CHAPTER II

Synthesis of (7-methyl-3-aza-4-oxo-6-octenyloxy)benzene

and Related Compounds
Bowers et al. (85) and Cerny et al. (86) were perhaps the pioneer workers in the field of juvenoids who were independently able to isolate, purify and characterize the first cyclic JH mimicking substance (+) juvabione (2.1) which was identified as the methyl ester of the already known todomatuic acid, a sesquiterpenic acid of the bisabolene series (87-89). In addition to juvabione, they were also able to isolate and identify another biologically more active substance, dehydrojuvabione (2.2) from Slovak fir.

It was almost a decade later that Manville and coworkers reported the isolation of a mixture of alcohols identified as (+) juvabiol (2.3) and (+)-isojuvabiole (2.4) from the wood of Balsam fir and (+) juvabiol and (+) epijuvabiol (2.5) from Alpine fir (148, 149). All these alcohols were found to exhibit insect JH activity. No other cyclic juvenoids seem to have
been found in nature.

\[
\text{(2-3)} \quad \text{OH} \quad \text{H} \quad \text{CH}_3 \\
\text{CH}_7 \\
\text{CO}_2 \text{CH}_3 \\
\]

\[
\text{(2-4)} \quad \text{OH} \quad \text{H} \quad \text{CH}_3 \\
\text{CH}_7 \\
\text{CO}_2 \text{CH}_3 \\
\]

\[
\text{(2-5)} \\
\text{OH} \quad \text{H} \quad \text{CH}_3 \\
\text{CH}_7 \\
\text{CO}_2 \text{CH}_3 \\
\]

Obviously, because of very small number of cyclic juvenoids available in nature, there was a very limited choice for extensive research in the application of these juvenoids for pest control. Further, all the natural cyclic juvenoids were found to possess very selective physiological action. It was therefore thought that various synthetic variations of the naturally occurring juvenoids could be synthesized in order to enhance/diversify the physiological action of such compounds. Also such variations could serve to study the structure activity relationship amongst this class of compounds. As such the
synthesis of various aromatic analogues of juvabione and dehydrojuvabione and also other structural variations were reported (93,98,99). Some of these compounds showed much higher biological activity than juvabione and dehydrojuvabione on hemipterans of the family Pyrrhocoridae and Dysdercus cingulatus. These findings prompted the synthetic organic chemists to explore possibilities of preparing other classes of cyclic JH like substances which also might show JH activity. This led to the syntheses of two particularly important type of compounds (2.6) and (2.7) in which an aromatic ring is attached to a terpenoid moiety through a hetero atom oxygen or nitrogen and their derivatives in which para substituent was varied from hydrogen to alkyl, hydroxy, alkoxy, carbethoxy or nitro group (104,111).

\[
\text{(2.6)}
\]

\[
\text{(2.7)}
\]
Results and Discussion:

The present work is a part of total synthetic programme undertaken in our laboratory to synthesize various classes of cyclic juvenoids with an intention to find out some such compounds that might show more universal JH activity on majority of the unrelated experimental insects. Such compounds, if successfully discovered, would serve as insecticides and pesticides which will act on physiological basis to control the insect problem.

A large number of cyclic juvenoids in which a phenyl group is attached to a terpenoid moiety through oxygen have been reported in the last two decades and some of the literature on such compounds has been reviewed in the introductory chapter. Quite a few structural changes like varying p-substituent in the phenyl ring, introducing additional structural features in the side chain and varying the length of the side chain, have also been reported. Such changes were observed to bring about changes in the JH activity also which at times were quite significant. The JH activities of a large number of juvenoids of various classes are listed in the book, "Insect Hormones and Bioanalogues" (150). The following table 2.1 (150) presents the JH activities of certain juvenoids of the type (2.6) and some of their synthetic variations already known in literature.

Juvenile hormone activity data are given in ID-50 Morph.
in μg per specimen. A triangle (Δ) indicates inactive or low activity compounds. PYR, DYS, GRA, TRI, TEN, DER, GAL, LYG respectively stand for *Pyrrhocoris apterus* (L) (Pyrrhocoridae), *Dysdercus cingulatus* (F) (Pyrrhocoridae), *Graphosoma italicum* (L) (Pentatomidae), *Triatoma infestans* (L) (Reduviidae), *Tenebrio molitor* (L) (Tenebrionidae), *Dermestes vulpinus* (F) (Fermestidae), *Galleria mellonella* (L) (Pyralidae), *Lygaeus equestris* (L) (Lygaeidae). Unless otherwise stated all the applications were performed topically, (i) or (e) stands for application through injection or topically. In *Galleria*, the symbol(7) and (P) stand for assays performed on larvae and on pupae respectively.
<table>
<thead>
<tr>
<th>S.No.</th>
<th>Compound</th>
<th>PYR</th>
<th>DYS</th>
<th>GRA</th>
<th>TRI</th>
<th>GRY</th>
<th>TEN</th>
<th>DER</th>
<th>GAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td><img src="" alt="Compound 1" /></td>
<td>Δ</td>
<td>100</td>
<td>Δ</td>
<td>-</td>
<td>-</td>
<td>Δ(e)</td>
<td>Δ(i)</td>
<td>-</td>
</tr>
<tr>
<td>2.</td>
<td><img src="" alt="Compound 2" /></td>
<td>50</td>
<td>10</td>
<td>5</td>
<td>-</td>
<td>-</td>
<td>7(e)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3.</td>
<td><img src="" alt="Compound 3" /></td>
<td>5</td>
<td>4</td>
<td>0.07</td>
<td>1</td>
<td>100</td>
<td>0.5(e)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>4.</td>
<td><img src="" alt="Compound 4" /></td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.08(e)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>5.</td>
<td><img src="" alt="Compound 5" /></td>
<td>-</td>
<td>0.05</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>0.005(e)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>6.</td>
<td><img src="" alt="Compound 6" /></td>
<td>8</td>
<td>4</td>
<td>0.8</td>
<td>-</td>
<td>100</td>
<td>30(e)</td>
<td>100(i)</td>
<td>-</td>
</tr>
<tr>
<td>S.No.</td>
<td>PYR</td>
<td>DYS</td>
<td>GRA</td>
<td>TRI</td>
<td>GRY</td>
<td>TEN</td>
<td>DER</td>
<td>GAL</td>
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<tr>
<td>7.</td>
<td></td>
<td></td>
<td>0.8</td>
<td></td>
<td>0.5</td>
<td>0.004</td>
<td>50</td>
<td>5(e)</td>
<td>100(e)</td>
</tr>
<tr>
<td>8.</td>
<td></td>
<td></td>
<td>5</td>
<td>1</td>
<td>10</td>
<td></td>
<td>-</td>
<td>Δ(e)</td>
<td>Δ(i)</td>
</tr>
<tr>
<td>9.</td>
<td></td>
<td></td>
<td>1</td>
<td>0.3</td>
<td>0.3</td>
<td></td>
<td>Δ</td>
<td>Δ(e)</td>
<td>Δ(i)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Δ</td>
<td>Δ(i)</td>
<td>Δ(7)</td>
</tr>
<tr>
<td>10.</td>
<td></td>
<td></td>
<td>0.5</td>
<td>0.5</td>
<td>0.8</td>
<td></td>
<td>100(e)</td>
<td>-</td>
<td>Δ(p)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>100(i)</td>
<td>-</td>
<td>Δ(7)</td>
</tr>
<tr>
<td>11.</td>
<td></td>
<td></td>
<td>0.05</td>
<td>0.05</td>
<td>0.01</td>
<td>0.08</td>
<td>100(e)</td>
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<td>Δ(7)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>100(i)</td>
<td>-</td>
<td></td>
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</tbody>
</table>

Abstracted from K. Slama, M. Romanuk, F. Sorm; "Insect Hormones and Bioanalogues".
Very often it has been reported that incorporation of a hetero atom produces significant changes in the biological activities of naturally occurring compounds (59, 60, 151-153). Although various structural variations in compounds of the type (2.6) have been reported in literature, not much work seems to have been reported in the direction of incorporating a hetero atom in the side chain of (2.6). It was therefore thought of interest to introduce a hetero atom in the side chain of (2.6).

In this chapter we are reporting the syntheses of certain analogues of (2.6) in which a nitrogen atom has been introduced in the side chain in the form of amide function in addition to varying the p-substituent in the phenyl ring and decreasing the length of the chain by one atom. Since some of the compounds of the type (2.6) have shown JH activities, the compounds synthesized in this chapter may be termed as JH-like substances.

The synthesis of (7-methyl-3-aza-4-oxo-6-octenyloxy) benzene (2.20), (7-methyl-3-aza-4-oxo-octyloxy)benzene (2.26) and related compounds was accomplished along the following lines (Fig. 2.1).
Fig. 2.1

2.8, 2.11, 2.14, 2.17, 2.20, 2.23, 2.26, 2.29 : R = H,
2.9, 2.12, 2.15, 2.18, 2.21, 2.24, 2.27, 2.30 : R = Cl,
2.10, 2.13, 2.16, 2.19, 2.22, 2.25, 2.28, 2.31 : R = CH₃.
Reagents: (a) NaOH; (b) (c) NH₂NH₂.H₂O; HCl; (d) (e) 3-Chloro perbenzoic acid; (f) \( \text{CH}_3\text{I} \).

The reaction of phenol with 1,2-dibromo ethane gave 2-phenoxyethyl bromide (2.11) by known procedure(154). The treatment of 2-phenoxyethyl bromide (2.11) with potassium phthalimide followed by hydrolysis with hydrazine hydrate resulted in the formation of 2-phenoxyethyl amine. The p-substituted amines (2.18) and (2.19) were also prepared from the respective p-substituted phenols as above. The yields of all these steps were satisfactory except the last hydrolysis step in which case the yields were only 30-35%.

For the synthesis of 2-phenoxyethyl bromide the reported procedure was to reflux the mixture of one mole of phenol with 1.25 mole of 1,2-dibromo ethane in presence of NaOH solution for 6 hr (154). However, in our hands this reaction performed under the above reported conditions yielded only about 25% product. In order to improve the yield of the products various changes in the experimental conditions were made. It was observed that when one mole of phenol was heated with 2 moles of 1,2-dibromo ethane for 15 hr in presence of NaOH solution the yield was considerably improved upto 60%.

Earlier, attempts were made to prepare 2-phenoxyethyl
amine (2.17-2.19) by the following method (Fig. 2.2).

**Fig. 2.2**

\[
\text{[Chemical structure image]}
\]

Reagents: (a) NaOH; (b) SOCl₂; (c) NH₃; (d) LAH.

2.8, 2.32, 2.35, 2.38, 2.17 : R = H,
2.9, 2.33, 2.36, 2.39, 2.18 : R = Cl,
2.10, 2.34, 2.37, 2.40, 2.19 : R = CH₃
p-Substituted phenoxyacetic acids (2.32-2.34) were prepared by the reaction of sodium salt of corresponding p-substituted phenols with the sodium salt of chloroacetic acid in alkaline medium(155). Their acid chlorides (2.35-2.37) were treated with ammonia to form corresponding amides (2.38-2.40). All these steps proceeded smoothly and gave good yields of products. The reduction of these amides with LAH gave very poor yield of the amines. In most of the cases the starting amides were recovered unreacted. Change of solvent from dry ether to THF or dioxane did not improve the yield.

Another method attempted to prepare the above amines was by the alkylation of the phenol with 2-bromo ethyl amine hydrobromide. This compound was prepared by the known method(156) (Fig. 2.3). Various attempts to alkylate the phenol with 2-bromo ethyl amine hydrobromide were unsuccessful.

Fig. 2.3

\[
\text{Reagents: (a) NaOH; (b) HBr 48\%}.
\]
4-Methyl-3-pentenoyl chloride (2.43) and 4-methyl pentanoyl chloride (2.47) required in the next step were prepared as follows (Fig. 2.4). Dobner reaction of 2-methyl propanal with malonic acid in pyridine formed 4-methyl-2-pentenoic acid (2.41) which was isomerized in presence of alkali to obtain 4-methyl-3-pentenoic acid (2.42). Its reaction with thionyl chloride gave the desired acid chloride (2.43) (157).

**Fig. 2.4**

\[
\text{CHO} + \begin{array}{c}
\text{CH}_2 \\
\text{COOH}
\end{array} \xrightarrow{a} \begin{array}{c}
\text{CHO} \\
\text{COOH}
\end{array} \xrightarrow{b} \begin{array}{c}
\text{CHO} \\
\text{COOH}
\end{array} \xrightarrow{c} \begin{array}{c}
\text{Cl}
\end{array}
\]

(2.41)  
(2.42)  
(2.43)

Reagents: (a) Pyridine; (b) KOH; (c) SOCl₂.
For the preparation of 4-methyl pentanoyl chloride (2.47), 3-methyl-1-butanol was treated with 48% HBr to form 3-methyl-1-bromo butane (2.44)(158) which on treatment with NaCN followed by alkaline hydrolysis gave 4-methyl pentanoic acid (2.46)(159). Its reaction with thionyl chloride gave the acid chloride (2.47)(160), (Fig. 2.5).

Fig. 2.5

Reagents : (a) 48% HBr; (b) NaCN; (c) KOH; (d) SOCl₂.

The reaction of 2-phenoxyethyl amine (2.17) with 4-methyl-3-pentenoyl chloride (2.43) and 4-methyl pentanoyl chloride
(2.47) in dry benzene using pyridine to bind the HCl formed gave juvenile hormone like substances (7-methyl-3-aza-4-oxo-6-octenyloxy)benzene (2.20) and (7-methyl-3-aza-4-oxo-octyloxy) benzene (2.26). A similar reaction of the amines (2.18 and 2.19) with the acid chloride (2.43 and 2.47) furnished the products (2.21, 2.22, 2.27 and 2.28).

It has been observed in literature that epoxides of various JH like substances generally increase the JH activity. The above compounds (2.20-2.22) containing the double bond were therefore subjected to epoxidation with 3-chloroperbenzoic acid. The reaction went smoothly to form the corresponding epoxides (6, 7-epoxy-7-methyl-3-aza-4-oxo-octyloxy)benzene (2.23) and its p-substituted products (2.24 and 2.25). Attempts to N-methylate the epoxy compounds with CH₃I in different conditions were unsuccessful.

The identification of all the above compounds was done by elemental analysis and spectroscopic studies. The salient features of proton magnetic resonance studies of the JH analogues prepared above are discussed below:

**PMR Studies:**

The PMR spectra of the above compounds (2.20-2.28) were recorded in CDCl₃ or CCl₄ solutions on the EM-390 spectrometer at 90 MHz and the data are presented in table 2.2.
Table 2.2: PMR Spectral Data of JH Analogues:

<table>
<thead>
<tr>
<th>Name of Compound</th>
<th>Compound No.</th>
<th>PMR Data (δ values)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(7-Methyl-3-aza-4-oxo-6-Octenyloxy) benzene.</td>
<td>2.20</td>
<td>7.0-7.52 (5H, Ar-H); 5.4 (1H, olefinic H)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4.1 (t, 2H, -OCH₂⁻); 3.75 (t, 2H, -CH₂-NH⁻);</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3.0 (d, 2H, -CO-CH₂⁻); 1.65 (s, 6H, gem dimethyl).</td>
</tr>
<tr>
<td>4-Chloro-1-(7-methyl-3-aza-4-oxo-6-octenyloxy) benzene.</td>
<td>2.21</td>
<td>6.75-7.4 (4H, Ar-H); 5.35 (1H, olefinic H);</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4.05 (t, 2H, -OCH₂⁻); 3.75 (t, 2H, -CH₂-NH⁻);</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3.03 (d, 2H, -COCH₂⁻); 1.65 (s, 6H, gem dimethyl).</td>
</tr>
<tr>
<td>4-Methyl-1-(7-methyl-3-aza-4-oxo-6-octenyloxy) benzene</td>
<td>2.22</td>
<td>6.8-7.25 (4H, Ar-H); 5.35 (t, 1H, olefinic H);</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4.01 (t, 2H, -OCH₂⁻); 3.7 (t, 2H, -CH₂-NH⁻);</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3.03 (d, 2H, -C-CH₂⁻); 2.35 (3H, CH₂-Ar); 1.65 (s, 6H, gem dimethyl).</td>
</tr>
<tr>
<td>(6,7-Epoxy-7-methyl-3-aza-4-oxo-octyloxy) benzene</td>
<td>2.23</td>
<td>6.9-7.55 (5H, Ar-H); 4.15 (2H, -OCH₂⁻);</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3.5 (2H, -CH₂-NH⁻); 3.35 (1H, -H-C=O-C=);</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.65 (2H, -CO-CH₂⁻); 1.3 (d, 6H, gem dimethyl).</td>
</tr>
<tr>
<td>Name of Compound</td>
<td>Compound No.</td>
<td>PMR Data (δ values)</td>
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<tr>
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</tr>
<tr>
<td>4-Chloro-1-(6,7-epoxy-7-methyl-3-aza-4-oxo-octyloxy)benzene</td>
<td>2.24</td>
<td>6.75-7.5 (4H, Ar-H); 4.08 (t, 2H, -OCH&lt;sub&gt;2&lt;/sub&gt;-); 3.58 (t, 2H, -CH&lt;sub&gt;2&lt;/sub&gt;-NH-); 3.31 (1H, C&lt;sup&gt;-&lt;/sup&gt;-C); 2.65 (2H, -CO-CH&lt;sub&gt;2&lt;/sub&gt;-); 1.3 (d, 6H, gem dimethyl).</td>
</tr>
<tr>
<td>4-Methyl-1-(6,7-epoxy-7-methyl-3-aza-4-oxo-octyloxy)benzene</td>
<td>2.25</td>
<td>6.7-7.5 (4H, Ar-H); 4.01 (2H, -OCH&lt;sub&gt;2&lt;/sub&gt;-); 3.58 (2H, -CH&lt;sub&gt;2&lt;/sub&gt;-NH-); 3.31 (1H, -C&lt;sup&gt;-&lt;/sup&gt;-C); 2.65 (2H, -CO-CH&lt;sub&gt;2&lt;/sub&gt;-); 2.3 (s, 3H, Ar-CH&lt;sub&gt;3&lt;/sub&gt;); 1.3 (d, 6H, gem dimethyl).</td>
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<tr>
<td>(7-Methyl-3-aza-4-oxo-octyloxy)benzene</td>
<td>2.26</td>
<td>7.0-7.5 (5H, Ar-H); 6.2 (1H, -NH-); 4.15 (t, 2H, -OCH&lt;sub&gt;2&lt;/sub&gt;-); 3.75 (t, 2H, -CH&lt;sub&gt;2&lt;/sub&gt;-NH-); 2.25 (t, 2H, -COCH&lt;sub&gt;2&lt;/sub&gt;-); 1.5 (m, 2H, -CH&lt;sub&gt;2&lt;/sub&gt;-CH&lt;sub&gt;2&lt;/sub&gt;-CH&lt;sub&gt;2&lt;/sub&gt;-CH&lt;sub&gt;2&lt;/sub&gt;-); 1.3 (m, 1H, -CH&lt;sub&gt;3&lt;/sub&gt;-); 0.95 (d, 6H, gem dimethyl).</td>
</tr>
<tr>
<td>4-Chloro-1-(7-methyl-3-aza-4-oxo-octyloxy)benzene</td>
<td>2.27</td>
<td>6.8-7.4 (4H, Ar-H); 6.25 (1H, -NH-); 4.01 (t, 2H, -OCH&lt;sub&gt;2&lt;/sub&gt;-); 3.78 (t, 2H, -CH&lt;sub&gt;2&lt;/sub&gt;-NH-); 2.23 (t, 2H, -CO-CH&lt;sub&gt;2&lt;/sub&gt;-); 1.5 (q, 2H, -CH&lt;sub&gt;2&lt;/sub&gt;-CH&lt;sub&gt;2&lt;/sub&gt;-CH&lt;sub&gt;2&lt;/sub&gt;-CH&lt;sub&gt;2&lt;/sub&gt;-); 1.3 (m, 1H, -CH&lt;sub&gt;3&lt;/sub&gt;-); 0.95 (d, 6H, gem dimethyl).</td>
</tr>
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Table 2.2 Contd...

<table>
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<tr>
<th>Name of the Compound</th>
<th>Compound No.</th>
<th>PMR Data ( δ values )</th>
</tr>
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<tbody>
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<td>4-Methyl-1-(7-methyl-3-aza-4-oxo-octyloxy)benzene</td>
<td>2.28</td>
<td>6.8-7.3(4H, Ar-H); 6.2(1H, -NH); 4.01(t, 2H, -O-CH₂-); 3.75(t, 2H, -CH₂-NH-); 2.25-2.30(5H, -OCH₂-, Ar-CH₃); 1.3-1.5(3H, -CH₂-CH₂); 0.95(d, 6H, gem dimethyl).</td>
</tr>
</tbody>
</table>
Considerable amount of work on the effect of substituents on the chemical shift of aromatic protons in benzene derivatives has been reported in literature\(^{(161)}\). Introduction of various substituents into the benzene nucleus results in characteristic chemical shifts at the ortho, meta and para-positions, and the magnitude of the latter two is related approximately to Hammett's substituent constant\(^{(162-166)}\). In meta and para disubstituted benzenes the substituent effects are approximately additive\(^{(167)}\).

In the PMR spectra of compounds (2.20, 2.23 and 2.26) in which there was no substituent at the para position of the benzene ring, a 5H complex signal was observed at approximately 7.0-7.5\(\delta\). When a chloro substituent was introduced in the above compounds the four aromatic protons in compounds (2.21, 2.24 and 2.27) were observed at 6.85-7.35\(\delta\) which could easily be split up into two different complexes, one at 6.85-7.0\(\delta\) (2H) due to two protons ortho to the ethereal oxygen and the other at 7.2-7.35\(\delta\) (2H) which could be attributed to two protons ortho to chloro group. In the spectra of compounds (2.22, 2.25 and 2.28) in which there was a methyl group at p-position, the 4-aromatic protons could again be observed at 6.85-7.0\(\delta\) (2H) due to two protons ortho to ethereal oxygen and at 7.10-7.25\(\delta\) (2H) due to two protons ortho to methyl group.

The two protons of phenoxyethylene group (Ar-O-CH\(_2\)-)
were observed as a triplet between 4.01-4.15 $\delta$ in all the above compounds, as expected. The methylene protons next to phenoxy methylene group attached directly to NH - $^0$O - group appeared as a triplet at almost 3.7-3.75 $\delta$ in all the above compounds, except the epoxy derivatives in which they appeared at 3.5-3.58 $\delta$. The values of chemical shifts of methylene protons in compounds of the type y-CH$_2$-X can be predicted by applying Shoolery rules(168). The Shoolery rules can be expressed as follows:

$$
\delta = 0.23 + \Sigma a
$$

where 'a' is the shielding constant of various groups 'X' and 'y'(169-170). While the observed values of Ar - O - CH$_2$ protons were very close to those calculated on the basis of Shoolery's rules, the chemical shift of - CH$_2$ - NH - $^0$O - was significantly below the value expected from compounds of the type R-CH$_2$-NH-$^0$O - where R is an alkyl group. It therefore appears that Ar-O-CH$_2$- group deshields the methylene group considerably and has a negative shielding constant of about 0.4-0.45 ppm. Further, the epoxide group present in compounds (2.23-2.25) seems to exert a lesser deshielding effect compared to double bond on the - CH$_2$ - NH - $^0$O - methylene protons shifting these protons upfield from 3.75 to 3.5 $\delta$ in (2.23) and to 3.58 $\delta$ in (2.24 and 2.25).
The methylene protons flanked by C - NH - group on one side and a double bond on the other side in compounds (2.20-2.22) appeared around 3.03 \( \delta \) which shifted upfield to about 2.65 \( \delta \) in compounds (2.23-2.25) where the double bond had been epoxidated. It shows that epoxide ring exerts lower deshielding effect than the double bond.

The olefinic proton in (2.20-2.22) was observed at 5.35-5.40 \( \delta \). However, on epoxidation this proton was observed much higher field at 3.35 \( \delta \) in compounds (2.23-2.25). The six protons of the terminal gem dimethyl group in compounds (2.20-2.22), appeared at 1.65 \( \delta \). In the case of epoxides (2.23-2.25) the six protons of the terminal gem dimethyl group appeared higher field at 1.3 \( \delta \) suggesting once again that the epoxide function exerts lower deshielding effect than the double bond.

In the spectra of the compounds (2.26-2.28) the terminal gem dimethyl group was observed at 0.95 \( \delta \) as a doublet \((J = 6Hz)\). The tertiary proton was observed as a multiplet at 1.3 \( \delta \) and the methylene group next to tertiary carbon was observed at 1.5 \( \delta \) as a multiplet. In compound (2.28) the tertiary proton and the methylene protons could not be observed as separate signal but was a 3H complex between 1.3-1.5 \( \delta \).
Treatment of 2-phenoxyethyl amines (2.17-2.19) with 4-methyl-2-pentenoyl chloride (2.48) furnished the products (7-methyl-3-aza-4-oxo-5-octenyloxy)benzene (2.49) and its p-substituted derivatives (2.50 and 2.51). 4-Methyl-2-pentenoyl chloride (2.49) was obtained by treatment of 4-methyl-2-pentenoic acid (2.41) with thionyl chloride. These products differed from compounds (2.20-2.22) by the position of double bond (Fig. 2.6). The identification of the above compounds was done by elemental analysis and spectroscopic studies.

Fig. 2.6

\[ \text{Reagents: (a)} \]

\[ (2.48) \]

\[ 2.17, 2.49 \quad R = H. \]

\[ 2.18, 2.50 \quad R = Cl. \]

\[ 2.19, 2.51 \quad R = CH_3 \]

\[ (2.17-2.19) \quad \xrightarrow{a} \quad (2.49-2.51) \]
Synthesis of Above Type of Compounds with Side Chain Shortened by One Carbon Atom:

A brief review of structure activity relationship in juvenoids is given in the book "Insect Hormones and Bio-analogues" by K. Slama; M. Romanuk and F. Sorm(171). Shortening or prolongation of the chain by a single or more carbon atoms has been reported to decrease the activity in sesammax type compounds, when the compounds were treated on Tenebrio(172-173). However, in certain insect species such as Pyrrhocorisd, juvabione or aromatic derivatives of juvabione having shortened side chain were approximately equal in activity, as also aromatic geranyl ethers having somewhat longer side chain or long chain aromatic farnesyl ethers(171). It therefore appears that the effect of shortening or prolongation of side chain might depend upon the type of juvenoid used and the insect species.

In view of this observation it was decided to synthesize (6-methyl-4-oxo-3-aza-5-heptenyloxy)benzene (2.52) and related compounds which would be one atom shorter than the normal length of compounds of the type (2.6). For this the following route was adopted (Fig. 2.7).
Fig. 2.7

Reagents:
(a) $\begin{array}{c} O \\ Cl \end{array}$
(b) $\begin{array}{c} O \\ ClC_6H_4 \end{array}$
(c) $\begin{array}{c} O \\ Cl \end{array}$

In this series the reaction of amines (2.17-2.19) with 3-methyl-2-butenoyl chloride (2.61) gave the amides (2.51-2.54).
which on epoxidation with 3-chloroperbenzoic acid afforded the products (2.55-2.57). Similar reaction of amines (2.17-2.19) with 3-methyl butanoyl chloride (2.62) afforded the products (2.58-2.60). The above acid chlorides (2.61 and 2.62) were obtained by treatment of 3-methyl-2-butenoic acid and 3-methyl butanoic acid with thionyl chloride.

The identification of all the above compounds was done by elemental analysis and spectroscopic studies. The salient features of proton magnetic resonance studies are discussed below:

PMR Studies:

The PMR spectra of compounds (2.52-2.60) were recorded in CDCl₃ or CCl₄ solutions. The PMR spectra of compounds (2.20-2.28) on page 82 (Table 2.2) have already been discussed above. The present compounds differed from the above compounds only in the nature of acyl group attached to nitrogen. The PMR spectra of these compounds differed from the above compounds in the following positions.

1. The olefinic proton in (2.52-2.54) appeared at 5.5 - 5.68 δ while in compounds (2.20-2.22) it had been observed at 5.35-5.40 δ. The lower field value of olefinic proton in (2.52-2.54) is attributed to the direct attachment of - C - NH- group on one side.
<table>
<thead>
<tr>
<th>Name of the Compound</th>
<th>Compound No.</th>
<th>PMR Data ( δ values )</th>
</tr>
</thead>
<tbody>
<tr>
<td>(6-Methyl-3-aza-4-oxo-5-heptyloxy)benzene</td>
<td>2.52</td>
<td>6.98-7.32(5H, Ar-H); 5.68(s, 1H, olefinic H); 4.01(t, 2H, -OCH₂-); 3.68(t, 2H, -CH₂-NH-); 2.18(s, 3H, Cis-CH₃); 1.8(s, 3H, trans-CH₃).</td>
</tr>
<tr>
<td>4-Chloro-1-(6-methyl-3-aza-4-oxo-5-heptyloxy)benzene</td>
<td>2.53</td>
<td>6.75-7.28(4H, Ar-H); 5.65(s, 1H, olefinic H); 3.98(t, 2H, -OCH₂-); 3.68(t, 2H, -CH₂-NH-); 2.18(s, 3H, Cis-CH₃); 1.8(s, 3H, trans-CH₃).</td>
</tr>
<tr>
<td>4-Methyl-1-(6-methyl-3-aza-4-oxo-5-heptyloxy)benzene</td>
<td>2.54</td>
<td>6.9-7.2(4H, Ar-H); 5.65(s, 1H, olefinic H); 4.01(t, 2H, -OCH₂-); 3.7(t, 2H, -CH₂-NH-); 2.31(s, 3H, Ar-CH₃); 2.2(s, 3H, Cis-CH₃); 1.85(s, 3H, trans-CH₃).</td>
</tr>
<tr>
<td>(5,6-Epoxy-6-methyl-3-aza-4-oxo-heptyloxy)benzene</td>
<td>2.55</td>
<td>6.98-7.4(5H, Ar-H); 4.05(t, 2H, -OCH₂-); 3.75(t, 2H, -CH₂-NH-); 3.38(s, 1H, C₂-O⁻C⁻⁻); 1.42(s, 3H, Cis-CH₃); 1.31(s, 3H, trans-CH₃).</td>
</tr>
<tr>
<td>Name of the Compound</td>
<td>Compound No.</td>
<td>PMR Data ( δ values )</td>
</tr>
<tr>
<td>----------------------</td>
<td>-------------</td>
<td>------------------------</td>
</tr>
<tr>
<td>4-Chloro-1-(5,6-epoxy-6-methyl-3-aza-4-oxo-heptyloxy)benzene</td>
<td>2.56</td>
<td>6.85-7.48(4H, Ar-H); 4.01(t, 2H, -OCH₂-); 3.75(t, 2H, -CH₂-NH-); 3.38(s, 1H, -CO₂H); 1.42(s, 3H, cis-CH₃); 1.31(s, 3H, trans-CH₃);</td>
</tr>
<tr>
<td>4-Methyl-1-(5,6-epoxy-6-methyl-3-aza-4-oxo-heptyloxy)benzene</td>
<td>2.57</td>
<td>6.78-7.25(4H, Ar-H); 4.01(t, 2H, -OCH₂-); 3.75(t, 2H, -CH₂-NH-); 3.4(s, 1H, H - C°°-C-); 2.31(s, 3H, Ar-CH₃); 1.41(s, 3H, cis-CH₃); 1.31(s, 3H, trans-CH₃);</td>
</tr>
<tr>
<td>(6-Methyl-3-aza-4-oxo-heptyloxy)benzene</td>
<td>2.58</td>
<td>6.9-7.32(5H, Ar-H); 4.01(t, 2H, -OCH₂-); 3.65(t, 2H, -CH₂-NH-); 2.1(d, 2H, -COCH₂-); 1.25(m, 1H, -CH₂-CH); 0.95(t, 6H, gem dimethyl);</td>
</tr>
<tr>
<td>4-Chloro-1-(6-methyl-3-aza-4-oxo-heptyloxy)benzene</td>
<td>2.59</td>
<td>6.85-7.4(4H, Ar-H); 4.01(t, 2H, -OCH₂-); 3.7(t, 2H, -CH₂-NH-); 2.12(d, 2H, -COCH₂-); 1.25(m, 1H, CH₂-CH); 0.95(d, 6H, gem dimethyl);</td>
</tr>
<tr>
<td>4-Methyl-1-(6-methyl-3-aza-4-oxo-heptyloxy)benzene</td>
<td>2.60</td>
<td>6.72-7.2(4H, Ar-H); 4.05(t, 2H, -OCH₂-); 3.65(t, 2H, -CH₂-NH-); 2.25(s, 3H, Ar-CH₃); 2.1(d, 2H, -COCH₂-); 1.2(m, 1H, -CH₂-CH); 0.95(d, 6H, gem dimethyl);</td>
</tr>
</tbody>
</table>
2. The 6 protons of the terminal gem dimethyl group in (2.52-2.54) were observed as two distinct sharp singlets (3H) because of the different configuration on double bond with respect to the carbonyl group. The cis-methyl group appeared at a lower field around 2.18-2.20 $\delta$ while the trans methyl group appeared around 1.80-1.85 $\delta$. Nearly same values have been reported for such cis and trans methyl groups in Ketones(174). Similarly in the epoxy compounds (2.55-2.57) the 6 protons of the terminal gem dimethyl group again showed two distinct 3H signals because here the rigid epoxide ring makes the configuration of the two methyl groups different with respect to carbonyl group. The methyl group cis to carbonyl group appeared slightly lower field at 1.42 $\delta$ while the trans methyl group appeared at 1.31 $\delta$. 
Biological Activities of (6-methyl-3-aza-4-oxo-5-heptyloxy) benzene (2.52):

Compounds of the type (2.6) have been shown to possess JH activity against various insect species (table 2.1). However, not much work seems to have been done on the synthesis of above type of compounds in which a hetero atom might have been incorporated in the side chain. Since we were contemplating to synthesize various JH like compounds of the above type by introduction of nitrogen atom in the form of amide function, we thought it desirable to undertake biological testing of one representative. (6-Methyl-3-aza-4-oxo-5-heptenyloxy) benzene (2.52) was tested for JH/insecticidal/chemosterilizing activity against potato tuber moth. The investigation was undertaken with the help of the Department of Bio-Sciences, Himachal Pradesh University, Shimla.

Materials and Methods:

Potato tuber moth, both sexes, were maintained on fresh potato/potato leaves in petridishes with covers, and bottles with muslin covers, in the laboratory under normal environmental conditions (ambient temperature 16-20°). These were kept under constant watch for the egg laying.

The eggs were collected and four sets (A,B,C and D) of control and treated eggs were prepared. Each petridish
contained 50 eggs on a filter paper round and slices of potatoes. Similarly larvae and pupae were obtained and were maintained for treatment. The compound was dissolved in 50% acetone to obtain solutions with concentration of 50 ug/ml, 25 ug/ml and 10 ug/ml respectively. Thus in each case the sets were managed as under.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Normal Controls</th>
<th>10 ug (B)</th>
<th>25 ug (C)</th>
<th>50 ug (D)</th>
</tr>
</thead>
<tbody>
<tr>
<td>egg</td>
<td>Untreated (A)</td>
<td>50</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>Larvae</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Pupa male</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Pupa female</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
</tr>
</tbody>
</table>

1 ml Acetone solution containing the compound was poured on the filter paper in each petridish and allowed to evaporate. Later the counted number of eggs/larvae/pupae to be treated were transferred to the petridishes.

Compound treatment through potato slices was also tried in which 1 ml of the compound solution was poured on two potato slices. After evaporation of acetone, counted number of specimen of the particular developmental stage were placed between them and maintained in jars covered with black muslin.
cloth. Fresh potato leaves were provided in each jar. In the control sets (A) 50% acetone without the compound was used.

**Results and Discussion:**

At a dose rate of 10 ug/ml, the eggs developed into normal larvae and pupae but at a dose rate of 25 ug/ml, various morphological changes were observed. The treated eggs developed into larvae with abnormal wings, generally short and curled. Their segments were fragile and the puparium was either perforated or was not fully formed. All these changes point to positive JH activity of the compound. Mortality rate was quite low. Similar but acute morphological changes were observed at a dose rate of 50 ug/ml. However, at a dose rate of 100 ug/ml the mortality rate in case of larvae and pupae was very high indicating that this compound can be a useful third generation pesticide.

To confirm the JH like activity of the compound, a histological investigation on the gonads of potato tuber moth was undertaken. The preliminary results have clearly revealed induction of numerous abnormalities not only in the morphology of the ovarioles but also in the structure of oocytes. Hematoxylin-eosin and Gomosis Trichrome staining methods have been employed to study these abberations, some of which are discussed below:
With 10 μg/ml treatment the female pupae exhibit alterations in the shape of the oocytes which do not present the normal oval structure. The epithelial layer is no longer regular in its appearance and may be more than a monolayer structure. Some of the oocytes exhibit abnormally large trophocytes, whereas others are devoid of the same. A few oocytes also depict one or more finger-like projections which involve the formation of cytoplasmic extensions. In some cases the interfollicular tissue forms a very thin partition between the two succeeding oocytes while at some places a thick multilayered plug-like structure is visualized. In a few specimen segregation of oocytes in the ovarioles has also been observed.

After 25 μg/ml treatment the histological profile of the ovarioles is grossly altered. The outer epithelial layer of the oocytes is usually interrupted at one or more places. In numerous oocytes the epithelial cells lose their structural integrity and get condensed to form a dense hematoxylin +ve membrane which is ruptured or broken. The oocytic cytoplasm may either get condensed to leave an empty space at one end of the oocyte or may form one or many vacuoles within. The germinal vesicle becomes highly basophilic. The number of cytoplasmic extensions is very large in many oocytes. Interfollicular tissue separating the successive oocytes is usually absent or may exhibit a feeble presence.
With 50 ug/ml treatment the above changes appear highly aggravated and no normal oocyte is seen in any ovariole. The epithelial cell layer, the cytoplasm, the germinal vesicle and the interfollicular tissue exhibit structural aberrations without exception. The germinal vesicle in the oocytes wherever observed in the sections, exhibits a multinucleolar condition and in many cases the oocyte is bi or multinucleate.

This is a preliminary study and the detailed results will be presented later.
Experimental:

2-Phenoxyethyl bromide (2.11):

In a 250 ml round bottom flask, a mixture of 1, 2-dibromo ethane (75.2 g; 400 mmol) and phenol (2.8; 18.8 g; 200 mmol) was heated to boiling in an oil bath. A solution of sodium hydroxide (8.8 g; 220 mmol) in 50 ml water was added to the above solution in small instalments during a period of 30 min. The reaction mixture was then refluxed for 15 hr. It was cooled and the upper layer was discarded. The lower layer was washed with 5% NaOH solution and then with water. It was then distilled under reduced pressure. The first fraction was collected up to 160°/50 mm which consisted of water and unreacted 1,2-dibromo ethane. The next fraction, b.p. 160-165°/50 mm, was 2-phenoxyethyl bromide (2.11; 24.2 g; 60%) Lit(154) b.p. 125-130°/18 mm. The residue contained a little 2-phenoxyethyl bromide and 1,2-diphenoxo ethane which separated out as a solid which was recrystallized from ethanol to get pure 1,2-diphenoxo ethane (5g) m.p. 97-98°, Lit(175) m.p. 98°.

2-(4-Chlorophenoxy)ethyl bromide (2.12):

The reaction of 4-chlorophenol (2.9, 25.7; 200 mmol), 1,2-dibromoethane (75.2 g; 400 mmol) and sodium hydroxide (8.8 g; 220 mmol) as above gave 2-(4-chlorophenoxy)ethyl
bromide (2.12; 24 g; 51%) b.p. 180-185°/40 mm. Rf 0.41 (system a)

PMR : 6.8-7.2 (4H, Ar-H); 4.15 (t, 2H, -OCH2-);
3.3 (t, 2H, -CH2Br).

Anal. Found : C, 40.96; H, 3.10%.

C8H6OClBr requires : C, 40.76; H, 3.39%.

2-(4-Methylphenoxy)ethyl bromide (2.13):

The reaction of 4-methylphenol (2.10; 21.6 g; 200 mmol), 1, 2-dibromoethane (75.2 g; 400 mmol) and sodium hydroxide (8.8 g; 220 mmol) as above furnished 2-(4-methylphenoxy)ethyl bromide (2.13; 21 g; 49%) b.p. 200-205°/45 mm, Rf 0.47 (system a).

Anal. Found : C, 50.05; H, 4.98%.

C9H11OBr requires : C, 50.23; H, 5.11%.

Potassium Phthalimide:

A solution of potassium hydroxide (7.6 g; 135 mmol) in 75% ethanol (30 ml) was added to a solution of phthalimide (20 g; 135 mmol) in anhydrous ethanol (400 ml). The mixture was cooled rapidly, the precipitated potassium phthalimide was filtered off and the filtrate was reheated. More phthalimide (20 g; 135 mmol) was added followed by potassium hydroxide (7.6 g; 135 mmol) in 75% ethanol (30 ml). The whole mixture
was cooled and filtered. The potassium phthalimide so obtained (176) was stirred with acetone, filtered off again and dried in the air (40 g; 80%).

**N-Phenoxyethyl phthalimide (2.14):**

Potassium phthalimide (20.0 g; 108 mmol) was added to a solution of 2-phenoxyethyl bromide (2.11; 20.1 g; 100 mmol) in 40 ml dry DMF. The mixture was refluxed for 4 hr in an oil bath. It was cooled and 100 ml cold water was added. A solid appeared which was filtered and the aqueous phase was extracted with chloroform twice. The solid product was dissolved in chloroform and added to the extraction. The whole organic phase was washed with 0.02 N NaOH to remove unreacted phthalimide and finally with water. The organic layer was dried over anhydrous Na₂SO₄ and the solvent was removed. The solid product obtained was recrystallized from ethanol to get N-phenoxyethyl phthalimide (2.14) as white crystals (20 g; 77%) m.p. 115-116°, Rᵢ 0.95 (system a).

Anal. Found : C, 71.45; H, 4.63; N, 5.11%.
C₁₆H₁₃NO₃ requires : C, 71.91; H, 4.86; N, 5.24%.

**N-(4-Chlorophenoxyethyl)phthalimide (2.15):**

The reaction of 2-(4-chlorophenoxy)ethyl bromide (2.12; 23.5 g; 100 mmol) with potassium phthalimide (20.0 g; 108 mmol)
as above furnished N-(4-chlorophenoxyethyl) phthalimide (2.15)
as a white solid (21.5 g; 72%) m.p. 143-145°, R_f 0.91 (system a).

Anal. Found : C, 63.92; H, 3.74; N, 4.34%.
C_{16}H_{12}O_3NCl requires : C, 63.68; H, 3.98; N, 4.64%.

N-(4-methylphenoxyethyl)phthalimide (2.16) :

The reaction of 2-(4-methylphenoxy)ethyl bromide (2.13; 21.5 g; 100 mmol) with potassium phthalimide (20.0 g; 108 mmol) as above gave N-(4-methylphenoxyethyl) phthalimide (2.16) as a white solid (22.2 g; 78%) m.p. 134-135°, R_f 0.85 (system a).

Anal. Found : C, 72.11; H, 5.45; N, 4.63%.
C_{17}H_{15}O_3N requires : C, 72.59; H, 5.33; N, 4.98%.

2-Phenoxyethyl amine (2.17) :

Finely powdered N-phenoxyethyl phthalimide (2.14; 26.7 g; 100 mmol) was suspended in 100 ml of ethanol containing hydrazine hydrate (5.0 g; 100 mmol). The mixture was warmed which caused separation of gelatinous precipitate. These precipitates were decomposed by warming with excess of conc. HCl (40 ml). A white precipitate separated out which was filtered and washed with water. Ethanol was distilled out from the filtrate. A solid again appeared which was filtered and made strongly alkaline by adding KCH (40 g). The organic layer
was separated out. The aqueous layer was extracted with ether twice. The combined organic layers were dried over KOH pallets. The solvent was removed and the residue was distilled to obtain 2-phenoxyethyl amine (2.17) as a colourless oil (5.2 g; 37%) b.p. 145-147°/50 mm, Lit(177), 104°/12 mm.

PMR

\[7.0-7.3(5H, \text{Ar-H}); \ 3.85(t, 2H, -OCH}_2^-); \ 3.2(m, 2H, -\text{CH}_2-\text{NH}_2 )\].

Anal. Found : C, 69.95; H, 7.95; N, 10.31%.

C\textsubscript{8}H\textsubscript{11}NO requires : C, 70.07; H, 8.02; N, 10.21%.

2-(4-Chlorophenoxy)ethyl amine (2.18) :

The hydrolysis of finely powdered N-(4-chlorophenoxyethyl) phthalimide (2.15, 30.15 g; 100 mmol) as above gave 2-(4-chlorophenoxy)ethyl amine (2.18) as a colourless oil (6 g; 35%) b.p. 170-173°/40 mm.

Anal. Found : C, 55.67, H, 5.53; N, 8.25%.

C\textsubscript{8}H\textsubscript{10}ONCl requires : C, 55.97; H, 5.83; N, 8.16%.

2-(4-Methylphenoxy)ethyl amine (2.19) :

The hydrolysis of finely powdered N-(4-methylphenoxyethyl) phthalimide (2.16; 28.1g; 100 mmol) as above gave 2-(4-methylphenoxy)ethyl amine (2.19) as a colourless liquid (5.5 g; 36%) b.p. 163-165°/40 mm.
Anal. Found : C, 71.24; H, 8.44; N, 8.96%.

C_{9}H_{13}ON requires : C, 71.52; H, 8.60; N, 9.27%.

4-Methyl-2-pentenoic acid (2.41):

To a solution of malonic acid (50 g; 460 mmol) in anhydrous pyridine (50 ml) was added freshly distilled 2-methyl propanal (32 g; 440 mmol). The reaction mixture was stirred at 25° for 24 hr, then at 45° for another 24 hr and finally at 60° for 3 hr. The reaction mixture was chilled and acidified with 6 N H_{2}SO_{4} (200 ml). The upper layer was separated and the lower aqueous layer was extracted with 30 ml portions of benzene. The combined organic layer was dried over anhydrous CaCl_{2}, filtered and the solvent was removed. The residue was distilled to get 4-methyl-2-pentenoic acid (2.41) as a colourless liquid (36 g; 66%), p.b. 135-137°/60 mm. Lit(157) b.p. 113°/20 mm; 104°/10 mm.

4-Methyl-3-pentenoic acid (2.42):

4-Methyl-2-pentenoic acid (2.41; 20 g; 175 mmol) was added to a solution of KOH (120 g; 2.14 mol) in water (250 ml). The reaction mixture was refluxed for 15 hr, cooled and acidified with HCl. The organic layer was separated and the aqueous layer was extracted thrice with 50 ml portions of benzene. The solvent was removed after drying it over Na_{2}SO_{4} and the residue was steam distilled. The organic layer was separated
from the distillate and the aqueous layer was extracted with benzene. The combined organic extract was dried over anhydrous Na$_2$SO$_4$ and distilled to give 4-methyl-3-pentenoic acid (2.42) as a colourless liquid (15 g; 75%) b.p. 130-132$^\circ$/60 mm. Lit(157) b.p. 99-100$^\circ$/10 mm.

4-Methyl-3-Pentenoyl chloride (2.43):

4-Methyl-3-pentenoic acid (2.42; 14.8 g; 130 mmol) was added dropwise with rapid stirring into freshly distilled thionyl chloride (23.8 g; 200 mmol). When the vigorous reaction ceased the reaction mixture was refluxed on water bath for 30 min. The excess of thionyl chloride was distilled off. Dry benzene (50 ml) was then added to the reaction mixture and the distillation continued until all excess SOCl$_2$ was removed with benzene. The residue was distilled to obtain 4-methyl-2-pentenoyl chloride (2.43; 10 g; 58%) b.p. 90-92$^\circ$/65 mm. Lit(157) 62$^\circ$/10 mm.

Isoamyl bromide (2.44):

A mixture of hydrobromic acid (48%; 105 g; 625 mmol) conc. H$_2$SO$_4$ (30.0 g) and isoamyl alcohol (44 g; 500 mmol) was refluxed for 6 hr. After one hr the separation of product was observed as a separate layer and the reaction was complete after 6 hr. The two layers were separated. The lower layer was successively washed with water, 3 ml dilute H$_2$SO$_4$, 10%
Na₂CO₃ solution and finally with water. The product was separated as completely as possible from the aqueous layer, dried over anhydrous CaCl₂ and distilled to give isoamyl bromide (2.44) as a colourless liquid (39 g; 88%) b.p. 112-114°. Lit(158) b.p. 116-120°.

**Isoamyl Cyanide (2.45):**

Finely powdered sodium cyanide (10.8 g; 220 mmol) was taken in 15 ml of water in a flask and warmed on a water bath till all the NaCN dissolved. To this solution was added a solution of isoamyl bromide (2.44; 30 g; 198 mmol) in pure methanol (40 ml). The reaction mixture was refluxed for 15 hr after which another lot of sodium cyanide (10.8 g; 220 mmol) was added and the refluxing continued for another 15 hr. The contents were cooled and the solid NaBr was removed by filtration. The methanol was distilled out from the reaction mixture. 100 ml of H₂O was then added to the residue and the distillation carried out until no more oily drops passed over to the distillate. The upper layer of isoamyl cyanide was separated from the distillate. The crude product was successively washed with conc. HCl, water, NaHCO₃ sol. and finally with water. The organic layer was then dried over anhydrous Na₂SO₄ and distilled to get isoamyl cyanide (2.45) as a colourless liquid (10 g; 51%) b.p. 147-150°, Lit(159) b.p. 154°.
4-Methyl pentanoic acid (2.46):

Isoamyl cyanide (2.45; 24.2 g; 250 mmol) was added to a solution of KOH (28 g; 500 mmol) in water (30 ml). The contents were refluxed for 10 hr and water (50 ml) was added through condenser. Sulfuric acid (50% v/v) was added with external cooling through condenser until the mixture became just acidic. The upper layer of crude product was separated, dried over anhydrous Na₂SO₄ and distilled to get 4-methyl-pentanoic acid (2.46) as a colourless liquid (17 g; 60%) b.p. 190-192°. Lit(159) b.p. 193°.

4-Methyl pentanoyl chloride (2.47):

4-Methyl pentanoic acid (2.46; 15 g; 130 mmol) was added dropwise with stirring into freshly distilled thionyl chloride (23.8 g; 200 mmol). When the vigorous reaction ceased the reaction mixture was refluxed on water bath for 30 min. The excess of thionyl chloride was distilled off. Dry benzene (50 ml) was then added to the reaction mixture and the distillation continued until all excess SOCl₂ was removed with benzene. The residue was distilled to obtain 4-methyl-pentanoyl chloride (2.47) as a colourless liquid (12 g; 69%) b.p. 140-142°, Lit(160) b.p. 144°.

(7-Methyl-3-aza-4-oxo-6-octenyloxy)benzene (2.20):

2-Phenoxyethyl amine (2.17; 2.74 g; 20 mmol) was taken
in 25 ml of dry benzene and pyridine (1.82 g; 20 mmol) was added to it. The mixture was cooled in an ice bath and 4-methyl-3-pentenoyl chloride (2.43; 2.65 g; 20 mmol) was added to it dropwise with constant stirring. The reaction mixture was stirred at room temperature for 5 hr. It was then decomposed with water (10 ml) and the organic layer was separated. The aqueous layer was extracted once with benzene. The combined extracts were washed with H₂O, NaHCO₃ and H₂O again. The solvent was distilled off to leave a residue. The residue was distilled to get (7-methyl-3-aza-4-oxo-6-octenyloxy) benzene (2.20) as a viscous oil (2.5 g; 54%) b.p. 225-227°/40 mm. Rᵣ 0.43 (system c).

PMR : 7.0-7.52 (5H, Ar-H); 5.4 (1H, olefinic H); 4.1 (t, 2H, -OCH₂-); 3.75 (t, 2H, -CH₂-NH-); 3.0 (d, 2H, -COCH₂-); 1.65 (s, 6H, gem dimethyl).

IR : 3304, 1640, 1605, 1540, 1510, 1294 cm⁻¹.

Anal. Found : C, 71.91; H, 8.25; N, 5.85%.

C₁₄H₁₉O₂N requires : C, 72.10; H, 8.15; N, 6.00%.

4-Chloro-1-(7-methyl-3-aza-4-oxo-6-octenyloxy)benzene (2.21) : To a solution of 2-(4-chlorophenoxy)ethyl amine (2.18; 3.4 g; 20 mmol) and pyridine (1.82 g; 20 mmol) in dry benzene (25 ml) was added 4-methyl-3-pentenoyl chloride (2.43; 2.65 g;
20 mmol) at 0° with constant stirring. After another 5 hr stirring at room temperature, it was worked up as above. The solid obtained was recrystallized from dry pet ether: benzene mixture (1:1) to give 4-chloro-1-(7-methyl-3-aza-4-oxo-6-octenyloxy)benzene (2.21) as a white solid (2.5 g; 46%) m.p. 54-56°, Rf 0.29 (system c).

PMR : 6.75-7.4(4H, Ar-H); 5.35(1H, olefinic H); 4.05(t, 2H, -OCH2-); 3.75(t, 2H, -CH2-NH-); 3.03(d, 2H, -CO-CH2-);

IR : 3310, 1644, 1605, 1525, 1520, 1290 cm⁻¹.

Anal. Found : C, 62.94; H, 6.48; N, 5.11%.

C14H18O2NCl requires : C, 62.80; H, 6.72; N, 5.23%.

4-Methyl-1-(7-methyl-3-aza-4-oxo-6-octenyloxy)benzene (2.22) :

The reaction of 2-(4-methylphenoxy)ethyl amine (2.19; 3.0 g; 20 mmol) with 4-methyl-3-pentenoyl chloride (2.43; 2.65 g; 20 mmol) in presence of pyridine as above gave 4-methyl-1-(7-methyl-3-aza-4-oxo-6-octenyloxy)benzene (2.22) which was recrystallized from pet. ether: benzene mixture (1:1) to obtain a white solid (2.6 g; 53%) m.p. 63-64°. Rf 0.27 (system c).

PMR : 6.8-7.25(4H, Ar-H); 5.35(t, 1H, olefinic H); 4.01(t, 2H, -OCH2-); 3.7(t, 2H, -CH2-NH-); 3.03(d, 2H, -CO-CH2-);
2.35(3H, CH$_3$-Ar); 1.65( s, 6H, gem dimethyl).

IR : 3298, 1640, 1595, 1536, 1512, 1293 cm$^{-1}$.

Anal. Found : C, 72.68; H, 8.35; N, 5.86%.

C$_{15}$H$_{21}$O$_2$N requires : C, 72.87; H, 8.50; N, 5.66%.

(6, 7-epoxy-7-methyl-3-aza-4-oxo-octyloxy)benzene (2.23):

A solution of 3-chloroperbenzoic acid (74 mg; 0.42 mmol) in dry methylene chloride (30 ml) was added to the solution of (7-methyl-4-oxo-3-aza-6-octenyloxy)benzene (2.20; 100 mg; 0.42 mmol) in dry methylene chloride (20 ml) at 0$^\circ$. The total addition was done during a period of 20 min. The reaction mixture was stirred at 0$^\circ$ for 2 hr and then at room temperature for 3 hr. It was poured into ice water with vigorous stirring. The organic layer was separated, washed successively with water, saturated solution of Na$_2$CO$_3$ and water again. It was then dried over anhydrous CaCl$_2$ and the solvent was distilled off to leave a residue which was crystallized from methanol to afford (6,7-epoxy-7-methyl-3-aza-4-oxo-octyloxy)benzene (2.23) as a white solid (50 mg; 47%) m.p. 36-38$^\circ$, R$_f$ 0.74 (system c).

PMR : 6.9-7.55(5H, Ar-H); 4.15(2H, -OCH$_2$-);
3.5(2H, -NH-CH$_2$-); 3.35(1H, -C-H-C$_2$);
2.65(2H, -COCH$_2$-); 1.3(d, 6H, gem dimethyl).
4-Chloro-1-(6, 7-epoxy-7-methyl-3-aza-4-oxo-octyloxy)benzene (2.24):

Epoxidation of 4-chloro-1-(7-methyl-3-aza-4-oxo-6-octenyloxy)benzene (2.21; 100 mg; 0.37 mmol) in methylene chloride with 3-chloroperbenzoic acid (64 mg; 0.37 mmol) as above gave 4-chloro-1-(6,7-epoxy-7-methyl-3-aza-4-oxo-octyloxy)benzene (2.24) as a white solid (42 mg; 40%) m.p. 76-78°, Rf 0.81 (system c).

PMR: 6.75-7.5(4H, Ar-H); 4.08(t, 2H, -OCH2-);
3.58(t, 2H, -CH2NH-); 3.32(1H, -C\(^{-}\)H-C\(^{\gamma}\));
2.65(2H, -COCH2-); 1.3(d, 6H, gem dimethyl).

Anal. Found: C, 59.01; H, 6.41; N, 4.65%.

C\(_{14}\)H\(_{18}\)O\(_2\)NCl requires: C, 59.25; H, 6.34; N, 4.93%.

4-Methyl-1-(6, 7-epoxy-7-methyl-3-aza-4-oxo-octyloxy)benzene (2.25): The epoxidation of 4-methyl-1-(7-methyl-3-aza-4-oxo-6-octenyloxy)benzene (2.22; 100 mg; 0.40 mmol) with 3-chloroperbenzoic acid (70 mg; 0.40 mmol) in methylene chloride as above...
gave 4-methyl-1-(6, 7-epoxy-7-methyl-3-aza-4-oxo-octyl)oxy) benzene (2.25) as a white solid (55 mg; 52%) m.p. 98-99°, R_f 0.78 (system c).

PMR : 6.75-7.5(4H, Ar-H); 4.01(t, 2H, -OCH_2-); 3.58(t, 2H, -CH_2NH-); 3.31(1H, -CO; -C_2); 2.65(2H, -COCH_2-); 2.3(s, 3H, Ar-CH_3); 1.3(d, 6H, gem dimethyl).

Anal. Found : C, 58.21; H, 7.63; N, 5.51%.

C_{15}H_{21}O_3N requires : C, 68.44; H, 7.98; N, 5.32%

(7-Methyl-3-aza-4-oxo-octyl)oxy)benzene (2.26) :

2-Phenoxyethyl amine (2.17; 2.74 g; 20 mmol) and pyridine (1.8 g; 20 mmol) were taken in dry benzene (25 ml) and 4-methyl pentanoyl chloride (2.47; 2.7 g; 20 mmol) was added to it dropwise with constant stirring at 0°. After another 3 hr stirring at room temperature it was worked up as above to give (7-methyl-3-aza-4-oxo-octyl)oxy)benzene (2.26) as a white crystalline solid (2.3 g; 49%) m.p. 50-51°, R_f 0.41 (system c).

PMR : 7.0-7.5(5H, Ar-H); 6.28(1H, -NH-C-); 4.15(t, 2H, -OCH_2-); 3.75(t, 2H, -CH_2NH-); 2.25(t, 2H, -CO-CH_2-); 1.5(m, 2H, -CH_2-CH_3-); 1.3(m, 1H, -CH_3); 0.95(d, 6H, gem dimethyl).
IR : 3298, 1629, 1602, 1536, 1494, 1305 cm⁻¹.

Anal. Found : C, 71.15; H, 8.75; N, 5.65%.

C₁₄H₂₁NO₂ requires : C, 71.48; H, 8.93; N, 5.95%.

4-Chloro-1-(7-methyl-3-aza-4-oxo-octyloxy)benzene (2.27) :

To a solution of 2-(4-chlorophenoxy) ethylamine (2.18; 3.4 g; 20 mmol) and pyridine (1.8 g; 20 mmol) in dry benzene (25 ml) was added 4-methyl pentanoyl chloride (2.47; 2.7 g; 20 mmol). The mixture was stirred at room temperature for 3 hr. It was then worked up as above to afford 4-chloro-1-(7-methyl-3-aza-4-oxo-octyloxy)benzene (2.27) as a white crystalline solid (2.8 g; 58%), m.p. 80-82°C, R_f 0.25 (system c).

PMR : 6.8-7.4 (4H, Ar-H); 6.25 (1H, -NH-);
   4.01 (t, 2H, -OCH₂-); 3.78 (t, 2H, CH₂NH);
   2.23 (t, 2H, -CO-CH₂-); 1.5 (q, 2H, -CH₂CH₂-);
   1.3 (m, 1H, -CH₃); 0.95 (d, 6H, gem dimethyl).

IR : 3252, 1632, 1596, 1554, 1492, 1282 cm⁻¹.

Anal. Found : C, 61.95; H, 7.22; N, 5.01%.

C₁₄H₂₀NO₂Cl requires : C, 62.33; H, 7.42; N, 5.19%.
4-Methyl-1-(7-methyl-3-aza-4-oxo-octyloxy)benzene (2.28):

2-(4-Methylphenoxy)ethyl amine (2.19; 3.0 g; 20 mmol) and pyridine (1.8 g; 20 mmol) were taken in dry benzene (25 ml) and 4-methyl pentanoyl chloride (2.47; 2.7 g; 20 mmol) was added to it. The mixture was stirred for 3 hr and worked up as above to obtain 4-methyl-1-(7-methyl-3-aza-4-oxo-octyloxy)benzene (2.28) as a crystalline white solid (2.8 g; 57%) m.p. 69-70°, Rf 0.30 (system c).

PMR: 6.8-7.3(4H, Ar-H); 6.2(1H, -NH); 4.01(t, 2H, -OCH2-); 3.75(t, 2H, -CH2-NH-); 2.25-2.30(5H, -OCH2-; Ar-CH3); 1.3-1.5(3H, -CH2-CH); 0.95(d, 6H, gem dimethyl).

IR: 3304, 1632, 1595, 1536, 1512, 1296 cm⁻¹.

Anal. Found: C, 72.05; H, 9.05; N, 5.45%.

C₁₅H₂₂N₂O₂ requires: C, 72.28; H, 9.23; N, 5.62%.

4-Methyl-2-pentenoyl chloride (2.48):

The treatment of 4-methyl-2-pentenoic acid (2.41; 10 g; 88 mmol) with thionyl chloride (15.5 g; 130 mmol) as above gave 4-methyl-2-pentenoyl chloride (2.48) as a colourless liquid (7 g; 60%) b.p. 90-93°/60 mm, Lit(157) b.p. 67°/20 mm.
(7-methyl-3-aza-4-oxo-5-octenyloxy)benzene (2.49):

The reaction of 2-phenoxyethyl amine (2.17; 2.74 g; 20 mmol) with 4-methyl-2-pentenoyl chloride (2.48; 2.65 g; 20 mmol) as above gave (7-methyl-3-aza-4-oxo-5-octenyloxy)benzene (2.49) as an oily liquid (2.1 g; 45%) b.p. 230-235°/60 mm. Rf 0.52 (system a).

PMR: 6.8-7.3(5H, Ar-H); 5.9(s, 1H, -COCH=); 5.6(s, 1H, -CCCH = CH-); 4.0(t, 2H, -OCH2-); 3.7(t, 2H, -CH2-NH-); 2.3(m, 1H,=CH=CH ); 0.98(d, 6H, gem dimethyl).

IR: 3304, 1655, 1605, 1545, 1520, 1290 cm⁻¹.

Anal. Found: C, 71.99; H, 8.25; N, 5.95%.

C14H19O2N requires: C, 72.10; H, 8.15; N, 6.00%.

4-Chloro-1-(7-methyl-3-aza-4-oxo-5-octenyloxy)benzene (2.50):

The reaction of 2-(4-chlorophenoxy)ethyl amine (2.18; 3.4 g; 20 mmol) with 4-methyl-2-pentenoyl chloride (2.48; 2.65 g; 20 mmol) as above furnished 4-chloro-1-(7-methyl-3-aza-4-oxo-5-octenyloxy)benzene (2.50) as a white solid (2.7 g; 52%) m.p. 65-67°, Rf 0.63 (system a).

PMR: 6.75-7.35(4H, Ar-H); 5.9(s, 1H, -COCH=CH-); 5.65(s, 1H, -COCH=CH-); 4.05(t, 2H, -OCH2-); 3.73(t, 2H, -CH2NH-);
2.3(m, 1H, =CH–CH ); 0.98(d, 6H, gem dimethyl).

IR : 3295, 1650, 1596, 1540, 1510, 1294 cm⁻¹.

Anal. Found : C, 62.84; H, 6.78; N, 5.41%.

C₁₄H₁₆C₂IN requires : C, 62.60; H, 6.72; N, 5.23%.

4-MethyI-1-(7-methyl-3-aza-4-oxo-5-octenyl oxy)benzene (2.51) :

The reaction of 2-(4-methylphenoxy)ethyl amine (2.19; 3.0 g; 20 mmol) with 4-methyl-2-pentenoyl chloride (2.48; 2.65 g; 20 mmol) as above gave 4-methyl-1-(7-methyl-3-aza-4-oxo-5-octenyl oxy)benzene (2.51) as a white solid (2.8 g; 57%) m.p. 80-82°, Rₖ 0.65 (system c).

PMR : 6.73-7.2(4H, Ar-H); 5.9(s, 1H, -COCH=CH); 5.65(s, 1H, -COCH=CH-); 4.01(t, 2H, -OCH₂-); 3.73(t, 2H, -CH₂NH-);
  2.3(m, 1H, =CH–CH ); 2.25(s, 3H, Ar-CH₃);
  0.99(d, 6H, gem dimethyl).

IR : 3298, 1656, 1595, 1535, 1512, 1292 cm⁻¹.

Anal. Found : C, 72.78; H, 8.85; N, 5.76%.

C₁₅H₂₁O₂N requires : C, 72.87; H, 8.50; N, 5.66%.
3-Methyl-2-butenoyl chloride (2.61) and 3-Methyl butanoyl chloride (2.62):

3-Methyl-2-butenoyl chloride (2.61) b.p. 62-65⁰/35 mm Lit(178), b.p. 59-61⁰/30 mm and 3-methyl butanoyl chloride (2.62) b.p. 110-112⁰, Lit(179), b.p. 116-117⁰ were prepared from 3-methyl-2-butenolic acid and 3-methyl butanoic acid as above respectively.

(6-Methyl-3-aza-4-oxo-5-heptenyloxy)benzene (2.52):

2-Phenoxyethyl amine (2.17; 2.74 g; 20 mmol) was taken in 30 ml of dry benzene and pyridine (1.82 g; 20 mmol) was added to it. The mixture was cooled in an ice bath and 3-methyl-2-butenoyl chloride (2.61; 2.4 g; 20 mmol) was added to it dropwise with constant stirring. The reaction mixture was stirred at room temperature for 5 hr. It was then decomposed with water (20 ml) and the organic layer was separated. The aqueous layer was extracted once with benzene. The combined extract was washed with water, NaHCO₃ and water again. The solvent was distilled off to leave a residue. To the residue was added pet ether (60-80⁰) which precipitated a solid. The solid was recrystallized from pet ether : benzene mixture (1:1) to obtain (6-methyl-3-aza-4-oxo-5-heptenyloxy) benzene (2.52) as a crystalline white solid (2.6 g; 59%) m.p. 64-65⁰, R₇ 0.52 (system c).
PMR : 6.98-7.32 (5H, Ar-H); 5.68 (s, 1H, olefinic H); 4.01 (t, 2H, -OCH₂-); 3.68 (t, 2H, -CH₂NH-); 2.18 (s, 3H, Cis-CH₃); 1.8 (s, 3H, trans-CH₃).

IR : 3304, 1632, 1599, 1536, 1293 cm⁻¹.

Anal. Found : C, 71.05; H, 7.55; N, 6.15%

C₁₅H₁₇O₂N requires : C, 71.23; H, 7.76; N, 6.39%.

4-Chloro-1-(6-methyl-3-aza-4-oxo-5-heptenyloxy)benzene (2.53):

The reaction of 2-(4-chlorophenoxy)ethyl amine (2.18; 3.4 g; 20 mmol) with 3-methyl-2-butenoyl chloride (2.61; 2.4 g; 20 mmol) in presence of pyridine (1.82 g; 20 mmol) gave 4-chloro-1-(6-methyl-3-aza-4-oxo-5-heptenyloxy)benzene (2.53) as a white needle shaped solid (2.4 g; 48%) m.p. 103-105°, Rᵢ 0.58 (system c).

PMR : 6.75-7.28 (4H, Ar-H); 5.65 (s, 1H, olefinic H); 3.98 (t, 2H, -OCH₂-); 3.68 (t, 2H, -CH₂NH-); 2.18 (s, 3H, Cis-CH₃); 1.8 (s, 3H, trans-CH₃).

IR : 3228, 1629, 1602, 1545, 1295 cm⁻¹.

Anal. Found : C, 61.33; H, 6.26; N, 5.35%

C₁₅H₁₆O₂NCl requires : C, 61.53; H, 6.31; N, 5.52%.
**4-Methyl-1-(6-methyl-3-aza-4-oxo-5-heptyloxy)benzene (2.54):**

The reaction of 2-(p-methylphenoxy)ethyl amine (2.19; 3.0 g; 20 mmol) with 3-methyl-2-butenoyl chloride (2.61; 2.4 g; 20 mmol) in presence of pyridine (1.82 g; 20 mmol) furnished 4-methyl-1-(6-methyl-3-aza-4-oxo-5-heptyloxy)benzene (2.54) as a white solid (2.6 g; 57%) m.p. 80-81°C, Rf 0.51 (system c).

**PMR:**
- 6.9-7.2 (4H, Ar-H);
- 5.65 (s, 1H, olefinic H);
- 4.01 (t, 2H, -OCH₂-);
- 3.75 (t, 2H, -NH₂-);
- 2.31 (s, 3H, Ar-CH₃);
- 2.2 (s, 3H, Cis-CH₃);
- 1.85 (s, 3H, trans-CH₃).

**IR:**
- 3310, 1635, 1596, 1540, 1290 cm⁻¹.

**Anal. Found:**
- C, 71.98; H, 7.95; N, 5.98%.

**C₁₄H₁₉O₂N requires:**
- C, 72.10; H, 8.15; N, 6.00%.

**A solution of 5, 6-Epoxy-6-methyl-3-aza-4-oxo-heptyloxy)benzene (2.55):**

A solution of 3-chloroperbenzoic acid (78 mg; 0.45 mmol) in dry methylene chloride was added to a solution of (6-methyl-3-aza-4-oxo-5-heptyloxy)benzene (2.52; 100 mg; 0.45 mmol) in dry methylene chloride (25 ml) at 0°C. It was then stirred at 0°C for 2 hr and at room temperature for 3 hr. It was then worked up as above to furnish (5, 6-epoxy-6-methyl-3-aza-4-oxo-heptyloxy)benzene (2.55) as a white solid (45 mg; 42%) m.p. 79-80°C, Rf 0.68 (system c).
PMR : 6.98-7.4(5H, Ar-H); 4.05(t, 2H, -OCH$_2$-); 3.75(t, 2H, -CH$_2$-NH-); 3.38(s, 1H, C$_1$-C$_2$); 1.42(s, 3H, Cis-CH$_3$); 1.31(s, 3H, trans-CH$_3$).

Anal. Found : C, 66.18; H, 7.08; N, 5.65%.

C$_{13}$H$_{17}$NO$_3$ requires : C, 66.38; H, 7.23; N, 5.95%.

4-Chloro-1-(5, 6-epoxy-6-methyl-3-aza-4-oxo-heptyloxy)benzene (2.56):

The epoxidation of 4-chloro-1-(6-methyl-3-aza-4-oxo-5-heptenyloxy)benzene (2.53; 100 mg; 0.39 mmol) with 3-chloroperbenzoic acid (67 mg; 0.39 mmol) as above afforded 4-chloro-1-(5, 6-epoxy-6-methyl-3-aza-4-oxo-heptyloxy)benzene (2.56) as a solid (40 mg; 38%) m.p. 135-137°, R$_f$ 0.84 (system c).

PMR : 6.85-7.48(4H, Ar-H); 4.01(t, 2H, -OCH$_2$-); 3.75(t, 2H, -CH$_2$NH-); 3.38(s, 1H, C$_1$-C$_2$); 1.42(s, 3H, Cis-CH$_3$); 1.31(s, 3H, trans-CH$_3$).

Anal. Found : C, 57.58; H, 5.73; N, 5.02%.

C$_{13}$H$_{16}$O$_3$NCl requires : C, 57.88; H, 5.93; N, 5.19%.
4-Methyl-1-(5, 6-epoxy-6-methyl-3-aza-4-oxo-heptyloxy)benzene (2.57):

The epoxidation of 4-methyl-1-(6-methyl-3-aza-4-oxo-5-heptenylloxy)benzene (2.54; 100 mg; 0.42 mmol) with 3-chloroperbenzoic acid (74 mg; 0.42 mmol) gave 4-methyl-1-(5, 6-epoxy-6-methyl-3-aza-4-oxo-heptyloxy)benzene (2.57) as a solid (50 mg; 47%) m.p. 120-121°C, Rf 0.79 (system c).

PMR: 6.78-7.25(4H, Ar-H); 4.01(t, 2H, -OCH₂-); 3.75(t, 2H, -NH-); 3.4(s, 1H, H - C - C ); 2.31(s, 3H, Ar-CH₃); 1.41(s, 3H, Cis-CH₃); 1.31(s, 3H, trans-CH₃).

Anal. Found: C, 67.21; H, 7.43; N, 5.33%.

C₁₄H₁₉O₃N requires: C, 67.46; H, 7.63; N, 5.62%.

(6-Methyl-3-aza-4-oxo-heptyloxy)benzene (2.58):

The reaction of 2-phenoxyethyl amine (2.17; 2.74 g; 20 mmol) with 3-methyl butanoyl chloride (2.62; 2.41 g; 20 mmol) in presence of pyridine (1.82 g; 20 mmol) in dry benzene afforded (6-methyl-3-aza-4-oxo-heptyloxy)benzene (2.58) as a liquid (2.6 g; 60%) b.p. 213-215°C/40 mm, Rf 0.59 (system c).
PMR : 6.9-7.32 (5H, Ar-H); 4.01 (t, 2H, -OCH_2-);
3.65 (t, 2H, -CH_2-NH-); 2.12 (d, 2H, -COCH_2-);
1.25 (m, 1H, -CH-CH ); 0.95 (d, 6H, gem dimethyl).

IR : 3310, 1644, 1599, 1542, 1302 cm^{-1}.

Anal. Found : C, 70.35; H, 8.25; N, 6.25%.

C_{13}H_{19}O_2N requires : C, 70.58; H, 8.59; N, 6.33%.

4-Chloro-1-(6-methyl-3-aza-4-oxo-hexyloxy)benzene (2.59):

The reaction of 2-(4-chlorophenoxy)ethyl amine (2.18; 3.4 g; 20 mmol) with 3-methyl butanoyl chloride (2.62; 2.41 g; 20 mmol) afforded 4-chloro-1-(6-methyl-3-aza-4-oxo-hexyloxy) benzene as a solid (2.3 g; 46%) m.p. 93-94°C, R_f 0.64 (system c).

PMR : 6.85-7.4 (4H, Ar-H); 4.01 (t, 2H, -OCH_2-);
3.7 (t, 2H, -CH_2-NH-); 2.12 (d, 2H, -COCH_2-);
1.25 (m, 1H, -CH-CH ); 0.95 (d, 6H, gem dimethyl).

IR : 3418, 1640, 1545, 1284 cm^{-1}.

Anal. Found : C, 60.91; H, 7.01; N, 5.31%.

C_{13}H_{18}O_2NCl requires : C, 61.05; H, 7.04; N, 5.47%.
4-Methyl-1-(6-methyl-3-aza-4-oxo-heptyloxy)benzene (2.60):

The reaction of 2-(4-methylphenoxy)ethyl amine (2.19; 3.0 g; 20 mmol) with 3-methyl butanoyl chloride (2.52; 2.41 g; 20 mmol) as above afforded 4-methyl-1-(6-methyl-3-aza-4-oxo-heptyloxy)benzene (2.60) as a white solid (2.4 g; 52%) m.p. 75-76°, Rf 0.75 (system a).

PMR: 6.75-7.2 (4H, Ar-H); 4.0 (t, 2H, -OCH2-);
3.65 (t, 2H, -CH2NH-); 2.26 (s, 3H, Ar-CH3);
2.1 (d, 2H, -COCH2-); 1.2 (m, 1H, -CH2-CH);
0.95 (d, 6H, gem dimethyl).

IR: 3298, 1635, 1585, 1539, 1293 cm⁻¹.

Anal. Found: C, 71.34; H, 8.73; N, 5.69%.

C14H21O2N requires: C, 71.48; H, 8.93; N, 5.95%.