SOME CYCLOHEXANE DERIVATIVES OF POTENTIAL BIOLOGICAL INTEREST

BY

GEORGE BRYAN AUSTIN VEITCH

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Pharmacy Department,

University of Aston in Birmingham,

Gosta Green,

Birmingham 4 7ET.

SUMMARY

Research involving the structural modifications of morphine, methadone, pethidine and prodine with emphasis on the structure-activity relationships has been reviewed. The mechanism of analgesic action including receptor site theory has been surveyed.

In the hope of obtaining compounds of biological interest some basic derivatives of 1-tetralin have been synthesised and assessed pharmacologically. The route adopted consisted of Mannich additions to 1-tetralone to give the basic ketones. These ketones were reduced to the corresponding tertiary alcohols, acylation of which was only partially successful. The alcohols and esters were theoretically capable of existing in stereoisomeric forms but successful separation of these was only achieved in the case of 2-(3-azabicyclo [3,2,2] nonylmethyl)-1-phenethynyl-1,2,3,4-tetrahydronaphth-1-ols.

Selected compounds were tested for pharmacological activity but the C.N.S. activity was found to be slight and no useful correlation between structure and activity could be made.

Some basic derivatives of cyclohexane have also been prepared and assessed pharmacologically. The route adopted consisted of the modified Tieman-Strecker synthesis to give α-aminocyclohexylnitriles in which the amino function is dimethylamino, piperidino, pyrrolidino, azabicyclo [3,2,2] nonano or N-methylpiperazino. Reactions of these α-aminonitriles with Grignard reagents and lithium aluminium hydride have been compared with respect to their ability to bring about nitrile replacement and an S_N1 mechanism is proposed for this reaction.

The α-aminonitriles were hydrolysed with sulphuric acid to give the corresponding amides, reduced with lithium aluminium hydride to give the primary amines and reduced with phenyl lithium to yield the arylimines.

The primary amines were formylated and reduced in a four stage synthesis, benzoylated and acetylated while the arylimines were hydrolysed to the corresponding arylketones which were reduced to secondary alcohols and acylated.

Selected compounds were tested for potential C.N.S. activity, several of which proved to have analgesic properties. Tentative correlations between structure and activity have been proposed.

The i.r. spectra of all, and the n.m.r. spectra of a few of the new compounds have been recorded.

A brief consideration of the mass spectra of a selection of the 1-tetralones, 1,2,3,4-tetrahydronaphth-1-ols and 1-(1-substituted cyclohexyl)-4-methylpiperazines has been recorded and possible fragmentation pathways for these compounds have been suggested.

To my parents

and my wife.

ACKNOWLEDGEMENTS

I wish to express my gratitude to Professor D. G. Wibberley and Dr. N. J. Harper for their help and encouragement throughout the course of this work.

I am also indebted to Allen and Hanburys Ltd. for carrying out the pharmacological screening reported in this thesis.

CONTENTS

PART II

PART I

SECTION I

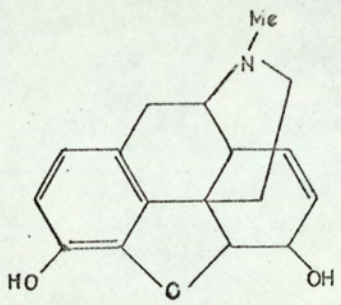
HISTORICAL

SECTION I

A: A general survey of analgesics

Pain is usually described as an unpleasant syndrome of sensations experienced by all members of the human race from time to time. This sensation of pain appears to vary in degrees of severity among individuals, some appearing to have a higher pain threshold than others and thus being better fitted to cope with the attendant physical and psychological stresses. The alleviation of pain has taxed the minds of medical scientists in every generation. A compound which depresses the sensation of pain by increasing the pain threshold without causing loss of consciousness is termed an analgesic. Most extant, historical documents describe the use of opium in the relief of pain from the time of the Sumerians about 5,500 years ago. With the isolation of the alkaloid morphine (1) from opium by Sertuerner in 1803 and the subsequent establishment of the prime importance of this compound as the analgesic ingredient, the first major breakthrough was achieved. Since then, many attempts have been made to produce a compound with similar analgesic properties but free from the undesirable, addictive and respiratory depressant side effects of morphine. Early attempts to overcome these side effects involved many modifications of the morphine molecule and concurrently, the synthesis of compounds based on fragments of the morphine structure was used as an alternative approach in order to incorporate certain structural features which were becoming important factors in structure-activity relationships (Small et al., 1938).[1] During the course of these investigations several compounds were produced which showed enhanced analgesic activity, but few were clinically useful.

In 1939, Eisleb and Schaumann[2] investigated pethidine (2) as a potential anti-spasmodic agent and made the fortuitous discovery that it possessed considerable analgesic activity. This provided the stimulus for research into structurally similar morphinomimetic compounds. During the course of this research Jensen et al.[3] 1943, discovered that the reversed ester of pethidine (3) was significantly more active than pethidine. An extensive study in this area by Ziering and Lee[4] led to the introduction in 1947 of the alpha- and beta-prodines (4 a,b) as potent analgesics.



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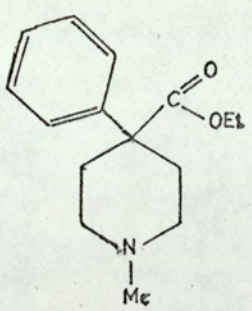

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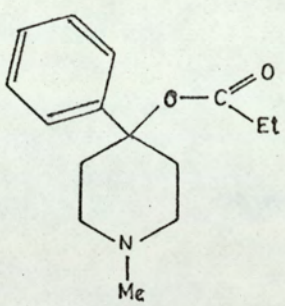

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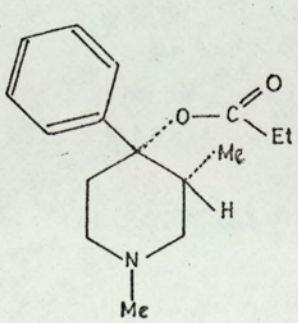

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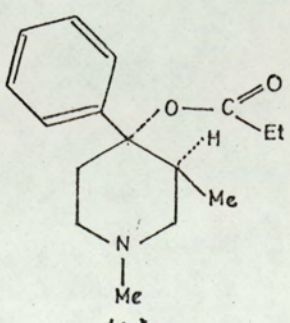
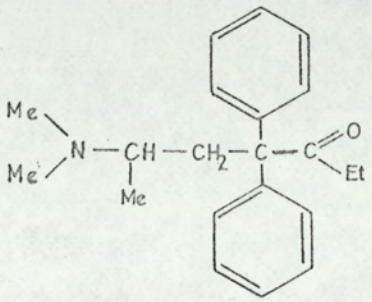


(b)

Meanwhile, during the course of World War II, Blockmühl, Ehrhart and Schaumann had investigated a new class of potent, synthetic analgesics, the diphenylpropylamines. With the cessation of hostilities a report was published in America (Kleiderer et al., 1945)[5] of war-time research in Germany. This described the synthesis of methadone (5) as the first basic, acyclic analgesic with a potency five to ten times that of pethidine.



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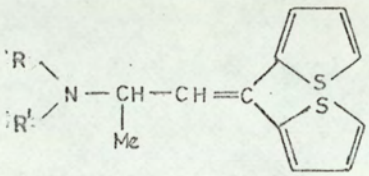

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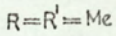
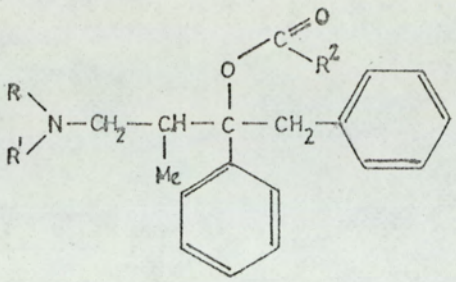


(7)

A number of independent groups then began working on methadone derivatives and in 1950, Adamson and Green[6] published their findings concerning a new series of potent analgesics, the dithienylbutenylamines (6). In this series, dimethylthiambutene (7) was found to be slightly less active than morphine.

Modification of the diphenylpropylamine analgesics by removal of one phenyl group from the quaternary carbon atom led to another series of moderately potent, orally effective analgesics, the 3-acyloxy-3-phenylbutylamines (8) or propoxyphenes. Compounds in this series were developed by Pohland and Sullivan[7] in 1953 and of these (+)-propoxyphene (9) has a fairly wide use.



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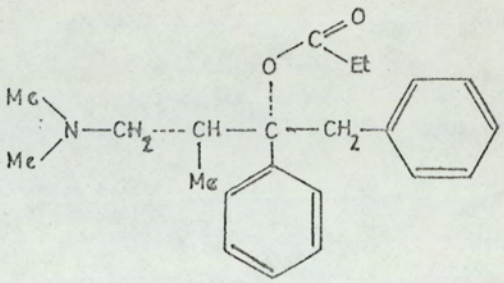

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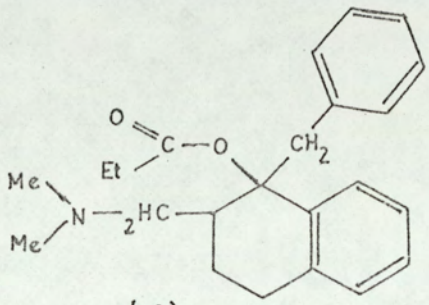

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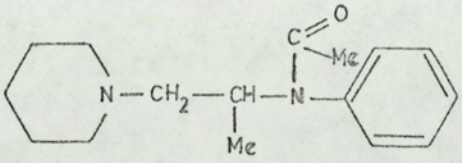
Cyclised propoxyphene analogues of tetrahydronaphthalene (10) have recently been reported independently by Patchett and Giarrusso[8] and de Stevens *et al.*[9]

In 1959, Wright *et al.*,[10] produced a new, more flexible series of analgesics in which the quaternary carbon atom and one of the phenyl groups of methadone were replaced by nitrogen. In this group of basic anilides, phenampromid (11) and diampromid (12) have been shown to be narcotic analgesics and extending this work Janssen [11,12] produced Fentanyl (13) with a potency 270 times that of morphine (rats, s.c.).



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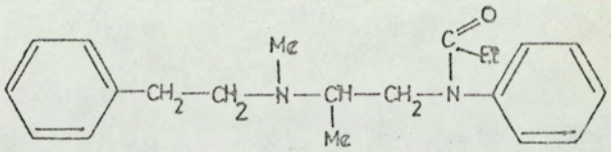

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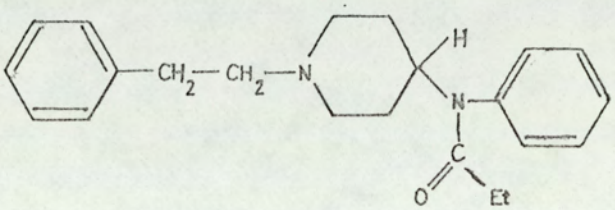
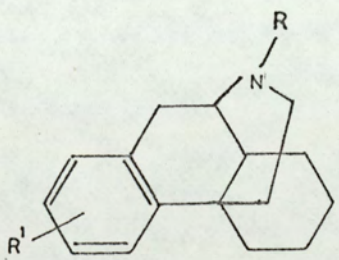


(13)

Concurrent with this synthetic work on morphinomimetics many attempts had been made to modify morphine by total synthetic procedures. As a result of this work some new, clinically useful narcotic analgesics have been introduced, eg. the morphinans (14) and the benzomorphans (15).



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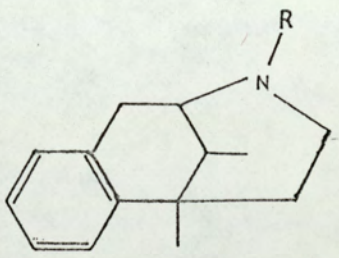

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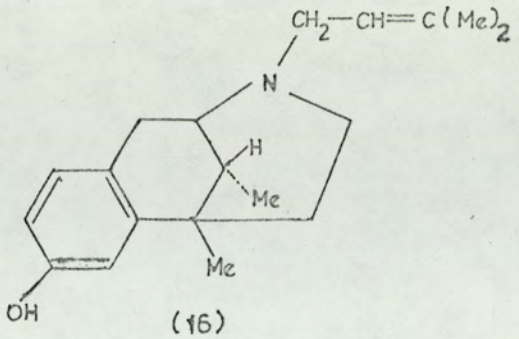
However, these compounds retain the undesirable properties of addiction liability and respiratory depression. When this work was extended to the narcotic antagonists, success was achieved with the synthesis of pentazocine (16).



(16)

Keats and Telford[13] (1964), reported the analgesic activity of pentazocine in the potency range of morphine. Jennett et al.,[14] (1968) have shown that it produces less respiratory depression than morphine in equianalgesic doses but De Nosaquo[15] and Neuschatz,[16] cast doubts on earlier claims of freedom from addiction liability on injection while Hart[17] has claimed this possibility even on oral administration.

A number of excellent reviews on morphine and synthetic analgesics have appeared (Bergel and Morrison,[18] 1948; Beckett,[19] 1952; Braenden, Eddy and Halbach,[20] 1955; Reynolds and Randall,[21] 1957; May,[22] 1960; Beckett and Casy,[23] 1962, 1965; de Stevens,[24] 1965; Portoghese,[25] 1966; Haller,[26] 1968; Janssen and Van der Eycken,[27] 1968; Harris and Dewey,[28] 1967.

In addition several citations occur in Portoghese[29] 1970 and a further review appeared in Ellis and West[30] Vol. 7, 1970. However, since the scope of the present work most closely approaches analogues of pethidine and methadone a more detailed discussion will be confined to these areas.

Pethidine and analogues.

The fortuitous discovery of the analgesic activity of pethidine (2) by Eisleb and Schaumann in 1939 provided the impetus for research into the 4-phenylpiperidines. Many analogues of pethidine were synthesised

and by about 1955 several general structure-activity relationships were recognised in this area.[31,23]

(a) With few exceptions any compound with a substituted 4-phenyl ring had lower activity, (m-hydroxy; bemidone; 1.5 times the activity of pethidine was one exception).

(b) Compounds with a 4-ethoxycarbonyl function proved to be more active than those containing methyl or higher alkyl esters. Derivatives with a "reversed ester" function usually had higher activity.

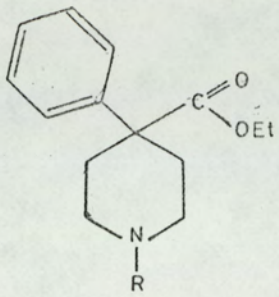
(c) Where compounds contained a phenyl and/or ethoxycarbonyl group in any position other than 4- they had less activity.

(d) Those compounds with a N-1-methyl group were considered to provide the structural conditions for optimal activity.

The discovery that N-phenethylnormorphine and N-phenethylnorpethidine had higher activity than their corresponding N-methyl compounds (Clark et al.,[32] 1953, Perrine and Eddy,[33] 1956) directed research efforts into investigating the effects of the nitrogen substituent. By this means large increases in potency were achieved (Table 1), but invariably accompanied by similar increases in the undesirable side effects.

TABLE 1.

1-Substituted Norpethidine Derivatives

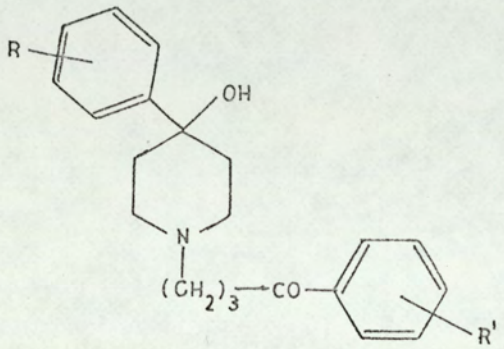


R	ACTIVITY*	CLINICAL COMPOUND
CH_3	1.0	Pethidine
$C_6H_5CH_2CH_2$	2 - 3	Pheneridine
$p\text{-}NH_2.C_6H_4CH_2CH_2$	3	Anileridine
$C_6H_5NH(CH_2)_3$	9	Piminodine
$C_6H_5NH(CH_2)_2$	60	Win. 13,797
$C_6H_5CO(CH_2)_2$	100	R. 951
$C_6H_5CH.OH(CH_2)_2$	150	Phenoperidine

* Compared with pethidine, using mice in the Eddy hot-plate test.

Compound R.951 was prepared as one of a series of 44 Mannich bases by Janssen *et al.*[34] (1959) using a variety of aromatic substituents but all were less active than this parent compound. Reduction to the corresponding alcohol phenoperidine, was reported by Janssen and Eddy[35] in 1960 and the enantiomers of this compound were resolved by Mazur[36] (1961). The (-)-isomer was found to be twice as active and the (+)-isomer half as active as the racemate, showing that the configuration of the side chain can play an important role.

Work by Janssen et al.[37] (1959), had produced a series of 4-piperidinols (17), where R = H, F; R^1 = H,F,Cl,CH_3. These compounds, although active in the hot-plate test, were not antagonised by nalorphine, were devoid of mydriatic activity and thus they were regarded as general C.N.S. depressants. Haloperidol (17, R = p-Cl, R^1 = p-F) was found to be a useful neuroleptic drug.



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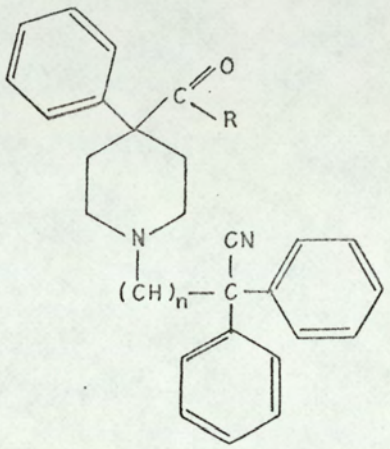

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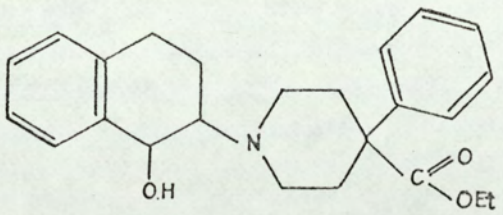


(19)

This work led to the synthesis of similar compounds by Janssen et al.[38] (1959) and Janssen[11] (1962) in series (18). An unusual feature of these compounds was a dissociation of morphine-like analgesic effects with a retention of physical dependence capacity and reduction of gastro-intestinal movement. Hence they were anti-diarrhoeal agents and also showed antitussive properties, the most effective being diphenoxylate (18, R = OC_2H_5, n = 2). This compound is related structurally to both

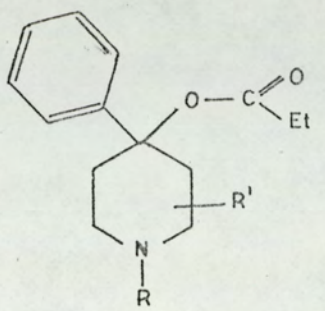
pethidine (2) and methadone (5). Of further interest to the present work was the synthesis of tetralin derivatives (19) by alkylation of norpethidine[39].

The reversed esters of pethidine

The enhancement of analgesic activity by replacing the ethoxycarbonyl group in pethidine with a reversed ester function was reported by Jensen et al.[3] in 1943. This compound was investigated independently at Roche Laboratories and in 1947 Ziering and Lee[4] described the synthesis and separation of the two diastereoisomeric forms of 1,3-dimethyl-4-phenyl-4-propionoxypiperidine (4 a,b). The hydrochlorides of these compounds were given the approved names of Alphaprodine and Betaprodine. Research in this prodine series, like work in the pethidine series, became directed towards changing structural features in order to enhance activity and minimise side effects. Structure-activity relationships were found to resemble those of the pethidine group :- the propionoxy esters were generally the most active, substitution on the 4-phenyl ring reduced activity and the 1-methyl group was thought to confer optimal activity. In addition the reversed esters were generally more active than the corresponding pethidine compounds and the 3-alkyl group increased the stereochemical complexity of the molecule and often increased analgesic activity. Research again paralleled that in the pethidine series with the investigation into nitrogen substituent effects (Table 2), in the presence and absence of the 3-alkyl function.

TABLE 2

1-substituted-4-acyloxy-4-phenylpiperidines



R	R^1	ACTIVITY *
PETHIDINE		1.0
CH_3	3-CH_3 (α -prodine)	5.0
CH_3	3-CH_3 (β -prodine)	14.0
$C_6H_5CH_2CH_2$	3-CH_3 (α)	23 **
$C_6H_5CH_2CH_2$	3-CH_3 (β)	110 **
$C_6H_5NH.CH_2CH_2$	H	1300 ***
$C_6H_5CH(OH)(CH_2)_2$	H	3200 ***

* Compared with Pethidine, using mice in the Eddy hot-plate test except where authors are quoted.

** Beckett et al.,[40] (1959)

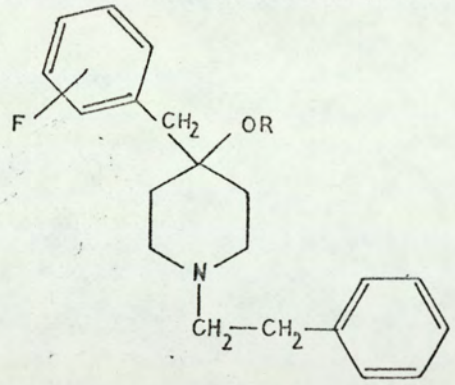
*** Carabateas and Grumbach,[41] (1962)

Therefore these results are not strictly comparable.

A lack of consistency was found between the relative activities of α- and β-isomers when variations were made in the 3-position, eg. the 3-C_2H_5(α) and 3-C_2H_5 (β) isomers showed activities of 8 : 1 and 5.5 : 6.3 respectively in different laboratories. The 3-allyl derivative was found to impose the upper size limit on 3-substituents with good activity.

The 1,3-diallyl derivative in these less rigid molecules did not produce antagonistic effects as in the rigid N-allylmorphine. In fact, the compound showed increased analgesic potency and a high physical dependence capacity in monkeys. The 3-phenyl compounds related to α- and β-prodine were investigated by Patchett and Giarrusso[42] in 1961. Synthesis and chromatographic separation of the 3-phenyl-4-acetoxy and 3-phenyl-4-propionoxy compounds gave a 7 : 1 preponderance of the α-isomers but all the compounds lacked analgesic activity. These compounds are of interest in that they may also be considered as cyclic analogues of the propoxyphenes (8) in which only the α-isomers show moderate analgesic activity.

With enhanced activity shown in the prodine class of analgesics where N-CH_3 was replaced by N-$CH_2CH_2.C_6H_5$ Harper and Simmonds[43] (1959) studied the effect of introducing fluorine in compounds (20) and (21).



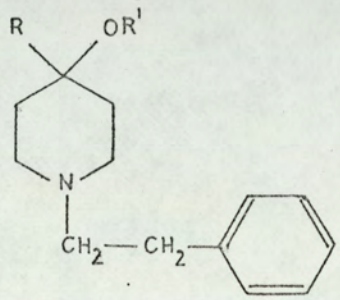
(20) R=H

(21) R=C(=O)Et

Two such compounds (20, p-F) and (20, o-F) in the hot-plate test showed high activity whereas the m-F isomer was inactive and all three lacked significant, mydriatic activity. It was therefore concluded that these compounds were C.N.S. depressants of a non-morphine type. The corresponding esters (21) of these compounds showed a marked loss of activity which is in contrast with morphine-like analgesics of the α- and β-prodine type.

Harper and Fullerton[44] (1961) then produced a similar series of N-phenethyl compounds in which the 4-phenyl group was replaced by

acetylene (22), substituted acetylenes (23, 24) and substituted ethylenes (25). The object was to investigate whether the aromatic function could be replaced by non-aromatic groups which nevertheless possessed a π-electron cloud.



(22) R= $HC\equiv C-$

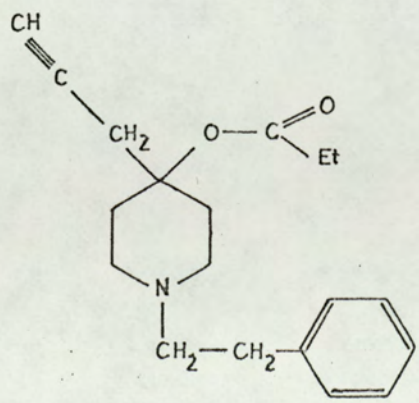
(23) R= $C_6H_5-C\equiv C-$

(24) R= $CH_3-(CH_2)_3-C\equiv C-$

(25) R= $C_6H_5-CH=CH-$

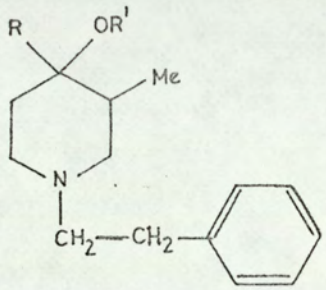
(26) R= $C_6H_5-CH_2-CH_2-$

A few of these compounds were reduced to the corresponding, fully saturated, phenethyl derivatives (26). When assessed by the hot-plate technique only the phenethynyl derivative (23, R^1 = H), butylethynyl derivative (24, R^1 = H) and 4-phenethyl derivatives (26, R^1 = H, $COCH_3$) showed significant activity. This activity was associated with a general depressant effect on the central nervous system rather than an analgesic effect. Reduction to the cis- and trans-styryl compounds (25) resulted in a loss of activity. In 1963, Deltour et al.[45] evaluated another compound very similar to those of Harper and Fullerton. This compound known under the generic name of propinetidine (27) has antitussive activity and no true morphine-like actions.



(27)

Thus, there is strong evidence that the 4-phenyl group cannot be successfully replaced by a non-aromatic group with a π-electron cloud, nor can it be separated from the 4-position by a vinyl, ethynyl or ethylene moiety with retention of morphine-like activity. This view received further support from Beckett *et al.*[46] (1960) who had successfully substituted a heterocyclic ring in the 4-position of compounds of type (28). This type of isosteric replacement resulted in a loss of analgesic activity which can also be attributed to steric as well as electronic factors.



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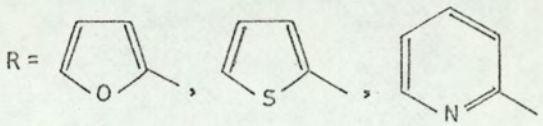
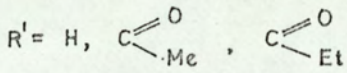
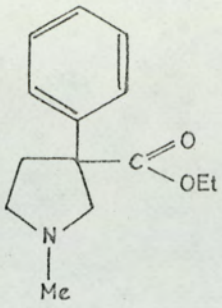


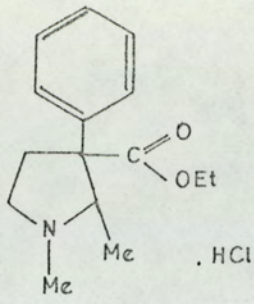


In this latter work several 4-alkoxy derivatives with significant activity were produced. The furyl derivative (28, R = 2-furyl, $R^1 = C_2H_5$) was several times more active than pethidine in mice and had a low toxicity. However, the higher and lower alkyl ethers were much less active as were those analogues with no 3-methyl substituent.[47]

In connection with both pethidine and its reversed esters attention has also been focussed on the five, seven- and eight-membered ring analogues. A pyrrolidine analogue (29) of pethidine was first described by Bergel *et al.*[48] in 1944, but was devoid of activity. When other related pyrrolidines were found to be inactive by Woods *et al.*[49] (1954) the area lay dormant for a number of years.

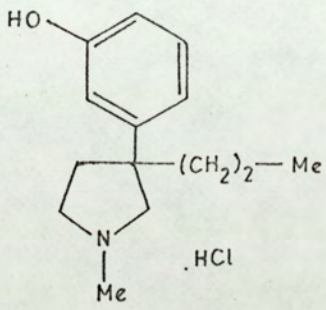


(29)

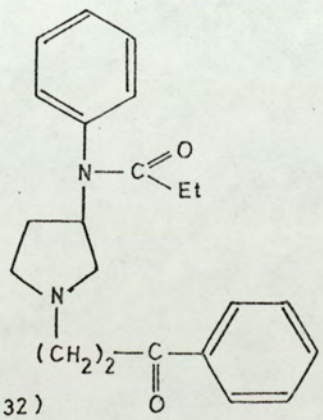


(30)

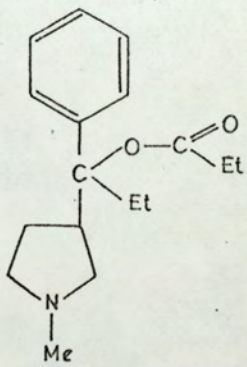
In 1961, Cavalla et al.[50] reported the synthesis, and Cass and Frederik[51] the screening, of the pyrrolidine analogue of α-prodine, prodilidine (30). The analgesic potency of this compound is very close to that of codeine when given orally, but much less potent when administered parenterally. This finding revitalised work in the pyrrolidine field which has culminated, to date, in the synthesis of profadol (31) by Cavalla et al.[52] Profadol has been shown to have one quarter the activity of morphine in clinical trials[53] and a detailed account of the compound was published by Bowman[54] in 1969. Two further pyrrolidines are worthy of note, (32) which was reported as being three times as active as morphine[55] and (33) judged to be as active as propoxyphene.[56]



(31)



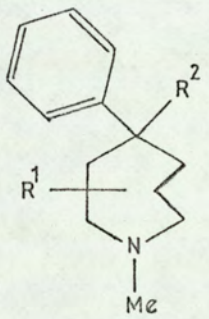
(32)



(33)

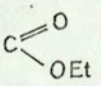
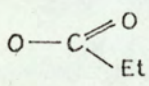
Seven- and eight-membered ring analogues of pethidine and prodine are less active than corresponding six-membered compounds and hence their study has been limited. The seven-membered ring analogue of pethidine,

ethoheptazine (34, $R^1 = H$, $R^2 = COOC_2H_5$), was synthesised independently in two laboratories[57,58] in 1953 and 1954. Activity was equal to that of codeine in man[59] and about half that of pethidine in mice,[60] but tests showed no evidence of addiction liability. The 3-methyl derivative of ethoheptazine (34, $R^1 = 3\text{-}CH_3$, $R^2 = COOC_2H_5$) has greater analgesic activity than the parent compound, in keeping with the improved activity shown when the 3-methyl substituent was introduced into pethidine. The activity results for the reversed ester (34, $R^1 = 3\alpha\text{-}CH_3$, $R^2 = OCOC_2H_5$), proheptazine,[61] also paralleled the prodine findings when it was found to have increased analgesic potency compared with the ethoxycarbonyl derivative, but it also showed high physical dependence in monkeys.



(34)

R^1 = H, 3–Me, 3α–Me

R^2 =  , 

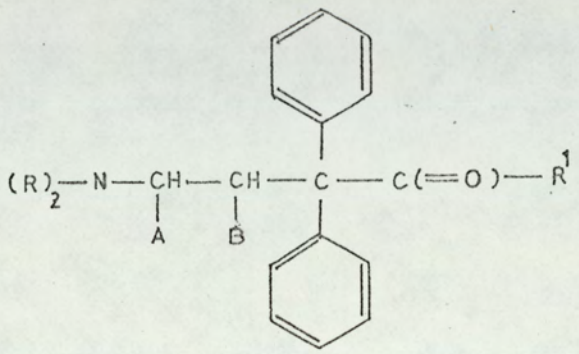
The eight-membered ring analogues of ethoheptazine and proheptazine were synthesised[62,63] but were of little analgesic interest.

Methadone and analogues

The diphenylpropylamine group of synthetic morphine-like analgesics was established in Germany during World War II. The American report[5] which included this work initiated the synthesis and analgesic screening of hundreds of diphenylpropylamines which have been reviewed through 1952 by Carney[64] and to mid-1958 by Janssen.[65] Methadone (5) was the parent clinical compound from which most of the work began. Table 3 illustrates some of the ketone derivatives of diphenylpropylamines which have clinical value.

TABLE 3.

Diphenylpropylamine Derivatives - Ketones



$(R)_2N$	A	B	$C(=O)R^1$	ACTIVITY *
MORPHINE				0.8
PETHIDINE				0.17
$(CH_3)_2N$	CH_3	H	COC_2H_5 (dl-methadone)	1.0
$(CH_3)_2N$	CH_3	H	COC_2H_5 (-)	2.0
$(CH_3)_2N$	CH_3	H	COC_2H_5 (+)	0.07
$(CH_3)_2N$	H	CH_3	COC_2H_5 (dl-isomethadone)	0.7
$(CH_3)_2N$	H	H	COC_2H_5 (normethadone)	0.7
$C_5H_{10}N$(a)	CH_3	H	COC_2H_5 (dipipanone)	0.9
$C_5H_{10}N$(a)	H	H	COC_2H_5 (hexalgon)	0.7
OC_4H_8N(b)	CH_3	H	COC_2H_5 (phenadoxone)	1.6

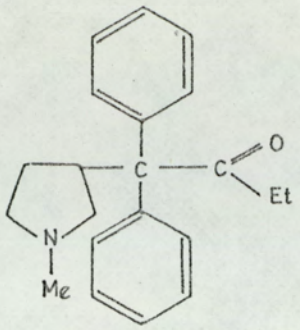
* Analgesic activity, compared with methadone, using mice in the Eddy hot-plate test.

(a) = piperidino.

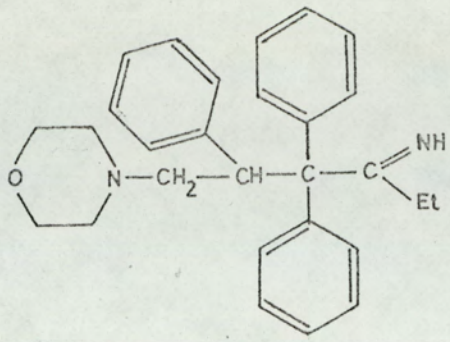
(b) = morpholino.

Methadone, while retaining the undesirable morphine-like side effects, showed less severe withdrawal symptoms and has been used in addiction

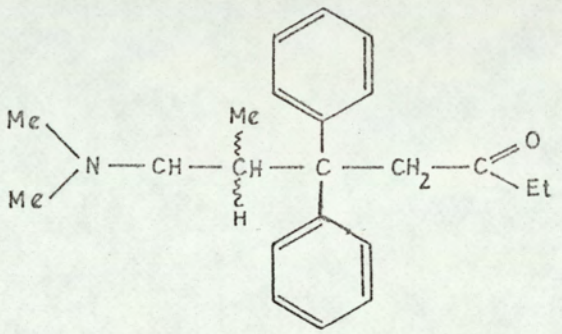
clinics for the withdrawal of patients from morphine. Separation of the (+) and (-) isomers revealed that the activity resided almost entirely in the (-) form. When the basic group was altered, clinically useful compounds were obtained from piperidino and morpholino variants (Table 3), but both of these major alternatives to methadone, dipipanone and phenadoxone, showed addiction liability. Most higher and lower alkyl variants at the ketone function of the molecule reduced activity. In the central C-chain of the molecule introduction of a methyl group at position B (isomethadone) or a lack of a methyl group at A and B (normethadone) had similar effects on analgesic potency and this is the limit of variation in the alkylene chain for retention of good activity. These general findings in structure-activity relations in the methadones are supported by more recent work by three groups of workers viz :- the pyrrolidine analogue (35) was synthesised by Ames,[66] (1960) and found to be less active than methadone while the corresponding N-phenethyl compound was inactive. In the second group Shapiro et al.[67] (1959) synthesised the methadone analogues with an additional aryl function, but limited success was obtained only in a ketimine derivative (36), which was one fifth as potent as methadone. Finally, Patchett and Giarrusso[68] were unsuccessful in their attempts to produce active methadone homologues (37).



(35)



(36)

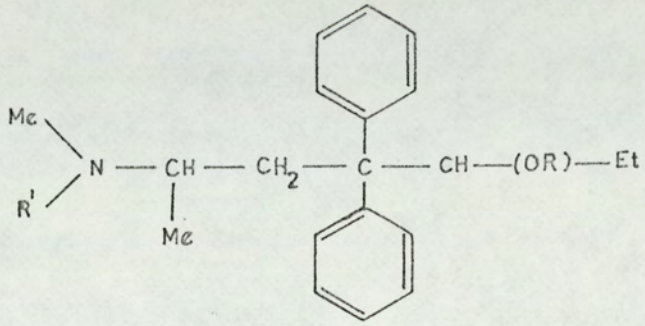


(37)

Reduction of methadone with catalysts or lithium aluminium hydride gave only one isomeric secondary alcohol but sodium/propanol reduction gave both α - and β-methadol. Subsequently both (+)- and (-)-methadone were reduced to give the four possible isomers of methadol[69] which were acetylated to give acetylmethadols (Table 4).

TABLE 4.

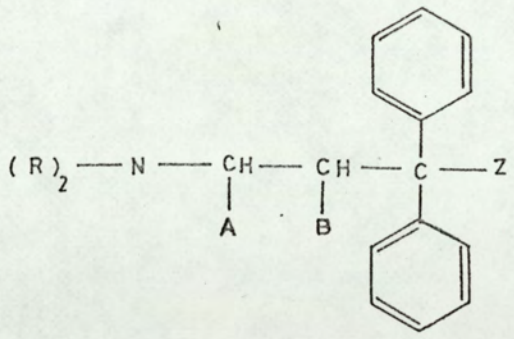
Diphenylpropylamine derivatives - Alcohols and Acylated Compounds



R	R'	ISOMER		ED.50 mg /kg
H	CH_3	α-(-)		3.5
H	CH_3	β-(+)	FROM	63.7
$COCH_3$	CH_3	α-(-)	(+)-METHADONE	1.8
$COCH_3$	CH_3	β-(+)		4.1
H	CH_3	α-(+)		24.7
H	CH_3	β-(-)	FROM	7.6
$COCH_3$	CH_3	α-(+)	(-)-METHADONE	0.3
$COCH_3$	CH_3	β-(-)		0.4
$COCH_3$	H	α-$(\overset{+}{-})$	(NORACIMETHADOL)	0.48

A detailed account of these isomers has been prepared by Janssen.[65] Clinical utility has been rather limited. α-acetylmethadols in the form of the racemate and both optical isomers were tried in 1952 and more recently the monomethylamino derivative, noracimethadol was studied.[70] This latter compound appeared to have some advantages over morphine such as longer duration of activity but it retained addiction liability.

Another closely related group of compounds (39-42) in which the alkyl ketone group was replaced by a tertiary amide moiety has also been shown to possess potent morphine-like activity. Although similar compounds (38) were known by Walton *et al.*[71] in 1949 it was not until 1956 that Janssen[72] demonstrated the analgesic properties of further derivatives in this series. Janssen and Jageneau[73] found that *N*-pyrrolidino and dimethylamino-amides were the most active and of these, dextromoramide (39) has been the subject of extensive clinical enquiry. This compound with an α-methyl group in the side chain has significantly more activity than its β-methyl isomer (cf. methadone-isomethadone). Compounds in this series containing a morpholino group were more active than those containing piperidino (40), pyrrolidino (41) and dimethylamino (42) groups. Those compounds containing quaternised amine functions were inactive.



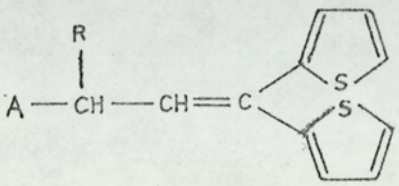
	$(R)_2N$	A	B	Z	
(38)	H_2N	(H,CH_3)	(H,CH_3)	$CONHC_4H_9$	
(39)	OC_4H_8N	H	CH_3	$CONC_4H_8$	(+)-DEXTROMORAMIDE
(40)	$C_5H_{10}N$	H	CH_3	$CON(CH_3)_2$	
(41)	C_4H_8N	H	CH_3	$CONC_4H_8$	
(42)	$(CH_3)_2N$	(H,CH_3)	(H,CH_3)	$CONC_4H_8$	

Dextromoramide was shown to have a short onset of action, very slow development of tolerance, no constipating effect and was almost as active on oral administration as by injection. In clinical trials in the United States and Europe it was shown to be a potent drug with similar actions to morphine and pethidine but without significant advantages over these well established drugs.

In 1950 during a period of intensive work on methadones and related structures Adamson and Green[6] used isosteric replacement of the phenyl groups of methadone in a new family of dithienylbutenylamines. Antispasmodic and local anaesthetic activity has been claimed for members of this group,[74] but reference is made only to those showing morphine-like activity. (Table 5). Analgesic potency in this series was limited to analogues of the tertiary amine function of which (44) was the most potent. The pyrrolidino (46) and piperidino (47) analogues also had good activity, but the morpholino compound (48) was less active. In the central carbon chain the branched methyl group was optimal as both hydrogen and other alkyl groups in this position resulted in less active compounds whilst hydrogenation of the double bond also reduced activity. If one of the thienyl groups is replaced by phenyl a compound with reduced activity is encountered. In the clinical trials,[75] ethylmethylthiambutene (44) was found to be the most potent and this required a 50 mg dose to equal the effect of 10 mg of morphine. Equipotent doses of ethylmethylthiambutene and morphine exhibited equivalent respiratory depressant and addiction liability effects. Dimethylthiambutene (43) has been used clinically in Japan.

TABLE 5

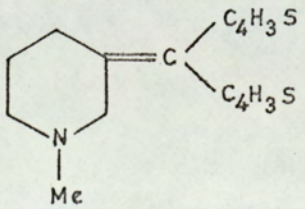
Dithienylbutenylamine derivatives



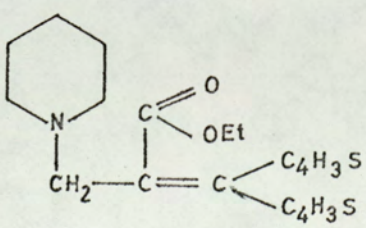
COMPOUND NO.	A	R	ACTIVITY *
MORPHINE			1.0
(43)	$(CH_3)_2N$	CH_3 (DIMETHYLTHIAMBUTENE)	0.7
(44)	$C_2H_5(CH_3)N$	CH_3	0.9
(45)	$(C_2H_5)_2N$	CH_3	0.5
(46)	C_4H_8N	CH_3	0.4
(47)	$C_5H_{10}N$	CH_3	1.0
(48)	OC_4H_8N	CH_3	0.3

* Analgesic activity, compared to morphine, Eddy hot-plate test in mice.

Few additional variations of the thiambutene structure have been reported but two piperidino compounds (49) and (50) have been claimed in Japan[76,77] to have analgesic or antitussive activity.



(49)

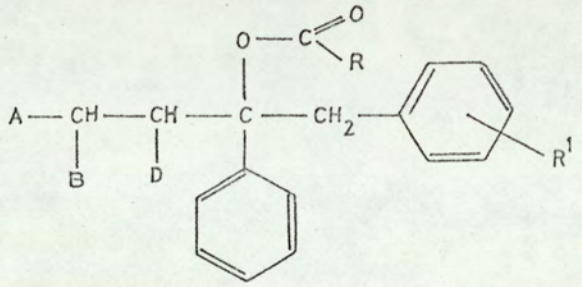


(50)

A further modification of diphenylpropylamine analgesics in the form of 3-phenyl-3-acyloxybutylamines or propoxyphenes (8) was introduced by Pohland and Sullivan[7] in 1953. Some members of this series are shown in Table 6 and it appears that retention of analgesic activity is associated with narrowly defined structural requirements.

TABLE 6

3-Phenyl-3-acyloxybutylamine derivatives



COMPOUND NO.	A	B	D	R	R^1	ACTIVITY*
PETHIDINE						1.0
(51)	$(CH_3)_2N$	H	CH_3	C_2H_5 (dl-α-; PROPOXYPHENE)	H	0.4
(52)	$(CH_3)_2N$	H	CH_3	C_2H_5 [(+)-α]	H	1.3
(53)	$(CH_3)_2N$	H	CH_3	C_2H_5 [(-)-α]	H	0
(54)	$(CH_3)_2N$	H	CH_3	C_2H_5 (dl-β)	H	0[7]
(55)	$(CH_3)_2N$	H	CH_3	CH_3[(+)-α]	H	1.9
(56)	PYRROLIDINO	H	CH_3	C_2H_5 (dl-α)	H	1.0[7]
(57)	PYRROLIDINO	H	CH_3	CH_3 (dl-α)	H	2.0

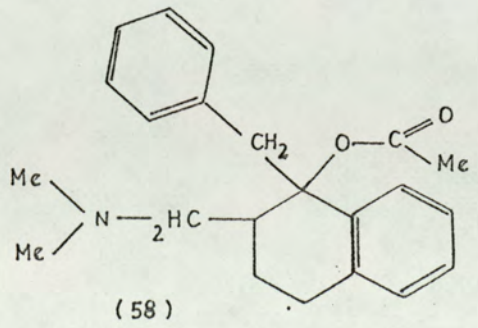
* Analgesic activity, compared to pethidine, Eddy hot-plate test except where marked with superscript reference number.

Variations of the amino function A other than $(CH_3)_2N$ and pyrrolidino (56 & 57) resulted in reduction or loss of activity eg. piperidino and

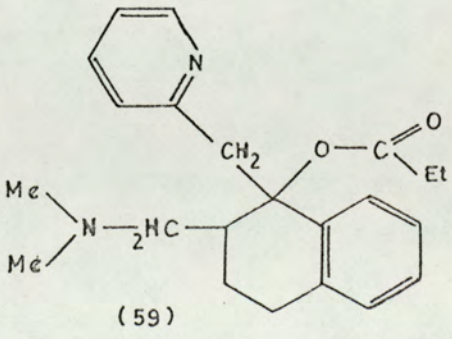
morpholino analogues. Variations in the carbon chain in which an ethyl group at position D and a methyl group in position B giving methadone-type isomers have also been synthesised and found to be much less active. Substitution in the aromatic ring (R^1 = alkyl, halogen) has given compounds of little interest. The parent member, dl-propoxyphene (51) was found to have a potency equal to that of codeine and its (+)-isomer (52) was wholly responsible for this activity, the (-)-isomer (53) being inactive analgesically, but having anti-tussive activity. An interesting indication of true morphine characteristics in the more potent members of the series was seen in the (+)-α-acetoxy derivative (55), for which a high physical dependence capacity was demonstrated in monkeys.

The cyclised propoxyphene analogues with a tetrahydronaphthalene structure (10), were synthesised and investigated independently [8,9] and are of interest to the present work. One group[8] reported the propionoxy compound (10) equipotent with d-propoxyphene but the onset of tolerance was very fast. They also claimed that the acetoxy analogue (58) had enhanced activity as in the propoxyphene series. The second group[9] also investigated the propionoxy compound (10), separated the diastereoisomeric racemates and discovered that analgesic activity was associated with only one isomer.

The same authors[9] also investigated the picolyl analogue (59) and only obtained one isomer which was 5-10 times as potent as morphine but had a high physical dependence capacity in monkeys.



(58)

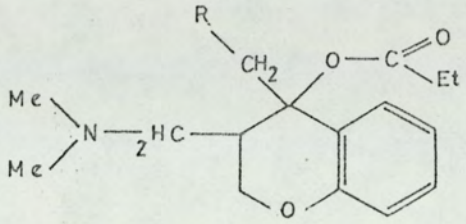


(59)

The corresponding chromane analogue (60) was found to be less active than

codeine, whereas the picolyl derivative (61) again increased the activity to twice that of codeine.

(60) R= C_6H_5

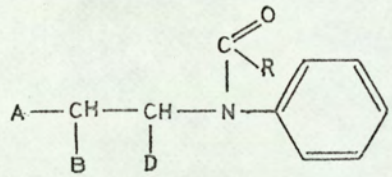


(61) R= C_5H_4N

A more flexible analgesic molecule was introduced by Wright[10] 1959. This compound (11) has some of the structural characteristics of pethidine and methadone. Some of the more important members of the series are shown in Table 7.

TABLE 7

Basic anilides



COMPOUND NO.	A	B	D	R	ACTIVITY*
PETHIDINE					1.0
(62)	$(CH_3)_2N$	H	CH_3	C_2H_5 (dl-PHENAMPROMID)	0.7
(63)	$(CH_3)_2N$	H	CH_3	C_2H_5 (-)	1.1[10]
(64)	$(CH_3)_2N$	H	CH_3	C_2H_5 (+)	0.3[10]
(65)	$C_2H_5(CH_3)N$	H	H	OC_2H_5	0.1[10]
(66)	$C_6H_5CH_2CH_2(CH_3)N$	CH_3	H	C_2H_5 (dl-DIAMPROMID)	4.0
(67)	p-$NH_2C_6H_4CH_2CH_2(CH_3)N$	CH_3	H	C_2H_5	0.8[10]
(68)	$C_6H_5CH_2(CH_3)N$	CH_3	H	C_2H_5	2.3
(69)	p-$ClC_6H_4CH_2(CH_3)N$	CH_3	H	C_2H_5	1.9
(70)	m-$CH_3C_6H_4CH_2(CH_3)N$	CH_3	H	C_2H_5	5.5[10]

* Analgesic activity, compared to Pethidine, Eddy hot-plate test except where marked with superscript reference number.

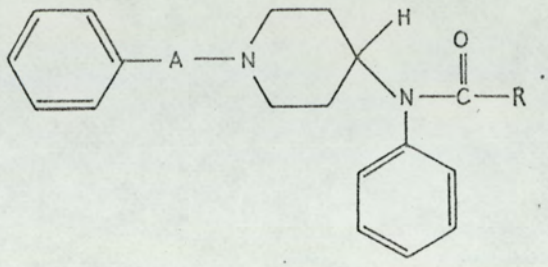
The racemic form of phenampromid (62) was found to have a codeine potency level and while both separated isomers retained analgesic activity the (-)-isomer (63) was more potent than the (+) isomer (64). The central alkylene chain was found to have an important structural influence on analgesic activity. This was exemplified by phenampromid itself which has an isomethadone-type chain and a potent analgesic effect whereas the isomeric N-(2-piperidino propyl) propionanilide with a methadone-type chain was analgesically inactive. A propionyl group in the acyl portion of the anilide moiety was optimal and any substitution in the anilide ring gave compounds with reduced activity. Variants of the tert-amino group retained activity but none approached the level attained with the piperidino derivative. Compound (65) was considered to be a nitrogen analogue derived from pethidine by substituting a nitrogen for the quaternary C-4 atom and opening the piperidine ring but it showed very weak activity.

A parallel can be found between dl-diampromid (66) and the pethidine series where, in general, a phenalkyl group on the basic nitrogen often increases analgesic potency. Activity was also associated with the central alkyl chain of the molecule where a methadone-type structure was found to be necessary (compare dl-phenampromid). Nalorphine antagonises the analgesic and respiratory depressant effects of these compounds,[78] all of which are liable to produce addiction. The introduction of heterocyclic moieties for the benzene ring in these compounds has been studied in Japan, notably using thiophene and thiazole.[79] A British Patent is registered for these and pyridine analogues.[80]

A new series of basic anilides, 4-anilinopiperidines by Janssen[11] was a development of this work in 1962, based on the prototype Fentanyl (13). Some members of this series are illustrated in Table 8, the most potent being 1000 times more active than pethidine.

TABLE 8.

Basic anilides related to Fentanyl



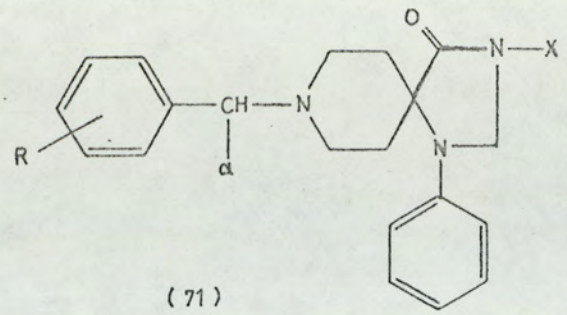
A	R	ACTIVITY *
PETHIDINE		1.0
CH_2	CH_3	0.6
CH_2	C_2H_5	0.7
$(CH_2)_2$	CH_3	50
$(CH_2)_2$	C_2H_5	700 ± 250^a (FENTANYL)
$(CH_2)_2$		280
$(CH_2)_3$	C_2H_5	14
$CH_2CH(CH_3)$	C_2H_5	1150 ± 150^a
$CHOHCH_2$	C_2H_5	150
$CHOHCH(CH_3)$	C_2H_5	1300
$CHOHCH(C_2H_5)$	C_2H_5	900

* Analgesic activity, compared to pethidine, Eddy hot-plate test in mice except a Janssen, unpublished results in rats.

All are short acting and characterised by an N-CH_2-X-aryl substituent, the clinical compound Fentanyl having X = CH_2. The anilide ring both here and in the phenampromid family of compounds must be unsubstituted and the propionyl amide is optimal, other amides being active but less potent.

A further recent development of these 4-anilino piperidines is a series containing basic amides that are as potent as Fentanyl but are very

long acting. These are of the triazaspirodecane type (71).



(71)

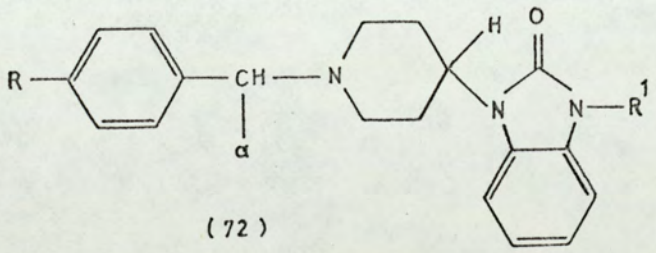
R = H, p-F, p-Cl, p-Me.

α = Me, Et, CH_2-CH_2-Me.

X = H, Me.

The important finding in this series was that the highest analgesic potency was associated with an alkyl-branched benzyl substituent on the basic nitrogen. Hence compound (71, α = CH_3, R = X = H) is 60 times, (71, α = CH_3, X = H, R = p-F) 240 times, (71, α = CH_3, X = H, R = p-Cl) 190 times and (71, α = CH_3, X = H, R = p-CH_3) 410 times as potent as pethidine. These potencies were improved in (71, α = CH_3, X = CH_3, R = H), this compound having a potency 450 times that of pethidine. Activity was greatly reduced with higher alkyl branching eg. where α = C_2H_5 or $CH_2CH_2CH_3$ except compound (71, α = C_2H_5, X = H, R = Cl) where the activity was nearly double that of its α-CH_3 analogue.

Another similar series of 4-benzimidazolonopiperidines (72) has been developed.



(72)

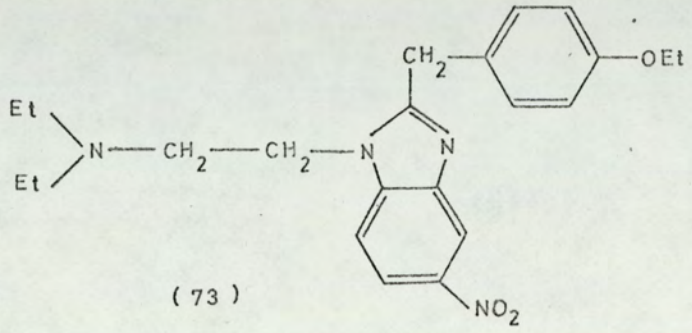
R = Me, Cl.

α = Me, Et, CH_2-CH_2-Me.

R^1 = H, Me, CH_2-O-Me, CH_2-OH.

The most potent derivatives in this series according to unpublished results by Janssen are the dimethyl compound (72, R = CH_3, α = CH_3, R^1 = H), the chlorophenyl compounds (72, R = Cl, α = CH_3, R^1 = H), (72, R = Cl, α = CH_3, R^1 = CH_3) and the ether compound (72, R = Cl, α = CH_3,

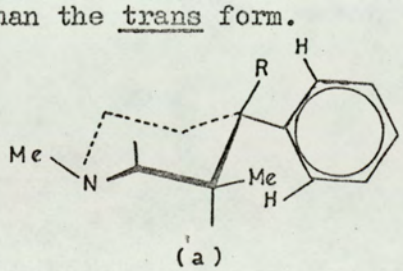
R^1 = CH_2OCH_3) which are respectively 290, 130, 170 and 130 times as active as pethidine. Hunger et al.[81] have also reported benzimidazole derivatives as potent analgesics. Etonitazene (73) was the most active in this series having a potency 1000 times that of morphine.



(73)

Contrary to activity findings in methadone and propoxyphene series, the diethylaminoethyl rather than the dimethylaminoethyl, basic function was optimal. Maximum activity was associated with a 5-nitro group in the benzimidazole nucleus and a 2-(4-alkoxybenzyl) substituent. Deviations from this structure gave less active compounds. All compounds were clinically unsuitable because of their addictive and respiratory depressant actions.

Casy et al.[82] (1969) have reported on structure-activity relations in a further series of Fentanyl analogues (75) and on the stereochemistry of 3-methyl analogues of pethidine (74 a, b). In the latter group the cis and trans forms of 3-methylpiperidine were both analgesically more active than the parent compound and the cis compound was ten times more potent than the trans form.

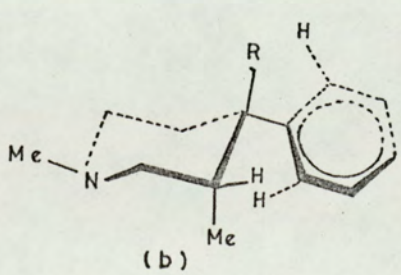


(a)

α—trans—3—Me/4—Ph

(74)

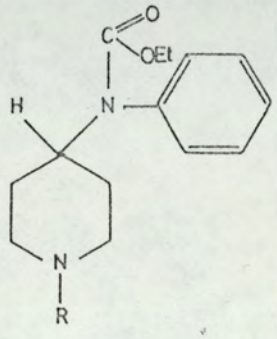
R = C(=O)OEt



(b)

β—cis—3—Me/4—Ph

The Fentanyl analogues were synthesised and subjected to the hot-plate test in mice in order to establish correlations between 4-phenylpiperidine analgesics and open-chain basic anilides such as Diampromid, Fentanyl possessing molecular features common to both.



R = Me, CH_2—Ph, $(CH_2)_2$—Ph.

(75)

Variationsin activity in the 1-methyl, 1-benzyl, and 1-phenethyl derivatives were found to resemble those of corresponding open-chain anilides rather than 4-phenyl piperidine analgesics. The extreme potency differences between the N-phenethyl derivatives, Diampromid and Fentanyl showed that the two classes were best regarded as mutually distinct types of analgesic. Separation of analgesic and detrimental side effects was not accomplished.

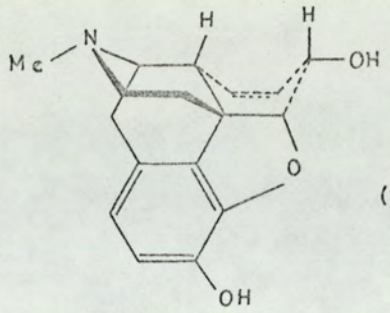
It is clear that none of the synthetic pethidine and methadone derivatives has approached pentazocine for non-addictive, oral, analgesic response.

B: The mechanism of analgesic action

Any theoretical attempt to explain the relationship between chemical structure and analgesic activity must account for the high activity of successful, clinical compounds as well as the lack of or low activity of the thousands of unsuccessful compounds which have been tested in animals. Among the numerous hypotheses advanced, many earlier theories stressed the importance of partial structures of morphine, but with the introduction of pethidine and methadone Macdonald[83] in 1946 considered the spatial

arrangements of analgesically active molecules of more importance. Pfeiffer and his colleagues[84] (1948) listed three factors common to then known analgesics: a prosthetic group consisting of a methyl group on a tertiary nitrogen, up to several oxygen functions separated from the nitrogen by a distance of 7 - 9 Å and blocking moieties making up the mass of the molecule (eg. phenyl, diphenyl or dibutyl).

In 1952, Beckett[19] considered the minimum requirement for activity in terms of a hydrophobic group (or collection of groups) containing a basic centre with an overall optimum spatial arrangement. He suggested the possibility of the stereochemical configuration of a drug being complementary to that of certain tissue surfaces or enzyme systems. Further work on the steric requirements of analgesics over the next four years resulted in the postulate of a "receptor site theory". In 1955, Braenden *et al.*[20] reported on structure-activity relationships to the United Nations Commission on Narcotics, at which time, all known, potent analgesics possessed the following chemical characteristics : a tertiary nitrogen with a relatively small attached group, a central carbon atom, none of whose valencies was connected with hydrogen, a phenyl group or isoster connected to the central carbon atom and a two-carbon chain between the central carbon atom and the nitrogen for maximum activity. Furthermore, all potent analgesics were antagonised by nalorphine. The remainder of the molecule was considered to be less important, although frequently an oxygen function was near the central atom. It was recognised that such features allowed considerable rotational or conformational freedom whereby the molecules could assume a configuration similar to that of morphine (76).



(76)

In particular, Beckett and Casy,[85, 86] used this important stereochemical implication to propose a tentative analgesic receptor surface consisting of 1) an anionic site (6.5Å x 7.5 - 8.5Å), which could be associated with a basic group,

2) a flat area, which allowed bonding with a flat aromatic ring through Van der Waals type forces and

3) a cavity, suitably orientated with sites 1) and 2) which accepted the projecting hydrocarbon moiety.

In this 'three-point' association only one member of an enantiomorphic pair could present the three features correctly orientated to the receptor site. However, the primary site of analgesic action was considered to be the association of drug donor groups with sites 1) and 2) i.e. a 'two-point' association. Whereas correct alignment of the hydrocarbon moiety of one enantiomorph at site 3) enhanced drug-receptor contact and in consequence the analgesic activity; so in the other enantiomorph the projecting group impaired or hindered drug-receptor contact. Although originally based on morphine, the convincing evidence of antagonism of most analgesics by nalorphine pointed to a common receptor, capable of accommodating other structural types. In 1959, Beckett[87] reviewed the asymmetry and stereochemical selectivity of such analgesic molecules, in which analgesic activity and other morphine-like properties were shown to reside mainly in one member of each enantiomorphic pair. (Table 10)

Further examples have since been described (Table 9)

TABLE 9

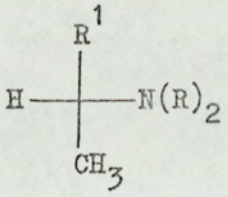
Compound	Isomer	Activity †
Phenazocine	(-)	0.11
	(+)	7.6
Phenampromid	(-)	9 *
	(+)	36 *
Diampromid	(+)	3.6 *
	(-)	11.7 *
Propoxyphene	α -(±)	25.4
	α -(+)	7.5
3-hydroxy-9-aza	(-)	4.28
-N-morphinan	(+)	INACTIVE

† ED_{50} mg /kg in mice

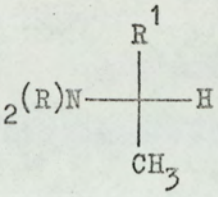
* AD_{50} in rat.

In order to establish the significance of stereospecificity in drug-receptor interactions it was then necessary to show that the more active isomers of enantiomorphic pairs have identical configurations. Beckett and Casy[88] related the more active isomers of the methadones and thiambutenes to D-(-)-alanine. (Table 10)

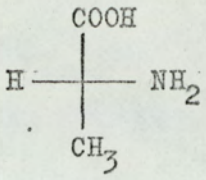
TABLE 10



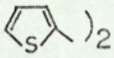
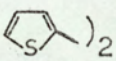
D-SERIES



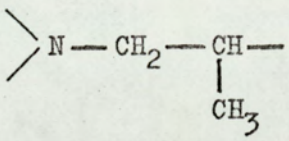
L-SERIES

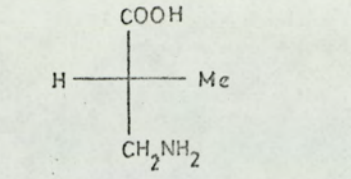


D-(-)-ALANINE

Compound	R^1	$(R)_2$	Isomer	Configuration	Activity*
Methadone	$CH_2.CPh_2COC_2H_5$	$(CH_3)_2$	-	D	180
			+	L	10
Phenadoxone	$CH_2.CPh_2COC_2H_5$		-	D	195
			+	L	5
Dimethylthiambutene	$CH = C($  $)_2$	$(CH_3)_2$	-	L	30
			+	D	170
Diethylthiambutene	$CH = C($  $)_2$	$(C_2H_5)_2$	-	L	50
			+	D	120

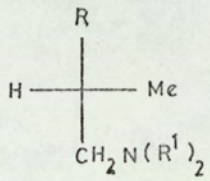
* Analgesic activity compared to (±)-Methadone = 100

Similarly, the more active isomers of those analgesics containing the central  structure were shown to possess identical configurations; hence, (-)-isomethadone,[89] (+)-propoxyphene[90] and (-)-phenampromid[91] were related to R-(-)-α-methyl-β-alanine. (77)



R-(-)-α-methyl-β-alanine

(77)

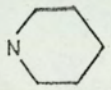


R= C(Ph)$_2$—COEt, N(R^1)$_2$= N(Me)$_2$.

(-)—isomethadone

R= C(OCOEt)—PhCH$_2$Ph, N(R^1)$_2$= N(Me)$_2$.

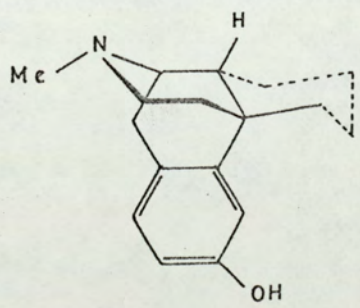
(+)—propoxyphene

R= N(COEt)—Ph, N(R^1)$_2$= 

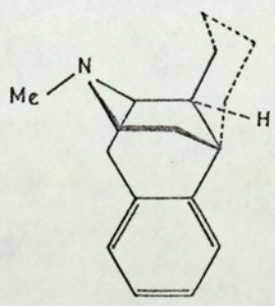
(-)—phenampromid

Only one report had contradicted these general findings of configurational identity in analgesically active enantiomorphs. Portoghese[92] showed the more active isomers of Diampromid (66) and the N-benzyl analogue to be related to L-(+) rather than D-(-)-alanine.

Hence the configurational identities and shapes of analgesically active molecules were considered important at the common receptor surface. From the original postulate based on (-)-morphine (76) the work was extended to levorphanol (78) which was expected to fit the receptor surface because the molecular shape closely resembles that of morphine.



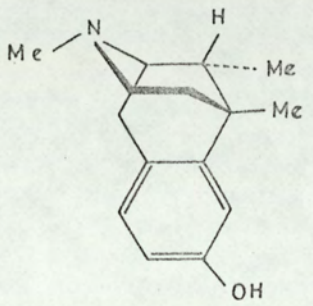
(78)



(79)

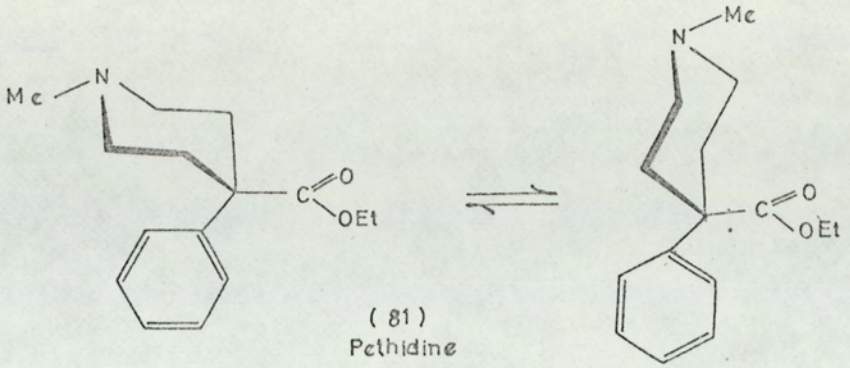
Further support came from the change from a morphinan (78) to an isomorphinan structure (79) without loss of potency. The difference in structure arises in the latter which has a trans juncture with rings B and

C but, since in both cases ring C is directed away from the receptor surface it should have little influence on drug-receptor contact. In benzomorphan derivatives such as methazocine (80) the methyl groups at C_5 and C_9 can be regarded as alkyl fragments of ring C in the morphinan molecule, but other structural and stereochemical features of the morphinan molecule are retained.[93] Thus, this molecule would also be expected to fit the proposed surface.

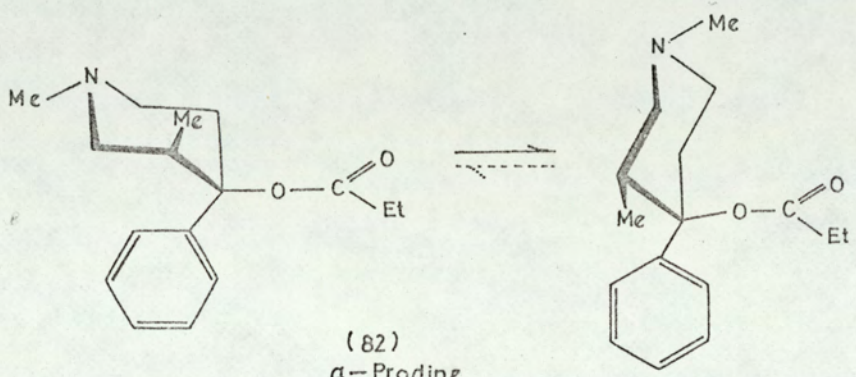


(80)

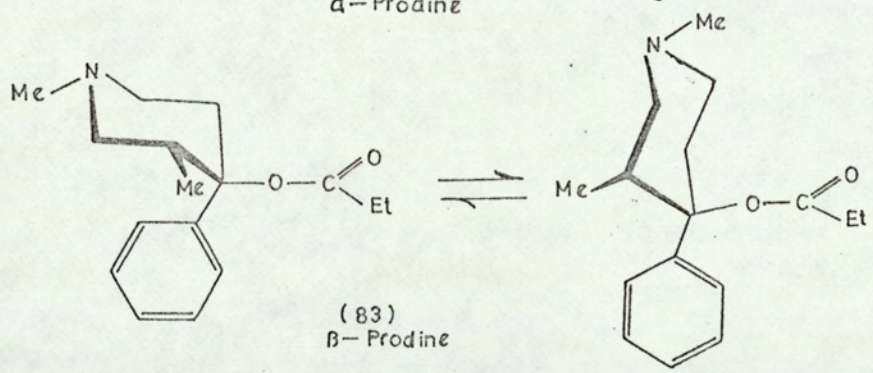
With less rigid molecules eg. 4-phenylpiperidine derivatives, the question of whether particular conformations were appropriate for drug-receptor contact as well as the possibility of the molecule adopting such conformations was important. The rigidity of the polycyclic molecules required the phenyl group to be linked axially to the 4-position of the piperidine ring but in the less rigid bicyclic systems an equatorial phenyl conformation is more likely. In fact, models showed that both axial and equatorial conformations could fit the receptor surface but the less favoured axial, phenyl conformer would fit more closely (81 - 83).



(81)
Pethidine

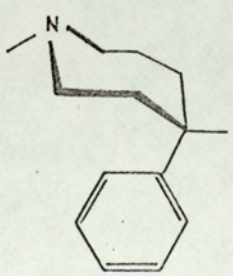


(82)
α-Prodine

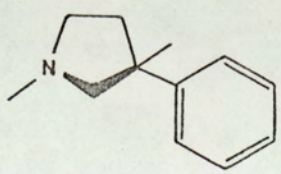


(83)
β-Prodine

With seven-ring analogues of piperidine derivatives (84) analgesic properties were reduced and in five-membered ring substances (85) activity was lost. This was taken to indicate that the orientation of, and the distance between, the basic centre and the aromatic group was optimal in the piperidine ring.



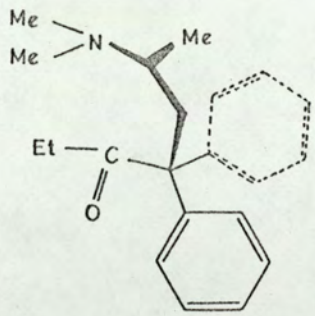
(84)



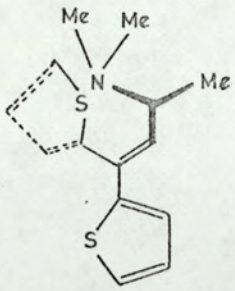
(85)

Replacement of phenyl with benzyl to give 4-benzylpiperidine analogues also resulted in potency falling[46] and the high potency of Fentanyl (13) synthesised later was unexpected since in this molecule the basic centre was separated from the aromatic moiety by four atoms. This was assuming Fentanyl to be related to pethidine compounds whereas it is perhaps more closely related to basic anilides eg. Diampromid.

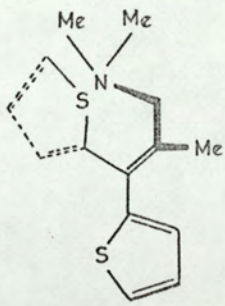
In acyclic, diphenylpropylamine analgesics where the basic centre and an aromatic ring are linked by three carbon atoms, models have shown that molecular conformations can exist where correct alignment at the common receptor surface is possible. Thus in methadone and thiambutene conformations shown in figures (86) and (87) the basic centre is in the same plane as one of the aromatic rings. Rotation of the ring out of this plane would increase steric interaction with the second aromatic ring and this second ring may possibly be holding "active" conformations.



(86)



(87)

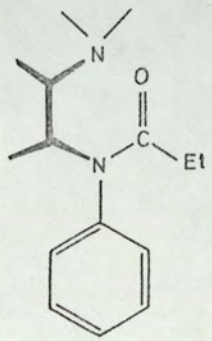


(88)

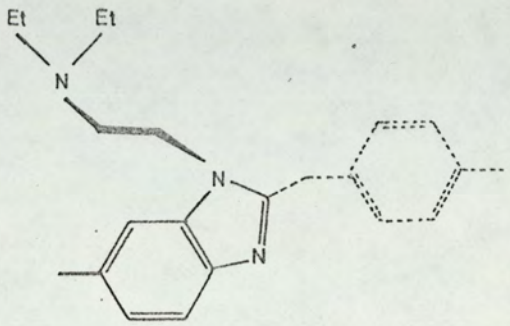
In compound (88) where the methyl is situated on carbon two thus becoming part of the alkene link, it has a fixed position and is much more restricted than the three-methyl substituent, resulting in a fall of activity which is not seen in the 1,1-diphenylpropylamines.

In the basic anilide analgesics (89) synthesised by Wright and his colleagues[10] suitable conformations for receptor association can be assumed. In the absence of a second, buttressing, phenyl group other factors such as hydrogen bonding between the amide carbonyl and protonated

nitrogen and rigidity arising from the partial sp^2 character of the acyl group may be the important factors in determining the more favourable conformations.



(89)



(90)

Essential features for fit at a common receptor site have also been shown in the 2-benzylbenzimidazoles.[94] In conformation (90) of such molecules the benzimidazole aryl ring is more likely to be associated at the receptor surface because it is linked through nitrogen (as with the quaternary carbon of other analgesics) to a 2-aminoethyl side chain. Some of these derivatives are exceedingly potent and it has been suggested that this may be related to a greater area of planarity in these molecules than exists in other analgesics.

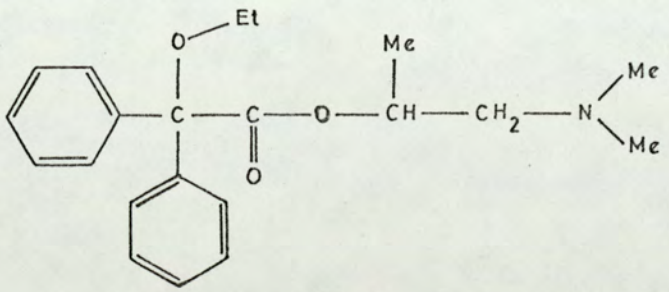
But, to be effective, an analgesic agent must not only possess the intrinsic capacity of associating with an envisaged, particular receptor site. Physico-chemical properties must be such that it reaches the locus of action in adequate concentration. That these were connected with the size and role of the basic group in the analgesic molecule was stressed by Beckett *et al.*[95] (1956) as part of their work on analgesic receptor theory. They suggested that an oxidative *N*-demethylation mechanism was involved in the mediation of an analgesic response. This was supported by Elliott *et al.*[96] (1954) and Burns *et al.*[97] (1955) using *N*-methyl C^{14} morphine and codeine, evidence for demethylation being based on $C^{14}O_2$ pulmonary

excretion and the isolation of the nor-compound from urine using counter-current techniques. Further evidence for the hypothesis came from Axelrod's [98] (1956) investigation of the dealkylation of analgesics by liver enzyme systems, the results indicating that analgesics may be demethylated by certain enzyme systems and, that the more active isomer was more readily demethylated. It was suggested that the hypothesis could be confirmed if the introduction of nor-compounds close to the receptor site produced an analgesic effect equal to that of the parent compound. Thus, the high activity of nor-morphine on intra-cisternal injection appeared to substantiate the claim. Later, Milthers[99] gave evidence for the transformation of both morphine and nalorphine to normorphine in the brain of hepatectomised rats. Oxidative dealkylation was previously unknown in the C.N.S. Dealkylation in the last analysis was considered to take place at the molecular level and it must be emphasised that the presence of the nor-compound upon the receptor site itself was regarded as the essential feature of the mechanism advanced for the mediation of analgesia.

The discovery that N- β-phenethylnormorphine and N- β-phenethyl-norpethidine possessed high analgesic activity,[32,33] led to renewed interest in the effect of the nitrogen substituent. In 1958 Elpern[100] showed that N-phenethyl and N-phenylpropyl derivatives of 4-phenylacyloxypiperidines were strong analgesics but the N-benzyl compound was virtually inactive. It was suggested later that activity differences between N-alkyl, N-aryl and N-aralkyl compounds could possibly be explained by a consideration of : 1) the steric limitations of the anionic site, 2) the rates of dealkylation and 3) the partition coefficients. A phenyl group in close proximity to the nitrogen atom might well exceed the steric requirements of the anionic site and hence tend to hinder drug-receptor complex formation. As the phenyl group is moved further from the focus of the anionic charge, the steric hindrance of the phenyl group decreases and this may allow the fit of

the drug at the receptor site. The polarity of the phenethyl group could also result in an increased rate of N-dealkylation. That this is the case is suggested by the high activity of the Mannich bases of norpethidine (Janssen et al.,[34] 1959) which are considered to be readily dealkylated due to polar factors. It also appears probable that the N-phenethyl substituent will alter the partition coefficient of the drug in favour of lipoid solubility and this should result in rapid penetration of the drug to the receptor site.

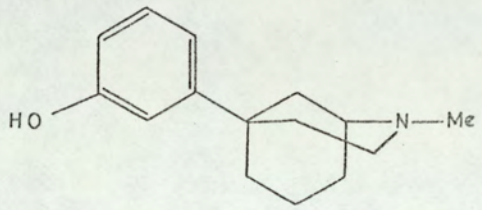
Among the many compounds found to possess analgesic activity it became clear that some were contravening the common receptor site theory of Beckett and Casy. A critical review by Adler and Way[101] appeared in 1960 which, while emphasising the vast amount of productive experimental research initiated by Beckett's hypothesis, pointed out many facts which were difficult to resolve both in this and the support work of Axelrod. Compounds with as many as five atoms between the aromatic ring and basic nitrogen are known to be equipotent with pethidine. Among such structurally diverse analgesics can be included (75, R = $(CH_2)_2C_6H_5$) and (91).



(91)

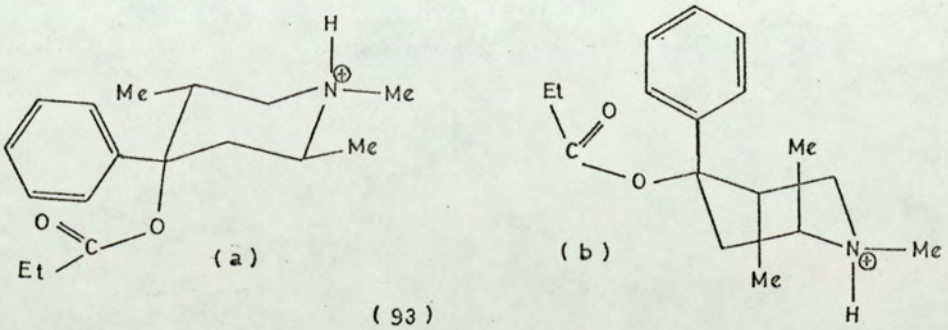
Beckett's approach to receptors in the correlation of absolute stereochemistry with analgesic potency has also been criticised in three recent reviews by Portoghese[102,25,29] (1965, 1966, 1970) while Martin,[103] and Fraser and Harris[104] have also commented on the current position. Portoghese has pointed out several perplexing aspects of the problem, for example the more active enantiomers of analgesic molecules which are

structurally somewhat similar and have a common asymmetric centre, are not all stereochemically related. Furthermore, it would appear that at least two conformations of the phenylpiperidine moiety in various compounds can exert high analgesic potency. Hence (92), a conformationally restricted compound, is as potent as morphine even though the aromatic ring is fixed in the equatorial position but the same moiety in morphine is axially constrained.



(92)

Presumably other phenylpiperidine compounds can be active as their equatorial conformers (93 a) and since the change in free energy of 7 k cal./mole in going from conformer (93 a) to conformer (93 b) is an unlikely consequence of analgesic-receptor interaction, (93 a) could be a biologically active conformation.



(93)

Another aspect not adequately explained by Beckett's theory was the finding that identical N-substituents on different analgesiophores could either enhance or diminish analgesic potency. Thus N-cinnamylnorpethidine was thirty times more active than pethidine but N-cinnamylnormorphine was inactive when compared with morphine. Similarly N-allylnorpethidine and pethidine were equipotent, the former being non-antagonistic but N-allyl-

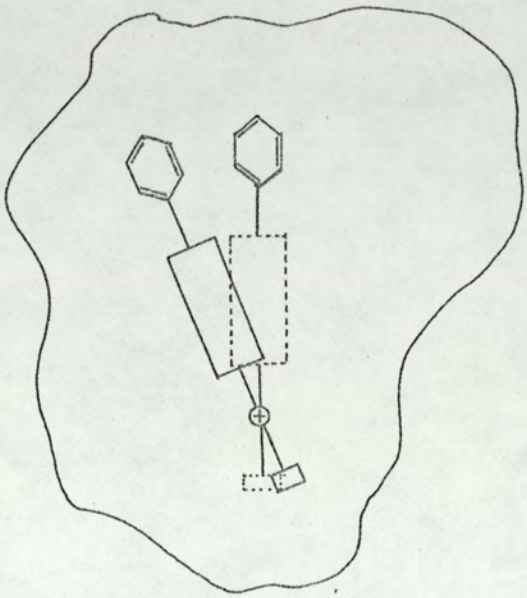
normorphine was less potent than morphine and had antagonistic effects.

Portoghese[102] introduced a new concept of the mode of interaction of narcotic analgesics with receptors in an attempt to explain the above findings. He postulated that analgesic-receptor complex formation may, in many cases, involve differing modes of interaction rather than a single, common drug-receptor site interaction, and allowed the possibility of induced fit as a contributory factor in receptor binding of diverse analgesics. The possible modes of interaction of different analgesics were described as :

1) interaction with a single species of receptors;
   (a) identical interaction, (b) differing interaction,
2) interaction with two or more common species of receptors
   (a) identical partitioning on the receptors by different analgesics
   (b) different partitioning on the receptors by different analgesics and
3) interaction with two or more species of receptors not common to the different analgesics.

Based on the evidence that certain highly potent compounds[105] are incompletely antagonised by nalorphine this concept allowed for a variety of analgesic receptor sites and a degree of flexibility[106] in these sites which permitted interaction with a greater variety of analgesic molecules than did the rigid receptor theory. It described the anionic site (94) as a pivotal point around which varying modes of binding could occur but specified that this might only occur in a small fraction of the 360° surrounding the site. Further, it allowed the structure of the analgesiophore to determine the position of binding of an N-substituent to a single, two or more common, or different species of receptors and

did not rule out the possibility of the N-substituent modifying the binding mode of the analgesiophore.



⊕ = Protonated amine nitrogen

□ = ⬚ = N-substituent

Heavy and dashed lines = different positions of binding.

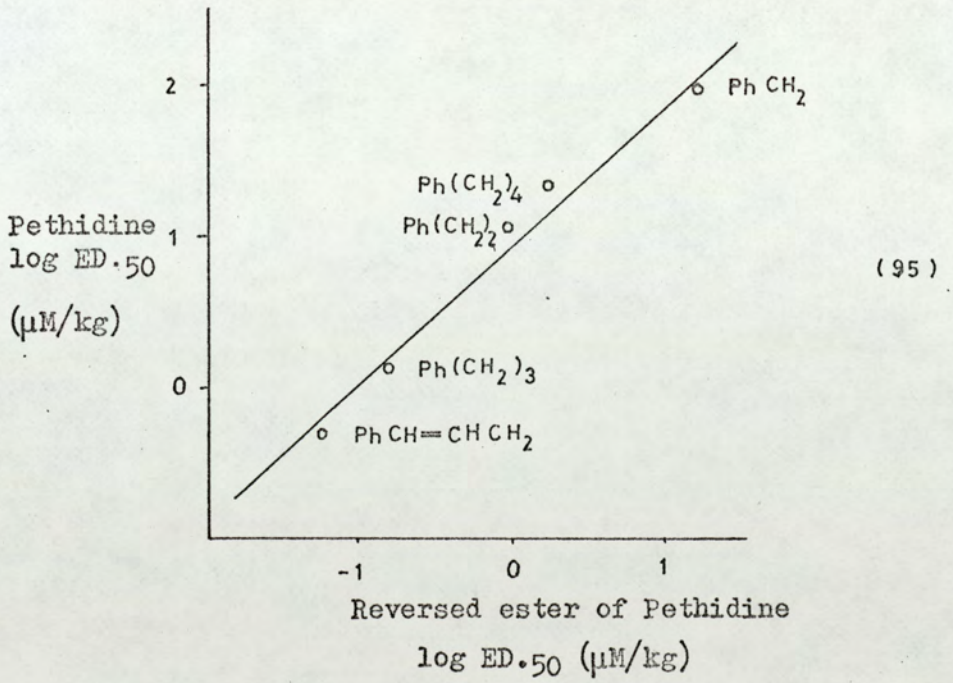
(94)

SCHEMATIC REPRESENTATION OF INTERACTION WITH A SINGLE SPECIES OF RECEPTOR, DIFFERING INTERACTION

Therefore, where identical changes of N-substituent in several series of compounds produced parallel potency changes, similar modes of binding of the different analgesiophores would be expected. Similarly, non-parallel changes in potency should result from dissimilar modes of binding. Portoghese[102] has produced evidence to demonstrate parallel relationships between pethidine and acyloxy analogues (group 1) and between morphine, morphinan, and benzomorphan compounds (group 2). Comparison of group 1 with group 2 has revealed non-parallel activity. Correlations have indicated that the analgesiophores of group 1 bind to receptors by similar modes and a similar situation exists for those of group 2. Further, the lack of parallel activity between structures of group 1 and group 2 has indicated that the interaction of identically substituted compounds in the former is different from those in the latter.

The same author has suggested that where identically N-substituted compounds in two different series (say within group 1) interacted with

receptors in a similar manner, then the quantitative contribution to the analgesic effect by the varying substituents should produce, in steady-state conditions, proportional variations of activity in both series. This proportionality would give a free energy relationship and the slope of this regression should be near unity because the identical basic groups would be expected to act by the same mechanism. The above quantitative approach assumed that identical changes in substitutents on two different analgesiophores would affect the distribution of the compounds in a similar way, an assumption held to be reasonable on the basis of the work of Hansch[107] who successfully applied substituent constants to the prediction of bio-availability of drugs. Thus, Portoghese[102,25] applied regression analysis to various N-substituted phenylpiperidines exemplified here (95) by pethidine and its reversed ester.



(95)

The data was obtained from the work of Janssen and Eddy,[35] since this was an extensive, single source with well-defined confidence limits. Point scattering and the absence of a regression would indicate dissimilar modes

of binding and a non-parallel relationship.

Also on the basis of this concept, reports by Portoghese and Larson,[92] and Portoghese and Riley[108] which proposed that the modes of interaction between Diampromid (and related N-substituted compounds) and receptors were different from that of methadone have been substantiated by Casy and Hassan.[109] Possible differences in preferred conformations between anilide analgesics[110] and methadone[111] have been used to rationalise the inversion of stereoselectivity by analgesic receptors. In connection with this Portoghese has stressed the importance of appreciating that an identical stereochemical relationship between more active enantiomers may be coincidental and does not necessarily imply that they have similar interactions with receptors. In addition, the pyrrolidine analgesics and closely related prodines have exhibited different patterns of activity on identical substituent variation, and non-parallel activity has also been found in the benzimidazole analgesics (73). In this latter group changing the basic substituent caused activity variations not observed in other analgesic compounds. These observations can be discussed in rational terms using the Portoghese concept of drug-receptor interactions.

Where different drug-receptor interactions were observed in compounds from a single series,[102] the binding mode of the analgesiophore would be expected to vary with the change of basic group. It was shown[108] that with increase of the number of methylenes in the N-aralkyl group of anilide analgesics the potency ratio approached unity. Large potency ratio changes are attributed to a decrease in the stereoselectivity of the receptors and hence to differing modes of binding.

The mechanism of analgesic action is obviously complex. At the present time it appears to be most accurately described as involving a dynamic interaction between a morphinomimetic compound and a macromolecular

receptor site at which a relatively rigid, small amine induces specific changes. The more flexible the analgesic structure is then the more difficult is the understanding of the dynamic interaction, since biologically important conformations of flexible molecules are largely unknown. A more precise, working theory requires a more detailed knowledge of the chemical anatomy of analgesics, their distribution, metabolism, site of action in the C.N.S. and conformations in the biological medium. In addition a knowledge of the constitution of macromolecular receptor sites is probably the key factor in any future progress.

PART I

SECTION II

EXPERIMENTAL AIMS AND OBJECTS OF THE PRESENT INVESTIGATION

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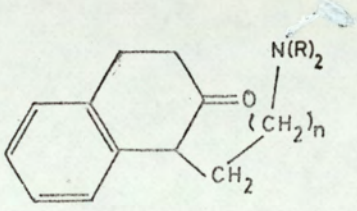
EXPERIMENTAL AIMS AND OBJECTS OF THE PRESENT INVESTIGATION

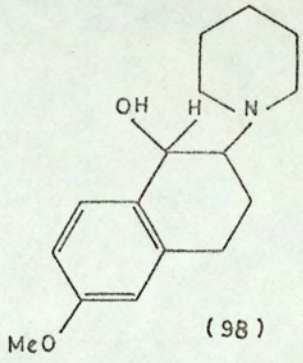
(A): Mannich bases of 1-tetralone

A tetralin nucleus alkylated in the 2-position with a dialkylaminoethyl group (96) comprises a part of the structure of the morphine molecule. Compounds derived from 1-tetralone (96, 97, 98) have been found to possess slight analgesic activity.



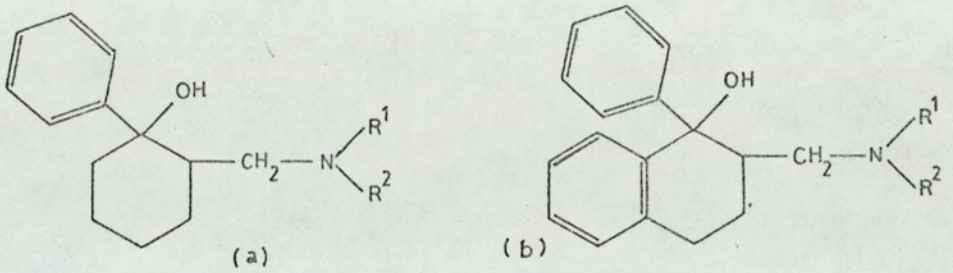
(96) $N(R)_2$ = diethylamino, piperidyl
n = 1

(97) $N(R)_2$ = piperidyl
n = 2

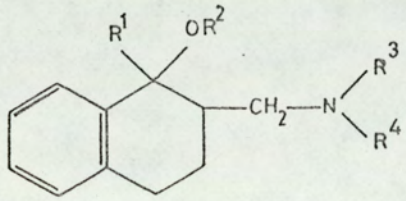


(98)

Cyclohexan-1-ols and 1,2,3,4-Tetrahydronaphth-1-ols (99 a,b) have been prepared by the action of arylmagnesium halides on Mannich bases derived from cyclohexanone and 1-tetralone. Analgesic activity is low in these compounds and their acyl analogues show no increase in potency over the parent carbinols. The initial aim of the present investigation was to extend the work on Mannich bases derived from 1-tetralone and synthesise a number of analogues (100) in order to investigate the effect on biological activity of introducing 4'-substituted heterocyclic bases in the 2-position.



(99)

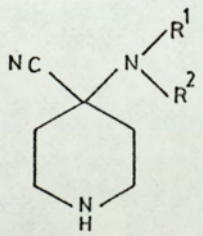


(100)

These analogues were expected to exist in isomeric forms which would require separation and configuration determination prior to biological screening for C.N.S. and cardiovascular effects.

(B): 1,1-Substituted cyclohexylamines

Analgesic activity has been reported in derivatives of N-benzyl-piperidine compounds (101). A further aim of the present work was to investigate the chemistry of a modified Strecker synthesis on 1-tetralone and cyclohexanone and synthesise a series of analogues (102, a b) by modifying the basic moiety and the nitrile group.



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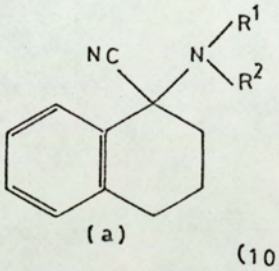
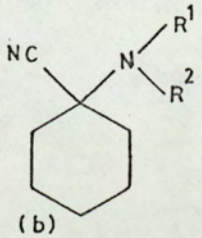


(102)



These compounds were synthesised in order to investigate their general C.N.S. activity and in particular their analgesic properties.

PART I

SECTION III

DISCUSSION

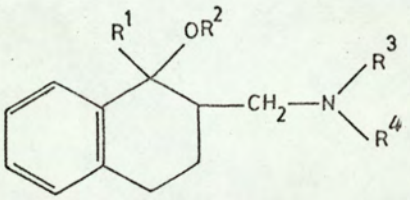
SECTION III

DISCUSSION

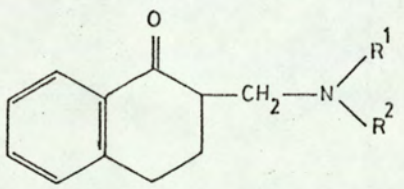
(A): Preparation of Mannich bases of 1-tetralone

Interest in tetralins as potential analgesics began with the recognition of 1-dialkylaminoethyl tetralins (96) constituting a part of the structure of morphine. Some tetralin derivatives have been synthesised[112-117] and found to possess mild analgesic activity but others[118,119] acted as selective, adrenal cortical and gonadal inhibitors.

Relatively few tetrahydronaphth-1-ols (103, NR^3R^4 = substituted heterocyclic functions) have been synthesised. 2-substituted 1-tetralones (104) appeared to be suitable starting materials since the reactive carbonyl group allows chemical modifications to be performed and such bases are readily synthesised via the Mannich reaction.



(103)



(104)

Mannich et al.[120] first synthesised the 2-dialkyl aminomethyl-1-tetralones eg.(104, $R^1 = R^2 = CH_3$) in 1937 and this particular compound was the subject of a German Patent[121] after it was obtained by a different synthetic route. During the present investigation both procedures were used initially but subsequently the Mannich technique was adopted because of the higher yields obtained.

When the Mannich reaction conditions for compound (104, $R^1 = R^2 = CH_3$) were applied to substituted heterocyclic bases the desired products were not obtained or were produced in very low yields. An increase in the molar ratio of ketone/base (3 : 1 or 5 : 1) and treatment of the mixture under

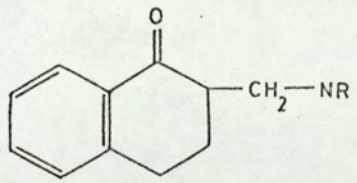
reflux gave the desired compounds in better yields in the acid-catalysed procedures (Table 11).

TABLE 11

Mannich reaction conditions

COMPOUND	MOLES 1-TETRALONE	MOLES BASE	MOLES FORMALIN	REFLUX TIME (HR)	YIELD %
(105)	5	1	2	0.5	30
(106)	3	1	1.2	0.5	18
(107)	5	1	2	3	66
(108)	5	1	3	0.75	16

Difficulty with low solubility of the N-methyl piperazine[122] derivative (105) in common organic solvents may in part, account for the low yield. When this compound was synthesised in base-catalysed conditions[123] no solvent extraction stage was involved and the yield was increased to 74%.



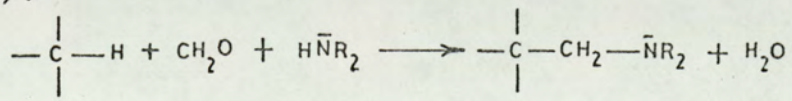
(105) NR = N^4-methylpiperazine

(106) NR = Azabicyclo[3,2,2]nonane

(107) NR = 4-phenylpiperidine

(108) NR = N^4-ethoxycarbonylpiperazine

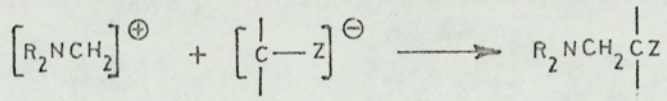
The mechanism of the Mannich reaction has been the subject of several recent reviews.[123-127] In the classical Mannich reaction between an active hydrogen, formaldehyde and ammonia or a primary or secondary amine the product is an asymmetrical derivative of methylene known as a "Mannich base" (109).



(109)

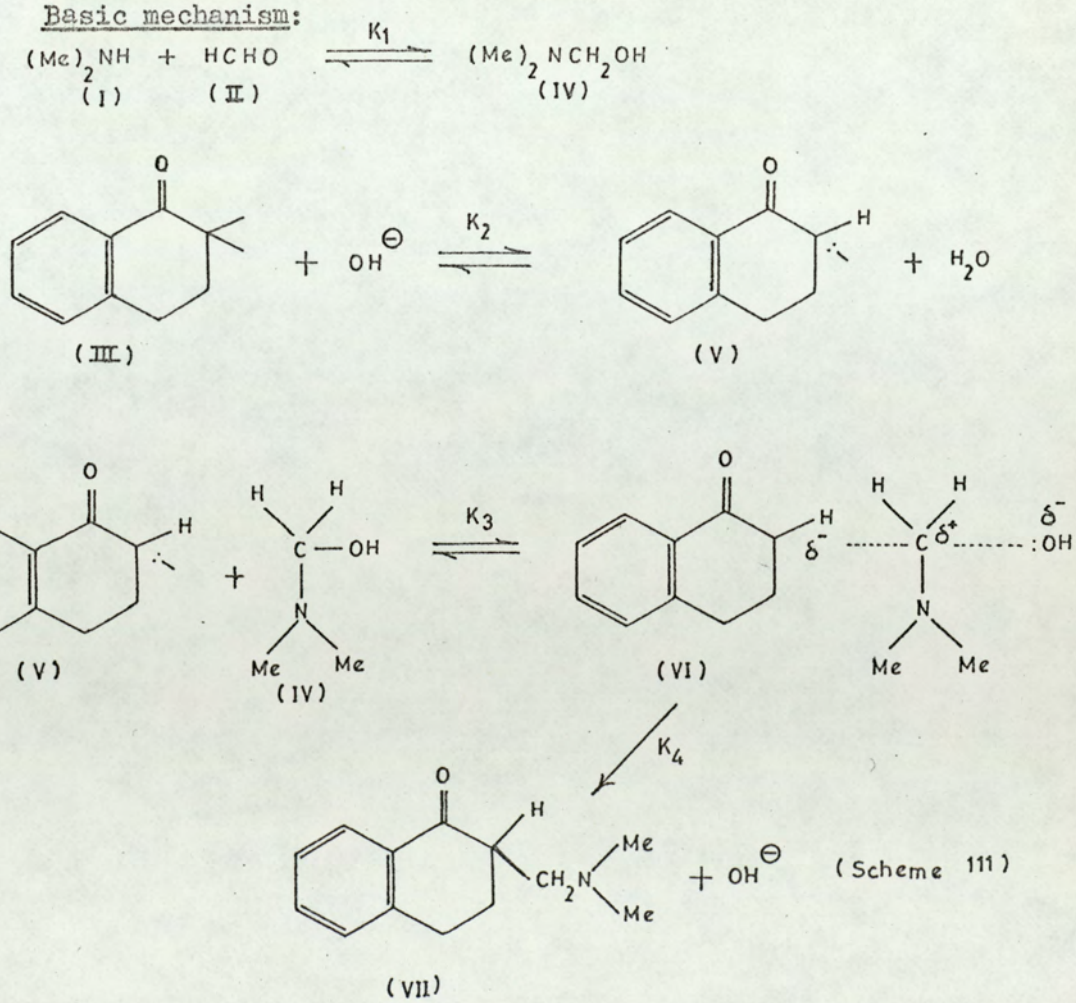
Prior to 1960 evidence for proposed mechanisms in this reaction was conflicting. In 1949 Lieberman and Wagner[123] presented a mechanism in

which a carbonium ion, $R_2N^+=CH_2$ formed from the amine combined irreversibly with a carbanion, Z^-: formed by removal of a proton from the active hydrogen compound to yield the Mannich base (Scheme 110).



(Scheme 110)

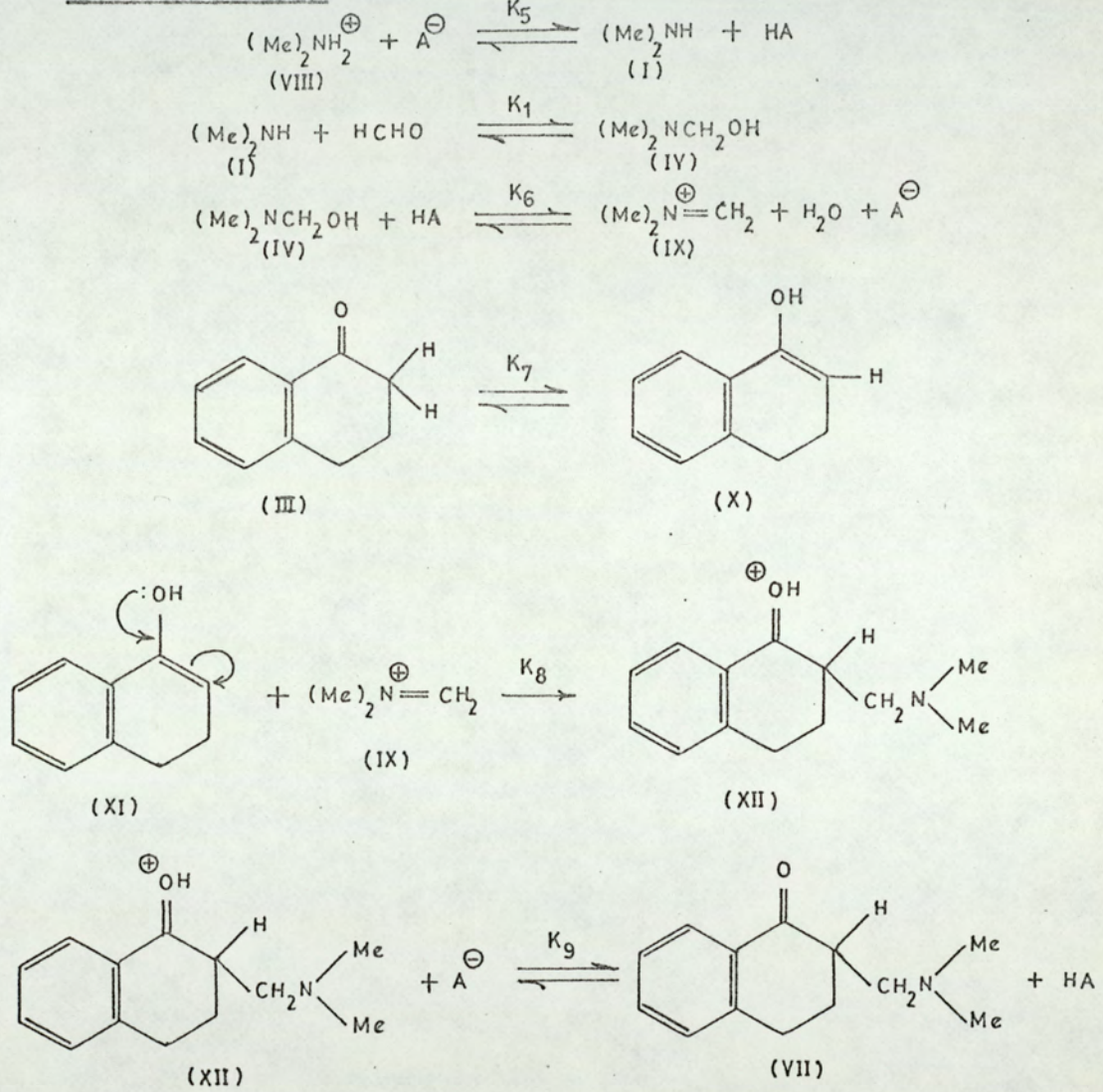
The kinetic studies of Alexander and Underhill[127] showed third order kinetics and no primary salt effect in the Mannich reaction, findings which contradict the mechanism proposed by Lieberman and Wagner. Cummings and Shelton[124] then performed a kinetic study on the Mannich reaction using cyclohexanone. The suggestion that 1-tetralone is likely to follow the sequence of events outlinedin schemes (111, 112) is based on the work of Cummings and Shelton.



(Scheme 111)

Intermediates (IV) and (V) react by an S_N2 mechanism to form an equilibrium concentration of the activated complex (VI) which decomposes by a relatively irreversible rate-controlling step to yield the Mannich base (VII).

Acidic mechanism:

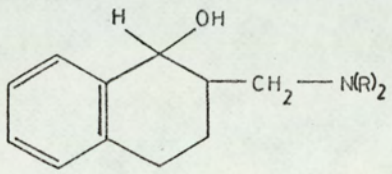


(Scheme 112)

The reaction in acid media appears to involve the reaction of a carbonium ion (IX) derived from the aminomethylol (IV) with the active hydrogen compound (XI). The rate is slower than for the reaction in basic media and is independent of pH at low pH values.

(B): Preparation of 1,2,3,4-tetrahydronaphth-1-ols

The first series of naphth-1-ols prepared (113-117) were secondary alcohols obtained by lithium aluminium hydride reduction (114, 116) or by sodium borohydride reduction (113, 115 & 117) of the appropriate ketones.



(113) $NR_2 = N(CH_3)_2$

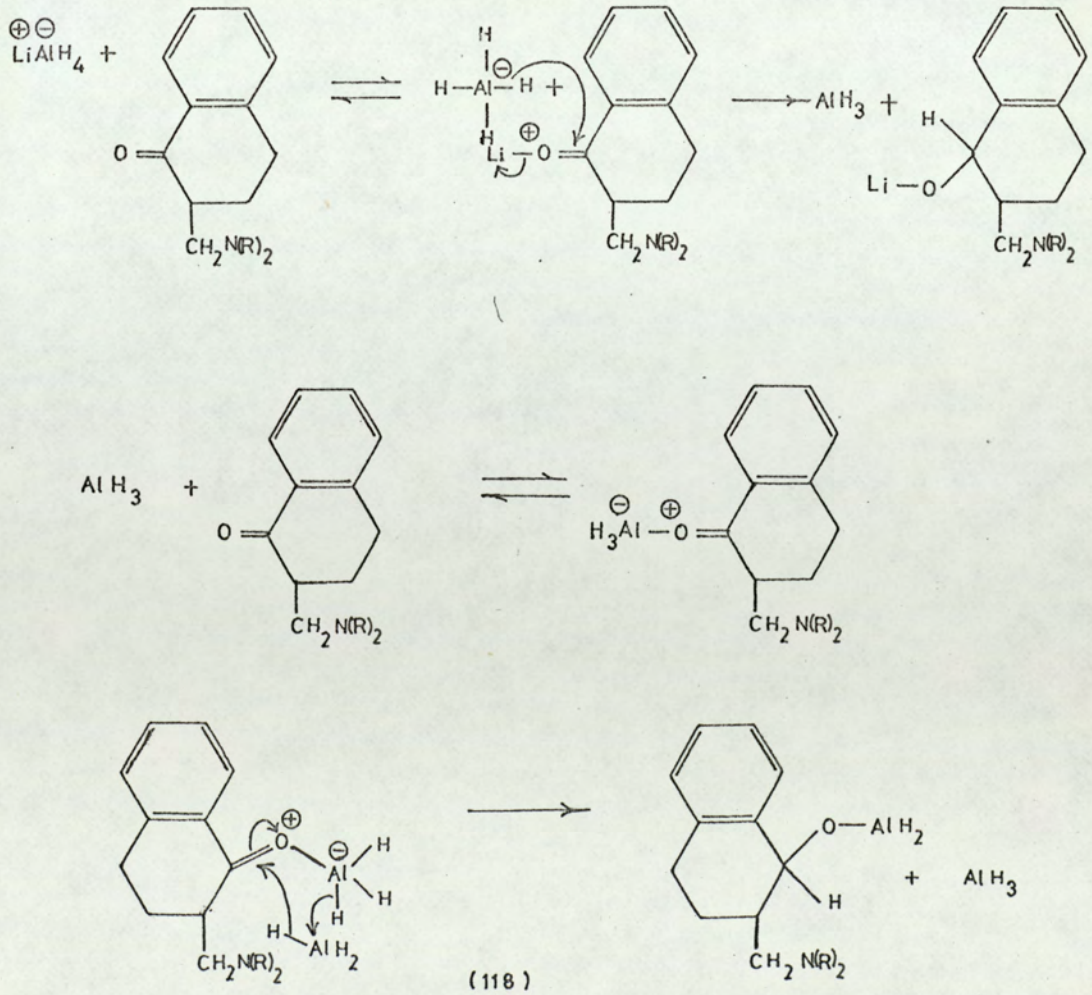
(114) NR_2 = $\underline{N}^4$-methylpiperazine

(115) NR_2 = Azabicyclo[3,2,2]nonane

(116) NR_2 = 4-phenylpiperidine

(117) NR_2 = $\underline{N}^4$-ethoxycarbonylpiperazine

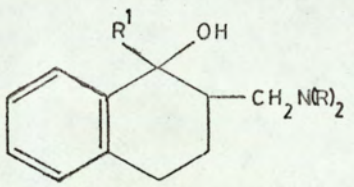
The reactions proceeded smoothly in all cases and gave good yields. The mechanisms (118) involve both lithium ions and various aluminium species complexing the carbonyl oxygen and aiding the nucleophilic transfer of hydride from aluminium to carbon.



(118)

The selective nature of the reducing properties of sodium borohydride was used to synthesise alcohol (117) from a keto-ester, leaving the ester function intact.

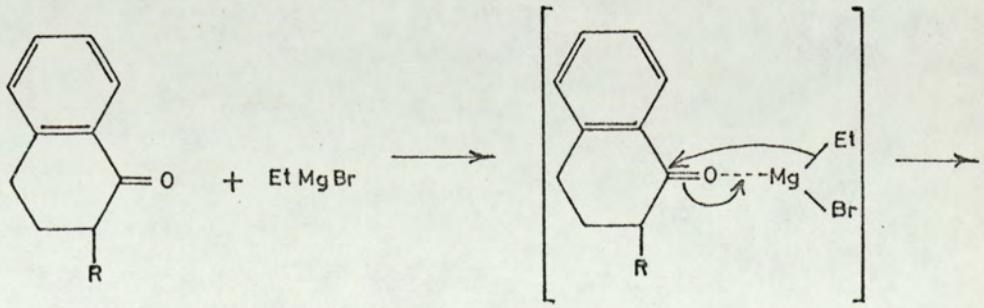
The tertiary alcohols reported in the present work were obtained by the addition of organolithium or Grignard reagents to the appropriate ketone. Organolithium compounds are known to be more reactive[128,129] and this enhanced reactivity is attributed to greater ease of cleavage of the C-Li bond, steric and electronic factors. The alcohol (119) was obtained as a crystalline base and the ethoxycarbonyl compound (120) as a crystalline hydrochloride.

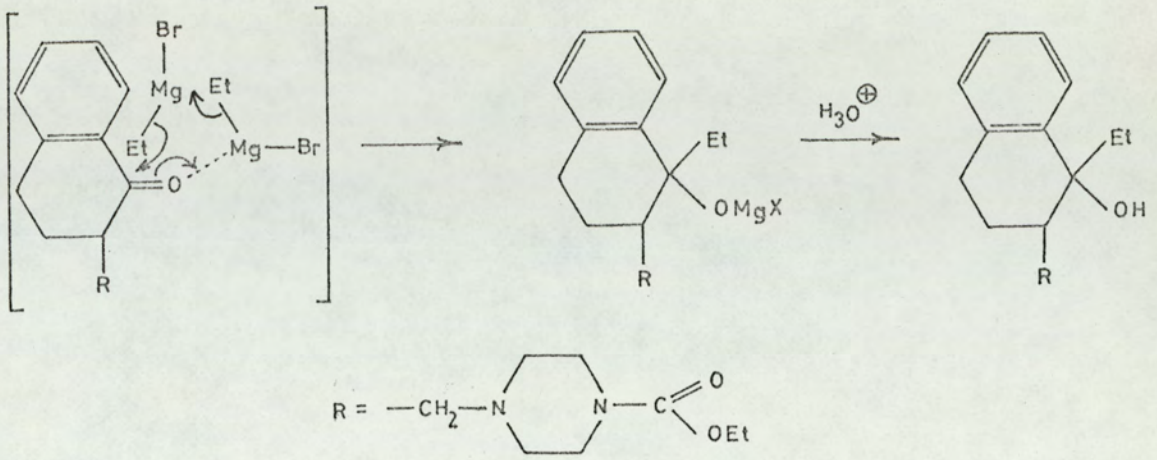


(119) NR_2 = $\underline{N}^4$-methylpiperazine, R^1 = Me

(120) NR_2 = $\underline{N}^4$-ethoxycarbonylpiperazine, R^1 = Et

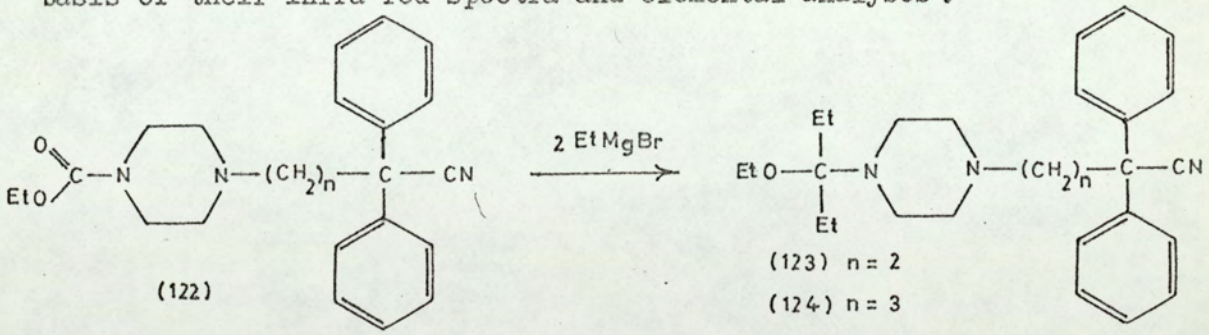
Attempts to attack the ethoxycarbonyl function in the alcohol (120) using excess Grignard reagent and refluxing in benzene returned the starting material unchanged. This conclusion was based on the evidence of an undepressed mixed m.p., superimposable infra red and superimposable nuclear magnetic resonance spectra of the starting material and product. The initial reaction therefore appears to be the normal, nucleophilic addition of Grignard reagent to the ketone function with the ester carbonyl remaining intact. This reaction proceeds via a six-membered cyclic transition state outlined in scheme (121) and first proposed by Swain.[131]



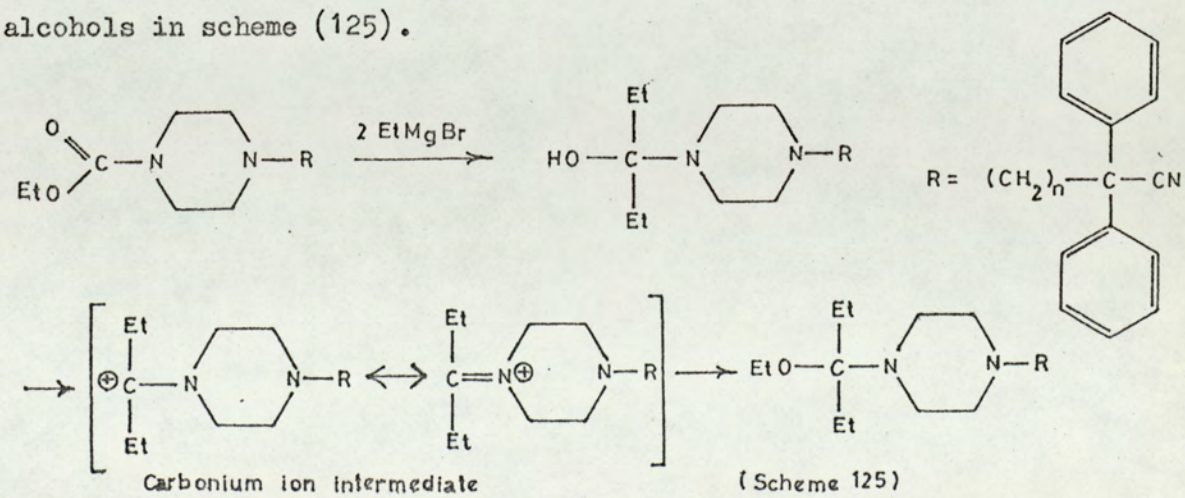


(Scheme 121)

These results are interesting when compared to those in N-ethoxycarbonyl piperazines synthesised by Islam[130] and Dimmock.[122] The base used by Islam (122) was complicated by the presence of a nitrile function also susceptible to Grignard reagents. Products (123, 124) were obtained from Grignard reactions and assigned ether structures on the basis of their infra red spectra and elemental analyses.

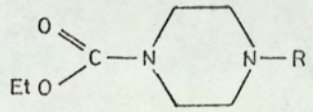


Islam considered these unexpected ethers to be formed via the corresponding alcohols in scheme (125).



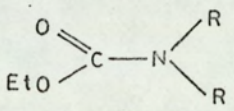
(Scheme 125)

Dimmock[122] investigated this unusual reaction using N-ethoxy carbonyl piperazines (126) lacking the nitrile function. On repeating Islam's exact Grignard conditions with these compounds he obtained two products, N-benzylpiperazine dihydrochloride (21%) and N^1-benzyl-N^4-ethoxycarbonyl piperazine dihydrochloride (27%). No evidence of ethers analogous to those obtained by Islam could be found.



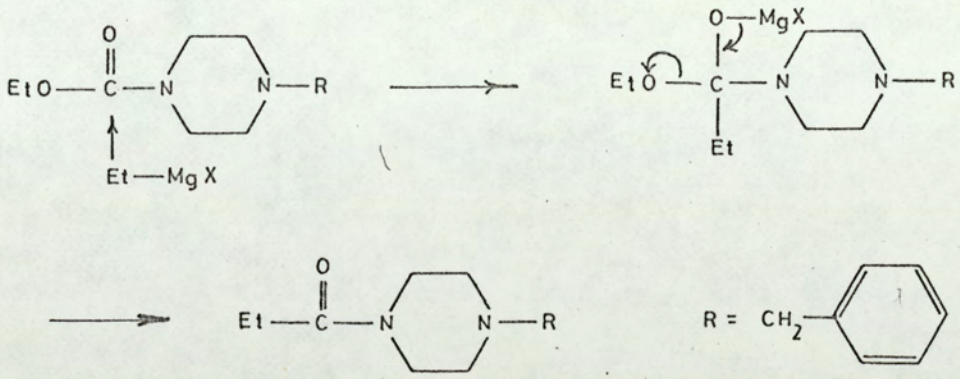
R = alkyl, arylalkyl

(126)



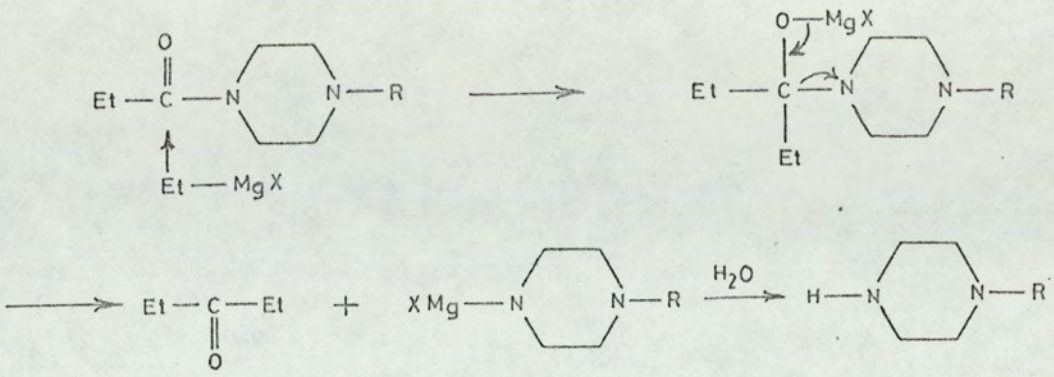
(127)

Dimmock considered that these compounds were substituted urethanes (127) and that their reactions with organometallic reagents should be assessed from this standpoint. Grignard reactions have been reviewed[132-134] but no reference to urethanes was made. The reaction sequence was considered to proceed via an amide (128).



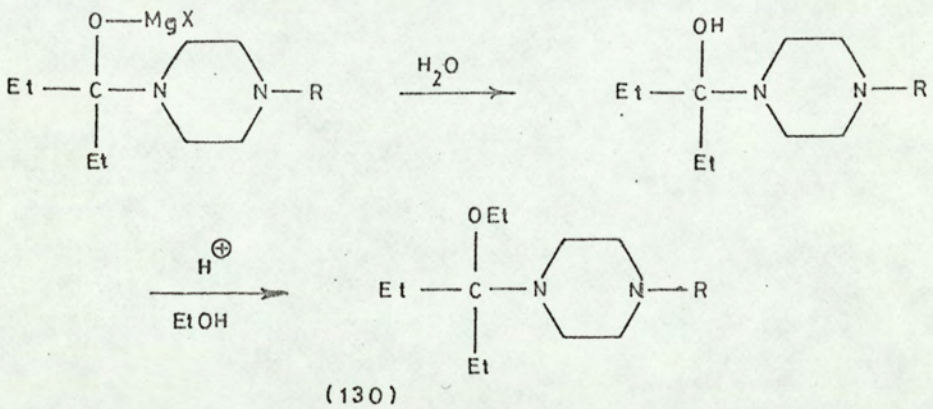
(128)

This amide could then react further as in sequence (129) where cleavage of the N-C bond gives a monosubstituted piperazine and a non-basic ketone.



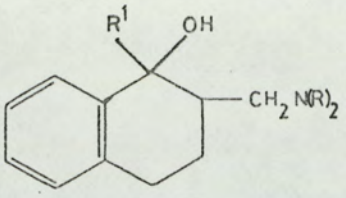
(129)

The N-C bond in the complex in (129) could possibly be stable in which case decomposition with water would yield a tertiary alcohol. The ethers reported by Islam are possibly produced by this route (130).



(130)

The tertiary alcohols (131, 132) were obtained by addition of aryl Grignard reagents to the appropriate ketones. The dimethylamine (131) was obtained as a basic oil and failed to give crystalline salts. The phenethyl compound (132) gave a crystalline hydrochloride but examination of the mother liquors and attempts to separate the original basic oil by column chromatography using alumina failed to give the possible isomeric phenethyl alcohols. The N-methylpiperazine derivative (133) was also obtained by the Grignard technique but the azabicyclo compound (134) was synthesised using phenyl lithium giving a crystalline basic product.



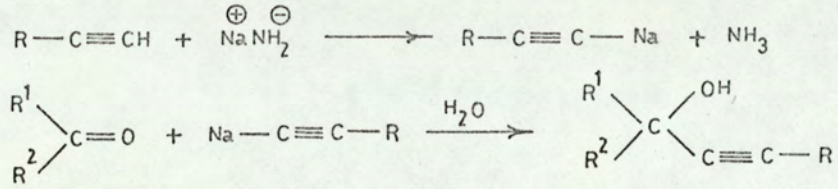
(131) $NR_2 = N(Me)_2$, R^1 = Ph

(132) $NR_2 = N(Me)_2$, $R^1 = CH_2CH_2Ph$

(133) $NR_2 = \underline{N}^4$-methylpiperazine, R^1 = Ph

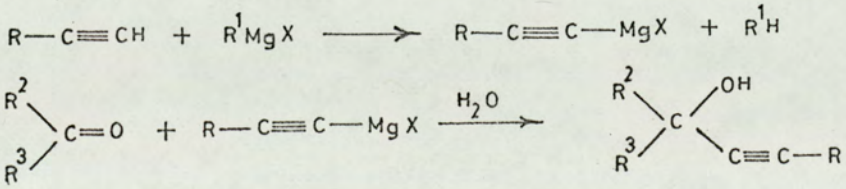
(134) NR_2 = Azabicyclo[3,2,2]nonane, R^1 = Ph

Three general methods are available for the preparation of acetylenic alcohols all depending on the acidic nature of the hydrogen attached to an acetylenic group. Hennion and O'Shea[135] used acetylene in a stirred suspension of sodamide in liquid ammonia then added an ethereal solution of the ketone, the reaction proceeding as in scheme (135).



(Scheme 135)

Nazarov et al.[136] prepared a series of N-substituted-4-ethynyl-4-piperidinols by addition of potassium hydroxide to dry ether, saturation of the solution at -7° with acetylene followed by addition of the ketone in ethanolic solution. N-substituted -4-phenethynyl-4-piperidinols have been prepared by the addition of the phenylacetylene Grignard reagent to the appropriate ketones. In this method and in Hennion's method only one isomer was isolated and the generalised sequence of reactions is shown in scheme (136).

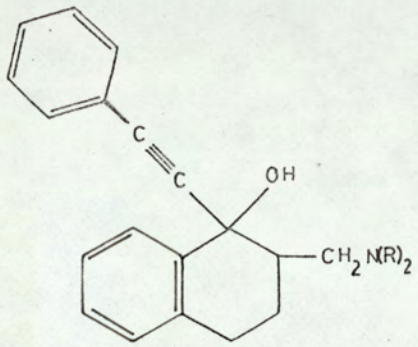


(Scheme 136)

Nazarov et al.[137] suggested that the substituent on the nitrogen exerts a profound effect on the proportion of isomers obtained by a screening

influence on the carbonyl group such that attack by the organometallic compound can take place from one side of the molecule only.

The method adopted to synthesise alcohols (137-140) was to add phenylacetylene to the Grignard reagent. Alcohols (138, 140) were obtained in good yields but the dimethylamino and azabicyclo analogues (137, 139) were produced in poor yields. All compounds gave crystalline hydrochlorides but the azabicyclo compound (139) crystallised as two basic isomers (trans: cis, 17 : 1) on the evidence of m.p., infra red and nuclear magnetic resonance spectra.



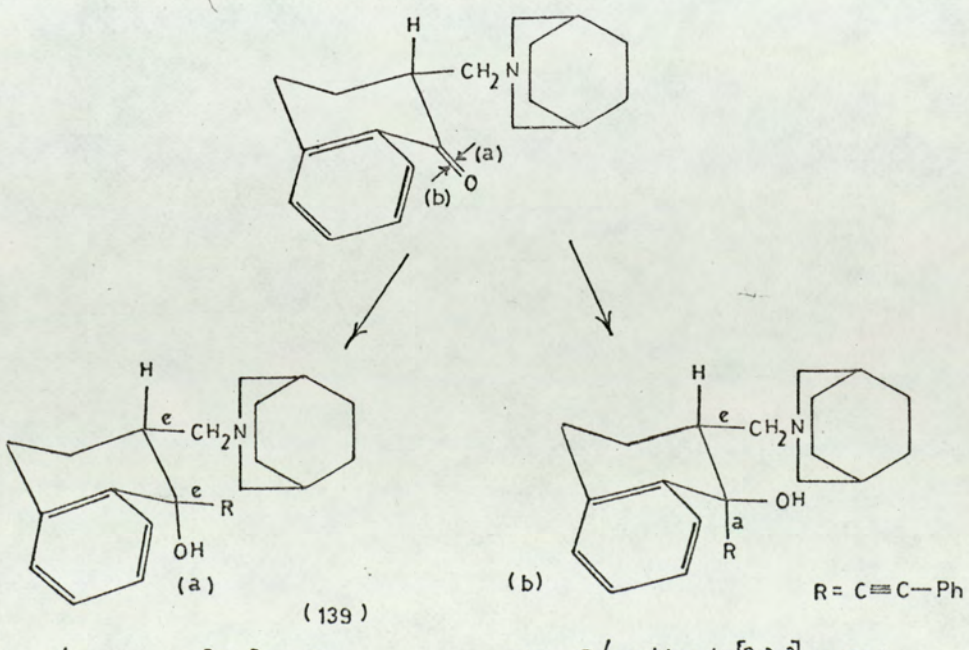
(137) NR_2= $N(Me)_2$

(138) NR_2= $\underline{N}^4$-methylpiperazine

(139) NR_2= Azabicyclo[3,2,2]nonane

(140) NR_2= 4-phenylpiperidine

In the absence of strong electrostatic effects it is generally accepted that a substituted cyclohexanone exists with the maximum number of groups in the equatorial position. Substituted 1-tetralones would be expected to exist in a similar conformation.



(139)

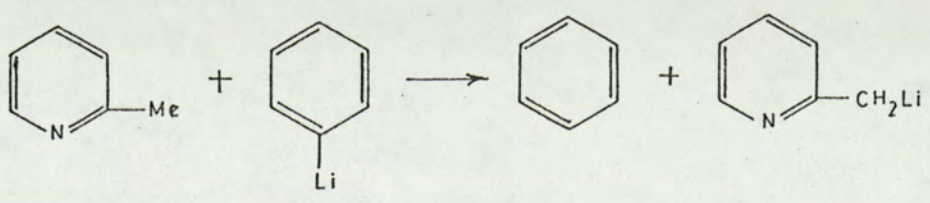
trans — R/azabicyclo [3,2,2] nonane

cis — R/azabicyclo [3,2,2] nonane

The trans-conformation (139a, R = C≡C-C_6H_5) is likely to be the most favoured and is the more thermodynamically stable conformer on the basis of the maximum number of groups larger than hydrogen in the equatorial position. In view of Nazarov's suggestion[137] the separation of these two isomers (139 a, b) is an interesting result, more particularly since the azabicyclo substituent is extremely bulky. Presumably the attacking species is more hindered by the 3-axial hydrogen and 5,6-fused phenyl ring than by the methylazabicyclo substituent at carbon 2 in this case, thus allowing formation of both isomers, the trans predominating.* Isomeric forms of no other tertiary alcohols were separated and it was tentatively assumed that the crystalline salts of the other alcohols synthesised had the trans-R/CH_2NR^1 conformation.

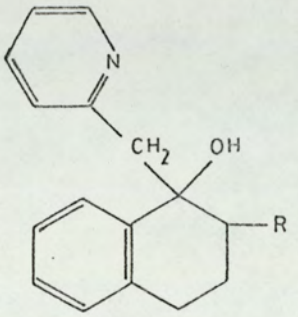
The introduction of acetylenic groups into potential analgesic molecules was of interest in view of reports that such groups have increased the stability, ease of absorption and activity in a number of biologically active compounds. Acetylenic groups contribute to the electron availability round the 1-substituent and allow the effects of replacing the 1-phenyl-substituent by a phenethynyl group to be investigated. The pharmacological reports (see pharmacology section) unfortunately indicated only very slight activity in the primary C.N.S. screen for all the naphthols described and hence no conclusions can be drawn concerning the value of the acetylenic group in enhancing pharmacological activity.

2-picolyl lithium was prepared by metallation of 2-picoline with lithium phenyl:



* In view of the stereochemistry of tetralone the benzene ring equally hinders approach above and below C=O

The process used was the method of Gilman[138] and Bebb (1939). In a preliminary investigation 1-tetralone was used and the reaction proceeded smoothly and gave a good yield of the picolyl alcohol (141).



(141) R = H

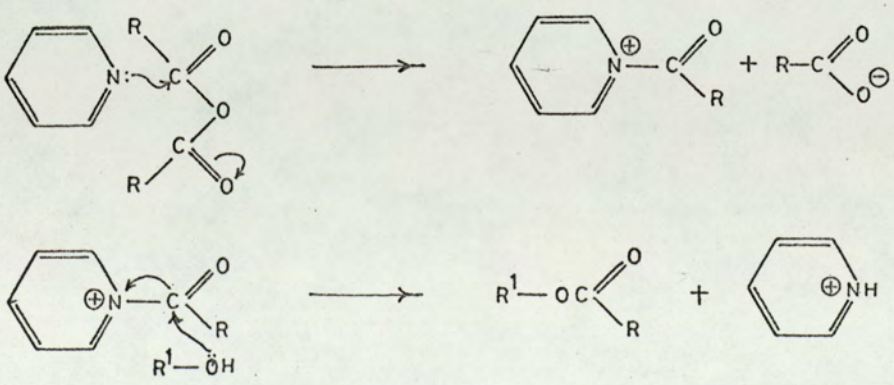
(142) R = CH_2—N N—Me

(143) R = CH_2—$N(Me)_2$

When the reaction was repeated using ketones (104, 105) almost identical yields of picolyl alcohols (142) and (143) were obtained as the crystalline base and diquaternary salt respectively but in neither case could isomers be isolated.

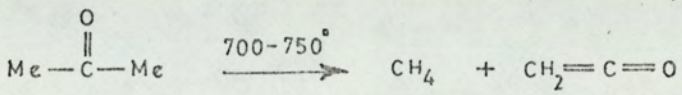
(C): Preparation of 1-acetoxy-1,2,3,4-tetrahydronaphthalenes

Esterification of 4-phenyl-4-piperidinols gave pethidine analogues with enhanced analgesic activity. The esterification of the tertiary alcohols previously described in the present work was therefore considered to be a logical development. Three general methods are available for the preparation of esters from basic, tertiary alcohols. The alcohol may be heated with acid anhydride in the presence of pyridine, a reaction which is considered to proceed via acylammonium ions produced by the basic catalyst shown in scheme (144).

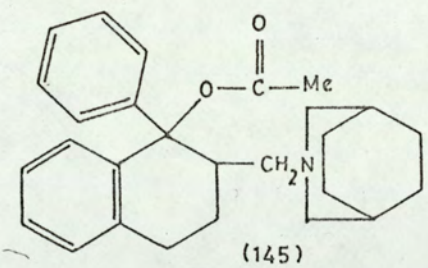


(Scheme 144)

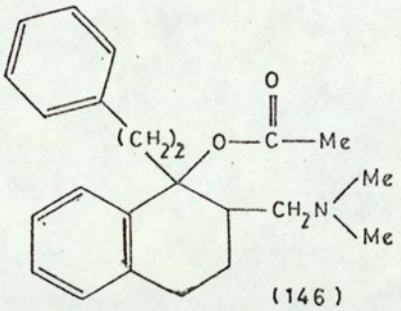
A milder lithium complex technique employs the addition of the alcohol (or ketone) to phenyl lithium and subsequent addition of acid anhydride at 0°. Ketene, a mild yet powerful acetylating agent (Rice[139] et al., 1934) may also be used and is obtained by thermal decomposition of acetone :



A preliminary investigation was carried out with the azabicyclo compound (134) using acetic anhydride/pyridine mixture but the product obtained was starting material and not the desired ester (145). A similar result was obtained with the phenyl lithium technique. Both methods were also unsuccessful when applied to alcohol (132) but when an ice-cold chloroform/acetone solution of this alcohol was treated with ketene the desired ester (146) was obtained in good yield.

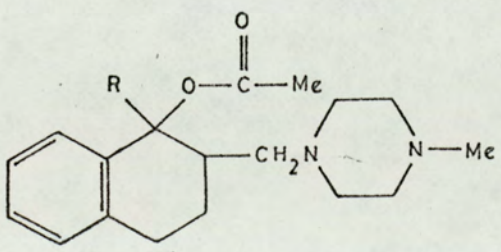


(145)

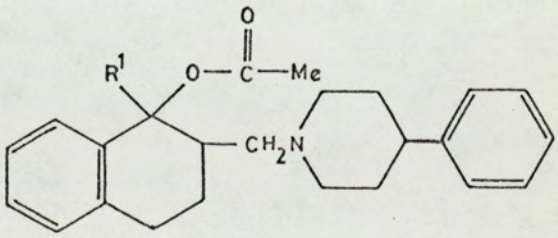


(146)

In further attempts to prepare esters (147-152) all three methods were unsuccessful.



(147) R = Ph
(148) R = C≡C—Ph
(149) R = Me
(150) R = H

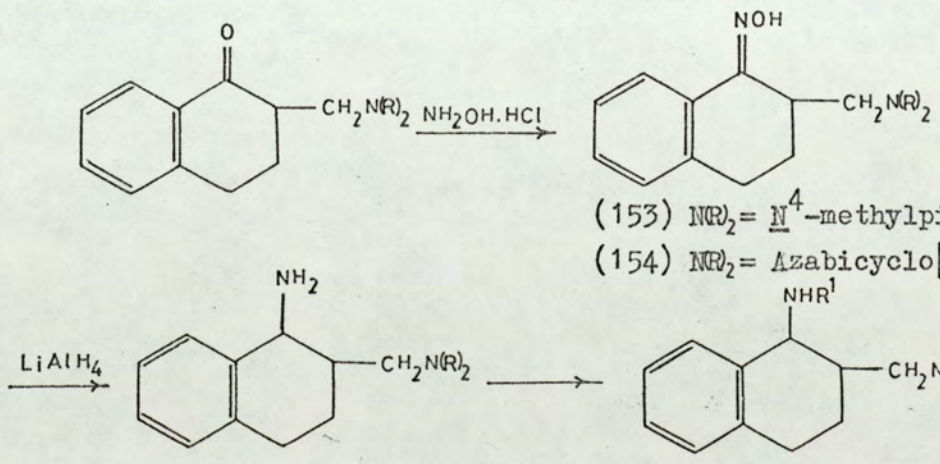


(151) R^1 = H
(152) R^1 = C≡C—Ph

Balon[140] reported many difficulties in his attempts to esterify tertiary piperidinols but occasionally the ketene method was successful when all other methods failed. Barton and Cookson[141] (1956) and Eliel and Lukach[142] (1957) have established that an equatorial hydroxyl group is subjected to less steric hindrance than an axial group. This results in the equatorial isomer having greater reactivity and leads to facile esterification. Isomeric forms of tertiary alcohols were not isolated in the present work and a tentative assumption of an axial hydroxyl group in the compounds obtained has been referred to earlier. This fact plus the very bulky form of the basic substituents in the two position may account for the lack of success in esterification procedures.

(D): 1,2,3,4-Tetrahydronaphthalene-1-oximes

An investigation of the effects of introducing substituted amines at position one was then commenced. The route chosen for the synthesis of these compounds was to prepare oximes (153, 154) from the corresponding ketones, reduce these to primary amines and then introduce a variety of substituents to the amine groups (scheme 155).



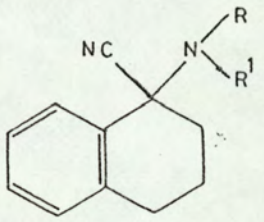
(153) NR_2 = N^4-methylpiperazine
(154) NR_2 = Azabicyclo[3,2,2]nonane

(Scheme 155)

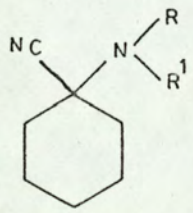
Due to difficulties in the synthesis of the oximes and reports of a lack of analgesic activity in the compounds previously described this work was discontinued.

(E): Preparation of some 1,1-substituted cyclohexylaminonitriles

Many cyclohexyl derivatives have been synthesised and assessed for potential biological activity. In recent years several papers[143-146] and patents[147] have been published on substituted cycylohexylamines particularly with regard to the C.N.S. activity of these compounds. The synthesis of related compounds outlined in the present work represents an attempt to make 1,1-substituted cyclohexylamines with specific analgesic properties. 1,1-substituted cyclicaminonitriles were considered to be good starting materials and originally it was proposed to synthesise tetrahydronaphthalene intermediates (156). These intermediates could not be obtained by the methods used, and starting materials were recovered in quantitative yields. Attention was then focussed on the less hindered cyclohexylaminonitriles (157).

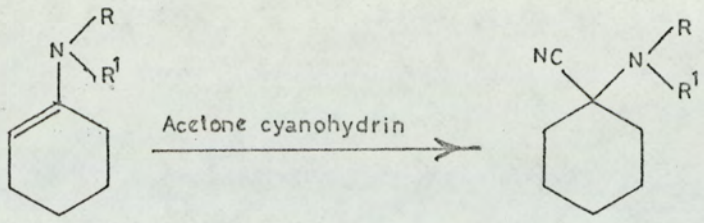


(156)



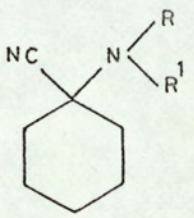
(157)

Several methods are available for the synthesis of aminonitriles. In the Knoevenagel synthesis,[147] an adduct of the ketone and sodium metabisulphite is formed first. This is then reacted with the amine and hydrogen cyanide in a one- or two-step reaction sequence. Kalir[146] used the same aqueous mixture of reagents without the metabisulphite and adjusted to pH 3-4 when the desired crystalline product was produced. Janssen[148] used the Tieman-Strecker synthesis and employed an aqueous ethanolic solution of these reagents to obtain a good yield of α-aminonitrile. Another variation by House et al.[149] was to treat the enamine (158) in chloroform solution with acetonecyanohydrin when the aminonitrile (159) was produced.



(158) (159)

All of these methods gave good yields but the method adopted in the present work to synthesise aminonitriles (160-164) was to reflux equimolar proportions of potassium cyanide, cyclohexanone and the hydrochloride salt of the appropriate base in aqueous ethanol for 24 hr. The reactions proceeded smoothly and good yields were obtained.



(160) NRR^1 = Dimethylamino

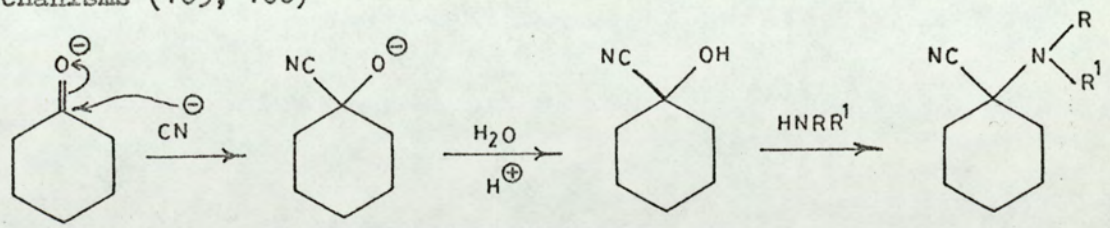
(161) NRR^1 = Piperidyl

(162) NRR^1 = Azabicyclo[3,2,2]nonyl

(163) NRR^1 = $\underline{N}^4$-methylpiperazinyl

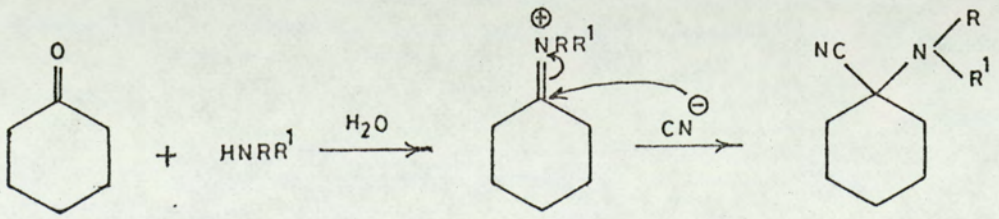
(164) NRR^1 = Pyrrolidinyl

This reaction is a modified Strecker synthesis and may proceed via two mechanisms (165, 166)



(Scheme 165)

In scheme (165) the cyanohydrin is produced first. The presence of a strong electron withdrawing group α to the hydroxy group causes the latter to be a much better leaving group and nucleophilic substitution occurs.

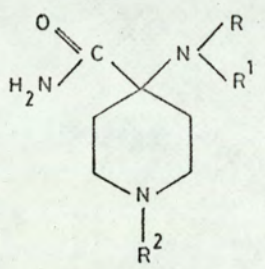


(Scheme 166)

In a second, more favoured mechanism shown in scheme (166) the amine may add first forming an imine followed by nucleophilic addition of the CN^-.

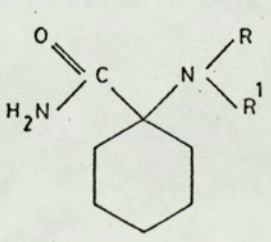
(F): Preparation of some 1,1-substituted aminocyclohexylamides

Janssen[148,150] has prepared a series of substituted aminoamides starting from N-substituted 4-piperidones. Although the simpler N-benzyl (167), nor-(168), N-arylalkyl (169) and N-aryloxyalkyl (170) derivatives of 4-piperidino-4-piperidinecarboxamide were devoid of C.N.S. - depressant activity, those compounds derived from α,α-diphenylbutyronitrile (171) had potent analgesic activity.



(167) R^2 = benzyl
(168) R^2 = H
(169) R^2 = arylalkyl
(170) R^2 = aryloxyalkyl
(171) R^2 = α,α-diphenylbutyronitrile

The nitrile intermediates (160-164) were therefore first used to synthesise the corresponding amides (172a-e). The chemical properties of α-amino nitriles are largely determined by the fact that they bear an electropositive and electronegative group on the same carbon atom. The properties of this class of compounds are unusual.[151, 152] The treatment of nitriles (160-164) with sulphuric acid gave the corresponding carboxamides (172 a-e) in very good yields.

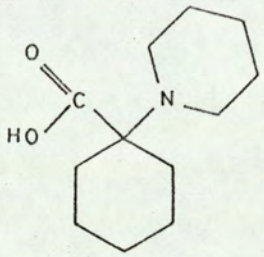


(172a) NRR^1 = Dimethylamino
(172b) NRR^1 = Piperidyl
(172c) NRR^1 = Azabicyclo[3,2,2]nonyl
(172d) NRR^1 = N^4-methylpiperazinyl
(172e) NRR^1 = Pyrrolidinyl

These compounds were submitted for primary C.N.S. screening and the detailed reports are presented in the pharmacology section. Amides (172 c-e) showed negligible activity with hyperthermia 0.5 - 0.9° in test

animals, amide (172a) was completely inactive and only amide (172e) showed moderate activity with a Straub tail response and raised posture in mice.

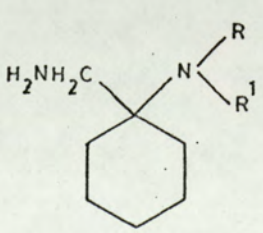
A literature search revealed no example of the direct alcoholysis of a ketone-derived α-amino nitrile to the corresponding ester. When this reaction was applied to nitrile (163) the desired ester was not obtained. A successful hydrolysis of α-tert-amino nitriles derived from ketones has been achieved only twice.[153,148] When both acid and alkaline hydrolysis procedures were applied to the nitrile (163) the desired acid was not obtained, but acid hydrolysis of the nitrile (161) to the corresponding acid (172f) has been reported[154] using a continuous chloroform extraction process to isolate the product.



(172f)

(G): Preparation of some substituted cyclohexyldiamines

Some of the diamino compounds reported by the Janssen group[144,148] are active analgesics. In many of these compounds both nitrogen atoms are part of heterocyclic structures. The compounds reported here have one primary amine function and one tertiary amine function separated by two carbon atoms one of which is carbon atom one of the cyclohexane ring. Nitriles (160-164) were treated with 2 moles of lithium aluminium hydride to give the corresponding cyclohexyldiamines (173-176) in excellent yields, but an anomalous result was obtained with nitrile (162)



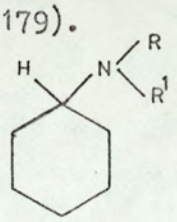
(173) NRR^1 = Dimethylamino

(174) NRR^1 = Piperidyl

(175) NRR^1 = N^4-methylpiperazinyl

(176) NRR^1 = Pyrrolidinyl

The nitrile (162) gave a monoamine (177) and this product was also synthesised from bromocyclohexane and azabicyclo [3,2,2] nonane in a condensation reaction. In both procedures the final product was characterised as the hydrochloride which had a m.p. undepressed on admixture and superimposable infra red spectra. Further anomalies were found with nitriles (161, 164) which in preliminary runs with small amounts of lithium aluminium hydride (0.02 mole) gave the diamines (174, 176) but in experiments using the same reducing agent (0.3 mole) gave monoamines(178, 179).

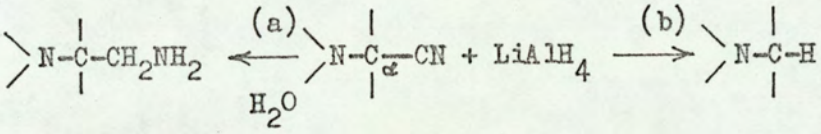


(177) NRR^1 = Azabicyclo[3,2,2]nonyl

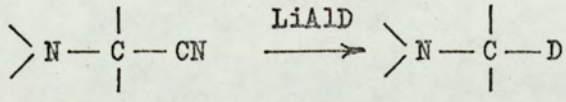
(178) NRR^1 = Piperidyl

(179) NRR^1 = Pyrrolidinyl

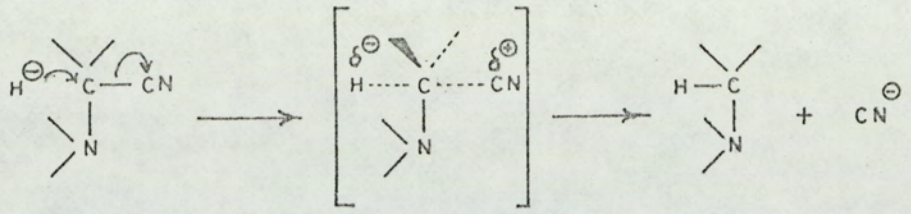
Few examples of this reaction could be found in the literature although dehalogenation with lithium aluminium hydride is reported.[155] Chauvière[167] et al. 1963 reported on this type of reaction in the α-aminonitriles.



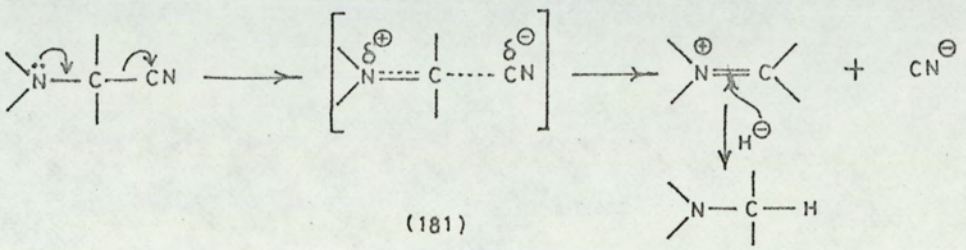
Where the α carbon is monosubstituted reaction (a) predominates and where it is disubstituted reaction (b) predominates. Competitive reactions can occur simultaneously. Reaction (a) is the normal sequence expected when nitriles are treated with lithium aluminium hydride. Reaction (b) is a replacement of CN with H since



a deutero product[167,168] is obtained when lithium aluminium deuteride is used. This nucleophilic substitution may follow either an S_N2 (180) or S_N1 mechanism (181).

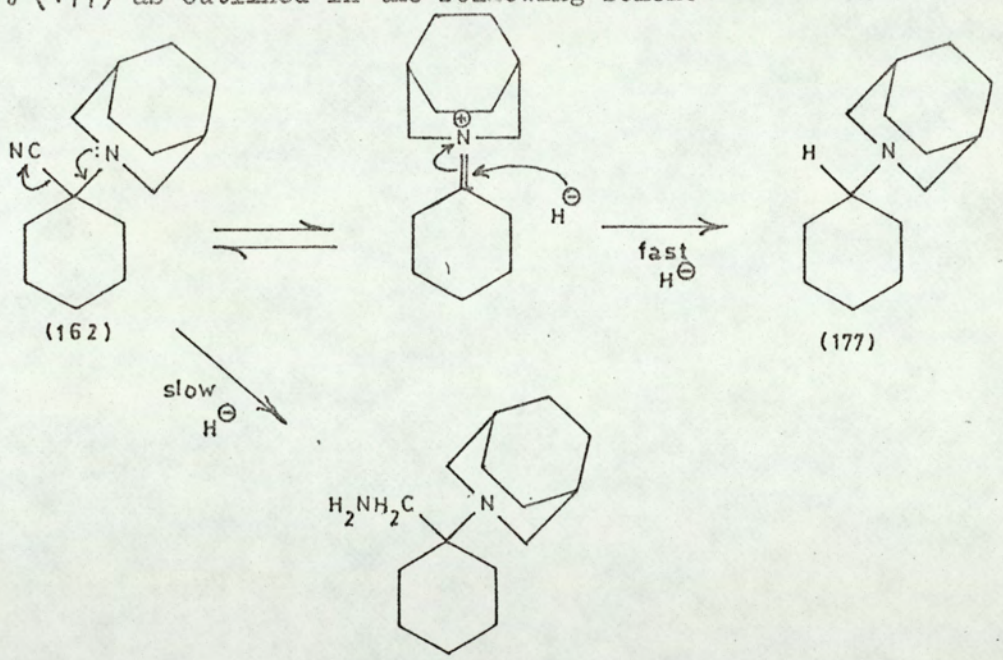


(180)

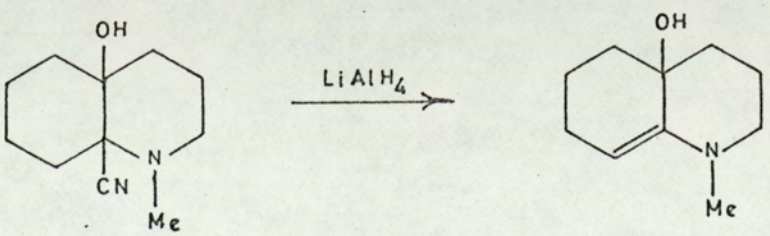


(181)

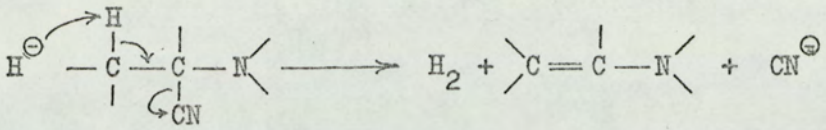
Therefore the nitrile (162) could give the normal amine or the anomalous product (177) as outlined in the following scheme.



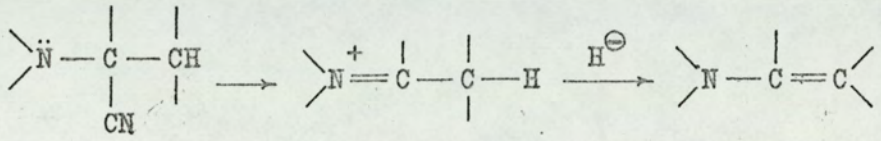
Leonard et al.[169,170] have proposed that the reaction of certain nitriles with lithium aluminium hydride proceeds via an enamine :-



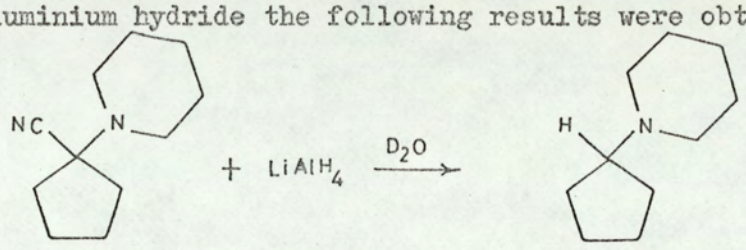
This may involve a one step sequence,

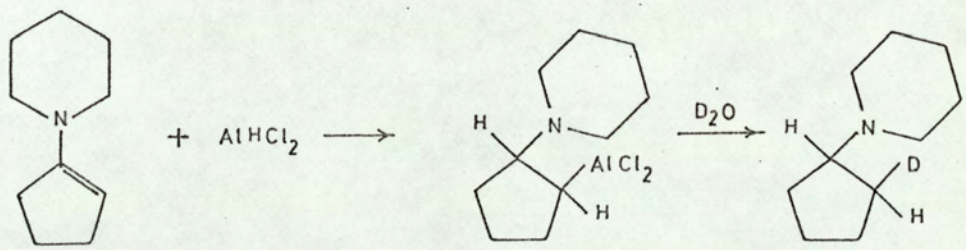


or a two step sequence :-



However in the reaction of α-aminonitriles with lithium aluminium hydride and dichloraluminium hydride the following results were obtained :-





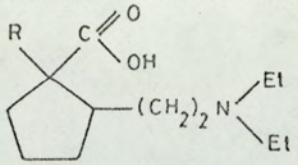
These results show that this type of reaction does not proceed via an enamine intermediate. The S_N1 sequence appears to be the most probable mechanism.

The diamines (173-176) were not tested for biological activity but one of the anomalous monoamines (177) was found to be inactive in the primary neuropharmacological screen.

(H): Preparation of methyl and formyl derivatives of some cyclohexyldiamines and triamines

Dialkylamino groups form a fundamental part of the structure of many biologically active compounds. Examples of such compounds related to

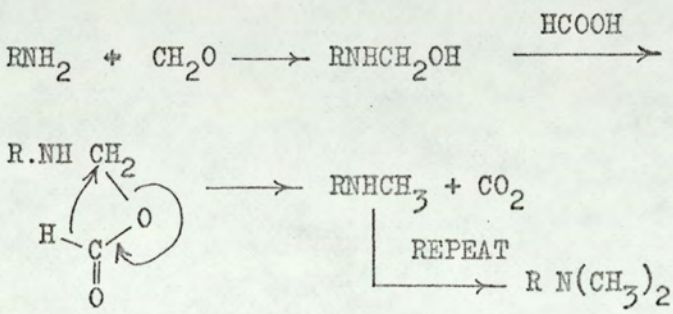
those reported in this work are the diethylamines (182, 183).



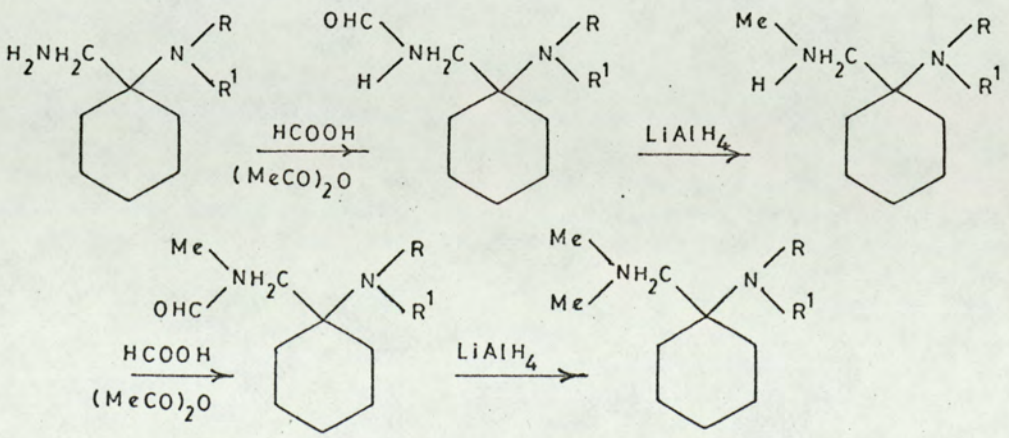
(182) R = Phenyl = CARAMIPHEN

(183) R = 2'-Methylphenyl

Dimethylamines may be prepared by the Eschweiler-Clarke procedure, a variant of the Leuckart reaction which gives high yields of tertiary amines. In this reaction the primary amine is treated with formic acid and formalin,[146] the reaction proceeding :-

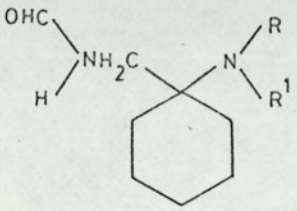


In the present work one of the aims was to investigate formyl as well as methylamine derivatives for C.N.S. effects and particularly the change in activity observed in compounds with the exocyclic nitrogen made non-basic. Formylation of amines using chloral hydrate was first reported by Hofmann[157] and used extensively by Blicke.[158] A mixture of formic acid and acetic anhydride also acts as a formylating agent by producing formic anhydride *in situ* and acting as a mixed anhydride. Erlich[159] reported the reduction of formylamines to methylamines using lithium aluminium hydride. A four-step procedure involving two formylation and two reduction steps is shown in scheme (184).



(Scheme 184)

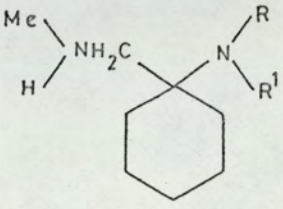
Although this procedure is more laborious it was adopted because both formyl and methyl derivatives can be prepared with advantage in good yields. The following series of compounds was synthesised using this four-step sequence.

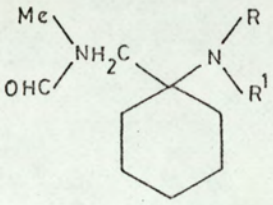


(185) NRR^1 = $\underline{N}^4$-methylpiperazinyl (188)

(186) NRR^1 = dimethylamino (189)

(187) NRR^1 = piperidyl (190)

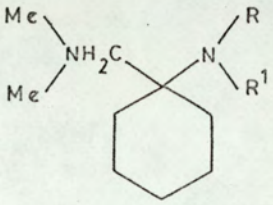




(191) NRR^1 = $\underline{N}^4$-methylpiperazinyl (194)

(192) NRR^1 = dimethylamino (195)

(193) NRR^1 = piperidyl (196)



The formylamines crystallised as solid basic compounds but the methyl and dimethylamines were characterised by conversion to solid hydrochlorides or quaternary iodides. A selection of these compounds was screened for C.N.S., antimicrobial, antimycoplasma and antianaphylactic activity. The detailed reports appear in the pharmacology section showing the compounds to be inactive in all areas except the C.N.S. Two of the $\underline{N}^4$-methylpiperazinyl derivatives, the monoformyl (185) and dimethyl (194) were also inactive in the C.N.S. However the dimethylamino (186, 189, 192, 195) and piperidyl (190, 193, 196) derivatives all showed some degree of C.N.S. activity notably in the direct hot-plate and phenylquinone induced writhing tests (Table 12).

TABLE 12

COMPOUND	DIRECT HOT-PLATE TEST	EFFECT ON PHENYL QUINONE INDUCED WRITHING	COMPOUND	DIRECT HOT-PLATE TEST	EFFECT ON PHENYL QUINONE INDUCED WRITHING
(186)	MODERATE ACTIVITY 55% INHIBITION SLIGHT TREMOR	INACTIVE			
(189)	NEGLIGIBLE ACTIVITY	MARKED ACTIVITY $\simeq$ ASPIRIN	(190)	MARKED ACTIVITY 100% INHIBITION	MARKED ACTIVITY $>>$ ASPIRIN
(192)	NEGLIGIBLE ACTIVITY	MARKED ACTIVITY 3/6 ANIMALS DIED	(193)	MARKED ACTIVITY 82% INHIBITION	MODERATE ACTIVITY $<$ ASPIRIN
(195)	MARKED ACTIVITY VIOLENT TREMORS	INACTIVE	(196)	NEGLIGIBLE ACTIVITY	MODERATE ACTIVITY

COMPOUND	DIRECT HOT-PLATE TEST	EFFECT ON PHENYL QUINONE INDUCED WRITHING
(185)	NEGLIGIBLE ACTIVITY	MODERATE ACTIVITY
(191)	MARKED ACTIVITY 77% INHIBITION	MARKED ACTIVITY $\geq$ ASPIRIN
(194)	INACTIVE	INACTIVE

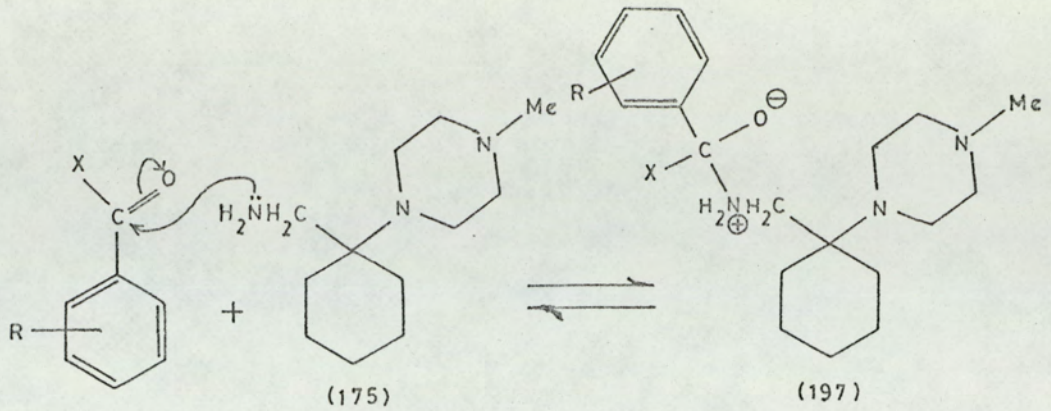
Several general comments can be made from these results. The N-formylmethylaminomethyl compound (192) shows mixed activity in the two principal results tabulated and the associated toxicity rules out any further interest in it. Since the most active compounds are the

N-formylmethylaminomethyl compound (191) and the N-methyl compound (190) no conclusion can be drawn about the importance of the formyl group in relation to C.N.S. activity in this series. The latter compound in particular is also of interest because it produces a reduced response to pain in mice, showing it to be a fairly good lead compound for analgesic activity. This compound is being investigated for analgesic activity in the dog using the dental pulp technique. A further interesting fact is that this compound does not contain an aromatic group which would be rather unusual if the compound is shown to be a narcotic analgesic. The dimethylamine (189) has also been tested in the rat adjuvant arthritis screen but no suppression of the disease was observed.

(I): Preparation of substituted benzamido derivatives of some cyclohexyldiamines and triamines

In a similar way to formylation, the primary amine function in these diamino molecules can be made non-basic by synthesising benzamido and substituted benzamido derivatives. This also introduces an aromatic substituent which is believed to be of structural significance in analgesic molecules. A well-documented technique in many chemical studies designed to enhance analgesic activity is to introduce halogens at the 3-, 4-, and 3,4-positions of the phenyl ring in the molecule. The substituted benzamido derivatives can therefore be 3-, 4-, and 3,4-halogen substituted benzamides. Acylation of amines was reviewed by Sonntag[160] and a mechanistic study reported by Bender and Jones.[161]

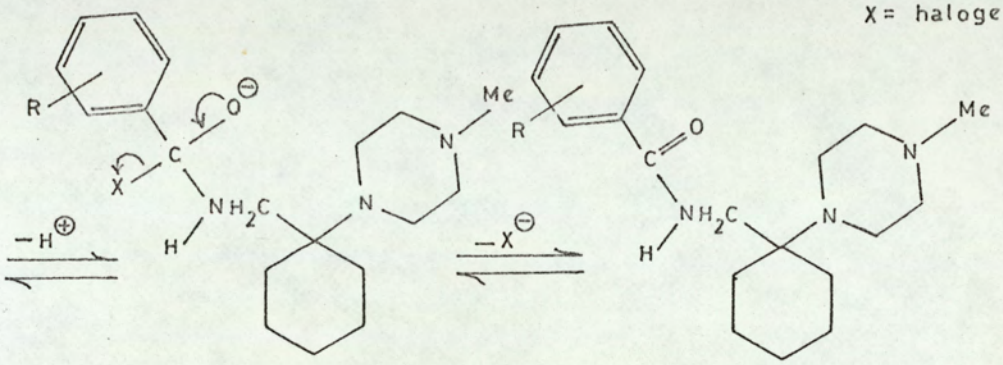
A preliminary study was made using the amine (175) and benzoyl chloride in the presence of pyridine when a good yield of the benzamide (198, R=H) was obtained. In the reaction mechanism the lone pair on the nitrogen plays a significant role in producing the intermediate (197) which by loss of a proton and elimination of the X^- gives the desired benzamide (198, R=H).



(175) (197)

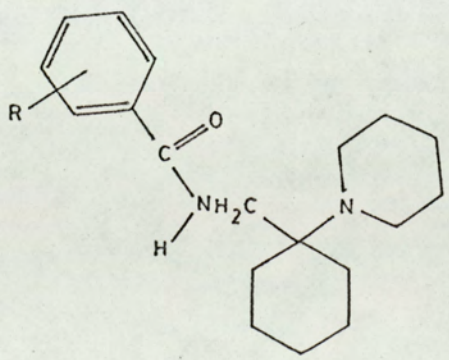
R = H, halogen

X = halogen



(198)

A further two series of substituted acyl derivatives of cyclohexylpiperidine (199-202) and cyclohexyldimethylamine (203-205) were then synthesised using the same procedure.

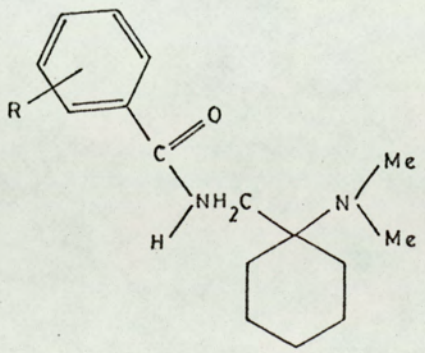


(199) R = H

(200) R = 4-F

(201) R = 3,4-di Cl

(202) R = 2-Cl



(203) R = H

(204) R = 4-F

(205) R = 3,4-di Cl

These compounds were submitted for primary C.N.S. screening and the detailed results appear in the pharmacology section. The piperidyl compounds were of little interest because the fluorobenzamide (200) was too toxic, the 2-chlorobenzamide (202) showed marked activity only in the phenylquinone induced writhing test and in the 3,4-dichlorobenzamide (201), although mice were reported to show the Straub tail effect, no activity was recorded for any other test. When the 2-chlorobenzamide (202) was reassessed for analgesic activity the oral ED_{50} value against phenyl quinone induced writhing was found to be 6.4 mg /kg and the subcutaneous ED_{50} value in the hot plate test 77 mg /kg. This compound possesses some analgesic activity without inducing Straub tail, moreover the compound has a long duration of action in the hot plate test. However, the compound is less potent and more toxic than its 3,4-dichlorobenzamide analogue (205). However, all three dimethylamino compounds showed well-marked and interesting activity. The unsubstituted benzamide (203) completely abolished the reflex response of a mouse placed on a hot plate and inhibited writhes induced by phenyl-quinone in the primary neuropharmacological screen. Table 13 shows that this activity was improved in the 4-fluoro (204) and 3,4-dichlorobenzamide (205) compounds and in addition both of these compounds produced a reduced response to pain in mice.

TABLE 13

COMPOUND	BEHAVIOUR IN THE MOUSE	DIRECT HOT PLATE TEST	EFFECT ON PHENYL QUINONE INDUCED WRITHING
(203)	MODERATE ACTIVITY STRAUB TAIL RAISED POSTURE	MARKED ACTIVITY 100% INHIBITION	MODERATE ACTIVITY $<$ ASPIRIN
(204)	REDUCED RESPONSE TO PAIN	MARKED ACTIVITY 100% INHIBITION	MARKED ACTIVITY $\gg$ ASPIRIN
(205)	REDUCED RESPONSE TO PAIN	MARKED ACTIVITY 100% INHIBITION	MARKED ACTIVITY $\gg$ ASPIRIN

The unsubstituted benzamide (203) has been investigated further and appears to possess some analgesic activity in the mouse with no indication of addiction liability when given intravenously at an LD.50 of 45 mg /kg body weight. These analgesic tests are to be extended to examine the activity of the compound in the dog using the dental pulp test. The dichlorobenzamide (205) is also being more extensively tested.

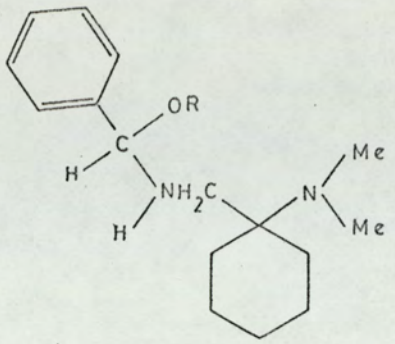
In a further attempt to assess the importance of the non-basic nitrogen in analgesic activity the active benzamide (203) was reduced to the corresponding alcohol (206) which in turn was esterified (207). Primary neuropharmacological reports on these compounds showed that activity was reduced. Table 14 shows that activity against phenylquinone induced writhing was completely absent in both the alcohol (206) and the ester (207). An interesting result is shown in the direct hot plate test where the diamino alcohol (206) reduces inhibition and in the ester (207) inhibition is increased to halfway between that of the alcohol (206) and the benzamide (203).

TABLE 14

COMPOUND	DIRECT HOT PLATE TEST	EFFECT ON PHENYL QUINONE INDUCED WRITHING
(203)	MARKED ACTIVITY 100% INHIBITION	MODERATE ACTIVITY < ASPIRIN
(206)	MODERATE ACTIVITY 55% INHIBITION	INACTIVE
(207)	MARKED ACTIVITY 77% INHIBITION	INACTIVE

In the dimethylamine series of compounds it seems clear that the non-basic nitrogen of the amide or ester group enhances biological activity and this

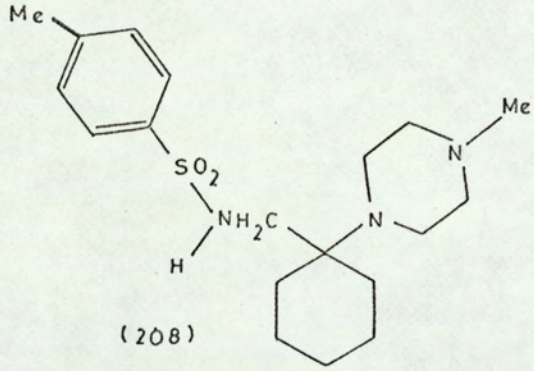
can be further improved by the introduction of halogens in the 3 or 4 positions of the benzamide function.



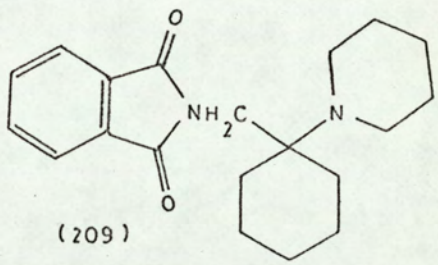
(206) R = H

(207) R = C(=O)Me

Two further amine derivatives were synthesised. The amine (175) was converted to the tosyl derivative (208) and the amine (174) was converted to a phthalimido derivative (209) where the non-basic nitrogen is now in a cyclic system. However, both compounds were inactive when tested in a primary C.N.S. screen.



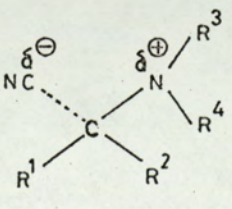
(208)



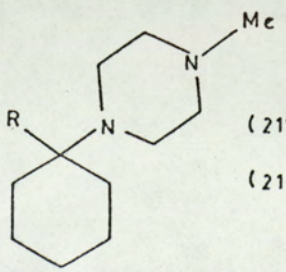
(209)

(J): Preparation of iminocyclohexylamines and their derivatives

The unusual properties of α-aminonitriles have been referred to previously,[151,152] and these are clearly demonstrated by the reaction of these compounds with Grignard reagents. In these reactions it has been found that ketone formation rarely occurs and that nitrile replacement frequently takes place. Welvart[162] has suggested that the α-aminonitriles act via an immonium ion (210).



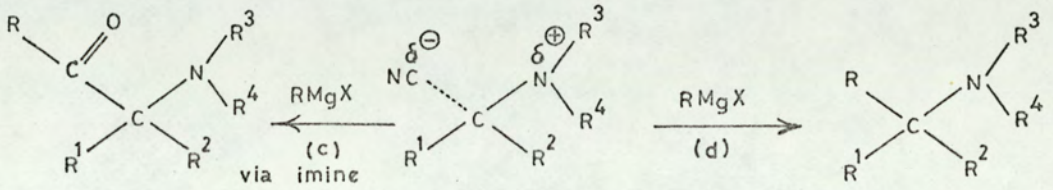
(210)



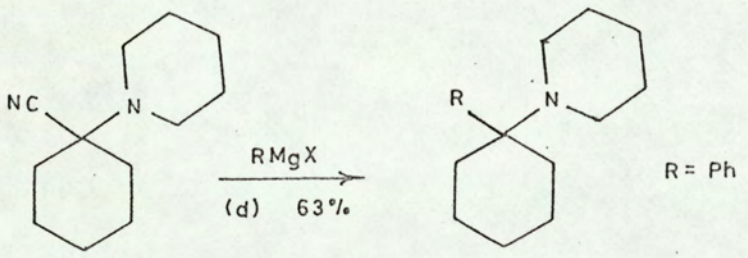
(211) R = Me

(212) R = Ph

Since in such an ion the chemical bond between α-C and CN has both electrovalent and covalent character, both carbon atoms can react with a nucleophilic reagent RMgX. The nature of R^1, R^2, R^3 and R^4 determines the course of the reaction such that where R^1 and R^2 are different from hydrogen the nitrile group is replaced by the radical of the Grignard complex. Later, Welvart[163,168] also implicated the type of Grignard reagent used in determining this course of events.

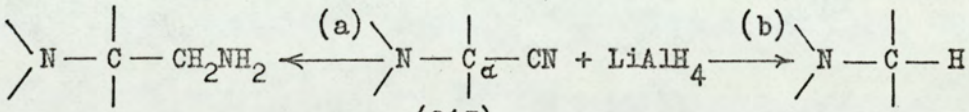


(213)



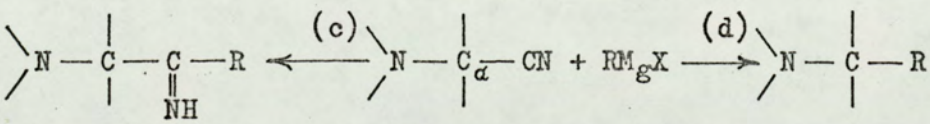
(161) (214)

The reactions of α-aminonitriles with Grignard reagents and lithium aluminium hydride are worth comparing. Reaction sequence (215)



(215)

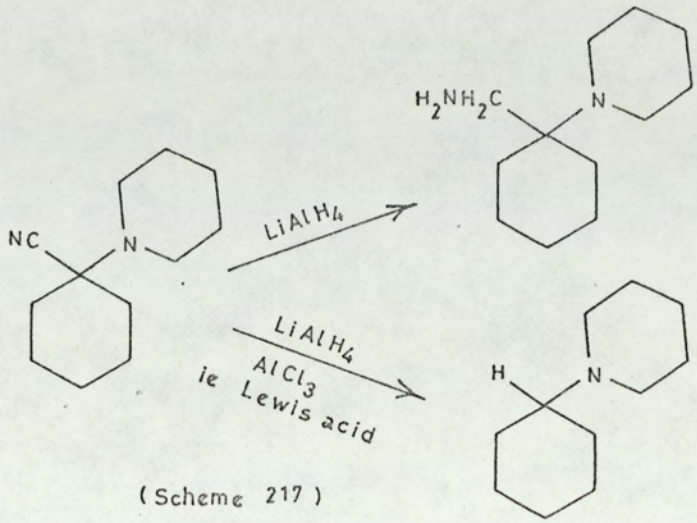
seems to be analagous to reaction sequence (216)



(216)

especially since in the lithium aluminium hydride reactions the presence of aluminium chloride alters the product obtained (scheme 217). The presence of a Lewis acid favours reaction (b) in the lithium aluminium hydride sequence and RM_gX acting as a Lewis acid similarly favours reaction (d) in

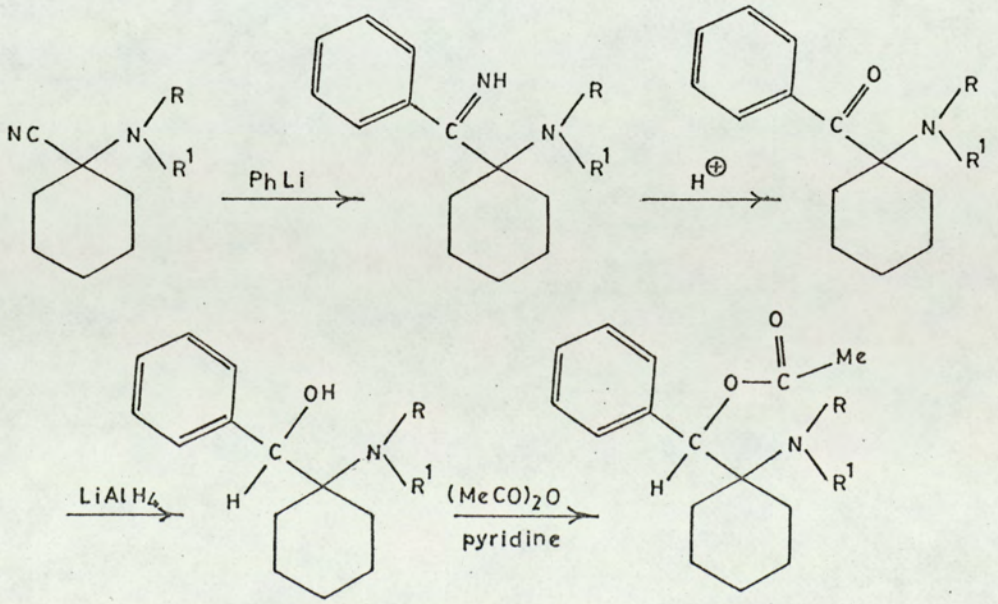
the Grignard reaction sequence. An S_N1 mechanism is proposed for both reactions (b) and (d).



(Scheme 217)

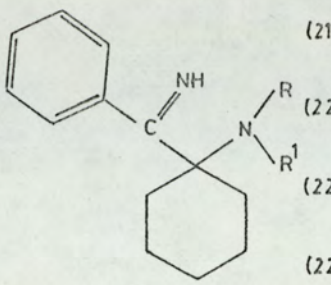
When the α-aminonitrile (163) was treated with aliphatic and aromatic Grignard reagents only nitrile replacement was found to occur giving alkyl (211) and aryl (212) compounds.

Since neither imines nor ketones were obtained in the Grignard reaction the α-aminonitriles were treated with organolithium compounds which are reported[164-167,144,146] to give only ketone formation. Theα-aminonitriles (160, 162-164) all reacted smoothly via imines to yield ketones which were reduced to their corresponding secondary alcohols which in turn were esterified (scheme 218)



(Scheme 218)

The imines were isolated pure in all cases and using the scheme as outlined the following series of compounds was made.

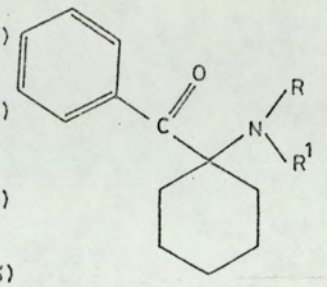


(219) NRR^1 = dimethylamino

(220) NRR^1 = azabicyclo[3,2,2]nonyl

(221) NRR^1 = $\underline{N}^4$-methylpiperazinyl

(222) NRR^1 = pyrrolidinyl

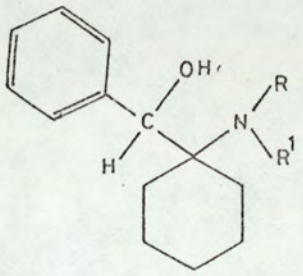


(223)

(224)

(225)

(226)

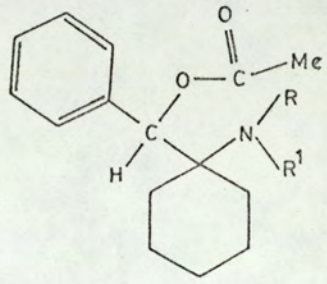


(227) NRR^1 = dimethylamino

(228) NRR^1 = azabicyclo[3,2,2]nonyl

(229) NRR^1 = $\underline{N}^4$-methylpiperazinyl

(230) NRR^1 = pyrrolidinyl



(231)

A selection of these compounds was sent for primary neuropharmacological screening. The only imine (220) tested was completely inactive. All of the ketones were screened, the azabicyclo (224) and the pyrrolidinyl (226) derivatives proving to be inactive. However a comparison of the dimethylamino (223) and $\underline{N}^4$-methylpiperazinyl (225) ketones in table 15 shows the former to have moderate activity in only one test but the latter to be markedly active in three tests. Unfortunately this latter compound was too toxic to be of further interest.

TABLE 15

COMPOUND	BEHAVIOUR IN THE MOUSE	EFFECT ON BODY TEMPERATURE	EFFECT ON PHENYL QUINONE INDUCED WRITHING
(223)	INACTIVE	INACTIVE	MODERATE ACTIVITY < ASPIRIN
(225)	MODERATE TO MARKED ACTIVITY CONVULSIONS, LIMB SPLAY, DEPRESSION	MARKED ACTIVITY HYPOTHERMIA 4.3°C 3/6 ANIMALS DIED	MARKED ACTIVITY $\underline{\Omega}$ ASPIRIN

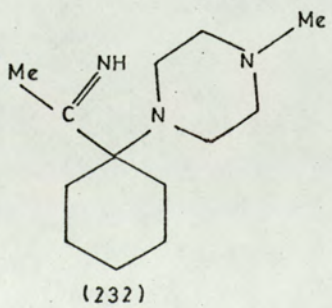
All four alcohols (227—230) were also tested. The N^4-methylpiperazinyl (229) and azabicyclo (228) alcohols showed negligible activity but both the dimethylamino (227) and pyrrolidinyl alcohols (230) showed interesting pharmacological properties. Table 16 shows this latter pair of compounds to have marked activity in two of the three standard tests for C.N.S. activity. In particular the dimethylamino alcohol (227) shows a general depressive effect upon the C.N.S. which could possibly be enhanced ~~by~~ in analogous compounds.

TABLE 16

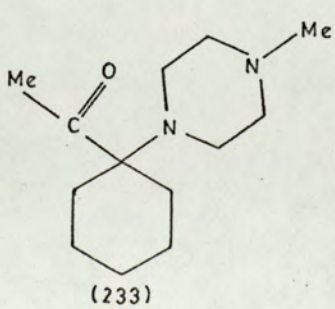
COMPOUND	ANTI-MAXIMUM ELECTRO SHOCK	DIRECT HOT PLATE TEST	EFFECT ON PHENYL QUINONE INDUCED WRITHING
(227)	MARKED ACTIVITY 100% INHIBITION OF TONIC EXTENSOR SEIZURES	NEGLIGIBLE ACTIVITY	MARKED ACTIVITY WRITHING ALMOST ABOLISHED
(230)	INACTIVE	MARKED ACTIVITY 92% INHIBITION	MARKED ACTIVITY ⎓ ASPIRIN

The one ester (231) synthesised in this series was inactive.

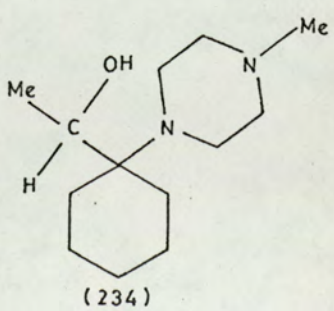
Two further series of compounds were prepared using the organo-lithium technique. The α-aminonitrile (163) on treatment with methyl lithium gave the corresponding methylimine (232) which on hydrolysis yielded the ketone (233) and on reduction gave the alcohol (234).



(232)



(233)

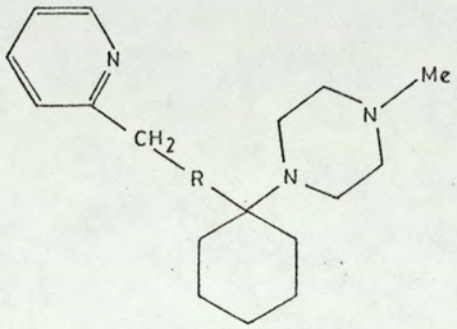


(234)

The alcohol (234) did show moderate activity in the effect on phenyl quinone induced writhing but otherwise these compounds were inactive and

therefore this study of the insertion of a methyl group was not extended to the other α-aminonitriles previously used.

The α-aminonitrile (163) was also treated with picolyl lithium and the imine product hydrolysed directly to the ketone (235). This was reduced with lithium aluminium hydride to the corresponding alcohol (236). These compounds have not been tested as yet and the study was not extended to the other α-aminonitriles.



(235) R = C=O

(236) R = CHOH

A further object of the present investigation was to attempt to verify structure-activity relationships based upon pharmacological results. In the presentation of each group of derivatives the tertiary amine moiety has been modified and comparative activities discussed where this was possible. Some general conclusions may now be drawn.

The aminocyclohexylamides (172a-e) were modified with five tertiary amine functions and all were inactive in the primary C.N.S. screen.

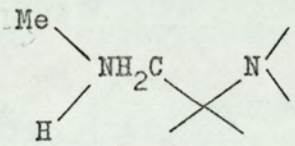
Only one of the two monoformyl derivatives (185, 186) tested showed moderate activity and hence this non-basic nitrogen function cannot be implicated as being essential for C.N.S. activity.

Both of the monomethylaminomethyl derivatives (189, 190) showed marked activity, the piperidyl compound (190) showing the greater activity. Clearly these diamino compounds show much better analgesic effects than their monoformyl analogues.

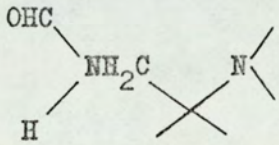
The N-formylmethylaminomethyl compounds (191 – 193) are all active. Although the dimethylamino compound (192) is toxic the overall analgesic properties do not seem to be markedly altered by changing the basic moiety. The dimethylamino (192) and piperidyl (193) compounds both show slightly

less activity than their monomethylaminomethyl analogues.

All the dimethylaminomethyl compounds (194-196) show only moderate activity. The proton on the monomethylaminomethyl derivatives may therefore be important in enhancing analgesic activity, particularly when it is attached to a basic nitrogen (237) rather than a non-basic nitrogen (238).

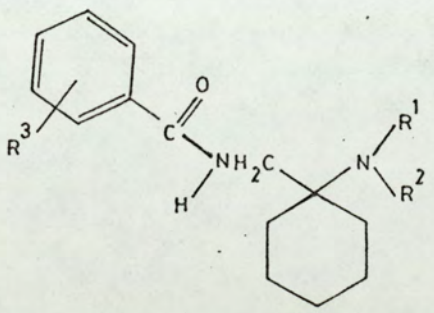


(237)



(238)

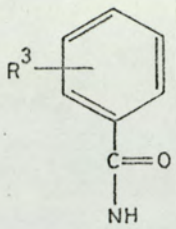
The benzamide and halogen substituted benzamides showed the most marked C.N.S. activity. The piperidyl compounds (200, 202) showed moderate to marked activity but the dimethylamino derivatives (203-205) were particularly active and all are being tested further. The importance of the non-basic nitrogen in this group of acylated compounds has been demonstrated by reducing the amide (203) to the alcohol (206) which shows reduced activity but on esterifying this alcohol, the ester (207) shows activity between that of the parent amide (203) and the alcohol (206).



(239)

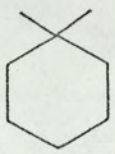
NR^1R^2 :- of the tertiary bases used, dimethylamino is preferred.

N-C=O
|
H
:- appears to be important in structure-activity relationships in two respects. First it introduces an exocyclic N atom which is non-basic (see the corresponding alcohol (206) and ester (207) studies). In addition the attached proton also seems to have significance.



:- Where R^3 = H, compound is active as an analgesic

R^3 = 4-F; 3,4-dichloro; analgesic activity is enhanced.



:- The importance of this part of the molecule has not been established either with regard to ring size or whether a carbocyclic system is necessary to retain activity.

Phenyl ketones (223-226) and phenyl alcohols (227-230) all showed at least moderate activity, the alcohols in most cases showing enhanced activity.

When the compounds are examined from the point of view of keeping the tertiary amine moiety the same and looking at the differences in activity induced by varying the other substitutents, some further conclusions can be drawn.

All the dimethylamino compounds are active with the exception of the amido derivative (172a). In particular where these compounds contain a second exocyclic nitrogen function which is non-basic, marked activity is found. This non-basic, exocyclic nitrogen with a proton attached to it may be significant in the relationship between structure and analgesic effect.

The piperidyl compounds show very variable activity. In derivatives with an exocyclic nitrogen function which is either basic (190) or non-basic (193) high levels of activity are recorded. However, in the benzamido derivatives (200-202) where good activity was expected, negligible activity was found. Clearly, since the rest of the molecule is identical in these benzamides the differences in activity must be associated with the tertiary amine function and dimethylamino is preferred to piperidyl.

Insufficient screening was carried out on the pyrrolidinyl compounds,

of which only one, the phenyl alcohol (230) showed marked activity.

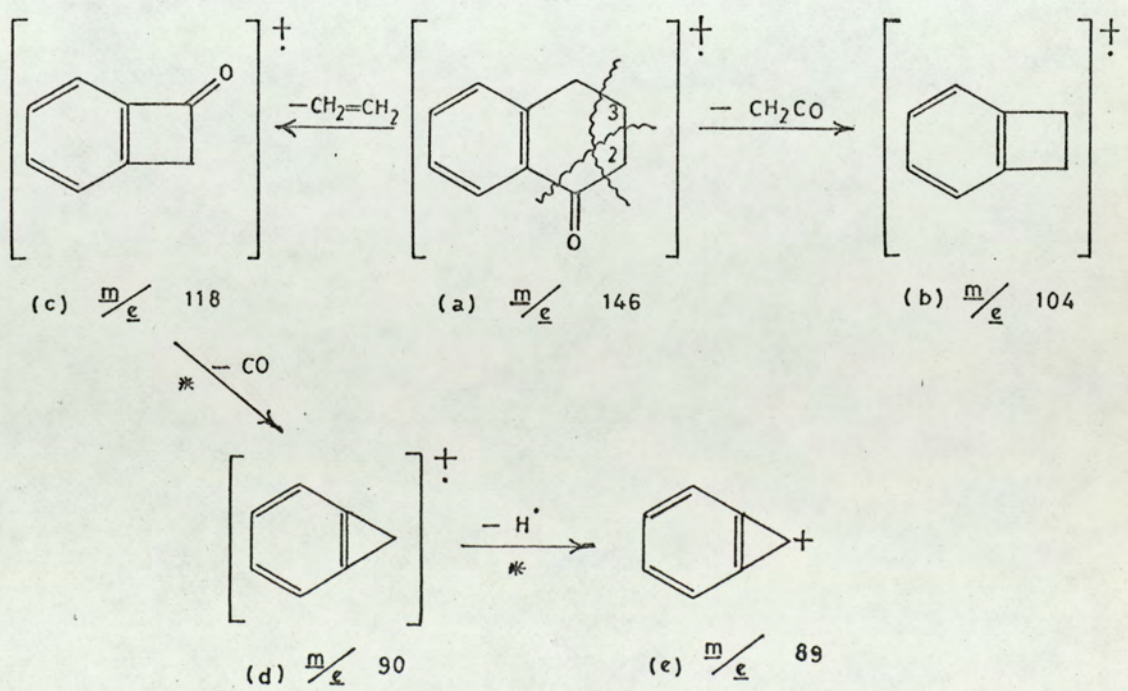
Although a wide variety of N-methylpiperazinyl compounds were tested only two of these, the phenyl ketone (225) and the N-formylmethyl-aminomethyl (191) showed marked activity and the latter was toxic. No clear pattern of activity is shown by these derivatives.

All the azabicyclo compounds showed negligible activity.

(K): Mass Spectrometry

In the present work a brief consideration of the mass spectra of a selection of the compounds synthesised is reported. Schemes for proposed degradation pathways are suggested on the basis of the major peaks observed, but some minor pathway possibilities are also outlined. In the more complex spectra some metastable peaks and certain fragments are unassigned.

The mass spectra of 1-tetralone and various deuterio-derivatives have been reported,[171] and the postulated fragmentation patterns are shown in scheme (240).

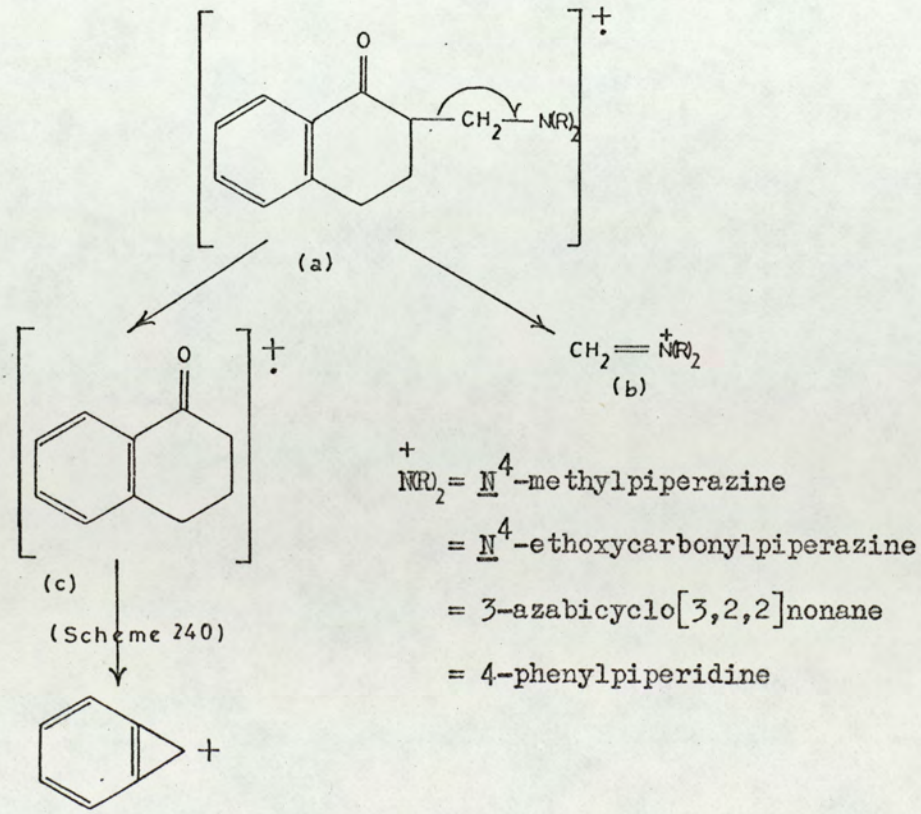


(Scheme 240)

From the spectrum of 1-tetralone (deuterated), the loss of ethylene from M^+ comes exclusively from the 2,3-position to form (c), ($\underline{m}/\underline{e}$ = 118). Subsequent fragmentation yields benzocyclopropenyl cation (e), ($\underline{m}/\underline{e}$ = 89). The loss of 15, 16, and 17 mass units equally from the 1-tetralone-d_2 molecular ion ($\underline{m}/\underline{e}$ = 148) shows that the loss of $Me^{\bullet}$ is a random process possibly involving all saturated centres. Although alkyl substituted 1-tetralones should follow this general fragmentation pattern caution should be taken in extending the analogy.

The mass spectra of piperidine and some derivatives have been reported.[172,173] These spectra are complex because of an increased number of possibilities for bond cleavage of the molecular ion and the hydrogen rearrangement products. The fragmentation behaviour of piperazine and derivatives[172] resembles that of piperidine.

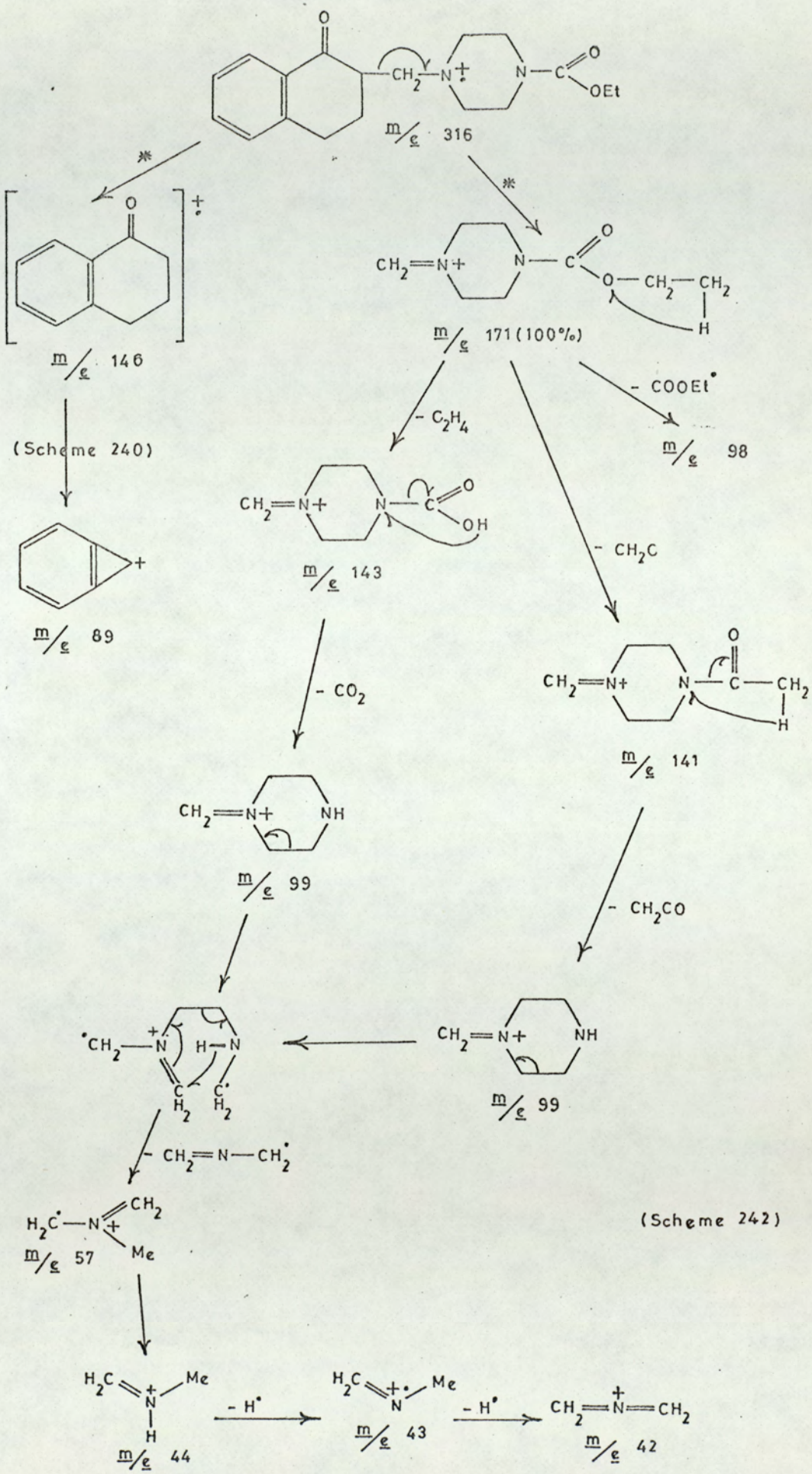
The Mannich bases of 1-tetralone (105-108) have been shown to undergo α-cleavage and $H^{\bullet}$ transfer to produce the main fragment ion (b) and (c) in scheme (241).



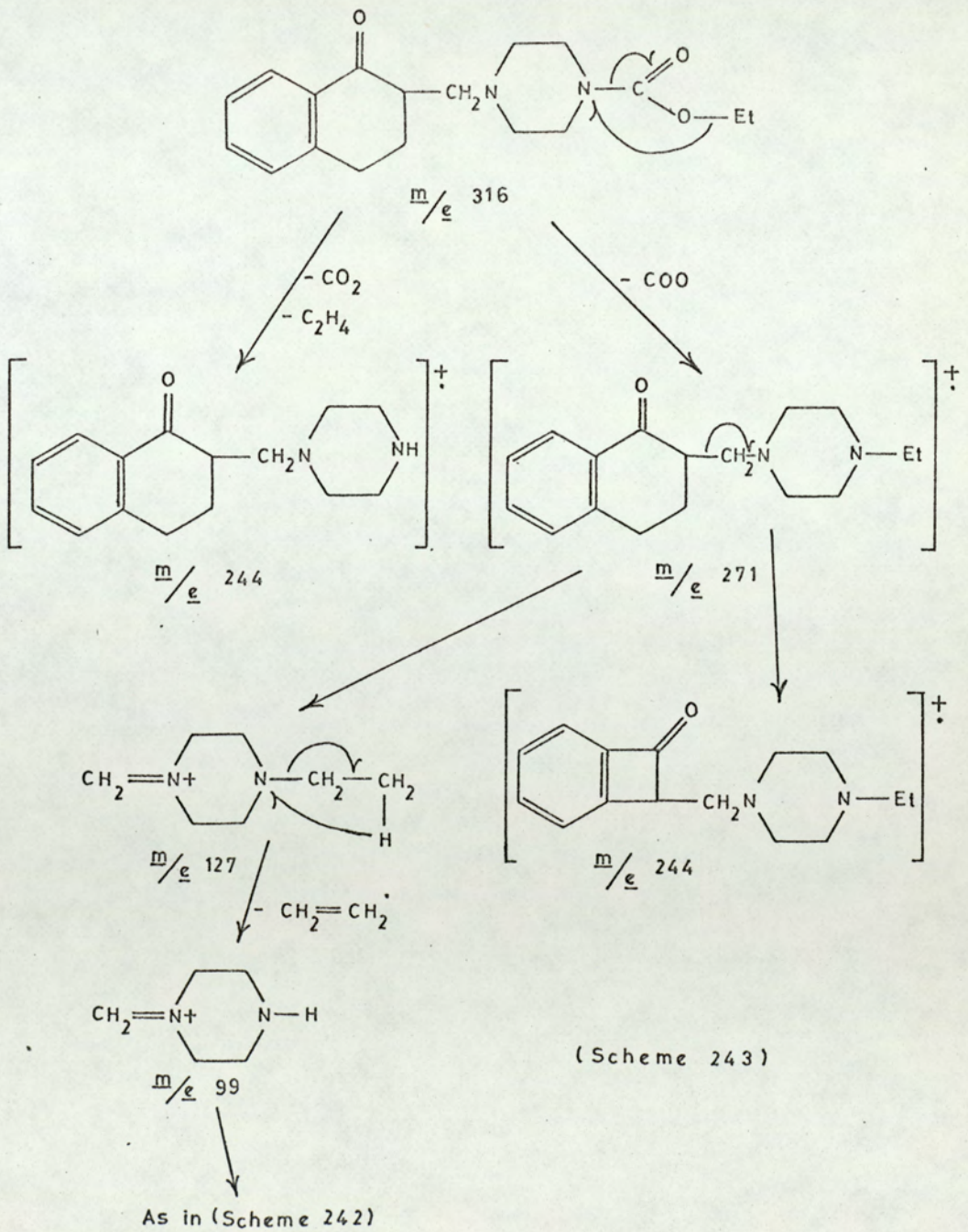
(Scheme 241)

2-(4-Ethoxycarbonylpiperazinylmethyl)-1-tetralone (108)

The mass spectrum of 2-(4-ethoxycarbonylpiperazinylmethyl)-1-tetralone shows a molecular ion peak at $^{m}/_{e}$ 316. This compound undergoes α-fission to give the cation fragment $^{m}/_{e}$ 171 as the base peak. Loss of ethylene from this fragment followed by loss of CO_2 yields the ion $^{m}/_{e}$ 99. β-cleavage accompanied by hydrogen transfer expels $CH_2{=}N{-}CH_2^{\bullet}$ to give fragment $^{m}/_{e}$ 57, scheme (242).

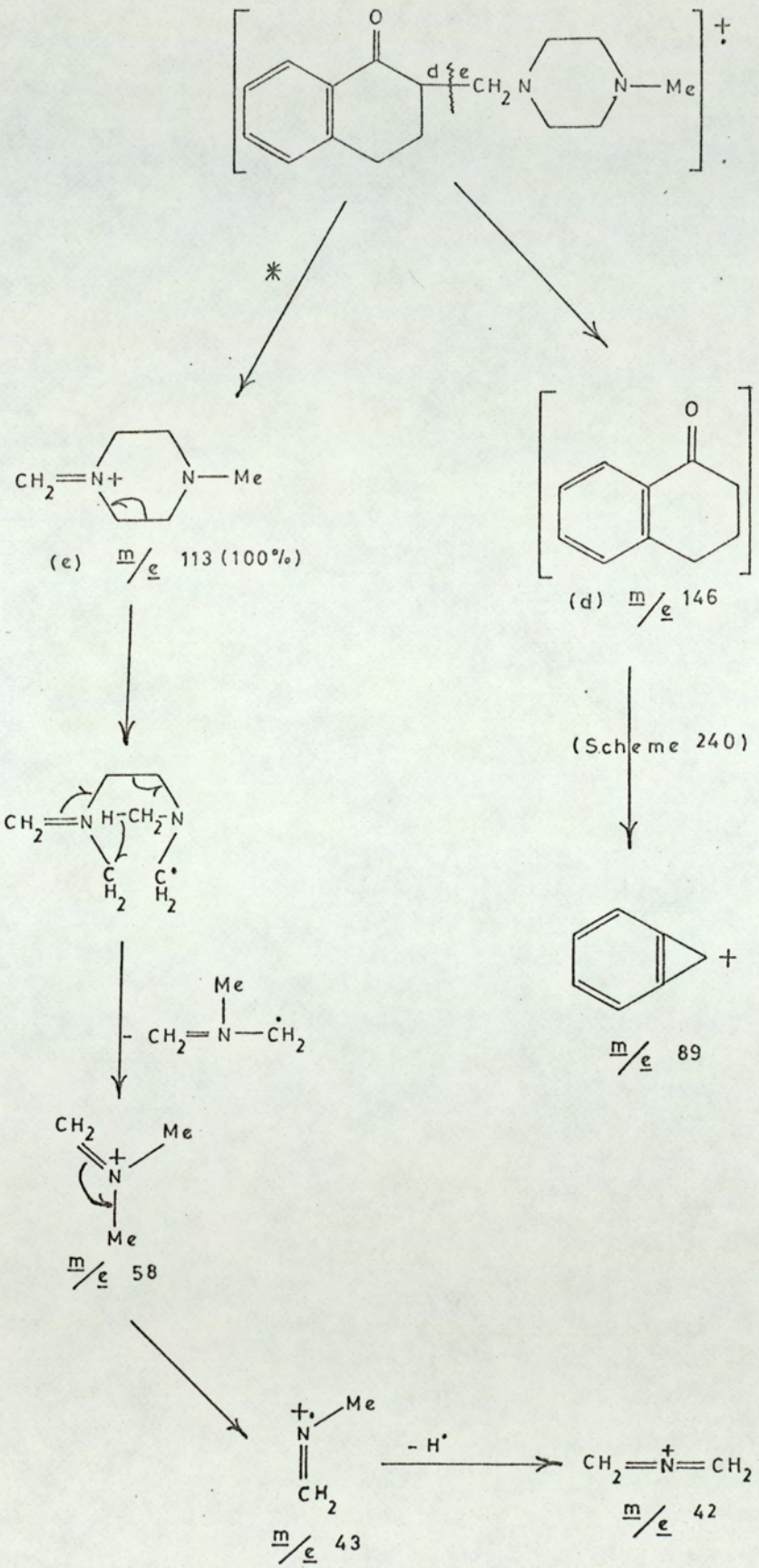

m/e 316
m/e 146
(Scheme 240)
m/e 89
m/e 171 (100%)
- C2H4
- COOEt•
m/e 98
m/e 143
- CH2C
- CO2
m/e 141
m/e 99
- CH2CO
m/e 99
- CH2=N—CH2•
m/e 57
(Scheme 242)
m/e 44
- H•
m/e 43
- H•
m/e 42

The ethoxycarbonyl group is susceptible to several modes of fragmentation and this is reflected in the complex spectrum obtained. Other possible minor pathways are shown in scheme (243). Loss of COOH by α-cleavage of the N-C bond and rearrangement of the ethyl radical gives the fragment $^{m}/_{e}$ 271. This fragment undergoes α-cleavage and H$^{\cdot}$ transfer to produce the cation $^{m}/_{e}$ 127 which by loss of ethylene gives the cation $^{m}/_{e}$ 99. The fragmentation of $^{m}/_{e}$ 99 then proceeds as outlined previously in scheme (242)



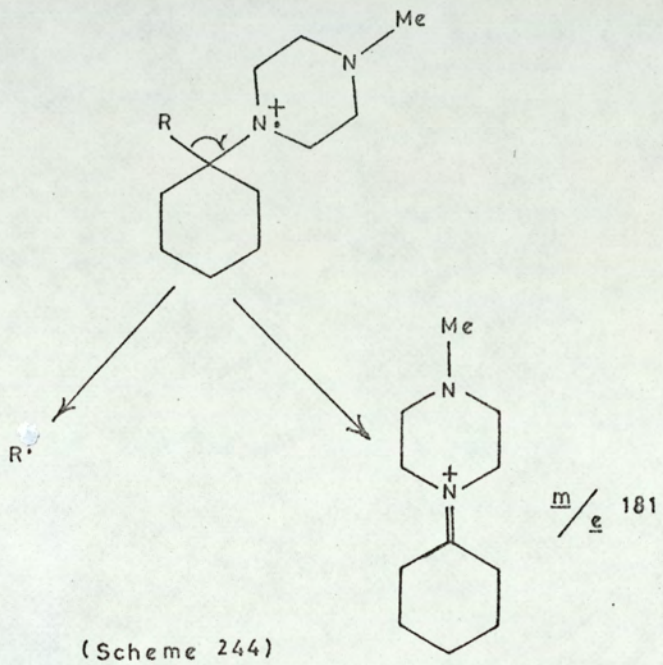
(Scheme 243)

Proposed degradation pathways for 2-(4-methylpiperazinylmethyl)-1-tetralone (105).



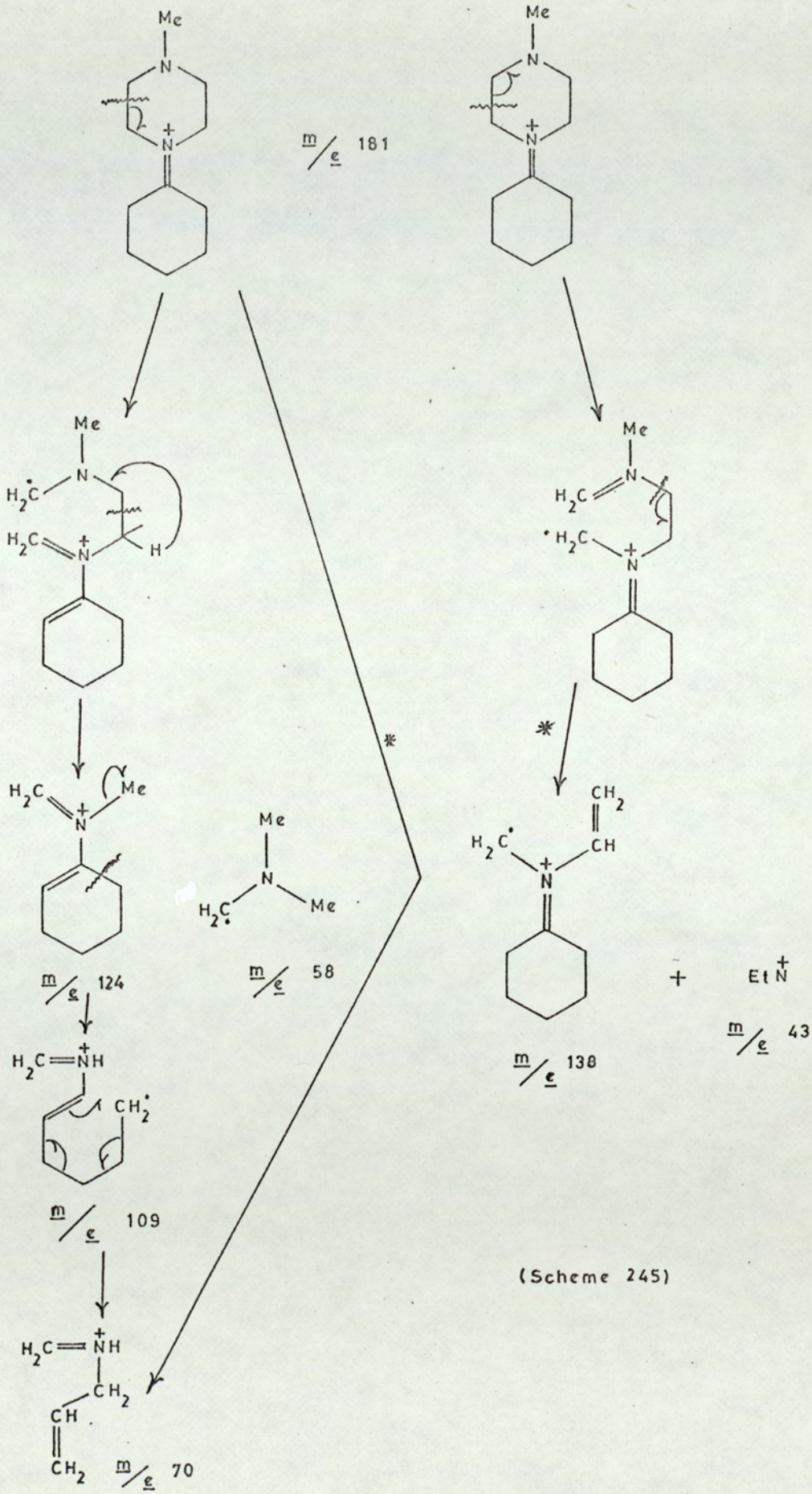
1-(1-R-substituted cyclohexyl)-4-methylpiperazines

Mass spectra of these compounds show a molecular ion peak and a common cation fragment at $^{m}/_{e}$ 181, scheme (244)



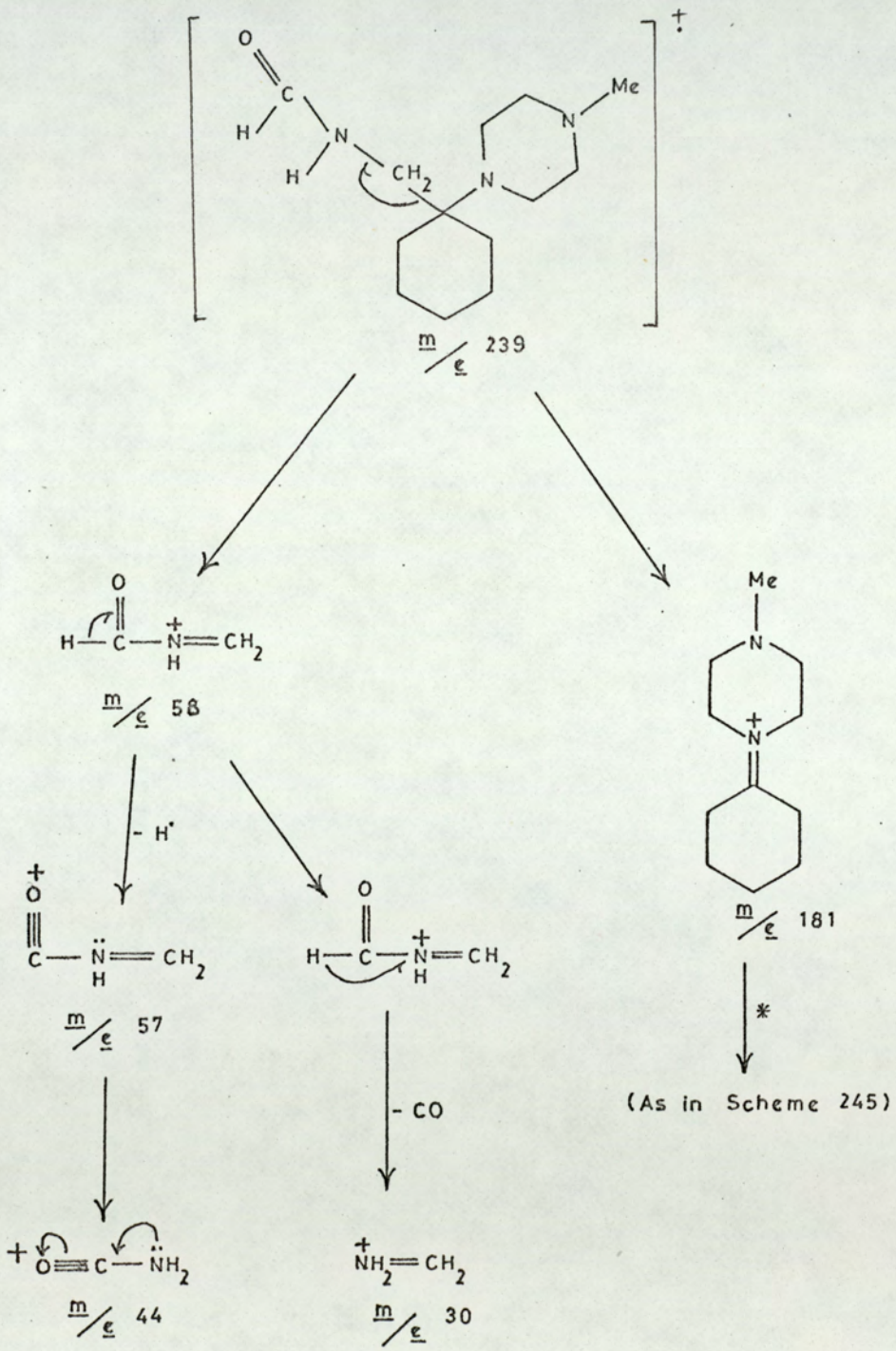
(Scheme 244)

The substituted piperazinium ion $^{m}/_{e}$ 181 could be involved in two degradation pathways, scheme (245). β-cleavage in the piperazine ring followed by allylic hydrogen transfer yields two fragments at $^{m}/_{e}$ 124 and $^{m}/_{e}$ 58. The cation $^{m}/_{e}$ 124 then undergoes α-fission accompanied by allylic hydrogen transfer to the primary radical site to give a major fragment at $^{m}/_{e}$ 70. Alternatively β-cleavage in the piperazine ring followed by cleavage α- to the methyl substituted nitrogen without hydrogen transfer gives the neutral fragment at $^{m}/_{e}$ 138 and the small cation at $^{m}/_{e}$ 43.

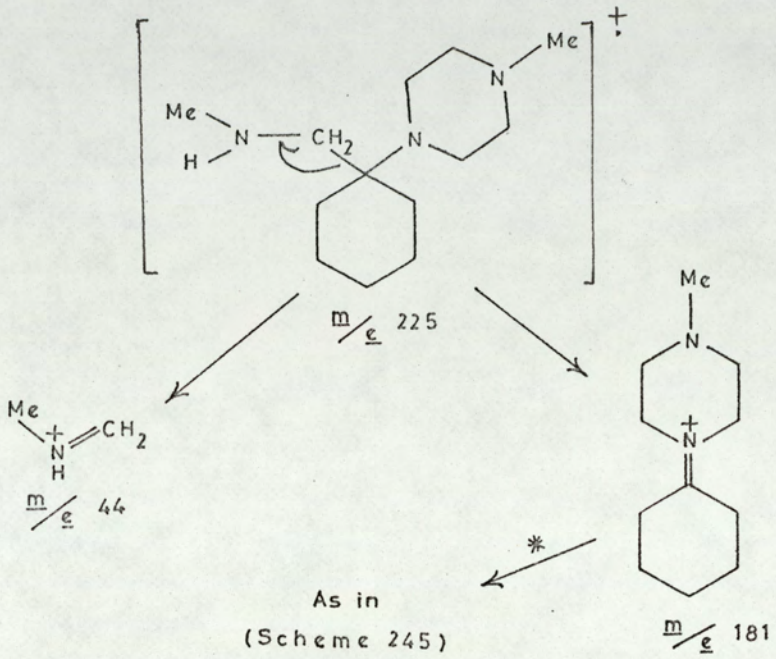

Me
N
+N
m/e 181
H2C
H
Me
m/e 124
m/e 58
m/e 138
CH2
CH
Et N
+
m/e 43
NH
m/e 109
m/e 70

(Scheme 245)

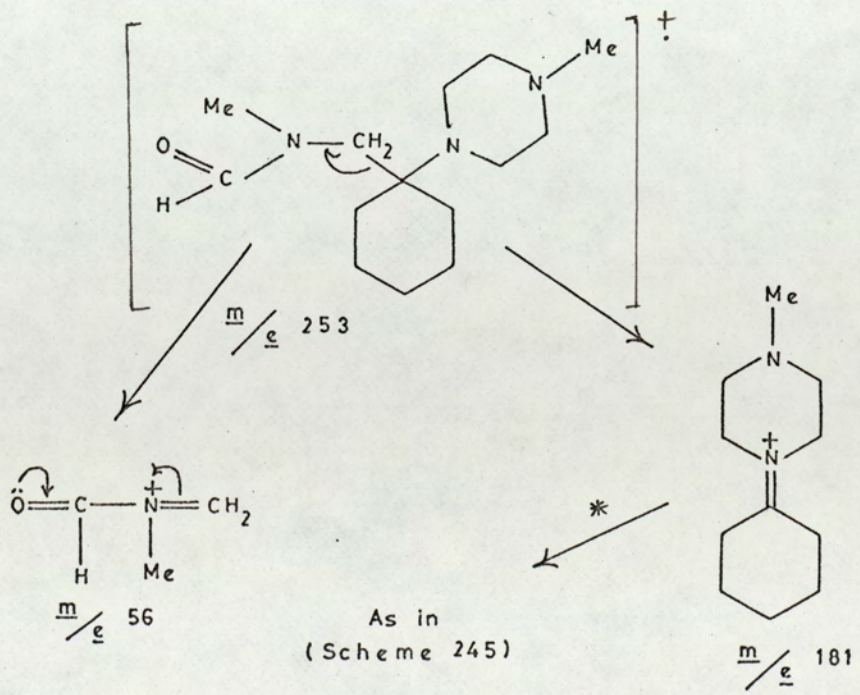
Proposed degradation pathway for 1-(1-formylaminomethylcyclohexyl)-4-methylpiperazine (185)



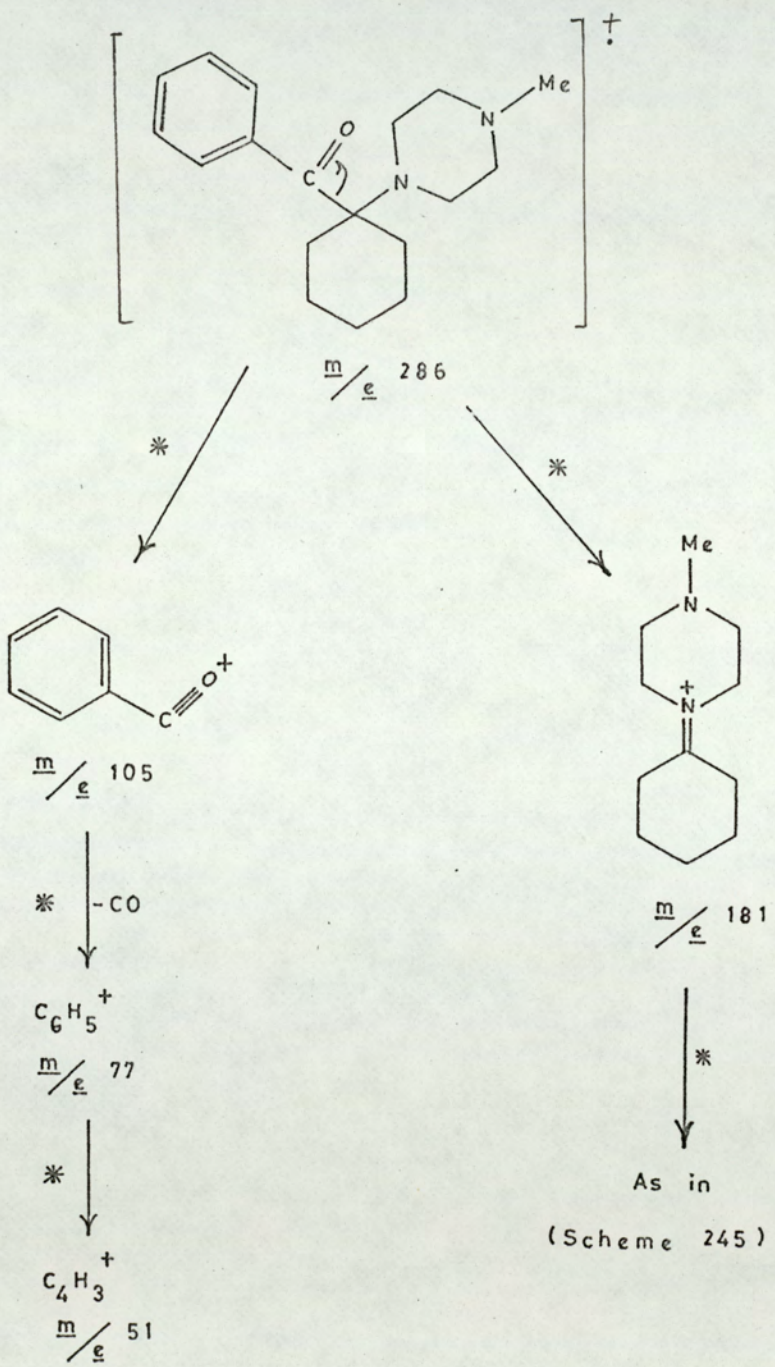
Proposed degradation pathway for 1-(1-methylaminomethylcyclohexyl)-4-methylpiperazine (188)



Proposed degradation pathway for 1-(N-formyl-1-methylaminomethyl cyclohexyl)-4-methylpiperazine (191)



Proposed degradation pathway for 1-(1-benzoylcyclohexyl)-4-methylpiperazine (225)



PART II

SECTION I

EXPERIMENTAL

SECTION I

EXPERIMENTAL

Determination of Equivalent Weights

The equivalent weights of bases were determined by titration with 0.1N perchloric acid in acetic acid using Oracet Blue B indicator. Titration of the hydrohalide and quaternary salts was carried out in the same solvent in the presence of 3% mercuric acetate.

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.

Infra-red absorption spectra

Infra-red spectra were recorded using a Unicam S.P. 200 spectrophotometer. The samples were run as liquid films, mulls in liquid paraffin or as solutions in chloroform. Some unassigned peaks are also recorded.

Nuclear Magnetic Resonance spectra

Nuclear magnetic resonance spectra were determined in chloroform-d, carbon tetrachloride or trifluoroacetic acid on a Varian A60 A spectrometer using tetra-methyl silane as an internal standard. All the peaks are assigned in τ values.

Mass spectra

Mass spectra were determined on an A.E.I. MS9 spectrometer.

Melting points

Melting points are uncorrected.

Microanalyses

Microanalyses were carried out by Dr. Alfred Bernhardt, Max-Planck Institut für Kohlenforschung, West Germany.

(A): DERIVATIVES OF THE MANNICH BASES OF 1-TETRALONE

2-Dimethylaminomethyl-1-tetralone (104)

1. 1-Tetralone (73 g, 0.5 mole), 40% formalin (50 g, 0.55 mole) and dimethylamine hydrochloride (45 g, 0.55 mole) were mixed and allowed to stand under nitrogen for 0.25 hr at room temperature. The stirred mixture was then placed in a boiling water bath for 0.5 hr, cooled and unreacted 1-tetralone removed by extraction with ether (2 x 100 ml). This left a concentrated acid solution which on standing gave colourless prisms of 2-dimethylaminomethyl-1-tetralone hydrochloride (59.5 g, 49.7%; lit. 84 g, 70.1%), m.p. 149.5-151.5° (lit. 144°)[120] (from acetone/alcohol 4:1) (Found: C, 65.1; H, 7.6; N, 5.9; equiv., 238.7. $C_{13}H_{18}ClNO$ requires C, 65.1; H, 7.7; N, 6.0%; equiv. 239.5), $\nu_{max.}$ (nujol), 2600-2450 (NH^+), 1680 (CO), 1600, 1230, 1160, 1140, 1015, 950, 910, 860, 770, 740 (Ph) cm^{-1}.

2. 1-Tetralone (24.3 g, 0.167 mole), 40% formalin (16.67 g, 0.18 mole), dimethylamine hydrochloride (15 g, 0.18 mole), water (2 ml) and HCl (4 ml) were refluxed for 1 hr. Unreacted 1-tetralone was removed from the cooled reaction mixture by extraction with ether (2 x 100 ml). The acid layer was then basified with ammonia, extracted with ether, the ether layer washed with water, dried (Na_2SO_4) and the solvent evaporated to give an amber oil. This base yielded colourless prisms of 2-dimethylaminomethyl-1-tetralone hydrochloride (13.0 g, 32.6%), m.p. 160-61° (from acetone/alcohol 4:1) (Found: C, 65.0; H, 7.5; N, 5.9; equiv., 238.5. $C_{13}H_{18}ClNO$ requires C, 65.1; H, 7.7; N, 6.0%; equiv., 239.5).

2-Dimethylaminomethyl-1-phenyl-1,2,3,4-tetrahydronaphth-1-ol. (131)

2-Dimethylaminomethyl-1-tetralone (11.0 g, 0.054 mole) in dry ether (100 ml) was added to a solution of phenyl magnesium bromide prepared from magnesium (2.9 g, 0.12 mole) and bromobenzene (18.8 g, 0.12 mole) in dry

ether (150 ml). The mixture was refluxed for 6 hr, cooled, and decomposed by the addition of a saturated ammonium chloride solution. The ether layer was separated, dried (Na_2SO_4), and the solvent evaporated to give a viscous, amber oil (11.1 g, 72.5%) which on distillation *in vacuo*. (185°/1 mm) gave 2-dimethylaminomethyl-1-phenyl-1,2,3,4-tetrahydronaphth-1-ol as a colourless, viscous oil (lit. 170°/0.6 mm)[115] (Found: C, 79.9; H, 8.0; N, 4.7; *equiv.*, 285.0. $C_{19}H_{23}NO$ requires C, 81.1; H, 8.2; N, 5.0%; *equiv.*, 281.0), $\nu_{max.}$(liq. film), 3400 (broad band OH), 1600, 1220, 1170, 1030 (OH), 760, 730, 700 (Ph) cm^{-1}.

2-Dimethylaminomethyl-1,2,3,4-tetrahydronaphth-1-ol. (113)
2-Dimethylaminomethyl-1-tetralone (10.15 g, 0.05 mole) was dissolved in methanol (100 ml) and sodium borohydride (1 g, 0.05 mole) in 2N. sodium hydroxide (2 ml) diluted with water (18 ml) was added 0.5 ml/min. The solvent was evaporated and the residue diluted with water (50 ml), extracted with ether, washed with water, dried (Na_2SO_4), and the ether evaporated to give a brown, mobile oil (6.5 g, 64.3%). Distillation *in vacuo*. gave 2-dimethylamino-1,2,3,4-tetrahydronaphth-1-ol as a colourless, mobile oil (5.2 g) (Found: C, 75.9; H, 9.1; N, 6.5; *equiv.*, 203.1. $C_{13}H_{19}NO$ requires C, 76.1; H, 9.3; N, 6.8%; *equiv.*, 205), $\nu_{max.}$(liq. film), 3350 (OH), 1480, 1260, 1155, 1040 (OH), 1000, 850, 745 (Ph) cm^{-1}.

2-Dimethylaminomethyl-1-phenethynyl-1,2,3,4-tetrahydronaphth-1-ol (137)
Phenylacetylene (10.4 g, 0.104 mole) in dry ether (30 ml) was added dropwise to a stirred solution of ethyl magnesium bromide prepared from ethyl bromide (11.3 g, 0.104 mole) and magnesium (2.5 g, 0.104 mole) in dry ether (150 ml). The mixture was stirred overnight and 2-dimethylaminomethyl-1-tetralone (10.15 g, 0.052 mole) in dry ether (30 ml) added dropwise then stirred for a further 24 hr. The complex was decomposed by pouring the solution onto crushed ice (100 g) and dil. hydrochloric acid (30 ml).

The separated aqueous layer was washed with ether then basified with ammonia and extracted with chloroform, the extract was washed with water, dried (Na_2SO_4), and the solvent evaporated to give a brown oil (5.41 g, 31.7%). Treatment with ethanolic hydrochloric acid gave colourless needles of 2-dimethylaminomethyl-1-phenethynyl-1,2,3,4-tetrahydronaphth-1-ol hydrochloride, m.p. 233.5-35° (decomp.) (from ethanol) (Found: C, 73.5; H, 6.5; N, 4.2; equiv., 334.0. $C_{21}H_{24}ClNO$ requires C, 73.8; H, 6.7; N, 4.1%; equiv., 341.5), $\nu_{max.}$(nujol), 3400 (OH), 2600-2400 (NH^+), 1140, 1020, 950, 760, 730, 700 (Ph) cm^{-1}. Attempts to separate the two possible isomers were unsuccessful. An attempt with acetic anhydride to make the acetoxy derivative was also unsuccessful.

2-Dimethylaminomethyl-1-phenethyl-1,2,3,4-tetrahydronaphth-1-ol (132)
2-Dimethylaminomethyl-1-tetralone hydrochloride (13.0 g, 0.054 mole) was finely powdered, vac. dried and added in small portions to a solution of phenethyl magnesium bromide prepared from magnesium (2.9 g, 0.12 mole) and phenethyl bromide (22.2 g, 0.12 mole) in dry ether (200 ml). The solution was refluxed overnight and worked up as in previous Grignard experiments when evaporation of the solvent gave a brown oil (17.0 g, 90.7%). Treatment with ethanolic hydrochloric acid gave fine colourless needles of 2-dimethylaminomethyl-1-phenethyl-1,2,3,4-tetrahydronaphth-1-ol hydrochloride, m.p. 205-205.5° (from ethanol/ether) (Found: C, 72.8; H, 8.0; N, 4.2; equiv., 343.2. $C_{21}H_{28}ClNO$ requires C, 72.9; H, 8.1; N, 4.1%; equiv., 345.5), $\nu_{max.}$(nujol), 3250 (OH), 2700-2400 (NH^+), 1600, 1220, 1140, 1060, 1040, 1030 (OH), 960, 870, 830, 750, 730, 700 (Ph) cm^{-1}. Attempts to separate the two possible isomeric forms were unsuccessful. An attempt with acetic anhydride to make the acetoxy derivative was also unsuccessful.

2-Dimethylaminomethyl-1-(2-picolyl)-1,2,3,4-tetrahydronaphth-1-ol (143)
2-Picoline (2.79 g, 0.03 mole) in dry ether (20 ml) was added dropwise to a solution of phenyl lithium prepared from lithium (0.5 g, 0.07 mole) and bromobenzene (6 g, 0.035 mole) in dry ether (75 ml). The resulting deep red solution was stirred for 1 hr, 2-dimethylaminomethyl-1-tetralone (4.7 g, 0.023 mole) in dry ether (50 ml) added dropwise and the mixture stirred for 5 hr. The complex was decomposed by dropwise addition of water, the ether layer separated, washed with water, dried (Na_2SO_4), and the solvent evaporated to give an orange, mobile oil (3.68 g, 59.4%). On standing in a slight excess of iodomethane this oil gave colourless pearly plates of 2-dimethylaminomethyl-1-(2-picolyl)-1,2,3,4-tetrahydronaphth-1-ol dimethiodide, m.p. 200.5-202° (from methanol/ether) (Found: C, 43.5; H, 5.5; N, 4.5; equiv., 298.1. $C_{21}H_{30}I_2N_2O$ requires C, 43.5; H, 5.2; N, 4.8%; equiv., 290), $\nu_{max.}$ (nujol), 3450 (OH), 1590, 1520, 1240, 1060, 1030 (OH), 940, 910, 790, 770, 740 (Ph) cm^{-1}.

1-Acetoxy-2-dimethylaminomethyl-1-phenethyl-1,2,3,4-tetrahydronaphthalene (146)
2-Dimethylaminomethyl-1-phenethyl-1,2,3,4-tetrahydronaphth-1-ol hydrochloride (1.0 g) was dissolved in a mixture of chloroform (30 ml) and acetone (10 ml). Two drops of 10% ethanolic hydrochloric acid were added, the solution cooled to 0° in an ice-bath and ketene passed into the solution for 1 hr. The solvents were distilled under reduced pressure leaving a yellowish solid (0.7 g, 64%). Recrystallisation from ethanol/ether gave buff needles of 1-acetoxy-2-dimethylaminomethyl-1-phenethyl-1,2,3,4-tetrahydronaphthalene hydrochloride, m.p. 171-172° (Found: C, 71.4; H, 7.7; N, 3.8; equiv., 385. $C_{23}H_{30}ClN_2O$ requires C, 71.2; H, 7.7; N, 3.6%; equiv., 387.5), $\nu_{max.}$ (nujol), 2600-2450 (NH^+), 1730 (ester CO), 735, 700 (Ph) cm^{-1}.

2-(4-Methylpiperazinylmethyl)-1-tetralone (105)

1. N-methylpiperazine (3.0 g, 0.03 mole) was treated with a slight excess of 10% ethanolic hydrochloric acid and the solvent removed under reduced pressure to give a pale yellow crystalline dihydrochloride. To this was added 40% formalin solution (5.6 ml, 0.075 mole), 1-tetralone (13.14 g, 0.09 mole) and the mixture refluxed for 0.5 hr. Water (15 ml) was added to the cooled, brown, homogeneous solution when two layers were formed. The upper layer was washed with water (2 x 10 ml) and these washings added to the original lower acid layer which was then extracted with ether (3 x 20 ml). The acid layer was then basified with a saturated solution of sodium hydroxide, extracted with ether, dried (Na_2SO_4), and the ether evaporated to yield N-methyl piperazine unchanged. (1-Tetralone was then recovered unchanged from the ether washings of the upper layer.)

2. The above method was repeated, running the reaction in a stream of nitrogen but again starting materials were isolated unchanged.

3. N-methylpiperazine (2.5 g, 0.025 mole) was converted to the dihydrochloride salt and refluxed with 40% formalin solution (4 ml, 0.05 mole), 1-tetralone (18.25 g, 0.125 mole), water (2 ml) and hydrochloric acid (4 ml) for 0.5 hr. Water (15 ml) was added to the cooled reaction mixture when two layers separated which were worked up as in method 1 to yield a dark brown oil (1.3 g, 30.0%) which failed to crystallise (Found: equiv., 125. $C_{16}H_{22}N_2O$ requires equiv., 129), $\nu_{max.}$ (liq. film), 1680 (CO), 760,740 (Ph) cm^{-1}. On treatment with 10% ethanolic hydrochloric acid this oil gave colourless needles of 2-(4-methylpiperazinylmethyl)-1-tetralone dihydrochloride, m. p. 242-243° (decomp.) (from ethanol ether) (Found: C, 58.3; H, 7.5; N, 8.3; equiv., 160.4. $C_{16}H_{24}Cl_2N_2O$ requires C, 58.0; H, 7.3; N, 8.6%;

equiv., 165.5), $\nu_{max.}$ (nujol), 2600-2300 (NH^+), 1680 (CO), 1600, 1220, 1120, 1080, 1070, 1020, 970, 950, 930, 860, 770, 740 (Ph) cm^{-1}.

4. 1-Tetralone (7.3 g, 0.05 mole) and N-methylpiperazine (5.0 g, 0.05 mole) were dissolved in ethanol (75 ml), 40% formalin solution (4.0 ml, 0.05 mole) added and the stirred solution refluxed for 18 hr. Ethanol was removed under reduced pressure and the resulting brown oil treated with 10% ethanolic hydrochloric acid to yield an amber, semi-crystalline mass (12.15 g, 73.6%) m.p. 243° (decomp.) undepressed on admixture with an authentic sample. This was basified with ammonia, extracted with chloroform, washed with water, dried (Na_2SO_4), and the solvent evaporated to give an amber oil which solidified on scratching. Recrystallisation from light petroleum (b.p. 60-80°) gave colourless prisms of 2-(4-methylpiperazinylmethyl)-1-tetralone, m.p. 94-95° (Found: C, 74.2; H, 8.4; N, 10.9; equiv., 127.5, M^+, 258. $C_{16}H_{22}N_2O$ requires C, 74.4; H, 8.5; N, 10.9%; equiv., 129, M^+, 258), $\nu_{max.}$ (nujol), 1680 (CO), 760, 740 (Ph) cm^{-1}.

2-(4-Methylpiperazinylmethyl)-1-phenyl-1,2,3,4-tetrahydronaphth-1-ol (133) Finely powdered 2-(4-methylpiperazinylmethyl)-1-tetralone (3.31 g, 0.01 mole) was added in small portions to a solution of phenylmagnesium bromide prepared from magnesium (0.97 g, 0.04 mole) and bromobenzene (6.28 g, 0.04 mole) in dry ether (100 ml). The mixture was refluxed for 24 hr, cooled and decomposed with a saturated solution of ammonium chloride. The ether layer was separated, washed with water, dried (Na_2SO_4), and the solvent evaporated to give a brown oil (2.9 g, 86.8%). Recrystallisation from ethanol gave colourless prisms of 2-(4-methylpiperazinylmethyl)-1-phenyl-1,2,3,4-tetrahydronaphth-1-ol, m.p. 179-181° (Found: C, 78.5; H, 8.4; N, 8.2; equiv., 171.2, M^+, 336. $C_{22}H_{28}N_2O$ requires C, 78.6;

H, 8.3; N, 8.3%; equiv., 168.0, M^+, 336), $\nu_{max.}$ (nujol), 3350 (OH), 755, 700 (Ph) cm^{-1}. Attempts to separate the possible isomeric forms were unsuccessful.

Attempted preparation of 1-acetoxy-2-(4-methylpiperazinylmethyl)-1-phenyl-1,2,3,4-tetrahydronaphthalene

2-(4-Methylpiperazinylmethyl)-1-phenyl-1,2,3,4-tetrahydronaphth-1-ol (1.0 g) was refluxed for 3 hr with pyridine (4 ml) and acetic anhydride (4 ml). The solvents were removed under reduced pressure to yield a brown residue (0.7 g) which failed to crystallise. $\nu_{max.}$ (liq. film), 3350 cm^{-1} (OH) showed impure starting material had been isolated.

Attempted preparation of 2-(4-Methylpiperazinylmethyl)-1-phenyl-3,4-dihydronaphthalene

2-(4-Methylpiperazinylmethyl)-1-phenyl-1,2,3,4-tetrahydronaphth-1-ol (5 g) was refluxed for 1 hr with hydrochloric acid (20 ml) and glacial acetic acid (50 ml). The solvents were removed under reduced pressure to give a charred mass which failed to yield either starting material or desired product.

2-(4-Methylpiperazinylmethyl)-1-phenethynyl-1,2,3,4-tetrahydronaphth-1-ol (138)

Phenylacetylene (5.2 g, 0.052 mole) in dry ether (30 ml) was added dropwise to a stirred solution of ethyl magnesium bromide prepared from ethyl bromide (5.65 g, 0.052 mole) and magnesium (1.25 g, 0.052 mole) in dry ether (100 ml). The mixture was stirred overnight and 2-(4-methylpiperazinylmethyl)-1-tetralone (3.0 g, 0.001 mole) in dry ether (30 ml) was added dropwise and stirring continued for a further 24 hr. The complex was decomposed by pouring the solution onto a mixture of crushed ice (100 g) and dil. hydrochloric acid (30 ml). The acid, aqueous layer was separated, washed with ether, basified with ammonia and extracted

with chloroform. This extract was washed with water, dried (Na_2SO_4), and the solvent evaporated to give a brown oil (2.4 g, 61.5%) which failed to crystallise. Treatment with ethanolic hydrochloric acid gave colourless crystals of 2-(4-methylpiperazinylmethyl)-1-phenethynyl-1,2,3,4-tetrahydronaphth-1-ol dihydrochloride, m.p. 249-251° (decomp.) (from methanol/ether) (Found: C, 66.3; H, 6.8; N, 6.6; equiv., 214.8. $C_{24}H_{30}Cl_2N_2O$ requires C, 66.5; H, 6.9; N, 6.5%; equiv., 216.5), $\nu_{max.}$(nujol), 3400 (OH), 2400-2300 (NH^+), 755, 740, 700 (Ph) cm^{-1}. Attempts to separate the possible isomeric forms were unsuccessful.

Attempted preparation of 1-acetoxy-2-(4-methylpiperazinylmethyl)-1-phenethynyl-1,2,3,4-tetrahydronaphthalene

1. 2-(4-Methylpiperazinylmethyl)-1-phenethynyl-1,2,3,4-tetrahydronaphth-1-ol (1.0 g) was refluxed for 3 hr with pyridine (4 ml) and acetic anhydride (4 ml). The solvents were removed under reduced pressure to yield a brown oil (0.8 g) which failed to crystallise as the base but gave colourless crystals of the dihydrochloride of the starting material, m.p. 249-251° (decomp.) undepressed on admixture with an authentic sample.

2. 2-(4-Methylpiperazinylmethyl)-1-phenethynyl-1,2,3,4-tetrahydronaphth-1-ol dihydrochloride (1.0 g) was dissolved in a mixture of chloroform (30 ml) and acetone (10 ml), cooled to 0° in an external ice-bath and ketene bubbled through it for 1.5 hr. The solvents were evaporated under reduced pressure to give a reddish brown oil (0.7 g) which failed to crystallise. On treatment with 10% ethanolic hydrochloric acid colourless prisms were obtained m.p. 230° (decomp.), $\nu_{max.}$(nujol), 1680 (CO), 770, 740 (Ph) cm^{-1}, but the sample failed to give the correct analysis figures.

1-Methyl-2-(4-methylpiperazinylmethyl)-1,2,3,4-tetrahydronaphth-1-ol (119)

2-(4-methylpiperazinylmethyl)-1-tetralone (6.0 g, 0.02 mole) in dry ether (30 ml) was added dropwise to a stirred solution of methylmagnesium iodide prepared from magnesium (1.7 g, 0.07 mole) and iodomethane (16.9 g, 0.07 mole) in dry ether (100 ml). The mixture was stirred overnight, decomposed with a saturated solution of ammonium chloride, the ether layer separated, washed with water, dried (Na_2SO_4), and the solvent evaporated to yield a mobile, amber oil (3.5 g, 55.1%). This oil crystallised from light petroleum (b.p. 80-100°) as pale buff prisms of 1-methyl-2-(4-methylpiperazinylmethyl)-1,2,3,4-tetrahydronaphth-1-ol, m.p. 114-115° (Found: C, 74.3; H, 9.6; N, 10.4; equiv., 136.0. $C_{17}H_{26}N_2O$ requires C, 74.4; H, 9.5; N, 10.2%; equiv., 137.0), $\nu_{max.}$ (nujol), 3450 (OH), 2800 (NCH_3), 1340, 1280, 1160, 1010, 830, 775, 740 (Ph) cm^{-1}. Attempts to separate the possible isomeric forms were unsuccessful.

Attempted preparation of 1-acetoxy-1-methyl-2-(4-methylpiperazinylmethyl)-1,2,3,4-tetrahydronaphthalene

1-Methyl-2-(4-methylpiperazinylmethyl)-1,2,3,4-tetrahydronapth-1-ol (1.5 g) was refluxed for 3 hr with pyridine (6 ml) and acetic anhydride (6 ml). The solvents were removed under reduced pressure to yield a viscous, brown oil (1.4 g) which failed to crystallise. Column chromatography yielded 13 fractions but the desired ester was not obtained from any one of these fractions on the basis of infra-red evidence.

2-(4-Methylpiperazinylmethyl)-1,2,3,4-tetrahydronaphth-1-ol (114)

1. 2-(4-Methylpiperazinylmethyl)-1-tetralone dihydrochloride (3.3 g, 0.01 mole) was converted to its base, dissolved in dry ether (30 ml) and added dropwise to a stirred suspension of lithium aluminium hydride (0.76 g, 0.02 mole) in dry ether (100 ml). The suspension was stirred overnight and the excess lithium aluminium hydride decomposed by dropwise

addition of 30% sodium hydroxide solution. The ether layer was separated, washed with water, dried (Na_2SO_4), and evaporated to yield a colourless oil (1.9 g, 57.6%) which failed to crystallise. The dihydrochloride recrystallised from ethanol/ether as colourless crystals of 2-(4-methylpiperazinylmethyl)-1,2,3,4-tetrahydronaphth-1-ol dihydrochloride, m.p. 271-272° (decomp.) (Found: C, 58.0; H, 8.0; N, 8.5; equiv., 163.7. $C_{16}H_{26}Cl_2N_2O$ requires C, 57,7; H, 7.8; N, 8.4%; equiv., 166.5), $\nu_{max.}$(nujol), 3500 (OH), 2600-2300 (NH^+), 1250, 1185, 1100, 1070, 1025, 970, 900, 760, 750, 730 (Ph) cm^{-1}.

2. Finely powdered, dry 2-(4-carbethoxypiperazinylmethyl)-1-tetralone hydrochloride (3.52 g, 0.01 mole) was added in small portions to a suspension of lithium aluminium hydride (0.76 g, 0.02 mole) in dry ether (100 ml). The suspension was stirred overnight and worked up as in the preceding method to give a colourless oil (2.0 g, 60.0%) which failed to crystallise. The dihydrochloride recrystallised from ethanol/ether as colourless crystals of 2-(4-methylpiperazinylmethyl)-1,2,3,4-tetrahydronaphth-1-ol dihydrochloride, m.p. 269-271° (decomp.) undepressed on admixture with authentic sample (Found: C, 57.8; H, 7.9; N, 8.3; equiv., 168.9. $C_{16}H_{26}Cl_2N_2O$ requires C, 57.7; H, 7.8; N, 8.4%; equiv., 166.5), $\nu_{max.}$(nujol), 3450 (OH), 2600-2300 (NH^+), 1260, 1190, 1100, 1070, 1040, 1025, 970, 900, 760, 740, 730 (Ph) cm^{-1}.

Attempted preparation of 1-acetoxy-2-(4-methylpiperazinylmethyl)-1,2,3,4-tetrahydronaphthalene

1. 2-(4-Methylpiperazinylmethyl)-1,2,3,4-tetrahydronaphth-1-ol dihydrochloride (1.56 g) was dissolved in acetone (15 ml) and chloroform (30 ml), cooled to 0° and ketene bubbled through the solution for 1.25 hr. The solvents were removed under reduced pressure to give a reddish brown,

viscous oil (1.4 g) which gave colourless crystals of starting material from ethanol/ether m.p. 269-270° (decomp.).

2. The preceding method was repeated at room temperature but again starting material was returned unchanged.

Attempted preparation of 2-(4-methylpiperazinylmethyl)-1,2,3,4-tetrahydronaphthalene-1-oxime

2-(4-Methylpiperazinylmethyl)-1-tetralone (3.3 g, 0.01 mole) and hydroxylamine hydrochloride (2.76 g, 0.04 mole) were refluxed for 24 hr in pyridine (75 ml). The solvent was evaporated under reduced pressure and the residue poured into water which was then extracted with ether (3 x 75 ml). The combined ether extracts were washed with dilute hydrochloric acid, sodium bicarbonate solution and water successively, dried (Na_2SO_4), and the solvent evaporated to give a brown oil (2.42 g), $\nu_{max.}$(liq. film), 3300 broad band (OH), 1210, 1115, 1040, 1030, 1010, 990, 920, 870, 760 (Ph) cm^{-1} with no evidence of C=O or C=N. An attempted non-aqueous titration gave precipitation and an inconclusive end point. 1g of the oil was placed on a chromatographic column and 7 x 50 ml collections of eluate were taken and evaporated to dryness. Infra-red analysis of the oily residues showed the original material to be absent but no evidence of C=N was obtained. The oily residues failed to crystallise.

2-(4-Methylpiperazinylmethyl)-1-(2-picolyl)-1,2,3,4-tetrahydronaphth-1-ol (142)

2-Picoline (9.3 g, 0.1 mole) in dry ether (30 ml) was added dropwise to a solution of phenyl lithium prepared from lithium (1.4 g, 0.2 mole) and bromobenzene (15.7 g, 0.1 mole) in dry ether (100 ml). The resulting deep red solution was stirred for 1 hr, 2-(4-methylpiperazinylmethyl)-

1-tetralone (18.0 g, 0.07 mole) in dry ether (100 ml) added dropwise and the solution stirred for 5 hr. The complex was then decomposed by dropwise addition of water, the ether layer separated, washed with water, dried (Na_2SO_4), and the ether evaporated to give a viscous, amber oil (14.0 g, 57.2%). Trituration with light petroleum (b.p. 60-80°) gave pale amber prisms of 2-(4-methylpiperazinylmethyl)-1-(2-picolyl)-1,2,3,4-tetrahydronaphth-1-ol, m.p. 76-77° (Found: C, 74.9; H, 8.3; N, 12.2; equiv., 120.5 end-point obscured by precipitation. $C_{22}H_{29}N_3O$ requires C, 75.2; H, 8.3; N, 12.0%; equiv., 117.0), $\nu_{max.}$ (nujol), 3350 (OH), 1592, 1290, 1280, 1160, 1140, 1050, 1010, 890, 820, 750, 730 (Ph) cm^{-1}.

2-(3-Azabicyclo [3,2,2] nonylmethyl)-1-tetralone (106)

1. 3-Azabicyclo [3,2,2] nonane (18.75 g, 0.15 mole) was treated with a slight excess of 10% ethanolic hydrochloric acid and the solvent removed under reduced pressure to give the colourless crystalline hydrochloride. To this was added 40% formalin solution (8 ml, 0.12 mole), 1-tetralone (14.6 g, 0.1 mole), water (2 ml), hydrochloric acid (5 ml) and the mixture refluxed for 0.5 hr. The cooled reaction mixture was washed with ether (3 x 100 ml), the extract dried and the ether evaporated to give a quantitative yield of 1-tetralone. The acid, aqueous residue of the reaction mixture was then basified with ammonia, extracted with ether and the extract washed with water, dried (Na_2SO_4), and evaporated to give a quantitative yield of solid 3-azabicyclo[3,2,2]nonane.

2. 3-Azabicyclo[3,2,2]nonane (12.5 g, 0.1 mole) was converted to the hydrochloride as in the preceding method. To this was added 40% formalin solution (8 ml, 0.12 mole), 1-tetralone (43.8 g, 0.3 mole), water (2 ml), hydrochloric acid (5 ml) and the mixture refluxed for 0.5 hr. The cooled

reaction mixture was extracted with ether (4 x 100 ml) which after drying (Na_2SO_4) and evaporation of ether gave an amber oil (33.3 g), $\nu_{max.}$ (liq. film), 1690 (CO), 1600, 1460, 1330, 1290, 1220, 760, 730 (Ph) cm^{-1}, which proved to be unreacted 1-tetralone. The acid residue of the reaction mixture was basified with ammonia, extracted with ether and the extract washed with water, dried (Na_2SO_4), and evaporated to give an almost colourless solid (15.0 g, 17.6%) which gave pearly plates of 2-(3-azabicyclo[3,2,2]nonylmethyl)-1-tetralone, m.p. 76-77° (from acetone/H_2O) (Found: C, 80.4; H, 8.6; N, 4.8; equiv., 282.6, M^+, 283. $C_{19}H_{25}NO$ requires C, 80.6; H, 8.8; N, 4.9%; equiv., 283, M^+, 283), $\nu_{max.}$ (nujol), 1680 (CO), 1600, 1310, 1210, 1150, 1140, 1000, 930, 860, 777, 740, 720 (Ph) cm^{-1}.

2-(3-Azabicyclo[3,2,2]nonylmethyl)-1-phenyl-1,2,3,4-tetrahydronaphth-1-ol

(134)

2-(3-Azabicyclo[3,2,2]nonylmethyl)-1-tetralone (7.0 g, 0.025 mole) was dissolved in dry ether (100 ml) and added dropwise to a solution of phenyl lithium prepared from lithium (1.4 g, 0.2 mole) and bromobenzene (15.7 g, 0.1 mole) in dry ether (150 ml). The solution was stirred overnight and the complex decomposed by the addition of damp ether. The ether layer was separated, dried (Na_2SO_4), and evaporated to give a white solid (4.6 g, 51.8%). On recrystallisation from acetone/water this gave pearly plates of 2-(3-azabicyclo[3,2,2]nonylmethyl)-1-phenyl-1,2,3,4-tetrahydronaphth-1-ol, m.p. 131-33° (Found: C, 83.1; H, 8.5; N, 3.9; equiv., 360.0. $C_{25}H_{31}NO$ requires C, 83.1; H, 8.6; N, 3.9%; equiv., 361.0), $\nu_{max.}$ (nujol), 3400 (OH), 760, 740, 700 (Ph) cm^{-1}. The compound was also obtained as the hydrochloride (Found: C, 75.7; H, 8.1; N, 3.6. $C_{25}H_{32}ClNO$ requires C, 75.5; H, 8.1; N, 3.5%).

Attempted preparation of 1-acetoxy-2-(3-azabicyclo[3,2,2]nonylmethyl-1-phenyl-1,2,3,4-tetrahydronaphthalene

1. 2-(3-Azabicyclo[3,2,2]nonylmethyl-1-phenyl-1,2,3,4-tetrahydronaphth-1-ol (1.0 g) was refluxed with acetic anydride (4 ml) and pyridine (4 ml) for 3 hr. The solvents were removed under reduced pressure to give a buff semi-solid (0.95 g) which gave pearly plate crystals m.p. 131-132° (from acetone/water), undepressed on admixture with an authentic sample of starting material.

2. 2-(3-Azabicyclo[3,2,2]nonylmethyl)-1-phenyl-1,2,3,4-tetrahydronaphth-1-ol (7.2 g, 0.02 mole) was dissolved in dry ether (50 ml) and added dropwise to a cooled ethereal solution of phenyl lithium prepared from lithium (1.4 g, 0.2 mole) and bromobenzene (16.5 g, 0.106 mole). The mixture was refluxed for 0.5 hr, cooled in an ice-bath and acetic anhydride (10.0 g, 0.102 mole) in dry ether (40 ml) added dropwise. The resulting thick suspension was stirred at room temperature overnight and the complex decomposed by addition of water. The separated ether layer was washed with water, dried (Na_2SO_4), and the solvent evaporated to give a brown, viscous oil which crystallised from acetone/water as pearly plates m.p. 131-133° undepressed on admixture with an authentic sample of starting material.

2-(3-Azabicyclo[3,2,2]nonylmethyl)-1,2,3,4-tetrahydronaphth-1-ol (115)

2-(3-Azabicyclo[3,2,2]nonylmethyl)-1-tetralone (3.03 g, 0.0125 mole) was dissolved in methanol (50 ml) and sodium borohydride (0.25 g, 0.0125 mole) in 2 N. sodium hydroxide solution (2 ml) diluted with water (18 ml) was added 0.5 ml/min with occasional cooling to keep the temperature about 18-25°. The solvents were evaporated under reduced pressure and the brownish, oily residue diluted with water (50 ml), extracted with ether,

washed with water, dried (Na_2SO_4), and the ether evaporated to give an amber, mobile oil (2.0 g, 66.7%). The base was characterised as colourless crystals of 2-(3-azabicyclo[3,2,2]nonylmethyl)-1,2,3,4-tetrahydronaphth-1-ol hydrochloride, m.p. 226-9° (from ethanol/ether) after standing in a refrigerator for 2 weeks (Found: C, 70.7; H, 8.9; N, 4.5; equiv., 321.9. $C_{19}H_{28}ClNO$ requires C, 70.9; H, 8.7; N, 4.4%; equiv., 321.5), $\nu_{max.}$ (nujol), 3300 broad band (OH), 2600-2400 (NH^+), 1240, 1200, 1110, 1040, 1015, 980, 860, 770, 740 (Ph) cm^{-1}. The lithium aluminium hydride reduction procedure as previously described for alcohol (114) gave colourless crystals, m.p. 227-9° undepressed on admixture with an authentic sample.

2-(3-Azabicyclo[3,2,2]nonylmethyl)-1-phenethynyl-1,2,3,4-tetrahydronaphth-1-ol (139)

Phenylacetylene (5.2 g, 0.052 mole) in dry ether (30 ml) was added dropwise to a stirred solution of ethyl magnesium bromide prepared from ethyl bromide (5.65 g, 0.052 mole) and magnesium (1.25 g, 0.052 mole) in dry ether (100 ml). The mixture was stirred overnight and 2-(3-azabicyclo[3,2,2]nonylmethyl)-1-tetralone (7.34 g, 0.026 mole) in dry ether (50 ml) was added dropwise and stirring continued for a further 24 hr. The complex was decomposed by addition of a cold, saturated solution of ammonium chloride when the product was formed as a solid between the aqueous and ether layers. The ether layer was separated and bulked with a chloroform extract of the aqueous layer. The combined ether/chloroform extract was dried (Na_2SO_4), and the solvents evaporated to give a colourless solid (3.6 g, 36.1%) which afforded colourless prisms of 2-(3-azabicyclo[3,2,2]nonylmethyl)-1-phenethynyl-1,2,3,4-tetrahydronaphth-1-ol, m.p. 171.5-73° (from acetone) (isomer A) (Found: C, 84.0; H, 8.1; N, 3.8; equiv., 377, M^+, 385. $C_{27}H_{31}NO$ requires C, 84.1; H, 8.1; N, 3.6%; equiv., 385, M^+, 385), $\nu_{max.}$ (nujol), 3300 broad band (OH), 1600, 1335, 1270, 1180, 1100, 1050 (equ. OH), 1030,

945, 880, 860, 850, 770, 760, 740, 700 (Ph) cm^{-1}.

$\tau_{(CDCl_3)}$ 7.45 (4H, d, CH_2-N-CH_2), 3.0-2.5 (9H, m, aromatic-H), OH difficult to distinguish. The mother liquor, on standing, gave long, colourless needles of 2-(3-azabicyclo[3,2,2]nonylmethyl)-1-phenethynyl-1,2,3,4-tetrahydronaphth-1-ol, m.p. 138.5-141° (isomer B) (0.21 g). Recrystallisation several times from acetone did not alter the m.p. of the product. (Found: C, 84.3; H, 8.0; N, 3.7; equiv., 379. $C_{27}H_{31}NO$ requires C, 84.1; H, 8.1; N, 3.6%; equiv., 385), $\nu_{max.}$(nujol), identical to isomer A.

$\tau_{(CDCl_3)}$ 3.0-2.5 (9H, m, aromatic-H), OH difficult to distinguish.

Attempted preparation of 2-(3-azabicyclo[3,2,2]nonylmethyl)-1-tetralone oxime

1. 2-(3-Azabicyclo[3,2,2]nonylmethyl)-1-tetralone (0.28 g, 0.001 mole) in ethanol (5 ml) was added to a solution of hydroxylamine hydrochloride (0.069 g, 0.01 mole) in water (4 ml) and the mixture stored at 0° for 48 hr but no crystalline product was formed. The solvents were removed and the residue azeotroped with benzene/ethanol but only starting materials were isolated unchanged.

2. 2-(3-Azabicyclo[3,2,2]nonylmethyl)-1-tetralone (2.83 g, 0.01 mole) in ethanol (20 ml) was added to a solution of hydroxylamine hydrochloride (0.69 g, 0.01 mole) in water (5 ml) and the stirred mixture refluxed for 48 hr during which time decomposition occurred.

3. Method 2 was repeated and the mixture refluxed for 3 hr only. The solvents were evaporated under reduced pressure and the residue azeotroped with benzene/ethanol to give a brown oil which failed to crystallise but gave colourless needles (1.5 g) from 10% ethanolic hydrochloric acid, m.p. 291° (decomp. from 277°), $\nu_{max.}$(nujol), 2600-2400 cm^{-1} (NH^+), equiv., 167.1, calc. for 3-azabicyclo[3,2,2]nonane 161.7.

Attempted preparation of 2-(3-azabicyclo[3,2,2]nonylmethyl)-1-phenyl-3,4-dihydronaphth-1-ol

1. 2-(3-Azabicyclo[3,2,2]nonylmethyl)-1-phenyl-1,2,3,4-tetrahydronaphth-1-ol (0.5 g) was refluxed with glacial acetic acid (9 ml) and hydrochloric acid (3 ml) for 1 hr and gave a completely charred mass.

2. 2-(3-Azabicyclo[3,2,2]nonylmethyl)-1-phenyl-1,2,3,4-tetrahydronaphth-1-ol (0.36 g, 0.001 mole) and phthalic anhydride (0.148 g, 0.001 mole) were refluxed in dry xylene (20 ml) for 3 hr using a Dean-Stark trap. The solvent was evaporated under reduced pressure to give an amber oil (0.4 g) from which starting materials were recovered unchanged.

3. 2-(3-Azabicyclo[3,2,2]nonylmethyl)-1-phenyl-1,2,3,4-tetrahydronaphth-1-ol (0.36 g, 0.001 mole) and anhydrous copper sulphate (1.0 g) were refluxed in dry xylene for 8 hr. The inorganic material was removed by filtration and the xylene evaporated under reduced pressure to give an amber oil (0.33 g) which crystallised from ethyl acetate as pearly plates (m.p. 131-33°) of unchanged starting material.

2-(4-Phenylpiperidylmethyl)-1-tetralone (107)

4-Phenylpiperidine (11.27 g, 0.07 mole) was converted to the hydrochloride, added to 40% formalin solution (11 ml, 0.140 mole), 1-tetralone (50 g, 0.34 mole), water (10 ml), hydrochloric acid (10 ml) and the mixture refluxed for 3 hr. The cooled reaction mixture was extracted with ether (4 x 100 ml), the extract dried (Na_2SO_4), and the solvent evaporated to give 1-tetralone (33 g) unchanged. The acid residue was basified with ammonia, extracted with ether, the extract washed with water, dried (Na_2SO_4), and evaporated to give a pale yellow solid (14.3 g, 65.6%). This was treated with 10% ethanolic hydrochloric acid to give colourless rosettes of 2-(4-phenylpiperidylmethyl)-1-tetralone hydrochloride,

m.p. 166-7° (from ethanol/ether) (Found: C, 74.1; H, 7.3; N, 3.8; equiv., 352.0. $C_{22}H_{26}ClNO$ requires C, 74.3; H, 7.3; N, 3.9%; equiv., 355.5), $\nu_{max.}$ (nujol), 2600-2400 (NH^+), 1680 (CO), 1600, 1300, 1230, 1190, 1060, 980, 960, 930, 780, 760, 750, 710 (Ph) cm^{-1}.

2-(4-Phenylpiperidylmethyl)-1,2,3,4-tetrahydronaphth-1-ol (116)

2-(4-Phenylpiperidylmethyl)-1-tetralone (3.19 g, 0.01 mole) in dry ether (50 ml) was added dropwise to a stirred suspension of lithium aluminium hydride (0.76 g, 0.02 mole) in dry ether (100 ml). The suspension was stirred overnight and worked up as in previous lithium aluminium hydride experiments to give a white solid (2.24 g, 70.2%) from 10% ethanolic hydrochloric acid. Recrystallisation from ethanol/ether gave colourless plates of 2-(4-phenylpiperidylmethyl)-1,2,3,4-tetrahydronaphth-1-ol hydrochloride, m.p. 253.5-54.5° (Found: C, 73.6; H, 7.8; N, 3.7; equiv., 355.2. $C_{22}H_{28}ClNO$ requires C, 73.8; H, 7.8; N, 3.9%; equiv., 357.5), $\nu_{max.}$ (nujol), 3300 (OH), 2600-2400 (NH^+), 1600, 1240, 1200, 1160, 1120, 1060, 970, 930, 840, 770, 750, 700 (Ph) cm^{-1}.

Attempted acetylation of 2-(4-phenylpiperidylmethyl)-1,2,3,4-tetrahydronaphth-1-ol.

2-(4-Phenylpiperidylmethyl)-1,2,3,4-tetrahydronaphth-1-ol (1.0 g) was refluxed with pyridine (3 ml) and acetic anhydride (3 ml) for 3 hr. The solvents were removed under reduced pressure to yield a brown oil (0.95 g) which proved to be the original material.

1-Phenethynyl-2-(4-phenylpiperidylmethyl)-1,2,3,4-tetrahydronaphth-1-ol (140)

Phenylacetylene (5.2 g, 0.052 mole) in dry ether (30 ml) was added dropwise to a stirred solution of ethyl magnesium bromide prepared from ethyl bromide (5.65 g, 0.052 mole) and magnesium (1.25 g, 0.052 mole) in dry

ether (100 ml). The mixture was stirred overnight and 2-(4-phenylpiperidylmethyl)-1-tetralone (8.29 g, 0.026 mole) in dry ether (100 ml) was added dropwise and stirring continued for a further 48 hr. The complex was decomposed and worked up as in previously described basic analogues and gave a brown oil (6.4 g, 60%) which on treatment with dry hydrogen chloride gas in ethereal solution gave colourless needles of 1-phenethynyl-2-(4-phenylpiperidylmethyl)-1,2,3,4-tetrahydronaphth-1-ol hydrochloride, m.p. 212.5-15° (from ethanol/ether at 0° for 3 days) (Found: C, 78.4; H, 7.2; N, 2.9; equiv., 462.7. $C_{30}H_{32}ClNO$ requires C, 78.7; H, 7.0; N, 3.0%; equiv., 457.5), $\nu_{max.}$ (nujol), 3400 broad band (OH), 2600-2400 (NH^+), 1320, 1155, 1070, 1030, 940, 770, 760, 730, 700 (Ph) cm^{-1}.

Attempted acetylation of 1-phenethynyl-2-(4-phenylpiperidylmethyl)-1,2,3,4-tetrahydronaphth-1-ol

Three previously described methods were used in attempts to prepare this acetyl derivative :-

1. Using pyridine and acetic anhydride,
2. Adding acetic anhydride to a Grignard complex of this alcohol,
3. Using the ketene lamp.

All methods failed to give the desired product. Methods 1 and 2 returned the starting material unchanged while method 3 gave a mixed product on T.L.C. evidence which proved incapable of separation by column chromatography.

Attempted preparation of 2-(4-phenylpiperidylmethyl)-1-tetralone oxime

1. 2-(4-phenylpiperidylmethyl)-1-tetralone hydrochloride (3.55 g, 0.01 mole) in ethanol (5 ml) was added to a solution of hydroxylamine hydrochloride (0.7 g, 0.01 mole) in water (4 ml) and the solution stored at 0° overnight. No crystalline product was obtained. The solution was refluxed for 3 hr

and stored at 0° overnight. No crystallisation occurred and only starting materials were obtained on evaporation of the solvents.

2. Method 1 was repeated but the proportion of hydroxylamine hydrochloride was trebled and the solution was refluxed for 5 hr then stored at 0° overnight. At first there was no crystallisation but after storing at 0° for several days rosette crystals of original material were obtained m.p. 167°, $\nu_{max.}$ (nujol), 2600-2400 (NH^{+}), 1680 (CO), 1600, 1300, 1230, 1190, 1060, 980, 960, 930, 780, 760, 750, 710 (Ph) cm^{-1}.

2-(4-Ethoxycarbonylpiperazinylmethyl)-1-tetralone (108)

1. N-Ethoxycarbonylpiperazine (15.7 g, 0.1 mole) was converted to the hydrochloride and refluxed with 40% formalin (7.5 ml, 0.1 mole), 1-tetralone (43.8 g, 0.3 mole), water (2 ml) and hydrochloric acid (4 ml) for 0.5 hr. The mixture was cooled and left at room temperature overnight. Water (40 ml) was added to the homogeneous solution and after shaking 2 layers separated. The upper layer was washed with water (2 x 20 ml) and the aqueous washings added to the lower acid layer which was then extracted with ether (3 x 50 ml) to remove traces of unreacted 1-tetralone. The acid layer was then basified with a 40% solution of sodium hydroxide, extracted with ether, dried (Na_2SO_4), and the ether evaporated to yield unchanged N-ethoxycarbonylpiperazine. 1-Tetralone was recovered unchanged from the upper layer.

2. N-Ethoxycarbonylpiperazine (7.85 g, 0.05 mole) was converted to the hydrochloride and refluxed with 40% formalin (11.25 ml, 0.15 mole), 1-tetralone (36.5 g, 0.25 mole), water (2 ml) and hydrochloric acid (4 ml) for 0.75 hr. The reaction mixture was worked up as in method 1 and evaporation of the ether gave a brown, mobile oil (12.6 g, 15.9%) which solidified on cooling to colourless needles of 2-(4-ethoxycarbonyl

piperazinylmethyl)-1-tetralone m.p. 72-3° (from 95% ethanol) (Found: C, 68.6; H, 7.6; N, 9.0; equiv., 312.1. $C_{18}H_{24}N_2O_3$ requires C, 68.4; H, 7.6; N, 8.9%; equiv., 316), $\nu_{max.}$ (nujol), 1700 (CO), 1680 (CO), 1600, 1290, 1240, 1150, 1120, 1050, 1010, 940, 770, 750 (Ph)cm^{-1}. Treatment with ethanolic hydrochloric acid gave colourless prisms of 2-(4-ethoxycarbonylpiperazinylmethyl)-1-tetralone hydrochloride, m.p. 167-8° (from ethanol/ether) (Found: C, 61.3; H, 7.0; N, 8.0; equiv., 346.4. $C_{18}H_{25}ClN_2O_3$ requires C, 61.3; H, 7.1; N, 7.9%; equiv., 352.5), $\nu_{max.}$ (nujol), 2700-2400 (NH^+), 1710 (CO), 1690 (CO), 1290, 1240, 1130, 1040, 1010, 970, 920, 770, 740 (Ph)cm^{-1}.

2-(4-Ethoxycarbonylpiperazinylmethyl)-1,2,3,4-tetrahydronaphth-1-ol (117) Sodium borohydride (0.5 g) was added to a cold solution of 2-(4-Ethoxycarbonylpiperazinylmethyl)-1-tetralone (1 g) in ethanol (50 ml). The mixture was stirred overnight, water (50 ml) added and the alcohol evaporated under reduced pressure. The remaining aqueous layer was extracted with benzene (4 x 50 ml), dried (Na_2SO_4), and the solvent evaporated to give a colourless oil (0.7 g, 70%) which on treatment with ethanolic hydrochloric acid gave colourless crystals of 2-(4-ethoxycarbonylpiperazinylmethyl)-1,2,3,4-tetrahydronaphth-1-ol hydrochloride, m.p. 193-4° (from methanol/ether) (Found: C, 60.8; H, 7.7; N, 7.8; equiv., 351.3. $C_{18}H_{27}ClN_2O_3$ requires C, 61.0; H, 7.6; N, 7.9%; equiv., 354.5), $\nu_{max.}$ (nujol), 3450 (OH), 2700-2400 (NH^+), 1710 (Ester CO), 1280, 1250, 1170, 1140, 1100, 1080, 1040, 970, 850, 770, 740, 730 (Ph)cm^{-1}.

1-Ethyl-2-(4-ethoxycarbonylpiperazinylmethyl)-1,2,3,4-tetrahydronaphth-1-ol (120)

2-(4-Ethoxycarbonylpiperazinylmethyl)-1-tetralone hydrochloride (3.52 g, 0.01 mole) was finely powdered, dried and added in small portions to a solution of ethylmagnesium iodide prepared from magnesium (0.96 g, 0.04 mole)

and ethyl iodide (6.24 g, 0.04 mole) in ether (100 ml). The solution was stirred and refluxed for 14 hr and the complex decomposed by addition of a cold, saturated solution of ammonium chloride. The ether layer was separated, dried (Na_2SO_4), and the solvent evaporated to give a viscous, amber oil (3.2 g, 89.3%). T.L.C. in benzene/acetone (8:1) gave a single spot (when exposed to iodine vapour) (Found: equiv., 353.4. $C_{20}H_{30}N_2O_3$ requires equiv., 346.0), $\nu_{max.}$ (liq. film), 3300 (OH), 1710 (ester CO), 1290, 1240, 1130, 1035, 1000, 760, 720 (Ph) cm^{-1}. Treatment with ethanolic hydrochloric acid gave colourless crystals of 1-ethyl-2-(4-ethoxycarbonylpiperazinylmethyl)-1,2,3,4-tetrahydronaphth-1-ol hydrochloride, m.p. 201.5-2.5° (from ethanol) (Found: C, 62.6; H, 8.2; N, 7.0; equiv., 380. $C_{20}H_{31}ClN_2O_3$ requires C, 62.7; H, 8.1; N, 7.3%; equiv., 382.5) $\nu_{max.}$ (nujol), 3320 (OH), 2650-2450 (NH^+), 1710 (ester CO), 1290, 1240, 1130, 1110, 1090, 1030, 1000, 970, 760, 720 (Ph) cm^{-1}. $\tau_{(CCl_4)}$ 5.8 (H, s, OH), 4.05 (2H, q, O-CH_2-CH_3), 3.0-2.3 (4H, m, aromatic-H).

2-Piperazinylmethyl-1-tetralone

1. 2-(4-Ethoxycarbonylpiperazinylmethyl)-1-tetralone (1.5 g) was refluxed with hydrochloric acid (15 ml) and water (15 ml) for 6 hr when some charring was observed. The solution was then evaporated to a low bulk, basified with ammonia, extracted with ether, the extract washed with water, dried (Na_2SO_4), and the solvent evaporated to give a yellow-brown oil (0.3 g). On conversion to the hydrochloride the oil gave colourless prisms of starting material as its hydrochloride m.p. 165-7°, $\nu_{max.}$ (nujol), 2700-2400 (NH^+), 1710 (CO), 1690 (CO), 770, 740 (Ph) cm^{-1}.

2. Method 1 was repeated using 2-(4-ethoxycarbonylpiperazinylmethyl)-1-tetralone (2 g), hydrochloric acid (10 ml), water (10 ml) and refluxing in a stream of nitrogen for 24 hr. Partial charring was again observed and a

slight brown oily residue. This residue was worked up as in Method 1 but extracted with benzene which after evaporation gave a dark brown varnish (0.4 g) which proved incapable of characterisation.

3. 2-(4-Ethoxycarbonylpiperazinylmethyl)-1-tetralone (2.5 g) was refluxed under nitrogen with potassium hydroxide (3 g), water (10 ml) and 95% alcohol (20 ml) for 3 hr. The solution darkened immediately to a dark red colour with some signs of charring. On evaporation of the ethanol, extraction of the residue with chloroform, drying the extract (Na_2SO_4), and evaporation of the solvent a dark brown mass was obtained which after conversion to the hydrochloride gave a dark brown, deliquescent, powdery precipitate which could not be characterised.

4. 2-(4-Ethoxycarbonylpiperazinylmethyl)-1-tetralone (3.1 g, 0.01 mole) and a 1.N solution of hydrogen bromide in glacial acetic acid (50 ml) were heated on a steam bath for 0.5 hr during which time carbon dioxide and hydrogen bromide were evolved. Heating on the steam bath was then continued for a further 2.5 hr. On cooling the solution, pale lemon crystals of piperazine dihydrobromide (0.8 g, 32.8%) were formed m.p. >300° equiv., 130. $C_4H_{12}Br_2N_2$ requires equiv., 124.0, $\nu_{max.}$ (nujol), 2600-2400 (NH^+), 1590, 1310, 1080, 1050, 930, 870 cm^{-1}. The mother liquor on cooling to 0° gave a pale buff solid which on recrystallisation from ethanol/ether gave white crystals of 2-piperazinylmethyl-1-tetralone dihydrobromide (1.3 g, 53.2%) m.p. 255° (decomp.) (Found: C, 44.0; H, 5.6; N, 6.9; equiv., 207.5. $C_{15}H_{22}Br_2N_2O$ requires C, 44.3; H, 5.4; N, 6.9%; equiv., 202.9), $\nu_{max.}$ (nujol), 2600-2400 (NH^+), 1690 (CO), 1600, 1320, 1270, 1230, 1080, 980, 950, 770, 740 (Ph) cm^{-1}.

2-(4-Benzoylpropylpiperazinylmethyl)-1-tetralone

2-Piperazinylmethyl-1-tetralone dihydrobromide (2.02 g, 0.005 mole) γ-chlorobutyrophenone (1.36 g, 0.0075 mole), sodium carbonate (3.18 g,

0.03 mole) and a few crystals of potassium iodide were refluxed in toluene (100 ml) for 48 hr. The mixture was cooled, water added, the organic phase separated, dried (Na_2SO_4), and evaporated under reduced pressure to give a brown oil (2.0 g) which solidified on cooling. Recrystallisation from ethanol/water gave buff crystals of 2-(4-benzoylpropylpiperazinylmethyl)-1-tetralone, m.p. 183-5° (decomp.) (Found: C, 76.6; H, 7.5; N, 7.0; equiv., 214.7. $C_{25}H_{30}N_2O_2$ requires C, 76.9; H, 7.7; N, 7.2%; equiv., 195.0), $\nu_{max.}$ (nujol), 1680 (CO), 1600, 1320, 1270, 1220, 1170, 1130, 1020, 1005, 770, 740 (Ph) cm^{-1}.

2-(4-Phenethylpiperazinylmethyl)-1-tetralone

2-Piperazinylmethyl-1-tetralone dihydrobromide (1.01 g, 0.0025 mole), 2-chloroethylbenzene (0.518 g, 0.0037 mole), sodium carbonate (1.59 g, 0.015 mole) and a few crystals of potassium iodide were refluxed in toluene (100 ml) for 48 hr. The product was worked up as in the preceding experiment to give small off-white prisms of 2-(4-phenethylpiperazinylmethyl)-1-tetralone, m.p. 183-4° (0.23 g, 26.8%) (Found: C, 79.0; H, 7.7; N, 7.7; equiv., 171.2. $C_{23}H_{28}N_2O$ requires C, 79.3; H, 8.0; N, 8.0%; equiv., 174.0), $\nu_{max.}$ (nujol), 1680 (CO), 780, 750, 680 (Ph) cm^{-1}.

(B): DERIVATIVES OF α-AMINOCYCLOHEXYLNITRILES.

1-(1-Cyanocyclohexyl)-4-methylpiperazine (163)

Methylpiperazine dihydrochloride (85.5 g, 0.5 mole) and potassium cyanide (32.5 g, 0.5 mole) were dissolved in water (200 ml) and ethanol (400 ml). To this stirred solution was added dropwise a solution of cyclohexanone (49 g, 0.5 mole) in ethanol (100 ml) and the whole refluxed for 24 hr. The cooled reaction mixture was extracted with chloroform, the extract dried (Na_2SO_4), and evaporated under reduced pressure to yield a

viscous, brown oil. On distillation *in vacuo*.(140°/3 mm) this gave a colourless oil (67.4 g, 65.1%) $\nu_{max.}$(liq. film), 2250 (C≡N) cm^{-1}. $\tau_{(neat\ liq.)}$ 7.8 (3H, s, N-CH_3). Treatment of an aliquot with ethanol/iodomethane yielded 1-(1-*cyanocylohexyl*)-4,4-*dimethylpiperazinium iodide* which crystallised from methanol as colourless prisms, m.p. 256-257° (decomp.) (Found: C, 44.8; H, 7.1; N, 11.8; I, 36.6; *equiv.*, 173.3. $C_{13}H_{24}N_3I$ requires C, 44.7; H, 6.9; N, 12.0; I, 36.4%; *equiv.*, 174.5), $\nu_{max.}$(nujol), 2750 (N-CH_3), 2600-2400 (NH^+), 2250 (C≡N), 1190, 1150, 1075, 1000, 970, 925, 860, 835, 800 cm^{-1}.

1-(1-Aminomethylcyclohexyl)-4-methylpiperazine (175)

1-(1-Cyanocyclohexyl)-4-methylpiperazine (4.1 g, 0.02 mole) was dissolved in dry ether (100 ml) and added dropwise to a stirred suspension of lithium aluminium hydride (1.52 g, 0.04 mole) in dry ether (200 ml). The suspension was stirred overnight and excess lithium aluminium hydride decomposed by dropwise addition of water (4 ml), 30% sodium hydroxide solution (3 ml), and water (14 ml). The ether layer was separated, dried (Na_2SO_4), and evaporated to yield a colourless, mobile oil (3.48 g, 82.9%), $\nu_{max.}$ (liq. film), 3350 cm^{-1} (NH). An aliquot was refluxed with ethanol (10 ml) and excess methyl iodide for 0.5 hr to give yellow needles of 1-(1-*methylaminocyclohexyl*)-4-*methylpiperazinedimethiodide* which was recrystallised from methanol/ether as pale yellow needles, m.p. 243-5° (Found: C, 33.7; H, 6.5; N, 8.3; I, 50.9; *equiv.*, 243.1. $C_{14}H_{31}I_2N_3$ requires C, 33.9; H, 6.3; N, 8.5; I, 51.3%; *equiv.*, 247.5), $\nu_{max.}$(nujol), 2600-2400 (NH^+), 1540, 1270, 1190, 1160, 1150, 1095, 1060, 1010, 1000, 970, 940, 910, 870, 810 cm^{-1}.

1-(4-Methylpiperazinyl)cyclohexylmethylbenzamide (198)

A mixture of 1-(1-aminomethylcyclohexyl)-4-methylpiperazine (1.5 g), benzoyl chloride (2 ml) and pyridine (10 ml) was allowed to stand at room

temperature for 1 hr. The dark red solution produced was diluted with water, basified with ammonia and extracted with chloroform (3 x 50 ml). The chloroform extract was washed with water, dried (Na_2SO_4), and evaporated under reduced pressure to yield a reddish-brown, viscous oil (2.4 g) which set to a hard mass on cooling. Crystallisation from light petroleum (b.p. 100-120°) afforded pale yellow prisms of 1-(4-Methylpiperazinyl) cyclohexylmethylbenzamide (1.53 g, 68.1%), m.p. 127-128° (Found: C, 72.4; H, 9.2; N, 13.1; equiv., 165.0. $C_{19}H_{29}N_3O$ requires C, 72.4; H, 9.2; N, 13.3%; equiv., 157.5), $\nu_{max.}$(nujol), 3300 (NH), 1640 (amide CO), 1230, 1170, 1090, 1005, 970, 830, 700 (Ph) cm^{-1}.

1-(1-Formylaminomethylcyclohexyl)-4-methylpiperazine (185)

Formic acid (6.9 g, 0.15 mole) and acetic anhydride (15.3 g, 0.15 mole) were mixed without cooling and kept at room temperature for 1 hr. 1-(1-aminomethylcyclohexyl)-4-methylpiperazine (8.4 g, 0.04 mole) was dissolved in formic acid (12 ml) and the formylating mixture (16 ml) added. This produced vigorous effervescence and a rise in temperature to 70°. The mixture was left at room temperature for 2 hr and then heated on a water bath at 55° for 0.75 hr. The solvents were removed under reduced pressure yielding a viscous, brown oil (6.0 g, 66.3%) which crystallised as colourless plates of 1-(1-formylaminomethylcyclohexyl)-4-methylpiperazine from light petroleum (b.p. 80-100°), m.p. 97-98° (Found: C, 65.2; H, 10.4; N, 17.6; equiv., 120.4, M^+, 239. $C_{13}H_{25}N_3O$ requires C, 65.3; H, 10.5; N, 17.6%; equiv., 119.5, M^+, 239), $\nu_{max.}$(nujol), 3150 (NH), 1660 (amide CO), 1540, 1280, 1220, 1170, 1150, 1130, 1090, 1070, 1000, 990, 970, 790 cm^{-1}. $\tau_{(CDCl_3)}$ 7.72 (3H, s, N-CH_3), 6.57 (2H, d, $\underline{CH_2}N\langle^{CHO}_{H}$) 1.75 (H, d, CHO).

1-(1-Methylaminomethylcyclohexyl)-4-methylpiperazine (188)

1-(1-Formylaminomethylcyclohexyl)-4-methylpiperazine (5.97 g, 0.025 mole)

was dissolved in dry benzene (100 ml) and added dropwise to a stirred suspension of lithium aluminium hydride (3.8 g, 0.1 mole) in dry ether (200 ml). The suspension was refluxed for four days and excess lithium aluminium hydride decomposed by the dropwise addition of water (8 ml), 30% sodium hydroxide solution (6 ml) and water (28 ml). The ether/benzene layer was separated, dried (Na_2SO_4), and evaporated to yield an amber, mobile oil (5.2 g, 93.0%) which failed to crystallise or produce stable salts. Distillation of this oil *in vacuo*. gave 1-(1-methylaminomethyl cyclohexyl)-4-methylpiperazine as a colourless oil (Found: C, 69.0; H, 11.8; N, 18.5; M^+, 225. $C_{13}H_{27}N_3$ requires C, 69.3; H, 12.0; N, 18.7%; M^+, 225), $\nu_{max.}$ (liq. film), 2300 (NH), 2770 ($N-CH_3$), 1460, 1290, 1160, 1010 cm^{-1}.

1-(N-Formyl-1-methylaminomethylcyclohexyl)-4-methylpiperazine (191)

Formic acid (3.45 g, 0.07 mole) and acetic anhydride (7.65 g, 0.07 mole) were mixed without cooling and kept at room temperature for 1 hr. 1-(1-methylaminomethylcyclohexyl)-4-methylpiperazine (2.25 g, 0.01 mole) was dissolved in formic acid (6 ml) and the formylating mixture (8 ml) added. This produced vigorous effervescence and a temperature rise to 60°. The mixture was left at room temperature for 2 hr and then heated on a water bath at 55° for 0.75 hr. The solvents were removed under reduced pressure to give a viscous, reddish-brown oil (2.13 g, 83.3%) which crystallised as colourless needles of 1-(N-formyl-1-methylaminomethylcyclohexyl)-4-methylpiperazine from light petroleum (b.p. 80-100°), m.p. 107-108° (Found: C, 66.2; H, 10.6; N, 16.7; equiv., 124.0, M^+, 253. $C_{14}H_{27}N_3O$ requires C, 66.4; H, 10.7; N, 16.6%; equiv., 126.5, M^+, 253), $\nu_{max.}$ (liq. film), 2780 ($N-CH_3$), 1660 (amide CO), 1460, 1390, 1285, 1160, 1080, 1010, 990, 800 cm^{-1}.

1-(1,1-Dimethylaminomethylcyclohexyl)-4-methylpiperazine (194)

1-(N-Formyl-1-methylaminomethylcyclohexyl)-4-methylpiperazine (0.76 g, 0.003 mole) was dissolved in dry ether (40 ml) and added dropwise to a stirred suspension of lithium aluminium hydride (0.23 g, 0.006 mole) in dry ether (100 ml). The suspension was refluxed for 48 hr and excess lithium aluminium hydride decomposed by dropwise addition of water (0.4 ml), 30% sodium hydroxide solution (0.3 ml) and water (1.4 ml). The ether layer was separated, dried (Na_2SO_4), and evaporated to yield a colourless, mobile oil (0.47 g, 72.2%) which failed to crystallise. Treatment with ethanol/methyl iodide gave colourless prisms of 1-(1,1,1-trimethylaminomethyl cyclohexyl)-4,4-dimethylpiperazinium diiodide, m.p. 171-172° (Found: C, 36.6; H, 6.8; N, 7.9; I, 48.7; equiv., 256.0. $C_{16}H_{35}N_3I_2$ requires C, 36.7; H, 6.7; N, 8.0; I, 48.6%; equiv., 261.5), $\nu_{max.}$ (nujol), 2820, 2780 (NCH_3), 1460, 1380, 1290, 1160, 1090, 1040, 1010, 990, 940, 860, 800 cm^{-1}.

1-(1-Tosylaminomethylcyclohexyl)-4-methylpiperazine (208)

1-(1-Aminomethylcyclohexyl)-4-methylpiperazine (0.5 g) was added to 10% sodium hydroxide solution (10 ml) and p-toluenesulphonyl chloride (0.5 g), and the mixture shaken vigorously. The solid was filtered, washed with water and recrystallised from 95% ethanol to give colourless needles (0.4 g, 46.2%) of 1-(1-tosylaminomethylcyclohexyl)-4-methylpiperazine, m.p. 128-130° (Found: C, 62.6; H, 8.5; N, 11.4. $C_{19}H_{31}N_3O_2S$ requires C, 62.5; H, 8.5; N, 11.5%), $\nu_{max.}$ (nujol), 3250 (NH), 2780 (NCH_3), 1330 (Asymm. SO_2), 1290, 1160 (Symm. SO_2), 1090, 1010, 980, 940, 920, 820, 720 (Ph) cm^{-1}.

1-(4-Methylpiperazinyl)cyclohexylamide (172d)

1-(1-Cyanocyclohexyl)-4-methylpiperazine (2.07 g, 0.01 mole) was heated on a steam bath with sulphuric acid (40 ml) for 0.25 hr, cooled, poured onto crushed ice (150 g), basified with ammonia and the resulting mixture

extracted with chloroform. The extract was washed with water, dried ($MgSo_4$), and evaporated under reduced pressure to give a viscous, amber oil (1.51 g, 67.7%). The oil solidified on standing and was crystallised from light petroleum (b.p. 80-100°) to yield colourless plates of 1-(4-methylpiperazinyl)cyclohexylamide, m.p. 107° (Found: C, 64.1; H, 10.3; N, 18.5; equiv., 110.0. $C_{12}H_{23}N_3O$ requires C, 64.0; H, 10.2; N, 18.7%; equiv., 112.5), $\nu_{max.}$(nujol), 3320, 3160 (NH), 2820 (N-CH_3), 1670 (amide CO), 1460, 1380, 1290, 1160, 1140, 1010, 980, 880, 790 cm^{-1}.

Attempts to prepare 1-(4-Methylpiperazinyl)cyclohexylcarboxylic acid

(1) 1-(1-Cyanocyclohexyl)-4-methylpiperazine (4.12 g, 0.02 mole) and sulphuric acid (80 ml) were heated on a steam bath for 0.25 hr. The solution was cooled, diluted with water (80 ml) and refluxed for 12 hr during which time charring slowly took place. The solution was cooled, poured onto crushed ice (150 g), basified with ammonia and extracted with chloroform using a continuous chloroform extractor. The extract was dried ($MgSO_4$), and the solvent distilled off to yield an intractable tar (0.84 g) which failed to give stable salts.

(2) 1-(4-Methylpiperazinyl)cyclohexylamide (1.0 g) was refluxed with 50% H_2SO_4 (40 ml) for 2.5 hr at which point charring just commenced. The solution was cooled, poured onto crushed ice (75 g), basified with ammonia, extracted with chloroform, dried (Na_2SO_4), and the solvent distilled to yield a brown, viscous oil (0.6 g, 60%), $\nu_{max.}$ 3300, 3120 (NH), 1670 (amide CO) cm^{-1}. The oil solidified on cooling and was recrystallised from light petroleum (b.p. 80-100°) to give colourless plates of the starting product m.p. 107°.

(3) 1-(4-Methylpiperazinyl)cyclohexylamide (1.0 g) was refluxed with freshly prepared 25% alcoholic potassium hydroxide (30 ml) for 27 hr.

The alcohol was distilled under reduced pressure and the alkaline residue extracted with benzene. The benzene extract was washed with water, dried (Na_2SO_4), and the solvent evaporated to give a brown oil (0.25 g), $\nu_{max.}$ (liq. film), 3320, 3160 (NH), 1670 (amide CO) cm^{-1}. All attempts to isolate the desired acid product from the residue failed.

1-(1-Benzylimidoylcyclohexyl)-4-methylpiperazine (221)

1-(1-Cyanocyclohexyl)-4-methylpiperazine (20.7 g, 0.1 mole) was dissolved in dry ether (150 ml) and added dropwise to a solution of phenyl lithium prepared from lithium (5.6 g, 0.8 mole) and bromobenzene (62.8 g, 0.4 mole) in dry ether (200 ml). The solution was stirred overnight, the complex decomposed by dropwise addition of damp ether and the ether layer separated. The ether layer was washed with water, dried (Na_2SO_4), and the ether evaporated to give a viscous, reddish-brown oil (23.9 g, 84.3%) which crystallised on cooling. Recrystallisation from light petroleum (b.p. 80-100°) afforded colourless needles of 1-(1-Benzylimidoylcyclohexyl)-4-methylpiperazine, m.p. 95-96° (Found: C, 75.9; H, 9.7; N, 14.8; equiv., 149.4. $C_{18}H_{27}N_3$ requires C, 75.8; H, 9.5; N, 14.7%; equiv., 142.5), $\nu_{max.}$ (nujol), 3200 (NH), 1620 (C=N), 1340, 1280, 1160, 1140, 1015, 970, 870, 760, 700 (Ph) cm^{-1}.

1-(1-Benzoylcyclohexyl)-4-methylpiperazine (225)

1-(1-Benzylimidoylcyclohexyl)-4-methylpiperazine (10.0 g) was refluxed with water (100 ml) and hydrochloric acid (100 ml) for 1 hr. The solution was cooled, made alkaline with ammonia and extracted with chloroform. The extract was washed with water, dried (Na_2SO_4), and the solvent evaporated to give a pale yellow solid (8.1 g, 81.0%). Recrystallisation from light petroleum (b.p. 100-120°) gave colourless needles of 1-(1-Benzoylcyclohexyl)-4-methylpiperazine, m.p. 121-122° (Found: C, 75.6; H, 9.2; N, 9.6; M^+, 286. $C_{18}H_{26}N_2O$ requires C, 75.5; H, 9.1; N, 9.8%; M^+, 286),

$\nu_{max.}$(nujol), 1670 (CO), 1420, 1290, 1220, 1160, 1140, 1015, 970, 880, 740, 715, 700 (Ph) cm^{-1}.

1-(1-1'-Hydroxybenzylcyclohexyl)-4-methylpiperazine (229)

1-(1-Benzoylcyclohexyl)-4-methylpiperazine (7.15 g, 0.025 mole) was dissolved in dry benzene (100 ml) and added dropwise to a stirred suspension of lithium aluminium hydride (1.90 g, 0.050 mole) in dry ether (100 ml). The suspension was refluxed for 4 hr, cooled, and excess lithium aluminium hydride decomposed by dropwise addition of water (4 ml), 30% sodium hydroxide solution (3 ml), and water (14 ml). The ether/benzene layer was separated, dried (Na_2SO_4), and evaporated to give an off-white solid (6.1 g, 84.8%) which was recrystallised from ethanol to yield colourless needles of 1-(1-1'-hydroxybenzylcyclohexyl)-4-methylpiperazine, m.p. 227-228° (Found: C, 74.8; H, 9.8; N, 9.6; equiv., 142.0, M^+, 288. $C_{18}H_{28}N_2O$ requires C, 75.0; H, 9.7; N, 9.7%; equiv., 144.0, M^+, 288), $\nu_{max.}$(nujol), 3400 broad band (OH), 1290, 1170, 1160, 1100, 1040, 980, 800, 770, 715, 700 (Ph) cm^{-1}.

1-(1-1'-Acetoxybenzylcyclohexyl)-4-methylpiperazine (231)

1-(1-1'-Hydroxybenzylcyclohexyl)-4-methylpiperazine (3 g) was refluxed for 3 hr with acetic anhydride (12 ml) and pyridine (12 ml). The unreacted reagents were evaporated under reduced pressure to yield a brown, viscous residue (4.1 g) which solidified on cooling. Recrystallisation from light petroleum (b.p. 60-80°) gave colourless prisms of 1-(1-1'-acetoxybenzylcyclohexyl)-4-methylpiperazine (1.5 g, 45.1%), m.p. 105° (Found: C, 72.6; H, 9.2; N, 8.3; equiv., 158.0. $C_{20}H_{30}N_2O_2$ requires C, 72.7; H, 9.1; N, 8.5%; equiv., 160.0), $\nu_{max.}$(nujol), 1730 (Ester CO), 1240, 1150, 1130, 1040, 990, 940, 730 (Ph) cm^{-1}.

1-(4-Methylpiperazinyl)cyclohexylphenylethanol

1-(1-Benzoylcyclohexyl)-4-methylpiperazine (5.72 g, 0.02 mole) was dissolved in dry ether (100 ml) and added dropwise to a solution of methylmagnesium iodide prepared from magnesium (2.2 g, 0.10 mole) and iodomethane (11.36 g, 0.10 mole) in dry ether (75 ml). The solution was stirred overnight and the complex decomposed by dropwise addition of a freshly prepared, saturated solution of ammonium chloride. The ether layer was separated, washed with water, dried (Na_2SO_4), and the solvent evaporated to give an amber, glassy solid (5.78 g, 95.3%). Recrystallisation from ethanol gave colourless needles of 1-(4-methylpiperazinyl)cyclohexylphenylethanol), m.p. 193-5° (Found: C, 75.2; H, 10.1; N, 9.1; $C_{19}H_{30}N_2O$ requires C, 75.5; H, 9.9; N, 9.3%), $\nu_{max.}$(nujol), 3400 broad (OH), 2780 (NCH_3), 1290, 1175, 1130, 1015, 990, 760, 700 (Ph) cm^{-1}.

1-(1-1'-Aminobenzylcyclohexyl)-4-methylpiperazine

1-(1-Benzylimidoylcyclohexyl)-4-methylpiperazine (5.7 g, 0.02 mole) was dissolved in dry ether (150 ml) and the solution added dropwise to a stirred suspension of lithium aluminium hydride (1.52 g, 0.04 mole) in dry ether (150 ml). The suspension was stirred overnight and excess lithium aluminium hydride decomposed by dropwise addition of water (4 ml), 30% sodium hydroxide solution (3 ml) and water (14 ml). The ether layer was separated, dried (Na_2SO_4), and evaporated to yield an amber, mobile oil (5.02 g, 87.6%) which solidified on cooling. The solid was recrystallised from acetone/water to give colourless needles of 1-(1-1'-aminobenzylcyclohexyl)-4-methylpiperazine, m.p. 182° (decomp.) (Found: C, 75.1; H, 9.9; N, 14.4; equiv., 142.1. $C_{18}H_{29}N_3$ requires C, 75.3; H, 10.1; N, 14.6%; equiv., 143.5), $\nu_{max.}$(nujol), 3355, 3265 (NH), 2780 (N-CH_3), 1280, 1160, 1090, 1070, 1040, 980, 800, 770, 700 (Ph) cm^{-1}.

1-(1-1'-Dimethylaminobenzylcyclohexyl)-4-methylpiperazine

1-(1-1'-Aminobenzylcyclohexyl)-4-methylpiperazine (2.87 g, 0.01 mole) was refluxed for 5 hr with formic acid (1.84 g, 0.04 mole) and formalin 40% (7.5 ml, 0.1 mole). The resulting solution was cooled, basified with ammonia, extracted with chloroform (3 x 100 ml), dried (Na_2SO_4), and the solvent evaporated under reduced pressure to give a bright yellow solid (2.3 g, 72.8%). Recrystallisation from ethanol gave colourless, feathery needles of 1-(1-1'-dimethylaminobenzylcyclohexyl)-4-methylpiperazine, m.p. 230-231° (Found: C, 75.9; H, 10.2; N, 13.1. $C_{20}H_{33}N_3$ requires C, 76.2; H, 10.5; N, 13.3%), $\nu_{max.}$ (nujol), 2800 (NCH_3), 1280, 1160, 1150, 1090, 1040, 980, 800, 780, 715, 700 (Ph) cm^{-1}.

1-(1-Phenylcyclohexyl)-4-methylpiperazine (212)

1-(1-Cyanocyclohexyl)-4-methylpiperazine (2.07 g, 0.01 mole) was dissolved in dry ether (50 ml) and added dropwise to a solution of phenylmagnesium bromide prepared from magnesium turnings (1.1 g, 0.05 mole) and bromobenzene (7.85 g, 0.05 mole) in dry ether (100 ml). The suspension was stirred overnight and the complex decomposed by dropwise addition of a freshly prepared, saturated solution of ammonium chloride. The ether layer was separated, washed with water, dried (Na_2SO_4), and the solvent evaporated to give an amber, mobile oil (1.9 g, 73.6%). On cooling, the oil crystallised and a recrystallisation from light petroleum (b.p. 60-80°) afforded colourless rosettes of 1-(1-Phenylcyclohexyl)-4-methylpiperazine, m.p. 90-91° (Found: C, 78.9; H, 9.9; N, 10.7; equiv., 127.8, M^+, 258. $C_{17}H_{26}N_2$ requires C, 79.1; H, 10.1; N, 10.9%; equiv., 129.0, M^+, 258), $\nu_{max.}$ (liq. film), 2780 (NCH_3), 1600, 1480, 1460, 1380, 1290, 1160, 1140, 1010, 980, 800, 760, 740, 700 (Ph) cm^{-1}.

1-(1-Methylcyclohexyl)-4-methylpiperazine (211)

1-(1-Cyanocyclohexyl)-4-methylpiperazine (4.14 g, 0.02 mole) was dissolved in dry ether (100 ml) and added dropwise to a solution of methylmagnesium bromide prepared from magnesium turnings (2.2 g, 0.1 mole) and iodomethane (11.36 g, 0.10 mole) in dry ether (100 ml). The resulting thick suspension was stirred for 3 hr and decomposed by pouring onto ice and ammonium chloride. The ether layer was separated, washed with water, extracted with dilute hydrochloric acid, the base liberated again with concentrated ammonia solution, extracted with ether, dried (Na_2SO_4), and evaporated to give a colourless oil (0.15 g) $\nu_{max.}$(liq. film), 2800 (NCH_3), 1460, 1380, 1290, 1160, 1120, 980, 920 cm^{-1} with no evidence for C≡N. This oil failed to crystallise but gave colourless needles with ethanol/methyl iodide m.p. 224°, which were identical to those obtained by extracting the inorganic residues with ethanol, evaporating off the solvent and recrystallising the residue from alcohol/acetone mixture. These colourless crystals (1.4 g), m.p. 225° proved to be 1-(1-methylcyclohexyl)-4,4-dimethylpiperazinium iodide (Found: C, 45.9; H, 7.7; N, 8.1; I, 37.1. $C_{13}H_{27}N_2I$ requires C, 46.1; H, 8.0; N, 8.3; I, 37.6%), $\nu_{max.}$(nujol), 2800 (NCH_3), 1160, 1120, 970 cm^{-1}.

$\tau_{(T.F.A.)}$ 8.75 (3H, s, cyclohexyl-CH_3), 6.87 (6H, s, $(CH_3)_2N^+$).

1-Cyclohexyl-4-methylpiperazine

1-(1-Cyanocyclohexyl)-4-methylpiperazine (4.17 g, 0.02 mole) was dissolved in dry benzene (75 ml) and added dropwise to a solution of ethyl magnesium iodide prepared from magnesium (2.4 g, 0.10 mole) and ethyl iodide (15.6 g, 0.10 mole) in dry ether (100 ml). The cream suspension produced was stirred overnight, the complex decomposed by addition of a saturated solution of ammonium chloride and the ether/benzene layer separated. This was washed with water, dried (Na_2SO_4), and the solvents evaporated to give an amber oil (0.86 g, 23.4%) which solidified on cooling. Crystallisation from

light petroleum (b.p. 100-120°) gave buff prisms of 1-cyclohexyl-4-methyl-4-ethyl piperazinium iodide, m.p. 187° (decomp.) (Found: C, 45.7; H, 7.9; N, 8.2; I, 38.0; equiv., 331. $C_{13}H_{27}N_2I$ requires C, 46.1; H, 8.0; N, 8.3; I, 37.6%; equiv., 338), $\nu_{max.}$(nujol), 2600-2400 (NH^+), 1430, 1280, 1260, 1190, 1160, 1130, 1100, 1060, 1030, 980, 930, 860 cm^{-1}.

1-(1-Acetylcyclohexyl)-4-methylpiperazine (233)

1-(1-Cyanocylohexyl)-4-methylpiperazine (10.35 g, 0.05 mole) was dissolved in dry benzene (150 ml) and added dropwise to a solution of methyl lithium prepared from lithium (3.04 g, 0.44 mole) and iodomethane (28.4 g, 0.22 mole) in dry etner (100 ml). The solution was refluxed for 48 hr, the complex decomposed by dropwise addition of damp ether and the ether/benzene layer separated. The inorganic residues were extracted again with benzene and the bulked ether/benzene extracts were washed with water, dried (Na_2SO_4), and evaporated to yield a viscous, red oil (10.1 g, 90.4%), $\nu_{max.}$(liq. film), 3300 (NH), 2780 ($N.CH_3$), 1630 (C=N) cm^{-1}. This was assumed to be the intermediate methylimine derivative 1-(1-methyliminocyclohexyl)-4-methylpiperazine (232). This oil (10.0 g) was refluxed with water (100 ml) and hydrochloric acid (100 ml) for 1 hr. The solution was cooled, basified with ammonia and extracted with chloroform. The extract was washed with water, dried (Na_2SO_4), and the solvent evaporated to give a dark brown, mobile oil (7.0 g, 70.0%) which failed to crystallise but gave a buff powdery precipitate of 1-(1-acetylcyclohexyl)-4,4-dimethylpiperazinium iodide, m.p. 243-244° (decomp.) from an ethanolic solution of iodomethane. (Found: C, 45.7; H, 7.2; N, 7.5; I, 35.0. $C_{14}H_{27}IN_2O$ requires C, 45.9; H, 7.4; N, 7.6; I, 34.7%), $\nu_{max.}$(nujol), 1690 (CO), 1255, 1185, 1140, 1020, 990, 960, 920, 840 cm^{-1}.

1-(1-Bromoacetylcyclohexyl)-4-methylpiperazine Hydrobromide

1-(1-Acetylcyclohexyl)-4-methylpiperazine (7.0 g) was converted to its hydrobromide and recrystallised from ethanol/ether to give pale brown prisms of 1-(1-acetylcyclohexyl)-4-methylpiperazine hydrobromide (9.42 g), m.p. 229-230°.

$\nu_{max.}$ (nujol), 2700-2400 (NH^+), 1705 (CO), 1620, 1175, 1120, 1010, 975, 900, 860 cm^{-1}.

This hydrobromide (9.42 g, 0.031 mole) was refluxed with acetic acid (25 ml) with stirring, and a solution of bromine (4.96 g, 0.031 mole) in acetic acid (15 ml) was added dropwise during 0.25 hr. The mixture was refluxed for a further 0.25 hr, the excess acetic acid distilled (20 ml), and ether (70 ml) added to the cooled residue which gave a brownish precipitate (7.6 g, 64.4%). Recrystallisation from ethanol gave buff prisms of 1-(1-bromoacetylcyclohexyl)-4-methylpiperazine hydrobromide, m.p. 216-217° (Found: C, 40.2; H, 6.1; N, 7.2; Br, 41.3. $C_{13}H_{24}Br_2N_2O$ requires C, 40.6; H, 6.2; N, 7.3; Br, 41.7%), $\nu_{max.}$ (nujol), 2700-2400 (NH^+), 1710 (CO), 1300, 1240, 1170, 1155, 1070, 1010, 980, 900, 860 cm^{-1}.

Attempt to cyclise 1-(1-bromoacetylcyclohexyl)-4-methylpiperazine

Ammonium hydroxide 28% (9 ml) was added to a cooled, stirred suspension of 1-(1-bromoacetylcyclohexyl)-4-methylpiperazine hydrobromide (7.6 g, 0.02 mole) in water (80 ml). A heavy precipitate was formed immediately but stirring was continued for 4 hr. The brown powdery product was filtered, washed with cold water and recrystallised from ethanol to give long feathery needles m.p. 164°. This crude product was recrystallised three times from ethanol/ether to give pale buff needles, m.p. 178-179° (Found: C, 33.8; H, 4.9; N, 5.6; Br, 49.3. Calc. for $C_{13}H_{24}BrN_2O$ C, 51.3; H, 7.9; N, 9.2; Br, 26.3%), $\nu_{max.}$ (nujol), 2700-2400 (NH^+), 1705 (CO), 1280, 1265, 1225, 1210, 1180, 1165, 1130, 1110, 1020, 1000, 985, 970, 920, 890, 870, 750 cm^{-1}.

1-(4-Methylpiperazinylcyclohexyl)ethanol (234)

1-(1-Acetylcyclohexyl)-4-methylpiperazine (2.85 g, 0.013 mole) was dissolved in dry benzene (75 ml) and added dropwise to a stirred suspension of lithium aluminium hydride (0.8 g, 0.026 mole) in dry ether (100 ml). The suspension was stirred overnight and excess lithium aluminium hydride decomposed by dropwise addition of water (2 ml), 30% sodium hydroxide solution (1.5 ml) and water (7 ml). The ether/benzene was separated, dried (Na_2SO_4), and evaporated to yield a pale cream solid (2.34 g, 82.1%). Recrystallisation from light petroleum (b.p. 60-80°) gave small cream needles of 1-(4-Methylpiperazinylcyclohexyl)ethanol, m.p. 138-139° (Found: C, 68.8; H, 11.4; N, 12.2. $C_{13}H_{26}N_2O$ requires C, 69.0; H, 11.5; N, 12.4%), $\nu_{max.}$(nujol), 3180 (OH), 1280, 1230, 1160, 1130, 1085, 1020, 1000, 975, 895, 875, 835, 790 cm^{-1}.

1-(2-Pyridylacetylcyclohexyl)-4-methylpiperazine (235)

2-Picoline (7.44 g, 0.08 mole) in dry ether (50 ml) was added dropwise to a solution of phenyl lithium prepared from lithium (1.12 g, 0.16 mole) and bromobenzene (12.56 g, 0.08 mole) in dry ether (100 ml). The dark red solution was stirred for 1 hr; 1-(1-cyanocyclohexyl)-4-methylpiperazine (4.12 g, 0.02 mole) in dry ether (50 ml) was then added dropwise and the solution stirred overnight. The complex was decomposed by cautious addition of water, the ether layer separated, washed, dried (Na_2SO_4), and the ether evaporated to give a reddish-brown oil (5.20 g, 87.1%), $\nu_{max.}$(liq. film), 3400, 3200 (NH), 2780 (NCH_3), 1620 (C=N), 1598, 1570, 1479, 766 cm^{-1}, indicating that the expected 1-(2-Pyridylacetyl cyclohexylimino)-4-methylpiperazine had been formed. This oil (5.15 g, 0.017 mole) was refluxed for 1 hr with 50% hydrochloric acid (60 ml), cooled, basified with ammonia and the alkaline layer extracted with chloroform (3 x 100 ml). The extract was washed, dried (Na_2SO_4), and the

solvent evaporated to give a viscous, brown oil (4.7 g, 91.2%). The oil was distilled *in vacuo*. to yield 1-(2-*pyridylacetylcyclohexyl*)-4-*methylpiperazine* as a pale amber oil (2.1 g) (Found: C, 71.5; H, 8.7; N, 13.8. $C_{18}H_{27}N_3O$ requires C, 71.8; H, 9.0; N, 14.0%), $\nu_{max.}$ (liq. film), 1710 (CO), 1598, 1570, 1480, 770 cm^{-1}.

1-(1-Hydroxy-2-picolylmethylcyclohexyl)-4-methylpiperazine (236)

1-(2-Pyridylacetylcyclohexyl)-4-methylpiperazine (2.0 g, 0.007 mole) was dissolved in dry ether (200 ml) and added dropwise to a stirred suspension of lithium aluminium hydride (0.5 g, 0.013 mole) in dry ether (100 ml). The deep orange-red suspension was stirred overnight and excess lithium aluminium hydride decomposed by addition of water (1 ml), 30% sodium hydroxide solution (1 ml) and water (5 ml). The ether layer was separated, dried (Na_2SO_4), and evaporated to yield an amber oil (1.61 g, 80.0%). This oil crystallised on cooling and on recrystallisation from light petroleum (b.p. 60-80°) gave colourless prisms of 1-(1-*hydroxy*-2-*picolylmethylcyclohexyl*)-4-*methylpiperazine*, m.p. 104-105° (Found: C, 71.4; H, 9.3; N, 13.6. $C_{18}H_{29}N_3O$ requires C, 71.3; H, 9.6; N, 13.9%), $\nu_{max.}$ (nujol), 3300 (OH), 1598, 1570 (pyridine), 1280, 1160, 1125, 1040 (OH), 1005, 990, 790, 770, 750 cm^{-1}.

1-(1-Cyanocyclohexyl)azabicyclo[3,2,2]nonane (162)

Azabicyclo[3,2,2]nonane hydrochloride (16.15 g, 0.1 mole) and potassium cyanide (6.5 g, 0.1 mole) were dissolved in water (100 ml) and ethanol (150 ml). To this stirred solution, cyclohexanone (9.8 g, 0.1 mole) in ethanol (50 ml) was added dropwise and the whole refluxed for 60 hr. On cooling, the reaction mixture gave a crystalline mass of 1-(1-*cyanocyclohexyl*)*azabicyclo*[3,2,2]*nonane* (9.44 g, 40.8%), m.p. 80-81° (from ethanol) (Found: C, 77.5; H, 10.4; N, 12.0; *equiv.*, 231.2. $C_{15}H_{24}N_2$ requires C, 77.6; H, 10.3; N, 12.1%; *equiv.*, 232.0), $\nu_{max.}$ (nujol),

2230 (C≡N), 1320, 1270, 1150, 1130, 1100, 960, 925, 870, 850 cm^{-1}.

$\tau_{(CDCl_3)}$ 7.35 (4H, d, CH_2-N-CH_2).

1-(1-Benzylimidoylcyclohexyl)azabicyclo[3,2,2]nonane (220)

1-(1-Cyanocyclohexyl)azabicyclo[3,2,2]nonane (9.28 g, 0.04 mole) was dissolved in dry ether (100 ml) and added dropwise to a solution of phenyl lithium prepared from lithium (2.24 g, 0.32 mole) and bromobenzene (25.12 g, 0.16 mole) in dry ether (100 ml). The solution was stirred overnight, the complex decomposed by addition of damp ether and the ether layer separated. This was washed with water, dried (Na_2SO_4), and the solvent evaporated to give a colourless crystalline solid (11.5 g, 93.2%), m.p. 107°. Recrystallisation from light petroleum (b.p. 80-100°) yielded colourless needles of 1-(1-benzylimidoylcyclohexyl)azabicyclo[3,2,2]nonane, m.p. 124-5° (Found: C, 81.5; H, 9.7; N, 9.1; equiv., 153.1. $C_{21}H_{30}N_2$ requires C, 81.3; H, 9.7; N, 9.0%; equiv., 155.0), $\nu_{max.}$(nujol), 1603 (C=N), 1330, 1280, 1170, 1095, 950, 870, 770, 740, 700 (Ph) cm^{-1}.

1-(1-Benzoylcyclohexyl)azabicyclo[3,2,2]nonane (224)

1-(1-Benzylimidoylcyclohexyl)azabicyclo[3,2,2]nonane (9.0 g) was refluxed with water (100 ml) and hydrochloric acid (100 ml) for 1 hr. The solution was cooled, basified with ammonia and extracted with chloroform. The extract was washed with water, dried (Na_2SO_4), and the solvent evaporated to give a pale yellow solid (7.8 g, 86.7%), m.p. 148°. Recrystallisation from light petroleum (b.p. 60-80°) gave colourless prisms of 1-(1-benzoylcyclohexyl)azabicyclo[3,2,2]nonane, m.p. 152° (Found: C, 81.1; H, 9.4; N, 4.4; equiv., 310.1. $C_{21}H_{29}NO$ requires C, 81.0; H, 9.3; N, 4.5%; equiv., 311.0), $\nu_{max.}$(nujol), 1670 (CO), 1598, 1320, 1240, 1210, 1170, 1120, 1100, 995, 960, 895, 790, 740, 700 (Ph) cm^{-1}.

1-(1-1'-Hydroxybenzylcyclohexyl)azabicyclo[3,2,2]nonane (228)

1-(1-Benzoylcyclohexyl)azabicyclo[3,2,2]nonane (6.2 g, 0.02 mole) was dissolved in dry benzene (100 ml) and added dropwise to a stirred suspension of lithium aluminium hydride (1.52 g, 0.04 mole) in dry ether (150 ml). The suspension was stirred overnight and excess lithium aluminium hydride decomposed by dropwise addition of water (4 ml), 30% sodium hydroxide solution (3 ml) and water (14 ml). The ether/benzene layer was separated, washed, dried (Na_2SO_4), and evaporated to give a pale amber oil (4.4 g, 71.0%). Crystallisation from light petroleum (b.p. 80-100°) gave colourless needles of 1-(1-1'-hydroxybenzylcyclohexyl)azabicyclo[3,2,2]nonane, m.p. 135-136° (Found: C, 80.6; H, 10.1; N, 4.4; equiv., 311.8. $C_{21}H_{31}NO$ requires C, 80.5; H, 9.9; N, 4.5%; equiv., 313.0), $\nu_{max.}$(nujol), 3400 (OH), 1270, 1200, 1145, 1090, 1030, 770, 740, 700 (Ph) cm^{-1}.

1-(1-Azabicyclo[3,2,2]nonyl)cyclohexylamide (167)

1-(1-Cyanocyclohexyl)azabicyclo[3,2,2]nonane (4.64 g, 0.02 mole) was heated on a steam bath with sulphuric acid (60 ml) for 0.25 hr, cooled, and the mixture poured onto crushed ice (150 g), basified with ammonia and the alkaline layer extracted with chloroform. The extract was washed with water, dried (Na_2SO_4), and the solvent evaporated to give a viscous, amber oil (2.18 g, 43.5%) which crystallised from light petroleum (b.p. 60-80°) as colourless prisms of 1-(1-Azabicyclo[3,2,2]nonyl)cyclohexylamide, m.p. 150° (Found: C, 71.8; H, 10.2; N, 11.2; equiv., 248.2. $C_{15}H_{26}N_2O$ requires C, 72.0; H, 10.4; N, 11.2%; equiv., 250.0), $\nu_{max.}$(nujol), 3310, 3180 (NH), 1670 (CO), 1225, 1160, 1120, 1070, 965, 920, 880, 865 cm^{-1}.

1-Cyclohexylazabicyclo[3,2,2]nonane (177)

(1) 1-(1-Cyanocyclohexyl)azabicyclo[3,2,2]nonane (16.24 g, 0.07 mole) was dissolved in dry benzene (200 ml) and added dropwise to a stirred

suspension of lithium aluminium hydride (5.68 g, 0.14 mole) in dry ether (200 ml). The suspension was stirred overnight and excess lithium aluminium hydride decomposed by dropwise addition of water (8 ml), 30% sodium hydroxide solution (6 ml), and water (28 ml). The ether/benzene layer was separated, washed with water, dried (Na_2SO_4), and evaporated to yield a colourless, mobile oil (12.18 g, 75.0%) which crystallised on cooling to pearly plates of 1-cyclohexylazabicyclo[3,2,2]nonane, m.p. 37-38° (Found: C, 81.2; H, 12.0; N, 6.6; equiv., 206.6, M^+, 207. $C_{14}H_{25}N$ requires C, 81.2; H, 12.1; N, 6.7%; equiv., 207.0, M^+, 207), $\nu_{max.}$(liq. film), 1460, 1315, 1270, 1220, 1190, 1170, 1140, 1090, 1015, 900, 870 cm^{-1}.

$\tau_{(CDCl_3)}$ 7.35 (4H, d, CH_2-N-CH_2).

This base was converted to colourless needles of 1-cyclohexylazabicyclo[3,2,2]nonane hydrochloride m.p. 310-15° (decomp.) (Found: C, 68.8; H, 10.7; N, 5.8; Cl, 14.5. $C_{14}H_{26}ClN$ requires C, 68.9; H, 10.7; N, 5.7; Cl, 14.6%), $\nu_{max.}$(nujol), 2600-2450 (NH^+), 1460, 1320, 1090, 900, 880 cm^{-1}.

(2) Azabicyclo[3,2,2]nonane (0.5 g, 0.004 mole), bromocyclohexane (0.98 g, 0.006 mole), sodium bicarbonate (0.16 g, 0.002 mole), and a crystal potassium iodide were refluxed in toluene (100 ml) for 48 hr. The mixture was cooled, washed with water, the organic phase separated, dried ($MgSO_4$), and the solvent evaporated under reduced pressure to yield a pasty product (0.25 g). The paste was converted to colourless needles of 1-cyclohexyl azabicyclo[3,2,2]nonane hydrochloride (from 10% ethanolic HCl/ether), m.p. 309-315° (decomp.) undepressed on admixture with authentic sample, $\nu_{max.}$(nujol), 2600-2450 (NH^+), 1460, 1320, 1220, 1190, 1090, 900, 870 cm^{-1} superimposable on the infra red of an authentic sample.

1-Cyanocyclohexyldimethylamine (160)

Dimethylamine hydrochloride (40.75 g, 0.5 mole) and potassium cyanide (32.5 g, 0.5 mole) were dissolved in water (200 ml) and ethanol (150 ml). To this stirred solution was added dropwise a solution of cyclohexanone (49.0 g, 0.5 mole) in ethanol (100 ml) and the whole refluxed for 24 hr. Ethanol was then removed under reduced pressure and the residue extracted with chloroform. The extract was washed with water, dried (Na_2SO_4), and evaporated under reduced pressure to give a reddish-brown,mobile oil (51.4 g, 62.4%). This oil was distilled in vacuo. ($88^{\circ}/3.5$ mm) yielding a colourless oil (38.3 g, 46.5%), $\nu_{max.}$(liq. film), 2780 (NCH_3), 2220 (C≡N), 1240, 1160, 1090, 810 cm^{-1}. The oil failed to crystallise but gave colourless needles of 1-cyanocyclohexyltrimethylammoniumiodide (from ethanol/iodomethane), m.p. 201-202° (Found: C, 40.7; H, 6.4; N, 9.3; I, 42.9; equiv., 284.9. $C_{10}H_{19}N_2I$ requires C, 40.8; H, 6.5; N, 9.5; I, 43.2%; equiv., 294), $\nu_{max.}$(nujol), 2220 (C≡N), 1405, 1030, 970, 950, 930, 890, 850 cm^{-1}.

1-Benzylimidoylcyclohexyldimethylamine (219)

1-Cyanocyclohexyldimethylamine (12.16 g, 0.08 mole) was dissolved in dry ether (75 ml) and added dropwise to a solution of phenyl lithium prepared from lithium (4.48 g, 0.64 mole) and bromobenzene (50.24 g, 0.32 mole) in dry ether (150 ml). The solution was stirred for 48 hr, the complex decomposed by addition of damp ether and the ether layer separated. This was washed with water, dried (Na_2SO_4), and the ether evaporated to give a pale amber, mobile oil (17.2 g, 94.5%) which failed to crystallise. The oil gave pale yellow needles of 1-benzylimidoylcyclohexyltrimethylammonium iodide (from ethanol/iodomethane) which on recrystallisation from ethanol/ether had a m.p. 161-162° (Found: C, 51.8; H, 7.0; N, 7.3; equiv., 375.8. $C_{16}H_{25}IN_2$ requires C, 51.6; H, 6.7; N, 7.5%; equiv., 372),

$\nu_{max.}$ (nujol), 3450, 3240 (NH), 1618 (C=N), 1340, 1190, 1030, 980, 950, 830, 760, 710 (Ph) cm^{-1}.

1-Benzoylcyclohexyldimethylamine (223)

1-Benzylimidoylcyclohexyldimethylamine (12.0 g) was refluxed with water (100 ml) and HCl (100 ml) for 1 hr. The solution was cooled, basified with ammonia and extracted with ether. The extract was washed with water, dried (Na_2SO_4), and the solvent evaporated to give an amber, mobile oil (11.2 g, 93.3%) which failed to crystallise but gave colourless needles of 1-benzoylcyclohexyldimethylamine hydrochloride (from 10% ethanolic HCl), m.p. 206-207° (Found: C, 67.6; H, 8.4; N, 5.3; equiv., 275.8. $C_{15}H_{22}ClNO$ requires C, 67.3; H, 8.2; N, 5.2%; equiv., 267.5), $\nu_{max.}$ (nujol), 2550-2300 (NH^+), 1670 (CO), 1600, 1310, 1250, 1230, 1140, 1015, 950, 890, 790, 730, 705 (Ph) cm^{-1}.

1-(1-Dimethylaminocyclohexyl)benzyl alcohol (227)

1-Benzoylcyclohexyldimethylamine (9.24 g, 0.04 mole) was dissolved in dry benzene (150 ml) and added dropwise to a stirred suspension of lithium aluminium hydride (3.04 g, 0.08 mole) in dry ether (200 ml). The suspension was stirred overnight and excess lithium aluminium hydride decomposed by dropwise addition of water (8 ml), 30% sodium hydroxide solution (6 ml), and water (28 ml). The ether/benzene layer was separated, washed with water, dried (Na_2SO_4), and evaporated to give a pale, amber oil (6.59 g, 71.9%) which crystallised on cooling. Recrystallisation from light petroleum (b.p. 60-80°) gave colourless, feathery needles of 1-(1-dimethylaminocyclohexyl)benzyl alcohol, m.p. 90-91° (Found: C, 77.5; H, 10.0; N, 6.2; equiv., 231.1. $C_{15}H_{23}NO$ requires C, 77.3; H, 9.9; N, 6.0%; equiv., 233.0), $\nu_{max.}$ (nujol), 3400 (OH), 1310, 1220, 1175, 1150, 1100, 1050, 1040, 1000, 960, 920, 850, 810, 780, 715, 700 (Ph) cm^{-1}.

1-Aminomethylcyclohexyldimethylamine (173)

1-Cyanocyclohexyldimethylamine (22.7 g, 0.15 mole) was dissolved in dry ether (200 ml) and added dropwise to a stirred suspension of lithium aluminium hydride (11.37 g, 0.3 mole) in dry ether (300 ml). The suspension was stirred overnight and excess lithium aluminium hydride decomposed by dropwise addition of water (28 ml), 30% sodium hydroxide solution (21 ml) and water (50 ml). The ether layer was separated, dried (Na_2SO_4), and evaporated to yield a colourless, mobile oil (21.4 g, 92.5%). Addition of 10% ethanolic hydrochloric acid to an ethereal solution of the oil gave a solid which was recrystallised from ethanol/ether as colourless needles of 1-aminomethylcyclohexyldimethylaminedihydrochloride, m.p. 251-3° (Found: C, 47.3; H, 9.5; N, 12.2; equiv., 117.3. $C_9H_{22}Cl_2N_2$ requires C, 47.2; H, 9.6; N, 12.2%; equiv., 114.5), $\nu_{max.}$(nujol), 3350 (NH), 2600-2400 (NH^+), 1270, 1200, 1160, 1050, 990, 820 cm^{-1}.

1-Formylaminomethylcyclohexyldimethylamine (186)

Formic acid (27.6 g, 0.60 mole) and acetic anhydride (61.2 g, 0.60 mole) were mixed without cooling and kept at room temperature for 1 hr. 1-aminomethylcyclohexyldimethylamine (18.3 g, 0.12 mole) was dissolved in formic acid (48 ml) and the formylating mixture (64 ml) added slowly. This produced vigorous effervescence and a temperature rise to 60°. The mixture was left at room temperature for 2 hr and then heated on a water bath at 55° for 0.75 hr. The solvents were removed under reduced pressure yielding an amber oil (14.0 g, 70.8%) which gave colourless needles of 1-formylaminomethylcyclohexyltrimethylammonium iodide, m.p. 156-8° (from ethanol/iodomethane) (Found: C, 40.4; H, 7.0; N, 8.6; I, 39.1; equiv., 323.1. $C_{11}H_{23}IN_2O$ requires C, 40.5; H, 7.1; N, 8.6; I, 39.0%; equiv., 326), $\nu_{max.}$(nujol), 3260 (NH), 1680 (CHO), 1530, 1210, 1135, 1065, 975, 950, 835, 825 cm^{-1}.

1-Methylaminomethylcyclohexyldimethylamine (189)

1-Formylaminomethylcyclohexyldimethylamine (9.0 g, 0.05 mole) was dissolved in dry ether (100 ml) and added dropwise to a stirred suspension of lithium aluminium hydride (3.8 g, 0.1 mole) in dry ether (200 ml). The suspension was refluxed for 24 hr and excess lithium aluminium hydride decomposed by dropwise addition of water (8 ml), 30% sodium hydroxide solution (6 ml), and water (28 ml). The ether layer was separated, dried (Na_2SO_4), and evaporated to give a colourless, mobile oil (7.8 g, 94.2%). An aliquot of this oil was treated with 10% ethanolic hydrochloric acid to give colourless needles of 1-methylaminomethylcyclohexyldimethylamine dihydrochloride, m.p. 232-233° (from ethanol/ether) (Found: C, 49.1; H, 9.8; N, 11.4; Cl, 29.0; equiv., 120.0. $C_{10}H_{24}Cl_2N_2$ requires C, 49.4; H, 9.9; N, 11.5; Cl, 29.2%; equiv., 121.5), $\nu_{max.}$ (nujol), 2600-2400 (NH^+), 1265, 1195, 1180, 1030, 1000, 975, 920, 855 cm^{-1}.

1-(N-Formyl-1-methylaminomethyl)cyclohexyldimethylamine (192)

Formic acid (6.9 g, 0.15 mole) and acetic anhydride (15.3 g, 0.15 mole) were mixed without cooling and kept at room temperature for 1 hr. 1-methylaminomethylcyclohexyldimethylamine (5.9 g, 0.034 mole) was dissolved in formic acid (12 ml) and the formylating mixture (16 ml) added slowly. This produced vigorous effervescence and a temperature rise to 75°. The mixture was then left at room temperature for 2 hr and then heated on a water bath at 55° for 0.75 hr. The solvents were removed under reduced pressure to give an amber oil (5.32 g, 77.7%) which crystallised as colourless prisms of 1-(N-formyl-1-methylaminomethyl)cyclohexyldimethylamine from light petroleum (b.p. 60-80°), m.p. 59-60° (Found: C, 66.8; H, 11.3; N, 14.0; equiv., 196.2. $C_{11}H_{22}N_2O$ requires C, 66.7; H, 11.1; N, 14.2%; equiv., 198), $\nu_{max.}$ (nujol), 2790 (NCH_3), 1680 (CO), 1220, 1150, 1080, 995, 960 cm^{-1}.

1-Dimethylaminomethylcyclohexyldimethylamine (195)

1-(N-formyl-1-methylaminomethyl) cyclohexyldimethylamine (2.88 g, 0.014 mole) was dissolved in dry ether (40 ml) and added dropwise to a stirred suspension of lithium aluminium hydride (1.14 g, 0.03 mole) in dry ether (150 ml). The suspension was stirred overnight and excess lithium aluminium hydride decomposed by dropwise addition of water (3 ml), 30% sodium hydroxide solution (2 ml) and water (10 ml). The ether layer was separated, dried (Na_2SO_4), and evaporated to give a pale amber oil (2.34 g, 87.6%), $\nu_{max.}$(liq. film), 2850, 2820, 2770 (NCH_3), 1455, 1200, 1150, 1045, 990 cm^{-1}. Treatment of this oil with 10% ethanolic hydrochloric acid gave colourless needles of 1-dimethylaminomethylcyclohexyldimethylamine dihydrochloride m.p. 232-4° (from ethanol/ether) (Found: C, 48.2; H, 10.6; N, 10.1. calc. $C_{11}H_{26}Cl_2N_2$ C, 51.4; H, 10.1; N, 10.9). The compound was slightly deliquescent.

1-Benzamidomethylcyclohexyldimethylamine (203)

A mixture of 1-aminomethylcyclohexyldimethylamine (1.5 g), benzoyl chloride (3 ml) and pyridine (10 ml) was allowed to stand at room temperature for 1 hr. The crystalline mass was filtered and recrystallised several times from 95% ethanol to give colourless prisms of 1-benzamidomethylcyclohexyldimethylaminehydrochloride m.p. 245-6° (Found: C, 65.1; H, 8.5; N, 9.3; equiv., 146.2. $C_{16}H_{25}ClN_2O$ requires C, 64.9; H, 8.4; N, 9.4%; equiv., 148.2), $\nu_{max.}$(nujol), 3220 (NH), 2600-2400 (NH^+), 1655 (CO), 1565, 1320, 1150, 1090, 950, 890, 820, 730, 710 (Ph) cm^{-1}.

1-(4-Fluorobenzamidomethyl)-cyclohexyldimethylamine (204)

A mixture of 1-aminomethylcyclohexyldimethylamine (1.0 g), 4-fluorobenzoyl chloride (2 ml) and pyridine (10 ml) was allowed to stand at room temperature for 1 hr. The crystalline material produced was filtered and

recrystallised several times from ethanol/ether to give colourless needles of 1-(4-fluorobenzamidomethyl)-cyclohexyldimethylaminehydrochloride, m.p. 238-239° (Found: C, 61.3; H, 7.5; N, 8.8; Cl, 11.4. $C_{16}H_{24}ClFN_2O$ requires C, 61.1; H, 7.6; N, 8.9; Cl, 11.3%), $\nu_{max.}$ (nujol), 3140 (NH), 2550-2400 (NH^+), 1660 (amide CO), 1500, 1310, 1290, 1230, 1160, 1140, 1010, 960, 875, 855, 765, 730, 700 (Ph) cm^{-1}.

1-(3,4-Dichlorobenzamidomethyl)-cyclohexyldimethylamine (205)

A mixture of 1-aminomethylcyclohexyldimethylamine (1.0 g), 3,4-dichlorobenzoyl chloride (2 ml) and pyridine (10 ml) was allowed to stand at room temperature for 1 hr. The pale yellow solid produced was filtered and recrystallised from ethanol/ether several times to give colourless microneedles of 1-(3,4-dichlorobenzamidomethyl)-cyclohexyldimethylamine hydrochloride, m.p. 215-216° (Found: C, 52.5; H, 6.3; N, 7.7; Cl, 29.0; equiv., 363.1. $C_{16}H_{23}Cl_3N_2O$ requires C, 52.5; H, 6.3; N, 7.7; Cl, 29.1%; equiv., 365.5), $\nu_{max.}$ (nujol), 3200 (NH), 2600-2400 (NH^+), 1660 (amide CO), 1590, 1540, 1430, 1300, 1240, 1140, 1080, 1030, 910, 860, 770, 740, 700 (Ph) cm^{-1}.

1-Dimethylaminocyclohexylamide (165)

1-Cyanocyclohexyldimethylamine (4 g, 0.026 mole) was heated on a steam bath with sulphuric acid (50 ml) for 10 min, cooled, the reaction mixture poured onto crushed ice (150 g), basified with ammonia and the alkaline material extracted with chloroform. The extract was washed with water, dried (Na_2SO_4), and evaporated under reduced pressure to give a colourless oil (3.2 g, 72.7%) which crystallised from light petroleum (b.p. 60-80°) as colourless prisms of 1-dimethylaminocyclohexylamide, m.p. 55-56° (Found: C, 63.4; H, 10.5; N, 16.7; equiv., 168.0. $C_9H_{18}N_2O$ requires C, 63.5; H, 10.6; N, 16.5%; equiv., 170), $\nu_{max.}$ (liq. film), 3370, 3200 (NH), 1670 (amide CO), 1460, 1390, 1250, 1200, 1150, 1060, 990, 900 cm^{-1}.

1-1'-Hydroxybenzyl-aminomethylcyclohexyldimethylamine (206)

1-Benzamidomethylcyclohexyldimethylamine (6.3 g, 0.025 mole) was dissolved in dry benzene (100 ml) and added dropwise to a stirred suspension of lithium aluminium hydride (1.9 g, 0.05 mole) in dry ether (200 ml). The suspension was refluxed overnight and excess lithium aluminium hydride decomposed by dropwise addition of water (4 ml), 30% sodium hydroxide solution (3 ml), and water (14 ml). The ether/benzene layer was separated, washed with water, dried (Na_2SO_4), and evaporated to yield an amber, mobile oil (5.43 g, 86.2%). On treatment with ethanol/iodomethane the oil gave colourless crystals of 1-1'-hydroxybenzyl-aminomethylcyclohexyl trimethylammonium di-iodide, m.p. 194-195° (decomp.) (from ethanol/ether) Found (C, 39.8; H, 6.1; N, 4.9; equiv., 269.2. $C_{18}H_{32}I_2N_2O$ requires C, 39.6; H, 5.9; N, 5.1%; equiv., 273.0), $\nu_{max.}$(nujol), 3400 broad band (OH), 2700-2500 (NH^+), 1260, 940, 890, 755, 705 (Ph) cm^{-1}.

1-1'-Acetoxybenzyl-aminomethylcyclohexyldimethylamine (207)

1-1'-Hydroxybenzyl-aminomethylcyclohexyldimethylamine (1.5 g, 0.0057 mole) was refluxed for 3 hr with acetic anhydride (5 ml) in pyridine (5 ml). The solvent was evaporated under reduced pressure and the residue azeotroped to give a brown, viscous oil (1.1 g, 63.2%). On treatment with 10% ethanolic hydrochloric acid this oil yielded pale buff prisms of 1-1'-acetoxybenzyl-aminomethylcyclohexyldimethylaminehydrochloride, m.p. 177-178° (from ethanol/ether) (Found: C, 63.4; H, 8.7; N, 8.1; Cl, 10.7; equiv., 336. $C_{18}H_{29}ClN_2O_2$ requires C, 63.5; H, 8.5; N, 8.2; Cl, 10.4%; equiv., 340.5), $\nu_{max.}$(nujol), 2600-2400 (NH^+), 1640 (ester CO), 1240, 1140, 1030, 980, 740, 700 (Ph) cm^{-1}.

1-(1-Cyanocyclohexyl)piperidine (161)

Piperidine hydrochloride (24.1 g, 0.2 mole) and potassium cyanide (13.0 g, 0.2 mole) were dissolved in water (80 ml) and ethanol (160 ml). To this

stirred solution was added dropwise a solution of cyclohexanone (19.62 g, 0.2 mole) in ethanol (40 ml) and the mixture refluxed for 24 hr. The ethanol was distilled under reduced pressure and the cooled aqueous residue was extracted with chloroform. The chloroform extract was washed with water, dried (Na_2SO_4), and evaporated under reduced pressure to give a pale, amber oil (27.0 g, 68.8%) which crystallised on standing. Recrystallisation from ethanol afforded colourless plates of 1-(1-cyanocyclohexyl)piperidine, m.p. 67-68° (lit. 67-8°)[143] (Found: C, 74.9; H, 10.3; N, 14.4; equiv., 189.7. $C_{12}H_{20}N_2$ requires C, 75.0; H, 10.4; N, 14.6%; equiv., 192), $\nu_{max.}$ (nujol), 2250 (C≡N), 1350, 1300, 1280, 1270, 1260, 1140, 1110, 1050, 1030, 980, 930, 880, 800 cm^{-1}.

1-Cyclohexylpiperidine (178)

1(1-Cyanocyclohexyl)piperidine (27.0 g, 0.14 mole) was dissolved in dry ether (200 ml) and added dropwise to a stirred suspension of lithium aluminium hydride (10.64 g, 0.28 mole) in dry ether (200 ml). The suspension was stirred overnight and excess lithium aluminium hydride decomposed by dropwise addition of water (28 ml), 30% sodium hydroxide solution (21 ml) and water (40 ml). The ether layer was separated, washed with water, dried (Na_2SO_4), and evaporated to yield a colourless, mobile oil (12.8 g, 47.5%) which failed to crystallise on cooling. On treatment with 10% ethanolic hydrochloric acid the oil yielded colourless prisms of 1-cyclohexylpiperidine hydrochloride, m.p. 296-298° (decomp.) (from ethanol/ether) (Found: C, 65.2; H, 10.6; N, 7.0; Cl, 17.2; equiv., 201.5. $C_{11}H_{22}ClN$ requires C, 64.9; H, 10.8; N, 6.9; Cl, 17.4%; equiv., 203.5), $\nu_{max.}$ (nujol), 2600-2400 (NH^+), 1320, 1190, 1080, 1010, 950, 870 cm^{-1}.

1-(1-Aminomethylcyclohexyl)piperidine (174)

1-(1-Cyanocyclohexyl)piperidine (1.92 g, 0.01 mole) was dissolved in dry ether (50 ml) and added dropwise to a stirred suspension of lithium aluminium

hydride (0.76 g, 0.02 mole) in dry ether (100 ml). The suspension was stirred overnight and the product worked up in an identical fashion to the preceding experiment. Removal of the ether gave a colourless oil (1.40 g, 74.4%) which yielded colourless needles of 1-(1-aminomethylcyclohexyl) piperidine dihydrochloride, m.p. 256-7° (from 10% ethanolic hydrochloric acid) (Found: C, 53.7; H, 9.7; N, 10.2; equiv., 132.7. $C_{12}H_{26}Cl_2N_2$ requires C, 53.5; H, 9.7; N, 10.4%; equiv., 134.5), $\nu_{max.}$ (nujol), 2600-2400 (NH^+), 1545, 1200, 1150, 1120, 1020, 950, 875, 860 cm^{-1}.

1-(1-Methylaminomethylcyclohexyl)piperidine (190)

Formic acid (13.8 g, 0.3 mole) and acetic anhydride (30.6 g, 0.3 mole) were mixed without cooling and kept at room temperature for 1 hr. 1-(1-aminomethylcyclohexyl)piperidine (5.88 g, 0.03 mole) was dissolved in formic acid (15 ml) and the formylating mixture (25 ml) added slowly. This produced effervescence and a rise in temperature to 50°. The mixture was left at room temperature for 2 hr and then refluxed for 48 hr. The solvents were removed under reduced pressure to give a viscous, brown oil (5.07 g, 75.7%), $\nu_{max.}$ (liq. film), 3300, 3080 (NH), 1660 (formyl CO), 1540, 1235, 1110, 1075, 980, 970 cm^{-1} which was assumed to be 1-(1-formylaminomethylcyclohexyl)piperidine. The oily product (4.48 g, 0.02 mole) was therefore reduced with lithium aluminium hydride (1.52 g, 0.04 mole) as previously described for reduction of a formyl group. The resultant amber, mobile oil (4.11 g, 93.0%) after treatment with 10% ethanolic hydrochloric acid gave colourless needles of 1-(1-methylaminomethylcyclohexyl) piperidine dihydrochloride, m.p. 259-60° (from ethanol/ether) (Found: C, 55.3; H, 9.9; N, 9.7; Cl, 24.9; equiv., 141.1. $C_{13}H_{28}Cl_2N_2$ requires C, 55.1; H, 9.9; N, 9.9; Cl, 25.1%; equiv., 141.5), $\nu_{max.}$ (nujol), 2600-2400, 1590 (NH^+), 1260, 1165, 1005, 890 cm^{-1}.

1-(N-Formyl-1-methylaminomethylcyclohexyl)piperidine (193)

Formic acid (13.8 g, 0.3 mole) and acetic anhydride (30.6 g, 0.3 mole) were mixed without cooling and kept at room temperature for 1 hr. 1-(1-methylaminomethylcyclohexyl) piperidine (4.2 g, 0.02 mole) was dissolved in formic acid (15 ml) and the formylating mixture (25 ml) added slowly. This produced effervescence and a rise in temperature to 60°. The mixture was allowed to stand at room temperature overnight and the solvents then evaporated under reduced pressure to yield a viscous, amber oil (3.79 g, 80%). This afforded colourless prisms of 1-(N-formyl-1-methylaminomethyl cyclohexyl) piperidine, m.p. 93-94° (from light petroleum b.p. 60-80°) (Found: C, 70.8; H, 11.0; N, 11.8; equiv., 235.1. $C_{14}H_{26}N_2O$ requires C, 70.6; H, 10.9; N, 11.8%; equiv., 238), $\nu_{max.}$(nujol), 1660 (formyl CO), 1220, 1070, 1030, 970, 955, 920, 860, 845, 710, 680 cm^{-1}.

1-(1-Dimethylaminomethylcyclohexyl)piperidine (196)

1-(N-Formyl-1-methylaminomethylcyclohexyl)piperidine (2.38 g, 0.01 mole) was dissolved in dry ether (50 ml) and added dropwise to a stirred suspension of lithium aluminium hydride (0.76 g, 0.02 mole) in dry ether (100 ml). The suspension was stirred overnight and the product worked up in a similar manner to previous lithium aluminium hydride experiments. Removal of ether gave a colourless, mobile oil (1.59 g, 72.1%) which on treatment with 10% ethanolic hydrochloric acid gave colourless needles of 1-(1-dimethylaminomethylcyclohexyl)piperidine dihydrochloride, m.p. 224° (from ethanol/ether) (Found: C, 56.4; H, 10.2; N, 9.2; Cl, 23.7; equiv., 148.1. $C_{14}H_{30}Cl_2N_2$ requires C, 56.6; H, 10.1; N, 9.4; Cl, 23.9%; equiv., 148.5), $\nu_{max.}$(nujol), 2850, 2780 (NCH_3), 2600-2400 (NH^+), 1250, 1205, 1145, 1135, 1100, 1070, 1035, 985, 970, 960, 860, 830 cm^{-1}.

1-(1-Benzamidomethylcyclohexyl)piperidine (199)

A mixture of 1-(1-aminomethylcyclohexyl)piperidine (1.5 g), benzoyl chloride (2 ml) and pyridine (10 ml) was allowed to stand at room temperature

for 1 hr. The dark red solution produced was diluted with water, basified with ammonia and extracted with chloroform. The extract was washed with water, dried (Na_2SO_4), and evaporated to give a dark red, viscous oil (0.32 g, 32.8%) which crystallised on cooling. On recrystallisation from light petroleum (b.p. 100-120°) colourless rosettes of 1-(1-benzamidomethylcyclohexyl)piperidine, m.p. 105-6° were obtained (Found: C, 75.8; H, 9.2; N, 9.3; equiv., 292. $C_{19}H_{28}N_2O$ requires C, 76.0; H, 9.3; N, 9.3%; equiv., 300), $\nu_{max.}$ (nujol), 3120 (NH), 1640 (amide CO), 1305, 1240, 1080, 975, 720, 710 (Ph) cm^{-1}.

1-(4-Fluorobenzamidomethylcyclohexyl)piperidine (200)

A mixture of 1-(1-aminomethylcyclohexyl)piperidine (1.5 g), 4-fluorobenzoyl chloride (2 ml) and pyridine (10 ml) was allowed to stand at room temperature for 1 hr. The crystalline material produced was filtered (2.35 g, 86.6%) and afforded pale lemon rosettes of 1-(4-fluorobenzamidomethylcyclohexyl) piperidine, m.p. 243-5° (decomp.) (Found: C, 64.5; H, 8.1; N, 7.7; Cl, 10.0; equiv., 349.6. $C_{19}H_{28}ClFN_2O$ requires C, 64.3; H, 7.9; N, 7.9; Cl, 10.0%; equiv., 354.5), $\nu_{max.}$ (nujol), 3170 (NH), 2650-2500 (NH^+), 1660 (amide CO), 1300, 1270, 1220, 1150, 1010, 850, 760, 700 (Ph) cm^{-1}.

1-(2-Chlorobenzamidomethylcyclohexyl)piperidine (202)

A mixture of 1-(1-aminomethylcyclohexyl)piperidine (1.5 g), 2-chlorobenzoyl chloride (2 ml) and pyridine (10 ml) was allowed to stand at room temperature for 1 hr with no apparent effect. The mixture was therefore refluxed for 1 hr, cooled, diluted with water, basified with ammonia and extracted with chloroform. This chloroform extract was washed with water, dried (Na_2SO_4), and evaporated to give a viscous, brown oil (3.0 g, 79.2%). On dissolving in ether and bubbling dry hydrogen chloride gas into the solution pale buff rosettes of 1-(2-chlorobenzamidomethylcyclohexyl)piperidine hydrochloride, m.p. 234-6° were obtained (from ethanol/ether) (Found: C, 61.2; H, 7.8;

N, 7.3; Cl, 19.5; equiv., 364.2. $C_{19}H_{28}Cl_2N_2O$ requires C, 61.4; H, 7.6; N, 7.6; Cl, 19.1%; equiv., 371), $\nu_{max.}$ (nujol), 2650-2400 (NH^+), 1640 (amide CO), 1590, 1060, 1045, 970, 780, 750 (Ph) cm^{-1}.

1-(3,4-Dichlorobenzamidomethylcyclohexyl)piperidine (201)

A mixture of 1-(1-aminomethylcyclohexyl)piperidine (1.5 g), 3,4-dichlorobenzoyl chloride (2 g) and pyridine (10 ml) was allowed to stand at room temperature for 1 hr when the whole mass solidified. Recrystallisation from ethanol/ether several times gave small colourless needles of 1-(3,4-dichlorobenzamidomethylcyclohexyl) piperidine hydrochloride (1.7 g, 54.8%), m.p. 235-236° (decomp.) (Found: C, 56.1; H, 6.6; N, 7.1; equiv., 401. $C_{19}H_{27}Cl_3N_2O$ requires C, 56.2; H, 6.7; N, 6.9%; equiv., 405.5), $\nu_{max.}$ (nujol), 3160 (NH), 2650-2500 (NH^+), 1665 (amide CO), 1030, 760, 700 (Ph) cm^{-1}.

1-(1-Phthalamidomethylcyclohexyl) piperidine (209)

A mixture of 1-(1-aminomethylcyclohexyl)piperidine (1.0 g), phthalic anhydride (1 g), and glacial acetic acid (10 ml) was refluxed for 1.5 hr. The resultant yellow solution did not crystallise on cooling. The acetic acid was removed under reduced pressure to yield a yellow oil (0.7 g, 42.1%) which crystallised on standing. Recrystallisation from 95% ethanol gave a felted mass of colourless needles of 1-(1-phthalamidomethylcyclohexyl) piperidine m.p. 141-143° (Found: C, 73.7; H, 8.0; N, 8.4; equiv., 320. $C_{20}H_{26}N_2O_3$ requires C, 73.6; H, 8.0; N, 8.6%; equiv., 326), $\nu_{max.}$ (nujol), 1760, 1700 (anhydride CO), 1120, 1045, 960, 930, 895, 800, 720, 700 (Ph) cm^{-1}.

1-(1-Cyanocyclohexyl)pyrrolidine (164)

Pyrrolidine hydrochloride (32.25 g, 0.3 mole) and potassium cyanide (19.5 g, 0.3 mole) were dissolved in water (150 ml) and ethanol (100 ml). To this stirred solution was added, dropwise, cyclohexanone (29.4 g, 0.3 mole) and the mixture refluxed for 24 hr. Ethanol was then removed under reduced

pressure and the cooled aqueous residue extracted with chloroform, washed with water, dried (Na_2SO_4), and evaporated to give a crude, amber oil (41.8 g, 78.3%). This crude product was distilled *in vacuo*. (100°/1.5 mm) to give a colourless, mobile oil (37.2 g), $\nu_{max.}$(liq. film), 2250 (C≡N) cm^{-1}. A small sample of the oil was dissolved in ether and treated with dry hydrogen chloride gas to give colourless plates of 1-(1-cyanocyclohexyl) pyrrolidine hydrochloride, m.p. 167-168° (from ethanol/ether) (Found: C, 61.3; H, 9.0; N, 13.0; Cl, 16.4; equiv., 212.2. $C_{11}H_{19}ClN_2$ requires C, 61.5; H, 8.9; N, 13.0; Cl, 16.6%; equiv., 214.5), $\nu_{max.}$(nujol), 2600-2400 (NH^+), 2250 (C≡N), 1260, 1120, 1050, 920, 880 cm^{-1}.

1-(1-Benzoylcyclohexyl)pyrrolidine (226)

1-(1-Cyanocyclohexyl)pyrrolidine (17.8 g, 0.1 mole) was dissolved in dry ether (150 ml) and added dropwise to a solution of phenyl lithium prepared from lithium (5.6 g, 0.8 mole) and bromobenzene (62.8 g, 0.4 mole) in dry ether (200 ml). The solution was stirred overnight and the mixture worked up as indicated in previous phenyl lithium reactions. Evaporation of the ether gave a red, mobile oil (26.0 g, 98%) which failed to crystallise but was assumed to be 1-(1-benzylimidoylcyclohexyl)pyrrolidine (222), $\nu_{max.}$(liq. film), 1620 (C=N), 760, 700 (Ph) cm^{-1}. This red oil (10.0 g) was refluxed with water (100 ml) and hydrochloric acid (100 ml) for 1 hr. The solution was cooled, basified with ammonia and extracted with chloroform. The extract was washed with water, dried (Na_2SO_4), and the solvent evaporated to give an amber oil (9.7 g, 97%) which crystallised on cooling. Recrystallisation from light petroleum (b.p. 60-80°) gave amber prisms of 1-(1-benzoylcyclohexyl)pyrrolidine, m.p. 50-51° (Found: C, 79.6; H, 8.8; N, 5.6; equiv., 254.9. $C_{17}H_{23}NO$ requires C, 79.4; H, 9.0; N, 5.4%; equiv., 257), $\nu_{max.}$(liq. film), 1680 (CO), 1460, 1230, 1160, 1130, 990, 890, 700 (Ph) cm^{-1}.

1-(1'-Hydroxybenzylcyclohexyl)pyrrolidine (230)

1-(1-Benzoylcyclohexyl) pyrrolidine (7.71 g, 0.03 mole) was dissolved in dry benzene (100 ml) and added dropwise to a stirred suspension of lithium aluminium hydride (2.28 g, 0.06 mole) in dry ether (100 ml). The suspension was refluxed overnight, cooled and worked up as in previous lithium aluminium hydride experiments to give a viscous amber oil (5.8 g, 75.3%). Treatment of an aliquot of the oil in ether with dry hydrogen chloride gas gave colourless needles of 1-(1'-hydroxybenzylcyclohexyl) pyrrolidine hydrochloride, m.p. 225° (decomp.) (from ethanol/ether) (Found: C, 68.7; H, 8.6; N, 5.0; Cl, 12.2; equiv., 291. $C_{17}H_{26}ClNO$ requires C, 69.0; H, 8.8; N, 4.7; Cl, 12.0%; equiv., 295.5), $\nu_{max.}$ (nujol), 3400 (broad OH), 2700-2500 (NH^+), 1350, 1260, 1190, 1140, 1100, 1050, 950, 770, 700 (Ph) cm^{-1}.

1-Pyrrolidinylcyclohexylamide (169)

1-(1-Cyanocyclohexyl)pyrrolidine (2.0 g) was heated on a steam bath with sulphuric acid (40 ml) for 10 min, cooled, poured onto crushed ice (150 g), basified with ammonia and extracted with chloroform. The extract was washed with water, dried (Na_2SO_4), and evaporated to yield a colourless oil (1.75 g, 96.1%) which crystallised on cooling. Recrystallisation from light petroleum (b.p. 80-100°) gave colourless plates of 1-pyrrolidinyl cyclohexylamide, m.p. 106-107° (Found: C, 67.2; H, 10.0; N, 14.3; equiv., 192.3 . $C_{11}H_{20}N_2O$ requires C, 67.4; H, 10.2; N, 14.3%; equiv., 196), $\nu_{max.}$ (liq. film), 3350, 3150 (NH), 1660 (amide CO), 1440, 1330, 1240, 1000, 960, 930, 910, 890, 850, 750, 700 cm^{-1}.

1-Cyclohexylpyrrolidine (179)

1-(1-Cyanocyclohexyl)pyrrolidine (15.6 g, 0.09 mole) was dissolved in dry ether (150 ml) and added dropwise to a stirred suspension of lithium aluminium hydride (7.31 g, 0.18 mole) in dry ether (200 ml). The suspension was stirred overnight and the mixture worked up as indicated in

previous lithium aluminium hydride experiments. This afforded a colourless oil (9.65 g, 53.1%) which on treatment with ethanol/iodomethane gave colourless prisms of 1-cyclohexyl-1-methylpyrrolidinium iodide, m.p. 220-222° (decomp.) (from ethanol/ether) (Found: C, 44.3; H, 7.3; N, 4.7; I, 43.3; equiv., 290. $C_{11}H_{22}NI$ requires C, 44.7; H, 7.5; N, 4.7; I, 43.1%; equiv., 295), $\nu_{max.}$(nujol), 1030, 1010, 930, 780 cm^{-1}.

1-(1-Aminomethylcyclohexyl) pyrrolidine (176)

1-Pyrrolidinylcyclohexylamide (1.17 g, 0.006 mole) was dissolved in dry benzene (40 ml) and added dropwise to a stirred suspension of lithium aluminium hydride (0.46 g, 0.012 mole) in dry ether (60 ml). The suspension was stirred overnight and the mixture worked up as indicated in previous lithium aluminium hydride experiments. This yielded a colourless oil (1.05 g), $\nu_{max.}$(liq. film), 1660 (amide CO) cm^{-1}. The oil was therefore resubjected to lithium aluminium hydride reduction but with refluxing overnight. The work up was as in previous lithium aluminium hydride experiments and yielded a colourless oil (0.75 g, 76.9%) which on treatment with dry hydrogen chloride gas in ethereal solution gave colourless needles of 1-(1-aminomethylcyclohexyl)pyrrolidine dihydrochloride, m.p. 206-207° (from ethanol/ether) (Found: C, 51.6; H, 9.3; N, 10.7; Cl, 27.7; equiv., 125.1. $C_{11}H_{24}Cl_2N_2$ requires C, 51.8; H, 9.4; N, 11.0; Cl, 27.9%; equiv., 127.5), $\nu_{max.}$(nujol), 2600-2400 (NH^+), 1530, 1120, 1020, 960, 900, 850 cm^{-1}.

PART II

SECTION II

MASS SPECTRAL DATA

SECTION II

MASS SPECTRAL DATA

2-(4-Ethoxycarbonylpiperazinylmethyl)-1-tetralone (108)

m/e (I%) 316 (30), 315 (3), 299 (3), 272 (5), 271 (25), 244 (2), 215 (5), 214 (24), 202 (13), 200 (4), 188 (5), 186 (4), 173 (14), 172 (96), 171 (100), 170 (52), 169 (22), 160 (6), 159 (47), 158 (96), 157 (31), 156 (5), 146 (12), 145 (11), 144 (13), 143 (57), 142 (31), 141 (57), 132 (11), 131 (49), 130 (75), 129 (75), 128 (57), 127 (36), 126 (9), 125 (31), 119 (8), 118 (53), 117 (17), 116 (68), 115 (64), 114 (11), 113 (31), 112 (2), 111 (5), 105 (11), 104 (14), 103 (20), 102 (23), 101 (8), 100 (10), 99 (41), 98 (26), 97 (58), 96 (7), 95 (4), 92 (5), 91 (60), 90 (67), 89 (52), 88 (16), 87 (5), 86 (6), 85 (43), 84 (21), 83 (18), 82 (11), 81 (4), 80 (2), 79 (3), 78 (13), 77 (37), 76 (15), 75 (14), 74 (16), 73 (3), 72 (46), 71 (15), 70 (57), 69 (55), 68 (18), 67 (5), 66 (2), 65 (16), 64 (32), 63 (35), 62 (11), 61 (3), 59 (3), 58 (40), 57 (57), 56 (96), 55 (57), 54 (18), 53 (12), 52 (9), 51 (41), 50 (18), 45 (11), 44 (96), 43 (53), 42 (78), 41 (37), 40 (9), 39 (31), 38 (6), 31 (3), 30 (52).

m^* 171 (173 → 172), 158 (160 → 159), 128 (130 → 129),
127 (129 → 128), 119.6 (171 → 143), 106.9 (158 → 130),
92.5 (316 → 171), 88.2 (90 → 89), 68.6 (118 → 90),
55.1 (57 → 56), 27.7 (70 → 44), 16.4 (316 → 72).

2-(3-Azabicyclo[3,2,2]nonylmethyl)-1-tetralone (106)

m/e (I%) 283 (9), 282 (3), 202 (5), 160 (12), 159 (67), 158 (63), 157 (50), 146 (11), 145 (8), 144 (11), 143 (14), 142 (4), 141 (14), 140 (9), 139 (53), 138 (65), 137 (53), 136 (13), 132 (24), 131 (64), 130 (100), 129 (96), 128 (96), 127 (64), 126 (47), 125 (83), 124 (68), 123 (7), 122 (16), 119 (20), 118 (79), 117 (11), 116 (49), 115 (83), 114 (7), 113 (39), 111 (7), 110 (41), 109 (12), 108 (15), 107 (5), 106 (5), 105 (32), 104 (38), 103 (44), 102 (49), 101 (22), 100 (11) 99 (5), 98 (9), 97 (40), 96 (83), 95 (48), 94 (63), 93 (33), 92 (13), 91 (69), 90 (83), 89 (75), 88 (10), 87 (17), 86 (12), 85 (4), 84 (34), 83 (39), 82 (70), 81 (63), 80 (40), 79 (71), 78 (56), 77 (78), 76 (48), 75 (47), 74 (41), 73 (4), 72 (3), 71 (39), 70 (80), 69 (67), 68 (75), 67 (78), 66 (27), 65 (58), 64 (70), 63 (78), 62 (44), 61 (11), 59 (13), 58 (87), 57 (70), 56 (65), 55 (83), 54 (62), 53 (63), 52 (43), 51 (82), 50 (53), 49 (6), 46 (14), 45 (65), 44 (96), 43 (92), 42 (79), 41 (93), 40 (52), 39 (85), 38 (30), 37 (9), 32 (48), 31 (9), 30 (83), 29 (58), 28 (67), 27 (75).

m^* 158 (160 → 159), 157 (159 → 158), 138 (140 → 139), 128 (130 → 129), 127.5 126 (130 → 128), 107.5 106.9 (158 → 130), 101.8 88.2 (283 → 158), 73.8 68.5 (130 → 94), 67.4 66.5 37.7 (130 → 70), 24.4 (70 → 41), 15.6 (130 → 45).

2-(4-Methylpiperazinylmethyl)-1-tetralone (105)

m/e (I%) 258 (38), 216 (3), 215 (11), 214 (10), 203 (3), 202 (18), 201 (2), 200 (3), 189 (2), 188 (14), 187 (2), 186 (3), 160 (6), 159 (36), 158 (86), 157 (19), 147 (2), 146 (13), 145 (11), 144 (22), 143 (5), 141 (5), 132 (8), 131 (29), 130 (72), 129 (69), 128 (57), 127 (27), 126 (7), 119 (8), 118 (48), 117 (7), 116 (23), 115 (62), 114 (46), 113 (100), 112 (14), 111 (32), 105 (11), 104 (11), 103 (13), 102 (16), 101 (10), 100 (63), 99 (14), 98 (26), 97 (10), 96 (4), 95 (3), 92 (3), 91 (36), 90 (63), 89 (49), 88 (3), 87 (4), 86 (3), 85 (13), 84 (9), 83 (12), 82 (10), 81 (3), 80 (2), 79 (2), 78 (12), 77 (31), 76 (11), 75 (11), 74 (10), 72 (10), 71 (39), 70 (94), 69 (8), 68 (8), 67 (4), 65 (14), 64 (24), 63 (33), 62 (10), 61 (2), 59 (12), 58 (94), 57 (41), 56 (58), 55 (16), 54 (13), 53 (8), 52 (8), 51 (32), 50 (15), 45 (4), 44 (54), 43 (70), 42 (70), 41 (25), 40 (8), 39 (18), 38 (6), 30 (25), 29 (25), 28 (37), 27 (24).

m*			
	158	128.5	113
	88.2 (90 → 89),	85.2	49.5 (258 → 113),
	43.4 (113 → 70),	33.7	33.4 (58 → 44).

2-(4-Phenylpiperidylmethyl)-1-tetralone (107)

m/e (I%) 319 (35), 318 (13), 317 (4), 316 (7), 214 (1), 201 (1), 200 (4), 189 (2), 188 (3), 186 (3), 176 (9), 175 (67), 174 (100), 173 (63), 172 (22), 171 (6), 170 (11), 163 (6), 162 (63), 161 (67), 160 (67), 159 (63), 158 (70), 157 (58), 156 (4), 155 (3), 147 (3), 146 (26), 145 (10), 144 (13), 143 (16), 142 (4), 141 (14), 140 (5), 139 (4),

133 (9), 132 (41), 131 (67), 130 (83), 129 (83), 128 (71), 127 (54), 126 (14), 120 (16), 119 (25), 118 (71), 117 (50), 116 (52), 115 (79), 114 (5), 113 (3), 108 (4), 107 (6), 106 (23), 105 (58), 104 (79), 103 (75), 102 (67), 101 (18), 99 (3), 98 (6), 97 (2), 96 (10), 95 (1), 94 (3), 92 (19), 91 (75), 90 (79), 89 (65), 88 (7), 87 (11), 86 (8), 85 (2), 84 (12), 83 (63), 82 (26), 81 (4), 80 (8), 79 (14), 78 (58), 77 (67), 76 (33), 75 (31), 74 (25), 73 (4), 71 (7), 70 (61), 69 (57), 67 (27), 66 (4), 65 (55). 64 (65), 63 (65), 62 (27), 61 (8), 58 (18), 57 (79), 56 (87), 55 (27), 54 (14), 53 (58), 52 (46), 51 (69), 50 (60), 45 (8), 44 (75), 43 (83), 42 (63), 41 (35), 40 (16), 39 (60), 38 (63), 37 (9), 36 (75), 35 (28), 31 (5), 30 (75), 29 (58), 28 (61), 27 (50).

m^*	174.4	160	157
	129	125	118
	117	115.2	114
	113	107.5	106.5
	104	103	102
	94.9 (319 → 174),	88.5	81.0 (131 → 103),
	68.8	63.4 (174 → 105),	55.1 (89 → 70),
	42.8	40.6	28.2 (174 → 70).

2-(3-Azabicyclo[3,2,2]nonylmethyl)-1-phenethynyl-1,2,3,4-tetrahydronaphth-1-ol (139)

m/e (I%) 385 (37), 384 (10), 369 (7), 368 (24), 367 (14), 308 (4), 302 (7), 294 (8), 290 (6), 283 (3), 282 (4), 281 (8), 280 (3), 277 (4), 266 (2), 261 (3), 260 (8), 259 (3), 245 (5), 244 (14), 243 (8),

242 (8), 241 (48), 240 (92), 239 (42), 238 (12), 231 (5), 230 (16), 229 (14), 228 (11), 227 (8), 226 (9), 219 (3), 218 (2), 217 (2), 216 (4), 215 (13), 212 (4), 211 (7), 191 (8), 190 (3), 189 (8), 171 (4), 166 (8), 165 (9), 164 (17), 162 (8), 161 (6), 160 (13), 159 (6), 158 (18), 157 (16), 156 (5), 155 (3), 154 (6), 153 (4), 152 (5), 150 (6), 146 (5), 145 (6), 144 (7), 143 (5), 141 (7), 140 (6), 139 (53), 138 (100), 137 (48), 136 (12), 132 (6), 131 (8), 130 (13), 129 (20), 128 (12), 127 (7), 126 (16), 125 (45), 124 (67), 122 (8), 118 (7), 117 (13), 116 (9), 115 (44), 110 (5), 109 (8), 108 (8), 105 (10), 104 (5), 103 (13), 102 (65), 101 (5), 96 (23), 95 (22), 94 (10), 93 (9), 92 (3), 91 (31), 90 (8), 89 (6), 84 (6), 83 (6), 82 (12), 81 (17), 80 (7), 79 (13), 78 (4), 77 (16), 76 (15), 75 (7), 74 (8), 70 (13), 69 (8), 68 (16), 67 (42), 65 (7), 63 (8), 59 (6), 58 (67), 57 (17), 56 (15), 55 (33), 54 (8), 53 (10), 52 (5), 51 (10), 50 (8), 44 (77), 43 (25), 42 (55), 41 (39), 39 (13), 30 (25), 29 (9), 28 (7), 27 (7).

m^* 351.7 (385 → 368), 240, 237, 225, 201, 189, 138.2, 49.5 (385 → 138), 24.4 (138 → 58).

2-(4-Methylpiperazinylmethyl)-1-phenyl-1,2,3,4-tetrahydronaphth-1-ol (133)

m/e (I%) 336 (74), 292 (3), 259 (3), 219 (2), 218 (2), 217 (4), 215 (3), 213 (3), 207 (13), 206 (43), 205 (16), 204 (11), 203 (14), 202 (14), 196 (5), 195 (23), 194 (13), 193 (3), 192 (5), 191 (20), 190 (5), 189 (8), 179 (8), 178 (16), 177 (10), 176 (3), 171 (3), 167 (3),

166 (7), 165 (21), 159 (3), 158 (8), 153 (3), 152 (12), 151 (3),
146 (3), 145 (4), 144 (3), 143 (2), 142 (3), 141 (18), 138 (8),
137 (2), 132 (2), 131 (11), 130 (8), 129 (20), 128 (19), 127 (9),
120 (2), 119 (7), 118 (6), 117 (8), 116 (9), 115 (22), 114 (73),
113 (100), 112 (11), 111 (34), 105 (32), 104 (3), 103 (8), 102 (5),
101 (13), 100 (75), 99 (17), 98 (40), 97 (11), 96 (8), 95 (4),
92 (6), 91 (62), 90 (8), 89 (8), 86 (12), 85 (21), 84 (8),
83 (11), 82 (15), 81 (4), 80 (3), 79 (6), 78 (8), 77 (44),
76 (5), 75 (3), 74 (3), 73 (3), 72 (12), 71 (43), 70 (92),
69 (10), 68 (8), 67 (4), 65 (8), 64 (2), 63 (5), 59 (8),
58 (79), 57 (33), 56 (68), 55 (17), 54 (8), 53 (4), 52 (3),
51 (10), 50 (4), 46 (3), 45 (8), 44 (50), 43 (67), 42 (73),
41 (25), 40 (3), 39 (8), 31 (14), 30 (14), 29 (13), 28 (23).

m^* 43.4 (113 → 70), 38 (336 → 113), 33.4 (58 → 44).

2-(4-Phenylpiperidylmethyl)-1,2,3,4-tetrahydronaphth-1-ol (116)

m/e (I%) 321 (97), 320 (22), 305 (8), 304 (27), 303 (17), 203 (3), 202 (14),
201 (2), 200 (10), 198 (3), 190 (4), 186 (8), 176 (35), 175 (92),
174 (100), 173 (28), 172 (23), 163 (8), 162 (62), 161 (69), 160 (67),
159 (13), 158 (17), 157 (5), 156 (4), 155 (5), 147 (8), 146 (23),
145 (47), 144 (20), 143 (36), 142 (21), 141 (31), 133 (9), 132 (33),
131 (75), 130 (65), 129 (70), 128 (67), 127 (29), 126 (4), 120 (8),
119 (23), 118 (25), 117 (57), 116 (43), 115 (68), 106 (5), 105 (29),
104 (48), 103 (75), 102 (15), 101 (3), 99 (3), 98 (10), 97 (37),
96 (25), 95 (4), 94 (8), 93 (2), 92 (23), 91 (83), 90 (17),
89 (15), 84 (21), 83 (32), 82 (21), 81 (6), 80 (6), 79 (16),

78 (27), 77 (48), 76 (8), 75 (5), 74 (6), 72 (5), 71 (33),
70 (83), 69 (36), 68 (22), 67 (8), 66 (4), 65 (31), 64 (8),
63 (13), 62 (3), 59 (3), 58 (20), 57 (65), 56 (70), 55 (29),
54 (16), 53 (21), 52 (8), 51 (24), 50 (9), 45 (13), 44 (73),
43 (67), 42 (73), 41 (57), 40 (6), 39 (27), 38 (63), 37 (13),
36 (75), 35 (38), 31 (10), 30 (58), 29 (21), 28 (33), 27 (21).

m^* 174.5 173.5 131.5
127.5 104.6 103
94.3 (321 → 174), 63.4 (174 → 105), 28.2 (174 → 70).

2-(4-Ethoxycarbonylpiperazinylmethyl)-1,2,3,4-tetrahydronaphth-1-ol (117)

m/e (I%) 318 (68), 317 (9), 302 (6), 301 (11), 300 (43), 299 (11), 260 (17),
259 (36), 257 (4), 246 (2), 242 (4), 241 (5), 228 (10), 227 (48),
216 (7), 206 (2), 205 (4), 202 (4), 199 (7), 198 (10), 188 (3),
187 (2), 186 (13), 185 (3), 184 (12), 183 (8), 182 (8), 174 (2),
173 (28), 172 (81), 171 (100), 170 (26), 169 (20), 168 (5), 163 (7),
161 (19), 160 (27), 159 (60), 158 (31), 157 (28), 156 (10), 155 (6),
146 (12), 145 (43), 144 (29), 143 (79), 142 (67), 141 (60), 139 (6),
133 (7), 132 (8), 131 (47), 130 (79), 129 (75), 128 (73), 127 (62),
126 (12), 125 (19), 123 (4), 120 (4), 119 (15), 118 (9), 117 (19).
116 (54), 115 (71), 114 (23), 113 (67), 112 (7), 111 (14), 109 (3),
106 (4), 105 (14), 104 (10), 103 (13), 102 (70), 101 (79), 100 (62),
99 (92), 98 (83), 97 (83), 96 (51), 95 (16), 94 (11), 93 (5),
92 (38), 91 (83), 90 (32), 89 (41), 88 (31), 87 (47), 86 (17),
85 (51), 84 (34), 83 (35), 82 (21), 81 (8), 80 (5), 79 (7),
78 (12), 77 (31), 76 (9), 75 (9), 74 (10), 73 (3), 72 (25),

71 (41), 70 (75), 69 (43), 68 (20), 67 (8), 65 (18), 64 (17), 63 (19), 62 (5), 59 (10), 58 (71), 57 (57), 56 (77), 55 (58), 54 (18), 53 (8), 52 (7), 51 (24), 50 (11), 45 (8), 44 (58), 43 (54), 42 (75), 41 (40), 40 (5), 39 (17), 38 (58), 37 (15), 36 (83), 35 (43), 31 (7), 30 (30), 29 (68), 28 (48), 27 (29).

m^* 171 (173 → 172), 128.0 (130 → 129), 119.6 (171 → 143), 114.7 101.7 (129 → 114), 98.8 (101 → 100), 97 (99 → 98), 92 (318 → 171), 80.4 55.4 (57 → 56).

1-(1-Methylcyclohexyl)-4-methylpiperazine (211).

m/e (I%) 196 (18), 181 (32), 154 (8), 153 (52), 142 (60), 141 (15), 128 (64), 127 (73), 125 (17), 123 (10), 114 (12), 111 (20), 109 (14), 100 (23), 99 (33), 98 (17), 97 (68), 96 (87), 95 (58), 93 (18), 91 (38), 85 (43), 84 (14), 83 (51), 82 (63), 81 (92), 80 (43), 79 (83), 78 (43), 77 (74), 72 (10), 71 (58), 70 (60), 69 (61), 68 (95), 67 (100), 66 (61), 65 (65), 63 (60), 62 (28), 61 (12), 58 (75), 57 (65), 56 (68), 55 (92), 54 (83), 53 (83), 52 (58), 51 (75), 50 (58), 44 (63), 43 (92), 42 (92), 41 (92), 40 (73), 39 (92), 38 (50), 37 (35), 36 (75), 35 (58), 30 (54), 29 (92), 28 (92), 27 (92).

m^* 68.0 (70 → 69), 67.0 (69 → 68), 54.1 (58 → 56), 37.2 27.1 (181 → 70).

1-(1-Phenylcyclohexyl)-4-methylpiperazine (212)

m/e (I%) 258 (56), 216 (31), 215 (100), 201 (8), 187 (9), 181 (85), 158 (42), 153 (23), 130 (47), 129 (48), 117 (53), 115 (55), 104 (23), 103 (29), 100 (38), 99 (47), 98 (18), 97 (14), 95 (21), 94 (80), 92 (21), 91 (90), 81 (36), 79 (20), 77 (51), 72 (20), 71 (28), 70 (56), 67 (27), 66 (46), 63 (23), 58 (80), 57 (39), 56 (90), 55 (62), 54 (26), 53 (28), 51 (32), 43 (70), 42 (80), 41 (58), 39 (38), 30 (26), 29 (40), 28 (65), 27 (44).

m^* 64.8 (67 → 66), 54.1 (58 → 56), 49.5
46.5 31.8 (58 → 43).

1-(1-Benzoylcyclohexyl)-4-methylpiperazine (225)

m/e (I%) 286 (7), 181 (100), 180 (72), 179 (68), 178 (30), 174 (26), 172 (18), 170 (28), 168 (26), 167 (44), 165 (33), 158 (35), 157 (53), 154 (23), 153 (18), 152 (19), 145 (29), 144 (17), 143 (22), 141 (18), 138 (32), 136 (18), 133 (48), 130 (19), 129 (37), 128 (25), 124 (91), 123 (32), 120 (28), 117 (22), 115 (38), 110 (52), 109 (44), 108 (32), 107 (27), 106 (84), 105 (95), 104 (90), 103 (44), 100 (36), 99 (96), 98 (99), 97 (45), 96 (37), 95 (55), 91 (69), 84 (38), 83 (58), 82 (65), 81 (96), 80 (46), 79 (74), 78 (88), 77 (98), 76 (38), 72 (28), 71 (63), 70 (98), 69 (49), 68 (32), 67 (43), 65 (23), 63 (20), 58 (92), 57 (48), 56 (98), 55 (92), 54 (72), 53 (63), 52 (43), 51 (88), 50 (55), 44 (80), 43 (98), 42 (98), 41 (88), 40 (26), 39 (72), 30 (44), 29 (40), 28 (95), 27 (70).

m^* 132.5 105.2 (181 → 138), 77.0 (79 → 78),
56.7 54.1 (58 → 56), 38.6 (286 → 105),
33.8 (77 → 51), 27.1 (181 → 70).

1-(1-1'-Hydroxybenzylcyclohexyl)-4-methylpiperazine (229)

m/e (I%) 288 (3), 270 (5), 189 (7), 183 (37), 181 (100), 180 (20), 179 (6),
172 (8), 165 (3), 139 (6), 138 (5), 129 (6), 124 (12), 123 (6),
115 (7), 113 (6), 110 (8), 106 (15), 105 (26), 104 (8), 99 (24),
98 (6), 97 (6), 91 (22), 85 (5), 84 (6), 83 (5), 82 (8),
81 (21), 80 (7), 79 (15), 78 (6), 77 (25), 72 (8), 71 (12),
70 (45), 69 (5), 68 (5), 67 (8), 58 (27), 57 (11), 56 (33),
55 (15), 54 (7), 53 (7), 51 (13), 50 (6), 44 (25), 43 (30),
42 (35), 41 (15), 39 (7), 31 (4), 30 (8), 29 (7), 28 (21).

m* 113.8 (288 → 181), 105.2 (181 → 138), 77.3
54.1 (58 → 56), 31.8 (58 → 43), 27.1 (181 → 70).

1-(1-Formylaminomethylcyclohexyl)-4-methylpiperazine (185)

m/e (I%) 239 (3), 181 (100), 179 (11), 165 (6), 139 (7), 138 (14), 125 (8),
124 (29), 123 (9), 111 (7), 110 (20), 109 (6), 108 (8), 101 (6),
100 (7), 99 (39), 98 (14), 97 (14), 96 (12), 95 (26), 94 (9),
93 (8), 85 (7), 84 (15), 83 (16), 82 (23), 81 (33), 80 (12),
79 (20), 77 (11), 72 (13), 71 (20), 70 (87), 69 (14), 68 (20),
67 (29), 66 (5), 65 (7), 59 (11), 58 (63), 57 (25), 56 (83),
55 (56), 54 (33), 53 (23), 46 (9), 44 (47), 43 (78), 42 (95),
41 (71), 40 (8), 39 (22), 30 (77), 29 (29), 28 (55), 27 (27).

m* 105.2 (181 → 138), 54.1 (58 → 56), 27.1 (181 → 70).

1-(1-Methylaminomethylcyclohexyl)-4-methylpiperazine (188)

m/e (I%) 225 (3), 181 (100), 180 (8), 179 (11), 165 (7), 151 (7), 139 (6), 138 (19), 137 (9), 136 (9), 126 (5), 125 (12), 124 (49), 123 (18), 122 (14), 112 (5), 111 (11), 110 (27), 109 (19), 108 (23), 107 (5), 106 (5), 105 (4), 99 (31), 98 (13), 97 (27), 96 (37), 95 (36), 94 (22), 93 (10), 91 (10), 85 (12), 84 (23), 83 (27), 82 (53), 81 (70), 80 (29), 79 (37), 78 (7), 77 (26), 72 (17), 71 (43), 70 (79), 69 (28), 68 (67), 67 (70), 66 (12), 65 (14), 58 (72), 57 (52), 56 (78), 55 (68), 54 (65), 53 (58), 52 (12), 51 (14), 50 (5), 45 (12), 44 (93), 43 (77), 42 (96), 41 (71), 40 (20), 39 (60), 38 (6), 32 (6), 30 (68), 29 (59), 28 (67), 27 (62).

m* 105.2 (181 → 138), 77.2 54.1 (58 → 56), 27.1 (181 → 70).

1-(N-Formyl-1-methylaminomethylcyclohexyl)-4-methylpiperazine (191)

m/e (I%) 253 (7), 194 (12), 193 (34), 182 (7), 181 (76), 180 (38), 179 (64), 165 (15), 153 (35), 152 (13), 151 (11), 150 (16), 139 (9), 138 (36), 137 (14), 136 (34), 125 (23), 124 (72), 123 (39), 122 (23), 113 (13), 112 (12), 111 (23), 110 (53), 109 (27), 108 (43), 107 (11), 100 (25), 99 (64), 98 (39), 97 (39), 96 (38), 95 (60), 94 (32), 93 (35), 91 (26), 85 (30), 84 (48), 83 (57), 82 (84), 81 (96), 80 (58), 79 (73), 78 (13), 77 (57), 73 (46), 72 (69), 71 (58), 70 (100), 69 (57), 68 (86), 67 (96), 66 (24), 65 (32), 60 (43), 59 (30), 58 (85), 57 (55), 56 (89), 55 (94), 54 (81), 53 (67), 52 (23), 51 (26), 50 (12), 45 (15), 44 (91), 43 (91), 42 (91), 41 (91),

40 (45), 39 (73), 38 (15), 30 (87), 29 (76), 28 (96), 27 (86).

m^* 105.2 (181 → 138), 84.9 (181 → 124), 54.1 (58 → 56), 27.1 (181 → 70).

1-(4-Methylpiperazinyl)cyclohexylamide (172d)

m/e (I%) 181 (100), 138 (21), 125 (11), 124 (29), 123 (11), 110 (28), 109 (18), 108 (27), 99 (50), 98 (24), 97 (25), 96 (21), 95 (15), 94 (15), 93 (6), 85 (10), 84 (14), 83 (20), 82 (30), 81 (75), 80 (23), 79 (28), 77 (26), 72 (17), 71 (38), 70 (76), 69 (19), 68 (33), 67 (44), 65 (13), 58 (65), 57 (42), 56 (77), 55 (67), 54 (72), 53 (63), 52 (15), 51 (16), 44 (36), 43 (69), 42 (84), 41 (76), 40 (15), 39 (53), 30 (43), 29 (60), 28 (75), 27 (68).

m^* 105.2 (181 → 138), 77.3 54.1 (58 → 56), 27.1 (181 → 70).

PART II

SECTION III

PHARMACOLOGICAL RESULTS

SECTION III

PHARMACOLOGICAL RESULTS

A number of compounds prepared in the present investigation were subjected to a primary pharmacological screen designed to detect a range of central nervous system effects. Several of these compounds proved sufficiently active to warrant further examination for analgesic activity and a provisional patent has been registered. For central nervous system and analgesic activity see tables 17-31.

In addition, a selection of the compounds have been screened for certain cardiovascular activities, antigastrin activity, antimicrobial activity, antimycoplasma activity and rat adjuvant arthritis effects.

(a) Central nervous system activity

In the following reports standard notation is used to indicate activity levels.

++ = marked activity

\+ = moderate activity

± = negligible activity

\- = inactive

TABLE 17

1-PHENETHYNYL-1,2,3,4-TETRAHYDRONAPHTH-1-OLS

ROUTE	TEST AND DOSE	COMPOUNDS		
		(137)	(138)	(140)
ORAL	1. Effects on behaviour in mouse 100 mg/kg	-	-	-
ORAL	2. LD. 50 mg/kg > 100			
ORAL	3. Effects on body temperature 100 mg/kg	-	±	-
ORAL	4. Antimaximal electroshock 100 mg/kg	-	-	-
ORAL	5. Antagonism of leptazol induced convulsions 100 mg/kg	-	-	-
S.C.	6. Hot plate 100 mg/kg a) Direct effect	±	+	-
	b) Interact. morphine	-	-	-
ORAL	7. Effects on phenylquinone induced writhing 100 mg/kg	++	+	-
ORAL	8. Effects on central cholinergic mechanisms 50 mg/kg a) Tremor		-	-
	b) Hypothermia		-	-
ORAL	9. Tail clip 100 mg/kg	±		±
ORAL	10. Anti-inflammatory a) U.V. mouse			
	b) U.V. G.pig			
	200 mg/kg c) Carrageenin	±		

Remarks:- a) Compound (138) induced hypothermia of 0.6° in test 3

b) Compound (138) produced 58% inhibition in test 6a

c) Compound (137) has an oral ED. 50 of 64 mg/kg and in the cardiovascular screen shows α-adrenergic blocking activity.

TABLE 18

MIXED 1,2,3,4-TETRAHYDRONAPHTH-1-OLS

ROUTE	TEST AND DOSE		COMPOUNDS (132)	COMPOUNDS (134)	COMPOUNDS (141)
ORAL	1. Effects on behaviour in mouse 100 mg/kg		-	-	±
ORAL	2. LD. 50 mg/kg	>100			
ORAL	3. Effects on body temperature 100 mg/kg		-	-	-
ORAL	4. Antimaximal electroshock 100 mg/kg		-	-	-
ORAL	5. Antagonism of leptazol induced convulsions 100 mg/kg		-	-	-
S.C.	6. Hot plate 100 mg/kg	a) Direct effect	+	-	±
		b) Interact. morphine	Convulsions	-	-
ORAL	7. Effects on phenylquinone induced writhing 100 mg/kg		+ → + +	+	+
ORAL	8. Effects on central cholinergic mechanisms 50 mg/kg	a) Tremor	-	-	-
		b) Hypothermia	-	±	-
ORAL	9. Tail clip 100 mg/kg		±	-	-
ORAL	10. Anti-inflammatory 200 mg/kg	a) U.V. mouse			
		b) U.V. G.pig			
		c) Carrageenin	+		
ORAL	11. Effects on central adrenergic receptors 50 mg/kg	a) Depression	-	-	-
		b) Hypothermia	+	+ → + +	-

Remarks:- a) Compound (141) produces a fast gait in the mouse in test 1.

b) Compound (132) produces convulsions with morphine in test 6b.

c) Compound (132) has activity ≤ aspirin and compound (134) has activity about half that of aspirin in test 7.

d) Compound (132) has activity < phenylbutazone in test 10c.

TABLE 19

CYCLOHEXYLAMIDES

ROUTE	TEST AND DOSE	COMPOUNDS			
		(172d)	(172c)	(172a)	(172e)
ORAL	1. Effects on behaviour of mouse 100 mg/kg	-	-	-	+
ORAL	2. LD. 50 mg/kg >100	-	-	-	-
ORAL	3. Effects on body temperature 100 mg/kg	±	±	-	±
ORAL	4. Antimaximal electroshock 100 mg/kg	-	-	-	-
ORAL	5. Antagonism of leptazol induced convulsions 100 mg/kg	-	-	-	-
S.C.	6. Hot plate 100 mg/kg a) Direct effect	±	±	-	-
	b) Interact. morphine	-	-	-	-
ORAL	7. Effects on phenylquinone induced writhing 100 mg/kg	-	-	-	±
ORAL	8. Effects on central cholinergic mechanisms 50 mg/kg a) Tremor	-	-	-	-
	b) Hypothermia	-	-	-	±

Remarks:- a) Compounds (172d), (172c) and (172e) induced hypothermia of 0.9°, 0.8° and 0.5° respectively in test 3

b) Compound (172e) produced a Straub tail and raised posture in the mice used in test 1.

TABLE 20

MONOFORMYL AND MONOMETHYLAMINOMETHYL CYCLOHEXYLAMINES

ROUTE	TEST AND DOSE	COMPOUNDS			
		(185)	(186)	(189)	(190)
ORAL	1. Effects on behaviour in mouse 100 mg/kg	-	-	±	±
ORAL	2. LD. 50 mg/kg	> 100			
ORAL	3. Effects on body temperature 100 mg/kg	-	±	-	-
ORAL	4. Antimaximal electroshock 100 mg/kg	-	-	-	-
ORAL	5. Antagonism of leptazol induced convulsions 100 mg/kg	-	-	-	-
S.C.	6. Hot plate a) Direct effect	-	+	±	++
	100 mg/kg b) Interact. morphine	-	±	-	+
ORAL	7. Effects on phenylquinone induced writhing 100 mg/kg	+	-	++	++
ORAL	8. Effects on central a) Tremor	-	-	-	-
	cholinergic b) Hypothermia	±	-	-	-
	mechanisms 50 mg/kg				

Remarks:- a) Compound (189) produced a slow gait and compound (190) produced a lowered posture and reduced response to pain ($+^{ve}$) in the mice used in test 1.

b) Compound (186) induced hyperthermia 0.7° in test 3.

c) Compound 186 produced 55% inhibition with slight tremor and compound (190) produced 100% inhibition in test 6a.

d) Compound (189) $\simeq$ aspirin and compound (190) has activity $\gg$ aspirin in test 7. Analgesic tests on compound (190) to be further quantified.

TABLE 21

METHYLFORMYLAMINOMETHYL CYCLOHEXYLAMINES

ROUTE	TEST AND DOSE	COMPOUNDS (191)	(192)	(193)
ORAL	1. Effects on behaviour in mouse 100 mg/kg	-	±	-
ORAL	2. LD. 50 mg/kg >100			
ORAL	3. Effects on body temperature 100 mg/kg	±	-	±
ORAL	4. Antimaximal electroshock 100 mg/kg	-	-	-
ORAL	5. Antagonism of leptazol induced convulsions 100 mg/kg	-	-	-
S.C.	6. Hot plate a) Direct effect	++	±	++
	100 mg/kg b) Interact. morphine	+	±	±
ORAL	7. Effects on phenylquinone induced writhing 100 mg/kg	++	++	+
ORAL	8. Effects on central a) Tremor	-	-	-
	cholinergic b) Hypothermia	-	-	-
	mechanisms 50 mg/kg			

Remarks:- a) Compound (192) produced slow gait and limb splay in the mice used in test 1.

b) Compounds (191) and (193) produced hyperthermia of 0.6° and 0.9° respectively in test 3.

c) Compound (192) killed 3/6 animals in test 5.

d) Compounds (191) and (193) produced 77% and 82% inhibition respectively in test 6a.

e) Compound (191) $\geqslant$ aspirin, compound (193) $<$ aspirin and compound (192) again killed 3/6 animals in test 7. Potential analgesic activity of (191) to be reassessed.

TABLE 22

DIMETHYLAMINOMETHYL CYCLOHEXYLAMINES

ROUTE	TEST AND DOSE	COMPOUNDS (194)	COMPOUNDS (195)	COMPOUNDS (196)
ORAL	1. Effects on behaviour in mouse 100 mg/kg	-	+	+/-
ORAL	2. LD. 50 mg/kg >100			
ORAL	3. Effects on body temperature 100 mg/kg	-	+	+/-
ORAL	4. Antimaximal electroshock 100 mg/kg	-	-	-
ORAL	5. Antagonism of leptazol induced convulsions 100 mg/kg	+/-	-	-
S.C.	6. Hot plate a) Direct effect 100 mg/kg b) Interact. morphine	-	++	+/-
		-	-	-
ORAL	7. Effects on phenylquinone induced writhing 100 mg/kg	-	-	+
ORAL	8. Effects on central cholinergic mechanisms 50 mg/kg a) Tremor	-	-	-
	b) Hypothermia	-	-	-

Remarks:- a) Compound (195) produced tremor, jumpy gait and midriasis, compound (196) produced a slow gait in the animals used in test 1.

b) Compounds (195) and (196) induced hyperthermia of 1.7° and 0.5° respectively in test 3.

c) Compound (195) caused violent tremors in the mice used in test 6a.

TABLE 23

1-BENZAMIDOMETHYLCYCLOHEXYL DIMETHYLAMINE (203)

ROUTE	TEST AND DOSE	RESULT	REMARKS
ORAL	1. Effects on behaviour in mouse 100 mg/kg	+	Straub tail, fast gait, raised posture
ORAL	2. LD. 50 mg/kg	>100	
ORAL	3. Effects on body temperature 100 mg/kg	±	Hyperthermia 6.5°
ORAL	4. Antimaximal electroshock 100 mg/kg	-	
ORAL	5. Antagonism of leptazol induced convulsions 100 mg/kg	-	
S.C.	6. Hot plate 100 mg/kg a) Direct effect	++	100% Inhibition
	b) Interact. morphine	-	
ORAL	7. Effects on phenylquinone induced writhing 100 mg/kg	+	< Aspirin
ORAL	8. Effects on central cholinergic mechanism 50 mg/kg a) Tremor	-	
	b) Hypothermia	-	

Remarks:- This compound completely abolished the reflex response of a mouse placed on a hotplate and inhibited writhes induced by phenylquinone in the primary neuropharmacological screen above. The compound was investigated further and the results are reported overleaf.

Secondary investigation of the analgesic activity of

1- Benzamidomethylcyclohexyldimethylamine (203)

Phenylquinone test :-

oral ED. 50 value = 32.8 (20.6 - 48.6) mg/kg

Aspirin oral ED. 50 value = 33.9 (14.0 - 70.0) mg/kg

Hot plate test :-

subcutaneous ED. 50 value = 15.5 (5.36 - 42.0) mg/kg

Morphine subcutaneous ED. 50 value = 2.2 (1.23 - 5.95) mg/kg

Straub Index :-

intravenous LD. 50 $\simeq$ 45 mg/kg. There were no Straub tails at this dose, thus the Straub Index is $\ll$ 1.0

The compound appears to possess some analgesic activity in the mouse with no indication of addiction liability. Analgesic studies on this compound are to be extended in the dog using the dental pulp test.

TABLE 24

HALOGEN SUBSTITUTED CYCLOHEXYLMETHYL BENZAMIDES

ROUTE	TEST AND DOSE	COMPOUNDS		
		(200)	(204)	(202)
ORAL	1. Effects on behaviour in mouse 100 mg/kg	±	±	-
ORAL	2. LD. 50 mg/kg >100			
ORAL	3. Effects on body temperature 100 mg/kg	+	-	±
ORAL	4. Antimaximal electroshock 100 mg/kg	-	-	-
ORAL	5. Antagonism of leptazol induced convulsions 100 mg/kg	-	-	-
S.C.	6. Hot plate 100 mg/kg a) Direct effect	±	++	-
	b) Interact. morphine	±	-	-
ORAL	7. Effects on phenylquinone induced writhing 100 mg/kg	+	++	++
ORAL	8. Effects on central cholinergic mechanism 50 mg/kg a) Tremor	+	+ → ++	-
	b) Hypothermia	-	-	-

Remarks:- a) Compound (200) produced ptosis and slow gait, compound (204) produced an unsteady gait, reduced response to pain and reduced reactivity in test 1.

b) Compounds (200) and (202) induced hyperthermia of 0.9° and 0.7° respectively in test 3.

c) Compound (204) produced 100% inhibition and the animals were incapacitated in test 6a.

d) Compound (200) < aspirin and killed 3/6 of the test animals, compound (204) ≫ aspirin and compound (202) has activity ≏ aspirin in test 7.

e) Compound (204) is to be investigated at lower doses in tests for analgesic activity.

Reinvestigation of compound (202) in the phenylquinone and hot plate tests in the mouse

In the primary neuropharmacological screen this compound caused some inhibition of writhing induced by phenylquinone and of the pain response of a mouse placed on a hot plate. The effects of compound (202) have been further investigated in these test situations and the results are summarised in table 25.

TABLE 25

TEST	ROUTE OF ADMINISTRATION	ED. 50 VALUE (95% FIDUCIAL LIMITS) mg/kg
Phenylquinone	Oral	6.4 (2.03 - 20.8)
Hot plate	S.C.	77.0 (32.6 - 170.2) duration $>$ 2 hr.

Compound (202) possesses some analgesic activity without inducing Straub tail and the compound has a long duration of action in the hot plate test. However, the compound is less potent and more toxic (LD. 50 is 10 mg/kg I.V.) than its analogue (205). No further work is planned with compound (202).

TABLE 26

HALOGEN SUBSTITUTED CYCLOHEXYLMETHYL BENZAMIDES

ROUTE	TEST AND DOSE	COMPOUND (205)	COMPOUND (201)
ORAL	1. Effects on behaviour in mouse 100 mg/kg	±	±
ORAL	2. LD. 50 mg/kg >100		
ORAL	3. Effects on body temperature 100 mg/kg	+	-
ORAL	4. Antimaximal electroshock 100 mg/kg	-	-
ORAL	5. Antagonism of leptazol induced convulsions 100 mg/kg	-	-
S.C.	6. Hot plate a) Direct effect	++	-
	100 mg/kg b) Interact. morphine	-	-
ORAL	7. Effects on phenylquinone induced writhing 100 mg/kg	++	±
ORAL	8. Effects on central cholinergic mechanisms a) Tremor	-	-
	50 mg/kg b) Hypothermia	-	-

Remarks:- a) Compound (205) produces unsteady gait, reduced reactivity and reduced response to pain. Compound (201) produces a Straub tail in test 1.

b) Compound (205) induces hypothermia 2°.

c) Compound (205) gives 100% inhibition and the animals are incapacitated in test 6a.

d) Compound (205) has activity $\gg$ aspirin in test 7 and is to be investigated at lower doses in tests for analgesic activity.

TABLE 27

TOSYL, PHTHALIMIDO AND IMINO CYCLOHEXYLAMINES

ROUTE	TEST AND DOSE	COMPOUNDS		
		(208)	(209)	(220)
ORAL	1. Effects on behaviour in mouse 100 mg/kg	+/-	-	-
ORAL	2. LD. 50 mg/kg >100			
ORAL	3. Effects on body temperature 100 mg/kg	+/-	+	-
ORAL	4. Antimaximal electroshock 100 mg/kg	-	-	-
ORAL	5. Antagonism of leptazol induced convulsions 100 mg/kg	-	-	-
S.C.	6. Hot plate 100 mg/kg a) Direct effect	-	-	+/-
	b) Interact. morphine	-	-	-
ORAL	7. Effects on phenylquinone induced writhing 100 mg/kg	-	-	-
ORAL	8. Effects on central cholinergic mechanisms 50 mg/kg a) Tremor	-	-	-
	b) Hypothermia	-	-	-

Remarks:- a) Compound (208) produced raised posture in the animals used in test 1.

b) Compounds (208) and (209) induced hyperthermia of 0.7° and 1.2° respectively.

TABLE 28

BENZOYL CYCLOHEXYLAMINES

ROUTE	TEST AND DOSE	COMPOUNDS (225)	(224)	(223)	(226)
ORAL	1. Effects on behaviour in mouse 100 mg/kg	+→++	-	-	-
ORAL	2. LD. 50 mg/kg >100				
ORAL	3. Effects on body temperature 100 mg/kg	++	±	-	±
ORAL	4. Antimaximal electroshock 100 mg/kg	-	-	-	-
ORAL	5. Antagonism of leptazol induced convulsions 100 mg/kg	-	-	-	-
S.C.	6. Hot plate a) Direct effect	±	±	±	-
	100 mg/kg b) Interact. morphine	-	-	-	-
ORAL	7. Effects on phenylquinone induced writhing 100 mg/kg	++	±	+	-
ORAL	8. Effects on central cholinergic mechanisms 50 mg/kg a) Tremor	-	-	-	-
	b) Hypothermia	-	-	-	-

Remarks:- a) Compound (225) produced convulsions and depression i.e. limb splay, lowered posture etc. in the animals used in test 1.

b) Compound (225) induced hypothermia of 4.3° and 3/6 of the test animals died. Compounds (224) and (226) induced hyperthermia of 0.8° and 0.6° respectively in test 3.

c) Compound (225) produced limb splay in the animals used in test 6a.

d) Compound (225) has activity $\simeq$ aspirin and compound (223) has activity $<$ aspirin in test 7.

TABLE 29

HYDROXY METHYLPHENYL CYCLOHEXYLAMINES

ROUTE	TEST AND DOSE	COMPOUNDS (229)	(228)	(227)	(230)
ORAL	1. Effects on behaviour in mouse 100 mg/kg	±	-	±	±
ORAL	2. LD. 50 mg/kg >100				
ORAL	3. Effects on body temperature 100 mg/kg	±	±	-	-
ORAL	4. Antimaximal electroshock 100 mg/kg	-	-	++	-
ORAL	5. Antagonism of leptazol induced convulsions 100 mg/kg	-	-	-	-
S.C.	6. Hot plate 100 mg/kg a) Direct effect	-	-	±	++
	b) Interact.morphine	-	-	-	±
ORAL	7. Effects on phenylquinone induced writhing 100 mg/kg	-	+	++	++
ORAL	8. Effects on central cholinergic mechanisms 50 mg/kg a) Tremor	-	-	+	-
	b) Hypothermia	-	-	-	+

Remarks:- a) Compound (229) showed Straub tail and raised posture, compound (227) showed slow gait and lowered posture and compound (230) showed limb splay in test 1.

b) Compounds (229) and (228) induced hyperthermia of 0.8° in both cases in test 3.

c) Compound (227) gave 100% inhibition of tonic extensor seizures in test 4.

d) Compound (230) gave 92% inhibition in test animals in test 6a.

e) Compound (228) has activity < aspirin, compound (227) almost abolished writhing and compound (230) has activity $\simeq$ aspirin in test 7.

TABLE 30

HYDROXYETHYL AND HYDROXYBENZYLAMINO METHYL CYCLOHEXYLAMINES

ROUTE	TEST AND DOSE		COMPOUNDS (234)	COMPOUNDS (206)
ORAL	1. Effects on behaviour in mouse 100 mg/kg		-	-
ORAL	2. LD.50 mg/kg >100			
ORAL	3. Effects on body temperature 100 mg/kg		±	±
ORAL	4. Antimaximal electroshock 100 mg/kg		-	-
ORAL	5. Antagonism of leptazol induced convulsions 100 mg/kg		±	-
S.C.	6. Hot plate 100 mg/kg	a) Direct effect	-	+
		b) Interact. morphine	-	+
ORAL	7. Effects on phenylquinone induced writhing 100 mg/kg		+	-
ORAL	8. Effects on central cholinergic mechanisms 50 mg/kg	a) Tremor	-	-
		b) Hypothermia	-	-

Remarks:- a) Compounds (234) and (206) induced hyperthermia of 0.7° and 0.9° respectively in the animals used in test 3.

b) Compound (206) produced 55% inhibition in the animals used in test 6a.

TABLE 31

ACETOXY DERIVATIVES AND A DECYANATED CYCLOHEXYLAMINE

ROUTE	TEST AND DOSE	COMPOUNDS (231)	(207)	(177)
ORAL	1. Effects on behaviour in mouse 100 mg/kg	-	±	±
ORAL	2. LD. 50 mg/kg >100			
ORAL	3. Effects on body temperature 100 mg/kg	-	+	-
ORAL	4. Antimaximal electroshock 100 mg/kg	-	-	-
ORAL	5. Antagonism of leptazol induced convulsions 100 mg/kg	-	-	-
S.C.	6. Hot plate 100 mg/kg a) Direct effect	±→+	++	-
	b) Interact.morphine	-	±	-
ORAL	7. Effects on phenylquinone induced writhing 100 mg/kg	-	-	-
ORAL	8. Effects on central cholinergic mechanisms 50 mg/kg a) Tremor	-	-	-
	b) Hypothermia	-	+	±

Remarks:- a) Compound (207) produces limb splay and compound (177) produces fast gait and raised posture in the animals used in test 1.

b) Compound (207) induced hyperthermia of 1.7°. in test 3.

c) Compound (207) produced 77% ibhibition and the animals were convulsed in test 6a.

(b) Cardiovascular activity :- Compounds (132), (134), (137), (138), (140) and (141) were tested for their effects in an anaesthetised dog, antispasmodic effects in an anaesthetised guinea-pig and effects in an anaesthetised cat (modification of vasopressor/depressor responses). The phenethynyl alcohol (137) showed some α-blocking activity *in vivo* and some spasmolytic activity *in vitro* but none of these compounds merit further interest.

(c) Anti-anaphylaxis activity :- Compounds (165), (177), (192), (195), (201), (207), (209), (223), (226) and (227) were tested in the anti-anaphylaxis screen at a dose level of 5 mg/kg I.V. with antigen. All the compounds were inactive.

(d) Antimicrobial and antimycoplasma activity :- Compounds (200), (220), (223), (224), (227) and (228) were tested in an antimicrobial screen and an antimycoplasma screen (using Mycoplasma gallisepticum X95). All the compounds were inactive.

(e) Rat adjuvant arthritis activity :- Two compounds (186) and (189) were tested in the rat adjuvant arthritis screen and found to be inactive.

COMPOUND	DOSE LEVEL mg/kg b.i.d.	PERIOD OF DOSING (DAYS)	SUPPRESSION OF DISEASE
(189)	25	15 - 28	-
INDOMETHACIN	1	15 - 28	+
(186)	25	19 - 32	-
INDOMETHACIN	1	19 - 32	+ → ++

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