  
was carried out by the candidate at  
The Australian National University.  
A thesis  
submitted for the  
Degree of Doctor of Philosophy  
in the  
Australian National University  
by  
Peter G. Tucker

Medical Chemistry Group  
John Curtin School of Medical Research  
Australian National University  
Canberra

January, 1979

I wish to express my gratitude to  
Dr W.D.F. Arncliffe for his enthusiastic  
encouragement and invaluable suggestions  
throughout this work, and to Dr D.J. Brown  
and the staff of the Medical Chemistry Group

The work described in this Thesis  
was carried out by the candidate at  
The Australian National University.  
Where the work of others was used,  
appropriate acknowledgement is given.

thanks for so ably typing this thesis.  
Finally, Peter G. Tucker for the  
award of a Commonwealth Postgraduate Research  
Scholarship.

I wish to express my gratitude to Dr W.L.F. Armarego for his enthusiastic encouragement and invaluable suggestions throughout this work, and to Dr D.J. Brown and the staff of the Medical Chemistry Group for helpful discussions and assistance.

I am most grateful to my wife for her tolerance and understanding during the course of this work.

Mrs S.M. Schenk is deserving of special thanks for so ably typing this thesis.

Finally, acknowledgement is made for the award of a Commonwealth Postgraduate Research Scholarship.

## SUMMARY

The following work describes the synthesis, properties and biological evaluation of adamantane analogues of tetrodotoxin. Studies toward the preparation of perhydropurine analogues of saxitoxin are also described.

2-Aminotetrahydroadamantano[2,1-*d*]pyrimidine sulphate was prepared by cyclization of 1-aminomethyladamantan-2-ylamine with  $\underline{\text{S}}$ -methyl-*iso*-thiouronium sulphate. 2-Aminomethyl-2-hydroxyadamantan-1-ylamine, on the other hand, afforded 5-hydroxytetrahydroadamantano[1,2-*d*]pyrimidin-2-iminium bromide when treated with cyanogen bromide, but failed to cyclize with  $\underline{\text{S}}$ -methyl-*iso*-thiouronium sulphate, guanidine hydrochloride or cyanamide. 2-Oxadamantane-1-carbonylchloride, prepared from bicyclo[3.3.1]nonane-3 $\alpha$ ,7 $\alpha$ -dicarboxylic acid and thionyl chloride, was the common intermediate in the synthesis of the adamantano[2,1-*d*] and [1,2-*d*]pyrimidines and related compounds.

The chemical shifts of bridgehead adamantane protons exhibited a consistent additivity effect, which proved to be useful in the interpretation of the p.m.r. spectra of 1,2-disubstituted adamantanes.

The photochemical syntheses of 1,2-disubstituted adamantanes were investigated, but were found to be unsuitable for the preparation of adamantanopyrimidines.

Adamantano[2,1-*d*]oxazolidin-2-one, prepared by the photolysis of adamantan-2-ylcarbonyl azide, was also prepared from 1-aminoadamantan-2-ol with phosgene and base. This independent synthesis afforded conclusive proof of the structure of the photochemical product.

In order to prepare 4-substituted 2,8-dioxo- and diimino-perhydropurines, the fusion of 5-substituted 4-aminoimidazol-2(3*H*)-ones with nitroacetic acid was investigated. The only detectable reactions were hydrolytic in nature; for example, 4-aminoimidazol-2(3*H*)-one gave only  $\alpha$ -ureidoacetamide by fission of the C-4-N-3 bond in the presence of moisture. Nitroacetic acid failed to react with a number of other enamines, including 2-amino-1-ethoxycarbonylcyclopent-1-ene and 2-amino-1-cyanocyclopent-1-ene, hydrolytic reactions again predominated.

A preliminary investigation of the toxicity (M.L.D. values in mice) of 2-iminoadamantanopyrimidine analogues of tetrodotoxin was carried out. These compounds possessed some of the biological properties of the natural toxin, but were much less active. The 2-oxoadamantanopyrimidines, on the other hand, had a different mode of action and were found to possess local anaesthetic and analgesic properties. The toxicity of a limited number of precursors to saxitoxin analogues were examined, and found to be relatively inactive.

Acknowledgements

Summary

For Rosette.

PART 1: General Introduction	1
PART 2: Tetrodotoxin Analogues	3
1) Nomenclature	5
2) Introduction	11
3) Synthesis of 3,5-diazatetracyclo (7.3.1.1 <sup>7,11</sup> .0 <sup>1,6</sup> )tetradecane (adamantane[2,1-d]pyrimidine) and related compounds	15
i) Discussion	15
ii) P.m.r. spectra	28
iii) Experimental	42
4) Synthesis of 2,4-diazatetracyclo (7.3.1.1 <sup>7,11</sup> .0 <sup>1,6</sup> )tetradecane (adamantane[1,2-d]pyrimidine) and related compounds	52
i) Discussion	52
ii) P.m.r. spectra	74
iii) Experimental	88
5) Photochemical synthesis of 1,2-disubstituted adamantane	93
i) Discussion	99
ii) P.m.r. spectra	113
iii) Experimental	118

## CONTENTS

PART 3: Saxitoxin analogues	125
Acknowledgements	125
Summary	128
PART 1: General Introduction	1
PART 2: Tetrodotoxin Analogues	9
1) Nomenclature	9
2) Introduction	13
3) Synthesis of 3,5-diazatetracyclo [7.3.1.1 <sup>7,11</sup> .0 <sup>1,6</sup> ]tetradecanes (adamantano[2,1- <i>d</i> ]pyrimidines)	15
and related compounds	15
i) Discussion	15
ii) P.m.r. spectra	28
iii) Experimental	42
4) Synthesis of 2,4-diazatetracyclo [7.3.1.1 <sup>7,11</sup> .0 <sup>1,6</sup> ]tetradecanes (adamantano[1,2- <i>d</i> ]pyrimidines)	52
and related compounds	52
i) Discussion	52
ii) P.m.r. spectra	74
iii) Experimental	86
5) Photochemical syntheses of 1,2-disubstituted adamantanes	99
i) Discussion	99
ii) P.m.r. spectra	113
iii) Experimental	118

PART 3: Saxitoxin analogues	125
1) Introduction	125
2) Preparation of 4-aminoimidazol-2(3H)-ones and their fusion with nitroacetic acid	128
i) Discussion	128
ii) P.m.r. spectra	137
iii) Experimental	142
3) Preparation of 2-aminocyclopent-1-enes and their fusion with nitroacetic acid	149
i) Discussion	149
ii) Experimental	160
PART 4: Biological evaluation of tetrodotoxin and saxitoxin analogues	165
1) Introduction	165
2) Tetrodotoxin analogues	166
3) Saxitoxin analogues	171
REFERENCES	174



## PART 1

## GENERAL INTRODUCTION

Tetrodotoxin and saxitoxin are among the most potent, non-protein neurotoxins known. Both have a minimum lethal dose of  $\sim 8 \mu\text{g}/\text{kg}$  in mice, and are thus considerably more toxic than sodium cyanide ( $\text{LD}_{50}$  10 mg/kg) and 160,000 times more potent than cocaine<sup>1-3</sup> in blocking axonal conduction. Their mode of action, however, differs from that of the local anaesthetics. Although chemically distinct, Kao<sup>4</sup> has shown that the toxins possess nearly identical biological properties. Thus, at nanomolar concentrations they block the early transient inflow of sodium ions associated with the passage of an action potential in nerve membrane, causing respiratory failure and complete neuromuscular block.<sup>5</sup> Even at relatively high concentrations the potassium current is unaffected and it is because of this specificity of action that the toxins have proved useful in the study of excitation phenomena<sup>6-8</sup> and the molecular nature of sodium channels in conducting tissue.<sup>9</sup> Their specific action has raised the possibility of using the toxins in the identification and characterization of membrane sodium channels.<sup>10</sup> Binding experiments<sup>11</sup> with radioactively labelled tetrodotoxin indicate a scanty distribution of sodium channels. The use of purer, more specifically labelled saxitoxin

preparations has given more reliable estimates of the sodium channel density in various nonmyelinated nerve preparations. For example garfish, lobster and rabbit nerve have sodium channel densities of 35,90 and 110/ $\mu\text{m}^2$  respectively.<sup>12</sup>

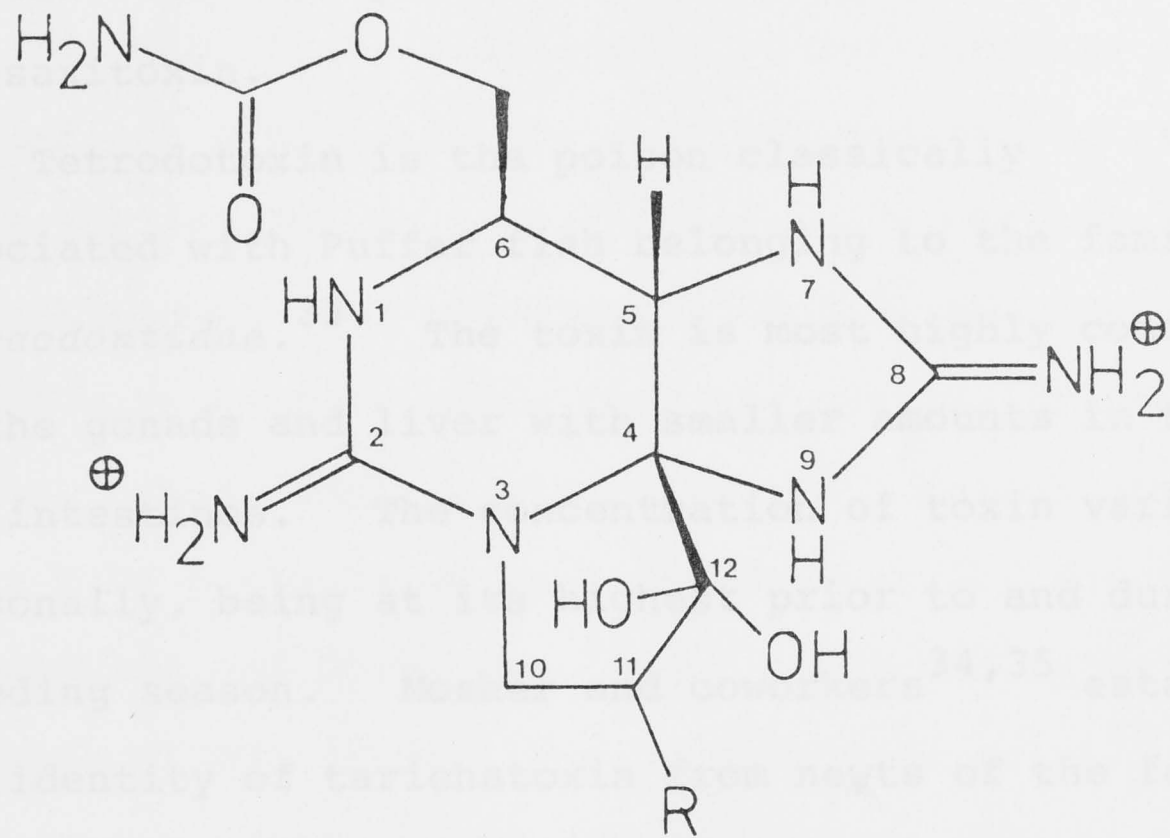
Both toxins have become valuable tools in neuropharmacological research. Tetrodotoxin has found clinical application as a muscle relaxant and pain-killer in cases of neurogenic leprosy and terminal cancer, and as a local anaesthetic in Japan.<sup>13</sup> Saxitoxin has found notoriety as a material held by the C.I.A.,<sup>14</sup> and its potential use in biological warfare has been suggested.<sup>15</sup>

Saxitoxin is a metabolite of certain types of dinoflagellate alga, notably *Gonyaulax catenella* and *Gonyaulax tamarensis*. When environmental conditions are favourable, these organisms reproduce rapidly and discolour the sea - a condition referred to as a "red-tide". Such phenomena are endemic to the East and West coasts of North America and most temperate coastal waters. Shellfish feeding on the dinoflagellates become toxic and may cause human and animal poisoning<sup>16</sup> and economic damage<sup>17</sup> to local shellfishing industries. Saxitoxin has been isolated as a dietary constituent of Alaskan butter clams (*Saxidomus giganteus*) and the Californian sea mussel (*Mytilus californianus*),<sup>18</sup> and as a metabolite of axenic cultures of *Gonyaulax catenella*.<sup>19</sup> Saxitoxin is a minor constituent of the toxins produced by *Gonyaulax tamarensis*,<sup>20</sup> the major components, gonyautoxins II and III are structurally related. The toxins were also

isolated from infested soft-shell clams, *Mya arenaria*.<sup>20</sup> Saxitoxin has also been found in a fresh water blue-green alga, *Aphanizomenon flos aquae*.<sup>21</sup>

Three species of xanthid crab, *Zosimus aeneus*, *Platypodia granulosa* and *Atergatis floridus* have been shown to contain saxitoxin.<sup>22-25</sup> The exoskeleton possesses the largest amount of toxin and large individual variations in crab toxicity are common. These observations suggest that the toxin is of exogenous origin but has not been positively ascribed to toxin producing dinoflagellate infestations. The sand crab, *Emerita analoga* contains saxitoxin in its digestive glands<sup>26</sup> and reportedly feeds on dinoflagellates (*Gonyaulax*-spp.).

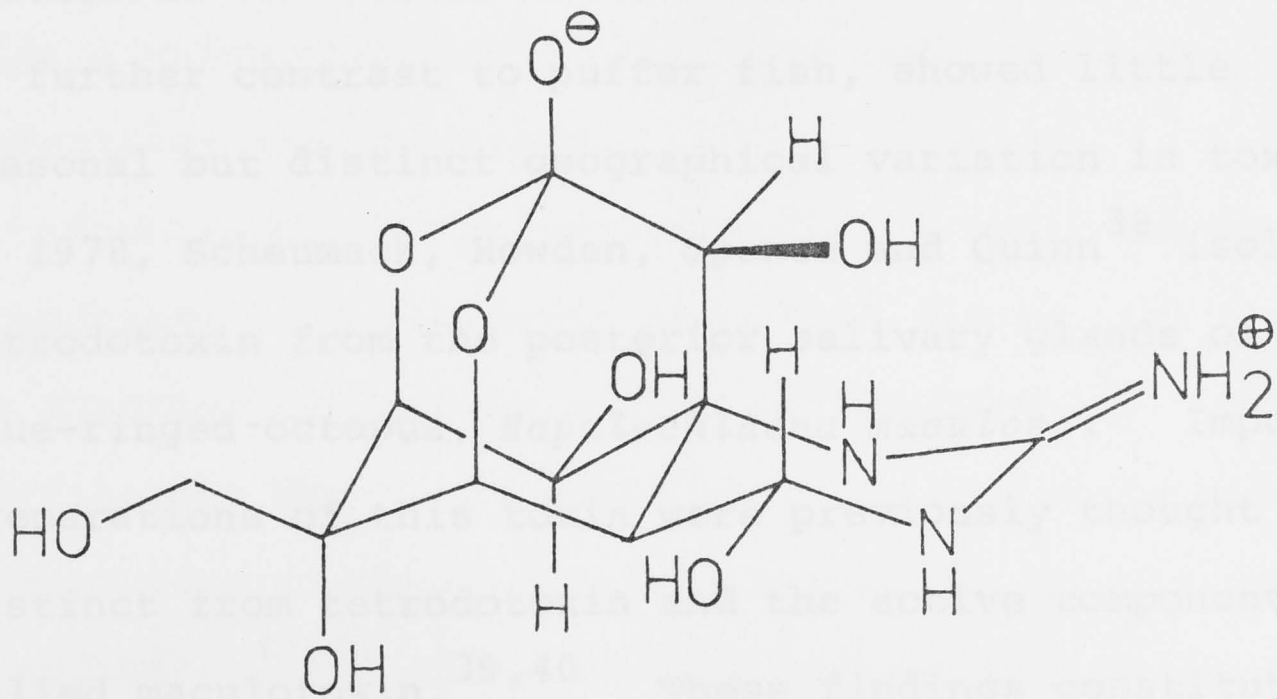
The determination of the structure of saxitoxin proved to be a formidable task. Initial investigations led to the proposal of incorrect structures, notably those of Russell<sup>27</sup> and Rapoport and coworkers.<sup>28</sup> The structure of saxitoxin was established by an X-ray crystallographic study<sup>29</sup> and subsequently confirmed<sup>30</sup> also by X-ray crystallography. It is a 3,4,6-trialkyl-2,8-diiminoperhydropurine with the structure illustrated in (1.1). The molecule has a perhydropurine skeleton, the N-3 and C-4 positions are joined by a three carbon bridge containing an hydrated ketone at C-12. Saxitoxin dehydrates under rigorous drying conditions, an observation which reconciles the difficulties in obtaining an accurate molecular formula. Another notable feature is the side-chain at C-6 which incorporates a carbamoyloxy group. The structures of gonyautoxins II and III were determined by Nakanishi and coworkers.<sup>31</sup>



(1.1) SAXITOXIN (R=H)

(1.2) GONYAUTOXIN II (R= $\alpha$ -OH)

(1.3) GONYAUTOXIN III (R= $\beta$ -OH)



(1.4) TETRODOTOXIN

They are  $11\alpha$ - and  $11\beta$ -hydroxysaxitoxins and are illustrated in (1.2) and (1.3). In 1977, Kishi and coworkers<sup>32</sup> reported the total synthesis of *d,l*-saxitoxin.

Tetrodotoxin is the poison classically associated with Puffer fish belonging to the family *Tetraodontidae*.<sup>33</sup> The toxin is most highly concentrated in the gonads and liver with smaller amounts in the skin and intestines. The concentration of toxin varies seasonally, being at its highest prior to and during the breeding season. Mosher and coworkers<sup>34,35</sup> established the identity of tarichatoxin from newts of the family *Salimandridae* with tetrodotoxin. Mosher and coworkers<sup>36</sup> also isolated tetrodotoxin from the skin of male and female Central American frogs of the genus *Atelopus*. A structurally related toxin was also obtained from one of the frogs, *Atelopus chiriquiensis*. Hashimoto and Noguchi<sup>37</sup> obtained tetrodotoxin from a goby, *Gobius criniger*. The goby exhibited greatest toxin concentration in the testes and skin but not the ovaries, and in further contrast to puffer fish, showed little seasonal but distinct geographical variation in toxicity. In 1978, Scheumack, Howden, Spence and Quinn<sup>38</sup> isolated tetrodotoxin from the posterior salivary glands of the blue-ringed octopus, *Hapalochlaena maculosa*. Impure preparations of this toxin were previously thought to be distinct from tetrodotoxin and the active component was called maculotoxin.<sup>39,40</sup> These findings constitute the

first case in which tetrodotoxin has been found in a venom. In all other known cases it occurs as a toxin in skin, muscle, liver, gonads and/or eggs.

The structural elucidation of tetrodotoxin was carried out simultaneously and independently in four laboratories, led by Mosher<sup>34</sup> working with toxin from the California newt and Tsuda,<sup>41</sup> Goto<sup>42</sup> and Woodward<sup>43</sup> all of whom used extracts from the ovaries of puffer fishes. The complete structure and absolute configuration were established by X-ray analysis of the toxin by Woodward and Gougoutas,<sup>44</sup> and confirmed by X-ray analysis of the crystalline hydrobromide salt.<sup>45</sup> Racemic tetrodotoxin was synthesized in 1972 by Kishi and coworkers.<sup>46</sup>

Tetrodotoxin is a zwitterionic polyhydroxy 2-iminoperhydroquinazoline with the structure illustrated in (1.4). Several features of the molecule are worthy of note, namely the *trans*-2-iminoperhydroquinazoline skeleton, a side-chain substituent (-CHOH-COO<sup>-</sup>) on the bridgehead carbon atom C-8a, the carboxyl group of which forms a unique hemilactal link and results in an adamantane-like structure.

Studies of the structure activity-relationships of tetrodotoxin and saxitoxin may yield information about the reactive components of the sodium channel. Direct modification of tetrodotoxin would appear productive because some minor alterations result in an attenuation of activity.<sup>47,48</sup> Tetrodotoxin derivatives of decreased

activity would be desirable clinically, but the cost of pure toxin and the laborious process of isolation make this approach unattractive. An alternative approach is the preparation of compounds bearing structural resemblances to some parts of the neurotoxin. Kao<sup>4</sup> has suggested that the guanidinium moiety of tetrodotoxin may be at least in part responsible for its highly specific physiological action. This hypothesis has been tested by several workers,<sup>49,50</sup> and in an extension of these studies Armarego and Reece<sup>51</sup> prepared various 2-imino- and 2-oxo-perhydroquinazolines and a zwitterionic 2-iminoperhydroquinazoline for biological evaluation. Tetrodotoxin has several unusual structural features none of which would appear to be individually responsible for the physiological activity of the toxin. The molecule may be described in steric terms as being spherical in shape with a protruding tongue - the guanidinium group, and it is possible that the toxicity of tetrodotoxin is at least in part due to its overall shape. The present work was directed toward the synthesis and biological evaluation of a number of 2-oxo- and 2-imino-adamantanopyrimidines\* incorporating a spherical non-penetrating moiety and a protruding hydrophilic

---

\* The term adamantane was abandoned by Chemical Abstracts in 1972 but will be retained in the General Introduction and Discussion for the sake of clarity (see also p. 9 ).

"tongue". The known biological activity of adamantane derivatives was a further consideration in the design of these analogues.

No systematic attempt has been made to study the structure-activity relationships of saxitoxin although Armarego and Reece<sup>52</sup> and Wegner and Rapoport<sup>53</sup> have investigated the preparation of 2,8-disubstituted perhydropurines. Schantz and coworkers<sup>54</sup> have prepared an acid hydrolysate of saxitoxin in which the carbamyl group at O-17 is absent. The derivative retains biological activity comparable to that of saxitoxin. Catalytic reduction of saxitoxin affords nontoxic dihydrosaxitoxin<sup>55</sup> in which the hydrated carbonyl function at C-12 has been replaced by a methylene group. From these observations it can be concluded that the guanidinium group at C-8 and the hydrated carbonyl at C-12 are indispensable for biological activity. The aim of this work was therefore to prepare saxitoxin analogues incorporating a 2,8-diiminoperhydropurine skeleton and a three carbon chain between N-3 and C-4 bearing a polar group at C-12.

It was anticipated that some of the analogues would be less toxic than tetrodotoxin and saxitoxin and thus more clinically useful compounds (e.g. as local anaesthetics and anticonvulsants).

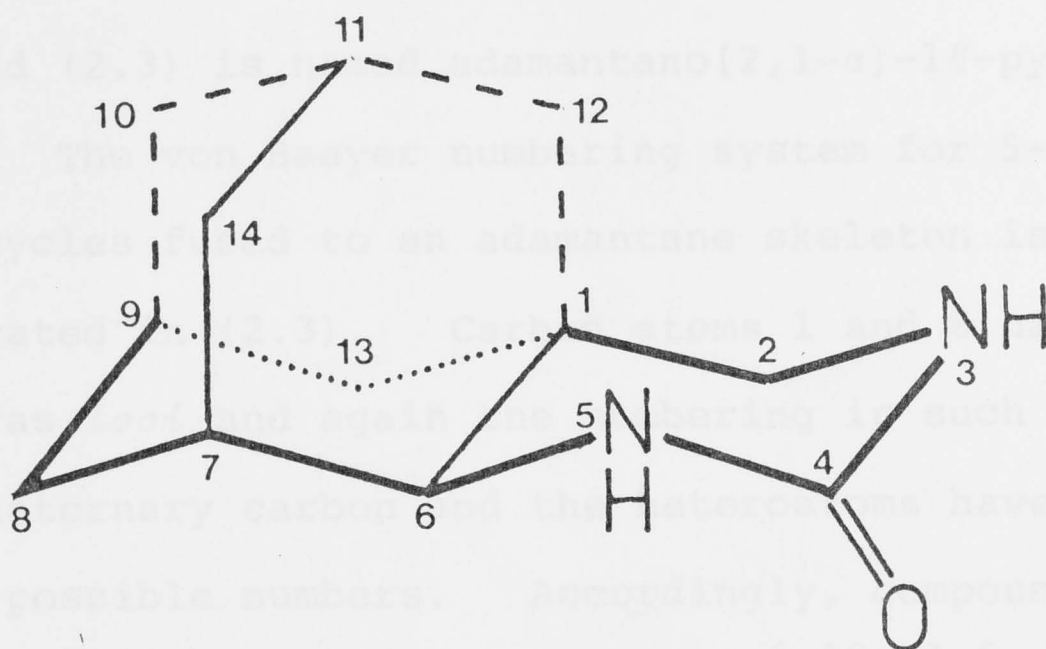


## PART 2

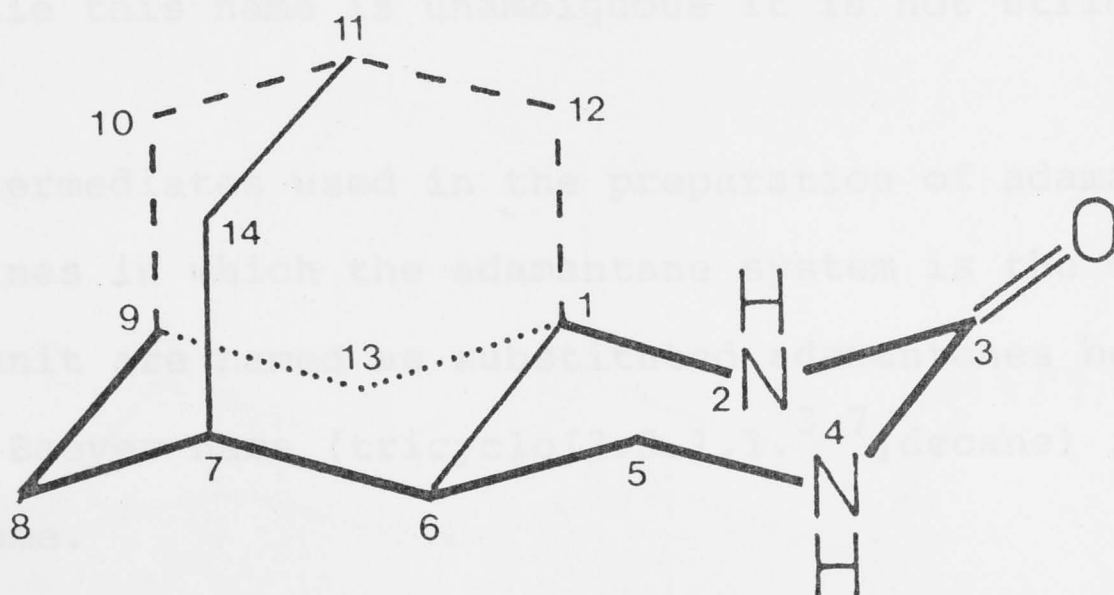
## TETRODOTOXIN ANALOGUES

1) Nomenclature

The term adamantane was abandoned by Chemical Abstracts in 1972 and replaced by tricyclo[3.3.1.1<sup>3,7</sup>]decane. However, in the general literature the systematic nomenclature has been widely adopted and will be retained in the present text. In the Experimental Sections, however, both the von Baeyer and the systematic nomenclature will be used, with the latter in brackets. Examples of the von Baeyer numbering system for adamantanopyrimidines are illustrated in (2.1) and (2.2). The carbon atoms numbered 1 and 9 have been chosen as *loci* such that C-1 is a quaternary carbon and the heteroatoms have the lowest possible numerical assignment. In both cases the heavy line passing through 7 atoms comprises the largest ring followed by the broken line (3 atoms) and the dotted line (1 atom). According to these conventions tetrahydroadamantano[2,1-*d*]pyrimidin-2(1*H*)-one (2.1) (systematic) is named 3,5-diazatetracyclo[7.3.1.1.<sup>7,11</sup>0<sup>1,6</sup>]tetradecan-4-one (von Baeyer), while tetrahydroadamantano[1,2-*d*]pyrimidin-2(1*H*)-one (2.2) is named 2,4-diazatetracyclo[7.3.1.1.<sup>7,11</sup>0<sup>1,6</sup>]tetradecan-3-one. A similar numbering system has been adopted for



(2.1)

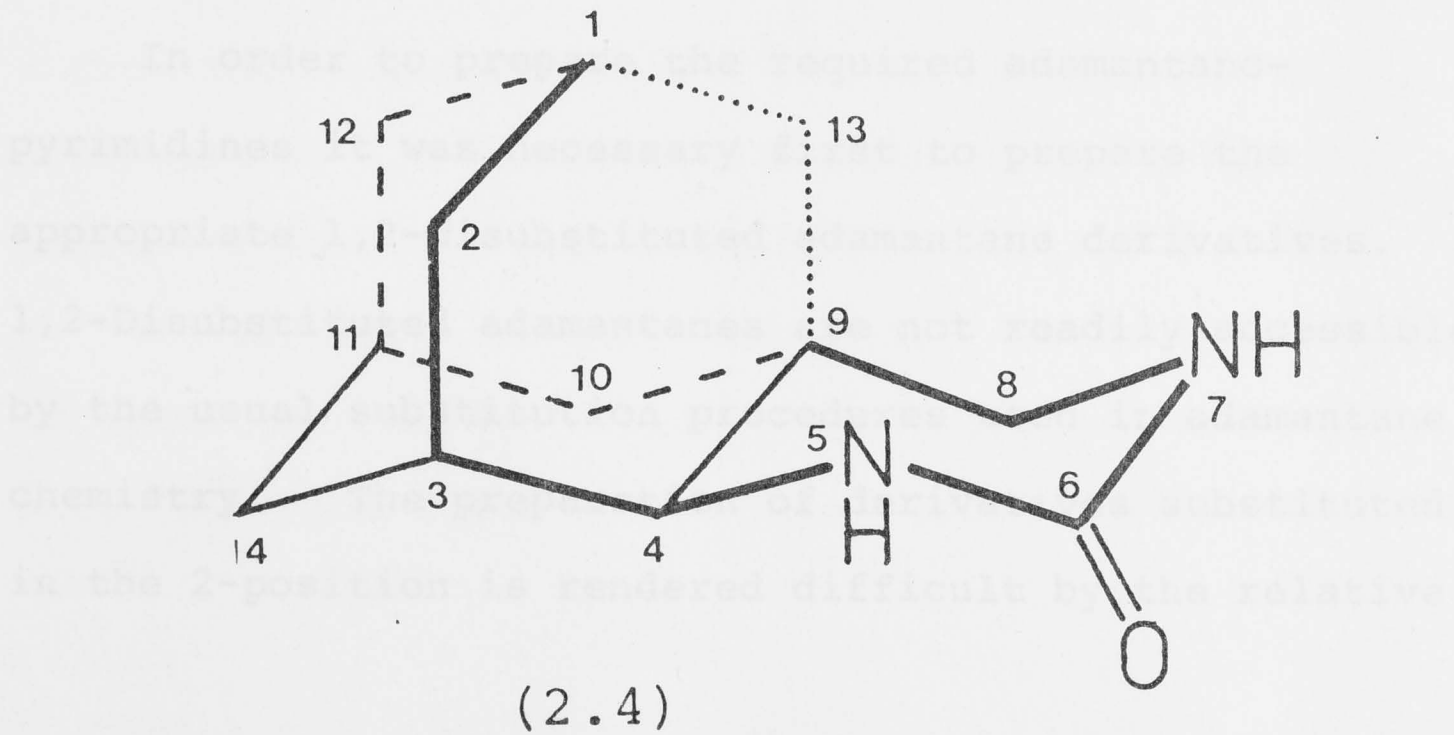
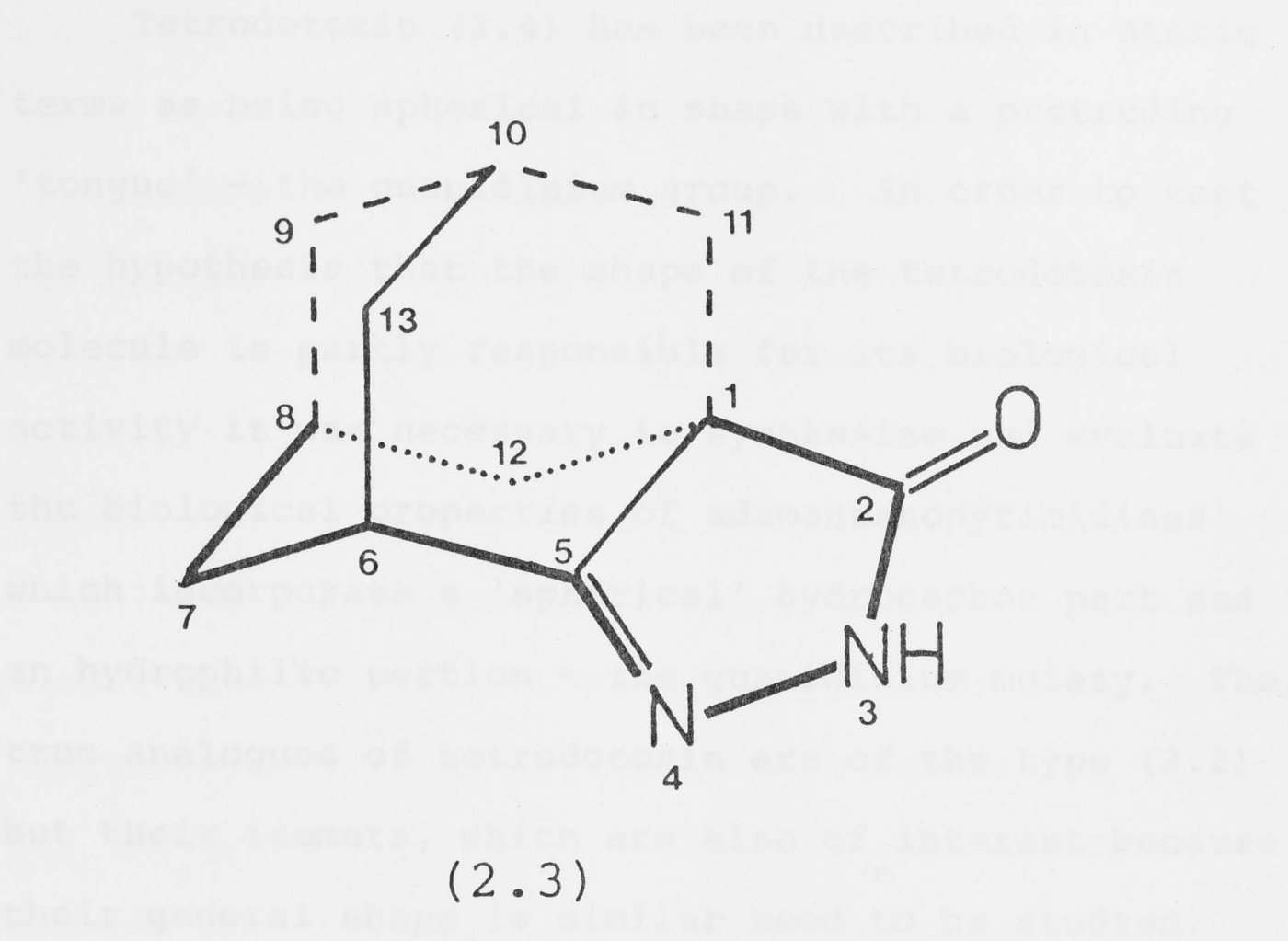


(2.2)

fused 5-membered heterocycles. In the systematic nomenclature a double bond within a ring (e.g. C=N) takes precedence over a substituent (e.g. C=O) and compound (2.3) is named adamantano[2,1-*c*]-1*H*-pyrazolin-5-one. The von Baeyer numbering system for 5-membered heterocycles fused to an adamantane skeleton is illustrated in (2.3). Carbon atoms 1 and 8 have been chosen as *loci* and again the numbering is such that C-1 is a quaternary carbon and the heteroatoms have the lowest possible numbers. Accordingly, compound (2.3) is named 3,4-diazatetracyclo[6.3.1.1<sup>6,10</sup>.0<sup>1,5</sup>]tridec-4,5-en-2-one in the von Baeyer nomenclature. This numbering system differs from that employed by Chakrabarti and coworkers<sup>56</sup> for adamantanopyrimidines. Their numbering is illustrated in figure (2.4). Carbon atoms 1 and 9 have been chosen as *loci* but C-1 is a tertiary carbon atom remote from the fused pyrimidine ring, consequently the heteroatoms cannot be given the lowest possible number. Tetrahydroadamantano[2,1-*d*]pyrimidin-2(1*H*)-one (2.4) has been called<sup>56</sup> 5,7-diazatetracyclo[7.3.1.1.<sup>3,11</sup>0<sup>4,9</sup>]tetradecan-6-one and, while this name is unambiguous it is not strictly correct.

Intermediates used in the preparation of adamantanopyrimidines in which the adamantane system is the only cyclic unit are named as substituted adamantanes because the von Baeyer name (tricyclo[3.3.1.1.<sup>3,7</sup>]decane) is cumbersome.

## 2) Introduction



## 2) Introduction

Tetrodotoxin (1.4) has been described in steric terms as being spherical in shape with a protruding 'tongue' - the guanidinium group. In order to test the hypothesis that the shape of the tetrodotoxin molecule is partly responsible for its biological activity it was necessary to synthesize and evaluate the biological properties of adamantanopyrimidines which incorporate a 'spherical' hydrocarbon part and an hydrophilic portion - the guanidinium moiety. The true analogues of tetrodotoxin are of the type (2.2) but their isomers, which are also of interest because their general shape is similar need to be studied.

If the hypothesis is correct the imino compounds should possess an activity and mode of action similar to that of tetrodotoxin though of lower intensity. The corresponding oxo-compounds (2.1) and (2.2) which lack the guanidinium function but retain the general shape and polar nature may possess different biological properties if they are active. The synthesis and chemical properties of the imino- and oxo-adamantano-pyrimidines are described in this Section.

In order to prepare the required adamantano-pyrimidines it was necessary first to prepare the appropriate 1,2-disubstituted adamantane derivatives. 1,2-Disubstituted adamantanes are not readily accessible by the usual substitution procedures used in adamantane chemistry. The preparation of derivatives substituted in the 2-position is rendered difficult by the relative

stability of radicals and carbonium ions at the 1-position (tertiary bridgehead carbon). Non-selective substitution of adamantane compounds leads primarily to reactions at the tertiary carbon atoms. For example, the treatment of adamantane with bromine under reflux affords 1-bromoadamantane by an ionic process, and in excellent yield.<sup>57-59</sup> The successful preparation of adamantan-2-one by Geluk and coworkers<sup>60-62</sup> has provided a useful intermediate in the synthesis of 2-substituted adamantanes. However, radical and ionic substitution reactions of adamantan-2-one are not generally suitable for the preparation of 1,2-disubstituted adamantanes because they usually give rise to mixtures. For example, radical bromination of adamantan-2-one affords a mixture of all possible monobrominated isomers.<sup>63</sup> The syntheses of a variety of 1,2-disubstituted adamantane derivatives appropriate to the present study have been reported since 1967. Successful general approaches have utilized intramolecular cyclization reactions of nitrenes,<sup>64-68</sup> carbenes<sup>68</sup> or free radicals,<sup>68-71</sup> the rearrangement of substituted protoadamantanes,<sup>72-75</sup> or the direct synthesis of the adamantane skeleton substituted in positions 1 and 2 from individual fragments.<sup>76</sup> Approaches to the synthesis of 1,2-disubstituted adamantanes involving nitrene insertions are described in section 5.

In 1971, Peters and coworkers,<sup>77</sup> in their attempts to epimerize bicyclo[3.3.1]nonane-3 $\alpha$ ,7 $\alpha$ -dicarboxylic acid (2.8) and its dimethyl ester found that these

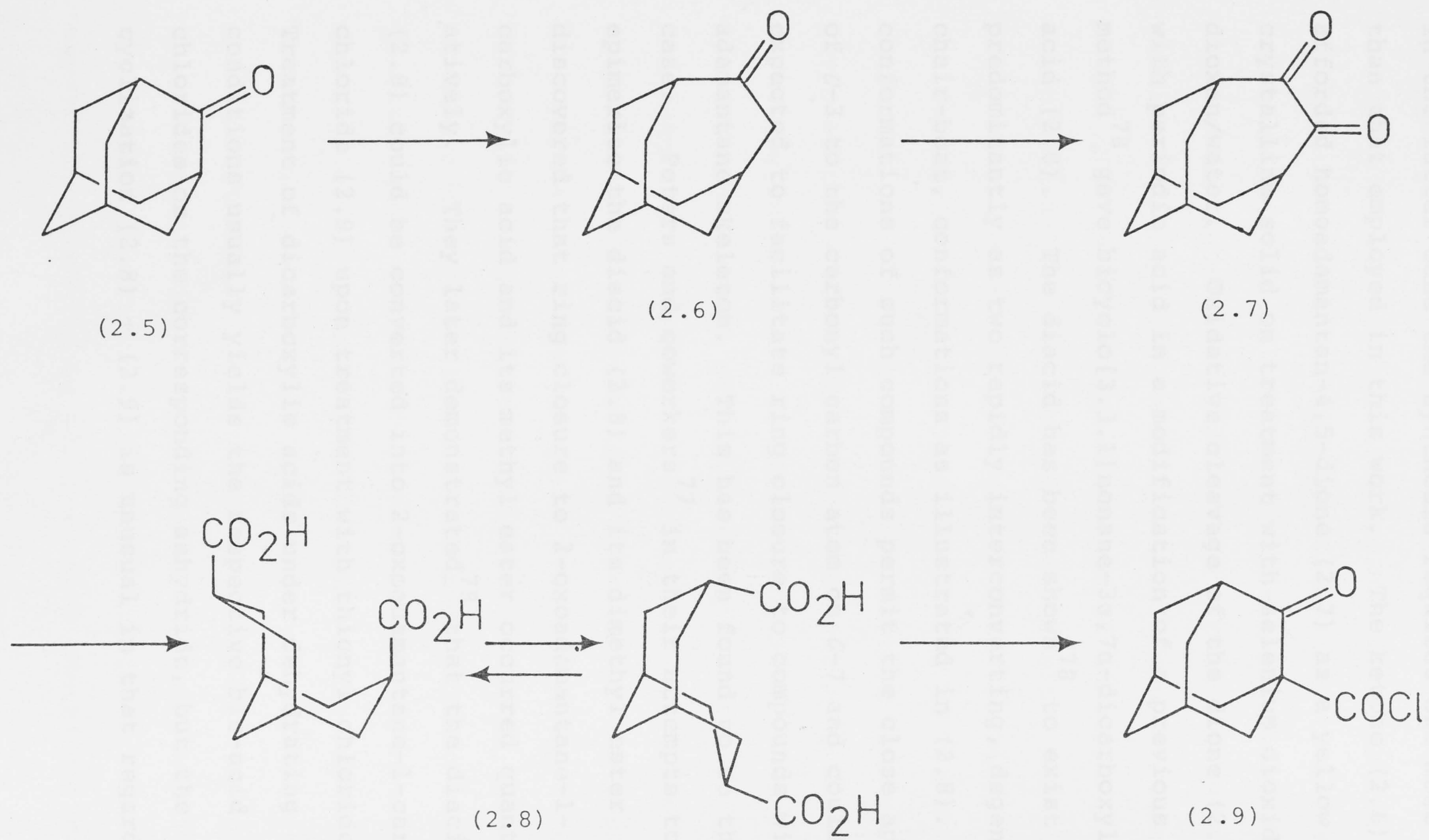
may also be prepared by the hydrolytic rearrangement of

bicyclononanes underwent facile ring closure to yield 2-oxoadamantane-1-carboxylic acid or its methyl ester. The reaction occurs in acidic or alkaline media and has proved useful for the preparation of 1,2-disubstituted adamantane derivatives.<sup>78-82</sup> The preparation of starting materials for the syntheses of adamantano-pyrimidines described in the following sections is based on earlier work.<sup>77,78</sup>

3) Synthesis of 3,5-diazatetracyclo[7.3.1.1.<sup>7,11</sup>0<sup>1,6</sup>] tetradecanes (adamantano[2,1-*d*]pyrimidines) and related compounds.

i) Discussion

Homoadamantane derivatives (e.g. (2.6)) are now readily accessible<sup>83-86,88</sup> and have proved to be convenient starting materials for the preparation of 3 $\alpha$ ,7 $\alpha$ -disubstituted-bicyclo[3.3.1]nonanes.<sup>77,78</sup> The facile cyclization of bicyclo[3.3.1]nonane-3 $\alpha$ ,7 $\alpha$ -dicarboxylic acid (2.8) to 2-oxoadamantane-1-carboxylic acid, methyl ester or acid chloride (see section 2) made this compound a good starting point for the synthesis of adamantano-pyrimidines. The diacid (2.8) was prepared by a two stage oxidative cleavage of homoadamantanone (2.6)<sup>77,78</sup> as illustrated in Scheme 2.1. Homoadamantanone (2.6) was obtained by ring enlargement of adamantanone (2.5) with diazomethane according to the procedure of Black and Gill.<sup>85</sup> Diazomethane was generated *in situ* from N-methyl-N-nitroso-*p*-toluenesulphonamide<sup>87</sup> and the product was isolated by steam distillation. Homoadamantanone may also be prepared by the hydrolytic rearrangement of



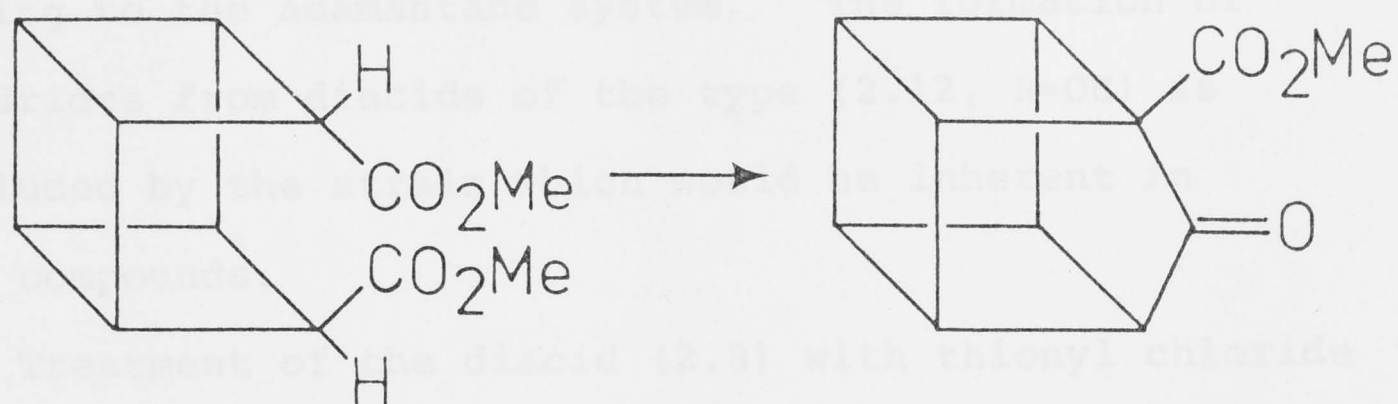
SCHEME 2.1



1-dichloromethyladamantane,<sup>88</sup> or by a Demjanov-Tiffeneau ring enlargement of 2-aminomethyl-2-hydroxyadamantane<sup>86</sup> but the yields are considerably lower and in the latter case the synthesis requires one more step than that employed in this work. The ketone (2.6) afforded homoadamantan-4,5-dione (2.7) as a yellow crystalline solid on treatment with selenium dioxide in dioxan/water. Oxidative cleavage of the dione (2.7) with periodic acid in a modification of a previous method<sup>78</sup> gave bicyclo[3.3.1]nonane-3 $\alpha$ ,7 $\alpha$ -dicarboxylic acid (2.8). The diacid has been shown<sup>78</sup> to exist predominantly as two rapidly interconverting, degenerate chair-boat, conformations as illustrated in (2.8). The conformations of such compounds permit the close approach of C-3 to the carbonyl carbon atom on C-7 and could be expected to facilitate ring closure to compounds with an adamantane skeleton. This has been found to be the case. Peters and coworkers<sup>77</sup> in their attempts to epimerize the diacid (2.8) and its dimethyl ester discovered that ring closure to 2-oxoadamantane-1-carboxylic acid and its methyl ester occurred quantitatively. They later demonstrated<sup>78</sup> that the diacid (2.8) could be converted into 2-oxoadamantane-1-carbonyl chloride (2.9) upon treatment with thionyl chloride. Treatment of dicarboxylic acids under dehydrating conditions usually yields the respective bis-acid chlorides or the corresponding anhydride, but the cyclization (2.8)  $\rightarrow$  (2.9) is unusual in that regard.

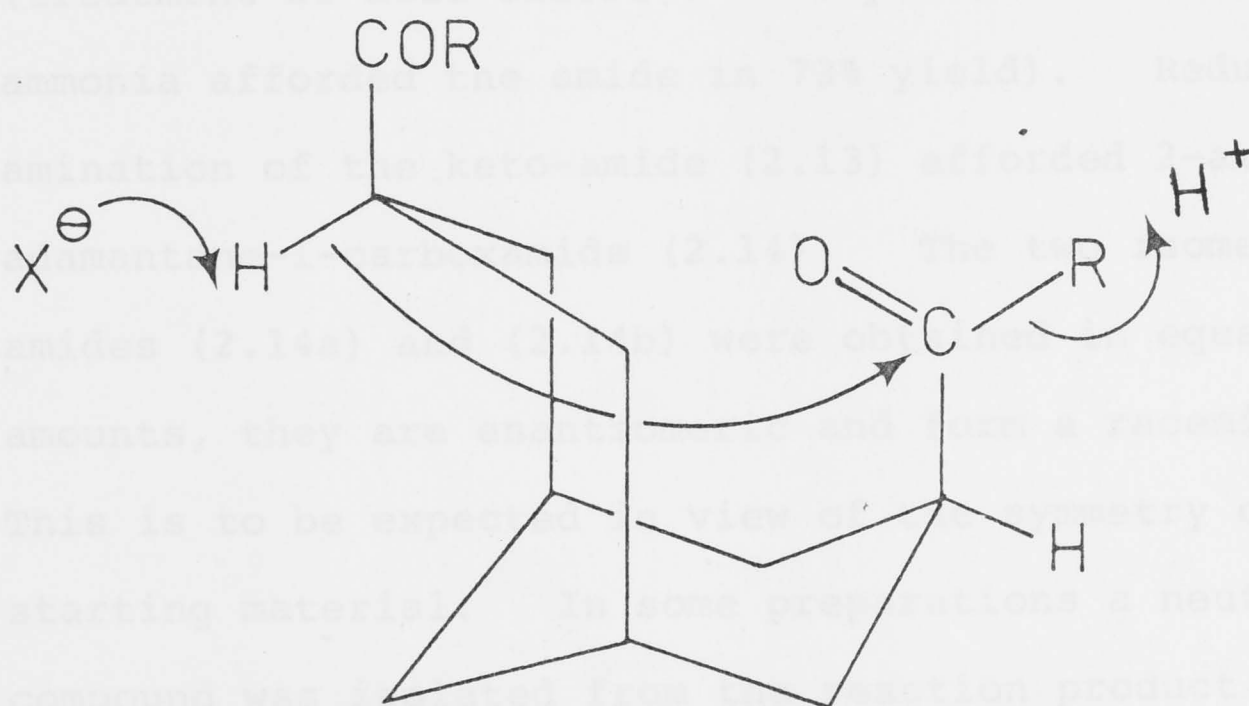
May be accounted for by the fact that the adamantane

Masamune *et al.*<sup>89</sup> have reported a similar reaction in which the endo-endo diester (2.10) undergoes an intramolecular Dieckmann condensation in the presence of methylsulphinyl carbanion to afford the keto-ester (2.11). Treatment of the diester with sodium methoxide resulted in epimerization to the exo-exo isomer presumably *via* the keto ester (2.11). Generally the Dieckmann reaction fails when the product cannot form a stable  $\beta$ -keto ester enolate. Exceptions to this general rule are cases such as the diester (2.10) and compounds of the type (2.12) in which cyclization is sterically favourable. The flexibility of the chair-boat conformation of the bicyclononane (2.12) enables the close approach of C-3 to the carbonyl carbon on C-7. The proximity of reactive centres predisposes these compounds to intramolecular cyclization reactions under acidic or basic conditions which probably involve the movement of electrons as depicted in (2.12). The species  $X^-$  represents a nucleophile ( $Cl^-$ ,  $MeO^-$  *etc.*) responsible for the removal of a proton or the generation of a partial negative charge at C-3, and R may be  $OSOCl$  or  $Cl$  when the diacid is treated with thionyl chloride,  $OH$  when a mixture of concentrated hydrochloric acid and glacial acetic acid (1:3) is used or  $OCH_3$  when the dimethyl ester is treated with sodium methoxide. A point of interest is that sodium methoxide failed to epimerize the dimethyl ester of bicyclo[3.3.1]nonane-3 $\alpha$ ,7 $\alpha$ -dicarboxylic acid, but under similar conditions the diester (2.10) was epimerized. This observation may be accounted for by the fact that the adamantane



(2.10)

(2.11)

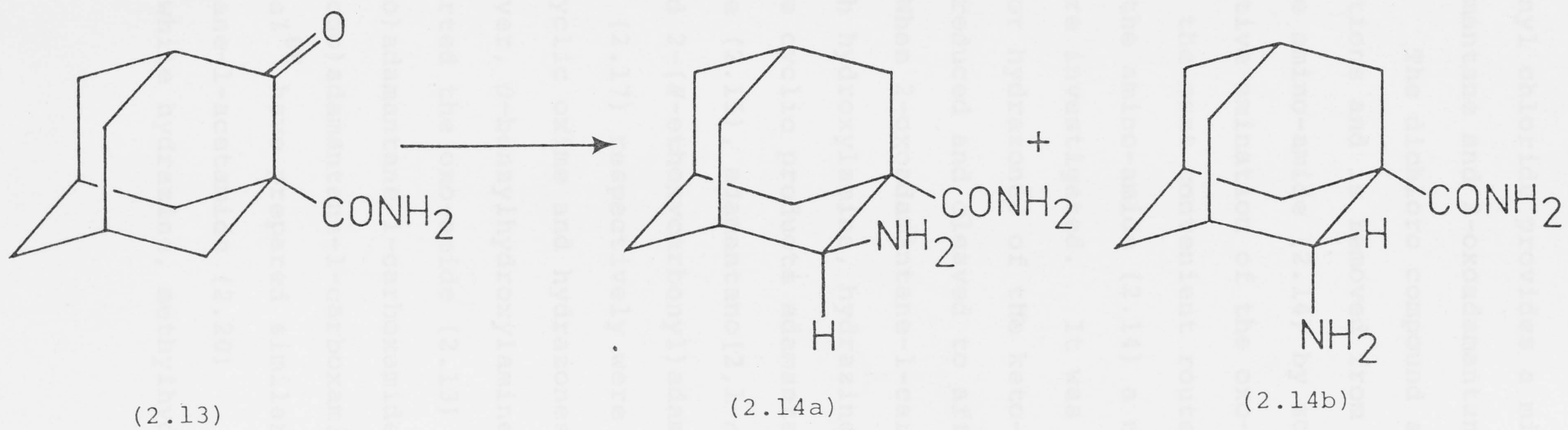


(2.12)

skeleton is relatively strain free<sup>90</sup> and rearrangements and ring closures leading to adamantane structures are facile. While the cyclization of the diester (2.10) to compound (2.11) is sterically favourable it would appear energetically less so compared with cyclizations leading to the adamantane system. The formation of anhydrides from diacids of the type (2.12, R=OH) is precluded by the strain which would be inherent in such compounds.

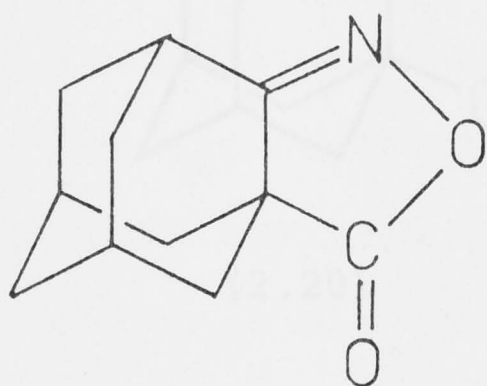
Treatment of the diacid (2.8) with thionyl chloride furnished 2-oxoadamantane-1-carbonyl chloride (2.9) in excellent yield. The acid chloride (2.9) is the key intermediate in the preparation of adamantanopyrimidines described below and in section 4. This acid chloride was converted into 2-oxoadamantane-1-carboxamide (2.13) in 90-95% yield with ammonia and ether, which is an improvement on the method of Tabushi and Aoyama,<sup>80</sup> (treatment of acid chloride in dry THF with 28% aqueous ammonia afforded the amide in 73% yield). Reductive amination of the keto-amide (2.13) afforded 2-amino-adamantane-1-carboxamide (2.14). The two isomeric amides (2.14a) and (2.14b) were obtained in equal amounts, they are enantiomeric and form a racemic mixture. This is to be expected in view of the symmetry of the starting material. In some preparations a neutral compound was isolated from the reaction product and was shown to be 2,2-dichloroadamantane by comparison with an authentic sample.<sup>91</sup> The diacid (2.8) was usually purified as its potassium salt, neutral impurities

SCHEME 2.2

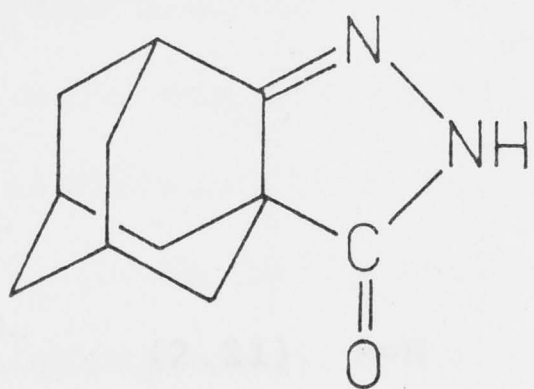


being extracted from aqueous solution with chloroform. Failure to execute this purification step leads to the retention of adamantanone (2.5) in the diacid (2.8) which with thionyl chloride provides a mixture of 2,2-dichloroadamantane and 2-oxoadamantane-1-carbonyl chloride (2.9). The dichloro compound survives subsequent reactions and is removed from acidic solutions of the amino-amide (2.14) by solvent extraction.

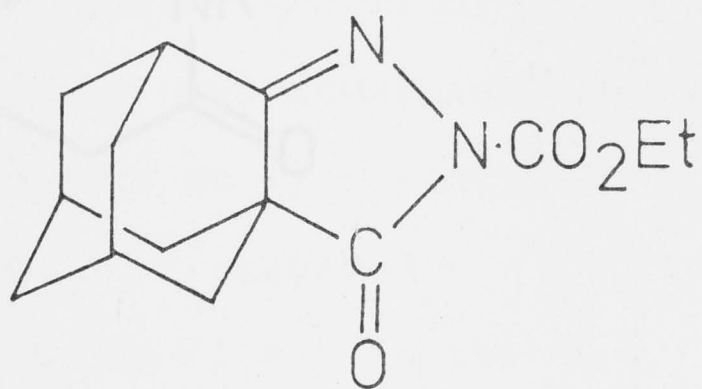
While reductive amination of the oxo-amide (2.13) was found to be the most convenient route for the preparation of the amino-amide (2.14) a number of alternatives were investigated. It was planned to prepare oximes or hydrazones of the keto-amide (2.13) which could be reduced and cleaved to afford the amino-amide (2.14). When 2-oxoadamantane-1-carboxamide (2.13) was treated with hydroxylamine, hydrazine or ethyl carbazate,<sup>92</sup> the cyclic products adamantano[2,1-*c*]isoxazolin-5-one (2.15), adamantano[2,1-*c*]-1*H*-pyrazolin-5-one (2.16) and 2-(*N*-ethoxycarbonyl)adamantano[2,1-*c*]pyrazolin-5-one (2.17) respectively were formed. The intermediate acyclic oxime and hydrazones could not be isolated. However, *O*-benzylhydroxylamine<sup>93</sup> and phenylhydrazine converted the oxo-amide (2.13) into 2-(benzyloximino)adamantane-1-carboxamide (2.19) and 2-(phenylhydrazono)adamantane-1-carboxamide (2.18). Chakrabarti *et al*<sup>68</sup> have prepared similar derivatives of 2-oxoadamantane-1-acetamide (2.20) and found that while hydrazine, methylhydrazine,



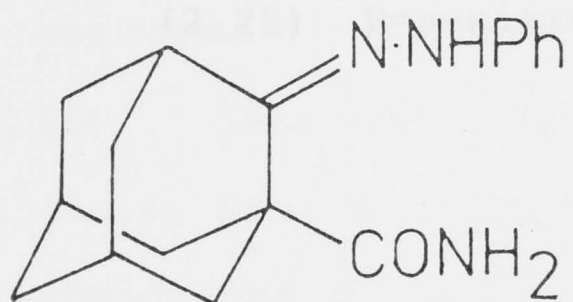
(2.15)



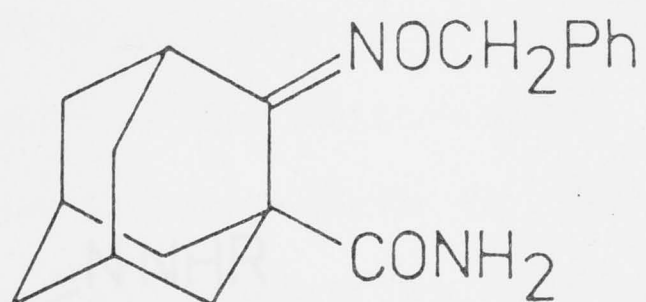
(2.16)



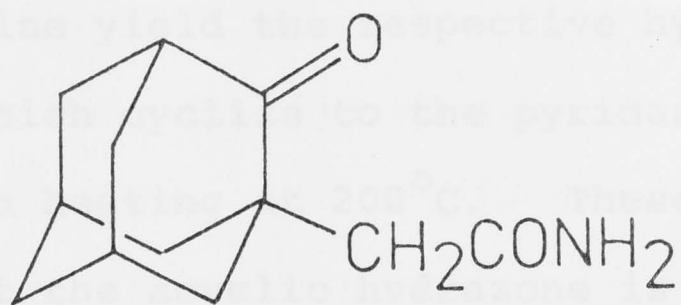
(2.17)



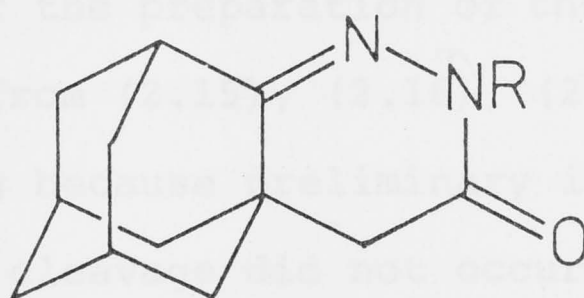
(2.18)



(2.19)



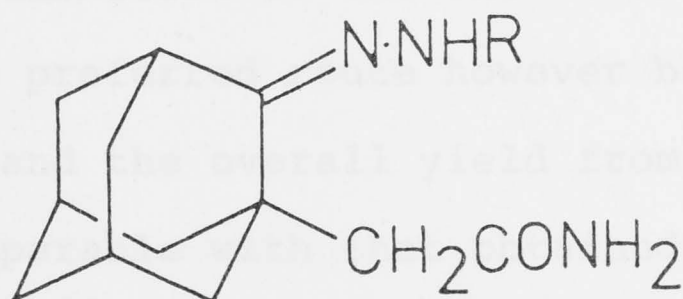
(2.20)



(2.21) R=H

(2.22) R=CH<sub>3</sub>(2.23) R=CH<sub>2</sub>CH<sub>2</sub>OH(2.24) R=*p*-chlorophenyl

(2.27) R=phenyl

(2.28) R=*p*-nitrophenyl

(2.25) R=phenyl

(2.26) R=*p*-nitrophenyl



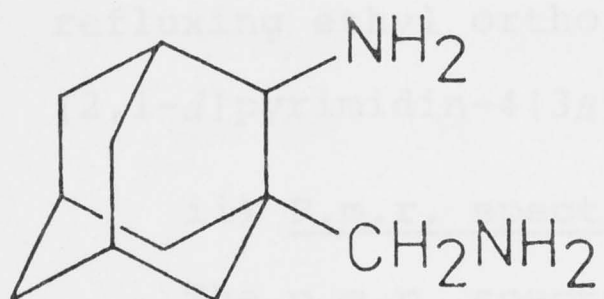
2-hydroxyethylhydrazine, and *p*-chlorophenylhydrazine afforded the respective cyclic products (pyridazinones) (2.21), (2.22), (2.23) and (2.24), phenylhydrazine and *p*-nitrophenylhydrazine yield the respective hydrazones (2.25) and (2.26) which cyclize to the pyridazinones (2.27) and (2.28) on heating at 200°C. These observations indicate that the acyclic hydrazone is formed first and subsequently cyclizes with elimination of ammonia. Chakrabarti *et al.*<sup>68</sup> were able to reduce the pyridazinones (2.21), (2.22), and (2.27) to deoxypyridazines with an excess of lithium aluminium hydride. Suitable methods for the preparation of the amino-amide (2.14) from (2.15), (2.16), (2.18) or (2.19) were not forthcoming because preliminary investigations indicated that ring cleavage did not occur readily.

In 1977, Stetter and coworkers<sup>82</sup> prepared adamantano[2,1-*c*]-1*H*-pyrazolin-5-one (2.16) by the reaction of 2-oxoadamantane-1-carboxylic acid methyl ester (from the acid chloride and methanol<sup>78,82</sup>) with hydrazine hydrate. They found that the pyrazolinone (2.16) could be converted into 2-aminoadamantane-1-carboxamide (2.14) in 82% yield with Raney nickel at 100°C in an autoclave. Synthesis of the amino-amide (2.14) by reductive amination of the oxo-amide (2.13) would seem to be the preferred route however because it is one step shorter and the overall yield from the acid chloride, 64% is comparable with that obtained by Stetter and coworkers.<sup>82</sup>

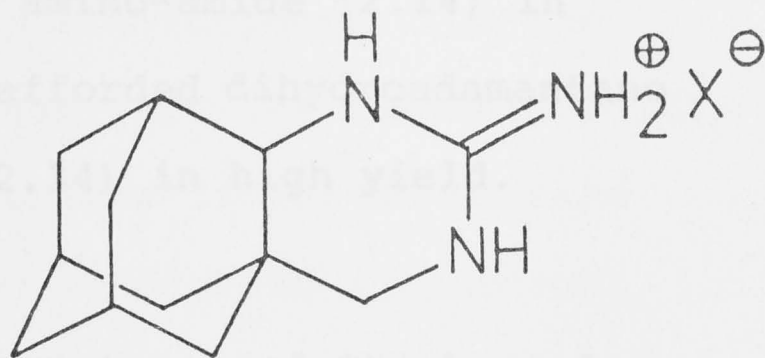
2-Aminoadamantane-1-carboxamide (2.14) was converted into 1-aminomethyladamantane-2-ylamine (2.29) by reduction with lithium aluminium hydride. The diamine (2.29) was characterized as the dihydrochloride salt because the free base readily absorbs carbon dioxide from the atmosphere. It was identical with the diamine obtained by Chakrabarti *et al.*<sup>68</sup> from the reductive amination of 2-oxo adamantane-1-methylamine, which was prepared by a Hoffmann rearrangement of the acetamide (2.20).

2-Aminotetrahydroadamantano[2,1-*d*]pyrimidine (2.30) sulphate and hydrochloride were prepared in good yields from the diamine (2.29) with S-methyl-*iso*-thiouronium sulphate and guanidine hydrochloride respectively. The hydrochloride salt was extremely hygroscopic, both the hydrochloride and the sulphate were characterized as identical picrates. Chakrabarti and coworkers<sup>68</sup> have prepared tetrahydroadamantano[2,1-*d*]pyrimidin-2(1*H*)-one (2.31) by two separate methods, namely i) the treatment of 2-aminoadamantane-1-acetamide with sodium hypobromite (56% yield) and ii) the reaction of 1-methylaminoadamantane-2-ylamine (2.29) with phosgene in toluene and pyridine (4% yield). In our hands the pyrimidinone (2.31) could be prepared in higher yields (93%) from the diamine (2.29) in a 2-phase system (2N.NaOH/phosgene in toluene).

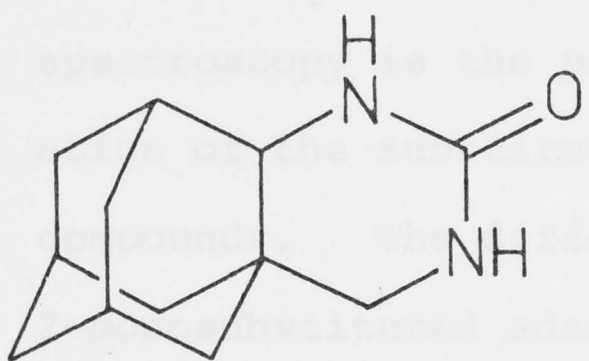
Under the same conditions 2-aminoadamantane-1-carboxamide (2.14) was converted into dihydroadamantano[2,1-*d*]pyrimidin-2,4(1*H*,3*H*)-dione (2.33).



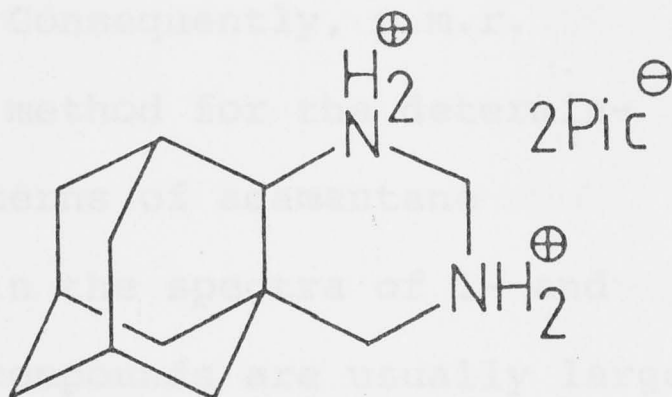
(2.29)



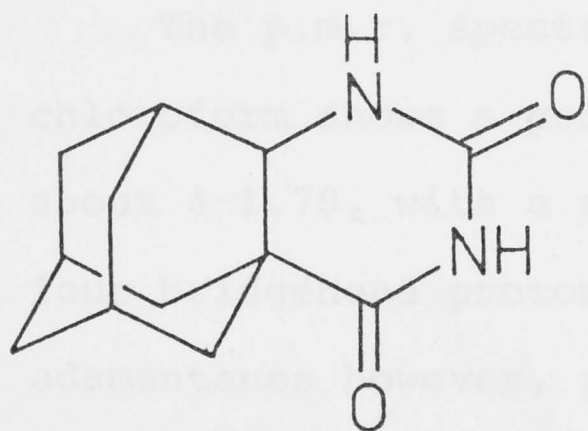
(2.30)



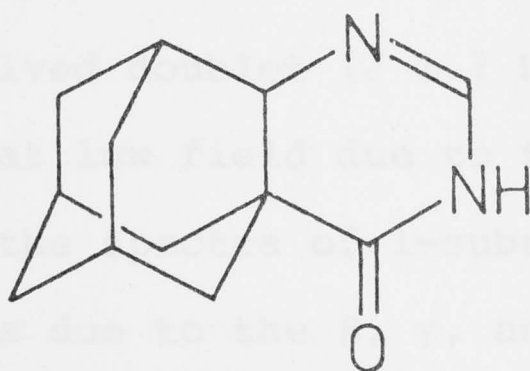
(2.31)



(2.32)



(2.33)



(2.34)

Hexahydroadamantano[2,1-*d*]pyrimidine (2.32) was prepared from the diamine (2.29) and 37% aqueous formaldehyde, the yield was low (10%) but may be improved by a different work up. The amino-amide (2.14) in refluxing ethyl orthoformate afforded dihydroadamantano[2,1-*d*]pyrimidin-4(3*H*)-one (2.34) in high yield.

ii) P.m.r. spectra

The p.m.r. spectra of adamantane and its 1- and 2-monosubstituted derivatives have been previously discussed.<sup>94,95</sup> The interpretation of the spectra of substituted adamantane compounds is facilitated by the absence of strong coupling and the relatively large chemical shift differences. Consequently, p.m.r. spectroscopy is the preferred method for the determination of the substitution patterns of adamantane compounds. The differences in the spectra of 1- and 2-monosubstituted adamantane compounds are usually large enough to allow compounds of the two types to be distinguished. The p.m.r. spectra of 1,2-disubstituted and 1,2,2-trisubstituted adamantanes are usually more complex due to the effects of additional substituents and to the asymmetry of the molecules.

The p.m.r. spectrum of adamantane in deuteriochloroform shows a poorly resolved doublet ( $J$  1.7 Hz) at about  $\delta$  1.78, with a shoulder at low field due to the four bridgehead protons. In the spectra of 1-substituted adamantanes however, resonances due to the  $\beta$ ,  $\gamma$ , and  $\delta$  protons are usually well separated, with the bridgehead ( $\gamma$ ) protons appearing as a broad band ( $W_{h/2}$  10 Hz) at

lower field than the other protons. The spectra of 1-adamantan-1-ylloxycarbonyl chloride (Fig. 2.1) and 1-adamantanylcyanamide (Fig. 2.2) are representative of 1-substituted adamantanes. In general, the chemical shifts of the  $\delta$  protons which are furthest from the substituent are displaced least from the chemical shift of the methylene protons of unsubstituted adamantane ( $\delta$  1.78) (see Fig. 2.1). The bridgehead ( $\gamma$ ) protons are displaced furthest from  $\delta$  1.78 (see Fig. 2.2) but the magnitude of the displacement is dependent upon the nature of the substituent. The p.m.r. spectrum of the 1-adamantyl cation<sup>96,97</sup> shows considerable deshielding of the bridgehead protons. This deshielding effect has been attributed to overlap of the vacant orbital lobe at the positively charged site with the inward projecting lobes of the bridgehead CH bonds. The electron deficiency at the 1-position is therefore shared among the other bridgehead positions, stabilizing the carbonium ion and deshielding the bridgehead protons. A similar mechanism may be operative in the deshielding of bridgehead protons in 1-substituted adamantanes. Substituent effects may be conveyed to the bridgehead protons by overlap of the inward projecting lobes of the  $sp^3$  orbitals of bridgehead CH bonds with the  $sp^3$  orbital of the carbon-substituent bond.

The C-2 proton is a distinguishing feature of the p.m.r. spectra of 2-monosubstituted adamantanes. Similarly, the bridgehead protons adjacent to the 2-position in adamantan-2-one and some of its derivatives are clearly discernible. The p.m.r. spectrum of

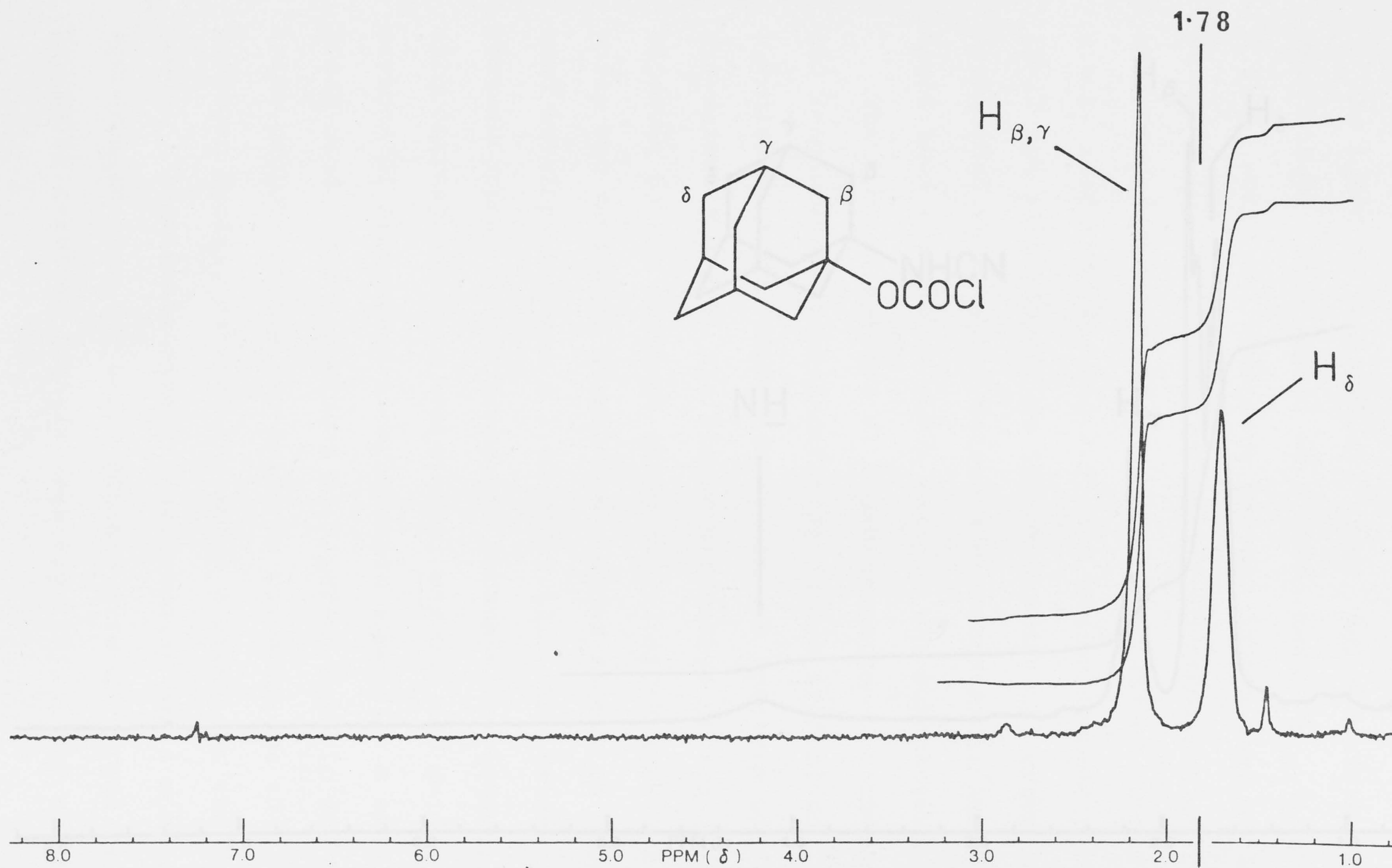


Fig. 2.1 P.m.r. spectrum of adamantan-1-oxycarbonyl chloride in  $CDCl_3$  at 60 MHz.

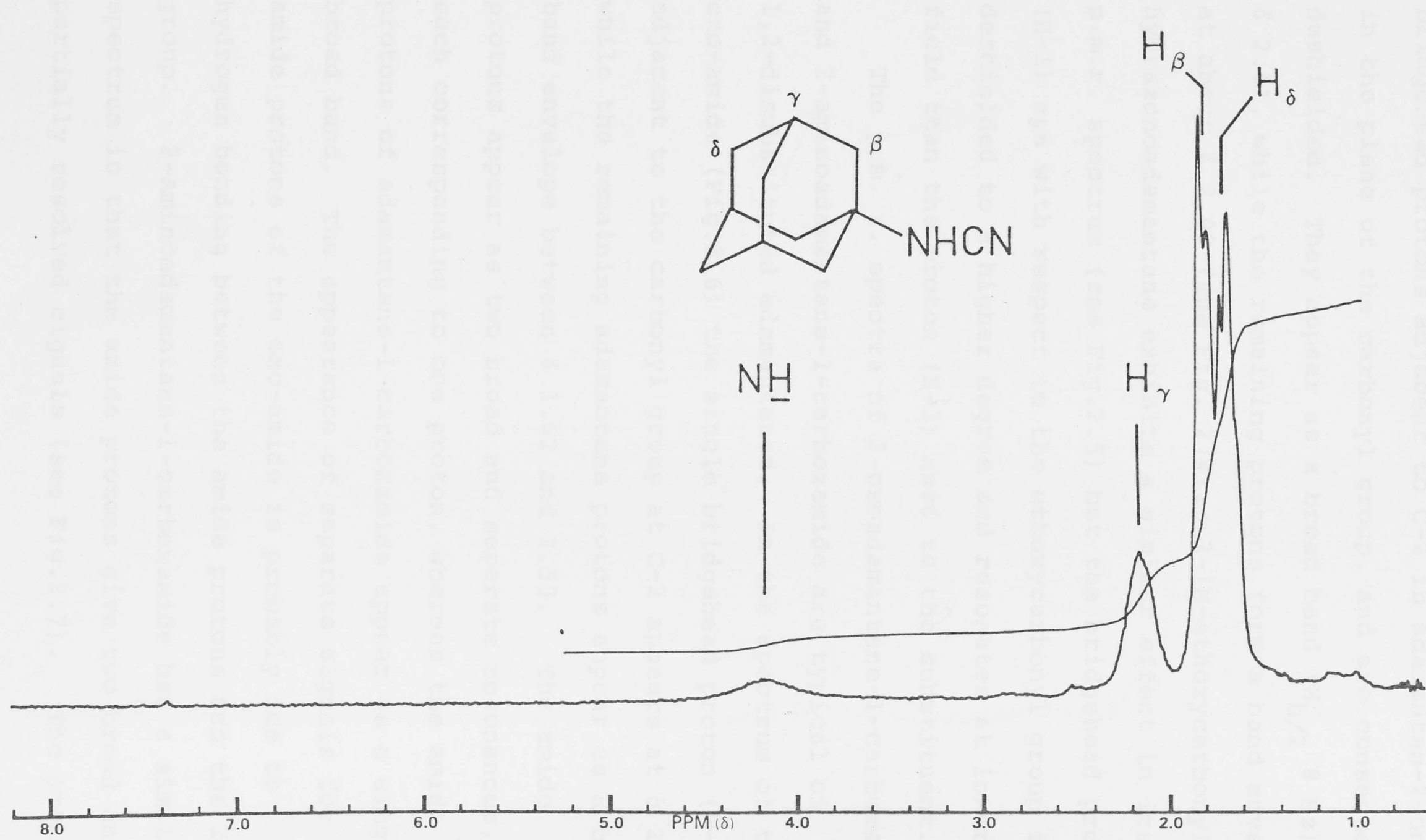


Fig. 2.2 P.m.r. spectrum of adamantan-1-ylcyanamide in  $\text{CDCl}_3$  at 60 MHz.

adamantan-2-ol (Fig. 2.3) exhibits a band envelope between  $\delta$  1.32 and 2.32 corresponding to 15 protons, whereas the proton at C-2, geminal to the hydroxy group appears at  $\delta$  3.83 and is thus easily assigned. The bridgehead protons adjacent to C-2 in adamantan-2-one lie in the plane of the carbonyl group, and are consequently deshielded. They appear as a broad band ( $W_{h/2}$  8 Hz) at  $\delta$  2.41, while the remaining protons form a band envelope at about  $\delta$  2.00 (see Fig. 2.4). 2-(N-ethoxycarbonyl)-hydrazonoadamantane exhibits a similar effect in its p.m.r. spectrum (see Fig. 2.5) but the bridgehead proton (H-1) *syn* with respect to the ethoxycarbonyl group is deshielded to a higher degree and resonates at lower field than the proton (H-3) *anti* to the substituent.

The p.m. r. spectra of 2-oxoadamantane-1-carboxamide and 2-aminoadamantane-1-carboxamide are typical of 1,2-disubstituted adamantanes. In the spectrum of the oxo-amide (Fig. 2.6) the single bridgehead proton (H-3) adjacent to the carbonyl group at C-2 appears at  $\delta$  2.67, while the remaining adamantane protons appear as a broad band envelope between  $\delta$  1.62 and 2.53. The amide protons appear as two broad and separate resonances, each corresponding to one proton, whereas the amide protons of adamantane-1-carboxamide appear as a single broad band. The appearance of separate signals for the amide protons of the oxo-amide is probably due to hydrogen bonding between the amide protons and the 2-oxo group. 2-Aminoadamantane-1-carboxamide has a similar spectrum in that the amide protons give two broad and partially resolved signals (see Fig. 2.7). The proton



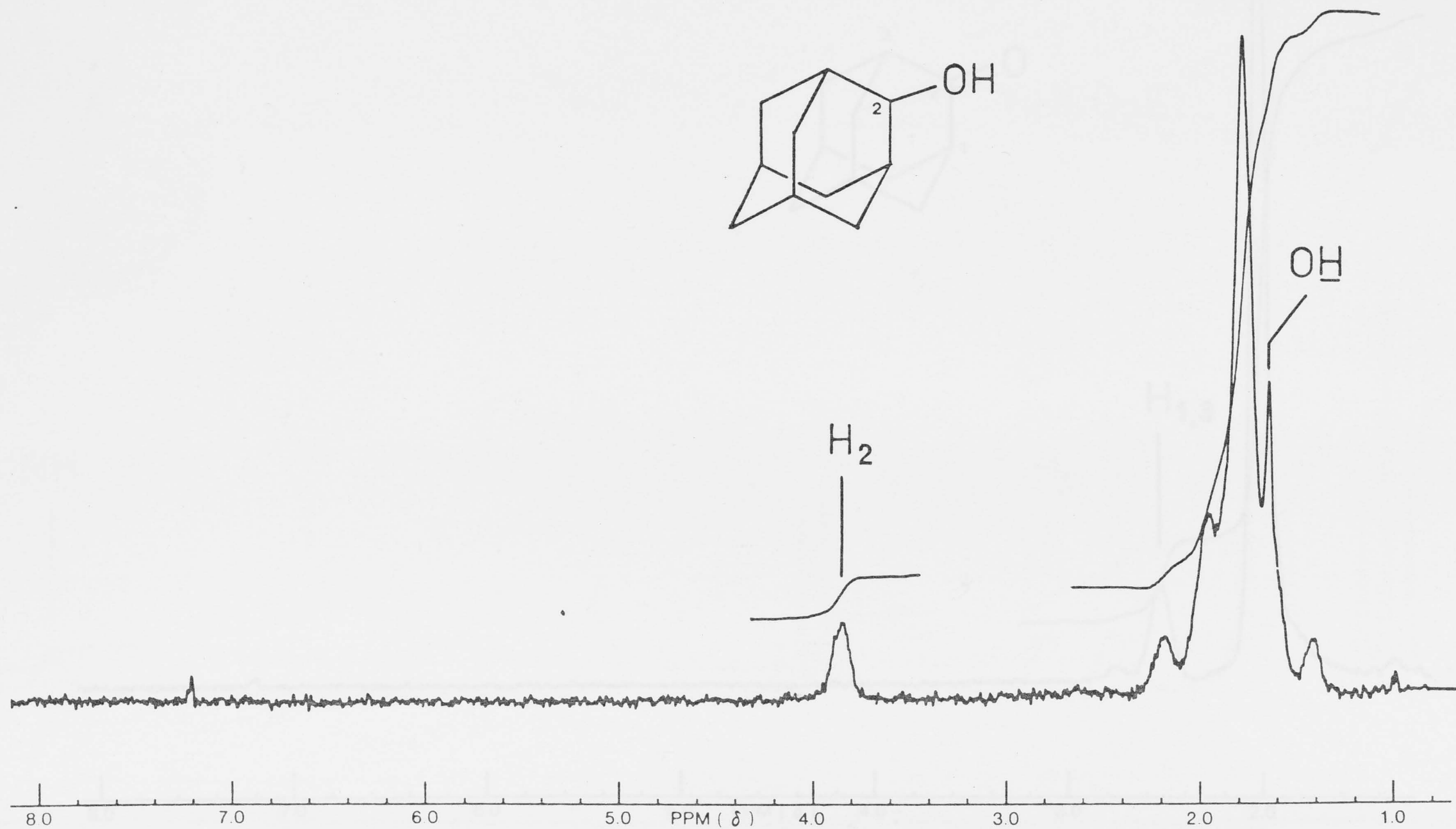


Fig. 2.3 P.m.r. spectrum of adamantan-2-ol in  $CDCl_3$  at 60 MHz.

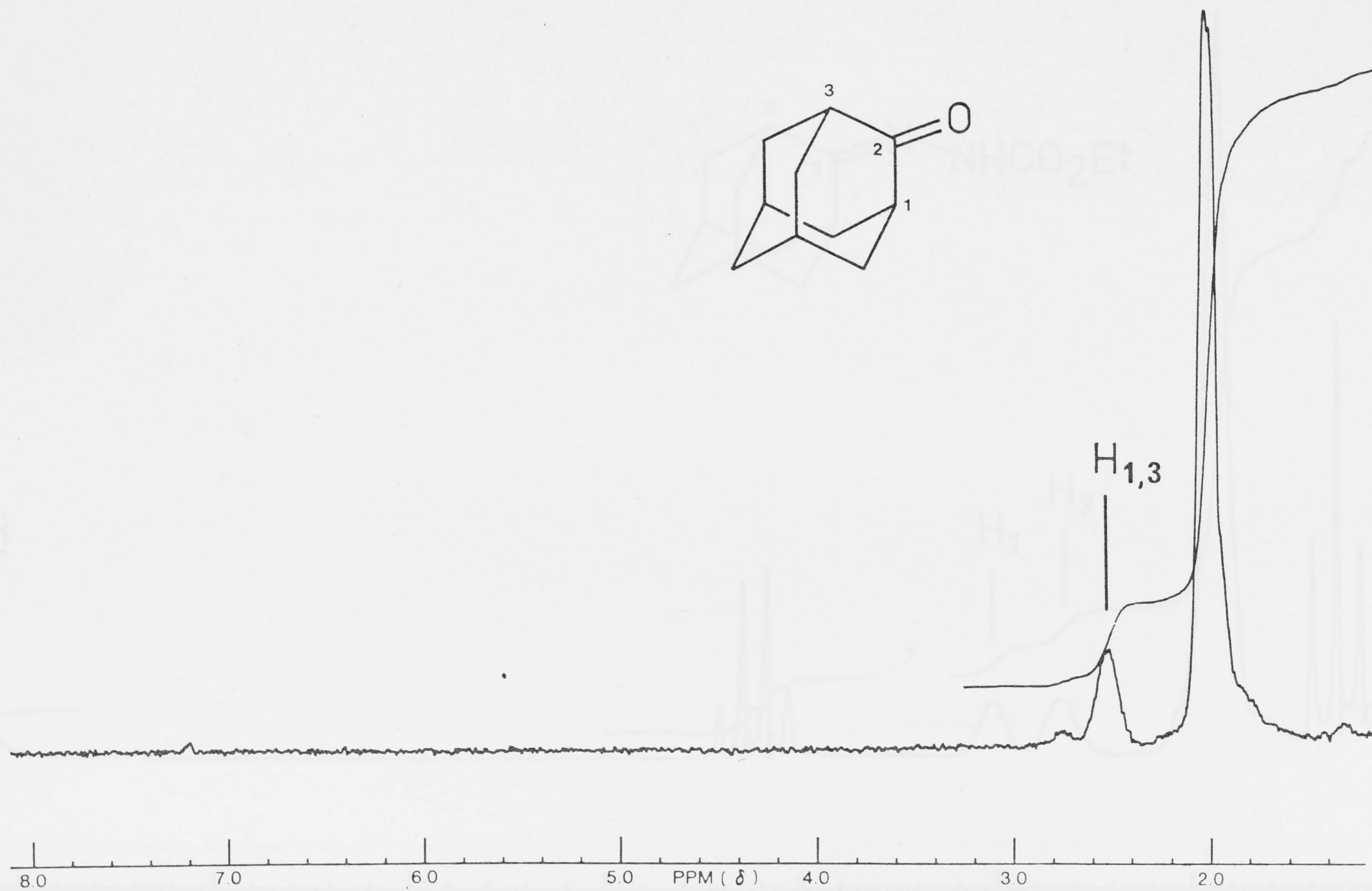


Fig. 2.4 P.m.r. spectrum of adamantan-2-one in  $\text{CDCl}_3$  at 60 MHz.

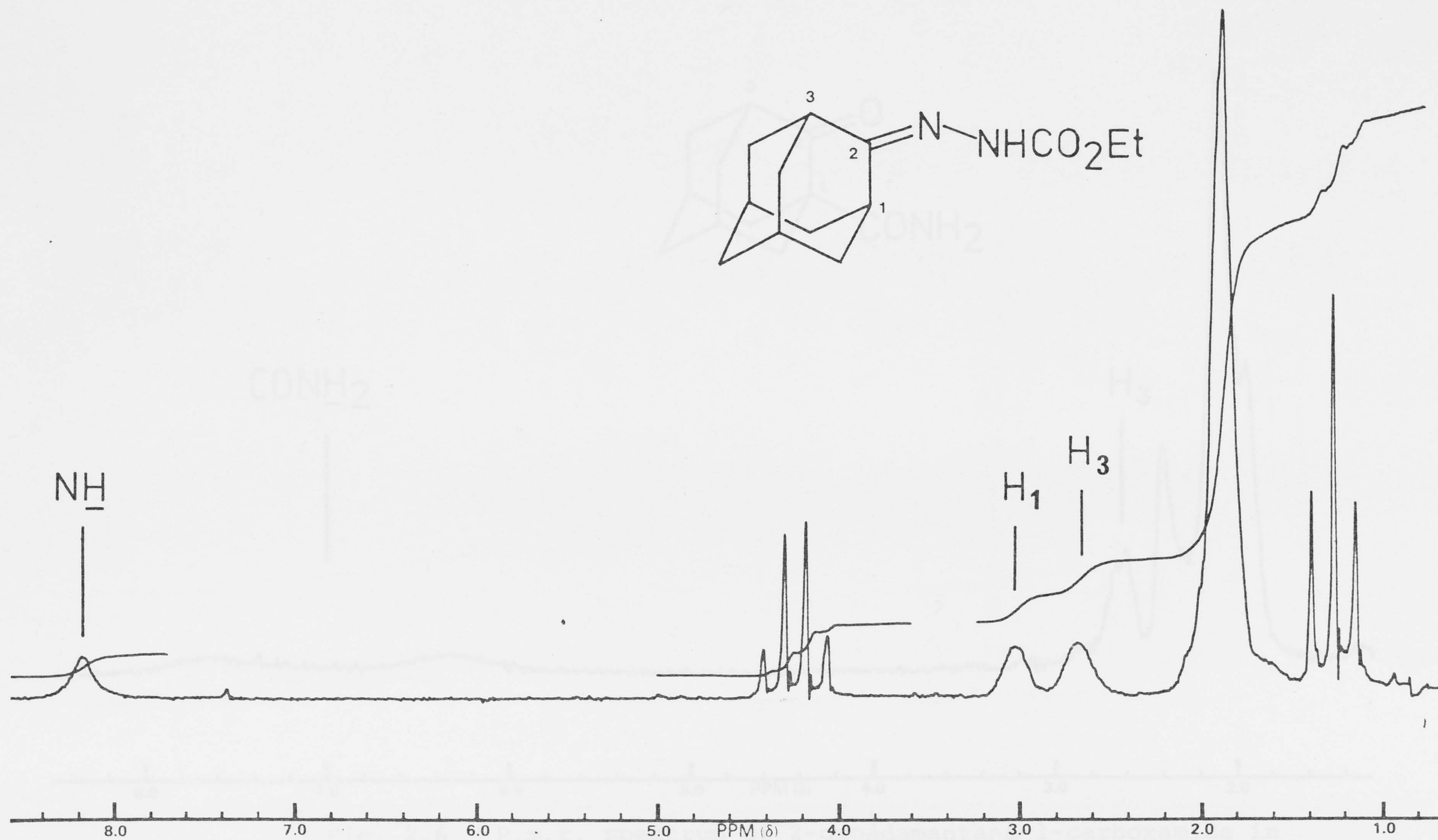
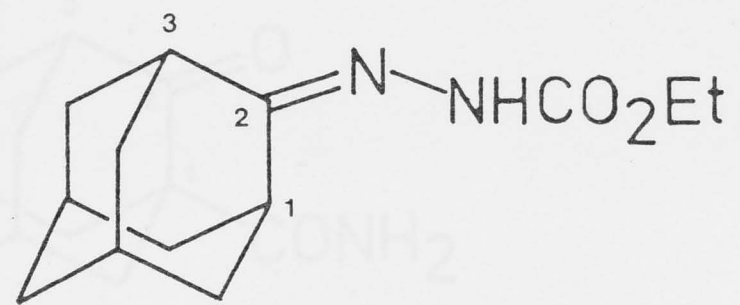


Fig. 2.5 P.m.r. spectrum of 2-(*N*-ethoxycarbonyl)hydrazonoadamantane in CDCl<sub>3</sub> at 60 MHz.

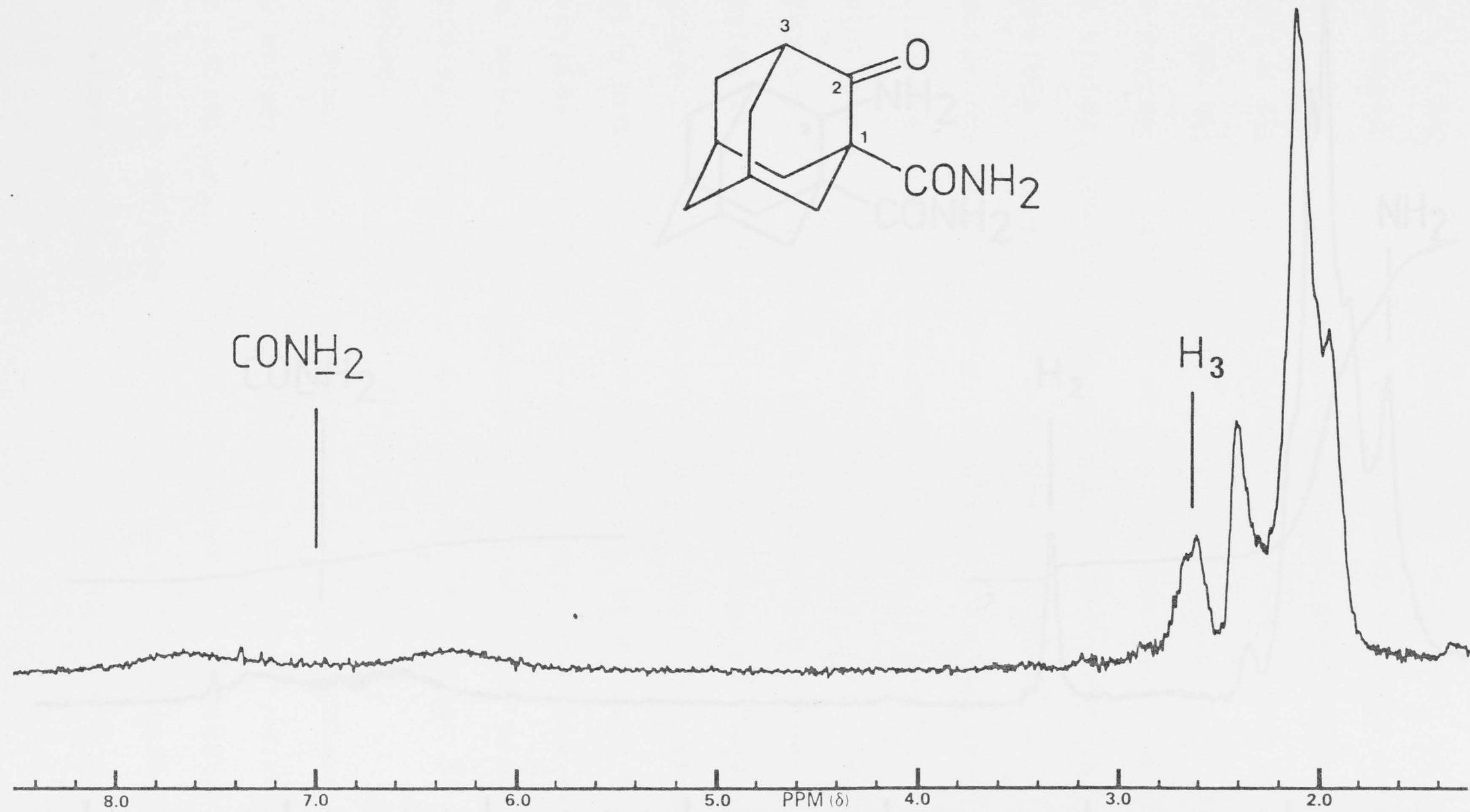


Fig. 2.6 P.m.r. spectrum of 2-oxadamantane-1-carboxamide in  $\text{CDCl}_3$  at 60 MHz.

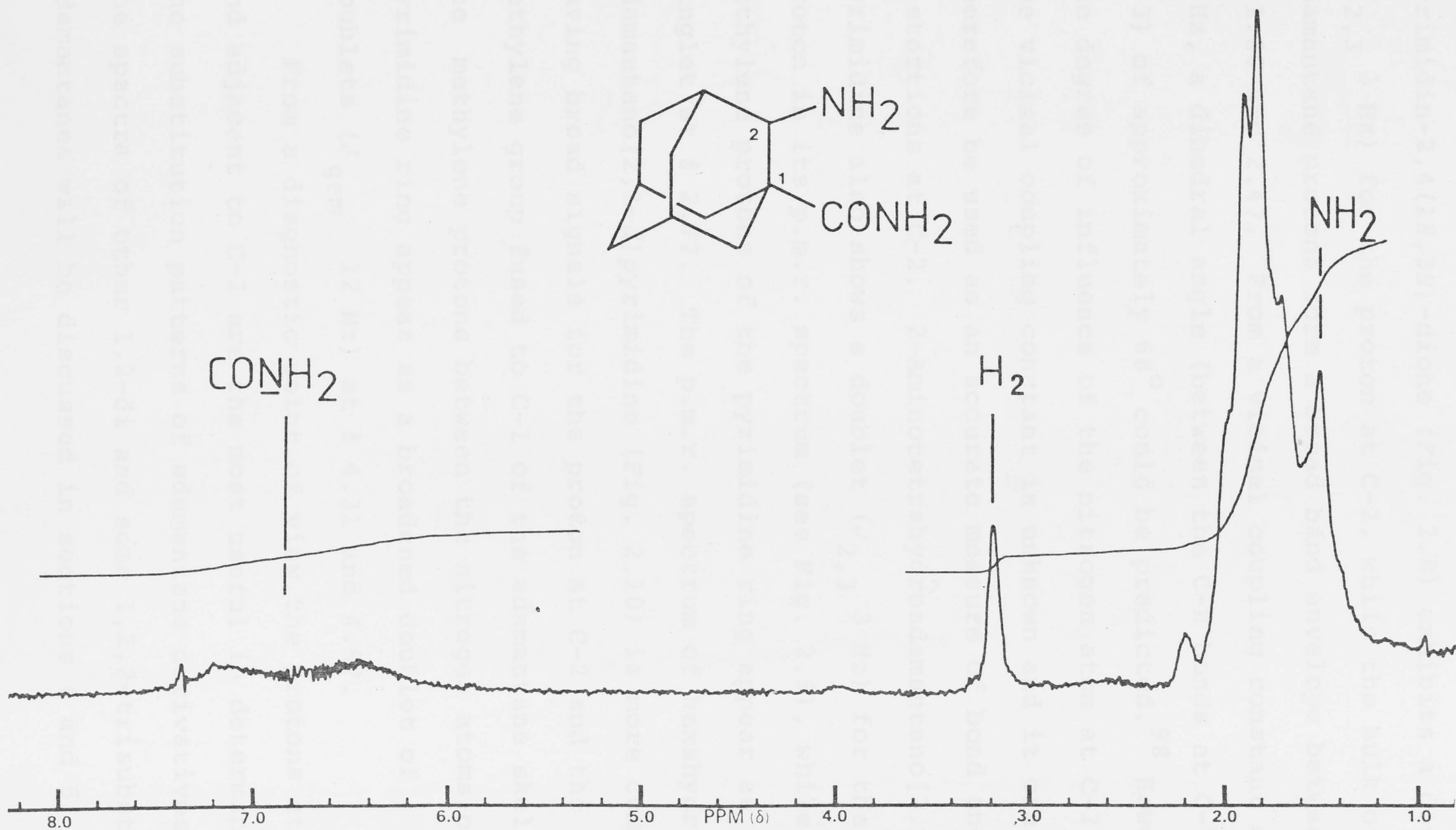


Fig. 2.7 P.m.r. spectrum of 2-aminoadamantane-1-carboxamide in  $\text{CDCl}_3$  at 60 MHz.

(H-2), geminal to the  $\text{NH}_2$  group appears as a broad singlet at  $\delta$  2.47, while the remaining protons form an unresolved multiplet between  $\delta$  1.53 and 2.13.

The p.m.r. spectrum of dihydroadamantano[2,1-*d*]pyrimidin-2,4(1*H*,3*H*)-dione (Fig. 2.8) exhibits a doublet ( $J_{2,3}$  3 Hz) for the proton at C-2, while the bulk of the adamantane protons form a broad band envelope between  $\delta$  1.30 and 2.47. From a vicinal coupling constant of 3 Hz, a dihedral angle (between the C-H bonds at C-2 and C-3) of approximately  $68^\circ$  could be predicted.<sup>98</sup> However, the degree of influence of the nitrogen atom at C-2 on the vicinal coupling constant is unknown and it cannot therefore be used as an accurate measure of bond angle distortions at C-2. 2-Aminotetrahydroadamantano[2,1-*d*]pyrimidine also shows a doublet ( $J_{2,3}$  3 Hz) for the C-2 proton in its p.m.r. spectrum (see Fig. 2.9), while the methylene protons of the pyrimidine ring appear as a singlet at  $\delta$  2.77. The p.m.r. spectrum of hexahydroadamantano[2,1-*d*]pyrimidine (Fig. 2.10) is more complex, having broad signals for the proton at C-2 and the methylene group fused to C-1 of the adamantane skeleton. The methylene protons between the nitrogen atoms of the pyrimidine ring appear as a broadened doublet of doublets ( $J_{\text{gem}}$  12 Hz) at  $\delta$  4.31 and 4.67.

From a diagnostic point of view the protons at C-2 and adjacent to C-2 are the most useful in determining the substitution patterns of adamantane derivatives. The spectra of other 1,2-di and some 1,2,2-trisubstituted adamantanes will be discussed in sections 4 and 5.

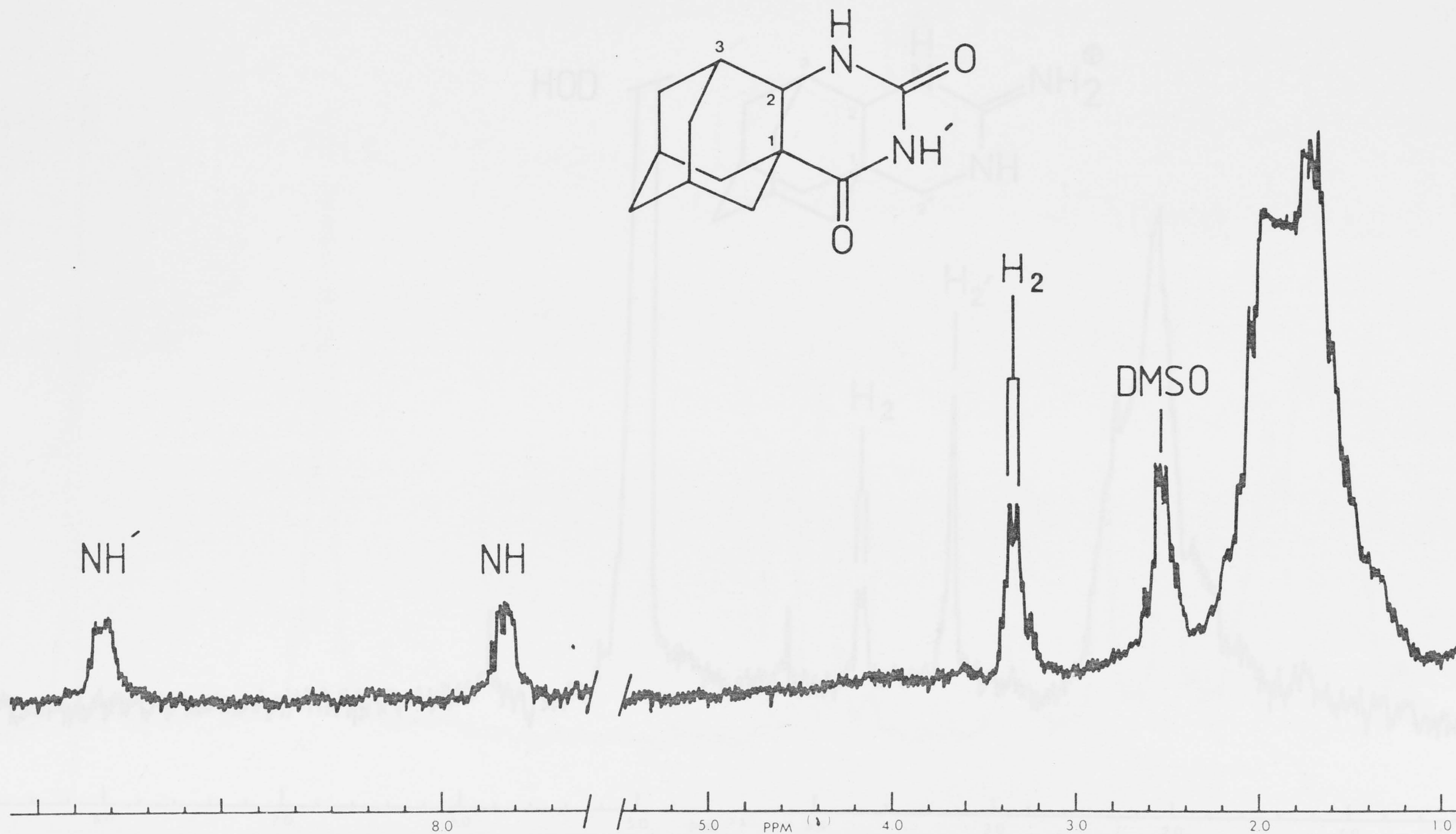


Fig. 2.8 P.m.r. spectrum of dihydroadamantano[2,1-*d*]pyrimidin-2,4(1*H*,3*H*)-dione in  $(\text{CD}_3)_2\text{SO}$  at 60 MHz.

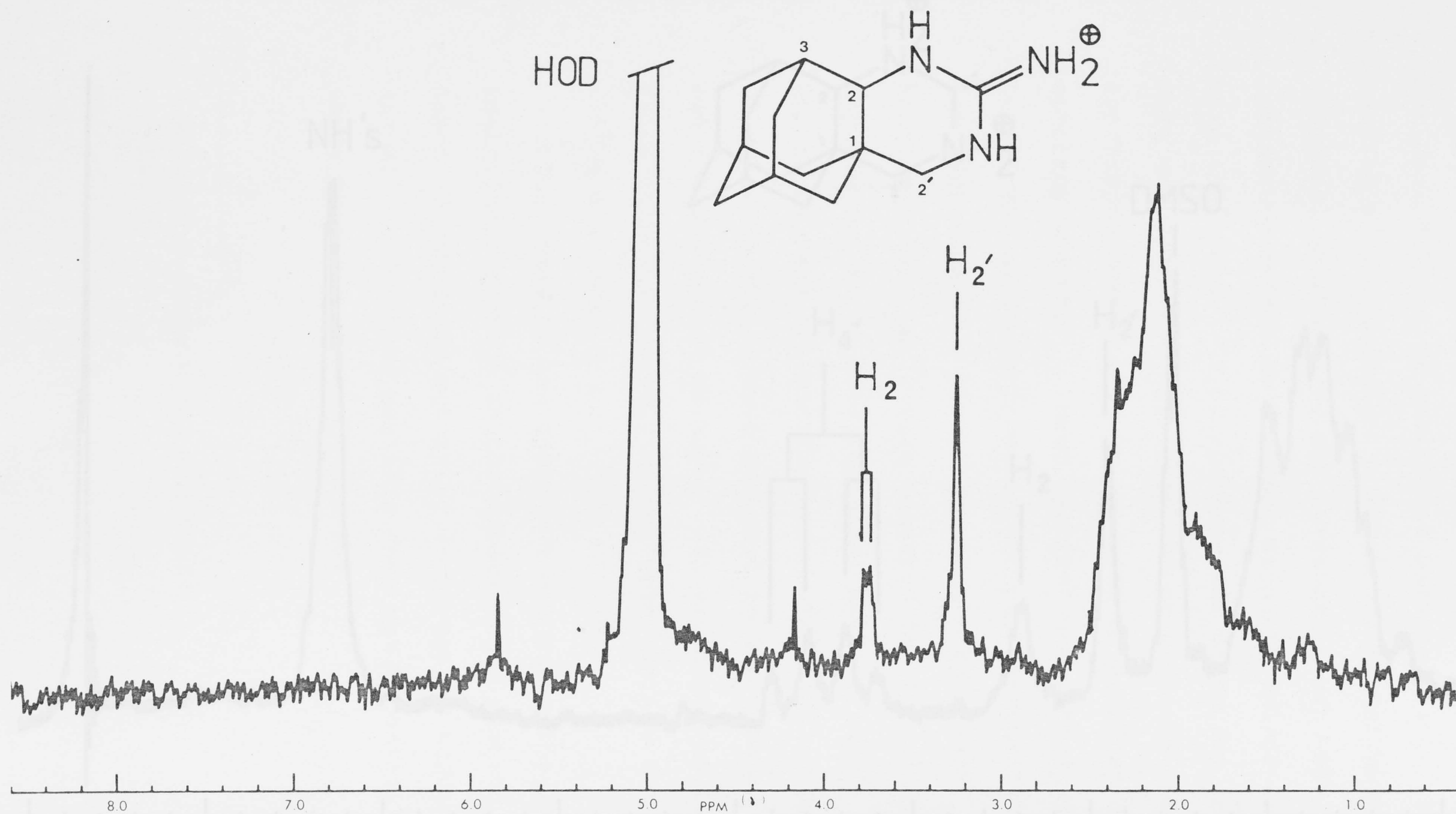


Fig. 2.9 P.m.r. spectrum of 2-aminotetrahydroadamantano[2,1-*d*]pyrimidine sulphate in D<sub>2</sub>O at 60 MHz.



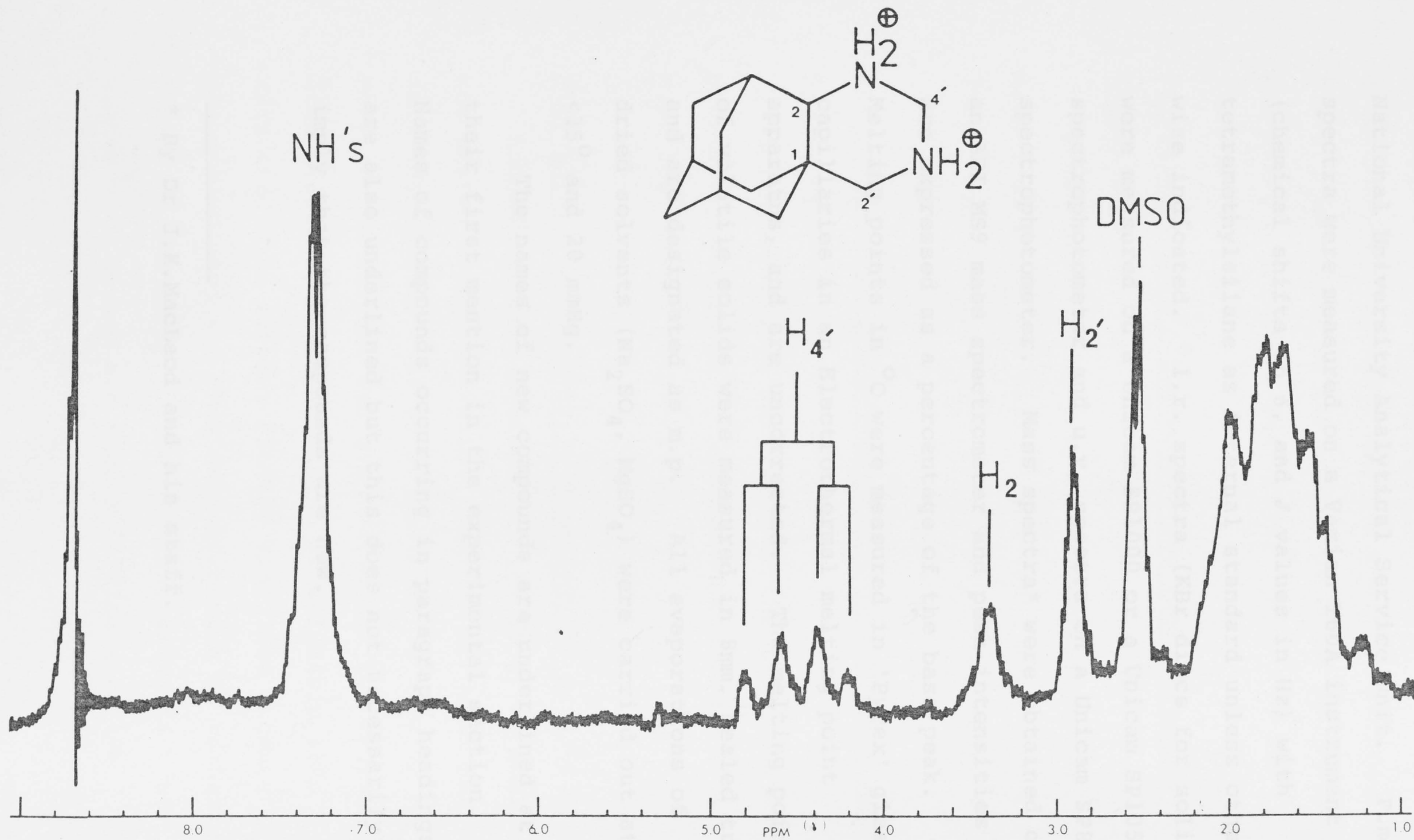


Fig. 2.10 P.m.r. spectrum of hexahydroadamantano[2,1,d]pyrimidine dipicrate in  $(\text{CD}_3)_2\text{SO}$  at 60 MHz.

iii) Experimental

Microanalyses were determined by the Australian National University Analytical Service Unit. P.m.r. spectra were measured on a Varian T60A instrument (chemical shifts in  $\delta$ , and  $J$  values in Hz) with tetramethylsilane as internal standard unless otherwise indicated. I.r. spectra (KBr discs for solids) were measured on a Unicam SP1000 or a Unicam SP1050 spectrophotometer and u.v. spectra on a Unicam SP800 spectrophotometer. Mass spectra\* were obtained on an AEI MS9 mass spectrometer and peak intensities are expressed as a percentage of the base peak. Melting points in  $^{\circ}\text{C}$  were measured in 'Pyrex' glass capillaries in an Electrothermal melting point apparatus, and are uncorrected. The melting points of volatile solids were measured in 8mm. sealed tubes and are designated as m.p. All evaporations of dried solvents ( $\text{Na}_2\text{SO}_4$ ,  $\text{MgSO}_4$ ) were carried out at  $<35^{\circ}$  and 20 mmHg.

The names of new compounds are underlined at their first mention in the experimental section. Names of compounds occurring in paragraph headings are also underlined but this does not necessarily imply that the compounds are new.

---

\* By Dr J.K.MacLeod and his staff.

Tricyclo[3.3.1.1<sup>3,7</sup>]decan-2-one (adamantanone) (2.5)

Adamantanone was prepared by sulphuric acid oxidation of adamantane and the reaction followed by g.l.c., according to the method of Geluk and Keizer.<sup>62</sup> (45-58%), m.p.\* 282.5-284<sup>o</sup> (lit.<sup>61</sup> m.p. 278-282<sup>o</sup>).

Tricyclo[4.3.1.1<sup>3,8</sup>]undecan-4-one (homoadamantan-4-one) (2.6)

This compound was prepared according to the method of Black and Gill.<sup>85</sup> (85-93%), m.p.\* 256-257<sup>o</sup> (lit.<sup>85</sup> m.p. 270.5-271<sup>o</sup>; lit.<sup>86</sup> m.p. 258-260<sup>o</sup>).

Tricyclo[4.3.1.1<sup>3,8</sup>]undecan-4,5-dione (homoadamantan-4,5-dione) (2.7)

Selenium dioxide oxidation of the ketone (2.6) as previously described<sup>86,78</sup> afforded the dione (82%), m.p. 286<sup>o</sup> (lit.<sup>86</sup> m.p. 287<sup>o</sup>).

Bicyclo[3.3.1]nonane-3 $\alpha$ ,7 $\alpha$ -dicarboxylic acid (2.8)

Homoadamantan-4,5-dione<sup>86,78</sup> (4.45 g, 25 mmol) was heated in dioxane/water (3:1, 25 ml) with periodic acid (dihydrate, 6.84 g, 30 mmol) at 70<sup>o</sup> for 72 h. Most of the solvent was evaporated and the residue in ether (200 ml) was washed with 1N sulphuric acid saturated with sulphur dioxide until the organic layer was colourless, and then extracted with 2N potassium hydroxide (3x35 ml). The alkaline extracts were washed with hexane and then acidified with 10N

hydrochloric acid (cooling). The white crystalline solid that separated was extracted into ethyl acetate (4x35 ml). The diacid (4.69 g, 87%), m.p. 180-181.5<sup>o</sup>, was obtained by evaporation of the washed and dried extracts (lit.<sup>78</sup> m.p. 180.5-181<sup>o</sup>)  $\nu_{\max}$  1690 (s, C=O), 1410, 1265, 1230.

2-Oxotricyclo[3.3.1.1<sup>3,7</sup>]decane-1-carbonylchloride  
(2-oxoadamantane-1-carbonylchloride) (2.9)

The diacid (2.8) was treated with thionylchloride by the method of Peters *et al.*<sup>78</sup> to afford the acid chloride (2.9) (95-98%), m.p. 84-86<sup>o</sup>.  $\nu_{\max}$  1795 (acid chloride C=O), 1716 (ketone).

2-Oxotricyclo[3.3.1.1<sup>3,7</sup>]decane-1-carboxamide  
(2-oxoadamantane-1-carboxamide) (2.13)

Ammonia gas was bubbled through an ice cold solution of 2-oxoadamantane-1-carbonylchloride (9.5 g, 44.8 mmol) in dry ether (290 mls) for 1 h. The mixture was evaporated and the residue partitioned between chloroform (100 ml) and water (75 ml). The aqueous phase was extracted with chloroform (3x50 ml) and the combined extracts were washed with 10% aqueous sodium carbonate (50 ml) and water (50 ml), and dried. Evaporation of the extracts afforded the oxo-amide (2.13) (8.5 g, 98%) which, when recrystallized from toluene had m.p. 170-171.5<sup>o</sup> (lit.<sup>80</sup> m.p. 177-177.5<sup>o</sup>).  $\nu_{\max}$  3440, 3360, 3305, 3210 (NH str), 1720 (C=O), 1675, 1624 (amide). P.m.r.  $\delta$ (CDCl<sub>3</sub>) 1.62-2.53 (m, 12H),

2.67 (m, 1H, H-3), 5.38-6.62 and 6.93-8.12 (very broad, each corresponding to 1H, NH<sub>2</sub>).

2-Aminotricyclo[3.3.1.1<sup>3,7</sup>]decane-1-carboxamide

(2-aminoadamantane-1-carboxamide) (2.14)

2-Oxoadamantane-1-carboxamide (2.13) (3.86 g, 20 mmol) was dissolved in ethanol (175 ml) and gaseous ammonia bubbled in for 30 min at 25° and at 5° for 30 min. 10% Palladium-on-charcoal (1.93 g) was added and the mixture shaken with hydrogen at 20° and 4 atm for 48 h. The catalyst was removed and the solvent evaporated. The residue was dissolved in chloroform and extracted into 4N hydrochloric acid. The aqueous solution was basified and extracted with chloroform (5x50 ml). Evaporation of the dried extracts gave 2-aminoadamantane-1-carboxamide (2.5 g, 65%) m.p. 140.5-142° (toluene) (lit.<sup>82</sup> m.p. 135°).  $\nu_{\max}$  3400 (NH str), 1655, 1610 (amide). P.m.r.  $\delta$ (CDCl<sub>3</sub>) 1.50 (s, NH<sub>2</sub>), 1.53-2.13 (m, 13H), 3.03 (s, 1H vicinal to NH<sub>2</sub>), 5.80-7.60 (v.br, 2H, CONH<sub>2</sub>).

Evaporation of the first chloroform extract occasionally gave small amounts of a neutral product which was shown to be dichloroadamantane by comparison with an authentic sample.<sup>90</sup> M.p. 201.5-203.5° (lit.<sup>90</sup> m.p. 203-204°) (Found: C, 58.3; H, 6.7; Cl, 34.0. Calc. for C<sub>10</sub>H<sub>14</sub>Cl<sub>2</sub>: C, 58.6; H, 6.9; Cl, 34.6).  $\nu_{\max}$  2970, 2940, 2880, 1455, 1358, 960, 907, 810, 795, 650. P.m.r. (CDCl<sub>3</sub>) 1.53-2.1 (m, 8H), 2.15-2.7 (m, 6H); m/e 208 (0.6%), 206 (2.7), 204 (3.4) (C<sub>10</sub>H<sub>14</sub>Cl<sub>2</sub><sup>+</sup>), 150 (100).

3-Oxa-4-azatetracyclo[6.3.1.1<sup>6,10</sup>.0<sup>1,5</sup>]tridec-4,5-en-2-one (adamantano[2,1-c]isoxazolin-5-one) (2.15)

A solution of the oxo-amide (2.13) (96 mg, 0.5 mmol) and hydroxylamine hydrochloride (139 mg, 2 mmol) in 95% ethanol containing potassium hydroxide (112 mg, 2 mmol) was heated under reflux for 20 min. The cooled solution was extracted with chloroform and the extracts were combined and washed with water. Evaporation of the dried extracts gave the isoxazolin-5-one (60 mg, 63%). It had m.p. 179-181<sup>o</sup> after sublimation at 70<sup>o</sup>/0.4 mm (Found: C, 69.5; H, 6.7; N, 7.1. C<sub>11</sub>H<sub>13</sub>NO<sub>2</sub> requires C, 69.1; H, 6.9; N, 7.3%).  
 $\nu_{\max}$  1790 (C=O), 1630 (C=N).

3,4-Diazatetracyclo[6.3.1.1<sup>6,10</sup>.0<sup>1,5</sup>]tridec-4,5-en-2-one (adamantano[2,1-c]-1H-pyrazolin-5-one) (2.16)

The oxo-amide (2.13) (96 mg, 0.5 mmol) was heated under reflux with hydrazine hydrate (10 ml) for 45 min. The solution was evaporated to dryness and the residue recrystallized from 95% ethanol to afford the pyrazolin-5-one (91 mg, 96%). M.p. 223-225<sup>o</sup> (lit.<sup>82</sup> m.p. 220<sup>o</sup>) (Found: C, 69.5; H, 7.3; N, 14.9. Calc. for C<sub>11</sub>H<sub>14</sub>N<sub>2</sub>O: C, 69.4; H, 7.4; N, 14.7%).  
 $\nu_{\max}$  3140 (br, NH str), 1690, 1660 (amide), 1630 (C=N).

3,4-Diazatetracyclo[6.3.1.1<sup>6,10</sup>.0<sup>1,5</sup>]tridec-4,5-en-2-on-3-ethyl carboxylate (adamantano-[2,1-c]-pyrazolin-5-on-3-ethyl carboxylate) (2.17)

2-Oxoadamantane-1-carboxamide (386 mg, 2 mmol) in ethanol (2.5 mls) was treated with ethyl carbazate (208 mg, 2 mmol) and the mixture heated under reflux for 3 h. The solution was cooled in ice and the crystalline pyrazolin-5-one was collected (438 mg, 83.6%). It had m.p. 126-127<sup>o</sup> after recrystallization from ethanol (Found: C, 63.1; H, 6.9; N, 10.6. C<sub>14</sub>H<sub>18</sub>N<sub>2</sub>O<sub>3</sub>·0.25H<sub>2</sub>O requires C, 63.0; H, 7.0; N, 10.5%).  $\nu_{\max}$  1799 (ester C=O), 1765 and 1754 (amide C=O), 1647 (C=N). P.m.r.  $\delta$ (CDCl<sub>3</sub>) 1.42 (t, 3H, CH<sub>2</sub>CH<sub>3</sub>), 1.60-2.50 (m, 12H), 3.05 (m, 1H, H-3), 4.46 (q, 2H, CH<sub>2</sub>CH<sub>3</sub>).

2-(Phenylhydrazono)tricyclo[3.3.1.1<sup>3,7</sup>]decane-1-carboxamide (2-(phenylhydrazono)adamantane-1-carboxamide) (2.18)

The oxo-amide (2.13) (96 mg, 0.5 mmol) in methanol (1 ml) was treated with phenylhydrazine (0.02 ml, 2 mmol) and the solution shaken until crystallization was complete. The colourless solid was collected, washed with cold methanol (5 ml) and dried in a vacuum to yield the phenylhydrazone (80 mg, 57%), m.p. 190-200<sup>o</sup> (dec.) (Found: C, 69.7; H, 7.6; N, 14.4. C<sub>17</sub>H<sub>21</sub>N<sub>3</sub>O, 0.5H<sub>2</sub>O requires C, 69.8; H, 7.6; N, 14.4%).

$\nu_{\max}$  3380, 3200 (NH str), 1675 (amide), 1610 (C=N).  
 P.m.r.  $\delta$ ( $C_2D_5OD$ ) 1.3-2.0 (m, 12H), 2.25 (m, 1H, H-3),  
 6.1-7.0 (m, 5H, aromatic protons).

2-(Benzyloximino)tricyclo[3.3.1.1<sup>3,7</sup>]decane-1-carboxamide (2-(benzyloximino)adamantane-1-carboxamide)  
 (2.19)

To a solution of O-benzylhydroxylamine<sup>93</sup> (86 mg, 0.7 mmol) in methanol (2.5 ml) was added the oxo-amide (2.13) (96 mg, 0.5 mmol) and the mixture boiled under reflux for 2 h. The solution was evaporated, dried in a vacuum, and the residue recrystallized from petroleum ether, b.p. 40-60°. The crystalline benzyloxime (108 mg, 73%) had m.p. 118-121° (Found: C, 73.1; H, 7.6; N, 9.2.  $C_{17}H_{22}N_2O_2$  requires C, 72.4; H, 7.4; N, 9.4%).  $\nu_{\max}$  3410 (NH str), 1670 (C=O). P.m.r.  $\delta$ ( $CDCl_3$ ) 1.5-2.4 (m, 13H), 5.13 (s, 2H,  $OCH_2$ ), 7.37 (d, 5H, aromatic protons).

2-Aminotricyclo[3.3.1.1<sup>3,7</sup>]decane-1-methylamine (1-aminomethyladamantan-2-ylamine) (2.29)

2-Aminoadamantane-1-carboxamide (500 mg, 2.6 mmol) in glyme (15 ml) was treated with lithium aluminium hydride (5.2 mmol) and the mixture heated at 80° for 3 days. To the cooled solution was added saturated aqueous sodium carbonate and the mixture boiled for 10 min. The solution was then extracted with chloroform. The extracts were dried ( $Na_2SO_4$ ), filtered, and the filtrate evaporated to afford the



diamine as a white solid (356 mg, 77%), m.p. 129-131<sup>o</sup>. The dihydrochloride had m.p. 314<sup>o</sup> (dec.) (lit.<sup>68</sup> m.p. 300-310<sup>o</sup> (dec.)).  $\nu_{\max}$  3400 (br, NH str), 1585, 1470, 1385, 1325: m/e 180 (M, 33%), 164 (100).

3,5-Diazatetracyclo[7.3.1.1<sup>7,11</sup>.0<sup>1,6</sup>]tetradecan-4-imine (2-amino-tetrahydroadamantano[2,1-d]pyrimidine)(2.30) sulphate, hydrochloride and picrate.

1-Aminomethyladamantan-2-ylamine (2.29) (90 mg, 0.5 mmol) in water (1 ml) was treated with S-methyl-*iso*-thiouronium sulphate (69 mg, 0.25 mmol) and the mixture heated under reflux for 1 h. The solution was evaporated to dryness and the residue recrystallized from water to yield the sulphate (125 mg, 98%), m.p. 355-357<sup>o</sup> (dec.) (Found: N, 16.3; S, 6.0. C<sub>24</sub>H<sub>40</sub>N<sub>6</sub>O<sub>4</sub>S requires N, 16.5; S, 6.3%).  $\nu_{\max}$  3260 (NH str), 1680, 1630 (cyclic guanidino). P.m.r. (D<sub>2</sub>O) 1.2-2.2 (m, 13H), 2.77 (s, 2H, CH<sub>2</sub> of heterocyclic ring), 3.28 (m, 1H vicinal to NH): m/e 205 (100) (C<sub>12</sub>H<sub>19</sub>N<sub>3</sub><sup>+</sup>). The picrate had m.p. 230-232<sup>o</sup> after recrystallization from ethanol (Found: C, 49.7; H, 4.8; N, 19.3. C<sub>18</sub>H<sub>22</sub>N<sub>6</sub>O<sub>7</sub> requires C, 49.8; H, 5.1; N, 19.4%).  $\nu_{\max}$  3440, 3323, 3200, 1680, 1660, 1640, 1625, 1582, 1376, 1345, 1324, 1275.

The diamine (2.29) (180 mg, 1 mmol) in water (1 ml) was treated with guanidine hydrochloride (95 mg, 1 mmol) and the mixture heated on a steam bath for 1.5 h. Evaporation of the solution afforded the hydrochloride as an hygroscopic glass (209 mg, 86.7%),  $\nu_{\max}$  3400, 3170 (NH str), 1670, the picrate of which had an infrared spectrum identical with that described above.

3,5-Diazatetracyclo[7.3.1.1<sup>7,11</sup>.0<sup>1,6</sup>]tetradecan-4-one  
(tetrahydroadamantano[2,1-d]pyrimidin-2(1H)-one) (2.31)

1-Aminomethyladamantan-2-ylamine (2.29) (900 mg, 5 mmol) was suspended in ice cold water (5 ml) and the vigorously stirred mixture treated with 20% phosgene in toluene (4.9 ml, 24 mmol) and 2N sodium hydroxide (8.4 ml, 48 mmol) simultaneously (over 20 min), ensuring that the solution remained alkaline. The solution was stirred at 20<sup>o</sup> for 18 h. The treatment was repeated and stirring continued for 12 h. The mixture was partitioned between chloroform and 1N hydrochloric acid. The aqueous layer was extracted with chloroform (3x50 ml) and the dried extracts afforded, on evaporation, the pyrimidin-2-one (2.31) (956 mg, 93%). It had m.p. 324-328<sup>o</sup> (dec.) after recrystallization from dimethylformamide (lit.<sup>68</sup> m.p. 310-320<sup>o</sup> (dec.); 4% yield from phosgene and pyridine) (Found: C, 70.0; H, 8.6; N, 13.7. Calc. for C<sub>12</sub>H<sub>17</sub>N<sub>2</sub>O: C, 69.9; H, 8.8; N, 13.6%)  $\nu_{\max}$  3250 (NH str), 2260, 1685 (C=O). P.m.r.  $\delta$ (CDCl<sub>3</sub>) 1.76-2.30 (m, 13H), 2.42 (m, 1H vicinal to NH), 2.63 (m,  $W_{h/2}$  14, 2H, CH<sub>2</sub> of heterocyclic ring).

3,5-Diazatetracyclo[7.3.1.1<sup>7,11</sup>.0<sup>1,6</sup>]tetradecane  
dipicrate (hexahydroadamantano[2,1-d]pyrimidine) (2.32)

1-Aminomethyladamantan-2-ylamine (180 mg, 1 mmol) was dissolved in 37% aqueous formaldehyde and set aside for 18 h. The solution was evaporated and the residue dissolved in saturated ethanolic picric acid. Water

was added until turbidity persisted and the mixture cooled. The dipicrate (66 mg, 10%) was recrystallized from aqueous ethanol and had m.p. 180.5-183<sup>o</sup> (Found: C, 44.4; H, 3.9; N, 17.1. C<sub>24</sub>H<sub>26</sub>N<sub>8</sub>O<sub>14</sub> requires C, 44.3; H, 4.0; N, 17.2%).  $\nu_{\max}$  3150 (NH str), 1635, 1610, 1575, 1540. P.m.r.  $\delta((\text{CD}_3)_2\text{SO})$  1.32-2.25 (m, 13H), 2.88 (m, 2H, CH<sub>2</sub>NH<sub>2</sub><sup>+</sup>), 3.50 (m, 1H vicinal to NH<sub>2</sub><sup>+</sup>), 4.67, 4.31 (dd, 2H,  $J$  12, NH<sub>2</sub><sup>+</sup>CH<sub>2</sub>NH<sub>2</sub><sup>+</sup>), 7.32 (m, 4H, 2NH<sub>2</sub><sup>+</sup>), 8.72 (s, 4H, aromatic protons).

3,5-Diazatetracyclo[7.3.1.1<sup>7,11</sup>.0<sup>1,6</sup>]tetradecan-2,4-dione(dihydroadamantano[2,1-d]pyrimidin-2,4(1H, 3H)-dione) (2.33)

2-Aminoadamantane-1-carboxamide (2.14) (388 mg, 2 mmol) was treated with phosgene in toluene and 2N sodium hydroxide as for the preparation of the pyrimidin-2(1H)-one (2.31) and gave the dione (299 mg, 68%); m.p. 290<sup>o</sup> after recrystallization from chloroform (Found: C, 63.7; H, 7.4; N, 12.4. C<sub>12</sub>H<sub>16</sub>N<sub>2</sub>O<sub>2</sub>·0.3H<sub>2</sub>O requires C, 63.6; H, 7.3; N, 12.0%).  $\nu_{\max}$  3340 (NH str), 1715 (s, C=O). P.m.r.  $\delta((\text{CD}_3)_2\text{SO})$  1.30-2.47 (m, 13H), 3.48 (d,  $J$  3, 1H vicinal to NH), 7.80 (m, 1H, NHCO), 10.03 (m, 1H, CONHCO).

3,5-Diazatetracyclo[7.3.1.1<sup>7,11</sup>.0<sup>1,6</sup>]tetradec-4,5-en-2-one  
(dihydroadamantano[2,1-d]pyrimidin-4(3H)-one) (2.34)

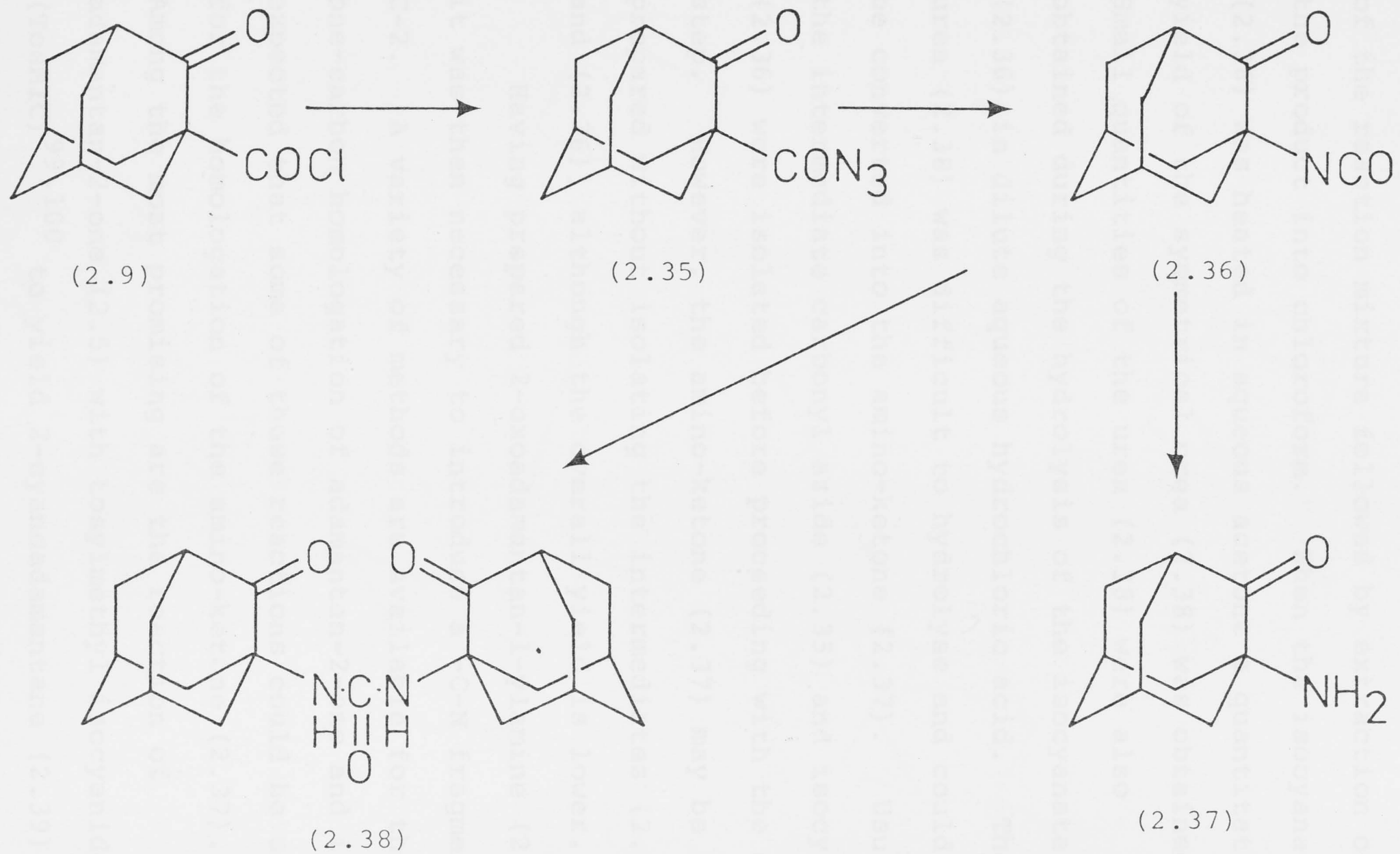
A solution of the amino amide (2.14) (100 mg, 0.52 mmol) in ethyl orthoformate (4 ml) was boiled under reflux for 2 h. and then kept at 20<sup>o</sup> for 12 h. The white solid was collected and recrystallized from ethyl orthoformate to yield the pyrimidinone (71.5 mg, 68%) m.p. 176-178<sup>o</sup> (d) (Found: C, 60.9; H, 8.6; N, 11.7. C<sub>12</sub>H<sub>16</sub>N<sub>2</sub>O<sub>1</sub>.2H<sub>2</sub>O requires C, 60.0; H, 8.4; N, 11.7%).

4) Synthesis of 2,4-diazatetracyclo[7.3.1.1<sup>7,11</sup>.0<sup>1,6</sup>]tetradecanes (adamantano[1,2-d]pyrimidines) and related compounds

i) Discussion

In order to prepare the second of the proposed analogues of tetrodotoxin it was necessary to convert 2-oxoadamantane-1-carbonyl chloride (2.9) into 2-oxoadamantan-1-ylamine (2.37), to perform a one-carbon homologation of the ketone at C-2, and finally, to cyclize the derived diamine.

2-Oxoadamantane-1-carbonyl azide (2.35) was prepared in high yield by treatment of the carbonyl chloride (2.9) with sodium azide at low temperature. Thermal rearrangement of the carbonyl azide (2.35) with elimination of nitrogen in dry benzene afforded 2-oxoadamantan-1-ylisocyanate (2.36) which, on hydrolysis



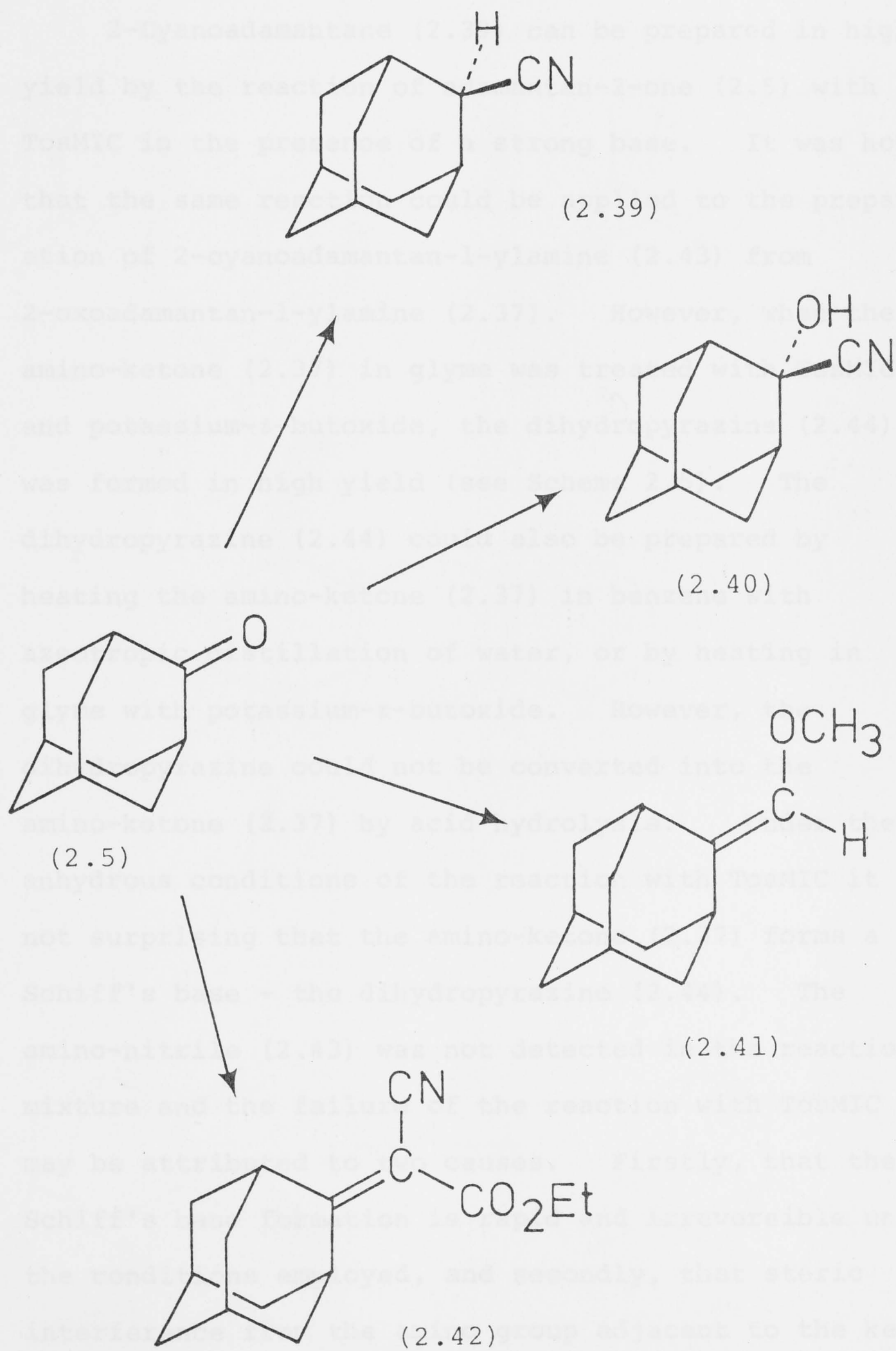
SCHEME 2.3

with dilute aqueous hydrochloric acid gave 2-oxoadamantan-1-ylamine (2.37) (see Scheme 2.3).

The amino-ketone (2.37) may be isolated as its hydrochloride salt by evaporation of the aqueous acid solution, or as the free base by basification of the reaction mixture followed by extraction of the product into chloroform. When the isocyanate (2.36) was heated in aqueous acetone a quantitative yield of the symmetrical urea (2.38) was obtained. Small quantities of the urea (2.38) were also obtained during the hydrolysis of the isocyanate (2.36) in dilute aqueous hydrochloric acid. The urea (2.38) was difficult to hydrolyse and could not be converted into the amino-ketone (2.37). Usually the intermediate carbonyl azide (2.35) and isocyanate (2.36) were isolated before proceeding with the next step. However, the amino-ketone (2.37) may be prepared without isolating the intermediates (2.35) and (2.36), although the overall yield is lower.

Having prepared 2-oxoadamantan-1-ylamine (2.37) it was then necessary to introduce a -C-N fragment at C-2. A variety of methods are available for the one-carbon homologation of adamantan-2-one and it was expected that some of these reactions could be useful for the homologation of the amino-ketone (2.37). Among the most promising are the reaction of adamantan-2-one (2.5) with tosylmethyl isocyanide (TosMIC)<sup>99,100</sup> to yield 2-cyanoadamantane (2.39), and hydrocyanation of the ketone with liquid hydrogen

SCHEME 2.4

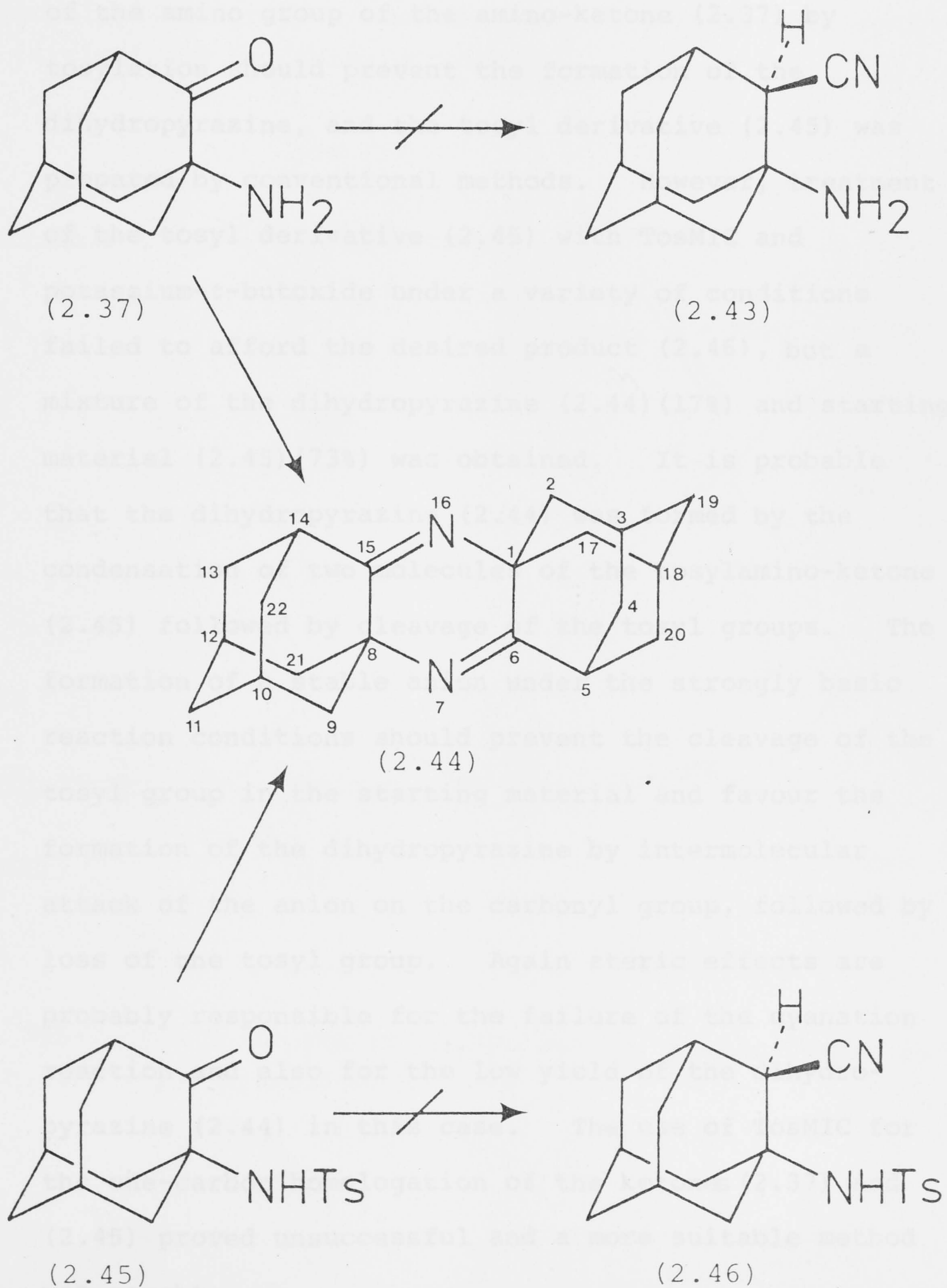


cyanide<sup>86</sup> or acetone cyanohydrin<sup>101</sup> to afford adamantanone cyanohydrin (2.40). The Wittig<sup>103</sup> and Cope<sup>104,105</sup> reactions of adamantan-2-one which afford adamantan-2-ylidenes of the type (2.41) and (2.42) are also potentially useful (see Scheme 2.4).

2-Cyanoadamantane (2.39) can be prepared in high yield by the reaction of adamantan-2-one (2.5) with TosMIC in the presence of a strong base. It was hoped that the same reaction could be applied to the preparation of 2-cyanoadamantan-1-ylamine (2.43) from 2-oxoadamantan-1-ylamine (2.37). However, when the amino-ketone (2.37) in glyme was treated with TosMIC and potassium-*t*-butoxide, the dihydropyrazine (2.44) was formed in high yield (see Scheme 2.5). The dihydropyrazine (2.44) could also be prepared by heating the amino-ketone (2.37) in benzene with azeotropic distillation of water, or by heating in glyme with potassium-*t*-butoxide. However, the dihydropyrazine could not be converted into the amino-ketone (2.37) by acid hydrolysis. Under the anhydrous conditions of the reaction with TosMIC it is not surprising that the amino-ketone (2.37) forms a Schiff's base - the dihydropyrazine (2.44). The amino-nitrile (2.43) was not detected in the reaction mixture and the failure of the reaction with TosMIC may be attributed to two causes. Firstly, that the Schiff's base formation is rapid and irreversible under the conditions employed, and secondly, that steric interference from the amino group adjacent to the ketone



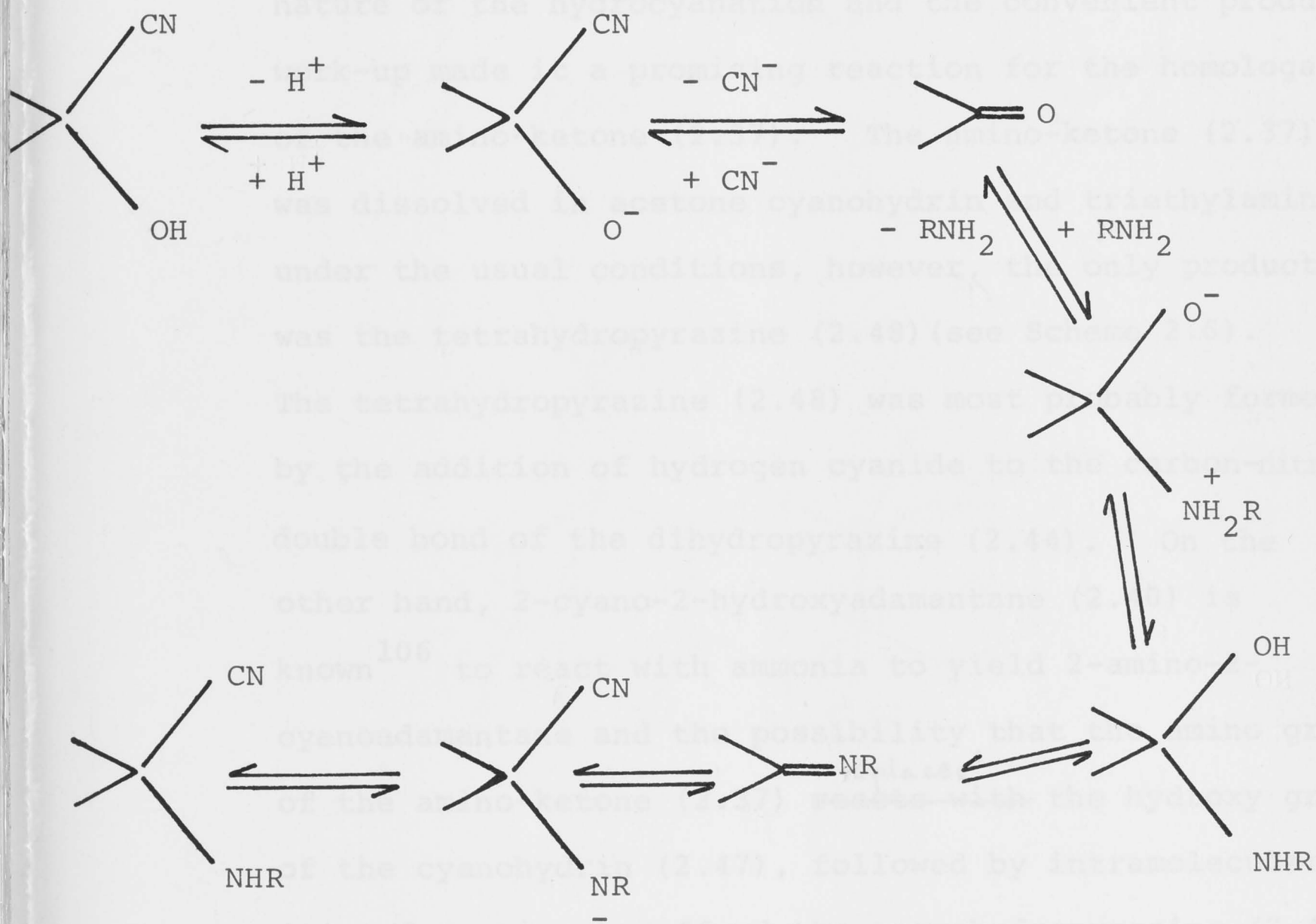
SCHEME 2.5



may destabilize the bulky intermediates formed by the reaction of the ketone with the TosMIC anion. These effects contribute to the preferential formation of the dihydropyrazine (2.44) in the TosMIC reaction rather than the desired product (2.43). Protection of the amino group of the amino-ketone (2.37) by tosylation should prevent the formation of the dihydropyrazine, and the tosyl derivative (2.45) was prepared by conventional methods. However, treatment of the tosyl derivative (2.45) with TosMIC and potassium-*t*-butoxide under a variety of conditions failed to afford the desired product (2.46), but a mixture of the dihydropyrazine (2.44) (17%) and starting material (2.45) (73%) was obtained. It is probable that the dihydropyrazine (2.44) was formed by the condensation of two molecules of the tosylamino-ketone (2.45) followed by cleavage of the tosyl groups. The formation of a stable anion under the strongly basic reaction conditions should prevent the cleavage of the tosyl group in the starting material and favour the formation of the dihydropyrazine by intermolecular attack of the anion on the carbonyl group, followed by loss of the tosyl group. Again steric effects are probably responsible for the failure of the cyanation reaction and also for the low yield of the dihydropyrazine (2.44) in this case. The use of TosMIC for the one-carbon homologation of the ketones (2.37) and (2.45) proved unsuccessful and a more suitable method was sought.

58a

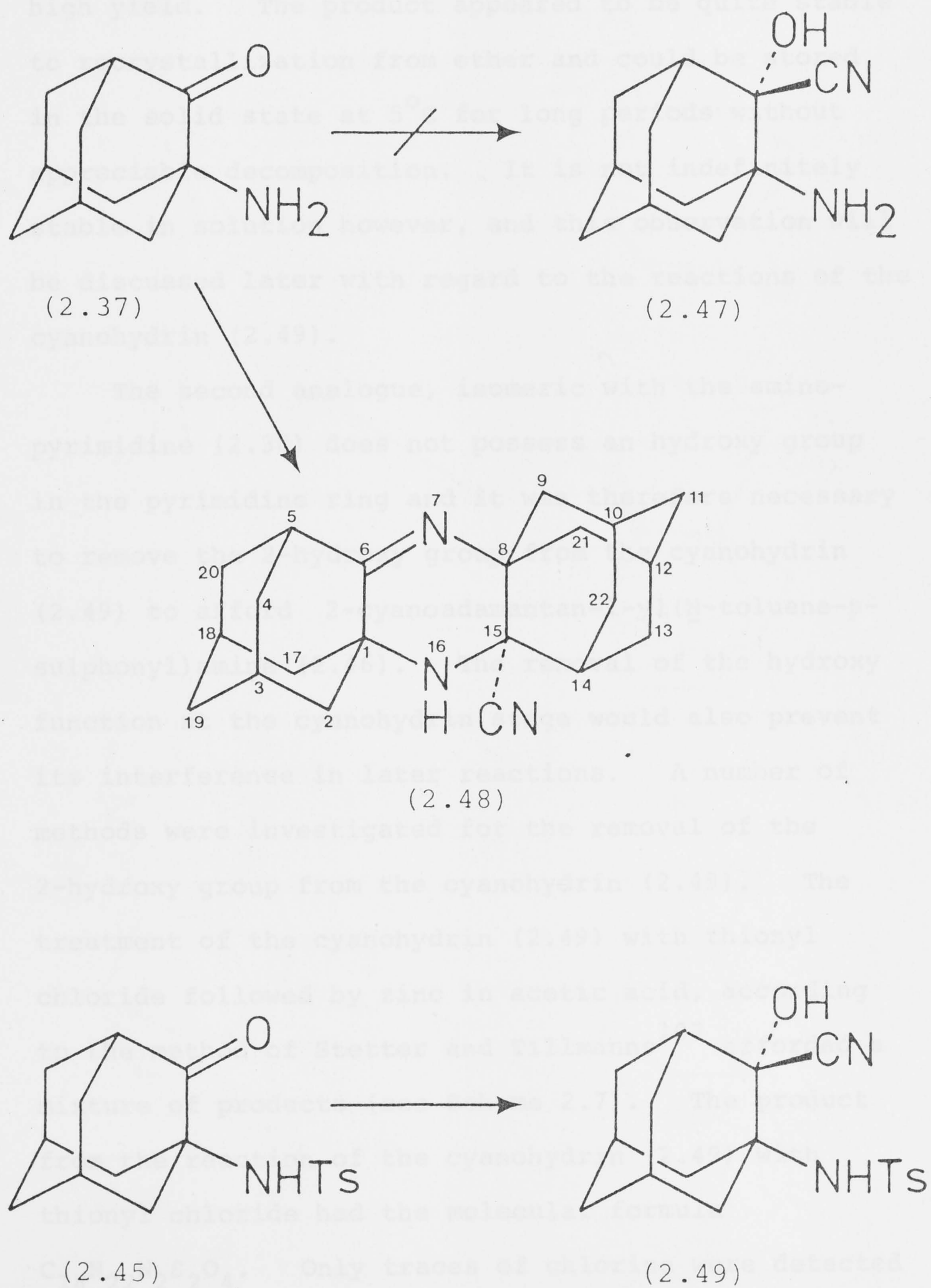
Replacement of the OH group by an NHR group in cyanohydrins most probably involves the following mechanism:\*



\* See P. Sykes, "A Guidebook to Mechanisms in Organic Chemistry", Longman, 1970, pp. 184-186

Schlatmann and coworkers<sup>86</sup> prepared 2-cyano-2-hydroxyadamantane (2.40) in 82% yield by treating adamantan-2-one (2.5) with liquid hydrogen cyanide in pyridine. We were able to prepare the cyanohydrin (2.40) in higher yields (91%) by using excess acetone cyanohydrin and a catalytic amount of triethylamine in the cold and under a nitrogen atmosphere. The facile nature of the hydrocyanation and the convenient product work-up made it a promising reaction for the homologation of the amino-ketone (2.37). The amino-ketone (2.37) was dissolved in acetone cyanohydrin and triethylamine under the usual conditions, however, the only product was the tetrahydropyrazine (2.48) (see Scheme 2.6). The tetrahydropyrazine (2.48) was most probably formed by the addition of hydrogen cyanide to the carbon-nitrogen double bond of the dihydropyrazine (2.44). On the other hand, 2-cyano-2-hydroxyadamantane (2.40) is known<sup>106</sup> to react with ammonia to yield 2-amino-2-cyanoadamantane and the possibility that the amino group of the amino-ketone (2.37) <sup>replaces</sup> ~~reacts with~~ the hydroxy group of the cyanohydrin (2.47), followed by intramolecular imine formation to afford the tetrahydropyrazine (2.48) should also be considered. The di-HCN adduct of the dihydropyrazine (2.44) could not be detected in the product by mass spectrometry. The tetrahydropyrazine (2.48) could be converted into the dihydropyrazine (2.44) by heating in solution or at the melting point whereby hydrogen cyanide was liberated. Protection of the amino group of the amino-ketone (2.37) was again

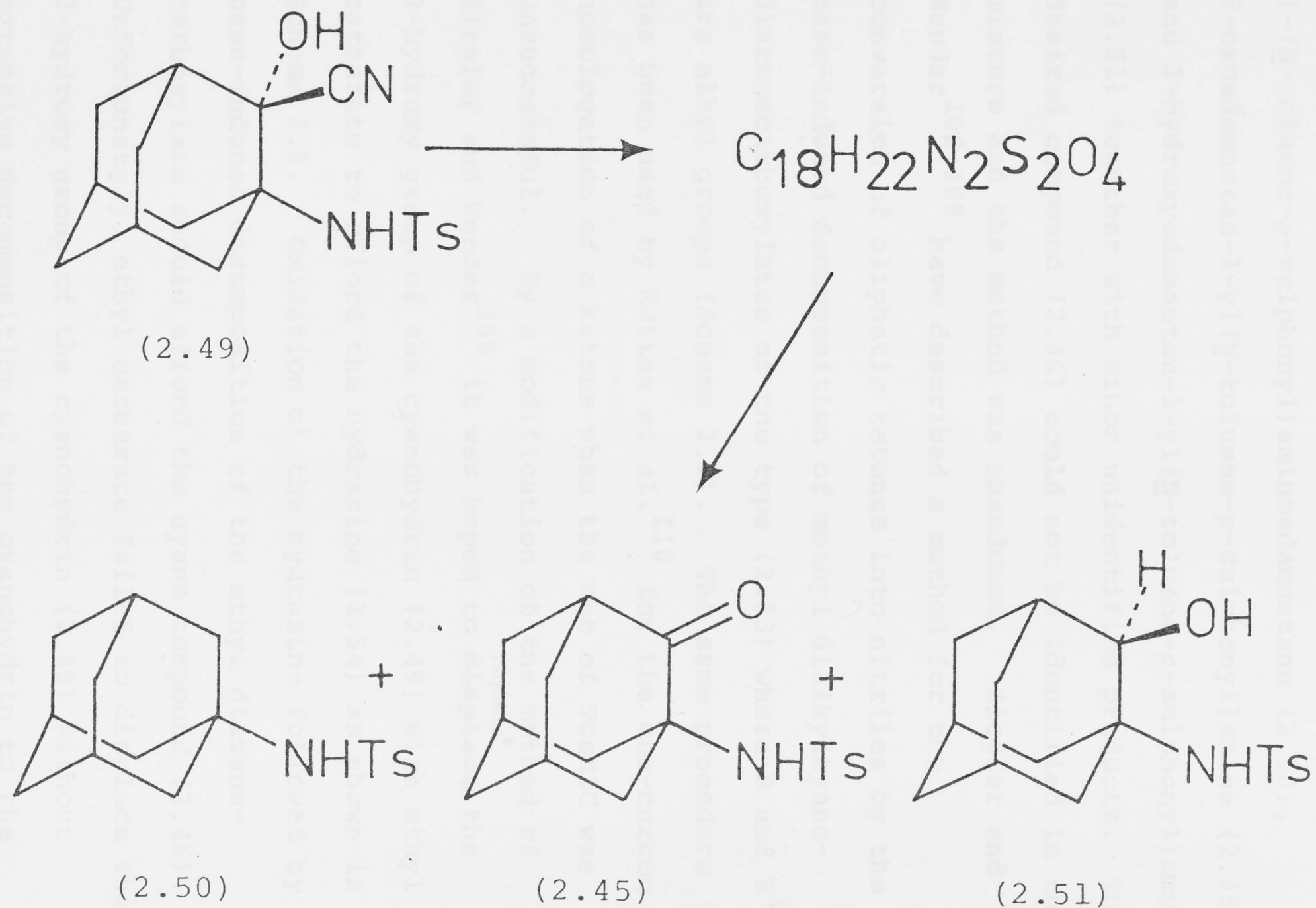
SCHEME 2.6



necessary to prevent the formation of the dihydro-pyrazine (2.44) and hence the tetrahydropyrazine (2.48). Treatment of the tosylamino-ketone (2.45) with acetone cyanohydrin and triethylamine under the usual conditions afforded the cyanohydrin (2.49) in high yield. The product appeared to be quite stable to recrystallization from ether and could be stored in the solid state at 5°C for long periods without appreciable decomposition. It is not indefinitely stable in solution however, and this observation will be discussed later with regard to the reactions of the cyanohydrin (2.49).

The second analogue, isomeric with the amino-pyrimidine (2.30) does not possess an hydroxy group in the pyrimidine ring and it was therefore necessary to remove the 2-hydroxy group from the cyanohydrin (2.49) to afford 2-cyanoadamantan-1-yl(N-toluene-*p*-sulphonyl)amine (2.46). The removal of the hydroxy function at the cyanohydrin stage would also prevent its interference in later reactions. A number of methods were investigated for the removal of the 2-hydroxy group from the cyanohydrin (2.49). The treatment of the cyanohydrin (2.49) with thionyl chloride followed by zinc in acetic acid, according to the method of Stetter and Tillmanns<sup>107</sup> afforded a mixture of products (see Scheme 2.7). The product from the reaction of the cyanohydrin (2.49) with thionyl chloride had the molecular formula  $C_{18}H_{22}N_2S_2O_4$ . Only traces of chlorine were detected

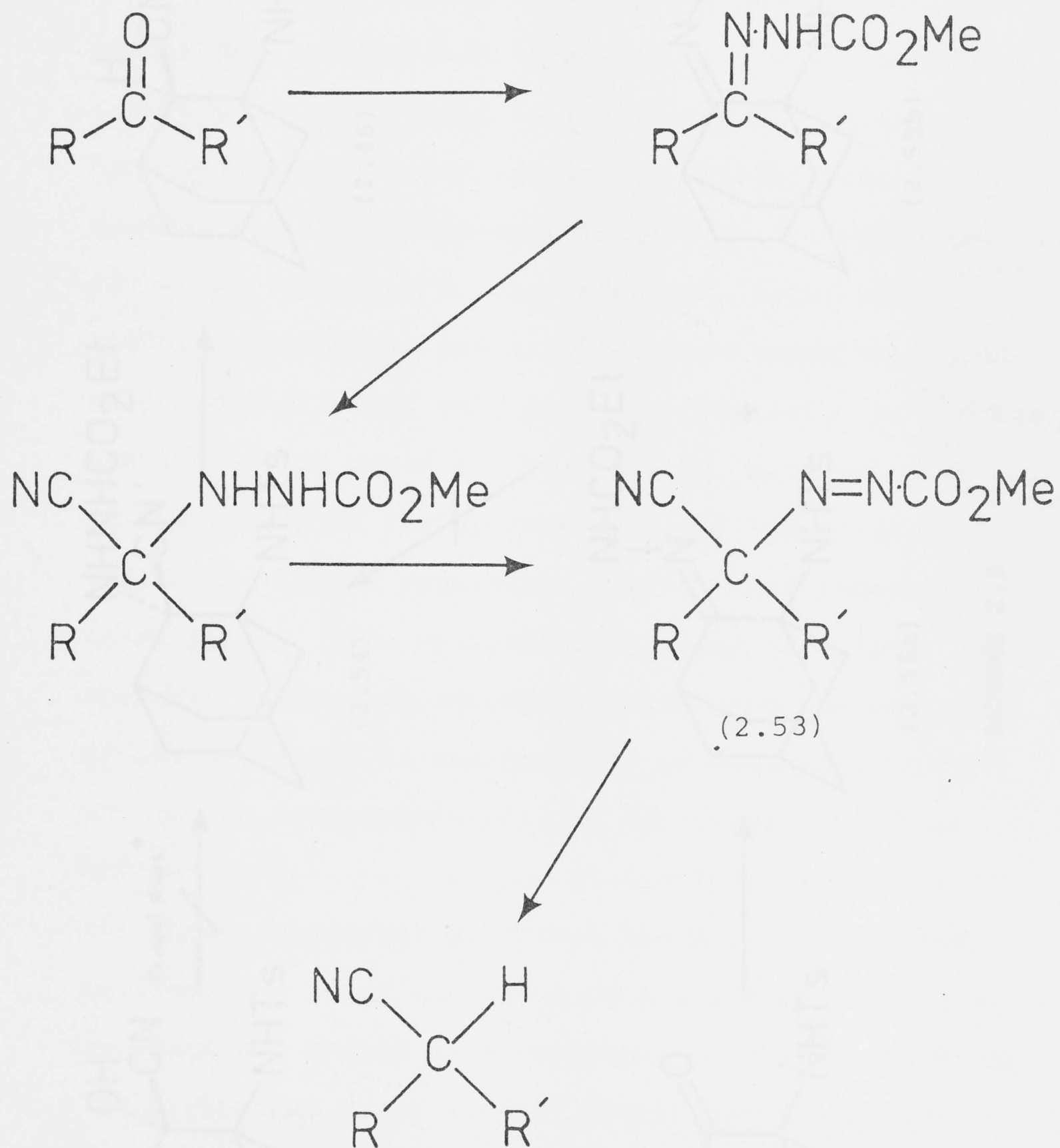
SCHEME 2.7

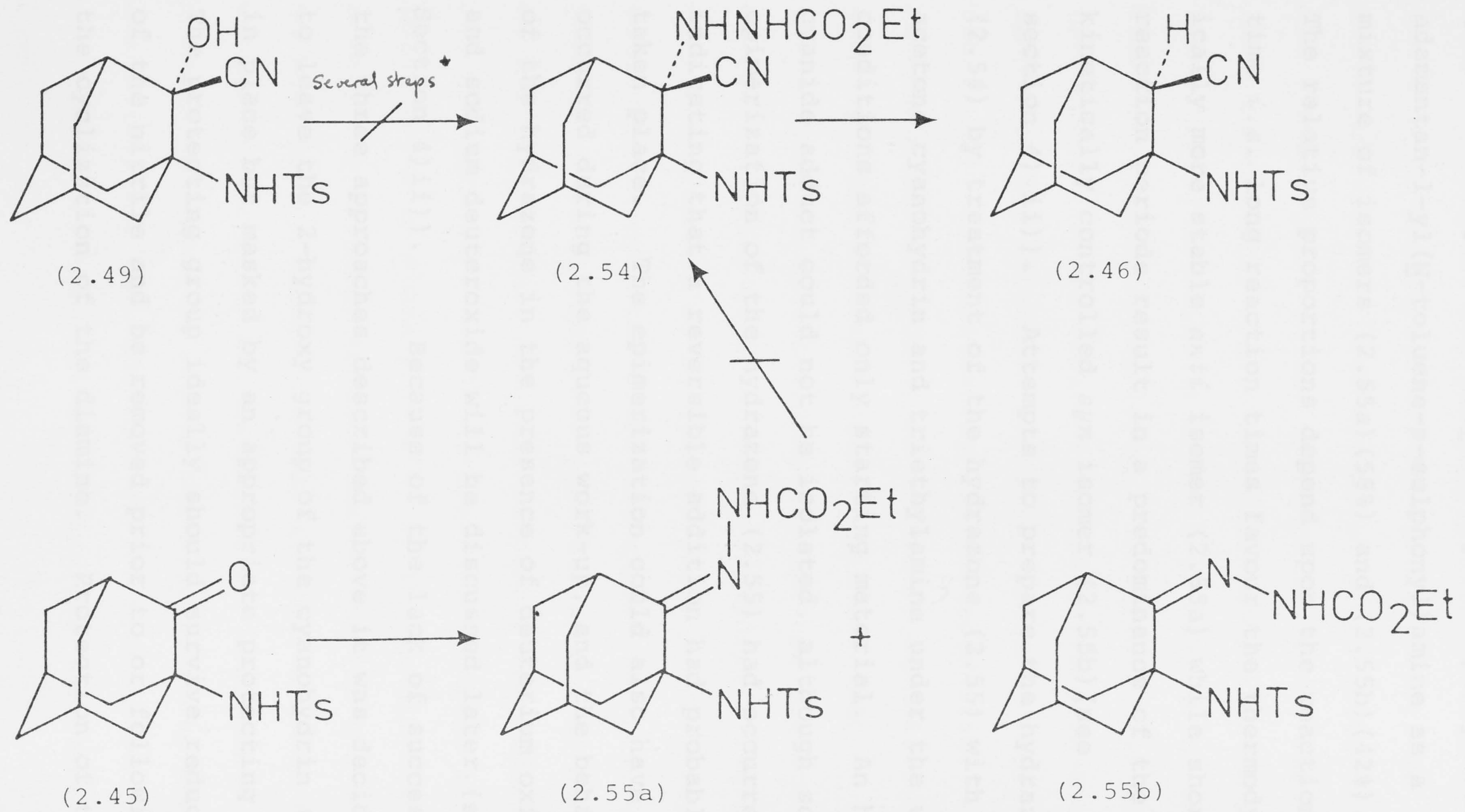


in the analysis and the product was probably a sulphonic acid. This compound, on treatment with zinc and acetic acid afforded a mixture which was shown by t.l.c. and p.m.r. to be composed of 1-(N-toluene-*p*-sulphonyl)aminoadamantane (2.50), 2-oxoadamantan-1-yl(N-toluene-*p*-sulphonyl)amine (2.45) and 2-hydroxyadamantan-1-yl(N-toluene-*p*-sulphonyl)amine (2.51) together with minor unidentified products. The desired compound (2.46) could not be identified in the mixture and the method was abandoned. Ziegler and Wender<sup>108,109</sup> have described a method for the conversion of aliphatic ketones into nitriles by the base-induced decomposition of methyl dialkylcyano-diazenecarboxylates of the type (2.53) where R and R<sup>1</sup> are alkyl groups (Scheme 2.8). The same procedure has been used by Mattes *et al.*<sup>110</sup> for the one-carbon homologation of a ketone when the use of TosMIC was unsuccessful. By a modification of the method of Ziegler and Wender<sup>109</sup> it was hoped to <sup>replace</sup> ~~displace~~ the 2-hydroxy group of the cyanohydrin (2.49) with ethyl carbazate to afford the hydrazine (2.54) as shown in Scheme 2.9. Oxidation of the hydrazine followed by base-induced decomposition of the ethyl diazenecarboxylate should afford the cyano compound (2.46). Unfortunately, ethyl carbazate failed to displace the 2-hydroxy group of the cyanohydrin (2.49) without extensive decomposition of the cyanohydrin to the ketone, and this approach was abandoned.



SCHEME 2.8





SCHEME 2.9

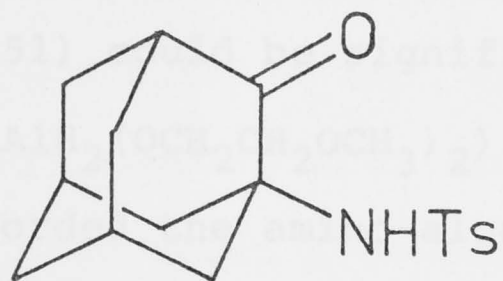
\* See p 58a

The tosylamino-ketone (2.45) reacts with ethyl carbazate in refluxing ethanol and affords a quantitative yield of 2-(N-ethoxycarbonyl)hydrazono-adamantan-1-yl(N-toluene-*p*-sulphonyl)amine as a mixture of isomers (2.55a) (58%) and (2.55b) (42%). The relative proportions depend upon the reaction time *i.e.* long reaction times favour the thermodynamically more stable *anti* isomer (2.55a) while shorter reaction periods result in a predominance of the kinetically controlled *syn* isomer (2.55b) (see section 4) ii)). Attempts to prepare the hydrazine (2.54) by treatment of the hydrazone (2.55) with acetone cyanohydrin and triethylamine under the usual conditions afforded only starting material. An hydrogen cyanide adduct could not be isolated, although some epimerization of the hydrazone (2.55) had occurred, indicating that a reversible addition had probably taken place. The epimerization could also have occurred during the aqueous work-up, and the behaviour of the hydrazone in the presence of deuterium oxide and sodium deuterioxide will be discussed later (see Section 4)ii)). Because of the lack of success in the three approaches described above it was decided to leave the 2-hydroxy group of the cyanohydrin (2.49) in place but masked by an appropriate protecting group. The protecting group ideally should survive reduction of the nitrile and be removed prior to or following the cyclization of the diamine. Protection of the

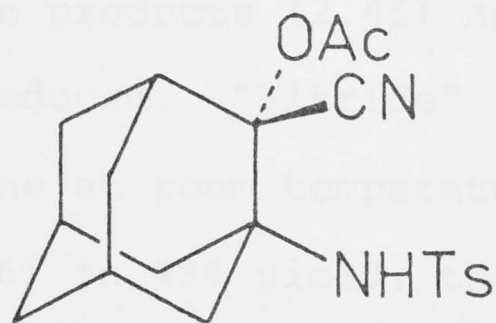
2-hydroxy group by tosylation or mesylation was unsuccessful because of the instability of the starting material and presumably also because of the ease of hydrolysis of the tertiary tosyl or mesyl derivative. The attempted preparation of the pyranyl ester of the cyanohydrin (2.49) was also unsuccessful due to rapid decomposition of the starting material (*i.e.* loss of HCN) under the reaction conditions employed. Acetylation of the cyanohydrin (2.49) occurs readily in pyridine-acetic anhydride and affords a promising protected derivative (2.52). Unfortunately its low solubility, slow rate of catalytic reduction and ready reductive cleavage with lithium aluminium hydride made acetylation an unsuitable method for the protection of the 2-hydroxy group of the cyanohydrin (2.49).

The presence of an hydroxy group in the proposed tetrodotoxin analogue would not appear to interfere with the initial postulate that the spherical shape of the tetrodotoxin molecule is partly responsible for its toxicity. Indeed, the incorporation of a polar group in close proximity to the guanidinium moiety may actually enhance the ability of the analogue to bind to the sodium channel, and thus enhance the biological activity of the molecule. For these reasons, attempts to remove the hydroxy group were abandoned, and the reduction of the cyanohydrin and cyclization of the derived diamine was undertaken.

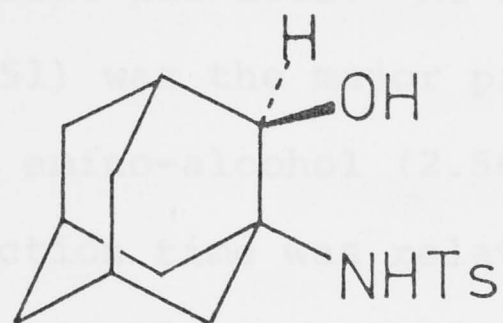
Several methods are available for the conversion of the cyanohydrin (2.49) into the corresponding amino-alcohol (2.56). For example, Schlatmann and coworkers<sup>86</sup> reduced 2-hydroxy-2-cyanoadamantane (2.40) with hydrogen over platinum oxide in ethanol-hydrochloric acid, while Sasaki *et al.*<sup>111,112</sup> prepared 2-hydroxy-2-aminomethyl homoadamantane by reduction of 2-hydroxy-2-cyanohomoadamantane with lithium aluminium hydride or by catalytic reduction over platinum oxide. Catalytic reduction of the cyanohydrin (2.49) according to the procedure of Schlatmann *et al.*<sup>86</sup> was attempted, but afforded a mixture of the amino-alcohol (2.56), the alcohol (2.51) and the ketone (2.45). The desired product (2.56) could be isolated from the mixture in an overall yield of 73%. The reaction time (~ 4 days) was quite long, and this was probably a consequence of steric hindrance, or of catalyst poisoning by the *p*-toluenesulphonyl protecting group, hydrogen cyanide liberated in the decomposition of the cyanohydrin (2.49) or by hydrochloric acid in the reaction medium. Fresh platinum oxide was added during the reaction to counter these effects. Apart from the long reaction time, the main difficulty arose from the instability of the cyanohydrin and the consequent formation of by-products. The catalytic reduction of the acetate (2.52) should proceed without the formation of the ketone (2.45) and the alcohol (2.51). Unfortunately, the reduction of the acetate (2.52) was extremely slow and was not pursued further.



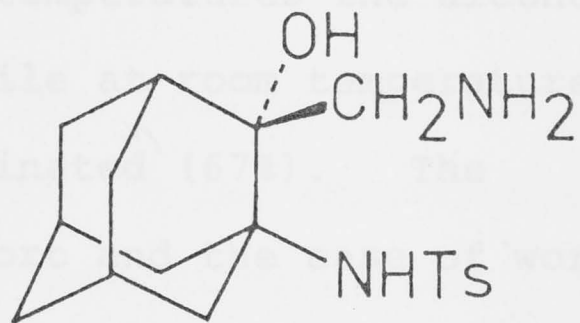
(2.45)



(2.52)



(2.51)



(2.56)

TABLE 2.1

Reagent	Starting material	Products (% yield)		
		Amino-alcohol (2.56)	Alcohol (2.51)	Ketone (2.45)
PtO <sub>2</sub> /H <sub>2</sub>	Cyanohydrin (2.49)	73	13.8	7
"Vitrade"*	Cyanohydrin (2.49)	45	51	-
LAH	Cyanohydrin (2.49)	67	28	-
B <sub>2</sub> H <sub>6</sub>	Cyanohydrin (2.49)	No reaction (94% recovery)		
PtO <sub>2</sub> /H <sub>2</sub>	Acetate (2.52)	No reaction (92% recovery)		
LAH	Acetate (2.52)	-	93	-

\* NaAlH<sub>2</sub>(OCH<sub>2</sub>CH<sub>2</sub>OCH<sub>3</sub>)<sub>2</sub>

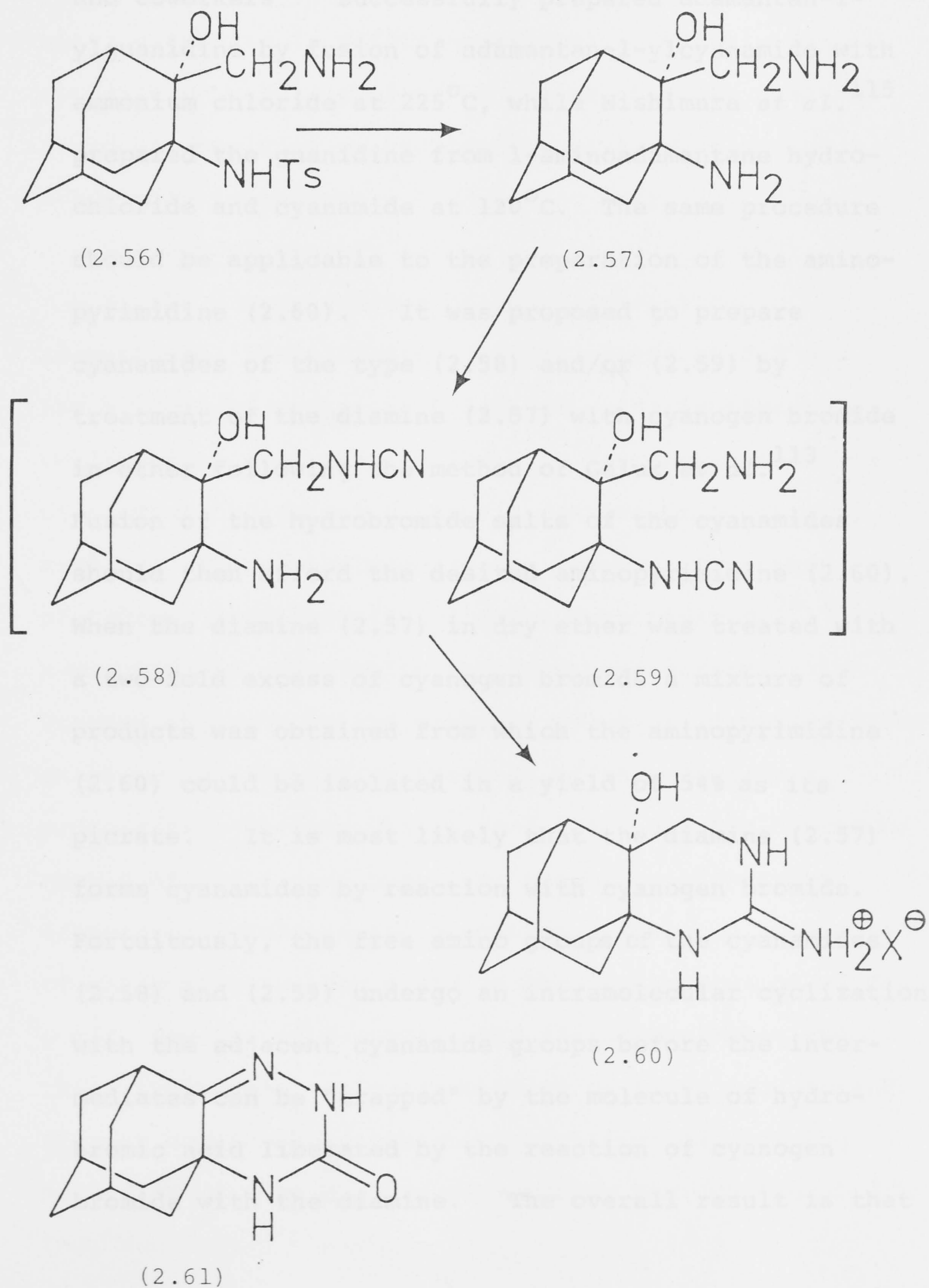
Reduction of the cyanohydrin (2.49) or its acetate (2.52) by a metal hydride should be more rapid than the catalytic methods described previously. Provided that the reduction of the cyanohydrin is sufficiently fast, the amounts of the decomposition products (2.45) and (2.51) could be significantly reduced. "Vitrade" ( $\text{NaAlH}_2(\text{OCH}_2\text{CH}_2\text{OCH}_3)_2$ ) in benzene at room temperature afforded the amino-alcohol (2.56) in 45% yield, the remainder of the product being the alcohol (2.51). The same products were obtained when lithium aluminium hydride was used. At elevated temperatures the alcohol (2.51) was the major product while at room temperature the amino-alcohol (2.56) predominated (67%). The reaction time was relatively short and the ease of work-up made lithium aluminium hydride reduction of the cyanohydrin (2.49) the preferred route to the amino-alcohol (2.56). An attempt was made to reduce the acetate (2.52) with lithium aluminium hydride in toluene at  $70^\circ$ . However, under these conditions reductive cleavage of the acetate ester to the cyanohydrin and ethanol followed by loss of hydrogen cyanide from the cyanohydrin occurred readily. The only product of the reaction was the alcohol (2.51) formed by the reduction of the ketone (2.45). The cyanohydrin (2.49) could not be reduced with diborane, the starting material was recovered almost quantitatively. The results of the attempted reductions of the cyanohydrin (2.49) and of its acetate (2.52) are summarised in Table 2.1.

The tosyl group of the amino-alcohol (2.56) was readily cleaved with sodium in liquid ammonia to afford 2-aminomethyl-2-hydroxyadamantan-1-ylamine (2.57) in quantitative yield (see Scheme 2.10). The reaction proceeded equally well whether the amino-alcohol or its hydrochloride salt was used. The diamine (2.57) reacts very readily with carbon dioxide and must therefore be stored under a carbon dioxide free nitrogen atmosphere, or converted into its dihydrochloride salt. Subsequent reactions of the free base were conducted under a nitrogen atmosphere.

A variety of methods were investigated for the cyclization of the diamine (2.57) to the aminopyrimidine (2.60). The reaction offered some difficulties however, because the conventional synthetic methods were unsuccessful. Guanidine hydrochloride, S-methyl-*iso*-thiouronium sulphate and cyanamide all failed to react with the diamine and the starting material could be recovered in all cases. These observations are in keeping with those of Geluk and coworkers<sup>113</sup> who found that 1-aminoadamantane did not react with cyanamide or S-methyl-*iso*-thiouronium sulphate even under vigorous conditions. Their observations on the lack of reactivity of 1-aminoadamantane toward these reagents were confirmed in our hands. Adamantan-1-ylguanidine could not be prepared by the conventional methods. It has been suggested<sup>114</sup> that the unsuccessful guanidination of sterically hindered amines is due to steric strain



SCHEME 2.10



caused by the bulky alkyl groups. However, this suggestion does not explain the lack of reactivity of the 2-aminomethyl group of the diamine (2.57) toward the usual reagents for guanidination. Geluk and coworkers<sup>113</sup> successfully prepared adamantan-1-ylguanidine by fusion of adamantan-1-ylcyanamide with ammonium chloride at 225°C, while Nishimura *et al.*<sup>115</sup> prepared the guanidine from 1-aminoadamantane hydrochloride and cyanamide at 120°C. The same procedure should be applicable to the preparation of the aminopyrimidine (2.60). It was proposed to prepare cyanamides of the type (2.58) and/or (2.59) by treatment of the diamine (2.57) with cyanogen bromide in ether following the method of Geluk *et al.*<sup>113</sup> Fusion of the hydrobromide salts of the cyanamides should then afford the desired aminopyrimidine (2.60). When the diamine (2.57) in dry ether was treated with a two-fold excess of cyanogen bromide a mixture of products was obtained from which the aminopyrimidine (2.60) could be isolated in a yield of 54% as its picrate. It is most likely that the diamine (2.57) forms cyanamides by reaction with cyanogen bromide. Fortuitously, the free amino groups of the cyanamides (2.58) and (2.59) undergo an intramolecular cyclization with the adjacent cyanamide groups before the intermediates can be "trapped" by the molecule of hydrobromic acid liberated by the reaction of cyanogen bromide with the diamine. The overall result is that

the aminopyrimidine (2.60) is formed and precipitates as the hydrobromide salt (2.60;  $X^- = Br^-$ ). The reaction is depicted in Scheme 2.10.

The oxo analogue (2.61) was prepared in high yield by the reaction of the amino-ketone (2.37) with ethyl carbazate in refluxing ethanol. Usually the cyclization was incomplete in ethanol but the reaction could be completed by heating the mixture as a suspension in toluene.

ii) P.m.r. spectra

In the p.m.r. spectra of 1,2-disubstituted adamantanes, identification of the proton at C-2 and the bridgehead proton at C-3 is of value in structural verification (see Section 3)ii)). The chemical shifts of adamantane protons display a consistent additivity, each substituent influencing the resonant frequency of protons independently of other substituents,<sup>94,116</sup> a significant observation for structure determination. Protons adjacent to the carbonyl group of adamantan-2-one resonate downfield from the bulk of the adamantane protons (see Section 3)ii)), and these downfield protons should afford a good probe for measuring additivity effects in 1-substituted adamantan-2-ones. A knowledge of these effects should aid in the interpretation of the p.m.r. spectra of 1-substituted adamantan-2-ones and their hydrazones. Interpretation of the p.m.r. spectra of such compounds is somewhat simplified because the molecules possess a plane of symmetry through C-1, C-2, C-3, and C-6.

The p.m.r. spectrum of 2-oxoadamantan-1-yl(N-toluene-*p*-sulphonyl)amine (fig. 2.11) exhibits a multiplet at  $\delta$  1.51-2.67 corresponding to the 10 methylene protons of the adamantane skeleton. A vicinal coupling constant  $J_{vic}$  2.6 Hz between the bridgehead and methylene protons can be observed, and is in excellent agreement with those determined by Fort and Schleyer<sup>94</sup> for 1-substituted adamantanes. The chemical shifts for the methylene protons are tentatively assigned as shown in Figure 2.11. The bridgehead protons resonate downfield from the methylene protons. By a comparison of their relative integrals, the chemical shifts  $\delta$  2.55 and  $\delta$  2.75 can be assigned to bridgehead protons H-3, and H-5 and H-7 respectively. The assignment of H-3 may be confirmed by application of the additivity principle described below.

If it is assumed that the bridgehead protons of adamantane resonate at  $\delta$  1.88,<sup>94</sup> then a measure of substituent effects on the chemical shifts of bridgehead protons in 1- and 2-mono, and 1,2-disubstituted adamantanes can be obtained relative to the bridgehead protons in unsubstituted adamantane. In adamantan-2-ones and -2-hydrazones and in 1-substituted adamantanes, the bridgehead protons are deshielded and are easily discernible as broad multiplets downfield from the bulk of the adamantane protons. For this reason they, and particularly H-3 can be used to measure additivity effects, and to aid in the assignment of chemical shifts for bridgehead protons. The chemical shift of the

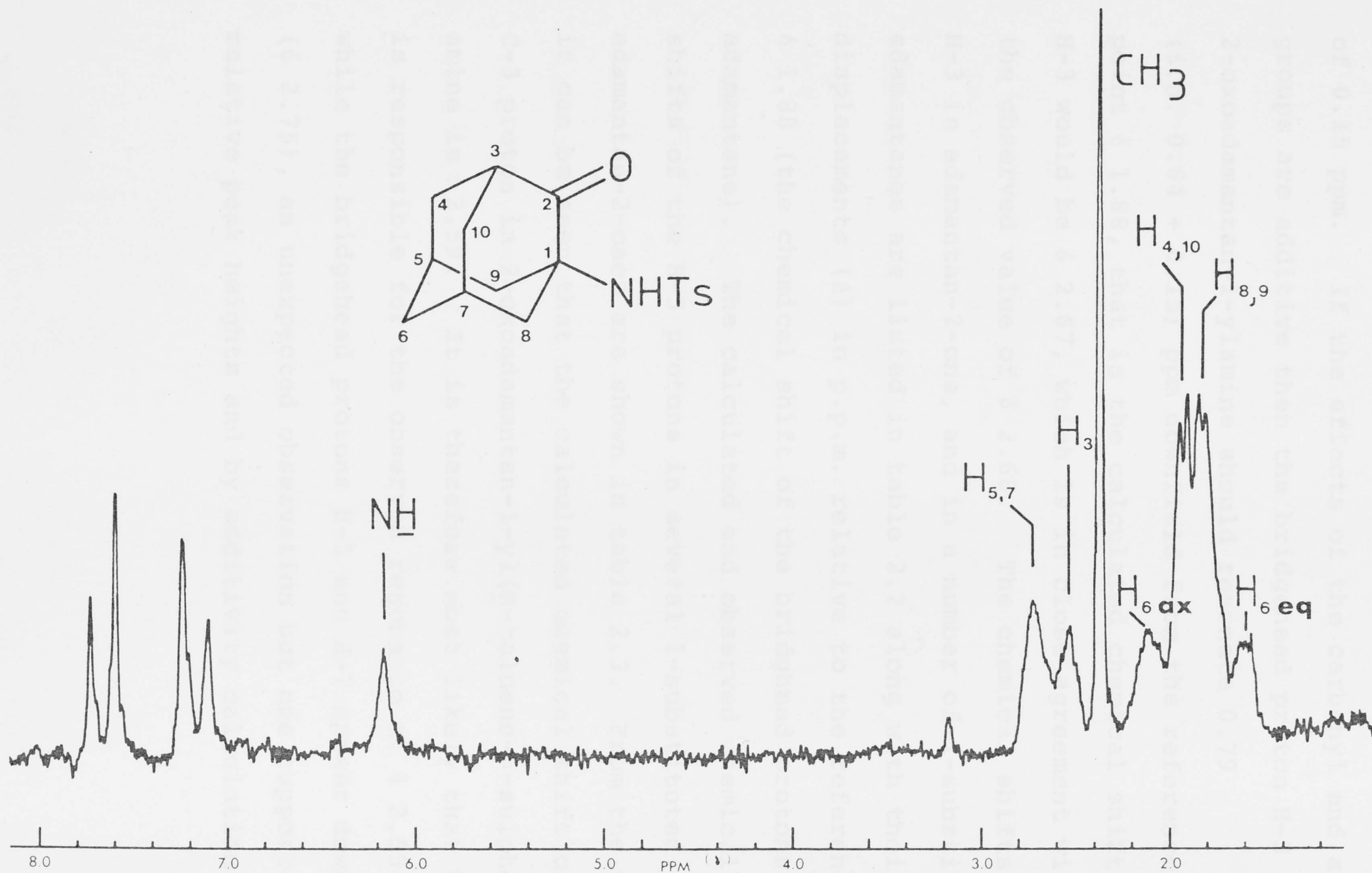


Fig. 2.11 P.m.r. spectrum of 2-oxoadamantan-1-yl  
(*N*-toluene-*p*-sulphonyl)amine in  $\text{CDCl}_3$  at 60 MHz.

bridgehead proton H-3 (and H-1) in adamantanone is  $\delta$  2.52, a difference of 0.64 ppm from  $\delta$  1.88 the reference point, while H-3 (and H-5 and H-7) in 1-aminoadamantane resonates at  $\delta$  2.03, a difference of 0.15 ppm. If the effects of the carbonyl and amino groups are additive then the bridgehead proton H-3 in 2-oxoadamantan-1-ylamine should resonate 0.79 (*i.e.* 0.64 + 0.15) ppm downfield from the reference point  $\delta$  1.88, that is the calculated chemical shift of H-3 would be  $\delta$  2.67, which is in close agreement with the observed value of  $\delta$  2.68. The chemical shifts of H-3 in adamantan-2-one, and in a number of 1-substituted adamantanes are listed in table 2.2 along with their displacements ( $\Delta$ ) in p.p.m. relative to the reference  $\delta$  1.88 (the chemical shift of the bridgehead protons in adamantane). The calculated and observed chemical shifts of the H-3 protons in several 1-substituted adamantan-2-ones are shown in table 2.3. From the table it can be seen that the calculated chemical shift of the C-3 proton in 2-oxoadamantan-1-yl(N-toluene-*p*-sulphonyl) amine is  $\delta$  2.59. It is therefore most likely that H-3 is responsible for the observed resonance at  $\delta$  2.55 while the bridgehead protons H-5 and H-7 appear downfield ( $\delta$  2.75), an unexpected observation but one supported by relative peak heights and by additivity calculations.

Table 2.2

	Chemical shift of H-3	
	Chemical shift of H-3 ( $\delta$ )	Observed $\Delta$ (ppm) *
adamantanone	2.52	0.64
1-aminoadamantane	2.03	0.15
1-( <i>N</i> -toluene- <i>p</i> -sulphonyl)- aminoadamantane	1.95	0.07
adamantane-1-carboxamide	2.02	0.14
adamantan-1-ol	2.10	0.22
2-( <i>N</i> -ethoxycarbonyl)- hydrazonoadamantane	<i>anti</i> 2.72	0.84
	<i>syn</i> 3.07	1.19

\* displacement of the observed chemical shift of H-3 from the chemical shift of the bridgehead protons of adamantane ( $\delta$  1.88).

Table 2.3

	Chemical shift of H-3	
	Calculated	Observed
2-oxoadamantan-1-ylamine	2.67	2.68
2-oxoadamantan-1-yl ( <i>N</i> -toluene- <i>p</i> -sulphonyl) amine	2.59	2.55
2-oxoadamantane-1-carboxamide	2.66	2.62
2-oxoadamantan-1-ol <sup>117</sup>	2.74	2.75
2-( <i>N</i> -ethoxycarbonyl)hydrazono- adamantan-1-yl ( <i>N</i> -toluene- <i>p</i> -sulphonyl) amine	<i>syn</i> 2.79	2.73
	<i>anti</i> 3.14	3.08

posed a problem in that three separate bridgehead proton resonances were observed. However their relative peak heights and additivity calculations allowed assignments to be made. 2-(*N*-ethoxycarbonyl)hydrazono-  
adamantane was prepared by the reaction of adamantane-2-one with ethyl carbazate. As previously described its p.m.r. spectrum (Fig. 2.3) exhibits separate signals (see page 32 )

<sup>117</sup> The relative integrals of the methylene protons of the ethyl groups were used as a measure of the proportion of each isomer. The appropriate methylene protons of the *anti* isomer resonate at  $\delta$  4.23 while the *syn* isomer methylene group appears as a quartet at  $\delta$  3.55 (see experimental).



As previously mentioned, the reaction of ethyl carbazate with 2-oxoadamantan-1-yl(*N*-toluene-*p*-sulphonyl)amine affords a mixture of *anti* and *syn* isomers, (2.55a) and (2.55b) respectively.<sup>†</sup> It was found that when this mixture was treated with acetone cyanohydrin followed by aqueous work the proportion of the more stable *anti* isomer increased slightly. Treatment of the same mixture with deuterium oxide and sodium deuterioxide led to a further increase in the proportion of the thermodynamically more stable *anti* isomer (see Fig. 2.12). The reversible addition of HCN, H<sub>2</sub>O or D<sub>2</sub>O to the C=N bond of the hydrazone enables isomerization to occur, with the more stable *anti* isomer being favoured over the *syn* isomer. The interpretation of the p.m.r. spectrum of the hydrazone posed a problem in that three separate bridgehead proton resonances were observed. However their relative peak heights and additivity calculations allowed assignments to be made. 2-(*N*-Ethoxycarbonyl)hydrazonoadamantane was prepared by the reaction of adamantan-2-one with ethyl carbazate. As previously described its p.m.r. spectrum (Fig. 2.5) exhibits separate signals (see page 32 )

---

<sup>†</sup> The relative integrals of the methylene protons of the ethyl groups were used as a measure of the proportion of each isomer. The appropriate methylene protons of the *anti* isomer resonate at  $\delta$  4.23 while the *syn* isomer methylene group appears as a quartet at  $\delta$  3.65 (see experimental).

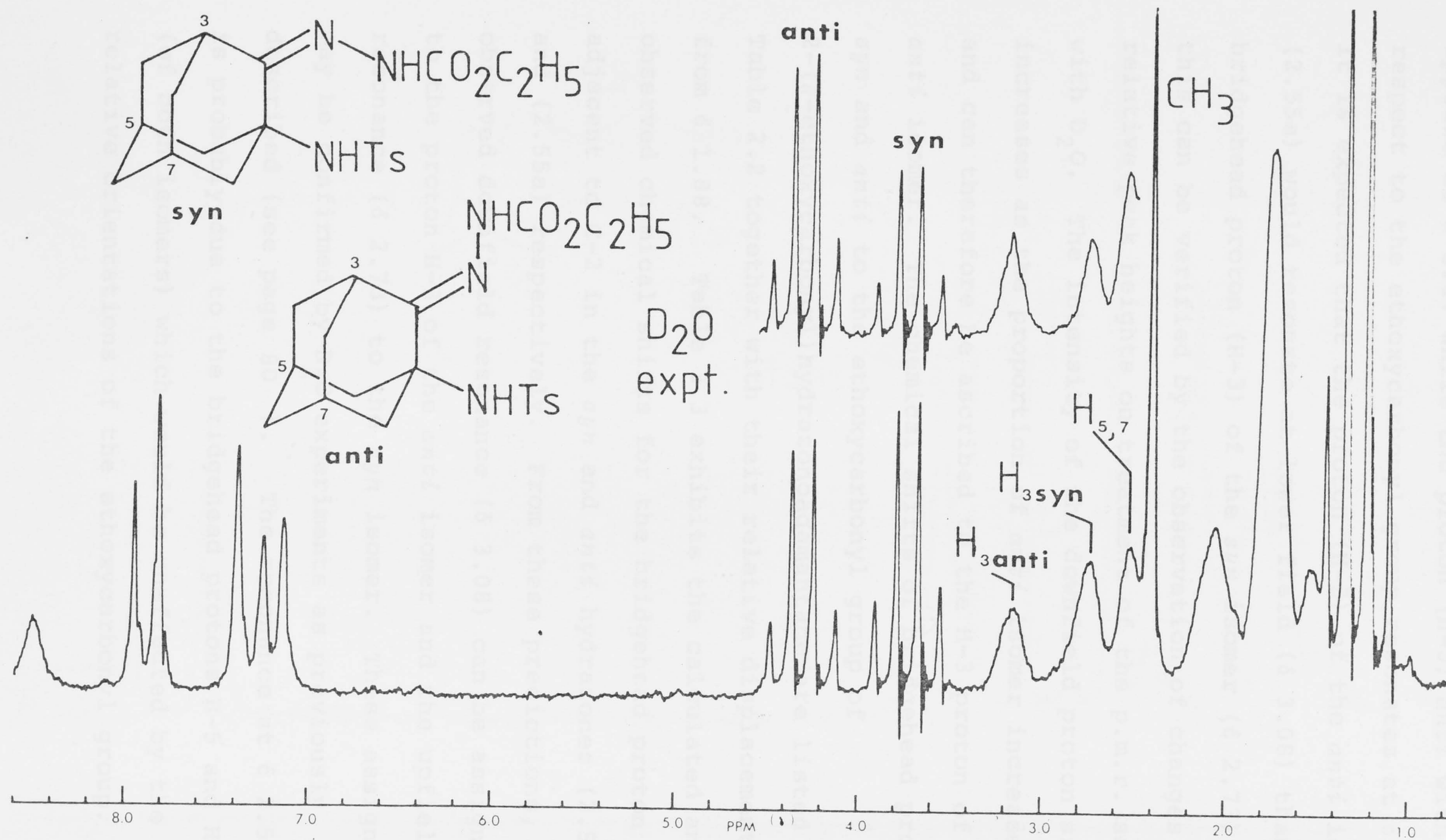


Fig. 2.12 P.m.r. spectrum of 2-(*N*-ethoxycarbonyl)hydrazonoadamantan-1-yl(*N*-toluene-*p*-sulphonyl)amine in  $\text{CDCl}_3$  at 60 MHz.

for bridgehead protons adjacent to C-2. The proton (H-1) *syn* with respect to the ethoxycarbonyl group appears at  $\delta$  3.07 while the proton (H-3) *anti* with respect to the ethoxycarbonyl group resonates at  $\delta$  2.72. It is expected that the proton (H-3) of the *anti* isomer (2.55a) would resonate at lower field ( $\delta$  3.08) than the bridgehead proton (H-3) of the *syn* isomer ( $\delta$  2.73), and this can be verified by the observation of changes in relative peak heights on treatment of the p.m.r. sample with D<sub>2</sub>O. The intensity of the downfield proton signal increases as the proportion of *anti* isomer increases, and can therefore be ascribed to the H-3 proton of the *anti* isomer. The chemical shifts of bridgehead protons *syn* and *anti* to the ethoxycarbonyl group of 2-(*N*-ethoxycarbonyl)hydrazonoadamantane are listed in Table 2.2 together with their relative displacements ( $\Delta$ ) from  $\delta$  1.88. Table 2.3 exhibits the calculated and observed chemical shifts for the bridgehead proton H-3 adjacent to C-2 in the *syn* and *anti* hydrazones (2.55b) and (2.55a) respectively. From these predictions, the observed downfield resonance ( $\delta$  3.08) can be assigned to the proton H-3 of the *anti* isomer and the upfield resonance ( $\delta$  2.73) to the *syn* isomer. These assignments may be confirmed by D<sub>2</sub>O experiments as previously described (see page 80 ). The resonance at  $\delta$  2.53 is probably due to the bridgehead protons H-5 and H-7 (of both isomers) which would be unaffected by the relative orientations of the ethoxycarbonyl group.

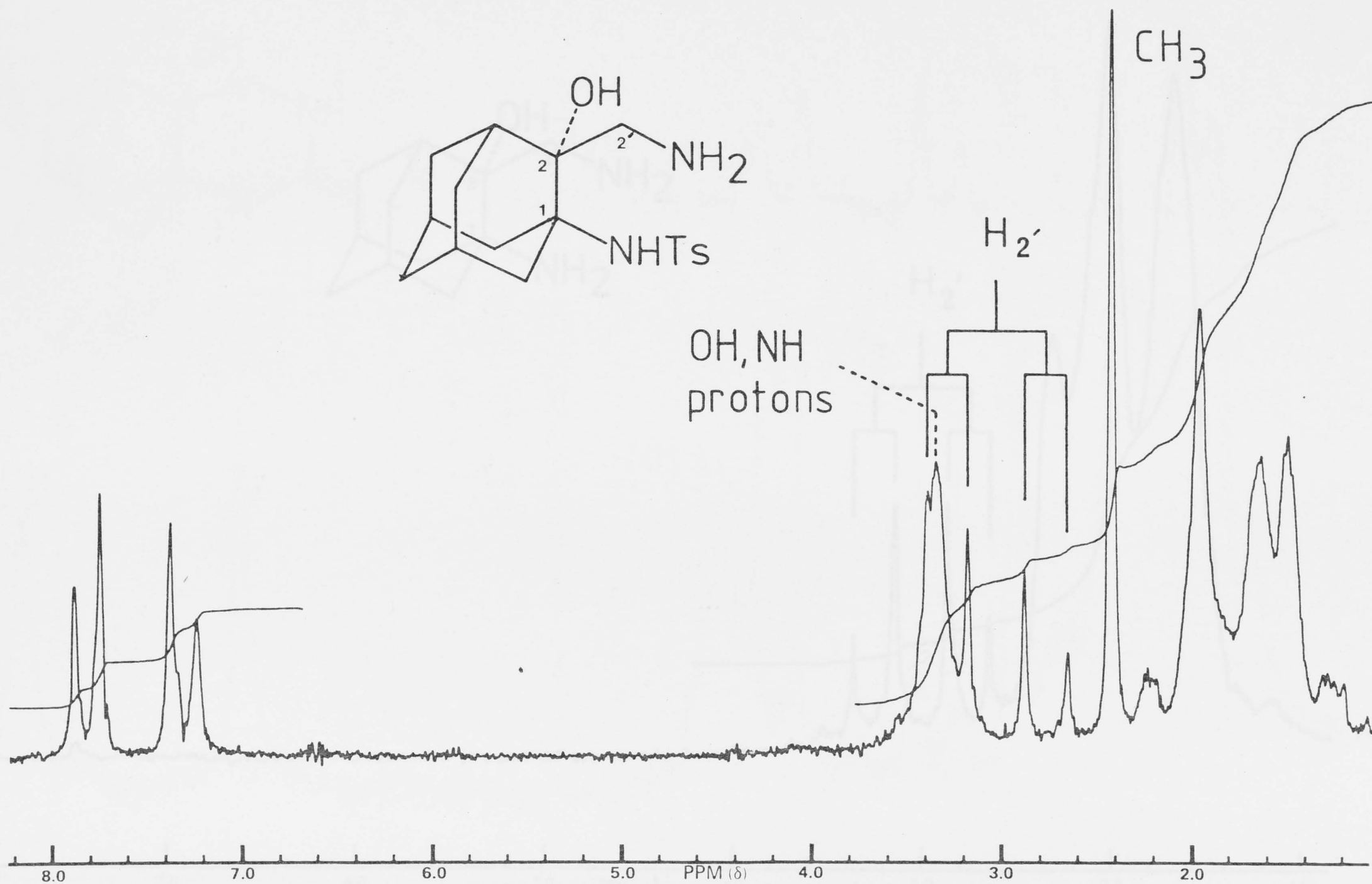


Fig. 2.13 P.m.r. spectra of 2-aminomethyl-2-hydroxyadamantan-1-yl(*N*-toluene-*p*-sulphonyl)amine in CDCl<sub>3</sub> at 60 MHz.

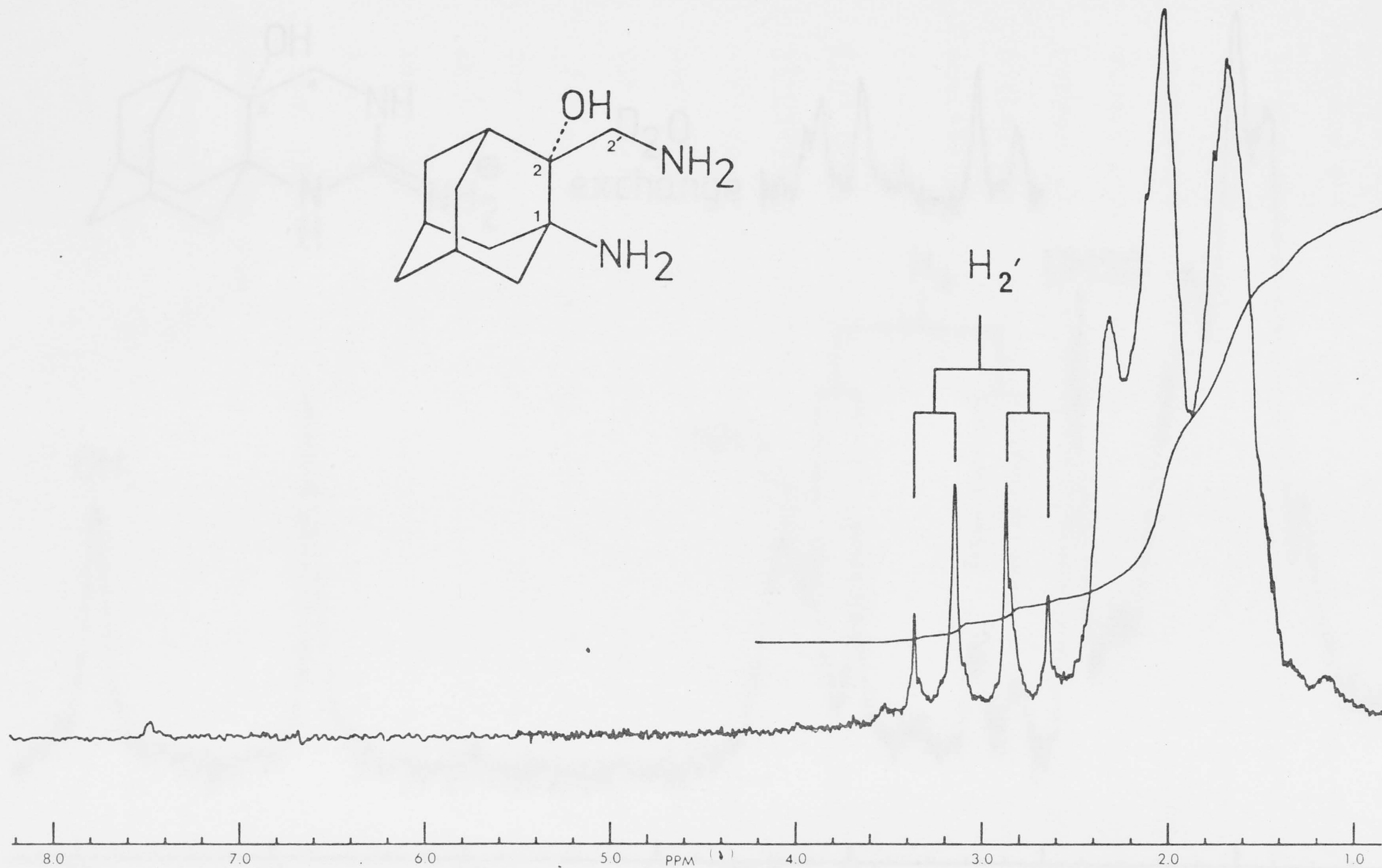


Fig. 2.14 P.m.r. spectrum of 2-aminomethyl-2-hydroxyadamantan-1-ylamine in  $\text{CDCl}_3$  at 60 MHz.

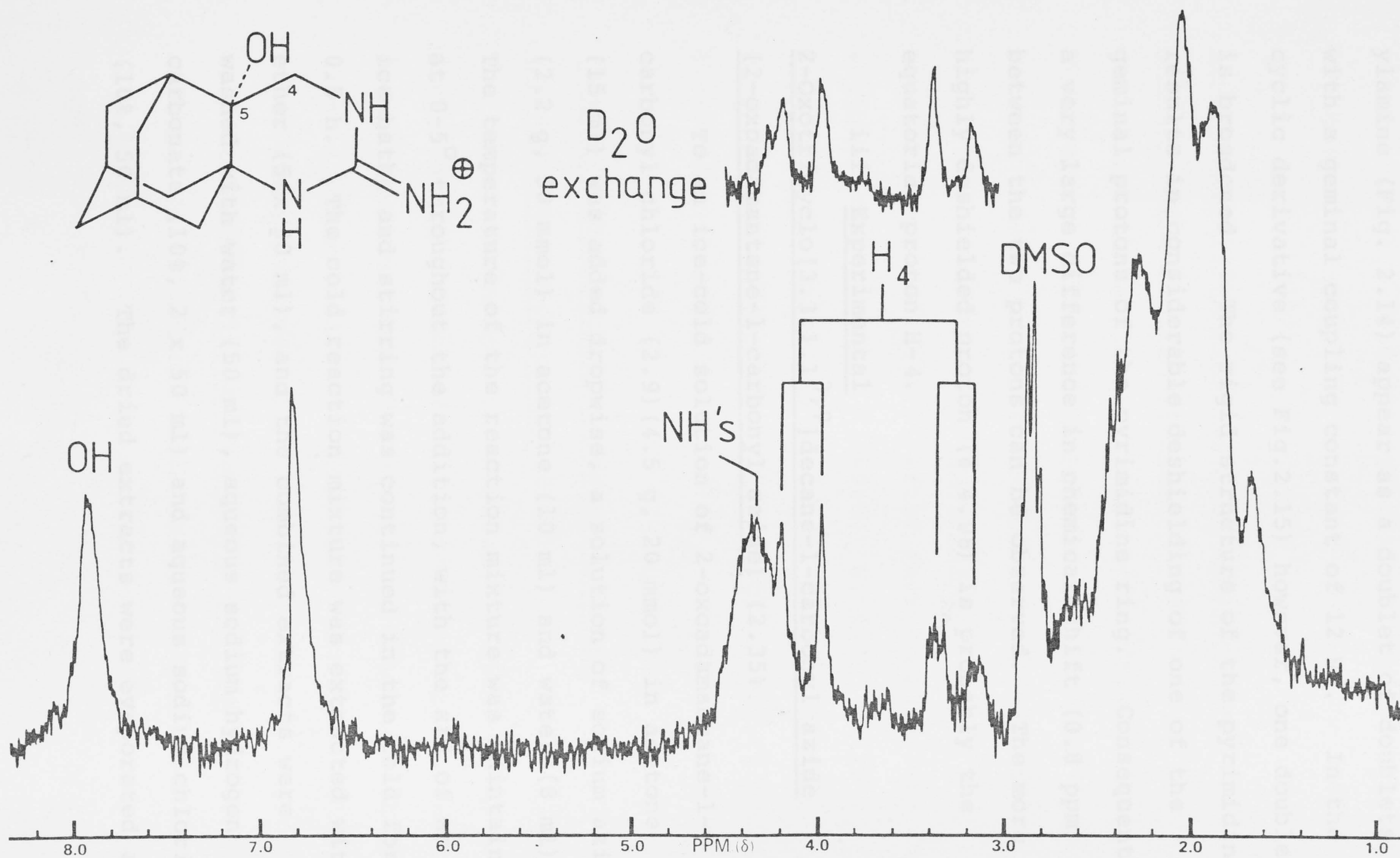


Fig. 2.15 P.m.r. spectrum of 5-hydroxytetrahydroadamantano[1,2-*d*]pyrimidine-2-iminium picrate in  $(\text{CD}_3)_2\text{SO}$  at 60 MHz.

The exocyclic methylene protons of 2-aminomethyl-2-hydroxyadamantan-1-yl(*N*-toluene-*p*-sulphonyl)amine (Fig. 2.13) and 2-aminomethyl-2-hydroxyadamantan-1-ylamine (Fig. 2.14) appear as a doublet of doublets with a geminal coupling constant of 12 Hz. In the cyclic derivative (see Fig. 2.15) however, one doublet is broadened. The rigid structure of the pyrimidine results in considerable deshielding of one of the geminal protons of the pyrimidine ring. Consequently a very large difference in chemical shift (0.8 ppm) between the two protons can be observed. The more highly deshielded proton ( $\delta$  4.08) is probably the equatorial proton H-4.

### iii) Experimental

2-Oxotricyclo[3.3.1.1<sup>3,7</sup>]decane-1-carbonyl azide  
(2-oxoadamantane-1-carbonyl azide) (2.35)

To an ice-cold solution of 2-oxoadamantane-1-carbonyl chloride (2.9) (4.5 g, 20 mmol) in acetone (15 ml) was added dropwise, a solution of sodium azide (2.2 g, 30 mmol) in acetone (10 ml) and water (8 ml). The temperature of the reaction mixture was maintained at 0-5<sup>o</sup> throughout the addition, with the aid of an ice-bath, and stirring was continued in the cold for 0.5 h. The cold reaction mixture was extracted with ether (5 x 30 ml), and the combined extracts were washed with water (50 ml), aqueous sodium hydrogen carbonate (10%, 2 x 50 ml) and aqueous sodium chloride (10%, 50 ml). The dried extracts were evaporated at

10-15<sup>o</sup> to afford the carbonyl azide as a white crystalline solid (3.87 g, 83%) melting at 63-64<sup>o</sup> (d).

$\nu_{\max}$  2160 (N<sub>3</sub>), 1720 (ketone), 1695 (carbonyl azide C=O).

P.m.r.  $\delta$ (CDCl<sub>3</sub>) 1.60-2.47 (m, 12H), 2.60 (m,  $W_{h/2}$  6Hz, 1H, H-3).

2-Oxotricyclo[3.3.1.1<sup>3,7</sup>]decan-1-ylisocyanate

(2-oxoadamantan-1-ylisocyanate) (2.36)

2-Oxoadamantane-1-carbonyl azide (2.35) (4.38g, 20 mmol) was dissolved in benzene (100 ml) and the solution heated under reflux for 2 h. Evaporation of the solution afforded the isocyanate (3.3 g, 94%) which had m.p. 151.5-153<sup>o</sup> after recrystallization from acetone-water (Found: C, 68.9; H, 6.7; N, 7.4.

C<sub>11</sub>H<sub>13</sub>N<sub>1</sub>O<sub>2</sub> requires C, 69.1; H, 6.9; N, 7.3%).

$\nu_{\max}$  2280, 2240 (s, NCO), 1730 (C=O). P.m.r.  $\delta$ (CDCl<sub>3</sub>) 1.50-2.63 (m, 12H), 2.87 (m,  $W_{h/2}$  6Hz, 1H, H-3).

2-Oxotricyclo[3.3.1.1<sup>3,7</sup>]decan-1-ylamine

(2-oxoadamantan-1-ylamine) (2.37)

2-Oxoadamantan-1-ylisocyanate (2 g, 11 mmol) was dissolved in toluene (40 ml) and the solution heated with 4*N* hydrochloric acid (75 ml) on a steam bath for 12 h. After cooling to room temperature the toluene layer was separated, dried, and evaporated to dryness to afford *N,N'*-di[2-oxoadamantan-1-yl]urea (2.38) (176 mg, 9%) identical with that described below.



The aqueous layer was basified (pH 9) with 5N potassium hydroxide and extracted with chloroform (4 x 50 ml). The combined extracts were washed with water (50 ml), dried, and evaporated to yield the amino-ketone (1.54 g; 85%). It had m.p.\* 215-216° after sublimation (75°/0.7 mmHg) (Found: C, 72.2; H, 9.2; N, 8.5.  $C_{10}H_{15}N_1O_1$  requires C, 72.7; H, 9.2; N, 8.5%).  $\nu_{max}$  3380, 3310, 3200 (NH str), 1720 (C=O). P.m.r.  $\delta$ (CDCl<sub>3</sub>) 1.45-2.40 (m, 15H), 1.72 (NH<sub>2</sub>, exchanges in D<sub>2</sub>O), 2.68 (m,  $W_{h/2}$  10 Hz, 1H, H-3). The hydrochloride salt could be prepared simply by evaporating the aqueous acid to dryness. Recrystallization of the residue from ethanol-ether afforded the amino-ketone hydrochloride as a white crystalline solid (1.96 g, 89%), m.p. 297-298° (Found: C, 59.1; H, 7.7; N, 6.7; Cl, 18.0.  $C_{10}H_{16}N_1O_1Cl_1$  requires C, 59.6; H, 8.0; N, 6.9; Cl, 17.6%).  $\nu_{max}$  3300-2300 (br, NH<sub>3</sub><sup>+</sup> and CH str), 1723 (C=O).

*N,N'*-Di[2-oxotricyclo[3.3.1.1<sup>3,7</sup>]decan-1-yl]urea

(*N,N'*-di[2-oxoadamantan-1-yl]urea) (2.38)

The isocyanate (2.36) (760 mg, 4 mmol) was dissolved in acetone (7 ml) and water added until cloudiness persisted. The mixture was heated under reflux for 5 min and cooled. The urea crystallized in fine needles

(630 mg, 89%), melting at 289.5-291<sup>o</sup> (d) (Found: C, 70.5; H, 7.7; N, 7.6. C<sub>21</sub>H<sub>28</sub>O<sub>3</sub>N<sub>2</sub> requires C, 70.8; H, 7.9; N, 7.9%).  $\nu_{\max}$  3350 (NH str), 1730 (ketone, C=O), 1628, 1560 (urea).

7,16-Diazaheptacyclo[11.3.3.1<sup>3,18</sup>.1<sup>8,12</sup>.1<sup>10,14</sup>.0<sup>1,6</sup>.0<sup>8,15</sup>]docosa-6(7),15(16)-diene (diadamantano[1,2-*b*:1',2'-*e*]-2,5-dihydropyrazine) (2.44)

(a) 2-Oxoadamantan-1-ylamine (330 mg, 2 mmol) and TosMIC (507 mg, 2.6 mmol) were dissolved in a mixture of ethanol (0.3 ml) and glyme (14 ml) and the solution cooled to -5<sup>o</sup>C. Potassium-*t*-butoxide (560 mg, 5 mmol) was added to the stirred mixture in portions over a period of 30 min. Stirring was continued at room temperature for 14 h. and then at 60<sup>o</sup> for 5 h. The suspension was filtered and the filtrate evaporated to dryness to afford a white solid. Recrystallization from petroleum ether (b.p. 40-60<sup>o</sup>) gave the dihydropyrazine (267 mg, 91%), m.p. 236-238<sup>o</sup> (Found: C, 82.0; H, 9.2; N, 9.3. C<sub>20</sub>H<sub>26</sub>N<sub>2</sub> requires C, 81.6; H, 8.9; N, 9.5%).  $\nu_{\max}$  1674 (C=N), 1454, 1176, 904. P.m.r.  $\delta$ (CDCl<sub>3</sub>) 1.53-2.33 (m, 24H), 2.53 (m,  $W_{h/2}$  12 Hz, 2H, H-3, H-3'); m/e 294 (M<sup>+</sup> 100%).

(b) A solution of the amino-ketone (82.5 mg, 0.5 mmol) in benzene (7 ml) was heated under reflux with slow and continuous distillation of the solvent. The volume of the solution was maintained by the occasional addition of dry benzene. After 1.5 h the starting material had almost completely disappeared (infra-red). Evaporation

of the solvent and recrystallization of the residue from petroleum ether (b.p. 40-60°) afforded the dihydropyrazine identical with that described above.

(c) The amino-ketone (82.5 mg, 0.5 mmol) in glyme (5 ml) was treated with potassium-*t*-butoxide (56 mg, 0.5 mmol) and the mixture heated under reflux for 7 h. The solution was filtered and the filtrate evaporated to dryness to afford the dihydropyrazine identical with that from (a) and (b).

(d) A mixture of 2-oxoadamantane-1-yl(*N*-toluene-*p*-sulphonyl)amine (2.45) (128 mg, .4 mmol) and TosMIC (100 mg, 0.5 mmol) in ethanol (0.1 ml) and glyme (4 ml) was treated with potassium-*t*-butoxide (112 mg, 1 mmol) according to the method described in (a). The residue from evaporation of the filtered reaction mixture was washed with a small quantity of cold methanol and the remaining white solid dissolved in ether. Evaporation of the filtered ethereal solution afforded the starting material (94 mg, 73%). The insoluble material (20 mg, 17%) was found to be identical with the dihydropyrazine described above.

2-Oxotricyclo[3.3.1.1<sup>3,7</sup>]decan -1-yl(*N*-toluene-*p*-sulphonyl)amine (2-oxoadamantan-1-yl(*N*-toluene-*p*-sulphonyl)amine) (2.45)

The amino-ketone (2.37) (4.98 g, 30 mmol) was added to pyridine (25 ml) containing toluene-*p*-sulphonyl chloride (11.4 g, 60 mmol) and the mixture stored in the cold. After 48 h the mixture was poured into

ice-cold water and the crystalline solid that separated was collected, washed with water and dried. The toluene-*p*-sulphonyl derivative (8.23 g, 86%) was recrystallized from ether and had m.p. 162-164<sup>o</sup>

(Found: C, 64.2; H, 6.6; N, 4.3; S, 9.7.

$C_{17}H_{21}N_1S_1O_3$  requires C, 63.9; H, 6.6; N, 4.4; S, 10.0%).  $\nu_{max}$  3322 (NH str), 1724 (C=O). P.m.r.  $\delta(CDCl_3)$  1.51-2.67 (m, 10H), 2.36 (s, 3H, toluene,  $CH_3$ ), 2.55 (m, 2H, H-5 & H-7), 2.75 (m, 1H, H-3), 6.21 (br, s, 1H, NH), 7.48 (q, aromatic H).

2-Hydroxy-2-cyanotricyclo[3.3.1.1<sup>3,7</sup>]decane  
(2-hydroxy-2-cyanoadamantane) (2.40)

Adamantanone (4 g, .027 mol) was dissolved in acetone cyanohydrin (25 ml) and triethylamine (25 drops). The mixture was kept under nitrogen in the cold for 24 h before being poured into ice-cold water. The precipitated solid was collected, washed with water and dried. Recrystallization from petroleum ether (b.p. 60-80<sup>o</sup>) afforded the cyanohydrin (4.3 g, 91%), m.p. 231-233<sup>o</sup> (lit.<sup>86</sup> 232-233.5<sup>o</sup>) (Found: C, 74.7; H, 8.7; N, 8.0. Calc. for  $C_{11}H_{15}N_1O_1$ : C, 74.5; H, 8.5; N, 7.9%).  $\nu_{max}$  3420 (OH str), 2235 (CN). P.m.r.  $\delta(CDCl_3)$  1.35-2.40 (m, 14H), 3.70 (s, 1H, OH).

15-Cyano-7,16-diazaheptacyclo[11.3.3.1<sup>3,18</sup>.1<sup>8,12</sup>.1<sup>10,14</sup>.0<sup>1,6</sup>.0<sup>8,15</sup>]docos-6(7)-ene (3-cyano-diadamantano[1,2-*b*:1',2'-*e*]2,3,4,5-tetrahydropyrazine) (2.48)

The amino-ketone (2.37) (200 mg, 1.2 mmol) was dissolved in acetone cyanohydrin (3 ml) and triethylamine (2 drops) added. The mixture was stored under nitrogen in the cold for 2 days. Evaporation of the solution at 30-35° under a stream of nitrogen afforded an oily solid, which on trituration with ether gave a white solid. The product recrystallized from ether in colourless elongated plates (148 mg, 77%), m.p. 243-244.5° (d) (Found: C, 78.7; H, 8.6; N, 12.9. C<sub>21</sub>H<sub>28</sub>N<sub>3</sub> requires C, 78.5; H, 8.5; N, 13.1%).  $\nu_{\max}$  3320 (NH str), 2200 (CN), 1655 (C=N). m/e 321 (M<sup>+</sup> 5%), 294 (100%).

2-Cyano-2-hydroxytricyclo[3.3.1.1<sup>3,7</sup>]decan -1-yl (*N*-toluene-*p*-sulphonyl)amine (2-cyano-2-hydroxyadamantan-1-yl(*N*-toluene-*p*-sulphonyl)amine) (2.49)

The tosylamino-ketone (2.45) (2.5 g, 7.8 mmol) was dissolved in acetone cyanohydrin (50 ml) and triethylamine (30 drops) and stirred under nitrogen in the cold for 2 days. The mixture was poured into ice-cold water and the solid collected and washed with water. The cyanohydrin (2.59 g, 96%) was recrystallized from ether and had m.p. 163-165° (d) (Found: C, 62.6; H, 6.3; N, 8.2; S, 9.2. C<sub>18</sub>H<sub>22</sub>N<sub>2</sub>S<sub>1</sub>O<sub>3</sub> requires C, 62.4; H, 6.4; N, 8.1; S, 9.3%).

$\nu_{\max}$  3379 (OH str), 3242 (NH str), 2250 (CN). P.m.r.  
 $\delta(\text{CDCl}_3)$  1.2-2.67 (m, 13H), 2.40 (s, 3H,  $\text{CH}_3$ ),  
 5.02 (br, s, 1H, OH), 5.77 (br, s, 1H, NH),  
 7.53 (q, 4H, aromatic H).

2-Acetoxy-2-cyanotricyclo[3.3.1.1<sup>3,7</sup>]decan-1-yl  
(*N*-toluene-*p*-sulphonyl) amine (2-acetoxy-2-  
cyanoadamantan-1-yl(*N*-toluene-*p*-sulphonyl) amine) (2.52)

The cyanohydrin (2.49) (1 g, 2.8 mmol) was dissolved in a mixture of acetic anhydride (4.6 g) and pyridine (5.8 ml). After standing at room temperature for 24 h the solution was poured into ice-cold water. The aqueous suspension was extracted with chloroform (5 x 40 ml) and the combined chloroform extracts washed with water, 2N HCl, 10% aqueous potassium carbonate and again with water. Evaporation of the dried extracts afforded a colourless semi-solid which when triturated with ether gave the acetate (980 mg, 88%), m.p.

224.5-226<sup>o</sup> (Found: C, 61.6; H, 6.6; N, 6.9; S, 8.1.

$\text{C}_{20}\text{H}_{24}\text{N}_2\text{S}_1\text{O}_4$  requires C, 61.8; H, 6.2; N, 7.2;

S, 8.3%).  $\nu_{\max}$  3250 (NH str), 1761 (C=O). P.m.r.

$\delta(\text{CDCl}_3)$  1.40-2.32 (m, 12H), 2.08 (s, 3H, acetate  $\text{CH}_3$ ),  
 2.42 (s, 3H, toluene  $\text{CH}_3$ ), 2.93 (br s, 1H, H-3),  
 5.75 (s, 1H, NH), 7.63 (q, 4H, aromatic H).

2-(N-Ethoxycarbonyl)hydrazonotricyclo[3.3.1.1<sup>3,7</sup>]decan-1-yl(N-toluene-p-sulphonyl)amine (2-(N-ethoxycarbonyl)hydrazonoadamantan-1-yl(N-toluene-p-sulphonyl)amine) (2.55)

The *N*-tosylamino-ketone (2.45) (200 mg, 0.63 mmol) in ethanol (3 ml) and a trace of acetic acid (1 drop) was treated with ethyl carbazate (66 mg, 0.63 mmol) and the mixture heated under reflux for 16 h. Evaporation of the solution gave the hydrazone (232 mg, 91%), m.p. 169.5-171<sup>o</sup> after recrystallization from ethanol (Found: C, 59.0; H, 6.8; N, 10.1; S, 7.7.

$C_{20}H_{27}N_3O_4S_1$  requires C, 59.2; H, 6.7; N, 10.4; S, 7.9%).  $\nu_{max}$  3460, 3350 (NH str), 1738 (C=O), 1530 (C=N). P.m.r.  $\delta$  (CDCl<sub>3</sub>) 1.33-2.60 (m, 12H), 1.15 (t, 1.4 H, CH<sub>2</sub>CH<sub>3</sub> *syn*), 1.27 (t, 1.6H, CH<sub>2</sub>CH<sub>3</sub> *anti*), 2.32 (s, 3H, toluene CH<sub>3</sub>), 2.53 (m, 2H, H-5 & H-7), 2.73 (m,  $W_{h/2}$  8 Hz, .47H, H-3 *syn*), 3.08 (m,  $W_{h/2}$  9 Hz, .53H, H-3 *anti*), 3.65 (q, .95H, CH<sub>2</sub>CH<sub>3</sub>, *syn*), 4.23 (q, 1.05H, CH<sub>2</sub>CH<sub>3</sub>, *anti*), 6.95 (s, 1H, NHTs), 7.50 (q, 4H, aromatic H), 7.78 (br s, 1H, NNH).

2-Aminomethyl-2-hydroxytricyclo[3.3.1.1<sup>3,7</sup>]decan-1-yl(N-toluene-p-sulphonyl)amine (2-aminomethyl-2-hydroxyadamantan-1-yl(N-toluene-p-sulphonyl)amine) (2.56)

(a) With platinum oxide: The *N*-tosylamino cyanohydrin (2.49) (1.15 g, 3.3 mmol) was dissolved in ethanol (30 ml) and ethanolic HCl (3.2 N, 5 ml), and platinum oxide (570 mg) was added. The mixture was

hydrogenated at 4 atmospheres for 2.5 days after which time a further quantity of platinum oxide (570 mg) was added and hydrogenation continued for 2 days.

Ethanol was added to dissolve the solid and the solution was filtered and reduced in volume to 30 ml at room temperature. Ether was added and the white precipitate was collected. Recrystallization from ethanol-ether afforded the amino-alcohol hydrochloride (1.06 g, 73%), m.p. 274-275° (Found: N, 7.3; Cl, 9.2.  $C_{18}H_{27}N_2S_1O_3Cl_1$  requires N, 7.2; Cl, 9.2%).  $\nu_{max}$  3660-2600 ( $NH_3^+$ , OH and CH str). P.m.r.  $\delta(D_2O)$  1.12-2.60 (m, 14H), 2.40 (s, 3H, toluene  $CH_3$ ), 3.60 (s, 2H,  $CH_2NH_2 \cdot HCl$ ), 7.68 (q, 4H, aromatic H). Evaporation of the mother liquors and fractional crystallization of the residue from ether gave the *N*-tosylamino-ketone (2.45) (84 mg, 7%), identified by comparison with an authentic sample, and the alcohol (2.51) (167 mg, 14%), identical with that described in (c).

(b) With "Vitrider" ( $NaAlH_2(OCH_2CH_2OCH_3)_2$ ): The cyanohydrin (346 mg, 1 mmol) in dry benzene (5 ml) was treated with "Vitrider" (2 ml) in benzene (5 ml) and the mixture was allowed to stand at room temperature for 18 h. To the solution was added saturated aqueous sodium carbonate and the mixture heated on a steam bath for 5 min. The solution was then extracted with chloroform. The extracts were dried ( $Na_2SO_4$ ), filtered, and the filtrate evaporated to afford an oil. Ether was added



and the product collected. It was found to be identical with the amino-alcohol (2.56) (158 mg, 45%) described below. Evaporation of the mother liquors gave the alcohol (2.51) (164 mg, 51%) which was identical with that described below.

(c) With lithium aluminium hydride: The cyanohydrin (1.3 g, 3.8 mmol) in glyme (15 mls) was treated with lithium aluminium hydride (400 mg) and the mixture stirred at room temperature for 24 h. To the solution was added saturated aqueous sodium carbonate and the mixture was stirred for 30 min. The solution was then extracted with chloroform. The extracts were dried ( $\text{Na}_2\text{SO}_4$ ), filtered and the filtrate evaporated. Ether (250 ml) was added to the oily residue and the crystalline amino-alcohol (891 mg, 67%) was collected, m.p. 133-134<sup>o</sup> (Found: C, 61.8; H, 7.3; N, 7.7; S, 9.1.  $\text{C}_{18}\text{H}_{26}\text{N}_2\text{S}_1\text{O}_3$  requires C, 61.7; H, 7.5; N, 8.0; S, 9.2%).  $\nu_{\text{max}}$  3427 (OH str), 3290 (NH str). P.m.r.  $\delta$  ( $\text{CDCl}_3$ ) 1.35-2.13 (m, 13H), 2.40 (s, 3H, toluene  $\text{CH}_3$ ), 2.55, 3.49 (dd,  $J$  12 Hz, 2H,  $-\text{CH}_2\text{NH}_2$ ), 3.35 (m, 4H, NH, OH,  $\text{NH}_2$ ), 7.55 (q, 4H, aromatic H). Evaporation of the filtrate afforded the alcohol (2.51) (338 mg, 28%) identical to that described in (e).

(d) With diborane: The cyanohydrin (173 mg, 0.5 mmol) in glyme (2.5 ml) was treated with diborane (1M in THF, 1.5 ml). After 2 h at room temperature, excess diborane was decomposed with ethanol. Ethanolic hydrogen chloride (1.5 ml) was added and the solution

evaporated. The residue was partitioned between chloroform and 4N aqueous ammonia. Evaporation of the dried chloroform extracts afforded the starting material (163 mg, 94%).

Reduction of 2-acetoxy-2-cyanoadamantan-1-yl  
(*N*-toluene-*p*-sulphonyl)amine (2.52)

The acetate (2.52) (388 mg, 1 mmol) in refluxing toluene was treated with lithium aluminium hydride (750 mg), and heating and stirring continued for 18 h. The usual work-up afforded the alcohol (2.51) (298 mg, 93%) which had m.p. 186.5-187.5<sup>o</sup> after recrystallization from ether (Found: C, 63.1; H, 7.0; N, 4.4; S, 10.0. C<sub>17</sub>H<sub>23</sub>N<sub>1</sub>S<sub>1</sub>O<sub>3</sub> requires C, 63.5; H, 7.2; N, 4.4; S, 10.0%).  $\nu_{\max}$  3580 (OH str), 3250 (NH str). P.m.r.  $\delta$ (CDCl<sub>3</sub>) 1.12-2.25 (m, 13H), 2.38 (s, 3H, toluene CH<sub>3</sub>), 3.85 (d, *J* 3 Hz, 1H, H-2), 3.33-5.33 (br, 1H, NH), 7.59 (q, 4H, aromatic H).

2-Aminomethyl-2-hydroxytricyclo[3.3.1.1<sup>3,7</sup>]decan-1-  
ylamine (2-aminomethyl-2-hydroxyadamantan-1-ylamine)  
(2.57)

2-Aminomethyl-2-hydroxyadamantan-1-yl(*N*-toluene-*p*-sulphonyl)amine (2.56) hydrochloride (500 mg, 1.29 mmol) in liquid ammonia (15 ml) was treated with sodium in small amounts until the blue colour persisted for at least 10 min. After standing for 20 min, ammonium chloride was added and the ammonia allowed to evaporate.

The residue was partitioned between 2N sodium hydroxide (30 ml) and chloroform and the dried chloroform extracts afforded, on evaporation, the diamine (250 mg, 98%), m.p. 133-134<sup>o</sup>. P.m.r.

$\delta(\text{CDCl}_3)$  1.33-2.53 (m, 18H, adamantyl, NH<sub>2</sub>, OH protons), 2.74, 3.20 (dd, 2H,  $J$  12 Hz, CH<sub>2</sub>NH<sub>2</sub>). The dihydrochloride had m.p. 340-343<sup>o</sup> (d) (Found: C, 48.7; H, 8.4; N, 10.0; Cl, 26.2. C<sub>11</sub>H<sub>22</sub>N<sub>2</sub>O<sub>1</sub>Cl<sub>2</sub> requires C, 49.1; H, 8.2; N, 10.4; Cl, 26.3%).  $\nu_{\text{max}}$  3610-2480 (br, NH<sub>3</sub><sup>+</sup>, OH, CH str), 2020 (NH<sub>3</sub><sup>+</sup>).

6-Hydroxy-2,4-diazatetracyclo[7.3.1.1<sup>7,11</sup>.0<sup>1,6</sup>]tetradecane-3-iminium (5-hydroxytetrahydroadamantano[1,2-*d*]pyrimidine-2-iminium)picrate (2.60)

To the diamine (2.57) (250 mg, 1.28 mmol) in ether (10 ml) was added cyanogen bromide (297 mg, 2.6 mmol) in ether (15 ml) with stirring. A white precipitate formed and stirring was continued for 30 min. The white solid was collected and dried *in vacuo*. The picrate (334 mg, 58%) had m.p. 261-262.5<sup>o</sup> (Found: C, 48.0; H, 5.2; N, 18.7. C<sub>18</sub>H<sub>22</sub>N<sub>6</sub>O<sub>8</sub> requires C, 48.0; H, 4.9; N, 18.7%).  $\nu_{\text{max}}$  3431, 3350, 3214 (NH, OH str), 1679, 1624 (cyclic guanidino). P.m.r.  $\delta((\text{CD}_3)_2\text{SO})$  1.47-2.67 (m, 13H), 3.28 and 4.08 (dd,  $J$  12, 2H, H-4).

2,4,5-Triazatetracyclo[7.3.1.1<sup>7,11</sup>.0<sup>1,6</sup>]tetradec-4,5-en-3-one(adamantano[2,1-e]-triazin-2-one) (2.61)

A solution of the amino-ketone (2.37) (330 mg, 2 mmol) and ethyl carbazate (208 mg, 2 mmol) in ethanol (3 ml) was heated under reflux for 6 h. The solution was evaporated to dryness and the residue suspended in toluene (5 ml). The mixture was heated under reflux for 30 min and the triazine (322 mg, 80%) was collected. It had m.p. 356.5-358° after recrystallization from ethanol (Found: C, 64.3; H, 7.3; N, 20.4.  $C_{11}H_{15}N_3O_1$  requires C, 64.4; H, 7.4; N, 20.5%).  $\nu_{max}$  3260, 3080 (NH str), 1699 (C=O), 1665 (C=N).

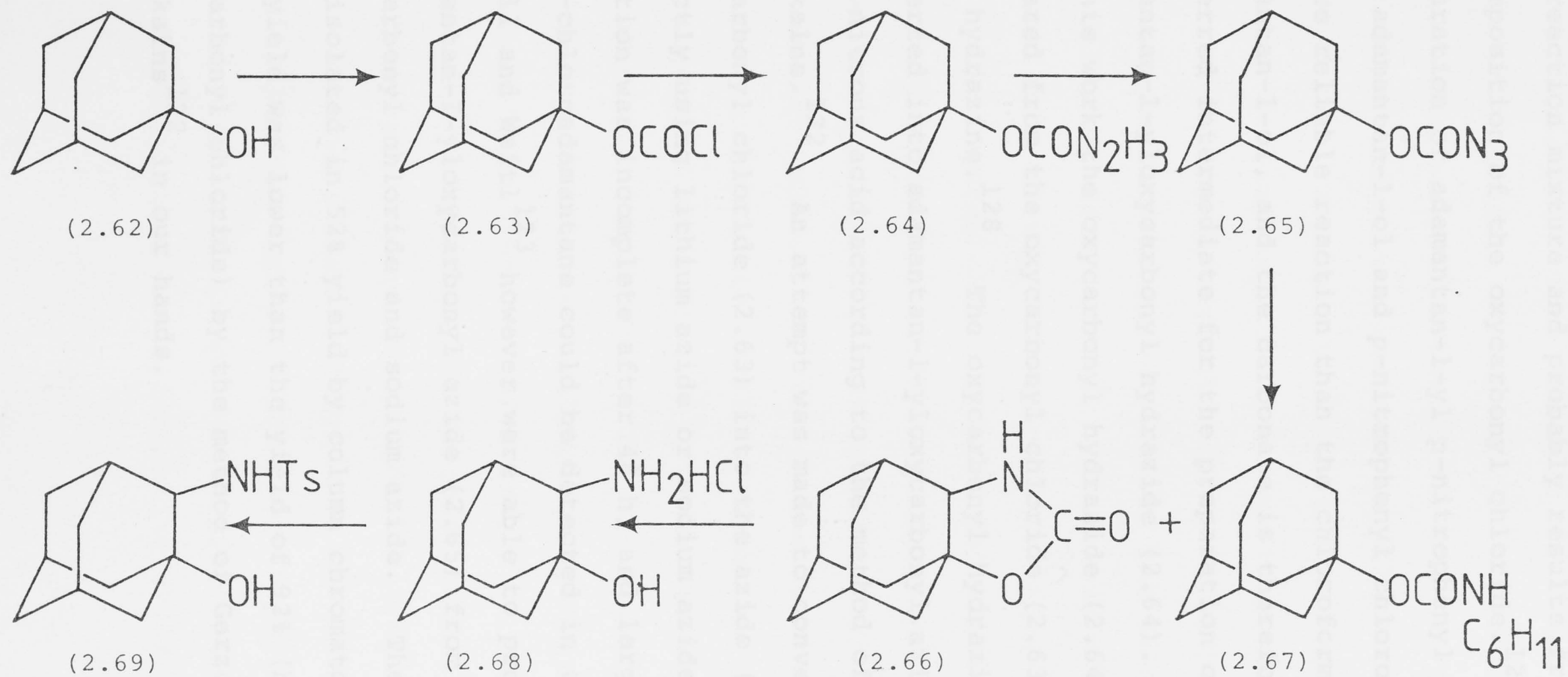
5) Photochemical Syntheses of 1,2-disubstituted adamantanes

i) Discussion

A number of other methods were investigated for the preparation of 1,2-disubstituted adamantanes as precursors to the isomeric adamantanopyrimidines described in Part 2, (Sections 3 and 4). As previously mentioned (Section 2), several successful approaches to the synthesis of 1,2-disubstituted adamantanes have utilized intramolecular cyclization reactions of nitrenes. These reactions were studied with a view toward the preparation of 1,2-disubstituted adamantanes appropriate to the present work.

Curran and Angier<sup>64,65</sup> have prepared adamantano[2,1-*d*]oxazolidin-2-one (2.66) in 45% yield by photolysis of adamantan-1-ylloxycarbonyl azide (2.65) in cyclohexane. The second product, cyclohexyl carbamate (2.67), was formed by insertion of the intermediate nitrene into a C-H bond of the solvent and was isolated from the reaction mixture in a yield of 4%. Both the oxazolidinone (2.66) and the cyclohexyl carbamate (2.67) are presumably formed *via* the singlet state nitrene intermediate,<sup>118,119,120</sup> rather than a triplet state nitrene. We were able to increase the yield of the oxazolidinone (2.66) to 65% by photolyzing the azide (2.65) in more concentrated cyclohexane solutions. Under such conditions the analytically pure product separates out of solution and is easily collected. The remaining product can be recovered by evaporating the solution and triturating the oily residue with cold cyclohexane. In 1974, Alewood and coworkers<sup>67</sup> obtained the oxazolidinone (2.66) in high yield (86%) by thermal decomposition of the azide (2.65) in chloroform containing a trace of ethanol. A small quantity of adamantan-1-yl *N*-ethoxy carbamate<sup>67</sup> was isolated from the reaction mixture and was probably formed by reaction of the nitrene with ethanol in the thermolysis.

Adamantan-1-ylloxycarbonyl azide (2.65) was prepared by the sequence of reactions illustrated in Scheme 2.11. Treatment of adamantan-1-ol (2.62) with phosgene in toluene and pyridine in a modification of the method of

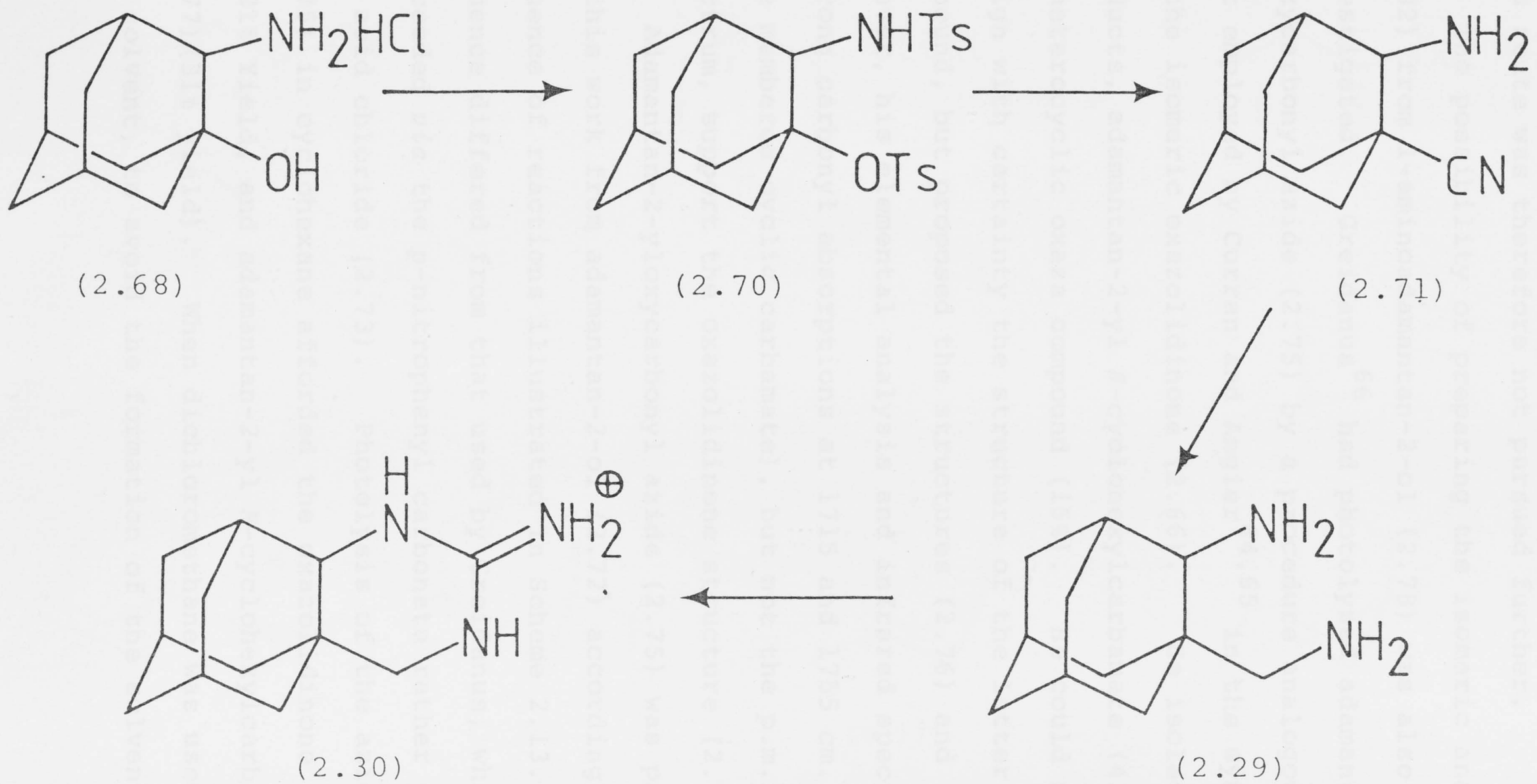


SCHEME 2.11

Kevill and Weitzl,<sup>121</sup> afforded adamantan-1-yloxycarbonyl chloride (2.63). The yields are variable however, and 1-chloroadamantane could occasionally be isolated from the reaction mixture and probably results from thermal decomposition of the oxycarbonyl chloride.<sup>121</sup> The preparation of adamantan-1-yl *p*-nitrophenyl carbonate<sup>65</sup> from adamantan-1-ol and *p*-nitrophenyl chloroformate is a more reliable reaction than the chloroformylation of adamantan-1-ol, and the carbonate is therefore the preferred intermediate for the preparation of adamantan-1-yloxycarbonyl hydrazide (2.64). However, in this work the oxycarbonyl hydrazide (2.64) was prepared from the oxycarbonyl chloride (2.63) by treatment with hydrazine.<sup>128</sup> The oxycarbonyl hydrazide was converted into adamantan-1-yloxycarbonyl azide (2.65) with nitrous acid according to the method of Gerzon and Krumkalns.<sup>122</sup> An attempt was made to convert the oxycarbonyl chloride (2.63) into the azide (2.65) directly using lithium azide or sodium azide but the reaction was incomplete after 48 h, and large quantities of 1-chloroadamantane could be detected in the products. Kevill and Weitzl<sup>123</sup> however were able to prepare adamantan-1-yloxycarbonyl azide (2.65) from the oxycarbonyl chloride and sodium azide. The azide (2.65) was isolated in 52% yield by column chromatography, but the yield was lower than the yield of 92% (based on the oxycarbonyl chloride) by the method of Gerzon and Krumkalns<sup>122</sup> in our hands.

Hydrolysis of the oxazolidinone (2.66) in 2N hydrochloric acid according to the procedure of Curran and Angier<sup>64,65</sup> afforded 2-aminoadamantan-1-ol hydrochloride (2.68) (see Scheme 2.11). The availability of the amino-alcohol (2.68) made it a promising precursor to the adamantanopyrimidine (2.30) and the proposed synthetic route to the analogue is illustrated in Scheme 2.12. Attempts to convert the 1-hydroxy group (by bromo or tosyloxy substitution) to yield 2-aminoadamantane-1-carbonitrile (2.71), the intended intermediate for the preparation of the diamine (2.29) were uniformly unsuccessful. Treatment of the oxazolidinone (2.66) or 2-aminoadamantan-1-ol (2.68) with fuming hydrobromic acid afforded mixtures of 2-aminoadamantan-1-ol (2.68) and 1-bromoadamantan-2-yl amine (as determined by mass spectrometry) as their hydrobromide salts. In view of the forcing conditions required to substitute tertiary adamantanyl bromides with a cyanide nucleophile<sup>124</sup> it was decided to abandon this approach. Although it is well known that adamantan-1-yl toluene-*p*-sulphonate hydrolyses very rapidly to adamantan-1-ol with traces of water,<sup>125</sup> it was planned to tosylate the amino-alcohol (2.68) and to substitute the *O*-tosyl group with the cyanide nucleophile. It was envisaged that hydrolysis of the tosyloxy group would be hindered by the adjacent amino group. Tosylation of 2-aminoadamantan-1-ol in pyridine, however, afforded only the *N*-tosyl derivative (2.69) (Scheme 2.11).



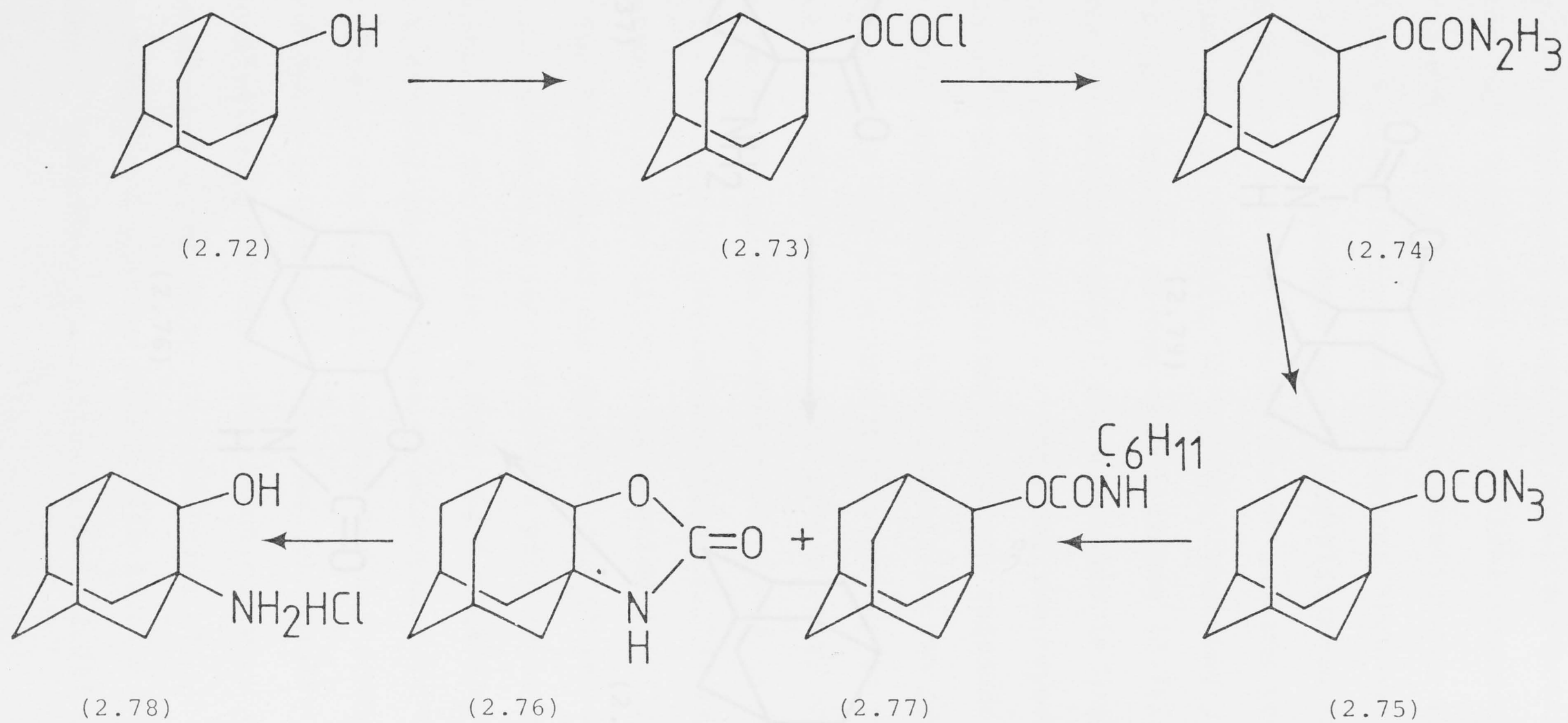


SCHEME 2.12

The *O*-tosyl group was clearly hydrolyzed extremely rapidly on contact with moisture and the vicinal amino group did not hinder the hydrolysis of the tosyl group. This route was therefore not pursued further.

The possibility of preparing the isomeric analogue (2.82) from 1-aminoadamantan-2-ol (2.78) was also investigated. Greidanus<sup>66</sup> had photolyzed adamantan-2-yloxycarbonyl azide (2.75) by a procedure analogous to that employed by Curran and Angier<sup>64,65</sup> in the synthesis of the isomeric oxazolidinone (2.66). He isolated two products, adamantan-2-yl *N*-cyclohexylcarbamate (41%) and an heterocyclic oxaza compound (15%). He could not assign with certainty the structure of the latter compound, but proposed the structures (2.76) and (2.79). However, his elemental analysis and infrared spectrum (strong carbonyl absorptions at 1715 and 1755  $\text{cm}^{-1}$ , five membered cyclic carbamate), but not the p.m.r. spectrum, support the oxazolidinone structure (2.76).

Adamantan-2-yloxycarbonyl azide (2.75) was prepared in this work from adamantan-2-ol (2.72) according to the sequence of reactions illustrated in Scheme 2.13. This sequence differed from that used by Greidanus, which proceeded *via* the *p*-nitrophenyl carbonate rather than the acid chloride (2.73). Photolysis of the azide (2.75) in cyclohexane afforded the oxazolidinone (2.76) in 21% Yield, and adamantan-2-yl *N*-cyclohexylcarbamate (2.77) (31% yield). When dichloromethane was used as the solvent, to avoid the formation of the solvent



SCHEME 2.13

insertion product (2.77), a 98:92 ratio of the oxazolidinone (2.76) was obtained together with an intractable tar.

Thus, in cyclohexane the solvent insertion product (2.77) was the major component, while in dichloromethane a brown tar was obtained.

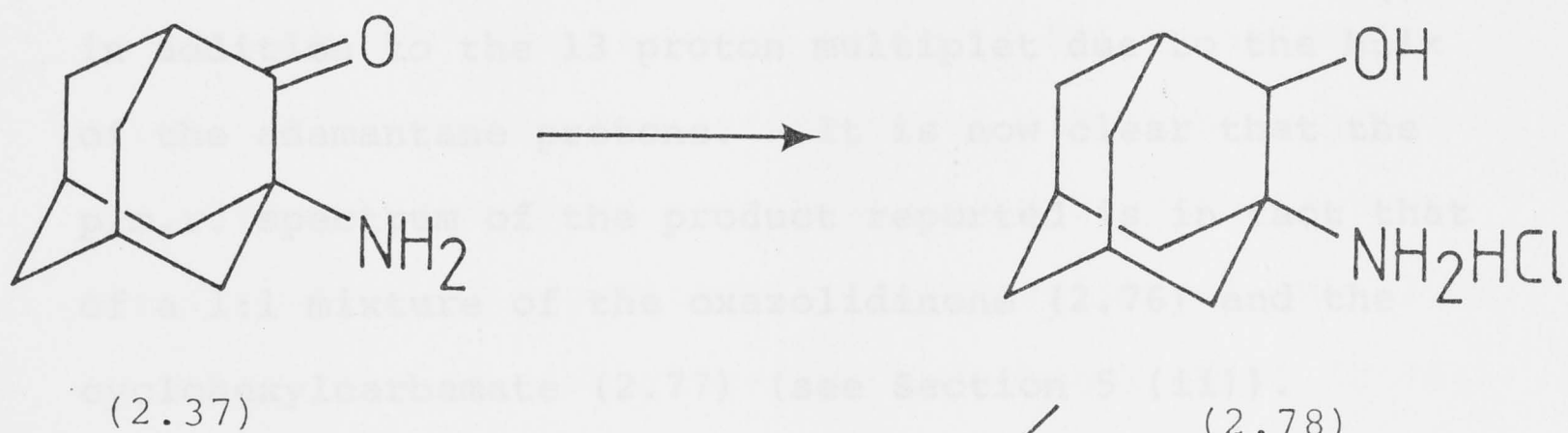
The p.d.r. spectra of the oxazolidinone (2.76) could be assigned by analogy to the corresponding

two peaks were observed in the region of the proton at 0-2, as well as a multiplet for the remaining protons.

The p.d.r. spectra of the oxazolidinone (2.76) and the cyclohexanecarboxamide (2.77) are discussed in greater detail in Section 5 (ii).

The spectra reported by Grubbs<sup>46</sup> for the heterocyclic amino bicyclic

systems are of interest in this connection.



The formation of the oxazolidinone (2.79) would appear unfavorable in view of the preference of

oxazolidinone for insertion into the bridgehead rather than the methylene groups of adamantane.

The structure of the oxazolidinone (2.76) was confirmed beyond doubt by analogy to the corresponding

hydrochloride (2.78) which is identical with the amino-alcohol obtained by the reduction of

2-oxo-2-aminobicyclo[2.2.1]heptane (2.77) with lithium aluminum hydride. Moreover, the amino-alcohol (2.78) obtained

insertion product (2.77), a 9% yield of the oxazolidinone (2.76) was obtained together with an intractable tar. Thus, in cyclohexane the solvent insertion product (2.77) was the major component, while in dichloromethane a brown tar was obtained from which the oxazolidinone (2.76) could be isolated by chromatography on alumina.

The p.m.r. spectrum of the oxazolidinone (2.76) has two peaks representing the NH proton and the proton at C-2, as well as a multiplet for the remaining protons. (The p.m.r. spectra of the oxazolidinone (2.76) and the cyclohexylcarbamate (2.77) are discussed in greater detail in Section 5 (ii) . The spectrum reported by Greidanus<sup>66</sup> for the heterocyclic oxaza compound showed four minor peaks representing a total of two protons, in addition to the 13 proton multiplet due to the bulk of the adamantane protons. It is now clear that the p.m.r. spectrum of the product reported is in fact that of a 1:1 mixture of the oxazolidinone (2.76) and the cyclohexylcarbamate (2.77) (see Section 5 (ii)).

The formation of the oxazin-2-one (2.79) would appear unfavourable in view of the preference of acylnitrenes for insertion into the bridgehead rather than the methylene C-H bonds of adamantane. The structure of the oxazolidinone (2.76) was confirmed beyond doubt by hydrolysis to 1-aminoadamantan-2-ol hydrochloride (2.78) which was identical with the amino-alcohol obtained by the reduction of 2-oxoadamantan-1-ylamine (2.37) with lithium aluminium hydride. Moreover, the amino-alcohol (2.78) obtained

by reduction of the amino-ketone (2.37) could be converted with phosgene in toluene and 2*N* sodium hydroxide into a compound having melting point, and infrared and p.m.r. spectra identical with those of the oxazolidinone (2.76).

The nitrene formed by the photolysis of adamantan-2-yloxycarbonyl azide (2.75) has two possible C-H bonds into which it may insert, assuming that the reaction takes place at the C-H bonds adjacent to the substituent. Nitrenes derived from the photolysis of adamantan-1-yloxycarbonyl azide (2.65) on the other hand have six adjacent C-H bonds into which they may insert. From a statistical point of view, the formation of adamantano[2,1-*d*]oxazolidin-2-one (2.66) by photolysis of adamantan-1-yloxycarbonyl azide (2.65) in solvents capable of trapping the intermediate nitrenes (*e.g.* cyclohexane) should be relatively more favourable than the formation of adamantano[1,2-*d*]oxazolidin-2-one (2.76) by photolysis of adamantan-2-yloxycarbonyl azide (2.75) under the same conditions. That is, the relative proportions of oxazolidinone and carbamate will be different in both cases, and statistical factors will result in a larger proportion of the intramolecular cyclization product from the photolysis of adamantan-1-yloxycarbonyl azide (2.65) because of the greater abundance of adjacent C-H bonds. However, oxycarbonyl nitrenes show a considerable preference for insertion

\* Oxycarbonylnitrenes were found to be six times more reactive toward the tertiary C-H bonds than the secondary C-H bonds of adamantane. 126

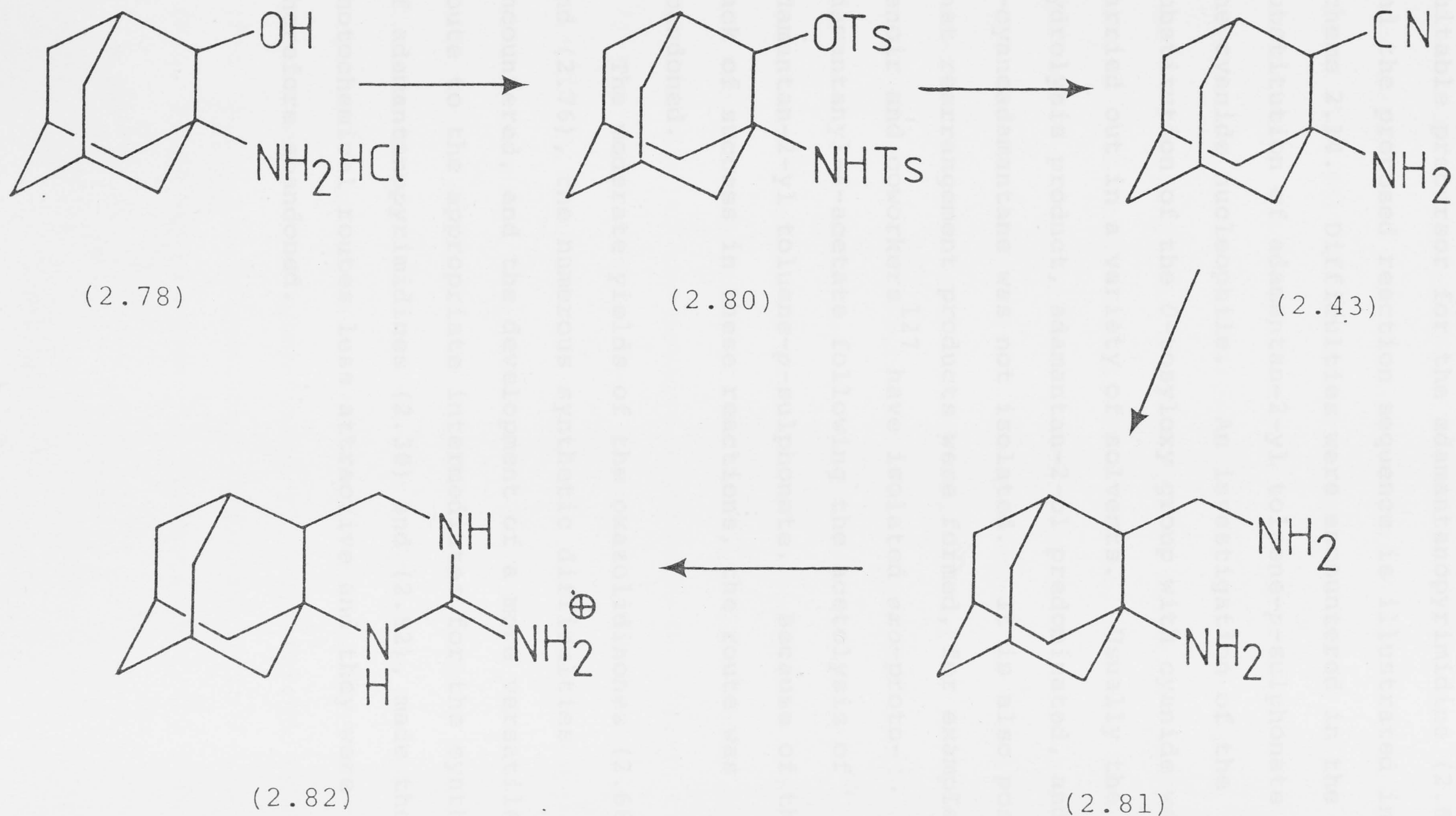
into bridgehead C-H bonds of adamantane\* and it was hoped that this factor would counteract the statistical bias against the formation of the oxazolidinone (2.76) sufficiently to result in a good yield. This, however, was not observed experimentally.

From the results described above it can be seen that the photolysis of adamantan-2-ylloxycarbonyl azide (2.75) was an unsatisfactory method for the preparation of adamantano[1,2-*d*]oxazolidin-2-one (2.76). Alewood and coworkers<sup>67</sup> however, were able to prepare the oxazolidinone (2.76) in high yields by thermal decomposition of the oxycarbonyl azide (2.75) in chloroform. Greidanus<sup>66</sup> and Alewood and coworkers<sup>67</sup> have also considered the cyclization of the intermediate nitrene to the tetrahydro-1,3-oxazin-2-one (2.79), but Alewood *et al.* were unable to detect any of the oxazin-2-one (2.79). Greidanus however was unable to assign the structure (2.76) to the intramolecular nitrene insertion product with certainty (see page 113).

Hydrolysis of the oxazolidinone (2.76) in 60% hydrobromic acid afforded a mixture of 1-amino-adamantan-2-ol (2.78) and 1-aminoadamantan-2-ylbromide (as determined by mass spectrometry). This observation is not unusual in view of the results described previously (see page 103) and the difficulties encountered by Tabushi and Aoyama<sup>80</sup> in replacing the hydroxy group of adamantan-2-ols with bromine.

---

\* Ethoxycarbonylnitrenes were found to be six times more reactive toward the tertiary C-H bonds than the secondary C-H bonds of adamantane.<sup>126</sup>



SCHEME 2.14



It was planned to tosylate the amino-alcohol (2.78) and to substitute the *O*-tosyloxy group with a cyanide nucleophile. The aminonitrile (2.43) would then be a suitable precursor for the adamantanopyrimidine (2.82), and the proposed reaction sequence is illustrated in Scheme 2.14. Difficulties were encountered in the substitution of adamantan-2-yl toluene-*p*-sulphonate with the cyanide nucleophile. An investigation of the substitution of the *O*-tosyloxy group with cyanide was carried out in a variety of solvents. Usually the hydrolysis product, adamantan-2-ol predominated, and 2-cyanoadamantane was not isolated. It is also possible that rearrangement products were formed, for example Lenoir and coworkers<sup>127</sup> have isolated *exo*-proto-adamantanyl-4-acetate following the acetolysis of adamantan-2-yl toluene-*p*-sulphonate. Because of the lack of success in these reactions, the route was abandoned.

The moderate yields of the oxazolidinones (2.66) and (2.76), the numerous synthetic difficulties encountered, and the development of a more versatile route to the appropriate intermediates for the syntheses of adamantanopyrimidines (2.30) and (2.82), made the photochemical routes less attractive and they were therefore abandoned.

ii) P.m.r. spectra

In the foregoing discussion the expected p.m.r. spectrum of adamantano[1,2-*d*]oxazolidin-2-one (2.76) was described. It should exhibit a thirteen proton multiplet for the adamantane protons and a broad signal for the single NH proton which should be exchangeable in deuterium oxide. The fourteenth proton, at C-2, can be expected to appear as a doublet ( $J_{2,3} \sim 3$  Hz) downfield from the bulk of the adamantane protons. The observed p.m.r. spectrum (Fig. 2.16) of the oxazolidinone (2.76) is consistent with the predicted spectrum described above, and is identical with the p.m.r. spectrum of adamantano[1,2-*d*]oxazolidin-2-one (2.76) reported by Alewood and coworkers.<sup>67</sup> Greidanus<sup>66</sup> however, reported that the p.m.r. spectrum of the oxazolidinone (2.76) exhibits four minor peaks in addition to the massive adamantane multiplet ( $\delta$  1.1 - 2.6, 13H). The minor peaks resonated at  $\delta$  6.22, 5.14, 4.79 and 4.11, and represent a total of 2 protons. The peaks at  $\delta$  5.14 and 4.78 are reportedly exchangeable in deuterium oxide - sodium deuterioxide and are broad. A comparison of the reported<sup>66</sup> spectrum of the oxazolidinone with the p.m.r. spectra of adamantan-2-yl *N*-cyclohexylcarbamate (Fig. 2.17) and adamantano[1,2-*d*]oxazolidin-2-one (Fig. 2.16) would appear to indicate that the p.m.r.

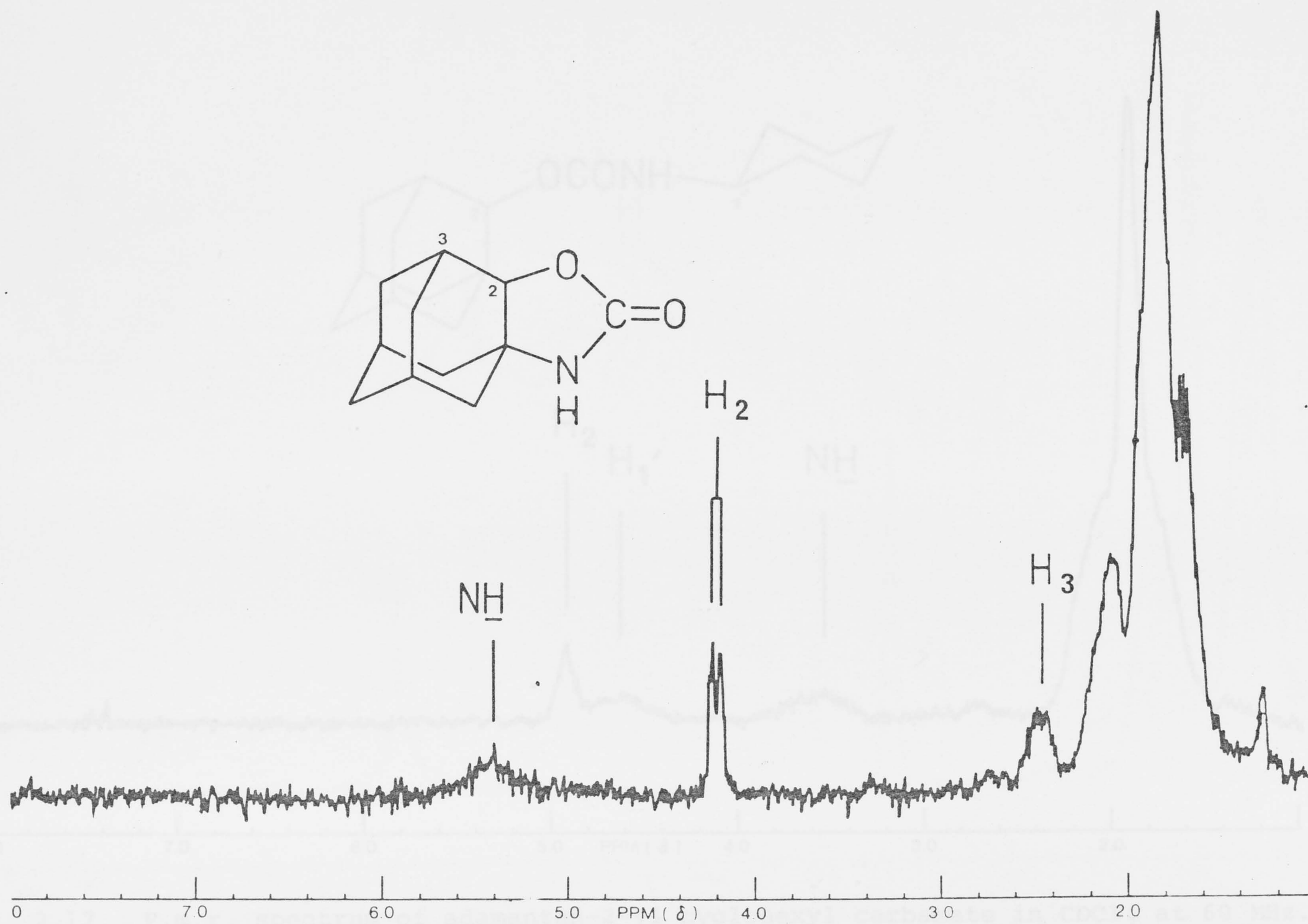


Fig. 2.16 P.m.r. spectrum of adamantano[1,2-*d*]oxazolidin-2-one in  $\text{CDCl}_3$  at 60 MHz.

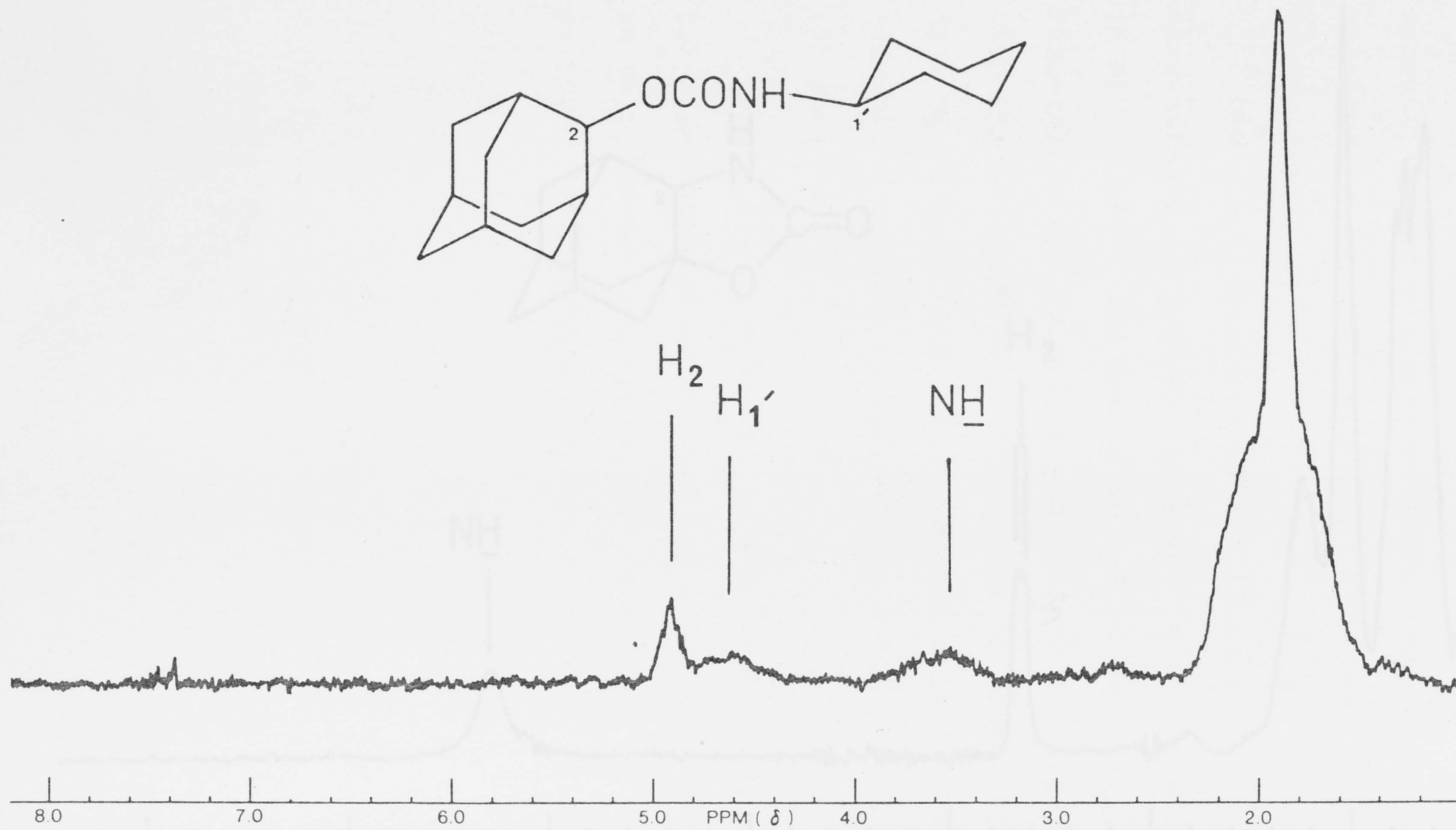


Fig. 2.17 P.m.r. spectrum of adamantan-2-yl cyclohexyl carbamate in  $CDCl_3$  at 60 MHz.

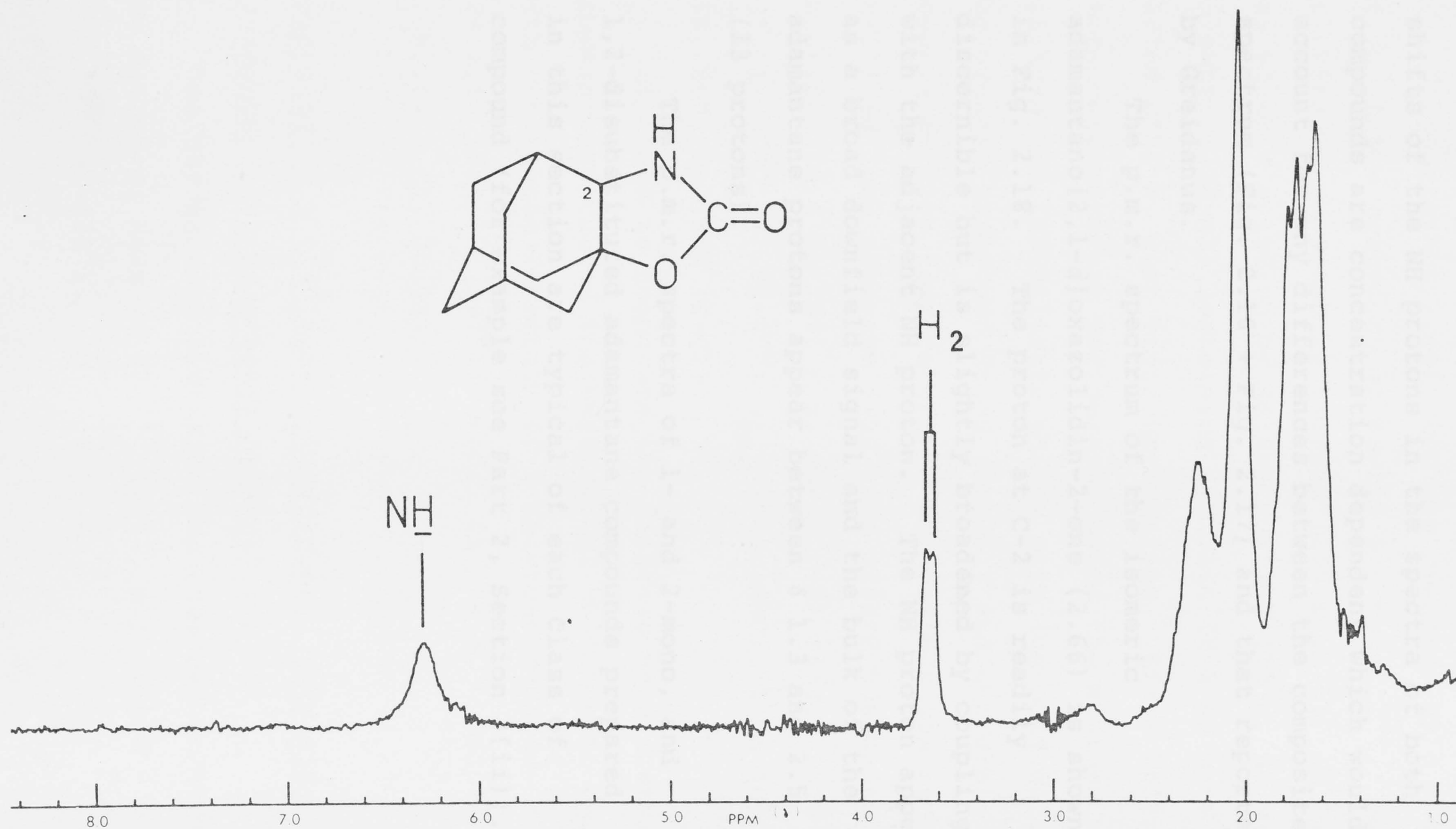


Fig. 2.18 P.m.r. spectrum of adamantano[2,1-d]oxazolidin-2-one in  $\text{CDCl}_3$  at 60 MHz.

spectrum reported by Greidanus<sup>66</sup> is in fact that of a 1/1 mixture of the oxazolidinone (2.76) and the cyclohexylcarbamate (2.77). The chemical shifts of the NH protons in the spectra of both compounds are concentration dependent which would account for any differences between the composite spectrum (Fig. 2.16 + Fig. 2.17) and that reported by Greidanus.

The p.m.r. spectrum of the isomeric adamantano[2,1-*d*]oxazolidin-2-one (2.66) is shown in Fig. 2.18. The proton at C-2 is readily discernible but is slightly broadened by coupling with the adjacent NH proton. The NH proton appears as a broad downfield signal and the bulk of the adamantane protons appear between  $\delta$  1.3 and 2.5 (13 protons).

The p.m.r. spectra of 1- and 2-mono, and 1,2-disubstituted adamantane compounds prepared in this section are typical of each class of compound (for example see Part 2, Section 3(ii)).

iii) ExperimentalTricyclo[3.3.1.1<sup>3,7</sup>]dec-1-yloxycarbonyl chloride  
(adamantan-1-yloxycarbonyl chloride) (2.63)

The oxycarbonyl chloride was prepared by a modification of the procedure of Kevill and Weitl.<sup>121</sup> To a solution of phosgene in toluene (150 ml, 25%) at 5-10° was added a solution of adamantan-1-ol (10 g, 65 mmol) in ether (300 ml) containing pyridine (8.8 g) over a period of 1 h. with vigorous stirring. After stirring at room temperature for several hours the mixture was filtered and the filtrate shaken with ice-cold water. The organic layer was dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated to dryness at room temperature. The residue was recrystallized from *n*-hexane (-20°) to afford the oxycarbonyl chloride (10.6 g, 75%) m.p. 48-50° (d) (lit.<sup>121</sup> 50-51° (d), lit.<sup>122,128</sup> 46-47°)  $\nu_{\max}$  1770 (C=O), 1155 (C-O), 840, 809, and 696 (C-Cl).

Attempts to evaporate the filtrate at elevated temperatures caused the oxycarbonyl chloride to decompose with consequent formation of 1-chloroadamantane, m.p.\* 164-165° (lit.<sup>129</sup> 165°) (Found: Cl, 20.4. Calc. for C<sub>10</sub>H<sub>15</sub>Cl<sub>1</sub>: Cl, 20.8%).

Tricyclo[3.3.1.1<sup>3,7</sup>]dec-1-yloxycarbonyl hydrazide  
(adamantan-1-yloxycarbonyl hydrazide) (2.64)

The oxycarbonyl hydrazide was prepared according to the method of Haas *et al.*<sup>128</sup> (97%), m.p. 135.5 - 138° (lit.<sup>128</sup> 141-142°).

Tricyclo[3.3.1.1<sup>3,7</sup>]dec-1-yloxycarbonyl azide  
 (adamantan-1-yloxycarbonyl azide) (2.65)

The azide was prepared according to the procedure of Curran and Angier,<sup>65</sup> but with the modification that extractions were done with cold cyclohexane and solvents were evaporated at 5-10°. The product was isolated as a colourless crystalline solid (95%) m.p. 40-42° (d) (lit.<sup>123</sup> 43-44°) (Curran and Angier<sup>65</sup> do not appear to have prepared the azide in pure form or to have characterized it).  $\nu_{\max}$  2200 & 2140 (N<sub>3</sub>), 1725 (C=O).

2-Oxa-4-azatetracyclo[6.3.1.1<sup>6,10</sup>.0<sup>1,5</sup>]tridecan-3-one  
 (adamantano[2,1-d]oxazolidin-2-one) (2.66)

Adamantan-1-yloxycarbonyl azide (5 g, 22.6 mmol) in cyclohexane (90 ml) was photolyzed (circular battery of low-pressure mercury lamps, 84% emission at 2537 Å, Rayonet photochemical chamber) for 6 h, after which time the azide absorptions in the infrared spectrum had disappeared. Some oxazolidinone (800 mg) had crystallized out at the end of the reaction and was collected. The filtrate was evaporated and the semi-crystalline residue was triturated with cyclohexane (25 ml) and filtered. The oxazolidinone was collected (2.9 g, total yield 65%) and had m.p. 127-130° (lit.<sup>65</sup> 130-133.5°, yield 43%, by using more dilute solutions) (Found: C, 68.3; H, 8.0; N, 7.1. Calc. for C<sub>11</sub>H<sub>15</sub>NO<sub>2</sub>: C, 68.4; H, 7.8; N, 7.3%).  $\nu_{\max}$  3360 (NH str), 1760, 1730 (C=O). P.m.r.  $\delta$ (CDCl<sub>3</sub>) 1.3-2.5 (m, 13H), 3.67 (m, 1H, H vicinal to NH), 5.67 (NH).



2-Amino-1-hydroxytricyclo[3.3.1.1<sup>3,7</sup>]decane

(2-aminoadamantan-1-ol)hydrochloride (2.68)

The oxazolidinone (2.66) was hydrolysed with 2*N* hydrochloric acid as described by Curran and Angier,<sup>65</sup> and gave a 71% yield of 2-aminoadamantan-1-ol hydrochloride (2.68), m.p. 310-360° (lit.<sup>65</sup> no m.p. recorded) (Found: C, 58.5; H, 9.1; N, 6.8; Cl, 17.3. Calc. for C<sub>10</sub>H<sub>18</sub>ClNO: C, 59.0; H, 8.9; N, 6.9; Cl, 17.4%).  $\nu_{\max}$  3234, 1610, 1540. P.m.r.  $\delta$ ((CD<sub>3</sub>)<sub>2</sub>SO) 1.23-2.37 (m, 13H), 3.03 (m, 1H vicinal to NH<sub>3</sub><sup>+</sup>), 4.20 (OH), 8.13 (NH<sub>3</sub><sup>+</sup>).

1-Hydroxytricyclo[3.3.1.1<sup>3,7</sup>]decan-2-yl(*N*-toluene-*p*-sulphonyl)amine (1-hydroxyadamantan-2-yl(*N*-toluene-*p*-sulphonyl)amine) (2.69)

The hydrochloride (2.68) (100 mg, 0.49 mmol) was dissolved in dry pyridine (5 ml) with warming, and toluene-*p*-sulphonyl chloride (380 mg, 2 mmol) was added to the solution. After 3 days at 0° the mixture was poured into ice-cold water and the crystalline solid that separated was collected, washed with water and dried. The toluene-*p*-sulphonyl derivative (105 mg, 67%) was recrystallized from ether/light petroleum, b.p. 40-60° and had m.p. 160-161.5° (Found: C, 63.7; H, 6.8; N, 4.3; S, 9.7. C<sub>17</sub>H<sub>22</sub>NO<sub>3</sub>S requires C, 63.7; H, 6.9; N, 4.4; S, 10.0%).  $\nu_{\max}$  3550 (OH str), 3380 (NH str). P.m.r.  $\delta$ (CDCl<sub>3</sub>) 1.2-2.2 (m, 13H), 2.40 (s, toluene CH<sub>3</sub>), 3.13 (d, *J* 7, 1H vicinal to NH), 7.23, 7.33, 7.72, 7.85 (aromatic H's).

2-Hydroxytricyclo[3.3.1.1<sup>3,7</sup>]decane (adamantan-2-ol)(2.72)

(a) Adamantan-2-one (10 g, 65 mmol) in methanol (200 ml) was treated with sodium borohydride (2.75 g, 290 mmol) in portions over a period of 1 h, while maintaining the reaction temperature at 10<sup>o</sup>. The solvent was evaporated and the residue partitioned between ether and 20% aqueous potassium hydrogen carbonate. The ethereal layer was separated and dried (Na<sub>2</sub>SO<sub>4</sub>). Evaporation of the solvent afforded the alcohol (9.87 g, 97%) m.p.\* 299-300<sup>o</sup> (lit.<sup>130</sup> 296.2-297.7<sup>o</sup>)  $\nu_{\max}$  3250 (OH str). P.m.r.  $\delta$ (CDCl<sub>3</sub>) 1.35-2.32 (m, 14H), 1.63 (s, 1H, OH), 4.18 (m, 1H, H2).

(b) Adamantan-2-ol was also prepared by the reduction of adamantan-2-one with lithium aluminium hydride according to the method of Schleyer and Nicholas<sup>130</sup> (91%).

Tricyclo[3.3.1.1<sup>3,7</sup>]dec-2-yloxycarbonyl chloride

(adamantan-2-yloxycarbonyl chloride)(2.73)

The oxycarbonyl chloride (2.73) was prepared in the same way as adamantan-1-yloxycarbonyl chloride (2.63) in a yield of 68%, and had m.p. 43-45<sup>o</sup> after recrystallization from petroleum ether (b.p. 40-60<sup>o</sup>) (Found: C, 61.5; H, 6.9; Cl, 16.5. Calc. for C<sub>11</sub>H<sub>15</sub>O<sub>2</sub>Cl<sub>1</sub>: C, 61.5; H, 7.0; Cl, 16.5%).  $\nu_{\max}$  1775 (C=O), 1176 (C-O str), 796, 765, 690 (C-Cl). P.m.r.  $\delta$ (CDCl<sub>3</sub>) 1.60-2.33 (m, 14H), 5.07 (m, 1H, H2).

Tricyclo[3.3.1.1<sup>3,7</sup>]dec-2-yloxycarbonyl hydrazide  
(adamantan-2-yloxycarbonyl hydrazide) (2.74)

The oxycarbonyl hydrazide (2.74) was prepared by the method described previously (see adamantan-1-yloxycarbonyl hydrazide) in 90% yield. After recrystallization from ether-cyclohexane the product had m.p. 67-68<sup>o</sup> (lit.<sup>66</sup> 69-70<sup>o</sup>) (Found: C, 62.7; H, 8.6; N, 13.3. Calc. for C<sub>11</sub>H<sub>18</sub>O<sub>2</sub>N<sub>2</sub>: C, 62.8; H, 8.6; N, 13.3%).  $\nu_{\max}$  3312 (NH str), 1695 (C=O). P.m.r.  $\delta$ (CDCl<sub>3</sub>) 1.37-2.25 (m, 14H), 3.73 (br m, 2H, NH<sub>2</sub>), 4.90 (br m, 1H H<sub>2</sub>), 6.22 (br m, 1H, NH).

Tricyclo[3.3.1.1<sup>3,7</sup>]dec-2-yloxycarbonyl azide  
(adamantan-2-yloxycarbonyl azide) (2.75)

The oxycarbonyl azide (2.75) was prepared from the hydrazide (2.74) according to the method of Greidanus<sup>66</sup> in a yield of 88%, and melted at 52-52.5<sup>o</sup> (d) (lit.<sup>66</sup> 52-54<sup>o</sup>) after recrystallization from ethyl acetate (at -18<sup>o</sup>) (Found: C, 60.1; H, 6.9; N, 19.2. Calc. for C<sub>11</sub>H<sub>15</sub>N<sub>3</sub>O<sub>2</sub>: C, 59.7; H, 6.8; N, 19.0%).  $\nu_{\max}$  2210, 2190 and 2150 (N<sub>3</sub>), 1720 (C=O). P.m.r.  $\delta$ (CDCl<sub>3</sub>) 1.37-2.13 (m, 14H), 6.63 (m, 1H, H<sub>2</sub>).

4-Oxa-2-azatetracyclo[6.3.1.1<sup>6,10</sup>.0<sup>1,5</sup>]tridecan-3-one  
(adamantano[1,2-d]oxazolidin-2-one) (2.76)

(a) Adamantan-1-yloxycarbonyl azide (6 g, 27 mmol) in cyclohexane was photolyzed for 15 h. The solvent was evaporated and the residue triturated with cold *n*-hexane. The solid was collected and recrystallized

from ethyl acetate to afford the oxazolidinone (1.09 g, 21%) m.p. 131-133<sup>o</sup> (lit.<sup>66</sup> 135-136<sup>o</sup>)  $\nu_{\max}$  3320 (NH str), 1760 and 1730 (C=O). P.m.r.  $\delta$ (CDCl<sub>3</sub>) 1.45-2.30 (m, 12H), 2.45 (m, 1H, H3), 4.20 (d, *J* 3, 1H, H2), 5.38 (m, 1H, NH).

The residue from the evaporation of the filtrate was chromatographed on an alumina column. Elution with benzene-*n*-hexane (1:1) afforded adamantan-2-ylcyclohexyl carbamate (2.77) (2.3 g, 31%) m.p. 115-117<sup>o</sup> (Found: C, 73.5; H, 9.2; N, 4.9. Calc. for C<sub>17</sub>H<sub>27</sub>NO<sub>2</sub>: C, 73.6; H, 9.8; N, 5.1%)  $\nu_{\max}$  3330 (NH str), 1680 (C=O). P.m.r.  $\delta$ (CDCl<sub>3</sub>) 1.48-2.33 (m, 24H), 3.52 (m, 1H, NH), 4.60 (m, 1H, H1'), 6.57 (m, 1H, H2).

(b) The oxycarbonyl azide (2.75) (500 mg, 2.3 mmol) in dichloromethane (10 ml) solution was irradiated as in (a). Evaporation of the solvent afforded a brown oil which was purified by chromatography on an alumina column. Elution with ether followed by benzene-ethanol (9/1) gave the oxazolidinone (25 mg, 9%), identical with that described in (a), and an intractable tar.

1-Amino-2-hydroxytricyclo[3.3.1.1<sup>3,7</sup>]decane

(1-aminoadamantan-2-ol)hydrochloride (2.78)

(a) The oxazolidinone (2.76) (1 g, 5.2 mmol) was added to 2N hydrochloric acid (100 ml) and the mixture heated on a steam bath for 2 h. The cooled solution was filtered and the filtrate evaporated to dryness to afford the hydrochloride (0.69 g, 65%) m.p. 305-306<sup>o</sup> identical with the product described in (b).

(b) 2-Oxoadamantan-1-ylamine (165 mg, 1 mmol) in ether (25 ml) was reduced with lithium aluminium hydride (150 mg, 3.9 mmol). After stirring for 8 h at room temperature saturated aqueous sodium carbonate was added. The mixture was extracted with chloroform and the dried ( $\text{Na}_2\text{SO}_4$ ) extracts evaporated to afford the amino-alcohol (159 mg, 95%) m.p.\* 271-273 $^\circ$ . P.m.r.  $\delta(\text{CDCl}_3)$  1.17-2.33 (m, 13H), 3.48 (m, 1H, H2). The hydrochloride had m.p. 305-306 $^\circ$  after recrystallization from ethanol-ether (Found: N, 6.7; Cl, 17.8.  $\text{C}_{10}\text{H}_{18}\text{NOCl}$  requires N, 6.9; Cl, 17.4%).  $\nu_{\text{max}}$  3660-2380 (OH,  $\text{NH}_3^+$  and CH str), 1990 ( $\text{NH}_3^+$ ).

Preparation of adamantano[1,2-d]oxazolidin-2-one (2.76)  
from 1-aminoadamantan-2-ol (2.78)

The amino-alcohol (70 mg, 0.42 mmol) was suspended in water (1 ml) and the mixture treated with phosgene in toluene (20%, 0.5 ml, 2.4 mmol) and 2*N* sodium hydroxide (0.84 ml, 4.8 mmol) at 5 $^\circ$ . The additions were carried out simultaneously, ensuring that the mixture remained alkaline. The mixture was stirred in the cold for 12 h after which time the additions were repeated and stirring continued for a further 6 h. The mixture was partitioned between chloroform and 1*N* hydrochloric acid. The chloroform layer was separated and the aqueous part extracted with chloroform. The combined extracts were dried ( $\text{Na}_2\text{SO}_4$ ) and evaporated to afford a white crystalline solid (55 mg, 68%). Recrystallization from ethyl acetate afforded a compound with m.p. 132-134 $^\circ$  (lit.<sup>66</sup> 135-136 $^\circ$ ) and having an infrared spectrum identical with that of adamantano[1,2-d]oxazolidin-2-one (2.76).

## PART 3

## SAXITOXIN ANALOGUES

1) Introduction

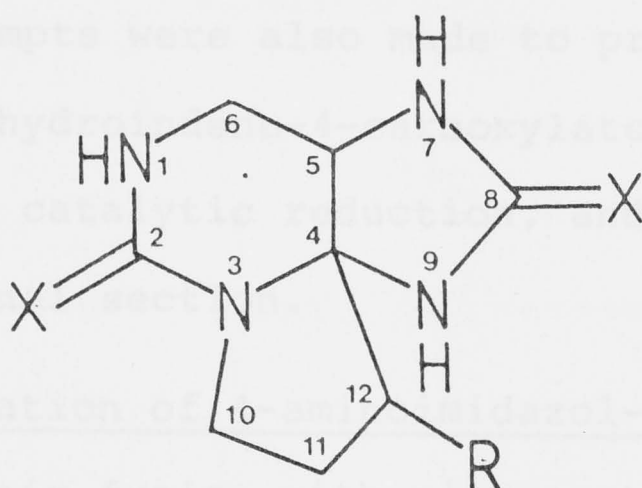
Saxitoxin (1.1) has a reduced purine skeleton, the *N*-3 and *C*-4 positions of which are linked by a three carbon bridge bearing an hydrated ketone at *C*-12. A carbamoyloxy side chain is present at *C*-6, and is *cis* with respect to H-5, the reduced imidazole and pyrimidine rings are also *cis* fused.

Armarego and Reece<sup>52</sup> and Wegner and Rapoport<sup>53</sup> have investigated the preparation of 2,8-diiminoperhydropurines, and the former demonstrated that the guanidinium groups play an important part in the activity of these analogues and of saxitoxin. Schantz and coworkers<sup>54</sup> have prepared a saxitoxin derivative in which the carbamyl group at *O*-17 is absent, but which retains biological activity comparable to that of saxitoxin. On the other hand, replacement of the hydrated carbonyl group at *C*-12 with a methylene group by catalytic reduction of saxitoxin affords nontoxic dihydrosaxitoxin.<sup>55</sup> According to Hille<sup>10</sup> it is the guanidinium moiety around *C*-8 of saxitoxin which enters the sodium channel, while the guanidinium group around *C*-2 remains in the 'antechamber' of the pore. From the observations described above it may be concluded that the guanidinium groups (particularly around *C*-8)

and the hydrated ketone at C-12 are essential for saxitoxin-like biological activity, while the carbamyl part of the C-6 substituent is dispensable. Based on these requirements, it was planned to prepare 2,8-dioxo- and 2,8-diiminoperhydropurines (3.1) and (3.2) with a three carbon chain between N-3 and C-4 bearing a polar group at C-12.

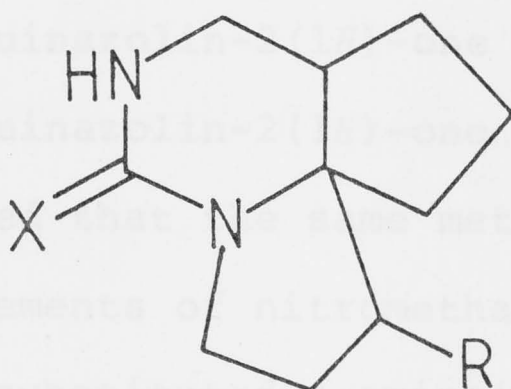
In order to prepare 4-substituted 2,8-dioxoperhydropurines it was planned to introduce a nitromethyl side-chain at the 4-position of 5-substituted 4-aminoimidazol-2(3H)-ones by fusion of the enamine with nitroacetic acid. Cyclization of the thus formed trisubstituted imidazolin-2-one was expected to afford 4-nitromethyl-2,8-dioxoperhydropurine, the nitromethyl group of which could be elaborated and cyclized to give a 2,8-dioxoperhydropurine (3.1) with a three carbon bridge between C-4 and N-3 and a polar group at C-12. The 2,8-diiminoperhydropurines were to be prepared similarly, or by conversion of the dioxo compounds directly into the diimino derivatives.

The following sections describe attempts to add the elements of nitromethane across the enamine-like part of 5-substituted-4-aminoimidazol-2(3H)-ones and 1-substituted-2-aminocyclopent-1-enes. The cyclopentane derivatives were required for the preparation of 3a-substituted-4,6-diaza-5-oxo- and 5-iminoperhydroindenes (3.3) and (3.4) which were to be compared with their heterocyclic analogues, the 4-substituted-2,8-dioxoperhydropurines (3.1) and (3.2). This



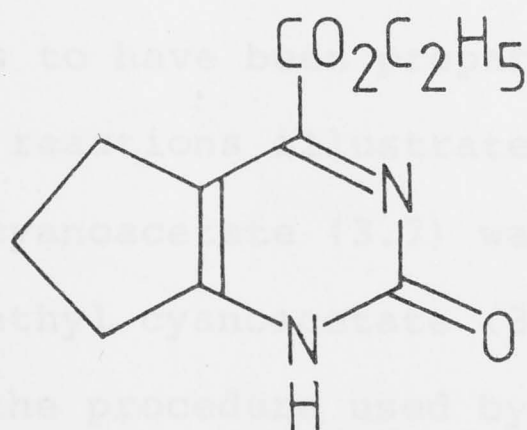
(3.1) X=O, R=polar group  
(e.g. hydrated ketone)

(3.2) X=NH, R=polar group  
(e.g. hydrated ketone)



(3.3) X=O, R=polar group  
(e.g. hydrated ketone)

(3.4) X=NH, R=polar group  
(e.g. hydrated ketone)



(3.5)



comparison should give an indication of the importance of the guanidinium group around C-8 in the 2,8-diimino-perhydropurine analogue (3.2) and in saxitoxin itself.

Attempts were also made to prepare ethyl 2-amino-5,6,7-trihydroindene-4-carboxylate (3.5) in order to study its catalytic reduction, and will be described in the final section.

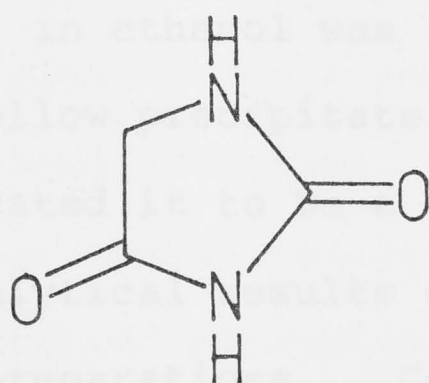
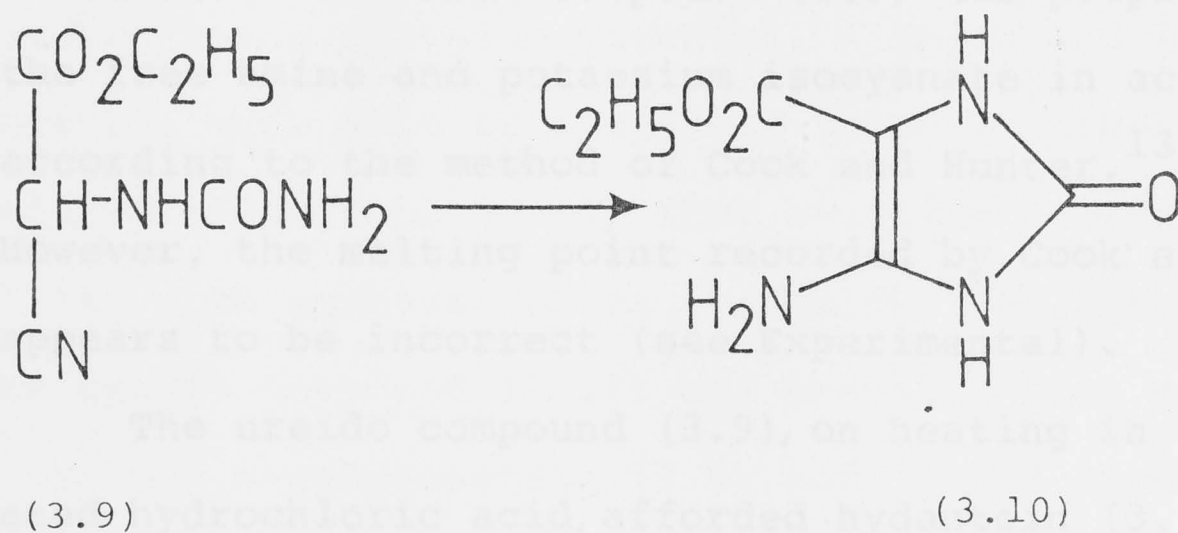
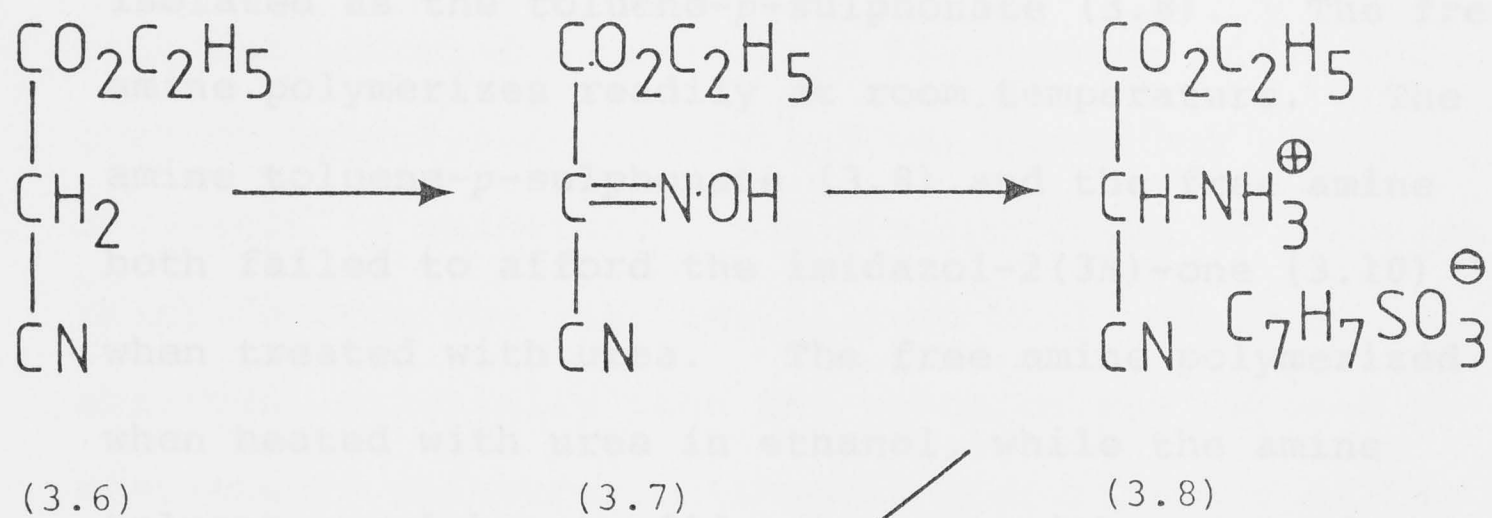
2) Preparation of 4-aminoimidazol-2(3H)-ones  
and their fusion with nitroacetic acid

i) Discussion

In 1969, Armarego<sup>131</sup> succeeded in adding the elements of nitromethane across the  $\alpha,\beta$ -double bond of enamines and enamides by fusing them with nitroacetic acid. Later, he prepared 8a-nitromethyl-*cis*-octahydroquinazolin-2(1H)-one by fusing 3,4,5,6,7,8-hexahydroquinazolin-2(1H)-one with nitroacetic acid.<sup>132</sup> It was hoped that the same methods could be used to add the elements of nitromethane across the 4,5-double bond of 5-substituted-4-aminoimidazol-2(3H)-ones. The adducts were then to be converted by a series of reactions into perhydropurines (3.1) and (3.2).

Initial efforts were directed toward the synthesis of 4-amino-5-ethoxycarbonylimidazol-2(3H)-one (3.10). The compound was to have been prepared according to the sequence of reactions illustrated in Scheme 3.1. Ethyl  $\alpha$ -oximinocynoacetate (3.7) was prepared by nitrosation of ethyl cyanoacetate (3.6) according to an adaptation of the procedure used by Ferris and

SCHEME 3.1



(3.11)

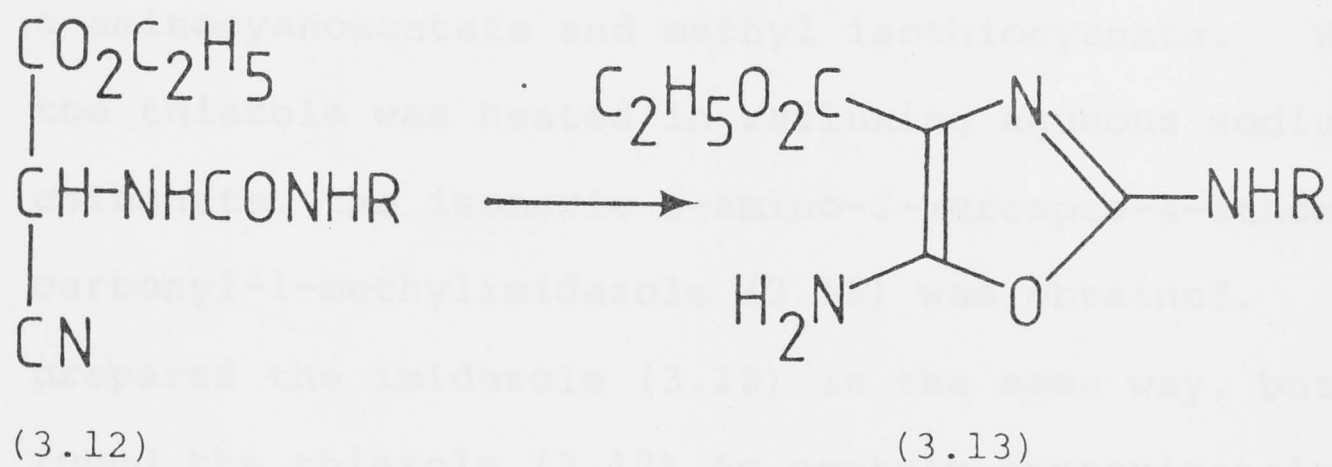
coworkers<sup>133</sup> for the nitrosation of malononitrile. The oximino compound was reduced with aluminium amalgam and water essentially by the method of Robinson and Shaw<sup>134</sup>, to afford ethyl  $\alpha$ -amino  $\alpha$ -cyanoacetate which was isolated as the toluene-*p*-sulphonate (3.8). The free amine polymerizes readily at room temperature. The amine toluene-*p*-sulphonate (3.8) and the free amine both failed to afford the imidazol-2(3*H*)-one (3.10) when treated with urea. The free amine polymerized when heated with urea in ethanol, while the amine toluene-*p*-sulphonate did not react with urea under a variety of conditions. When potassium isocyanate and the toluene-*p*-sulphonate (3.8) were heated in water, a high yield of ethyl  $\alpha$ -ureido  $\alpha$ -cyanoacetate (3.9) was obtained. The same compound (3.9) was prepared from the free amine and potassium isocyanate in acetic acid according to the method of Cook and Hunter.<sup>135</sup> However, the melting point recorded by Cook and Hunter appears to be incorrect (see Experimental).

The ureido compound (3.9), on heating in concentrated hydrochloric acid, afforded hydantoin (3.11) which probably arises from the hydrolysis and decarboxylation of the imidazol-2(3*H*)-one (3.10). When the ureido compound (3.9) in ethanol was treated with sodium ethoxide, a yellow precipitate was formed. Microanalyses indicated it to be a sodium salt although consistent analytical results could not be obtained for separate preparations. Cook and Hunter<sup>135</sup> found that ureas of the type (3.12) were converted into the

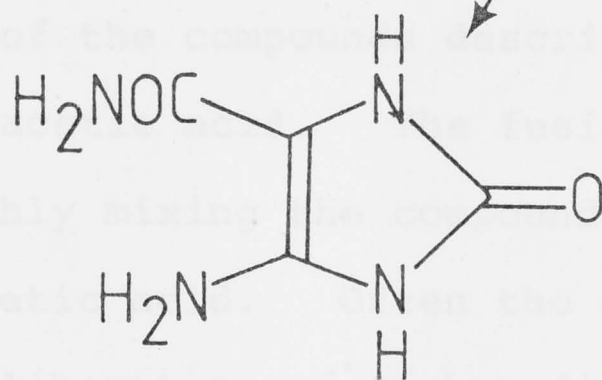
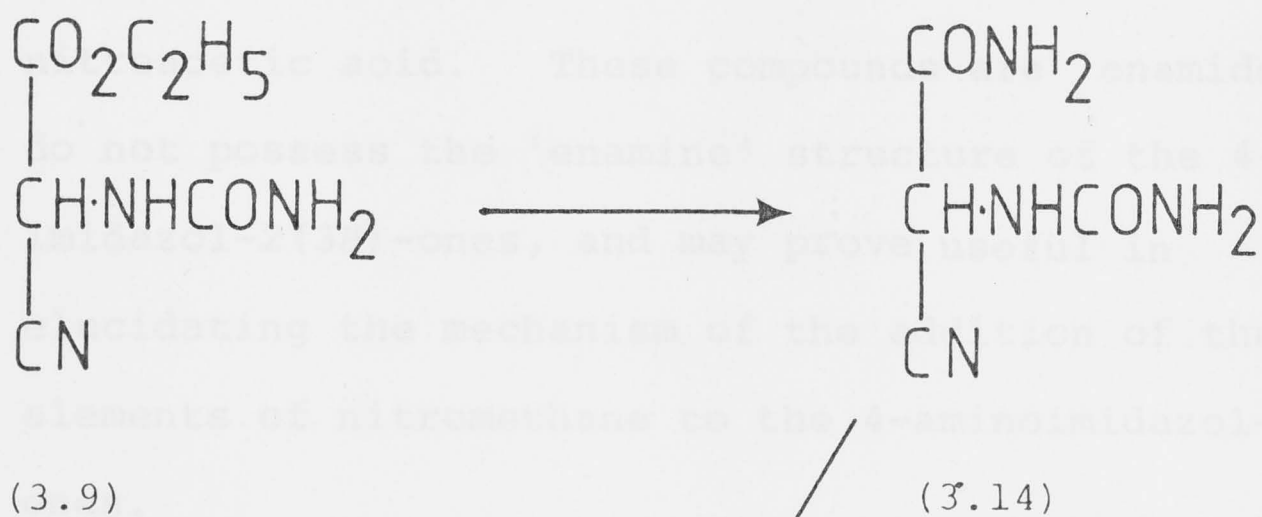
corresponding oxazoles (3.13) with sodium ethoxide. Acidification of the sodium salt described above however, afforded a complex mixture of products which could not be adequately separated. Treatment of the ureido compound (3.9) with ethanolic hydrogen chloride afforded an extremely hygroscopic oil. The product hydrolysed rapidly and was converted into hydantoin in solution. The precipitation of ammonium chloride from the reaction mixture could often be observed, especially when the solution was exposed to atmospheric moisture. Attempted picratization of the product was unsuccessful and it was not characterized.

Treatment of the ureido compound (3.9) with aqueous potassium hydroxide resulted in the formation of a small quantity of a potassium salt, the remainder of the product being starting material. Smith and Yates<sup>136</sup> however, were able to prepare 4-amino-5-carboxamidoimidazol-2(3H)-one (3.15) from  $\alpha$ -ureido  $\alpha$ -cyanoacetamide (3.14) with aqueous sodium hydroxide (5%) (see Scheme 3.2). The ureido compound (3.14) was prepared from ethyl  $\alpha$ -ureido  $\alpha$ -cyanoacetate (3.9) and liquid ammonia. 4-Amino-5-carboxamidoimidazol-2(3H)-one (3.15) appeared to be a suitable compound for the study of enamine - nitroacetic acid fusion reactions, but other enamines were prepared for a comparative study.

4-Aminoimidazol-2(3H)-one (3.16) was prepared by heating equimolar quantities of aminoacetonitrile hydrogen sulphate and potassium isocyanate in water



R =  $\alpha$ -naphthyl



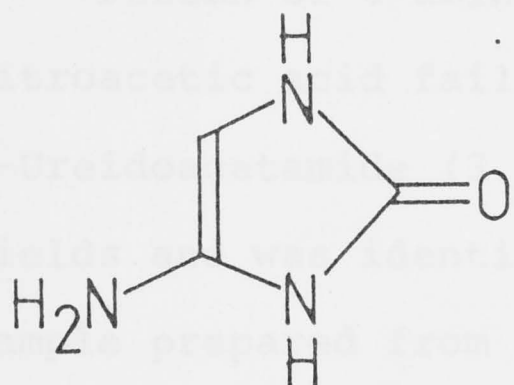
Scheme 3.2

on a steam bath. The compound was hydrolysed to hydantoin on heating in concentrated hydrochloric acid.

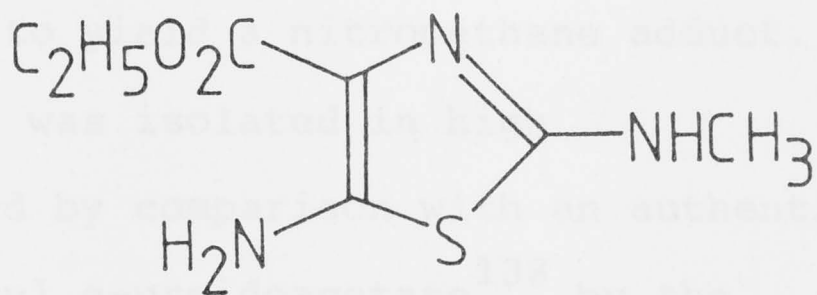
Cook and coworkers<sup>137</sup> prepared 5-amino-2-methyl-amino-4-ethoxycarbonylthiazole (3.17) from ethyl  $\alpha$ -aminocynoacetate and methyl isothiocyanate. When the thiazole was heated in refluxing aqueous sodium carbonate, the isomeric 5-amino-2-mercapto-4-ethoxycarbonyl-1-methylimidazole (3.18) was obtained. We prepared the imidazole (3.18) in the same way, but found the thiazole (3.17) to contain approximately 15% of the imidazole.

4-Methyl-5-ethoxycarbonylimidazol-2(3H)-one (3.19) and 4-ethoxycarbonylimidazol-2(3H)-one (3.20) were prepared, by known methods,<sup>143,144</sup> for fusion with nitroacetic acid. These compounds are 'enamides' but do not possess the 'enamine' structure of the 4-aminoimidazol-2(3H)-ones, and may prove useful in elucidating the mechanism of the addition of the elements of nitromethane to the 4-aminoimidazol-2(3H)-ones.

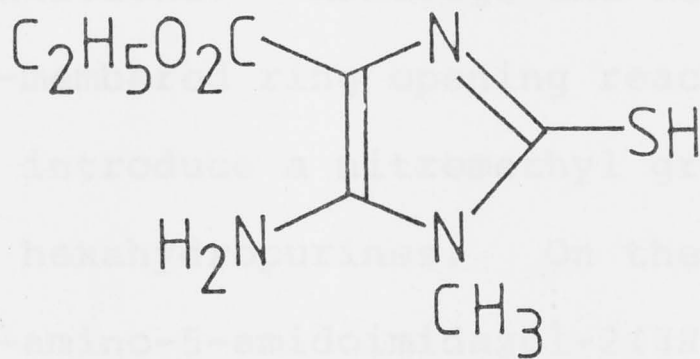
Each of the compounds described above was fused with nitroacetic acid. The fusions were carried out by thoroughly mixing the compound with two equivalents of nitroacetic acid. Often the decomposition of the acid with liberation of carbon dioxide occurred at room temperature, while in other cases elevated temperatures were necessary. The fusions were repeated before the product was isolated by evaporation of nitromethane formed in the reaction. The p.m.r. spectra



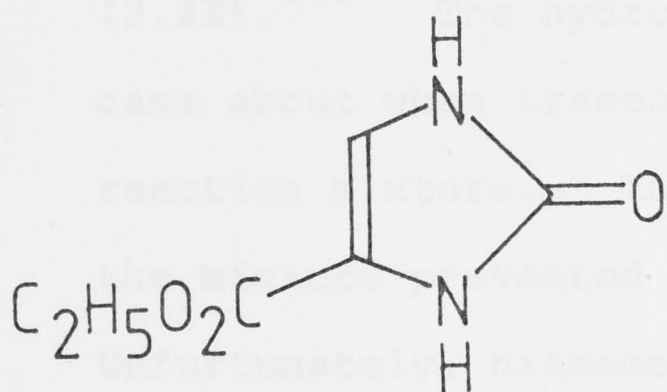
(3.16)



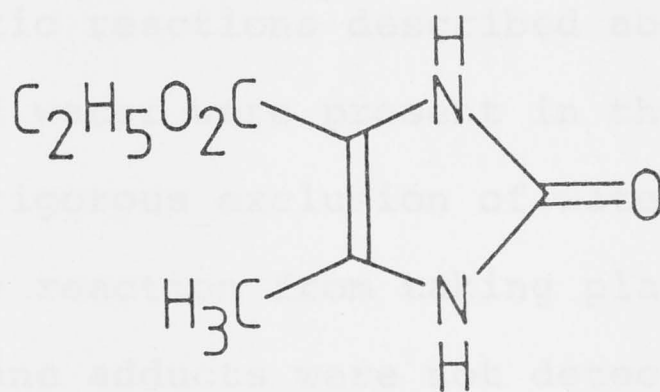
(3.17)



(3.18)



(3.20)



(3.19)

of the crude residues were measured before work up. The protons of the nitromethyl group of the fusion products should resonate in the region of  $\delta$  4.60 ppm,<sup>132</sup> and provide an indication of the extent of reaction.

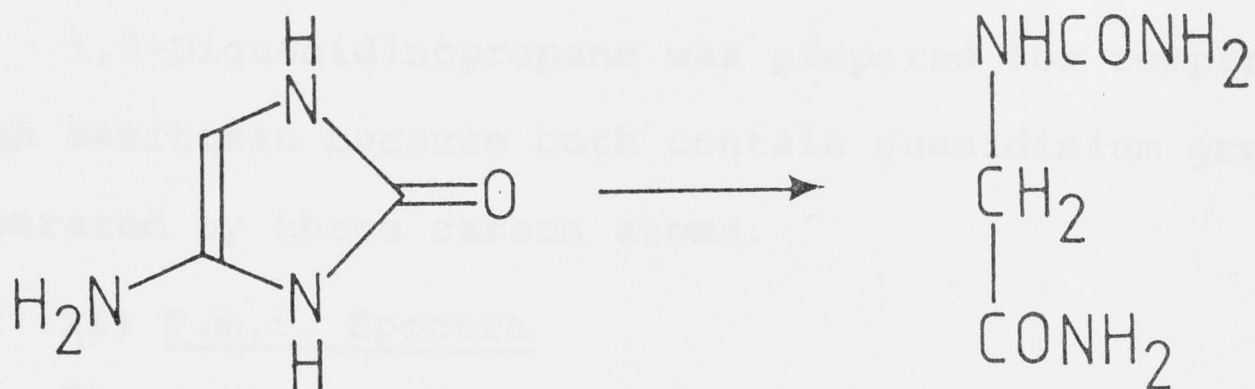
Fusion of 4-aminoimidazol-2(3H)-one (3.16) with nitroacetic acid failed to yield a nitromethane adduct.  $\alpha$ -Ureidoacetamide (3.21) was isolated in high yields and was identified by comparison with an authentic sample prepared from ethyl  $\alpha$ -ureidoacetate<sup>138</sup> by the method of Bailey.<sup>139</sup> The product probably comes about through hydrolytic ring opening of the imidazol-2(3H)-one (3.16) with traces of water under the strongly acidic reaction conditions. Armarego and Reece<sup>52</sup> have reported a similar 5-membered ring opening reaction in their attempts to introduce a nitromethyl group at the C-4 position of hexahydropurines. On the other hand, the fusion of 4-amino-5-amidoimidazol-2(3H)-one (3.15) with nitroacetic acid afforded a small proportion of starting material with a larger quantity of 4-amidohydantoin (3.22).<sup>140</sup> The hydrolytic reactions described above came about when traces of water were present in the reaction mixture. The rigorous exclusion of water from the mixture prevented any reaction from taking place. Unfortunately, nitromethane adducts were not detected in the reaction products.

5-Amino-2-methylamino-4-ethoxycarbonylthiazole (3.17), 5-amino-2-mercapto-4-ethoxycarbonyl-1-methylimidazole (3.18), 4-methyl-5-ethoxycarbonylimidazol-2(3H)-one (3.19) and 4-ethoxycarbonylimidazol-2(3H)-one



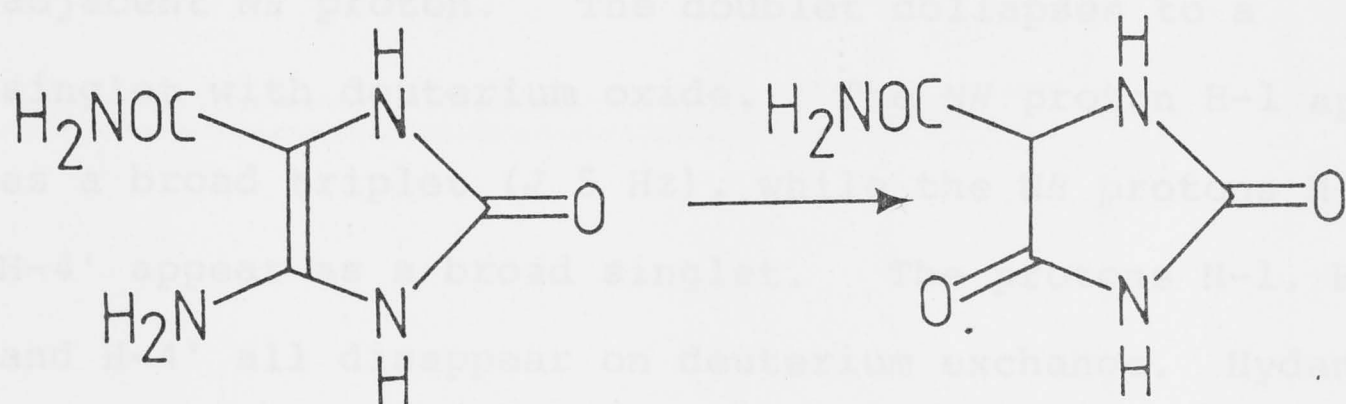
(3.20) all failed to react with nitrosous acid and the starting materials were recovered unchanged.

Attempts to introduce a nitromethyl group into the 4-position of 4-aminimidazole-2(1H)-one were abandoned because of the lack of reactivity of these compounds toward nitrosous acid.



(3.16)

(3.21)



(3.15)

(3.22)

4-Aminimidazole-2(1H)-one (3.16) would therefore be more correctly called 4-aminimidazole-1-one, however, the former name will be retained for consistency.

(3.20) all failed to react with nitroacetic acid and the starting materials were recovered unchanged.

Attempts to introduce a nitromethyl group into the 4-position of 4-aminoimidazol-2(3H)-ones were abandoned because of the lack of reactivity of these compounds toward nitroacetic acid.

1,3-Diguanidinopropane was prepared for comparison with saxitoxin because both contain guanidinium groups separated by three carbon atoms.

ii) P.m.r. Spectra

The p.m.r. spectrum of 4-aminoimidazol-2(3H)-one (Fig. 3-1) indicates that the compound exists predominantly, if not entirely in the imino form rather than the enamine form (3.16)\*. The protons at C-5 appear as a doublet ( $J$  5 Hz) probably because of coupling with the adjacent NH proton. The doublet collapses to a singlet with deuterium oxide. The NH proton H-1 appears as a broad triplet ( $J$  5 Hz), while the NH protons H-2 and H-4' appear as a broad singlet. The protons H-1, H-2, and H-4' all disappear on deuterium exchange. Hydantoin on the other hand exhibits no coupling for the C-5 protons, although a chemical shift difference of approximately 0.7 Hz can be observed, while the NH protons H-1 and H-3 appear as broad signals at  $\delta$  8.03 and  $\delta$  11.0 respectively. It is of interest to compare the p.m.r.

---

\* 4-Aminoimidazol-2(3H)-one (3.16) would therefore be more correctly called 4-iminoimidazolidin-2-one, however, the former name will be retained for consistency.

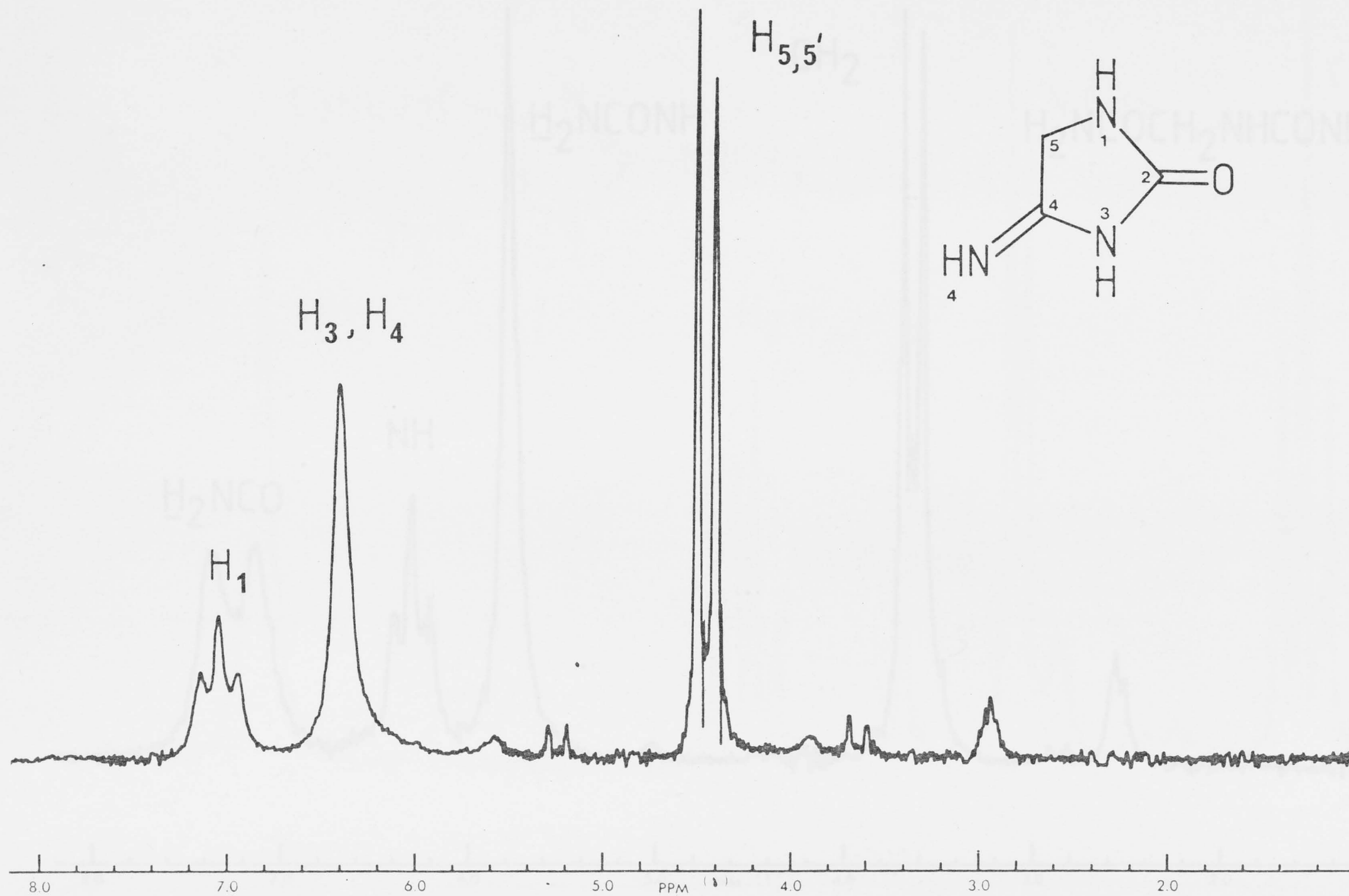


Fig. 3.1 The p.m.r. spectrum of 4-aminoimidazol-2(3H)-one in  $(\text{CD}_3)_2\text{SO}$  at 60 MHz.

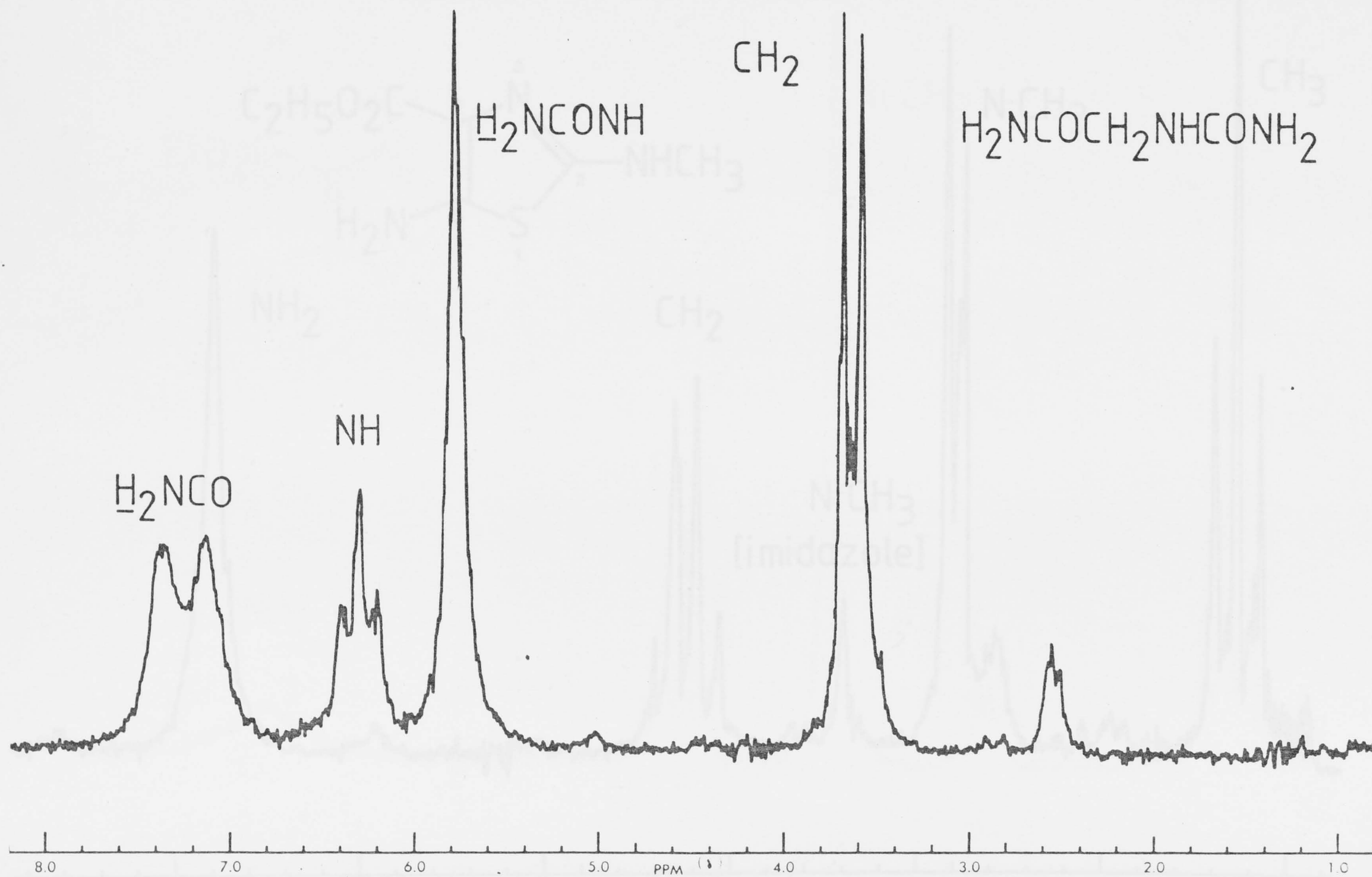


Fig. 3.2 The p.m.r. spectrum of  $\alpha$ -ureidoacetamide in  $(\text{CD}_3)_2\text{SO}$  at 60 MHz.

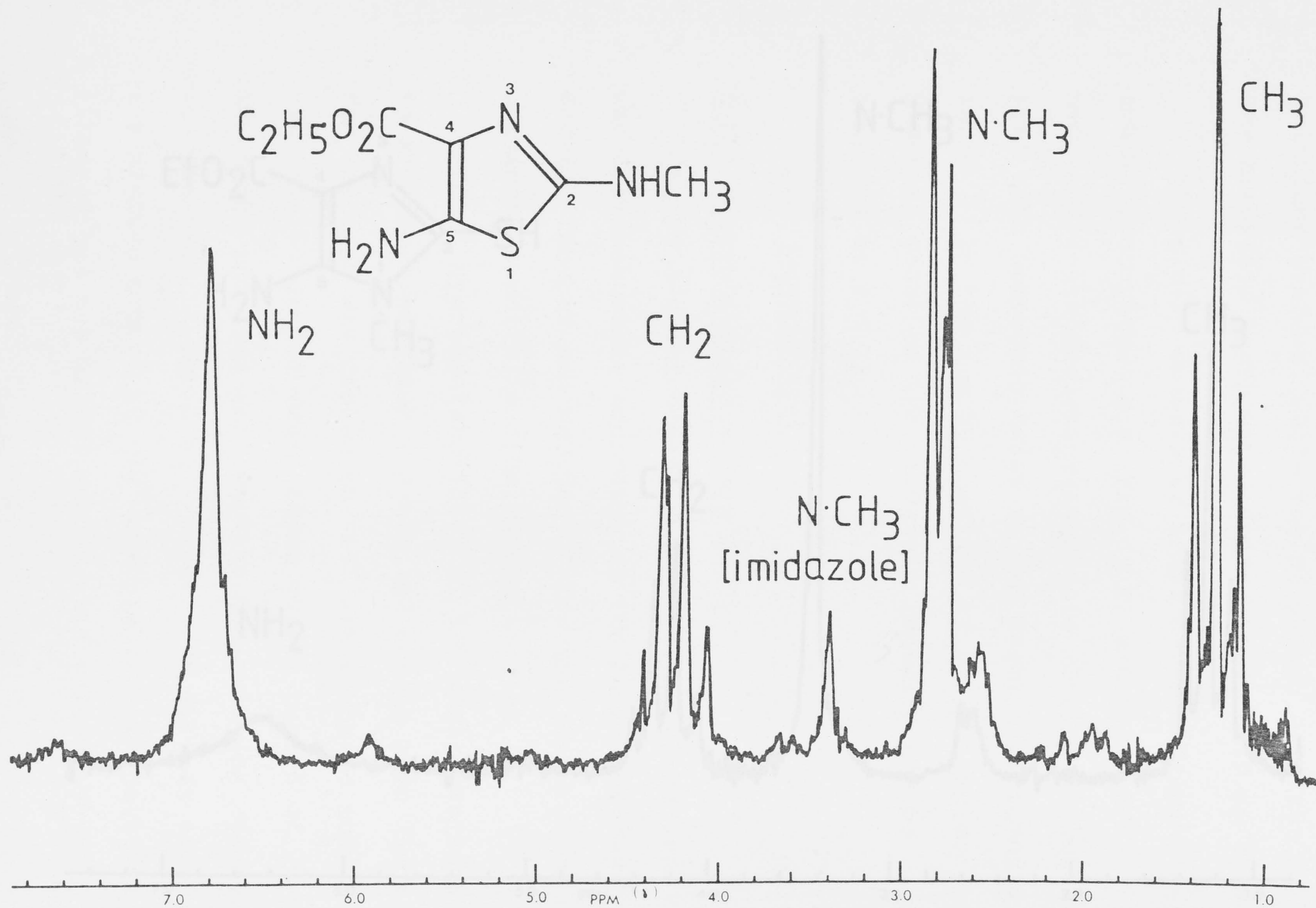


Fig. 3.3 The p.m.r. spectrum of 5-amino-2-methylamino-4-ethoxycarbonylthiazole in  $(\text{CD}_3)_2\text{SO}$  at 60 MHz.

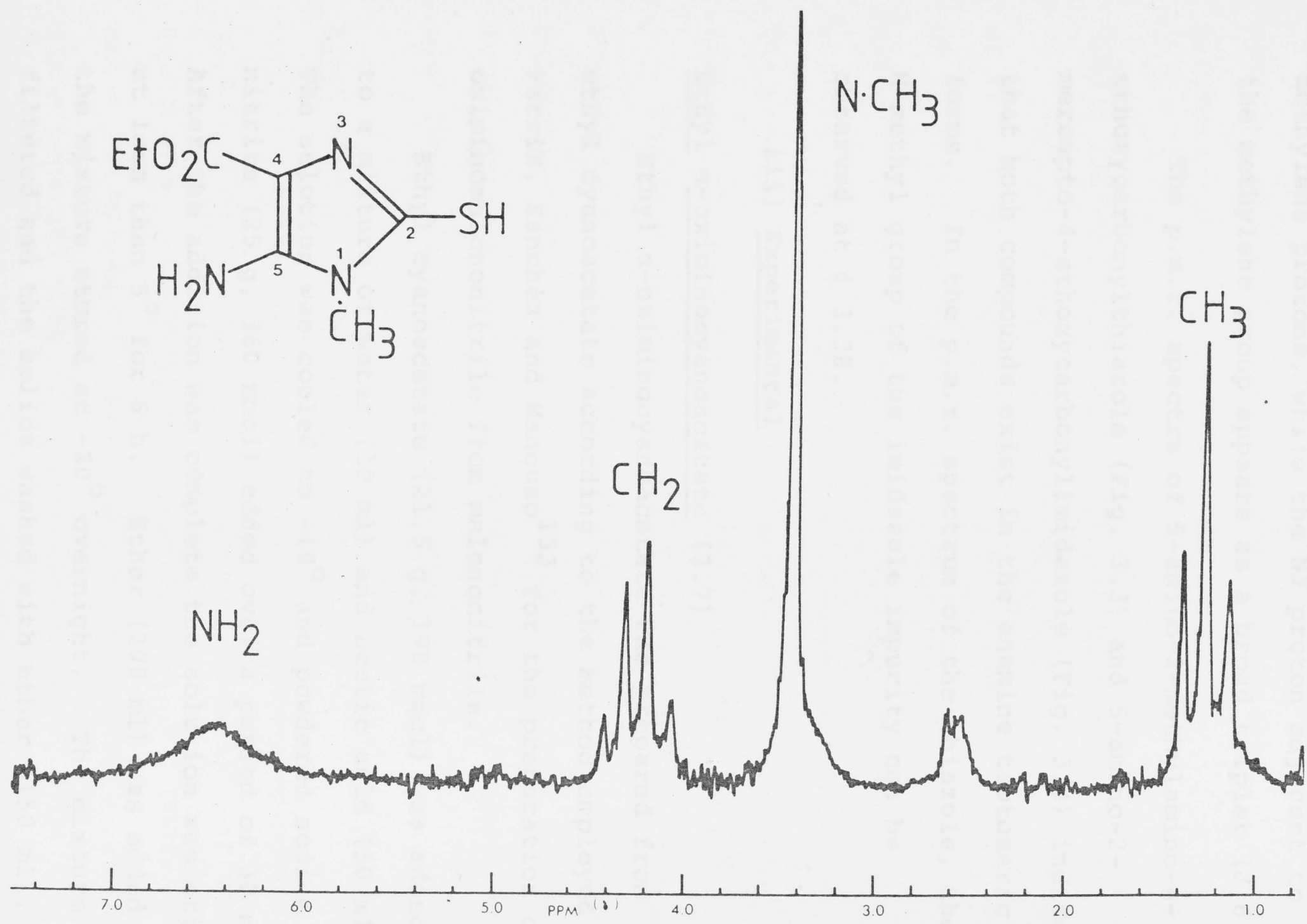


Fig. 3.4 The p.m.r. spectrum of 5-amino-2-mercapto-4-ethoxycarbonylimidazole in  $(\text{CD}_3)_2\text{SO}$  at 60 MHz.

spectrum of  $\alpha$ -ureidoacetamide (Fig. 3.2) with that of 4-aminoimidazol-2(3H)-one (Fig. 3.1). The acetamide also exhibits a doublet ( $J$  6 Hz) for the methylene protons, while the NH proton adjacent to the methylene group appears as a broad triplet ( $J$  6 Hz).

The p.m.r. spectra of 5-amino-2-methylamino-4-ethoxycarbonylthiazole (Fig. 3.3) and 5-amino-2-mercapto-4-ethoxycarbonylimidazole (Fig. 3.4) indicate that both compounds exist in the enamine tautomeric forms. In the p.m.r. spectrum of the thiazole, the N-methyl group of the imidazole impurity can be observed at  $\delta$  3.38.

### iii) Experimental

#### Ethyl $\alpha$ -oximinocyanoacetate (3.7)

Ethyl  $\alpha$ -oximinocyanoacetate was prepared from ethyl cyanoacetate according to the method employed by Ferris, Sanchez and Mancuso<sup>133</sup> for the preparation of oximinomalononitrile from malononitrile.

Ethyl cyanoacetate (21.5 g, 190 mmol) was added to a mixture of water (10 ml) and acetic acid (50 ml). The solution was cooled to  $-10^{\circ}$  and powdered sodium nitrite (25 g, 360 mmol) added over a period of 30 m. After the addition was complete the solution was stirred at less than  $5^{\circ}$  for 6 h. Ether (200 ml) was added and the mixture stored at  $-20^{\circ}$  overnight. The mixture was filtered and the solids washed with ether (150 ml).

The filtrate was evaporated to dryness under reduced pressure. The crystalline residue was suspended in water and collected by vacuum filtration. Recrystallization of the residue from water afforded the oxime (14.7 g, 55%) melting at 135-137° (lit.<sup>141</sup> 133°, 87% yield from the addition of acetic acid to a solution of ethyl cyanoacetate and sodium nitrite).

Ethyl  $\alpha$ -aminocyanoacetate toluene-*p*-sulphonate (3.8)

Ethyl  $\alpha$ -aminocyanoacetate was prepared by reduction of the oxime (3.7) with aluminium amalgam by the method of Robinson and Shaw,<sup>134</sup> with the modification that the aluminium used in the preparation of the amalgam was activated by etching with dilute aqueous sodium hydroxide. The product was isolated as the toluene-*p*-sulphonate (61% yield) and had m.p. 119-121° (lit.<sup>134</sup> 115-117°).

The free amine was prepared by treating the toluene-*p*-sulphonate with 2*N* sodium hydroxide and the solution extracted with chloroform. Evaporation (<25°) of the dried extracts gave the amine as a yellow oil which was used immediately in subsequent reactions.

Ethyl  $\alpha$ -ureidocyanoacetate (3.9)

(a) Ethyl  $\alpha$ -aminocyanoacetate toluene-*p*-sulphonate (1.5 g, 5 mmol) was dissolved in hot water (35 ml) and a solution of potassium isocyanate (0.45 g, 5.5 mmol) in water (10 ml) added. The solution was heated to 75° on a steam bath and then allowed to cool in ice. The precipitate was collected and recrystallized from ethanol to afford the ureido compound (0.85 g, 95%) melting at 193-194° (d) (lit.<sup>135</sup> 166°).



(b) The ureido compound was also prepared by the method of Cook and Hunter<sup>135</sup> in 75% yield and had m.p. 193-194° (d) (lit.<sup>135</sup> 166°) (Found: C, 41.8; H, 5.2; N, 24.3. Calc. for C<sub>6</sub>H<sub>9</sub>N<sub>3</sub>O<sub>3</sub>: C, 42.1; H, 5.3; N, 24.6%).  $\nu_{\max}$  3490, 3350 (NH str), 1725 (ester C=O), 1670 (amide C=O), 1585, 1563 (NH bend). P.m.r.  $\delta$ ((CD)<sub>3</sub>SO) 1.55 (t, 3H, CH<sub>2</sub>CH<sub>3</sub>), 4.18 (q, 2H, CH<sub>2</sub>CH<sub>3</sub>), 5.49 (d, *J* 6.5, 1H, H- $\alpha$ ), 6.03 (br s, 2H, CONH<sub>2</sub>), 7.12 (d, *J* 6.5, 1H, NHCO).

When the ureido compound (171 mg, 1 mmol) was heated under reflux in concentrated hydrochloric acid (5 ml) a white solid precipitated from the solution on cooling. Recrystallization from ethanol afforded a crystalline solid (89 mg, 89%) melting at 218-219.5°, and having infrared and p.m.r. spectra identical with those of hydantoin (m.p. 222-224°).

#### 4-Aminoimidazol-2(3H)-one (3.16)

Aminoacetonitrile hydrogen sulphate (15.4 g, 0.1 mmol) in water (100 ml) was treated with potassium isocyanate (8.1 g, 0.1 mmol). The mixture was heated on a steam bath for 1 h. Evaporation of the solution afforded a white solid which was dried *in vacuo* before being extracted with ethylacetate in a soxhlet extractor for 12 h. During the extraction the product separated, and crystallization continued on cooling. Recrystallization of the product from ethanol afforded the imidazolone (3.2 g, 32%) melting at 122-123° (Found: C, 36.0; H, 5.1; N, 41.9.

$C_3H_5N_3O_1$  requires: C, 36.3; H, 5.1; N, 42.4%.

$\nu_{\max}$  3400 (NH str), 1660, 1620 (amide). P.m.r.

$\delta((CD_3)_2SO)$  4.43 (d,  $J$  6, 2H, H-5), 6.38 (br s, 2H, H-3 and H-4'), 7.03 (t,  $J$  6, 1H, H-1).

The aminoimidazolone (200 mg, 2 mmol) was heated under reflux with concentrated hydrochloric acid (10 ml). Evaporation of the solution and recrystallization of the residue from ethanol afforded hydantoin, m.p. 221-223 $^{\circ}$  (m.p. 222-224 $^{\circ}$ ) identical with an authentic sample.

#### $\alpha$ -Ureidocyanoacetamide (3.14)

Ethyl  $\alpha$ -ureidocyanoacetate (200 mg, 1.17 mmol) was dissolved in ethanol (30 ml) and liquid ammonia (10 ml) added. After standing for several hours the solution was evaporated to dryness and the residue was recrystallized from ethanol to afford the amide as colourless needles (105 mg, 63%) m.p. 204-206 $^{\circ}$  (lit.<sup>136</sup> 202-203 $^{\circ}$  from  $\alpha$ -oximinocyanoacetamide).

#### 4-Amino-5-carboxamido-imidazol-2(3H)-one (3.15)

The imidazolone was prepared according to the method of Smith and Yates<sup>136</sup> (76%) from  $\alpha$ -ureidocyanoacetamide and 5% aqueous sodium hydroxide and had m.p. >360 $^{\circ}$  (lit.<sup>136</sup> >370 $^{\circ}$ ).

#### 5-Amino-2-methylamino-4-ethoxycarbonylthiazole (3.17)

The thiazole was prepared by the method of Cook, Downer and Heilbron<sup>137</sup> in 80% yield by the condensation of ethyl  $\alpha$ -aminocyanoacetate and methylisothiocyanate,

m.p.  $164^{\circ}$  (ethanol) (lit.<sup>137</sup>  $162^{\circ}$ ).  $\nu_{\max}$  3400, 3275, 3150 (NH str), 1650, 1600 (ester C=O, C=N). P.m.r.  $\delta$ (CDCl<sub>3</sub>) 1.23 (t, 3H, CH<sub>2</sub>CH<sub>3</sub>), 2.80 (d, 3H, NCH<sub>3</sub>), 3.20 (br s, 0.25H, NCH<sub>3</sub> rearrangement product, see below), 4.23 (q, 2H, CH<sub>2</sub>CH<sub>3</sub>), 6.76 (br s, 3H, NH's).

5-Amino-2-mercapto-4-ethoxycarbonyl-1-methyl imidazole (3.18)

The imidazole was prepared by base catalyzed rearrangement of the above thiazole as described by Cook *et al.*<sup>137</sup> in a yield of 88%, m.p.  $212-213^{\circ}$  (d) (lit.<sup>137</sup>  $211^{\circ}$  (d)).  $\nu_{\max}$  3460, 3330, 3130 (NH and SH str), 1680 (ester), 1645 (amide). P.m.r.  $\delta$ (CDCl<sub>3</sub>) 1.23 (t, 3H, CH<sub>2</sub>CH<sub>3</sub>), 3.36 (s, 3H, NCH<sub>3</sub>), 4.23 (q, 2H, CH<sub>2</sub>CH<sub>3</sub>), 6.43 (br, 2H, NH<sub>2</sub>).

4-Methyl-5-ethoxycarbonylimidazol-2(3H)-one (3.19)

Ethyl  $\alpha$ -oximino-acetoacetate was prepared in 89% yield from ethyl acetoacetate according to the method of Adkins and Reeve.<sup>142</sup> The oximino compound (4.77 g, 30 mmol) was dissolved in ethanol (15 ml) and 0.5N hydrochloric acid (60 ml) and the mixture shaken with 10% palladium-on-charcoal (200 mg) and hydrogen at 5 atmospheres pressure. After 3 days, the mixture was filtered, and 5N hydrochloric acid (3 ml) added to the filtrate, followed by potassium isocyanate (3.65 g, 45 mmol) in water (14 ml). The solution was heated to  $65^{\circ}$  and on cooling, the product precipitated. Recrystallization from water afforded the imidazol-2(3H)-one

(1.06 g, 21%) melting at 229-231<sup>o</sup> (lit.<sup>143</sup> 225-226<sup>o</sup>).  
 $\nu_{\max}$  1720 (ester C=O), 1700 (amide C=O). P.m.r.  
 $\delta((\text{CD}_3)_2\text{SO})$  1.08 (t, 3H,  $\text{CH}_2\text{CH}_3$ ), 2.20 (s, 3H,  $\text{CH}_3$ ),  
 4.18 (q, 2H,  $\text{CH}_2\text{CH}_3$ ), 10.20 (br s, 1H, NH), 10.63  
 (br s, 1H, NH).

4-Ethoxycarbonylimidazol-2(3H)-one (3.20)

The ethoxycarbonylimidazolone was prepared by esterification of 4-carboxy-imidazol-2(3H)-one with ethanol and concentrated sulphuric acid according to the method of Hilbert.<sup>144</sup>

$\alpha$ -Ureidoacetamide (3.21)

(a) Ethyl  $\alpha$ -ureidoacetate (500 mg, 3.4 mmol) was dissolved in a minimum of ethanol and ammonia gas bubbled into the solution for 1 h. The solution was refrigerated for 2 days and the amide (186 mg, 61.6%) was collected. It had m.p. 201-202<sup>o</sup> (eff.) (lit.<sup>139</sup> 204<sup>o</sup> (eff.)) (Found: C, 30.8; H, 6.1; N, 35.8. Calc. for  $\text{C}_3\text{H}_7\text{N}_3\text{O}_2$ : C, 30.8; H, 6.0; N, 35.9%). P.m.r:  $\delta((\text{CD}_3)_2\text{SO})$  3.62 (d,  $J$  6, 2H,  $\text{CH}_2$ ), 5.77 (s, 2H,  $\text{NHCONH}_2$ ), 6.28 (t,  $J$  6, 1H,  $\text{NHCO}$ ), 7.35 and 7.12 (m, 2H,  $\text{H}_2\text{NCO}$ ).

When ethyl  $\alpha$ -ureidoacetate (500 mg, 3.4 mmol) in ethanolic ammonia (30 ml) was heated in a sealed tube at 95<sup>o</sup> for 12 h, hydantoin was obtained in quantitative yield.

(b) 4-Aminoimidazol-2(3H)-one (99 mg, 1 mmol) and nitroacetic acid (206 mg, 2 mmol) were stirred and warmed until effervescence began. The temperature was

maintained at 35-45° until effervescence ceased. The excess of nitromethane was removed *in vacuo*, and the residue was fused with a further quantity of nitroacetic acid. After the removal of excess nitromethane, the residue was recrystallized from ethanol. It had m.p. 198-200° (eff.) (lit.<sup>139</sup> 204°) and infrared and p.m.r. spectra were identical with those described above.

Hydantoin-4-carboxamide (3.22)

4-Amino-5-carboxamidoimidazol-2(3H)-one (142 mg, 1 mmol) was fused with nitroacetic acid (203 mg, 2 mmol) by the procedure described above (see  $\alpha$ -ureidoacetamide (b)). The residue was triturated with ethanol and the solid collected. Recrystallization from ethanol afforded the hydantoin (100 mg, 70%), m.p. 251-253° (eff.) (lit.<sup>140</sup> 249° (eff.)) (Found: N, 28.0. Calc. for  $C_4H_5N_3O_3 \cdot 0.5H_2O$ : N, 27.6%).

1,3-Diguanidinopropane sulphate

A mixture of 1,3-diaminopropane (3.7 g, 50 mmol), S-methyl-isothiuronium sulphate and water (25 ml) was heated under reflux for 3 h. After standing at room temperature for 24 h the product was collected by vacuum filtration (4.1 g, 60%) m.p. 321° (d) (Found: C, 23.5; H, 6.2; N, 32.7; S, 12.6.  $C_5H_{16}N_6S_1O_4$  requires: C, 23.4; H, 6.3; N, 32.8; S, 12.5%). The dipicrate had m.p. 235° (Found: C, 33.2; H, 3.3; N, 27.2.  $C_{17}H_{20}N_{12}O_{14}$  requires: C, 33.1; H, 3.3; N, 27.3%).

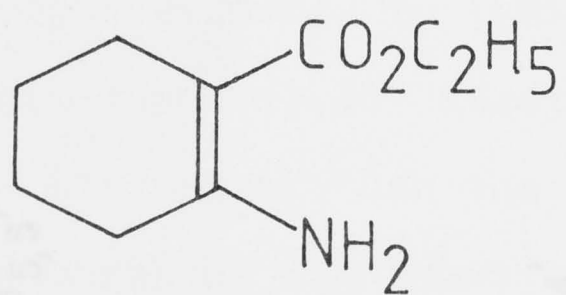
3) Preparation of 2-aminocyclopent-1-enes  
and their fusion with nitroacetic acid

i) Discussion

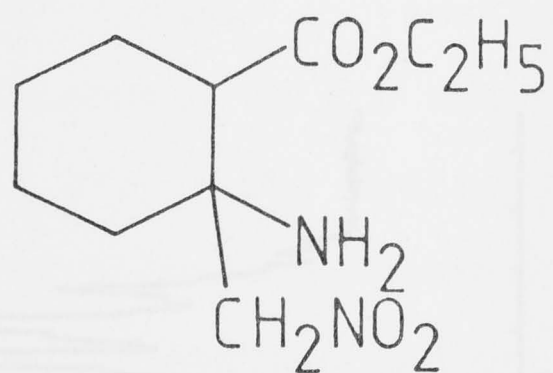
In an approach to the synthesis of 8a-substituted quinazolines with a reactive side-chain, Armarego and Kobayashi<sup>145</sup> fused 2-amino-1-ethoxycarbonylcyclohex-1-ene (3.23) with nitroacetic acid and obtained ethyl *cis*-2-amino-*trans*-2-nitromethylcyclohexane-1-carboxylate (3.24). The adduct readily lost the elements of nitromethane on heating or on mild treatment with acid or base.

We attempted the addition of the elements of nitromethane to the enamines; 2-amino-1-cyanocyclopent-1-ene (3.25) and 2-amino-1-ethoxycarbonylcyclopent-1-ene (3.26) in an approach to the preparation of 3a-substituted-4,6-diaza-5-oxoperhydroindenes and their 5-imino analogues.

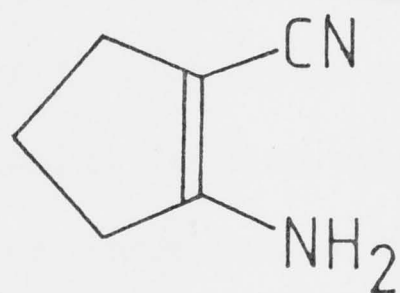
Thorpe<sup>146</sup> claimed to have prepared 2-amino-1-cyanocyclopent-1-ene (3.25) in 84% yield by cyclizing adiponitrile in ethanol with a catalytic amount of sodium ethoxide. Our attempts to repeat Thorpe's preparation were unsuccessful, and no cyclization was detected even after extended reaction times. Catalytic amounts of potassium *t*-butoxide also failed to bring about cyclization. However, Thompson<sup>147</sup> was able to prepare 2-amino-1-cyanocyclopent-1-ene in 85% yield by treatment of adiponitrile with a molecular equivalent of sodium *t*-butoxide under heterogeneous conditions. Thompson prepared the heterogeneous mixture by the addition of



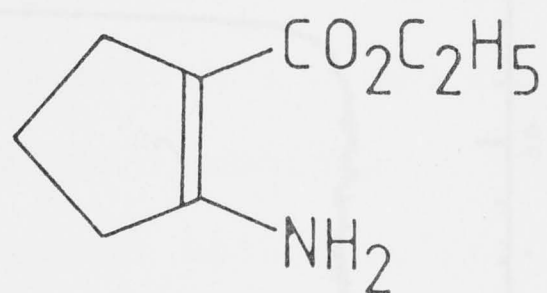
(3.23)



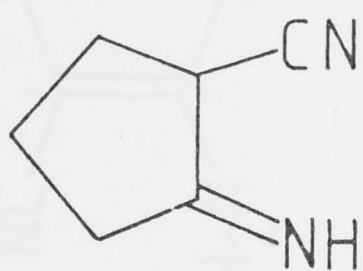
(3.24)



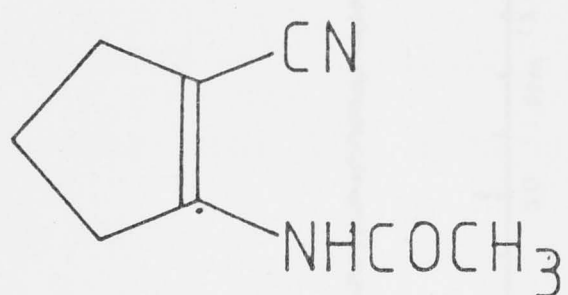
(3.25)



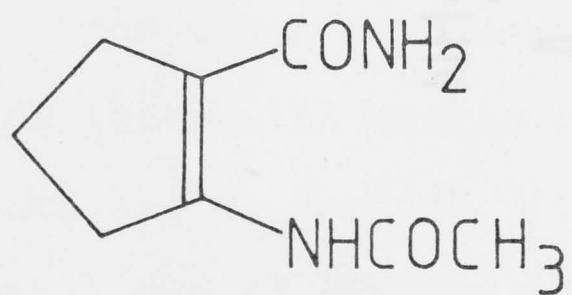
(3.26)



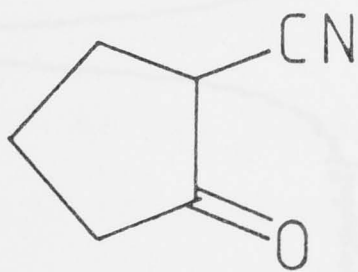
(3.27)



(3.28)



(3.30)



(3.29)

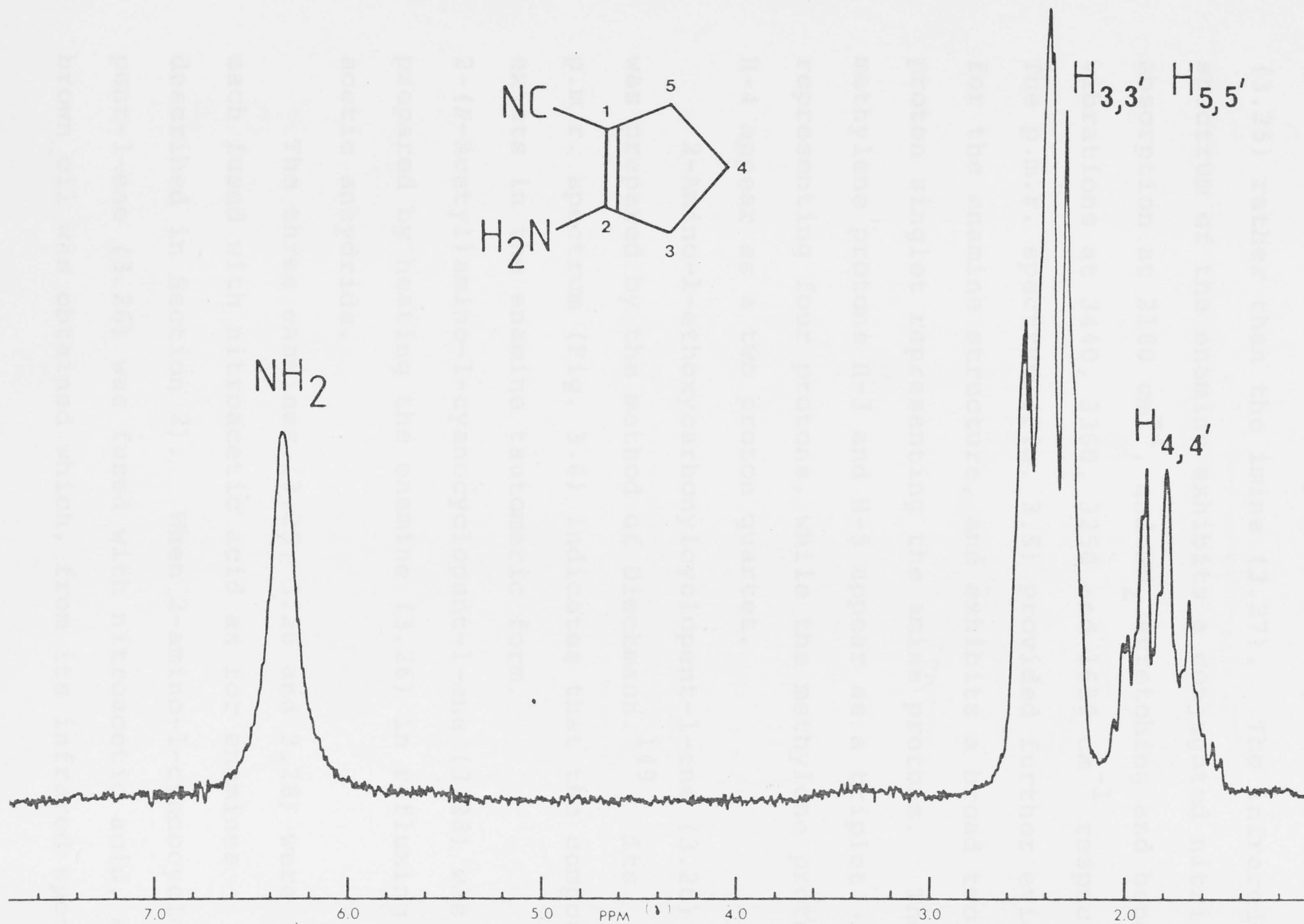


Fig. 3.5 The p.m.r. spectrum of 2-amino-1-cyanocyclopent-1-ene in  $(\text{CD}_3)_2\text{SO}$  at 60 MHz.



*t*-butanol to a suspension of sodium in toluene. However, we found potassium *t*-butoxide in toluene to be equally effective in facilitating the cyclization. Hammer and Hines<sup>148</sup> have presented infrared spectroscopic evidence to indicate that 2-amino-1-cyanocyclopent-1-ene (3.25) exists predominantly as the enamine (3.25) rather than the imine (3.27). The infrared spectrum of the enamine exhibits a conjugated nitrile absorption at  $2180\text{ cm}^{-1}$ , and  $\text{NH}_2$  stretching and bending vibrations at 3440, 3360, 3250 and  $1650\text{ cm}^{-1}$  respectively. The p.m.r. spectrum (Fig. 3.5) provided further evidence for the enamine structure, and exhibits a broad two proton singlet representing the amine protons. The methylene protons H-3 and H-5 appear as a triplet representing four protons, while the methylene protons H-4 appear as a two proton quartet.

2-Amino-1-ethoxycarbonylcyclopent-1-ene (3.26) was prepared by the method of Dieckmann.<sup>149</sup> Its p.m.r. spectrum (Fig. 3.6) indicates that the compound exists in the enamine tautomeric form.

2-(*N*-Acetyl)amino-1-cyanocyclopent-1-ene (3.28) was prepared by heating the enamine (3.26) in refluxing acetic anhydride.

The three enamines (3.25, 3.26 and 3.28) were each fused with nitroacetic acid as for enamines described in Section 2). When 2-amino-1-cyanocyclopent-1-ene (3.26) was fused with nitroacetic acid, a brown oil was obtained which, from its infrared spectrum,

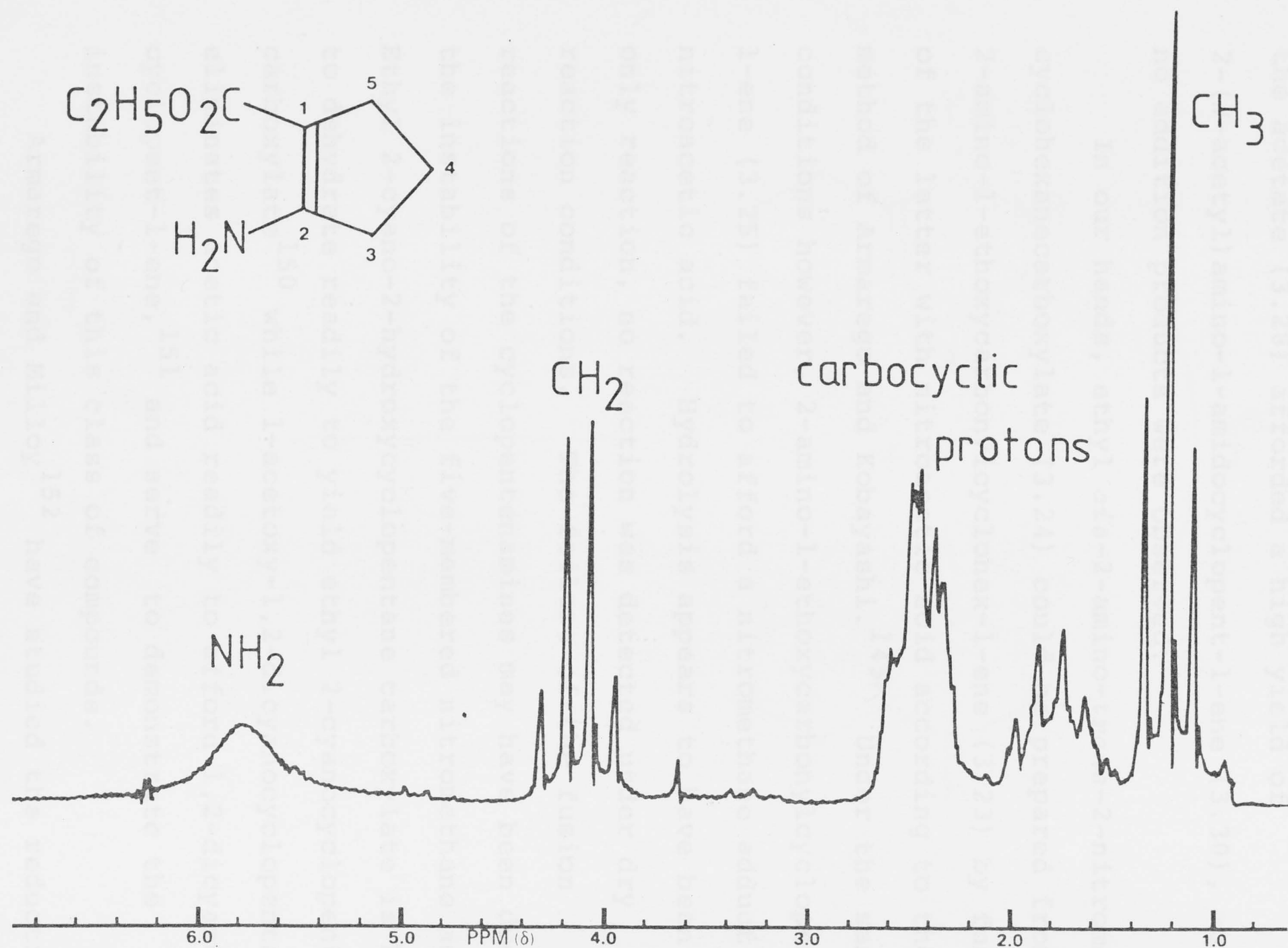
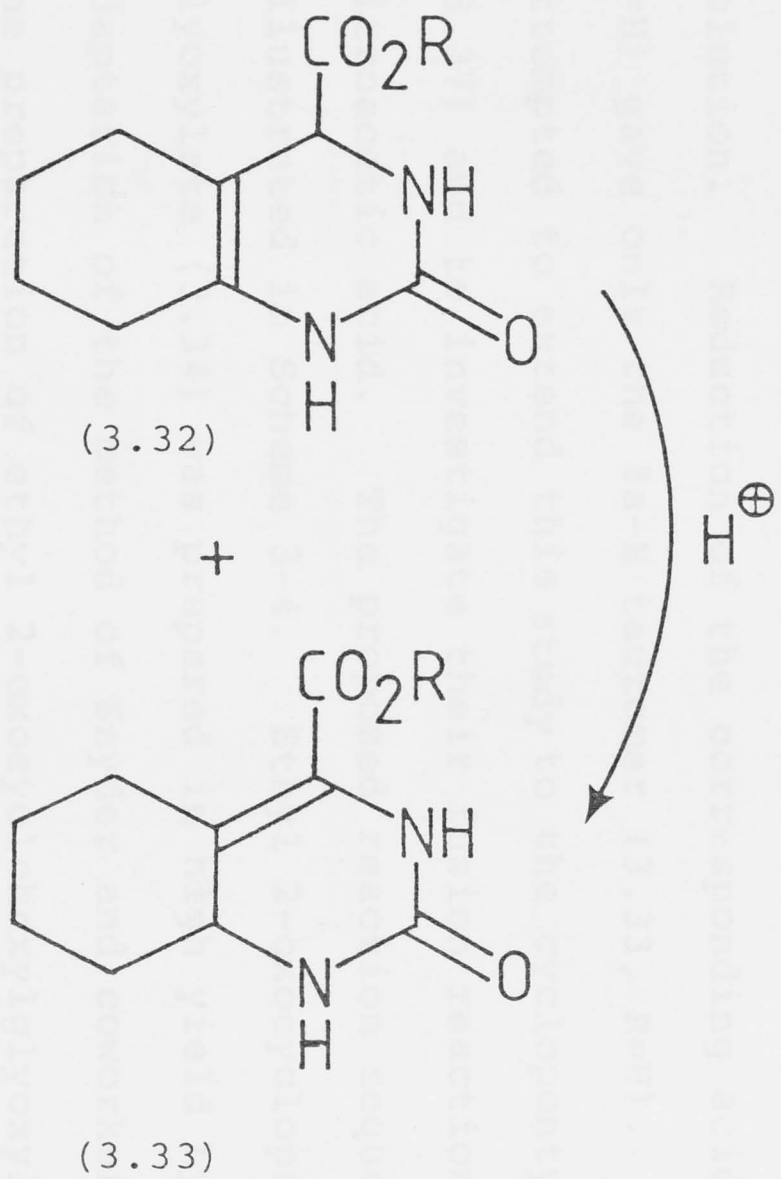
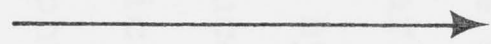
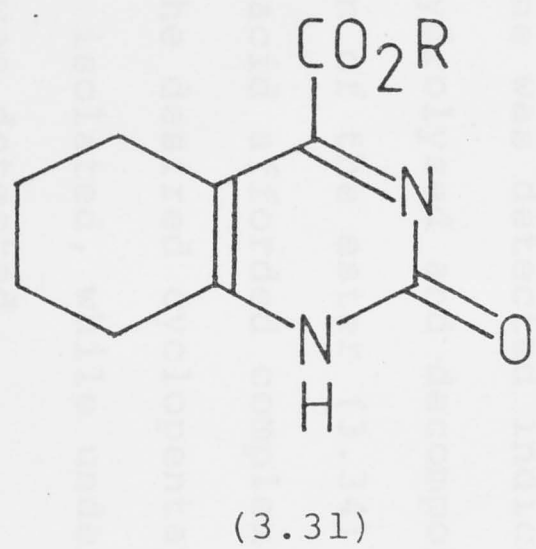


Fig. 3.6 The p.m.r. spectrum of 2-amino-1-ethoxycarbonylcyclopent-1-ene in  $\text{CDCl}_3$  at 60 MHz.

appeared to be a mixture of the starting material and 2-cyanocyclopentanone (3.29) (ketone absorption  $1760\text{ cm}^{-1}$  (lit.<sup>148</sup>  $1755\text{ cm}^{-1}$ ) and unconjugated nitrile  $2243\text{ cm}^{-1}$  (lit.<sup>148</sup>  $2250\text{ cm}^{-1}$ )). No addition products could be detected by p.m.r. spectroscopy. With nitroacetic acid, the acetate (3.28) afforded a high yield of 2-(*N*-acetyl)amino-1-amidocyclopent-1-ene (3.30), again no addition products were observed.

In our hands, ethyl *cis*-2-amino-*trans*-2-nitromethylcyclohexanecarboxylate (3.24) could be prepared from 2-amino-1-ethoxycarbonylcyclohex-1-ene (3.23) by fusion of the latter with nitroacetic acid according to the method of Armarego and Kobayashi.<sup>145</sup> Under the same conditions however, 2-amino-1-ethoxycarbonylcyclopent-1-ene (3.25) failed to afford a nitromethane adduct with nitroacetic acid. Hydrolysis appears to have been the only reaction, no reaction was detected under dry reaction conditions. The failure of the fusion reactions of the cyclopentenamines may have been due to the instability of the five-membered nitromethane adducts. Ethyl 2-cyano-2-hydroxycyclopentane carboxylate is known to dehydrate readily to yield ethyl 2-cyanocyclopent-1-ene carboxylate<sup>150</sup> while 1-acetoxy-1,2-dicyanocyclopentane eliminates acetic acid readily to afford 1,2-dicyanocyclopent-1-ene,<sup>151</sup> and serve to demonstrate the instability of this class of compounds.

Armarego and Milloy<sup>152</sup> have studied the reduction of quinazolinecarboxylic acids which were prepared from

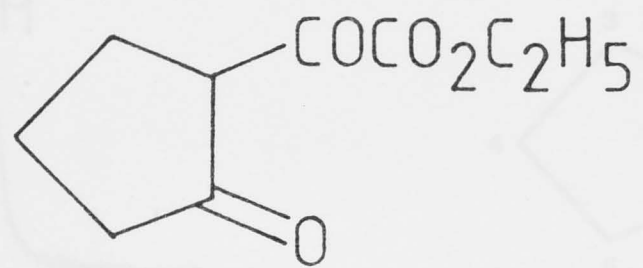


Scheme 3.3

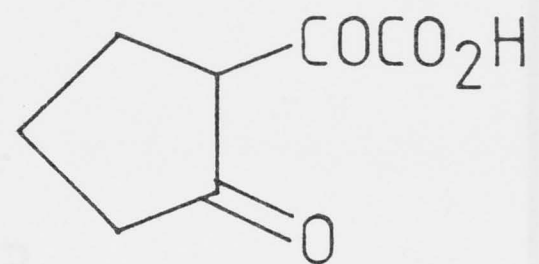
2-oxocyclohexylglyoxylic acid and urea. They found that when methyl 1,2,5,6,7,8-hexahydro-2-oxoquinazoline-4-carboxylate (3.31, R=CH<sub>3</sub>) was reduced catalytically, a mixture of the ester (3.32, R=CH<sub>3</sub>) and its 8a-H tautomer (3.33, R=CH<sub>3</sub>) was obtained (see Scheme 3.3). The ester was rapidly converted into the 8a-H tautomer in acid solution. Reduction of the corresponding acid (3.31, R=H) gave only the 8a-H tautomer (3.33, R=H). We attempted to extend this study to the cyclopentyl analogues (3.37) and to investigate their fusion reactions with nitroacetic acid. The proposed reaction sequence is illustrated in Scheme 3-4. Ethyl 2-oxocyclopentylglyoxylate (3.34) was prepared in high yield by an adaptation of the method of Snyder and coworkers<sup>153</sup> for the preparation of ethyl 2-oxocyclohexylglyoxylate. The p.m.r. spectrum of ethyl 2-oxocyclopentylglyoxylate is illustrated in Figure 3.6, and indicates that the compound exists primarily in the enol tautomeric form.

All attempts to hydrolyse the ester (3.34) to the acid (3.35) were unsuccessful. Under mild conditions (*e.g.* dilute sulphuric acid, dilute potassium hydroxide, or chloroform-1*M* sulphuric acid-silica gel) the ester was unchanged, while in refluxing dilute sulphuric acid, cyclopentanone was detected indicating that the ester (3.34) had hydrolysed and decomposed.

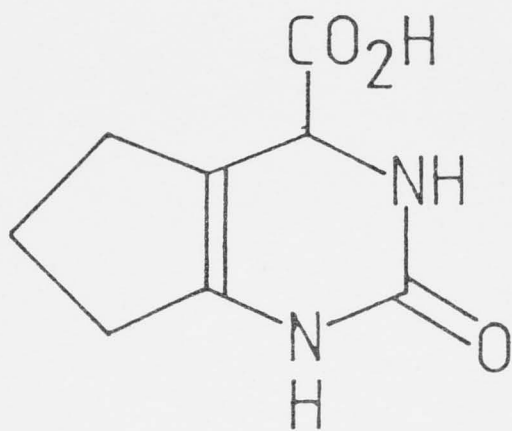
Reaction of the ester (3.34) with urea in the presence of acid afforded complex mixtures of products from which the desired cyclopentapyrimidinone (3.36) could not be isolated, while under neutral conditions, no reaction was detected.



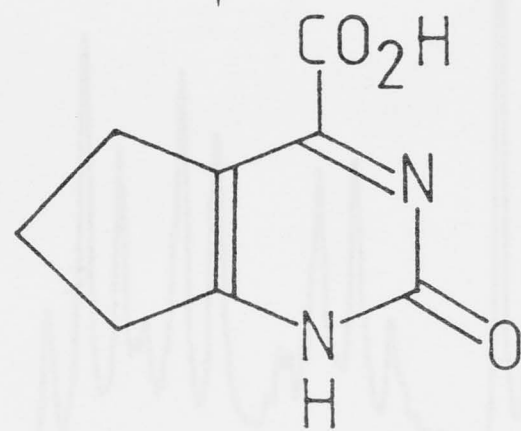
(3.34)



(3.35)



(3.37)



(3.36)

Scheme 3.4

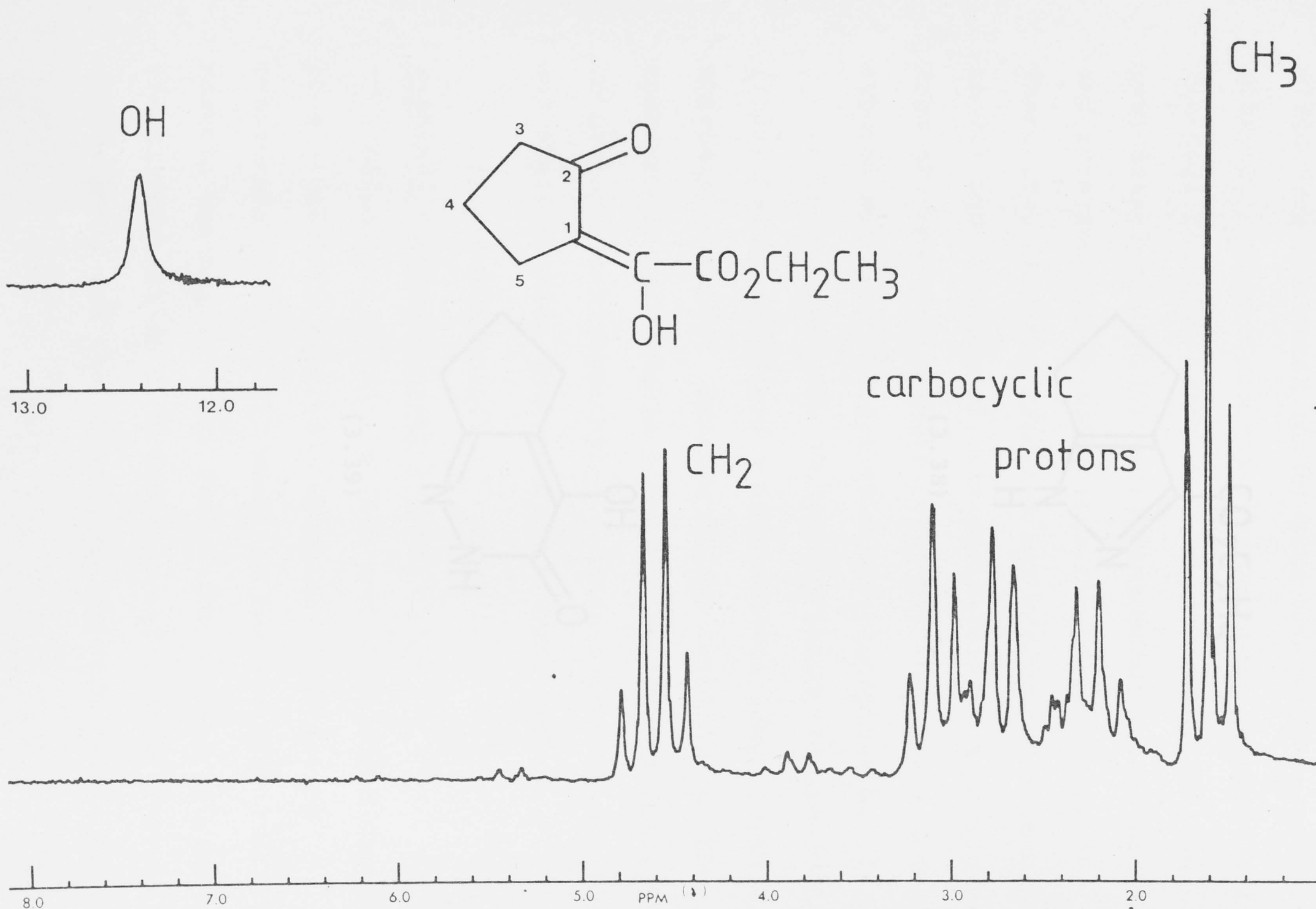
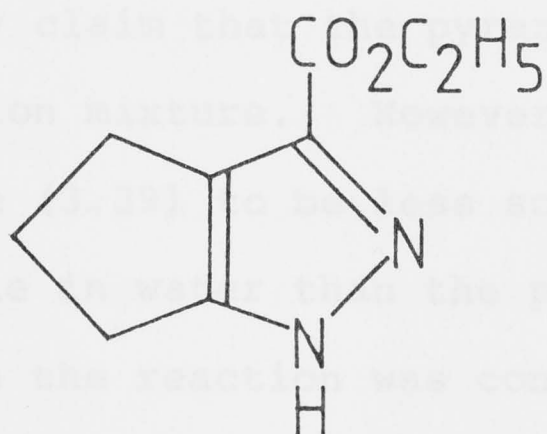
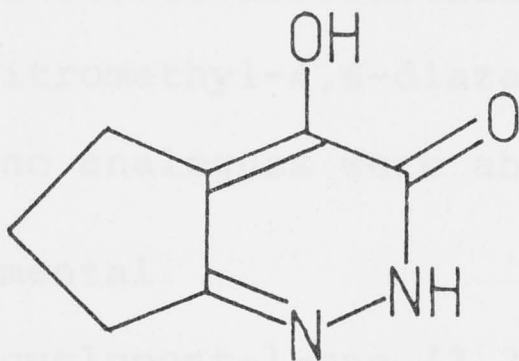


Fig. 3.7 The p.m.r. spectrum of ethyl 2-oxocyclopentyl glyoxalate in  $\text{CDCl}_3$  at 60 MHz.



(3.38)



(3.39)



When treated with hydrazine in aqueous ethanol (~30%) the ester (3.34) afforded ethyl 4,5-trimethylene-pyrazole-3-carboxylate (3.38) (57%) and 5,6-trimethylene-4-oxypyridazin-3-one (3.39) (29%). Elguero and coworkers<sup>154</sup> have prepared the pyrazole (3.38) in 62% yield from the ester (3.38) with hydrazine in aqueous ethanol. They claim that the pyrazole precipitates from the cool reaction mixture. However, we found the pyridazin-3-one (3.39) to be less soluble in ethanol and more soluble in water than the pyrazole (3.38). Therefore, when the reaction was conducted in absolute to 75% aqueous ethanol, the pyridazin-3-one precipitated from the reaction mixture, whereas, when 25% aqueous ethanol was used the pyrazole was precipitated.

Both the pyrazole (3.38) and the pyridazin-3-one (3.39) failed to afford a nitromethane adduct with nitroacetic acid. Because of the inability of the enamines to form stable nitromethane adducts attempts to prepare 3a-nitromethyl-4,6-diaza-5-oxoperhydroindenes and their 5-imino analogues were abandoned.

#### ii) Experimental

##### 2-Amino-1-cyanocyclopent-1-ene (3.25)

Adiponitrile (10.8 g, 0.1 mmol) was added dropwise to a vigorously stirred suspension of potassium *t*-butoxide (11.3 g, 0.1 mmol) in benzene (120 ml). The mixture was heated under reflux for 2 h and allowed to stand overnight at room temperature. Water (50 ml) was added slowly and the organic solids were collected by

vacuum filtration. The benzene phase was washed with water (50 ml) and more crystals separated. The aqueous phases were extracted with chloroform and the combined organic phases washed with water (50 ml), dried and evaporated to dryness. Recrystallization of the crystalline products and residue afforded 2-amino-1-cyanocyclopent-1-ene (84 g, 78%), m.p. 148-149<sup>o</sup> (lit.<sup>147</sup> 147-148<sup>o</sup>).  $\nu_{\max}$  3440, 3360, 3250 (NH str), 2180 (nitrile), 1650 (NH bend). P.m.r.  $\delta$ (CDCl<sub>3</sub>) 1.80 (m, 2H, H-4), 2.33 (m, 4H, H-3, H-5), 6.30 (br s, 2H, NH<sub>2</sub>).

2-Amino-1-ethoxycarbonylcyclopent-1-ene (3.26)

This was prepared from ethyl 2-oxocyclopentane-carboxylate<sup>155</sup> and ethanolic ammonia according to the method of Dieckmann,<sup>149</sup> m.p. 57-59<sup>o</sup> (lit.<sup>149</sup> 60<sup>o</sup>).  $\nu_{\max}$  3460, 3350 (NH str), 1737 (ester), 1670 (NH bend). P.m.r.  $\delta$ (CDCl<sub>3</sub>) 1.25 (t, 3H, -OCH<sub>2</sub>CH<sub>3</sub>), 1.83 (m, 2H, H-4), 2.47 (m, 4H, H-3, H-5), 4.17 (q, 2H, -OCH<sub>2</sub>CH<sub>3</sub>), 5.82 (br s, 2H, NH<sub>2</sub>).

2-(N-Acetyl)amino-1-cyanocyclopent-1-ene (3.28)

2-Amino-1-cyanocyclopent-1-ene (432 mg, 4 mmol) was heated in gently refluxing acetic anhydride (6 ml) for 45 min. and then cooled in ice. After standing in the cold for 12 h the crystals were collected and recrystallized from ether to afford the acetate (335 mg, 56%), m.p. 130-132<sup>o</sup> (Found: C, 64.5; H, 6.8; N, 18.7. C<sub>8</sub>H<sub>10</sub>N<sub>2</sub>O<sub>1</sub> requires C, 64.0; H, 6.7; N, 18.7%).

$\nu_{\max}$  3290, 3220, 3130 (NH str), 2195 (nitrile), 1720 (acetate C=O). P.m.r.  $\delta(\text{CDCl}_3)$  1.77-3.4 (m's, 6H, methylene protons), 2.13 (s, 3H, acetyl  $\text{CH}_3$ ), 8.53 (br, 1H, NH).

2-(N-Acetyl)amino-1-carboxamidocyclopent-1-ene (3.30)

The acetate (3.28) (75 mg, 0.5 mmol) was fused with nitroacetic acid (1.03 mg, 1 mmol) at  $45^\circ$ . After the evolution of carbon dioxide had ceased, the excess of nitromethane was evaporated *in vacuo*. The fusion was repeated and the crystalline residue dissolved in benzene. The benzene solution was filtered and the filtrate evaporated to afford the amide (80 mg, 95%), m.p.  $195-196^\circ$  (Found: C, 57.2; H, 7.3; N, 16.8.  $\text{C}_8\text{H}_{12}\text{N}_2\text{O}_2$  requires C, 57.1; H, 7.2; N, 16.7%).  $\nu_{\max}$  3372, 3180 (NH str), 1673, 1644 (acetate C=O and amide). P.m.r.  $\delta(\text{CDCl}_3)$  1.93-3.57 (m's, 6H, methylene protons), 2.35 (s, 3H, acetyl  $\text{CH}_3$ ), 7.40 (br s, 2H,  $\text{CONH}_2$ ), 11.7 (br s, 1H, NHAc).

Ethyl 2-oxocyclopentylglyoxylate (3.34)

A solution of sodium ethoxide was prepared by the cautious addition of clean sodium (23 g, 1 gm atom) to anhydrous ethanol (300 ml) in a 1 litre three necked round bottom flask with a dropping funnel, oil sealed stirrer and reflux condenser carrying a calcium chloride drying tube. The solution was cooled to  $10^\circ$  and an ice-cold mixture of cyclopentanone (84 g, 1 mmol) and ethyl oxalate (146 g, 1 mmol) added over a period of 15 min. Vigorous stirring was maintained throughout the addition,

for 1 h at ice-bath temperature and for 5 h at room temperature. The mixture was carefully decomposed with cold dilute sulphuric acid (28 ml conc. sulphuric acid and 220 gm ice) keeping the internal temperature at 5-10°C. The solution was diluted with cold water to a volume of 2L. and the supernatant decanted from the precipitated product. The aqueous part was extracted with benzene (4 x 250 ml) and the extracts combined with the precipitate. The extracts were washed with water (2 x 100 ml), dried (MgSO<sub>4</sub>) and evaporated to afford the crude product. Distillation gave the ethyl glyoxylate (157.4 g, 85%), b.p. 156-158°, 17 mmHg, m.p. 30-31° (lit.<sup>156</sup> b.p. 138-139°, 14 mmHg, oil, 13% yield; lit.<sup>157</sup> m.p. 26-27° from sodium ethoxide in ether). P.m.r.  $\delta$ (CDCl<sub>3</sub>) 1.58 (t, 3H, -OCH<sub>2</sub>CH<sub>3</sub>), 1.93-3.33 (m, 6H, methylene protons), 4.59 (q, 2H, -OCH<sub>2</sub>CH<sub>3</sub>), 12.4 (br s, 1H, OH).

3-Ethoxycarbonyl-trimethylene-4,5-pyrazole (3.38) and  
5,6-trimethylene-4-oxypyridazin-3-one (3.39)

(a) Ethyl 2-oxocyclopentylglyoxylate (4.7 g, 2.5 mmol) was dissolved in hot 30% aqueous ethanol (30 ml). Hydrazine hydrate (1.5 ml) was then added and the mixture heated under reflux for 1 h. The solution was cooled and the precipitate was collected and recrystallized from benzene to afford the pyrazole (2.6 g, 57%), m.p. 122-123° (lit.<sup>154</sup> 124-125°).

$\nu_{\max}$  1730 (ester C=O). P.m.r.  $\delta$ (CDCl<sub>3</sub>) 1.33 (t, 3H, -OCH<sub>2</sub>CH<sub>3</sub>), 2.23-3.00 (m, 6H, methylene protons), 4.37 (q, 2H, -OCH<sub>2</sub>CH<sub>3</sub>), 12.37 (br s, 1H, NH). Evaporation of

the filtrate and recrystallization from ethanol afforded the pyridazinone (1.1 g, 28.9%) m.p. 257-259<sup>o</sup> (lit.<sup>158</sup> 254-256<sup>o</sup>).  $\nu_{\max}$  3320, 3250 (OH and NH str), 1665, 1608 (amide, and C=N).

(b) The ester (1.84 g, 10 mmol), hydrazine hydrate (0.6 g) and 95% ethanol (10 ml) were heated under reflux for 30 minutes. The mixture was cooled and the crystals collected. Two further crops were obtained by evaporation of the filtrates to a small volume. The combined product (1.28 g, 84%) was recrystallized from ethanol to afford the pyridazinone melting at 257-259<sup>o</sup> and identical with that described in (a).

## PART 4

BIOLOGICAL EVALUATION OF TETRODOTOXIN  
AND SAXITOXIN ANALOGUES1) Introduction

Tetrodotoxin and saxitoxin have proved to be valuable tools in neurophysiology, and have yielded important information about the sodium channels of excitable membranes. Studies of the structure-activity relationships of each toxin are potentially useful in elucidating the mechanisms of action and nature of binding at the sodium channel, and could lead to the design of potent new drugs. However, as has been previously noted,<sup>159</sup> even minor modifications of the tetrodotoxin molecule result in an almost complete loss of biological activity,<sup>4</sup> and a direct approach by modification of the structure of the toxins and observation of the biological activities of the analogues would appear to be unproductive. The presence of the guanidinium moiety would seem to be essential for the pharmacological actions of the toxins. Kao and Nishiyama<sup>1</sup> were first to make the now generally accepted suggestion that the guanidinium group found in both toxins enters the sodium channel where it becomes "stuck" because the remainder of the molecule is too bulky to pass through. Thus, an alternative approach to structure-activity studies is the synthesis and

evaluation of cyclic guanidinium and urea analogues of the toxins. Compounds of these types were selected because in common with the toxins, they contain a cyclic guanidinium group, although they are otherwise structurally different.

The most suitable preliminary method for evaluating the activity of the analogues was to determine their minimum lethal doses (M.L.D.) in mice. The analogues were administered to mice by intraperitoneal injection as emulsions or solutions in 0.9N sterile saline. The analgesic and local anaesthetic properties of some compounds were investigated by treating mice with sub-lethal doses of the compound. Fifteen minutes later the mice were challenged with 0.5% acetic acid and observed for writhing normally resultant from such a challenge. When no writhing was observed the compound was judged as having analgesic or local anaesthetic effects. The mode of death, death time and other macroscopic effects yielded useful information about the injected compounds and gave some indication of their site of action.

## 2) Tetrodotoxin analogues

The tetrodotoxin molecule has been described in steric terms as being spherical in shape with a protruding tongue - the guanidinium group. 2-Oxo- and 2-imino-adamantanopyrimidines incorporating a spherical non-penetrating hydrocarbon moiety and a protruding hydrophilic "tongue" were prepared in an effort to duplicate the shape of the tetrodotoxin molecule.

The known biological activity of adamantane derivatives was a further consideration in the design of these analogues. Since the initial reports of the antiviral activity of 1-aminoadamantane<sup>160-166</sup> hundreds of other adamantane derivatives have been screened for antiviral, antiinflammatory, antitumor, insecticidal, analgesic and other activities. Several reviews on the biological activity of adamantane-containing drugs have appeared in recent years.<sup>167-169</sup> With some exceptions, the adamantane moiety has been used primarily to modify the potency of substances already recognised as drugs. The adamantane substituent increases the lipophilic character of these substances and hence enables them to be more easily transported through membranes. The adamantane moiety is not metabolized in man and therefore has the capacity to persist as an effective drug in a biological system. In 1969, Chakrabarti and coworkers<sup>56</sup> described the preparation of tetrahydroadamantano[2,1-*d*]-pyrimidin-2(1*H*)-one (2.31) and derivatives and claimed them to be useful as analgesics and local anaesthetics.

The minimum lethal doses of the tetrodotoxin analogues which were synthesized ( see sections 3 and 4 ) are listed in Table 4.1. Although the 2-iminoadamantanopyrimidines were considerably less toxic than tetrodotoxin, their toxicities were nevertheless comparable with those of the most active cyclic guanidines known.<sup>49,51,159</sup>



Table 4.1

## TETRODOTOXIN ANALOGUES

Minimum lethal doses for male mice

Compound	Approximate M.L.D. (mg/kg)
2-aminotetrahydroadamantano[2,1- <i>d</i> ]pyrimidine sulphate (2.30)*	246
tetrahydroadamantano[2,1- <i>d</i> ]pyrimidin-2(1 <i>H</i> )-one (2.31)*†	300
dihydroadamantano[2,1- <i>d</i> ]pyrimidin-2,4(1 <i>H</i> ,3 <i>H</i> )-dione (2.33)*†	76
adamantan-1-ylguanidine.HCl <sup>113</sup>	~180
<i>N</i> -[adamantan-1-yl]-urea*† <sup>170</sup>	>750
5-hydroxytetrahydroadamantano[1,2- <i>d</i> ]pyrimidin-2-iminium bromide (2.60)	125
adamantano[2,1- <i>e</i> ]triazin-2-one (2.61)*	>750
<i>trans</i> -2-amino-3,4,4a,5,6,7,8,8a-octahydroquinazoline hydrochloride <sup>51</sup>	110
<i>cis</i> -2-amino-3-methyl-3,4,4a,5,6,7,8,8a-octahydroquinazoline <sup>51</sup>	90
<i>cis</i> -8a-methoxycarbonyl methyl-2-amino-3,4,4a,5,6,7,8,8a-octahydroquinazoline <sup>51</sup>	210
<i>cis</i> -3-methylperhydroquinazolin-2-one <sup>51</sup>	75
tetrodotoxin <sup>51</sup>	0.013

\* Administered as an emulsion in Tween 80—0.9N sterile saline (1:9).

† Exhibited analgesic and local anaesthetic properties.

Paralysis of the hind limbs was apparent soon after injection and death occurred within 1-10 minutes by respiratory paralysis. The macroscopic effects of the analogues appear to be qualitatively similar to those of tetrodotoxin. The oxo-compound (2.31) was of comparable toxicity to the amino-compound (2.30), but the dioxo-compound (2.33) was considerably more toxic. However, the oxo- and dioxo- derivatives killed the mice by affecting the central nervous system, causing severe convulsions and pain.\* Mice treated with sub-lethal doses of the oxo- and dioxo- compounds were challenged with an intraperitoneal injection of 0.5% acetic acid and observed for writhing normally resultant from such a challenge. The mice were completely protected from writhing and the compounds were judged to possess analgesic and local anaesthetic properties. The triazine-one (2.61) was apparently inactive, the mice being unaffected by doses of 750 mg/kg or less. Adamantan-1-ylguanidine<sup>113</sup> and *N*-[adamantan-1-yl]-urea<sup>170</sup> were prepared for comparison with the cyclic guanidine and urea analogues. The guanidino compound had a toxicity comparable with that of the cyclic guanidino compounds and killed the mice in the same way. *N*-[Adamantan-1-yl]-urea was nontoxic at the levels administered (<750 mg/kg). It was

---

\* Similar effects were observed with *cis*-3-methylperhydroquinazolin-2-one.<sup>171</sup>

Table 4.2

AMINO-ADAMANTANES<sup>†</sup>

Minimum lethal doses in male mice

Compound	Approximate M.L.D. (mg/kg)
2-aminoadamantan-1-ol.HCl	260
2-oxoadamantane-1-ylamine.HCl	540
1-aminoadamantane.HBr*	295

<sup>†</sup> Potential antiviral and anti-Parkinsonian agents.

\* A known antiviral and anti-Parkinsonian agent.

effective as a local anaesthetic and analgesic, but appeared to cause long term central nervous system damage. The latter was deduced from the behaviour of test animals four or more hours after injection. They were sedate, their movements were uncoordinated and the mice did not appear to recover from the effects of the compound.

Several amino-adamantanes (potential antiviral agents or antidepressants) were tested and showed varying degrees of toxicity (see Table 4.2). The compounds caused central nervous damage in those mice that survived large doses, otherwise the mice suffered prolonged convulsions followed by death.

### 3) Saxitoxin Analogues

A limited number of compounds were examined and the minimum lethal doses for the saxitoxin analogues are illustrated in Table 4.3. The imidazolone (3.16) and its ring-opened analogue (3.21) were nontoxic at doses below 500 mg/kg although the imidazolone did induce mild convulsions. 1,3-Diguanidinopropane sulphate killed mice by respiratory inhibition and mice which survived were sedate for long periods. These results should be compared with those of the simple analogues prepared by Armarego and Reece<sup>52</sup> (see Table 4.3).

Table 4.3

## SAXITOXIN ANALOGUES

Minimum lethal doses for male mice

Compound	Approximate M.L.D. (mg/kg)
4(5)-aminoimidazol-2(3H)-one (3.16)	>750
$\alpha$ -ureidoacetamide (3.21)	>500
1,3-diguanidinopropane sulphate*	350
<i>N</i> -methylguanidine.HCl	600
2-amino-4,4a,5,6,7,8,8a-hexahydro-3H-cyclopenta[ <i>d</i> ]pyrimidine <sup>52</sup>	170
2-amino-4,5-dihydroimidazole <sup>52</sup>	120

\* See Part 3, Section 2 (iii) Experimental.

From these observations it may be concluded that the guanidinium moiety has a significant part to play in the saxitoxin- and tetrodotoxin- like activity of the analogues described above. The analogues incorporating cyclic guanidinium moieties are considerably less toxic than tetrodotoxin but have the same mode of action, and it can therefore be concluded that the polar groups of tetrodotoxin are essential for its extreme toxicity. The spherical shape of the adamantane moiety does not appear to enhance the activity of the analogues although some possess analgesic and local anaesthetic properties.

1. H. P. J. H. J., *Percept. Biol. Med.*, 19, 539 (1976).
2. Hille, B., *J. Gen. Physiol.*, 35, 539 (1971).
3. Hille, B., *Biophys. J.*, 15, 615 (1973).
4. Keynes, R.D., J.M. Ritchie and K. Rojas, *J. Physiol. (London)*, 213, 235 (1971).
5. Ritchie, J.M., R.D. Rogers and G. Strichartz, *J. Physiol. (London)*, 261, 477 (1976).
6. Ogura, Y., and Y. Mori, *Exp. J. Pharmacol.*, 3, 55 (1968).
7. Robinson, R.A., *J. Chem. Educ.*, 54, 345 (1977).
8. Martin, B.F., and S.B. Martin, *J. Chem. Educ.*, 53, 614 (1976).
9. Schantz, F.J., in "Microbial Toxins", S. Kadis, A. Cieglarz and S.J. Ajl, eds. Vol. VII, p.1, Academic Press, N.Y. (1971).

## REFERENCES

- 1 Kao, C.Y., and A. Nishiyama,  
*J. Physiol.* (London), 180, 50 (1965).
- 2 Dettbarn, W.D., H. Higman, P. Rosenberg and  
D. Nachmansohn, *Science*, 132, 300 (1960).
- 3 Kao, C.Y., and F.A. Fuhrman,  
*J. Pharmacol. Exp. Therap.*, 140, 31 (1963).
- 4 Kao, C.Y., *Federation Proc.*, 31, 1117 (1972).
- 5 Narahashi, T., *Federation Proc.*, 31, 1124 (1972).
- 6 Kao, C.Y., *Pharmacol. Rev.*, 18, 997 (1966).
- 7 Evans, M.H., *Int. Rev. Neurobiol.*, 15, 83 (1972).
- 8 Blankenship, J.E., *Perspect. Biol. Med.*  
19, 509 (1976).
- 9 Hille, B., *J. Gen. Physiol.*, 58, 599 (1971).
- 10 Hille, B., *Biophys. J.*, 15, 615 (1975).
- 11 Keynes, R.D., J.M. Ritchie and E. Rojas,  
*J. Physiol.* (London), 213, 235 (1971).
- 12 Ritchie, J.M., R.B. Rogart and G. Strichartz,  
*J. Physiol.* (London), 261, 477 (1976).
- 13 Ogura, Y., and Y. Mori,  
*Eur. J. Pharmacol.*, 3, 58 (1968).
- 14 Rubinson, K.A., *J. Chem. Educ.*, 54, 345 (1977).
- 15 Martin, D.F., and B.B. Martin,  
*J. Chem. Educ.*, 53, 614 (1976).
- 16 Schantz, E.J., in "Microbial Toxins",  
S. Kadis, A. Ciegler and S.J. Ajl, eds.  
Vol. VII, p.3, Academic Press, N.Y. (1971).

- 17 Lo Cicero, V.R. (Ed.)  
Proc. 1st Intl. Conf. Toxic Dinoflagellate Blooms,  
Mass. Sci. Technol. Found., Wakeford (1975).
- 18 Schantz, E.J., J.D. Mold, D.W. Stanger,  
J. Shavel, F.J. Riel, J.P. Bowden, J.M. Lynch,  
R.S. Wyler, B. Riegel and H. Sommer,  
*J. Am. Chem. Soc.*, 79, 5230 (1957).
- 19 Schantz, E.J., J.M. Lynch, G. Vayvada,  
K. Matsumoto and H. Rapoport,  
*Biochemistry*, 5, 1191 (1966).
- 20 Shimizu, Y., M. Alam, Y. Oshima and W.E. Fallon,  
*Biochem. Biophys. Res. Commun.*, 66, 731 (1975).
- 21 Jackim, E., and J. Gentile,  
*Science*, 162, 915 (1968).
- 22 Hashimoto, Y., S. Konosu, T. Yasumoto, A. Inoue  
and T. Noguchi, *Toxicon*, 5, 85 (1967).
- 23 Inoue, A., T. Noguchi, S. Konosu and  
Y. Hashimoto, *Toxicon*, 6, 119 (1968).
- 24 Konosu, S., A. Inoue, T. Noguchi and  
Y. Hashimoto, *Toxicon*, 6, 113 (1968).
- 25 Noguchi, T., S. Konosu and Y. Hashimoto,  
*Toxicon*, 7, 325 (1969).
- 26 Sommer, H., *Science*, 76, 574 (1932).
- 27 Russell, F.E., *Federation Proc.*, 26, 1206 (1967).
- 28 Wong, J.L., R. Oesterlin and H. Rapoport,  
*J. Am. Chem. Soc.*, 93, 7344 (1971).
- 29 Schantz, E.J., V.E. Ghazarossian, H.K. Schnoes,  
F.M. Strong, J.P. Springer, J.O. Pezzanite and  
J. Clardy, *J. Am. Chem. Soc.*, 97, 1238 (1975).



- 30 Bordner, J., W.E. Thiessen, H.A. Bates and  
H. Rapoport, *J. Am. Chem. Soc.*, 97, 6008 (1975).
- 31 Shimizu, Y., L.J. Buckley, M. Alam, Y. Oshima,  
W.E. Fallon, H. Kasai, I. Miura, V. Gullo and  
K. Nakanishi, *J. Am. Chem. Soc.*, 98, 5414 (1976).
- 32 Tanino, H., T. Nakata, T. Kaneko and Y. Kishi.  
*J. Am. Chem. Soc.*, 99, 2818 (1977).
- 33 Fuhrman, F.A., *Sci. Am.*, 217, (2), 60 (1967).
- 34 Mosher, H.S., F.A. Fuhrman, H.D. Buchwald and  
H.G. Fischer, *Science*, 144, 1100 (1964).
- 35 Buchwald, H.D., L. Durham, H.G. Fischer,  
R. Harada, H.S. Mosher, C.Y. Kao and  
F.A. Fuhrman, *Science*, 143, 474 (1964).
- 36 Kim, Y.H., G.B. Brown, H.S. Mosher and  
F.A. Fuhrman, *Science*, 189, 151 (1975).
- 37 Noguchi, T., and Y. Hashimoto,  
*Toxicon*, 11, 305 (1973).
- 38 Scheumack, D.D., M.E.H. Howden, I. Spence and  
R.J. Quinn, *Science*, 199, 188 (1978).
- 39 Gage, P.W., J.W. Moore and M. Westerfield,  
*J. Physiol.* (London), 259, 427 (1976).
- 40 Crofe, J.A., and M.E.H. Howden,  
*Toxicon*, 10, 645 (1972).
- 41 Tsuda, K., S. Ikuma, M. Kawamura, R. Tachikawa,  
K. Sakai, C. Tamura and O. Amakasu,  
*Chem. Pharm. Bull.*, 12, 1357 (1964).
- 42 Goto, T., Y. Kishi, S. Takahashi and Y. Hirata,  
*Tetrahedron*, 21, 2059 (1965).

- 43 Woodward, R.B., *Pure and Appl. Chem.*, 9, 49 (1964).
- 44 Woodward, R.B., and J.Z. Gougoutas,  
*J. Am. Chem. Soc.*, 86, 5030 (1964).
- 45 Furusaki, A., Y. Tomiie and I. Nitta,  
*Bull. Chem. Soc. Jpn.*, 43, 3332 (1970).
- 46 Kishi, Y., T. Fukuyama, M. Aratani, F. Nakatsubo,  
T. Goto, S. Inoue, H. Tanino, S. Sugiura and  
H. Kakoi, *J. Am. Chem. Soc.*, 94, 9219 (1972).
- 47 Deguchi, T., *Jap. J. Pharmacol.*, 17, 267 (1967).
- 48 Narahashi, T., J.W. Moore and R.N. Poston,  
*Science*, 156, 976 (1967).
- 49 Ranney, B.K., F.A. Fuhrman, J.L. Schmiegel  
and H.S. Mosher, *Arch. Int. Pharmacodyn. Ther.*,  
175, 193 (1968).
- 50 Schmiegel, J.L.,  
*Dissertation Abst. B.*, 28, 4507 (1968).
- 51 Armarego, W.L.F., and P.A. Reece,  
*J. Chem. Soc., Perkin Trans 1*, 1470 (1975).
- 52 Armarego, W.L.F., and P.A. Reece,  
*J. Chem. Soc., Perkin Trans 1*, 1414 (1976).
- 53 Wegner, M.M., and H. Rapoport,  
*J. Org. Chem.*, 42, 3065 (1977).
- 54 Ghazarossian, V.E., E.J. Schantz, H.K. Schnoes  
and F.M. Strong, *Biochem. and Biophys. Res.*  
*Commun.*, 68, 776 (1976).
- 55 Mold, J.D., J.P. Bowden, D.W. Stanger,  
J.E. Maurer, J.M. Lynch, R.S. Wyler,  
E.J. Schantz and B. Riegel,  
*J. Am. Chem. Soc.*, 79, 5235 (1957).

- 56 Chakrabarti, J.K.,  
S.S. Szinai, U.S. Patent, 3,746,761 (1973).
- 57 Landa, S., S. Kriebel, and E. Knobloch,  
*Chem. Listy*, 48, 61 (1954).
- 58 Stetter, H., M. Schwarz, and A. Hirschhorn,  
*Angew. Chem.*, 71, 429 (1959).
- 59 Stetter, H., M. Schwarz, and A. Hirschhorn,  
*Chem. Ber.*, 92, 1629 (1959).
- 60 Geluk, H.W., and J.L.M.A. Schlatmann,  
*Chem. Commun.*, 426 (1967).
- 61 Geluk, H.W., and J.L.M.A. Schlatmann,  
*Tetrahedron*, 24, 5361 (1968).
- 62 Geluk, H.W., and V.G. Keizer,  
*Org. Synth.*, 53, 8 (1973).
- 63 Tabushi, I., Y. Aoyama, and Z. Yoshida,  
*J. Am. Chem. Soc.*, 93, 2077 (1971).
- 64 Curran, W.V., and R.B. Angier,  
*Chem. Commun.*, 563 (1967).
- 65 Curran, W.V., and R.B. Angier,  
*J. Org. Chem.*, 34, 3668 (1969).
- 66 Greidanus, J.W., *Can. J. Chem.*, 52, 1062 (1974).
- 67 Alewood, P.F., M. Benn, and R. Reinfried,  
*Can. J. Chem.*, 52, 4083 (1974).
- 68 Chakrabarti, J.K., S.S. Szinai, and A. Todd,  
*J. Chem. Soc. (C)*, 1303 (1970).
- 69 Lunn, W.H.W., W.D. Podmore, and S.S. Szinai,  
*J. Chem. Soc. (C)*, 1657 (1968).
- 70 McKervey, M.A., *Chem. Ind. (London)*, 1791 (1967).

- 71 Chakrabarti, J.K., M.J. Foulis,  
T.M. Hotten, S.S. Szinai, and A. Todd,  
*J. Med. Chem.*, 17, 602 (1974).
- 72 Lenoir, D., R. Glaser,  
P. Mison, and P. von R. Schleyer,  
*J. Org. Chem.*, 36, 1821 (1971).
- 73 Cuddy, B.D., D. Grant, and M.A. McKervey,  
*Chem. Commun.*, 27 (1971).
- 74 Chakrabarti, J.K., T.M. Hotten, and D.E. Tupper,  
*Tetrahedron Lett.*, 27, 2241 (1975).
- 75 Chakrabarti, J.K., T.M. Hotten,  
D.M. Rackham, and D.E. Tupper,  
*J. Chem. Soc., Perkin Trans.1*, 1893 (1976).
- 76 Stetter, H., H.G. Thomas, and K. Meyer,  
*Chem. Ber.*, 103, 863 (1970).
- 77 Peters, J.A., J.D. Remijnse,  
A. van der Wiele, and H. van Bekkum,  
*Tetrahedron Lett.*, 32, 3065 (1971).
- 78 Peters, J.A., J.M. van der Toorn, and  
H. van Bekkum, *Tetrahedron*, 31, 2273 (1975).
- 79 Alberts, A.H., H. Wynberg, and J. Strating,  
*Tetrahedron Lett.*, 8, 543 (1973).
- 80 Tabushi, I., and Y. Aoyama,  
*J. Org. Chem.*, 38, 3447 (1973).
- 81 Bagal, M.L., T.K. Klindukhova, and V.I. Lantvoev,  
*Zh. Org. Khim.*, 11, 1645 (1975).
- 82 Stetter, H., V. Löhr, and A. Simos,  
*Justus Liebigs Ann. Chem.*, 999 (1977).

- 83 Nordlander, J.E., F.Y.-H. Wu,  
S.P. Jindal, and J.B. Hamilton,  
*J. Am. Chem. Soc.*, 91, 3962 (1969).
- 84 Schleyer, P. von R., E. Funke, and S.H. Liggero,  
*J. Am. Chem. Soc.*, 91, 3965 (1969).
- 85 Black, R.M., and G.B. Gill,  
*J. Chem. Soc. (C)*, 671 (1970).
- 86 Schlatmann, J.L.M.A., J.G. Korsloot, and  
J. Schut, *Tetrahedron*, 26, 949 (1970).
- 87 de Boer, Th. J., and H.J. Backer,  
*Org. Synth.*, Coll. Vol.IV, 943 (1963).
- 88 Tabushi, I., Z. Yoshida, and N. Takahashi,  
*J. Am. Chem. Soc.*, 92, 6670 (1970).
- 89 Chin, C.G., H.W. Cuts, and S. Masamune,  
*Chem. Commun.*, 880 (1966).
- 90 Fort, Jr., R.C., *Studies in Organic Chemistry*  
Volume 5, pp.2-4. Ed., P.G. Gaussman.
- 91 Cuddy, B.D., D. Grant, A. Karim,  
M.A. McKervey, and E.J.F. Rea,  
*J. Chem. Soc., Perkin Trans.1*, 2701 (1972).
- 92 Gillis, B.T., and J.D. Hagarty,  
*J. Org. Chem.*, 32, 330 (1967).
- 93 Janny, A., *Ber. Dtsch. Chem. Ges.*, 16, 170 (1883).
- 94 Fort, R.C., and P. von R. Schleyer,  
*J. Org. Chem.*, 30, 789 (1965).
- 95 van Deursen, F.W., and P.K. Korver,  
*Tetrahedron Lett.*, 40, 3923 (1967).

- 96 Schleyer, P. von R., R.C. Fort, Jr., W.E. Watts,  
M.B. Comisarow, and G.A. Olah.  
*J. Am. Chem. Soc.*, 86, 4195 (1964).
- 97 Olah, G.A., and J. Lukas,  
*J. Am. Chem. Soc.*, 90, 933 (1968).
- 98 Becker, E.D., "High Resolution NMR",  
p. 103-105, Academic Press, N.Y. (1970).
- 99 Oldenziel, O.H., and A.M. van Leusen,  
*Tetrahedron Lett.*, 16, 1357 (1973).
- 100 Oldenziel, O.H., D. van Leusen, and A.M. van Leusen,  
*J. Org. Chem.*, 42, 3114 (1977).
- 101 Armarego, W.L.F., and P.G. Tucker,  
unpublished work.
- 102 Alberts, A.H., H. Wynberg, and J. Strating,  
*Synth. Commun.*, 2, 79 (1972).
- 103 Lundahl, K., J. Schut, J.L.M.A. Schlatmann,  
G.B. Paerels, and A. Peters,  
*J. Med. Chem.*, 15, 129 (1972).
- 104 Burkhard, J., J. Vais, and S. Landa,  
*Collect. Czech. Chem. Commun.*, 38, 1263 (1973).
- 105 Gašpert, B., S. Hromadko, and B. Vranešić,  
*Croat. Chem. Acta*, 48, 169 (1976).
- 106 de Bock, C.A., and J.L.M.A. Schlatmann,  
*Ger., Offen.* 1,910,560 (1969).
- 107 Stetter, H., and V. Tillmanns,  
*Chem. Ber.*, 105, 735 (1972).
- 108 Ziegler, F.E., and P.A. Wender,  
*J. Am. Chem. Soc.*, 93, 4318 (1971).

- 109 Ziegler, F.E., and P.A. Wender,  
*J. Org. Chem.*, 42, 2001 (1977).
- 110 Mattes, K.C., M.T. Hisa, C.R. Hutchinson, and  
S.A. Sisk, *Tetrahedron Lett.*, 40, 3541 (1977).
- 111 Sasaki, T., S. Eguchi, and S. Hattori,  
*Tetrahedron Lett.*, 1, 97 (1977).
- 112 Sasaki, T., S. Eguchi, and S. Hattori,  
*Tetrahedron*, 34, 67 (1978).
- 113 Geluk, H.W., J. Schut, and J.L.M.A. Schlatmann,  
*J. Med. Chem.*, 12, 712 (1969).
- 114 Tsuji, T., and T. Ueda,  
*Chem. Pharm. Bull.*, 12, 946 (1964).
- 115 Nishimura, T., H. Toku, N. Ueno, and K. Kenmotsu,  
*Yuki Gosei Kagaku Kyokai Shi*, 30, 1024 (1972).
- 116 van Deursen, F.W., and J. Bakker,  
*Tetrahedron*, 27, 4593 (1971).
- 117 Buss, V., R. Gleiter, and P. von R. Schleyer,  
*J. Am. Chem. Soc.*, 93, 3927 (1971).
- 118 Lwowski, W., and F.P. Woerner,  
*J. Am. Chem. Soc.*, 87, 5491 (1965).
- 119 Breslow, D.S., T.J. Prosser, A.F. Marcantonio,  
and C.A. Genge, *J. Am. Chem. Soc.*, 89, 2384 (1967).
- 120 Lwowski, W.,  
*Angew. Chem. Int. Ed. Engl.*, 6, 897 (1967).
- 121 Kevill, D.N., and F.L. Weitzl,  
*J. Am. Chem. Soc.*, 90, 6416 (1968).
- 122 Gerzon, K., and E.V. Krumkalns,  
U.S. Patent, 3,369,041 (1968).

- 123 Kevill, D.N., and F.L. Weigl,  
*J. Org. Chem.*, 35, 2526 (1970).
- 124 Owens, P.H., G. J. Gleicher, and L.M. Smith,  
*J. Am. Chem. Soc.*, 90, 4122 (1968).
- 125 Sinnot, M.L., and M.C. Whiting,  
*J. Chem. Soc. (B)*, 965 (1971).
- 126 Breslow, D.S., E.I. Edwards, R. Leone, and  
P. von R. Schleyer,  
*J. Am. Chem. Soc.*, 90, 7097 (1968).
- 127 Lenoir, D., R.E. Hall, and P. von R. Schleyer,  
*J. Am. Chem. Soc.*, 96, 2138 (1974).
- 128 Haas, W.L., E.V. Krumkalns, and K. Gerzon,  
*J. Am. Chem. Soc.*, 88, 1988 (1966).
- 129 Stetter, H., M. Schwarz, and A. Hirschhorn,  
*Chem. Ber.*, 92, 1629 (1959).
- 130 Schleyer, P. von R., and R.D. Nicholas,  
*J. Am. Chem. Soc.*, 83, 182 (1961).
- 131 Armarego, W.L.F., *J. Chem. Soc. (C)*, 986 (1969).
- 132 Armarego, W.L.F., *J. Chem. Soc. (C)*, 1812 (1971).
- 133 Ferris, J.P., R.A. Sanchez, and R.W. Mancuso,  
*Org. Synth. Coll. Vol. V*, 32 (1973).
- 134 Robinson, D.H., and G. Shaw,  
*J. Chem. Soc., Perkin Trans. 1*, 1715 (1972).
- 135 Cook, A.H., and G.D. Hunter,  
*J. Chem. Soc.*, 3789 (1952).
- 136 Smith, L.H., and P. Yates,  
*J. Am. Chem. Soc.*, 76, 6080 (1954).



- 137 Cook, A.H., J.D. Downer, and Sir I. Heilbron,  
*J. Chem. Soc.*, 2028 (1948).
- 138 Harries, C., and M. Weiss,  
*Ber. Dtsch. Chem. Ges.*, 33, 3418 (1900).
- 139 Bailey, J.R., *J. Am. Chem. Soc.*, 28, 386 (1902).
- 140 Johnson, T.B., and B.H. Nicolet,  
*J. Am. Chem. Soc.*, 36, 362 (1914).
- 141 Conrad, M., and A. Schulze,  
*Ber. Dtsch. Chem. Ges.*, 42, 735 (1909).
- 142 Adkins, H., and E.W. Reeve,  
*J. Am. Chem. Soc.*, 60, 1329 (1938).
- 143 Duschinsky, R., and L.A. Dolan,  
*J. Am. Chem. Soc.*, 67, 2079 (1945).
- 144 Hilbert, G.E., *J. Am. Chem. Soc.*, 54, 3413 (1932).
- 145 Armarego, W.L.F., and T. Kobayashi,  
*J. Chem. Soc. (C)*, 3222 (1971).
- 146 Thorpe, J.F., *J. Chem. Soc.*, 1901 (1909).
- 147 Thompson, Q.E., *J. Am. Chem. Soc.*, 80, 5483 (1958).
- 148 Hammer, C.F., and R.A. Hines,  
*J. Am. Chem. Soc.*, 77, 3649 (1955).
- 149 Dieckmann, von W.,  
*Justus Liebigs Ann. Chem.*, 317, 27 (1901).
- 150 Takaya, T., H. Yoshimoto, and E. Imoto,  
*Bull. Chem. Soc.*, 40, 2844 (1967).
- 151 Cariou, M., and M. Lamant,  
*C. R. Acad. Sci., Ser. C*, 278, 1457 (1974).
- 152 Armarego, W.L.F., and B.A. Milloy,  
*J. Chem. Soc. Perkin Trans. 1*, 2814 (1973).

- 153 Snyder, H.R., L.A. Brooks, and S.H. Shapiro,  
*Org. Synth.*, Coll. Vol.II, 531 (1943).
- 154 Elguero, J., G. Guiraud, and R. Jacquier,  
*Bull. Soc. Chim. Fr.*, 12, 619 (1966).
- 155 Pinkey, P.S., *Org. Synth.* Coll. Vol.II, 116 (1943).
- 156 Kötzt, von A.,  
*Justus Liebigs Ann. Chem.*, 348, 111 (1906).
- 157 Ruhemann, S., *J. Chem. Soc.*, 1729 (1912).
- 158 von Auwers, von K., and W. Noll,  
*Justus Liebigs Ann. Chem.*, 536, 97 (1938).
- 159 Goldberg, P.B., and C.Y. Kao,  
*J. Pharm. and Exp. Ther.*, 186, 569 (1973).
- 160 Davies, W.L., R.R. Grunert, R.F. Haff,  
J.W. McGahen, E.M. Neumayer, E. Paulshock,  
J.C. Watts, T.R. Word, E.C. Hermann and  
C.E. Hoffmann, *Science*, 144, 862 (1964).
- 161 Stanley, E.D., L.W. Muldoon, L.W. Akers, and  
G.G. Jackson, *Ann. N.Y. Acad. Sci.*, 130, 44 (1965).
- 162 Wood, T. R., *Ann. N.Y. Acad. Sci.*, 130, 419 (1965).
- 163 Sabin, A.B., *J. Am. Med. Assoc.*, 200, 943 (1967).
- 164 Galegov, G.A., N.L. Pushkarskaya, and  
S.V. Lavrov, *Lancet*, 2, 1086 (1967).
- 165 Kato, N., and H.J. Eggers,  
*Virology*, 37, 632 (1969).
- 166 Brown, F., and P.H. Redfern,  
*Br. J. Pharmacol.*, 58, 561 (1976).
- 167 Majerski, Z., D. Skare, J. Janjatovic,  
Z. Hamerask, and B. Vinkovic,  
*Arh. Hig. Rada Toksikol*, 27, 335 (1976).

- 168 Kovalev, I.E.,  
*Khim.-Farm. Zh.*, 11, 19 (1977).
- 169 Indulena, M., V. Kalnina,  
G.M. Ryazatseva, and V.I. Bubovica,  
*Latv. PSR Zinat, Akad. Vestis*, 3, 17 (1977).
- 170 Stetter, H., and C. Wulff,  
*Chem. Ber.*, 95, 2302 (1962).
- 171 Armarego, W.L.F., and P.A. Reece,  
private communication.