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 MHz, 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 (\(\delta\)), multiplicity, s (singlet), b (broad), d (doublet), t (triplet), q (quartet), dd (doublet of doublets), m (multiplet), removed with D\(_2\)O means that the signal disappears on shaking with the sample with D\(_2\)O, complex means that this part of the spectrum could not be interpreted; first-order coupling coupling constant (J) is expressed in Hz.

(4) Ultraviolet spectra (uv) were determined using a Unicam SP 300A 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% Kiesel G and HF 254 applied to the glass plates as a suspension in water and activated at 120°C 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 4Å 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\textsuperscript{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 convolution within one hour

* 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\textsuperscript{98}.

**Regression Analysis:** The data was analysed by computer using the Polyanna Curve-fitting package for optimal orthogonal polynomial fit.
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-di-hydroxypyridine-5-carboxylic acid (18) was collected (3.50g, 70%); mp 308$^\circ$ (lit$^{32}$ 310$^\circ$).

Acid 18 (1.90g) was then heated at 190-200$^\circ$ 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$^\circ$ for 6 hrs. The decarboxylated product was collected as yellow needles (0.10g, 11%) mp 258-262$^\circ$ (lit$^{33}$ 265$^\circ$-267$^\circ$).

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$^\circ$/0.05 to give 22 as colourless needles (16g, 90%); mp 241-242$^\circ$ (lit$^{49}$ 243$^\circ$).

QUINOLINAMIDE (23)

A solution of methyl quinolinate (21) or quinolinimide (2g) in methanol (20ml) was added to liquid ammonia (20ml) at 0$^\circ$, the
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° (lit34 209°).

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

PYRIDOPYRIMIDINE (24)

Pyridopyrimidine (24) was prepared by the method of Beckwith and Hickman35 in 80% yield, mp > 350° (lit35 365°)

ir (nujol) 3180, 3060, 1730 and 1680 cm⁻¹.
Mass spectrum (70eV): m/e (M+163 C₇H₅N₃O₂ 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 fluorosulpho-
-nate (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,
the product separated. Recrystallisation of the crude product from ethanol gave colourless needles (0.12g, 51%) mp 161-162° (lit²⁴ 164-165°). This compound was identified as 26 by spectral analysis.

nmr (CDCl₃): 6 5.50 (2H, N-CH=CH-); 7.20 (1H, N-CH=CH-CH); 3.72 (s, 3H, CO-NCH₂-CO); 3.50 (s, 3H, CH₃N CO).

Mass spectrum (70eV): m/e (M¹+191 C₉H₁₉N₃O₂ requires M¹+191) (30)

3-BENZOYL-1-METHYLNYRID-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 (3N; 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°
\text{ir (nujol)}: 1645 \text{ cm}^{-1}

\text{nmr (CDCl}_3\text{): } \delta 7.9-7.4 (\text{complex, 7H}); 6.20 (t, J7Hz, 1H, N-CH=CH-CH); 3.50 (s, 3H, N-CH}_3\text{).

\text{Mass Spectrum (70eV): } m/e (M^+213, C}_{13}\text{H}_{11}\text{NO}_2 \text{ requires } M^+213 (55), 185 (100), 136 (65), 105 (33), 77 (73).

\text{Anal. Calcd for } C_{13}\text{H}_{11}\text{NO}_2: \begin{align*}
\text{C: } & 73.22 \quad \text{H: } 5.20 \quad \text{N: } 6.57 \\
\text{Found: } & \begin{align*}
\text{C: } & 73.22 \quad \text{H: } 5.32 \quad \text{N: } 6.45\%
\end{align*}
\end{align*}

\text{ATTEMPTED PREPARATION OF 16 FROM PHENYLLITHIUM.}

\text{N-methyl-2-pyridone-3-carboxylic acid\textsuperscript{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^\circ \text{C 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).}
Table 2: Attempted Phenylation of N-Methyl-2-Pyridone-3-Carboxylic Acid.

<table>
<thead>
<tr>
<th>Acid</th>
<th>Ph Li</th>
<th>Solvent</th>
<th>Time</th>
<th>Cond. of exp.</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 equiv.</td>
<td>Et₂O</td>
<td>24 hrs</td>
<td>0⁰</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>2 equiv.</td>
<td>Et₂O</td>
<td>7 days</td>
<td>R.T.</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>4 equiv.</td>
<td>Et₂O</td>
<td>7 days</td>
<td>Refl.</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>15</td>
<td>2 equiv.</td>
<td>THF</td>
<td>24 hrs</td>
<td>0⁰</td>
<td>-</td>
</tr>
<tr>
<td>2 equiv.</td>
<td>THF</td>
<td>24 hrs</td>
<td>0⁰</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>4 equiv.</td>
<td>THF</td>
<td>24 hrs</td>
<td>R.T.</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>4 equiv.</td>
<td>THF</td>
<td>24 hrs</td>
<td>Refl.</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>2 equiv.</td>
<td>THF</td>
<td>4 days</td>
<td>R.T.</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>27</td>
<td>2 equiv.</td>
<td>Et₂O</td>
<td>4 hrs</td>
<td>0⁰</td>
<td>trace</td>
</tr>
<tr>
<td>2 equiv.</td>
<td>Et₂O</td>
<td>2 days</td>
<td>Refl.</td>
<td></td>
<td>trace</td>
</tr>
</tbody>
</table>

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 0.6M solution of thallium (111) trifluoroacetate (TTF) in trifluoroacetic acid (TFA) was prepared according to the method of McKillop et al.²⁹

Compound 16 (0.266g) was added to TTF 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 116°)

ir (nujol): 2250, 1720, 1620 and 1590 cm⁻¹.
nmr (CDCl₃): 8 8.10 (t, J = 6H₂, 1H, -CH = CH -);
7.80 - 7.30 (complex, 7H); 4.40 (q, J = 8H₂, 2H, COO-CH₂-CH₂);
1.40 (t, J = 7H₂, 3H, COO-CH₂-CH₂).

(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-fluorenone¹⁷ (4) (0.30g), 4-aminoveratrole(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 C₂₀H₁₆N₂O₃Cl₂Zn: 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°C 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 ethyliodide 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\textsuperscript{17} (0.60g) in dry tetrahydrofuran (30ml) was added over 2 hrs. to the stirred Grignard reagent at 0°C. During this addition the colour changed from yellow to green. The reaction mixture was stirred for another hour at 0°C 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-d₆) : δ 7.30-7.20 (complex, 7H); 6.70 (m, 3H);
5.60 (b, 1H, OH, removed with D₂O); 3. 80 (6H, 2OCH₃).
Mass spectrum (70eV) : m/e (M⁺335, C₂₀H₁₇NO₄ requires M⁺325) (20):
Anal. Calcd for C₂₀H₁₇NO₄ : 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 (CDCl₃) : 8 7.40 (complex, 7H), 6.20 (t, J = 7Hz, 1H, -CH = CH - CH =), 5.81 (b, 1H, -CH - OH), 5.08 (b, 1H, CH - OH, removed with D₂O), 5.60 (s, 3H, N - CH₃).

Anal. Calcd for C₁₅H₁₅NO₂ : 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 (CDCl₃) : 8 9.30 (b, 1H, NH), 8.60 (d, d, J = 7Hz, 2H₂, 1H, CH - NH₂), 8.00 (complex, 2H, CH = CO - CH - Ar), 7.50 (complex, 3H, 3H (Ar)), 7.10 (d, d, J = 7Hz, 2H₂, 1H, CH = C - NH), 6.30 (t, J = 7Hz, 1H, N - CH = CH - CH =), 3.60 (s, 3H, N - CH₃).

Anal. Calcd for C₁₃H₁₂N₂O₂ : C, 68.41 ; H, 5.30 ; N, 12.27
Found : C, 68.50 ; H, 5.46 ; N, 12.02 %
THE SCHMIDT REACTION OF 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-pyridones-3-carbaldehyde (42) as colourless needles (0.05g, 70%).

mp 97-97.5°

nmr (CDCl3) δ 10.50 (s, 1H, -CHO), 8.18 (d, d, J = 7Hz)
J = 2Hz, 1H, -CH=N-CH3); 7.70 (d, d, J = 7Hz, J = 2Hz, 1H,
-CH = C - CHO); 6.40 (t, J = 7Hz, 1H, -CH = CH - CH =);
3.67 (s, 3H, N-CH3).

Anal. Calc'd for C7H7NO2: C, 61.31; H, 5.15; N, 10.21
Found: C, 60.57; 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-CARBOXYANILIDE (45)

A solution of aniline (2.0g) in benzene (10ml) was added to the crude acid chloride 27 (prepared from 1-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 (CDCl₃): δ 12.00 (t, 1H, NH); 8.66 (d, d, J = 7Hz, J = 2Hz, 1H, -CH-NCH₃); 7.70 (complex, 5H, aromatic protons); 7.30, (doublet J = 7Hz, 2Hz, 1H, CH = C - C = 0); 6.50 (t, J = 7Hz, 1H, N - CH = CH - CH = ); 3.70 (s, 3H, N - CH₃)

Anal. Calcd for C₁₃H₁₂N₂O₂: C, 68.41; H, 5.30; N, 12.27
Found: C, 68.46; H, 5.42; N, 11.95%
THE SCHMIDT REACTION ON FLUCREXOL 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, C₂₀H₁₆N₂O₃ requires M+332) (100), 317 (57).
Uv (95% EtOH) : 240 mp ( ε 27,600); 254 ( ε 21,600); 268 ( ε 15,600); 280 ( ε 9,960); 326 ( ε 9,600).
Anal Calcd for C₂₀H₁₆N₂O₃ : 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 \(\text{II} \) (0.012g, 40\%):

\[\text{mp } 273 - 274^\circ\]

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

Mass spectrum (70eV) : \(m/e\) (M\(^+\) 348 \(\text{C}_{20}\text{H}_{16}\text{N}_2\text{O}_4\) 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 \(\text{C}_{20}\text{H}_{16}\text{N}_2\text{O}_4\cdot\frac{1}{2}\text{H}_2\text{O}\) : C, 67.26; H, 4.79; N, 7.84

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

**DEHYDROPERLOLINE (3)**

The N-oxide \(\text{II} \) (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\%):

\[\text{mp } 285 - 287^\circ \quad \text{(lit 288\textsuperscript{13,4})}\]

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

UV (EtOH) : 238 (\(\text{E} 28,800\)); 255 (\(\text{E} 19,000\)); 275 (\(\text{E} 11,000\)); 340 (\(\text{E} 8,000\)); 350 (\(\text{E} 8,700\)); 370 (\(\text{E} 6,000\)).

Mass spectrum (70eV) : \(m/e\) (M\(^+\) 348 \(\text{C}_{20}\text{H}_{16}\text{N}_2\text{O}_4\) requires M\(^+\)348)

(100).

Accurate mass calcd mol.wt for \(\text{C}_{20}\text{H}_{16}\text{N}_2\text{O}_4\) : 348.1109

Found 348.1099

* The sample was supplied by Prof. William I. Taylor (International Flavors and Fragrances)
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 : 30-82°/0.6 (lit 137-140°/17)  
nmr (CCl₄) : 8 3.30 (m, 4H, -CH₂-N-CH₂-); 2.30 (b, 2H, CH₂-CC); 1.70-1.20 (complex, 10H); 0.90 (m, 3H, -CH₂-CH₃).

**N-i-Butylcaprolactam (9d)**

Appeared as colourless oil. A small sample was redistilled before analysis.  
yield : 55\%  
bp : 148-150°/25  
nmr (CCl₄) : 8 3.50 (m, -CH₂-N-CH₂-, 4H); 2.50 (b, 2H, CH₂-CC); 1.80-1.20 (complex, 7H); 0.84 (d, J=6H₂, 6H, CH (CH₃)₂).  
Anal. Calcd for C₁₀H₁₉N⁰ : C, 70.96; H, 11.32; N, 8.28  
Found : C, 71.08; H, 11.59; N, 7.12 \%

**N-Benzylcaprolactam (9e)**

Appeared as colourless needles from pentane.
yield : 55%
mp : 56-57° (lit 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 (CCl4) : 8 3.50 (m, 4H, -CH2-N-CH2-); 2.40 (b, 2H, CH2CO); 2.00-1.30 (complex, 9H); 0.85 (d, J=6H, 6H, -CH (CH3)2).
Anal. calcd for C11H21NO : 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 C14H27NO : 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 purification.
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° (lit114 75°).

nmr (CDCl₃) : 8 7.2 (m, 5H, aromatic protons), 3.70 (b, 2H, CH₂-N-), 2.50 (b, 2H, CH₂CO), 1.70 (b, 6H).

(ii) FROM BENZYL WITH LITHIUM SALT OF E-CAPROLACTAM: To a solution of E-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 (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 (MgSO₄) and solvent removed. The residue (0.50g) was chromatographed on alumina in petroleum, each fraction being examined by ir spectroscopy. Fractions 15-17 (0.10g) were the only ones to contain a lactam carbonyl group, but thin layer chromatography on silica 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 (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 caprolactam appears to have occurred on the column. Fractions from the second column were examined as above and fractions 1-2 contained \( \epsilon \)-methylcaprolactam while fractions 9-11, eluted with ethyl acetate, had nmr and ir spectra consistent with \( \Lambda \)-phenylcaprolactam. They were combined and the resulting oil (0.15g) was subjected to preparative tlc to give pure \( \Lambda \)-phenylcaprolactam as colourless needles (0.08g, 15%), mp 74-75\(^\circ\).

(iv) from benzyne and \( \epsilon \)-caprolactam: A mixture of \( \epsilon \)-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 \( \Lambda \)-phenylcaprolactam. Fractions 7-13 were essentially free of unreacted caprolactam.

\( \Lambda \)-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° (lit114 68-69°)

Attempted preparation of N-p-methoxyphenylcaprolactam:

Prepared from cyclohexanone (10.00g), p-enisidine (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 (lla):

Treatment of N-isobutylcaprolactam (9d) (0.50g) with phosphorus
pentasulphide (1.00g) in toluene (30ml) according to the above
general method gave lla as pale yellow liquid (0.40g, 72%).
bp 118-120°/0.01

\[ \text{nmr (CDCl}_3\text{)}: 8 \text{ 3.70 (m, 4H, CH}_2\text{-N-CH}_2\text{); 3.04 (b, 2H, -CH}_2\text{-CS); 2.20 (m, 1H, CH}_2\text{-CH (CH}_3\text{)}_2\text{); 1.80 (b, 6H, (CH}_2\text{)}_3\text{); 0.95 (d, J = 7Hz, 6H, CH (CH}_3\text{)}_2\text{).} \]

Anal. Calcd for C\text{10H}_{19}\text{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)

\[ \text{nmr (CDCl}_3\text{)}: 8 \text{ 3.90 (m, 4H, -CH}_2\text{-N-CH}_2\text{); 3.10 (b, 2H, CH}_2\text{-CS); 1.90 - 1.50 (complex, 10H); 1.00 (m, 3H, CH}_2\text{-CH}_3\text{).} \]

Anal. Calcd for C\text{10H}_{19}\text{NS}: C, 64.83; H, 10.34; N, 7.36 Found: C, 64.58; H, 10.17; N, 7.79 %

**N-Isopentylthiopropylcaprolactam (11c):**

Yield: 60%

bp: 120°/0.01

ir (film): 1120 and 1070 cm\(^{-1}\) (strong)

\[ \text{nmr (CCl}_4\text{)}: 8 \text{ 3.80 (m, 4H, CH}_2\text{-N-CH}_2\text{); 3.10 (b, 2H, CH}_2\text{-CS); 2.20-1.40 (complex, 9H); 0.90 (d, J = 6Hz, 6H, CH (CH}_3\text{)}_2\text{).} \]

Anal. Calcd for C\text{11H}_{21}\text{NS}: C, 66.29; H, 10.62; N, 7.03 Found: C, 66.27; H, 10.59; N, 6.97 %

**N-Octylthiopropylcaprolactam (11d):**

Yield: 85%
bp : 110-112°C/0.01

Anal. Calcd for C_{14}H_{27}NS : C, 69.66 ; H, 11.28 ; N, 5.60

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)\textsuperscript{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 infra-red spectrum (\( \nu \) 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.)\textsuperscript{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 5M 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 (Na2SO4) 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 g.l.c and pure 1,3-dimethylcaprolactam was obtained as colourless liquid,

bp 96-97°/13

ir (film) : 1660 cm⁻¹

nmr (CDCl3) : 8.3.40 (m, 2H, CH₂-N); 3.00 (s, 3H, N-CH₃);
2.60 (d, 1H, CH₃-CO); 2.00-1.30 (complex, 6H, (CH₂)₅); 1.15 (s, J = 7Hz, 3H, -CH₂-CH₂⋅)

Mass spectrum (70eV) : m/e 141 (M⁺, C₈H₁₅NO requires M⁺141)
Anal. Calcd for C₈H₁₅NO : C, 68.04; H, 10.71; N, 9.92
Found : C, 68.00; H, 10.51; N, 9.87 %

G.C. Apiezon w (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 (CDCl₃) : δ 3.40 (m, 2H, CH₂-N CH₃); 3.00 (s, 3H, N-CH₃)
2.40 (m, 1H, CH-CO); 2.00-1.20 (complex, 8H, (CH₂)₄); 1.00
(3H, -CH₂-CH₃).

Anal. Calcd for C₉H₁₇NO : 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 (CDCl₃) : δ 3.40 (m, 2H, CH₂-N CH₃); 3.00 (s, 3H, N-CH₃)
2.40 (b, 1H, CH-CO); 2.00-1.10 (complex, 10H, (CH₂)₅); 0.90
(m, 3H, -CH₂-CH₃).
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 (CDCl₃): 8 5.40 (m, 2H, CH₂-NCH₂); 2.98 (s, 3H, H CH₃); 2.30 (b, 1H, CHCO); 2.00-1.00 (complex, 12H, (CH₂)₆); 0.82 (m, 3H, -CH₂-CH₂).
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 1-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 L-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 E-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° (lit43 111°)

nmr (CDCl$_3$): 8 7.00 (b, 1H, NH); 4.70 (b, 1H, CH-Br); 3.40 (b, 2H, CH$_2$NH); 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 (CDCl₃) : δ 4.70 (s, 1H, CH-Br); 3.40 (m, 2H, \_CH₂-NCH₂); 3.00 (s, 3H, N-CH₃); 2.40-1.50 (complex, 6H, \( \text{CH}_2 \_ \)) . 3-bromocaprolactam and 8-caprolactam were identified by comparison with authentic specimen.

Schmidt Rearrangement of 2-Oxocyclohexane-1-spiro-2',1',3'-dioxolan (22)

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 22 (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 24 (0.05g, 2.2%); nmr (CDCl₃) : δ 6.60 (s, 1H, NH); 2.50-1.60 (complex, 8H, 4(CH₂)).
(ii) Elution with ethyl acetate gave 25 \((0.03\text{g}, 1.6\%)\); nmr \((\text{CDCl}_3\) : 
\[\delta\ 6.80\ (b, 1\text{H, NH});\ 4.30\ (2\text{H});\ 3.80\ (2\text{H, -O-CH}_2-\text{CH}_2-0-);\ 2.60-1.80\ (\text{complex, 8H})].

(iii) Elution with ethyl acetate-methanol \((9:1)\) gave 26 \((0.03\text{g}, 1.6\%)\); nmr \((\text{CDCl}_3\) : 
\[\delta\ 7.20\ (b, 1\text{H, NH});\ 4.30\ (2\text{H, -O-CH}_2-\text{CH}_2-0-);\ 3.70\ (2\text{H, -O-CH}_2-\text{CH}_2-0-);\ 3.30\ (b, 2\text{H, -CH}_2-\text{NH});\ 2.80-1.80\ (\text{complex, 6H})].

(iv) Elution with ethyl acetate-methanol \((1:1)\) gave 21 \((0.02\text{g}, 2.0\%)\); nmr \((\text{CDCl}_3\) : 
\[\delta\ 6.80\ (b, 1\text{H, NH});\ 3.50\ (b, 2\text{H, -CH}_2-\text{NH});\ 2.80-1.80\ (\text{complex, 6H})].

3-Alkyl-0-methylcaprolactam (28) and 3-Alkylcaprolactam (14)

The general method for the alkylation of 0-methylcaprolactam is shown below:

Anhydrous tetrahydrofuran \((20\text{ml})\) and diisopropylamine \((2.0\text{g}; 0.02\text{ mole})\) were added to a dry flask purged with nitrogen and maintained under a nitrogen atmosphere. After cooling the mixture to \(-5^\circ\), butyllithium in hexane solution \((10\text{ml}, 2.0\text{M}, 0.02\text{ mole})\) was added in a controlled manner to prevent the temperature from exceeding \(0^\circ\). 0-Methylcaprolactam \((1.80\text{g}, 0.015\text{ mmole})\) was added dropwise while maintaining the temperature of reaction below \(0^\circ\). The reaction was stirred at \(0^\circ\) for another 3 hrs. Alkyl halide \((2.0-2.5\text{ equiv.})\) 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°C/12
ir (film) : 1670 cm⁻¹

nmr (CDCl₃): δ 3.50 (s, 3H, OCH₃); 3.40 (b, 2H, CH₂-NC); 2.7 (b, 1H, -CH-CH₃); 1.80-1.20 (complex, 6H, 3(CH₂)); 1.10 (d, J = 7Hz, 3H, CH-CH₃).

Anal. Calc'd for C₇H₁₅NO: C, 68.04; H, 10.71; N, 9.92
Found : C, 67.71; H, 10.91; N, 10.29%
G.C. OV101 (110°C), 4/45.
3-Ethyl-O-methylcaprolactim (28b):

Yield : 65%
bp : 70-72°/11
ir (film): 1670 cm⁻¹

nmr (CDCl₃): δ 3.60 (s, 3H, OCH₃); 3.50 (b, 2H, CH₂-NCO); 2.40 (m, 1H, -CH-CH₂-); 2.00-1.20 (complex, 8H, 4(CH₂));
0.95 (m, 3H, -CH₂-CH₂-).

Anal. Calcd for C₉H₁₇NO : 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 (CDCl₃): δ 3.50 (s, 3H, OCH₃); 3.50 (b, 2H, CH₂-NCO); 2.40 (b, 1H, -CH-CH₂-); 1.90-1.10 (complex, 10H, 5(CH₂));
0.90 (m, 3H, -CH₂-CH₂-).

Anal. Calcd for C₁₀H₁₉NO : C, 70.96; H, 11.32; N, 8.28
Found : C, 71.06; H, 11.26; N, 8.00%

G.C. OV101 (130°), 5/20

3-Methylcaprolactam (14a):

Yield : 16%
mp : 92-93° (lit 94°).
ir (nujol): 3200, 3050 and 1665 cm⁻¹

nmr (CCl₄): δ 6.40 (b, 1H, NH); 3.20 (b, 2H, CH₂NH); 2.50 (b, 1H, CH–CH₂); 1.90–1.30 (m, 6H, 3(CH₂)); 1.18 (d, J = 7Hz, –CH–CH₃).

3-Ethylcaprolactam (14b):

Yield : 15%
mp : 98–99°C (lit 99–100°C)

ir (nujol): 3180, 3050 and 1665 cm⁻¹

nmr (CCl₄): δ 6.30 (b, 1H, NH); 3.25 (b, 2H, –CH₂–NH); 2.40–1.20 (complex, 8H).

3-Proxylcaprolactam (14c):

Yield : 15%
mp : 79–80°C (lit 80–81°C)

ir (nujol): 3200, 3050 and 1665 cm⁻¹

nmr (CCl₄): δ 5.50 (b, 1H, NH); 5.20 (b, 2H, –CH₂–NH).

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

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

(1) 3-Methoxy-5,5-dimethyl-2-cyclohexen-1-one oxime (35)
A solution of dinedone (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% K₂CO₃ and extracted with methylene chloride. The combined extracts were dried and concentrated in vacuo to give the crude product (35.00g) 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 1520 cm⁻¹

nmr (CCl₄) : δ 8.67 (b, 1H, OH, removed with D₂O); 6.05 (s, 1H, -CH=C); 3.70 (s, 3H, OCH₃); 2.08 (4H, 2(CH₂)); 1.01 (s 6H, gem-di CH₃).

Anal. Calc'd for C₉H₁₅NO₂ : 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 (lit⁵³ 104-110°/0.07).

(ii) The above syn- and anti-oximes were treated with polyphosphoric acid according to the procedure of Tamura et al⁵³ to afford 36 in 75% yield, mp 146-147° (lit⁵³ 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 (CDCl₃) : 8.90-7.30 (complex, 7H, NH, aromatic protons); 3.18 (d, J = 7Hz, 2H, CH₂-NH); 2.60 (s, 2H, CH₂-CO); 1.10 (s, 6H, gem-diCH₃),

Mass spectrum (70eV) : m/e (M⁺ 243 C₁₅H₁₇NO requires M⁺ 243).

Anal. Calcd for C₁₅H₁₇NO : 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 (37c)

Appeared as pale yellow needles.

Yield : 52%

mp : 193-194°
ir (nujol) : 3200, 1700, 1650, 1608, and 1590 cm⁻¹

nmr (CDCl₃) : δ 8.50 (d, J = 9Hz, 2H, aromatic protons); 7.80 (3H, aromatic protons, methine proton); 7.30 (b, 1H, NH); 3.15 (d, J = 7Hz, 2H, -CH₂-NH); 2.60 (s, 2H, -CH₂C(CH₃)₂); 1.10 (s, 6H, gem-diCH₃).

Anal. Calcd for C₁₅H₁₆N₂O₄ : 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 (CDCl₃) : δ 7.80-7.30 (6H, aromatic protons, NH and methine proton); 3.10 (d, J = 7Hz, 2H, CH₂-NH); 2.60 (s, 2H, (CH₃)₂C CH₂-); 5.12 (s, 6H, gem-diCH₃).

Anal. Calcd for C₁₅H₁₆N₂O₂Cl : C, 64.87; H, 5.81; N, 5.05

Found : C, 64.90; H, 5.85; N, 4.73%

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 (CDCl₃) : 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, $J = 7$ Hz, 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, 57.31; 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-atm) 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 15 and 30% yield respectively of the 4-C-alkylated product. The C- and O-alkylocaprolactams 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 C-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$_3$): $\delta$ 7.00 (b, 1H, NH); 5.50 (m, 2H, CH$_2$NH);
3.00 (s, J = 8H₂, 1H, CH-CH₃), 2.50 (s, 2H, CH₂CO), 1.30 (d, J = 8Hz, 3H, CH-CH₂), 1.02-1.00 (6H, 2(CH₃)₂).

Anal. Calcd for C₉H₁₅NO₂: C, 63.88; H, 8.94; N, 3.28
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, 3030, 1708 and 1675 cm⁻¹

nmr (CDCl₃): 8 7.20 (b, 1H, NH), 3.40 (m, 2H, CH₂-NH), 3.00 (m, 1H, -OH-CH₂-), 2.47 (s, 2H, -CH₂-CO), 1.84 (6, q, J = 7Hz, 2H, -CH-CH₂-CH₃), 1.02-1.00 (6H, gem-diCH₃), C.90 (3H, CH₂-CH₃).

Anal. Calcd for C₁₀H₁₉NO₂: C, 65.54; H, 9.35; N, 7.54
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 16% yield. A small sample was recrystallised from petroleum ether before analysis.
mp : 112-113°
ir (nujol) : 3180, 1650 and 1610 cm⁻¹
nmr (CCl₄) : 8 8.53 (b, 1H, NH); 4.87 (d, J = 2Hz, allylic proton, C = CH⁻); 3.80 (q, J = 7Hz, 2H, -O-CH₂-CH₃); 3.84 (d, J = 7Hz, -CH₂-NH); 2.18 (s, 2H, -CH₂-C(CH₃)₂); 1.35 (t, J = 7Hz, 3H, -O-CH₂-CH₃); 1.00 (s, 6H, sem-dich₂)
Anal. Calcd for C₁₀H₁₇NO₂ : 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-isopropanoyl-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 (CDCl₃) : 8 6.70 (b, 1H, NH); 3.34 (m, 2H, -CH₂-NH); 2.95 (m, 1H, -CH-CH(CH₃)₂); 2.45 (s, 2H, -CH₂-CO); 1.65 (b, 1H, -CH (CH₃)₂); 1.00-0.90 (complex, 12H)
Anal. Calcd for C₁₁H₁₉NO₂ : 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 (CDCl₃) : 6 6.80 (b, 1H, NH), 5.00 (d, J = 2H₂, -CH = C-), 4.30 (q, J = 6H₂, 1H, -O-CH₂), 2.90 (d, J = 6H₂, 2H, -CH₂-NH), 2.20 (s, 2H, -CH₂C(CH₃)₂), 1.30 (d, J = 7H₂, 6H, CH(CH₃)₂), 1.00 (s, 6H, gem-diCH₃).

Anal. Calcd for C₁₁H₁₉NO₂ : C, 66.97; H, 9.71; N, 7.10
Found : C, 67.30; H, 9.55; 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 (CCl₄) : 8.70 (b, 1H, NH); 3.20 (b, 2H, -CH₂NH); 2.63 (m, 2H, -CH₂CCl); 2.00 (complex, 5H, CH₃ and methylene protons)
Anal. Calcd for C₇H₁₀NOCl: C, 52.51; H, 6.31; N, 8.77
Found  i.e., C, 53.00; H, 6.20; N, 8.43 %

3-Methylcaprolactam from the reduction of 3la

Chloro-amide 3la (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. 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 $\delta$ 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-methylcaprolactams. Attempts to separate these two lactams by fraction recrystallisation, tlc or preparative glc were unsuccessful.

The Grignard reaction on 6,6-Dimethyl-4-ketocaprolactam (35)

Ethyl magnesium bromide was prepared from magnesium (1.20g) and ethyl bromide (6.00g) in dry tetrahydrofuran (50ml) in the usual way. The Grignard reagent was cooled to 0° and keto-amide (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 \( \nu_{\text{max}} \) (nujol) 1710 indicating the presence only of starting keto-amide 36.

The mixture was treated twice more with ethyl magnesium bromide at 0\(^{\circ}\), 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-\((\text{Benzylamino})-6,6\text{-dimethyl}-2,5,6,7\text{-tetrahydrobenzoxazin-2-one (40a}\))

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,

\[ \text{mp} : \quad 206-207^\circ \]
ir (nujol) : 3180, 1605, 1580 and 1530 cm⁻¹

nmr (CDCl₃) : 6 7.36 (s, 5H, aromatic protons); 5.85 (b, 1H, NH, removed with D₂O); 4.70 (d, J = 2H₂, allylic coupling, 1H, -CH₂-C = CH); 4.20 (s, 2H, NH-CH₂-C₆H₅); 2.90 (s, 2H, -CH₂C(CH₃)₂); 1.00 (s, 6H, gem-diCH₃).

Anal. Calcd for C₁₉H₂₀N₂O : 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 C₁₄H₁₈N₂O : C, 73.01; H, 7.88; N, 12.17
Found : C, 73.33; H, 7.84; N, 12.28%

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

⁵-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 C₁₅H₂₀N₂O : 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 56 (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 (CDCl₃) : 8 6.80 (m, 3H, aromatic protons); 5.82 (b, NH, 1H); 4.70, (d, J = 2H₂, allylic coupling, 1H, -CH₂-C = CH⁻); 3.90 (s, 6H, 2(OCH₃)); 3.30 (m, 2H, -CH₂-Ar); 2.90 (d, J = 7H₂, 4H, -CH₂-N-CH₂); 2.10 (s, 2H, -CH₂-C(CH₃)₂); 1.00 (s, 6H, gem-diCH₃).

Anal. Calcd for C₁₈H₂₆O₂N₂ : C, 67.90; H, 8.23; N, 8.80
Found : C, 67.97; H, 8.24; N, 8.64 %

4-(m-Nitropheny lamino)-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 C₁₄H₁₇N₂O₃ : 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 \( \text{C}_{14}\text{H}_{17}\text{N}_{3}\text{O}_{3} \): C, 61.08; H, 6.22; N, 15.26
Found : C, 60.83; H, 6.10; N, 15.41%

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

 Prepared according to the general method.
 Yield : 88%
mp : 176 - 178°

*Anal. Calcd for \( \text{C}_{14}\text{H}_{17}\text{N}_{2}\text{OCl} \): C, 63.51; H, 5.47; N, 10.56
Found : C, 62.35; H, 7.03; N, 9.13%

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%).

* 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 C₁₄H₂₀N₂O : 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 4lc. Recrystallisation of the crude product from ethyl acetate afforded 4lc as colourless needles (0.25g, 83%),
ir (nujol) : 3200, 3050, 1660 and 1606 cm⁻¹
Anal. Calcd for C₁₅H₂₂N₂O : 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 (CDCl₃) : 8 7.50 (b, 1H, NH) ; 5.02 (d, J = 2H₂, allylic coupling, 1H, CH₂-O-C=CH−) ; 3.07 (s, 3H, -OCH₂−) ; 2.97 (d, J = 7H₂, 2H, -CH₂-NH) ; 2.23 (s, 2H, (CH₃)₂C CH₂−) ; 1.00
(s, 6H, gem-diCH₂).
Anal. Calcd for C₉H₁₅NO₂: C, 63.88; H, 8.94; N, 8.28
Found: C, 63.38; H, 9.05; N, 7.74%

6,6-Dimethyl-4-methoxy-2,5,6,7-tetrahydroazegenin-2-one (65) from
4-Chloro-6,6-dimethyl-2,5,6,7-tetrahydroazegenin-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 Na₂CO₃ 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 re-
arangement 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 (2cm1) 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-bromo-caprolactam (12) according to the literature procedure68. The crude product was vacuum distilled giving a colourless liquid bp 55°/0.2 (lit68 65°/0.5). 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 (CCl₄) : 7.91 (b, 1H, NH); 3.13 (b, 2H, CH₂-NH); 2.23 (b, 2H, -CH₂-CO); 1.90-1.10 (complex, 12H); 0.90 (m, 3H, -CH₂-CH₂).

Mass spectrum (70eV) : m/e 169 (M⁺C₁₀H₁₉NO requires M⁺169) (18), 112 (M-C₄H₉) (100), 84 (M-C₄H₉+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. 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 oximes (43)

These were prepared according to the procedure of Koch et al. 7c 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° (lit72,74 112-115°, lit73 103-109°).

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 iso-
phorone 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° (lit72 92-95°, lit73 90.1-90.7°).
4,6,6-Trimethylcaprolactam (46).

Lactam 44 (0.612g; 4 mmole) in ethanol (50ml) 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° (lit72 110-111°)
ir (nujol) : 3180, 3020 and 1670 cm-1
nrm (CDCl3) : 8 8.00 (b, 1H, NH); 3.10 (b, 2H, CH2NH);
2.08 (b, 2H, -CH2CO); 1.08-1.00 (complex, 12H).

4,4,6-Trimethylcaprolactam (47)

The preparation was similar to that above.
Yield : 92%
mp : 108-108.5° (lit72 109-111°)
ir (nujol) : 3130, 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 (CCl₄) : $\delta$ 5.70 (d, J = 2Hz, allylic coupling, 1H, CH₂-C=CH-); 3.02 (s, 3H, N-CH₃); 3.00 (s, 2H, CH₂-N-); 2.00 - 1.98 (5H, methylene and methyl protons); 1.00 (s, 6H, gem-diCH₃).

Anal. Calcd for C₁₀H₁₇NO : 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 (CCl₄) : $\delta$ 5.80 (d, J = 2Hz, 1H, allylic proton); 2.90 (s, 3H, N-CH₃); 2.20 (s, 2H, -CH₂CO); 1.90-1.85 (5H, methylene and methyl protons); 1.05 (s, 6H, gem-diCH₃).

Anal. Calcd for C₁₀H₁₇NO : 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 H-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 (CDCl\(_3\)) : S 6.40 (d, J = 2H, 1H, allylic proton); 3.00 (d, J = 6H, 2H, CH\(_2\)-NH).
Anal. Calcd for C\(_7\)H\(_{15}\)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\(_7\)H\(_{15}\)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-Trimethylthiobianprolactam (49)

4,6,6-Trimethylthiobianprolactam (49) was prepared from 46
(0.50g), phosphorus pentasulphide (1.0g) and toluene (30ml) by the 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 C₁₉H₁₇NS : C, 63.13 ; H, 10.00 ; N, 8.18
Found : C, 63.18 ; H, 9.55 ; N, 8.10%

4,4,6-Trimesitylthiocaprolactam (52)

4,4,6-Trimesitylthiocaprolactam (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 C₉H₁₇NS : 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 ketone¹¹⁹ 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 (CCl₄) δ 9.00 (b, N-ÖH removed with D₂O), 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 K₂CO₃ and evaporated to give a brown solid which was recrystallised from petroleum ether to yield lactam 56 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 (CCl₄) : δ 8.30 (b, 1H, NH); 5.70 (1H, -CH=CH-); 3.30 (m, 2H, CH₂-NH).

Anal. Calcd for C₉H₁₅NO : C, 71.59 ; H, 8.67 ; N, 9.27

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

Hydrogenation of Lactam 56

Lactam 56 (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 58 as small colourless prisms after recrystallisation from petroleum ether.

mp : 95-95.5°

nmr (CCl₄) : δ 8.13 (b, 1H, NH); 3.18 (b, 2H, CH₂-NH).

Anal. Calcd for C₉H₁₅NO : 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\textsuperscript{49} from 3-chloro-5, 5-dimethyl-2-cyclohexen-1-one (bp 88-90\textdegree/12 lit\textsuperscript{120} 109-110\textdegree/14) with PPA by the Schmidt reaction. The crude product was absorbed on a column of alumina.

(i) Elution with 90% C\textsubscript{6}H\textsubscript{6}-10% EtOA\textsubscript{c} gave 61 as colourless needles. mp 94-95\textdegree (lit\textsuperscript{49} 95-96\textdegree)

ir (nujol): 3200, 3130 and 1660 cm\textsuperscript{-1}

nrm (CCl\textsubscript{4}): S 10.20 (b, 1H, NH); 6.20 (d, J = 4Hz, 1H, -C=CH); 2.40 (s, 4H, CH\textsubscript{2}-CO and CH\textsubscript{2}-C=); 1.05 (s, 6H, gem-diCH\textsubscript{3}).

(ii) Elution with ethyl acetate gave 60 as colourless needles after recrystallisation from petroleum ether.

mp 84-85\textdegree (lit\textsuperscript{49,53} 84.5-85.5\textdegree)

nrm (CCl\textsubscript{4}): S 8.70 (b, 1H, NH); 6.02 (d, J = 2Hz, 1H, -C=CH-); 2.92 (d, J = 7Hz, 2H, CH\textsubscript{2}-NH); 2.46 (s, 2H, CH\textsubscript{2}O(CH\textsubscript{3})\textsubscript{2}); 1.02 (s, 6H, gem-diCH\textsubscript{3}).

4,4-Dimethylcanrolactam (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\textdegree

ir (nujol): 3180, 3080 and 1660 cm\textsuperscript{-1}
nmr (CCl₄): S 6.90 (b, 1H, NH); 3.20 (b, 2H, CH₂NH); 2.42 (b, 2H, –CH₂CO); 1.67 (m, 4H); 1.02 (s, 6H, gem-diCH₃).
Anal. Calcd for C₈H₁₅NO: 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⁺, C₈H₁₃NS₂ requires M⁺ 187).
Anal. Calcd for C₈H₁₃NS₂: 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 (150.1g), 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⁺, C₁₀H₁₈N₂O requires M⁺182).
Anal. Calcd for C₁₀H₁₈N₂O: C, 55.89; 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-tetrahydrazepin-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 (20:1) 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\textsuperscript{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\textdegree (lit\textsuperscript{50} 41-42\textdegree).

ir (nujol) : 3200, 3080 and 1660 cm\textsuperscript{-1}

nmr (CCl\textsubscript{4}) : 6 6.34 (b, 1H, NH); 3.20 (m, 2H, CH\textsubscript{2}NH); 2.42 (m, 2H, CH\textsubscript{2}CO).

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

5-Ethylcaprolactam (71b)

\begin{itemize}
  \item Yield : 90%
  \item mp : 55-56\textdegree (lit\textsuperscript{121} 56-57\textdegree)
  \item ir (nujol) : 3200, 3090 and 1660 cm\textsuperscript{-1}
  \item nmr (CCl\textsubscript{4}) : 6 6.90 (b, 1H, NH); 3.30 (m, 2H, CH\textsubscript{2}NH); 2.50 (m, 2H, CH\textsubscript{2}CO).
\end{itemize}

5. Isopropylcaprolactam (71c)

\begin{itemize}
  \item Yield : 85%
  \item mp : 84-85\textdegree (lit\textsuperscript{121} 84\textdegree)
  \item ir (nujol) : 3200, 3080 and 1660 cm\textsuperscript{-1}
  \item nmr (CCl\textsubscript{4}) : 6 8.00 (b, 1H, NH); 3.20 (m, 2H, CH\textsubscript{2}NH); 2.40 (m, 2H, CH\textsubscript{2}CO); 2.00-1.10 (complex, 6H); 0.90 (d, J=7Hz, 6H, CH(CH\textsubscript{3})\textsubscript{2}).
\end{itemize}
5-t-Butylcaprolactam (71d):

Yield: 87%  
mp: 152-154° (lit121 156-157°)  
\( \text{ir (nujol)} : 3.200, 3.080 \text{ and } 1.660 \text{ cm}^{-1} \)  
\( \text{nmr (CCl}\_4) : S 6.50 (b, 1H, NH); 3.20 (m, 2H, CH\_2NH); 2.44 (m, 2H, CH\_2CO); 0.84 (s, 9H, CH\_3) \).

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-carbethoxy-cyclohexanone (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, 68\%):  
bp 158°/43 (lit86 122-4°/9)  
\( \text{ir (film)} : 1748 \text{ and } 1724 \text{ cm}^{-1} \)

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 78⁰/16 (lit⁸⁶ 90-94⁰/40)
ir (film) : 1724 cm⁻¹

In a similar manner the following compounds were prepared.

2-n-Propylcyclohexanone (73b)

Yield : 74%
bp 82-84⁰/12 (lit³⁴ 96-97⁰/25)

2-n-Butylcyclohexanone (73c)

Yield : 70%
bp 92-94⁰/15 (lit¹²⁴ 90-92⁰/13)
ir (film) : 1724 cm⁻¹

7-Methylcaprolactam (74a)

The method was adapted from that used by Conley³³ from 2-methylcyclohexanone (4.95g), polyphosphoric acid (95g) and sodium azide (3.40g), giving 7-methylcaprolactam (74a) as colourless needles (4.75g, 96%);

mp 88-89⁰ (lit³³ 90-91⁰)
ir (nujol) : 3200, 3080 and 1670 cm⁻¹
nmr (CCl₄) : 6.90 (t, 1H, NH); 3.50 (b, 1H, CH-NH); 2.38 (m, 2H, CH₂CO); 2.00-1.40 (complex, 6H); 1.20 (d, J=8Hz, 3H, -CH₂CH₃).

7-Ethylcaprolactam (74b)

This was prepared according to the procedure above.
Yield : 95%
mp 91-92° (lit 91.5-92°)
ir (nujol) : 3180, 3060 and 1660 cm⁻¹

7-n-Pryonylacrolactam (74c)

Yield : 95%
mp 97-98° (lit 97-98°)
ir (nujol) : 3180, 3050 and 1660 cm⁻¹
nmmr (CCl₄) : S 7.80 (b, 1H, NH); 3.25 (b, 1H, CH-NH); 2.30 (m, 2H, CH₂CO); 2.20-1.30 (complex, 1OH) and 1.00 (m, 3H, \( \text{CH}_{2}-\text{CH}_{2} \)).

7-n-Butyllacrolactam (74d)

Yield : 94%
mp 73-75°5 (lit 70°)
ir (nujol) : 3200, 3050 and 1660 cm⁻¹
nmmr (CCl₄) : S 7.70 (b, 1H, NH); 3.20 (b, 1H, CH-NH); 2.30 (b, 2H, CH₂-CO); 2.00-1.20 (complex, 12H) and 0.95 (m, 3H, \( \text{CH}_{2}-\text{CH}_{2} \)).

4-Methyl-7-isoprynylacrolactam (76)

Yield : 98%
mp 120-121° (lit 119-120°)
ir (nujol) : 3200, 3050 and 1660 cm⁻¹

7-Methylthiacyprolactam (75a)

7-Methylthioacrolactam (75a) was prepared according to the general method described earlier for \( \text{H} \)-alkythioacrolactam (Chapter 1) from 7-methylacrolactam (1.0g), phosphorus pentasulphide (4.0g)
and toluene (20ml). The residue was chromatographed on alumina (40%)
Elution with ethyl acetate gave 75a as white solid (0.75g, 67%).
The analytical sample was prepared as colourless needles by recryst-
tallisation from petroleum ether.

mp 87.5 - 88°

ir (nujol): 3180 and 1060 cm⁻¹ (strong)
nmr (CCl₄): δ 8.20 (b, 1H, NH); 3.80 (b, 1H, CH₂-NH); 3.00 (b,
2H, CH₂CS); 1.65 (m, 6H, (CH₂)₃); 1.30 (d, J=7Hz, 3H, CH-CH₃).
Anal. Calcd for C₇H₁₃NS: 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 pre-
pared and their analytical and spectral data are obtained as below.

7-n-Propylthiocaprolactam (75c)

Yield 89%

mp 85-85.5°

ir (nujol): 3180 and 1070 cm⁻¹ (strong)
nmr (CCl₄): δ 8.83 (b, 1H, NH); 3.40 (b, 1H, CH₂-NH); 2.80 (b,
2H, CH₂CS); 2.00-1.30 (complex, 10H); 1.00 (3H, CH₂-CH₃).
Anal. Calcd for C₉H₁₇NS: C, 63.13; H, 10.00; N, 8.18
Found: C, 63.35; H, 9.37; N, 8.03%

4-Methyl-7-isopropylthiocaprolactam (77)

Yield 82%

mp 106-107°

ir (nujol): 3180, 1108 and 1100 cm⁻¹

Anal. Calcd for C₁₀H₁₉NS: 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) : 3130 and 1660 cm⁻¹

nmr (CCl₄) : 8 8.00 (b, 1H, NH); 2.95 (b, 2H, CH₂-NH); 2.30 (b, 2H, -CH₂ CO); 1.50 (m, 4H, (CH₂)₂); 1.00 (s, 6H, gem-diCH₃).

Anal. Calcd for C₈H₁₅NO : C, 68.04; H, 10.71; N, 9.92

Found : C, 68.24; H, 10.32; N, 9.50%

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

The method was adapted from that used by Fieser. 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 thio-ketal 79 as colourless needles (0.80g, 77%), mp 229-230°

ir (nujol) : 3200, 3030 and 1670 cm⁻¹

nmr (CDCl₃) : 8 6.70 (b, 1H, NH); 3.40 (s, 4H, S(CH₂)₂S); 3.10 (s, 2H, CH₂ CO); 3.06 (d, J=7Hz, 2H, CH₂ NH); 2.30 (s, 2H,
\[
\text{CH}_2\text{C}(\text{CH}_3)_{2}; 1.04 (s, 6\text{H, gem-diCH}_3).
\]

Anal. calcd for \(\text{C}_{10}\text{H}_{17}\text{NOS}_2\) : 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°C. 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°C 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°C.

mp : 70°C

ir (nujol) : 3160, 3040 and 1660 cm\(^{-1}\)


\(\text{nmr (CCl}_4\) : S 6.50 (b, 1H, N\text{H}); 4.05 (2H, CH\text{2-NH}); 3.35 (s, 6H, 2(OCH}_3\); 1.95 (s, 2H, CH\text{2CO}); 1.40 (m, 2H); 1.00 (s, 6H, gem-diCH}_3\)).

Anal. Calcd for \(\text{C}_{10}\text{H}_{19}\text{NOS}_3\) : C, 59.67; H, 9.52; N, 6.95

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.
To a solution of lactam 61 (0.172g, 1 mmole) in freshly distille
tetrahydrofuran (20ml) was added butyllithium (2ml, 1.0M, 2 mmole)
at 0° under nitrogen and to the resultant suspension was added tri-
ethylborane (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 tetrachydrofuran
(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 Baron97 from glutaric anhydride mp 150-152° (lit97
152-153°).
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.