12/10/76

SYNTHESIS OF DEHYDROPERLOLINE

AND

OF LACTAM ANTAGONISTS OF

γ-AMINOBUTYRIC ACID (GABA)

A THESIS

PRESENTED FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

IN

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BY

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C O N T E N T S

Erratum

The reader's attention is drawn to the fact that pp. 91 and 92 have been inadvertently bound before p. 90 and are out of order. Similarly p. 155 has been bound in front of p. 154.

Thach Duong.

Chapter 6 contains the results of testing of some lactams and thiolactams as well as their structure-activity relationships.

* * *

STATEMENT

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

THACH DUONG

ACKNOWLEDGEMENTS

I wish to express my sincere thanks to Dr. R.H. Prager for his guidance, encouragement and enthusiasm during the supervision of this work. I also wish to thank my colleagues in the laboratory and some staff members for their help. In particular, I am indebted to Dr. A.D. Ward for very helpful discussions and to Mr. G. Frith for preparing caprolactams 9, 10 and 11.

The biological testing of synthetic compounds has been conducted by Dr. D.I.B. Kerr and Miss E. Breuker of the Department of Human Physiology and Pharmacology, University of Adelaide, South Australia, and I am happy to acknowledge this help.

This research was carried out during the tenure of a Colombo Plan Award sponsored by Australian Government for which I am grateful.

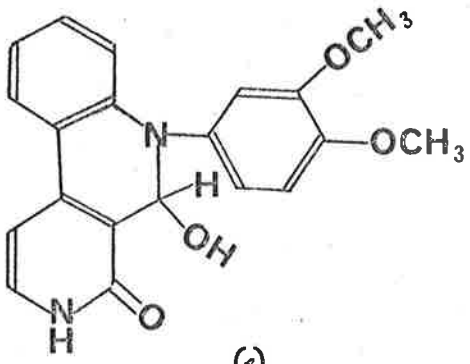
* * *

PART 1

SYNTHESIS OF DEHYDROPERLOLINE

INTRODUCTION

Several alkaloids containing a diazaphenanthrene skeleton have been discovered in various species of grass. Perloline, the most abundant member of this family was first isolated by Melville and Grimmett[1] from Lolium perenne L (New Zealand rye-grass) and became the target for most structural investigations. After studying its ultraviolet spectra and the analytical data, Metcalf[2] concluded that perloline contained a dimethoxyphenyl group and its structure was subsequently shown to be 1 by x-ray analysis[3].

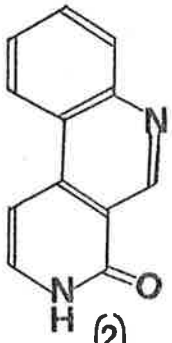


(1)

Because of the widespread use of L-perenne in pastures, a detailed investigation of perloline has been made[4]. This alkaloid has been subjected to a number of investigations dealing with the extraction of perloline and other bases from grass[5], its estimation in grass[6], its characterisation and chemistry[7], its toxicity and physiological effects[8,9], its effect on plant growth[10], and the effect of genetic differences on the perloline content of rye-grass herbage[11].

It was reported[12] that the oxidation of perloline proceeded easily and afforded a variety of products all of which contained nitrogen. The degradation[13] of perloline gave perlolidine (2) and a colourless non basic material dehydroperloline (3).

Perlolidine was first isolated and characterised in New Zealand [14,15] and it was the base responsible for the blue fluorescence



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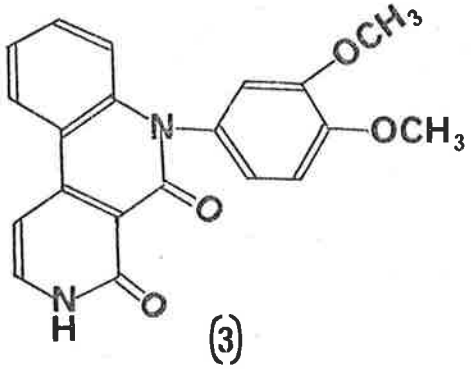


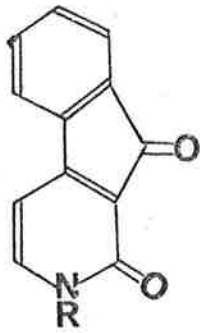
(3)

of zone 3 on the paper chromatograms described by Jeffreys[16]. This alkaloid has been synthesised by two different routes[17,18].

Because of the physiological activity of these alkaloids, intensive studies have been reported on the extraction of perloline from other species of grass[4], but no synthetic work has yet been reported on either perloline or on dehydroperloline (3). It was therefore the aim of this work to synthesise the latter. The methods used are easily adaptable to the synthesis of the former, although this has not been pursued.

DISCUSSION

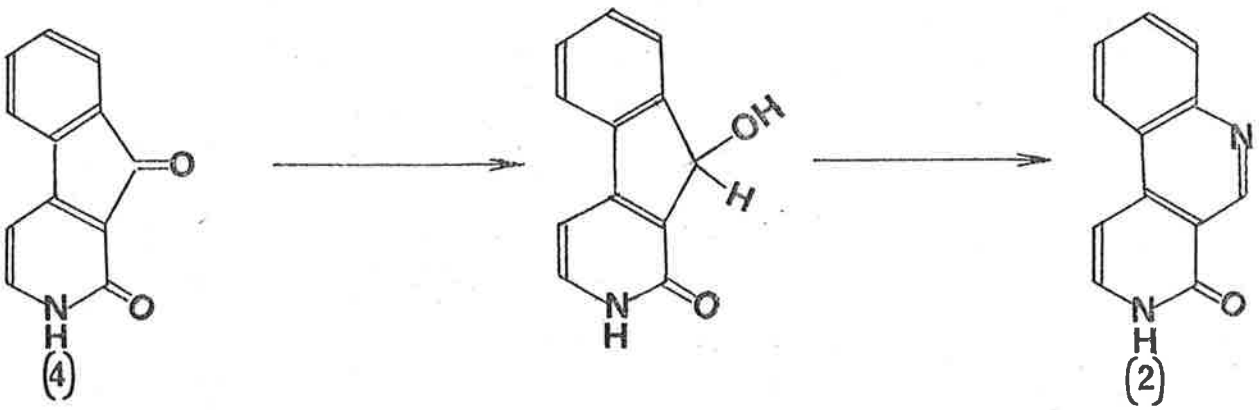
A suitable starting compound for the proposed synthesis appeared to be the fluorenones 4 or 5.



4 R=H

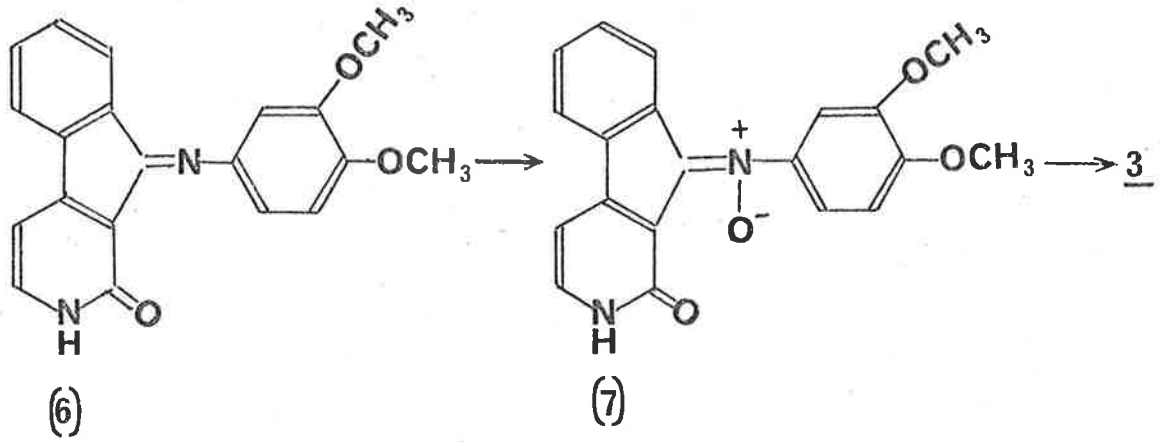
5 R=CH_3

Compound 4 had been used by Powers and Ponticello[17] as the key intermediate for the synthesis of perlolidine (2) (scheme 1).



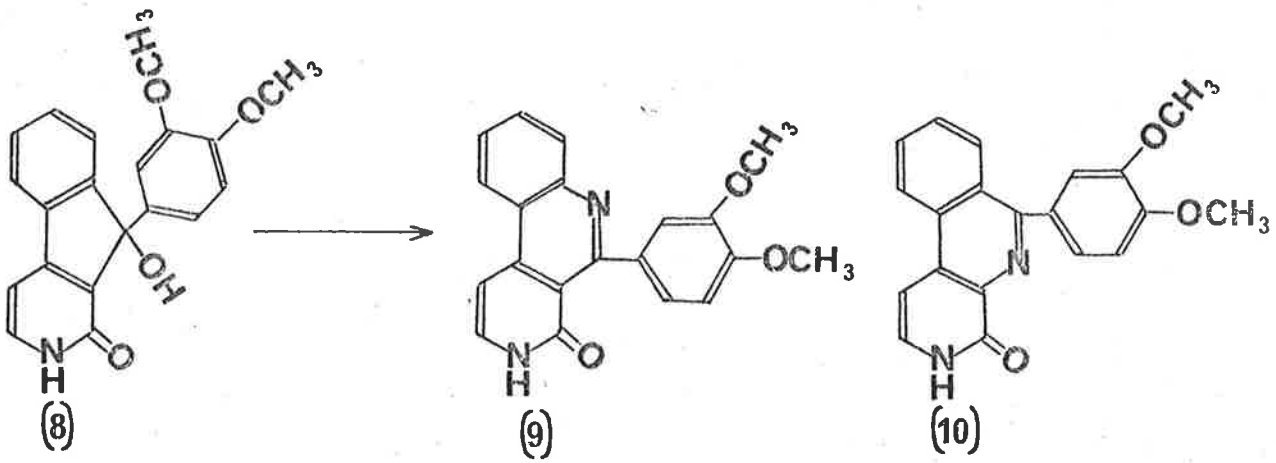
Scheme 1

Two methods for the conversion of 4 to 3 were considered. Conversion of 4 or 5 to a Schiff base 6 by the method of Reddlien[19] with 4-aminoveratrole followed by treatment with m-chloroperoxybenzoic acid[20] (m-CPBA) would give the N-oxide 7 (Scheme 2). Irradiation[21] of 7 would subsequently afford the required product 3, although other products are possible (see below).



Scheme 2

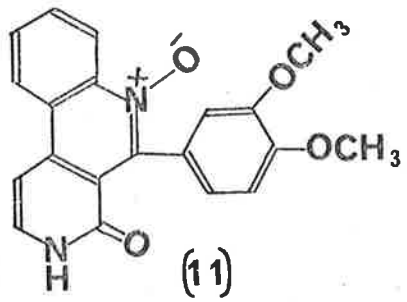
Alternatively, reaction of ketone 4 with the Grignard reagent derived from 4-bromoveratrole would lead to the fluorenol 8 which should undergo the Schmidt reaction to produce 9 and/or 10 (Scheme 3).



Scheme 3

Recent reviews[22,23,24] on the mechanism and migratory aptitude of the Schmidt reaction have indicated that in the case of alcohols and 9-fluorenols in particular, the ring having the

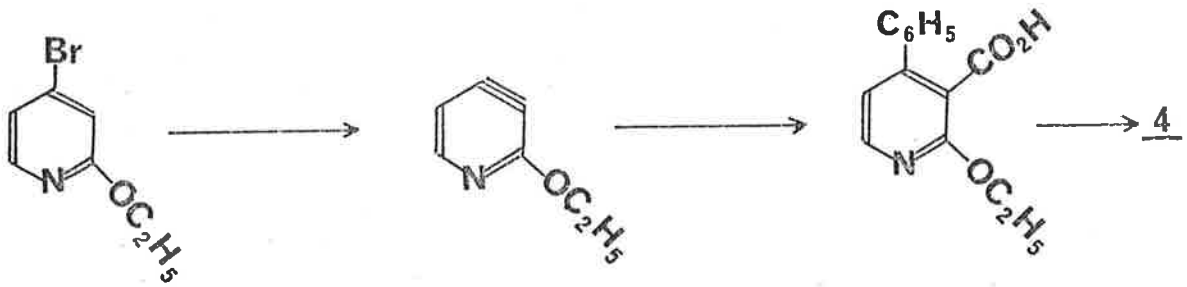
greater electron-release will migrate predominantly and therefore compound 9 is likely to be the major product. With m-CPBA in chloroform, 9 should give the N-oxide 11, irradiation of which would yield 3.



(11)

A consideration of the synthetic routes to the intermediates 4 and 5 is also in order. Although 4 had been prepared by Powers and Ponticello[17], alternative routes were investigated.

Conversion of 3-carboxy-2-ethoxy-4-phenylpyridine (12) into 4 by acid cyclisation[25] appeared to be a promising route (Scheme 4).



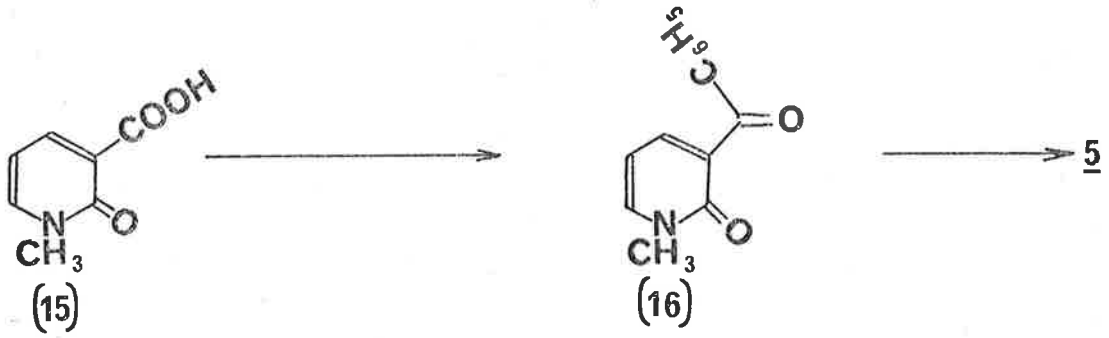
(13) (14) (12)

Scheme 4

However, the success of this Scheme depends on an efficient synthesis of acid 12. It was hoped that 3, 4-dehydro-pyridine 14

could be formed selectively from 4-bromo-2-ethoxy-pyridine[26] (13) and the addition of phenyllithium to 14 would lead to the desired product 12.

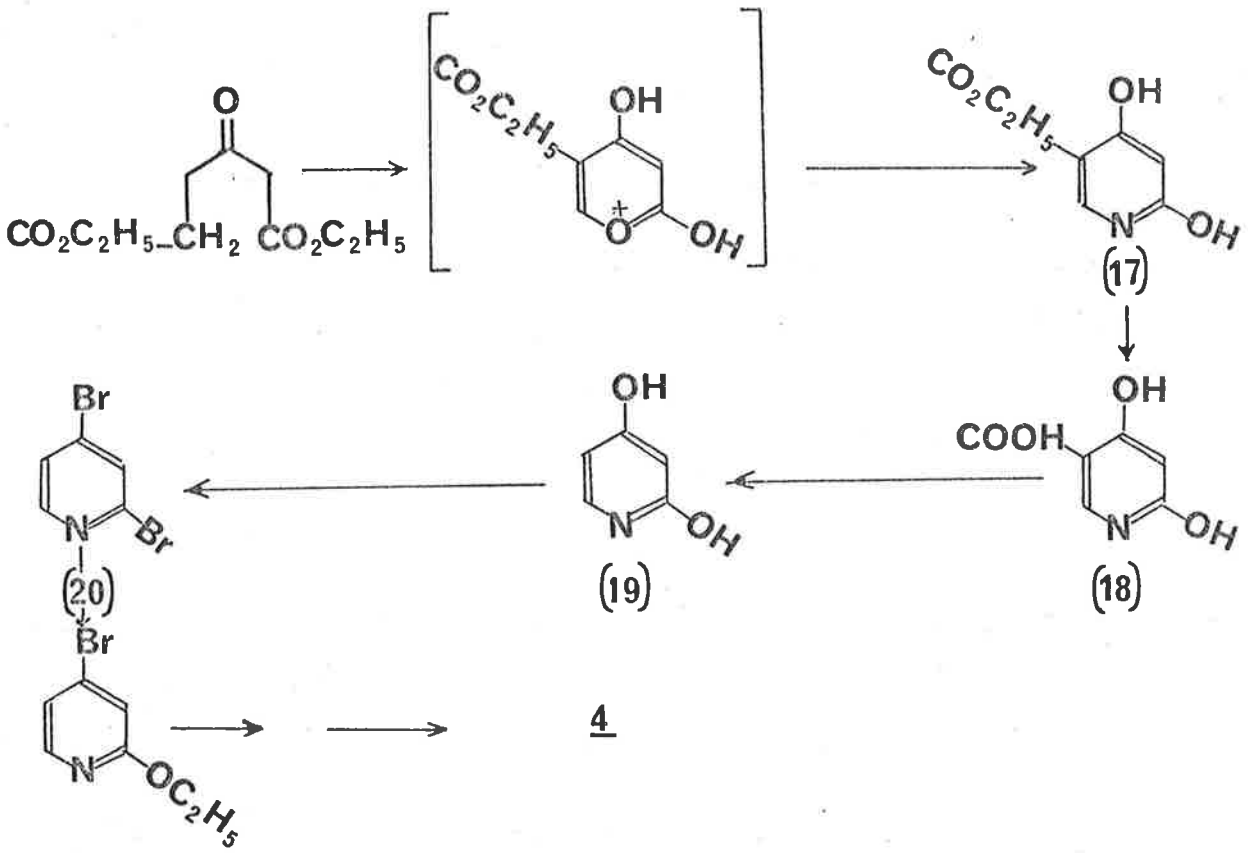
An alternative route was also investigated. Conversion of N-methyl-2-pyridone-3-carboxylic acid (15) to 5 by photolysis[27,28] of 16 or via the thallium (111) trifluoroacetate (TTFA) adduct[29] appeared to be hopeful routes (Scheme 5).



Scheme 5

Application of these synthetic routes to an eventual synthesis of dehydroperloline 3 are now discussed in full detail.

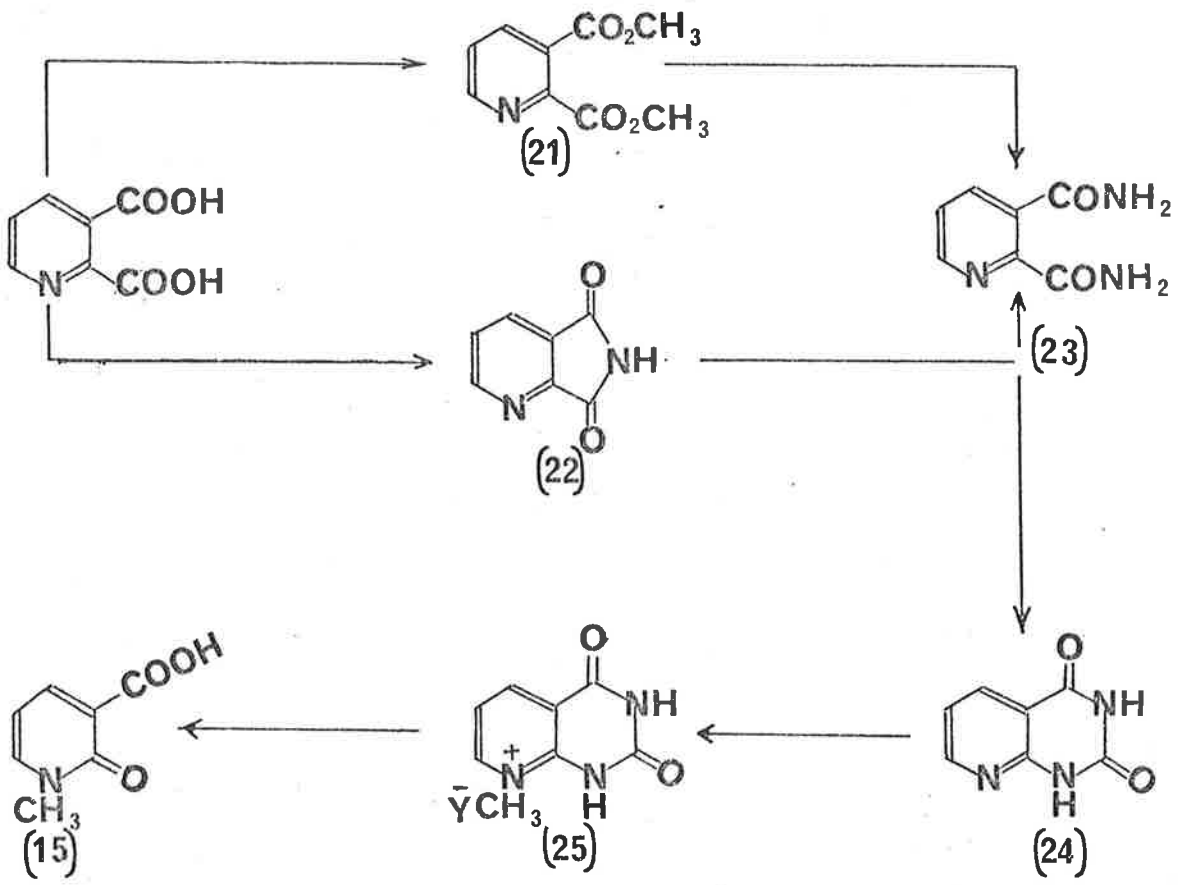
Ethyl-2, 4-dihydroxypyridine-5-carboxylate (17) was prepared by condensation of ethyl acetonedicarboxylate with ethyl orthoformate under the influence of acetic anhydride and concentrated ammonia[32] (Scheme 6), but attempts to convert this ester to 2, 4-dihydroxypyridine (19) were only partially successful. The decarboxylation method used was that of Errera[33] who obtained 19 by heating the acid 18 at 190-200°, but in the present study no decarboxylation was observed. On subliming a mixture of 18 and



Scheme 6

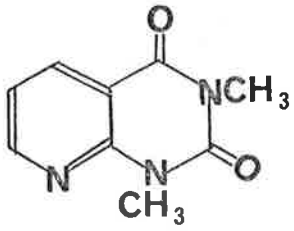
copper powder at 280-300° under reduced pressure, again only a small amount of the desired product was collected. Because of the above mentioned low-yield step in this route, the proposal outlined in Scheme 4 has not been pursued and other methods of synthesis have been investigated.

Although N-methyl-2-pyridone-3-carboxylic acid 15 had been prepared by Holman and Wiegand[30] in low yield from nicotinamide, another method was examined in order to obtain a more convenient supply. It was hoped to synthesise acid 15 from quinolinic acid following the reactions shown in Scheme 7.



Scheme 7

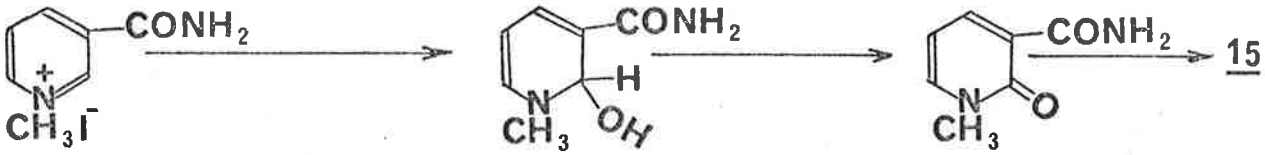
Saturating a methanolic solution of methylquinolate (21) or quinolinimide (22) with ammonia at 0^{o} gave quinolinamide (23). Treatment of this amide with alkaline potassium hypobromite gave only a low yield of pyridopyrimidine (24) together with 2-amino-nicotinic acid[34]. More recently, Beckwith and Hickman[35] have been able to convert quinolinamide (23) into 24 in high yield by using lead tetraacetate in dimethyl formamide (DMF). It was hoped that the hydrolysis of quaternary salt 25 would yield the expected product 15. Unfortunately, 24 could not be converted to its salt 25 by any means tried including methyl fluorosulphonate. In all cases, it was observed that only the 1- and 3- positions were methylated to give 26 in moderate yield. This product was identical with an authentic specimen prepared according to the



(26)

procedure of McLean and Spring[34].

As the above method was unsuccessful, acid 15 was finally prepared following the method of Holman and Wiegand[30] (Scheme 8).

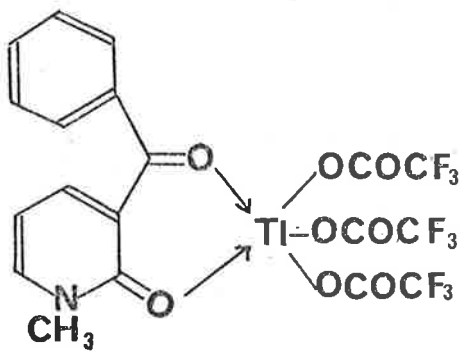


Scheme 8

The condensation of acid chlorides with a variety of aromatic compounds via an intermolecular Friedel-Crafts reaction has been described[36]. The acid chloride 27 derived from 15 reacted with benzene in the presence of aluminum chloride to give 16 in 45% yield. Because of the unsatisfactory yield of this condensation, the preparation of 16 was attempted from 15 or 27 by reaction with two equivalents or excess of phenyllithium [37] but in both solvents

ether and tetrahydrofuran over a range of temperature only very low yields of product were isolated. Thin layer chromatography examination of the reaction mixture showed that it did indeed contain the product 16 obtained previously by Friedel-Crafts reaction. Unfortunately, all attempts to cyclise 16 photochemically[27] by using benzene as solvent in the presence of a small amount of iodine failed to yield the expected product. Repetition of this method with methanol[28] as solvent was also unsuccessful.

Using a method analogous to that of McKillop et al[29], the preparation of 5 by thallation of 16 with thallium (111) trifluoroacetate (TTFA) in trifluoroacetic acid (TFA), followed by photolysis[38] of the intermediate thallium compound 28 in benzene was investigated (Scheme 9), but this, too, was fruitless. After reaction of 16 with TTFA/TFA, an intermediate organo-thallium compound was obtained which is believed to have the structure 29 since aqueous work up regenerated the benzoyl pyridone 16



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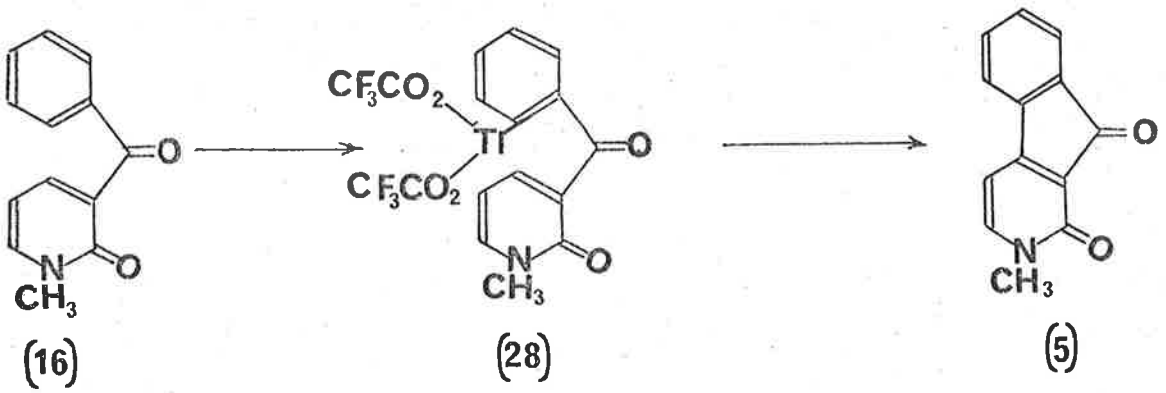
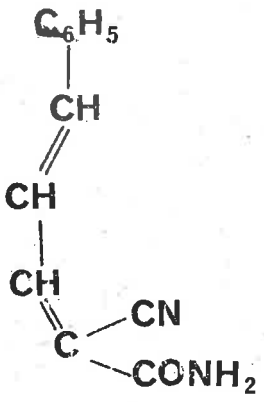


(16) (28) (5)

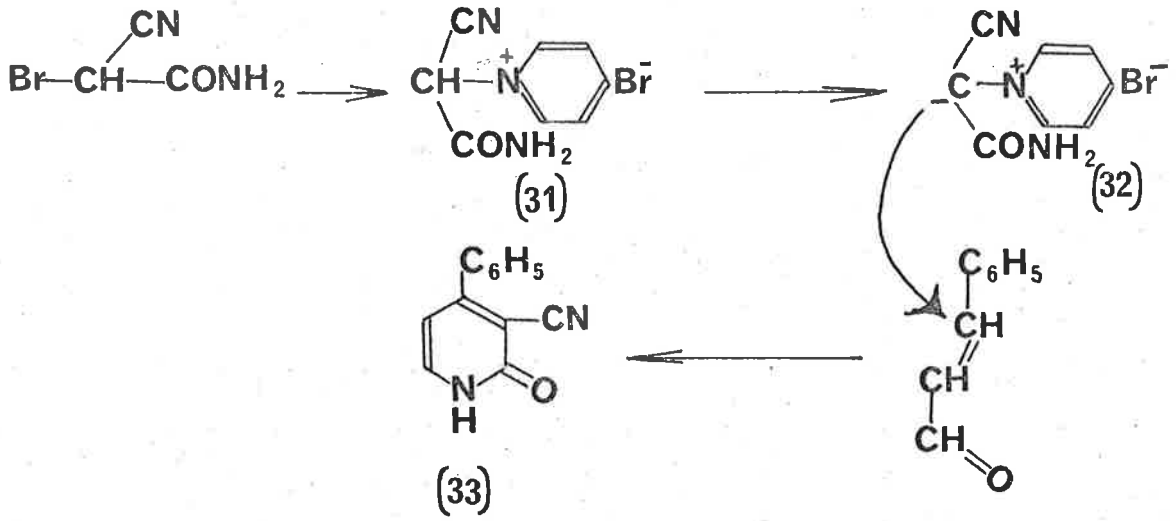
Scheme 9

Although the key intermediate 4 has been prepared in low yield[17], it was hoped that alternative methods for its preparation could be developed. With N-bromosuccinimide (NBS) in boiling chloroform, cyanoacetamide gave a good yield of bromocyanoacetamide. Using a method analogous to that of Thesing and Lüler[31], the preparation of 4 from pyridine, bromocyanoacetamide and cinnamaldehyde in the presence of sodium hydroxide was attempted but this was unsuccessful and gave a quantitative yield of a yellow product which was identified as 30 by spectroscopic analysis and by mixed melting point with an authentic specimen prepared according to the procedure of Curtis et al[39].



(30)

In this Scheme, it was hoped that pyridine would react with bromocyanoacetamide to give pyridinium salt 31 (Scheme 10) which formsthe ylid 32 in the presence of base and would add in a 1,4 manner to cinnamaldehyde to give 3-cyano-4-phenyl-2-pyridone (33) which was easily cyclised to 4 by heating with polyphosphoric

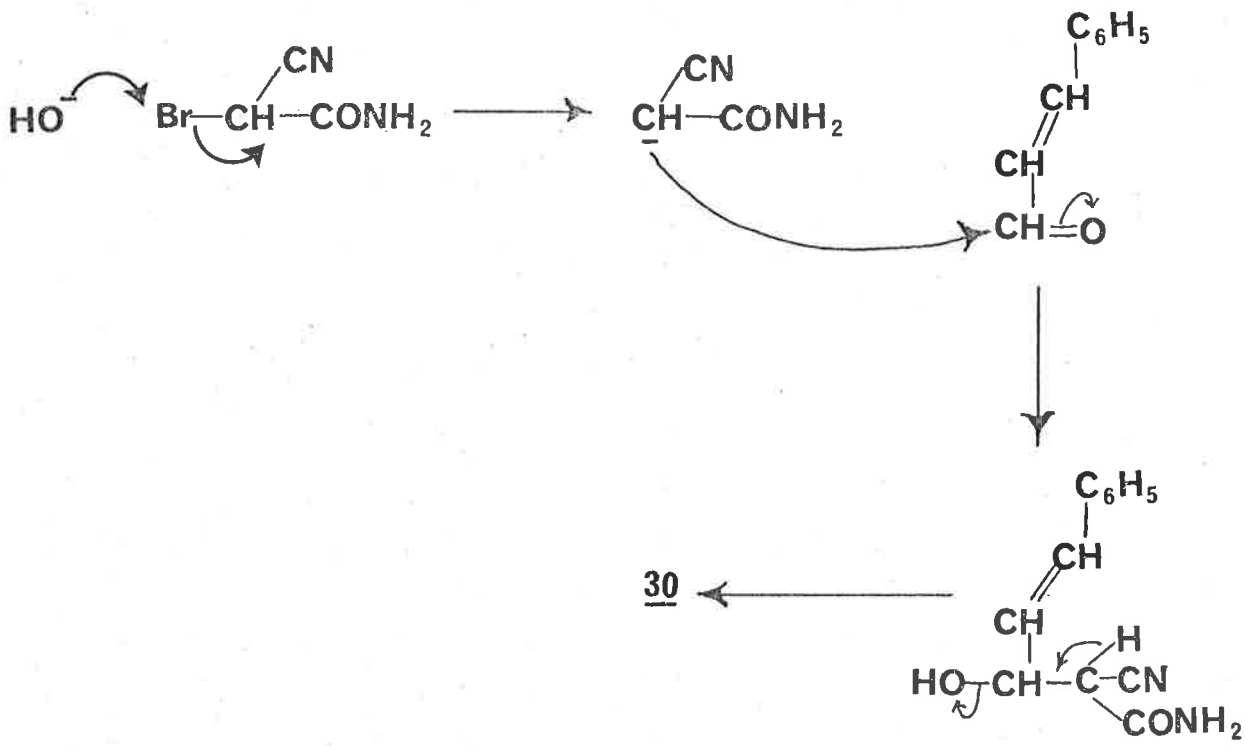


Scheme 10

acid (PPA)[17]. However, under the conditions used, the intermediate pyridinium salt 31 did not form and the formation of 30 is suggested to arise by the following pathway (Scheme 11).

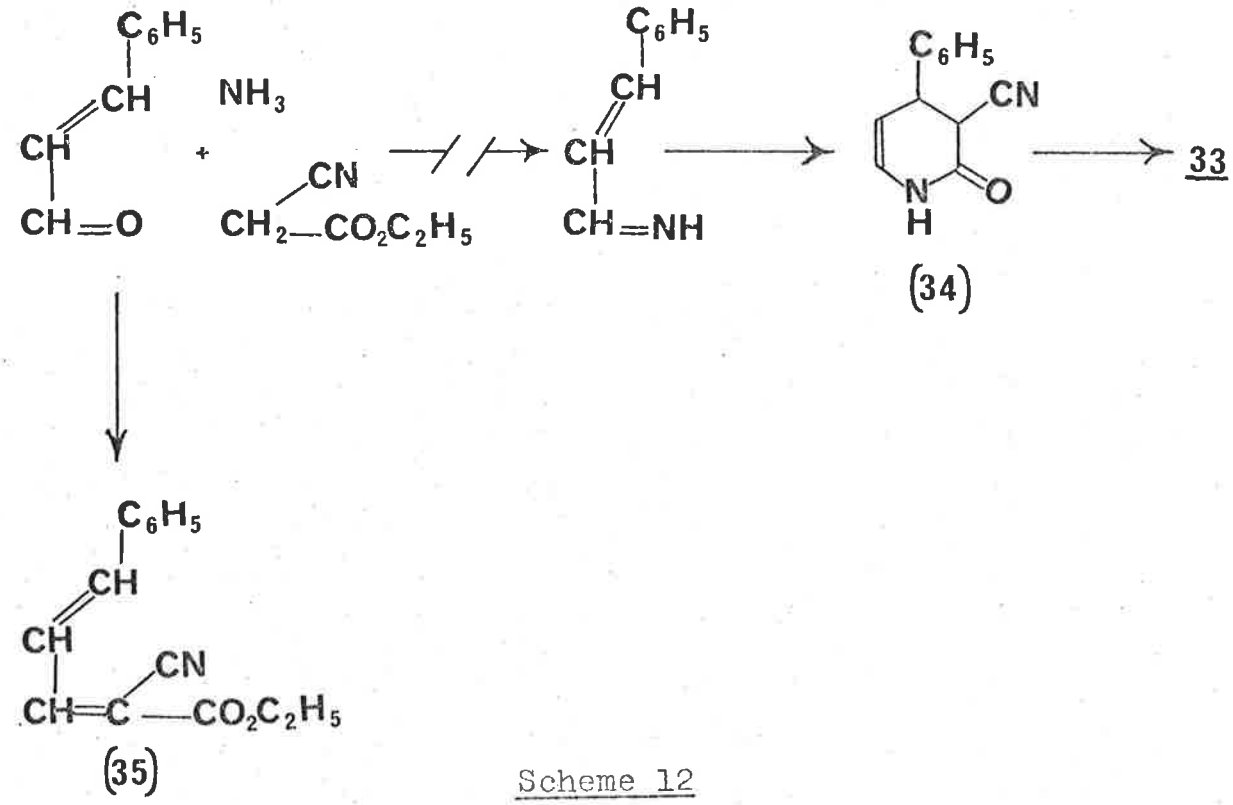
When 31 was prepared independently no apparent reaction with cinnamaldehyde occurred under basic conditions. The experiences of Ahktar et al[18] are thus confirmed.

Alternatively, it was planned to prepare 33 by condensation



Scheme 11

of cinnamaldehyde with ethylcyanoacetate in the presence of ammonia. The expected intermediate product was 34 but again the pathway followed was not the Michael 1,4 addition but 1,2 addition

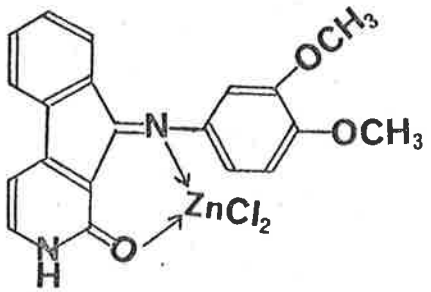


Scheme 12

to the cinnamaldehyde to give 35 in quantitative yield (Scheme 12).

Because of the lack of success in the previously described reactions, it was decided to prepare 4 by the method of Powers and Ponticello[17] from ethylcyanoacetate and 1-amino-2-benzoyl-ethylene.

Reddlien[19] had successfully converted ketones to anils by heating with aniline in the presence of zinc chloride at 170°. Thus, refluxing a mixture of 4, 4-aminoveratrole and zinc chloride in toluene gave the zinc chloride complex of the desired product which spectroscopic analysis and microanalysis suggested had structure 36.



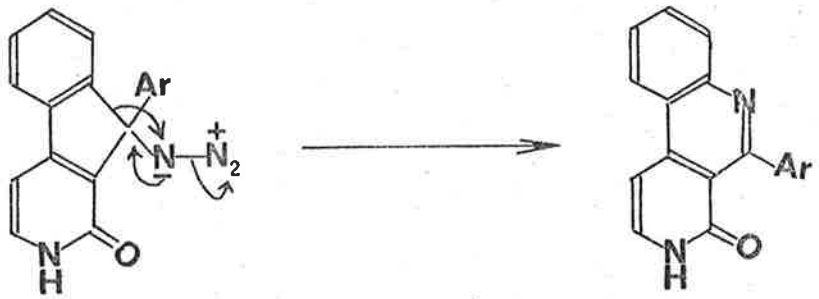
(36)

Attempts to remove zinc chloride from the complex by washing with cold water or dilute acid led to the unchanged complex and with concentrated acid led to decomposition to the parent ketone. When the complex was treated with m-CPBA in the hope it would form an N-oxide 11, the reaction was unsuccessful; presumably the lone pair of electrons on the nitrogen atom were unavailable for reaction with m-CPBA because of co-ordination with zinc

chloride. In view of these difficulties, this route was not pursued.

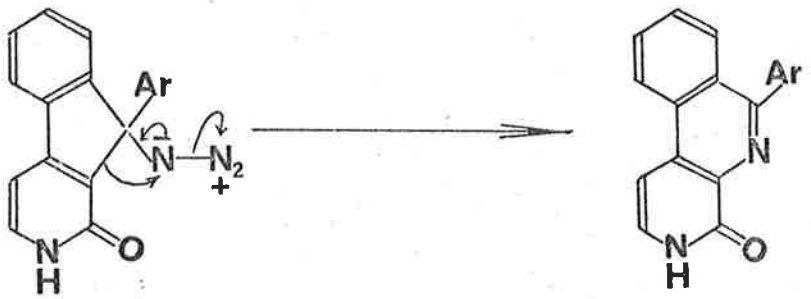
A practical route to dehydroperloline (3) was based on the reaction of fluorenone 4 with the Grignard reagent derived from 4-bromoveratrole to give fluorenol 8 in 63% yield. It was hoped that the Schmidt reaction on this alcohol would give the desired product 8-aza-7,8-dihydro-6-(3',4'-dimethoxyphenyl)-phenanthridine-7-one (9). There are three possible modes of rearrangements in this reaction.

(i) Pathway a : phenyl ring migrates to give 9



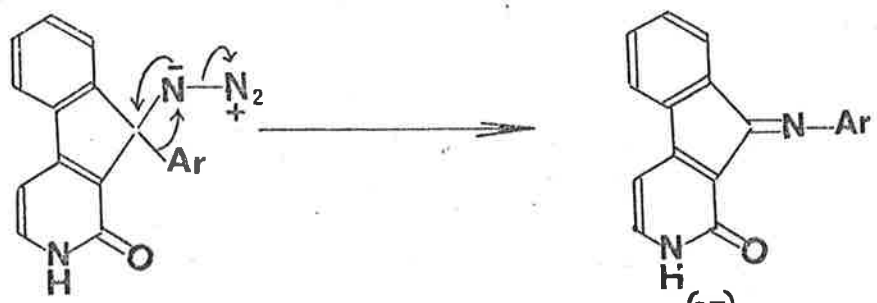
(9)

(ii) Pathway b : pyridone ring migrates to give 10



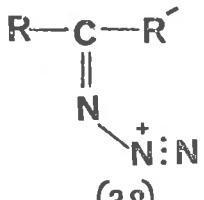
(10)

(iii) Pathway c : aryl group migrates to give 37



(37)

For the Schmidt reaction with ketones, Smith and his co-workers[41,42,43] have proposed an oxime-like intermediate 38 formed by elimination of water from the adduct of hydrazoic acid and the protonated ketone. These authors proposed that the group having the greater bulk in the neighbourhood of the C=N

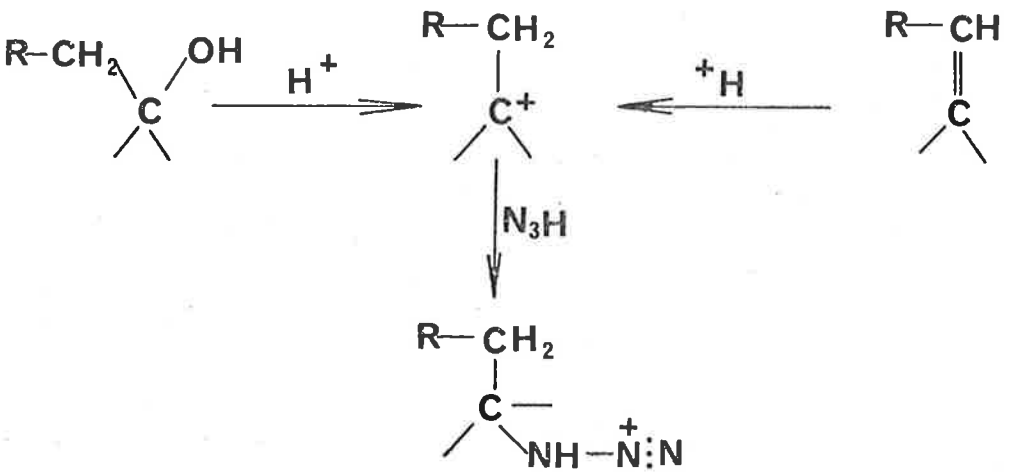


(38)

group is anti to the $-\overset{+}{N}:N$ group, nitrogen separates and this group R migrates. Sch echter and Kirk[44] have provided further evidence on 2-substituted cyclopentanones and cyclohexanones which accords with Smith's mechanism.

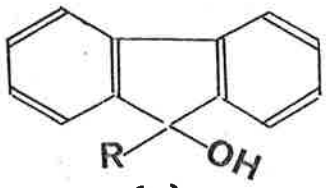
According to Arcus and Coombs[22], the mechanism above is inapplicable to the reaction with alcohols and olefins because

the intermediate 38 cannot be formed (Scheme 13). However, they



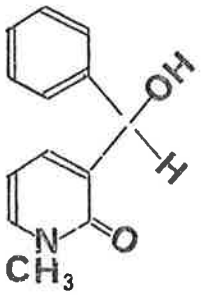
Scheme 13

pointed out that the ring having the greater electron-release will migrate. McEwen and Mehta[23] also found the migratory aptitude to be directly related to the electron-release of the group. After studying the reaction of fluoren-9-ols with hydrazoic acid and sulphuric acid, Arcus and Coombs[22] concluded that, for tertiary alcohols such as 39, the rearrangement is independent of the R group, and always leads to ring expansion to the phenanthridine system. Again the most electron-rich ring migrated.



(39)

The above observations suggest that pathway a is most likely and pathway c would be only minor. To obtain further evidence for this reaction mechanism, the Schmidt reaction on two model compounds 40 and 16 was studied. Alcohol 40 was prepared in 70%



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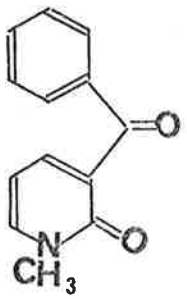
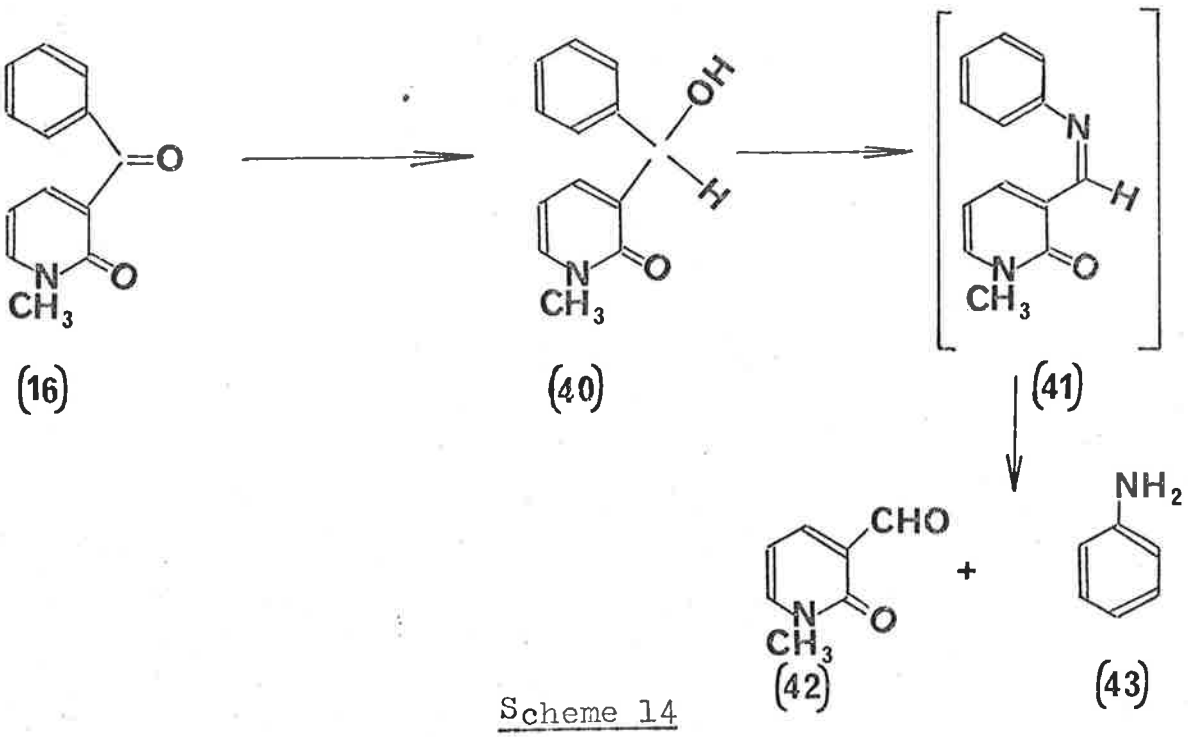


(16)

yield by the reduction of 16 with sodium borohydride in methanol[17]. Compound 40 gave exclusively N-methyl-3-pyridonecarbaldehyde (42) and aniline (43) upon reaction with hydrazoic acid in polyphosphoric acid (Scheme 14).

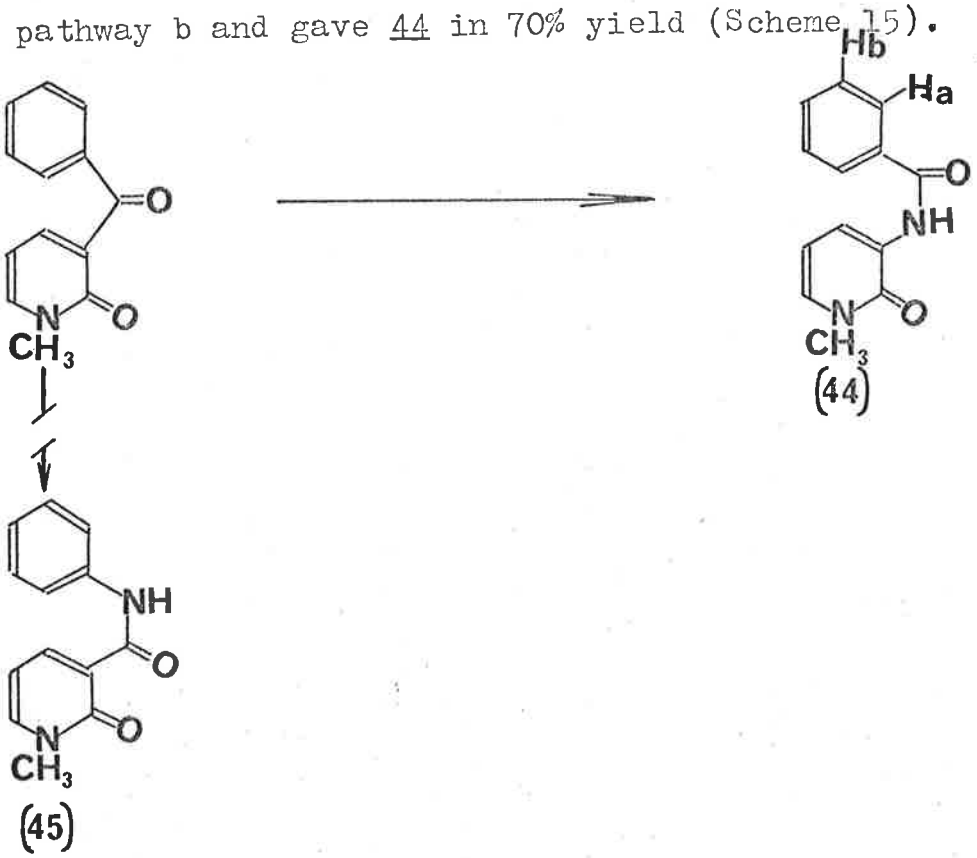


Scheme 14

The products are considered to arise from hydrolysis of the imine 41. This result confirms that the reaction followed pathway a as expected; that is, the phenyl ring has a greater migratory aptitude than the pyridone ring and therefore migrates preferentially to the positive nitrogen in the transition state[17].

There is no evidence for migration of the pyridone ring; thin layer chromatography of the residues showed only 42 and aniline. It was thought possible that the course of the reaction might be influenced by the nature of the acid used. To test this point the experiment was then carried out in concentrated sulphuric acid-chloroform and the same results were obtained as in the previous reaction.

On the contrary, the Schmidt reaction on ketone 16 followed pathway b and gave 44 in 70% yield (Scheme 15).



Scheme 15

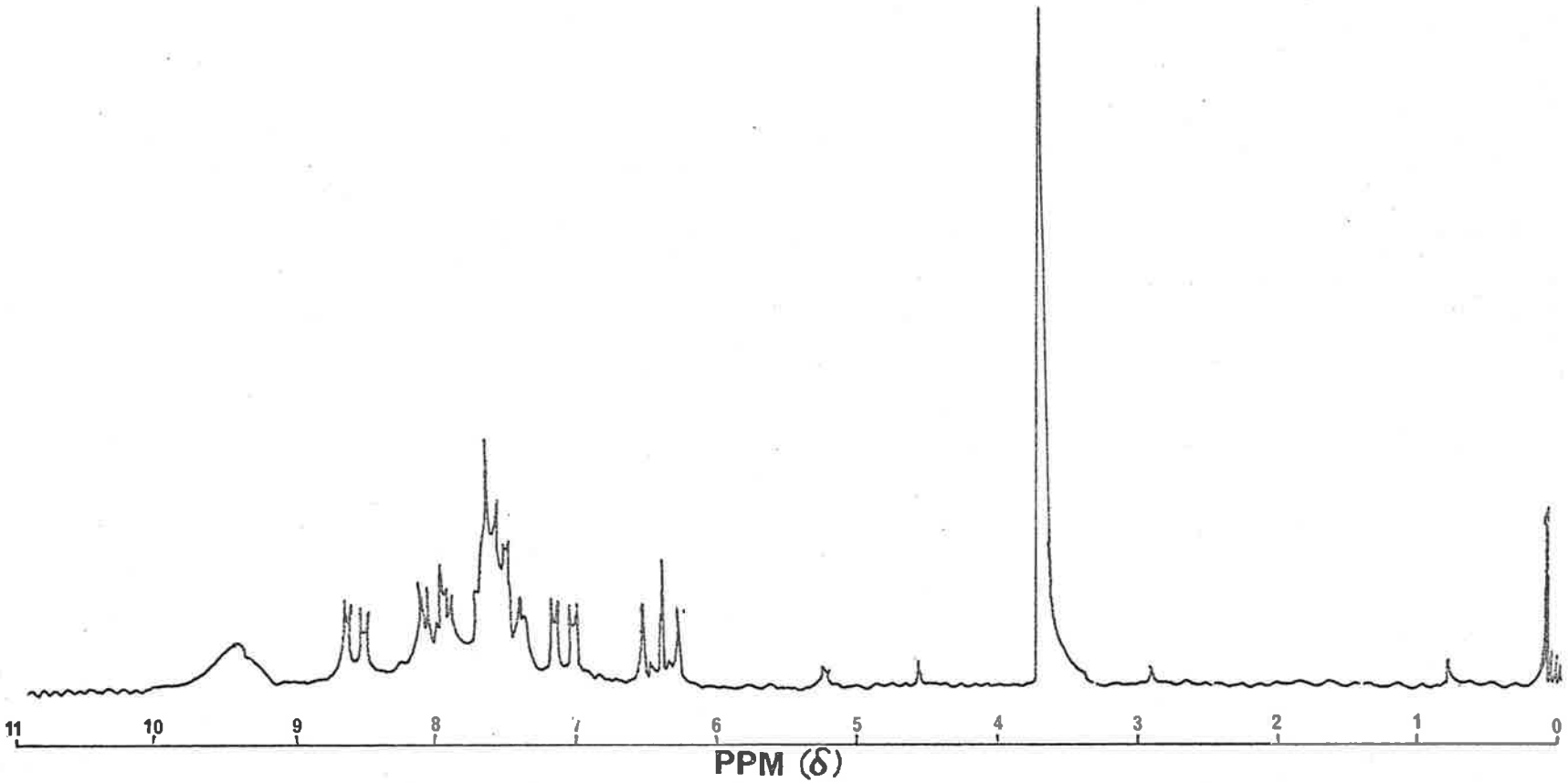
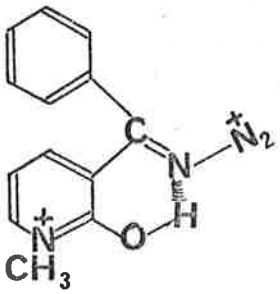


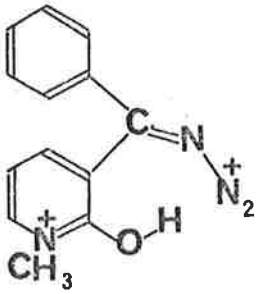
FIG.1 NMR spectrum of 44 in $CDCl_3$

Thin-layer chromatography on the crude product showed only one spot and the nuclear magnetic resonance spectrum suggested the structure 44 rather than 45, and this was confirmed by an independent synthesis of 45 which was shown to be totally absent. A broad peak at δ8.0 ppm has been attributed to the two protons H_a and at 7.5 ppm to the three protons H_b. This result can be rationalised by an oxime-like intermediate as suggested by Smith and his colleagues[41,42,43,44].

Two intermediate products may be represented by 46 and 47. With the evolution of N_2, the group anti to the leaving nitrogen



(46)



(47)

migrates and thus the isomers 46 and 47 give rise to the amides 44 and 45. It is suggested that only intermediate 46 is formed because of the effect of hydrogen bonding.

To confirm the identification of 44, compound 45 was prepared by the reaction of acid chloride 27 with aniline. Its nmr spectra showed that it was completely different to 45. A broad multiplet centred at about 7.70 ppm has been attributed to protons belonging to the phenyl group. (Fig 2)

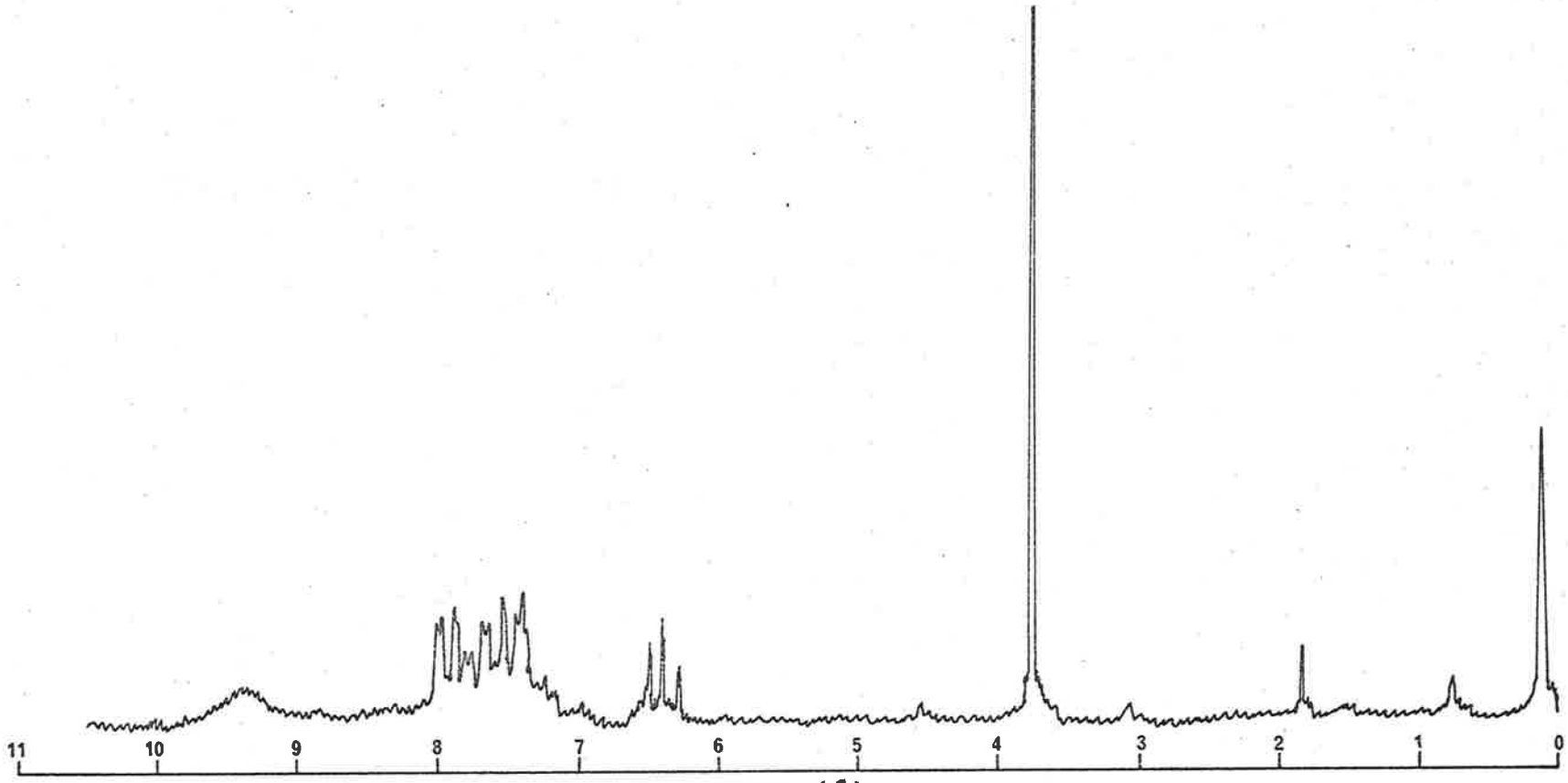
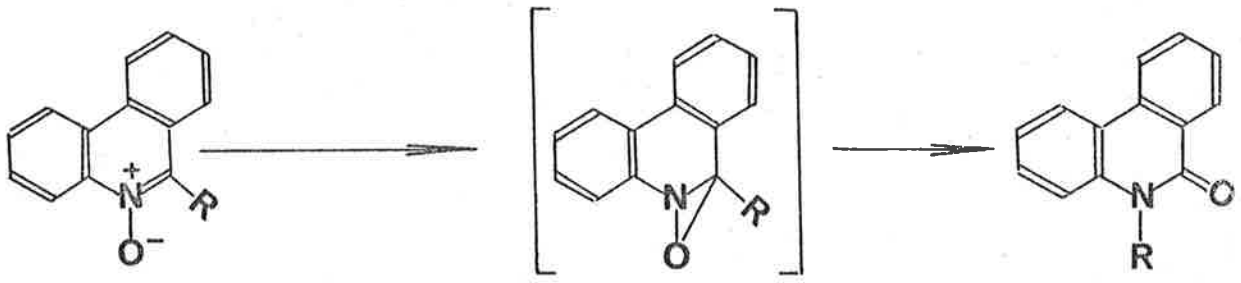


FIG. 2 NMR spectrum of 45 in $CDCl_3$

These observations strongly favour structure 9 as the product from alcohol 8. With m-CPBA in chloroform, 9 gave N-oxide 11 in moderate yield as a hemi-hydrate.

In 1966, Taylor and Spence[21] described the photoisomerisation of phenanthridine N-oxide 48 to phenanthridone 50 formed from the intermediate oxaziridine 49 (Scheme 16). A study of the rate[21]



Scheme 16

of the product formation showed that the photolysis was essentially complete within 30 sec. and that further irradiation served only to effect decomposition of 50. Irradiation of 11 could lead to at least three products. Examination of the reaction mixture by ultraviolet spectroscopy showed that the reaction was complete in 30 min. after the exposure to sunlight (Fig 4). The suggested mechanism[21] for this reaction involves the oxaziridine 51, homolysis of the N-O bond in which gives radical 52 (Scheme 17).

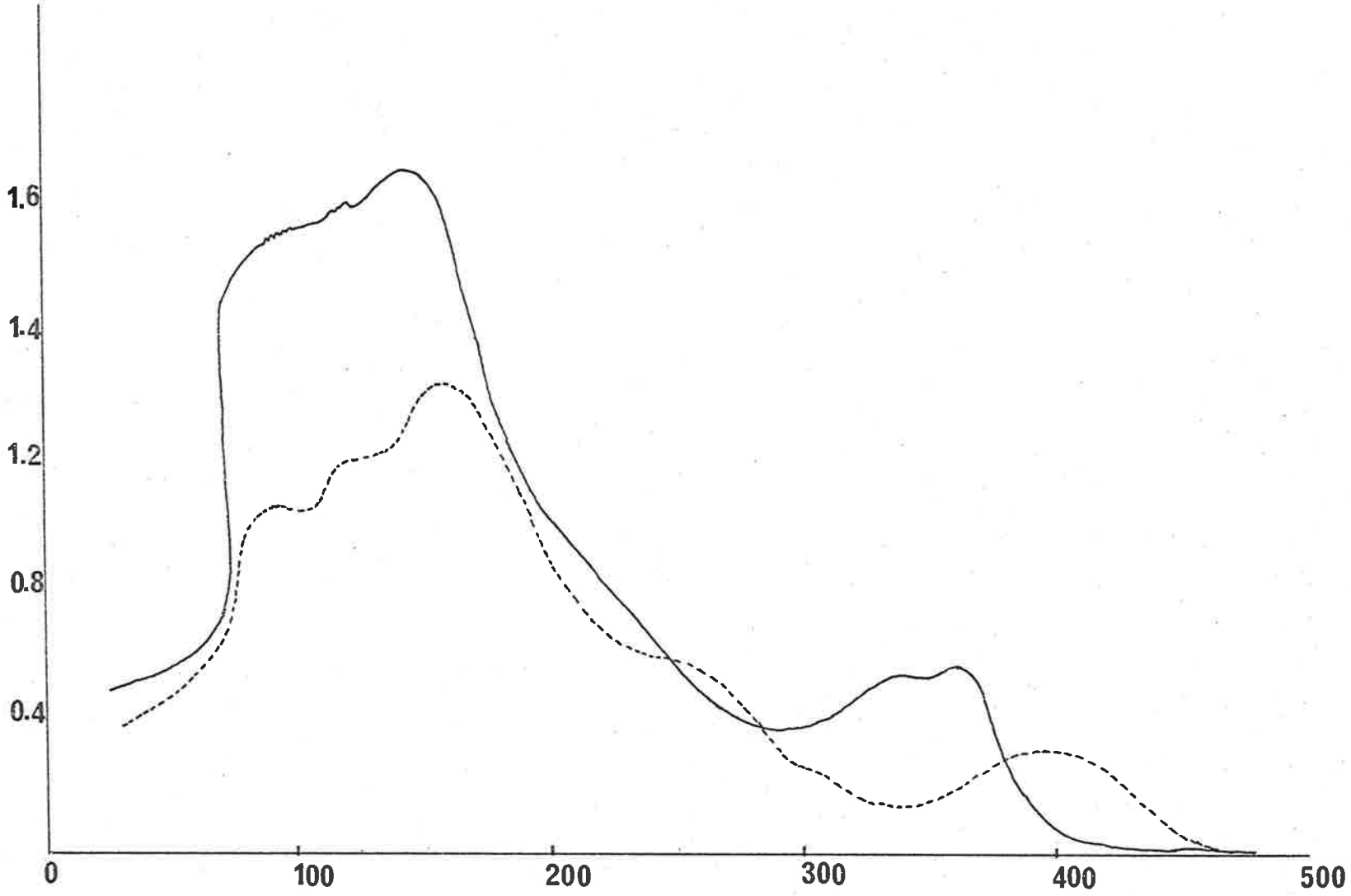
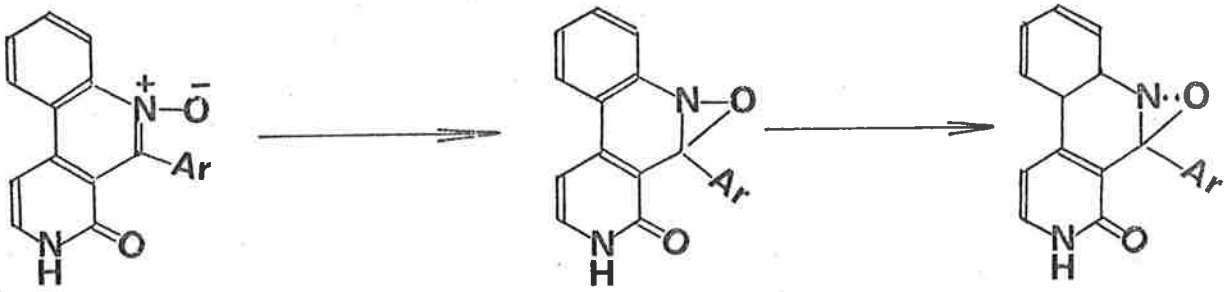


FIG.4. Ultraviolet spectra of 11 (---) and 3 (—).

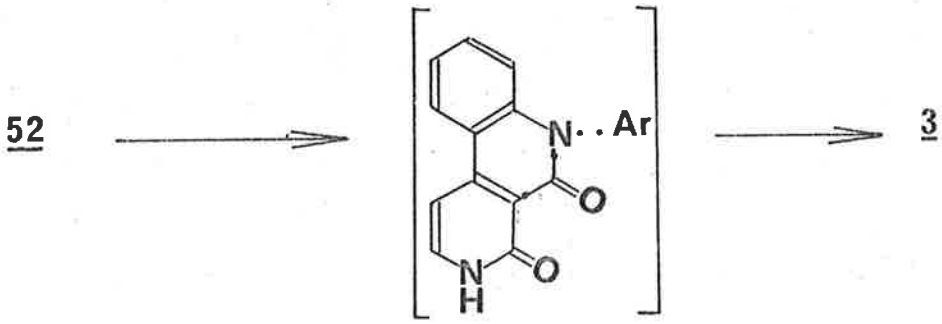


(11) (51) (52)

Scheme 17

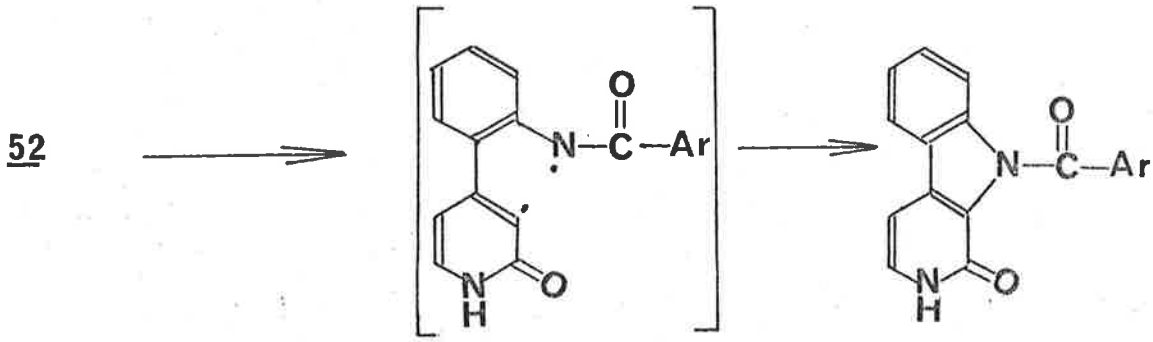
This diradical then could rearrange by three pathways :

(i) Pathway a :



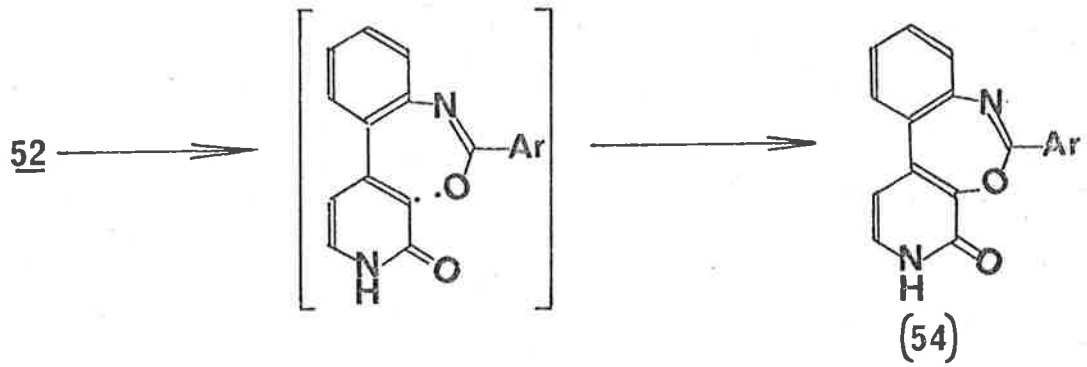
52 3

(ii) Pathway b :



52 (53)

(iii) Pathway c :



(54)

The reaction mixture by thin-layer chromatography showed only one product which can be either 3, 53, or 54. All of the major ions of the photo-product are listed in Table 1.

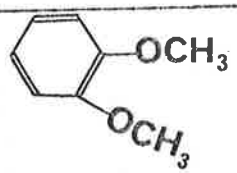
Table 1 : Mass Spectral Data of the Photo-Product

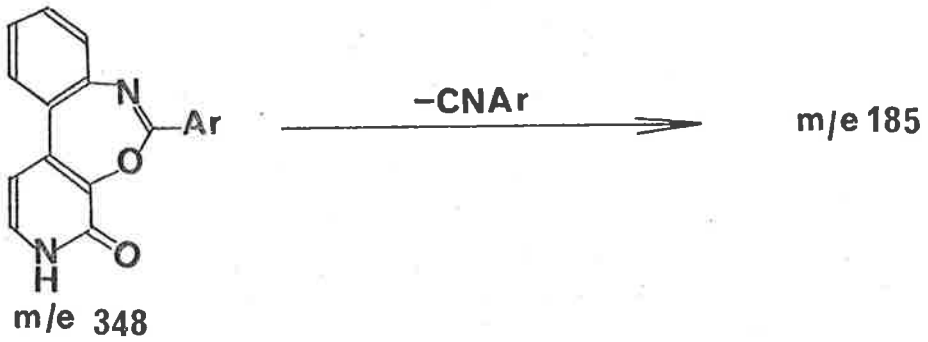
M/e	Relative Intensity
349	20.9
348 M^+	100.0
347 M-H	44.8
333 M-CH_3	19.1
332 M-O	1.6
317 M- (CHO+2H) or M- NOH	4.8
195 M- (O+Ar)*	38.6
167 M- (O+Ar+CO)	12.4

As reported[28,46], the peak at M/e 195 can be regarded as the loss of (O + Ar) in 3.

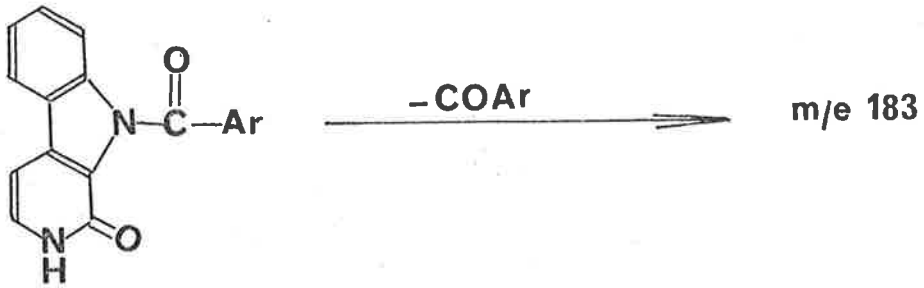
Scheme 18 shows a mechanistic rationalisation[47,48] for the principal peaks to be expected in the spectrum of 53 and 54.

---

* Ar = Aryl group : 



m/e 348



m/e 348

Scheme 18

The absence of m/e ions at 185 and 183 in Fig. 3 indicates that it is unlikely the product is 53 or 54 and therefore the product from photolysis of 11 can be regarded as the expected product 3. Furthermore, its melting point and ultraviolet spectra were identical with that of an authentic sample*.

---

* Sample was kindly supplied by Prof. William I. Taylor

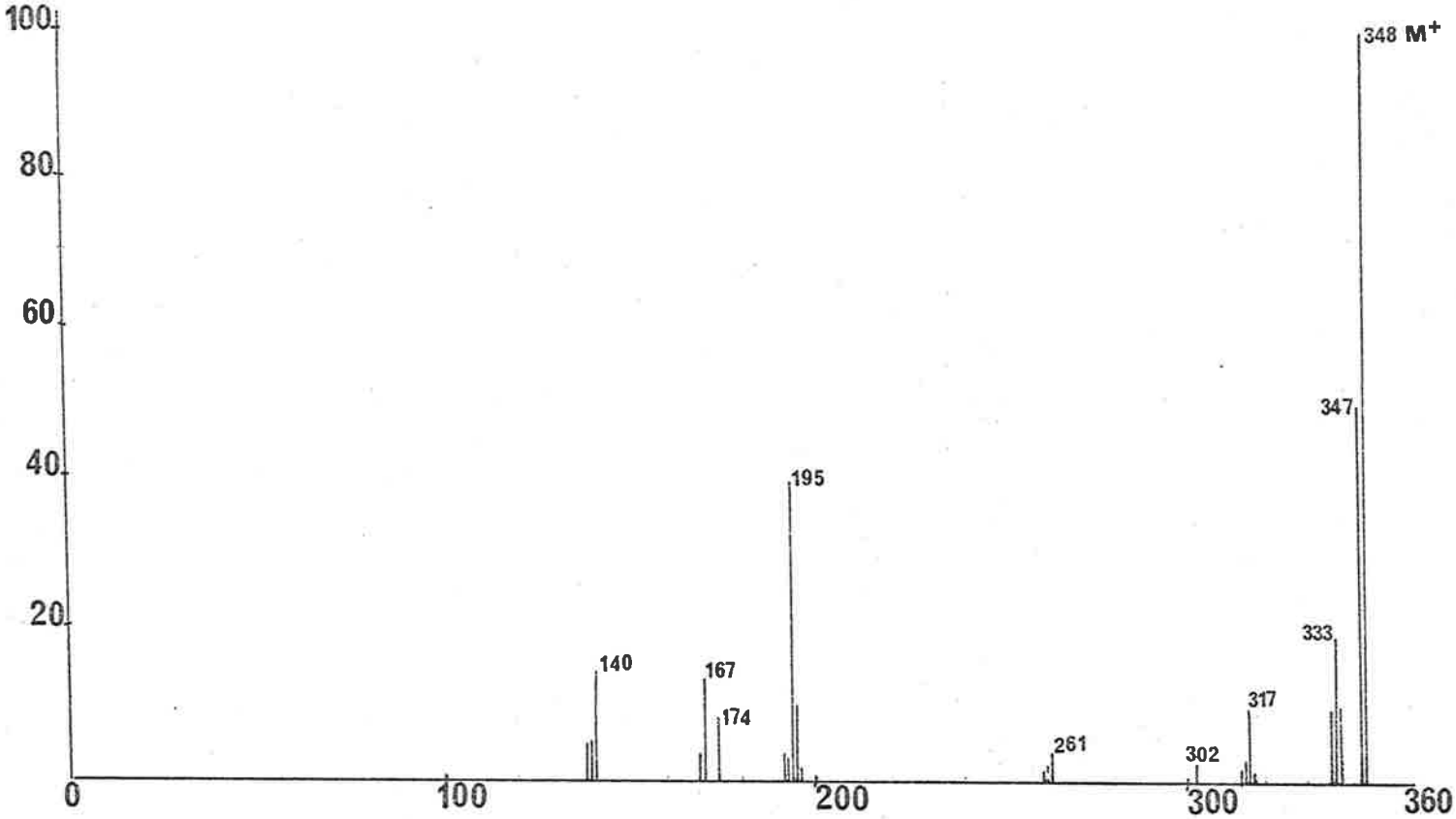


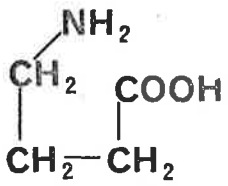
FIG.3. Mass spectrum of dehydroperloline

PART II

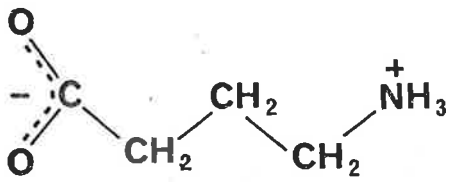
SYNTHESIS OF LACTAM ANTAGONISTS OF GAMMA - AMINOBUTYRIC ACID (GABA)

INTRODUCTION

To date only a small number of compounds have been characterised as being transmitters in the mammalian central nervous system[1]. One of these, γ-aminobutyric acid (GABA) (1) has been found to have a potent inhibitory action against epileptic seizures[2]. A considerable amount of work has been published on the synthesis and activity of GABA analogues[3,4,5,6], yet no satisfactory structure-activity relationship has emerged. It would appear that both the intramolecular distance between the zwitterionic centres(2) and the rotational freedom of the molecules are



(1)

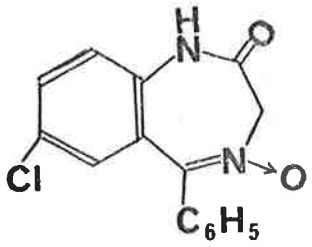


(2)

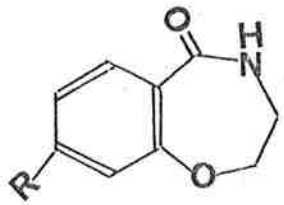
important factors governing the synaptic activities of these substances[7].

Molecular orbital calculations suggested that GABA can assume a zwitterionic conformation with the charged centre at least 5Å or more likely 6Å apart[8]. X-ray crystallography indicated that GABA exists in a partially folded conformation in the solid state[9].

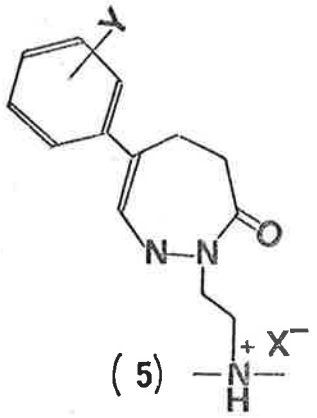
A number of cyclic amides have been shown to be active on the central nervous system, particularly the seven-membered lactam system. Examples included demoxepam (3) and the related anticonvulsants and sedatives[10,11], β-adrenergic blocking agents such as 4,[12,13], analgesics 5[14,15] and hypnotics 6[16].



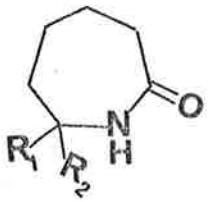
(3)



(4)



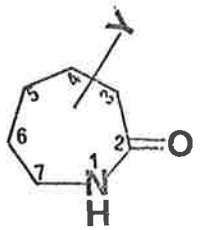
(5)



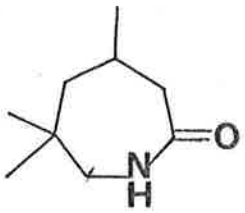
(6)

A search of the literature for central nervous system activity of simple lactams reveals isolated instances of activity, but no detailed examination appears to have been made. Thus Lien and co-workers[17, 18], have shown that lactams lacking N-substituents are CNS stimulants, the most active being 2-azacyclononanone. The effect of ring size is not straightforward, however. Thus, valerolactam appears to be CNS inactive, but possesses some bactericidal activity[19,20].

Although the preliminary study of Lien[17,18] suggested that lactams containing a nine or ten-membered ring exhibited most central nervous system activity, a number of reports in the literature suggested that caprolactam derivatives 7 might merit further study.



(7)



(46)

Because of its industrial importance in the synthesis of nylon, caprolactam has been subjected to considerable pharmacological scrutiny. Thus Poluskin[21] has shown that caprolactam led to epileptic spasms in mice although its L D_{50} at 580 mg/kg is fairly high. Goldblatt and his co-workers[22] also showed that caprolactam is an effective convulsing agent, acting particularly on the cortex of the rhinencephalon.

Caprolactam is sufficiently lipid soluble to penetrate the central nervous system relatively rapidly. Lactams of the amino acids of longer chain length are more lipid soluble and more effective convulsants as are their thio-derivatives[17,18]. This has prompted a search for more active compounds with better lipid solubility but based on caprolactam 7. Using convulsant activity for preliminary screening, the most active compounds found have substituents on carbons 4 and 6 of the ring. Thus 4,6,6-trimethylcaprolactam (46) is a potent convulsant with a CD_{50} of 4 - 6 mg / kg representing some one hundred-fold improvement over the parent lactam. Surprisingly, in view of the commercial importance of caprolactam, relatively few C-alkylated derivatives have been

described and general methods of synthesis are not common.

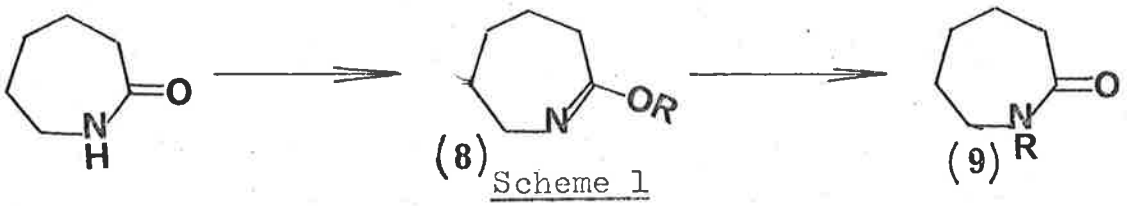
This thesis will describe synthetic methods for the preparation of caprolactams substituted at N-1, C-2, C-3, C-4, C-5, C-6 and C-7. Most of the lactams in this study were obtained from the corresponding ketones by the Schmidt reaction or Beckmann rearrangement. The former reaction was used with saturated ketones while unsaturated lactams were more conveniently prepared by the latter rearrangement. These lactams together with the corresponding thiocaprolactams have been tested for GABA-antagonism in the Department of Human Physiology and Pharmacology of this University, using the strio-nigral pathway in which GABA is a recognised transmitter readily blocked by picrotoxin[23].

D I S C U S S I O N

CHAPTER I SUBSTITUTION ON N OR O

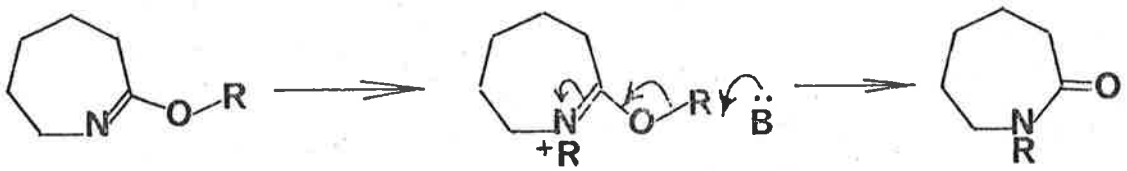
In connection with our investigation of convulsant activities of caprolactam derivatives, the preparation of N-alkylated products was necessary. It was reported[24] that caprolactam can be alkylated on nitrogen or oxygen by alkyl sulphates in benzene. The first-formed product (major) was O-alkylcaprolactim (8) which can be easily converted to N-alkylcaprolactam (9) by heating with a catalytic amount of alkyl sulphate (Scheme 1). Direct thermal

(a) $R = CH_3$
(b) $R = C_2H_5$



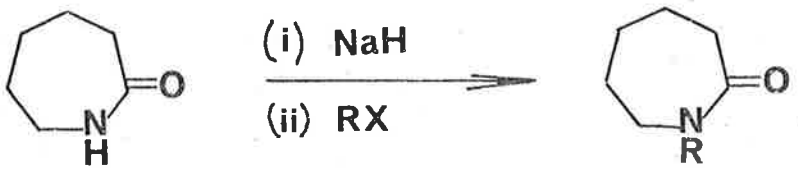
Scheme 1

interconversion of these isomers requires much higher temperature than the refluxing benzene used in this case[24]. The conversion of O-alkylcaprolactim into N-alkylcaprolactam probably proceeds as shown in Scheme 2.



Scheme 2

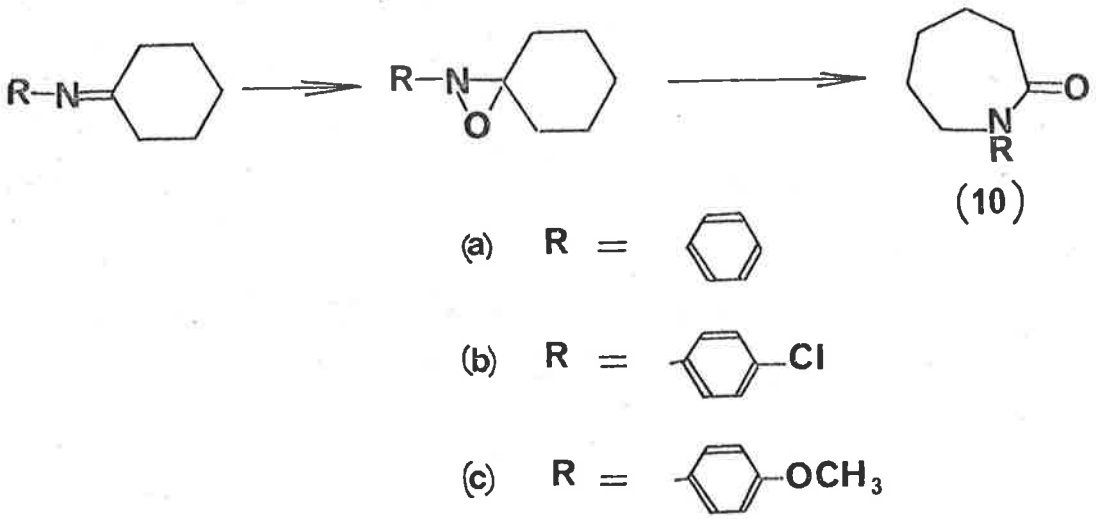
With an alkyl halide or sulphate in the presence of sodium hydride, lactams generally give N-alkylated products.[25,26] The N-alkylated caprolactams prepared in this way are shown below :



(9)

(a) R = CH_3
(b) R = C_2H_5
(c) R = n-C_4H_9
(d) R = i-C_4H_9
(e) R = i-C_5H_{11}
(f) R = n-C_8H_{17}
(g) R = $-CH_2-C_6H_5$

Other N-alkyl derivatives have been prepared by the reaction of caprolactam with epoxides[27], acetylenes[27] and by the Mannich reaction. It appeared that an adaptation of the reported photochemical rearrangement of oxaziridines[28,29] (Scheme 3) could be a useful general method for the synthesis of N-arylcaprolactams (10).



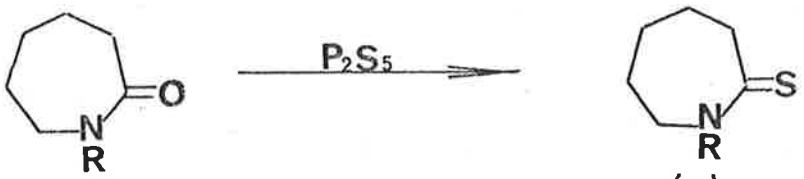
Scheme 3

However, the method gave only poor yields of N-phenyl and N-p-chlorophenylcaprolactam and failed to give any N-p-methoxyphenylcaprolactam (10c). Because of the complex nature of the products obtained in these reactions, it was felt that the method was not a suitable general route to these compounds.

Another possible method for the preparation of N-arylcaprolactams might be obtained in the reaction of arynes and lactams. Arynes have been generated under a variety of conditions by fragmentation of suitable ortho-disubstituted benzenes[30]. Most of the methods suffer from either limited availability of benzyne precursor, involved experimental techniques and/or low yield of benzene-derived products. One of the more attractive benzyne precursors is benzenediazonium-2-carboxylate[31] obtained from

anthranilic acid and an alkyl nitrite. It was hoped that the intermediate benzyne would react with Ɛ-caprolactam or O-methylcaprolactim to give the desired product 10a. Again this method gave only a poor yield of N-phenylcaprolactam (10a) upon reaction with O-methylcaprolactim and failed to give any trace of 10a with Ɛ-caprolactam. This is probably in part a result of reactions of benzyne and benzenediazonium-2-carboxylate with each other[32] and other products[32]. Since the testing programme has shown that N-alkylation or N-arylation leads to a marked decrease in convulsant activity; further investigation of potential routes to N-arylderivatives was not made. This finding is similar to that observed in the case of cyclic lactams by Elison et al[18].

Because of the reported higher biological activities of thiolactams compared to the corresponding lactams[17,18], it was decided to convert all of these compounds to their thio-derivatives 11 by reaction with phosphorus pentasulphide. The reaction proceeded smoothly and gave 11 in high yield :



(11)

(a) R = i-C_4H_9

(b) R = nC_4H_9

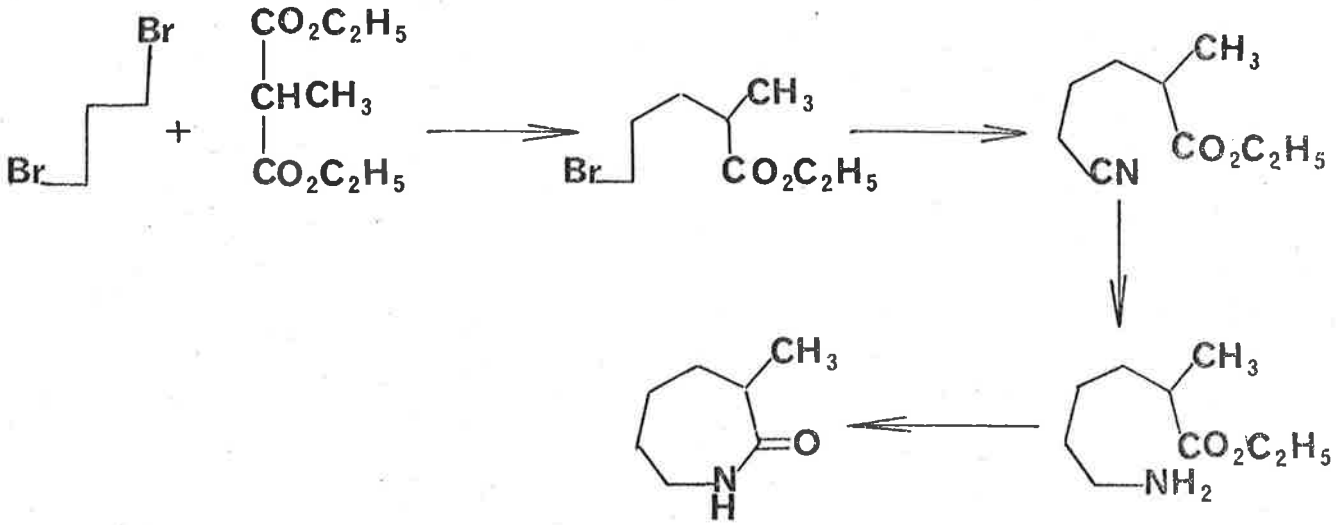
(c) R = i C_5H_{11}

(d) R = n C_8H_{17}

CHAPTER 2 : SUBSTITUTION AT C - 3

Very few derivatives of caprolactam substituted at C-3 have been prepared. The Schmidt reaction on 2-alkylcyclohexanones gave mainly 7-alkylcaprolactam[33] and there is no evidence for the formation of 3-alkylderivatives[34].

Cefelin et al[35] have reported the synthesis of 3-alkylcaprolactam in low yield by more round-about routes such as that for 3-methylcaprolactam (Scheme 5).

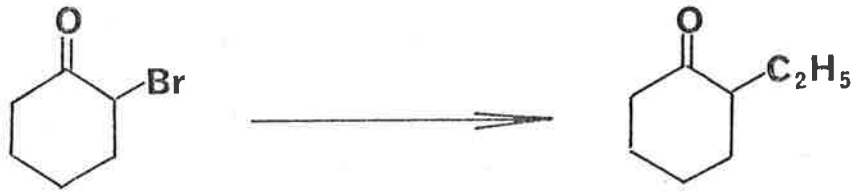


Scheme 5

Fabrichnyi and his co-workers[36] also reported the preparation of 3-ethyl and 3-propylcaprolactams in better yield but their methods are difficult and not general. It was thought therefore

alternative general methods should be investigated for this synthesis

Brown et al[37] found that the 2-bromocyclohexanone reacted readily with organoboranesunder the influence of potassium-t-butoxide in tetrahydrofuran to produce the corresponding 2-alkyl derivatives (Scheme 6). This reaction has recently been extended by Prager and Reece[38]. It seemed possible that alkylation of

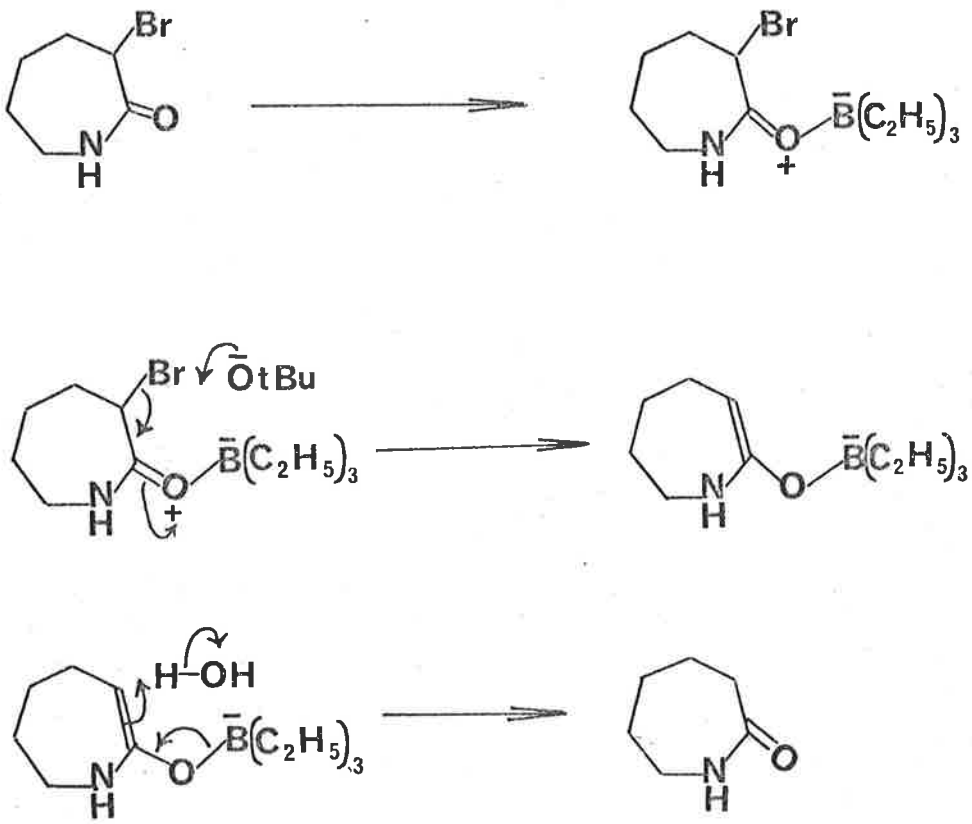


Scheme 6

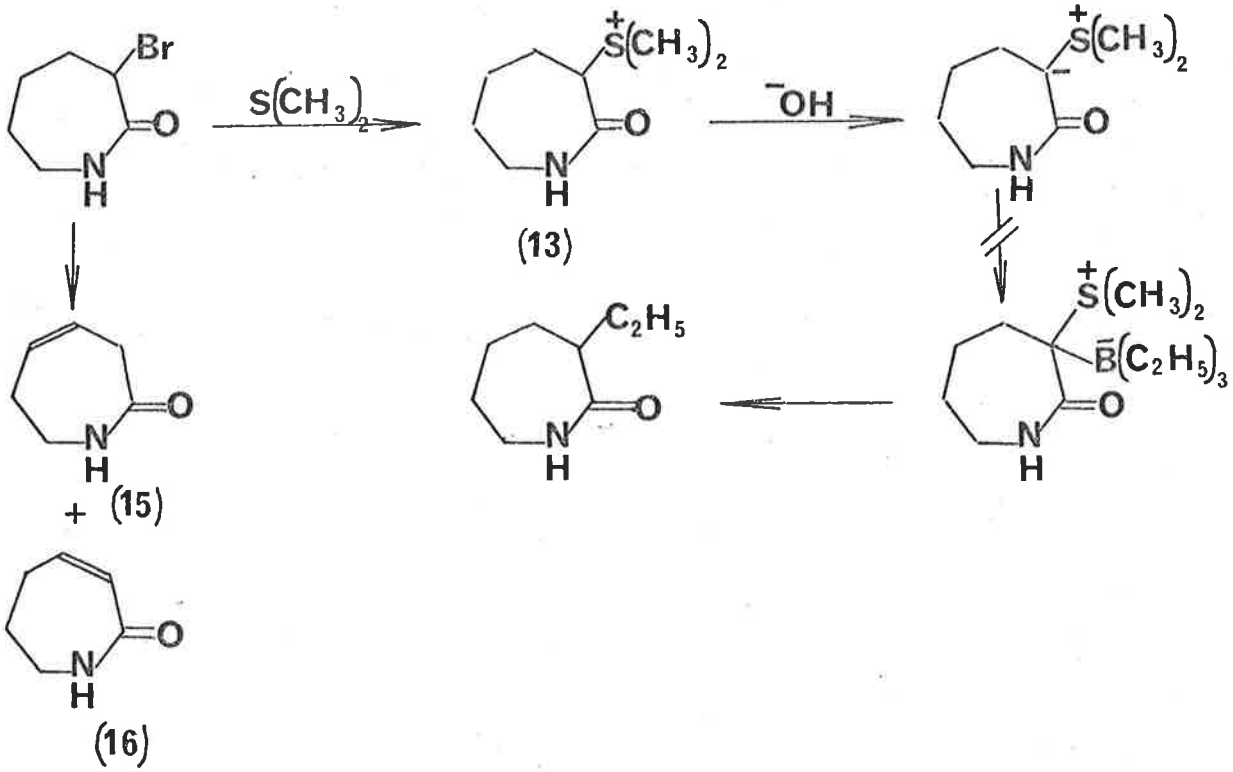
amides (e.g. 3-bromocaprolactam (12)) could similarly be achieved as shown below :

The key compound 3-bromocaprolactam (12) was easily obtained by the procedure of Francis et al[43]. When 12 was treated with triethylborane and potassium-t-butoxide in THF at 0^{o}, thin layer

chromatography, after oxidation or hydrolysis, showed a mixture of ε-caprolactam and the starting material. The formation of the former is suggested to arise by the following pathway:

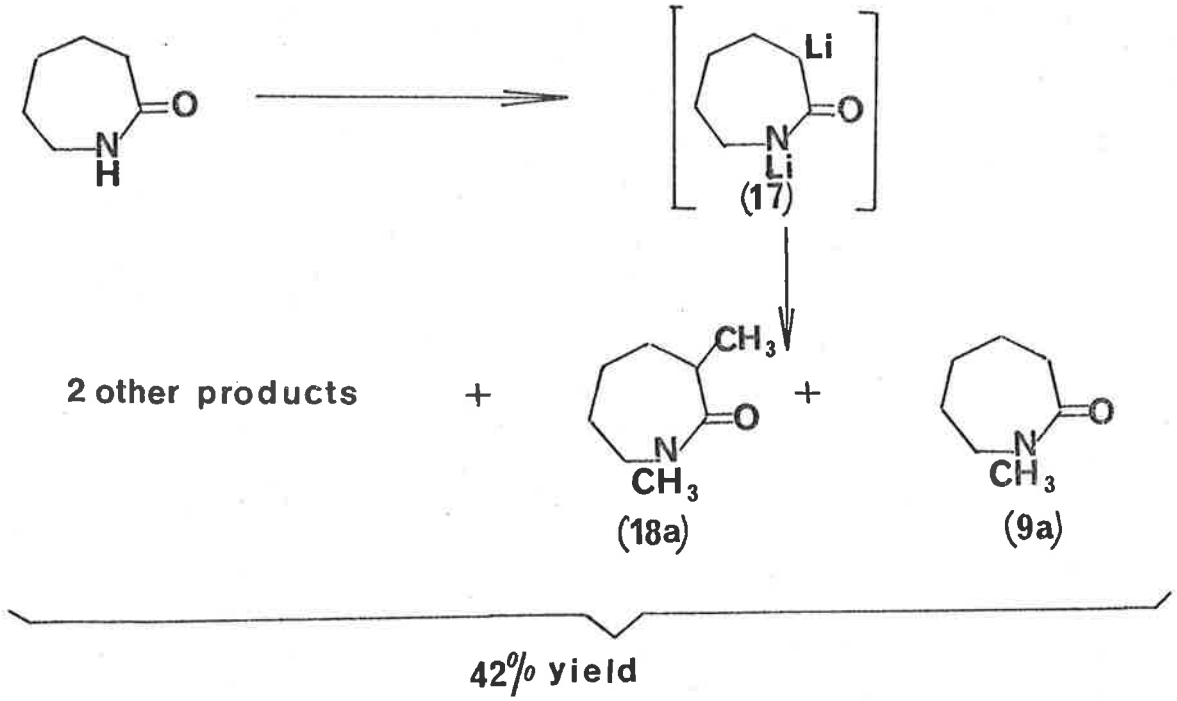


An attractive alternative was that the ylid-organoborane reaction[39] of sulphonium salt 13 might lead to the desired product 14b (Scheme 7) but again the reaction was fruitless and nmr spectral examination showed the product to be a mixture of ylid and the elimination products 2, 3, 6, 7-tetrahydro-azepin-2-one (15) and 2, 5, 6, 7-tetrahydro-azepin-2-one (16).



Scheme 7

Because of the lack of success in the previously described reactions, it was decided to prepare 14b by direct alkylation of Ɛ-caprolactam with strong base. Although lactones can be successfully alkylated ∝- to the carbonyl group[40], this method appears to have been adapted mainly to acyclic amides[41]. Attempts to directly alkylate Ɛ-caprolactam were only moderately successful, the product being mainly the 1, 3-dialkylcaprolactam. With butyllithium in tetrahydrofuran, Ɛ-caprolactam forms the dilithio salt 17 which was methylated at room temperature to afford equal amounts of the dimethylated derivative 18a and N-methylcaprolactam (9a) and two other products (Scheme 8).



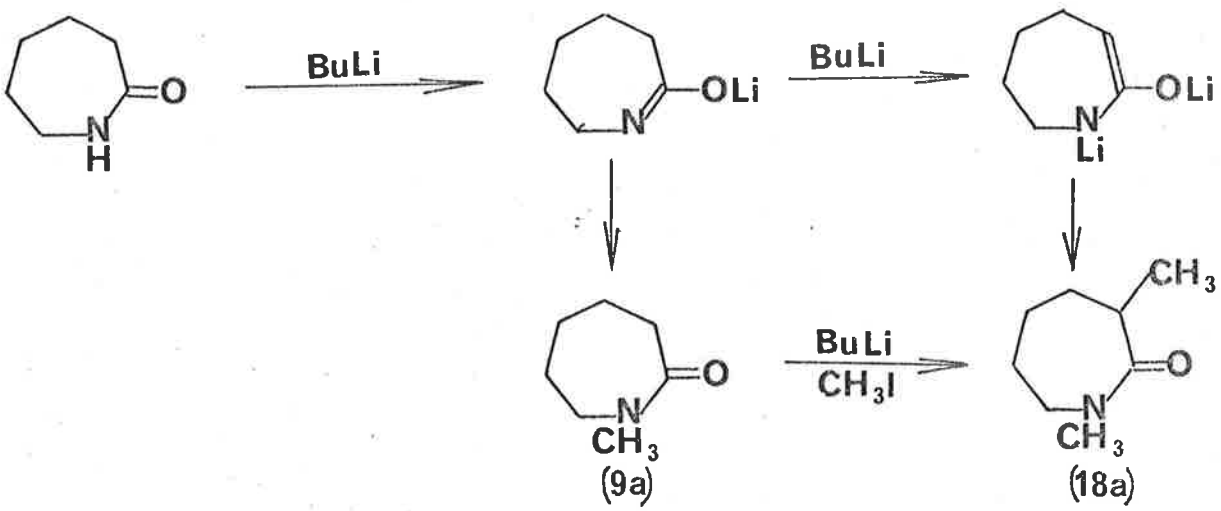
Scheme 8

Attempts to get a better yield of 18a by varying the conditions of the experiment were only partially successful. In all cases, it was observed that the major product was 9a. The conditions of the experiment and products isolated are summarised in Table 1.

Table 1. Alkylation of Caprolactam

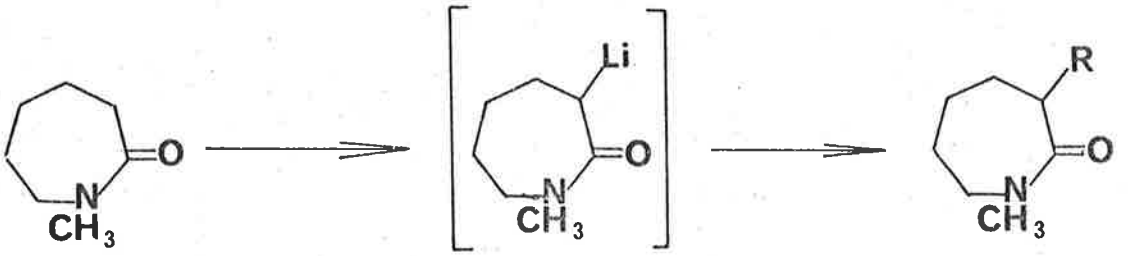
temp. °C	Yield %	Product: % of the mixture 9a	18a
-70	-	-	-
0	42	32	34
R.T.	38	36	20
Reflux	37	36	18

From this table, it seems that the best temperature for this alkylation is 0°. Increasing the temperature of the experiment decreased the yield of the products. This is probably due to side reactions such as direct attack of butyllithium on the amide carbonyl group. However, when the reaction was carried out at -70°, no alkylation was observed and the starting lactam returned. This finding suggested that the dianion 17 is not easily formed until the temperature is 0°. The formation of 9a and 18a in Scheme 8 can be explained as follows (Scheme 9)



Scheme 9

1, 3-Dimethylcaprolactam (18a) or in general 1-methyl-3-alkylcaprolactam (18) can also be prepared in moderate yield from 9a with one equivalent of butyllithium in tetrahydrofuran at 0°, followed by alkylation of the intermediate monolithio salt 19 at room temperature (Scheme 9a).



(9a) (19) (18)

(a) R= CH_3 (c) R=n-C_3H_7

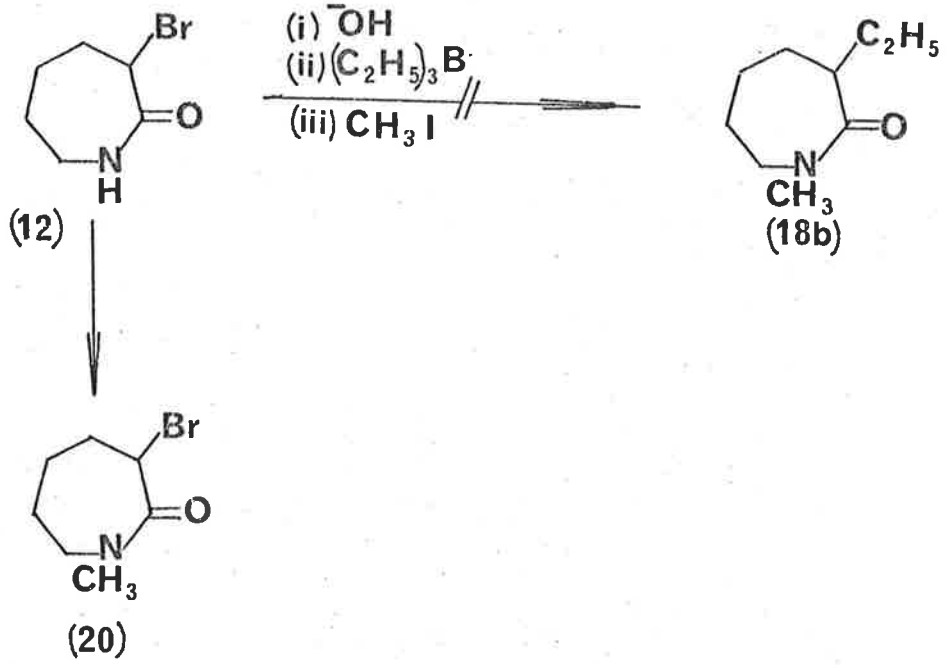
(b) R= C_2H_5 (d) R=n-C_4H_9

Scheme 9a

Because of the unsatisfactory yield of this method, and particularly the constant formation of the undesirable N-methylation products, the preparation of 18 was attempted from 3-bromocaprolactam or its N-methyl derivative 20. For this synthesis to be useful, a convenient preparation N-methyl-3-bromocaprolactam (20) is necessary. Bromination of 9a using cupric bromide in ethyl acetate-chloroform[42] or bromine-phosphorus tribromide in benzene[43] was attempted but no bromination at the 3- position was observed by thin layer chromatography or nmr analysis, and the reaction returned starting lactam. Because of the lack of success in the preparation of 20, it was thought 18b could be obtained from 3-bromocaprolactam (12) by the organoborane reaction followed by methylation (Scheme 10).

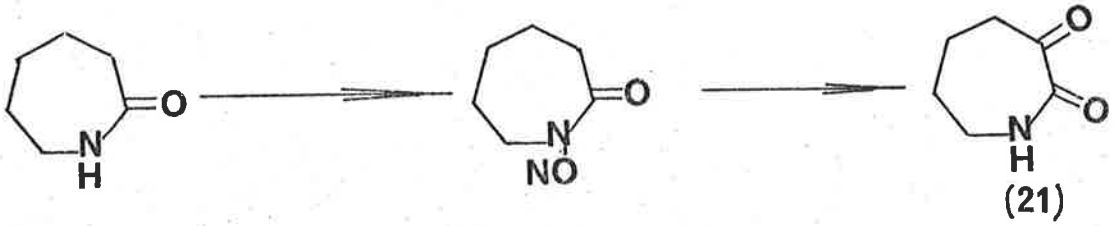
When 12 was treated with triethylborane and potassium-t-butoxide in THF at 0° and the reaction worked up by methylation, thin layer chromatography after oxidation or hydrolysis showed a mixture of two products : E-caprolactam and N-methyl-3-bromocaprolactam (20). The latter was identified by its nmr spectrum.

The sharp peak at δ3.40 was assigned to the N-CH_3.



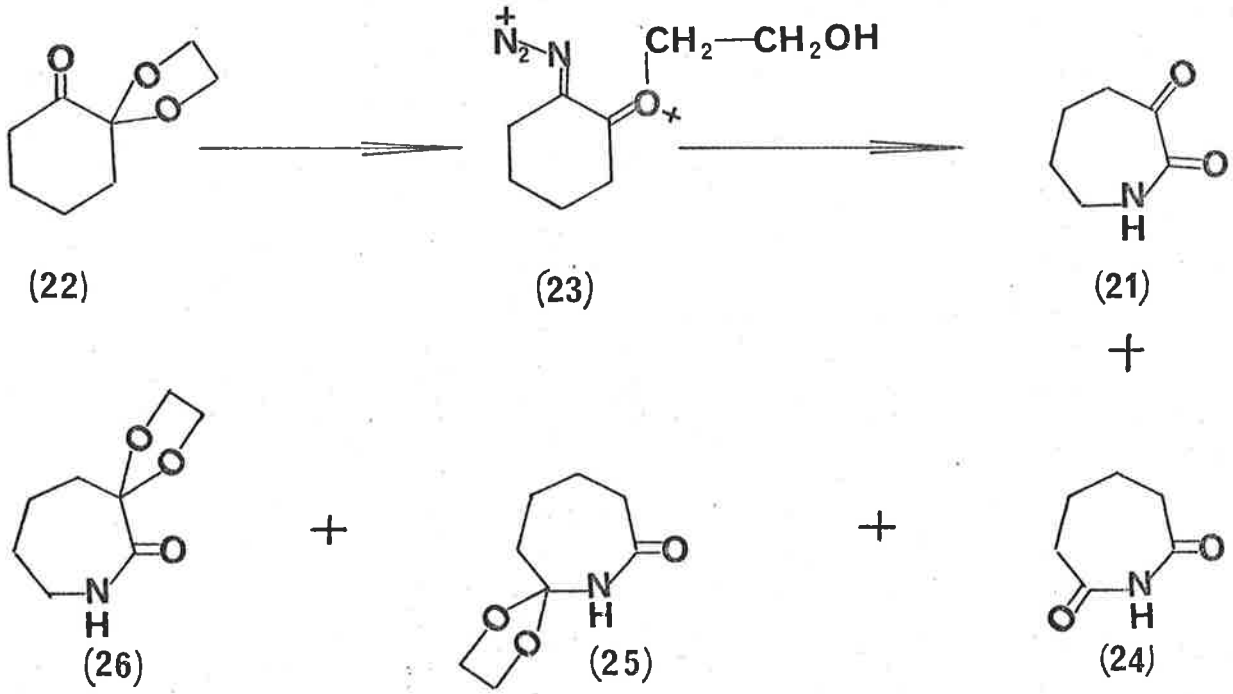
Scheme 10

Because of the failure of the above schemes, it was planned to prepare 3-oxocaprolactam (21) in the hope that it would act as a useful intermediate to other lactam substituted at C-3. Although this compound had been prepared by Murakani et al[45] in low yield from N-nitrosocaprolactam (Scheme 11), another method was examined in order to obtain a more convenient supply. The Beckman or Schmidt rearrangement of cyclohexan-1, 2-dione appears to be a promising route. Unfortunately, all attempts at the Schmidt



Scheme 11

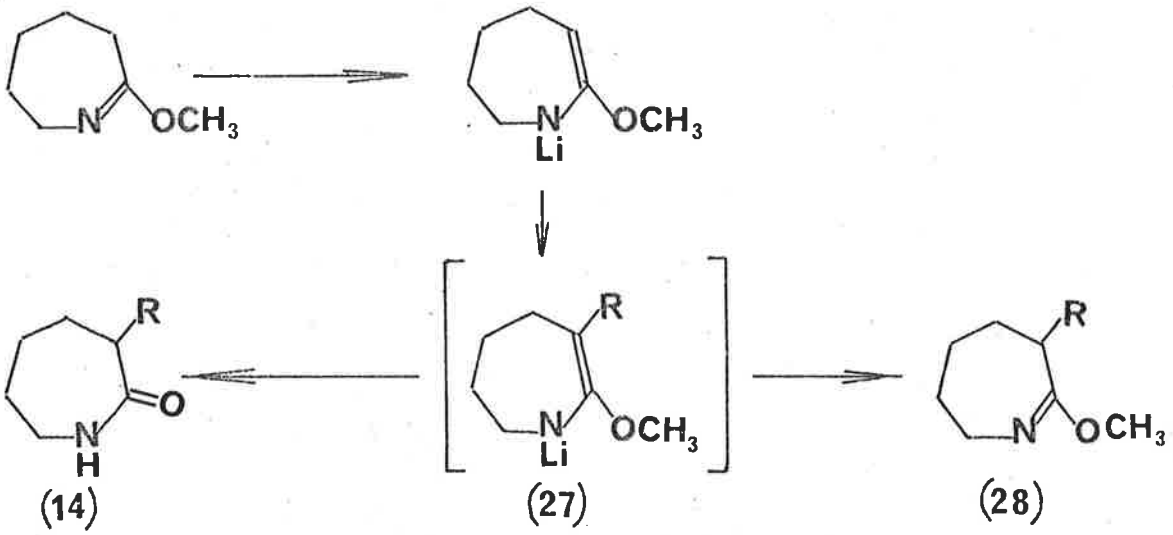
reaction led to the formation of small amounts of 5-cyanopentanoic acid together with large amounts of tar. Also the Beckman rearrangement of 1, 2-cyclohexan-1,2-dione mono-oxime yielded only tar. It could be concluded, therefore, that tar formation is caused by the decomposition of the starting ketone since it was reported to be very unstable[46]. We therefore considered that the Schmidt reaction on the monoacetal of cyclohexan-1,2-dione[47] (22) might lead to more useful products on the grounds that the intermediate could have a structure similar to 23 and would prefer to migrate the more electron-rich 1,6-bond rather than the 1,2-bond which might be preferred on steric grounds. In the event the reaction proceeded in only moderate yield to give essentially equal proportions of the four possible products which we believe to be 21, 24, 25 and 26 (Scheme 12). The structure of these lactams was supported by nmr spectral analysis. No pure compounds



Scheme 12

could be isolated from the mixture even after chromatography.

The recently published procedure for alkylation of lactams described by Trost and Kunz[48] has been extended to the caprolactam area and this method has resulted in the synthesis of some 3-alkylcaprolactams and their corresponding lactim ethers (Scheme 13). The metallated lactim was generated by treatment of O-methylcaprolactim with lithium diisopropylamide in dry tetrahydrofuran at 0°. One unresolved feature of this reaction is the nature of the product formed on protonation of the lithio-intermediate 27; acidification with the weak acid ammonium chloride gave the lactim ether 28 in high yield but 28 did not give 3-alkylcaprolactam (14) with mineral acid. Instead a dark polymeric material was obtained. Direct acidification of the alkylation reaction mixture with mineral acid leads to the lactam 14



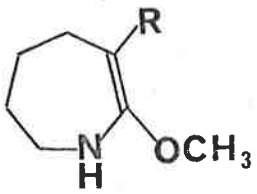
(a) $R = CH_3$

(b) $R = C_2H_5$

(c) $R = n\text{-}C_3H_7$

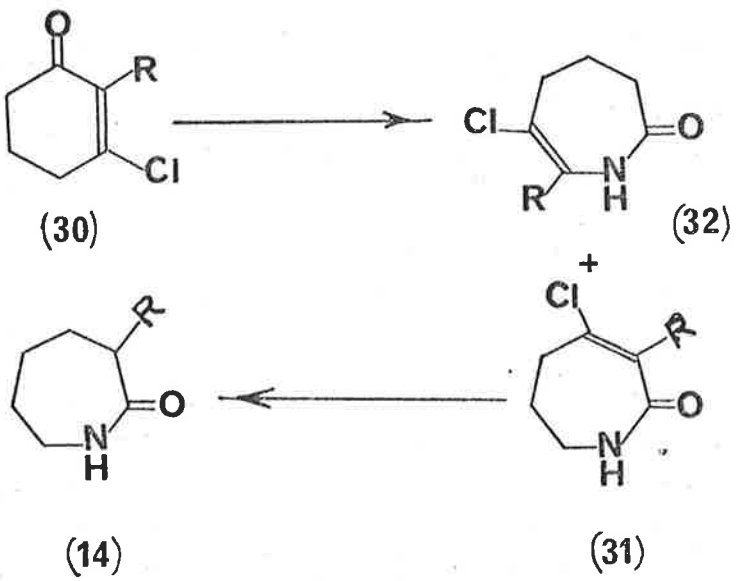
Scheme 13

in poor yield. One possible reason for the low yield in this reaction could be that acidification of the reaction mixture with 10% HCl leads to the formation of 28 and 29 and the former polymerised in acidic solution while the latter hydrolysed to the desired product 14.



(29)

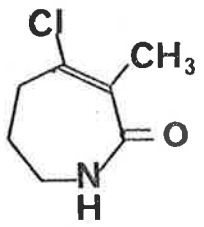
Another possible method for the preparation of 14 was based on the reduction of 3-alkyl-4-chloro-2,5,6,7-tetrahydro-azepin-2-one (31) with platinum oxide in ethanol (Scheme 14). Chloro compound 31 was easily obtained from 3-chloro-2-alkylcyclohexen-1-one (30) by the Schmidt reaction. It has been reported[49] that



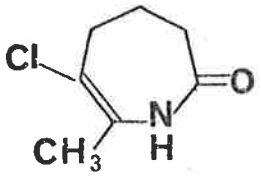
Scheme 14

in the Schmidt rearrangement of 3-chloro-2-cyclohexen-1-one with

polyphosphoric acid, migration of the alkyl site and the double bond site are competitive and thus nearly equal amounts of 4-chloro-2,5,6,7-tetrahydro-azepin-2-one (33) and 6-chloro-2,3,4,5-tetrahydro-azepin-2-one (34) were obtained. However, when the Schmidt reaction was performed on 2-methyl-3-chloro-cyclohexen-1-one, only one product was isolated in 50-55% yield. It is possible that the other isomer is formed but decomposes in acidic solution. Two structure 31a ($R=CH_3$) and 32a ($R=CH_3$) are possible for the product. The nuclear magnetic resonance (nmr) spectrum suggests



(31a)

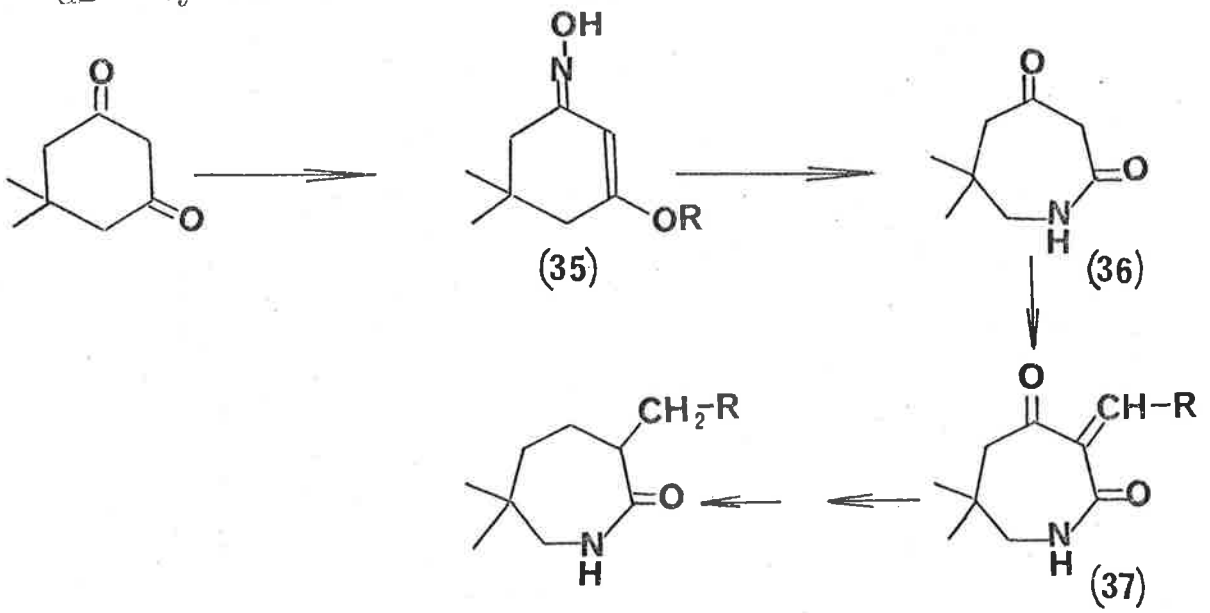


(32a)

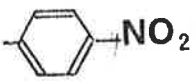
the structure 31a rather than 32a. A broad multiplet centred at about δ 3.20 can be attributed to the two protons belonging to the methylene group next to nitrogen. Furthermore, structure 31a was supported by its hydrogenation to give 3-methylcaprolactam (14a), the structure of which was confirmed by its nmr spectrum and by mixed melting point with an authentic specimen. This scheme appeared to offer a general method for the preparation of 3-alkylcaprolactam (14). Unfortunately, this method suffers from the difficult preparation of the key compound 3-chloro-2-alkylcyclohexen-1-one. A difficulty that frequently arises in the alkylation of 1,3-dicarbonyl compounds is the concurrent formation of both C-alkylated and O-alkylated products[50,51,52]

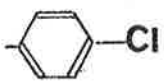
which separated with difficulty. The C-alkylated material is generally only the minor component. In view of these difficulties, it was felt that the method was not a suitable general route to these compounds.

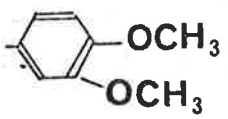
Since dimedone has been successfully converted to the corresponding caprolactam by Beckmannrearrangement[53], it seemed worthwhile to attempt to explore this reaction for the synthesis of 3-substituted caprolactam (Scheme 15). The keto-amide 36 was prepared from oximes 35 according to the procedure of Tamura et al[53] by the Beckmannrearrangement in polyphosphoric acid. In



(a) R = 

(b) R = 

(c) R = 

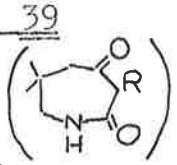
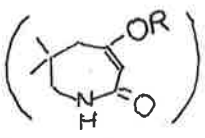
(d) R = 

Scheme 15

this reaction only the saturated group migrated and this, together with easy interconversion of syn- and anti-oximes in the reaction medium, led to a high yield of 36. The keto-amide 36 readily reacted with aromatic aldehydes to form the benzylidene derivative[54] 37. Reduction of the carbonyl group at the 4-position of 37 is currently being investigated.

Direct alkylation of keto-amide 36 would be a useful procedure for the preparation of 3-substituted caprolactams[55]. The alkylation of 1,3-diketone has been reported to give C and O-alkylated products[51,52], with the proportion of these two compounds depending on the nature of an alkylating agent[56,57]. Usually more O-alkylation is obtained with secondary alkyl halides than with primary halides[58,59]. This may be explained by the increase in steric hindrance at the formation of C-alkylated products. Searles and Ressler[57] showed that C-alkylation was favoured when the entering group was small or activated (as methyl or benzyl), while O-alkylation gradually predominated when the bulk of the entering group increased. The results of alkylation of 36, summarised in table 2, show that the proportion of C-alkylation decreases as the alkyl chain changes from C_1 to C_3. Pure samples of the C- and O-alkylated products were easily obtained by chromatography and their percentages were calculated on the basis of isolated yields.

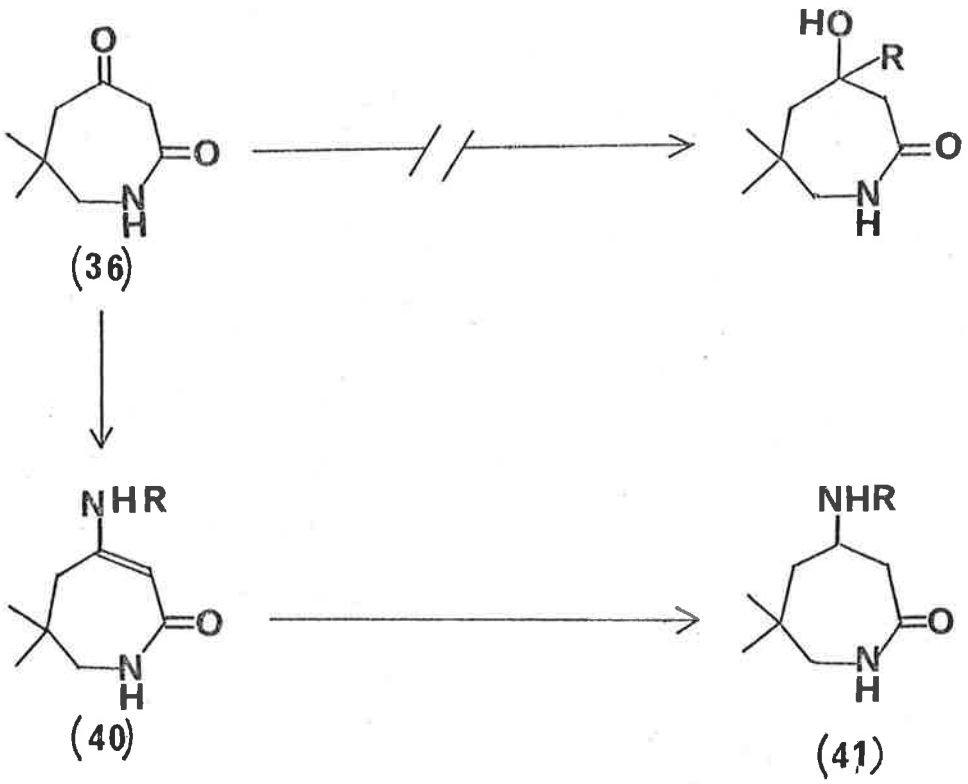
Table 2. The Proportion of 38 and 39

	R	Total Yield %	38 	39 
a	CH_3	69	100	0
b	C_2H_5	53	66	34
c	$i\text{-}C_3H_7$	60	50	50

CHAPTER 3 : SUBSTITUTION AT C-4

Caprolactams substituted at C-4 are not generally accessible. The Beckmann rearrangement[60] or Schmidt reaction[61] of 3-methylcyclohexanone gave mixtures of 4- and 6-alkylcaprolactams which are very difficult to separate. We have therefore investigated alternative general methods for their synthesis. The 6,6-dimethyl-4-keto-caprolactam (36) derived from dimedone[53] did not undergo addition reactions with organo-metallic reagents, and treatment with Grignard reagents or organolithium compounds resulted only in an ionisation. However, 36 did react smoothly with arylamines to give enamines 40 (Scheme 18). When an electron-withdrawing group was present on the aryl ring of these compounds, they showed a considerable sensitivity to moisture and were readily hydrolysed to 36. This water sensitivity would clearly preclude their physiological use and as a consequence the corresponding dihydro derivatives 41 were prepared by catalytic reduction (Scheme 16). Thus saturated lactam 41b caused depression in mice with the dose of 60 mg/Kg.

Two other methods were investigated for the synthesis of 4-substituted caprolactams. The addition of lithium dialkylcuprates or Grignard reagent in the presence of a catalytic amount of copper salt to α,β-unsaturated ketones[62,63,64,65] and esters[66] has been achieved with high success. The wide scope and effectiveness of such reagents have encouraged us to examine the possibility of conjugated addition to the unsaturated amide 16, although similar reactions do not appear to have been previously reported.



(a) R = CH_2–C$_6$H$_5$

(b) R = C$_6$H$_5$

(b) R = C$_6$H$_5$

(c) R = 2-CH_3-C$_6$H$_4$

(c) R = 2-CH_3-C$_6$H$_4$

(d) R = 3,4-dimethoxyphenethyl

(e) R = 2-NO_2-C$_6$H$_4$

(f) R = 4-NO_2-C$_6$H$_4$

(g) R = 4-Cl-C$_6$H$_4$

Scheme 16

The unsaturated caprolactam 16 had been synthesised by Donat and Nelson[67]. Reimschussel et al[68] have also prepared 16 by dehydrobromination of 3-bromocaprolactam (12) by treatment of the latter with bases such as lutidine or sodium alkoxides. Unfortunately, we were unable to obtain a pure compound 16 from the dehydrobromination of 12 under varying conditions and on each attempt only the mixture of 15 and 16 was observed. The work of Paquette[69] and Vogel[70] suggested that the unconjugated isomer 15 is actually the more stable. When the mixture of 15 and 16 was treated with lithium dibutylcuprate[71], a small yield of conjugated addition product 4-butylcaprolactam (42) was obtained and a large amount of starting material returned. With butylmagnesium bromide in the presence of cuprous chloride, no evidence for conjugate addition could be observed and only starting materials were returned.

Since it appeared possible that the cuprate and Grignard addition reactions were unsuccessful due to the formation of insoluble metal complexes with the amide group, another possible route to the useful intermediate unsaturated lactams was through the Schmidt or Beckmannreaction on the conjugated cyclohexanone. Although some instances of successful rearrangements of such systems have been reported, the reactions do not appear to be general.* Thus both isomeric oximes (43) of isophorone can be successfully rearranged to the corresponding amides 44 and 45[72,73] (Scheme 17). The Schmidt reaction on isophorone, however, gives

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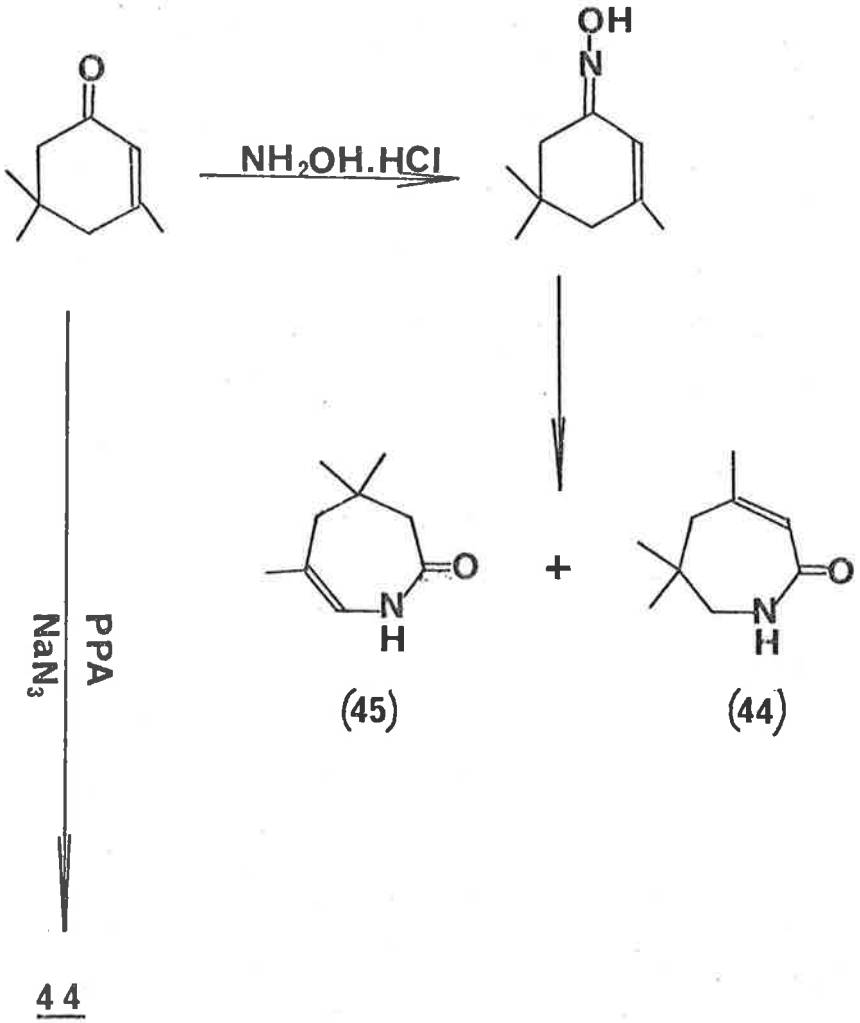
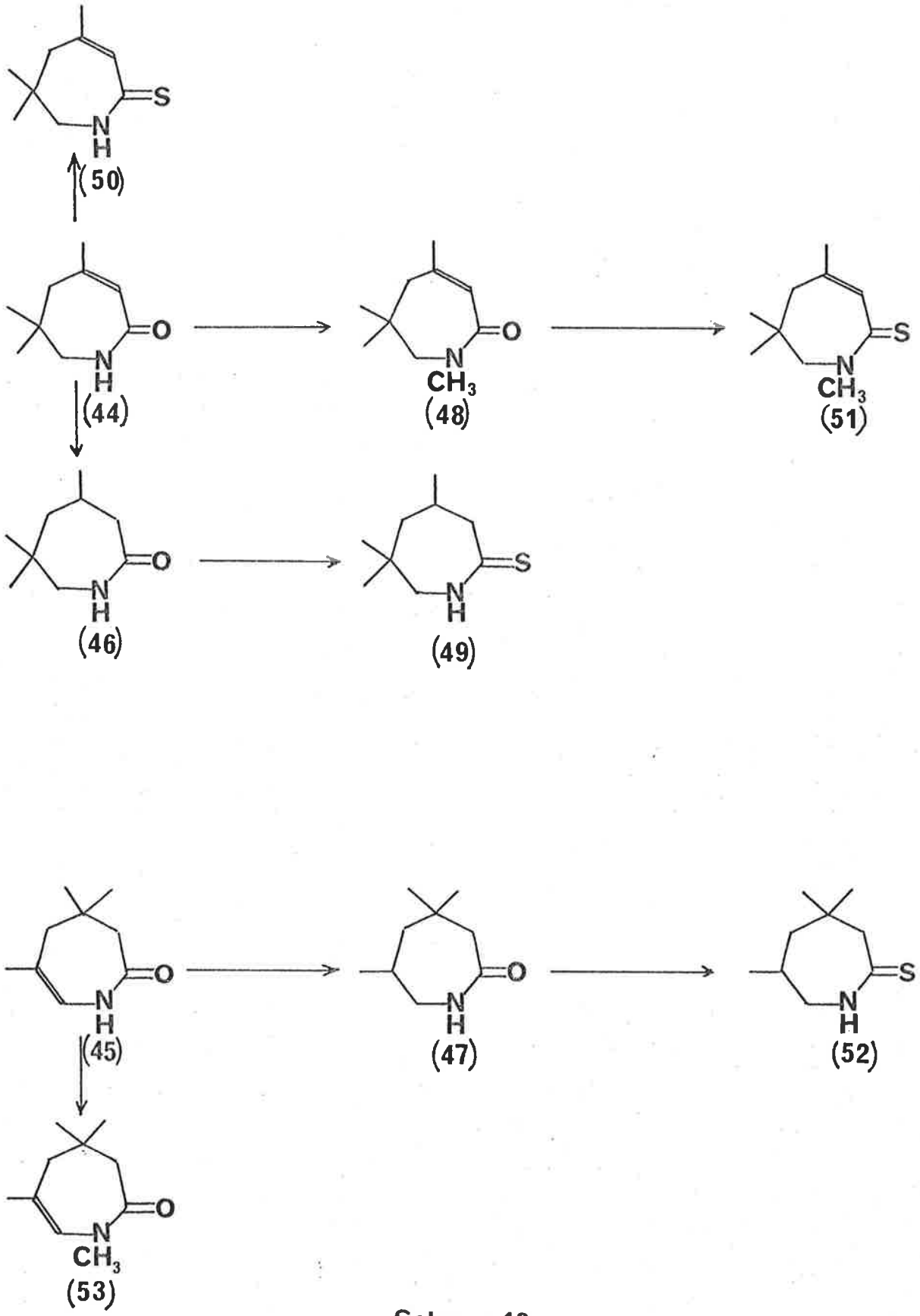
* only the syn-oxime of cyclohexene-1-one undergoes rearrangement[67].



Scheme 17



Scheme18

only the conjugated lactam 44[74]. Each lactam was successively hydrogenated to the saturated product 46 and 47. The above lactams were then methylated by the method described by Jones[26] and were next converted to their thio compounds by reaction with phosphorus pentasulphide (Scheme 18).

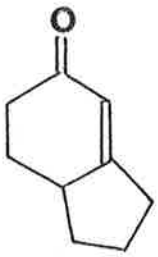
The preliminary testing of 44 and its dihydroderivative 46 caused strong convulsions in mice and the results are summarised in Table 3.

Table 3 : Convulsant Activity of Lactams 44 and 46.

Lactam	Dose mg/Kg	Observation	Final Result
44	10	Clonic convulsion	Died
	20	Clonic convulsion in 1 min. after injection	Died in 4 min., blood came through the nose
46	10	Clonic convulsion, salivation, urination	Died
	20	Clonic convulsion, straub tail	Died in 1 min.

The high convulsant activity of the lactams 44 and 46 suggests that lactams with similar substitution patterns (4- and/or 6-positions) should be prepared.

The oximes 55 prepared from ketone 54 were shown to be a mixture of syn- and anti- isomers by nuclear magnetic resonance spectral analysis. It has been reported[75,76] that in the nmr



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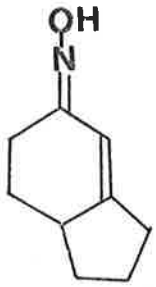
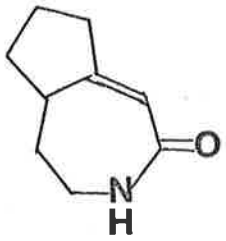


(55)

spectra of the α,β-unsaturated keto-oximes the vinyl proton of syn-isomer shifts to lower field than that of the anti-isomer. The nmr of keto-oximes 55 shows two singlet absorptions for the vinyl proton at δ 6.70 ascribed to syn-isomer and δ 6.60 ascribed to anti-isomer. Further, from the inte grated value of their vinyl protons, it is determined that the ratio of the mixtures of anti- and syn- isomers is 3:2. Attempts to separate these two oximes by repeating fractional crystallisation from different solvents or by column chromatography were unsuccessful. Treating these two isomers with polyphosphoric acid at 130-135^{o} caused the Beckman rearrangement and afforded product in 52% yield. Thin layer chromatography of the residue showed only one product and therefore the product can be regarded as 56 or 57. Nuclear magnetic resonance spectral analysis supports strongly structure 56. A broad multiplet centred at δ 3.28 was assigned to the methylene protonsadjacent to the nitrogen. Lactam 56 was then hydrogenated to its dihydroderivative 58. From this result, it appears that the anti-isomer easily isomerises in the reaction



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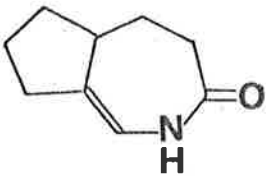

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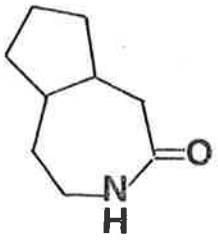
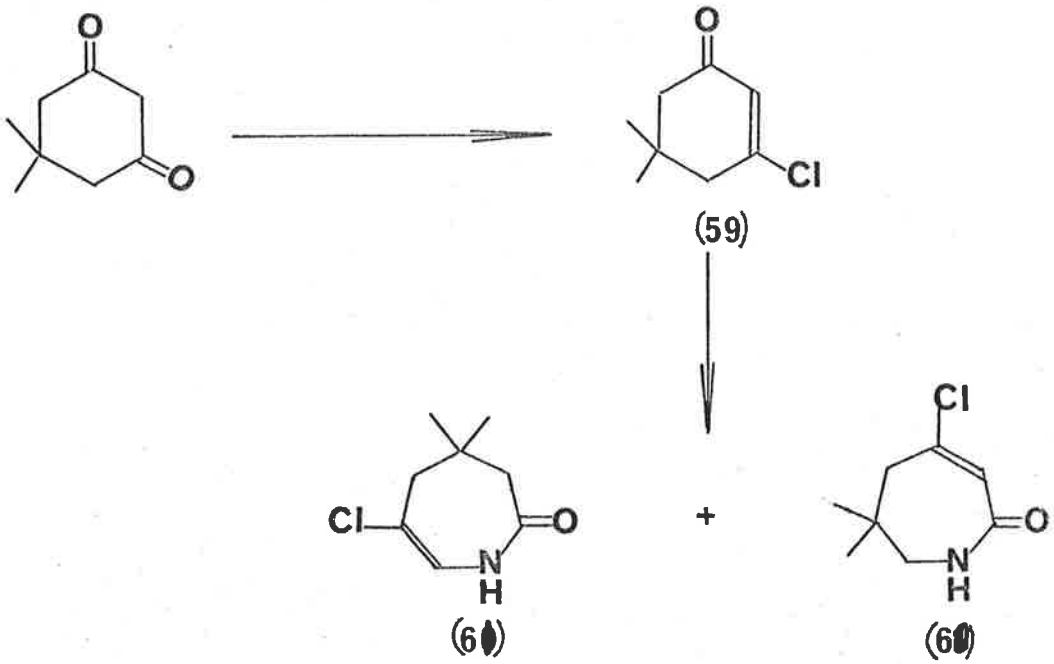


(58)

medium to give syn-isomer which undergoes anti-migration[53] to give 56. Alternatively, the absence of lactam 57 may well be accounted for by the acid-catalysed polymerisation of such systems.

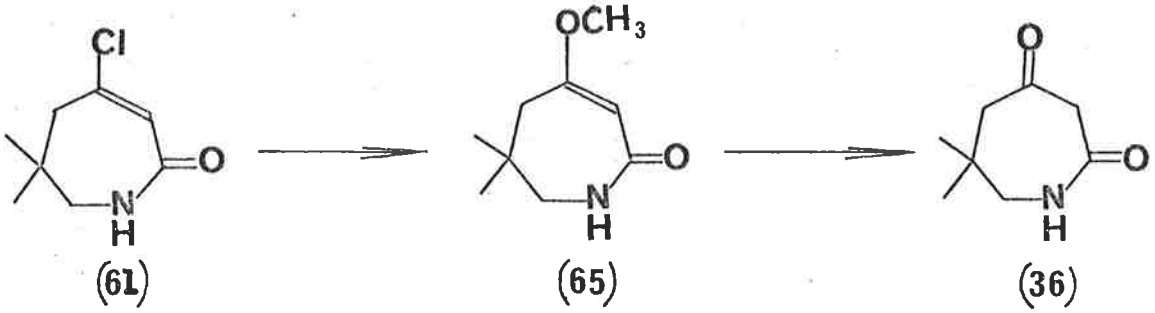
The Schmidt reaction on the chloro derivative of dimedone 59 gave the lactams 60 and 61[49] which seem capable of offering analogues of 44 (Scheme 19). Hydrogenation of lactam 61 in the



Scheme 19

presence of platinum oxide in ethanol at room temperature and at atmospheric pressure led to reduction of the chlorine also; none of the 6-chloro-4,4-dimethylcaprolactam (62) was isolated. The following spectral and chemical data support the structure of 4,4-dimethylcaprolactam (63). The infrared spectrum shows the absence of carbon-carbon double bond at 1625 and the chloro group at 740 cm-1. Its nmr spectrum has a broad peak of two protons at 3.20 assigned to the methylene group adjacent to the nitrogen. Mass spectrum shows molecular ion at 141. Similarly, 60 gave 6,6-dimethylcaprolactam (64) in high yield upon reduction with platinum oxide.

The successful dehalogenation of halo ketones[77,78,79] by silver-promoted zinc dust in methanol or zinc dust and potassium iodide suggests the reaction might prove useful for the reduction of lactams 60 and 61. Unfortunately, all attempts at these methods were unsuccessful and the reaction returned starting material. In view of our inability to remove the chlorine to provide a direct route to 4- or 6- substituted products, a replacement of chlorine by other groups was considered. Thus treatment of 60 with sodium methoxide in methanol gave 6,6-dimethyl-4-methoxy-2,5,6,7-tetrahydro-azepin-2-one (65) in 74% yield (Scheme 20). Its structure was supported by analytical and spectral data. A sharp singlet peak at δ 3.70 ppm was assigned to the methoxy group. Hydrolysis of 65 with 10% HCl gave 36 in high yield. Lactam 65 was also easily obtained by refluxing a methanolic solution of 36 in benzene.



(61) (65) (36)

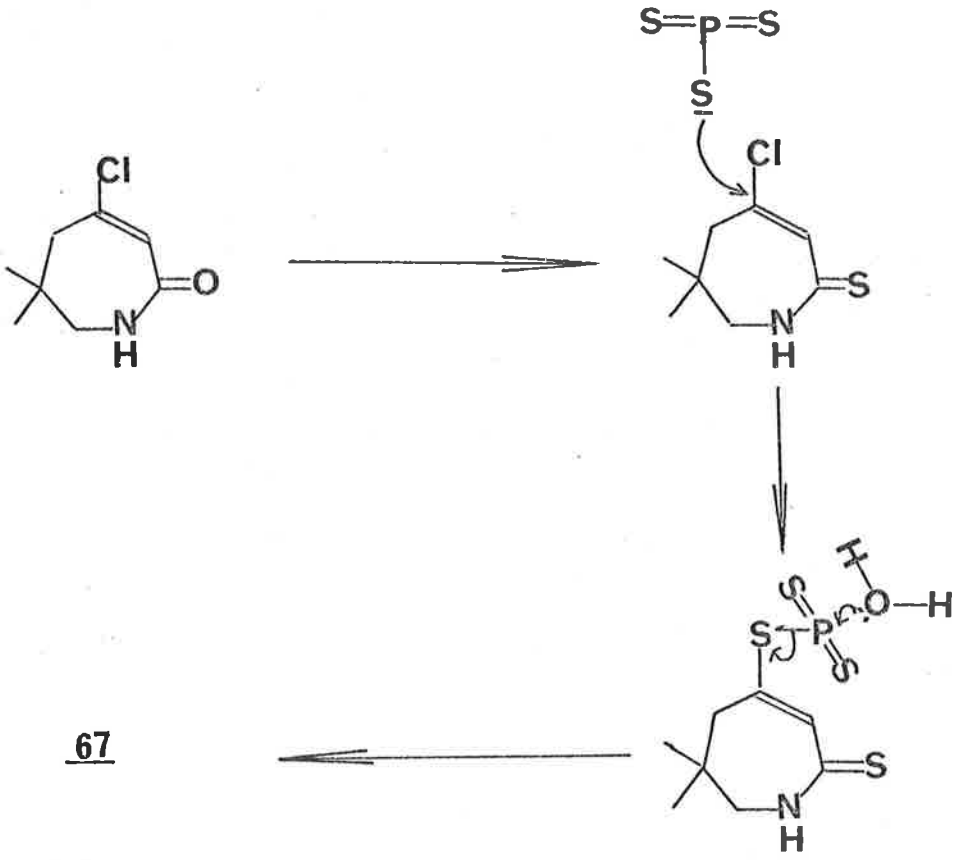
Scheme 20

Refluxing of 61 with phosphorus pentasulphide in toluene gave a thio derivative in 79% yield. Two structures 66 and 67 are possible for the products, but mass spectral and elemental analysis strongly supported the structure 67. To explain the

(66) (67)

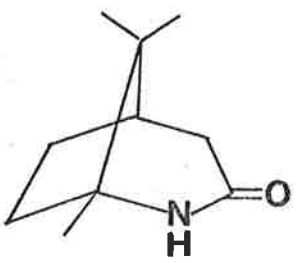
formation of 67, it is suggested the intermediate product is 66 which further rearranges to give 67 as shown below (Scheme 21).

Camphor, which has been observed[80] to give no amide-type product under the Beckman reaction of its oxime, has been found to rearrange to an amide in 34% yield under the Schmidt reaction. Together with the product from this procedure, a large amount of the starting material was recovered. Thin layer chromatography

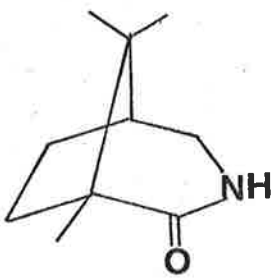


Scheme 21

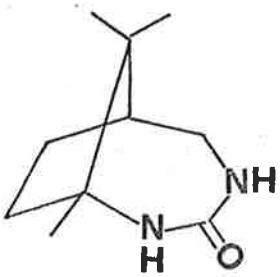
of the residue showed only one product and therefore the product can be regarded as 68, 69 or 70. The two methylene protons at δ2.95 suggested the product from the rearrangement of camphor has structure 69 or 70 rather than 68. The latter structure is strongly supported by elemental analysis and mass spectroscopy



(68)

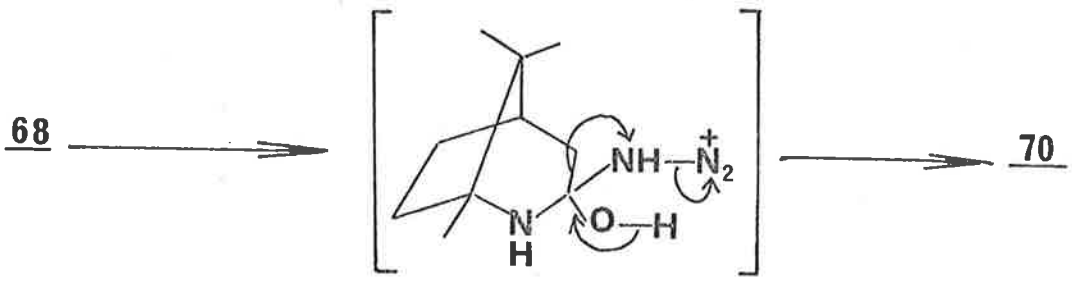


(69)



(70)

(M^+ 182). To explain the formation of 70, it is suggested that the product from the Schmidt reaction which could be 68 or 69, further rearranges to give 70. The mechanistic scheme for its formation is believed to proceed as shown below :



The reason for this reaction pathway is not clear, since most amides react with hydrazoic acid to give tetrazoles[81]. In fact, camphortetrazole is a powerful convulsant[82].

CHAPTER 4 : SUBSTITUTION AT C-5 AND C-7

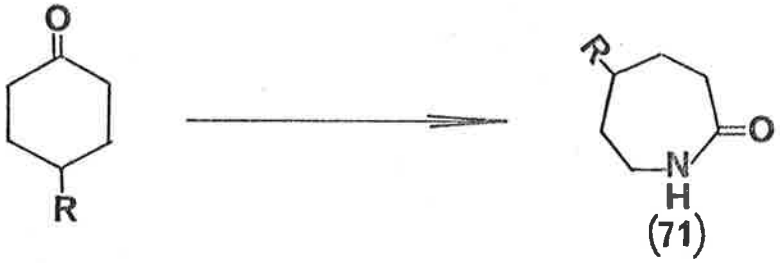
Derivatives of caprolactam substituted at C-5 are most easily available through rearrangement of 4-substituted cyclohexanones by the Schmidt reaction. Since those derivatives prepared showed little activity, the number of such compounds prepared was few.

7-Substituted caprolactams were also obtained from 2-alkylcyclohexanones through the Schmidt reaction. In this rearrangement, it was found[83,84] that the direction of rearrangement is dependent on the steric environment of the carbonyl group and not on "migratory aptitude" of groups. In their reaction with hydrazoic acid using polyphosphoric acid as both solvent and catalyst, cyclohexanones substituted in the 2-position with groups releasing electrons (e.g. methyl, ethyl . . .) gave the corresponding 7-alkylcaprolactam (74) in high yield; there was no evidence of the formation of the isomeric 3-alkylcaprolactams and again these lactams were converted to their thioderivatives 75 in high yield by the method described earlier.

2-Alkylcyclohexanones (73) in this study were prepared from 2-carbethoxycyclohexanone[86] by two steps via the intermediate 2-alkyl-2-carbethoxycyclohexanone (72). Ketones 73 can also be obtained from 2-bromocycloalkanones with organoboranes under the influence of potassium-t-butoxide in tetrahydrofuran[40] but this method is not particularly facile for cyclohexanones. Recently Prager and Tippett[87] have investigated the reaction of α,α'-dibromocycloalkanones with organoboranes and found that the reaction

yields monoalkylated ketones faster and in better yield than ∝-bromocycloalkanones.

Since preliminary testing of caprolactam derivatives suggests that optimum activity is attained with lactams substituted at C-7 and/or C-4, the Schmidt reaction on dl-menthone was performed and gave 4-methyl-7-isopropylcaprolactam (76) in 98% yield and this lactam was also converted to its thioderivative (77) in the usual way.



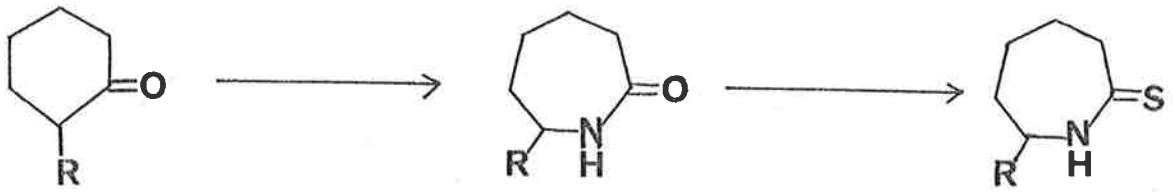
(71)

(a) R= CH_3

(b) R= C_2H_5

(c) R= i-C_3H_7

(d) R= t-C_4H_9



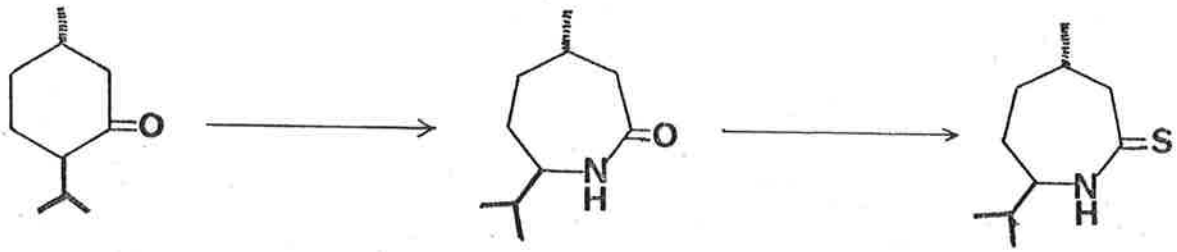
(73) (74) (75)

(a) R=CH_3

(b) R=C_2H_5

(c) R=n-C_3H_7

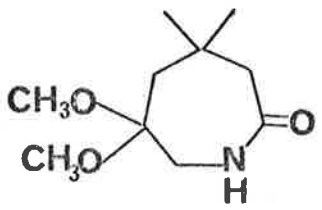
(d) R=n-C_4H_9



(76) (77)

CHAPTER 5 : SUBSTITUTION AT C-6

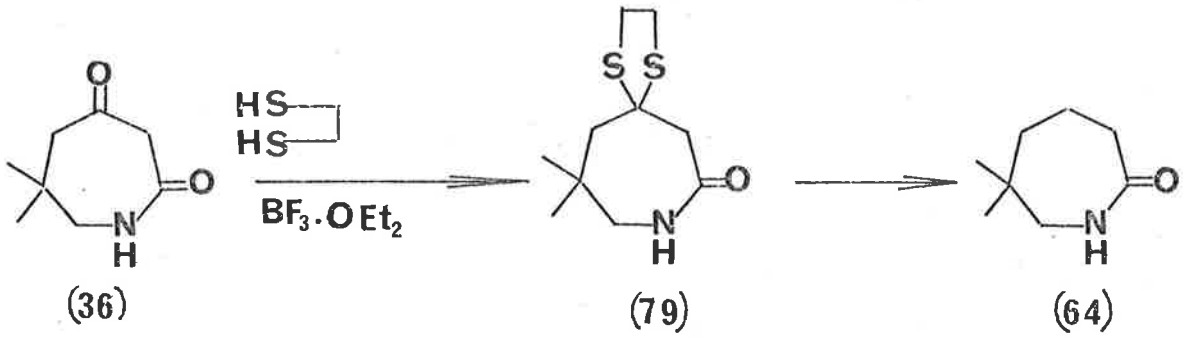
As in the case of 4-alkylated derivatives of caprolactam, no general method of synthesis appeared to be available in the literature. The high activity of the derivatives 44 and 46 suggested that synthetic efforts to solve this problem were merited. As mentioned in Chapter 3, the reduction of 4-chloro-6, 6-dimethyl-2,5,6,7-tetrahydro-azepin-2-one (60) gave 64 in high yield. Its structure was supported by the nmr spectrum. A broad peak centred at δ2.65 ppm was assigned to the methylene protons adjacent to the carbonyl group. Its mass spectrum shows molecular ion at 141. Similar to chlorocaprolactam 60, the replacement of chlorine by another functional group would be a useful procedure for the preparation of 6-substituted caprolactam. Surprisingly, 61 did not give any trace of 4,4-dimethyl-6-methoxy-2,3,4,5-tetrahydro-azepin-2-one when heated with sodium methoxide in methanol, (nmr analysis) but yielded 4,4-dimethyl-6,6-dimethoxycaprolactam (78). The structure of 78 was assigned by elemental analysis and



(78)

spectral data. The nuclear magnetic resonance spectrum shows 2 methoxy groups at δ3.50.

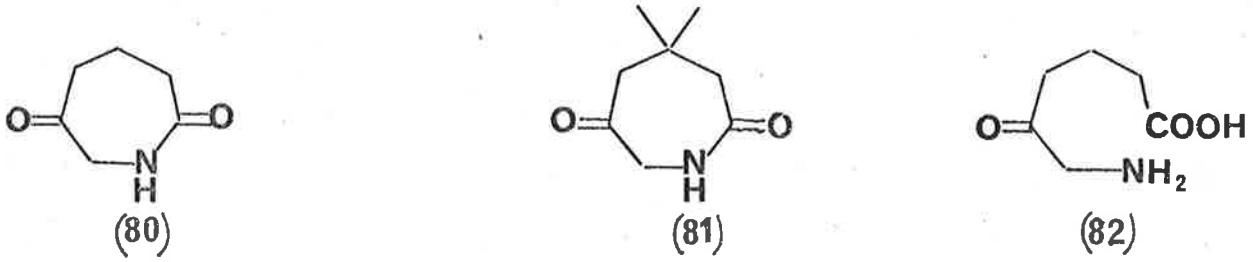
The simplest active compound was obtained from 36 by reduction of the carbonyl group at the 4-position. Indeed there are a great variety of methods[88,89,90,91,92] for this reduction but the simplest procedure was based on the desulphurisation of the corresponding thio-ketal 79 with Raney nickel in boiling ethanol[93,94,95,96] (Scheme 22). The structure of 64 was confirmed by comparison



(36) (79) (64)

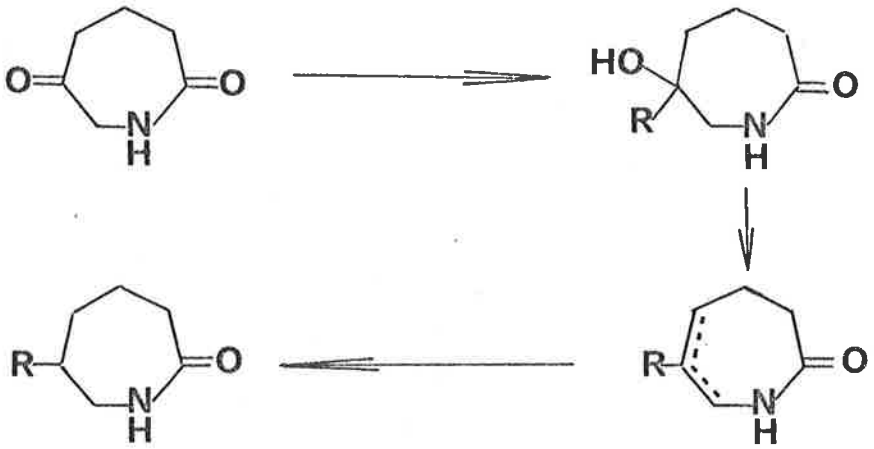
Scheme 22

of its ir, nmr with that obtained by the hydrogenation of 60 as mentioned earlier. However, this procedure is not general and therefore it is hoped to find a key product which could act as a useful intermediate to other lactams substituted at C-6. A suitable starting compound for this synthesis appeared to be the 6-ketoamide 80 or 81 which are completely absent in the literature. The proposed scheme for the synthesis of 6-alkylcaprolactams is out-



(80) (81) (82)

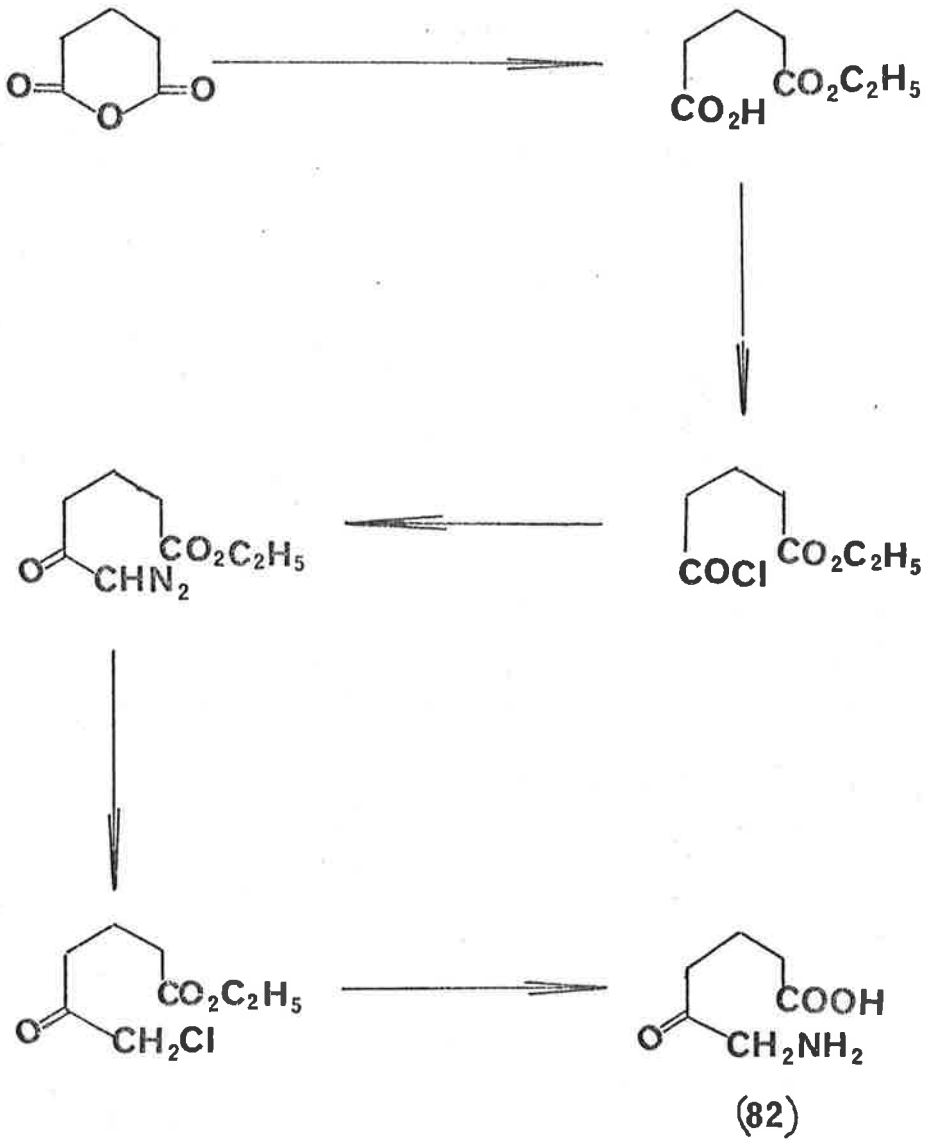
lined in Scheme 23. The cyclisation of aminoacid 82 would be a



Scheme 23

promising route in obtaining compound 80. Lartillot and Baron[97] have reported that 82 can be prepared by round-about route from glutaric anhydride as shown in Scheme 24. However, attempts to cyclise 82 by using dicyclohexylcarbodiimide (DCC) in chloroform or DCC in chloroform in the presence of triethylamine were unsuccessful. In all cases, unchanged amino-acid 82 was recovered and further work in this area is required. An attractive alternative was that hydroboration/oxidation of 6D might lead to compound 81 but again the reaction was fruitless and the starting chloroamide 6D was returned even after long reaction times.

In view of the failure of these schemes, a directed alkylation of lactam 6D with trialkylborane was attempted but the reaction failed to give any trace of the desired product and the unchanged amide was recovered. It seems that different methods for the required keto-amide 80 or 81 will be needed.


O
O
O
CO2H
CO2C2H5
COCl
CO2C2H5
O
CHN2
CO2C2H5
O
CH2Cl
CO2C2H5
O
CH2NH2
COOH

(82)

Scheme 24

CHAPTER 6 : CONVULSANT ACTIVITY OF SOME CAPROLACTAMS. STRUCTURE - ACTIVITY RELATIONSHIPS.

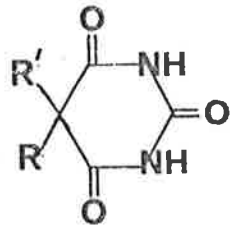
The substituted caprolactams and their corresponding thio-derivatives in this study were screened for convulsant activity on the intact animal and any convulsants were then further tested on isolated preparations.

Caprolactams which caused convulsion at 200 mg/Kg or less, did so within the first 10 min. The convulsions persisted for only 1 - 2 min. and were generally followed by a period of decreased activity. In some cases, the clonic convulsions were followed by a tonic extensor seizure and occasionally resulted in death. The lactams which did not cause convulsions at 200 mg/Kg or less, generally did not have any other effects. Their median convulsant doses (CD_{50}) were estimated by the method of Litchfield and Wilcoxon[98], a rapid graphic method with 95% confidence limits. Subsequent work has shown that the activity of these compounds is anti-GABA[99]. Picrotoxin which had a CD_{50} of 5.40 mg/Kg was also screened. The onset of convulsions was longer than with the lactam and the convulsions persisted for a longer period. In a large proportion of mice injected with picrotoxin, tonic extensor seizures and death also occurred.

STRUCTURE - ACTIVITY RELATIONSHIP

The Hansch approach to correlating chemical structure with biological activity has been widely accepted and recognised as a

versatile way to understand drug action by analysing the structure-activity relationship in various biological systems[100,101,102]. This approach assumes that the physicochemical factors governing the transport and drug-receptor interaction can be factored into electronic, hydrophobic and steric components. The partition coefficient, log P, as measured by the octanol-water partition coefficient is widely regarded as the best measure of the hydrophobic factor governing drug transport. After studying the hypnotic activity of groups of barbiturates (81) Hansch and his colleagues[103] have shown that the acute lethal toxicity (log $(\frac{1}{C})$ of drugs



(83)

is highly correlated with log (P), the correlation having the form :

$$\log (\frac{1}{C}) = - K (\log P)^2 + K' (\log P) + K'' \qquad (1)$$

where:

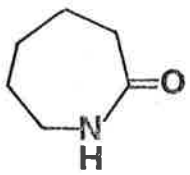
C is the molar concentration of applied drug producing a standard biological response.

K, K' and K" are constants obtained via the method of least squares.

Setting the derivative of equation (1) equal to zero and solving the resulting equation for log P, yields log (P_o) which Hansch and his colleagues[103] called the ideal lipophilic character

for the set of congeners under the specific test conditions. The log P_o is a useful parameter for designing the most potent drug in a set of congeners as well as for illustrating the character of barriers through which drugs have to travel[104,105].

In this study, Ɛ-caprolactam was chosen as the base reference. In a recent review, Hansch, Leo and Elkins[106] have estimated log P value of Ɛ-caprolactam at - 0.19, and this value has been used in several reports[12,18]. We have measured the log P of Ɛ-caprolactam, apparently for the first time and have found it to be - 0.90. This value was used in the investigation of convulsant activity of substituted caprolactams. The measured values for



logP= -0.90

Ɛ-caprolactam

other cyclic amides are likewise lower than estimated by Lien[17]. The additivity of π constants (π_x= log $P_{parent\ molecule\ -x}$ - log $P_{parent\ molecule}$) was found to be quite good, if the value of CH_3 or CH_2 was 0.40 instead of 0.42[107], except lactams 44, 45, 48, 60, 61, which are all unsaturated caprolactams and had log P values considerably higher than expected. The reasons for this are not yet understood. The estimated CD_{50} values and the physicochemical constants used in the correlation are assembled in Table 4.

Our attempts to correlate structure with activity have brought to light some important facts. After studying a limited number of unsubstituted lactams and their thio-derivatives, Lien and his colleagues[17] concluded that these lactams could be correlated by one equation but our work suggests that this is not so. If all the lactams are considered, the data is best correlated with equation (2) Fig 1. No satisfactory correlation at all could be found if the thiocaprolactams were also included. We prefer, at the moment, to consider the correlation of equation (2) to be made up of two separate curves corresponding to lactams and their thio-derivatives.

Table 4 : Convulsive Doses and Partition Coefficients of Caprolactams and Thiocaprolactams

	Structure	CD_{50} mg/Kg	$\log\frac{I}{C}$ mol/Kg	log P exp	log P calcd
7	Caprolactam	580.0	2.28	-0.90	-
9a	1-CH_3-	> 200.0	-	-0.40	-0.50
12	3-Br*-	400.0	2.67	-0.56	-0.30
63	4,4-$(CH_3)_2$-	> 200.0	-	-0.25	-0.10
71a	5-CH_3-	> 200.0	-	-0.46	-0.50
71d	5-t-Bu-	> 200.0	-	0.73	0.70
64	6,6-$(CH_3)_2$-	6.0	4.33	-0.18	-0.10
74a	7-CH_3-	> 200.0	-	-0.46	-0.50
74b	7-C_2H_5-	34.0	3.62	-0.01	-0.10
74c	7-nC_3H_7	60.0	3.41	0.30	0.30
74d	7-nC_4H_9	> 200.0	-	0.64	0.70
46	4,6,6-$(CH_3)_3$-	6.0	4.41	0.45	0.30
47	4,4,6-$(CH_3)_3$-	9.0	4.25	0.40	0.30
44	4,6,6-$(CH_3)_3$-Δ3-	6.7	4.36	1.21	0
45	4,4,6-$(CH_3)_3$-Δ6-	17.0	3.95	1.28	0
48	1,4,6,6-$(CH_3)_4$-Δ3-	41.0	3.61	1.31	0.40
61**	4,4-$(CH_3)_2$-6-Cl-Δ6-	29.0	3.77	1.36	0
60	6,6-$(CH_3)_2$-4-Cl-Δ3-	4.2	4.61	0.96	0

Table 4 : Convulsive Doses and Partition Coefficients of Caprolactams and Thiocaprolactams (continued)

	Structure	CD_{50} mg/Kg	$\log\frac{I}{C}$ mol/Kg	log P exp	log P calcd
	Thiocaprolactam	36.0	3.55	0.72[17]	-
75a	7-CH_3-	33.5	3.63	1.07	1.12
75b	7-C_2H_5-	15.0	4.02	1.45	1.52
75c	7-nC_3H_7-	> 200.0	-	1.76	1.92
	4-CH_3- 6-CH_3-	16.0	3.95	1.02	1.12
49	4,6,6-$(CH_3)_3$-	7.2	4.38	1.74	1.92
50	4,6,6-$(CH_3)_3$-Δ3-	11.5	4.16	1.30	1.63
51	1,4,6,6-$(CH_3)_4$-Δ3-	82.0	3.35	2.09	2.03
36	6,6-$(CH_3)_2$-4CO-	84.0	3.27	-0.83	-
38a	3,6,6-$(CH_3)_3$-4CO-	41.2	3.60	-0.33	-0.43

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* $\pi_{Br}^{106} = 0.60$

* $\pi_{Cl} = 0.40$

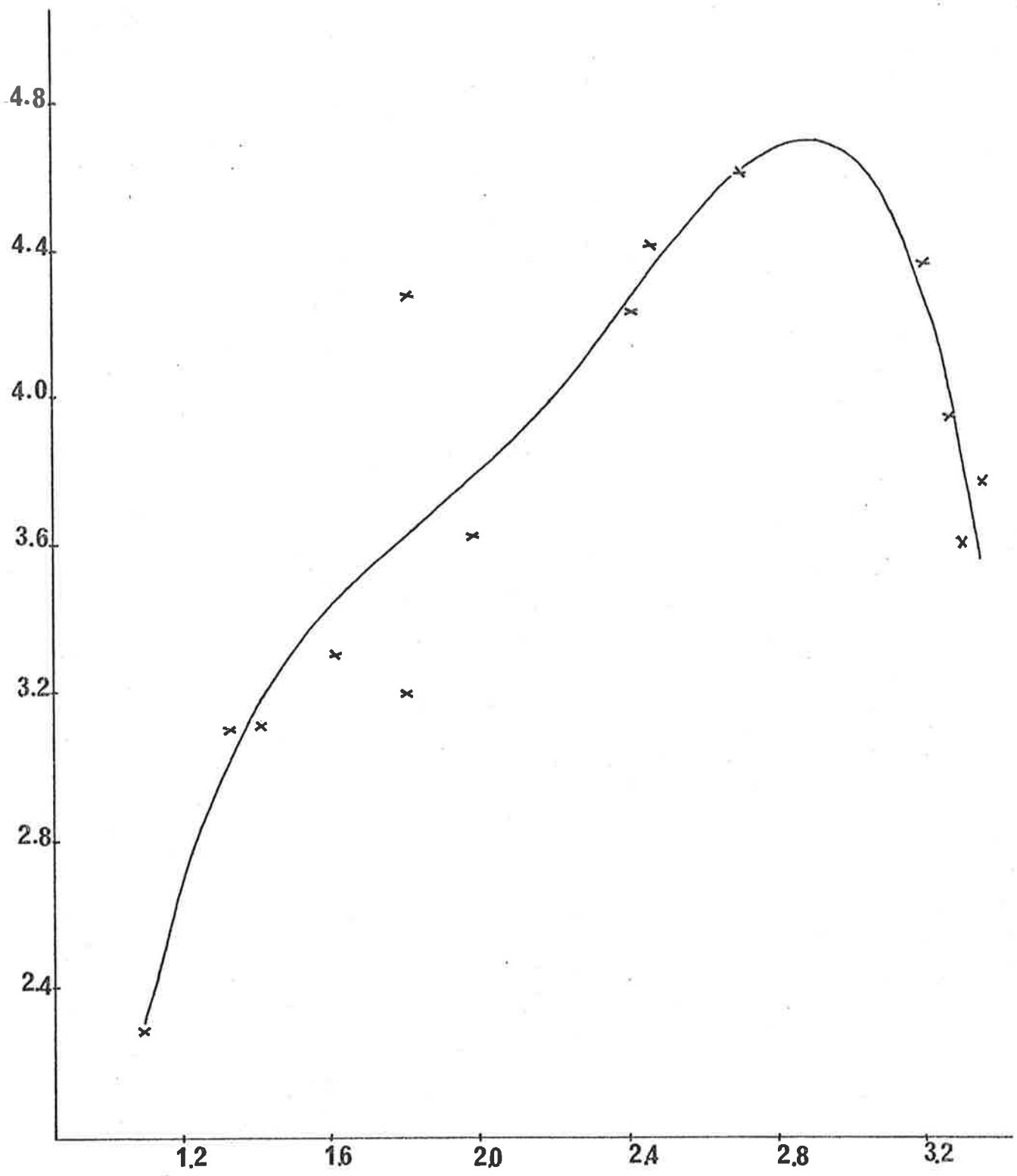


Fig 1. Plot of $\log\frac{I}{C}$ against log P of caprolactams and thio-caprolactams, where C is concentration expressed in moles per kilogram mouse and P is the partition coefficient (1-octanol-water).

$$\log \left(\frac{I}{C}\right) = - 1.02 (\log P)^4 + 8.63 (\log P)^3 - 26.80 (\log P)^2 + 37.28 (\log P) - 16.27 \quad (2)$$

n	s	r
13	0.102	0.822

where :

n is the number of points used in the regression

s is the standard deviation and

r the correlation coefficient.

Fitting the data of all caprolactams in Table 4 to equation (1) yield equation (3) which is strong support for Hansch's hypothesis that, biological response is parabolically dependent on log P[108]. For convenience of computing, each log P in equation (2) and (3) has 2.0 added to it and therefore (3) becomes (4).

$$\log \left(\frac{I}{C}\right) = - 3.06 (\log P)^2 + 17.04 (\log P) - 19.02 \quad (3)$$

n	s	r
14	0.124	0.914 ,

$$\log \left(\frac{I}{C}\right) = - 3.06 (\log P)^2 + 4.80 (\log P) + 2.82 \quad (4)$$

and $\log P_o = 0.79$. This value turns out to be quite close to that reported by Lien and his co-workers[17] ($\log P_o = 0.89$). Indeed, on the basis only of drawing curves of best fit, it would appear that there are three distinct groups : those caprolactams substituted at only one carbon atom, those substituted at two carbon atoms and thiocaprolactams. And therefore, three sets of congeners were considered in this study with three different values of $\log P_o$.

(i) Caprolactam substituted at one carbon atom.

Substitution at 4- or 5- position of the ring gave inactive compounds although they show near optimum log P values (e.g. 4,4-dimethylcaprolactam and 5-alkylcaprolactam) (see Table 4). The reasons for this are not well understood. However, the most active compounds were substituted at C-6 or C-7; thus 6,6-dimethylcaprolactam (64) is potent convulsant with a CD_{50} of 6 mg/Kg (Table 4). The activity of 7-alkylcaprolactam was found to be chiefly dependent on the size of the substituents. By increasing the length of the side-chain, the substitution first enhances the convulsant activity (e.g. 7-ethylcaprolactam with CD_{50} = 34) and then decreases the convulsant activity of the compound (e.g. 7-n-propylcaprolactam with CD_{50} = 60.0) until finally the compound no longer is a convulsant (e.g. 7-Butylcaprolactam). In fact, 7-butylcaprolactam, with dose at 110 mg/Kg, causes paralysis in the hind limbs and also causes an increase in motor activity in the mice. Kerr and Dennis[99] report that, in marked contrast to the convulsant lactams which antagonise the activity of barbiturates, the 7-butyl compound potentiates barbiturate-induced anaesthesia very markedly. Thus in the case of 7-alkylcaprolactam, a steric factor is clearly at work, and a full analysis must wait for the synthesis of a larger group of such derivatives.

(ii) Caprolactams substituted at two carbon atoms.

Using convulsant activity for preliminary screening, the most effective compounds so far found are substituted on carbon 4 and 6 of the ring. Fitting the data of caprolactams substituted at two carbon atoms in Table 4 to equation (1) yield equation (5) (Fig 2.)

From Table 4 the most active compound is 4-chloro-6,6-dimethyl-2,5,6,7-tetrahydro-azepin-2-one (60) with CD_{50} of 4.20 mg/Kg

$$\log \left(\frac{I}{C}\right) = -1.074 (\log P)^2 + 1.20 (\log P) + 4.18 \quad (5)$$

n	s	r
11	0.206	0.870

representing some hundred-fold improvement over the parent lactam (CD_{50} is about 580 mg/Kg)[22]. Replacing a single bond with a double bond results in a constant change in log P ($\Delta\pi$) of about -0.30[100] which according to Hansch[109], should cause a decrease in the ease with which the compounds enter the nervous system (e.g. 44 with CD_{50} = 6.70 c.f. 46 with CD_{50} = 6.00 etc...). When the nitrogen in the ring is alkylated the activity dropped (e.g. 48 with CD_{50} = 41.00 c.f. 44 with CD_{50} = 6.70). This finding is in agreement with the observation by Elison et al[18] in the study of CNS activities of lactam derivatives. The reason for this decrease in activity may be due to interference of dipole-dipole interaction at the receptor sites by N-alkyl group or the requirement for hydrogen bond formation.

One possible reason for the difference in log P_o requirement for mono- and disubstituted caprolactams may lie in the secondary hydrophobic bonding, as shown below which suggests that the three-point binding in the case of disubstituted derivatives favours binding of the amide group as shown, but monosubstituted derivatives possibly bind a different site.

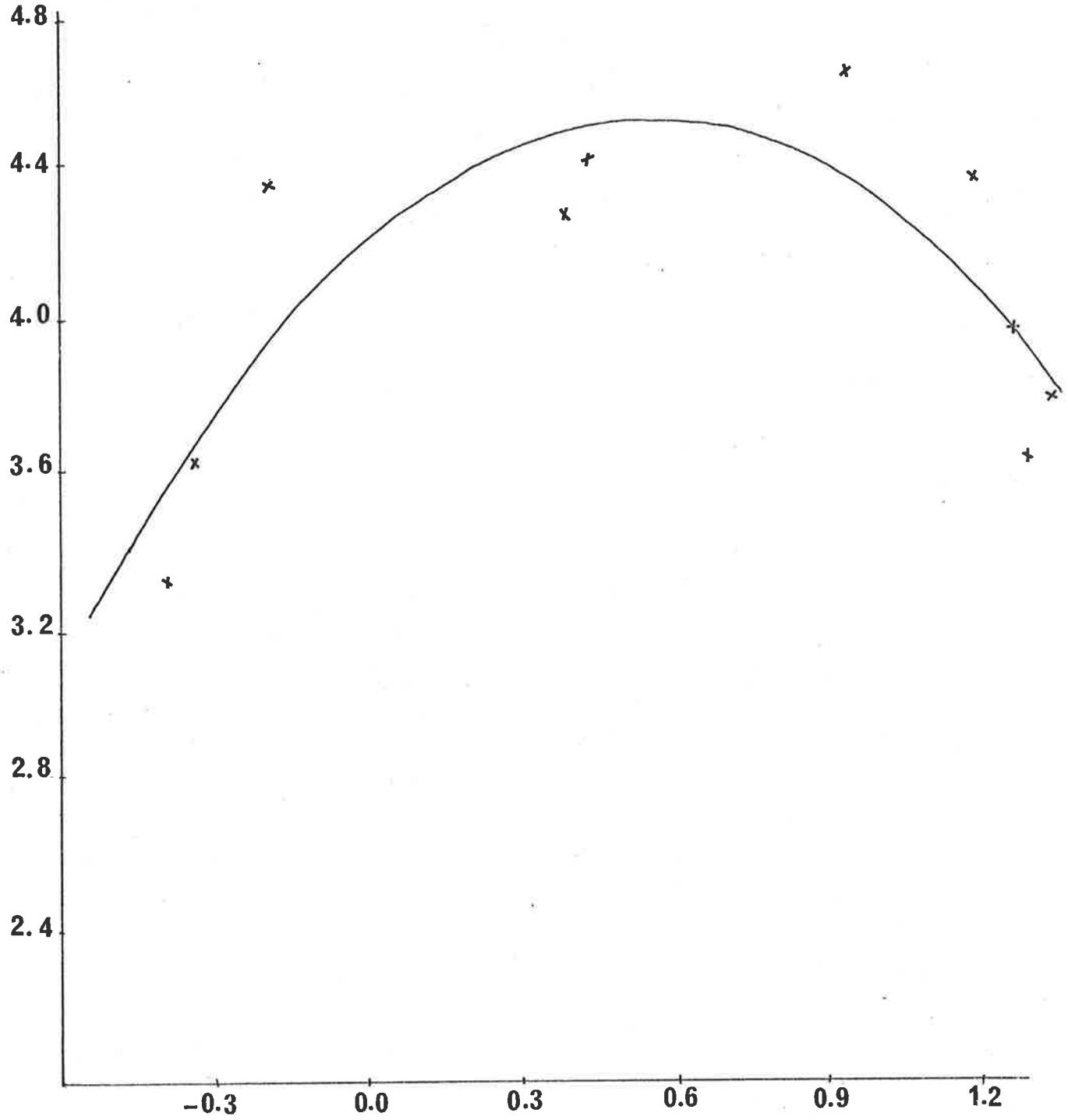
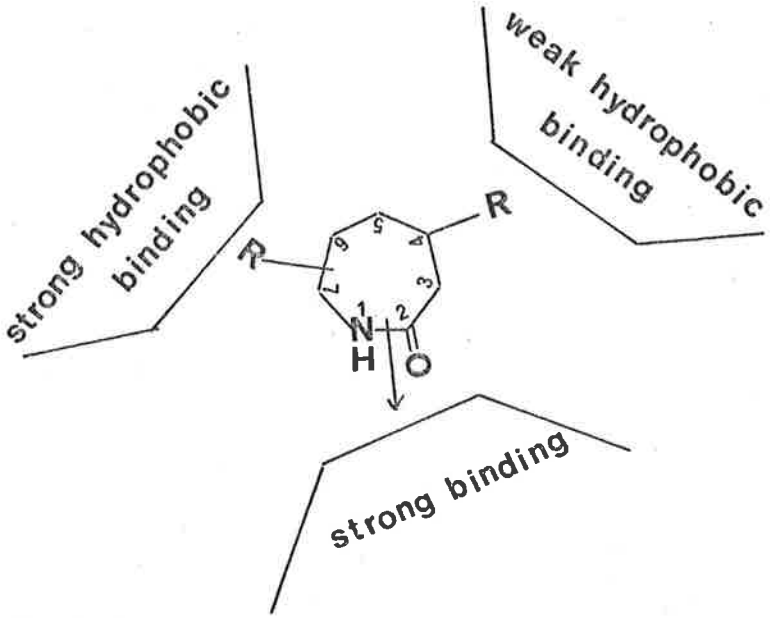


Fig 2 : Plot of log $\frac{I}{C}$ against log P of caprolactams substituted at two carbon atoms.



(iii) Thiocaprolactam

Substituting the oxygen atom with a sulphur atom does not always increase the potency as thought by Lien and his colleagues[17,18]. Although 7-alkylthiocaprolactam follows this pattern, the thio-derivatives such as 2,5,6,7-tetrahydro-4,6,6-trimethylazepin-2-thione (50) and 4,6,6-trimethylthiocaprolactam (49) were not as potent as the oxygen analogue. Fitting the data of all thiocaprolactams in Table 4 to equation (1) yield equation (6) (Fig 3.) in which the optimum lipophilic character for maximum toxicity (log P_o) is 1.43. This value is in agreement with the observation by Lien et al[17].

$$\log \left(\frac{I}{C}\right) = - 1.609 \ (\log P)^2 + 4.607 \ (\log P) + 0.907 \quad (6)$$

n	s	r
6	0.259	0.976

It seems very likely that it is imprudent to compare the relative activities of the thiolactams with those of the lactams, since the activities refer to whole-animal studies and the high

log P values of the thioamides* result in a very rapid and high concentration of drug in the brain, resulting in rapid onset of convulsions. With caprolactams, the lower log P results in overall lower concentrations in the brain, resulting in slower onset of convulsions lasting for longer periods. Clearly the relative activities should be compared in an isolated system where transport is not important. As in the case of caprolactam derivatives, the most active compounds found in this series have substituents on carbon 4 and 6 of the ring. Double bond or alkylation on N tend to decrease activity of the compounds (see Table 4).

The pharmacology of the caprolactam derivatives reported in this thesis have been studied in further detail by Kerr[99] who has found that they inhibit the action of GABA in the central nervous system.

Finally, it should be pointed out that these ring structures with resonant-NH-CO- and -NH-CS- groups raise certain questions concerning the nature of the GABA receptor, and of the active conformation of the GABA molecule, at a time when an "extended" rather than "folded" GABA molecule is becoming favoured[110] as the preferred conformation involved in GABA-mediated inhibitions in the CNS.

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* Normally, sulfur compounds are considered to be more lipophilic than their oxygen analogs.

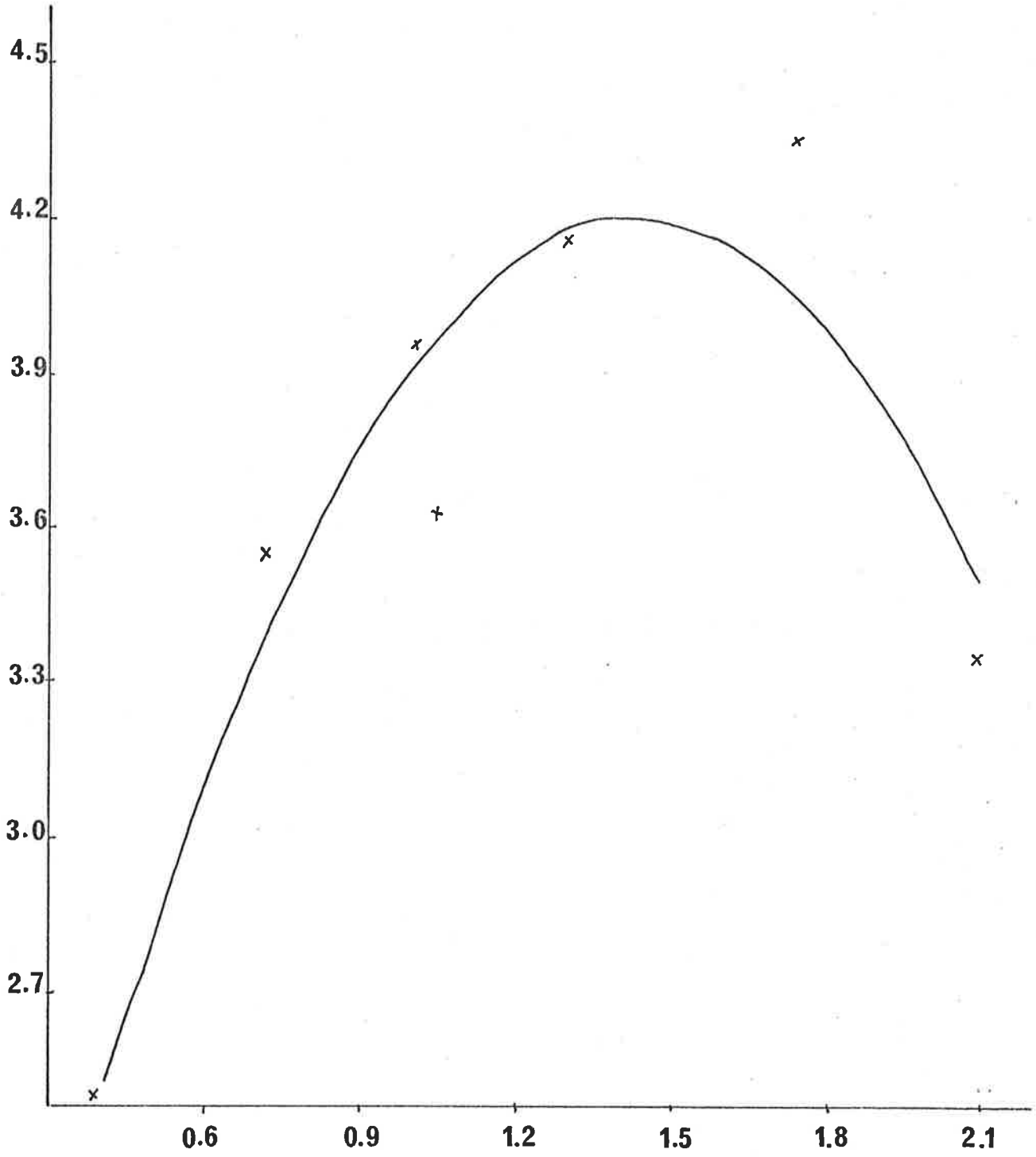

Fig 3 : Plot of $\log\frac{I}{C}$ against log P of thiocaprolactams.

EXPERIMENTAL

GENERAL

(1) Melting points (mp) were measured using a Kofler hot-stage apparatus. Melting points and boiling points (bp) are uncorrected.

(2) Infrared spectra (ir) were recorded on either a Perkin-Elmer 337, a Unicam SP 200, or a Jasco IRA-1 grating infrared spectrophotometer, using the 1603 cm^{-1} bond of polystyrene as a reference.

(3) Nuclear magnetic resonance (nmr) spectra were recorded on a Varian T60 spectrometer operating at 60 MH_z, using tetramethylsilane as an internal reference. All spectra were determined in carbon tetrachloride unless stated otherwise. Data are given in the following order : solvent; chemical shift (δ), multiplicity, s (singlet), b (broad), d (doublet), t (triplet), q (quartet), dd (doublet of doublets), m (multiplet), removed with D_2O means that the signal disappears on shaking with the sample with D_2O, complex means that this part of the spectrum could not be interpreted; first-order coupling coupling constant (J) is expressed in H_z.

(4) Ultraviolet spectra (uv) were determined using a Unicam SP 800A spectrophotometer.

(5) Mass spectra were recorded with a Hitachi Perkin-Elmer RMU-6D double focussing mass spectrometer operating at 70eV. The data are recorded in the following order : operating voltage; m/e value; assignment with metastable peak (where observed); relative

intensity to base peak (100).

(6) Gas chromatographic analyses (G.C.) were performed on Autoprep 700 and 705 models or Pye 104 chromatograph using nitrogen carrier gas. The columns, constructed of stainless steel or pyrex glass, were (1) Apiezon M 5%, 6M x 12mm, (2) Carbowax 20M 10%, 3.6M x 2.0mm, (3) OV 101 20% 2M x 6.0mm. The relative areas of peaks have been determined by triangulation. Data are recorded in the order : column; temperature; retention time (mins/sec.).

(7) Microanalyses were performed by the Australian Microanalytical Service, Melbourne.

(8) Analytical and preparative-thin layer chromatography (tlc) plates were prepared from 50% Kiesegel G and HF 254 applied to the glass plates as a suspension in water and activated at 120° for 12 hr. Column chromatography was carried out on sorbsil silica gel or Spence neutral alumina, using dry redistilled solvents.

(9) The commonly used anhydrous solvents were purified as follows : Ether was dried over calcium chloride granules for 48 hr., distilled from phosphorus pentoxide and stored over sodium wire. When required further drying was achieved by distillation from lithium aluminium hydride. Reagent grade tetrahydrofuran was distilled from lithium aluminium hydride immediately before use. Benzene was dried by refluxing over a water separator until no more water was collected, then distilled and stored over sodium wire. Petroleum ether and hexane of sufficient dryness were obtained by distillation. Pyridine

was heated under reflux over potassium hydroxide pellets for 24 hrs., then distilled from fresh potassium hydroxide and stored over 4A° molecular sieves. Chloroform and methylene chloride were distilled from phosphorus pentoxide. Acetic anhydride was distilled from calcium carbide. Dioxan was purified and dried as described by Hess and Frahm[111,112] and stored over sodium wire. Dimethyl formamide (DMF) and dimethylsulphoxide (DMSO) were distilled under reduced pressure from calcium hydride.

(10) In this text, petroleum ether refers to the fraction of bp 50-65°.

(11) All organic extracts were dried over anhydrous magnesium sulphate, unless stated otherwise. Redistilled solvents were used for all extractions.

(12) All glassware for reactions involving organometallics was flame dried under vacuum.

WORK DESCRIBED IN CHAPTER 6

Partition Coefficients : The analyses of the concentrations of partitioned substances were made using a Unicam SP 800 spectrometer. The 1-octanol was purified by washing with dilute sulfuric acid and then sodium hydroxide followed by distillation. For the partitioning, octanol saturated with distilled water and distilled water saturated with octanol were used, and therefore no corrections

for volume change after equilibrium were necessary. Usually, 50-150 ml portions of octanol were used with 50-400 ml portions of water. The volume ratio of the two phases and the amount of sample were chosen so that, in most cases, the absorbance of a sample from the water after partitioning had a value between 0.20 and 0.90. Only the concentration of the sample in the water layer was determined, and that in the octanol was obtained by difference. Each determination was done at least in duplicate at two different volume ratios and the average value for log P has been reported.

Preliminary Test for CD_{50}:

Mice weighing 20-42g were injected intraperitoneally with a series of doses (10, 20, 40, 60, 100, 200 mg/kg body weight) of the relevant compound. Signs of CNS stimulant activity were observed continuously for at least one hour. All drugs were dissolved in saline (9% NaCl) or propylene glycol* and administered in a volume of 0.25-0.50 ml.

Estimation of CD_{50}:

For a given drug known to cause convulsions at 200 mg/kg or less, a group of five mice were injected intraperitoneally with each appropriate dose to be tested. Clonic convulsion within one hour

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* Propylene glycol was used in cases to dissolve those drugs which were insoluble in saline. This did not affect the administration of the drug in any significant way.

after injection was used to determine the effective convulsant dose. The CD_{50} was estimated for each lactam according to the method of Litchfield and Wilcoxon[98].

Regression Analysis: The data was analysed by computer using the Polyanna Curve-fitting package for optimal orthogonal polynomial fit.

PART I

2, 4- DIHYDROXYPYRIDINE (19)

Ethyl-2,4-dihydroxypyridine-5-carboxylate[32] (17) (6.00g), ethanol (30ml) and dilute sodium hydroxide (30ml) were refluxed for 30 min. The solution was cooled and then acidified slowly with concentrated hydrochloric acid. On cooling, the product 2,4-dihydroxypyridine-5-carboxylic acid (18) was collected (3.50g, 70%); mp 308° (lit[32] 310°).

Acid 18 (1.90g) was then heated at 190-200° for 1 hr. The infrared spectrum indicated that the product was the starting material. This acid was then mixed with copper powder and sublimed at temperature 280-300° for 6 hrs. The decarboxylated product was collected as yellow needles (0.10g, 11%) mp 258-262° (lit[33] 265°-267°).

QUINOLINIMIDE (22)

Quinolinic acid (20g), acetic anhydride (20ml), acetamide (20g) and pyridine (0.20ml) were refluxed for 4 hrs. The acetic acid was removed by distillation. The crude product was collected and sublimed at 160°/0.05 to give 22 as colourless needles (16g, 90%) mp 241-242° (lit[49] 243°).

QUINOLINAMIDE (23)

A solution of methyl quinolinate (21) or quinolinimide (2g) in methanol (20ml) was added to liquid ammonia (20ml) at 0°, the

ir (nujol) : 1645 cm-1

nmr ($CDCl_3$) : δ 7.9-7.4 (complex, 7H); 6.20 (t , $J7H_z$, 1H, N-CH=CH-CH); 3.50 (s, 3H, $N-CH_3$).

Mass Spectrum (70eV) : m/e (M^+213, $C_{13}H_{11}NO_2$ requires M^+213) (55), 185 (100), 136 (65), 105 (33), 77 (73).

Anal. Calcd for $C_{13}H_{11}NO_2$: C, 73.22 ; H, 5.20 ; N, 6.57

Found : C, 73.22 ; H, 5.32 ; N, 6.45%

ATTEMPTED PREPARATION OF 16 FROM PHENYLLITHIUM.

N-methyl-2-pyridone-3-carboxylic acid[30] (0.153g, 1 mmol) in dry ether or tetrahydrofuran (20ml) was added during 15 min. to phenyllithium in ether (1ml, 2M). The mixture was stirred at 0° for 4 hrs. The reaction was poured onto ice and then extracted with ether. The ether extracts were dried and evaporated to yield a solid which was shown to be starting material by its infrared spectrum. This reaction was repeated under varying conditions of temperature and solvent (Table 2).

the product separated. Recrystallisation of the crude product from ethanol gave colourless needles (0.12g, 51%) mp 161-162° (lit[34] 164-165°). This compound was identified as 26 by spectral analysis.

nmr ($CDCl_3$) : δ 8.50 (2H, N-CH=CH-); 7.20 (1H, N-CH=CH-CH); 3.72 (s, 3H, CO-NCH_3-CO); 3.50 (s, 3H, CH_3N CO).

Mass spectrum (70eV) : m/e (M^+191 $C_9H_{19}N_3O_2$ requires M^+191) (30)

3-BENZOYL-1-METHYLPYRID-2-ONE (16)

N-methyl-2-pyridone-3-carboxylic acid (0.153g; 1 mmol) was added in small portions, over half an hour, at room temperature, to a stirred solution of oxalyl chloride (1.02g, 8 mmol) in dry benzene (20ml). The mixture was stirred at room temperature for 3 hrs., during which time the acid slowly dissolved. The reaction was completed by warming to 50-55° for 30 min. The mixture was cooled and the solvents removed by rotary evaporation and the crude acid chloride (νmax 1780-cm-1) was dissolved in benzene (10ml) at 0°. Aluminium chloride (0.4g) was added to this solution over 1.5 hrs., and the reaction allowed to warm to room temperature, then refluxed for 6 hrs. On cooling, crushed ice (20g) was added followed by hydrochloric acid (3M; 20ml). The aqueous phase was washed with ether, basified and extracted with chloroform. The combined chloroform extracts were washed with water, dried, filtered and the solvent was removed. Recrystallisation of the solid product from ethanol gave 16 as yellow needles (0.09g, 44%),

mp 114-115°

quinolinamide separating as needles after being left overnight. Recrystallisation of the crude product from hot water gave quinolinamide (23) as colourless needles (1.2g, 77%); mp 207-208° (lit[34] 209°).

ir (nujol) 3350, 3150, 1700, 1650 and 1608 cm-1.

PYRIDOPYRIMIDINE (24)

Pyridopyrimidine (24) was prepared by the method of Beckwith and Hickman[35] in 80% yield, mp > 350° (lit[35] 365°)

ir (nujol) 3180, 3060, 1730 and 1680 cm-1.

Mass spectrum (70eV) : m/e (M^+163 $C_7H_5N_3O_2$ requires M^+163) (100) 130 (75).

ATTEMPTED PREPARATION OF PYRIDOPYRIMIDINE METHIODIDE (25)

Pyridopyrimidine (1.63g), methyl iodide (2.84g) and dimethylformamide (20ml) were stirred in the dark at room temperature for 3 days. Removal of the solvent gave a solid which was shown to be the starting material by infrared spectroscopy.

METHYLATION OF PYRIDOPYRIMIDINE

A mixture of pyridopyrimidine (0.20g) and methyl fluorosulphonate (1.5 ml) was stirred at room temperature for 1 hr. 10% Sodium hydroxide (10ml) was added to the solution and then the mixture was refluxed for 1 hr. After cooling and adjusting the pH to 5-6,

Table 2 : Attempted Pheny lation of N-Methyl-2-Pyridone-3-Carboxylic Acid.

Acid	Ph Li	Solvent	Time	Cond. of exp.	Product
	2 equiv.	Et_2O	24 hrs	0^o	-
	2 equiv.	Et_2O	7 days	R.T.	-
	4 equiv.	Et_2O	7 days	Refl.	-
15	2 equiv.	THF	24 hrs	0^o	-
	2 equiv.	THF	24 hrs	0^o	-
	4 equiv.	THF	24 hrs	R.T.	-
	4 equiv.	THF	24 hrs	Refl.	-
	2 equiv.	THF	4 days	R.T.	-
27	2 equiv.	Et_2O	4 hrs	0^o	trace
	2 equiv.	Et_2O	2 days	Refl.	trace

ATTEMPTED CYCLISATION OF 16 BY PHOTOLYSIS

Compound 16 (0.10g) in methanol (200ml) was irradiated using a low pressure mercury lamp in a quartz flask at room temperature for 3 days. Thin layer chromatography of the reaction mixture showed only unchanged starting material. This reaction was repeated with benzene as solvent in the presence of a little iodine but again no reaction occurred.

ATTEMPTED CYCLISATION OF 16 BY THALLATION.

A 0.8M solution of thallium (111) trifluoroacetate (TTFA) in trifluoacetic acid (TFA) was prepared according to the method of McKillop et al[29].

Compound 16 (0.266g) was added to TTFA in TFA (7ml) and the reaction mixture allowed to stand at room temperature overnight. The solvent was removed under reduced pressure and the mixture was then diluted with ether and 1,2-dichloroethane followed by evaporation under reduced pressure to remove solvents and excess TFA. The residual oil was suspended in benzene (200ml) in a quartz flask under nitrogen and the suspension then irradiated for 2 days. The benzene solution was evaporated to dryness to give a brown oil which was identified as starting material by its infrared spectrum.

ATTEMPTED PREPARATION OF 3-CYANO-4-PHENYL-2-PYRIDONE (33)

(i) Bromocyanoacetamide (2.0g) was heated with pyridine (4.0g) for 1 hr. To the cooled mixture was added 1 M NaOH (15ml), methanol (30ml) and cinnamaldehyde (1.32g). After 10 min. acetic acid (30ml) was added and after cooling, the reaction mixture was extracted with benzene. The solvent was removed from the dried extract to yield a yellow solid which was identified as 30 (1.75g, 80%)

mp 155° (lit[39] 156°)

ir (nujol) : 3400, 3200, 2220 and 1690 cm-1

(ii) Cinnamaldehyde (6.5g) and ethylcyanoacetate (5.6g) were dissolved in ethanol (50ml) and various concentrations of ammonia (S.G. 0.880) added at temperatures from 0° to 80°. Working up of the reaction gave a high yield of the product 35.

mp 114-116° (lit[40] 116°)

ir (nujol) : 2250, 1720, 1620 and 1590 cm-1.

nmr ($CDCl_3$) : δ 8.10 (t, J= $6H_z$, 1H, = CH - CH = CH-); 7.80 - 7.30 (complex, 7H); 4.40 (q, J= $8H_z$, 2H, COO-CH_2-CH_3); 1.40 (t, J= $7H_z$, 3H, COO-CH_2-CH_3).

(iii) Repetition of the experiment (ii) from cinnamaldehyde (6.5g) and cyanoacetamide (2.00g) gave quantitative yield of a yellow solid which was identical in all respects to the compound 30 obtained in the above experiment.

ZINC CHLORIDE COMPLEX OF 6

A mixture of 2-aza-1-keto-fluorenone[17] (4) (0.30g), 4-amino-veratrole (0.45g) and zinc chloride (0.20g) was refluxed in toluene (50ml) for 7 days. The reaction mixture was cooled and filtration gave an orange solid which was washed with a little cold water or dilute acid. The analysis of this solid was consistent with the zinc chloride complex 35.

ir (nujol) : 3100 and 1645 cm-1.

Anal. Calcd for $C_{20}H_{16}N_2O_3Cl_2Z_n$: C, 51.28; H, 3.41; N, 6.01

Found : C, 51.36 ; H, 3.42 ; N, 6.42 %

The complex was dissolved in concentrated acid and the solution was extracted with chloroform. The solvent was removed to give a yellow solid which was identified as the ketone 4 by its nmr and ir spectra.

REACTION OF ZINC CHLORIDE COMPLEX WITH m-CHLOROPEROXYBENZOIC ACID

m-Chloroperoxybenzoic acid (0.80g) was added to a solution of the zinc chloride complex (0.50g) in chloroform (30ml) and the resulting mixture stirred at room temperature for 3 days. During this period the solution darkened in colour. The dark solution was then poured through a column of neutral alumina and the eluate evaporated to dryness under reduced pressure to yield a dark oil which polymerised rapidly on standing.

REACTION OF 2-AZA-1-KETOFLUORENONE WITH 4-BROMOVERATROLE

Magnesium turnings (1.2g) were washed with a little sodium dried ether to remove surface grease, dried at 100-120° and allowed to cool in a desiccator. Portion of a solution of redistilled 4-bromoveratrole (5.40g) in anhydrous tetrahydrofuran (20ml) was added to the turnings and the reaction was stirred and heated under nitrogen. To start the reaction, a few drops of redistilled ethyl iodide were added, and when the reaction had commenced, the remainder of the halide was added and the mixture refluxed overnight. After cooling, the reaction was stirred at room temperature for another day. Addition of dry tetrahydrofuran (200ml) was necessary to keep the Grignard reagent in solution when it was cooled. A solution of 2-aza-1-ketofluorenone[17] (0.60g) in dry tetrahydrofuran (30ml) was added over 2 hrs. to the stirred Grignard reagent at 0°. During this addition the colour changed from yellow to green. The reaction mixture was stirred for another hour at 0° and then left overnight

at room temperature when the colour of the reaction changed from green to brown. The reaction was quenched with crushed ice and saturated ammonium chloride. The organic phase was separated and the aqueous phase was extracted with chloroform (3 x 50ml). The combined extracts were dried, the solvent removed, and the residue recrystallised from ethanol to yield 8 as yellow needles (0.60g, 63%). A small sample was recrystallised from ethanol before analysis.

mp 225°

ir (nujol) : 3250, 3150 and 1640 cm-1

nmr (DMSO-d_6) : δ 7.80-7.20 (complex, 7H); 6.70 (m, 3H); 5.60 (b, 1H, OH, removed with D_2O); 3. 80 (6H, $2(OCH_3)$).

Mass spectrum (70eV) : m/e (M^+ 335, $C_{20}H_{17}NO_4$ requires M^+ 335) (20)

Anal. Calcd for $C_{20}H_{17}NO_4$: C, 71.63 ; H, 5.11 ; N, 4.18

Found : C, 71.66 ; H, 5.33 ; N, 4.06 %

REDUCTION OF 16 BY SODIUM BOROHYDRIDE IN ETHANOL

A solution of sodium borohydride (0.40g) in ethanol (10ml) was added to 16 (0.64g) in ethanol (20ml). The bright yellow colour of the ketone was discharged by the borohydride to yield a clear colourless solution. After stirring for 30-45 mins., the solution was poured into water and the pH adjusted to 4-5 with 10% HCl. Extraction with chloroform, followed by the usual work-up gave the crude product 40 which was recrystallised from ether as colourless needles (0.50g, 70%).

mp 108 - 109°

ir (nujol) : 3260 and 1640 cm-1

nmr ($CDCl_3$) : δ 7.40 (complex, 7H), 6.20 (t, J= $7H_z$, 1H, -CH= CH - CH=), 5.81 (b, 1H, -CH-OH), 5.08 (b, 1H, CH-OH, removed with D_2O), 3.60 (s, 3H, N-CH_3).

Anal. Calcd for $C_{13}H_{13}NO_2$: C, 72.54 ; H, 6.09 ; N, 6.51

Found : C, 72.58 ; H, 6.19 ; N, 6.49 %

THE SCHMIDT REACTION ON 16

To a stirred suspension of sodium azide (0.80g) in chloroform (10ml), cooled in ice, sulphuric acid (98%) (10ml) was slowly added and the stirring continued for 30 min at 0°. The ice was replaced by a water-bath maintained at 20-25° and a solution of 16 (0.10g) in chloroform (10ml) added during 20 min. The reaction mixture was stirred at room temperature overnight and then at 50° for another hour. The mixture was cooled and poured onto ice (75g). Extraction with chloroform and evaporation gave crude product (0.095g) which was recrystallised from ether as bright yellow needles (0.075g, 70%).

mp 125-126°

ir (nujol) : 3320 and 1640 cm-1

nmr ($CDCl_3$) : δ 9.30 (b, 1H, NH), 8.60 (d, d, J = $7H_z$, $2H_z$, 1H, CH-NCH_3), 8.00 (complex, 2H, CH=CO-CH-Ar), 7.50 (complex, 3H, 3H (Ar)), 7.10 (d, d, J = $7H_z$, $2H_z$, 1H, CH = C-NH), 6.30 (t, J = $7H_z$, 1H, N - CH = CH - CH =), 3.60 (s, 3H, N- CH_3).

Anal. Calcd for $C_{13}H_{12}N_2O_2$: C, 68.41 ; H, 5.30 ; N, 12.27

Found : C, 68.50 ; H, 5.46 ; N, 12.02 %

THE SCHMIDT REACTION ON ALCOHOL 40

(i) With hydrazoic acid in concentrated sulfuric acid-chloroform.

The reaction was carried out similarly to that above using 40 (0.10g), concentrated sulfuric acid (10ml), sodium azide (0.10g) and chloroform (15ml). Sublimation of the crude product at 110°/0.4 gave pure N-methyl-2-pyridone-3-carbaldehyde (42) as colourless needles (0.05g, 70%).

mp 97-97.5°

nmr ($CDCl_3$) δ 10.50 (s, 1H, -CHO); 8.18 (d, d, J = $7H_z$ J = $2H_z$, 1H, -CH-N-CH_3); 7.70 (d, d, J = $7H_z$, J = $2H_z$, 1H, -CH = C - CHO); 6.40 (t, J = $7H_z$, 1H, -CH = CH - CH =); 3.67 (s, 3H, N-CH_3).

Anal. Calcd for $C_7H_7NO_2$: C, 61.31 ; H, 5.15 ; N, 10.21

Found : C, 60.67 ; H, 5.14 ; N, 10.25 %

(ii) With Hydrazoic acid in Polyphosphoric acid

To a mixture of 40 (0.45g) in polyphosphoric acid (20g), sodium azide (0.16g) was added in small portions over 40 mins. with slow agitation. The temperature was slowly increased to 50-55° on a water bath, and maintained at this level overnight. The reaction mixture was cooled and then poured onto ice-water. Extraction with chloroform and evaporation gave the crude product which, after recrystallisation from ether, afforded the same product 42 (0.26g, 57%) as shown by tlc and nmr spectrum. The acid aqueous solution

(above) was made alkaline with sodium hydroxide solution and extracted with chloroform. Evaporation of the solvent yielded a brown liquid (0.085g) which was shown to be aniline by its ir and nmr spectra.

1-METHYL-2-PYRIDONE-3-CARBOXANILIDE (45)

A solution of aniline (2.0g) in benzene (10ml) was added to the crude acid chloride 27 (prepared from N-methyl-2-pyridone-3-carboxylic acid (0.46g, 3mmol) in benzene (30ml) and oxalyl chloride (3.06g)) in benzene (30ml) until the odour of the acid chloride disappeared. The mixture was then stirred at room temperature for 10 mins., 10% HCl added and the mixture then extracted with benzene. The combined benzene extracts were washed with water (15ml), dried, and the solvent was removed to give a crude solid (0.52g) which after recrystallisation from benzene-ether afforded 45 as colourless needles (0.48g, 70%).

mp 169 - 170°

ir (nujol) : 3050 and 1680 cm-1.

nmr ($CDCl_3$) : δ 12.00 (b, 1H, NH); 8.66 (d, d, J= $7H_z$, J=$2H_z$, 1H, -CH-NCH_3); 7.70 (complex, 5H, aromatic protons); 7.30, (d of d J= $7H_z$, $2H_z$, 1H, CH = C - C = O); 6.50 (t, J= $7H_z$, 1H, N - CH = CH - CH =); 3.70 (s, 3H, N - CH_3)

Anal. Calcd for $C_{13}H_{12}N_2O_2$: C, 68.41 ; H, 5.30 ; N, 12.27

Found : C, 68.46 ; H, 5.42 ; N, 11.95 %

THE SCHMIDT REACTION ON FLUORENOL 8

To a mixture of 8 (0.06g) in polyphosphoric acid (1.20g) was added sodium azide (0.05g) in small portions over 2 hrs. with slow agitation. The temperature was slowly increased to 45-47° on a water bath and this reaction temperature maintained at this level overnight. The reaction mixture was cooled, poured onto crushed ice, and made alkaline with 50% NaOH. The solution was then extracted with chloroform (5 x 10ml). The combined chloroform extracts were dried and evaporated to give a brown solid which after recrystallisation from ethanol afforded 9 as pale pink crystals (0.05g, 87%),

mp 280 - 281°

ir (nujol) : 1645 and 1628 cm-1

Mass spectrum (70eV) : m/e (M^+332, $C_{20}H_{16}N_2O_3$ requires M^+332) (100), 317 (57).

Uv (95% EtOH) : 240 mμ (ε 27,600); 254 (ε 21,600); 268 (ε 15,600); 280 (ε 9,960); 326 (ε 9,600).

Anal Calcd for $C_{20}H_{16}N_2O_3$: C, 72.28 ; H, 4.85 ; N, 8.43

Found : C, 71.96 ; H, 4.89 ; N, 8.27 %

PREPARATION OF N-OXIDE 11

The amide 9 (0.03g) and m-chloroperoxybenzoic acid (0.045g) were dissolved in chloroform (10ml) and the mixture was stirred at room temperature for 3 days. The yellow solution was poured through a column of neutral alumina and the eluate evaporated. Recrystallisation of the crude product from ethanol gave yellowish

needles of the partially hydrated N-oxide 11 (0.012g, 40%),

mp 273 - 274°

UV (95% EtOH) 242 (ε 26,800), 280 (ε 9,400), 288 (ε 8,000), 310 (ε 4,500), 364 (ε 6,600), 404 (ε 4,200)

Mass spectrum (70eV) : m/e (M^+ 348 $C_{20}H_{16}N_2O_4$ requires M^+348) (25), 332 (20), 331 (25), 330 (100), 315, 316, 317 (10), 287 (25), 195 (15), 165 (15), 149 (15), 103 (50).

Anal calcd for $C_{20}H_{16}N_2O_4 \cdot \frac{1}{2}H_2O$: C, 67.26 ; H, 4.79 ; N, 7.84

Found : C, 67.23 ; H, 4.95 ; N, 7.26 %

DEHYDROPERLOLINE (3)

The N-oxide 11 (0.008g) in ethanol (400ml) was exposed to sunlight. After 1 hr. of irradiation, examination of the solution by ultraviolet spectroscopy gave evidence that most of the starting material had disappeared. Evaporation of the solvent gave a white solid which crystallised from ethanol as fine needles (0.004g, 50%),

mp 285 - 287° (lit 288[13,4])

The ultraviolet spectrum was identical with that of an authentic sample of dehydroperloline*

UV (EtOH) : 238 (ε 28,800); 255 (ε 19,000); 275 (ε 11,000) 340 (ε 8,000); 350 (ε 8,700); 370 (ε 6,000).

Mass spectrum (70eV) : m/e (M^+ 348 $C_{20}H_{16}N_2O_4$ requires M^+348) (100).

Accurate mass calcd mol.wt for $C_{20}H_{16}N_2O_4$: 348.1109

Found 348.1099

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* The sample was supplied by Prof. William I. Taylor (International Flavors and Fragrances)

PART II

CHAPTER 1 : SUBSTITUTION ON N OR O

N-Methylcaprolactam (9a) :

N-methylcaprolactam (9a) bp 100-102°/18 (lit[24] 50-51/4) was prepared according to the procedure of Benson and Cairns[24] in 68% yield from ε-caprolactam and dimethyl sulphate in dry benzene. G.C. Apiezon M (180°), 2/15.

O-Ethylcaprolactim (8b) :

This compound bp 82-84°/20 (lit[113] 70°/15, lit[24] 81-82°/26) was prepared according to the procedure of Brown and Ienaga[113] in 68% yield from ε-caprolactam and ethyl chloroformate.

N-Ethylcaprolactam (9b) :

Lactim 8b was heated for 2 h at 200-250° in an atmosphere of nitrogen. Distillation gave N-ethylcaprolactam (60%) as a colourless oil bp 110-113°/8 (lit[24] 97°/5.5).

N-Alkylcaprolactam (9)

The general method for alkylation of caprolactam is given below :

A mixture of caprolactam (1mmole), sodium hydride (1.2 mmole) and dry xylene (10ml) were stirred at room temperature under

nitrogen overnight. A solution of alkyl halide (2 mmole) in xylene (5ml) was added over 20 mins. The reaction mixture was stirred at 100-105° for another 3 h. The hot mixture was filtered, the residual sodium halide was washed with benzene and the solvent evaporated. Applying this method, the following compounds were prepared.

N-Butylcaprolactam (9c)

yield : 92%

bp : 80-82°/0.6 (lit[25] 137-140°/17)

nmr (CCl_4) : δ 3.30 (m, 4H, $-\underline{CH_2}-N-\underline{CH_2}-$); 2.30 (b, 2H, $\underline{CH_2}-CO$); 1.70-1.20 (complex, 10H); 0.90 (m, 3H, $-CH_2-\underline{CH_3}$).

N-i-Butylcaprolactam (9d)

Appeared as colourless oil. A small sample was redistilled before analysis.

yield : 55%

bp : 148-150°/25

nmr (CCl_4) : δ 3.30 (m, $-\underline{CH_2}-N-\underline{CH_2}-$, 4H); 2.30 (b, 2H, $\underline{CH_2}CO$); 1.80-1.20 (complex, 7H); 0.84 (d, J=6H_z, 6H, $CH(\underline{CH_3})_2$).

Anal. Calcd for $C_{10}H_{19}NO$: C, 70.96 ; H, 11.32 ; N, 8.28

Found : C, 71.08 ; H, 11.59 ; N, 7.12 %

N-Benzylcaprolactam (9g)

Appeared as colourless needles from pentane

yield : 55%

mp : 56-57° (lit[29] 55-57°)

N-Isopentylcaprolactam (9e) :

Appeared as colourless oil. A small amount of sample was redistilled in a bulb to bulb apparatus before analysis.

yield : 55%

bp : 148-150°/18

nmr (CCl_4) : δ 3.30 (m, 4H, $-CH_2-N-CH_2-$); 2.40 (b, 2H, CH_2CO); 2.00-1.30 (complex, 9H); 0.85 (d, J=6H_z; 6H, $-CH(CH_3)_2$).

Anal. calcd for $C_{11}H_{21}NO$: C, 72.08 ; H, 11.55 ; N, 7.64

Found : C, 72.48 ; H, 11.06 ; N, 7.98 %

N-Octylcaprolactam (9f) :

yield : 60%

bp : 152-154°/2.5

Anal. calcd for $C_{14}H_{27}NO$: C, 74.61 ; H, 12.08 ; N, 6.22

Found : C, 74.52 ; H, 12.10 ; N, 6.32 %

N-Phenylcaprolactam (10a):

(i) from cyclohexylphenylimine : Cyclohexanone (10.0g), redistilled aniline (10.0 g) and zinc chloride (0.5g) were heated in an oil bath at 155° for 20 mins. The resulting oil was dissolved in chloroform and filtered. The chloroform was removed to give cyclohexylphenylimine (12.0g, 68%) which was used in the next step without purificatio

To the above imine (12.0g) in chloroform (50ml), m-chloroperoxybenzoic acid (14.0g) in chloroform (200ml) was added over a period of 30 min. The resulting mixture was stirred at room temperature for 20 hrs and then filtered through an alumina column, washed with dilute acid and then water. The chloroform was removed and the residue taken up in cyclohexane and placed in a silica flask and exposed to sunlight for 2 days. The cyclohexane was then removed and the brown oil distilled giving N-phenylcaprolactam as colourless solid (4.0g, 30%).

mp : 75° (lit[114] 75°).

nmr ($CDCl_3$) : δ 7.2 (m, 5H, aromatic protons), 3.70 (b, 2H, $\underline{CH_2}$-N-), 2.50 (b, 2H, $\underline{CH_2}CO$), 1.70 (b, 6H).

(ii) from Benzyne with lithium salt of ε-caprolactam : To a solution of ε-caprolactam (0.34g, 3 mmole) in freshly distilled tetrahydrofuran (20ml) was added butyllithium (3ml, 1.0M, 3 mmole) and to the resultant suspension was added benzenediazonium-2-carboxylate[31] (3.0g). The mixture was refluxed for 30 mins., methanol (5ml) added and the solvent evaporated. The residue was partitioned between methylene chloride and water and the organic phase was dried ($MgSO_4$) and solvent removed. The residue (0.50g) was chromatographed on alumina in petroleum, each fraction being examined by ir spectroscopy. Fractions15-17 (0.10g) were the only ones to contain a lactam carbonyl group, but thin layer chromatography on silica and spectroscopic analysis showed the product was the starting material.

(iii) from benzyne with O-Methylcaprolactim : A mixture of O-methylcaprolactim (0.40g) and benzene-diazonium-2-carboxylate[31] (3.0g) in ethylene chloride (50ml) was brought to reflux and heating

was continued for further 30 mins, after the mixture became homogeneous (5 mins.) After removal of solvent, the residue was chromatographed on alumina in light petroleum, eluting with light petroleum-methylene chloride mixtures and finally ethyl acetate. Each fraction was examined by ir and nmr spectroscopy and on this basis fractions 1-6 were combined and rechromatographed. Fraction 7-12 contained mainly caprolactam; hydrolysis of the caprolactim appears to have occurred on the column. Fractions from the second column were examined as above and fractions 1-2 contained O-methylcaprolactim while fractions 9-11, eluted with ethyl acetate, had nmr and ir spectra consistent with N-phenylcaprolactam. They were combined and the resulting oil (0.15g) was subjected to preparative tlc to give pure N-phenylcaprolactam as colourless needles (0.08g, 15%), mp 74-75°.

(iv) from benzyne and Ɛ-caprolactam : A mixture of Ɛ-caprolactam (2.00g) and benzenediazonium-2-carboxylate (3.50g) in ethylene chloride (30ml) was brought to the boiling point and refluxed for 20 mins. after a homogeneous solution had formed (5 mins.). The solvent was removed and the dark residue was chromatographed on alumina in light petroleum, eluting with light petroleum-methylene chloride mixtures and ethyl acetate. Fractions 1-4, eluted with light petroleum - 1% methylene chloride were shown by ir and nmr spectroscopy to contain some N-phenylcaprolactam. Fractions 7-13 were essentially free of unreacted caprolactam.

N-p-Chlorophenylcaprolactam : (10b) :

This was prepared according to the above method (i) from cyclo-

hexanone (10.0g), p-chloroaniline (10.00g), zinc chloride (0.50g), giving a solid product which was purified by sublimation (0.75g, 3%).

mp 67° (lit[114] 68-69°)

Attempted preparation of N-p-methoxyphenylcaprolactam :

Prepared from cyclohexanone (10.00g), p-anisidine (10.00g) and zinc chloride (0.50g) by the method (i) described for the preparation of N-phenylcaprolactam. Work up of the reaction in the usual way gave a dark oil which polymerised rapidly on standing.

General Method for Preparation of Thiolactams.

A mixture of lactam (Ag), phosphorus pentasulphide (2 x Ag), toluene (a x x) was stirred and refluxed for 3-5 hrs. The solvent was removed by filtration, the residue added to water and the mixture was then extracted with chloroform. The chloroform was washed with water, dried and evaporated to give a brown solid which was absorbed on a column of alumina. The column was treated successively with petroleum ether, benzene, benzene-ethyl acetate, ethyl acetate.

N-Isobutylthiocaprolactam (11a):

Treatment of N-isobutylcaprolactam (9d) (0.50g) with phosphorus pentasulphide (1.00g) in toluene (30ml) according to the above general method gave 11a as pale yellow liquid (0.40g, 72%).

bp 118-120°/0.01

nmr ($CDCl_3$) : δ 3.70 (m, 4H, $\underline{CH_2}$-N-$\underline{CH_2}$); 3.04 (b, 2H, -$\underline{CH_2}$-CS); 2.20 (m, 1H, CH_2-$\underline{CH}$ $(CH_3)_2$); 1.80 (b, 6H, $(CH_2)_3$); 0.95 (d, J = $7H_z$, 6H, CH $(\underline{CH_3})_2$).

Anal. Calcd for $C_{10}H_{19}NO_2$: C, 64.83 ; H, 10.34 ; N, 7.56

Found : C, 65.47 ; H, 10.02 ; N, 7.55 %

N-Butylcaprolactam (11b) :

Yield : 73%

bp : 110°/0.01

ir (film) : 1120 and 1070 cm-1 (strong)

nmr ($CDCl_3$) : δ 3.90 (m, 4H, -$\underline{CH_2}$-N-$\underline{CH_2}$); 3.10 (b, 2H, $\underline{CH_2}$-CS); 1.90 - 1.50 (complex, 10H); 1.00 (m, 3H, CH_2-$\underline{CH_3}$).

Anal. Calcd for $C_{10}H_{19}NS$: C, 64.83 ; H, 10.34 ; N, 7.36

Found : C, 64.58 ; H, 10.17 ; N, 7.79 %

N-Isopentylthiocaprolactam (11c) :

Yield : 60%

bp : 120°/0.01

ir (film) : 1120 and 1070 cm-1 (strong)

nmr (CCl_4) : δ 3.80 (m, 4H, $\underline{CH_2}$-N-$\underline{CH_2}$); 3.10 (b, 2H, $\underline{CH_2}$-CS); 2.20-1.40 (complex, 9H); 0.90 (d, J = $6H_z$, 6H, $\underline{CH}$ $(CH_3)_2$).

Anal. Calcd for $C_{11}H_{21}NS$: C, 66.29 ; H, 10.62 ; N, 7.03

Found : C, 66.27 ; H, 10.59 ; N, 6.97 %

N-Octylthiocaprolactam (11d) :

Yield : 85%

bp : 110-112°/0.01

Anal. Calcd for $C_{14}H_{27}NS$: C, 69.66 ; H, 11.28; N, 5.80

Found : C, 69.63 ; H, 11.35 ; N, 5.70 %

CHAPTER 2 : SUBSTITUTION AT C-3

Reaction of Sulphonium Ylid with Triethylborane

A mixture of 3-bromocaprolactam (12) (0.50g)[43] and dimethylsulphide (1.50g) in ethanol (10ml) was heated in a sealed tube at 100° for 24 hrs. On cooling, the sulphonium salt 13 crystallised as a colourless deliquescent solid, characterised only by its infrared spectrum (ν_{max} 1640 cm-1). The sulphonium salt 13 (0.50g) was suspended in freshly distilled THF (10ml) and stirred with sodium hydride (0.20g) at 20° until evolution of nitrogen ceased (2 hrs.)[115]. To the yellow suspension was added triethylborane (4.50 mmole) in THF (3ml) and the mixture stirred for 4 hrs. at 20°. The reaction was quenched by the addition of 3M sodium hydroxide (5ml) followed by 30% hydrogen peroxide (2ml). After 3 hrs. stirring at 20°, extraction with ether gave a colourless oil (0.70g) which was chromatographed on alumina in benzene to remove the paraffin oil. The main fraction (0.30g) was eluted with methylene chloride and appeared from its nmr spectrum, to be a mixture of the ylid and the elimination products, 2, 3, 6, 7-tetrahydroazepin-2-one (15) and 2,5,6,7-tetrahydroazepin-2-one (16). Neither earlier or later fractions indicated the presence of any alkylated material.

1, 3-Dimethylcaprolactam (18a) from E-caprolactam.

A suspension of E-caprolactam (1.13g, 10 mmole) in freshly distilled tetrahydrofuran (20ml) under nitrogen at 0° was treated during 10 mins. with butyllithium in hexane (10ml, 2.0M, 20 mmole).

The first equivalent of the reagent produced a voluminous white precipitate which dissolved on adding the second equivalent of butyllithium to afford a yellow solution. The mixture was stirred at 0° under nitrogen for 30 mins. A solution of methyl iodide (2.84g) in tetrahydrofuran (10 ml) was added over 10 mins. During the addition of this reagent, a white precipitate formed. The reaction mixture was stirred at room temperature for another hour, then hydrolysed by the addition of 3N HCl. The organic layer was separated and the aqueous layer was extracted with ether (3 x 20ml). The combined extracts were dried ($NgSO_4$) and the solvent was removed to afford a yellow orange liquid in 42% yield. G.l.c. analysis of this liquid showed 4 products, the major component being identified as 1,3-dimethylcaprolactam (18a). The products were separated by preparative glc and pure 1,3-dimethylcaprolactam was obtained as colourless liquid,

bp 96-97°/13

ir (film) : 1660 cm-1

nmr ($CDCl_3$) :δ3.40 (m, 2H, $\underline{CH_2}$-N); 3.00 (s, 3H, N-$\underline{CH_3}$); 2.60 (b, 1H, $\underline{CH}$-CO); 2.00-1.30 (complex, 6H, $(CH_2)_3$); 1.15 (d, J = 7H_z, 3H, -CH-$\underline{CH_3}$).

Mass spectrum (70eV) : m/e 141 (M^+, $C_8H_{15}NO$ requires M^+141)

Anal. Calcd for $C_8H_{15}NO$: C, 68.04 ; H, 10.71 ; N, 9.92

Found : C, 68.00 ; H, 10.51 ; N, 9.87 %

G.C. Apiezon M (180°), 1/51

1,3-Dimethylcaprolactam (18a) from 1-Methylcaprolactam (9a)

The reaction of 1-methylcaprolactam with butyllithium is

described as an example of the procedure used. The method adapted was similar to the above but in this case only one equivalent of butyllithium was used. Working up the reaction mixture in the usual way gave a colourless oil in 34% yield which was identical in all respects to the caprolactam 18a obtained in the above experiment.

In a similar manner, the following compounds were prepared.

1-Methyl-3-ethylcaprolactam (18b)

Yield : 34%

bp : 110-111°/28

ir (film) : 1650 cm-1

nmr ($CDCl_3$) : δ 3.40 (m, 2H, $\underline{CH_2}$-N CH_3); 3.00 (s, 3H, N-$\underline{CH_3}$) 2.40 (m, 1H, $\underline{CH}$-CO); 2.00-1.20 (complex, 8H, $(CH_2)_4$); 1.00 (3H, -CH_2-$\underline{CH_3}$).

Anal. Calcd for $C_9H_{17}NO$: C, 69.63 ; H, 11.04 ; N, 9.02

Found : C, 69.65 ; H, 10.92 ; N, 8.89 %

1-Methyl-3-propylcaprolactam (18c)

Yield : 30%

bp : 116-118°/23

ir (film) : 1650 cm-1

nmr ($CDCl_3$) : δ 3.40 (m, 2H, $\underline{CH_2}$-N CH_3); 3.00 (s, 3H, -N-$\underline{CH_3}$); 2.40 (b, 1H, $\underline{CH}$-CO); 2.00-1.10 (complex, 10H, $(CH_2)_5$); 0.90 (m, 3H, -CH_2-$\underline{CH_3}$).

Anal. Calcd for $C_{10}H_{19}NO$: C, 70.96 ; H, 11.32 ; N, 8.28

Found : C, 70.98 ; H, 11.28 ; N, 8.44 %

1-Methyl-3-butylcaprolactam (18d)

bp : 124°/23

Yield : 35%

ir (film) : 1650 cm-1

nmr ($CDCl_3$) : δ 3.40 (m, 2H, $\underline{CH_2}$-NCH_3); 2.98 (s, 3H, N $\underline{CH_3}$); 2.30 (b, 1H, C$\underline{H}$CO); 2.00-1.00 (complex, 12H, $(CH_2)_6$); 0.82 (m, 3H, $-CH_2-\underline{CH_3}$).

Anal. Calcd for $C_{11}H_{21}NO$: C, 72.08 ; H, 11.55 ; N, 7.64

Found : C, 72.33 ; H, 11.28 ; N, 7.35 %

Attempted Preparation of 1-Methyl-3-bromocaprolactam (20) from 1-Methylcaprolactam.

(i) 1-Methylcaprolactam (0.38g) in chloroform (25ml) was added to a refluxing suspension of cupric bromide(0.60g) in ethyl acetate (25ml). The resulting reaction mixture was refluxed with vigorous stirring for 7 days. The black colour of copper II bromide was unchanged. Evaporation of the solvent after filtering gave liquid identical in all respects to the starting material (i.r., n.m.r.). No trace of 20 could be detected by examination of the nmr spectrum.

(ii) A solution of N-methylcaprolactam (1.70g) in dry benzene (10ml) was added to a mixture of bromine (4.80g) and phosphorus tribromide (8.10g) in benzene (15ml). The addition was carried out while stirring and cooling to maintain the temperature at 10-15°.

The reaction mixture was diluted with benzene (20ml) and heated at 45-57° overnight. The lower layer was added to chipped ice. After warming to room temperature, the hydrolysed solution was extracted with chloroform. The solvent was removed to give a brown liquid which was shown to be starting material only by its i.r. spectrum.

Attempted Preparation of N-Methyl-3-ethylcaprolactam (18b) from 3-Bromocaprolactam with Triethylborane in the presence of potassium-t-butoxide.

The method for the preparation of 3-bromocaprolactam was similar to the above (ii) from ε-caprolactam (8.50g), bromine (24.00g), phosphorus tribromide (40.50g) and benzene (20ml). The solvent was removed to give a brown solid which was recrystallised from benzene-hexane at -70° affording 12 as colourless solid (9.0g, 65%),

mp 110°-111° (lit[43] 111°)

nmr ($CDCl_3$) : δ 7.00 (b, 1H, NH); 4.70 (b, 1H, CH-Br); 3.40 (b, 2H, CH_2NH); 2.70-1.50 (complex, 6H).

A suspension of 3-bromocaprolactam (0.119g) in anhydrous tetrahydrofuran (15ml) under nitrogen at 0° was treated with triethylborane (2.2ml, 0.9M) in tetrahydrofuran followed by slow addition of potassium-t-butoxide (3ml, 0.25M) in dry tetrahydrofuran. The reaction mixture was stirred at room temperature for 1 hr. A solution of methyl iodide (0.213g, 1.5 equiv.) in dry tetrahydrofuran (5ml) was added over 10 mins., the reaction mixture was stirred at room temperature overnight, added to water (15ml) and then extracted with chloroform. Evaporation of the solvent gave a mixture of

3 products (0.08g) which were separated by means of preparative thin layer chromatography. 1-Methyl-3-bromocaprolactam (20) was identified by its nmr spectrum. nmr ($CDCl_3$) :δ4.70 (b, 1H, C<u>H</u>-Br); 3.40 (m, 2H, <u>CH_2</u>-NCH_3); 3.00 (s, 3H, N-<u>CH_3</u>); 2.40-1.50 (complex, 6H, $(CH_2)_3$). 3-bromocaprolactam and ε-caprolactam were identified by comparison with authentic specimen.

<u>Schmidt Rearrangement of 2-Oxocyclohexane-1-spiro-2',1',3'-dioxolan (22)</u>

2-Oxocyclohexane-1-spiro-2',1',3'-dioxolan (22) was prepared from cyclohexane 1,2-dione and ethylene glycol in dry benzene according to literature procedure[47] bp 105-107°/10 (lit[47] 115-116°/22)

To a stirred mixture of <u>22</u> (1.56g) in polyphosphoric acid (45.00g) was added in portions sodium azide (0.68g) over a period of 40 mins. The mixture was heated at 50-55° overnight with occasional shaking. It was then cooled and poured into a mixture of crushed ice and water (50ml) and extracted with chloroform. The extract was dried and concentrated in vacuo giving a gummy residue (0.30g). The crude product was chromatographed on alumina (25.00g). The column was treated successively with petroleum ether (30ml), benzene (50ml), ethyl acetate-benzene (1:9) (60ml), ethyl acetate (80ml), ethyl acetate-methanol (9:1) (80ml), ethyl acetate-methanol (1:1) and methanol.

(i) Elution with benzene-ethyl acetate (9:1) gave <u>24</u> (0.03g, 2.2%); nmr ($CDCl_3$) : δ 6.60 (b, 1H, N<u>H</u>); 2.60-1.60 (complex, 8H, 4(CH_2)).

(ii) Elution with ethyl acetate gave 25 (0.03g, 1.6%); nmr ($CDCl_3$) : δ 6.80 (b, 1H, NH); 4.30 (2H); 3.80 (2H, $-O-CH_2-CH_2-O-$); 2.60-1.80 (complex, 8H).

(iii) Elution with ethyl acetate-methanol (9:1) gave 26 (0.03g, 1.6%); nmr ($CDCl_3$) δ 7.20 (b, 1H, NH); 4.30 (2H, $-O-CH_2-CH_2-O-$); 3.70 (2H, $-O-CH_2-CH_2-O-$); 3.30 (b, 2H, $-CH_2-NH$); 2.60-1.60 (complex, 6H).

(iv) Elution with ethyl acetate-methanol (1:1) gave 21 (0.028, 2.0%); nmr ($CDCl_3$) : δ 6.80 (b, 1H, NH); 3.50 (b, 2H, CH_2-NH); 2.80-1.80 (complex, 6H).

3-Alkyl-O-methylcaprolactim (28) and 3-Alkylcaprolactam (14)

The general method for the alkylation of O-methylcaprolactim is shown below :

Anhydrous tetrahydrofuran (20ml) and diisopropylamine (2.00g; 0.02 mole) were added to a dry flask purged with nitrogen and maintained under a nitrogen atmosphere. After cooling the mixture to -5°, butyllithium in hexane solution (10ml, 2.0M, 0.02 mole) was added in a controlled manner to prevent the temperature from exceeding 0°. O-Methylcaprolactim (1.80g, 0.015 mmole) was added dropwise while maintaining the temperature of reaction below 0°. The reaction was stirred at 0° for another 3 hrs. Alkyl halide (2.0-2.5 equiv.) was added either neat or in THF solution. The reaction was completed by stirring at room temperature for 5 hrs.

Isolation of 3-Alkyl-O-methylcaprolactim (28). Half of the volume of the reaction mixture was neutralised with saturated ammonium chloride, and then extracted with 3 portions of ether. The combined organic layers were washed with water, dried and evaporated to give 3-alkyl-O-methylcaprolactim (28) in high yield.

Isolation of 3-Alkylcaprolactam (14). The remaining solution mixture was neutralised with ice-cold 10% HCl and then extracted with three portions of ether. The combined organic layers were dried and the solvent was removed to afford 3-alkylcaprolactam (14) in moderate yield.

Application of the above method prepared the following compounds :

3-Methyl-O-methylcaprolactim (28a) :

Appeared as colourless oil.

Yield : 68%

bp : 60-62°/12

ir (film): 1670 cm-1

nmr ($CDCl_3$): δ 3.50 (s, 3H, OCH_3); 3.40 (b, 2H, CH_2-NC); 2.7 (b, 1H, -CH-CH_3); 1.80-1.20 (complex, 6H, 3(CH_2)); 1.10 (d, J = 7H_z, 3H, CH-CH_3).

Anal. Calcd for $C_8H_{15}NO$: C, 68.04 ; H, 10.71 ; N, 9.92

Found : C, 67.71 ; H, 10.91 ; N, 10.29 %

G.C. OV101 (110°), 4/45.

3-Ethyl-O-methylcaprolactim (28b) :

Yield : 65%

bp : 70-72°/11

ir (film): 1670 cm-1

nmr ($CDCl_3$) : δ 3.60 (s, 3H, OCH_3); 3.50 (b, 2H, CH_2-NC); 2.40 (m, 1H, -CH-CH_2-); 2.00-1.20 (complex, 8H, 4(CH_2)); 0.95 (m, 3H, -CH_2-CH_3),

Anal. Calcd for $C_9H_{17}NO$: C, 69.63 ; H, 11.04 ; N, 9.02

Found : C, 69.45 ; H, 11.01 ; N, 9.43 %

G.C. OV101 (130°), 4/15.

3-Propyl-O-methylcaprolactim (28c) :

Yield : 70%

bp : 89-90°/10

ir (film) : 1670 cm-1

nmr ($CDCl_3$) : δ 3.60 (s, 3H, OCH_3); 3.50 (b, 2H, -CH_2-NC); 2.40 (b, 1H, -CH-CH_2-); 1.90-1.10 (complex, 10H, 5(CH_2)); 0.90 (m, 3H, -CH_2-CH_3),

Anal. Calcd for $C_{10}H_{19}NO$: C, 70.96 ; H, 11.32 ; N, 8.28

Found : C, 71.06 ; H, 11.26 ; N, 8.00 %

G.C. OV101 (130°), 6/20

3-Methylcaprolactam (14a):

Yield : 16%

mp : 92-93° (lit[35] 94°).

ir (nujol) : 3200, 3050 and 1665 cm-1

nmr (CCl_4) : δ 6.40 (b, 1H, NH); 3.20 (b, 2H, CH_2NH); 2.50 (b, 1H, $CH-CH_3$); 1.90-1.30 (m, 6H, $3(CH_2)$); 1.18 (d, J = 7H_z, $-CH-CH_3$).

3-Ethylcaprolactam (14b) :

Yield : 15%

mp : 98-99° (lit[36] 99-100°)

ir (nujol) : 3180, 3050 and 1665 cm-1

nmr (CCl_4) : δ 6.30 (b, 1H, NH); 3.25 (b, 2H, $-CH_2-NH$); 2.40-1.20 (complex, 8H).

3-Propylcaprolactam (14c) :

Yield : 15%

mp : 79-80° (lit[36] 80-81°)

ir (nujol) : 3200, 3050 and 1665 cm-1

nmr (CCl_4) : δ 6.50 (b, 1H, NH); 3.20 (b, 2H, $-CH_2-NH$).

6,6-Dimethyl-4-ketocaprolactam (36)

6,6-Dimethyl-4-ketocaprolactam (36) was prepared in two steps from dimedone by the method of Tamura et al[53,116]. The preparation is summarised below :

(i) 3-Methoxy-5,5-dimethyl-2-cyclohexen-1-one oxime (35)

A solution of dimedone (42.00g) and hydroxylamine hydrochloride (20.80g) in methanol (250ml) was heated at 100° for 3 hrs. The methanol was removed to give the crude hydrochloride as brown syrup. The syrup was taken up in methylene chloride, shaken with 10% K_2CO_3 and extracted with methylene chloride. The combined extracts were dried and concentrated in vacuo to give the crude product (33.00g) which was absorbed on a column of alumina (250g). The column was treated successively with benzene, benzene-ethyl-acetate (9:1), ethyl acetate and methanol. Elution with benzene (300ml) gave mixture of syn- and anti-isomers in the ratio 6:1. The pure syn-oxime (3.00g, 7.1%) was obtained by recrystallising a few times from petroleum ether, as colourless needles,

mp : 106-107°

ir (nujol) : 3,200, 3050, 1640 and 1620 cm-1

nmr (CCl_4) : δ 8.67 (b, 1H, O<u>H</u>, removed with D_2O); 6.05 (s, 1H, -C<u>H</u>=C); 3.70 (s, 3H, OC<u>H</u>$_3$); 2.08 (4H, 2(CH_2)); 1.01 (s 6H, gem-di CH_3).

Anal. Calcd for $C_9H_{15}NO_2$: C, 64.17 ; H, 9.01 ; N, 8.16

Found : C, 63.88 ; H, 8.94 ; N, 8.24 %

Elution with benzene-ethyl acetate (9:1) gave mixture of equal amount of oximes as brown oil (23.00g, 55%) bp 90-100°/0.05 (lit[53] 104-110°/0.07).

(ii) The above syn- and anti-oximes were treated with polyphosphoric acid according to the procedure of Tamura et al[53] to afford <u>36</u> in 75% yield, mp 146-147° (lit[53] 145.5-146 .5°).

General Method for the preparation of Benzylidenelactams (37)

Aldehyde (1.00g) was added to the keto-amide 36 (2.00g) in concentrated hydrochloric acid (60ml). The reaction mixture was stirred at room temperature for 36 hrs. The yellow solution was extracted with chloroform which was washed with a little water. The extract was dried and concentrated in vacuo to give a solid which can be recrystallised from ethanol. Applying this method, the following compounds were prepared.

3-Benzylidene-6,6-dimethyl-4-oxo-hexahydroazepin-2-one (37a)

Appeared as colourless prisms from ethanol.

Yield : 95%

mp : 217-218°

ir (nujol) : 325), 318), 1690, 1650 and 1610 cm-1

nmr ($CDCl_3$) :δ7.90-7.30 (complex, 7H, NH, aromatic protons); 3.18 (d, J = 7H_z, 2H, CH_2-NH); 2.60 (s, 2H, -CH_2-CO); 1.10 (s, 6H, gem-diCH_3),

Mass spectrum (70eV) : m/e (M^+243 $C_{15}H_{17}NO$ requires M^+243).

Anal. Calcd for $C_{15}H_{17}NO$: C, 74.05 ; H, 7.04 ; N, 5.76

Found : C, 74.23 ; H, 7.04 ; N, 5.51 %

3-(p-Nitrobenzylidene)-6,6-dimethyl-4-oxo-hexahydroazepin-2-one(37b)

Appeared as pale yellow needles.

Yield : 52%

mp : 193-194°

ir (nujol) : 3200, 1700, 1660, 1608, and 1590 cm-1

nmr ($CDCl_3$) : δ 8.30 (d, J = $9H_z$, 2H, aromatic protons); 7.80 (3H, aromatic protons, methine proton); 7.30 (b, 1H, NH); 3.15 (d, J = $7H_z$, 2H, $-\underline{CH_2}-NH$); 2.60 (s, 2H, $-CH_2C(CH_3)_2$), 1.10 (s, 6H, gem-diCH_3).

Anal. Calcd for $C_{15}H_{16}N_2O_4$: C, 62.49 ; H, 5.59 ; N, 9.72

Found : C, 62.49 ; H, 5.60 ; N, 9.80 %

3-(p-Chlorobenzylidene)-6,6-dimethyl-4-oxo-hexahydro azepin-2-one (37c)

Appeared as yellow prisms from ethanol.

Yield : 54%

mp : 189-190°

ir (nujol) : 3180, 3050, 1700, 1660, 1608 and 1585 cm-1

nmr ($CDCl_3$) : δ 7.80-7.30 (6H, aromatic protons, NH and methineproton); 3.10 (d, J = $7H_z$, 2H, $\underline{CH_2}-NH$); 2.60 (s, 2H, $(CH_3)_2$ C $\underline{CH_2}$-); 3.12 (s, 6H, gem-diCH_3).

Anal. Calcd for $C_{15}H_{16}NO_2Cl$: C, 64.87 ; H, 5.81 ; N, 5.05

Found : C, 64.90 ; H, 5.85 ; N, 4.78 %

3-(3',4'-Dimethoxybenzylidene)-6,6-dimethyl-4-oxo-hexahydro azepin-2-one (37d)

Yield : 61%

mp : 187-188°

ir (nujol) : 3180, 3050, 1690 1620 and 1590 cm-1

nmr ($CDCl_3$) : δ 7.80 (s, 1H, methine proton), 7.40-6.80

(complex, 4H, aromatic protons and NH); 3.90 (6H, $2(OCH_3)$); 3.06 (d, J = 7H_z, 2H, CH_2-NH); 2.50 (s, 2H $(CH_3)_2$ C CH_2-); 1.00 (s, 6H, gem-diCH_3).

Anal. Calcd for $C_{17}H_{21}NO_4$: C, 67.31 ; H, 6.98 ; N, 4.62

Found : C, 67.41 ; H, 6.86 ; N, 4.60 %

General Procedure for Alkylation of 6,6-dimethyl-4-ketocaprolactam (36)

To a mixture of keto-amide 36 (0.10 mole), sodium (0.10 g-atn) and methanol (20ml) was added alkyl halide (0.20 mole) in portions with stirring at room temperature. The reaction mixture was heated at 80-82° for 10 hrs. and concentrated in vacuo. Chloroform was added to the residue and the precipitated sodium halide was removed to yield a crude product which was recrystallised from petroleum ether. In the case of ethyl- and isopropyl halides, C-alkylation was accompanied by about 18 and 3o% yield respectively of the 4-O-alkylated product. The C- and O-alkylcaprolactams were prepared and their spectral and analytical data are shown below.

6,6-Dimethyl-4-keto-3-methylcaprolactam (38a)

6,6-Dimethyl-4-keto-3-methylcaprolactam (38a) was prepared in 69% yield according to the above procedure. No trace of the O-alkylated product could be detected by examination of the nmr spectrum or the mp 124-125°,

ir (nujol) : 328), 1708 and 1670 cm-1.

nmr ($CDCl_3$) : δ 7.00 (b, 1H, NH); 3.50 (m, 2H, CH_2NH);

3.00 (, J = 8H_z, 1H, $\underline{CH}$-CH_3), 2.50 (s, 2H, $\underline{CH_2}CO$), 1.30 (d, J = 8H_z, 3H, CH-$\underline{CH_3}$), 1.02-1.00 (6H, 2$(CH_3)_2$).

Anal. Calcd for $C_9H_{15}NO_2$: C, 63.88 ; H, 8.94 ; N, 8.28

Found : C, 63.98 ; H, 8.90 ; N, 8.28 %

6,6-Dimethyl-3-ethyl-4-ketocaprolactam (38b) and 4-ethoxy-6,6-dimethyl-2,5,6,7-tetrahydroazepin-2-one (39b)

These were prepared in 60% yield. The two lactams were separated by preparative thin layer chromatography using chloroform-ethanol (95:5).

(i) 6,6-Dimethyl-3-ethyl-4-ketocaprolactam (38b) was isolated in 35% yield from the crude product as white solid. The analytical sample was prepared as colourless needles by recrystallisation from ether-benzene.

mp : 132-133°

ir (nujol) : 3200, 3080, 1708 and 1675 cm-1

nmr ($CDCl_3$) : δ 7.20 (b, 1H, $\underline{NH}$), 3.40 (m, 2H, $\underline{CH_2}$-NH), 3.00 (m, 1H, -$\underline{CH}$-CH_2-), 2.47 (s, 2H, -$\underline{CH_2}$-CO), 1.84 (d, q, J = 7H_z, 2H_z, -CH-$\underline{CH_2}$-CH_3), 1.02-1.00 (6H, gem-diCH_3), 0.90 (3H, CH_2-$\underline{CH_3}$).

Anal. Calcd for $C_{10}H_{19}NO_2$: C, 65.54 ; H, 9.35 ; N, 7.64

Found : C, 65.76 ; H, 9.33 ; N, 7.53 %

(ii) 4-Ethoxy-6,6-dimethyl-2,5,6,7-tetrahydroazepin-2-one (39b) was also isolated in 18% yield. A small sample was recrystallised from petroleum ether before analysis.

mp : 112-113°

ir (nujol) : 3180, 1650 and 1610 cm-1

nmr (CCl_4) : δ 8.53 (b, 1H, NH); 4.87 (d, J = $2H_z$, allylic proton, C = CH-); 3.80 (q, J = $7H_z$, 2H, -O-CH_2-CH_3); 3.84 (d, J = $7H_z$, -CH_2-NH); 2.18 (s, 2H, -CH_2-$C(CH_3)_2$); 1.35 (t, J = $7H_z$, 3H, -O-CH_2-CH_3); 1.00 (s, 6H, gem-diCH_3).

Anal. Calcd for $C_{10}H_{17}NO_2$: C, 65.54 ; H, 9.35 ; N, 7.64

Found : C, 65.46 ; H, 9.08 ; N, 7.60 %

6,6-Dimethyl-3-isopropyl-4-ketocaprolactam (38c) and 6,6-dimethyl-4-isopropoxy-2,5,6,7-tetrahydroazepin-2-one (39c).

These were obtained in 70% yield. Their separation was similar to the above method.

(i) 6,6-Dimethyl-3-isopropyl-4-ketocaprolactam (38c) was obtained in 30% yield from the crude product. An analytical sample, colourless needles, was obtained by one more recrystallisation from petroleum ether,

mp : 150-151°

ir (nujol) : 3200, 3080, 1708 and 1660 cm-1

nmr ($CDCl_3$) : δ 6.70 (b, 1H, NH); 3.34 (m, 2H, -CH_2-NH); 2.95 (m, 1H, -CH-$CH(CH_3)_2$); 2.45 (s, 2H, -CH_2-CO); 1.65 (b, 1H, -CH $(CH_3)_2$); 1.00-0.90 (complex, 12H).

Anal. Calcd for $C_{11}H_{19}NO_2$: C, 66.97 ; H, 9.71 ; N, 7.10

Found : C, 66.72 ; H, 9.64 ; N, 7.02 %

(ii) 6,6-Dimethyl-4-isopropoxy-2,5,6,7-tetrahydro-azepin-2-one (39c) was also isolated in 30% yield. A small amount of the product was recrystallised from petroleum ether before analysis.

mp : 124-125°

ir (nujol) : 3180, 1650 and 1610 cm-1

nmr ($CDCl_3$) : δ 6.80 (b, 1H, NH), 5.00 (d, J = $2H_z$, -CH = C-), 4.30 (q, J = $6H_z$, 1H, -O-CH $(CH_3)_2$), 2.90 (d, J = $6H_z$, 2H, $-CH_2$-NH), 2.20 (s, 2H, $-CH_2C(CH_3)_2$), 1.30 (d, J = $7H_z$, 6H, CH $(CH_3)_2$), 1.00 (s, 6H, gem-diCH_3).

Anal. Calcd for $C_{11}H_{19}NO_2$: C, 66.97 ; H, 9.71 ; N, 7.10

Found : C, 67.30 ; H, 9.65 ; N, 7.21 %

Schmidt rearrangement of 3-chloro-2-methylcyclohexen-1-one (30).

To a stirred mixture of 3-chloro-2-methylcyclohexen-1-one (1.00g) and polyphosphoric acid (40.00g) was added in small portions, sodium azide (0.70g), over a period of 40 mins. The mixture was then heated at 120° for 2 hrs. with occasional shaking. It was cooled and poured into a mixture of crushed ice and water and extracted with chloroform. The extract was dried and concentrated in vacuo to give a white solid which was recrystallised from petroleum ether affording 4-chloro-3-methyl-2,5,6,7-tetrahydro-azepin-2-one (31a) as colourless needles (0.60g, 54%). No trace of the isomeric 6-chloro-7-methyl-2,3,4,5-tetrahydroazepin-2-one (32a) could be detected by examination of the nmr spectrum or tlc,

mp : 105-106°

nmr (CCl_4) :δ 8.70 (b, 1H, NH); 3.20 (b, 2H, $-CH_2$NH); 2.63 (m, 2H, $-CH_2$-CCl); 2.00 (complex, 5H, CH_3 and methylene protons).

Anal. Calcd for $C_7H_{10}NOCl$: C, 52.61 ; H, 6.31 ; N, 8.77

Found : C, 53.00 ; H, 6.20 ; N, 8.43 %

3-Methylcaprolactam from the reduction of 31a

Chloro-amide 31a (0.10g) in ethanol (10ml) was hydrogenated over platinum oxide at room temperature and at atmospheric pressure overnight. The filtrate, after removal of catalyst by filtration, was removed under vacuum to give a white solid which was recrystallised from petroleum ether affording 3-methylcaprolactam as colourless needles (0.065g, 81%). Its spectral data were identical in all respects to the previous experiment.

CHAPTER 3 : SUBSTITUTION AT C-4

The Schmidt reaction on 3-Methylcyclohexanone. The method was adapted from that used by Conley[33].

To a mixture of 3-methylcyclohexanone (19.60g) in polyphosphoric acid (380g), sodium azide (13.60g) was added in small portions over one hour with slow agitation. The temperature was slowly increased to 50° and maintained for 9 hrs. It was then poured into crushed ice and water, then made alkaline with cold 50% sodium hydroxide and the resulting solution extracted with chloroform. The chloroform extracts were combined, dried and evaporated to give a gummy residue (17.00g) whose nmr signals at δ 3.47 and 3.04 were assigned to the methylene protons adjacent to the NH. Integration of these signals indicated an approximately 2:1 ratio of the two products : 6- and 4-methycaprolactams. Attempts to separate these two lactams by fraction recrystallisation, tlc or preparative glc were unsuccessful.

The Grignard reaction on 6,6-Dimethyl-4-ketocaprolactam (36)

Ethyl magnesium bromide was prepared from magnesium (1.20g) and ethyl bromide (6.00g) in dry tetrahydrofuran (30ml) in the usual way[117]. The Grignard reagent was cooled to 0° and keto-amide 36 (2.00g) in tetrahydrofuran (20ml) was added dropwise with stirring. The mixture was kept at 0° under nitrogen for 4 hrs. and then at room temperature overnight. Saturated aqueous ammonium chloride was added and the organic layer separated. The aqueous layer was

extracted with ether and the combined extract was washed with water, dried and evaporated. The crude solid (2.10g) showed ν_{max} (nujol) 1710 indicating the presence only of starting keto-amide 36.

The mixture was treated twice more with ethyl magnesium bromide at 0°, using the procedure described above. Upon working-up the reaction product gave starting material 36.

General method for the preparation of Lactam 40

The method was adapted from that used by Crabbé et al[118].

The amine (1 equiv.) was dissolved in an anhydrous organic solvent (chloroform, benzene) and keto-amide 36 (1.1 equiv.) was added. This solution was allowed to reflux for 24 hrs. using a Dean-Stark separator. After cooling, the precipitate was filtered off and washed with chloroform. The crude product was recrystallised from ethyl acetate or methanol.

4-(Benzylamino)-6,6-dimethyl-2,5,6,7-tetrahydroazepin-2-one (40a)

Benzylamine (0.10g) and keto-amide 36 (0.15g) were dissolved in chloroform and the solution was left at room temperature for 3 days. After removal of the solvent in vacuo, the residue was recrystallised from methylene chloride-hexane yielding 40a (0.220g, 93%) as colourless needles. An analytical sample was obtained by one more recrystallisation,

mp : 206-207°

ir (nujol) : 3180, 1605, 1580 and 1530 cm-1

nmr ($CDCl_3$) : δ 7.36 (s, 5H, aromatic protons); 5.85 (b, 1H, NH, removed with D_2O); 4.70 (d, J = $2H_z$, allylic coupling, 1H, $-CH_2-C=CH$); 4.20 (s, 2H, $NH-CH_2-C_6H_5$); 2.90 (s, 2H, $-CH_2C(CH_3)_2$); 1.00 (s, 6H, gem-diCH_3).

Anal. Calcd for $C_{15}H_{20}N_2O$: C, 73.73 ; H, 8.25 ; N, 11.47

Found : C, 73.49 ; H, 8.07 ; N, 11.12 %

4-Phenylamino-6,6-dimethyl-2,5,6,7-tetrahydroazepin-2-one (40b)

The procedure described for the preparation of 40a was applied to aniline (0.15g) and keto-amide 36 (0.20g) to afford, after recrystallisation from ethyl acetate-methylene chloride, the pure sample 40b (0.225g, 76%),

mp : 232°

ir (nujol) : 3200, 1630, 1580 and 1530 cm-1

Anal. Calcd for $C_{14}H_{18}N_2O$: C, 73.01 ; H, 7.88 ; N, 12.17

Found : C, 73.33 ; H, 7.84 ; N, 12.28 %

4-β-Tolylamino-6,6-dimethyl-2,5,6,7-tetrahydroazepin-2-one (40c)

β-Toluidine (0.80g) and keto-amide 36 (1.10g) were treated in chloroform solution according to the above general method. Recrystallisation of the crude product from methanol gave pure sample 40c as colourless needles (1.00g, 80%),

mp : 227-228°

ir (nujol) : 3250, 3150, 1620 and 1590 cm-1.

Anal. Calcd for $C_{15}H_{20}N_2O$: C, 73.73 ; H, 8.25 ; N, 11.47

Found : C, 73.88 ; H, 8.29 ; N, 11.58%

4-Homoveratrylamino-6,6-dimethyl-2,5,6,7-tetrahydroazepin-2-one(40d)

The procedure describes for the preparation of 40c was applied to homoveratrylamine (0.15g) and keto-amide 36 (0.30g), to afford, after recrystallisation from methylene chloride-hexane, the sample 40d. An analytical sample, colourless needles, was obtained by one more recrystallisation (0.35g, 60%),

mp : 174-175°

ir (nujol) : 3280, 3150, 1608 and 1590 cm-1

nmr ($CDCl_3$) : δ 6.80 (m, 3H, aromatic protons); 5.82 (b, NH, 1H); 4.70, (d, J = $2H_z$, allylic coupling, 1H, $-CH_2-C = CH-$); 3.90 (s, 6H, $2(OCH_3)$); 3.30 (m, 2H, $-CH_2-Ar$); 2.90 (d, J = $7H_z$, 4H, $-CH_2-N-CH_2$); 2.10 (s, 2H, $-CH_2-C(CH_3)_2$); 1.00 (s, 6H, gem-diCH_3).

Anal. Calcd for $C_{18}H_{26}O_3N_2$: C, 67.90 ; H, 8.23 ; N, 8.80

Found : C, 67.97 ; H, 8.24 ; N, 8.64 %

4-(m-Nitrophenylamino)-6,6-dimethyl-2,5,6,7-tetrahydroazepin-2-one (40e)

Prepared according to the general method.

Yield : 58%

mp : 228-230°

Anal. Calcd for $C_{14}H_{17}N_3O_3$: C, 61.08 ; H, 6.22 ; N, 15.26

Found : C, 61.07 ; H, 6.21 ; N, 15.41 %

4-(p-Nitrophenylamino)-6,6-dimethyl-2,5,6,7-tetrahydroazepin-2-one (40f)

prepared according to the general method.

yield : 55%

mp : 242 - 243°

Anal. Calcd for $C_{14}H_{17}N_3O_3$: C, 61.08 ; H, 6.22 ; N, 15.26

Found : C, 60.83 ; H, 6.10 ; N, 15.41%

4-(p-Chlorophenylamino)-6,6-dimethyl-2,5,6,7-tetrahydroazepin-2-one (40g)

Prepared according to the general method.

Yield : 88%

mp : 176 - 178°

*Anal. Calcd for $C_{14}H_{17}N_2OCl$: C, 63.51 ; H, 6.47 ; N, 10.50

Found : C, 62.35 ; H, 7.03 ; N, 9.18%

Reduction of Lactam 40b

Lactam 40b (0.220g) in ethanol (20ml) was hydrogenated over platinum oxide at room temperature and at atmospheric pressure overnight. The filtrate, after removal of catalyst by filtration, was removed under vacuum to give a white solid. Recrystallisation of the crude product from ethyl acetate afforded the saturated amine 41b as colourless needles (0.195g, 88%),

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* It appeared that the product is decomposing during crystallisation to give a mixture of the chloro compound and the starting material. This was verified by tlc examination.

mp : 214 - 215°

ir (nujol) : 3350, 3240, 1660 and 1605 cm-1

Anal. Calcd for $C_{14}H_{20}N_2O$: C, 72.38 ; H, 8.66 ; N, 12.06

Found : C, 72.31 ; H, 8.53 ; N, 11.94%

Reduction of Lactam 40c

The preparation was similar to that of 40b from 40c (0.30g) gave white solid of saturated amine 41c. Recrystallisation of the crude product from ethyl acetate afforded 41c as colourless needles (0.25g, 83%),

ir (nujol) : 3200, 3050, 1660 and 1606 cm-1

Anal. Calcd for $C_{15}H_{22}N_2O$: C, 73.13 ; H, 9.00 ; N, 11.37

Found : C, 72.82 ; H, 8.89 ; N, 11.60%

6,6-Dimethyl-4-methoxy-2,5,6,7-tetrahydroazepin-2-one (65) from Keto-amide 36

Keto-amide 36 (0.50g), methanol (10ml) and p-toluenesulphonic acid (0.05g) were heated together under nitrogen in refluxing benzene (20ml) using a Dean-Stark apparatus. After 12 hrs., the reaction mixture was washed with water, dried and evaporated. Recrystallisation of the crude product from petroleum ether gave 65 as colourless needles (0.25g, 56%),

mp : 148 - 149°

ir (nujol) : 3150, 1660 and 1602 cm-1

nmr ($CDCl_3$) : δ 7.50 (b, 1H, NH); 5.02 (d, J = $2H_z$, allylic coupling, 1H, CH_3O-C=CH-); 3.07 (s, 3H, -OCH_3-); 2.97 (d, J = $7H_z$, 2H, -CH_2-NH); 2.23 (s, 2H, $(CH_3)_2C$ CH_2-); 1.00

(s, 6H, gem-diCH_3).

Anal. Calcd for $C_9H_{15}NO_2$: C, 63.88 ; H, 8.94 ; N, 8.28

Found : C, 63.88 ; H, 9.05 ; N, 7.74%

6,6-Dimethyl-4-methoxy-2,5,6,7-tetrahydroazepin-2-one (65) from 4-Chloro-6,6-dimethyl-2,5,6,7-tetrahydroazepin-2-one (60)

Sodium (0.05g), methanol (20ml) and 60 (0.33g) were heated at 55-60° for 48 hrs. The methanol was removed and chloroform added to the residue and the precipitate sodium chloride was filtered. The chloroform solution was evaporated in vacuo to give quantitative yield of crude product 65. Recrystallisation of this white solid from petroleum ether gave 65 as colourless needles (0.25g, 74%). This compound was identical to the previous sample obtained by refluxing keto-amide 36 and methanol in benzene.

Hydrolysis of 65 to Keto-amide 36

Compound 65 (0.05g) in 10% HCl (10ml) was stirred at room temperature overnight and then at 60° for 30 mins. The reaction mixture was neutralised with 10% aqueous Na_2CO_3 and extracted with chloroform. The extract was dried and concentrated in vacuo. Recrystallisation of the residue from benzene-ether gave 36 as colourless needles (0.035g, 73%). This compound was identical in all respects to the previous sample obtained by the Beckman rearrangement of oximes 35.

6,6-Dimethyl-4-ethoxy-2,5,6,7-tetrahydroazepin-2-one (39b) from Keto-amide 36

The preparation was similar to that of 65. Ketone 36 (0.20g), ethanol (5ml), p-toluenesulphonic acid (0.01g) in dry benzene (20ml) gave a white solid. Recrystallisation of the crude product from petroleum ether gave 65 as colourless needles (0.175g, 89%),

mp : 112-113°

ir (nujol) : 3180, 1650 and 1605 cm-1

This compound was identical to the previous sample obtained by alkylation of 36 (Chapter 2).

1,5,6,7-Tetrahydro-2H-azepin-2-one (16) and 1,3,6,7-tetrahydro-2H-azepin-2-one (15)

These were prepared in one step from 3-bromocaprolactam (12) according to the literature procedure[68]. The crude product was vacuum distilled giving a colourless liquid bp 55°/0.2 (lit[68] 65°/0.3). Nmr spectroscopy showed the mixture to consist of 16 and 15 in the ratio of 3:2. Attempts to separate these two isomers were unsuccessful.

4-Butylcaprolactam (42) :

To a stirred mixture of cuprous chloride (2.50g) in dry tetrahydrofuran (15ml) at 0° (under nitrogen) was added butyllithium (2.0M, 10ml). The mixture was then stirred an additional 15 mins. at 0°. A solution of 15 and 16 in dry tetrahydrofuran (10ml) was

then added over 20 mins. After stirring at 0° for 5 hrs., the reaction mixture was poured into 1.2M HCl (30ml) with vigorous stirring. Concentrated ammonium hydroxide was slowly added until the solution became blue and clear. The layers were separated and the aqueous portion was extracted with ether. Removal of the solvent gave an oily material (0.22g) which still contained starting material, as shown by tlc. The crude product was separated by preparative tlc giving 4-butylcaprolactam as colourless oil (0.15g, 15%) based on the total mixture of 15 and 16.

bp : 118-119°/8

ir (film) : 3300 and 1660 cm-1

nmr (CCl_4) : 7.91 (b, 1H, NH); 3.13 (b, 2H, CH_2-NH); 2.23 (b, 2H, -CH_2-CO); 1.90-1.10 (complex, 12H); 0,90 (m, 3H, -CH_2-CH_3).

Mass spectrum (70eV) : m/e 169 ($M^+C_{10}H_{19}NO$ requires M^+169) (18), 112 ($M-C_4H_9$) (100), 84 ($M-C_4H_9+CO$) (70).

The oil was redistilled under reduced pressure (115-120°/0.9) in a bulb to bulb apparatus but failed to give an analytically pure sample.

4-Butylcaprolactam from 15 and 16 with Butylmagnesium bromide and Cuprous chloride

Butylmagnesium bromide was prepared from magnesium (1.20g) and butyl bromide (6.75g) in dry tetrahydrofuran (100ml) in the usual way[65]. The Grignard reagent was cooled to 0° and the cuprous chloride was added to produce a bluish-green colour. After the mixture 15 and 16 (2.50g) was added, no visible reaction seemed to

take place. The reaction was left at 0° under nitrogen for 5 hrs. and then at room temperature for 48 hrs. Upon working up the reaction product gave an oil (2.20g), the ir and nmr spectra of which indicated only the presence of starting material 15 and 16.

Isophorone oxines (43)

These were prepared according to the procedure of Koch et al[74] from freshly distilled isophorone (69.00g), hydroxylamine hydrochloride (34.00g), 20% sodium hydroxide, water and ethanol.

4,6,6-Trimethyl-2,5,6,7-tetrahydroazepin-2-one (44)

4,6,6-Trimethyl-2,5,6,7-tetrahydroazepin-2-one (44) was prepared by the Beckman rearrangement of the syn-oxime of isophorone with polyphosphoric acid according to the procedure reported by Mazure[72]. The crude product was recrystallised from light petroleum giving colourless needles mp 111-112° (lit[72,74] 112-113°, lit[73] 108-109°).

4,4,6-Trimethyl-2,3,4,5-tetrahydroazepin-2-one (45).

4,4,6-Trimethyl-2,3,4,5-tetrahydroazepin-2-one (45) was obtained by the Beckman rearrangement of the anti-oxime of isophorone with polyphosphoric acid according to the method of Mazure[72]. The crude product was recrystallised from aqueous methanol yielding 45 as small colourless needles mp 91-92° (lit[72] 92-93°, lit[73] 90.1-90.7°).

4,6,6-Trimethylcaprolactam (46).

Lactam 44 (0.612g ; 4 mmole) in ethanol (30ml) was hydrogenated over platinum oxide at room temperature and at atmospheric pressure for 3 hrs. The filtrate, after removal of catalyst by filtration, was evaporated under vacuum to give a white solid. Recrystallisation of the crude product from light petroleum gave the saturated lactam 46 as colourless needles (0.53g, 84%),

mp : 109-110° (lit[72] 110-111°)

ir (nujol) : 3180, 3020 and 1670 cm-1

nmr ($CDCl_3$) : δ 8.00 (b, 1H, NH); 3.10 (b, 2H, CH_2NH); 2.08 (b, 2H, $-CH_2CO$); 1.08-1.00 (complex, 12H).

4,4,6-Trimethylcaprolactam (47)

The preparation was similar to that above.

Yield : 92%

mp : 108-108.5°(lit[72] 109-111°)

ir (nujol) : 3180, 3020 and 1660 cm-1

1,4,6,6-Tetramethyl-2,5,6,7-tetrahydroazepin-2-one (48)

1,4,6,6-Tetramethyl-2,5,6,7-tetrahydroazepin-2-one (48) was prepared from 44 (0.153g), sodium hydride (0.024g), methyl iodide (0.274g) and xylene (10ml) by the general method described earlier for N-alkylation of caprolactams (Chapter 1) giving product as a colourless liquid (0.12g, 72%). A small sample was distilled under reduced pressure in a bulb to bulb apparatus before analysis.

bp : 100-102°/2.3

ir (film) : 1660 and 1620 cm-1

nmr (CCl_4) : δ 5.70 (d, J = $2H_z$, allylic coupling, 1H, CH_3-C= CH-); 3.02 (s, 3H, N-CH_3); 3.00 (s, 2H, CH_2-N-); 2.00 - 1.98 (5H, methylene and methyl protons); 1.00 (s, 6H, gem-diCH_3).

Anal. Calcd for $C_{10}H_{17}NO$: C, 71.81 ; H, 10.25 ; N, 8.38

Found : C, 71.46 ; H, 10.39 ; N, 8.39%

G.C. Carbowax (190°), 4/20.

1,4,4,6-Tetramethyl-2,3,4,5-tetrahydroazepin-2-one (53)

1,4,4,6-Tetramethyl-2,3,4,5-tetrahydroazepin-2-one (53) was prepared from 45 (0.153g), sodium hydride (0.024g), methyl iodide (0.274g), and xylene (10ml) by the general method described earlier. Distillation of the crude product gave 53 as a colourless oil (0.14g, 84%). An analytical sample was redistilled before analysis.

bp : 50°/0.4

ir (film) : 1660 and 1635 cm-1

nmr (CCl_4) : δ 5.80 (d, J = $2H_z$, 1H, allylic proton); 2.90 (s, 3H, N-CH_3); 2.20 (s, 2H, -CH_2CO); 1.90-1.85 (5H, methylene and methyl protons); 1.05 (s, 6H, gem-diCH_3).

Anal. Calcd for $C_{10}H_{17}NO$: C, 71.81 ; H, 10.25 ; N, 8.38

Found : C, 71.72 ; H, 10.40 ; N, 8.17%.

G.C. Carbowax 20M (190°), 1/45.

4,6,6-Trimethyl-2,5,6,7-tetrahydroazepin-2-thione (50)

4,6,6-Trimethyl-2,5,6,7-tetrahydroazepin-2-thione (50) was

obtained from 44 (0.50g), phosphorus pentasulphide (1.0g) and dry toluene (30ml) according to the general procedure described earlier for the preparation of N-alkyl-thiocaprolactams (Chapter 1). Recrystallisation of the brown solid from petroleum ether gave 50 as yellow needles (0.30g, 54%). An analytical sample, bright yellow needles, was obtained by one more recrystallisation from the same solvent.

mp : 131-132°

ir (nujol) : 3150, 1620, 1140 and 1120 cm-1 (strong)

nmr (CCl_4) : δ 6.40 (d, J = $2H_z$, 1H, allylic proton); 3.00 (d, J = $6H_z$, 2H, $\underline{CH_2}$-NH).

Anal. Calcd for $C_9H_{15}NS$: C, 63.88 ; H, 8.94 ; N, 8.28

Found : C, 63.98 ; H, 8.72 ; N, 8.04%

Mass spectrum (70eV) : m/e 169 (M^+, $C_9H_{15}NS$ requires M^+169).

1,4,6,6-Tetramethyl-2,5,6,7-tetrahydroazepin-2-thione (51)

1,4,6,6-Tetramethyl-2,5,6,7-tetrahydroazepin-2-thione (51) was prepared as described earlier from 48 (1.0g), phosphorus pentasulphide (2.0g) and toluene (30ml). Recrystallisation of the crude product from petroleum ether gave 51 as bright orange needles (0.80g, 73%). A small sample was recrystallised before analysis.

mp ; 131-132°

ir (nujol) : 1620, 1120 and 1110 cm-1 (strong)

Anal. Calcd for $C_{10}H_{17}NS$: C, 65.54 ; H, 9.35 ; N, 7.64

Found : C, 65.53 ; H, 9.11 ; N, 7.37%

4,6,6-Trimethylthiocaprolactam (49)

4,6,6-Trimethylthiocaprolactam (49) was prepared from 46

(0.50g), phosphorus pentasulphide (1.0g) and toluene (30ml) by general method described earlier. Recrystallisation of the crude product from petroleum ether gave 49 as colourless needles (0.50g, 89%), mp : 133.5 - 134°

ir (nujol) : 3180, 3050, 1160 and 1115 cm-1

Anal. Calcd for $C_{19}H_{17}NS$: C, 63.13 ; H, 10.00 ; N, 8.18

Found : C, 63.18 ; H, 9.65 ; N, 8.10%

4,4,6-Trimethylthiocaprolactam (52)

4,4,6-Trimethylthiocaprolactam (52) was prepared from 47 (0.25g), phosphorus pentasulphide (0.50g) and dry toluene (20ml) by the general method described earlier. Recrystallisation of the crude product from petroleum ether gave 52 as colourless needles (0.23g, 83%),

mp : 121-121.5°

ir (nujol) : 3180, 3020, 1150 and 1115 cm-1 (strong)

Anal. Calcd for $C_9H_{17}NS$: C, 63.13 ; H, 10.00 ; N, 8.18

Found : C, 63.30 ; H, 9.66 ; N, 7.83%

Beckmann rearrangement of Ketone 54

Redistilled ketone[119] 54 (4.08g), was added to a mixture of hydroxylamine hydrochloride (2.0g), 20% sodium hydroxide (6.5ml) and water (13.0ml). Ethanol (30ml) was added to make a homogeneous solution which was then refluxed for 3 hrs. and allowed to stand overnight. The ethanol was evaporated and the residue was then extracted with ether (3 x 20ml) and the combined extract was dried. The solvent was removed under vacuum to give a gummy product (3.5g,

84%). The nmr spectrum indicated the product was a mixture of syn- and anti-oximes. Attempted separations of these two oximes by recrystallisation were unsuccessful. nmr (CCl_4) δ 9.00 (b, N-O<u>H</u> removed with D_2O), 6.70 (b, 1H, syn-oxime), 5.95 (b, 1H, anti-oxime). The crude oxime (0.30g) which is believed to be a mixture of two possible stereoisomers was heated with manual stirring in polyphosphoric acid (3ml) for 20 mins. at 130-135°. The mixture was cooled and poured into water (100ml) and then extracted with chloroform (4 x 20ml). The combined extract was dried over K_2CO_3 and evaporated to give a brown solid which was recrystallised from petroleum ether to yield lactam <u>56</u> as colourless prisms (0.15g, 50%). A small amount of sample was recrystallised from the same solvent before analysis.

mp : 120-121°

ir (nujol) : 3180, 3120, 1660 and 1610 cm-1

nmr (CCl_4) : δ 8.30 (b, 1H, N<u>H</u>); 5.70 (1H, -C<u>H</u>=C-); 3.30 (m, 2H, <u>C</u>H_2-NH).

Anal. Calcd for $C_9H_{13}NO$: C, 71.59 ; H, 8.67 ; N, 9.27

Found : C, 71.39 ; H, 8.53 ; N, 8.99%

<u>Hydrogenation of Lactam 56</u>

Lactam <u>56</u> (0.05g) in ethanol (10ml) was hydrogenated over platinum oxide at room temperature and at atmospheric pressure for 4 hrs. Working up the reaction as described earlier gave <u>58</u> as small colourless prisms after recrystallisation from petroleum ether.

mp : 95-95.5°

nmr (CCl_4) : δ 8.13 (b, 1H, N<u>H</u>); 3.18 (b, 2H, <u>C</u>H_2NH).

Anal. Calcd for $C_9H_{15}NO$: C, 70.55, H, 9.87 ; N, 9.14

Found : C, 70.20 ; H, 9.65 ; N, 8.89%

4-Chloro-6,6-dimethyl-2,5,6,7-tetrahydroazepin-2-one (60) and 6-Chloro-4,4-dimethyl-2,3,4,5-tetrahydroazepin-2-one (61)

These lactams were prepared according to the procedure of Tamura and Kita[49] from 3-chloro-5,5-dimethyl-2-cyclohexen-1-one (bp 88-90°/12 lit[120] 109-110°/14) with PPA by the Schmidt reaction. The crude product was absorbed on a column of alumina.

(i) Elution with 90% C_6H_6-10% $EtOA_c$ gave 61 as colourless needles.
mp 94-95° (lit[49] 95-96°)
ir (nujol) : 3200, 3180 and 1660 cm-1
nmr (CCl_4) : δ 10.20 (b, 1H, NH); 6.20 (d, J = $4H_z$, 1H, -C=CH); 2.40 (s, 4H, CH_2-CO and CH_2-C=); 1.05 (s, 6H, gem-diCH_3).

(ii) Elution with ethyl acetate gave 60 as colourless needles after recrystallisation from petroleum ether.
mp 84-85° (lit[49,53] 84.5-85.5°)
nmr (CCl_4) : δ 8.70 (b, 1H, NH); 6.02 (d, J = $2H_z$, 1H, -C=CH-); 2.92 (d, J = $7H_z$, 2H, CH_2-NH); 2.46 (s, 2H, $CH_2C(CH_3)_2$); 1.02 (s, 6H, gem-diCH_3).

4,4-Dimethylcaprolactam (63)

Lactam 61 (0.10g) in ethanol (15ml) was hydrogenated over platinum oxide at room temperature and at atmospheric pressure for 4 hrs. Upon working up the reaction in the usual way, 63 was obtained as a colourless solid. The analytical sample was prepared as colourless needles by recrystallisation from petroleum ether (0.075g, 90%),
mp 103-104°
ir (nujol) : 3180, 3080 and 1660 cm-1

nmr (CCl_4) : δ 6.90 (b, 1H, NH); 3.20 (b, 2H, CH_2NH); 2.42 (b, 2H, $-CH_2CO$); 1.67 (m, 4H); 1.02 (s, 6H, gem-diCH_3).

Anal. Calcd for $C_8H_{15}NO$: C, 68.04 ; H, 10.71 ; N, 9.92

Found : C, 68.15 ; H, 10.74 ; N, 9.96%

Reaction of 60 with Phosphorus pentasulphide

4-Chloro-6,6-dimethyl-2,5,6,7-tetrahydroazepin-2-one (60) (0.70g), phosphorus pentasulphide (2.0g) and toluene (25ml) were refluxed overnight. Work up of the reaction mixture as described earlier gave a brown solid. The analytical sample, orange yellow needles, was obtained by one more recrystallisation from ethyl acetate (0.60, 79%).

mp 187-188°

ir (nujol) : 3170, 1585 and 1120 cm-1

Mass spectrum (70eV) : m/e 187 (M^+, $C_8H_{13}NS_2$ requires M^+ 187).

Anal. Calcd for $C_8H_{13}NS_2$: C, 51.37 ; H, 6.95 ; N, 7.48

Found : C, 51.40 ; H, 6.66 ; N, 7.68%

The Schmidt reaction on Camphor

To a mixture of camphor (7.60g), in polyphosphoric acid (160.0g) sodium azide (4.0g) was added in small portions over 90 mins. with slow agitation. The mixture was then kept at 60-64° for 48 hrs. Work up of the reaction mixture as described earlier gave a crude product which was recrystallised from petroleum ether as colourless prisms (2.90g, 34%). A small sample was recrystallised before analysis.

mp 180-182°

ir (nujol) : 3300, 3170 and 1660 cm-1

Mass spectrum (70eV) : m/e 182 (M^+, $C_{10}H_{18}N_2O$ requires M^+182).

Anal. Calcd for $C_{10}H_{18}N_2O$: C, 65.89 ; H, 9.96 ; N, 15.37

Found : C, 65.99 ; H, 9.96 ; N, 15.72%

Attempted Dechlorination of 4-Chloro-6,6-dimethyl-2,5,6,7-tetrahydroazepin-2-one (60)

(i) by Zn-KI in ethanol.

Zinc dust (2.0g) was stirred for 4 mins. with 10% HCl (10ml). The supernatant liquid was decanted and the zinc was washed with acetone (2 x 20ml) and ether (10ml). Lactam 60 (0.30g) in methanol (15ml) and potassium iodide (0.25g) in methanol (10ml) were added and the mixture was then stirred overnight. The reaction was then filtered and the filtrate evaporated. The residue was shaken vigorously (till it dissolved) with a mixture of 5% HCl (20ml) and ether (50ml). The ether layer was dried and removed to give white solid (0.28g) identical in all respects to the starting material. No trace of the desired product could be detected by examination of the nmr spectrum or tlc.

Repetition of the above experiment by refluxing the reaction mixture for 2 days gave none of the expected product, and only starting chloro-amide was recovered.

(ii) by Tri-n-butyltin hydride.

To a solution of 60 (0.170g, 1 mmole) in dry benzene (20ml) was added dropwise tri-n-butyltin hydride (0.30g, 1 mmole) with stirring under nitrogen during 30 mins. The temperature was maintained below 40° by external cooling. After the addition had been completed, the mixture was stirred at room temperature overnight.

Working up the reaction in the usual way failed to give any trace of the expected product and most of the starting material was recovered.

CHAPTER 4 : SUBSTITUTION AT C-5 AND C-7

5-Methylcaprolactam (71a)

The method was adapted from that used by Conley[33] from 4-methylcyclohexanone (10.0g) in polyphosphoric acid (200g) and sodium azide (6.8g). Working up the reaction mixture in the usual way gave 71a as colourless needles (10g, 90%),

mp 40-41° (lit[60] 41-42°).

ir (nujol) : 3200, 3080 and 1660 cm-1

nmr (CCl_4) : δ 6.84 (b, 1H, NH); 3.20 (m, 2H, CH_2NH); 2.42 (m, 2H, CH_2CO).

In a similar manner, the following compounds were prepared and their spectral data are shown below :

5-Ethylcaprolactam (71b)

Yield : 90%

mp : 55-56° (lit[121] 56-57°)

ir (nujol) : 3200, 3090 and 1660 cm-1

nmr (CCl_4) : δ 6.90 (b, 1H, NH); 3.30 (m, 2H, CH_2NH); 2.50 (m, 2H, CH_2CO).

5. Isopropylcaprolactam (71c)

Yield : 85%

mp : 84-85° (lit[121] 84°)

ir (nujol) : 3200, 3080 and 1660 cm-1

nmr (CCl_4) : δ 8.00 (b, 1H, NH); 3.20 (m, 2H, CH_2NH); 2.40 (m, 2H, CH_2CO); 2.00-1.10 (complex, 6H); 0.90 (d, J=7H_z, 6H, $CH(CH_3)_2$).

5-t-Butylcaprolactam (71d) :

Yield : 87%

mp : 152-154° (lit[121] 156-157°)

ir (nujol) : 3.200, 3080 and 1660 cm-1

nmr (CCl_4) : δ 6.50 (b, 1H, NH); 3.20 (m, 2H, CH_2NH); 2.44 (m, 2H, CH_2CO); 0.84 (s, 9H, CCH_3).

2-Carbethoxy-2-ethylcyclohexanone (72a)

The method was adapted from that used by Jikek and Protira[18] and is summarised below :

A solution of sodium methoxide was prepared by addition of sodium (1.22g, 0.053 mole) in small portions to absolute methanol (15ml). When the sodium had completely dissolved, 2-carbethoxycyclohexanone (9.0g) was introduced over 15 mins. and stirring began while the flask was brought to reflux. Ethyl iodide (9.6g) was added slowly to the refluxing mixture over 30 mins. The refluxing and stirring were continued for 12-15 hrs. The solvent was removed, the residue added to water (50ml) and the mixture was then extracted with ether (4 x 30ml) and the combined extract was dried. Distillation of the liquid gave 2-carbethoxy-2-ethylcyclohexanone (6.0g, 60%).

bp 158°/48 (lit[86] 122-4°/9)

ir (film) : 1748 and 1724 cm-1

2-Ethylcyclohexanone (73a)

A mixture of 2-carbethoxy-2-ethylcyclohexanone(72a) (4.08g), potassium hydroxide (4.08g), methanol (40ml) and water (40ml) was refluxed for 15-17 hrs. After cooling, concentrated hydrochloric acid (11ml) was added. The mixture was then refluxed for another

2 hrs. On cooling water (50ml) was added and the mixture was then extracted with petroleum ether (4 x 20ml) and the combined extract was dried. Evaporation of the solvent gave an oil (2.10g, 75%).

bp $78^{\circ}/16$ (lit[86] $90-94^{\circ}/40$)

ir (film) : 1724 cm-1

In a similar manner the following compounds were prepared.

2-n-Propylcyclohexanone (73b)

Yield : 74%

bp $82-84^{\circ}/12$ (lit[34] $96-97^{\circ}/25$)

2-n-Butylcyclohexanone (73c)

Yield : 70%

bp $92-94^{\circ}/15$ (lit[124] $90-92^{\circ}/13$)

ir (film) : 1724 cm-1

7-Methylcaprolactam (74a)

The method was adapted from that used by Conley[33] from 2-methylcyclohexanone (4.95g), polyphosphoric acid (95g) and sodium azide (3.40g), giving 7-methylcaprolactam (74a) as colourless needles (4.75g, 96%),

mp $88-89^{\circ}$ (lit[33] $90-91^{\circ}$)

ir (nujol) : 3200, 3080 and 1670 cm-1

nmr (CCl_4) : δ7.90 (b, 1H, NH); 3.50 (b,. 1H, CH-NH); 2.38 (m, 2H, CH_2CO); 2.00-1.40 (complex, 6H); 1.20 (d, $J=8H_z$, 3H, $-CH-CH_3$).

7-Ethylcaprolactam (74b)

This was prepared according to the procedure above.

Yield : 95%

mp 91-92° (lit[34] 91.5-92°)

ir (nujol) : 3180, 3060 and 1660 cm-1

7-n-Propylcaprolactam (74c)

Yield : 95%

mp 97-98° (lit[33] 97-98°)

ir (nujol) : 3180, 3050 and 1660 cm-1

nmr (CCl_4) : δ 7.80 (b, 1H, NH); 3.23 (b, 1H, CH-NH); 2.30 (m, 2H, CH_2CO); 2.20-1.30 (complex, 10H) and 1.00 (m, 3H, CH_2-CH_3).

7-n-Butylcaprolactam (74d)

Yield : 94%

mp 73-73°5 (lit[124] 70°)

ir (nujol) : 3200, 3050 and 1660 cm-1

nmr (CCl_4) : δ 7.70 (b, 1H, NH); 3.20 (b, 1H, CH-NH); 2.30 (b, 2H, CH_2-CO); 2.00-1.20 (complex, 12H) and 0.95 (m, 3H, -CH_2-CH_3).

4-Methyl-7-isopropylcaprolactam (76)

Yield : 98%

mp 120-121° (lit[122] 119-120°)

ir (nujol) : 3200, 3050 and 1660 cm-1

7-Methylthiocaprolactam (75a)

7-Methylthiocaprolactam (75a) was prepared according to the general method described earlier for N-alkylthiocaprolactam (Chapter 1) from 7-methylcaprolactam (1.0g), phosphorus pentasulphide (4.0g)

and toluene (20ml). The residue was chromatographed on alumina (40g). Elution with ethyl acetate gave 75a as white solid (0.75g, 67%). The analytical sample was prepared as colourless needles by recrystallisation from petroleum ether.

mp 87.5 - 88°

ir (nujol) : 3180 and 1060 cm-1 (strong)

nmr (CCl_4) : δ 8.20 (b, 1H, NH); 3.80 (b, 1H, CH-NH); 3.00 (b, 2H, CH_2CS); 1.65 (m, 6H, $(CH_2)_3$); 1.30 (d, J=7H_z, 3H, CH-CH_3).

Anal. Calcd for $C_7H_{13}NS$: C, 58.72 ; H, 9.15 ; N, 9.78

Found : C, 58.77 ; H, 8.96 ; N, 9.07%

In a similar manner, the following thiocaprolactams were prepared and their analytical and spectral data are obtained as below.

7-n-Propylthiocaprolactam (75c)

Yield 89%

mp 83-83.5°

ir (nujol) : 3180 and 1070 cm-1 (strong)

nmr (CCl_4) : δ 8.83 (b, 1H, NH); 3.40 (b, 1H, CH-NH); 2.80 (b, 2H, CH_2CS); 2.00-1.30 (complex, 10H); 1.00 (3H, CH_2-CH_3).

Anal. Calcd for $C_9H_{17}NS$: C, 63.13 ; H, 10.00 ; N, 8.18

Found : C, 63.35 ; H, 9.87 ; N, 8.03%

4-Methyl-7-isopropylthiocaprolactam (77)

Yield : 82%

mp 106-107°

ir (nujol) : 3180, 1108 and 1100 cm-1

Anal. Calcd for $C_{10}H_{19}NS$: C, 64.83 ; H, 10.34 ; N, 7.56

Found : C, 65.21 ; H, 10.44 ; N, 7.56%

CHAPTER 5 : SUBSTITUTION AT C-6

6,6-Dimethylcaprolactam from 6,6-Dimethyl-4-chloro-2,5,6,7-tetrahydroazepin-2-one (60)

The preparation was similar to that of 4,4-dimethyl-caprolactam (Chapter 4) from 60 (0.20g), platinum oxide (0.02g) and ethanol (20ml). Distillation (110°, 0.07mm, cold finger) gave analytically pure 6,6-dimethylcaprolactam (64) as colourless needles (0.155g, 95%),

mp 100-101°

ir (nujol) : 3180 and 1660 cm-1

nmr (CCl_4) : δ 8.00 (b, 1H, NH); 2.95 (b, 2H, CH_2-NH); 2.30 (b, 2H, $-CH_2CO$); 1.60 (m, 4H, $(CH_2)_2$); 1.00 (s, 6H, gem-diCH_3).

Anal. Calcd for $C_8H_{15}NO$: C, 68.04; H, 10.71 ; N, 9.92

Found : C, 68.24 ; H, 10.82 ; N, 9.50%

6,6-Dimethylcaprolactam (64) from Keto-amide 36

The method was adapted from that used by Fieser[94]. A mixture of keto-amide 36 (0.70g) and ethane-1,2-dithiol (0.5ml) in a test-tube at 0° was treated with boron fluoride etherate (0.5ml) and the mixture homogenised with a stirring rod. The mixture became warm and soon set to a white solid. After 10 mins., methanol (10ml) was added, the mixture was stirred well and cooled and the solid collected and washed with a little cold methanol giving a white solid. Recrystallisation of the crude product from ethyl acetate afforded thioketal 79 as colourless needles (0.80g, 77%),

mp 229-230°

ir (nujol) : 3200, 3080 and 1670 cm-1

nmr ($CDCl_3$) : δ 6.70 (b, 1H, NH); 3.40 (s, 4H, $S(CH_2)_2S$); 3.10 (s, 2H, CH_2CO); 3.06 (d, J=7H_z, 2H, CH_2NH); 2.30 (s, 2H,

To a solution of lactam 61 (0.172g, 1 mmole) in freshly distilled tetrahydrofuran (20ml) was added butyllithium (2ml, 1.0M, 2 mmole) at 0° under nitrogen and to the resultant suspension was added triethylborane (2ml, 1.0M, 2 mmole). The mixture was stirred at 0° for 1 hr., then at room temperature for 2 hrs. and then refluxed for 1 hr. Water (10ml) was added, followed by 10% sodium hydroxide (10ml) and 30% hydrogen peroxide (7ml). The aqueous mixture was extracted with ether (2 x 20ml), and the extract was washed with water, dried and evaporated, affording solid (0.165g) which was identical with the starting material lactam 61. No trace of the desired product could be detected by examination of the nmr spectrum or tlc.

Attempted preparation of 4,4-Dimethyl-6-ketocaprolactam (81) from 61 with Diborane

Diborane (4 mmole) generated in the usual way in diglyme (20ml) was carried by a slow stream of nitrogen into a chilled, stirred solution of chloro-amide 61 (0.344g, 2 mmole) in dry tetrahydrofuran (30ml). The solution was stirred under nitrogen at room temperature overnight. Working up the reaction mixture in the usual way gave a gummy residue (0.30g) whose infrared spectrum was almost identical with that of the starting material 61. Work on this reaction was not pursued.

6-Amino-5-keto-hexanoic acid (82)

This aminoacid was prepared according to the procedure of Lartillot and Baron[97] from glutaric anhydride mp 150-152° (lit[97] 152-153°).

$CH_2C(CH_3)_2$); 1.04 (s, 6H, gem-diCH_3).

Anal. calcd for $C_{10}H_{17}NOS_2$: C, 51.94 ; H, 7.41 ; N, 6.06

Found : C, 52.10 ; H, 7.45 ; N, 5.91%

Thioketal 79 (0.10g) was refluxed with Raney nickel in ethanol overnight. The solution was filtered and the nickel washed thoroughly with ethanol and then with ether. Evaporation of the solvents gave a white solid. Recrystallisation of the crude product from light petroleum gave 64 as colourless needles (0.050g, 82%), mp 100-101°. This material was identical with the authentic sample obtained from the reduction of 60 in all respects.

4,4-Dimethyl-6,6-dimethoxycaprolactam (78)

Sodium (0.06g) was dissolved in methanol (10ml), 4,4-dimethyl-6-chloro-2,3,4,5-tetrahydroazepin-2-one (61) (0.172g) was added and the mixture heated at 100-102° overnight. The methanol was removed and chloroform added to the residue and filtered. The chloroform solution was evaporated in vacuo to give a white solid. The analytical sample was prepared as colourless needles by recrystallisation from n-hexane at -70°.

mp : 70°

ir (nujol) : 3160, 3040 and 1660 cm-1

nmr (CCl_4) : δ 6.50 (b, 1H, NH); 4.03 (2H, CH_2-NH); 3.35 (s, 6H, 2(OCH_3)); 1.95 (s, 2H, CH_2CO); 1.40 (m, 2H); 1.00 (s, 6H, gem-diCH_3).

Anal. Calcd for $C_{10}H_{19}NO_3$: C, 59.67 ; H, 9.52 ; N, 6.96

Found : C, 59.59 ; H, 9.60 ; N, 6.82%

Attempted preparation of 4,4-Dimethyl-6-ethylcaprolactam from 4,4-Dimethyl-6-chloro-2,3,4,5-tetrahydroazepin-2-one with Triethylborane and Butyllithium

Attempted cyclisation of 82

Dicyclohexylcarbodiimide (DCC) (0.26g, 1.5 mmole), 82 (0.13g, 1 mmole) in chloroform (15ml) was stirred at room temperature overnight. Working up the reaction mixture in the usual way failed to give any trace of the desired product and only starting material was returned.

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