THE SYNTHESIS AND STEREOCHEMISTRY OF SOME AZETIDINES

A THESIS

PRESENTED FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

in the

UNIVERSITY OF ADELAIDE

by

MERVYN BENJAMIN JACKSON, B.Sc.(Hons.)

Department of Organic Chemistry

January, 1969.

CONTENTS

SUMMARY

A convenient one-step synthesis of *N*-substituted azetidines from 2-azetidinones by the reduction of the latter with aluminium hydride or diborane has been developed. With aluminium hydride, all *N*-substituted 2-azetidinones investigated were reduced to the corresponding azetidines in about 80% yield while with diborane, all *N*-substituted 2-azetidinones, except *N*-methyl-2-azetidinones, were reduced in only slightly lower yields to azetidines. These reductions were in contrast to those observed with lithium aluminium hydride in which only ring cleavage products were detected, and the difference is discussed in terms of the nature of the intermediate organometallic complexes.

Several other potential routes to azetidines were investigated although none of these were found to be of any synthetic importance. The base treatment of 3-halopropylamines or tosylates, obtained in very poor yields from the corresponding 3-aminopropanols, gave only trace amounts of azetidines. The reduction of 1,4-diphenyl-2-azetidinethione with Raney nickel or aluminium amalgam gave only ring cleavage products with no evidence of any azetidine. Irradiation of a mixture of a Schiff's base and an olefin or of *N*,*N*-diethylphenacylamine (in benzene) also failed to yield any azetidine derivatives.

The *cis* and *trans* isomers and the ring substituents and protons in the n.m.r. spectra of azetidines were assigned by analogy with the spectra of 2-azetidinones and by qualitative interpretation of the shielding effects of various substituents. Vicinal coupling constants

of the order of 7.7 to 8.8 c.p.s. for *cis* ring protons and 4.9 to 7.7 c.p.s. for *trans* protons were found and these provided further evidence for the stereochemical assignments. Geminal coupling constants for the 2- and 4-protons in the azetidine ring of the order of -5.85 to -7.2 c.p.s. were found, while a value of about -10.0 c.p.s. for the 3-protons was found. Changes in chemical shifts and coupling constants were interpreted in terms of probable conformations of the azetidine ring and the nitrogen substituents.

The benzylic protons of 1-benzyl-4-substituted-azetidines and 1-benzyl-2,2,4-trimethylazetidine were magnetically non-equivalent. The origin of this non-equivalence is discussed.

The rates of nitrogen inversion could be measured directly by variable temperature n.m.r. spectroscopy for only 1-bromo- and 1-chloro-2,2,3,3-tetramethylazetidine, the rates for all other azetidines being too fast down to -67°C, the limit of the equipment available. The rates of nitrogen inversion for 1,2,2,3,3-pentamethylazetidine and 1-benzyl-2,2,3,3-tetramethylazetidine were measured by studying their variable temperature n.m.r. spectra in solutions of low pH.

The mass spectra of azetidines and 2-azetidinones were studied. The fragmentation modes were found to depend largely upon the substitution pattern and involved specific cleavage of the four-membered ring. In 2-azetidinones, the predominant ring cleavage process occurred in such a manner as to produce the olefin radical ion in contrast to the azetidines, in which fragmentation to produce the Schiff's base radical ion predominated. The major peaks in the spectra

of 2-azetidinones were not affected by the group attached to the nitrogen atom whereas the spectra of azetidines were largely dependent upon the nature of the nitrogen substituent. Several hydrogen rearrangement reactions occurred. In some cases, *cis* and *trans* isomers could be distinguished by large differences in the relative abundances of certain fragment ions.

STATEMENT

This thesis contains no material which has been accepted for the award of any other degree or diploma in any University, and to the best of my knowledge and belief contains no material previously published or written by another person, except where due reference is made in the text.

Mervyn B. Jackson

ACKNOWLEDGEMENTS

I wish to thank sincerely Dr. T.M. Spotswood for his guidance and encouragement, and for the many stimulating discussions during his supervision of this work.

I wish to thank all other staff members and especially Dr. L.N. Mander for his generous help and encouragement and valuable discussions during Dr. Spotswood's sabbatical leave, and Dr. J.H. Bowie for assistance in the interpretation of the mass spectra.

I also wish to thank Mr. R.L. Paltridge for help in determining the n.m.r. spectra. I am grateful to Mr. D.B. Cobb for determining the mass spectra.

This research was carried out during the tenure of a C.S.I.R.O. Senior Post-Graduate Studentship, for which I am very grateful.

PUBLICATIONS

Part of the work described in this thesis has been accepted for publication in the paper:

"Mass Spectra of Azetidines and 2-Azetidinones", M.B. Jackson, T.M. Spotswood and J.H. Bowie, *Journal of Organic Mass Spectrometry*, (1968).

CHAPTER 1. THE SYNTHESIS OF AZETIDINES

I. INTRODUCTION

1. The Synthesis of Azetidines

Azetidines, which are saturated four-membered nitrogen heterocycles, have received relatively little attention, mainly because of the low yields often encountered in their preparation. The rate of cyclization of 3-bromopropylamine is much less than the rate of cyclization of either 2-bromoethylamine or 4-bromobutylamine.[1] It has been suggested[2] that the ease of ring closure depends on the distance between the bonding centres and the ring strain of the product. Each of these factors reinforce each other with the result that the formation of the four-membered ring compared with other small and medium sized rings is the most difficult. We were particularly interested in the synthesis, stereochemistry and mass spectra of azetidines.

The first member of the azetidine series to be described was the parent compound, azetidine, prepared by Gabriel and Weiner[3] in 1888 by treatment of 3-bromopropylamine with alkali. In 1890 it was found that the dry distillation of 1,3-diamino-propane dihydrochloride also yielded azetidine.[4] Neither of these reactions yielded a pure product and azetidine was not fully characterized until the formation of the *N*-*p*-toluenesulphonamide, followed by reductive cleavage to azetidine, was described by Marckwald.[5,6]

Until recently, there were only two general methods of synthesis of azetidines: (1) the formation of the cyclic amine by cyclization of a suitable acyclic precursor and (2) the formation of the azetidine by reduction of a 2-azetidinone or malonimide. The first of these methods may be represented by the reaction shown in Scheme 1, which involves an internal nucleophilic displacement by an

Scheme 1

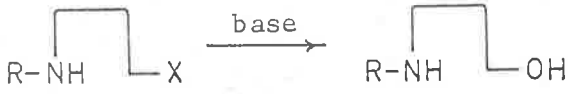
amino group of a suitable leaving group X in the 3-position of a three carbon chain. Several examples involving different leaving groups X are discussed below.

(1) Cyclization of 3-haloamines

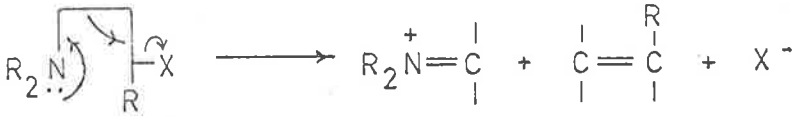
As previously mentioned, this method has been used for the synthesis of azetidine itself,[3] with yields ranging from six to twenty-six per cent.[7] Treatment of 3-chloro- and 3-bromoamines with a strong base has been the most widely used method. In many cases the yields were very low and other products were not mentioned. A number of competing reactions are possible, thus reducing the yield of the azetidine or in some cases preventing its formation. These competing reactions may include

(a) the formation of cyclic dimers and polymers *via* an intermolecular nucleophilic substitution reaction rather than the desired intramolecular one,

(b) solvolysis of the alkyl halide,



(c) elimination and fragmentation[13] reactions, and



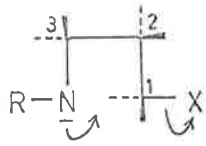
(d) the yield of *N*-unsubstituted azetidines (secondary amines) may be reduced by further alkylation.

In general, a primary halide cyclizes more readily than does a secondary halide and this in turn cyclizes more readily than a tertiary halide. This is what would be expected, with side reactions from an S_N1 type process and from fragmentation[13] being less for a primary halide.

Mannich[8] and Kohn[9-12] have prepared 1,3,3-trimethylazetidine and 4-alkyl-1,2-dimethylazetidines respectively from the corresponding haloamines in reasonable yields although the purity of the products may be open to question.

Vaughan[15] has considered that cyclization to the azetidine system is a conformational problem. However, since the ring closure is much slower than the interconversion of conformers in these systems it would appear that the cyclization should be discussed in relation to the energy of the transition state according to the Curtin-Hammett Principle.[14(a),14(b)] Vaughan[15] has suggested that the most favourable

situation for effective cyclization to the azetidine system will be found in the 3-aminopropyl system (1) in which there are no substituents

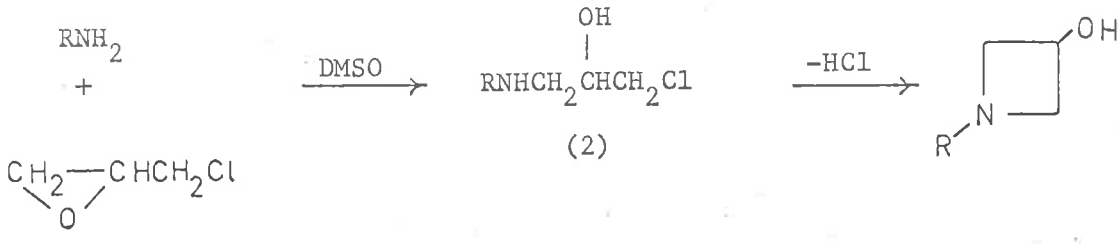


(1)

Figure 1

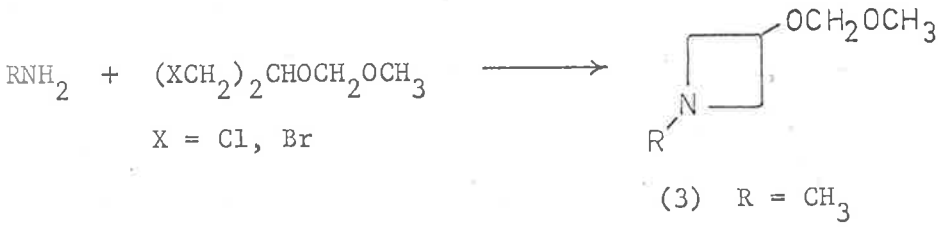
on any of the carbons and a large substituent on nitrogen. Symmetrical *gem* substitution on C_2 (provided the groups are not too large) with no substituents on C_1 and C_3 or with *gem* substitution on C_3 with no substituents on C_1 and C_2 should have little effect on the success of the cyclization. *Threo* substituents on C_1 and C_2 or on C_2 and C_3 (or on all three carbon atoms) should not interfere with cyclization. *Erythro* substituents at C_2 and C_3 should result in a slower rate of cyclization since in the transition state they will be partially eclipsed thus raising the energy of the transition state. *Erythro* substituents at C_1 and C_2 should affect mainly the stability of the product.

A very convenient two-step synthesis of 1-alkyl-3-azetidinols from primary alkylamines and epichlorohydrins has recently been reported.[16,17] The reaction involves a spontaneous cyclization of the 1-alkylamino-3-chloro-2-alkanol (2) carrying tertiary, secondary or hindering primary *N*-alkyl groups. *n*-Alkyl or aryl groups do not provide sufficient hindrance or nucleophilicity for cyclization to



Scheme 2

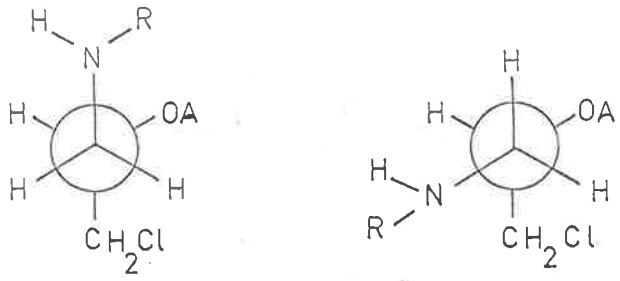
occur. 1-*tert*-Alkylamino-3-chloro-2-propyl acetates were found to cyclize sluggishly and in lower yields than the propanols. This contradicts the generalisation of Vaughan[15] mentioned above that groups in the 2-position of 3-haloamines will hinder cyclization only if they eclipse in the transition state with substituents in the 1 and 3 positions. The preparation of 1-methyl-3-(methoxymethoxy)-azetidine (3)[19] from methylamine and 1,3-dichloro-2-(methoxymethoxy)-propane is claimed to clarify the steric requirements for cyclization.[19]



(3) R = CH_3

Scheme 3

However, Gaertner[16,17] and Gaj and Moore[19] have discussed these steric requirements in terms of preferred staggered conformations depending on the total steric bulk of the *N*-substituent and the oxygen containing group. They further suggest that one conformation (A) favours intermolecular reactions and another (B) favours cyclization.

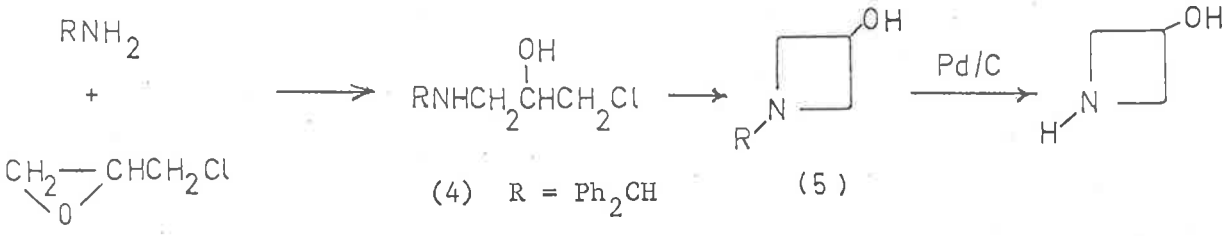


(A) (B)

Figure 2

Such an approach would appear to violate the Curtin-Hammett Principle [14(a),14(b)] which states that provided the activation energy of the reaction is large compared with the barrier to rotation (which is almost certainly the case), the proportion of the products in no way reflects the relative population of the ground state conformations but depends only on the activation energies of the processes leading to these products. It thus appears that the steric requirements for azetidine formation are considerably more complex than the approach of Gaertner[16,17] and Gaj and Moore[19] would suggest. Furthermore, the yields obtained by the latter[19] for R ≠ CH_3 (Scheme 3) were low (4-23%) thus making it difficult to assess the mechanistic significance which may be placed on these yields, especially in view of the fact that the other products were not determined. Since fragmentation is unlikely for primary halides,[13] the major side reaction would be expected to be that of dimerization or polymerization. These could presumably be minimized by using high dilution techniques.

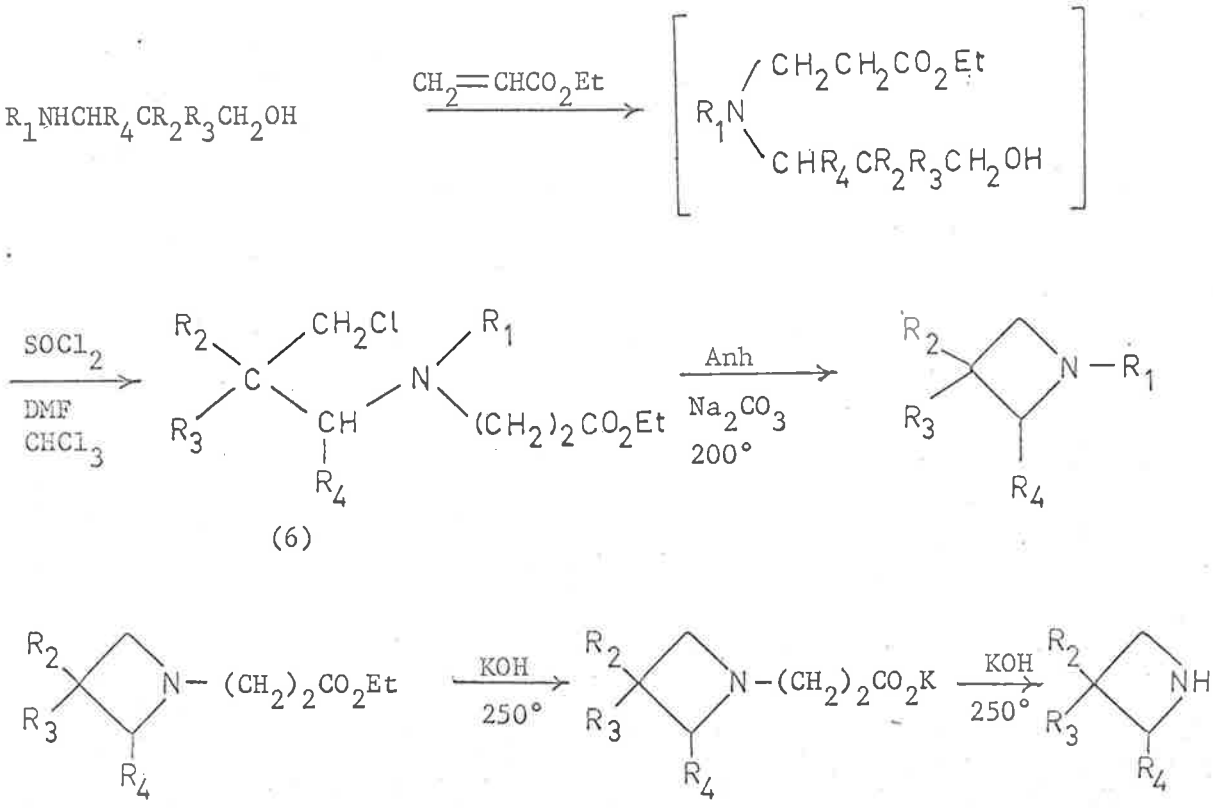
The parent azetidin-3-ol has recently been prepared[18] by the cyclization of 3-chloro-1-diphenylmethylamino-2-hydroxypropane (4) to give 1-diphenylmethylazetidin-3-ol (5), followed by hydrogenolysis with palladium/carbon.



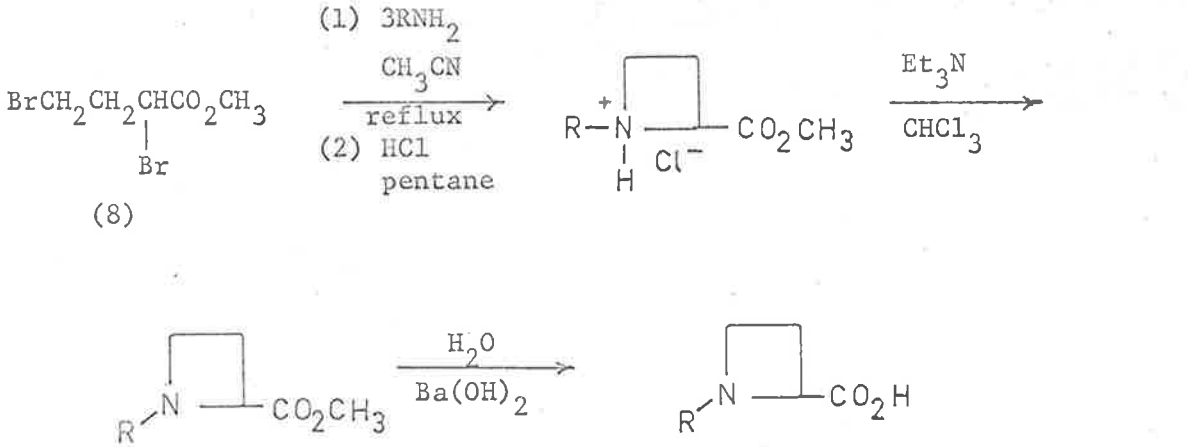
Scheme 4

A method for the preparation of azetidine and its lower homologs by the cyclization of the appropriate *N*-substituted *N*-(2-carbethoxy-ethyl)-3-aminopropyl chlorides (6) in the presence of sodium carbonate followed by saponification and subsequent cleavage of 1-(2-carbethoxyethyl)azetidines has been described.[20] This sequence is summarized in Scheme 5.

1-Alkyl-2-carbomethoxyazetidines (7) have been prepared by refluxing methyl α,γ-dibromobutyrate (8) with alkylamines.[21] Basic hydrolysis of the esters gave the corresponding acids.

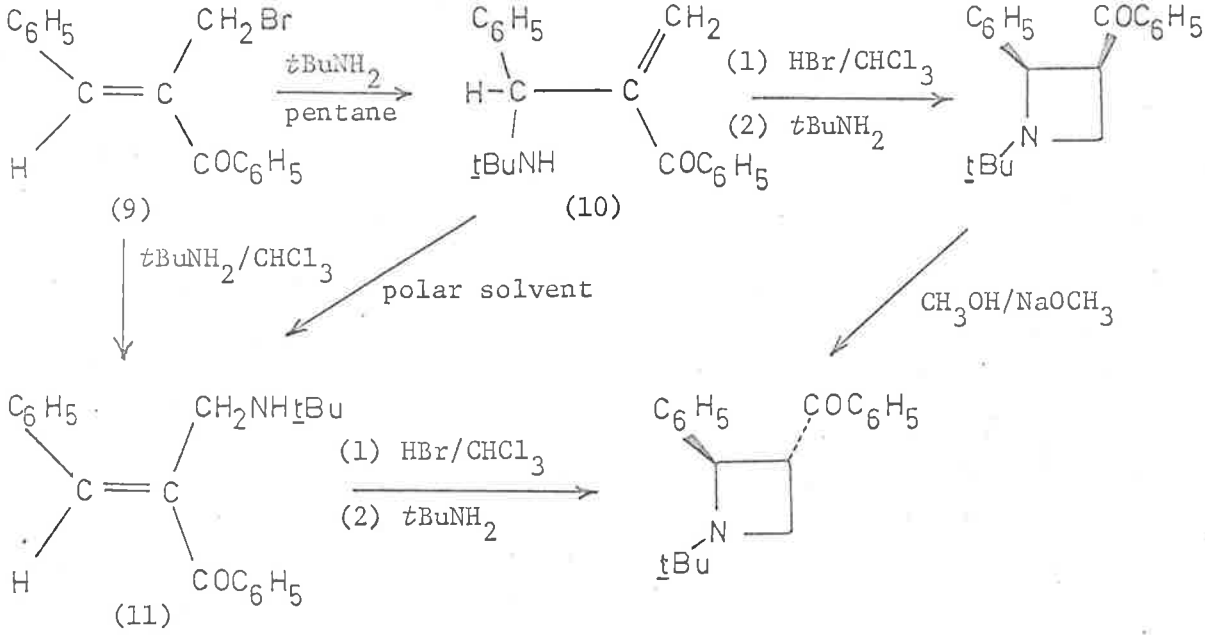


Scheme 5



Scheme 6

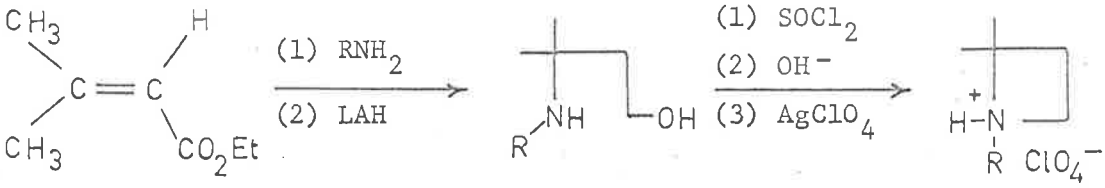
Cromwell[22,23] has found that *trans*-α-(bromomethyl)chalcone (9) reacts with *tert*-butylamine in pentane to give 2-[α-(N-*tert*-butylamino)-benzyl]acrylophenone (10) as the kinetically favoured product which readily rearranges in more polar solvents to the thermodynamically more stable α-[(-*tert*-butylamino)methyl]chalcone (11). Treatment of the acrylophenone or chalcone with hydrogen bromide followed by reaction with base produced the *cis*- and *trans*-1-*tert*-butyl-2-phenyl-3-benzoylazetidines respectively. The mechanism of



Scheme 7

the reaction leading to these stereospecific cyclizations to produce the arylaroylazetidines are discussed by Cromwell[23] by applying the views of Grob[13] and Vaughan.[15]

Silver perchlorate has been found to facilitate the cyclization of some γ-chloroamines to the azetidinium salts.[24] A typical scheme is shown below.

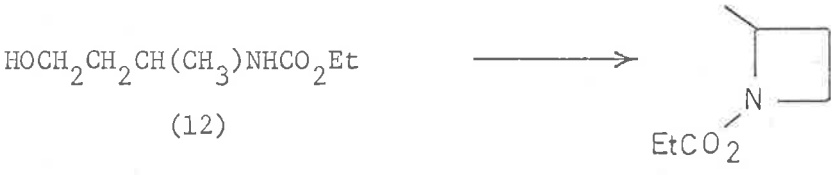


Scheme 8

(2) Cyclization of 3-aminoalkylsulphates

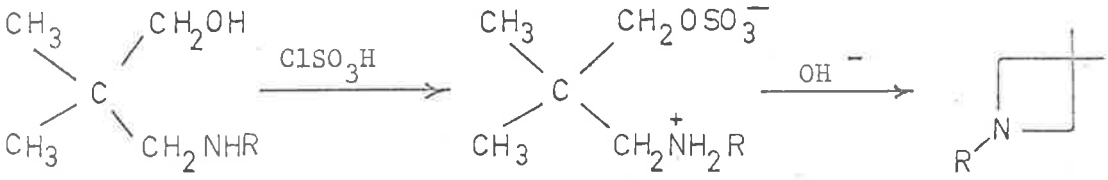
Treatment of a 3-amino-alcohol with concentrated sulphuric acid or treatment of the amine hydrochloride with chlorosulphonic acid[25] gives the sulphate esters which, on treatment with base, give the azetidines, generally in very low yields. This should be compared with the cyclization of β-aminoethyl hydrogen sulphate to the aziridine in nearly quantitative yield.[26]

The direct conversion of a 3-amino alcohol into an azetidine has not been reported although a hydroxyurethane (12) undergoes ring closure to the azetidine on heating.[29]



Scheme 9

Anderson[27(a)] found that dipolar salts were obtained in good yields when amino alcohols were treated according to the procedure of Reeves and Guthrie[28] (chlorosulphonic acid and carbon tetrachloride). Treatment of these inner salts (13) with aqueous alkali formed the corresponding azetidines in excellent yields (84-92%). The sequence is shown in Scheme 10.



(13)

R = CH_3, CH_2Ph, $CH(Ph)CH_2Ph$

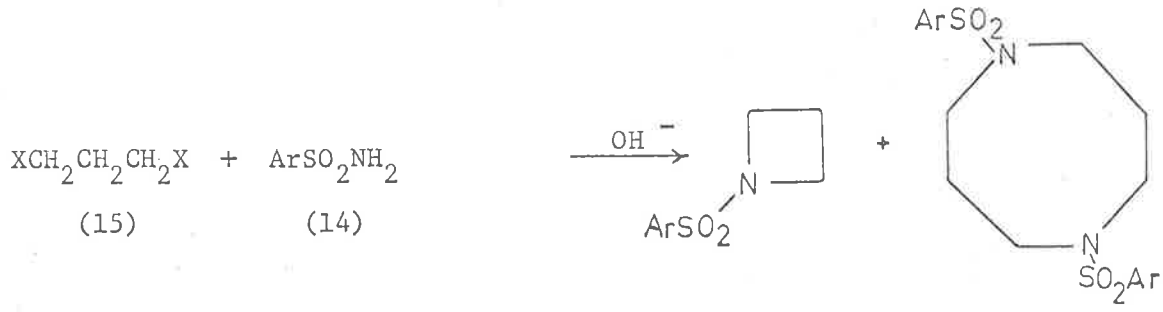
Scheme 10

(3) Cyclization of 1,3-diamines

Although five- and six-membered cyclic amines have often been successfully prepared by the thermal decomposition of diamine hydrochlorides, no satisfactory syntheses of azetidines have been reported by this method.[29]

(4) Cyclization to 1-(arylsulphonyl)azetidines

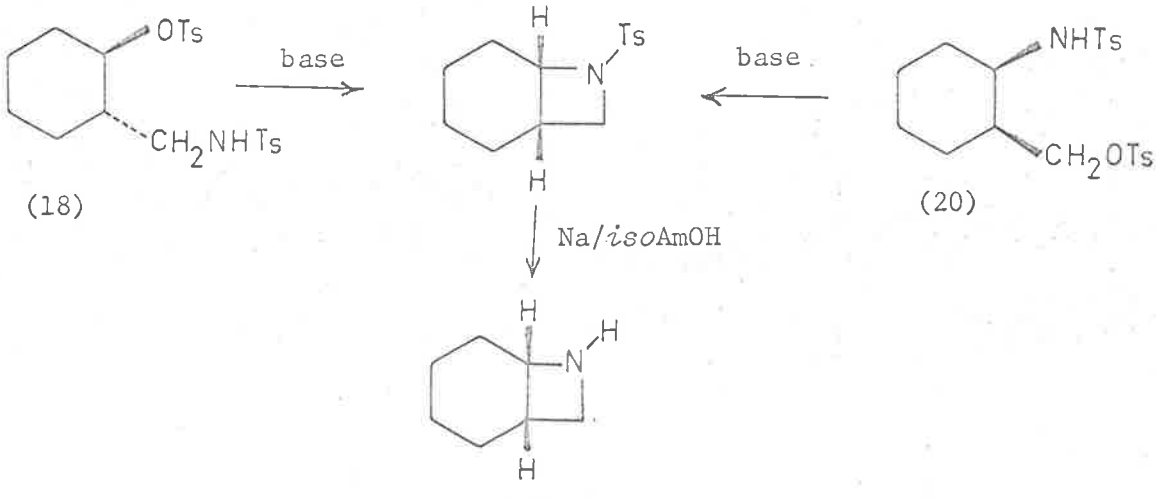
This method involves dialkylation of a sulphonamide (14) by a 1,3-dihalide (15)[5] and is particularly useful for the synthesis of the parent azetidine since it is possible to reduce the sulphonamide to the free amine. The reduction has been accomplished in low yield

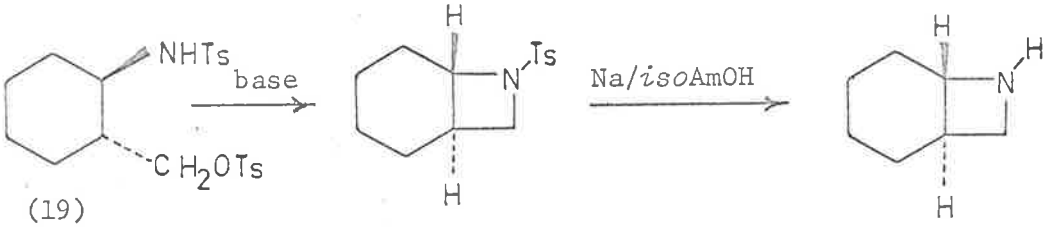


Scheme 11

with sodium in liquid ammonia[30] and with lithium aluminium hydride.[31] Reduction with sodium and pentanol has been reported to occur in yields ranging from 14 to 80%.[7,32] Consistently good yields of azetidine have been obtained using sodium and amyl alcohol as the reducing agent under conditions of moderately high dilution.[15]

The preparation of *cis*- and *trans*-7-azabicyclo[4,2,0]-octane (16)(17) has been reported by Moriconi[53] by base treatment of *N*,*O*-ditosyl-*trans*-2-aminomethyl cyclohexanol (18) and *N*,*O*-ditosyl-*trans*-2-amino-cyclohexanemethanol (19) respectively followed by reductive detosylation with sodium and isoamyl alcohol. *N*,*O*-Ditosyl-*cis*-2-aminocyclohexanemethanol (20) also gave the *cis* azacyclobutane.



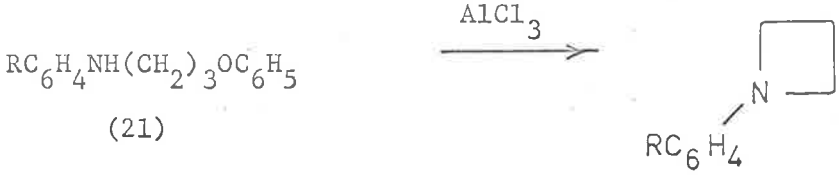


(19) (17)

Scheme 12

(5) 1-arylazetidines

A number of 1-arylazetidines have been synthesized in low yields by treating *N*-aryl-3-aminopropyl phenyl ethers (21) with aluminium chloride[34] as shown in Scheme 13.



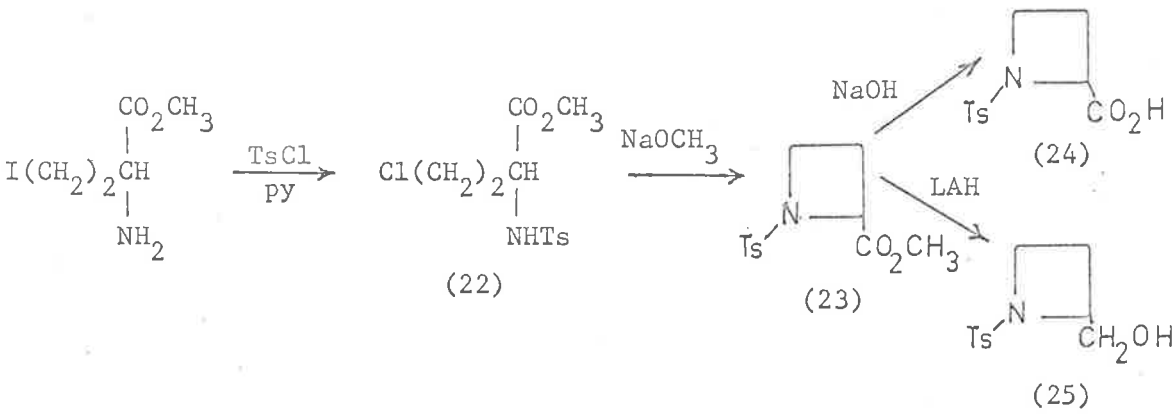
(21)

Scheme 13

(6) Functional derivatives of azetidines

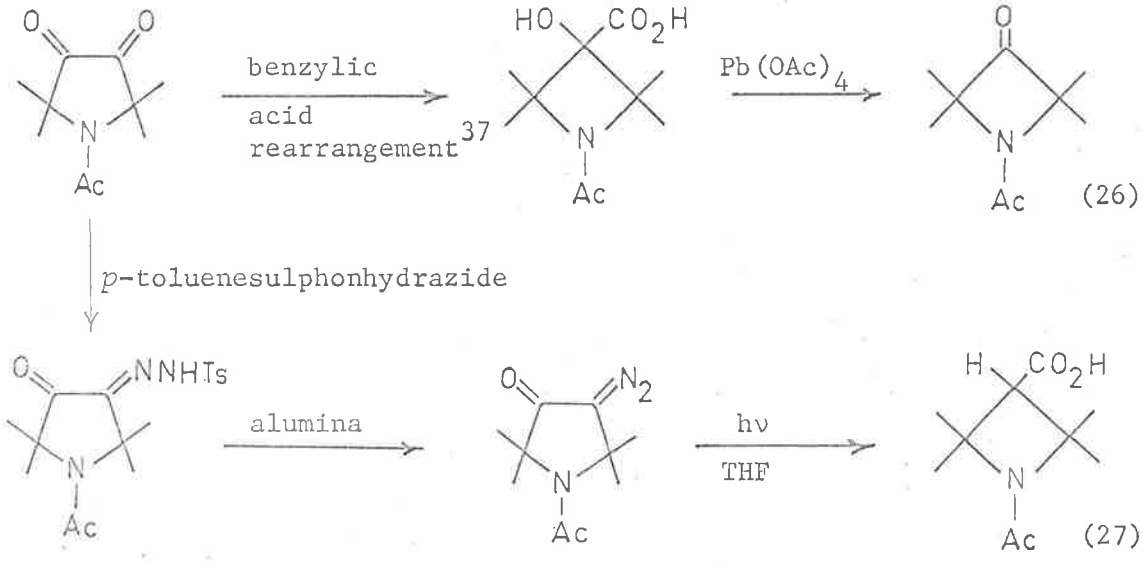
Except for 2-azetidinones, which are discussed below, there have been very few reports of azetidine derivatives with functional groups attached to the ring. Until the recently reported 2-carbomethoxyazetidines,[21] 3-acylazetidines[23] and 3-azetidinols,[16,17] which have been mentioned above, the only such derivatives known were condensed 3-azetidinones,[35,36] 1-acetyl-3-hydroxytetramethylazetidine-3-carboxylic acid[37] and azetidine-2-carboxylic acid.[38]

The sodium methoxide catalysed cyclization of methyl α-tosylamino-γ-chlorobutyrate (22) has been shown to give methyl 1-tosylazetidine-2-carboxylate (23).[39] Hydrolysis or lithium aluminium hydride reduction of the ester gave the corresponding acid (24) or carbinol (25) respectively. 1-Acetyl-2,2,4,4-tetramethyl-3-azetidinone



Scheme 14

(26) and 1-acetyl-2,2,4,4-tetramethyl-3-carboxylic acid (27) have been prepared by the same workers[39] by the methods shown in Scheme 15.

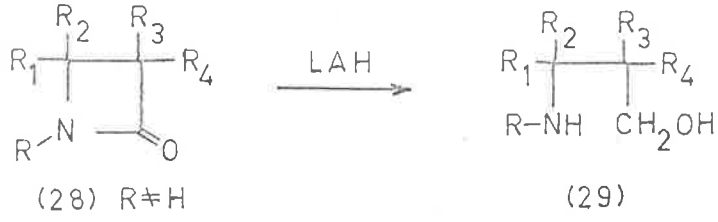


Scheme 15

During a study of the tosylation of 1-substituted 3-azetidinols it was found that 1-*tert*-butyl-3-azetidinol gave predominantly 1-*tert*-butylazetidinyl-3-tosylate[40] (although 1-cyclohexyl-3-azetidinol gave mainly *N*-tosyl-1-cyclohexylamino-3-chloro-2-propanol). Treatment of the 1-*tert*-butylazetidinyl-3-tosylate with potassium cyanide in methanol gave the corresponding 3-cyanoazetidine which on subsequent hydrolysis with barium hydroxide afforded 1-*tert*-butylazetidine-3-carboxylic acid in good yield.[40] Similarly, 3-amino and 3-mercapto azetidine derivatives were obtained by the reaction of 1-*tert*-butylazetidinyl-3-tosylate with ammonia, primary and secondary amines, and mercaptans.[41]

(7) Reduction of 2-azetidinones

Although the reduction of lactams to the corresponding cyclic imines with lithium aluminium hydride proceeds in good yield with five-, six- and seven-membered rings, similar reduction of *N*-substituted 2-azetidinones (28) consistently yields the corresponding amino-propanols (29)[15,42,43] (Scheme 16). Reductive cleavage has also been



(28) R≠H (29)

Scheme 16

reported to occur with the reducing agents sodium borohydride, lithium borohydride, sodium borohydride-aluminium chloride and lithium borohydride-aluminium chloride.[15]

However, lithium aluminium hydride reduction of *N*-unsubstituted 2-azetidinones readily affords the corresponding azetidines in good yields.[44]

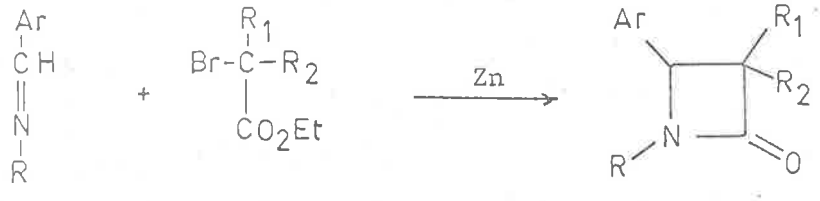
Lithium aluminium hydride reduction of 2-azetidinones is discussed in greater detail below.

2. The Synthesis of 2-Azetidinones

A number of methods are available for the preparation of 2-azetidinones and these have been reviewed elsewhere.[45,46] Only a brief mention will be made of those methods which were used to synthesize 2-azetidinones as starting materials for this work.

(1) The Reformatsky reaction

The reaction between an anil (30) and an α-bromoester (31) in the presence of zinc to yield a 2-azetidinone (32) was first observed by Gilman and Speeter[47] (scheme 17). Recent work has



(30) (31) (32)

Scheme 17

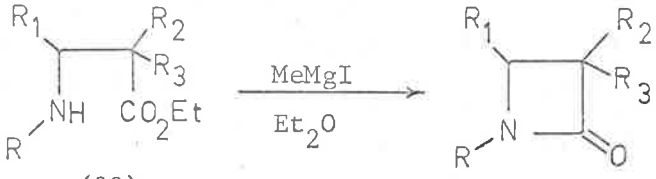
examined the reaction in greater detail so that the range of starting materials which may be used and also the stereochemistry of the products is now known.[46,48] It was anticipated that it should be possible to convert a 2-azetidinone into the corresponding azetidine

without cleavage of the ring or rearrangement of the substituents. In such a case, the stereochemistry of the azetidine would be known by correlation with the corresponding 2-azetidinone. Accordingly, the Reformatsky reaction was the method chosen for the synthesis of the 2-azetidinones.

However, the Reformatsky reaction can be used only for the preparation of *N*-substituted 2-azetidinones and therefore alternative procedures were required for the synthesis of *N*-unsubstituted 2-azetidinones.

(2) Cyclization of β-amino acid esters

Treatment of a β-amino acid ester (33) with a Grignard reagent, usually methyl magnesium iodide, results in the formation of the corresponding 2-azetidinone (Scheme 18). This reaction, which



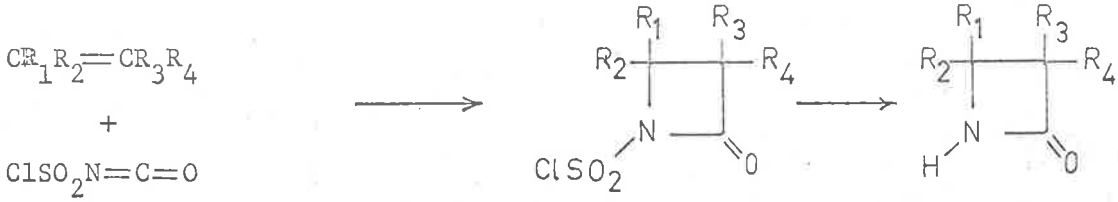
(33)

Scheme 18

has been studied in detail by Testa and coworkers,[49,50] provides the only general method of preparing *N*-unsubstituted 2-azetidinones, although the yields are frequently poor. Several compounds required in the present work were synthesized by this route.

(3) Cyclization of isocyanates and olefins

Graf[51,52] has found that chlorosulphonylisocyanate (34) reacts with olefins to form 1-chlorosulphonyl-2-azetidinones (35). Subsequent removal of the chlorosulphonyl group has been accomplished



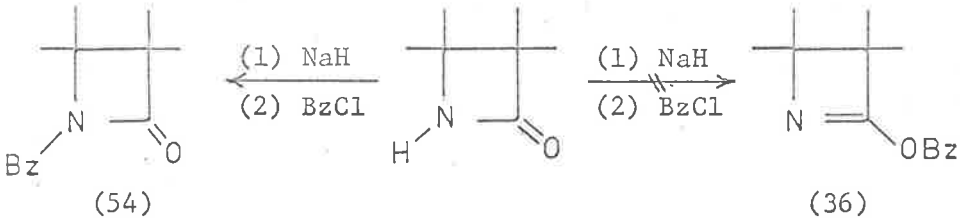
Scheme 19

using thiophenol or sodium hydroxide under controlled conditions of temperature and pH.[51] This useful method of preparation of *N*-unsubstituted 2-azetidinones is limited only by the availability of suitable olefins. Moriconi[33] has discussed possible mechanisms of this addition reaction.

II. DISCUSSION AND RESULTS

1. *N*-Methylation and *N*-benzylation of 2-azetidinones

For reasons mentioned below it was found necessary in one case and advantageous in the others to convert the *N*-unsubstituted 2-azetidinone into its corresponding *N*-methyl or *N*-benzyl derivative. This was accomplished by adding the 2-azetidinone dissolved in benzene, or better, dimethoxyethane, to a suspension of sodium hydride in the same solvent followed by methyl iodide or benzyl chloride.

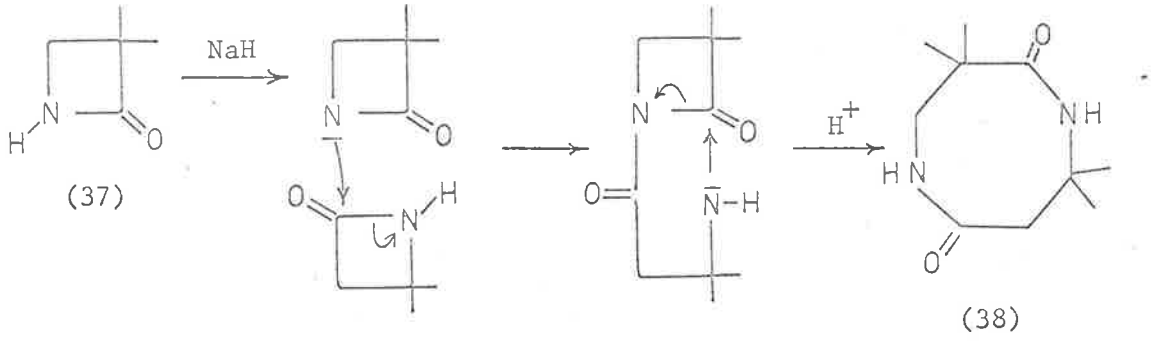


(54) (36)

Scheme 20

Theoretically, it would be possible for either *N*-alkylation or *O*-alkylation to result. As expected, only *N*-alkylation was observed as shown by the characteristic carbonyl absorption of the 2-azetidinone in the i.r. spectrum as well as the presence of an *N*-substituent in the n.m.r. spectrum. *O*-Alkylation would have resulted in the formation of a 1-azetine (36), where synthesis has only recently been accomplished under completely different conditions.[54]

In one case, a concentrated solution of 3,3-dimethyl-2-azetidinone (37) in dimethoxyethane was added to sodium hydride in dimethoxyethane and, instead of the expected product, a white solid, m.p. 235-240°, was obtained and tentatively assigned the structure (38). The n.m.r. spectrum of compound (38) showed a singlet at

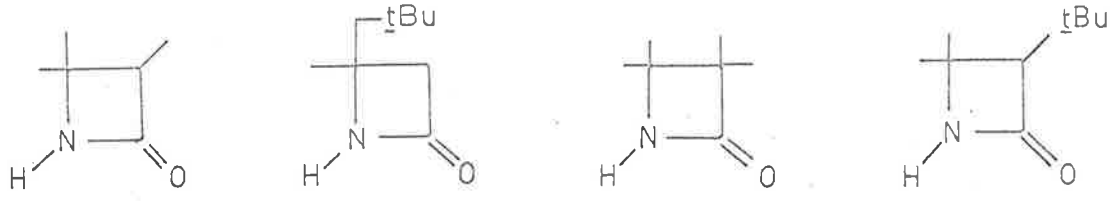


Scheme 21

δ 1.17 and a broad doublet centred at δ 3.25 in the ratio of 3:1. Since it was not sufficiently soluble in *o*-dichlorobenzene it was not possible to observe the effect on the doublet of increasing the temperature. The i.r. spectrum of compound (38) showed intense bands at 3380 cm^{-1} and 1648 cm^{-1} which were assigned to the N-H str. and the C=O str. respectively in the cyclic amide. It is equally probable that the compound may be a linear polyamide.

2. *N*-Unsubstituted azetidines

The reduction with lithium aluminium hydride (LAH) of *N*-unsubstituted 2-azetidinones,[44] which were prepared by the method of Testa,[49,50] proceeded in good yields. Using similar reaction



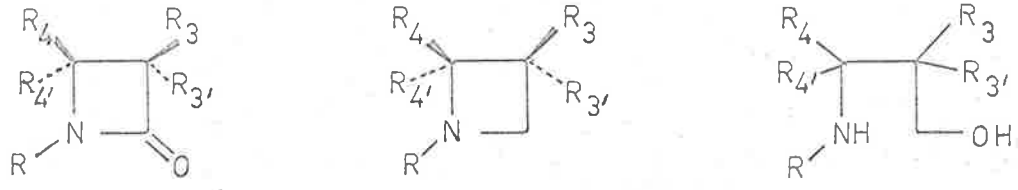
(39) (40) (41) (42)

Figure 3

conditions, compounds (39) and (40) were reduced in fair yields after refluxing in ether for 4 hours whereas compound (41) was reduced in low yield (30%) under the same conditions. 3-*tert*-Butyl-4,4-dimethyl-2-azetidinone (42) did not react even after refluxing with LAH in ether for 24 hours. Presumably the steric bulk of the *tert*-butyl group prevents the attack by LAH. In this case the oxygen atom is at position 6 relative to a hydrogen atom of the *tert*-butyl group and so, according to Newman's "rule of six",[55,56] reaction at this position would be expected to be slow. The azetidine corresponding to the 2-azetidinone (42) was desired since it would be expected to give a moderately simple ABX type n.m.r. spectrum. Accordingly, in view of the method of reduction of *N*-substituted 2-azetidinones discussed below, the 2-azetidinone (42) was converted to the *N*-benzyl derivative by the method outlined above.

3. *N*-Substituted azetidines

In spite of the repeated failures[15,42,43] to reduce 2-azetidinones [(43), R≠H] to the corresponding azetidines (44) [the corresponding



(43) (44) (45)

Figure 4

3-aminopropanol derivatives (45) were obtained in every case], this method still appeared to be the most attractive.

Brown[57] has reported that the reduction of tertiary amides to the corresponding amines with diborane proceeds without reductive cleavage of the carbon-nitrogen bond. Accordingly, the reaction of a number of 2-azetidinones with diborane was investigated. Since the use of sodium borohydride is known to result in the reductive cleavage of the carbon-nitrogen bond[15] in 2-azetidinones the diborane was generated externally. Initially diborane was generated from sodium borohydride and boron trifluoride etherate[58] but subsequently it was prepared from iodine and sodium borohydride in diglyme.[59]

Table I shows the results obtained on the reduction of several 2-azetidinones. The amino-alcohols were identified by comparison with authentic samples which were obtained by lithium aluminium hydride

TABLE I. Reduction of 2-Azetidinones with Diborane

Cpd.No.	2-Azetidinone (43) Substituents					% Azetidine (compound no.)		% Amino Alcohol	% Recovered 2-azetidinone
	R	R_3	$R_{3'}$	R_4	$R_{4'}$				
(46)	C_6H_5	CH_3	CH_3	C_6H_5	H	70%	(61)	0	5
(47)	C_6H_5	H	H	C_6H_5	H	60	(62)	5	30
(48)	C_6H_5	CH_3	CH_3	$(CH_3)_3C$	H	67	(63)	0	trace
(49c)	C_6H_5	CH_3	H	C_6H_5	H	70	(64)	trace	0
(50t)	C_6H_5	H	C_6H_5	C_6H_5	H	30[a]	(65)	20	0
(51)	C_6H_5	C_6H_5	C_6H_5	C_6H_5	C_6H_5	0	-	0	100
(52)	$(CH_3)_3C$	CH_3	CH_3	C_6H_5	H	70	(66)	0	10
(53)	$C_6H_5CH_2$	CH_3	CH_3	C_6H_5	H	60	(67)	0	5
(54)	$C_6H_5CH_2$	CH_3	CH_3	CH_3	CH_3	75	(68)	0	trace
(55)	$C_6H_5CH_2$	H	H	C_6H_5	H	35[a]	(69)	35	0
(56)	$C_6H_5CH_2$	$(CH_3)_3C$	H	CH_3	CH_3	60	(70)	0	0

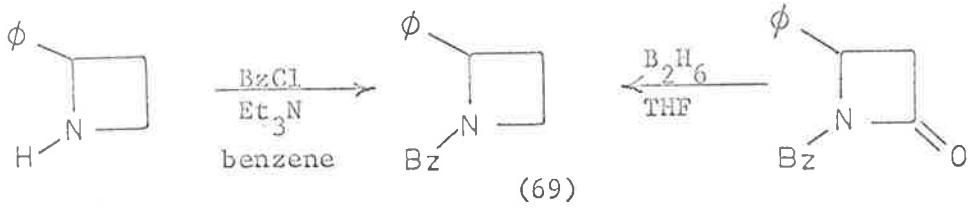
cont'd

cont'd

(57)	$pCH_3OC_6H_4CH_2$	CH_3	CH_3	C_6H_5	H	50	(71)	0	0
(58)	$C_6H_5(CH_2)_2$	CH_3	CH_3	C_6H_5	H	30	(72)	0	trace
(59)	$(CH_3)_2CH$	CH_3	CH_3	C_6H_5	H	40	(73)	0	45
(60)	$CH_3CH_2CH_2$	CH_3	CH_3	C_6H_5	H	30	(74)	0	0

[a] Yield estimated by v.p.c. and n.m.r. spectroscopy

reduction of the corresponding 2-azetidinone. The structures of the azetidines were confirmed by the usual physical methods, and, in particular, by the absence of bands in the i.r. spectra in the C=O str., N-H str. and O-H str. regions and their n.m.r. and mass spectra which are discussed in detail in Chapters 2 and 3 respectively. *N*-Benzyl-2-phenyl azetidine (69), prepared in this manner, was identical in all respects with an authentic sample of *N*-benzyl-2-phenyl azetidine[60] which was prepared from 2-phenyl azetidine and benzyl chloride (Scheme 22).



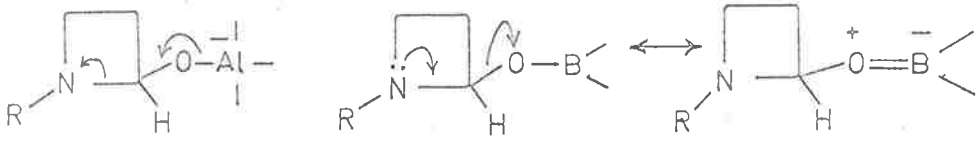
(69)

Scheme 22

From Table I it can be seen that diborane reduces a variety of *N*-substituted 2-azetidinones to the corresponding azetidines in good yields, and since diastereomeric pairs of 2-substituted 2-azetidinones are readily available,[46,48] reduction with diborane provides a convenient and versatile synthesis of azetidine derivatives of known stereochemistry.

Attempted reduction of *N*-unsubstituted 2-azetidinones and *N*-methyl-2-azetidinones with diborane yielded only aminopropanol derivatives, unchanged starting material and, occasionally, polymeric material.

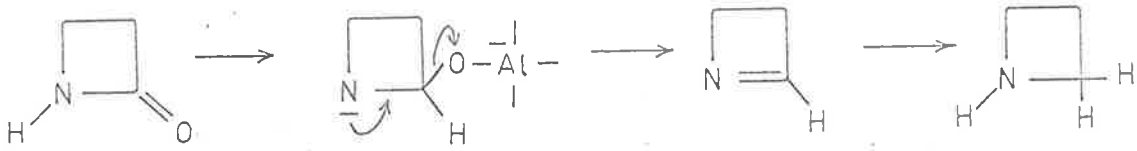
The behaviour of diborane in the reduction of 2-azetidinones is almost complementary to that of lithium aluminium hydride and the nature of the intermediate organometallic complexes (75) and (76) in the two reactions provides a plausible explanation for this behaviour.



(75) (76) (77)

Figure 5

The decomposition of the complexes (75) and (76) would be expected to be controlled by the availability of the lone pair of electrons on the nitrogen atom and the strength of the O-Al- or O-B bond. It is well-known that reductive cleavage[61] is favoured in *N*,*N*-disubstituted acyclic amides when at least one of the groups is electron-withdrawing. In the case where the nitrogen substituent is hydrogen, reduction of the 2-azetidinone to the azetidine with LAH may be explained by considering that the relatively easy loss of a proton from the nitrogen atom would favour carbon-oxygen bond cleavage rather than carbon-nitrogen bond cleavage (Scheme 23).[62]



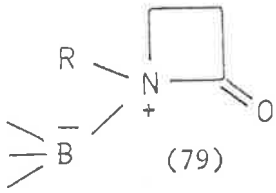
(78)

Scheme 23

For a particular nitrogen substituent, R, the difference in the reduction products obtained with lithium aluminium hydride and diborane must depend on the relative bond strengths of the O-Al- and O-B bonds. Dipolar structures such as (77) (Figure 5) would contribute to the strength of the B-O bond and facilitate the elimination reaction (76) to give the intermediate ketimines, which on further reduction would yield the *N*-substituted azetidine, in contrast to the cleavage of the relatively weaker O-Al bond (75) to form the amino-aldehyde. Further reduction of amino-aldehydes would produce the 3-aminopropanols. Dipolar structures such as (77) have recently been considered to be one of the contributing factors to the driving force involved in the conversion of ketones to hydrocarbons by diborane.[63] There has also been some recent evidence supporting B-O π-bonding in dimethylboric anhydride.[64]

The reductive cleavage of *N*-unsubstituted or *N*-methyl-2-azetidinones with diborane may reasonably be ascribed to the formation of a complex between borine (BH_3) and the amide nitrogen (79) which

would be sterically unfavourable in compounds with bulkier nitrogen and ring substituents.[65] The ring cleavage reaction would then be favoured by the presence of a quaternary nitrogen atom.



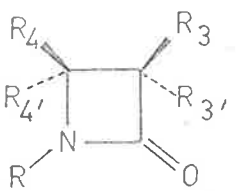
(79)

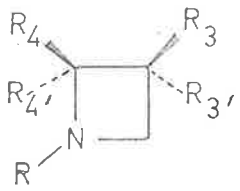
Figure 6

It was thought that since aluminium hydride is related to lithium aluminium hydride as diborane is to sodium borohydride and since lithium aluminium hydride[15,42,43,44] and sodium borohydride[15] both result in reductive cleavage of the *N*-substituted 2-azetidinones then aluminium hydride might have the same reducing properties as diborane. One might conceivably imagine that the initial attack by the Lewis acids aluminium hydride and diborane would be on the oxygen atom whereas that of the ionic hydrides might be on the carbon atom of the carbonyl group.[66] Thus a number of 2-azetidinones were treated with aluminium hydride and the results obtained are shown in Table II.

The results recorded in Table II show that aluminium hydride is a very good reducing agent for converting *N*-substituted 2-azetidinones to the corresponding azetidines. A comparison of the yield of a particular azetidine from the corresponding 2-azetidinone using aluminium hydride as the reducing agent (Table II) with that obtained using diborane as the reducing agent (Table I) reveals that the yield using the former

TABLE II. Reduction of 2-Azetidinones with Aluminium Hydride





Substituents					2-Azetidinone	% yield of	Azetidine
R	R_3	$R_{3'}$	R_4	$R_{4'}$	Cpd.No.	Azetidine	Cpd.No.
$C_6H_5CH_2$	CH_3	CH_3	CH_3	CH_3	(54)	80%	(68)
$(CH_3)_2CH$	CH_3	CH_3	C_6H_5	H	(59)	80	(73)
$CH_3CH_2CH_2$	CH_3	CH_3	C_6H_5	H	(60)	70	(74)
CH_3	C_6H_5	H	H	C_6H_5	(80t)	50	(86t)
CH_3	CH_3	CH_3	C_6H_5	H	(81)	65	(87)
C_6H_5	$(CH_3)_3C$	H	C_6H_5	H	(82c)	75	(88c)
C_6H_5	H	$(CH_3)_3C$	C_6H_5	H	(82t)	70	(88t)

cont'd

cont'd

$CH_3CH_2CH_2$	CH_3	CH_3	CH_3	H	(83)	73	(89)
CH_3	$(CH_3)_2CH$	H	H	C_6H_5	(84t)	73	(90t)
C_6H_5	C_6H_5	H	H	C_6H_5	(50t)	70	(65t)
C_6H_5	CH_3	CH_3	C_6H_5	H	(46)	75	(61)
$(CH_3)_3C$	CH_3	CH_3	C_6H_5	H	(52)	80	(66)
$C_6H_5CH_2CH_2$	CH_3	CH_3	C_6H_5	H	(58)	75	(72)
C_6H_5	CH_3	CH_3	$(CH_3)_3C$	H	(48)	75	(63)
$C_6H_5CH_2$	CH_3	CH_3	C_6H_5	H	(53)	60	(67)
$C_6H_5CH_2$	$(CH_3)_3C$	H	CH_3	CH_3	(56)	79	(70)
C_6H_5	CH_3	H	C_6H_5	H	(49c)	70	(64c)
CH_3	CH_3	CH_3	CH_3	CH_3	(85)	50	(91)

is always as good as, and in most cases better than that obtained with the latter. Furthermore, 3-aminoalcohols were detected in the reduction with aluminium hydride of only two 2-azetidinones (46) and (50t) [t means the *trans* isomer, c the *cis* isomer]. The yields of azetidines reported in Table II are those of the pure compound, except for the azetidines (61) and (65t), which were contaminated by about 15% and less than 3% of the corresponding 3-aminoalcohols, respectively, as shown by v.p.c. and n.m.r. spectroscopy.

It may be significant mechanistically, and it is certainly useful synthetically, that *N*-methyl 2-azetidinones [(80t), (81), (84t) and (85)] are reduced with aluminium hydride in satisfactory yields to the corresponding azetidines (86t), (87), (90t) and (91). The physical characteristics of compound (87) were identical to those reported for 1,3,3-trimethyl-2-phenylazetidine[27(b)] prepared by a completely different procedure. No azetidines could be isolated from the reaction of *N*-unsubstituted 2-azetidinones. If our postulate that *N*-methyl 2-azetidinones complex with borine in the reduction with diborane, thus favouring ring cleavage, is correct, then the successful reduction of *N*-methyl 2-azetidinones with aluminium hydride would imply that aluminium hydride does not complex with the nitrogen atom of 2-azetidinones as readily as does borine. If it is assumed that a 2-azetidinone is a soft base then, according to Pearson's principle of hard and soft acids and bases (HSAB),[67,68] it should complex more readily with the soft acid borine than with the hard

acid aluminium hydride. However, the use of this argument requires considerable caution.[68,69] Although we have no direct evidence that borine complexes more readily than aluminium hydride to the nitrogen atom of 2-azetidinones it would seem fairly clear that borine complexes more readily than aluminium hydride to azetidines, (this is the opposite to that predicted by HSAB if an azetidine is assumed to be a hard base). When *N*-benzyl-3-*tert*-butyl-4,4-dimethyl-2-azetidinone (56) was treated with an excess of diborane it gave a white solid whose analysis figures best fitted the molecular formula $C_{16}H_{25}N.BH_3$ which was assigned structure (92). This complex was very stable to treatment

(92) (93)

Figure 7

with 10% sodium hydroxide solution and decomposed slowly on heating under reduced pressure (0.5 mm) to the azetidine (70) and diborane. The i.r. spectrum showed a very intense band at 2400 cm^{-1} with shoulders at 2340 cm^{-1} and 2300 cm^{-1} in carbon tetrachloride which may be assigned to the B-H str. vibrations.[70] Treatment of *N*-benzyl-2,2,3,3-tetramethylazetidine (68) with a solution of diborane also yielded the corresponding borine complex (93), which was reasonably stable.

It decomposed on treatment with 10% sodium hydroxide solution and also on heating under reduced pressure to the azetidine (68). Again the i.r. spectrum showed intense bands at 2410 cm^{-1} with shoulders at 2350 cm^{-1} and 2290 cm^{-1}. The n.m.r. spectrum of compound (93) showed sharp singlets at δ 1.50 (two methyl groups), δ 1.44 (one methyl group) and δ 1.07 (one methyl group) and two AB quartets, one for the ring methylene protons and one for the benzylic methylene protons with a coupling constant of -10.0 c.p.s. for the ring methylene protons. This value is numerically greater (more negative) than that for normal azetidines [-6 to -7 c.p.s. (see below)], as would be expected if the nitrogen atom has some positive charge.[71] A coupling constant of -10.0 c.p.s. for the ring methylene protons of the hydrochloride of compound (68) was also observed. The treatment of compound (56) with excess aluminium hydride under similar conditions gave the pure azetidine (70) with no complex being observed, i.e. the aluminium hydride complex appears to be much less stable than the borine complex.

The solutions of aluminium hydride used in this study were prepared by treating three moles of lithium aluminium hydride in ether with one mole of aluminium chloride[72] and filtering the solution to

$$3LiAlH_4 + AlCl_3 \longrightarrow 4AlH_3 + 3LiCl$$

remove the precipitated lithium chloride. It is known that ether solutions of aluminium hydride prepared in this manner are metastable with the aluminium hydride forming a polymer which precipitates out

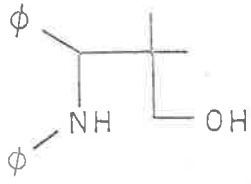
$$xAlH_3 \longrightarrow (AlH_3)_x$$

of solution.[72,73] However, this was not a major problem in this case since the reduction of the 2-azetidinones occurred more rapidly than the polymerization. In most cases reduction was essentially complete after fifteen minutes whereas formation of a white precipitate from the filtered solution of aluminium hydride in ether did not usually become serious until after this time. Accordingly, it was not found necessary to prepare the aluminium hydride solutions from 100% sulphuric acid and lithium aluminium hydride in tetrahydrofuran,[66] a method which is reported to give more stable solutions of aluminium hydride. Brown[66,75] has recently studied some applications of aluminium hydride for the reduction of other organic compounds.

Since diborane and aluminium hydride both reduce *N*-substituted 2-azetidinones to the azetidines, without carbon-nitrogen bond cleavage to the 3-aminopropanols, it seemed difficult to explain why Vaughan[15] obtained only the 3-aminoalcohol when 3,3-dimethyl-1,4-diphenyl-2-azetidinone (46) was reduced with mixed hydrides such as sodium borohydride and aluminium chloride. We found that the reduction of compound (46) with sodium borohydride and aluminium chloride in the

$$3NaBH_4 + AlCl_3 \longrightarrow 3NaCl + AlH_3 + 3BH_3$$

molar ratio of 3:1 gave a mixture of the azetidine (61) and the 3-aminopropanol (94) in the ratio of 1:2. Although Vaughan did not report the molar ratios of sodium borohydride to aluminium chloride



(94)

Figure 8

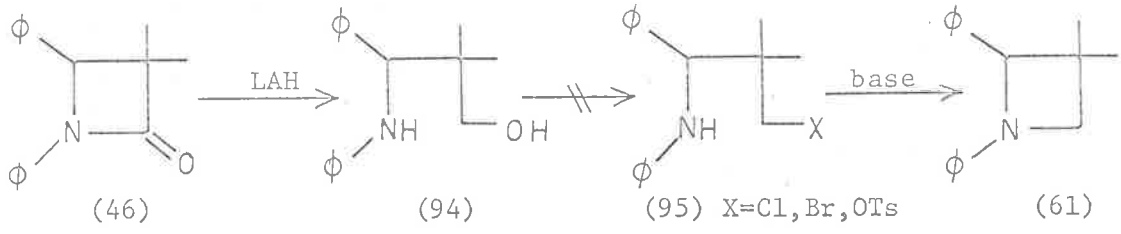
which he used, it is probable that he used a ratio different from that of 3:1, in which case the 3-aminopropanol could well be the only observed product. V.p.c. and n.m.r. spectroscopy showed that only pure azetidine was formed when the 2-azetidinone (46) was treated with a mixture of lithium aluminium hydride and aluminium chloride (3:1).

4. Attempted Syntheses of Azetidines

(1) 3-Haloamines and tosylates of aminopropanols

It was mentioned above that in the preparation of azetidines from 3-haloamines by treatment with base ~~that~~ a number of competing reactions reduced the yield or even precluded the formation of the azetidines. Apart from these factors, it is often difficult to prepare suitably substituted 3-haloamines for conversion to an azetidine with the desired substituents. Therefore it was thought that the lithium aluminium hydride reduction of an *N*-substituted 2-azetidinone to the corresponding 3-aminopropanol would provide a suitable starting material which could subsequently be converted to the azetidine *via* the

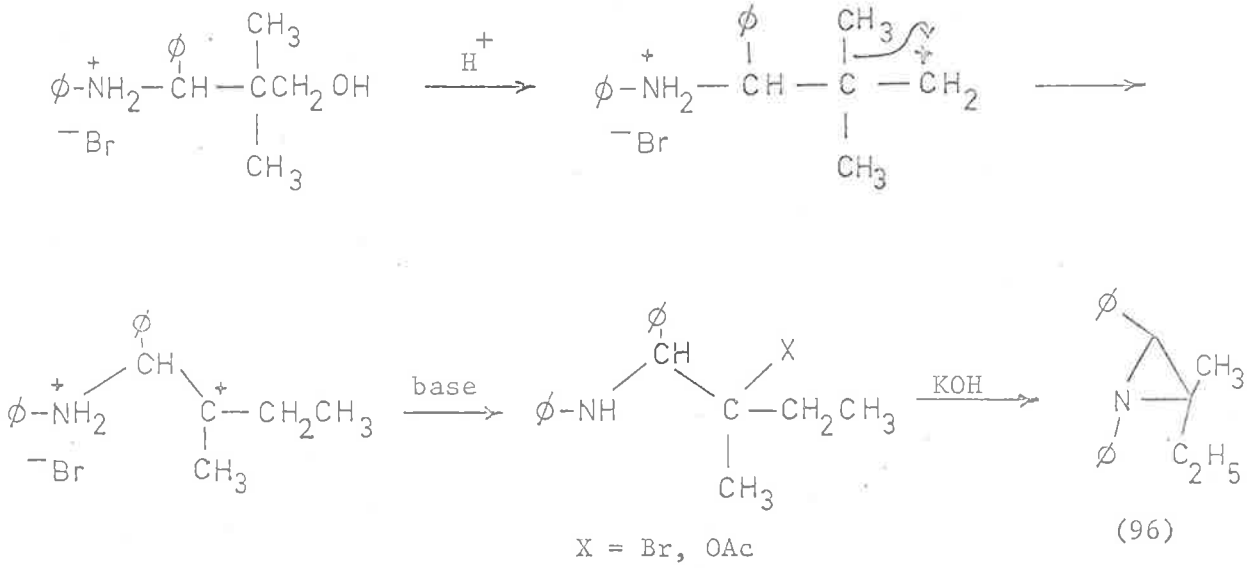
3-haloamine. Initially, 3,3-dimethyl-4-phenyl-2-azetidinone (46) was chosen as the starting material since it was thought that the 3-haloamine (95) would then undergo ring closure on treatment with base, rather than a β-elimination reaction.



(46) (94) (95) X=Cl,Br,OTs (61)

Scheme 24

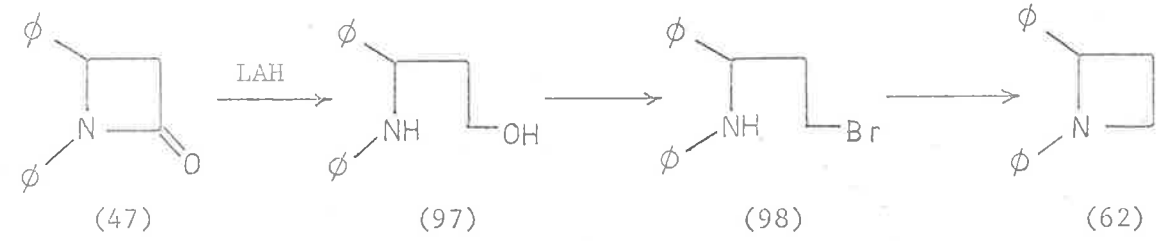
All attempts to convert the 3-aminoalcohol (94) into the 3-haloamine (95) using either hydrogen bromide in acetic acid,[8] 48% hydrobromic acid or phosphorous tribromide in ether[77] were unsuccessful; a blue oil, from which no pure compound could be isolated, was obtained in each case. Since the alcohol (94) resembles *neo*-pentyl alcohol, it might be expected that some methyl migration could occur. The n.m.r. spectrum of the mixture of compounds, which were obtained after treating the blue oil with base, indicated that some methyl migration had occurred, since there was now an ethyl group present. There were also other peaks which could have been assigned to the aziridine (96). The sequence shown in Scheme 25 is merely a suggested possible one with even the final product (96) doubtful. The reaction.



Scheme 25

of compound (94) with thionyl chloride gave several compounds from which a colourless liquid was obtained but the structures of these compounds have not been established.

Attempts to convert the amino-alcohol (97), obtained from 1,4-diphenyl-2-azetidinone (47), to the corresponding 3-bromoamine (98)

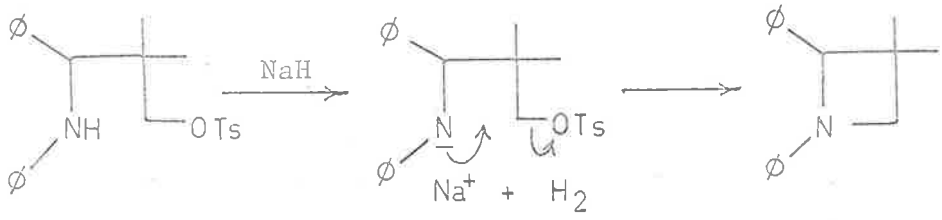


Scheme 26

were only slightly more successful. The hydrobromide of compound (98) was obtained in good yield by heating compound (97) in a sealed tube with 48% hydrobromic acid for 10 hours at 170°. Compound (98) was then obtained by treating the hydrobromide with dilute sodium bicarbonate solution and quickly extracting it with ether. Compound (98) was treated under a variety of conditions with base without further purification. The best yield of a yellow liquid was obtained by leaving compound (98) at room temperature for 10 hours with a 25% solution of potassium hydroxide although even then the yield was only 10%. However, much of the other material was the amino-alcohol (97) which could then be recycled. The colourless liquid was subsequently shown to be the azetidine (62) by comparison with a sample prepared by aluminium hydride reduction of compound (47).

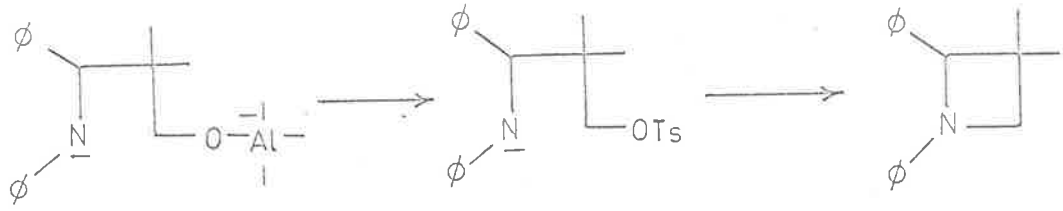
Only trace amounts of what was presumably the tosylate of compound (94) could be detected by t.l.c. when the amino-alcohol (94) (Scheme 24) was treated with *p*-toluenesulphonyl chloride in pyridine under a number of different conditions. In every case an almost quantitative recovery of the amino-alcohol (94) was obtained. In one case, when the 2-azetidinone (46) was reduced with lithium aluminium hydride and then the reaction mixture treated with *p*-toluenesulphonyl chloride, very small amounts of the azetidine (61) were detected by t.l.c. and v.p.c. together with the amino-alcohol (94). No azetidine (61) could be detected on subsequent reactions. Benzyl alcohols have been converted to their tosylates using sodium hydride[78] and therefore the amino-alcohol (94) was treated with sodium hydride at -20° under nitrogen and then a solution of *p*-toluenesulphonyl chloride added.

The isolated material was shown to be a mixture of two compounds by t.l.c. and they were separated by preparative t.l.c. under nitrogen and shown to be recovered starting material (85%) and the azetidine (61) (5%) by comparison with authentic samples. The formation of the azetidine could be explained by a base catalyzed ring closure as shown in Scheme 27. However, it is difficult to explain why no



Scheme 27

ditosylate was detected nor why such a small yield of the azetidine (61) was obtained if this is a favoured reaction. Apparently the only possible explanation must be that the monotosylate is very difficult to form under these conditions and that the ditosylate is even more difficult. The formation of the small amount of the azetidine (61) observed in the reaction of *p*-toluenesulphonyl chloride with the crude LAH reduction mixture could also possibly be explained by a similar base catalyzed ring closure as shown in Scheme 28.



Scheme 28

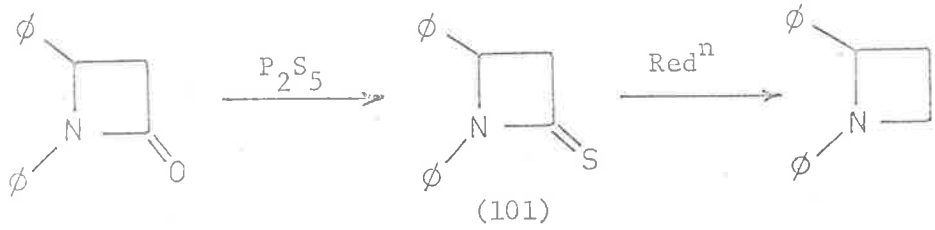
(2) Reduction of 2-azetidinethiones

Thioamides (99) have been reduced under a variety of conditions to the corresponding amines (100).[79,80] Several 2-azetidinones have

(99) (100)

Scheme 29

been converted to the 2-azetidinethiones with phosphorus pentasulphide.[81,82] Accordingly, it was thought that the sequence shown in Scheme 30 might be a possible method of preparing azetidines.



(101)

Scheme 30

Since it was known that some azetidines are unstable under acid conditions[29] it was decided that a neutral or basic medium would be desirable and therefore the reduction of the 2-azetidinethione (101) with Raney nickel was investigated.

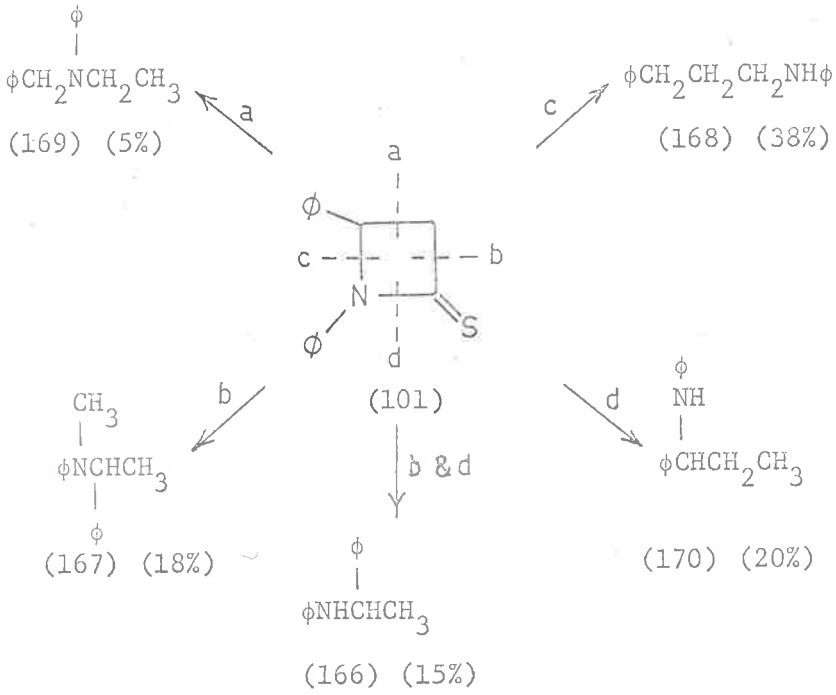
When compound (101) was treated with Raney nickel (W4) or degassed Raney nickel under a variety of different conditions either the 2-azetidinethione was recovered unchanged or a mixture of at least six products were obtained, none of which was the required azetidine. In the latter case five fractions were collected by preparative v.p.c. and three compounds were obtained in the pure state. The n.m.r. spectral data and structures of these compounds (166), (167) and (168) are given in Table III and Scheme 31 respectively. All compounds were basic and contained nitrogen. There was an intense band at 3400-3500 cm^{-1} in the i.r. spectra of all compounds except compound (167) corresponding to an N-H str. vibration and all compounds had similar u.v. spectra. The n.m.r. spectrum of one of the impure compounds showed the presence of an *N*-benzyl and possibly an *N*-ethyl group and therefore one of the compounds was assigned structure (169). The n.m.r. spectrum of the other impure fraction indicated the presence of a $-CHCH_2CH_3$ group and therefore the major component in this fraction was assigned structure (170). On the basis of the above facts it would appear that the products were derived from the cleavage of each of the four bonds of the four-membered ring as shown in Scheme 31.

TABLE III. N.m.r. Spectral Data of Compounds (166), (167) and (168)

Cpd.No.	Absorption (δ from TMS)		Assignment	Multiplicity
(166)	1.5	(3 protons)	CH_3	doublet (J = 7 c.p.s.)
	3.4	(1)	N-H	singlet
	4.4	(1)	CH	quartet (J = 7)
	6.4-7.2	(10)	Aromatics	multiplet
(167)	1.5	(3)	CH_3	doublet (J = 7)
	3.0	(3)	$N-CH_3$	singlet
	4.7	(1)	CH	quartet (J = 7)
	6.5-7.2	(10)	Aromatics	multiplet
(168)	1.8	(2)	CH_2	quartet*
	2.6	(2)	CH_2	doublet*
	3.0	(2)	CH_2	triplet*
	2.8	(1)	N-H	singlet
	6.4-7.2	(10)	Aromatics	multiplet

* Under fast scan

The approximate yields, which varied slightly with conditions of the reactions, are shown in brackets. Compound (168) was identical in all respects to that obtained by hydrogenation of the anil of cinnamaldehyde and aniline. It is possible that one of the other products in either of the two impure fractions was an acyclic thioamide



Scheme 31

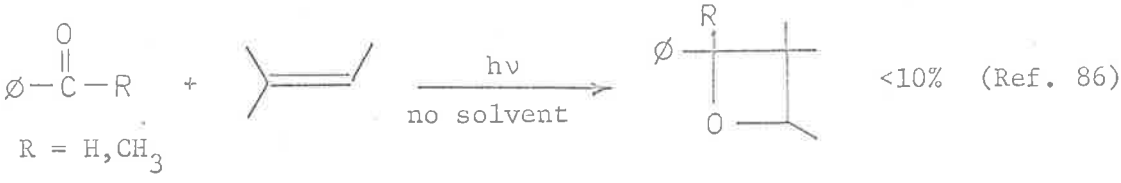
since in several runs, although not in most of them, the presence of sulphur was detected in one of these two fractions.

Aluminium amalgam[83] has been used to reduce thioamides to the corresponding amine. However, in this case the reaction of the compound (101) with aluminium amalgam gave the same mixture of at least six compounds in about the same ratio as did Raney nickel.

(3) Photochemical methods

A number of four-membered ring compounds have been synthesized by photochemical methods[84,85] although when this work was commenced there had been no reports on the synthesis of azetidines by this means. In view of the readily available potential starting materials the possibility of a photochemical synthesis appeared to be an attractive one.

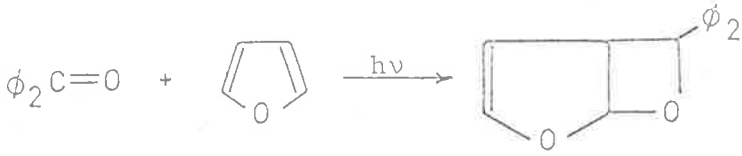
The photolysis of aldehydes or ketones in the presence of an olefin has been found to be a good method of preparing oxetans. Several examples are given in Scheme 32. There appear to be two

(a) 

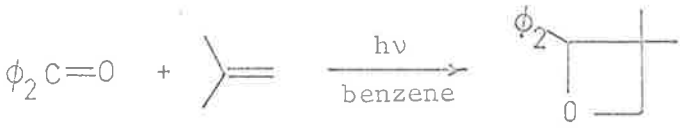
<10% (Ref. 86)

(b) 

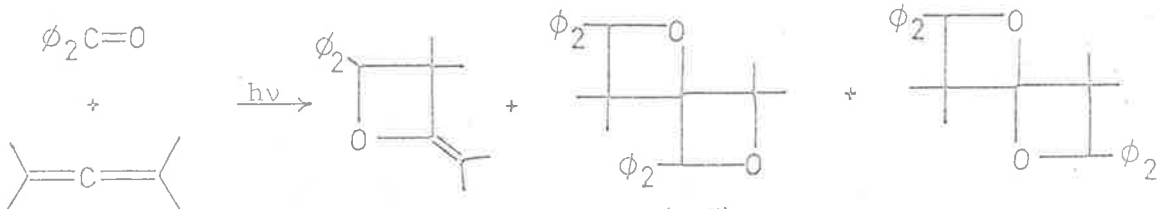
(Ref. 87)

(c) 

(94%) (Ref. 88,89)

(d) 

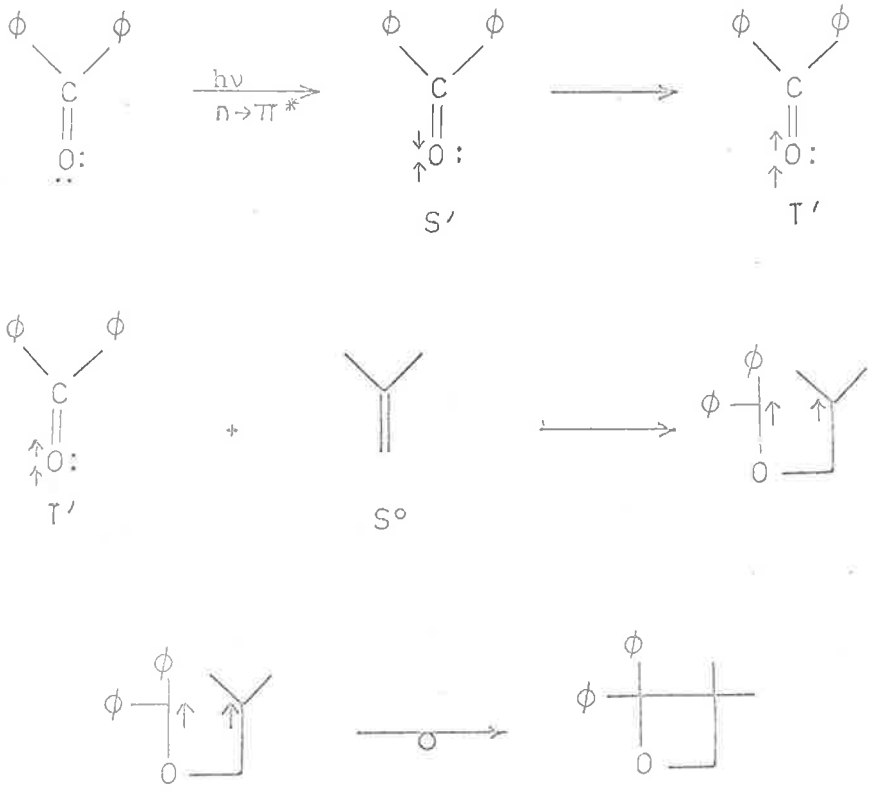
(93%) (Ref. 90)

(e) 

(37%) (28%) (15%) (Ref. 91)

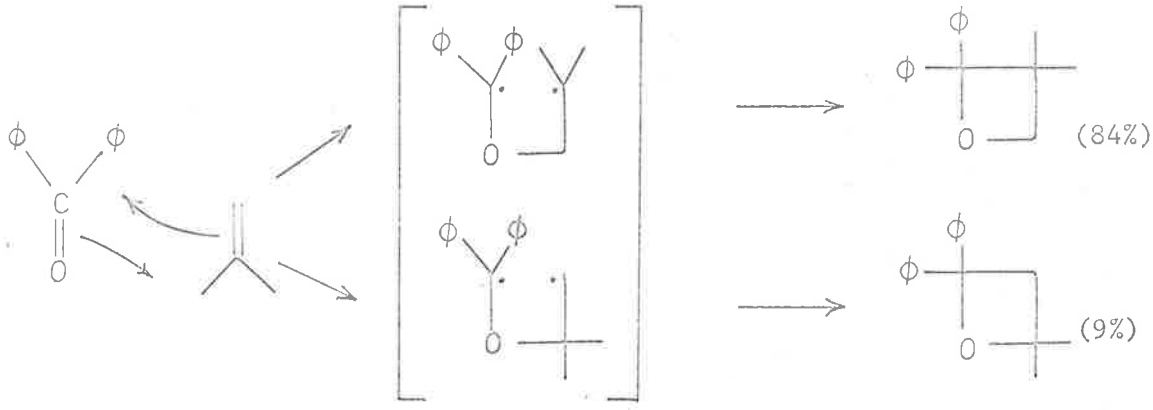
Scheme 32

factors which influence these cycloaddition reactions.[90,92,93] The first is that only carbonyl compounds whose lowest triplet state is of the $n\rightarrow\pi^*$ type react and second is that cycloaddition depends on the triplet energy of the olefin. If this energy is below that of the carbonyl compound than triplet-triplet energy transfer occurs and no oxetan is formed. On the other hand, if the triplet energy of the olefin is greater than that of the carbonyl compound, the oxetan is formed. The favoured mechanism[90,91,92,93] for such cycloadditions is shown in Scheme 33. The orientation of the substituents in the



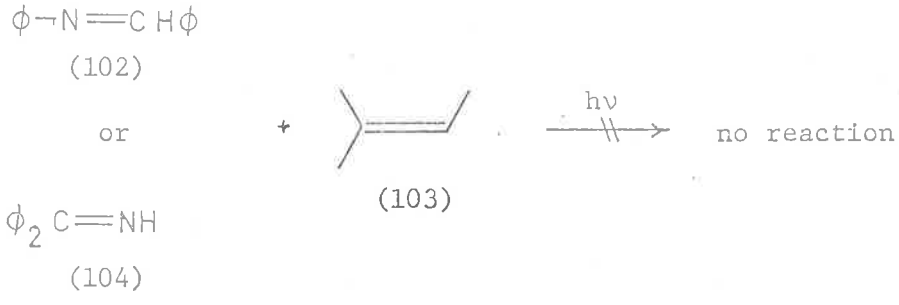
Scheme 33

resulting oxetan appears to be governed by the relative stabilities of the intermediate diradicals.[90] Arnold[90] has shown that both isomers are formed and that the isomer which has the most stable diradical precursor predominates (Scheme 34).



Scheme 34

In view of the facile cycloadditions of carbonyl compounds to olefins to form oxetans it was decided to investigate the reaction of Schiff's bases with olefins. Several studies of photochemical reactions of Schiff's bases have been reported in the literature,[94-99] but no cases were found where a Schiff's base was irradiated in the presence of an olefin. After the irradiation of a mixture of the Schiff's base (102) and 2-methyl-2-butene (103) by the use of a high pressure mercury lamp or by exposure to sunlight in toluene, benzene or ether as solvents for periods of up to 10 days the Schiff's base was recovered quantitatively. The Schiff's base was also recovered when triphenylene[100] was used as a photosensitizer. The irradiation



Scheme 35

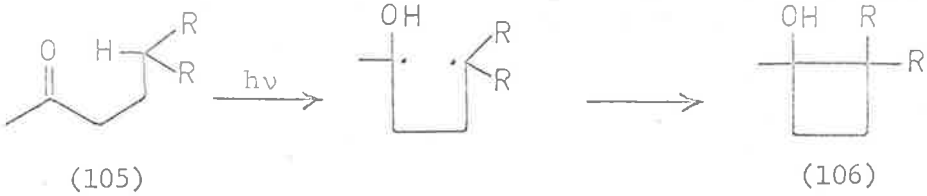
of diphenylketimine (104), whose u.v. spectral characteristics very closely resemble those of benzophenone [209 mμ (ε 17,000), 250 mμ (ε 15,000) and 325 mμ (ε 880) and 205 mμ (ε 21,000) and 253 mμ (ε 16,000) respectively (in ethanol)], and the olefin (103) under the same variety of conditions also failed to yield any azetidine. The diphenylketimine was recovered quantitatively in each case. On one occasion, when a low pressure mercury lamp was used, a small amount of polymeric olefin was obtained together with the quantitative recovery of compound (104). It is not easy to explain why these attempted reactions failed. If the conditions for cycloaddition of Schiff's bases to olefins are the same as the conditions for cycloaddition of analogous carbonyl compounds to similar olefins,[90,92,93] then either the lowest triplet state of the Schiff's base may not be of the $n\rightarrow\pi^*$ type or the triplet energy of the Schiff's base may be greater than that of the olefin. There does not appear to be sufficient data available to determine which, if either or both, of these factors apply. *Prima facie*, one might expect the triplet energy of a Schiff's base to be lower than that

of a carbonyl compound,[100] thus eliminating the latter possibility. However, the isolation of a small amount of the polymeric olefin mentioned above suggests that the latter condition is the more likely, since this type of reaction would presumably be a photosensitized polymerization, by the Schiff's base, of the olefin.[101]

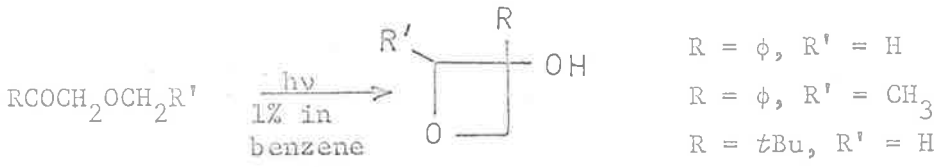
Clasen[102] has also been unable to detect the formation of azetidines when Schiff's bases and olefins were irradiated together.

In a photochemical study of the dimethyl maleate-dimethyl fumarate-acetone system, Albone[109] has presented evidence which supports a mechanism involving the attack of the excited unsaturated diester on the ground state ketone to form the oxetan. Also, studies of the photochemical additions of alkyl ketones to the electron deficient double bond of α,β-unsaturated nitriles indicate that this reaction proceeds *via* a singlet ($n\pi^*$) state of the ketone and that the orientation of the resulting oxetan is not that expected from consideration of the more stable biradical intermediate.[74] It thus appears that the mechanism proposed by Arnold[90] to account for the formation of oxetans is not always adequate. In view of the complex nature of this reaction it is perhaps not so surprising that Schiff's bases and olefins failed to react.

Another useful photochemical method of preparing four-membered ring compounds involves the photolysis of ketones (105) with a γ-hydrogen atom to cyclobutanols (106).[103,104] If the β-carbon atom is replaced by an oxygen atom then the 3-oxetanol (107) is formed.[105] Clearly, the next step would be an examination of the photolysis of



(105) (106)

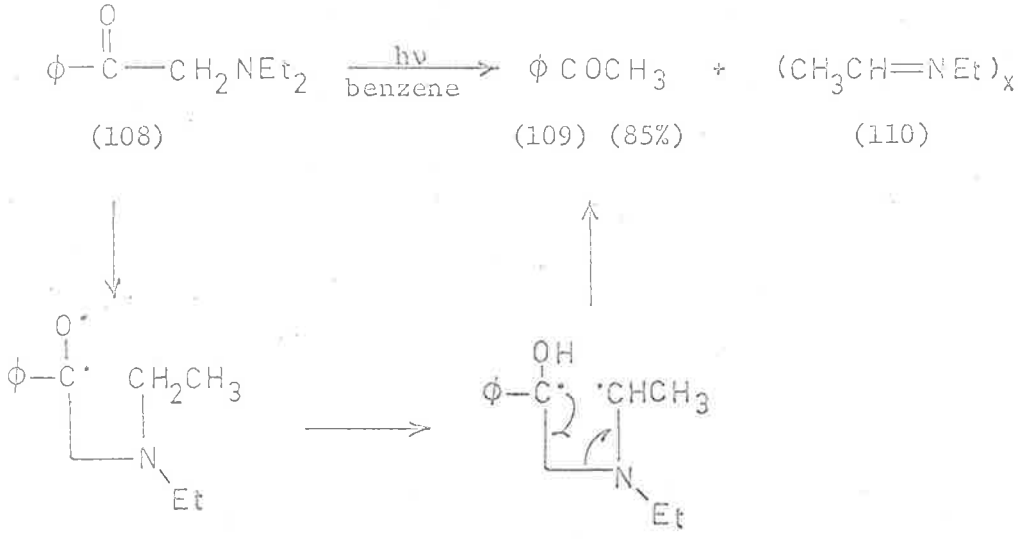


R = φ, R' = H
R = φ, R' = CH_3
R = *t*Bu, R' = H

(107) (29%)

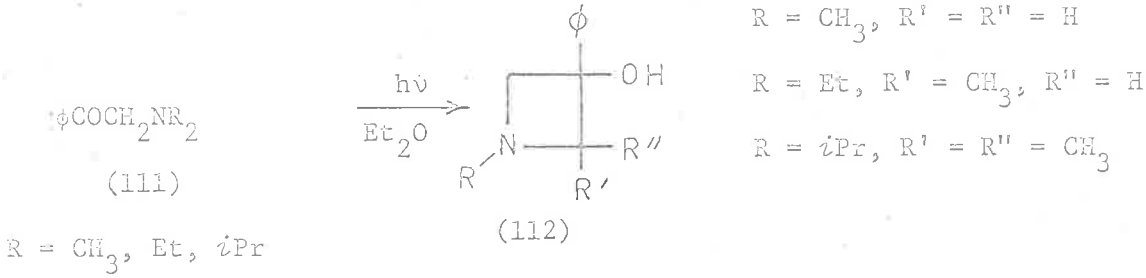
Scheme 36

the carbonyl compound (105) with a nitrogen atom replacing the β-carbon atom. Accordingly, the photolysis of *N*,*N*-diethylphenacylamine (108) in benzene using a high pressure mercury lamp was studied. The solution was irradiated for 135 hours, by which time no *N*,*N*-diethylphenacylamine remained in the reaction mixture. Only two products could be detected and these were separated by chromatography and subsequently shown to be acetophenone (109) (85% yield) and a polymer of *N*-ethylacetaldimine (110). These are the expected products from a Norrish Type II cleavage as shown in Scheme 37. After this work had been completed, Clasen and Searles[106] reported the successful cyclization of *N*,*N*-dimethyl-, *N*,*N*-diethyl- and *N*,*N*-di*iso*propyl-phenacylamines (111) in ether to the azetidinols (112) in yields of 9, 26 and 22% respectively. Acetophenone was obtained as a by-product in 30-50% yield.



(108) (109) (85%) (110)

Scheme 37



(111)

R = CH_3, Et, *i*Pr

(112)

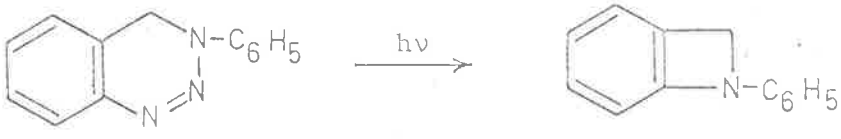
R = CH_3, R' = R'' = H

R = Et, R' = CH_3, R'' = H

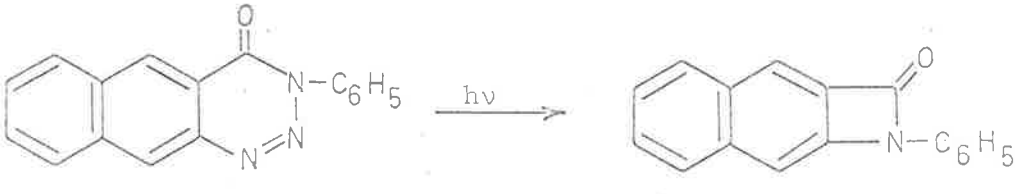
R = *i*Pr, R' = R'' = CH_3

Scheme 38

N-Phenylbenzoazetine (171) has been prepared by the irradiation of a solution of 3-phenyl-4H-benzo-1,2,3-triazine (172) in benzene[107] and *N*-phenylnaphtho[2,3-b]azetinone (173) by the irradiation of a solution of 3-phenyl-3,4-dihydronaphtho[2,3-d]-1,2,3-triazin-4-one (174) in tetrahydrofuran.[108(a)] The existence of *N*-phenylbenzoazetinone (175) in solution has been proved by trapping reactions[108(b)] and by i.r. spectroscopy.[110]

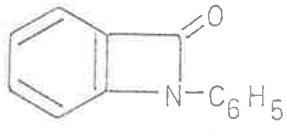


(172) (171)



(174) (173)

Scheme 39



(175)

Figure 9

CHAPTER 2. NUCLEAR MAGNETIC RESONANCE (N.M.R.) SPECTRA AND STEREOCHEMISTRY OF AZETIDINES

I. INTRODUCTION

1. N.M.R. Spectroscopy

The successful application of n.m.r. spectroscopy to stereochemical problems involves the measurement and interpretation of one or more of three effects: (1) the chemical shift, (2) coupling constants and (3) exchange effects. These effects have been discussed at length in texts[111] and reviews[112-117] and only a brief summary of some of the factors influencing these variables is given below.

(1) The chemical shift

A spinning positive charge such as a proton has a magnetic moment $\underline{\mu}$ associated with it. The magnetic moment vector is collinear with and directly proportional to that of the angular momentum $\underline{p}$.[118] When the proton with its magnetic moment is placed in a magnetic field $\underline{H}$ the magnetic moment may align with or against the field thus creating two different energy levels. A radio frequency now applied to this system may induce a transition from the lower to higher energy level and this absorption may be detected as the resonance signal. The resonance frequency depends on the applied magnetic field, the gyromagnetic ratio ($\gamma = \underline{\mu}/\underline{p}$) and to a small but very important extent on its nuclear environment. As a result, nuclei of the same species resonate at

slightly different applied fields depending on their nuclear environment. This arises from the magnetic screening effect of the extra-nuclear electrons and the magnetic field experienced by the nucleus is not quite the same as the applied field. In general, the following relationship holds:[119]

$$H_A = H_{app}(1 - \sigma_A) \qquad (2\text{-}1)$$

where H_A is the applied magnetic field at the nucleus (i.e. effective field), H_{app} is the applied magnetic field and σ_A is a dimensionless number known as the shielding coefficient or shielding constant. The value of the shielding constant is determined by local fields at the nucleus which arise from electron circulations induced by the applied magnetic field. These electron circulations can be broken down on an atomic basis in the following way:[120]

$$\sigma_A = \sigma_{AA}^{dia} + \sigma_{AA}^{para} + \sum_{B \neq A} \sigma_{AB} + \sigma_A^{deloc} \qquad (2\text{-}2)$$

where σ_{AA} corresponds to the local diamagnetic currents which are induced by the applied magnetic field and which are caused by the circulation of electrons around the nucleus in a plane perpendicular to the applied field, thereby producing a field which is in opposition to the applied field. As a result, shielding at the nucleus is increased and the resonance is shifted to higher field. Local diamagnetic circulations about one nucleus in the liquid or gaseous state (σ_{AA}^{dia}) average to zero and therefore make no contribution to the shielding of a neighbouring nucleus.

σ_{AA}^{para} is the contribution to σ_A of induced paramagnetic currents on the nucleus A, and arises as a consequence of the mixing of the ground and excited electronic states by the applied magnetic field.[120]

The term $\sum_{B \neq A} \sigma_{AB}$ is the contribution to σ_A from local induced currents on atoms other than A and can be expressed approximately as:[120]

$$\sigma_{AB} = \frac{1}{3R_{AB}^3 N_o} [(1 - 3\cos^2 \theta_x) \psi_{xx} + (1 - 3\cos^2 \theta_y) \psi_{yy} + (1 - 3\cos^2 \theta_z) \psi_{zz}] \qquad (2\text{-}3)$$

where N_o is Avagadro's number; ψ_{xx}, ψ_{yy} and ψ_{zz} are the three principle axes of the magnetic susceptibility tensor of the atom or bond B; θ_x, θ_y and θ_z are the angles between the principal axes and the AB internuclear vector and R_{AB} is the magnitude of the internuclear vector. σ_{AB} is zero unless the magnetic susceptibility tensor is anisotropic (neighbour anisotropy effect).

The last term, σ_A^{deloc}, in Equation (2-2) arises from induced currents involving electrons which are not localised on any one atom or bond in the molecule and includes, for example, the deshielding of the aromatic protons of the benzene ring. When a benzene molecule is oriented with its plane perpendicular to the applied field, extensive circulations of delocalised electrons occur and this circulation produces an opposing magnetic field at the centre of the ring as shown in Figure 10. The peripheral hydrogen atoms lie in the region where the induced field reinforces the applied field thus causing the

aromatic protons to resonate at a lower field than would otherwise be the case.

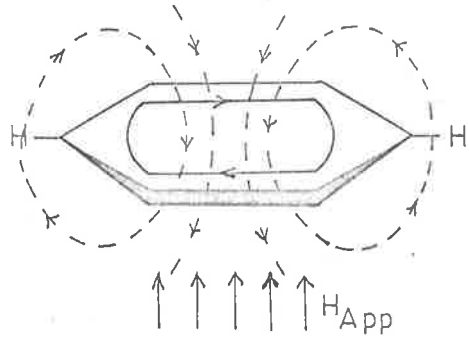


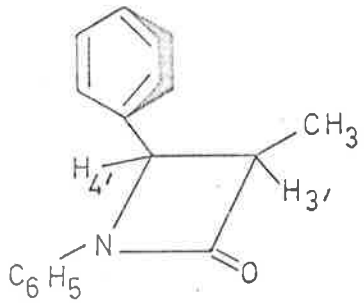
Figure 10. The deshielding of aromatic protons

The ring current effect (σ^{ring}) can be approximated by an expression similar to that for σ_{AB} and for an axially symmetrical electron distribution $\psi_{xx} = \psi_{yy} = \psi_{\perp}$ (perpendicular to the rotational axis) and $\psi_{zz} = \psi_{||}$ (parallel to the rotational axis) and hence[121]

$$\sigma^{ring} = \frac{\Delta\psi}{3R^3 N_o} (1 - 3\cos^2 \theta) \qquad (2\text{-}4)$$

where $\Delta\psi = \psi_{\perp} - \psi_{||}$ and θ is the angle between the axis and the vector R. This expression can satisfactorily approximate (for distances greater than about 3Å) the ring current effect in benzene derivatives where $\Delta\psi$ is now the diamagnetic anisotropy of the aromatic ring, θ is the angle between the vector joining the proton to the centre of the ring and the six-fold rotational axis of the ring and R is the distance of the proton from the centre of the benzene ring. More refined methods[122] of calculation are unnecessary for the present work.

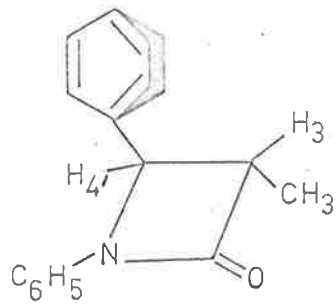
Much of the stereochemical information reported in this work has been either obtained or confirmed by a qualitative application of known anisotropies of functional groups.[123] Such a procedure has been used in the assignment of *cis* and *trans* isomers in, for example, benzocyclobutenes[124] and 2-azetidinones.[46] The compounds (49c) and



(49c)

CH_3: 0.86

$H_{3'}$: 3.67



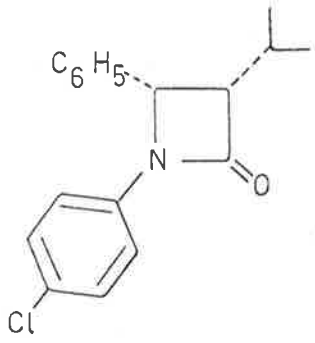
(49t)

CH_3: 1.48

H_3 : 3.12

Figure 11. The shielding effect of a phenyl substitutuent in 2-azetidinones

(49t) in Figure 11 illustrate this method and it requires the assumption that the 4-phenyl group exists in a preferred conformation in which the plane of the aromatic ring is approximately at right angles to the plane of the 2-azetidinone ring in its equilibrium position. Recent X-ray analysis has shown this angle to be 79 ± 2° in compound (164).[125] Thus, from Equation (2-4) and from models it is clear that the methyl group in compound (49c) is in the shielding region of the aromatic ring and thus resonates at a higher field



(164)

than does the methyl group in compound (49t). [Both R and θ are smaller for compound (49c) than for compound (49t) and therefore σ^{ring} is greater.]

(2) Coupling constants

Resonance lines which under low resolution appear as only single lines can show considerable multiplicity or fine structure under higher resolution and this results from spin-spin splitting. Spin-spin splitting proceeds by the Fermi contact term between an electron and the nuclear spin and is transmitted by bonding electrons. As would be expected on the basis of this explanation, spin-spin splitting is independent of the applied magnetic field but the effect of one proton on another depends on the number and kind of intervening chemical bonds and the stereochemical relationships of the interacting groups. These effects are discussed below.

(a) Vicinal Coupling Constants (H—C—C'—H')

Karplus[126,127] has discussed the factors influencing vicinal coupling constants and the main ones are the magnitude of the dihedral angle ϕ (Figure 12), the presence of electronegative substituents, the bond angles θ and θ' (Figure 12) and the C—C' bond length.

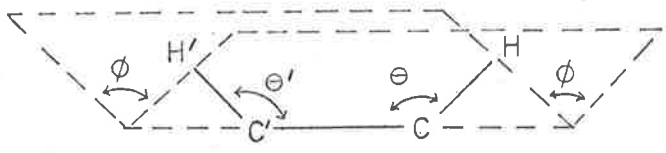


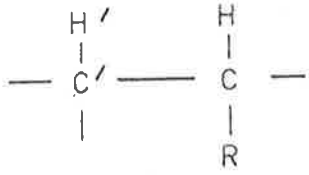
Figure 12

Using valence bond calculations, Karplus has derived an equation (2-5) relating the dihedral angle ϕ to the vicinal coupling constant J_{vic}. From this it can be seen that J_{vic} will have a maximum

$$J_{vic} = A + B\cos\phi + C\cos^2\phi \qquad (2\text{-}5)$$

at 0° and 180° [actually $J_{vic}(\phi = 0°)$ is usually less than $J_{vic}(\phi = 180°)$] and a value of 0 when $\phi = 90°$. Clearly, values of A, B and C will vary with the particular system and so it is dangerous to attempt to obtain quantitive measures of ϕ from measured values of J_{vic}. A modified Karplus equation has also been applied to olefins, where it was predicted that J_{vic} for the *trans* olefinic protons is greater than J_{vic} for the *cis* olefinic protons.[128]

Theoretical calculations[126] suggest that the coupling constant J_{vic} depends on the electronegativity of the substituent R in the system (143). The direct inductive effect on the polarity of the C—H and C'—H' bonds involved is relatively small; the changes in



(143)

Figure 13

the hybridisation of the C and C' carbon atoms (Figure 13) on substitution have a greater effect. The calculations suggest that the observed couplings will decrease slightly with the increased electronegativity of R (Figure 13). (See, for example, the effect of substituent electronegativity on vicinal coupling constants in hexachlorobicyclo[2,2,1]heptenes[129,130]).

This electronegativity effect shows a stereochemical dependence, and Booth[131] has suggested that the maximum electronegativity effect appears to coincide with the *trans* coplanarity of the system R—C—C'—H'. The three most important consequences of this generalization are:

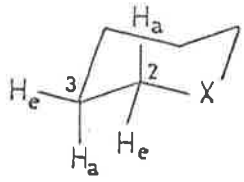
(i) When R is an electronegative substituent attached to a cyclohexane ring, the maximum effect on J_{vic} occurs in conformation (144) rather than (145) with $J_{e_1a_2}$ [Figure 14, (144)] being smaller than $J_{a_1e_2}$

(144) (145)

Figure 14

[Figure 14, (145)] (provided that other factors such as bond angles, bond lengths, etc. remain constant).

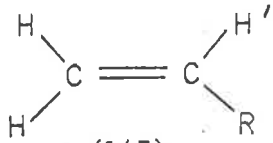
(ii) In a reduced six-membered heterocycle, the maximum electronegativity effect will be experienced at position 3 [compound (146), Figure 15]. Thus it is anticipated that $J_{a_2e_3}$ will be less than $J_{e_2a_3}$.



(146)

Figure 15

(iii) In a substituted ethylene (147) any variation in R will affect J_{vic} *cis* more than J_{vic} *trans*.[132] This effect is only



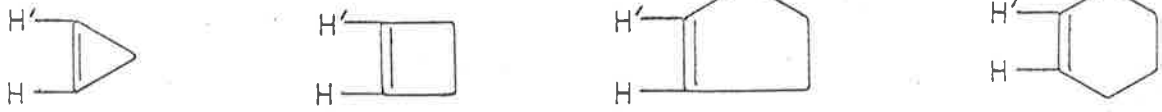
(147)

Figure 16

slight although J_{vic} *cis* usually shows more variation with electronegativity of R than does J_{vic} *trans*. It should be noted, however, that in five membered heterocycles J_{vic} increases with increasing electronegativity of the heteroatom,[133] in contrast to the above rule.

Cohen and Schaefer[134] have compiled sets of values of vicinal coupling constants between the protons HC_2 and HC_3, and HC_3 and HC_4 in the fragment $RHC_1-HC_2-HC_3-HC_4$, where R is a substituent of varying electronegativity for several acyclic, alicyclic and aromatic systems. For increasing electronegativity of R, an increase in coupling between HC_2-HC_3 was observed, while coupling between HC_3 and HC_4 showed a slight decrease.

Valence bond calculations have shown that J_{vic} should decrease for most dihedral angles ϕ as the angles θ and θ' (Figure 12) increase.[126] This prediction is more easily confirmed in the case where $\phi = 0°$ and $\theta = \theta'$, i.e. in symmetrically substituted *cis* olefins (148)-(151).[135]



J_{vic} = 0.5-2 c.p.s.; 2.5-4 c.p.s.; 5.1-7 c.p.s.; 8.8-10.5 c.p.s.

(148) (149) (150) (151)

Figure 17

A decrease in J_{vic} is predicted for an increase in bond length (for constant bond angles and hybridisation) and for vinylic systems calculations yield an almost linear dependence.[126] There is some experimental evidence in agreement with these theoretical calculations.[136]

(b) Geminal Coupling Constants (H—C—H')

Pople and Bothner-By[71] have given a molecular orbital treatment of geminal coupling constants and this has provided a

qualitative rationalization for the signs of observed coupling constants. It is suggested that the value of the geminal coupling constant provides a means of distinguishing between inductive and hyperconjugative electron transfer. An excellent correlation of experimental and theoretical data was obtained by Barfield and Grant[138,139] using a semi-empirical valence bond description of hyperconjugative effects.

Empirical regularities in geminal coupling constants have now been established with some certainty,[71] the principal trends being:

(i) In the simplest hydrocarbons, the geminal proton-proton coupling constant J_{gem} increases (becomes more positive) as the hybridization of the C—H bonds increases in s character. Thus, the value for methane (sp^3 hybridization) is ±12.4 c.p.s. (most probably -12.4 c.p.s.), while that for ethylene (sp^2 hybridization) is +2.5 c.p.s. The value for cyclopropane rings (intermediate between sp^2 and sp^3 hybridization) is about -4 c.p.s.

(ii) The substitution of an electronegative atom in a position α to the $-CH_2-$ group leads to a positive shift in the geminal coupling constant. This applies to both sp^2 hybridization[140,141] and to sp^3 hybridisation.[142]

(iii) Substitution of an electronegative atom in a position β to the $-CH_2-$ group leads to a negative shift in J_{gem}. There is evidence that the trend applies to both sp^2 hybridized compounds[132,143] and to sp^3 hybridized compounds.[129,130]

(iv) The presence of a π-electron system next to a $-CH_2$ group generally leads to a decrease of J_{gem} (becomes more negative).[138,144,145] This shift seems to be greatest when the H—H axis (the axis bisecting the $C\lessgtr^{H}_{H}$ bond angle) is perpendicular to the nodal plane of the π-electrons. Grant[138] has calculated the effect of changing the angle between the H—H axis and the nodal plane of the π-electrons.

(c) Long Range Coupling Constants (i.e. coupling across four or more chemical bonds)

Theoretical valence bond treatments using electron spin resonance (e.s.r.) hyperfine coupling data for estimating σ-π exchange terms have been successful in correlating a variety of n.m.r. long range coupling constant data in unsaturated and aromatic systems.[146-151] These treatments use only those coupling paths associated with the 2p π-electrons. The principal trends have been summarized in Sternhell's extensive review[112] and are as follows:

(i) *Cis*oid and *trans*oid allylic and homoallylic coupling constants should be of a similar magnitude.

(ii) The magnitude of the long-range coupling constants should depend on the angle made by the bond joining the proton(s) to the sp^3 hybridized carbon atom(s) and the plane of the multiple bond.

(iii) Coupling constants for protons separated by an odd number of bonds should be positive and for protons separated by an even number of bonds, negative in sign.

(iv) The replacement of a $=C-H$ grouping by $=C-CH_3$ should alter the sign but not the magnitude of the coupling across the intervening π system.

All of these predictions have been verified experimentally in allylic, homoallylic and allenic systems.

Compounds which exhibit long range coupling may be divided into a number of groups[112] based on the type of structure involved and include allylic, homoallylic, allenic, acetylenic, saturated, ^4J where some of the intervening carbon atoms are sp^2 hybridized, conjugated systems, long range *meta* and *para* coupling in aromatic rings, protons situated on different rings of polynuclear heterocyclic compounds, long-range coupling between ring and α-protons and long range coupling across heteroatoms. All of these groups have been extensively reviewed.[112] Only coupling through 4σ-bonds is discussed here since it is the main long-range coupling observed in compounds discussed in Part II of this Chapter.

The occurrence of significant long range coupling constants across four single bonds in saturated systems, together with the observation of appreciable positive couplings across four bonds of substituted norbornenes and norbornadienes where the protons are in the nodal plane of the π electrons (the above theoretical predictions[146-151] predict negligible long range coupling),[152-154] led Barfield[155] to formulate a semi-empirical valence bond treatment which was used in conjunction with the spin-spin coupling formulation of Karplus and Anderson[156] to determine the angular dependence of long range coupling

constants across four bonds in saturated (and unsaturated) hydrocarbons. It was predicted that in saturated hydrocarbons ~~that~~ the maximum long range coupling constant should correspond to a planar zig-zag arrangement ("M", "W" or "tail-to-tail"). This is analogous to the explanation suggested earlier by Meinwald and Lewis[157] that long-range interaction may be due to a direct overlap between the small orbitals of the carbon atoms 1 and 3. Experimental evidence (e.g. [112, 157,158,159]) supports Barfield's[155] predictions. For allylic long range coupling, Barfield's[155] formulation predicts that *cis*oid coupling constants are slightly less than *trans*oid and that there are positive maxima for dihedral angles of 90° and 270°. For example, in propene the calculated *cis*oid and *trans*oid allylic long range couplings are -0.9 c.p.s. and -1.3 c.p.s. respectively while the experimental values are -1.3 and -1.7 c.p.s.

(3) Exchange effects

The n.m.r. spectrum of a molecule may be modified if the molecules present are taking part in some rate process.[160] Chemical exchange or hindered internal rotation, for example, may affect the n.m.r. spectrum. One important application of n.m.r. spectroscopy involves conclusions which can be drawn about the conformations of molecules, such as cyclohexanes and substituted ethanes, by a study of the n.m.r. spectra at varying temperatures. In general three types of rate processes may arbitrarily be distinguished.[161] These are:

(i) the slow rate processes in which the observed spectrum is a superposition of spectra corresponding to the individual species or environments present,

(ii) the intermediate rate processes for which, in general, rather complex spectra are obtained and for which detailed mathematical treatment is necessary for interpretation and

(iii) the rapid rate processes in which the observed spectrum is the weighted average of the individual species or environments present.

These three processes correspond to different ratios of the frequency of exchange (Δt sec^{-1}) to the differences in chemical shift ($\Delta\nu$ c.p.s.) of the groups involved in the exchange process. Where $\Delta t >> \frac{1}{2}\pi\Delta\nu$ (fast exchange) only a single weighted average spectrum is observed [type (iii)]. Where $\Delta t \approx \frac{1}{2}\pi\Delta\nu$ (intermediate rate process) broad bands result [type (ii)] and where $\Delta t << \frac{1}{2}\pi\Delta\nu$ (slow exchange) the spectra of the individual species present are observed [type (i)].

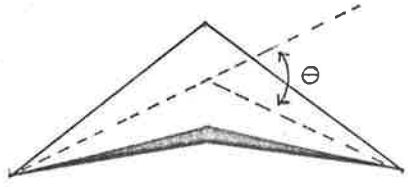
The theoretical methods of analysis of such systems and the qualitative and quantitative results have been extensively reviewed.[162,163,164] Some of these aspects are discussed in more detail below (Section I.4).

2. The Conformation of Four-Membered Rings

The non-planarity of cyclohexane and the resulting axial and equatorial orientation of substituents were first suggested in 1890[165] but were not generally accepted until 1925.[166] The conformational properties of cyclohexanes have been extensively studied (e.g.[167]) and

require no further discussion here. On the other hand, until recently, the planar character of the skeletal carbon atoms of the cyclobutane ring has been accepted as a fact[168] in spite of physical evidence to the contrary.[169-174]

Recent evidence, particularly from X-ray diffraction and n.m.r. spectral studies, has shown that most cyclobutanes are non-planar. For example, an angle of puckering (θ) of about 20° has been found by electron diffraction studies in cyclobutane itself. Several further



examples of the angle of puckering for several substituted cyclobutanes, together with the technique used to determine the angle, are given in Table IV.

TABLE IV. Angle of Puckering in Cyclobutane Rings

Compound	Angle θ	Technique (Ref.)
cyclobutane	20°	electron diffraction (170)
cyclobutane	35°	n.m.r. spectroscopy (175)
octafluorocyclobutane	20±4°	electron diffraction (176)
octachlorocyclobutane	22°,27°	X-ray diffraction (177,179)
bromocyclobutane	29°22'±08'	microwave spectroscopy (173)

cis-1,3-cyclobutane-dicarboxylic acid	31°	X-ray diffraction (178)
trans-1,2-dibromo-1,2-di-carbomethoxycyclobutane	27°	X-ray diffraction (180)
cis-1,2-dibromo-1,2-dicarbo-methoxycyclobutane	30°	X-ray diffraction (180)
chlorobutane	20°	microwave spectroscopy (181)
trans-1,3-cyclobutanedi-carboxylic acid	0°	X-ray diffraction (182)
trans-1,3-cyclobutanedi-carboxylic acid (with an equimolar amount of di-sodium salt)	25°	X-ray diffraction (183)
octahydroxycyclobutane	0°	X-ray diffraction (184)
1,1-difluoro-3-phenyl-cyclobutane	27°	dipole moment (185)
trans-1,3-dicyano-2,2,4,4-tetramethylcyclobutane	24°	dipole moment (186)
cis-1,3-dicyano-2,2,4,4-tetramethylcyclobutane	42°	dipole moment (186)

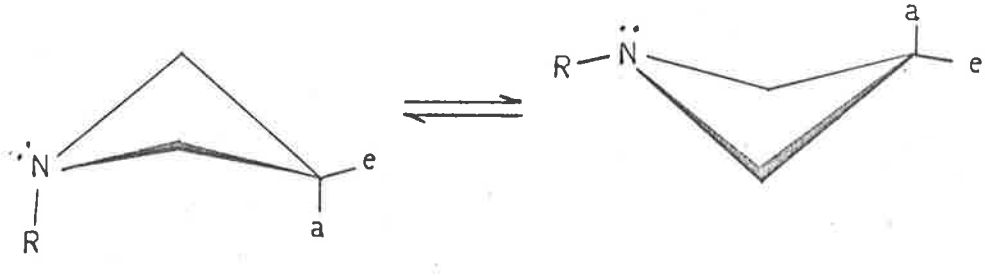
The replacement of a methylene group by a heteroatom, as in oxetan, removes two 1,3-(cross-ring) interactions and four 1,2-(vicinal) interactions. Oxetan has been shown by microwave spectroscopy to be planar with an energy barrier to ring inversion being estimated at only 35 cms^{-1} (0.1 kcal).[187,188] Similarly, steric interactions in cyclobutanone and cyclobutene would be less than in cyclobutane. These compounds would therefore be expected to be planar and this has, in fact, been found to be the case.[185,189] Thus it has been concluded[185] that the non-planarity of the four-membered ring system is due to steric interactions; the replacement of a carbon atom by a carbonyl group or an oxygen atom reducing the steric interactions and hence enabling the system to become planar. A comparison of the puckering caused in the two 1,3-dicyano compounds (penultimate and last compound in Table IV) illustrates this suggestion, where steric interactions result in a greater degree of puckering in the *cis* compound. Furthermore, non-planarity may arise in highly substituted four-membered rings even if one methylene group has been replaced by a carbonyl group, provided the substituent interactions elsewhere in the molecule are high.[190]

In Table V are summarized the barriers to inversion of some four-membered rings obtained from far-infrared spectral measurements and also the corresponding dihedral angle (θ). In cyclohexanes, it is found that the replacement of a $-CH_2-$ group with either a nitrogen or sulphur atom results in an increase in the ring inversion energy

TABLE V. Puckering Data for some Four-Membered Rings

Compound	Barrier height (cm^{-1})	Dihedral Angle (θ)	Ref.
cyclobutane	400,448	$20°$[170], $35°$[175]	171,192
cyclobutanone	5	planar	194,195
oxetan	15.3,35±5	planar	196,197,187,188
thietan	274	28°	194,195,198
silacyclobutane	440	35.9°±2°	193
2-bromocyclobutanone	153	-	199

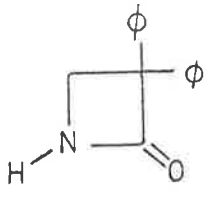
whereas the replacement of the methylene group with an oxygen atom lowers it.[200] In the case of four-membered rings it can be seen that the barrier is considerably lower for oxetan than for thietan. The energy barrier for azetidine does not appear to have been reported but it is probably about the same as for thietan. This means that, although we may adopt the model of interconverting conformers by analogy with that of cyclohexane, the size of the barrier is such that the model is more closely related to that of rapidly interconverting



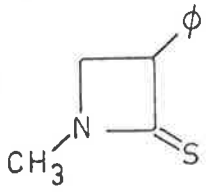
ethane rotamers (the possibility of simultaneous inversion of the nitrogen substituted is discussed below). In other words, "freezing out" the two possible conformers at low temperature would not be expected to be feasible. However, it was hoped by n.m.r. spectroscopy to observe temperature dependent vicinal coupling constants and chemical shifts of ring protons and substituents corresponding to changes in conformer populations.

Several azetidines reported in this work are crystalline solids and therefore X-ray diffraction studies would be useful in determination of the conformation of azetidines in the solid state. Unfortunately, neither time nor equipment was available for this to be done at present. Similarly, microwave studies on azetidine itself would give useful information.

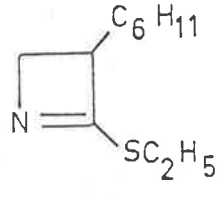
The absence of any significant change of chemical shift difference between the methylene protons in the 2-azetidinone (161), 2-azetidinethione (162), and 1-azetine (163) has been taken as conclusive evidence that these three ring systems are planar.[201] However, the results would also be consistent with non-planar interconverting conformers if the chemical shifts of the methylene protons were very similar.



(161)

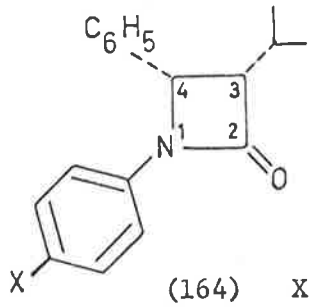


(162)



(163)

A study of the u.v. spectra[202] and n.m.r. spectra[46,125,202,203] of 2-azetidinones indicates that the heterocyclic ring is planar and that in *N*-aryl-2-azetidinones the three valences of nitrogen are planar with the *N*-aryl ring in the plane of the 2-azetidinone ring. These features have been conclusively confirmed by X-ray diffraction studies of the chloro and bromo 2-azetidinones (164).[125] Some of



(164) X = Cl, Br

the parameters obtained for these compounds are listed in Table VI.

TABLE VI. X-ray Diffraction Data for Compound (164)[125]

		X = Br	X = Cl
Distances (Å) of atom to the mean plane	O	-0.007	+0.018
	N	-0.013	-0.001
	C_4	+0.036	+0.004
	C_3	-0.025	-0.009
	C_2	+0.011	+0.006

Angle between the four-membered ring and aryl groups	C_4-Ph	80±2°	79±2°
	N-Ar	5±1°	8±1°
Angle between the N-Ar bond and mean plane of 2-azetidinone ring		8.5°	9.3°
Angle between the plane of Ar group and mean plane of 2-azetidinone ring		5.6°	8.0°

A detailed study of the X-ray diffraction data of 1-benzyl-1,2,2-trimethyl azetidinium bromide indicates that the heterocyclic ring bears a close resemblance in bond distances, bond angles and conformation to the 2-azetidinone ring found in penicillin.[204]

3. Nitrogen Inversion Rates in *N*-Substituted Aziridines and Azetidines

The repeated failures to resolve amines which would owe their asymmetry solely to the non-planar trivalent nitrogen atom[205,206] indicates that the nitrogen inversion rate is rapid. However, in certain cases, the inversion rate may be sufficiently slow to allow it to be measured by n.m.r. spectroscopy or even possibly to allow the resolution of optical isomers. Such a situation is found, for example, in aziridines. Table VII lists the coalescence temperature (Tc) for several aziridines (i.e. where the inversion rate is approximately equal to $\pi\Delta\nu_{AB}/\sqrt{2}$[207]). Recently Brois[218] has isolated

TABLE VII. Coalescence Temperature (Tc) for Aziridines

Aziridine substituent(s)	Tc	Ref.
1-ethyl	108°	208,209
1-cyclohexyl	95°	209
1,2,2-trimethyl	97°	210
1-ethyl-2-methylene	-65°	209
1-phenyl	<-77°	209
	-65° (in methanol)	209
1-trifluoromethyl-2,2-difluoro	-50°	211
1-methansulphonyl	-25°	212
1-carbomethoxy	-138°	212
1-$SO_2C_6H_5$	-30°	213
1-SOC_6H_5	0°	213
1-SC_6H_5	-11°	213
1-$PO(C_6H_5)_2$	-108°	213
2,2,3,3-tetramethyl	52°	214
1-CF_3CFHCF_2	11°	215
1-*t*-butyl	<-77°	209
	52°	216
1-chloro-2,2-dimethyl	>180°	217
1-bromo-2,2-dimethyl	>140°	217

the *cis* (165c) and *trans* (165t) isomers of 1-chloro-2-methylaziridine. A similar separation of diastereomeric isomers of 7-chloro-7-azabicyclo[4,1,0]heptanes has been accomplished.[219]

(165c) (165t)

The above results have enabled some of the important factors which influence the rates of nitrogen inversion in aziridines to be determined, and they may be summarized as follows:-[76,209,213]

(1) Steric effects

An increase in the size of the group attached to the nitrogen atom or to a ring-carbon atom should result in an increase in the rate of inversion since the nitrogen substituent should be more compressed in the non-planar ground state than in the presumably planar transition state for the nitrogen inversion. For example, compare 1-ethylaziridine and 1-*t*-butylaziridine (Table VII).

(2) Inductive effects

Electronegative substituents on nitrogen would be expected to decrease the rate of inversion because of the tendency of such substituents to increase the s character of the unshared electron

pair on nitrogen.[220] In the planar transition state this electron pair must be in a p orbital.[213] This would explain the high Tc for *N*-chloro and *N*-bromo aziridines although it was considered that the transition state would be stabilized by d-orbital resonance[221] prior to the experimental proof that the rate of inversion for the *N*-chloro and *N*-bromo aziridines was slower than for *N*-alkyl aziridines.

(3) Conjugative effects

Since conjugation, especially of the p-p type, is greater in a planar system than in a non-planar one, a group on the nitrogen atom or on a ring-carbon atom which is capable of conjugation should lower the energy of the transition state more than that of the ground state and so increase the inversion rate. A comparison of Tc for 1-ethylaziridine with that for 1-ethyl-2-methyleneaziridine or of Tc for the former with that for 1-phenylaziridine supports this view (Table VII).

(4) Electrostatic effects

When the atom attached to the nitrogen atom carries an unshared electron pair, repulsion between this pair and that on the nitrogen is less in the ground state than in the transition state. Thus Tc for 1-$SO_2C_6H_5$ should be lower than for 1-SC_6H_5 but other factors may also be important.

(5) Effect of solvent

Inversion rates most probably are decreased in hydroxylic solvents because of the stabilization of the separate conformations

by hydrogen bonding between the solvent and the nitrogen atom.

Roberts[209] observed that nitrogen inversion rates of *N*-substituted azetidines were too great to be measurable by nuclear magnetic resonance techniques at temperatures above -77°. Lehn[217] has reported the only examples of hindered nitrogen inversion in azetidines and the coalescence temperature for these azetidines are given in Table VIII. When this work was commenced, no cases of

TABLE VIII. Nitrogen Inversion in Azetidines[217]

Compound	Solvent	Tc	ΔGc*	Group
1,3,3-trimethyl-	$CFCl_3$	-98±3°	8.85 kcals/mole	CH_3
azetidine		-93±3°	8.5	CH_2
1-chloro-3,3-	$CFCl_3$	-54±2°	11.5	CH_3
dimethylazetidine		-46±3°	11.4	CH_2
	CH_2Cl_2	-47±2°	11.9	CH_3
		-43±2°	11.6	CH_2
1-bromo-3,3-	CH_2Cl_2	-56±2°	11.5	CH_3
dimethylazetidine		singlet(-71°)	-	CH_2

hindered nitrogen inversion in azetidines had been reported and we were interested in studying this phenomena in a series of azetidines to determine what factors affect the inversion rate.

4. Measurement of Rate Processes by N.M.R. Spectroscopy

When a magnetic nucleus can undergo exchange between two structural sites in a molecule it may have a different chemical shift in each of the two environments. If the exchange process is slow two separate signals will be observed for the resonance of this nucleus. If the process is accelerated (e.g. by increasing the temperature) eventually the rate of exchange will be sufficiently rapid to give a single resonance line appearing at an intermediate position. Similar reasoning applies to the averaging of spin-spin multiplets. At intermediate rates of exchange broad lines may result. From a measurement of line widths and shapes it is possible to determine the rate of the process responsible for the line broadening.

Mathematical expressions have been developed which describe the relationship between line shapes and rate processes and these have been discussed elsewhere.[160-164] These expressions may be used to calculate rate processes from observed spectra although several assumptions must be made to simplify the expressions for convenient use. Errors involved in these assumptions have been discussed[164] and it appears that, where possible, the use of computer programs, based on the complete density matrix, is preferable to the simplified equations. However, in this work, a suitable program was not available. Accordingly, simplified equations were used and these are discussed very briefly below.

Consider two equally populated uncoupled sites A and B with a rate of exchange $k(=\frac{1}{2\tau})$. If k is too slow to coalesce the AB doublet to a singlet k is related to the measured peak separation $\Delta\nu_e$ or the maximum to central minimum intensity ratio r by Equations (2-6)[242] and (2-7)[243-245] respectively where $\Delta\nu_{AB}$ is the chemical shift difference between the doublet when the exchange rate is very slow.

$$\frac{1}{2\tau} = (\pi/\sqrt{2})(\Delta\nu_{AB}^2 - \Delta\nu_e^2)^{\frac{1}{2}} \qquad (2\text{-}6)$$

$$\frac{1}{2\tau} = (\pi\Delta\nu_{AB}/\sqrt{2})[r + (r^2 - r)^{\frac{1}{2}}]^{\frac{1}{2}} \qquad (2\text{-}7)$$

These equations require

$$\frac{1}{\tau} \text{ and } \Delta\nu_{AB} >> (1/\pi T_2'') \equiv W'' \qquad (2\text{-}8)$$

where $(1/T_2'') = (1/T_2^{o}) + (1/T_2')$,

$(1/T_2^{o})$ represents the relaxation contribution to W''

and $(1/T_2')$ represents the inhomogeneity, instability and other instrumental contributions to W'', the effective line width in the absence of exchange; line width here is defined as the full width in c.p.s. at half-maximum intensity.[164] Equations (2-6) and (2-7) are only applicable up to and at the coalescence point.

Equation (2-9)[246] is a somewhat more general expression which is valid at and above coalescence provided expression (2-8) is

$$\frac{1}{2\tau} = (\pi\Delta\nu_{AB}/2)[(\Delta\nu_{AB}/W^*)^2 - (W^*/\Delta\nu_{AB})^2 + 2]^{\frac{1}{2}} \qquad (2\text{-}9)$$

satisfied. W* is the full width at half-maximum intensity, in c.p.s., and if it is further defined as the width of the spectrum at the point where it possesses an amplitude one-half of the central intensity, Equation (2-9) is also valid below coalescence.

Uncoupled line-shape equations are often used to obtain intramolecular exchange rates for a coupled AB system. It has been shown[164] that the error in k, obtained by the use of Equation (2-9), is less than 5% if

$$\frac{1}{2\tau} = k \gtrsim 15J \qquad (2\text{-}10)$$

In the case of two coupled and equally populated sites, k, at coalescence, becomes:[247]

$$k = \pi(6J_{AB}^2 + \Delta\nu_{AB}^2)^{\frac{1}{2}}/\sqrt{2} \qquad (2\text{-}11)$$

Eyring's rate equation is

$$k = \frac{fk'T}{h} e^{-\Delta G^*/RT} \qquad (2\text{-}12)$$

where k = rate, k′ = Boltzman's constant, h = Planck's constant and ΔG^* = free energy of activation. If the transmission coefficient f = 1,

$$\Delta G^* = 4.57T\,[10.32 + \log(T/k)] \qquad (2\text{-}13)$$

or, since $\Delta G^* = \Delta H^* - T\Delta S^*$,

$$\log\,(k/T) = 10.32 + \frac{\Delta S^*}{4.57} - \frac{\Delta H^*}{4.57T} \qquad (2\text{-}14)$$

Thus a plot of log (k/T) against $\frac{1}{T}$ should give a straight line, and from the slope and intercept ΔH^* and ΔS^* values may be obtained. However, unless the rates are obtained by a complete line shape analysis using a computer, the errors in k may result in considerable errors in ΔH^* and ΔS^*.

The line-width changes appreciably only over a small temperature range, and as a result, k values can be measured over only a small range. This may result in an appreciable error in the slope and intercept of a plot of log (k/T) vs $\frac{1}{T}$ and thus in ΔH^* and ΔS^* values. Other sources of error have been discussed in detail elsewhere.[164]

II. DISCUSSION AND RESULTS

1. N.M.R. Spectra and Stereochemistry of 2-Azetidinones and Azetidines

(1) 2-Azetidinones

(a) Chemical Shifts (2-Azetidinones)

The chemical shifts of 2-azetidinones are listed in Table IX. The compound numbers refer to those allotted in the discussion of their synthesis in Chapter 1 or in the details of their synthesis in Chapter 4. The numbering system for the 2-azetidinone ring is shown in Figure 18.

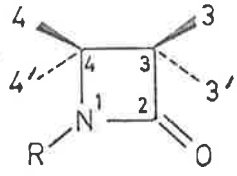


Figure 18

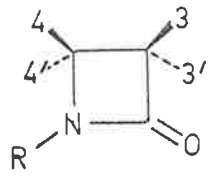
Only 2-azetidinones for which chemical shifts have apparently not been reported previously are given here. All spectra were recorded as approximately 10% $CDCl_3$ solutions containing tetramethysilane as an internal reference (δ in ppm from TMS).

(i) Assignment of the 3 and 4 protons and substituents in 2-azetidinones.

Barrow[46] found that a substituent in the 3 or 4 position of the 2-azetidinone ring induces a marked non-equivalence in the neighbouring $-CH_2-$ group, the proton *cis* to the substituent being

shifted to higher field and that *trans* to the substituent to lower field. A methyl group in the 3 or 4 position of the azetidinone ring was found to cause a separation of approximately 0.5 ppm between the adjacent *cis* and *trans* protons. A smaller, but corresponding difference in chemical shift (0.16 ppm) was shown by the effect of

TABLE IX. Chemical Shifts of 2-Azetidinones in $CDCl_3$ (δ in ppm from Tetramethylsilane)



Cpd.No.	Substituents and Chemical Shifts				
	N	3	3'	4	4'
(115)	H: 7.2	C_6H_5: 7.3	CH_3: 1.60	H: 3.46	H: 3.34
(57)	*p*MeO$C_6H_4CH_2$	CH_3: 0.76	CH_3: 1.30	C_6H_5: 7-7.4	H: 4.10
	MeO: 3.74				
	C_6H_4: 7-7.4				
	CH_2: 3.81,4.86				
(118)	SO_2Cl	H: 2.92	H: 3.26	CH_3: 1.85	$(CH_3)_3CCH_2$
					$(CH_3)_3C$: 1.04
					CH_2: 2.02

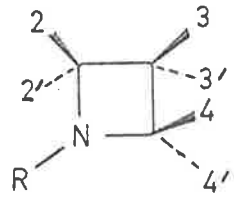
(40)	H: 7.3	H: *c.* 2.7	H: *c.* 2.7	CH_3: 1.47	$(CH_3)_3CCH_2$ $(CH_3)_3$: 0.97 CH_2: 1.68
(121)	SO_2Cl	CH_3: 1.30	H: 3.27	CH_3: 1.62	CH_3: 1.75
(39)	H: 6.7	CH_3: 1.16	H: 2.88	CH_3: 1.27	CH_3: 1.40
(120)	SO_2Cl	$(CH_3)_3C$: 1.15	H: 3.07	CH_3: 1.76	CH_3: 1.85
(42)	H: 7.0	$(CH_3)_3C$: 1.08	H: 2.70	CH_3: 1.40	CH_3: 1.50
(119)	SO_2Cl	CH_3: 1.33	CH_3: 1.33	CH_3: 1.64	CH_3: 1.64
(41)	H: 6.2	CH_3: 1.18	CH_3: 1.18	CH_3: 1.46	CH_3: 1.46
(48)	C_6H_5: 7.1-7.3	CH_3: 1.17	CH_3: 1.22	$(CH_3)_3C$: 1.02	H: 3.68
(54)	$C_6H_5CH_2$ C_6H_5: 7.3 CH_2: 4.25	CH_3: 1.08	CH_3: 1.08	CH_3: 1.18	CH_3: 1.18
(56)	$C_6H_5CH_2$ C_6H_5: 7.23 CH_2: 4.21	$(CH_3)_3C$: 1.08	H: 2.64	CH_3: 1.18	CH_3: 1.27
(85)	CH_3: 2.58	CH_3: 1.12	CH_3: 1.12	CH_3: 1.21	CH_3: 1.21

TABLE X. Coupling Constants in 2-Azetidinones (c.p.s.)

Compound No.	Value	Type
(115)	- 5.2	J_{44}, geminal
(57)	-15.0	geminal benzylic CH_2
(118)	-16.0	J_{33}, geminal
(121)	7.7	CH_3-CH vicinal

(39)	7.4	CH_3-CH vicinal
	1.1	N-H to C_3-H_3, long range
(42)	0.9	N-H to C_3-H_3, long range

TABLE XI. Chemical Shifts of Azetidines in CCl_4 (δ in ppm from Tetramethylsilane)



Cpd.No.	Substituents and Chemical Shifts						
	N	2	2'	3	3'	4	4'
(124)	H	H	H	C_6H_5	CH_3	H	H
	1.7	3.83	3.72	7.1	1.58	3.83	3.72
(125)	$C_6H_5CH_2$	H	H	C_6H_5	CH_3	H	H
	C_6H_5: 7-7.3	3.32	3.20	7-7.3	1.58	3.32	3.20
	CH_2: 3.51						
(61)	C_6H_5	C_6H_5	H	CH_3	CH_3	H	H
	6.3-7.3	7.3	4.61	0.85	1.28	3.70	3.50
(66)	$(CH_3)_3C$	C_6H_5	H	CH_3	CH_3	H	H
	0.88	7.1-7.4	4.02	0.71	1.08	2.97	2.83
(73)	$(CH_3)_2CH$	C_6H_5	H	CH_3	CH_3	H	H
	CH: 2.37	7.2	3.67	0.72	1.11	3.12	2.58
	$(CH_3)_2$						
	0.70,0.92						

(67)	$C_6H_5CH_2$	C_6H_5	H	CH_3	CH_3	H	H
	C_6H_5: 7.3	7.3	3.85	0.80	1.17	3.03	2.59
	CH_2						
	3.33,3.89						
(87) (c.f. Ref. 27(b))	CH_3	C_6H_5	H	CH_3	CH_3	H	H
	2.26	7.15	3.54	0.76	1.13	3.11	2.58
(74)	$CH_3CH_2CH_2$	C_6H_5	H	CH_3	CH_3	H	H
	CH_3: 0.86	7.3	3.69	0.78	1.16	3.18	2.62
(72)	$C_6H_5(CH_2)_2$	C_6H_5	H	CH_3	CH_3	H	H
	C_6H_5: 7.2-7.3	7.2-7.3	3.77	0.78	1.15	3.19	2.67
	$(CH_2)_2$: *c.* 2.7						
(71)	*p*MeO$C_6H_4CH_2$	C_6H_5	H	CH_3	CH_3	H	H
	C_6H_4: 6.7-7.4	6.7-7.4	3.79	0.78	1.15	2.97	2.56
	CH_2: 3.22,3.79						
	MeO: 3.67						
(132)	H	CH_3	CH_3	CH_3	CH_3	H	H
	2.2	1.17	1.17	1.10	1.10	3.08	3.08
(130)	H	CH_3	CH_3	CH_3	H	H	H
	1.8	1.10	1.18	0.98	2.31	2.95	3.40
(131)	$C_6H_5CH_2$	CH_3	CH_3	CH_3	H	H	H
	C_6H_5: 7.2	0.99	1.07	0.97	2.11	2.57	3.20
	CH_2: 3.42						
(70)	$C_6H_5CH_2$	CH_3	CH_3	$(CH_3)_3C$	H	H	H
	C_6H_5: 7.2	1.14	1.19	0.90	1.99	2.76	3.06
	CH_2: 3.36,3.52						
(88t)	C_6H_5	C_6H_5	H	H	$(CH_3)_3C$	H	H
	6.1-7.5	7.3-7.5	4.56	2.46	0.87	3.93	3.44

(88c)	C_6H_5	C_6H_5	H	$(CH_3)_3C$	H	H	H
	6.1-7.5	7.3-7.5	5.09	0.73	2.71	3.87	3.71
(63)	C_6H_5	$(CH_3)_3C$	H	CH_3	CH_3	H	H
	6.3-7.2	1.05	3.35	1.13	1.25	3.26	3.83
(68)	$C_6H_5CH_2$	CH_3	CH_3	CH_3	CH_3	H	H
	C_6H_5: 7.1-7.2	1.05	1.05	1.00	1.00	2.73	2.73
	CH_2: 3.44						
(128)	H	H	H	CH_3	CH_3	H	H
	1.6	3.19	3.19	1.18	1.18	3.19	3.19
(140)	Br	CH_3	CH_3	CH_3	CH_3	H	H
		1.14	1.14	1.09	1.09	3.47	3.47
(141)	Cl	CH_3	CH_3	CH_3	CH_3	H	H
		1.21	1.21	1.13	1.13	3.56	3.56
(135)	H	CH_3	$(CH_3)_3CCH_2$	H	H	D	D
	1.1	1.39	$(CH_3)_3C$: 0.93	1.84	2.13		
			CH_2: 1.55				
(91)	CH_3	CH_3	CH_3	CH_3	CH_3	H	H
	1.98	1.01	1.01	0.93	0.93	2.67	2.67

TABLE XII. Chemical Shifts of Selected Groupings in Azetidines in CCl_4 (δ in ppm from Tetramethylsilane)

Cpd.No.	Substituents and Chemical Shifts						
	N	2	2'	3	3'	4	4'
(139)	$C_6H_5CH_2$	CH_3	CH_3	H	H	CH_3	H
	C_6H_5: 7.3	1.02	1.15	-	-	0.91	-
	CH_2: 3.41,3.61						
(69)	$C_6H_5CH_2$	C_6H_5	H	H	H	H	H
	CH_2	-	-	-	-	-	-
	3.33,3.77						
(89)	$CH_3CH_2CH_2$	CH_3	H	CH_3	CH_3	H	H
	-	-	-	-	-	2.30	2.97
(90t)	CH_3	C_6H_5	H	H	$(CH_3)_2CH$	H	H
	2.17	7.3	-	-	$(CH_3)_2$	-	-
					0.70,0.77		
(64t)	C_6H_5	C_6H_5	H	H	CH_3	H	H
	6.3-7.2	7.2	4.38	-	1.22	-	-
(64c)	C_6H_5	C_6H_5	H	CH_3	H	H	H
	6.3-7.2	7.2	5.02	0.85	-	-	-
(138)	$(CH_3)_2CH$	H	H	OH	H	H	H
	$(CH_3)_2$: 0.91	-	-	5.5	4.33	-	-
	CH: 2.32						
(137)	$(CH_3)_3C$	H	H	OH	H	H	H
	0.95	-	-	5.2	4.37	-	-

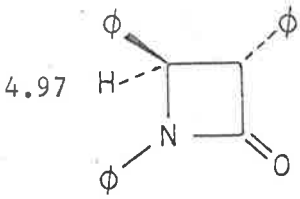
(142)	$C_6H_5CH_2$	H	H	C_6H_5	H	H	H
	CH_2: 3.56	-	-	-	-	-	-
(86t)	CH_3	C_6H_5	H	H	C_6H_5	H	H
	2.33	7.0-7.3	-	-	7.0-7.3	-	-

one methyl group on an adjacent *cis* or *trans* methyl group. Similarly, the asymmetry induced by a phenyl group in the 3 or 4 position on adjacent protons was found to be in the range 0.41-0.82 ppm and on adjacent methyl groups it was found to be in the range 0.60-0.80 ppm. The origin of the non-equivalence induced by a methyl group lies in the anisotropy of the $C-CH_3$ bond which shields a *cis* substituent or proton relative to a *trans* substituent or proton. This is analogous to the greater shielding of axial protons relative to equatorial protons in cyclohexane derivatives by the anisotropy of the C_2-C_3 bond.[137] Similarly, the anisotropy of the phenyl group is responsible for the shielding of a *cis* substituent or proton relative to a *trans* substituent or proton. This effect has been discussed in more detail above [Section I 1.(1), Equation (2-4) and Figure 11].

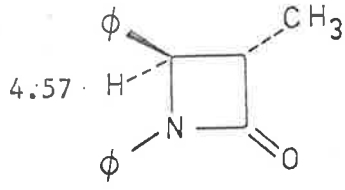
The chemical shifts of protons and methyl groups in position 3 or 4 of the 2-azetidinone ring of the compounds listed in Table IX were assigned on the basis of these observations. The higher field methyl signal was assigned to the methyl group *cis* to the phenyl group in compound (57). Similarly, the methyl group *cis* to the *tert*-butyl group in the spectra of compounds (48), (42), (120) and (56) was

assigned to the higher field signal in each case. The assignment of the methyl groups for compounds (85), (54), (41) and (119) [Table IX] was made on the basis of a comparison with compounds (39) and (121), which revealed that in such systems the 4-methyl group resonates at lower field than do 3-methyl groups. In the latter compounds, (39) and (121), again the 4-methyl group *cis* to the 3-methyl group was attributed to the higher of the two low field methyl groups.

Several assignments cannot be made with certainty. In the spectrum of compound (115), the higher field doublet of the AB system was assigned to the hydrogen atom at position 4 *cis* to the methyl group as a result of a comparison of the chemical shift of



(50t)



(49t)

(Ref. 46)

the 4-proton in compounds (50t) and (49t). This indicated that a 3-methyl group shielded a 4-proton *cis* to it more than did a 3-phenyl group. For compound (118), there did not appear to be sufficient information available here to determine which of the two protons at position 3 resonated at higher field. Accordingly, the correct assignment could well be the reverse to that given in Table IX for

the 3 protons of compound (118). The surprising thing, however, is that in compound (118) there is a chemical shift difference of 0.34 ppm between the two protons at position 3 whereas in compound (40), which lacks the *N*-chlorosulphonyl substituent, the corresponding protons have nearly identical chemical shifts, with the resonance signal being a broad singlet. This could be explained if it is assumed that the $-SO_2Cl$ group is out of the plane of the 2-azetidinone ring, in which case the proton at position 3 and *cis* to the $-SO_2Cl$ group should be deshielded relative to the proton *trans* to the $-SO_2Cl$ group. The $-SO_2Cl$ group should have a higher probability of lying on the opposite side of the ring to the $-CH_2C(CH_3)_3$ group.

An $-SO_2Cl$ group on the nitrogen atom of 2-azetidinones causes a large downfield shift of substituents at position 4, relative to the N—H unsubstituted 2-azetidinone, of the order of 0.18-0.38 ppm and usually a somewhat smaller, but definite, downfield shift of substituents at position 3 of the order of 0.07-0.56 ppm. [Compare the spectra of compounds (118), (121), (120) and (119) with those of compounds (40), (39), (42) and (41).]

A comparison of the spectra of compounds (42) and (120) with those of compounds (39) and (121) indicates that a methyl group *cis* to another methyl group resonates at a higher field than does a methyl group *cis* to a *tert*-butyl group. Furthermore, comparison of the 4,4-dimethyl resonance signals of compounds (39) and (42) with that of 4,4-dimethyl-2-azetidinone (δ CH_3 = 1.46 ppm[46]) suggests that a

methyl group at position 3 results in an upfield shift of both *cis* and *trans* methyl groups at position 4 with the effect on the *cis* methyl group being the larger. On the other hand, a *tert*-butyl group at position 3 causes only a small upfield shift of a *cis* methyl group at position 4 and a similar small downfield shift of a *trans* methyl group.

(ii) Non-equivalence of benzylic protons in 2-azetidinones.

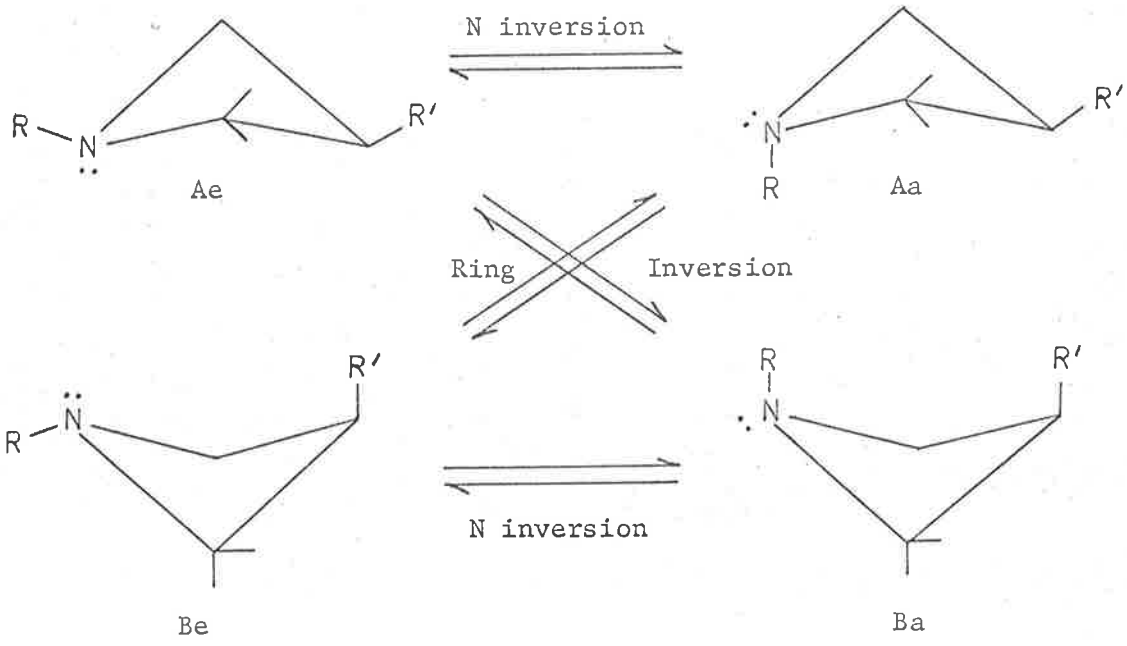
As in the case of other 1-benzyl-2-azetidinones,[46,203] a marked magnetic non-equivalence of the benzylic $-CH_2$ protons was observed in the spectrum of compound (57) [1.05 ppm]. In view of the non-equivalence of the benzylic $-CH_2$ protons in the azetidine (70), which was derived from compound (56), it is worth noting that the benzylic $-CH_2$ protons of compound (56) are equivalent. The non-equivalence of the benzylic $-CH_2$ protons in the azetidine (70) is discussed in more detail below.

(b) Coupling Constants in 2-Azetidinones

Coupling constants for the 2-azetidinones listed in Table IX are given in Table X.

A long range coupling of the proton at position 3 to the proton on the nitrogen atom was clearly resolvable in the spectra of compounds (39) and (42) with values of 1.1 c.p.s. and 0.9 c.p.s. respectively. This long range coupling has been observed in a number of other 2-azetidinones.[46]

(2) Azetidines



Scheme 40. Conformations of the azetidine ring

The possible conformations of a 3-substituted azetidine are shown in Scheme 40. Although nothing is known of the conformational preferences of ring substituents for azetidines and very little for cyclobutanes it is reasonable to expect the pseudo-equatorial position to be preferred. On this basis Ae would be the preferred conformation while Ba, with two axial substituents, should be unimportant. Aa and Be may be significantly populated. It has been shown that the phenyl group has an "equatorial" preference of ∿1 kcal/mole in *gem*-difluoro-cyclobutane[185] (c.f. 3.1 kcals/mole in cyclohexane[248]).

The ring inversion in four-membered ring compounds and nitrogen inversion in aziridines and azetidines have been discussed above in

Sections I. 2 and I. 3, respectively of this Chapter. In piperidines the usual chair inversions are much slower than bond-inversion at nitrogen (e.g.[248]). In fact, the latter is so much faster in six-membered ring compounds that the rate cannot, as a rule, be obtained directly by variable temperature n.m.r. spectroscopy whereas the rate of the former can. On the other hand, the rate of inversion of the nitrogen substituent in aziridines is readily measured by n.m.r. spectroscopy (see Section I. 3). In the case of cyclobutanes, however, the barrier to ring inversion is low and therefore the rate of ring inversion high. On the basis of these observations it was anticipated that azetidines would represent an intermediate situation as regards the rate of nitrogen inversion, the rate being somewhere between that in piperidines and aziridines. As far as ring inversion is concerned, it was anticipated that the rate of ring inversion of azetidines would be much greater than that of cyclohexanes; possibly about the same as cyclobutanes.

(a) Chemical Shifts (Azetidines)

The chemical shifts of the azetidines are given in Tables XI and XII. The compound numbers refer to those allotted in the discussion of their synthesis in Chapter 1 or in the details of their synthesis in Chapter 4. The numbering for the azetidine ring is shown in Figure 19. All spectra were recorded as approximately 10% carbon tetrachloride solutions containing tetramethylsilane (TMS) as an internal reference. Chemical shifts are expressed as δ in ppm from TMS.

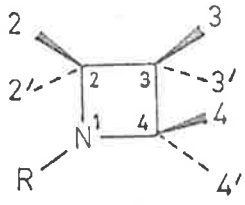


Figure 19

The spectra of all compounds given in Table XI were analysed as AB or ABX systems in the usual way[111] or in cases where the spectra were more complex (ABXY or A_3MXY) by using the Ferguson[222] or Bothner-By[223] n.m.r. programs adapted for use on the University of Adelaide CDC6400 computer and in the former case chemical shifts quoted to 2 decimal places are accurate to at least 0.01 ppm. The errors in the chemical shifts obtained using the iterative programs were less than 0.001 ppm for all cases recorded in Table XI. The chemical shifts reported in Table XII are those for selected groupings in azetidines whose spectra were not completely analysed.

(i) Assignment of 2,3 and 4 protons and substituents in azetidines.

A priori, in the series of compounds (61), (66), (71), (73), (67), (72), (74) and (87), for example, one would be tempted to assign the methyl group at position 3 and *cis* to the 2-phenyl group to the higher field signal by analogy with the 2-azetidinones.[46] In these azetidines the phenyl group induces asymmetry of the order of

0.37-0.43 ppm in the adjacent methyl groups and this shift arises by a combination of the effects of the anisotropies of the phenyl group and the C—C bond joining the phenyl group to the azetidine ring. A *cis* methyl group can lie well within the shielding region of the aromatic ring current, whereas the *trans* methyl group will probably be in the deshielding region[122] if it is assumed that the phenyl group exists in a preferred conformation in which the plane of the aromatic ring is approximately at right angles to the plane of the azetidine ring in its equilibrium position. The anisotropy of the C—C bond should shield the *cis* methyl group relative to the *trans* methyl group. Thus the methyl group at position 3 and *cis* to the phenyl group in the compounds (61), (66), (71), (73), (67), (72), (74) and (87) was considered to resonate at the higher field. Such an assignment is further substantiated by a comparison of the spectra of the two compounds (64c) and (64t) [Table XII] in which the 3-methyl group in compound (64c) is shielded relative to the same group in compound (64t).

The proton at position 2 in compound (64t) [Table XII] resonates 0.64 ppm higher than does the corresponding proton in compound (64c) thus showing that a proton at position 2 and *cis* to a methyl group resonates at a higher field than does a corresponding proton which is *trans* to the methyl group. Accordingly, the protons at position 4 and *cis* to the methyl group in compounds (130) and (131) were considered to resonate at higher field than the ones *trans* to the methyl group. The higher of the two lower-field methyl

signals was assigned to the 2-methyl group which is *cis* to the 3-methyl group in these two compounds (130) and (131).

The stereochemistry of the azetidines (88t) and (88c) is *trans* and *cis* respectively since they were prepared from the corresponding 2-azetidinones (82t) and (82c), the stereochemistry of which has been well established,[48,125] by a method which does not result in any stereochemical change of the ring substituents. It can be seen that in the *trans* azetidine the 3-proton is more shielded than the corresponding proton in the *cis* compound by 0.25 ppm. Similarly, in the *trans* azetidine the *tert*-butyl group at position 3 is deshielded relative to the *tert*-butyl group in the *cis* compound. In other words, a proton and a *tert*-butyl group *cis* to a phenyl group are shielded relative to the same groups in a *trans* relationship. Furthermore, the proton at position 2 in compound (88t) resonates 0.53 ppm higher than does the corresponding proton in compound (88c) showing that protons *cis* to a *tert*-butyl group resonate at higher field than do protons *trans* to a *tert*-butyl group and it seems justified to extend this to the case of the effect of *tert*-butyl groups on adjacent methyl groups. On the basis of these observations, the methyl groups at positions 2 or 3 in compounds (63) and (70) and the protons at position 4 in compounds (70) and (88t) were assigned as indicated in Table XI. However, satisfactory analysis of the spectrum of compound (88c) required making the opposite assignment for the 4-protons to that expected on the basis of the above discussion. This may reflect some conformational feature of the azetidine ring or its substituents and is discussed in more detail below.

In the series of compound (61), (66), (71), (73), (67), (72), (74) and (87) not only are the methyl groups at position 3 non-equivalent but also the two protons at position 4. Thus the phenyl group at position 2 also induces asymmetry at position 4. Again, if it is assumed that the phenyl group exists in a preferred conformation in which the plane of the aromatic ring is approximately at right angles to the plane of the azetidine ring, it appears from models that the proton at position 4 and *cis* to the phenyl group would be deshielded relative to the proton *trans* to the phenyl group. On this basis, the protons at position 4 in this series were assigned as indicated in Table XI. Further support for these assignments is given by an examination of long-range coupling constants which are discussed below [Section (b)(iii)].

A *tert*-butyl group at position 2 also induces non-equivalence of the protons at position 4. Since a 2-*tert*-butyl group should shield a proton at position 4 and *cis* to it, the assignment of the 4-protons in compound (63) was made as shown in Table XI, with the 4-proton *cis* to the *tert*-butyl group being shielded relative to the *trans* proton. Similarly, the 4-methyl group in compound (139) should shield the 2-methyl group which is *cis* to it relative to the *trans* methyl group and thus the 2-methyl groups were assigned accordingly.

The relative assignments of the protons at positions 2 and 4 in compounds (124) and (125) and of the protons at position 3 in compound (135) are more or less arbitrary. The final decisions for

compounds (124) and (125) were made by analogy with the corresponding 2-azetidinone (115) [Table IX, Section 1.(1)(a)] and by an examination of a model of compound (124).

(ii) Chemical Shifts in *N*-Benzylazetidines.

The replacement of the N—H of azetidines with an *N*-benzyl group results in an upfield shift of protons or methyl groups in positions 2 or 4. A similar effect is observed for protons at position 3 but the effect is negligible for 3-methyl groups. Thus, a comparison of the chemical shifts of the 3-methyl groups in compounds (124) and (125), in compounds (132) and (68) and in compounds (130) and (131) shows upfield shifts of this group in the *N*-benzyl compound relative to the N—H compound of 0.00, 0.10 and -0.01 ppm. In compounds (124) and (125), upfield shifts of 0.51 and 0.52 ppm are found for 2 (and 4) and 2' (and 4') protons respectively. Similarly, upfield shifts of the 2-methyl groups of 0.12 ppm are observed in compounds (132) and (68) and 0.35 ppm in the case of the 2-protons. Again, upfield shifts of 0.11 and 0.11 are observed for the 2 and 2' methyl groups respectively and upfield shifts of 0.20, 0.38 and 0.20 ppm for the 3', 4 and 4' protons respectively in compounds (130) and (131).

The long range shielding effect may be explained in part by assuming that one of the more preferred conformations of the benzyl group is one in which the phenyl ring lies underneath the azetidine ring thus shielding the 2- and 4- protons and methyl groups and, to a lesser extent, the 3-protons and methyl groups. This explanation

has been used to account for similar observations in 2-azetidinones[46] [compare, for example, spectra of compounds (41) with (54) and (42) with (56) in Table IX]. However, there are apparently other important factors involved, since the 3-methyl groups and 4-protons in compound (91) (an *N*-methyl azetidine) are more shielded than these groups in the corresponding *N*-benzylazetidine (68) [compare (41), (54) and (85) in Table IX].

(iii) Magnetic non-equivalence of Benzylic $-CH_2$ Protons in Azetidines.

The protons of a methylene group (or an isopropyl group) removed by one or more bonds from a centre of molecular asymmetry may be magnetically non-equivalent and display AB-type nuclear magnetic resonance spectra.[224-227] The existence of preferred conformations of the methylene group (or the isopropyl group) with respect to the asymmetric centre is generally considered necessary for magnetic non-equivalence, but the possibility of small contributions to magnetic non-equivalence arising from "intrinsic" asymmetry which are independent of rotational conformer populations has been pointed out.[228,229]

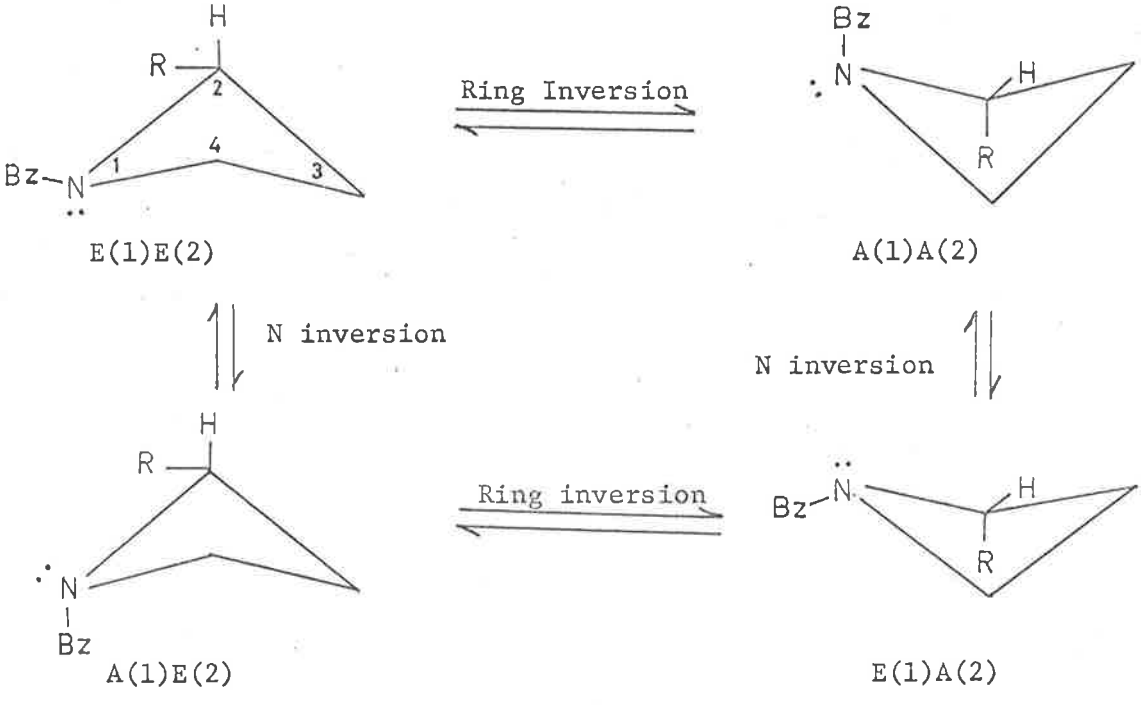
Non-equivalence of benzylic protons and methyl groups of isopropyl substituents has been observed in 2-azetidinones[46,203] [see also Section 1.(1)(a)]. Magnetic non-equivalence has also been recorded in a number of other *N*-benzyl cyclic amides.[230,231]

As in the case of 2-azetidinones,[46] the presence of a phenyl group in the 2-position of an azetidine ring induces a marked magnetic non-equivalence of the *N*-benzylic protons with a chemical shift

difference of about 0.44-0.56 ppm [compounds (67), (69) and (71)]. The chemical shift difference for the corresponding 2-azetidinones is nearly twice this value.[46] This difference may be caused, in part, by the removal of the C=O group in the azetidine and/or a change in the ring geometry. A phenyl group in the 3-position does not cause magnetic non-equivalence [compounds (125) and (142)].

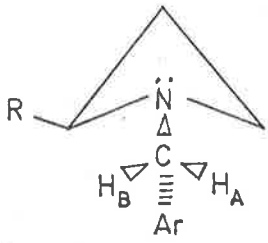
The non-equivalence of the benzylic $-CH_2$ protons may be explained as follows. The possible conformations of a 2-substituted azetidine are given in Scheme 41. In order to simplify the argument it is assumed that -

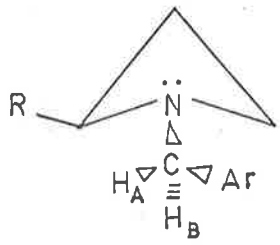
(a) in the general case the benzyl groups and the C(2) substituents will have about the same conformational preferences so that A(1)E(2) and E(1)A(2) are approximately equally probable.



Scheme 41. Conformations of a 2-substituted azetidine

E(1)E(2)





NC4

RE: high

AC: negligible

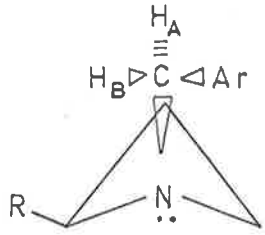
lp RE: low

AC: H_B+ (shielding)

NC2 RE: low

AC: H_A+, H_B-

A(1)E(2)



lp

RE: high

AC: H_A++, H_B--

NC4

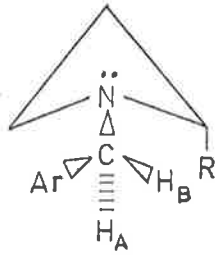
RE: very high

AC: small

NC2 RE: low

AC: H_A-, H_B-?

E(1)A(2)



lp

RE: very high

AC: small

NC4

RE: high

AC: H_B+

NC2 RE: low

AC: H_A+, H_B--

RE ≡ estimated relative energy, AC ≡ estimated asymmetry contribution

Figure 20

(b) A(1)A(2) will be of considerably higher energy than the other conformations. This is not self evident. The 1,2-interactions will be relieved by ring distortion and there is only one major 1,3-interaction destabilizing the axial form. However, it seems to be a reasonable simplifying assumption - and the contribution to the non-equivalence of the $-CH_2$ protons of this form will be small, in any case, and therefore A(1)A(2) will not be considered any further.

(c) E(1)E(2) should be the lowest energy and predominant conformation.

It is now necessary to consider the 3 possible staggered rotamers of the *N*-benzyl group for each of the conformers E(1)E(2), E(1)A(2) and A(1)E(2), of which the important ones are shown in Figure 20. The rotamers are classified as lp (the CH_2 group staggered about the nitrogen lone pair), NC2 (the CH_2 group staggered about the N−C(2) bond) and NC4 (the CH_2 group staggered about the N−C(4) bond). The estimated relative energy (RE) and asymmetry contribution (AC) to the benzylic $-CH_2$ group of each conformer is also shown in Figure 20. If we now neglect conformations of high energy, it seems that the $-CH_2$ asymmetry would be produced by either or both (a) unequal populations of E(1)E(2)lp and E(1)E(2)NC2 and (b) equal population of the above two, but with some contribution from E(1)A(2)NC2.

From compound (139) [Table XII] it can be seen that three methyl groups at positions 2, 2' and 4 are sufficient to cause a magnetic non-equivalence of the benzylic $-CH_2$ protons of 0.20 ppm although three methyl groups at positions 2, 2' and 3 [compound (131)] do not cause magnetic non-equivalence. The benzylic $-CH_2$ protons

of compound (70) show a chemical shift difference of 0.16 ppm although in the corresponding 2-azetidinone (56) these protons are equivalent. This aspect is further discussed in Section 2.(2).

The methyl groups of an *N*-*iso*propyl group are also non-equivalent provided there is a phenyl group at position 2 as shown by compound (73) where the chemical shift difference is 0.22 ppm. The preferred conformation in this case would be the one in which the proton of the *iso*propyl group approximately eclipses the phenyl group. The methyl groups of the *N*-*iso*propyl group of compound (138), which lacks a 2- or 4-substituent, are equivalent. The magnetic non-equivalence is not confined to the *N*-substituent as the methyl groups of a 3-*iso*propyl group are also non-equivalent in compound (90t) [Table XII], which bears a 2-phenyl group.

(iv) Effect of the *N*-Substituent on the Chemical Shifts of Groups in the 2-Phenyl-3,3-dimethylazetidine Series.

The effect of varying the *N*-substituent of *N*-substituted 2-phenyl-3,3-dimethylazetidines and 4-phenyl-3,3-dimethyl-2-azetidinones on the chemical shifts of the 2'- and 4'-protons respectively is shown in Table XIII. From the table is can be seen that there is a marked upfield shift of the 2'-proton in an azetidine compared to the 4'-proton in the 2-azetidinone. In view of the well-known deshielding effect of the carbonyl group[111(a)] this would be expected. The nature of the *N*-substituent does not appear to have any systematic effect on the chemical shift of the 4'-proton in the 2-azetidinones (except that the *N*-phenyl group markedly deshields

TABLE XIII. Chemical Shifts of the 2'- and 4'-Protons in *N*-Substituted 2-Phenyl-3,3-dimethylazetidines and *N*-Substituted 4-Phenyl-3,3-dimethyl-2-azetidinones, Respectively

	Azetidine		2-Azetidinone		
N-substituent	Cpd.No.	2'	Cpd.No	4'	$\Delta\nu_{2'4'}$
CH_3	(87)	3.54	(81)	4.31[46]	0.77
*n*Pr	(74)	3.69	(60)	4.38[46]	0.69
*i*Pr	(73)	3.67	(59)	4.34[46]	0.67
$C_6H_5CH_2CH_2$	(72)	3.77	(58)	4.07	0.30
$pMeOC_6H_4CH_2$	(71)	3.79	(57)	4.10	0.31
$C_6H_5CH_2$	(67)	3.85	(53)	4.15[46]	0.30
C_6H_5	(61)	4.61	(46)	4.80[46]	0.19
*t*Bu	(66)	4.02	(52)	4.34[46]	0.32

the 4'-proton). However, in the case of the azetidines there appears to be a marked trend in which the 2'-proton moves to lower field as the size of the *N*-substituent increases. The preferred conformation for all of these substituents would be expected to be the one in which the substituent is *trans* to the phenyl group and so the order of shielding of the *cis* proton by the *N*-substituents is Me > *n*Pr ∿ *i*Pr > $C_6H_5CH_2CH_2$ ∿ $pMeOC_6H_4CH_2$ ∿ $C_6H_5CH_2$ > C_6H_5 > *t*Bu. A similar effect has been observed in aziridines[216] in which protons *cis* to magnetically anisotropic *N*-alkyl groups are shifted upfield relative to the N—H aziridine.

The effect of varying the *N*-substituent of 2-phenyl-3,3-dimethylazetidines on the chemical shifts of protons 4 and 4' is shown in Table XIV. From this table it can be seen that as the size of the *N*-substituent increases the chemical shift difference $\Delta\nu_{44'}$

TABLE XIV. Chemical Shifts of 4- and 4'-Protons in *N*-Substituted 2-Phenyl-3,3-dimethylazetidines

N-substituent	Cpd.No.	4	4'	$\Delta\nu_{44'}$
CH_3	(87)	3.11	2.58	0.53
*n*Pr	(74)	3.18	2.62	0.56
*i*Pr	(73)	3.12	2.58	0.54
$C_6H_5CH_2CH_2$	(72)	3.19	2.67	0.52
$C_6H_5CH_2$	(67)	3.03	2.59	0.44
$pMeOC_6H_4CH_2$	(71)	2.97	2.56	0.41
C_6H_5	(61)	3.70	3.50	0.20
*t*Bu	(66)	2.97	2.83	0.14

decreases. Thus the magnitude of the anisotropic shift decreases with increased steric requirements of the *N*-substituent in an order similar to that given above (i.e. anisotropic shift decreases in the order Me > *n*Pr ∿ *i*Pr > $C_6H_5CH_2CH_2$ ∿ $pMeOC_6H_4CH_2$ ∿ $C_6H_5CH_2$ > C_6H_5 > *t*Bu). Again a similar effect has been observed in *N*-substituted

aziridines[216] where it was proposed that the somewhat unexpected [128,232,233] decreased shielding of the larger alkyl groups could be accounted for by intramolecular van der Waals (dispersion) interactions between the *N*-alkyl and ring protons.[216,234-236] Furthermore, a comparison of the change in the chemical shifts of the 4- and 4'-protons (Table XIV) as one descends the series *N*-methyl- to *N*-*tert*-butyl-2-phenyl-3,3-dimethylazetidine reveals that it is the chemical shift of the 4'-proton which changes the more. This would be the expected result if the 4'-proton were *cis* to the *tert*-butyl group which were in turn *trans* to the 2-phenyl group, since the shielding of the *cis* proton at position 2 (Table XIII) follows the same trend [i.e. the 2'- and 4'-protons in compound (66) are both deshielded relative to the 2'- and 4'-protons in compound (87)]. The observation that both the 2'- and 4'-protons in compound (66) are deshielded relative to the same protons in compound (87), together with the fact that $\Delta\nu_{44'}$ decreases as one descends the series from the *N*-methyl to the *N*-*tert*-butyl compound, may be taken as further evidence that the assignment of the 4-proton *cis* to the phenyl group as the one which resonates at lower field in this series is the correct one.

(v) Chemical Shifts of the 3,3'-Methyl Groups in Azetidines and 2-Azetidinones.

A comparison of the chemical shift difference of the 3- and 3'-methyl groups in the same series of azetidines (Table XV) shows that the *N*-substituent has no significant effect. However, a comparison of the chemical shift difference between the 3- and 3'-methyl groups in azetidines with those in 2-azetidinones [Table XV] reveals that

TABLE XV. The Chemical Shifts of the 3 and 3' Methyl Groups in *N*-Substituted 2-Phenylazetidines and 4-Phenyl-2-azetidinones

	Azetidine				2-Azetidinone			
N-substituent	Cpd.No.	CH_3	CH_3	$\Delta\nu_{CH_3}$	Cpd.No.	CH_3	CH_3	$\Delta\nu_{CH_3}$
CH_3	(87)	0.76	1.13	0.37	(81)	0.76	1.43[46]	0.67
*n*Pr	(74)	0.78	1.16	0.38	(60)	0.77	1.44[46]	0.67
*i*Pr	(73)	0.72	1.11	0.39	(59)	0.76	1.38[46]	0.62
$C_6H_5CH_2CH_2$	(72)	0.78	1.15	0.37	(58)	0.69	1.22	0.53
$pMeOC_6H_4CH_2$	(71)	0.78	1.15	0.37	(57)	0.76	1.30	0.54
$C_6H_5CH_2$	(67)	0.80	1.17	0.37	(53)	0.79	1.35[46]	0.56
C_6H_5	(61)	0.85	1.28	0.43	(46)	0.85	1.52[46]	0.67
*t*Bu	(66)	0.71	1.08	0.37	(52)	0.71	1.32[46]	0.61

the chemical shift difference in the latter compounds is nearly twice that in the former compounds. There are at least three possible explanations for this observation. Firstly, the conformation of the phenyl group in its equilibrium position in the azetidine may be different from that in the 2-azetidinone. As has been discussed above, the 2-azetidinone ring has been shown to be planar and the 2-phenyl group makes an angle of about 90° with the 2-azetidinone ring.[46,125,203] From models, there seems to be no reason why this angle should change appreciably. Furthermore, any change in the conformation of the phenyl group might be expected to affect the

cis methyl group (higher field) to a greater extent than the *trans* methyl group whereas, in fact, it is the *trans* methyl group which moves upfield in the azetidine. Secondly, there may be a change in the conformation of the *N*-substituent. That this is an unlikely explanation may be seen by comparing the spectra of compounds (67) and (53). It has been shown that the $N-CH_2$ bond does not lie in the plane of the 2-azetidinone ring[46,203] and it seems that its conformation would be fairly similar in the azetidine (67). However, there is a chemical shift difference of 0.18 ppm for the 3'-methyl group in the spectra of compounds (67) and (53). Thirdly, the difference between $\Delta\nu_{CH_3}$ for the azetidines and 2-azetidinones may reflect a change in the conformation of the ring. Clearly, if the azetidine and 2-azetidinone were both planar, reduction of the C = O group to the CH_2 group would not affect the chemical shift difference $\Delta\nu_{CH_3}$. On the other hand, if the azetidine ring were non-planar, the two methyl groups would experience different diamagnetic anisotropic effects of the two C—N bonds, the two C_4—H bonds, the C_2—C phenyl bond and the C_2—H bond providing the 2-phenyl group was fixed in the pseudo-equatorial position.

No systematic attempt was made to study the effects of various solvents or changes in concentrations of solutions on the chemical shifts.

(b) Coupling Constants in Azetidines

Geminal and vicinal coupling constants for the protons of the azetidine ring are given in Table XVI. The compound number corresponds

TABLE XVI. Coupling Constants of Ring Protons in Azetidines (in c.p.s.)

Cpd.No.	$J_{3,3'}$	$J_{4,4'}$	$J_{2,3}$ *cis*	$J_{2,3}$ *trans*	$J_{3,4}$ *cis* (or $J_{3,4'}$)	$J_{3,4}$ *trans* (or $J_{3,4'}$)
(61)	-	-6.4	-	-	-	-
(63)	-	-7.2	-	-	-	-
(64t)	-	?	-	6.4	?	?
(64c)	-	?	8.1	-	?	?
(66)	-	-6.2	-	-	-	-
(67)	-	-6.2	-	-	-	-
(70)	-	-6.1	-	-	8.11	7.68
(71)	-	-6.2	-	-	-	-
(72)	-	-6.0	-	-	-	-
(73)	-	-6.0	-	-	-	-
(74)	-	-6.3	-	-	-	-
(87)	-	-5.85	-	-	-	-
(88t)	-	-7.03	-	6.79	8.01	7.47
(88c)	-	-7.15	8.84	-	8.72	4.92
(89)	-	-6.0	-	-	-	-
(124)	-	-6.9	-	-	-	-

(125)	-	-6.7	-	-	-	-
(130)	-	-7.10	-	-	8.18	7.16
(131)	-	-6.01	-	-	7.69	6.63
(135)	-10.0	-	-	-	-	-

to that given in Tables XI or XII. The values are accurate to ±0.05 c.p.s. and in cases where a computer program was used the error was less than ±0.02 in all cases. The error in the geminal coupling constant $J_{33'}$ for compound (135) may be somewhat larger since the AB quartet was broadened due to the deuterium coupling of the deuterium atoms at position 4. All geminal coupling constants have been assumed to be negative although the signs were not determined experimentally.

(i) Vicinal Coupling Constants in the Azetidine Ring.

The relative magnitudes of the *cis* and *trans* couplings (J_{cis} = 7.7-8.8 c.p.s. and J_{trans} = 4.9-7.7 c.p.s.) are in qualitative agreement with the predictions of the Karplus equation[126,127] (although obviously the same constants in the $\cos^2\theta$ relationship do not apply in the strained azetidine ring) as the dihedral angles of close to 0° and 120° for the *cis* and *trans* configurations (Figure 21) would be expected to result in $J_{cis} > J_{trans}$.

The magnitude of the vicinal coupling constants in these azetidines are very similar to those observed in cyclobutanes[237] and cyclobutanones.[237,238] However, in the case of the reported

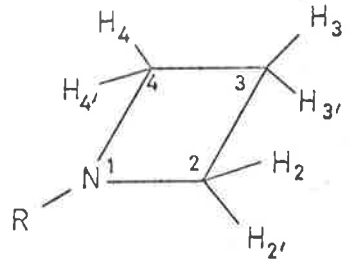


Figure 21

cyclobutanes and cyclobutanones there is considerable overlap of the ranges of vicinal *cis* (4.6-11.38 c.p.s.) and *trans* (2.24-10.72 c.p.s.) coupling constants. These compounds contained a wide range of substituents of differing electronegativity which would have had a major effect in determining the magnitude of the coupling constants. In the azetidines considered here there is no overlap in the ranges of the vicinal *cis* and *trans* coupling constants and therefore they may be used with some degree of certainty in assigning the stereochemistry of azetidines which do not carry highly electronegative groups.

The magnitude of *cis* and *trans* vicinal coupling constants in these azetidines are considerably greater than those observed in 2-azetidinones where the ranges of the *cis* and *trans* coupling constants are 4.9-6.0 c.p.s. and 2-2.8 c.p.s. respectively.[46,48,125] One explanation for this might be that the conformation of the azetidine is different from that of the 2-azetidinone, i.e. the azetidine is puckered or non-planar, although the removal of the C=O group may also have an effect. Unfortunately, conformational and electronegativity

effects as well as the effect of the carbonyl group in cyclobutanes and cyclobutanones on vicinal coupling constants have not been adequately investigated.[237] Therefore a comparison of azetidines and the corresponding 2-azetidinones with cyclobutanes and the corresponding cyclobutanones was not possible.

Inspection of the usual curve associated with the Karplus equation[126,127] (Figure 22) reveals that small changes in the dihedral

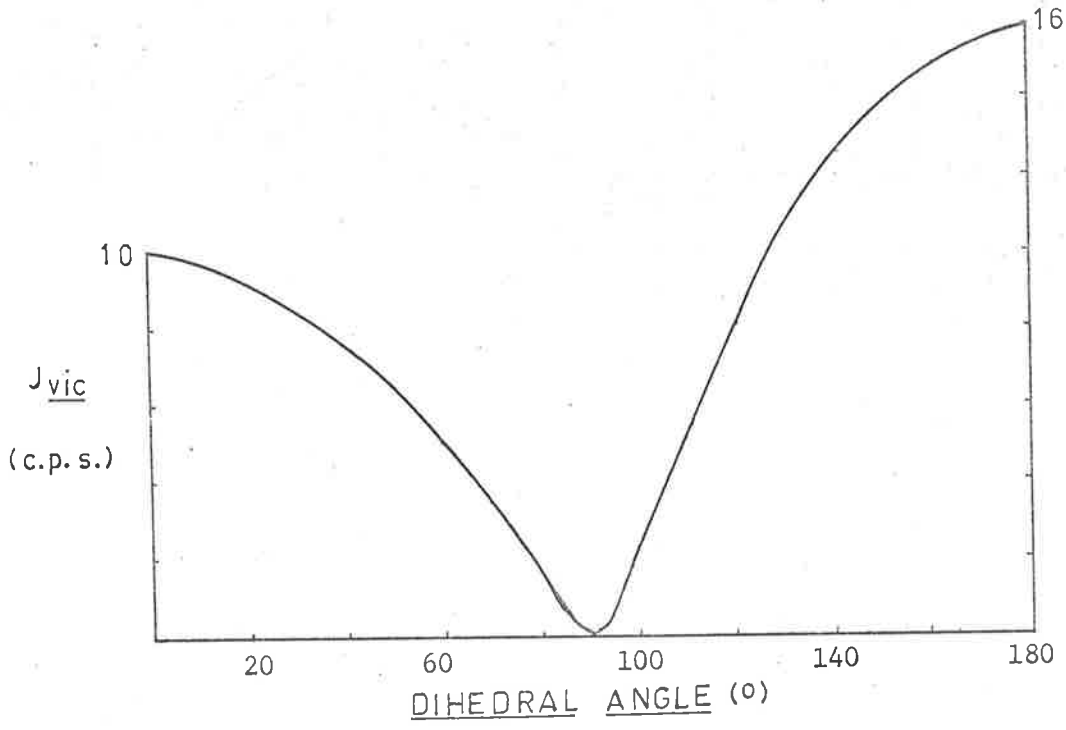


Figure 22

angle between the *cis* protons (e.g. 0° to 20°) produces a smaller change in J_{vic} (in this case <1 c.p.s.) compared to a similar change in the dihedral angle between the *trans* protons (e.g. 120° to 140° results in a change in J_{vic} of ∿3 c.p.s.). Thus it was anticipated

that changes in the ring conformation of the azetidine should be reflected to the greater extent by the *trans* vicinal coupling constant. Table XVI, does, in fact, indicate that there is a greater variation in *trans* vicinal coupling constants than in *cis* vicinal coupling constants and this may therefore be due to conformational ring changes (compare[239]). The preferred conformation for compound (88t) should be the one in which both the phenyl and *tert*-butyl groups occupy pseudo-equatorial positions. A comparison of the *cis* and *trans* vicinal coupling constants for compounds (88t) and (88c) shows that the *cis* coupling constant is greater and the *trans* coupling constant much smaller in compound (88c) than in compound (88t). From Figure 22, this suggests that the dihedral angle between both the *cis* and the *trans* protons in compound (88c) are smaller than in compound (88t). In other words, the *cis* compound (88c) would appear to be considerably less puckered than the *trans* compound (88t).

The effect of varying the temperature on vicinal coupling constants is discussed below [Section 2.(1)].

No systematic studies of the n.m.r. spectra of azetidines appear to have been reported. The n.m.r. spectra of several isolated azetidines have been reported[18,21,23,27(a),27(b),39,41,201,217] and in cases where they have been analysed have values in fair agreement with similar compounds reported here.

(ii) Geminal Coupling Constants in the Azetidine Ring.

The geminal coupling constants $J_{22'}$ and $J_{44'}$ were found to be in the range -5.85 to -7.2 c.p.s. The geminal coupling constant

in a four-membered ring would be expected to be more positive than methane (J_{gem} = -12.4 c.p.s.) because of the hybridization of the carbon atoms in the strained ring.[71] The effect of the nitrogen atom on the adjacent carbon atom of the azetidine ring would be to withdraw electrons through the σ bond (the C_2-N bond) which would remove electrons from the symmetric bonding orbital of the $-CH_2-$ group and lead to a further positive contribution to the geminal coupling constants $J_{22'}$ and $J_{44'}$.[71] Since the electronegativity of the N-atom in the azetidine is less than in the 2-azetidinone[201] it would be expected that $J_{22'}$ and $J_{44'}$ should be more negative in the azetidines than $J_{44'}$ in 2-azetidinones and this is found to be the case ($J_{44'}$ in 2-azetidinones = -5.5,[46] -5.2- -5.7 c.p.s.[201]). The values reported for $J_{22'}$ and $J_{44'}$ for several 3,3-disubstituted azetidines are somewhat more negative (-7.4- -8 c.p.s.) than the values obtained in this work.[201]

A geminal coupling constant of -10.0 c.p.s. for $J_{33'}$ in azetidines compared with a value of about -14.5 c.p.s.[46] for $J_{33'}$ in 2-azetidinones is reasonable since removal of the π electron system[138,144,145] and a decrease in the electronegativity of the N-atom at a β-position to C_3[71,129,130] would both be expected to result in a positive shift in the geminal coupling constant.

(iii) Long Range Coupling Constants across the Azetidine Ring.

Coupling across four bonds occurs between the proton at position 2 and the low-field proton in position 4 and the values are listed in Table XVII. Although all 2-phenyl azetidines showed evidence

TABLE XVII. Long Range Coupling Constants (c.p.s.) in Azetidines

Compound No.	H_4	Coupled group
(73)	0.9	$H_{2'}$
(74)	0.8	$H_{2'}$
(89)	0.7	$H_{2'}$
(72)	0.7	$H_{2'}$
(124)	1.1	$H_{2'}$

of this long-range coupling to the 4-proton only those cases in which clearly resolved splitting was observed are given in Table XVII. Irradiation of the 2'-proton removed the coupling to the low-field proton at position 4 showing that the 4-proton is coupled to the 2'-proton. Although the resonance signal of the high-field proton at position 4 was broad, the broadening was less than that for the low-field proton. Again spin-decoupling showed that the 2'-proton is also coupled to the high-field proton at position 4. Thus the 2'-proton is coupled to both the 4- and 4'-protons but the magnitude of the coupling to the lower field proton is the greater. In cyclobutanones[237,238] and 2-azetidinones[240] (Figure 23) there is some evidence that the *transoid* coupling constant is greater than the *cisoid* coupling constant. If a similar relationship holds for azetidines, the low-field proton at position 4 should be in a *transoid* relationship to the 2'-proton. This would mean that the low-field proton must be the one *cis* to the phenyl group (i.e. the

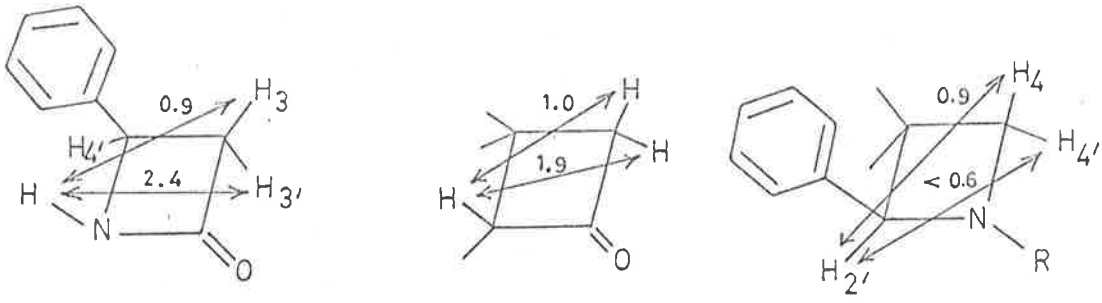


Figure 23

4-proton) thus providing further evidence that the 4-proton *cis* to the 2-phenyl group resonates at a lower field than does the *trans* proton. Of course, it is not possible to determine whether the long-range coupling is transmitted *via* the carbon atom C_3 or by the nitrogen atom.[112]

It has been suggested that the long range coupling of the proton at position 3 to the proton on the nitrogen atom in 2-azetidinones is transmitted *via* the sp^2 carbon of the carbonyl group (or possibly by direct orbital overlap).[241] The absence of any detectable long range coupling of this type in the azetidines (130) and (131) (<0.4 c.p.s.) compared with the 2-azetidinones (39) and (42) (Table X) (1.1 and 0.9 c.p.s. respectively) tends to support this view.

(iv) Other Coupling Constants.

Other coupling constants for azetidines are listed in Table XVIII.

TABLE XVIII. Other Coupling Constants for Azetidines (c.p.s.)

Compound No.	*N*-substituents	Methyl Substituents	Others
(67)	-13.2	-	-
(70)	-12.8	-	-
(71)	-12.8	-	-
(73)	-	-	CH_3-CH; 6.0
(74)	-	-	CH_3-CH_2; 6.6
(64t)	-	CH_3-CH; 7.0	-
(64c)	-	CH_3-CH; 7.0	-
(69)	-13.0	-	-
(90t)	-	-	CH_3-CH; 6.0
(130)	-	CH_3-CH; 6.93	-
(131)	-	CH_3-CH; 6.70	-
(139)	-13.5	CH_3-CH; 6.0	-

The geminal benzylic coupling constants of -12.8 to -13.2 c.p.s. in the azetidines (67), (71) and (69) are less negative than those for the corresponding 2-azetidinones (53), (57) and (55) [-14.9 to -15.1 c.p.s.[46] and Table X]. This suggests that the positive shift (J_{gem} becoming more positive), which would be expected on reducing the carbonyl group at the β-position,[137,132,143] outweighs the negative effect which a decrease in the electronegativity of the nitrogen atom in the azetidine compared to that in the 2-azetidinone would produce.[137,142]

2. Variable Temperature N.M.R. Spectra of Azetidines

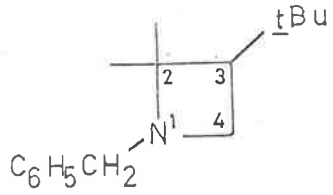
The possible conformations of a 3-substituted azetidine ring are shown in Scheme 40 (page 93) and of a 2-substituted azetidine ring in Scheme 41 (page 101). Variable temperature n.m.r. spectral studies designed to elucidate conformational properties of azetidines are discussed below.

(1) Effect of Temperature on Vicinal Coupling Constants

In an attempt to investigate possible conformational changes of the azetidine ring the spectra of several of the azetidines were recorded at various temperatures from -60° to 165°. In most cases only very minor changes in vicinal coupling constants were observed.

However, the spectrum of 1-benzyl-3-*tert*-butyl-2,2-dimethyl-azetidine (70) showed small changes as the temperature was increased and the results are shown in Table XIX. If the population of the

TABLE XIX. Chemical Shifts (δ) and Coupling Constants of Compound (70) at 40° and 165° in *o*-dichlorobenzene



(70)

Tempt	ν_4	$\nu_{4'}$	$\nu_{3'}$	$J_{44'}$	$J_{3'4}$	$J_{3'4'}$
40°	2.72	3.02	1.94	-6.2	7.65	8.24
165°	2.79	3.03	1.94	-6.4	7.90	8.00

conformer with the *tert*-butyl group in the *pseudo*-axial position increases as the temperature is increased then, on an average, the dihedral angle between the C_3-H_3, bond and the C_4-H_4 bond and also the dihedral angle between the C_3-H_3, bond and the C_4-H_4, bond should decrease and therefore $J_{3',4'}$ should increase and $J_{3',4}$ should decrease. This is the opposite to that observed and so presumably other factors must be important.

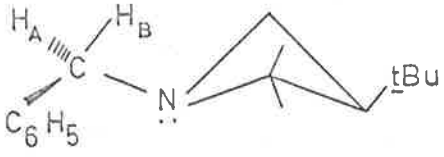
(2) Non-equivalence of the Benzylic CH_2 Protons in 1-Benzyl-3-*tert*-butyl-2,2-dimethylazetidine (70).

The benzylic CH_2 protons of compound (70) show a chemical shift difference of 0.16 ppm although in the corresponding 2-azetidinone (56) these protons are equivalent. If the magnetic non-equivalence in compound (70) were a result of restricted rotation about the H_2C-N bond with rotation being unrestricted in compound (56) the energy barrier to free rotation in compound (70) should be small. However, variable temperature n.m.r. spectral studies from 40° to 165°, in *o*-dichlorobenzene as solvent, of compound (70) do not support the view that the non-equivalence is due to restricted rotation in compound (70). The AB quartet was still apparent at 165° although the separation between the two central peaks had decreased from 3.3 c.p.s. at 40° to 1.2 c.p.s. at 165° and this indicates a free energy of activation $\Delta G^* \geq 22$ Kcals, which is much too high for rotation about a single bond.[248]

An alternative explanation is as follows. The ring conformations for the azetidine (70) are shown in Scheme 40 (page 93) where

R = $CH_2C_6H_5$ and R' = *tert*-Bu. The high preference of a *tert*-Bu group for the equatorial position in cyclohexanes suggests that conformations Be and Ba will be unimportant. Accordingly, the rotational conformations of only conformers Ae and Aa will be considered. The preferred rotational conformations A, B and C for the conformer Ae and D, E and F for the conformer Aa are shown in Figure 24. A consideration of the steric effects indicate that conformers A, B and E are the most likely. Conformers A and D appear to contribute most to non-equivalence of protons H_A and H_B but conformer D appears to be unimportant on steric considerations. If ΔG^* for the nitrogen inversion Ae → Aa and for Aa → Ae (Scheme 40) is small in each case but not equal, then it seems that the effect of temperature will be determined by $\Delta G°$, the difference between the free energy of conformers Ae and Aa, rather than ΔG^*. If, for example, $\Delta G° \simeq 1.0$ Kcal/mole then the ratio of the concentration of conformer Ae to Aa will be about 85/15 at 25° and 80/20 at 85°, i.e. only a small change in conformer populations with temperature will be observed. This means that the population of conformer A (Figure 24), the one responsible for the non-equivalence of the benzylic protons, will decrease only slightly at higher temperatures with the result that the chemical shift difference will change only slightly.

Rotational preferences for Ae

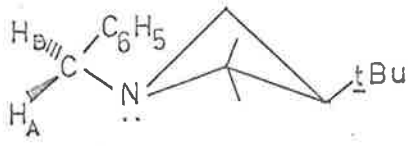


A

likely; source of non-equivalence

B

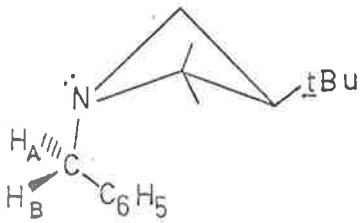
preferred



C

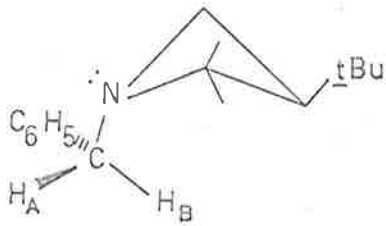
less favoured

Rotational preferences for Aa



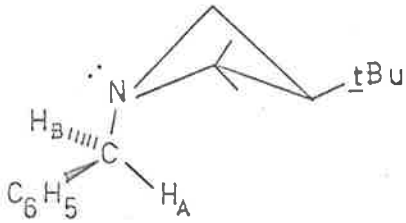
D

unfavourable: source of non-equivalence



E

preferred



F

less favourable

Figure 24

(3) Nitrogen Substituent Inversion Rates in Azetidines

No evidence of hindered nitrogen inversion was detected by variable temperature n.m.r. spectroscopy in any of the *N*-methyl, *N*-*iso*-propyl, *N*-*n*-propyl, *N*-benzyl, *N*-phenyl or *N*-*t*-butyl azetidines reported in this work, in $CDCl_3$ solutions, down to temperatures of -67°C.

Since the rate of inversion of nitrogen substituents in aziridines decreases markedly when the substituent is changed from methyl to bromine or chlorine,[217] the variable temperature n.m.r. spectra of 1-bromo and 1-chloro-2,2,3,3-tetramethylazetidine [(140) and (141) respectively] were studied. Since these compounds were not distilled before use, they were washed thoroughly with water to remove any trace of acid. Any trace of acid would greatly affect the observed rate.

The spectra of the methylene protons and methyl groups of compound (140) at several temperatures are shown in Figure 25. The signal from the methylene protons split into the expected AB quartet at a temperature where the rate of inversion became slow. That of the methyl groups split into three peaks although four peaks would be expected theoretically. This may be explained by assuming that there was an accidental magnetic equivalence of two of the methyl groups or at least the chemical shift between these two was very small. The methylene group of compound (141) behaved similarly although there was no change in the appearance of the methyl signals.

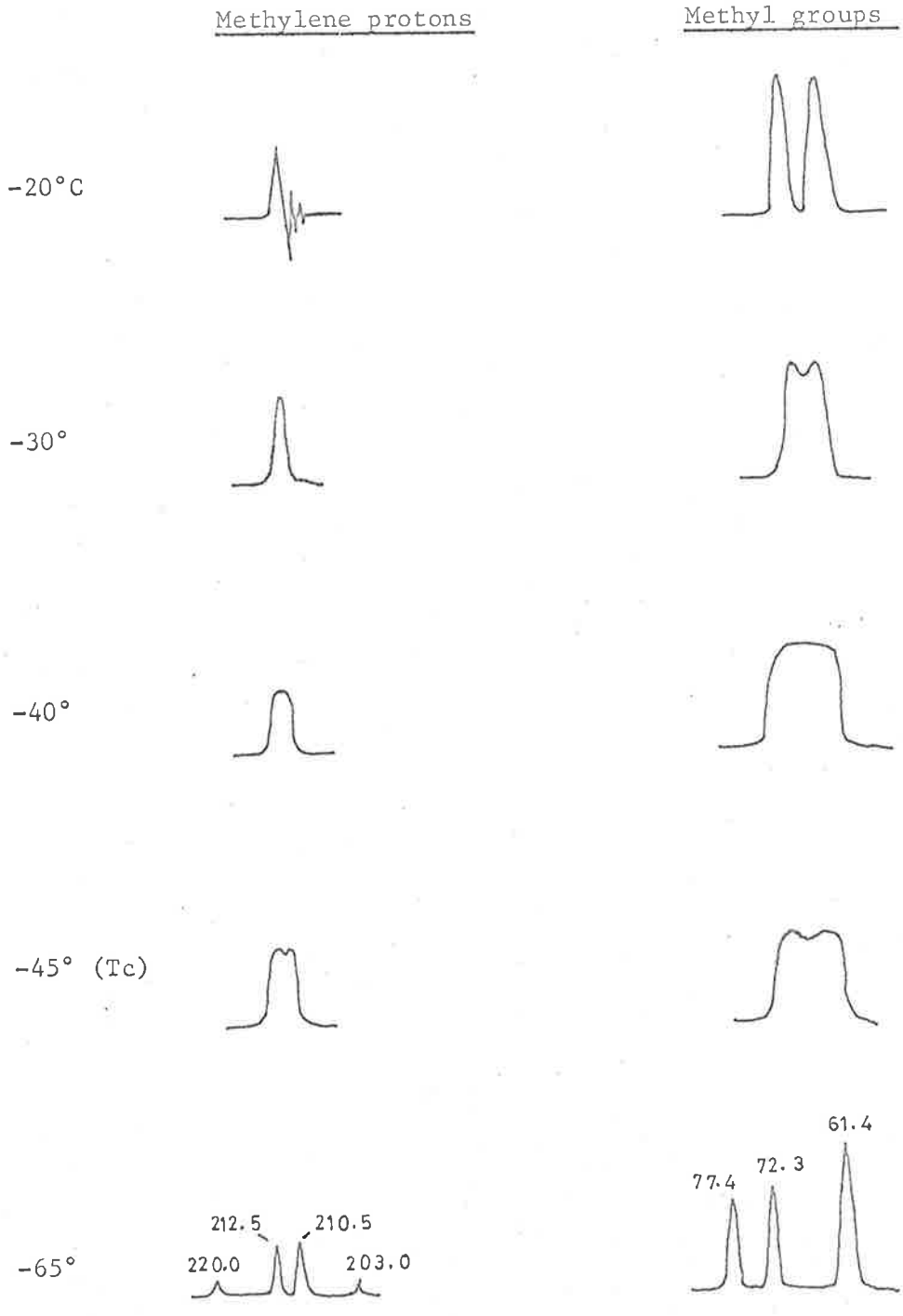
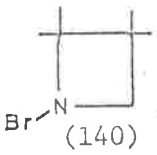
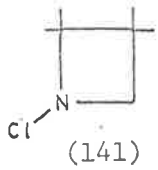


Figure 25. N.M.R. Spectra of 1-Bromo-2,2,3,3-tetramethylazetidine (140) [at 60 Mc/sec]

TABLE XX. Variable Temperature N.M.R. Spectral Data at Coalescence

(solvent: $CDCl_3$)

Compound	Group	Appearance when k slow	Tc	ΔGc* (kcals/mole)
 (140)	CH_2	quartet	-45±1°	11.5±0.1
	CH_3	three peaks	-43±1°	11.6±0.1
 (141)	CH_2	quartet	-37±1°	11.9±0.1
	CH_3	two peaks	-	-

At a given temperature, near Tc, the half-width at half maximum intensity of either the signal from the methylene protons or the methyl groups of compound (140) did not change significantly over a four-fold concentration range of the azetidine. This confirms that the inversion process is first order.

The free energies of activation ΔGc* (Table XX) at the coalescence temperature (Tc) were calculated using Equations (2-11) [J = 0 for the methyl groups, J = 7.5 c.p.s. for compound (140) and J = 7.0 c.p.s. for compound (141)] and (2-13) [Section I.4]. The slower rate of inversion in the chloro compound is in accord with the postulate that electronegative substituents on nitrogen decrease the rate of inversion.[213]

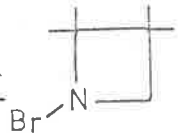
Equation (2-9) [Section I.4] was used to calculate the rate of inversion at several different temperatures near Tc for compound (140) from changes in the width of the methyl signals. A study of the coalescence of the two outside peaks of the three signals (Figure 25) suggested that these represented one of the doublets and the central

peak and the highest field peak the other doublet. Measurement of the full-width at half-height (W*) was possible for the narrowing of the two outside peaks above Tc but notbelow Tc due to the fact that changes in the other doublet (centre and highest field signals) obscured the central intensity. This is required for the measurement of W* below Tc. The values of k are summarized in Table XXI. The values of ΔH^* and ΔS^* were obtained from a plot of log (k/T) versus 1/T (Figure 26).

TABLE XXI. Rate Constants and Thermodynamic Properties of Nitrogen Inversion in 1-Bromo-2,2,3,3-tetramethylazetidine (140) [calculated from changes in the methyl group resonances]

T	°K	$\frac{1}{T} \times 10^3$	$k = \frac{1}{2\tau}$ (sec^{-1})	ΔGc^*	ΔH^*	ΔS^*
-30°	243°	4.12	75.4	11.7 kcals/mole	5.7 kcals/mole	-26 eu
-40°	233°	4.29	45.0	(at -43°C)		
-45°	228°	4.39	33.2			

Similar calculations were carried out for the methylene protons in compound (140) and (141) using Equation (2-9) to obtain rates at temperatures above Tc. However, the justification for the use of this equation in this case is extremely doubtful since 15J is 112 and 105 whereas k at Tc is 42.9 and 43.4 sec^{-1} for compounds (140) and (141) respectively. Thus Equation (2-10) is not satisfied. Accordingly,

The rates of nitrogen inversion in  in $CDCl_3$

A Plot of log (k/T) vs 1/T [k calculated from changes in line width of methyl (⊙——⊙) and methylene (△– –△) resonances.]

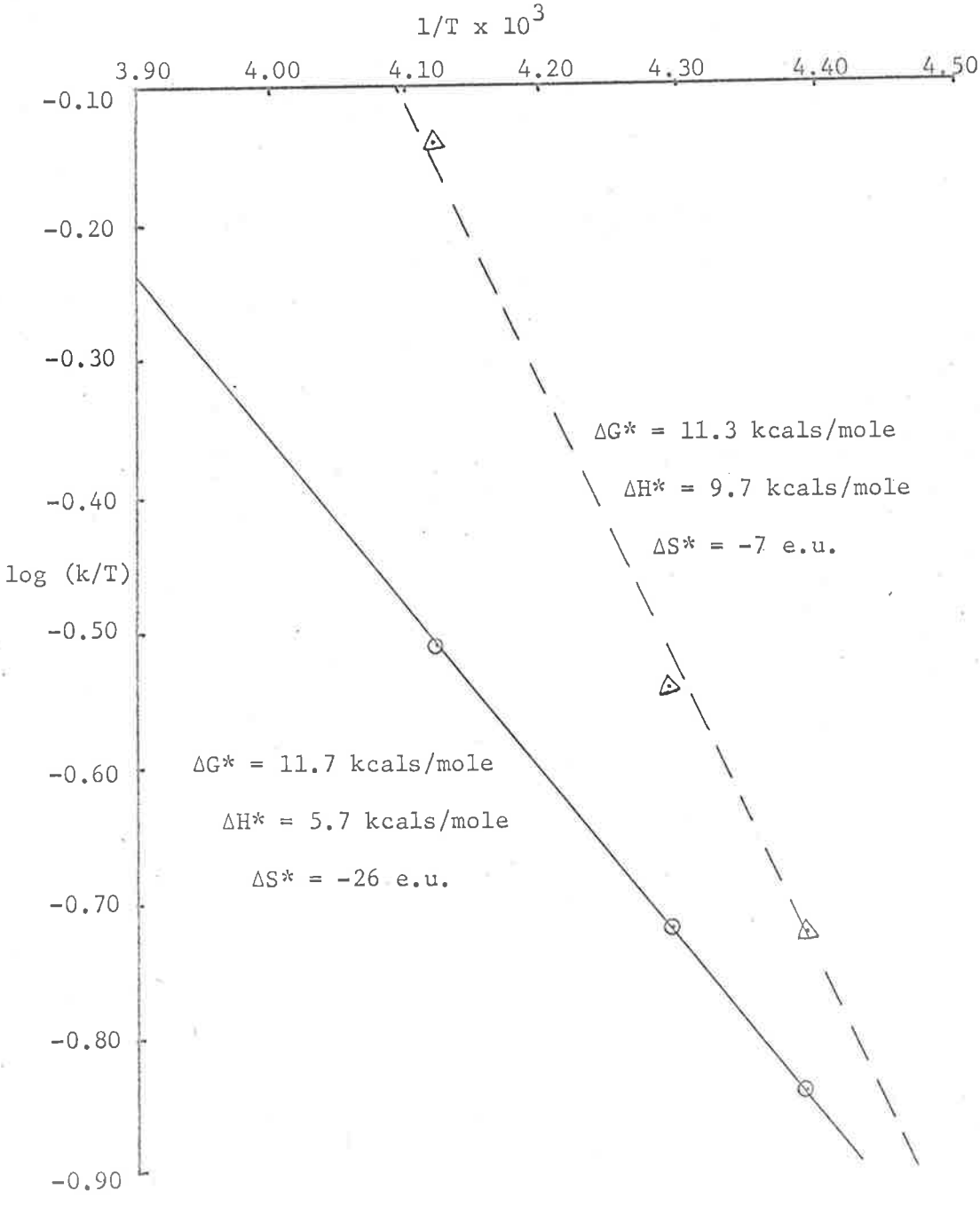


Figure 26. ⊙——⊙ values obtained from methyl groups

△ — △ values obtained from methylene groups

the errors in ΔG^*, ΔH^* and ΔS^*, the values of which are recorded in Table XXII, are probably greater than for those given in Table XXI.

TABLE XXII. Thermodynamic Properties of Nitrogen Inversion in 1-Bromo- and 1-Chloro-2,2,3,3-tetramethylazetidines [calculated from changes in the methylene group resonances]

Compound	ΔGc^*[a] (kcals/mole)	ΔH^* (kcals/mole)	ΔS^* (e.u.)
(140)	11.3[b]	9.7	-7
(141)	12.0[c]	10.6	-6

[a] calculated from $\Delta G^* = \Delta H^* - T\Delta S^*$

[b] $T = -45°$

[c] $T = -37°$

A plot of log (k/T) versus 1/T for compound (140), the values of k being obtained from changes in the methylene group resonances, is shown in Figure 26.

(4) Measurement of Nitrogen Inversion Rates in low pH media

Saunders and Yamada[249] have shown that proton exchange rates and nitrogen inversion rates of suitable amines can be measured in acidic aqueous solution by n.m.r. spectroscopy. Recently this technique has been applied and extended to the measurement of nitrogen inversion rates in six-membered nitrogen heterocyclic compounds.[250-252]

We have made preliminary studies of the effect of pH on n.m.r. and variable temperature n.m.r. spectra of 1,2,2,3,3-pentamethylazetidine (91) and 1-benzyl-2,2,3,3-tetramethylazetidine (68) in D_2O/pyridine solutions and the results are discussed below.

(a) 1,2,2,3,3-Pentamethylazetidine (91)

The n.m.r. spectra of compound (91) in D_2O/pyridine/H^+ at pH 6.60 (20°C) at various temperatures are shown in Figure 27. The *N*-methyl, ring methyls and methylene protons of compound (91) in D_2O each gave rise to singlets in the n.m.r. spectrum at δ 2.17, 1.07 and 2.83 respectively [δ = 0.00 for the sodium salt of 3-(trimethylsilyl)-1-propane-sulphonic acid (TMP)]. The addition of hydrochloric acid caused a downfield shift, as expected,[253] of each of these peaks with those arising from the ring methyl groups splitting into two peaks. The further splitting of these two peaks into four peaks on decreasing the temperature (or pH) was the expected result of reduction in the observed rate process. The outside peaks of the expected quartet for the methylene protons were not visible at low temperature (or pH).

In concentrated hydrochloric acid/pyridine (*no* D_2O present) the *N*-methyl signal of compound (91) split into a doublet (J = 6 c.p.s.) due to coupling to the proton on the quaternary nitrogen atom. Under the same conditions, the ring methyl groups gave four peaks which were identical to those mentioned above [Figure 27 at 4°C]. These facts indicate that the rate of proton exchange and nitrogen inversion are both slow in concentrated hydrochloric acid. When the pH was

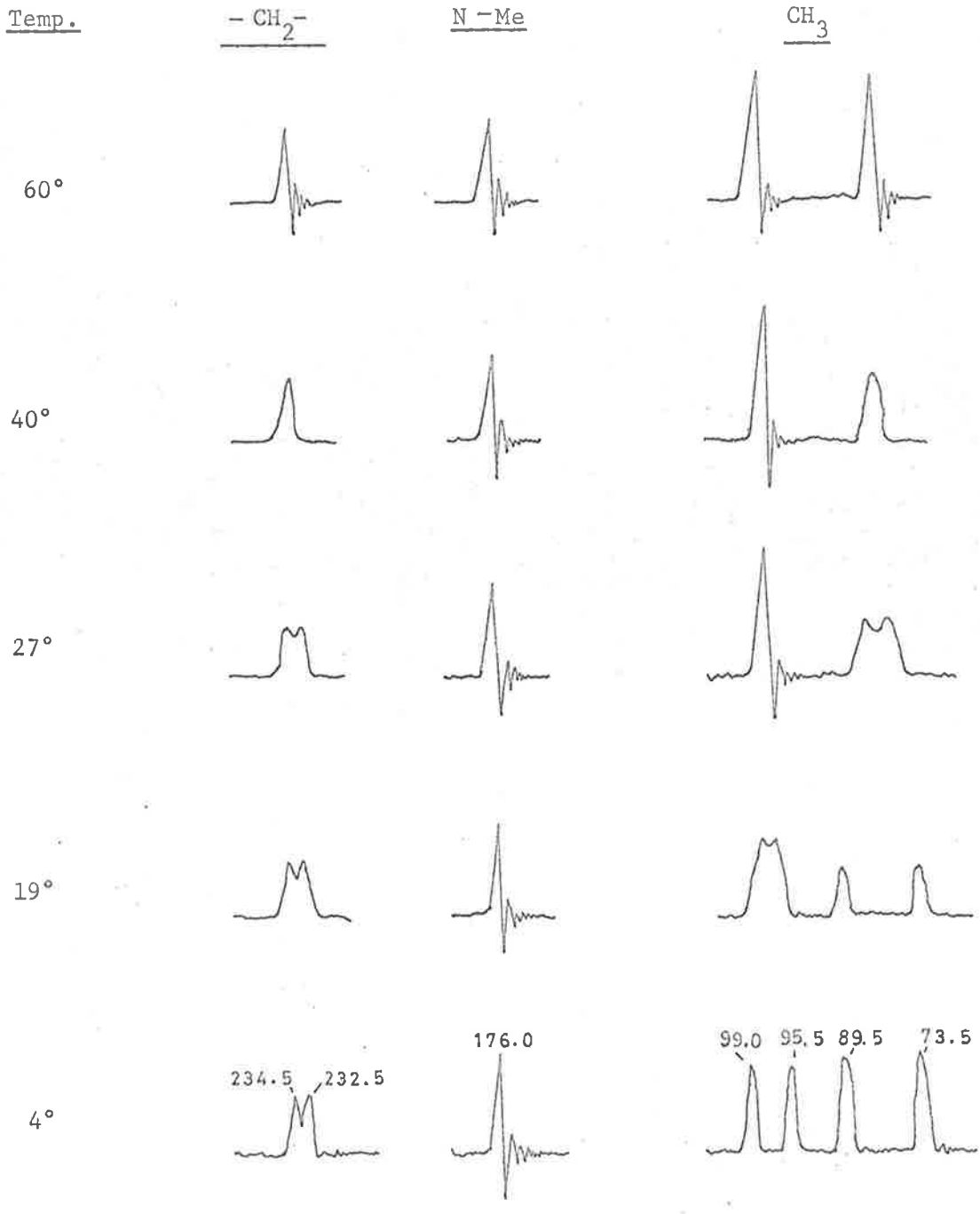


Figure 27. Variable temperature N.m.r. Spectra of 1,2,2,3,3-pentamethylazetidine (91) in D_2O/pyridine at pH 6.60 (20°C)

[Shifts in c.p.s. from TMP, spectrum at 60 Mc/sec.]

gradually increased, the *N*-methyl signal coalesced to a single peak long before the ring methyl groups commenced to coalesce, thus indicating that the rate of proton exchange is considerably greater than the rate of nitrogen inversion.

At low temperature (or pH) the average lifetime of the azetidine is too short to allow inversion of the *N*-substituent before reprotonation (provided the rate of inversion k_i << rate of protonation). Inversion is possible only for the unprotonated azetidine. As the temperature (or pH) is increased the rate of protonation and of nitrogen inversion will increase. This will result in a spectrum typical of one arising from an intermediate rate process (not very fast or very slow) from which a rate constant k_{meas} may be obtained. Provided the rate of protonation >> k_i and the acid dissociation constant, K_1, of the protonated azetidine is small ($K_1 \leq 10^{-2}$) the rate of inversion is given by the approximate Equation (2-15),[163,250]

$$k_i = \frac{k_{meas}\,[H^+]}{K_1} \qquad (2\text{-}15)$$

It has been shown above that the rate of protonation for compound (91) is considerably greater than the rate of nitrogen inversion. The rate of protonation for other amines has been found to be in the range 10^8-10^9 1/mole sec[249,244] and, if the rate of protonation of azetidines is also of this order, the rate of protonation is, in most cases, very much greater than the rate of nitrogen inversion k_i, as seen from values of k_i recorded below.

Clearly, the same effect on the n.m.r. spectrum will be observed whether the pH is varied over a particular range or the temperature is varied over a given range while the pH is kept constant (the pH will change slightly with temperature, but this change can be measured).

Since the coalescence temperature (Tc) for one set of methyl signals was different from the other set (because $\Delta\nu_{AB}$ was different) for compound (91), values of k_i and therefore ΔGc^*, calculated from Equations (2-11) and (2-13) respectively, may theoretically be used to determine values of ΔS^* and ΔH^*. However, since values at only two temperatures were known, such a procedure resulted in large uncertainties in the values of ΔS^* and ΔH^*. Nitrogen inversion rates and the free energy of activation at the coalescence temperatures are given in Table XXIII. In all cases, K_1 was measured potentiometrically

TABLE XXIII. Rates of Nitrogen Inversion and ΔGc^* at Tc for Compound (91) [in D_2O/pyridine]

Substituents	Tc	pH	K_1	k_i (sec^{-1})	ΔGc^* (Kcals/mole)
Higher field methyls	28°C	6.37	1.07×10^{-10}	7.78×10^{4}	10.9±0.1
Lower field methyls	19°	6.60	3.47×10^{-11}	5.64×10^{4}	10.7±0.1

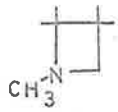
in the same solvent at approximately the same concentrations as were used in the variable temperature n.m.r. spectral studies.

The rates of nitrogen inversion were measured at temperatures above Tc for the high-field methyls using Equations (2-9) [Section I.4] and (2-15). Similarly, the rates of nitrogen inversion above and below Tc for the low-field methyls of compound (91) were also determined. Values of k_i obtained by these means are recorded in Table XXIV and a plot of log (k_i/T) versus 1/T is shown in Figure 28. The values

TABLE XXIV. Rates of Nitrogen Inversion for Compound (91) in D_2O/pyridine as Measured from Changes in Width of Methyl Resonances

Methyl resonances	Temp.	pH	pK_1	k_i (sec^{-1})
Higher field	42°	6.02	9.24	2.98×10^5
"	39°	6.10	9.40	2.44 "
"	37°	6.15	9.50	2.11 "
"	34.5°	6.22	9.62	1.81 "
"	32.5°	6.28	9.74	1.81 "
"	30°	6.33	9.86	1.41 "
Lower field	21.5°	6.54	10.32	9.09×10^4
"	19.5	6.60	10.42	7.43 "
"	16	6.68	10.61	7.49 "
"	14	6.74	10.72	6.24 "
"	12	6.80	10.82	5.13 "

of ΔH^* and ΔS^* obtained by a least squares fit of these values are 9.34 kcals/mole and -4.0 e.u. respectively. The values of ΔH^* and ΔS^*

The rates of nitrogen inversion in  (91) in D_2O/pyridine.

A Plot of log (ki/T) vs 1/T [ki calculated from changes in the shape of higher and lower field ring methyl doublets using Eqs. (2-9) and (2-15)]

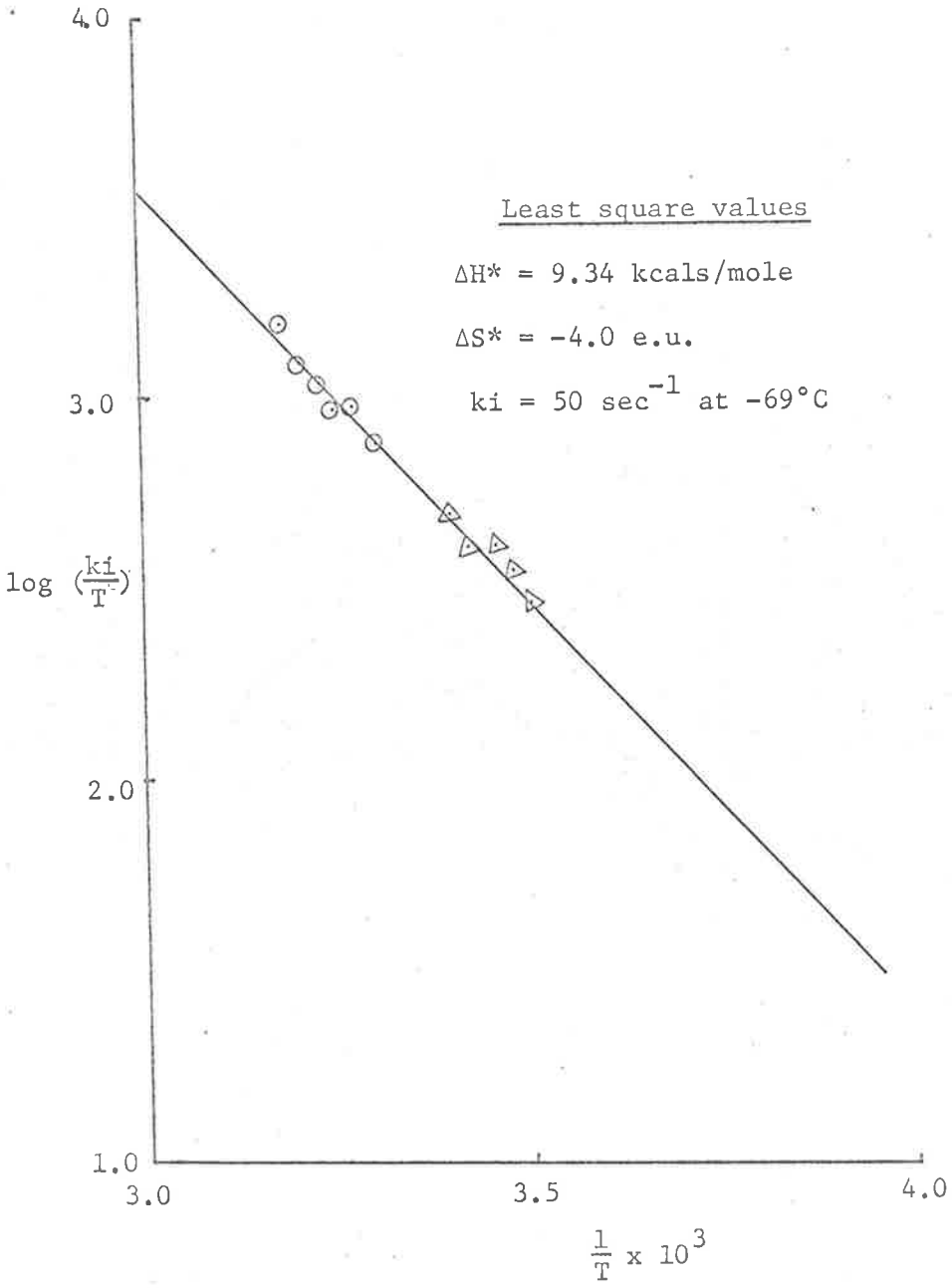


Figure 28. ⊙—⊙ values from high field methyls

△—△ values from low field methyls

were substituted in the expression $\Delta G^* = \Delta H^* - T\Delta S^*$ and this value of ΔG^* equated with that of Equation (2-13). The resulting equation was solved for $k_i \approx 50$ sec^{-1} to give $T \approx -70°C$. This indicates that a theoretical coalescence should be observed at about -70° by n.m.r. spectroscopy in D_2O/pyridine. However, the solvent freezes above this temperature. In any case, it may be concluded that coalescence in the absence of acid and in a non-hydrogen-bonding solvent will be below -70°. Unfortunately, equipment was not available to study n.m.r. spectra below -67°.

(b) 1-Benzyl-2,2,3,3-tetramethylazetidine (68)

It can be seen from the variable temperature spectra (Figure 29) of 1-benzyl-2,2,3,3-tetramethylazetidine (68) in D_2O/pyridine at pH 5.25 (22°) that the spectra are similar to those for compound (91). Again coalescence of different groups occurred at different temperatures (because $\Delta\nu_{AB}$ was different) thus suggesting that it should be possible to obtain values of ΔH^* and ΔS^* from the three different values of ΔGc^*. However, the error in ΔGc^* (± 0.1 kcals/mole) resulted in such large errors in ΔH^* and ΔS^* that these values were not very useful. The values of ΔGc^* at the coalescence of the respective groups are listed in Table XXV.

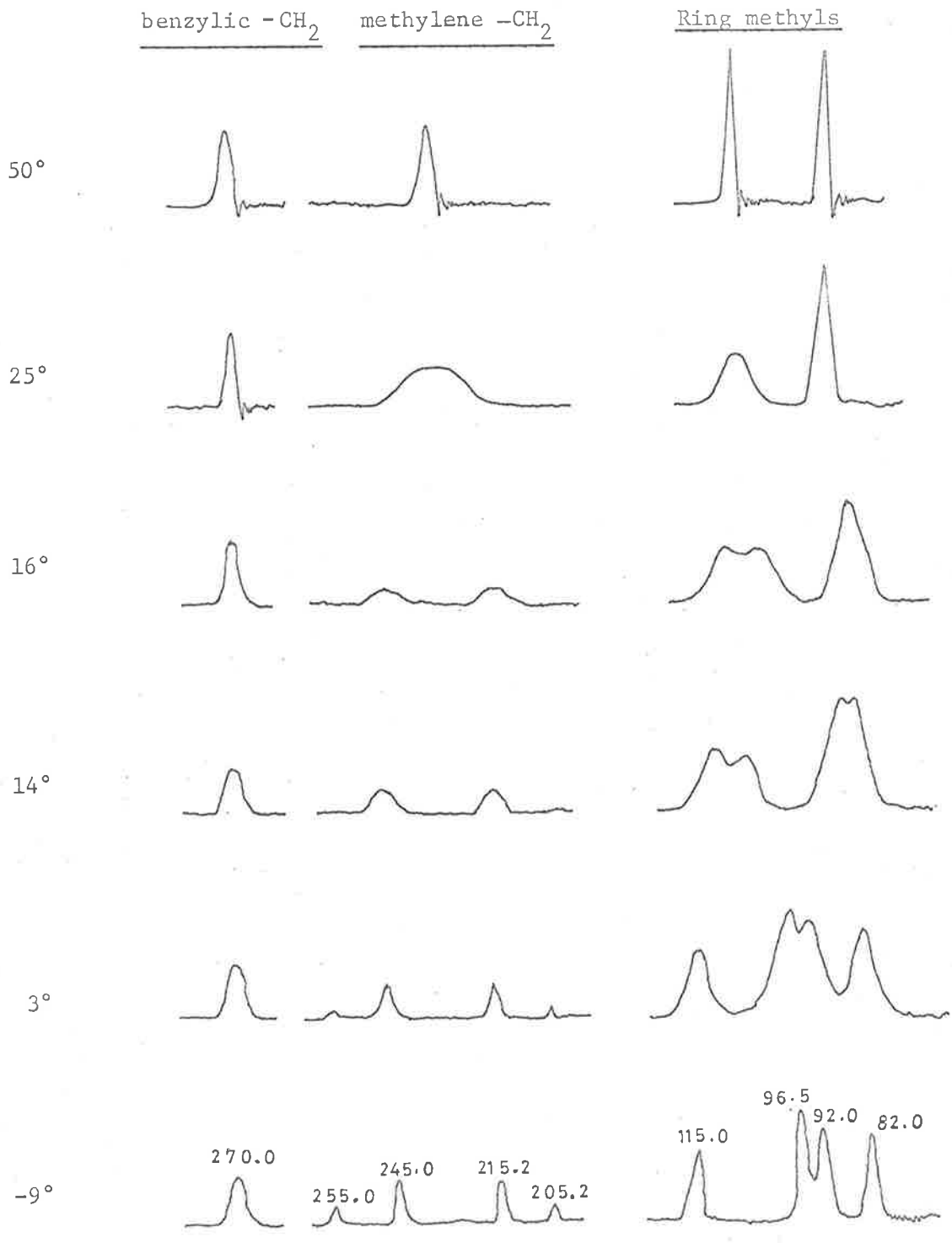
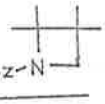


Figure 29. Variable temperature N.M.R. Spectra of 1-benzyl-2,2,3,3-tetramethylazetidine (68) in D_2O/pyridine at pH 5.25 (22°C) [Shifts from TMP] [60 Mc/sec]

TABLE XXV. Rates of Nitrogen Inversion and ΔGc* at Tc for Compound (68) in D_2O/pyridine solution

Substituents	Tc	pH	pK_1	k_i (sec^{-1})	ΔGc* (Kcals/mole)
Higher field methyls	14°	5.06	9.82	1.28×10^6	8.8
Lower field methyls	19°	4.94	9.64	2.07 "	8.6
Methylene (ring)	25°	4.80	9.40	3.93 "	8.4

The rates of nitrogen inversion were measured at temperatures above Tc using Equations (2-9) and (2-15) from changes in the line width of both the higher and lower methyl resonance doublets. Values of k_i, which were calculated in this way, are listed in Table XXVI and a plot of log $(\frac{k_i}{T})$ versus $\frac{1}{T}$ is shown in Figure 30. From Table XXVI or Figure 30 it can be seen that at a given temperature the rate obtained from measurements of the lower field methyls gave a value of k_i almost double that obtained from measurements of the higher field methyls. However, within each set of values, values of k_i are consistent. It thus appears that the systematic error[164] changes in going from one set of signals to another. A comparison of the rate of inversion for compound (68) at a given temperature [Table XXVI] with that for compound (91) at the same temperature [Table XXIV] indicates that the former is more than 10 times greater than the latter. The rate of inversion for compound (91) is similar to

The rates of nitrogen inversion in  (68) in D_2O/pyridine

A Plot of log (ki/T) vs 1/T [ki calculated from changes in the shape of higher and lower field methyl doublets using Equs. (2-9) and (2-15)]

Least squares values

	ΔH* (kcals/mole)	ΔS* (e.u.)	T (where ki ≈50 sec^{-1})
Higher field methyls	8.87	0.00	-96°
Lower field methyls	9.00	+1.6	-98°

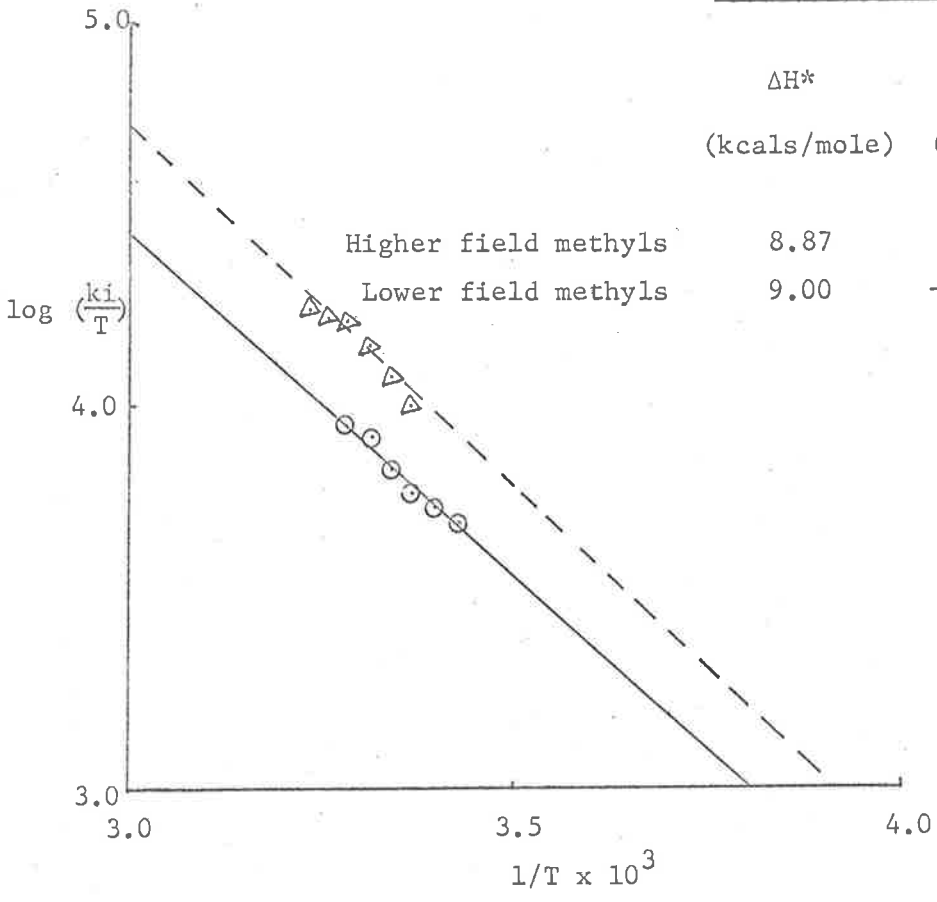


Figure 30. ⊙—⊙ higher field methyls

△ — △ lower field methyls

TABLE XXVI. Rates of Nitrogen Inversion for Compound (68) in D_2O/pyridine as Measured from Changes in Width of Methyl Resonances

Methyl resonances	Temp.	pH	pK_1	k_i (sec^{-1})
Higher field	31°	4.64	9.20	2.71×10^6
"	28.6°	4.71	9.28	2.47 "
"	26°	4.77	9.38	2.03 "
"	23.6°	4.83	9.48	1.76 "
"	21.2°	4.88	9.56	1.59 "
"	18.8°	4.94	9.65	1.44 "
Lower field	36°	4.52	9.00	5.55 "
"	33.6°	4.58	9.09	5.12 "
"	31°	4.64	9.20	5.11 "
"	28.6°	4.71	9.28	4.26 "
"	26°	4.77	9.38	3.52 "
"	23.6°	4.83	9.48	2.93 "

that found for dibenzylamine[249] [$2\pm1 \times 10^5$ sec^{-1} at 25°]. The greater rate of nitrogen inversion for the benzyl compound (68) is in accord with the postulate that a bulky group will invert more rapidly than a less bulky one.[209,213] This increased rate may, in part, account for the inconsistency observed in values of k_i obtained from the changes in width of the two different sets of methyl groups. Equation (2-15) is valid only if the rate of protonation >> k_i and if the latter increases

and the former remains about the same, the use of Equation (2-15) may introduce greater errors when applied to calculations of k_i for compound (68) than when used to calculate k_i for compound (91).

A least squares fit for the points obtained from the higher field methyl groups [Figure 30] gave values of 8.87 kcals/mole and 0.0 e.u. for ΔH^* and ΔS^* respectively. The theoretical coalescence temperature for these signals in D_2O/pyridine in the absence of acid was calculated to be about-96°C [i.e. where $k_i \approx 50$ sec^{-1}]. Similarly, a least squares fit for the points obtained from the lower field methyl groups gave values of 9.00 kcals/mole, 1.6 e.u. and -98°C for ΔH^*, ΔS^* and Tc respectively.

The 1-methyl group of 1,3,3-trimethyl-2-phenylazetidine (87) may exist either in the *pseudo*-equatorial or *pseudo*-axial conformation. In an attempt to investigate this possibility, variable temperature n.m.r. spectra of compound (87) in acidic solutions were recorded and studied. However, in all cases, the methyl group remained a singlet. This may be interpreted as follows. Either the chemical shift difference between the methyl group in the two possible conformations is too small to be observed or there is predominantly one conformer present (i.e. the one with the methyl group *trans* to the phenyl group). In concentrated acid the methyl group should split into a doublet due to coupling to the N—H proton. The latter coupling was, of course, not observed in this case since the solvent was D_2O.

Further study of these topics is planned with a complete line shape analysis being performed in order to obtain more satisfactory rate constants k_i. It is further intended to study the rates of protonation in some of these azetidines.

CHAPTER 3. THE MASS SPECTRA OF AZETIDINES AND 2-AZETIDINONES

I. INTRODUCTION

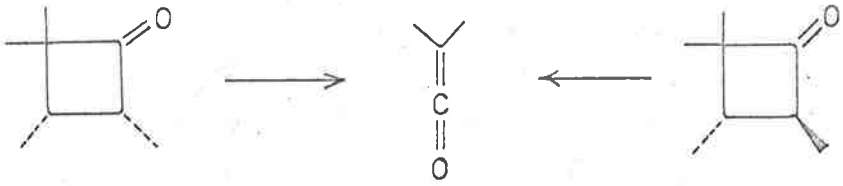
During the past decade, mass spectrometry has become a useful physical aid to the elucidation of the structures of organic molecules. The application of high resolution data and labelling studies has assisted in the interpretation of fragmentation processes in the mass spectra of many types of organic molecules. Details of the theory, mode and application of fragmentation processes in organic molecules have been extensively discussed in texts[255-263] and require no further discussion here.

The mass spectra of the parent compounds azetidine,[264] oxetan[264,265] and thietan[264] and also of cyclobutanes,[266] cyclobutanones,[267,268] 2,2,4,4-tetramethylcyclobutan-1,3-dione,[269] cyclobutanol,[270] 3-aroylazetidines,[271] 1,3-diazetidines,[99] 2-azetidinones[272-277] and 4,4-diphenyl-1,2-oxazetidin-3-ones[278] have been reported. The major fragmentation process of these four-membered ring compounds is that of ring cleavage, examples of which are given below.

The fragmentation process involving cleavage of the four-membered ring in cyclobutanone[267,268] to form the ionized ketene (*m/e* 42, 100%) and neutral ethylene is typical of four-membered ring compounds and constitutes the main mode of decomposition in

cyclobutanol,[270] thietan[264] and oxetan[264,265] to give the ions $\cdot CH_2CH=\overset{+}{O}H$, $CH_2=\overset{+}{S}\cdot$ and $CH_2=\overset{+}{O}\cdot$, respectively, and ethylene. In the latter case, however, the charge resides predominantly on the hydrocarbon fragment.

A study of the mass spectra of cyclobutanone[267,268] and several substituted cyclobutanones[268] has shown that the number and position of substituents have a pronounced effect on the observed fragments. A small, but distinct, influence of stereochemistry was observed with the peak at *m/e* 70 from compound (154) being more intense than from compound (155). Similarly, several cyclobutanecarboxylates have been

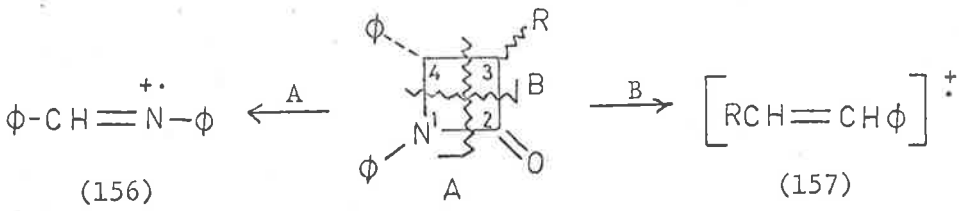


(154) *m/e* 70 (155)

Scheme 42

shown to undergo characteristic ring cleavage[266] where it was noted that *cis* substituents on adjacent carbon atoms caused characteristic cleavage of the ring between the two substituents.

Again, in the case of 2-azetidinones it has been observed[272] that the four-membered ring may cleave in either of two ways to give either ion (156) or (157). It was found that as the size of the R group [CH_3, CH_3CH_2, $(CH_3)_2CH$, $(CH_3)_3C$] increased the intensity of the



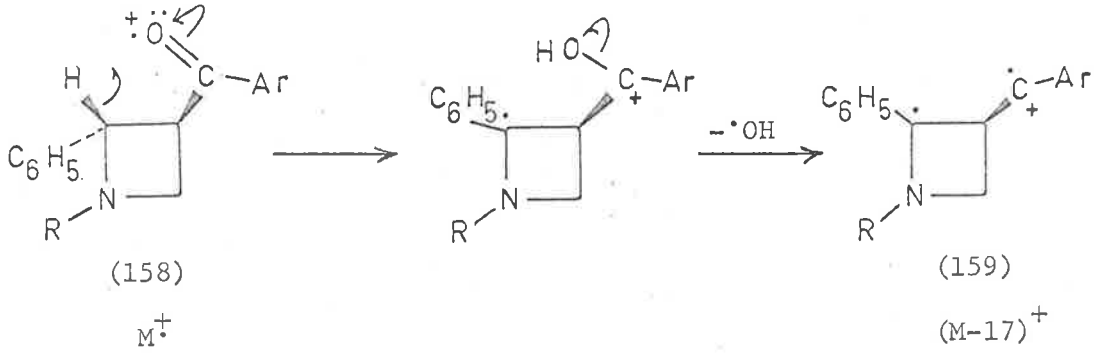
Scheme 43

molecular ion from the *trans* compound gained in intensity relative to that of the *cis* compound. Furthermore, the ratio of the intensities of the ions (156) to (157) was greater in each case for the *cis* isomer and this ratio increased as the size of the R group increased. Thus it was concluded that, at a given energy of electron bombardment, increasing steric interaction between the substituents favoured the rupture of the bonds holding them. Similar stereochemical differences have been observed in *cis*- and *trans*-3,4-diphenyl-2-azetidinones.[273]

Apart from the mass spectrum of azetidine itself[264] there appears to have been only one other mass spectral study of azetidines and that was of some 3-aroylazetidines.[271] Since these azetidines contain two heteroatoms it is not certain whether the fragmentation pattern is controlled by the nitrogen or oxygen atom. Although it is generally accepted that nitrogen is capable of stabilizing a positive charge more readily than oxygen[279] there is reason to suspect that in this case fragmentation, controlled by removal of an electron

from the oxygen atom, is also a possible process. Since the carbonyl group is adjacent to an aromatic system a positive charge on the oxygen atom would be stabilized by resonance interaction with the aromatic ring. A difference between the spectra of *cis* and *trans* isomers was observed and this can best be explained by considering the removal of an electron from the oxygen atom.

The mass spectrum of each *trans* compound shows an ion at M-17 which is absent in the corresponding *cis* isomer. This obvious difference in the spectra may be rationalized on the basis of a rearrangement of the hydrogen atom at position 2 onto the carbonyl group in the isomer (158), followed by loss of hydroxyl radical to yield the



(158) $M^{+\cdot}$ (159) $(M-17)^+$

Scheme 44

diradical (159). Since the β-hydrogen is geometrically unavailable in the *cis* isomer, the rearrangement cannot occur. It appears that aroylazetidines fragment mainly by α-cleavage to the carbonyl group, and ring fission is generally minor in comparison.

We were particularly interested, therefore, in studying the mass spectra of azetidines containing only the one heteroatom and observing the relationship between substitution pattern and ring cleavage. We were further interested in comparing the mass spectra of the azetidines with the corresponding 2-azetidinones.

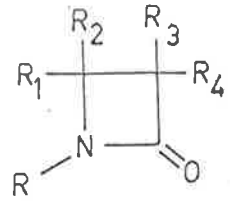
II. DISCUSSION AND RESULTS

1. The Mass Spectra of Azetidines

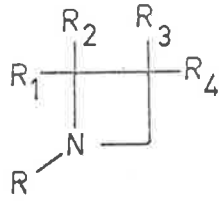
The mass spectra of the azetidines are given in Table XXVII or Figures 31-41. Figures 31-41 are collected at the end of this Chapter. The composition of fragment ions determined by exact mass measurements are listed in Table XXVIII. Compound numbers correspond to those assigned in Chapter 1. The symbolism used throughout this chapter is that developed by Budzikiewicz, Djerassi and Williams[258, 259,263] from initial proposals by McLafferty[260,261] and Shannon.[284] Although it is recognized that the structures written for fragment ions are nominal, they have been used here since they serve the purpose of relating the decomposition modes to the structure of the intact molecule. The presence of a metastable ion for a particular process is represented both in the text or in a figure by an asterisk (*).

The mass spectra of azetidines which contain either one or two substituents are often quite complex. The interpretation of the spectrum (Figure 31) of 2-phenylazetidine (122) was aided by the spectra of the labelled derivatives, 4,4-d_2-2-phenylazetidine (133) and 1-d-2-phenylazetidine (160). The base peak (m/e 104) in the spectrum of compound (122) is a doublet, and labelling studies are consistent with the isobaric fragments being formed by the processes $a \rightarrow b$ and $a \rightarrow d$ as shown in Scheme 45. Fragments b and d then lose C_2H_2 and HCN respectively as shown in Figure 31. As can

Compound Numbers for Some of the Compounds Discussed in this Chapter



2-Azetidinone



Azetidine

Substituents	2-Azetidinone	Azetidine
$R_1 = C_6H_5$, $R_2 = H$, $R_3 = R_4 = CH_3$		
$R = C_6H_5$	(46)	(61)
$R = (CH_3)_3C$	(52)	(66)
$R = C_6H_5CH_2$	(53)	(67)
$R = pCH_3OC_6H_4CH_2$	(57)	(71)
$R = C_6H_5CH_2CH_2$	(58)	(72)
$R = (CH_3)_2CH$	(59)	(73)
$R = CH_3CH_2CH_2$	(60)	(74)
$R = CH_3$	(81)	(87)
$R_1 = R_2 = R_3 = R_4 = CH_3$		
$R = H$	(41)	(132)
$R = CH_3$	(85)	(91)
$R = C_6H_5CH_2$	(54)	(68)

$R_1 = R_2 = CH_3$		
$R_3 = CH_3$, $R = R_4 = H$	(39)	-
$R_3 = (CH_3)_3C$, $R_4 = H$, $R = C_6H_5CH_2$	(56)	(70)
$R_1 = R_2 = H$, $R_3 = C_6H_5$, $R_4 = CH_3$		
$R = H$	(115)	(124)
$R = C_6H_5CH_2$	-	(125)
$R_1 = CH_3$, $R_2 = (CH_3)_3CCH_2$, $R_3 = R_4 = R = H$	(40)	(129)
$R_1 = C_6H_5$, $R_2 = H$		
$R_3 = (CH_3)_2CH$, $R_4 = H$, $R = CH_3$	(84t)	(90t)
$R_3 = R_4 = R = H$	(113)	(122)
$R_3 = R_4 = R = H$, 4-d_2	-	(133)
$R_3 = R_4 = H$, $R = D$	-	(160)
$R_3 = R_4 = H$, $R = C_6H_5CH_2$	-	(69)
$R_3 = CH_3$, $R_4 = H$, $R = C_6H_5$	(49c)	(64c)
$R_3 = C_6H_5$, $R_4 = H$, $R = CH_3$	(80t)	(86t)
$R_3 = (CH_3)_3C$, $R_4 = H$, $R = C_6H_5$	-	(88c) and (88t)
$R_1 = (CH_3)_3C$, $R_2 = H$, $R_3 = R_4 = CH_3$		
$R = C_6H_5$	(48)	(63)

TABLE XXVII. The Mass Spectra of Azetidines [All peaks greater than 5% of the base peak (100%) (and molecular and M+1 ions less than this value) are recorded]

Cpd.No.											
(133)	*m/e*	28	29	39	50	51	52	63	77	78	79	103
	I(%)	9	9	7	9	23	8	6	26	35	6	39

		105	134	135(M)								
		28	15	9								
(91)	*m/e*	39	41	42	43	44	55	56	57	69	70	71
	I(%)	10	25	15	5	21	9	100	5	29	5	20
		72	112	127(M)								
		8	9	6								
(90t)	*m/e*	42	77	78	91	118	119	120	131	132	133	146
	I(%)	7	7.5	5	15	100	34	10	24	10	18	7
		174	188	189(M)	190(M+1)							
		7	5	9	1							
(63)	*m/e*	39	41	51	55	57	77	78	91	104	105	106
	I(%)	7	17	13	10	5	56	7	13	48	14	7
		118	119	130	131	132	144	145	146	160	161	217(M)
		12	5	7	6	5	14	6	14	100	18	9
		218(M+1)										
		2										
(129)	*m/e*	39	41	42	43	44	55	56	57	58	70	71
	I(%)	12	31	28	6	6	11	7	55	6	100	7
		84	85	97	126	127	141(M)					
		15	12	7	13	2	0					
(124)	*m/e*	77	78	91	103	115	117	118	147(M)			
	I(%)	13	18	17	30	11	52	100	1			

(68)	*m/e*	39	41	56	65	69	91	92	120	132	146	147
	I(%)	6	15	16	6	18	100	8	6	5	8	13
		203(M)										
		4										

(70)	*m/e*	41	55	56	57	65	69	91	92	97	120	132
	I(%)	21	10	12	10	10	11	100	10	14	8	6
		146	147	160	216	231(M)						
		18	10	5	34	5						

(125)	*m/e*	39	51	77	78	91	92	102	115	117	118	119
	I(%)	12	21	16	17	62	8	20	8	35	100	18
		120	237(M)		238(M+1)							
		14	12		3							

(137)	*m/e*	39	41	42	43	55	56	57	58	70	71	114
	I(%)	17	36	19	11	6	6	100	6	57	6	60
		129(M)										
		11										

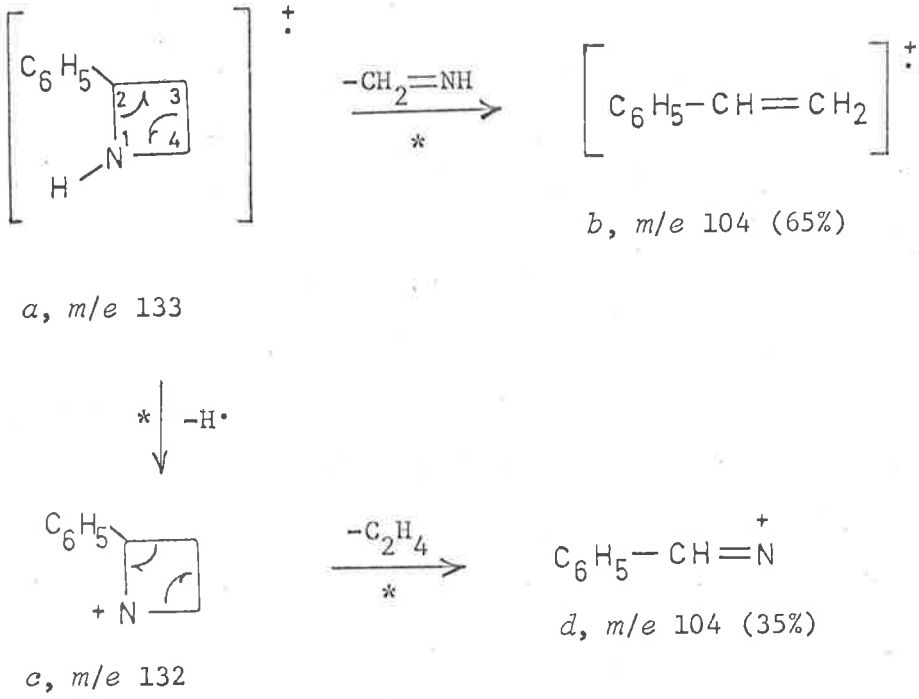
(87)	*m/e*	39	41	42	51	65	77	78	91	117	118	119
	I(%)	6	9	23	6	5	10	8	15	16	100	29
		120	132	175(M)								
		8	11	20								

(66)	*m/e*	39	41	55	56	57	70	77	91	104	105	106
	I(%)	10	30	14	10	56	86	10	20	20	40	46

		117	132	146	147	160	161	202	217(M)		
		24	36	100	10	16	22	32	5		
(67)	*m/e*	65	91	92	115	116	117	132	194	195	251(M)
	I(%)	12	100	32	7	8	30	16	26	14	11
(71)	*m/e*	91	92	121	122	132	160	195	225	251	281(M) 282(M+1)
	I(%)	7	10	100	13	7	8	7	16	13	33 8
(72)	*m/e*	39	41	42	51	65	70	77	79	91	92 103
	I(%)	13	15	100	14	14	30	27	9	83	8 6
		104	105	117	118	119	132	145	174	175	265(M)
		7	45	18	84	10	18	6	56	9	7

TABLE XXVIII. Compositions of Some Ions in the Spectra of Azetidines

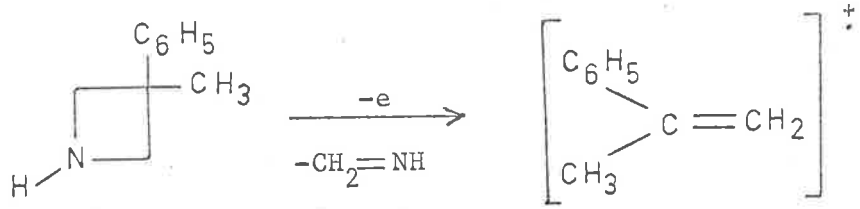
Compound	*m/e*	Composition	Compound	*m/e*	Composition
(122)	104	(C_8H_8 (65%) (C_7H_6N (35%)	(87)	132	$C_{10}H_{12}$
			(74)	118	C_8H_8N
	105	(C_8H_9 (70%) (C_7H_7N (30%)		132	($C_9H_{10}N$ (95%) ($C_{10}H_{12}$ (5%)
(69)	104	(C_8H_8 (60%) (C_7H_6N (40%)	(73)	132	($C_9H_{10}N$ (95%) ($C_{10}H_{12}$ (5%)
(132)	58	C_3H_8N	(66)	132	$C_{10}H_{12}$
(86t)	104	C_8H_8	(61)	104	C_7H_6N
	118	C_8H_8N		117	C_9H_9



Scheme 45

be seen from Figure 31 and Scheme 45, the major fragments originate by either 1,2 and 3,4 or 2,3 and 1,4 bond-cleavages. This is a feature of the spectra of azetidines and is also a feature of other four-membered rings as discussed above.[264-270,272-277] The spectrum (Figure 32) of 1-benzyl-2-phenylazetidine (69) retains the features of the spectrum of compound (122). The peak at *m/e* 104 is again a doublet with the fragments being produced by the processes $M-C_8H_9N$ (60%) and $M-C_6H_5CH_2^{\bullet}-C_2H_4$ (40%). These cleavages are analogous to the processes *a* → *b* and *a* → *d* shown in Scheme 45 and the fragments decompose further in the same way losing C_2H_2 and HCN respectively. α-Cleavage to nitrogen produces the tropylium cation

(*m/e* 91) which is the base peak in this spectrum. When there is a phenyl substituent at C-3 but not at C-2 the 1,2 and 3,4 bond cleavages predominate, because stabilization of a nitrogen-containing fragment can no longer occur. This effect is noted in the spectrum (Table XXVII) of compound (124) in which the base peak is produced by the process (124) → *e* as shown in Scheme 46. A similar process is responsible for the base peak in the spectrum (Table XXVII) of the 1-benzyl derivative of compound (124) [i.e. compound (125)] being at *m/e* 118.



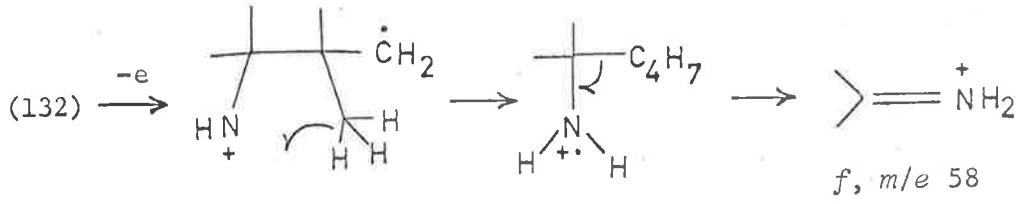
(124)

e, *m/e* 118 (100%)

Scheme 46

The spectrum (Figure 33) of 2,2,3,3-tetramethylazetidine (132) contains the tetramethylethylene radical ion (*m/e* 84, 42% of the base peak) which is produced by cleavage of the 1,2 and 3,4 bonds. However, the base peak is *m/e* 58 and was shown by accurate mass measurement to have the composition C_3H_8N. This ion can be produced only by cleavage of the 2,3 and 1,4 bonds with accompanying hydrogen rearrangement and the spectrum (Figure 33) of compound (134) shows that a specific hydrogen rearrangement is involved with the hydrogen

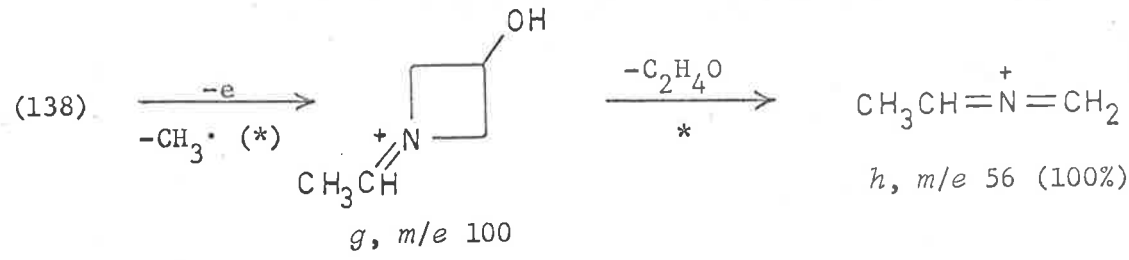
from the methyl groups at C-3 being involved. A possible mechanism for the formation of *m/e* 58 is given in Scheme 47. When a methyl or



Scheme 47

benzyl substituent is attached to nitrogen as in 1,2,2,3,3-pentamethylazetidine (91), 1-benzyl-2,2,3,3-tetramethylazetidine (68) and 1-benzyl-3-*tert*—butyl-2,2-dimethylazetidine (70) [all in Table XXVII] the hydrogen rearrangement no longer occurs. Instead the processes $M-C_4H_8-CH_3^{\cdot}$ [compounds (91) and (68)] and $M-C_6H_{12}$ [(70)] are observed.

The fragmentation of 1-*iso*propyl-3-hydroxyazetidine (138) is shown in Figure 34 and that of 1-*tert*-butyl-3-hydroxyazetidine (137) in Table XXVII. The major breakdown process of compound (138) involves β-cleavage of the *iso*propyl substituent to produce the cation *g* which then loses C_2H_4O to give *h* (base peak). A similar process occurs for compound (137) except that α-cleavage is also important giving *m/e* 57 as the base peak.



g, *m/e* 100

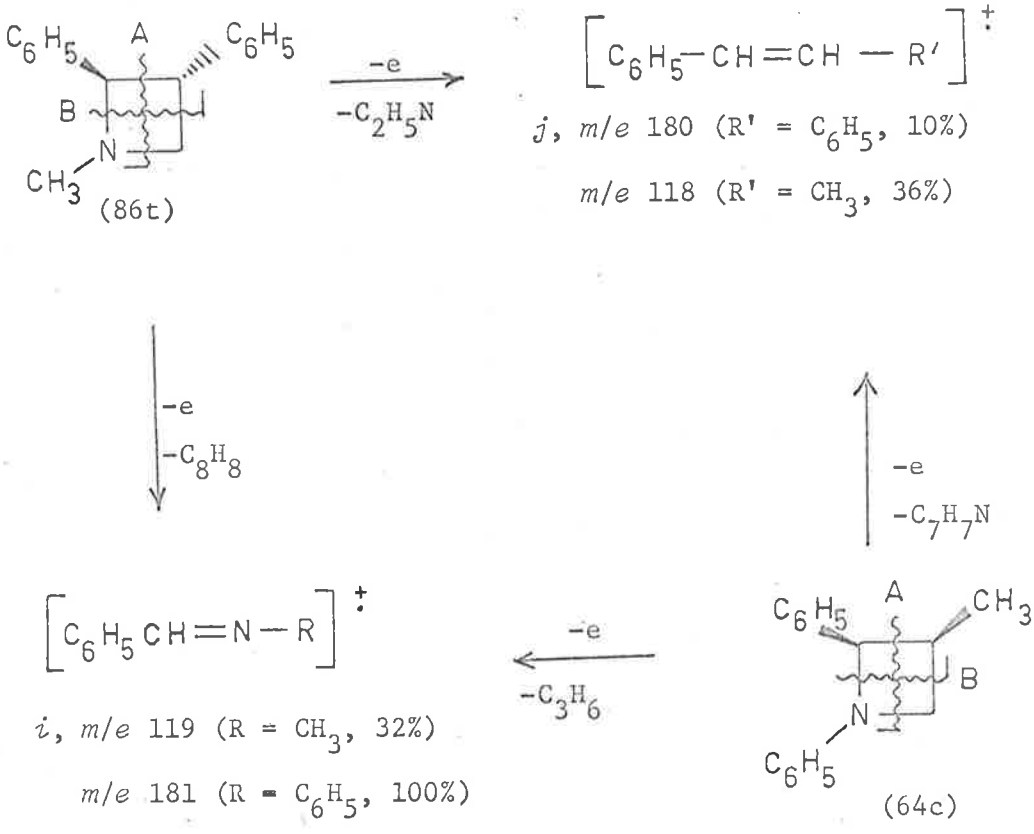
h, *m/e* 56 (100%)

Scheme 48

The mass spectra of azetidines with more than two substituents are generally much simpler than those which contain only one or two substituents. Again the most important mode of fragmentation involves ring cleavage although when alkyl substituents (other than methyl) are present, additional fragmentation of the side chain is also noted and this may make the spectrum more complex than normal. The completely different spectra (Figures 35 and 36) observed for the isomers 1-methyl-2,3-diphenylazetidine (86t) and 3-methyl-1,2-diphenylazetidine (64c) indicate the ease with which mass spectrometry can differentiate between, and identify these compounds.

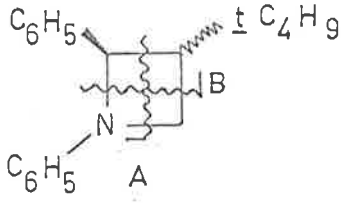
When a phenyl group occupies C-2 and when there is a substituent attached to nitrogen, the species (or an ion derived from it) produced by 2,3/4,1 fragmentation (process A) constitutes the base peak of the spectrum. The alternative 1,2/3,4 fragmentation (process B) is only minor in comparison. For example, the base peak (*m/e* 118) in the spectrum (Figure 35) of compound (86t) is produced

by loss of a hydrogen atom from fragment *i* (*m/e* 119) which in turn results from the fragmentation process A whereas the stilbene radical ion *j* (*m/e* 180), produced by the fragmentation process B has an abundance of only 10%. Similarly, the base peak (*m/e* 181) in the spectrum (Figure 36) of compound (64c) is produced by process A while the peak at *m/e* 118 produced by process B has an abundance of only 36%.



Scheme 49

In the case of 2-azetidinones it has been shown that a change in the stereochemistry of highly substituted derivatives affects the mass spectrum.[272,273] A similar effect was also found to occur in the case of azetidines and is illustrated by the spectra (Figures 37 and 38) of *cis* and *trans* 3-*tert*-butyl-1,2-diphenylazetidine [(88c) and (88t) respectively]. The ring may again cleave by processes A and B and the difference between the spectra lies in the relative abundances of ions produced by these processes. Although the Schiff's base radical ion (process A) is the base peak in both spectra, the



(88c) and (88t)

formation of the hydrocarbon species (process B) is only 6% for the sterically-hindered *cis* isomer but 25% for the *trans* isomer. This suggests that in the sterically-hindered azetidine process A is an even more preferred one than in the less hindered compound. In other words, the steric interaction of the bulky *cis* groups favours cleavage of the 2,3 (and therefore 4,1) bond. This feature may therefore be used in specific cases to differentiate between geometrical isomers.

As noted above for other *N*-substituted-2-phenylazetidines, the abundances of the ions produced by cleavage A are generally greater than those formed by cleavage B for the *N*-substituted 3,3-

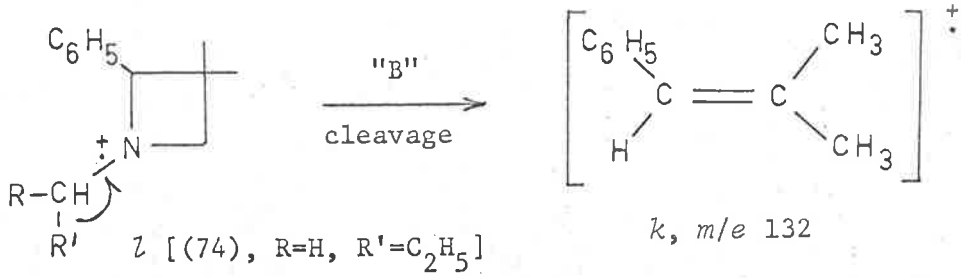
dimethyl-2-azetidines [(87), (74), (73), (66), (61), (67), (71) and (72)] as shown in Tables XXVII and XXIX and/or in Figures 39, 40 and 41. In compounds (66) and (72) fragmentations of the side chains complicate the issue. In the spectrum (Figure 41) of compound (61) cleavage A is especially pronounced. The effect of changing the substituent on the nitrogen atom is demonstrated by the differences between the spectra (Figures 39 and 40 or Tables XXVII and XXIX) of the compounds (87), (74), (73), (66), (61), (67), (71) and (72). A considerable variation in abundances of those ions and their decomposition products produced by the two ring cleavages A and B are observed. The abundances of ions produced by these processes are listed in Table XXIX.

TABLE XXIX. Abundances of Some Fragment Ions in the Spectra of *N*-substituted-3,3-dimethyl-2-phenylazetidines

Cpd.No	*N*-subst (R)	$M^{+\cdot}$	R^+	Process A ($M-C_4H_8$)	Process B ($M-RCH_2N$)
(87)	CH_3	20	-	28	12
(74)	$CH_3CH_2CH_2$	9	18	5	2
(73)	$(CH_3)_2CH$	6	21	22	10
(66)	$(CH_3)_3C$	5	56	22	36
(61)	C_6H_5	10	30*	100	9
(67)	$C_6H_5CH_2$	11	100	16	15
(71)	pMeO$C_6H_4CH_2$	33	100	16	8
(72)	$C_6H_5CH_2CH_2$	7	45	0	18

* Some of this species may originate from the 2-phenyl group.

Apart from the variations in abundances of ions resulting from the two ring cleavages A and B as the nitrogen substituent changes from a methyl to a phenyl group, a very large difference from changing the nitrogen substituent from an *n*-propyl to an *iso*-propyl group is also observed. This effect is illustrated by the spectra (Figures 39 and 40) of the propyl compounds (74) and (73). The peak at *m/e* 132 in the spectra of compounds (87), (66), (61), (67), (71) and (72) corresponds to $C_{10}H_{12}$ (*k*), which is formed by cleavage B. However,

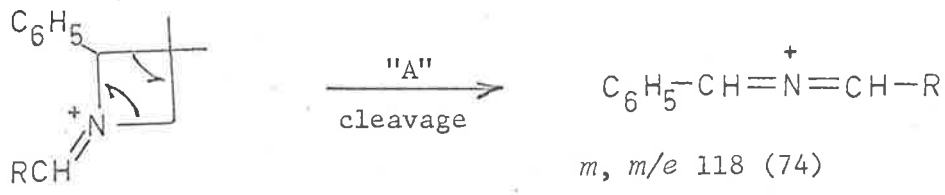


l [(74), R=H, R'=C_2H_5]

[(73), R=R'=CH_3]

k, *m/e* 132

-R'·



m/e 174 (74)

m/e 188 (73)

m, *m/e* 118 (74)

m/e 132 (73)

Scheme 50

m/e 132 is a doublet in the spectrum of compound (73), with *k* being the minor component (5%). The major component ($C_9H_{10}N$) is produced by fragmentation of the *N*-alkyl group followed by loss of C_4H_8 by ring cleavage. The base peaks in the spectra of compounds (74) and (73) originate from the decomposition process *l* → *m*. Although *m* is drawn as a linear structure, it is of course equally probably that rearrangement may produce the appropriate azirine cation. Other fragmentations are indicated in Figures 39 and 40.

The spectra of compounds (64c), (69), (88c) and (88t) were obtained by the direct-insertion procedure in addition to recording them by the heated inlet system method. In all cases, the "heated" and "direct" spectra were very similar, except for some very small differences in the abundances of several fragment ions. This observation precludes the possibility of thermal decomposition.

2. The Mass Spectra of 2-Azetidinones

The mass spectra of 2-azetidinones are listed in Table XXX or are shown in Figures 42 to 46. Figures 42-46 are collected at the end of this Chapter. The composition of fragment ions determined by exact mass measurements are given in Table XXXI.

TABLE XXX. The Mass Spectra of 2-Azetidinones [All peaks greater than 5% of the base peak (100%) (and the molecular and M+1 ions less than this value) are recorded]

Cpd.No.												
(40)	*m/e*	39	41	42	43	53	55	56	57	58	69	70
	I(%)	10	23	35	8	5	14	15	100	9	5	5

		83	84	97	98	99	112	140	155(M)			
		6	65	28	18	19	24	4	0			
(115)	*m/e*	39	50	51	52	63	65	76	77	78	91	102
	I(%)	9	8	18	5	9	6	5	26	29	19	7
		103	104	105	115	117	118	119	132	161(M)		
		44	15	5	11	48	100	10	6	0		
(85)	*m/e*	39	41	42	55	56	69	70	72	84	85	141(M)
	I(%)	13	37	14	10	35	100	14	30	78	6	0
(84t)	*m/e*	42	69	77	91	115	116	117	118	120	130	131	132
	I(%)	5	5	9	20	11	6	5	18	13	6	100	13
		146	147	203(M)									
		61	8	3									
(39)	*m/e*	39	41	42	55	56	58	70	71	113(M)			
	I(%)	8	12	36	77	14	28	100	6	0			
(54)	*m/e*	41	65	69	70	84	85	91	217(M)				
	I(%)	7	6	57	6	100	7	23	2				
(56)	*m/e*	55	91	97	98	112	113	245(M)	246(M+1)				
	I(%)	11	29	100	8	43	6	1	1				
(48)	*m/e*	69	97	98	104	112	118	146	231(M)	232(M+1)			
	I(%)	6	100	8	23	25	7	46	8	3			

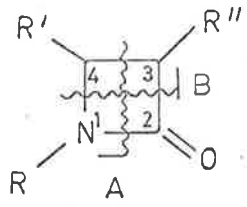
(60)	*m/e*	91	115	117	118	131	132	133	148	217(M)	218(M+1)	
	I(%)	17	6	52	14	8	100	13	12	2	3	
(59)	*m/e*	41	70	77	91	104	105	115	117	118	131	132
	I(%)	12	12	14	24	12	8	16	83	9	12	100
		133	146	218(M+1)								
		12	5	1								
(52)	*m/e*	41	57	77	84	91	104	115	117	118	131	132
	I(%)	9	9	7	9	16	6	11	64	7	10	100
		133	146	232(M+1)								
		10	8	1								
(46)	*m/e*	51	77	78	91	104	115	117	118	131	132	133
	I(%)	7	29	7	14	10	12	62	7	9	100	11
		180	181	182	251(M)	252(M+1)						
		48	76	14	23	5						
(53)	*m/e*	65	77	91	92	104	115	117	131	132	133	194
	I(%)	7	7	100	11	6	6	63	9	100	11	15
		196	265(M)	266(M+1)								
		23	1	2								
(57)	*m/e*	77	91	117	121	131	132	133	295(M)	296(M+1)		
	I(%)	6	9	32	44	6	100	11	1	1		

(58)	*m/e*	42	65	77	91	92	103	104	105	115	117	118
	I(%)	6	8	13	68	7	7	8	12	11	48	26
		131	132	133	210	279(M)		280(M+1)				
		10	100	11	6	1		2				

TABLE XXXI. Compositions of Some Ions in the Spectra of 2-Azetidinones

Compound No.	*m/e*	Composition	Compound No.	*m/e*	Composition
(113)	104	C_8H_8	(80t)	120	$C_8H_{10}N$
	119	C_8H_9N	(81)	120	$C_8H_{10}N$
(41)	58	C_3H_8N		132	$C_{10}H_{12}$
(48)	146	$C_{10}H_{12}N$	(59)	132	$C_{10}H_{12}$

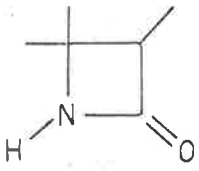
A comparison of the mass spectra of 2-azetidinones with those of azetidines reveals that those of the former differ from those of the latter in three distinct ways. These are: (1) many of the spectra of 2-azetidinones are devoid of molecular ions but instead contain M+1 ions in contrast to the spectra of azetidines which invariably contain molecular ions but no M+1 ions (other than the isotope peaks), (2) in 2-azetidinones ring cleavage by process B produces the more abundant fragment ions in contrast to azetidines in which fragmentation by process A generally produces the more abundant fragment ions and (3) because of the extreme proclivity of process B in 2-azetidinones, the major peaks in the 2-azetidinone

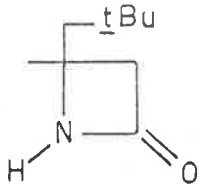


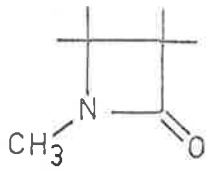
spectra are not affected by the group attached to the nitrogen atom whereas the spectra of azetidines are largely dependent upon the nature of the *N*-substituent. Each of these features will now be discussed in more detail.

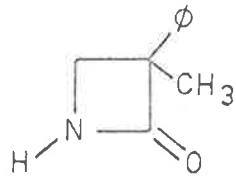
(1) The Appearance of M+1 ions in 2-Azetidinones

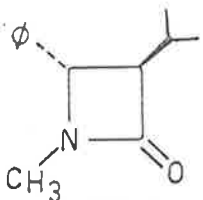
Although the mass spectra (Table XXX) of compounds (39), (40), (85) and (115) showed neither an M or M+1 peak and the spectrum (Table XXX) of compound (84t) showed an M but no M+1 peak, in general, all other 2-azetidinones gave spectra either with no M peak but a small (about 2%) M+1 peak or an M and M+1 peak. The only exceptions among this group were observed when the nitrogen substituent was a phenyl group. In this case the spectra (Table XXX or Figure 44) of such compounds [e.g. (46), (48) and (49c)] showed M but no M+1 peaks. It is of interest to note that X-ray evidence[125] has established the approximate coplanarity of the phenyl and 2-azetidinone rings in *N*-aryl-2-azetidinones. In other *N*-substituted-2-azetidinones n.m.r. spectral evidence[46,203] suggests that the *N*-substituent bond lies out

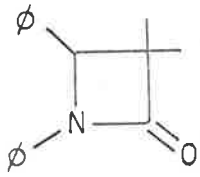

(39)

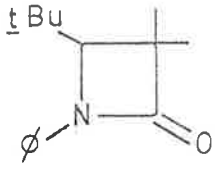

(40)

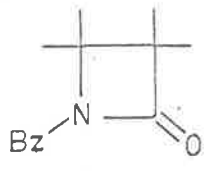

(85)


(115)


(84t)


(46)


(48)


(54)

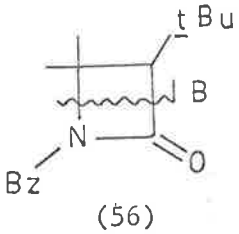
of the plane of the 2-azetidinone ring. If these stereochemical features are retained in the molecular ions it seems reasonable to suppose that the abstracted hydrogen atom may bond to nitrogen. The appearance of M+1 ions have not been observed in the spectra of amides,[280,281] 2-pyrrolidones[282] or barbiturates.[283]

(2) Ring Cleavage

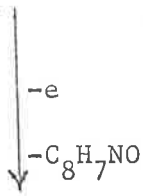
The olefin radical ion formed by process B, or a decomposition product of that olefin radical ion, is always the base peak in the spectra of 2-azetidinones. In azetidines the nitrogen containing fragment produced by process A is generally the more abundant. The

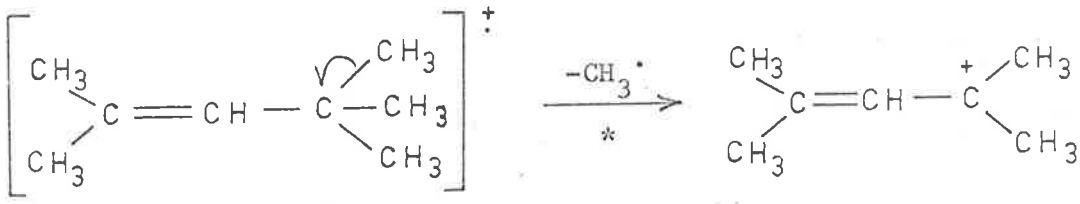
spectrum (Figure 42) of 4-phenyl-2-azetidinone (113) exhibits only "cleavage B" fragments. The peak at *m/e* 104 is a singlet due to *b* (C_8H_8, Scheme 45). Of all the compounds reported here, the loss of CO was observed from only compounds (113) and (84t).

The major peaks in the spectra (Table XXX or Figure 43) of compounds (39), (41) [Figure 43], (54), (56) and (48) are produced by olefin radical ions. For example, in the spectrum (Table XXX) of 1-benzyl-3-*tert*-butyl-4,4-dimethyl-2-azetidinone (56), cleavage B produces the olefin radical ion *n* (*m/e* 112) which fragments by loss of a methyl radical to produce *o* (*m/e* 97, base peak). The olefin fragment (e.g. *n*) is always the base peak of the spectrum when the energy of the electron beam is lowered to 15 eV.



(56)





n, *m/e* 112 *o*, *m/e* 97

Scheme 51

Again, in the spectrum (Figure 43) of compound (41) the base peak at *m/e* 69 is derived from the olefin radical ion (*m/e* 84). The peak at *m/e* 58 results from type A cleavage with accompanying hydrogen rearrangement and is formed by an analogous rearrangement to that which occurs to give an *m/e* 58 peak in the spectrum (Figure 33) of 2,2,4,4-tetramethylazetidine (132) [Scheme 47, fragment *f*]. The same process gives rise to an *m/e* 58 (*f*) fragment in the spectrum (Table XXX) of 3,4,4-trimethyl-2-azetidinone (39).

A comparison of the spectrum (Figure 35) of *trans*-1-methyl-2,3-diphenylazetidine (86t) with the spectrum (Figure 45) of *trans*-1-methyl-3,4-diphenyl-2-azetidinone (80t) again emphasizes the relative ease of cleavages by processes A and B. The difference in the spectra (Figures 44 and 45) of the two isomeric 2-azetidinones (49c) and (80t) demonstrates further the ease with which mass spectrometry allows the differentiation of structural isomers. Compound (80t) undergoes type A cleavage (although type B predominates) with hydrogen rearrangement, but it is not clear from Figure 45 whether the transferred hydrogen originates from the phenyl group or hydrogen atom at C-3 [reaction of (80t) with sodium/D_2O/dioxan failed to exchange the hydrogen atom at C-3]. A feature of the spectrum (Figure 45) of compound (80t) is the appearance of a stabilized phenylketene radical ion *p* produced by cleavage A. Although the spectrum (Table XXX) of 1-*iso*propyl-3,3-dimethyl-4-phenyl-2-azetidinone (59) and the spectrum (Figure 46) of compound (81) both contain small peaks due to dimethylketene radical ions, in the spectra of 2-azetidinones reported here it is unusual for the ketene species to retain the charge, although it has

(80t) $\xrightarrow[-C_8H_9N]{-e}$ $\left[C_6H_5CH{=}C{=}O\right]^{+\cdot}$

p, *m/e* 118

Scheme 52

been reported to occur in the spectra of *cis*- and *trans*-3,4-diphenyl-2-azetidinone.[273]

Process A occurs in the spectra of 1-phenyl-2-azetidinones [e.g. compounds (46) and (48) (Table XXX) and (49c) (Figure 44)] but, as mentioned above, in the spectra of other 2-azetidinones it occurs with hydrogen rearrangement to the nitrogen containing fragment. This aspect is further illustrated for 3,3-dimethyl-4-phenyl-2-azetidinones in Table XXXII. Figure 46 illustrates the general fragmentations of

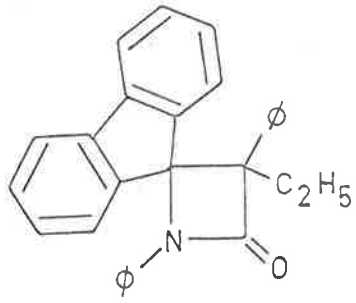
TABLE XXXII. Relative Abundances of Molecular(M), M+1 and Fragment Ions in the Spectra of *N*-Substituted-3,3-dimethyl-4-phenyl-2-azetidinones

Cpd.No.	*N*-subst. (R)	$M^{+\cdot}$	M+1	R^+	Process A ($M-C_4H_6O$)	$M-C_4H_5O^{\cdot}$	Process B ($M-RCNO$)
(81)	CH_3	7	4	-	-	36	100
(60)	$CH_3CH_2CH_2$	2	3	3	-	13	100
(59)	$(CH_3)_2CH$	-	1	6	-	5	100

(52)	$(CH_3)_3C$	-	1	8	-	-	100
(46)	C_6H_5	23	-	29*	76	-	100
(53)	$C_6H_5CH_2$	1	2	80	-	23	100
(57)	$pMeOC_6H_4CH_2$	1	1	44	-	-	100
(58)	$C_6H_5CH_2CH_2$	1	2	11	-	5	100

* Some of this species may originate from the 4-phenyl group.

2-azetidinones. A comparison of Tables XXVII and XXX and especially of Tables XXIX and XXXII further illustrate the differences outlined above. It is interesting to note that it has been reported that the 2-azetidinone (160) gives the fluorenone anil radical ion as the base peak with no peaks due to the olefin.[274]



(160)

(3) Effect of the Nitrogen Substituent on Ring Cleavage

In the spectra (Table XXVII or Figure 32) of the 1-benzyl-azetidines (67), (68), (69) and (70) the tropylium cation (*m/e* 91) dominates the spectrum. However, in the spectra (Tables XXX and/or XXXII) of the 1-benzyl-2-azetidinones (53) and (56) this is no longer

the case. Similarly, the spectrum (Table XXVII) of 1-*tert*-butyl-3,3-dimethyl-2-phenylazetidine (66) is extremely complex due to fragmentation of the *tert*-butyl group whereas the spectrum (Table XXX) of the corresponding 2-azetidinone (52) is very simple. Thus it appears that the tendency for the 2-azetidinones to cleave by process B is so great that it masks any effect which the nitrogen substituent may have on the fragmentation process. A comparison of the two very different spectra (Figures 39 and 40) of the two propyl-azetidines (74) and (73) with those of the two very similar spectra (Table XXX) of the corresponding propyl-2-azetidinones (60) and (59) again demonstrates that the nitrogen substituent of 2-azetidinones has little effect on their cleavage.

The spectra of compounds (46) and (49c) were obtained by the direct insertion procedure in addition to obtaining them by the usual heated inlet system method. The "heated" and "direct" spectra were very similar, except for some very small differences in the abundances of several fragment ions. This observation precludes the possibility of thermal decomposition.

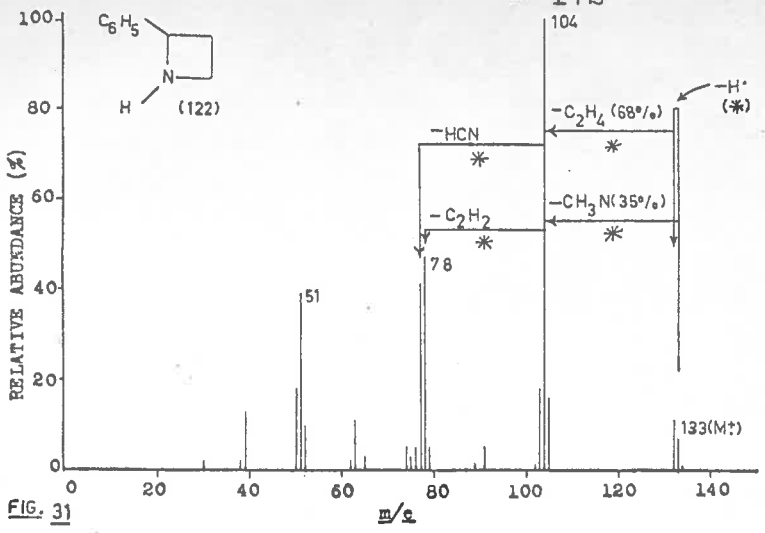


FIG. 31

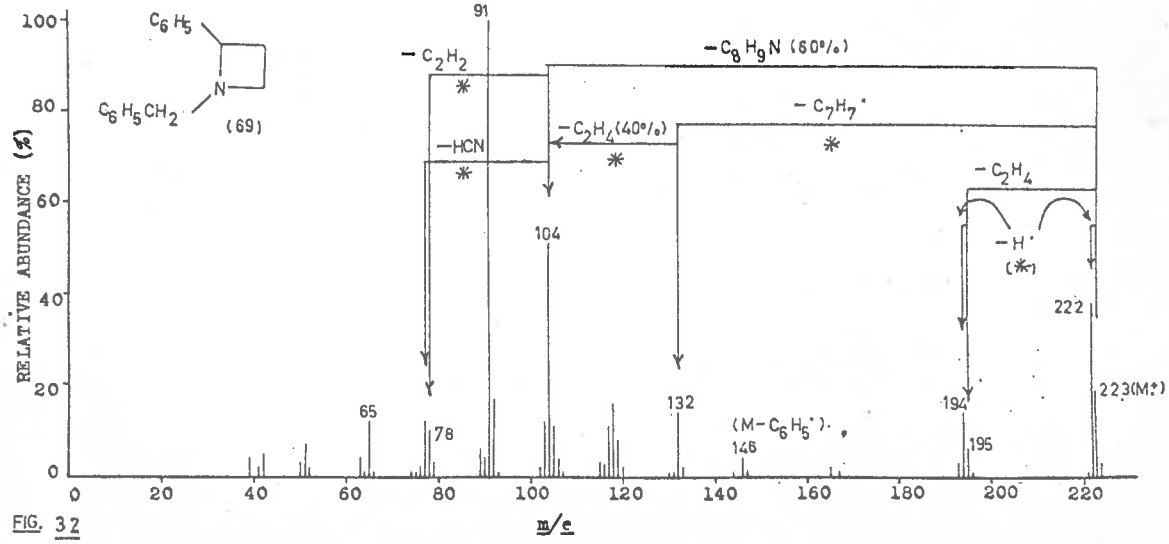


FIG. 32

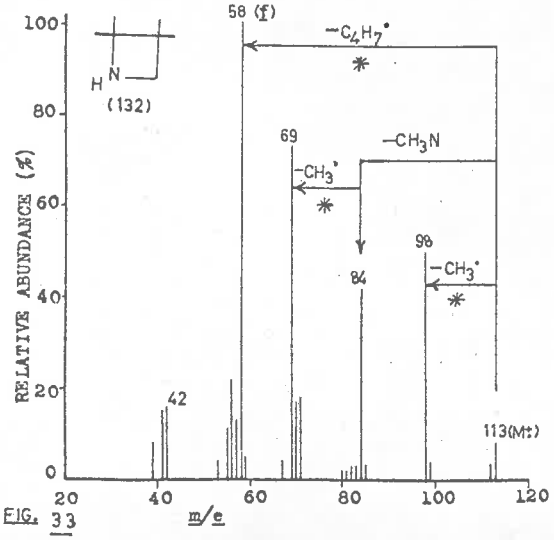
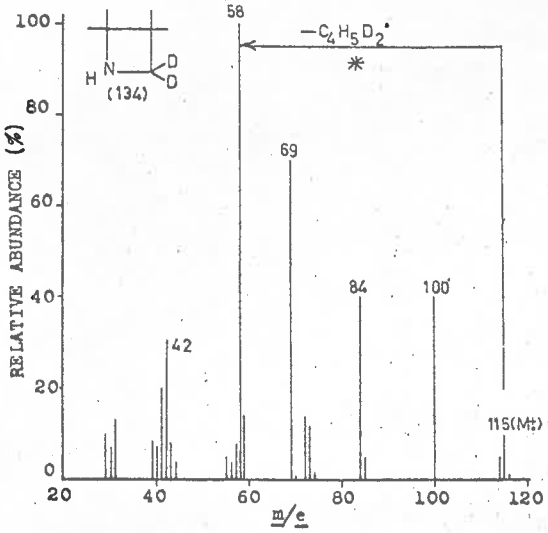


FIG. 33



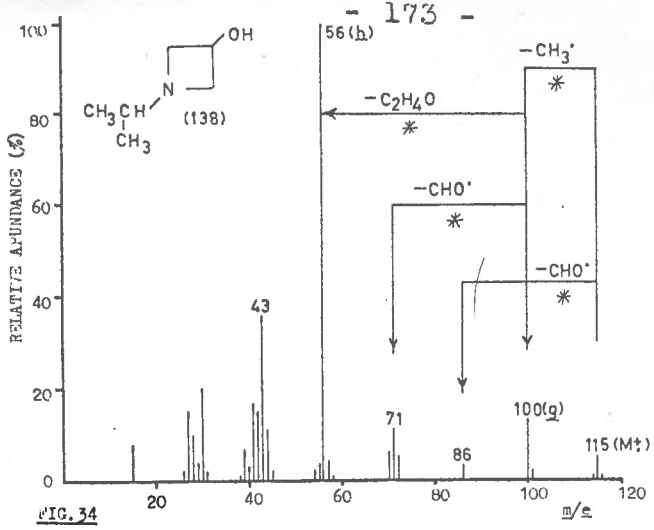


FIG. 34

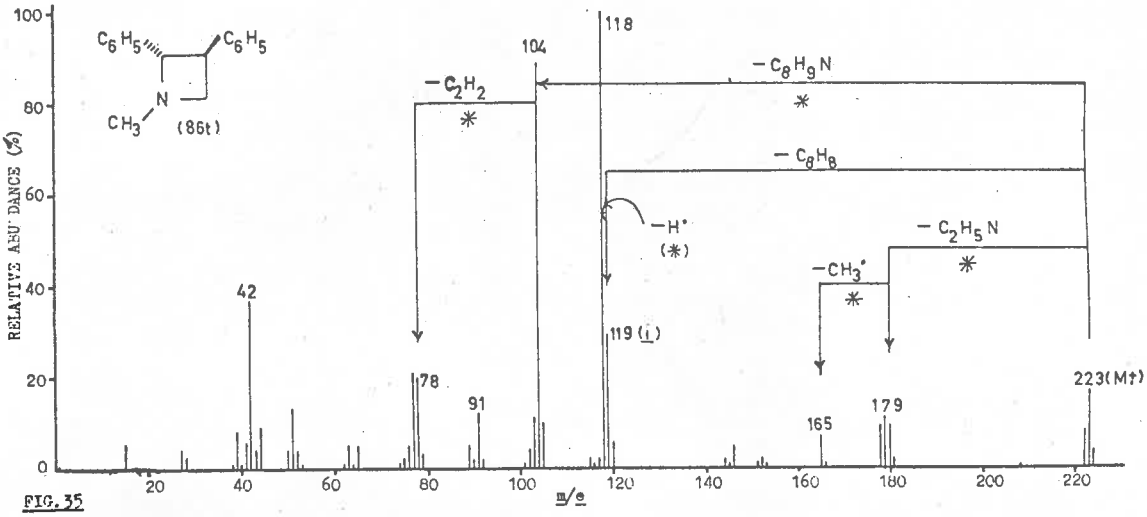


FIG. 35

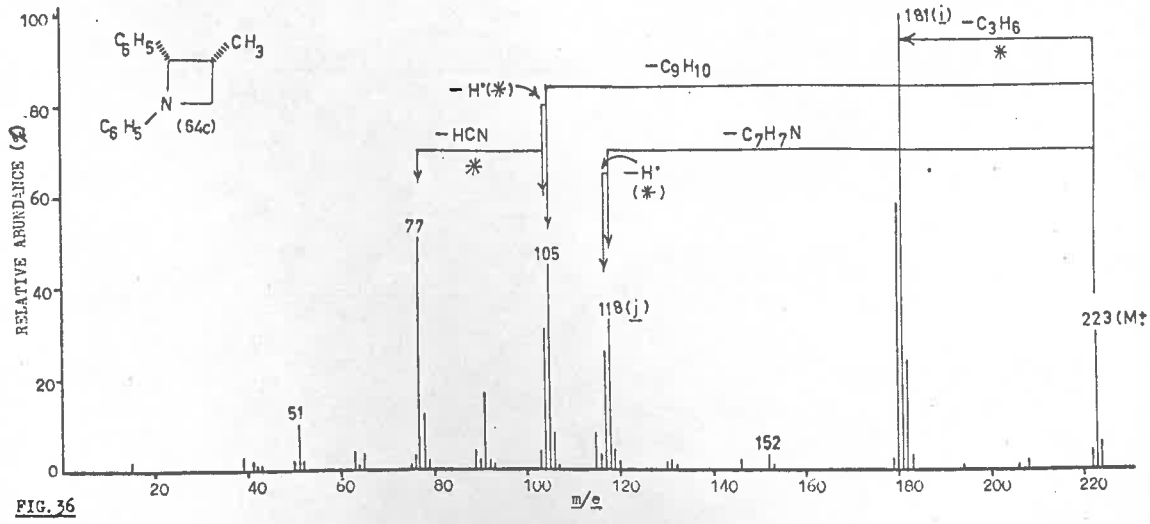


FIG. 36

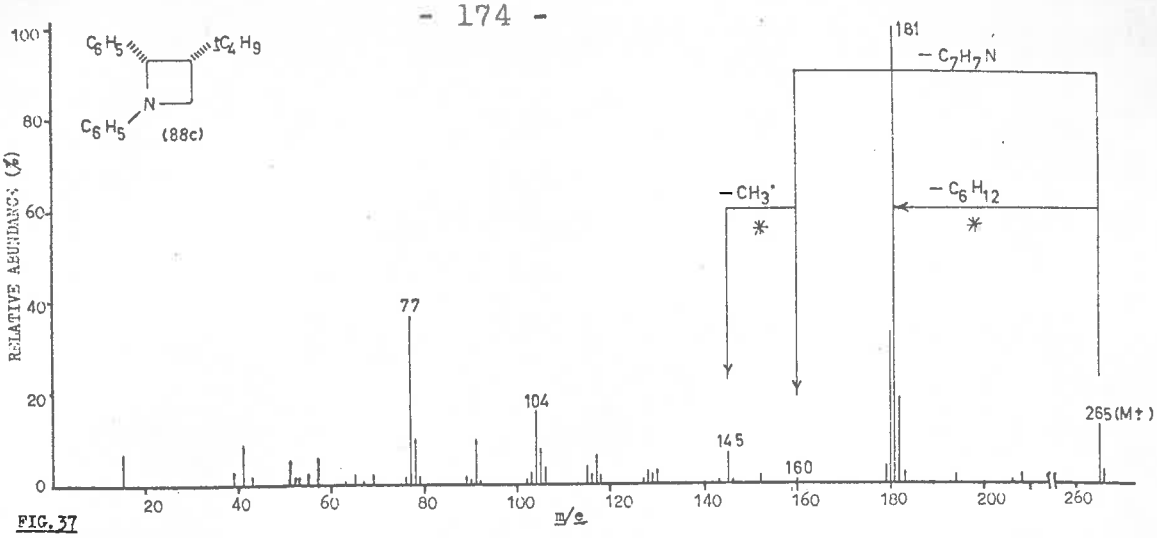


FIG. 37

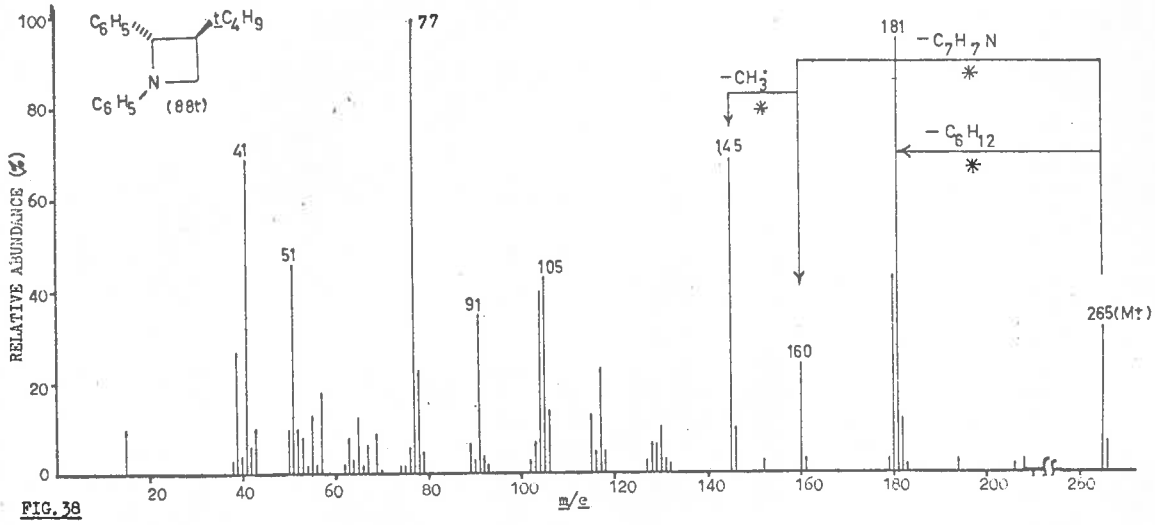


FIG. 38

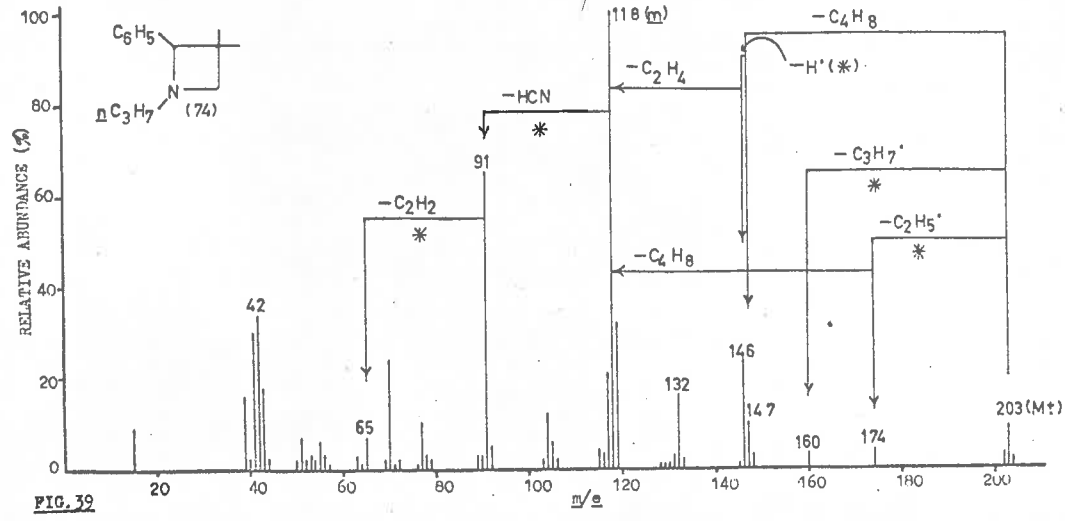


FIG. 39

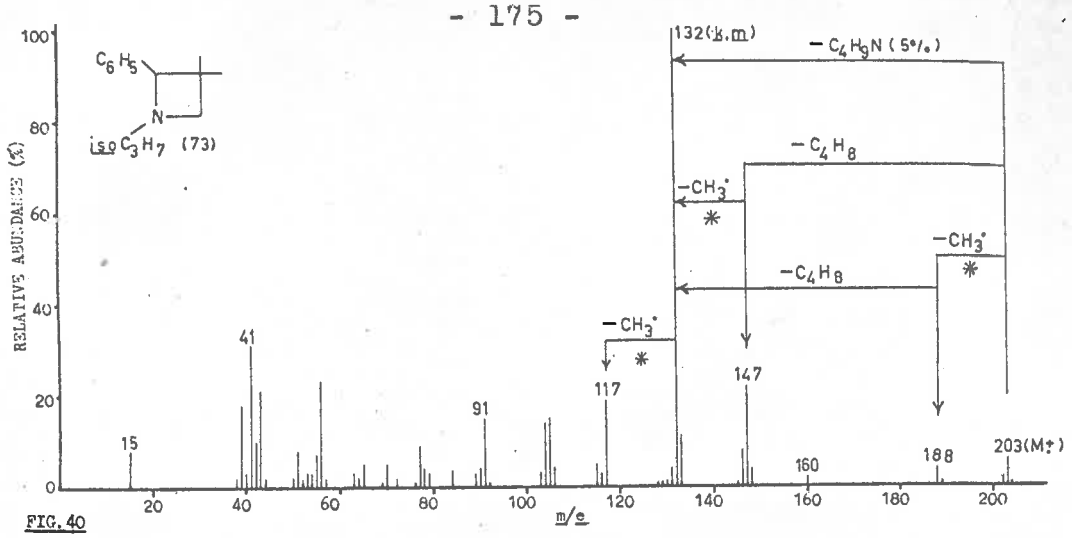


FIG. 40

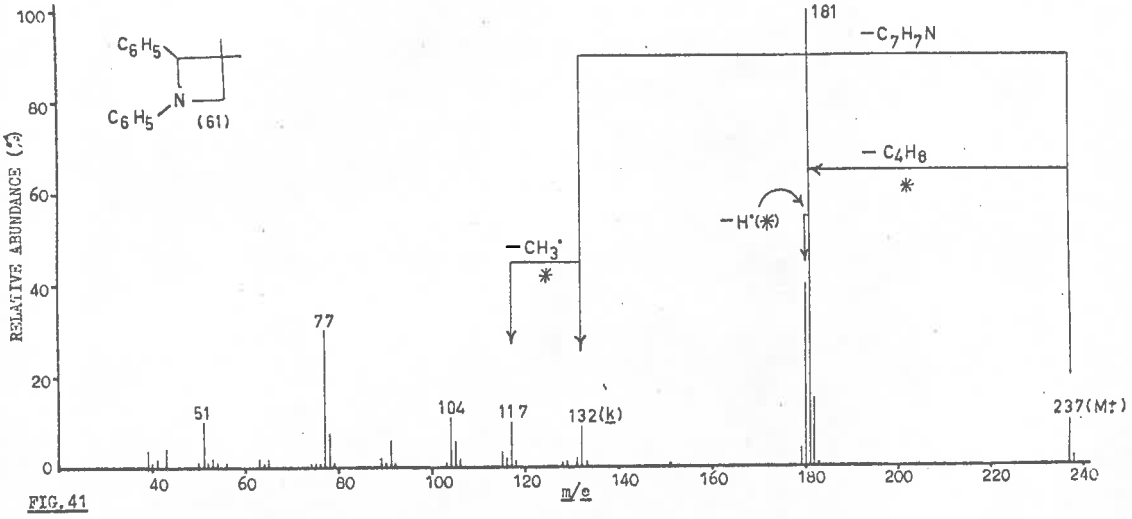


FIG. 41

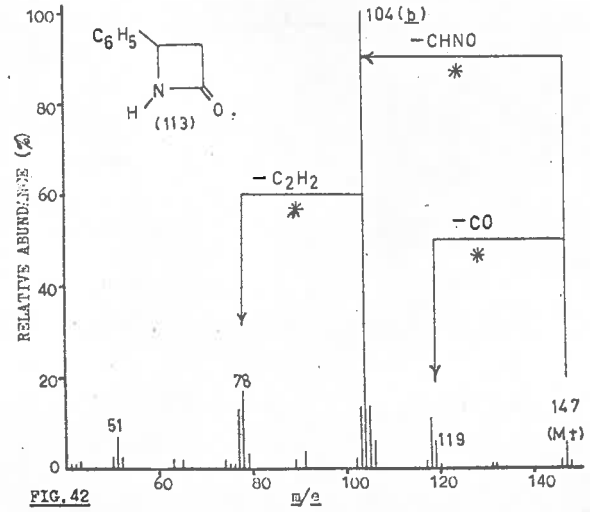


FIG. 42

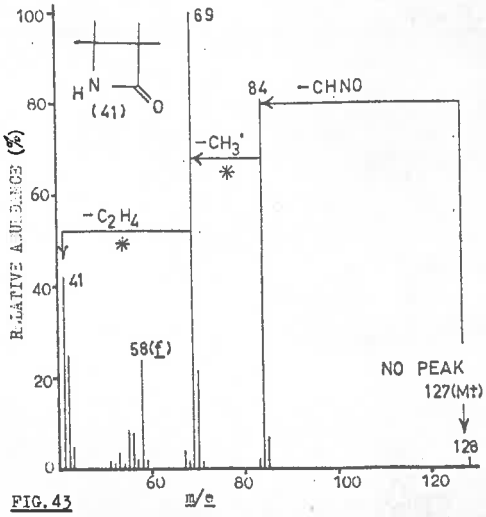


FIG. 43

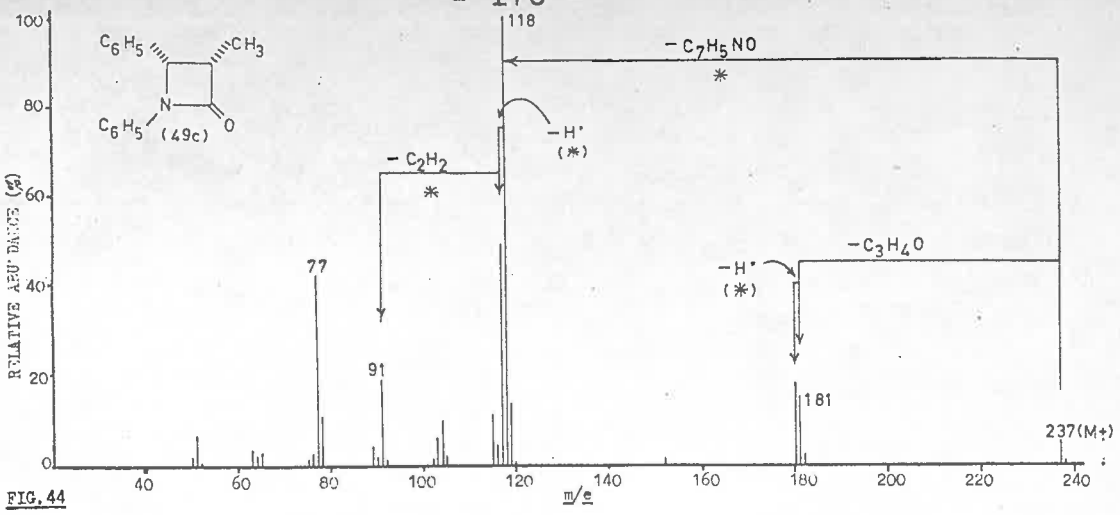


FIG. 44

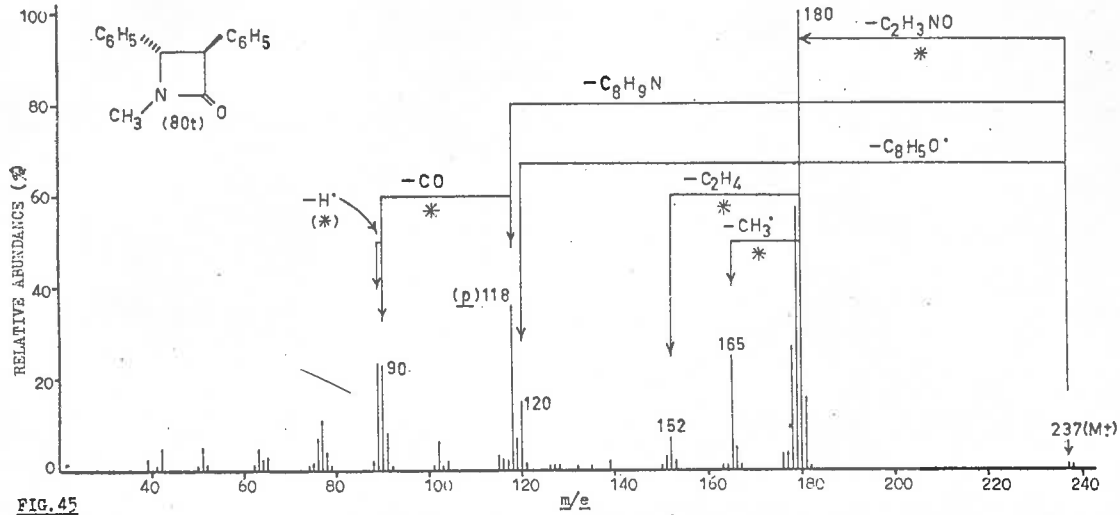


FIG. 45

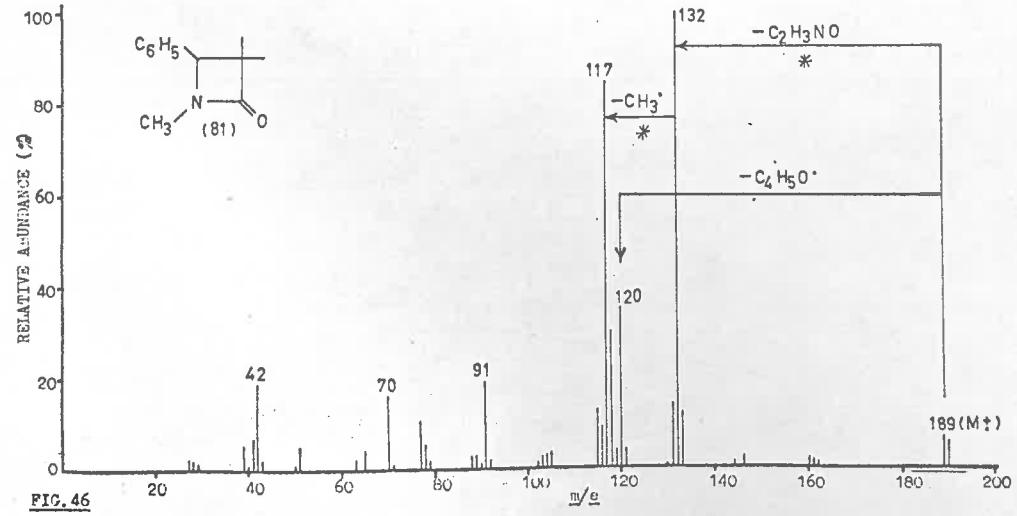


FIG. 46

CHAPTER 4. EXPERIMENTAL

1. Instrumentation

Melting points were determined using either a Gallenkamp melting point apparatus or a Reichert-Kofler Micro Heating Stage and are uncorrected.

Infrared (i.r.) spectra were recorded on either a Perkin-Elmer 237 IR Spectrophotometer, a Perkin-Elmer 337 IR Spectrophotometer or an Unicam SP200 IR Spectrophotometer.

Ultraviolet (u.v.) spectra were recorded on a Perkin-Elmer 137 UV Spectrophotometer.

Nuclear magnetic resonance (n.m.r.) spectra were recorded on a Varian DA-60-IL Spectrometer operating at 60 Mc/s. The spectra were calibrated by locking on tetramethylsilane as an internal reference using the internal reference n.m.r. stabilized controller V4354A. The spectra were run in the frequency sweep mode. Variable temperature spectra were run using the variable temperature accessory V6040 and the temperature was calibrated using methanol or glycerol and the graphs in the Varian manual.

Mass spectra (MS) were measured with an Hitachi Perkin-Elmer RMU 6D double-focussing mass spectrometer, using the heated inlet system (temperature 100-150°). The spectra of the compounds (46), (49c), (64c), (69), (88c) and (88t) were additionally obtained by the direct insertion procedure at 70°. Exact mass measurements were

performed at a resolution (M/ΔM) of 10,000 (40% valley definition). This is the maximum resolution (for this particular instrument) obtainable on the peak matcher. Heptacosafluorotributylamine provided the reference masses. After calibration of the voltage range using standard masses an accuracy of ±0.002 (*m/e*) was obtained for masses less than *m/e* 250. All measurements quoted in Tables XXVIII and XXXI are accurate to within these limits.

Vapour phase chromatography (v.p.c.) was carried out using a Perkin-Elmer 800 Gas Chromatograph. An Aerograph Autoprep Model A-700 was used for preparative v.p.c.

Microanalyses were performed by the Australian Microanalytical Service, Melbourne.

2. 2-Azetidinones by the Reformatsky Reaction

Schiff's bases were prepared by the standard methods and had melting points and boiling points in agreement with those reported in the literature.

α-*Bromoesters* were prepared by the standard methods and had boiling points in agreement with those reported in the literature.

The following 2-azetidinones were prepared by the Reformatsky reaction using techniques fully described elsewhere.[46,47,48] The physical data for all these compounds were identical to the reported values and consistent with the proposed structures.

3,3-Dimethyl-1,4-diphenyl-2-azetidinone (46), m.p. 149° (lit.[46,48] 149°), was obtained from benzal-aniline and ethyl α-bromo*iso*butyrate in 85% yield.

1,4-Diphenyl-2-azetidinone (47), m.p. 154° (lit.[46,47] m.p. 154°), was prepared from benzal-aniline and ethyl α-bromoacetate in 70% yield.

4-t-Butyl-3,3-dimethyl-1-phenyl-2-azetidinone (48)

The reaction between *neo*-pentylidene-aniline (2.2 gm, 0.014 mole) and ethyl α-bromo*iso*butyrate (3.0 gm, 0.017 mole) gave 2.0 gm (65%) (recrystallized from aqueous ethanol) of *4-t-butyl-3,3-dimethyl-1-phenyl-2-azetidinone*, m.p. 76-77°, ν_{max} (nujol) 1753 cm^{-1}. [Found: C, 77.47; H, 9.17; N, 6.56; O, 6.97. $C_{15}H_{21}NO$ requires C, 77.88; H, 9.15; N, 6.05; O, 6.92%].

1,4-Diphenyl-3-methyl-2-azetidinone (49c), m.p. 108-110° (lit.[46,48] m.p. 107-110°, 111°), was prepared from benzal-aniline and ethyl α-bromopropionate in 85% yield. The n.m.r. spectrum showed the product to be a mixture of 92% of the *cis* isomer and 8% of the *trans* isomer (lit.[46] 70% of the *cis* isomer and 30% of the *trans* isomer).

1,3,4-Triphenyl-2-azetidinone (50t), m.p. 133° (lit.[46,43] m.p. 133°), was prepared from benzal-aniline and ethyl α-bromophenyl-acetate in 70% yield.

1-t-Butyl-3,3-dimethyl-4-phenyl-2-azetidinone (52), m.p. 86° (lit.[46] m.p. 85-86°), was prepared from benzal-*t*-butylamine and ethyl α-bromo*iso*butyrate in 75% yield.

1-Benzyl-3,3-dimethyl-4-phenyl-2-azetidinone (53), m.p. 40° (lit.[43,46] m.p. 38°, 42°), was prepared from benzal-benzylamine and ethyl α-bromo*iso*butyrate in 85% yield.

1-Benzyl-4-phenyl-2-azetidinone (55), b.p. 140-142°/0.1 mm (lit.[46] b.p. 140-142°/0.1 mm), was prepared from benzal-benzylamine and ethyl α-bromoacetate in 70% yield.

1-(p-Methoxybenzyl)-3,3-dimethyl-4-phenyl-2-azetidinone (57)

The reaction between benzal-*p*-methoxybenzylamine (4.5 gm, 0.020 mole) and ethyl α-bromo*iso*butyrate (4.6 gm, 0.026 mole) gave 3.7 gm (63%) of *1-(p-methoxybenzyl)-3,3-dimethyl-4-phenyl-2-azetidinone* as a yellow oil, b.p. 180°/0.5 mm, ν_{max} (film) 1755 cm^{-1}. [Found: C, 76.67; H, 7.21; N, 4.56. $C_{19}H_{21}NO$ requires C, 77.29; H, 7.14; N, 4.75%.]

3,3-Dimethyl-1-β-phenylethyl-4-phenyl-2-azetidinone (58), m.p. 72-74° (lit.[46] m.p. 72-74°), was prepared from benzal-β-phenylethylamine and ethyl α-bromo*iso*butyrate in 70% yield.

*3,3-Dimethyl-4-phenyl-1-*isopropyl*-2-azetidinone* (59), m.p. 41° (lit.[46] m.p. 40-41°), was prepared from benzal-*iso*propylamine and ethyl α-bromo*iso*butyrate in 85% yield.

*3,3-Dimethyl-4-phenyl-1-*n*-propyl-2-azetidinone* (60), b.p. 128°/0.3 mm (lit.[46] b.p. 128°/0.3 mm), was prepared from benzal-*n*-propylamine and ethyl α-bromo*iso*butyrate in 85% yield.

3,4-Diphenyl-1-methyl-2-azetidinone (80t), m.p. 67-69° (lit.[46] m.p. 68-69°), was prepared from benzal-methylamine and ethyl-α-bromophenylacetate in 80% yield.

1,3,3-Trimethyl-4-phenyl-2-azetidinone (81), b.p. 112°/0.5 mm (lit.[46,285] b.p. 112°/0.5 mm, 139°/13.5 mm), was prepared from benzal-methylamine and ethyl α-bromo*iso*butyrate in 85% yield.

3-t-Butyl-1,4-diphenyl-2-azetidinone (82c) (82t) was prepared from benzal-aniline and ethyl α-bromo-*t*-butylacetate in 85% yield. The n.m.r. spectrum showed the product to be a mixture of 67% of the *trans* isomer (82t) and 33% of the *cis* isomer (82c) (lit.[48] 75% of the *trans* isomer and 25% of the *cis* isomer). The mixture (3 gm) was adsorbed on to Spence alumina (250 gm) and eluted with a mixture of light petroleum, ether and benzene (6:1:1). 100 ml fractions were collected. Fractions 4-8 yielded 1.2 gm of pure trans-*3-t-butyl-1,4-diphenyl-2-azetidinone* as long colourless needles, m.p. 151° (lit.[48] m.p. 151-152°). Fractions 9-16 yielded 1.45 gm of a mixture of the *cis* and *trans* isomer with each succeeding fraction yielding an increasing amount of the *cis* isomer. Fractions 17-26 yielded 0.3 gm of pure cis-*3-t-butyl-1,4-diphenyl-2-azetidinone* as colourless prisms, m.p. 174-175° (lit.[48] m.p. for a 1:1 mixture of the *cis* and *trans* isomer 138°).

1-n-Propyl-3,3,4-trimethyl-2-azetidinone (83), b.p. 77°/1.4 mm (lit.[46] b.p. 77°/1.4 mm), was prepared from ethylidene-*n*-propylamine and ethyl α-bromo*iso*butyrate in 75% yield.

1-Methyl-4-phenyl-3-isopropyl-2-azetidinone (84t) and (84c), b.p. 138°/0.8mm (lit.[46] b.p. 138°/0.8 mm) and m.p. 98-99° (lit.[46] m.p. 98-99°) respectively, were prepared from benzal-methylamine and ethyl α-bromo*iso*valerate in 85% yield and separated by chromatography on a Spence alumina column.

3. 2-Azetidinones by Other Methods

(1) Grignard Cyclization of a β-Aminoester

General procedure for the Grignard cyclization.[50,286]

To a Grignard solution of methyl magnesium iodide prepared from magnesium (2.6 mg), methyl iodide (16 gm) and ether (60 mls) was added the aminoester (0.025 mole) in ether (30 mls) at 0° with stirring over a period of one hour. The whole was allowed to reach room temperature, stirred for 4 hours, kept for 12 hours and then cooled to 0°. The mixture was treated dropwise with 20% ammonium chloride solution (13 mls) at 0° and then acidified to pH 5 with cold dilute hydrochloric acid solution (10%, 50 mls). The ether layer was separated, the aqueous layer extracted with ether, the combined ether layers washed with dilute hydrochloric acid solution, water until neutral and the organic layer dried. The ether was removed and the residue redistilled under reduced pressure or recrystallized from a suitable solvent.

In this way, the following 2-azetidinones were prepared. The intermediate aminoesters were prepared by previously reported methods and their physical properties were in agreement with those reported in the literature.

4-Phenyl-2-azetidinone (113), m.p. 107-108° (lit.[60] m.p. 107-108°), was prepared from ethyl β-aminohydrocinnamate[287] in 19% yield. Attempts to cyclize ethyl β-aminohydrocinnamate to compound (113) with anhydrous potassium carbonate in dimethylformamide under a variety of conditions were unsuccessful.

3-Phenyl-2-azetidinone (114), m.p. 115° (lit.[288] m.p. 115-116°) was prepared from ethyl α-phenyl-β-aminopropionate[288] in 10% yield. Attempts to cyclize ethyl α-phenyl-β-aminopropionate to compound (114) with anhydrous potassium carbonate in dimethylformamide were also unsuccessful.

3-Methyl-3-phenyl-2-azetidinone (115) m.p. 95-97° (lit.[50] m.p. 96-97°) was prepared from ethyl α-methyl-α-phenyl-β-aminopropionate[50] in 40% yield.

3-Benzyl-2-azetidinone (116) m.p. 89-93° (lit.[49] m.p. 90-92°) was prepared from ethyl α-benzyl-β-amino-propionate[49] in 35% yield.

3,3-Dimethyl-2-azetidinone (37) b.p. 70-72°/0.2-0.4 mm (lit.[289] b.p. 70-73°/0.8 mm) was prepared from ethyl α,α-dimethyl-β-aminopropionate in 55% yield.

Trans-*3,4-diphenyl-2-azetidinone* (117), m.p. 122-124° (lit.[46] m.p. 123-124°), was prepared from *threo* methyl α,β-diphenyl-β-aminopropionate[290] in 27% yield.

(2) *1,3,3,4,4-Pentaphenyl-2-azetidinone* (51) was prepared from benzophenone-anil[291] and diphenylketene[292] according to the method of Staudinger,[293] m.p. 192-192.5° (lit.[293] m.p. 190-191°), in 68% yield.

(3) Olefins and chlorosulphonylisocyanate

The following 2-azetidinones were prepared from chlorosulphonyl-isocyanate and the appropriate olefin by the method of Graf.[51] The

N-chlorosulphonyl-2-azetidinone was hydrolysed to the *N*-unsubstituted-2-azetidinone with sodium hydroxide solution (33%) according to the method of Graf.[51]

1-Chlorosulphonyl-4-methyl-4-neo-pentyl-2-azetidinone (118) was prepared from diisobutylene and chlorosulphonylisocyanate, and on hydrolysis it yielded *4-methyl-4-neo-pentyl-2-azetidinone* (40), b.p. 114°/0.5 mm (lit.[51] b.p. 108°/0.1 mm), in 85% yield.

1-Chlorosulphonyl-3,3,4,4-tetramethyl-2-azetidinone (119) was prepared from tetramethyl-ethylene[294] and chlorosulphonylisocyanate, and on hydrolysis it yielded *3,3,4,4-tetramethyl-2-azetidinone* (41), m.p. 104° (lit.[51] m.p. 104°), in 85% yield.

3-t-Butyl-1-chlorosulphonyl-4,4-dimethyl-2-azetidinone (120) was prepared from 2,4,4-trimethyl-2-pentene and chlorosulphonylisocyanate, and on hydrolysis it yielded *3-t-butyl-4,4-dimethyl-2-azetidinone* (42), m.p. 75-76° (lit.[51] m.p. 76°), in 90% yield.

1-Chlorosulphonyl-3,4,4-trimethyl-2-azetidinone (121) was prepared from 2-methyl-2-butene and chlorosulphonylisocyanate, and on hydrolysis it gave *3,4,4-trimethyl-2-azetidinone* (39), b.p. 84-86°/2.0-2.5 mm (lit.[51] b.p. 74-75°/0.5 mm), in 80% yield.

(4) *N*-Benzylation and *N*-Methylation of 2-Azetidinones

1-Benzyl-3,3,4,4-tetramethyl-2-azetidinone (54)

3,3,4,4-Tetramethyl-2-azetidinone (9.6 gm, 0.075 mole) in dry dimethoxyethane (90 mls) was added dropwise to sodium hydride (3.0 gm,

0.125 mole) in dimethoxyethane (25 mls) under nitrogen with vigorous stirring. The suspension was stirred for 6 hours while heating at 60° on a water-bath. After cooling, benzyl chloride (19.2 gm, 17.5 mls, 0.15 moles) was added dropwise and the resulting suspension heated with stirring on a water-bath for 12 hours. The white slurry was evaporated under reduced pressure, the residue mixed with water and the suspension extracted twice with chloroform. The chloroform was dried (magnesium sulphate) and removed and the residue fractionated under vacuum. *1-Benzyl-3,3,4,4-tetramethyl-2-azetidinone* (11.6 gm, 71%), b.p. 136-137°/1 mm, was obtained as colourless needles, m.p. 53.5-54°, ν_{max} (CCl_4) 1750 cm^{-1}. [Found: C, 77.50; H, 8.70; N, 6.51; O, 7.29. $C_{14}H_{19}NO$ requires C, 77.38; H, 8.81; N, 6.45; O, 7.36%.]

1-Benzyl-3-t-butyl-4,4-dimethyl-2-azetidinone (56)

The reaction of 3-*t*-butyl-4,4-dimethyl-2-azetidinone (3.1 gm, 0.02 mole) with sodium hydride (1.0 gm, 0.04 mole) and then with benzyl chloride (5.7 gm, 0.045 mole) under similar conditions to those used above gave *1-benzyl-3-t-butyl-4,4-dimethyl-2-azetidinone* (4.3 gm, 87%), b.p. 142°/0.7 mm, as a colourless liquid, ν_{max} (CCl_4) 1740 cm^{-1}. [Found: C, 77.76; H, 9.45; N, 5.70; O, 6.8. $C_{16}H_{23}NO$ requires C, 78.32; H, 9.45; N, 5.71; O, 6.52%.]

1,3,3,4,4-Pentamethyl-2-azetidinone (85).

The reaction of 3,3,4,4-tetramethyl-2-azetidinone (2.5 gm, 0.02 mole) with sodium hydride (0.72 gm, 0.03 mole) and then with methyl iodide (5.7 gm, 0.04 mole) under similar conditions to those given above gave *1,3,3,4,4-pentamethyl-2-azetidinone* (2.2 gm, 80%),

m.p. 57.5-59° (from light petroleum), as colourless plates, ν_{max} (CCl_4) 1740 cm^{-1}. [Found: C, 67.42; H, 10.68; N, 9.79. $C_8H_{15}NO$ requires C, 68.04; H, 10.71; N, 9.92%.]

4. The Reduction of 2-Azetidinones to Azetidines

(1) Lithium Aluminium Hydride (LAH) Reduction of *N*-Unsubstituted 2-Azetidinones

General procedure for the LAH reductions.[44]

The 2-azetidinone (0.014 mole) was added gradually (portion-wise if a solid, as a solution in ether if the 2-azetidinone was a liquid) to LAH (0.05 mole) suspended in absolute ether (35 mls) with stirring. The mixture was refluxed for 4 hours (longer if necessary), cooled to 0°, treated dropwise with 20% ammonium chloride solution (7.9 mls) below 5°, the solid filtered off, washed with ether, the combined organic solutions dried and then fractionated under nitrogen. Since all of these azetidines readily absorbed carbon dioxide it was found necessary to distil and store them under nitrogen. This property also made it impracticable to obtain satisfactory analytical results for the azetidines but, analysis as the picrates, gave satisfactory results.

2-Phenylazetidine (122), b.p. 76-79°/2.5 mm (lit.[60] b.p. 76-78°/2.5 mm) was obtained in 46% yield from 4-phenyl-2-azetidinone.

1-Benzyl-2-phenylazetidine (69), b.p. 120-122°/0.4 mm (lit.[60] b.p. 120-122°/0.4 mm) was prepared in 60% yield from 2-phenylazetidine and benzyl chloride according to the method of Testa.[60]

3-Phenylazetidine (123), b.p. 87-89°/3.5 mm (lit.[295] b.p. 87-89°/3.5 mm), was obtained in 45% yield from 3-phenyl-2-azetidinone.

3-Methyl-3-phenylazetidine (124), b.p. 83°/0.9 mm (lit.[44] b.p. 73°/0.9 mm), was obtained in 55% yield from 3-methyl-3-phenyl-2-azetidinone. *1-Benzyl-3-methyl-3-phenylazetidine* (125) was prepared from 3-methyl-3-phenylazetidine and benzyl chloride by the method of Testa[60] as a colourless liquid, b.p. 145-146°/0.7 mm (Yield 66%). [Found: C, 85.60; H, 8.08; N, 6.10. $C_{17}H_{19}N$ requires C, 86.03; H, 8.07; N, 5.90%.]

3-Benzylazetidine (126), b.p. 98-100°/0.9 mm (lit.[49] b.p. 98°/0.8 mm), was prepared in 45% yield from 3-benzyl-2-azetidinone. *3-Benzyl-1-carbamoylazetidine* (127) was obtained by reacting 3-benzylazetidine with sodium cyanate, according to the method of Testa,[49] as colourless plates (from aqueous ethanol), m.p. 207-208° (95% yield). [Found: C, 69.41; H, 7.29; O, 9.0; N, 15.09. $C_{11}H_{14}N_2O$ requires C, 69.46; H, 7.37; O, 8.42; N, 14.74%.]

3,3-Dimethylazetidine (128), b.p. 90° (lit.[44] b.p. 90-92°), was prepared from 3,3-dimethyl-2-azetidinone in 40% yield.

*2-Methyl-2-*neo*pentylazetidine* (129)

LAH reduction of 4-methyl-4-*neo*pentyl-2-azetidinone (8 hours reflux in ether) gave *2-methyl-2-*neo*pentylazetidine* as a colourless liquid, b.p. 72°/38 mm, in 70% yield. The *picrate* was obtained as yellow

crystals, m.p. 139-140.5° (recrystallized from water). [Found: C, 48.57; H, 5.99; N, 15.34; O, 30.1. $C_{15}H_{22}N_4O_7$ requires C, 48.64; H, 5.99; N, 15.13; O, 30.24%.]

2,2,3-Trimethylazetidine (130)

LAH reduction of 3,4,4-trimethyl-2-azetidinone gave *2,2,3-trimethylazetidine* as a colourless liquid, b.p. 97°, in 50% yield. Under the conditions used, no picrate could be isolated. The reaction of 2,2,3-trimethylazetidine with benzyl chloride under the conditions used by Testa[60] yielded *1-benzyl-2,2,3-trimethylazetidine* (131) as a colourless liquid in about 80% yield. However, it was not possible to separate completely this compound from benzyl chloride, with which it was contaminated.

2,2,3,3-Tetramethylazetidine (132)

LAH reduction of 3,3,4,4-tetramethyl-2-azetidinone (refluxed in ether for 24 hours) gave *2,2,3,3-tetramethylazetidine* as a colourless liquid, b.p. 118°, in 35% yield. The *picrate* was obtained as yellow needles, m.p. 157-158.5° (recrystallized from aqueous ethanol). [Found: C, 45.75; H, 5.45; N, 16.07; O, 32.6. $C_{13}H_{18}O_7N_4$ requires C, 45.61; H, 5.30; N, 16.37; O, 32.75%.]

Attempted reduction of 3-t-butyl-4,4-dimethyl-2-azetidinone (42)

3-*t*-Butyl-4,4-dimethyl-2-azetidinone (0.014 mole) and LAH (0.05 mole) were refluxed in ether for up to 72 hours. In every case the 2-azetidinone was recovered unchanged. Compound (42) was also recovered when it was refluxed in tetrahydrofuran for 4 hours with LAH.

4,4-d_2-2-Phenylazetidine (133), 4,4-d_2-3-phenylazetidine (136), 4,4-d_2-2-methyl-2-*neo*pentylazetidine (135) and 4,4-d_2-2,2,3,3-tetramethylazetidine (134) were prepared by reducing compounds (113), (114), (40) and (41) respectively with lithium aluminium deuteride.

1-Bromo-2,2,3,3-tetramethylazetidine (140)

To a cold sodium hypobromite solution prepared by adding bromine (0.16 gm, 1.1mmole) to a solution of sodium hydroxide (0.09 gm, 2.2 mmoles) in water (0.4 mls) at -5° to -10° was added cold 2,2,3,3-tetramethylazetidine (113 mg, 1 mmole) at -10° with stirring (c.f.[254]). The mixture was extracted with deuterochloroform, the organic layer washed five times with water and dried (magnesium sulphate). The chloroform solution was filtered and transferred to an n.m.r. tube.

1-Chloro-2,2,3,3-tetramethylazetidine (141) was prepared similarly from sodium hypochlorite and 2,2,3,3-tetramethylazetidine.

(2) Diborane Reduction of 2-Azetidinones to Azetidines

Solutions of diborane in tetrahydrofuran were prepared from sodium borohydride and iodine in the usual way.[58,59] The concentration of the diborane solutions was measured[296] by forming diisopropoxyborane by reaction of an aliquot of the diborane solution with acetone followed by hydrolysis in water. The solution was then titrated for boric acid.

The solvents, diglyme and tetrahydrofuran, were purified in the usual way.[58]

General procedure for the diborane reductions

A solution of the 2-azetidinone (0.015 mole) in absolute tetrahydrofuran (15 mls) was added dropwise to a stirred solution of diborane in tetrahydrofuran [30 mls, 0.75M] at 0° under a nitrogen atmosphere. The resulting solution was stirred at room temperature for 15 minutes and then at 50° for 30 minutes to 2 hours. The solution was cooled and maintained at 5-10° during the dropwise addition of a 10% sodium hydroxide solution (12 mls). The reaction mixture was then stirred at room temperature for 30 minutes, the organic layer separated, the aqueous layer extracted with ether and the combined organic layers dried (magnesium sulphate). After removal of the solvent the residue was fractionated under nitrogen.

3,3-Dimethyl-1,2-diphenylazetidine (61)

The reduction of 3,3-dimethyl-1,4-diphenyl-2-azetidinone (3.0 gm) with diborane gave *3,3-dimethyl-1,2-diphenylazetidine* (2.1 gm, 70%) as a colourless liquid, b.p. 130-131°/1 mm. [Found: C, 85.24; H, 8.11; N, 5.99. $C_{17}H_{19}N$ requires C, 86.03; H, 8.07; N, 5.90%.] The *picrate* was obtained as fine yellow needles, m.p. 117-118.5°, after recrystallization from ethanol. [Found: C, 59.00; H, 4.87; N, 12.02; O, 24.1. $C_{23}H_{22}N_4O_7$ requires C, 59.22; H, 4.75; N, 12.01; O, 24.01%.]

1,2-Diphenylazetidine (62)

The reduction of 1,4-diphenyl-2-azetidinone (2.5gm) with diborane yielded 2.3 gm (95%) of a mixture of *1,2-diphenylazetidine* (60%), 3-anilino-3-phenyl-1-propanol (5%) and starting material (30%). These ratios were determined by n.m.r. spectra and v.p.c. This mixture gave

three separate peaks on v.p.c. but because of the tendency of the azetidine (62) to absorb carbon dioxide and since both the azetidine and aminoalcohol may be prepared by alternative routes [Section 4.(3) and 5.(1) respectively] no attempt was made to separate the components by preparative v.p.c.

2-t-Butyl-3,3-dimethyl-1-phenylazetidine (63)

The reduction of 4-*t*-butyl-3,3-dimethyl-1-phenyl-2-azetidinone (2.0 gm) with diborane gave *2-t-butyl-3,3-dimethyl-1-phenylazetidine* (1.3 gm, 67%) as a colourless liquid, b.p. 99-100°/2 mm. [Found: C, 82.46; H, 10.56. $C_{15}H_{23}N$ requires C, 82.89; H, 10.67%.] The *picrate* was obtained as a yellow crystalline solid, m.p. 153-162° (Recrystallized from ethanol). [Found: C, 56.52; H, 5.92; N, 12.67; O, 24.8. $C_{21}H_{26}N_4O_7$ requires C, 56.49; H, 5.87; N, 12.55; O, 25.09%.]

3-Methyl-1,2-diphenylazetidine (64c)

The reduction of *cis*-3-methyl-1,4-diphenyl-2-azetidinone (3.0 gm) with diborane gave cis-*3-methyl-1,2-diphenylazetidine* (2.1 gm, 70%) as colourless liquid, b.p. 134°/ 1.5 mm. [Found: C, 85.89; H, 7.78; N, 6.42. $C_{16}H_{17}N$ requires C, 86.05; H, 7.67; N, 6.27%.]

Attempted reduction of 1,3,3,4,4-pentaphenyl-2-azetidinone (51) with diborane resulted in quantitative recovery of compound (51).

1-t-Butyl-3,3-dimethyl-2-phenylazetidine (66)

The reduction of 1-*t*-butyl-3,3-dimethyl-4-phenyl-2-azetidinone (2.5 gm) with diborane gave *1-t-butyl-3,3-dimethyl-2-phenylazetidine* (1.7 gm, 70%) as a colourless liquid, b.p. 71°/1 mm. [Found: C, 82.52; H, 10.32; N, 6.66. $C_{15}H_{23}N$ requires C, 82.89; H, 10.67; N, 6.45%.]

1-Benzyl-3,3-dimethyl-2-phenylazetidine (67)

The reduction of 1-benzyl-3,3-dimethyl-4-phenyl-2-azetidinone (3.2 gm) with diborane gave *1-benzyl-3,3-dimethyl-2-phenylazetidine* (1.9 gm, 60%) as a colourless liquid, b.p. 136-138°/2 mm. The *picrate* was obtained as a yellow crystalline solid, m.p. 177.5-179° (recrystallized from ethanol). [Found: C, 59.94; H, 5.13; N, 11.74; O, 23.2. $C_{24}H_{24}N_4O_7$ requires C, 59.99; H, 5.04; N, 11.66; O, 23.31%.]

1-Benzyl-2,2,3,3-tetramethylazetidine (68)

The reduction of 1-benzyl-3,3,4,4-tetramethyl-2-azetidinone (3.0 gm) with diborane gave *1-benzyl-2,2,3,3-tetramethylazetidine* (2.2 gm, 75%) as a colourless liquid, b.p. 82°/ 0.3 mm. The *picrate* was obtained as a yellow crystalline solid, m.p. 168.5-170° (recrystallized from ethanol). [Found: C, 55.12; H, 5.48; N, 12.79; O, 25.6. $C_{20}H_{24}O_7N_4$ requires C, 55.55; H, 5.59; N, 12.96; O, 25.90%.]
Treatment of compound (68) with a solution of diborane in tetrahydrofuran gave a white crystalline solid, m.p. 98-99° (recrystallized from dry light petroleum ether). This compound was shown to be the borine complex of 1-benzyl-2,2,3,3-tetramethylazetidine (93). [Found: C, 77.87; H, 10.78; N, 6.45; B, 4.9. $C_{14}H_{21}N.BH_3$ requires C, 77.43; H, 11.14; N, 6.45; B, 4.98%.]

1-Benzyl-2-phenylazetidine (69)

The reduction of 1-benzyl-4-phenyl-2-azetidinone (2.6 gm) with diborane gave 1.7 gm (70%) of a mixture of *1-benzyl-2-phenylazetidine* (35%) and 3-benzylamino-3-phenyl-1-propanol (35%). These two compounds were separated by preparative v.p.c. and identified by comparison with authentic samples prepared as described in Sections 4.(1) and 5.(1) respectively.

1-Benzyl-3-t-butyl-2,2-dimethylazetidine (70)

The reduction of 1-benzyl-3-*t*-butyl-4,4-dimethyl-2-azetidinone (56) (3.1 gm) with diborane gave *1-benzyl-3-t-butyl-2,2-dimethylazetidine* (1.8 gm, 60%) as a colourless liquid, b.p. 101-102°/0.2-0.4 mm. [Found: C, 82.57; H, 10.67; N, 6.31. $C_{16}H_{25}N$ requires C, 83.05; H, 10.89; N, 6.05%.] The *picrate* was obtained as a yellow crystalline solid, m.p. 174-175° (recrystallized from chloroform/ethanol). [Found: C, 57.74; H, 6.27; N, 12.63. $C_{22}H_{28}N_4O_7$ requires C, 57.38; H, 6.13; N, 12.17%.] When compound (56) was reduced with a large excess of diborane, a colourless crystalline solid, m.p. 87-89° (recrystallized from light petroleum ether), was obtained and this was shown to be the borine complex of 1-benzyl-3-*t*-butyl-2,2-dimethylazetidine (92). [Found: C, 77.84; H, 11.37; N, 6.25; B, 4.3. $C_{16}H_{25}N.BH_3$ requires C, 78.36; H, 11.46; N, 5.71; B, 4.41%.]

1-(p-Methoxybenzyl)-3,3-dimethyl-2-phenylazetidine (71)

The reduction of 1-(*p*-methoxybenzyl)-3,3-dimethyl-4-phenyl-2-azetidinone (2.95 gm) with diborane gave *1-(p-methoxybenzyl)-3,3-dimethyl-2-phenylazetidine* (1.4 gm, 50%) as a colourless liquid,

b.p. 150°/0.4 mm. This compound was contaminated by a very small amount of a similar boiling point impurity which prevented satisfactory analysis figures from being obtained and also precluded the formation of a picrate derivative.

3,3-Dimethyl-1-β-phenylethyl-2-phenylazetidine (72)

The reduction of 3,3-dimethyl-1-β-phenylethyl-4-phenyl-2-azetidinone (3.0 gm) with diborane gave *3,3-dimethyl-1-β-phenylethyl-2-phenylazetidine* (0.9 gm, 30%) as a colourless liquid, b.p. 144-146°/1.5 mm. [Found: C, 86.24; H, 8.80; N, 5.42. $C_{19}H_{23}N$ requires C, 85.98; H, 8.74; N, 5.28%.] The *picrate* was obtained as a yellow crystalline solid, m.p. 195-197° (recrystallized from ethanol). [Found: C, 60.40; H, 5.34; N, 11.48; O, 22.2. $C_{25}H_{26}N_4O_7$ requires C, 60.72; H, 5.30; N, 11.33; O, 22.65%.]

*3,3-Dimethyl-2-phenyl-1-*iso*-propylazetidine* (73)

The reduction of 3,3-dimethyl-4-phenyl-1-*iso*-propyl-2-azetidinone (3.0 gm) with diborane gave *3,3-dimethyl-2-phenyl-1-*iso*-propylazetidine* (1.2 gm, 40%) as a colourless liquid, b.p. 80°/2.5 mm. The *picrate* was obtained as yellow plates, m.p. 163.5-165.5° (recrystallized from ethanol). [Found: C, 55.51; H, 5.72; N, 13.09; O, 25.6. $C_{20}H_{24}N_4O_7$ requires C, 55.55; H, 5.59; N, 12.96; O, 25.90%.]

*3,3-Dimethyl-2-phenyl-1-*n*-propylazetidine* (74)

The reduction of 3,3-dimethyl-4-phenyl-1-*n*-propyl-2-azetidinone (3.0 gm) with diborane gave *3,3-dimethyl-2-phenyl-1-*n*-propylazetidine*

(0.9 gm, 30%) as a colourless liquid, b.p. 70-73°/2-2.5 mm. The *picrate* was obtained as a yellow crystalline solid, m.p. 147-148.5° (recrystallized from ethanol). [Found: C, 55.73; H, 5.67; N, 12.88; O, 25.3. $C_{20}H_{24}N_4O_7$ requires C, 55.55; H, 5.59; N, 12.96; O, 25.90%.]

1,2,3-Triphenylazetidine (65t)

The reduction of *trans*-1,3,4-triphenyl-2-azetidinone (2.5 gm) with diborane gave 1.2 gm(50%) of a yellow liquid, b.p. 180-200°/1 mm, which was shown to be a mixture of trans-*1,2,3-triphenylazetidine* (30%) and 3-anilino-2,3-diphenyl-1-propanol (20%). These yields were estimated by "spiking" with an authentic sample of the amino-alcohol using v.p.c. and by n.m.r. spectroscopy. Although separation of these two compounds by preparative v.p.c. should present few difficulties, no attempt was made to do so.

The reduction of *trans*-1-methyl-3,4-diphenyl-2-azetidinone with diborane yielded 3-methylamino-2,3-diphenyl-1-propanol as the only product which could be isolated. This was identified by comparison with an authentic sample prepared as described in Section 5.(1).

Similarly, the reduction of 1,3,3-trimethyl-4-phenyl-2-azetidinone gave only the corresponding amino-alcohol.

(3) Aluminium Hydride Reduction of 2-Azetidinones to Azetidines

General procedure for the aluminium hydride reductions

A solution containing LAH (0.12 gm, 2.9 mmoles) in ether (2 mls) was diluted with ether (3 mls) and treated portionwise with aluminium chloride (0.13 gm, 0.95 mmoles) under nitrogen at 0°. After stirring

at 0° for 20 minutes the solution was filtered under nitrogen through a celite pad.

The 2-azetidinone (0.6 mmoles) in tetrahydrofuran was added dropwise to the above solution of aluminium hydride in ether under nitrogen at 0°. A white precipitate formed immediately. The suspension was stirred at 0° for 45 minutes, 10% sodium hydroxide solution (3 mls) was added dropwise at 0° and then the mixture stirred at 0° for 30 minutes. The organic layer was separated, the aqueous phase extracted with ether and the combined organic layers washed with a small amount of water and dried (magnesium sulphate). The ether was removed and the residue fractionated under nitrogen.

All of the 2-azetidinones in Section 4.(2) which were reduced with diborane were also reduced with aluminium hydride. The yield of the azetidine using aluminium hydride was always as good as and in most cases better than that obtained when the reducing agent, diborane, was used. The yields of these azetidines are given in Table II of Chapter 1 and will not be repeated here.

The following azetidines were also prepared by reduction with aluminium hydride.

1-Methyl-2,3-diphenylazetidine (86t)

The reduction of *trans*-1-methyl-3,4-diphenyl-2-azetidinone (1.4 gm) with aluminium hydride gave trans-*1-methyl-2,3-diphenylazetidine* (0.65 gm, 50%) as a very light-yellow liquid, b.p. 130°/0.3 mm. This compound rapidly absorbed carbon dioxide, thus preventing satisfactory analytical figures being obtained. [Found: C, 84.86; H, 7.84;

N, 6.16. $C_{16}H_{17}N$ requires C, 86.05; H, 7.67; N, 6.27%.] Under the conditions used, it was not possible to obtain a crystalline picrate derivative.

1,3,3-Trimethyl-2-phenylazetidine (87)

The reduction of 1,3,3-trimethyl-4-phenyl-2-azetidinone (1.0 gm) with aluminium hydride gave *1,3,3-trimethyl-2-phenylazetidine* (0.6 gm, 65%) as a colourless liquid, b.p. 56°/0.5 mm (lit.[27(b)] b.p. 85-89°/9 mm). Since this compound rapidly absorbed carbon dioxide, it was difficult to obtain satisfactory analytical values. [Found: N, 7.74. $C_{21}H_{17}N$ requires N, 7.99%.]

trans-*3*-t-*Butyl-1,2-diphenylazetidine* (88t)

The reduction of *trans*-3-*t*-butyl-1,4-diphenyl-2-azetidinone (1.1 gm) with aluminium hydride gave trans-*3*-t-*butyl-1,2-diphenyl-azetidine* (0.7 g, 70%) as colourless needles, sublimed at 90°/0.3 mm, m.p. 74.5-75.5° (recrystallized from ethanol). [Found: C, 85.56; H, 8.80; N, 5.50. $C_{19}H_{23}N$ requires C, 85.98; H, 8.74; N, 5.28%.]

cis-*3*-t-*Butyl-1,2-diphenylazetidine* (88c)

The reduction of *cis*-3-*t*-butyl-1,4-diphenyl-2-azetidinone (2.0 gm) with aluminium hydride gave cis-*3*-t-*butyl-1,2-diphenylazetidine* (1.4 gm, 75%) as colourless needles, sublimed at 90-95°/0.2 mm, m.p. 87-88.5° (recrystallized from light petroleum ether). [Found: C, 85.62; H, 8.58; N, 5.19. $C_{19}H_{23}N$ requires C, 85.98; H, 8.74; N, 5.28%.]

2,3,3-Trimethyl-1-n-propylazetidine (89)

The reduction of 3,3,4-trimethyl-1-*n*-propyl-2-azetidinone (1.6 gm) with aluminium hydride gave *2,3,3-trimethyl-1-n-propylazetidine* (1.1 gm, 73%) as a colourless liquid, b.p. 50°/35 mm. The *picrate* was obtained as yellow plates, m.p. 88-89° (recrystallized from aqueous ethanol). [Found: C, 48.87; H, 6.13; N, 14.81; O, 30.3. $C_{15}H_{22}N_4O_7$ requires C, 48.64; H, 5.99; N, 15.13; O, 30.24%.]

1-Methyl-2-phenyl-3-iso-propylazetidine (90t)

The reduction of *trans*-1-methyl-4-phenyl-*iso*-propyl-2-azetidinone (1.2 gm) with aluminium hydride gave trans-*1-methyl-2-phenyl-3-iso-propylazetidine* (0.8 gm, 73%) as a colourless liquid, b.p. 68-70°/0.4-0.5 mm. The *picrate* was obtained as yellow needles, m.p. 125.5-127° (recrystallized from ethanol). [Found: C, 54.68; H, 5.38; N, 13.55; O, 26.4. $C_{19}H_{22}N_4O_7$ requires C, 54.54; H, 5.30; N, 13.39; O, 26.77%.]

1,2,2,3,3-Pentamethylazetidine (91)

The reduction of 1,3,3,4,4-pentamethyl-2-azetidinone (1.5 gm) with aluminium hydride gave *1,2,2,3,3-pentamethylazetidine* (0.65 gm 50%) as a colourless liquid, b.p. 120°. The *picrate* was obtained as a yellow crystalline solid, m.p. 207-209° (recrystallized from ethanol). [Found: C, 46.60; H, 5.44; N, 15.69. $C_{14}H_{20}N_4O_7$ requires C, 47.19; H, 5.66; N, 15.72%.]

(4) A solution containing sodium borohydride (0.12 gm) in tetrahydrofuran (7 mls) was treated portionwise with aluminium chloride (0.13 gm) under nitrogen at 0°. After stirring for 20 minutes compound

(46) (150 mg) in tetrahydrofuran was added. The suspension was stirred at less than 10° for 45 minutes, wet ether (2 mls) and 10% sodium hydroxide solution (3 mls) was added dropwise. After stirring for 15 minutes the organic layer was separated, dried and the solvent removed. The n.m.r. spectrum of the residue showed it to be a mixture of the amino-alcohol (94) and the azetidine (61) in the ratio of 2:1.

A similar reduction of compound (46) using LAH (0.12 gm) and aluminium chloride (0.13 gm) instead of sodium borohydride and aluminium chloride gave exclusively the azetidine (61).

5. Some Attempted Syntheses of Azetidines

(1) LAH Reduction of 2-Azetidinones to γ-Aminoalcohols

General procedure for LAH reductions.[15]

The 2-azetidinone (10 mmoles), dissolved in absolute tetrahydrofuran, was added dropwise to a stirred solution of LAH (8 mmoles) in tetrahydrofuran. The solution was refluxed for 45 minutes, cooled and 25% sodium hydroxide solution (30 ml) added. After stirring for 30 minutes the suspension was filtered through a sintered glass funnel (celite) and the organic layer separated from the filtrate. The aqueous layer was extracted with ether and the combined organic layers dried (magnesium sulphate). The organic solvent was removed under reduced pressure and the residue recrystallised from a suitable solvent (usually ethanol).

3-Anilino-3-phenyl-1-propanol (97), m.p. 88-90° (lit.[42,15] m.p. 87-88°, 89-90°), was prepared from 1,4-diphenyl-2-azetidinone in 80% yield.

3-Anilino-2,2-dimethyl-3-phenyl-1-propanol (94), m.p. 103-105° (lit.[15] m.p. 105-105.5°), was prepared from 3,3-dimethyl-1,4-diphenyl-2-azetidinone in 90% yield.

3-Methylamino-2,3-diphenyl-1-propanol

The reduction of *trans*-1-methyl-3,4-diphenyl-2-azetidinone gave *3-methylamino-2,3-diphenyl-1-propanol* (65%) as colourless needles, m.p. 90-90.5° (recrystallised from hexane). [Found: C, 79.08; H, 7.84; N, 5.51. $C_{16}H_{19}NO$ requires C, 79.63; H, 7.94; N, 5.80%.]

All 2-azetidinones which were reduced with diborane or aluminium hydride [Sections 4.(2) and 4.(3)] were also reduced with LAH to the corresponding γ-aminoalcohol. The latter compounds were characterised by only their i.r. and n.m.r. spectra and therefore will not be discussed here.

(2) Attempts to Prepare and to Cyclize γ-Haloamines to Azetidines

(a) *3-Anilino-2,2-dimethyl-3-phenyl-1-propanol hydrobromide*, m.p. 194-197° (recrystallized from absolute ethanol), was obtained as a white crystalline solid by bubbling dry hydrogen bromide into an ethereal solution of compound (94). The hydrobromide precipitated quantitatively.

The above hydrobromide salt (8.4 gm, 0.025 mole) was heated with a solution of hydrogen bromide (8.1 gm, 0.10 mole) in glacial acetic acid (80 mls) at 160° under nitrogen for 10 hours (compare[8]) and then left at room temperature for 10 hours. [After about 10 minutes at 160° the solution became dark blue. If the reaction mixture was worked up just before this time only the hydrobromide could be isolated.] The acetic acid was removed under reduced pressure to give a dark-blue oil. Normal purification techniques (boiling with charcoal in ethanol, distillation and chromatography) failed to give any pure compound.

The blue oil from above (4.0 gm) was dissolved in water (4 mls) and a solution of 50% potassium hydroxide added (4 mls) (compare[8]). The mixture was heated on a water-bath for 2 hours and then steam-distilled. The distillate was extracted with ether, the ether solution dried and then the ether removed. Distillation of the residue gave a small amount (0.2 gm) of a colourless liquid. Subsequent comparison with an authentic sample of 3,3-dimethyl-1,2-diphenylazetidine, an expected product, showed that there was no azetidine.

3-Anilino-2,2-dimethyl-3-phenyl-1-propanol hydrobromide (100 mg) was heated with an excess of hydrobromic acid (48% in water) for periods up to 3 hours. [After 5 minutes the solution became pink.] The water was removed under reduced pressure to give a green-blue oil. Again normal purification techniques failed to give any pure compounds while base treatment (potassium hydroxide) failed to yield any 3,3-dimethyl-1,2-diphenylazetidine.

Treatment of 3-anilino-2,2-dimethyl-3-phenyl-1-propanol with phosphorus tribromide according to the method of Black[77] also gave a similar green-blue oil.

3-Anilino-2,2-dimethyl-3-phenyl-1-propanol was treated with excess thionyl chloride, the red solution left at room temperature for 12 hours and then the thionyl chloride removed under reduced pressure. The residue was treated with a sodium bicarbonate solution and extracted with ether. The ether solution was dried and the ether removed to give a red oil which on distillation yielded a colourless liquid, the structure of which is not known.

(b) 3-Anilino-3-phenyl-1-propanol (1.1 gm, 0.005 mole) was heated with 48% aqueous hydrobromic acid (15 mls) in a sealed tube at 170° for 10 hours and then the water removed to give crude *3-anilino-3-phenyl-1-propylbromide hydrobromide* (1.5 gm, 83%), m.p. >230°, as a light yellow solid. The latter compound (1.5 gm) was mixed with a 25% solution of potassium hydroxide (50 mls) without purification and left at room temperature for 10 hours. The mixture was steam distilled, the distillate saturated with solid potassium hydroxide pellets and extracted with ether. The solution was dried over potassium hydroxide pellets and the ether removed. The residue was fractionated under reduced pressure. *1,2-Diphenylazetidine* (80 mg, 10%) was obtained as a yellow liquid, b.p. 140-142°/1 mm. The compound was identified by the usual physical techniques (i.r., n.m.r., MS) and later by comparison with an authentic sample.

(3) Attempts to Prepare Tosylates and to Cyclise them to Azetidines

(a) A solution of 3-anilino-2,2-dimethyl-3-phenyl-1-propanol (2.6 gm, 0.01 mole) in dry pyridine (15 mls) was cooled in an ice-salt bath and *p*-toluenesulphonyl chloride (1.6 gm, 0.01 mole) was added in portions (compare[8]), keeping the temperature below 5°. The solution was stirred at room temperature for 14 hours, filtered and the filtrate poured on to a mixture of ice and water (100 mls). After standing for several hours -

(i) a portion of the separated oil was removed and washed with light petroleum to give a grey solid. Recrystallisation from ethanol gave 3-anilino-2,2-dimethyl-3-phenyl-1-propanol (1.2 gm).

(ii) the remainder of the aqueous solution and oil was extracted with chloroform, the chloroform solution washed with water and dried (magnesium sulphate). Removal of the chloroform gave a green semi-solid, m.p. 80-95°. The material showed two spots at Rf = 0.47 and Rf = 0.60 (50% ether in hexane). Recrystallisation of this semi-solid from ethanol gave 3-anilino-2,2-dimethyl-3-phenyl-1-propanol (1.2 gm) (Rf = 0.47). The compound at Rf = 0.60 may be the mono- or ditosylate but the yield was very small (less than 0.2 gm). Similar attempts to prepare the tosylate under a number of different conditions were equally unsuccessful.

(b) 3,3-Dimethyl-1,4-diphenyl-2-azetidinone (1.0 gm) in tetrahydrofuran was added dropwise to LAH (0.12 gm) in tetrahydrofuran (10 mls) with stirring. The mixture was refluxed for 45 minutes,

cooled in ice and *p*-toluenesulphonylchloride (0.7 gm) in tetrahydrofuran added dropwise over a period of 15 minutes. The mixture was stirred at room temperature for 30 minutes and then refluxed for 13 hours. After cooling, 5% sodium hydroxide solution (20 mls) was added and the solution stirred for 15 minutes. The mixture was filtered through a sintered glass funnel (celite), the organic layer separated and the aqueous phase extracted with toluene. The combined organic layers were dried (magnesium sulphate) and the solvent removed. T.l.c. and v.p.c. of the distilled residue showed it to be a mixture of the amino-alcohol (94) (>98%) and the azetidine (61)(<2%).

(c) 3-Anilino-2,2-dimethyl-3-phenyl-1-propanol (2.6 gm, 0.01 mole) was dissolved in dry ether (30 mls) and added with stirring to a suspension of sodium hydride (0.3 gm) in ether under nitrogen (compare[78]). The mixture was refluxed for 18 hours, cooled to -20° and a solution of *p*-toluenesulphonylchloride (1.6 gm, 0.01 mole) in ether (35 mls) was added dropwise to the suspension. After the addition, the reaction mixture was stirred for 30 minutes at -20° and then 4 hours at 0°. The suspension was filtered and the ether removed from the filtrate to give 2.5 gm of a yellow oil, which was shown to be a mixture of 2 compounds by t.l.c. A portion of this oil (600 mg) was dissolved in acetone and chromatographed under nitrogen on a preparative t.l.c. plate to give 560 mg of starting material and 40 mg of *3,3-dimethyl-1,2-diphenylazetidine*.

(4) The Reduction of 2-Azetidinethiones

1,4-Diphenyl-2-azetidinethione (101), m.p. 118-120° (lit.[81,82] m.p. 121-122°, 121-122.5°) was prepared from 1,4-diphenyl-2-azetidinone in 60% yield.

1,4-Diphenyl-2-azetidinethione was reduced with Raney nickel under a variety of conditions of which the following is typical. 1,4-Diphenyl-2-azetidinethione (3.0 gm) was refluxed with Raney nickel (18.0 gm) in absolute ethanol (300 mls) for 35 minutes, and the solution then filtered while hot. The Raney nickel was washed thoroughly with ethanol. The ethanol was removed under reduced pressure from the combined ethanol solutions to give a light yellow oil. V.p.c. analysis showed 5 separate peaks and these fractions were collected by preparative v.p.c. The nature of these fractions, none of which was the expected 1,2-diphenylazetidine, is discussed in Section 4.(2) of Chapter 1.

1,4-Diphenyl-2-azetidinethione (2.0 gm) in absolute ethanol (80 mls) was mixed with aluminium amalgam (1.3 gm) and water (1.4 mls) slowly added to the reaction mixture with shaking. The reduction was completed by heating on a water-bath at 60-70° for 3 hours (compare[83]). The solution was made strongly alkaline with sodium hydroxide solution and steam-distilled. The distillate was made strongly alkaline with a few pellets of sodium hydroxide and extracted with ether. The ether solution was dried (magnesium sulphate) and then the ether removed. Analysis of the residue showed it to be very similar to that obtained when compound (101) was reduced with Raney nickel (see above).

(5) Photochemical Approaches to Azetidines

The photochemical reactors employed for reactions not done in the sun were of the water-cooled Pyrex type.[297] Irradiations were carried out with Philips HP 125-W high-pressure mercury-quartz lamps or with Hanovia type low-pressure mercury lamps.

(a) Irradiation of Schiff's bases with an olefin

In a typical experiment, benzal-aniline (3.6 gm, 0.02 mole) and 2-methyl-2-butene (1.4 gm, 0.02 mole) were irradiated with a high pressure mercury lamp in dry benzene (200 mls, 0.1M solution of each reactant) for 7 days. Aliquots, which were examined by i.r. and n.m.r. spectroscopy at regular intervals, showed that no reaction had taken place.

Similar experiments were carried out in benzene, toluene or ether for periods of up to 10 days using reactant concentrations in the range 0.005 to 1.0 M but no reaction was observed. The solutions were irradiated using high and low pressure mercury lamps and were also irradiated in the sun. Triphenylene was used as a photosensitizer in several experiments without success.

The irradiation of diphenylketimine and 2-methyl-2-butene under a similar range of experimental conditions as those used above also failed to yield any observable products.

(b) Irradiation of *N*,*N*-diethylphenacylamine

A solution of *N*,*N*-diethylphenacylamine (5.0 gm) in dry benzene (100 mls) was irradiated with a high-pressure mercury lamp until i.r.

and n.m.r. spectra of aliquots showed that *N*,*N*-diethylphenacylamine had completely reacted (135 hours). The benzene was removed under reduced pressure and the residue chromatographed on Spence alumina to give, as the only observable products, a brown oil (1.5 gm, 85%), which was shown to be a polymer of *N*-ethylacetaldimine, and acetophenone (2.6 gm, 85%).

6. Miscellaneous Reactions

(1) *1-t-Butyl-3-azetidinol* (137) and *1-iso-propyl-3-azetidinol* (138) were prepared by the method of Gaertner.[16,17]

(2) *2,2,4-Trimethylazetidine* was prepared by the method of Kohn.[9] However, it was not possible to obtain it in sufficient purity for n.m.r. study. 2,2,4-Trimethylazetidine was converted to *1-benzyl-2,2,4-trimethylazetidine* (139) with benzyl chloride by a method previously described[60] and obtained as a light yellow liquid, b.p. 80-90°/25 mm. This compound was also contaminated by at least two similar boiling compounds.

REFERENCES

REFERENCES

1. H. Freundlich and H. Kroepelin, *Z.Physik.Chem.*, *122*, 39 (1926).
2. L. Ruzicka, *Helv.Chim.Acta*, *9*, 230 (1926).
3. S. Gabriel and J. Weiner, *Ber.*, *21*, 2669 (1888).
4. A. Ladenburg and J. Sieber, *ibid.*, *23*, 2727 (1890).
5. W. Marckwald and A.F. van Droste-Huelshoff, *ibid.*, *31*, 3261 (1898).
6. C.C. Howard and W. Marckwald, *ibid.*, *32*, 2031 (1899).
7. F.C. Schaefer, *J.Am.Chem.Soc.*, *77*, 5928 (1955).
8. C. Mannich and G. Baumgarten, *Ber.*, *70*, 210 (1937).
9. M. Kohn, *Ann.*, *351*, 134 (1906).
10. M. Kohn, *Monatsh.Chem.*, *28*, 430 (1907).
11. M. Kohn and J. Giaconi, *ibid.*, *28*, 461 (1907).
12. M. Kohn and O. Morgenstern, *ibid.*, *28*, 479 (1907).
13. C.A. Grob, *Experientia*, *13*, 126 (1957).
    C.A. Grob, "Kekulé Symposium of Theoretical Organic Chemistry", Butterworths Scientific Publications, London, 1959, pp. 114-127.
14. (a) E.L. Eliel, "Stereochemistry of Carbon Compounds", McGraw-Hill Book Co., Inc., New York, 1962, p. 149.
    (b) D.Y. Curtin, Stereochemical Control of Organic Reactions, *Record Chem.Progress*, *15*, 111 (1954).
15. W.R. Vaughan, R.S. Klonowski, R.S. McElhinney and B.B. Millward, *J.Org.Chem.*, *26*, 138 (1961).
16. V.R. Gaertner, *Tetrahedron Letters*, 4691 (1966).
17. V.R. Gaertner, *J.Org.Chem.*, *32*, 2972 (1967).

18. S.S. Chatterjee and D.J. Triggle, *Chem.Commun.*, 93 (1968).

19. B.J. Gaj and D.R. Moore, *Tetrahedron Letters*, 2155 (1967).

20. D.H. Wadsworth, *J.Org.Chem.*, *32*, 1184 (1967).

21. R.M. Rodebaugh and N.H. Cromwell, *J.Heterocyclic Chem.*, *5*, 309 (1968).

22. N.H. Cromwell and E. Doomes, *Tetrahedron Letters*, 4037 (1966).

23. J.-L. Imbach, E. Doomes, R.P. Rebman and N.H. Cromwell, *J.Org.Chem.*, *32*, 78 (1967).

24. N.J. Leonard and D.A. Durand, *ibid.*, *33*, 1322 (1968).

25. R.C. Elderfield and H.A. Hageman, *ibid.*, *14*, 605 (1949).

26. V.P. Wystrach, D.W. Kaiser and F.C. Schaefer, *J.Am.Chem.Soc.*, *77*, 5915 (1955).

27. (a) A.G. Anderson Jr. and M.T. Wills, *J.Org.Chem.*, *33*, 2123 (1968).
(b) A.G. Anderson Jr. and M.T. Wills, *ibid.*, 536 (1968).

28. W.A. Reeves and J.D. Guthrie, *J.Am.Chem.Soc.*, *75*, 4101 (1953).

29. J.A. Moore in "Heterocyclic Compounds with Three- and Four-Membered Rings", A. Weissberger, Ed., Interscience Publishers, New York, 1964, p.897.

30. A.B. Burg and C.D. Good, *J.Inorg.Nuclear Chem.*, *2*, 237 (1956).

31. R.S. Klonowski, Ph.D. Thesis, University of Michigan, 1959.

32. G.D. Jones, *J.Org.Chem.*, *9*, 484 (1944).

33. E.J. Moriconi and J.F. Kelly, *Tetrahedron Letters*, 1435 (1968).

34. L.W. Deady, R.D. Topsom, R.E.J. Hutchinson, J. Vaughan and G.J. Wright, *ibid.*, 1773 (1968).

35. J.A. Moore and R.W. Medeiros, *J.Am.Chem.Soc.*, *81*, 6026 (1959).

36. F.J. Marascia, J.A. Moore, R.W. Medeiros and E. Wyss, *ibid.*, *84*, 3022 (1962).

37. C. Sandris and G. Ourisson, *Bull.Soc.Chim.France*, 345 (1958).

38. L. Fowden, *Biochem.J.*, *64*, 323 (1956).

39. T. Chen, T. Sanjiki, H. Kato and M. Ohta, *Bull.Chem.Soc.Jap.*, *40*, 2398 (1967).

40. T. Chen, T. Sanjiki, H. Kato and M. Ohta, *ibid.*, *40*, 2401 (1967).

41. T. Chen, H. Kato and M. Ohta, *ibid.*, *41*, 712 (1968).

42. M.E. Speeter and W.H. Maroney, *J.Am.Chem.Soc.*, *76*, 5810 (1954).

43. F.F. Blicke and W.A. Gould, *J.Org.Chem.*, *23*, 1102 (1958).

44. E. Testa, L. Fontanella and G.F. Cristiani, *Ann.*, *626*, 114 (1959).

45. Ref. 29, p. 918.

46. K.D. Barrow, Ph.D. Thesis, University of Adelaide, 1966.

47. H. Gilman and M. Speeter, *J.Am.Chem.Soc.*, *65*, 2255 (1943).

48. H.B. Kagan, J.-J. Basselier and J.-L. Luche, *Tetrahedron Letters*, 941 (1964).

49. E. Testa, A. Bonati, G. Pagani and E. Gatti, *Ann.*, *647*, 92 (1961).

50. E. Testa, L. Fontanella, G.F. Cristiani and F. Fava, *ibid.*, *614*, 158 (1958).

51. R. Graf, *ibid.*, *661*, 111 (1963); *Organic Synthesis*, *46*, 51 (1966).

52. R. Graf, *Angew.Chem.Intern.Ed.Engl.*, *7*, 172 (1968).

53. E.J. Moriconi and P.H. Mazzocchi, *J.Org.Chem.*, *31*, 1372 (1966).

54. G. Pifferi, P. Consonni, G. Pelizza and E. Testa, *J.Heterocyclic Chem.*, *4*, 619 (1967).

55. M.S. Newman, *J.Am.Chem.Soc.*, *72*, 4783 (1950).

56. M.S. Newman in "Steric Effects in Organic Chemistry", M.S. Newman, Ed., John Wiley and Sons, Inc., New York, 1956, p. 206.

57. H.C. Brown and P. Heim, *J.Am.Chem.Soc.*, *86*, 3566 (1964).

58. G. Zweifel and H.C. Brown in "Organic Reactions", A.C. Cope, Ed., John Wiley and Sons, Inc., New York, 1963, Vol. 13, p.1.

59. G.F. Freeguard and L.H. Long, *Chem.Ind.*(London), 471 (1965).

60. E. Testa, L. Fontanella and V. Aresi, *Ann.*, *656*, 114 (1962).

61. N.G. Gaylord, "Reduction with Complex Metal Hydrides", Interscience, New York, 1956, Ch. 10.

62. Ref. 29, p. 947.

63. E. Breuer, *Tetrahedron Letters*, 1849 (1967).

64. G.F. Lanthier and W.A.G. Graham, *Chem.Commun.*, 715 (1968).

65. H.C. Brown, "Hydroboration", Benjamin, New York, 1962.

66. H.C. Brown and N.M. Yoon, *J.Am.Chem.Soc.*, *88*, 1464 (1966).

67. R.G. Pearson, *ibid.*, *85*, 3533 (1963); *J.Chem.Education*, *45*, 581 (1968).

68. R.G. Pearson and J. Songstad, *J.Am.Chem.Soc.*, *89*, 1827 (1967).

69. W.S. Trahanovsky and M.P. Doyle, *Chem.Commun.*, 1021 (1967).

70. M.F. Hawthorne, *J.Am.Chem.Soc.*, *80*, 4291 (1958).

71. J.A. Pople and A.A. Bothner-By, *J.Chem.Phys.*, *42*, 1339 (1965).

72. A.E. Finholt, A.C. Bond and H.I. Schlesinger, *J.Am.Chem.Soc.*, *69*, 1199 (1947).

73. E. Wiberg, H. Graf, M. Schmidt and R. Uson, *Z.Naturforsch.*, *7B*, 578 (1952).

74. J.A. Barltrop and H.A.J. Carless, *Tetrahedron Letters*, 3901 (1968).

75. N.M. Yoon and H.C. Brown, *J.Am.Chem.Soc.*, *90*, 2927 (1968).

76. D.J. Cram, "Fundamentals of Carbanion Chemistry", Academic Press Inc., New York, N.Y., 1965, pp. 80-83, 113.

77. D.K. Black, S.R. Landor, A.N. Patel and P.F. Whiter, *Tetrahedron Letters*, 483 (1963).

78. J.K. Kochi and G.S. Hammond, *J.Am.Chem.Soc.*, *75*, 3443 (1953). c.f. D. Wege, Ph.D. Thesis, University of Adelaide, 1965, pp. 95 and 96.

79. R.N. Hurd and G. De La Mater, *Chem.Rev.*, *61*, 45 (1961).

80. H. Hauptmann and W.F. Walter, *ibid.*, *62*, 347 (1962).

81. A. Spasov, B. Panaiotova and E. Golovinskii, *Dokl.Akad.Nauk SSSR*, *158*(2), 429 (1964) through *Chem.Abstracts*, *61*, 11949h (1964).

82. Ref. 46, p. 230.

83. K. Kindler and W. Dehn, *Ber.*, *54*, 1080 (1921).

84. R.N. Warrener and J.B. Bremner, *Rev.Pure and Appl.Chem.*, *16*, 117 (1966).

85. G.S. Hammond and N.J. Turro, *Science*, *142*, 1541 (1963).

86. G. Büchi, C.G. Inman and E.S. Lipinsky, *J.Am.Chem.Soc.*, *76*, 4327 (1954).

87. R. Srinivasan, *ibid.*, *82*, 775 (1960).

88. G.O. Schenck, W. Hartmann and R. Steinmetz, *Ber.*, *96*, 498 (1963).

89. D. Gagnaire and E. Payo-Subiza, *Bull.Soc.Chim.France*, 2623 (1963).

90. D.R. Arnold, R.L. Hinman and A.H. Glick, *Tetrahedron Letters*, 1425 (1964).

91. H. Gotthardt, R. Steinmetz and G.S. Hammond, *J.Org.Chem.*, *33*, 2774 (1968).

92. N.C. Yang, *Pure and Appl.Chem.*, *9*, 591 (1964).

93. J. Saltiel, R.M. Coates and W.G. Dauben, *J.Am.Chem.Soc.*, *88*, 2745 (1966).

94. S. Searles and R.A. Clasen, *Tetrahedron Letters*, 1627 (1965).

95. J.S. Shannon, H. Silberman and S. Sternhell, *ibid.*, 659 (1964).

96. P.J. Collin, H. Silberman, S. Sternhell and G. Sugowdz, *ibid.*, 2063 (1965).

97. M.P. Cava and R.H. Schlessinger, *ibid.*, 2109 (1964).

98. G.M. Badger, C.P. Joshua and G.E. Lewis, *ibid.*, 3711 (1964).

99. R.O. Kan and R.L. Furey, *J.Am.Chem.Soc.*, *90*, 1666 (1968).

100. W.G. Herkstroeter, A.A. Lamola and G.S. Hammond, *ibid.*, *86*, 4537 (1964).

101. G.S. Hammond, N.J. Turro and R.S.H. Liu, *J.Org.Chem.*, *28*, 3297 (1968).

102. R.A. Clasen, *Dissertation Abstracts*, *27*(B), 1411 (1967).

103. N.C. Yang, A. Morduchowitz and D.H. Yang, *J.Am.Chem.Soc.*, *85*, 1017 (1963).

104. I. Orban, K. Schaffner and O. Jeger, *ibid.*, *85*, 3033 (1963).

105. P. Yates and A.G. Szabo, *Tetrahedron Letters*, 485 (1965).

106. R.A. Clasen and S. Searles Jr., *Chem.Commun.*, 289 (1966).

107. E.M. Burgess and L. McCullagh, *J.Am.Chem.Soc.*, *88*, 1580 (1966).

108. (a) G. Ege and E. Beisiegel, *Angew.Chem.Intern.Ed.Engl.*, *7*, 303 (1968).

(b) G. Ege, *ibid.*, *4*, 699 (1965).

109. E.S. Albone, *J.Am.Chem.Soc.*, *90*, 4663 (1968).

110. E.M. Burgess and G. Milne, *Tetrahedron Letters*, 93 (1966).

111. (a) L.M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", Pergamon Press, London, 1959.

(b) J.A. Pople, W.G. Schneider and H.J. Bernstein, "High-resolution Nuclear Magnetic Resonance", McGraw-Hill Book Co., Inc., New York, 1959.

(c) N.S. Bhacca and D.H. Williams, "Applications of N.M.R. Spectroscopy in Organic Chemistry", Holden-Day, Inc., San Francisco, 1964.

(d) J.W. Emsley, J. Feeney and L.H. Sutcliffe, "High-Resolution Nuclear Magnetic Resonance Spectroscopy", Pergamon Press, New York, 1965, Vols. I and II.

(e) J.S. Waugh (Ed.), "Advances in Magnetic Resonance", Academic Press, London, 1965, Vol. I.

(f) J.D. Roberts, "Nuclear Magnetic Resonance. Applications to Problems in Organic Chemistry", McGraw-Hill Book Co., Inc., New York, 1959.

(g) J.D. Roberts, "An Introduction to the Analysis of Spin-Spin Splitting in High-Resolution Nuclear Magnetic Resonance Spectra", W.A. Benjamin, Inc., New York, 1962.

112. S. Sternhell, *Rev.Pure Appl.Chem.*, *14*, 15 (1964).

113. J.E. Anderson, *Quart.Rev.*, *19*, 426 (1965).

114. J.E. Wertz, *Chem.Rev.*, *55*, 829 (1955).

115. S. Browstein, *ibid.*, *59*, 463 (1959).

116. P.L. Corio, *ibid.*, *60*, 363 (1960).

117. J.D. Baldeschwieler and E.W. Randall, *ibid.*, *63*, 81 (1963).

118. Ref. 111 (d), p. 10.

119. Ref. 111 (d), p. 59.

120. Ref. 111 (d), p. 130.

121. H.M. McConnell, *J.Chem.Phys.*, *27*, 226 (1957).

122. C.E. Johnson and F.A. Bovey, *ibid.*, *29*, 1012 (1958).

123. A.A. Bothner-By and J.A. Pople, *Ann.Rev. of Phys.Chem*, *16*, 43 (1965).

124. A.T. Blomquist and C.G. Bottomley, *Ann.*, *653*, 67 (1962).

125. J.L. Luche, H.B. Kagan, R. Parthasarathy, G. Tsoucaris, C. de Rango and C. Zelwer, *Tetrahedron*, *24*, 1275 (1968).

126. M. Karplus, *J.Am.Chem.Soc.*, *85*, 2870 (1963).

127. H.S. Gutowsky, M. Karplus and D.M. Grant, *J.Chem.Phys.*, *31*, 1278 (1959).

128. A.A. Bothner-By and [illegible].C. Naar-Colin, *J.Am.Chem.Soc.*, *83*, 231 (1961).

129. K.L. Williamson, *ibid.*, *85*, 516 (1963).

130. P. Laszlo and P. von R. Schleyer, *ibid.*, *85*, 2709 (1963).

131. H. Booth, *Tetrahedron Letters*, 411 (1965).

132. C.N. Banwell and N. Sheppard, *Disc.Faraday Soc.*, *34*, 115 (1962).

133. R.J. Abraham and W.A. Thomas, *Chem.Commun.*, 431 (1965).

134. A.D. Cohen and T. Schaefer, *Mol.Phys.*, *10*, 209 (1966).

135. Ref. 111 (c), p. 54 .

136. N. Jonathan, S. Gordon and B.P. Dailey, *J.Chem.Phys.*, *36*, 2443 (1962).

137. Ref. 111 (a), pp. 115-119.

138. M. Barfield and D.M. Grant, *J.Am.Chem.Soc.*, *85*, 1899 (1963).

139. M. Barfield and D.M. Grant, in Ref. 111 (e), p. 149.

140. D.M. Graham and C.E. Holloway, *Can.J.Chem.*, *41*, 2114 (1963).

141. B.L. Shapiro, R.M. Kopchik and S.J. Ebersole, *J.Chem.Phys.*, *39*, 3154 (1963).

142. H.J. Bernstein and N. Sheppard, *ibid.*, *37*, 3012 (1962).

143. R.T. Hobgood, G.S. Reddy and J.H. Goldstein, *J.Phys.Chem.*, *67*, 110 (1963).

144. M. Barfield and D.M. Grant, *J.Am.Chem.Soc.*, *83*, 4726 (1961).

145. M. Barfield and D.M. Grant, *J.Chem.Phys.*, *36*, 2054 (1962).

146. R.A. Hoffman and S. Gronowitz, *Arkiv.Kemi.*, *16*, 471 (1961).

147. H.M. McConnell, *J.Mol.Spectroscopy*, *1*, 11 (1957).

148. J.V. Acrivos, *Mol.Phys.*, *5*, 1 (1962).

149. A.D. McLachlan, *ibid.*, *1*, 233 (1958).

150. M. Karplus, *J.Chem.Phys.*, *33*, 1842 (1960).

151. M.J.S. Dewar and R.C. Fahey, *J.Am.Chem.Soc.*, *85*, 2704 (1963).

152. E.I. Snyder and B. Franzus, *ibid.*, *86*, 1166 (1964).

153. P. Laszlo and P. von R. Schleyer, *ibid.*, *86*, 1171 (1964).

154. F.S. Mortimer, *J.Mol.Spectroscopy*, *3*, 528 (1959).

155. M. Barfield, *J.Chem.Phys.*, *41*, 3825 (1964).

156. M. Karplus and D.H. Anderson, *ibid.*, *30*, 6 (1959).

157. J. Meinwald and A. Lewis, *J.Am.Chem.Soc.*, *83*, 2769 (1961).

158. A. Rassat, C.W. Jefford, J.M. Lehn and B. Waegell, *Tetrahedron Letters*, 233 (1964).

159. H. Wehrli, M.S. Heller, K. Schaffner and O. Jeger, *Helv.Chim. Acta.*, *44*, 2162 (1961).

160. Ref. 111 (d), p. 481.

161. Ref. 111 (b), p. 365.

162. L.W. Reeves in "Advances in Physical Organic Chemistry", V. Gold, Ed., Academic Press, London, 1965, Vol. 3, p. 187.

163. C.S. Johnson Jr., in Ref. 111 (e), p. 33.

164. A. Allerhand, H.S. Gutowsky, J. Jonas and R.A. Meinzer, *J.Am.Chem.Soc.*, *88*, 3185 (1966).

165. H. Sachse, *Ber.*, *23*, 1368 (1890).

166. W. Hückel, *Ann.*, *441*, 42 (1925).

167. Ref. 14 (a), Chapter 8.

168. A. Wilson and D. Goldhamer, *J.Chem.Education*, *40*, 504 (1963).

169. A. Almenningen, D. Bastiansen and P.N. Skancke, *Acta Chem.Scand.*, *15*, 711 (1961).

170. J.D. Dunitz and V. Schomaker, *J.Chem.Phys.*, *20*, 1703 (1952).

171. G.W. Rathjens, N.K. Freeman, W.D. Gwinn and K.S. Pitzer, *J.Am.Chem.Soc.*, *75*, 5634 (1953).

172. R.C. Lord and I. Nakagawa, *J.Chem.Phys.*, *39*, 2951 (1963).

173. W.G. Rothschild and B.P. Dailey, *ibid.*, *36*, 2931 (1962).

174. L.C. Snyder and S. Meiboom, *Chem.Eng.News*, *44*, 51 (1966).

175. S. Meiboom and L.C. Snyder, *J.Am.Chem.Soc.*, *89*, 1038 (1967).

176. H.P. Lemaire, R.L. Livingston, *ibid.*, *74*, 5732 (1952).

177. T.B. Owen and J.L. Hoard, *Acta Cryst.*, *4*, 172 (1951).

178. E. Adman and T.N. Margulis, *Chem.Commun.*, 641 (1967).

179. T.N. Margulis, *Acta Cryst.*, *19*, 857 (1965).

180. I.L. Karle, J. Karle and K. Britts, *J.Am.Chem.Soc.*, *88*, 2918 (1966).

181. H. Kim and W.D. Gwinn, *J.Chem.Phys.*, *44*, 865 (1966).

182. T.N. Margulis and M.S. Fischer, *J.Am.Chem.Soc.*, *89*, 223 (1967).

183. E. Adman and T.N. Margulis, *ibid.*, *90*, 4517 (1968).

184. C.M. Bock, *ibid.*, *90*, 2748 (1968).

185. J.B. Lambert and J.D. Roberts, *ibid.*, *87*, 3884 (1965).

186. F. Lautenschlaeger and G.F. Wright, *Can.J.Chem.*, *41*, 863 (1963).

187. S.I. Chan, J. Zinn, J. Fernandez and W.D. Gwinn, *J.Chem.Phys.*, *33*, 1643 (1960).

188. S.I. Chan, J. Zinn, W.D. Gwinn, *ibid.*, *34*, 1319 (1961).

189. A. Bauder , F. Tank and Hs.H. Günthard, *Helv.Chim.Acta*, *46*, 1453 (1963).

190. J.-M. Conia and J. Gorē, *Tetrahedron Letters*, 1379 (1963).

191. J.-M. Conia and J. Goré, *Bull.Soc.Chim.France*, 1968 (1964).

192. T. Ueda, communication to Ref. 193.

193. J. Laane and R.C. Lord, *J.Chem.Phys.*, *48*, 1508 (1968).

194. J.R. Durig and R.C. Lord, *ibid.*, *45*, 61 (1966).

195. T.R. Borgers and H.L. Strauss, *ibid.*, *45*, 947 (1966).

196. S.I. Chan, T.R. Borgers, J.W. Russell, J.L. Strauss and W.D. Gwinn, *ibid.*, *44*, 1103 (1966).

197. A. Danti, W.J. Lafferty and R.C. Lord, *ibid.*, *33*, 294 (1960).

198. D.O. Harris, H.W. Harrington, A.C. Luntz and W.D. Gwinn, *ibid.*, *44*, 3467 (1966).

199. J.R. Durig and A.C. Morrissey, *ibid.*, *47*, 4455 (1967).

200. F.G. Riddell, *Quart.Rev.*, *21*, 364 (1967).

201. A. Vigevani and G.G. Gallo, *J.Heterocyclic Chem.*, *4*, 583 (1967).

202. M.S. Manhas, S. Jeng, and A.K. Bose, *Tetrahedron*, *24*, 1237 (1968).

203. K.D. Barrow and T.M. Spotswood, *Tetrahedron Letters*, 3325 (1965).

204. C.L. Moret and L.M. Trefonas, *J. Heterocyclic Chem*, *5*, 549 (1968).

205. R.L. Shriner, R. Adams and C.S. Marvel in "Organic Chemistry, An Advanced Treatise", H. Gilman, Ed., John Wiley and Sons, Inc., New York, 1943, Vol. I, pp. 402-413.

206. V. Prelog and P. Wieland, *Helv.Chim.Acta*, *27*, 1127 (1944).

207. Ref. 111 (b), p. 218.

208. A.T. Bottini and J.D. Roberts, *J.Am.Chem.Soc.*, *78*, 5126 (1956).

209. A.T. Bottini and J.D. Roberts, *ibid.*, *80*, 5203 (1958).

210. A. Loewenstein, J.F. Neumer and J.D. Roberts, *ibid.*, *82*, 3599 (1960).

211. A.L. Logothetis, *J.Org.Chem.*, *29*, 3049 (1964).

212. F.A.L. Anet and J.M. Osyany, *J.Am.Chem.Soc.*, *89*, 352 (1967).

213. F.A.L. Anet, R.D. Trepka and D.J. Cram, *ibid.*, *89*, 357 (1967).

214. T.J. Bardos, C. Szantay and C.K. Navada, *ibid.*, *87*, 5796 (1965).

215. R.G. Kostyanovsky, Z.E. Samojlova and I.I. Tchervin, *Tetrahedron Letters*, 3025 (1968).

216. S.J. Brois, *J.Am.Chem.Soc.*, *89*, 4242 (1967).

217. J.M. Lehn and J. Wagner, *Chem.Commun.*, 148 (1968).

218. S.J. Brois, *J.Am.Chem.Soc.*, *90*, 508 (1968).

219. D. Felix and A. Eschenmoser, *Angew.Chem.Intern.Ed.Engl.*, *7*, 224 (1968).

220. H.A. Bent, *Chem.Rev.*, *61*, 275 (1961).

221. V.F. Bystrov, R.G. Kostyanovskii, O.A. Panshin, A.U. Stepanyants and O.A. Iuzhakova, *Opt.Spectry.* (USSR), *19*, 122 (1965).

222. R.M. Stanley, D.W. Marquardt and R.C. Ferguson, "Analysis of N.M.R. Spectra", E.I. Du Pont De Nemours and Co., Inc., Programs 33 and 34, Quantum Chemistry Program Exchange, Indiana University, 1967.

223. A.A. Bothner-By and S. Castellano, "LAOCN 3", Program 111, Quantum Chemistry Program Exchange, Indiana University, 1968.

224. E.I. Snyder, *J.Am.Chem.Soc.*, *85*, 2624 (1963).

225. K. Deutsch and I. Deutsch, *Ann.Physik*, *16*, 30 (1965) and references therein.

226. R.K. Hill and T. Chan, *Tetrahedron*, *21*, 2015 (1965).

227. N.S. Bowman, D.E. Rice and B.R. Switzer, *J.Am.Chem.Soc.*, *87*, 4477 (1965).

228. J.A. Pople, *Mol.Phys.*, *1*, 3 (1958).

229. J.S. Waugh and F.A. Cotton, *J.Phys.Chem.*, *65*, 562 (1961).

230. A.H. Lewin, J. Lipowitz and T. Cohen, *Tetrahedron Letters*, 1241 (1965).

231. P.L. Southwick, J.A. Fitzgerald and G.E. Milliman, *ibid.*, 1247 (1965).

232. A.A. Bothner-By, C. Naar-Colin and H. Günther, *J.Am.Chem.Soc.*, *84*, 2748 (1962).

233. F.A. Bovey, F.P. Hood, III, E. Pier and H.E. Weaver, *ibid.*, *87*, 2060 (1965).

234. A.D. Buckingham, T. Schaefer and W.G. Schneider, *J.Chem.Phys.*, *32*, 1227 (1960).

235. T. Schaefer, W.F. Reynolds and T. Yonemoto, *Can.J.Chem.*, *41*, 2969 (1963).

236. V.M.S. Gil and W.A. Gibbons, *Mol.Phys.*, *8*, 199 (1964).

237. I. Fleming and D.H. Williams, *Tetrahedron*, *23*, 2747 (1967).

238. B. Braillon, J. Salaün, J. Gore and J.-M. Conia, *BullSoc. Chim.France*, 1981 (1964).

239. Ref. 46, p. 124.

240. Ref. 46, p. 138.

241. Ref. 46, p. 135.

242. H.S. Gutowsky and C.H. Holm, *J.Chem.Phys.*, *25*, 1228 (1956).

243. E. Grunwald, A. Loewenstein and S. Meiboom, *ibid.*, *27*, 630 (1957).

244. A. Loewenstein and S. Meiboom, *ibid.*, *27*, 1067 (1957).

245. M.T. Rogers and J.C. Woodbrey, *J.Phys.Chem.*, *66*, 540 (1962).

246. M. Takeda and E.O. Stejskal, *J.Am.Chem.Soc.*, *82*, 25 (1960).

247. R.J. Kurland, M.B. Rubin and W.B. Wise, *J.Chem.Phys.*, *40*, 2426 (1964); M. Oki, H. Iwamura and N. Hayakawa, *Bull.Chem.Soc. Jap.*, *37*, 1865 (1964).

248. J. McKenna, The Royal Institute of Chemistry, Lecture Series, 1966, No. 1, Conformational Analysis of Organic Compounds.

249. M. Saunders and F. Yamada, *J.Am.Chem.Soc.*, *85*, 1882 (1963).

250. J.J. Delpuech and M.N. Deschamps, *Chem.Commun.*, 1188 (1967).

251. J.J. Delpuech and Y. Martinet, *ibid.*, 478 (1968).

252. J.L. Sudmeier and G. Occupati, *J.Am.Chem.Soc.*, *90*, 154 (1968).

253. E. Grunwald, A. Loewenstein and S. Meiboom, *J.Chem.Phys.*, *27*, 641 (1957).

254. A.F. Graefe and R.E. Meyer, *J.Am.Chem.Soc.*, *80*, 3939 (1958).

255. K. Biemann, "Mass Spectrometry: Organic Chemical Applications", McGraw-Hill Book Co., Inc., New York, 1962.

256. J.H. Beynon, "Mass Spectrometry and Its Applications to Organic Chemistry", Elsevier Publishing Co., Amsterdam, 1960.

257. J.D. Waldron (Ed.), "Advances in Mass Spectrometry", Pergamon Press, London, 1959.

258. H. Budzikiewicz, C. Djerassi and D.H. Williams, "Interpretation of Mass Spectra of Organic Compounds", Holden-Day, Inc., San Francisco, 1964.

259. H. Budzikiewicz, C. Djerassi and D.H. Williams, "Structural Elucidation of Natural Products by Mass Spectrometry", Holden-Day, Inc., San Francisco, 1964, Vol. I and II.

260. F.W. McLafferty, "Mass Spectrometry of Organic Ions", Academic Press, New York, 1963.

261. F.W. McLafferty, "Interpretation of Mass Spectra", W.A. Benjamin, Inc., New York, 1966.

262. H.C. Hill, "Introduction to Mass Spectrometry", Heyden and Son , Ltd., London, 1966.

263. H. Budzikiewicz, C. Djerassi and D.H. Williams, "Mass Spectrometry of Organic Compounds", Holden-Day, Inc., San Francisco, 1967.

264. E.J. Gallegos and R.W. Kiser, *J.Phys.Chem.*, *66*, 136 (1962).

265. Ref. 257, p. 328.

266. D.A. Bak and K. Conrow, *J.Org.Chem.*, *31*, 3608 (1966).

267. H.J. Hofman, *Tetrahedron Letters*, 2329 (1964).

268. H. Audier, J.-M. Conia, M. Fétizon and J. Goré, *Bull.Soc. Chim.France*, 787 (1967).

269. N.J. Turro, D.C. Neckers, P.A. Leermakers, D. Seldner and P. D'Angelo, *J.Am.Chem.Soc.*, *87*, 4097 (1965).

270. P. Natalis, *Bull.Soc.Roy.Sci.Liege*, *31*, 790 (1962).

271. J.-L. Imbach, E. Doomes, N.H. Cromwell, H.E. Baumgarten and R.G. Parker, *J.Org.Chem.*, *32*, 3123 (1967).

272. H.E. Audier, M. Fétizon, H.B. Kagan and J.L. Luche, *Bull. Soc.Chim.France*, 2297 (1967).

273. O.L. Chapman and W.R. Adams, *J.Am.Chem.Soc.*, *90*, 2333 (1968).

274. L.A. Singer and G.A. Davis, *ibid.*, *89*, 941 (1967).

275. M.S. Manhas, B.N. Ghosh-Mazumdar and A.K. Bose, *Chem.Commun.*, 349 (1967).

276. M. Fischer, *Ber.*, *101*, 2669 (1968).

277. E.J. Moriconi, J.F. Kelly and R.A. Salomone, *J.Org.Chem.*, *33*, 3448 (1968).

278. T. Sheradsky, U. Reichman and M. Frankel, *ibid.*, *33*, 3619 (1968).

279. Ref. 255, p. 117.

280. J.A. Gilpin, *Anal.Chem.*, *31*, 935 (1959).

281. Z. Pelak, M.A. Kielczewski, J.M. Wilson, M. Ohashi, H. Budzikiewicz and C. Djerassi, *J.Am.Chem.Soc.*, *85*, 2470 (1963).

282. A.M. Duffield, H. Budzikiewicz and C. Djerassi, *J.Am.Chem.Soc.*, *86*, 5536 (1964); *87*, 2913 (1965).

283. A. Costopanagiotis and H. Budzikiewicz, *Monatsh.Chem.*, *96*, 1800 (1965).

284. J.S. Shannon, *Proc.Royal Australian Chem.Inst.*, *31*, 323 (1964).

285. H. Staudinger, H.W. Klever and P. Kober, *Ann.*, *374*, 1 (1910).

286. E. Testa, L. Fontanella and F. Fava, *Il.Farmaco Ed.sci.*, *13*, 152 (1968) through *Chem.Abstracts*, *53*, 324c (1959).

287. R.W. Holley and A.D. Holley, *J.Am.Chem.Soc.*, *71*, 2124 (1949).

288. E. Testa, F. Fava and L. Fontanella, *Ann.*, *614*, 167 (1958).

289. E. Testa and L. Fontanella, *ibid.*, *625*, 95 (1959).

290. B.J. Kurter, N.M. Mollov, M.J. Ljapova and A.S. Orahovats, *Monatsh.Chem.*, *94*, 904 (1963).

291. A.W. Weston and R.J. Michaels Jr., *J.Am.Chem.Soc.*, *73*, 1381 (1951).

292. L.I. Smith and H.H. Hoehn, *Organic Synthesis*, Coll.Vol. *3*, 356 (1955).

293. H. Staudenger and S. Jelagin, *Ber.*, *44*, 365 (1911).

294. G. Crank and F.W. Eastwood, *Australian J.Chem.*, *17*, 1392 (1964).

295. E. Testa, L. Fontanella, L. Mariani and G.F. Cristiani, *Ann.*, *639*, 157 (1961).

296. H.C. Brown and B.C. Subba Rao, *J.Am.Chem.Soc.*, *81*, 6428 (1959).

297. G.M. Badger, R.J. Drewer and G.E. Lewis, *Australian J.Chem.*, *16*, 1042 (1963).