THE SYNTHESIS AND STRUCTURE-ACTIVITY RELATIONS OF SOME BENZOMORPHAN ANALOGUES

BY

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SUMMARY

A brief review of the history of analgesics leading to the introduction of the 6,7-benzomorphans is presented.

In the hope of obtaining compounds of biological interest, some 6-cycloalkylamino derivatives of 3-methyl-3-azabicyclo[3.3.1] nonan-9-one have been synthesised and submitted for pharmacological testing. The route adopted consisted of the addition of acrolein to the various cycloalkylamino enamines of N-methyl-4-piperidone, to give in each case, a mixture of two stereoisomeric ketones. A successful separation of these pairs of ketones was not achieved. However, after reduction of each pair of ketones to the corresponding tertiary alcohols, a successful route has been established to the isolation of three of the four possible stereoisomeric alcohols. The stereochemistry of each of the amino-alcohols has been defined by a study of their chemical properties, pKa values, NMR, infrared, and mass spectra. Of special interest, is the discovery of a new band in the infrared spectra of certain amino-alcohol salts which confirms their stereochemistry. In addition, each series of alcohols contains at least one compound containing the piperidine ring in a boat form. Further proof of the boat form is at present being sought by X-ray analysis.

A further series of compounds have also been prepared by the reaction between cinnamaldehyde and the pyrrolidine enamine of

N-methyl-4-piperidone, to yield, 3-methyl-3-azabicyclo [3.3.1] nonan-9-one derivatives substituted at the 6- and 8- positions. In order to facilitate the interpretation of the NMR spectra of the 6- and 6,8-disubstituted compounds obtained, a number of model compounds of known stereochemistry were prepared. The reaction between the morpholine enamine of cyclohexanone and acrolein yielded 6-substituted bicyclo [3.3.1] nonanes, and the reaction with cinnamaldehyde yielded 6,8-disubstituted bicyclo [3.3.1] nonanes of known stereochemistry.

The infrared spectra of all, and the NMR spectra of a number of the new compounds have been recorded.

A brief consideration of the mass spectra of the 6-substituted and 6,8-disubstituted 3-methyl-3-azabicyclo [3.3.1] nonananes and bicyclo [3.3.1] nonanes has been recorded, and possible fragmentation pathways for these compounds have been suggested. A correlation between the stereochemistry of the amino-alcohols and their fragmentation pathways has been discovered.

Selected compounds were tested for pharmacological activity, but a variety of differing results have been obtained.

To Chris and Michael.

ACKNOWLEDGEMENTS

I wish to express my gratitude to Doctor A.Z. Britten for his help and encouragement throughout the course of this work.

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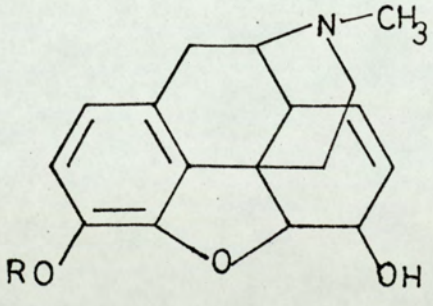
CONTENTS

INTRODUCTION

A. Analgesics

Much of medicine is concerned with the treatment of symptoms of injury and disease. Of these symptoms probably the most important is pain, a syndrome of unpleasant sensations experienced by nearly all mankind. Because of the constant need for the immediate relief of pain, the search for analgesics has been one of the great challenges for scientists in every generation. An analgesic is the term given to a compound that produces insensibility to, or a decreased awareness of pain without significantly impairing consciousness.

The use of preparations of the opium poppy in medicine for the relief of pain and distress dates from antiquity. In 1803 Sertuerner isolated the alkaloid morphine (1a, R = H) from opium.



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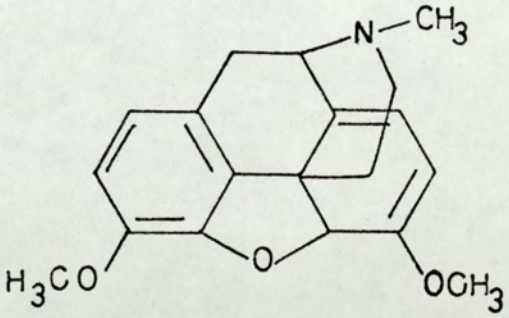


(2)

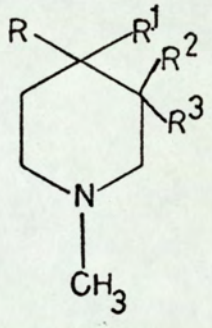
Morphine was subsequently shown to be the major analgesic ingredient, although opium contains some 25 alkaloids. Opposed to the valuable analgesic activities of morphine are several inherent

deficiencies that necessitate circumscribing its use in clinical practice. Chief among these are its addiction potential and respiratory-depressant action. Less serious but of importance are such effects as emetic action, circulatory depression and gastrointestinal disturbances.

Early attempts to abolish or significantly reduce the dependence potential and respiratory-depressant action while still retaining the morphine-like analgesic action consisted principally of modifications of morphine or codeine (1b, R = CH_3) or the toxic, medically useless thebaine (2). Thebaine occurs in opium along with morphine and codeine and is related chemically. Of the hundreds of congeners made, none has attained more than limited medical use, usually in restricted clinical situations. In addition, any change in analgesic potency has been paralleled in general, by changes in deleterious effects including those of dependence liability. Equally discouraging were efforts directed towards the total synthesis of structures simulating various portions of morphine. In these efforts, morphine was considered as a phenanthrene, a piperidine, a dibenzofuran, an isoquinoline, a benzodihydrofuran, a furan or other ring system. Phenanthrene was the most frequently used fundamental structure. During the course of these investigations, [1] several compounds were produced which showed enhanced analgesic activity but in general as

the analgesic activity increased, so did the side effects.

A breakthrough was made in 1939 by Eisleb and Schaumann [2] who prepared a number of piperidine derivatives as anti-spasmodic agents and discovered that several of these showed marked analgesic activity in addition to their atropine-like action. The most important of these is pethidine (3a) which has become widely used as a substitute for morphine for moderate to severe pain.

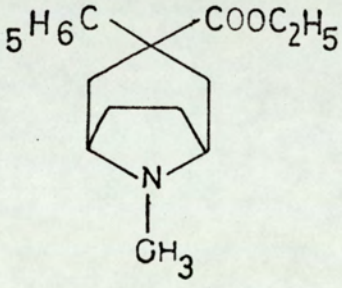


(3)

R	R_1	R_2	R_3	
C_6H_5	$COOC_2H_5$	H	H	3a
C_6H_5	$OCOC_2H_5$	H	H	3b
C_6H_5	$OCOC_2H_5$	CH_3	H	3c
C_6H_5	$OCOC_2H_5$	H	CH_3	3d

A large number of pethidine analogues have been prepared and in 1943 Jensen [3] discovered that the "reversed ester" of pethidine (3b) was significantly more active than pethidine. Introduction of a methyl group into the 3-position of the "reversed ester" of pethidine by Ziering and Lee [4] led to the introduction in 1947 of the alpha- and beta-prodines (3c) and (3d). Interesting tropane analogues of pethidine were prepared by Bell and Archer [5] which indicated the possibility of finding some analgesic compounds in this series. 3-Phenyl-3-ethoxycarbonyl-tropane hydrochloride (4)

showed twice the activity of pethidine hydrochloride in rats. Other structures related to tropanes which show analgesic activity are derivatives of 3,8-diazabicyclo[3.2.1] octane synthesised by Cignarella. [6] 3-Cinnamyl-8-propionyl-3,8-diazabicyclo[3.2.1] octane (5) was the most active compound in this series, with a potency ten times that of morphine.



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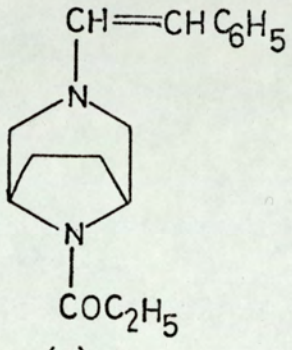
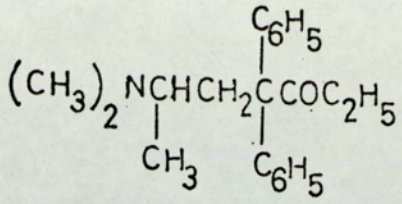


(5)

Over 4000 pethidine derivatives have been made and tested. Some of these, especially pethidine itself, are useful drugs, but none show the desired separation of strong analgesic activity from unwanted side effects. More importantly the advent of pethidine stimulated not only the synthesis of analogues, but more divergent structures such as methadone (6) which was developed during World War II by Bockmuhl and Erhart. [7] A report published after the war by Kleider [8] described the war-time research and the synthesis of methadone which has a potency five times that of pethidine.



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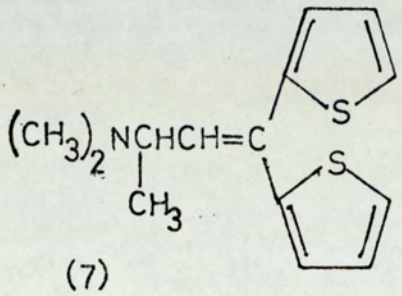

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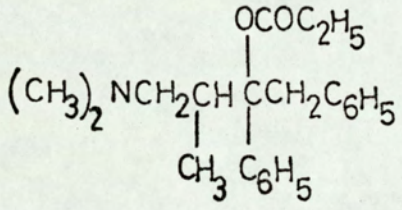


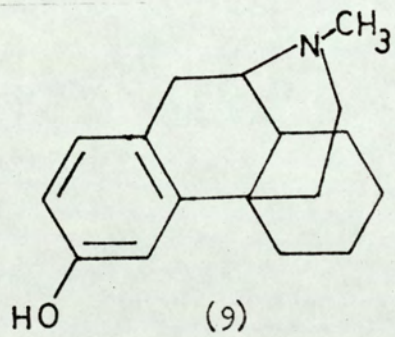
(8)

Pharmacologically, methadone resembles morphine in most respects and clinically reproduces every detail of the action of morphine, including its dependence liability. The search for methadone analogues that would have high analgesic activity and little dependence liability has proved fruitless but methadone has found a clinical use as a substitute for morphine with dependent individuals.

During the search for methadone analogues, two interesting classes of compounds were investigated. Adamson and Green [9] originated the synthesis of the dithienylbutenylamines in which

dimethylthiambutene (7) was found to be slightly less active than morphine. Pohland and Sullivan [10] developed the 3-acyloxy-3-phenylbutylamines or propoxyphenes. In this series, (+)-propoxyphene (8) has a fairly wide use.

Almost simultaneously with the emergence of methadone came another important advance in synthesis, the morphinans, synthesised by Grewe [11,12] in 1946. This marked the beginning of the era of research on "simplified morphines". The best-known analgesic of this series (-)-3-hydroxy-N-methylmorphinan (9) contains the complete carbon-nitrogen framework of morphine but lacks several of morphine's peripheral functional groups.



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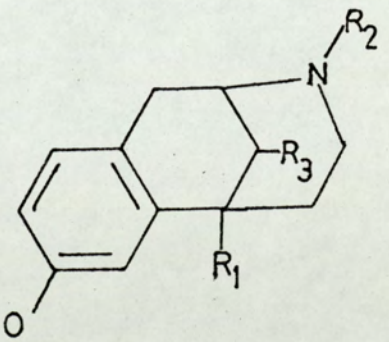
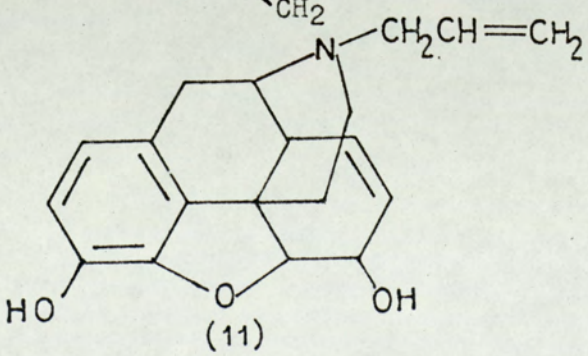


(10)

	R_1	R_2	R_3
10a)	CH_3	$CH_2CH=C(CH_3)_2$	CH_3
10b)	CH_3	$-CH_2-CH-CH_2-CH_2-$	CH_3



(11)

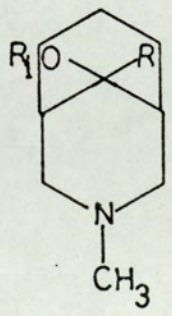
Several clinically active compounds are found in the morphinan group, all of which have the drawbacks of morphine.

The simplification of the morphine structure was carried a step further by May et al [13] who in 1954 initiated their work on the 6,7-benzomorphans (10) which contain the intact iminoethano system and other structural features of morphine believed essential for strong, central analgesic action. [14] The clinically useful compounds found in this series show a definite separation of analgesic activity and dependence liability. Based on these findings, and on the discovery of strong analgesic activity for the non-dependence producing narcotic antagonist nalorphine (11), Archer et al. [15] synthesised a series of antagonists by substitution on the nitrogen atom (R_2). Introduction of an allyl or cyclopropyl moiety on the nitrogen produces benzomorphans that are narcotic antagonists. A narcotic antagonist may be defined as an agent that will cancel or reverse most of the pharmacological effects of morphine-like substances. Pentazocine, (10a) although a weak antagonist, was found to be comparable to morphine in controlling pain and is now widely used as a substitute for morphine. Early reports claimed it to be free from addiction liability. Doubts have been cast on the claims of freedom from addiction liability[16,17,18] but it has been shown [19] to produce less respiratory depression than morphine in equi-analgesic doses. Cyclazocine (10b), although a very

strong antagonist is forty times as potent as morphine in post-operative pain.

The 6,7-benzomorphans are potentially the most interesting system. Even if the earlier claims of no addiction potential are disproved, they still have far less addiction potential and respiratory depressant action than morphine while still retaining potent analgesic action.

A study of the 6,7-benzomorphans, in addition to morphine, shows that they can be considered as azabicyclo [3.3.1] nonane derivatives, and a number of azabicyclo [3.3.1] nonanes have recently been shown to possess analgesic activity. 3-Methyl-3-azabicyclo [3.3.1] nonane and a number of analogues have been prepared (12)[20,21] with variations in both the ester or ether group and substituents on the benzene ring, and are found to possess analgesic activity. It has been shown that (12a) has an analgesic potency and therapeutic index three times that of pethidine.[22,23]



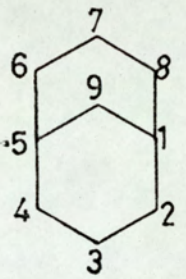
a) R = C_6H_5, R_1 = CH_3

(12)

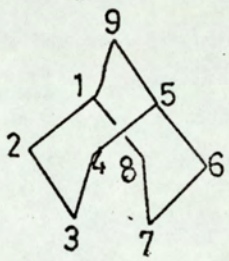
In addition to analgesic activity, hypotensive,[24] local anaesthetic[20] and psychotropic activity[25] have been found in derivatives of azabicyclo[3.3.1]nonanes.

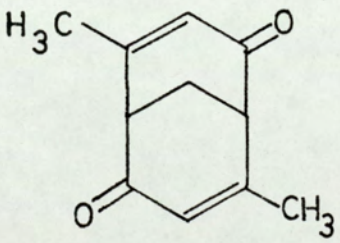
B. Bicyclononanes

The bicyclo[3.3.1]nonane ring system (13) has been known for over 70 years. [26] As early as 1894 Knoevenagel [27] obtained a bis enone by condensing acetyl-acetone with benzaldehyde and cyclising the resulting product with acid. He formulated the product as the diketone (14) or (15) and provided some supporting evidence.



(13)





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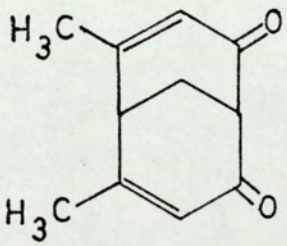
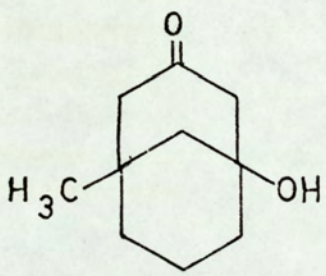


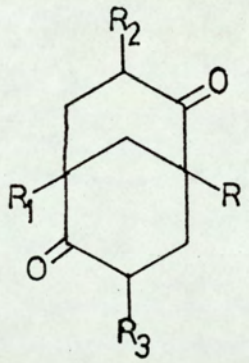
(15)

Another early synthesis was described by Rabe [28] in 1908. The addition of ethyl acetoacetate to 3-methylcyclohexanone gave the expected Michael product and thus afforded the bridgehead alcohol (16). Of the early syntheses, the preparation of the diketone

(17), by Meerwein [26] in a one-step synthesis from malonic ester and formaldehyde is of special interest. In a paper presented in 1922 he argued out its structure (without any spectroscopic aid) and prepared from it the bicyclononan-2,6-dione (18) and then the parent hydrocarbon (13) whose structure has since been verified. In a prophetic footnote he commented on what is now termed the conformation of the ring system. Although later generations have improved on these preparations, the synthetic routes pioneered by Meerwein and Rabe have played major roles in the chemistry of bicyclononanes.



(16)

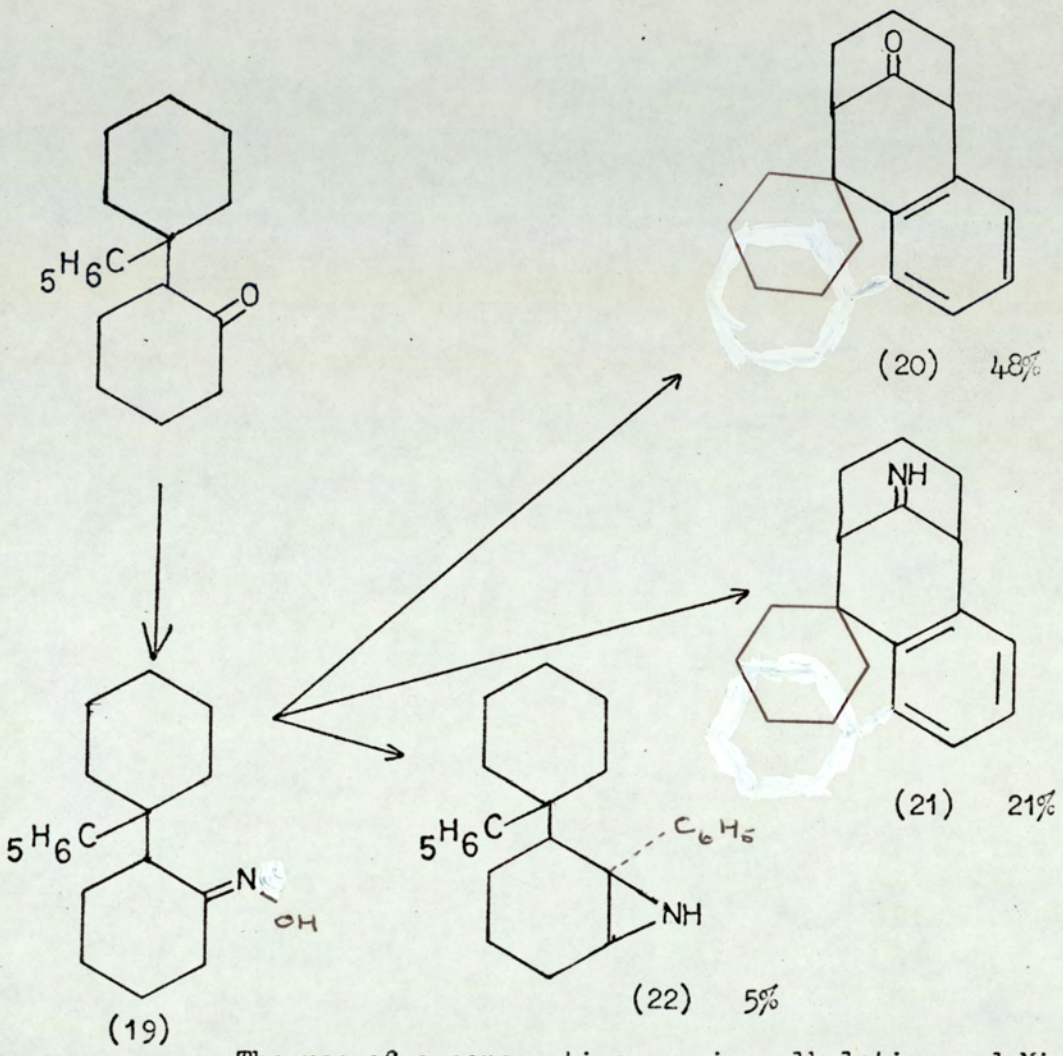


(17) $R = R_1 = COOCH_3$, $R_2 = R_3 = COOCH_3$

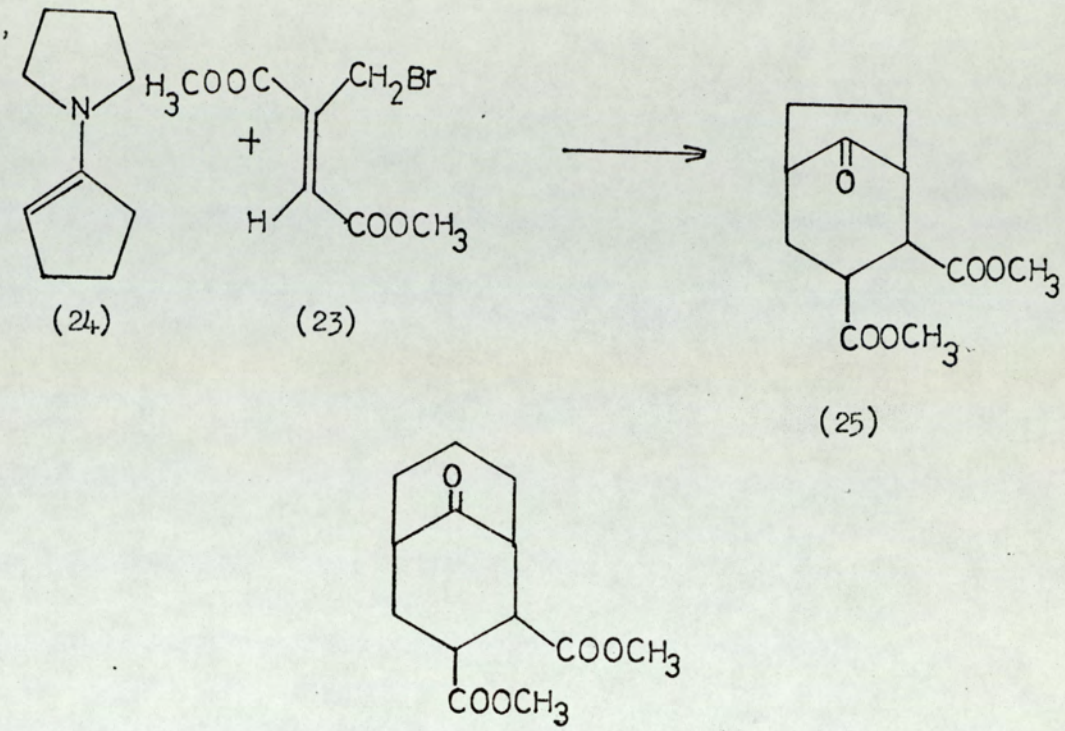
(18) $R = R_1 = H$, $R_2 = R_3 = COOCH_3$

More recently a novel intramolecular cyclisation reaction has been reported [27] in which 2(1'-phenyl)-cyclohexylcyclohexanone oxime (19) is reacted with aromatic Grignard reagents, either phenyl or p-tolylmagnesium bromide, to give spiro[bicyclo[3.3.1]-3,4-benzononan-9-one-2,1'cyclohexane] (20). In addition, two other

basic compounds (21) and (22) are also obtained.



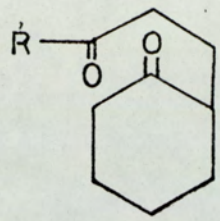
The use of a consecutive enamine alkylation and Michael addition has allowed a new synthetic approach to bicyclic ketones to be developed.[28] Dimethyl γ-bromomesaconate (23) reacted with the pyrrolidine enamine of cyclopentanone (24) to give the bicyclic ketone (25). In a similar condensation of bromomesaconic ester (23) with the pyrrolidine enamine of cyclohexanone, a 71% yield of 2,3-dimethyl bicyclo[3.3.1]nonan-9-one-dicarboxylate (26) was obtained.



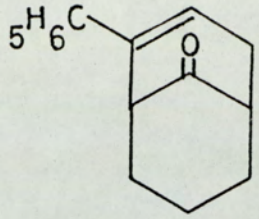
(24) (23) (25)

(26)

Bicyclononanes containing a 9-keto group are often prepared by the cyclisation of 1,5-diones of type (27) and these are available by the Michael reaction (R = aryl, H or alkyl). However, formation of the bicyclic compound is not always smooth or uncomplicated. Aryl ketones are generally cyclised under acid conditions [29] and give rise to the fewest complications. The initial aldol product, a tertiary benzylic alcohol, is readily dehydrated and affords a $\beta\gamma$-enone. Consequently the enone (28) is readily prepared from cyclohexanone.

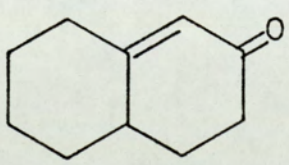


(27)



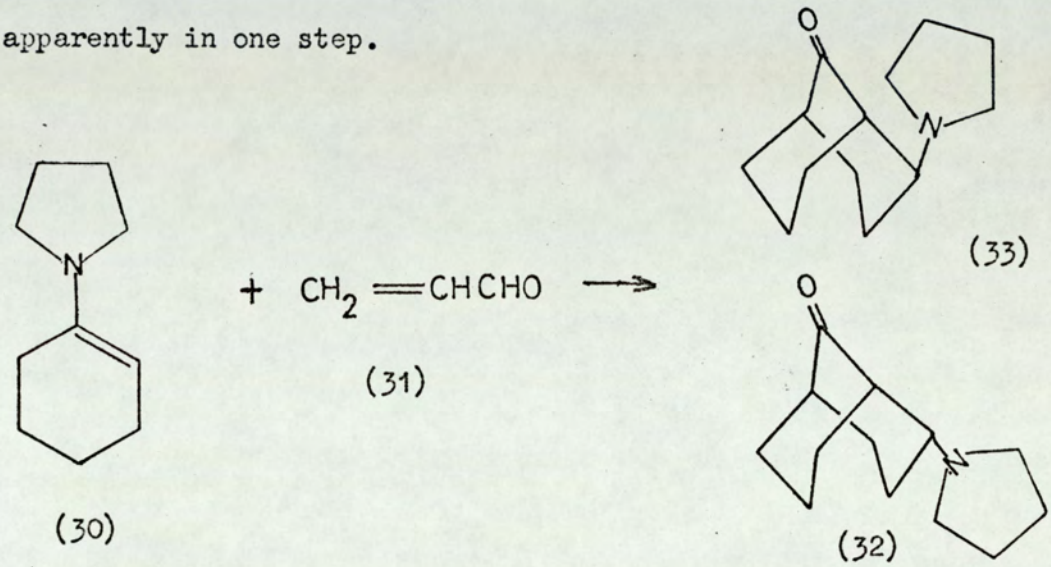
(28)

Another method of preparing bicyclic ketones is *via* the enamine. The term enamine was coined by Wittig and Blumenthal [30] in order to indicate a general structural feature in which a nitrogen atom replaces an oxygen atom in the familiar "enol." The structual moiety represented by enamine has been known in the litcrature for a long time, although its full chemical potentiality remained dormant until 1954.[31] The use of enamines as a route to bicyclic systems was pioneered by Stork [31-35] and the first reported cyclisation involving an enamine was the 1,4 cycloaddition of methyl vinyl ketone with the enamine of cyclohexanone to give, after hydrolysis, $\Delta^{1,9}$-decal-2-one (29). [32]



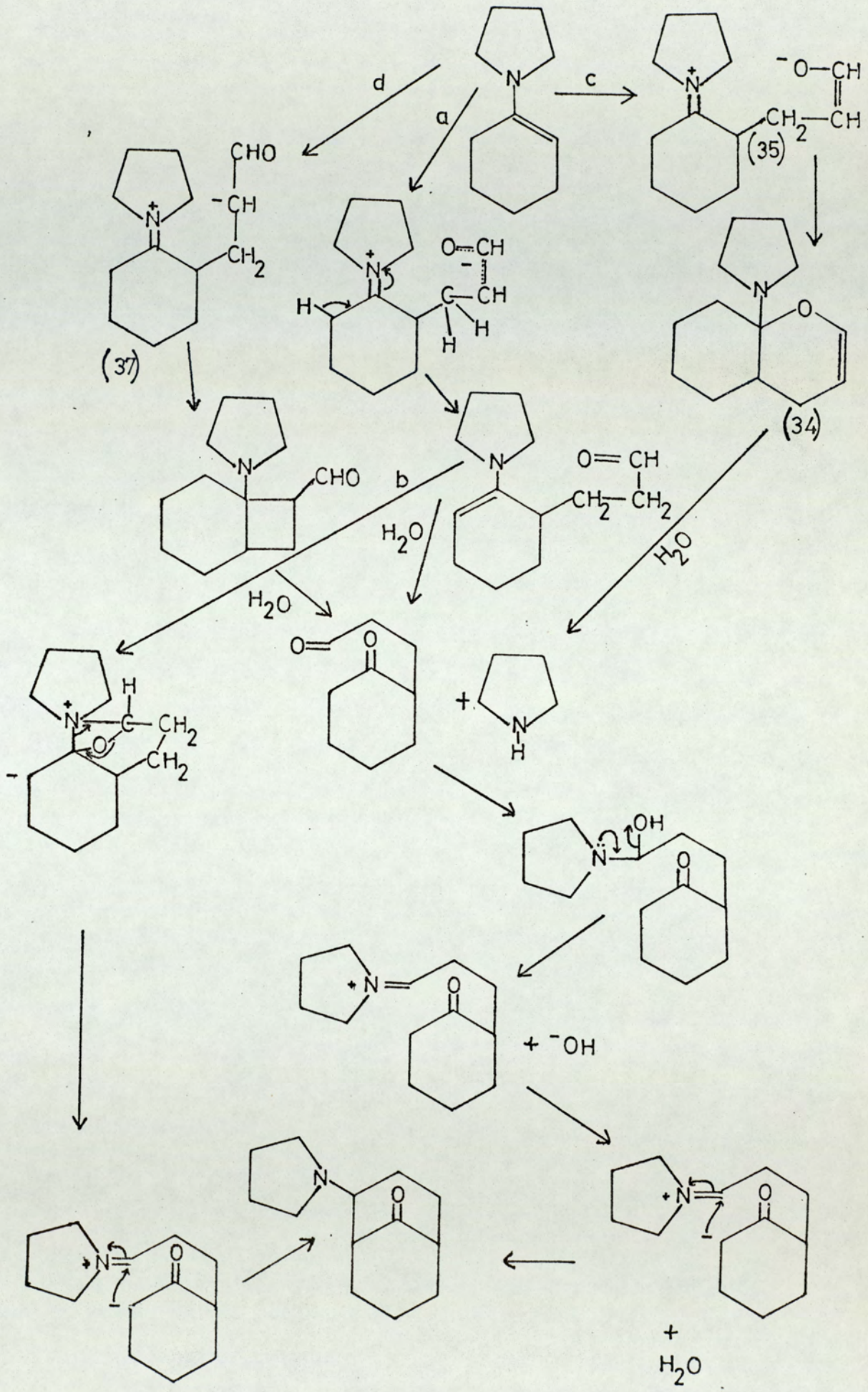
(29)

When an α β-unsaturated aldehyde is reacted with a cyclic enamine, the product is a 2-substituted bicyclic ketone. [33,36] Thus the reaction of the pyrrolidine enamine of cyclohexanone (30) with acrolein (31) gives the bicyclic amino-ketones (32) and (33), apparently in one step.

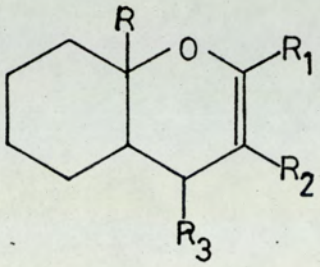


The composition of the mixture of (32) and (33) varied between 70 and 80% of the α-epimer (32) and 30 and 20% of the β-epimer (33), which approximates to the likely thermodynamic equilibrium composition expected. [37] The α-epimer (32) has one diaxial-type repulsion (with 8α-H) to balance the similar repulsion (with 4β-H) in the β-epimer. This leaves one extra skew interaction of the π-skew butanol type [38] in the β-epimer. Since this is likely to be somewhat less than the hydrogen-dialkylamine repulsion, (1 kcal/mole), [39] about 75% of the α-epimer at equilibrium is reasonable [37] and is in agreement with a non stereospecific ring closure. A thorough investigation of the course of this reaction

has not been reported. Any mechanism postulated has to account for an apparent rearrangement, the pyrrolidine group becoming attached to the carbon that was the aldehyde and the oxygen becoming attached to the carbon that had been bonded to the pyrrolidinyl group in the enamine. The versatility of the reaction and its usefulness in the synthesis of medium-size rings was studied in detail by Untch [36] but only a limited investigation was described. Untch used mixtures of different enamines of cyclohexanone to show that the reaction occurred via a bimolecular process and suggested a possible mechanism (path a). In this route, following the first electrophilic attack, the reaction occurs intermolecularly with transfer of the amine from the ketonic enamine to the aldehyde followed by cyclisation. It has been shown that the ratio of 2α-amino-ketone to 2β-amino-ketone is in reasonable correspondance with the expected thermodynamic equilibrium between the two compounds, thus indicating that the rearrangement is an intermolecular process. One alternative pathway (path b) must be discounted since this involves an intramolecular rearrangement and would be expected to give a single preferred configuration at C2. A recent study on the reaction [40,41] has shown that an intermediate dihydropyran (34) (path c) is produced, presumably through the zwitterion (35) [42] and a number of dihydropyrans with the general formula (36) have been isolated and


d
a
c
(37)
(35)
(34)
b
H_2O
H_2O
H_2O
+ ^-OH
+
H_2O

characterised from reactions of enamines with acrolein.



(36)

R = 4-Phenyl-1-piperazinyl, or morpholinyl,

R_1 = H, or C_6H_5,

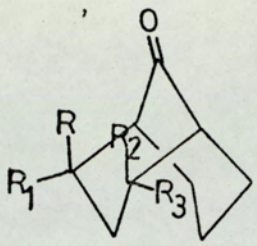
R_2 = H, or CH_3,

R_3 = H, or C_6H_5.

That the stereochemical requirements for formation of aminohexahydrobenzopyran intermediates are quite stringent is shown by the fact that whereas the intermediate aminohexahydrobenzopyran could be isolated from the reaction between 1-(1-cyclohexen-1-yl)-4-phenylpiperazine and acrolein, no intermediate was isolated from the reaction between 1-(1-cyclopenten-1-yl)-4-phenylpiperazine or 1-(1-cyclohepten-1-yl)-4-phenylpiperazine and acrolein, both reactions going directly to the bicyclic ketones. Furthermore, no intermediate was obtained from the reaction of 1-(1-cyclohexen-1-yl)-4-phenylpiperazine and cinnamaldehyde, the bicyclic ketones being produced in good yield. A possible route (path d) *via* a cyclobutane adduct could proceed either from the intermediate (37) by an intramolecular attack or by direct cycloaddition of the enamine to the electrophilic olefin. Cyclobutane intermediates have been isolated from enamine reactions,[40] especially when the aldehyde-

enamine adduct cannot become neutral by proton transfer as with α,α-disubstituted aldehydes. Such a course was observed by Brannock [43] in the reaction of enamines derived from secondary aldehydes with many electrophilic olefins. In these cases an intermediate zwitterion following path(a) could not lose a proton to regenerate an enamine. Although the reaction is carried out under nominally anhydrous conditions, the presence of a small amount of hydrolytic agents cannot be excluded. A small amount of secondary amine mixed with the enamine could react with acraldehyde to generate water which could then cause the hydrolysis stage in each of the three pathways to produce a mixture of amine and dicarbonyl compound as shown. There are a number of variations possible on these suggested mechanisms, all of which would incorporate the general features of ring fission followed by recyclisation.

A number of different cyclic secondary amines as well as substituted cyclohexanones and substituted acroleins have been used [36] to produce substituted bicyclononanes. The reaction between cyclohexanone and an α,β-unsaturated aldehyde has recently been extended to include cinnamaldehyde as the aldehyde and a mixture of three ketones was produced (38-40). [54,55]

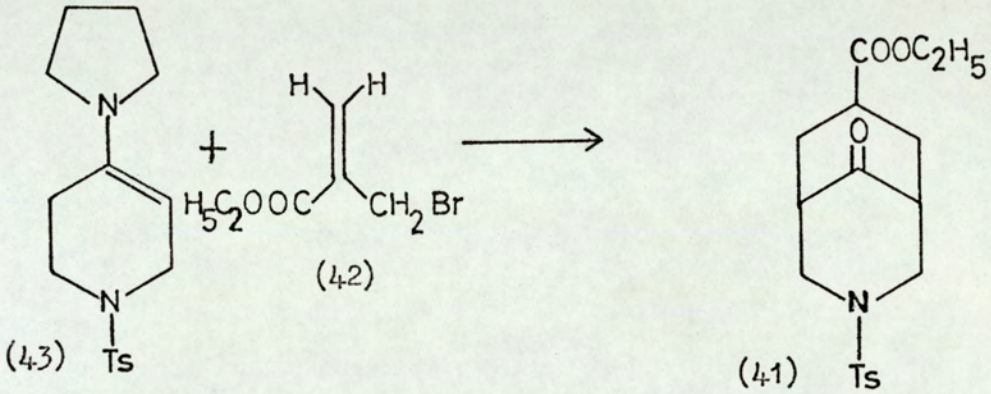


	R	R_1	R_2	R_3
38)	C_6H_5	H	H	Morpholine
39)	H	C_6H_5	Morpholine	H
40)	C_6H_5	H	Morpholine	H

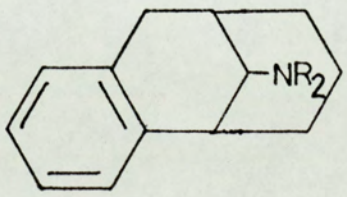
The similarity between these ketones and the 6,7-benzomorphans make this a potentially important route to various substituted benzomorphan analogues when applied to piperidone rather than cyclohexanone enamines.

C. Azabicyclononanes

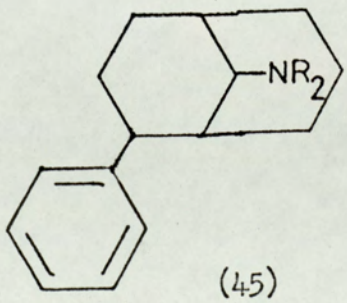
The use of enamines to prepare azabicyclo[3.3.1]nonanes has not received the same attention as the corresponding deaza compounds. Speckamp [44-46] synthesised several 3-azabicyclo[3.3.1]nonanes (41) via the addition of α-bromomethylacrylate (42) to the enamine of N-tosylpiperidone (43).



Mitsuhashi [47] used the enamines of β-tetralone and 4-phenylcyclohexanone to produce derivatives of 11-amino-2,3-benzobicyclo[3.3.1]nonane (44) and 2-phenyl-9-aminobicyclo[3.3.1]nonane (45) as analogues of benzomorphan.



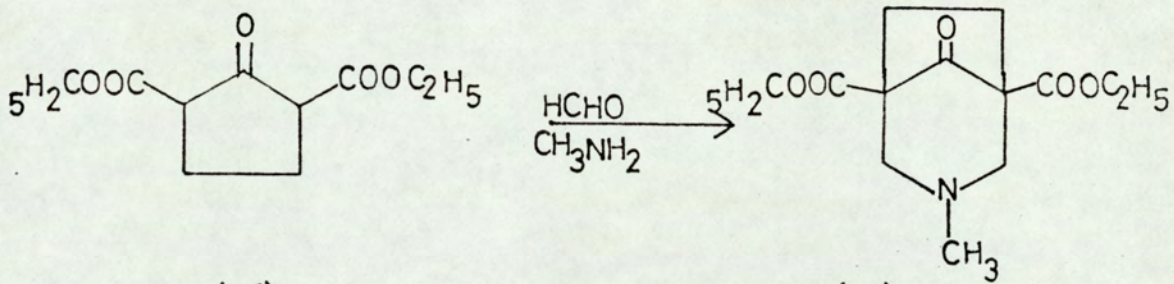
(44)



(45)

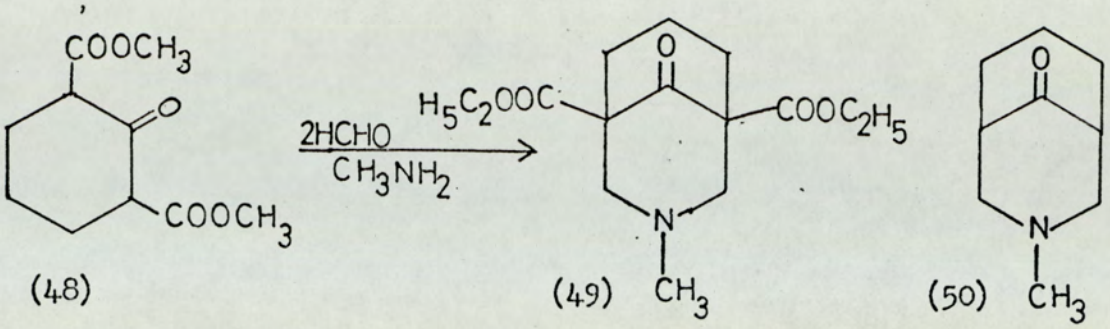
The azabicyclononanes reported to possess hypoglycaemic and psychoanaleptic activity [21] were prepared from 4-piperidones *via* the enamine.

One of the most widely used methods of synthesising azabicyclic ketones was reported by Anet. [56] Diethyl cyclopentanone-2,5-dicarboxylate (46) condensed with formalin and aqueous methylamine in alcohol at room temperature to yield diethyl 3-methyl-3-azabicyclo[3.2.1]octan-8-one-1,5-dicarboxylate (47) in 50% yield.



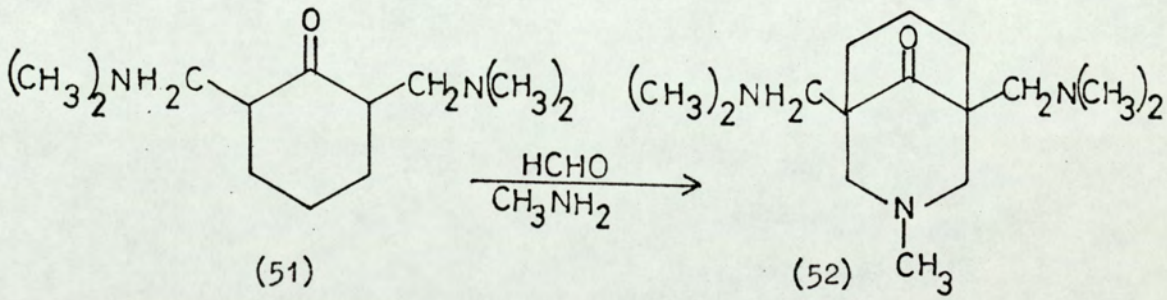
(46) (47)

This reaction was then extended to be a route to 3-azabicyclo[3.3.1]nonanes. Dimethyl cyclohexanone-2,6-dicarboxylate (48) was found to react with formalin and aqueous methylamine in methanol at room temperature to give dimethyl 3-methyl-3-azabicyclo[3.3.1]nonan-9-one-1,5-dicarboxylate (49) in 80% yield. [57] The unsubstituted amino ketone (50) was prepared [48] by decarboxylation of the keto diester (49) in boiling hydrochloric acid.



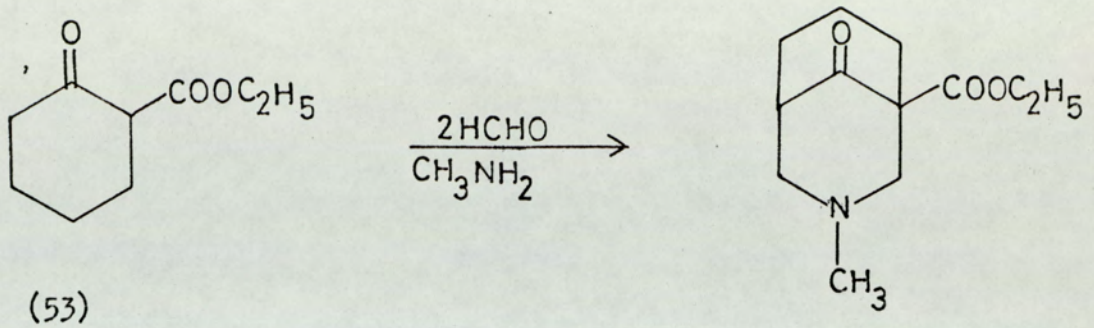
(48) (49) (50)

The reaction between cyclohexanone, paraformaldehyde and dimethylamine hydrochloride produced 2,6-bis(dimethylaminomethyl) cyclohexanone dihydrochloride (51). When this substance was allowed to react with formalin and methylamine hydrochloride, 1,5-bis (dimethylaminomethyl)-3-methyl-3-azabicyclo[3.3.1]nonan-9-one trihydrochloride (52) was formed.



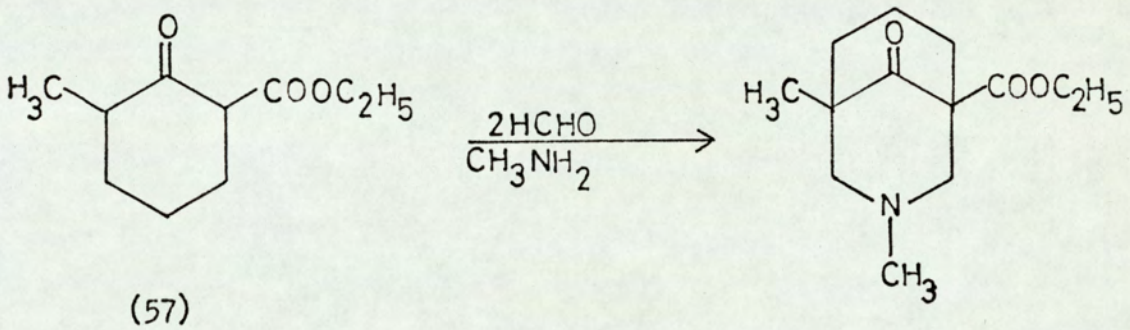
(51) (52)

Many substituted derivatives have been produced by the reaction of formalin and methylamine with substituted cyclohexanones.[49] When ethyl cyclohexanone-2-carboxylate (53) was reacted in this manner, ethyl 3-methyl-3-azabicyclo[3.3.1]nonan-9-one-1-carboxylate (54) was produced and could be hydrolysed to the acid and decarboxylated to the unsubstituted amino ketone (50).



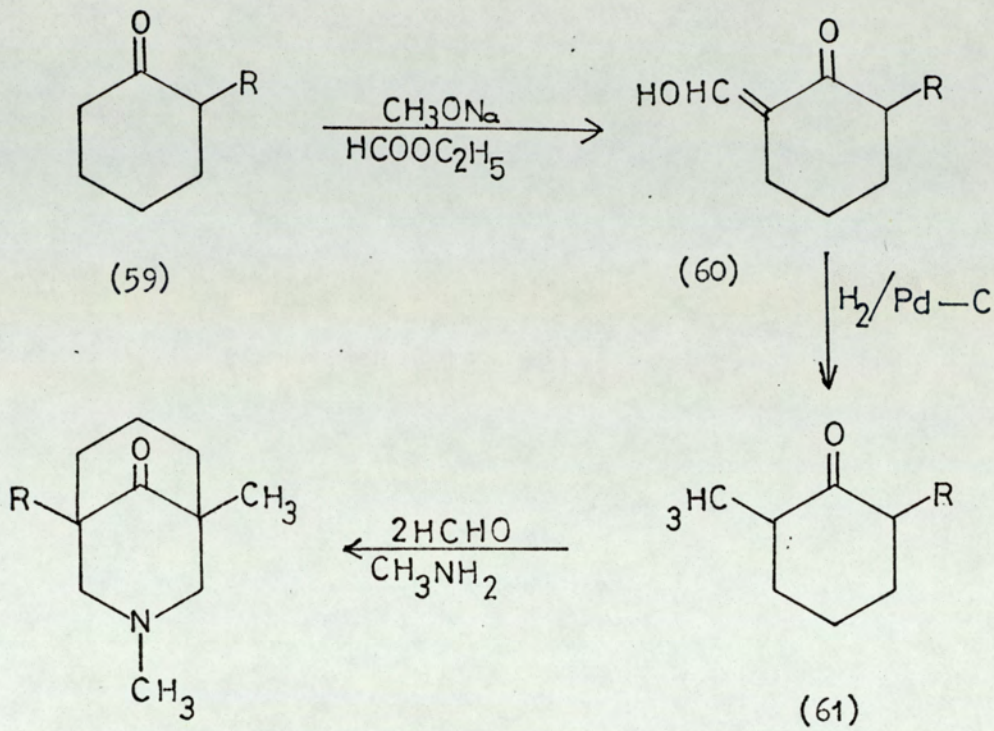
(53) (54)

Use of ethyl 2-methylcyclohexanone-6-carboxylate (57) together with formalin and methylamine gives ethyl 1,3-dimethyl-3-azabicyclo[3.3.1]nonan-9-one-5-carboxylate (58).



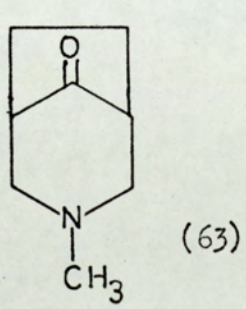
(57) (58)

The reaction was then extended to the synthesis of 3-azabicyclo[3.3.1]nonane derivatives by the same condensation from keto-compounds without a carboxylic group in the α-position. 2-(p-Methoxyphenyl)cyclohexanone (59) was treated with ethyl formate to give a 6-formyl derivative (60). This was hydrogenated to give (61) and a similar ring formation carried out to give the 3-azabicyclo[3.3.1]nonane (62).

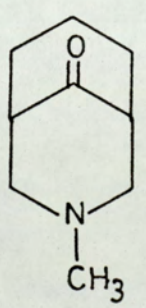


R = p-Methoxyphenyl

In a search for a synthetic route to the three azabicyclic ketones (63-65) House [50] reinvestigated the claim [51] that the reaction of cyclohexanone with formaldehyde and methylamine afforded the diketo amine (66) but not the desired ketone (64).



(63)



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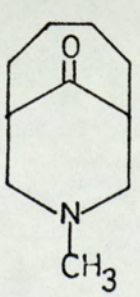
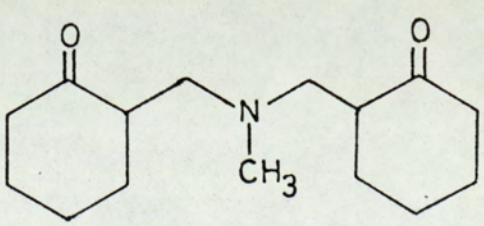


(65)

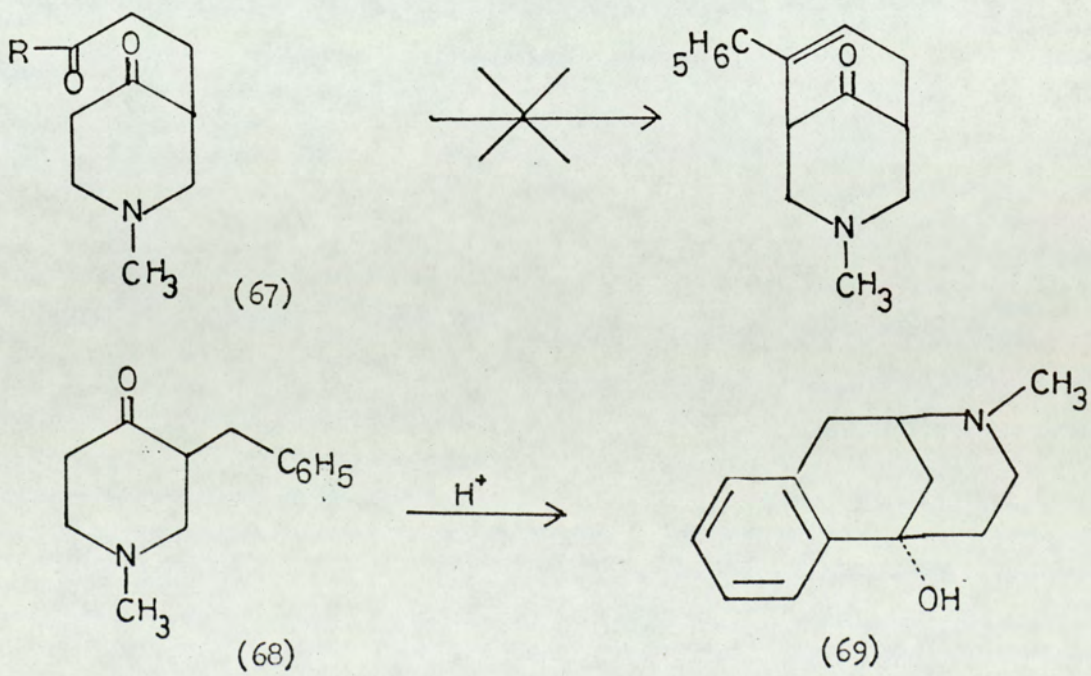


(66)

Each of the desired ketones (63-65) was isolated from the reaction of the monocyclic ketone with formaldehyde and methylamine in acetic acid, although each was formed in low yield.

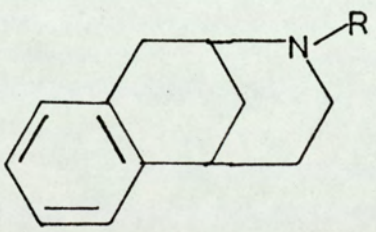
Another possible route to the 3-azabicyclo[3.3.1]nonane system would be the ring closure of the 1,5 diones of type (67) derived from 4-piperidone. The reaction in the deaza series is known (page 13) but is not always a smooth uncomplicated procedure. The reaction as a route to azabicyclo[3.3.1]nonanes is not reported and attempts to ring close the dione (67, R = C_6H_5) under either acid or alkaline conditions resulted in unreacted starting material.[52]

May[53] has recently reported a one-step synthesis of azabicyclo[3.3.1]nonanes which contain the 6,7-benzomorphan skeleton. 2-Benzyl-1-methyl-4-piperidone (68) and boiling hydrobromic acid react to give 5-hydroxy-2-methyl-6,7-benzomorphan (69) in 84% yield.

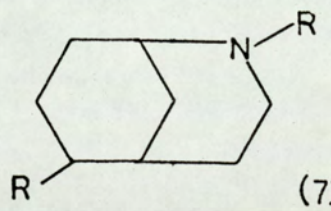


D. Aims and objects of the present investigations

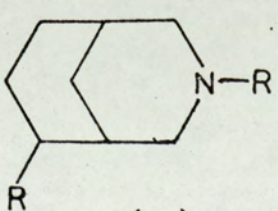
The 6,7-benzomorphans (70) are 2-azabicyclo[3.3.1]nonane derivatives with a benzene ring fused in the 6,7-position. A related series of compounds possessing the nitrogen in the 3-position, the 3-azabicyclo[3.3.1]nonanes (71), have also been shown to possess analgesic activity [20-24]. The initial aim of the present investigation was the preparation of azabicyclononanes synthesised by the addition of αβ-unsaturated aldehydes to the enamines of 1-methyl-4-piperidone to give 6-substituted 3-azabicyclo[3.3.1]nonanes (72). In this way the effect on biological activity of a second basic centre could be examined. These compounds were expected to exist in isomeric forms which would require separation, and configuration determination, prior to biological screening.



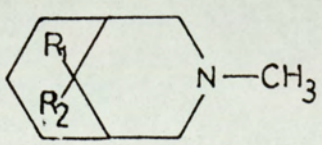
(70)



(73)



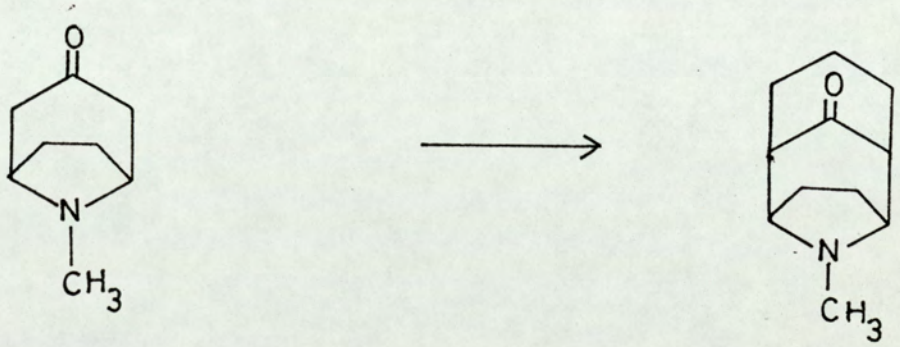
(72)



(71)

These compounds, as derivatives of 3-azabicyclo[3.3.1]nonane might be expected to exhibit some analgesic activity. They also possess a saturated bicyclic ring system isomeric with the saturated bicyclic ring of the 6,7-benzomorphans. 2-Azabicyclo[3.3.1]nonane derivatives (73) could also be prepared by the same route, from 1-methyl-3-piperidone and would contain the same saturated bicyclic ring system as occurs in the 6,7-benzomorphans.

Analgesic activity has also been reported in tropane derivatives [5,6]. A further aim of the present work was to extend the scope of the enamine ring-formation procedure to the tropane system and thereby form substituted azatricyclo compounds.

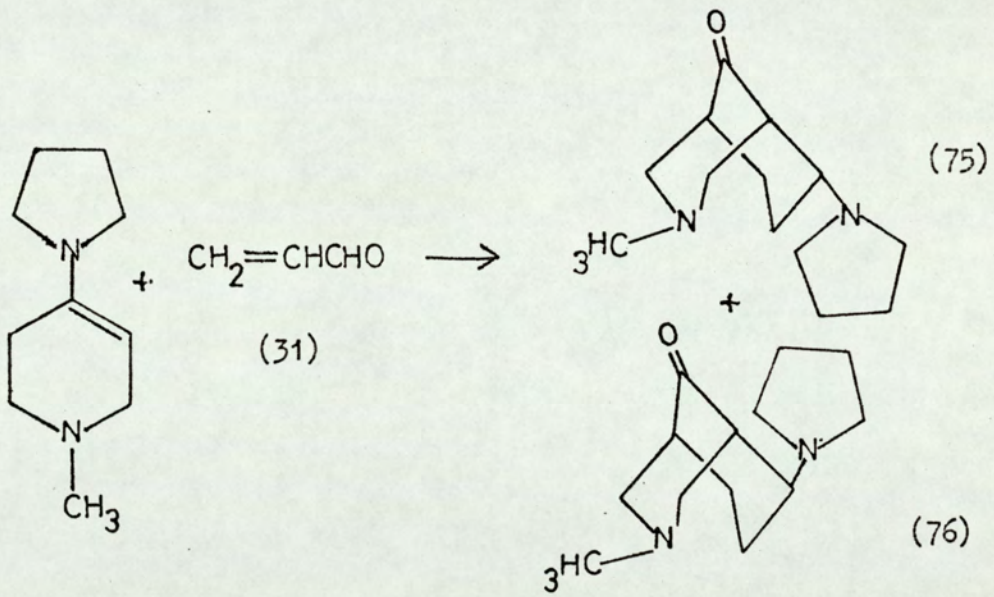


DISCUSSION

A. Synthesis of some 6-Cycloalkylamino-3-azabicyclo[3.3.1]nonanes.

1. Pyrrolidine derivatives.

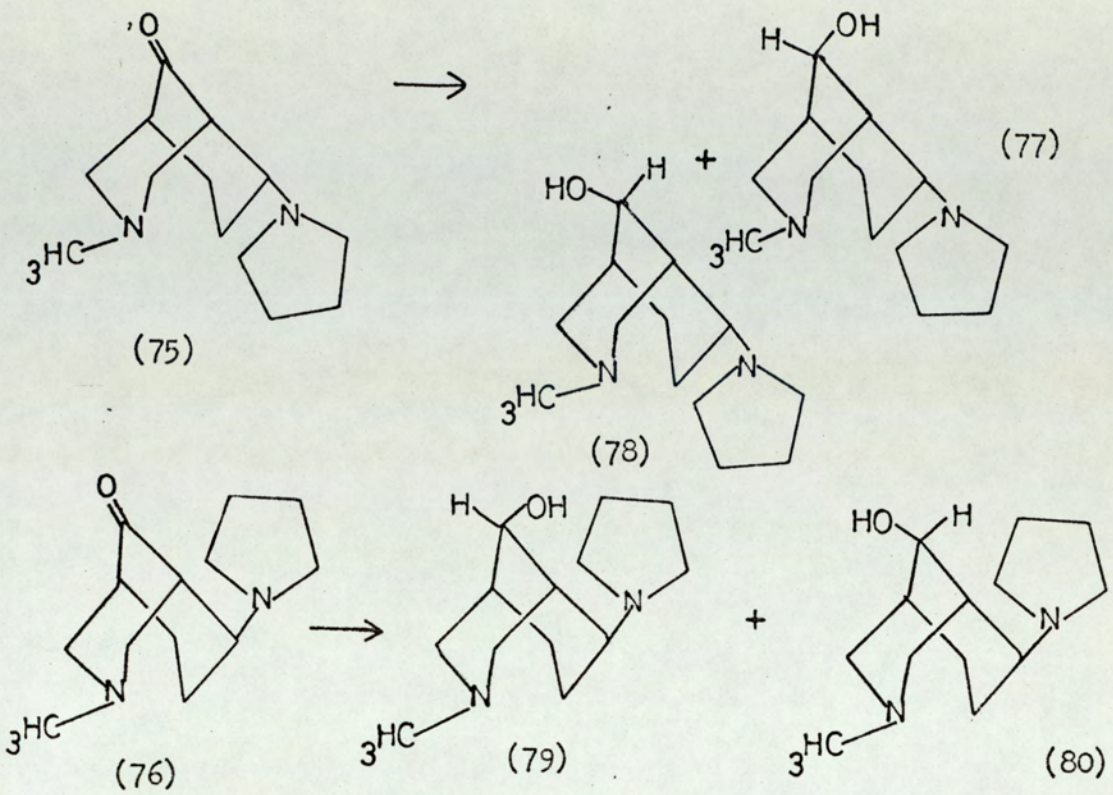
When acrolein (31) and 1-methyl-4-(N-pyrrolidinyl)-1,2,3,6-tetrahydropyridine (74) were reacted, the product obtained was a mixture of stereoisomeric ketones (75) and (76). (The structures as shown are configurationally correct but do not necessarily indicate the preferred conformations. The 6-cycloalkylamino group is referred to as 6α as in (75) and 6β as in (76).)



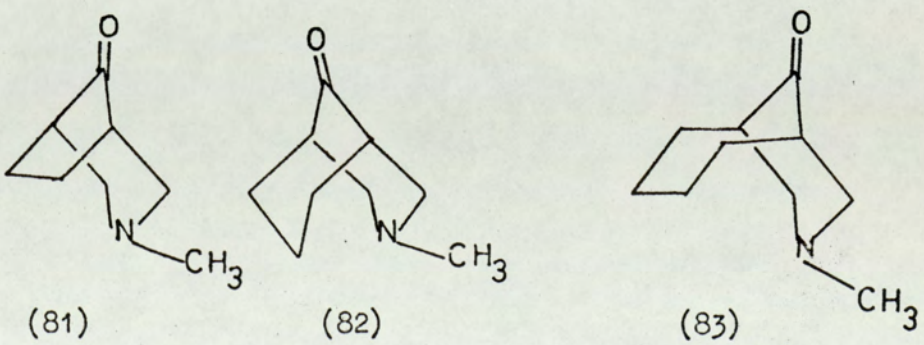
The presence of two ketones was demonstrated by tlc but could not be shown by glc. Densitometry of the tlc, in conjunction with the isolation of subsequent reduction products, indicated a 3-4 : 1 ratio of 6α : 6β isomers. This is in agreement with results on the analogous deaza ketones [37] and appears to be the expected

yield based on calculations (see page 15). The small difference in the Rf values of the ketones made chromatographic separation difficult and column chromatography failed to yield a pure isomer. The mixed pair of ketones were reduced to the alcohols (Fig. 1) by a variety of reducing agents in an attempt to vary the amount of the isomers produced. The reduction mixtures were investigated by glc and each reduction was found to give rise to two peaks. Sodium borohydride reduction gave a ratio of 1 : 1.2 for the ratio of the fast-moving component to the slow-moving component, and lithium aluminium hydride reduction gave a similar ratio of 1 : 1.3 . Catalytic hydrogenation over platinum oxide gave a ratio of 1 : 3.6 while reduction with sodium and isopropyl alcohol gave a ratio of 1 : 3.6 . Each of the ketones (75) and (76) can give rise to two alcohols by reduction, and subsequent isolation of the four alcohols showed that the two alcohols with the hydroxyl group anti to the pyrrolidine gave rise to the fast-moving component. The two alcohols with the hydroxyl group syn to the pyrrolidine group gave rise to the slow-moving component. A precise interpretation of these results was not possible because each peak represented the sum of the contribution of two isomers.

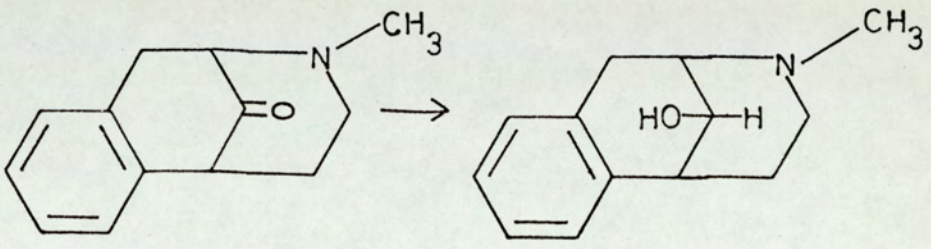
Figure 1



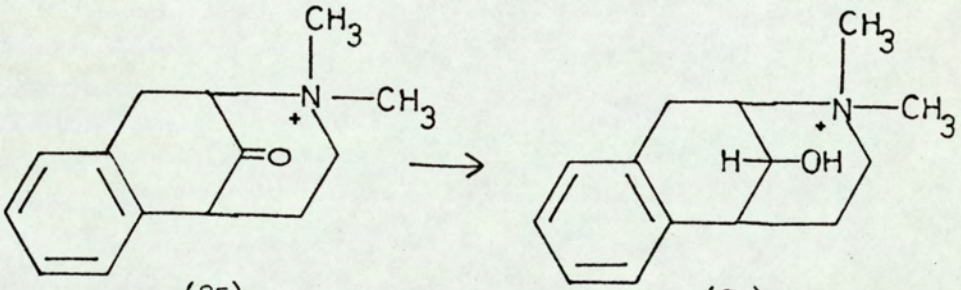
A study of the reduction of the amino ketones (81), (82) and (83) has been carried out using sodium and alcohol, sodium borohydride, and hydrogen and platinum.[58] The various reductions of the azabicyclooctane (81) produced primarily the β-amino alcohol (hydroxyl group syn to the amino function), whereas the azabicyclodecanone (83) yielded primarily the α-amino alcohol. Reductions of the azabicyclononane (82) afforded mixtures of the α- and β-isomers.



Studies of the benzomorphan (84) and its quaternary salt (85) [59-63] proved of special interest since the free base (84) was converted to the α-isomer (86) by either catalytic hydrogenation or hydride reduction, whereas the β-isomer (87) was produced from the salt (85) under comparable conditions.



(84) (86)



(85) (87)

Two factors might be considered important in determining the course of amino ketone reductions. The results may be attributed to steric factors which either hinder approach of the catalyst or complex metal hydride (steric approach control) or destabilise the transition state (product-development control). Alternatively, the results may be attributed to a prior complexing of the amine function with the catalyst surface (Fig. 2) or the borane (Fig. 3),

allowing participation of the amine function in the hydride ion transfer.

Figure 2

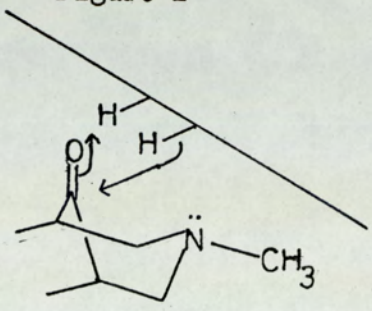
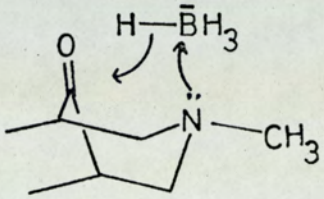
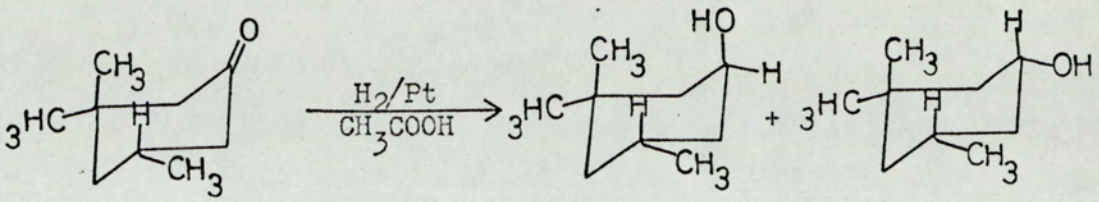


Figure 3



Early studies by Linstead et al.[64] on the hydrogenation of phenanthrene and diphenic acid derivatives over platinum led to the concept that the less hindered side of an unsaturated molecule is adsorbed onto the catalyst surface. This adsorption was thought to be followed by the simultaneous transfer of two or more hydrogen atoms from the catalyst to the adsorbed molecule and subsequent desorption of the reduced molecule. This concept has led to the useful generalisation that catalytic hydrogenation of a multiple bond results in cis addition of two hydrogen atoms from the least hindered side of the multiple bond. In addition, the reduction of ketones is predicted to take place from the least hindered side, as shown by the reduction of the ketone (88).[65]



(88) 83% 17%

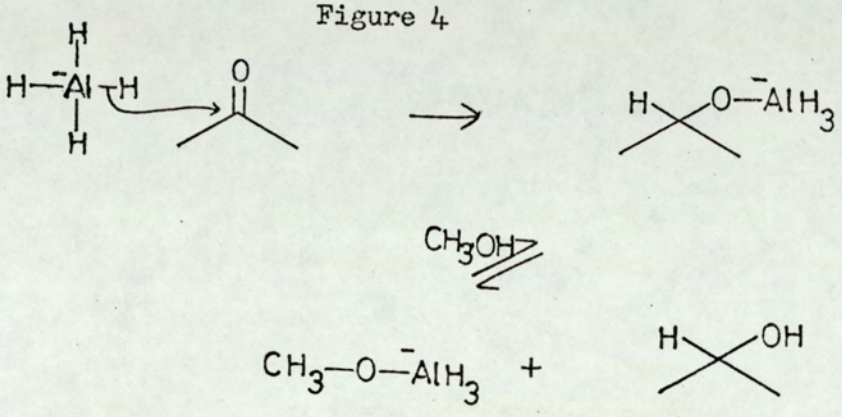
Studies of catalytic reductions have established that the transfer of hydrogen atoms to an adsorbed molecule must occur in a stepwise manner.[66]

Ketone (76), on catalytic reduction would be expected to give rise almost exclusively to the syn-alcohol (79) and produce very little of the anti-alcohol (80). The ketone (75) would be expected to favour formation of the syn-alcohol (77) since the bulky pyrrolidine group would force the less hindered side of the molecule to be adsorbed onto the catalyst surface. This would allow attack on the carbonyl group from the side anti to the pyrrolidine group and produce the syn-alcohol. The experimental results obtained from the mixed ketones (75) and (76) by catalytic reduction are in agreement with this concept, the syn-alcohols comprising 78% of the reduction mixture.

Reduction with metal hydrides of aluminium or boron involves the AlH_4^- (or BH_4^-) ion as the attacking species, which, in effect, transfers H^- to the carbon. The freed AlH_3 then complexes

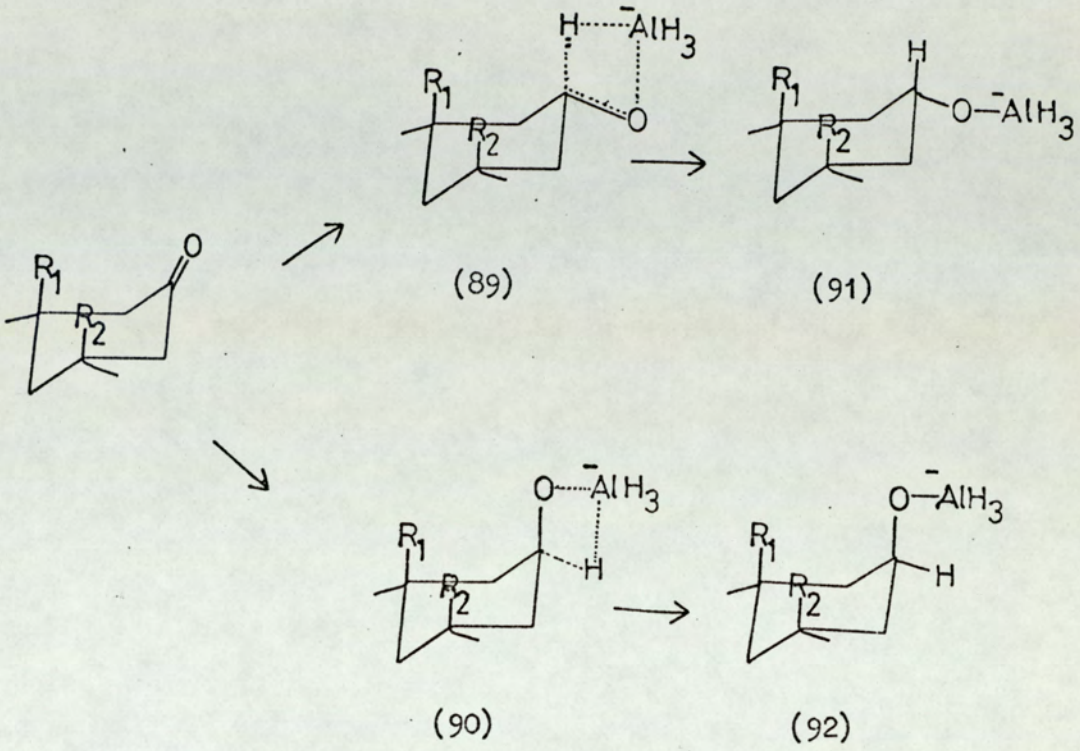
with the oxygen from the same molecule or from a different one. The complex must then be hydrolysed to the alcohol. If the reaction is performed in a protic solvent, then AlH_3 co-ordinates with the solvent instead, and a proton from the solvent goes to the oxygen (Fig. 4).

Figure 4



Free H^- cannot be the attacking species in most reductions with boron or aluminium hydride, because the reactions are frequently sensitive to the size of the MH_4^-. It has been shown [67] that $NaBH_4$ molecules are not the attacking species either, since they react only in solvents in which they are ionised to Na^+ and BH_4^-. If structures (89) and (90) are used to represent the transition states for the two possible directions of reduction of a conformationally rigid cyclohexanone derivative, it can be seen that steric interference between the R_1 and R_2 groups in (89) and the metal hydride (steric approach control) will oppose the

formation of the equatorial alcohol (91).



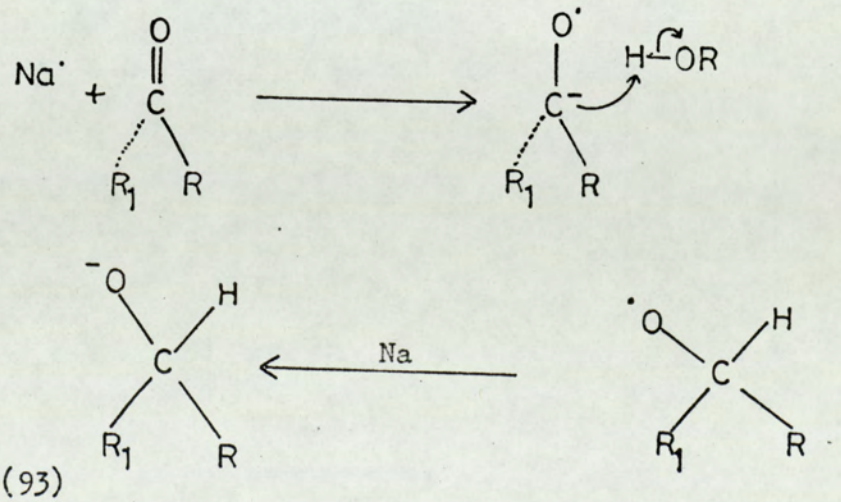
Alternatively, steric interference between the developing alkoxy-aluminium function and the R_1 and R_2 groups in (90) (product-development control) will oppose the formation of the axial alcohol (92). Unless approach to one side of the carbonyl function is clearly much more hindered than approach to the other side, the usual result of a metal hydride reduction is the formation of a mixture of alcohols.

Ketone (76) would be expected to favour formation of the syn-alcohol because the pyrrolidine group would seriously hinder attack of the carbonyl from the pyrrolidine side of the molecule. Approach to ketone (75), although more hindered on the pyrrolidine

side, is still possible from both sides of the molecule and would be expected to give both the syn- and anti-alcohols. This postulate is borne out by the results for both sodium borohydride and lithium aluminium hydride reductions of the ketones. The syn-alcohols form 55-60% of the mixture and the anti-alcohols 40-45%. If ketone (76) is assumed to give a large proportion of the syn-alcohol relative to the anti-alcohol, this would indicate that ketone (75) gives approximately equal amounts of the syn- and anti-alcohols.

The reduction of ketones with sodium and isopropyl alcohol in refluxing toluene offers the stereochemical advantage that the more stable alcohol is frequently, but not always, the predominant product. [68] Since the apparent violations of the rule appear to be found with ketones which possess either strained or hindered carbonyl functions, [69] the reaction may follow the course indicated (Fig. 5).

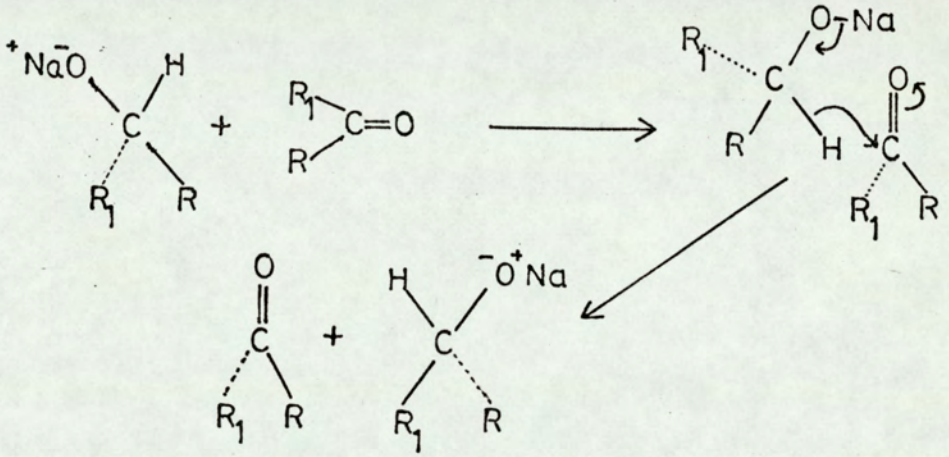
Figure 5



(93)

The initial reaction of the ketone with a metal to form a radical ion is followed by a sterically controlled protonation in which the proton is added from the least hindered side and then reacts further with the metal to form the alkoxide (93). The alkoxide, once formed, can react with the starting ketone (Fig. 6), analogous to the Meerwein-Pondorf-Verley reduction, to produce the isomeric (and usually more stable) alkoxide (94).

Figure 6



(94)

However, if the starting ketone is strained or if it is sterically hindered, then the conversion of the initially formed tetrahedral alkoxide back to the trigonal ketone would be especially slow (for either steric or energetic reasons) and isolation of the initial alcohol formed in a kinetically controlled protonation process would be expected.

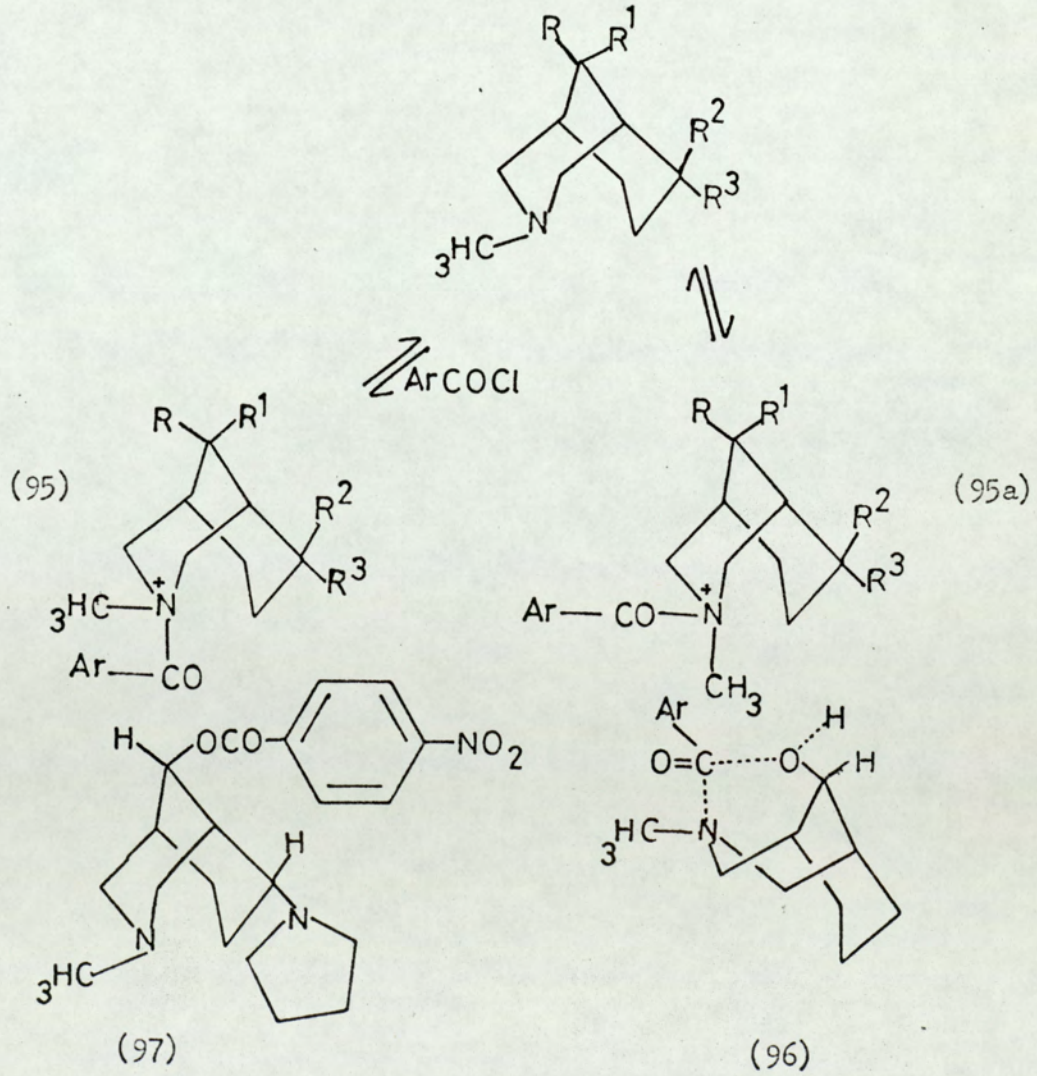
The syn-alcohols obtained from the ketones (75) and (76) by reduction with sodium and isopropyl alcohol constituted 78% of the

mixture. This indicates attack on the carbonyl group from the least hindered side (anti to the pyrrolidine group), with little or no conversion of the initially formed alkoxide back to the ketone. In agreement with this, the epimerisation of the syn-alcohol (77) derived from ketone (75) was found to occur very slowly, if at all.

From the crude sodium borohydride reduction mixture an alcohol (77) was obtained by fractional crystallisation. This alcohol was shown to be pure by tlc, and glc identified it as a "slow-moving" component of the mixture. This isomer was also isolated by fractional crystallisations of the crude reduction mixtures from the other reductions. The isolation of this alcohol as 27% of the total reduction mixture indicates that the 6-cycloalkylamino group is in an α-position since the 6β-ketone forms at the most only 25% of the mixture of ketones. The stereochemistry about C9 is revealed by the resistance of this alcohol to esterification under mild conditions. It has been reported [58] that unsubstituted 3-methyl-3-azabicyclo[3.3.1]nonan-9-ols and analogues in which the hydroxyl group is syn to the amino function, react with p-nitrobenzoyl chloride in chloroform at room temperature to yield the corresponding p-nitrobenzoates. Their anti-isomers are inert under these mild conditions and this has been used as a method of defining the stereochemistry of these

compounds. The very marked difference in esterification rates has been attributed to the reversible formation of the acyl ammonium salts (95) and (95a) followed by an intramolecular acyl transfer (i.e. 96 from 95a, R = OH, R^1 = H) (Fig. 7). When intramolecular acyl transfer is not possible (i.e. 95, R = H, R^1 = OH) the acyl function is attacked by either the chloride ion, or by the ethanol or water present in the chloroform more rapidly than it is attacked intermolecularly by a second alcohol molecule.

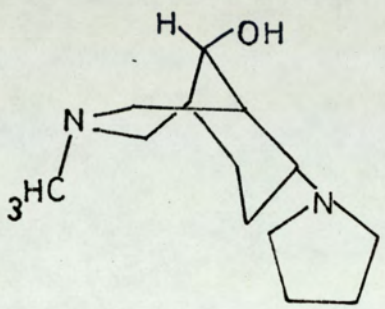
Figure 7



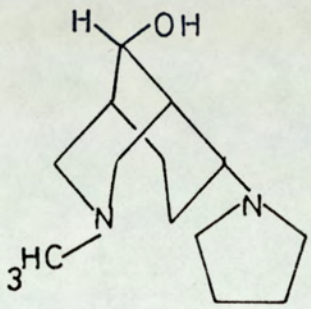
An intermediate comparable to (95a) has been suggested to explain the conversion of benzoyl chloride to benzaldehyde on reaction with tropine and alkali.[70] It has also been shown[58] that the unsubstituted 3-methyl-3-azabicyclo[3.3.1]nonan-syn-9-ols showed a detectable degree of hydrogen-bonding in dilute carbon disulphide, whereas their anti-isomers exhibited only free hydroxyl absorption. The alcohol (77) on dilution to 0.0025M in carbon disulphide showed only free hydroxyl absorption in the infrared at 3610 cm.$^{-1}$ The resistance to esterification under mild conditions and the absence of any intramolecular hydrogen-bonding indicate that the alcohol (77) possesses a hydroxyl group anti to the methylamino group and syn to the pyrrolidine. A p-nitrobenzoate ester (97) was prepared from the alcohol (77) by reaction of its lithium alkoxide salt with p-nitrobenzoyl chloride.

Various chemical methods were attempted to prove the structure of the alcohol (77). The reaction with chloroacetyl chloride failed to yield the desired ester and therefore no attempt could be made at preparing the lactone, which would have been possible had the hydroxyl group been syn to the methylamino group. Attempts to epimerise the alcohol with aluminium isopropoxide and isopropyl alcohol to the corresponding alcohol (78) gave only starting materials. All attempts to prepare the mesylate or

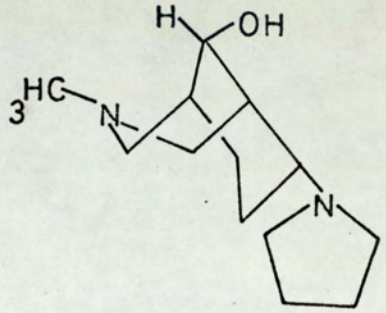
tosylate, and thus isomerise the alcohol, yielded unreacted starting material. The mass spectrum and NMR spectrum are discussed in their respective sections. The structure of alcohol (77) is therefore represented, as far as its configuration is concerned by (77).



(77b)



(77)



(77c)

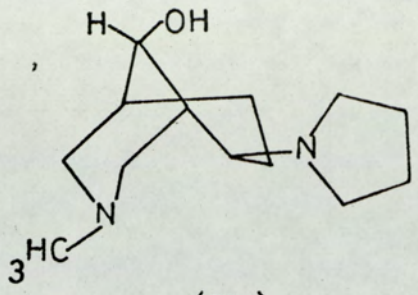
The carbocyclic ring with the 6α-pyrrolidine group is almost certainly in a chair form as shown. Any departure from this towards a flattened or boat form is shown by models to introduce further steric crowding of the 6α-cycloalkylamino group with the $4CH_2$ and methylamino group. Puckering of the ring is shown by models to increase the interaction between the methylamino group and the $7CH_2$ position. The heterocyclic ring can relieve this interaction by adopting either a half-chair (77b), or a boat form (77c).

It has been demonstrated by X-ray and other methods [71-75] that, contrary to earlier qualitative expectations, several compounds having two hydrogen atoms at the hindered endo-positions at atoms

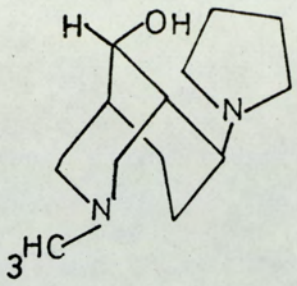
3 and 7 or one hydrogen atom and one lone-electron pair, exist preferentially in conformations analogous to (77), but with partly flattened chairs. In view of this, and because the presence of the 6α-cycloalkylamino group prevents the carbocyclic ring from flattening, the structure of the alcohol (77) is best represented by (77b) or (77c).

The reduction product residue remaining after removal of the alcohol (77), on subjection to the mild esterification procedure, [58] yielded a colourless precipitate, shown to be the dihydrochloride salt (98) of an alcohol isomeric with the amino-alcohol (77). Basification of the dihydrochloride (98) yielded the parent base (79) which was shown to have a retention time on glc identical to that of alcohol (77). Melting point, mixed melting point, tlc, mass spectrum and NMR data all showed this alcohol to be a single isomer and not an impure sample of the amino-alcohol (77). This alcohol was therefore also resistant to the mild esterification procedure and must have the hydroxyl group anti to the methylamino group and syn to the pyrrolidine group. On dilution infrared at 0.0025M in carbon disulphide, both free and intramolecularly hydrogen-bonded hydroxyl absorption were observed at 3610 and 3335 $cm.^{-1}$ Since the hydroxyl group is syn to the pyrrolidine group, which must now be axial, the intramolecular hydrogen-bonding must arise as a result of the

proximity of the hydroxyl group to the pyrrolidine group. This isomer was isolated in 15% yield of the total reduction mixture, which would be expected, because the 6β-cycloalkylamino ketone isomer is produced in only 20-25% of the total ketone mixture. A study of stereochemical models shows that in the idealised dichair form, this isomer would exist entirely in a hydrogen-bonded form. However, this is found to be a sterically overcrowded conformation with strong interactions between the pyrrolidine group and both the 5CH and $8CH_2$ functions. The hydroxyl group being seen to exist largely in a non hydrogen-bonded form, would indicate a departure from the ideal chair form of the carbocyclic ring of this isomer. The steric overcrowding can be relieved by a flattening of this ring to give a skew form (79a) which is probably the preferred form, and accounts for the large proportion of free hydroxyl absorption in the infrared. Since some intramolecular hydrogen-bonding is observed, the presence of a structure (79b) is indicated. The heterocyclic ring is most likely in a chair form since the flattening of the carbocyclic ring would relieve any strain due to the interaction of the methylamino group and the $7CH_2$ group. In addition, any flattening of the heterocyclic ring would introduce a serious flagpole interaction between the methylamino group and the 9CH position.

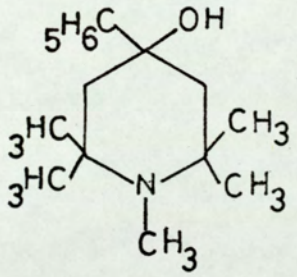


(79a)

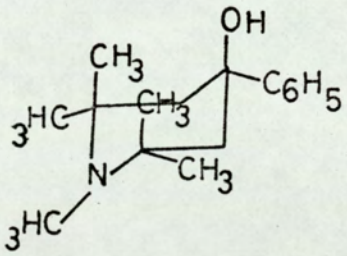


(79b)

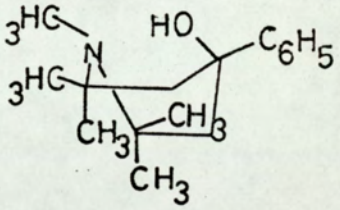
The intramolecular hydrogen bond is seen to be as strong as that produced by 1,2,2,6,6-pentamethyl-4-phenylpiperidin-4-ol (99) [80] which shows bands due to both free and intramolecularly hydrogen-bonded hydroxyl absorption in the infrared. The $\Delta \nu$(OH) value which is related to the strength of the hydrogen bond is 205 cm.$^{-1}$ for alcohol (99) and 275 cm.$^{-1}$ for alcohol (79).



(99)



(100)



(101)

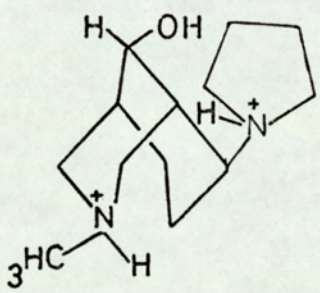
The strain resulting from the presence of three axial groups in the chair conformation (100) is so great that the molecule adopts the boat form (101). Several open chair amino-alcohols show both free and intramolecular hydrogen-bonding to a similar degree (see table 1). [76]

Table 1

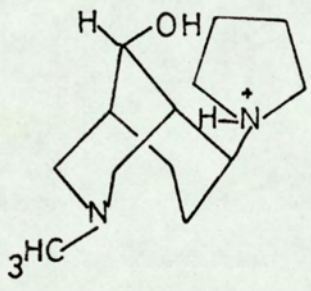
Amino alcohol	Free ($cm.^{-1}$)	Bound ($cm.^{-1}$)	$\Delta\nu$(OH) ($cm.^{-1}$)
$(C_2H_5)_2N(CH_2)_2OH$	3630	3477	153
$(C_2H_5)_2NCH_2CHOHCH_3$	3600	3468	132
$(nC_3H_7)_2N(CH_2)_2OH$	3629	3497	132
$(nC_4H_9)_2N(CH_2)_2OH$	3631	3497	134
$(C_2H_5)_2N(CH_2)_3OH$	3628	3288	340
$(nC_3H_7)_2N(CH_2)_3OH$	3632	3304	328

The dihydrochloride (98) on infrared analysis showed a medium intensity band at 1630 $cm.^{-1}$ Analysis showed the presence of a hydrate. However, on preparing the monohydrochloride (102) for an NMR study, the same band was present, although analysis showed the molecule was not hydrated. The dihydrochloride (103) of alcohol (77) showed no such band. This absorption is in the correct region and of sufficient intensity to be assigned to the in-plane bending vibration of a water molecule and such a band is known for the infrared spectra of hydrated salts.[77,78,79] It is possible that the band arises from the presence of a "pseudo-water molecule" in this compound. This could result from an intramolecular hydrogen-bond from the hydrogen on the pyrrolidine

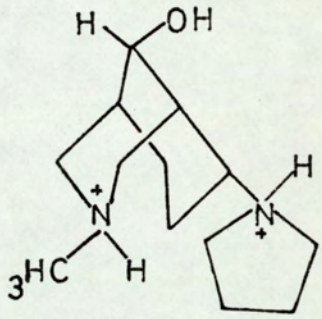
nitrogen to the oxygen of the hydroxyl group which is suitably placed (102). NMR and pKa data show that the amino-alcohols (79) and (77) protonate first on the pyrrolidine nitrogen. This further confirms the position of the pyrrolidine syn to the hydroxyl function in the alcohol (79). The dihydrochloride (103) does not show this absorption, presumably because the distance between the hydroxyl group and the proton on the α-pyrrolidine nitrogen is too great for intramolecular hydrogen-bonding to occur.



(98)

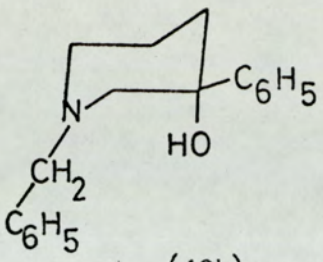


(102)

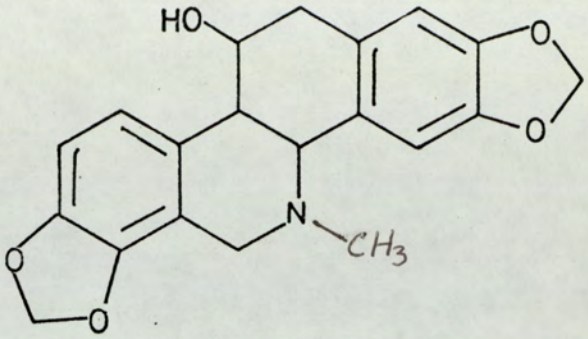


(103)

The presence of such a band for piperidinol hydrochlorides has not been reported in the literature. Several compounds known to show hydrogen bonding to nitrogen could show this band in the infrared spectrum of their hydrochlorides. Two such compounds are N-benzyl-3β-hydroxy -3α-phenylpiperidine (104) and chelidonine (105).[80]



(104)

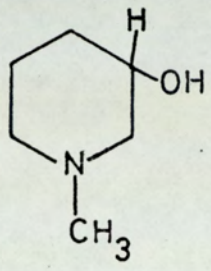


(105)

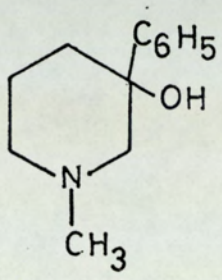
N-Benzyl-3β-hydroxy -3α-phenylpiperidine (104) was prepared by reaction of the Grignard obtained from bromobenzene on N-benzyl-3-piperidone. On recrystallisation only one isomer was obtained, which showed intramolecular hydrogen-bonded hydroxyl only at 3480 cm.$^{-1}$ indicating it was the 3β-hydroxy compound, and not the 3α-hydroxy which could not show this intramolecular hydrogen bonding. N-Methyl-3-hydroxypiperidine (106) shows bands in the infrared at 3623 and 3539 cm.$^{-1}$ due to the presence of a mixture of α- and β-alcohols. 3-Hydroxy-1-methyl-3-phenylpiperidine (107) shows one band at 3496 cm.$^{-1}$ due to intramolecular hydrogen bonding which is in close agreement with the result for the amino-alcohol (104). The hydrochloride (108) prepared from the alcohol (104) did not show any absorption in the 1610-1700 cm.$^{-1}$ region. This could be caused by the hydrogen bond in alcohol (104) being weaker than that in alcohol (79) and therefore the distance between the hydroxyl group and the proton on the nitrogen is too great for the bond to be formed. This indicates that stringent steric

requirements are necessary for the formation of this bond.

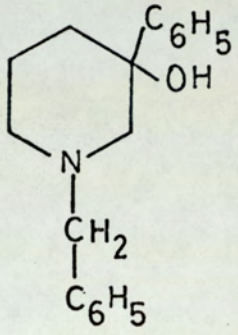
Chelidonine was converted to the hydrochloride but again no band was observed in the 1610-1700 cm.$^{-1}$ region.*



(106)

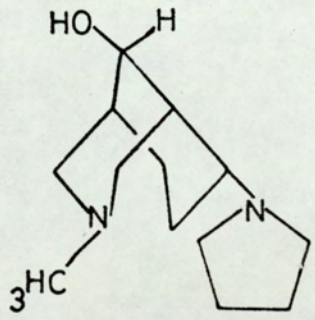


(107)

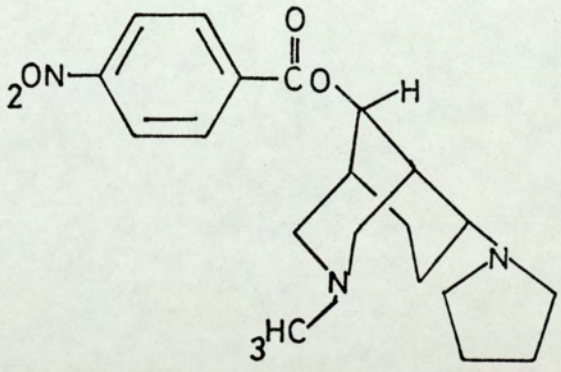


(104)

The chloroform solution from the esterification reaction, after the removal of the dihydrochloride (98) gave the expected p-nitrobenzoate (109). Acid hydrolysis of this ester gave the alcohol (78), isomeric with alcohols (77) and (79).



(78)



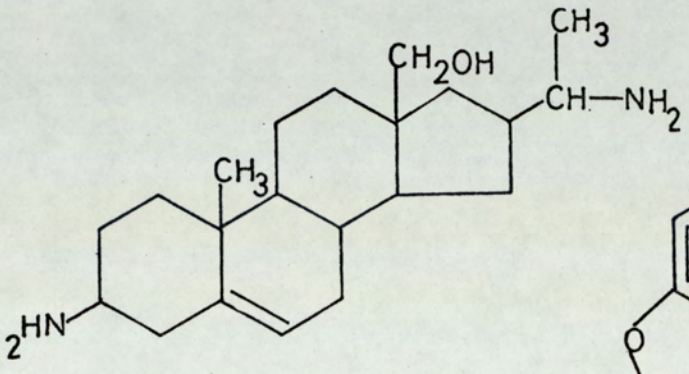
(109)

Glc showed this alcohol to be a fast-moving component of the reduction mixture. Because of the ease of esterification, this alcohol must have the hydroxyl group syn to the methylamino group.

* See addendum, p.200.

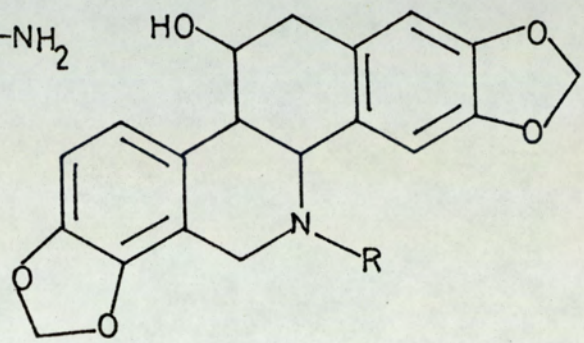
This then facilitates the intramolecular acyl transfer (see page 40). On dilution to 0.0025M in carbon disulphide, this alcohol exhibits no free hydroxyl absorption in the infrared but only strongly bound hydroxyl absorption at 3200 cm.$^{-1}$ The complete absence of any free hydroxyl and the large shift in the hydroxyl absorption (free hydroxyl absorption being at about 3610 cm.$^{-1}$) at this dilution ($\Delta \nu(OH) \simeq 400$ cm.$^{-1}$) indicate a very strong hydrogen bond. Hydrogen-bonding of this magnitude has been reported for relatively few compounds. [80]

3α-Hollarhidin (110) and 3β-hollarhidin (111) [81] show a shift of about 350 cm.$^{-1}$ and the steroidal compound (112) shows a shift of 303 cm.$^{-1}$ 2-Hydroxydiphenylamine shows a shift of 416 cm.$^{-1}$ Norchelidonine (113) [82] shows only bound hydroxyl at 3210 cm.$^{-1}$ and chelidonine (114) shows a shift of 410 cm.$^{-1}$ The steroidal compounds (115) also show a large shift. All these examples have a rigid structure with the hydroxyl group held in close proximity to a nitrogen atom. However, the alcohol (78) can only give rise to an intramolecular hydrogen bond by the existence in this isomer of the heterocyclic ring in a boat form. The corresponding 3-methyl-3-azabicyclononan-9-ols without a 6-substituent, and with the hydroxyl group syn to the methylamino group, showed a detectable amount of intramolecular hydrogen-bonding on dilution in carbon



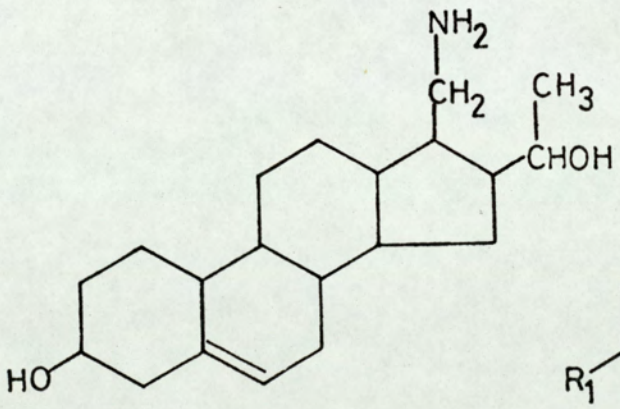
(110) 3α-NH_2

(111) 3β-NH_2

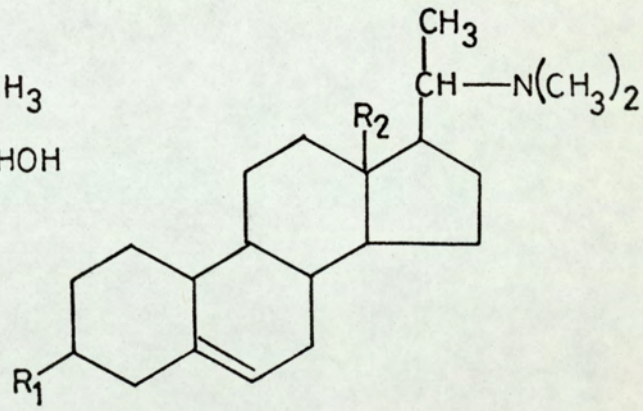


(113) R = H

(114) R = CH_3



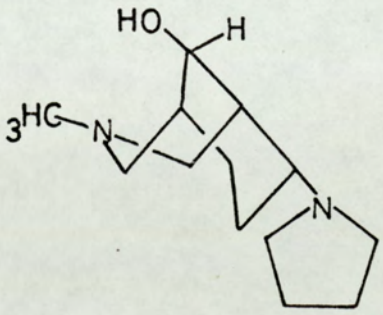
(112)



(115)

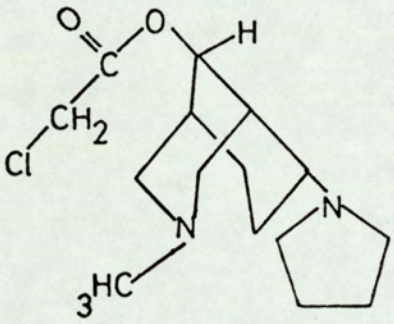
R_1	R_2	ν(OH)
α-$N(CH_3)_2$	CH_2OH	487
β-$N(CH_3)_2$	CH_2OH	485
α-$N(CH_3)_2$	$CH(OH)CH_3$	436
β-$N(CH_3)_2$	$CH(OH)CH_3$	467

disulphide. It was concluded [58,59] that the energy gained by the formation of an intramolecular hydrogen-bond would not be sufficient to force the piperidine ring into a boat conformation unless the boat form is favoured because of appreciable steric repulsions which exist in the chair form. [83,84,85] However, when a cycloalkylamino group is placed in the 6α-position, it is seen from stereochemical models that severe steric crowding results. There is an interaction between the 6α-substituent and the $4CH_2$ in addition to the methylamino group. The interaction of the 6α-amino group and the heterocyclic ring could be relieved by a puckering of the chair form, but this would increase the interaction between the methylamino group and the $7CH_2$ position. The interaction between the pyrrolidine group and the $4CH_2$ and methylamino group as well as the methylamino and $7CH_2$ interaction can all be relieved by the heterocyclic ring adopting a boat form (78a).

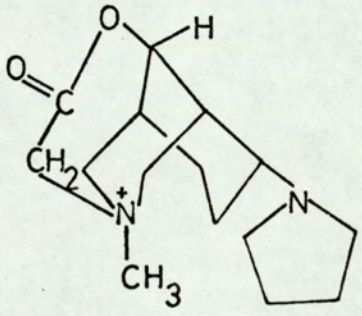


(78a)

Further evidence which points to the pyrrolidine group in alcohol (78) being in the α-position, is its isolation in a proportion of the reduction mixture greater than the alcohol (79), and comparable with the amount of alcohol (77). This indicates the origin of the alcohol being the amino-ketone (75). Chemical attempts to prove the presence of the hydroxyl group syn to the methylamino group involved the preparation of the chloroacetate (116). Attempts to form the lactone (117) from the chloroacetate yielded only the amino-alcohol (78).

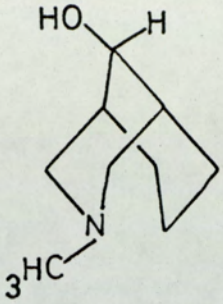


(116)

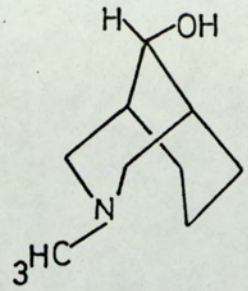


(117)

This reaction sequence has been used [86] to determine unequivocally the stereochemistry of certain 3-azabicyclo[3.3.1] nonanols (118) and (119) and also to assign stereochemistry to the N-alkylated products derived from various tropane derivatives. [87]

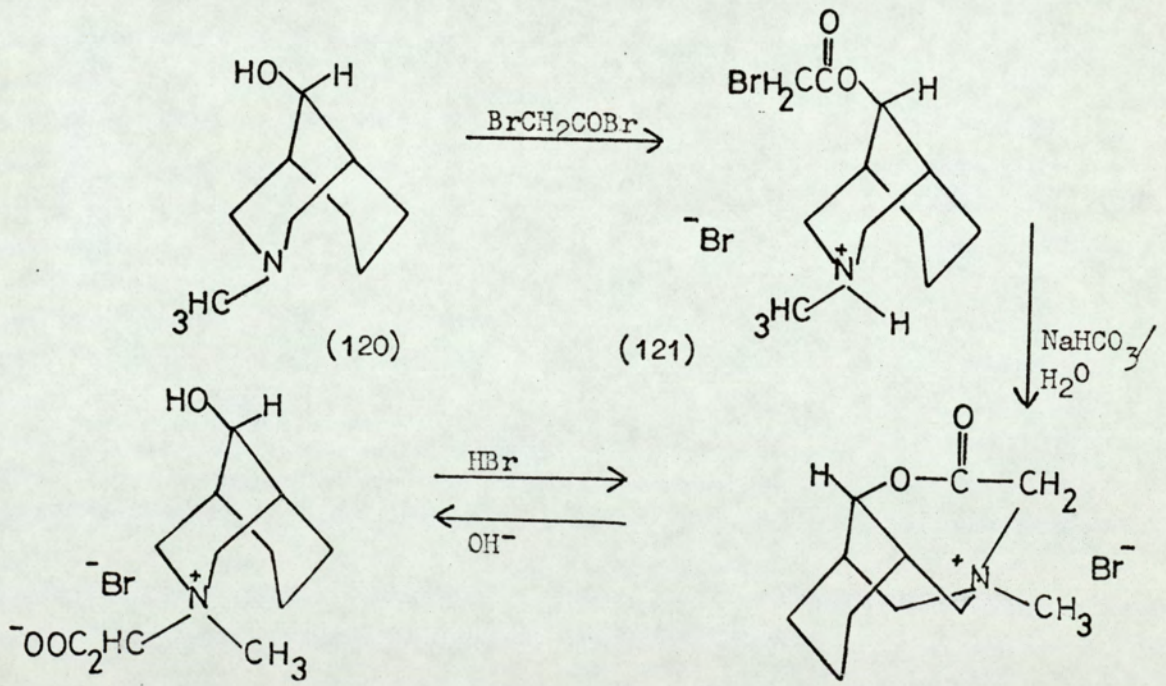


(118)



(119)

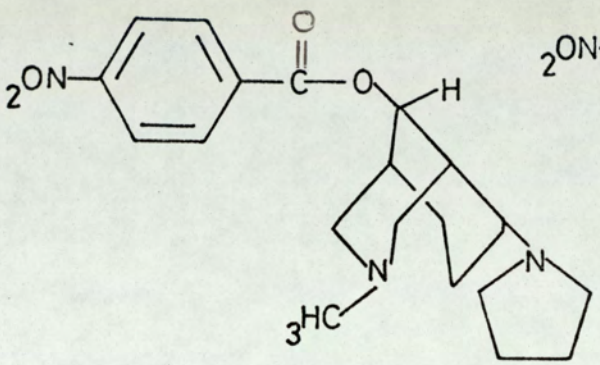
The amino-alcohol (120) reacted with bromoacetyl bromide to give the ester hydrobromide (121) which on neutralisation gave the lactone (122) which could be reversibly converted to the betaine (123).



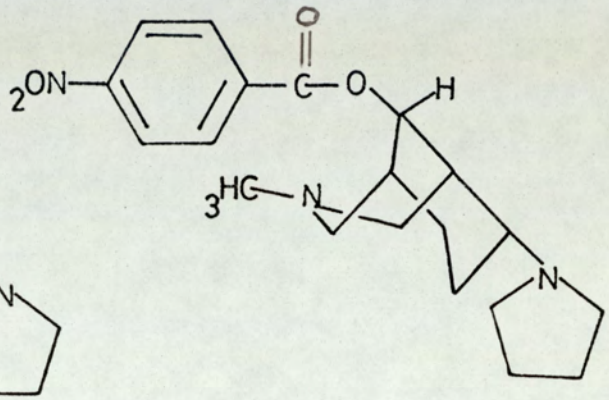
(120) (121) (123) (122)

The ease of hydrolysis of the chloroacetate (116) may be explained by a backside displacement by nitrogen in a mechanism similar to that for intramolecular acyl transfer.

The p-nitrobenzoate ester (109) is not believed to exist with the heterocyclic ring in the boat form (109a). This is concluded from the UV spectrum of the ester (109) which is identical to the absorption of the p-nitrobenzoate ester (97) and of ethyl p-nitrobenzoate.

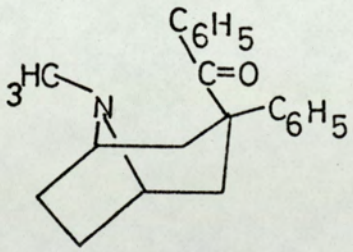


(109)



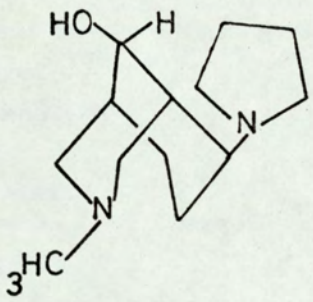
(109a)

Such an interaction has been demonstrated for the tropine derivative (124).[69] The heterocyclic ring in the ester (109) must adopt the chair form presumably to relieve the severe crowding obtained in the boat form due to the bulky p-nitrobenzoate group.

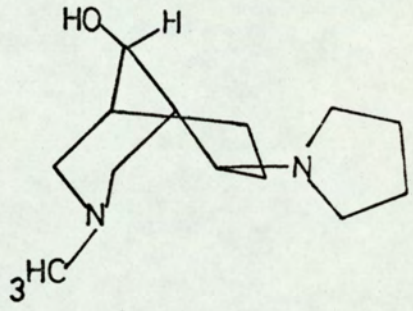


(124)

During a large scale preparation of the ester (109), a very small amount of an alcohol was obtained. This was found to be isomeric with the alcohols (77), (78) and (79). Tlc showed it to be pure and glc showed it to have the same retention time as the alcohol (78). Insufficient material was obtained for a dilution infrared study but its accurate mass determination and melting point showed it to be the fourth alcohol (80). This alcohol was also resistant to the esterification procedure employed and also had the highest melting point (215°) of the four isomeric alcohols.



(80)



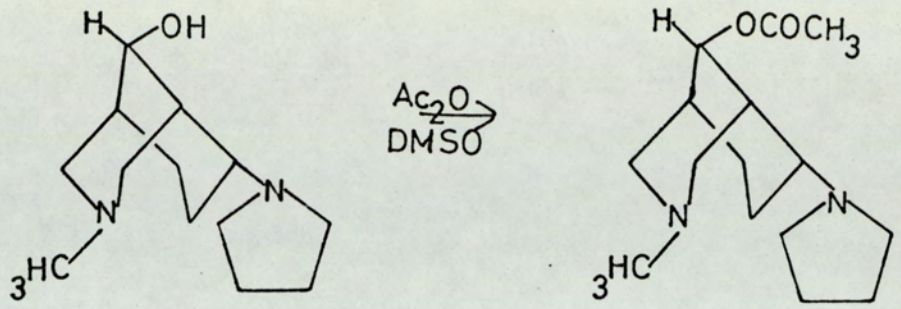
(80a)

Both these facts indicate that in this isomer the heterocyclic ring is in a chair or near chair form and therefore unable to allow hydrogen bonding between the hydroxyl group and the methylamino group. However, the carbocyclic ring is unlikely to be in a chair form because the 6β-cycloalkylamino group causes severe steric overcrowding in this conformation, with interactions between the C5 and C8 hydrogens . This steric overcrowding can be

overcome (as with alcohol 79) by a flattening of the carbocyclic ring to give a skew form (80a) which is probably the preferred form. The heterocyclic ring is most likely in a chair form since the flattening of the carbocyclic ring would relieve any strain due to interaction between the methylamino group and the $7CH_2$ position. This is further indication that the production of an intramolecular hydrogen bond alone is insufficient to force a piperidine ring into the boat form.

The melting points of the alcohols may be useful guides to their stereochemistry. Alcohol (80) of which there was insufficient for a dilution infrared study had the highest melting point (215°) and was expected to exist in a non hydrogen-bonded form. Alcohol (77) also had a high melting point (170°) and shows only free hydroxyl absorption in the infrared. The alcohol (79) shows both free and intramolecularly bonded hydroxyl in the infrared and has a lower melting point of 135°. The alcohol (78) which shows only intramolecular hydrogen-bonding in the infrared has the lowest melting point of 60°.

Attempts to prepare the ketone (75) by chromic oxidation of the alcohol (77) resulted only in unchanged starting material. An alternative method of oxidation using acetic anhydride in dimethyl sulphoxide gave the acetate (125).

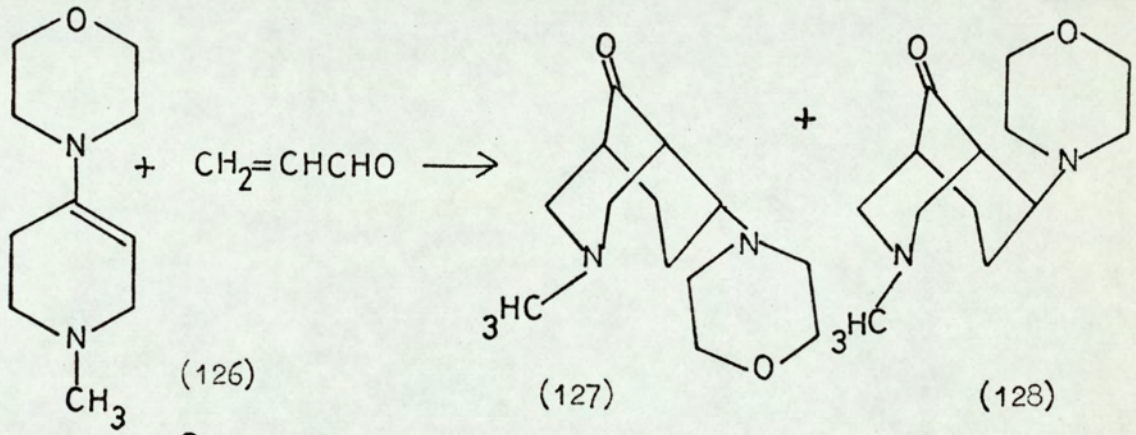


(77) (125)

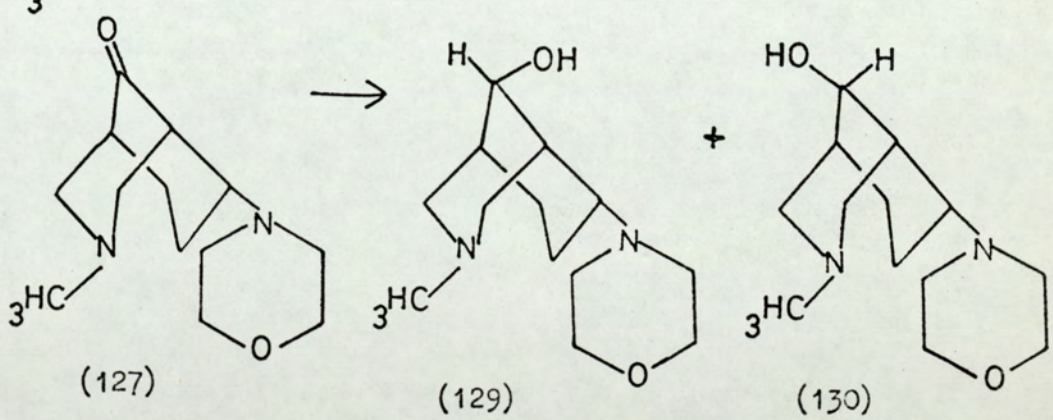
Ruthenium tetroxide oxidation of the alcohol resulted in an intractable tar from which no product could be isolated.

2. Morpholine derivatives

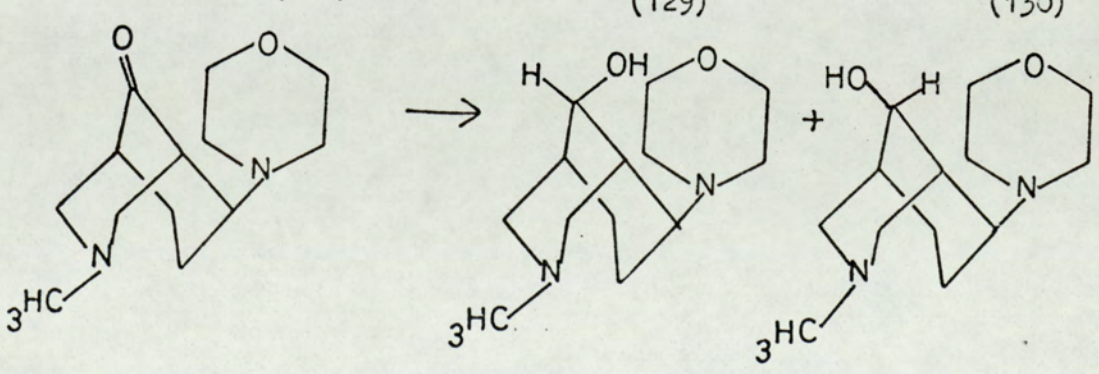
The reaction between acrolein and the morpholine enamine of N-methyl-4-piperidone (126) gave the expected mixture of ketones (127) and (128). The ketones were not separated but reduced to the alcohols and worked up in an identical fashion to that previously described for the 6α- and 6β-pyrrolidinyl ketones (75) and (76). The work-up yielded three of the four possible alcohols (129), (130), (131) but not alcohol (132).



(126) (127) (128)

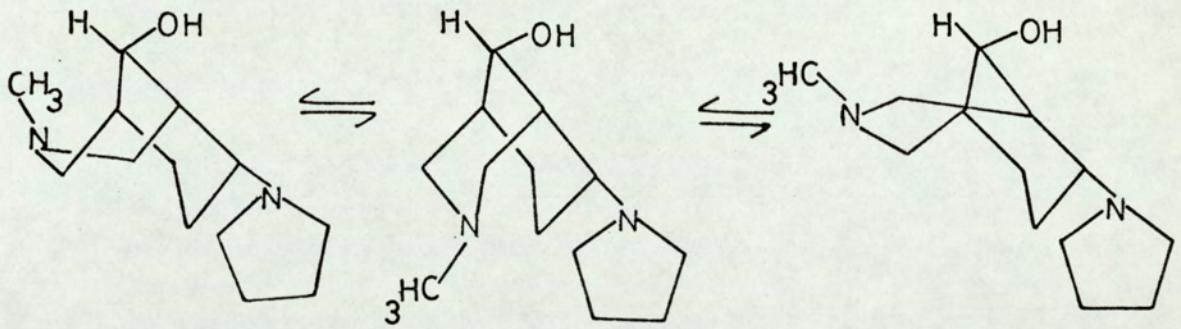


(127) (129) (130)

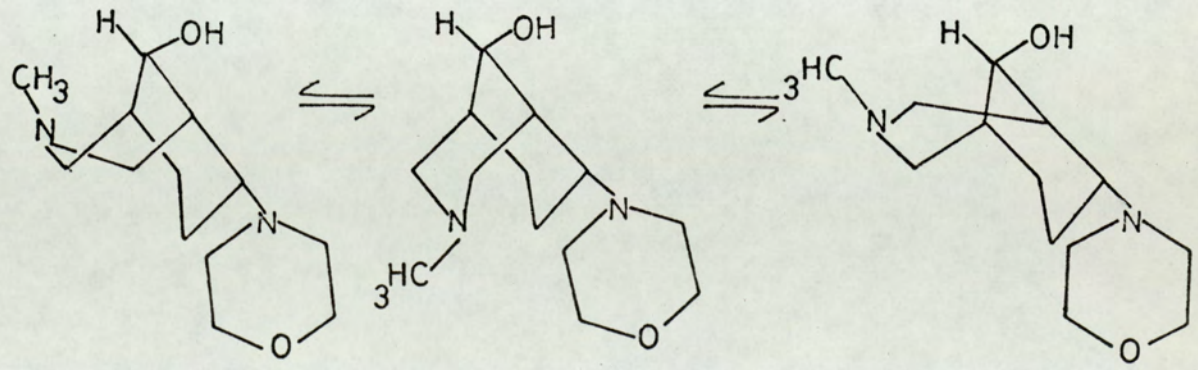


(128) (131) (132)

Alcohol (129) was obtained by fractional crystallisation of the crude reduction mixture and on dilution infrared in carbon disulphide at 0.0025M, only free hydroxyl absorption was observed at 3610 cm.$^{-1}$ This alcohol proved resistant to the mild esterification procedure using p-nitrobenzoyl chloride in chloroform. By analogy with the pyrrolidine derivatives this alcohol can be assumed to have the same conformation as alcohol (77) with the heterocyclic ring in a skew or boat form, the carbocyclic ring in the chair form, and the hydroxyl group syn to the morpholine substituent, which is in an equatorial position.



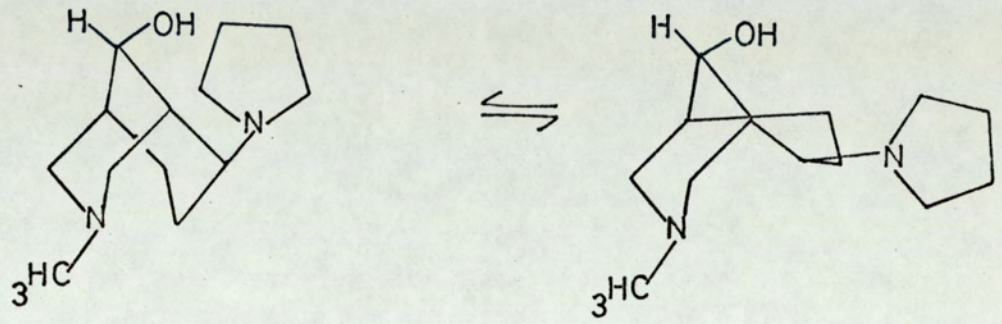
(77)



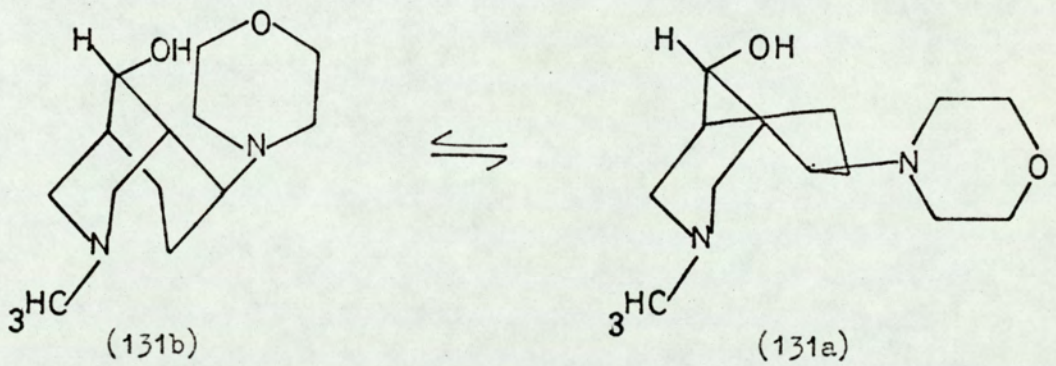
(129)

The amino-alcohol (131) was obtained by basification of the dihydrochloride salt (133), which was precipitated when the reduction mixture, after the removal of alcohol (129), was subjected to the mild esterification procedure.[58] The dihydrochloride while hydrated showed a peak in the infrared at 1630 cm.$^{-1}$, but after drying at 110°, the peak was no longer observed in the infrared spectrum. In the hydrated form the in-plane bending vibration due to the "pseudo-water molecule" may have been possible by an intramolecular bond between the hydrogen on the nitrogen and the oxygen of the water molecule, holding the water in a tight bond. That no band at 1630 cm.$^{-1}$ was seen after drying could again indicate that the steric requirements for this band to be produced are quite stringent. This alcohol (131) was resistant to the mild esterification procedure and on dilution infrared in carbon disulphide at 0.0025M showed absorption due to both free and intramolecular hydrogen-bonding hydroxyl at 3610 and 3480 cm.$^{-1}$ By analogy with the pyrrolidine derivatives this alcohol can be assumed to have the same conformation as alcohol (79) with the heterocyclic ring in a chair form, the morpholine group axial and the carbocyclic ring in a flattened or skew form (131a) but with structure (131b) also present, allowing the intramolecular hydrogen-bonding. The intramolecular hydrogen bond in this alcohol

(131) ($\Delta\nu$(OH) = 130 cm.$^{-1}$) is not as strong as in the pyrrolidine series ($\Delta\nu$(OH) = 275 cm.$^{-1}$). This could be because the larger bulk of the morpholine group does not allow as close a fit as the pyrrolidine group to the hydroxyl group.

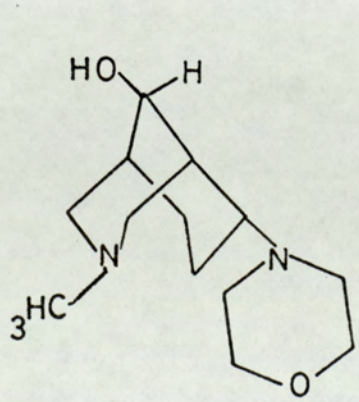


(79)

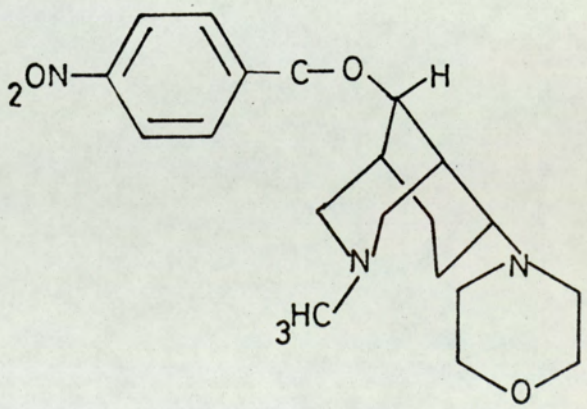


(131b) (131a)

Alcohol (130) was obtained by acid hydrolysis of the ester (134) which was formed by the mild esterification procedure.

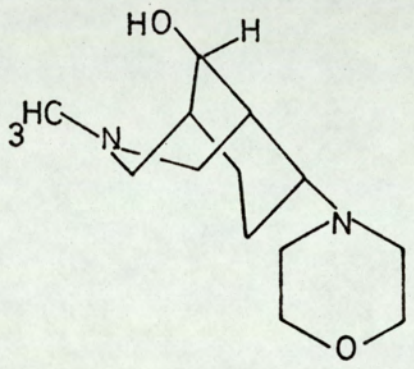


(130)



(134)

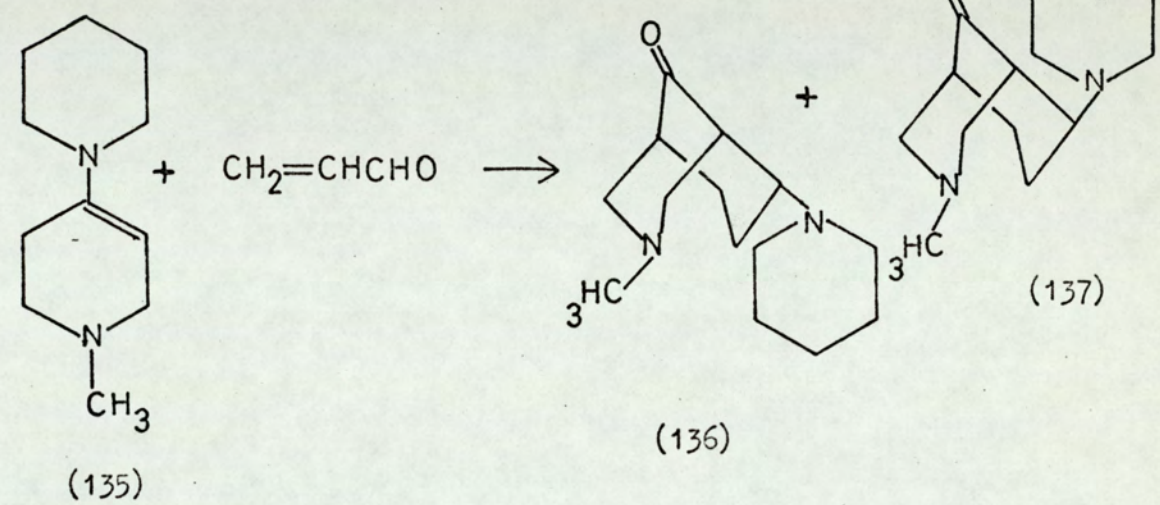
The ease of esterification and the presence in the infrared of only intramolecular hydrogen-bonded hydroxyl absorption at 3200 cm.$^{-1}$ point to this alcohol having the same conformation (130a) as the corresponding alcohol (78) in the pyrrolidine series. The heterocyclic ring is in a boat form, the hydroxyl group anti to the morpholine group and the morpholine in an equatorial position.

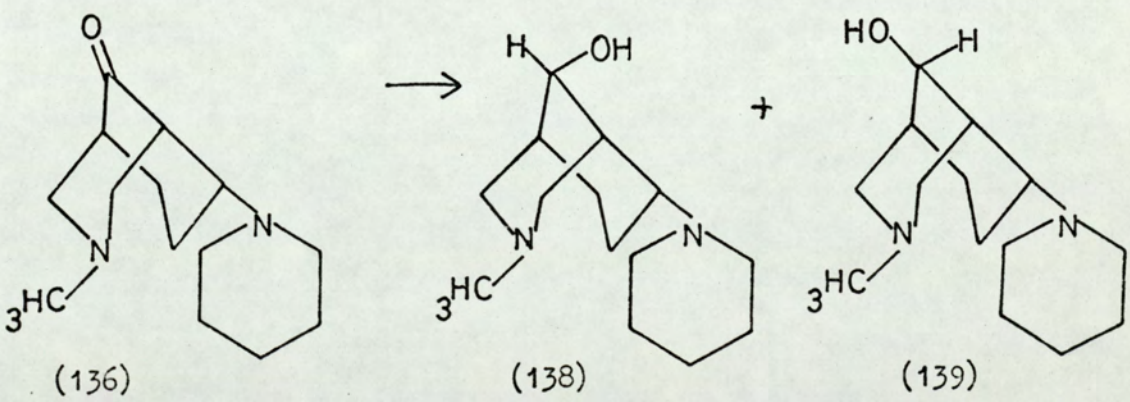


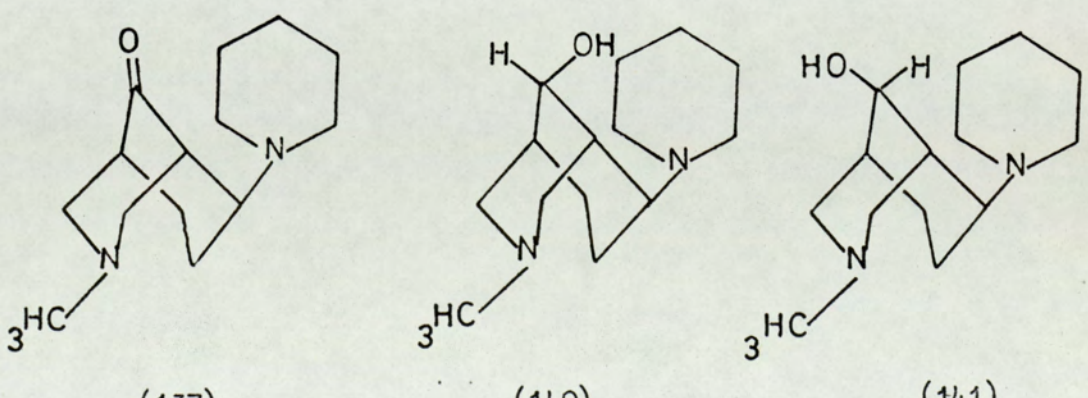
(130a)

3. Piperidine derivatives

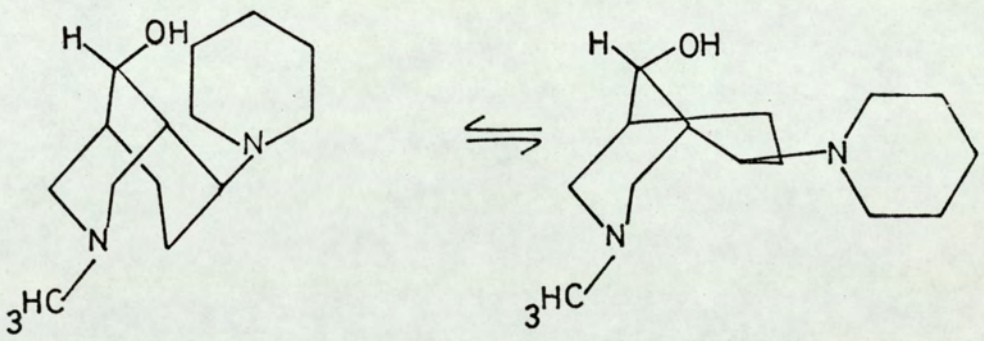
In a similar manner to that described for the pyrrolidine and morpholine derivatives, the reaction between acrolein and the piperidine enamine of N-methyl-4-piperidone (135) gave the mixture of ketones (136) and (137). The ketones were not separated but reduced to a mixture of isomeric alcohols.







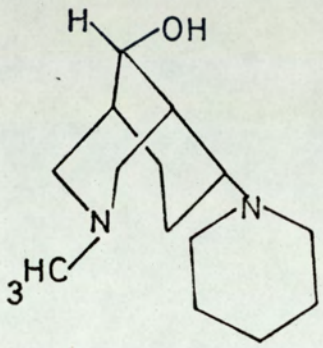
The crude reduction mixture failed to yield a crystalline isomer as occurred with the pyrrolidine and morpholine series. However, on subjection of the reduction mixture to the mild esterification procedure,[58] a crystalline dihydrochloride (142) was obtained. On basification the parent alcohol (140) was obtained. The dihydrochloride, as occurred with the dihydrochloride of alcohol (131) in the piperidine series, showed a peak at 1630 cm.$^{-1}$ while hydrated, but this was removed after drying at 110°, indicating that the stringent steric requirements had not been fulfilled for the formation of a "pseudo-water molecule." This could possibly be because of the increased bulk of the piperidine group when compared to pyrrolidine.



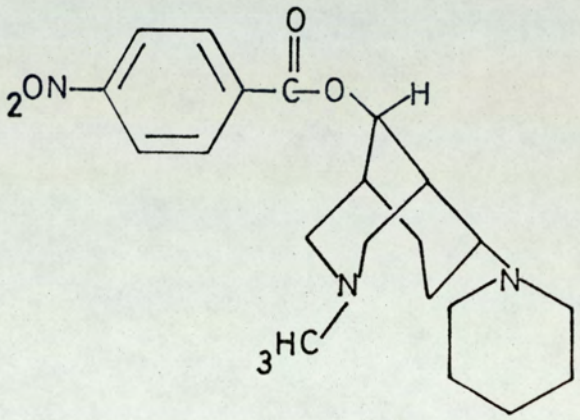
(140b) (140a)

The alcohol (140) must have been resistant to the mild esterification procedure and on dilution infrared showed both free and intramolecular hydrogen-bonding at 3610 and 3335 cm.$^{-1}$ This points to the alcohol having the same conformation as the

pyrrolidine alcohol (79) and the morpholine alcohol (131) with the carbocyclic ring in a skew form (140a) but with some structure (140b) present, accounting for the intramolecularly bound hydroxyl in the infrared.

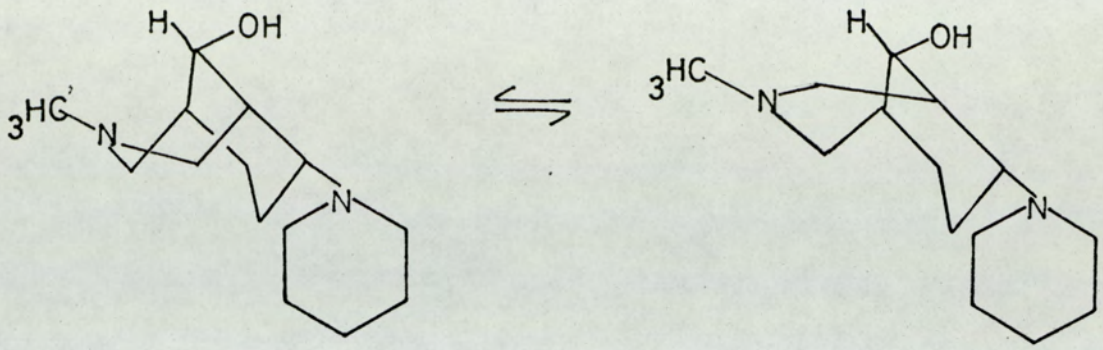


(138)



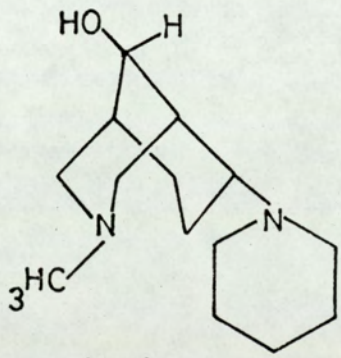
(143)

The esterification mixture after removal of the dihydrochloride (142) yielded the alcohol (138) and the ester (143) by fractional crystallisation. The alcohol (138) was resistant to the mild esterification procedure and on dilution infrared showed absorption due to free hydroxyl only at 3610 $cm.^{-1}$ By analogy with the pyrrolidine and morpholine series, this alcohol would be expected to have the carbocyclic ring in a chair form, the piperidine group equatorial, the hydroxyl group syn to the piperidine and the heterocyclic ring in a skew or boat form (138a).

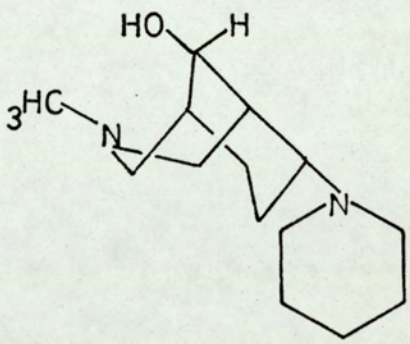


(138a)

The ester (143) on acid hydrolysis yielded the alcohol (139). The conformation of this alcohol follows from its ease of esterification and the presence of only intramolecularly bound hydroxyl absorption on dilution infrared analysis. This alcohol must exist with the heterocyclic ring in a boat form, the hydroxyl group anti to the piperidine ring and the piperidine ring in an equatorial position (139a).



(139)



(139a)

The fourth possible alcohol (141) was not isolated.

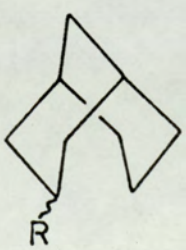
In each of the three series of alcohols it is seen that the alcohol exhibiting only intramolecularly bound hydroxyl on dilution infrared analysis (78, 130, 139) has in each case the lowest melting point in that series. The highest melting point alcohols show in

each case only free hydroxyl absorption (77, 80, 129, 138) and those alcohols exhibiting both free and intramolecular hydrogen-bonding have intermediate melting points (79, 131, 140).

The pairs of syn-alcohols (77 and 79), (129 and 131) and (138 and 140) all showed the same retention times on glc and the anti-alcohols (78, 80, 130 and 139) had a shorter retention time. Thus the retention time on glc is determined not only by hydrogen-bonding but by the orientation of the hydroxyl group towards the cycloalkylamino group. It has been reported [88] that amino alcohols which exhibit substantial intramolecular hydrogen-bonding are eluted from a Carbowax 20M gas chromatography column much more rapidly than their epimers, which do not exhibit significant intramolecular hydrogen-bonding. In the present study, the amino-alcohols showing strong intramolecular hydrogen-bonding were eluted faster than their epimers but the alcohols showing both free and intramolecular hydrogen-bonding were eluted at the same rate as the alcohols showing no intramolecular hydrogen-bonding at all. This indicates that the strength of the hydrogen bond is important in determining the rate of elution of the amino alcohols.

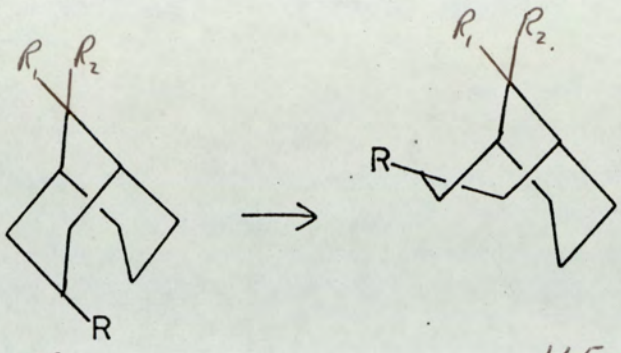
The present study in the azabicyclononane system shows that an α-substituent in the 2(4, 6, 8) position exerts a transannular effect and forces the ring to which it is not

attached into a boat form (alcohols 77, 78, 129, 130, 138, 139). The ring to which the α-substituent is attached cannot become flattened without introducing further steric crowding of the 6α-group with the $4CH_2$ and methylamino group. Puckering of the ring only suffices to increase the interaction between the methylamino group and the $7CH_2$ position. However, the heterocyclic ring can relieve this interaction by adopting a boat form. This effect is absent in the 6β-substituted compounds (79, 80, 131, 140) and the substituent exerts an effect on the ring to which it is attached. Flattening of the ring reduces the $7CH_2$ and methylamino interaction and also reduces the 5CH and $8CH_2$ interaction. The ring to which it is not attached stays in the chair form because the interaction between the methylamino group and the $7CH_2$ position is reduced and because any boat conformer will introduce a further interaction between the 9CH position and the methylamino group. The discovery that substituents on a bicyclononane ring can force one of the rings into a boat form has been shown with 3-substituted bicyclononanes (144).[88,89,90,91]



R = CH, Br, CH_3, COOH

(144)



145 R = Cl.
146 $R_1 R_2$ = O.

(144)

145a R = Cl.
147 R = Cl, $R_1 R_2$ = O

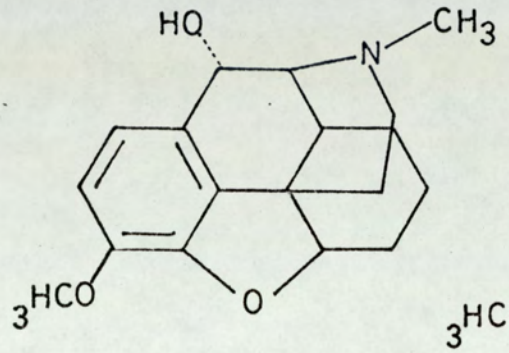
The ring with the substituent is found to adopt a chair form if the substituent is in an α-position. However, a β-substituent forces the ring to which it is attached to adopt a boat conformation. An α-substituent (R) has interaction with C2 and C4 hydrogens but any tendency towards a boat form for the ring would introduce a severe interaction between the C3 and C9 hydrogens. Puckering of the ring would only increase the interaction between the $3CH_2$ and the $7CH_2$ groups. However, a β-substituent has a severe interaction with the C7 hydrogen which can be relieved by either ring adopting a boat form. If the ring to which the substituent is not attached adopts a boat form then interactions are introduced between the substituent (R) and both the 6CH and 8CH positions which are likely to be greater than the initial interactions. If the ring to which the substituent is attached adopts a boat form then the interaction between the substituent and the 7CH position is replaced by interactions between the C2 and C7 hydrogens and also between the C4 and C7 hydrogens which are likely to be less severe

and account for the ring adopting a boat form.

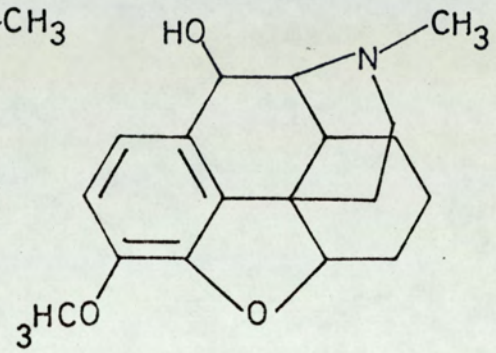
It has been reported that even in the presence of a bulky axial substituent at the 2-position, the bicyclo[3.3.1]nonan-9-one (145) appears to prefer the twin-chair conformation, [92] despite the absence of interaction between the 3CH and the 9CH groups in the boat form (145a). This has since been verified by X-ray analysis, [93] which showed that both the 2α- and 2β-substituted chloro-compounds (146) and (147) preferred the twin-chair conformation. Since the present study shows that a 2β-substituent forces the azabicyclo- and bicyclononane systems to have one ring in a boat form, this would indicate that the chlorine atom is not sufficiently bulky to force the ring to which it is not attached into a boat form. The much larger pyrrolidine, morpholine or piperidine ring however, causes more severe interactions resulting in the adoption of a boat-chair system.

The pKa values for each of the dibasic amino-alcohols (with the exception of alcohol (107) of which there was insufficient sample available) were obtained, in order to find a correlation with either the stereochemistry of the molecules or the intramolecular hydrogen-bonding. NMR proved that for both alcohols (77) and (79), the initial site of protonation was the pyrrolidine nitrogen. These alcohols have the pyrrolidine group in different

orientations (α- in alcohol (77) and β- in alcohol (79)) and therefore, because of the increased shielding of the pyrrolidine group in alcohol (79), might have been expected to protonate preferentially on the methylamino nitrogen.



(148)



(149)

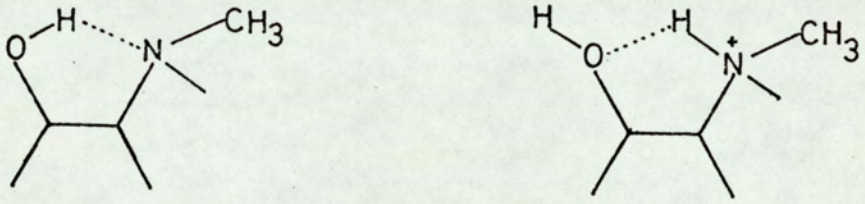
It can be seen that within each series of alcohols the spread of pKa values is not exceptionally large and a strict correlation between pKa and hydrogen-bonding or stereochemistry cannot be drawn. The 10-hydroxydihydrodesoxycodeine derivatives (148) and (149) showed a correlation between the hydrogen bonding and the pKa value.[94]

pKa Values of Amino-Alcohols.

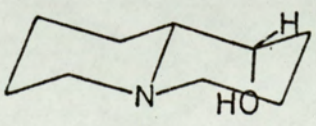
Amino alcohol	Hydrogen bonding	pKa in CH_3OH/H_2O
77, 129, 138	Free	a) 10.1, 6.1 c) 10.2, 6.2 b) 8.8, 5.0
78, 130, 139	Bonded	a) 10.1, 6.6 c) 10.1, 6.7 b) 8.6, 5.0
79, 131, 140	Free and Bonded	a) 9.9, 6.6 c) 9.8, 6.3 b) 8.0, 5.5

The trans-form (148) showed only free hydroxyl on dilution infrared at 3600 cm.$^{-1}$ whereas the cis (149) showed only intramolecularly bound hydroxyl at 3333 cm.$^{-1}$ However, the cis had a pKa of 9.41 compared with 7.71 for the trans. Hydrogen-bonding may be interpreted as base-weakening if it occurs in the amine form or base-strengthening if it occurs in the ammonium form, stabilising the ion (Fig. 8). [95]

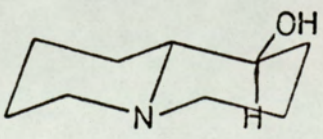
Figure 8



Since hydrogen-bonding is most probably greater to the ion than to the amine, [96] a base-strengthening effect would be expected and agrees with the above practical result. Another example of hydrogen-bonding increasing the pKa value is found in the 1-hydroxyquinolizidines (150) and (151). [97]



(150)

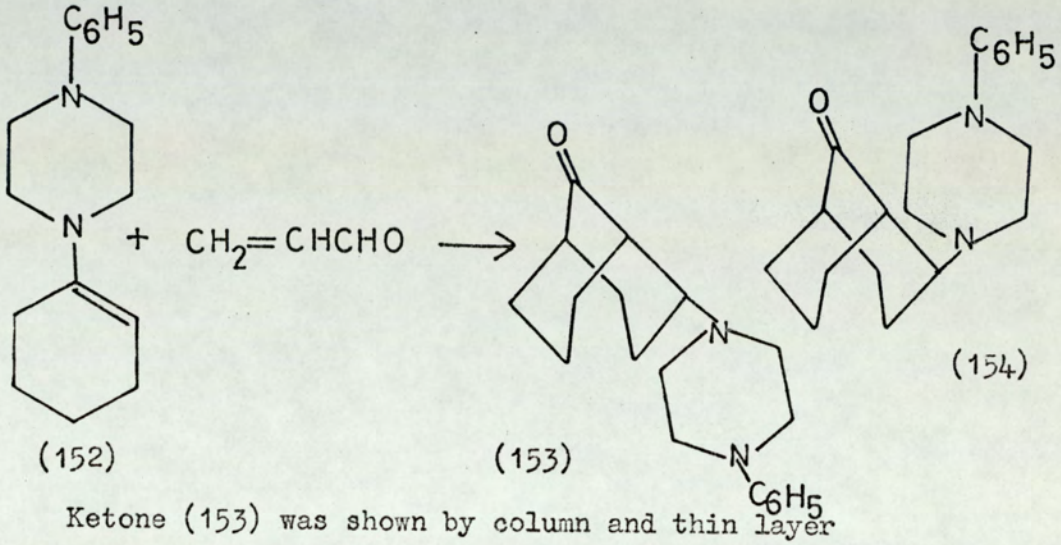


(151)

The alcohol (150) shows only intramolecularly bound hydroxyl at 3527 cm.$^{-1}$ whereas the alcohol (151) shows only free hydroxyl at 3609 cm.$^{-1}$ The free-hydroxyl containing alcohol (151) has a pKa of 8.7, whereas the alcohol exhibiting intramolecular hydrogen-bonding (150) has a pKa of 10.2. It has been shown however, [98] that hydrogen-bonding does not always increase base strength. Tropine, a stronger base than pseudotropine, has the trans configuration and pseudotropine the cis configuration and thus a sound interpretation of the differences between the base strengths of tropine and pseudotropine cannot be based upon a consideration only of the configuration of the hydroxyl group. It is possible that the strain imposed upon the ring system by the ethylene bridge is affected by the position of the hydroxyl group with respect to the bridge and thus the tendency for the nitrogen atom to assume the tetrahedral form by ionisation is affected by the configuration of the hydroxyl group. In a similar way the pKa of the azabicyclononan-9-ols may be determined not only by the extent of any intramolecular hydrogen-bonding but also by the amount of shielding of the amino group.

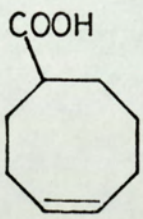
B. Synthesis of some 2-substituted bicyclo [3.3.1] nonanes.

The reaction between 1-(1-cyclohexen-1-yl)-4-phenylpiperazine (152) and acrolein in benzene at 10° has been reported [41] to give a mixture of bicyclic ketones (153) and (154).



(152) (153) (154)

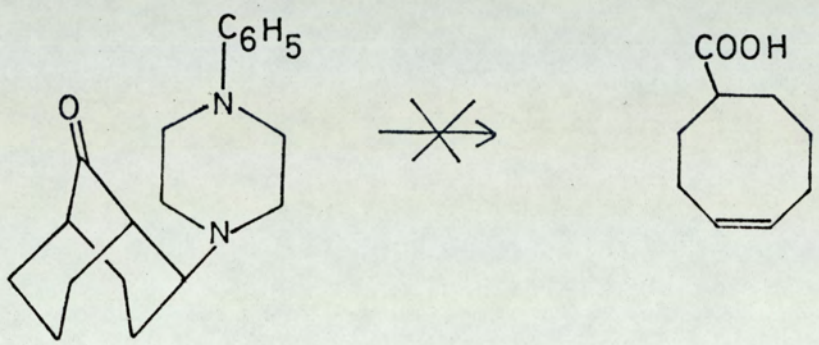
Ketone (153) was shown by column and thin layer chromatography to be present in at least 75% of the mixture of ketones. The ketones were separated by column chromatography and their stereochemistry determined by both degradation studies and reduction to the alcohols. Ketone (153) was degraded to 4-cyclooctene-1-carboxylic acid (154') and then to the known carboxamide. [32]



(154')

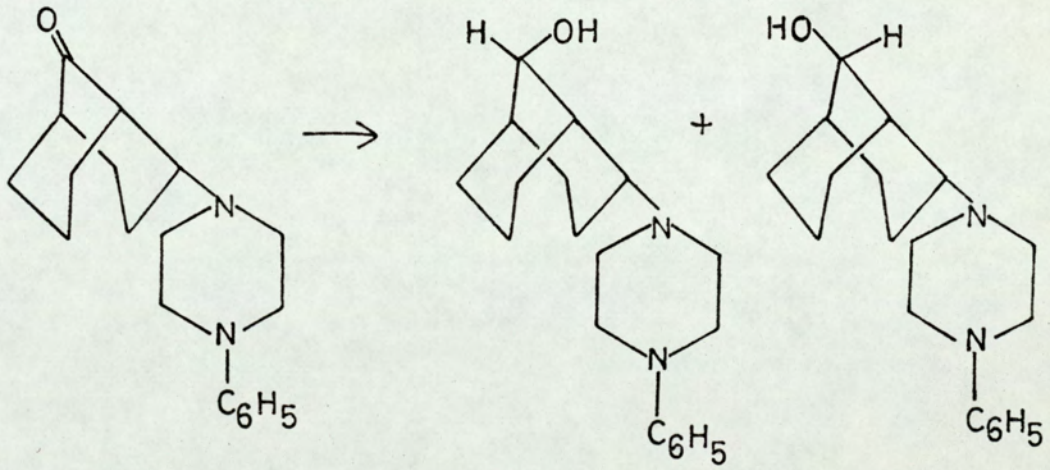
The ketone (154) could not be degraded in this manner. The geometry of the fragmentation process necessitates coplanarity

of N, C-2, C-1 and C-9, [98] which is attainable only when the 2-substituent is α-orientated. It was therefore assumed that in ketone (153) the 2-substituent was α-orientated.



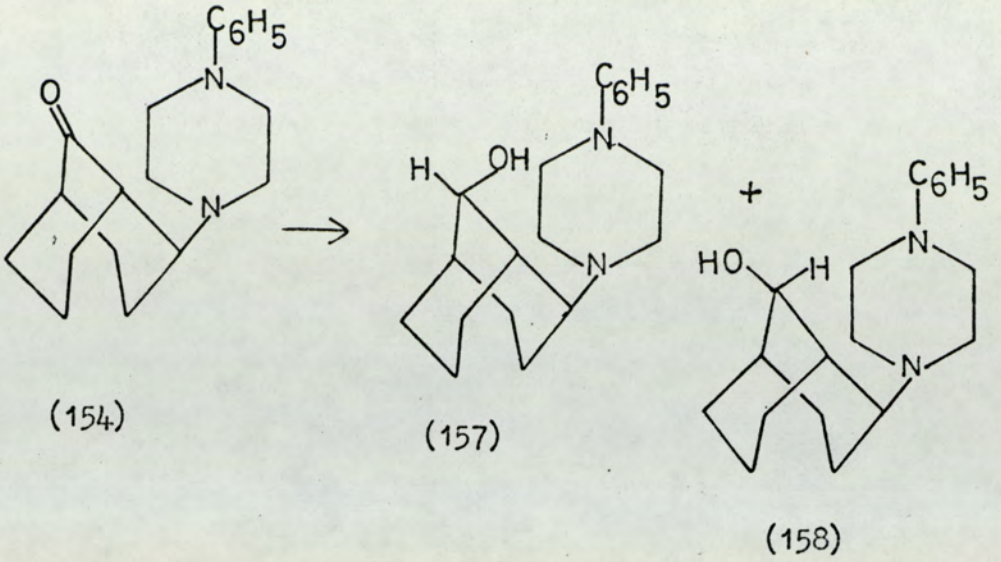
(154) (154')

Reduction of the ketone (153) with sodium borohydride gave one of the two possible alcohols in 75% yield.



(153) (155) (156)

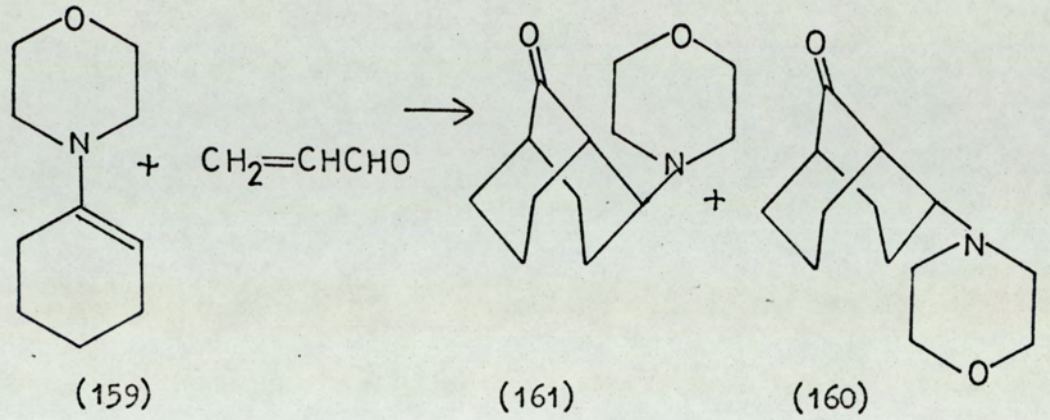
Its infrared spectrum exhibited bands due to both free and bonded hydroxyl at 3620 and 3440 cm.$^{-1}$ respectively. Reduction of ketone (154) gave an amino alcohol (76% yield) whose infrared showed no free hydroxyl but a broad intense band centred at 3175 cm.$^{-1}$ due to intramolecular hydrogen-bonding.



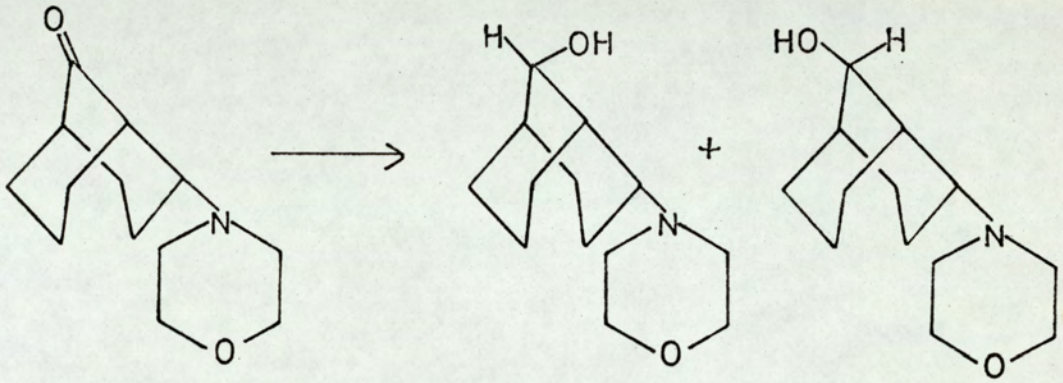
(154) (157) (158)

This spectral result was interpreted as being possible only when the bicyclo[3.3.1]nonane system was in the double chair conformation allowing hydrogen-bonding between the axially orientated amino-group and the C-9 hydroxyl group. No comment was made on the intramolecular hydrogen-bonding observed for the alcohol (155 or 156) which was obtained from the ketone (153). An inspection of stereochemical models shows that neither of the alcohols obtained from the reduction of ketone (153) can show intramolecular hydrogen-bonding, regardless of whether the bicyclo [3.3.1]nonane system is in a dichair, chair-boat, boat-chair or diboat conformation and the hydroxyl group is syn or anti to the amine function. However, to investigate the possibility of intramolecular hydrogen-bonding occurring in more than one bicyclo [3.3.1]nonan-9-ol derived from an isomeric pair of ketones, and to obtain model compounds for an NMR study, the bicyclo[3.3.1]nonanes (160) and (161) were prepared by the reaction between acrolein and the morpholine enamine of cyclohexanone (159). [37] The ketones were

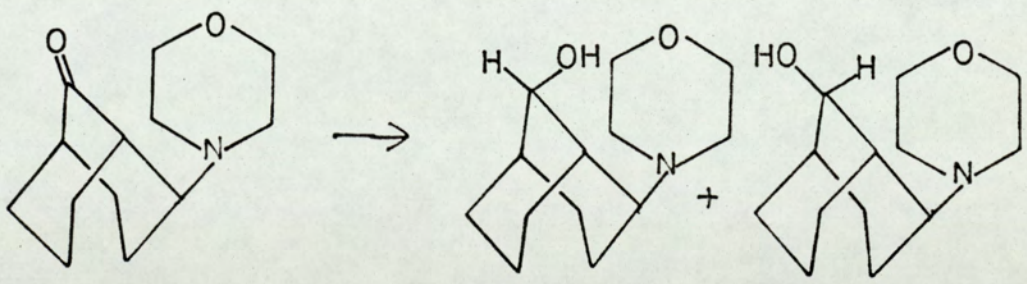
not separated but reduced to a mixture of amino-alcohols.



(159) (161) (160)



(160) (162) (163)

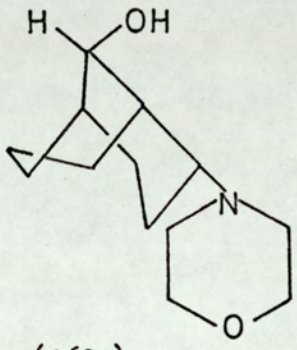


(161) (164) (165)

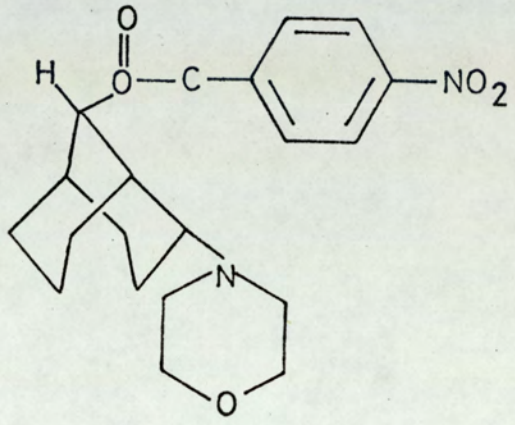
No crystalline alcohol could be isolated from the crude reduction mixture which was then subjected to the mild esterification procedure.[58] A crystalline hydrochloride (166) was

precipitated after a short time and on basification yielded a crystalline alcohol. This was shown by tlc and NMR to be a pure isomer. This alcohol was resistant to the esterification procedure although an ester (167) was prepared by reaction of its lithium alkoxide salt and p-nitrobenzoyl chloride. On dilution infrared in carbon disulphide at 0.0025M only free hydroxyl absorption was observed at 3600 $cm.^{-1}$ This alcohol must therefore be alcohol (162) obtained from ketone (160). The morpholine group must be equatorial because of its isolation as 31% of the total reduction mixture and also because on dilution infrared no intramolecular hydrogen-bonding was observed, as could be expected for alcohol (164). Alcohol (165) could not be present in such a high proportion of the reduction mixture. [37] Alcohol (163) would not be expected to form a p-nitrobenzoate ester even with the lithium alkoxide salt. This follows because the presence of a 6α-cycloalkylamino group would be expected to force the ring to which it is not attached into a boat form. The absence in this series of a methylamino group means that the ring to which the cycloalkylamino group is not attached cannot participate in the intramolecular acyl transfer mechanism, [58] and would prevent any approach of the acid chloride to the alkoxide. Alcohol (162) however, would be available to attack on the lithium alkoxide salt

by p-nitrobenzoyl chloride although the ring to which the cycloalkylamino group is not attached would be expected to be in a boat form. The structure for this alcohol is therefore best represented by (162a).

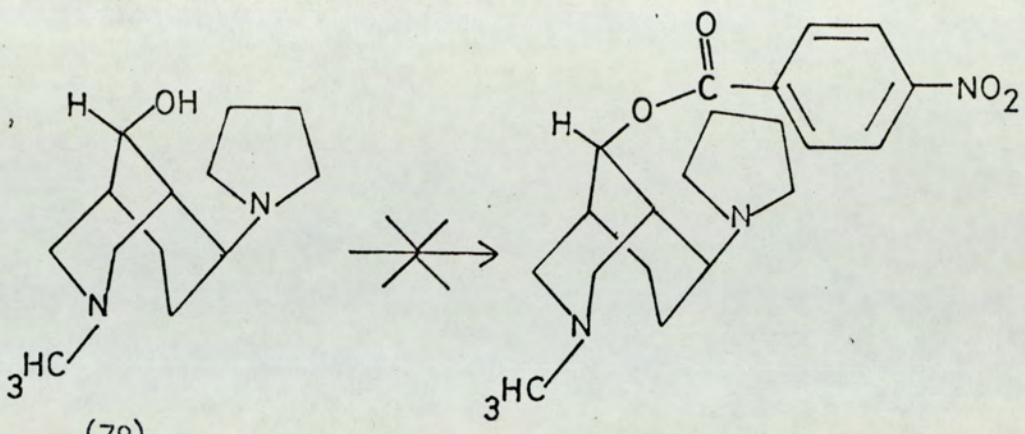


(162a)



(167)

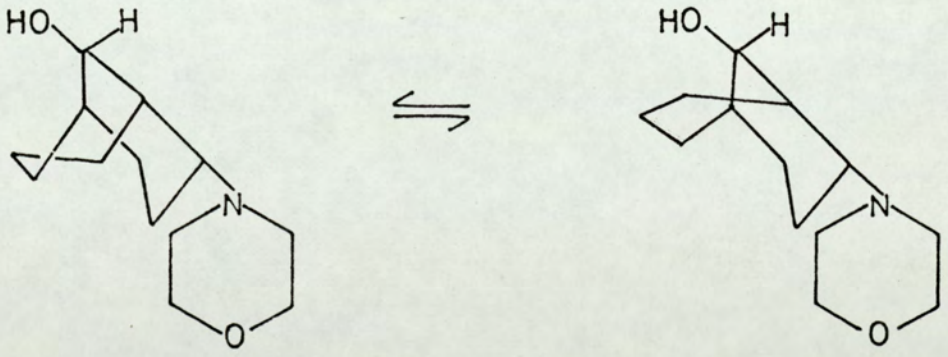
Work-up of the esterification mixture for basic material gave an oil, the infrared of which showed no C = O absorption. This further indicates that the ready esterification of the pyrrolidine (78), morpholine (139) and piperidine (130) alcohols was due to the participation of the methylamino group and not the cycloalkylamino group. If the cycloalkylamino group had participated in an intramolecular acyl transfer then the conformations of the pairs of alcohols (78 and 79), (130 and 131) and (139 and 140) could be reversed and the hydrogen-bonding and ready esterification be caused by the cycloalkylamino group.



(79)

The crude reduction mixture remaining was converted to a mixture of hydrochlorides from which a hydrochloride (168) was isolated by fractional crystallisation. This hydrochloride had a lower melting point than hydrochloride (166). The infrared of this hydrochloride showed a peak at 1640 cm.$^{-1}$ but analysis showed the presence of a hydrate. After drying at 110° the infrared showed the absence of any absorption in this region. The hydrochloride (166) also showed no absorption in this region. On converting the hydrochloride (168) to the parent base, a crystalline solid was obtained, isomeric with the previously obtained alcohol (162) with a melting point differing by only 4° and with very similar Rf values. NMR showed the presence of only one isomer in each case. This alcohol must also have been resistant to the esterification procedure [58] and could not be esterified even by means of its lithium alkoxide salt. Dilution infrared in carbon disulphide at 0.0025M showed the presence of free hydroxyl only. This alcohol must therefore be alcohol (163). This follows

because the morpholine group must be equatorial because of its isolation as 32% of the reduction mixture and also because, on dilution infrared, no intramolecular hydrogen bond was observed which would be expected for alcohol (164). Alcohol (165) could not be present in such a high proportion of the reduction mixture. The resistance to ester formation indicates that in this isomer the ring to which the 6α-morpholine group is not attached is in fact in a boat or near boat form thus preventing approach of the reagent. The structure of this amino-alcohol is therefore best represented by (163a). This further demonstrates that a 6(2, 4 or 8)α-substituent forces the ring to which it is not attached into a boat form. Alcohol (164) could not be isolated as a pure isomer.



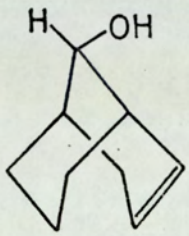
(163a)

Previous work [37] on the reaction between the morpholine enamine of cyclohexanone and acrolein had involved the separation of the ketones (160) and (161) by column chromatography. The ketones

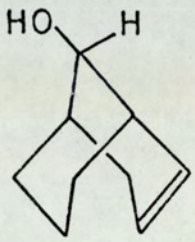
had been reduced to the alcohols but no crystalline compounds had been isolated from the alcohol mixtures. The mixture of alcohols had been converted to the N-oxides and pyrolysed. Reduction of ketone (161) and pyrolysis of the N-oxide was reported to give exclusively the syn-enol (169). This was the expected result because the axial 2-substituent would block approach of the reagent from that side of the molecule. However, after reduction of ketone (160), the alcohols could not be separated and were converted to a mixture of N-oxides and pyrolysed to give a mixture of syn- and anti-enols, with a preponderance of the syn-enol (69%). Because the Rf values were so similar, it was not possible to analyse the mixture of amino-alcohols prior to the preparation of their N-oxides and consequent pyrolysis. It was not possible therefore to determine to which extent the preferential formation of the syn-enol (169) from ketone (160) reflected selectivity at the reduction or elimination stage.

Both the alcohols isolated in the present study were subjected to the same degradation procedure. The fact that in alcohol (162) the hydroxyl group is syn to the morpholine group was confirmed by preparing the N-oxide which could be isolated and purified, and pyrolysing it to the known syn-bicyclo[3.3.1] non-2-en-9-ol (169). Attempts to form the N-oxide of alcohol (163)

failed to give an N-oxide which could be isolated, and pyrolysis of the product failed to give either the syn- (169) or anti-enol (170).



(169)



(170)

It might be argued that the elimination of N-hydroxymorpholine would proceed more efficiently from the N-oxides of alcohol (162) than that of alcohol (163) because in the former case the steric interactions due to the hydroxyl-group would be diminished in the transition state. However, since in the present study the alcohols (162) and (163) were isolated in approximately equal amounts, and alcohol (162) proved far easier to convert to the enol than alcohol (163), it seems likely that the selectivity occurred at the elimination stage rather than at the reduction stage. Alcohol (164) which was not isolated could be expected to show intramolecular hydrogen-bonding between the morpholine nitrogen and the hydroxyl group. Neither of the two alcohols isolated showed any intramolecular hydrogen-bonding, which would be expected since

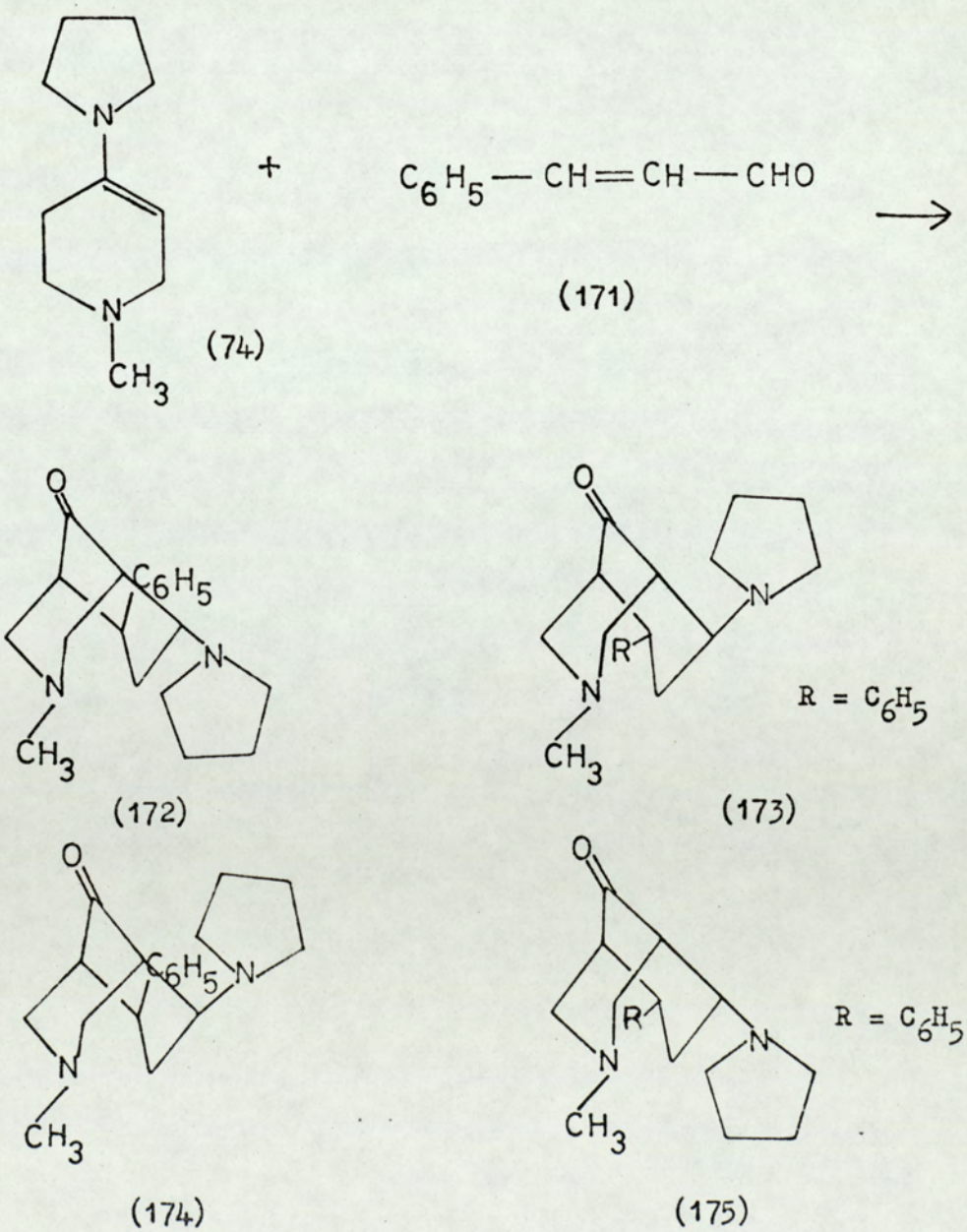
the nitrogen of the 6α-substituent cannot approach sufficiently close to the hydroxyl group to allow formation of a hydrogen bond. The fourth alcohol (165) would be expected to be present as a small percentage of the total reduction mixture and show no hydrogen-bonding. The results obtained for the 6-substituted 3-azabicyclo[3.3.1]nonan-9-ols and the 2-substituted bicyclo[3.3.1]nonan-9-ols appear to be contradictory to that reported [41] for the 4-phenylpiperazinyl bicyclo[3.3.1]nonan-9-ols and cast doubts on the claim of hydrogen-bonding in the two alcohols isolated.

The pKa of each of the amino-alcohols (162 and 163) was determined but the difference in their values (7.1 for alcohol (162) and 7.3 for alcohol (163)) was too small to allow any conclusions to be drawn as to their relative stereochemistries. Since both alcohols showed the absence of any intramolecular hydrogen-bonding, both have equatorial cycloalkylamino groups, and therefore approach of a hydrogen ion is equally hindered in both, the results would not be expected to differ markedly.

C. Synthesis of some 3-methyl-6-phenyl-8-(N-pyrrolidinyl)-3-azabicyclo[3.3.1]nonanes.

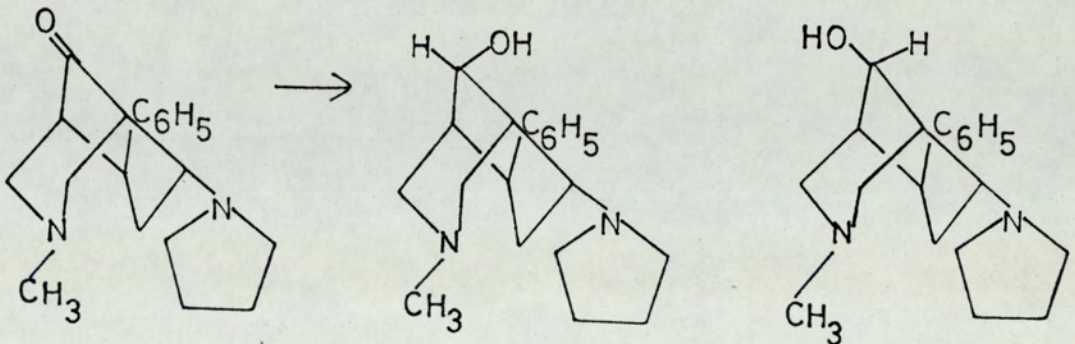
The reaction between the pyrrolidine enamine of N-methyl-4-piperidone (74) and cinnamaldehyde (171) gave a mixture of ketones, shown by tlc to consist of at least three components. The four ketones believed to be formed in the reaction are shown in fig. 9. The major component of the mixture was obtained by fractional crystallisation and was isolated as 52% of the reaction mixture.

Figure 9



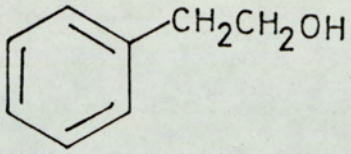
The corresponding reaction of cinnamaldehyde with the morpholine enamine of cyclohexanone is known to give a mixture of three isomeric ketones, [54,55] the major product being the 2β-phenyl-4α-(N-morpholinyl)-ketone. The structure of this ketone was proved by degradation studies. By analogy, the major isomer of the mixture of ketones (172-175) would be expected to be ketone (172). The preferential formation of (172) is in accord with the preferred formation of the erythro-isomer in the addition of cyclic enamines to β-nitrostyrene. [99] That this is the correct configurational assignment for ketone (172) was shown by sodium borohydride reduction of the ketone to the alcohols (176) and (177) and a study of their properties. The mixture of alcohols was shown by tlc to consist principally of alcohol (176) with only a small amount of another alcohol, presumed to be alcohol (177), present. The alcohol (177) could not be isolated either by fractional crystallisation or as a dihydrochloride or an ester from the reaction of a mixture of the alcohols with p-nitrobenzoyl chloride. Neither alcohol (176) or (177) formed an ester by this method. Alcohol (176) was obtained by fractional crystallisation of the mixture of alcohols.

Each of the ketones (172-175) would be expected to reduce principally from the side anti to the pyrrolidine and phenyl substituents and give predominantly the syn-isomer.

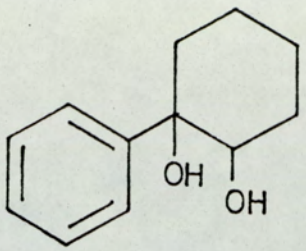


(172) (176) (177)

The stereochemistry of alcohol (176) follows from its isolation as the major component of a reduction mixture indicating that the hydroxyl group is syn to both the pyrrolidine and phenyl substituents. The alcohol proved resistant to esterification both under the mild conditions [58] or *via* the lithium alkoxide salt. This indicates the presence of either the phenyl or pyrrolidine substituent or both in an axial position and blocking approach of the reagent. On dilution infrared in carbon disulphide at 0.0025M, both free and intramolecularly bound hydroxyl were observed at 3595 and 3478 $cm.^{-1}$ respectively. This hydrogen bond could be due to an interaction between the hydroxyl group and the pyrrolidine nitrogen or with the π-electron components of the phenyl group, as observed for the alcohols (178) [100] and (179) [101] if the phenyl substituent is in an axial position and therefore in close proximity to the hydroxyl group.



(178)

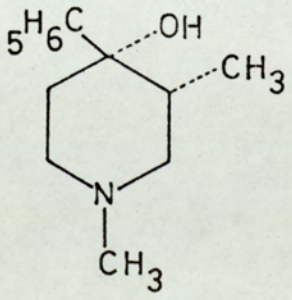


(179)

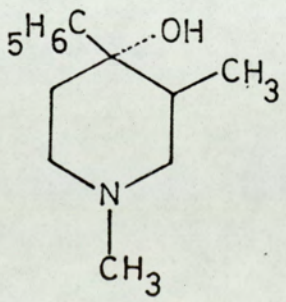
$\Delta\nu(OH) = 30$ cm.$^{-1}$

$\Delta\nu(OH) = 35$ cm.$^{-1}$

The phenyl substituent was shown to be in an axial position by the NMR spectrum which showed a broad splitting pattern for the aromatic protons, different to that for the ketone. This is believed to be due to the proximity of the electronegative oxygen of the hydroxyl group to the phenyl group. This can only occur if the hydroxyl group is syn to a phenyl substituent in an axial position. A similar effect on the splitting pattern of a phenyl group due to the proximity of a hydroxyl group has been reported [102] for the α- and β-prodinols (180) and (181).



(180)



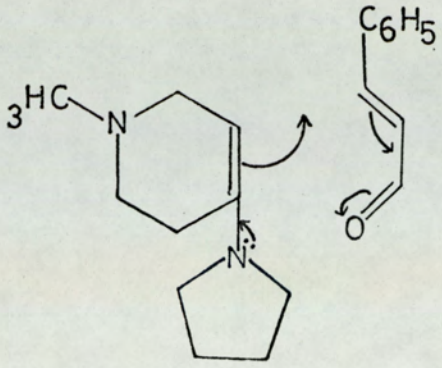
(181)

In α-prodinol (180) the preferred orientation of the phenyl group is in a plane approximately at right angles to that of the piperidine ring, the equatorial 3-methyl/ortho aromatic hydrogen interactions being minimal in this conformation. In β-prodinol (181) however, the same orientation is not preferred since it would bring aromatic hydrogens into close proximity to an axial methyl group, and the preferred orientation of the 4-phenyl group is when it is approximately coplanar with the piperidine. Averaged environments are experienced by all the hydrogen atoms as a result of rapid rotation about the bond linking the two-rings, but it is probable that the populations of conformers akin to α- (180) and β- (181) will be higher than all others at any one time. In α-conformers the environments of the ortho aromatic hydrogens are expected to differ markedly from the corresponding meta and para atoms because an ortho proton is close to the electronegative oxygen of the 4-hydroxyl group in the preferred conformation α- (180) and the equivalent form in which the ortho hydrogens are interchanged. In β-conformers, the ortho hydrogens are further removed from the hydroxyl group, and hence the chemical shift will be closer to the other aryl hydrogens. The chemical shift differences were thus anticipated to make the trans aromatic signal more complex than that of the corresponding cis isomer. This conclusion

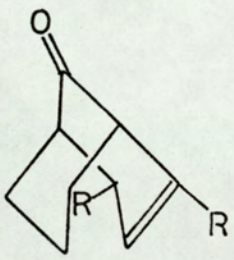
was confirmed experimentally with the aromatic signal of the α-isomer being markedly broader than the corresponding β-signal.

The splitting observed in the NMR of the amino-alcohol (176) must be caused by the hydroxyl group being in close proximity to the phenyl substituent, which must arise from the phenyl substituent being in an axial position. The pyrrolidine group can be either in an equatorial or axial position but it is likely that in this isomer the pyrrolidine is equatorial. This follows from the preparation of the alcohol (176) from the ketone (172) which was formed in greatest bulk of the mixture of ketones. It would seem unlikely that the ketone formed most favourably was that with both phenyl and pyrrolidine substituents in an axial position, and in the corresponding deaza series the ketone formed in greatest bulk had an axial phenyl group and an equatorial morpholine group. [54] A tentative suggestion for the preparation of the ketone (172) in greatest bulk is that the enamine reactions involve the production and neutralisation of unlike charges, and it has been suggested [103] that this occurs with the molecules orientated as shown (Fig. 10) so as to minimise the separation between the charges (possibly to make all the electron transfers very nearly concerted). The trans geometry of the cinnamaldehyde then imposes the erythro-configuration at the new carbon-carbon bond.

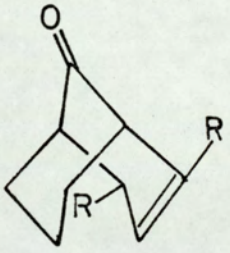
Figure 10



The base-catalysed addition of cyclohexanone to chalcone leads mainly to the threo-isomer, however, for cyclisation of the adduct gives (182) and (183) as the major and minor products respectively.



(182)

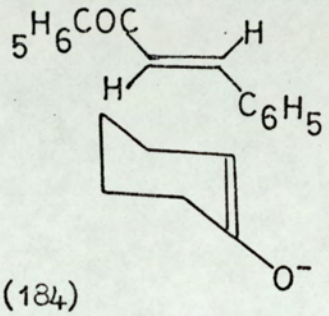


(183)

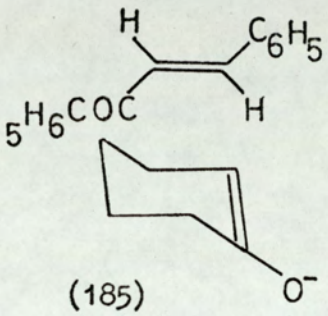
$R = C_6H_5$

Quite different considerations apply to the addition to the enolate ion; it has been suggested that the two π-electron systems must adopt an anti-periplanar conformation about the developing single bond (as do the leaving groups in an E2 reaction) and further, that the developing bond will be axial (as in other enolate additions).[103]

Two relative orientations of the reacting molecules meet these conditions. That leading to erythro-product (184) has severe steric interactions, and that leading to threo-product (185) has not.

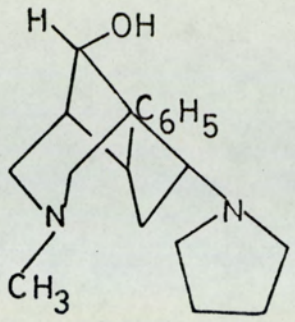


(184)

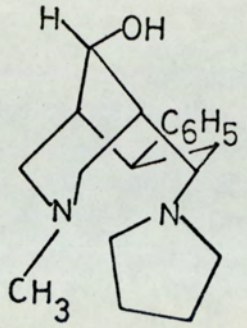


(185)

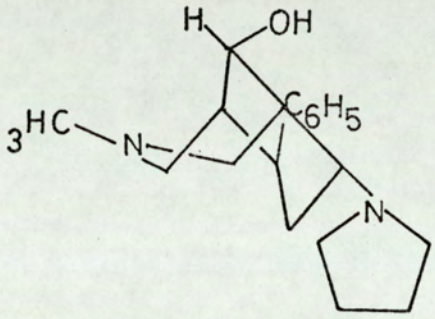
The splitting of the aromatic protons must be caused by the hydroxyl group in close proximity to the phenyl group. From stereochemical models this can be seen to occur both when the carbocyclic ring is in a chair form and also when the carbocyclic ring is in a near-boat form. In either of these conformations, the hydroxyl group would not be expected to esterify readily. In the chair form, the phenyl group would block approach of the reagent and in the boat form, the $7CH_2$ group would prevent approach of the p-nitrobenzoyl chloride.



(176a)



(176b)



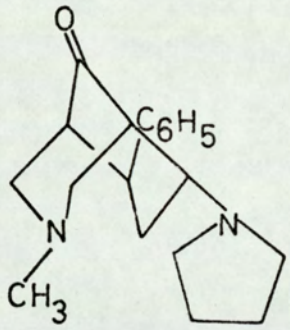
(176c)

In the twin-chair conformer (176a) there are interactions between; (a), the $7CH_2$ protons and the methylamino group; (b), the pyrrolidine ring and both the $7CH_2$ and 5CH positions; (c), the phenyl substituent and the 9COH, 5CH and 8CH groups. If the carbocyclic ring were to adopt the boat form (176b) then severe interactions would occur between the pyrrolidine ring and the $2CH_2$, $7CH_2$, 6CH and methylamino groups in addition to interactions between; (a), the methylamino group and the 6CH proton and (b), the phenyl group with the 5CH and $7CH_2$ positions. These would be expected to prevent the carbocyclic ring adopting a boat form. Puckering of the rings would only increase the interactions between the

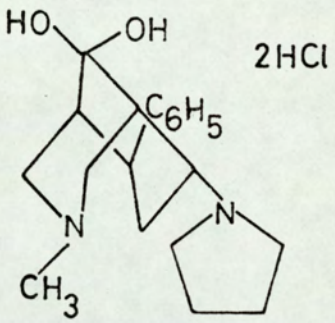
methylamino position and the C7 hydrogens and give little or no relief to the interactions already present. If the heterocyclic ring were to adopt a boat form (176c) then interactions would occur between; (a), the methylamino and 9CH positions; (b), the pyrrolidine group and both the C2 and C7 hydrogens ; (c), the phenyl group and 8CH, 9COH and 5CH positions. Thus the heterocyclic ring,by adopting a boat form,would relieve the interaction between the $7CH_2$ and methylamino group but replace it with equally severe interactions which make it unlikely that the heterocyclic ring should adopt a boat form. The preferred conformation of the alcohol is thus believed to be (176a) but because of the many interactions, the carbocyclic ring will probably be in a flattened or half-chair conformation. This conformation is in agreement with the hydrogen-bonding, the resistance to esterification, the splitting of the benzene ring in the NMR spectrum and comparisons with the comparable deaza system. [55] The hydrogen-bonding is believed to exist between the hydroxyl group and π-electron components of the phenyl group which is in close proximity, as shown by the NMR. Hydrogen-bonding to aromatic systems is not usually found to be as strong as shown by this alcohol [80] which would indicate that the phenyl group is in close proximity to the hydroxyl group. The dihydrochloride (186) of the alcohol (176) does not show any absorption between 1600 and 1700 $cm.^{-1}$

in agreement with the proposed structure.

The ketone (172) might also be expected to exist in a twin-chair conformation although the absence of any hydrogens at the C9 position would mean the absence of flagpole-interactions between the 9CH and the methylamino group or the $7CH_2$ and the 9CH position if either ring were to adopt a boat form, and therefore the interaction between the methylamino group and the C7 hydrogen could be relieved in this way. The proposed structure of the ketone is thus shown by (172a).



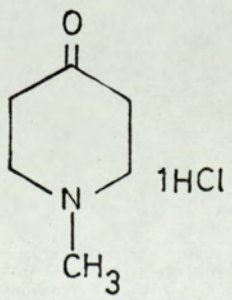
(172a)



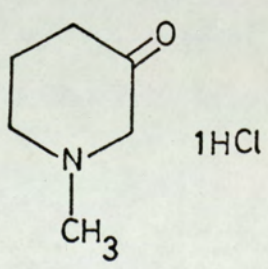
(187a)

The dihydrochloride of the ketone (187) showed an absence of any C = O absorption in the infrared and instead showed an intense absorption at 3200 $cm.^{-1}$ Analysis showed the presence of a hydrate which must exist as (187a). The addition of water to the carbonyl group of aldehydes or ketones leads to stable hydrates in only a few cases. Those examples of stable hydrates that are known have in common one or more strongly electron-attracting groups

attached to the carbonyl, and this structural feature is considered necessary for a stable hydrate. The formal positive charge of an amine salt, therefore, would be expected to stabilise the hydrate of a carbonyl located in the same molecule. Ketals have been reported to be formed by the reaction of 4-piperidone hydrochloride, [104] 1-alkyl-4-piperidone quaternary salts [105] and 1-alkyl-4-piperidone hydrochlorides [106] with alcohol. This reaction is promoted by the positive charge in the salt; however, the strain inherent in a tercovalent carbon within a six-membered ring [107] alone appears to provide the driving force for the formation of the ketal. Thus, unlike other ketones which undergo partial reaction with alcohols by addition, [108] cyclohexanone is converted to the ketal. [109] 1-Methyl-4-piperidone hydrochloride (188) and 1-methyl-3-piperidone hydrochloride (189) both have the structural features expected to promote the stability of a ketone hydrate and both these compounds have been shown to crystallise from aqueous solvents with a molecule of water. [115]



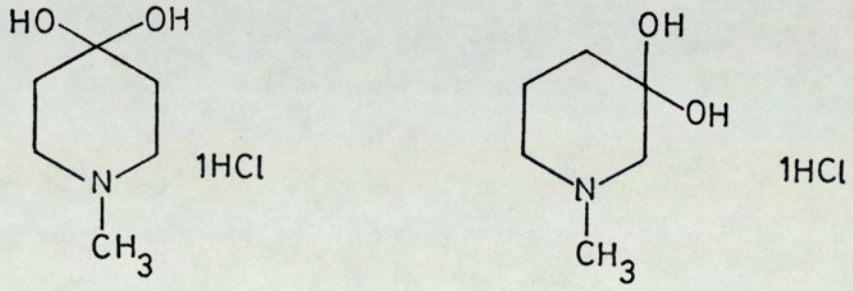
(188)



(189)

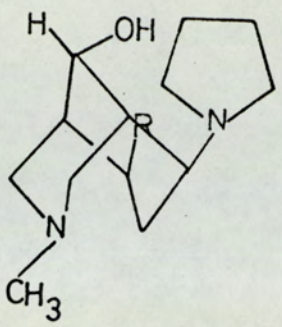
The structure determination of these hydrates was accomplished by a study of the infrared absorption spectra. The spectrum of the amines showed strong absorption at 1715-1716 cm.$^{-1}$ characteristic of carbon to oxygen double bond stretching, and no absorption above 3100 cm.$^{-1}$ The spectra of the hydrochlorides showed no absorption between 1500 and 2000 cm.$^{-1}$ but had large broad bands at about 3300 cm.$^{-1}$ The possibility of a hydrated enol of the ketone hydrochlorides was removed by the failure of the hydrochlorides to give a reaction with ferric chloride and the absence of absorption in the infrared spectrum characteristic of carbon to carbon double bond. The possibility of a hydrated product of transannular interaction between the nitrogen and the carbonyl is unlikely in view of Leonard's results with related compounds [110] and such interactions would be impossible with the quaternary salts of 1-methyl-3- and -4-piperidone. The methiodides of the ketones showed similar properties to the hydrochlorides. Thus the hydrates of 1-methyl-3- and -4-piperidone hydrochlorides must be represented by the gem-diols (Fig. 11).

Figure 11



The results for the 3-methyl-6β-phenyl-8α-(N-pyrrolidinyl)-3-azabicyclo[3.3.1]nonan-9-one (172) parallel the results for the hydrochlorides of 1-methyl-3- and -4-piperidone and thus it can be assumed that the water is present as the hydrate of the carbonyl group.

The mixture of ketones remaining after removal of the ketone (172) was reduced with sodium borohydride to give a mixture of alcohols. On subjecting a sample of the crude reduction mixture to the mild esterification procedure no dihydrochlorides or esters were formed. From the mixture, fractional crystallisation yielded three alcohols (190), (191) and (192). Alcohol (192) was obtained because of its low solubility in light petrol (60-80°) and alcohols (190) and (191) had differing solubilities in ether. The configuration of alcohol (190) was determined to be (190a) for the following reasons.

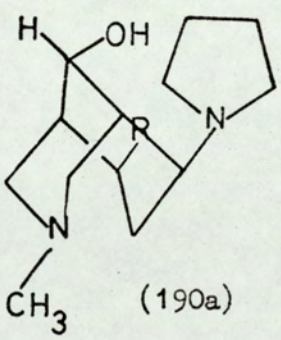


R = C_6H_5

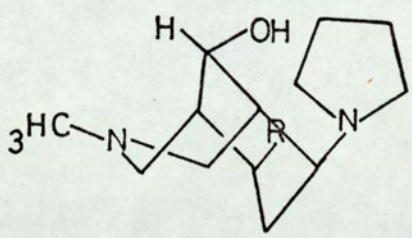
(190a)

The NMR spectrum of alcohol (190) showed the same splitting and broadening of the aromatic protons due to the close proximity of an hydroxyl group as for alcohol (176). This indicates that the phenyl substituent is axial and the hydroxyl group syn to the pyrrolidine and phenyl substituents. Since the pyrrolidine group was equatorial in alcohol (176) when the phenyl group was axial, it follows that this alcohol the pyrrolidine group must be axial. Thus in the alcohol (190) both substituents are axially positioned, which seems doubtful given their steric requirements. However, the analagous deaza ketone was formed containing both an axial phenyl group and an axial morpholine group. [55] It was concluded that a small deformation of the ideal chair led to sufficient spacial separation of the substituents to allow both in an axial position. In addition, three 2,4-diphenylbicyclo[3.3.1] nonan-9-ones have been prepared, one of which contained both the phenyl groups in an axial position. Examination of stereochemical

models shows that for alcohol (190), only a small deformation of the ideal chair form is sufficient to allow both substituents in the β-position. On reacting the lithium alkoxide salt of the alcohol with p-nitrobenzoyl chloride, an ester (193) was produced. This would further confirm that the carbocyclic ring is not in an ideal chair form. On dilution infrared in carbon disulphide at 0.0025M, only free hydroxyl absorption was observed at 3600 $cm.^{-1}$ indicating that hydrogen-bonding was not possible to either the phenyl group or the pyrrolidine group. The carbocyclic ring can therefore be assumed to be in a boat or near-boat form.

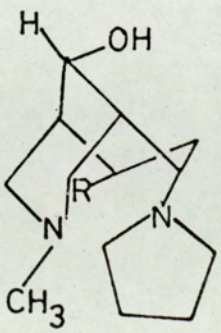


(190a)

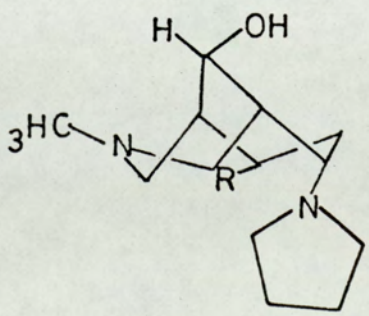


(190b)

R = C_6H_5



(190c)



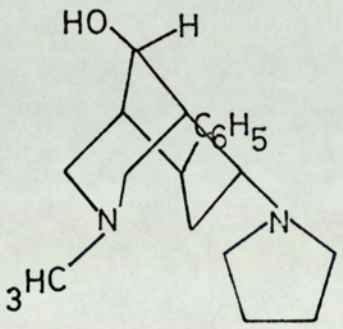
(190d)

Of the possible conformations for alcohol (190), the ideal twin-chair conformation (190a) can be excluded because an examination of stereochemical models shows this to be a sterically overcrowded molecule with severe interactions between the pyrrolidine and phenyl substituents as well as interactions between (a), the phenyl group and 5CH, $7CH_2$ and 9COH positions and (b), the pyrrolidine group with 1CH, $7CH_2$ and 9COH. If the heterocyclic ring were to adopt a boat form with the carbocyclic ring in a chair form (190b), these interactions would still exist and an additional interaction between the 9CH and methylamino group would be introduced. If the carbocyclic ring were to adopt a boat form with the heterocyclic ring in a chair form (190c), then the severe interactions between pyrrolidine and phenyl substituents would be removed and their only interactions would be with the bridgehead hydrogens at C1 and C5 respectively. An interaction between 9COH and $7CH_2$ would be introduced but the corresponding interaction between the $7CH_2$ and the methylamino group would be relieved. No extra relief of interaction is obtained by adopting the twin-boat conformation (190d) and from stereochemical models it can be seen that new interactions between 9CH and the methylamino position as well as severe C2-C6 and C4-C8 interactions are introduced. In view of this, it is proposed that alcohol (190) exists in a conformation in which the carbocyclic ring is in a boat

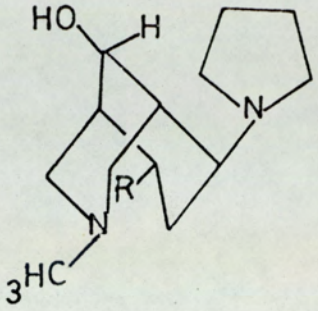
or near-boat form and the heterocyclic ring in a chair form. This is in agreement with the splitting of the aromatic protons in the NMR, the absence of hydrogen-bonding, and the formation of an ester. The dihydrochloride of this alcohol (194) showed no absorption in the 1610-1700 $cm.^{-1}$ region in the infrared, although analysis showed the molecule to be hydrated, which is in agreement with the pyrrolidine ring being removed from the hydroxyl group by a flattening of the carbocyclic ring.

Alcohol (191), isolated because of its difference in solubility in ether to alcohol (190), did not show the same splitting of the aromatic protons in the NMR as was observed for alcohols (176) and (190), indicating that either the benzene ring was in an equatorial position or that the hydroxyl group was anti to the phenyl group. On reaction of its lithium alkoxide salt with p-nitrobenzoyl chloride, this alcohol formed an ester (195) and on dilution infrared in carbon disulphide both free and intramolecularly bound hydroxyl absorption was observed at 3600 and 3330 $cm.^{-1}$

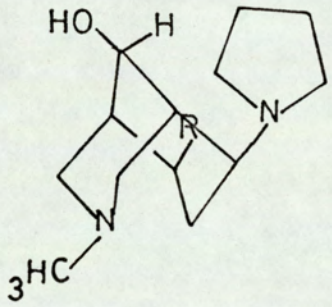
Of the possible configurations for this alcohol (1 - V1), (1) has been shown to be the minor product of the reduction of ketone (172) and thus this alcohol is not likely to be present in the mixture of alcohols, due to the removal of the bulk of the ketones from which it is formed, prior to reduction.



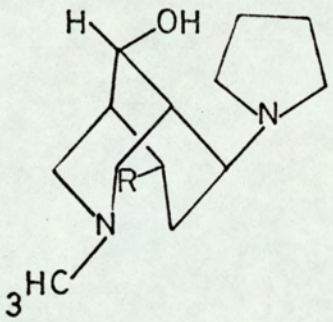
(1)



(11)

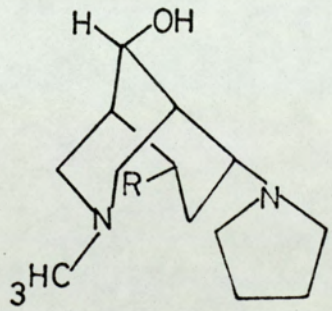


(111)

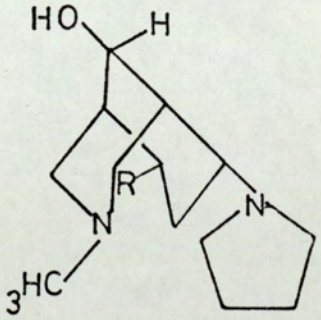


(1V)

R = C_6H_5



(V)

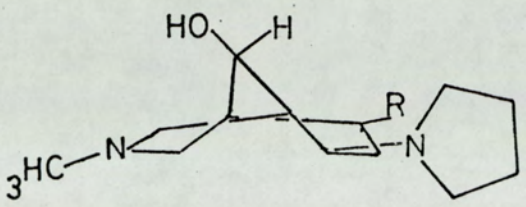


(V1)

Configurations (V) and (V1) are unlikely because in the corresponding deaza series, [55] the ketone from which these alcohols would be formed was not isolated and was shown to be present in trace amounts only. Since this alcohol forms an ester (195), (1V) is an unlikely structure because, to accommodate the ester, the carbocyclic ring would have to assume a flattened, half-boat form, and this would bring the phenyl group into severe interactions with the methylamino group, $2CH_2$, 6CH and $7CH_2$ hydrogens. In view of the severity of these interactions configuration (1V) can be excluded. Of the two remaining structures (11) and (111), the alcohol (11) would be obtained from ketone (173) by reduction from the sterically hindered side of the molecule, syn to the pyrrolidine group. This has been shown in the 6β-substituted 3-methyl-3-azabicyclo [3.3.1] nonane to produce very little of the alcohol anti to the pyrrolidine group. However, ketone (174) can be expected to reduce from both sides of the carbonyl function since alcohol (190) was isolated and shown to be capable of accommodating an ester group syn to the phenyl and pyrrolidinyl groups. In view of this, approach of the reducing agent should also be possible from the side syn to the pyrrolidine group and therefore give rise to the anti-alcohol. It is proposed that alcohol (191) has the configuration (111). The hydrogen bond formed is between the hydroxyl group and the methylamino

group, both the pyrrolidine and phenyl groups are axial and the carbocyclic ring is in a boat or near-boat form. This allows the esterification *via* the lithium alkoxide salt.

The carbocyclic ring would be expected to exist in a boat or near-boat form for the same reasons as outlined for alcohol (190). The heterocyclic ring cannot be in a full-boat form because of the extra interactions introduced between the 2CH and 8CH groups and also 4CH and 6CH positions. This offers an explanation as to why the alcohol does not esterify under the mild reaction conditions, since the heterocyclic ring has to adopt a boat form for the intramolecular acyl transfer to occur, and the complex produced is very crowded. However, a dilution infrared study indicates the presence of some intramolecular hydrogen-bonding, indicating that the heterocyclic ring may exist in a half-boat form, especially if the carbocyclic ring is not in a full-boat form. Because of this, alcohol (191) is believed to exist in the conformation (191a) with both the carbocyclic ring and the heterocyclic ring in a half- boat form.

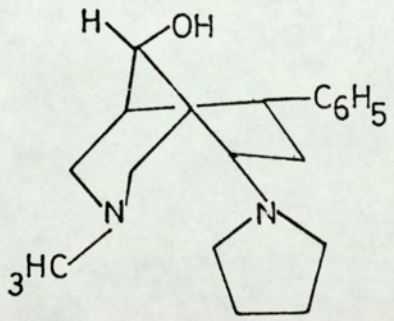


(191a) R = C_6H_5

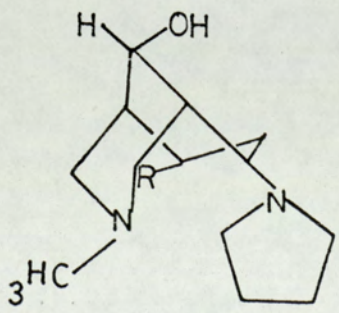
The dihydrochloride of this alcohol (196) showed no absorption in the 1610-1700 cm.$^{-1}$ region in the infrared. This is in agreement with the proposed structure.

Alcohol (192) can have the configuration depicted by (1, 11, 1V,V or V1). For the reasons already stated, structures (1), (V) and (V1) are unlikely, indicating that (11) or (1V) is the likely structure. The alcohol (192) failed to esterify under the mild conditions or via the lithium alkoxide salt and, on dilution infrared, only free hydroxyl absorption was observed at 3600 cm.$^{-1}$ The NMR of this alcohol does not show the characteristic broadening and splitting of the aromatic protons due to the close proximity of a hydroxyl group, indicating that the phenyl substituent is in an equatorial position or that the hydroxyl group is anti to the phenyl substituent. An alcohol with configuration (11) would be expected to form an ester, whereas an alcohol with configuration

(1V) would not be expected to form an ester due to the presence of the pyrrolidine group blocking approach of the reagent In addition, by comparison with the analogous 6-substituted 3-methyl-3-azabicyclo [3.3.1] nonanes, the ketone (173) would not be expected to produce a significant amount of the alcohol with structure (11). The alcohol (192) is therefore concluded to have the configuration (1V). The absence of marked splitting of the aromatic protons in the NMR is accounted for by the phenyl substituent being in an equatorial position and therefore not being in close proximity to the syn-hydroxyl group. The absence of any intramolecular hydrogen-bonding indicates that the carbocyclic ring exists in a flattened form (192b)



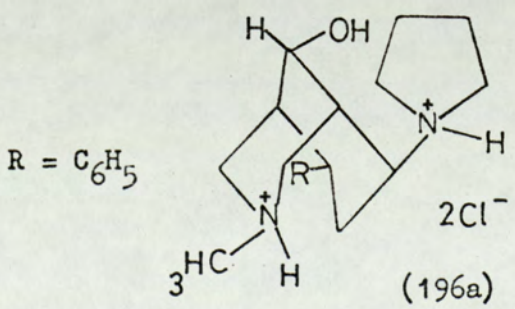
(192b)



R = C_6H_5

(192c)

In the twin-chair form the pyrrolidine group interacts with the 1CH, $7CH_2$, 9COH and the 6CH positions. By a flattening of the carbocyclic ring (192b), all the interactions with exception of that with the 1CH position are removed. The carbocyclic ring is unlikely to adopt a boat form (192c) because of the severe interactions which would be set up between the phenyl group and the $7CH_2$, $4CH_2$, 6CH and methylamino group. These are expected to be greater than the $4CH_2$ and $7CH_2$ interactions with the phenyl group which are present in the chair form. The heterocyclic ring is probably in a chair form since production of a boat form would introduce new interactions between the phenyl ring and the $2CH_2$, $4CH_2$ and methylamino group. The probable structure of the alcohol is therefore (192b). The dihydrochloride of this alcohol (196a), shows no absorption between 1600 and 1700 cm. $^{-1}$ in the infrared, although analysis shows that the molecule is hydrated. Since this alcohol showed no hydrogen-bonding to the pyrrolidine nitrogen, the possibility of forming a "pseudo-water molecule" can no longer exist.

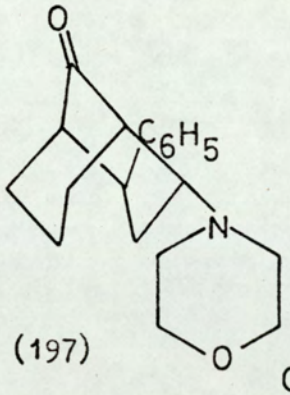


R = C_6H_5

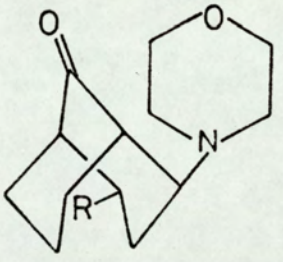
(196a)

D. Synthesis of some 2-Phenyl-4-(N-morpholinyl)-bicyclo[3.3.1]nonanes.

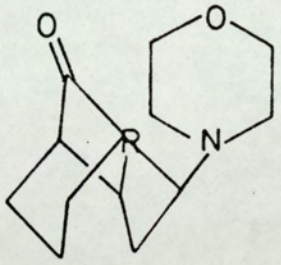
In order to test the validity of the hypothesis that the splitting in the NMR of the aromatic protons in alcohols (176) and (190) and not in alcohols (191) and (192) was in fact due to the hydroxyl group and not another hetero atom such as the heterocyclic nitrogen atom, the deaza ketones (197, 198, 199) were prepared by the method of Dressler and Bodendorf.[55] The alcohols derived from these ketones of known structure would also show whether the hydrogen-bonding in alcohol (172) was to the phenyl group or not.



(197)



(198)



R = C_6H_5

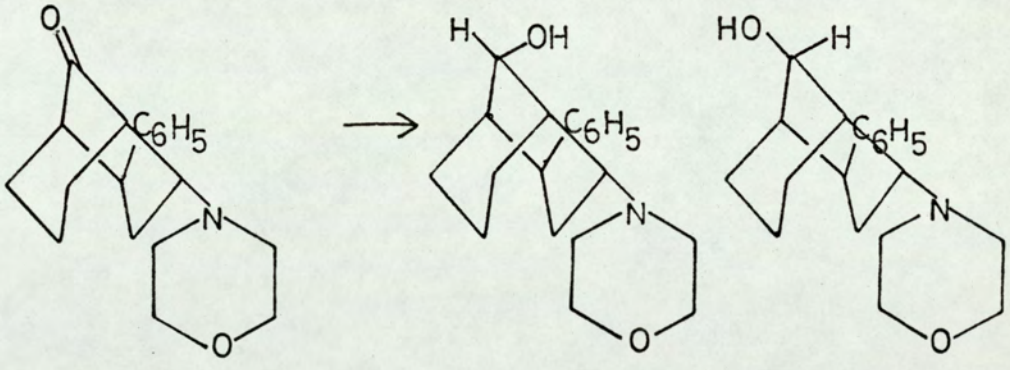
(199)

Each of the ketones (197-199) failed to show the broadening and splitting of the aromatic protons as exhibited by

the alcohols (176) and (190), further indicating that the hydroxyl group was necessary for the splitting to occur.

On reduction, each of the ketones was expected to produce principally one alcohol, formed by reduction from the side anti to the phenyl and morpholine groups. Each of the ketones on reduction was found to produce one isomer in bulk and a small amount of what was assumed to be the alcohol formed by reduction from the morpholine side of the molecule.

Ketone (197) on reduction gave almost exclusively one alcohol (200) which was purified by repetitive crystallisations.

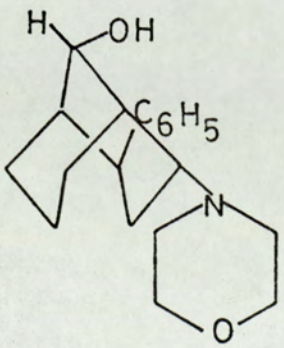


(197) (200) (201)

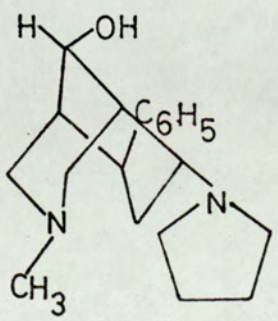
Since ketone (197) would be expected to yield the syn-alcohol on reduction, the configuration of this alcohol can be assumed to be (200). This is also the same alcohol obtained by lithium aluminium hydride reduction of ketone (197) and shown to have structure (200). [103] The 220 MHz NMR of the alcohol showed the expected broadening and splitting of the aromatic signal

indicating that the splitting was in fact caused by the hydroxyl group. On preparing the hydrochloride (202), the NMR showed the same splitting pattern and the infrared showed no absorption in the 1610-1700 $cm.^{-1}$ region. On dilution infrared in carbon disulphide at 0.0025M both free and intramolecular hydrogen-bonding was observed at 3600 and 3440 $cm.^{-1}$ This intramolecular hydrogen-bond must be due to the interaction between the hydroxyl group and the π-electrons of the phenyl substituent since it is impossible in this alcohol to form a hydrogen-bond between the hydroxyl group and the pyrrolidine ring. Since the alcohol (176) obtained from the analogous ketone (172) in the piperidine series of compounds showed all these properties, it can be concluded that alcohol (176) does in fact exist with the hydroxyl group syn to a phenyl substituent in an axial position and a pyrrolidine group in an equatorial position. The conformation of alcohol (200) is assumed to be the same as for alcohol (176) as shown in Fig. 12.

Figure 12



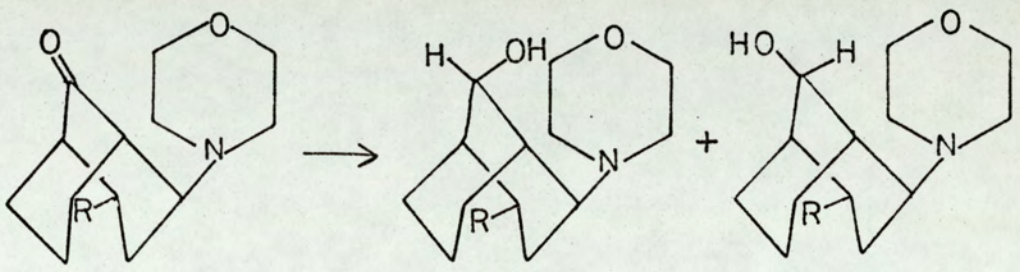
(200)



(176)

Attempts to isolate the alcohol formed in least amount in the reduction (201) failed to produce any pure isomer.

Ketone (198) on reduction with sodium borohydride yielded a mixture of alcohols consisting principally of alcohol (203) with only a small amount of what was assumed to be alcohol (204) present.

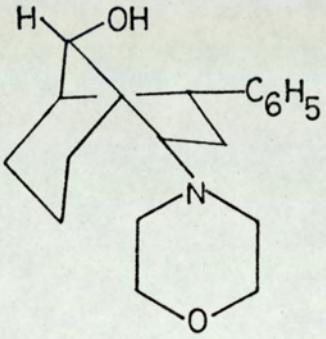


(198) (203) (204)

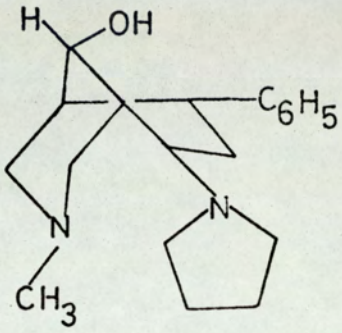
$R = C_6H_5$

Fractional crystallisation yielded a chromatographically pure sample of alcohol (203). On dilution infrared this alcohol showed the absence of intramolecular hydrogen-bonding and only free hydroxyl absorption was observed at 3600 $cm.^{-1}$ Since this alcohol was the major product from the reduction of the ketone (198), it is probable that the alcohol group is syn to the phenyl and morpholine group. The NMR failed to show the broadening and splitting observed for the alcohol (200). This is in agreement with the conclusion that the splitting is caused by a hydroxyl group syn to a phenyl group in an axial position. This alcohol must have structure (203a), which has the phenyl group in an α-position and thus unable to

interact with the electronegative oxygen of the hydroxyl group. The conformation of this alcohol (203a) was assumed to be the same as for alcohol (192) in the piperidine series.



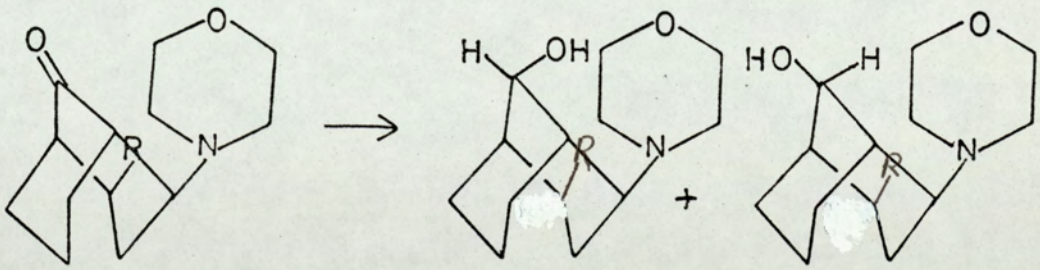
(203a)



(192)

The alcohol (204) formed as a minor product in the reaction could not be isolated from the reduction mixture.

Ketone (199) on reduction gave a mixture of two alcohols, consisting largely of alcohol (205) with a small amount of another alcohol presumed to be alcohol (206) present.

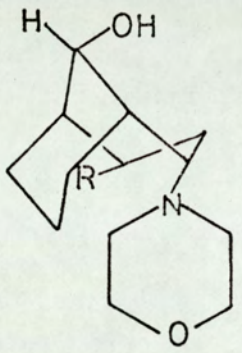


(199) (205) (206)

R = C_6H_5

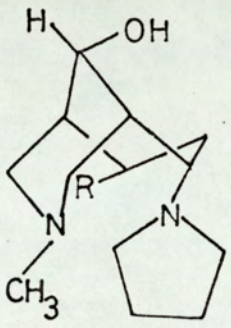
Alcohol (205) was isolated by repetitive crystallisations and shown to be pure by tlc, although alcohol (206) could not be

obtained in a pure state. On dilution infrared at 0.0025M in carbon disulphide, only free hydroxyl absorption was observed at 3600 cm.$^{-1}$ Alcohol (205) would be expected to have the hydroxyl group syn to the phenyl and morpholine groups. The structure of this alcohol would thus be expected to be (205).



(205)

R = C_6H_5



(190)

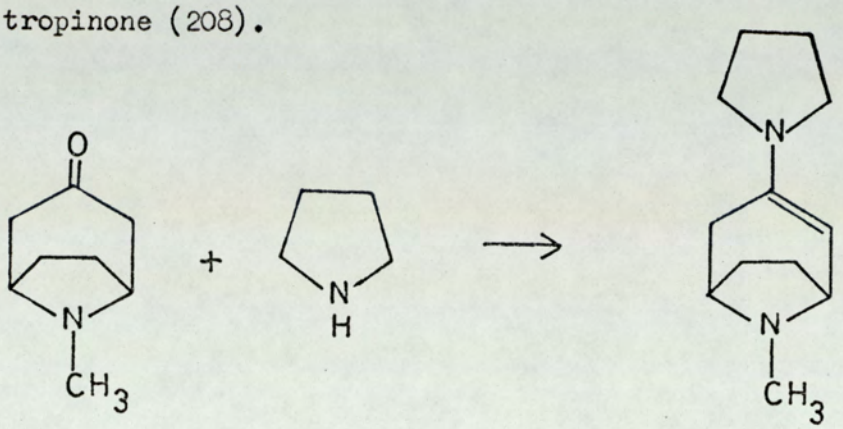
This alcohol (205) has the hydroxyl group syn to an axial phenyl and axial morpholine group, although the ring containing the two substituents would be expected to be in a flattened or near-boat form. The NMR spectrum of this alcohol was expected to show the broadening and splitting of the aromatic protons due to the close proximity of the electronegative oxygen of the hydroxyl group to the phenyl substituent. The NMR spectrum showed this splitting and broadening effect of the aromatic protons in the same way as for alcohol (200) thus showing the splitting was entirely caused by the close proximity of the hydroxyl group to the phenyl group. The splitting in these deaza compounds could

not have been caused by a heterocyclic nitrogen and the position of the morpholine group was known to be such that it could not have this effect on the phenyl substituent in both alcohol (200) and (205).

Both alcohols (205) and (203) showed an absence of intramolecular hydrogen-bonding on dilution infrared in carbon disulphide at 0.0025M, which was the same result obtained for the analogous amino-alcohols in the piperidine series. The three alcohols (200), (203) and (205) obtained from ketones of known stereochemistry showed identical behaviour towards the splitting pattern of the aromatic protons in the NMR and intramolecular hydrogen-bonding as the alcohols with the same postulated stereochemistry in the piperidine series. The pairs of alcohols are therefore assumed to have the same stereochemistries.

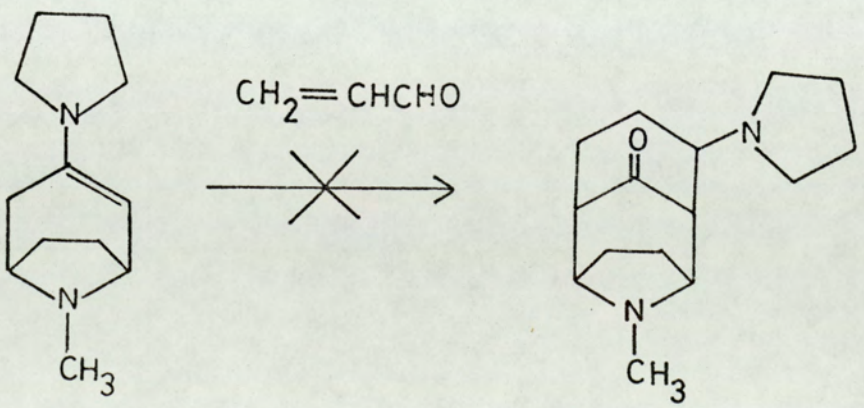
E. Synthesis of some tropinone derivatives.

Tropinone (207) reacted with pyrrolidine in refluxing benzene under a water separator to give the pyrrolidine enamine of tropinone (208).



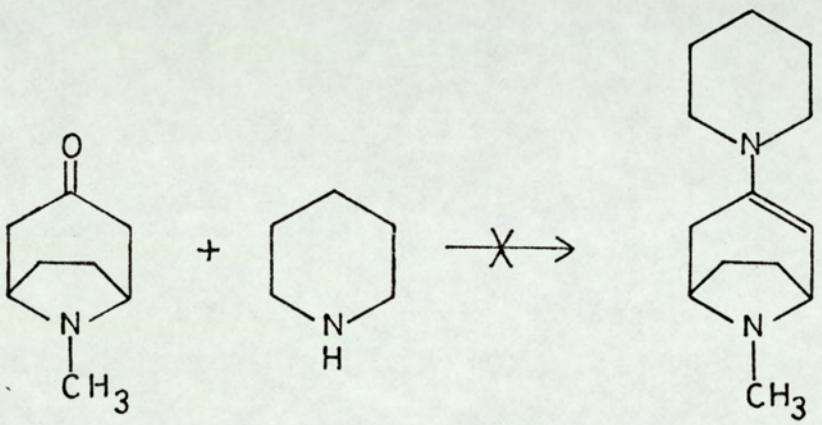
(207) (208)

The enamine was treated at 0 - 10° with acrolein but the desired ketone (209) could not be isolated. The infrared spectrum of the oil produced showed absorption at 1710 (C = O) and 1630 (C = C) $cm.^{-1}$ The mass spectrum of the oil showed a peak at $^{m}/e$ 248 which corresponded to the molecular weight of the desired ketone (209), but also contained peaks at $^{m}/e$ 272 and $^{m}/e$ 301.



(208) (209)

The reaction was repeated at room temperature in a stream of nitrogen and also at 100° but in both instances, no identifiable product could be isolated. In an attempt to vary the reaction and use a less reactive enamine, but with the possibility of a more stable intermediate being produced, the reaction between tropinone (207) and piperidine in benzene was attempted but no reaction occurred.

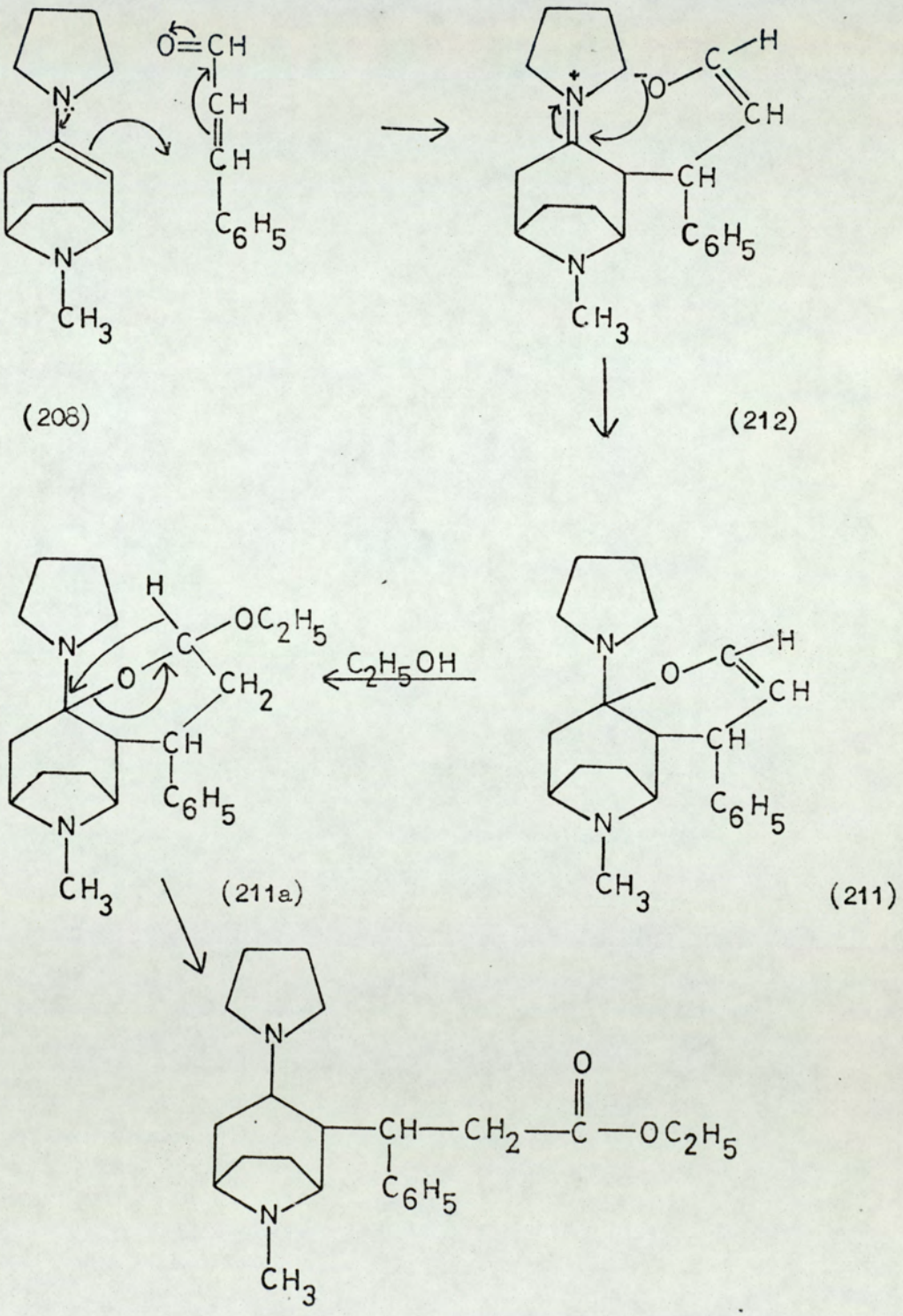


(207)

The reaction was then varied, using cinnamaldehyde as the aldehyde, in the reaction with pyrrolidine enamine of tropinone. After stirring for 1 hr at 0 - 10° followed by heating for 1 hr at 100°, no product was isolated. However, when the reaction of the tropinone enamine and cinnamaldehyde was carried out in ethanol, a crystalline compound was isolated, the infrared spectrum of which showed absorption at 1720 (C = O) $cm.^{-1}$ and also showed the presence of an aromatic group with absorptions at 1600 and 1500 $cm.^{-1}$ The NMR spectrum of this compound however, showed the presence of an

ester-type ethyl group. Analysis and mass spectral data confirmed the structure of the compound as (210). A possible mechanism for this reaction is outlined in fig. 12.

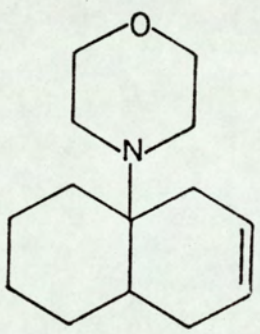
Figure 12



This reaction is of interest since it represents an internal oxidation-reduction system. Other hydride-transfer reactions range from the Cannizzaro reaction with strong alkali to the very rapid interchanges between iso-paraffins and organic halides brought about by aluminium bromide or chloride. The driving force in the former example is derived from a negative ion which stabilises itself by the formation of a carbonyl group by losing a hydride ion. In the latter example, the driving force comes from the positive charge on a carbonium ion going to a hydrocarbon. Concerted processes which are intermediate and probably more closely related to the reaction described include the Meerwein-Pondorf-Verley and Oppenauer reactions. Another hydride transfer reaction has been proposed for the mechanism of the isomerisation of steroidal sapogenins at C - 25 by Woodward and Sondheimer. [111]

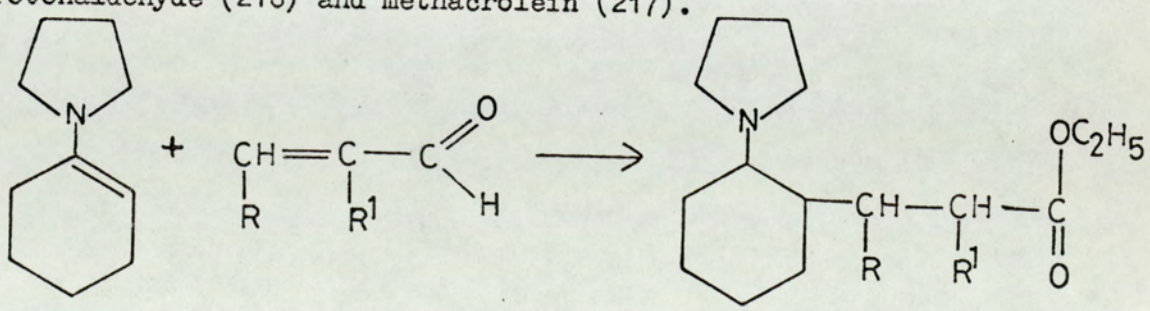
The mechanism outlined in fig. 12 involves the production of a dihydropyran intermediate (211). Dihydropyrans have been isolated from the reactions of enamines with αβ-unsaturated aldehydes, [112] and may be formed via a two-step mechanism with formation of a common dipolar intermediate (e.g. 212). Alternatively, the formation of the dihydropyrans could be regarded as a Diels-Alder-type reaction occurring with a one-step multicentre mechanism by synchronous attack of the heterodiene system of the αβ-unsaturated aldehyde on the enamine

double bond. A similar course, via a dihydropyran, has been postulated for the reaction of several enamines with 2-chlorovinyl ketones. [113] In addition, the aminohexahydropyran (213) has been shown to be precursor of the 2-morpholinobicyclo[3.3.1]nonan-9-ones (160 and 161). [41] The dihydropyran intermediate, once formed, can add ethanol across the double bond and a hydride shift gives rise to the tropine derivative (210). Addition of alcohols to dihydropyrans is known to give rise to ethers. [114]



(213)

Untch [36] prepared the esters (214, R = CH_3, R^1 = H) and (215, R = H, R^1 = CH_3) by reaction of the pyrrolidine enamine of cyclohexanone (159) with the substituted αβ-unsaturated aldehydes, crotonaldehyde (216) and methacrolein (217).



(159)

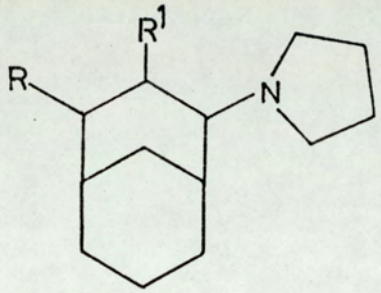
216 R=CH_3, R^1=H

217 R=H, R^1=CH_3

214 R=CH_3, R^1=H

215 R=H, R^1=CH_3

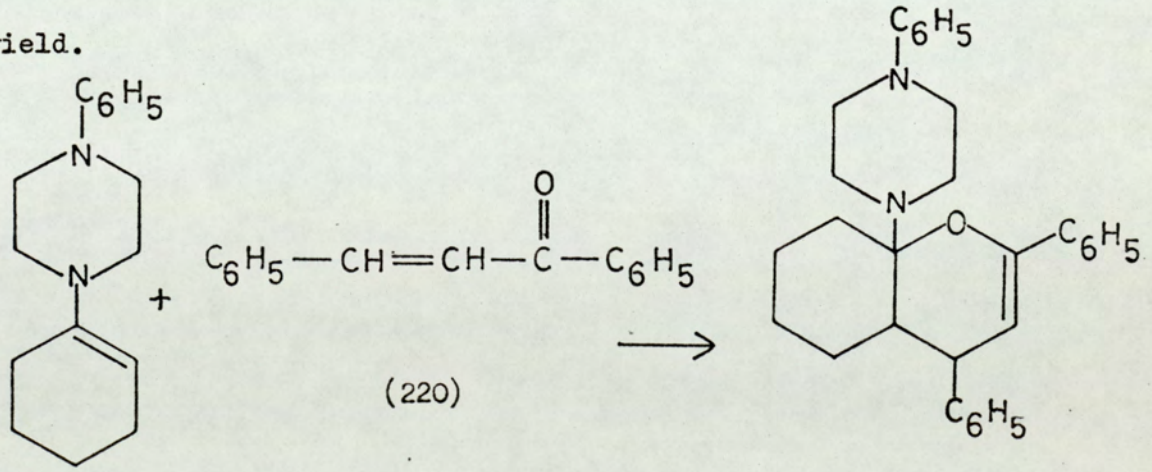
A similar mechanism to that proposed for the formation of the tropine derivative (210) can be used to explain the formation of the cyclohexanone derivatives (214) and (215). If the reaction is carried out in benzene then the substituted bicyclo[3.3.1]nonan-9-ones (218) and (219) are prepared in high yield.



218) $R = CH_3$, $R^1 = H$

219) $R = H$, $R^1 = CH_3$

A related reaction has been reported [41] for the reaction of chalcone (220) with 1-(1-cyclohexen-1-yl)-4-phenylpiperazine (221) in dry benzene to give the aminohexahydrobenzopyran (222) in 44% yield.

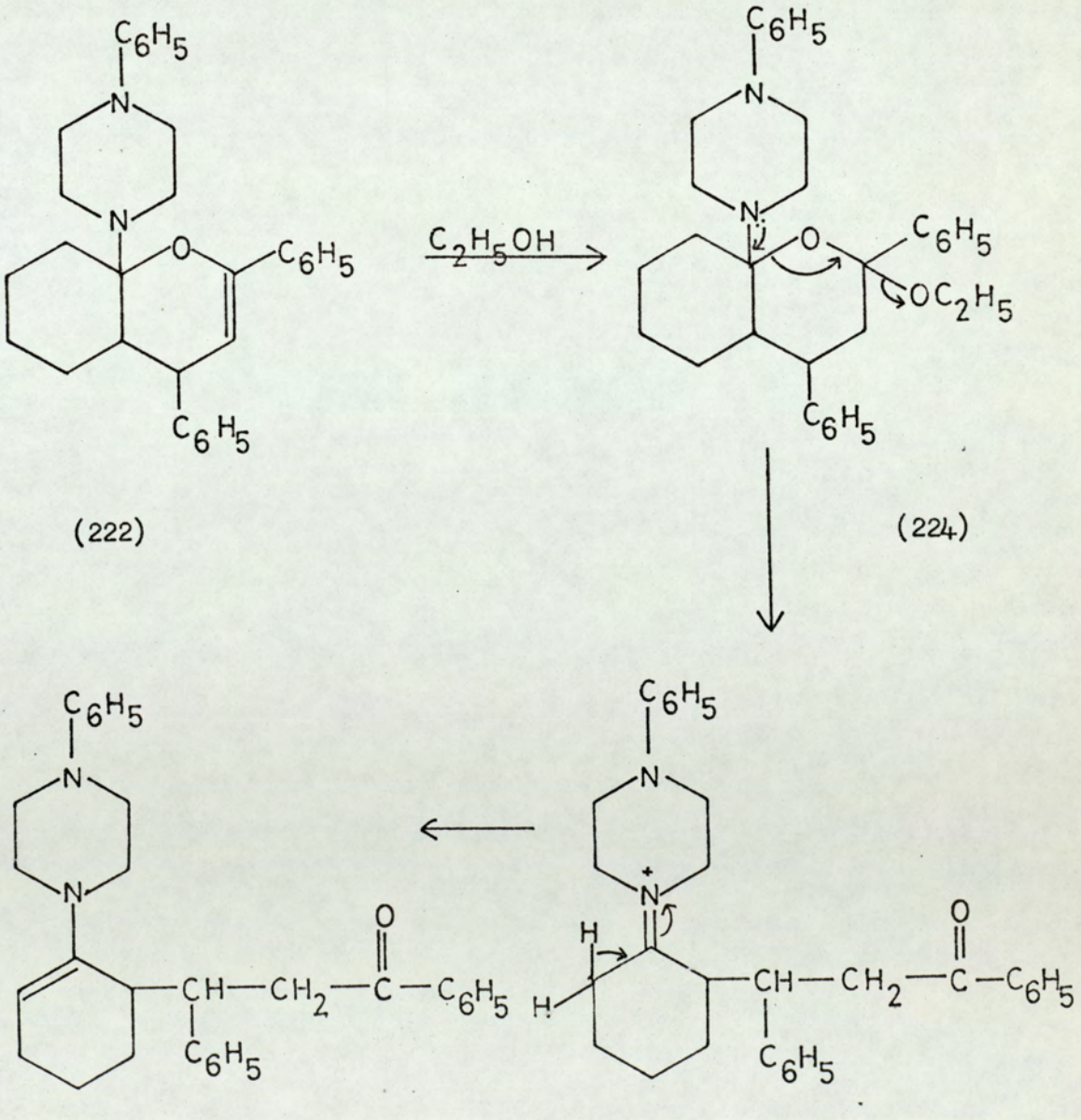


(221) (222)

Isomerisation to the bicyclic ketone (223) was accomplished

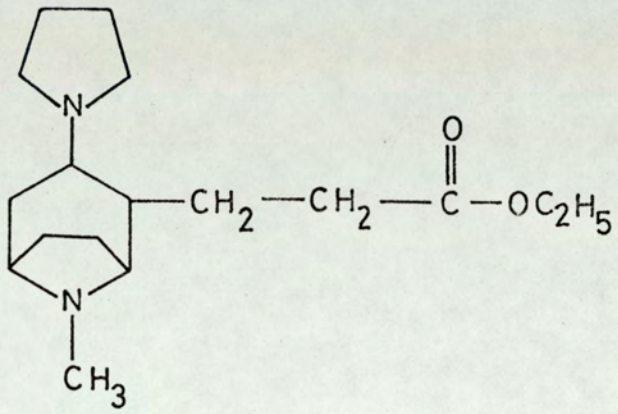
by merely recrystallising a sample of the aminohexahydrobenzopyran (222) from absolute alcohol. In this case the reaction mechanism may be as outlined in fig. 13. Addition of ethanol across the double bond of the dihydropyran (222) to give the intermediate (224) cannot be followed by the same hydride transfer as in the case of the analogous intermediate (211a, fig. 12), and loss of ethanol results in the product (223).

Figure 13



(223)

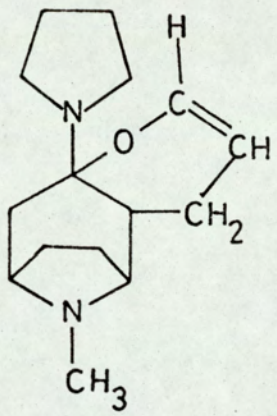
The reaction between the pyrrolidine enamine of tropinone (208) and acrolein, in ethanol, gave a dark red oil from which was distilled tropinone (207). The expected ester (225) could not be shown to be present in the mixture.



(225)

It is interesting to note that although Untch [36] prepared the esters (214) and (215) by reacting the substituted αβ-unsaturated aldehydes, crotonaldehyde and methacrolein, with the pyrrolidine enamine of cyclohexanone in alcohol, the reaction with acrolein in alcohol gave the bicyclic ketones (160 and 161 page 78). The reaction in ethanol of an enamine and an αβ-unsaturated aldehyde may require the presence of a substituent on the aldehyde for the reaction to proceed to the ester. In the absence of the possible stabilising influence of a substituent, the intermediate dihydropyran may not be formed or may be readily hydrolysed to the starting ketone. The reaction of the tropinone enamine (208) with cinnamaldehyde would appear to give the expected dihydropyran intermediate (211) since

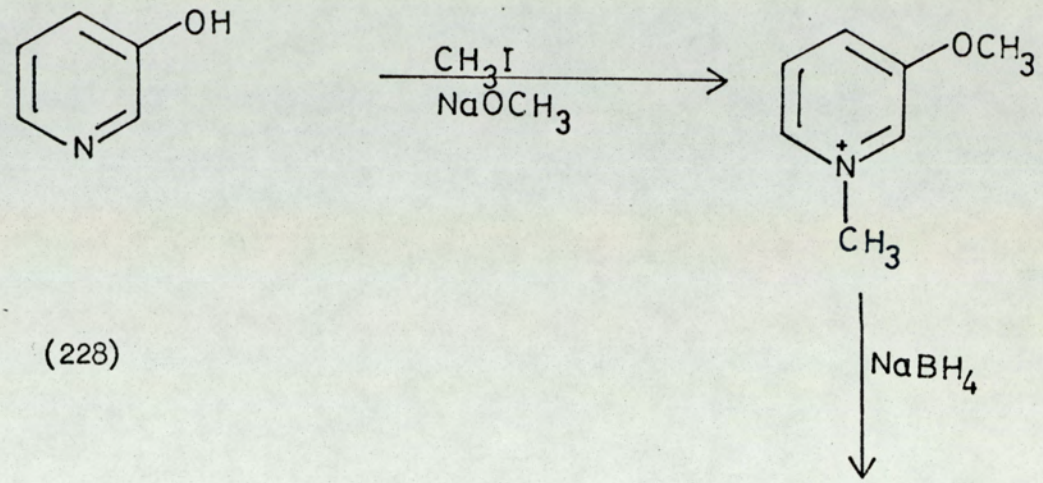
the ester (210) was produced, indicating that the initial reaction to give the intermediate (212) had occurred. Cyclisation to the tricyclic ketone however could not be accomplished. The reaction of the tropinone enamine could not be shown to give the intermediate dihydropyran (226) because the expected ester (225) could not be formed when the reaction was carried out in ethanol.



(226)

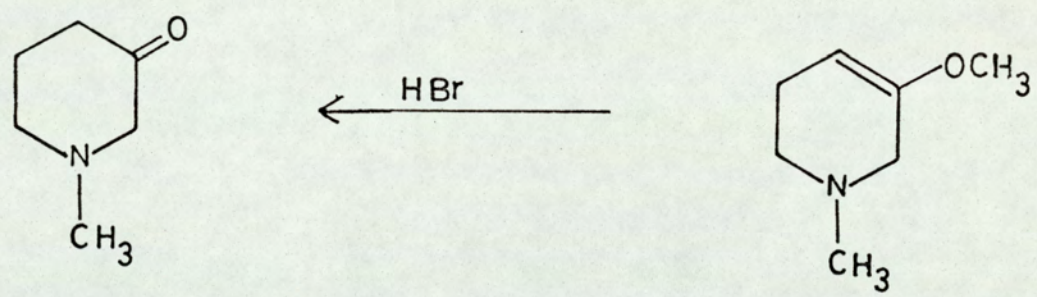
F. Synthesis of some N-substituted 3-piperidone derivatives.

1-Methyl-3-piperidone (227) was prepared by a modification of the method of Lyle, Adel, and Lyle.[115] The previous methods of synthesis of N-methyl-3-piperidone[116,117,118] are complex due to the necessity of preparing an unsymmetrical amino diester for the Dieckmann cyclisation, the conventional procedure for preparing piperidones. Lyle, Adel and Lyle however, used the selective reduction of pyridinium salts to tetrahydropyridines by sodium borohydride as a means of a shorter route to 1-methyl-3-piperidone (227).[119,120] 3-Hydroxypyridine (228) was alkylated simultaneously on nitrogen and oxygen with methyl iodide, and, without isolation, the pyridinium salt (229) was reduced with sodium borohydride to 1-methyl-1,2,5,6-tetrahydro-3-pyridyl methyl ether (230). By carrying out the reduction in isopropyl alcohol, instead of methanol as reported by Lyle et al.,[115] the overall yield can be increased to 53% from 28%. On hydrolysis with hydrobromic acid, (230) gave 1-methyl-3-piperidone (227). Using the method of Lyle et al. a crystalline compound was isolated, whose infrared showed absorption at 2350 and 1670 (C = C) $cm.^{-1}$ The mass spectrum showed a molecular ion of $^{m}/e$ 140 and also the presence of boron. Analysis confirmed the presence of a boron intermediate such as (231). The compound was found to be stable in the crystalline form and could be stored as such.



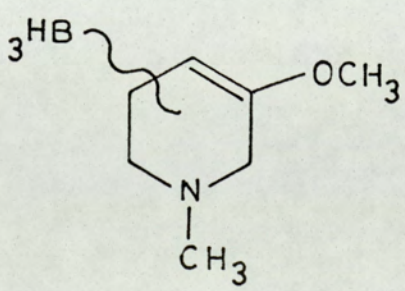
(228)

(229)



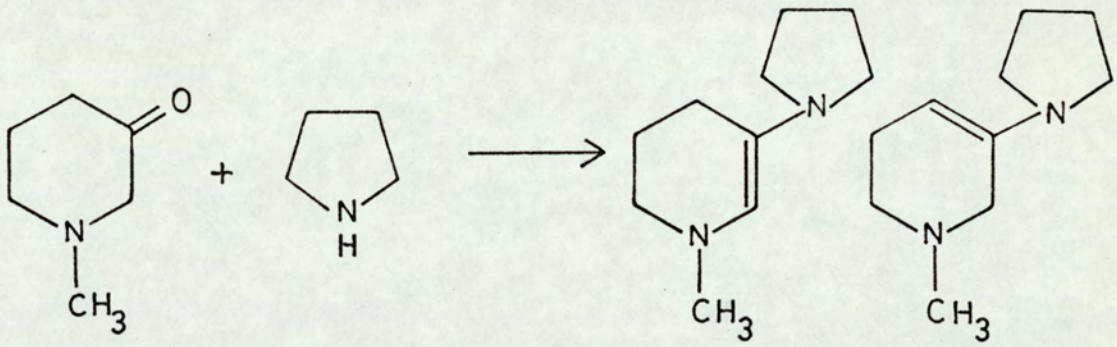
(227)

(230)

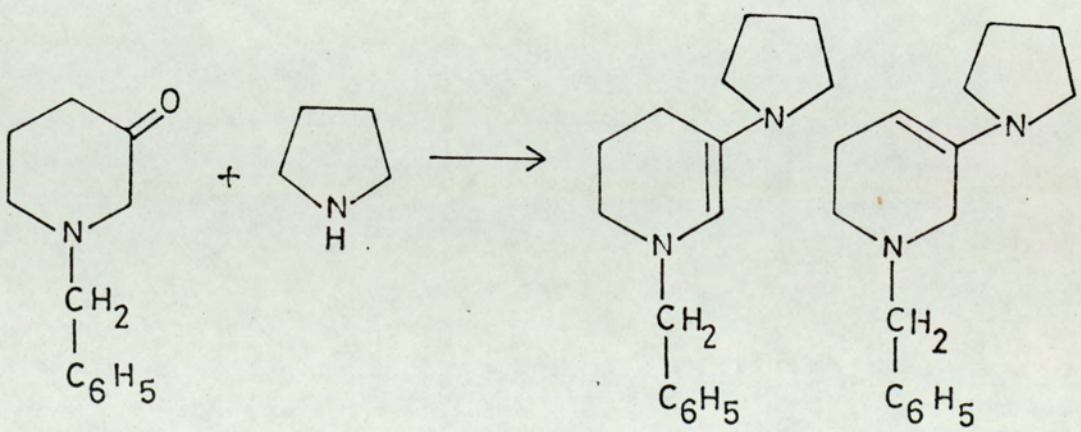


(231)

On refluxing the N-methyl-3-piperidone (227) in benzene with excess pyrrolidine under a water separator, the enamine (232) was prepared, as shown by its mass spectrum. The reaction might, in principle, have given rise to the enamine (232) or its isomer (233) or a mixture of these compounds. It has been shown however, [121] that the reaction of pyrrolidine with 1-benzyl-3-piperidone (234) gave an unstable enamine (84% yield) whose structure was shown to be (235) and not (236).



(227) (232) (233)

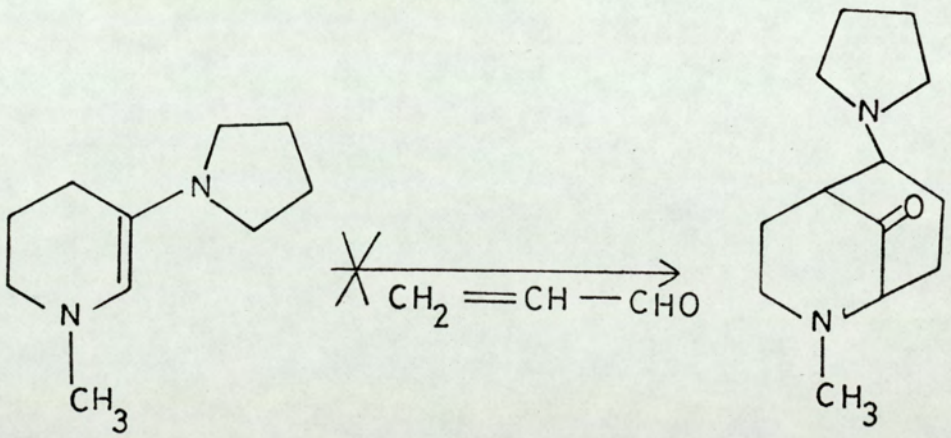


(234) (235) (236)

This was clearly demonstrated by the NMR spectrum which contained a singlet encompassing one proton at τ 5.15. It was not decided whether the enamine (232) arose from kinetic or thermodynamic control, but it might be assumed that it is the more stable of the two enamines since it contains conjugation of the "lone pair" of the N-methyl nitrogen atom with the double bond. From these results it seems likely that the enamine formed by the reaction of 1-methyl-3-piperidone (227) with pyrrolidine was (232) and not (233).

The reaction of the enamine (232) with acrolein did not lead to the ketone (237) but gave a dark reaction mixture from which no products could be isolated, fig. 14.

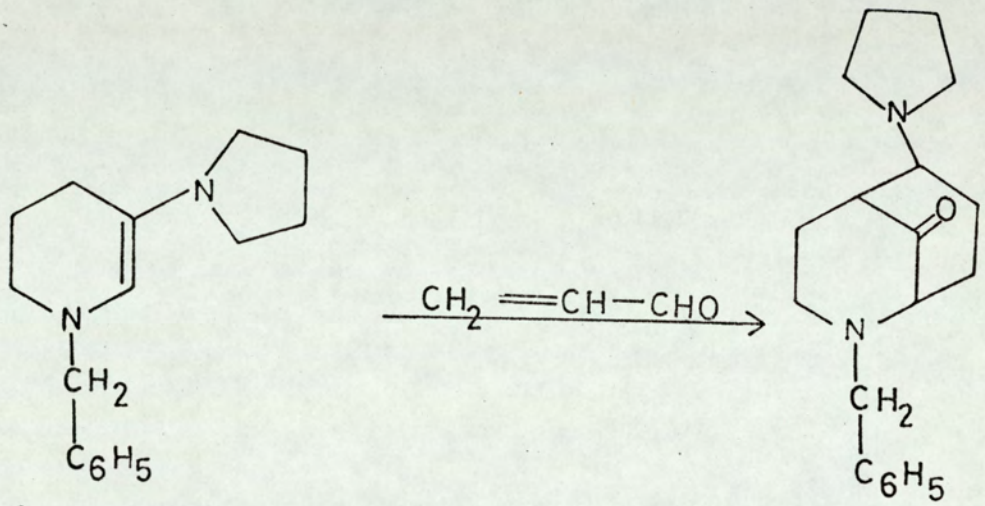
Figure 14



(232) (237)

The reaction was repeated using the piperidine enamine of N-methyl-3-piperidone (239)[1] but again no identifiable product could be isolated.

N-Benzyl-3-piperidone (234) reacted with pyrrolidine to give the enamine (235). This enamine reacted with acrolein to give a dark red oil, the infrared of which showed absorption at 1720 (C = O) $cm.^{-1}$ which indicated that the desired bicyclic ketone (239) had been formed.



(235) (239)

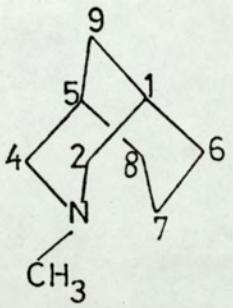
Tlc of the oil showed a mixture of three or more components. Column chromatography of a sample of the oil on a neutral alumina column allowed the fastest moving component of the mixture to be separated. The mass spectrum of this product showed it to be the ketone (239). Tlc of the product failed to show the presence of two ketones, but in view of the difficulty of separation of the pyrrolidine ketones (75) and (76) (page 30) this does not necessarily prove the presence of one isomer only.

As a route to the bicyclic ketone (239) this is not a clean, quick route as found for the bicyclic ketones derived from 4-piperidones

and as such is not a convenient method of preparing 2-azabicyclo[3.3.1] nonanes.

G. NMR study.

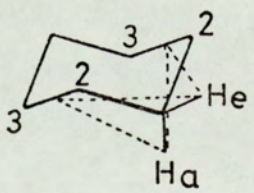
There is at present no reported systematic study of the NMR spectra of the bicyclo[3.3.1]nonane skeleton. The ring proton signals of cyclic derivatives are more complex when substituents are present and when rings are heterocyclic, and are particularly difficult to resolve in compounds which show pronounced conformational preferences. In these cases, axial and equatorial environments are not averaged and complex coupling patterns arise. It is not surprising that many of the hydrogens in a bicyclo[3.3.1]nonane system will have similar chemical shifts. Each proton has several close neighbours, the bridgehead C - 1 and C - 5 hydrogens for example having a possibility of four vicinal interactions with the methylene hydrogens attached to C - 2 and C - 8 or C - 5 and C - 6.



Also, all the methylene hydrogens have a unique chemical environment, and have a distinctive, similar chemical shift. The result is extensive spin-spin coupling, which manifests itself in a very large number of unresolved multiplets, sometimes referred to as the methylene envelope.

A single proton geminal to an electronegative substituent may, however, often be moved sufficiently downfield to be clear of the main proton band, and data of stereochemical value may be obtained from the resolution of such signals. Since the frequency of the chemical shift is directly proportional to the applied field, the use of high field strengths and appropiately larger radio frequencies further enhances the resolution. For this reason, the spectra of the azabicyclononanes and bicyclononanes presented for discussion have been obtained at 220 MHz. Further, it has been established for a wide variety of six-membered ring systems that axial ring protons absorb at higher field than do their epimeric equatorial counterparts. These chemical shifts (δae) have their origin in a long-range shielding effect associated with anisotropies of the magnetic susceptibilities of the carbon-carbon single bonds bearing a 2 - 3 relation to the absorbing protons. [121] The situation for a simple cyclohexane ring is summarised in fig. 15.

Figure 15

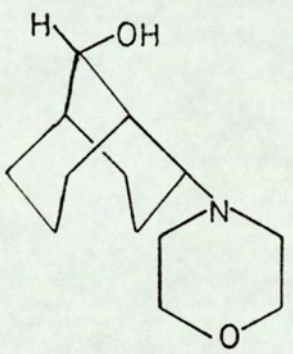


He (Deshielded by 2-3 bonds)

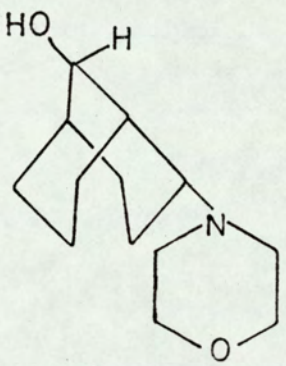
Ha (Shielded by 2-3 bonds)

Experimental values of δae lie in the range 0.1 - 0.7τ, [122] although even larger values may be observed when the axial/equatorial protons are further influenced by the anisotropy of neighbouring substituents. Thus the proton signals which are moved sufficiently to be outside the methylene envelope are discussed although in some instances peaks such as the $N\text{-}CH_3$, which are found within the methylene envelope are assigned.

1) 2-Substituted bicyclo[3.3.1]nonanes.



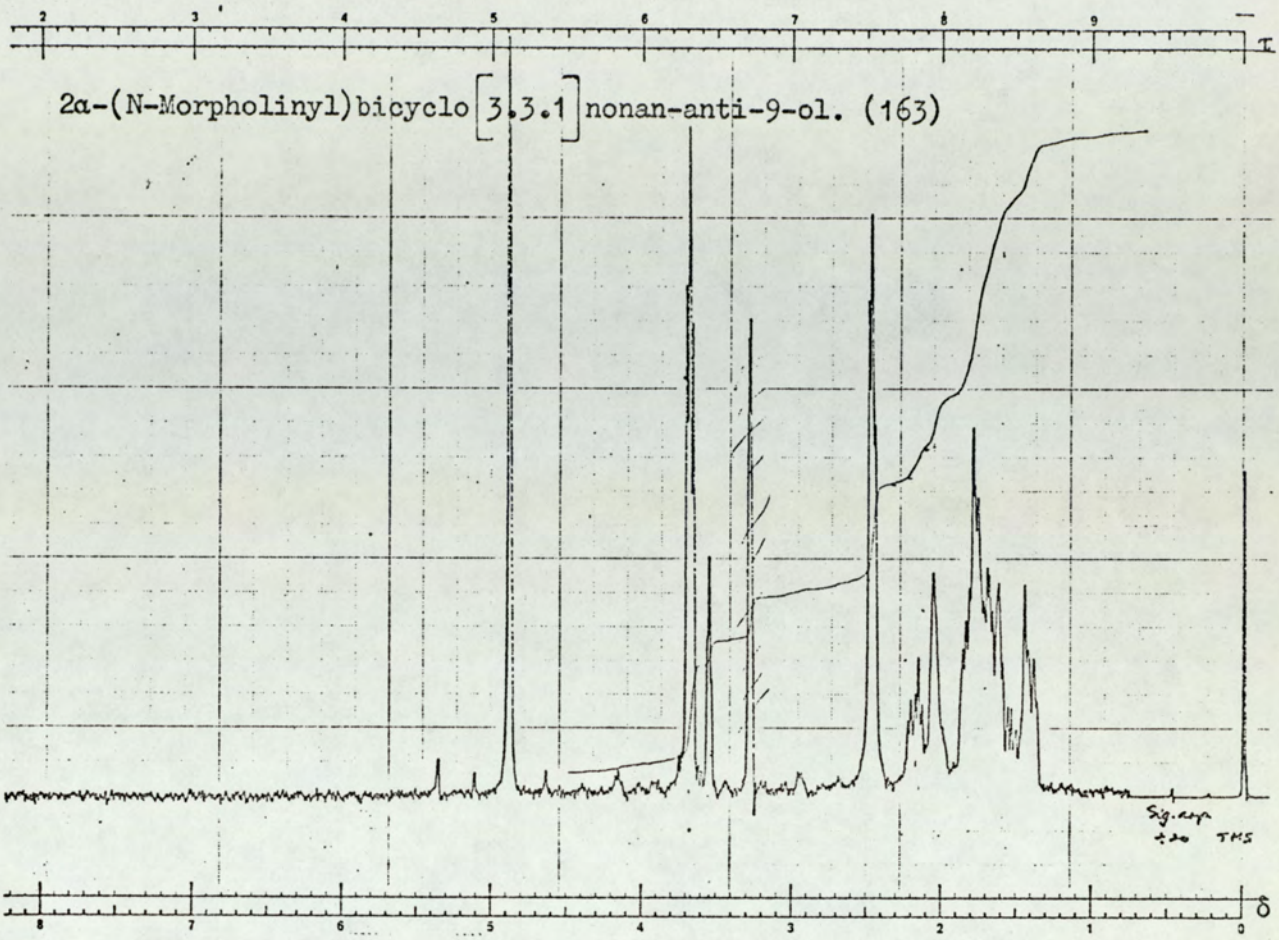
(162)



(163)

The 9CH proton resonates at 6.2τ in alcohol (162) and 6.45τ in alcohol (163), fig. 16. Both compounds are believed to exist with the carbocyclic ring not containing the morpholine group in a skew or boat form. Thus an interaction can occur in alcohol (162) between the $7CH_2$ and the 9CH protons resulting in a deshielding effect caused by mutual repulsion of the electron clouds surrounding each proton. A similar effect has been reported by Robinson [123] to account for the low τ-values of the endo 7-hydrogen atoms in the spectrum of

Figure 16


2α-(N-Morpholinyl)bicyclo[3.3.1]nonan-anti-9-ol. (163)
τ
δ
Sig. exp.
± 2σ TMS

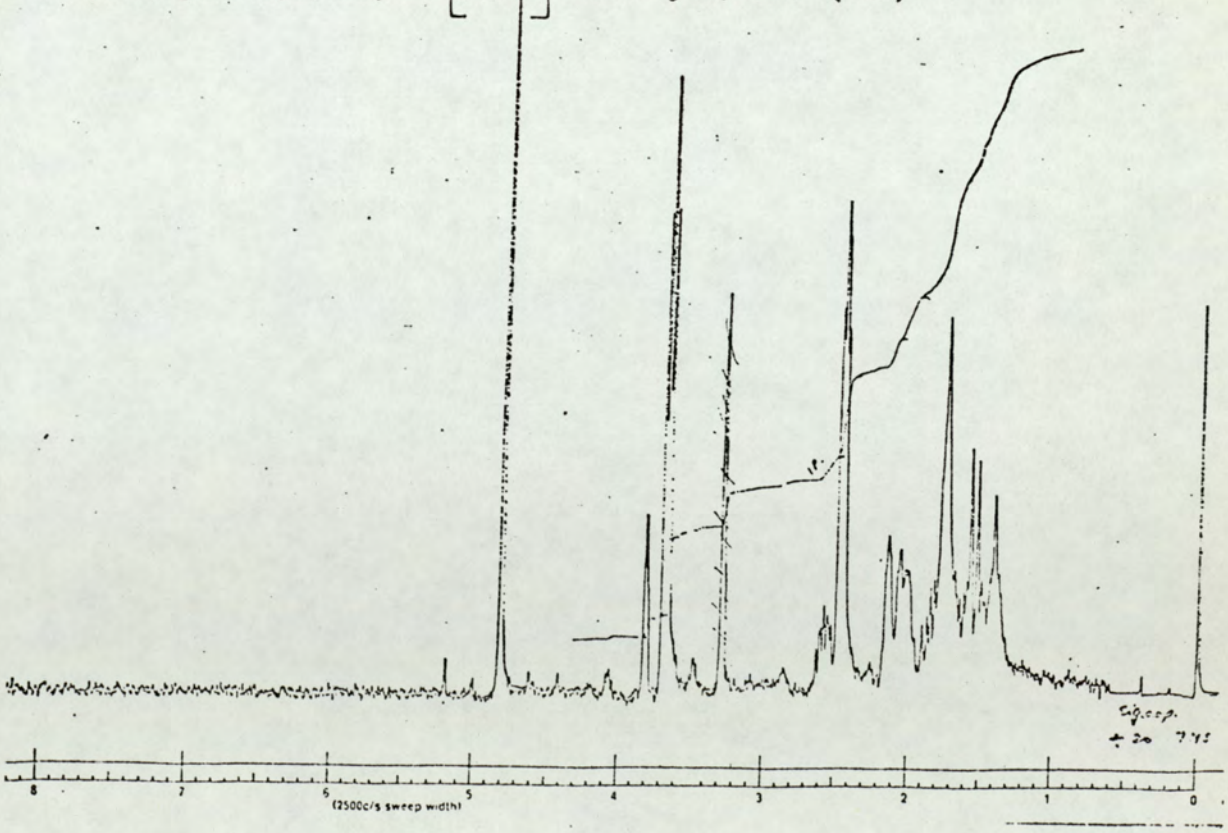
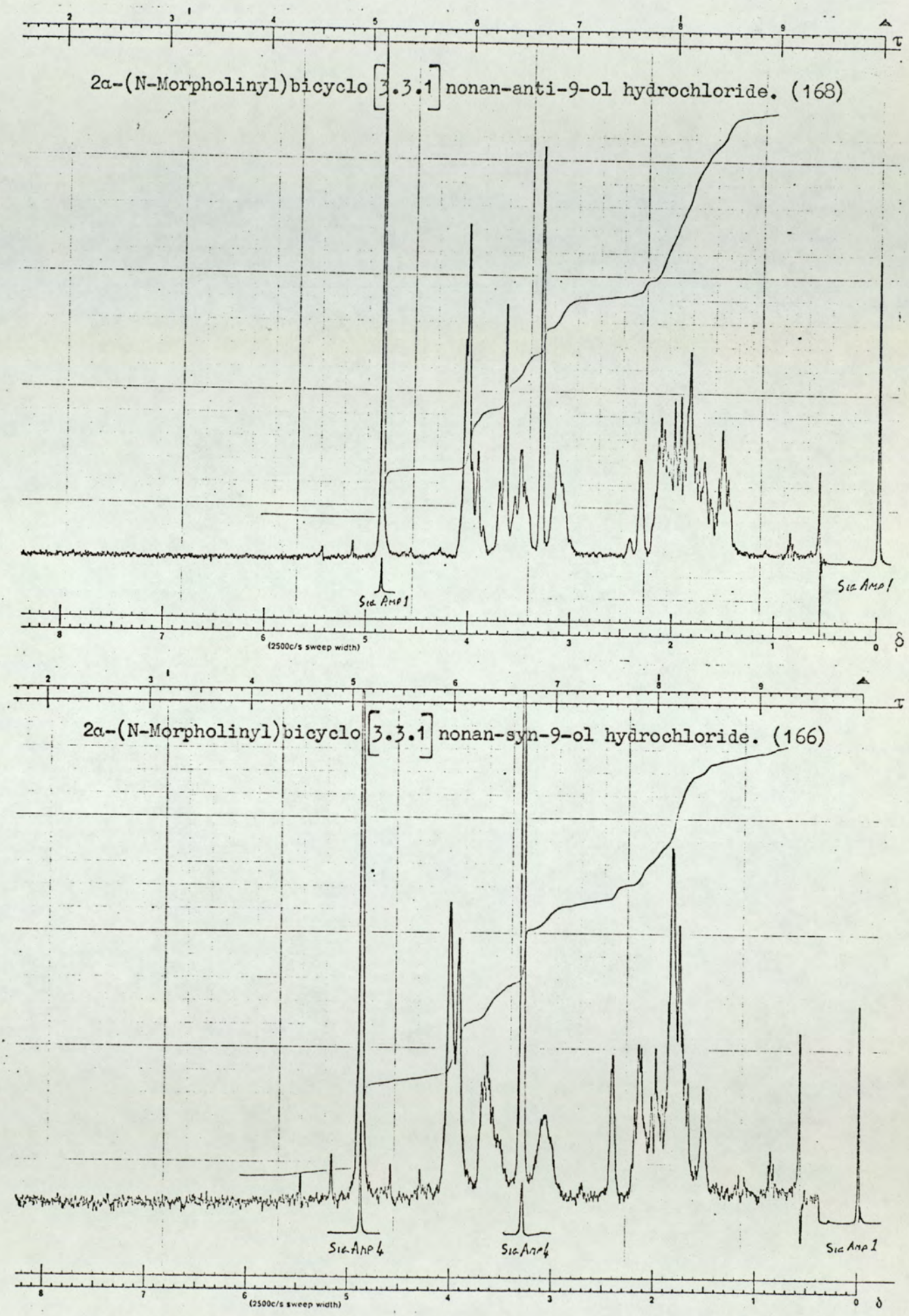

2α-(N-Morpholinyl)bicyclo[3.3.1]nonan-syn-9-ol. (162)
δ
(2500c/s sweep width)

Figure 17


2α-(N-Morpholinyl)bicyclo [3.3.1] nonan-anti-9-ol hydrochloride. (168)
τ
Sig Amp 1
Sig Amp 1
δ
(2500c/s sweep width)
2α-(N-Morpholinyl)bicyclo [3.3.1] nonan-syn-9-ol hydrochloride. (166)
τ
Sig Amp 4
Sig Amp 4
Sig Amp 1
δ
(2500c/s sweep width)

3-azabicyclo[3.3.1]nonane. Qualitatively similar deshielding is found in the 3-oxa- and 3-thia-bicyclo[3.3.1]nonanes.[124] This deshielding effect is attributed to the proximity of an unshared pair of electrons on the heteroatom to the endo 7-hydrogen atom because (a) similar effects are found whenever heteroatoms with unshared pairs are close to hydrogen atoms, (b) the effect is not found in the salts of azabicyclononanes, and (c) the chemical shifts of the endo 7-hydrogen atom is very sensitive to the addition of methanol, which causes large shifts to high field. In alcohol (162) the deshielding is explained by an interaction between the $7CH_2$ and 9CH protons. Alcohol (163) has the 9CH proton syn to the morpholine group and not deshielded to the same extent, explaining the chemical shift of 0.25τ to higher field. The 9CH proton is seen to be a triplet, J = 2.5 Hz, which is presumably caused by two overlapping doublets produced by splitting with the 1CH and 5CH protons.

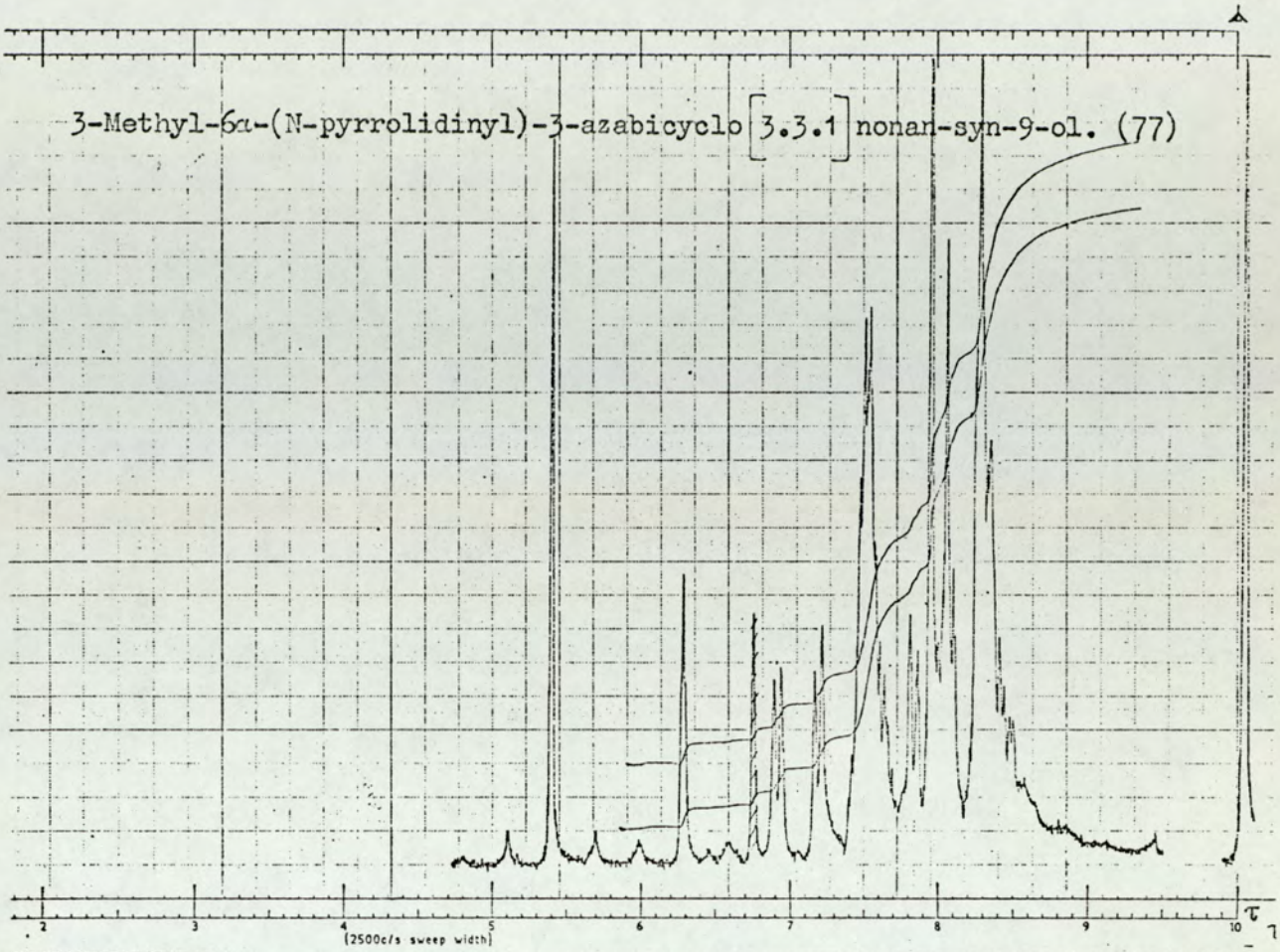
Both the compounds show a multiplet (1H) between 7.4 and 7.9τ. In alcohol (162) this occurs at 7.45τ and in alcohol (163) at 7.85τ. This multiplet is believed to be caused by the resonance of the 2CH proton. The difference in chemical shift is the expected result of the deshielding action of the hydroxyl group at C - 9 on the C - 2 proton. In alcohol (162) the hydroxyl group deshields the C - 2 proton, moving it downfield. In alcohol (163) however, the

C - 2 proton cannot be deshielded in this manner and resonates at 0.4τ higher field. The hydrochlorides of these alcohols (Fig. 17) no longer show these multiplets, but the integrated spectrum shows an additional proton absorbing at lower field, obscured by the morpholine protons. The O - CH_2 protons of the morpholine are seen at 6.35τ and the N - CH_2 protons of the morpholine at 7.6τ in the spectra of the bases. Both alcohols show complex absorption and splitting patterns in the 8.1 to 9.0τ region of the spectra due to the methylene envelope.

11) 6-Substituted 3-methyl-3-azabicyclo [3.3.1] nonanes.

A comparison of the spectra of alcohols (77) and (261) fig. 18, confirms that the 9CH proton is a triplet at 6.25τ, since this peak is absent in the spectrum of the deuterated alcohol. Two doublets (J = 10 Hz) are observed in the spectra of these alcohols at 6.9τ (1H) and 7.2τ (1H). Scale expansion showed that each of these doublets shows a further, very small splitting. An identical pair of doublets are observed in the spectrum of alcohol (138), fig. 19, each integrating for one proton. By comparison with the deaza alcohols (162) and (163), fig. 16, only the 9CH, 2CH, and morpholine protons resonate below 7.9τ. The 2CH proton in alcohols (162) and (163) is a multiplet above 7.4τ. By analogy, the 6CH proton in alcohols (77) and (138) would not be expected to resonate as low as 7.2τ. The doublets

Figure 18


3-Methyl-6a-(N-pyrrolidinyl)-3-azabicyclo [3.3.1] nonan-syn-9-ol. (77)
2
3
4
5
6
7
8
9
10
τ
(2500c/s sweep width)

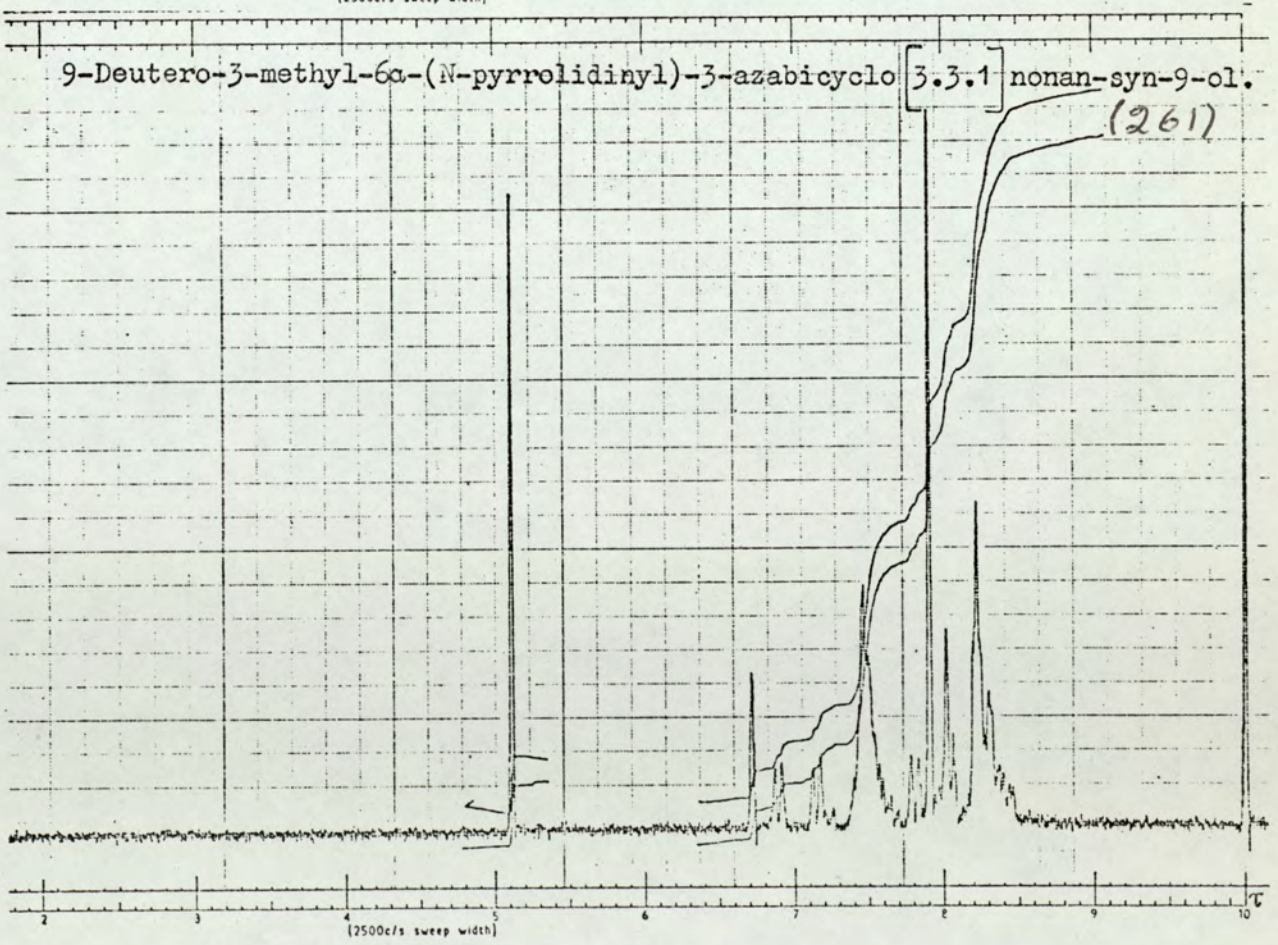
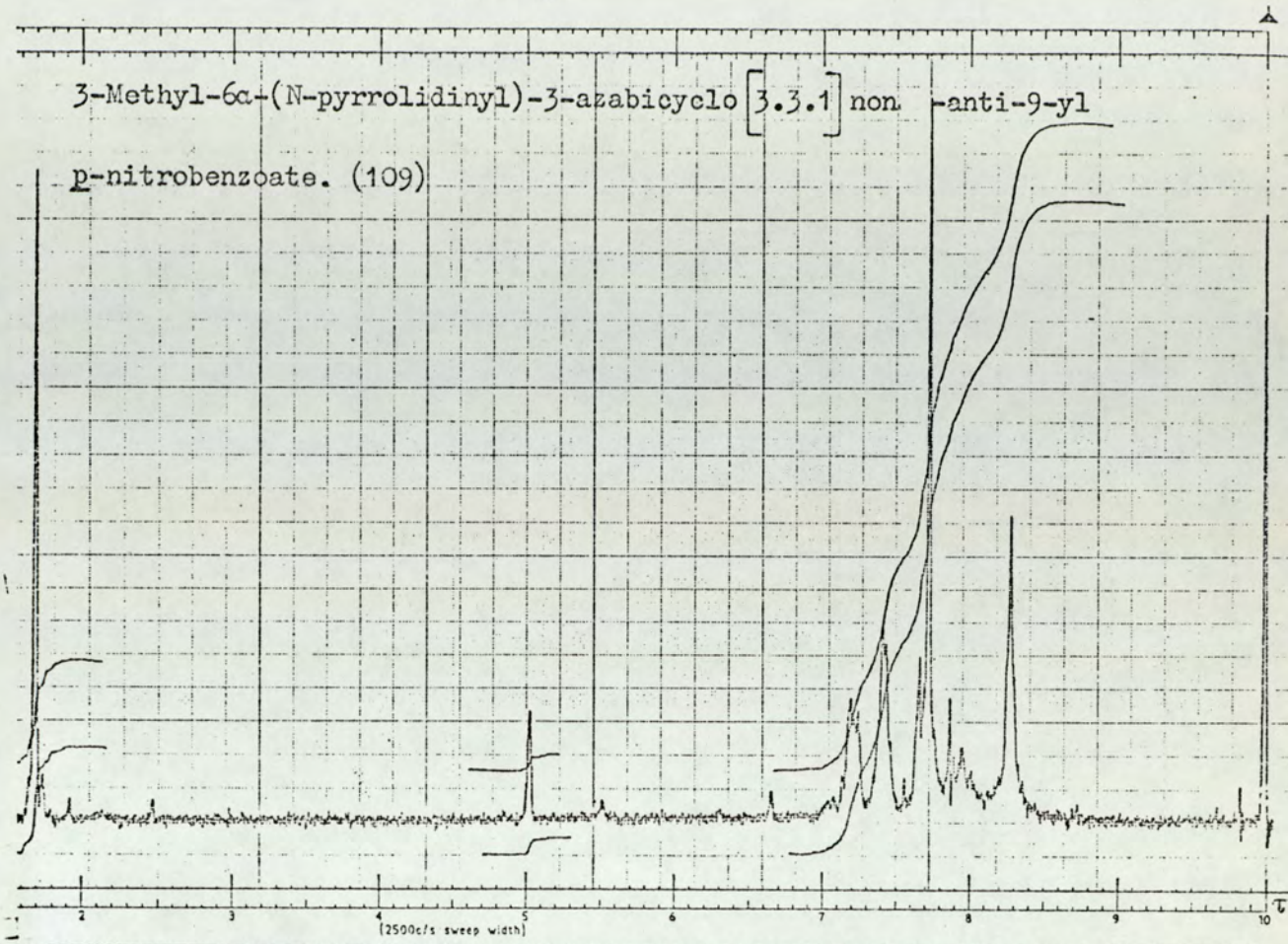

9-Deutero-3-methyl-6a-(N-pyrrolidinyl)-3-azabicyclo [3.3.1] nonan-syn-9-ol.
(261)
2
3
4
5
6
7
8
9
10
τ
(2500c/s sweep width)

Figure 19


3-Methyl-6α-(N-pyrrolidinyl)-3-azabicyclo[3.3.1]non-anti-9-yl
p-nitrobenzoate. (109)
2
3
4
5
6
7
8
9
10
τ
(2500c/s sweep width)

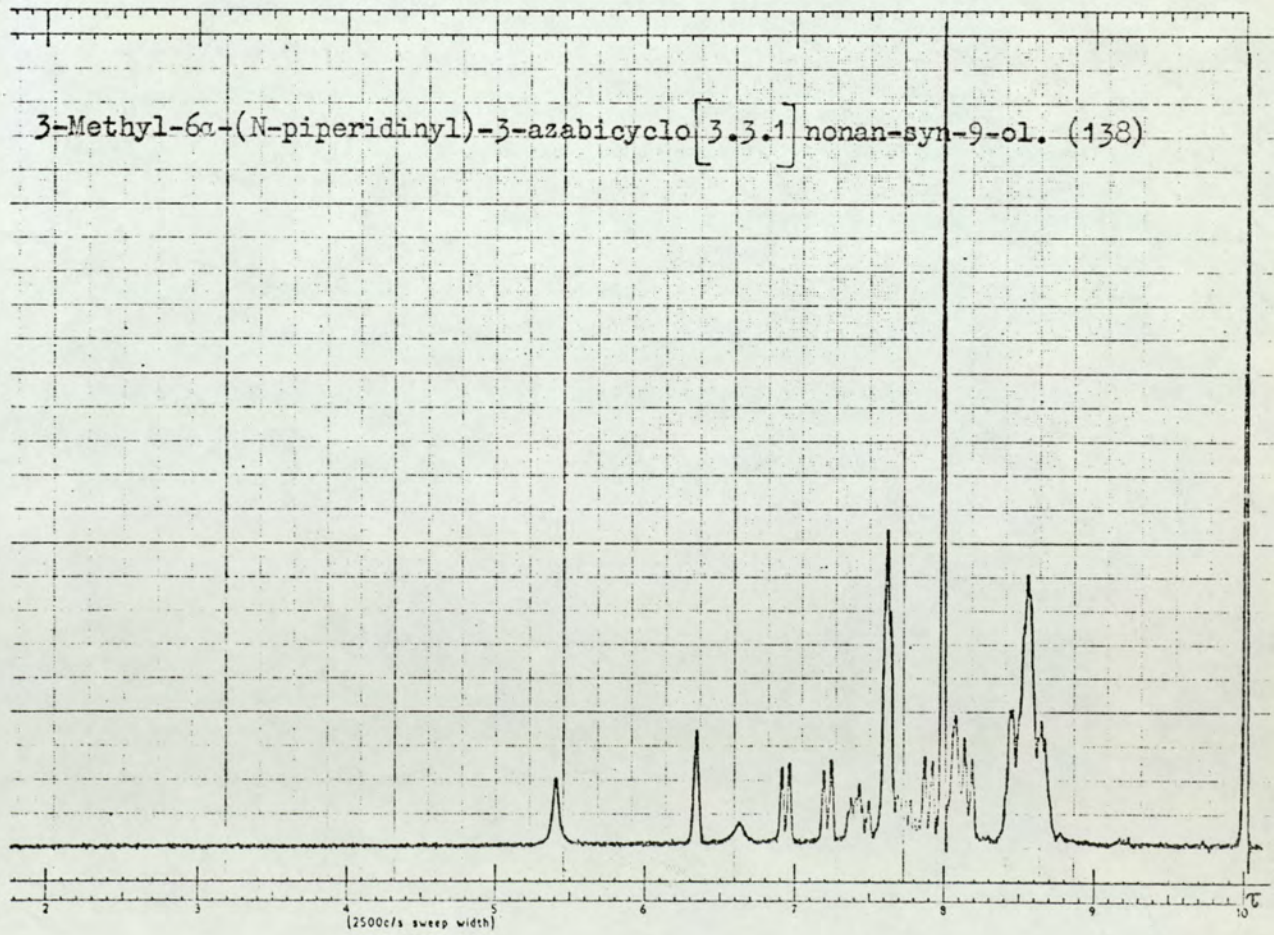
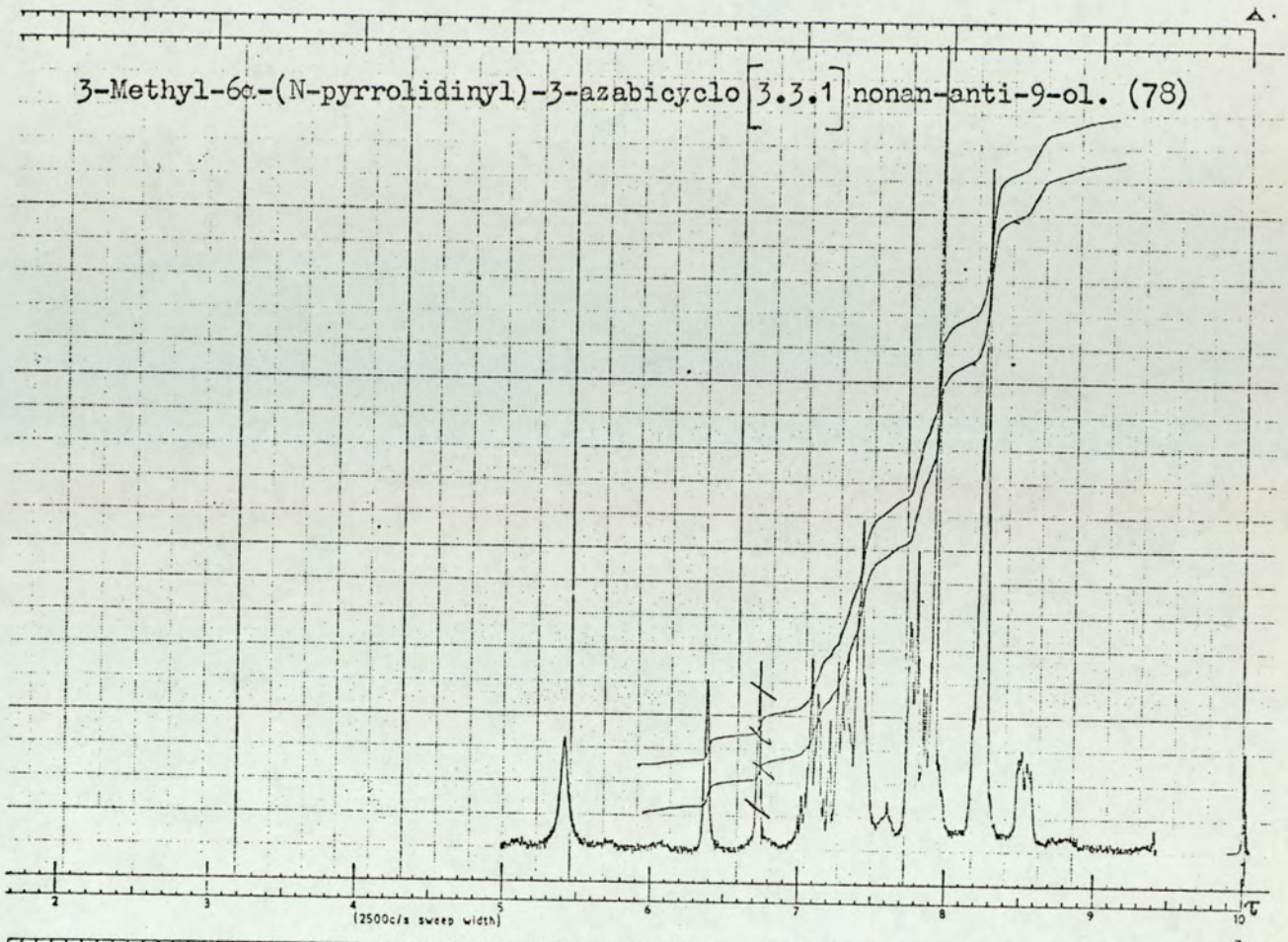

3-Methyl-6α-(N-piperidinyl)-3-azabicyclo[3.3.1]nonan-syn-9-ol. (138)
2
3
4
5
6
7
8
9
10
τ
(2500c/s sweep width)

Figure 20


3-Methyl-6α-(N-pyrrolidinyl)-3-azabicyclo[3.3.1]nonan-anti-9-ol. (78)
(2500c/s sweep width)
τ

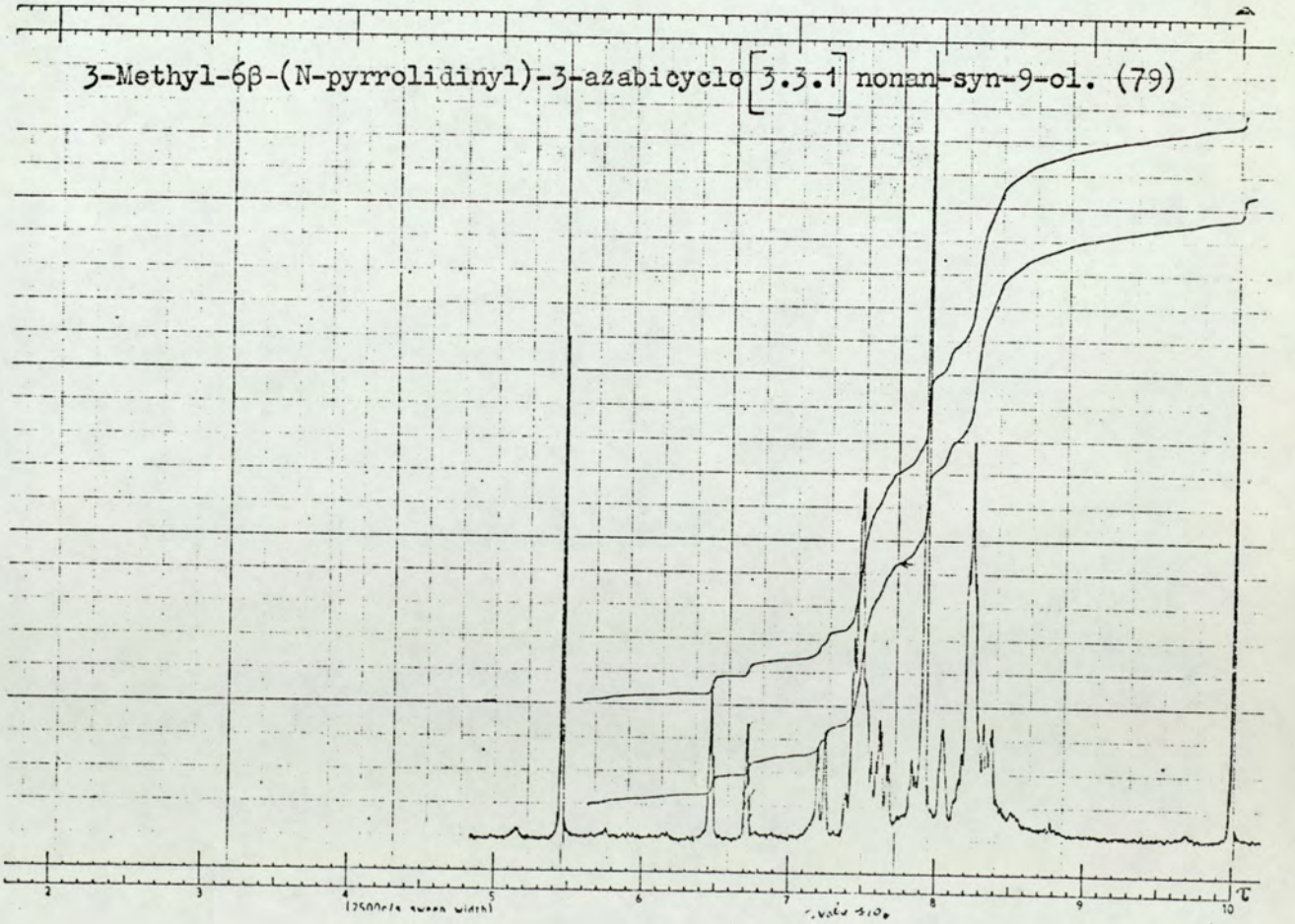
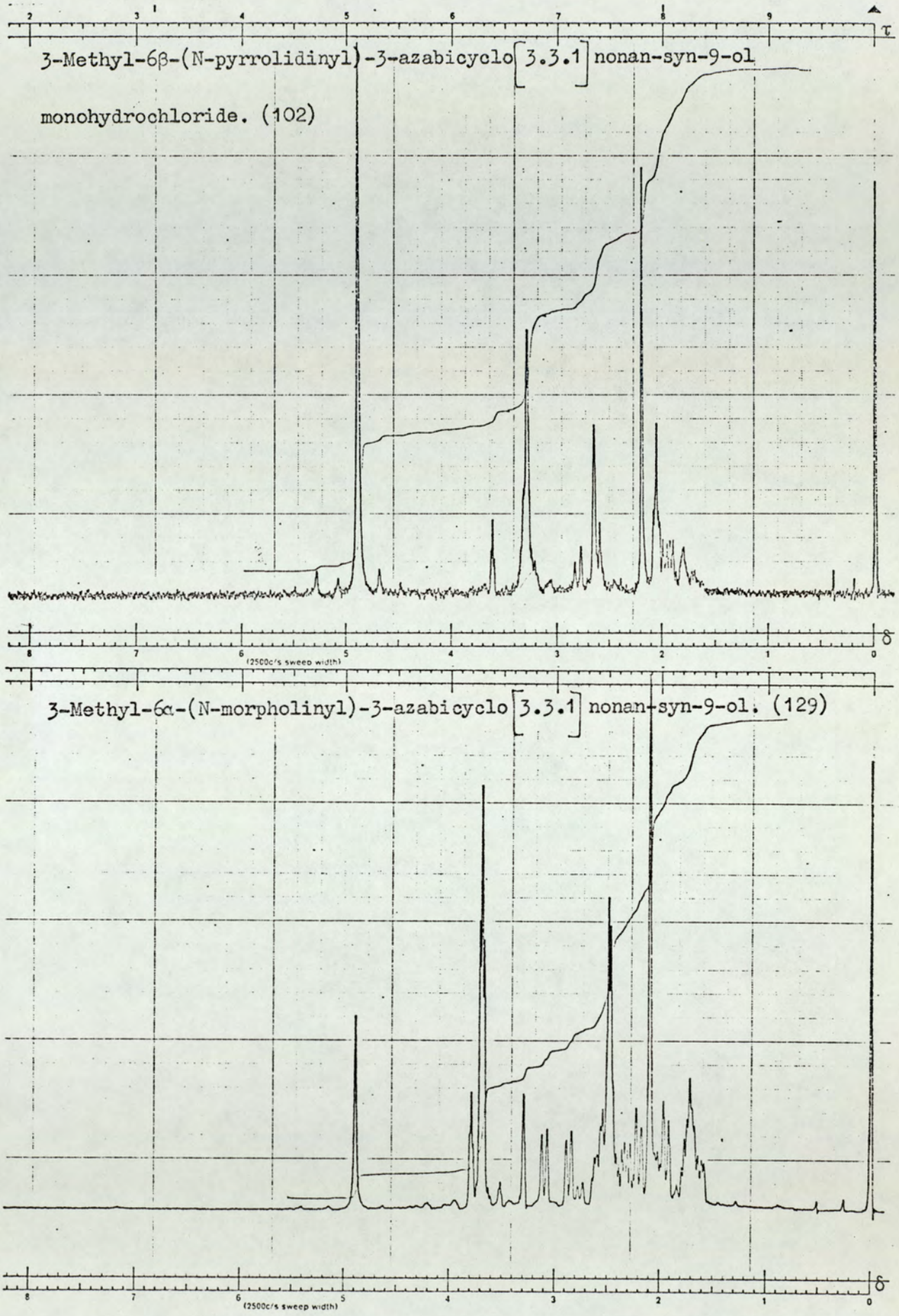

3-Methyl-6β-(N-pyrrolidinyl)-3-azabicyclo[3.3.1]nonan-syn-9-ol. (79)
τ

Figure 21


τ
3-Methyl-6β-(N-pyrrolidinyl)-3-azabicyclo[3.3.1]nonan-syn-9-ol
monohydrochloride. (102)
δ
(2500c/s sweep width)
3-Methyl-6α-(N-morpholinyl)-3-azabicyclo[3.3.1]nonan-syn-9-ol. (129)
δ
(2500c/s sweep width)

are believed to be outside the methylene envelope due to the deshielding effect of the methylamino group. The choice of protons giving rise to these resonances is believed to be either the C - 2 and C - 4 methylene protons or the C1 and C5 protons. Since each doublet integrates for one proton, they are unlikely to be the C - 2 and C - 4 protons since they would be expected to have very similar chemical shifts for both the axial protons and also for the equatorial protons. House [50] found that in 6-unsubstituted azabcicyclo[3.3.1]nonanes, the C - 2 and C - 4 protons resonated as a broad multiplet at 7.73τ. It is therefore proposed that the C - 1 and C - 5 hydrogens give rise to the doublets in the alcohols (77) and (138). Unlike the 6-unsubstituted deaza compounds (162) and (163) both these protons are now influenced by a hetero-atom at the 3-position, which produces a deshielding effect. In the alcohols (77) and (138), the low doublets at 6.9τ would be expected to be the 5CH proton because this proton is subject to the influence of an additional heteroatom, the pyrrolidine or piperidine nitrogen, producing an extra deshielding effect. The doublet at 7.2τ would therefore arise because of the resonance of the C - 1 proton.

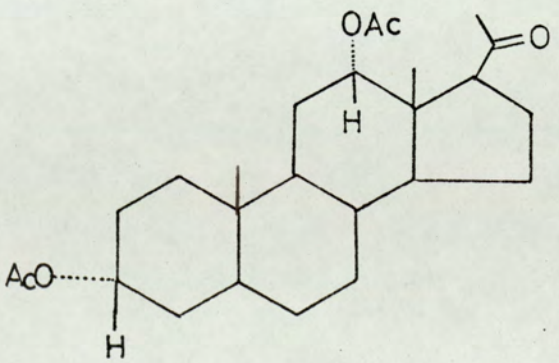
In the spectrum of alcohol (79), fig.20, a doublet (1H), J = 10 Hz, is seen at 7.23τ and the 9CH proton resonates at 6.45τ as a triplet, J = 2.5 Hz. The monohydrochloride (102), fig. 21, of alcohol

(79) also shows the doublet at 7.2τ, indicating that the proton resonating at 7.2τ is far removed from the pyrrolidine group and therefore this resonance cannot be caused by the 6CH proton. This doublet is in a similar position to the higher field doublet in alcohols (77) and (138) and similarly can be assigned to the 1CH proton. However, the 5CH proton would be expected to resonate at lower field than the 1CH proton. However, since no resonance is seen at lower field than this doublet, only a tentative assignment can be made as to the position of the 1CH proton. This doublet however, can not be the 5CH proton.

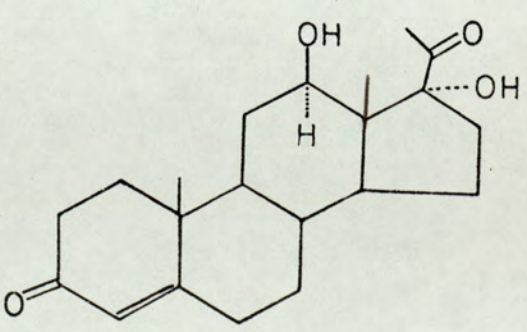
Due to the width of the methylene envelope in alcohol (78), fig. 20, no doublets are clearly visible, although a doublet may be present at 7.1τ, somewhat obscured by the methylene envelope. The 9CH proton is a triplet, J = 2.5 Hz, at 6.4τ. Similarly no doublets are observed in the spectrum of the ester (109), fig. 19, although the 9CH proton is moved downfield to 5.01τ as expected.

Although no multiplet is clearly discernible in the spectrum of alcohol (77), fig. 18, between 7.0 and 8.0τ, a multiplet (1H) can be seen in the spectrum of alcohol (138) at 7.4τ. This is in the same region as the 6CH multiplet for the deaza alcohol (162) which is believed to have the same conformation. It is therefore proposed that the 6CH proton occurs in the region of 7.4τ when the proton is

axial and syn to a hydroxyl group at the C - 9 position. When the 6CH proton is axial and anti to a hydroxyl group at C - 9, the position of the multiplet is 7.7-7.8τ. Due to the width of the methylene envelope in both alcohol (79) and (78), no multiplet in the 7-8τ region is discernible. An important factor in determining the axial or equatorial nature of protons relies upon observations of the half-band width of the proton signal. [125] The axial proton in general has a broader signal than the equatorial proton because diaxial vicinal coupling is larger than axial-equatorial or diequatorial coupling. However, the spectra of the alcohols (77), (78) and (79) do not allow a measurement to be taken. The spectra of alcohols (138), (162) and (163) show a half band width of 23 Hz for alcohol (138), 23 Hz for alcohol (162) and 21 Hz for alcohol (163). These alcohols are believed to exist with the C6 hydrogen in an axial position and in similar environments. These would therefore be expected to give similar coupling patterns. This point is well illustrated by the spectrum of 5β-pregnane-3α, 12α-diol-20-one acetate (240). [126]



(240)



(241)

The axial 3β-proton in the steroid (240) is subjected to two large diaxial and two smaller axial-equatorial vicinal couplings. This combination of splittings results in a broad signal (half-band width 15 Hz) at 5.29τ. The 12β-proton is equatorial however, and its resonance, centred at 4.85τ, is split by relatively small equatorial-axial and diequatorial couplings. The half-band width in this case is only 4 Hz. It can be appreciated that the greatly reduced half-band width of the 12β-proton can be attributed to a combination of two factors; first, its equatorial nature and second, the presence of only two vicinal neighbours. However, even if only the former factor is operative, the large differences in the broadness of patterns due to axial and equatorial hydrogens are readily discernible. This difference may be seen by comparison of the 12β-proton resonances for the steroid (240) and Δ^4-pregnene-12β,17α-diol-3,20-dione (241) which shows a broad signal at 6.0τ (half-band width ≈ 10 Hz). Thus by inspection of the large half-band widths encountered in alcohols (162), (163) and (138) for the C - 6 proton resonance, it can be concluded that in each case the proton is axial.

The position of the N-CH_3 peak is not seen to vary for any of the alcohols studied, resonating between 7.9 and 8.0τ. The ester (109) however shows a downfield shift of 0.2τ. This could be due to an interaction between the methylamino group and the p-nitrobenzoate

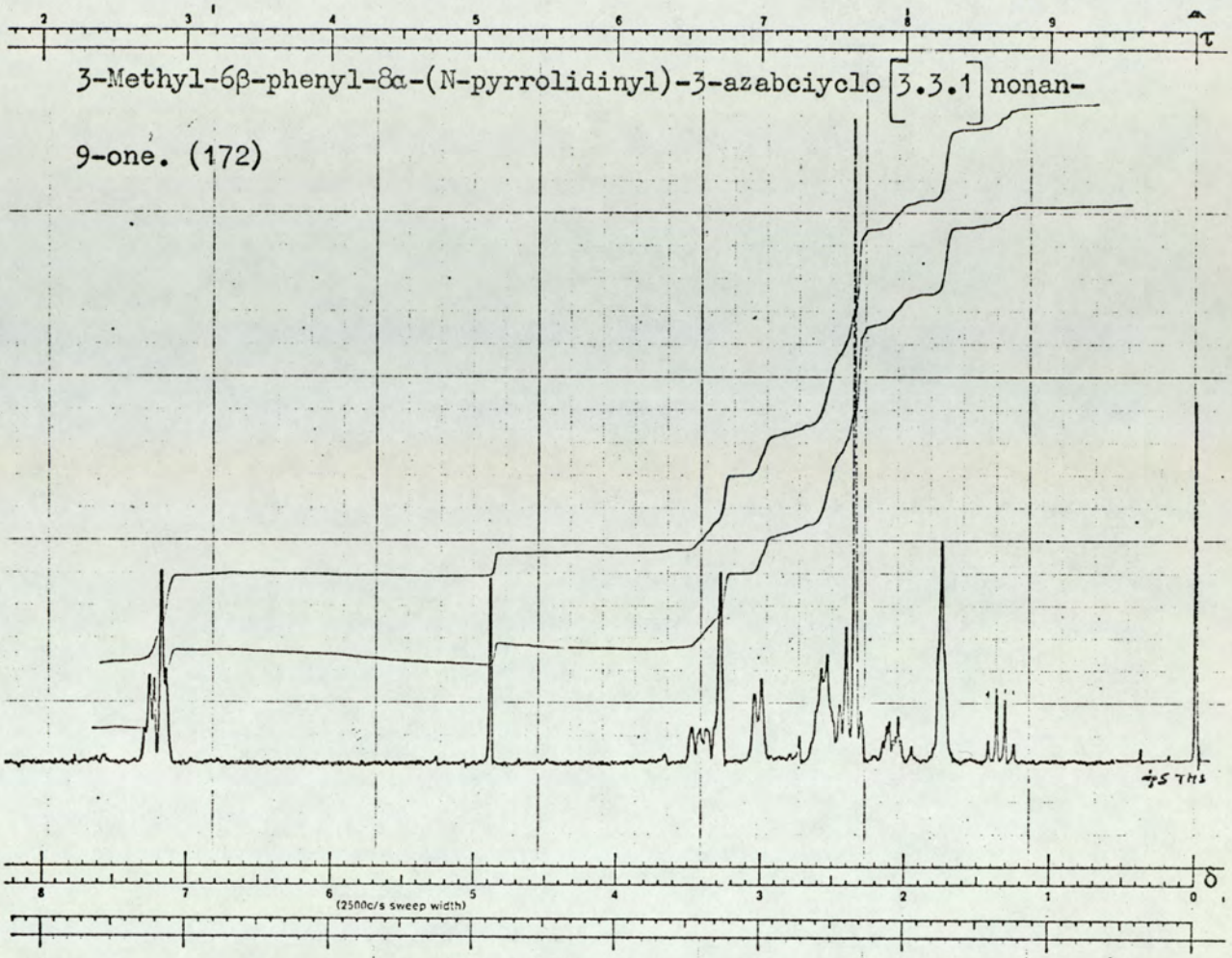
function although the UV spectrum indicated no such interaction.

111) 2-Phenyl-6-cycloalkylamino-bicyclo[3.3.1]nonanes.

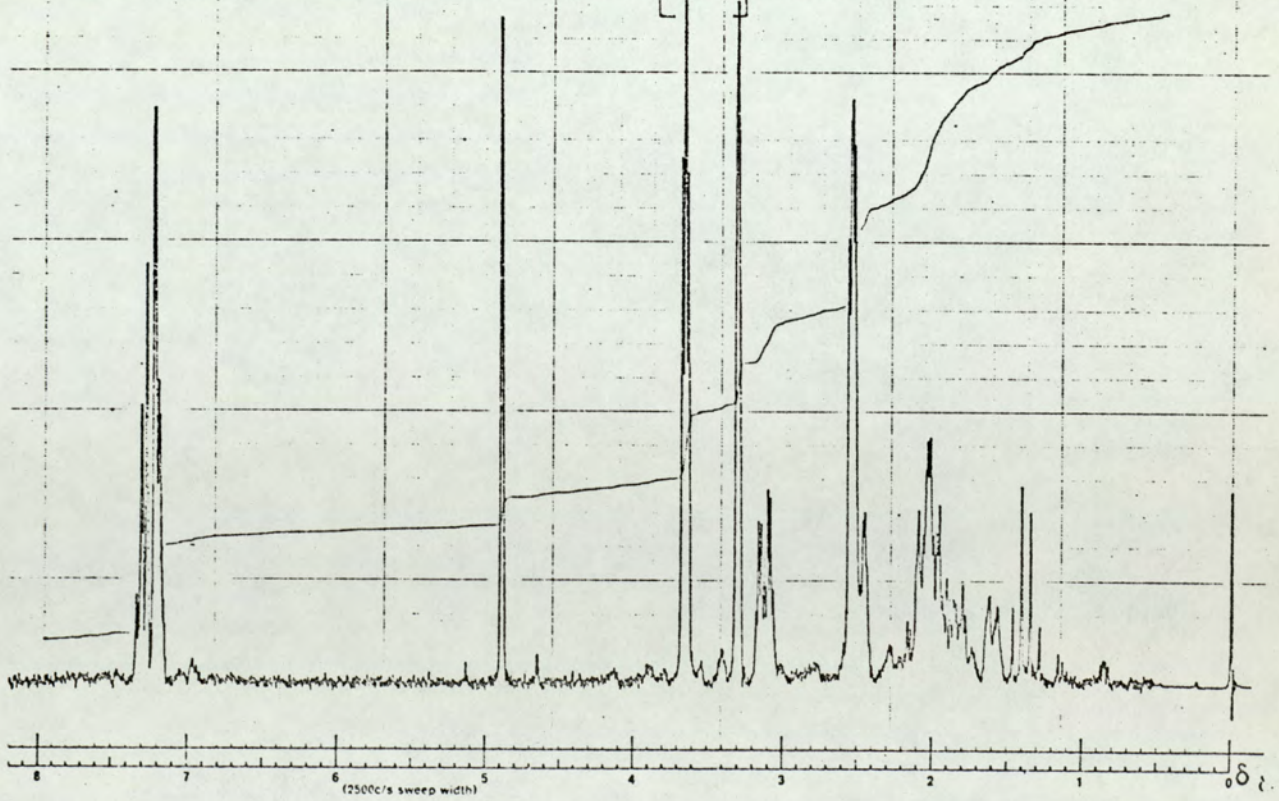
It was considered that from a comparison of the spectra of the ketones (197), (198) and (199) and the alcohols (200), (203) and (205), of known configuration, data of general stereochemical values and applicable to the related 3-azabciyclo[3.3.1]nonane system could be obtained.

The use of the coupling pattern of the benzene ring to determine the stereochemistry of the hydroxyl group and the phenyl substituent has been discussed (page 89). The spectrum of the ketone (197), fig. 22, shows a broad multiplet (2H) at 6.9τ. On scale expansion, seven peaks are seen and appear to be two overlapping quartets. The C - 1 and C - 5 protons of this ketone, by analogy with the deaza alcohols (162) and (163), would not be expected to resonate as low-field as 6.9τ. The resonance at 6.9τ could be due to overlapping resonances of the C - 2 and C - 4 protons, each of which might be expected to be a multiplet due to the presence of three vicinal protons. Of special interest is a quartet centred at 8.65τ. This same quartet is observed in the spectrum of the alcohol (200), fig. 24, although moved downfield to 7.65τ, and is observed at 7.45τ in the hydrochloride (202), fig. 24. This quartet is believed to be the C - 3 axial proton. If this proton was coupled only to the

Figure 22



3-Methyl-6β-phenyl-8α-(N-pyrrolidinyl)-3-azabciyclo [3.3.1] nonan-9-one. (172)



2β-Phenyl-4α-(N-morpholinyl)bicyclo [3.3.1] nonan-9-one. (197)

Figure 23

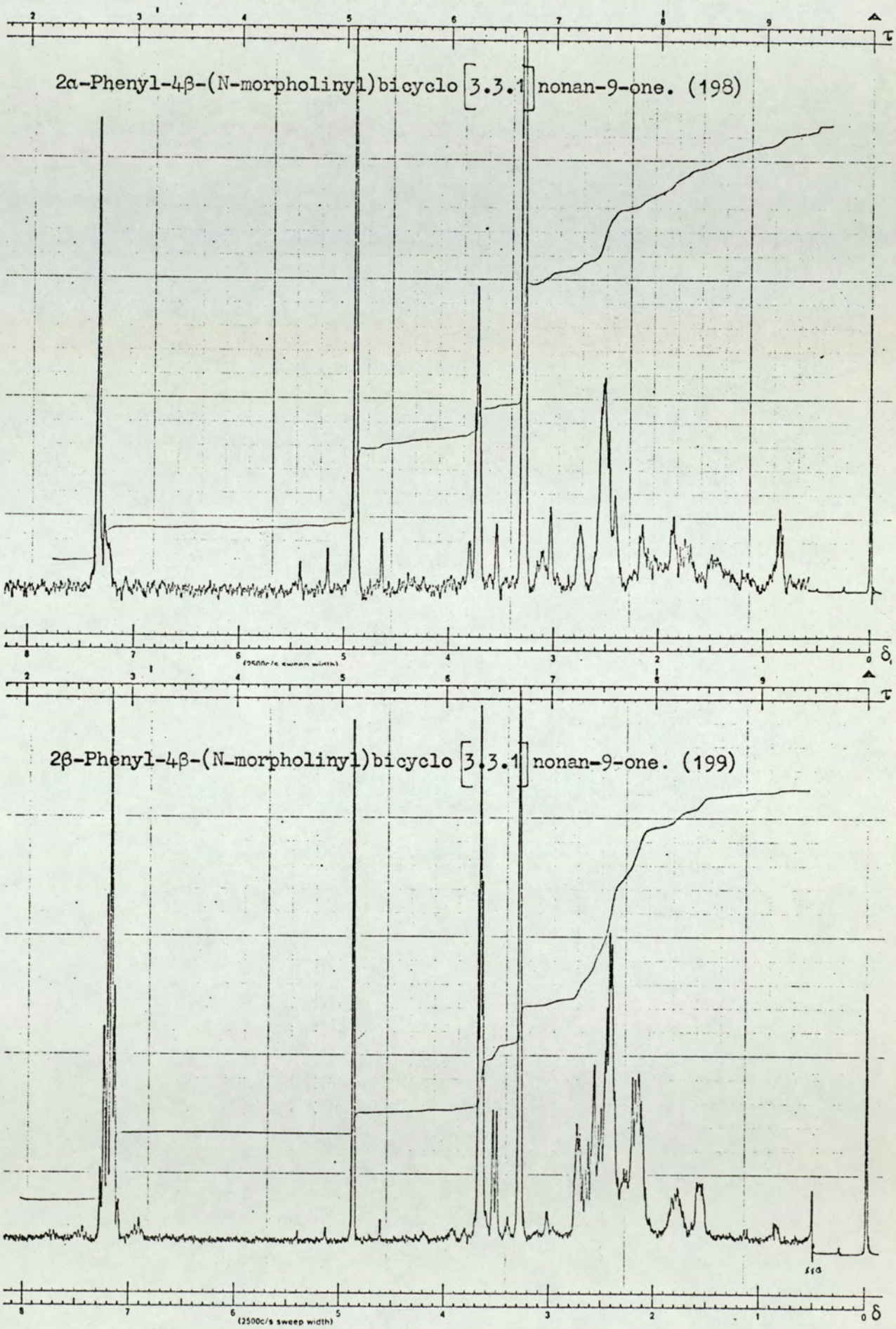
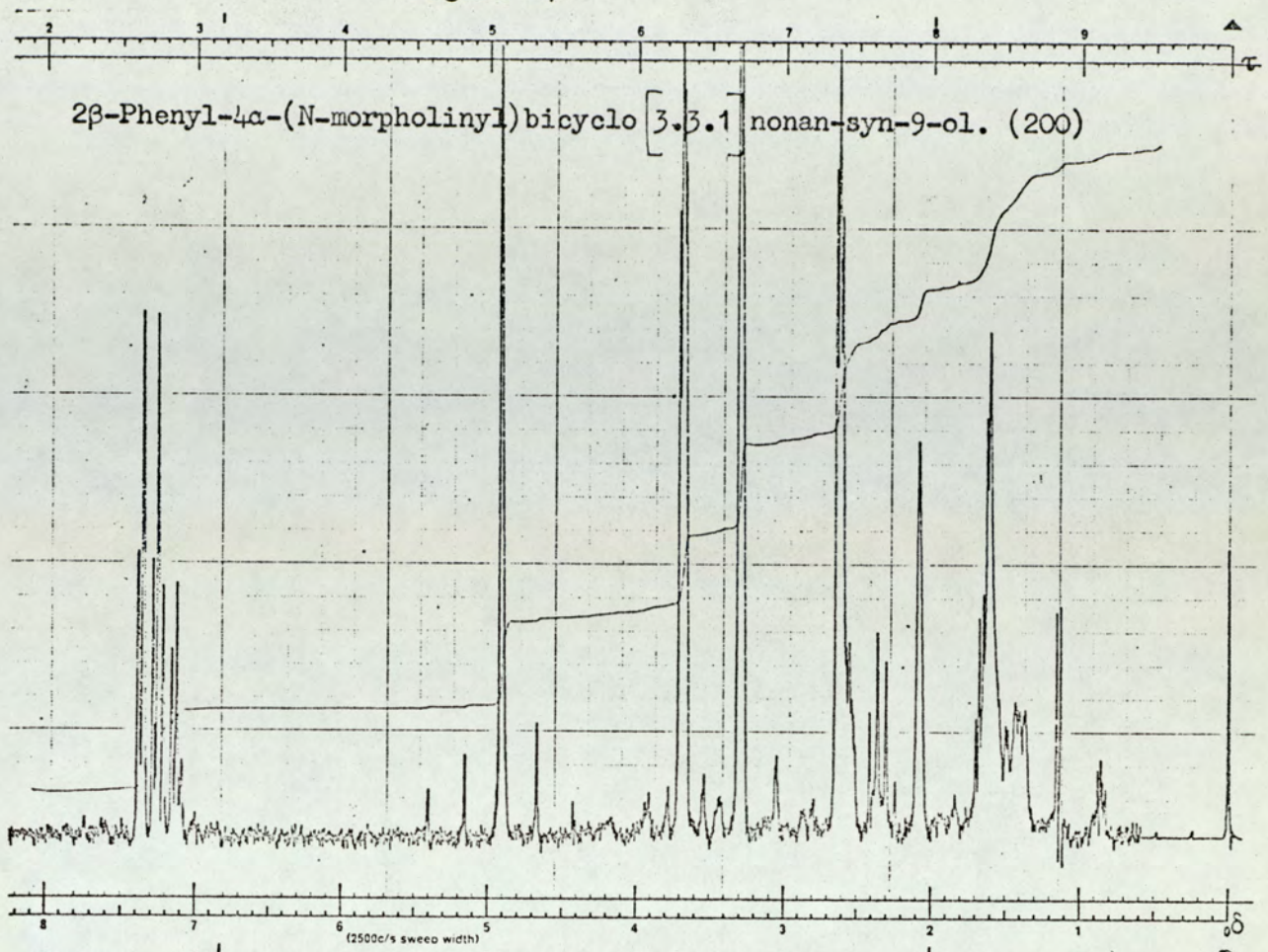

τ
2α-Phenyl-4β-(N-morpholinyl)bicyclo [3.3.1] nonan-9-one. (198)
δ
τ
2β-Phenyl-4β-(N-morpholinyl)bicyclo [3.3.1] nonan-9-one. (199)
(2500c/s sweep width)
δ

Figure 24


2β-Phenyl-4a-(N-morpholinyl)bicyclo [3.3.1] nonan-syn-9-ol. (200)
τ
δ
(2500c/s sweep width)

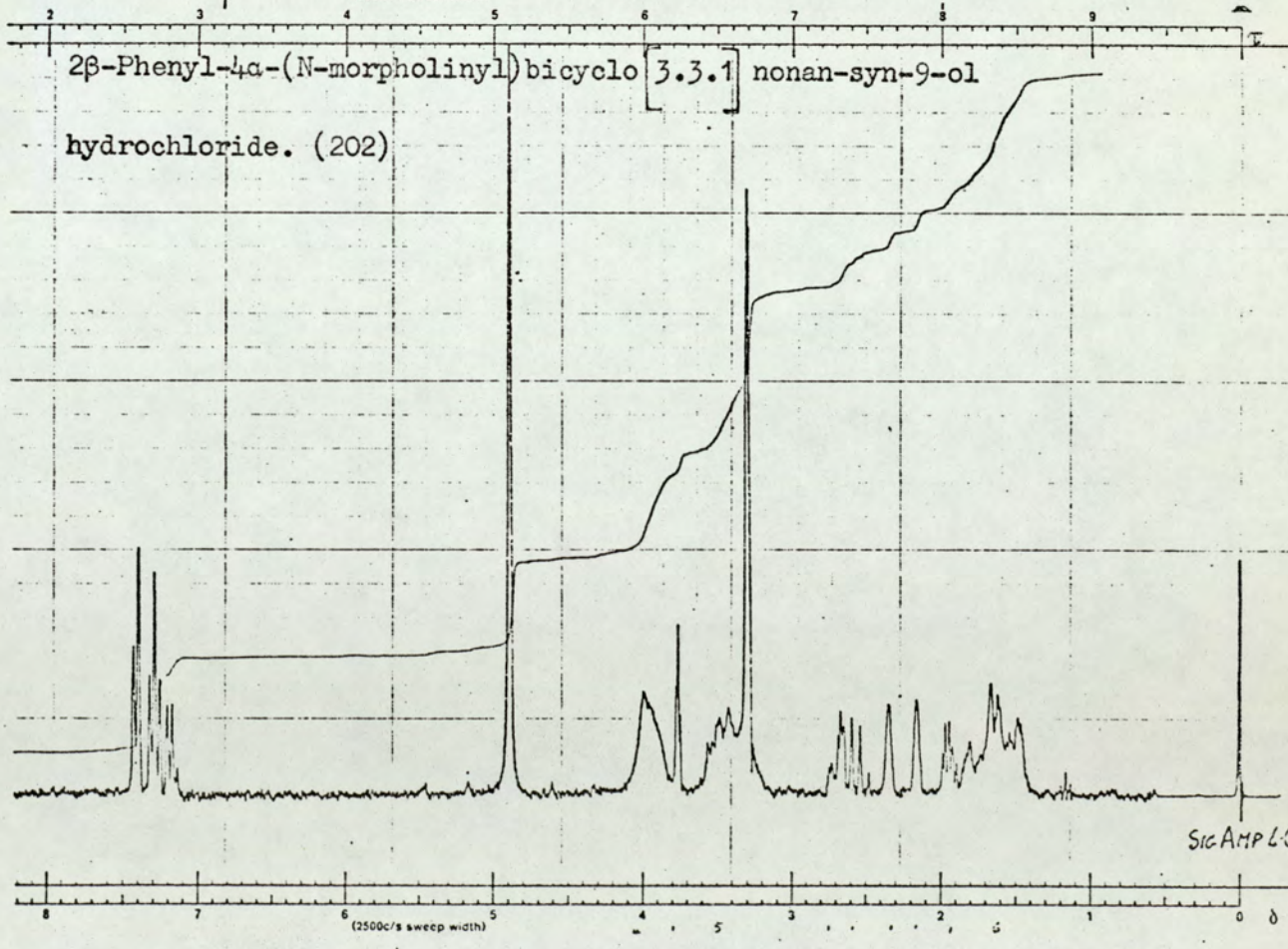
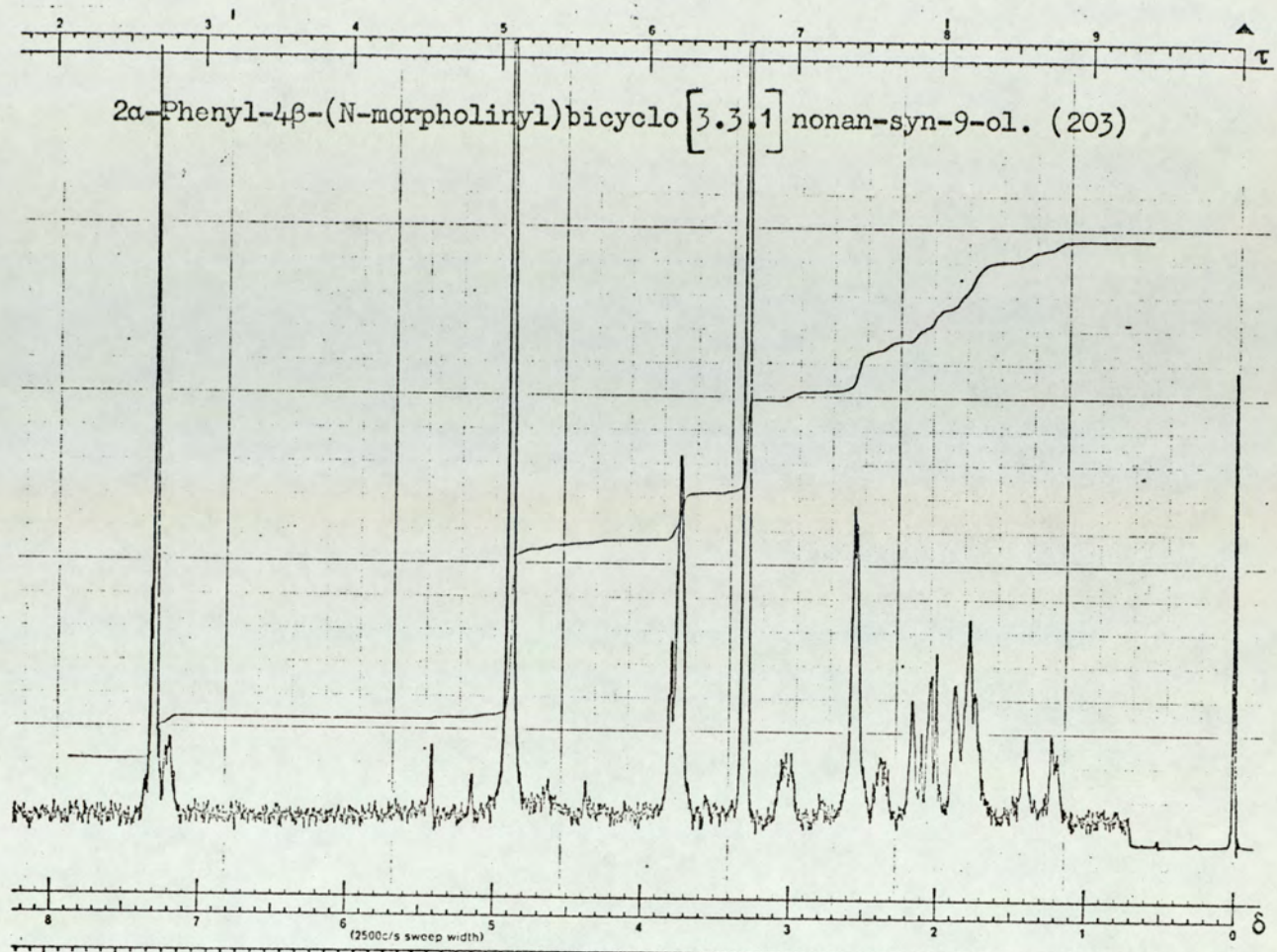
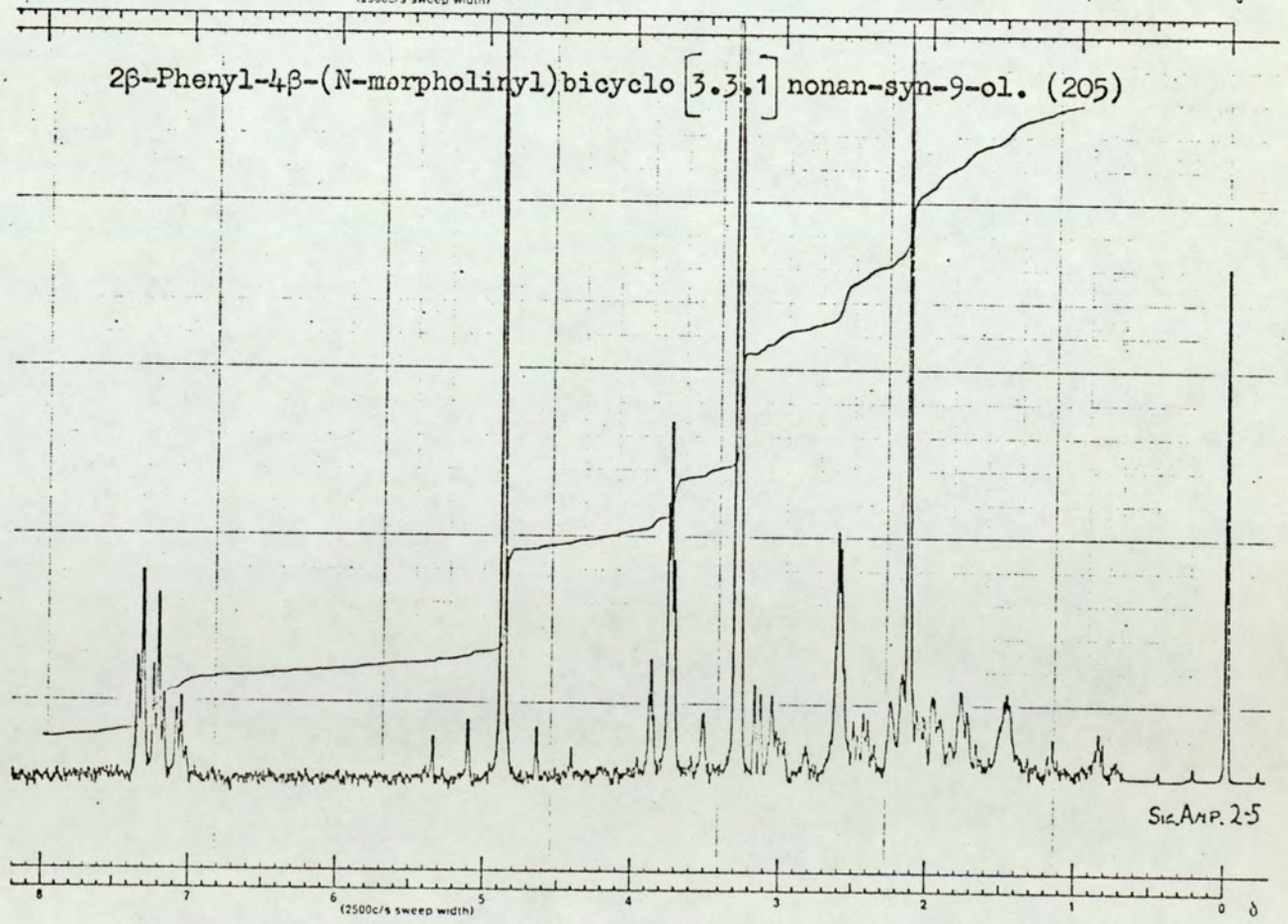

2β-Phenyl-4a-(N-morpholinyl)bicyclo [3.3.1] nonan-syn-9-ol
hydrochloride. (202)
τ
δ
(2500c/s sweep width)
SIG AMP L-C

Figure 25


2α-Phenyl-4β-(N-morpholinyl)bicyclo[3.3.1]nonan-syn-9-ol. (203)
τ
δ
(2500c/s sweep width)


2β-Phenyl-4β-(N-morpholinyl)bicyclo[3.3.1]nonan-syn-9-ol. (205)
SIC AMP. 2-5
(2500c/s sweep width)
δ

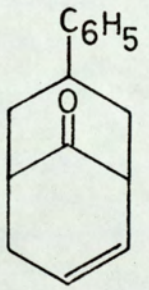
equatorial C - 3 proton and the axial C - 4 proton, then it would correspond to an AMX system and the X-portion would give rise to four lines of equal intensity. However this is not observed, possibly due to further splitting with the C - 2 proton, and for this reason the assignment of the C - 3 axial proton is only tentative. The quartet is seen to move downfield on converting the ketone (197) to the alcohol (200), fig. 24, and is in agreement with the assignment of the C - 3 axial proton to this quartet. In the ketone, the carbocyclic ring can assume a flattened form without introducing flagpole interactions with any protons at C - 9. However, the introduction of a secondary alcohol group at the C - 9 position would introduce a flagpole interaction and cause the ring to adopt a chair-form again. This would bring the axial C - 7 proton in close proximity to the C - 3 proton and cause the deshielding effect. Such an interaction has already been described (page 134) [123] to account for the low-field position of the C - 7 hydrogen atoms in 3-azabicyclo [3.3.1] nonane. The hydrochloride (202) shows a downfield shift of 0.2τ of the quartet, indicating that it is removed from the positively charged nitrogen atom by at least two carbon atoms, again in agreement with the above assignment. In the ketone (197), the $O-CH_2$ morpholine protons resonate at 6.35τ and the $N-CH_2$ morpholine protons resonate at 7.45τ. In the alcohol (200) the $O-CH_2$ protons resonate at 6.3τ and the $N-CH_2$

morpholine protons resonate at 7.35τ. In the spectrum of the hydrochloride (202), fig. 24, the O-CH_2 morpholine protons resonate at 6.0τ as a broad hump and the N-CH_2 morpholine protons are seen as a broad multiplet centred at 6.5τ.

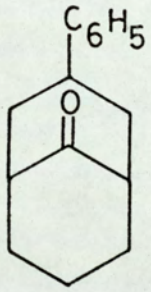
The spectrum of the ketone (198), fig. 23, shows a broad multiplet (1H) at 6.9τ, with a half-band width of 21 Hz, indicating that this is an axial proton. This ketone is known to have the C - 2 proton axial and the C - 4 proton equatorial. This would indicate that the multiplet is caused by the resonance of the C - 2 proton. A broad singlet at 7.25τ (1H) could be the resonance of the C - 4 proton. Both ketone (197) and (198) show a singlet at 7.5τ (2H). This could be tentatively assigned to the C - 1 and C - 5 bridgehead protons. No high-field quartet is observed in the spectrum of ketone (198). The alcohol (203), fig. 25, obtained from this ketone, shows a triplet, J = 2.5 Hz, at 6.2τ (1H), due to the 9CH resonance. Two broad multiplets are seen at 7.0τ and 7.6τ. The low-field multiplet can be assigned to the C - 2 proton and the higher-field multiplet to the C - 4 proton. However, the half-band widths are both about 20 Hz, which is in agreement with the assignment of the C - 2 proton, but larger than anticipated for the C - 4 proton. The broad singlet observed in the parent ketone (198) at 7.6τ (2H) is now seen at 7.85τ. Again this may be tentatively assigned to the C - 1 and C - 5

bridgehead protons. The spectrum of the ketone (198) shows the morpholine O-CH_2 protons at 6.3τ and the N-CH_2 protons at 7.5τ, whereas in the alcohol (203) the O-CH_2 protons are seen at 6.25τ and the N-CH_2 protons at 7.45τ.

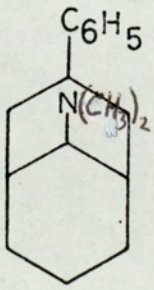
The third isomeric ketone (199), fig. 23, shows a doublet, J = 7.5 Hz, at 6.48τ. This could be due to either the C - 2 or C - 4 proton but is lower than previously found for either of these protons. By comparison with other bicyclo [3.3.1] nonanes, it could also be assigned to the benzylic proton. Conformation and configuration of the phenyl-bicyclic compounds (242), (243), (244) and (245) were elucidated by examination of their NMR spectra. [47]



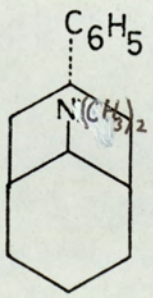
(242)



(243)



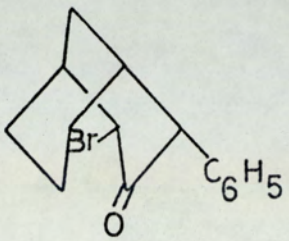
(244)



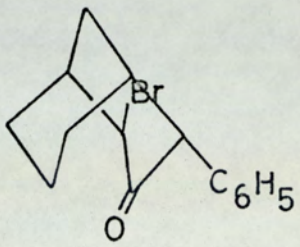
(245)

The NMR spectra of (242), (243), (244) and (245) exhibited a multiplet signal of similar pattern at 6.57τ, 6.28τ, 6.77τ and 6.65τ respectively which was ascribed to the C - 7 proton in each case. The phenyl orientation in these compounds was assumed to be equatorial in chair conformation. The difference (0.2 ppm) in the chemical shift of the C - 7 proton between the ketones (242) and (243) would be due to the paramagnetic effect of the carbon-carbon double bond which influences the C - 7 hydrogen only when the phenyl substituted ring has a chair conformation. Moreover, the difference (0.49 or 0.37 ppm) between(243), and(244)or(245) would be the result of a diamagnetic effect of the carbonyl group on the C - 7 hydrogen in the chair conformation. The configuration of the amino group in (244) and (245) could not be determined by NMR examination because only a small difference (0.04 ppm) in chemical shift of the $N\text{-}CH_3$ signals was found. However, it was concluded from the glc retention times that the isomer (244) has cis orientation of the phenyl group and that the isomer (245) had the trans, from the general relationship that the retention time of compounds having a axial substituent tend to be shorter than that of the compounds with equatorial groups.[127] The results indicate that for a cyclohexane ring with a phenyl substituent, the phenyl C-H proton resonates at 6.5τ. Other results[128,129,130] for phenyl substituted bicyclo[3.3.1]

nonanes show a range of 5.48τ to 6.3τ for the benzylic proton, depending on the electronegativity of the substituents present.



(247)

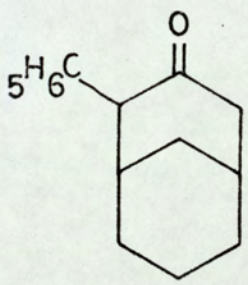


(246)

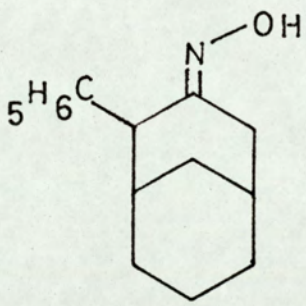
C_6H_5-C<u>H</u>- 6.12τ, d, J = 5 Hz ------(247)

C_6H_5-C<u>H</u>- 5.48τ, d, J = 5 Hz ------(246)

The benzylic proton in the spectrum of the isomer (246) is deshielded with respect to that of the isomer (247) by a 1,3-diaxial interaction with the bromine atom.



(249)

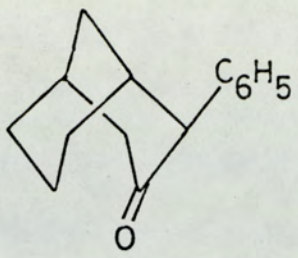


(248)

C_6H_5-C<u>H</u> 6.15τ, s

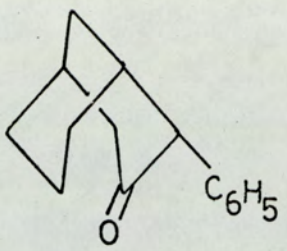
The phenyl group in the oxime (248) occupies the β-position, as shown by its NMR spectrum where the signal of the benzylic proton is a singlet, just as in the ketone (249) from which it is derived.

(250)



C_6H_5-C<u>H</u> 6.3τ

(251)



C_6H_5-C<u>H</u> 6.3τ($CDCl_3$)
6.6τ(C_6H_6)

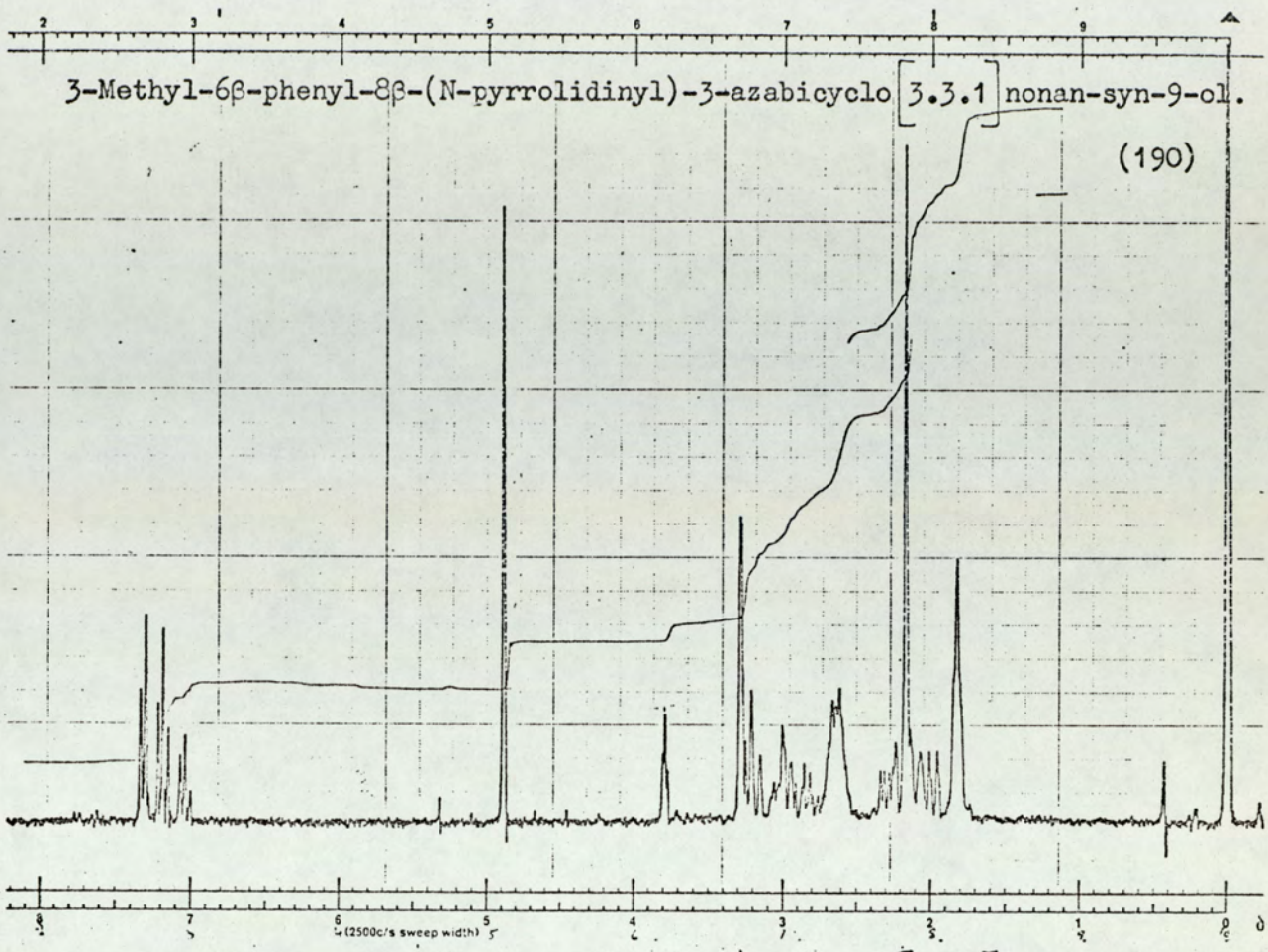
The benzylic proton in the isomer (250) was assigned the equatorial position and in the isomer (251) the axial position. From these results it can be seen that the position of the doublet in the spectrum of the ketone (199) could be due to the benzylic proton. In the absence of data for suitably labelled derivatives, a firm assignment cannot be made to the proton giving this resonance. The alcohol (205) derived from the ketone (199) does not exhibit the same low-field doublet, but a triplet (1H), J = 2.5 Hz, is seen at 6.15τ and corresponds to the C9H. A doublet, (1H), J = 9 Hz, is observed at 6.85τ and a multiplet at 7.0τ (1H). The doublet has a different coupling constant to the doublet found in the parent ketone, indicating that they are not the same resonance. The peaks at 6.45τ and 6.95τ are believed to be spinning side-bands and are therefore not assigned. Since both the C-2 and C-4 hydrogens are in an equatorial position, it is believed that the doublet at 6.85τ is caused by the 2CH resonance and the multiplet at 7.0τ is due to the 4CH resonance.

The spectrum of the ketone (199) shows the morpholine O-CH_2 protons at 6.35τ and the N-CH_2 protons within the methylene envelope. The alcohol (205) however, shows the O-CH_2 morpholine protons at 6.25τ and the N-CH_2 protons at 7.4τ.

IV) 3-Methyl-6-phenyl-8-cycloalkylamino-3-azabicyclo[3.3.1]nonanes.

The spectrum of the ketone (172), fig. 22, (page 148), resembles the spectrum of the ketone (197), fig. 23, in one important way. The quartet found at 8.7τ in the ketone (197) is again present at almost the same position (8.75τ) and has identical separation of the peaks. The spectrum of the alcohol (176), fig. 26, derived from this ketone shows the quartet moved downfield to 7.75τ. By analogy with the deaza compounds (197) and (200), the resonance can therefore be assigned to the axial C7 hydrogen, the deshielding found in the alcohol in this case resulting from an interaction between the C - 7 proton and the "lone pair" of electrons on the methylamino nitrogen, as found by Lygo *et al.* [131] The spectrum of the ketone shows four broad singlets, one of which is seen as a shoulder of the solvent peak, centred at 6.5τ. Two broad overlapping singlets are also seen, centred at 7.0τ. By analogy with the spectrum of the deaza ketone (197) which is believed to have the same structure, the broad singlets are assigned to the C - 6 and C - 8 protons, and the overlapping singlets at 6.5τ are assigned to the C - 1 and C - 5 bridgehead protons. These are at

Figure 26


3-Methyl-6β-phenyl-8β-(N-pyrrolidinyl)-3-azabicyclo [3.3.1] nonan-syn-9-ol.
(190)
(2500c/s sweep width)
δ

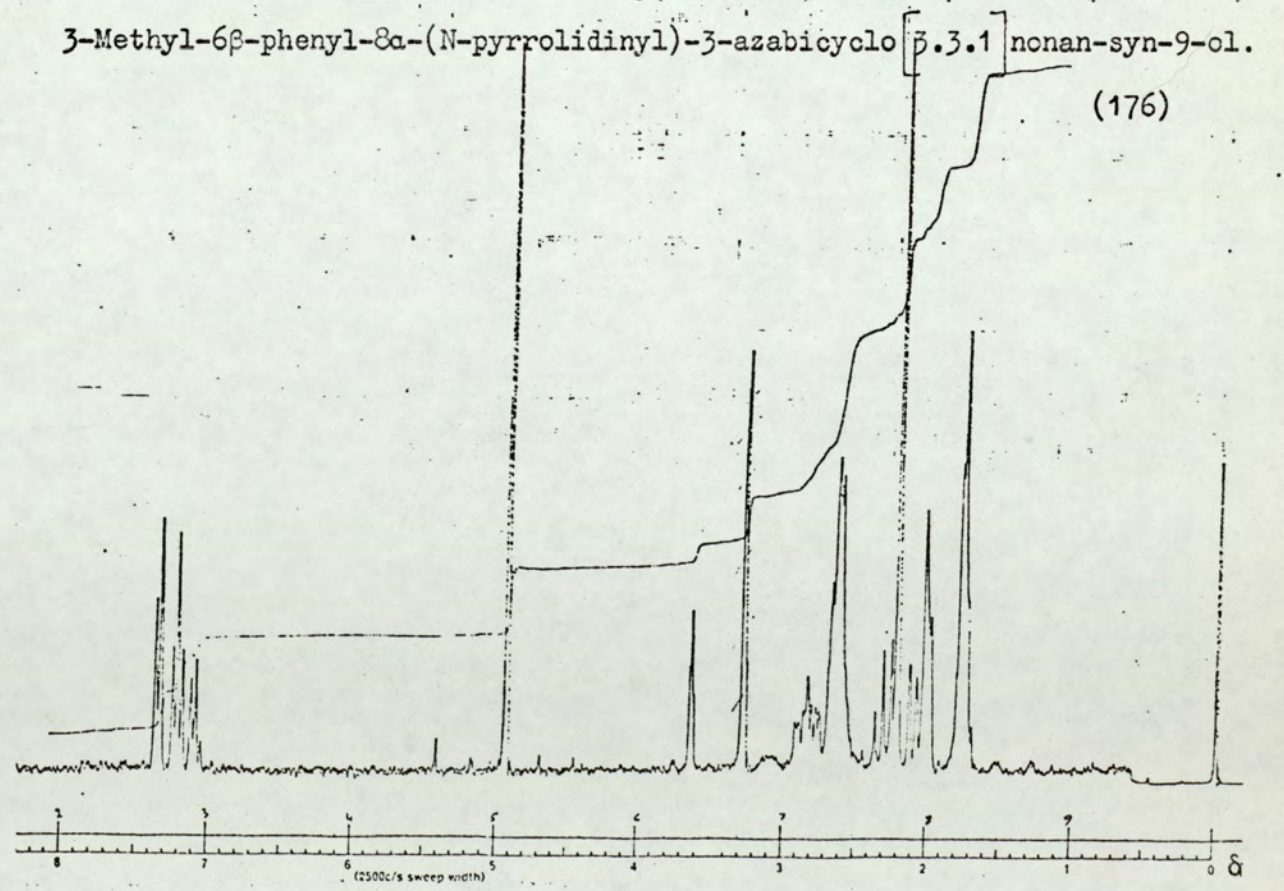
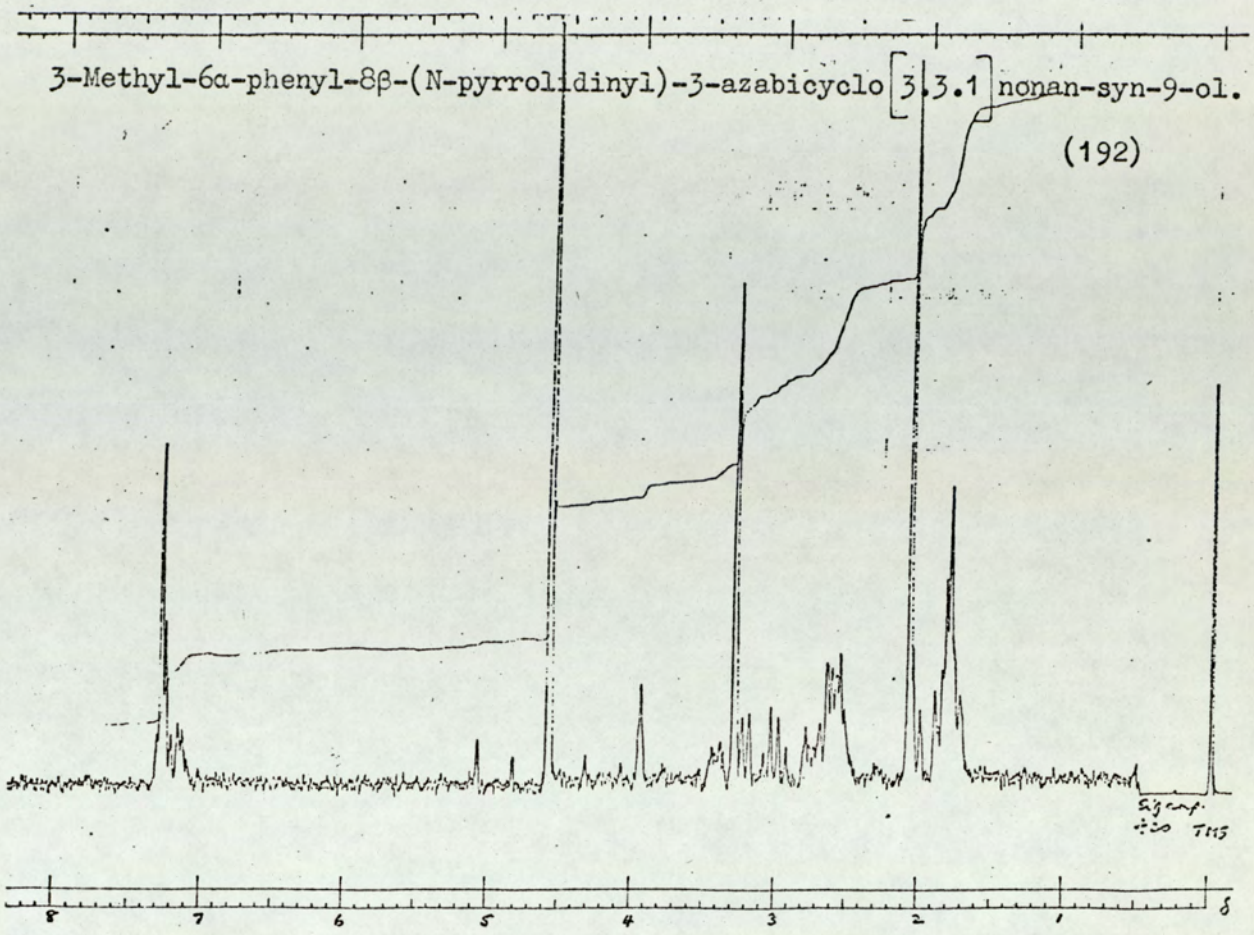

3-Methyl-6β-phenyl-8α-(N-pyrrolidinyl)-3-azabicyclo [3.3.1] nonan-syn-9-ol.
(176)
(2500c/s sweep width)
δ

Figure 27


3-Methyl-6α-phenyl-8β-(N-pyrrolidinyl)-3-azabicyclo[3.3.1]nonan-syn-9-ol.
(192)
8
7
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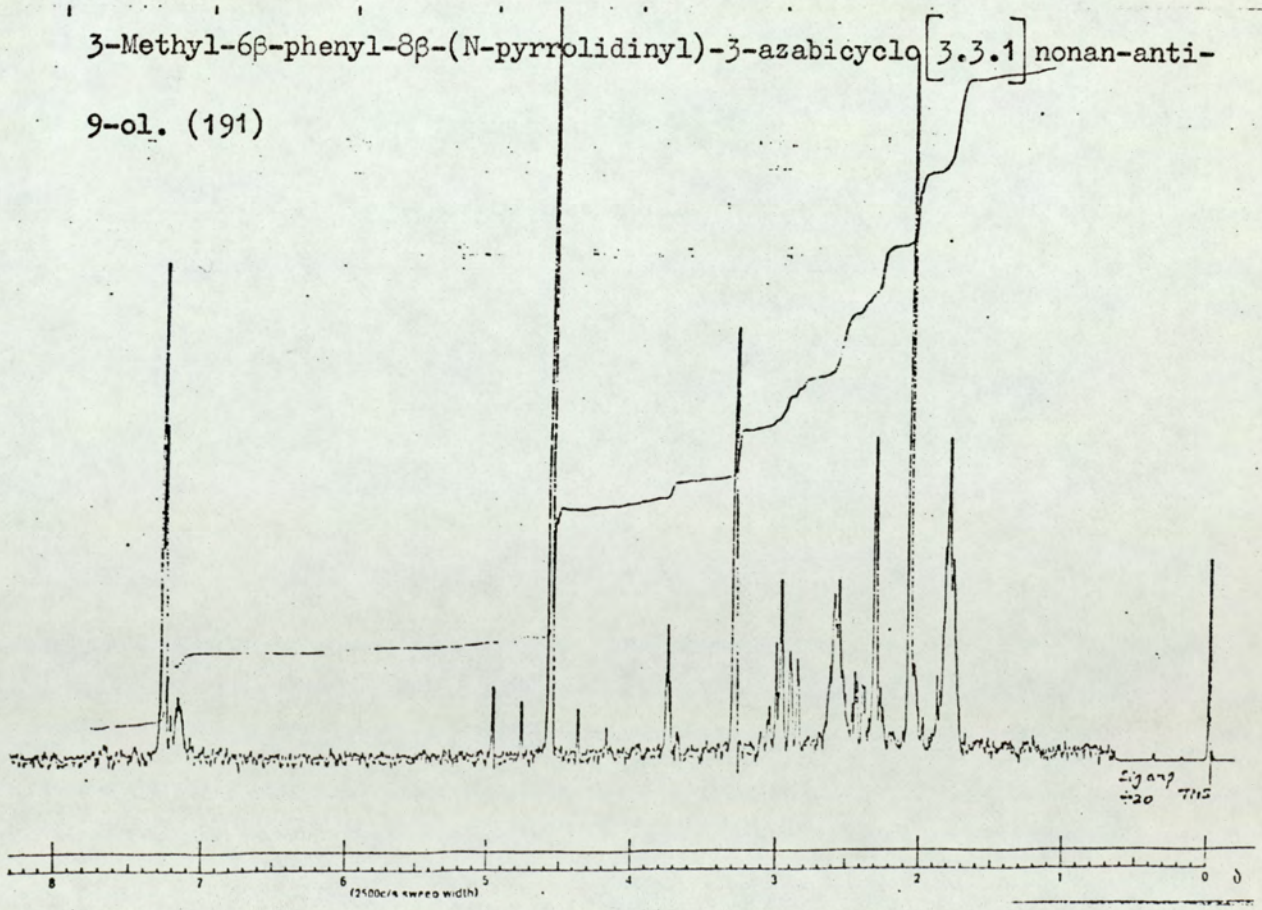
δ


3-Methyl-6β-phenyl-8β-(N-pyrrolidinyl)-3-azabicyclo[3.3.1]nonan-anti-
9-ol. (191)
8
7
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δ

lower field than in the spectrum of the deaza ketone, which is the expected effect of the methylamino nitrogen. The alcohol (176) derived from the ketone (172) shows the C - 9 proton as a triplet at 6.35τ and a broad multiplet (2H) at 7.2τ, believed to be a combination of overlapping multiplets due to the resonances of the C - 6 and C - 8 protons. The quartet (1H) due to the axial C - 7 proton is seen at 7.75τ and a doublet (1H), J = 11 Hz, at 7.95τ.

The alcohol (190), fig. 26, shows a complex splitting pattern above 6.7τ for which no assignments are possible. The resonance of the C - 9 proton is seen however at 6.2τ as a triplet, J = 2.5 Hz.

The spectrum of the alcohol (192), fig. 27, shows the C - 9 proton as a triplet at 6.1τ, J = 2.5 Hz. A multiplet is seen at 6.7τ (1H), a doublet at 6.8τ (1H) and a quartet at 7.0τ (1H). This quartet is identical to those quartets already discussed for ketones (172) and (197), and alcohols (176) and (200), and is thus assigned to the C-7 axial hydrogen. However, in this alcohol it is at lower field (0.75τ than for either of the other alcohols. The alcohol (203), fig. 25, shows no such quartet although both alcohols are believed to have the same structure. The multiplet is assigned to the C - 6 proton, because of its half-band width (25 Hz). The C - 6 proton is axial and thus would be expected to have a greater half-band width than the equatorial C - 8 proton. The doublet at 6.8τ is presumed to be the resonance of

the C - 8 proton, although the coupling constant, J = 11 Hz, would appear to be outside the normal limits for either equatorial-equatorial or axial-equatorial coupling. Observed results for diaxial coupling are usually in the range 8-14 Hz, whereas axial-equatorial and diequatorial coupling constants are usually found in the range 1-7 Hz.[125] The important conclusion to be derived from these values is that large vicinal coupling constants (8-14 Hz) may be identified with an approximate diaxial orientation of the atoms, while smaller splittings (usually 1-5 Hz and only infrequently appreciably larger) are associated with axial-equatorial or diequatorial interactions. Some doubt is therefore cast on the validity of assigning the doublet at 6.8τ to the C - 8 proton since it is believed to be in an equatorial position and therefore capable of only axial-equatorial or diequatorial coupling.

The spectrum of the alcohol (191), fig. 27, shows the resonance of the C - 9 proton as a triplet, J = 2.5 Hz, at 6.25τ. A multiplet is visible at 7.0τ (2H) in addition to a doublet (1H), J = 11 Hz, at 7.15τ and a quartet at 7.6τ with apparent J values of 11 and 3 Hz. Since the doublet has a J value of 11 Hz then it is unlikely to be the resonance of either the C - 6 or C - 8 protons since both of these are believed to be in an equatorial position and therefore incapable of giving rise to this coupling constant. It is therefore proposed that

the multiplet at 7.0τ is due to the overlapping resonances of the C - 6 and C - 8 protons which are both believed to be equatorial.

The position of the N-CH_3 signal is seen to show little difference in the series resonating at 7.65τ in the spectrum of the ketone (172) and at 7.80τ in the alcohol (176), 7.80τ in the alcohol (190), 7.95τ in alcohol (191) and 7.95τ in alcohol (192).

It can be seen that the number of protons whose resonance can be unambiguously assigned is severely restricted by the complex splitting which occurs, and also by the width of the methylene envelope. In general, the only protons which can be assigned are those which are geminal or vicinal to electronegative substituents, such as the 6-cycloalkylamino group or the C - 9 hydroxy group.

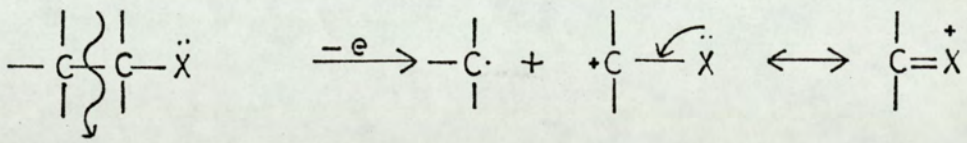
H. Mass spectra.

Frequent attempts have been made to solve stereochemical problems with the aid of mass spectrometry. Normally, however, stereoisomeric compounds have similar mass spectra, due to the fact that the main fragmentation reactions do not involve the centre of stereoisomerism. Thus, stereoisomeric differences have been found to lead to only slight variations in peak intensity, particularly when the centre of stereoisomerism is remote from the bonds which are preferentially cleaved. It is only when bonds participating in the centre of stereoisomerism are broken in the main fragmentation reactions that the mass spectra differ sufficiently for stereochemical conclusions to be drawn.

While in a chemical reaction the reagent attacks a particular group or bond, the electronic attack in the mass spectrometer is directed towards no particular site of the molecule. Fragments are formed preferentially with a minimum expenditure of energy. Because of this, weaker bonds are ruptured rather than stronger ones, and cleavage reactions in which stable fragments are formed are preferred, because in these the energy required for rupture is, at least partially, balanced by the gain in stabilisation energy. In saturated aliphatic hydrocarbons, for example, the weaker C-C bonds are therefore split more readily than the stronger C-H bonds. By cleavage of a C-C bond in a straight-chain saturated hydrocarbon,

primary carbonium ions of approximately equal stability are formed and thus all C-C bonds in such a hydrocarbon have an equal probability of being ruptured. The C-C bonds in a branched saturated hydrocarbon are likewise approximately equal in strengh. By fission of bonds at branching points, however, secondary and tertiary carbonium ions are formed. Because of the inductive electron donor effect of alkyl groups, a positive charge is better stabilised in such intermediates than in primary carbonium ions. For this reason, less energy is required to split branched saturated hydrocarbons than their straight-chain isomers.[132]

Functional groups containing a singly bonded hetero-atom with a lone pair of electrons have a much stronger effect on fragmentation than alkyl groups. Such compounds are cleaved with high probability at one of the C-C bonds adjacent to the hetero-atom, since in this way stabilised ions can be formed.



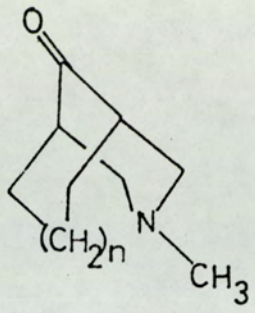
X = NH_2, NHR, NR_2, OH, OR, SH, SR, Halogen.

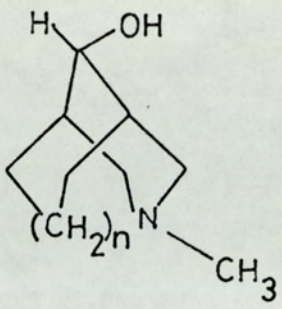
Not only is the stability of positively charged fragments important, but also the stability of the uncharged particles which

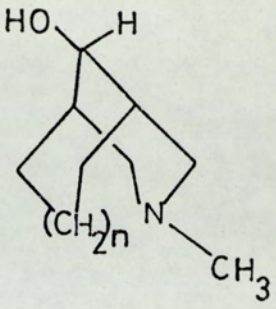
are formed simultaneously. Since the total energy balance determines the course of a decomposition reaction, this consideration is valid only when fissions are compared in which particles of roughly equal stability are formed.

The interpretation of the cleavage of alicyclic compounds is appreciably more difficult than that of their non-cyclic analogues due to the many possible decomposition reactions shown by the former.[132] Except when fragments are formed by hydrogen abstraction, at least two carbon-carbon bonds must be broken, and this obviously requires more energy than the rupture of a single bond.

The fragmentation of a number of unsubstituted azabicycloalkanols, including the nonanols (255-260) differing in stereochemistry about the bridgehead CHOH position have been discussed and the postulated fragmentation pathways outlined.[133] The stereochemistry of the epimeric pairs of alcohols could be assigned by comparison of their M-1 peak, M-17 peak, and the $^{m}/_{e}$ 58 and 44 peaks.







β-isomers

α-isomers

252) n = 0

253) n = 1

254) n = 2

255) n = 0

256) n = 1

257) n = 2

258) n = 0

259) n = 1

260) n = 2

For the various pairs of epimers studied, the M-1 peak was more abundant for the epimer in which the larger substituent at C9 was oriented towards the nitrogen. In each of the alcohols (255-260), M-17 fragments were observed which were frequently comparable in abundance with the molecular ions. The relative intensities of these fragment peaks in the various amino-alcohols showed little, if any, difference which was useful for assigning stereochemistry to the amino-alcohols. This behaviour is unusual in that alcohols normally lose the elements of water [134] rather than a hydroxyl group. The most abundant peaks in the spectra of the alcohols were found at $^{m}/e$ 58 and $^{m}/e$ 44. The β-secondary alcohols had an $^{m}/e$ 44 ion which was comparable in intensity with, or more abundant

than, that of $^{m}/e$ 58. However, the α-secondary alcohols tended to have an $^{m}/e$ 58 peak which was either comparable in intensity or more intense than that at $^{m}/e$ 44. From these peaks the relative stereochemistries of the alcohols (255-260) could be determined.

The mass spectra of the 3-methyl-6-cycloalkylamino-3-azabicyclononanes and the related deaza compounda have been studied with a view to correlating the observed breakdown and the stereochemistry of each of the isomers. To simplify discussion of these spectra, corresponding or related fragment peaks which occur in a number of the spectra are considered together. The elemental compositions of the fragments were determined by accurate mass measurements. In order to clarify certain breakdown pathways a number of deuterated compounds were prepared. Lithium aluminium deuteride reduction of the azabicyclononan-9-ones (75 and 76) gave 9-deutero-3-methyl-6α-(N-pyrrolidinyl)-3-azabicyclo[3.3.1]nonan-syn-9-ol (261). Addition of p-nitrobenzoyl chloride to the mother liquors remaining after removal of the alcohol (261) gave 9-deutero-3-methyl-6α-(N-pyrrolidinyl)-3-azabicyclo[3.3.1]non-anti-9-yl p-nitrobenzoate (262). 9-Deutero-3-methyl-6α-(N-pyrrolidinyl)-3-azabicyclo[3.3.1]non-syn-9-yl p-nitrobenzoate (263) was prepared by reaction of the lithium salt of the deuterated alcohol (261) with p-nitrobenzoyl chloride. An attempt to prepare 1,5-dideutero-3-methyl-6α- and 1,5-dideutero-3-

methyl-6β-(N-pyrrolidinyl)-3-azabicyclo[3.3.1]nonan-9-ones by the method of House and Muller [135] gave a black tar from which the ketones could not be distilled.

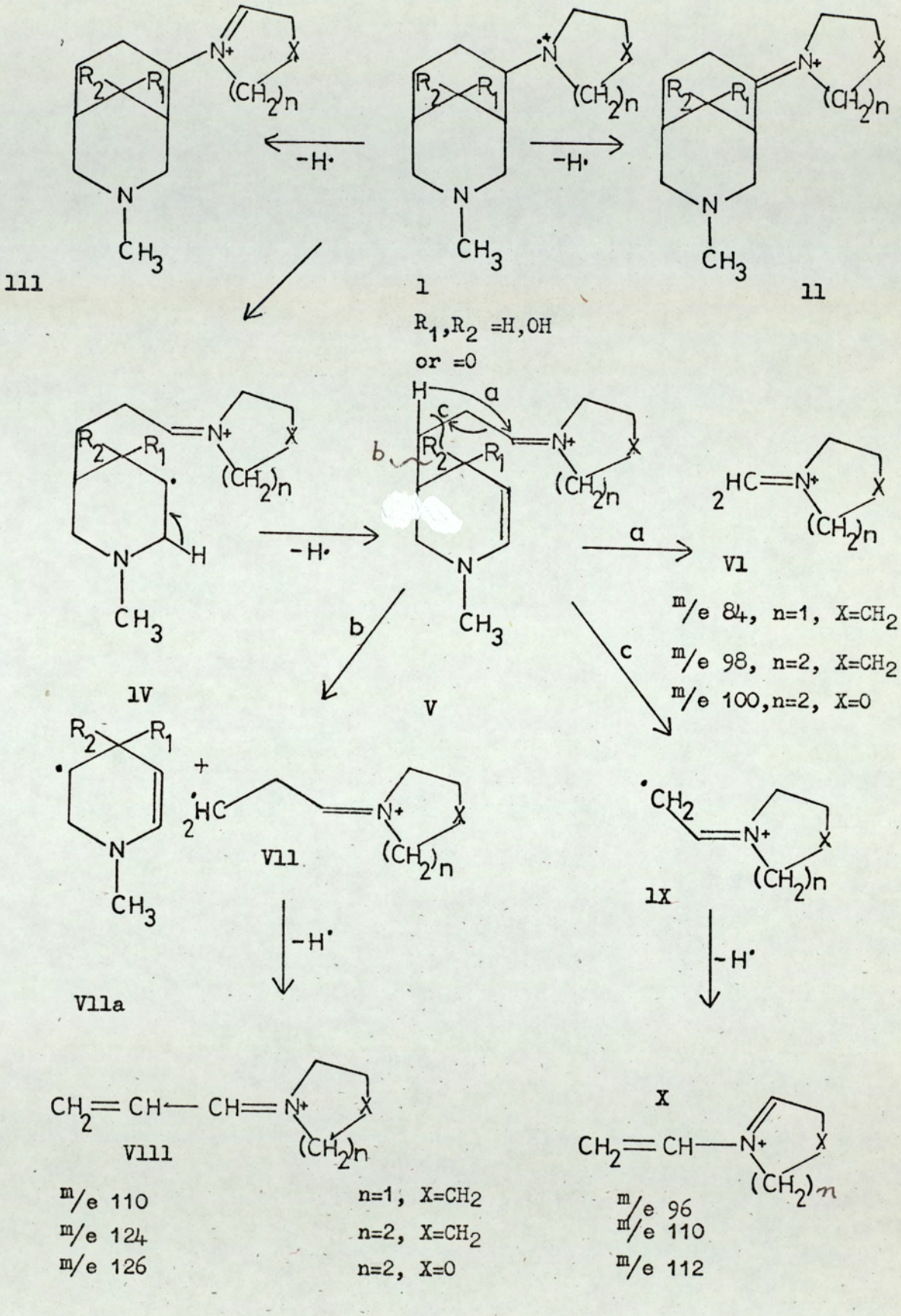
1) 3-Methyl-6-Cycloalkylamino-3-azabicyclo[3.3.1]nonanes.

In these series of compounds the introduction of a 6-cycloalkylamino group was found to bring about a marked alteration in fragmentation to that reported for the unsubstituted compounds. [131] The observed breakdown for the 6-cycloalkylamino-3-azabicyclo[3.3.1] nonanes can be discussed in terms of two major fragmentation pathways, A and B, which are outlined in Schemes A and B. The interpretation of the cleavage of these cyclic compounds was complicated by the many possible decomposition reactions. This was shown by the discovery not only of metastable ions which support the proposed breakdowns but also of metastable ions for many minor fragmentation pathways which lead ultimately to the same products. The fragmentation pathways described are based therefore not only on the location of metastable ions, but also on the assumption that the presence of functional groups, in this case the heterocyclic nitrogen atoms, plays a major role in the decomposition under electron impact.

Fragmentation pathway A.

In this fragmentation pathway, the breakdown occurs most probably through the molecular ion 1. The loss of a hydrogen can occur from this molecular ion in a number of ways and give rise to the M - 1 ions 11, 111 and V. The epimeric pairs of ketones (75 and 76, 127 and 128 and 136 and 137) are found to give rise to a more abundant M - 1 peak than the alcohols or esters derived from them. This can be seen by a comparison of the spectrum of a typical ketone mixture (75 and 76), Fig. 28a, and Figs. 28b, 28c, 29a, 29b, and 29c, (page 184), which show the fragmentation pattern for the alcohols obtained from the ketones. Analogy with the known fragmentation pattern of amines [134] and the fact that the deuterated compounds (261, 262 and 263) lose only one mass unit, strongly suggest that the hydrogen atom is lost from one of the carbon atoms α to a nitrogen. Structure V is preferred for the M - 1 ion since in the ketones, Fig. 28a, the formation of 1V and V would be expected, due to resonance stabilisation, to be easier relative to the corresponding hydroxyl and ester compounds. Other possible M - 1 ions such as 11 or 111 would be expected to be equally favoured by both alcohols and ketones alike and can therefore be regarded as possible minor pathways. No correlation could be found between the abundance of the M - 1 peak and the stereochemistry of the alcohols as was demonstrated for the unsubstituted azabicyclononanols. [133] The unsubstituted compounds

Fragmentation Pathway A



were found to lose a hydrogen atom α to the methylamino group, without any breakdown of the bicyclic system, and therefore the loss of the α-H atom was dependent on the stereochemistry of the parent ion. In the present series, lack of this dependence points to breakdown of the bicyclic system prior to loss of the hydrogen. This further indicates that the M - 1 ion arises via structure IV rather than II or III, both of which retain the azabicyclononane ring system.

The alcohols and esters, with the exception of the 6-morpholinyl compounds, exhibit a base peak which is shown by VI and can be obtained from V by the rearrangement pathway (a). The 6-morpholinyl alcohols, Figs. 30c, 32c and 34b, show a peak corresponding to VI which is comparable in abundance to the base peak. The alcohols and esters also show another rearrangement pathway (b) to give the relatively stable neutral fragment VIIa and the radical ion VII which can lose a hydrogen toyield the ion VIII. This route (b) is seen to be the preferred route for the pairs of ketones (75 and 76, 127 and 128, and 136 and 137) and not route (a) as seen for the alcohols and esters. In the breakdown of the ketones by path (b), the radical VIIa can be resonance stabilised whereas the alcohols and esters do not have this possibility. In this case therefore it is the stability of the neutral fragment produced which is important in determining the breakdown pathway. Another rearrangement (c) from V accounts for

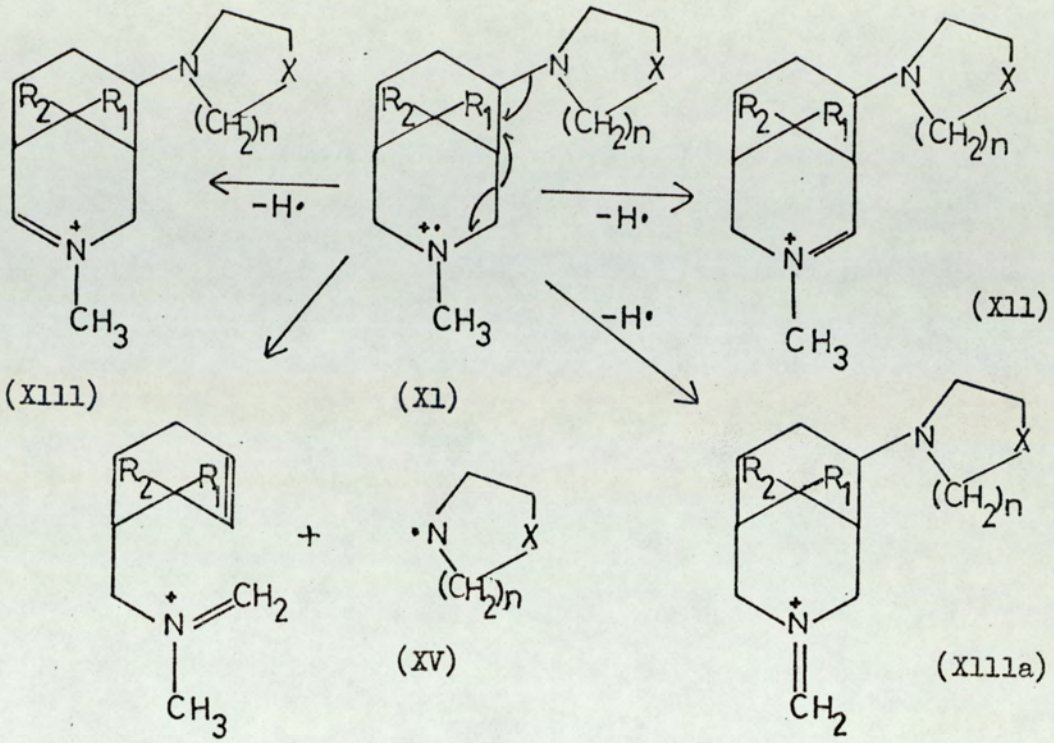
the presence of a relatively abundant ion X via the intermediacy of the radical ion 1X. Ions with this structure have been shown to occur in the fragmentation of cyclic amines and enamines.[136] These ions V1, V111 and X also occur in the spectra of the deuterated alcohol (261), Fig. 29c, and deuterated esters (262 and 263), further indicating the validity of the structure assigned to these breakdown products.

The spectra of the deaza compounds (162 and 163), Figs. 35a and 35b, show the presence of the same ions V1 and V111 but not the presence of the ion X to any large extent. This further indicates that the methylamino group is not involved in the breakdown leading to these particular ions. The notable difference between the deaza alcohols (162 and 163) with respect to the abundance of their $^{m}/_{e}$ 100 ion cannot readily be explained by the difference in their stereochemistry.

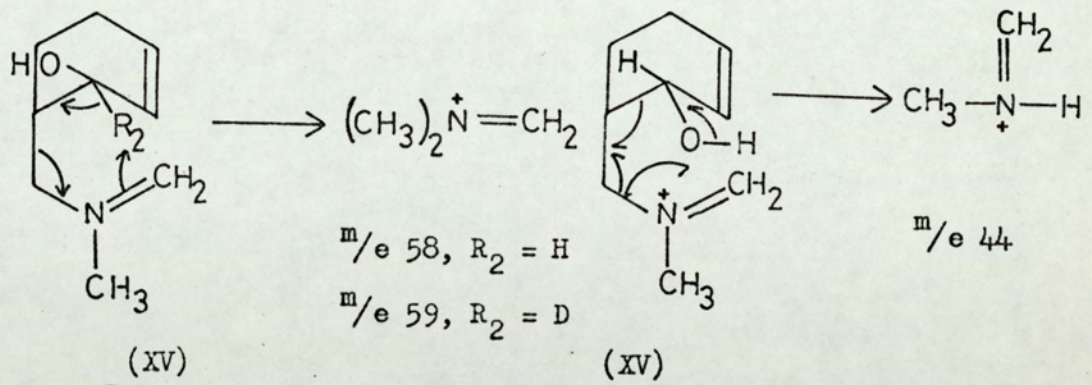
Fragmentation pathway B.

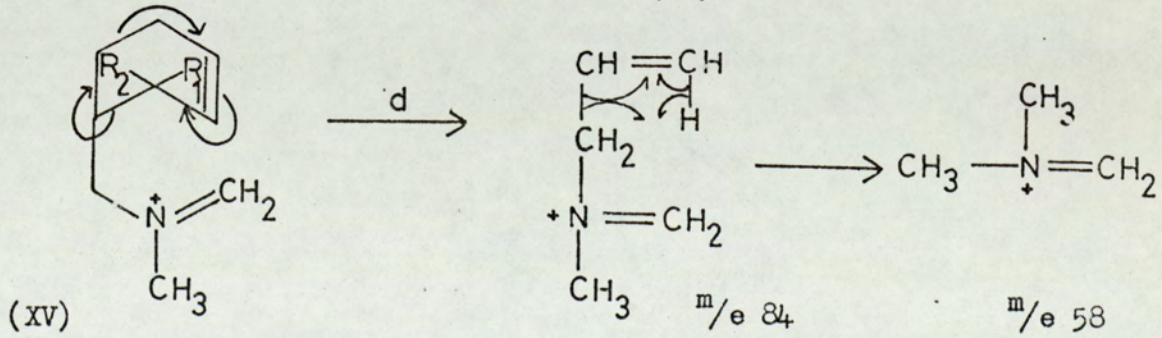
In this case the breakdown occurs most probably through the molecular ion X1, formed by the loss of an electron from the methylamino nitrogen. In a similar manner to that described in the fragmentation pathway A, M - 1 ions X11, X111 or X111a are all possible but the major breakdown is believed to be that involving loss of the cycloalkylamino group to give the ion XV which may arise

Fragmentation Pathway B

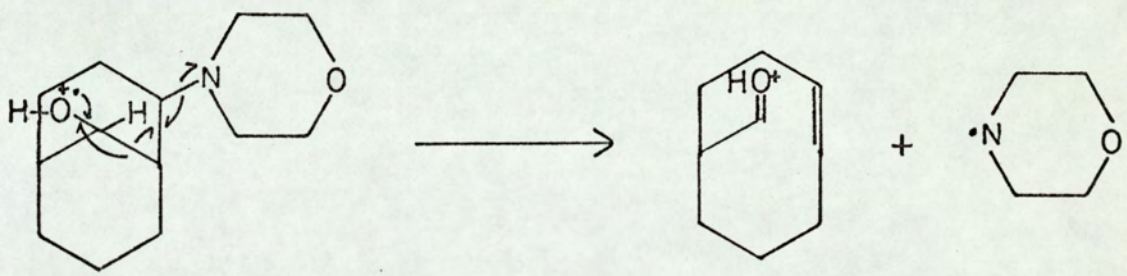


n = 1, X = CH_2	m/e 154	R_2, R_1 = H, OH
n = 2, X = CH_2	m/e 155	R_2, R_1 = D, OH
n = 2, X = O	m/e 303	R_2, R_1 = H, p-NO_2-$C_6H_4CO_2$-
	m/e 304	R_2, R_1 = D, p-NO_2-$C_6H_4CO_2$-
	m/e 152	R_2, R_1 = O





directly from XI. This ion is of high abundance in all the alcohols, esters and ketones but is absent in the spectra of the deaza compounds Figs. 35a and 35b, which do not contain the methylamino group necessary for this fragmentation to arise. Loss of the cycloalkylamino group could in theory arise from a molecular ion formed by loss of an electron from the oxygen of the hydroxyl group but the absence of this peak in the spectra of the deaza alcohols indicates that this is not a preferred route.



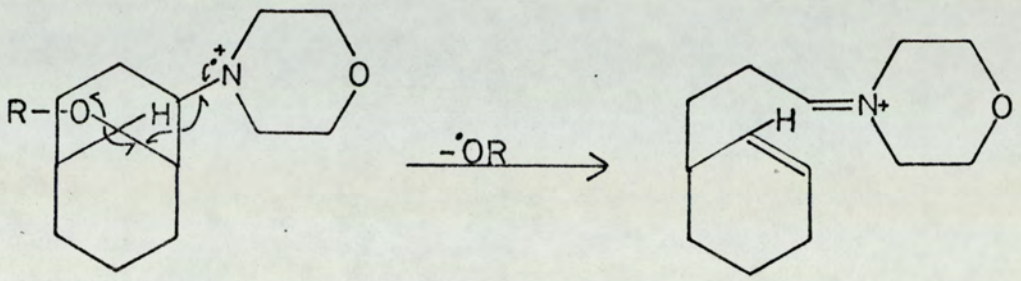
The peak due to XV occurs at $^{m}/e$ 154 in all the alcohols and at $^{m}/e$ 152 in the ketones. However, the deuterated alcohol (261), Fig. 29c, exhibits a peak at $^{m}/e$ 155, whereas the deuterated esters (262 and 263) show a peak at $^{m}/e$ 304 compared with the non-deuterated ester peak at $^{m}/e$ 303. More importantly, the abundance of this ion is seen to vary with the stereochemistry about C-6 and C-9 of the alcohols. The compounds with the cycloalkylamino group in an equatorial position show a moderately intense peak for the loss of the

cycloalkylamino group,Figs. 28b, 28c, 29a, 30b, 31b, 32c and 34b. This loss is independent of whether the 6-cycloalkylamino group is syn or anti to the hydroxyl group at C-9. However, when the cycloalkylamino group is in an axial position and syn to the hydroxyl group, this ion reaches an abundance comparable to the base peak, Figs. 29b, 30c and 31c. The ease of formation of this ion can be related to the 1,3-diaxial interaction of the hydroxyl at C-9 and the C-6 amino group. This mode of fragmentation would thus be expected to be favoured in order to relieve this interaction. This would appear to confirm that the parent ion is represented by XI and not XIV since only in XI is the stereochemistry retained. In XIV the bridged rigid bicyclic system is broken and any initial steric strain due to a 1,3-diaxial interaction is likely to be so reduced as to make its effect not felt in the decomposition. The fragmentation of XI to XV is further demonstrated by the presence of metastable peaks for this loss. The deuterated alcohol (261), Fig. 29c, showed a metastable peak at 106.8 for this loss, compared with the metastable at 105.9 for the alcohols (77, 78, 79 and 80). The alcohol containing an axial pyrrolidine group anti to the hydroxyl function at C-9 (80), Fig. 29a, does not show the same abundant loss of the cycloalkylamino group as alcohol (79), Fig. 29b, in which the hydroxyl group is syn to an axial pyrrolidine group. This must arise because the 1,3-diaxial

repulsion cannot be as severe when the bulky hydroxyl group is replaced by a hydrogen atom.

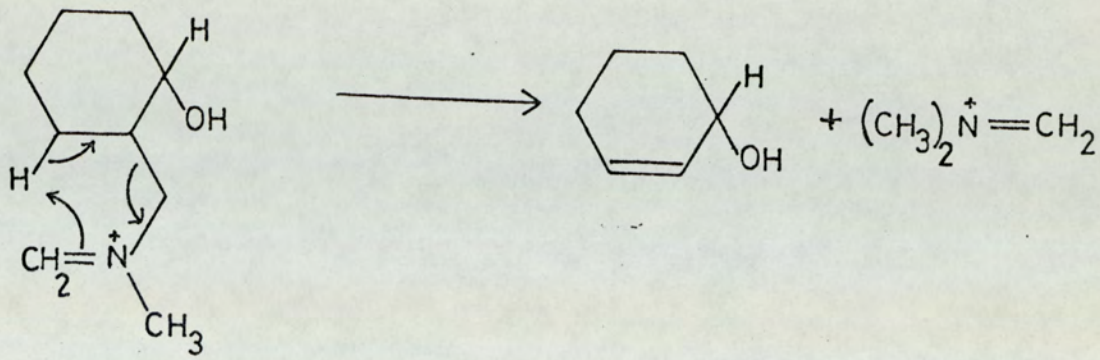
The unsubstituted alcohols (255-260) [133] (page 167) showed an M - 17 peak, the size of which could be related to their stereochemistry. The deaza alcohols (162) and (163) also show a small M - 17 peak. The 6-substituted azabicyclononanols however, are found to give a very small M - 18 peak, but an intense metastable peak corresponding to this loss. This indicates that the ion produced is either not very stable and therefore fragments easily or that the product of fragmentation is very stable, making the fragmentation favoured. The deuterated alcohol (261), Fig. 29c, also showed an M - 18 peak, indicating that the C-9 hydrogen was not involved in this loss. The absence of any M - 17 ion in these alcohols is therefore in contrast to the 6-unsubstituted compounds. The esters however, show a significant peak at M - 166 due to loss of the p-nitrobenzoate radical which corresponds to an M - 17 loss for the alcohols. This indicates that in the alcohols the preferred loss is of the cycloalkylamino group and not the hydroxyl group. However, in the esters, loss of the cycloalkylamino group is accompanied by the loss of the p-nitrobenzoate radical, presumably because this is a more stable radical than the hydroxyl radical and can compete more favourably. The deaza ester (167) shows a large M - 166 peak. In this

ester, no loss of the cycloalkylamino group occurs and therefore the loss of the p-nitrobenzoate radical is not suppressed.



R = p-NO_2-C_6H_4CO-

Other notably abundant ions common to both the unsubstituted alcohols (255-260) and the present series are $^{m}/e$ 58 and $^{m}/e$ 44 peaks, shown by XVl and XVll respectively. These are believed to arise as a result of the rearrangement shown in fragmentation pathway B. In the deuterated alcohol (261), Fig. 29c, the $^{m}/e$ 58 ion is no longer as intense as for the parent alcohol (77), Fig. 28b, but an intense $^{m}/e$ 59 ion occurs. This shows that one of the sites for abstraction of the hydrogen atom for the formation of the $^{m}/e$ 58 ion is from C-9. The stereochemistry of the 6-unsubstituted alcohols (255-260), (page 167), could be determined by the preferential formation of the $^{m}/e$ 58 or $^{m}/e$ 44 peak. However, no correlation can be found between the intensities of the $^{m}/e$ 58 and $^{m}/e$ 44 peaks and the stereochemistry of the alcohols in the present series. Abstraction of the proton to form the $^{m}/e$ 58 ion can occur not only from C9 but also from C8.



Each of the alcohols and esters with a 6-cycloalkylamino group show a peak at $^{m}/e$ 84. In the 6-pyrrolidinyl derivatives this can be explained by the presence of the ion VI. However, the non-pyrrolidine containing derivatives also show this peak which can arise from the ion XV by an alternative pathway, and can also represent a new route to the $^{m}/e$ 58 ion (path d, fragmentation pathway B).

The alcohols in the present series show a relatively abundant ion at $^{m}/e$ 136 which occurs as a result of loss of water from $^{m}/e$ 154. Metastable peaks are found in some of the alcohols at $^{m}/e$ 120.1 accounting for this loss. In the deuterated alcohol (261), Fig. 29c, this moderately intense peak now occurs at $^{m}/e$ 137 as expected, once again indicating that the loss of water does not involve the C-9 hydrogen.

Loss of the methyl group from the methylamino position is indicated for the ketones, alcohols and esters by the presence of an M - 15 peak of low abundance. This loss is not reported for the

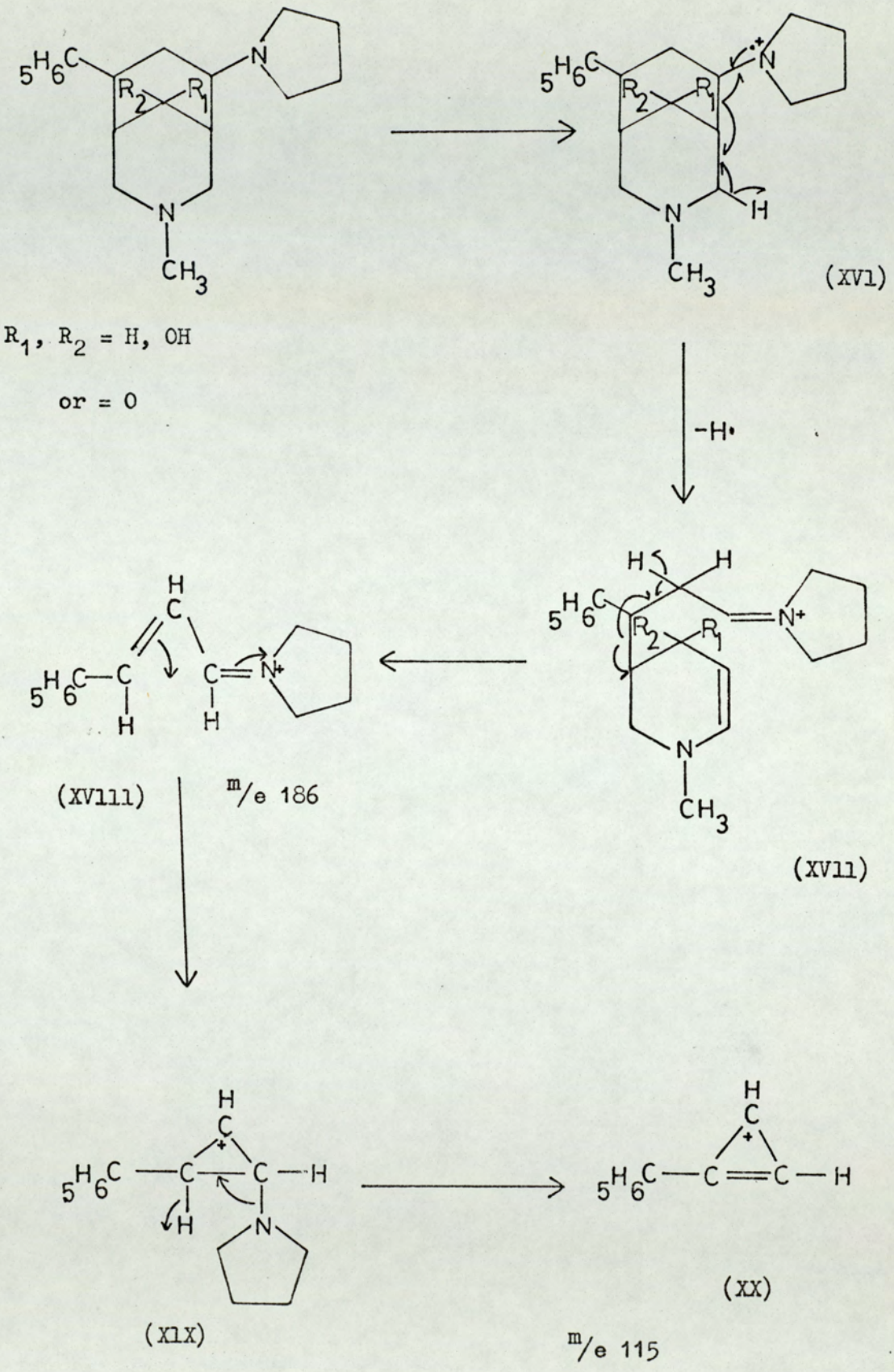
6-unsubstituted compounds (252-260) [133] and it is not believed to involve a rearrangement because it is absent in the spectra of the deaza compounds (162) and (163).

11) 6-Phenyl-8-cycloalkylamino-3-azabicyclo[3.3.1]nonane derivatives.

The ketone (172), alcohols (176, 190, 191 and 192) and esters (193 and 195) in this series of compounds showed the same fragmentation pathways (A and B) previously described. In addition to these routes, a new breakdown pathway is also observed, fragmentation pathway C.

The conjugated ion XVlll can give rise to the base peak in the ketone (172), Fig. 32b, and the alcohols, with the exception of alcohol (190) in which it is present in a comparable abundance to the base peak, and alcohol (191), Fig. 34c, where it represents an abundance of less than 40% that of the base peak. This alcohol (191) however, shows a very large peak at M - 70 which represents a loss of the cycloalkylamino group, indicating that fragmentation pathway B was the preferred breakdown pathway and path A was suppressed. Alcohol (190), the other alcohol which did not show this ion as the base peak, must also be suppressing path A due to the preferred loss of the pyrrolidine group. In both these alcohols, the pyrrolidine and phenyl substituents are axial and in close proximity to one another. A 1,3-diaxial interaction exists which can be relieved by loss of the pyrrolidine group to give the ion XV (pathway B). This can be used as

Fragmentation Pathway C



a guide to the stereochemistries of these alcohols.

Each of the alcohols, esters and ketones shows a peak at $^{m}/e$ 115 which can be derived from the $^{m}/e$ 186 ion by the rearrangement shown in pathway C.

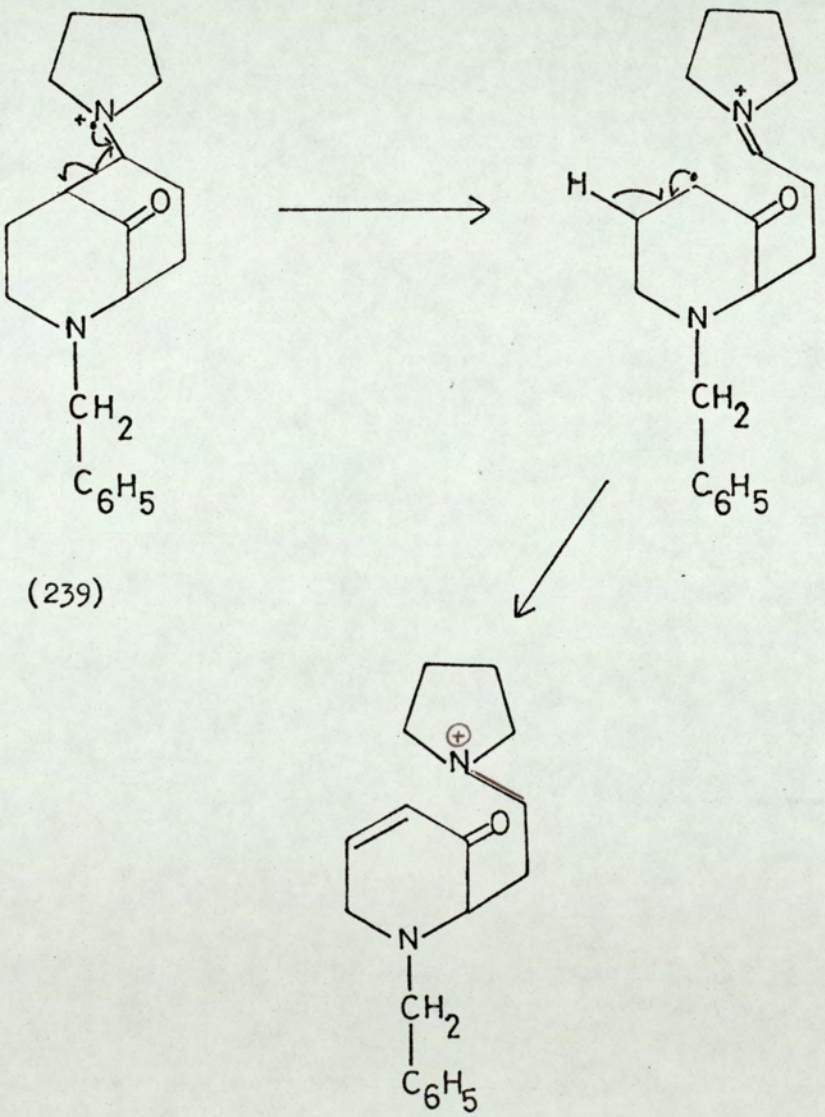
The deaza ketones and alcohols (197, 198, 199, 200, 203 and 205), Figs. 33c, 34a, 35c, 36a, 36b and 36c, show only one major peak in their breakdown at $^{m}/e$ 202. This is due to the ion XVlll. Other losses are suppressed because of the stability of this ion. Fragmentation to give the $^{m}/e$ 115 ion is seen as a minor breakdown pathway from this ion.

2-Benzyl-6-(N-pyrrolidinyl)-2-azabicyclo[3.3.1]nonan-9-one. (239)

The breakdown of this ketone is seen to resemble in some respects the breakdown of the pairs of ketones (75 and 76, 127 and 128, and 136 and 137) and gives rise to a base peak at $^{m}/e$ 110 due to ion Vlll. This is seen to be the base peak for the epimeric pairs of ketones (75 and 76, 127 and 128, and 136 and 137) and can arise in a similar fashion (fragmentation pathway A). However, this ketone (239) shows no appreciable loss of the cycloalkylamino group. This occurs because the methylamino group is no longer in a position to enable fragmentation pathway B to occur. This results in retention of the cycloalkylamino group. This ketone also shows no M - 1 peak, in contrast to the related ketones derived from N-methyl-4-piperidone,

which lost a hydrogen atom to give a radical which could be resonance stabilised. However, loss of a hydrogen atom from the ketone (239) would give a radical ion which could not be resonance stabilised to the same extent, Fig. 37. and this is therefore no longer a preferred loss.

Figure 37



(239)

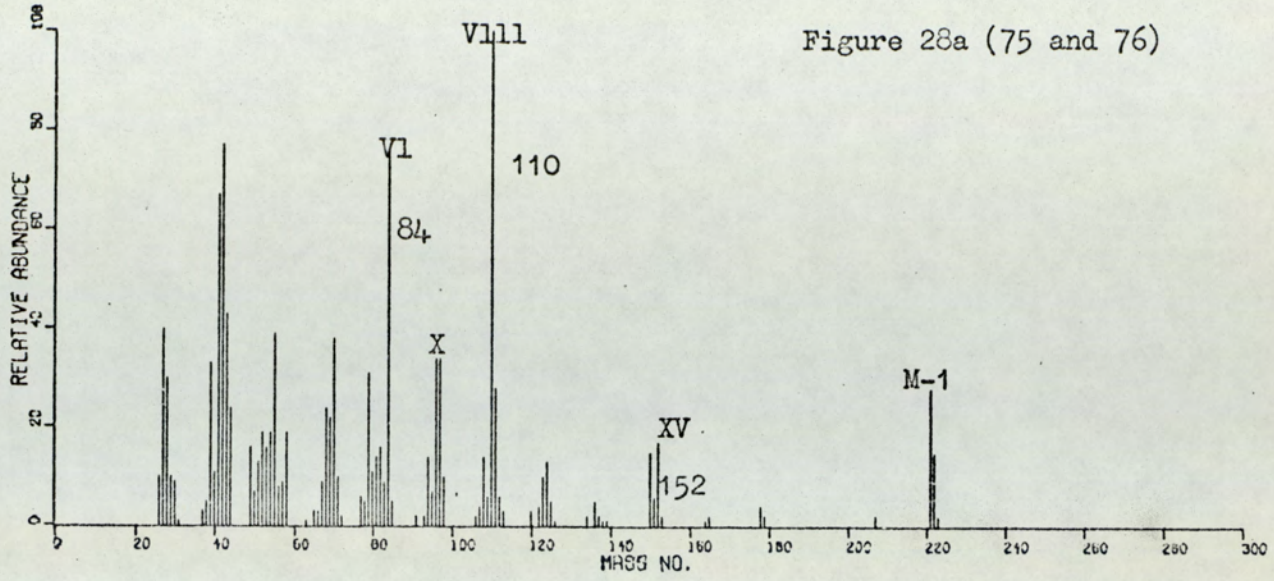


Figure 28a (75 and 76)

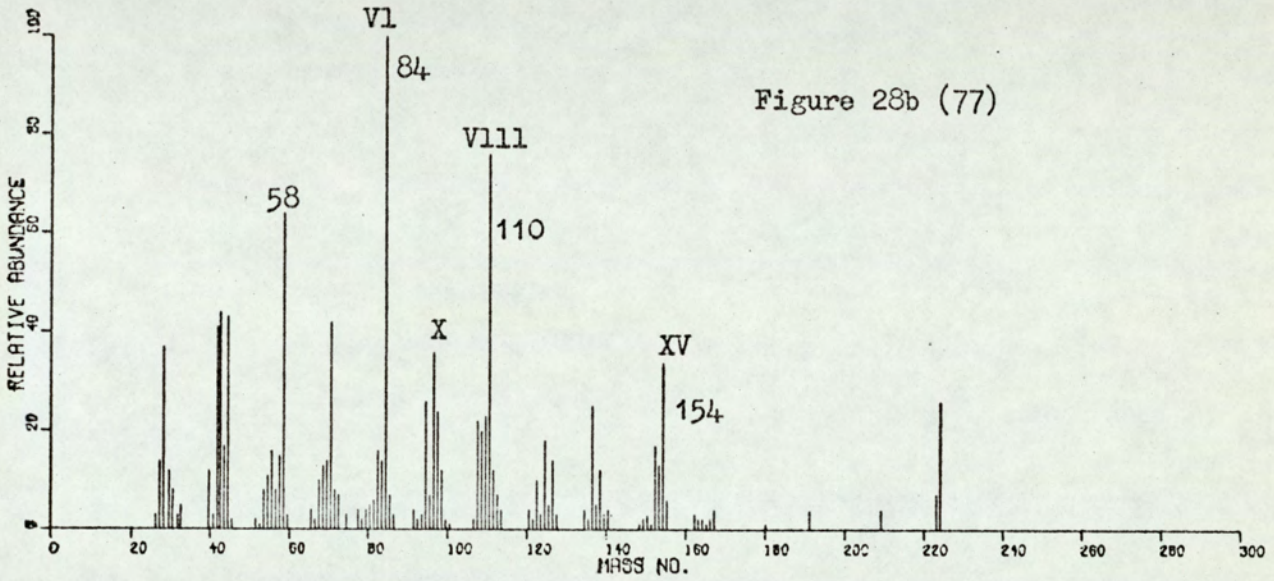


Figure 28b (77)

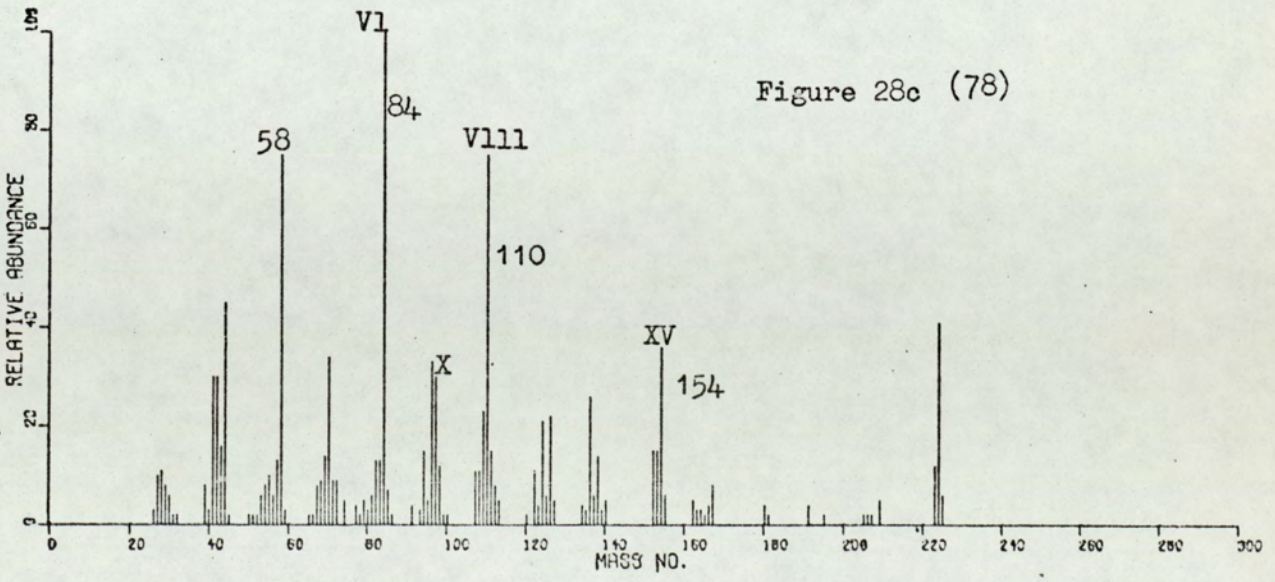


Figure 28c (78)

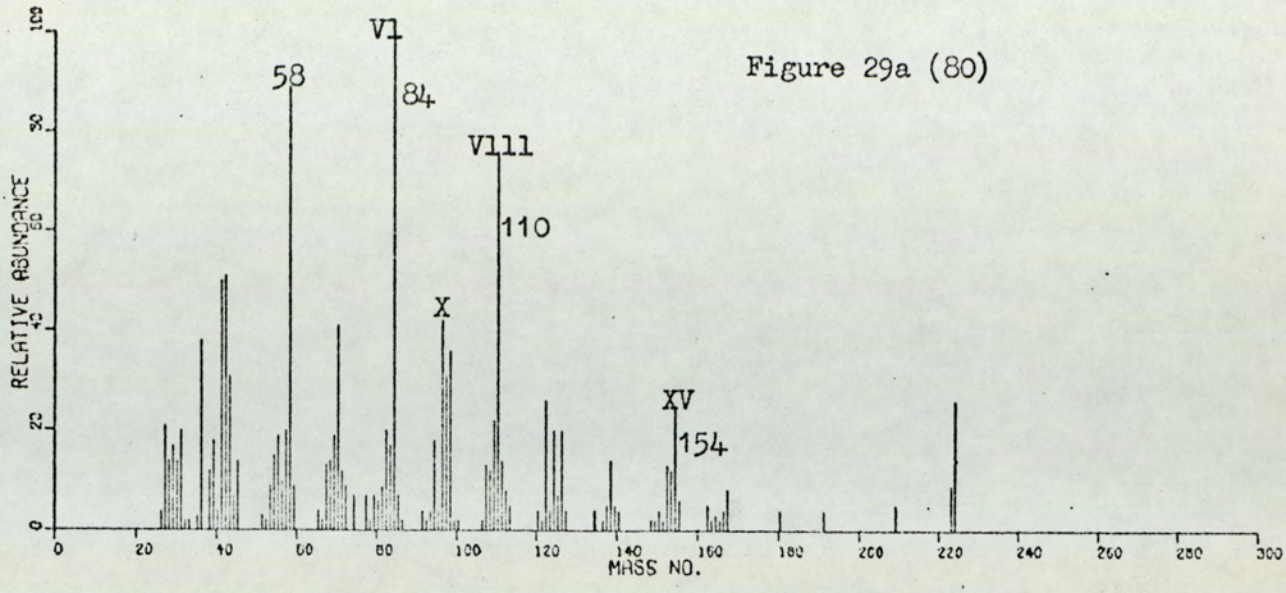


Figure 29a (80)

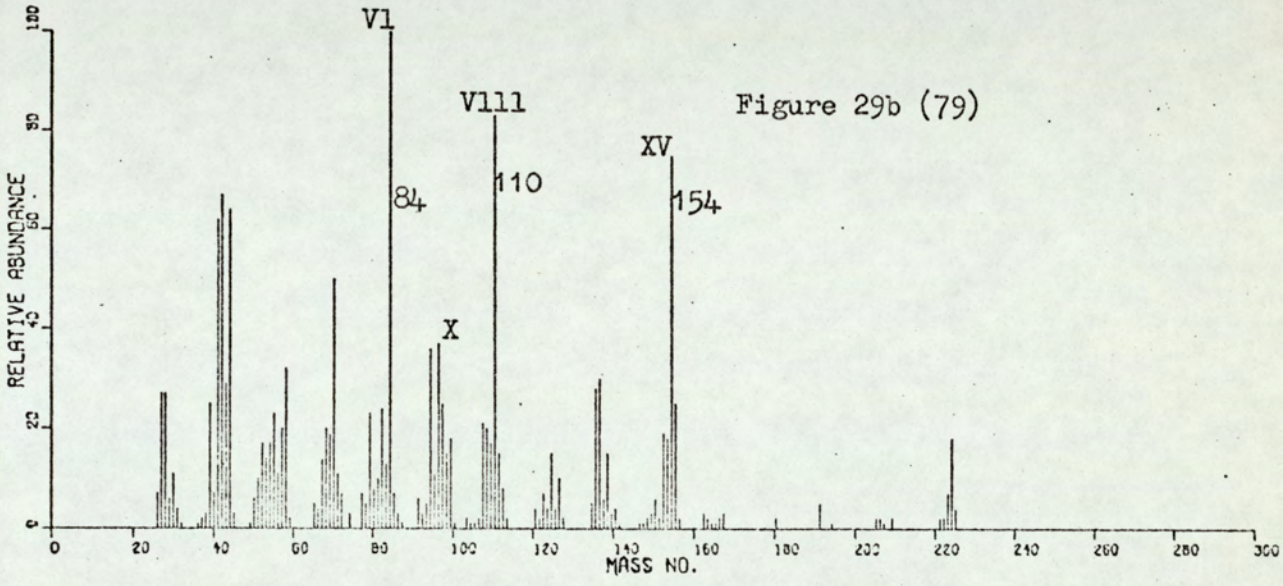


Figure 29b (79)

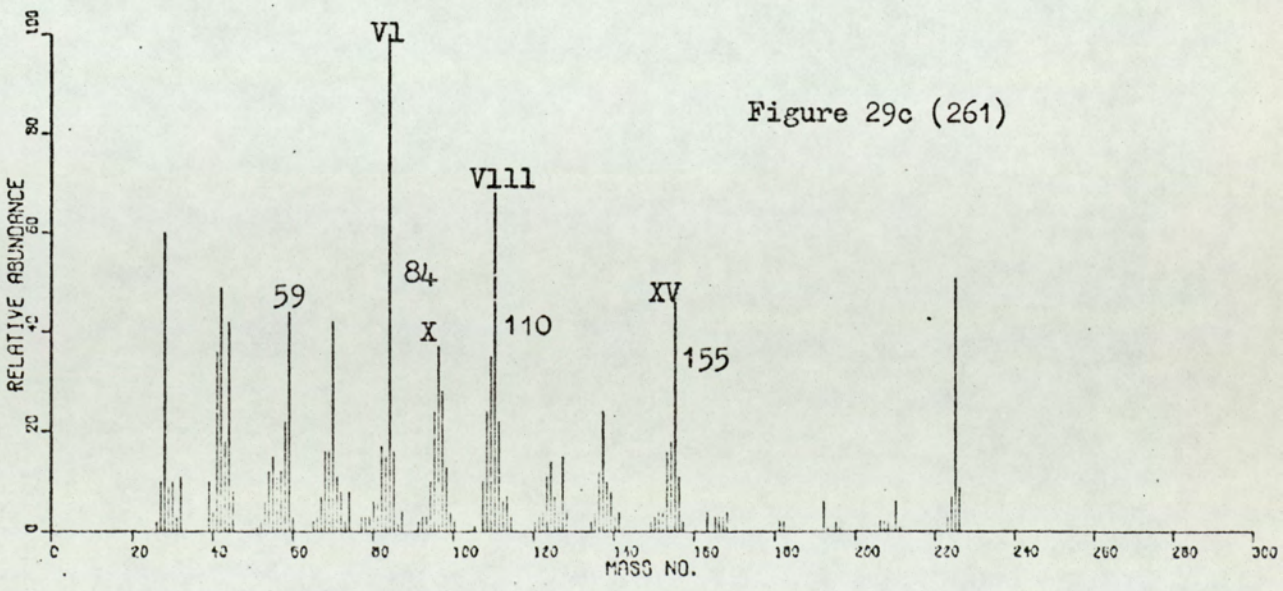


Figure 29c (261)

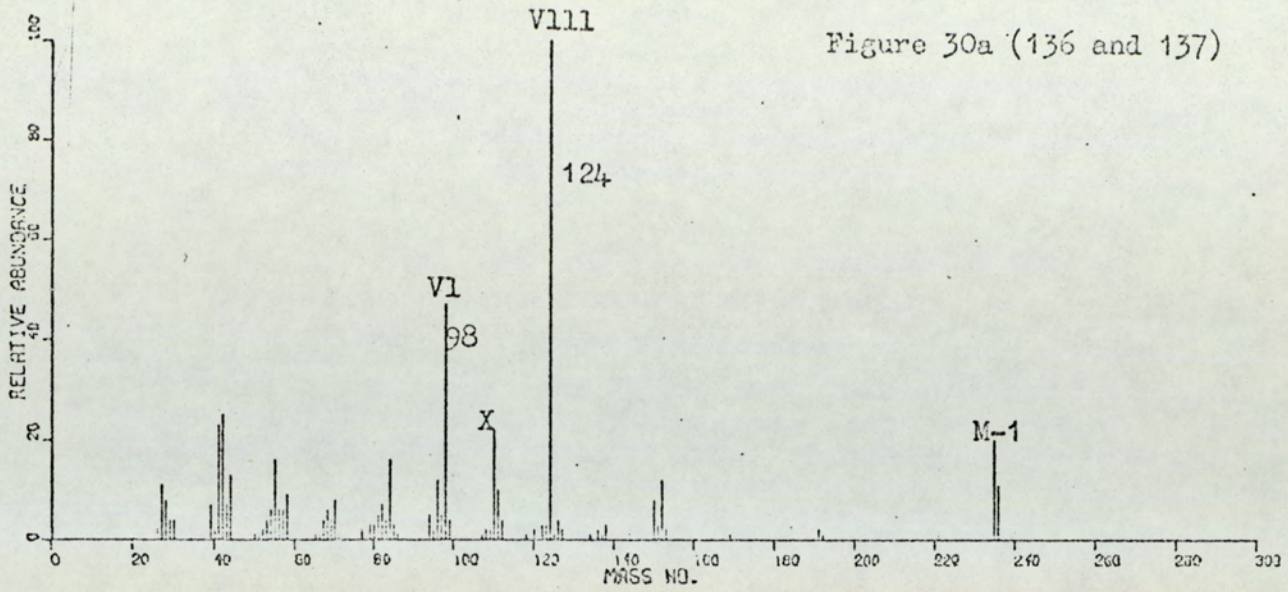


Figure 30a (136 and 137)

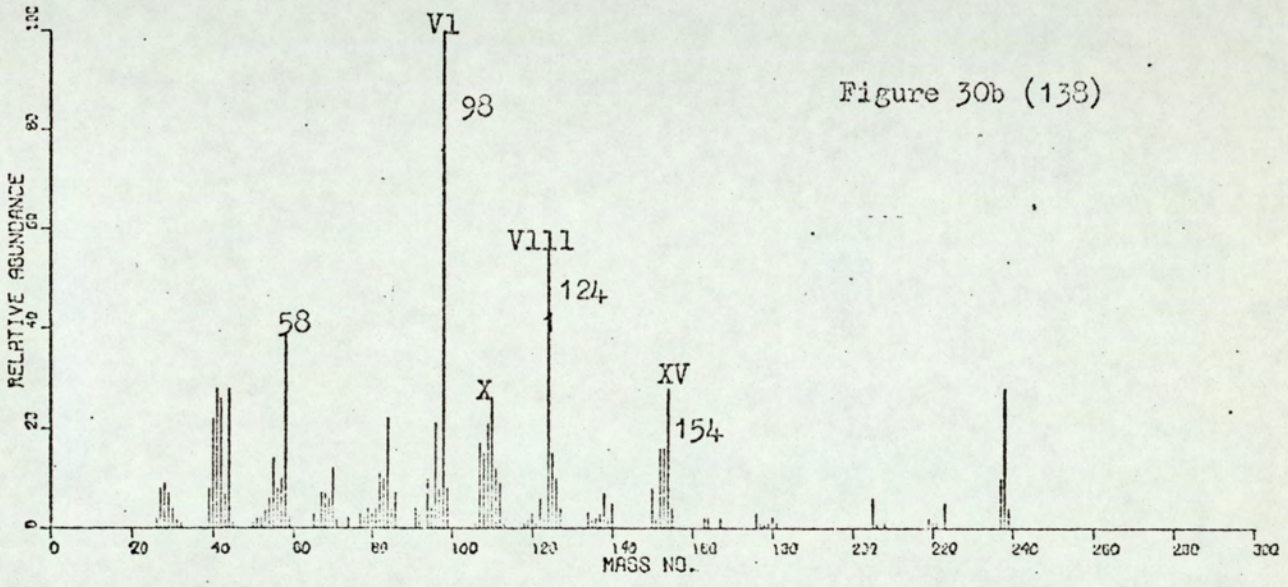


Figure 30b (138)

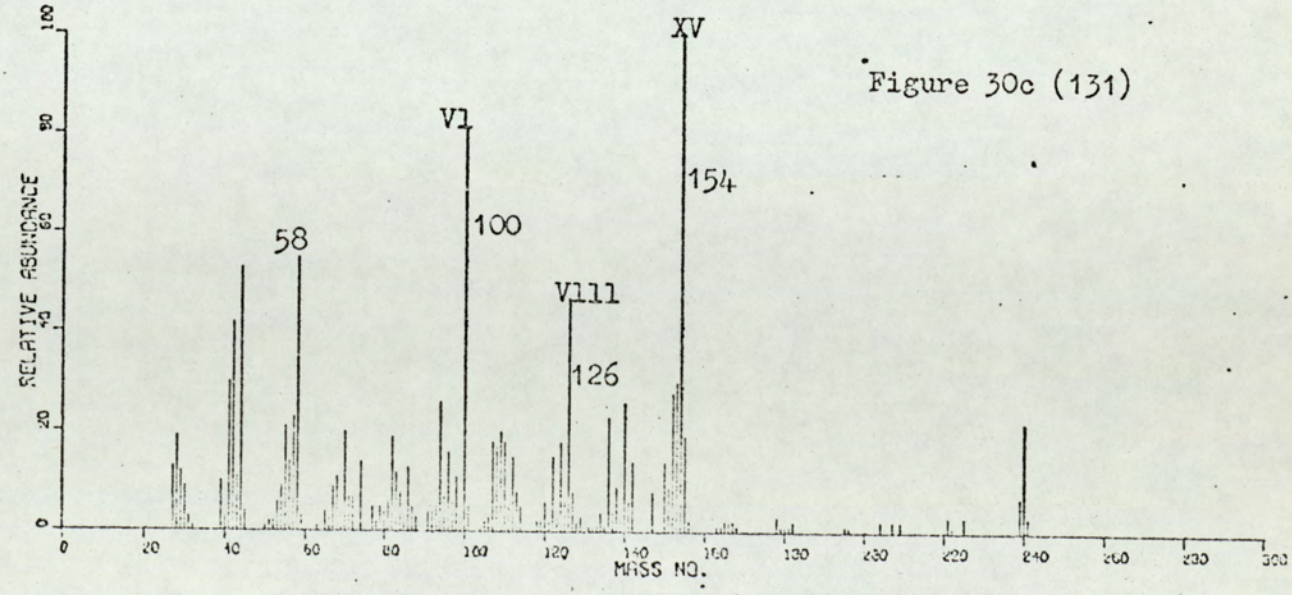


Figure 30c (131)

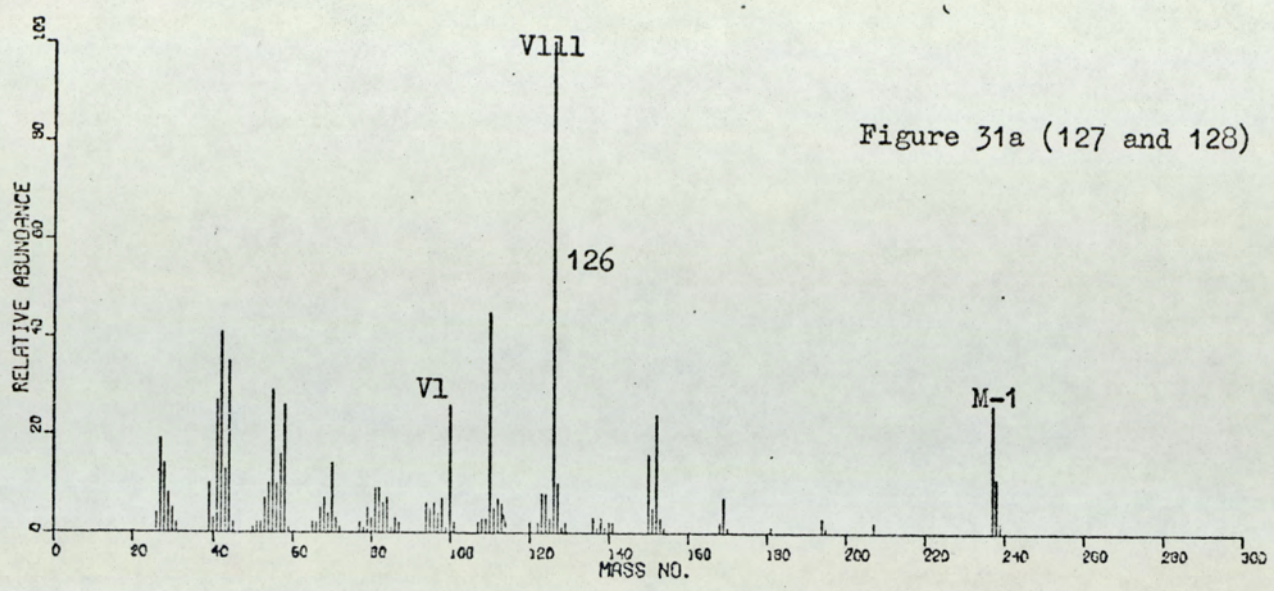


Figure 31a (127 and 128)

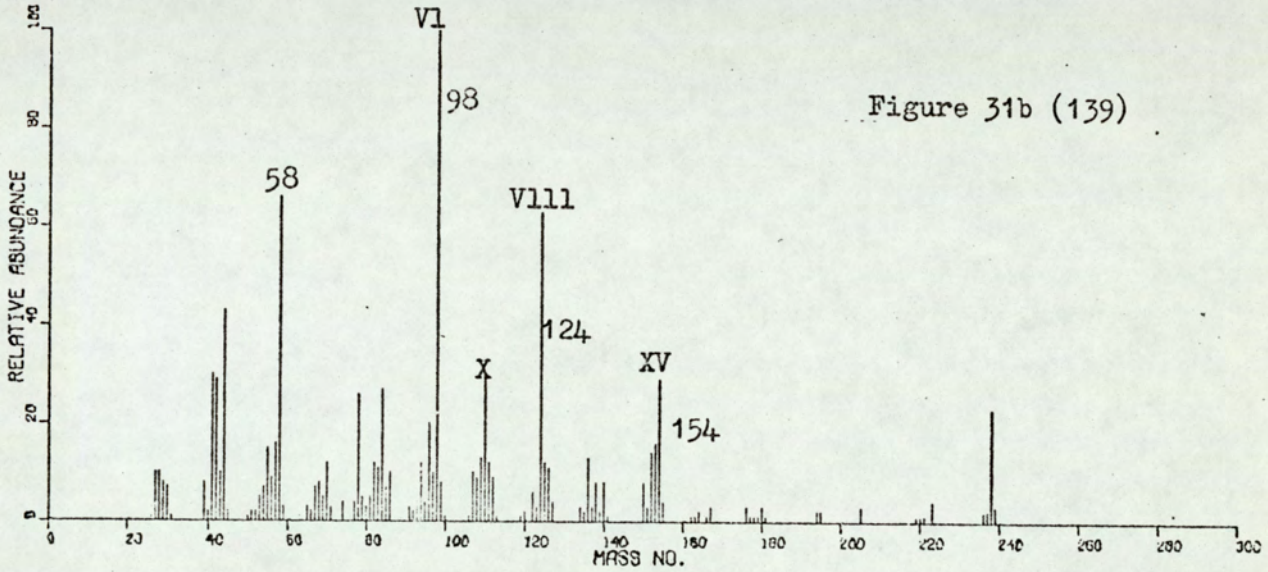


Figure 31b (139)

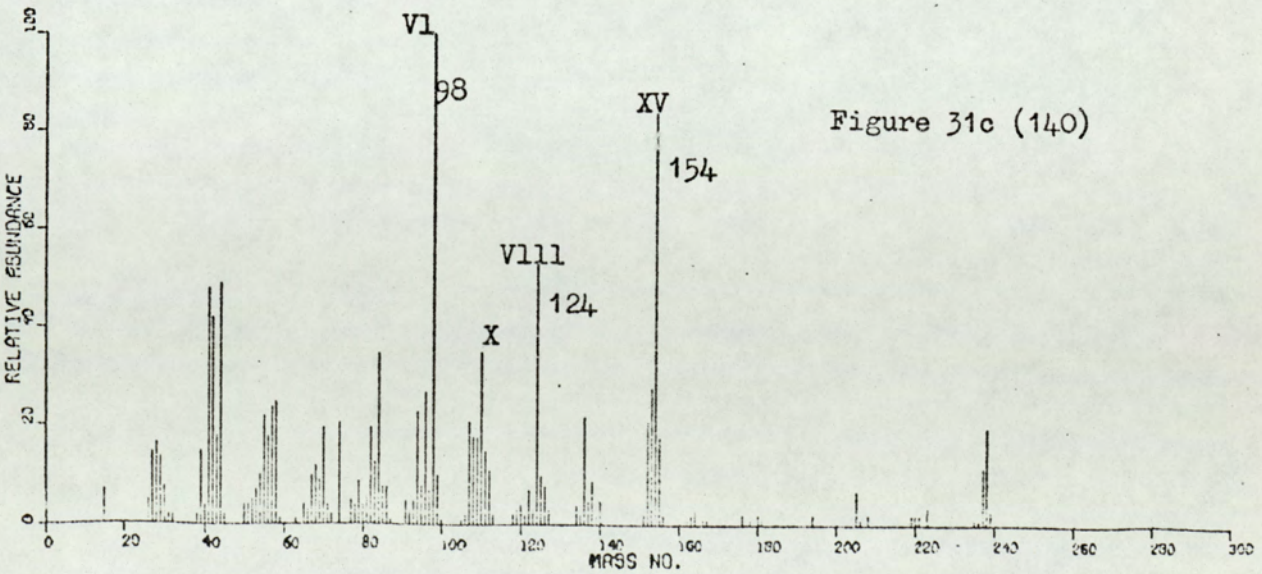


Figure 31c (140)

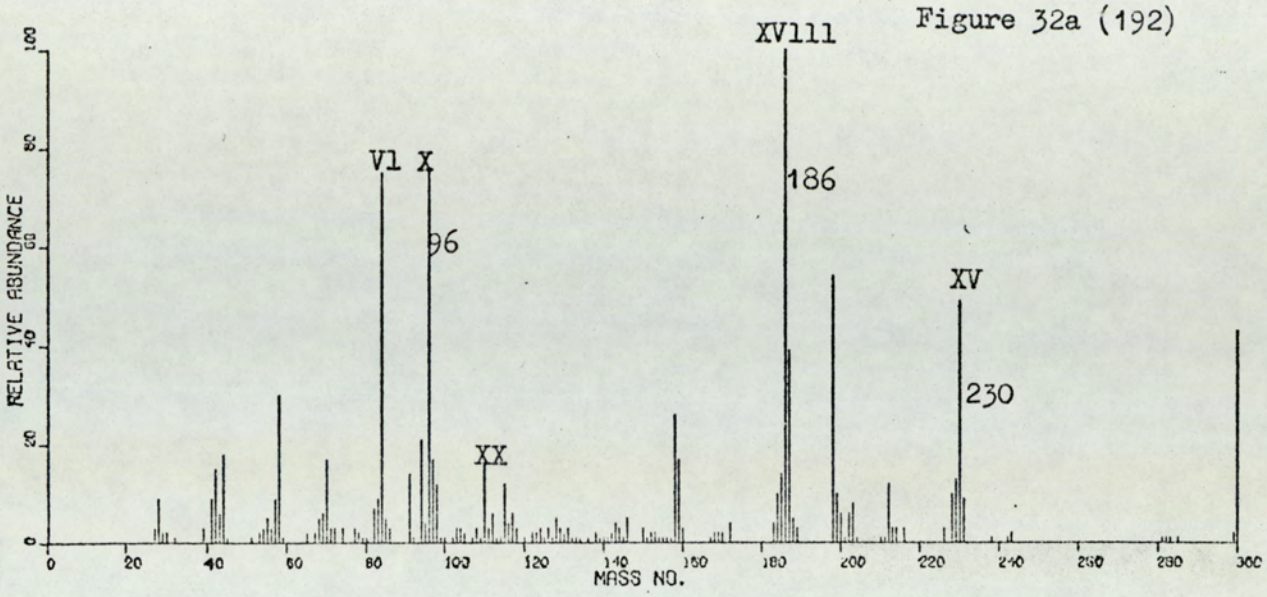


Figure 32a (192)

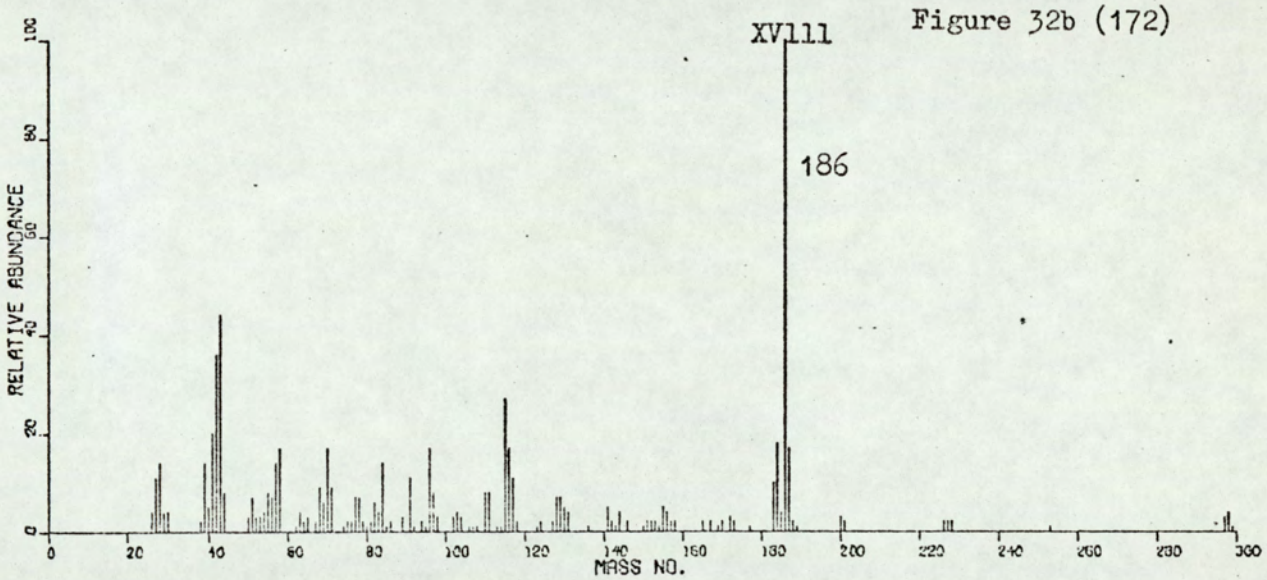


Figure 32b (172)

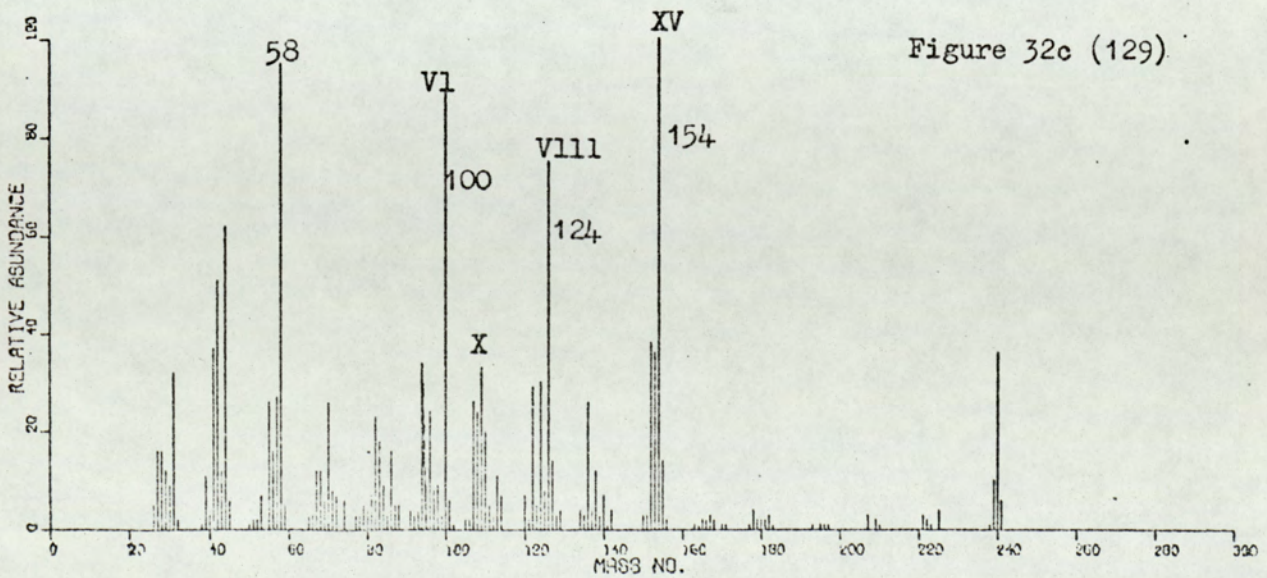
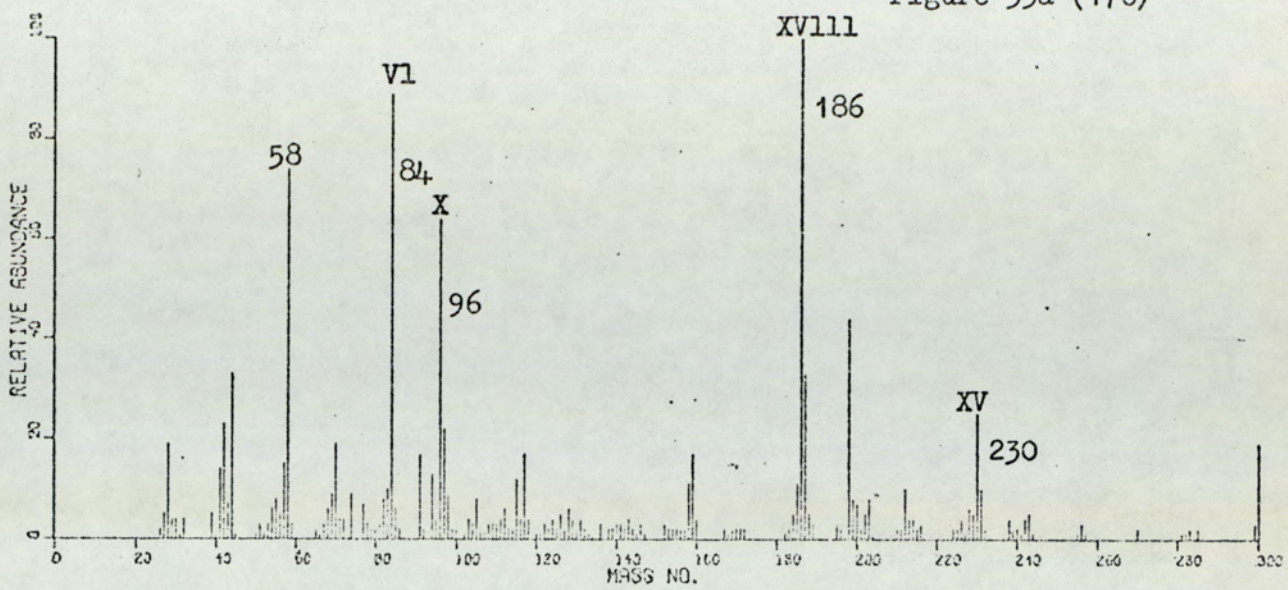


Figure 32c (129)

Figure 33a (176)



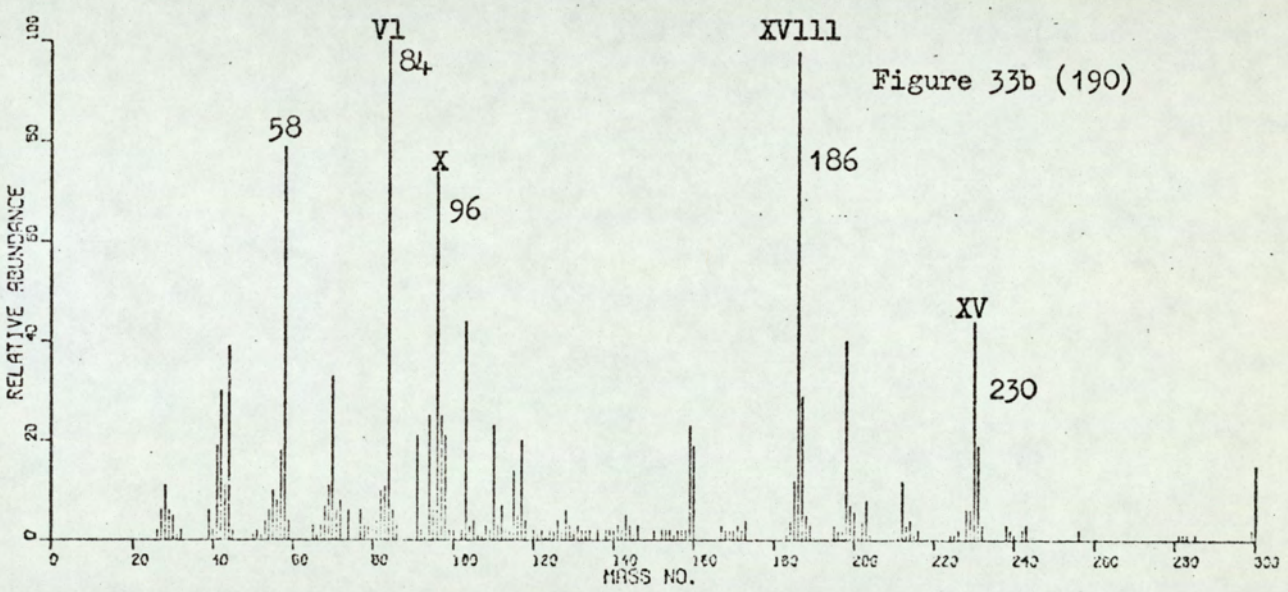
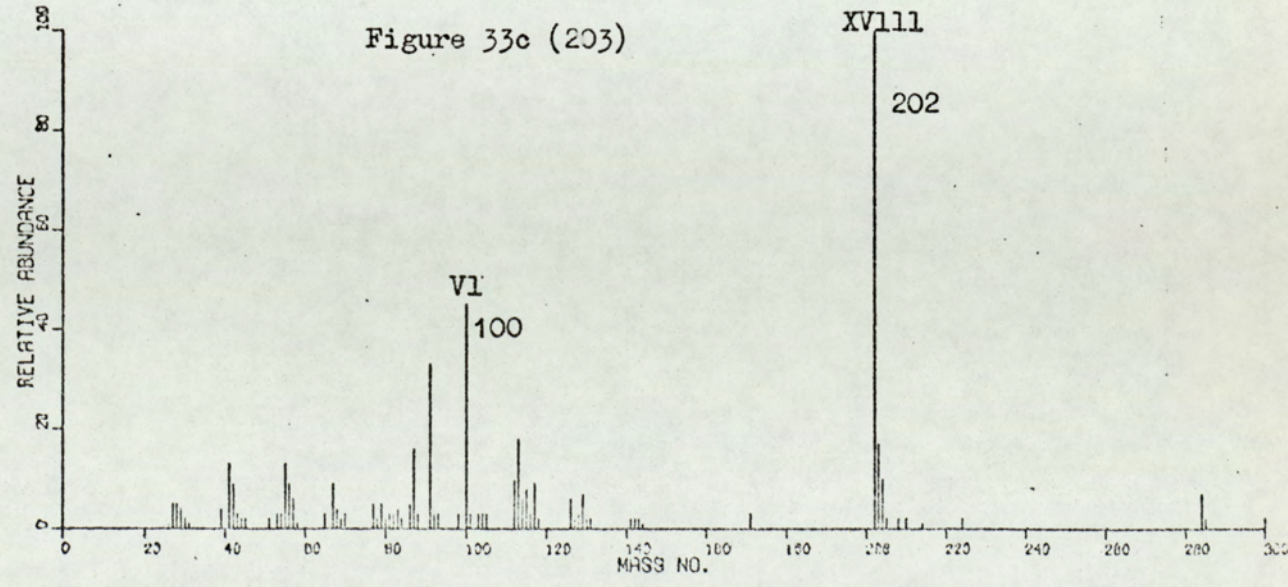


Figure 33c (203)



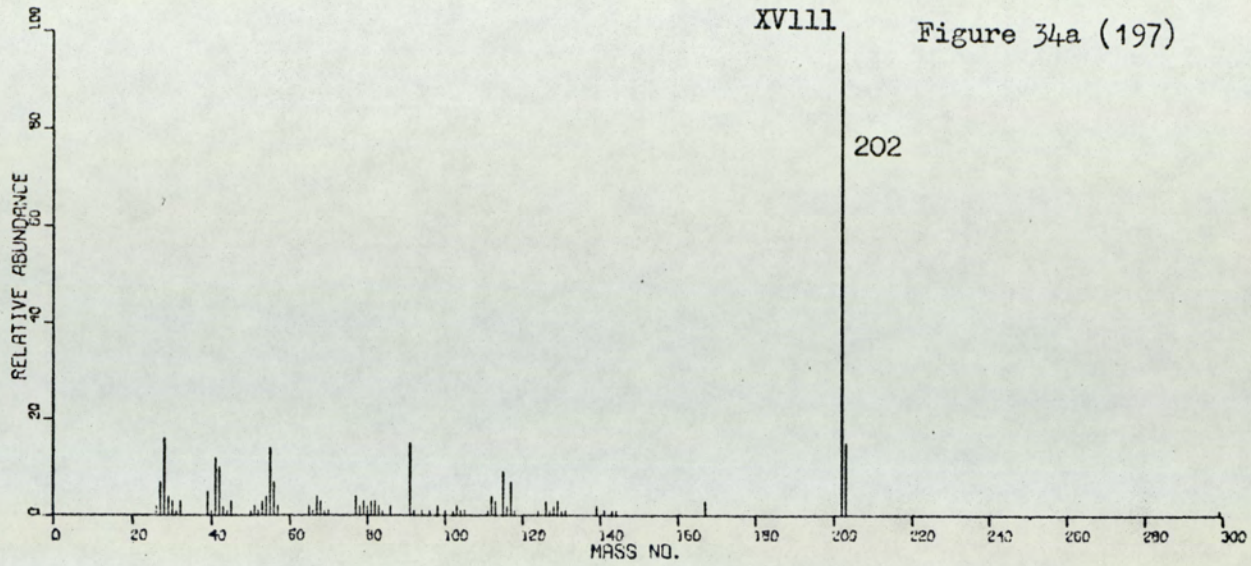


Figure 34a (197)

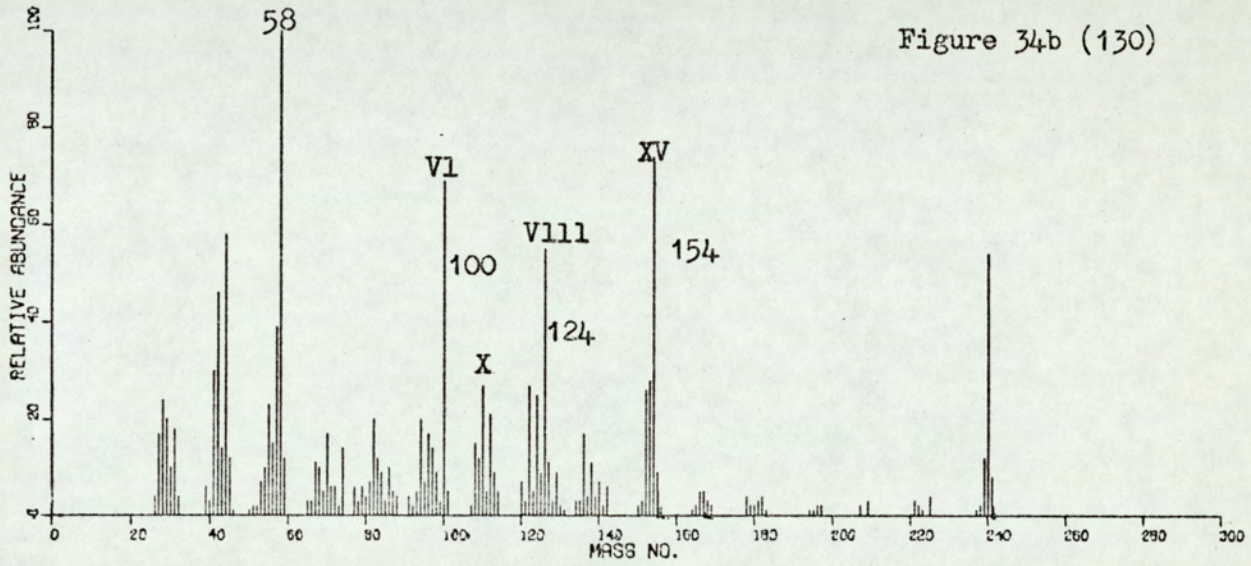


Figure 34b (130)

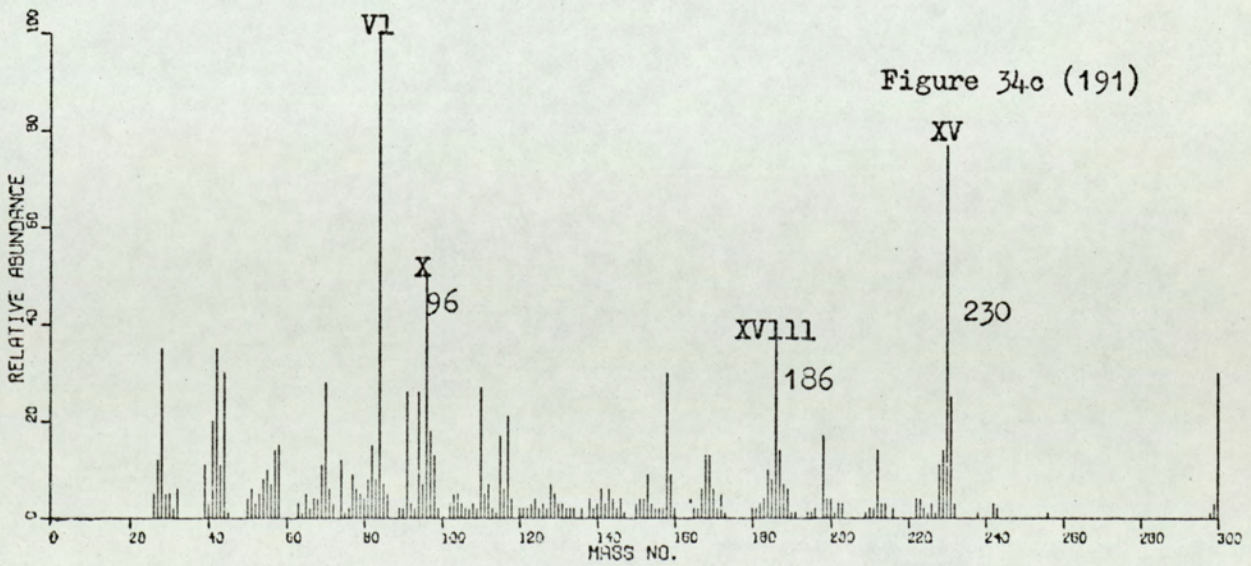


Figure 34c (191)

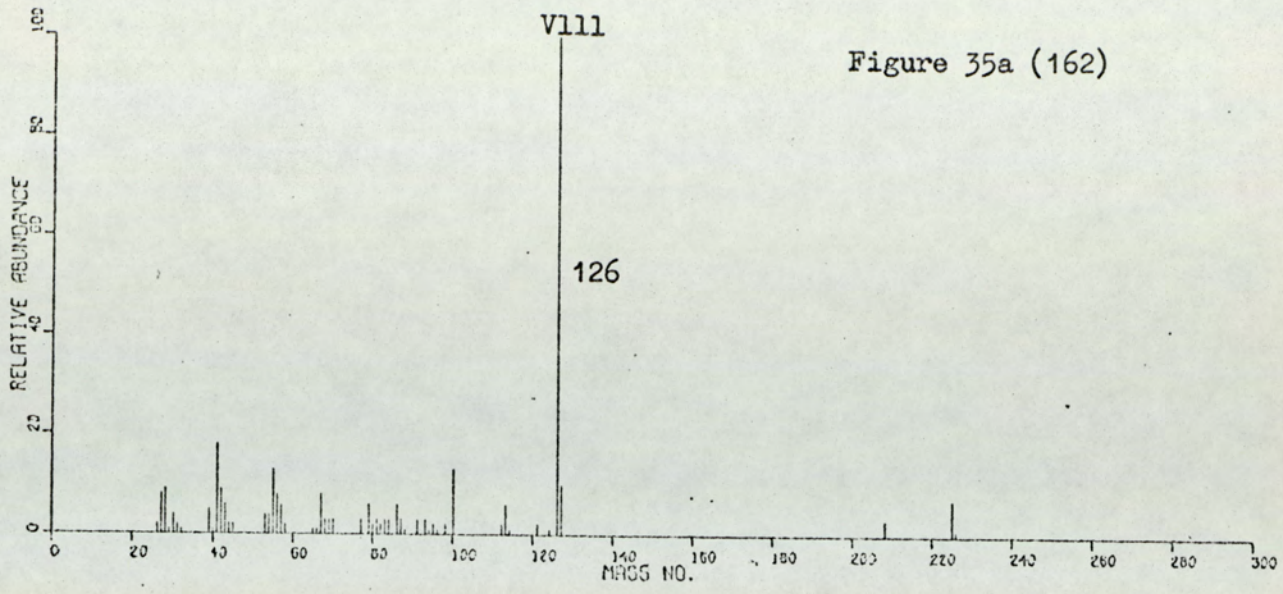


Figure 35a (162)

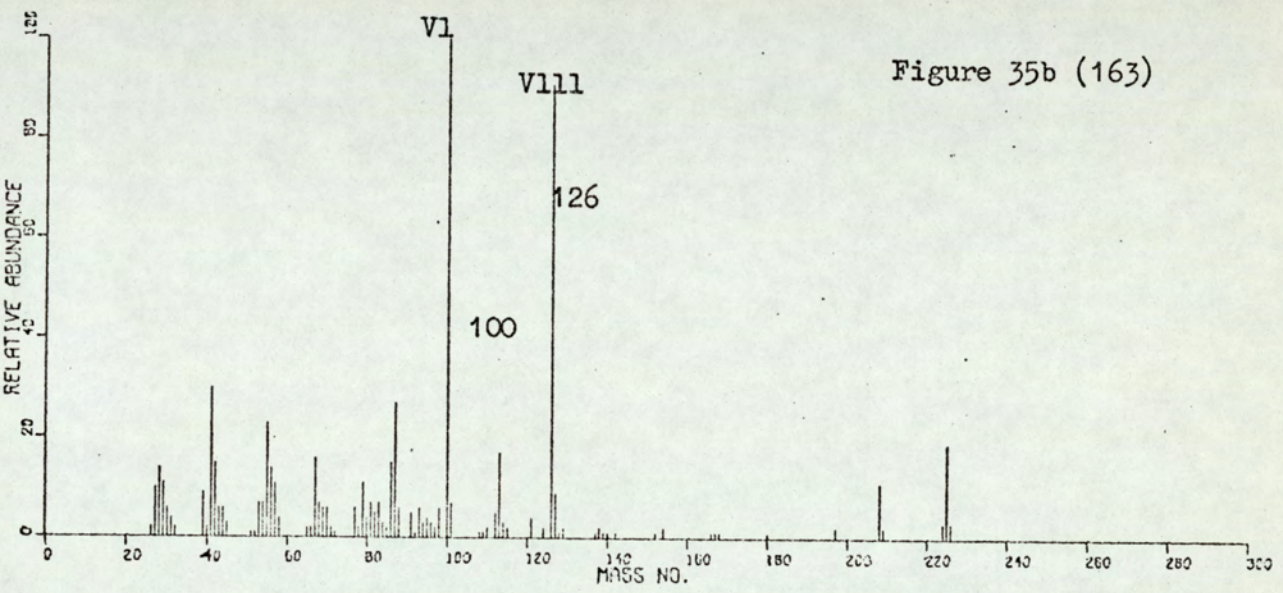


Figure 35b (163)

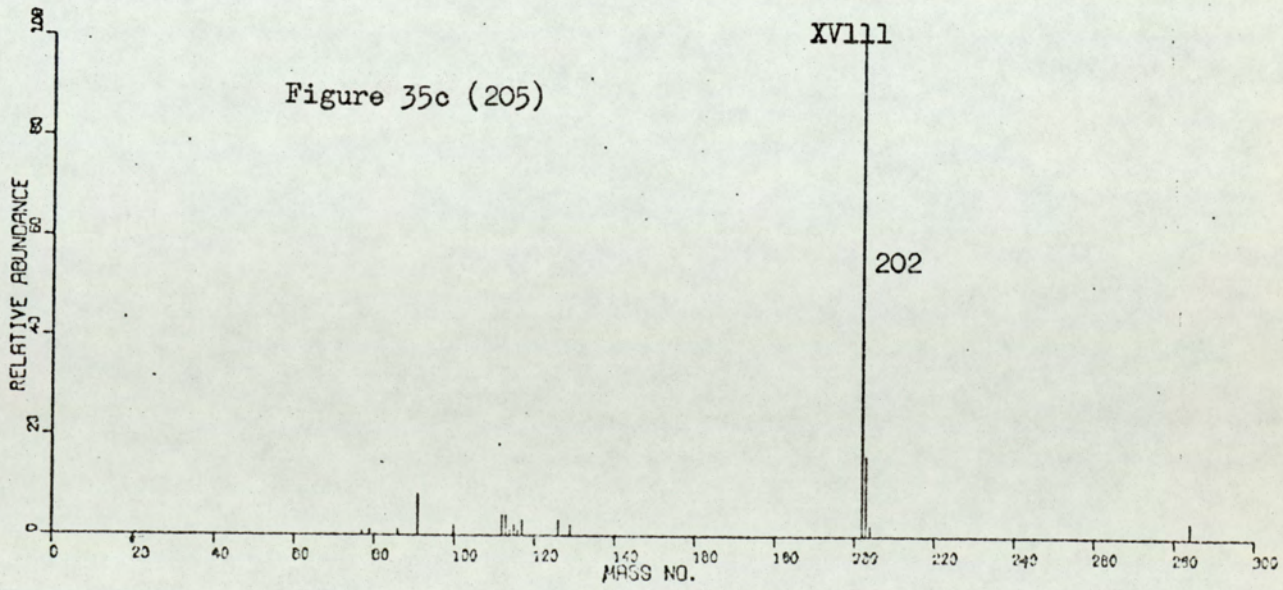


Figure 35c (205)

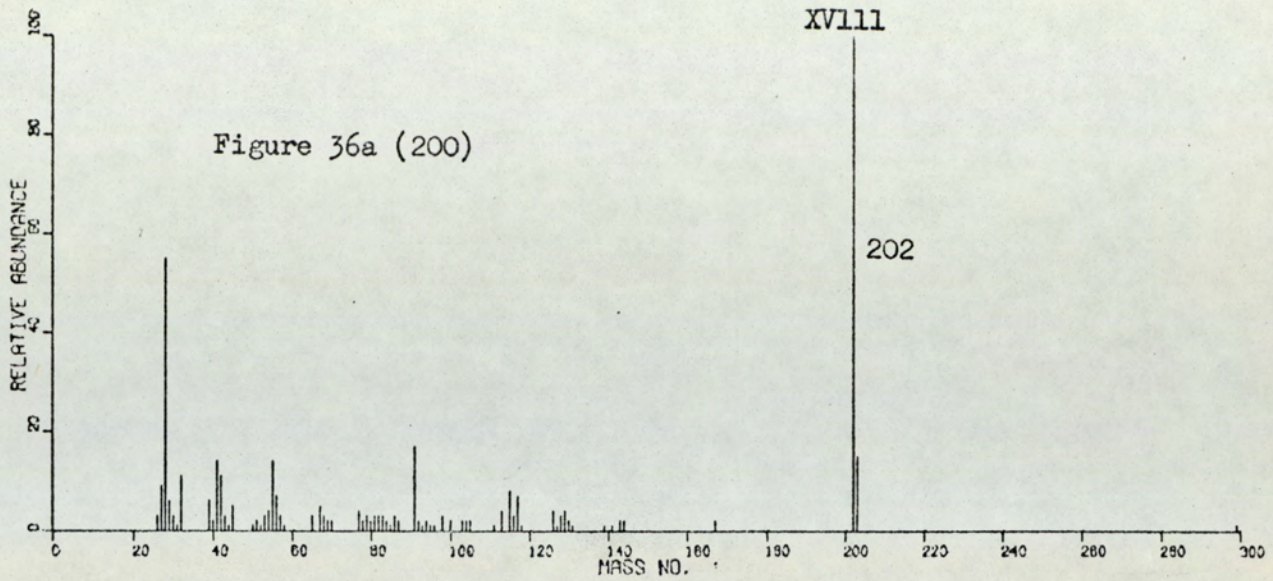


Figure 36a (200)

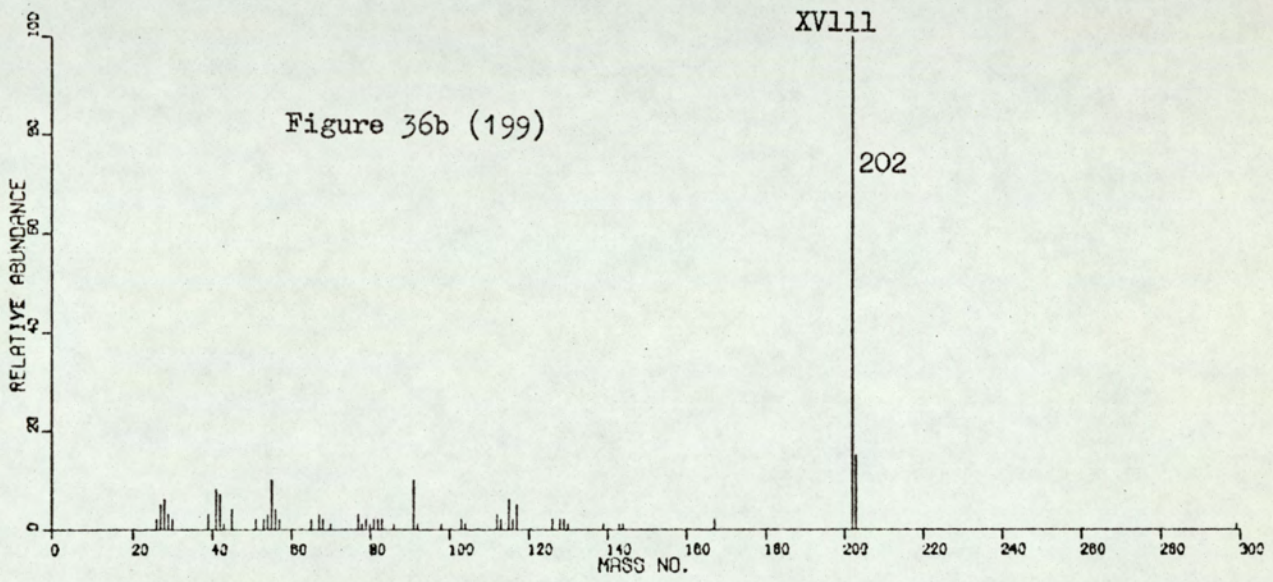


Figure 36b (199)

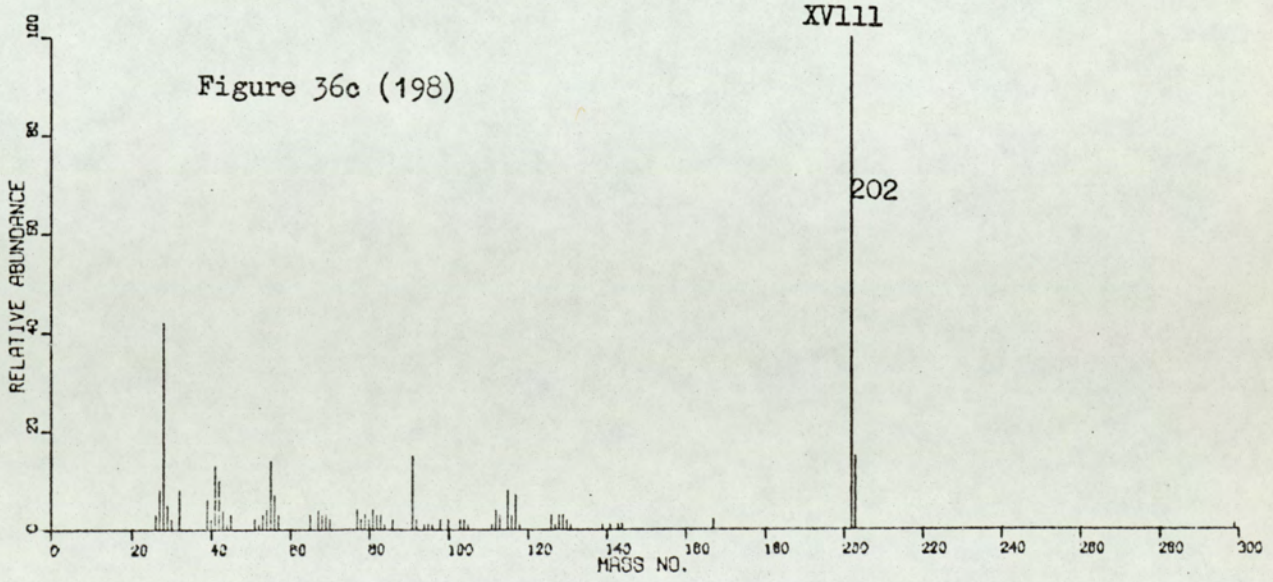


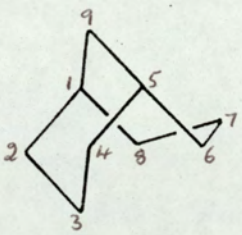
Figure 36c (198)

I. Conformational properties of bicyclo[3.3.1]nonane derivatives.

The conformational mobility of the bicyclo[3.3.1]nonane ring system has made it an interesting system for study.[137-139] The possible conformations of the bicyclo[3.3.1]nonane skeleton, and the more serious interactions involved therein, may be described briefly as follows.

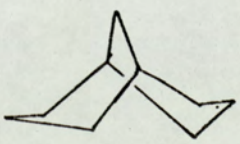
In the dichair conformer (264a), one very serious interaction occurs between the endo-hydrogens on C3 and C7. From a Dreiding model composed of ideal chairs, the H-H internuclear distance is 0.8 Å, but in reality this conformer would, of necessity, be distorted to accomodate these hydrogens.[71]

(264a)



(264b)

(264c)



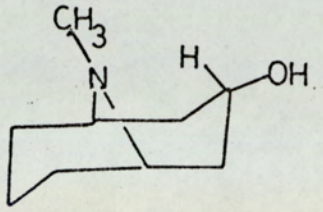
(264d)

Relief of the 3-7 methylene interaction can be brought about if the molecule assumes the boat-chair form (264b), but the creation of a 3,9 "bowsprit" interaction in the boat and also 3,6- and 3,8-hydrogen interactions of comparable severity below the molecule, would offset the easement of crowding. In any structure having a boat-chair conformation (264b), the boat portion cannot assume the lower energy twist modification because of the fused and rigid chair half of the structure. Consideration of a twin-boat conformer (264c) cannot be excluded in such a crowded system. In addition to the obvious 3,9- and 7,9- interactions, two less serious ones between the 2,8- and 4,6- hydrogens must be considered. The ideal twin-boat conformer is the only one which has any rotational freedom in the carbon framework, and permissible distortion produces the "twin-twist boat" conformer (264d). A slight, but probably negligible, relief of the bowsprit interactions is accompanied by the creation of a serious transverse 2,6- interaction below the rings as they are depicted.

The 1,5- dimethylbicyclo [3.3.1] nonanes are believed to exist in distorted twin-chair conformations,[137] where the 3,7- transannular hydrogen interactions are relieved either by carbon-carbon bond-angle changes, as in the medium-sized carbocycles, or by localised H-C-H bond-angle disturbances.

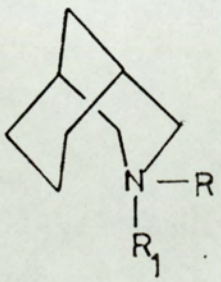
Chen and Le Fevre[140] however, have concluded that 3a-

granatanol is a mixture of conformers in which the chair-boat (265) is preferred.

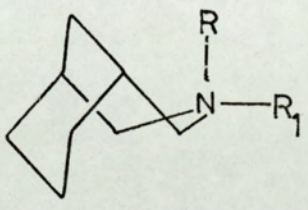


(265)

Examination of the n.m.r. spectra [131] of the hydrochloride and the methiodide of 3-methyl-3-azabicyclo[3.3.1]nonane has shown that the main configurational isomer in solutions of the hydrochloride has conformation (266, $R=CH_3$, $R_1=H$) corresponding to that found (266, R=H, $R^1=H$) for 3-azabicyclo[3.3.1]nonane hydrobromide in the solid phase. [139] The methiodide however is apparently almost exclusively (267, $R=R_1=CH_3$).



(266)

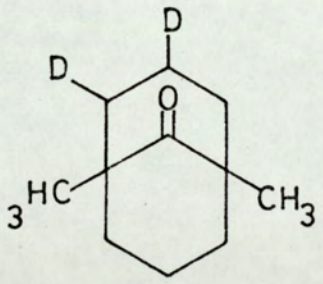


(267)

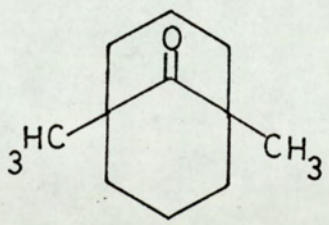
The boat ring, like the chairs in (266), is probably flattened, a process which has little initial effect on torsional angles. The single boat in this bridged system cannot easily be twisted, and the n.m.r. evidence also excluded the possibility of an appreciable proportion of a twin-twist-boat conformation.

Another method for determining the configuration of bicyclo [3.3.1] nonanes has been use of their infrared spectra. A detailed survey of the infrared spectra of bicyclo [3.3.1] nonanes has revealed unusual absorptions which can be related to the stereochemistry and conformation of the system. Models of the saturated bicyclo [3.3.1] nonane system show that no matter which conformation the molecule adopts (conformational sketches 264a-264d), there exists strong non-bonded hydrogen-hydrogen interactions. Evidence of such interactions has been afforded by an examination of the CH stretching and bending regions in the infrared region. De Vris and Ryason [141] have found ν(C-H) bands at abnormally high frequencies (3055-2980 cm. $^{-1}$) in a variety of fused polycyclic compounds in which two or more methylene groups are forced into close proximity. The bands are generally rather indistinct shoulders on the high frequency side of the main ν(C-H) absorption and assignment is difficult when the molecule contains double bonds. Eglinton et al. [137] have shown the infrared spectra of certain bicyclo [3.3.1] nonanes to contain bands near 2990

and 1490 cm. $^{-1}$ In the bicyclo-series, the 1490 cm. $^{-1}$ bands would appear to be more diagnostic as they are well separated from the normal methylene scissoring absorption. The infrared spectra of pertinent bicyclo[3.3.1]nonane compounds reported by Stoll et al. [142] also show high frequency scissoring bands. In the bicyclo[3.3.1]nonane series reported by Eglinton [137] it was concluded that the interacting methylenes were 3- and 7- methylenes on the grounds that they show closest approach in conformation (264a). It was also shown that any change in the molecule which relieved the interaction, resulted in the disappearance of the band at 1490 cm.$^{-1}$ In an attempt to confirm that the 3- and 7- methylene groups were responsible for the abnormally high frequency bands at 2990 cm.$^{-1}$ and 1490 cm.$^{-1}$, the bisdeutero-ketone (268) was prepared and its infrared compared with that of the non-deuterated ketone (269).



(268)



(269)

It was expected that the substitution of a CDH grouping in the 3-position would affect the intensities of both abnormal bands.

The spectrum in fact showed a reduction of approximately one-half in the intensity of the 1490 cm.$^{-1}$ band, an effect attributable to the replacement of the H-C-H scissoring band of the 3-methylene groups by a D-C-H scissoring absorption elsewhere in the spectrum. A further indication that the 1490 cm.$^{-1}$ peak is due to the interaction of the 3- and 7- methylenes is found by an inspection of the infrared spectrum of adamantone [143] which shows no significant absorption at this frequency. This compound is clearly analogous in its stereochemistry to the twin-chair conformer (264a), and is formally derivable by insertion of one methylene group between carbons 3 and 7, thereby eliminating the 3,7- methylene hydrogen-hydrogen interactions.

In view of this, the infrared spectra of a number of azabicyclononanes were obtained as 10% $^{w}/_{v}$ solutions in chloroform to ascertain whether any absorption at unusually high frequencies could be observed. The results are summarised in table 2.

The results show that only three of the compounds examined showed an absorption at unusually high frequencies, (191, 162, and 198). The peak at 1494 cm.$^{-1}$ in the phenyl substituted compounds can be attributed to the benzene ring. Two of the three compounds exhibiting the high frequency band are seen to be deaza compounds (162 and 198). However, the majority of the compounds examined failed to show any absorption at unusually high frequency in the 1400-1500 cm.$^{-1}$ region.

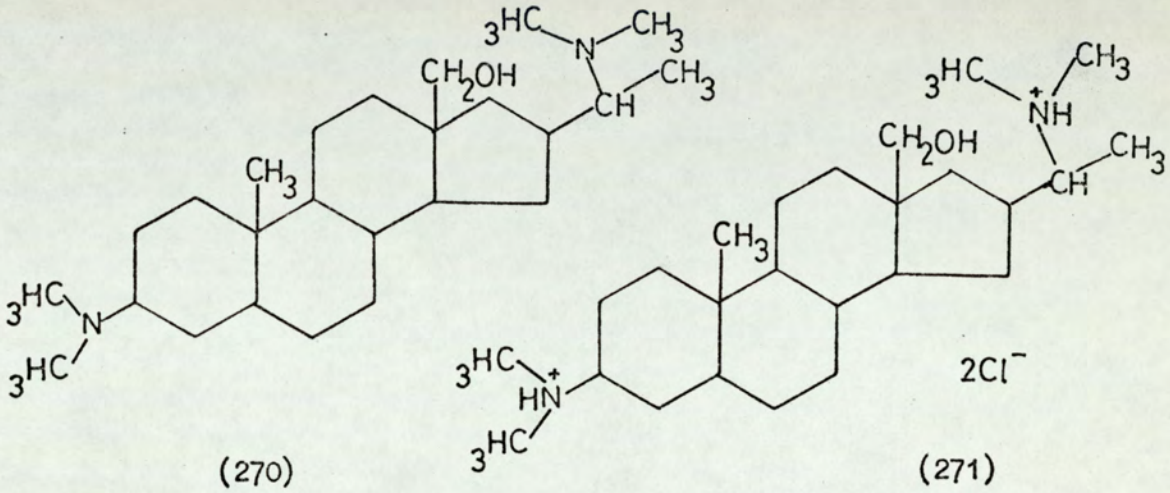
This would indicate that although hydrogen-hydrogen interactions produce bands in the infrared at abnormally high frequencies, interactions between hydrogens and the "lone pair" of the methylamino group do not produce the same band or produce a band in a different region of the spectrum. However, before any firm conclusion can be drawn, a more general extensive survey of the interaction between the "lone-pair" on nitrogen and hydrogen atoms is required.

Table 2

Compound number.	Position of peaks ($cm.^{-1}$).
77	1467
172	1494,1467,1454
176	1494,1467,1454
192	1494,1467,1454
190	1494,1467,1454
191	1492,1481,1453
197	1494,1454
198	1494,1488,1454
199	1494,1454
200	1494,1454
203	1494,1454
162	1488,1454

ADDENDUM

In a further attempt to prove that the band at 1630 cm. $^{-1}$ in the infrared spectrum of the amino-alcohol salt (98) was due to the in-plane bending vibration of a "pseudo-water molecule", dihydrotetramethylholarrhimine (270), was converted to the dihydrochloride (271), and its infrared spectrum examined. [144]



(270) (271)

Dihydrotetramethylholarrhimine is known to show only intramolecular hydrogen-bonding on a dilution infrared study. [81] The infrared of the dihydrochloride salt (271) after drying at 115° showed a sharp band at 1630 cm.$^{-1}$ in the infrared spectrum, in good agreement with the result for the amino-alcohol salt (98), which also showed this band. Analysis of the amino-alcohol salt (271), showed the molecule not to be hydrated. The band at 1630 cm.$^{-1}$ in the infrared spectrum of the dihydrochloride salt (271) cannot be produced by any C=C, C=N or C=O absorption, and this is believed to clearly demonstrate that the peak at 1630 cm.$^{-1}$ in the spectra of both the amino-alcohol

salts (271) and (98) is due to the presence of a "pseudo-water molecule." The use of this band can thus be used in the structure determination of amino-alcohols which exhibit intramolecular hydrogen-bonding.

EXPERIMENTAL

Infrared spectra were recorded using a Unicam S.P. 200 spectrophotometer. The samples were run as liquid films or as mulls in liquid paraffin. Dilution infrared spectra were measured with a Grubb-Parsons spectromaster, (carbon disulphide).

Nuclear magnetic resonance spectra were determined at 220 MHz using tetramethylsilane as internal standard. All the peaks are assigned in τ values. Abbreviations used in the interpretation of n.m.r. spectra: s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet; and J = coupling constant.

Mass spectra were determined with an A.E.I. MS9 instrument operating at 70eV with direct introduction of the samples into the heated inlet system.

Melting points are uncorrected.

Microanalyses were determined by Dr. F.B. Strauss, Oxford, England, or by Dr. A. Bernhardt, Max-Planck Institut fur Kohlenforschung, Mulheim, West Germany.

Glc results were obtained on a Perkin Elmer F-11 instrument, operated at a nitrogen pressure of 15 p.s.i.

General method for the preparation of the enamines.

The ketone (1.0 equivalent) and the amine (1.8 equivalents) were refluxed under a water separator in dry benzene (300 ml per mole) for 3 hr. The benzene and excess amine were removed under reduced pressure and the residue distilled in vacuo to give the product.

General method for the preparation of hydrochloride salts.

The base was dissolved in a 10% $^{w}/_{v}$ solution of hydrochloric acid in ethanol, the ethanol evaporated and the residue crystallised from ethanol/ether unless otherwise indicated.

1-Methyl-4-(N-pyrrolidinyl)-1,2,3,6-tetrahydropyridine (74).

1-Methyl-4-piperidone (11.3 g, 0.10 mole) and pyrrolidine (12.4 g, 0.18 mole) were refluxed in dry benzene (30 ml) for 3 hr to give 1-methyl-4-(N-pyrrolidinyl)-1,2,3,6-tetrahydropyridine b.p. 84-86°/1.5 mm (13.3 g, 80%) (lit. 73-75°/0.2 mm)[43] according to the general method.

$\nu_{max.}$ (Thin liquid film), 2760 (N-CH_3), 1650 (C=C) $cm.^{-1}$

3-Methyl-6α- and 3-Methyl-6β-(N-pyrrolidinyl)-3-azabicyclo[3.3.1]nonan-9-ones (75, 76).

1-Methyl-4-(N-pyrrolidinyl)-1,2,3,6-tetrahydropyridine (8.3 g, 0.05 mole) in dry dioxan (15 ml) was cooled to 0 - 5° and acrolein (2.8 g, 0.05 mole) in dry dioxan (10 ml) was added dropwise with stirring during 1 hr. The mixture was stirred at 0° for 1 hr,

and then allowed to stand at room temperature for 1 hr. The dioxan was removed at 20 mm to give a viscous amber oil (8.3 g, 75%) which on distillation gave a straw coloured liquid (7.8 g, 70%) b.p. 124-126°/0.75 mm, which crystallised on cooling as colourless needles of a mixture of 3-methyl-6α- and 3-methyl-6β-(N-pyrrolidinyl)-3-azabicyclo[3.3.1]nonan-9-ones m.p. 42-44° (from petrol b.p. 60-80°). (Found: C, 70.1; H, 9.9; N, 12.7; $C_{13}H_{22}N_2O$ requires C, 70.2; H, 10.0; N, 12.6%),

$\nu_{max.}$ (Nujol), 2770 (N-CH_3), 1720 (C=O) $cm.^{-1}$

τ ($CDCl_3$): 7.78 (3H, s, N-CH_3).

3-Methyl-6α-(N-pyrrolidinyl)-3-azabicyclo[3.3.1]nonan-syn-9-ol (77).

To a solution of 3-methyl-6α- and 3-methyl-6β-(N-pyrrolidinyl)-3-azabicyclo[3.3.1]nonan-9-ones (2.2 g, 0.01 mole) in isopropyl alcohol (10 ml) was added sodium borohydride (0.33 g) and the resulting mixture stirred at room temperature for 3 hr. After the excess sodium borohydride had been destroyed by the addition of glacial acetic acid, hydrochloric acid (1 ml) was added. The mixture was concentrated, made basic with aqueous sodium hydroxide, saturated with sodium chloride and extracted with ether. The ether layer was separated, washed with water, dried ($MgSO_4$), concentrated to 20 ml and allowed to stand for 1 hr. The crystalline material produced was filtered (0.6 g, 27%) and afforded colourless needles of

3-methyl-6α-(N-pyrrolidinyl)-3-azabicyclo[3.3.1] nonan-syn-9-ol

m.p. 169-170° (from ethyl acetate).

(Found: C, 69.4; H, 10.7; N, 12.7; $C_{13}H_{24}N_2O$ requires

C, 69.4; H, 10.8; N, 12.5%),

$\nu_{max.}$ (Nujol), 3200 (OH), 2760 (N-CH_3) cm.$^{-1}$

$\nu_{max.}$ (CS_2, 0.0025M), 3610 (OH) cm.$^{-1}$

τ (CD_3OD): 6.2 (1H, t, J=2.5 Hz, C<u>H</u>-O-), 7.9 (3H, s, N-C<u>H</u>$_3$).

3-Methyl-6β-(N-pyrrolidinyl)-3-azabicyclo[3.3.1] nonan-syn-9-ol (79).

The dihydrochloride (98).

The mother liquors from the preceding reaction were evaporated and the residue dissolved in chloroform (20 ml). To this was added p-nitrobenzoyl chloride (1.5 g) in chloroform (15 ml) and the mixture stirred for 12 hr. The resulting precipitate (450 mg) of 3-methyl-6β-(N-pyrrolidinyl)-3-azabicyclo[3.3.1] nonan-syn-9-ol dihydrochloride monohydrate was filtered and dried, m.p. 271° (from methanol/ether).

(Found: C, 49.5; H, 8.5; N, 8.9; Cl, 22.2; $C_{13}H_{28}N_2Cl_2O_2$ requires

C, 49.8; H, 8.9; N, 8.9; Cl, 22.7%).

$\nu_{max.}$ (Nujol), 3400 (OH), 2600 (N^+H), 1635 (H-O-H) cm.$^{-1}$

τ (D_2O): 7.1 (3H, s, N-C<u>H</u>$_3$).

The base (79).

The dihydrochloride after basification with aqueous sodium hydroxide and extraction with ether gave a quantitative yield of

3-methyl-6β-(N-pyrrolidinyl)-3-azabicyclo[3.3.1]nonan-syn-9-ol

m.p. 135-136° (from ethyl acetate).

(Found: C, 69.7; H, 10.8; N, 12.5; $C_{13}H_{24}N_2O$ requires

C, 69.6; H, 10.8; N, 12.5%),

$\nu_{max.}$ (Nujol), 3200 (OH), 2760 (N-CH_3) cm.$^{-1}$

$\nu_{max.}$ (CS_2, 0.0025M), 3610, 3335 (OH) cm.$^{-1}$

τ (CD_3OD): 6.45 (1H, t, J=3Hz, C<u>H</u>-O-), 7.9 (3H, s, N-C<u>H</u>$_3$).

<u>The monohydrochloride (102)</u>.

3-Methyl-6β-(N-pyrrolidinyl)-3-azabicyclo[3.3.1]nonan-syn-9-ol (50 mg) in methanol/water (25 ml, 1:1) was titrated with $^N/_{50}$ hydrochloric acid to pH 8.2. The solution was then evaporated to dryness and the residual solid (41 mg, 88%) recrystallised to yield the <u>monohydrochloride</u> m.p. 235° (from methanol/ether).

(Found: C, 59.3; H, 9.9; N, 10.3; Cl, 13.3; $C_{13}H_{25}N_2ClO$ requires

C, 59.8; H, 9.6; N, 10.7; Cl, 13.6%).

$\nu_{max.}$ (Nujol), 3600 (OH), 2740 (N-CH_3), 1635 (H-O-H) cm.$^{-1}$

τ (CD_3OD): 6.4 (1H, t, J=2.5 Hz, C<u>H</u>-O-), 7.9 (3H, s, N-C<u>H</u>$_3$).

<u>3-Methyl-6α-(N-pyrrolidinyl)-3-azabicyclo[3.3.1]non-anti-9-yl P-nitrobenzoate (109)</u>.

The chloroform solution remaining after the removal of the dihydrochloride (98) was extracted with dilute hydrochloric acid. The aqueous extract was made basic with aqueous sodium hydroxide

and extracted with ether. The ethereal solution was dried ($MgSO_4$) and evaporated to yield a yellow oil, the infra-red of which indicated a mixture with absorptions at 3300 (OH) and 1720 (C=O) $cm.^{-1}$ This product was dissolved in ether and on scratching yielded yellow needles (0.75 g) of 3-methyl-6α-(N-pyrrolidinyl)-3-azabicyclo[3.3.1] non-anti-9-yl p-nitrobenzoate m.p. 152-153° (from petrol b.p. 60-80°).

(Found: C, 64.3; H, 7.0; N, 11.5; $C_{20}H_{27}N_3O_4$ requires
C, 64.3; H, 7.3; N, 11.3%).

$\nu_{max.}$ (Nujol), 2780 ($N-CH_3$), 1720 (C=O), 1610,1500 (aromatic ring), 1535,1350 (NO_2) $cm.^{-1}$

τ ($CDCl_3$): 1.7 (4H, s, Ph), 5.0 (1H, t, J=2.5 Hz, CH-O-), 7.7 (3H, s, $N-CH_3$).

3-Methyl-6β-(N-pyrrolidinyl)-3-azabicyclo[3.3.1] nonan-anti-9-ol (80).

The mother liquors remaining after a large scale preparation of 3-methyl-6α-(N-pyrrolidinyl)-3-azabicyclo[3.3.1] non-anti-9-yl p-nitrobenzoate were dissolved in acetone and on cooling yielded colourless needles (50 mg) of 3-methyl-6β-(N-pyrrolidinyl)-3-azabicyclo[3.3.1]nonan-anti-9-ol m.p. 215-216°.

(Found: M^+, 224.188933; $C_{13}H_{24}N_2O$ requires
M^+, 224.188853).

$\nu_{max.}$ (Nujol), 3200 (OH), 2780 ($N-CH_3$) $cm.^{-1}$

3-Methyl-6α-(N-pyrrolidinyl)-3-azabicyclo[3.3.1]nonan-anti-9-ol (78).

A solution of 3-methyl-6α-(N-pyrrolidinyl)-3-azabicyclo[3.3.1]non-anti-9-yl p-nitrobenzoate (0.75 g) in hydrochloric acid (20 ml, 20%) was refluxed for 12 hr and then filtered free from the liberated p-nitrobenzoic acid, made basic with aqueous sodium hydroxide and extracted with chloroform. The chloroform solution was dried ($MgSO_4$) and evaporated to leave a clear oil which crystallised on cooling to give 3-methyl-6α-(N-pyrrolidinyl)-3-azabicyclo[3.3.1]nonan-anti-9-ol (0.44 g, 100%) as colourless plates m.p. 59-60° (from petrol b.p. 60-80°).

(Found: C, 69.6; H, 10.9; N, 12.4; $C_{13}H_{24}N_2O$ requires

C, 69.6; H, 10.8; N, 12.6%).

$\nu_{max.}$ (Nujol), 3200 (OH), 2780 ($N-CH_3$) $cm.^{-1}$

$\nu_{max.}$ (CS_2, 0.0025M), 3200 (OH) $cm.^{-1}$

τ (CD_3OD): 6.35 (1H, t, J=3 Hz, $C\underline{H}$-O-), 7.95 (3H, s, $N-C\underline{H}_3$).

3-Methyl-6α-(N-pyrrolidinyl)-3-azabicyclo[3.3.1]nonan-syn-9-yl p-nitrobenzoate (97).

3-Methyl-6α-(N-pyrrolidinyl)-3-azabicyclo[3.3.1]nonan-syn-9-ol (2 g) in dry ether (100 ml) was added dropwise to a stirred solution of methyl lithium prepared from lithium (0.56 g) and methyl iodide (5.2 g) in dry ether (20 ml). The mixture was stirred for 1 hr and p-nitrobenzoyl chloride (1.7 g) in dry ether (20 ml) added dropwise and the mixture stirred for a further 16 hr. The ethereal solution

was concentrated to half volume and extracted with water. The ether layer was dried ($MgSO_4$), and evaporated to leave a yellow solid (2.37 g, 71%). Recrystallisation from ether gave yellow needles of 3-methyl-6α-(N-pyrrolidinyl)-3-azabicyclo[3.3.1]nonan-syn-9-yl p-nitrobenzoate m.p. 135-136° (from ether).

(Found: C, 64.2; H, 7.4; N, 11.4; $C_{20}H_{27}N_3O_4$ requires

C, 64.3; H, 7.3; N, 11.3%).

$\nu_{max.}$ (Nujol), 2760 ($N-CH_3$), 1720 (C=O), 1600,1500 (aromatic ring), 1525,1350 (NO_2) $cm.^{-1}$

1-Methyl-4-(N-piperidinyl)-1,2,3,6-tetrahydropyridine (135).

1-Methyl-4-piperidone (22.6 g, 0.20 mole) and piperidine (29.8 g, 0.35 mole) were refluxed in dry benzene (60 ml) for 3 hr to give 1-methyl-4-(N-piperidinyl)-1,2,3,6-tetrahydropyridine b.p. 94-96°/2 mm (34 g, 94%) according to the general method.

$\nu_{max.}$ (Thin liquid film), 2760 ($N-CH_3$), 1640 (C=C) $cm.^{-1}$

3-Methyl-6α- and 3-Methyl-6β-(N-piperidinyl)-3-azabicyclo[3.3.1]nonan-9-ones (136, 137).

1-Methyl-4-(N-piperidinyl)-1,2,3,6-tetrahydropyridine (34 g) in dry dioxan (40 ml) was cooled to 0 - 5° and acrolein (11.2 g) in dry dioxan (30 ml) added dropwise with stirring during 1 hr. The mixture was stirred at 0° for 1 hr, and then allowed to stand at room temperature for 1 hr. The dioxan was removed at 20 mm to give

a yellow oil (37.2 g, 81%) which on distillation *in vacuo* gave a mixture of 3-*methyl*-6α- and 3-*methyl*-6β-(N-*piperidinyl*)-3-*azabicyclo* [3.3.1] *nonan*-9-*ones* as a pale yellow liquid b.p. 158°/0.2 mm (32.7 g, 70.6%).

(Found: M^+, 236, $C_{14}H_{24}N_2O$ requires

M^+, 236).

$\nu_{max.}$ (Thin liquid film), 2760 (N-CH_3), 1720 (C=O) $cm.^{-1}$

3-Methyl-6β-(N-piperidinyl)-3-azabicyclo [3.3.1] *nonan-syn-9-ol (140).*

To a solution of 3-methyl-6α- and 3-methyl-6β-(N-piperidinyl)-3-azabicyclo [3.3.1] nonan-9-ones (14.84 g) in isopropyl alcohol (40 ml) was added sodium borohydride (2.1 g) and the resulting mixture stirred at room temperature for 3 hr. After the excess sodium borohydride had been destroyed by the addition of glacial acetic acid, hydrochloric acid (1 ml) was added. The mixture was concentrated, made basic with aqueous sodium hydroxide, saturated with sodium chloride and extracted with ether. The ether layer was washed with water, dried ($MgSO_4$), and evaporated to yield a colourless oil (12.98 g, 88%) which could not be induced to crystallise. This oil was dissolved in chloroform (50 ml) and *p*-nitrobenzoyl chloride (10 g) in chloroform (50 ml) was added and the mixture stirred for 12 hr at room temperature. The resulting dihydrochloride precipitate (3.08 g) was filtered, dried, dissolved in water, basified with aqueous

sodium hydroxide and extracted with ether. The ether layer was washed with water, dried ($MgSO_4$) and evaporated to yield a white solid (2.36 g). Recrystallisation from petrol (b.p. 60-80°) gave colourless needles of 3-methyl-6β-(N-piperidinyl)-3-azabicyclo[3.3.1]nonan-syn-9-ol m.p. 102-103°.

(Found: C, 70.7; H, 11.0; N, 11.7; $C_{14}H_{26}N_2O$ requires
C, 70.6; H, 11.0; N, 11.8%).

$\nu_{max.}$ (Nujol), 3200 (OH), 2780 (N-CH_3) cm.$^{-1}$

$\nu_{max.}$ (CS_2, 0.0025M), 3610,3335 (OH) cm.$^{-1}$

3-Methyl-6α-(N-piperidinyl)-3-azabicyclo[3.3.1]nonan-syn-9-ol (138).

The chloroform solution remaining after removal of the dihydrochloride from the preceding reaction was extracted with dilute hydrochloric acid. The aqueous extract was made basic with aqueous sodium hydroxide and extracted with ether. The ethereal solution was washed with water, dried ($MgSO_4$), and evaporated to leave a yellow oil. The oil was dissolved in ether and on scratching yielded colourless needles (3.07 g) of 3-methyl-6α-(N-piperidinyl)-3-azabicyclo[3.3.1]nonan-syn-9-ol m.p. 114-115° (from petrol b.p. 60-80°).

(Found: C, 70.5; H, 10.9; N, 11.9; $C_{14}H_{26}N_2O$ requires
C, 70.6; H, 10.9; N, 11.8%).

$\nu_{max.}$ (Nujol), 3200 (OH), 2760 (N-CH_3) cm.$^{-1}$

$\nu_{max.}$ (CS_2, 0.0025M), 3610 (OH) cm.$^{-1}$

τ (DMSO): 6.35 (1H, t, J=2 Hz, C<u>H</u>-O-), 8.0 (3H, s, N-C<u>H</u>$_3$).

3-Methyl-6α-(N-piperidinyl)-3-azabicyclo[3.3.1]non -anti-9-yl p-nitrobenzoate (143).

The ethereal solution remaining after removal of 3-methyl-6α-(N-piperidinyl)-3-azabicyclo[3.3.1]nonan-syn-9-ol from the preceding reaction was evaporated to leave a yellow oil (8.3 g) which was triturated with petrol (b.p. 60-80°) to give 3-methyl-6α-(N-piperidinyl)-3-azabicyclo[3.3.1]non -anti-9-yl p-nitrobenzoate (3.2 g) as pale yellow needles m.p. 114-115° (from petrol b.p. 60-80°). (Found: C, 65.2; H, 10.5; N, 7.4; $C_{21}H_{29}N_3O_4$ requires C, 65.1; H, 10.9; N, 7.5%).

$\nu_{max.}$ (Nujol), 2760 (N-CH_3), 1710 (C=O), 1600,1500 (aromatic ring), 1545,1350 (NO_2) $cm.^{-1}$

3-Methyl-6α-(N-piperidinyl)-3-azabicyclo[3.3.1]nonan-anti-9-ol (139).

A solution of 3-methyl-6α-(N-piperidinyl)-3-azabicyclo[3.3.1] non-anti-9-yl p-nitrobenzoate (3.2 g) in hydrochloric acid (20 ml, 20%) was refluxed for 12 hr and then filtered free from the liberated p-nitrobenzoic acid, made basic with aqueous sodium hydroxide and extracted with chloroform. The chloroform solution was dried ($MgSO_4$) and evaporated to leave a colourless oil which crystallised on cooling to give 3-methyl-6α-(N-piperidinyl)-3-azabicyclo[3.3.1]nonan-anti-9-ol (1.92 g, 100%) as colourless needles m.p. 44-45° (from petrol 60-80°).

(Found: C, 70.3; H, 10.8; N, 11.5; $C_{14}H_{26}N_2O$ requires

C, 70.6; H, 10.9; N, 11.8%).

$\nu_{max.}$ (Nujol), 3150 (OH), 2760 (N-CH_3) cm.$^{-1}$

$\nu_{max.}$ (CS_2, 0.0025M), 3135 (OH) cm.$^{-1}$

1-Methyl-4-(N-Morpholinyl)-1,2,3,6-tetrahydropyridine (126).

1-Methyl-4-piperidone (56.5 g, 0.5 mole) and morpholine (77 g, 0.9 mole) were refluxed in dry benzene (150 ml) for 5 hr to give 1-methyl-4-(N-morpholinyl)-1,2,3,6-tetrahydropyridine 112-114°/2mm (lit. 96-97°/0.7 mm)[143] (63.5 g, 70%) according to the general method.

$\nu_{max.}$ (Thin liquid film), 2770 (N-CH_3), 1645 (C=C) cm.$^{-1}$

3-Methyl-6α- and 3-Methyl-6β-(N-morpholinyl)-3-azabicyclo[3.3.1]nonan-9-ones (127, 128).

To 1-Methyl-4-(N-morpholinyl)-1,2,3,6-tetrahydropyridine (15 g, 0.07 mole) in dry dioxan (30 ml) was added acrolein (3.9 g, 0.07 mole) in dioxan (20 ml) and the solution refluxed for 8 hr. Evaporation of the dioxan solution and distillation of the residue in vacuo (159°/0.2 mm) gave a mixture of 3-methyl-6α- and 3-methyl-6β-(N-morpholinyl)-3-azabicyclo[3.3.1]nonan-9-ones as a colourless, viscous oil (11.3 g, 57.3%).

(Found: C, 65.5; H, 9.2; $C_{13}H_{22}N_2O_2$ requires

C, 65.5; H, 9.1%).

$\nu_{max.}$ (Thin liquid film), 2780 (N-CH_3), 1720 (C=O) cm.$^{-1}$

3-Methyl-6α-(N-Morpholinyl)-3-azabicyclo[3.3.1]nonan-syn-9-ol (129).

To a solution of 3-methyl-6α- and 3-methyl-6β-(N-morpholinyl)-3-azabicyclo[3.3.1]nonan-9-ones (5.6 g) in isopropyl alcohol (45 ml) was added sodium borohydride (1.3 g) and the resulting mixture stirred at room temperature for 3 hr. After the excess sodium borohydride had been destroyed by the addition of glacial acetic acid, hydrochloric acid (1 ml) was added. The mixture was concentrated, made basic with aqueous sodium hydroxide, saturated with sodium chloride and extracted with ether. The ether layer was washed with water, dried ($MgSO_4$) and evaporated to leave a colourless oil (5.2 g, 94%) which on redissolving in ether (20 ml) and cooling gave 3-methyl-6α-(N-morpholinyl)-3-azabicyclo[3.3.1]nonan-syn-9-ol (1.2 g, 23%) as colourless needles m.p. 99-101°.

(Found: C, 65.1; H, 10.0; N, 11.6; $C_{13}H_{24}N_2O_2$ requires

C, 65.0; H, 10.0; N, 11.7%).

$\nu_{max.}$ (Nujol), 3300 (OH), 2760 ($N-CH_3$) $cm.^{-1}$

$\nu_{max.}$ (CS_2, 0.0025M), 3610 (OH) $cm.^{-1}$

3-Methyl-6β-(N-morpholinyl)-3-azabicyclo[3.3.1]nonan-syn-9-ol (131). The dihydrochloride (133).

The mother liquors from the preceding reaction were evaporated and the residue dissolved in chloroform (25 ml). To this was added p-nitrobenzoyl chloride (1.5 g) in chloroform (15 ml) and the mixture

stirred for 12 hr. The resulting precipitate (1.48 g) of 3-methyl-6β-(N-morpholinyl)-3-azabicyclo[3.3.1] nonan-syn-9-ol dihydrochloride was filtered, and dried at 110°, m.p. 230° (from methanol/ether).

(Found: C, 49.5; H, 8.2; N, 8.9; Cl, 22.9; $C_{13}H_{26}N_2Cl_2O_2$ requires C, 49.8; H, 8.3; N, 9.0; Cl, 22.7%).

$\nu_{max.}$ (Nujol), 3400 (OH), 2600 (N^+H) cm.$^{-1}$

The base (131).

The dihydrochloride after basification with aqueous sodium hydroxide and extraction with ether gave a quantitative yield of 3-methyl-6β-(N-morpholinyl)-3-azabicyclo[3.3.1] nonan-syn-9-ol m.p. 97-98° (from petrol b.p. 60-80°).

(Found: C, 65.4; H, 10.0; N, 11.5; $C_{13}H_{24}N_2O_2$ requires C, 65.0; H, 10.0; N, 11.7%).

$\nu_{max.}$ (Nujol), 3200 (OH), 2750 ($N-CH_3$) cm.$^{-1}$

$\nu_{max.}$ (CS_2, 0.0025M), 3610,3480 (OH) cm.$^{-1}$

3-Methyl-6α-(N-morpholinyl)-3-azabicyclo[3.3.1] non-anti-9-yl p-nitrobenzoate (134).

The ethereal solution remaining after removal of the dihydrochloride from the preceding reaction was extracted with hydrochloric acid, the aqueous extract was made basic with aqueous sodium hydroxide and extracted with ether. The ethereal solution was dried ($MgSO_4$) and evaporated to yield a yellow oil (3.3 g) which on

dissolving in petrol (b.p. 60-80°) and cooling yielded yellow needles (1.28 g) of 3-methyl-6α-(N-morpholinyl)-3-azabicyclo[3.3.1]non-anti-9-yl p-nitrobenzoate m.p. 127° (from petrol b.p. 60-80°).

(Found: C, 61.6; H, 7.1; N, 10.8; $C_{20}H_{27}N_3O_5$ requires

C, 61.7; H, 6.9; N, 10.8%).

$\nu_{max.}$ (Nujol), 2760 (N-CH_3), 1700 (C=O), 1600,1500 (aromatic ring), 1520,1345 (NO_2) $cm.^{-1}$

3-Methyl-6α-(N-morpholinyl)-3-azabicyclo[3.3.1]nonan-anti-9-ol (130).

A solution of 3-methyl-6α-(N-morpholinyl)-3-azabicyclo[3.3.1]non-anti-9-yl p-nitrobenzoate (1.28 g) in hydrochloric acid (20 ml, 20%) was refluxed for 12 hr and then filtered free from the liberated p-nitrobenzoic acid, made basic with aqueous sodium hydroxide and extracted with chloroform. The chloroform solution was dried ($MgSO_4$) and evaporated to leave a colourless oil which crystallised on cooling to give 3-methyl-6α-(N-morpholinyl)-3-azabicyclo[3.3.1]nonan-anti-9-ol (0.78 g, 100%) as colourless needles m.p. 84° (from petrol b.p. 60-80°).

(Found: C, 65.3; H, 10.2; N, 11.4; $C_{13}H_{24}N_2O_2$ requires

C, 65.0; H, 10.0; N, 11.7%).

$\nu_{max.}$ (Nujol), 3100 (OH), 2750 (N-CH_3) $cm.^{-1}$

$\nu_{max.}$ (CS_2, 0.0025M), 3200 (OH) $cm.^{-1}$

9-Deutero-3-methyl-6α-(N-pyrrolidinyl)-3-azabicyclo[3.3.1]nonan-syn-9-ol (261).

3-Methyl-6α and 3-Methyl-6β-(N-pyrrolidinyl)-3-azabicyclo [3.3.1]nonan-9-ones (1.1 g) were dissolved in dry ether (20 ml) and added dropwise to a stirred suspension of lithium aluminium deuteride (0.10 g) in dry ether (20 ml). The suspension was stirred overnight and excess lithium aluminium deuteride decomposed by dropwise addition of a 10% solution of ammonium chloride. The ether layer was separated, dried ($MgSO_4$), and evaporated to yield a colourless oil (0.9 g, 82%). The oil was dissolved in ether (15 ml) and on cooling yielded colourless needles (0.25 g) of 9-deutero-3-methyl-6α-(N-pyrrolidinyl)-3-azabicyclo[3.3.1]nonan-syn-9-ol m.p. 170° (from ethyl acetate). (Found: M^+, 225.195131, $C_{13}H_{23}DN_2O$ requires

M^+, 225.194956).

$\nu_{max.}$ (Nujol), 3200 (OH), 2760 ($N-CH_3$) $cm.^{-1}$

τ (CD_3OD): 6.9 (3H, s, $N-C\underline{H}_3$).

9-Deutero-3-methyl-6α-(N-pyrrolidinyl)-3-azabicyclo[3.3.1]non-anti-9-yl p-nitrobenzoate (262).

The ethereal solution from the preceding reaction was evaporated and the residue dissolved in chloroform (10 ml) and p-nitrobenzoyl chloride (1 g) in chloroform (20 ml) was added. The mixture was stirred for 12 hr and worked up as for the ester (109)

Yellow needles (0.13 g) of 9-deutero-3-methyl-6α-(N-pyrrolidinyl)-3-azabicyclo[3.3.1]non-anti-9-yl p-nitrobenzoate were obtained m.p. 152° (from petrol b.p. 60-80°).

(Found: M^+, 374.206421, $C_{20}H_{26}DN_3O_4$ requires

M^+, 374.206588).

$\nu_{max.}$ (Nujol), 2780 ($N-CH_3$), 1720 (C=O), 1610,1500 (aromatic ring), 1535,1350 (NO_2) $cm.^{-1}$

9-Deutero-3-methyl-6α-(N-pyrrolidinyl)-3-azabicyclo[3.3.1]non-syn-9-yl p-nitrobenzoate (263).

To the methyl lithium in dry ether (150 ml) generated from lithium metal (0.1 g) and methyl iodide (1.05 g), was added 9-deutero-3-methyl-6α-(N-pyrrolidinyl)-3-azabicyclo[3.3.1]nonan-9-ol (100 mg) in dry ether (20 ml) and the mixture stirred for 1 hr. p-Nitrobenzoyl chloride (0.15 g) in dry ether (20 ml) was then added and the resulting mixture stirred for 16 hr. On working the reaction up as for the ester (97) , yellow needles (110 mg, 67%) of 9-deutero-3-methyl-6α-(N-pyrrolidinyl)-3-azabicyclo[3.3.1]non-syn-9-yl p-nitrobenzoate were obtained m.p. 135° (from petrol b.p. 60-80°).

(Found: M^+, 374.206421, $C_{20}H_{26}DN_3O_4$ requires

M^+, 374.206588).

$\nu_{max.}$ (Nujol), 2760 ($N-CH_3$), 1720 (C=O), 1610,1500 (aromatic ring), 1535,1350 (NO_2) $cm.^{-1}$

Attempted preparation of 3-methyl-6α-(N-pyrrolidinyl)-3-azabicyclo [3.3.1] non-syn-9-yl chloroacetate

To a solution of 3-methyl-6α-(N-pyrrolidinyl)-3-azabicyclo [3.3.1] nonan-syn-9-ol (0.45 g) in chloroform (20 ml) was added chloroacetyl chloride (0.34 g) in chloroform (10 ml) and the mixture stirred for 3 hr. The precipitate (380 mg) was filtered, washed with chloroform and recrystallised from ethanol/ether to give colourless needles of 3-methyl-6α-(N-pyrrolidinyl)-3-azabicyclo [3.3.1] nonan-syn-9-ol dihydrochloride m.p. 260-262° .

(Found: C, 52.5; H, 8.9; N, 9.2; Cl, 23.6; $C_{13}H_{26}N_2Cl_2$ requires C, 52.5; H, 8.8; N, 9.4; Cl, 23.9%).

$\nu_{max.}$ (Nujol), 3100 (OH), 2650 (N^+H) $cm.^{-1}$

3-Methyl-6α-(N-pyrrolidinyl)-3-azabicyclo [3.3.1] non-anti-9-yl chloroacetate (116).

To a solution of 3-methyl-6α-(N-pyrrolidinyl)-3-azabicyclo [3.3.1] nonan-anti-9-ol (0.54 g) in chloroform (20 ml) was added chloroacetyl chloride (0.42 g) in chloroform (20 ml) and the mixture stirred for 3 hr. The resulting precipitate (0.7 g) was collected and recrystallised from ethanol/ether to give 3-methyl-6α-(N-pyrrolidinyl)-3-azabicyclo [3.3.1] non-anti-9-yl chloroacetate dihydrochloride m.p. 217°.

(Found: M^+, 302, $C_{15}H_{25}N_2Cl$ requires

M^+, 302).

$\nu_{max.}$ (Nujol), 2600 (N^+H), 1750 (C=O) $cm.^{-1}$

Attempted preparation of a lactone from 3-methyl-6α-(N-pyrrolidinyl)-3-azabicyclo[3.3.1]non-anti-9-yl chloroacetate.

To a solution of 3-methyl-6α-(N-pyrrolidinyl)-3-azabicyclo [3.3.1] non-anti-9-yl chloroacetate dihydrochloride (0.65 g) in water (25 ml) was added sodium bicarbonate to pH 8.1 and the solution extracted with chloroform. The chloroform extract was washed with water, dried ($MgSO_4$), and evaporated to leave a yellow residue (0.3 g) which failed to crystallise. The infrared spectrum of the oil was identical to the original alcohol.

Reductions of 3-methyl-6α- and 3-methyl-6β-(N-pyrrolidinyl)-3-azabicyclo[3.3.1]nonan-9-ones.

In addition to the reduction of the ketones by sodium borohydride (previously described) the ketones were also reduced a further three different ways. In each case the crude reduced mixture was examined by Glc on Carbowax 20M KOH with an oven temperature of 180°. For each reduction mixture, two peaks were observed, one after 12 minutes and the other after 19 minutes. The ratio of the fast-moving components to the slow-moving components was obtained.

1. Reduction with sodium borohydride.

Ratio = 1 : 1.2

2. Reduction with lithium aluminium hydride.

Method as given for the lithium aluminium deuteride reduction of the ketones (75 and 76).

Ratio = 1 : 1.3

3. Reduction with sodium and isopropyl alcohol.

To a mixture of sodium (6.9 g) in boiling toluene (150 ml) was added a solution of the ketones (13.2 g) in isopropyl alcohol (35 ml). After the resulting mixture had been refluxed for 4 hr, it was cooled and extracted with aqueous hydrochloric acid. The aqueous extract was made basic with aqueous sodium hydroxide, saturated with sodium chloride and extracted with ether. The ether solution was washed with water, dried ($MgSO_4$), and evaporated to leave 7.8 g (59%) of a mixture of alcohols.

Ratio = 1 : 3.6

4. Catalytic reduction.

A solution of the ketones (1 g) in glacial acetic acid (30 ml) was hydrogenated at room temperature and atmospheric pressure over the catalyst obtained from platinum oxide (100 mg). After the absorption of hydrogen was complete (110 ml, 1.01 equiv., 3 hr), the solution was filtered, concentrated, made basic with aqueous sodium hydroxide and extracted with ether. The ether layer was removed,

washed with water, dried ($MgSO_4$), and evaporated to leave 0.5 g (50%) of a mixture of alcohols.

Ratio = 1 : 3.6

Attempted preparation of 3-methyl-6β-(N-pyrrolidinyl)-3-azabicyclo [3.3.1] non-syn-9-yl p-nitrobenzoate.

1. To a solution of 3-methyl-6β-(N-pyrrolidinyl)-3-azabicyclo [3.3.1] nonan-syn-9-ol (0.2 g) in chloroform (10 ml) was added p-nitrobenzoyl chloride (0.2 g) in chloroform (10 ml) and the resulting mixture stirred for 1 hr. The resulting precipitate (0.27 g) was shown by m.p. and infrared to be the dihydrochloride of the starting material.

2. To the methyl lithium in dry ether (150 ml) generated from lithium metal (0.1 g) and methyl iodide (1.05 g) was added 3-methyl-6β-(N-pyrrolidinyl)-3-azabicyclo [3.3.1] nonan-syn-9-ol (0.1 g) in dry ether (20 ml) and the mixture stirred for 1 hr. p-Nitrobenzoyl chloride (0.15 g) in dry ether was then added and the resulting mixture stirred for 16 hr. The ethereal solution was concentrated to half volume and extracted with water. The ether layer was dried ($MgSO_4$) and evaporated to leave a yellow oil (85 mg) which gave colourless crystals of starting material(from ethyl acetate m.p. 135-136°.

Attempted isomerisation of 3-methyl-6α-(N-pyrrolidinyl)-3-azabicyclo [3.3.1] nonan-syn-9-ol.

Method A: A solution of 3-methyl-6α-(N-pyrrolidinyl)-3-azabicyclo [3.3.1] nonan-syn-9-ol (1.1 g, 0.005 mole) in pyridine (15 ml) was cooled to 0 - 5° and treated dropwise with a cold solution of methanesulphonyl chloride (3.9 ml) in pyridine (5 ml). The mixture was stirred at 0° for 4 hr, poured slowly onto crushed ice and extracted with chloroform. The aqueous extract was evaporated, made basic with aqueous sodium hydroxide and extracted with chloroform. The chloroform solution was washed with water, dried ($MgSO_4$), and evaporated to leave a buff semi-solid (0.8 g) which gave colourless needles m.p. 170-171° (from ethyl acetate) undepressed on admixture with an authentic sample of starting material.

Method B: To the methyl lithium in dry ether (150 ml) generated from lithium metal (0.4 g) and methyl iodide (3.5 g) was added 3-methyl-6α-(N-pyrrolidinyl)-3-azabicyclo [3.3.1] nonan-syn-9-ol (1 g) in dry ether (100 ml) and the mixture stirred for 1 hr. Methanesulphonyl chloride (0.5 g) in dry ether (30 ml) was then added and the resulting mixture stirred for 16 hr. The ethereal solution was concentrated to half volume and extracted with water. The ether layer was washed with water, dried ($MgSO_4$), and evaporated

to leave a yellow oil (0.8 g) which crystallised from ethyl acetate as colourless needles m.p. 170° undepressed on admixture with an authentic sample of starting material.

Method C: Method B was repeated using p-toluenesulphonyl chloride as the acid chloride. An oil was produced from which the starting material was recovered unreacted.

Attempted preparation of syn-9-chloro-3-methyl-6α-(N-pyrrolidinyl)-3-azabicyclo[3.3.1]nonane.

To a solution of 3-methyl-6α-(N-pyrrolidinyl)-3-azabicyclo[3.3.1]nonan-syn-9-ol (1 g) in ether (50 ml) at -10° was added pyridine (0.3 g) and thionyl chloride (0.25 g) and the mixture stirred for 1 hr. The precipitate was filtered, made basic with aqueous sodium hydroxide and extracted with ether. The ethereal extract was washed with water, dried ($MgSO_4$), and evaporated to leave a brown oil (0.7 g) which crystallised from ethyl acetate as colourless needles m.p. 170° undepressed on admixture with an authentic sample of starting material.

Attempted epimerisation of 3-methyl-6α-(N-pyrrolidinyl)-3-azabicyclo[3.3.1]nonan-syn-9-ol.

Method A: 3-methyl-6α-(N-pyrrolidinyl)-3-azabicyclo[3.3.1]nonan-syn-9-ol (0.45 g) was stirred with freshly distilled aluminium

isopropoxide (0.45 g) in anhydrous isopropyl alcohol (40 ml) containing acetone (1 ml) for 4 weeks. The solvents were evaporated and the residue extracted with ether. Tlc of the ether extract showed only starting material present.

Method B: Method A was repeated and the mixture refluxed for 60 hr. The solvents were evaporated and the residue extracted with ether. Tlc of the ether extract showed only starting material present.

Attempted oxidation of 3-methyl-6α-(N-pyrrolidinyl)-3-azabicyclo [3.3.1] nonan-syn-9-ol.

Method A: To a stirred solution of 3-methyl-6α-(N-pyrrolidinyl)-3-azabicyclo[3.3.1] nonan-syn-9-ol (0.1 g) in acetone (20 ml) was added dropwise a solution of chromium trioxide (2.6 g) and sulphuric acid (2.2 ml) in water (7.5 ml). After stirring for 5 min., sodium carbonate was added until the solution was basic. The solvents were then evaporated and the residue extracted with ether to give a yellow oil (80 mg) which gave colourless needles m.p. 169-170° (from ethyl acetate) undepressed on admixture with authentic starting material.

Method B: Method A was repeated and the mixture stirred for 30 min.

The solvents were removed and the residue extracted with ether but only unchanged starting material was isolated. Continued stirring for up to 66 hr yielded only starting material.

Method C: Method A was repeated and the mixture heated on a water bath for 4 hr. The solvents were removed and the residue extracted with ether but only unreacted starting material was recovered.

Method D: A solution of 3-methyl-6α-(N-pyrrolidinyl)-3-azabicyclo [3.3.1] nonan-syn-9-ol (0.4 g) in dimethyl sulphoxide (5 ml) was added dropwise to acetic anhydride (4 ml). The mixture was stirred at room temperature for 18 hr and then poured slowly onto crushed ice. The mixture was made basic with aqueous sodium hydroxide and extracted with chloroform. Evaporation of the dried ($MgSO_4$) chloroform solution gave an oil (0.35 g) which was shown to be 3-methyl-6α-(N-pyrrolidinyl)-3-azabicyclo[3.3.1] non-syn-9-yl acetate. (Found: M^+, 266.199417, $C_{15}H_{26}N_2O_2$ requires M^+, 266.199047).

$\nu_{max.}$ (Thin liquid film) 2760 (N-CH_3), 1720 (C=O) $cm.^{-1}$

Method E: Ruthenium tetroxide[146] (0.5 g) in carbon tetrachloride (10 ml) was added dropwise with stirring to a solution of 3-methyl-

6α-(N-pyrrolidinyl)-3-azabicyclo[3.3.1]nonan-syn-9-ol (200 mg) in carbon tetrachloride (20 ml), cooled in ice, at a rate slow enough to maintain a temperature of 10 - 15°. The reaction mixture was allowed to stand overnight at room temperature. The precipitated ruthenium dioxide was filtered off and washed with carbon tetrochloride. Continuous chloroform extraction of the ruthenium dioxide gave 40 mg of organic residue. This was combined with the residue (0.14 g) found in the carbon tetrochloride filtrate. Removal of the solvents left a dark red oil (0.18 g) which failed to yield either starting material or desired products.

Attempted preparation of 1,5-dideutero-3-methyl-6α- and 1,5-dideutero-6β-(N-pyrrolidinyl)-3-azabicyclo[3.3.1]nonan-9-ones.

3-Methyl-6α- and 3-methyl-6β-(N-pyrrolidinyl)-3-azabicyclo[3.3.1]nonan-9-ones (0.8 g) were heated in a solution of deuterium chloride in deuterium oxide (10 ml, 20%) in a sealed tube at 105° for 14 days. The solution was made basic with aqueous sodium hydroxide and extracted with ether. The ether solution was washed with water, dried ($MgSO_4$), and evaporated to yield an intractable black tar (0.55 g) which proved incapable of characterisation.

1-(N-Morpholinyl)cyclohexene (159).

Cyclohexanone (58.6 g, 0.6 mole) and morpholine (65.4 g, 0.75 mole) were refluxed in dry benzene (200 ml) for 6 hr to give

1-(N-morpholinyl)cyclohexene b.p. 120-122°/10 mm (lit. 121-125°/10-14 mm)[36] (78.6 g, 78.4%) according to the general method.

2α- and 2β-(N-Morpholinyl)bicyclo[3.3.1]nonan-9-ones (160, 161).

The ketones were prepared by the same method as 3-methyl-6α- and 3-methyl-6β-(N-pyrrolidinyl)-3-azabicyclo[3.3.1]nonan-9-ones (75, 76). Distillation at 132-135°/2 mm gave 2α- and 2β-(N-morpholinyl)bicyclo[3.3.1]nonan-9-ones (88 g, 48%) as a viscous pale yellow liquid.

$\nu_{max.}$ (Thin liquid film), 1705 (C=O) $cm.^{-1}$

2α-(N-Morpholinyl)bicyclo[3.3.1]nonan-syn-9-ol (162).

To a solution of 2α- and 2β-(N-morpholinyl)bicyclo[3.3.1]nonan-9-ones (21 g) in isopropyl alcohol (40 ml) was added sodium borohydride (5 g) and the resulting mixture stirred at room temperature for 12 hr. After the excess sodium borohydride had been destroyed by the addition of glacial acetic acid, hydrochloric acid (1 ml) was added. The mixture was concentrated, made basic with aqueous sodium hydroxide, saturated with sodium chloride and extracted with ether. The ether layer was washed with water, dried ($MgSO_4$), and evaporated to yield a colourless oil (20 g, 95%) which could not be induced to crystallise. This oil was dissolved in chloroform (150 ml) and p-nitrobenzoyl chloride (17.5 g) in chloroform (100 ml) was added. The resulting precipitate (7.2 g) of 2α-(N-morpholinyl)bicyclo[3.3.1]

nonan-syn-9-ol hydrochloride was filtered and dried m.p. 283° (from methanol/ether).

(Found: C, 59.4; H, 9.1; N, 5.3; Cl, 13.8; $C_{13}H_{24}NClO_2$ requires C, 59.7; H, 9.2; N, 5.4; Cl, 13.6%).

$\nu_{max.}$ (Nujol), 3350 (OH), 2600 (N^+H) $cm.^{-1}$

τ (CD_3OD): 6.4 (1H, t, J=2.5 Hz, C<u>H</u>-O-).

The hydrochloride after basification with aqueous sodium hydroxide and extraction with ether gave a quantitative yield of 2α-(N-<u>morpholinyl</u>)<u>bicyclo</u>[3.3.1] <u>nonan</u>-<u>syn</u>-9-<u>ol</u> m.p. 77-78° (from petrol b.p. 60-80°).

(Found: C, 69.1; H, 10.1; N, 6.1; $C_{13}H_{23}NO_2$ requires C, 69.3; H, 10.2; N, 6.2%).

$\nu_{max.}$ (Nujol), 3300 (OH) $cm.^{-1}$

$\nu_{max.}$ (CS_2, 0.0025M), 3610 (OH) $cm.^{-1}$

τ (CD_3OD): 6.2 (1H, t, J=2.5 Hz, C<u>H</u>-O-).

Tlc (Alumina, 50% chloroform-petrol), rf = 0.43

<u>2α-(N-Morpholinyl)bicyclo[3.3.1]nonan-anti-9-ol (163)</u>.

The mother liquors remaining after removal of the hydrochloride from the preceding reaction were extracted with hydrochloric acid, the aqueous extract was made basic with aqueous sodium hydroxide and extracted with ether. The dried ($MgSO_4$) ethereal solution was evaporated to yield a pale yellow oil (11.8 g). The infrared spectrum of the oil showed an absence of peaks in the 1650-1750 $cm.^{-1}$ range

showing that no ester had been formed in the reaction. The oil was converted to the hydrochloride by the general method and repeated recrystallisations from methanol/ether yielded 2α-(N-morpholinyl) bicyclo[3.3.1]nonan-anti-9-ol (7.5 g) as colourless needles m.p. 215°.

(Found: C, 59.8; H, 9.2; N, 5.3; $C_{13}H_{24}NClO_2$ requires

C, 59.7; H, 9.2; N, 5.4%).

$\nu_{max.}$ (Nujol), 3350 (OH), 2500 (N^+H) cm.$^{-1}$

τ (CD_3OD): 6.05 (1H, t, J=2.5 Hz, C<u>H</u>-O-).

The hydrochloride after basification with aqueous sodium hydroxide and extraction with ether gave a quantitative yield of 2α-(N-morpholinyl)bicyclo[3.3.1]nonan-anti-9-ol m.p. 82-83° (from petrol b.p. 60-80°).

(Found: C, 69.6; H, 10.3; N, 6.4; $C_{13}H_{23}NO_2$ requires

C, 69.3; H, 10.2; N, 6.2%).

$\nu_{max.}$ (Nujol), 3450 (OH) cm.$^{-1}$

$\nu_{max.}$ (CS_2, 0.0025M), 3610 (OH) cm.$^{-1}$

τ (CD_3OD): 6.5 (1H, t, J=2.5 Hz, C<u>H</u>-O-).

Tlc (Alumina, 50% chloroform-petrol), rf = 0.45

<u>Syn-bicyclo[3.3.1]non-2-en-9-ol (169).</u>

2α-(N-Morpholinyl)bicyclo[3.3.1]nonan-syn-9-ol (3 g) in methanol (6 ml) was treated at 0° with hydrogen peroxide solution (6 ml, 30%) and the solution kept at room temperature for 24 hr.

The solvent was then evaporated and the oil produced was dissolved in ethanol. Addition of ether precipitated the N-oxide (2.30 g) as colourless needles m.p. 175°.

(Found: M -16, 225.172869 $C_{13}H_{23}NO_2$ requires

M -16, 225.171744).

The N-oxide (1 g) was heated at 200°/0.5 mm, and the products collected in a cold trap. The distillate was partitioned between ether and dilute hydrochloric acid. The dried ($MgSO_4$) ether layer was evaporated to leave syn-bicyclo[3.3.1]non-2-en-9-ol (0.3 g) m.p. 155-157° (lit. 156-158°)[37].

(Found: C, 76.7; H, 9.8%; M -18, 120.093896 C_9H_{14} requires

C, 78.3; H, 10.1%; M -18, 120.093995).

$\nu_{max.}$ (Nujol), 3250 (OH), 1640 (C=C) $cm.^{-1}$

Attempted preparation of anti-bicyclo[3.3.1]non-2-en-9-ol

2α-(N-Morpholinyl)bicyclo[3.3.1]nonan-anti-9-ol (2 g) in methanol (4 ml) was treated at 0° with hydrogen peroxide solution (4 ml, 30%) and the solution kept at room temperature for 24 hr. The solvents were evaporated to leave an oil which could not be induced to crystallise. The product was not purified further but was utilised in the next reaction.

The above N-oxide (1 g) was heated at 200°/0.5 mm, and the products collected in a cold trap. The distillate was partitioned between

ether and dilute hydrochloric acid. The dried ($MgSO_4$) solution was evaporated to leave an oil (0.3 g). The infrared spectrum of the oil showed:

$\nu_{max.}$ (Thin liquid film), 3350 (OH), 1700 (C=O) $cm.^{-1}$

2α-(N-Morpholinyl)bicyclo[3.3.1]non-syn-9-yl p-nitrobenzoate (167).

To the methyl lithium in dry ether (100 ml) generated from lithium metal (0.3 g) and methyl iodide (2.5 g) was added 2α-(N-Morpholinyl)bicyclo[3.3.1]nonan-syn-9-ol (1 g) in dry ether (50 ml) and the mixture stirred for 1 hr. p-Nitrobenzoyl chloride (1 g) in dry ether (30 ml) was then added and the resulting mixture stirred for 16 hr. The ethereal solution was concentrated to half volume and extracted with water. The ether layer was washed with water, dried ($MgSO_4$), and evaporated to leave a yellow oil (1.3 g, 80%) which crystallised from ether as yellow needles m.p. 150-151° of 2α-(N-morpholinyl)bicyclo[3.3.1]non-syn-9-yl p-nitrobenzoate. (Found: C, 64.4; H, 7.0; N, 7.4; $C_{20}H_{26}N_2O_5$ requires C, 64.2; H, 7.0; N, 7.5%).

$\nu_{max.}$ (Nujol), 1710 (C=O), 1605,1500 (aromatic ring), 1530,1350 (NO_2) $cm.^{-1}$

Attempted preparation of 2α-(N-morpholinyl)bicyclo[3.3.1]non-anti-9-yl P-nitrobenzoate.

The method used was the same as in the preceding reaction

but only unreacted starting material was recovered.

3-Methyl-6β-phenyl-8α-(N-pyrrolidinyl)-3-azabicyclo[3.3.1]nonan-9-one (172).

1-Methyl-4-(N-pyrrolidinyl)-1,2,3,6-tetrahydropyridine (21 g) in dry dioxan (50 ml) was cooled to 0 - 5° and freshly distilled cinnamaldehyde (16.5 g) in dry dioxan (30 ml) was added dropwise with stirring during 1 hr. The mixture was stirred at 0° for 1 hr, and then allowed to stand at room temperature for 1 hr. The dioxan was removed at 20 mm to give a viscous dark red oil (31 g, 87.2%) which on triturating with petrol (b.p. 40-60°) gave colourless needles (16.1 g, 52%) of 3-methyl-6β-phenyl-8α-(N-pyrrolidinyl)-3-azabicyclo[3.3.1]nonan-9-one m.p. 104-105° (from petrol b.p. 60-80°).

(Found: C, 76.5; H, 8.8; N, 9.4; $C_{19}H_{26}N_2O$ requires

C, 76.5; H, 8.7; N, 9.4%).

$\nu_{max.}$ (Nujol), 2760 (N-CH_3), 1720 (C=O), 1600,1500 (aromatic ring) $cm.^{-1}$

τ (CD_3OD): 2.8 (5H, m, Ph), 7.62 (3H, s, N-CH_3).

Tlc (Alumina, ether), rf = 0.58.

The oil showed three spots with rf values of 0.58, 0.79 and 0.83.

The ketone was converted to the dihydrochloride by the general method and yielded colourless needles m.p. 217° of the dihydrochloride monohydrate (187).

(Found: C, 58.8; H, 7.8; N, 7.1; Cl, 18.0; $C_{19}H_{30}N_2Cl_2O_2$ requires

C, 58.6; H, 7.7; N, 7.2; Cl, 18.3%).

$\nu_{max.}$ (Nujol), 3200 (OH), 2600 (N^+H), 1600,1500 (aromatic ring) $cm.^{-1}$

3-Methyl-6α-phenyl-8β-(N-pyrrolidinyl)-3-azabicyclo[3.3.1]nonan-syn-9-ol (192).

The mother liquors from the preceding reaction were combined and evaporated to leave a dark red oil. This oil was partitioned between ether and hydrochloric acid. The acid layer was basified, extracted with ether, dried ($MgSO_4$), and the ether solution evaporated to leave a red oil (12.6 g). To the oil in isopropyl alcohol (100 ml) was added sodium borohydride (3.5 g) and the resulting mixture stirred for 3 hr at room temperature. After the excess sodium borohydride had been destroyed by the addition of glacial acetic acid, hydrochloric acid (1 ml) was added. The mixture was concentrated, made basic with aqueous sodium hydroxide, saturated with sodium chloride and extracted with ether. The ether layer was washed with water, dried ($MgSO_4$), concentrated to 20 ml and allowed to stand for 12 hr. The crystalline material produced was filtered (2.7 g, 22.5%) and afforded colourless needles of 3-methyl-6α-phenyl-8β-(N-pyrrolidinyl)-3-azabicyclo[3.3.1]nonan-anti-9-ol m.p. 197-198° (from ethyl acetate).

(Found: C, 75.8; H, 9.4; N, 9.2; $C_{19}H_{28}N_2O$ requires

C, 76.0; H, 9.3; N, 9.3%).

$\nu_{max.}$ (Nujol), 3200 (OH), 2760 (N-CH_3), 1600,1500 (aromatic ring) $cm.^{-1}$

$\nu_{max.}$ (CS_2, 0.0025M), 3595 (OH) $cm.^{-1}$

τ (CD_3OD): 8.7 (5H, m, Ph), 7.9 (3H, s, N-CH_3).

Tlc (Alumina, chloroform-ether 50%), rf = 0.25.

The amino alcohol was converted to the dihydrochloride by the general method to give colourless needles m.p. 234-236° of the dihydrochloride monohydrate (196a).

(Found: C, 58.6; H, 8.3; N, 7.1; $C_{19}H_{32}N_2Cl_2O_2$ requires

C, 58.3; H, 8.2; N, 7.2%).

$\nu_{max.}$ (Nujol), 3300 (OH), 2600 (N^+H), 1610,1500 (aromatic ring) $cm.^{-1}$

3-Methyl-6β-phenyl-8β-(N-pyrrolidinyl)-3-azabicyclo[3.3.1]nonan-syn-9-ol (190).

The mother liquors from the preceding reaction, after removal of the amino alcohol, were evaporated to give a pale yellow oil (9.1 g) which crystallised from petrol (b.p. 60-80°) as a mixture of long colourless needles and microprisms. Repeated recrystallisations from petrol (b.p. 60-80°) yielded long colourless needles (1.7 g, 14.3%) of 3-methyl-6β-phenyl-8β-(N-pyrrolidinyl)-3-azabicyclo[3.3.1]nonan-syn-9-ol m.p. 133-134°.

(Found: C, 76.0; H, 9.5; N, 9.3; $C_{19}H_{28}N_2O$ requires

C, 76.0; H, 9.3; N, 9.3%).

$\nu_{max.}$ (Nujol), 3200 (OH), 2770 (N-CH_3), 1600,1500 (aromatic ring) $cm.^{-1}$

$\nu_{max.}$ (CS_2, 0.0025M), 3595 (OH) $cm.^{-1}$

τ (CD_3OD): 2.8 (5H, m, Ph), 6.2 (1H, t, J=2.5 Hz, C<u>H</u>-O-),

7.8 (3H, s, N-C<u>H</u>$_3$).

Tlc (Alumina, chloroform-ether 50%), rf = 0.35.

The amino-alcohol was converted to the dihydrochloride by the general method to give colourless microprisms m.p. 185° of the <u>dihydrochloride monohydrate (194)</u>.

(Found: C, 58.6; H, 8.4; N, 7.0; Cl, 18.0; $C_{19}H_{32}N_2Cl_2O_2$ requires

C, 58.3; H, 8.2; N, 7.2; Cl, 18.2%).

$\nu_{max.}$ (Nujol), 3250 (OH), 2600 (N^+H), 1600,1500 (aromatic ring) $cm.^{-1}$

<u>3-Methyl-6β-phenyl-8β-(N-pyrrolidinyl)-3-azabicyclo[3.3.1]nonan-anti-9-ol (191)</u>.

The mother liquors from the preceding reaction, after removal of the amino alcohol, were concentrated to 20 ml and refrigerated for 12 hr. Colourless microprisms (0.8 g, 8%) of 3-<u>methyl</u>-6β-<u>phenyl</u>-8β-(N-<u>pyrrolidinyl</u>)-3-<u>azabicyclo[3.3.1]nonan-syn</u>-9-<u>ol</u> m.p. 168-170° were obtained.

(Found: C, 76.0; H, 9.5; N, 9.5; $C_{19}H_{28}N_2O$ requires

C, 76.0; H, 9.3; N, 9.3%).

$\nu_{max.}$ (Nujol), 3200 (OH), 2760 (N-CH_3), 1605,1500 (aromatic ring) $cm.^{-1}$

$\nu_{max.}$ (CS_2, 0.0025M), 3595,3340 (OH) $cm.^{-1}$

τ (CD_3OD): 2.7 (5H, m, Ph), 6.25 (1H, t, J=2.5 Hz, C<u>H</u>-O-),

7.9 (3H, s, N-C<u>H</u>$_3$)

Tlc (Alumina, chloroform-ether 50%), rf = 0.31.

<u>3-Methyl-6β-phenyl-8α-(N-pyrrolidinyl)-3-azabicyclo[3.3.1]nonan-syn-9-ol (176)</u>.

To a solution of 3-methyl-6β-phenyl-8α-(N-pyrrolidinyl)-3-azabicyclo[3.3.1]nonan-9-one (5 g) in isopropyl alcohol (50 ml) was added sodium borohydride (1.3 g) and the resulting mixture stirred for 3 hr. After the excess sodium borohydride had been destroyed by the addition of glacial acetic acid, hydrochloric acid (1 ml) was added. The mixture was concentrated, made basic with aqueous sodium hydroxide, saturated with sodium chloride and extracted with ether. The dried ($MgSO_4$) ethereal solution was evaporated to leave a white solid (4.7 g, 94%). Tlc on this product (Alumina, chloroform-ether 50%) showed it to be a mixture of two components, a faster running major component rf = 0.21 and a slower component rf = 0.13. Repeated recrystallisations gave colourless microprisms of 3-<u>methyl</u>-6β-<u>phenyl</u>-8α-(N-<u>pyrrolidinyl</u>)-3-<u>azabicyclo</u>[3.3.1]<u>nonan-syn-9-ol</u> m.p. 135° (from petrol b.p. 60-80°).

(Found: C, 75.7; H, 9.4; N, 9.4; $C_{19}H_{28}N_2O$ requires

C, 76.0; H, 9.3; N, 9.3%).

$\nu_{max.}$ (Nujol), 3200 (OH), 2780 (N-CH_3), 1600,1500 (aromatic ring) $cm.^{-1}$

$\nu_{max.}$ (CS_2, 0.0025M), 3595,3460 (OH) $cm.^{-1}$

τ (CD_3OD): 2.7 (5H, m, Ph), 6.35 (1H, t, J=2.5 Hz, C<u>H</u>-O-),
7.78 (3H, s, N-C<u>H</u>$_3$).

The amino alcohol was converted to the dihydrochloride by the general method to give colourless microprisms of the <u>dihydrochloride</u> m.p. 293-295°.

(Found: C, 61.6; H, 8.2; N, 7.7; Cl, 18.8; $C_{19}H_{30}N_2Cl_2O$ requires
C, 61.1; H, 8.0; N, 7.5; Cl, 19.0%).

$\nu_{max.}$ (Nujol), 3300 (OH), 2500 (N^+H), 1600,1500 (aromatic ring) $cm.^{-1}$

<u>3-Methyl-6β-phenyl-8β-(N-pyrrolidinyl)-3-azabicyclo[3.3.1]non-syn-9-yl p-nitrobenzoate (193)</u>.

Method A: To a solution of 3-methyl-6β-phenyl-8β-(N-pyrrolidinyl)-3-azabicyclo[3.3.1]nonan-syn-9-ol (1 g) in chloroform (20 ml) was added <u>p</u>-nitrobenzoyl chloride (1.2 g) in chloroform (20 ml) and the mixture stirred at room temperature for 24 hr. The solution was extracted with aqueous sodium hydroxide and the chloroform extract washed with water. The dried ($MgSO_4$) chloroform solution was evaporated to leave a white solid (0.9 g) which gave colourless needles m.p. 133° (from petrol b.p. 60-80°) undepressed on admixture with an authentic sample of starting material.

Method B: To the methyl lithium in dry ether (100 ml) generated from

lithium metal (0.14 g) and methyl iodide (1.3 g) was added 3-methyl-6β-phenyl-8β-(N-pyrrolidinyl)-3-azabicyclo[3.3.1]nonan-syn-9-ol (0.5 g) in dry ether (50 ml) and the mixture stirred for 1 hr. p-Nitrobenzoyl chloride (0.5 g) in dry ether (50 ml) was then added and the resulting mixture stirred for 16 hr. The ethereal solution was concentrated to half volume and extracted with water. The dried ($MgSO_4$) ethereal solution was evaporated to leave a yellow oil which crystallised from petrol (b.p. 60-80°) as yellow needles (0.57 g, 74.8%) of 3-methyl-6β-phenyl-8β-(N-pyrrolidinyl)-3-azabicyclo[3.3.1]non-syn-9-yl p-nitrobenzoate m.p. 179° (from petrol b.p. 60-80°).

(Found: C, 69.5; H, 7.0; N, 9.2; $C_{26}H_{31}N_3O_4$ requires
C, 69.5; H, 6.9; N, 9.4%).

$\nu_{max.}$ (Nujol), 2770 (N-CH_3), 1710 (C=O), 1605,1505 (aromatic ring), 1535,1350 (NO_2) $cm.^{-1}$

3-Methyl-6β-phenyl-8β-(N-pyrrolidinyl)-3-azabicyclo[3.3.1]non-anti-9-yl p-nitrobenzoate (195).

Method A: Method A as in the preceding reaction was used but only unreacted starting material was recovered.

Method B: Method B as in the preceding reaction gave yellow needles of 3-methyl-6β-phenyl-8β-(N-pyrrolidinyl)-3-azabicyclo[3.3.1]non-anti-9-yl p-nitrobenzoate m.p. 162° (from petrol b.p. 60-80°).

(Found: C, 69.0; H, 7.0; N, 9.2; $C_{26}H_{31}N_3O_4$ requires

C, 69.5; H, 6.9; N, 9.4%).

$\nu_{max.}$ (Nujol), 2800 ($N-CH_3$), 1715 (C=O), 1605,1500 (aromatic ring), 1530,1350 (NO_2) $cm.^{-1}$

Attempted preparation of 3-methyl-6β-phenyl-8α-(N-pyrrolidinyl)-3-azabicyclo[3.3.1]non-syn-9-yl p-nitrobenzoate.

Method A as used in the preceding reaction gave a precipitate of the dihydrochloride m.p. 293-295°, undepressed on admixture with an authentic sample.

Method B as used in the preceding reaction gave only unreacted starting material.

Attempted preparation of 3-methyl-6α-phenyl-8β-(N-pyrrolidinyl)-3-azabicyclo[3.3.1]non-syn-9-yl p-nitrobenzoate.

Both method A and method B as used in the preceding reaction gave only unreacted starting material.

2β-Phenyl-4α-(N-morpholinyl)bicyclo[3.3.1]nonan-9-one (197).

The method used was a combination of V. Dressler's[55] and K. Untch's[36] procedures.

Cyclohexanone (196 g) and morpholine (195 g) in sodium-dried benzene (300 ml) were refluxed under a water separator for 24 hr. The solution was cooled to room temperature and a solution of cinnamaldehyde (252 g) in dry benzene (200 ml) was slowly added, with cooling *via* an ice bath to 10 - 20°. The solution was then

heated on a water bath for 4 hr, under nitrogen. The solvent was removed at 20 mm to give a dark red oil which was dissolved in isopropyl alcohol (1.5 litre) and the solution made acidic with hydrochloric acid (6N). The solution was refrigerated overnight and then filtered to give a mixture of ketone hydrochlorides (383 g). This mixture of solids was dissolved in water, basified with aqueous sodium hydroxide and extracted with chloroform. The dried ($MgSO_4$) chloroform extract was evaporated to give an oil which crystallised from isopropyl alcohol to give 2β-phenyl-4α-(N-morpholinyl)bicyclo [3.3.1] nonan-9-one (245 g, 42.5%) as colourless needles m.p. 120° (lit. 130°).[103]

(Found: M^+, 299, $C_{19}H_{25}NO_2$ requires

M^+, 299).

$\nu_{max.}$ (Nujol), 1705 (C=O), 1600,1500 (aromatic ring) $cm.^{-1}$

τ (CD_3OD): 2.75 (5H, m, Ph).

Tlc (Silica, benzene-ethyl acetate 50%), rf = 0.4.

The isopropyl alcohol solution remaining after removal of the ketone was made acidic with hydrochloric acid (6N) and refrigerated for 24 hr. The precipitate obtained was twice recrystallised from water and then basified with aqueous sodium hydroxide to give 2β-phenyl-4β-(N-morpholinyl)bicyclo [3.3.1] nonan-9-one (11.2 g, 2.5%) as colourless needles m.p. 110° (lit. 95°).[103]

(Found: M^+, 299, $C_{19}H_{25}NO_2$ requires

M^+, 299).

$\nu_{max.}$ (Nujol), 1710 (C=O), 1600,1500 (aromatic ring) $cm.^{-1}$

τ (CD_3OD): 2.8 (5H, m, Ph).

Tlc (Silica, benzene-ethyl acetate 50%), rf = 0.5.

The isopropyl alcohol solution remaining after removal of the mixture of ketone hydrochlorides was evaporated to leave an oil which was dissolved in water, basified with aqueous sodium hydroxide and extracted with ether. The dried ($MgSO_4$) ethereal extract was evaporated to leave a dark brown oil which was redissolved in ether and refrigerated overnight. The precipitate was collected and recrystallised from isopropyl alcohol to give 2α-phenyl-4β-(N-morpholinyl)bicyclo[3.3.1]nonan-9-one (29.5 g, 5%) as colourless needles m.p. 143-144° (lit. 145°).[55]

(Found: M^+, 299, $C_{19}H_{25}NO_2$ requires

M^+, 299).

$\nu_{max.}$ (Nujol), 1705 (C=O), 1600,1500 (aromatic ring) $cm.^{-1}$

τ (CD_3OD): 2.7 (5H, m, Ph).

Tlc (Silica, benzene-ethyl acetate), rf = 0.65.

2β-Phenyl-4α-(N-morpholinyl)bicyclo[3.3.1]nonan-syn-9-ol (200).

To a solution of 2β-phenyl-4α-(N-morpholinyl)bicyclo[3.3.1]nonan-9-one (5 g) in isopropyl alcohol (75 ml) was added sodium

borohydride (1.3 g) and the resulting mixture stirred at room temperature for 20 hr. After the excess sodium borohydride had been destroyed by the addition of glacial acetic acid, hydrochloric acid (1 ml) was added. The mixture was concentrated, made basic with aqueous sodium hydroxide, saturated with sodium chloride and extracted with ether. The ether layer was washed with water, dried ($MgSO_4$), and evaporated to leave a colourless oil (4.8 g, 95%) which solidified on cooling. Repeated recrystallisations from isopropyl alcohol gave 2β-phenyl-4α-(N-morpholinyl)bicyclo[3.3.1]nonan-syn-9-ol as colourless needles m.p. 160-161°. Tlc on the product (silica, methanol) showed only one compound.

(Found: C, 75.6; H, 9.1; N, 4.6; $C_{19}H_{27}NO_2$ requires
C, 75.8; H, 9.0; N, 4.7%).

$\nu_{max.}$ (Nujol), 3550 (OH), 1600,1495 (aromatic ring) $cm.^{-1}$

$\nu_{max.}$ (CS_2, 0.0025M), 3605,3450 (OH) $cm.^{-1}$

τ (CD_3OD): 2.7 (5H, m, Ph).

The amino alcohol was converted to the hydrochloride by the general method to give colourless plates m.p. 275-277°.

(Found: C, 67.6; H, 8.2; N, 4.1; Cl, 10.3; $C_{19}H_{28}NClO_2$ requires
C, 67.6; H, 8.3; N, 4.2; Cl, 10.5%).

$\nu_{max.}$ (Nujol), 3400 (OH), 2600 (N^+H), 1600,1500 (aromatic ring) $cm.^{-1}$

τ (CD_3OD): 2.7 (5H, m, Ph), 6.2 (1H, t, J=2.5 Hz, C<u>H</u>-O-).

2α-Phenyl-4β-(N-morpholinyl)bicyclo[3.3.1]nonan-syn-9-ol (203).

Method A: 2α-Phenyl-4β-(N-morpholinyl)bicyclo[3.3.1] nonan-9-one (5 g) was reduced with sodium borohydride and the reaction worked up as in the preceding experiment to give an oil (4.75 g) which crystallised on scratching. Tlc (silica, methanol) showed a mixture of two components, a faster running major component rf = 0.65 and a slower component rf = 0.50. Repeated recrystallisations continued to give a mixture.

Method B: A solution of 2α-phenyl-4β-(N-morpholinyl)bicyclo[3.3.1] nonan-9-one (2 g) in glacial acetic acid (50 ml) was hydrogenated at room temperature and atmospheric pressure over the catalyst obtained from platinum oxide (300 mg). After the absorption of hydrogen was complete (150 ml, 1.01 equiv., 3 hr), the solution was filtered, concentrated, made basic with aqueous sodium hydroxide and extracted with ether. Evaporation of the dried ($MgSO_4$) ethereal solution gave an oil (1.5 g, 74%) which crystallised on scratching. Recrystallisation from isopropyl alcohol gave 2α-phenyl-4β-(N-morpholinyl)bicyclo[3.3.1]nonan-syn-9-ol as colourless microprisms m.p. 190-191°.

(Found: C, 75.8; H, 9.0; N, 4.8; $C_{19}H_{27}NO_2$ requires

C, 75.8; H, 9.0; N, 4.7%).

$\nu_{max.}$ (Nujol), 3400 (OH), 1600,1500 (aromatic ring) $cm.^{-1}$

$\nu_{max.}$ (CS_2, 0.0025M), 3600 (OH) $cm.^{-1}$

τ (CD_3OD): 2.75 (5H, m, Ph), 4.2 (1H, t, J=2.5 Hz, C<u>H</u>-O-).

<u>2β-phenyl-4β-(N-morpholinyl)bicyclo[3.3.1]nonan-syn-9-ol (205)</u>.

Method A: 2β-phenyl-4β-(N-morpholinyl)bicyclo[3.3.1]nonan-9-one (1 g) was reduced with sodium borohydride and worked up as in the previous experiment to give an oil (0.9 g, 90%) which crystallised on scratching. Tlc (silica, methanol) showed a mixture of two components, a faster running minor component rf = 0.55 and a slower running major component rf = 0.45. Repeated recrystallisations failed to give a pure compound.

Method B: A solution of 2β-phenyl-4β-(N-morpholinyl)bicyclo[3.3.1]nonan-9-one (0.35 g) in dry ether (50 ml) was added dropwise to a stirred suspension of lithium aluminium hydride (50 mg) in dry ether (25 ml). The suspension was stirred overnight and excess lithium aluminium hydride decomposed by dropwise addition of a solution of ammonium chloride (20 ml, 10%). The ether layer was separated, dried ($MgSO_4$), and evaporated to yield a colourless oil (0.32 g, 92%) which crystallised on scratching. Recrystallisation from ether gave 2β-<u>phenyl</u>-4β-(N-<u>morpholinyl</u>)<u>bicyclo</u>[3.3.1]<u>nonan-syn-9-ol</u> as colourless microprisms m.p. 152-153°.

(Found: C, 75.8; H, 8.9; N, 4.7; $C_{19}H_{27}NO_2$ requires

C, 75.8; H, 9.0; N, 4.7%).

$\nu_{max.}$ (Nujol), 3300 (OH), 1600,1495 (aromatic ring) $cm.^{-1}$

$\nu_{max.}$ (CS_2, 0.0025M), 3600 (OH) $cm.^{-1}$

τ (CD_3OD): 2.7 (5H, m, Ph), 4.13 (1H, t, J=2.5 Hz, CH-O-).

8-Methyl-3-(N-pyrrolidinyl)-8-azabicyclo[3.2.1]oct-2-ene (208).

Tropinone[147] (29 g) and pyrrolidine (29 g) were refluxed in dry benzene (200 ml) for 12 hr to give 8-methyl-3-(N-pyrrolidinyl)-8-azabicyclo[3.2.1]oct-2-ene b.p. 114-116/2 mm (31.5 g, 76%) according to the general method.

(Found: M^+, 192, $C_{12}H_{20}N_2$ requires

M^+, 192).

$\nu_{max.}$ (Thin liquid film), 1625 (C=C) $cm.^{-1}$

Attempted preparation of 11-methyl-7-(N-pyrrolidinyl)-11-azatricyclo[3.2.1.1]undecan-10-one.

Method A: 8-Methyl-3-(N-pyrrolidinyl)-8-azabicyclo[3.2.1]oct-2-ene (31.5 g) in dry dioxan (100 ml) was cooled to 0 - 5° and acrolein (9.3 g) in dry dioxan (50 ml) was added dropwise with stirring during 1 hr. The mixture was stirred at 0° for 1 hr, and then allowed to stand at room temperature for 1 hr. The dioxan was removed at 20 mm to give a dark red viscous oil (34.3 g) which was dissolved in ether and extracted with hydrochloric acid. The acid

layer was basified with aqueous sodium hydroxide and extracted with ether. Evaporation of the dried ($MgSO_4$) ethereal solution gave a dark red oil (27.5 g) which showed the following infrared spectrum:

$\nu_{max.}$ (Thin liquid film), 1710 (C=O), 1630 (C=C) cm.$^{-1}$

The mass spectrum of the oil showed in addition to the desired peak at $^{m}/e$ 248, two peaks at higher $^{m}/e$ values; $^{m}/e$ 272 and $^{m}/e$ 301. Further purification of the oil did not yield any pure compound.

Method B: Method A was repeated, running the reaction in a stream of nitrogen but again no identifiable product was obtained.

Method C: The above method was repeated but after stirring the solution for 1 hr at room temperature it was heated on a water bath for 1 hr. Again no pure compound was isolated.

Attempted preparation of 11-methyl-9-phenyl-7-(N-pyrrolidinyl)-11-azatricyclo[3.2.1.1] undecan-10-one.

8-methyl-3-(N-pyrrolidinyl)-8-azabicyclo[3.2.1] oct-2-ene (19 g) in dry dioxan (100 ml) was treated at 0 - 5° with cinnamaldehyde (13 g) in dry dioxan (25 ml) and worked up as for method C in the preceding reaction. A dark red oil was produced (22.3 g) which showed the following infrared spectrum:

$\nu_{max.}$ (Thin liquid film), 1720 (C=O), 1630 (C=C) $cm.^{-1}$

The oil did not yield any pure compound on further purification.

Attempted preparation of 8-methyl-3-(N-piperidinyl)-8-azabicyclo [3.2.1] oct-2-ene.

Tropinone (14 g) and piperidine (17 g) were refluxed in dry benzene (150 ml) for 12 hr and worked up, according to the general method, to give unreacted starting materials.

Ethyl-3-phenyl-3-(8-methyl-3-(N-pyrrolidinyl)-8-azabicyclo [3.2.1] oct-2-yl)propionate (210).

8-Methyl-3-(N-pyrrolidinyl)-8-azabicyclo [3.2.1] oct-2-ene (32 g) in absolute ethanol (150 ml) was cooled to 0 - 5° and cinnamaldehyde (25 g) in absolute ethanol (50 ml) was added dropwise with stirring during 1 hr. The mixture was stirred at 0° for 1 hr, and then allowed to stand for 1 hr at room temperature. The ethanol was evaporated to leave a dark brown oil (51.2 g, 84%) which crystallised on cooling. Recrystallisation from petrol (b.p. 60-80°) gave long colourless needles m.p. 83-84°, of the ester.

(Found: C, 74.7; H, 9.3; N, 7.5; $C_{23}H_{34}N_2O_2$ requires

C, 74.6; H, 9.2; N, 7.6%).

$\nu_{max.}$ (Nujol), 2760 ($N-CH_3$), 1720 (C=O), 1600,1500 (aromatic ring) $cm.^{-1}$

Attempted preparation of ethyl-3-(8-methyl-3-(N-pyrrolidinyl)-8-azabicyclo[3.2.1]oct-2-yl)propionate.

8-Methyl-3-(N-pyrrolidinyl)-8-azabicyclo[3.2.1]oct-2-ene (19 g) in absolute ethanol (100 ml) was cooled to 0 - 5° and acrolein (6 g) in absolute ethanol (50 ml) was added dropwise with stirring during 1 hr. The mixture was stirred at 0° for 1 hr, and then allowed to stand for 1 hr at room temperature. The ethanol was evaporated to leave a dark brown oil (21.3 g) which on distillation at 80°/1 mm gave tropinone m.p. 43-44° (lit. 45°).[147]

1-Methyl-3-piperidone (227).

The method used was a modification of the procedure of Lyle.[115]

A solution of 3-hydroxypyridine (36 g) and sodium methoxide (23 g) in methanol (150 ml) was treated with methyl iodide (100 g). The resulting mixture was heated under reflux for 7 hr, cooled, and the solvent evaporated to give a viscous oil which was dissolved in isopropyl alcohol (500 ml). Sodium borohydride (30 g) was then added and the mixture stirred at room temperature for 48 hr. After the excess sodium borohydride had been destroyed by the addition of glacial acetic acid, hydrochloric acid (5 ml) was added. The mixture was concentrated, made basic with aqueous sodium hydroxide and extracted with chloroform. Evaporation of the dried ($MgSO_4$) chloroform solution gave 1,2,5,6-tetrahydro-3-pyridyl methyl ether (45.6 g) as a

mobile red oil.

The original method[115] gave a colourless, crystalline compound (3.6 g) m.p. 62°, the infrared spectrum of which showed:

$\nu_{max.}$ (Nujol), 2350,1670 (C=C) cm.$^{-1}$

(Found: C, 61.1; H, 11.2; N, 9.8; M^+, 140.121498; $C_7H_{15}NBO$ requires C, 60.0; H, 10.7; N, 10.0%; M^+, 140.120843).

A solution of 1,2,5,6-tetrahydro-3-pyridyl methyl ether (45.6 g) in hydrobromic acid (140 ml, 50%) was heated under reflux for 6 hr. The solution was then neutralised with aqueous sodium hydroxide and extracted with ether. Evaporation of the dried ($MgSO_4$) ethereal solution gave an oil (25.9 g) which was distilled b.p. 46-48°/2 mm (lit. 65-70°/15 mm)[115], to give 1-methyl-3-piperidone (22.67 g, 53% overall from 3-hydroxypyridine).

$\nu_{max.}$ (Thin liquid film), 2770 (N-CH_3), 1720 (C=O) cm.$^{-1}$

1-Methyl-3-(N-pyrrolidinyl)-1,2,3,4-tetrahydropyridine (232).

1-Methyl-3-piperidone (11 g) and pyrrolidine (15 g) were refluxed in dry benzene (150 ml) for 12 hr to give 1-methyl-3-(N-pyrrolidinyl)-1,2,3,4-tetrahydropyridine (13.1 g, 79%) according to the general method. Distillation of the oil produced much charring. The product was not purified further but was utilised in a further reaction.

(Found: M^+, 166, $C_{10}H_{18}N_2$ requires

M^+, 166).

$\nu_{max.}$ (Thin liquid film), 1605 (C=C) $cm.^{-1}$

1-Methyl-3-(N-piperidinyl)-1,2,3,4-tetrahydropyridine (239).

1-Methyl-3-piperidone (11 g) and piperidine (16 g) were refluxed in dry benzene (150 ml) for 12 hr to give 1-methyl-3-(N-piperidinyl)-1,2,3,4-tetrahydropyridine (13.8 g, 78%) according to the general method. The product was not distilled but on refrigeration for 1 hr produced yellow needles. The product was not purified further but was utilised in a further reaction.

(Found: M^+, 180, $C_{11}H_{20}N_2$ requires

M^+, 180).

$\nu_{max.}$ (Nujol), 1500 (C=C) $cm.^{-1}$

Attempted preparation of 2-methyl-6-(N-pyrrolidinyl)-2-azabicyclo [3.3.1] nonan-9-one.

1-Methyl-3-(N-pyrrolidinyl)-1,2,3,4-tetrahydropyridine (13.1 g) in dry dioxan (50 ml) was cooled to 0 - 5° and acrolein (6 g) in dry dioxan (100 ml) was added dropwise with stirring during 1 hr. The mixture was stirred at 0° for 1 hr, and then allowed to stand at room temperature for 1 hr. The dioxan was removed at 20 mm to give a dark brown oil (14.4 g) which on distillation produced much charring and no pure products were isolated. An aliquot

was dissolved in chloroform and extracted with hydrochloric acid. The acid layer was separated, made basic with aqueous sodium hydroxide and extracted with chloroform. Evaporation of the dried ($MgSO_4$) chloroform solution gave a red oil which could not be characterised.

Attempted preparation of 2-methyl-6-(N-piperidinyl)-2-azabicyclo [3.3.1] nonan-9-one.

The method was the same as in the preceding experiment. A dark brown oil was produced which could not be characterised.

1-Benzyl-3-(N-pyrrolidinyl)-1,2,3,4-tetrahydropyridine (238).

1-Benzyl-3-piperidone (10 g) and pyrrolidine (15 g) were refluxed in dry benzene for 3 hr to give 1-benzyl-3-(N-pyrrolidinyl)-1,2,3,4-tetrahydropyridine (9 g, 70%) according to the general method. The product was not distilled but on refrigeration for 1 hr produced yellow needles. The product was not purified further but was utilised in the next reaction.

2-Benzyl-6-(N-pyrrolidinyl)-2-azabicyclo [3.3.1] nonan-9-one (239).

1-Benzyl-3-(N-pyrrolidinyl)-1,2,3,4-tetrahydropyridine (9 g) in dry dioxan (50 ml) was cooled to 0 - 5° and acrolein (5.8 g) in dry dioxan (100 ml) was added dropwise with stirring. The mixture was stirred at 0° for 1 hr, and then allowed to stand at room temperature for 1 hr. The dioxan was removed at 20 mm to give a dark brown oil (9 g, 80%). 1 g of the oil was placed on a chromatographic column

(neutral alumina) and eluted with ether. 15 x 50 ml collections of eluate were taken and evaporated to dryness giving an oil (0.4 g) of 2-benzyl-6-(N-pyrrolidinyl)-2-azabicyclo[3.3.1]nonan-9-one.

(Found: M^+, 298.204503, $C_{19}H_{26}N_2O$ requires

M^+, 298.203496).

$\nu_{max.}$ (Thin liquid film), 1720 (C=O), 1600,1495 (aromatic ring) $cm.^{-1}$

1-Benzyl-3β-hydroxy-3α-phenyl-piperidine (104).

1-Benzyl-3-piperidone (10 g) was dissolved in dry ether (100 ml) and added dropwise to a solution of phenyl lithium prepared from lithium (1.05 g) and bromobenzene (12 g) in dry ether (100 ml). The solution was stirred overnight and the complex decomposed by the addition of damp ether. The ether layer was separated, dried ($MgSO_4$), and evaporated to give a yellow oil (12 g, 85%) which crystallised on scratching. On recrystallisation from petrol (b.p. 60-80°) this gave colourless needles of 1-benzyl-3β-hydroxy-3α-phenyl-piperidine m.p. 70-71°.

(Found: C, 81.1; H, 7.9; N, 5.3; $C_{18}H_{21}NO$ requires

C, 80.9; H, 7.9; N, 5.2%).

$\nu_{max.}$ (Nujol), 3500 (OH), 1605,1500 (aromatic ring) $cm.^{-1}$

$\nu_{max.}$ (CS_2, 0.0025M), 3480 (OH) $cm.^{-1}$

The amino-alcohol was converted to the hydrochloride by the general method, to give colourless needles of the hydrochloride (108)

m.p. 237-239°.

(Found: C, 70.9; H, 7.2; N, 4.6; Cl, 8.7; $C_{18}H_{22}NClO$ requires

C, 71.2; H, 7.2; N, 4.6; Cl, 8.6%).

$\nu_{max.}$ (Nujol), 3380 (OH), 2600 (N^+H), 1600,1500 (aromatic ring) $cm.^{-1}$

Dihydrotetramethylholarrhimine dihydrochloride (271).

Dihydrotetramethylholarrhimine (270) was converted to the dihydrochloride by the general method, to give colourless needles of the dihydrochloride (271) m.p. 305-307°.

(Found: C, 63.83; H, 9.85; N, 5.96; $C_{24}H_{45}N_2Cl_2O$ requires

C, 64.29; H, 10.04; N, 6.25%).

$\nu_{max.}$ (Nujol), 3300 (OH), 2500 (N^+H), 1630 (H-O-H) $cm.^{-1}$

MASS SPECTRAL TABLES

3-Methyl-6α- and 3-methyl-6β-(N-pyrrolidinyl)-3-azabicyclo[3.3.1] nonan-9-ones.

m/e	223	222	221	152	151	150	136	125	124	123	112	111	110
I%	2	15	28	17	6	15	5	5	13	10	6	28	100
m/e	109	108	98	97	96	95	94	85	84	83	82	81	80
I%	6	14	10	34	34	7	14	5	76	9	16	14	11
m/e	79	78	77	71	70	69	68	67	58	57	56	55	54
I%	31	5	6	10	38	22	24	9	19	9	8	39	19
m/e	53	52	51	50	49	44	43	42	41	40	39	30	29
I%	16	19	13	7	16	24	43	77	67	11	33	9	10
m/e	28	27	26										
I%	30	40	10										

m^* 220 (222 221), 101.9, 54.9.

3-Methyl-6α-(N-pyrrolidinyl)-3-azabicyclo[3.3.1] nonan-syn-9-ol.

m/e	224	223	209	155	154	153	152	138	137	136	126	125	124
I%	26	7	4	6	34	13	17	12	5	25	14	5	18
m/e	122	112	111	110	109	108	107	98	97	96	95	94	85
I%	10	7	12	76	23	20	22	12	24	36	7	26	7
m/e	84	83	82	81	80	72	71	70	69	68	67	58	57
I%	100	14	16	6	5	7	8	42	14	13	10	64	15

m/e	56	55	54	53	44	43	42	41	39	30	29	28	27
I%	8	16	11	8	43	17	44	41	12	8	12	37	14

m^* 189.5 (224 206).

Ion source determinations. Meta-stable scan at 2-8 kv.

m/e 154		m/e 110		m/e 96	
221	154 (0.144 m)	125	110 (0.046 vs)	110	96 (0.050 vl)
		136	110 (0.079 vs)	124	96 (0.096 m)
		151	110 (0.125 vs)	136	96 (0.138 m)

9-Deutero-3-methyl-6α-(N-pyrrolidinyl)-3-azabicyclo[3.3.1]nonan-syn-9-ol.

m/e	226	225	224	210	208	207	206	192	156	155	154	153	139
I%	9	51	7	6	2	2	2	6	11	46	18	16	8
m/e	138	137	136	127	125	124	123	113	112	111	110	109	108
I%	10	24	12	15	7	14	11	7	6	22	68	35	24
m/e	98	97	96	95	94	85	84	83	82	81	80	74	72
I%	13	28	37	24	10	16	100	15	17	6	6	8	8
m/e	71	70	69	68	67	59	58	57	56	55	54	53	45
I%	11	42	16	16	7	44	22	12	11	15	12	6	8
m/e	44	43	42	41	39	32	30	29	28	27			
I%	42	18	49	36	10	11	10	9	60	10			

m^* 190.5 (225 207), 106.9 (225 155), 62.5.

3-Methyl-6α-(N-pyrrolodinyl)-3-azabicyclo[3.3.1] nonan-anti-9-ol.

m/e	225	224	223	209	207	206	167	162	155	154	153	152	140
I%	6	41	12	5	2	2	8	5	6	36	15	15	5
m/e	138	137	136	126	125	124	122	112	111	110	109	108	107
I%	14	6	26	22	6	21	11	8	15	75	23	11	11
m/e	98	97	96	95	94	85	84	83	82	81	72	71	70
I%	12	30	33	5	15	7	100	13	13	6	9	9	34
m/e	69	68	67	58	57	56	55	54	53	44	43	42	41
I%	14	9	8	75	13	6	10	8	6	45	16	30	30
m/e	39	30	29	28	27								
I%	8	6	8	11	10								

m^* 189.5 (224 → 206), 106 (224 → 154), 62.5

Ion source determinations. Meta-stable scan at 4-8 kv.

m/e 136

224 → 136 (0.646 m)

206 → 136 (0.520 l)

153 → 136 (0.128 vl)

3-Methyl-6β-(N-pyrrolidinyl)-3-azabicyclo[3.3.1] nonan-anti-9-ol.

m/e	224	223	209	167	162	155	154	153	152	139	138	137	126
I%	26	9	5	8	5	6	25	12	13	5	14	5	20
m/e	125	124	122	112	111	110	109	108	107	98	97	96	94
I%	7	20	26	8	14	76	22	12	13	36	31	42	18

m/e	85	84	83	82	81	80	79	77	74	72	71	70	69
I%	7	100	17	20	9	6	7	7	7	9	12	41	19
m/e	68	67	59	58	57	56	55	54	53	45	44	43	42
I%	14	13	9	89	20	10	19	15	9	14	7	31	51
m/e	41	39	38	36	31	30	29	28	27				
I%	50	18	12	38	20	14	17	14	21				

m^* 189.5 (224 206).

3-Methyl-6β-(N-pyrrolidinyl)-3-azabicyclo[3.3.1]nonan-syn-9-ol.

m/e	225	224	223	222	209	207	206	191	155	154	153	152	150
I%	4	18	7	2	2	1	2	5	25	75	18	19	6
m/e	138	137	136	135	134	126	124	122	112	111	110	109	108
I%	15	6	30	28	5	10	15	7	8	15	83	17	20
m/e	107	99	98	97	96	95	94	93	91	85	84	83	82
I%	21	18	15	25	37	11	36	5	6	7	100	13	24
m/e	81	80	79	78	77	72	71	70	69	68	67	58	57
I%	10	8	23	5	7	7	11	50	19	20	14	32	20
m/e	56	55	54	53	52	51	50	44	43	42	41	40	39
I%	11	23	17	14	17	10	6	64	29	67	62	7	25
m/e	30	29	28	27	26								
I%	11	6	27	27	7								

m^* 189.5 (224 206), 106 (224 154).

3-Methyl-6α- and 3-methyl-6β-(N-piperidinyl)-3-azabicyclo[3.3.1]nonan-9-ones.

m/e	236	235	152	150	124	111	110	98	97	96	94	84	82
I%	11	20	12	8	100	10	22	47	5	12	5	16	7
m/e	81	70	68	58	57	56	55	54	44	43	42	41	39
I%	5	8	6	9	6	6	16	6	13	7	25	23	7
m/e	28	27											
I%	8	11											

Accurate mass measurements on selected ions:

m/e	Found	Empirical Formula	Required
152	152.107533	$C_9H_{14}NO$	152.107374
124	124.112619	$C_8H_{14}N$	124.113398

3-Methyl-6α-(N-piperidinyl)-3-azabicyclo[3.3.1]nonan-syn-9-ol.

m/e	239	238	237	223	221	220	219	205	154	153	152	150	140
I%	4	28	10	5	1	1	2	6	28	16	16	8	5
m/e	138	126	125	124	122	112	111	110	109	108	107	99	98
I%	7	10	15	56	6	9	12	26	21	15	17	8	100
m/e	97	96	94	86	84	83	82	70	69	68	67	58	57
I%	8	21	10	7	22	10	11	12	6	7	7	39	10
m/e	56	55	54	44	43	42	41	40	39	29	28	27	
I%	8	14	6	28	7	26	28	22	8	7	9	8	

m^* 203.4 (238 → 220), 67.8.

Accurate mass measurements on selected ions:

m/e	Found	Empirical Formula	Required
44	44.050022	C_2H_6N	44.048230
58	58.065671	C_3H_8N	58.064734
136	136.112619	$C_9H_{14}N$	136.112094

Ion source determinations. Meta-stable scan at 4-8 kv.

m/e 124

139 124 (0.121 vw)

152 124 (0.230 w)

238 124 (0.898 1)

3-Methyl-6β-(N-piperidinyl)-3-azabicyclo[3.3.1]nonan-syn-9-ol.

m/e	239	238	237	236	235	223	221	220	205	155	154	153	152
I%	3	20	12	1	1	4	2	2	7	18	84	28	21
m/e	150	140	138	137	136	126	125	124	122	112	111	110	109
I%	7	5	9	5	22	8	10	53	7	11	15	35	18
m/e	108	107	99	98	97	96	95	94	93	91	86	85	84
I%	18	21	10	100	7	27	8	23	5	5	8	8	35
m/e	83	82	81	79	74	70	69	68	67	58	57	56	55
I%	13	20	6	9	21	20	9	12	10	25	24	18	22
m/e	54	53	44	43	42	41	39	30	29	28	27	26	
I%	10	7	49	18	42	48	15	8	14	17	15	5	

m^* 203.4 (238 220), 99.6 (238 154).

Accurate mass measurements on selected ions:

m/e	Found	Empirical Formula	Required
84	84.081320	$C_5H_{10}N$	84.082392

Ion source determinations. Meta-stable scan at 2-8 kv.

m/e	84
99	84 (0.183)
112	84 (0.339)
125	84 (0.489)
138	84 (0.648)
152	84 (0.813)
238	84 (1.83)

3-Methyl-6α-(N-piperidinyl)-3-azabicyclo[3.3.1]nonan-anti-9-ol.

m/e	239	238	237	236	223	221	220	154	153	152	150	140	138
I%	3	23	2	2	4	1	1	29	16	14	8	8	8
m/e	136	126	125	124	122	112	111	110	109	108	107	99	98
I%	13	11	12	63	6	9	12	30	13	9	10	8	100
m/e	97	96	94	86	85	84	83	82	81	79	78	70	69
I%	10	20	12	10	7	27	11	12	5	5	26	12	5
m/e	68	67	58	57	56	55	54	53	44	43	42	41	39
I%	8	7	66	16	9	15	7	5	43	10	29	30	8
m/e	30	29	28	27									
I%	7	8	10	10									

m^* 203.4 (238 220).

Accurate mass measurements on selected ions:

m/e	Found	Empirical Formula	Required
74	74.060318	C_3H_8NO	74.060585

3-Methyl-6α and 3-methyl-6β-(N-morpholinyl)-3-azabicyclo[3.3.1] nonan-9-ones.

m/e	239	238	237	169	152	151	150	127	126	124	123	113	112
I%	2	11	26	7	24	5	16	10	100	8	8	6	7
m/e	111	110	100	98	96	95	94	84	83	82	81	79	70
I%	5	45	26	7	6	5	6	7	6	9	9	5	14
m/e	68	67	58	57	56	55	54	53	44	43	42	41	39
I%	7	5	26	16	10	29	10	7	35	13	41	27	10
m/e	30	29	28	27									
I%	5	8	14	19									

m^* 236 (238 237), 94.9.

3-Methyl-6α-(N-morpholinyl)-3-azabicyclo[3.3.1] nonan-syn-9-ol.

m/e	241	240	239	238	225	223	222	221	155	154	153	152	140
I%	6	36	10	1	4	1	2	3	14	100	36	38	7
m/e	138	136	127	126	125	124	123	122	120	114	113	111	110
I%	12	26	14	75	8	30	5	29	7	7	11	5	20
m/e	109	108	107	101	100	98	97	96	95	94	88	87	86
I%	33	24	26	6	89	9	8	24	9	34	5	5	16

m/e	84	83	82	81	79	74	72	71	70	69	68	67	59
I%	9	18	23	7	5	6	7	8	26	6	12	12	5
m/e	58	57	56	55	54	53	45	44	43	42	41	39	31
I%	95	27	16	26	11	7	6	62	12	51	37	11	32
m/e	30	29	28	27	26								
I%	9	12	16	16	5								

m^* 205.5 (240 222), 98.9 (240 154), 77.6.

Accurate mass measurements on selected ions:

m/e	Found	Empirical Formula	Required
124	124.076234	$C_7H_{10}NO$	124.076485
124	124.112619	$C_8H_{14}N$	124.112693
70	70.065671	C_4H_8N	70.065797

Ion source determinations. Meta-stable scan at 2-8 kv.

m/e 124

152 124 (0.076 1).

3-Methyl-6β-(N-morpholinyl)-3-azabicyclo[3.3.1]nonan-syn-9-ol.

m/e	241	240	239	225	222	221	155	154	153	152	151	150	147
I%	3	22	7	3	1	3	19	100	30	28	9	14	8
m/e	142	141	140	138	136	127	126	125	124	122	120	114	113
I%	14	6	26	9	23	8	47	6	18	15	6	5	8
m/e	112	111	110	109	108	107	101	100	98	97	96	95	94
I%	15	5	18	20	17	18	5	81	11	6	16	7	26

m/e	93	87	86	84	83	82	81	79	77	74	72	71	70
I%	5	5	13	8	12	19	6	5	5	14	7	7	20
m/e	69	68	67	58	57	56	55	54	53	45	44	43	42
I%	5	11	9	55	23	14	21	9	6	4	53	11	42
m/e	41	39	30	29	28	27							
I%	30	10	9	12	19	13							

m^* 205.5 (240 222), 99 (240 154), 77.6.

Accurate mass measurements on selected ions:

m/e	Found	Empirical Formula	Required
74	74.060585	C_3H_8NO	74.060603

Ion source determinations. Meta-stable scan at 2-8 kv.

m/e 74		m/e 152		m/e 70	
154	74 (0.360 l)	240	152 (0.193 vl)	240	70 (0.811 s)
		223	152 (0.156 s)	222	70 (0.726 s)
		183	152 (0.068 m)	154	70 (0.398 vl)
		168	152 (0.035 m)	138	70 (0.322 m)
				126	70 (0.269 l)
				114	70 (0.211 l)
				99	70 (0.139 l)
				88	70 (0.086 m)
				85	70 (0.072 m)

3-Methyl-6α-(N-morpholinyl)-3-azabicyclo[3.3.1]nonan-anti-9-ol.

m/e	241	240	239	238	237	225	223	222	221	167	166	155	154
I%	8	54	12	2	1	4	1	2	3	5	5	9	74
m/e	153	152	142	140	138	136	129	127	126	125	124	123	122
I%	28	26	6	7	11	17	9	11	55	9	25	5	27
m/e	120	114	113	112	111	110	109	108	101	100	98	97	96
I%	7	5	9	21	5	27	12	15	5	69	9	14	17
m/e	95	94	93	87	86	84	83	82	81	79	77	72	71
I%	7	20	5	5	10	9	12	20	7	6	6	6	6
m/e	70	69	68	67	59	58	57	56	55	54	53	45	44
I%	17	5	10	11	12	100	39	15	23	10	7	12	58
m/e	43	42	41	31	30	29	28	27					
I%	14	46	30	18	10	20	24	17					

m^* 205.4 (240 222), 98.9 (240 154), 77.5, 69.5.

Ion source determinations. Meta-stable scan at 4-8 kv.

m/e 126

141 126 (0.119 s)

155 126 (0.227 m)

223 126 (0.773 vs)

238 126 (0.886 s)

3-Methyl-6α-(N-pyrrolidinyl)-3-azabicyclo[3.3.1]non-anti-9-yl p-nitrobenzoate.

m/e	374	373	304	303	224	223	207	206	205	191	163	162	152
I%	5	21	7	27	6	28	17	17	6	11	5	14	8
m/e	150	149	139	138	137	136	135	134	123	122	120	111	110
I%	16	8	7	9	6	27	7	8	7	23	9	7	52
m/e	109	108	107	104	97	96	95	94	93	92	91	85	84
I%	10	16	24	15	13	17	8	18	7	6	7	6	100
m/e	83	82	81	79	78	77	71	70	69	68	66	58	57
I%	5	7	6	5	9	8	14	8	7	9	6	31	9
m/e	55	44	43	42	41	39	28	26					
I%	7	13	18	17	15	7	8	7					

m^* 246 (373 → 303), 133.3 (373 → 223).

9-Deutero-3-methyl-6α-(N-pyrrolidinyl)-3-azabicyclo[3.3.1]non-anti-9-yl p-nitrobenzoate.

m/e	375	374	304	282	281	252	224	208	207	192	163	150	139
I%	2	8	11	15	8	7	15	10	10	7	9	13	8
m/e	138	137	136	135	124	123	111	110	109	108	107	104	97
I%	6	21	7	7	7	21	19	46	16	21	10	16	16
m/e	96	95	94	85	84	83	82	81	80	77	76	70	69
I%	21	19	9	13	100	6	6	5	5	5	10	16	11

m/e	68	59	58	57	55	54	44	43	42	41	39	29	28
I%	13	13	26	11	8	6	21	16	26	16	5	5	16

m^* 247 (374 304), 90.2.

3-Methyl-6α-(N-pyrrolidinyl)-3-azabicyclo[3.3.1] non-syn-9-yl p-nitrobenzoate.

m/e	373	303	223	207	191	152	150	138	136	135	134	122	120
I%	4	13	6	7	5	6	5	6	24	5	5	18	7
m/e	111	110	109	108	107	104	97	96	95	94	93	85	84
I%	7	48	8	15	25	9	10	18	10	21	6	7	100
m/e	83	82	81	76	70	69	68	67	65	58	57	56	55
I%	5	7	5	6	18	7	6	6	7	26	6	5	10
m/e	54	50	44	43	42	41	39	29	27				
I%	10	5	50	43	26	21	11	5	8				

m^* 246 (373 303), 133.3 (373 223), 114, 72.2.

Accurate mass measurements on selected ions:

m/e	Found	Empirical Formula	Required
110	110.096970	$C_7H_{12}N$	110.095564
84	84.081320	$C_5H_{10}N$	84.079288

9-Deutero-3-methyl-6α-(N-pyrrolidinyl)-3-azabicyclo[3.3.1] non-syn-9-yl p-nitrobenzoate.

m/e	374	305	304	224	208	207	192	153	150	139	138	137	123
I%	14	7	25	9	9	8	7	6	8	7	6	20	20

m/e	111	110	109	108	107	104	97	96	95	94	85	84	76
I%	13	43	13	20	9	8	10	14	19	6	10	100	5
m/e	70	69	68	59	58	44	43	42	41	32	28		
I%	12	5	7	6	9	9	5	13	8	8	45		

m^* 247 (374 304), 73.

3-Methyl-6α-(N-piperidinyl)-3-azabicyclo[3.3.1]non-anti-9-yl P-nitrobenzoate.

m/e	387	303	237	221	220	167	150	136	124	122	120	110	109
I%	4	8	6	7	5	8	23	9	22	8	7	15	8
m/e	108	107	104	99	98	96	94	84	74	65	59	58	57
I%	7	12	12	7	100	6	8	7	26	6	33	23	8
m/e	55	50	45	44	43	42	41	29	28	27			
I%	6	5	21	12	5	13	12	22	24	13			

m^* 162.5 (303 222), 43.5.

3-Methyl-6α-(N-morpholinyl)-3-azabicyclo[3.3.1]non-anti-9-yl P-nitrobenzoate.

m/e	389	304	303	239	223	222	221	178	152	150	138	137	136
I%	6	8	39	10	11	14	6	8	14	17	7	5	23
m/e	135	134	126	123	122	121	120	111	110	109	108	107	104
I%	7	8	35	11	100	6	12	6	14	13	17	29	15
m/e	100	98	96	95	94	93	92	91	83	82	79	77	76
I%	70	5	7	9	25	10	6	7	5	7	5	8	8

m/e	70	68	67	65	58	57	56	55	43	42	41	39	28
I%	7	5	9	6	53	18	9	12	6	24	14	5	36

m^* 236 (389 303), 67.

2α-(N-Morpholinyl)bicyclo[3.3.1]nonan-syn-9-ol.

m/e	226	225	127	126	113	100	86	81	79	67	57	56	55
I%	1	7	10	100	6	13	6	3	6	8	6	8	13
m/e	43	42	41	39	28	27							
I%	6	9	18	5	9	8							

m^* 85.

2α-(N-Morpholinyl)bicyclo[3.3.1]nonan-anti-9-ol.

m/e	225	224	208	127	126	113	112	101	100	98	93	91	88
I%	19	3	11	9	91	17	5	7	100	6	6	5	6
m/e	87	86	83	82	81	79	77	70	69	68	67	57	56
I%	27	15	7	5	7	11	6	6	6	7	16	11	14
m/e	55	54	53	44	43	42	41	39	30	29	28	27	
I%	23	7	7	6	6	15	30	9	6	11	14	10	

m^* 172.5, 85.

3-Methyl-6β-phenyl-8α-(N-pyrrolidinyl)-3-azabicyclo[3.3.1]nonan-9-one.

m/e	299	298	297	187	186	184	183	141	130	129	128	117	116
I%	1	4	3	17	100	18	10	5	5	7	7	11	17
m/e	115	111	110	97	96	91	84	82	78	77	71	70	69
I%	27	8	8	8	17	11	14	6	7	7	9	17	6

m/e	68	58	57	56	55	51	44	43	42	41	40	39	28
I%	9	17	14	7	8	7	8	44	36	20	5	14	14
m/e	27												
I%	11												

m^* 115.

3-Methyl-6β-phenyl-8α-(N-pyrrolidinyl)-3-azabicyclo[3.3.1]nonan-syn-9-ol.

m/e	301	300	299	285	283	282	231	230	229	228	212	203	202
I%	4	19	3	2	2	1	10	25	5	6	10	8	5
m/e	200	199	198	188	187	186	185	184	159	158	128	126	117
I%	7	8	44	5	33	100	11	5	17	11	6	5	17
m/e	115	112	105	98	97	96	94	91	85	84	83	77	74
I%	12	6	8	9	22	64	13	17	6	89	10	7	9
m/e	70	69	68	58	57	56	55	54	44	43	42	41	28
I%	19	9	6	74	15	5	8	6	33	7	23	14	19

m^* 265 (300 → 282), 176 (300 → 230), 113 (117 → 115), 49.2.

3-Methyl-6α-phenyl-8β-(N-pyrrolidinyl)-3-azabicyclo[3.3.1]nonan-syn-9-ol.

m/e	301	300	299	285	283	282	281	231	230	229	228	212	203
I%	9	43	2	1	1	1	1	9	49	13	10	12	8
m/e	202	200	199	198	188	187	186	185	184	159	158	128	117
I%	6	6	10	54	5	39	100	14	10	17	26	5	6

m/e	115	112	110	98	97	96	94	91	85	84	83	82	70
I%	12	6	16	12	17	76	21	14	5	75	9	7	17
m/e	69	68	58	57	55	44	43	42	41	28			
I%	6	5	30	9	5	18	6	15	9	9			

m^* 265 (300 282), 176.2 (300 230), 113 (117 115), 49.2.

3-Methyl-6β-phenyl-8β-(N-pyrrolidinyl)-3-azabicyclo[3.3.1] nonan-syn-9-ol.

m/e	301	300	299	285	283	282	281	231	230	229	228	212	203
I%	3	15	2	1	1	1	1	19	44	6	6	12	8
m/e	200	199	198	188	187	186	185	160	159	128	117	116	115
I%	6	7	40	5	29	98	12	19	23	6	20	5	14
m/e	112	110	103	98	97	96	95	94	91	85	84	83	82
I%	7	23	44	21	25	74	6	25	21	6	100	11	10
m/e	77	74	72	71	70	69	68	58	57	56	55	54	44
I%	6	6	8	6	33	11	7	79	18	8	10	6	39
m/e	43	42	41	39	30	29	28	27					
I%	11	30	19	6	5	6	11	6					

m^* 265 (300 282), 176.2 (300 230), 113 (117 115), 92.3, 49.2.

3-Methyl-6β-phenyl-8β-(N-pyrrolidinyl)-3-azabicyclo[3.3.1] nonan-anti-9-ol.

m/e	301	300	231	230	229	228	212	198	189	188	187	186	185
I%	6	30	25	77	14	11	14	17	6	7	14	37	8

m/e	184	172	170	169	168	167	159	158	153	152	151	150	147
I%	10	5	6	13	13	6	9	30	9	4	4	3	3
m/e	143	141	129	128	117	116	115	112	111	110	104	103	98
I%	6	6	5	7	21	6	17	7	5	27	5	5	13
m/e	97	96	95	94	91	86	85	84	83	82	81	79	78
I%	18	50	7	26	26	5	7	100	8	15	8	5	6
m/e	77	74	71	70	69	58	57	56	55	54	53	51	44
I%	9	12	6	28	11	15	14	7	10	8	5	6	30
m/e	43	42	41	39	32	30	29	28	27	26			
I%	11	35	20	11	6	5	5	35	12	5			

m^* 265 (300 282), 176.2, 113 (117 115), 49.2.

2β-Phenyl-4α-(N-morpholinyl)bicyclo[3.3.1]nonan-9-one.

m/e	299	203	202	117	115	91	56	55	42	41	39	28	27
I%	1	15	100	7	9	15	7	14	10	12	5	16	7

m^* 113 (117 115).

2α-Phenyl-4β-(N-morpholinyl)bicyclo[3.3.1]nonan-9-one.

m/e	299	203	202	117	115	91	56	55	42	41	39	32	29
I%	1	15	100	7	8	15	7	14	10	13	6	8	5
m/e	28	27											
I%	42	8											

m^* 113 (117 115).

2β-Phenyl-4β-(N-morpholinyl)bicyclo[3.3.1]nonan-9-one.

m/e	299	203	202	117	115	91	55	42	41	28	27
I%	1	15	100	5	6	10	10	7	8	6	5

m^* 113 (117 115).

2β-Phenyl-4α-(N-morpholinyl)bicyclo[3.3.1]nonan-syn-9-ol.

m/e	301	203	202	117	115	91	67	56	55	45	42	41	39
I%	1	15	100	7	8	17	5	7	14	5	11	14	6
m/e	32	29	28	27									
I%	11	6	55	9									

m^* 113 (117 115).

2α-Phenyl-4β-(N-morpholinyl)bicyclo[3.3.1]nonan-syn-9-ol.

m/e	302	301	300	285	284	204	203	202	129	126	117	115	114
I%	2	11	2	2	7	10	17	100	7	6	9	8	6
m/e	113	112	100	91	87	86	79	77	67	57	56	55	42
I%	18	10	45	33	16	5	5	5	9	6	9	13	9
m/e	41	28	27										
I%	13	5	5										

m^* 85.

2β-Phenyl-4β-(N-morpholinyl)bicyclo[3.3.1]nonan-syn-9-ol.

m/e	301	284	203	202	91
I%	2	3	16	100	8

m^* 135.5 (301 202).

3-Methyl-6β-phenyl-8β-(N-pyrrolidinyl)-3-azabicyclo[3.3.1]non-syn-9-yl p-nitrobenzoate.

m/e	449	380	379	350	283	228	214	212	199	187	186	185	184
I%	4	12	25	6	7	10	9	19	6	21	74	9	17
m/e	183	158	150	141	129	128	117	115	110	108	104	98	97
I%	11	9	12	6	5	11	15	13	12	7	15	7	17
m/e	96	95	94	92	91	85	84	83	82	81	77	76	72
I%	80	12	59	8	25	7	100	10	9	8	6	8	6
m/e	71	70	69	68	67	65	58	57	56	55	54	44	43
I%	6	31	10	7	5	6	62	15	6	10	7	27	11
m/e	42	41	39	32	28	27							
I%	28	14	39	32	28	27							

m^* 320 (449 → 379), 113 (117 → 115), 49.3.

3-Methyl-6α-phenyl-8β-(N-pyrrolidinyl)-3-azabicyclo[3.3.1]non-anti-9-yl p-nitrobenzoate.

m/e	449	380	379	299	283	228	226	214	213	212	211	210	198
I%	11	9	29	9	11	5	7	7	9	34	10	7	21
m/e	188	187	186	185	184	183	167	158	150	143	141	137	136
I%	6	26	71	13	26	14	9	9	29	9	6	11	6
m/e	129	128	121	120	117	116	115	110	108	107	105	104	103
I%	5	12	6	25	20	5	17	14	9	6	5	21	6

m/e	98	97	96	95	94	93	92	91	85	84	83	82	81
I%	9	15	66	19	94	5	14	29	7	100	8	11	13
m/e	80	79	78	77	76	75	71	70	69	68	67	65	58
I%	6	7	6	10	13	8	28	51	14	13	7	19	13
m/e	57	56	55	54	53	52	51	50	44	43	42	41	40
I%	16	12	13	8	7	6	9	11	46	69	51	40	6
m/e	39	38	36	32	30	29	28	27	26				
I%	24	5	8	10	13	9	57	19	7				

m^* 320 (449 379), 49.3.

Accurate mass measurements on selected ions:

m/e	Found	Empirical Formula	Required
212	212.143918	$C_{15}H_{18}N$	212.143790
186	186.128268	$C_{13}H_{16}N$	186.127273
158	158.096970	$C_{11}H_{12}N$	158.097557
115	115.054773	C_9H_7	115.054455

2α-(N-Morpholinyl)bicyclo[3.3.1] non-syn-9-yl P-nitrobenzoate.

m/e	374	209	208	150	127	126	121	104	100	93	86	81	79
I%	9	9	62	7	9	100	7	9	5	7	14	7	11
m/e	67	56	55	42	41								
I%	15	7	14	7	11								

m^* 70.3, 35.7.

Ethyl-3-phenyl-3-(8-methyl-3-(N-pyrrolidinyl)-8-azabicyclo[3.2.1]oct-2-yl)propionate.

m/e	370	300	194	193	186	136	122	98	97	96	94	91	84
I%	1	11	14	100	23	7	10	5	30	27	7	6	9
m/e	83	82	70	69	57	56	55	44	43	42	41	32	29
I%	45	38	9	5	22	23	7	5	12	16	20	7	22
m/e	28	27											
I%	36	9											

m^* 95.8, 77.1, 69.3.

2-Benzyl-6-(N-pyrrolidinyl)-2-azabicyclo[3.3.1]nonan-9-one.

m/e	299	298	189	188	179	178	173	172	160	146	136	124	111
I%	4	18	6	34	9	15	12	5	5	7	9	5	12
m/e	110	98	97	96	92	91	84	70	69	68	65	55	54
I%	100	7	53	14	10	7	7	10	10	8	7	8	6
m/e	43	42	41	39	28	27							
I%	9	13	19	8	10	6							

3-Methyl-6α-(N-pyrrolidinyl)-3-azabicyclo[3.3.1]non-anti-9-yl chloroacetate.

m/e	302	300	230	207	206	205	191	162	150	149	148	146	138
I%	2	5	8	7	12	12	5	9	11	6	5	9	12
m/e	137	136	135	134	123	122	120	111	110	109	108	107	98
I%	6	27	8	10	6	19	7	9	60	13	18	19	5

m/e	97	96	95	94	93	91	85	84	83	82	81	80	79
I%	13	19	9	19	9	10	7	100	7	8	7	6	8
m/e	78	77	70	69	68	67	58	57	55	54	53	50	49
I%	5	12	16	9	9	11	50	13	10	8	6	5	5
m/e	44	43	42	41	39	38	37	35	32	31	29	28	27
I%	27	12	27	25	10	94	13	35	5	7	6	24	12

Syn-bicyclo[3.3.1]non-2-en-9-ol.

m/e	121	120	119	105	95	93	92	91	83	81	80	79	78
I%	12	96	6	16	7	10	83	100	6	9	7	41	22
m/e	77	70	69	67	66	65	57	55	54	53	51	40	31
I%	14	15	5	22	9	8	14	11	7	13	8	5	5
m/e	29	27											
I%	8	19											

1-Benzyl-3β-hydroxy-3α-phenyl-piperidine.

m/e	267	176	148	147	146	135	134	120	105	92	91	78	77
I%	1	6	5	38	10	5	48	6	20	10	100	7	17
m/e	65	51	43	42	41	39	38	36	28				
I%	12	6	5	12	9	7	7	24	11				

m^* 145.5, 123, 61.8, 46.5.

X-Ray Results

Two alcohols (77) and (78) were submitted for X-ray analysis. The results are summarised in table 4.

Table 4

Properties	(77)	(78)
Crystal habit	Needles	Needles
Space group	$P2_1/c$	P or $P\bar{1}$
	Needle axis along c.	Irregular form.
Unit cell dimensions		
a	9.69 ± 0.04 Å	9.39 ± 0.09 Å
b	10.60 ± 0.06 Å	9.67 ± 0.10 Å
c	11.87 ± 0.06 Å	12.29 ± 0.12 Å
α	90°	$90.6^\circ \pm 1^\circ$
β	$93^\circ \pm 1^\circ$	$90.4^\circ \pm 1^\circ$
γ	90°	$86^\circ \pm 1^\circ$

Amino-alcohol (78) is most conveniently indexed in the non-standard space group F1 (or $F\bar{1}$). Using the F1 ($F\bar{1}$) axes there is some similarity between the two amino-alcohols, although not enough similarity of axes to infer any similarity of conformation in the molecules.

PHARMACOLOGICAL RESULTS

A number of compounds prepared in the present investigation were subjected to a primary pharmacological screen designed to detect analgesic activity, antimicrobial activity, inhibition of epinephrine biosynthesis, hypo/hyperglycaemic activity, adjuvant arthritis effects, effects on gastric acid secretion and effects on gluconeogenesis.

In the following reports standard notation is used to indicate activity levels.

++ = marked activity

+ = moderate activity

± = negligible activity

- = inactive

(a) Rat adjuvant arthritis activity :- Two compounds (77) and (109) were tested in the rat adjuvant arthritis screen.

COMPOUND	DOSE LEVEL (mg)	PERIOD OF DOSING (DAYS)	SUPPRESSION OF DISEASE
(77)	42	17	+
(109)	23	17	-
Prednisolone	20	17	++

(b) Gastric acid secretion - pylorus ligation :- Two compounds (77) and (143) were tested in the gastric acid secretion test for their effect on gastric juice pH and gastric juice volume. One of the compounds, (143), showed some activity.

COMPOUND	DOSE mg/kg	GASTRIC JUICE pH Increased	GASTRIC JUICE VOLUME Decreased
(77)	50	-	-
(143)	50	-	++

(c) In vitro effect on gluconeogenesis :- Two compounds (75 and 76) and (97) were tested for their effects on gluconeogenesis. Both showed a significant effect at a concentration of $1x10^{-4}M$.

(d) In vivo hypo/hyperglycaemia activity :- Compounds (77) and (143) were tested for their hypo/hyperglycaemia activity at a dose level of 150 mg/kg. Whereas compound (143) was inactive, compound (77) showed decreased blood glucose levels at 1,2, and 4 hours.

(e) Antimicrobial activity :- Compounds (97) and (143) were tested in an antimicrobial screen but both compounds were found to be inactive.

(f) Oxygen transport - in vitro activity :- Compound (97) was tested for its effect on oxygen transport but was found to be inactive.

(g) Parasitological activity :- Compound (143) was tested for its parasitological activity on N. dubius, H. nana, and S. obvelata but was inactive.

(h) Analgesic activity :- Compounds (172) and (176) were tested for analgesic activity by the hot wire tail withdrawal test at a dose level of 100 mg/kg but both failed to produce analgesia when administered to rats.

Table 3

Results for Compound (210).

DOSE mg/kg	ROUTE	TEST	RESULT
100	Oral	Effects on behaviour in mouse	-
100	Oral	Effects on body temperature	-
100	Oral	Effects on pupil diameter	-
	Oral	LD. 50 mg/kg 100	
50	Oral	Anti-maximal electroshock	-
50	S.C.	Antagonism of leptazol induced convulsions	-
50	S.C.	Hot plate a) Direct effect	-
		b) Interact. morphine	-
50	Oral	Effects on phenylquinone induced writhing	-
25	I.P.	Effects on hyper-reactivity of anterior hypothalamic rats	-

BIBLIOGRAPHY

1. L.F. Small, N.B. Eddy, E. Mosettig and C.K. Himmelsbach, "Studies on Drug Addiction", Suppl. No. 138, Washington, D.C., 1938.
2. O. Eisleb and O. Schaumann, Deut. medicin. Woch., 1939, 65, 967.
3. K.A. Jensen, F. Lindquist, E. Rekling and C.G. Wolfbrandt, Dansk. Tidssk. Farm., 1943, 17, 173.
4. A. Ziering and J. Lee, J. Org. Chem., 1947, 12, 911.
5. M.R. Bell and S. Archer, U.S.P. 3058984/1962.
6. C. Cignarella, E. Occelli, G. Maffii and E. Testa, J. Medicin. Chem., 1961, 6, 29.
7. M. Bockmuhl and G. Erhart, Liebigs Annalen der Chemie, 1948, 52, 561.
8. E.C. Kleiderer, J.B. Rice, V. Conquest and J.H. Williams, Report No. PP-981, Office of the Publication Board, Dept. of Commerce, Washington, D.C., 1945.
9. D.W. Adamson and A.F. Green, Nature, 1950, 165, 122.
10. A. Pohland and H.R. Sullivan, J. Amer. Chem. Soc., 1953, 75, 4458.
11. R. Grewe, Naturwissenschaften, 1946, 33, 333.
12. R. Grewe and A. Mondon, Chem. Ber., 1948, 81, 279.
13. E.L. May and L.J. Sargent in "Analgetics", ed. G. de Stevens, Academic Press, New York-London, 1965, vol. 5, p 171.
14. O. Schaumann, Pharmazie, 1949, 4, 364.

15. S. Archer, N.F. Albertson, L.S. Harris, A.K. Pierson and J.G. Bird, J. Medicin. Chem., 1964, 7, 123.

16. N. De Nosaquo, J. Amer. Med. Assoc., 1969, 210, 502.

17. R.H. Hart, Lancet, 1969, ii, 690, 851.

18. S. Jennett, J.G. Barker and J.B. Forrest, Brit. J. Anaesthesia, 1968, 40, 864.

19. J. Neuschatz, J. Amer. Med. Assoc., 1969, 209, 112.

20. Sanky Co. Ltd., B.P. 952,137/1962,
B.P.1142,415/1967.

21. Yoshitomi Pharmaceutical Industries Ltd., F.P. 1,557,671/1969.

22. S. Ohki, S. Oida, Y. Ohashi, H. Takagi and I. Iwai, Chem. Pharmaceut. Bull. (Tokyo), 1970, 18, 2050.

23. S. Kobayashi, K. Hasegawa, T. Oshima and H. Takagi, Toxicol. Appl. Pharmacol., 1970, 17, 344.

24. L.M. Rice and C.H. Grogan, J. Org. Chem., 1958, 23, 844.

25. R.N. Schut, F.E. Ward and R. Rodriguez, J. Medicin. Chem., 1972, 15, 301.

26. H. Meerwein, J. Prakt. Chem., 1922, 104, 161.

27. E. Knoevenagel, Liebigs Annalen der Chemie, 1903, 39, 281.

28. P. Rabe, R.E. Ehrenstein and M. Jahr, Liebigs Annalen der Chemie, 1908, 360, 265.

27[1]. K. Miyano and T. Tagachi, Chem. Pharmaceut. Bull. (Tokyo), 1970, 18, 1806.

28. R.P. Nelson and R.G. Lawton, J. Amer. Chem. Soc., 1966, 88, 3884.

29. E. Buchta and S. Billenstein, Naturwissenschaften, 1964, 51, 383.

30. G. Wittig and H. Blumenthal, Chem. Ber., 1922, 60, 1085.

31. G. Stork, R. Terrell and J. Szmuszkovic, J. Amer. Chem. Soc., 1954, 76, 2029.

32. G. Stork and H.K. Landesman, J. Amer. Chem. Soc., 1956, 78, 5128.

33. G. Stork and H.K. Landesman, J. Amer. Chem. Soc., 1956, 78, 5129.

34. H. Landesman, Ph.D. Thesis, Columbia University, 1957.

35. G. Stork, A. Brizzolara, H.K. Landesman, J. Szmuszkovic and R. Terrell, J. Amer. Chem. Soc., 1963, 85, 207.

36. K. Untch, Ph.D. Thesis, Columbia University, 1959.

37. C.S. Dean, J.R. Dixon, S.H. Graham and D.O. Lewis, J. Chem. Soc.(C), 1968, 1491.

38. W.D. Cotterhill and M.J.T. Robinson, Tetrahedron, 1964, 20, 777.

39. J. Sicher, J. Jonas and M. Tichy, Tet. letts., 1963, 825.

40. I. Fleming and J. Harley-Mason, J. Chem. Soc., 1965, 2165.

41. R.N. Schut and T.M.H. Liu, J. Org. Chem., 1965, 30, 2845.

42. I. Fleming and M.H. Karger, J. Chem. Soc.(C), 1967, 226.

43. K.C. Brannock, A. Bell, R.D. Burpitt and C.A. Kelly, J. Org. Chem., 1964, 29, 801.

44. W.N. Speckamp, J. Dijnink, A.W.J.D. Dekkers and H.O. Huisman, Tetrahedron, 1971, 27, 3143.

45. A.W.J.D. Deckers, W.N. Speckamp and H.O. Huisman, Tet. letts., 1971, 489.

46. W.N. Speckamp, J. Dijkink and H.O. Huisman, J. Chem. Soc.(D), 1970, 196.

47. K. Mitsuhashi and S. Shiotani, Chem. Pharmaceut. Bull. (Tokyo), 1970, 18, 75.

48. W. Schneider and H. Gotz, Naturwissenschaften, 1960, 47, 397.

49. B. Shimizu, A. Ogiso and I. Iwai, Chem. Pharmaceut. Bull. (Tokyo), 1963, 11, 333.

50. H.O. House, P.P. Whickham and H.C. Muller, J. Amer. Chem. Soc., 1962, 84, 3139.

51. C. Weatherbee, W.E. Adcock and D. Winter, J. Org. Chem., 1957, 22, 465.

52. A.Z. Britten, Personal Communication.

53. M. Takeda and E.L. May, J. Medicin. Chem., 1970, 15, 1223.

54. V. Dressler and K. Bodendorf, Tet. letts., 1967, 4243.

55. V. Dressler and K. Bodendorf, Liebigs Annalen der Chemie, 1968, 71, 720.

56. E.F.L.J. Anet, G.K. Hughes, D. Marmion and E. Ritchie, J. Sci. Research (Australia), Ser. A, 1950, 3, 330.

57. F.F. Blicke and F.J. McCarthy, J. Org. Chem., 1959, 24, 1379.

58. H.O. House, H.C. Muller, C.G, Pitt and P.P. Whickham, J. Amer. Chem. Soc., 1963, 28, 2407.

59. E.L. May and H. Kugita, J. Org. Chem., 1961, 26, 188.

60. E.L. May, H. Kugita and J.H. Ager, J. Org. Chem., 1961, 26, 1621.

61. H. Kugita and E.L. May, J. Org. Chem., 1961, 26, 1954.

62. S. Saito and E.L. May, J. Org. Chem., 1961, 26, 4536.

63. S.E. Fullerton, E.L. May and E.D. Becker, J. Org. Chem., 1962, 27, 2144.

64. R.P. Linstead, W.E. Doering, S.B. Davies, P. Levine and R.P. Whetstone, J. Amer. Chem. Soc., 1942, 64, 1985.

65. E.L. Eliel and R.S. Ro, J. Amer. Chem. Soc., 1957, 79, 5992.

66. R.L. Burwell and G.V. Smith, J. Amer. Chem. Soc., 1962, 84, 925.

67. H.C. Brown and K. Ichikawa, J. Amer. Chem. Soc., 1961, 83, 4372.

68. G. Ourisson and A. Russat, Tet. letts., 1960, 21, 16.

69. M.R. Bell and S. Archer, J. Amer. Chem. Soc., 1958, 80, 6147.

70. B.J. Calvert and J.D. Hobson, Proc. Chem. Soc., 1962, 19.

71. W.A.C. Brown, G. Eglinton, J. Martin, W. Parker and G.A. Sim, Proc. Chem. Soc., 1964, 57.

72. W.A.C. Brown, J. Martin and G.A. Sim, J. Chem. Soc. (C), 1965, 1844.

73. I. Laszlo, Rec. Trav. Chim., 1965, 84, 251.

74. N.W. Pumphrey and M.J.T. Robinson, Chem. and Ind., 1963, 1903.

75. M. Dobler and J.D. Dunitz, Helv. Chim. Acta., 1964, 47, 695.

76. M.St.C. Flett, Spectrochim. Acta., 1957, 10, 21.

77. H.E. Hallam, IR Spectroscopy and Mol. Structure, Elsevier, 1963, p. 414.

78. F.A. Mifler and C.H. Wilkins, Analyt. Chem., 1952, 24, 1253

79. G. Brimk and M. Falk, Spectrochim. Acta., 1971, 27A, 1811

80. M. Tichy, in "Advances in Organic Chemistry", Interscience, 1965, vol. 5, p. 115

81. V. Cerny, A. Kassal, and F. Sorm, Coll. Czech. Chem. Comm., 1970, 35, 1235.

82. F. Santavy, M. Horak, M. Maturova and J. Brabenec, Coll. Czech. 1960, 25, 1344.

83. R.E. Lyle, J. Org. Chem., 1957, 22, 1280.

84. M. Svoboda, M. Tichy, J. Fajkos and J. Sicher, Tet. letts., 1962, 717.

85. M. Balasubramanian, Chem. Rev., 1962, 62, 591.

86. H.O. House and B.E. Tefertiller, J. Org. Chem., 1966, 31, 1068.

87. G. Fodor, in "The Alkaloids", ed. R.H.F. Manske, Academic Press Inc., New York, N.Y. 1966, vol. 6, pp. 145-177

88. R.A. Appleton, C. Egan, J.M. Evans, S.H. Graham and J.R. Dixon, J. Chem. Soc.(C), 1968, 1110.

89. J.D. Connolly, R. Henderson, R. McCrindle, K.H. Overton and N.S. Bhacca, J. Chem. Soc., 1965, 6935.

90. A.T. McPhail and G.A. Sim, Tet. letts., 1964, 2599.

91. W.D.D. Macrossan, J. Martin and W. Parker, Tet. letts., 1965, 2589

92. W.F. Erman and H.C. Kretschmar, J. Org. Chem., 1968, 33, 1545.

93. N.C. Webb and M.R. Becker, J. Chem. Soc.(B), 1967, 1319.

94. H. Rapoport and S. Masamune, J. Amer. Chem. Soc., 1955, 77, 4330.

95. T.A. Geissman, B.D. Wilson and R.B. Medz, J. Amer. Chem. Soc., 1954, 76, 4183.

96. L. Pauling, "Nature of the Chemical Bond", Cornell University Press, Ithaca, N.Y. 1949, p. 287.

97. C.P. Rader, G.E. Wicks and H.S. Aaron, Abstracts of Papers, National Meeting of the American Chemical Society, Los Angeles, Calif., April 1963, 40M.

98. C.A. Grob, I.U.P.A.C. Kekule Symposium, Butterworths, London, 1959, p. 114.

99. A. Risaliti, M. Forchiassin and E. Valentin, Tet. letts., 1966, 6331.

100. F. Dalton, G.D. Meakins, J.H. Robinson and W. Zacharia, J. Chem. Soc., 1962, 1556.

101. M.T. Davis, D.F. Dobson, D.F. Hayman, G.B. Jackmann, M.G. Lester, V. Petrow, D. Stephenson and A.A. Webb, Tetrahedron, 1962, 18, 751.

102. A.F. Casy, Tetrahedron, 1966, 22, 2711.

103. R.A. Appleton, K.H. Baggaley, C. Egan, J.M. Davies, S.H. Graham and D.O. Lewis, J. Chem. Soc.(C), 1968, 2032.

104. S.M. McElvain and R. McMahon, J. Amer. Chem. Soc., 1949, 71, 901.

105. H.M.E. Cardwell, J. Chem. Soc., 1950, 1059.

106. P. Brookes and J. Walker, J. Chem. Soc., 1957, 3171.

107. H.C. Brown, R.S. Fletcher and R.B. Johannesen, J. Amer. Chem. Soc., 1951, 73, 212.

108. O.H. Wheeler, J. Amer. Chem. Soc., 1957, 79, 4191.

109. R.E. McCoy, A.W. Baker and R.S. Gohlke, J. Org. Chem., 1957, 22, 1175.

110. N.J. Leonard, R.C. Fox and M. Oki, J. Amer. Chem. Soc., 1954, 76, 5708.

111. R.B. Woodward, F. Sondheimer and Y. Nagur, J. Amer. Chem. Soc., 1958, 80, 6693.

112. G. Opitz and I. Loschmann, Angew. Chem., 1960, 72, 523.

113. W. Schroth and G. Fischer, Angew. Chem., Internat. edn., 1963, 2, 394.

114. R. Noller, "Chemistry of Organic Compounds", p. 810.

115. R.E. Lyle, R.E. Adel and G.G. Lyle, J. Org. Chem., 1959, 24, 342.

116. E.A. Prill and S.M. McElvain, J. Amer. Chem. Soc., 1933, 55, 1233.

117. S.M. McElvain and J.F. Vozza, J. Amer. Chem. Soc., 1949, 71, 896.

118. N.J. Leonard and E. Barthel, J. Amer. Chem. Soc., 1950, 72, 3632.

119. A.E. Kerlin, B.S. Thesis, University of New Hampshire, 1956.

120. R.E. Lyle, E. Perlowski, H. Troscianiec and G.G. Lyle, J. Org. Chem., 1955, 20, 1761.

121. S. Danishefsky and R. Cavanaugh, J. Org. Chem., 1968, 33, 2959.

121[1]. R.F. Zurcher, Helv. Chim. Acta., 1961, 44, 1755.

122. L.M. Jackman, "Applications of NMR Spectroscopy in Organic Chemistry", Pergamon Press, London, 1959, pp. 115-119.

123. M.J.T. Robinson, Tet. letts., 1968, 10, 1153.

124. N.W.J. Pumphrey and M.J.T. Robinson, Chem. and Ind., 1963, 1903.

125. N.S. Bhacca and D.H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry", Holden-Day, Inc., London, 1964, p. 79

126. NMR Spectra Catalog, Varian Associates, Palo Alto, California, Spectrum No. 361.

127. I. Matsuo, K. Sugimoto and S. Ohki, Chem. Pharmaceut. Bull. (Tokyo), 1968, 16, 1680.

128. L. Baiocchi, M. Giannangeli and G. Palazzo, Gazz. Chim. Ital., 1972, 102, 36.

129. L. Baiocchi and M. Giannangeli, Annali Di Chemica, 1970, 60, 454.

130. G. Palazzo and L. Baiocchi, Gazz. Chim. Ital., 1969, 99, 1068.

131. R. Lygo, J. McKenna and I.O. Sutherland, Chem. Comm., 1965, 356.

132. G. Spiteller and M. Spiteller-Friedmann, Angew. Chem., 1965, 4, 383.

133. W.M. Bryant, A.L. Burlingame, H.O. House, G.G. Pitt and B.E. Tefertiller, J. Org. Chem., 1966, 31, 3120.

134. J.H. Beynon, "Mass Spectrometry and its Applications to Organic Chemistry", Elsevier Publishing Co., New York, N.Y. 1960.

135. H.O. House and H.C. Muller, J. Org. Chem., 1962, 27, 4436.

136. H. Budzikiewicz, C. Djerassi and D. Williams, "Mass Spectrometry of Organic Compounds", Holden-Day, Inc., London, 1967, pp. 297, 394.

137. G. Eglinton, J. Martin and W. Parker, J. Chem. Soc., 1965, 1243.

138. W.A.C. Brown, J. Martin and G.A. Sim, J. Chem. Soc., 1965, 1844.

139. M. Dobler and J.D. Dunitz, Helv. Chim. Acta., 1964, 47, 695.

140. C.Y. Chen and R.J.W. Le Fevre, Tet. letts., 1965, 737.

141. L. De Vries and C.P. Ryason, J. Org. Chem., 1961, 26, 621.

142. M. Stoll, B. Willhalm and G. Buchi, Helv. Chim. Acta., 1955, 38, 1573.

143. R. Mecke and H. Spiesecke, Chem. Ber., 1955, 88, 1977.

144. Supplied by Prof. V. Cerny, cf. ref. 81.

145. L.A. Paquette, J. Org. Chem., 1964, 29, 2854.

146. L.M. Berkowitz and P.N. Tylander, J. Amer. Chem. Soc., 1958, 80, 6682.

147. N. Elming and P. Nedenskov, B.P. 791,770/1958.