PIPERIDINE DERIVATIVES OF

POTENTIAL BIOLOGICAL INTEREST

A thesis presented by

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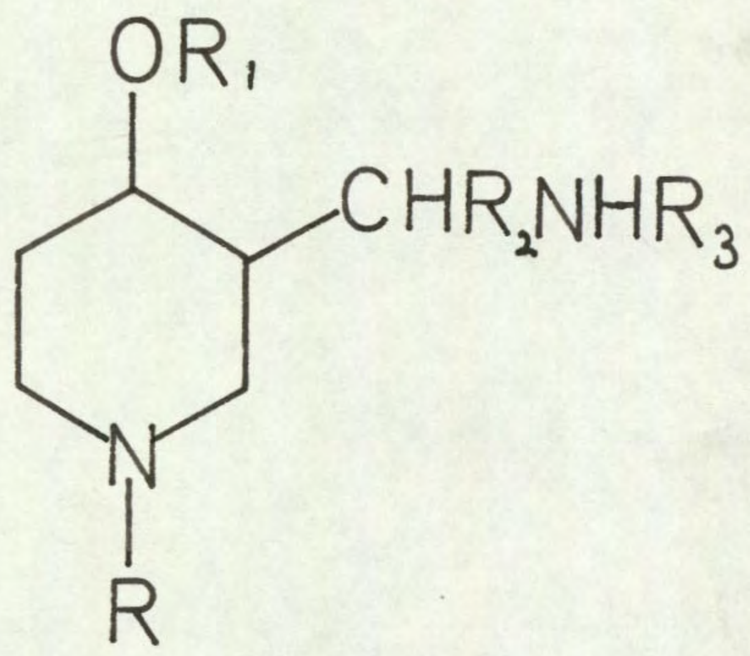
SUMMARY

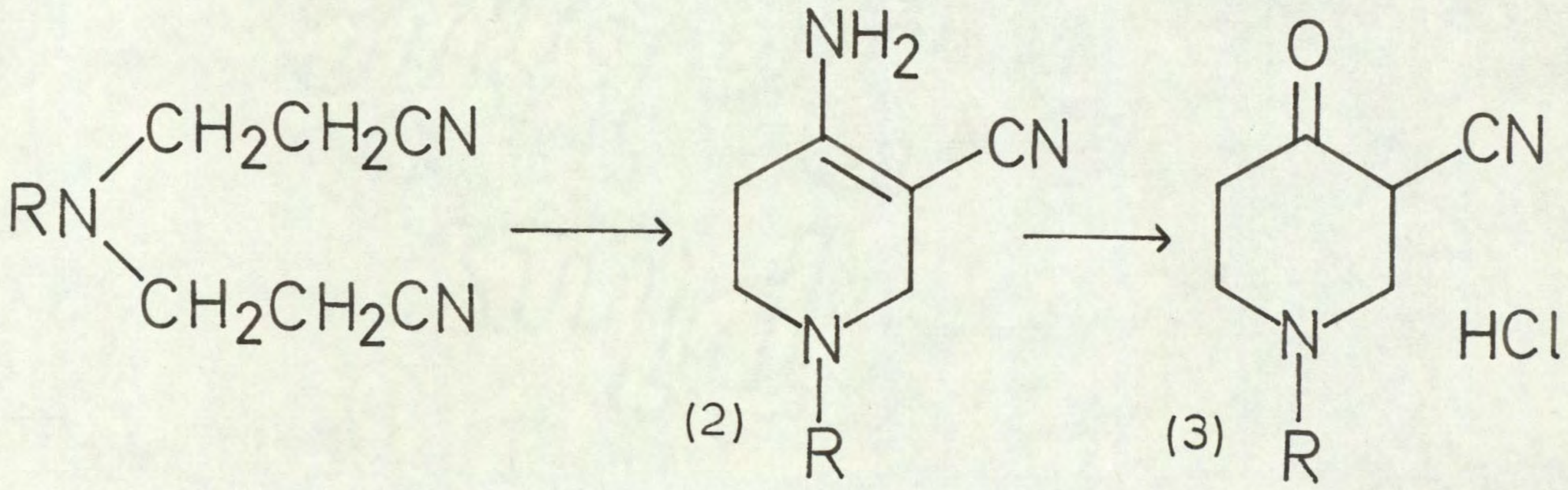
Research involving the structural modification of pethidines and prodines with emphasis on the structure-activity relationships has been reviewed.

In the hope of obtaining compounds of pharmacological interest, compounds of type (1), where R = alkyl or aralkyl,



(1)

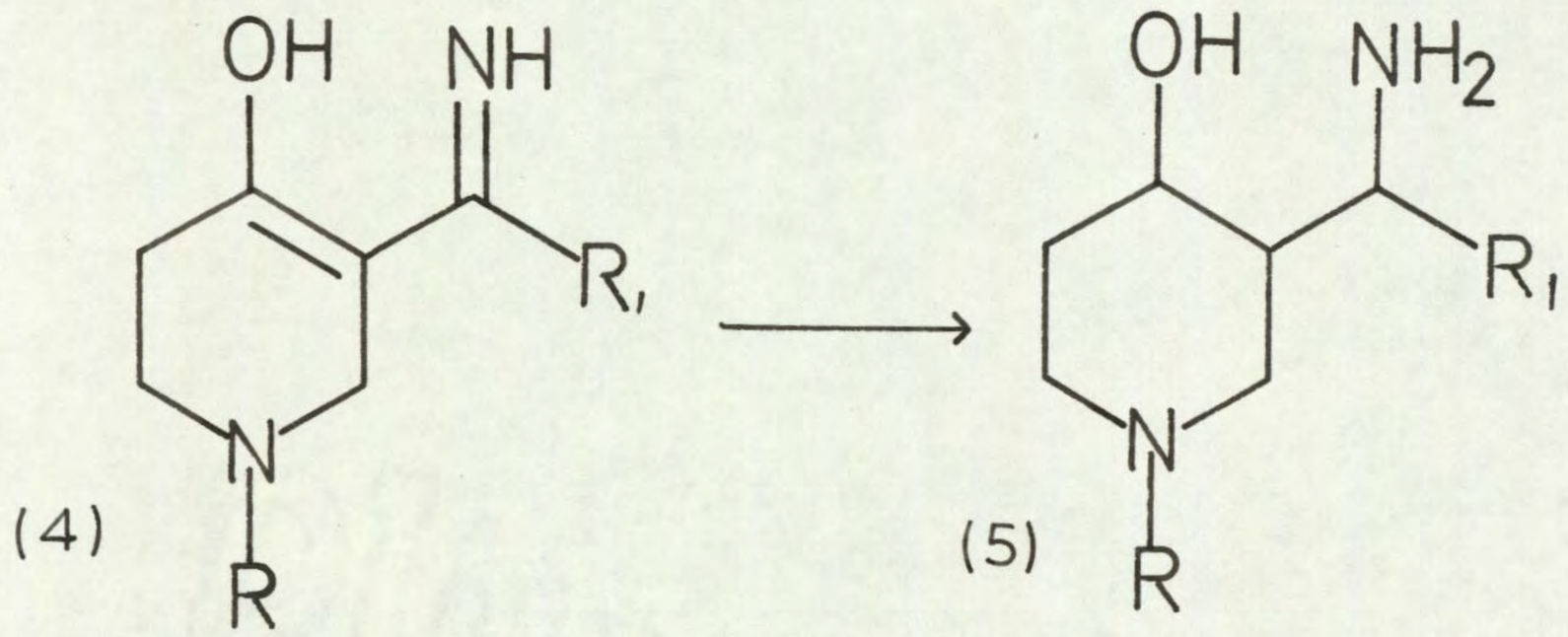
R_1 = H or acyl, R_2 = H or C_6H_5 and R_3 = H or acyl, have been prepared and assessed pharmacologically. The synthetic route adopted consisted of Grignard addition to the corresponding 1-substituted 3-cyano-4-piperidone (3),



(2) (3)

prepared by Thorpe cyclisation of a dinitrile to give an enamine (2) and subsequent hydrolysis.

The reaction with Grignard reagents gave a compound which was found to be a tetrahydro-pyridine (4). Possible methods of reduction of the compound were reviewed and the

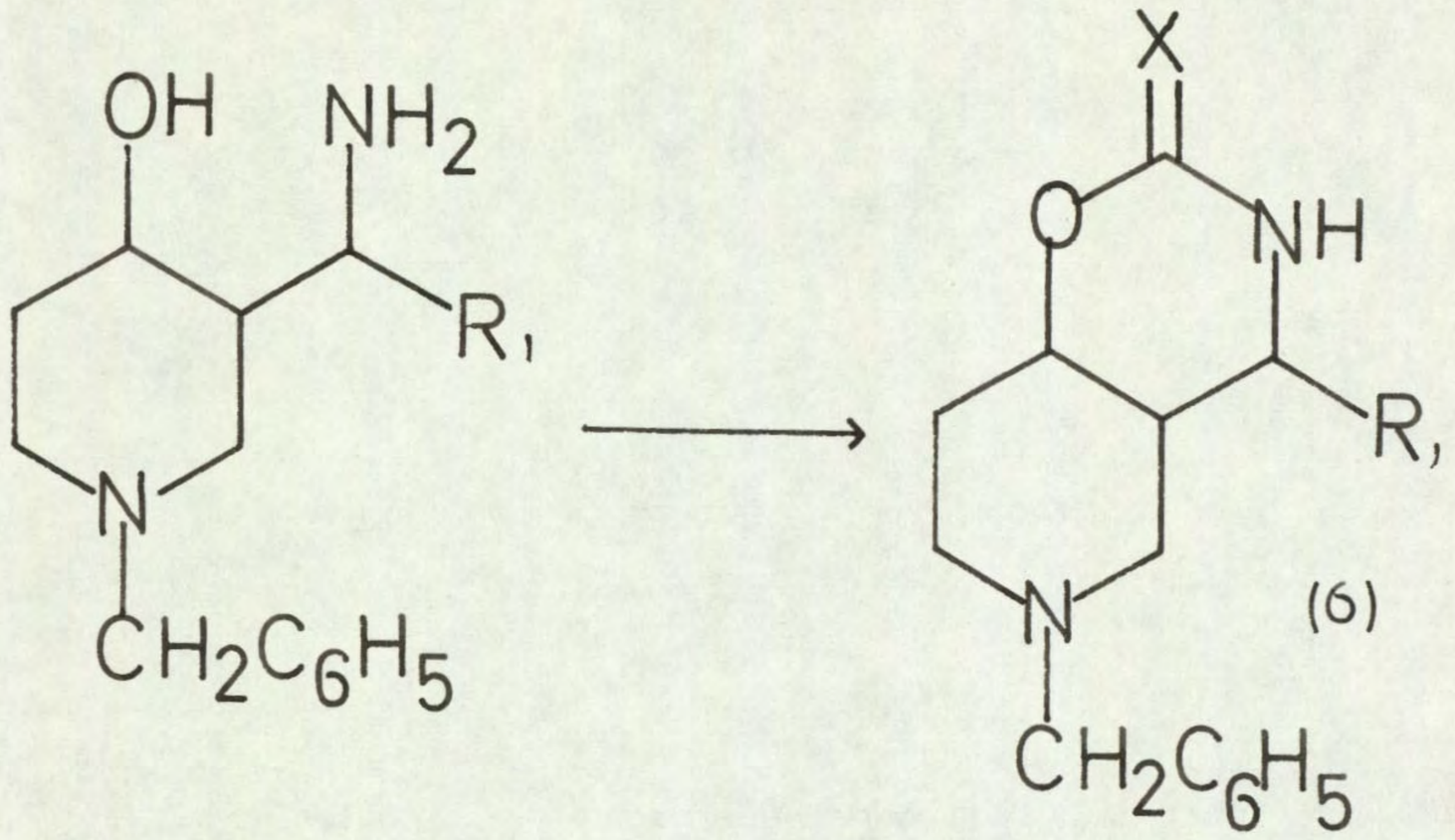


compound reduced with $NaBH_4$ to give the amino-alcohol (5, $R_1 = C_6H_5$). A second route giving amino-alcohols of type (5, $R_1 = H$) consisted of stepwise reduction of the cyano-ketone (3).

The amino-alcohols were capable of existing in stereo-isomers, and a study of the stereochemistry led to the provisional assignment of configurations using methods which included hydrolysis and a consideration of the absorption spectra.

The amino-alcohols (5) were reacted with aldehydes and ketones to give the cyclic structures (6), where $R_1 = C_6H_5$ or H, and X = C_6H_4Y, O or S. Y = OH, OCH_3, F, NMe_2. A consideration of the N.M.R. spectra of these compounds is

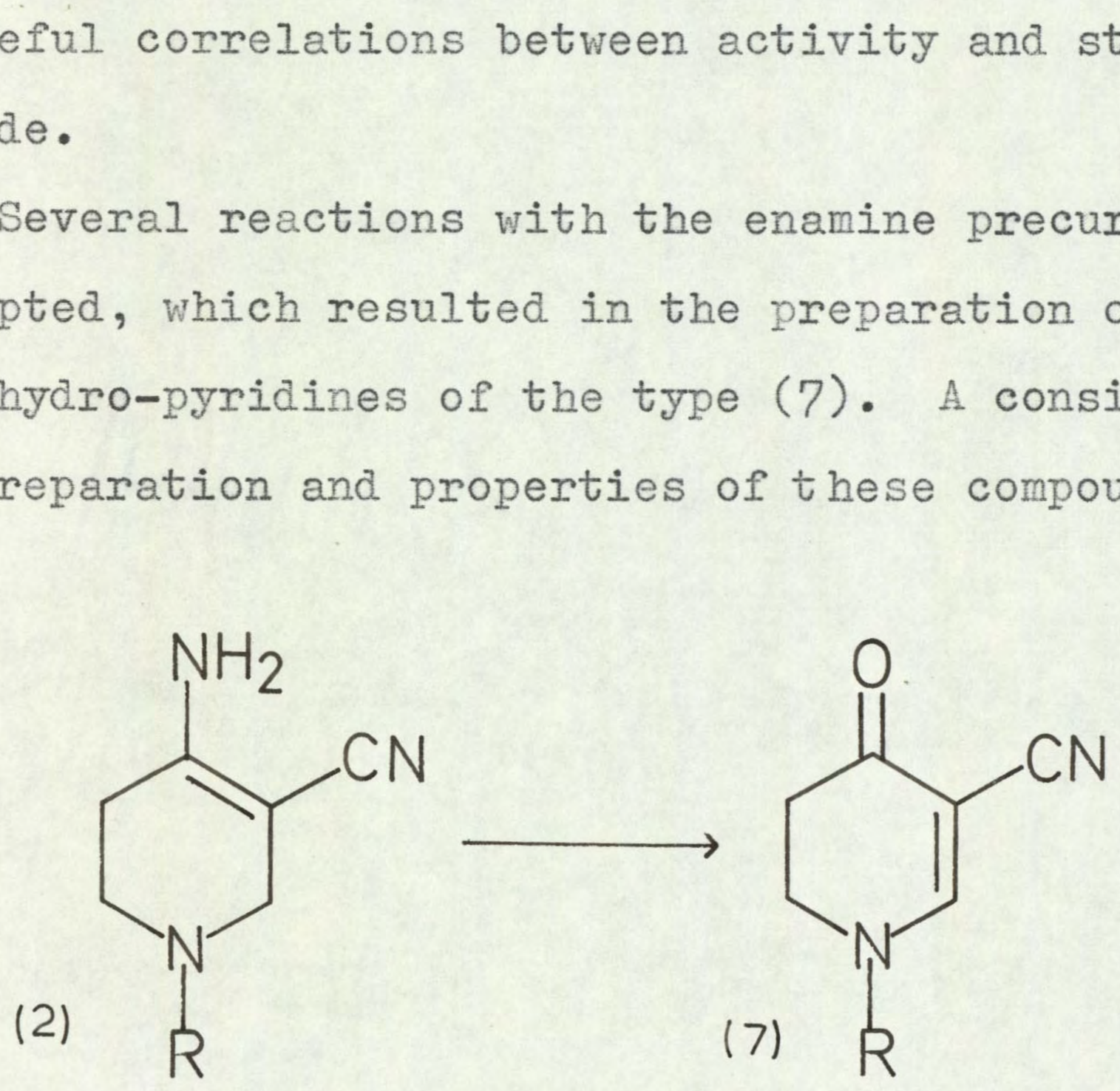
given.



(6)

Several of the amino-alcohols and their derivatives were tested for pharmacological activity but the central nervous system activity of these compounds was slight and no useful correlations between activity and structure could be made.

Several reactions with the enamine precursor (2) were attempted, which resulted in the preparation of novel tetrahydro-pyridines of the type (7). A consideration of the preparation and properties of these compounds was given.



The pharmacological activity of a few of these compounds and their derivatives was investigated, but the compounds were devoid of any significant activity.

To my parents.

ACKNOWLEDGEMENTS

I would like to thank Professor N. J. Harper for his help and encouragement throughout the course of this work.

I would also like to thank Allen and Hanbury's Limited for the award of a scholarship.

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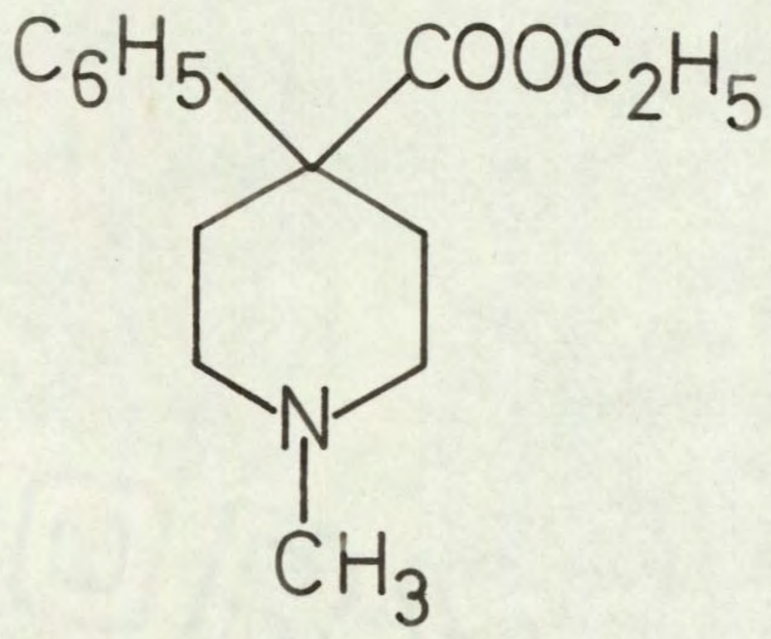
Section I

Part I

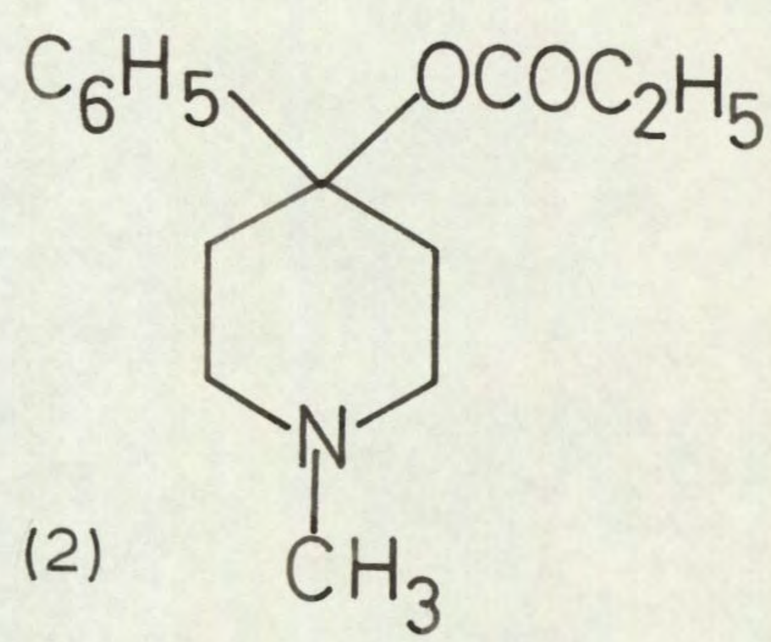
Introduction

INTRODUCTION

Piperidine derivatives, and in particular the 4-phenyl-piperidines have long been regarded as being potentially biologically active and are historically the oldest synthetic group of morphine-like analgesic agents. The discovery of pethidine (Eisleb and Schaumann, 1939)



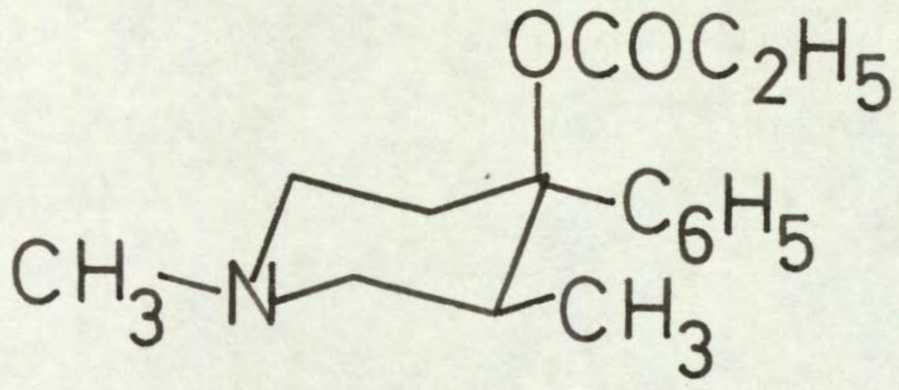
(1)



(2)

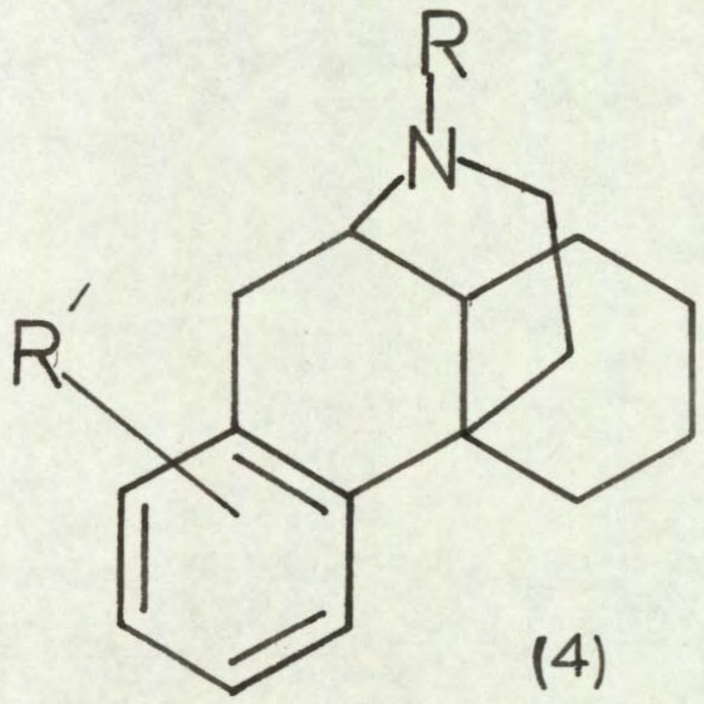
(1) attracted research towards related compounds, the research continuing to expand today even though pethidine itself is still one of the more widely accepted substitutes for morphine. The reversed ester of pethidine (2), first described by Jensen et al. (1943), was found to be significantly more active than pethidine and led to the introduction of a methyl group into the 3-position (Ziering and Lee, 1947), giving rise to the alpha- and beta-prodines (3), both of which are potent analgesics.

Many attempts have been made to modify morphine



'α' (3) 'β'

and the synthetic narcotic analgesics with the aim of eliminating or at least minimising the undesirable side effects of the compounds, in particular the addiction liability and respiratory depression. Although as a result of this work new and clinically useful narcotic analgesics have been introduced, e.g. the morphinans (4)



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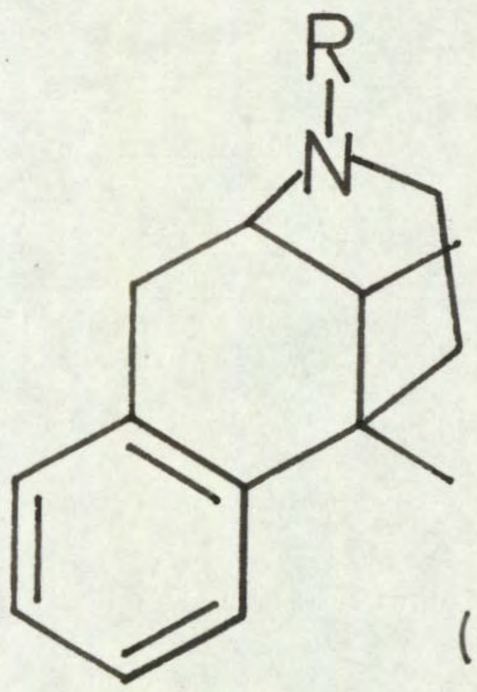
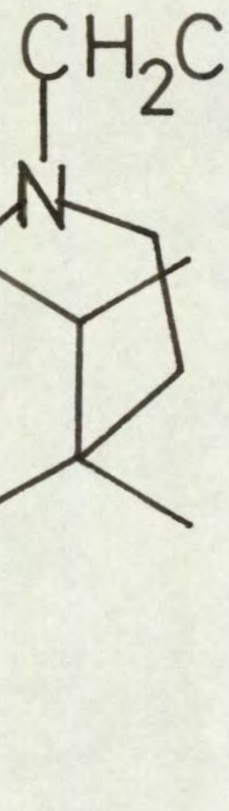


(5)

and benzmorphans (5), these are still drugs with addiction liability and produce respiratory depression. It is only in very recent years with continued research on analgesic antagonists that measurable success appears to have been achieved with the introduction of compounds

like pentazocine (6), which, given by injection to



(6)

post-operative patients, was reported to be an analgesic in the potency range of morphine (Keats and Telford, 1964).

The earlier lack of success in producing a non-addictive analgesic might in part be attributed to the fact that the pharmacological methods used in the assessment of the relief of such a subjective phenomenon as pain are those which are most likely to indicate morphine-like properties and perhaps fail to show analgesia or central nervous system depression other than the morphine type. For example, the "hot plate" method of testing for analgesics (Janssen et. al. 1957) does not distinguish between morphine-like analgesics and other compounds which may increase reaction time, though Janssen and Jageneau (1956) suggested the measurement of mydriatic activity since it has been shown that there is a significant correlation between morphine-

like activity and mydriatic activity in mice.

Despite the lack of success in preparing a suitable analgesic, it was possible, after extensive studies of structure and morphine-like activity, to make predictions concerning the structural requirements for a compound to possess analgesic activity. In 1955, Braenden et al. made a comparison of chemical structure and analgesic action for the United Nations Commission on Narcotics. At that time, no potent analgesic was known which did not possess certain chemical characteristics, namely:

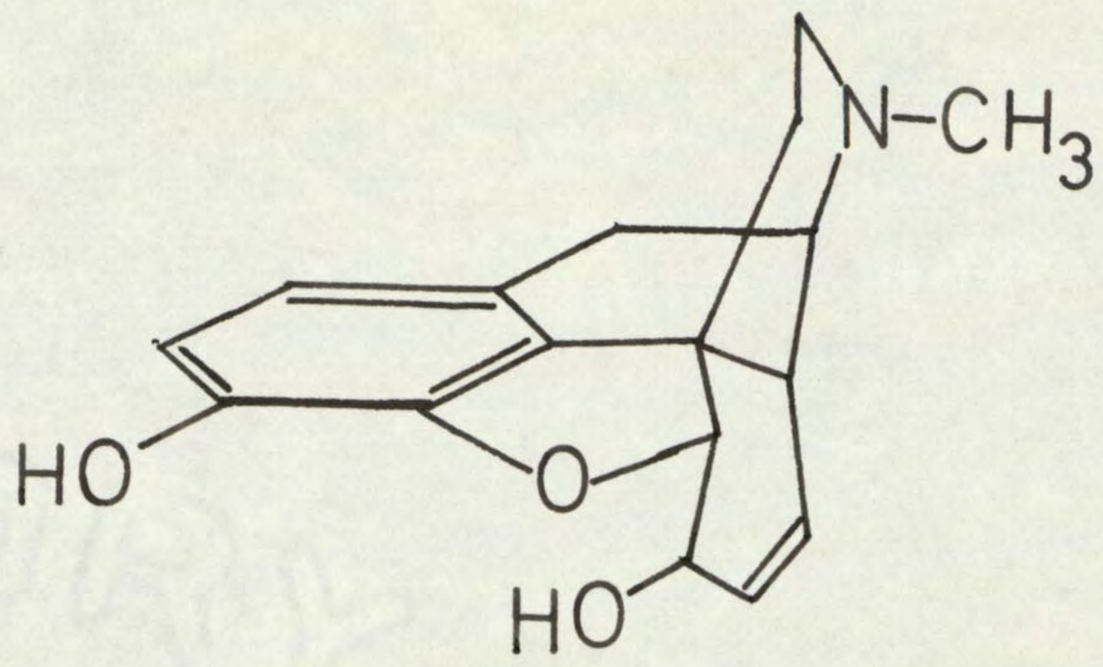
a) A tertiary nitrogen, the group on the nitrogen being relatively small.

b) A central carbon atom, none of whose valencies were connected with hydrogen.

c) A phenyl group or a group isoteric with phenyl connected with the central carbon atom.

d) A two-carbon chain separating the central carbon atom from nitrogen for maximal activity.

In addition, all potent analgesics were antagonised by nalorphine. The remainder of the molecule is less critical, but frequently has an oxygen function in the vicinity of the central atom. These requirements allow considerable rotational or conformational freedom for the synthetic structures, which are thus capable of forming a



(7)

morphine-like configuration (7). This ability to form similar configurations was regarded by Beckett and Casy (1954), who postulated that analgesic compounds fit a receptor surface, initiating a reaction sequence the outcome of which effect is analgesic action. Hence stereochemical factors appeared extremely important in analgesic action, and by considering surfaces common to different chemical types of analgesics, certain tentative conclusions were drawn. These suggested that the most probable analgesic receptor surface contained:

a) a flat portion allowing Van der Waals forces to bond to a flat aromatic ring,

b) an anionic site, which can associate with a basic group, and

c) a cavity in which a suitably oriented moiety can fit.

To be effective, an analgesic agent must not only

possess the intrinsic capacity of associating with the particular receptor site, but also its physicochemical properties must be such that it reaches the locus of action in an adequate concentration. Since it is generally agreed that morphine-like analgesics exert their effect in the central nervous system, an attempt to base the design of potential central nervous system drugs on the skeletal structure of existing analgesics seemed a realistic approach in that the physico-chemical properties of the resulting compounds, for example, lipoid solubility and pKa, might be expected to be such as would allow penetration into the central nervous system.

At this time, the change in structure-activity relationships could be summarised in that,

a) substitution in the 4-phenyl ring generally reduced activity except for a few special cases,

b) the carbethoxy functions proved to be more active than the methyl and higher alkyl esters, with replacement of the ester by other groupings generally diminishing activity, and

c) shifting the phenyl and carbethoxy groups from the 4-position reduced or eliminated activity.

It was also claimed that the N-methyl grouping was optimum for achieving high narcotic analgesic activity

and was stressed by Beckett et al. (1956) as part of their work on analgesic receptor theory, which suggested that an oxidative N-demethylation mechanism was involved in the mediation of an analgesic response. This was substantiated by Burns et al. (1955) and Elliot et al. (1954) using N-methyl C^{14} morphine and codeine, the evidence for demethylation being based on $C^{14}O_2$ pulmonary excretion and the isolation of the nor-compound from urine by counter-current techniques. Axelrod (1956) also substantiated the hypothesis by investigating dealkylations of analgesics by liver enzyme systems, the results indicating that analgesics may be demethylated by the enzyme systems studied and that the more analgesically active isomer is more readily demethylated than the less active isomer. If the dealkylation hypothesis is valid, the introduction of nor-compounds close to the analgesic receptor site should produce an analgesic effect at least equal to the parent compound. The high activity of nor-morphine on intra-cisternal injection appeared to further substantiate the proposed hypothesis (Beckett et al. 1956).

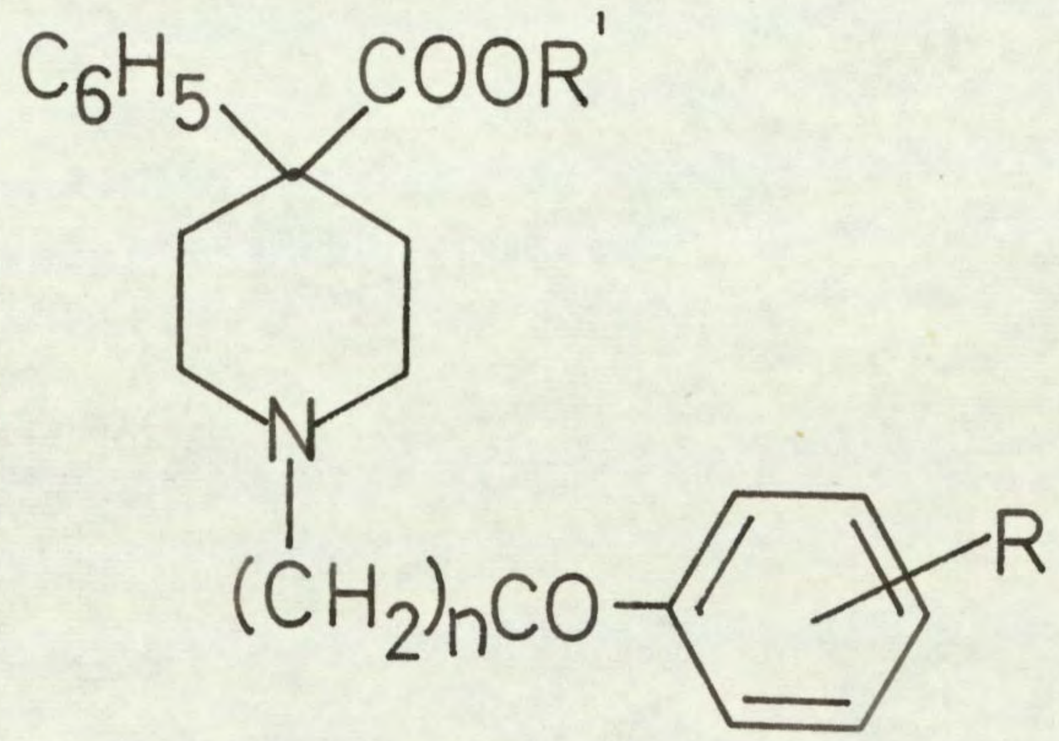
The discovery that N-phenethylnor-morphine and N-phenethyl pethidine possessed high analgesic activity

in animals (Clark et al. 1953, Perrine and Eddy, 1956) led to renewed interest in the effect of the nitrogen substituent, and while most early structural modifications of the piperidine moieties were made in a fairly empirical manner, some of the more recent work has been specifically designed to investigate the basic features which appear necessary for analgesic activity.

Modification of the N-substituent of pethidine led Janssen et al. (1959) to prepare a series of Mannich bases of the type (6), where R'=alkyl, in particular, C_2H_5, and R=H or a substituent such as alkyl, hydroxyl

(6) n=2

(7) n=1,3,4



or halogen. These compounds had increased analgesic potency in mice; for example, the compound R951 (6, R'=C_2H_5, R=H) had between 8 and 200 times the activity of pethidine. This encouraged Janssen et al. (1960) to prepare further derivatives with a variety of basic ketones to give type (7), where R' was an unsubstituted alkyl or aralkyl group, and R was H, alkyl,

hydroxyl or halogen. However, it was found that a shortening of the chain length from propiophenone derivatives (n = 2) to acetophenone derivatives (n = 1) led to a decrease in analgesic and mydriatic activity. Lengthening the chain (n >2) progressively decreased analgesic and mydriatic activity, the butyrophenones (n = 3) for example, having about an eighth of the potency of the propiophenones, with the exception of compounds of the type (7, R=F, R'=C_2H_5, n = 3). These compounds were found to have low mydriatic activity but were more active in the hot plate test than the unsubstituted homologue, and were less antagonised by nalorphine than were classical morphine-like analgesics. This suggested that these compounds were acting as central nervous system depressants rather than typical morphine-like analgesics.

Further work by Janssen et al. (1959a) resulted in the preparation of 4-piperidinols (8), where R = H, F; R = H, F, Cl, CH_3. Once again these compounds were found to be active in the hot plate test, were not antagonised by nalorphine and were devoid of mydriatic activity and thus were regarded as general nervous system depressants, the most successful compound of this type, Haloperidol (8, R=p-Cl, R'=p-F), being useful as a neuroleptic drug.

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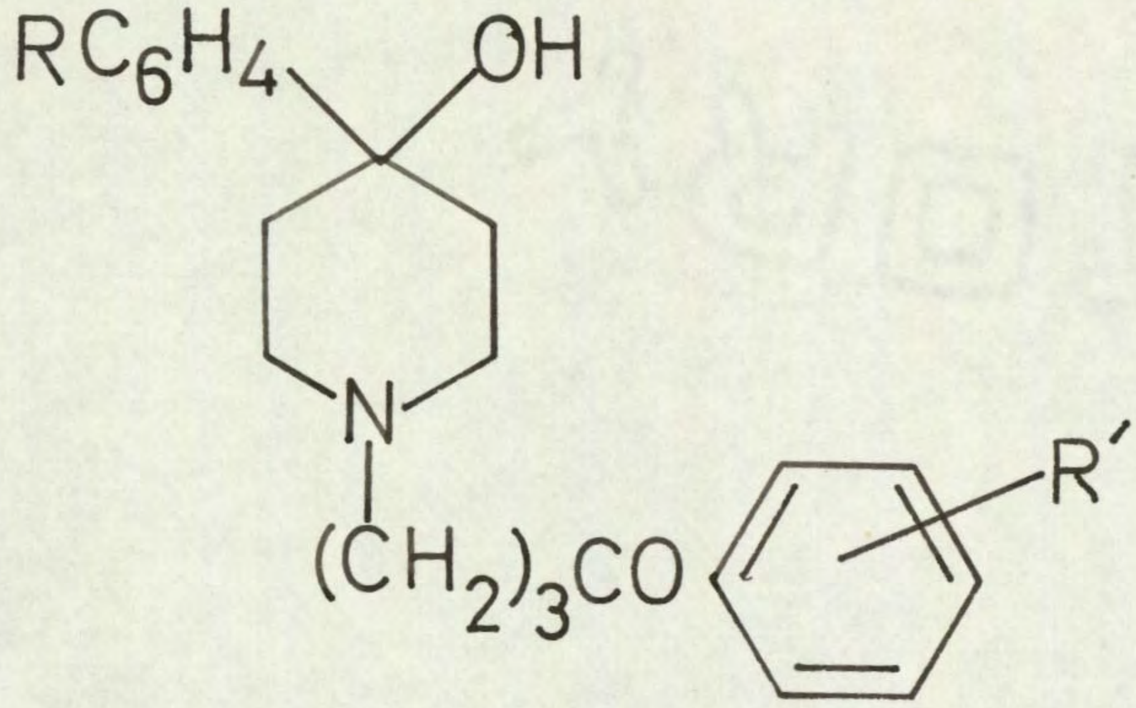
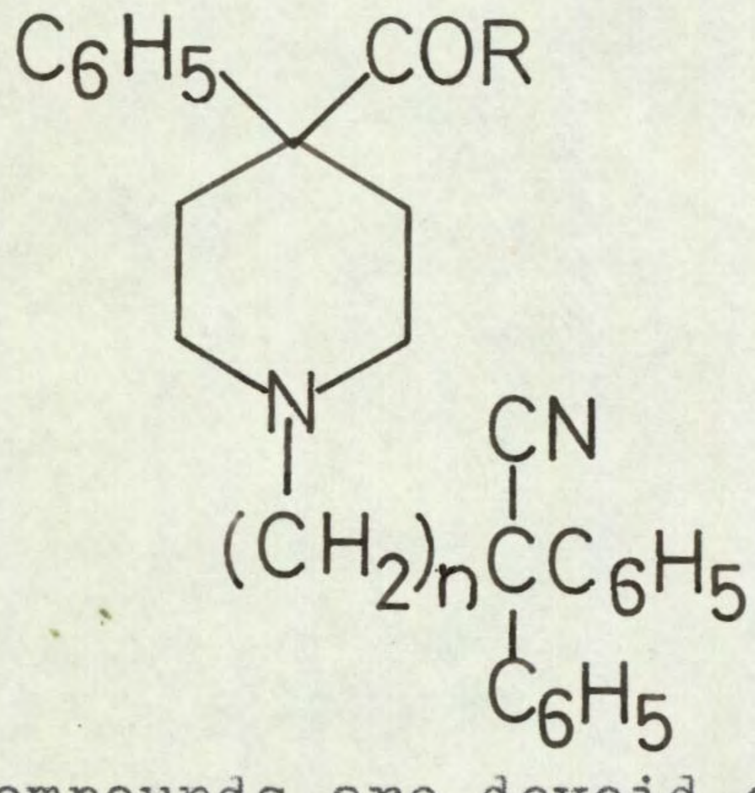
(8)



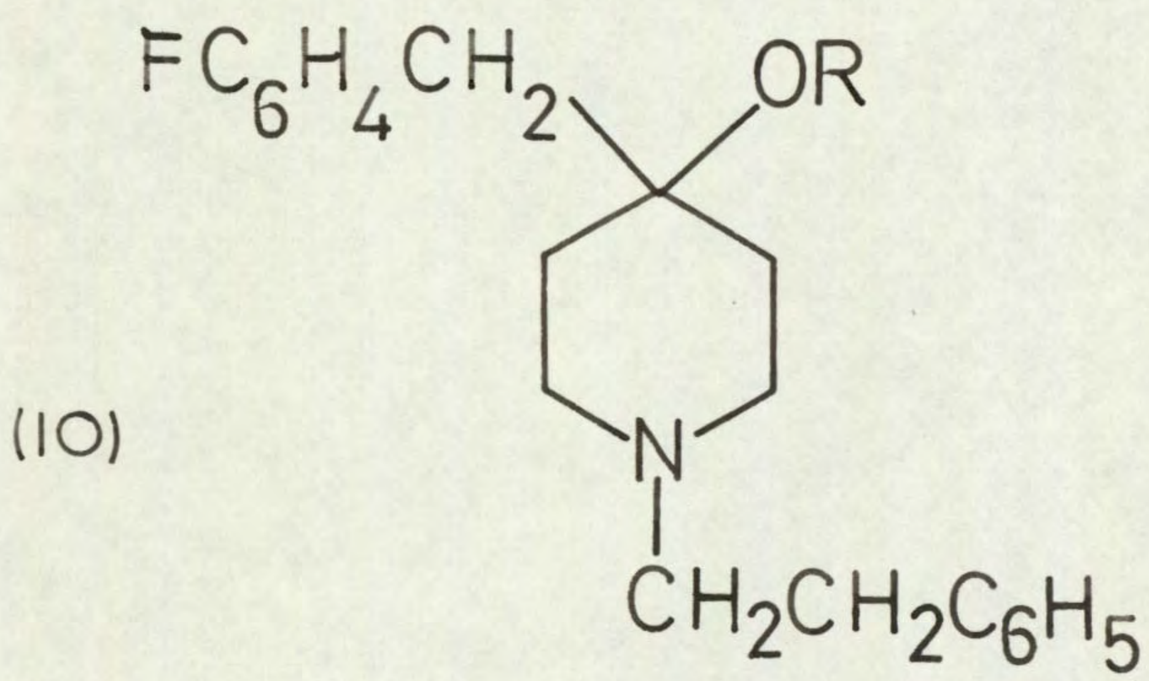
A similar type of compound, also developed by Janssen (1962) and Janssen et al. (1959b), which shows a dissociation of morphine like effects, though the physical dependence capacity is still present, is that of type (9), where COR represents an ester or ketone and

(9)



n=2-4. These compounds are devoid of significant analgesic or parasympatholytic activity but are active in reducing the rate of defaecation and gastro-intestinal propulsion. Thus these are effective anti-diarrheal agents which also show anti-tussive properties, the most useful being Diphenoxylate (9, R=OC_2H_5, n = 2).

The preparation of alpha and beta prodines by Ziering and Lee, and the resulting activity of these compounds led several workers to consider the effect of changing the 4-phenyl substituents. Harper et al. (1959) studied the effect of introducing fluorine into

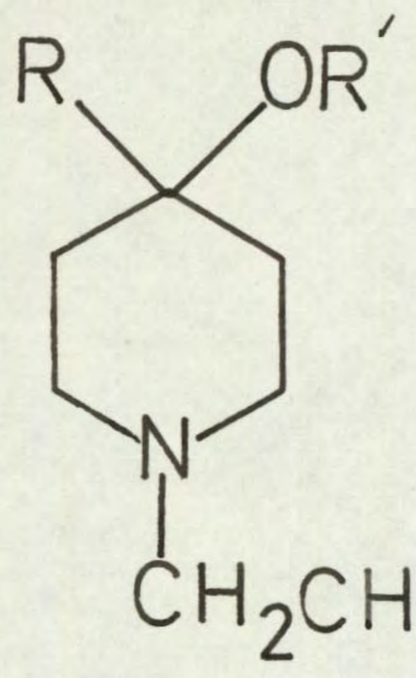


(10)

prodine-type analgesics, giving compounds of the type (10, R=H or COC_2H_5). Two of these compounds (10, p-F, R=H) and (10, O-F, R=H) showed high activity with the hot plate test, while the m-F derivative was devoid of hot plate activity. None of the compounds showed any appreciable mydriatic activity. It was concluded that the compounds were non-morphine-like central nervous system depressants. The corresponding esters of these compounds showed a marked loss in activity which is in contrast with morphine-like analgesics of the alpha- and beta-prodine type.

Harper and Fullerton (1961) studied a series of ethynyl (11), phenethynyl (12) and styryl compounds (13)

derived from prodine in order to determine whether the



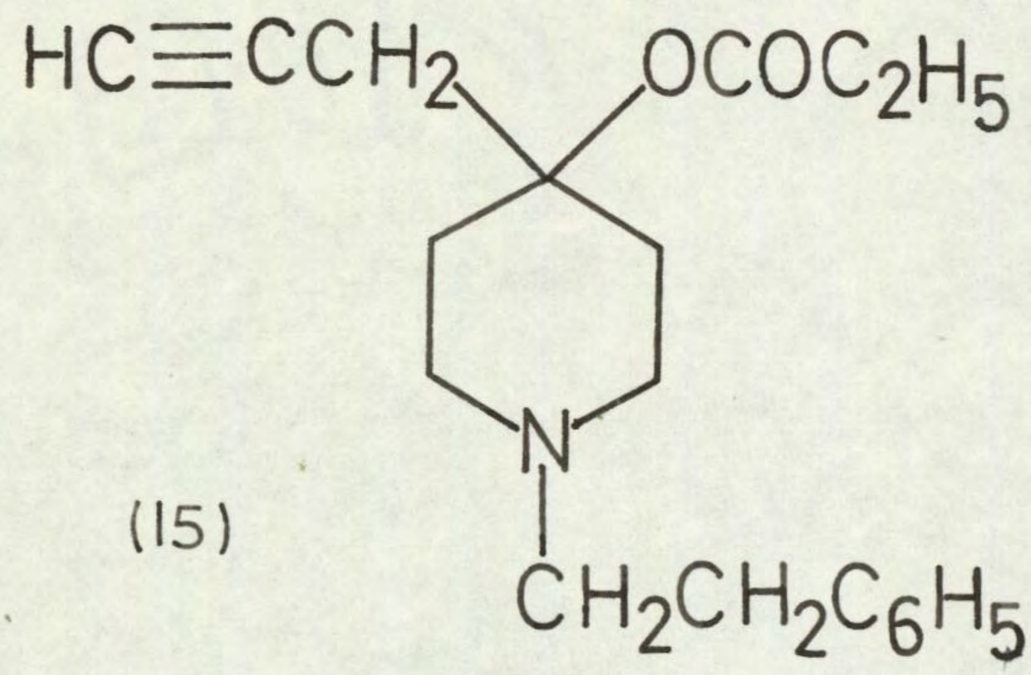
(11) R= $HC\equiv C-$

(12) R= $C_6H_5C\equiv C-$

(13) R= $C_6H_5CH=CH-$

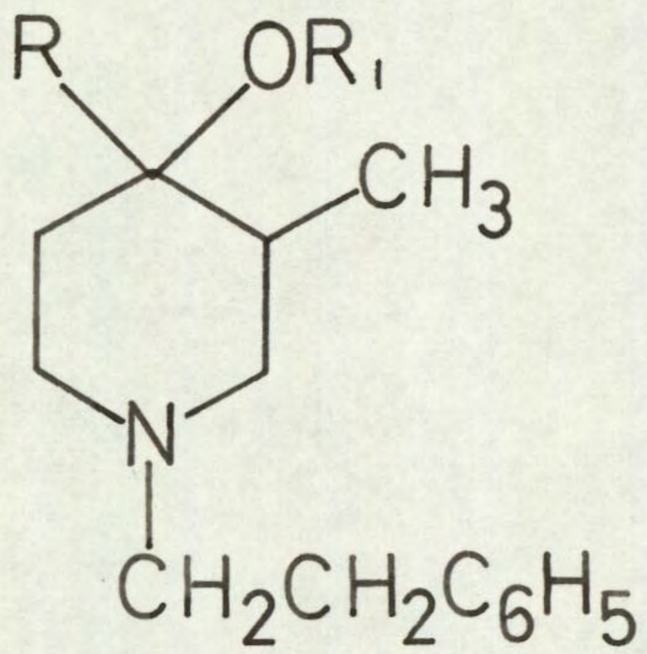
(14) R= $C_6H_5CH_2CH_2-$

aromatic ring could be replaced by other groups which were not aromatic but which possessed a π cloud of electrons. Some of the compounds were reduced to the corresponding fully-saturated phenethyl derivatives (14). Only the phenethynyl derivative (12, R'=H) and the 4-phenethyl derivatives (14, R=H,$COCH_3$) have pronounced activity when assessed by the hot plate method. The activity is judged to be general central nervous system depressing rather than morphine-like. Another compound related to the work of Harper and Fullerton is Propenitidine (15) which has been evaluated as an anti-tussive (Deltour et al. 1963). This also did not seem to have morphine-like actions. The evidence suggests that a 4-phenyl substituent is necessary for its bonding capacity with the morphine-like analgesic receptor and can not be replaced by a non-aromatic group with a π-electron cloud. Nor can the phenyl



(15)

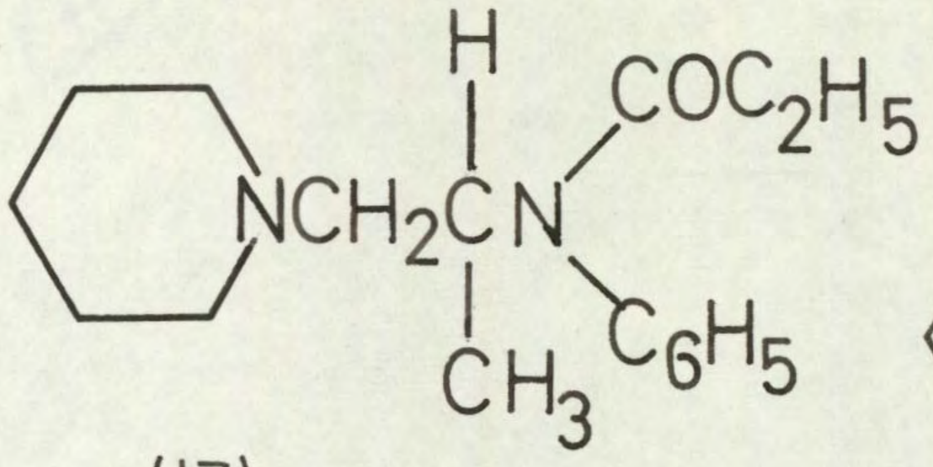
group be separated from the 4-position by an ethylene, vinyl or ethynyl moiety. A successful attempt by Beckett et al. (1960) to substitute a heterocylic ring in the 4-position, giving compounds of type (16), where R = pyridyl or thienyl and R_1=$COCH_3$ and COC_2H_5, resulting



(16)

in loss of narcotic analgesic activity, supported this view.

In 1959, Wright et al. described two members of a new system of basic anilides, phenampromide (17) and diampromide (18) which were selected for clinical trial. The results indicated that both compounds were narcotic



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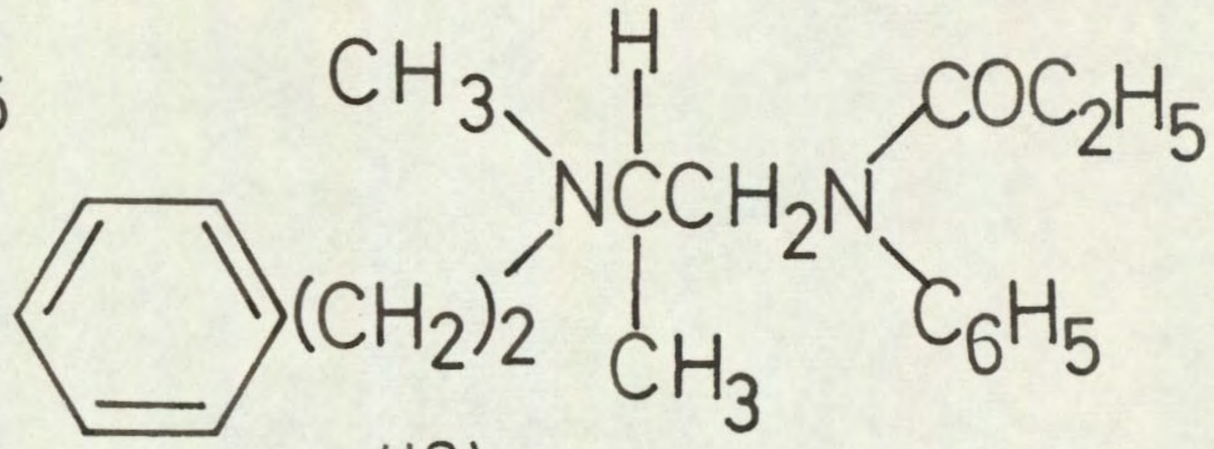
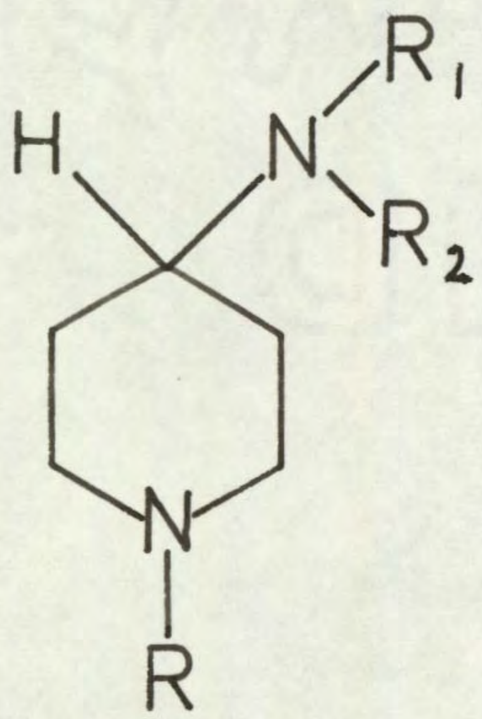


(18)

type analgesics. These compounds retain the steric requirements postulated for the potent analgesics and would be expected to fit the same analgesic receptor as methadone or morphine. In an attempt to prepare central nervous system type drugs acting as anti-depressants, Harper and Chignell (1964) synthesised compounds of the type (19), where R = alkyl or aralkyl, R_1= aralkyl and



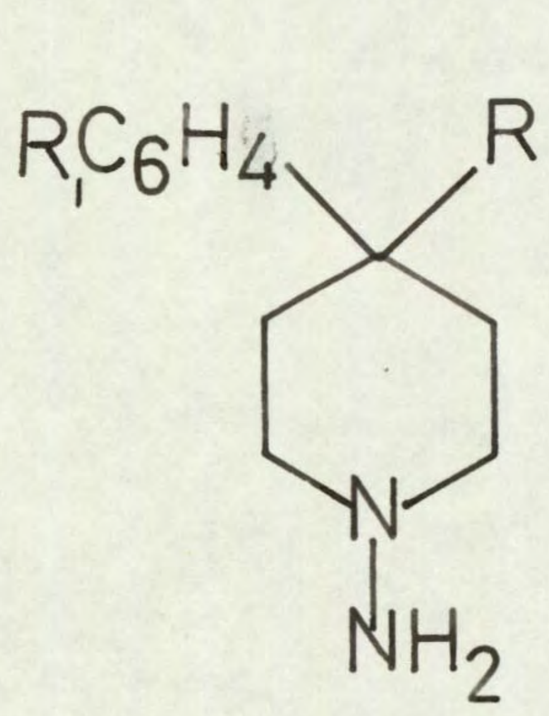
(19)

R_2=H or acyl. However these piperidines showed little anti-depressant activity, though some were found to be narcotic analgesics with activities comparable with pethidine. Janssen et al. (1963) also prepared piperidines of the type (19), one compound, Phenatyl

(19, R=$C_6H_5CH_2CH_2$, R_1=C_6H_5, R_2=COC_2H_5) being a potent morphine-like analgesic with the usual concomitant side effects, and is claimed to be about 270 times as active as morphine when subcutaneously injected in rats.

Further research has been carried out with the object of obtaining compounds exhibiting general central nervous system depressant effects rather than narcotic analgesic activity. Harper et al. (1967) in a search for an anti-depressant drug of the imipramine type, synthesised compounds of the type (20), where R=OH and R_1=H, F, Cl, CF_3. The compound (20, R=OH, R_1=H) was

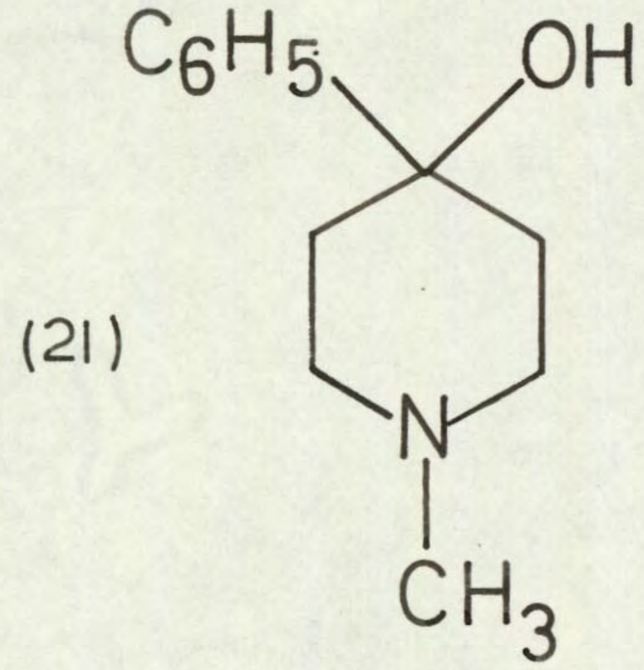
(20)



found to be more active than imipramine as an anti-depressant. Homologues with substituents on the nitrogen and with various groups for R, however, did not exhibit any exceptional activity.

The simple alcohol (20, R=OH, R_1=H) led to the suggestion that the simple piperidinol (21) may have been useful as an anti-depressant. The compound has

been found to have 3-5 times more anti-depressive activity than imipramine and can be used for psychotic



(21)

and psychoneurotic diseases (Allen and Hanburys, 1965).

From their pharmacological actions, it would appear that many of the compounds are capable of forming excellent complexes with the stereospecific receptor postulated for analgesic actions. However, the significant modification of the accepted requirements found in the morphine-like analgesics suggests that potent morphine-like actions may be found in molecules less closely related to the previously postulated structural requirements for analgesics than thought possible, and may require additional modification of the optimum dimensions and arrangement of the stereospecific receptor postulated for analgesic activity.

Section I

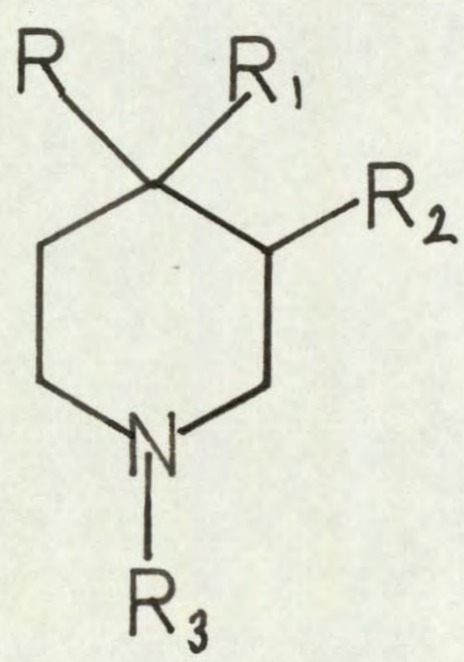
Part II

Experimental Aims and Objects of the present investigation

EXPERIMENTAL AIMS AND OBJECTS OF THE PRESENT INVESTIGATION

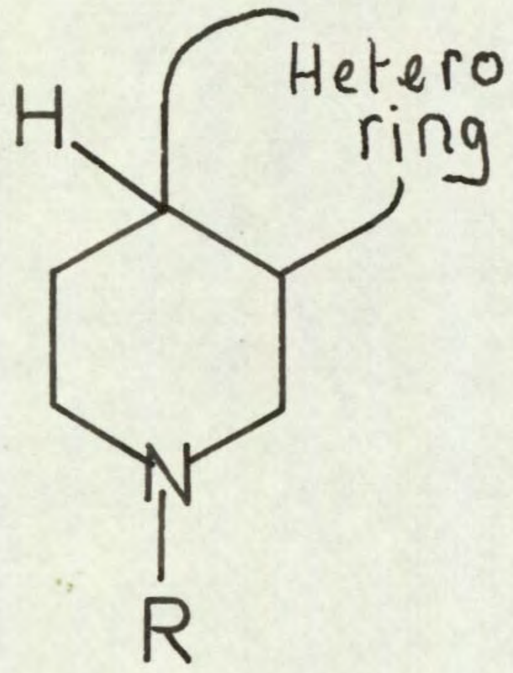
Piperidine derivatives have been shown to have widely different biological activities. In a number of cases, the nature of the substituent in the 3-position of the piperidine ring appears to have a marked qualitative and quantitative effect on the biological activity. In spite of this, a limited range of 3-substituents have been investigated, and these largely have an alkyl or carbethoxy group in the 3-position. It was therefore considered desirable to investigate the effect on biological activity of the introduction of other novel groups, particularly reactive functional groups which would allow a variety of compounds to be prepared. With this in mind, it was decided to prepare compounds of the type (1), where R=C_6H_5 or H; R_1=OH or NH_2; R_2=CN, CH_2NH_2, $CONH_2$, $CH_2NHCOCH_3$; R_3=CH_3, C_2H_5, $CH_2C_6H_5$, $(CH_2)_2C_6H_5$.

(1)



From these compounds, the possibility would appear to exist of ring closure between the 3- and 4-positions of the piperidine ring so as to give compounds of the type (2).

(2)



It was envisaged that the piperidines substituted in the 3- and 4-positions, and the compounds resulting from the ring-closure of these positions, would give rise to isomers, and it appeared desirable to attempt the determination of the configuration of such compounds, since some of the compounds resulting from the investigation would be subjected to a biological screen and in particular to central nervous system and cardio-vascular testing.

A number of the compounds prepared during the course of the present work were novel, and it was considered desirable to attempt the study of the N.M.R. spectra and possibly the mass spectra of such compounds.

Section II

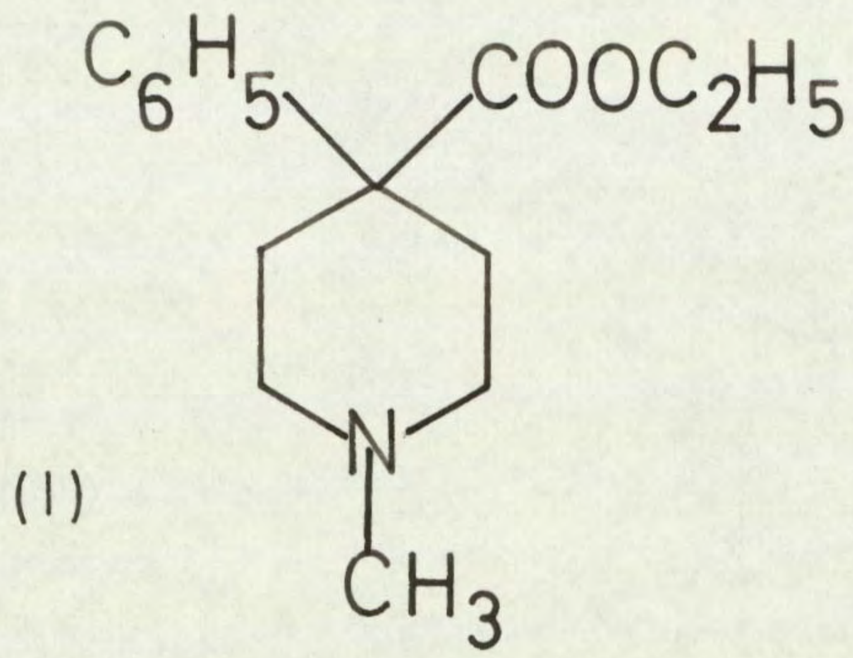
Part I

Description and discussion of the experimental

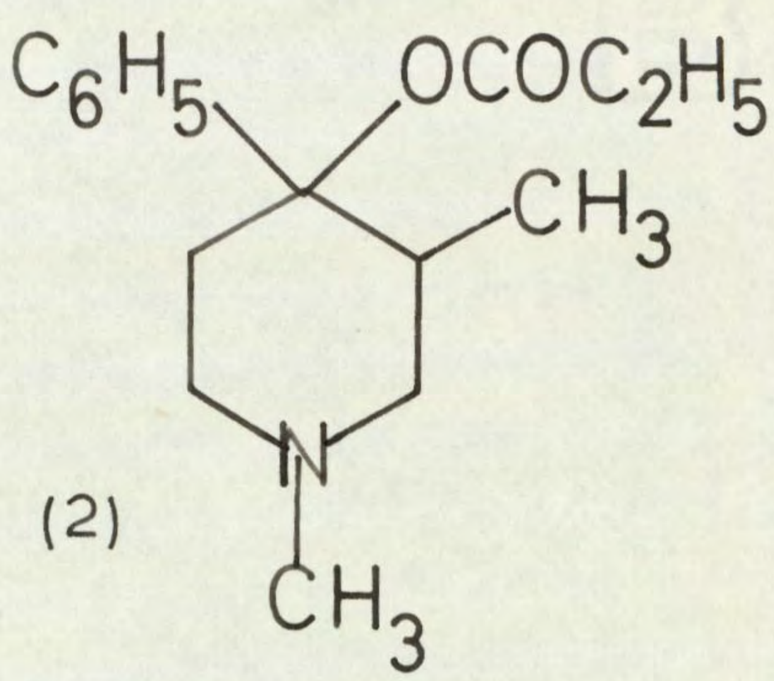
DESCRIPTION AND DISCUSSION OF THE EXPERIMENTAL

PREPARATION OF 1-BENZYL-3-CYANO-4-PIPERIDONE

The great interest in piperidines disubstituted in the 4-position began with the discoveries of the analgesic pethidine (1).



(1)

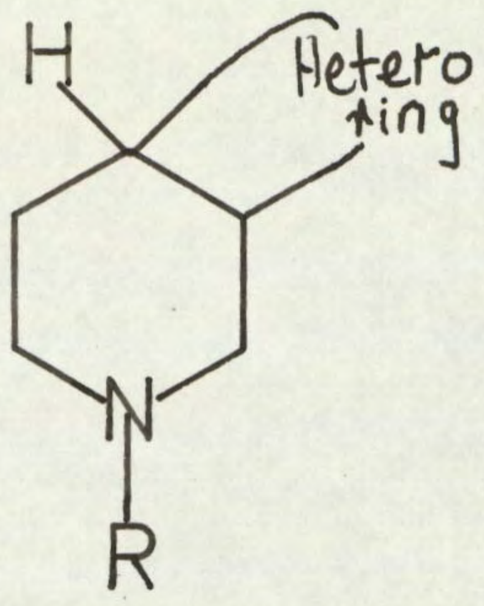


(2)

Much effort subsequently went into preparing piperidines with a variety of substituents in the 4-position. The analgesics alpha- and beta-prodine (2) emphasised the effect of a 3-substituent on biological activity. Piperidines substituted mono- or di- in the 4-positions and also bearing a 3-substituent are less well known. The following are typical of those which have been described: 3-phenyl-3,4-dialkyl-(Kugita *et al.*, 1964),3-hydroxy-(Lyle *et al.* 1966, Branquet *et al.* 1965),3-aralkyl-(CIBA, 1967) and 3-acetamido-(Lasslo *et al.* 1956, Lasslo *et al.* 1957, Beasley *et al.* 1967, Quintana *et al.* 1967). Relatively few compounds with a heterocyclic

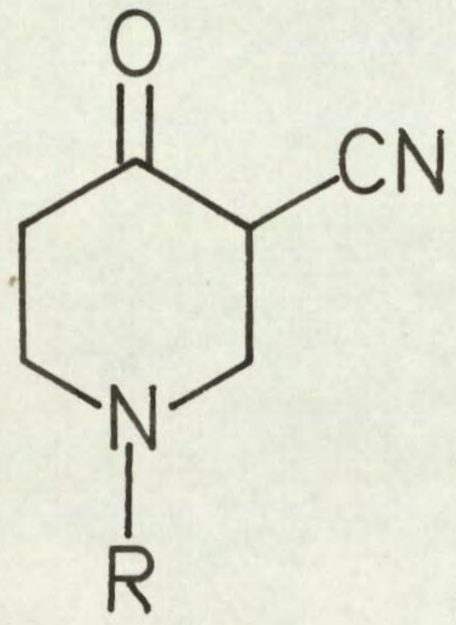
bridge between the 3 and 4 positions (3) have been described.

(3)

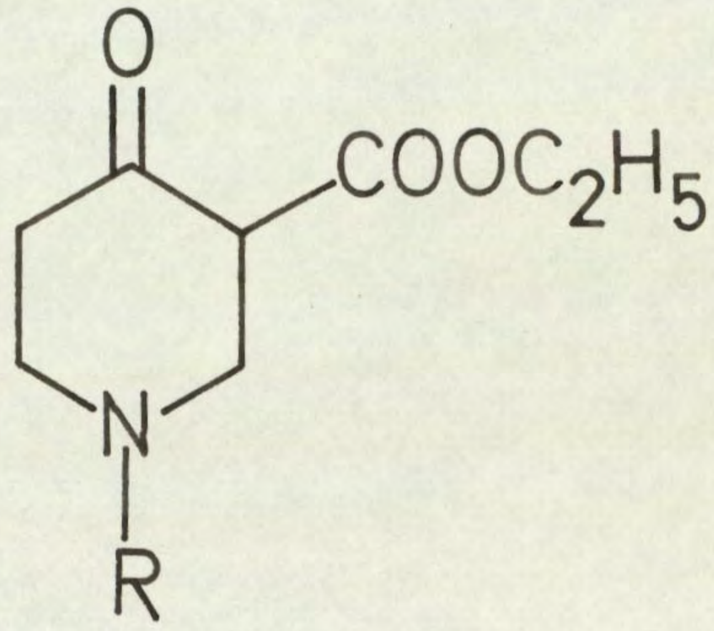


3-Substituted 4-piperidones appeared to be suitable starting materials since the very reactive carbonyl group presented the possibility of extensive chemical modification. The 3-cyano-4-piperidones (4) and the 3-carbethoxy-4-piperidones (5), both of which appeared to

(4)

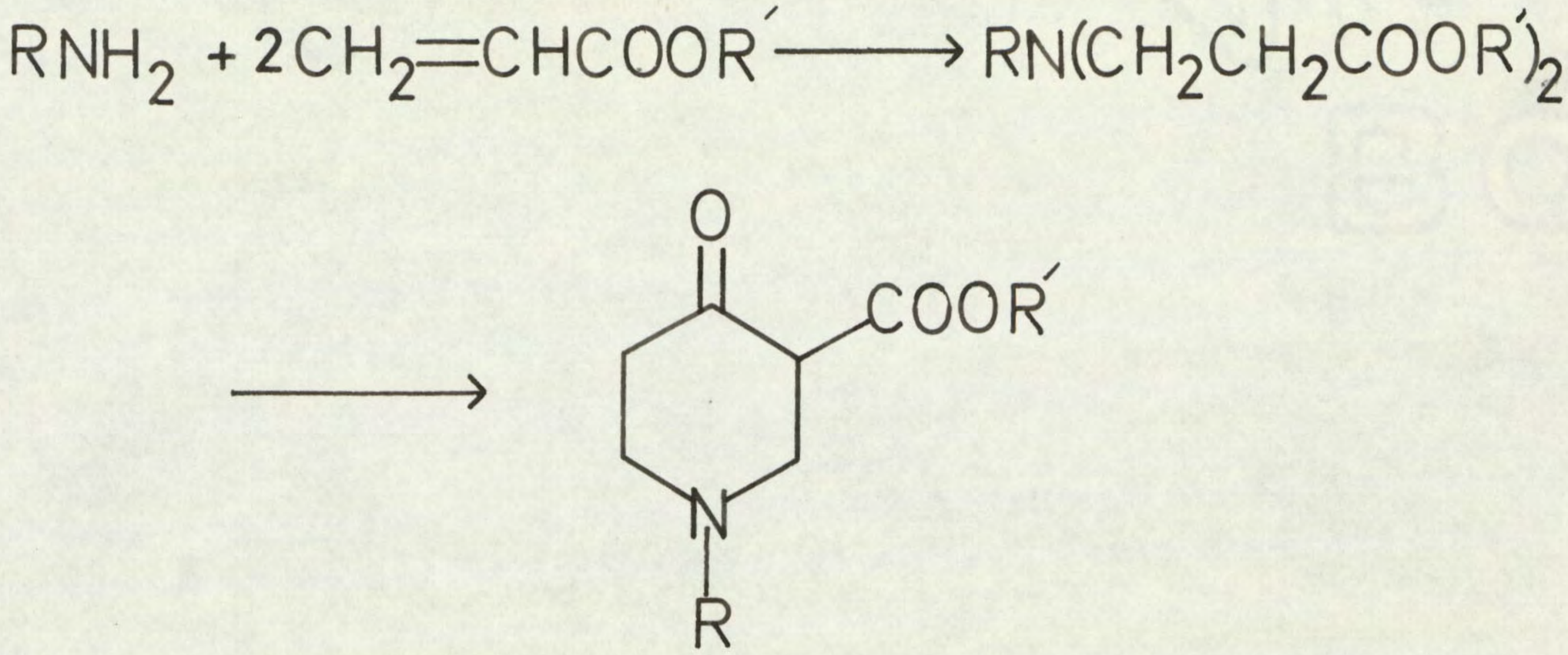


(5)

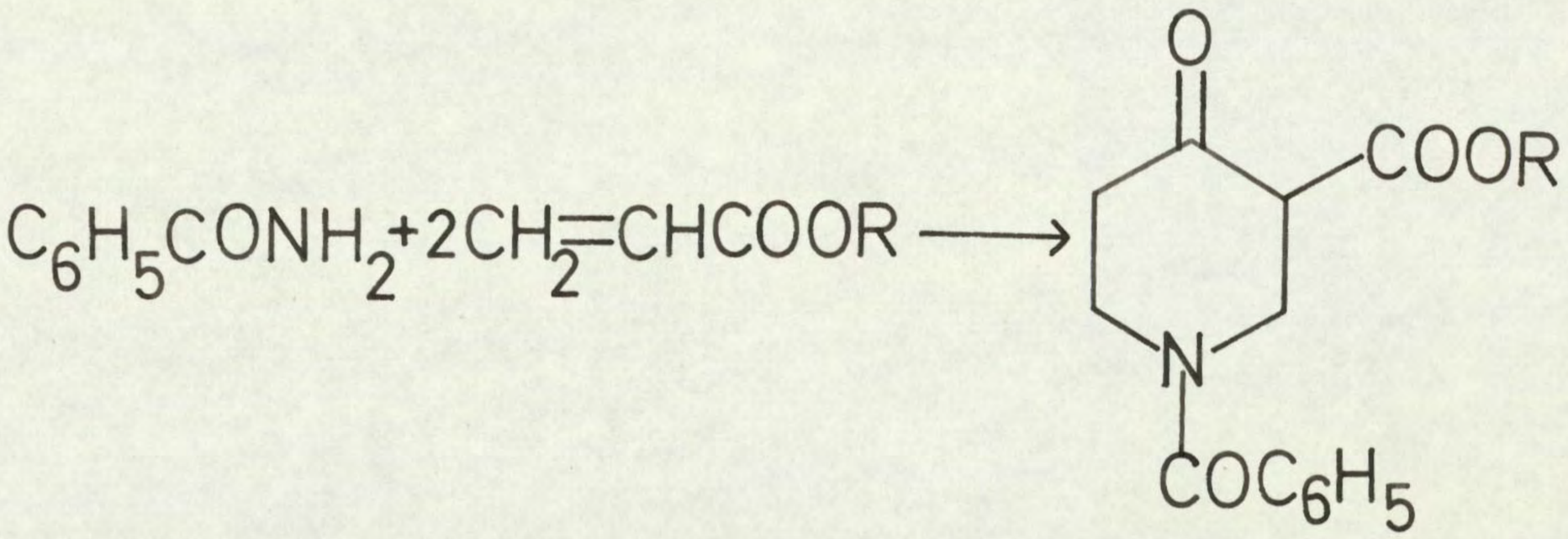


be relatively easily synthesised from readily available starting material, seemed to offer advantages for the present investigation. This was particularly true of the type (5), which could be synthesised as shown. (McElvain, 1924, Bolyard and McElvain, 1929).

This involved the condensation of an α,β-unsaturated

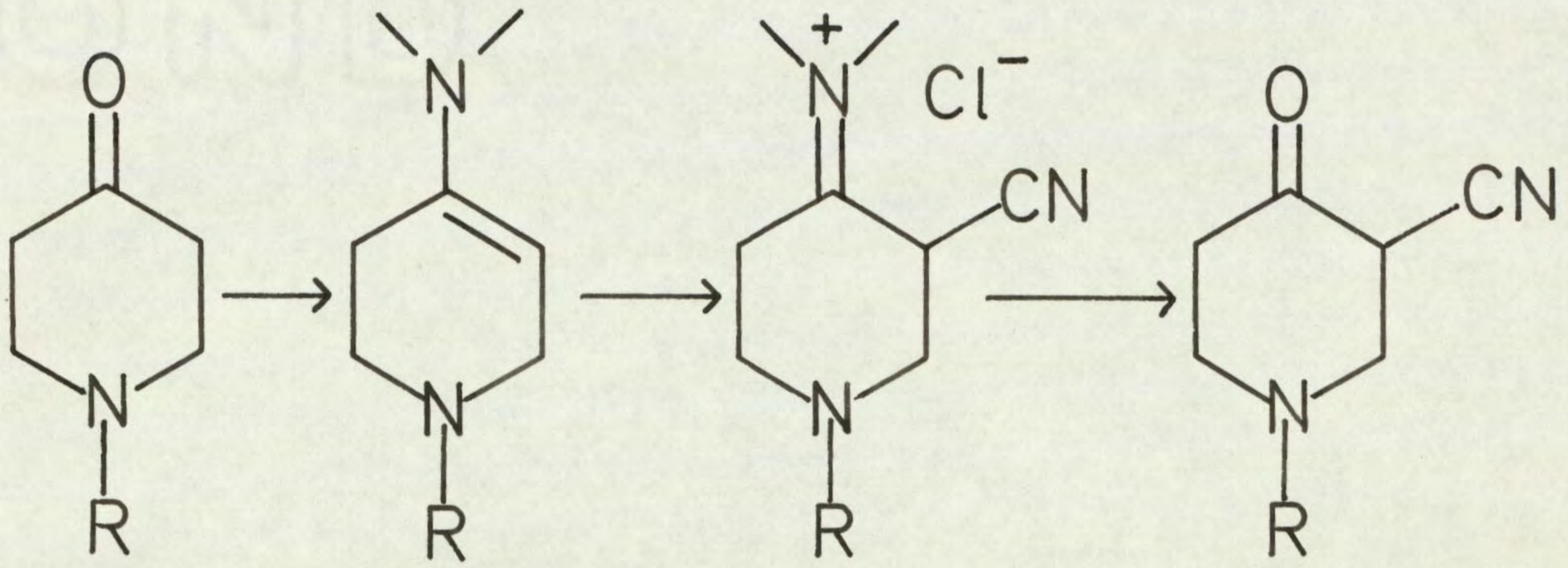


ester, such as methyl acrylate or ethyl crotonate, with a primary amine or ammonia, by allowing to stand for up to 42 days, and fractionally distilling the products. The tertiary amine obtained could then be cyclised using "bird-shot" sodium in xylene, to give the desired 3-carbethoxy-4-piperidone. A second method, where the desired 1-substituent was to be an amide, involved direct condensation and cyclisation onto an amide (Baty et al. 1967, Gavellin and Spickett, 1965) using sodium hydride as a condensing agent.



The carbethoxy compounds (5) have, of course, already been extensively exploited, a situation less true for the 3-cyano-4-piperidones (4). If these compounds could be prepared, it appeared possible that reactions of the types illustrated in flow sheet I could be undertaken.

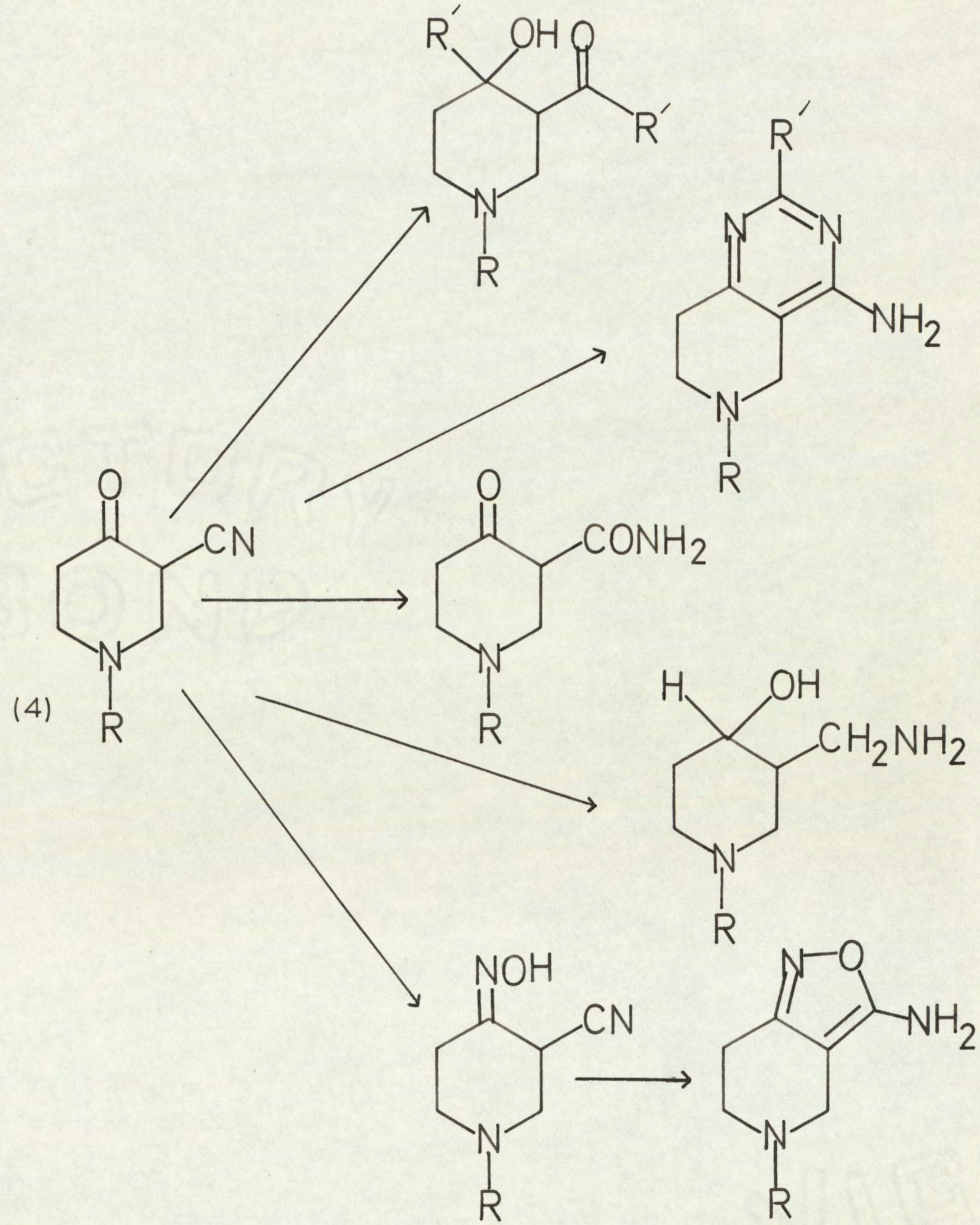
To obtain compounds of the type (4), two routes could be used. The first involved formation of an enamine, using a secondary amine with an acid catalyst



and water separation. This could be reacted with a cyanogen halide to give a salt, which on acid hydrolysis would yield the 3-cyano-ketone (Kuehne, 1959). This method, however, would require the preparation of the 4-piperidones beforehand, which would involve the preparation of the 3-carbethoxy-4-piperidones described previously, followed by decarboxylation to give the starting ketone.

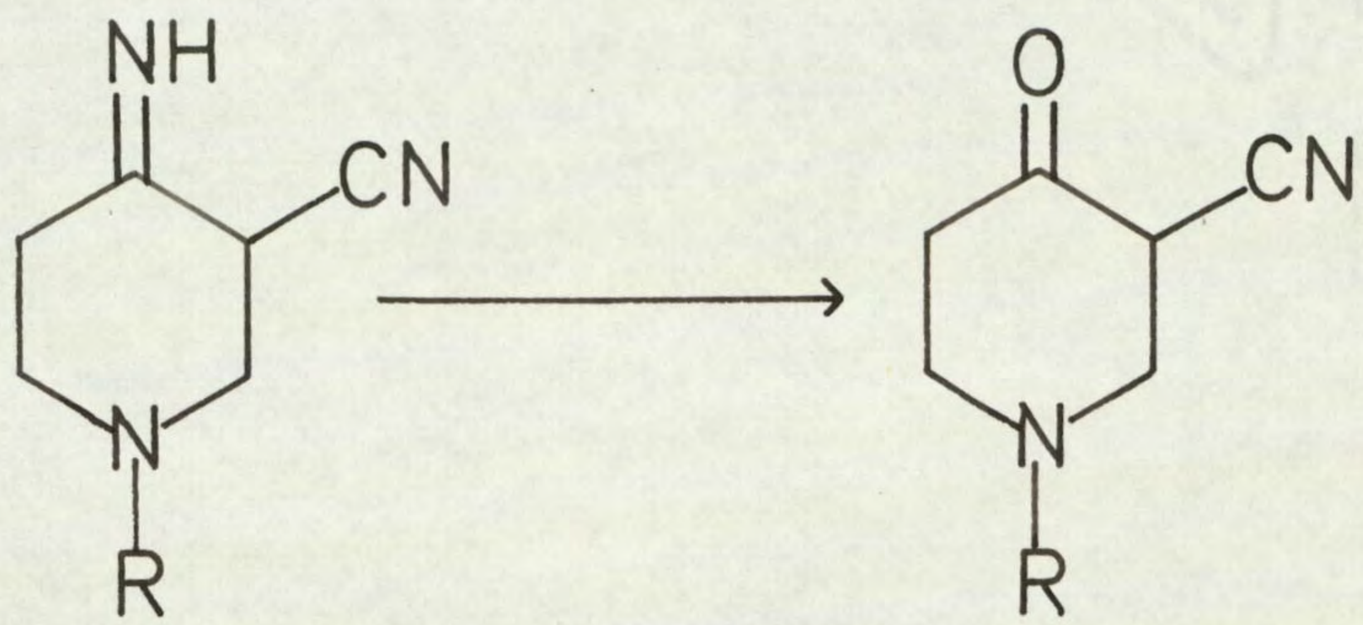
A shorter route, which also gives a useful inter-

Flow Sheet I


R´
OH
O
R´
N
R
R´
N
N
NH2
N
R
O
CN
CONH2
N
R
(4)
H
OH
CH2NH2
N
R
NOH
CN
N
R
N
O
NH2
N
R

mediate, involves the cyclisation of a dicyanide with sodium in toluene (Thorpe cyclisation) (Cook and Reed, 1945, Bachman and Barker, 1947).

$$RNH_2 + 2CH_2{=}CHCN \longrightarrow RN(CH_2CH_2CN)_2 \longrightarrow$$



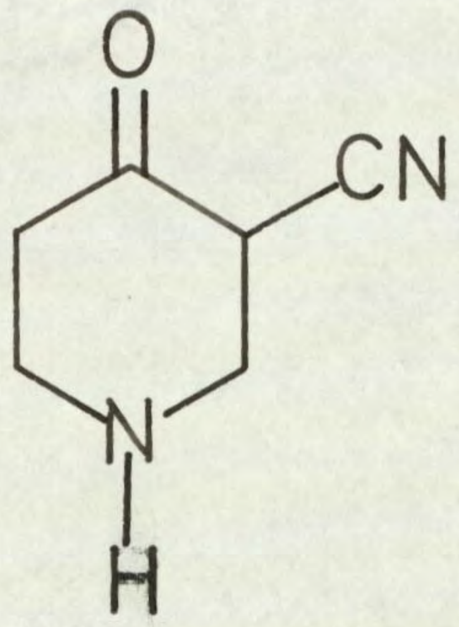
The tertiary amine can be obtained by refluxing a primary amine with 2 moles of acrylonitrile (Adams, 1951) for several hours, followed by distillation of the products. In the case of simple aliphatic amines, the reaction proceeds exothermically to give the required tertiary amine (or secondary amine if ammonia is used) (Wiedeman and Montgomery, 1945, Ford et al. 1947, Buc et al. 1945). Use of more complex aliphatic amines or aromatic amines tends to give the mono-substituted secondary amine. This can be overcome by addition of a catalyst (Whitmore et al., 1944) such as acetic acid or hydrated $CuSO_4$ (Braunholtz and Mann, 1952).

The tertiary amine could be added dropwise to a suspension of sodium in toluene to obtain a solid which

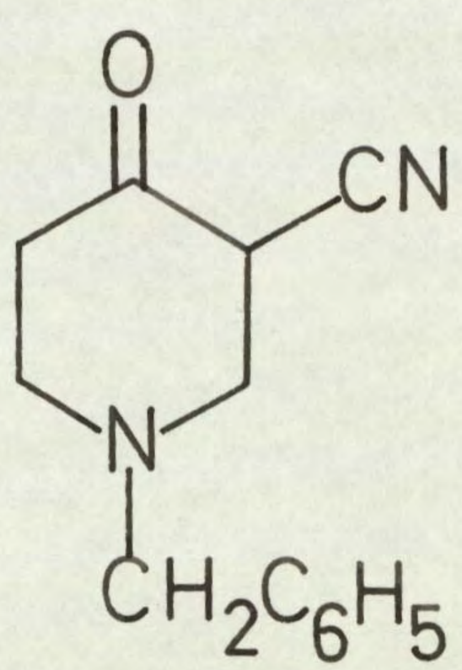
is claimed to be the 3-cyano-4-ketimine, hydrolysis of which might be expected to give the cyano ketone as the hydrochloride salt.

In the present investigation, it was considered highly desirable to prepare compounds with a variety of groups in the 1-position. There appeared to be two methods of achieving this, namely an attempt to prepare an intermediate of type (6), which could be converted to

(6)



(7)

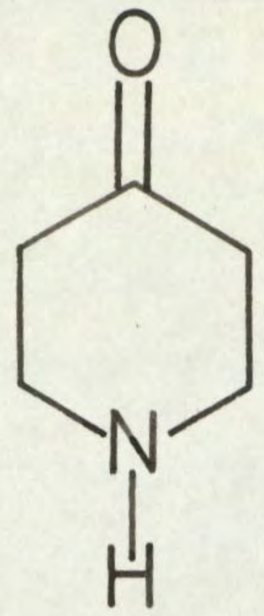


the required tertiary base, or the synthesis of compound (7), from which the benzyl group could be removed by catalytic debenzylation at some suitable stage.

Bachman and Barker (1947) prepared the compound (6), 3-cyano-4-piperidone, as the free base, but the stability of this compound is a matter of conjecture in view of the well-known instability of compound (8) due to polymerisation (Nazarov and Rudenko, 1948).

An attempt was made to synthesise 3-cyano-4-piperidone (6) using the method of Bachman and Barker.

(8)



This involved addition of ββ'-iminodipropionitrile to a refluxing stirred suspension of sodium in dioxan containing naphthalene as a metal carrier. The mixture was poured into benzene, when the piperidine separated. Reaction of the piperidine with 5N HCl and neutralisation with conc. NaOH solution gave the piperidine in 70% yield, based on the dinitrile used. However, in the present investigation, attempts to attain this high yield using identical conditions failed, even though the experiment was repeated several times. At a later stage, another method due to Taub et al. (1967) using potassium tert. butoxide in toluene was investigated. This method tended to give much better yields of a cleaner product, but in view of the generally low yields of ketone obtained, and of the doubtful stability, it was decided to attempt the preparation of 1-benzyl-3-cyano-4-piperidone. This was supported by the opinion that, with the 1-benzyl compound, further reactions could be attempted without

the piperidine nitrogen being attacked, until the final stage after the complete molecule had been debenzylated.

ββ'-Benzyliminodipropionitrile has been made by two synthetic methods. The first was by reaction of benzylamine with acrylonitrile (Preobrazhenskii et al. 1957) and distillation of the products. The second method involved the use of ββ'iminodipropionitrile with benzyl chloride (Frost and Martell, 1950).

$$C_6H_5CH_2NH_2 + 2CH_2{=}CHCN \rightarrow C_6H_5CH_2N(CH_2CH_2CN)_2$$

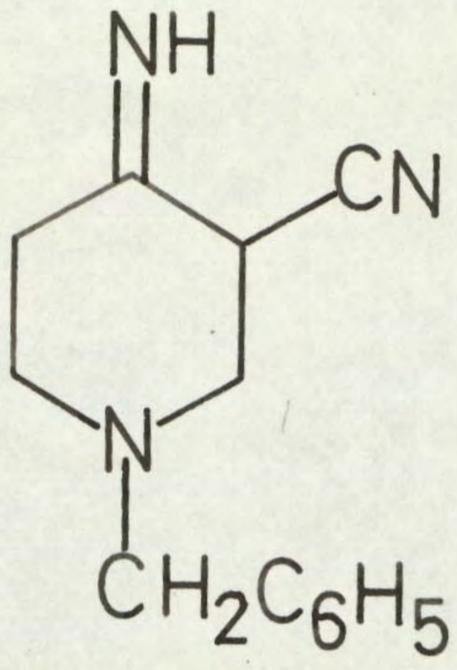
$$C_6H_5CH_2Cl + HN(CH_2CH_2CN)_2$$

The one-step reaction was attempted, involving refluxing benzylamine with excess of acrylonitrile for 48 hours, when two fractions were obtained on distillation. The first was acrylonitrile, while the second fraction was considered to be β-benzylamino-propionitrile. An infra-red spectrum of this compound showed a peak at 2250 $cm.^{-1}$, attributed to C≡N, and a peak at 3300 $cm.^{-1}$, attributed to NH. Non-aqueous titration of the oil gave an equivalent weight of 163 ($C_{10}H_{12}N_2$ requires 160). Hence it appeared that only the mono-substituted product was obtained. Heating benzylamine and acrylonitrile in a sealed tube to 80°

for 20 hours gave the mono-substituted product, as did heating in a sealed tube with $CuSO_4$ (Whitmore *et al*. 1944). Refluxing benzylamine and excess acrylonitrile with 10% w./v. of acetic acid, however, gave after 3 hours a yellow liquid which gave 3 fractions when distilled. The first was acrylonitrile, the second, acetic acid, unreacted benzylamine and mono-substituted product, while the third was a pale yellow oil. The infra-red spectrum of this oil showed a peak at 2250 $cm.^{-1}$, attributed to C≡N, but no other major peak except for mono-substituted aromatic absorption. The equivalent weight of this compound was found to be 216 (calc. for $C_{13}H_{15}N_3$, 213). The N.M.R. spectrum of the compound showed a singlet peak at $\tau = 2.6$, a singlet at $\tau = 6.35$ and two triplets at $\tau = 7.23$ and 7.64. The ratio of protons in the peaks were 5 : 2 : 4 : 4. The evidence strongly suggested that the compound was the desired dicyanide.

The cyclisation of the dicyanide was attempted using the method of Cook and Reed, the dicyanide being added dropwise to a stirred refluxing suspension of "molecular" sodium in toluene, the solution refluxed for a further 10 minutes, decanted from remaining sodium and allowed to stand. The compound obtained had an equivalent weight of 211, agreeing with 213 calculated

for the structure (9) instead of 235 expected for the



(9)

sodium salt of the imine.

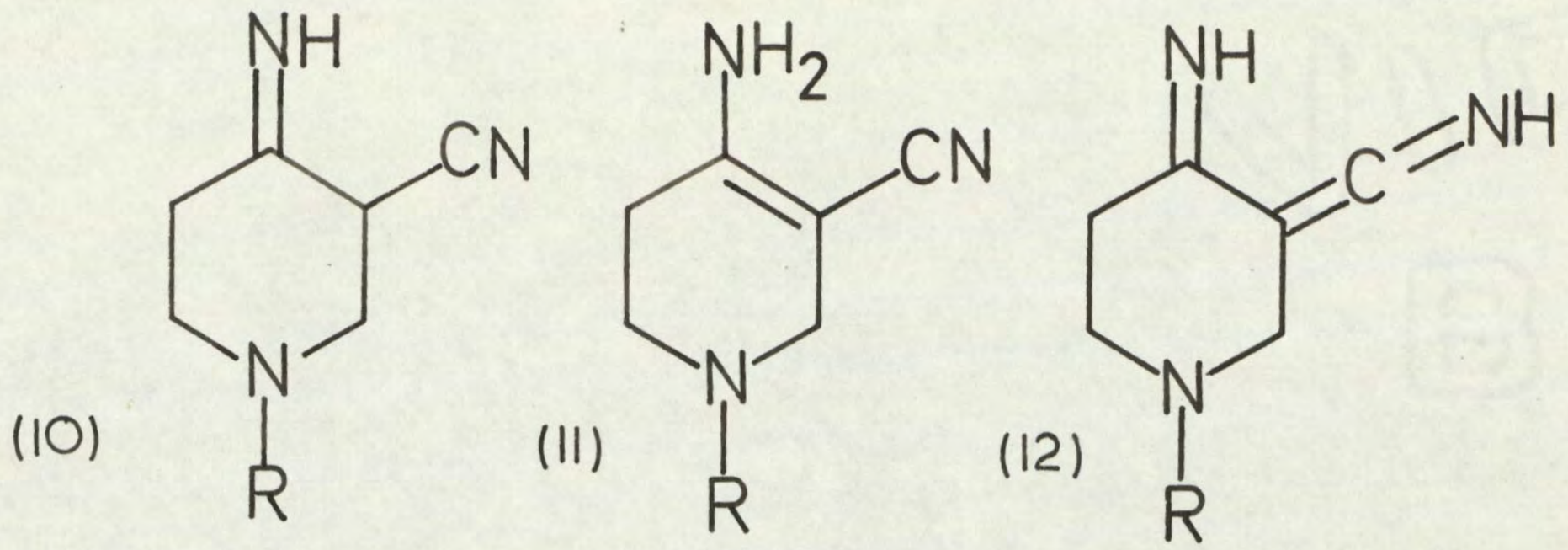
The infra-red spectrum of the compound showed the following peaks in Nujol: 3200 cm.$^{-1}$, 3300 cm.$^{-1}$, 3400 cm.$^{-1}$, 2190 cm.$^{-1}$, (C≡N); 1640 cm.$^{-1}$, 1620 cm.$^{-1}$, 700 cm.$^{-1}$, 760 cm.$^{-1}$ (C_6H_5).

The N.M.R. spectrum showed the following peaks: τ($CDCl_3$), 2.6 (S, 5H), 5.6 (S, 2H), 6.37 (S, 2H), 6.9 (S, 2H), 7.45 (T, 2H), 7.72 (T, 2H).

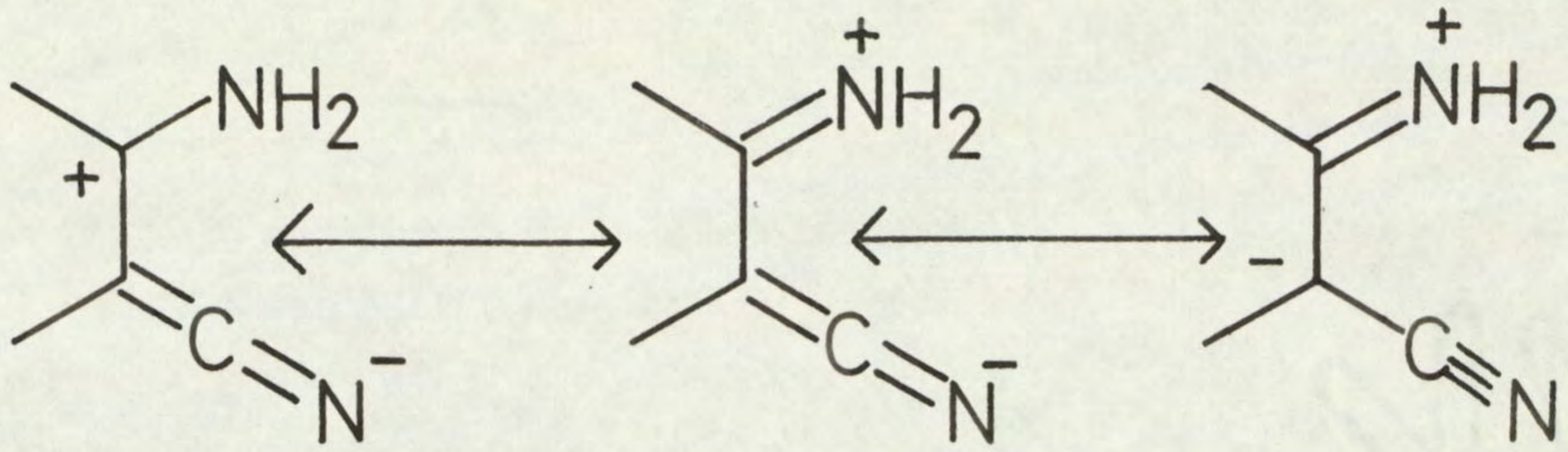
The ultra-violet spectrum of this compound had the following maxima: $\lambda_{max.}$ (EtOH), 264 mμ (11300); $\lambda_{max.}$ (HCl), 234 mμ (2480).

The physical data was not compatible with the structure being the 3-cyano-4-ketimine, as suggested by Cook and Reed. The system, however, can exist in the following three tautomeric forms; 10, 11 and 12.

The infra-red data obtained agreed with the enamine structure (11) instead of the expected ketimine (10). A



large number of enamines have been made previously and during the course of the present investigation, including three piperidine homologues (Cologne et al. 1963) (11, R=CH_3, C_2H_5, C_6H_5). In all of these compounds, it was found that they existed solely as the enamine (Baldwin, 1961), even for five-membered rings, where the imino-nitrile was expected to be the more favoured (Brown et al. 1954, Brown, 1957). In these compounds the C≡N peak occurs between 2165 $cm.^{-1}$ and 2198 $cm.^{-1}$, which corresponded to 2190 $cm.^{-1}$ found in the prepared compound. The low stretching frequency observed (Bellamy lists 2215 $cm.^{-1}$ and 2220 $cm.^{-1}$ as the lower limits for C≡N stretching frequencies) could be explained by the increased interaction between the p-electrons on the nitrogen atom and the π-electrons of the double bond and of the nitrile group, which allows charge-separated resonance forms to contribute to the ground state:



The appearance of more than one peak in the region 3100 $cm.^{-1}$ - 3500 $cm.^{-1}$ also suggested that the compound did not contain an imine group but had an amine group.

The N.M.R. spectrum was in agreement with the proposed enamine structure, showing two triplets due to the spin-coupling of the neighbouring methylene groups, a broad singlet of integral value two protons, due to $N\underline{H}_2$ and three singlets, which are attributed to $C_6\underline{H}_5$, $C_6H_5C\underline{H}_2$ and $NC\underline{H}_2C{=}C$.

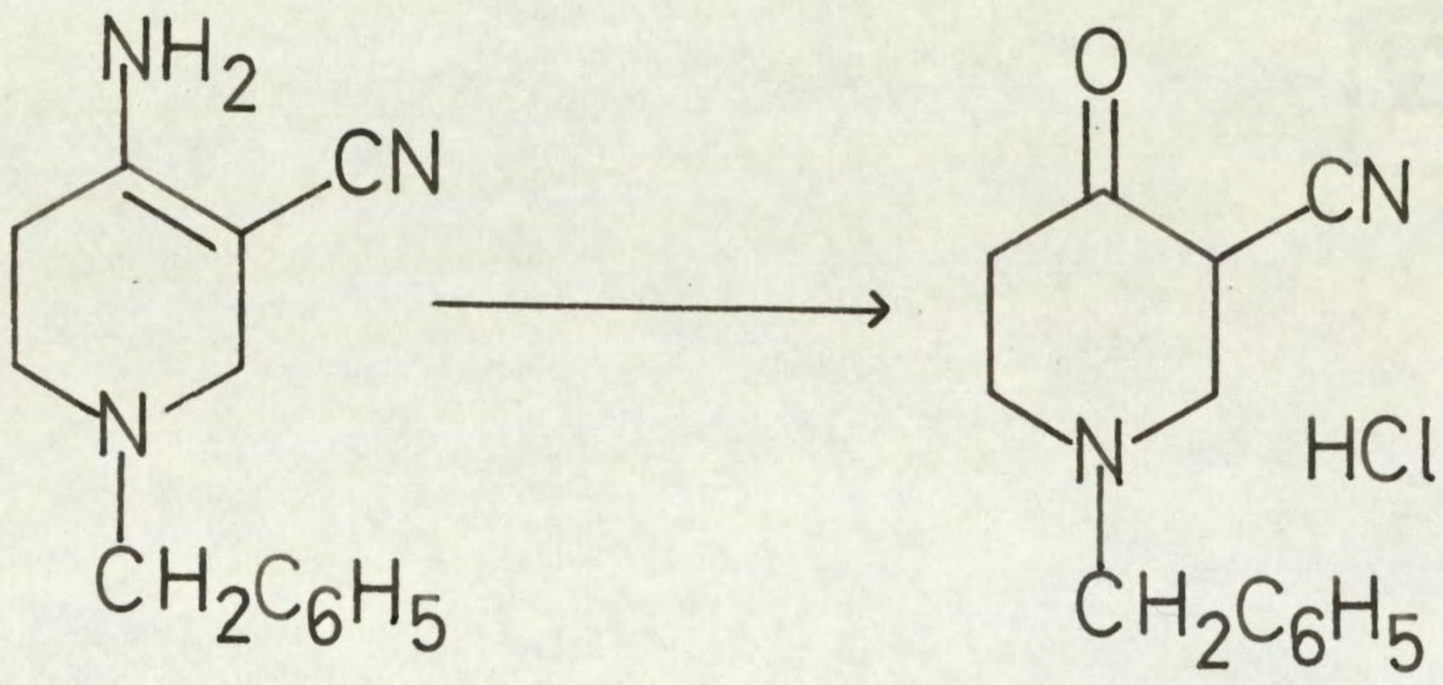
The ultra-violet spectrum of the compound, showing a peak at $\lambda_{max.}$ = 264 mμ (11300), suggested a conjugated system which could not be accounted for by the imino-nitrile structure, and was in agreement with other enamino-nitrile structures (Baldwin, 1961). Dissolving the enamine in dilute HCl reduced the intensity of the absorption and shifted the maximum to 234 mμ. This was due to the quaternisation of the amine group, preventing

the p-electrons on the nitrogen atom from taking part in the resonant structure.

The third tautomer (12) was not considered to be present in view of the fact that the C=C=N- group absorbs around 2045 $cm.^{-1}$ and no bands were observed in this region.

4-Amino-1-benzyl-3-cyano-1,2,5,6-tetrahydropyridine has since been reported (Taylor and Vromen, 1966, Aviram and Vromen, 1967) and was made by a similar method using potassium tert. butoxide as the condensing agent.

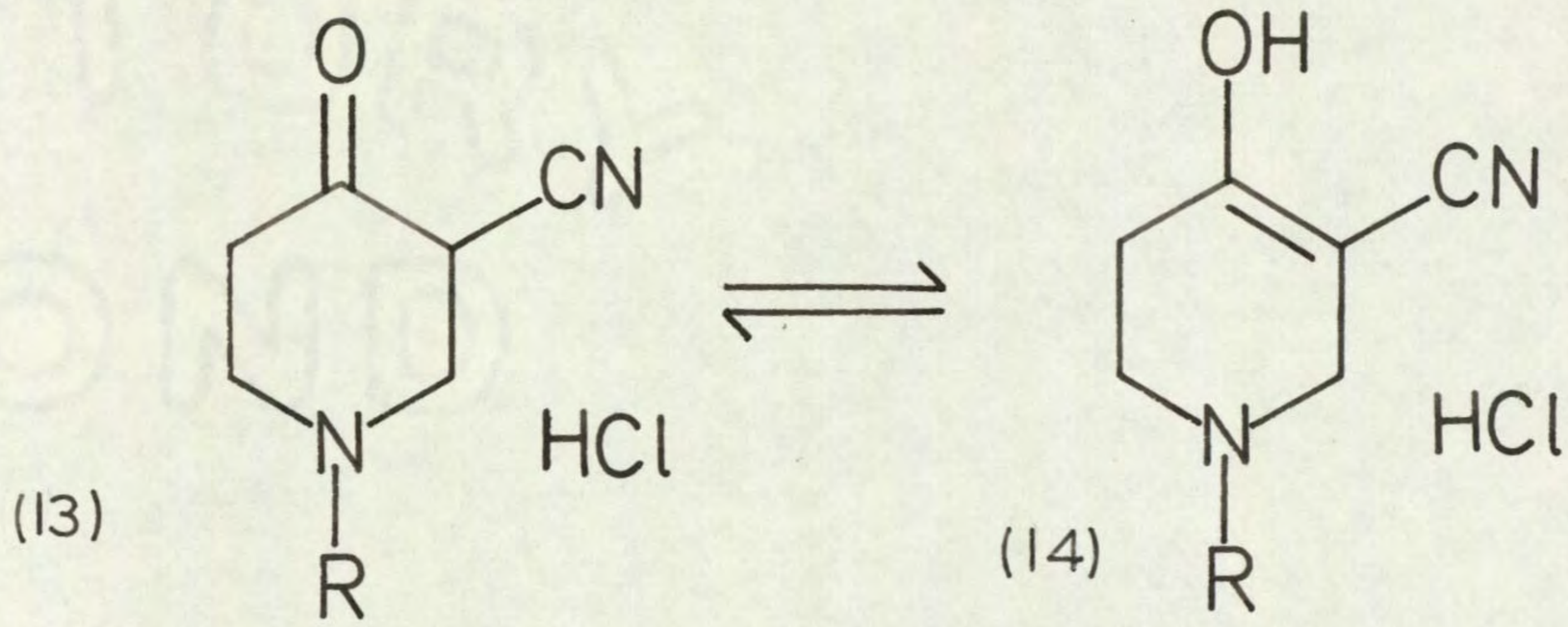
In the present investigation, the enamine was hydrolysed to the piperidone by warming with conc. HCl on a steam bath. On cooling, the hydrochloride



crystallised and was filtered. Ammonium chloride formed as a by-product was found difficult to remove.

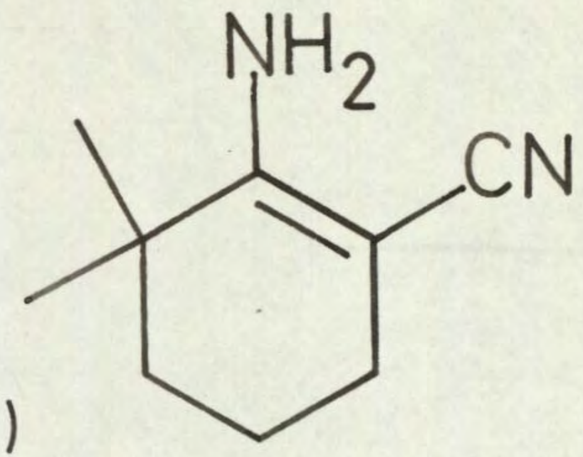
The infra-red spectrum of 1-benzyl-3-cyano-4-piperidone hydrochloride suggested that the compound was existing partly in the tautomeric enolic form (14) as well

as the expected ketonic form (13), since the band attributed to the ketone group appeared at 1650 cm.$^{-1}$ as

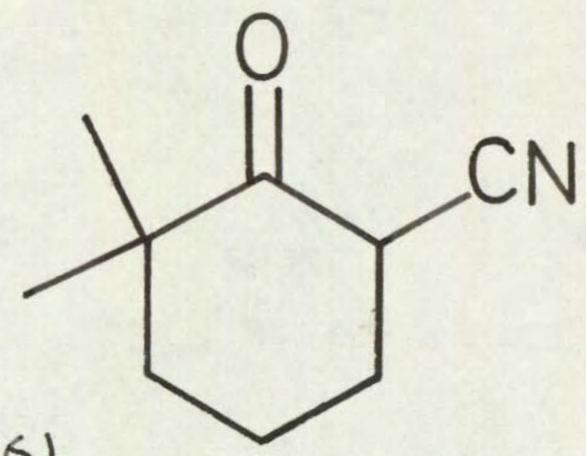


(13) ⇌ (14)

a very strong peak. This is rather low for an α - substituted carbonyl, since these absorb in the region 1680 cm.$^{-1}$ - 1700 cm.$^{-1}$ (Bellamy). There was also a broad band centred on 3000 cm.$^{-1}$, attributed to enolic OH stretch. The ultra-violet spectrum obtained tended to confirm the possibility of a proportion of enol form, having a maximum at $\lambda_{max.}$ = 241 mμ (4100), indicative of a conjugated double bond. In neutral or basic media, the compound exhibited a bathochromic shift of 22 mμ, having a maximum at 263 mμ (14000), which was due to the formation of the enolate anion. The spectra compared favourably with the cyclohexane derivatives (15) and (16), prepared by Kulp (1967) who quoted the following figures for the ultra-violet spectra: (15) 262 mμ (10900), (16) neutral 236 mμ (4800) basic 264 mμ (11800); c.f. (11) 264 mμ (11300), (13) neutral



(15)



(16)

241 mμ (4100) basic 263 mμ (14000).

Homologues of the cyano-piperidone generally exhibited the same enolisation, as shown by the main infra-red bands:

Compound	OH	CN	C=O	=C-OH
1-Benzyl	3000 cm.$^{-1}$	2205 cm.$^{-1}$	1650 cm.$^{-1}$	1220 cm.$^{-1}$ 1095 cm.$^{-1}$
1-Methyl	3000 cm.$^{-1}$	2220 cm.$^{-1}$	1645 cm.$^{-1}$	1220 cm.$^{-1}$ 1100 cm.$^{-1}$
1-Ethyl	3000 cm.$^{-1}$	2250 cm.$^{-1}$	1650 cm.$^{-1}$	1230 cm.$^{-1}$ 1105 cm.$^{-1}$
1-Phen-ethyl	3000 cm.$^{-1}$	2210 cm.$^{-1}$	1670 cm.$^{-1}$	1210 cm.$^{-1}$ -
1-Benzyl-5-methyl	3300 cm.$^{-1}$	2250 cm.$^{-1}$	-	1180 cm.$^{-1}$ -

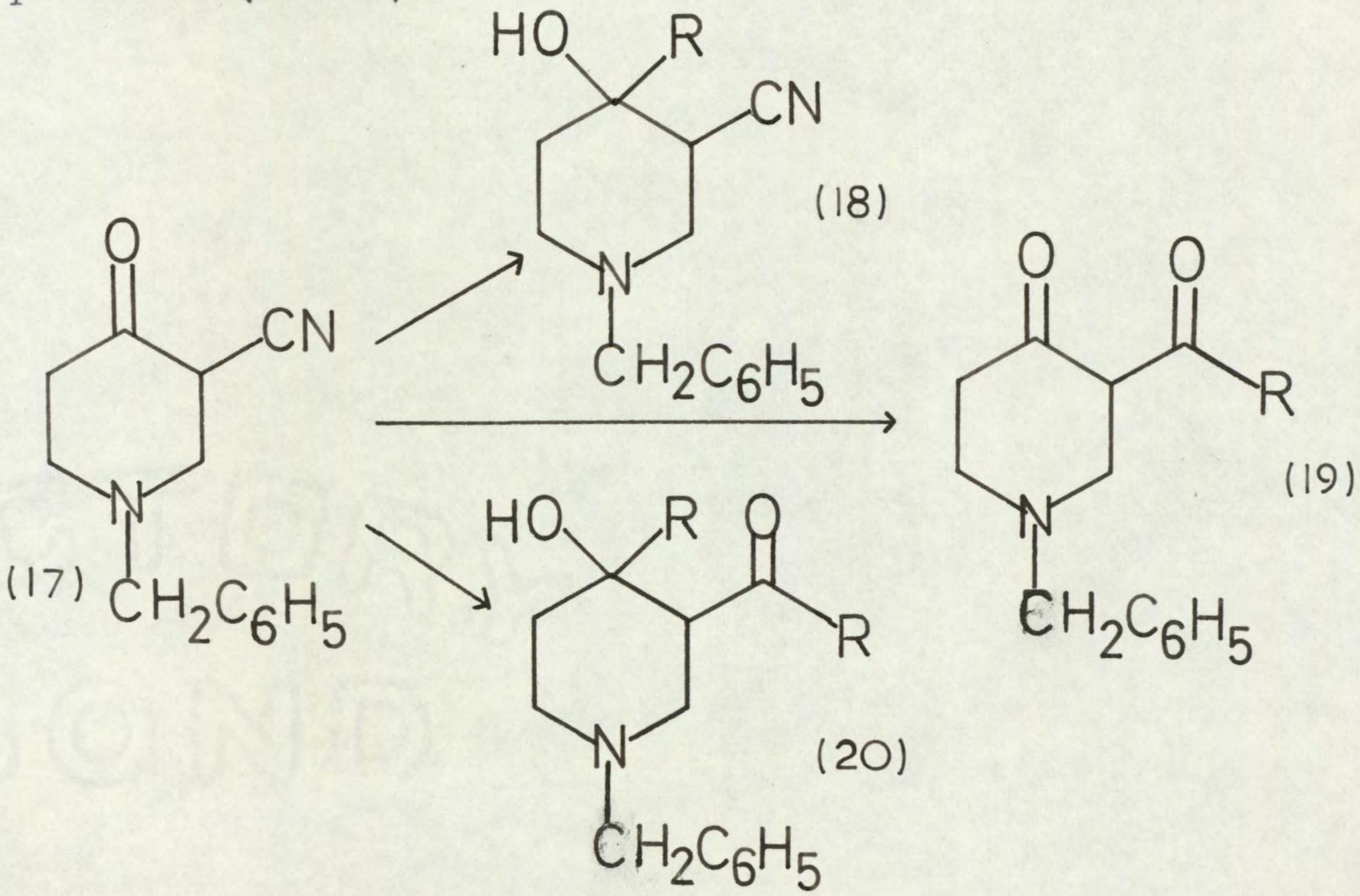
The 1-benzyl, 1-methyl and 1-ethyl compounds exhibited almost identical spectra. 1-Phenethyl-3-cyano-4-piperidone hydrochloride, however, did not conform, the carbonyl peak being shifted to a higher wave~~length~~ number, suggesting that the compound existed rather more as the ketone than the enol, as compared to the other three

compounds. The 5-methyl compound had an infra-red spectrum which suggested that this compound was in the completely enolised form, though the peak at 2250 cm.$^{-1}$, attributed to the nitrile, is higher than that expected for an unsaturated nitrile.

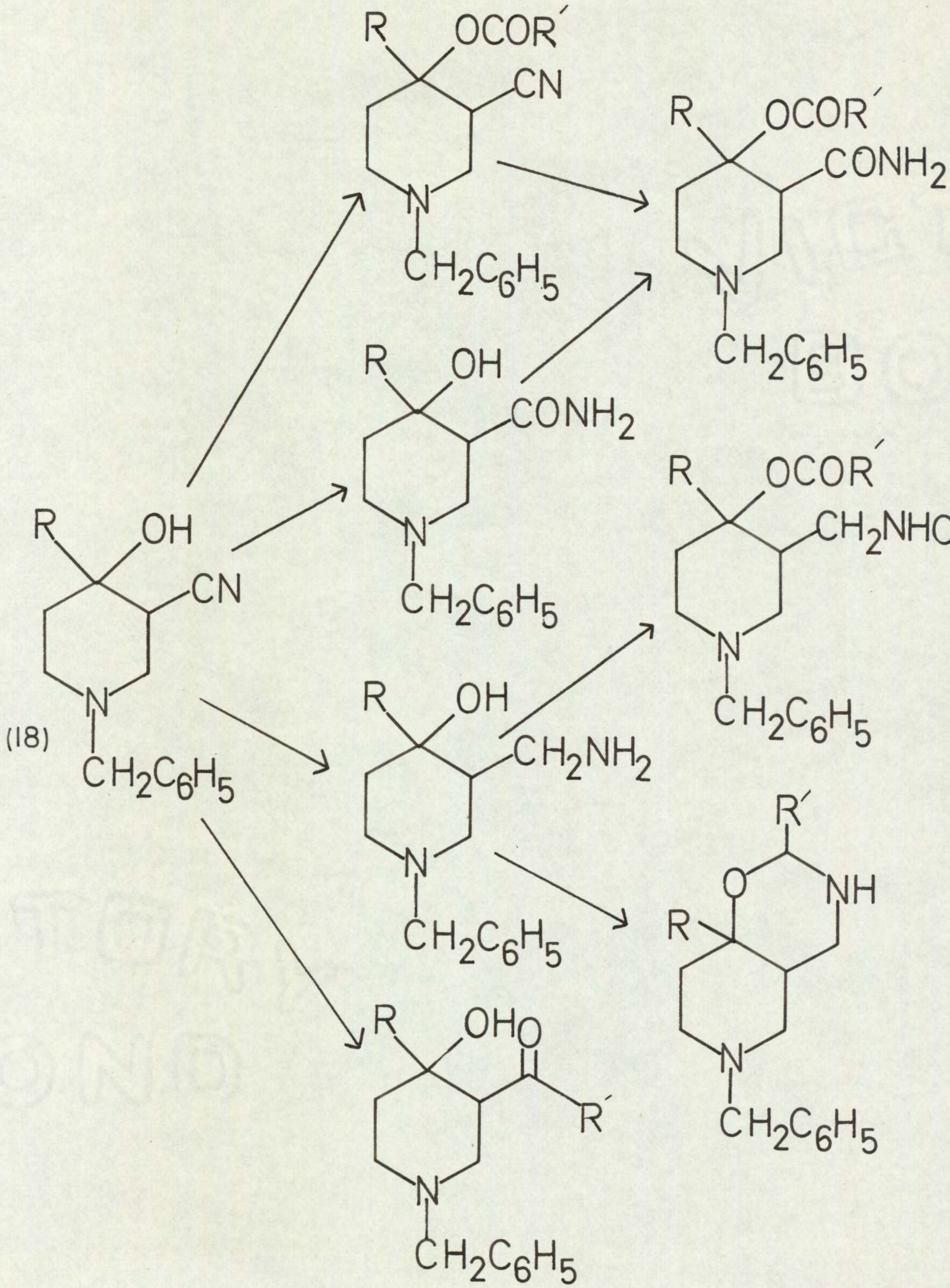
SOME REACTIONS WITH 1-BENZYL-3-CYANO-4-PIPERIDONE

A. Reaction with organometallic reagents. i Phenyl magnesium bromide

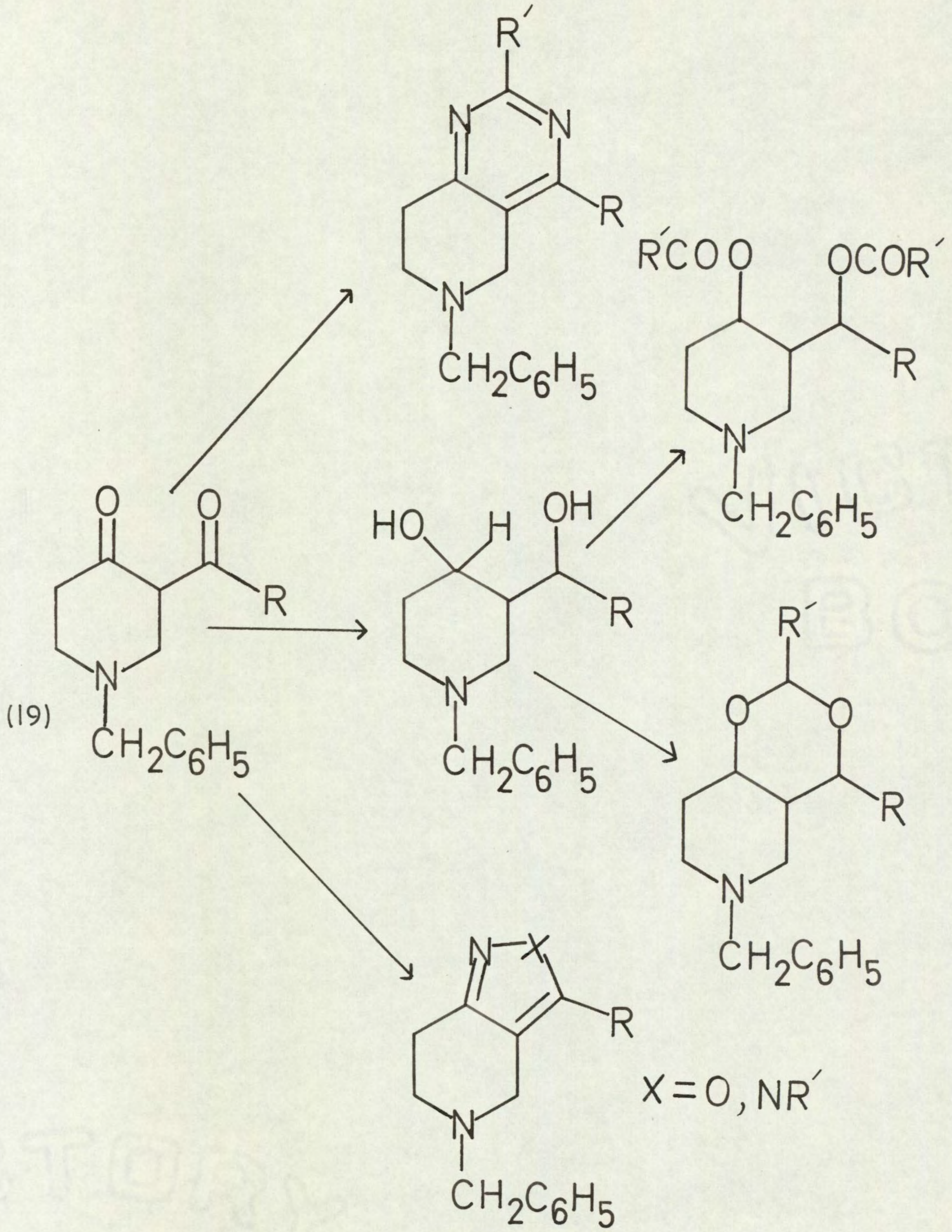
The reaction of 1-benzyl-3-cyano-4-piperidone hydrochloride (17) could possibly be expected to give, by reaction with organometallic reagents, one of three products (18-20):



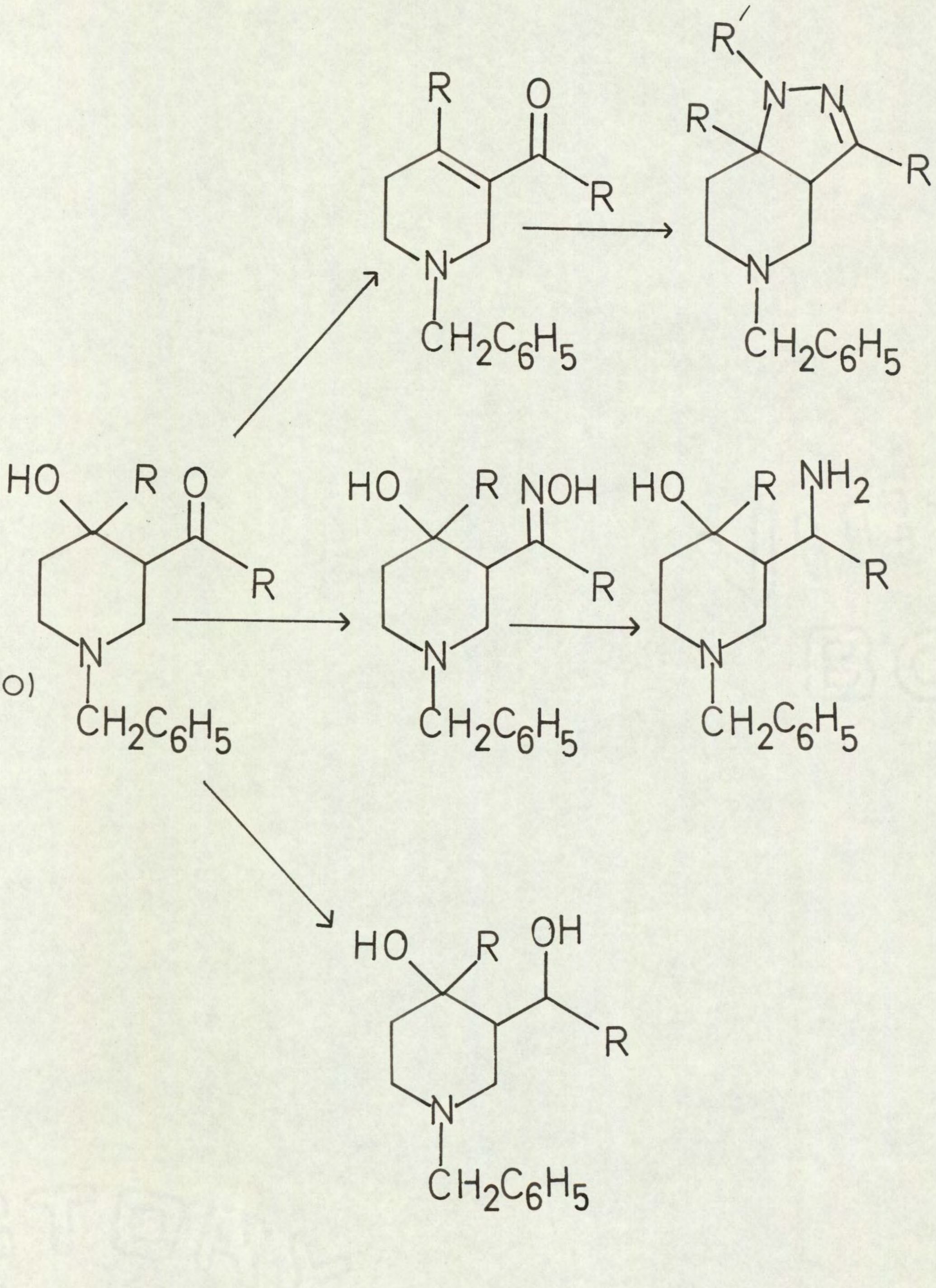
Flow Sheet II



Flow Sheet III

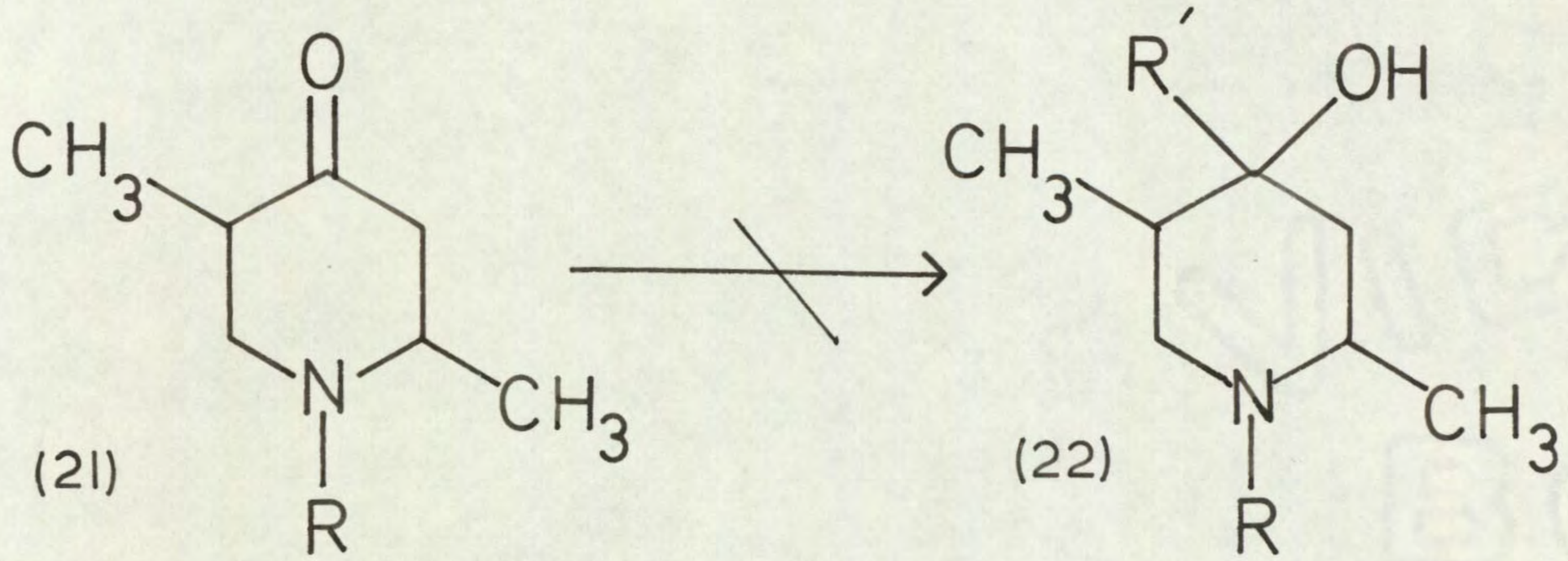


Flow Sheet IV



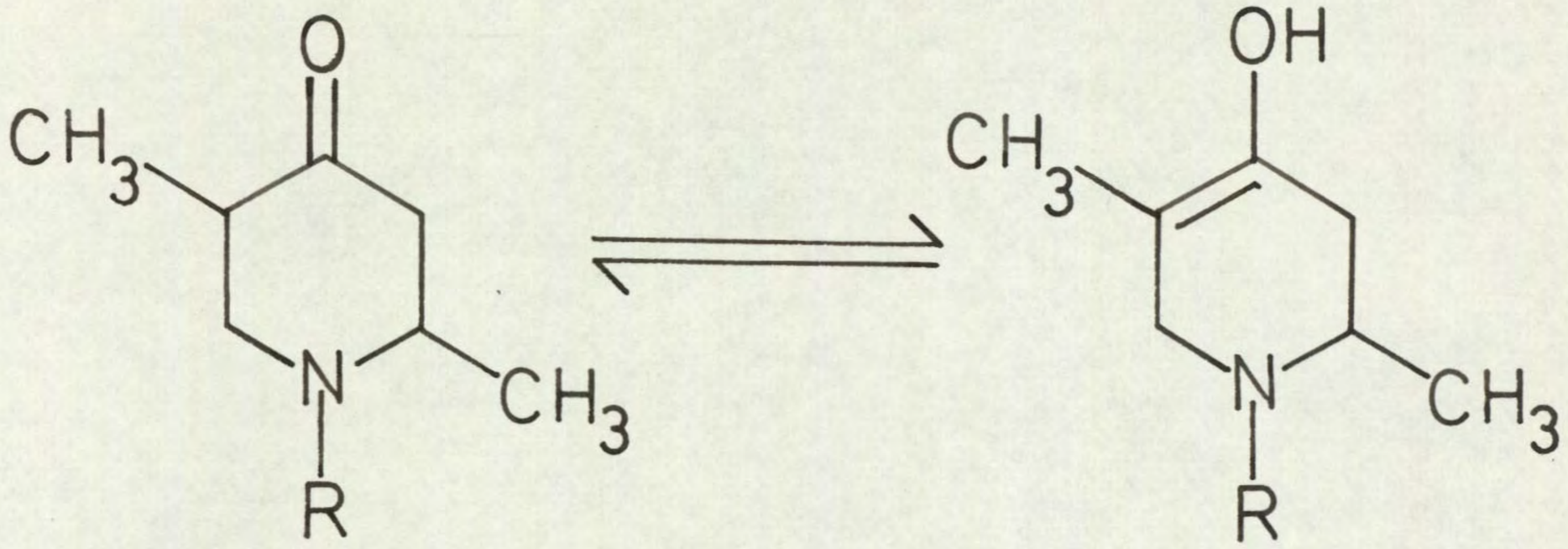
If only one mole of the organometallic reagent reacted, either the tertiary alcohol (18) or the diketone (19) might be obtained, the course of the reaction depending upon the relative rates of addition of the organometallic reagent to the reactive moieties. If these compounds were obtained, they could then be reacted further to give the compounds illustrated in flow sheets II and III. Excess organometallic reagent would be expected to yield the keto-alcohol (20), which might then take part in the reaction sequences shown in flow sheet IV.

Phenyllithium appeared to be the organometallic reagent of choice because Grignard reagents sometimes gave anomalous results. Nazarov (1956), for example, found that some 4-piperidones, such as (21) gave unchanged starting material when reactions with Grignard

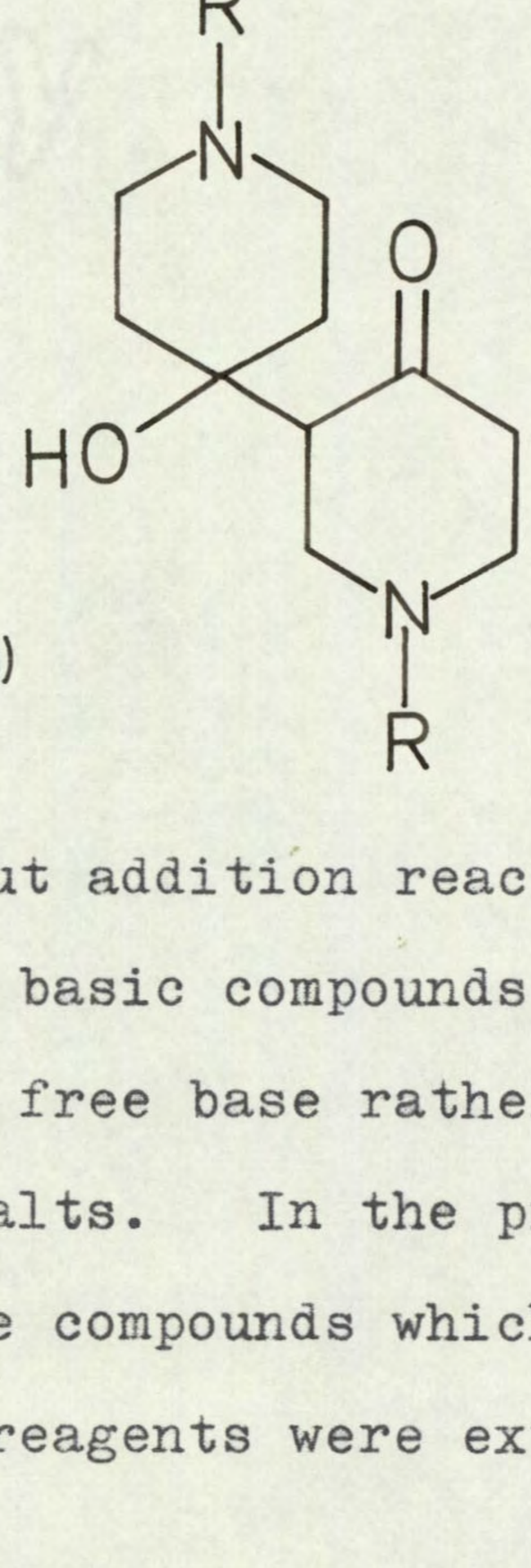


reagents were attempted. This was attributed to the facile enolisation of the 4-piperidone. Reaction with

phenyllithium however gave the corresponding 4-piperidinol (22). Berger et al. (1947) obtained compounds



of the type (23) via aldol-like condensations when 4-piperidones were reacted with Grignard reagents.



(23)

When carrying out addition reactions with organometallic reagents on basic compounds, it is generally advisable to use the free base rather than the hydrochlorides or other salts. In the present investigation, the free bases of the compounds which were to be reacted with organometallic reagents were extremely soluble

in water and consequently were very difficult to extract into an organic solvent even using continuous extraction methods. This resulted in a serious loss of material. To avoid this, the hydrochloride salts were used when reactions were attempted with organometallic reagents, an extra mole of the reagent being employed.

1-Benzyl-3-cyano-4-piperidone hydrochloride was reacted with phenyllithium and the reaction mixture worked up. A brown oil was obtained which failed to solidify and could not be crystallised. Attempts to make a hydrochloride salt also failed to yield a solid. Thin layer chromatography on the free bases indicated the presence of six separate spots, one of which could be correlated with starting material. An infra-red spectrum showed peaks attributed to OH, C≡N and C=O, which suggested that the reaction was incomplete. A second attempt using phenyllithium and a longer reaction time merely reduced the amount of unreacted starting material.

While it is generally recognised that phenyllithium is a more reactive and specific reagent for keto groups than the corresponding Grignard reagent, it was considered that in the present instance the greater bulk of the Grignard reagent offered an advantage in that the size factor alone may prevent the reaction with both functional groups. In the event, a two-fold excess of

Grignard reagent was used in the hope that this would enable all of the cyano-ketone to react. Decomposition of the reaction mixture with ammonium chloride facilitated extraction of the free bases and gave a solid in good yield. This compound exhibited the following spectra:

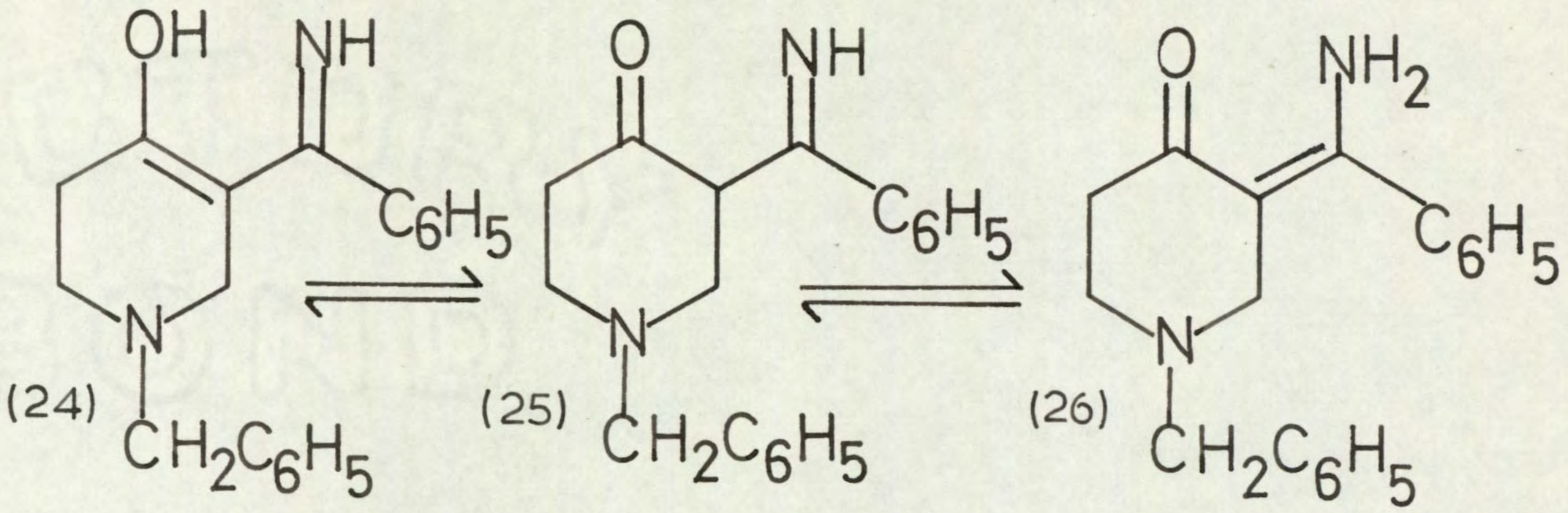
Infra-red: $\nu_{max.}$ ($CHCl_3$), 3450 cm.$^{-1}$, 1605 cm.$^{-1}$, 1570 cm.$^{-1}$, 1280 cm.$^{-1}$, 1140 cm.$^{-1}$.

Ultra-violet: $\lambda_{max.}$ (EtOH), 317 mμ (14800), 250 mμ (13500).

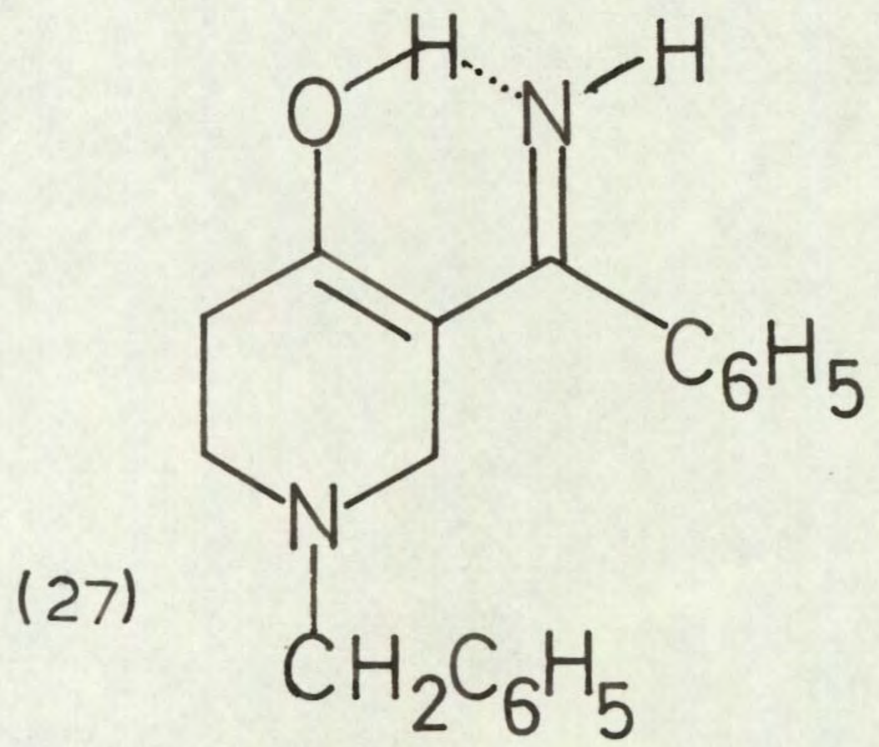
N.M.R.: τ($CDCl_3$), 2.5 (S, 5H, $C_6\underline{H}_5$), 2.6 (S, 5H, $C_6\underline{H}_5$), 6.48 (S, 2H), 6.85 (S, 2H), 7.4 (M, 4H), 4.5 (S, H), - 0.8 (S, H). The latter two peaks disappeared on shaking the $CDCl_3$ solution with D_2O.

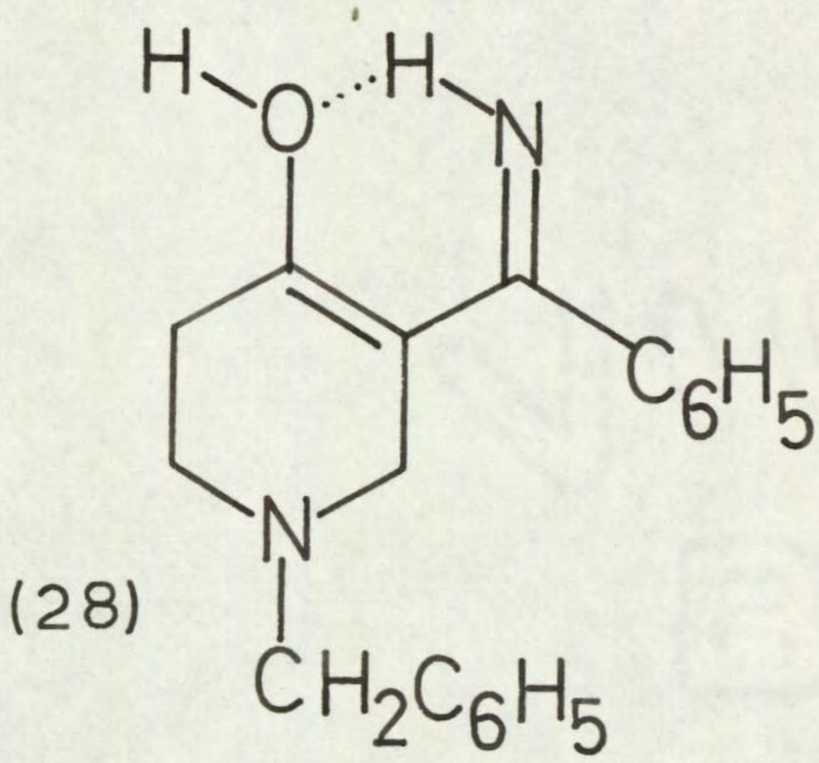
An analysis corresponded to an empirical formula of $C_{19}H_{20}N_2O$, and a mass spectrum gave a molecular weight of 292.

A compound which fitted the evidence was 1-benzyl-1,2,5,6-tetrahydro-4-hydroxy-3-phenylimino-pyridine (24) which is the enolic form of 1-benzyl-3-phenylimino-4-piperidone (25). The N.M.R. spectrum suggested (24) rather than (25), since the peak at τ = -0.8 could be assigned to the enolic O$\underline{H}$ and the peak at τ = 4.5 to N$\underline{H}$. This spectrum also eliminated the possibility of the third tautomeric form (26). The infra-red spectrum

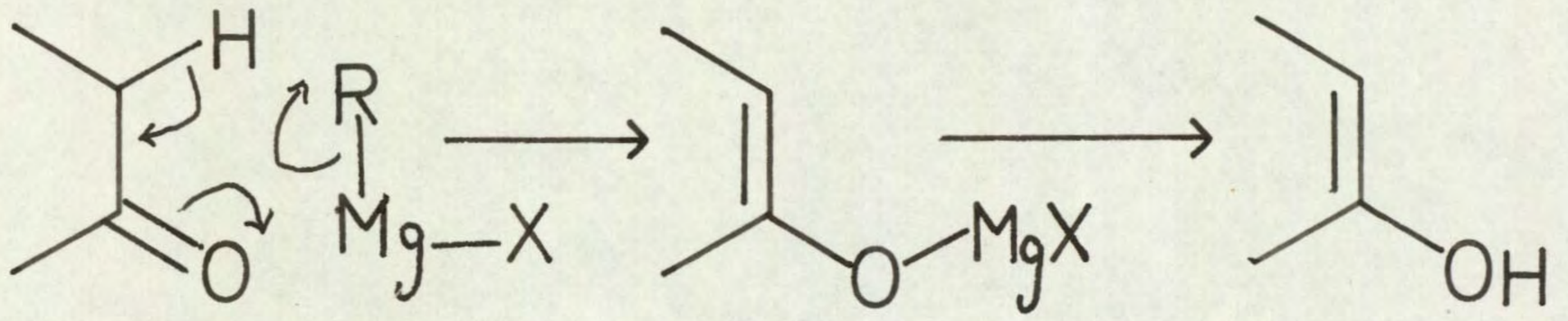


suggested that there was intra-molecular hydrogen bonding, since dilution of the chloroform solution did not shift the OH peak from a broad band at 3200 $cm.^{-1}$. The molecule was probably in the form (27) rather than (28).

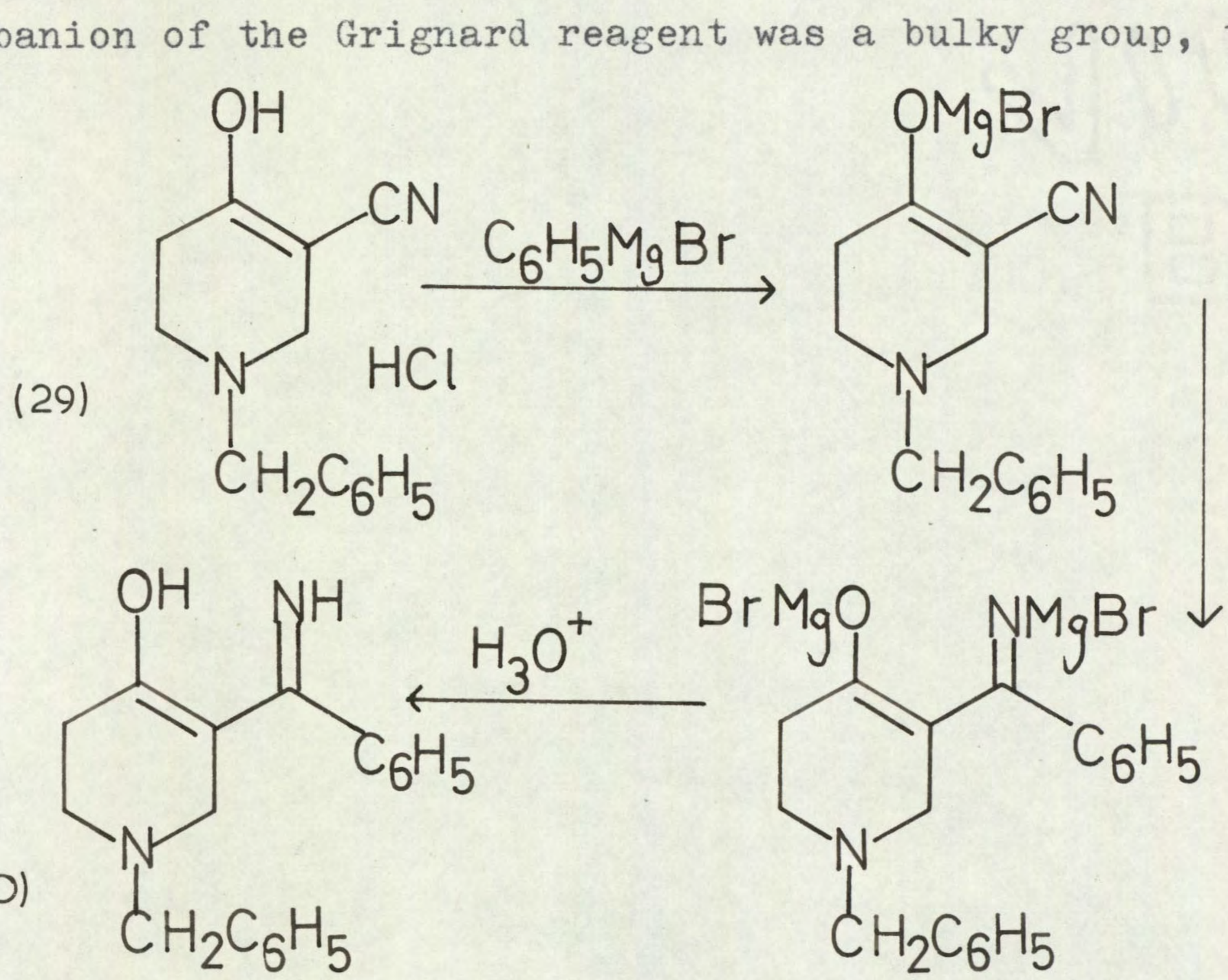




One of the less normal reactions of Grignard reagents with carbonyls is the formation of an enol salt. If the R group of the Grignard reagent is bulky, and there is an *a* proton on the carbonyl compound, enolisation can compete successfully with addition reaction, giving the magnesium halide salt of the enol.

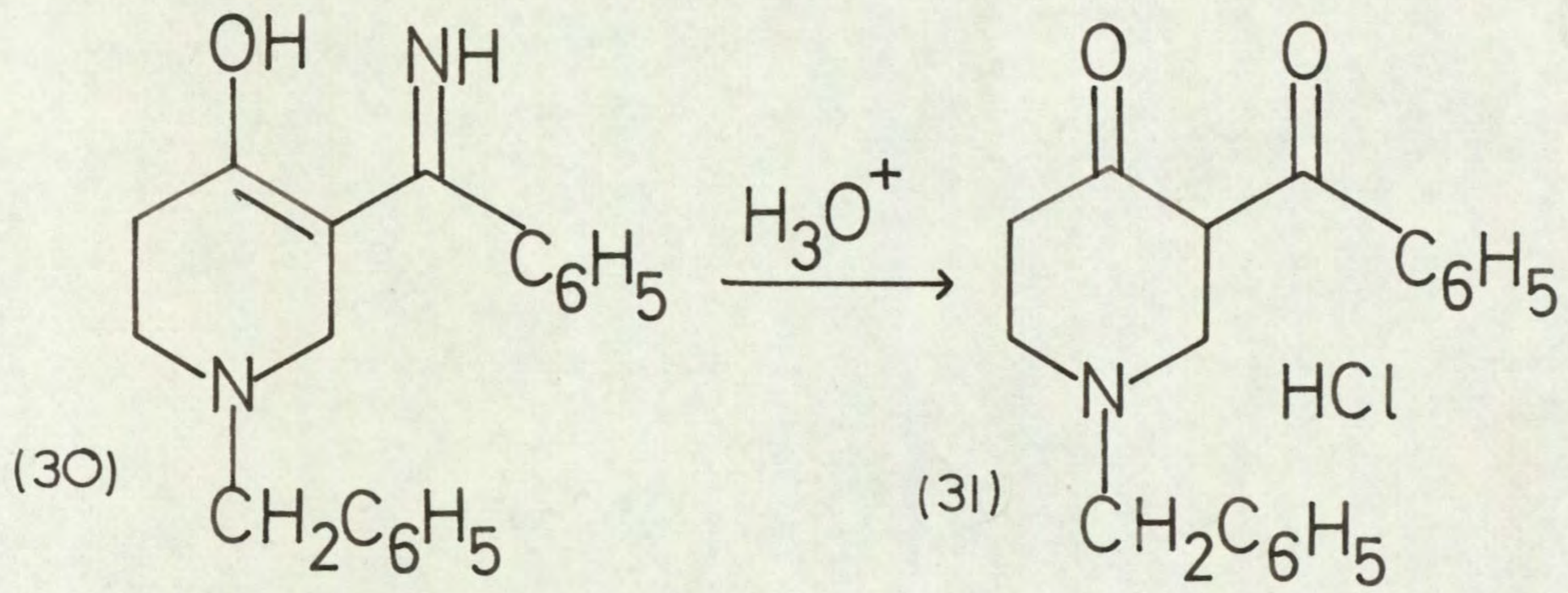


It had previously been demonstrated that the starting cyano-ketone existed partly in the enolic form (29). Since there was an α proton and the carbanion of the Grignard reagent was a bulky group, the



first stage in the reaction between phenyl magnesium bromide and the cyano-ketone was most likely to be the formation of the metal enolate, followed by attack on the nitrile, forming the imino-enol di-metal salt, which on

mild hydrolysis merely gave the imine instead of the ketone. As further proof of the structure, the imino-enol (30) was hydrolysed in conc. HCl, forming a β-diketone (31). The infra-red spectrum of the hydrolysed product showed two carbonyl peaks, 1690 cm.$^{-1}$ and



(30) (31)

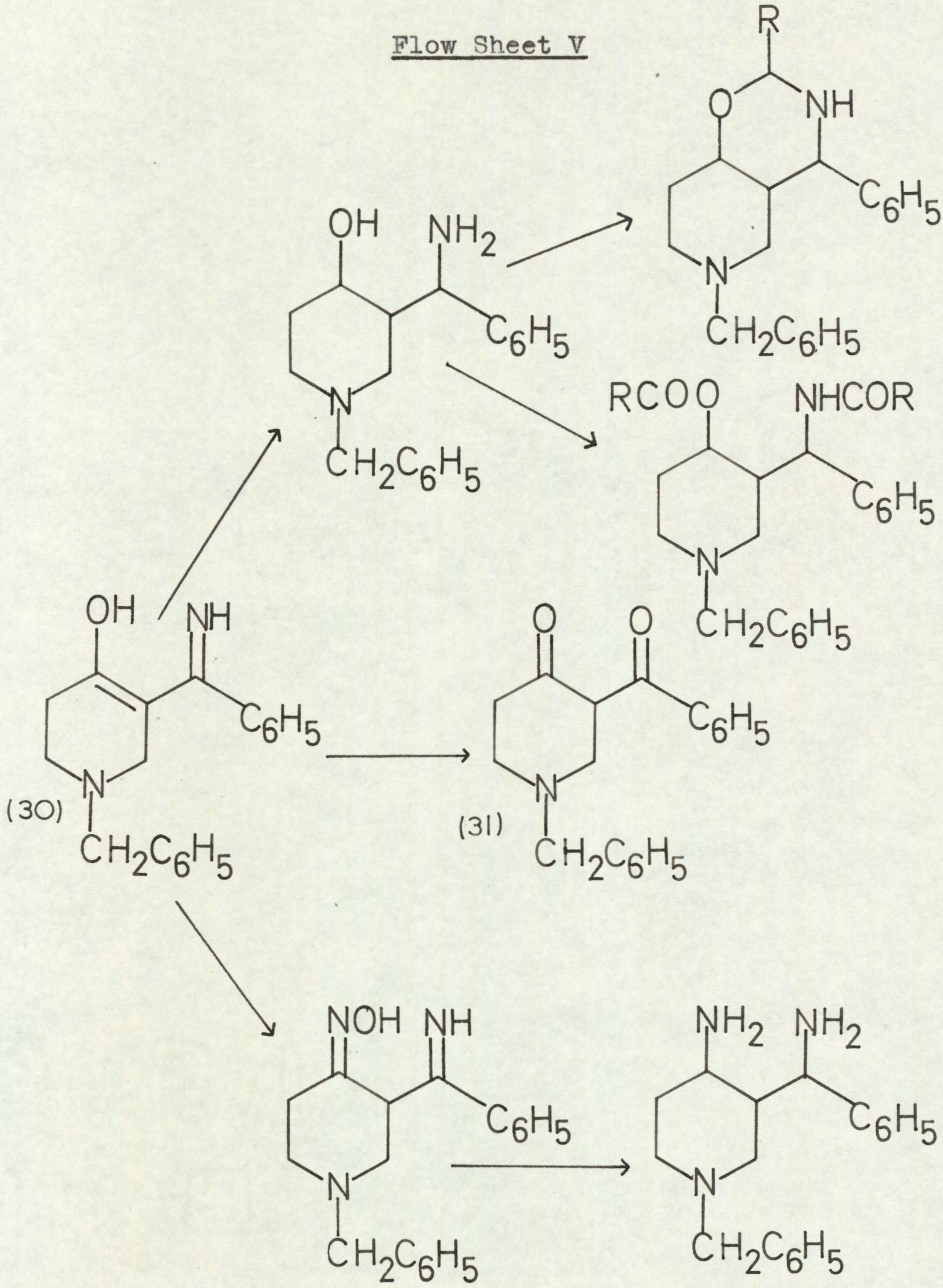
1720 cm.$^{-1}$, two mono-substituted benzene rings and a lack of peaks at 3200 cm.$^{-1}$ - 3400 cm.$^{-1}$ attributable to OH or NH.

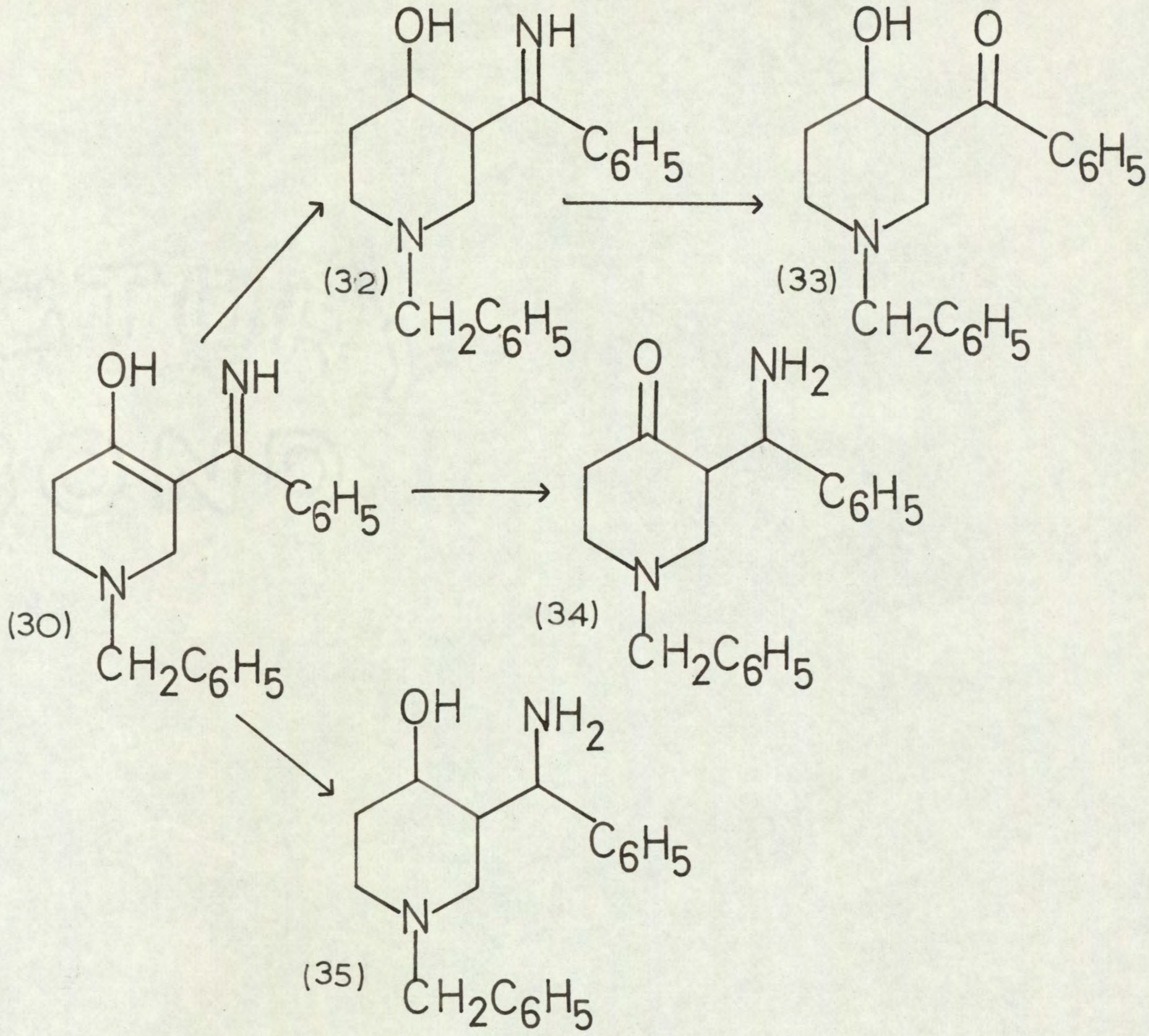
Having obtained the imino-enol, several reactions at first sight appeared possible, as illustrated in flow sheet V.

Reduction of 1-benzyl-1,2,5,6-tetrahydro-4-hydroxy 3-phenylimino-pyridine

It was thought that an attempt at reducing 1-benzyl-1,2,5,6-tetrahydro-4-hydroxy-3-phenylimino-pyridine might be of interest since at least three products were possible. Partial reduction might have been expected to yield the imino-alcohol (32) which might be expected to

Flow Sheet V

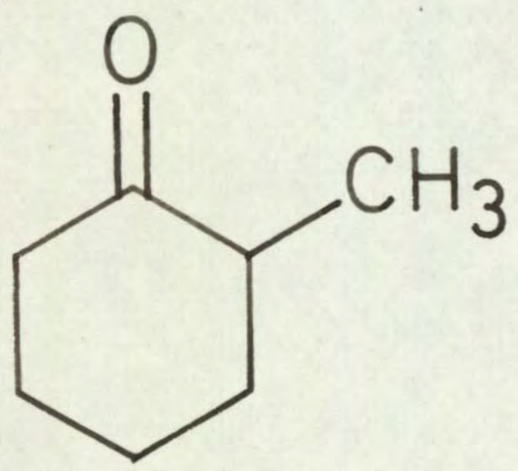

OH
NH2
C6H5
N
CH2C6H5
R
O
NH
C6H5
N
CH2C6H5
RCOO
NHCOR
C6H5
N
CH2C6H5
OH
NH
C6H5
N
CH2C6H5
(30)
O
O
C6H5
N
CH2C6H5
(31)
NOH
NH
C6H5
N
CH2C6H5
NH2
NH2
C6H5
N
CH2C6H5



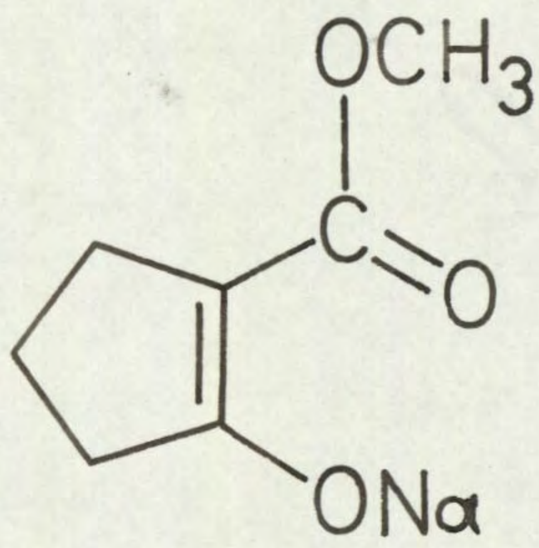
hydrolyse to the keto-alcohol (33). Alternatively, the amino-ketone (34) might have resulted, whereas complete reduction might be expected to yield the amino-alcohol (35).

Reduction of enols with complex metal hydrides, in particular lithium aluminium hydride, tends to give low yields, due to the intermediate formation of a lithium

aluminium enolate (Gaylord), which on hydrolysis regenerates the original functional group. Dreiding and Hartman (1953), for example, found that $LiAlH_4$ reduction of the sodium enolate of 2-methyl<u>cyclo</u>-hexanone (36) gave the starting material in almost quantitative yield, though the sodium enolate of

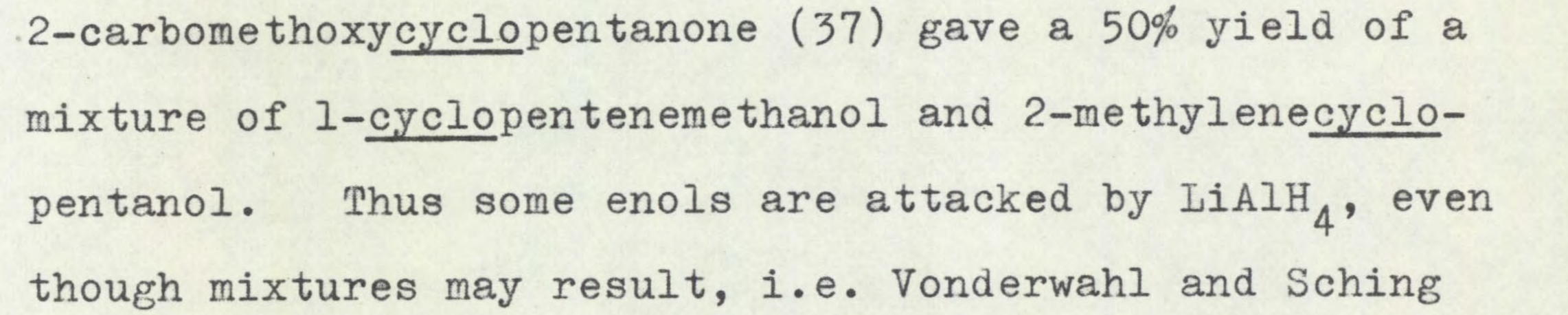


(36)



(37)

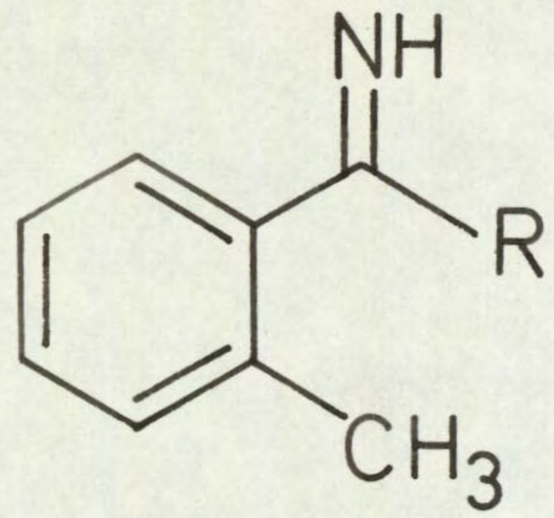
2-carbomethoxy<u>cyclo</u>pentanone (37) gave a 50% yield of a mixture of 1-<u>cyclo</u>pentenemethanol and 2-methylene<u>cyclo</u>-pentanol. Thus some enols are attacked by $LiAlH_4$, even though mixtures may result, i.e. Vonderwahl and Sching (1952) reported that the $LiAlH_4$ reduction of 1,1,5,5-tetramethyl-4-hydroxymethyl-<u>cyclo</u>hexan-3-one (38) gave a 49% yield of a mixture of three products:



(38)

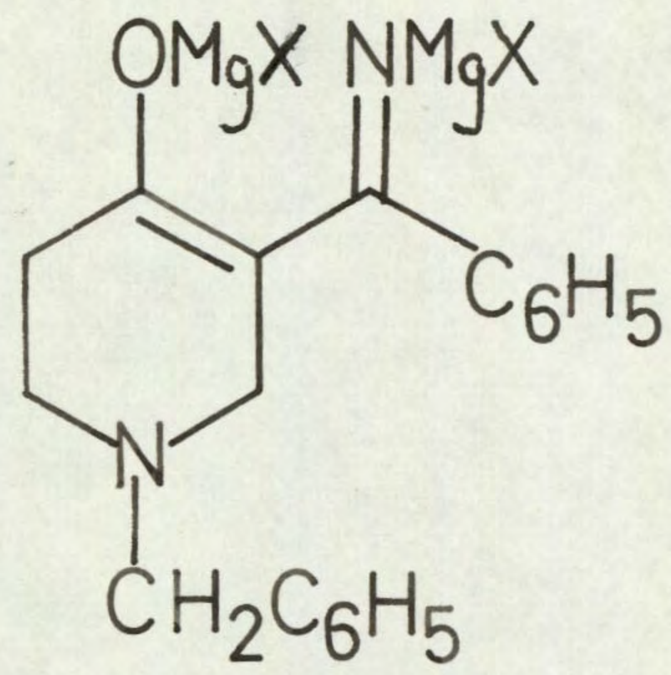
In view of the low yields and mixed products

obtained by previous workers, it was decided to attempt, in the first instance, catalytic hydrogenation. Imines had been successfully reduced over platinum metal catalysts such as palladium and platinum (Rylander, 1967) in neutral, acidic and basic media. Though reductions could be carried out in acidic media, in the present investigation no attempt was made at reduction of the imino-enol in acidic media in order to avoid the possible hydrolysis of the imine to the ketone. Platinum oxide in ethanol was the catalyst of choice since palladium on charcoal might have debenzylated the compound, while Raney nickel catalysts tend to give none of the desired amine (Campbell et al. 1944). However, attempts to hydrogenate the imino-enol using platinum oxide in ethanol failed, starting material being recovered, no uptake of hydrogen being observed after 24 hours. Steric hindrance probably played a large part in preventing the reaction, since Pickard and Jenkins (1953) found that the relative rates of catalytic hydrogenation of o-tolylimines (39) decreased as the substituent size increased, being very small when the group was sec. butyl. Palladium on carbon (5%) was used in the hope that this would be successful, although side reactions were expected, especially the debenzylation of either the reduced or the non-reduced compounds

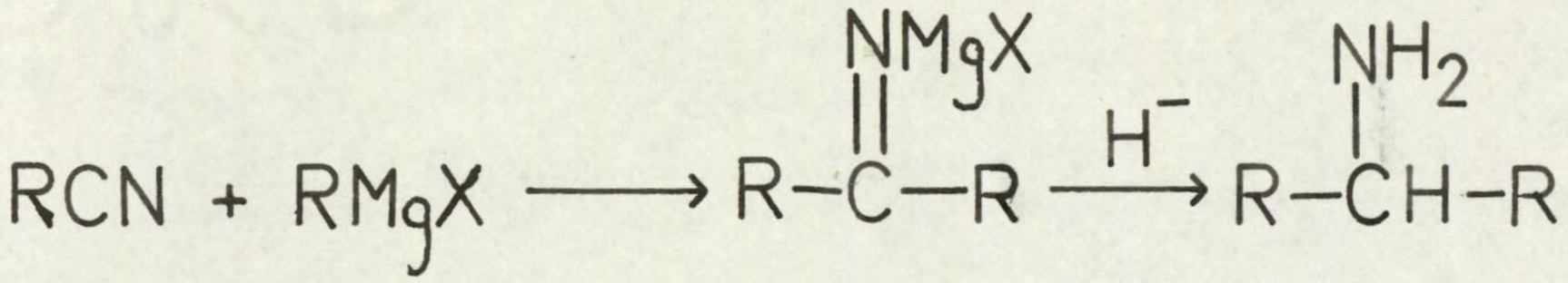
(39) 

(Hartung and Simenoff, 1953). Work-up of the reaction gave a pale green oil which would not crystallise. Thin layer chromatography of this oil showed the presence of five spots, one of which compared with the starting material. In view of this, catalytic reduction was abandoned.

A possible route to reduction of the imino-enol could have been the $LiAlH_4$ reduction of the Grignard complex formed from the cyano-ketone (40), since Pohland and Sullivan (1953) successfully reduced the complex

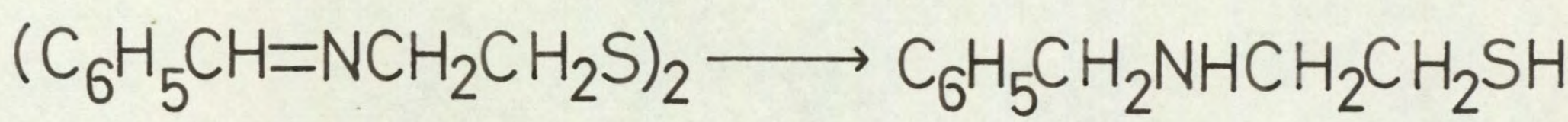
(40) 

magnesium salts derived from the reaction of various nitriles with Grignard reagents:

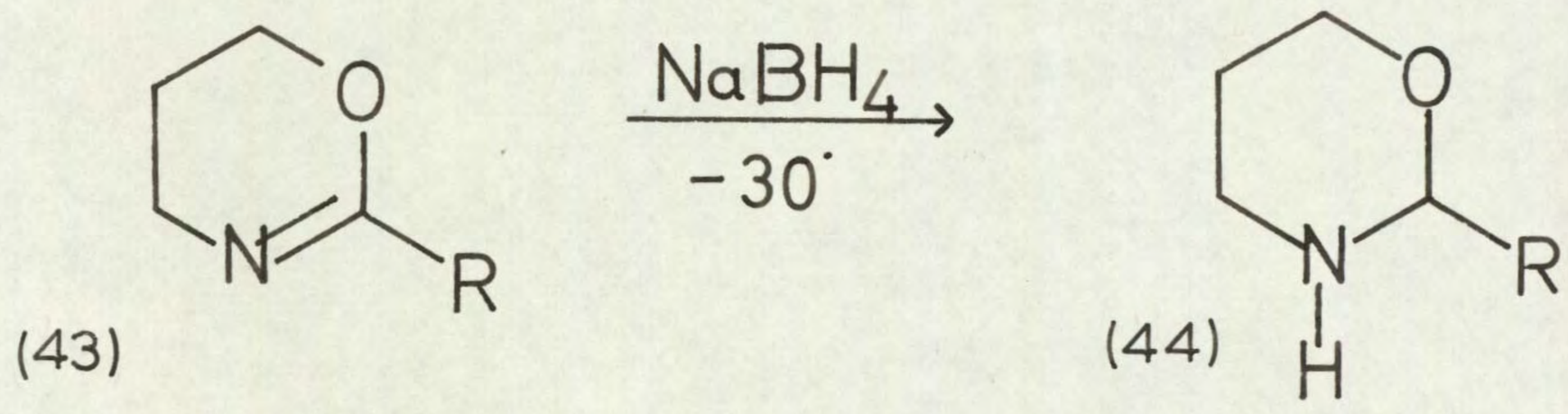


The experiment was not attempted, however, in view of the fact that a metal enolate was also formed, which may not have reduced, and because the side products possibly formed, both in the course of the Grignard reaction and in the following reduction, might have made isolation of the desired products difficult.

Imines have been reduced with sodium borohydride in ethanol, methanol or water. Johnston and Gallagher (1962), for example, reduced the disulphide (41) with $NaBH_4$ to give an amino-thiol (42). Reduction of the



(41) (42)

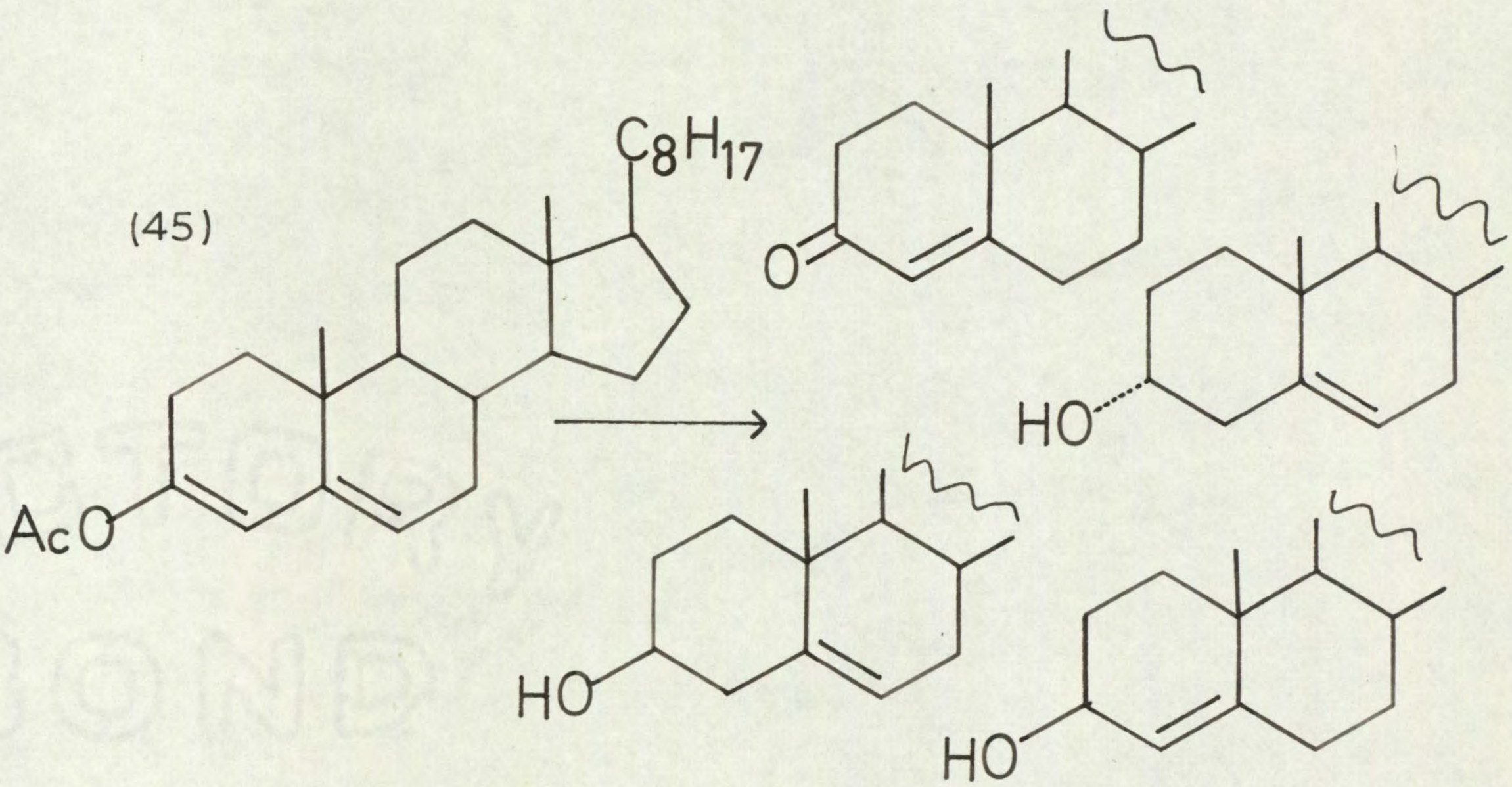


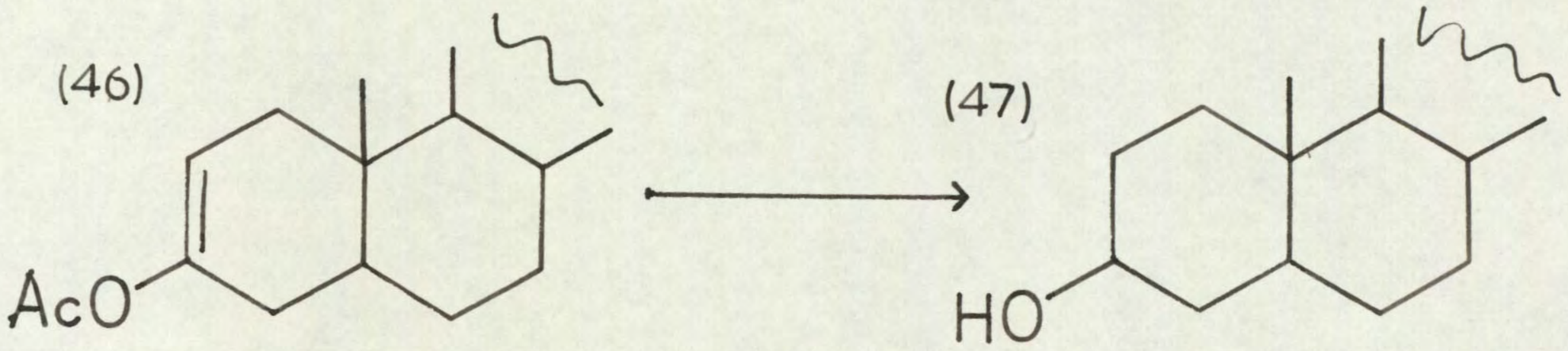
(43) (44)

carbon-nitrogen double-bond in dihydro-oxazines (43), giving the tetrahydro-oxazines (44) has been achieved

using $NaBH_4$ at a low temperature (Meyers and Nabeya, 1967).

Enol esters have been reduced with $NaBH_4$, though many mixed products were obtained. Dauben and Eastham (1950, 1951) reduced the enol acetate of 4-cholestene-3-one (45) with both $LiAlH_4$ and $NaBH_4$ under a variety of conditions to give various products.



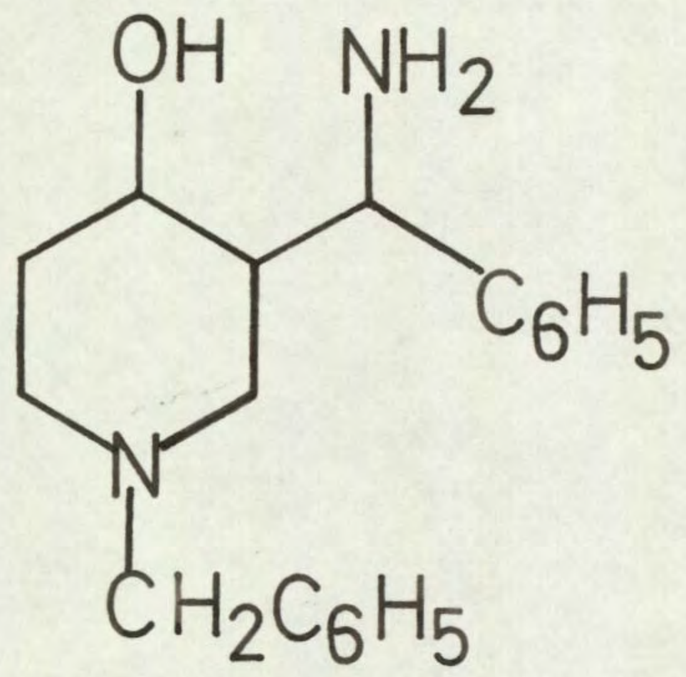


However, sodium borohydride reduction of 3-acetoxy-2-cholestene (46) gave one isomer of cholestanol (47) in good yield (Dauben et al. 1952).

In view of these results, reduction with sodium

borohydride in ethanol seemed to merit some attention. Since 1-benzyl-1,2,5,6-tetrahydro-4-hydroxy-3-phenyl-imino-pyridine was only slightly soluble in cold ethanol, reduction in hot ethanol was tried, although $NaBH_4$ reacts with hot ethanol to some extent (Gaylord). The first trial run using $NaBH_4$ in ethanol yielded a pale green oil with an equivalent weight of 151. The infra-red spectrum suggested that the amino-alcohol was obtained, but attempts to crystallise the compound or to form a solid hydrochloride failed. A second attempt, but evaporating the solvent in vacuo, gave a 50% yield of needle crystals of 1-benzyl-3-α-phenylaminomethyl-4-piperidinol (48), which was subsequently proved to be a single isomer and was designated isomer A. The other isomer, designated B, was obtained in 20% yield on further evaporation of the solvent. A detailed

(48)



consideration of the configuration and conformation of these alcohols will be presented later.

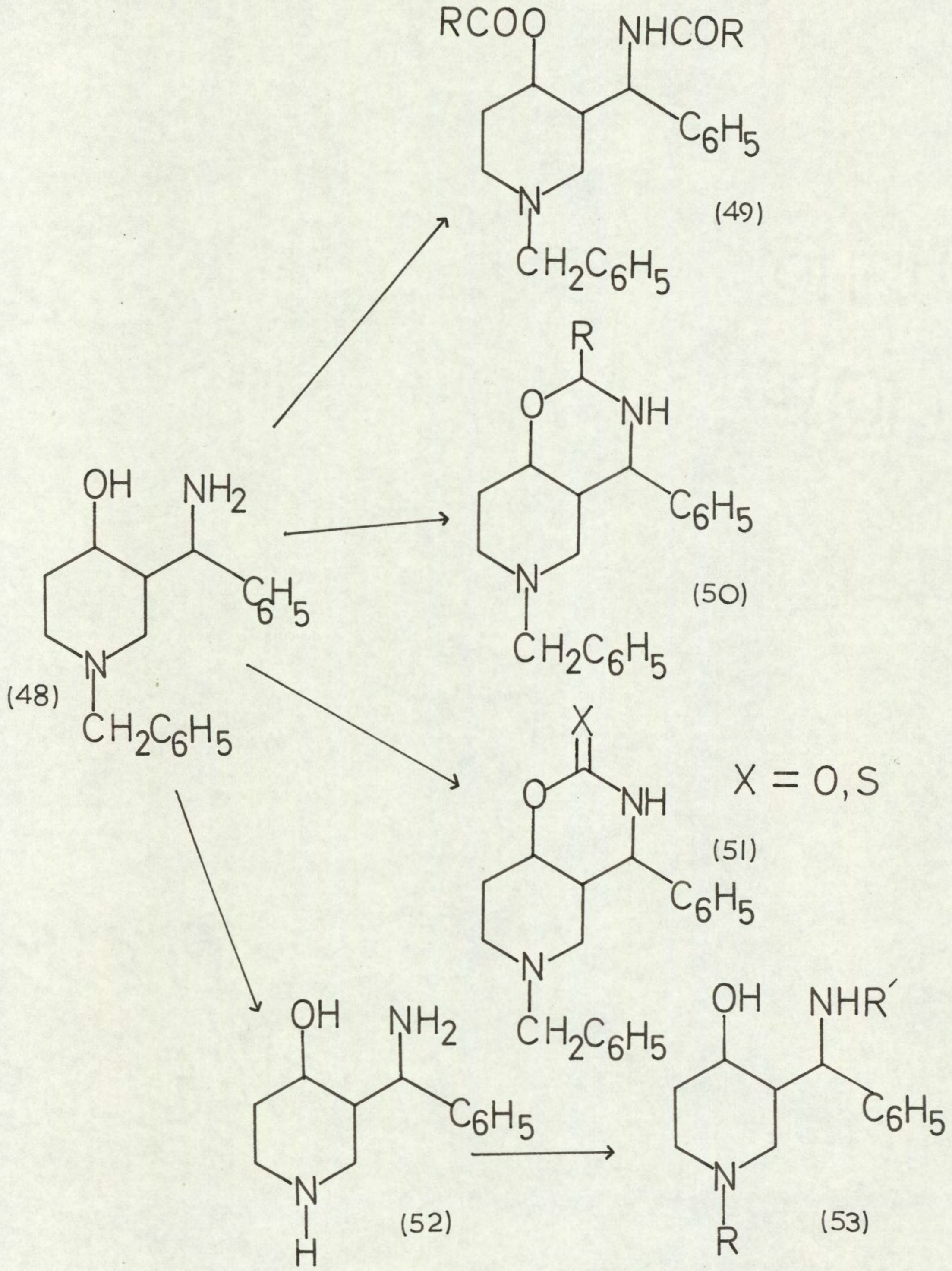
Reactions of the amino alcohol

The 1-benzyl-3-α-phenylaminomethyl-4-piperidinols (48) could be reacted further as illustrated in flow sheet VI.

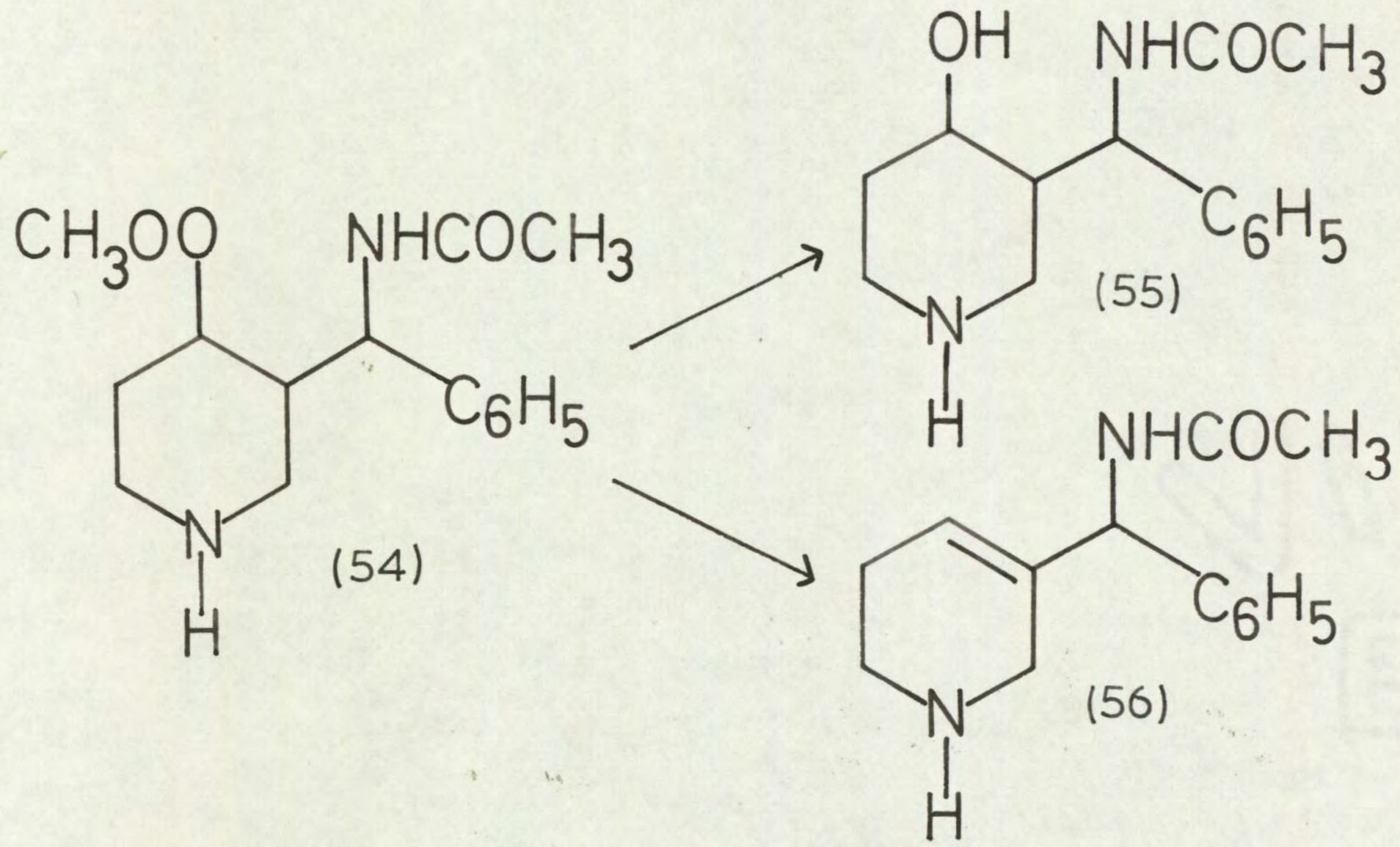
Reaction of the amino-alcohol (48) with anhydrides in pyridine (Kirk, 1958) could possibly be expected to give the di-substituted products, e.g. the amido esters (49). Azeotropic distillation with an aldehyde or ketone might yield the oxazines (50), or reaction with carbon disulphide or phosgene to give the oxazolone (51) was possible. Finally, the amino alcohol afforded the possibility of being debenzylated to give the secondary amine (52), which might be expected to react for example with alkyl or aralkyl halides to give the tertiary amines (53).

1-Benzyl-3-α-phenylaminomethyl-4-piperidinol (48) was refluxed in pyridine with acetic anhydride for 3 hours (Kirk, 1958). Evaporation of the solvent yielded N{α[4-acetoxy-1-benzyl-3-piperidyl]benzyl}acetamide (49, R=CH_3). It was thought that debenzylation of this compound and subsequent reaction with alkyl or aralkyl halides could produce 1-substituted piperidines. However, an attempt at hydrogenolysis gave a clear colourless oil, with an equivalent weight of 293 ($C_{16}H_{22}N_2O_3$ requires 290). The infra-red spectrum showed the

Flow sheet VI



presence of both ester and amide functions and the presence of only one mono-substituted benzene ring. The compound did not solidify and could not be induced to crystallise. An attempt to form the hydrochloride gave an oil, the infra-red spectrum of which showed that the relative amount of ester to amide had been reduced and showed the possible presence of an OH group. Thus either the compound after debenzylation had hydrolysed to give the amido-alcohol (55), which seemed quite



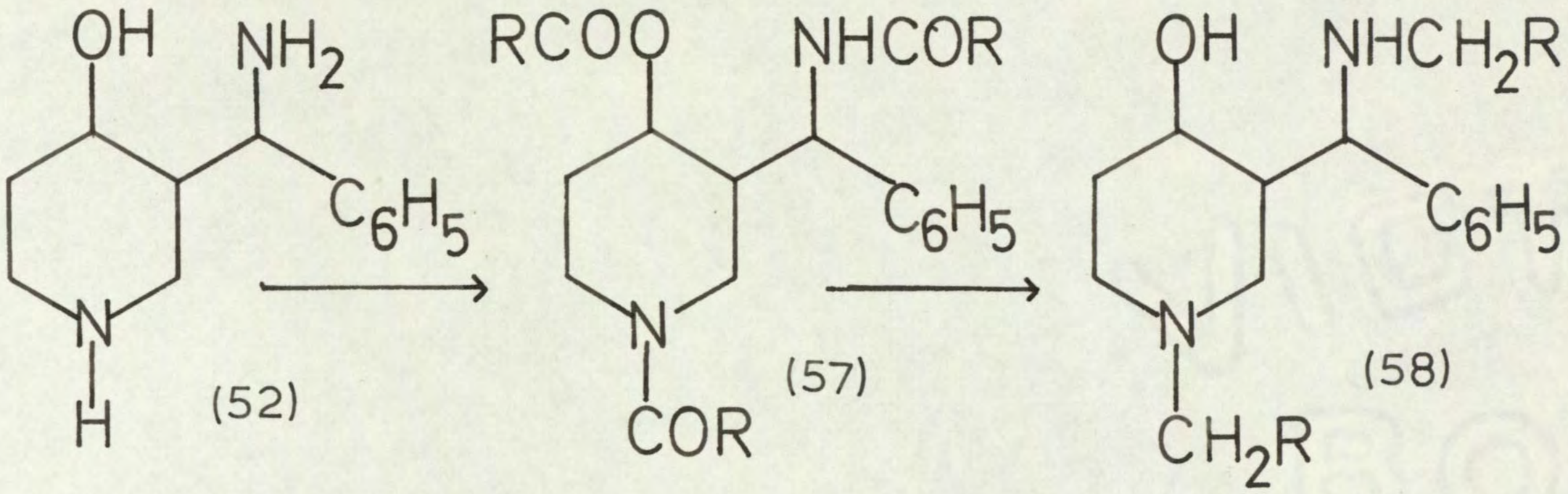
possible, or the compound (54) had eliminated, forming the unsaturated amide (56), since Badger et al. (1950) found that ethanolic hydrogen chloride caused facile elimination of various 4-piperidinol esters. An attempt was made to react the free base with phenethyl bromide, in the hope that preparation of a tertiary amine might

give a solid compound. Work-up of the reaction mixture once more gave an oil that did not solidify. Thin layer chromatography showed the presence of three spots, one of which compared with starting material.

Following these results, 1-benzyl-3-α-phenylaminomethyl-4-piperidinol was debenzylated by the same method to give 3-α-phenylaminomethyl-4-piperidinol (52) in good yield, characterised as the dihydrochloride.

This might be expected to react with alkyl and aralkyl halides to give either the mono-substituted tertiary amine (53, R'=H) if only one mole of alkyl halide was used, or the disubstituted tertiary amine (53, R'=R), if two moles of alkyl halide reacted. The mono-substituted compound (53, R'=H) might then be acylated to give the 1-substituted amido esters which were unobtainable by a previous method. However, reaction of the amido-alcohol (52) with one or two moles of phenethyl bromide in chloroform failed to give any solid product, and thin layer chromatography showed mixed products.

An alternative method of preparing NN'-disubstituted amino-alcohols from the secondary amine (52) was considered. This involved the acylation of the three reactive centres to give a di-carboxamido ester (57), followed by $LiAlH_4$ reduction to give the NN'-di-substituted compound (58). Reaction of 3-α-phenyl-



aminomethyl-4-piperidinol (52) with acetic anhydride gave the compound (57, R=CH_3). Reduction of this compound with $LiAlH_4$ gave the required compound (58, R=CH_3) as a deliquescent dihydrochloride.

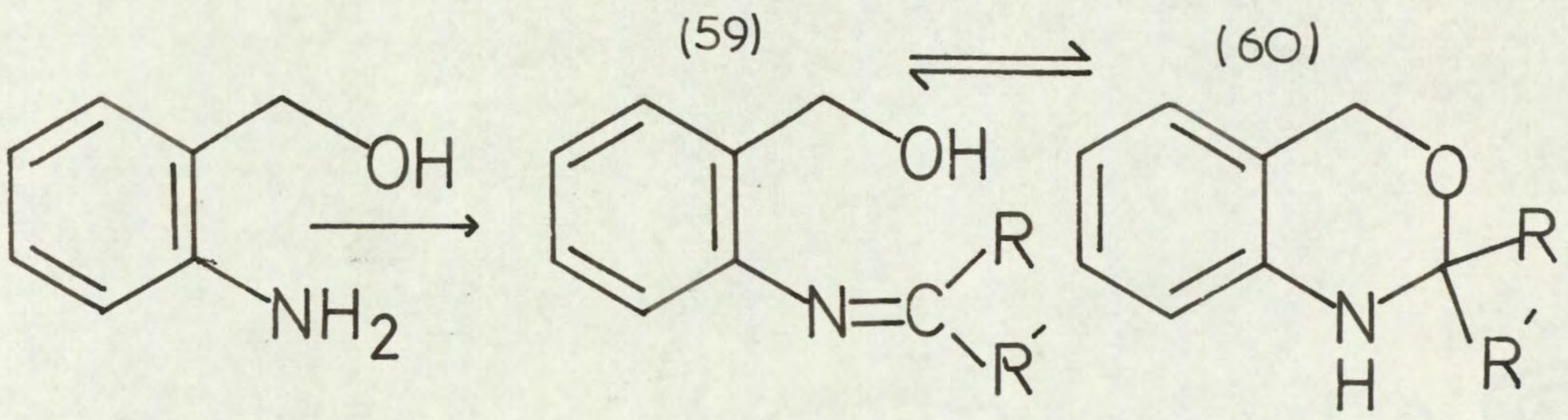
Preparation of the NN'-dimethyl compound was attempted. Two methods at first sight appeared possible. Firstly, with formic anhydride (Waley, 1953, Waley and Watson, 1954) or with chloral (Hoffman, 1872), both of which result in the introduction of a formyl

$$CCl_3CHO + RNH_2 \longrightarrow RNHCHO + CHCl_3$$

group. Reaction of the secondary amino-alcohol (52) with formic acid and acetic anhydride was attempted, giving a clear colourless oil which did not titrate under non-aqueous conditions. The infra-red spectrum suggested that the compound formed was the triformyl derivative (57, R=H) rather than the NN'-diformyl-piperidinol. This intermediate was reduced with $LiAlH_4$

to give the dimethyl compound (58, R=H) as a very deliquescent hydrochloride.

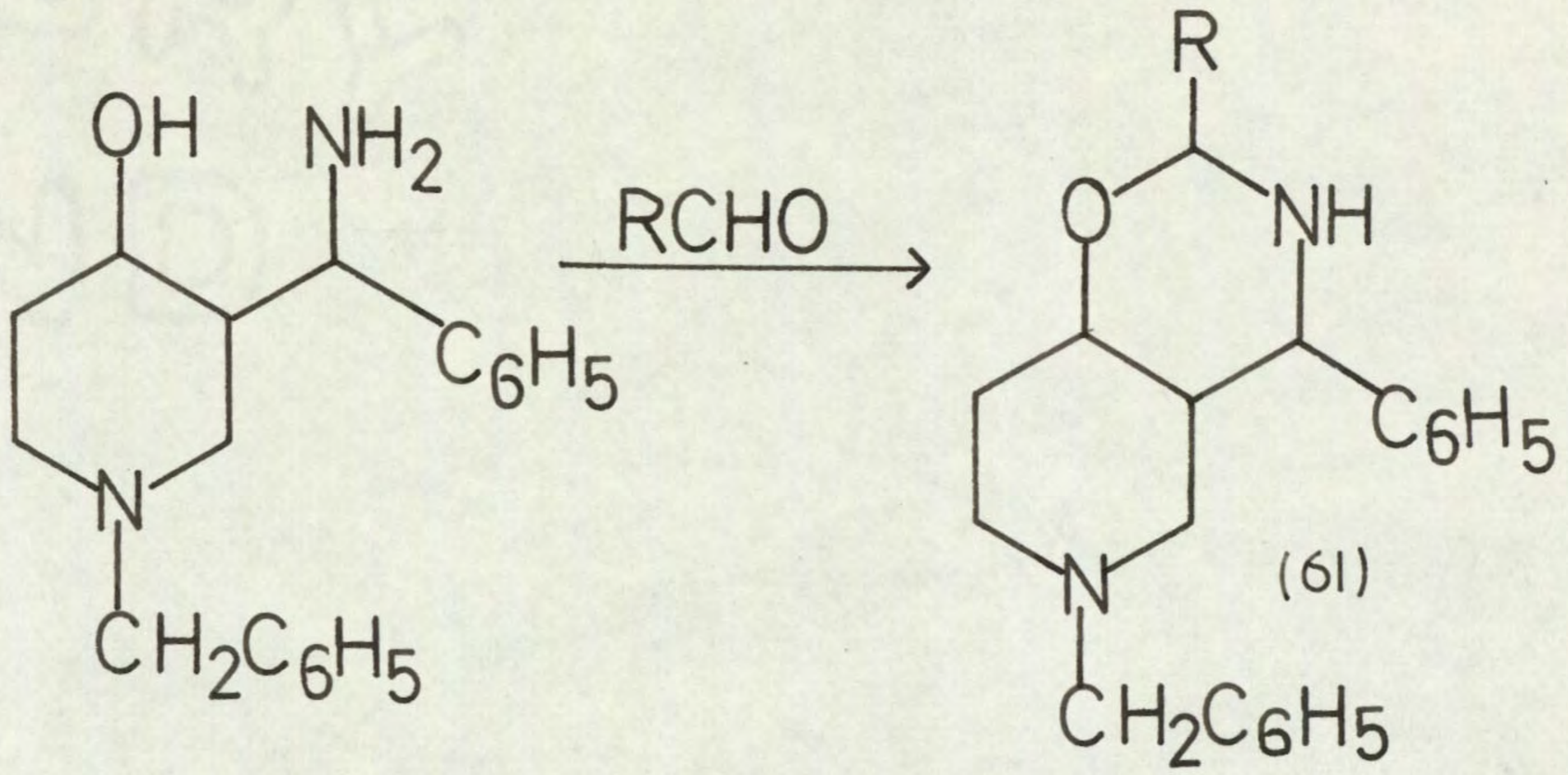
Paal and Laudenheimer (1892) described the condensation of carbonyl compounds with o-amino-benzyl alcohol, forming azomethines (59). It was subsequently



shown (Holly and Cope, 1944) that the azomethine (59) could exist in equilibrium with a tautomeric structure, a benzoxazine (60), depending upon the structure of the starting ketone, the more sterically hindered ones forming the uncyclised Schiff bases (59). The condensation of aldehydes with o-hydroxybenzylamine has also been described (McDonagh and Smith, 1968). It was found that, in general, aliphatic aldehydes and ketones gave predominantly the open chain structures.

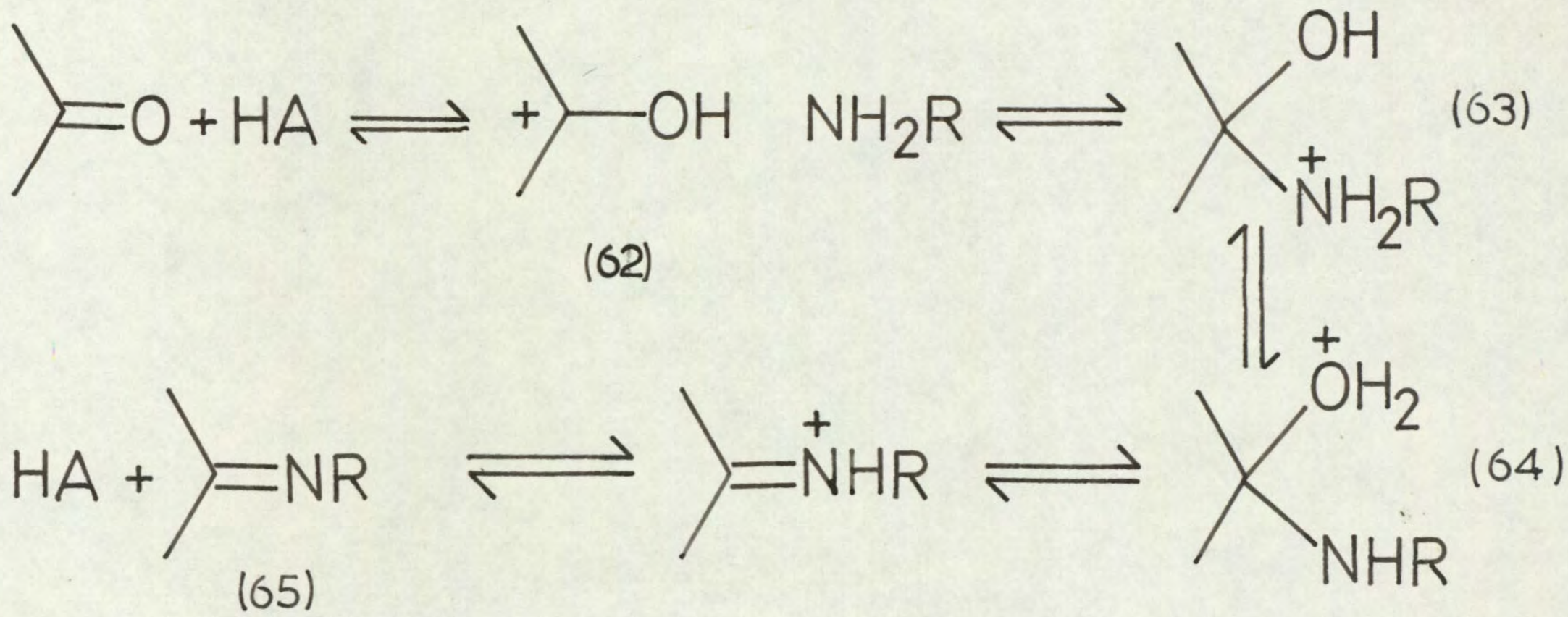
Condensation of the isomeric 1-benzyl-3- α -phenyl aminomethyl-4-piperidinols with a variety of aldehydes and ketones was obtained by refluxing the components in dry benzene, water of condensation being removed either by azotropic distillation to dryness or by the use of a water separator to give octahydro-pyrido[3,4,e][1,3]

oxazines (61). A small quantity of acetic acid was

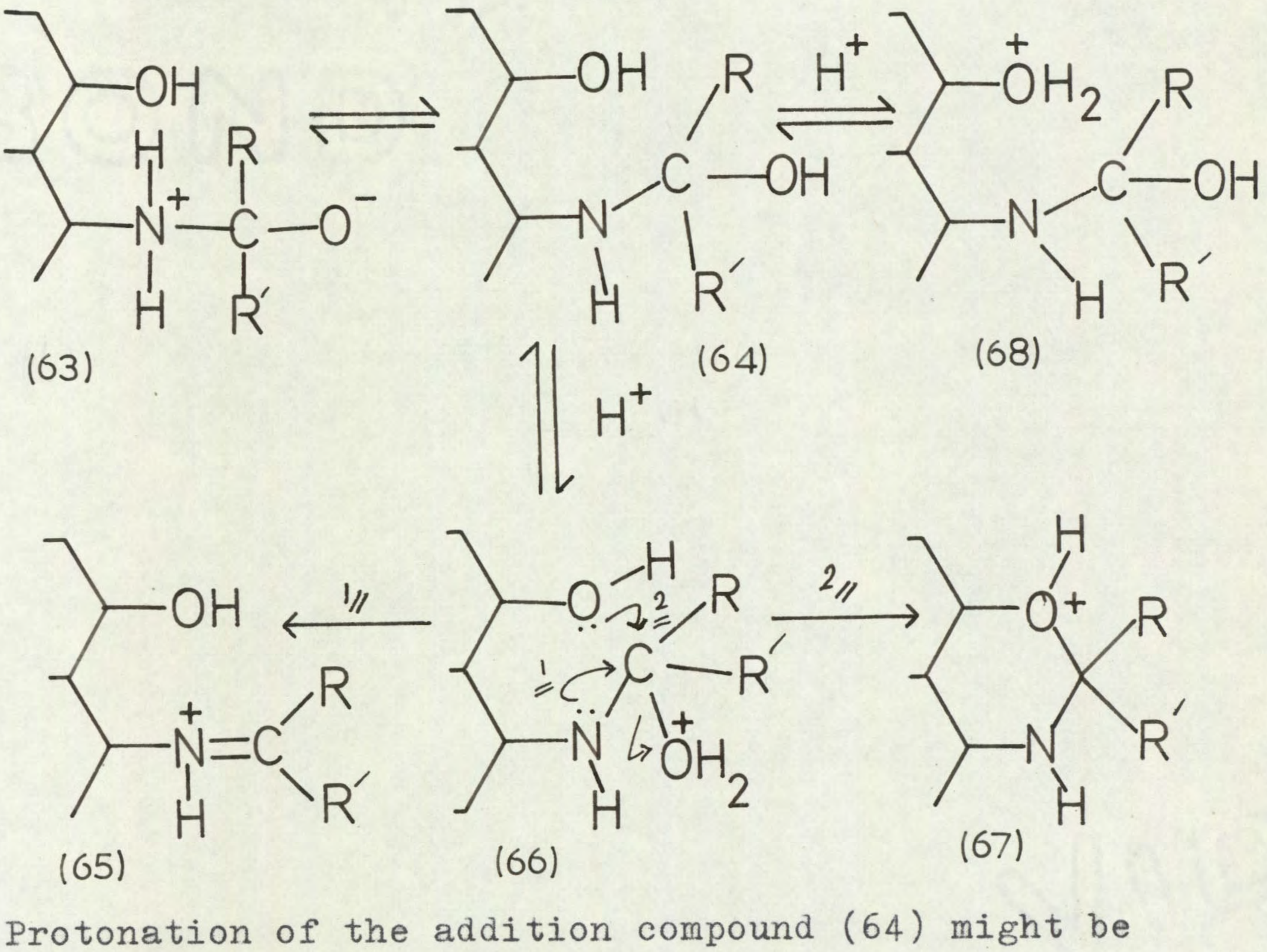


(61)

added to the reaction mixture (Hancock and Cope, 1944, Goodsen and Moffett, 1950) when the aldehyde used was p-dimethylaminobenzaldehyde. Addition of an acid to the reaction between a carbonyl and a nucleophile partially converts the carbonyl to its conjugate acid (62), or perhaps to a hydrogen bonded complex. In either case the carbon atom becomes more electropositive and attack by the nucleophile is facilitated. The rate-determining step is the formation of (63) from (62).

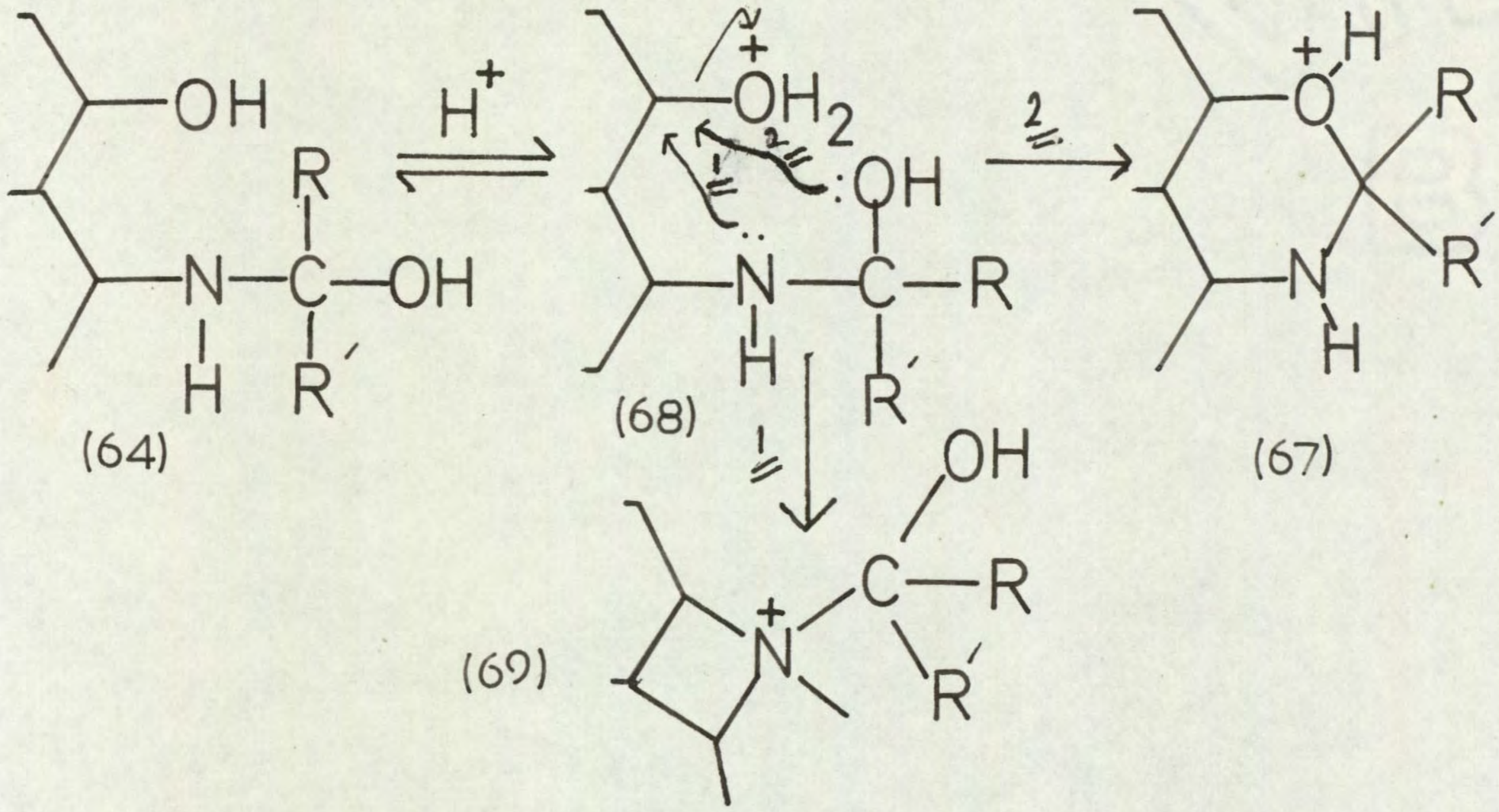


Transfer of a proton from the nitrogen to the oxygen is assumed to be rapid. In the simple addition of an amine to a carbonyl, a further fast step follows. The gem hydroxyamine eliminates the elements of water to give the imine (65). In the case of hydroxy amines, however, a second reaction sequence could occur:



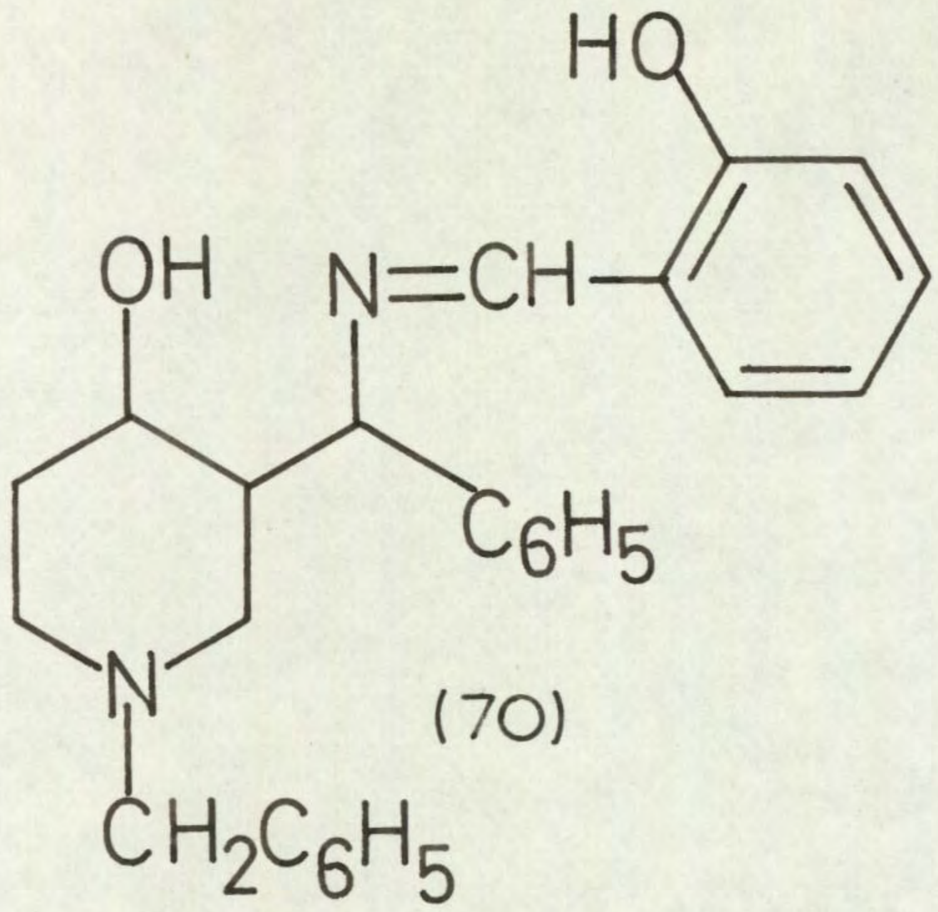
Protonation of the addition compound (64) might be expected to give (66). Elimination of the elements of water could then occur in one of two ways: by formation of an immonium complex and subsequent loss of proton to give (65), or by nucleophilic attack by the neighbouring hydroxyl group, forming a six-membered ring (67), which

could eliminate a proton to form an oxazine. A third mechanism, involving protonation of (64) to give an oxonium salt of the secondary alcohol (68) as opposed to

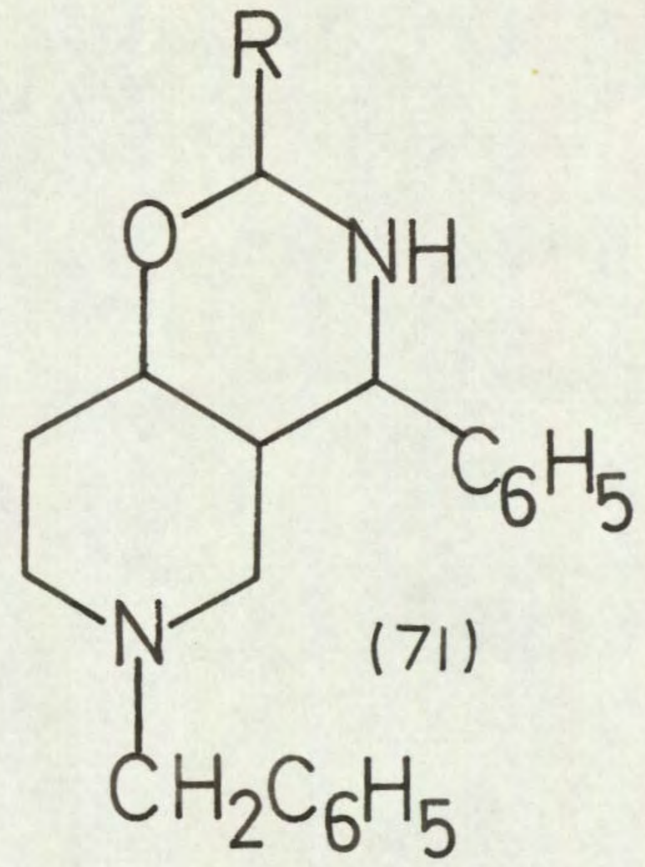


the oxonium salt of the tertiary alcohol (66) would not be expected to occur, since elimination is more difficult for secondary alcohols. Also formation of an immonium salt would involve the preparation of an azetane (69) which would be more strained than a six-membered ring.

Condensation between o-hydroxybenzaldehyde and 1-benzyl-3-α-phenylaminomethyl-4-piperidinol gave a yellow solid which showed a peak at 1620 $cm.^{-1}$ in an infra-red spectrum. This was attributed to C=N, the compound being assigned the open Schiff base structure (70).



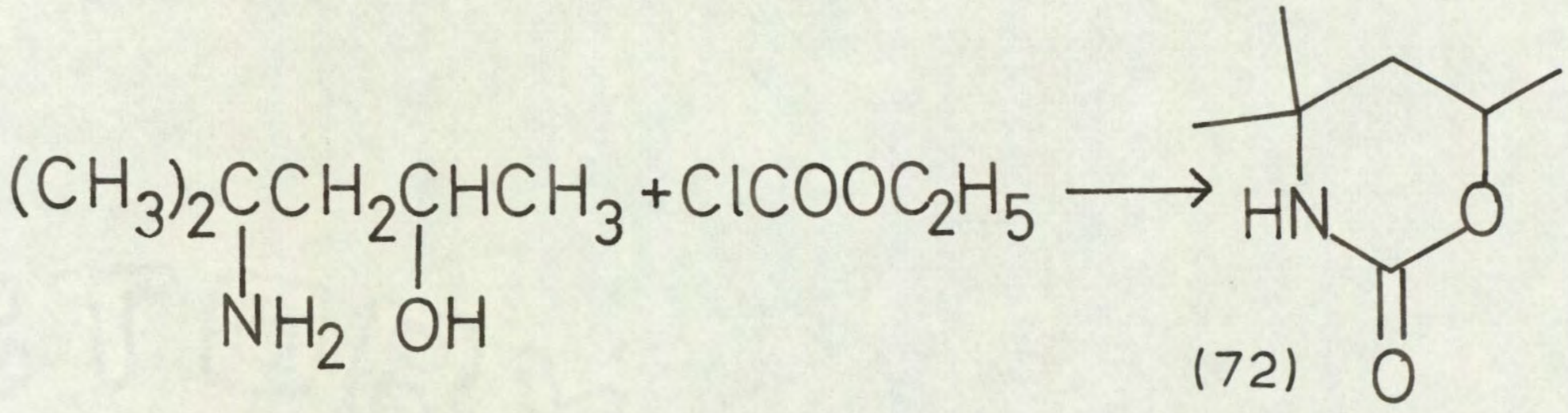
(70)



(71)

Condensation of the amino-alcohol with other aldehydes and ketones gave compounds with the general structure (71), based on their infra-red and nuclear magnetic resonance spectra. These compounds will be discussed later.

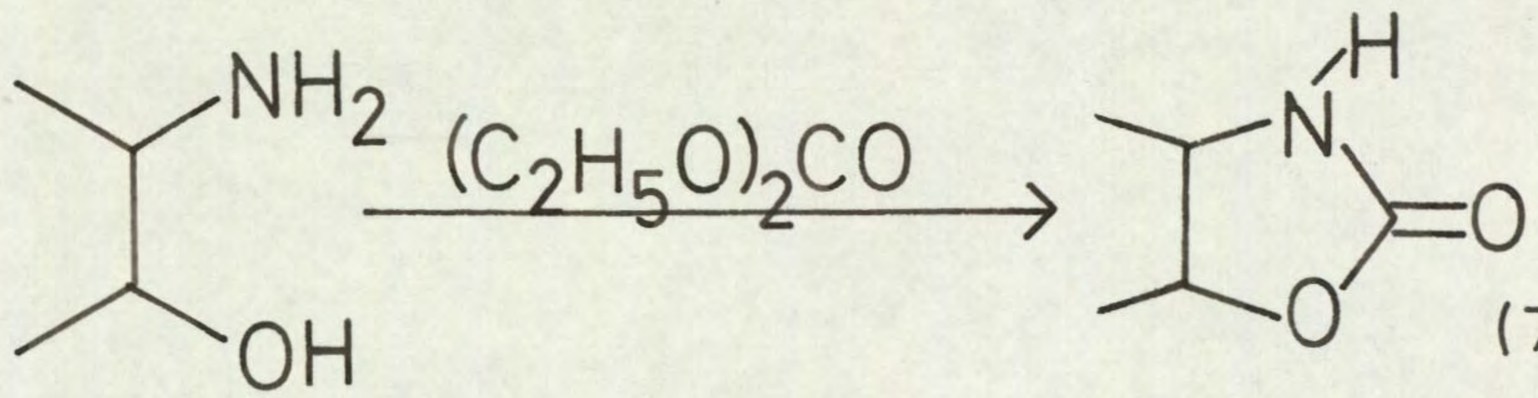
Kohn (1905) prepared 2-keto-4,4,6-trimethyl tetrahydro-1,3-oxazine (72) by reacting ethyl chloro-formate and sodium carbonate with 2-amino-4-hydroxy-1-



(72)

methylpentane. Foglia and Swern (1967) condensed amino-alcohols with ethyl carbonate in the presence of sodium

methoxide to give substituted oxazolidones (73). 1-Oxa-2-oxo-3,8-diazaspiro(4,5)decanes (74) were also obtained



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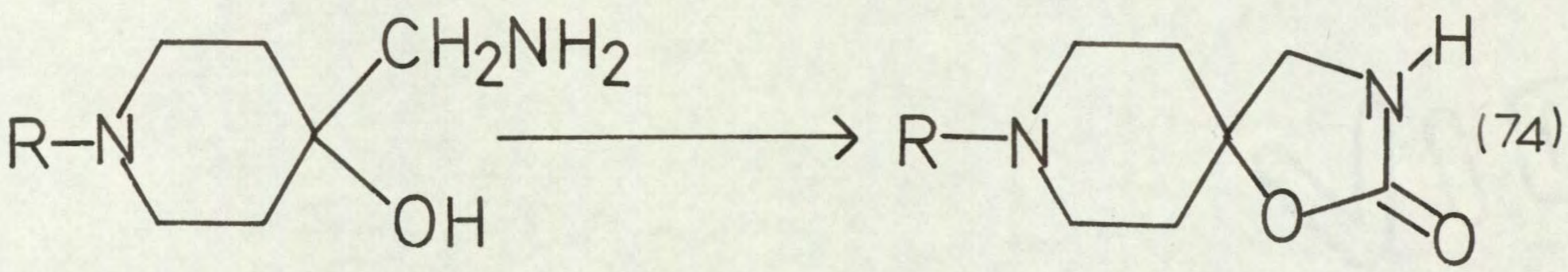
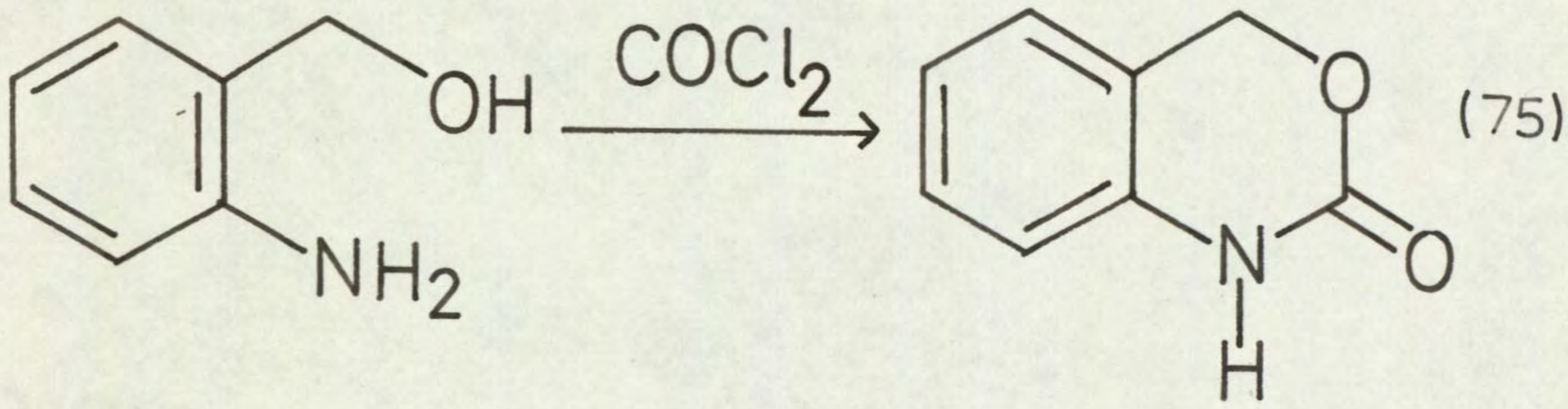


(74)

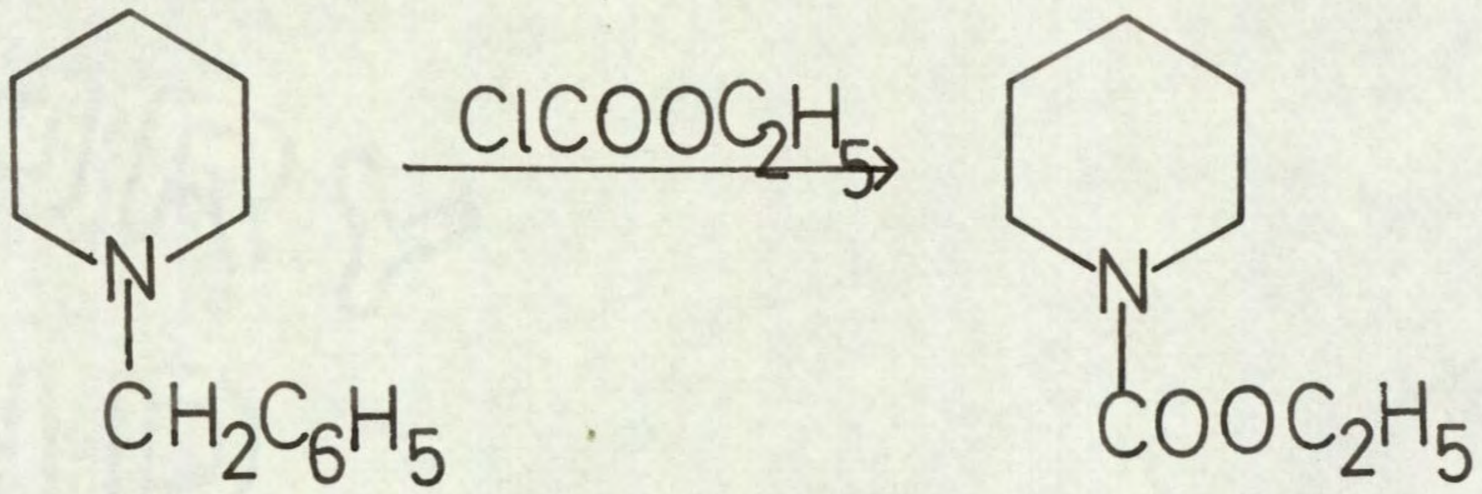
by the condensation of ethyl carbonate with amino-alcohols (Science Union et Cie, 1966). A third method, involving addition of phosgene with the elimination of two moles of HCl, was used by Kitamura (1934) to obtain 2-oxo-3,1,4-benzoxazine (75).



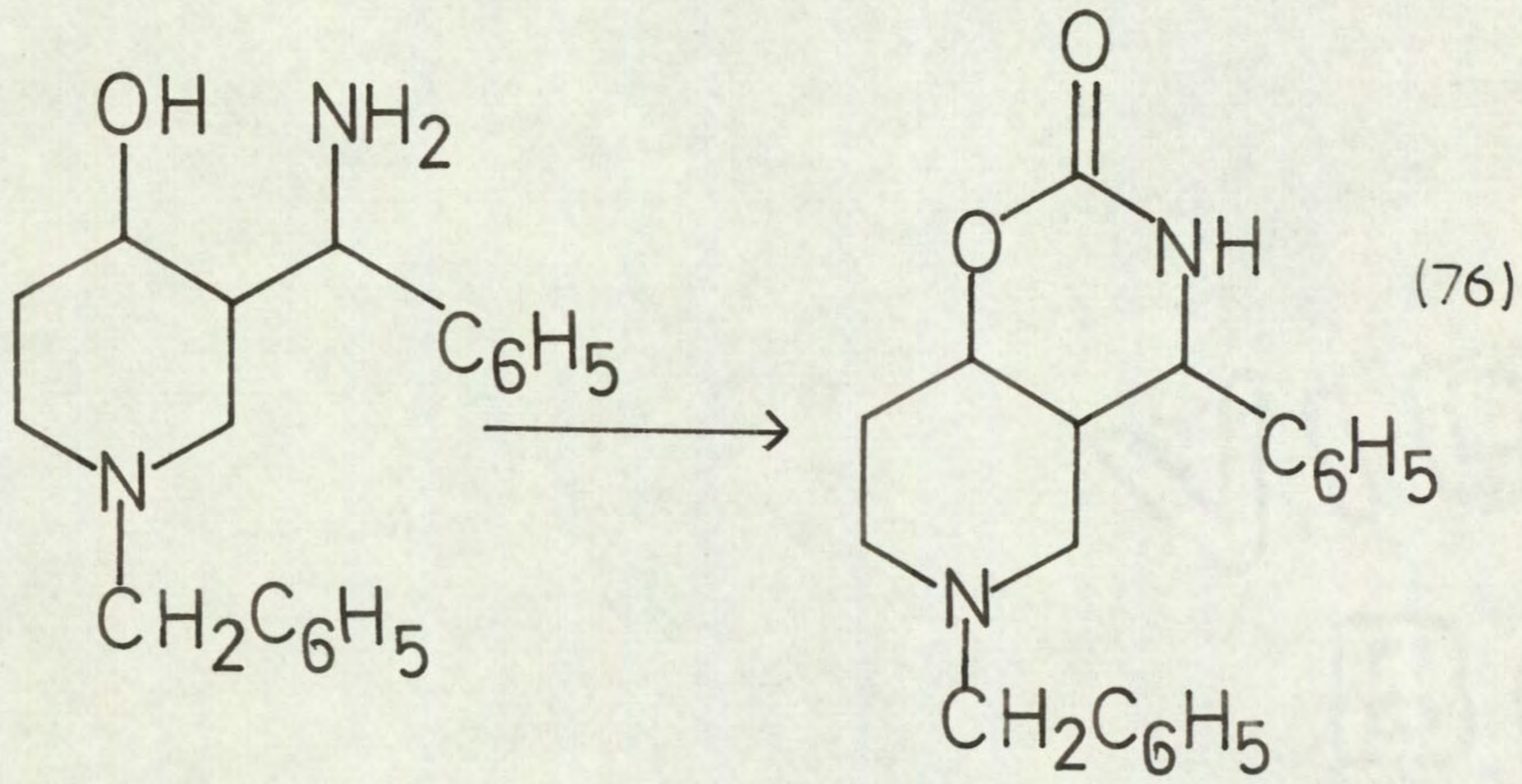
(75)

Ethyl chloroformate can react with tertiary amines to form urethans (Wright and Brabander, 1961). The reaction is not limited to ethyl esters (Hobsen and McCluskey, 1967). This reaction made ethyl chloro-formate unsuitable for cyclisation. Phosgene was the

reagent of choice for ease of reaction and gave with 1-benzyl-3-α-phenylaminomethyl-4-piperidinol a white solid which was found to be 6-benzyl-octahydro-2-oxo-



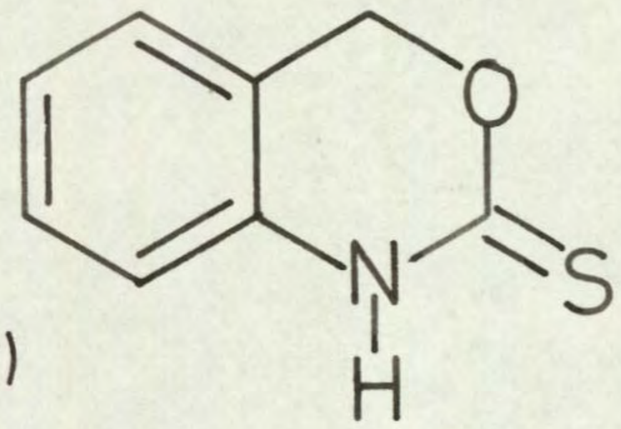
4-phenyl-pyrido[3,4,e][1,3]oxazine (76).



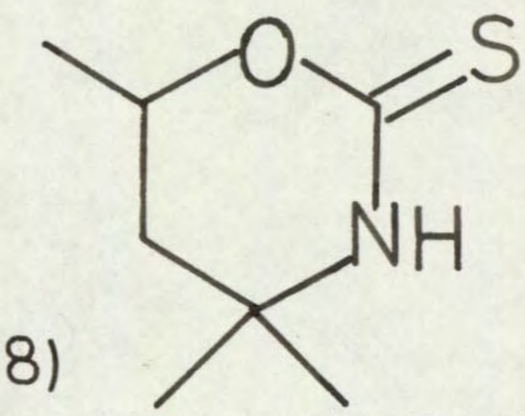
(76)

Paal and Commerell (1894) obtained 2-thio-dihydrobenzoxazine (77) on refluxing o-amino benzyl alcohol with carbon disulphide and potassium hydroxide, while Fisher (1944) refluxed potassium

(77)



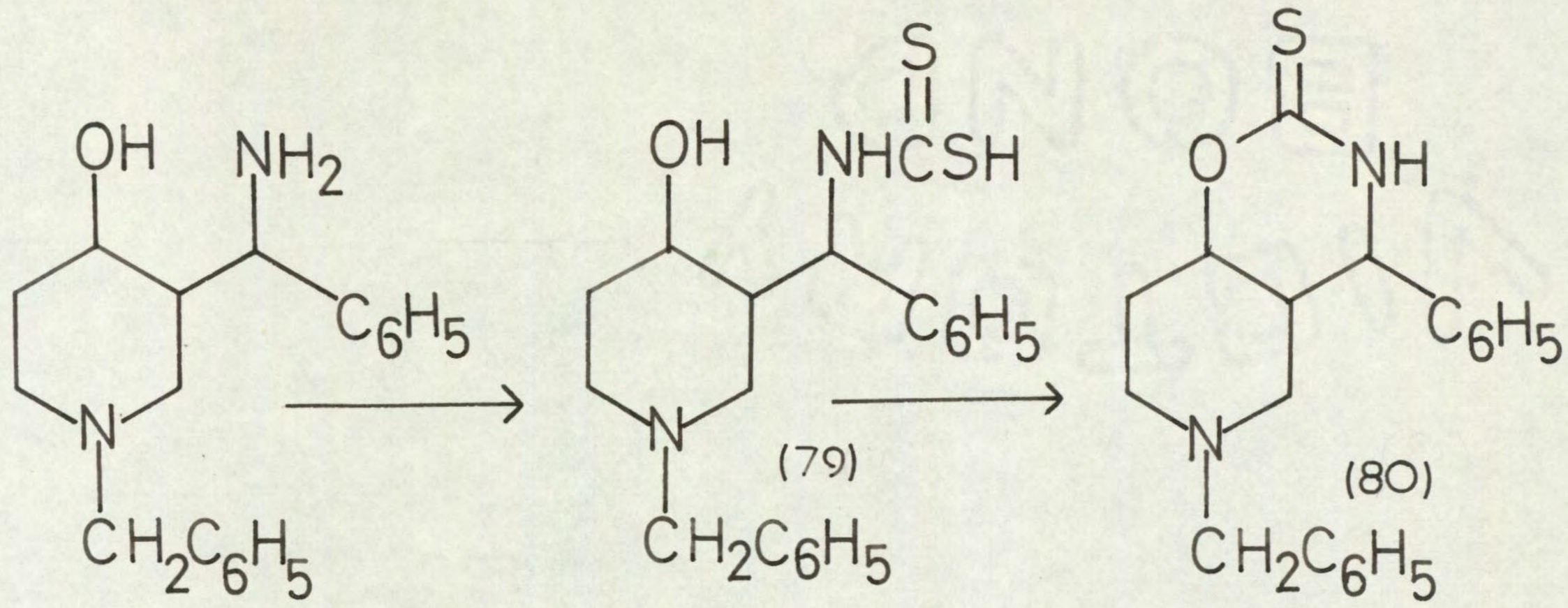
(78)



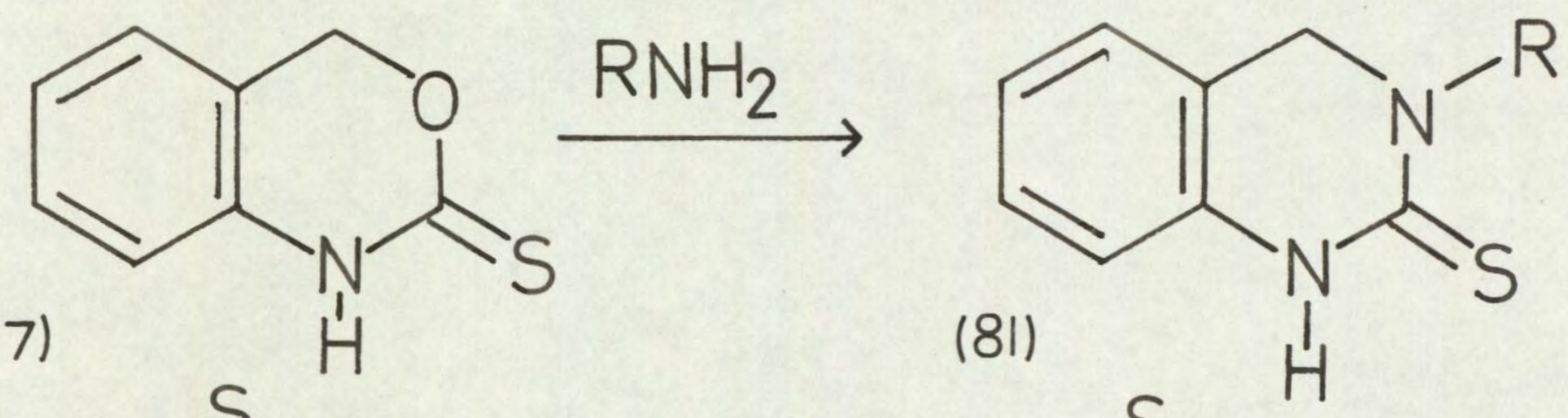
hydroxide, 2-amino-4-hydroxy-1-methylpentane and carbon disulphide in absolute ethanol to obtain 4,4,6-trimethyl-2-thio-tetrahydro-1,3-oxazine (78).

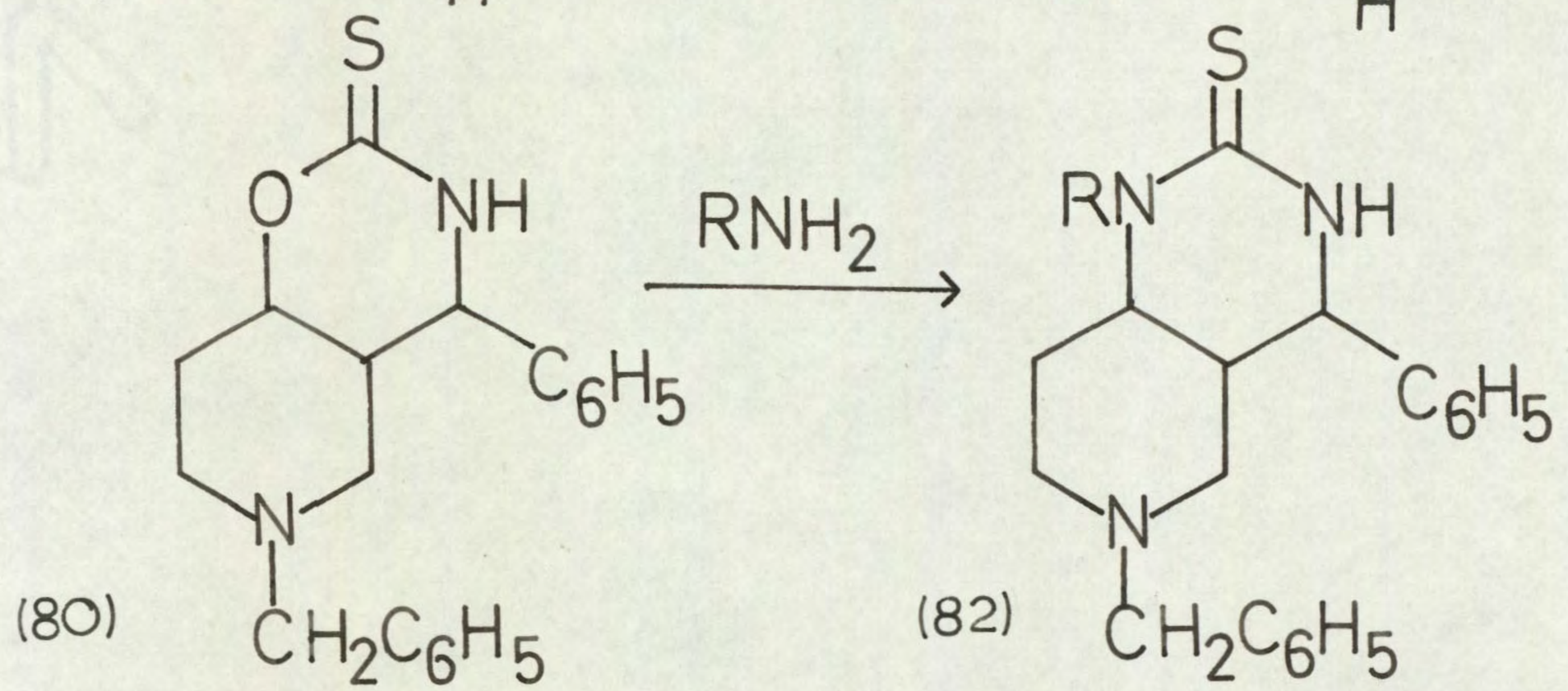
Refluxing 1-benzyl-3- α -phenylaminomethyl-4-piperidinol in benzene with carbon disulphide gave a fine white precipitate. An equivalent weight was not obtained as the compound was insoluble in acetic acid, but an infra-red spectrum did not agree with that expected of a cyclic oxazine but suggested the uncyclised compound (79), a dithio-carbamic acid. The compound was not characterised but dissolved on heating in digol, evolving H_2S and giving a small yield of a white crystalline compound on cooling. The infra-red spectrum of this compound showed the expected bands, and analysed correctly for 1-benzyl-octahydro-4-phenyl-2-sulphinyl-pyrido[3,4,e][1,3]oxazine (80).

Paal and Commerell heated the thiobenzoxazine (77)



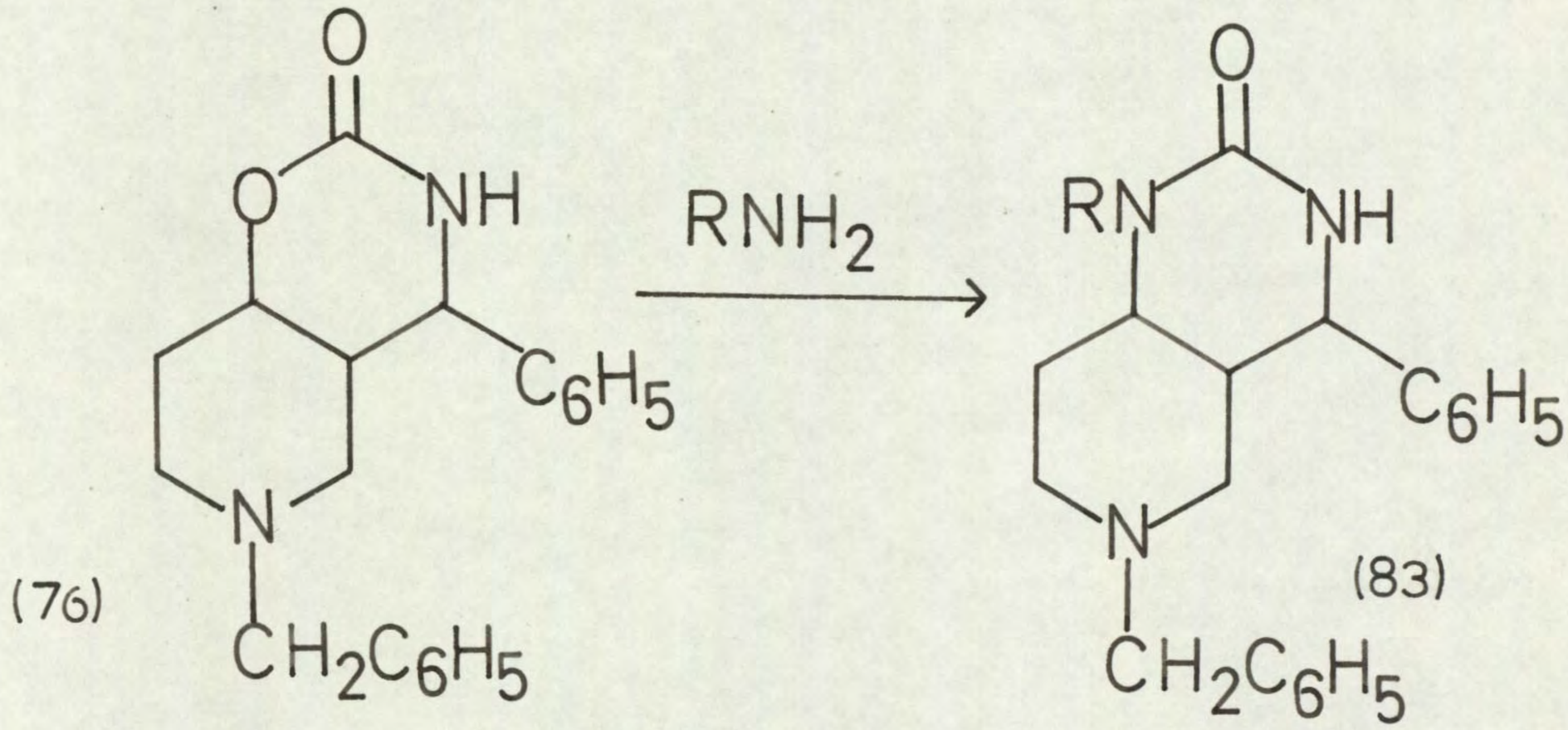
with aniline and toluidines to obtain the 1-substituted dihydro-thio-quinazolines (81). Consequently, the pyrido-oxazine (80) was refluxed in toluene with benzyl-





amine and in toluene with hydrazine in order to obtain the corresponding octahydropyrido-pyrimidine (82), but

the starting material was recovered unchanged. This was followed by an attempt to attack the 2-oxo-pyrido-oxazine (76) with benzylamine or hydrazine to obtain the 1-substituted-2-oxo-pyrido-pyrimidines (83). Once



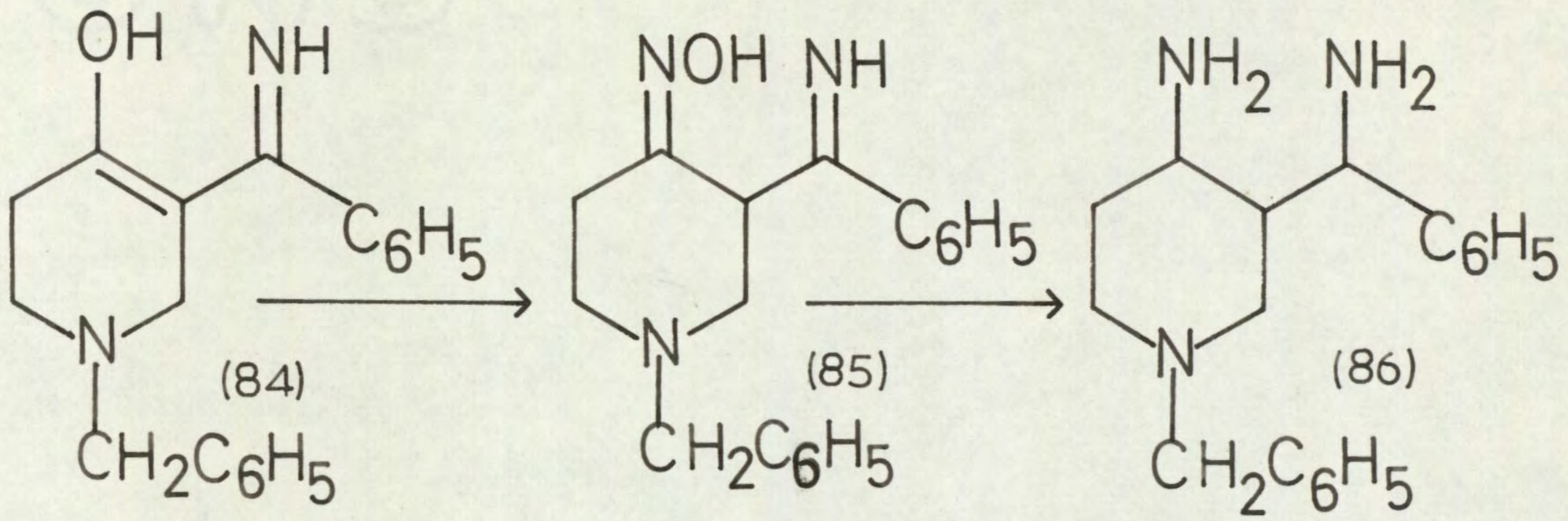
(76) (83)

again the starting material was recovered unchanged. Finally, both the 2-oxo- and 2-thio-pyrido-oxazines were heated in sealed tubes with an ethanolic solution of ammonia to 140° for 40 hours. Evaporation of the solvent gave yellow oils which could not be crystallised. The method of synthesising pyrido-pyrimidines was abandoned.

Further reactions with 1-benzyl-1,2,5,6-tetrahydro-4-hydroxy-3-phenylimino-pyridine

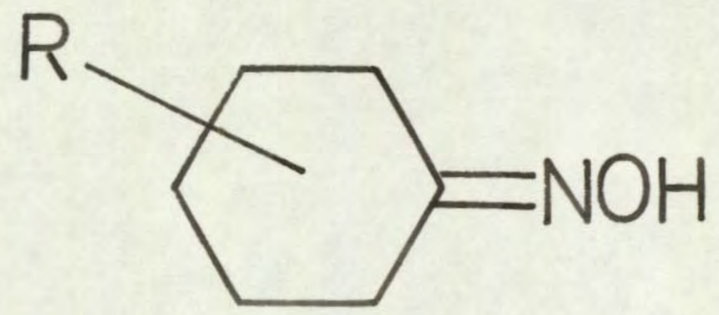
1-Benzyl-1,2,5,6-tetrahydro-4-hydroxy-3-phenylimino-pyridine (84) was reacted with hydroxylamine hydrochloride to give the 4-ketoxime (85). It was hoped that

reduction of this oxime would give the triamine (86)



which might be dialkylated or diacylated. The product from the enolimine (84) and hydroxylamine could not, however, be crystallised. The infra-red spectrum showed a different structure from the starting material, with the possible presence of an oxime =N-OH. The compound was not characterised but used directly.

Oximes have been reduced under a variety of conditions. Smith et al. (1952) reduced the oximes of benzaldehyde, butanone, cyclohexanone and propiophenone with $LiAlH_4$ to give varying yields of the primary amines. Catalytic reduction of various cyclohexanone oximes have been successful (Bose, 1952) using platinum in acid media. Sodium in ethanol has also been used. Nightingale (1952) reduced oximes of the type shown to give the trans amines in reasonable yields.



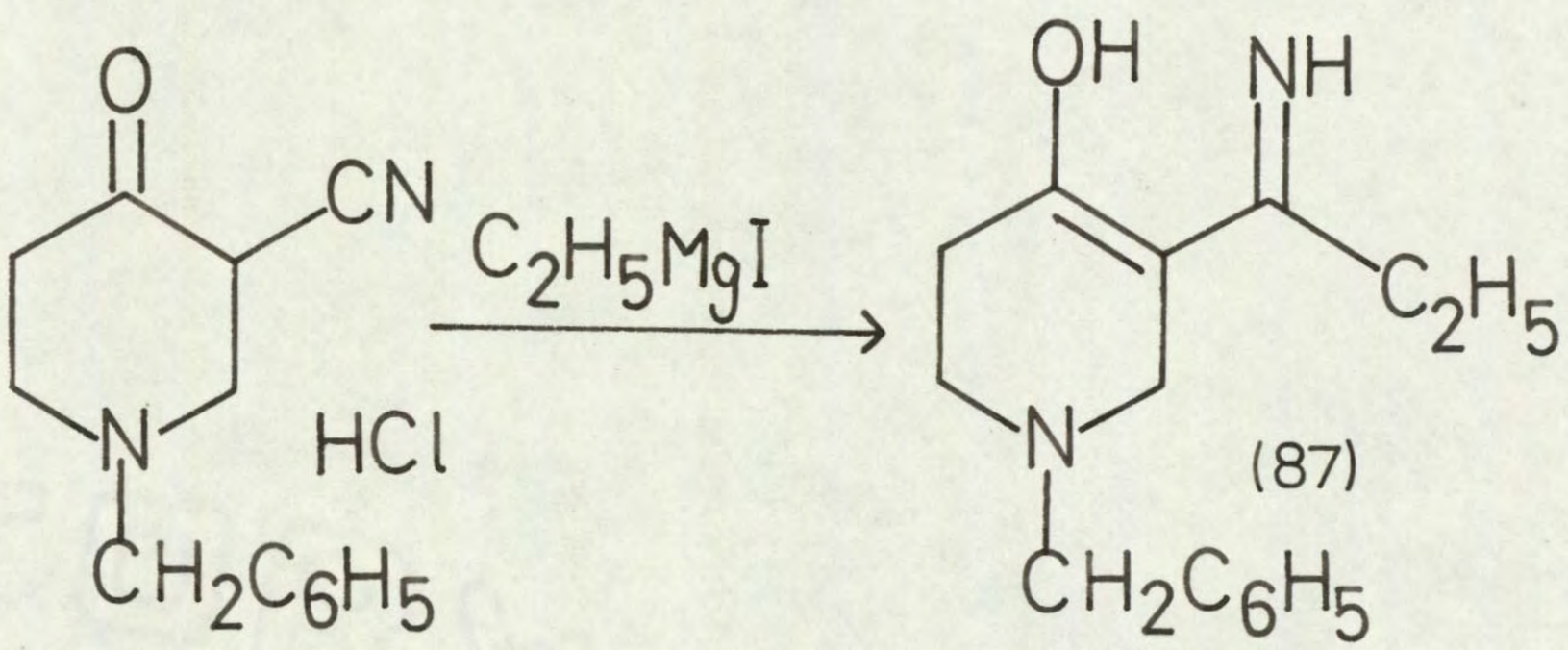
The presence of the imine group presented a little difficulty, since reactions in acid media might be expected to hydrolyse the group to the ketone. An attempt at reducing the compound over hydrogen in the presence of platinum failed, no hydrogen uptake being observed. The presence of the N-benzyl group precluded the use of palladised charcoal.

Reduction of the impure oxime with $LiAlH_4$ gave a pale yellow oil which had an infra-red spectrum similar to that of 1-benzyl-3-α-phenylaminomethyl-4-piperidinol. Thin layer chromatography showed the presence of three major spots, two of which compared favourably with similar spots obtained from the two isomers of the amino-alcohol. An attempt at reduction of the oxime in ethanol with sodium borohydride gave a similar result. The presence of a strong base during the reaction may have hydrolysed the oxime back to the imino-enol, which then reduced to give the amino-alcohol.

SOME REACTIONS OF 1-BENZYL-3-CYANO-4-PIPERIDONE

A. Reaction with organometallic reagents. ii Ethyl magnesium iodide

1-Benzyl-3-cyano-4-piperidone reacted with ethyl magnesium iodide in a similar manner to the reaction with phenyl magnesium bromide giving 1-benzyl-3-ethylimino-1,2,5,6-tetrahydro-4-hydroxy-pyridine (87).



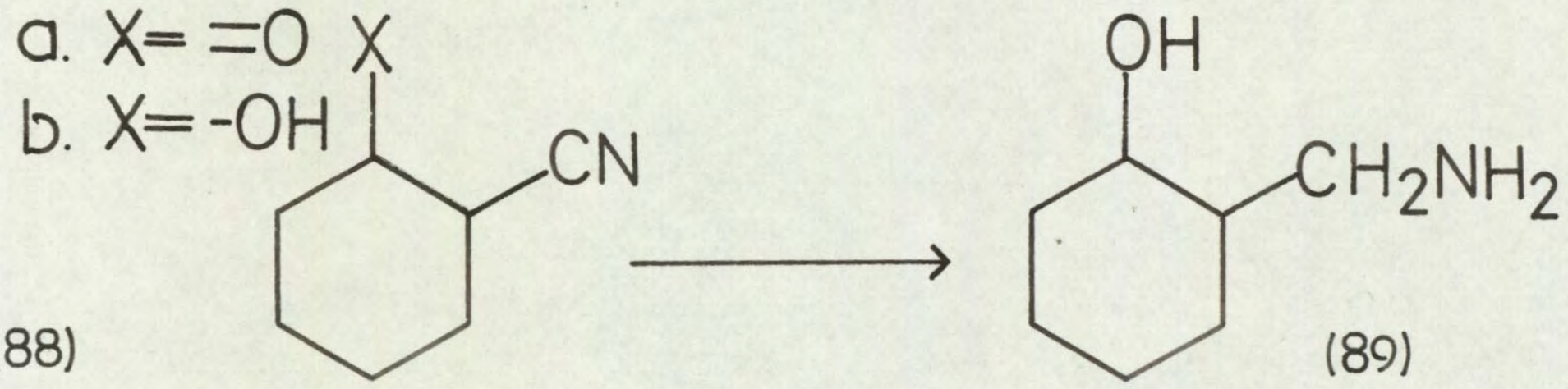
Attempted hydrolysis of the enolimine (87) to the corresponding diketone gave an oil from which no solid material could be obtained. An infra-red spectrum showed the presence of one peak corresponding to a carbonyl stretching frequency, which suggested that the reaction had succeeded.

Reduction of the enolimine with $NaBH_4$ gave an oil which could not be crystallised, neither could a solid salt be obtained. An infra-red spectrum of the product suggested that the reaction had been successful, but as

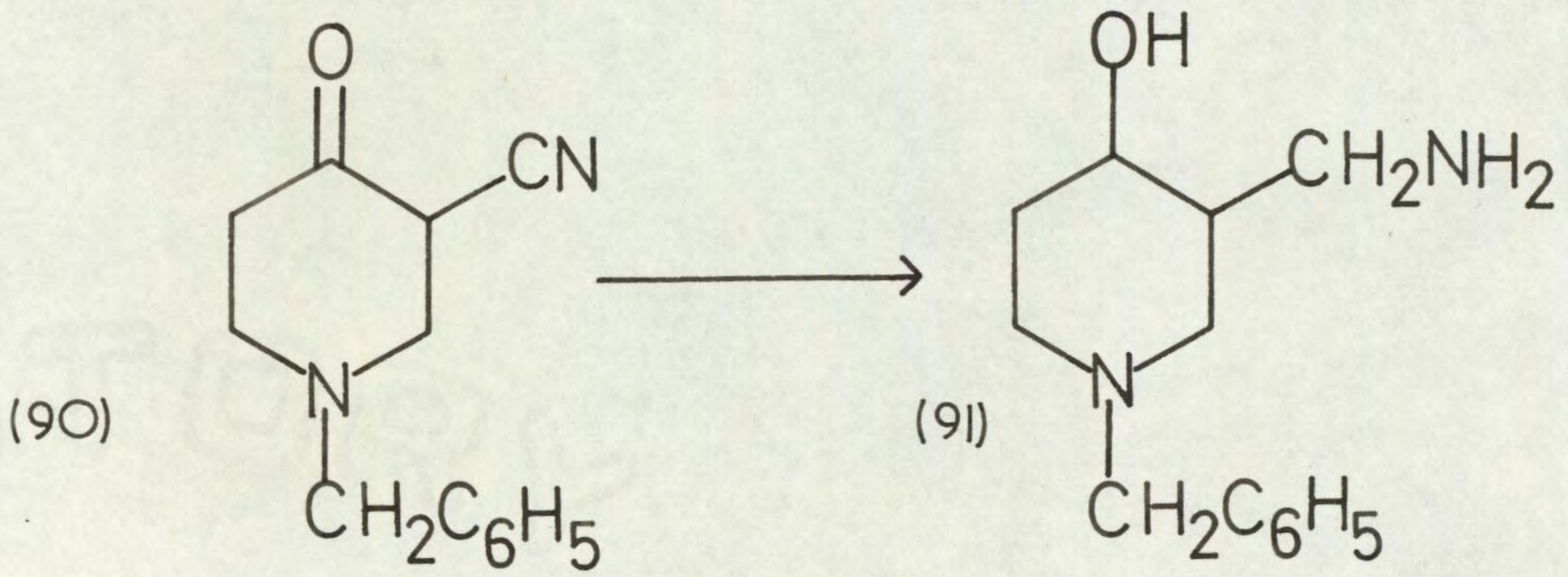
the compound could not be obtained pure, preparation of derivatives was not attempted.

B. Reduction

Under reducing conditions, α -cyano-ketones have given rise to both the amino-ketone and the fully-reduced amino-alcohol. Wiley and Adkins (1938) after many unsuccessful attempts obtained both products using Raney nickel catalysed hydrogenation at 270 atmospheres pressure and a variety of temperature conditions. A milder method involved reduction with complex metal hydrides. Mousseron et al. (1952) reduced 2-cyanocyclohexanone (88a) and 2-cyanocyclohexanol (88b) with $LiAlH_4$ to give trans-2-aminomethylcyclohexanol (89).



(88) (89)



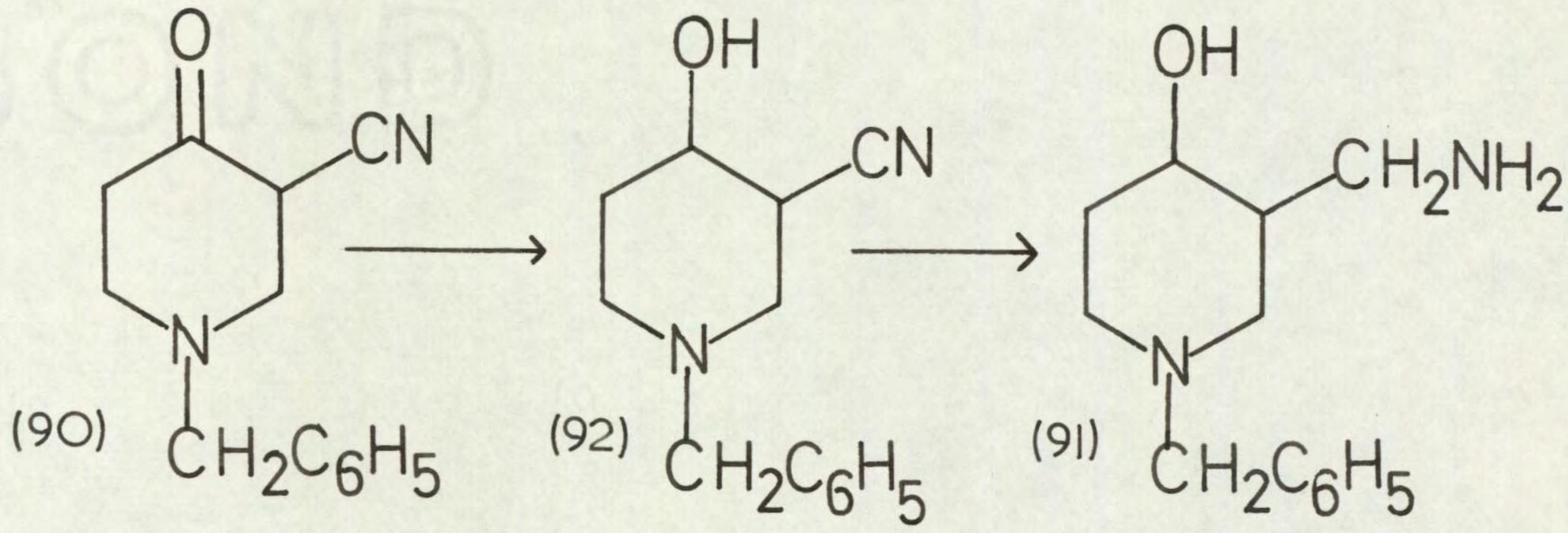
(90) (91)

In view of the apparent ease of reduction with $LiAlH_4$, the solid hydrochloride salt of 1-benzyl-3-cyano-4-piperidone (90) was reacted in ether with $LiAlH_4$, excess hydride being used in order to allow for the hydrogen chloride, and to suppress possible side reactions, such as aldehyde formation from the nitrile (Nystrom and Brown, 1948). Work-up of the mixture gave a clear colourless oil with an equivalent weight of 112 ($C_{13}H_{20}N_2O$ requires 110). The infra-red spectrum showed the possible presence of OH and NH_2 bands absorbing in the region 3200 $cm.^{-1}$ - 3400 $cm.^{-1}$, and the absence of a C≡N band absorbing in the region of 2250 $cm.^{-1}$. The peak at 1650 $cm.^{-1}$, attributed to C=O had also disappeared. Attempts to solidify and crystallise the 3-aminomethyl-1-benzyl-4-piperidinol (91) or to prepare a salt failed. Attempts to synthesise a solid derivative by reaction with acetic anhydride to form the amido-ester resulted in the formation of intractable tars.

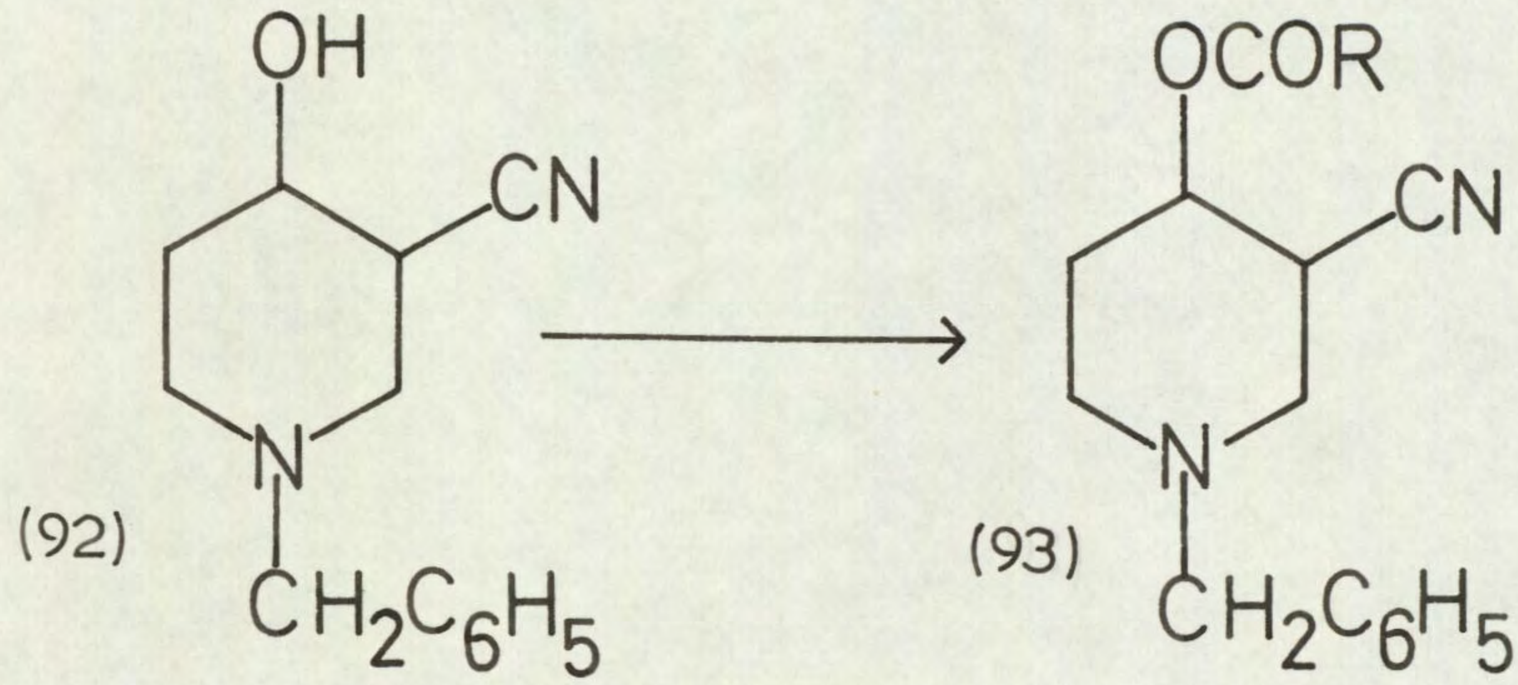
The failure to crystallise the amino-alcohol may have been due to the presence of isomers. Examination of the compound indicated that it could exist in the form of <u>cis</u> and <u>trans</u> isomers. Thin layer chromatography of the oil showed the presence of more than one spot.

It was decided to attempt a step-wise reduction of

the cyano-ketone. Sodium borohydride reduces ketones to alcohols but does not reduce nitriles (House, Gaylord). Consequently, the reaction of the cyano-ketone (90) with $NaBH_4$ in methanol gave 1-benzyl-3-cyano-

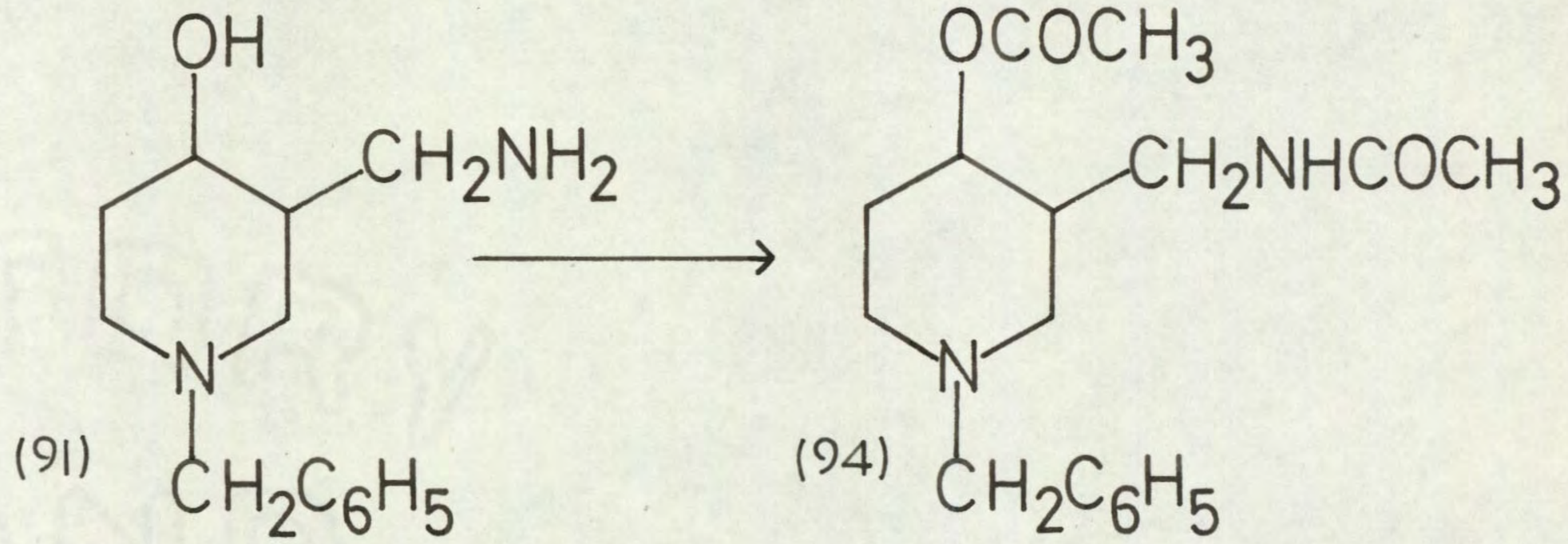


4-piperidinol (92) with an equivalent weight of 215 ($C_{13}H_{16}N_2O$ requires 216). An infra-red spectrum showed the presence of OH at 3300 $cm.^{-1}$, C≡N at 2250 $cm.^{-1}$ and loss of C=O at 1650 $cm.^{-1}$. The compound, on refluxing with acetic anhydride and pyridine gave the hydrochloride salt of 4-acetoxy-1-benzyl-3-cyano-piperidine (93, R=CH_3). Reduction of the piperidinol with $LiAlH_4$ in ether gave



3-aminomethyl-1-benzyl-4-piperidinol (91), characterised as the dihydrochloride. Only one isomer was obtained. The residue did not crystallise and no solid derivative could be prepared. Thin layer chromatography showed the presence of three spots, one of which appeared identical with that from the solid isomer.

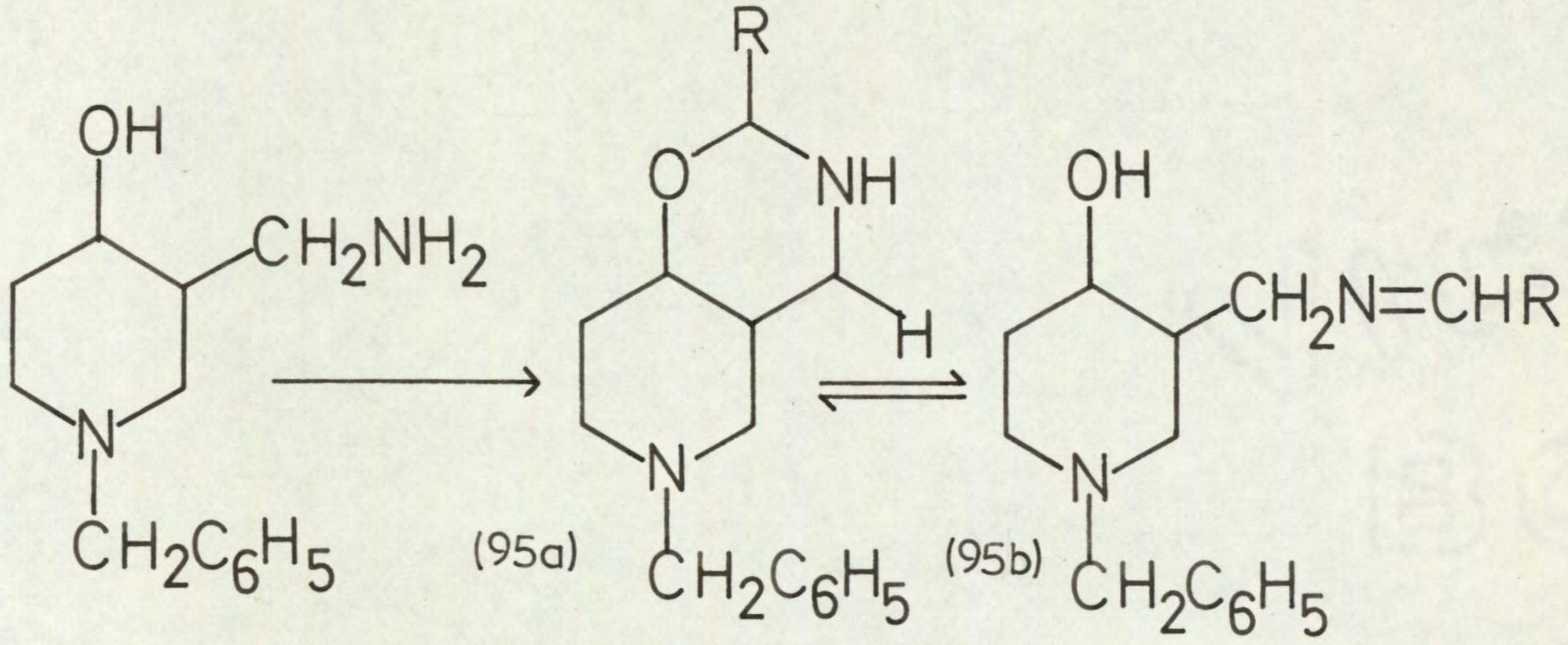
Refluxing the amino-alcohol (91) with acetic anhydride and pyridine gave the amido-ester (94) in good yield. In a preliminary attempt to prepare the amido-



ester, a brown oil with the expected infra-red spectrum was obtained. An attempt to prepare the hydrochloride of this compound gave a small yield of a solid, the infra-red spectrum and equivalent weight of which suggested that the ester had been hydrolysed to the alcohol.

3-Aminomethyl-1-benzyl-4-piperidinol was refluxed in benzene with p-fluorobenzaldehyde and with benzaldehyde in order to obtain the corresponding 6-benzyl-2-

substituted-octahydro-pyrido[3,4,e][1,3]oxazines (95a).



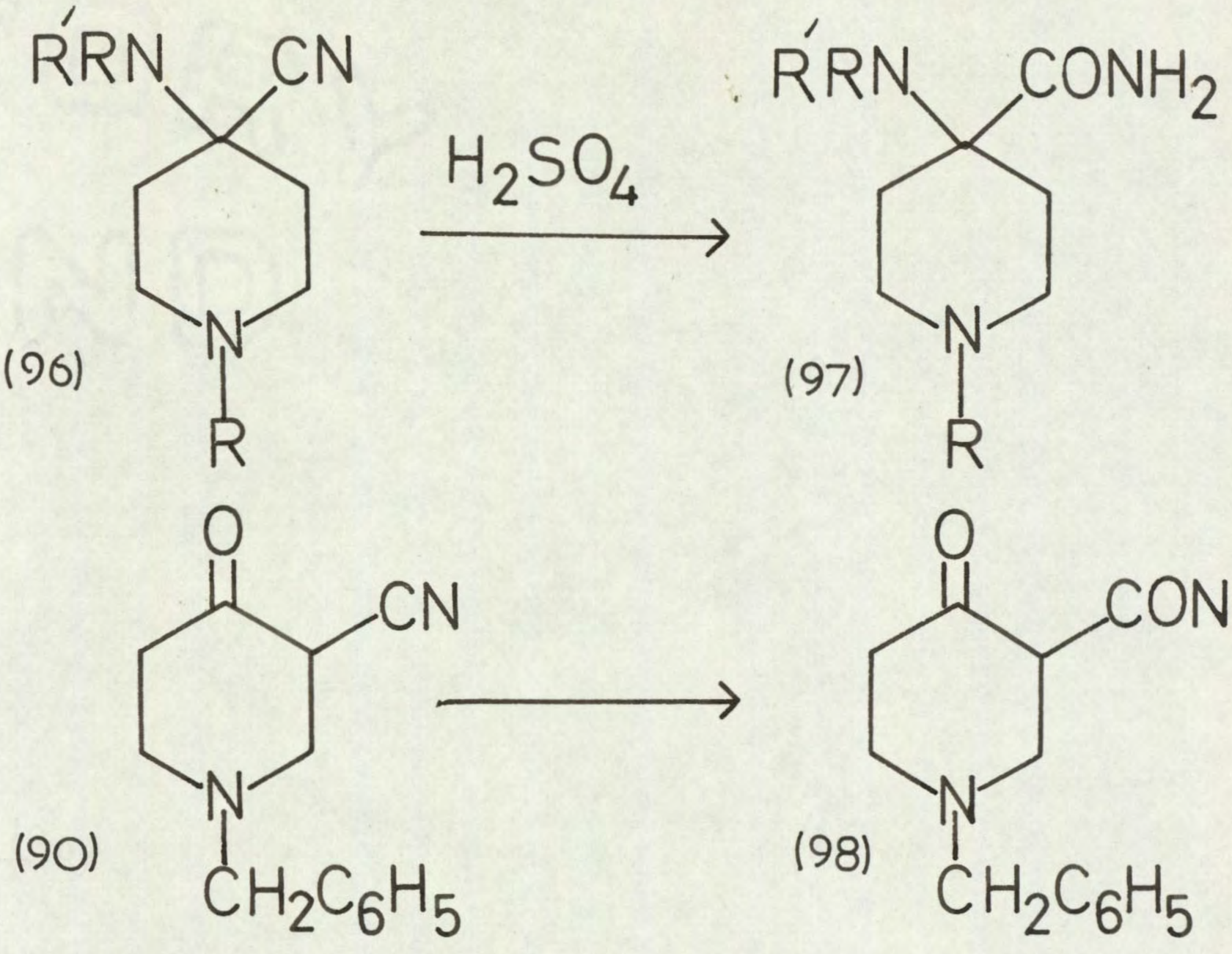
(95a) (95b)

However, on work-up, pale yellow oils were obtained which could not be solidified or induced to crystallise. Infra-red spectra of these products showed peaks in the region of 1640 $cm.^{-1}$ suggestive of the uncyclised compounds (95b). Distillation under reduced pressure tended to decompose the products. A second attempt, using molecular sieves to remove the water formed, thus enabling the temperature to be kept low, was successful. p-Nitrobenzaldehyde gave the cyclised oxazine (95a, R=p-$NO_2C_6H_4$) while p-fluorobenzaldehyde and p-dimethyl-aminobenzaldehyde gave the uncyclised benzylidine (95b, R=p-FC_6H_4, p-$N(CH_3)_2C_6H_4$). These compounds will be discussed later.

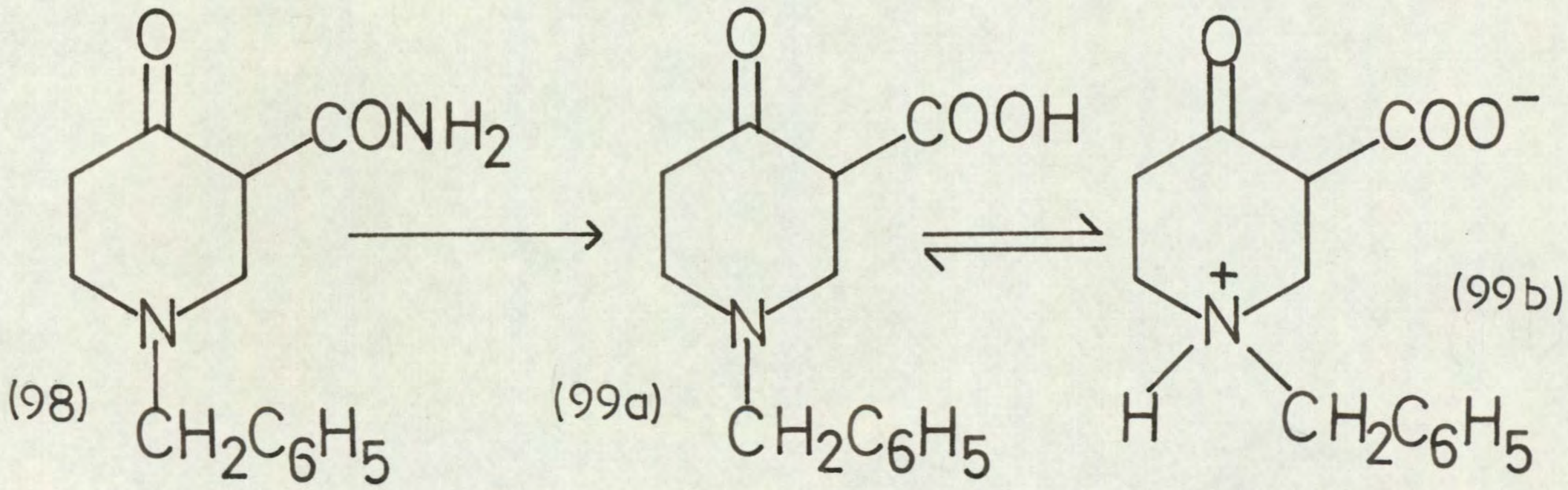
C. Attempted hydrolysis

Janssen et al. (1964, 1965) obtained 4-tertiary amino

4-piperidine carboxamides (97) by treating 4-tertiary



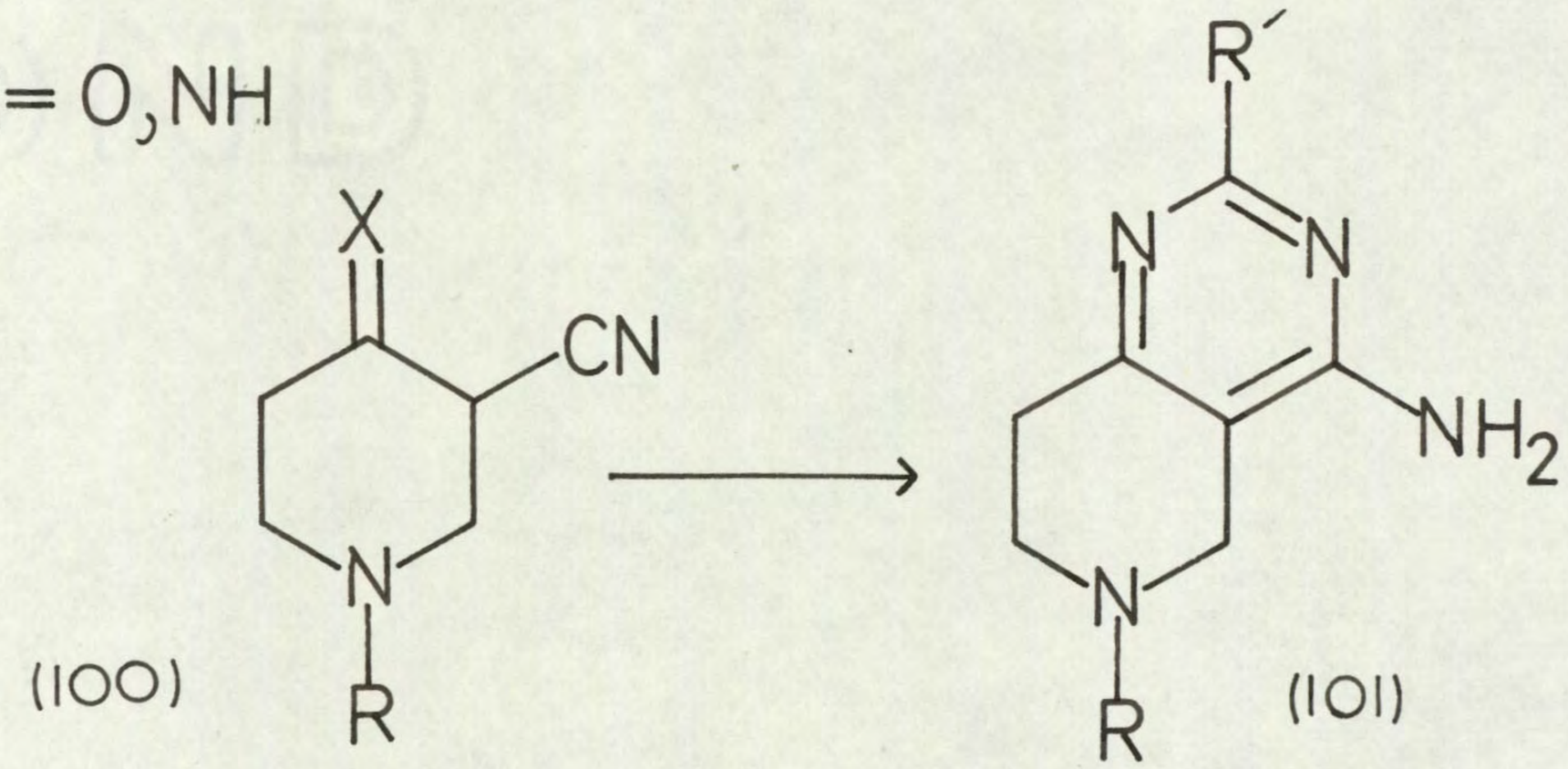
amino-4-cyano-piperidines with 90% H_2SO_4. A similar attempt was carried out using the cyano-ketone (90). The product, however, was difficult to isolate, about 10% of the weight being recovered as a brown oil of indeterminate structure. This may have been due to the complete hydrolysis of the nitrile to the acid and subsequent zwitterion formation (99, a b) which might



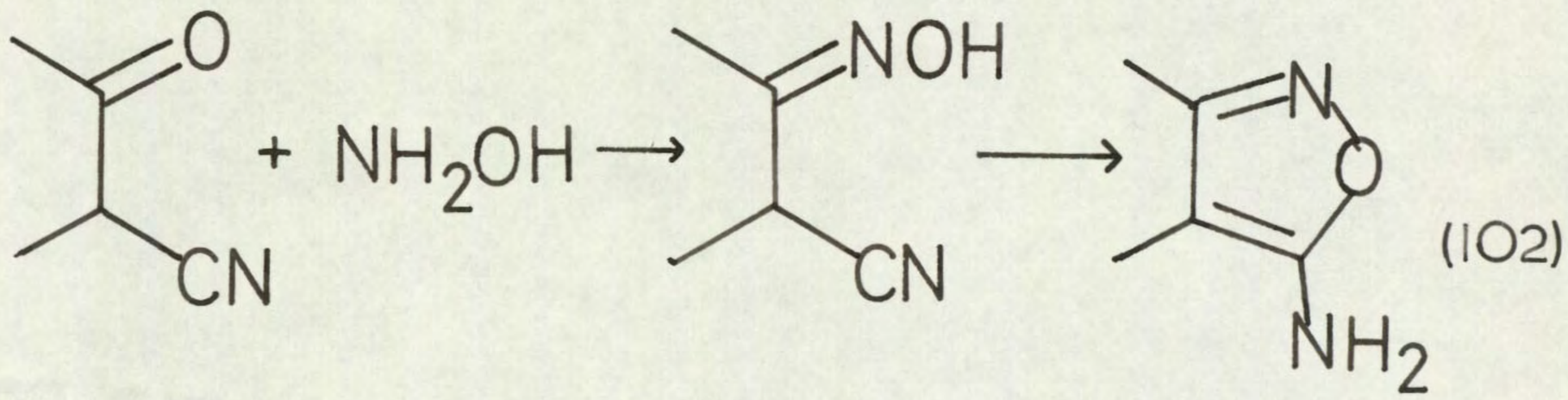
be expected to make extraction difficult.

D. Cyclisations with the cyano-ketone

β-Keto-nitriles can cyclise in a number of ways. Reaction with ureas and amidines have been successfully attempted by Ohnacker (U.S. Pat. 3248395) forming pyrido-pyrimidines with various substituents (101), the starting material being either the cyano-ketone (100, X=O) or the imino-nitrile (100, X=NH). Both these starting materials gave pyrimidines in fair yield.

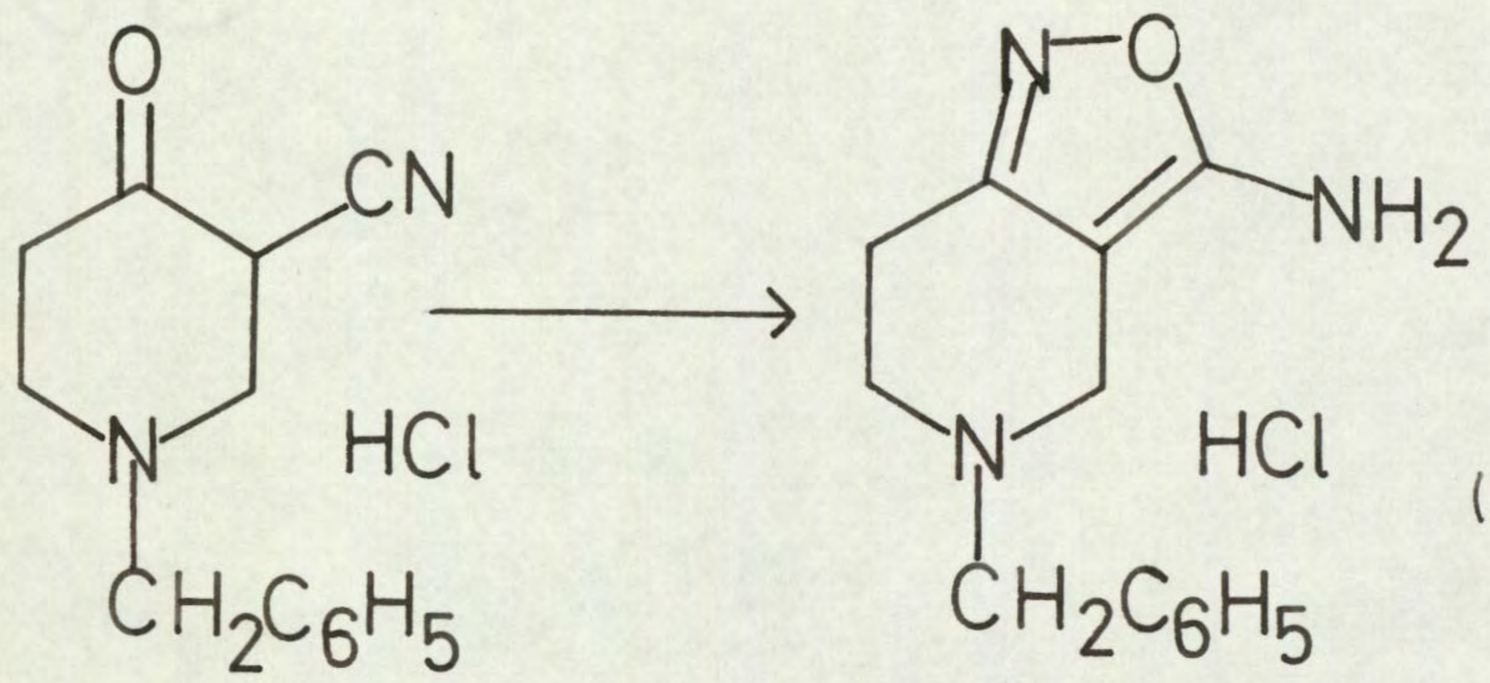


Hydroxylamine reacts with β-keto-nitriles to give oxazolidines (102) (Dunstan and Dymond, 1891, Morgan and Burgess, 1921). It appeared such compounds had not been prepared from 1-benzyl-3-cyano-4-piperidone. The reaction was attempted and 7-amino-5-benzyl-3,4,5,6-



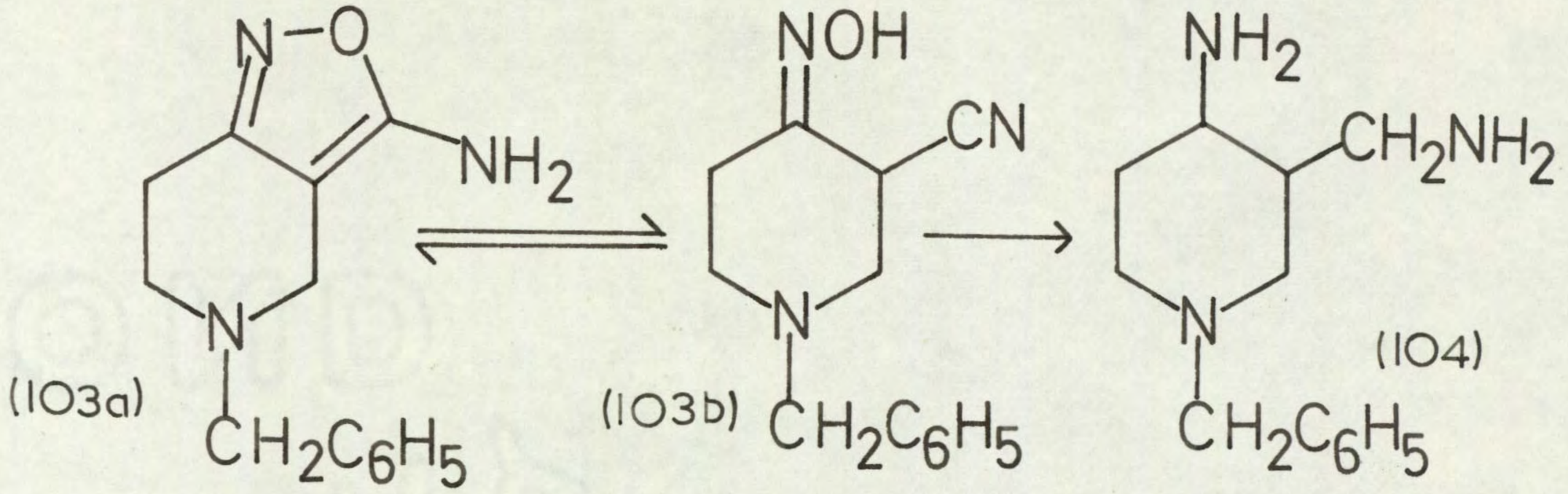
(102)

tetrahydro-isoxazolo[4,3,c]pyridine hydrochloride obtained (103).

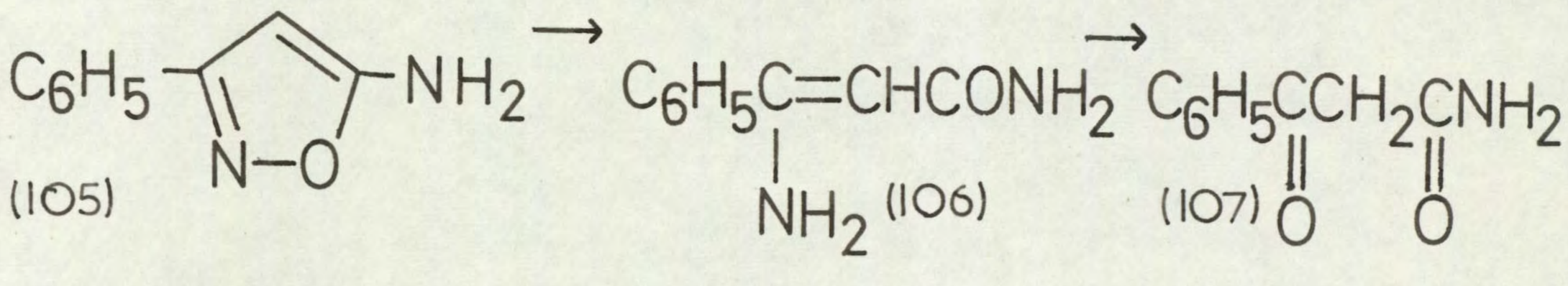


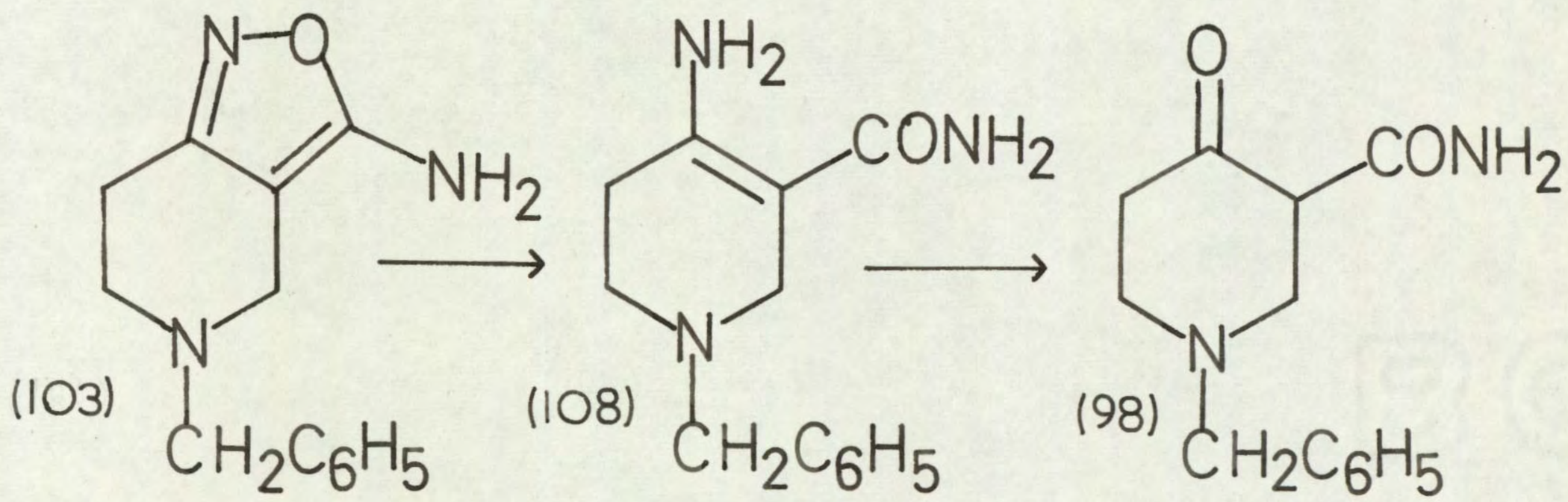
(103)

It was thought that reduction of the isoxazolo pyridine (103) with $LiAlH_4$ might produce the triamine (104) by formation of the open-chain cyano-oxime (103b) which might reduce normally. However, it has been shown (Shaw and Sugowdz, 1954, Awers and Wunderling, 1934) that reduction of isoxazolidines (105) form unsaturated amino-amides (106) by N-O fission and consequent reduction of the imino-enol. The enamine



(106) so formed can be hydrolysed under mild conditions to give the β-keto-amide (107). This method might have

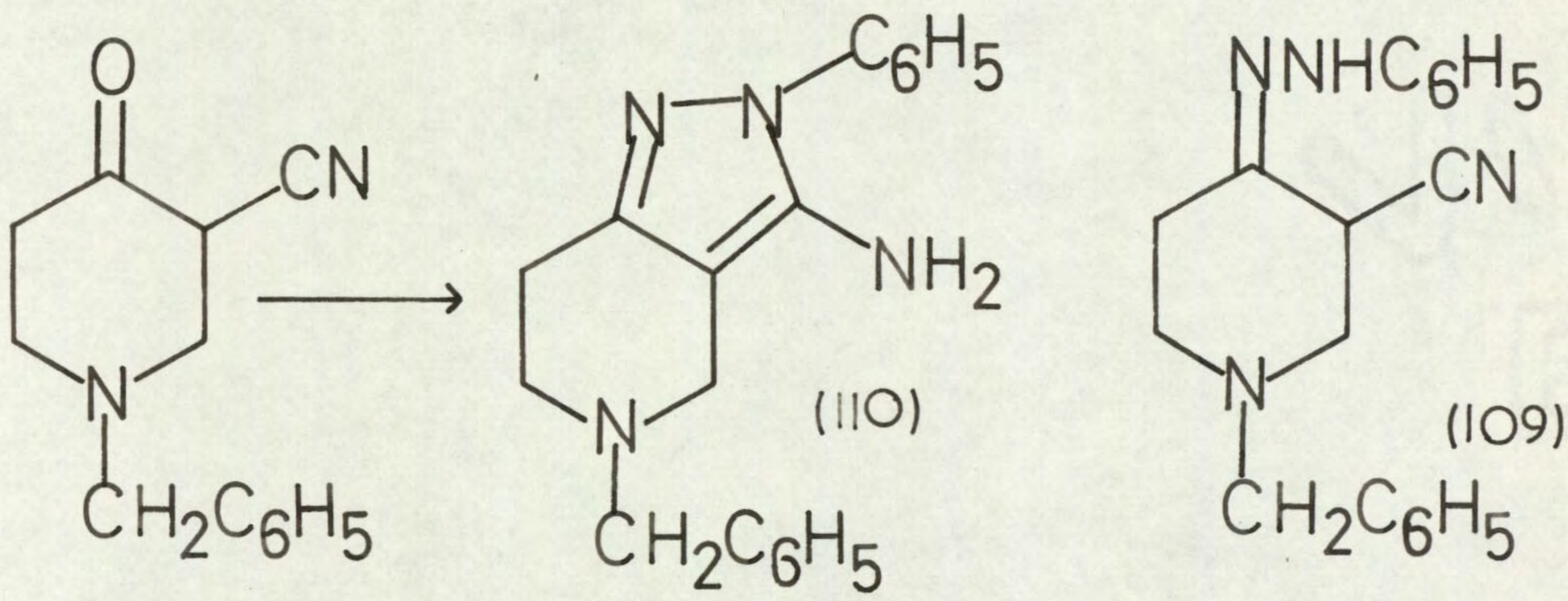




been useful as a route to the β-keto-amide (98) which was not obtainable previously. However, an attempt to reduce the isoxazolo-pyridine (103) with $LiAlH_4$ gave a mixture of products (by thin layer chromatography) which could not be separated. An attempt to form a hydrochloride of the reduction products or their possible

hydrolysis products also failed.

1-Benzyl-3-cyano-4-piperidone was also reacted with phenylhydrazine in an attempt to form the pyrazolo-pyridine (110). The crystalline compound obtained had an equivalent weight of 155 ($C_{19}H_{20}N_4$ requires 152), but the infra-red spectrum showed the presence of a C≡N stretch at 2250 cm.$^{-1}$ and an NH stretch at 3300 cm.$^{-1}$,

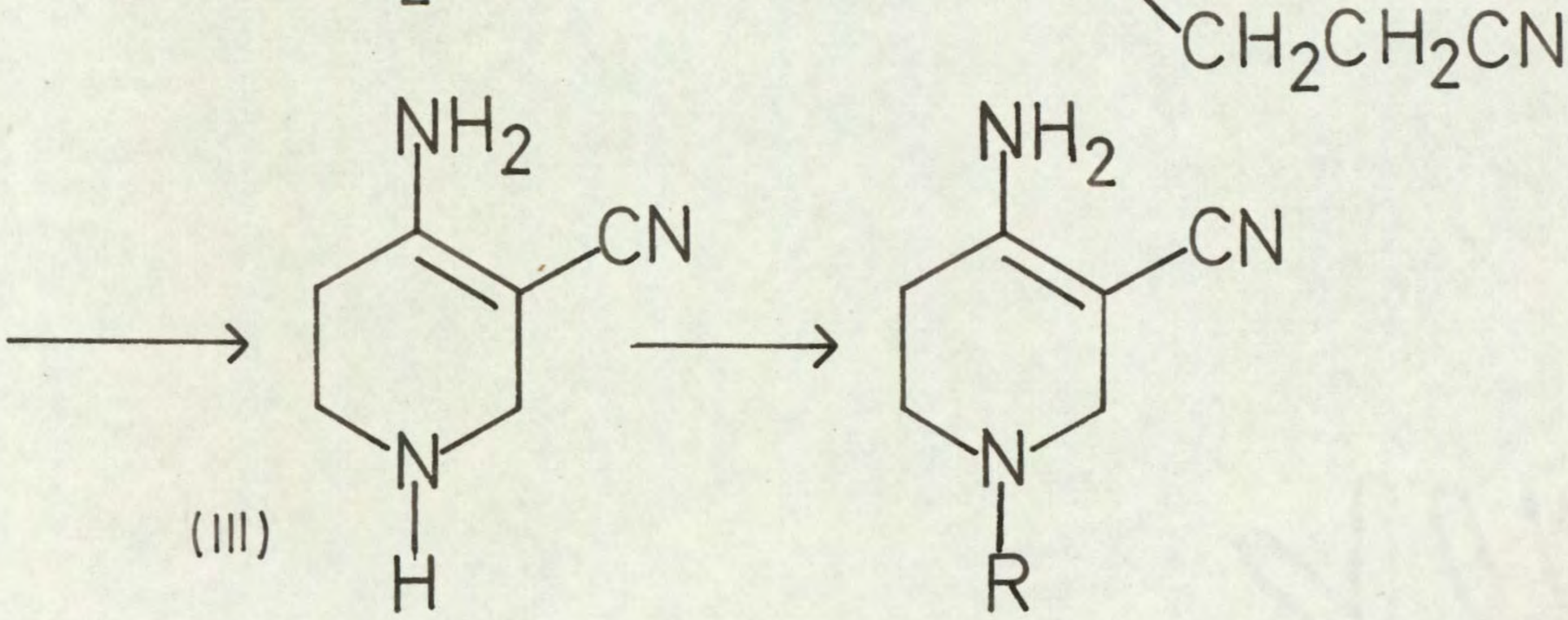


which suggested that the compound was 1-benzyl-3-cyano-4-piperidone phenylhydrazone (109). Attempts to cyclise the hydrazone failed, intractable tars being obtained.

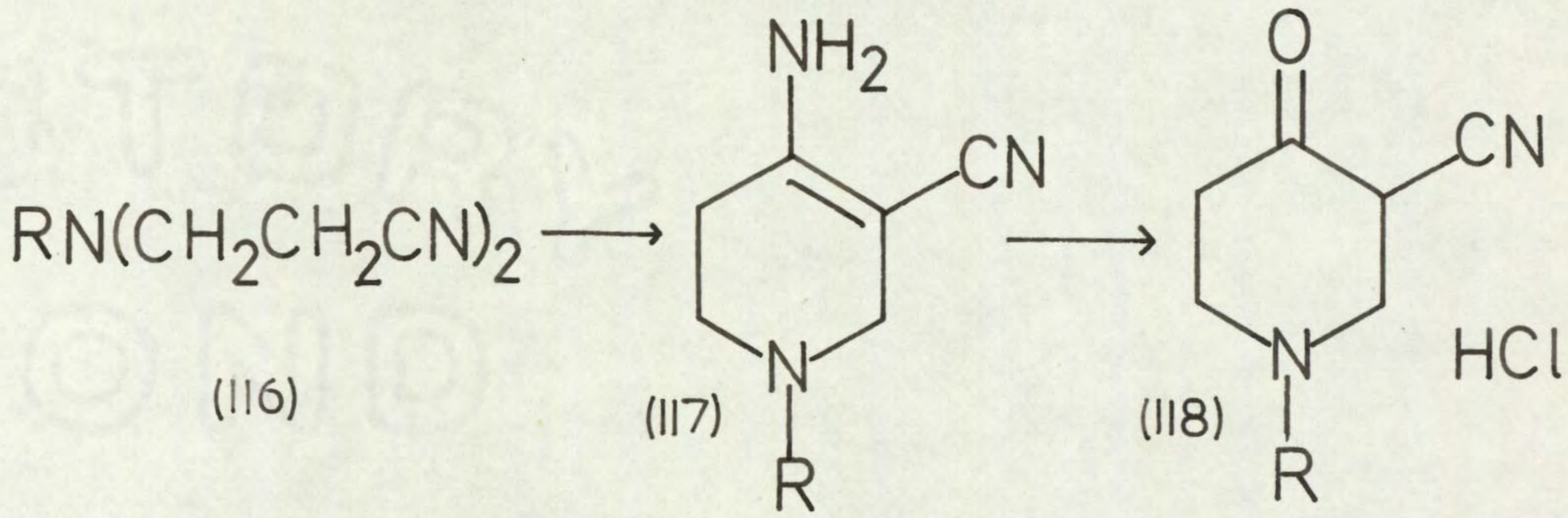
SYNTHESIS OF SOME HOMOLOGUES

A substantial proportion of the compounds prepared in the earlier stages of the present investigation were 1-benzyl-piperidines. The reasons for carrying out initial work with this particular type of compound have been discussed.

The concept that the 1-benzyl group could be catalytically removed and the secondary base reacted with alkyl or aralkyl halides proved less wide in its application than might have been anticipated. In the event it became obvious that independent synthesis of the 1-substituents would prove more fruitful and less troublesome. The difficulties associated with one alternative route, namely the preparation of 4-amino-3-cyano-1,2,5,6-tetrahydro-pyridine (111) for subsequent alkylation have been discussed.



In view of these facts, it was thought that preparation of homologues substituted on the piperidine nitrogen, starting from an amine and acrylonitrile, offered the best alternative. 1-Methyl piperidines were the compounds of choice. Consequently, 3-cyano-1-methyl-4-piperidone hydrochloride (118, R=CH_3) was prepared by the method of Cook and Reed (1945), via the

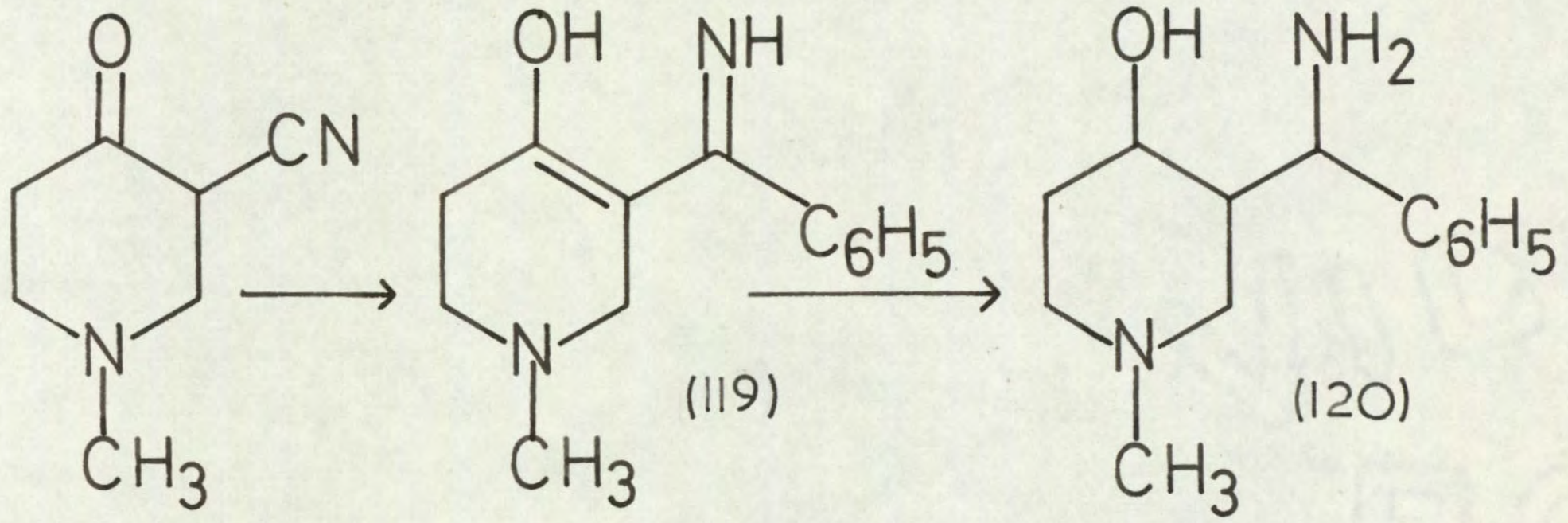


dicyanide (116), cyclisation to give the enamino nitrile (117) and subsequent hydrolysis. 3-Cyano-1-ethyl-4-piperidone hydrochloride (118, R=C_2H_5) and 3-cyano-1-phenethyl-4-piperidone hydrochloride (118, R=$C_6H_5CH_2CH_2$) were prepared similarly.

1. <u>1-Methyl piperidines</u>

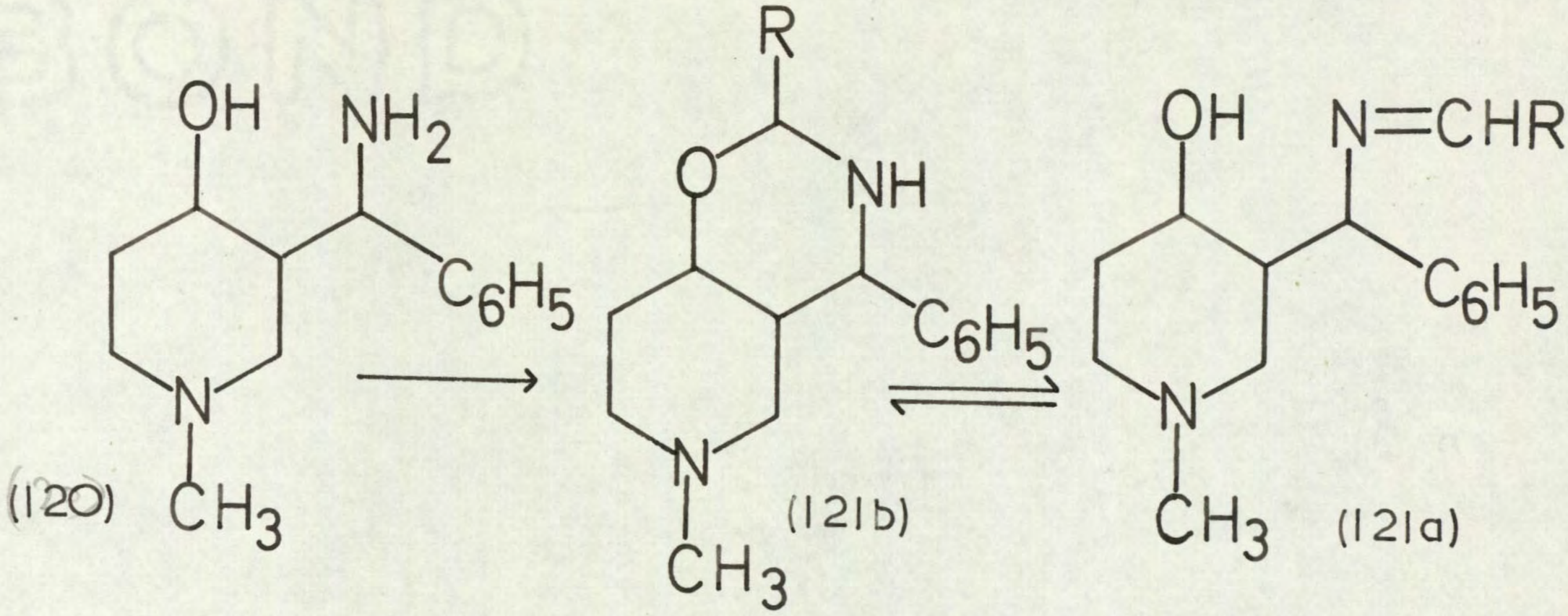
3-Cyano-1-methyl-4-piperidone (118, R=CH_3) was reacted with phenyl magnesium bromide to give a dark red oil which was crystallised with difficulty to give a small yield of 1,2,5,6-tetrahydro-4-hydroxy-1-methyl-3-

phenylimino-pyridine (119). Reduction of the tetrahydro-pyridine with $NaBH_4$ gave an oil from which one isomer (isomer A) of 1-methyl-3-α-phenylaminomethyl-4-piperidinol (120) was obtained in a small yield. Thin

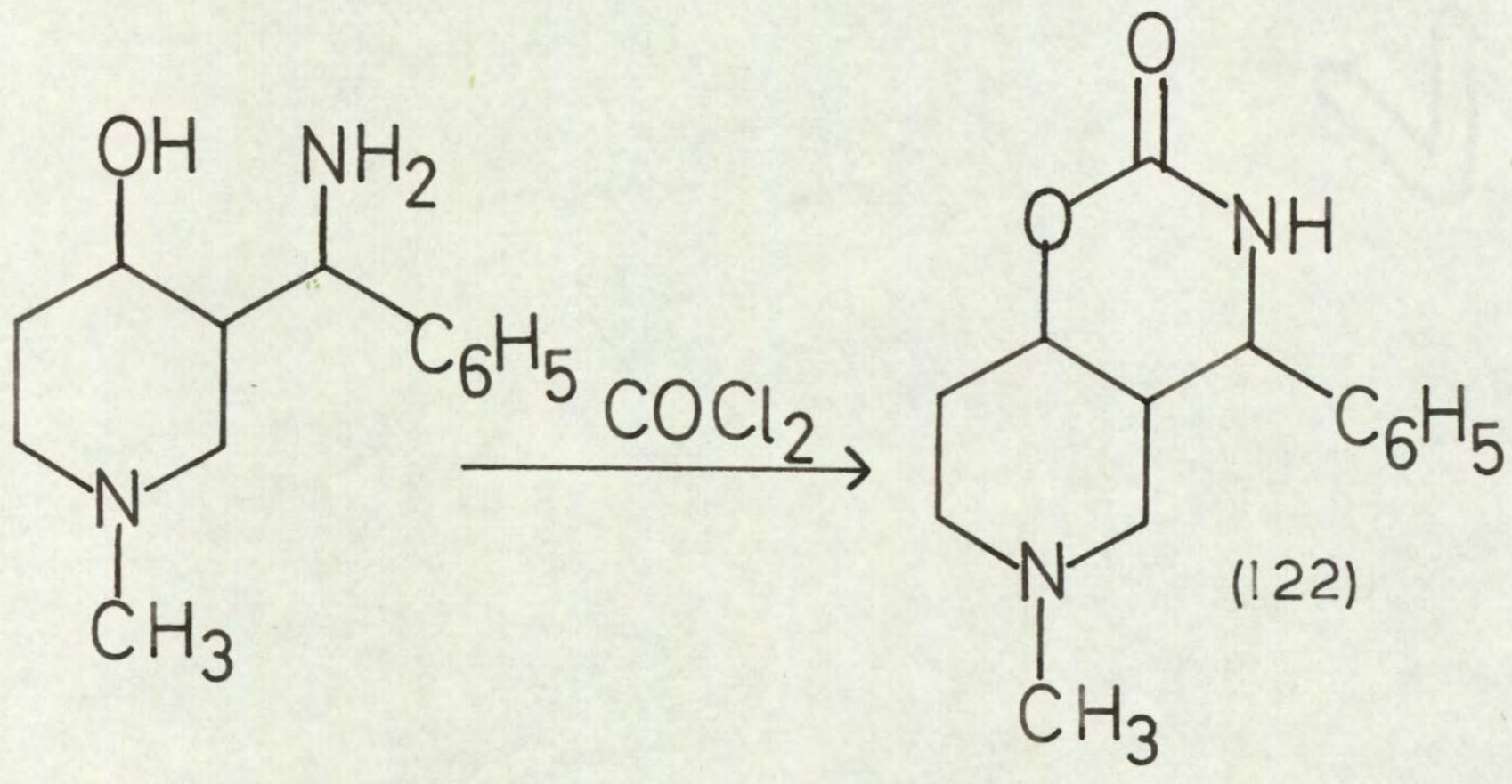


layer chromatography of the remaining oil showed the possible presence of the second isomer as well as two spots, one of which indicated the further presence of isomer A. Attempts to obtain isomer B failed.

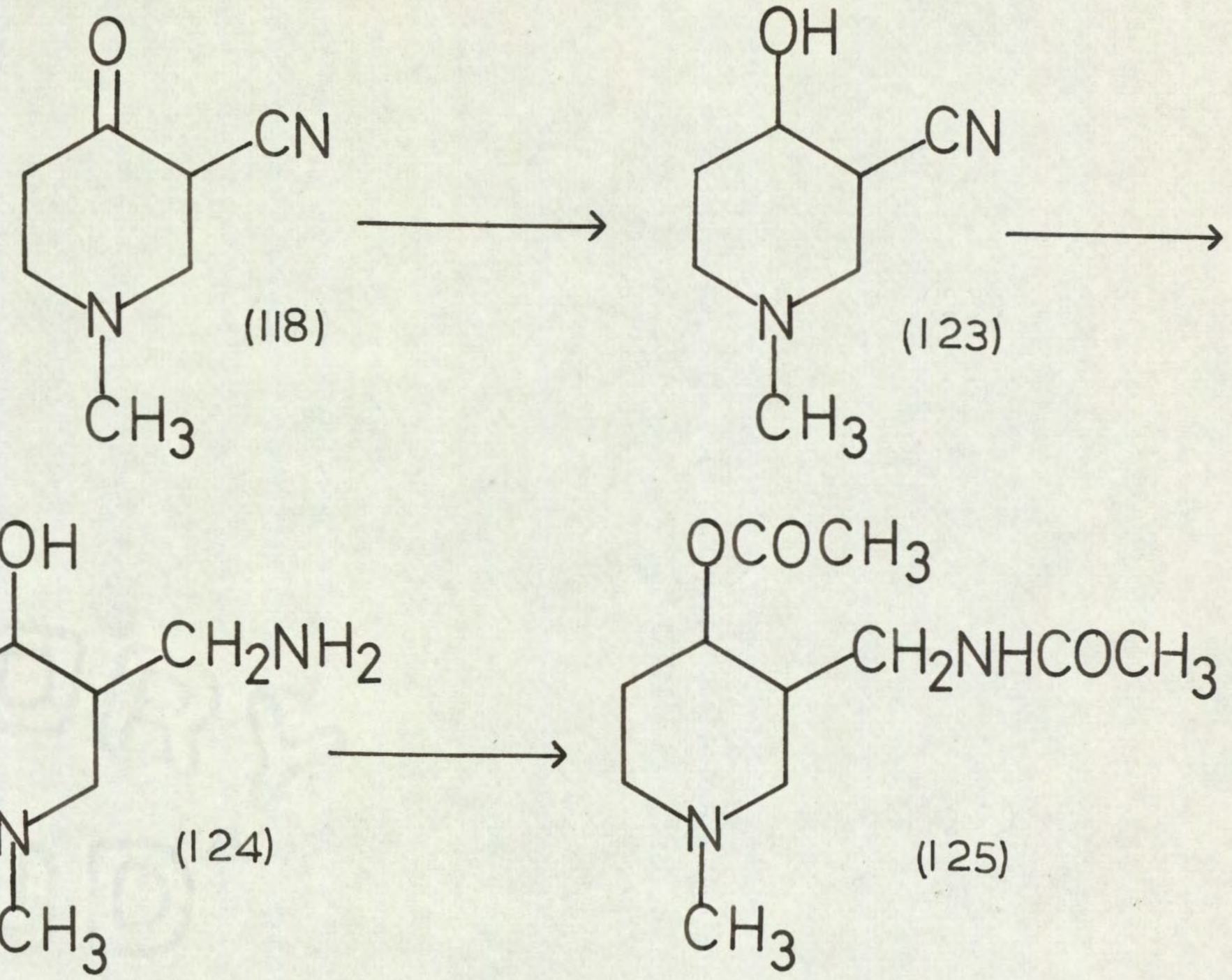
The amido-alcohol (120) was reacted with benzaldehyde and with o-methoxybenzaldehyde. The infra-red spectra of the oils obtained suggested that the non-cyclic Schiff bases (121a) were obtained rather than the oxazines (121b). Attempts to purify the products failed. Reaction with p-nitrobenzaldehyde yielded the imine (121a, R=p-$NO_2C_6H_4$) in small yield when milder conditions prevailed. The 2-oxo-pyrido-



oxazine (122) was also obtained in a small yield on reaction of the amino-alcohol with phosgene.

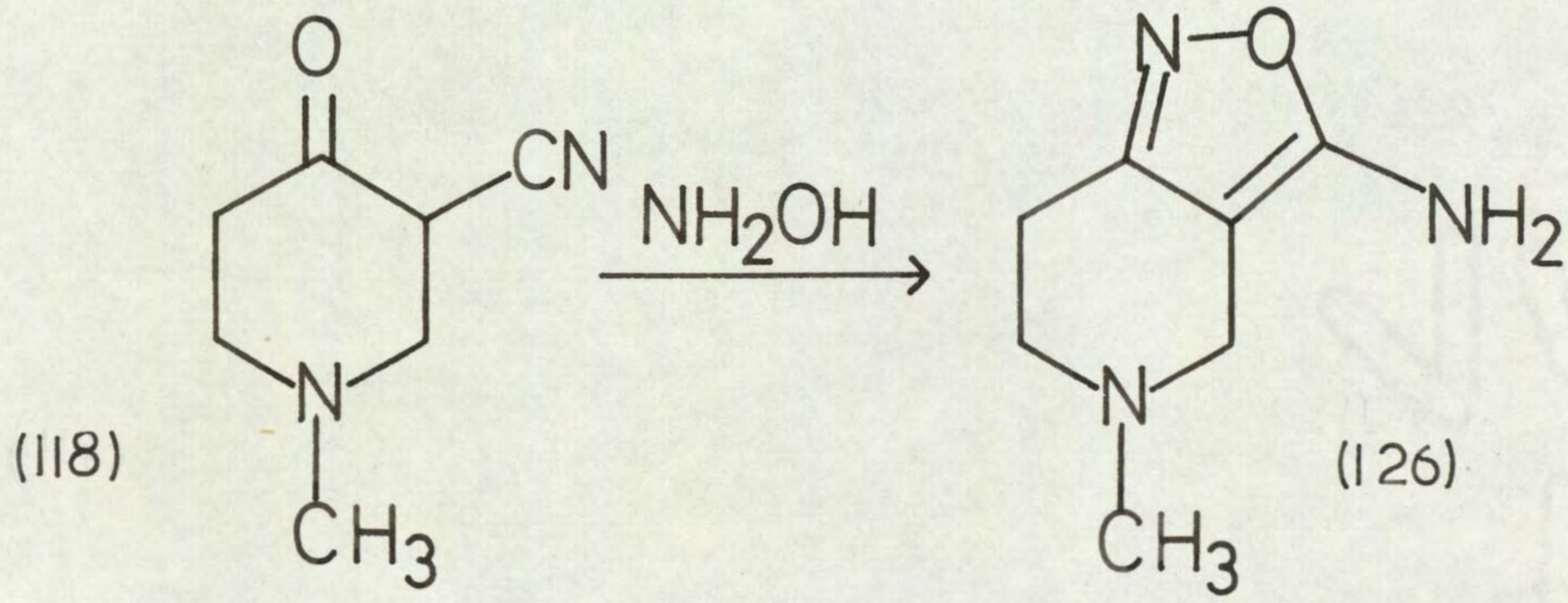


Reduction of the cyano-ketone (118, R=CH_3) to the amino-alcohol (124) was achieved using $NaBH_4$ and subsequent reduction of the cyano-alcohol (123) with $LiAlH_4$. The amino-alcohol was acetylated with acetic anhydride to give 3-acetamidomethyl-4-acetoxy-1-methyl-piperidine (125). Attempts at cyclisation with aldehydes



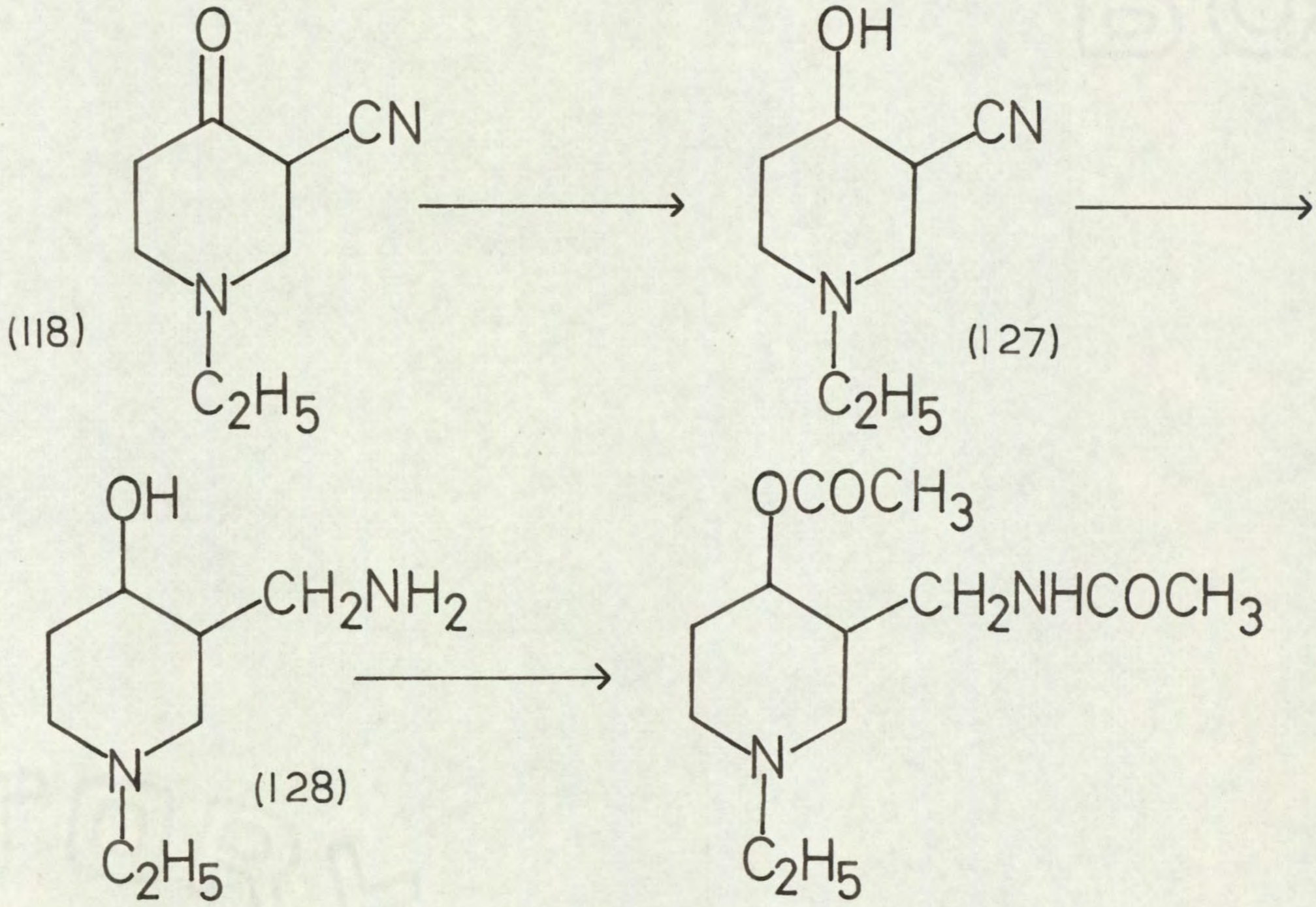
yielded tarry oils from which no pure compounds were obtained. Infra-red spectra of these products indicated that the uncyclised compound predominated.

Finally, 3-cyano-1-methyl-4-piperidone was reacted with hydroxylamine to give the oxazolo-pyridine (126).



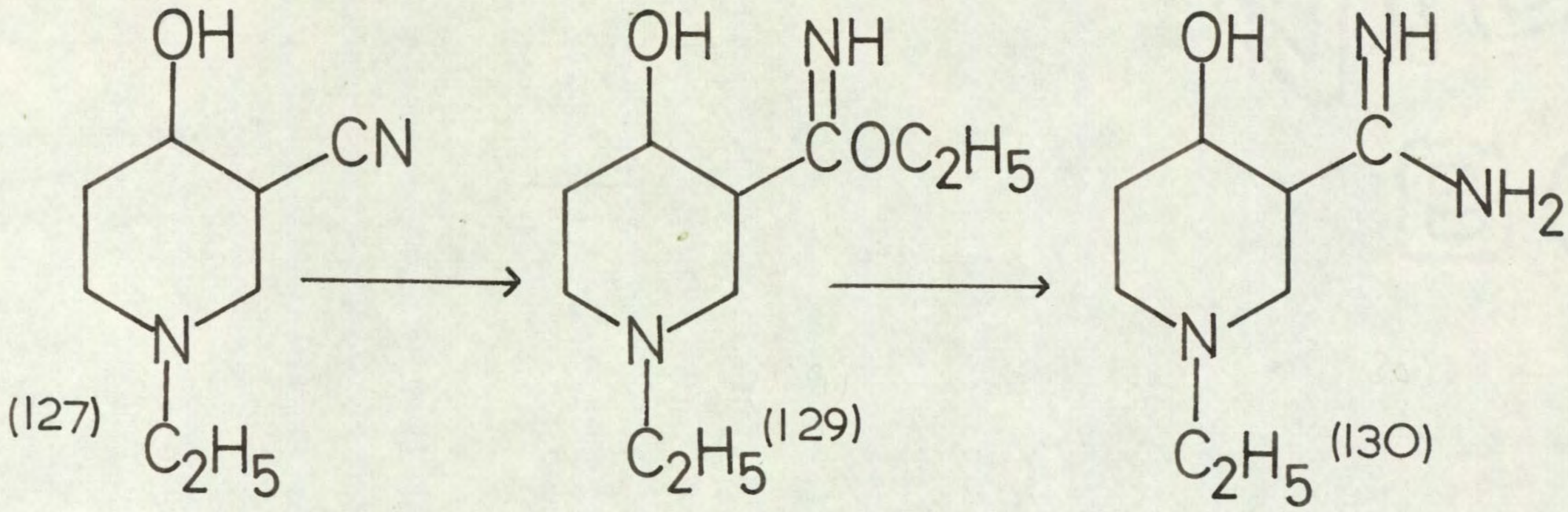
2. <u>1-Ethyl piperidines</u>

3-Cyano-1-ethyl-4-piperidone (118, R=C_2H_5) was reduced with $NaBH_4$ to the cyano-alcohol (127), which was further reduced with $LiAlH_4$ to the amino-alcohol (128).



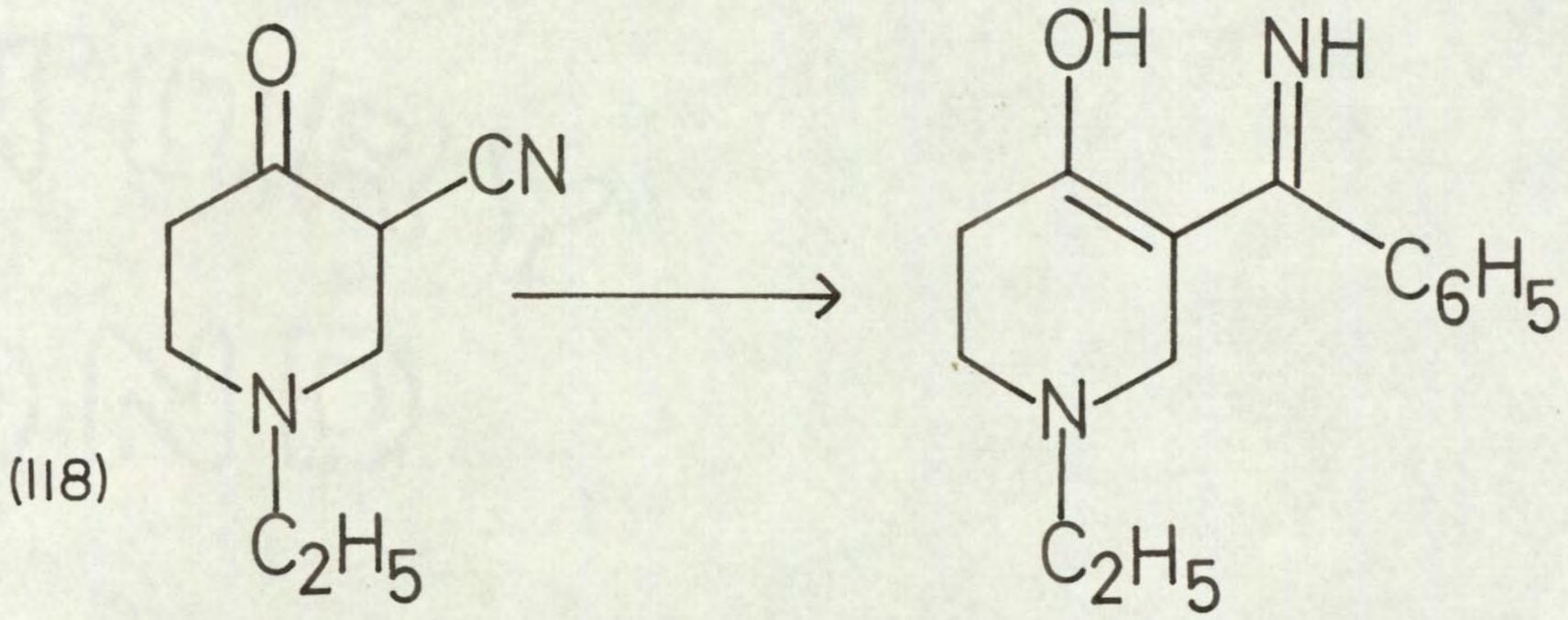
Acylation with acetic anhydride gave 3-acetamidomethyl-4-acetoxy-1-ethyl-piperidine. Reaction of the amino-alcohol (128) with benzaldehyde gave an oil with an infra-red spectrum suggestive of the uncyclised Schiff base. No pure product was obtained.

3-Cyano-1-ethyl-4-piperidinol (127) was dissolved in dry ethanolic hydrogen chloride in an attempt to form the imino-ether (129), which could subsequently be reacted with ammonia to give a hydroxy-amidine (130). The only product isolated, however, was the hydroxy -



cyanide hydrochloride.

Attempted synthesis of the imino-enol from the cyano-ketone (118) gave a dark red oil which had the expected infra-red spectrum. The oil did not solidify

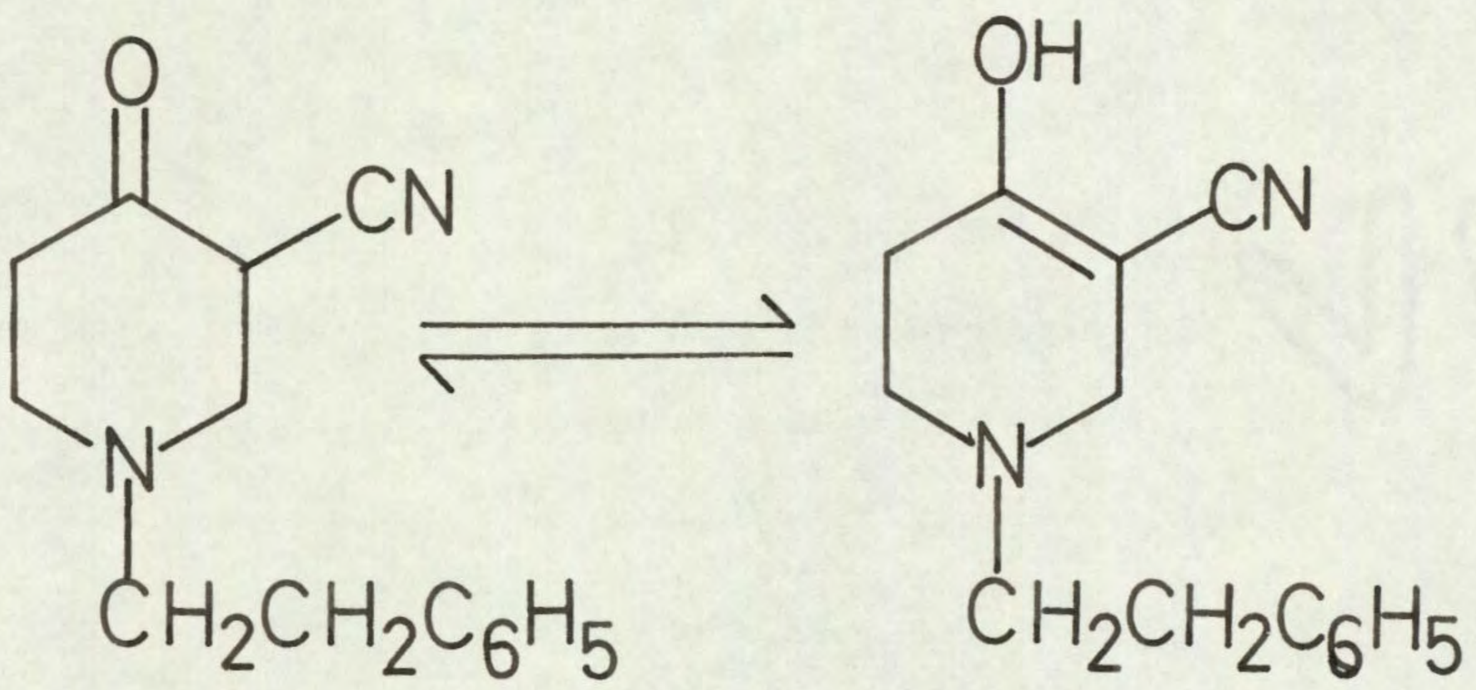


or cystallise and was not characterised. In view of the possible number of side products, reduction of the impure compound was not attempted.

3. <u>1-Phenethyl compounds</u>

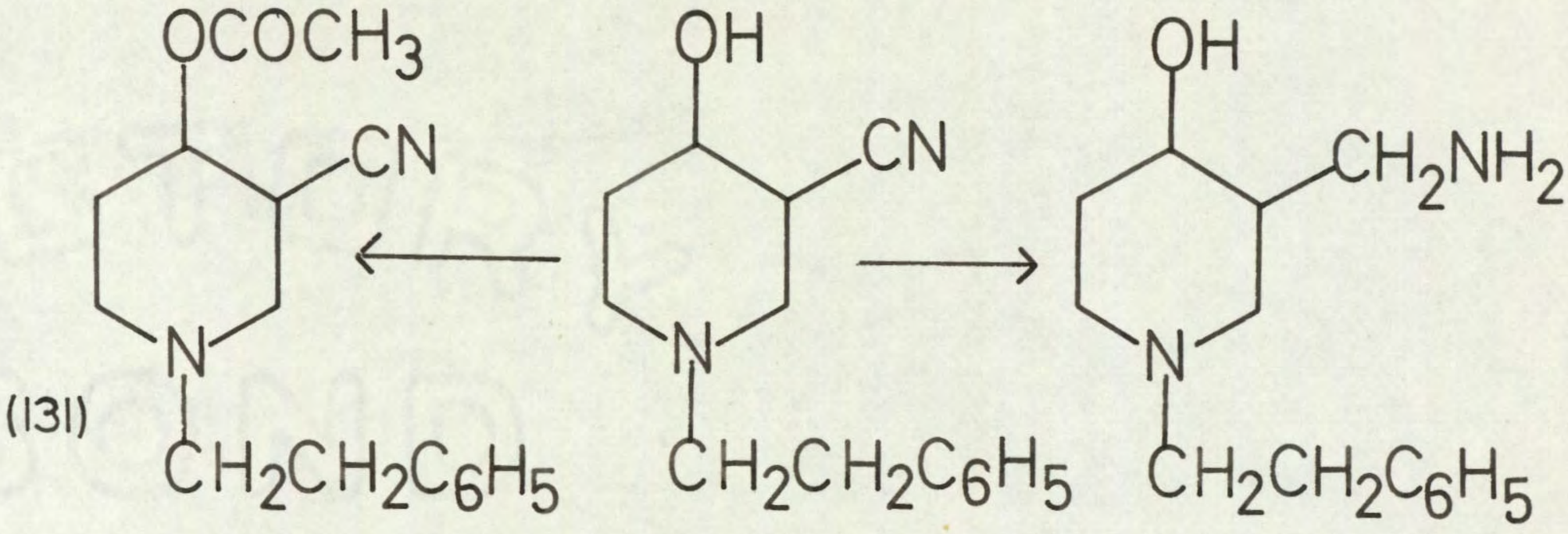
3-Cyano-1-phenethyl-4-piperidone (118, R=$C_6H_5CH_2CH_2$)

similarly did not give an imino-enol when reacted with phenyl magnesium bromide. The infra-red spectrum of the products obtained was not the expected one, but suggested that some addition had occurred on the carbonyl to give the tertiary alcohol. Thin layer chromatography showed the presence of multiple products, none of which could be obtained pure. This anomalous result may have been due to the 3-cyano-1-phenethyl-piperidone being more in the keto form than in the enol form suggested for



the other piperidones.

Reduction of the cyano-ketone with $NaBH_4$ gave the cyano-alcohol as a white pasty mass which could not be crystallised, neither could a crystalline salt be obtained. Reaction of the alcohol with acetic anhydride gave the ester (131) characterised as the hydrochloride. Reduction of the cyano-alcohol gave a clear colourless oil with an equivalent weight of 230 ($C_{14}H_{22}N_2O$ requires 234). The infra-red spectrum



(131)

showed lack of C≡N absorption, indicating that the nitrile had been reduced. The amino-alcohol could not be induced to solidify or crystallise and no derivative such as a dihydrochloride or diacetate could be obtained pure.

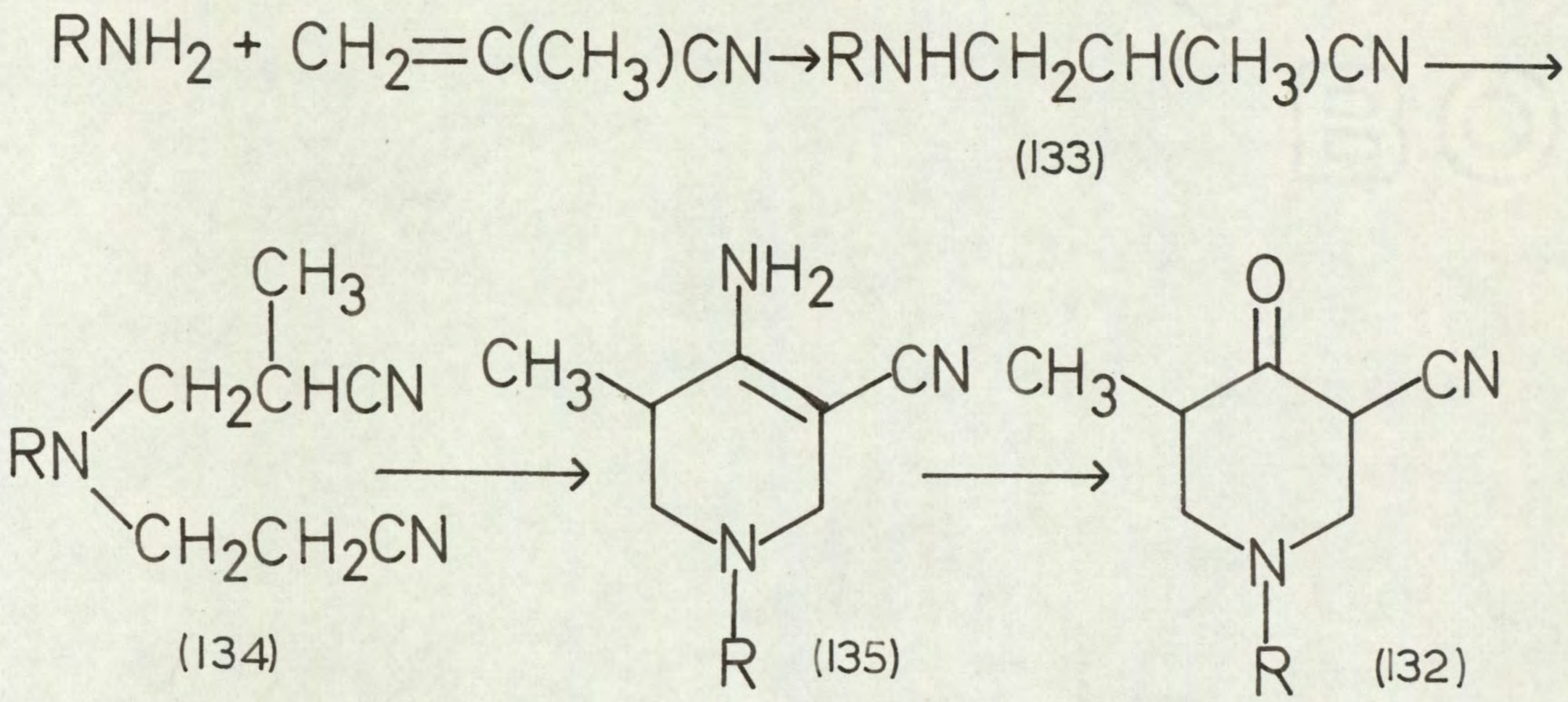
The cyano-ketone reacted with hydroxylamine to give 7-amino-3,4,5,6-tetrahydro-5-phenethyl-isoxazolo [4,3,c] pyridine, characterised as the hydrochloride.

4. 1-Benzyl-5-methyl piperidines

It was decided in the present work to attempt the synthesis of some 5-methyl piperidones of the type (132), following a route similar to that used previously (see flow sheet VII).

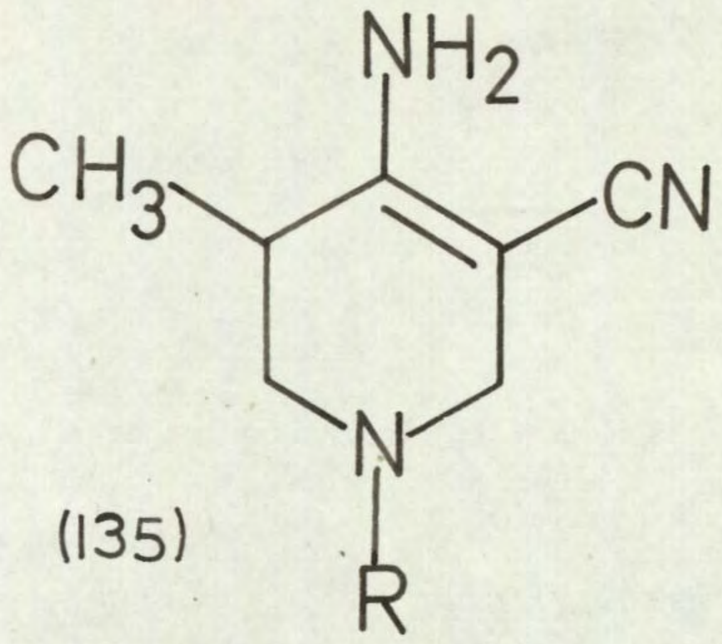
Benzylamine was refluxed with excess methacryl-onitrile, yielding β-benzylamino-α-methyl-propionitrile (133, R=$C_6H_5CH_2$). Reaction of benzylamine with 2 moles

Flow Sheet VII

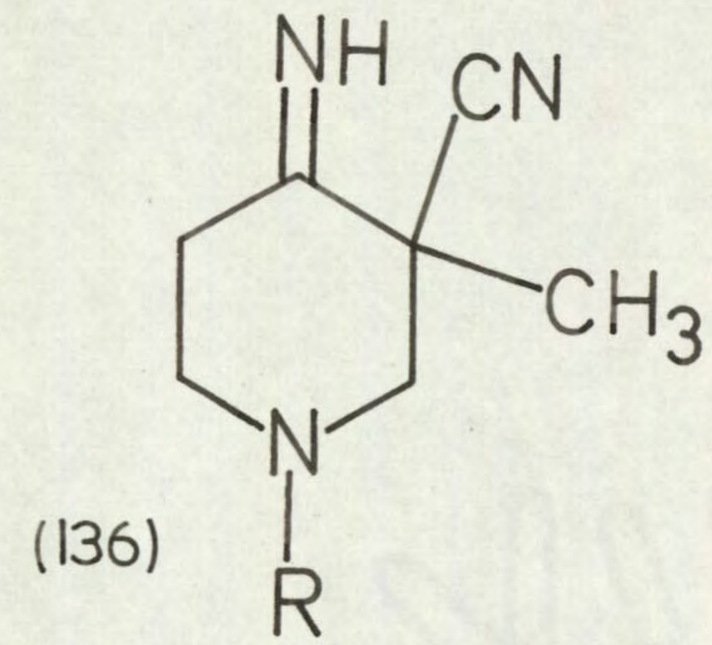


of methacrylonitrile to give the disubstituted tertiary amine was not expected to occur due to the decrease in the reactivity of the acrylic derivative on introducing a methyl group into the α position. Refluxing the aminonitrile (133) with excess acrylonitrile and 10% by weight of acetic acid gave the tertiary amine (134). This was cyclised with sodium in toluene to give the expected enaminonitrile (135, R=$C_6H_5CH_2$) in fair yield.

The cyclisation might have proceeded in one of two directions, to give the expected compound (135) or the imino nitrile (136) by cyclising on the opposite nitrile group. The latter would not be expected to occur due to the inductive effect of the methyl group, which would destabilise the intermediate II formed during the cyclising reaction, the intermediate I being more stable

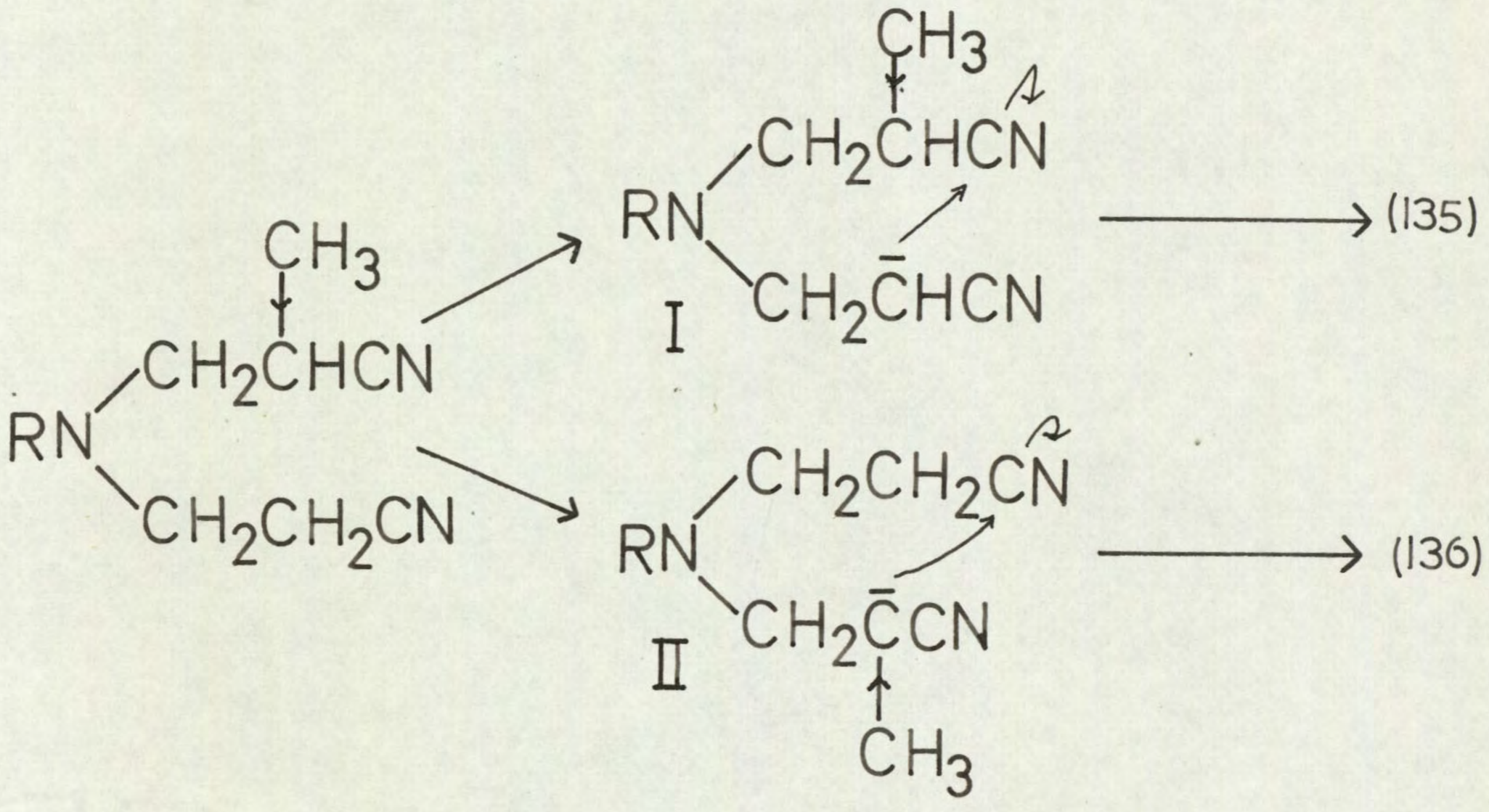


(135)

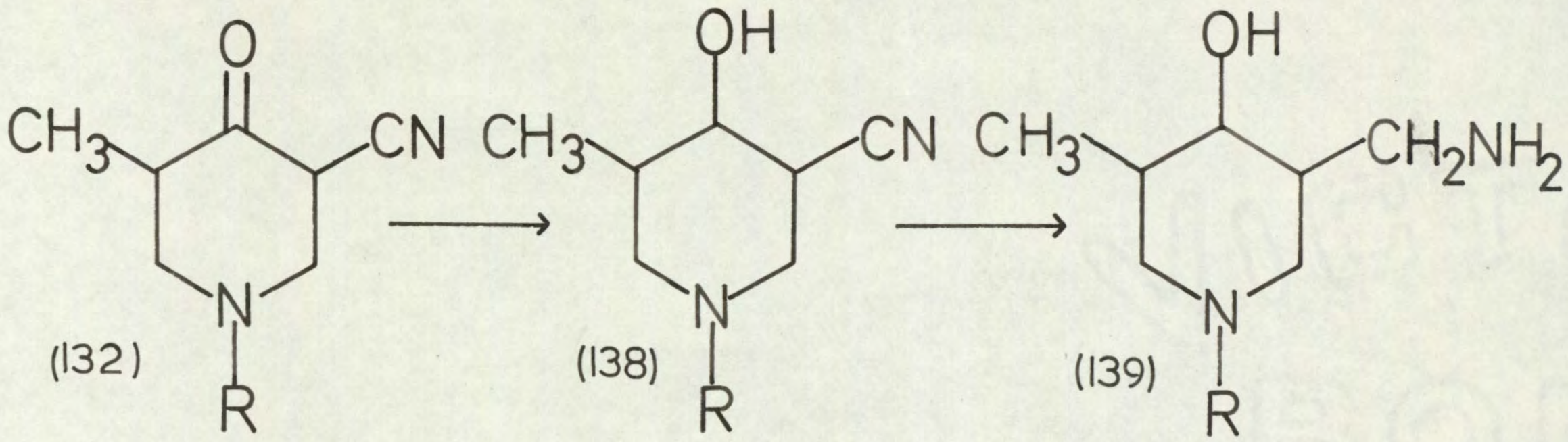


(136)

and so more easily formed.



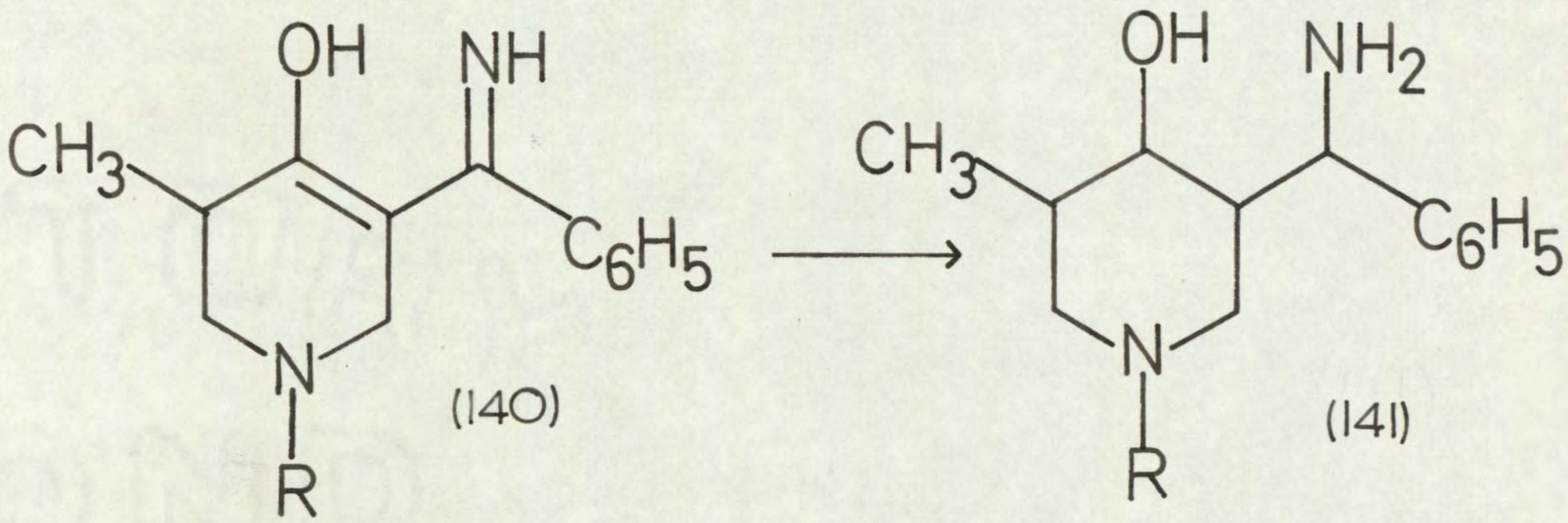
The enamine was hydrolysed to give 1-benzyl-3-cyano-5-methyl-4-piperidone hydrochloride (132, R=$C_6H_5CH_2$). Reduction with $NaBH_4$ gave 1-benzyl-3-cyano-5-methyl-4-piperidinol (138) as an oil. A small fraction of this compound crystallised. Thin layer chromatography on the residue showed a number of spots. Reduction of the



cyano-alcohol was not attempted in view of the low yield.

Reaction of the cyano-ketone (132, R=$C_6H_5CH_2$) with phenyl magnesium bromide gave a red oil which crystallised with difficulty to give 1-benzyl-1,2,5,6-tetrahydro-4-hydroxy-5-methyl-3-phenylimino-pyridine (140).

Reduction with $NaBH_4$ gave the amino-alcohol (141).



Examination of the amino-alcohol reveals the possible existence of four geometric isomers. Thin layer chromatography on the product of the reduction of the imino-enol revealed the possible presence of all four isomers. Attempts at obtaining a solid failed.

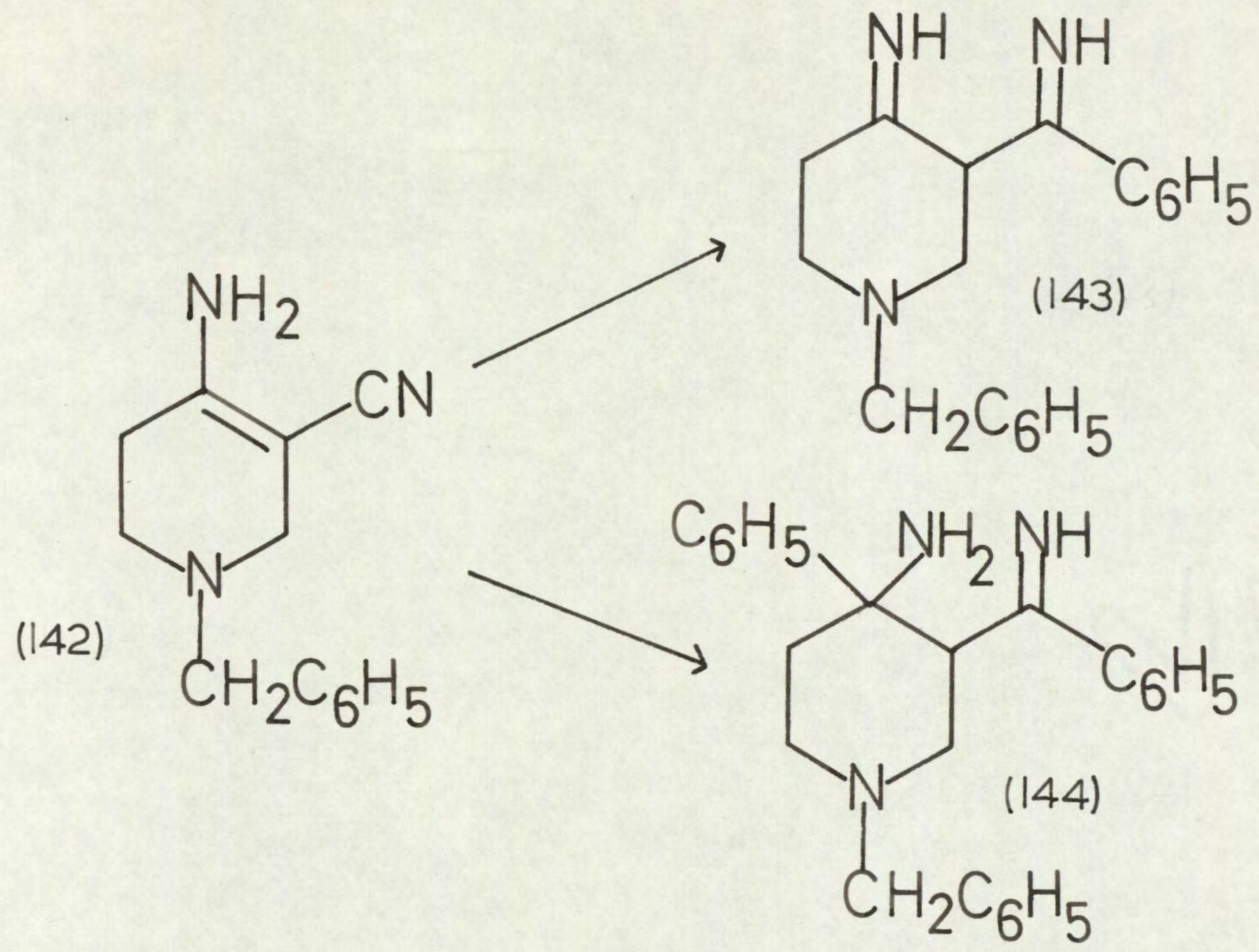
4-Amino-3-cyano-1,2,5,6-tetrahydro-5-methyl-1-phenethyl-pyridine (135, R=$C_6H_5CH_2CH_2$) was synthesised in a similar manner to the 1-benzyl compound. Hydrolysis of the enamine gave a pasty solid which could not be obtained pure.

In view of the results obtained, further work in this section was not pursued.

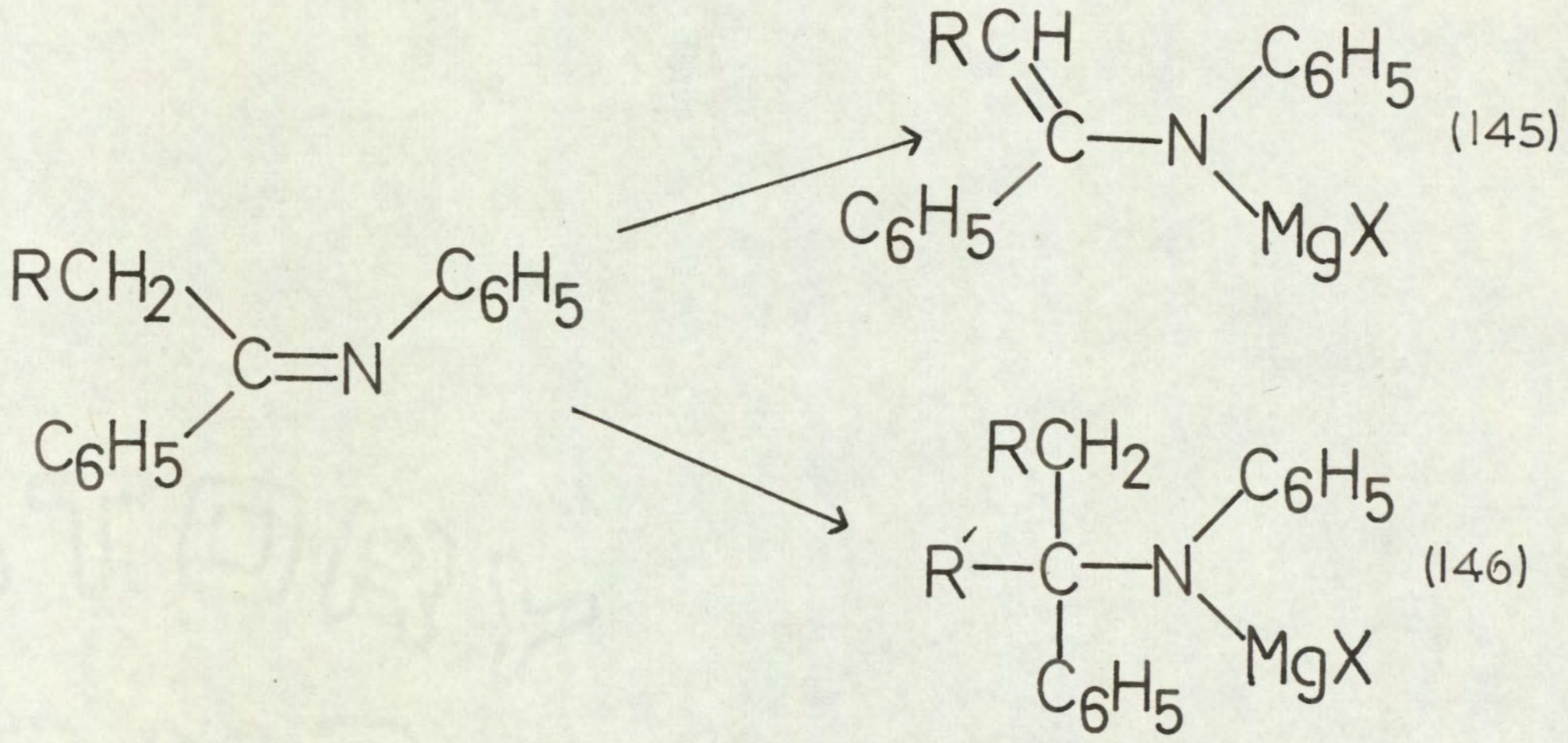
SOME REACTIONS WITH 4-AMINO-1-BENZYL-3-CYANO 1,2,5,6-TETRAHYDRO-PYRIDINE

Some reactions were attempted using the intermediate enamine (142) formed in the preparation of 1-benzyl-3-cyano-4-piperidone.

An attempt was made to react the enamine with organometallic reagents. The compounds which might have been expected were either the di-imine (143), due to reaction with one mole of organometallic reagent, or the aminoimine (144) on reaction with 2 moles of organometallic reagent. Plancher *et al.* (1907) found that addition of Grignard reagents to imines gave an enolate salt (145) rather than the addition product

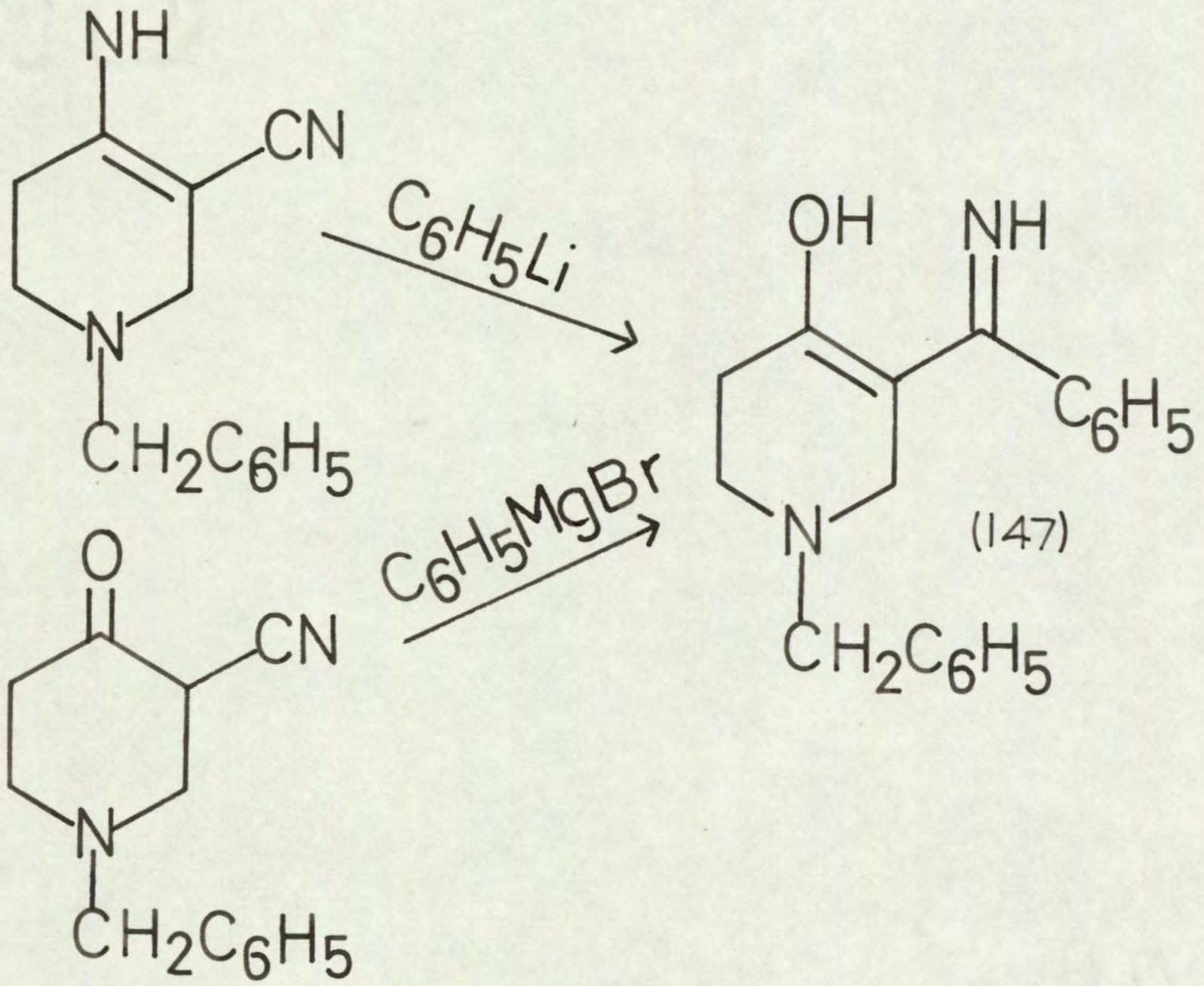


(146), although this was obtained by Gilman and Eisch (1957).



In view of this, 4-amino-1-benzyl-3-cyano-1,2,5,6-tetrahydro-pyridine was reacted with phenyllithium to give a dark red oil, smelling strongly of bromobenzene.

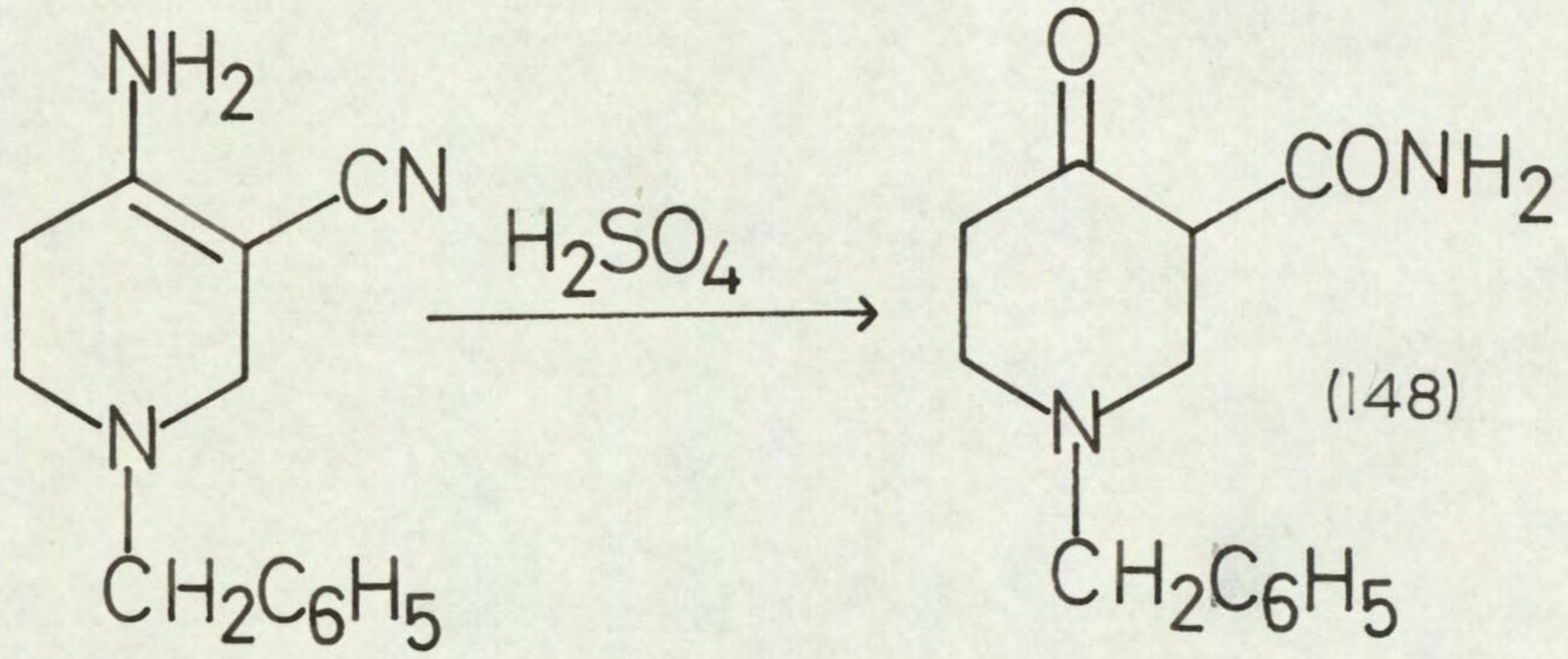
Thin layer chromatography showed the presence of four products. Acid extraction left a solid which was found to be diphenyl (C_6H_5-C_6H_5), a common by-product of phenyl metallic reactions. Basification of the acid solution and separation of the resulting oil on an alumina column gave a small yield of a solid which was identical with 1-benzyl-1,2,5,6-tetrahydro-4-hydroxy-3-phenylimino-



pyridine (147) which had been obtained from 1-benzyl-3-cyano-4-piperidone. The presence of the imino-enol (147) was probably due to the formation of the di-imine (143) and subsequent hydrolysis of this under the conditions used in the work-up of the reaction mixture. The three remaining fractions could not be crystallised.

Hydrolysis of the enamine under conditions similar

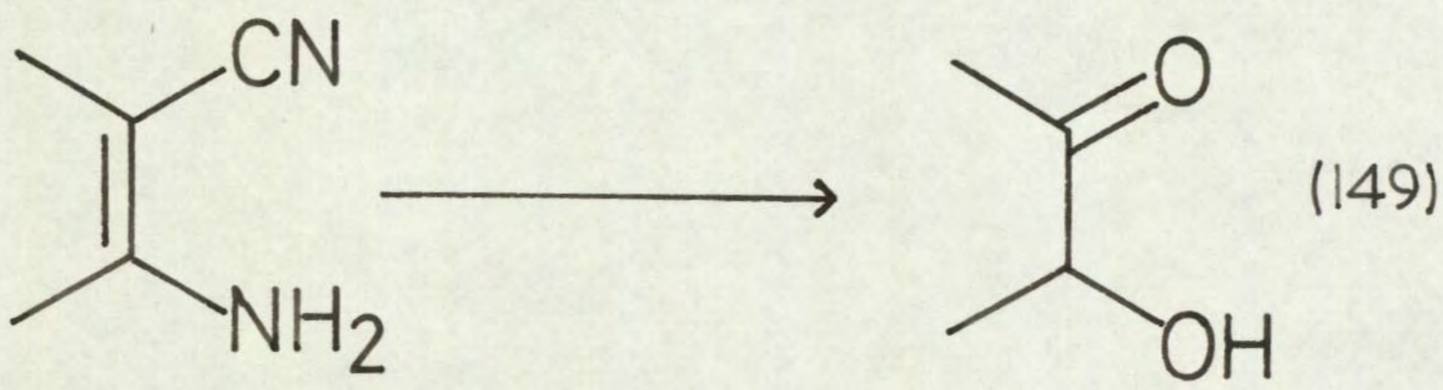
to those used by Janssen *et al*. (1964) might have been expected to yield the keto-amide (148). However, on dissolving in conc. H_2SO_4, the compound tended to char,



(148)

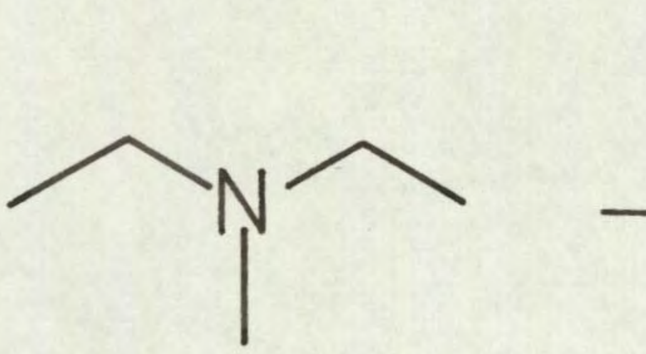
and reaction at low temperatures gave a small yield of 1-benzyl-3-cyano-4-piperidone.

Oxidation of double bonds with potassium permanganate in neutral solution can give a variety of products. Tull *et al*. (1955), for example, found that oxidation of enamines gave α-hydroxy ketones (149). Cavé *et al*. (1967) found that oxidation of tertiary amines tended to give amides. This was supported by Ayes *et al*. (1964), who oxidised (151) to give (152).

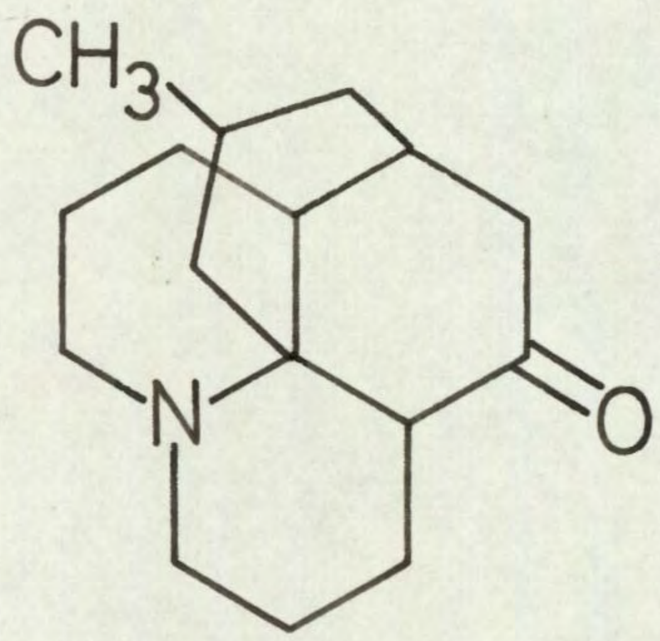


(149)

Freundenberg (1918) obtained a diol on reaction of alkaline permanganate with a tetrahydro-pyridine (153).



(150)



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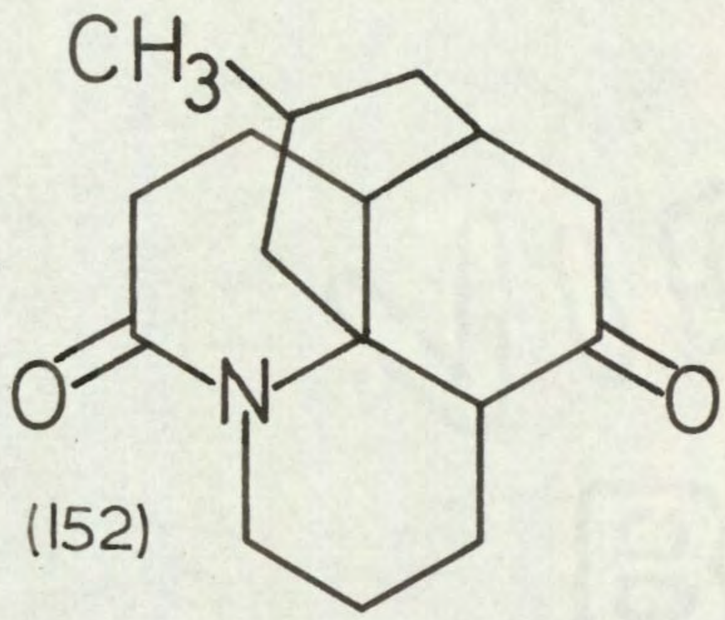
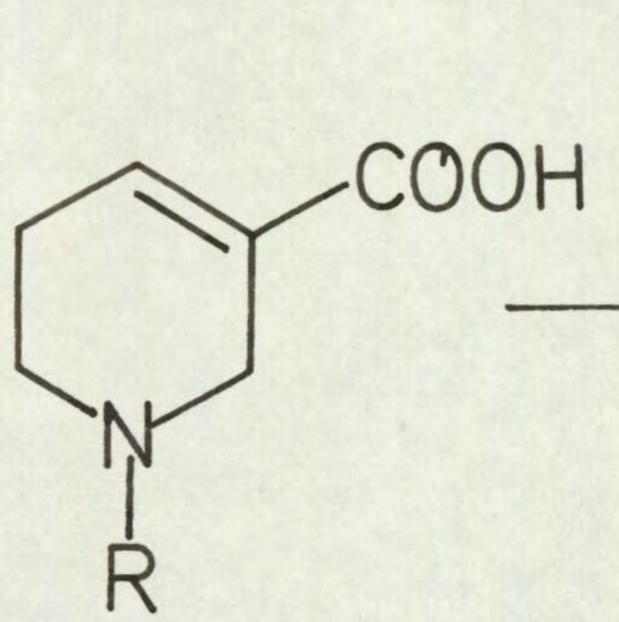
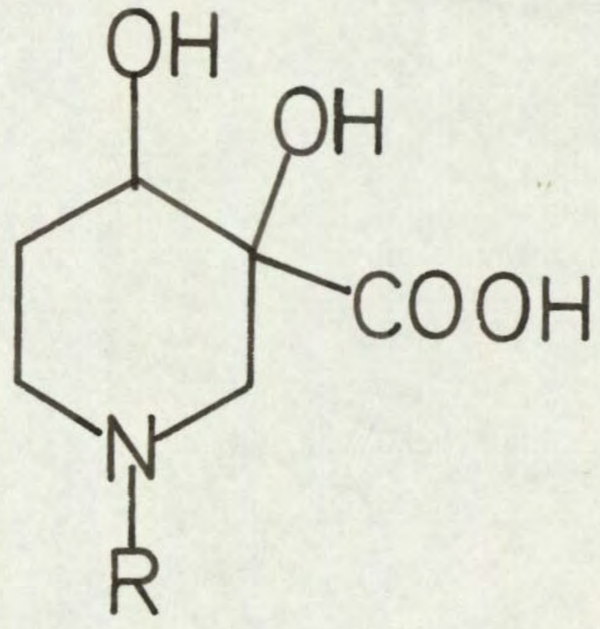


(152)



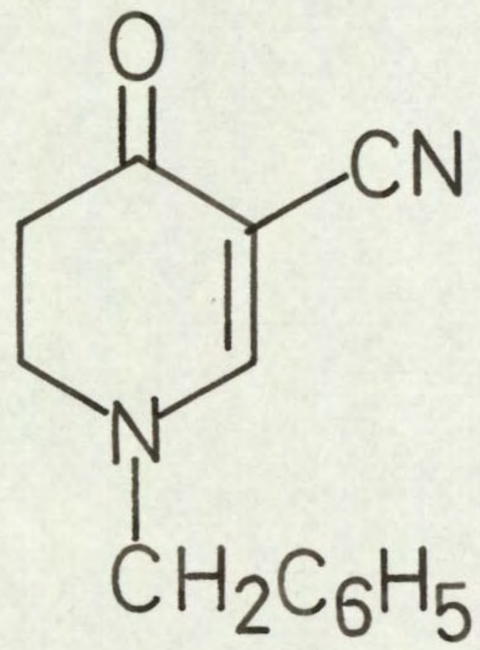
(153)



In the event, 4-amino-1-benzyl-3-cyano-1,2,5,6-tetrahydro-pyridine was reacted in acetone with potassium permanganate. The compound obtained did not titrate in non-aqueous solvents and gave an analysis of $C_{13}H_{12}N_2O$. The infra-red spectrum had the following main peaks: 2200 cm.$^{-1}$ (C≡N), 700 cm.$^{-1}$, 760 cm.$^{-1}$ (C_6H_5), 1620 cm.$^{-1}$, 1640 cm.$^{-1}$. The ultra-violet spectrum showed two peaks, $\lambda_{max.}$ (EtOH), 312.5 mμ (15800) and 228.5 (11900).

A suggested structure which fitted the physical data was 1-benzyl-5-cyano-1,2,3,4-tetrahydro-4-oxo-pyridine (154). A consideration of the preparation and properties of this unsaturated compound will appear later.

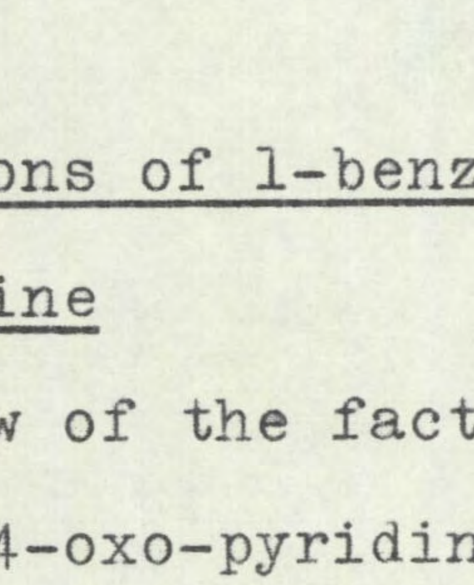
(154)



Reactions of 1-benzyl-5-cyano-1,2,3,4-tetrahydro-4-oxo-pyridine

In view of the fact that 1-benzyl-5-cyano-1,2,3,4-tetrahydro-4-oxo-pyridine (164) bears some resemblance to 1-benzyl-3-cyano-4-piperidone (165), some similar reactions

(164)



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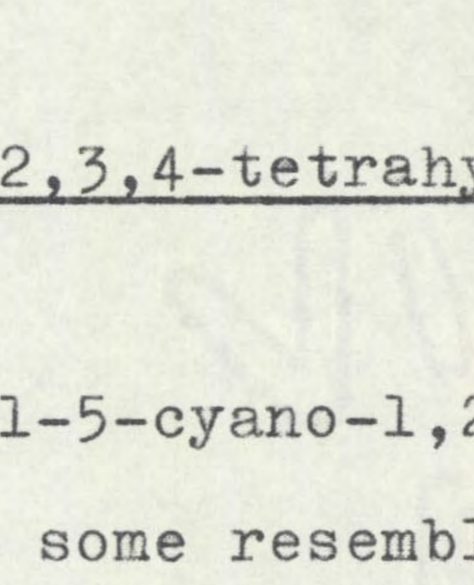
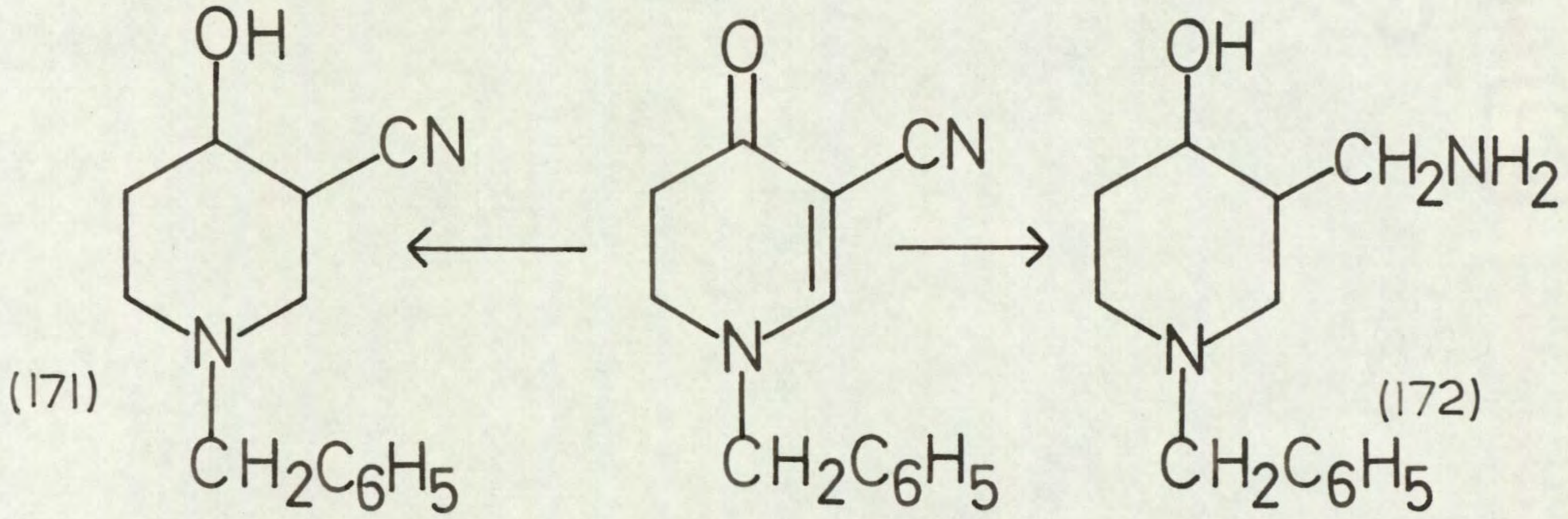


were attempted in order to compare the chemical reactivities of the two compounds.

While 1-benzyl-3-cyano-4-piperidone hydrochloride (165) reacted with phenyl magnesium bromide to give 1-benzyl-1,2,5,6-tetrahydro-4-hydroxy-3-phenylimino-pyridine, reaction of phenyl magnesium bromide with the unsaturated ketone (164) gave, in the first instance, unchanged starting material. A second attempt in a higher boiling solvent gave a brown oil from which no solid compound was obtained.

Reduction of the unsaturated ketone was attempted.

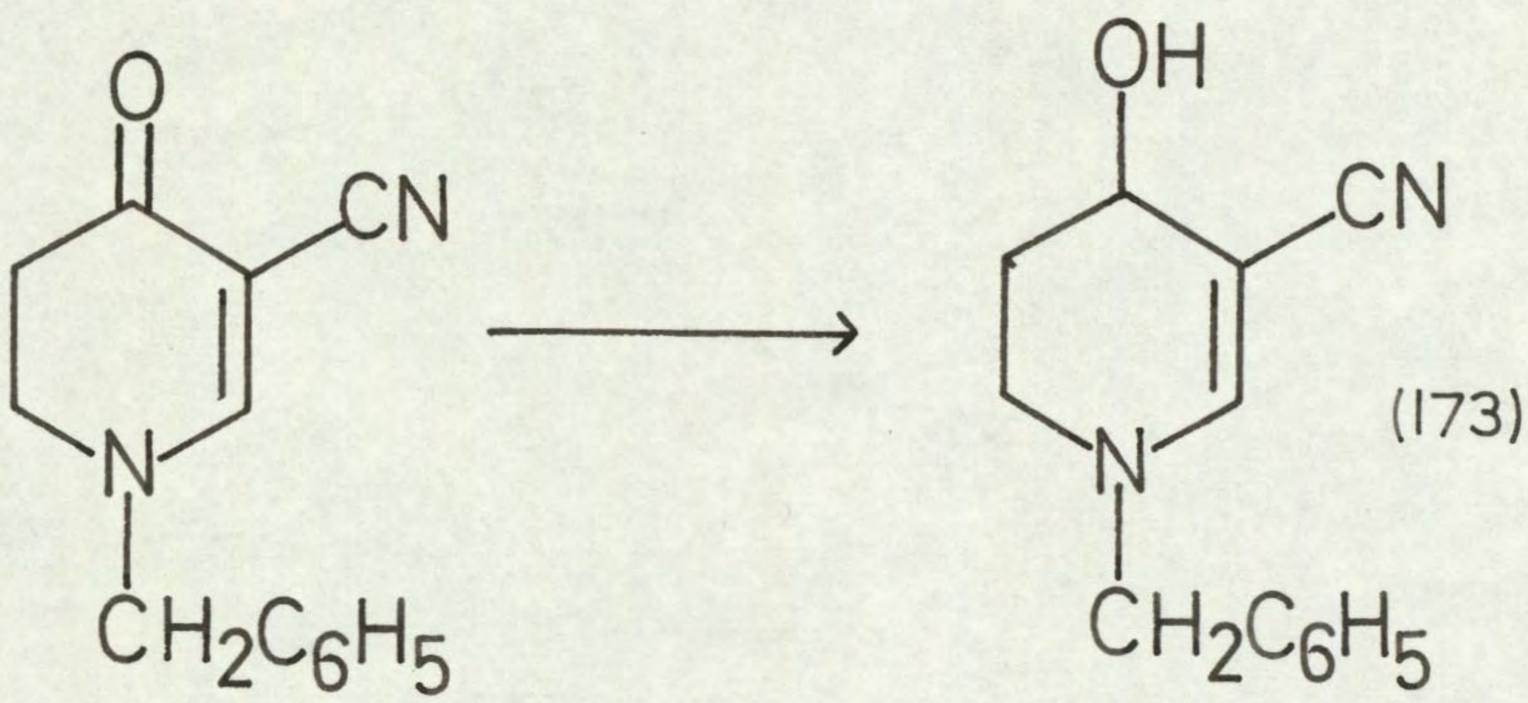


(171) (172)

Reduction with $NaBH_4$ gave the saturated cyano-alcohol (171), identical with that obtained from the saturated cyano-ketone (165). $LiAlH_4$ reduction yielded the saturated amino-alcohol (172), although, as in the case of the reduction of the cyano-ketone (165), no solid product could be obtained.

An attempt was made to obtain the unsaturated

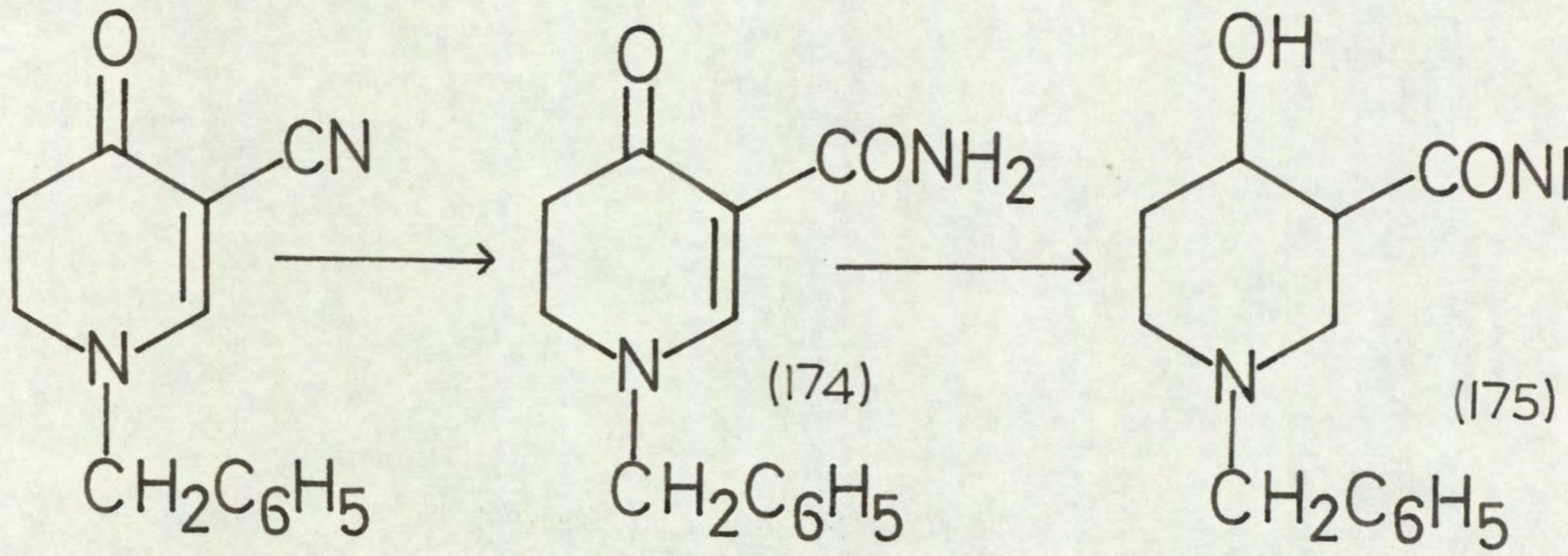
cyano-alcohol (173), using aluminium isopropoxide (Bachmann and Struve, 1939), but only starting material was isolated from the reaction mixture. Reduction with



(173)

sodium in ethanol proved fruitless, starting material being recovered.

Dissolving 1-benzyl-3-cyano-4-piperidone in conc. H_2SO_4, with a view to hydrolysis to the amide, resulted in a small yield of uncharacterisable material. 1-Benzyl-5-cyano-1,2,3,4-tetrahydro-4-oxo-pyridine, however, gave

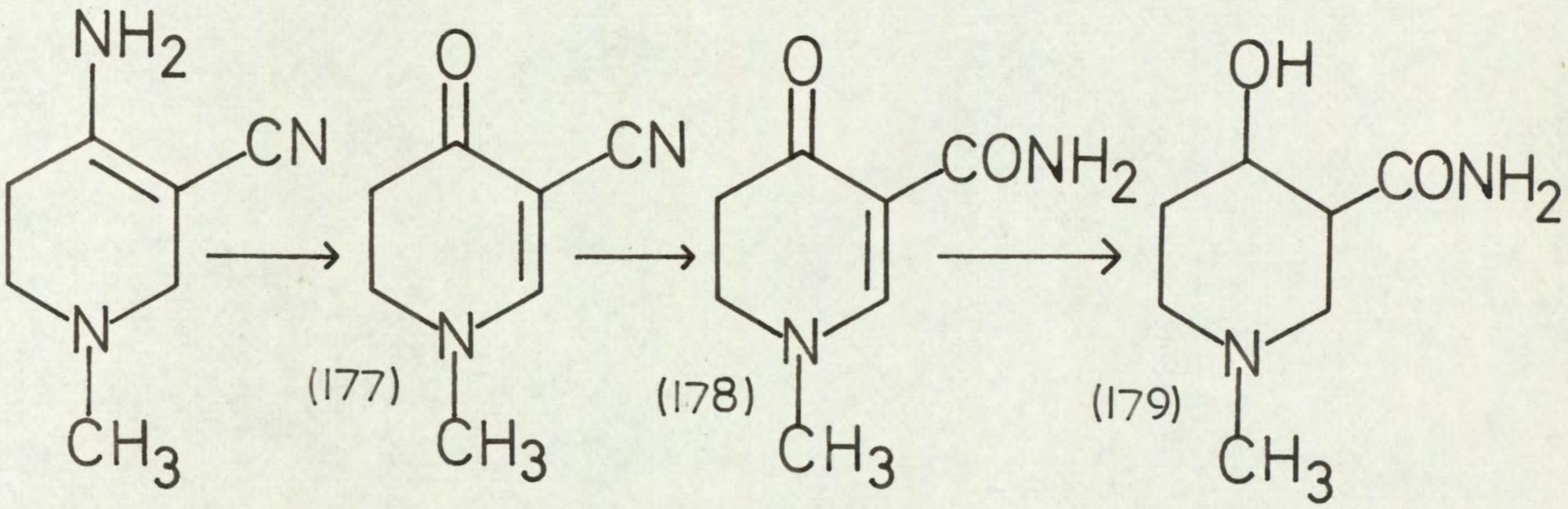


(174) (175)

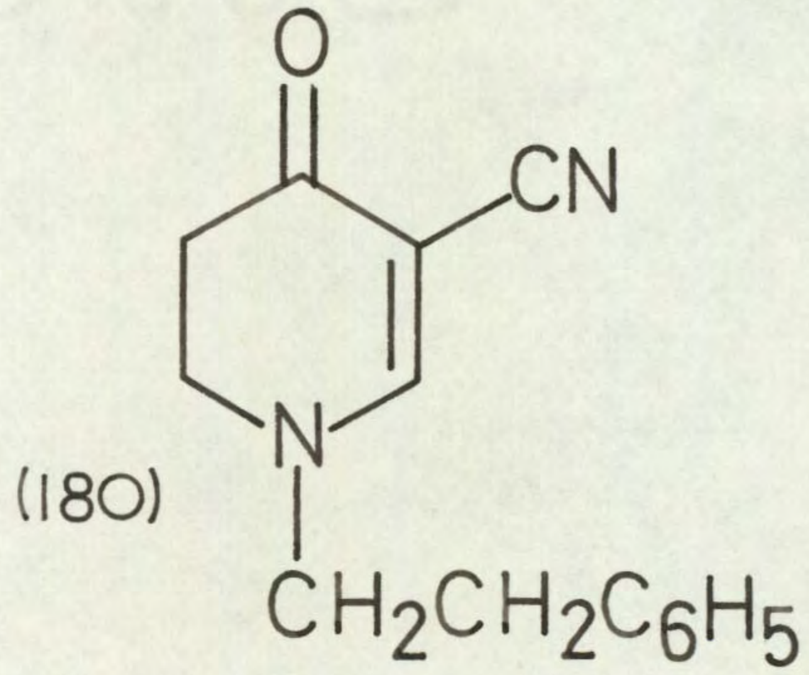
the corresponding amido-ketone (174) in good yield. The compound did not titrate in non-aqueous solvents,

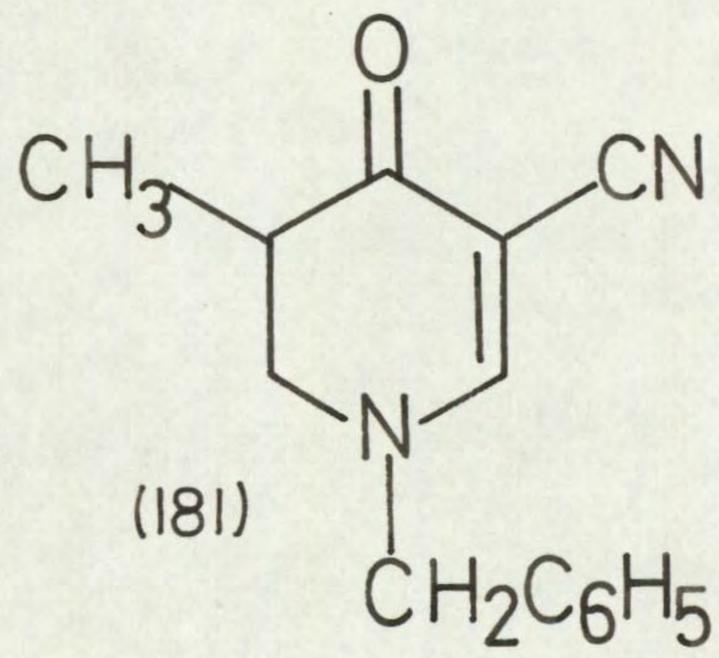
but had the correct infra-red spectrum and molecular weight by mass spectrum. Reduction of the amido-ketone with $NaBH_4$ gave the saturated amido-alcohol (175).

5-Cyano-1,2,3,4-tetrahydro-1-methyl-4-oxo-pyridine (177) was prepared in a similar manner by a potassium permanganate oxidation of 4-amino-3-cyano-1,2,5,6-tetrahydro-1-methyl-pyridine. Hydrolysis

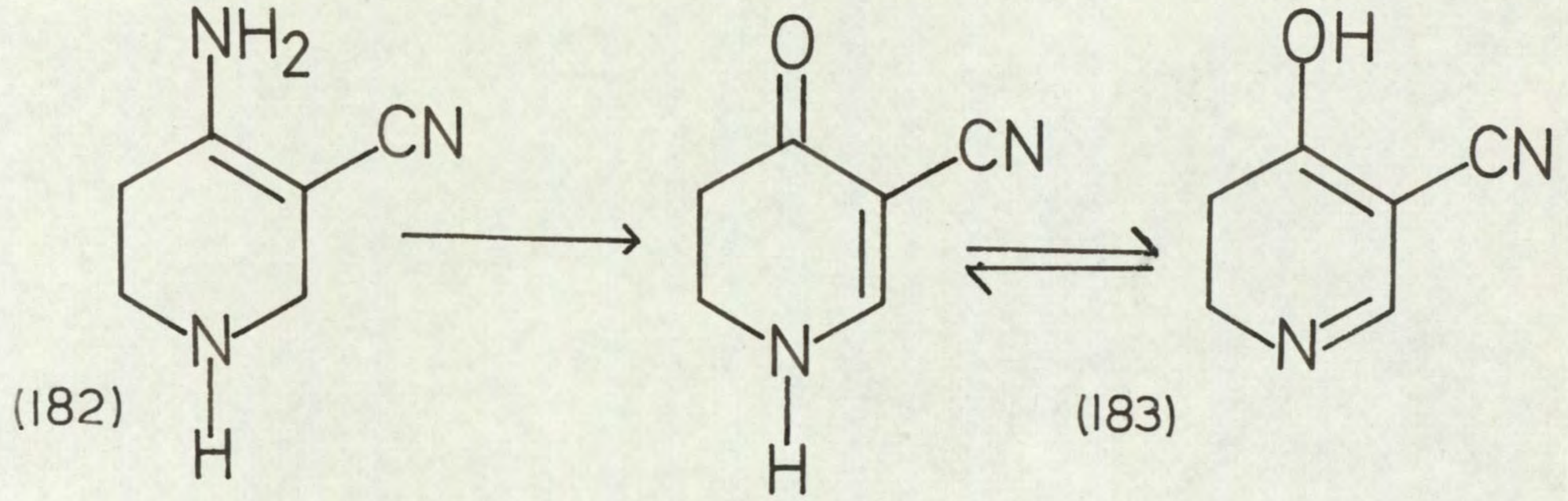


yielded the unsaturated amido-ketone (178), which reduced with $NaBH_4$ to give the saturated amido-alcohol (179). Similarly, 5-cyano-1,2,3,4-tetrahydro-4-oxo-1-phenethyl-pyridine (180), and 1-benzyl-5-cyano-1,2,3,4-



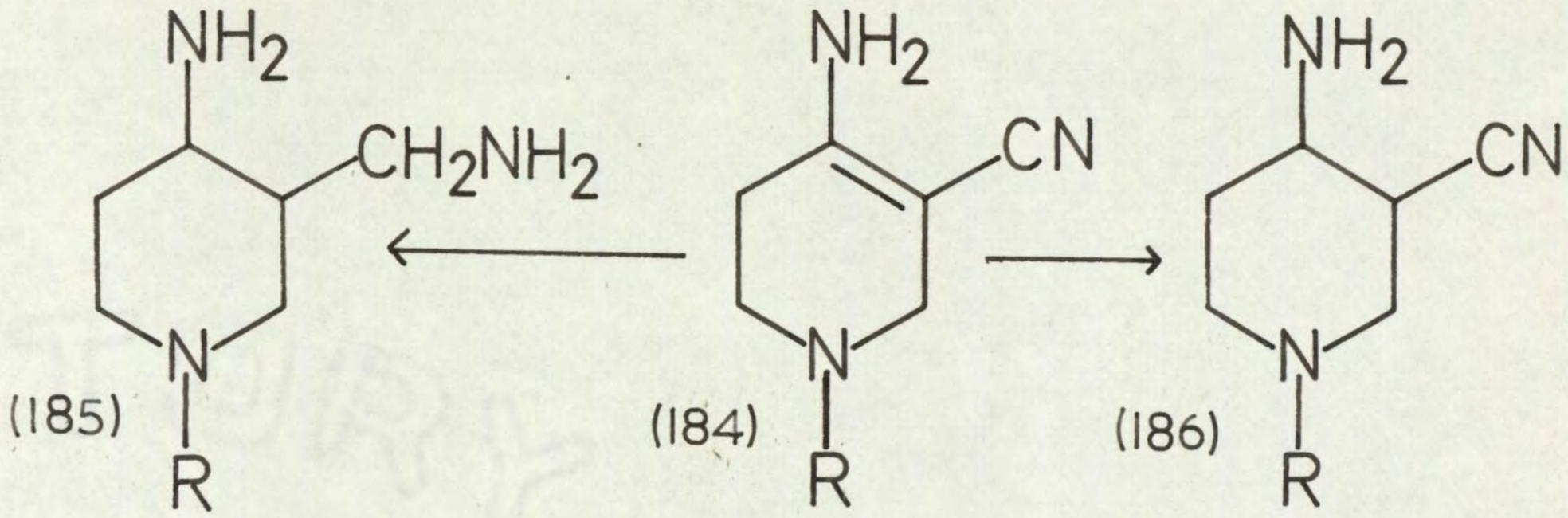


tetrahydro-3-methyl-4-oxo-pyridine (181), were prepared using identical conditions.

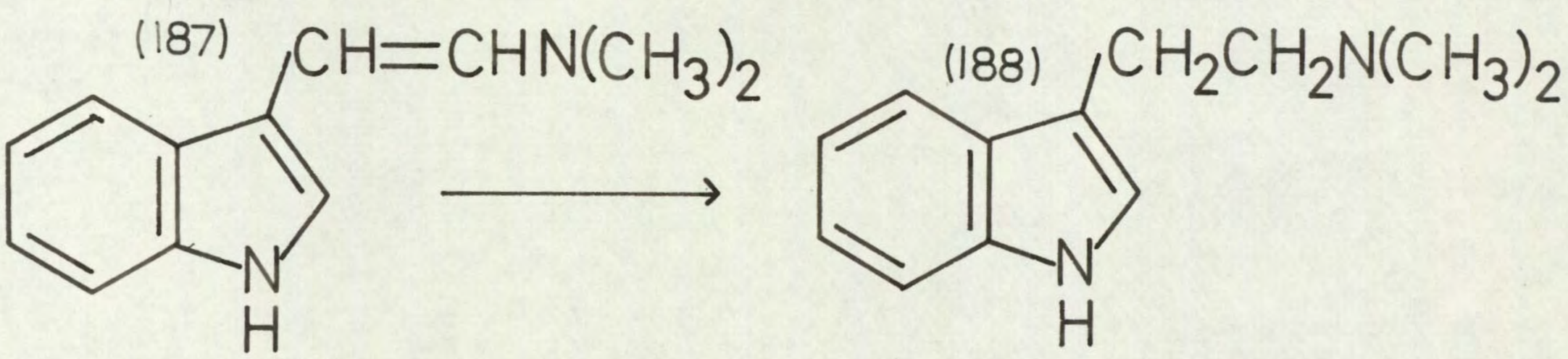


Synthesis of the nor-compound (183) from 4-amino-3-cyano-1,2,5,6-tetrahydro-pyridine (182) was not successful, starting material being the only compound recovered. Attempts to debenzylate 1-benzyl-5-cyano-1,2,3,4-tetrahydro-4-oxo-pyridine were not successful, as too many products were obtained, none of which could be clearly characterised.

While 4-amino-3-cyano-1,2,5,6-tetrahydro-pyridines (184) had been successfully reduced with sodium in ethanol (Cologne et al.) to give the triamines (185), no attempt had been made to synthesise 4-amino-3-cyano-piperidines (186). Daly and Witkop (1962) reduced the vinylamine (187) to NN-dimethyltryptamine (188) with both $LiAlH_4$ and $NaBH_4$. Since $LiAlH_4$ was expected to reduce the nitrile group, $NaBH_4$ was used. Starting



material was the only compound recovered. An attempt using $NaBH_4$ in isopropanol and in diglyme (Brown et al.



1955) also gave starting material. West (1963) reduced enamines to amines by catalytic hydrogenation over platinum oxide. Hydrogenation of 4-amino-1-benzyl-3-cyano-1,2,5,6-tetrahydro-pyridine failed, no uptake of hydrogen being observed.

Diels-Alder reactions were attempted with a view to cyclising across the double bond of the enamine, although the nature and number of the substituents suggested that the reaction may be difficult (Norton, 1942; Martin and Hill, 1961), especially since a heterocyclic nitrogen

was present. In the event, 4-amino-1-benzyl-3-cyano-1,2,5,6-tetrahydro-pyridine was heated under a variety of conditions with isoprene, furan and with cyclo-pentadiene, but no reaction was observed, starting materials being recovered in quantitative yield.

Section II

Part II

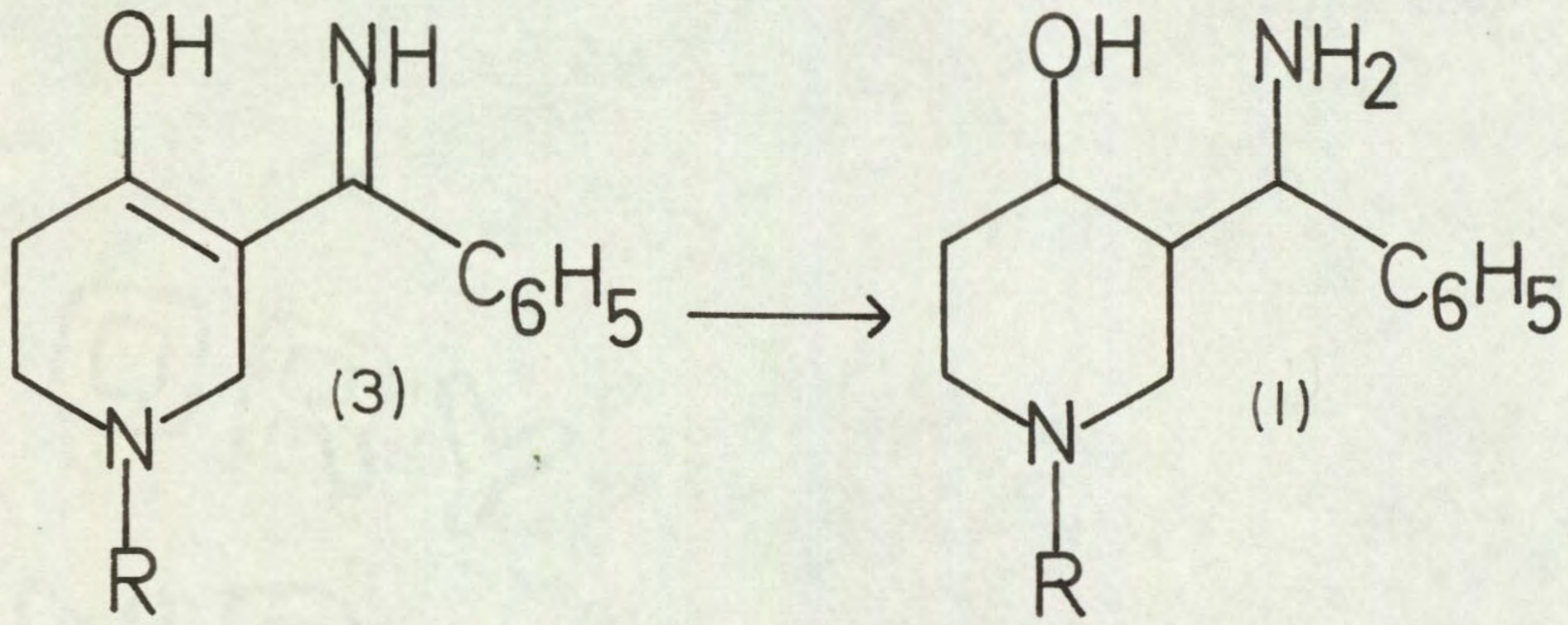
Some theoretical considerations

SOME THEORETICAL CONSIDERATIONS

There are several facets of the present work which appear to merit further attention.

1. A configurational study of 1-benzyl-3-α-phenyl-aminomethyl-4-piperidinol and related compounds

During the course of the present work, amino-alcohols of the type (1) and (2) have been synthesised by reduction of either an imino-enol (3) to give type (1), or a cyano-ketone (4) to give type (2) via a cyano-



alcohol (5). The amino-alcohols and their derivatives are potential analgesics, and a knowledge of their

configuration and conformation may be of importance in a study of structure-activity relationships. An attempt was made to establish the configurations using the following methods:

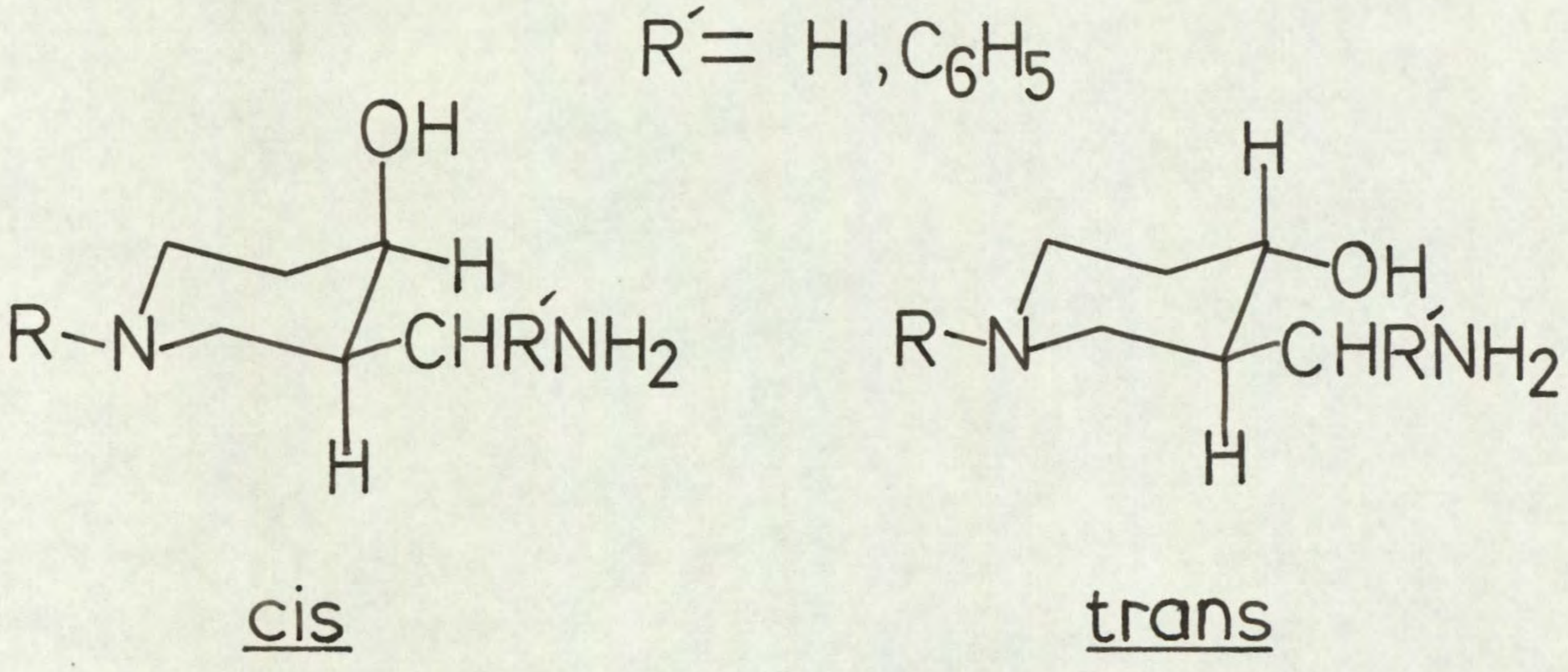
a) A consideration of the stereospecific reduction.

b) A study of the hydrolysis of the esters.

c) An interpretation of the infra-red spectra.

d) An interpretation of the N.M.R. spectra.

Assuming that the nitrogen valencies have no fixed configuration, the compounds (1) and (2) can exist in two epimeric forms, with the 3 and 4 substituents either cis or trans.

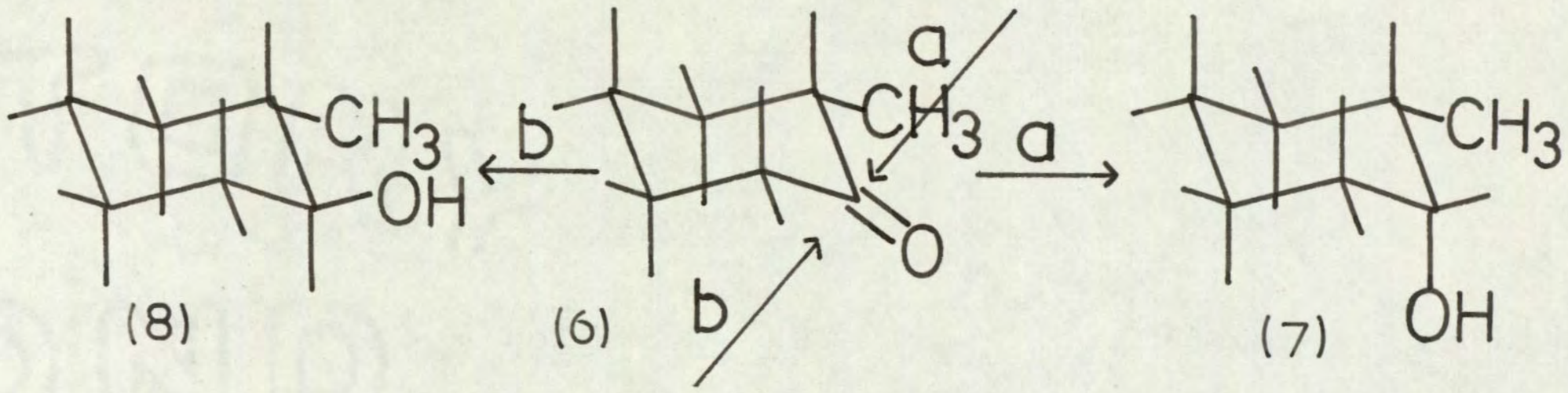


Since it has been shown that, in the absence of strong electrostatic effects, substituted cyclohexanes exist mainly in the chair conformation with the maximum number of equitorial substituents (Barton and Cookson, 1956) and that, if one equitorial and one axial group are present, the molecule will adopt the

chair form with the larger group equitorial, it can be assumed that the two geometrical isomers are in the form shown. Thus the trans isomer of the amino-alcohol will probably have both the 3- α -phenylaminomethyl group and the 4-hydroxy group equitorial, while the cis isomer will probably have the 3-aminomethyl group equitorial and the 4-hydroxy group axial.

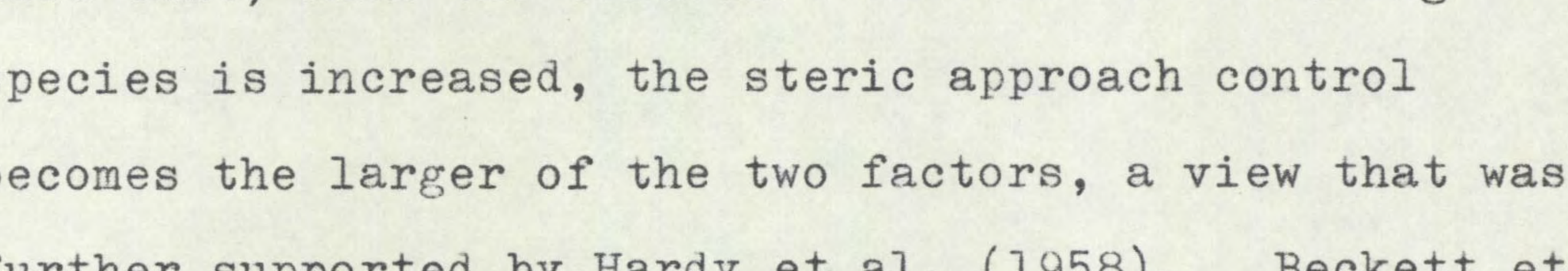
a) Stereospecific Reduction

The reduction of alicyclic and polycyclic ketones has been well investigated and has been summarised by Barton (1953) who emphasised the importance of the thermodynamic factor, which gives the more stable equitorial isomer as predominant in the reduction product from unhindered ketones. Dauben et al. (1956) investigated the stereochemistry of the hydride reduction of alkyl cyclohexanones and suggested that two factors were involved, termed "steric approach control", which involved competitive attack from a hindered or unhindered side, and "product development control", which was a measure of the relative stabilities of the two isomeric products. For example, in the reduction of 2-methylcyclohexanone (6), existing mainly in the conformation shown, attack from side 'b' is sterically hindered, resulting in the preferential



(8) (6) (7)

formation of the cis isomer (7), though the trans isomer (8) is the more stable, and hence the more thermodynamically favoured, as shown by equilibrium studies. This suggests that the two factors are in opposition to one another. This is supported by the fact that, when the effective size of the reducing species is increased, the steric approach control becomes the larger of the two factors, a view that was further supported by Hardy et al. (1958). Beckett et al. (1959) found that heterocyclic ketones, for example tropinone (9), behaved in a similar manner, giving two



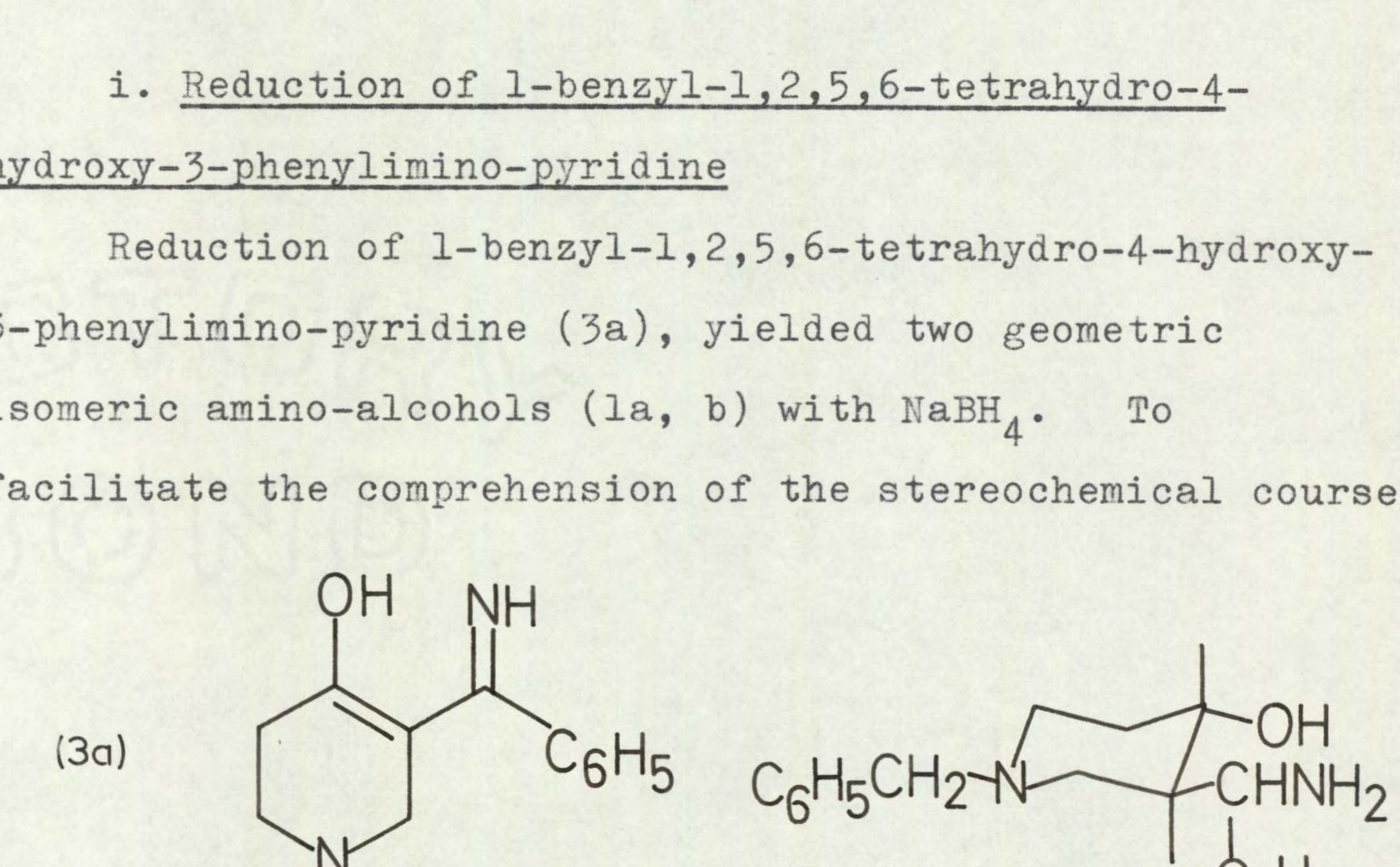
(9) (10) (11)

isomeric alcohols, tropine (10) and ψ tropine (11), the yield ratio of which was found to vary with change in size of the reducing agent. Equilibration, using sodium

in n-pentanol and isobutanol, showed that the equitorial isomer (11) was the thermodynamically more stable product, while increase in the size of the reducing agent tended to give a greater proportion of tropine (10), the kinetically favoured product.

i. Reduction of 1-benzyl-1,2,5,6-tetrahydro-4-hydroxy-3-phenylimino-pyridine

Reduction of 1-benzyl-1,2,5,6-tetrahydro-4-hydroxy-3-phenylimino-pyridine (3a), yielded two geometric isomeric amino-alcohols (1a, b) with $NaBH_4$. To facilitate the comprehension of the stereochemical course



of the reduction, it is necessary to assume that the

imino-ketone (3b) is the moiety being reduced, rather than the flatter imino-enol (3a). Models indicate that attack from side 'a' is the more sterically hindered due to the presence of the 2 and 6 axial hydrogens, as well as the substituent in the 3 position. This will result in preferential approach of the reducing agent from side 'b', leading to formation of the less stable cis isomer, having an axial hydroxy group. Hence, in the first instance, the cis isomer should predominate, while under more vigorous conditions, suitable to cause equilibration of the alcohols, the trans isomer (equitorial OH group) should appear in the greater proportion.

In the event, the two isomers (A) and (B) appeared in the ratio 3 :1, in a total yield of 80%, with a further amount of both isomers present in the remaining uncrystallised material. Since equilibration is not expected to occur using sodium borohydride in ethanol (Beckett et al. 1959), the isomer formed in the major amount is expected to be the axial-hydroxy cis isomer. Thus isomer (A) is assigned the cis configuration (1b), while the isomer in smaller yield, isomer (B), is assigned the trans configuration (1a).

In an earlier experiment, reduction of 1-benzyl-1,2,5,6-tetrahydro-4-hydroxy-3-phenylimino-pyridine with

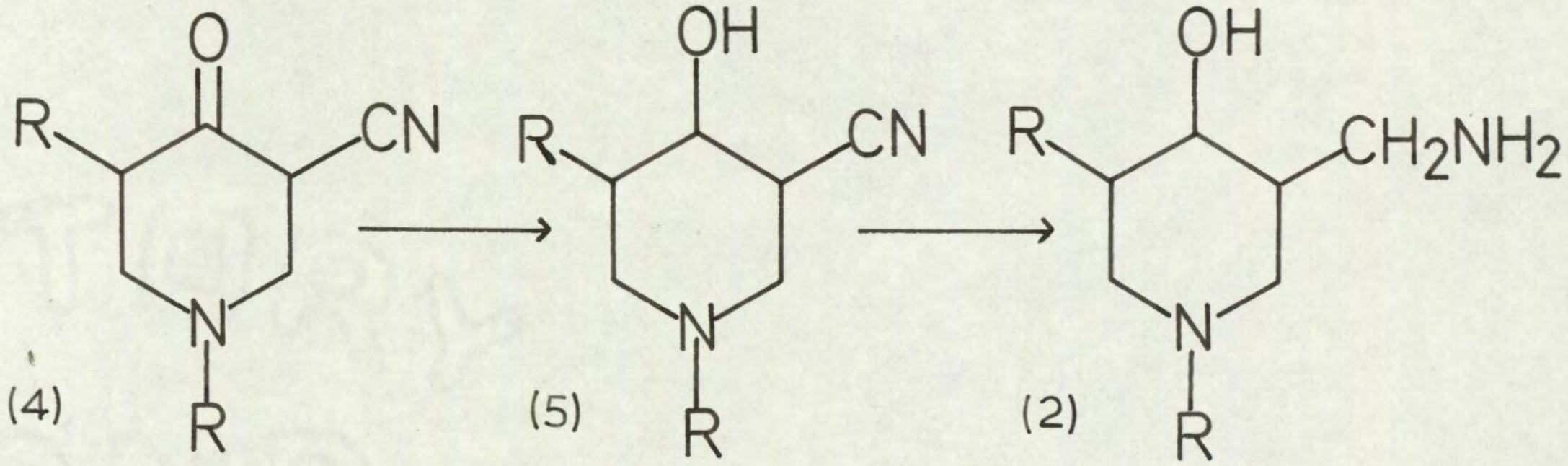
$NaBH_4$ in ethanol, under more vigorous work-up conditions, gave an oil which could not be crystallised. Thin layer chromatography showed the presence of two major spots. The results suggested that under the conditions of the work-up of the reaction mixture, partial equilibration had occurred, giving a larger amount of the trans isomer than had been obtained previously, which caused the separation of the two isomers to be less facile. This result tended to support the view that the major component obtained in the initial reaction was the less stable isomer, viz. the cis isomer.

ii. Reduction of 1,2,5,6-tetrahydro-4-hydroxy-1-methyl-3-phenylimino-pyridine

The reduction with $NaBH_4$ of 1,2,5,6-tetrahydro-4-hydroxy-1-methyl-3-phenylimino-pyridine gave a green oil from which was obtained, with great difficulty, a low yield of one isomer, (A). Inspection of the mother liquors revealed the presence of a further quantity of the isomer (A) with a second isomer, (B). Attempts to obtain the second isomer were not successful. In this case, lack of a second isomer and the low yield of isomer obtained prevented any provisional configurations from being assigned.

iii. Reduction of cyano-ketones

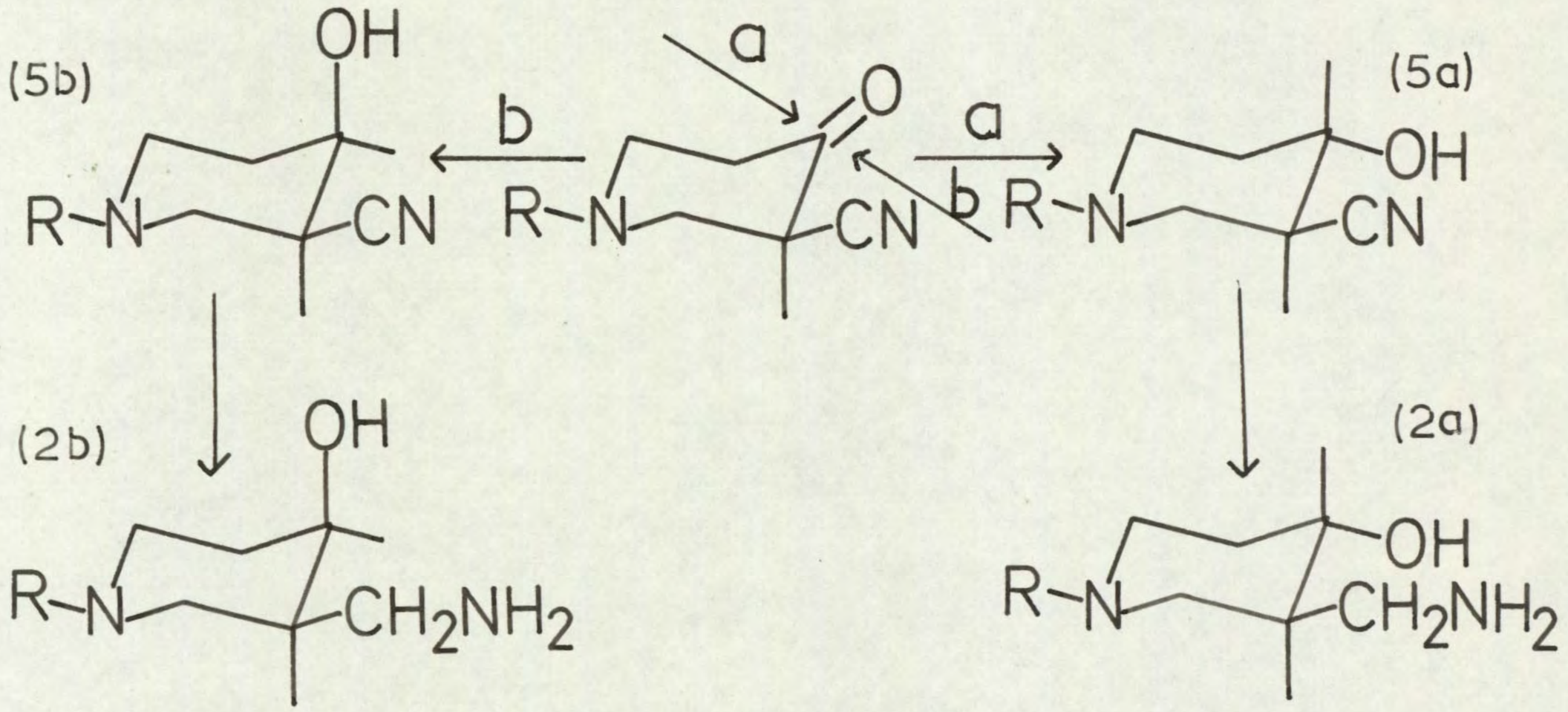
The reduction of the cyano-ketones (4) to give the amino-alcohols (2) was achieved in two ways. The first,



involving a single stage reduction using $LiAlH_4$ did not result in the separation of the isomers from the oil obtained, though their presence was detected with the aid of infra-red spectra and thin layer chromatography. Reduction of the cyano-ketone with $NaBH_4$, however, gave an oil from which crystals were eventually obtained in a 40% yield. Examination of the mother liquors showed that the isomer obtained also formed the greater part of the uncrystallised residue. Reduction of the cyano-alcohol with $LiAlH_4$ gave the corresponding amino-alcohol (2). The second stage is not expected to alter the configuration of the molecule, under the conditions used in the experiment.

The $NaBH_4$ reduction is expected to proceed in two ways; to give the stable equitorial OH, <u>trans</u> cyano-

alcohol (5a), which would be expected to reduce to give the trans amino-alcohol (2a); or to give the less stable, axial OH, cis cyano-alcohol (5b) which would be expected to reduce to give the cis amino-alcohol (2b).



The cis compound would be expected to give the greater yield initially, due to the smaller steric hindrance (route b) as shown by models. However, the reduction was carried out in an aqueous/ethanolic medium, which may have influenced the thermodynamic ratio of the two geometric isomers, since the reduction of the imino-enol (3) gave a ratio of alcohols which was altered under the influence of the solvent, going from mostly axial OH to a higher proportion of equitorial OH. Because of this, at this stage no assignment was made until further evidence presented itself.

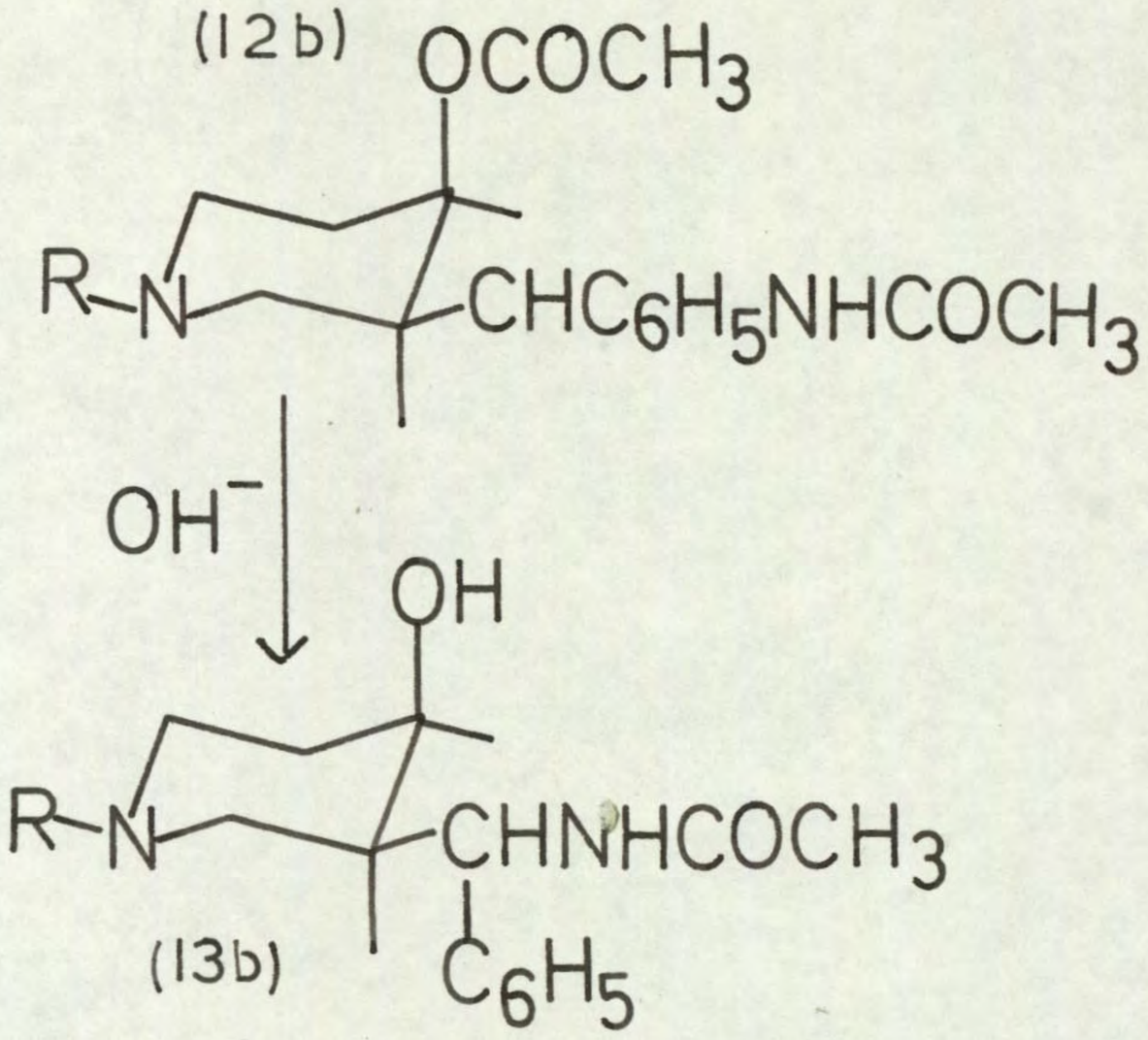
b) Hydrolysis of the amido-esters

At a given carbon atom in a cyclohexane ring system, an axial hydroxyl group is more hindered towards acylation than an equitorial group and the ester of an axial grouping is more slowly hydrolysed. Eliel (1953) postulated that, in such cases, the reaction proceeds via the conformation of the molecule in which the reactive hydroxyl group is equitorial, and that the rate differences in isomers should be attributed to that energy necessary to place the other substituent into an axial conformation. The rates of esterification of the isomeric menthols, for example, based upon the postulates of Eliel, would be in the order of menthol/isomenthol/neoisomenthol/neomenthol. The relative rates actually found are 16.5/12.3/3.1/1 respectively (Read and Grubb, 1934).

i. N {α [4-Acetoxy-1-benzyl-3-piperidyl] benzyl} acetamide

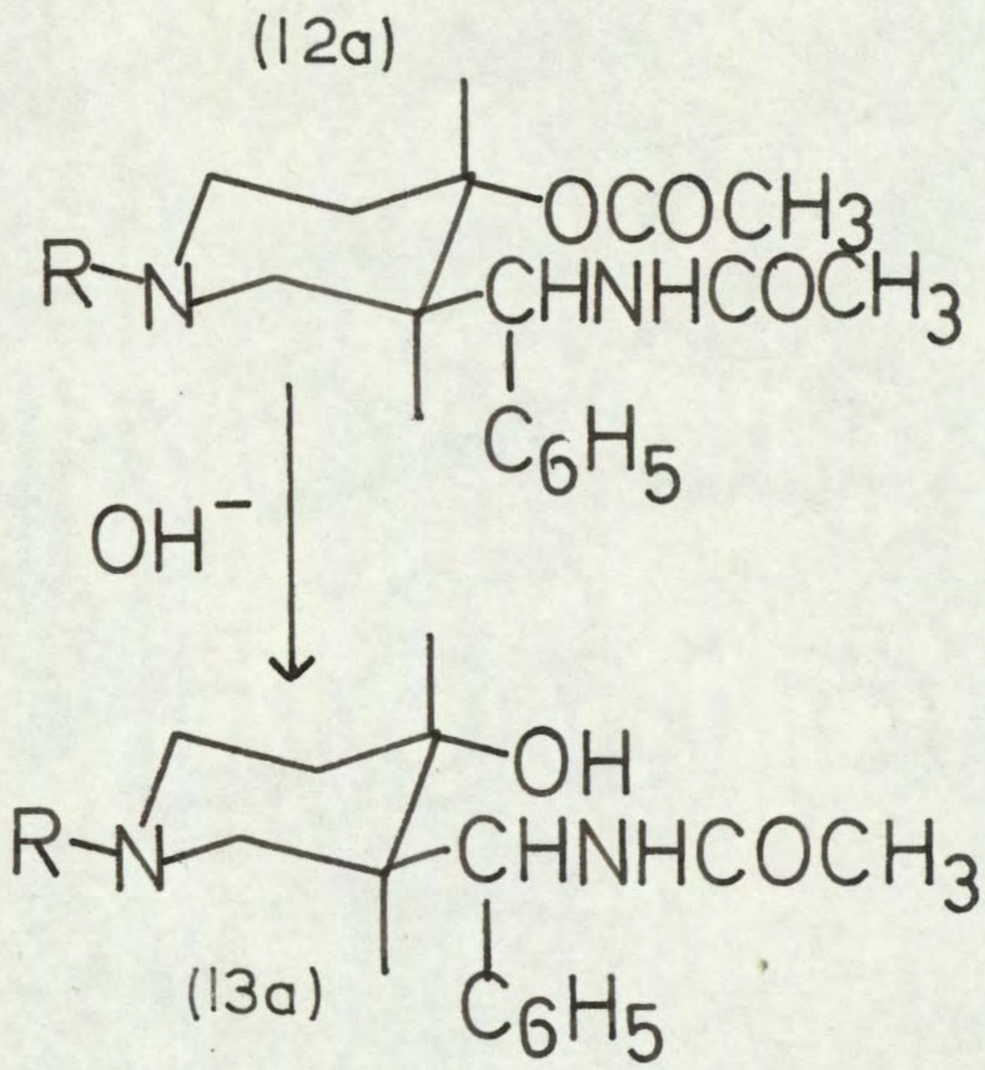
In view of this, an attempt was made to hydrolyse differentially the two geometric isomeric N {α [4-acetoxy-1-benzyl-3-piperidyl] benzyl} acetamides (12a, b) to give the corresponding N {α [1-benzyl-4-hydroxy-3-piperidyl] benzyl} acetamides (13a, b). This was achieved using 0.5% KOH in ethanol at 0^{o}.

(12b)



(13b)

(12a)



(13a)

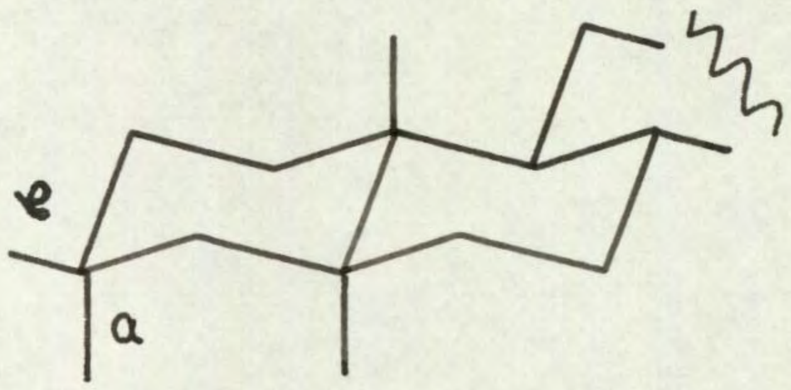
Isomer (B), provisionally designated the <u>trans</u> 3-amine/4-alcohol (equitorial OH) configuration, would be expected to hydrolyse faster than isomer (A), provisionally designated the <u>cis</u> (axial OH) configuration based on an inspection of the stereospecific reduction of the precursor. A preliminary reaction was attempted with samples being removed every few minutes and the result followed on a thin layer chromatograph. Isomer (B) appeared to have completely hydrolysed after 40 minutes, hence the experiment was repeated, but the reaction stopped after 40 minutes by dilution of the solution and rapid extraction of the organic material. From the reaction, isomer (B) gave the hydroxy amide (13a) while isomer (A) merely gave starting material (12b). The result is in agreement with the provisional assignments made.

ii. 3-Acetamidomethyl-4-acetoxy-piperidines

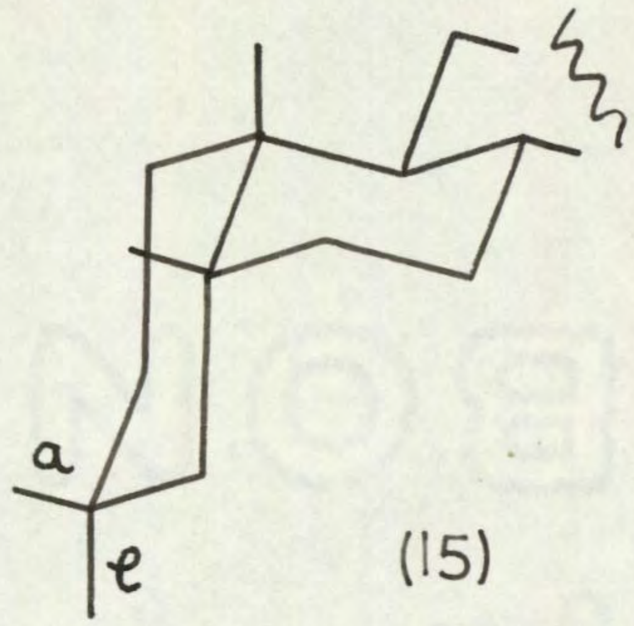
In view of the fact that only one isomer of the 3-aminomethyl-4-hydroxy-piperidines (2) were obtained, no attempt was made to hydrolyse the esters derived from these compounds. This also included 1-methyl-3-α-phenylaminomethyl-4-piperidinol.

c) Interpretation of the infra-red spectra

Infra-red absorption spectroscopy can provide a very useful method for distinguishing configurations, since many workers have observed a pattern of absorption in infra-red regions which are characteristic for similar conformational forms. Cole et al. (1952) found that, for a variety of hydroxy steroids, the equitorial and axial C-O stretching frequencies occurred at different, well-defined positions. For example, for compounds of type (14), equitorial hydroxy groups absorbed in the region 1037 $cm.^{-1}$ - 1040 $cm.^{-1}$, while axial hydroxy groups absorbed at a lower frequency, in the region 996 $cm.^{-1}$ - 1002 $cm.^{-1}$; while for compounds of type (15), equitorial hydroxy absorption occurs in the region of 1037 $cm.^{-1}$ - 1044 $cm.^{-1}$, and axial hydroxy absorption occurs in the region 1032 $cm.^{-1}$ - 1036 $cm.^{-1}$. Page (1955) explained this with the idea that a stretching motion of an equitorial 3-substituent causes



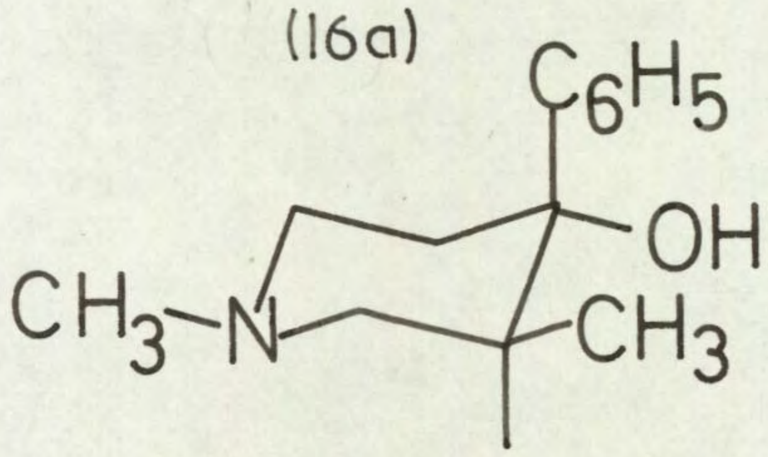
(14)



(15)

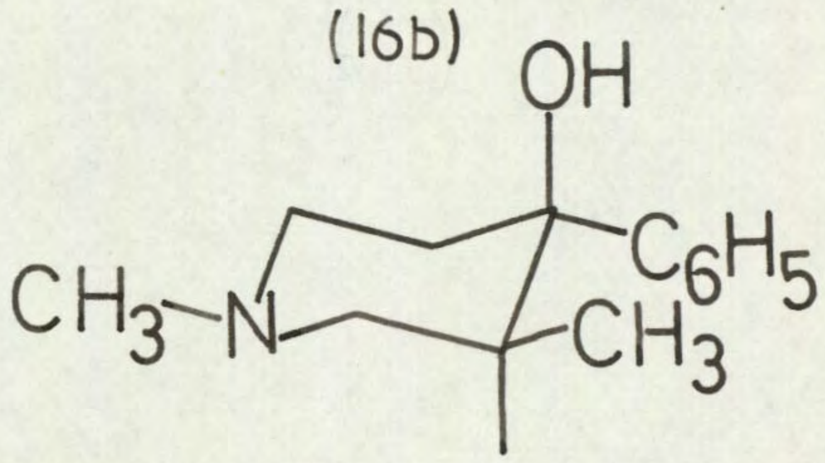
appreciable expansion and contraction of the ring, whereas an axial 3-substituent is normal to the ring and thus requires less effort to stretch the C-O bond, thus less energy is needed and so axial C-O stretches occur at a lower frequency. It has also been shown (Rosenkrantz and Zablow, 1953) that acetates of equitorial hydroxy groups have a singlet acetate band absorbing in the region of 1240 $cm.^{-1}$, whereas acetates of axial hydroxy groups exhibit multiplet bands in the region of 1240 $cm.^{-1}$. An example of a differential absorption in a heterocycle is provided by alpha and beta prodines (16a, b) (Beckett et al. 1959), where the cis compound, with an equitorial OH group, absorbs in the

(16a)



cis

(16b)

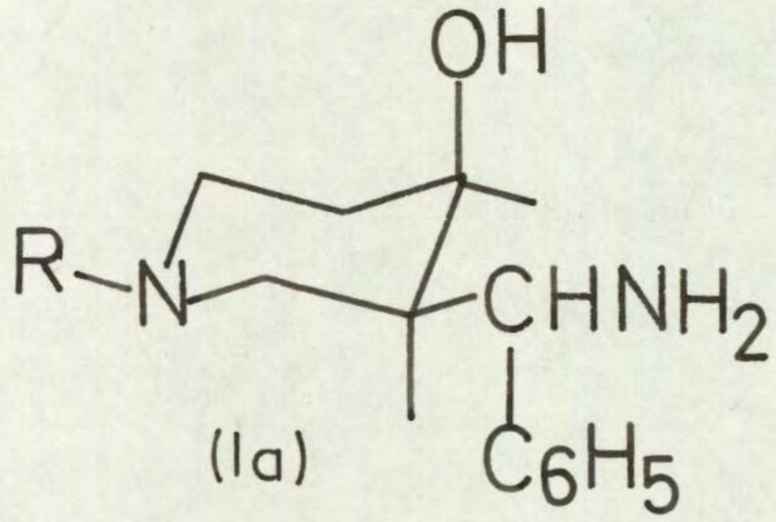


trans

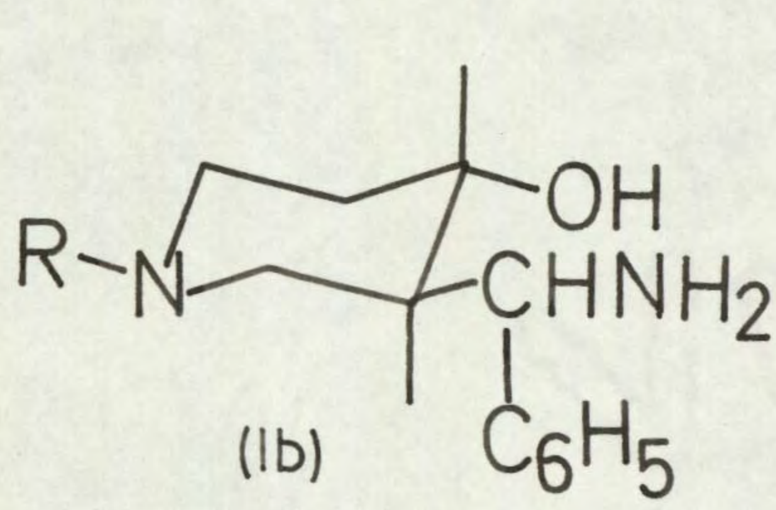
region 1040 cm.$^{-1}$ - 1055 cm.$^{-1}$, while the <u>trans</u> compound, with an axial OH group, did not have a consistent region of absorption. With the regions of absorption in mind, the infra-red spectra of the prepared compounds were inspected.

i. <u>1-Benzyl-3-α-phenylaminomethyl-4-piperidinols</u>

Inspection of the infra-red spectra of the two isomers of 1-benzyl-3-α-phenylaminomethyl-4-piperidinol (1a, b) reveals a difference in absorption in the region



(1a)



(1b)

950 cm.$^{-1}$ - 1100 cm.$^{-1}$. Isomer (A), designated <u>cis</u> (axial OH) absorbs in the region of 980 cm.$^{-1}$, while isomer (B) (equitorial OH) absorbs in the region of 1045 cm.$^{-1}$. Thus it can be concluded that isomer (A) has the structure shown (1a), with a <u>cis</u> 4-OH/3-substituent arrangement, giving an axial OH group, and isomer (B) has the structure shown (1b), with a <u>trans</u> 4-OH/3-substituent arrangement, giving an equitorial OH. An inspection of the isomeric acetates (12a, b) in the hope of strengthening the infra-red spectra confirmations

was disappointing, since the two isomers have practically identical spectra, there being no multiplicity of bands for the axial ester compared with the equitorial ester.

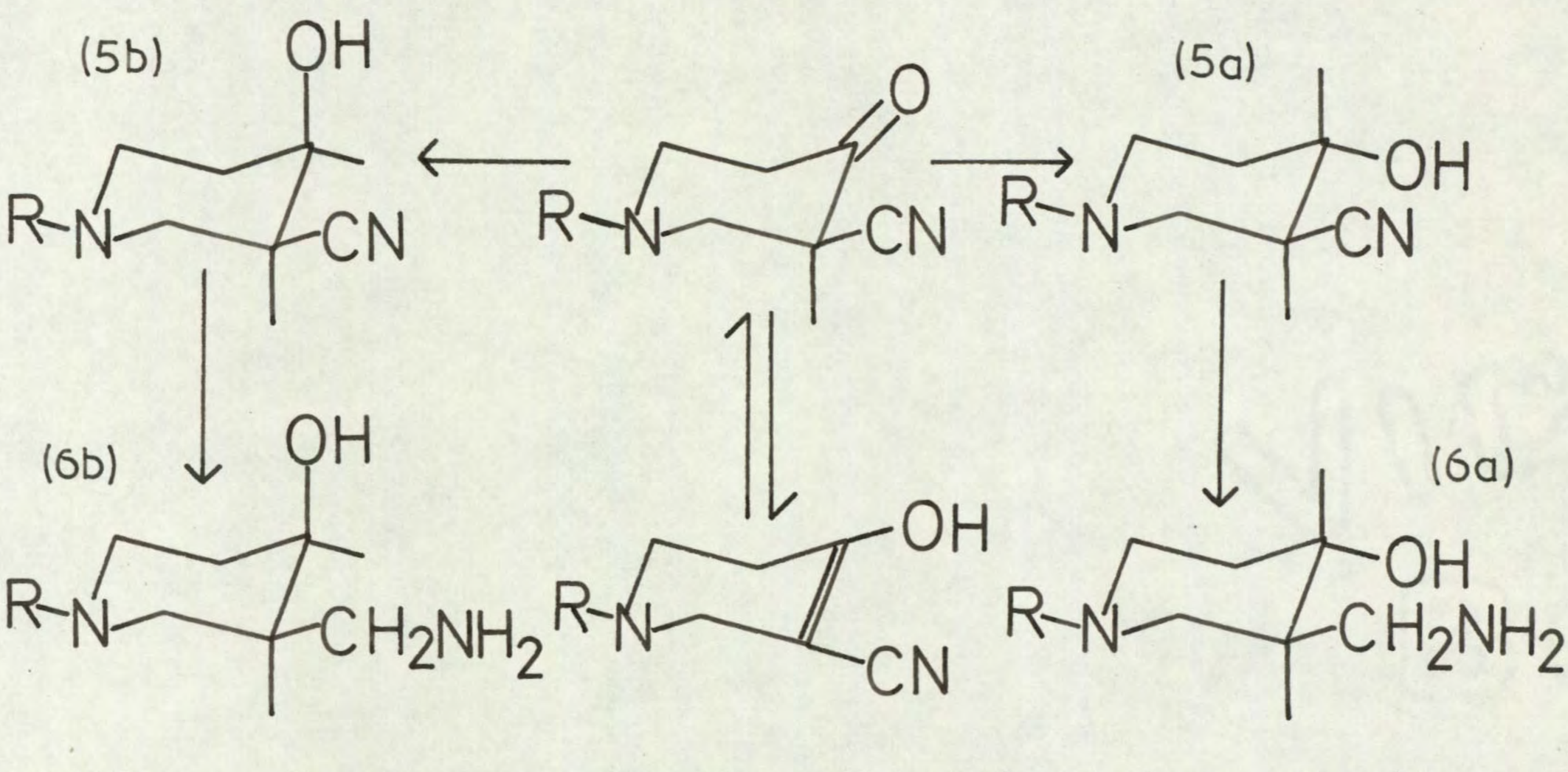
ii. 1-Methyl-3-α-phenylaminomethyl-4-piperidinol

This compound (1, R=CH_3), of which only one isomer was obtained in a crystalline form, has not yet been configurationally characterised. Comparison of the whole of the infra-red spectrum of the single isomer with the infra-red spectra of the two isomers obtained for the 1-benzyl homologue suggests very strongly that the isomer obtained is the (B) isomer, i.e. the trans 4-OH/3-substituted compound, having an equitorial OH (1b, R=CH_3). Examination of the infra-red spectrum of the hydrochloride of the amino-alcohol again reveals the presence of an equitorial OH, absorbing at 1045 $cm.^{-1}$ and 1070 $cm.^{-1}$. Hence it appears that, in the stereo-specific reduction of the imino-enol precursor, the thermodynamically more stable equitorial alcohol predominated. It is thought that this may be due to the work-up conditions, in forming NaOH on addition of water, caused equilibration of the isomeric piperidinols, enabling the thermodynamically more stable isomer to appear in greater quantity and thus to preferentially crystallise. The higher solubility of the 1-methyl

amino-alcohol, compared with the 1-benzyl compound, would tend to enhance this effect, since the 1-methyl compound would tend to remain in solution longer and thus have a greater chance of being equilibrated.

iii. 3-Aminomethyl-4-piperidinols

The compounds from the $NaBH_4$ reduction in aqueous ethanol of the 3-cyano-4-piperidones (4) were isolated in one geometric isomeric form of the cyano-alcohol (5a, b). These were then reduced to the amino-alcohols (6a, b) with

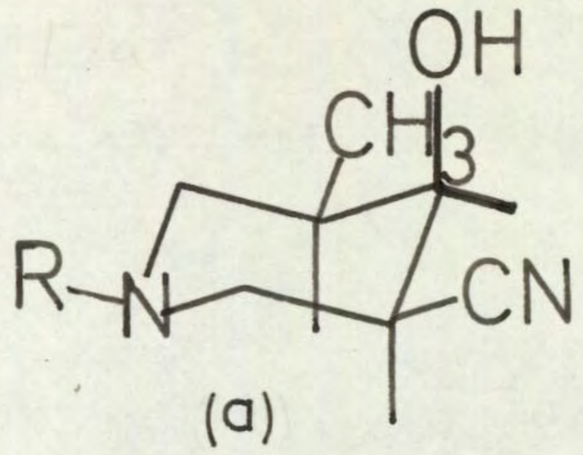


$LiAlH_4$. So far, no configurational assignments have been made due to the lack of the second isomer to compare with. An inspection of the infra-red spectra of the cyano-alcohols (5) show, in all cases, a large single or double peak in the region 1050 $cm.^{-1}$ - 1090 $cm.^{-1}$, with no peak in the region 980 $cm.^{-1}$ - 1040 $cm.^{-1}$, attributable to axial OH. Hence it is concluded that

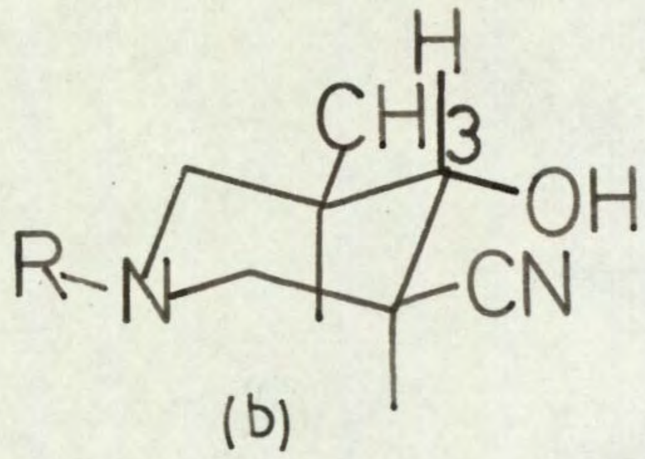
the isomers obtained are the trans 4-OH/3-CN piperidines, having an equitorial OH group. These could be obtained by hydride attack from the more sterically hindered side (a), but it is thought that the conditions used for the reaction, viz. aqueous ethanolic $NaBH_4$, permitted the initially-formed axial alcohol to equilibrate under the influence of the strong base present, giving the equitorial isomer. This is supported by the fact that single stage reductions with $LiAlH_4$, under conditions where very little equilibration is expected to occur, yield oils, the infra-red spectra of which show the presence of peaks in the region 1050 $cm.^{-1}$ - 1090 $cm.^{-1}$ and in the region 980 $cm.^{-1}$ - 1000 $cm.^{-1}$, suggesting the presence of both isomers. Thin layer chromatography agrees with this, showing spots attributed to the cis and trans alcohols.

$LiAlH_4$ reduction of the cyano-alcohols (5a) gave the amino-alcohols (6a). The infra-red spectra of the bases and their hydrochloride salts confirmed the designation of the configuration, having peaks in the region 1060 cm.-1 - 1090 $cm.^{-1}$, attributable to equitorial C-O stretching.

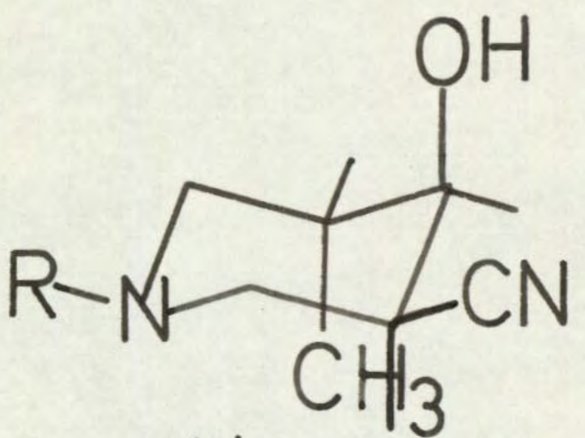
In the case of 1-benzyl-3-cyano-5-methyl-4-piperidinol (17), the presence of the extra substituent tends to complicate the stereochemistry, since four



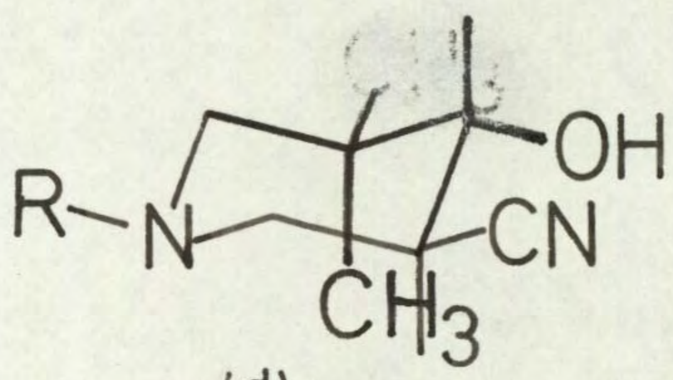
(17a)



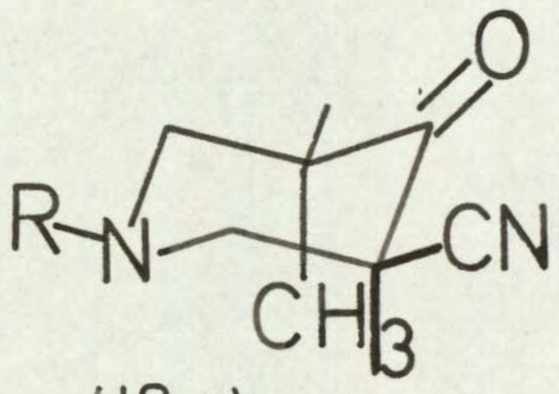
(17b)



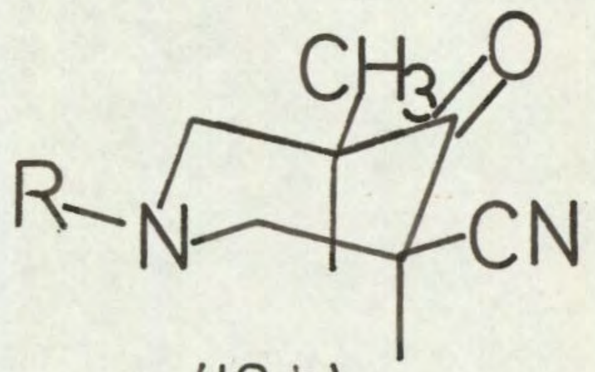
(17c)



(17d)

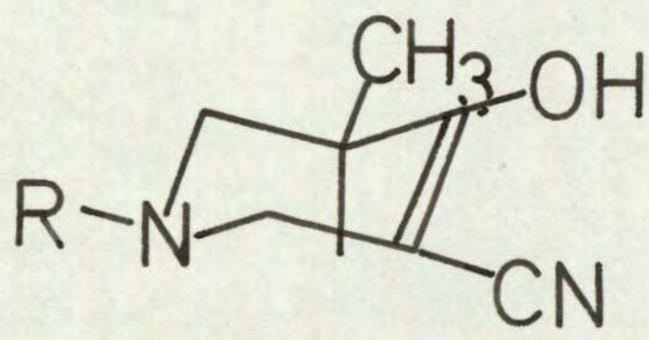


(18a)



(18b)

geometric isomers are theoretically possible (17 a-d), arising from the cyano-ketones (18a, b). The situation can be simplified by assuming that, due to the presence of the ketone, which has been shown by infra-red spectroscopy to exist in the enolic form (18c), both the 3-CN and the 5-CH_3 are in the equitorial position (18b) while



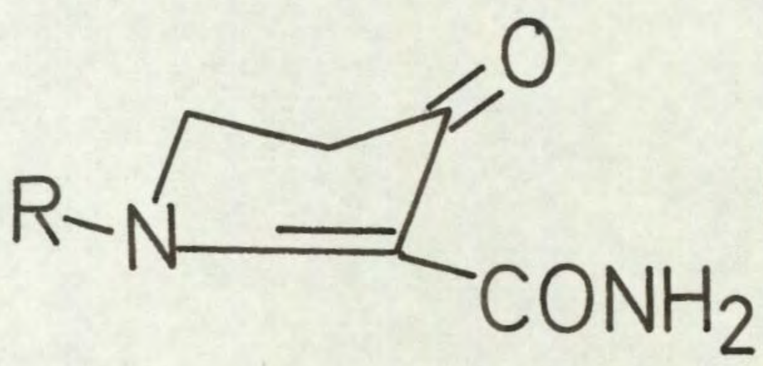
(18c)

the ketone is being reduced. This would tend to lead to the synthesis of alcohols (17a, b), and under the conditions used for the reduction, namely aqueous ethanolic $NaBH_4$, the equitorial alcohol (17b) is expected to predominate. An attempt at reduction of the cyano-ketone (18c) gave a mixture of compounds, one of which

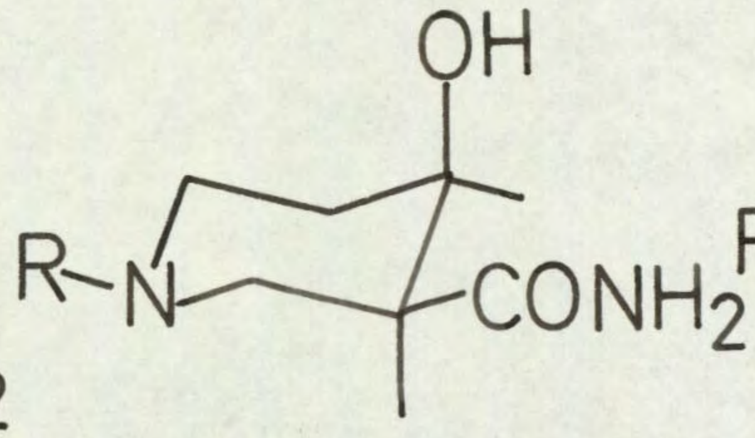
was obtained pure in a very small yield (6%). An infra-red spectrum of this alcohol showed a doublet at 1060 cm.$^{-1}$ - 1080 cm.$^{-1}$, which was attributed to equitorial OH. Hence the compound was provisionally assigned the <u>cis</u> 3-CN/5-CH_3, <u>trans</u> 3-CN/4-OH configuration (17b), though further evidence is required to substantiate this assignment.

iv. <u>3-Amido-4-piperidinols</u>

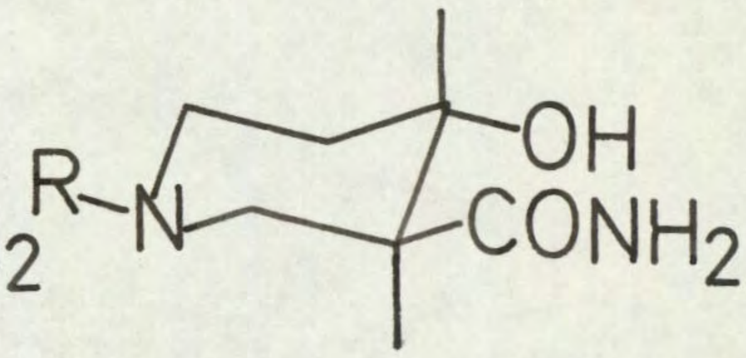
Two further compounds can be discussed in this section. These are 3-amido-1-benzyl-4-piperidinol (19, R=$C_6H_5CH_2$) and 3-amido-1-methyl-4-piperidinol (19, R=CH_3) obtained from the corresponding 5-amido-1,2,3,4-tetrahydro-4-oxo-pyridines (20) via a $NaBH_4$ reduction. The presence of the 5,6 double bond tends to complicate the course of the reduction, and so no assignments were attempted from a consideration of the stereospecificity of the reduction. The infra-red spectra of the products, however, suggest that the isomer obtained in each case is the stable equitorial alcohol (19b), with the 3-$CONH_2$/



(20)



(19a)



(19b)

4-OH being <u>trans</u>, having an absorption in the region 1050 cm.$^{-1}$ - 1070 cm.$^{-1}$. Examination of the mother liquors indicated the possible presence of the second isomer, the axial alcohol, with a small peak in the region of 990 cm.$^{-1}$, attributed to axial C-O stretch. Once again, further evidence would be needed to substantiate the assignment.

d) <u>N.M.R. Spectra interpretation</u>

It was hoped that an examination of the N.M.R. spectra of some of the alcohols and their esters would provide a fourth method for determining the configurations of the piperidinols.

Casy (1966) assigned the configuration of the <u>cis</u> and <u>trans</u> isomers of 1-alkyl-4-aryl-3-methyl-4-piperidinols using N.M.R. spectroscopy. For determining the configuration of the alcohols, either a comparison of the shift in the τ value of the α proton on esterification (Schoolery and Rodgers, 1958, Sheehan and Yang, 1958) or a measure of the half-height width of the signal due to the α proton on esterification (Chan and Taylor, 1967) can be used.

The N.M.R. spectra of the alcohols and their acetates, however, were not sufficiently clear to make any absolute assignments of configuration. This was due in the

first instance to the low solubility of some of the compounds in the solvent used ($CDCl_3$), and secondly to the rapid interchange of the conformations causing the shielding of the protons to be averaged out, with consequent line broadening. The spectra could, however, be correlated roughly with the known configurations by comparing the positions of the protons *a* to the hydroxyl group and their shifts on esterification of the alcohol. The compounds and the positions of the *a* protons are shown in table I.

The absence of any values for the position of the *a* proton in compounds (25) were due to the formation of a di-hydrochloride, which protonated the nitrogens and lowered the frequencies of the protons adjacent to the nitrogens to coincide with the positions of the *a* proton absorptions. The low frequencies for the *a* protons observed in compounds (24) were also attributed to the presence of the protonated nitrogens causing general lowering of the absorption of the adjacent protons.

Jackman (1959) found that, for substituted <u>cyclo</u>-hexanes, the equitorial and axial protons exhibit separate signals, and made the generalisation that, in each case, the axial proton absorbs at higher frequencies than its equitorial counterpart. This is found to be true in the case of compounds (21). Isomer 'A', with

TABLE I

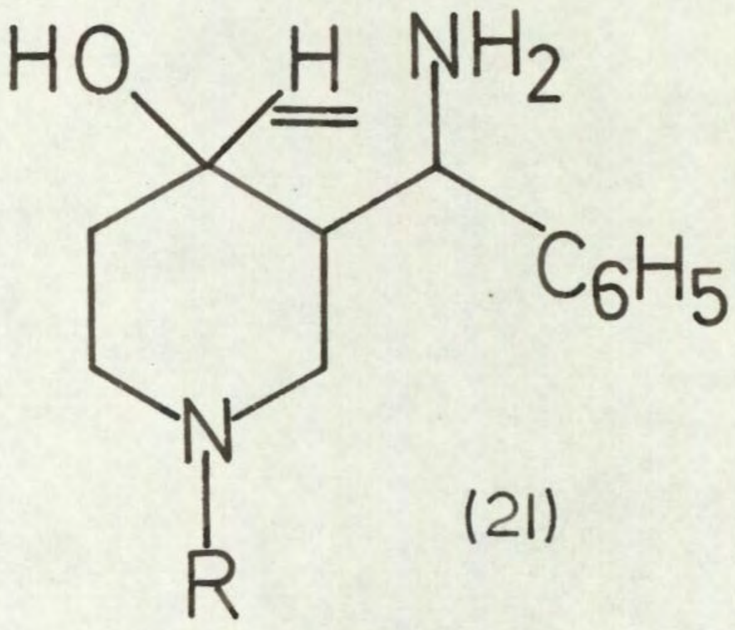
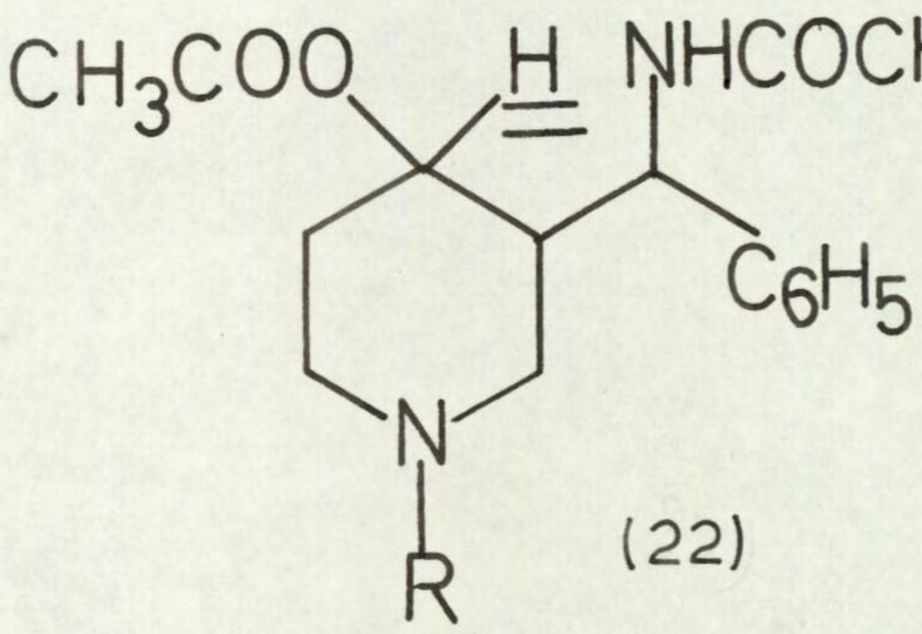
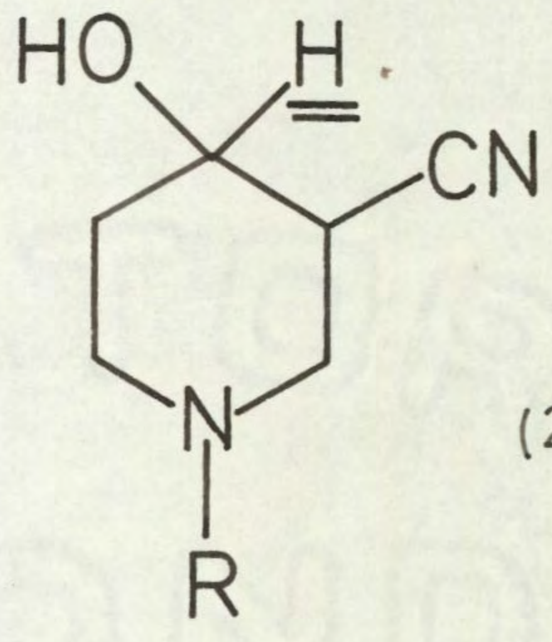
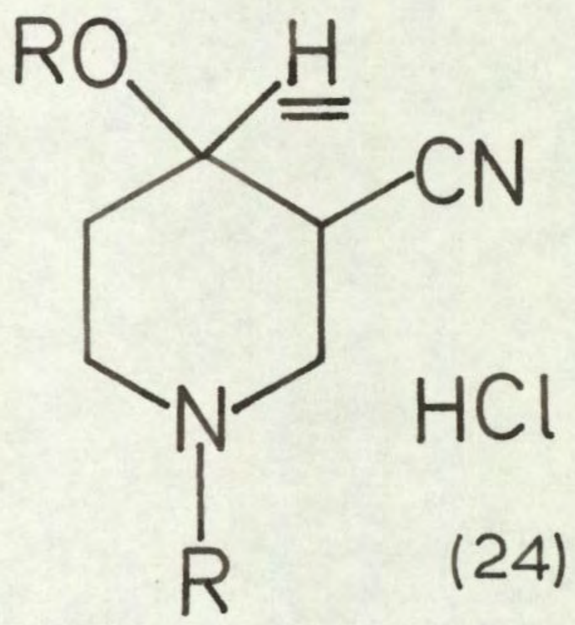
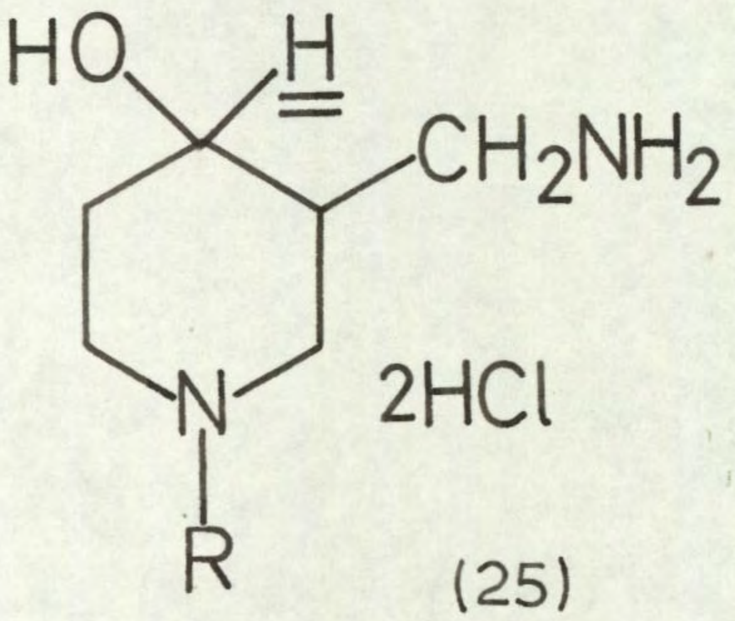
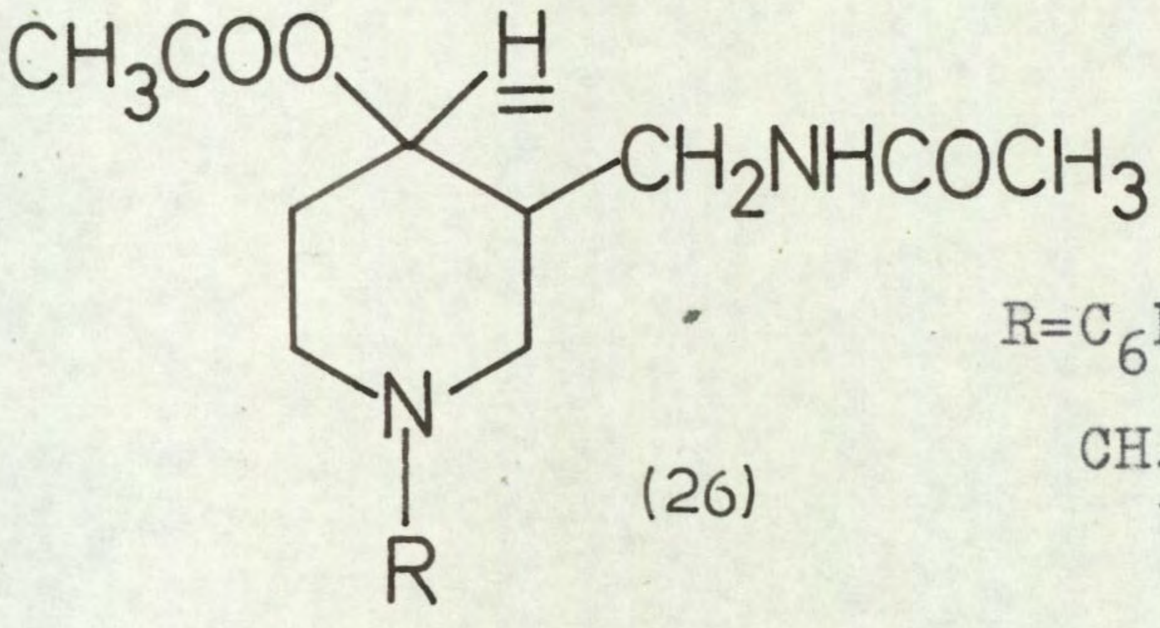
Compound	Substituents	Isomer	τ p.p.m.	τ c.p.s.
 (21)	$R=C_6H_5CH_2$	'A'	5.8	253
	$C_6H_5CH_2$	'B'	6.4	215
 (22)	$C_6H_5CH_2$	'A'	5.4	276
	$C_6H_5CH_2$	'B'	5.1	295
	CH_3CO	'A'	5.2	288
	CH_3CO	'B'	5.0	300
 (23)	CH_3	'B'	6.3	222
	C_2H_5	'B'	6.4	216
	$C_6H_5CH_2$	'B'	6.2	228

TABLE I CONT'D.

Compound	Substituents	Isomer	p.p.m.	c.p.s.
 (24)	$R=C_6H_5CH_2$ $R'=CH_3CO$	'B'	4.6	324
	$R=C_6H_5CH_2$ $R'=C_2H_5CO$	'B'	4.6	324
 (25)	$R=CH_3$	'B'	-	
	C_2H_5	'B'	-	
	$C_6H_5CH_2$	'B'	-	
 (26)	$R=C_6H_5CH_2$	'B'	5.3	282
	CH_3	'B'	5.25	285

axial OH, hence an equitorial *a* proton, absorbs at τ=5.8, while isomer 'B' absorbs at τ=6.4. Thus N.M.R. spectroscopy substantiates the suggestion that isomer (A) is the <u>cis</u> epimer.

Careful inspection of the spectra of the isomeric acetates (compounds 22), however, do not agree with Jackman's theory. Isomers 'A', with equitorial protons, absorb in the region τ=5.2-5.4, while isomers 'B' absorb in the region τ=5.0-5.1. Schoolery and Rodgers, however, suggested that the shift in the value for the *a* proton of the alcohol on esterification was greater for axial protons than for equitorial protons. A calculation reveals that the axial *a* protons (isomer B) do shift to a greater extent than do isomers (A). Thus while the two opposing results do not substantiate the designations of the isomers, neither do they deduct from them.

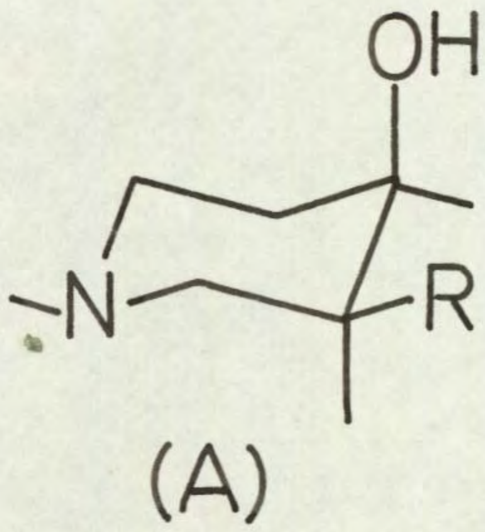
The compounds (23) and (25) were suggested as having the <u>trans</u> 3-substituent/4-OH configuration by a comparison of the infra-red spectra of the single isomers with the spectra of the two isomers with confirmed configurations. Similarly, a comparison of the position of the absorption due to the *a* proton in the single isomers of compounds (23) and (25) with the position due to the *a* proton of the two isomers of

compound (21) may be expected to yield useful information . The absorption due to the suggested axial α protons in the compounds (23) occur in the region τ=6.2-6.4. This agrees with the absorption due to the axial α proton in isomer (B) of compounds (21), which absorbed at τ=6.4. Thus the N.M.R. spectra of these compounds substantiate the suggested configuration.

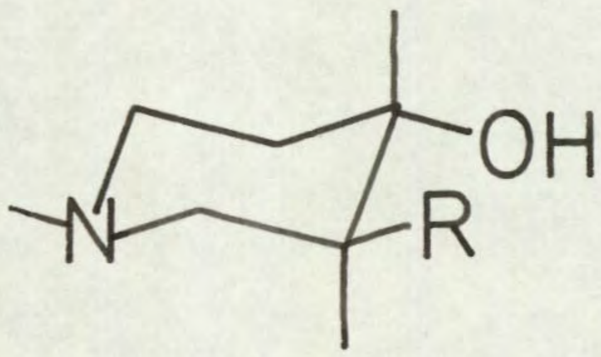
A summary of the results

In conclusion, the results of the above investigation are summarised.

1-Benzyl-3- α -phenylaminomethyl-4-piperidinol yielded two isomers, designated (A) and (B). Hydrolysis of the esters of the two isomeric alcohols provided the most concrete evidence for the designation of configurations, and led to the (B) isomer being given the trans 3-$C_6H_5CHNH_2$/4-OH configuration. A consideration of the stereospecific reduction did not, in itself, lead



(A)

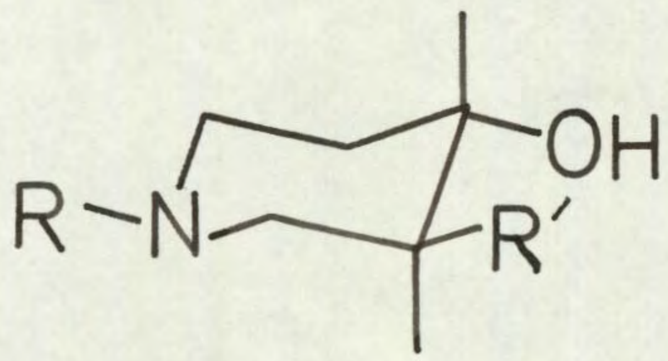


(B)

to any definite conclusion but substantiated the evidence given by the hydrolysis. Infra-red and N.M.R. spectros-

copy further substantiated the idea that isomer (B) had the suggested configuration.

The other compounds were not obtained in more than one isomeric form, and so both hydrolysis studies and stereospecific reduction studies were not considered to be of importance. Infra-red and N.M.R. spectroscopy proved to be useful in as much as the spectra of the single isomers could be compared with the spectra of the two isomers of suggested configuration. The infra-red and N.M.R. spectra tended to agree and led to the suggestion that the compounds existed as the (B) isomers,



$R = CH_3, C_2H_5, C_6H_5CH_2.$

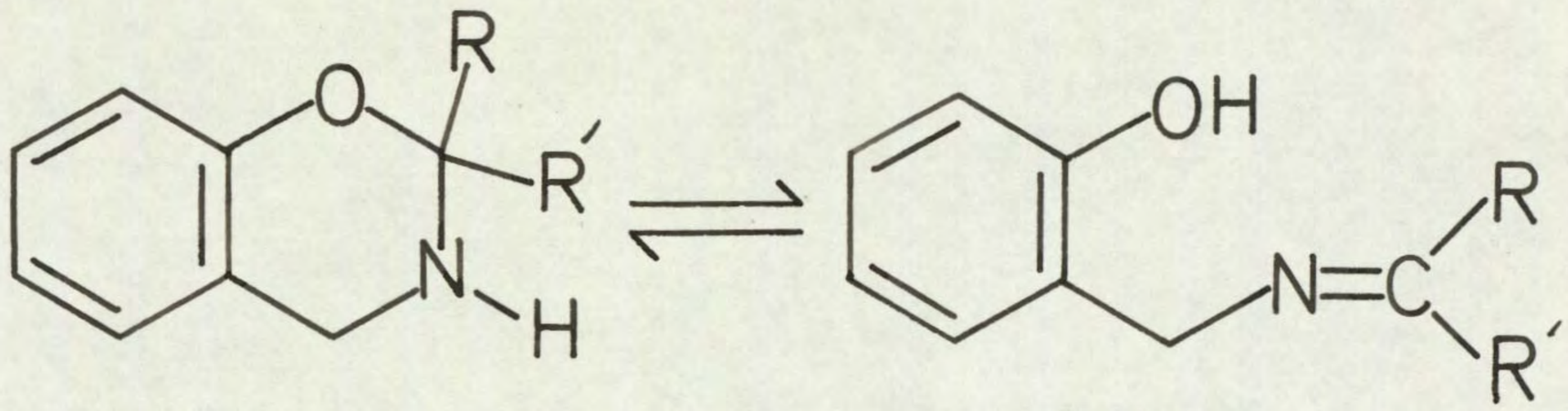
$R = CN, CH_2NH_2, CONH_2.$

with the 3 and 4 substituents being axial.

Further work is necessary before configurations can be definitely assigned to some of the compounds.

2 <u>A brief consideration of the oxazine syntheses</u>

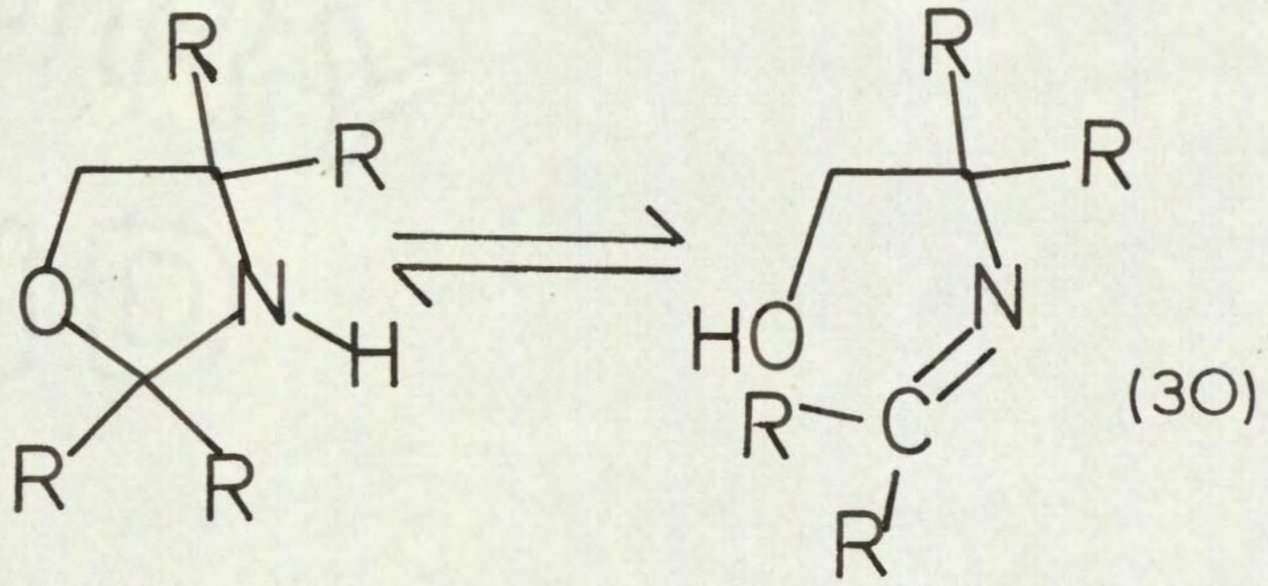
McDonagh and Smith (1968) condensed aldehydes and ketones with o-hydroxybenzylamine to obtain a tautomeric system consisting of either an oxazine (27), an open chain Schiff base (28) or a mixture of both. The



(27) (28)

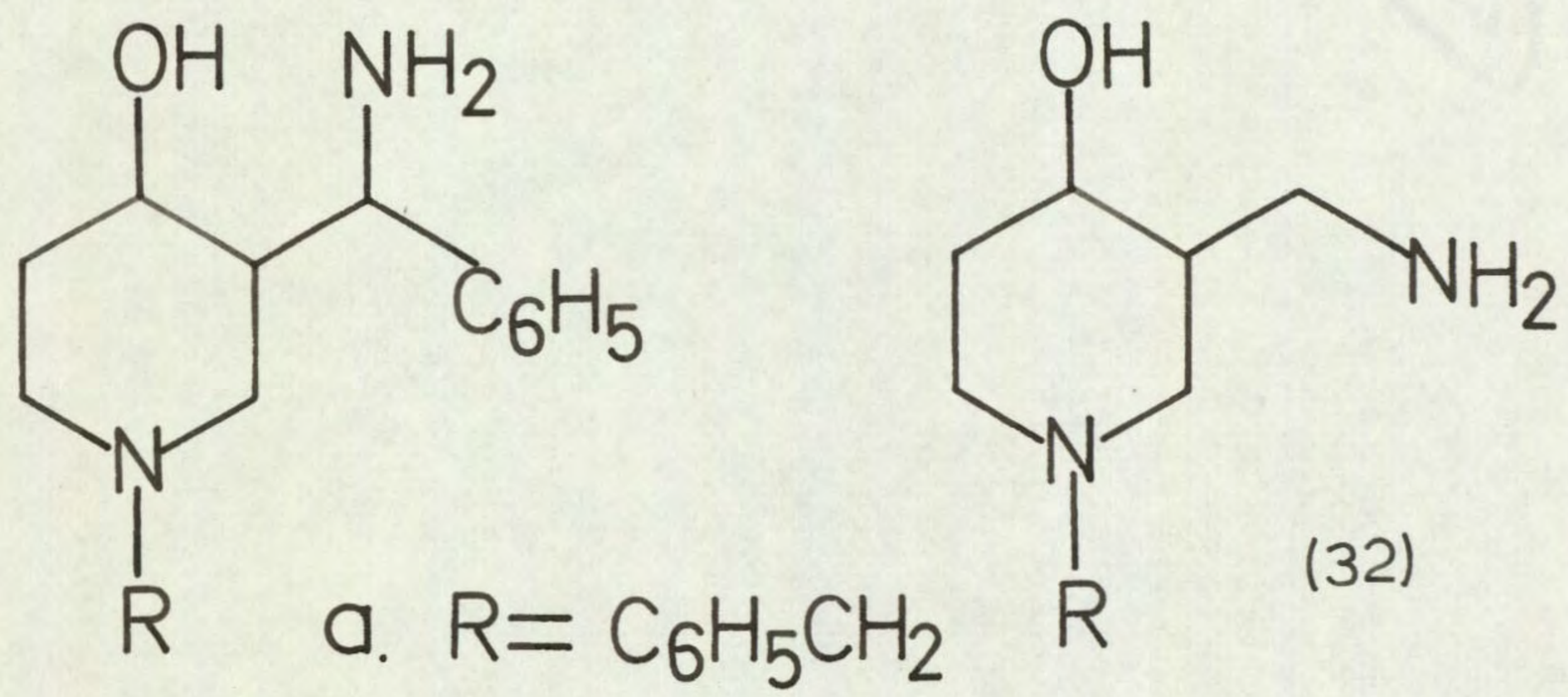
compounds obtained were studied by physical methods, especially nuclear magnetic resonance spectroscopy, in order to elucidate the equilibrium constants of the synthesis, and to draw some conclusions from these constants. In general, it was found that aliphatic aldehydes and ketones tended to give predominantly cyclic structures, while aromatic aldehydes and ketones tended to give open-chain structures. However, in the case of substituted benzaldehydes, there existed an equilibrium which was found to be dependant upon the benzaldehyde substituent and upon the solvent used for the equilibrium determination. One conclusion drawn was that the greater the electron-withdrawing power of the substituent in the aldehyde, the greater the ring/chain ratio, a plot of log K/Ko (K = equilibrium constant for substituted benzaldehyde, Ko = equilibrium constant for benzaldehyde) against the substituant constant σ being found to be roughly linear. A second conclusion was that the equilibrium was solvent sensitive, but was not

correlatable with the dipole moment or dielectric constant of the solvent. Paukstelis and Hammaker (1968), in a study of the equilibrium constants of oxazolidines (29) and their open-chain analogues (30),

(29)  (30)

again using N.M.R. spectroscopy, also found a change in the equilibrium with change of solvent, and related this with the ability of the solvent to hydrogen bond with the OH group in the Schiff base. Further work in this field is indicated.

The amino-alcohols (31) and (32), synthesised in the present work, were reacted with a variety of aldehydes and ketones. The results are summarised in



(31) (32)

a. R= $C_6H_5CH_2$
b. CH_3
c. C_2H_5

Table II.

TABLE II

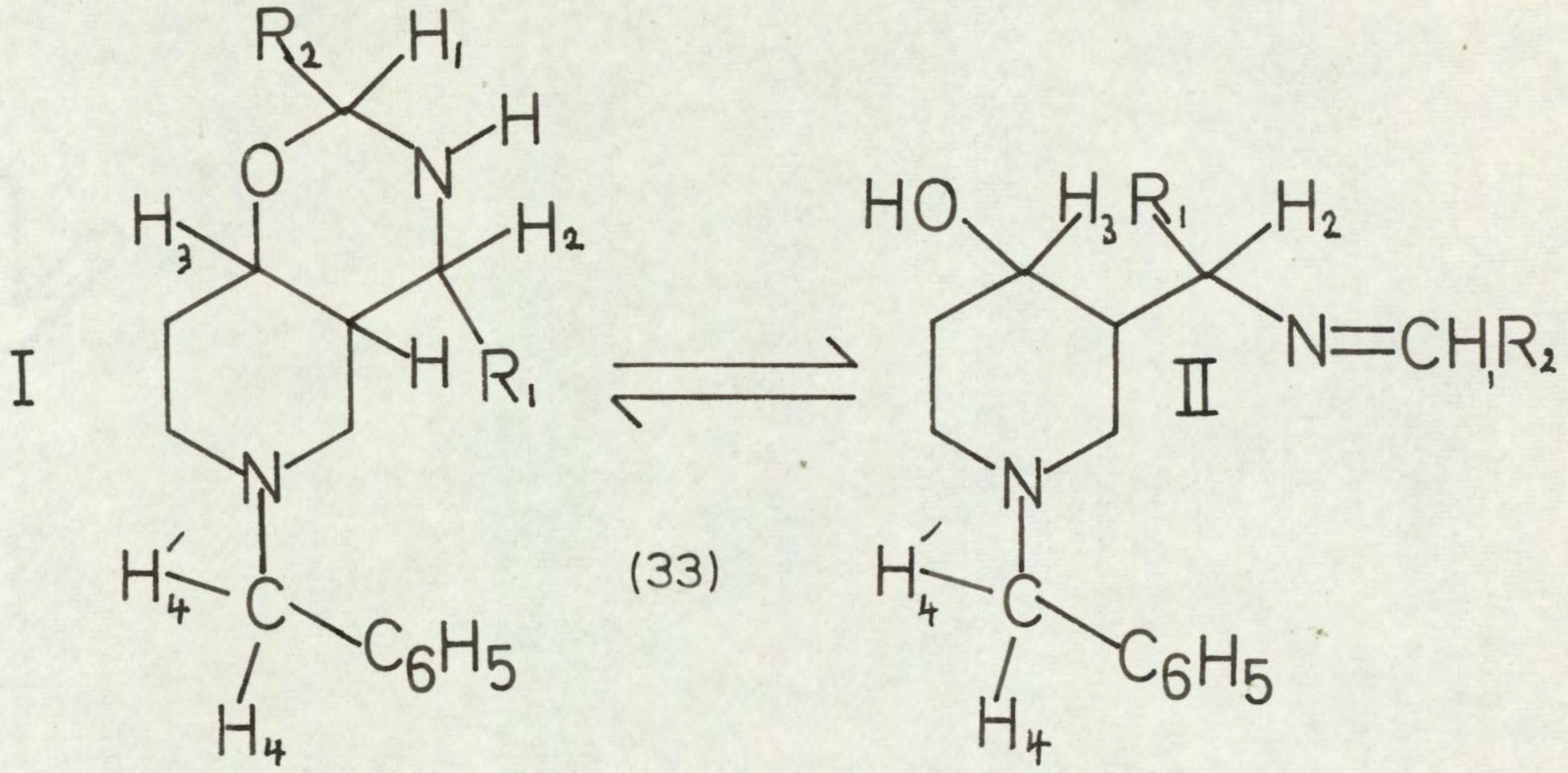
Compound	Isomer	Reagent	Form	M.p.
31a	A	Benzaldehyde	Ring	134°
"	B	"	"	117°
"	A	n-Butyraldehyde	"	84°(i
"	A	Acetaldehyde	"	98°(i
"	A	o-Methoxybenzaldehyde	"	155°
"	A	m-Methoxybenzaldehyde	"	133°
"	A	p-Methoxybenzaldehyde	"	110°
"	A	3,4-Dimethoxybenz-aldehyde	"	112°
"	A	p-Fluorobenzaldehyde	"	124°
"	B	"	"	121°
"	A	p-Dimethylaminobenz-aldehyde	"	136°
"	A	o-Hydroxybenzalde-hyde	Chain	142.5°
"	A	m-Hydroxybenzalde-hyde	Ring	179°
"	B	"	"	- (ii
"	A	Cyclohexanone	"	94°(i
"	A	Acetophenone	-	-(iii
"	A	Formaldehyde	Ring	- (i
"	A	3,4-Dihydroxybenz-aldehyde	-	-(iii
"	A	p-Hydroxybenzalde-hyde	Chain	- (ii
"	A	Acetone	-	-(iii
"	A	Phosgene	Ring	243°
"	A	Carbon disulphide	"	273°
32a	B	p-Nitrobenzaldehyde	"	153-156°
"	B	p-Fluorobenzaldehyde	Equilibrium	
"	B	p-Dimethylamino-		

Compound	Isomer	Reagent	Form	M.p.
32a	B	Benzaldehyde	Chain	- (ii
31b	B	p-Nitrobenzaldehyde	"	- (i
"	B	o-Methoxybenz-aldehyde	"	- (ii
"	B	Benzaldehyde	"	- (ii
32b	B	"	"	- (ii
"	B	n-Butyraldehyde	"	- (ii
32c	B	Benzaldehyde	"	- (ii

(i) Decomposed on allowing to stand.
(ii) Could not be solidified or crystallised.
(iii) Did not react.

It was found that, in general, aliphatic aldehydes and ketones gave compounds that were difficult to crystallise and tended to decompose on allowing to stand, giving brown resins. No attempt was made to obtain N.M.R. spectra of these compounds because of their dubious state of purity. Aromatic aldehydes, on the other hand, gave good crystalline compounds which were stable. N.M.R. spectra of these compounds were obtained, the relevant peaks of which are shown in Table III.

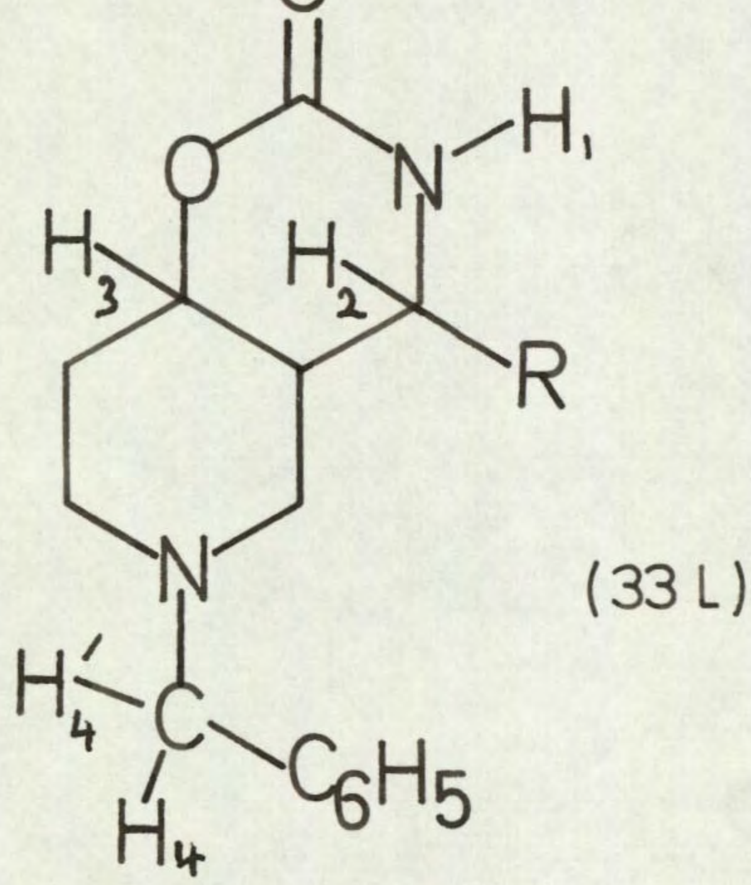
TABLE III



Compound	R_1	R_2	Isomer	H_1 τ	H_2 τ	H_3 τ	H_4 τ	H_4' τ	$\delta_4-\delta_4$ c.p.s
33a	C_6H_5	C_6H_5	A	4.63	5.6	5.9	6.5	6.7	14
"	"	"	B	4.63	6.3	6.5	6.45	6.75	18
b	"	m-$C_6H_4OCH_3$	A	4.67	5.6	5.9	6.5	6.7	14
c	"	3,4-$C_6H_3(OCH_3)_2$	A	4.67	5.6	5.87	6.5	6.7	14
d	"	p-$C_6H_4N(CH_3)_2$	A	4.7	5.6	5.9	6.5	6.7	14
e	"	o-C_6H_4OH	A	1.7	5.63	6.45	6.35	6.72	21.5
f	"	o-$C_6H_4OCH_3$	A	4.38	5.6	5.87	6.45	6.65	14
g	"	p-$C_6H_4OCH_3$	A	4.39	5.6	5.88	6.5	6.7	14
h	"	p-C_6H_4F	A	4.69	5.62	5.9	6.5	6.7	14
	"	"	B	4.65	6.3	6.5	6.45	6.75	18
i	H	p-$C_6H_4NO_2$	B	4.88	(i)	6.7	6.56		(ii)
j	"	p-$C_6H_4N(CH_3)_2$	B	2.2	(i)	6.5	6.6		(ii)
k	"	p-C_6H_4F	B	{2.07 4.95}	(i)	6.6	6.6		(ii)
l	C_6H_5	-	A	3.83	5.14	5.3	6.56	6.76	11

(i) Occurs in the region 6.9-7.5

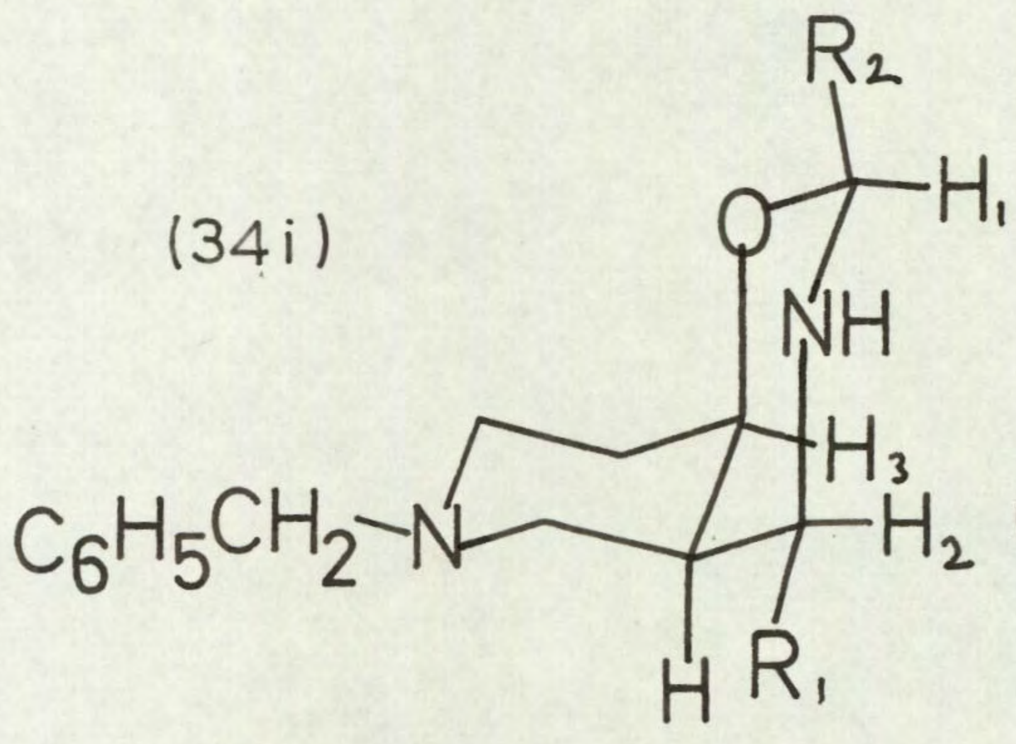
(ii) Single peak obtained, $\delta_4 - \delta_4' = 0$



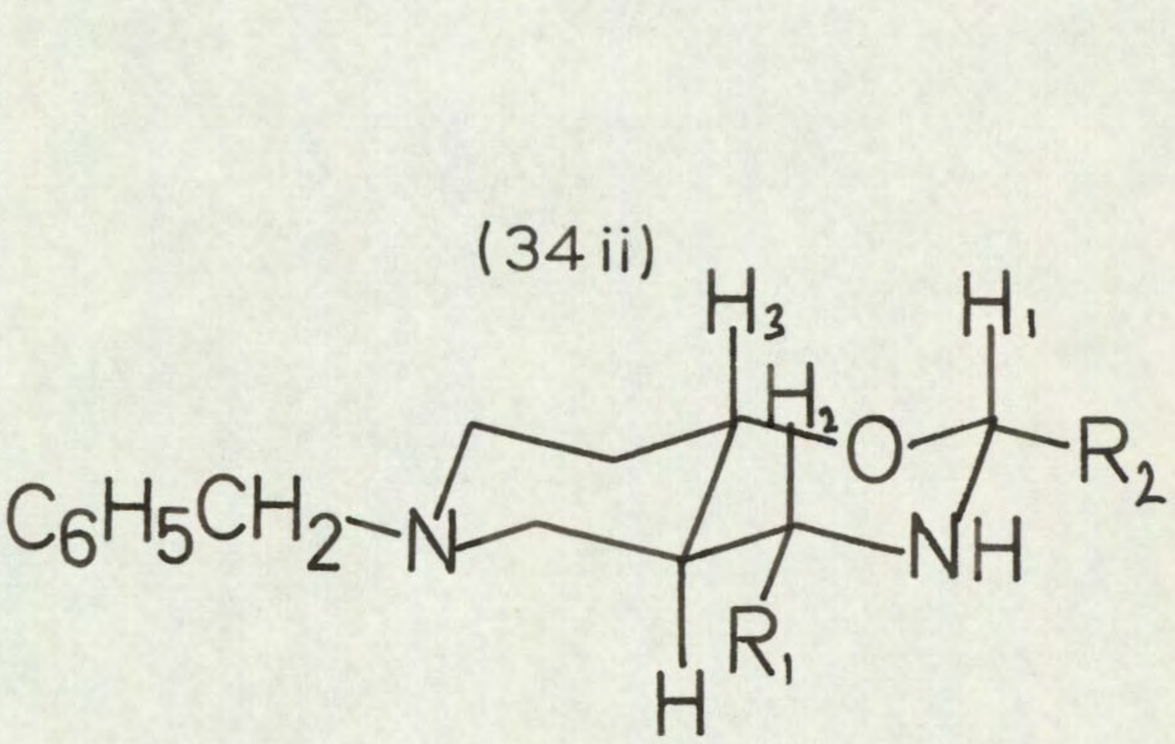
(33 L)

Assuming that a chair/chair form is the most stable, the two configurations for the pyrido-oxazines are expected to be (34 i, ii). This is in agreement with the

(34 i)



(34 ii)

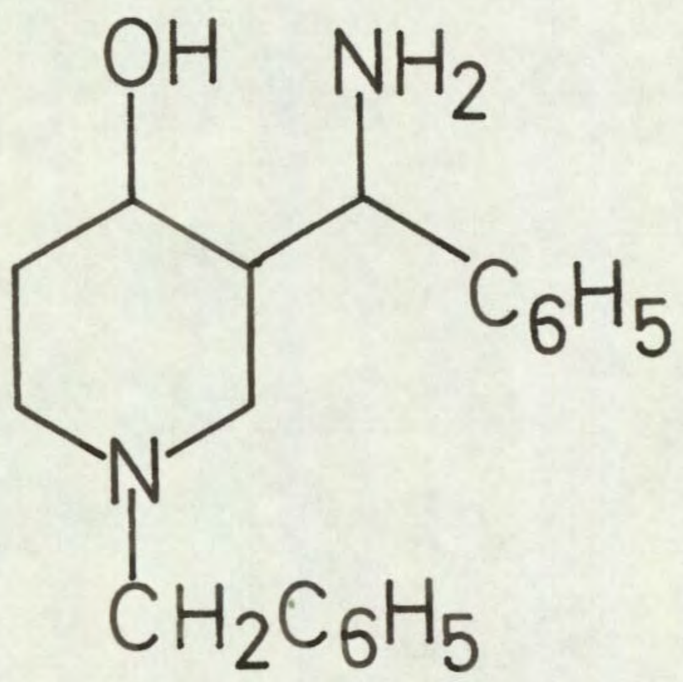


absorption found for the proton H_3, the absorption for the equitorial proton (34, i) at τ = 5.68-5.9 being lower than that for the axial proton (34 ii) at τ = 6.5 (The values for the equitorial and axial protons in the

amino-alcohol precursors were τ = 5.8 and $\tau \sim$ 6.8 respectively.). The only anomalous result is that for (33e), obtained from the condensation of the (A) isomer of (31a) with salicylaldehyde. This was found to be in the chain form (33 II) and gave a value of τ = 6.45 for the absorption of the proton H_3. It was thought that the presence of the o-hydroxyl, coupled with the compound being in the chain form, might have constituted a large bulky group. This, with the bulky α-phenyl group, might tend to force the piperidine ring into the other conformation, with the 3-substituent axial and the 4-hydroxy group equitorial, making the α proton axial. However, this conformation is not expected to be stable, and the presence of C-O-H stretch in the infra-red at 995 $cm.^{-1}$ suggests that the compound is still in the more stable 3-equitorial/4-axial form.

That this compound is anomalous is shown by the absorption due to the H_4 protons. In a magnetic field, a pair of equivalent nuclei, A_2, i.e. CH_2, gives rise to a single absorption line. If the two nuclei are different, AB, they give rise to a pair of doublets of equal intensity. The intermediate case, in which the difference in chemical shift $\delta_B - \delta_A$ is comparable to the spin-spin coupling constant J_{AB}, also consists of a pair of doublets, but the intensities of the four lines

are no longer equal, the intensities of the inner lines increasing at the expense of the outer pair. The non-equivalence can arise from the restricted rotation of a single bond, if the rate of rotation is slow on the N.M.R. time scale, and has been observed in a number of compounds containing a benzyl group (Price and Sutherland 1967, Whiteside et al. 1965). This effect can be observed in the spectra of the compounds derived from the



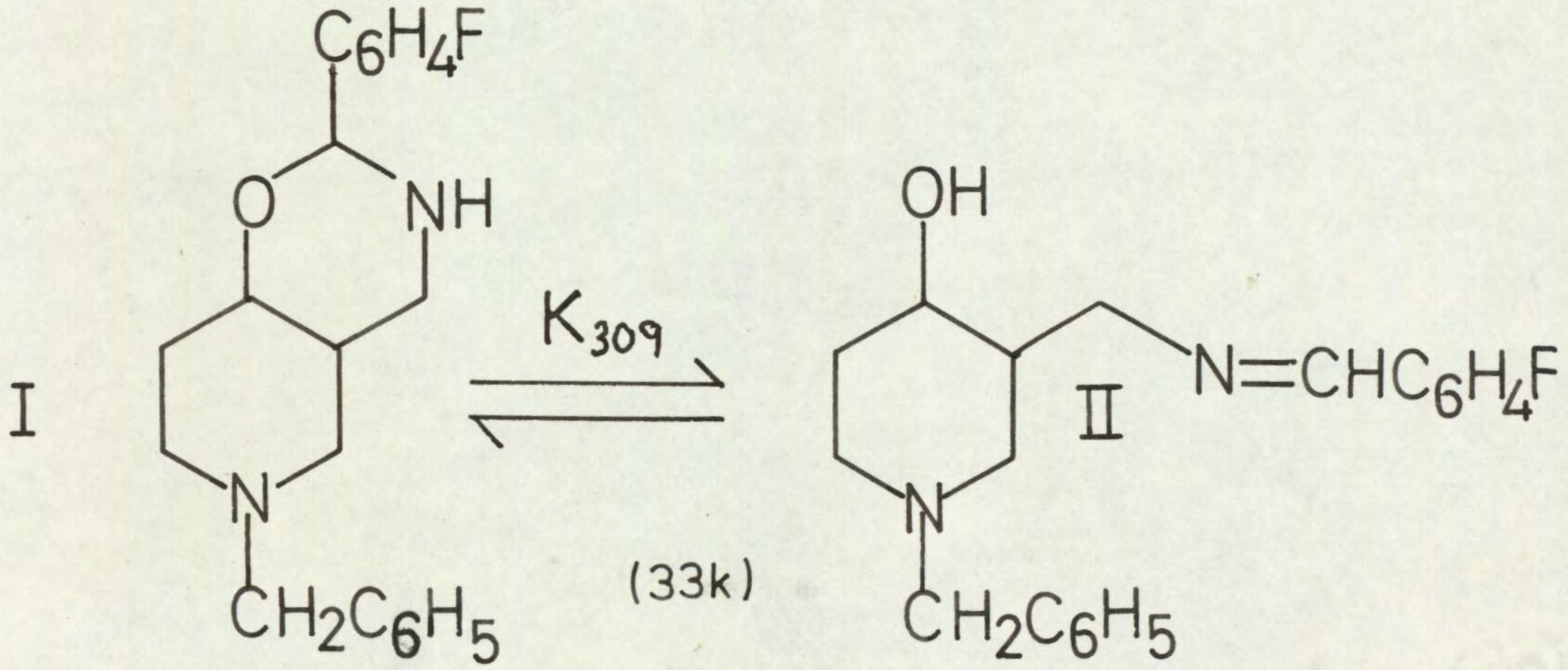
(31a)

(31d)

amino-alcohols (31a). The absorption due to the methylene protons (labelled H_4 and H_4') all found in the region τ = 6.3-6.8 and occur due to the restricted rotation around the C-N bond. The restriction is possibly caused by the presence of the phenyl group (R_1) on the side chain, since compounds without this side-chain, viz. those derived from the amino-alcohol (32a), appear to be unhindered and freely rotate about the C-N bond, as shown by a single peak for the CH_2 which is found in the region of 6.6τ. The differences in chemical shift ($\delta_4 - \delta_4'$) for the two isomers are

constant, the value for the (B) isomer being the larger. In the case of (33e), arising from the condensation of salicylaldehyde with the amino-alcohol, however, the difference in chemical shift is found to be 21.5 c.p.s., 8 c.p.s. greater than that expected of an (A) isomer. The larger splitting could be attributed either to the greater difference in magnetic field experienced by the methylene protons, due to rotation about the C-C bond attached to the 3-position of the piperidine, or to the greater amount of hindrance due to the free $C_6H_5CH-N=CHR$ group. The former effect may also explain the anomalous absorption of the H_3 proton, which could be shielded by the large group.

An equilibrium mixture was noticed in only one of the compounds obtained as a crystalline solid (33k). The presence of either the ring or chain tautomer is detected by a consideration of the position of the H_1



proton absorption. For the ring (I), the absorption appears around τ = 4.3-4.9 as a broadened singlet or triplet, while the H_1 proton for the chain (II) absorbs in the region τ = 1.7-2.2. The infra-red spectra can be used to detect the presence or absence of the chain (II) by inspection of the region 1650 $cm.^{-1}$ - 1620 $cm.^{-1}$ for the C=N absorption, while the OH absorption appears as a broad hump centred on 3300 $cm.^{-1}$. The equilibrium constant for the compound (33k) is determined by a comparison of the areas of the two absorptions in the N.M.R. spectrum and is found to be K (ring/chain) = 1.32 (57% ring).

The other compounds exist entirely as the ring structure (33a-d, 33f-i) or as the chain structure (33e, 33j), which is contrary to expectations. A closer inspection of the crystallisable compounds reveals that they fall into two categories:

a) the compounds with R_1=H.

b) the compounds with R_1=C_6H_5.

The first class of compound behaves normally, i.e. as the substitution constant σ decreases (e.g. from R_2=p-nitrobenzaldehyde to p-dimethylaminobenzaldehyde) the ring/chain ratio decreases. The second class of compound, on the other hand, gives ring structures with the majority of aldehydes, the two exceptions being

o-hydroxybenzaldehyde, resulting in a chain structure, and p-dimethylaminobenzaldehyde, resulting initially in a chain structure, but is converted to the ring form by reaction in acetic acid, which probably protonates the nitrogen atom of the substituent, forming an electron-withdrawing group instead of an electron-donating group, with consequent change in the substitution constant. The compounds may exist primarily in the ring tautomer because the presence of the phenyl group, constituting a large steric factor, might tend to force the primary amine group of the amino-alcohol into a position such that the ring tautomer is more easily formed and more stable than the chain form. In the first class of compound the phenyl group is absent and so the steric effect is lessened and electronic factors predominate. N.M.R. spectra of the reaction products of the condensation between benzaldehyde and (32a, b, c), where the phenyl group is missing in the amino-alcohol, show the presence of both the ring and chain tautomers, though the equilibria were not ascertained as the compounds are not thought to be pure. This tends to substantiate the idea that steric factors may play a part in determining the tautomeric ratio. N.M.R. spectra of the impure products of the reactions between (31b) and p-nitrobenzaldehyde and benzaldehyde also show

equilibrium mixtures, suggesting the possibility that the N-benzyl group is also involved. The presence of the equilibria may also explain why the compounds were unobtainable in a crystalline form.

The ultra-violet spectra of three of the compounds (33a, e, f) are unexceptional, two giving simple aromatic or substituted aromatic absorption spectra, while (33e) gives a spectrum attributable in part to substituted benzylidine absorption.

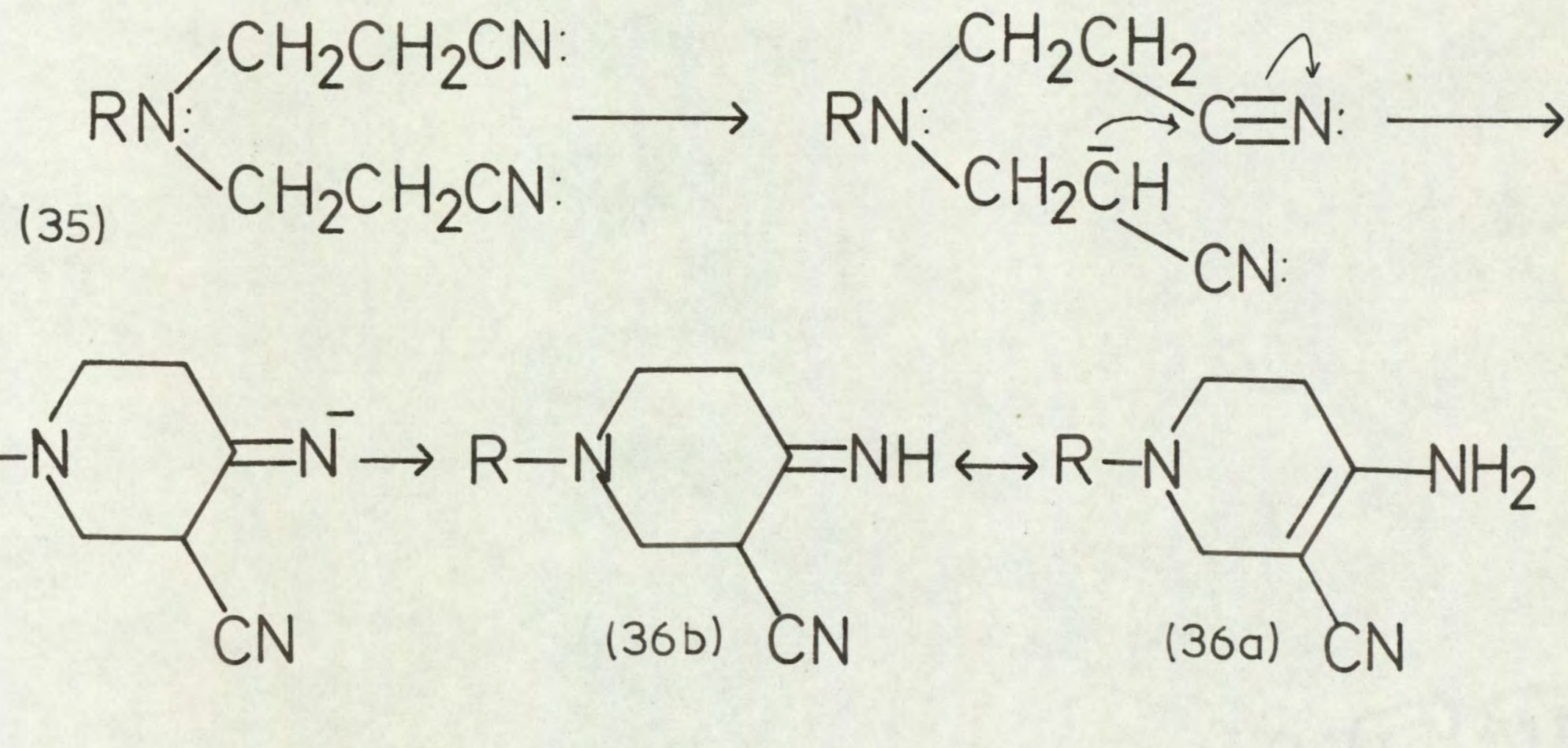
The compound obtained by the action of phosgene on the amino-alcohol (331), gave a similar N.M.R. spectrum to those obtained from the ring tautomers. The proton on the nitrogen was found at $\tau = 3.83$ as a broad hump which disappeared on deuteration. The proton H_2 was found at $\tau = 5.14$ as a broad hump which split into a doublet on deuteration. The proton α to the O-C=O group appeared at $\tau = 5.3$, midway between the absorption of the proton α to the amino-alcohol ($5.8\,\tau$) and that of the amido-ester ($4.8\,\tau$). The AB splitting due to hindered rotation is again observed, but the difference in chemical shift ($\delta_4 - \delta_4'$) appears to be smaller. This may be due to lack of a large substituent in the 2-position causing the difference in magnetic environment to be smaller.

The N.M.R. spectrum of the corresponding 2 -

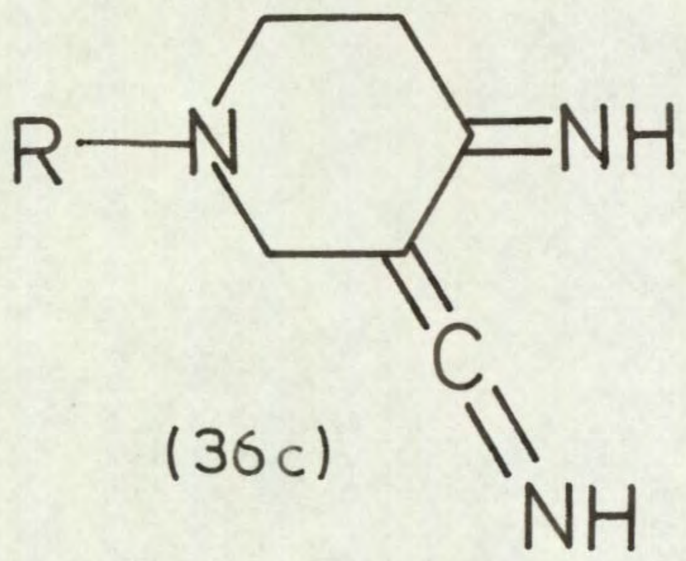
sulphinyl homologue was not obtained owing to the low solubility of the compound in common solvents.

3 The preparation and properties of 4-amino-3-cyano-1,2,5,6-tetrahydro-pyridines

The 4-amino-3-cyano-1,2,5,6-tetrahydro-pyridines (36a) are synthesised by the Thorpe cyclisation of a dinitrile (35) with the aid of a catalytic amount of a condensing agent such as sodium, sodium hydride or potassium tert. butoxide in an inert solvent. The mechanism probably involves the initial formation of a carbanion and subsequent intra-molecular attack on the



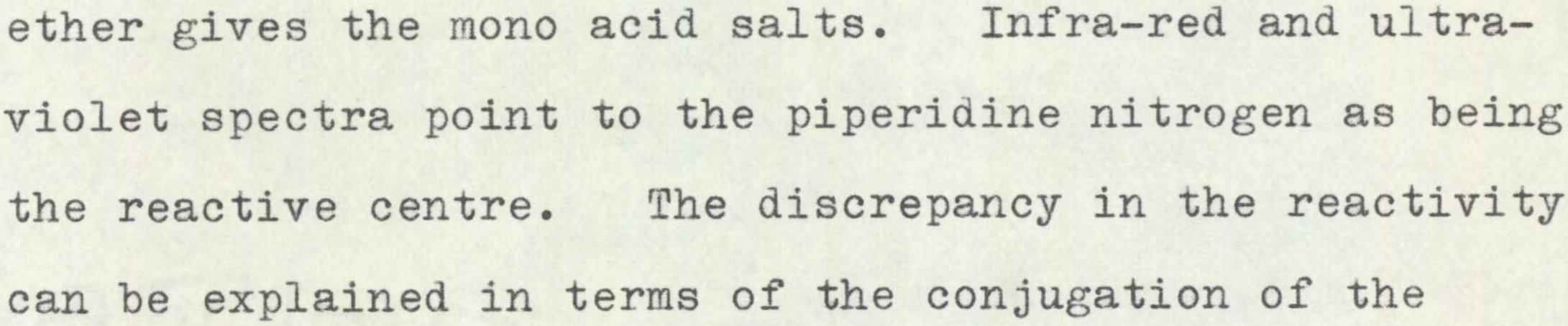
nitrile to give an iminonitrile (36b) which can tautomerise to the enaminonitrile (36a). The prevalence of an enaminonitrile rather than an iminonitrile (36b) or even an iminoketenimine (36c) has been discussed previously with the aid of absorption spectroscopy.



(36c)

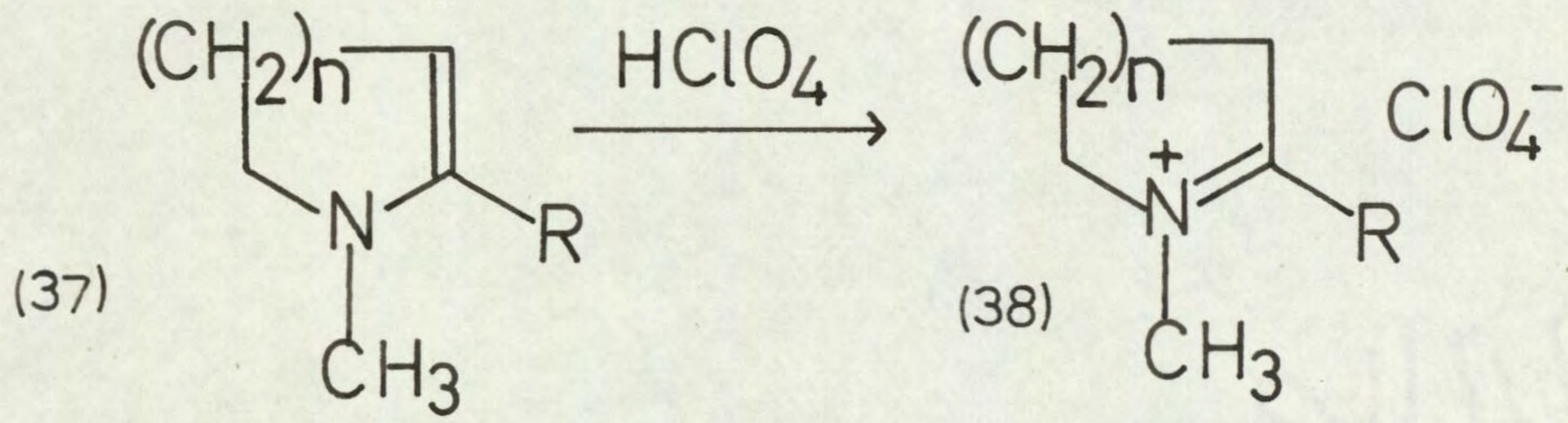
Although the enamines (36a) have the characteristic spectra of an amine group, the reactions of the compounds are not typical of an amine. They titrate as monobasic compounds and reaction with hydrogen halides in ether gives the mono acid salts. Infra-red and ultra-violet spectra point to the piperidine nitrogen as being the reactive centre. The discrepancy in the reactivity can be explained in terms of the conjugation of the enaminonitrile. The increased interaction between the p-electrons on the nitrogen atom with the π-electrons of

(36)

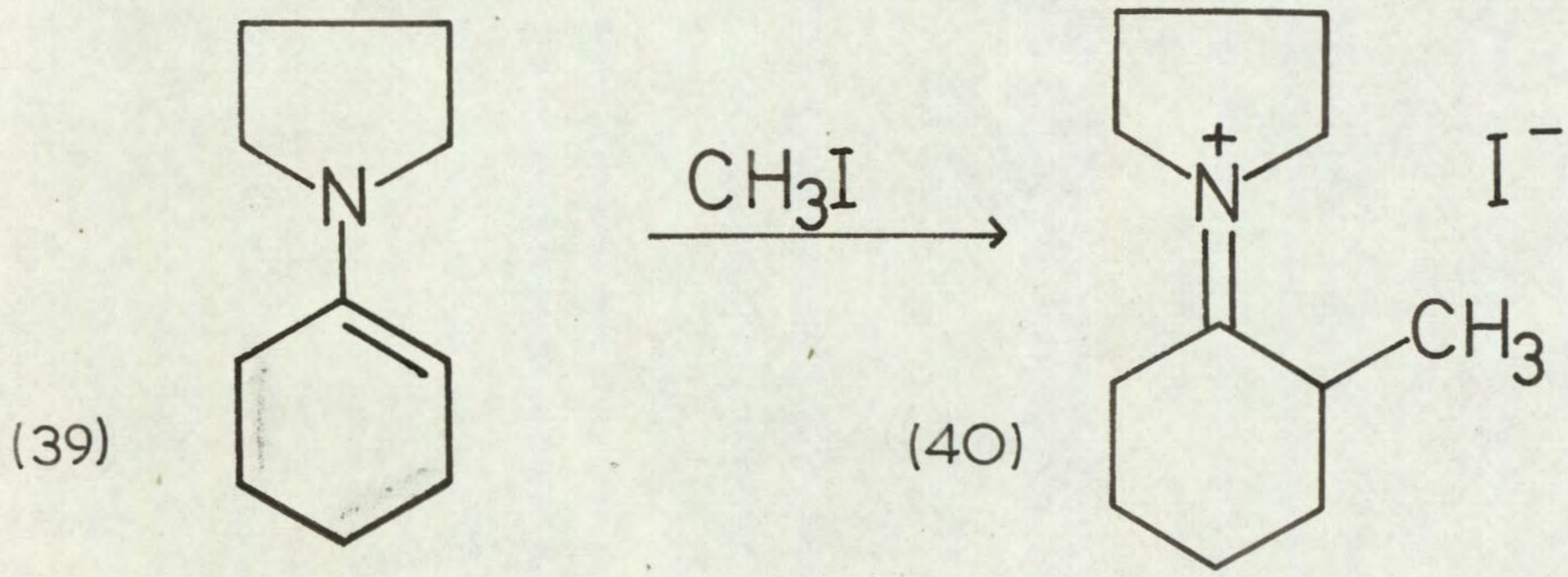


the double bond and in turn with the π-electrons of the nitrile group allows charge-separated resonance forms,

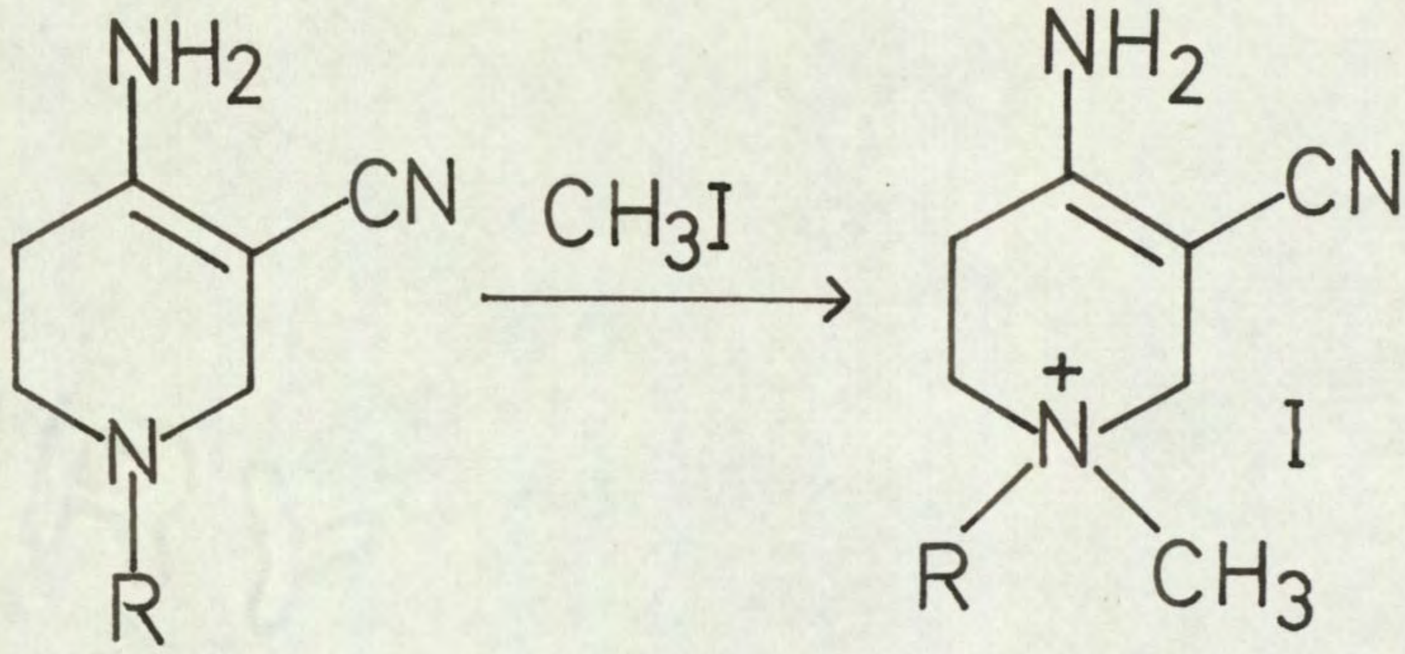
i.e. (36d, e, f) to contribute to the ground state of the molecule. This results in a lowering of available charge on the nitrogen with consequent lowering of the nucleophilicity. That the nitrile group plays a part in the conjugation is assumed from the fact that simple enamines readily protonate, forming immonium salts (37-38) (Hellmann et al. 1956).



Amines and enamines are readily alkylated under a variety of conditions. Amines give the corresponding substituted amine, while enamines usually give C-alkylation, to give a C-substituted immonium ion (Stork et al. 1963) (39-40). Reaction of the enamines with methyl

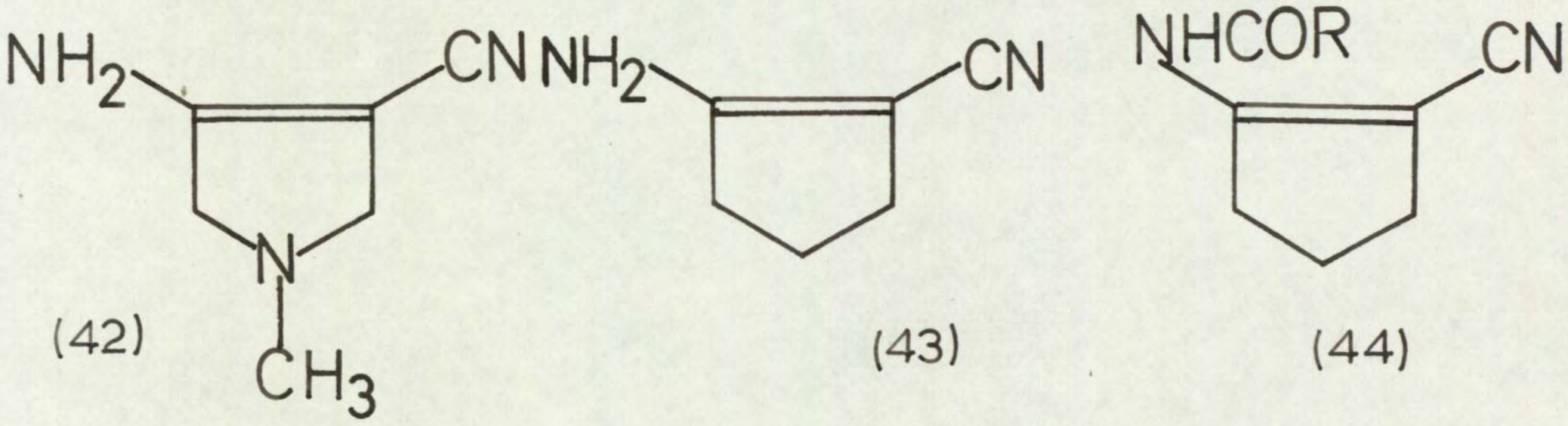


iodide gave the mono-methiodide, the piperidine nitrogen again forming the quaternary salt (41).



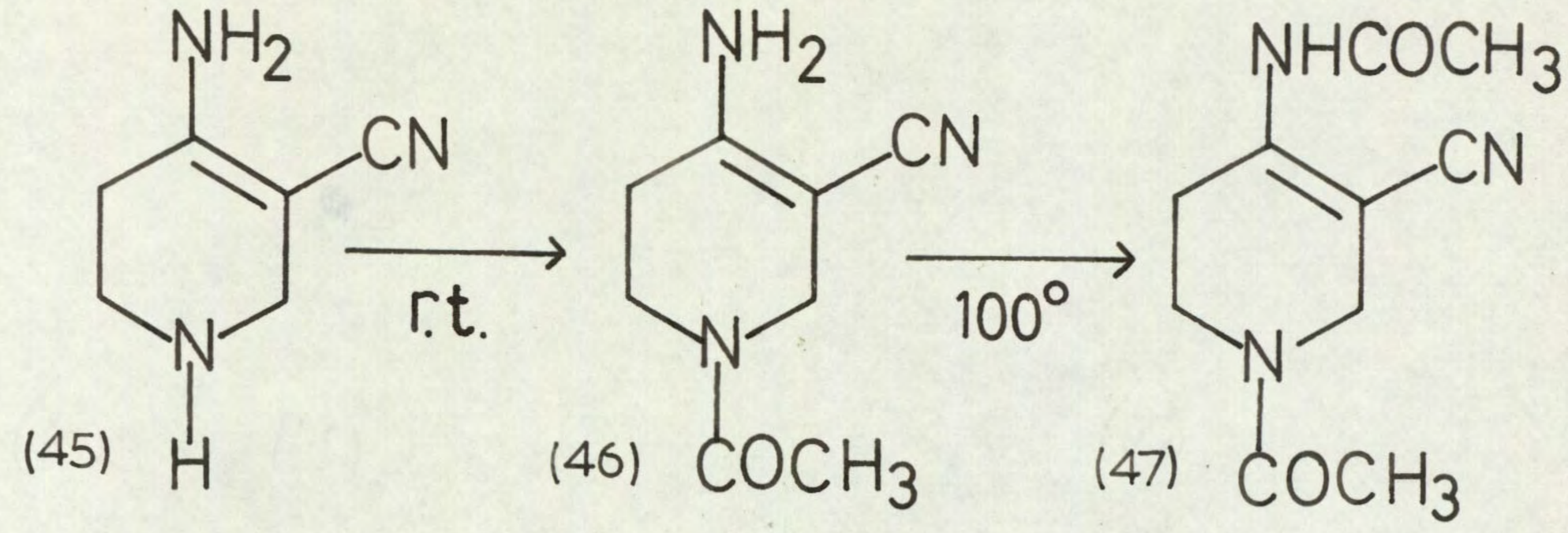
(41)

Acylation is to a great extent similar to alkylation. Amines give amides and enamines give C-acylated immonium

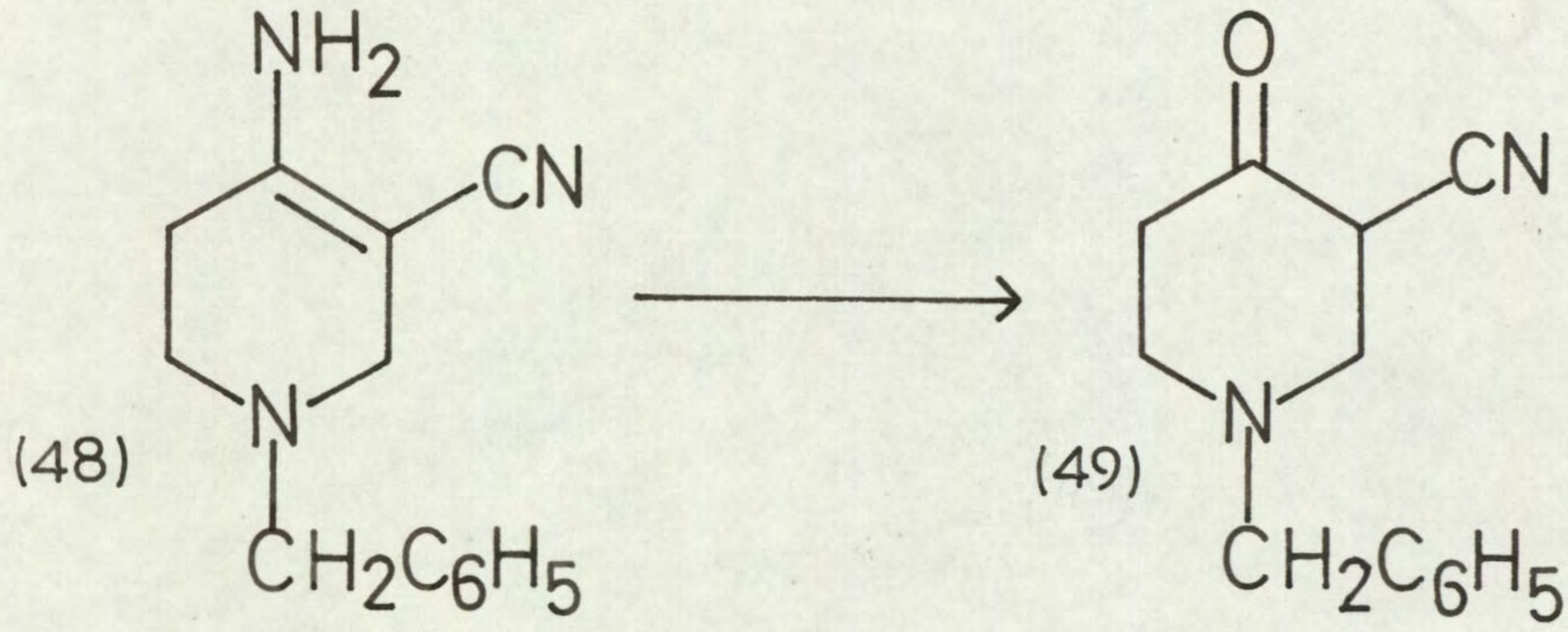


(42) (43) (44)

salts. Enaminonitriles behave differently. Cavalla (1962), for example, found that pyrrolidines of type (42) could not be acetylated, while Thompson (1955) found that compounds of type (43) reacted with acetic anhydride or benzoyl chloride in pyridine to give very low yields of the corresponding enamidonitrile (44). Taub et al. (1967) obtained the monoacetate (46) under mild conditions from the secondary enaminonitrile (45). Stronger conditions were needed, however, to effect the diacetylation of this compound, giving (47). An



attempt to form the amide of the N-benzyl homologue (48) was unsuccessful, acetic anhydride in pyridine giving black tars, while acetyl chloride in chloroform gave mixtures from which no solid products were

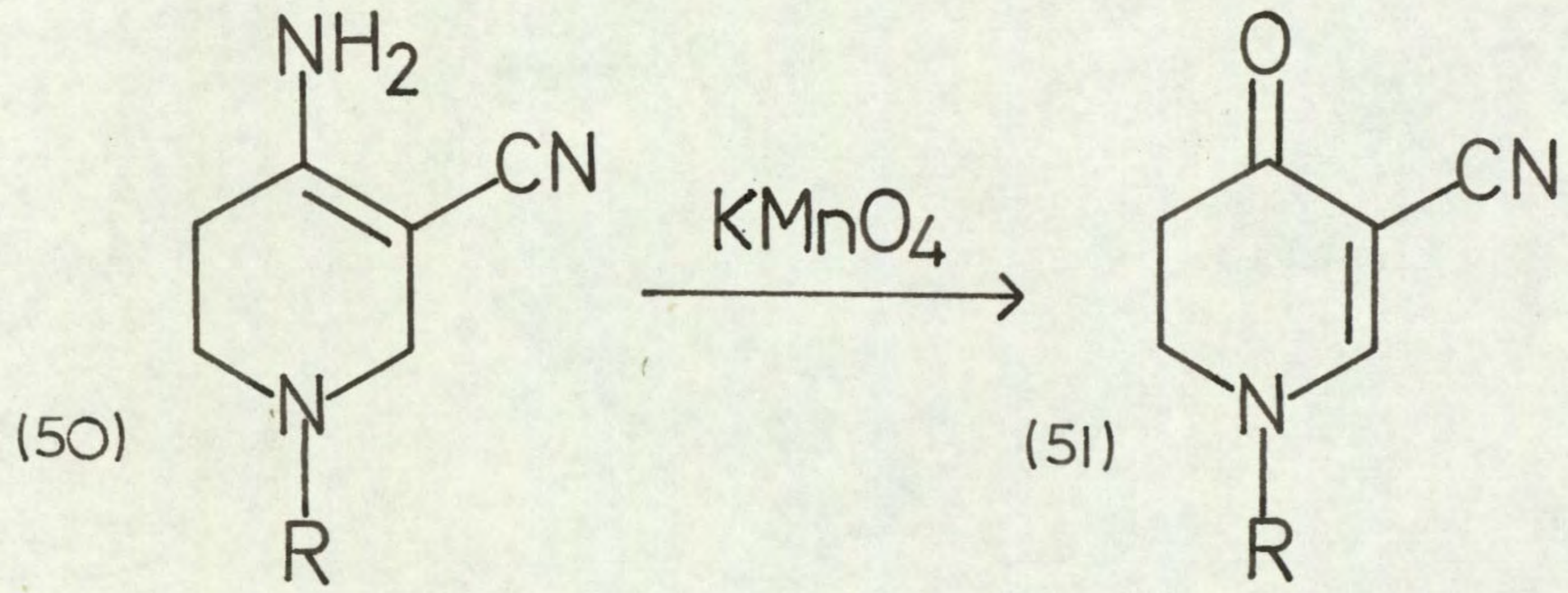


obtainable, but the infra-red spectrum suggested that the enamino-nitrile may have hydrolysed in part to the cyano-ketone (49) (Kloetzel and Pinkus, 1958).

The failure of the attempted Diels-Alder reactions may possibly be attributed to the delocalisation of the p-electrons of the nitrogen into the π-electron system of the double bond, with consequent deactivation of the double bond.

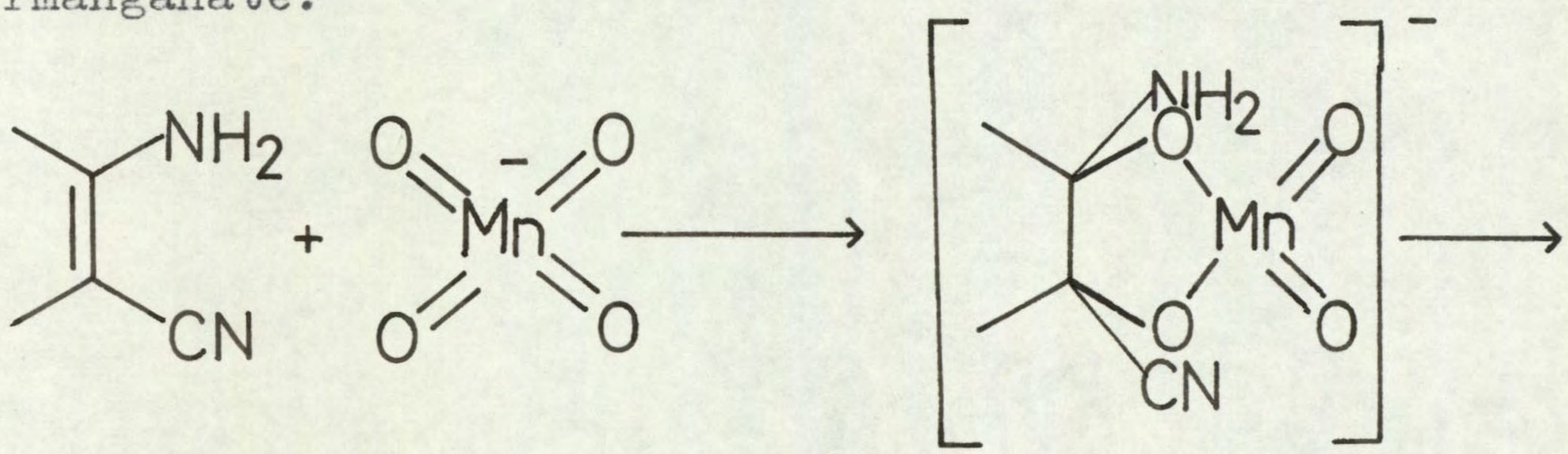
4 The preparation and properties of 5-cyano-1,2,3,4-tetrahydro-4-oxo-pyridines

During the course of the present work, enamines of the type (50) were reacted with potassium permanganate in acetone to give compounds with the suggested structure (51).



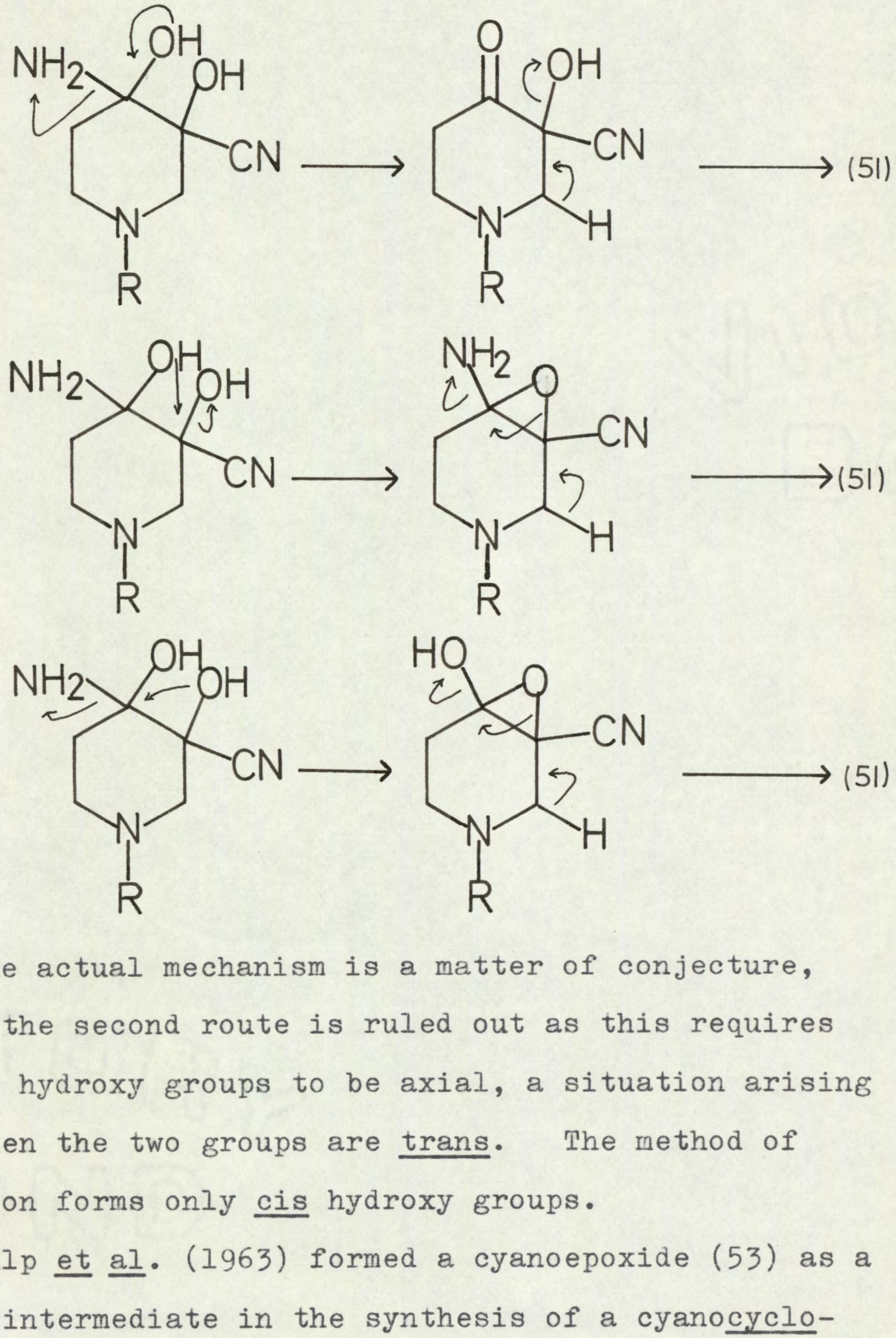
(50) (51)

The formation of 1-benzyl-5-cyano-1,2,3,4-tetrahydro-4-oxo-pyridine was thought to form by way of the diol (52), formed by reaction of the double bond with permanganate:



(52)

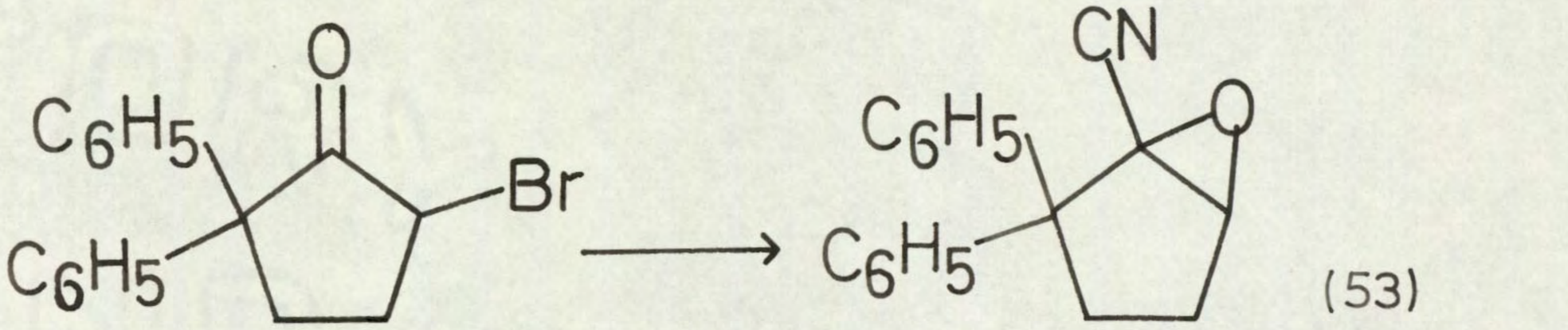
From the diol, three routes of elimination seemed possible:



The actual mechanism is a matter of conjecture, though the second route is ruled out as this requires the two hydroxy groups to be axial, a situation arising only when the two groups are <u>trans</u>. The method of oxidation forms only <u>cis</u> hydroxy groups.

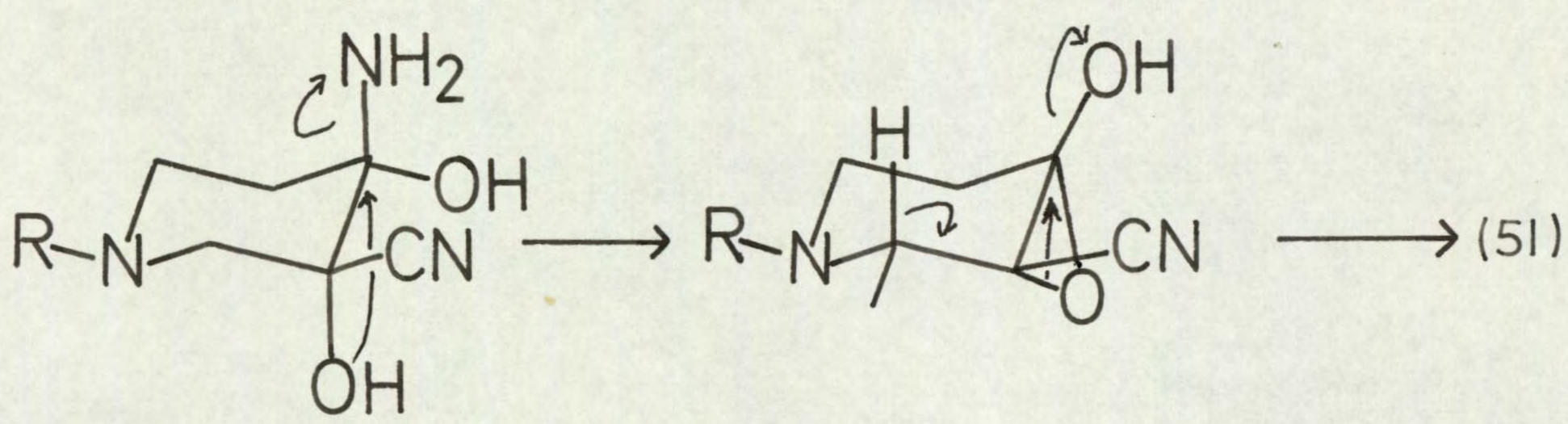
Kulp <u>et al</u>. (1963) formed a cyanoepoxide (53) as a stable intermediate in the synthesis of a cyano<u>cyclo</u>-

pentane. Thus the formation of an epoxide, as in

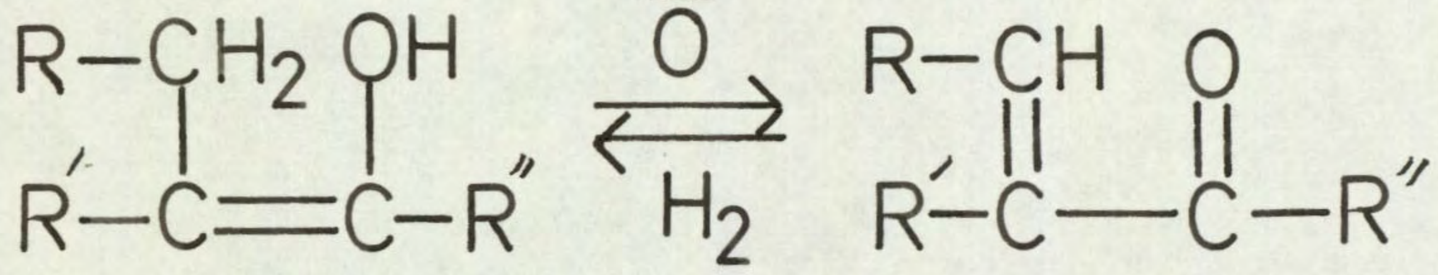


(53)

route 3, is feasible via a β-elimination and enables a second facile β-elimination to take place with subsequent formation of the α,β-unsaturated ketone.

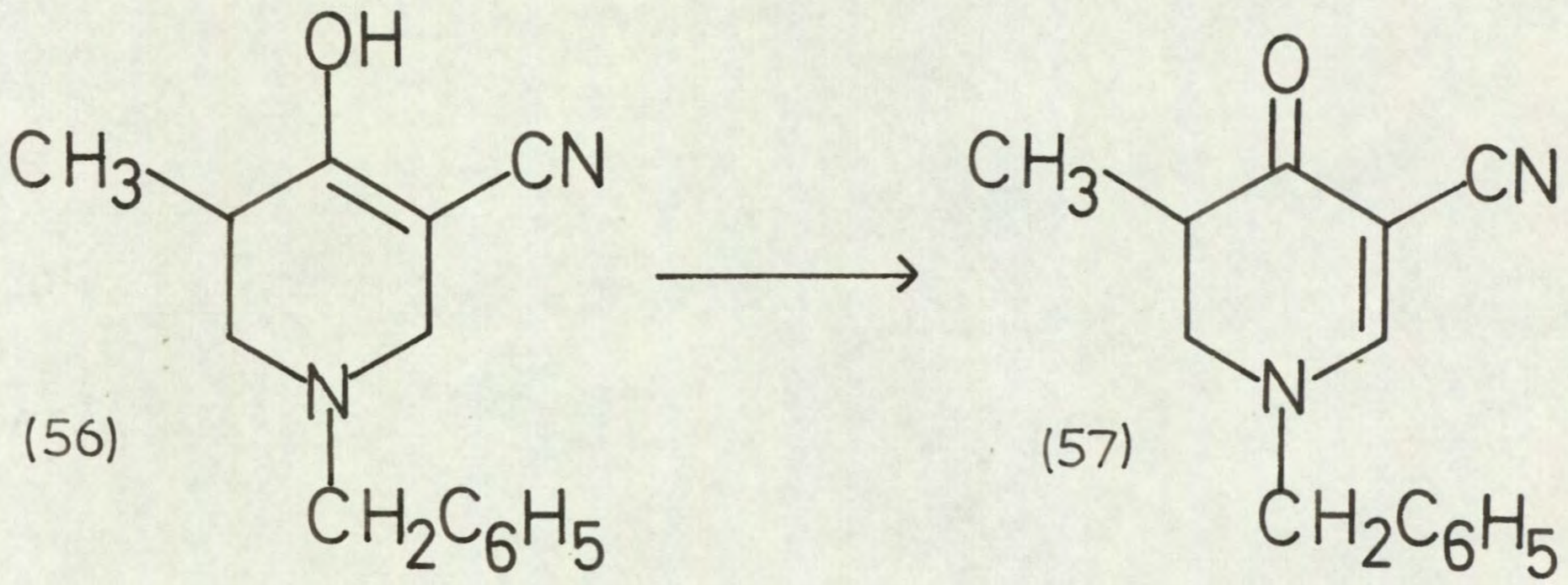


Fuson et al. (1944) found that reaction of the enol (54) with potassium permanganate in acetone gave the



corresponding α,β-unsaturated ketone (55). In view of this, the cyano-ketone (56), which is thought to

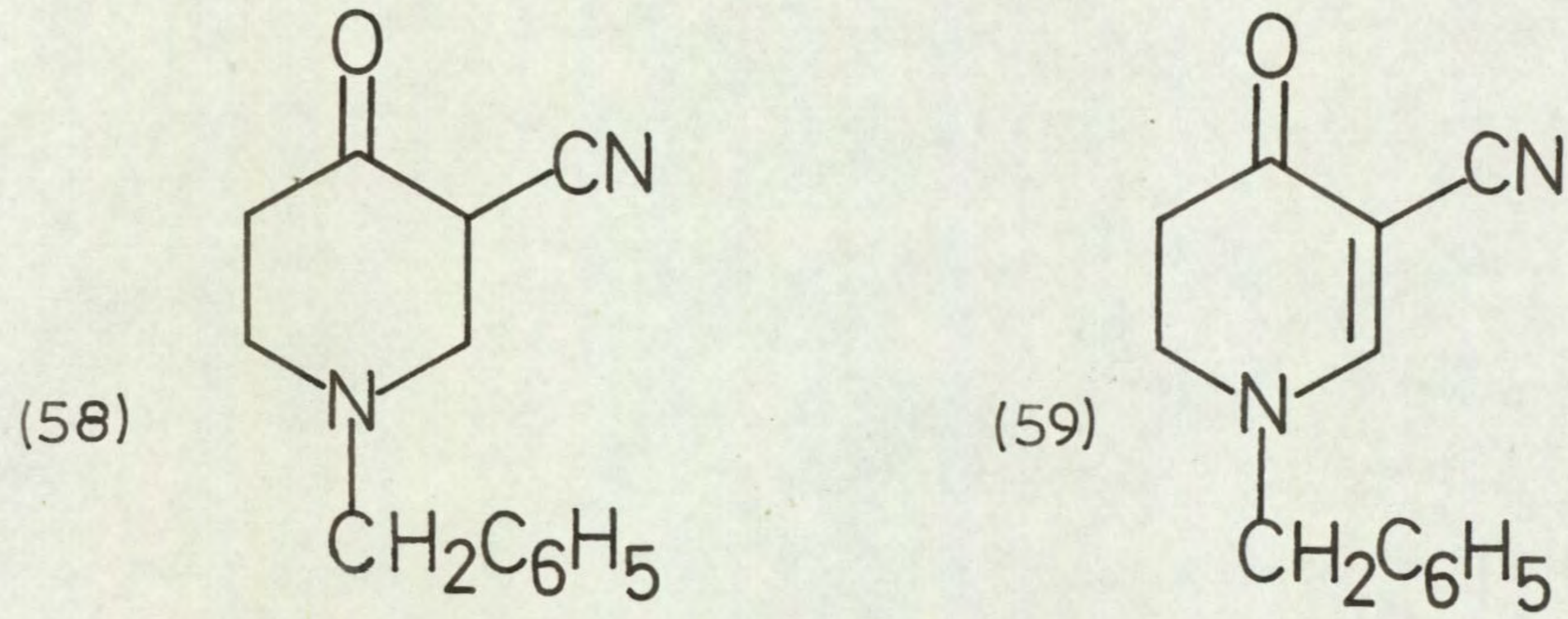
exist in the enol form, was reacted with potassium permanganate in neutral aqueous solution and gave the



(56) (57)

expected α,β-unsaturated ketone (57). Thus this reaction supported the view that the compound obtained had the suggested structure.

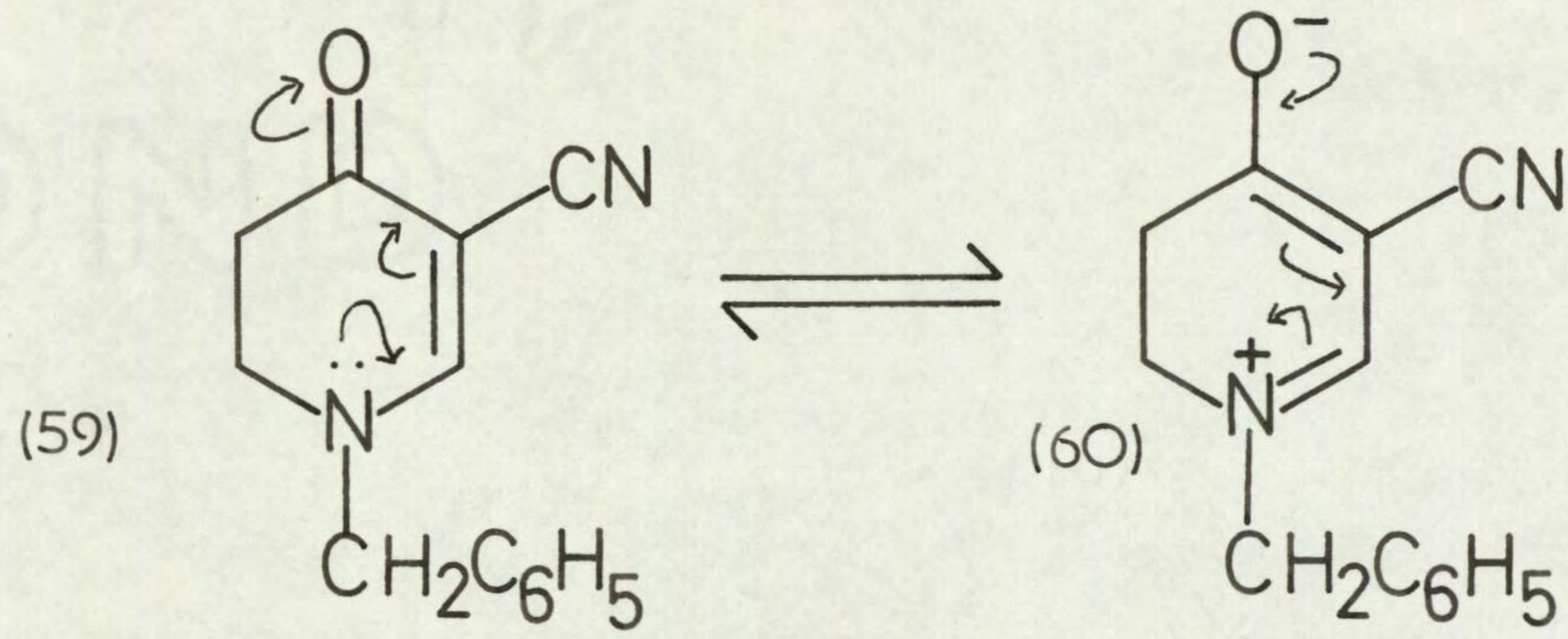
In contrast to the saturated cyano-ketone (58), 1-benzyl-5-cyano-1,2,3,4-tetrahydro-4-oxo-pyridine (59) did not titrate in non-aqueous solvents and did not form a salt. This was attributed to the double bond forming



(58) (59)

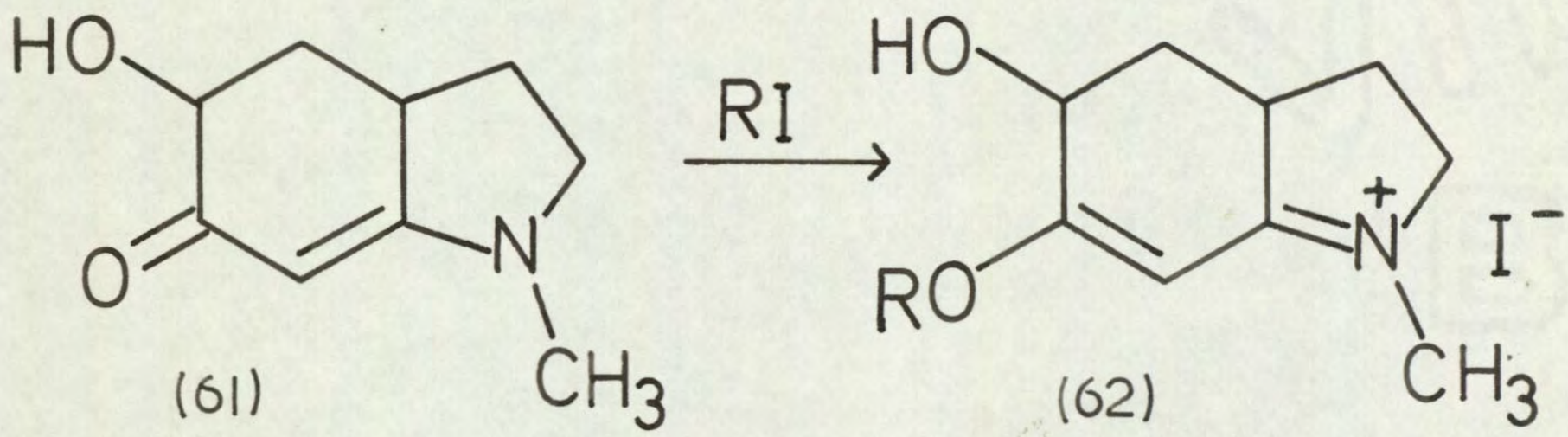
a conjugated system between the nitrogen and the carbonyl, with consequent delocalisation of the lone pair on the

nitrogen (59-60). An attempt to form a derivative with



(59) (60)

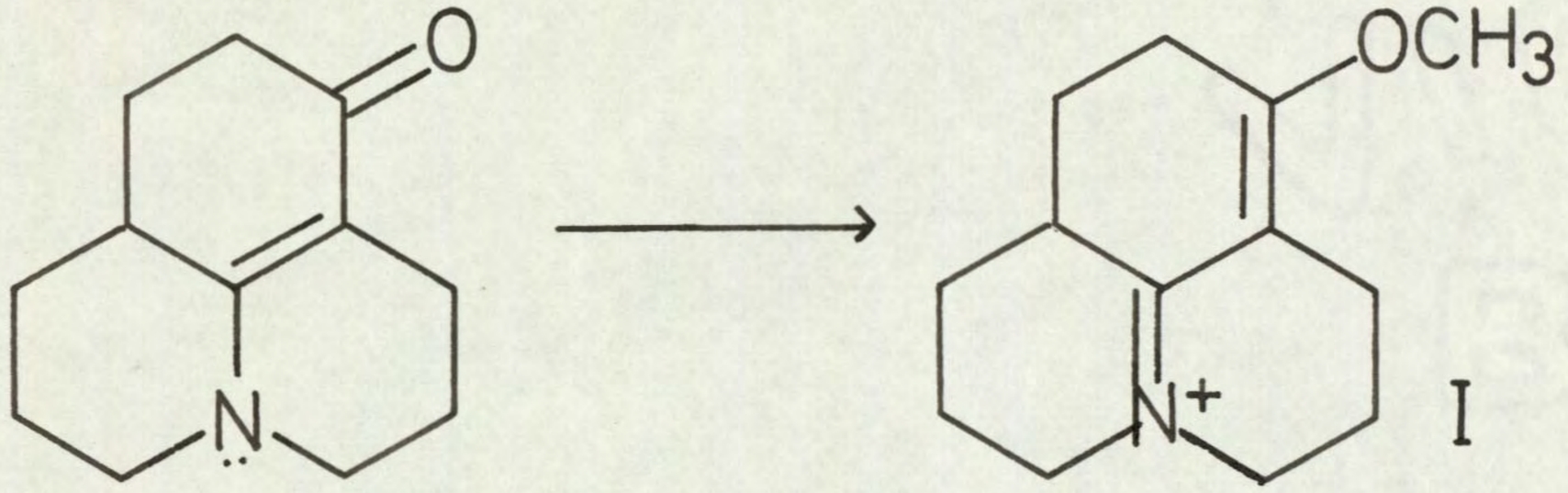
2,4-dinitrophenylhydrazine failed. Austin et al. (1951) found that compounds such as (61) did not react with reagents for the carbonyl group. They did, however, find that the compounds gave a colouration with ferric chloride solution and reacted with alkyl halides to give



(61) (62)

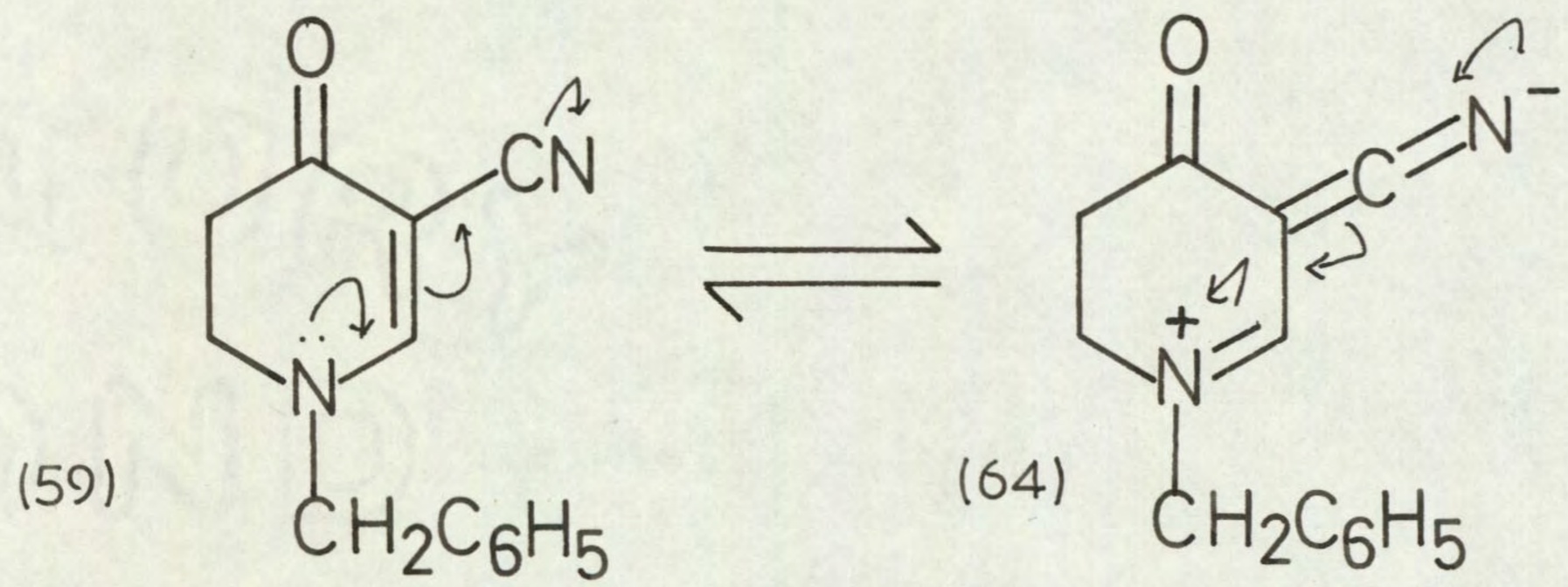
a halide salt, the structure of which was suggested to be (62). Valenta et al. (1964) also found that compounds such as (63) gave salts when refluxed with methyl iodide. Reaction of 1-benzyl-5-cyano-1,2,3,4-tetrahydro-4-oxo-pyridine with alkyl halides failed, unchanged starting material being recovered. Also, no colouration was detected with ferric chloride solution.

(63)



I

It was thought that the lack of reactivity of the compound, even compared with compounds with similar reactive groups, was due to the electronic charge being delocalised over two conjugate systems, encompassing either the carbonyl group (59-60), or the nitrile group

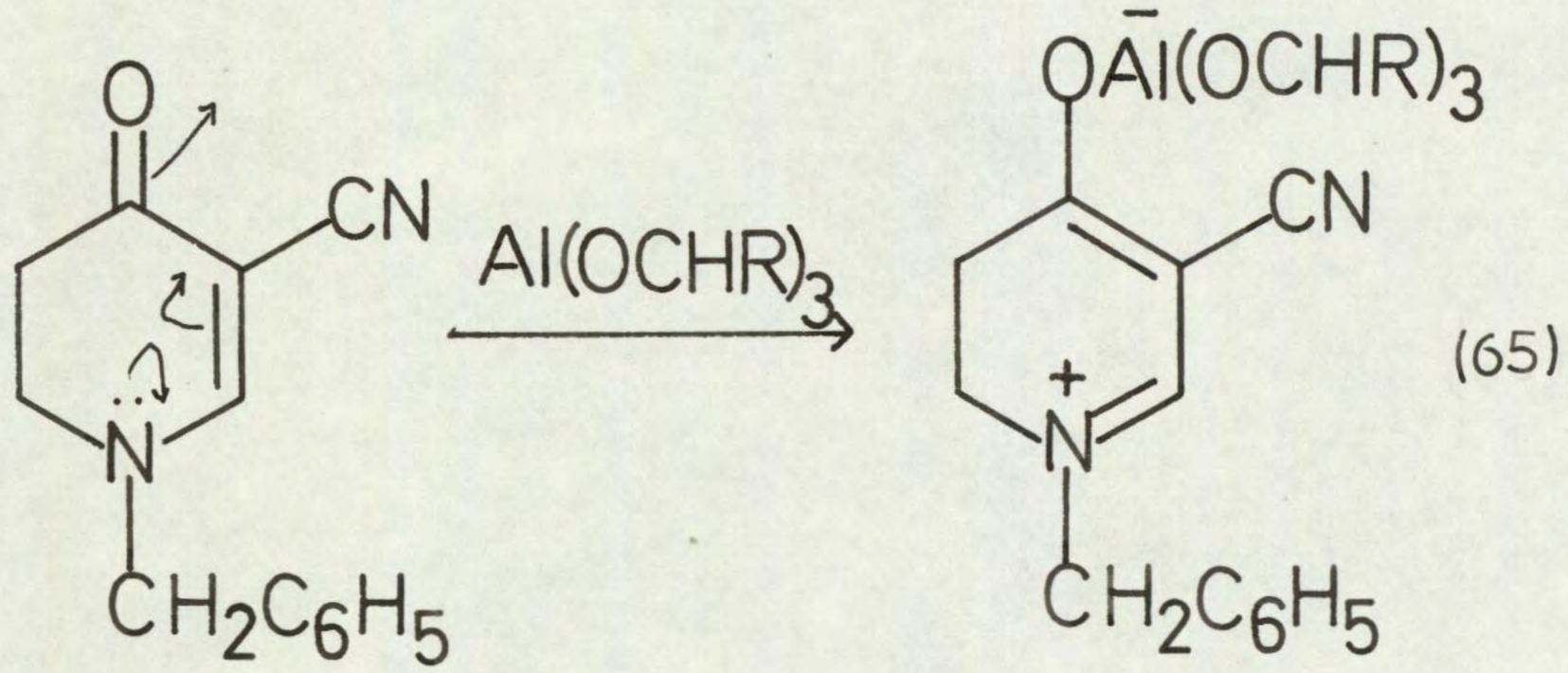


(59) (64)

(59-64), which resulted in a lowering of available charge. An attempt to cyclise, using amidines, which succeeded with 1-benzyl-3-cyano-4-piperidone (Ohnacker 1963) was not successful with the unsaturated cyano-ketone. This was also attributed to the delocalisation of the electronic charge reducing the electrophilic

characters of the carbonyl and nitrile groups.

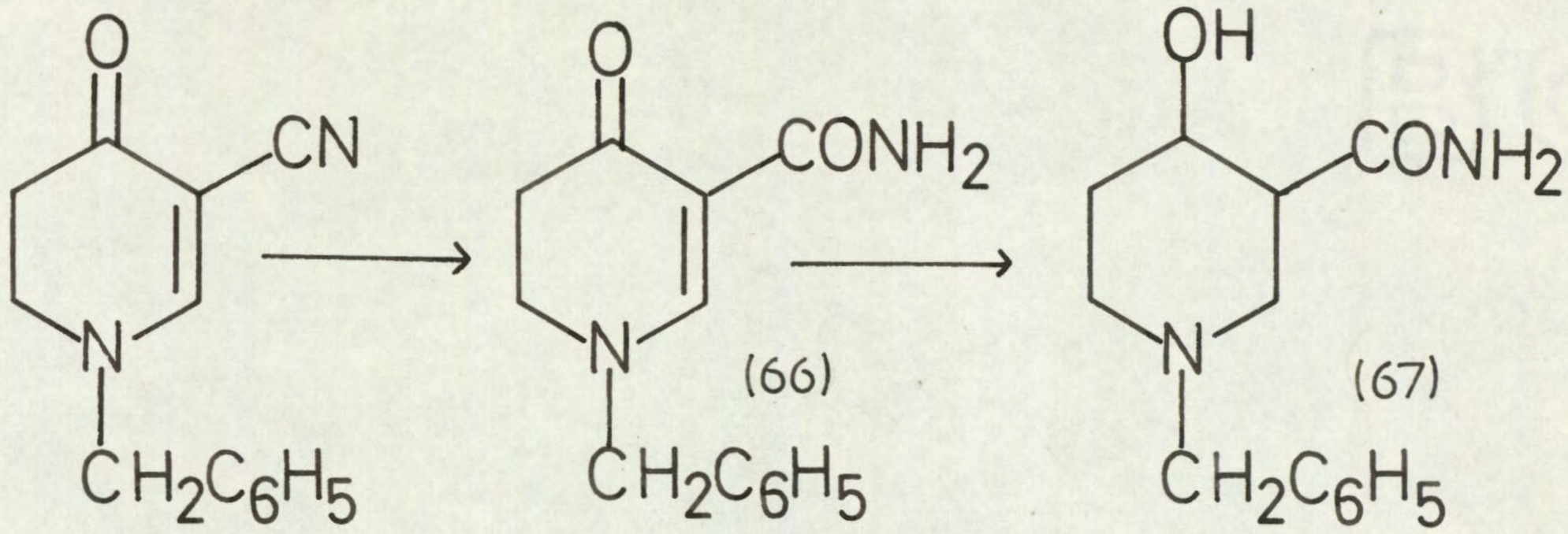
The compound was, however, attackable by some reducing agents, $LiAlH_4$ and $NaBH_4$ giving identical compounds to those obtained by the equivalent reduction of the saturated cyano-ketone. This provided an additional item of proof for the structure of the unsaturated cyano-ketone, though an attempt at obtaining the corresponding unsaturated alcohol via a Meerwein-Ponndorf-Verley reduction failed. The failure was attributed to the formation of an aluminium salt (65), with delocalisation preventing attack by the hydride anion.



(65)

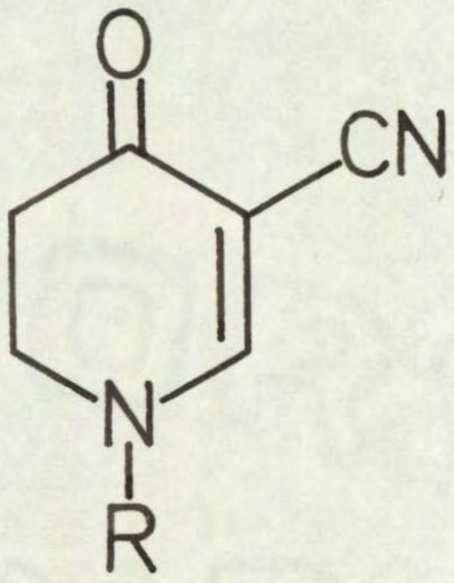
The unsaturated cyano-ketone reacted normally with hydrolysing agents to give the unsaturated amido-ketone (66), which was reducible to the saturated amido-alcohol (67).

Comparison with literature supported the assignment of the unsaturated cyano-ketone structure. Unsaturated



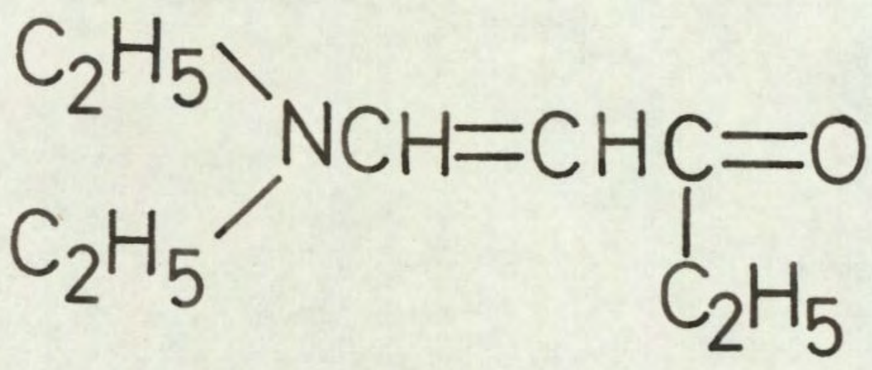
(66) (67)

amines (68, 69, 70) have the following infra-red spectra (Leonard and Adamick, 1959):



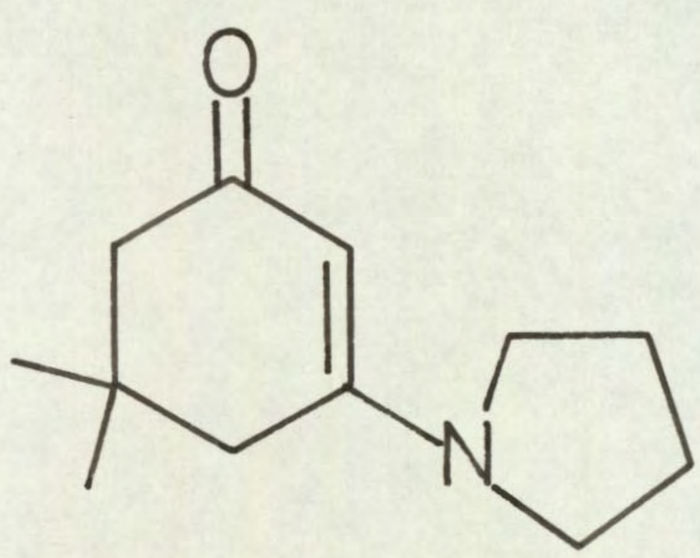
$\nu_{max.}$ = 1645 $cm.^{-1}$ 1620 $cm.^{-1}$ 1600 $cm.^{-1}$

(69)



1664 $cm.^{-1}$ 1616 $cm.^{-1}$ 1574 $cm.^{-1}$

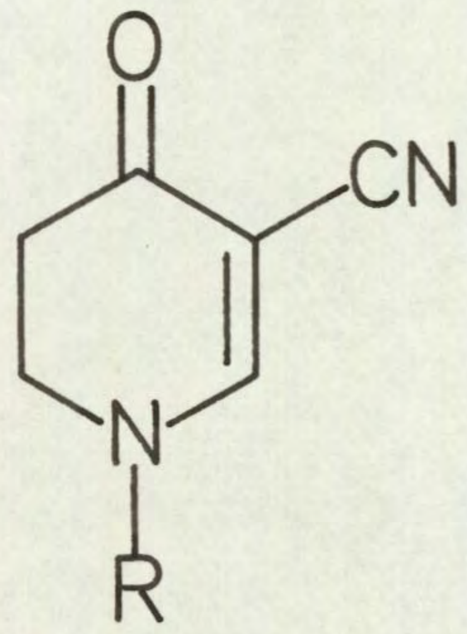
(70)



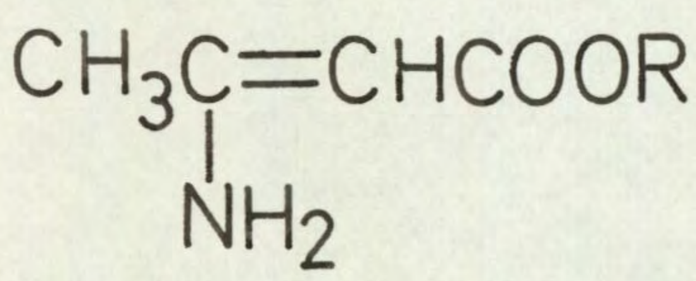
1607 $cm.^{-1}$ 1560 $cm.^{-1}$

The nitrile absorption, appearing at 2200 cm.$^{-1}$, is rather low for simple unsaturated nitriles (Bellamy), but is in keeping with the values obtained for a similar system - the enaminonitriles (see earlier work), whose nitrile absorptions appear in the region of 2190 cm.$^{-1}$.

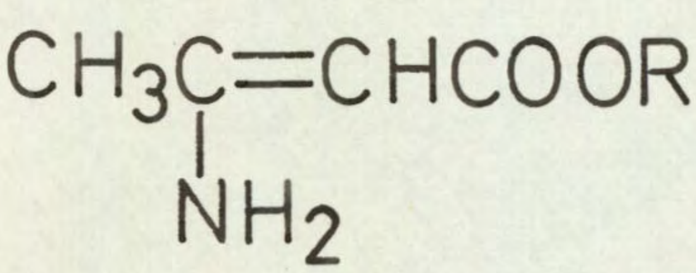
The ultra-violet spectra of some β-amino-α,β-unsaturated ~~ketones~~ esters exhibit a similar absorption to the compound obtained (Gliekman and Cope, 1945):



$\lambda_{max.}$ = 312·5 mμ (15800)
228·5 mμ (11900)



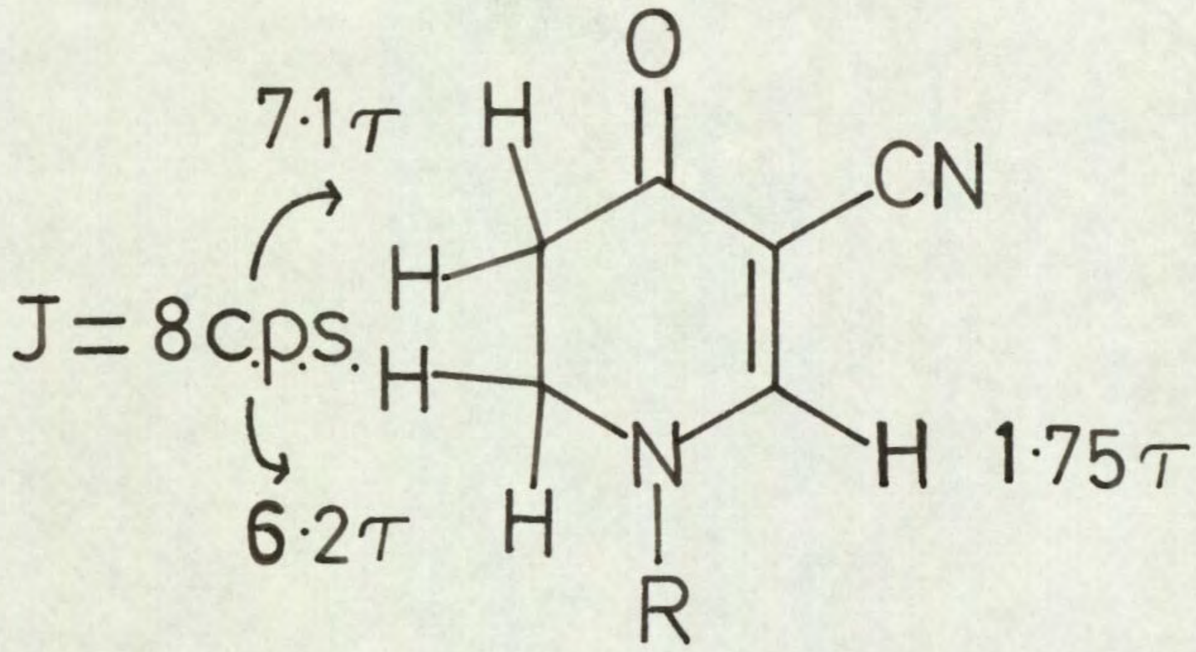
375 mμ (16220)



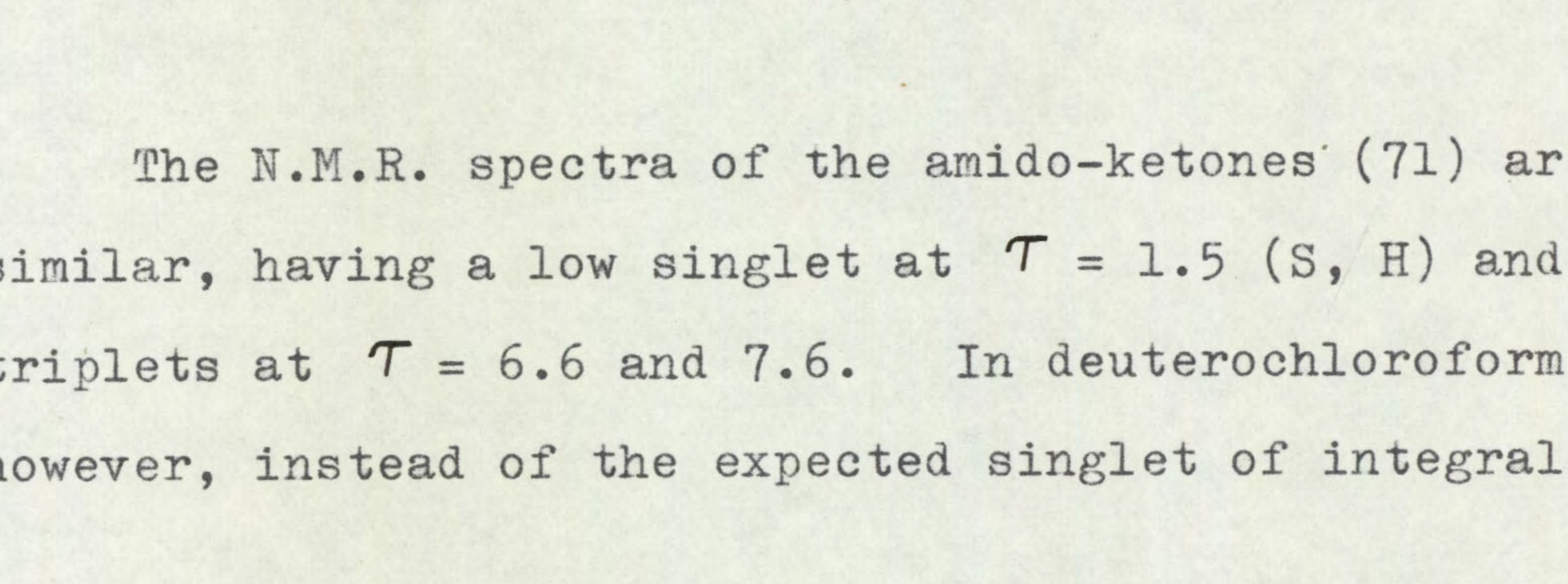
355 mμ (17780)

The lower absorption and extinction coefficient of the prepared compound compared with the literature compounds may be attributed to the crossed conjugate system.

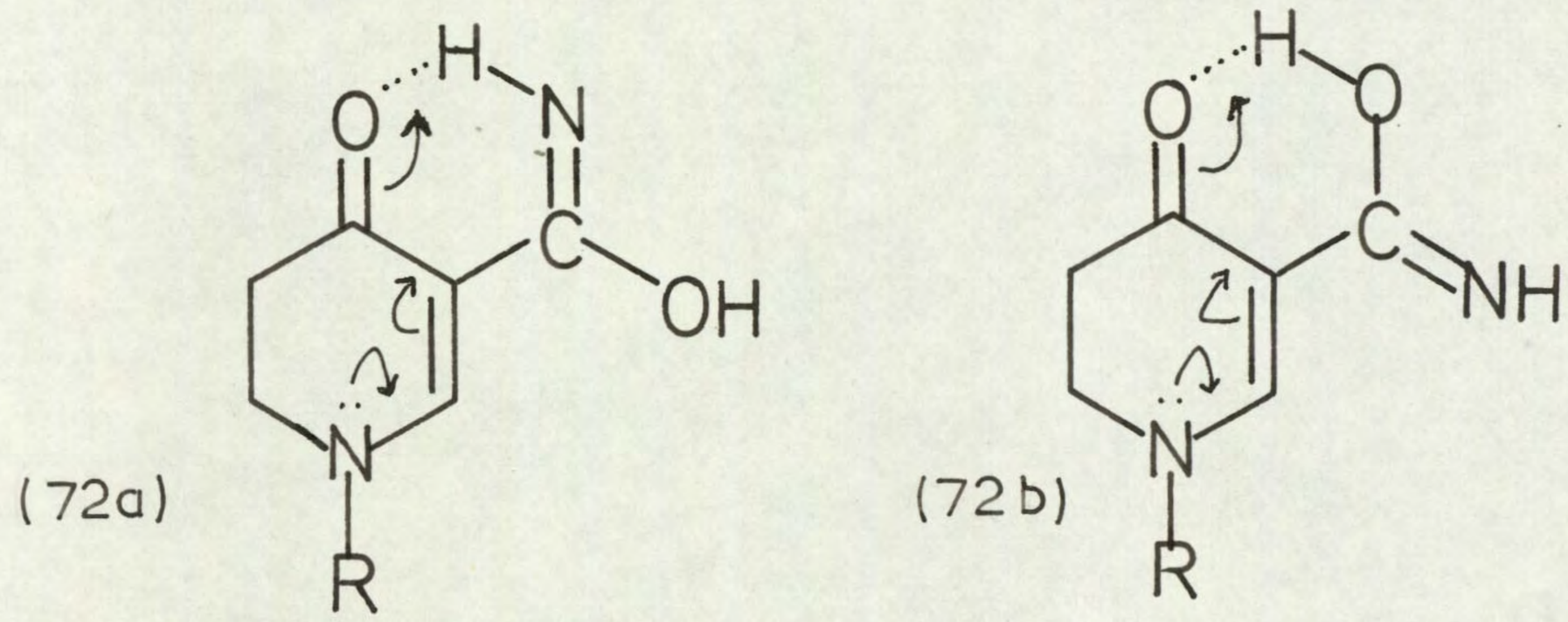
The N.M.R. spectra are consistant with the proposed structures, having the following peaks: τ = 1.75 (S, H), 6.2 (T, 2H, J=8 c.p.s.), 7.1 (T, 2H, J=8 c.p.s.). The large downfield shift of the C_6 proton was attributed to the diamagnetic deshielding of the conjugate double bond.



The N.M.R. spectra of the amido-ketones (71) are similar, having a low singlet at τ = 1.5 (S, H) and two triplets at τ = 6.6 and 7.6. In deuterochloroform, however, instead of the expected singlet of integral

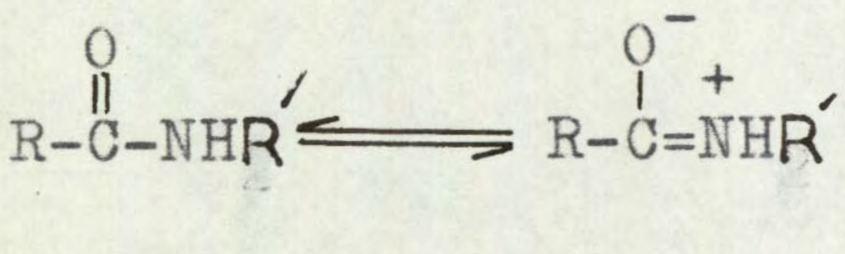


value 2 protons for the primary amide, two singlet peaks of integral value 1 proton each appear at τ = 1.5 and τ = 4.4. With trifluoroacetic acid as solvent, the two peaks disappear. These results can be explained if the amide is assumed to exist in the tautomeric enolimine form (72), which can be stabilised by hydrogen bonding between the conjugated ketone and either the imino (72a) or enolic (72b) hydrogen. That an amide can



canonical structures

exist in ~~a tautomeric form~~ is not unknown, since Carpenter and Donahue (1950) found a 50% equilibrium between the two ~~tautomers~~: structures:



$R = CH_3$

$R' = CH_2COOH$.

Section III

Experimental

EXPERIMENTAL

A. PREPARATION OF SOME 4-PIPERIDONES

ββ Benzyliminodipropionitrile

$$C_6H_5CH_2N(CH_2CH_2CN)_2$$

A number of attempts were made to prepare this compound, one of which was successful.

a) Benzylamine (290 g.) was added to acrylonitrile (320 g.), followed by the addition of acetic acid (60 g.) and the mixture refluxed for 4 hours. Distillation under reduced pressure gave ββ'-benzyliminodipropionitrile (490 g.) b.p. 173°/3 mm. (Frost and Martell (1950) quote b.p. 173-5°/3-4 mm.) Found: equiv., 216. Calc. for $C_{13}H_{15}N_3$, equiv., 213. $\nu_{max.}$ 2250 cm.$^{-1}$ (C≡N), 700 cm.$^{-1}$, 740 cm.$^{-1}$ (C_6H_5).

The picrate, recrystallised from ethanol, had m.p. 88°.

Analysis Found: C, 51.7; H, 4.1; N, 18.9%; equiv., 430. $C_{19}H_{18}N_6O_7$ requires C, 51.6; H, 4.1; N, 19.0%; equiv., 442.

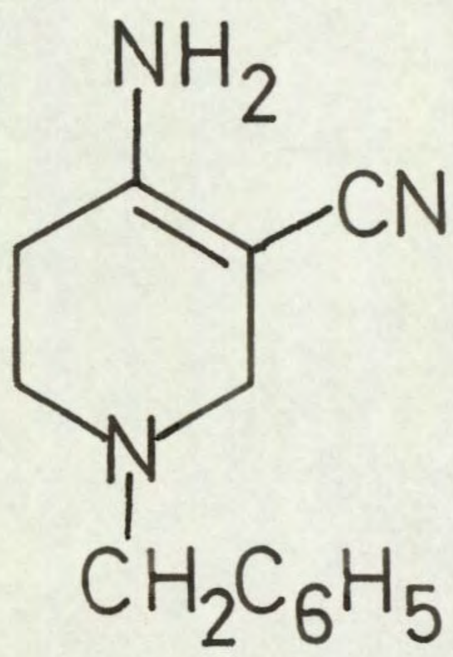
b) Benzylamine (20 g.) was added dropwise to acryl-

onitrile (30 g.), the mixture heated on a steam bath for 3 hours and allowed to stand for 48 hours. Distillation under reduced pressure gave acrylonitrile, (19 g.) b.p. 36°/150 mm. and a second fraction, b.p. 236-240°/135 mm. (28 g.) which was considered to be β-benzylaminopropionitrile. $\nu_{max.}$ 3300 cm.$^{-1}$ (NH). Found: equiv., 163, calc. for $C_{10}H_{12}N_2$, 160.

c) β-Benzylaminopropionitrile (28 g.) was refluxed with acrylonitrile (28 g.) for 48 hours. Distillation under reduced pressure gave β-benzylaminopropionitrile (26 g.), b.p. 142°/10 mm.

d) Benzylamine (10 g.) and acrylonitrile (15 g.) were heated to 80° in a sealed tube for 20 hours. Distillation under reduced pressure gave β-benzylaminopropionitrile, b.p. 142°/10 mm. The experiment was repeated with the addition of $CuSO_4$ (1 g.) to the reaction mixture. Distillation under reduced pressure gave β-benzylaminopropionitrile, b.p. 142°/10 mm.

4-Amino-1-benzyl-3-cyano-1,2,5,6-tetrahydropyridine



$\beta\beta'$-Benzyliminodipropionitrile (90 g.) was added dropwise to a refluxing suspension of sodium (2 g.) in toluene (500 ml.). The mixture was refluxed for a further 10 minutes, decanted from remaining sodium and allowed to stand. On cooling, crystals were obtained, which recrystallised from methanol to give 4-amino-1-benzyl-3-cyano-1,2,5,6-tetrahydro-pyridine (75 g.), m.p. 154°, as white plates (Taylor and Vromen quote m.p. 154°.).

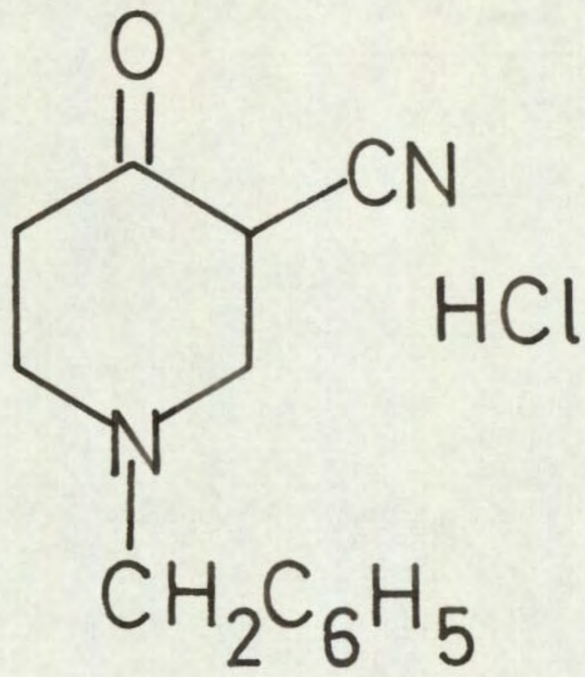
Infra-red: $\nu_{max.}$ (Nujol), 3200 cm.$^{-1}$, 3300 cm.$^{-1}$, 3450 cm.$^{-1}$ (NH_2), 2190 cm.$^{-1}$ (C≡N), 1640 cm.$^{-1}$ (C=C), 1620 cm.$^{-1}$ (C-N).

Ultra-violet: $\lambda_{max.}$ (EtOH), 264 mμ (11300); $\lambda_{max.}$ (HCl), 233 mμ (2480) and 215 mμ (5200).

N.M.R.: τ ($CDCl_3$), 2.6 (S, 5H, $C_6\underline{H}_5$); 5.6 (S, 2H, $N\underline{H}_2$), 6.37 (S, 2H, $C_6H_5C\underline{H}_2$), 6.9 (S, 2H, $NC\underline{H}_2C=$), 7.45 (T, 2H, $NC\underline{H}_2CH_2$), 7.72 (T, 2H, $NCH_2C\underline{H}_2$).

Analysis Found: C, 72.7; H, 7.4; N, 19.6%; equiv., 211. Calc. for $C_{13}H_{15}N_3$: C, 73.3; H, 7.1; N, 19.7%; equiv., 213.

1-Benzyl-3-cyano-4-piperidone hydrochloride



4-Amino-1-benzyl-3-cyano-1,2,5,6-tetrahydropyridine (20 g.) was dissolved in conc. HCl (50 ml.). On warming the solution, a white solid separated (28.5 g.), crystallised from methanol/ether to give 1-benzyl-3-cyano-4-piperidone hydrochloride, m.p. 199°.

Infra-red: $\nu_{max.}$ (Nujol), 1650 cm.$^{-1}$ (C=O), 2200 cm.$^{-1}$ (C≡N), 2500 cm.$^{-1}$ - 2700 cm.$^{-1}$ ($\overset{+}{N}H$).

Analysis Found: C, 60.2; H, 6.3; N, 11.2%; equiv., 260. $C_{13}H_{15}ClN_2O$ requires: C, 62.4; H, 6.0; N, 11.2%; equiv., 251.

ββ-Iminodipropionitrile

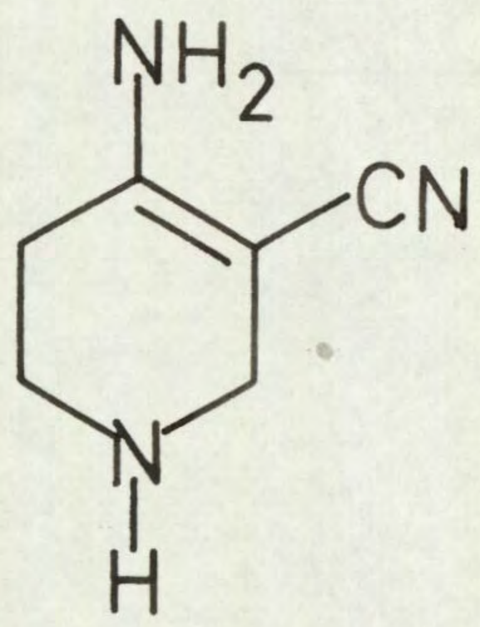
$HN(CH_2CH_2CN)_2$

Acrylonitrile (424 g.) was added to aqueous ammonia (200 ml. of a 35% aqueous solution) at such a rate that two layers did not appear, the temperature being kept below 30°. Distillation under reduced pressure gave ββ′-iminodipropionitrile (276 g.), b.p. 190°/6 mm. (Whitmore et. al. quote b.p. 140-160°/2-5 mm.). $\nu_{max.}$ 3350 cm.$^{-1}$ (NH), 2250 cm.$^{-1}$ (C≡N). Found: equiv., 125. Calc. for $C_6H_9N_3$, 123.

The benzoyl derivative, recrystallised from ethanol/benzene, had m.p. 112° (Whitmore et. al. quote m.p. 112°).

Analysis Found: C, 68.7; H, 6.0; N, 18.7%.
Calc. for $C_{13}H_{13}N_3O$: C, 68.7; H, 5.9; N, 18.5%.

4-Amino-3-cyano-1,2,5,6-tetrahydropyridine



a) ββ′-Iminodipropionitrile (50 g.) was added dropwise to a suspension of sodium (2 g.) in dioxan (400 ml.) and naphthalene (25 g.). The air was displaced with

nitrogen and the mixture stirred on a steam bath for several hours. A small amount of a solid was obtained. The solution was poured into hot benzene (1 litre) and allowed to stand. A small amount of solid was obtained on cooling, crystallised from ethanol to give 4-amino-3-cyano-1,2,5,6-tetrahydro-pyridine (2 g.), m.p. 192°. (Taub et. al. quote m.p. 193°.) $\nu_{max.}$ (Nujol), 3200 cm.$^{-1}$, 3300 cm.$^{-1}$ (NH_2), 2198 cm.$^{-1}$ (C≡N).

Analysis Found: C, 58.4; H, 7.2; N, 34.3%; equiv., 124. Calc. for $C_6H_9N_3$: C, 58.5; H, 7.3; N, 34.2%; equiv., 123.

b) ββ′-Iminodipropionitrile (100 g.) was added dropwise to a refluxing suspension of sodium (4 g.) in toluene (500 ml.). The solution was refluxed for 30 minutes and allowed to stand. The solid obtained was crystallised from ethanol to give 4-amino-3-cyano-1,2,5,6-tetrahydro-pyridine (5 g.), m.p. 192°, undepressed on admixture with authentic sample.

An alternative method of preparing 4-amino-3-cyano-1,2,5,6-tetrahydro-pyridine

4-Amino-1-benzyl-3-cyano-1,2,5,6-tetrahydro-pyridine (1 g.) in ethanol (100 ml.) was shaken with hydrogen at atmospheric pressure in the presence of 5% palladised charcoal (1 g.). After the absorption of a

mole of hydrogen, the mixture was filtered, the filtrate evaporated to dryness and the residue crystallised from ethanol to give 4-amino-3-cyano-1,2,5,6-tetrahydropyridine (.5 g.), m.p. 192°, undepressed with an authentic sample.

<u>ββ′-Methyliminodipropionitrile</u>

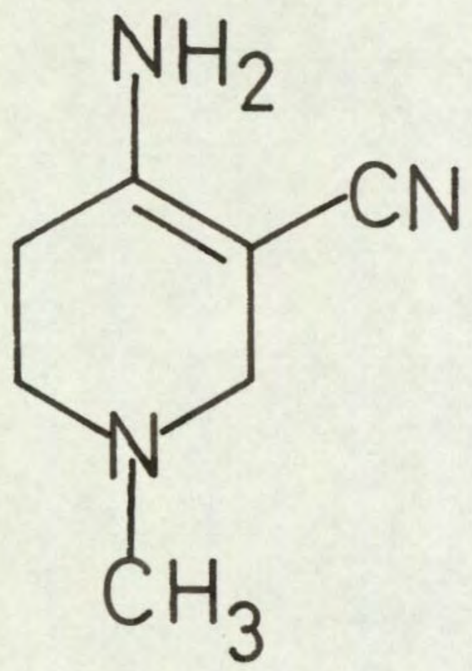
$$CH_3N(CH_2CH_2CN)_2$$

Acrylonitrile (250 g.) was added dropwise to 33% aqueous methylamine (238 ml.). Acetic acid (30 g.) was added and the mixture refluxed for 3 hours. Distillation under reduced pressure gave ββ′-methyliminodipropionitrile (280 g.), b.p. 195-198°/20 mm. (Cook and Reed quote b.p. 195-198°/20 mm.). Found: equiv., 137. Calc. for $C_7H_{11}N_3$, 137. $\nu_{max.}$ 2250 cm.$^{-1}$ (C≡N).

The picrate, from ethanol, m.p. 172° (Cook and Reed quote m.p. 172°).

<u>Analysis</u> Found: C, 42.7; H, 3.9; N, 23.0%; equiv., 260. Calc. for $C_{13}H_{14}N_6O_7$: C, 42.6; H, 3.8; N, 23.0%; equiv., 266.

4-Amino-3-cyano-1,2,5,6-tetrahydro-1-methyl-pyridine



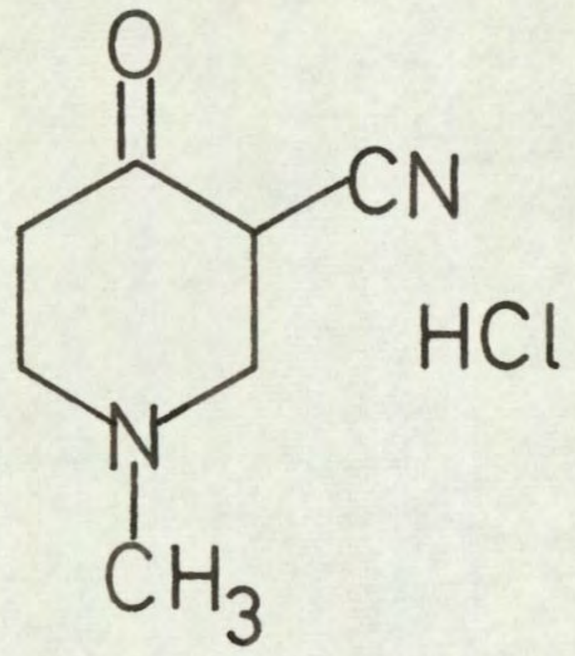
ββ́-Methyliminodipropionitrile (50 g.) was added dropwise to a refluxing suspension of sodium (1 g.) in toluene (250 ml.). The mixture was refluxed for 10 minutes, decanted from the remaining sodium and allowed to stand. On cooling, crystals were obtained which recrystallised from acetone to give 4-amino-3-cyano-1,2,5,6-tetrahydro-1-methyl-pyridine (42 g.), m.p. 124° (Cook and Reed quote m.p. 122-123°).

Infra-red: $\nu_{max.}$ (Nujol) 3150 cm.$^{-1}$, 3350 cm.$^{-1}$ (NH_2), 2180 cm.$^{-1}$ (C≡N), 1660 cm.$^{-1}$ (C=C), 1610 cm.$^{-1}$ (C-N).

N.M.R.: τ($CDCl_3$), 5.2 (S, 2H, $N\underline{H}_2$), 7 (S, 2H, $NC\underline{H}_2C$=), 7.4-7.7 (M, 7H, $NC\underline{H}_2C\underline{H}_2$ and $C\underline{H}_3$).

Analysis Found: C, 61.8; H, 8.7; N, 29.8%; equiv., 129. Calc. for $C_7H_{11}N_3$: C, 61.4; H, 8.0; N, 30.6%; equiv., 137.

3-Cyano-1-methyl-4-piperidone hydrochloride



4-Amino-3-cyano-1,2,5,6-tetrahydro-1-methyl-pyridine (20 g.) was added to 25% HCl (35 ml.) and warmed to complete solution. Evaporation of the solvent in vacuo, extraction of the residue with ethanol and partial evaporation of the solvent gave a white solid (25 g.) on allowing to stand, which crystallised from ethanol/ether to give 3-cyano-1-methyl-4-piperidone hydrochloride (20 g.), m.p. 167°. (Cook and Reed quote m.p. 167°.). $\nu_{max.}$ (Nujol), 2400 cm.$^{-1}$ - 2700 cm.$^{-1}$ ($\overset{+}{N}H$), 1645 cm.$^{-1}$ (C=O). Found: equiv., 171. Calc. for $C_7H_{11}ClN_2O$: equiv., 175.

ββ´-Ethyliminodipropionitrile

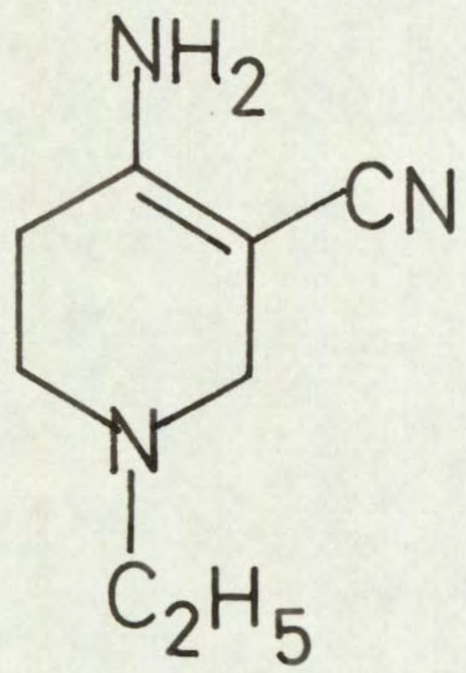
$$C_2H_5N(CH_2CH_2CN)_2$$

Acrylonitrile (800 ml.) was added dropwise to a 70% aqueous solution of ethylamine (500 ml.) and the mixture refluxed for 14 hours. Distillation under reduced pressure gave $\beta\beta'$-ethyliminodipropionitrile (265 g.), b.p. 140°/1 mm. (Cologne et al. quote b.p. 136-139°/.9 mm.) $\nu_{max.}$ 2250 cm.$^{-1}$ (C≡N).

The hydrochloride, recrystallised from ethanol/ether as white plates, had m.p. 161°.

Analysis Found: C, 51.4; H, 7.5; N, 22.2%; equiv., 190. Calc. for $C_8H_{14}ClN_3$: C, 51.2; H, 7.5; N, 22.4%; equiv., 188.

4-Amino-3-cyano-1-ethyl-1,2,5,6-tetrahydro-pyridine



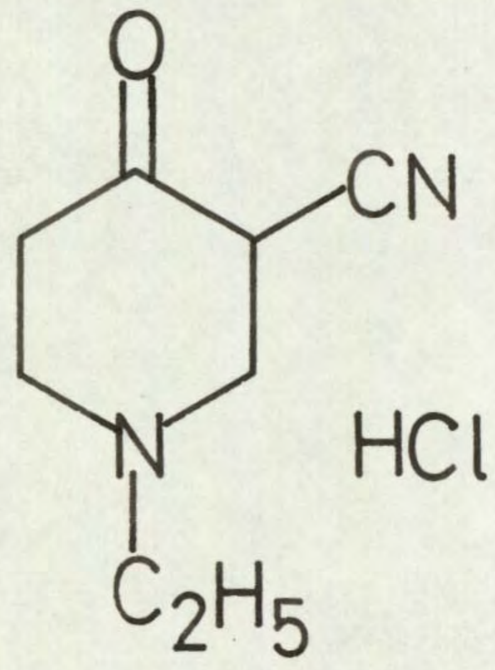
$\beta\beta'$-Ethyliminodipropionitrile (265 g.) was added dropwise to a stirred refluxing suspension of sodium (4 g.) in toluene (500 ml.). The mixture was refluxed for a further 30 minutes, decanted and allowed to stand. On cooling, a yellow solid was obtained, which

crystallised from benzene to give 4-amino-3-cyano-1-ethyl-1,2,5,6-tetrahydropyridine (80 g.) as colourless prisms, m.p. 98°. (Cologne et al. quote m.p. 98°.)

Infra-red: $\nu_{max.}$ (Nujol) 3180 cm.$^{-1}$, 3320 cm.$^{-1}$, 3370 cm.$^{-1}$ (NH_2), 2210 cm.$^{-1}$ (C≡N), 1660 cm.$^{-1}$ (C=C), 1620 cm.$^{-1}$ (C-N).

Analysis Found: C, 63.5; H, 8.5; N, 27.8%; equiv., 150. Calc. for $C_8H_{11}N_3$: C, 63.6; H, 8.6; N, 27.8%; equiv., 151.

3-Cyano-1-ethyl-4-piperidone hydrochloride



4-Amino-3-cyano-1-ethyl-1,2,5,6-tetrahydropyridine (40 g.) was dissolved in conc. HCl (100 ml.). The solution was warmed and allowed to stand. On cooling, a white solid was obtained, which crystallised from ethanol/ether to give 3-cyano-1-ethyl-4-piperidone hydrochloride, m.p. 195° (decomp.).

Infra-red: $\nu_{max.}$ (Nujol), 2470 cm.$^{-1}$ - 2850 cm.$^{-1}$

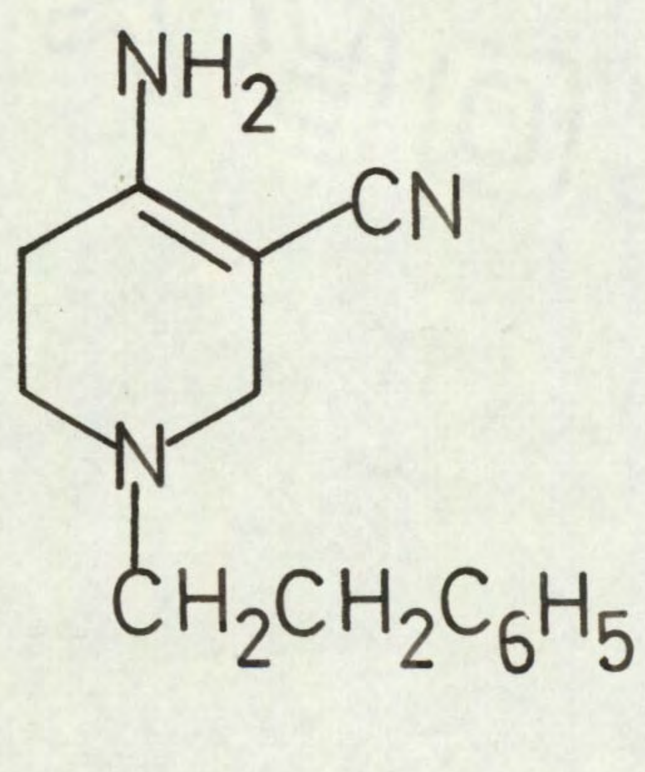
($\overset{+}{N}H$), 2250 cm.$^{-1}$ (C≡N), 1650 cm.$^{-1}$ (C=O). Found: equiv., 193. $C_8H_{13}ClN_2O$ requires 189.

<u>ββ′-Phenethyliminodipropionitrile</u>

$$C_6H_5CH_2CH_2N(CH_2CH_2CN)_2$$

Acrylonitrile (150 g.) was refluxed with phenethylamine (130 g.) and acetic acid (30 g.) for 4 hours. Distillation under reduced pressure gave ββ′-phenethyliminodipropionitrile (200 g.), b.p. 228°/2.4 mm. $\nu_{max.}$ 2250 cm.$^{-1}$ (C≡N). Found: equiv., 220. Calc. for $C_{14}H_{17}N_3$, 227.

<u>4-Amino-3-cyano-1,2,5,6-tetrahydro-1-phenethylpyridine</u>



Two methods were used to prepare this compound.

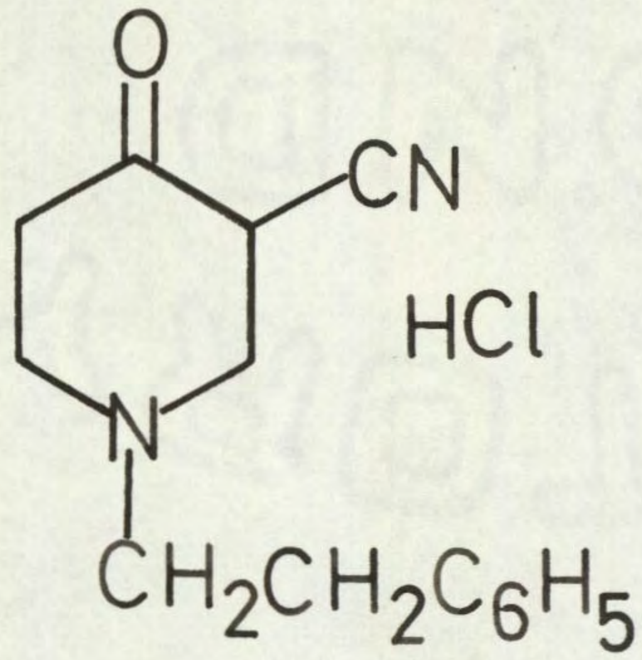
a) ββ́-Phenethyliminodipropionitrile (18 g.) was added dropwise to a stirred refluxing suspension of sodium (.2 g.) in toluene (60 ml.). The mixture was refluxed for 20 minutes, decanted and allowed to stand. On cooling, crystals were obtained which recrystallised from ethanol to give 4-amino-3-cyano-1,2,5,6-tetrahydro-1-phenethyl-pyridine (3.4 g.), m.p. 142°, as white plates. (Ohnacker quotes m.p. 142°.)

Infra-red: $\nu_{max.}$ (Nujol), 3250 cm.$^{-1}$, 3350 cm.$^{-1}$, 3450 cm.$^{-1}$ (NH_2), 2190 cm.$^{-1}$ (C≡N), 1650 cm.$^{-1}$ (C=C), 1615 cm.$^{-1}$ (C-N), 700 cm.$^{-1}$, 760 cm.$^{-1}$ (C_6H_5).

Analysis Found: C, 73.9; H, 7.5; N, 18.7%; equiv., 225. Calc. for $C_{14}H_{17}N_3$: C, 74.0; H, 7.5; N, 18.5%; equiv., 227.

b) 4-Amino-3-cyano-1,2,5,6-tetrahydro-pyridine (2 g.) was refluxed in acetone/chloroform (200 ml.) with phenethyl bromide (3 g.), sodium bicarbonate (20 g.) and a crystal of KI for 24 hours. The mixture was filtered, the filtrate evaporated and the residue crystallised from ethanol to give 4-amino-3-cyano-1,2,5,6-tetrahydro-1-phenethyl-pyridine (1.45 g.), m.p. 142°, undepressed on admixture with an authentic sample.

3-Cyano-1-phenethyl-4-piperidone hydrochloride



4-Amino-3-cyano-1,2,5,6-tetrahydro-1-phenethyl-pyridine (5 g.) was dissolved in 50% HCl (10 ml.) and the solution warmed. On cooling, a white solid was obtained of 3-cyano-1-phenethyl-4-piperidone hydrochloride (5 g.).

Infra-red: $\nu_{max.}$ (Nujol), 2210 cm.$^{-1}$ (C≡N), 2600 cm.$^{-1}$ - 2700 cm.$^{-1}$ ($\overset{+}{N}$H), 1670 cm.$^{-1}$ (C=O), 700 cm.$^{-1}$, 760 cm.$^{-1}$ (C_6H_5).

Found: equiv., 254. $C_{14}H_{17}ClN_2O$ requires equiv., 265.

The compound could not be crystallised successfully.

β-Benzylamino-α-methyl-propionitrile

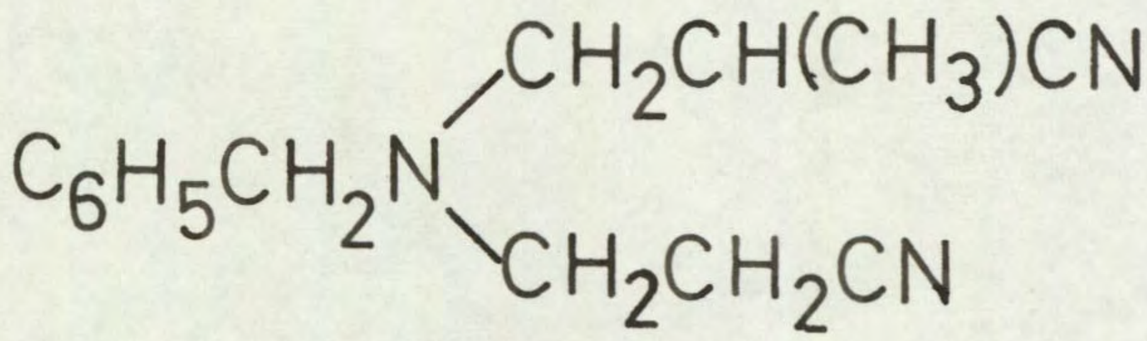
$$C_6H_5CH_2NHCH_2CH(CH_3)CN$$

Methacrylonitrile (20 g.) was added dropwise to benzylamine (40 g.) and acetic acid (6 g.). The mixture was refluxed for 2.5 hours and allowed to stand for 12 hours. Distillation under reduced pressure gave <u>β-benzylamino-α-methyl-propionitrile</u> (15 g.), b.p. 154°/3.5 mm. $\nu_{max.}$ 3300 cm.$^{-1}$ (NH), 2250 cm.$^{-1}$ (C≡N). Found: equiv., 180. $C_{11}H_{14}N_2$ requires equiv., 174.

<u>The hydrochloride</u>, recrystallised from ethanol, had m.p. 202°.

<u>Analysis</u> Found: C, 62.6; H, 7.1; N, 13.5%; equiv., 210. $C_{11}H_{15}ClN_2$ requires: C, 62.6; H, 7.1; N, 13.3%; equiv., 211.

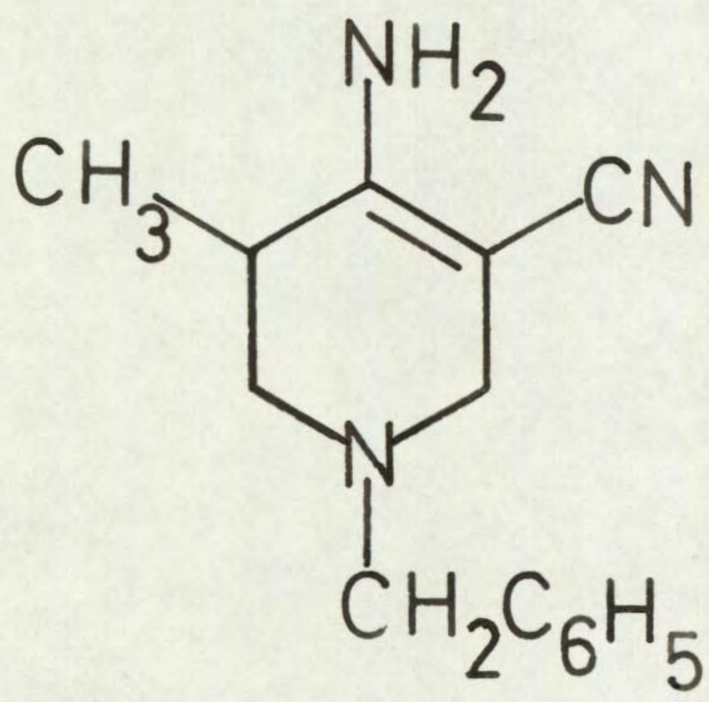
<u>ββ́-Benzylimino-α-methyl-dipropionitrile</u>



β-Benzylamino-α-methyl-propionitrile (40 g.), acrylonitrile (30 g.) and acetic acid (7 g.) were refluxed for 48 hours. Distillation under reduced pressure gave <u>ββ́-benzylimino-α-methyl-dipropionitrile</u>

(34.5 g.), b.p. 210°/3.5 mm. $\nu_{max.}$ 2250 cm.$^{-1}$ (C≡N). Found: equiv., 230. $C_{14}H_{17}N_3$ requires equiv. 227.

4-Amino-1-benzyl-3-cyano-1,2,5,6-tetrahydro-5-methyl-pyridine



ββ′-Benzylimino-α-methyl-dipropionitrile (10 g.) was added dropwise to a refluxing suspension of sodium (.2 g.) in toluene (25 ml.). The mixture was refluxed for .5 hours and allowed to stand. On cooling, a solid was obtained which crystallised from ethanol/water to give 4-amino-1-benzyl-3-cyano-1,2,5,6-tetrahydro-5-methyl-pyridine (5.2 g.), m.p. 124°, depressed when mixed with a sample of 4-amino-1-benzyl-3-cyano-1,2,5,6-tetrahydro-pyridine.

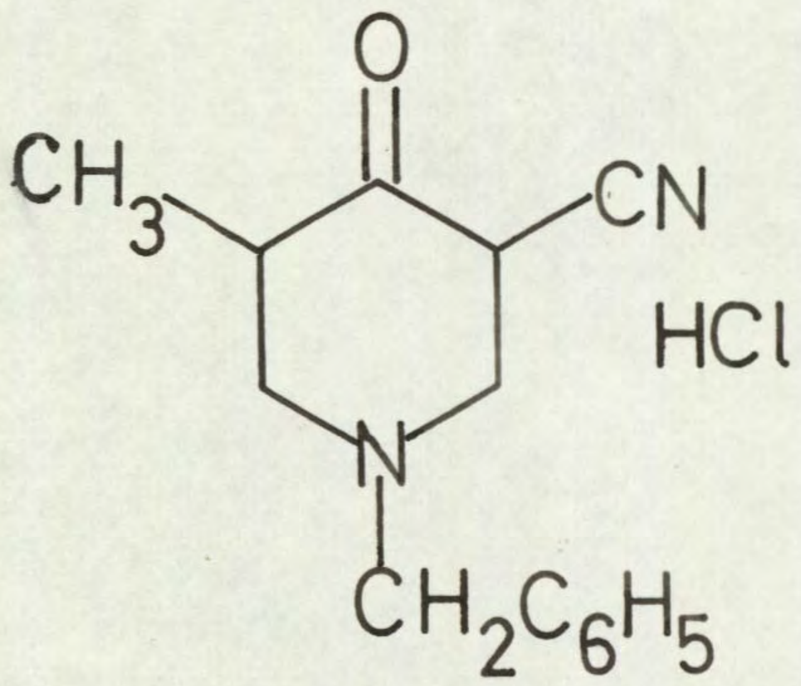
Infra-red: $\nu_{max.}$ (Nujol), 3270 cm.$^{-1}$, 3370 cm.$^{-1}$, 3450 cm.$^{-1}$ (NH_2), 2190 cm.$^{-1}$ (C≡N), 1650 cm.$^{-1}$ (C=C), 1640 cm.$^{-1}$ (C-N).

N.M.R.: τ($CDCl_3$), 2.7 (S, 5H, $C_6\underline{H}_5$), 5.7 (S, 2H,

$N\underline{H}_2$), 6.55 (S, 2H, $C_6H_5C\underline{H}_2$), 7.05 (S, 2H, $NC\underline{H}_2$), 7.05 (S, 2H, $NC\underline{H}_2C=$), 7.2-8.2 (M, 3H, $CH_2C\underline{H}$), 8.95 (D, 3H, $C\underline{H}_3$).

Analysis Found: C, 73.7; H, 7.5; N, 18.8%; equiv., 224. $C_{14}H_{17}N_3$ requires : C, 74.0; H, 7.5; N, 18.5%; equiv., 227.

1-Benzyl-3-cyano-5-methyl-4-piperidone hydrochloride



4-Amino-1-benzyl-3-cyano-1,2,5,6-tetrahydro-5-methyl-pyridine (40 g.) was dissolved in conc. HCl (80 ml.) and water (120 ml.) and warmed for 15 minutes on a steam bath. On cooling, a white solid was obtained (48 g.), which crystallised from ethanol/ether to give 1-benzyl-3-cyano-5-methyl-4-piperidone hydrochloride, m.p. 181° (decomp.).

Infra-red: $\nu_{max.}$ (Nujol), 3300 cm.$^{-1}$ (OH), 2500 cm.$^{-1}$ - 2700 cm.$^{-1}$ ($\overset{+}{N}H$), 2250 cm.$^{-1}$ (C≡N), 700 cm.$^{-1}$ and 745 cm.$^{-1}$ (C_6H_5).

Analysis Found: C, 62.1; H, 7.0; N, 10.3%; equiv., 270. $C_{14}H_{17}ClN_2O$ requires : C, 63.5; H, 6.4; N, 10.6%; equiv., 265.

β-Phenethylamino-α-methyl-propionitrile

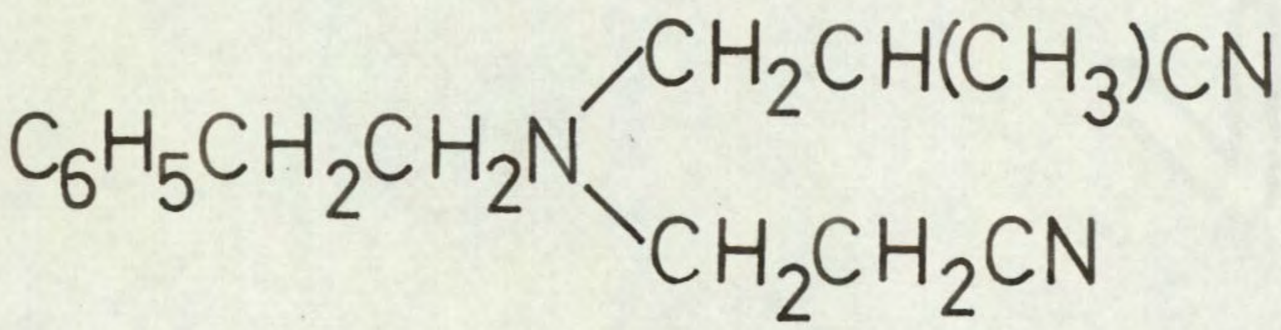
$$C_6H_5CH_2CH_2NHCH_2CH(CH_3)CN$$

Phenethylamine (70 g.), methacrylonitrile (39 g.) and acetic acid (2 g.) were refluxed for 24 hours. Distillation under reduced pressure gave β-phenethylamino-α-methyl-propionitrile (62 g.), b.p. 133°/2 mm. $\nu_{max.}$ 3350 cm.$^{-1}$ (NH), 2250 cm.$^{-1}$ (C≡N).

The hydrochloride, recrystallised from ethanol, had m.p. 193°.

Analysis Found: C, 64.0; H, 7.8; N, 12.5%; equiv., 218. $C_{12}H_{17}ClN_2$ requires : C, 64.2; H, 7.6; N, 12.5%; equiv., 225.

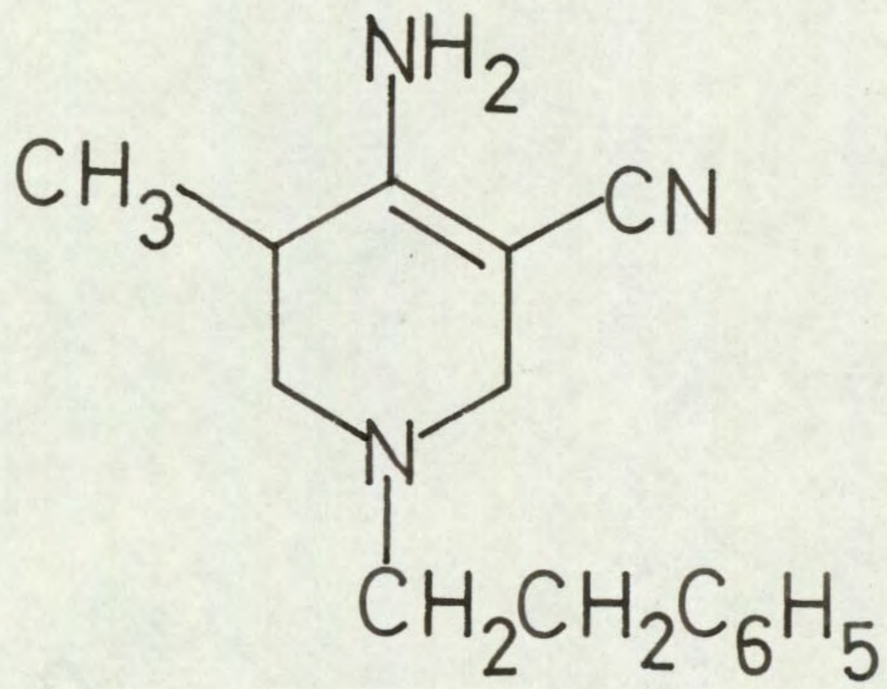
ββ'-Phenethylimino-α-methyl-dipropionitrile



β-Phenethylamino-α-methyl-propionitrile (50 g.), acrylonitrile (20 g.) and acetic acid (7 g.) were refluxed for 24 hours. Distillation under reduced pressure gave ββ'phenethylimino-α-methyl-dipropionitrile (48 g.), b.p. 218-220°/3 mm. $\nu_{max.}$ 2250 cm.$^{-1}$ (C≡N).

Found: equiv., 245. $C_{15}H_{19}N_3$ requires equiv., 241.

4-Amino-3-cyano-1,2,5,6-tetrahydro-5-methyl-1-phenethyl-pyridine



ββ́-Phenethylimino-α-methyl-dipropionitrile (40 g.) was added dropwise to a refluxing suspension of sodium (.1 g.) in toluene (50 ml.). The solution was refluxed for 1 hour and allowed to stand. On cooling, an oil was obtained which solidified. The solid was crystallised from ethyl acetate to give 4-amino-3-cyano-1,2,5,6-tetrahydro-5-methyl-1-phenethyl-pyridine (30 g.) as white plates, m.p. 108°.

Infra-red: $\nu_{max.}$ (Nujol), 3240 cm.$^{-1}$, 3350 cm.$^{-1}$,

3420 cm.$^{-1}$ (NH_2), 2180 cm.$^{-1}$ (C≡N), 1645 cm.$^{-1}$ (C=C), 1610 cm.$^{-1}$ (C-N).

Analysis Found: C, 74.6; H, 7.7; N, 17.6%; equiv., 247. $C_{15}H_{19}N_3$ requires : C, 74.7; H, 7.9; N, 17.5% equiv., 241.

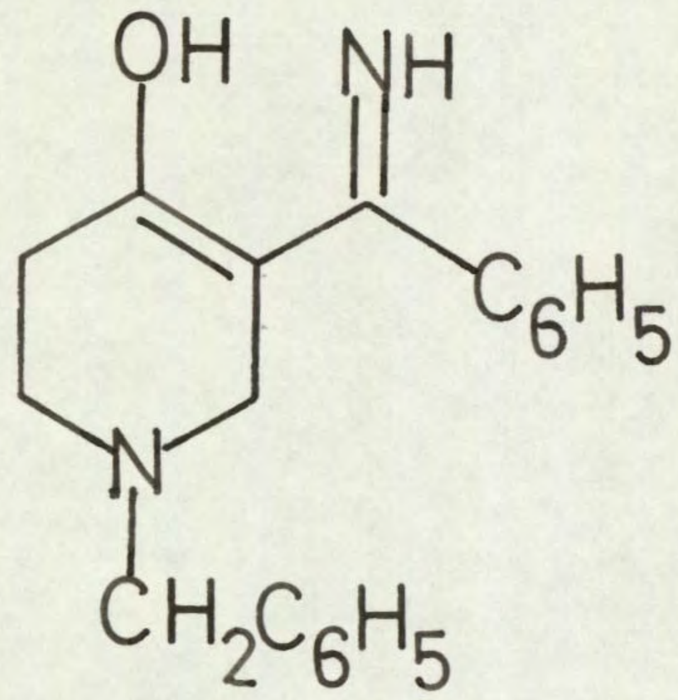
Attempted preparation of 3-cyano-5-methyl-1-phenethyl 4-piperidone hydrochloride

4-Amino-3-cyano-1,2,5,6-tetrahydro-5-methyl-1-phenethyl-pyridine (20 g.) was dissolved in conc. HCl (40 ml.) and water (40 ml.) and warmed on a steam bath for 15 minutes. On cooling a brown oil separated (10 g.) which could not be induced to solidify. Attempts to crystallise the oil failed.

B.(i) PREPARATION OF SOME DERIVATIVES OF 1-BENZYL-3-CYANO 4-PIPERIDONE HYDROCHLORIDE

Two attempts were made to react 1-benzyl-3-cyano-4-piperidone hydrochloride with organometallic reagents, one of which was successful.

a) <u>1-Benzyl-1,2,5,6-tetrahydro-4-hydroxy-3-phenylimino-pyridine</u>



Finely powdered 1-benzyl-3-cyano-4-piperidone hydrochloride (40 g.) was added in small portions to a solution of a Grignard reagent made from magnesium turnings (23 g.) and bromobenzene (150 g.) in ether (500 ml.). The mixture was refluxed for 24 hours and decomposed with a saturated NH_4Cl solution. Chloroform (600 ml.) was added to prevent precipitation of the organic compound, the organic layers separated and dried (anhy. Na_2SO_4) and evaporated, yielding a brown solid, crystallised from ethanol/water to give <u>1-benzyl-1,2,5,6-tetrahydro-4-hydroxy-3-phenylimino-pyridine</u> (36 g.) as pale yellow needles, m.p. 178°.

<u>Infra-red</u>: $\nu_{max.}$ (Nujol), 3300 $cm.^{-1}$ (NH), 3100 $cm.^{-1}$ (OH), 1620 $cm.^{-1}$ (C=C), 1600 $cm.^{-1}$ (C=N), 700 $cm.^{-1}$, 760 $cm.^{-1}$ (C_6H_5)

$\nu_{max.}$ ($CHCl_3$), 3460 $cm.^{-1}$ (bonded OH),

3300 cm.$^{-1}$ (NH).

Ultra-violet: $\lambda_{max.}$ (EtOH), 317 mμ (14800), 250 mμ (13500).

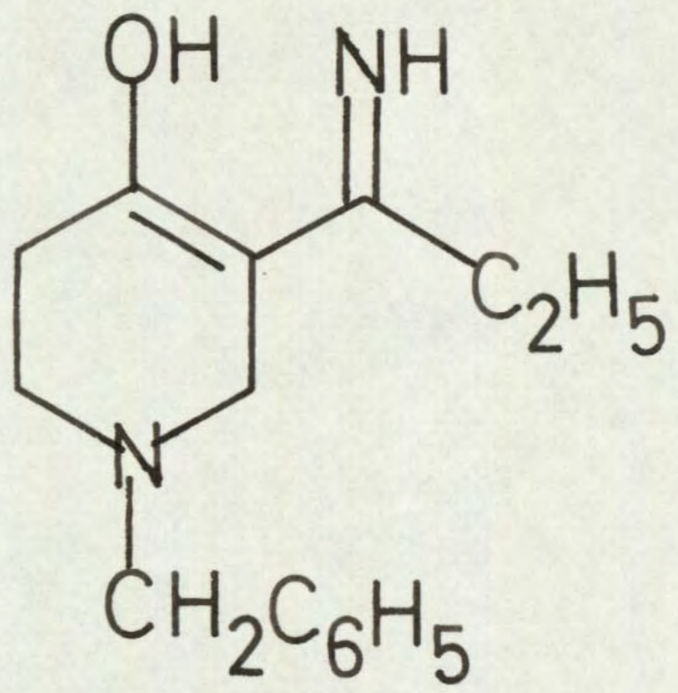
N.M.R.: τ($CDCl_3$), -0.8 (S, H, O<u>H</u>), 2.5 (S, 5H, $C_6\underline{H}_5$), 2.6 (S, 5H, $C_6\underline{H}_5$), 4.5 (S, H, N<u>H</u>), 6.48 (S, 2H, $C_6H_5C\underline{H}_2$), 6.85 (S, 2H, $NC\underline{H}_2C$=), 7.4 (M, 4H, 2 x $C\underline{H}_2$).

Analysis Found: C, 77.8; H, 7.0; N, 9.7%; equiv., 287. $C_{19}H_{20}N_2O$ requires : C, 78.1; H, 6.9; N, 9.6%; equiv., 292.

b) Finely powdered 1-benzyl-3-cyano-4-piperidone hydrochloride (6 g.) was added in small portions to a solution of lithium (1 g.) and bromobenzene (11 g.) in ether (100 ml.). The mixture was stirred for 1 hour, decomposed with water, the organic layer separated and dried (anhy. Na_2SO_4). Evaporation of the solvent yielded a dark brown oil (5 g.) which could not be induced to crystallise. An infra-red spectrum of the product showed the presence of C≡N, OH and C=O, which suggested that a mixture was present. Thin layer chromatography showed the presence of six separate spots, one of which could be compared with starting material.

c) A second attempt, using the same quantities but refluxing for 24 hours, gave a similar product.

1-Benzyl-3-ethylimino-1,2,5,6-tetrahydro-4-hydroxy pyridine



Finely-powdered 1-benzyl-3-cyano-4-piperidone hydrochloride (20 g.) was added in small portions to a solution of a Grignard reagent made from magnesium turnings (12 g.) and ethyl iodide (76 g.) in ether (400 ml.). The mixture was refluxed for 24 hours, decomposed with a saturated solution of NH_4Cl and the organic layer separated and dried (anhy. Na_2SO_4). Evaporation of the solvent gave a solid which crystallised from ethanol/water to give 1-benzyl-3-ethylimino-1,2,5,6-tetrahydro-4-hydroxy-pyridine (11.5 g.), m.p. 130.5°.

Infra-red: $\nu_{max.}$ (Nujol), 3300 cm.$^{-1}$ (NH), 3100 cm.$^{-1}$ (OH), 1620 cm.$^{-1}$ (C=C), 1600 cm.$^{-1}$ (C=N), 695 cm.$^{-1}$, 750 cm.$^{-1}$ (C_6H_5).

$\nu_{max.}$ ($CHCl_3$), 3460 cm.$^{-1}$ (OH), 3350 cm.$^{-1}$ (NH).

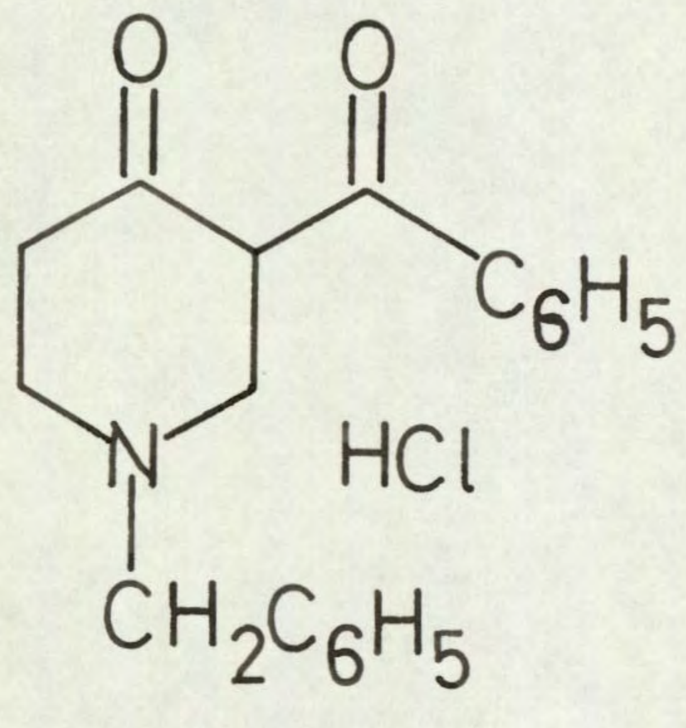
Ultra-violet: $\lambda_{max.}$ (EtOH), 317 mμ (14800), 250 mμ (13500).

N.M.R.: τ ($CDCl_3$), -0.8 (S, H, O<u>H</u>), 2.78 (S, 5H, $C_6\underline{H}_5$), 4.5 (S, H, N<u>H</u>), 6.4 (S, 2H, $C_6H_5C\underline{H}_2$), 6.8 (S, 2H, $NC\underline{H}_2C$=), 7.5 (M, 4H, 2 x $C\underline{H}_2$), 7.9 (Q, 2H, $C\underline{H}_2$), 8.93 (T, 3H, $C\underline{H}_3$).

Analysis Found: C, 73.3; H, 8.4; N, 11.5%. $C_{15}H_{20}N_2O$ requires : C, 73.8; H, 8.2; N, 11.5%; equiv., 244.

The compound did not titrate to a distinct end point.

3-Benzoyl-1-benzyl-4-piperidone hydrochloride



1-Benzyl-1,2,5,6-tetrahydro-4-hydroxy-3-phenyl-imino-pyridine (1.5 g.) was dissolved in conc. HCl (10 ml.) and water (10 ml.) and warmed on a steam bath. On allowing to stand, a solid was obtained which crystallised from water to give 3-benzoyl-1-benzyl-4-piperidone hydrochloride (1 g.), m.p. 161° (decomp.).

Infra-red: $\nu_{max.}$ (Nujol), 1720 cm.$^{-1}$ (C=O), 1690 cm.$^{-1}$ (C=O), 2500 cm.$^{-1}$ - 2700 cm.$^{-1}$ ($\overset{+}{N}H$), 690 cm.$^{-1}$, 760 cm.$^{-1}$ (C_6H_5).

Ultra-violet: $\lambda_{max.}$ (EtOH), 246 mμ (13200).

Analysis Found: C, 65.2; H, 6.5; N, 4.1%; equiv., 333. $C_{19}H_{20}ClN_2O$ requires C, 69.2; H, 6.1; N, 4.3%; equiv., 330.

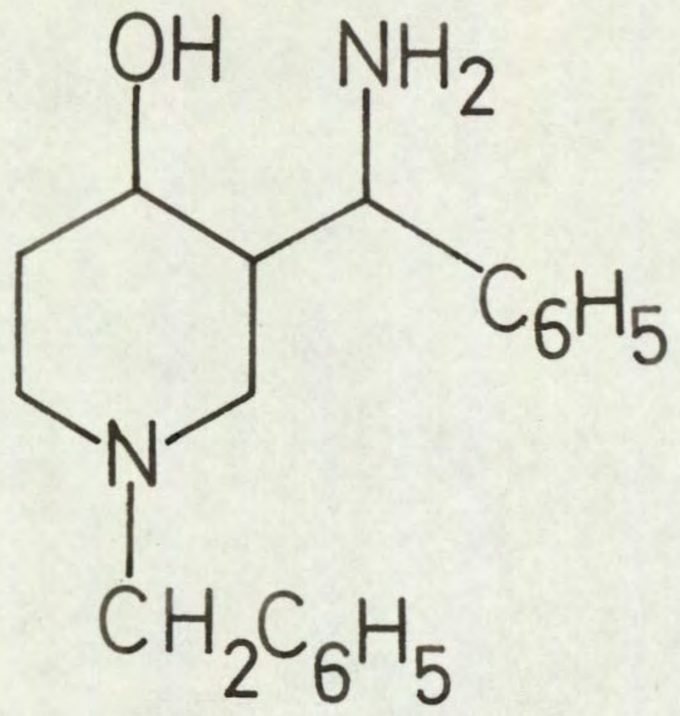
Attempted hydrolysis of 1-benzyl-3-ethylimino-1,2,5,6-tetrahydro-4-hydroxy-pyridine

1-Benzyl-3-ethylimino-1,2,5,6-tetrahydro-4-hydroxy-pyridine (1 g.) was dissolved in conc. HCl (10 ml.) and water (10 ml.) and warmed on a steam bath. On cooling no solid separated. The solvent was evaporated under reduced pressure, the residue extracted with hot ethanol which was concentrated and allowed to stand. Addition of ether precipitated a tacky solid which could not be crystallised. An infra-red spectrum showed a band at 1715 cm.$^{-1}$ (C=O) and lack of either OH or NH peaks.

Attempted reduction of 1-benzyl-1,2,5,6-tetrahydro-4-hydroxy-3-phenylimino-pyridine

Several attempts were made to reduce this compound, one of which was successful.

a) <u>1-Benzyl-3-α-phenylaminomethyl-4-piperidinol</u>



Sodium borohydride (2 g.) was added to a hot solution of 1-benzyl-1,2,5,6-tetrahydro-4-hydroxy-3-phenylimino-pyridine (5 g.) in ethanol (200 ml.). The mixture was stirred for 2 hours, water (100 ml.) added and the ethanol evaporated under reduced pressure. The solid which separated out was crystallised from ethanol/water to give <u>isomer A</u> of <u>1-benzyl-3-α-phenyl-aminomethyl-4-piperidinol monohydrate</u> (3 g.), as white needles, m.p. 100°.

<u>Infra-red</u>: $\nu_{max.}$ (Nujol), 3400 cm.$^{-1}$ (OH), 3200 cm.$^{-1}$ (NH).

$\nu_{max.}$ ($CHCl_3$), 3300 cm.$^{-1}$ (OH and NH), 980 cm.$^{-1}$ (axial C-O).

<u>Analysis</u> Found: C, 72.2; H, 8.6; N, 9.0%; equiv., 154. $C_{19}H_{26}N_2O_2$ requires : C, 72.6; H, 8.3; N, 8.9%; equiv., 157.

Further dilution of the reaction mixture with

water caused a solid to separate out, which crystallised from ethanol/water to give <u>isomer B</u> of <u>1-benzyl-3-α-phenylaminomethyl-4-piperidinol</u> (1 g.), as white needles, m.p. 148°.

<u>Infra-red</u>: $\nu_{max.}$ (Nujol), 3350 cm.$^{-1}$ (OH), 3250 cm.$^{-1}$ (NH).

$\nu_{max.}$ ($CHCl_3$), 3200 cm.$^{-1}$ (OH and NH), 1045 cm.$^{-1}$ (equ. C-O).

<u>Analysis</u> Found: C, 75.9; H, 8.5; N, 9.8%; equiv., 148. $C_{19}H_{24}N_2O$ requires : C, 77.0; H, 8.3; N, 9.5%; equiv., 148.

Mass spectra of the two isomers are identical and have a peak at M-1 $^{+}$.

b) 1-Benzyl-1,2,5,6-tetrahydro-4-hydroxy-3-phenylimino-pyridine (1 g.) in methanol (100 ml.) was shaken with hydrogen at atmospheric pressure in the presence of platinum oxide (500 mg.). No uptake of hydrogen was observed. After 24 hours, the solution was filtered, the filtrate evaporated to dryness and the residue crystallised from ethanol, yielding starting material (1 g.), the m.p. of which was undepressed on admixture with an authentic sample of 1-benzyl-1,2,5,6-tetrahydro-4-hydroxy-3-phenylimino-pyridine.

c) 1-Benzyl-1,2,5,6-tetrahydro-4-hydroxy-3-phenylimino-pyridine (1 g.) in methanol (200 ml.) was shaken with

hydrogen at atmospheric pressure in the presence of 5% palladised charcoal (1 g.). When the uptake of hydrogen had ceased, the solution was filtered and the solvent evaporated, yielding a green oil (1 g.) which could not be induced to crystallise. Thin layer chromatography of this oil showed at least five spots. Comparison with a spot of starting material suggested that one of the compounds present was unreduced starting material.

d) Sodium borohydride (.5 g.) was added to a hot solution of 1-benzyl-1,2,5,6-tetrahydro-4-hydroxy-3-phenylimino-pyridine (1 g.) in ethanol (50 ml.). The mixture was stirred hot for 2 hours, water (100 ml.) added and the alcohol evaporated, yielding a pale green oil. The aqueous layer was extracted with benzene (3 x 50 ml.), the organic layers combined, dried (anhy. Na_2SO_4) and evaporated, yielding a pale green oil (1 g.), The infra-red spectrum of this oil showed a broad band at 3200 $cm.^{-1}$ - 3400 $cm.^{-1}$, suggesting OH and NH_2, but all attempts to crystallise this compound failed. The oil (.5 g.) was dissolved in ethanolic HCl and allowed to stand. No solid was obtained. Evaporation of the solvent gave a gummy solid which would not crystallise and tended to be very deliquescent.

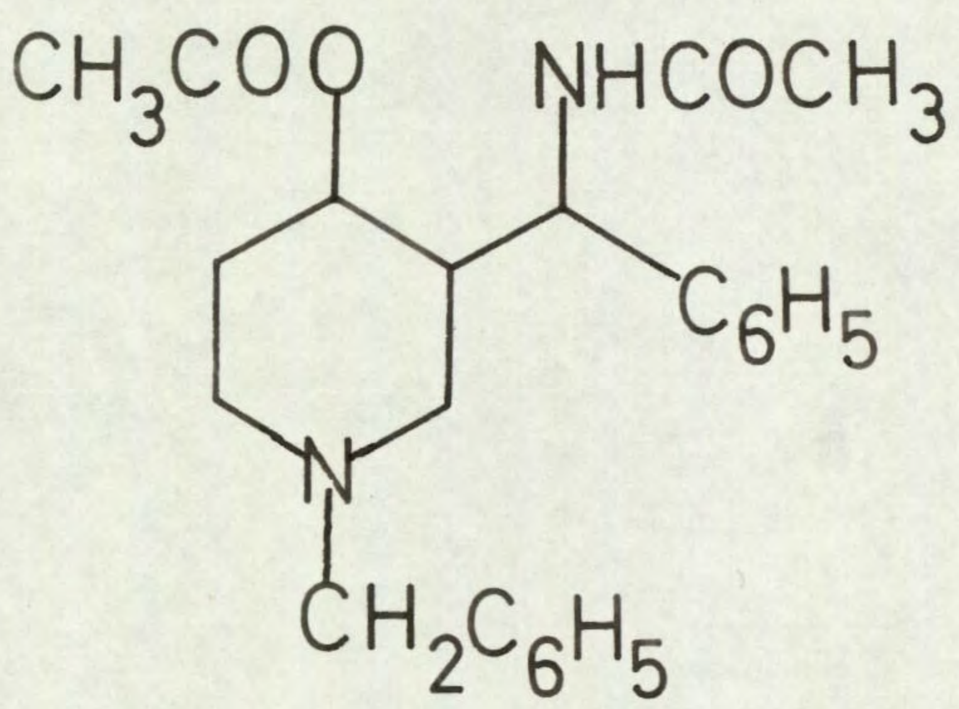
Attempted reduction of 1-benzyl-3-ethylimino-1,2,5,6-tetrahydro-4-hydroxy-pyridine

a) Sodium borohydride (1 g.) was added to a cold solution of 1-benzyl-3-ethylimino-1,2,5,6-tetrahydro-4-hydroxy-pyridine (3 g.) in ethanol (100 ml.). The mixture was stirred for 2 hours, water (50 ml.) added and the alcohol evaporated under reduced pressure, yielding a pale green oil, which solidified, and crystallised from ethanol to give starting material (1.7 g.), m.p. undepressed on admixture with authentic sample of 1-benzyl-3-ethylimino-1,2,5,6-tetrahydro-4-hydroxy-pyridine.

b) Sodium borohydride (.5 g.) was added to a solution of 1-benzyl-3-ethylimino-1,2,5,6-tetrahydro-4-hydroxy-pyridine (1 g.) in ethanol (100 ml.). The mixture was refluxed for 2 hours, water (50 ml.) added and the alcohol evaporated under reduced pressure, yielding a pale green oil. Extraction of the aqueous solution with ether (2 x 100 ml.) and evaporation of the organic solvents gave an oil (1 g.) which could not be induced to crystallise. An infra-red spectrum showed the presence of OH and NH_2. An attempt to form a hydrochloride also failed.

B.(ii) PREPARATION OF SOME DERIVATIVES OF 1-BENZYL-3-α-PHENYLAMINOMETHYL-4-PIPERIDINOL

N{α[4-Acetoxy-1-benzyl-3-piperidyl] benzyl}acetamide



Isomer A — 1-Benzyl-3-α-phenylaminomethyl-4-piperidinol (isomer A) (1 g.) was dissolved in pyridine (5 ml.) and acetic anhydride (5 ml.). The solution was refluxed for 3 hours, the solvents evaporated and the residue crystallised from absolute ethanol to give N{α[4-acetoxy-1-benzyl-3-piperidyl] benzyl}acetamide (isomer A) (.5 g.), as white plates, m.p. 227-8°.

Infra-red: $\nu_{max.}$ (Nujol), 3300 cm.$^{-1}$ (NH), 1740 cm.$^{-1}$ (ester C=O), 1660 cm.$^{-1}$ (amide I), 1560 cm.$^{-1}$ (amide II), 1250 cm.$^{-1}$ (C-O).

Analysis Found: C, 72.4; H, 7.8; N, 7.5%; equiv., 390. $C_{23}H_{28}N_2O_3$ requires : C, 72.6; H, 7.4; N, 7.4%; equiv., 380.

Isomer B — In a similar manner, 1-benzyl-3-α-

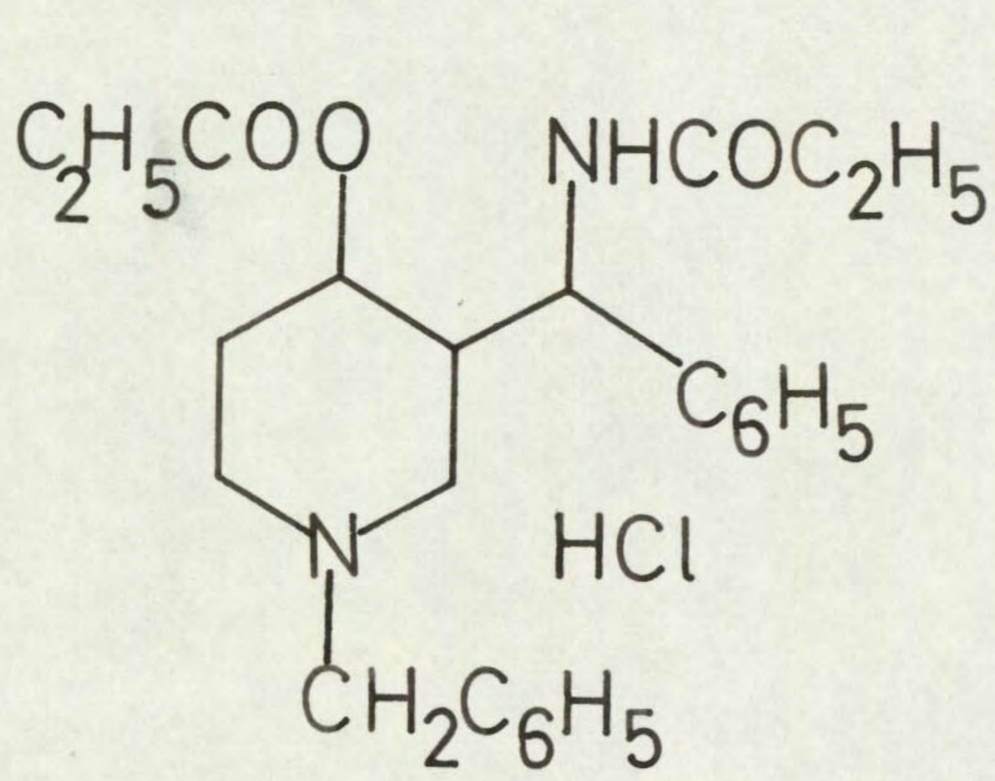
phenylaminomethyl-4-piperidinol (isomer B) (1 g.) was refluxed in pyridine (5 ml.) and acetic anhydride (5 ml.) for 3 hours to give a solid, crystallised from ethanol to give N{α[4-acetoxy-1-benzyl-3-piperidyl]benzyl} acetamide (isomer B) (.6 g.), as white plates, m.p. 145°, depressed on admixture with isomer A.

Infra-red: $\nu_{max.}$ (Nujol), 3250 cm.$^{-1}$ (NH), 1730 cm.$^{-1}$ (ester C=O), 1640 cm.$^{-1}$ (amide I), 1540 cm.$^{-1}$ (amide II), 1250 cm.$^{-1}$ (C-O).

N.M.R.: τ ($CDCl_3$), 2.8 (D, 10H); 3.1 (D, H), 4.7 (Q, H), 5.1 (Q, H), 6.7 (T, 2H), 7.2-8.4 (M, 7H), 8.0 (S, 3H), 8.3 (S, 3H).

Analysis Found: C, 72.3; H, 7.7; N, 7.5%; equiv., 375. $C_{23}H_{28}N_2O_3$ requires : C, 72.6; H, 7.4; N, 7.4%; equiv., 380.

N{α[1-Benzyl-4-propionoxy-3-piperidyl]benzyl} propionamide hydrochloride



Isomer A 1-Benzyl-3-α-phenylaminomethyl-4-piperidinol (isomer A) (1 g.) was dissolved in pyridine (3 ml.) and propionic anhydride (2 ml.). The mixture was refluxed for 1 hour, the solvents evaporated and the residue dissolved in ethanolic HCl. On allowing to stand, a solid was obtained which crystallised from ethanol/ether to give N{α[1-benzyl-4-propionoxy-3-piperidyl]benzyl}propionamide hydrochloride (isomer A) (.45 g.), as white leaves, m.p. 238°.

Infra-red: $\nu_{max.}$ (Nujol), 3200 cm.$^{-1}$ (NH), 2500 cm.$^{-1}$ ($\overset{+}{N}H$), 1740 cm.$^{-1}$ (ester C=O), 1660 cm.$^{-1}$ (amide I), 1540 cm.$^{-1}$ (amide II), 1260 cm.$^{-1}$ (C-O).

Analysis Found: C, 67.3; H, 7.5; N, 6.1%; equiv., 463. $C_{25}H_{33}ClN_2O_3$ requires : C, 67.5; H, 7.4; N, 6.3%; equiv., 445.

Isomer B In a similar manner, 1-benzyl-3-α-phenylaminomethyl-4-piperidinol (isomer B) (1 g.) in pyridine (5 ml.) and propionic anhydride (2 ml.) refluxing for 1.5 hours gave a solid, crystallised from ethanol/ether to give N{α[1-benzyl-4-propionoxy-3-piperidyl]benzyl}propionamide hydrochloride (isomer B) (.25 g.) as white prisms, m.p. 220°.

Infra-red: $\nu_{max.}$ (Nujol), 3250 cm.$^{-1}$ (NH), 2500 cm.$^{-1}$ ($\overset{+}{N}H$), 1720 cm.$^{-1}$ (ester C=O), 1680 cm.$^{-1}$ (amide I), 1540 cm.$^{-1}$ (amide II), 1180 cm.$^{-1}$ (C-O).

Analysis Found: C, 66.7; H, 7.4; N, 6.4%; equiv., 432. $C_{25}H_{33}ClN_2O_3$ requires : C, 67.5; H, 7.4; N, 6.3%; equiv., 445.

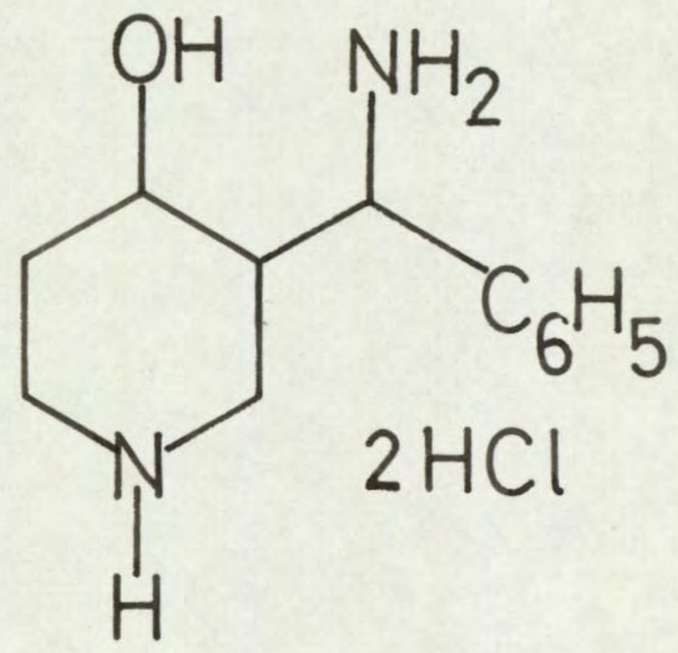
Attempted debenzylation of N{α [4-acetoxy-1-benzyl-3-piperidyl] benzyl} acetamide

N {α [4-Acetoxy-1-benzyl-3-piperidyl] benzyl} acetamide (isomer A) (.57 g.) in methanol (50 ml.) was shaken with hydrogen at atmospheric pressure in the presence of 10% palladised charcoal (.026 g.). When the uptake of hydrogen had ceased, the solution was filtered and the filtrate evaporated, yielding a clear oil (.5 g.) with an equivalent weight of 293 ($C_{16}H_{22}N_2O_3$ requires 290). The infra-red spectrum showed the presence of both ester and amide functions. The compound could not be solidified or crystallised. A small portion in ethanolic HCl did not form a solid hydrochloride. An infra-red of the hydrochloride showed lack of bands assigned to an ester.

The reduced product (.47 g.) in chloroform (50 ml.) was refluxed with phenethyl bromide (.3 g.), sodium bicarbonate (2 g.) and a crystal of potassium iodide for 24 hours. Filtration of the solution and evaporation of the filtrate yielded an oil (.7 g.) which could not be solidified. An infra-red spectrum of the oil

suggested that the reaction may have worked. Thin layer chromatography indicated the presence of three compounds, one of which compared with starting material.

3-α-Phenylaminomethyl-4-piperidinol dihydrochloride



Isomer A 1-Benzyl-3-α-phenylaminomethyl-4-piperidinol (isomer A) (2 g.) in methanol (125 ml.) was shaken with hydrogen at atmospheric pressure in the presence of 10% palladised charcoal (2 g.). When one mole of hydrogen had been absorbed, the solution was filtered and the filtrate evaporated to give a clear oil (1.5 g.). This was dissolved in ethanolic HCl and allowed to stand. The crystals obtained were recrystallised from ethanol/ether to give 3-α-phenylaminomethyl-4-piperidinol dihydrochloride (isomer A) (1.3 g.), as white needles, m.p. $>360^{\circ}$.

Infra-red: $\nu_{max.}$ (Nujol), 3380 $cm.^{-1}$ (OH), 2400 $cm.^{-1}$ - 2700 $cm.^{-1}$ ($\overset{+}{N}H$), 1535 $cm.^{-1}$, 1575 $cm.^{-1}$,

1620 cm.$^{-1}$ ($C\overset{+}{-}N$), 990 cm.$^{-1}$ (axial OH), 705 cm.$^{-1}$, 770 cm.$^{-1}$ (C_6H_5).

Analysis Found: C, 51.7; H, 7.3; N, 10.2%; equiv., 147. $C_{12}H_{20}Cl_2N_2O$ requires : C, 51.6; H, 7.2; N, 10.0%; equiv., 140.

Isomer B 1-Benzyl-3-α-phenylaminomethyl-4-piperidinol (isomer B) (5 g.) in methanol (200 ml.) with 10% palladised charcoal (2 g.) reacted similarly to give 3-α-phenylaminomethyl-4-piperidinol dihydrochloride (isomer B) (3.5 g.), as white needles from ethanol, m.p. $>360^{\circ}$.

Infra-red: $\nu_{max.}$ (Nujol), 3320 cm.$^{-1}$ (OH), 2500 cm.$^{-1}$ - 2700 cm.$^{-1}$ ($\overset{+}{N}H$), 1510 cm.$^{-1}$, 1575 cm.$^{-1}$, 1620 cm.$^{-1}$ ($C\overset{+}{-}N$), 1090 cm.$^{-1}$ (equ. OH), 700 cm.$^{-1}$, 760 cm.$^{-1}$, (C_6H_5).

Analysis Found: C, 51.4; H, 7.1; N, 10.2%; equiv., 143. $C_{12}H_{20}Cl_2N_2O$ requires : C, 51.6; H, 7.2; N, 10.0%; equiv., 140.

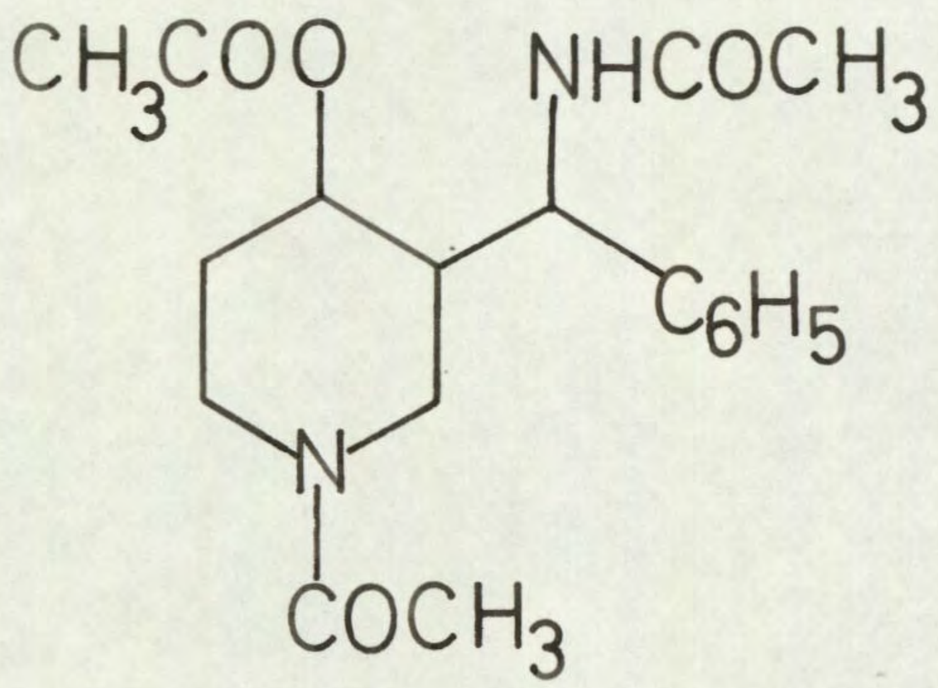
Attempted reaction of 3-α-phenylaminomethyl-4-piperidinol with phenethyl bromide

a) 3-α-Phenylaminomethyl-4-piperidinol dihydrochloride (1 g.) was refluxed in ethanol (200 ml.) with phenethyl bromide (.7 g.), sodium bicarbonate (10 g.) and a crystal of KI for 140 hours. Filtration of the

solution and evaporation of the solvent yielded a light brown oil (1.5 g.), which could not be induced to crystallise. The oil was dissolved in ethanolic HCl and allowed to stand. No solid product was obtained. Evaporation of the solvent gave a colourless oil which did not solidify.

b) The experiment was repeated, using 3-α-phenylamino-methyl-4-piperidinol dihydrochloride (1 g.), phenethyl bromide (1.4 g.), sodium bicarbonate (10 g.), and a crystal of KI in ethanol (200 ml.) refluxing for 60 hours. Once again no solid product was obtained.

N{α[1-Acetamido-4-acetoxy-3-piperidyl]benzyl} acetamide



Isomer A 3-α-Phenylaminomethyl-4-piperidinol (isomer A) (1.8 g.) was refluxed in pyridine (10 ml.) and acetic anhydride (5 ml.) for 3 hours. Evaporation of the solvents gave a brown solid (1.8 g.) which

crystallised from ethanol to give N{α[1-acetamido-4-acetoxy-3-piperidyl]benzyl}acetamide (isomer A) (1.1 g.) as colourless leaves, m.p. 245°.

Infra-red: $\nu_{max.}$ (Nujol), 3250 cm.$^{-1}$ (NH), 1730 cm.$^{-1}$ (ester C=O), 1640 cm.$^{-1}$ (amide I), 1575 cm.$^{-1}$ (amide II), 1240 cm.$^{-1}$ (C-O).

Analysis Found: C, 64.9; H, 7.4; N, 8.5%.

$C_{18}H_{24}N_2O_4$ requires : C, 65.1; H, 7.2; N, 8.4%.

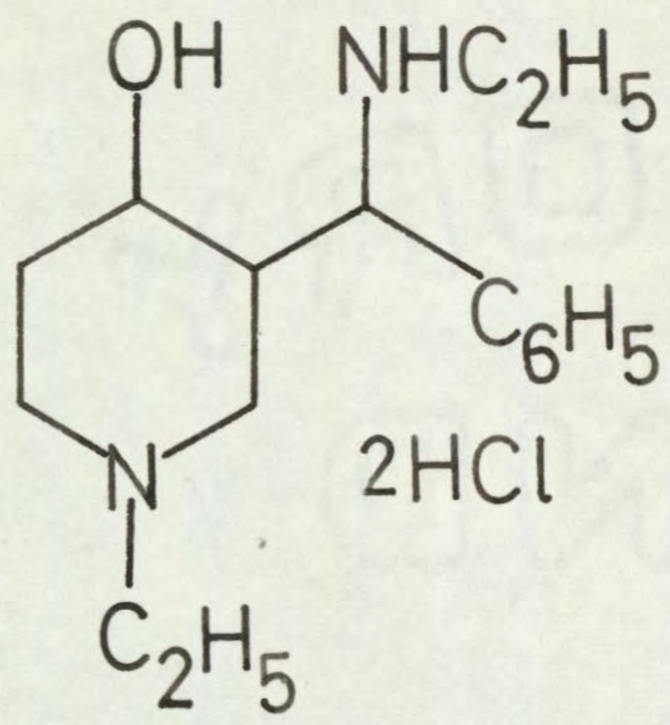
Isomer B In a similar manner, refluxing 3-α-phenylamino-methyl-4-piperidinol (isomer B) (2.5 g.) with pyridine (10 ml.) and acetic anhydride (5 ml.) for 3 hours gave, on crystallising from ethanol, N{α[1-acetamido-4-acetoxy-3-piperidyl]benzyl}acetamide (isomer B) (2.2 g.), as colourless needles, m.p. 168°-169°.

Infra-red: $\nu_{max.}$ (Nujol), 3350 cm.$^{-1}$ (NH), 1725 cm.$^{-1}$ (ester C=O), 1660 cm.$^{-1}$, 1630 cm.$^{-1}$ (amide I), 1540 cm.$^{-1}$ (amide II), 1250 cm.$^{-1}$ (C-O).

Analysis Found: C, 64.9; H, 7.2; N, 8.6%.

$C_{18}H_{24}N_2O_4$ requires : C, 65.1; H, 7.2; N, 8.4%.

NN'-Diethyl-3-α-phenylaminomethyl-4-piperidinol dihydrochloride



Isomer A N{α [1-Acetamido-4-acetoxy-3-piperidyl] benzyl} acetamide (isomer A) (.5 g.) in benzene (50 ml.) was added dropwise to a stirred solution of $LiAlH_4$ (1 g.) in ether (50 ml.). The mixture was refluxed overnight, decomposed with a saturated solution of sodium potassium tartrate, the inorganic precipitate filtered off, the organic layer dried (anhy. Na_2SO_4) and evaporated, yielding a pale yellow oil (.4 g.). The infra-red spectrum of this oil showed the loss of amide and ester peaks in the region 1540 $cm.^{-1}$ - 1740 $cm.^{-1}$, and the presence of OH and NH peaks in the region 3200 $cm.^{-1}$ - 3400 $cm.^{-1}$. The oil was dissolved in ethanolic HCl and allowed to stand. A white solid was obtained (.35 g.), which was crystallised from ethanol/ether to give NN'-diethyl-3-α-phenylaminomethyl-4-piperidinol dihydrochloride (isomer A) (.3 g.), as

colourless prisms, m.p. 265°.

Infra-red: $\nu_{max.}$ (Nujol), 3200 cm.$^{-1}$ (OH), 2400 cm.$^{-1}$ - 2700 cm.$^{-1}$ ($\overset{+}{N}$H), 990 cm.$^{-1}$ (axial OH).

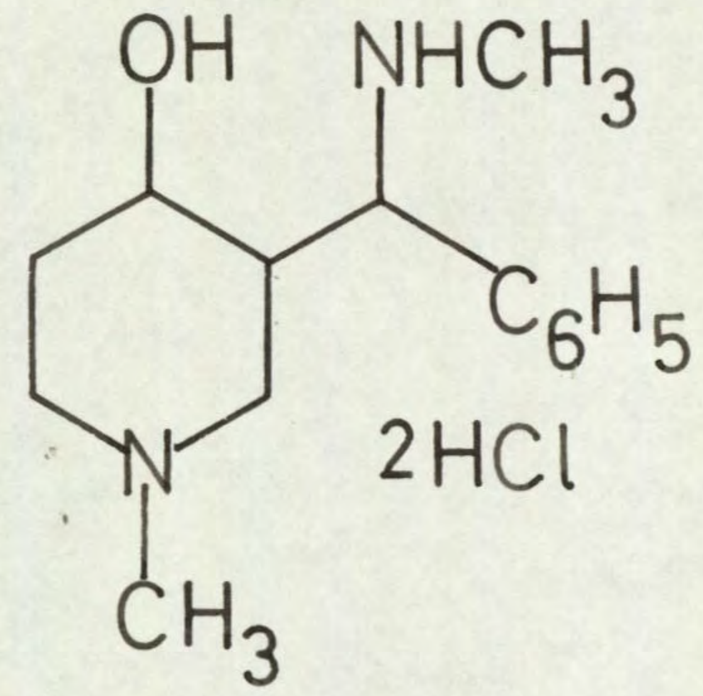
Analysis Found: C, 57.1; H, 8.5; N, 8.0%; equiv., 163. $C_{16}H_{28}Cl_2N_2O$ requires : C, 57.3; H, 8.4; N, 8.4%; equiv., 168.

Isomer B In a similar manner, N{α [1-acetamido-4-acetoxy-3-piperidyl] benzyl} acetamide (isomer B) (1 g.) in benzene (50 ml.) with $LiAlH_4$ (1 g.) gave NN'-diethyl-3-α-phenylaminomethyl-4-piperidinol dihydrochloride (isomer B) (.55 g.) from ethanol/ether as colourless needles, m.p. 264°.

Infra-red: $\nu_{max.}$ (Nujol), 3250 cm.$^{-1}$ (OH), 2400 cm.$^{-1}$ - 2800 cm.$^{-1}$ ($\overset{+}{N}$H), 1050 cm.$^{-1}$ (equ. OH).

Analysis Found: C, 57.4; H, 8.6; N, 8.1%; equiv. 164. $C_{16}H_{28}Cl_2N_2O$ requires : C, 57.3; H, 8.4; N, 8.4%; equiv., 168.

NN'-Dimethyl-3-α-phenylaminomethyl-4-piperidinol dihydrochloride



3-α-Phenylaminomethyl-4-piperidinol (isomer A) (1.2 g.) was dissolved in formic acid (10 ml.). An equimolar mixture of acetic anhydride and formic acid (10 ml.) was added, the solution allowed to stand for 1 hour and the solvents evaporated, yielding a brown oil (2.03 g.). This was dissolved in benzene (10 ml.) and added to $LiAlH_4$ (2 g.) in ether (50 ml.). The mixture was stirred overnight and decomposed with sodium potassium tartrate solution. The inorganic deposit was filtered, the organic layer dried (anhy. Na_2SO_4) and evaporated, yielding a yellow oil (.8 g.). This was dissolved in ethanolic HCl and allowed to stand. A white solid was obtained, which on crystallisation from ethanol/ether gave NN'-dimethyl-3-α-phenylaminomethyl-4-piperidinol dihydrochloride (isomer A) (.2 g.) as white needles, m.p. 271°.

Infra-red: $\nu_{max.}$ (Nujol), 3380 cm.$^{-1}$ (OH),

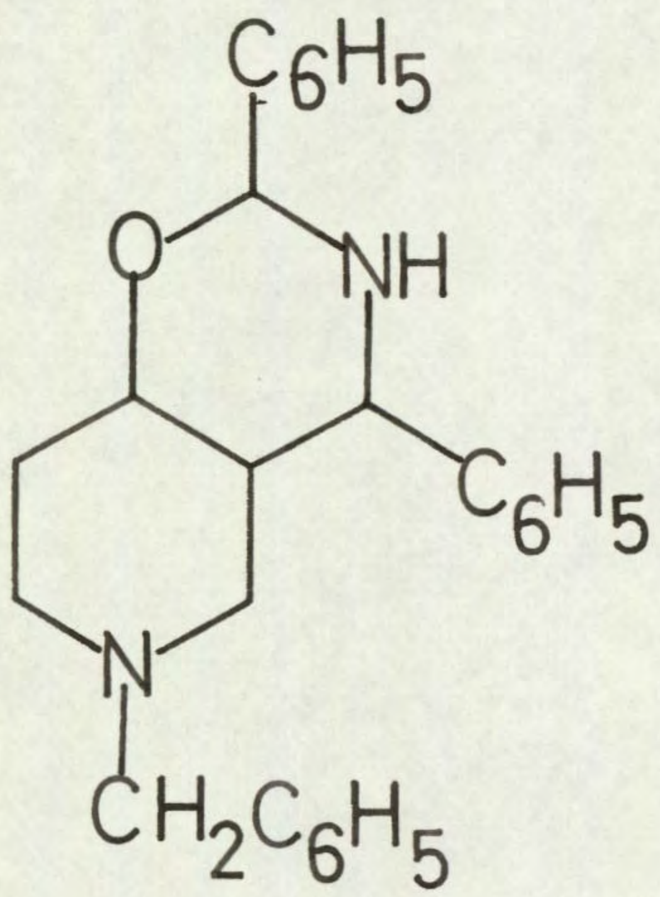
2500 cm.$^{-1}$ - 2800 cm.$^{-1}$ ($\overset{+}{N}H$), 980 cm.$^{-1}$ (axial OH).

<u>Analysis</u> Found: C, 54.1; H, 8.4; N, 8.3%; equiv., 161. $C_{14}H_{24}Cl_2N_2O$ requires : C, 54.7; H, 7.8; N, 9.1%; equiv., 154.

The poor analysis was attributed to the deliquescence of the compound.

B.(iii) PREPARATION OF PYRIDO[3,4,e][1,3]OXAZINES

<u>6-Benzyl-octahydro-2H-2,4-diphenyl-pyrido[3,4,e][1,3]oxazine</u>



<u>Isomer A</u> 1-Benzyl-3-α-phenylaminomethyl-4-piperidinol (isomer A) (3 g.), benzaldehyde (1 g.) and toluene (50 ml.) were refluxed, the water present being removed in a water separator. When all the water had been removed, the solvent was evaporated, yielding a

clear colourless oil (4 g.) which solidified on scratching and crystallised from ethanol/pet. ether (80°-100°) to give 6-benzyl-octahydro-2H-2,4-diphenyl-pyrido[3,4,e][1,3]oxazine (isomer A) (3.8 g.), as white needles, m.p. 134°.

Infra-red: $\nu_{max.}$ (Nujol), 3300 cm.$^{-1}$ (NH), 700 cm.$^{-1}$, 750 cm.$^{-1}$ (C_6H_5).

Ultra-violet: $\lambda_{max.}$ (EtOH), 214 mμ (12200), 250 mμ (840).

N.M.R.: τ($CDCl_3$), 2.7 (M, 15H), 4.6 (D, H), 5.6 (D, H), 5.9 (S, H), 6.6 (Q, 2H), 7.4-8.4 (M, 8H).

τ ($CDCl_3$ + D_2O), 2.7 (M, 15H), 4.6 (S, H), 5.6 (S, H), 5.9 (S, H), 6.6 (Q, 2H), 7.4-8.4 (M, 7H).

Analysis Found: C, 81.1; H, 7.4; N, 7.2%; equiv., 189. $C_{26}H_{28}N_2O$ requires : C, 81.3; H, 7.3; N, 7.3%; equiv., 192.

Isomer B 1-Benzyl-3-α-phenylaminomethyl-4-piperidinol (isomer B) (1 g.), benzaldehyde (.32 g.) in toluene (50 ml.) similarly gave 6-benzyl-octahydro-2H-2,4-diphenyl-pyrido[3,4,e][1,3]oxazine (isomer B) (1.1 g.), as white needles from ethanol/pet. ether (80°-100°), m.p. 117°.

Infra-red: $\nu_{max.}$ ($CHCl_3$), 3300 cm.$^{-1}$ (NH).

Ultra-violet: $\lambda_{max.}$ (EtOH), 210.5 mμ (17200),

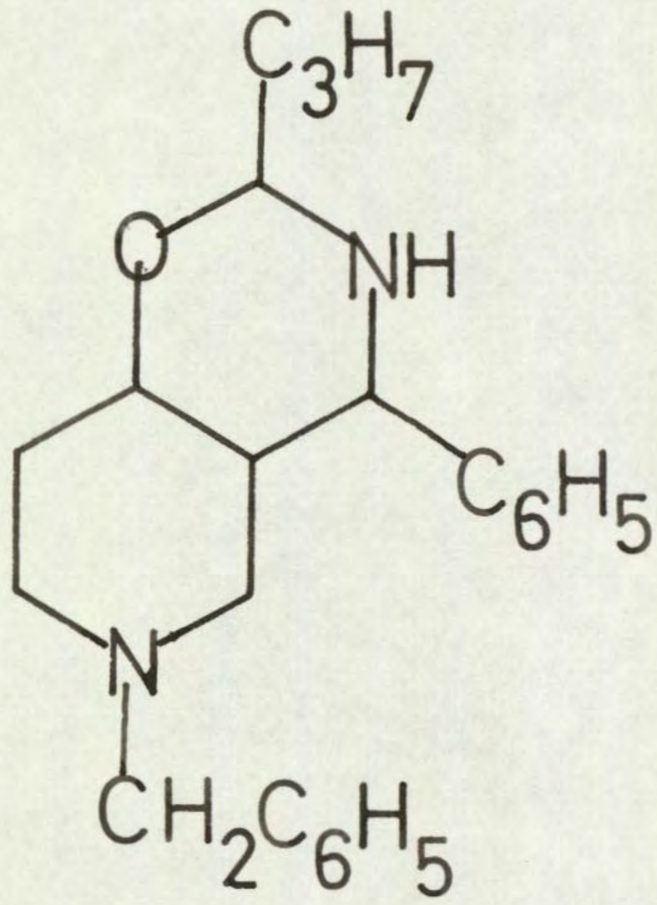
250 mμ (1720).

N.M.R.: τ($CDCl_3$), 2.7 (M, 15H), 4.6 (S, H), 6.2 (D, H), 6.7 (Q, 2H), 7.0-8.4 (M, 9H).

Analysis Found: C, 81.3; H, 7.4; N, 7.4%; equiv., 189. $C_{26}H_{28}N_2O$ requires : C, 81.3; H, 7.3; N, 7.3%; equiv., 192.

The mass spectra of isomers A and B are identical.

6-Benzyl-octahydro-2H-2-phenyl-4-propyl-pyrido [3,4,e][1,3]oxazine



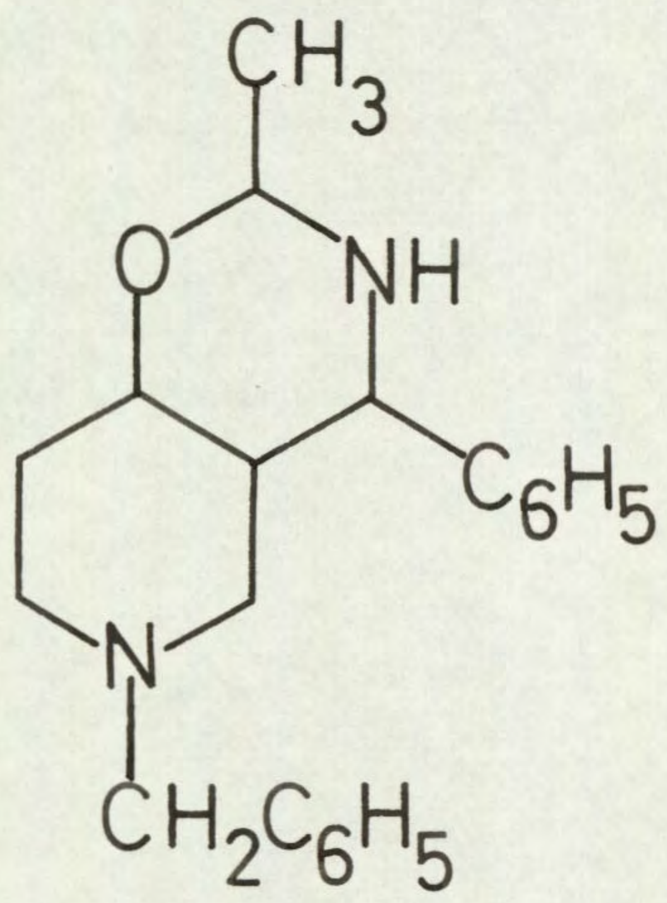
1-Benzyl-3-α-phenylaminomethyl-4-piperidinol (isomer A) (1 g.) in benzene (50 ml.) and n-butyraldehyde (.5 ml.) gave in a similar manner 6-benzyl-octahydro-2H-2-phenyl-4-propyl-pyrido[3,4,e][1,3]oxazine (isomer A) (1 g.), as white leaves from pentane, m.p. 84°.

Infra-red: $\nu_{max.}$ (film), 3350 cm.$^{-1}$ (NH).

Analysis Found: C, 79.1; H, 8.6; N, 8.0%; equiv., 170. $C_{23}H_{30}N_2O$ requires : C, 78.9; H, 8.6; N, 8.0%; equiv., 175.

The compound was unstable and gradually turned yellow.

6-Benzyl-octahydro-2H-2-methyl-4-phenyl-pyrido [3,4,e][1,3]oxazine

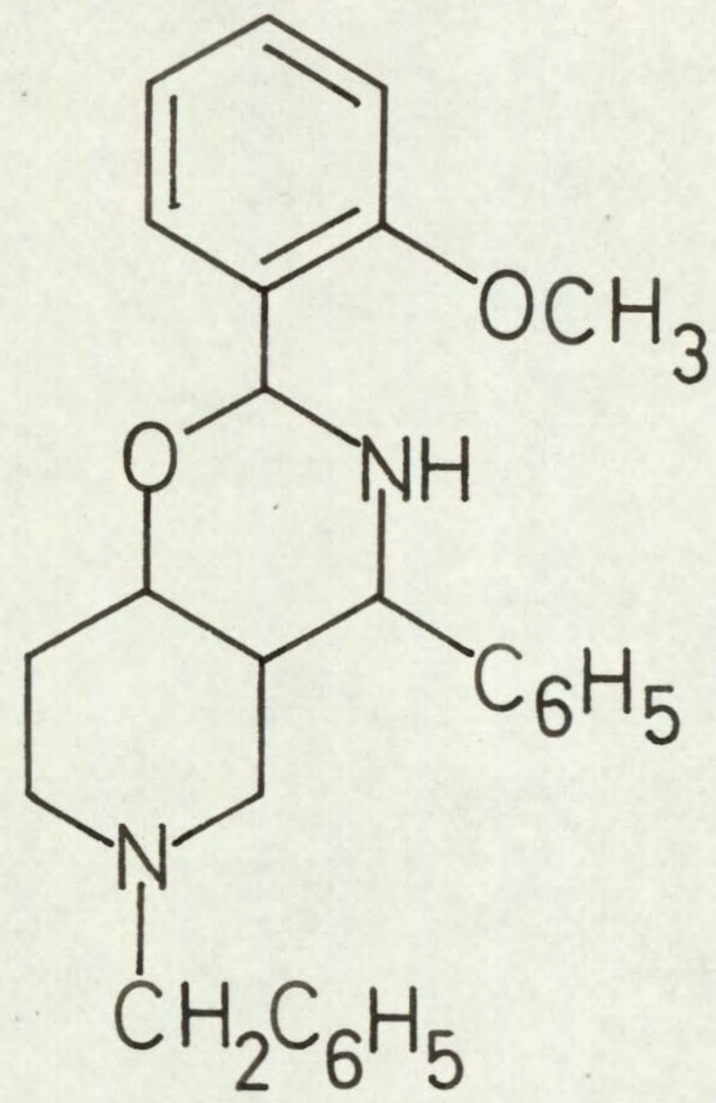


In a similar manner, 1-benzyl-3-α-phenylamino-methyl-4-piperidinol (isomer A) (1 g.), acetaldehyde (1 ml.) and benzene (50 ml.) gave an oil which crystallised from pentane to give 6-benzyl-octahydro-2H-2-methyl-4-phenyl-pyrido[3,4,e][1,3]oxazine (isomer A) (.5 g.) as white needles, m.p. 98°.

Infra-red: $\nu_{max.}$ (film), 3300 cm.$^{-1}$ (NH).

Analysis Found: C, 78.4; H, 8.3; N, 8.6%; equiv., 168. $C_{21}H_{26}N_2O$ requires : C, 78.3; H, 8.1; N, 8.7%; equiv., 161.

6-Benzyl-octahydro-2H-2-(o-methoxyphenyl)-4-phenyl-pyrido[3,4,e][1,3]oxazine



1-Benzyl-3-α-phenylaminomethyl-4-piperidinol (isomer A) (1 g.), o-methoxybenzaldehyde (.46 g.) and toluene (50 ml.) gave in a similar manner a yellow solid which crystallised from ethanol to give 6-benzyl-octahydro-2H-2-(o-methoxyphenyl)-4-phenyl-pyrido[3,4,e][1,3]oxazine (isomer A) (1.12 g.), as white needles, m.p. 155°.

Infra-red: $\nu_{max.}$ (Nujol), 3300 cm.$^{-1}$ (NH), 1240 cm.$^{-1}$ (C-O-C).

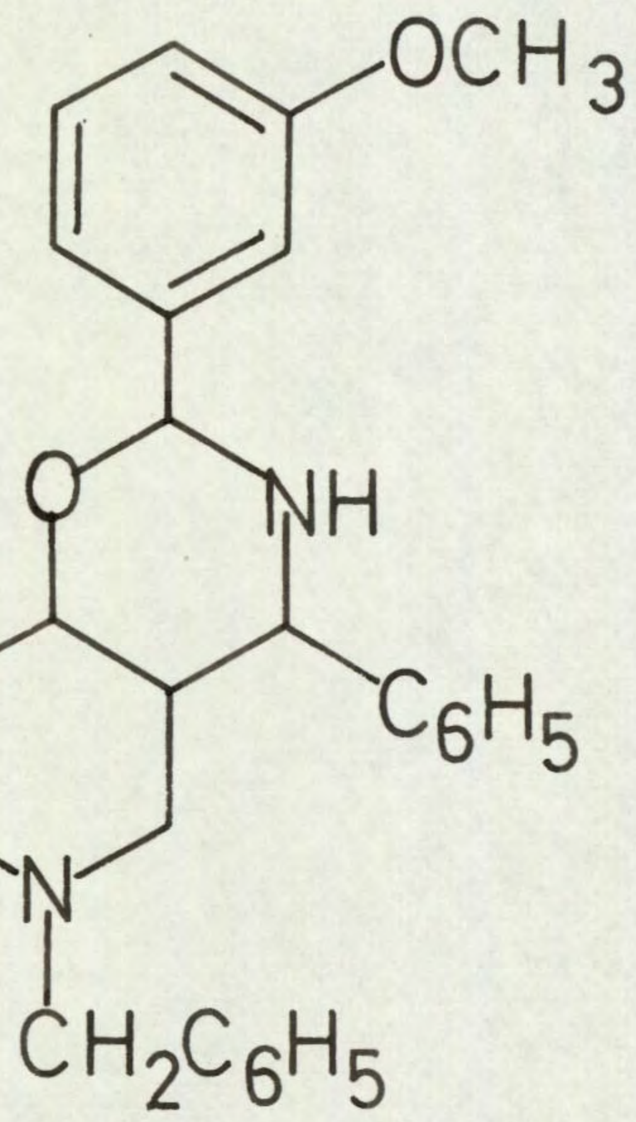
Ultra-violet: $\lambda_{max.}$ (EtOH), 214 mμ (16800), 252 mμ (4840), 305 mμ (1700).

N.M.R.: τ($CDCl_3$), 2.75 (M, 14H), 4.35 (S, H), 5.6 (S, H), 6.2 (S, 3H), 6.6 (Q, 2H), 7.2-8.3 (M, 9H).

Analysis Found: C, 78.3; H, 7.4; N, 6.9%;

equiv., 202. $C_{27}H_{30}N_2O_2$ requires : C, 78.3; H, 7.2; N, 6.8%; equiv., 207.

6-Benzyl-octahydro-2H-2-(m-methoxyphenyl)-4-phenyl-pyrido[3,4,e][1,3]oxazine



In a similar manner, 1-benzyl-3-α-phenylamino-methyl-4-piperidinol (isomer A) (4 g.), m-methoxy-benzaldehyde (1.75 g.) and toluene (50 ml.) gave a solid (5.8 g.) which crystallised from ethanol/pet. ether (100-120°) to give 6-benzyl-octahydro-2H-2-(m-methoxy-phenyl)-4-phenyl-pyrido[3,4,e][1,3]oxazine (isomer A) (5 g.), as white needles, m.p. 133°.

Infra-red: $\nu_{max.}$ (Nujol), 1290 cm.$^{-1}$ (C-O-C).

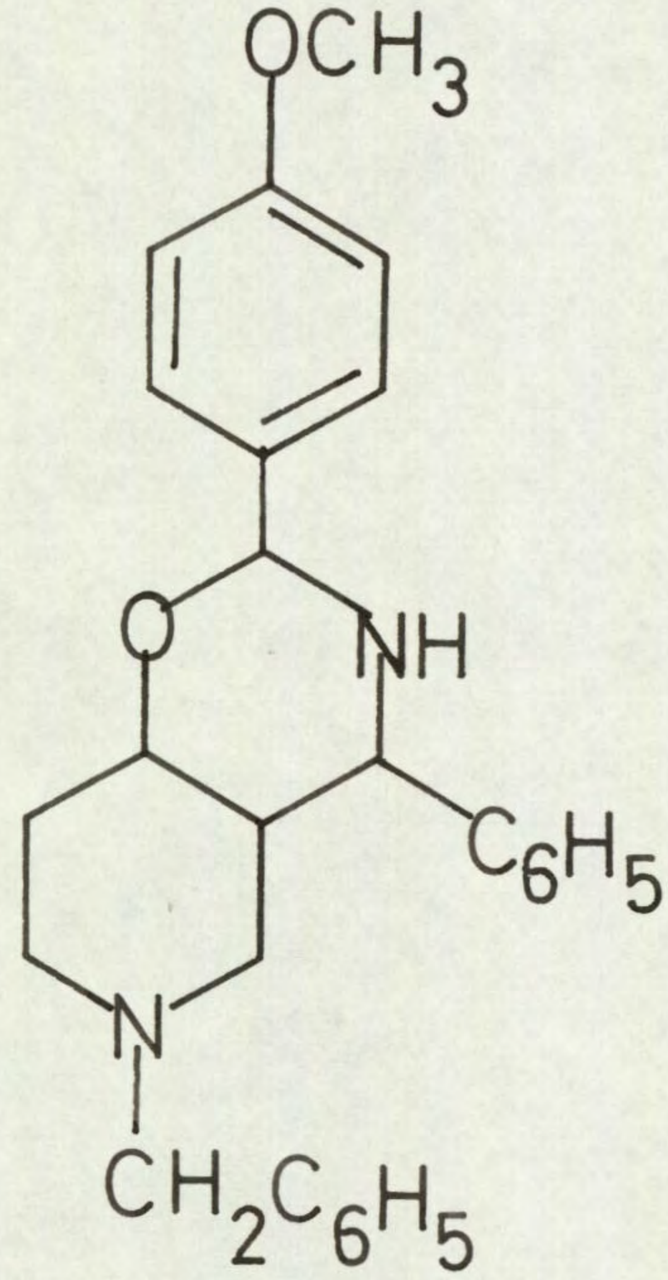
N.M.R.: τ ($CDCl_3$), 2.8 (M, 14H), 4.7 (D, H), 5.7 (D, H), 5.9 (S, H), 6.25 (S, 3H), 6.6 (Q, 2H), 7.4-8.3

(M, 8H).

τ ($CDCl_3$ + D_2O), 2.8 (M, 14H), 4.7 (S, H), 5.7 (S, H), 5.9 (S, H), 6.25 (S, 3H), 6.6 (Q, 2H), 7.4-8.3 (M, 7H).

Analysis Found: C, 78.4; H, 7.2; N, 6.9%; equiv., 207. $C_{27}H_{30}N_2O_2$ requires : C, 78.3; H, 7.2; N, 6.8%; equiv., 207.

6-Benzyl-octahydro-2H-2-(p-methoxyphenyl)-4-phenyl-pyrido[3,4,e][1,3]oxazine



In a similar manner, 1-benzyl-3-α-phenylaminomethyl-4-piperidinol (isomer A) (3 g.), anisaldehyde (1.23 ml.) and toluene (50 ml.) gave a solid (4.25 g.) which crystallised from ethanol/pet. ether (100-120°) to give

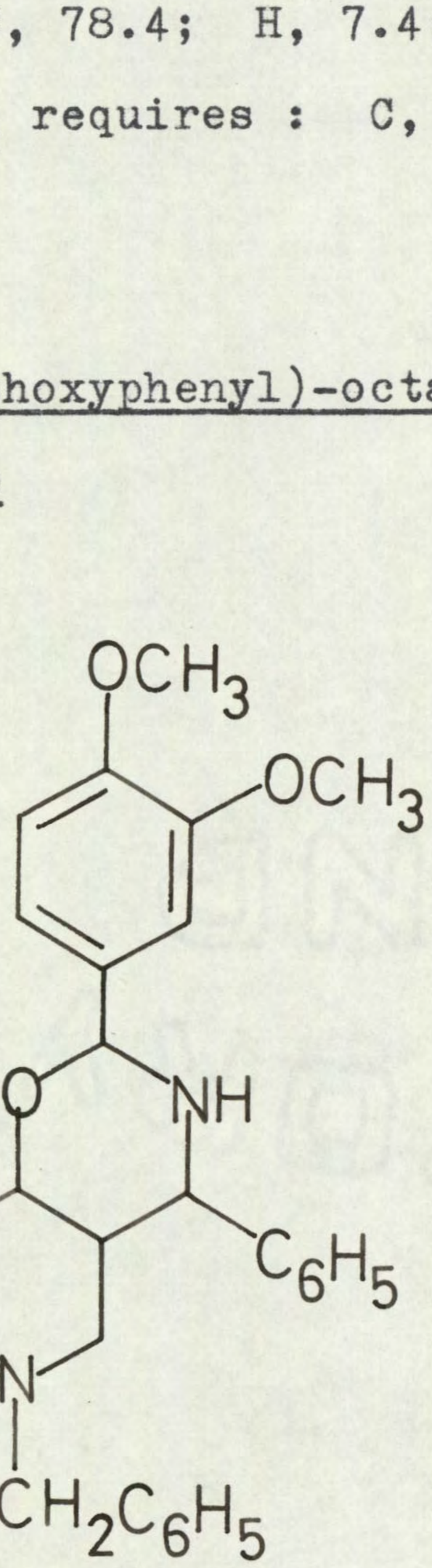
<u>6-benzyl-octahydro-2H-2-(p-methoxyphenyl)-4-phenyl-pyrido[3,4,e][1,3]oxazine (isomer A)</u> (3.21 g.), as white needles, m.p. 110°.

<u>Infra-red</u>: $\nu_{max.}$ (Nujol), 1250 cm.$^{-1}$ (C-O-C).

<u>N.M.R.</u>: τ ($CDCl_3$), 2.75 (M, 14H), 4.7 (D, H), 5.6 (D, H), 5.9 (S, H), 6.25 (S, 3H), 6.6 (Q, 2H), 7.2-8.3 (M, 8H).

<u>Analysis</u> Found: C, 78.4; H, 7.4; N, 6.8%; equiv., 203. $C_{27}H_{30}N_2O_2$ requires : C, 78.3; H, 7.2; N, 6.8%; equiv., 207.

<u>6-Benzyl-2(3,4-dimethoxyphenyl)-octahydro-2H-4-phenyl-pyrido[3,4,e][1,3]oxazine</u>



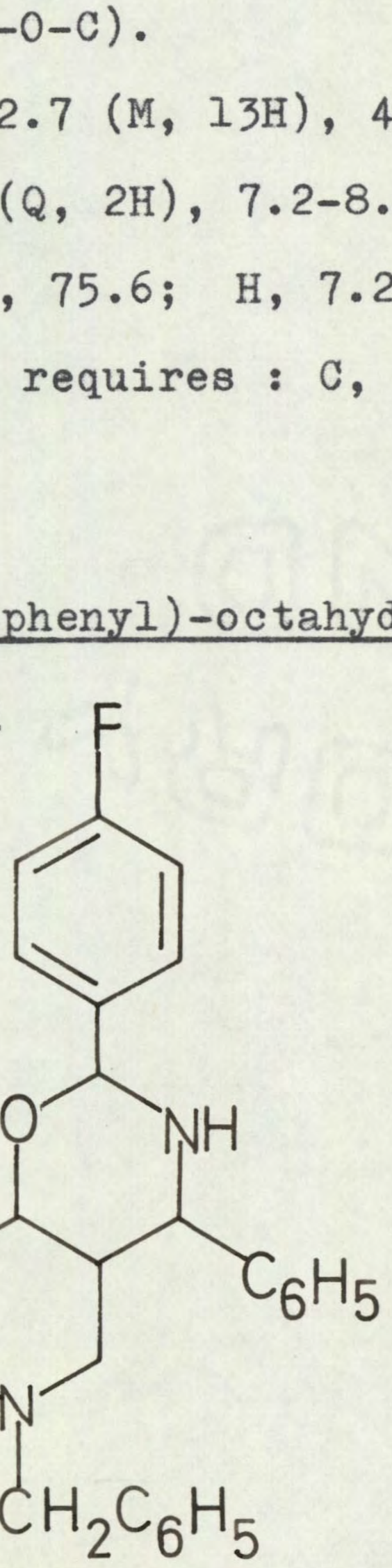
1-Benzyl-3-α-phenylaminomethyl-4-piperidinol (isomer A) (4 g.), 3,4-dimethoxybenzaldehyde (2.12 g.) and toluene (150 ml.) gave in a similar manner a brown solid (6.2 g.) which crystallised from pet. ether (100-120°) to give 6-benzyl-2-(3,4-dimethoxyphenyl)-octahydro-2H-4-phenyl-pyrido[3,4,e][1,3]oxazine (isomer A) (5.5 g.), as white needles, m.p. 112°.

Infra-red: $\nu_{max.}$ (Nujol), 3300 cm.$^{-1}$ (NH), 1240 cm.$^{-1}$, 1260 cm.$^{-1}$ (C-O-C).

N.M.R.: τ($CDCl_3$), 2.7 (M, 13H), 4.7 (S, H), 5.9 (S, H), 6.1 (S, 6H), 6.6 (Q, 2H), 7.2-8.3 (M, 8H).

Analysis Found: C, 75.6; H, 7.2; N, 6.5%; equiv., 220. $C_{28}H_{32}N_2O_3$ requires : C, 75.7; H, 7.2; N, 6.3%; equiv., 222.

6-Benzyl-2-(p-fluorophenyl)-octahydro-2H-4-phenyl-pyrido[3,4,e][1,3]oxazine



Isomer A In a similar manner, 1-benzyl-3-α-phenylaminomethyl-4-piperidinol (isomer A) (1 g.), p-fluorobenzaldehyde (.4 g.) and toluene (50 ml.) gave a pale yellow solid, which crystallised from pet. ether (100-120°), to give 6-benzyl-2-(p-fluorophenyl)-octahydro-2H-4-phenyl-pyrido[3,4,e][1,3]oxazine (isomer A) (1.35 g.), as white prisms, m.p. 124°.

N.M.R.: $\tau(CDCl_3)$, 2.7 (M, 14H), 4.6 (S, H), 5.6 (S, H), 5.9 (D, H), 6.6 (Q, 2H), 7.2-8.3 (M, 8H).

Analysis Found: C, 77.7; H, 6.7; N, 6.8%; equiv., 203. $C_{26}H_{27}FN_2O$ requires : C, 77.6; H, 6.7; N, 7.0%; equiv., 201.

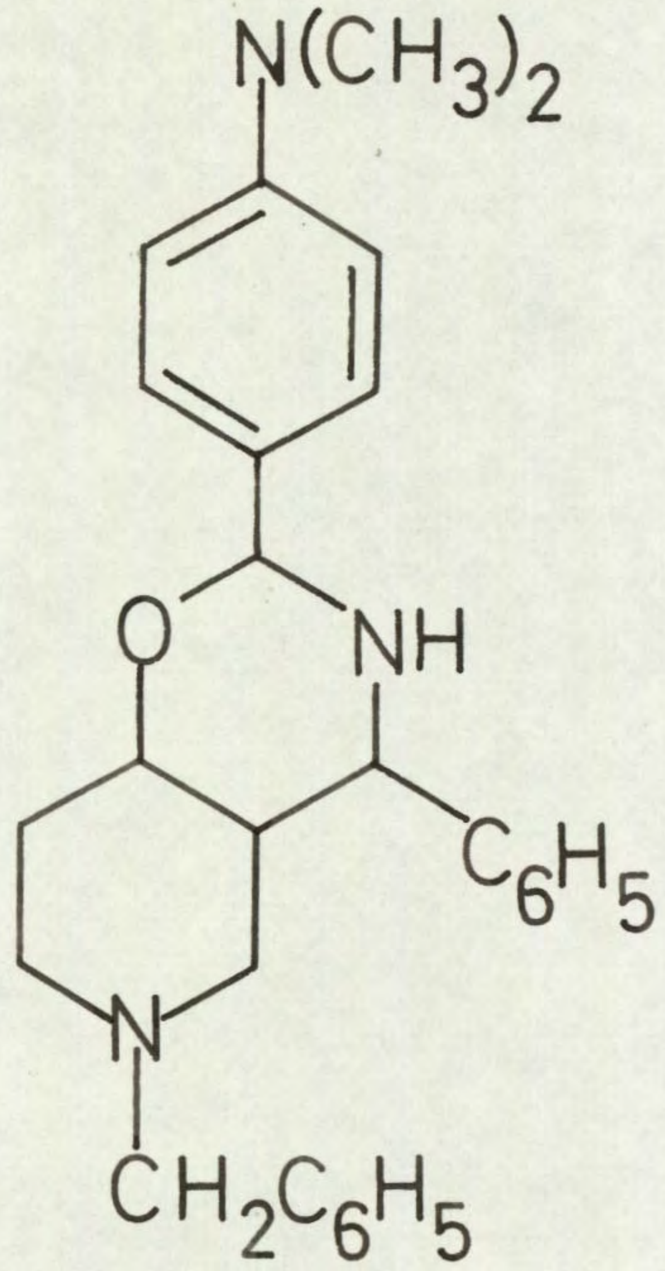
Isomer B 1-Benzyl-3-α-phenylaminomethyl-4-piperidinol (isomer B) (3 g.), p-fluorobenzaldehyde (1.26 g.) and toluene (50 ml.) gave by the same method a white solid which crystallised from pet. ether (100-120°) to give 6-benzyl-2-(p-fluorophenyl)-octahydro-2H-4-phenyl-pyrido[3,4,e][1,3]oxazine (isomer B) (4 g.), as white leaves, m.p. 121°.

Infra-red: $\nu_{max.}$ (Nujol), 3300 $cm.^{-1}$ (NH).

N.M.R.: $\tau(CDCl_3)$, 2.75 (M, 14H), 4.6 (S, H), 6.2 (S, H), 6.4 (S, H), 6.6 (Q, 2H), 7.0-8.4 (M, 8H).

Analysis Found: C, 77.6; H, 6.8; N, 7.1%; equiv., 206. $C_{26}H_{27}FN_2O$ requires : C, 77.6; H, 6.7; N, 7.0%; equiv., 201.

6-Benzyl-2(p-dimethylaminophenyl)-octahydro-2H-4-phenyl-pyrido[3,4,e][1,3]oxazine



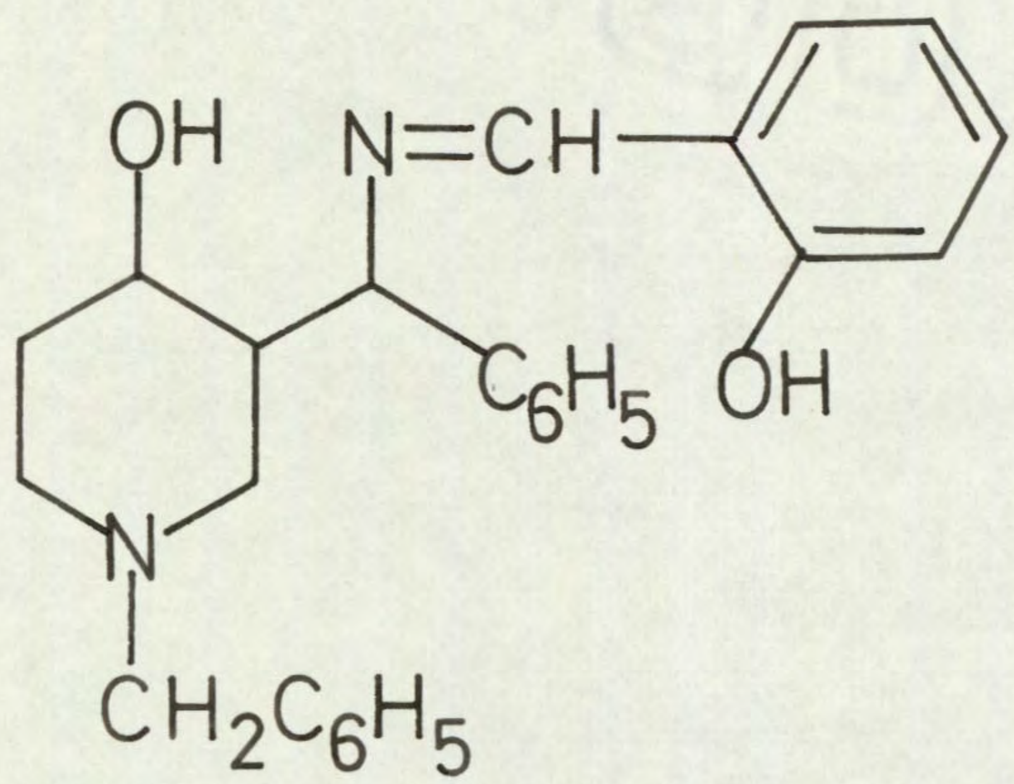
1-Benzyl-3-α-phenylaminomethyl-4-piperidinol (isomer A) (1 g.) was refluxed with p-dimethylamino-benzaldehyde (.505 g.) in toluene (50 ml.), with a water separator, until dry. The solvent was evaporated, yielding a clear colourless oil (1.5 g.). The infra-red spectrum of this oil had a broad peak centred on 3300 $cm.^{-1}$, suggestive of OH, and a sharp peak at 1640 $cm.^{-1}$, suggestive of C=N. The oil was dissolved in toluene (50 ml.), acetic acid (1 ml.) added and the mixture refluxed for 1 hour. Evaporation of the solvents gave a red oil which solidified on scratching. Crystallisation of the solid from pet. ether (100-120°) gave 6-benzyl-2-

(p-dimethylaminophenyl)-octahydro-2H-4-phenyl-pyrido [3,4,e] [1,3] oxazine (isomer A) (1.2 g.), as white needles, m.p. 136°.

N.M.R.: τ($CDCl_3$), 2.75 (M, 14H), 4.6 (S, H), 5.6 (S, H), 5.9 (S, H), 6.6 (Q, 2H), 7.1 (S, 6H), 7.3-8.3 (M, 8H).

Analysis Found: C, 78.7; H, 7.8; N, 10.0%; equiv., 150. $C_{28}H_{33}N_3O$ requires : C, 78.7; H, 7.7; N, 9.8%; equiv., 142.

α(1-Benzyl-4-hydroxy-3-piperidyl)-N-(o-hydroxybenzylidine)benzylamine



1-Benzyl-3-α-phenylaminomethyl-4-piperidinol (isomer A) (1 g.) in toluene (50 ml.) was refluxed with salicylaldehyde (.36 ml.) with a water separator until dry. Evaporation of the solvent gave a yellow oil which crystallised from ethanol/pet. ether (100-120°) to give

α(1-benzyl-4-hydroxy-3-piperidyl)-N-(o-hydroxybenzylidine)benzylamine (isomer A) (1.11 g.), as yellow prisms, m.p. 142.5°.

Infra-red: $\nu_{max.}$ (Nujol), 3550 cm.$^{-1}$ (OH), 1620 cm.$^{-1}$ (C=N), 1290 cm.$^{-1}$ (C-O-C).

$\nu_{max.}$ ($CHCl_3$), 3600 cm.$^{-1}$ (OH), 3450 cm.$^{-1}$ (OH), 1630 cm.$^{-1}$ (C=N).

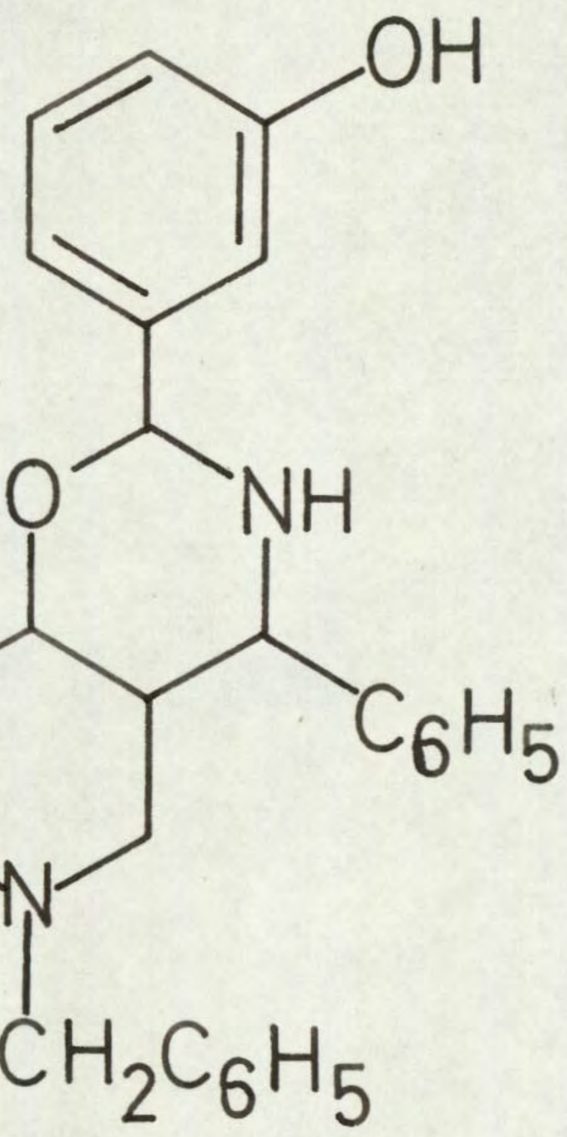
Ultra-violet: $\lambda_{max.}$ (EtOH), 208 mμ (31000), 223 mμ (21100), 256 mμ (14400), 262 mμ (12700), 316 mμ (4220).

N.M.R.: τ($CDCl_3$), -3.4 (S, H), 1.7 (S, H), 2.7 (M, 14H), 5.6 (D, H), 6.6 (Q, 2H), 7.0-8.8 (M, 8H).

τ($CDCl_3$ + D_2O), ---, 1.7 (S, H), 2.7 (M, 14H), 5.6 (D, H), 6.6 (Q, 2H), 7.0-8.8 (M, 7H).

Analysis Found: C, 78.1; H, 7.0; N, 7.0%; equiv., 198. $C_{26}H_{28}N_2O_2$ requires : C, 78.0; H, 7.0; N, 7.0%; equiv., 200.

6-Benzyl-octahydro-2H-2-(m-hydroxyphenyl)-4-phenyl-pyrido[3,4,e][1,3]oxazine



Isomer A 1-Benzyl-3-α-phenylaminomethyl-4-piperidinol (isomer A) (1 g.) in toluene (50 ml.) with m-hydroxybenzaldehyde (.39 g.) gave in a similar manner a pale yellow solid which crystallised from ethanol to give 6-benzyl-octahydro-2H-2-(m-hydroxyphenyl)-4-phenyl-pyrido[3,4,e][1,3]oxazine (isomer A) (1.03 g.), as colourless prisms, m.p. 179°.

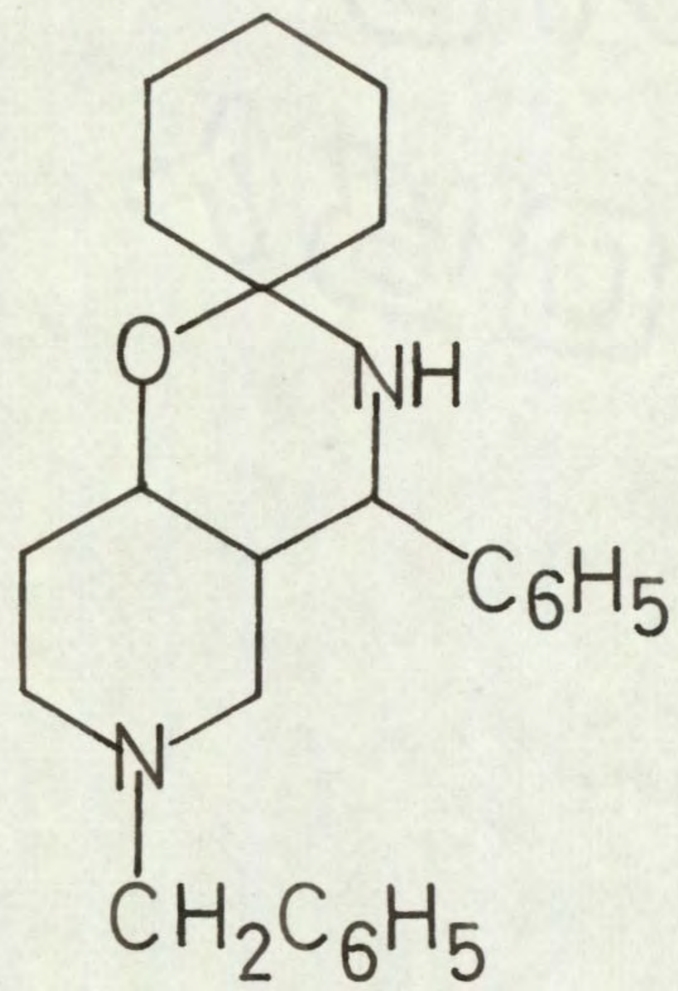
Infra-red: $\nu_{max.}$ (Nujol), 3300 cm.$^{-1}$ (NH), 2400 cm.$^{-1}$-3400 cm.$^{-1}$ (OH).

Analysis Found: C, 77.9; H, 7.2; N, 6.8%; equiv., 193. $C_{26}H_{28}N_2O_2$ requires : C, 78.0; H, 7.0; N, 7.0%; equiv., 200.

Isomer B 1-Benzyl-3-α-phenylaminomethyl-4-

piperidinol (isomer B) (1 g.) in toluene (50 ml.) was reacted similarly with m-hydroxybenzaldehyde (.39 g.). Evaporation of the solvent gave a pale brown oil (1.3 g.) which could not be crystallised. An infra-red spectrum of this oil was similar to that of isomer A, but no solid was obtained.

Spiro{cyclohexyl(1,2'-6'-benzyl-octahydro-2'H-4'-phenyl-pyrido[3',4'e][1',3']oxazine)}



1-Benzyl-3-α-phenylaminomethyl-4-piperidinol (isomer A) (1 g.) was refluxed with toluene (50 ml.) and cyclohexanone (.35 ml.), with a water separator, until dry. Evaporation of the solvents yielded a colourless oil which solidified with difficulty. Crystallisation of the solid from pentane gave spiro{cyclohexyl(1,2'-6'-

benzyl-octahydro-2'H-4'-phenyl-pyrido[3',4',e'][1',3'] oxazine)}(isomer A) (1.05 g.) as white needles, m.p. 94°.

Analysis Found: C, 78.4; H, 8.5; N, 7.2%; equiv., 200. $C_{25}H_{32}N_2O_2$ requires : C, 76.5; H, 8.2; N, 7.2%; equiv., 196.

The compound proved difficult to crystallise and gradually decomposed, on allowing to stand, to a yellow tacky solid.

Attempted cyclisation with acetophenone

1-Benzyl-3-α-phenylaminomethyl-4-piperidinol (isomer A) (1 g.) was reacted in a similar manner with acetophenone (.4 ml.) in toluene (50 ml.) to give a clear colourless oil which did not solidify. Thin layer chromatography and an infra-red spectrum suggested that the oil contained unreacted starting material.

Attempted cyclisation with formaldehyde

1-Benzyl-3-α-phenylaminomethyl-4-piperidinol (isomer A) (1 g.) was reacted in a similar manner with 40% formalin (1 ml.) in toluene (50 ml.) to yield a white solid (1 g.) on evaporation of the solvents. The solid proved difficult to crystallise and tended to decompose on standing. An infra-red spectrum suggested that the oxazine had been synthesised, but due to the

instability the compound was not characterised.

Attempted cyclisation with 3,4-dihydroxybenzaldehyde

1-Benzyl-3- α -phenylaminomethyl-4-piperidinol (isomer A) (3 g.) in toluene (50 ml.) was refluxed in a similar manner with 3,4-dihydroxybenzaldehyde (1.4 g.), yielding a black tar. An infra-red spectrum showed the presence of unreacted material. The products could not be crystallised.

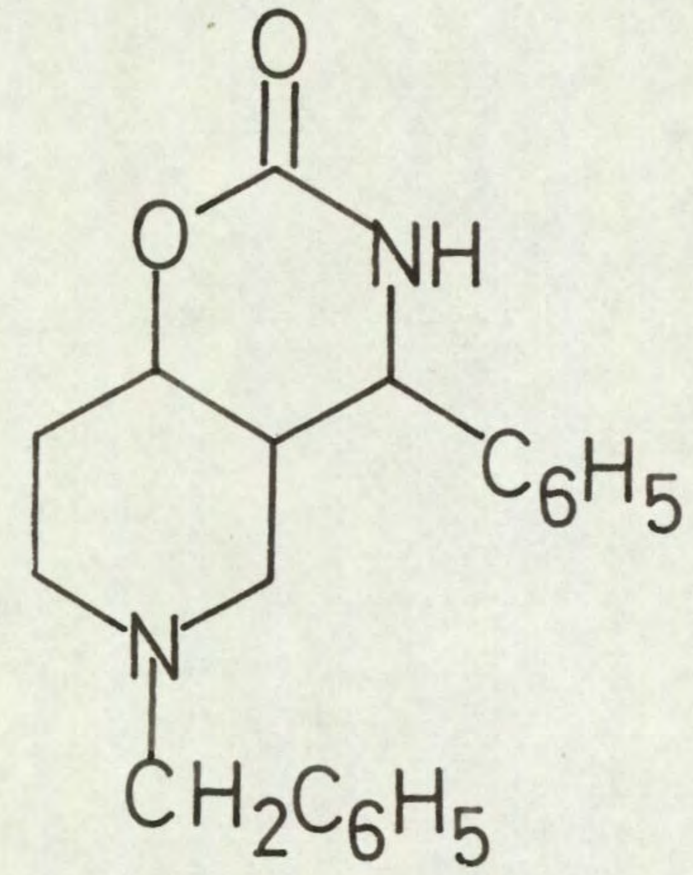
Attempted cyclisation with p-hydroxybenzaldehyde

1-Benzyl-3-α-phenylaminomethyl-4-piperidinol (isomer A) (1 g.) was reacted in a similar manner in toluene (50 ml.) with p-hydroxybenzaldehyde (.412 g.) to give a brown oil which would not crystallise. An infra-red spectrum suggested that the uncyclised product had been obtained.

Attempted cyclisation with acetone

1-Benzyl-3- α -phenylaminomethyl-4-piperidinol (isomer A) (1 g.) was refluxed in acetone (50 ml.) for 1 hour. Benzene (50 ml.) was added and the solvents distilled slowly, yielding starting material (1 g.), identical with authentic material by infra-red spectroscopy and thin layer chromatography.

6-Benzyl-octahydro-2-oxo-4-phenyl-pyrido[3,4,e][1,3]oxazine



1-Benzyl-3-α-phenylaminomethyl-4-piperidinol (isomer A) (1 g.) was dissolved in benzene (100 ml.), sodium bicarbonate (5 g.) added and 12% w/v of phosgene in benzene (20 ml.) added dropwise to the stirred solution. The solution was stirred for .5 hours, filtered, the precipitate washed in benzene and extracted with boiling ethanol (3 x 50 ml.). Evaporation of the alcohol and crystallisation of the residue in alcohol gave 6-benzyl-octahydro-2-oxo-4-phenyl-pyrido[3,4,e][1,3] oxazine (isomer A) (.7 g.), as white prisms, m.p. 243°.

Infra-red: $\nu_{max.}$ (Nujol), 3230 cm.$^{-1}$, 3100 cm.$^{-1}$ (NH), 1690 cm.$^{-1}$ (C=O), 1295 cm.$^{-1}$ (C-O).

$\nu_{max.}$ ($CHCl_3$), 3450 cm.$^{-1}$, 3250 cm.$^{-1}$ (NH), 1700 cm.$^{-1}$ (C=O).

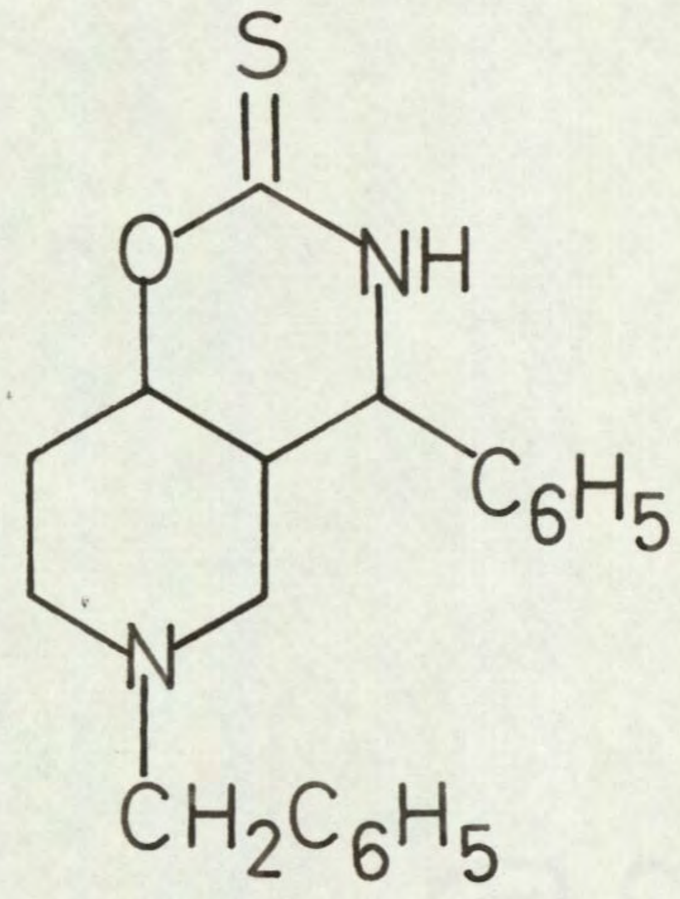
N.M.R.: τ($CDCl_3$), 2.8 (D, 10H), 3.8 (S, H), 5.2 (D, H), 5.3 (S, H), 6.6 (Q, 2H), 7.4-8.3 (M, 7H).

τ ($CDCl_3$ + D_2O), 2.8 (D, 10H), ---, 5.2 (D, H), 5.3 (S, H), 6.6 (Q, 2H), 7.4-8.3 (M, 7H).

A mass spectrum gives a M^+ peak at 322.

Analysis Found: C, 74.8; H, 6.7; N, 8.8%; equiv., 312. $C_{20}H_{22}N_2O_2$ requires : C, 74.5; H, 6.8; N, 8.7%; equiv., 322.

6-Benzyl-octahydro-4-phenyl-2-sulphinyl-pyrido [3,4,e][1,3]oxazine



To a solution of 1-benzyl-3-α-phenylaminomethyl-4-piperidinol (isomer A) (5 g.) in benzene (100 ml.) carbon disulphide (10 ml.) was added and the mixture refluxed for .5 hours. A white solid separated (5.1 g.), which was filtered and dissolved in digol (10 ml.), H_2S being evolved. On allowing to stand, a small amount of colourless crystals were obtained (1.4 g.), which crystallised from toluene to give 6-benzyl-octahydro-4-

<u>phenyl-2-sulphinyl-pyrido[3,4,e][1,3]oxazine (isomer A)</u>

as white needles, m.p. 273°.

<u>Infra-red</u>: $\nu_{max.}$ (Nujol), 3150 cm.$^{-1}$ (NH), 1550 cm.$^{-1}$ (C-N), 1300 cm.$^{-1}$ (C=S), 1170 cm.$^{-1}$ (C=S), 700 cm.$^{-1}$, 740 cm.$^{-1}$, 765 cm.$^{-1}$ (C_6H_5).

<u>Analysis</u> Found: C, 71.1; H, 6.6; N, 8.3%; equiv., 326. $C_{20}H_{22}N_2OS$ requires : C, 71.0; H, 6.5; N, 8.3%; equiv., 338.

<u>Attempted reactions of 6-benzyl-octahydro-2-oxo-4-phenyl-pyrido[3,4,e][1,3]oxazine with amines</u>

a) Dry ammonia was passed into a cooled suspension of 6-benzyl-octahydro-2-oxo-4-phenyl-pyrido[3,4,e][1,3] oxazine (.5 g.) in absolute ethanol (100 ml.). The solution was allowed to stand for 24 hours and the solvent evaporated to give starting material (.5 g.), m.p. undepressed on admixture with an authentic sample.

b) 6-Benzyl-octahydro-2-oxo-4-phenyl-pyrido[3,4,e][1,3] oxazine (.5 g.) was refluxed in toluene (25 ml.) with benzylamine (.2 g.) for 4 hours. The presence of water was not observed. The solvents were evaporated to give starting material (.5 g.), m.p. undepressed on admixture with an authentic sample.

c) 6-Benzyl-octahydro-2-oxo-4-phenyl-pyrido[3,4,e][1,3] oxazine (.25 g.) in ethanol (100 ml.) and hydrazine

hydrate (.25 g.) was allowed to stand for 100 hours. Evaporation of the solvents gave starting material (.25 g.), m.p. undepressed on admixture with an authentic sample.

d) Dry ammonia was passed into a suspension of 6-benzyl-octahydro-2-oxo-4-phenyl-pyrido[3,4,e][1,3]oxazine (1 g.) in ethanol (50 ml.) in a tube cooled in acetone/CO_2. The tube was sealed and heated to 140° for 24 hours. Evaporation of the solvent gave a yellow oil (1 g.) from which no solid compound could be obtained.

Attempted reactions of 6-benzyl-octahydro-4-phenyl-2-sulphinyl-pyrido[3,4,e][1,3]oxazine

a) 6-Benzyl-octahydro-4-phenyl-2-sulphinyl-pyrido [3,4,e][1,3]oxazine (.5 g.) and benzylamine (1 ml.) were refluxed in toluene (50 ml.) for 24 hours. Evaporation of the solvent gave starting material (.5 g.), m.p. undepressed on admixture with an authentic sample.

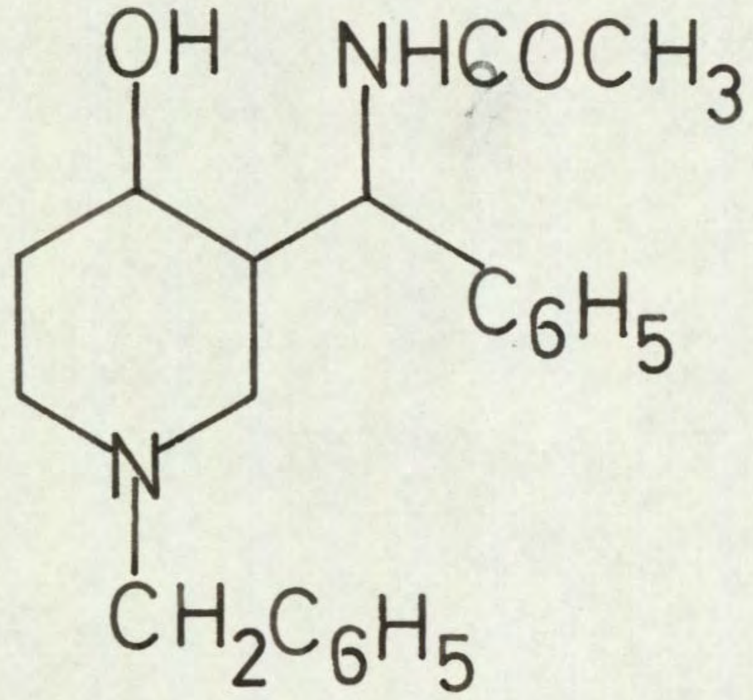
b) 6-Benzyl-octahydro-4-phenyl-2-sulphinyl-pyrido[3,4,e] [1,3]oxazine (.5 g.), hydrazine hydrate (.5 ml.) in toluene (50 ml.) refluxed for 24 hours gave, on evaporation of the solvent, starting material (.5 g.), m.p. undepressed on admixture with an authentic sample.

c) 6-Benzyl-octahydro-4-phenyl-2-sulphinyl-pyrido

[3,4,e][1,3]oxazine (.5 g.) was suspended in a saturated solution of ammonia in ethanol (50 ml.). The mixture was placed in a sealed tube and heated to 140° for 24 hours. Evaporation of the solvent gave an oil, thin layer chromatography of which showed a number of spots, one of which could be compared with starting material.

Hydrolysis of N{α[4-acetoxy-1-benzyl-3-piperidyl]benzyl}acetamide

N{α[1-Benzyl-4-hydroxy-3-piperidyl]benzyl}acetamide



Isomer B To a solution of N{α[4-acetoxy-1-benzyl-3-piperidyl]benzyl}acetamide (isomer B) (500 mg.) in absolute ethanol (90 ml.) kept at 0°C was added 5% KOH in ethanol (10 ml.). The solution was stirred while aliquots were taken every 3 minutes and chromatographed on a thin layer plate. After 40 minutes, the solution was diluted with water (200 ml.) and extracted with

chloroform (2 x 50 ml.). Evaporation of the chloroform yielded a clear colourless oil which crystallised from ethyl acetate/pet. ether (80-100°) to give N{α[1-benzyl-4-hydroxy-3-piperidyl]benzyl}acetamide (isomer B) (0.3 g.), m.p. 176°.

Infra-red: $\nu_{max.}$ (Nujol), 3240 cm.$^{-1}$ (NH), 3080 cm.$^{-1}$ (OH), 1630 cm.$^{-1}$ (amide I), 1555 cm.$^{-1}$ (amide II), 1070 cm.$^{-1}$ (equ. OH).

Analysis Found: C, 74.7; H, 7.6; N, 8.2%; equiv., 331. $C_{21}H_{26}N_2O_2$ requires : C, 74.6; H, 7.7; N, 8.3%; equiv., 338.

Isomer A N{α[4-Acetoxy-1-benzyl-3-piperidyl]benzyl}acetamide (isomer A) (500 mg.) in absolute ethanol (90 ml.) with 5% KOH in ethanol (10 ml.) at 0° under identical conditions gave starting material (.4 g.), m.p. undepressed with an authentic sample.

Attempted reaction of 1-benzyl-1,2,5,6-tetrahydro-4-hydroxy-3-phenylimino-pyridine with hydroxylamine

To a solution of hydroxylamine hydrochloride (0.5 g.) and sodium acetate (1 g.) in water (10 ml.) was added 1-benzyl-1,2,5,6-tetrahydro-4-hydroxy-3-phenyl-imino-pyridine (1 g.) in ethanol (50 ml.). The mixture was warmed on a steam bath, allowed to stand for 24 hours, the alcohol evaporated under reduced pressure and the

aqueous solution extracted with chloroform (2 x 20 ml.), yielding a yellow oil on evaporation of the organic extract. An infra-red spectrum of this oil showed a band at 3300 $cm.^{-1}$, attributed to enolic OH. Attempts to solidify the oil failed.

The impure oxime (.1 g.) in ethanol (50 ml.) was shaken with hydrogen at atmospheric pressure in the presence of platinum oxide (50 mg.). No uptake of hydrogen was observed. Filtration of the solution and evaporation of the solvent yielded a pale yellow oil (.1 g.), an infra-red spectrum of which was identical with the starting oil.

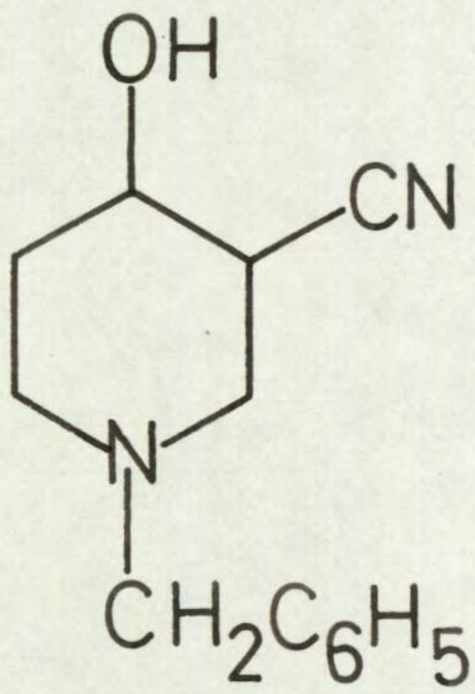
Sodium borohydride (.5 g.) was added to the oxime oil (.7 g.) in ethanol (10 ml.) and stirred for 1 hour. Addition of water (20 ml.), evaporation of the ethanol, extraction of the aqueous solution with ether and evaporation of the ether extracts gave an oil (.5 g.), an infra-red spectrum of which was similar to one of 1-benzyl-3-α-phenylaminomethyl-4-piperidinol. Thin layer chromatography of the oil showed three major spots, two of which were similar to the two isomers of 1-benzyl-3-α-phenylaminomethyl-4-piperidinol. Attempts to crystallise the oil failed.

The impure oxime (.7 g.) in benzene (50 ml.) was added dropwise to a stirred solution of $LiAlH_4$ (.5 g.) in

ether (20 ml.). The solution was refluxed for 1 hour and decomposed with a saturated solution of sodium potassium tartrate. Separation and evaporation of the organic layers yielded a pale yellow oil (.6 g.) with an infra-red spectrum similar to 1-benzyl-3-α-phenyl-aminomethyl-4-piperidinol. Once again thin layer chromatography showed the presence of three major spots. All attempts to crystallise the compound failed.

B(iv) REDUCTION OF 1-BENZYL-3-CYANO-4-PIPERIDONE HYDRO-CHLORIDE

1-Benzyl-3-cyano-4-piperidinol



Sodium borohydride (3 g.) was added to 1-benzyl-3-cyano-4-piperidone hydrochloride (5 g.) in methanol (100 ml.) and water (100 ml.). The mixture was allowed to stand for 18 hours, the inorganic solid filtered off and the filtrate extracted with benzene (2 x 100 ml.).

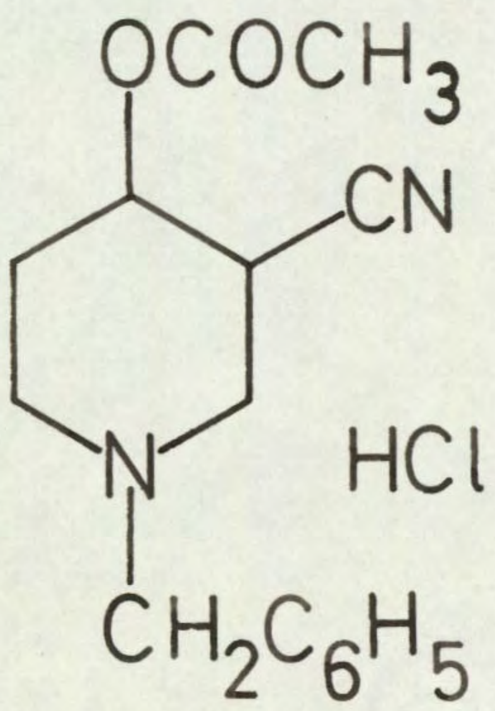
The benzene extracts were dried (anhy. Na_2SO_4) and evaporated, yielding a colourless oil (2.9 g.) which crystallised on allowing to stand. Recrystallisation from ethyl acetate gave 1-benzyl-3-cyano-4-piperidinol (2.05 g.), as colourless needles, m.p. 108°.

Infra-red: $\nu_{max.}$ (Nujol), 3200 cm.$^{-1}$ (OH), 2250 cm.$^{-1}$ (C≡N), 1070 cm.$^{-1}$ (equ. OH).

Analysis Found: C, 72.5; H, 7.5; N, 12.9%; equiv., 215. $C_{13}H_{16}N_2O$ requires : C, 72.2; H, 7.4; N, 13.0%; equiv., 216.

Attempts to obtain a second isomer from the oil, after evaporation of the solvent, failed. Thin layer chromatography on the oil, compared with the solid obtained, suggested that the isomer obtained as a solid also formed the greater part of the oil. An attempt to form a solid hydrochloride of the oil failed.

4-Acetoxy-1-benzyl-3-cyano-piperidine hydrochloride

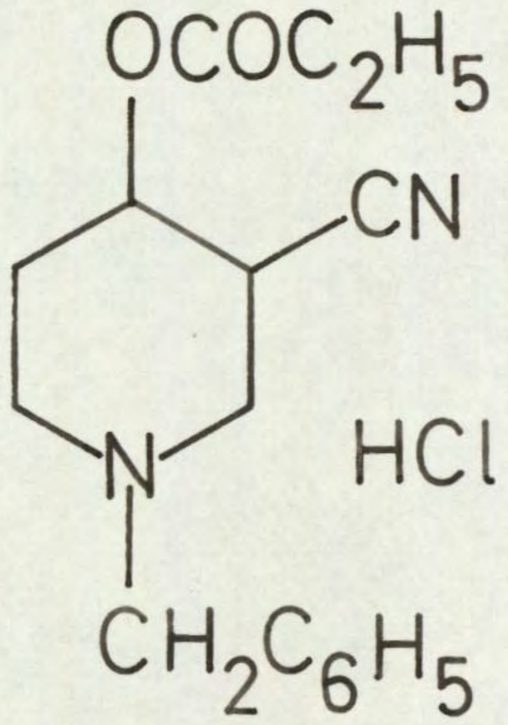


1-Benzyl-3-cyano-4-piperidinol (2 g.) was refluxed in pyridine (3 ml.) and acetic anhydride (3 ml.) for 3 hours. Evaporation of the solvent under reduced pressure gave a brown oil, which was dissolved in ethanolic HCl and allowed to stand. A solid was obtained which gave on crystallisation from ethanol/ether 4-acetoxy-1-benzyl-3-cyano-piperidine hydrochloride (1.4 g.), as white plates, m.p. 224°.

Infra-red: $\nu_{max.}$ (Nujol), 2500 cm.$^{-1}$ - 2700 cm.$^{-1}$ ($\overset{+}{N}H$), 2250 cm.$^{-1}$ (C≡N), 1740 cm.$^{-1}$ (C=O), 1220 cm.$^{-1}$ (C-O).

Analysis Found: C, 61.4; H, 6.9; N, 9.6%; equiv., 295. $C_{15}H_{19}ClN_2O_2$ requires : C, 61.1; H, 6.5; N, 9.5%; equiv., 295.

1-Benzyl-3-cyano-4-propionoxy-piperidine hydrochloride

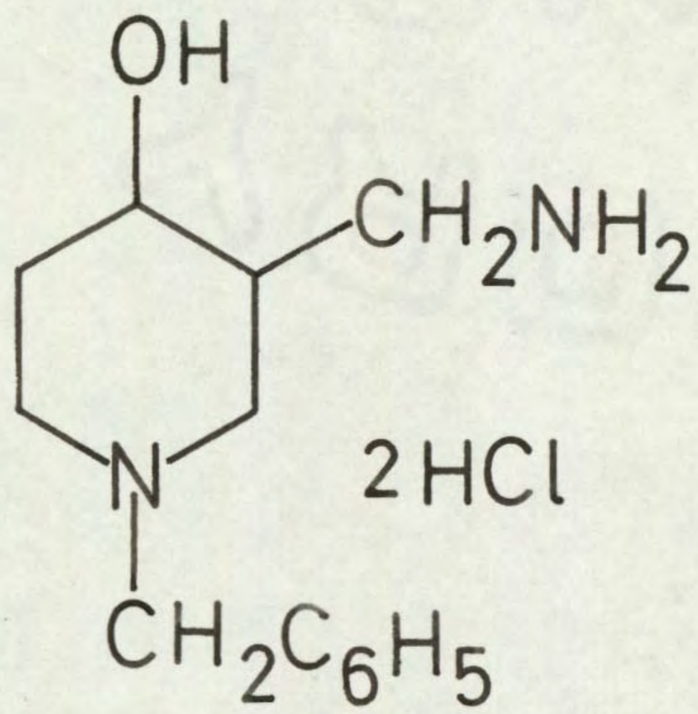


1-Benzyl-3-cyano-4-piperidinol (1 g.) refluxed for 1 hour in pyridine (3 ml.) and propionic anhydride (3 ml.) similarly gave 1-benzyl-3-cyano-4-propionoxy-piperidine hydrochloride (.2 g.), as white prisms from ethanol/ether, m.p. 198°.

Infra-red: $\nu_{max.}$ (Nujol), 2500 cm.$^{-1}$ ($\overset{+}{N}H$), 2250 cm.$^{-1}$ (C≡N), 1740 cm.$^{-1}$ (C=O), 1180 cm.$^{-1}$ (C-O).

Analysis Found: C, 62.3; H, 6.9; N, 8.9%; equiv., 320. $C_{16}H_{21}ClN_2O_2$ requires : C, 62.2; H, 6.9; N, 9.1%; equiv., 309.

3-Aminomethyl-1-benzyl-4-piperidinol dihydrochloride



Two methods of synthesising this compound were tried, one of which was successful.

a) 1-Benzyl-3-cyano-4-piperidinol (14 g.) in benzene (200 ml.) was added dropwise to a stirred solution of $LiAlH_4$ (5 g.) in ether (100 ml.). The mixture was stirred for 14 hours, decomposed with a saturated

solution of sodium potassium tartrate and the organic layers separated and dried (anhy. Na_2SO_4). Evaporation of the solvent gave a pale yellow oil (14 g.) which solidified on standing. The solid (4 g.) was dissolved in ethanolic HCl and allowed to stand. A white crystalline solid was obtained, which recrystallised from ethanol to give 3-aminomethyl-1-benzyl-4-piperidinol dihydrochloride (2 g.), as white needles, m.p. 265°.

Infra-red (Base): $\nu_{max.}$ (Nujol), 3350 cm.$^{-1}$, 3200 cm.$^{-1}$ (OH, NH_2), 1620 cm.$^{-1}$ (C-N), 1060 cm.$^{-1}$ (equ. OH).

(Salt): $\nu_{max.}$ (Nujol), 3350 cm.$^{-1}$ (OH), $\overset{+}{(NH)}$ 2500 cm.$^{-1}$ - 2800 cm.$^{-1}$, 1080 cm.$^{-1}$ (equ. OH).

Ultra-violet: $\lambda_{max.}$ (EtOH), 258 mμ (313), 220 mμ (1750).

Analysis Found: C, 531; H, 7.7; N, 9.4%; equiv., 152. $C_{13}H_{22}Cl_2N_2O$ requires : C, 53.2; H, 7.5; N, 9.6%; equiv., 147.

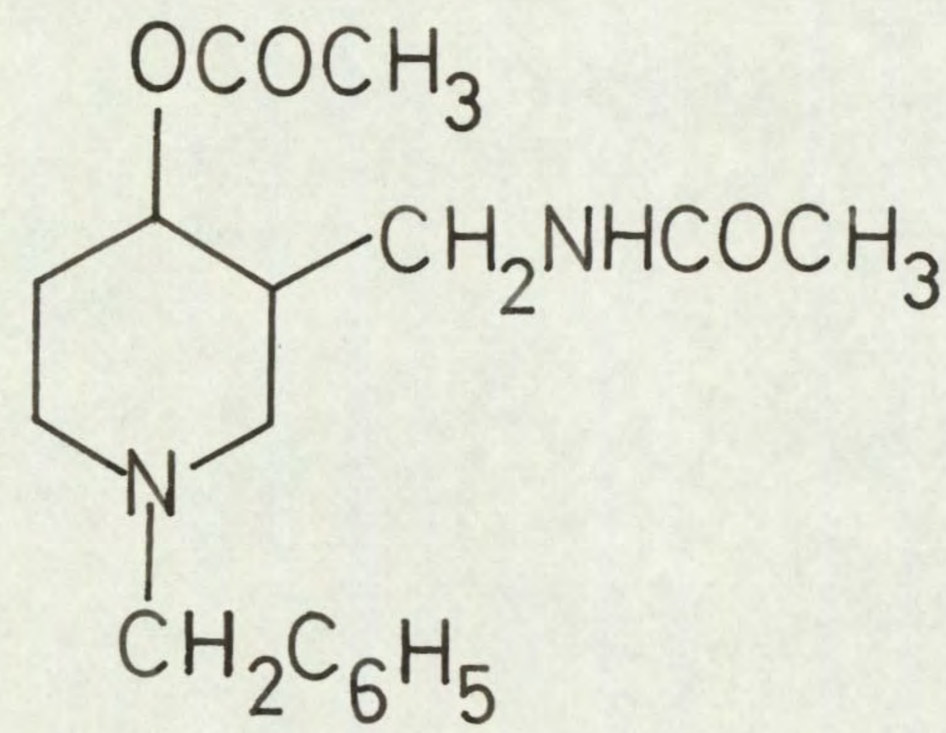
b) Finely powdered 1-benzyl-3-cyano-4-piperidone hydrochloride (5 g.) was added in small portions to a stirred suspension of $LiAlH_4$ (1 g.) in ether (200 ml.) and benzene (200 ml.). The solution was stirred for 2 hours and decomposed with a saturated solution of sodium potassium tartrate. The organic layer was separated, dried (anhy. Na_2SO_4) and evaporated, yielding

a colourless oil (3 g.). An infra-red spectrum of the product showed a band at 3300 cm.$^{-1}$, attributed to OH, and a peak at 2250 cm.$^{-1}$, attributed to C≡N. An equivalent weight determination gave 113 ($C_{13}H_{20}N_2O$ requires 110). Attempts to crystallise the oil failed. Dissolving the oil in ethanolic HCl failed to yield a solid hydrochloride.

The oil (.5 g.) was refluxed with pyridine (1 ml.) and acetic anhydride (1 ml.). After 1 hour the solution had darkened considerably, and evaporation of the solvents yielded a dark intractable bar which did not yield a solid.

Distillation of the oil under reduced pressure (1 mm.) merely decomposed the compound.

3-Acetamidomethyl-4-acetoxy-1-benzyl-piperidine



3-Aminomethyl-1-benzyl-4-piperidinol (8 g.) was refluxed in pyridine (15 ml.) and acetic anhydride (10 ml.) for 3 hours. Evaporation of the solvent gave a brown

oil which crystallised from ethyl acetate to give 3-acetamidomethyl-4-acetoxy-1-benzyl-piperidine (5 g.), as white needles, m.p. 121°.

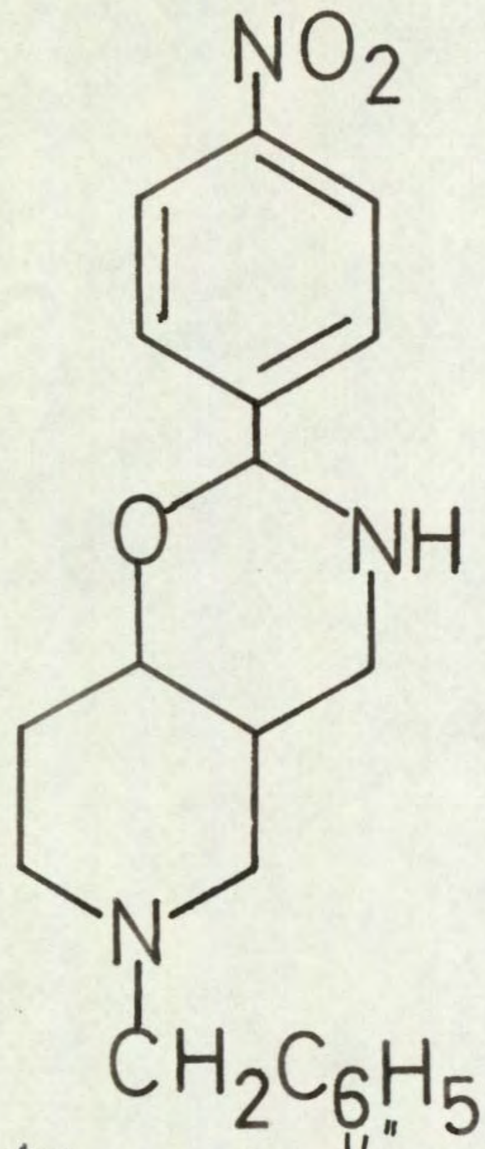
Infra-red: $\nu_{max.}$ (Nujol), 3350 cm.$^{-1}$ (NH), 1720 cm.$^{-1}$ (ester C=O), 1655 cm.$^{-1}$ (amide I), 1560 cm.$^{-1}$ (amide II), 1260 cm.$^{-1}$ (C-O).

Analysis Found: C, 67.0; H, 7.9; N, 9.2%; equiv., 298. $C_{17}H_{24}N_2O_3$ requires : C, 67.1; H, 7.9; N, 9.2%; equiv., 304.

An attempt to prepare the hydrochloride salt of this compound gave a very small yield of an impure solid, the infra-red spectrum of which did not contain an ester C=O at 1740 cm.$^{-1}$ but had a broad band at 3300 cm.$^{-1}$, attributable to OH. Titration in non-aqueous solvent gave an equiv. of 290 ($C_{15}H_{23}ClN_2O_2$ requires 299). This suggested that the ester had hydrolysed to the alcohol.

Condensations with aldehydes were attempted, one of which was successful.

a) <u>6-Benzyl-octahydro-2H-2-(p-nitrophenyl)-pyrido [3,4,e][1,3]oxazine</u>



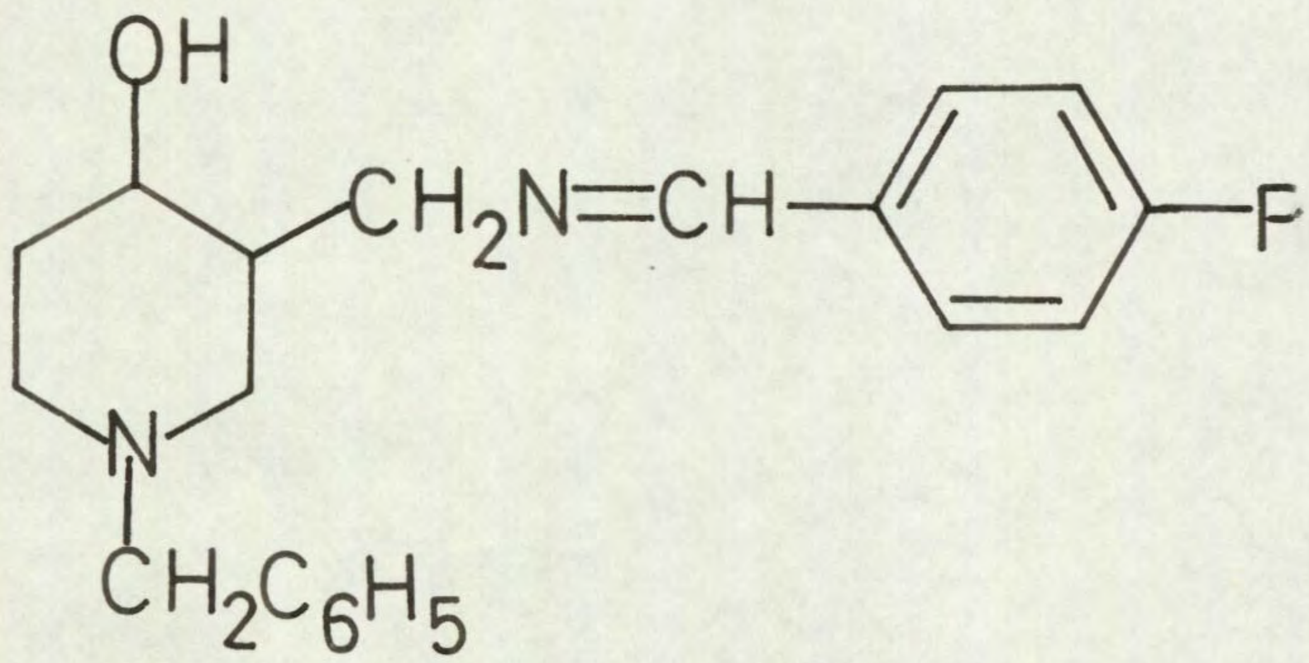
Molecular sieves (Type A, 1/16" mesh) (1 g.) were added to a solution of 3-aminomethyl-1-benzyl-4-piperidinol (.5 g.) and p-nitrobenzaldehyde (.344 g.) in benzene (10 ml.). The solution was allowed to stand for 16 hours, the solid filtered and the filtrate evaporated under reduced pressure to give a pale yellow oil (.8 g.), which was crystallised from ethyl acetate to give <u>6-benzyl-octahydro-2H-2-(p-nitrophenyl)-pyrido [3,4,e][1,3]oxazine</u> (.7 g.), as yellow prisms, m.p. 153-156°.

<u>Infra-red</u>: $\nu_{max.}$ (Nujol), 3300 cm.$^{-1}$ (NH), 1530 cm.$^{-1}$, 1350 cm.$^{-1}$ (NO_2), 800 cm.$^{-1}$ (p-C_6H_4).

<u>N.M.R.</u>: τ($CDCl_3$), 2.3 (Q, 4H), 2.9 (S, 5H), 4.88 (S, H), 6.6 (S, 2H), 6.6-8.7 (M, 11H).

Analysis Found: C, 67.8; H, 6.6; N, 12.0%; equiv., 176. $C_{20}H_{23}N_3O_3$ requires : C, 68.0; H, 6.5; N, 11.9%; equiv., 177.

α(1-Benzyl-4-hydroxy-3-piperidyl)-N-(p-fluoro-benzylidine)methylamine



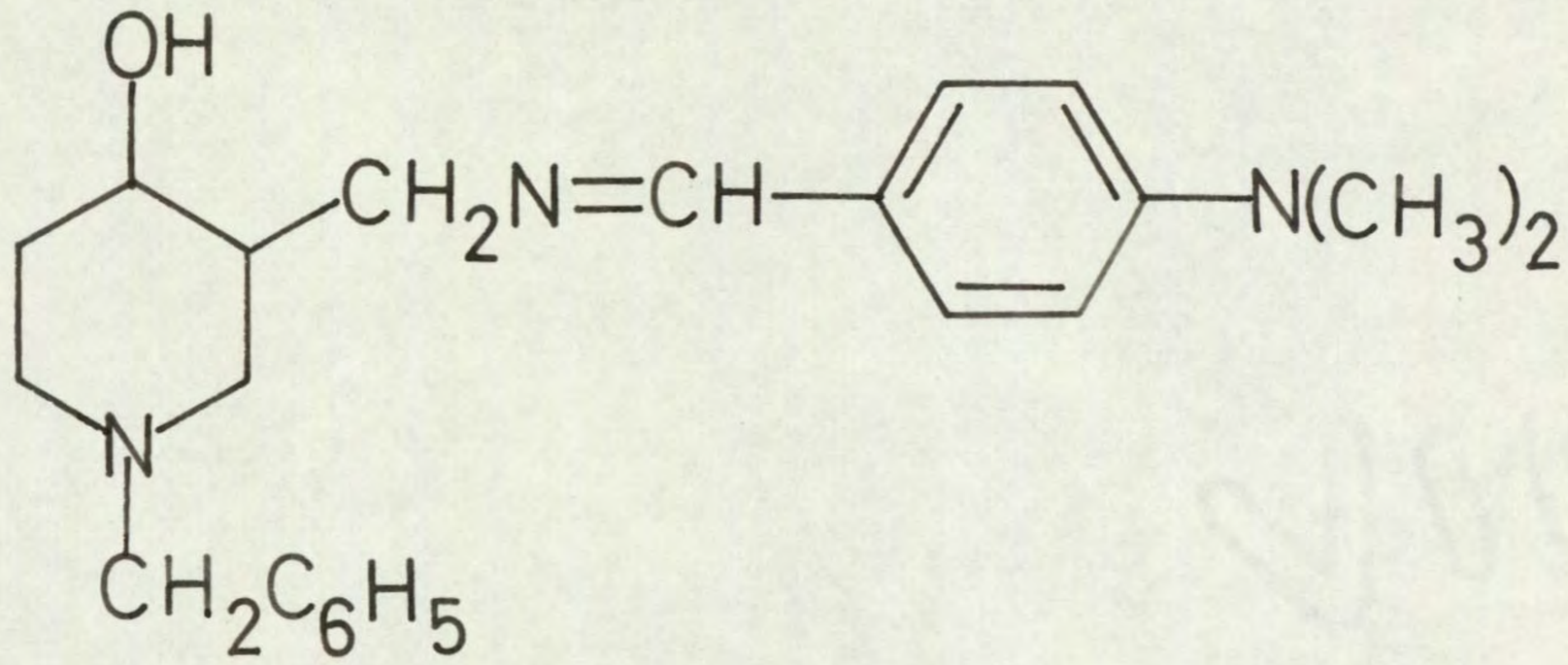
In a similar manner, 3-aminomethyl-1-benzyl-4-piperidinol (1.15 g.), p-fluorobenzaldehyde (.65 g.) and molecular sieves (Type A, 1/16" mesh) (2 g.) in benzene (20 ml.) gave α(1-benzyl-4-hydroxy-3-piperidyl)-N-(p-fluoro-benzylidine)methylamine (1.4 g.), as colourless needles from pet. ether (100-120°), m.p. 95°.

Infra-red: $\nu_{max.}$ (Nujol), 3350 cm.$^{-1}$ (OH), 1655 cm.$^{-1}$ (C=N), 1065 cm.$^{-1}$ (equ. OH), 840 cm.$^{-1}$ (p-C_6H_4).

N.M.R.: τ($CDCl_3$), 2.08 (0.43H, S), 2.9 (M, 9H), 5.01 (S, 0.57H), 6.6 (S, 2H), 6.5-8.8 (M, 11H).

Analysis Found: C, 73.5; H, 7.2; N, 8.4%; equiv., 165. $C_{20}H_{23}FN_2O$ requires : C, 73.6; H, 7.1; N, 8.6%; equiv., 163.

<u>α(1-Benzyl-4-hydroxy-3-piperidyl)-N-(p-dimethyl-aminobenzylidine)methylamine</u>



In a similar manner, 3-aminomethyl-1-benzyl-4-piperidinol (.5 g.), p-dimethylaminobenzaldehyde (.34 g.) and molecular sieves (Type A, 1/16" mesh) (1 g.) in dry benzene (10 ml.) gave <u>α(1-benzyl-4-hydroxy-3-piperidyl)-N-(p-dimethylaminobenzylidine)methylamine</u> (.7 g.), as pale yellow needles from ethyl acetate/pet. ether (40-60°) m.p. 119°.

<u>Infra-red</u>: $\nu_{max.}$ (Nujol), 3350 cm.$^{-1}$ (OH), 1645 cm.$^{-1}$ (C=N).

<u>N.M.R.</u>: τ ($CDCl_3$), 2.2 (S, H), 2.91 (S, 5H), 3.1 (Q, 4H), 6.6 (S, 2H), 7.1 (S, 6H), 6.2-8.4 (M, 11H).

<u>Analysis</u> Found: C, 75.1; H, 8.1; N, 12.1%; equiv., 173. $C_{22}H_{28}N_3O$ requires : C, 75.2; H, 8.3; N, 12.0%; equiv., 175.

b) 3-Aminomethyl-1-benzyl-4-piperidinol (.5 g.) and p-fluorobenzaldehyde (.29 g.) were refluxed in benzene (20 ml.) with a water separator until dry. Evaporation

of the solvent gave a pale yellow oil which could not be crystallised. An infra-red spectrum showed the presence of unreacted aldehyde and of uncyclised product.

3-Aminomethyl-1-benzyl-4-piperidinol (.55 g.) in benzene (25 ml.) with benzaldehyde (.27 g.) similarly gave a dark brown oil (.7 g.) which did not crystallise. An infra-red spectrum showed the presence of unreacted materials and the probable presence of uncyclised compound.

3-Aminomethyl-1-benzyl-4-piperidinol (.25 g.) in toluene (10 ml.) was refluxed with carbon disulphide (2 ml.). A brown tarry compound was obtained which could not be solidified. The infra-red spectrum of the product suggested that the product was very impure.

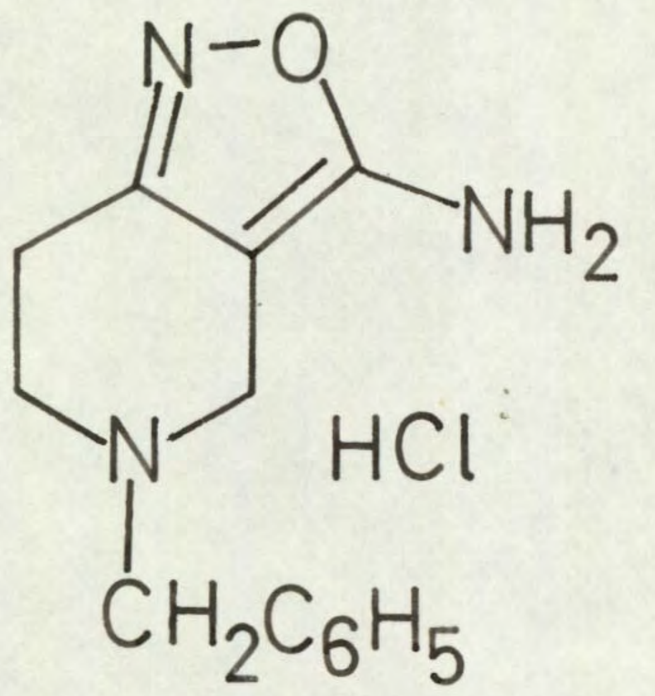
B(v) FURTHER REACTIONS OF 1-BENZYL-3-CYANO-4-PIPERIDONE

a) <u>Attempted hydrolysis</u>

1-Benzyl-3-cyano-4-piperidone hydrochloride (5 g.) was dissolved in 85% sulphuric acid in ethanol (50 ml.) and allowed to stand for 48 hours. The solution was poured on to ice, made alkaline with sodium hydroxide solution and extracted with chloroform (2 x 100 ml.).

The chloroform extracts were dried (anhy. Na_2SO_4) and evaporated, yielding a brown oil (.53 g.). The aqueous solution was saturated with potassium carbonate and extracted again with chloroform (2 x 100 ml.). Evaporation of the organic layer did not yield any product.

b) 7-Amino-5-benzyl-3,4,5,6-tetrahydro-isoxazolo [4,3,c] pyridine hydrochloride



Hydroxylamine hydrochloride (7 g.) and sodium acetate (12 g.) in water (5 ml.) was added to a solution of 1-benzyl-3-cyano-4-piperidone hydrochloride (12 g.) in water (20 ml.) and ethanol (10 ml.). The solution was warmed and allowed to stand. A white solid was obtained (9 g.) which crystallised from ethanol/water to give 7-amino-5-benzyl-3,4,5,6-tetrahydro-isoxazolo [4,3,c] pyridine hydrochloride, as a flocculent white solid, m.p. 217-218°.

Infra-red (Salt): $\nu_{max.}$ (Nujol), 3300 $cm.^{-1}$

3100 cm.$^{-1}$ (NH_2), 2570 cm.$^{-1}$ ($\overset{+}{N}H$), 1650 cm.$^{-1}$ (C=N), 1620 cm.$^{-1}$ (C=C).

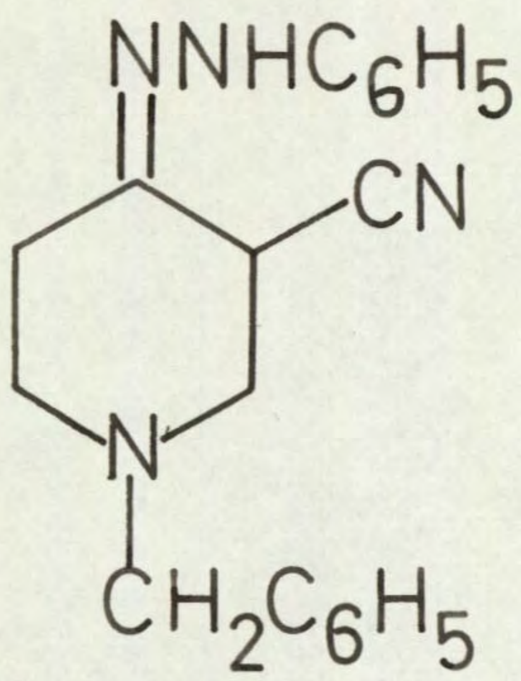
(Base): $\nu_{max.}$ (Nujol), 3390 cm.$^{-1}$, 3100 cm.$^{-1}$ (NH_2), 1655 cm.$^{-1}$ (C=N), 710 cm.$^{-1}$, 745 cm.$^{-1}$ (C_6H_5).

Analysis Found: C, 58.6; H, 6.0; N, 16.0%; equiv., 272. $C_{13}H_{16}ClN_3O$ requires : C, 58.8; H, 6.0; N, 15.8%; equiv., 266.

Attempted reduction of the isoxazolo-pyridine

Finely powdered 7-amino-5-benzyl-3,4,5,6-tetrahydro-isoxazolo[4,3,c]pyridine hydrochloride (2 g.) was added to a suspension of $LiAlH_4$ (1 g.) in ether (200 ml.). The mixture was refluxed for 1 hour and decomposed with sodium potassium tartrate solution. The ether layer was separated, dried (anhy. Na_2SO_4) and evaporated, yielding a pale yellow oil (2 g.). Attempts to crystallise this oil failed. Thin layer chromatography of the oil showed the presence of five major spots. An attempt to form a solid hydrochloride by dissolving part of the oil in ethanolic HCl also failed.

c) 1-Benzyl-3-cyano-4-piperidone phenylhydrazone



Phenylhydrazine (.5 g.) in ethanol (1 ml.) was added to a solution of 1-benzyl-3-cyano-4-piperidone hydrochloride (1 g.) and sodium acetate (2 g.) in water (5 ml.). The solution was warmed and allowed to stand. A white solid separated, which was crystallised from ethanol to give 1-benzyl-3-cyano-4-piperidone phenyl-hydrazone (1.1 g.), as white plates, m.p. 161°.

Infra-red: $\nu_{max.}$ (Nujol), 3300 cm.$^{-1}$ (NH), 2250 cm.$^{-1}$ (C≡N), 1610 cm.$^{-1}$ (C=N), 700 cm.$^{-1}$, 750 cm.$^{-1}$, 760 cm.$^{-1}$ (2 x C_6H_5).

Analysis Found: C, 74.8; H, 6.4; N, 18.6%; equiv., 155. $C_{19}H_{20}N_4$ requires : C, 75.0; H, 6.6; N, 18.4%; equiv., 152.

Attempted cyclisation of the phenylhydrazone

a) 1-Benzyl-3-cyano-4-piperidone phenylhydrazone (1 g.) was heated to 170° for 1 hour. The compound turned a dark brown and did not crystallise on cooling.

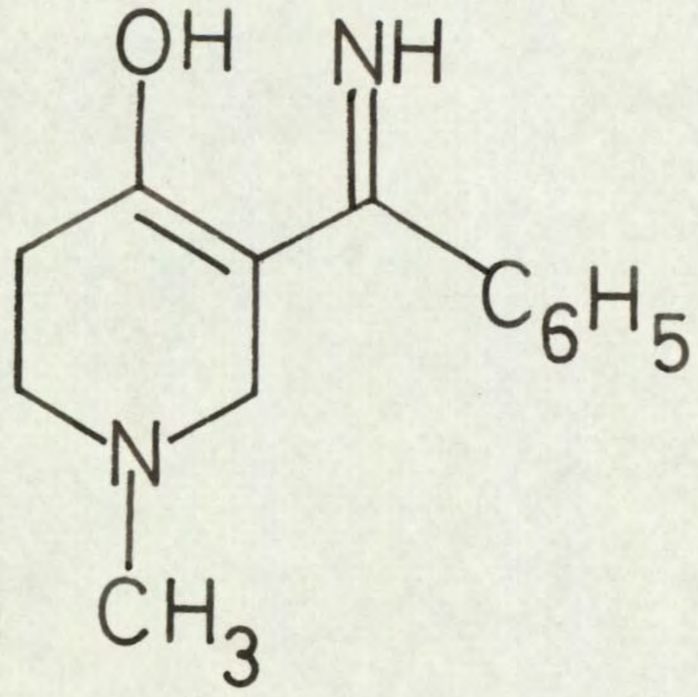
Attempts to solidify the product failed.

b) 1-Benzyl-3-cyano-4-piperidone phenylhydrazone (1 g.) was refluxed for 2 hours in a solution of sodium (.1 g.) in absolute ethanol (50 ml.). The solution turned brown. Dilution with water (50 ml.), evaporation of the alcohol under reduced pressure and extraction with chloroform (2 x 50 ml.) yielded a brown solution which gave, on evaporation of the chloroform, a black tar. This was discarded.

C. REACTIONS OF SOME OTHER N-SUBSTITUTED-3-CYANO-4-PIPERIDONES

1-Methyl derivatives

1,2,5,6-Tetrahydro-4-hydroxy-1-methyl-3-phenylimino pyridine



Finely powdered 3-cyano-1-methyl-4-piperidone hydrochloride (5 g.) was added in small portions to a solution of a Grignard reagent made from magnesium turnings (4 g.) and bromobenzene (27 g.) in ether (100 ml.) and benzene (200 ml.). The mixture was stirred for 4 hours and decomposed with a saturated solution of ammonium chloride. The organic layer was separated, the aqueous layer extracted with chloroform (2 x 100 ml.), the organic layers combined and dried (anhy. Na_2SO_4). Evaporation of the organic layers gave a dark red oil (8 g.) which partially crystallised with difficulty and recrystallised from ethyl acetate to give 1,2,5,6-tetrahydro-4-hydroxy-1-methyl-3-phenylimino-pyridine (2.1 g.), as colourless needles, m.p. 143°.

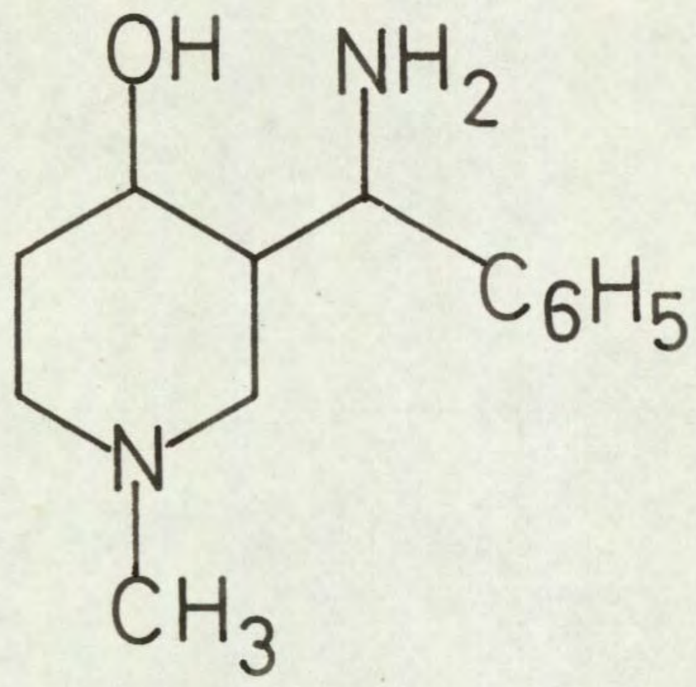
Infra-red: $\nu_{max.}$ (Nujol), 3100 cm.$^{-1}$ - 3350 cm.$^{-1}$ (OH, NH), 2780 cm.$^{-1}$ ($\rangle N-CH_3$), 1570 cm.$^{-1}$ - 1610 cm.$^{-1}$ (C=C, C=N), 1290 cm.$^{-1}$ (C-O).

N.M.R.: τ ($CDCl_3$), -0.5 (S, H, O$\underline{H}$), 2.65 (S, 5H, $C_6\underline{H}_5$), 4.2 (S, H, N$\underline{H}$), 7.08 (S, 2H, NC$\underline{H}_2$C=), 7.52 (M, 4H, NC$\underline{H}_2$C$\underline{H}_2$-), 7.82 (S, 3H, C$\underline{H}_3$).

Analysis Found: C, 72.1; H, 7.5; N, 12.9%. $C_{13}H_{16}N_2O$ requires : C, 72.2; H, 7.4; N, 13.0%; equiv., 216.

The compound did not titrate to a definite end-point in non-aqueous solvents.

1-Methyl-3- α -phenylaminomethyl-4-piperidinol



Isomer A Sodium borohydride (4 g.) was added to a solution of 1,2,5,6-tetrahydro-4-hydroxy-1-methyl-3-phenylimino-pyridine (8 g.) in ethanol (100 ml.). The mixture was refluxed for 2 hours, the alcohol evaporated under reduced pressure, water (100 ml.) added and the solution extracted with benzene (2 x 100 ml.), the benzene extracts dried (anhy. Na_2SO_4) and evaporated, yielding a yellow oil (8 g.) which crystallised with difficulty. The solid was recrystallised from ethyl acetate to give 1-methyl-3- α -phenylaminomethyl-4-piperidinol (2 g.), as white needles, m.p. 132°.

Infra-red: $\nu_{max.}$ (Nujol), 3300 cm.$^{-1}$, 3380 cm.$^{-1}$ (NH_2), 2700 cm.$^{-1}$ - 3300 cm.$^{-1}$ (OH), 2790 cm.$^{-1}$ ($>N-CH_3$), 1060 cm.$^{-1}$ (equ. OH).

Analysis Found: C, 71.0; H, 9.3; N, 12.7%; equiv., 107. $C_{13}H_{20}N_2O$ requires : C, 70.9; H, 9.1; N, 12.7%; equiv., 110.

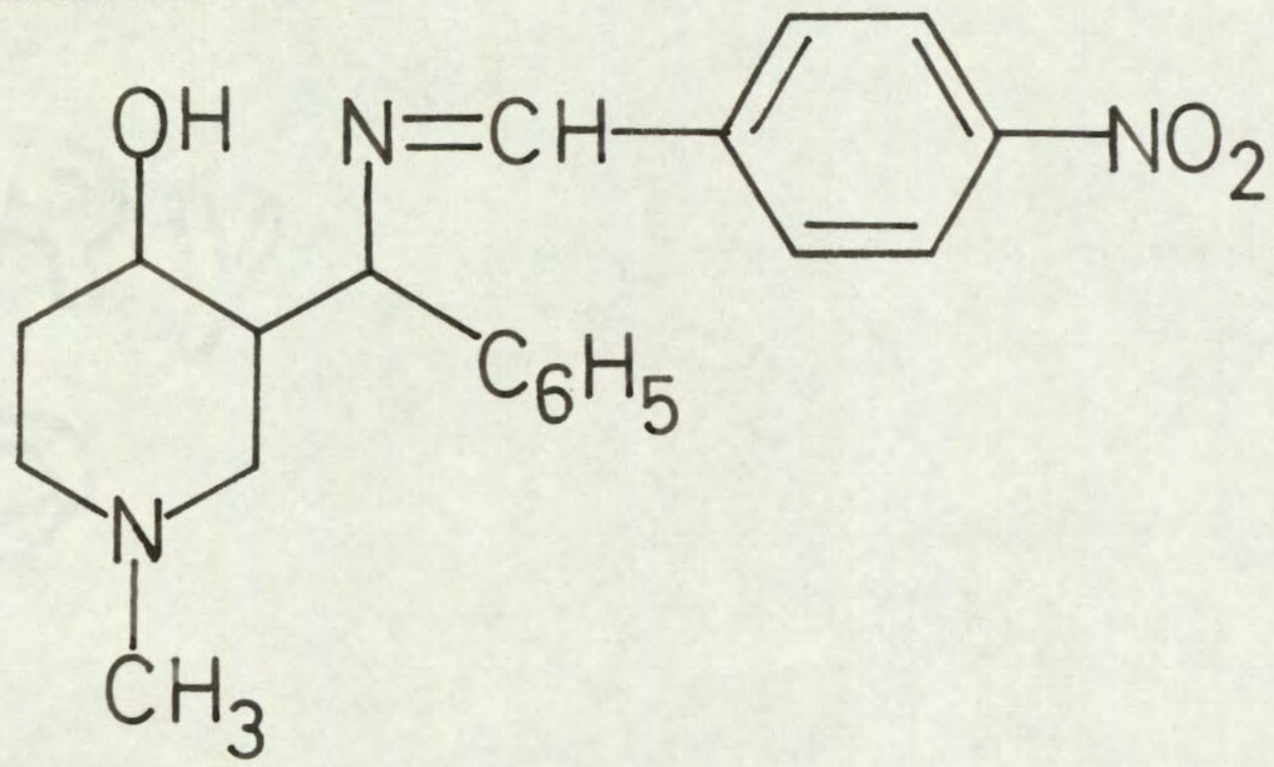
Examination of the mother liquors revealed, by thin

layer chromatography, the possible presence of a second isomer (B), as well as a large fraction of the isomer (A) obtained. Attempts to obtain isomer (B) by chromatography or by preparation of a hydrochloride salt failed, the compound obtained being the hydrochloride of isomer A.

Attempted reaction with substituted benzaldehydes

Reactions with substituted benzaldehydes was attempted, one of which was partially successful.

a) α(4-Hydroxy-1-methyl-3-piperidyl)-N-(p-nitrobenzylidine)benzylamine



1-Methyl-3-α-phenylaminomethyl-4-piperidinol (.678 g.) was dissolved in benzene (10 ml.). p-Nitrobenzaldehyde (.466 g.) and molecular sieves (Type A, 1/16" mesh) (1.2 g.) added and the mixture allowed to stand. Filtration of the solid and evaporation of the filtrate yielded a yellow oil (1.05 g.) which partially solidified.

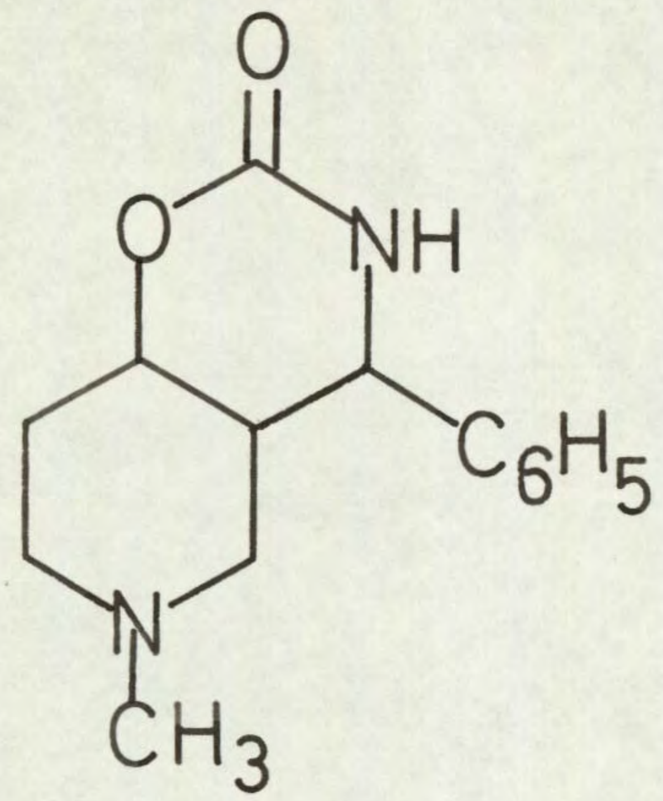
The solid was crystallised with difficulty from ethyl acetate to give α(4-hydroxy-1-methyl-3-piperidyl)-N-(p-nitrobenzylidine)benzylamine (.1 g.).

Infra-red: $\nu_{max.}$ (Nujol), 2700 cm.$^{-1}$ - 3100 cm.$^{-1}$ (bonded OH), 1645 cm.$^{-1}$ (C=N), 1350 cm.$^{-1}$, 1530 cm.$^{-1}$ (NO_2), 860 cm.$^{-1}$ (p-C_6H_4).

b) 1-Methyl-3-α-phenylaminomethyl-4-piperidinol (1 g.) was refluxed in benzene (50 ml.) with o-methoxybenzaldehyde (.62 g.) with water separation. Evaporation of the solvent yielded a pale yellow oil (1.53 g.) which could not be crystallised. An infra-red spectrum showed the presence of unreacted aldehyde and uncyclised product (C=N peak at 1635 cm.$^{-1}$).

c) 1-Methyl-3-α-phenylaminomethyl-4-piperidinol (1 g.) with benzaldehyde (.48 g.) in benzene (50 ml.) similarly gave an oil (1.4 g.) which could not be crystallised. An infra-red spectrum showed the presence of peaks at 1630 cm.$^{-1}$ (C=N) and 1700 cm.$^{-1}$ (CHO).

Octahydro-6-methyl-2-oxo-4-phenyl-pyrido[3,4,e][1,3]oxazine

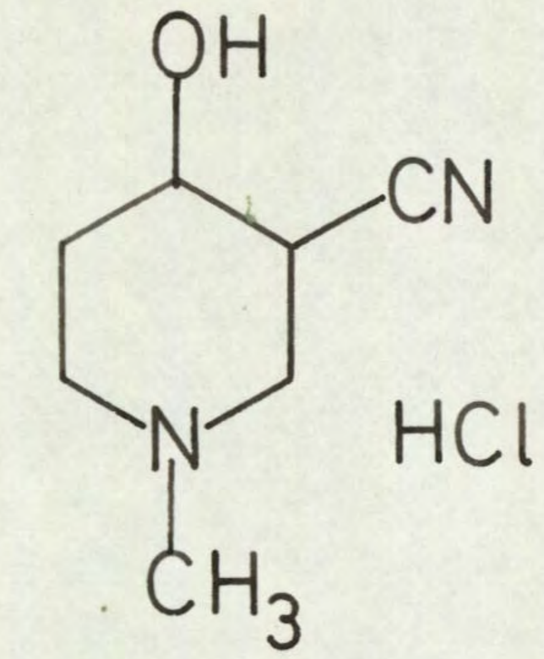


A 12% solution of phosgene in benzene (20 ml.) was added dropwise to 1-methyl-3-α-phenylaminomethyl-4-piperidinol (1 g.) and sodium bicarbonate (5 g.) in benzene (100 ml.). The solution was refluxed for .5 hours, filtered and the precipitate extracted with hot ethanol (2 x 100 ml.). Evaporation of the extracts gave a clear colourless oil (1.1 g.) which partially solidified, and was crystallised from ethyl acetate/pet. ether (60-80°) to give octahydro-6-methyl-2-oxo-4-phenyl-pyrido[3,4,e][1,3]oxazine (.2 g.), as flocculent white needles, m.p. 216°.

Infra-red: $\nu_{max.}$ (Nujol), 3100 cm.$^{-1}$, 3200 cm.$^{-1}$ (NH), 1690 cm.$^{-1}$ (C=O).

Analysis Found: C, 66.1; H, 7.4; N, 10.7%; equiv., 249. $C_{14}H_{18}N_2O_2$ requires : C, 68.3; H, 7.3; N, 11.4%; equiv., 246.

3-Cyano-1-methyl-4-piperidinol hydrochloride

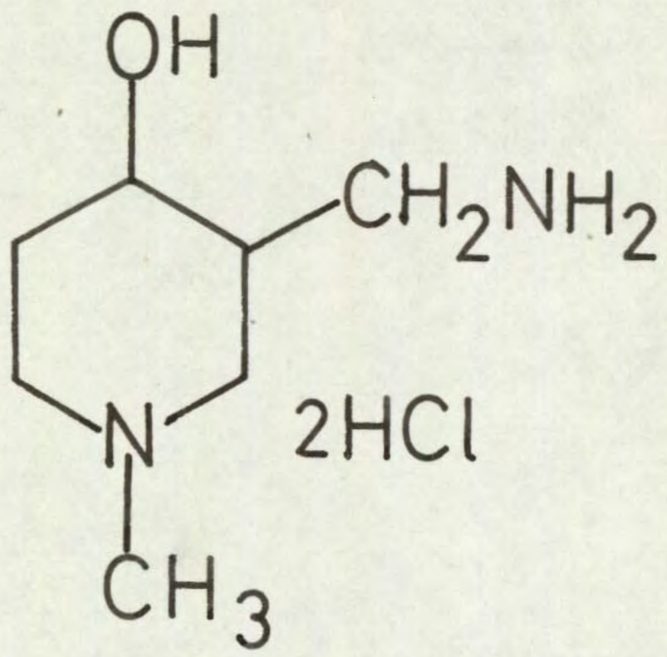


Sodium borohydride (3 g.) was added to 3-cyano-1-methyl-4-piperidone hydrochloride (5 g.) in water (10 ml.). The mixture was stirred for 2 hours, saturated with anhy. Na_2CO_3 and extracted with chloroform (3 x 50 ml.). The organic extracts were dried (anhy. Na_2SO_4) and evaporated to give a pale yellow oil (5 g.), ($\nu_{max.}$ 3450 cm.$^{-1}$ (OH)), which was dissolved in ethanolic HCl and allowed to stand. A white solid (2 g.) was obtained which crystallised from ethanol/ether to give 3-cyano-1-methyl-4-piperidinol hydrochloride (1.8 g.), as white needles, m.p. 168°.

Infra-red (base): $\nu_{max.}$ (film), 3450 cm.$^{-1}$ (OH), 2250 cm.$^{-1}$ (C≡N). 1090 cm.$^{-1}$ (equ. OH), 2800 cm.$^{-1}$ ($\rangle$N-CH_3).

Analysis Found: C, 47.5; H, 7.5; N, 15.9%; equiv., 174. $C_7H_{13}ClN_2O$ requires : C, 47.6; H, 7.4; N, 15.9%; equiv., 177.

3-Aminomethyl-1-methyl-4-piperidinol dihydrochloride



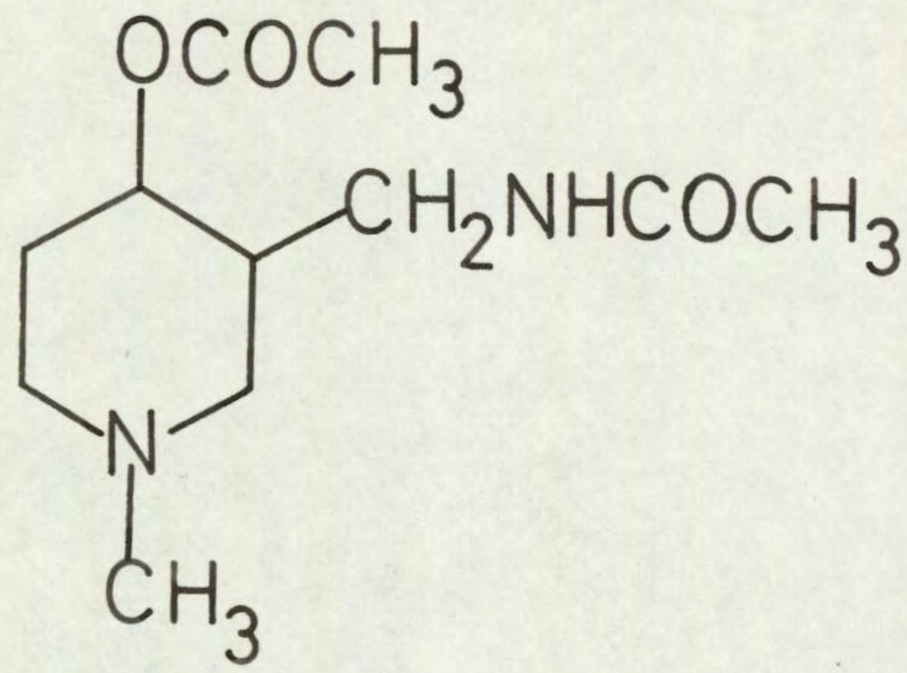
3-Cyano-1-methyl-4-piperidinol (5 g.) in benzene (50 ml.) was added dropwise to $LiAlH_4$ (2 g.) in ether (100 ml.). A white flocculent precipitate was noticed. The mixture was refluxed for 2 hours and decomposed with a saturated solution of sodium potassium tartrate. The inorganic precipitate was filtered off and extracted with benzene (2 x 50 ml.). The combined organic extracts were dried (anhy. Na_2SO_4) and evaporated, the pale green oil obtained dissolved in ethanolic HCl and allowed to stand. The white solid which precipitated was crystallised from ethanol/ether to give 3-amino-methyl-1-methyl-4-piperidinol dihydrochloride (3 g.), as white needles, m.p. 245°.

Infra-red (base); $\nu_{max.}$ (film), 3200 cm.$^{-1}$ - 3400 cm.$^{-1}$ (OH, NH_2), 2800 cm.$^{-1}$ ($>N-CH_3$), 1610 cm.$^{-1}$ (C-N), 1080 cm.$^{-1}$ (equ. OH).

Analysis Found: C, 38.5; H, 8.1; N, 12.8%; equiv., 108. $C_7H_{18}Cl_2N_2O$ requires : C, 38.7; H, 8.3;

N, 12.9%; equiv., 109.

3-Acetamidomethyl-4-acetoxy-1-methyl-piperidine



3-Aminomethyl-1-methyl-4-piperidinol (4 g.) was refluxed in pyridine (10 ml.) and acetic anhydride (5 ml.) for 3 hours. Evaporation of the solvent gave a brown oil which solidified with difficulty. The solid was recrystallised from ethyl acetate to give 3-acetamidomethyl-4-acetoxy-1-methyl-piperidine (.7 g.), as white needles, m.p. 134°.

Infra-red: $\nu_{max.}$ (Nujol), 3310 cm.$^{-1}$ (NH), 2800 cm.$^{-1}$ ($\rangle$N-CH$_3$), 1720 cm.$^{-1}$ (ester C=O), 1650 cm.$^{-1}$ (amide I), 1570 cm.$^{-1}$ (amide II), 1250 cm.$^{-1}$ (C-O).

Analysis Found: C, 57.9; H, 8.9; N, 12.2%; equiv., 225. $C_{11}H_{20}N_2O_3$ requires : C, 57.9; H, 8.8; N, 12.3%; equiv., 228.

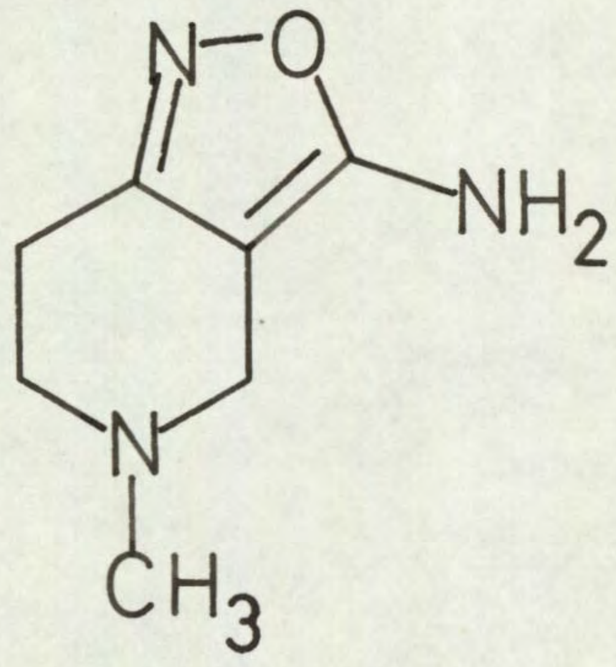
Attempted cyclisations with aldehydes

a) 3-Aminomethyl-1-methyl-4-piperidinol (1.4 g.) was refluxed in toluene (50 ml.) with benzaldehyde (1.03 g.)

until no more water was removed in a water separator. Evaporation of the solvent gave a brown tarry compound which could not be solidified. An infra-red spectrum of this product had a peak at 1640 cm.$^{-1}$, attributed to C=N.

b) n-Butyraldehyde (1 ml.) was added to 3-aminomethyl-1-methyl-4-piperidinol (1 g.). The mixture became warm. Benzene (50 ml.) was added, the mixture refluxed for .5 hours and the solvents evaporated, yielding a brown oil which did not solidify. An infra-red spectrum had a band at 3300 cm.$^{-1}$ (OH), and a peak at 1650 cm.$^{-1}$ (C=N). An attempt to distil the compound under reduced pressure gave a dark-brown tar.

7-Amino-3,4,5,6-tetrahydro-5-methyl-isoxazolo [4,3,c] pyridine



3-Cyano-1-methyl-4-piperidone hydrochloride (4 g.) was added to a solution of hydroxylamine hydrochloride (2 g.) and sodium acetate (4 g.) in water

(10 ml.). The solution was stirred for 16 hours, saturated with anhy. Na_2CO_3 and extracted with chloroform (3 x 50 ml.). The combined extracts were dried (anhy. Na_2SO_4), evaporated and the residue crystallised from ethanol to give 7-amino-3,4,5,6-tetrahydro-5-methyl-isoxazolo[4,3,c]pyridine (3 g.), as colourless prismatic needles, m.p. 192-193°.

Infra-red: $\nu_{max.}$ (Nujol), 3250 cm.$^{-1}$, 3100 cm.$^{-1}$ (NH_2), 2790 cm.$^{-1}$ ($\rangle N-CH_3$), 1660 cm.$^{-1}$ (C=N), 1640 cm.$^{-1}$ (C=C).

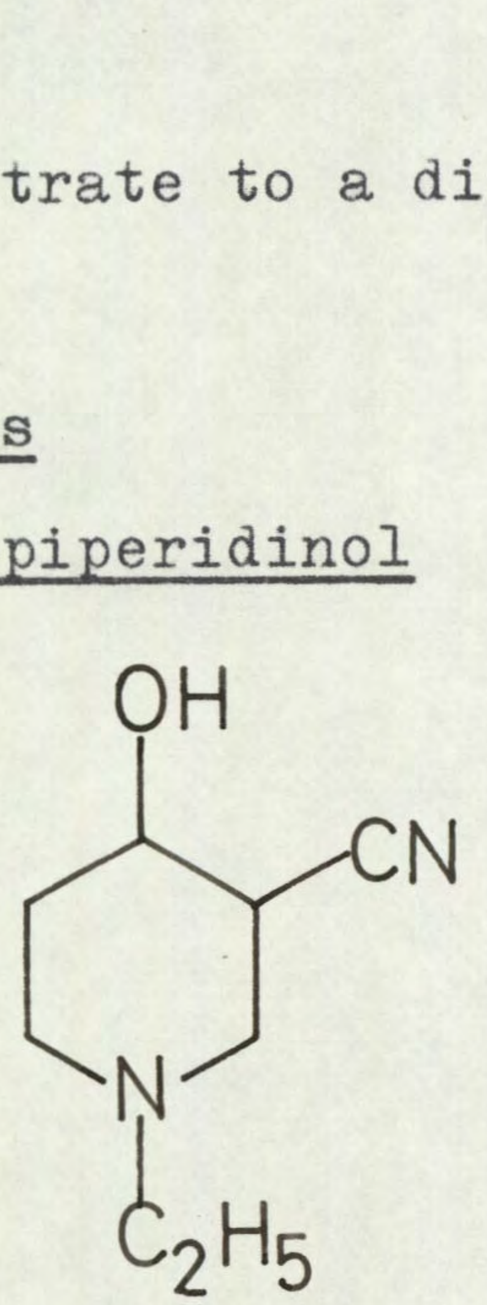
Analysis Found: C, 55.0; H, 7.1; N, 27.4%.

$C_7H_{11}N_3O$ requires : C, 54.9; H, 7.2; N, 27.5%; equiv., 153.

The compound did not titrate to a distinct end point.

2. 1-Ethyl derivatives

3-Cyano-1-ethyl-4-piperidinol



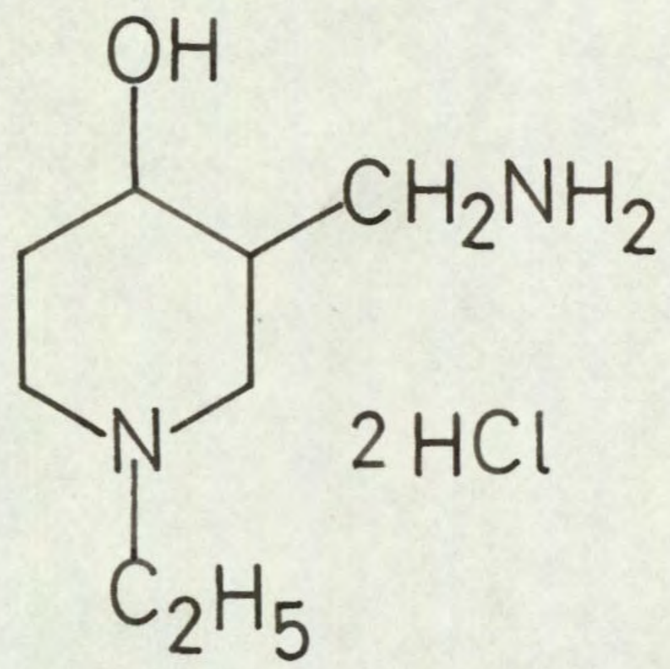
Sodium borohydride (2 g.) was added to a solution of 3-cyano-1-ethyl-4-piperidone hydrochloride (4 g.) in

water (20 ml.). The mixture was stirred for 3 hours, saturated with anhy. Na_2CO_3 and extracted with chloroform (3 x 50 ml.). The combined chloroform extracts were dried (anhy. Na_2SO_4) and evaporated, yielding a clear colourless oil (2.5 g.) which partly solidified, and was crystallised from benzene/pet. ether (60-80°) to give 3-cyano-1-ethyl-4-piperidinol (1.7 g.), as white needles, m.p. 75°.

Infra-red: $\nu_{max.}$ (Nujol), 3450 cm.$^{-1}$ (OH), 2250 cm.$^{-1}$ (C≡N), 1090 cm.$^{-1}$ (equ. OH).

Analysis Found: C, 62.2; H, 8.9; N, 18.3%; equiv., 152. $C_8H_{14}N_2O$ requires : C, 62.3; H, 9.1; N, 18.2%; equiv., 154.

3-Aminomethyl-1-ethyl-4-piperidinol dihydrochloride



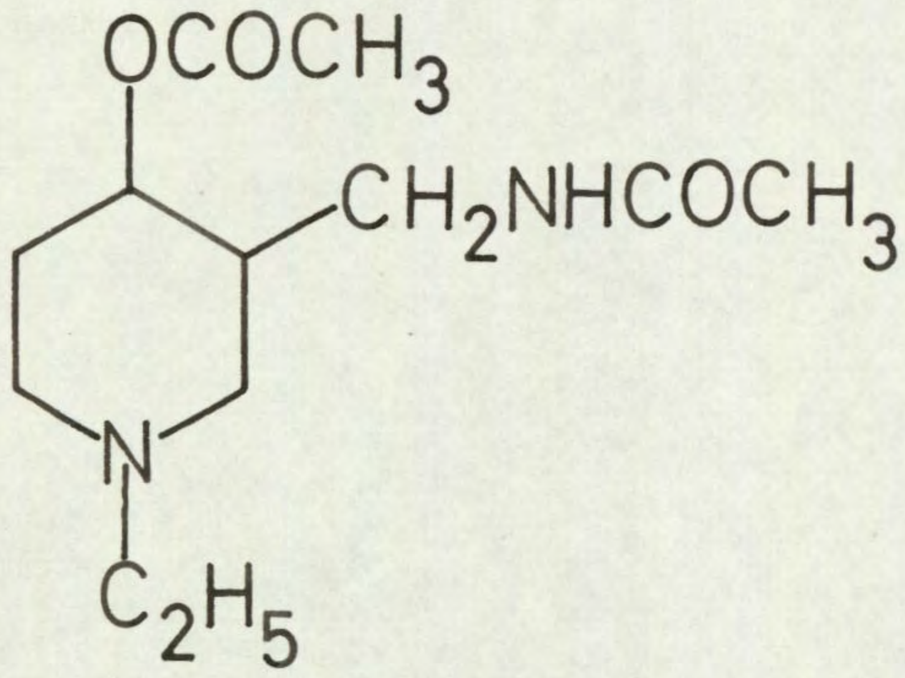
3-Cyano-1-ethyl-4-piperidinol (.5 g.) in benzene (50 ml.) was added dropwise to a stirred suspension of $LiAlH_4$ (.2 g.) in ether (10 ml.). The mixture was stirred for 16 hours and decomposed with a saturated

solution of sodium potassium tartrate. Filtration of the inorganic solid and evaporation of the organic solvent gave a green oil (.5 g.) which was dissolved in ethanolic HCl and allowed to stand. The white solid obtained was crystallised from ethanol to give 3-amino-methyl-1-ethyl-4-piperidinol dihydrochloride (.3 g.), as white prisms, m.p. 200°.

Infra-red (base): $\nu_{max.}$ (film), 3200 cm.$^{-1}$ - 3400 cm.$^{-1}$ (OH, NH_2), 1600 cm.$^{-1}$ (C-N), 1090 cm.$^{-1}$ (equ. OH).

Analysis Found: C, 41.4; H, 8.6; N, 12.2%; equiv., 116. $C_8H_{20}Cl_2N_2O$ requires : C, 41.6; H, 8.7; N, 12.1%; equiv., 116.

3-Acetamidomethyl-4-acetoxy-1-ethyl-piperidine



3-Aminomethyl-1-ethyl-4-piperidinol (3 g.) was refluxed with pyridine (10 ml.) and acetic anhydride (5 ml.) for 3 hours. On cooling, a white solid was obtained which crystallised from ethyl acetate to give

3-acetamidomethyl-4-acetoxy-1-ethyl-piperidine (1.05 g.), as white needles, m.p. 117°.

Infra-red: $\nu_{max.}$ (Nujol), 3310 cm.$^{-1}$ (NH), 1720 cm.$^{-1}$ (ester C=O), 1650 cm.$^{-1}$ (amide I), 1570 cm.$^{-1}$ (amide II), 1250 cm.$^{-1}$ (C-O).

Analysis Found: C, 59.4; H, 9.2; N, 11.5%; equiv., 237. $C_{12}H_{22}N_2O_3$ requires : C, 59.5; H, 9.1; N, 11.6%; equiv., 242.

Attempted reaction with benzaldehyde

3-Aminomethyl-1-ethyl-4-piperidinol (1 g.) and benzaldehyde (.67 g.) were refluxed in benzene (50 ml.) with a water separator until dry. Evaporation of the solvent yielded a dark yellow oil (1.5 g.) which could not be induced to solidify. An infra-red spectrum showed a peak at 1635 cm.$^{-1}$, attributed to C=N.

Attempted preparation of an imino-ether

3-Cyano-1-ethyl-4-piperidinol (2 g.) was dissolved in dry ethanol (100 ml.). The cooled solution was saturated with dry hydrogen chloride and allowed to stand for 7 days. A white solid was obtained which crystallised from ethanol/ether to give 3-cyano-1-ethyl-4-piperidinol hydrochloride $\nu_{max.}$ (Nujol), 2250 cm.$^{-1}$ (C≡N), 3350 cm.$^{-1}$ (OH). . Evaporation of

the solution gave a further crop of the hydrochloride.

Attempted reaction of 3-cyano-1-ethyl-4-piperidone hydrochloride with phenyl magnesium bromide

Finely powdered 3-cyano-1-ethyl-4-piperidone hydrochloride (5 g.) was added in small portions to a solution of a Grignard reagent prepared from magnesium (4 g.) and bromobenzene (25 g.) in ether (200 ml.). The solution was stirred for 16 hours, decomposed with a saturated solution of ammonium chloride, the organic layer separated, dried (anhy. Na_2SO_4) and evaporated, yielding a dark red oil (5 g.). The infra-red spectrum of this oil showed a band at 1600 cm.$^{-1}$ (C=C, C=N), a broad band at 3300 cm.$^{-1}$ (OH, NH) and peaks at 710 cm.$^{-1}$ and 750 cm.$^{-1}$ attributed to C_6H_5. Non-aqueous titration gave an equiv. 250 ($C_{14}H_{18}N_2O$ requires 230). All attempts to solidify the compound failed.

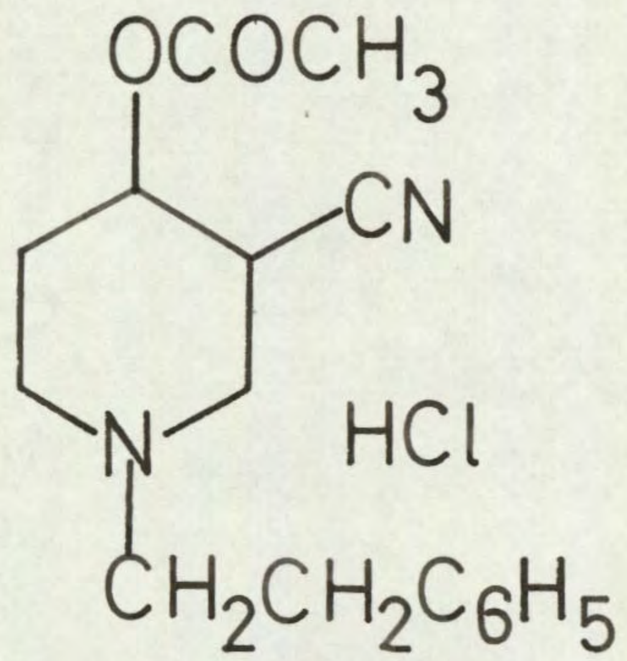
3. 1-Phenethyl derivatives

Attempted reaction of 3-cyano-1-phenethyl-4-piperidone hydrochloride with phenyl magnesium bromide

Finely powdered 3-cyano-1-phenethyl-4-piperidone hydrochloride (4 g.) was added in small portions to a solution of a Grignard reagent made from magnesium (1.5 g.) and bromobenzene (9 g.) in ether (100 ml.).

Benzene (200 ml.) was added to the mixture which was refluxed for 16 hours, decomposed with a saturated solution of ammonium chloride, the organic layer separated, dried (anhy. Na_2SO_4) and evaporated, yielding a dark brown oil (6 g.). An infra-red spectrum of this product had a small peak at 3300 $cm.^{-1}$ (OH or NH), a small peak at 2250 $cm.^{-1}$ (C≡N), a peak centred on 1680 $cm.^{-1}$ (C=O or C=N), and peaks suggesting mono-substituted benzene. Thin layer chromatography showed at least six major spots. Attempts to obtain a solid product from the mixture were not successful.

4-Acetoxy-3-cyano-1-phenethyl-piperidine hydrochloride



Sodium borohydride (3 g.) was added to a solution of 3-cyano-1-phenethyl-4-piperidone hydrochloride (20 g.) in water (200 ml.). The mixture was stirred for 17 hours, extracted with chloroform (3 x 200 ml.), the combined chloroform extracts dried (anhy. Na_2SO_4) and extracted, yielding a yellow oil (13.2 g.), equiv. 240 ($C_{14}H_{18}N_2O$ requires 230). An infra-red spectrum

gave the following peaks: $\nu_{max.}$ (film), 3450 cm.$^{-1}$ (OH), 2250 cm.$^{-1}$ (C≡N). The compound could not be crystallised. Dissolving an aliquot in ethanolic HCl and allowing to stand did not yield a solid hydrochloride. The compound was not characterised but used directly.

Impure 3-cyano-1-phenethyl-4-piperidinol (2 g.) was refluxed with pyridine (3 ml.) and acetic anhydride (3 ml.) for 3 hours. Evaporation of the solvent yielded a brown oil (2.2 g.) which was dissolved in ethanolic HCl and allowed to stand. The solid obtained crystallised from ethanol/ether to give 4-acetoxy-3-cyano-1-phenethyl-piperidine hydrochloride (1.2 g.), as white needles, m.p. 240°.

Infra-red: $\nu_{max.}$ (Nujol), 2400 cm.$^{-1}$ ($\overset{+}{N}H$), 1735 cm.$^{-1}$ (C=O).

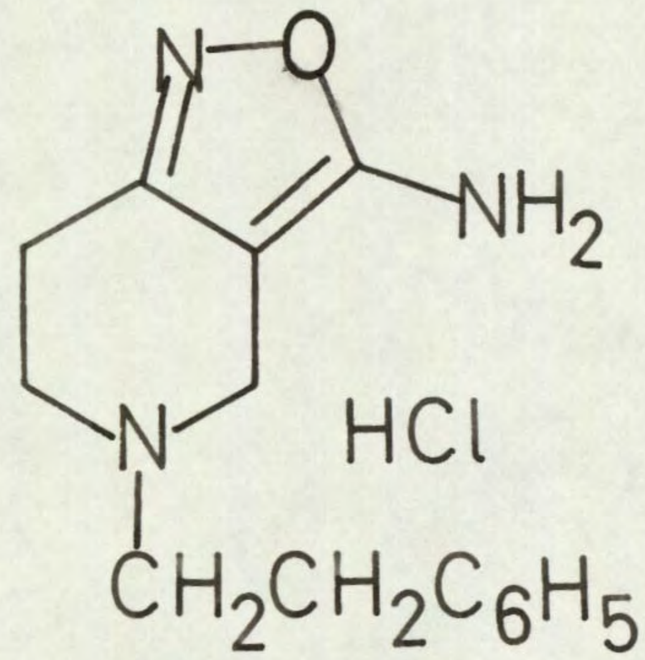
Analysis Found: C, 62.0; H, 7.0; N, 9.0%; equiv., 318. $C_{16}H_{21}ClN_2O_2$ requires : C, 62.2; H, 6.8; N, 9.0%; equiv., 309.

Attempted reduction of the cyano-alcohol

Impure 3-cyano-1-phenethyl-4-piperidinol (2 g.) in benzene (20 ml.) was added dropwise to a suspension of $LiAlH_4$ (1 g.) in ether (50 ml.). The solution was stirred for 4 hours, decomposed with a saturated solution

of sodium potassium tartrate, the inorganic solid filtered and the organic layer evaporated to give a clear colourless oil (2 g.), equiv., 230 ($C_{14}H_{22}N_2O$ requires 234). An infra-red spectrum had a broad band centred on 3200 cm.$^{-1}$ (OH, NH_2), and did not contain a peak at 2250 cm.$^{-1}$ (C≡N). Attempts to solidify the compound failed. Dissolving the oil in ethanolic HCl did not give a solid.

<u>7-Amino-3,4,5,6-tetrahydro-5-phenethyl-isoxazolo [4,3,c] pyridine hydrochloride</u>



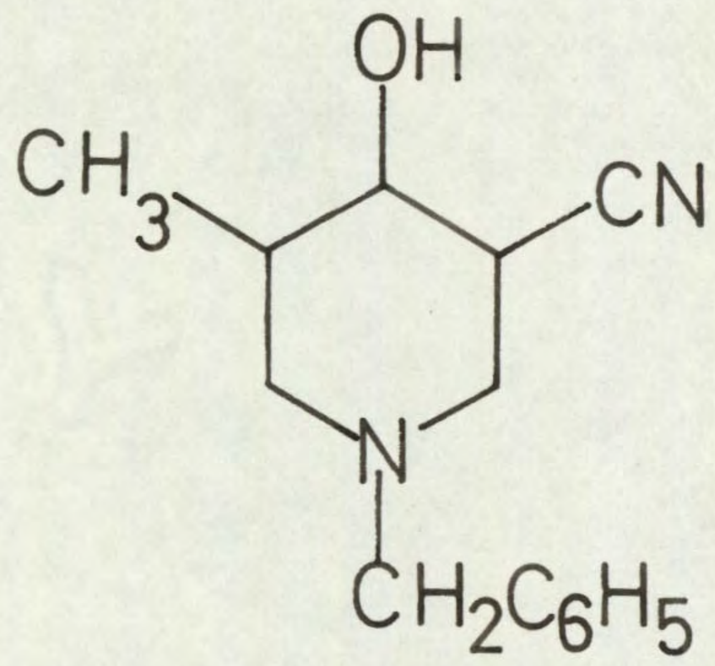
Hydroxylamine hydrochloride (5 g.) and sodium acetate (10 g.) in water (20 ml.) were added to a suspension of 3-cyano-1-phenethyl-4-piperidone hydrochloride (10 g.) in ethanol (40 ml.). The solution was warmed for 10 minutes and allowed to stand. The white precipitate was crystallised from ethanol to give <u>7-amino-3,4,5,6-tetrahydro-5-phenethyl-isoxazolo[4,3,c] pyridine hydrochloride</u> (5 g.), as white needles, m.p. 172°.

Infra-red: $\nu_{max.}$ (Nujol), 3150 cm.$^{-1}$, 3330 cm.$^{-1}$ (NH_2), 2580 cm.$^{-1}$ (NH), 1665 cm.$^{-1}$ (C=N), 1630 cm.$^{-1}$ (C=C).

Analysis Found: C, 60.0; H, 6.4; N, 15.2%; equiv., 288. $C_{14}H_{18}ClN_3O$ requires: C, 60.1; H, 6.4; N, 15.0%; equiv., 280.

4. 1-Benzyl-5-methyl derivatives

1-Benzyl-3-cyano-5-methyl-4-piperidinol



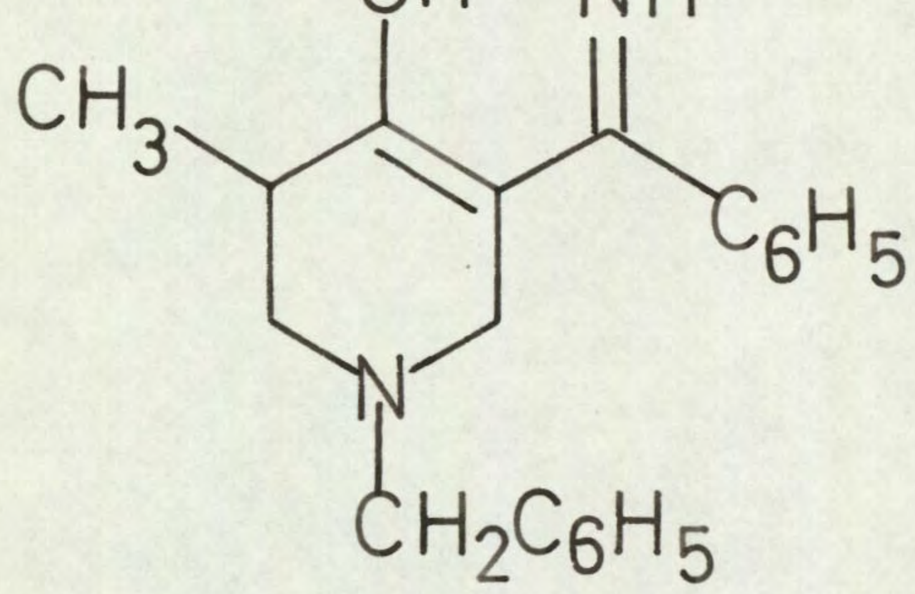
Sodium borohydride (2 g.) was added to a stirred solution of 1-benzyl-3-cyano-5-methyl-4-piperidone hydrochloride (10 g.) in water (100 ml.) and ethanol (50 ml.). The mixture was allowed to stand for 14 hours, extracted with chloroform (3 x 100 ml.), the combined chloroform extracts dried (anhy. Na_2SO_4) and evaporated, yielding a pale yellow oil (9.2 g.) which partially crystallised with difficulty and was crystallised from acetone/cyclohexane to give 1-benzyl-3-cyano-5-methyl-4-piperidinol (.6 g.), as white needles, m.p. 163°.

Infra-red: $\nu_{max.}$ (Nujol), 3450 cm.$^{-1}$ (OH), 2250 cm.$^{-1}$ (C≡N), 1070 cm.$^{-1}$ (equ. OH).

Analysis Found: C, 73.0; H, 8.0; N, 12.3%; equiv., 224. $C_{14}H_{18}N_2O$ requires : C, 73.1; H, 7.8; N, 12.2%; equiv., 230.

Examination of the residual oil showed a number of compounds by thin layer chromatography, none of which could be obtained pure.

1-Benzyl-1,2,5,6-tetrahydro-4-hydroxy-5-methyl-3-phenylimino-pyridine



Finely powdered 1-benzyl-3-cyano-5-methyl-4-piperidone hydrochloride (10 g.) was added to a solution of a Grignard reagent prepared from magnesium (5.45 g.) and bromobenzene (35.6 g.) in ether (200 ml.). The mixture was stirred for 4 hours and decomposed with a saturated solution of ammonium chloride. The aqueous layer was extracted with benzene (2 x 100 ml.), the combined organic layers dried (anhy. Na_2SO_4) and evaporated, yielding a red oil (12 g.), which partially

solidified to give a red solid, crystallised from ethyl acetate, giving 1-benzyl-1,2,5,6-tetrahydro-4-hydroxy-5-methyl-3-phenylimino-pyridine (3.6 g.), as pale yellow needles, m.p. 134°.

Infra-red: $\nu_{max.}$ (Nujol), 3300 cm.$^{-1}$, 3100 cm.$^{-1}$ (NH, OH), 1600 cm.$^{-1}$ (C=C, C=N), 700 cm.$^{-1}$, 750 cm.$^{-1}$, 780 cm.$^{-1}$ (2 x C_6H_5).

N.M.R.: τ ($CDCl_3$), 0 (S, H, OH), 2.7 (S, 5H, C_6H_5), 2.8 (S, 5H, C_6H_5), 5 (S, H, NH), 6.6 (S, 2H, $C_6H_5CH_2$), 6.95 (S, 2H, $NCH_2C=$), 7.1-8.0 (M, 3H, N-CH_2CH), 8.9 (D, 3H, CH_3).

The signals at τ=0 and τ=5 disappear on shaking with D_2O.

Analysis Found: C, 78.4; H, 7.2; N, 9.0%; equiv., 293. $C_{20}H_{22}N_2O$ requires : C, 78.4; H, 7.2; N, 9.2%; equiv., 306.

Attempted reduction of the 5-methyl imino-enol

Sodium borohydride (1 g.) was added to a stirred solution of 1-benzyl-1,2,5,6-tetrahydro-4-hydroxy-5-methyl-3-phenylimino-pyridine (1 g.) in ethanol (100 ml.). The mixture was warmed and stirred for 2 hours and allowed to stand for 48 hours. Evaporation of the solvent under reduced pressure, addition of water (50 ml.), extraction of the aqueous solution with benzene (2 x

50 ml.) and evaporation of the organic extracts yielded a yellow oil (1 g.), equiv., 168 ($C_{20}H_{26}N_2O$ requires 155). An infra-red spectrum showed a band centred on 3300 $cm.^{-1}$ (OH, NH_2) and loss of the band at 1600 $cm.^{-1}$ (C=C, C=N). The compound could not be crystallised. An attempt to form a solid hydrochloride also failed. Thin layer chromatography showed the presence of five spots. Further attempts at isolating a solid compound were abandoned.

D. REACTIONS WITH 4-AMINO-1-BENZYL-3-CYANO-1,2,5,6-TETRAHYDRO-PYRIDINE

Attempted reaction with phenyl-lithium

Finely powdered 4-amino-1-benzyl-3-cyano-1,2,5,6-tetrahydro-pyridine (20 g.) was added in small portions to a solution of phenyl-lithium made from lithium (8.4 g.) and bromobenzene (94 g.) in dry ether (200 ml.). Dry benzene (400 ml.) was added and the mixture stirred for 24 hours. The solution was decomposed with water, the organic layer separated, dried (anhy. Na_2SO_4) and evaporated, yielding a dark brown oil with a strong smell of bromobenzene. The oil was heated to 100^{o} under vacuum for 1 hour, dissolved in benzene (100 ml.) and extracted with cold conc. HCl (2 x 50 ml.). Evaporation

of the benzene layer yielded a brown solid (12 g.) which was sublimed at 70°/8 mm. to give biphenyl, m.p. 71° (lit. m.p. 71°). The acid layer was made alkaline with 5N NaOH solution and extracted with chloroform (2 x 50 ml.). The combined chloroform extracts were dried (anhy. Na_2SO_4) and evaporated, yielding a dark brown oil (20 g.). The oil was dissolved in benzene (50 ml.) and pet. ether (80-100°) (50 ml.), and passed over an alumina column 20 cm. in length and 2 cm. in diameter. An increasing percentage of benzene in pet. ether (80-100°) was used as the eluant. In all, four fractions were collected, the flow rate being approximately 2 cc./minute.

The material recovered from the column amounted to 12 g., i.e. approximately 60% recovery. The details of the chromatographic separation are summarised in table I.

The residue III solidified with difficulty and crystallised from ethanol to give 1-benzyl-1,2,5,6-tetrahydro-4-hydroxy-3-phenylimino-pyridine (1.8 g.), m.p. 178°, undepressed on admixture with authentic sample.

No crystalline solid could be obtained from the other fractions.

Table I

Fraction	Volume of solvent	Solvent	Weight of residue	
1	50 ml.	50% v/v benzene in pet. ether.		
2	50 ml.	75% v/v benzene in pet. ether	4 g.	I
3	20 ml.	"		
4	25 ml.	80% v/v benzene in pet. ether.		
5	25 ml.	90% v/v benzene in pet. ether	5 g.	II
6	40 ml.	benzene	— 2 g.	III
7	40 ml.	acetone	— 1 g.	IV

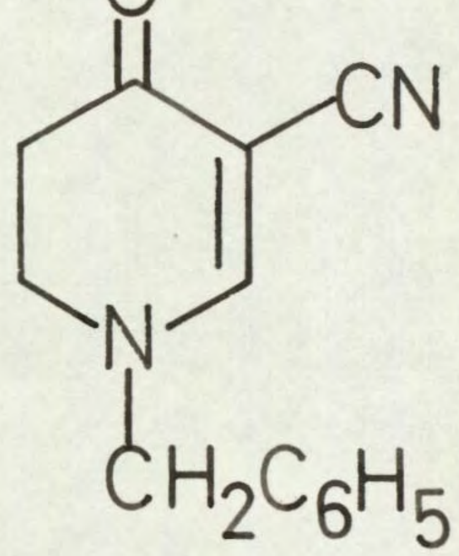
Attempted hydrolysis of 4-amino-1-benzyl-3-cyano-1,2,5,6-tetrahydro-pyridine

a) 4-Amino-1-benzyl-3-cyano-1,2,5,6-tetrahydro-pyridine (1 g.) was dissolved in conc. H_2SO_4 (10 ml.). The solution became hot and turned black.

b) 4-Amino-1-benzyl-3-cyano-1,2,5,6-tetrahydro-pyridine (1 g.) was dissolved in conc. H_2SO_4 (10 ml.) cooled to a low temperature in acetone/CO_2. A brown solution was obtained. The stirred solution was

allowed to warm to room temperature and was poured onto ice. The aqueous solution was saturated with anhy. Na_2CO_3 and extracted with chloroform (2 x 20 ml.). The combined chloroform extracts were dried and evaporated, yielding a dark brown oil (.1 g.), an infra-red spectrum of which suggested that the major component was 1-benzyl-3-cyano-4-piperidone $\nu_{max.}$ 2200 cm.$^{-1}$ (C≡N), 1650 cm.$^{-1}$ (C=O) .

<u>1-Benzyl-5-cyano-1,2,3,4-tetrahydro-4-oxo-pyridine</u>



Potassium permanganate (3 g.) in acetone (200 ml.) was added dropwise to a stirred solution of 4-amino-1-benzyl-3-cyano-1,2,5,6-tetrahydro-pyridine (5 g.) in acetone (200 ml.), until the solution was permanently pink. The precipitate of manganese dioxide was filtered, water (50 ml.) was added to the filtrate and the acetone evaporated. The brown solid was crystallised from ethanol/water to give starting material (1 g.) and <u>1-benzyl-5-cyano-1,2,3,4-tetrahydro-4-oxo-pyridine</u> (3.5 g.), as white leaves, m.p. 189°.

Infra-red: $\nu_{max.}$ (Nujol), 2200 cm.$^{-1}$ (C≡N), 1640 cm.$^{-1}$ (C=C), 1620 cm.$^{-1}$ (C=O).

Ultra-violet: $\lambda_{max.}$ (EtOH), 312.5 mμ (15800), 228.5 mμ (11900).

N.M.R.: τ (T.F.A.), 1.8 (S, H), 2.56 (S, 5H), 5.2 (S, 2H), 6.18 (T, 2H), 7.15 (T, 2H).

Analysis Found: C, 73.7; H, 5.9; N, 13.1%. $C_{13}H_{12}N_2O$ requires : C, 73.9; H, 5.7; N, 13.3%; equiv., 212.

The compound did not titrate in non-aqueous solvents, did not form a halide salt and did not give a colouration with $FeCl_3$ solution.

Attempted reaction with methyl iodide

1-Benzyl-5-cyano-1,2,3,4-tetrahydro-4-oxo-pyridine (1 g.) was refluxed in methyl iodide (10 ml.) and ethanol (50 ml.) for 100 hours. Evaporation of the solvents yielded starting material (1 g.), m.p. undepressed on admixture with authentic sample.

Attempted reaction with phenyl magnesium bromide

Finely powdered 1-benzyl-5-cyano-1,2,3,4-tetrahydro-4-oxo-pyridine (3 g.) was added in small portions to a solution of a Grignard reagent made from magnesium (1.8 g.) and bromobenzene (11.5 g.) in ether (100 ml.).

The solution was stirred for 4 hours and decomposed with a saturated solution of ammonium chloride. Evaporation of the organic layer yielded starting material (2 g.), m.p. undepressed on admixture with authentic sample.

A second reaction with identical quantities but including benzene (400 ml.), after refluxing for 17 hours, gave, on work-up, a brown oil (4 g.) which could not be solidified or crystallised. An aliquot, dissolved in ethanolic HCl, did not give a solid salt.

Attempted ring closures of 1-benzyl-5-cyano-1,2,3,4-tetrahydro-4-oxo-pyridine with amidines

Some attempts were made to form pyrido-pyrimidines using amidines. None were successful.

a) 1-Benzyl-5-cyano-1,2,3,4-tetrahydro-4-oxo-pyridine (.5 g.) was fused with urea (.15 g.) for 10 minutes. The resulting solid was dissolved in ethanol and water and allowed to stand. Starting material (.45 g.) was obtained, m.p. undepressed on admixture with authentic sample.

b) The compound (.5 g.) was refluxed in alcohol (100 ml.) with urea (.15 g.) for 4 hours. Starting material was returned.

c) The compound (.5 g.) in glacial acetic acid (5 ml.)

was refluxed with urea (.5 g.) for 2 hours. Distillation of the acetic acid and subsequent work-up yielded only starting material.

d) Benzamidine and thiourea, under similar conditions, merely returned the starting material unchanged.

Reduction of 1-benzyl-5-cyano-1,2,3,4-tetrahydro-4-oxo-pyridine

Several attempts were made to reduce this compound, two of which were successful.

a) Sodium borohydride (1 g.) was added to a solution of 1-benzyl-5-cyano-1,2,3,4-tetrahydro-4-oxo-pyridine (2 g.) in methanol (100 ml.). The solution was stirred for 16 hours, water (200 ml.) added and the methanol evaporated under reduced pressure. The aqueous solution was extracted with benzene (2 x 100 ml.), the combined organic extracts dried (anhy. Na_2SO_4) and evaporated, yielding a pale yellow liquid (1.8 g.). This was crystallised from acetone/pet. ether (60-80°) to give 1-benzyl-3-cyano-4-piperidinol (1 g.), m.p. undepressed on admixture with authentic sample.

b) Finely powdered 1-benzyl-5-cyano-1,2,3,4-tetrahydro-4-oxo-pyridine (2 g.) was added in small portions to a suspension of $LiAlH_4$ (.6 g.) in ether (50 ml.) and benzene (100 ml.). The mixture was stirred for 16

hours, decomposed with a solution of sodium potassium tartrate, the organic layer separated, dried (anhy. Na_2SO_4) and evaporated to give a pale yellow oil (1.8 g.), equiv., 115 ($C_{13}H_{20}N_2O$ requires 110). An infra-red spectrum was identical with that obtained from the product of the $LiAlH_4$ reduction of 1-benzyl-3-cyano-4-piperidone hydrochloride, which was thought to be the saturated amino-alcohol. No solid was obtained from this reaction product, and no solid HCl salt was obtained.

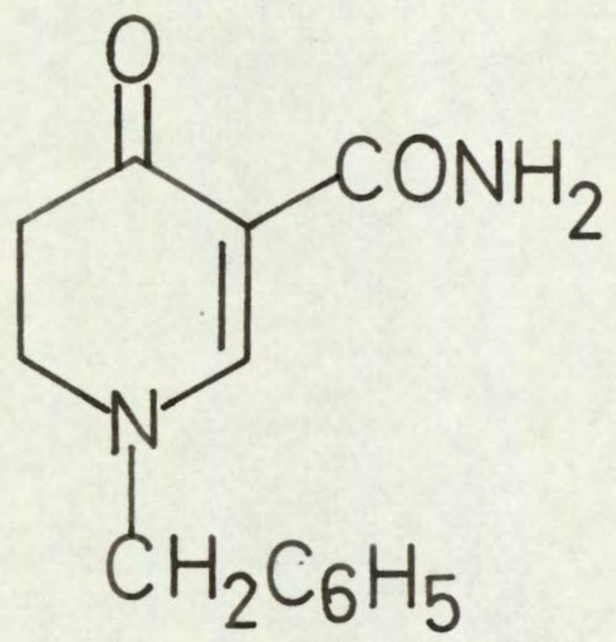
c) 1-Benzyl-5-cyano-1,2,3,4-tetrahydro-4-oxo-pyridine (2 g.) was refluxed with aluminium isopropoxide (3 g.) in dry isopropanol (100 ml.) for 1 hour. Distillation of the solvent gave no acetone in the distillate. Addition of water and distillation of the remaining alcohol yielded starting material (1.8 g.), m.p. undepressed with an authentic sample of the tetrahydro-pyridine.

d) 1-Benzyl-5-cyano-1,2,3,4-tetrahydro-4-oxo-pyridine (2 g.) was refluxed with aluminium isopropoxide (2 g.) in toluene (250 ml.) for 6 hours. Isopropanol (10 ml.) was added dropwise to the slowly-distilling solution. Work-up of the solution returned unchanged starting material.

e) Sodium (2 g.) was added in small pieces to a

solution of 1-benzyl-5-cyano-1,2,3,4-tetrahydro-4-oxo-pyridine (1 g.) in ethanol (50 ml.). The solution was refluxed for .5 hours, cooled and water (20 ml.) added. The ethanol was distilled under reduced pressure, yielding starting material.

1-Benzyl-5-carboxamido-1,2,3,4-tetrahydro-4-oxo-pyridine



1-Benzyl-5-cyano-1,2,3,4-tetrahydro-4-oxo-pyridine (.9 g.) was dissolved in 90% H_2SO_4 in ethanol (10 ml.). The mixture was allowed to stand for 24 hours, poured onto ice and neutralised with 5N NaOH solution. The solid was crystallised from ethanol/pet. ether (60-80°) to give 1-benzyl-5-carboxamido-1,2,3,4-tetrahydro-4-oxo-pyridine (.9 g.), as white prisms, m.p. 176°.

Infra-red: $\nu_{max.}$ (Nujol), 3300 cm.$^{-1}$, 3150 cm.$^{-1}$ (NH_2), 1560 cm.$^{-1}$ - 1650 cm.$^{-1}$ (C=O, C=C, amide I and II).

N.M.R.: τ($CDCl_3$), 1.45 (S, 2H), 2.6 (S, 5H), 4.2 (S, H), 6.5 (T, 2H), 7.5 (T, 2H).

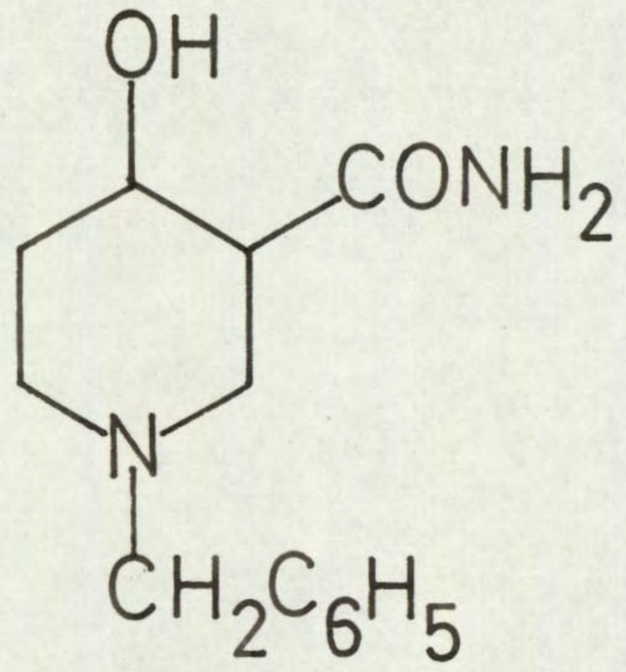
τ(T.F.A.), 1.45 (S, H), 2.6 (S, 5H), 6.5 (T, 2H), 7.5 (T, 2H).

Ultra-violet: $\lambda_{max.}$ (EtOH), 314 mμ (17650), 241 mμ (16050).

Analysis Found: C, 67.7; H, 6.1; N, 12.0%. $C_{13}H_{14}N_2O_2$ requires: C, 67.8; H, 6.1; N, 12.2%; equiv., 230.

The compound did not titrate in non-aqueous solvents.

1-Benzyl-3-carboxamido-4-piperidinol



Sodium borohydride (.5 g.) was added to a solution of 1-benzyl-5-carboxamido-1,2,3,4-tetrahydro-4-oxo-pyridine (1 g.) in ethanol (50 ml.). The mixture was stirred for 20 hours, water (100 ml.) added and the ethanol removed under reduced pressure. The aqueous solution was saturated with anhy. Na_2CO_3, extracted with chloroform (3 x 50 ml.), the combined chloroform extracts dried (anhy. Na_2SO_4) and evaporated, yielding a

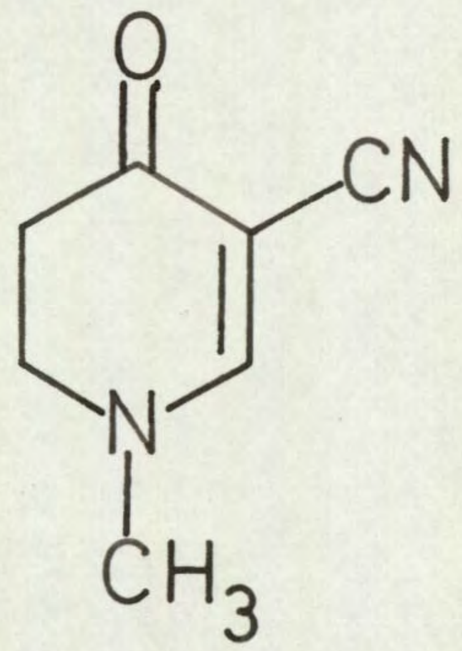
colourless oil (1 g.) which was crystallised from ethanol to give 1-benzyl-3-carboxamido-4-piperidinol (.8 g.), as white plates, m.p. 148°.

Infra-red: $\nu_{max.}$ (Nujol), 3400 cm.$^{-1}$, 3250 cm.$^{-1}$ (OH, NH_2), 1660 cm.$^{-1}$ (amide I), 1600 cm.$^{-1}$ (amide II), 1100 cm.$^{-1}$ (equ. OH).

Analysis Found: C, 66.9; H, 7.9; N, 11.9%; equiv., 235. $C_{13}H_{18}N_2O_2$ requires : C, 66.7; H, 7.7; N, 12.0%; equiv., 234.

Preparation of some N-substituted homologues

5-Cyano-1,2,3,4-tetrahydro-1-methyl-4-oxo-pyridine



Potassium permanganate (5.7 g.) in water (200 ml.) was added dropwise to 4-amino-3-cyano-1,2,5,6-tetrahydro-1-methyl-pyridine (5 g.) in water (200 ml.). The precipitate of manganese dioxide was filtered off, the aqueous solution saturated with anhy. K_2CO_3 and extracted

with chloroform (3 x 100 ml.). The combined chloroform extracts were dried (anhy. Na_2SO_4) and evaporated, yielding a mixture (3 g.). This was dissolved in conc. HCl (10 ml.), saturated with anhy. K_2CO_3 and extracted with chloroform (3 x 100 ml.). The combined chloroform extracts were dried (anhy. Na_2SO_4) and evaporated, yielding a solid (1 g.), crystallised from benzene to give 5-cyano-1,2,3,4-tetrahydro-1-methyl-4-oxo-pyridine (.5 g.), as white needles, m.p. 124°.

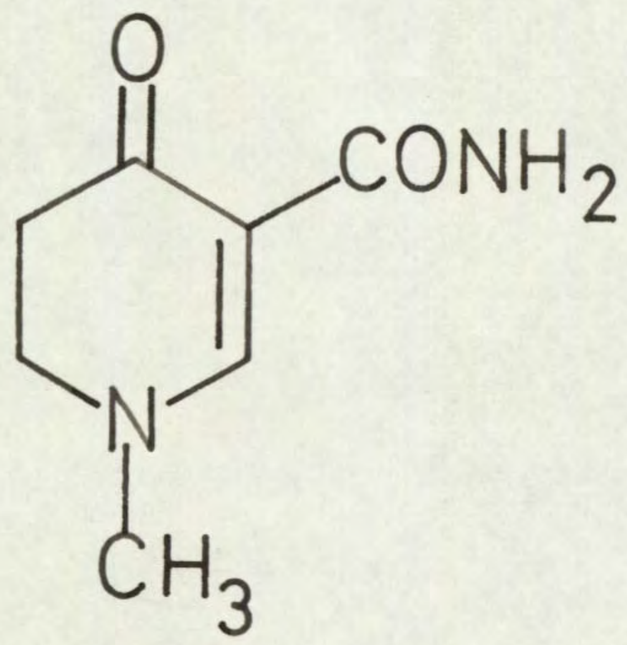
Infra-red: $\nu_{max.}$ (Nujol), 2210 cm.$^{-1}$ (C≡N), 1590 cm.$^{-1}$ - 1650 cm.$^{-1}$ (C=C, C=O).

N.M.R.: τ($CDCl_3$), 2.28 (S, H), 6.3 (T, 2H), 6.7 (S, 3H), 7.47 (T, 2H).

Analysis Found: C, 61.9; H, 5.9; N, 20.8%. $C_7H_8N_2O$ requires : C, 61.8; H, 5.9; N, 20.6%; equiv., 136.

The compound did not titrate in non-aqueous solvents.

5-Carboxamido-1,2,3,4-tetrahydro-1-methyl-4-oxo-pyridine



5-Cyano-1,2,3,4-tetrahydro-1-methyl-4-oxo-pyridine (1 g.) was dissolved in conc. H_2SO_4 (5 ml.) and allowed to stand for 24 hours. The solution was poured onto ice, saturated with anhy. Na_2CO_3 and extracted with chloroform (3 x 50 ml.). The combined chloroform extracts were dried (anhy. Na_2SO_4) and evaporated, yielding a yellow solid (1 g.) which crystallised from benzene to give 5-carboxamido-1,2,3,4-tetrahydro-1-methyl-4-oxo-pyridine (.5 g.), as white needles, m.p. 176°.

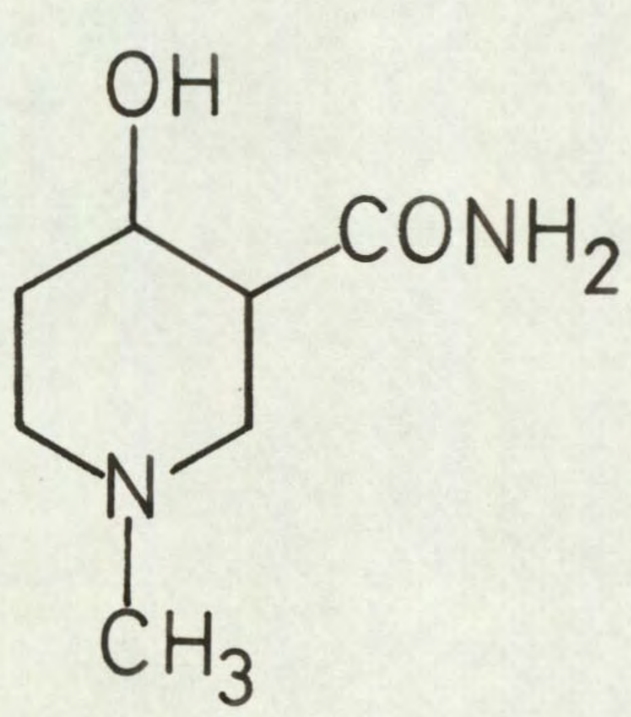
Infra-red: $\nu_{max.}$ (Nujol), 3200 cm.$^{-1}$ - 3400 cm.$^{-1}$ (NH_2), 1550 cm.$^{-1}$ - 1650 cm.$^{-1}$ (C=O, C=C, amide I and II).

N.M.R.: τ ($CDCl_3$), 1.45 (S, H), 1.72 (S, H), 3.95 (S, H), 6.40 (T, 2H), 6.73 (S, 3H), 7.43 (T, 2H).

Analysis Found: C, 54.4; H, 6.6; N, 18.3%.

$C_7H_{10}N_2O_2$ requires : C, 54.6; H, 6.5; N, 18.2%.

3-Carboxamido-1-methyl-4-piperidinol

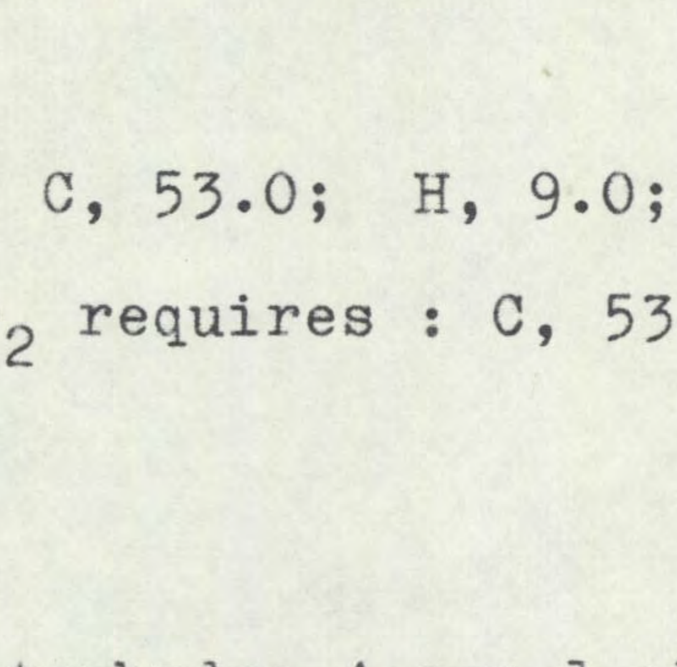


Sodium borohydride (.5 g.) was added to a solution of 5-carboxamido-1,2,3,4-tetrahydro-1-methyl-4-oxo-pyridine (2 g.) in water (10 ml.). The solution was stirred for 12 hours, saturated with K_2CO_3 and extracted with chloroform (3 x 20 ml.). The combined chloroform extracts were dried (anhy. Na_2SO_4) and evaporated, yielding a clear colourless oil (2 g.) which crystallised from ethyl acetate/pet. ether (80-100°) to give 3-carboxamido-1-methyl-4-piperidinol (1.2 g.), as colourless prisms, m.p. 145°.

Infra-red: $\nu_{max.}$ (film), 3200 cm.$^{-1}$, 3400 cm.$^{-1}$, 3460 cm.$^{-1}$ (OH, NH_2), 2790 cm.$^{-1}$ ($>N-CH_3$), 1665 cm.$^{-1}$ (amide I), 1635 cm.$^{-1}$ (amide II), 1050 cm.$^{-1}$, 1075 cm.$^{-1}$ (OH).

Analysis Found: C, 53.0; H, 9.0; N, 17.7%; equiv., 163. $C_7H_{14}N_2O_2$ requires : C, 53.2; H, 8.9; N, 17.7%; equiv., 158.

5-Cyano-1,2,3,4-tetrahydro-4-oxo-1-phenethyl-pyridine



Potassium permanganate (3.5 g.) in acetone (200 ml.) was added dropwise to a stirred solution of 4-amino-3-cyano-1,2,5,6-tetrahydro-1-phenethyl-pyridine (5 g.) in acetone (100 ml.). Water (100 ml.) was added, the manganese dioxide filtered off and the acetone evaporated under reduced pressure. The precipitate was crystallised from ethanol to give 5-cyano-1,2,3,4-tetrahydro-4-oxo-1-phenethyl-pyridine (3 g.), as pale yellow needles, m.p. 169°.

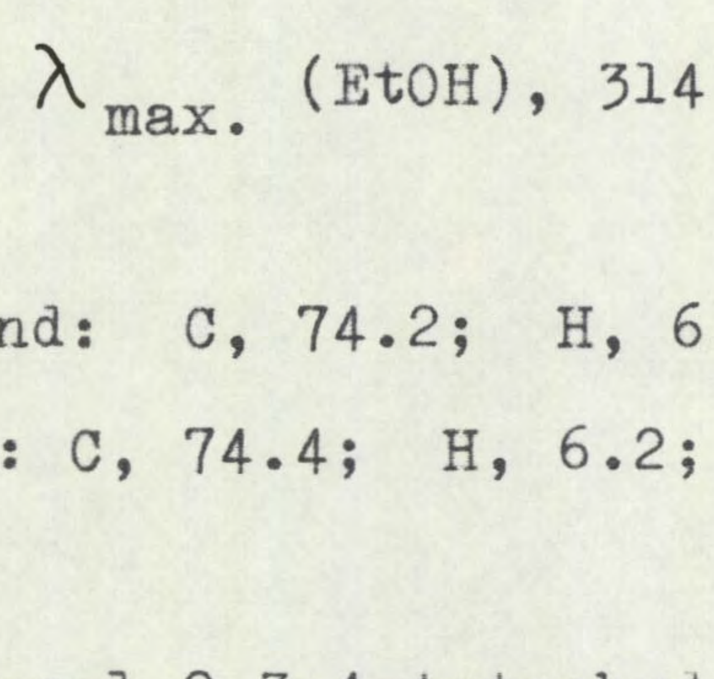
Infra-red: $\nu_{max.}$ (Nujol), 2200 cm.$^{-1}$ (C≡N), 1650 cm.$^{-1}$ (C=C), 1620 cm.$^{-1}$ (C=O).

N.M.R.: τ(T.F.A.), 2.1 (S, H), 2.7 (S, 5H), 6.2 (Q, 4H), 7.1 (M, 4H).

Ultra-violet: $\lambda_{max.}$ (EtOH), 314 mμ (15300), 229 mμ (11100).

Analysis Found: C, 74.2; H, 6.6; N, 12.3%.
$C_{14}H_{14}N_2O$ requires : C, 74.4; H, 6.2; N, 12.4%.

1-Benzyl-5-cyano-1,2,3,4-tetrahydro-3-methyl-4-oxo-pyridine



a) 4-Amino-1-benzyl-3-cyano-1,2,5,6-tetrahydro-5-methyl-pyridine (3 g.) in acetone (100 ml.) with potassium permanganate (2.1 g.) in acetone (200 ml.) similarly gave a solid which crystallised from benzene/pet. ether (40-60°) to give 1-benzyl-5-cyano-1,2,3,4-tetrahydro-3-methyl-4-oxo-pyridine (.5 g.), as white needles, m.p. 104°.

Infra-red: $\nu_{max.}$ (Nujol), 2210 cm.$^{-1}$ (C≡N), 1590 cm.$^{-1}$ - 1660 cm.$^{-1}$ (C=C, C=O).

N.M.R.: τ ($CDCl_3$), 2.14 (S, H), 2.6 (S, 5H), 5.38 (S, 2H), 6.2-7.7 (M, 3H), 8.9 (D, 3H).

Analysis Found: C, 74.2; H, 6.1, N, 12.4%.
$C_{14}H_{14}N_2O$ requires : C, 74.3; H, 6.2; N, 12.4%.

b) Potassium permanganate (1.2 g.) in water (200 ml.) was added dropwise to a stirred solution of 1-benzyl-3-cyano-5-methyl-4-piperidone hydrochloride (2 g.) and sodium bicarbonate (2 g.) in water (50 ml.). The solution was extracted with chloroform (3 x 100 ml.), the organic layers combined, dried (anhy. Na_2SO_4) and evaporated, yielding a pale yellow oil which solidified and crystallised from ethyl acetate to give 1-benzyl-5-cyano-1,2,3,4-tetrahydro-3-methyl-4-oxo-pyridine (1 g.), m.p. undepressed on admixture with an authentic sample.

Attempted preparation of 5-cyano-1,2,3,4-tetrahydro-4-oxo-pyridine

a) Potassium permanganate (2.6 g.) in acetone (400 ml.) was added dropwise to a stirred solution of 4-amino-3-cyano-1,2,5,6-tetrahydro-pyridine (2 g.) in acetone (200 ml.) and water (11 ml.). The manganese dioxide was filtered off and the acetone evaporated, yielding starting material (1 g.), m.p. undepressed on admixture with authentic material.

b) Potassium permanganate (1.3 g.) in water (50 ml.) was added dropwise to a stirred solution of 4-amino-3-cyano-1,2,5,6-tetrahydro-pyridine (1 g.) in water (10 ml.). The precipitated manganese dioxide was filtered off, the filtrate saturated with K_2CO_3 and continuously extracted with chloroform. The chloroform extract was dried (anhy. Na_2SO_4) and evaporated, yielding starting material (.6 g.), m.p. undepressed with an authentic sample.

c) 1-Benzyl-5-cyano-1,2,3,4-tetrahydro-4-oxo-pyridine (1 g.) in ethanol (150 ml.) was shaken with hydrogen at atmospheric pressure in the presence of 10% palladised charcoal (1 g.). After 4 hours, 450 ml. of hydrogen had been absorbed. The catalyst was filtered off and the solvent evaporated, yielding a yellow oil (1 g.). Thin layer chromatography of the oil showed the presence

of six major spots. Attempts to solidify the oil failed.

Further reactions with 4-amino-1-benzyl-3-cyano-1,2,5,6-tetrahydro-pyridine

Attempted reduction of the enamine function

a) Sodium borohydride (.5 g.) was added to a solution of 4-amino-1-benzyl-3-cyano-1,2,5,6-tetrahydro-pyridine (2 g.) in ethanol (200 ml.). The solution was stirred for 17 hours, water (100 ml.) added and the ethanol removed under reduced pressure to give starting material (2 g.), m.p. 154°, undepressed on mixing with an authentic sample.

b) Sodium borohydride (.5 g.) was added to a solution of 4-amino-1-benzyl-3-cyano-1,2,5,6-tetrahydro-pyridine (2 g.) in isopropanol (100 ml.). The solution was refluxed for 4 hours, water (100 ml.) added and the solution allowed to stand. Starting material (2 g.) was recovered.

c) Sodium borohydride (1 g.) and 4-amino-1-benzyl-3-cyano-1,2,5,6-tetrahydro-pyridine (2 g.) were refluxed in diglyme (100 ml.) for 24 hours, yielding starting material (2 g.).

d) 4-Amino-1-benzyl-3-cyano-1,2,5,6-tetrahydro-pyridine (1 g.) in ethanol (200 ml.) was shaken with hydrogen at atmospheric pressure in the presence of

platinum oxide (100 mg.). After 24 hours, a negligible amount of hydrogen had been absorbed. The catalyst was filtered off and the solvent evaporated, yielding starting material.

Attempted Diels-Alder cyclisations with 4-amino-1-benzyl-3-cyano-1,2,5,6-tetrahydro-pyridine

a) 4-Amino-1-benzyl-3-cyano-1,2,5,6-tetrahydro-pyridine (2 g.) was refluxed with furan (2 ml.) in ethanol (50 ml.) for 2 hours. Evaporation of the solvents yielded starting material (2 g.), m.p. undepressed on admixture with authentic sample.

b) The enamine (2 g.) was refluxed with furan (2 ml.) in benzene (50 ml.) for 24 hours, yielding starting material.

c) The enamine (1 g.) was heated with isoprene (5 ml.) and xylene (50 ml.) in a sealed tube to 104° for 60 hours to yield starting material.

d) The enamine (1 g.), cyclopentadiene (20 ml.) and ethanol (20 ml.) were refluxed for 60 hours, yielding starting material.

e) The enamine (1 g.) was refluxed in cyclopentadiene (50 ml.) for 5 hours, yielding starting material.

Attempted reaction with acetic anhydride

4-Amino-1-benzyl-3-cyano-1,2,5,6-tetrahydro-pyridine (2 g.) was refluxed in acetic anhydride (2 ml.) and pyridine (5 ml.) for 3 hours. Evaporation of the solvent gave a black tar, which could not be induced to solidify. Attempts to form a solid hydrochloride salt failed.

Attempted reaction with acetyl chloride

Acetyl chloride (.75 gm.) in chloroform (10 ml.) was added dropwise to a stirred solution of 4-amino-1-benzyl-3-cyano-1,2,5,6-tetrahydro-pyridine (2 g.) and sodium bicarbonate (2 g.) in chloroform (50 ml.). The mixture was refluxed for 2 hours, the inorganic layer filtered off and the solvent evaporated, yielding a yellow oil (2.2 g.) which could not be induced to solidify or crystallise. An attempt to form a hydrochloride failed. Infra-red spectra suggest that a C=O group is present.

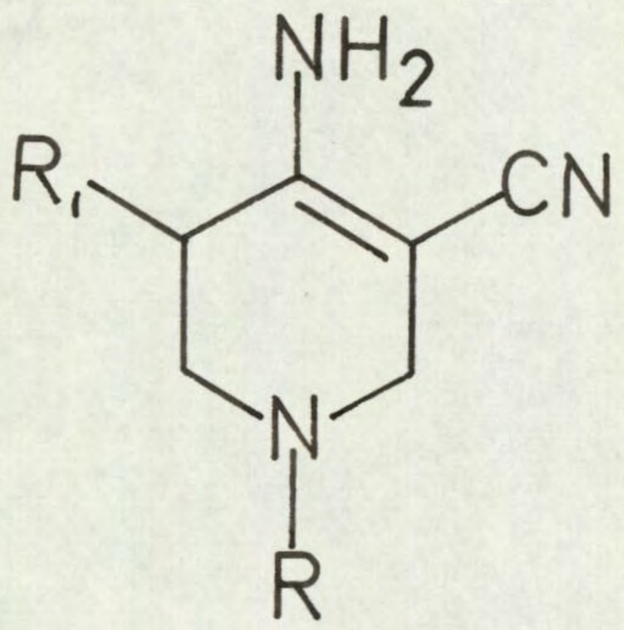
Section IV

Pharmacological Results

Pharmacological Results

A number of compounds prepared in the present investigation were subjected to a pharmacological screen designed to detect a range of central nervous system effects, certain cardiovascular activities, the effect on smooth muscle and useful antibacterial activity.

Compounds of type 1



Compound	R	R_1
I	$C_6H_5CH_2$	H
II	$C_6H_5CH_2$	CH_3
III	$C_6H_5CH_2CH_2$	H
IV	CH_3	H

a) Central Nervous System Activity

At an oral dose of 100 mg./kg., compounds I and IV were found to be inactive while compound II induced

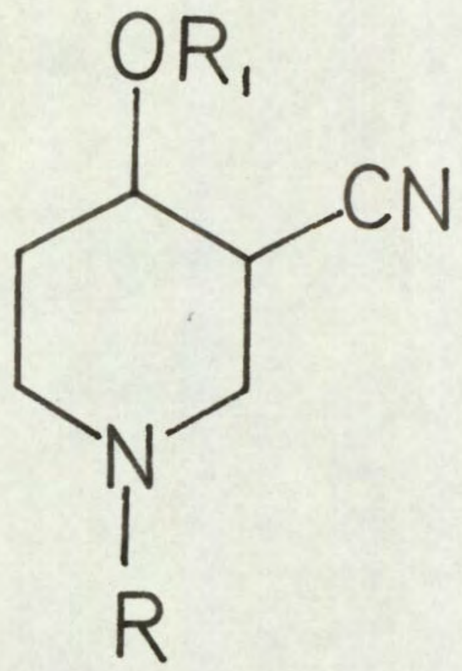
hypothermia (0.9°), was active in inhibiting the effect on 5-hydroxy-tryptamine-induced head twitch response and in the tail clip test brought about 60% inhibition.

Compound III at an oral dose of 100 mg./kg. showed 67% inhibition in a tail clip test while at 100 mg./kg. (S.C.) it showed 60% inhibition in a hot plate test.

b) Cardiovascular Activity

Compound II, when tested at 9 mg./kg. I.V. was inactive when tested for effects in anaesthetised dog. At 10 mg./kg. it had no effect on smooth muscle. Compound IV was also found to be inactive. Compounds I and III were not tested.

Compounds of type 2



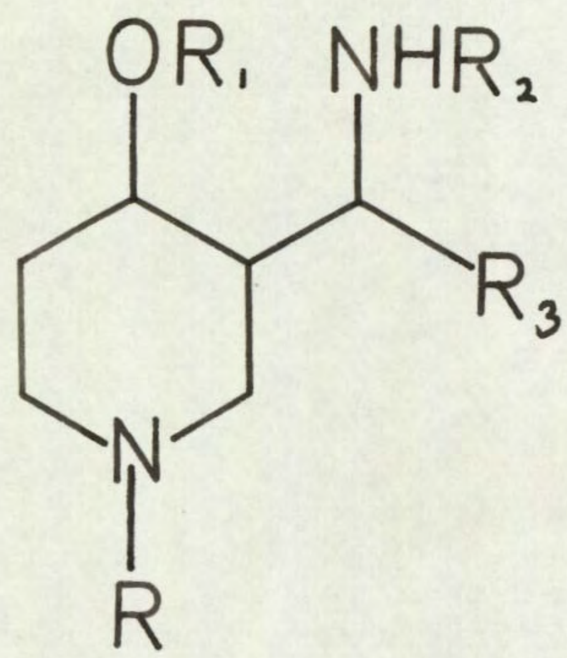
Compound	R	R_1
V	$C_6H_5CH_2$	H
VI	$C_6H_5CH_2$	$COCH_3$
VII	$C_6H_5CH_2CH_2$	$COCH_3$

Central Nervous System Activity

Compounds V and VI, when tested orally at 100 mg./kg. were found to be inactive.

Compound VII, at 50 mg./kg. orally, when tested for effects on central cholinergic mechanism had no effect in terms of tremor but produced marked hypothermia.

Compounds of type 3



Compound	R	R_1	R_2	R_3
VIII	$C_6H_5CH_2$	H	H	H
IX	$C_6H_5CH_2$	$COCH_3$	$COCH_3$	H
X	$C_6H_5CH_2$	H	H	C_6H_5
XI	$C_6H_5CH_2$	$COCH_3$	$COCH_3$	C_6H_5
XII	CH_3	H	H	H
XIII	CH_3	$COCH_3$	$COCH_3$	H
XIV	CH_3	H	H	C_6H_5
XV	C_2H_5	H	H	H
XVI	C_2H_5	$COCH_3$	$COCH_3$	H

Compounds X and XI were obtained in two geometric isomeric forms, isomer A being cis 3/4 disubstituted and isomer B being trans 3/4 disubstituted.

a) Central Nervous System Activity

Compounds X (isomer A), XI (isomer A), IX, XII, XV and XVI showed only negligible activity in the tests applied.

Compound VII, tested at 50 mg./kg. orally for effects on central adrenergic receptors, produced moderate hypothermia.

Compound X (isomer B) at 100 mg./kg. orally showed moderate activity in inhibiting the effect on 5-hydroxy-tryptamine-induced head twitch response, while at 50 mg./kg.

orally, when tested for effects on central cholinergic mechanism, produced moderate hypothermia.

Compound XIII, at a dose of 100 mg./kg. (S.C.) produced 87% inhibition in a hot plate test and was markedly active at 50 mg./kg. orally when tested for effects on central adrenergic receptors, producing moderate hypothermia.

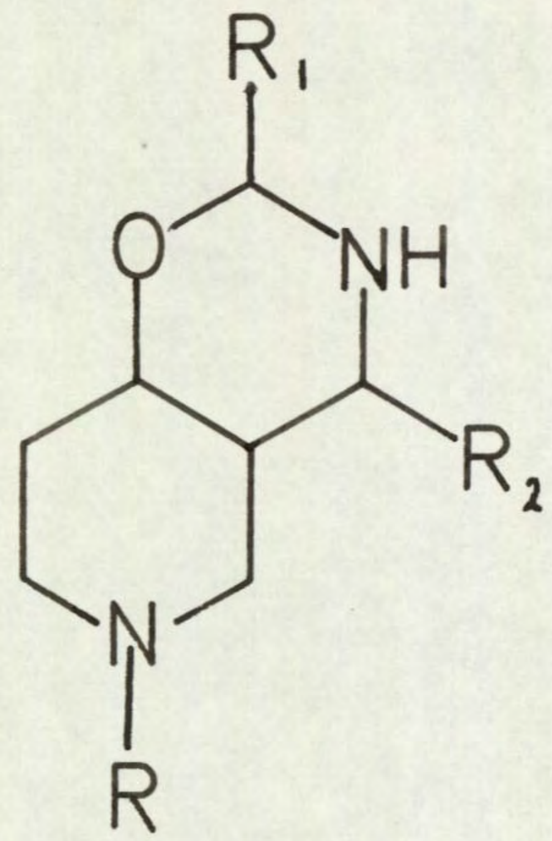
b) Cardiovascular Activity

At 10 mg./kg. I.V. in anaesthetised dog, compounds VIII, XVI, XII and XIV were inactive.

Compound X (isomer B), when tested at 10 mg./kg. I.V. in anaesthetised dog, produced a fall in blood pressure of 20 mm. Hg which lasted 20 minutes. The heart rate was decreased over a similar period of time while the respiration rate increased. It had no effect on either C.O. reflex or isoprenaline however.

The (A) isomer of compound X, at 9 mg./kg. I.V. in anaesthetised dog, was found to be virtually inactive, though the heart rate was reduced.

Compounds of type 4



Compound	R	R_1	R_2	isomers
XVII	$C_6H_5CH_2$	C_6H_5	C_6H_5	A, B
XVIII	$C_6H_5CH_2$	p-$C_6H_4N(CH_3)_2$	C_6H_5	A
XIX	$C_6H_5CH_2$	o-$C_6H_4OCH_3$	C_6H_5	A
XX	$C_6H_5CH_2$	p-C_6H_4F	C_6H_5	A, B
XXI	$C_6H_5CH_2$	3,4-$C_6H_3(OCH_3)_2$	C_6H_5	A
XXII	$C_6H_5CH_2$	m-$C_6H_4OCH_3$	C_6H_5	A
XXIII	$C_6H_5CH_2$	$CH_3CH_2CH_2$	C_6H_5	A
XXIV	$C_6H_5CH_2$	p-$C_6H_4OCH_3$	C_6H_5	A
XXV	$C_6H_5CH_2$	= O	C_6H_5	A
✱ XXVI	$C_6H_5CH_2$	o-C_6H_4OH	C_6H_5	A

✱ Compound XXVI is thought to exist as the open chain analogue rather than the cyclic oxazine.

a) Central Nervous System Activity

At 100 mg./kg. oral dose, compounds XVII (isomer B), XXIII, XXVI, XX (isomer B), XXII and XXIV were inactive or showed only negligible activity in the tests applied.

Compound XXI was inactive in all the tests applied except the tail clip test, where 52% inhibition (equivalent to a fifth of the activity of codeine) occurred. Under similar conditions compound XVII (isomer A) showed only slight activity.

Compound XX (isomer A) had an oral L.D.50 mg./kg. >100. When given orally at 100 mg./kg. this compound showed only a slight Straub tail effect, had slight activity in the tail clip test and had a marked effect on phenylquinone-induced writhing, the activity being approximately equal to that of aspirin.

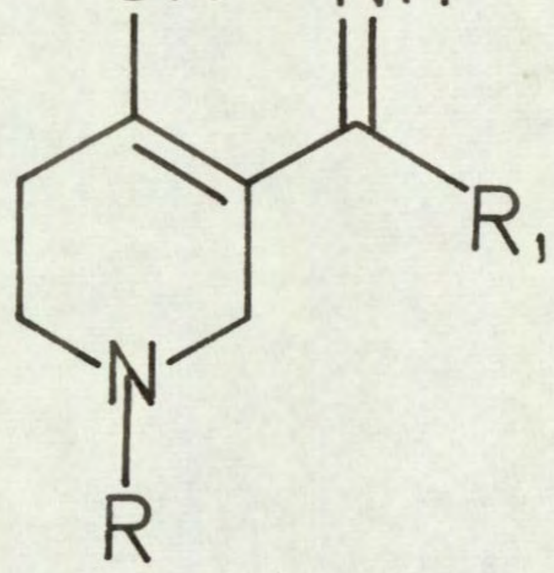
A similar effect and of the same order was found in compound XIX on phenylquinone-induced writhing. In addition, in a test for antiinflammatory activity using carrageenin , the compound exhibited a moderate activity at 200 mg./kg., being about a tenth as active as Indomethacin. At 100 mg./kg. orally there was antagonism of leptazol-induced convulsions, the activity being of the order of a tenth that of chlordiazepoxide.

Compound XVIII, when tested for effects on central adrenergic receptors, at a dose of 50 mg./kg. orally,

produced moderate hypothermia.

There was a fall in body temperature of 1^{o} when compound XXV was given orally at 100 mg./kg. In addition, the compound had marked activity at 100 mg./kg. orally in the effects on phenylquinone-induced writhing, and in an antiinflammatory test at 200 mg./kg. orally using carrageenin, exhibited about one tenth the activity of Indomethacin.

Compounds of type 5



Compound	R	R_1
XXVII	$C_6H_5CH_2$	C_6H_5
XXVIII	$C_6H_5CH_2$	C_2H_5
XXIX	CH_3	C_6H_5

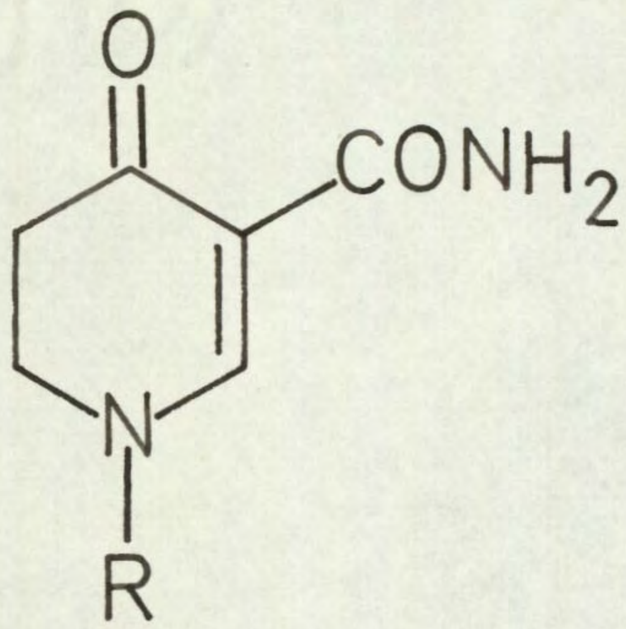
Central Nervous System Activity

Compound XXIX, when tested at 100 mg./kg. orally in mice, produced a jerky gait and hypothermia of 0.7°.

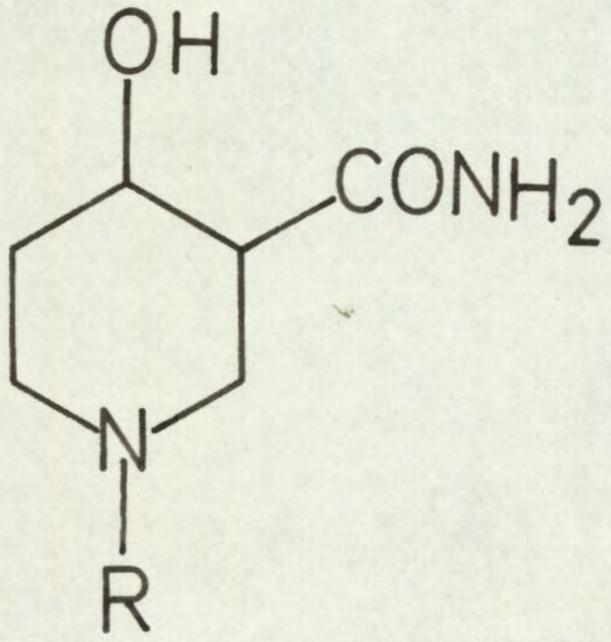
Compound XXVIII under similar conditions in the mouse induced a slow gait and there were indications of the limbs being splayed.

Compound XXVII at 100 mg./kg. orally in a phenylquinone-induced writhing test was moderately active. A dose of 50 mg./kg. orally produced marked hypothermia when testing for effects on central adrenergic receptors.

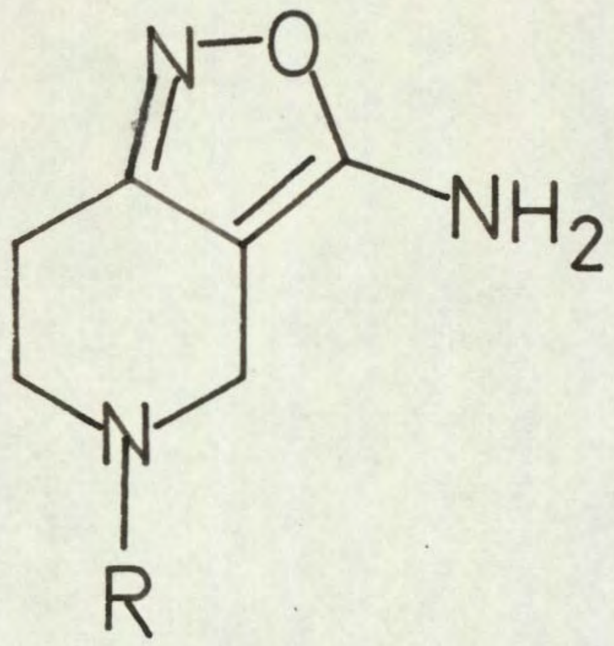
Miscellaneous Compounds



Compound	R
XXX	$C_6H_5CH_2$
XXXI	CH_3



XXXII	$C_6H_5CH_2$



Compound	R
XXXIII	$C_6H_5CH_2$
XXXIV	$C_6H_5CH_2CH_2$

a) Central Nervous System Activity

Compounds XXX, XXXI and XXXII, at 100 mg./kg. orally, had no significant activity.

b) Cardiovascular Activity

Compound XXXI, at 10 mg./kg. I.V. had no effect on anaesthetised dog.

In an anaesthetised dog at 10 mg./kg. I.V., compound XXXIV reduced the blood pressure by 30 mm. Hg for a short period. The heart rate was reduced by 30% and the respiration rate increased.

Under similar conditions, compound XXXIII showed no significant effect on the cardiovascular system. At 5 g./kg. in an atria preparation using guinea pig ileum, acetylcholine response was reduced by 30% and there was no effect on 5-hydroxy-tryptamine. A similar dose on rabbit duodenum proved negative. The compound probably had weak anticholinergic activity.

Antibacterial activity

All the compounds mentioned in the preceding reports were found to have no useful anti-bacterial properties.

Appendix

APPENDIX

Determination of Equivalent Weights

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

Preparation of Picrate Salts

A 10% excess of picric acid was dissolved in a minimum quantity of boiling ethanol and the solution added to a hot solution of the base in ethanol. The picrate which separated on cooling was crystallised from a suitable solvent.

Preparation of Hydrochloride Salts

The base was dissolved in a warm 10% w/v solution of HCl in ethanol and allowed to stand. The salt which separated was generally crystallised from ethanol/ether.

Ultra-violet Absorption Spectra

Ultra-violet spectra were recorded, usually in ethanol, using a Unicam S.P. 800 spectrophotometer.

Infra-red Absorption Spectra

Infra-red spectra were recorded using a Unicam S.P. 200 spectrophotometer. The samples were run as mulls in liquid paraffin or as a solution in chloroform. Major peaks only are recorded except when assignment of a minor peak is obvious.

Nuclear Magnetic Resonance Spectra

Nuclear Magnetic Resonance spectra were determined in chloroform-d on a Varian A60A spectrometer using tetra-methyl silane as an internal standard. All the peaks are assigned in terms of τ values.

Mass spectra

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

Compounds were deemed to be starting materials when their melting points were undepressed on admixture with an authentic sample of the starting compound. Mixed melting points were taken also of compounds suspected to be isomers.

I wish to thank Allen and Hanbury's Ltd. for carrying out the pharmacological screening reported in the thesis.

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