PART IV

GENERAL INTRODUCTION
Pain is mankind's oldest enemy and it is also mankind's oldest friend. In general, it may be said that pain is a sensation produced by some external or internal agents, which may menace the integrity of the normal human tissue.

The two principal types of pain are (a) superficial pain and (b) deep pain. Since ancient times attempts have been made to abolish this pain. The Egyptians probably used narcotics during surgery. The Chinese employed Hashish (cannabis indica) for its analgesic properties. Pliny, Dioscorides and Apuleius recommended mandragora (Belladonna alkaloids) for use before operation. Mandragora was in use till the middle of nineteenth century as a pain reliever. Opium and alcohol have been used for many centuries to ease the pain of surgery.

The use of anesthetics for complete and safe abolition of pain in surgery is an achievement of an epoch-making five year period between 1842 and 1847. The first gaseous anesthetic to be discovered was nitrous oxide by Priestley in 1776. In 1795 Pearson controlled the pain of colic by ether inhalation and Beddoes in the next year reported production of deep sleep by ether. In 1818 Farady showed that ether possessed analgesic activity. Ether was first prepared by Valerious Cordus in 1540 but successfully used as an anesthetic agent on 16th October, 1846 by Morton.
The search for other anesthetics was soon under way, chloroform was discovered in 1831 and was tried on animals by Flourens in 1847. In the same year Simpson in Edinburgh successfully tried chloroform anesthesia on human beings.

A period of rapid development now followed and many new anesthetics were introduced. Some important general anesthetics along with their important characteristics are described below.

Nitrous oxide (N$_2$O), diethyl ether (C$_2$H$_5$OC$_2$H$_5$), chloroform (CHCl$_3$), divinyl ether (CH$_2$=CH)$_2$O, cyclopropane (CH$_2$CH$_2$CH$_2$), ethyl chloride (C$_2$H$_5$Cl), ethylene (CH$_2$=CH$_2$), acetylene (CH=CH$_2$), trichloroethylene (Cl.CH=CCl$_2$), fluothane (CHBrCl-CF$_3$), floroxy (trifluoro ethyl vinyl ethane) and halopropene (1,1-2,2 tetrafluoro-3-bromopropene) have also been tried as general anesthetic agents.

Pentothal (Sodium), Thiopental (Sodium):

Pentothal sodium e.g. sodium salt of 5-ethyl-5-(2-amyl)-2-thiobarbituric acid was introduced in 1935 by Lundy(57). It is used as an intravenous anesthetic agent.
21-Hydroxypregnane 3,20-dione succinate:

Hydroxy dione, Viadril:

It is a steroid derivative which has been found to exhibit anesthetic activity (47).

\[
\text{COCH}_2\text{O}_2\left(\text{CH}_2\right)_2\text{COONa}
\]

**LOCAL ANESTHETICS:**

Local anesthetics are drugs that block nerve conduction when applied locally to nerve tissue in appropriate concentration. If the site of application is near the peripheral nerve ending, they prevent nervous reaction in this area. If applied to a central nervous organ, they block the transmission of impulses only from the portion of the central organ involved or stimuli received by it, thus definite local region may be anesthetised without affecting other part of nervous system. Many kinds of compounds interfere with nervous conduction but they often permanently damage the nerve cell. The great practical advantage of the local anesthetics is that their action is reversible; their use is followed by complete recovery in nerve function with no evidence of structural damage of nerve fibers or cells.
The history of the discovery of local anesthetics is no less interesting as compared to that of general anesthetics. The first local anesthetic to be discovered was cocaine, an alkaloid present in the leaves of Erythroxylon coca, a shrub growing in the Andes Mountains at a height of 1500 to 6000 feet above sea level. High priests of several American Indian tribes chewed leaves from this plant and spat the juice on the patient's body at the spot where an operation had to be performed. It made the particular part insensitive to pain. Köller was the first person to introduce cocaine in eye surgery.

During the past seventy years thousands of compounds have been synthesized and tested experimentally. The intensive effort has given us some very potent and comparatively less toxic local anesthetics. This search will continue so long as an ideal anesthetic is not discovered.

An ideal local anesthetic is one whose onset of action is rapid. The duration of the anesthetic effect must be long enough. It should be soluble in water if it is to be injected. It should be stable, should withstand boiling when sterilized and should have a high therapeutic index.

The local anesthesia is classified according to the site of application of the anesthetic agent as follows:
(1) The topical anesthesia-surface application to skin or mucous membrane.

(2) Infiltration anesthesia-injecting the agent into the tissues.

(3) Field-block anesthesia-injecting the agent into the tissue about the periphery of the area to be operated.

(4) Conduction anesthesia-depositing a solution along the course of nerves supplying a portion where elimination of sensation is required.

Chemistry and important properties of commonly used local anesthetics are discussed below:

**Natural anesthetic:**

Cocaine-Benzoyl methyl ecgonine:

![Chemical Structure of Cocaine](image)

The most important action of cocaine clinically is its ability to block nerve conduction upon local application. Cocaine at present is used only in ophthalmology because of its mydriatic action in addition to its local anesthetic activity.
Synthetic anesthetics:

Esters not containing nitrogen in the alcohol part:

(i) Benzocaine (Ethyl-p-amino benzoate)

and Butesine (Butyl-p-amino benzoate):

\[ \text{Benzocaine} \quad \text{Butesine} \]

\[ \text{p-NH}_2 \text{C}_6\text{H}_4\text{-OOCH}_2\text{H}_5 \quad \text{p-NH}_2 \text{C}_6\text{H}_4\text{-OOCH}_2\text{H}_5\]

These are mainly used in dusting powders and in dilute solutions and ointment. Benzocaine was introduced by Ritsert (70).

Esters containing tertiary nitrogen in the alcohol part:

Procaine: Novocaine:

Diethylaminoethyl ester of p-aminobenzoic acid.

\[ \text{p-NH}_2 \text{C}_6\text{H}_4\text{-OOCH}_2\text{CH}_2\text{N(C}_2\text{H}_5)_2 \]

This was introduced by Einhorn and Uhlfelder (34).

Procaine has weak anesthetic action of short duration. It is used for infiltration, nerve block and spinal anesthesia. It is too weak for topical application.

Stovaine: Amylocaine:

Methylethyldimethylamino methylcarbinol benzoate.

\[ \text{It is a local anesthetic with potency and toxicity a little less than that of cocaine. It is irritant and hence can not be used for surface anesthesia.} \]
Esters with secondary nitrogen in the alcohol part:

Butethamine: Monocaine:

2-Isobutylaminoethyl p-aminobenzoate.

\[ p-\text{NH}_2 \cdot \text{C}_6\text{H}_4 \cdot \text{OOCCH}_2 \text{NHCH}_2 \text{CH(CH}_3)_2 \]

It is used for topical or infiltration anesthesia.

Ethers containing nitrogen:

Pramoxine: Tronothane:

4-Butoxyphenyl-(3-morpholino propyl)ether.

\[ p-\text{C}_4\text{H}_9\text{O} \cdot \text{C}_6\text{H}_5 \cdot \text{O} \cdot (\text{CH}_2)_3\text{N} \]

It is well tolerated on the skin and less delicate mucous membrane but not in the eye or in the nose.

Amides:

Lidocaine: Xylocaine: Lignocaine:

Diethylamino-2,6-dimethylacetanilide.

\[
\begin{array}{c}
\text{CH}_3 \\
\text{NHCH}_2 \text{N} \cdot \text{C}_2\text{H}_5 \text{CH}_3 \\
\end{array}
\]

It produces more prompt, more intense, longer lasting, and more extensive anesthesia than an equal concentration of procaine. It is widely used for both topical and injection anesthesia.
Dibucaine: Nupercaine: Percaine:

2-Diethylaminoethylamide of 2-butoxycinchoninic acid:

\[
\begin{align*}
\text{N} & \quad \text{O}_4\text{H}_9 \\
\text{OONHCH}_2\text{CH}_2\text{N(C}_2\text{H}_5)_2
\end{align*}
\]

It is the most potent, most toxic and longest acting of the commonly employed local anesthetics. It is used topically as well as in the form of injection.

Miscellaneous types of local anesthetics.

Diperodon: Dithane:

Di-N-phenylcarbamate of 1-piperidino propane-1,3-diol.

\[
\begin{align*}
\text{CH}_2\text{N} & \\
\text{CHOONH}_6\text{H}_5 & \\
\text{CH}_2\text{CHOONH}_6\text{H}_5
\end{align*}
\]

It is applied topically for the relief of surface pain and irritation of the skin and mucous membrane.

Phenacaine: Halocaine: Tancaine:

Diphenetidine amidine.
It was one of the earliest anesthetics to be introduced. It is equal, to twice as toxic as cocaine. It is mainly used for topical anesthesia of the eye.

**MECHANISM OF ACTION OF LOCAL ANESTHETICS:**

Local anesthetics prevent both the generation and the conduction of the nerve impulse. Their main site of action is the cell membrane, and there is seemingly little action of physiological importance on the axoplasm. Local anesthetics are said to block conduction in nerve fibres through interference with electrical depolarisation.

The effectiveness of a local anesthetic is measured not only by the degree of insensibility of the anesthetised area but also by the duration of its action. Majority of local anesthetics are basic compounds. They are used in the form of their salts most commonly as their soluble hydrochlorides or sulphates. The tissue fluids (pH 7.4) liberates the free bases from these salts. The administration of the free bases has been undertaken in several instances and it has been found that they anesthetised tissues more readily than the corresponding salts but the free bases are frequently oily and easily oxidisable. Hence these stable salts of local anesthetics are used for the sake of greater safety and ease of application.
Structure of cocaine was elucidated by Willstatter who synthesized it and made it possible to get the compound free from isomers (93). Cocaine possesses in addition to local anesthetic properties, some undesirable properties like high toxicity, liability to addiction and cortical stimulation. A number of experiments based on the structural model of cocaine were carried out to determine which of the portions of the molecule were responsible for its local anesthetic action. During this study it was found that either the hydrolysis of the carboxyethyl group $-COOCH_3$ or benzoyl group gave inactive compounds but the restoration of the benzoyl group in the cocaine molecule restored the local anesthetic properties. The importance of the tertiary nitrogen atom was not clear in the significance of the tropene ring system for local anesthetic effect of cocaine.

$\alpha$-Eucaine and $\beta$-Eucaine were the first of the synthetic compounds to come into general use. These are related to open chain compounds of cocaine, retaining the piperidine ring and at least one of the ester groupings.

( $\beta$-Eucaine displaced $\alpha$-Eucaine, which was more toxic )
Basic esters of \textit{p-alkoxybenzoic} acid show greater activity as compared to basic esters of \textit{p-hydroxybenzoic} acid and this activity increases with the increase in size of the alkyl group (26, 27, 36, 61, 71, 72). A large number of basic esters containing heterocyclic rings are also active as local anesthetic. The order of activity increases generally from furan to thiophene and pyrazole to benzene.

(b) \textbf{VARIATION IN THE SIDE CHAIN:}

The length of the side chain has been varied generally upto four carbon atoms. Tertiary amino groups with two unequal alkyl groups (12) and cyclic tertiary amino groups have also been introduced. Steric hindrance in the aromatic ring plays an interesting part in modifying the local anesthetic activity. \textit{\textit{p-Diethylamino ethyl-2,3,5,6-tetramethyl benzoate}} is hydrolysed with difficulty because of steric hindrance, and consequently the duration of action is also prolonged (68).
If oxygen of a basic ester is replaced by NH, a basic amide would be obtained:

\[ \text{ROOR}^1 \quad \text{ROONHR}^1 \]

Ester Amide

**Xylocaine: Lidocaine:**

α-Diethylamino-2,6-dimethylacetanilide synthesized by Lofgren is a very active, stable local anesthetic (34a).

Following the discovery of Xylocaine a very large number of basic amides has been synthesized. Some of these along with relevant references are summarised below:

**Alkylaminoacylanilides** \( \text{ArNO}_2 \text{R}^2 \text{NR}_3 \text{R}_4 \) (33), **N-aryl-**

α-diethylamino acetamides \( \text{RC}_6\text{H}_4\text{NHCOCH}_2\text{NET}_2 \) (4), \( \text{ArNHCOCH}_2\text{NET}_2 \)

(\( \text{Ar}=\text{p-ClC}_6\text{H}_4, \text{p-BrC}_6\text{H}_4, 2,5-\text{Cl}_2\text{C}_6\text{H}_3 \)) (88), piperidino alkanoic acid anilides \( 2,6-\text{Me}_2\text{RC}_6\text{H}_2\text{NHCOZN-pip R}_1\text{R}_2 \)

(\( \text{R}=\text{H}; \text{R}_1=\text{H} \) or \( 2,5-\text{Me}_2; \text{R}_2=4-\text{OH} \) or \( 4-(\text{CH}_2)_3\text{OH} \); \( Z=\text{CH}_2 \) or \( -\text{CH}_2\text{CH}_2 \text{etc.} \)) (89). aromatic acylamides substituted in both ortho positions
4,2,6-R-Me-\(\text{C}_6\text{H}_2\text{ONH}(\text{CH}_2)_{\text{n}}\text{NR}_2\) (R=H or alkoxy; R' = alkyl with 1-4 carbon atoms; n=2 or 3) (40), 2,4-dimethyl-6-bromo-a-diethylamino acetanilide 2,4,6, Me_2, Br. \(\text{C}_6\text{H}_2\text{NHOCCH}_2\text{NEt}_2\) (48), 2,4,6-triisopropyl-a-diethylamino (or other tertiary base) acetanilide 2,4,6-(Me_2CH)_3\(\text{C}_6\text{H}_2\text{NHOCCH}_2\text{X}\) (X=tertiary base as hydrochloride salt), 4-amino-a-diethylamino acetanilide 4-\(\text{H}_2\text{NHNOCCH}_2\text{NEt}_2\) (85), a-(2-methyl-1-piperidyl)-acylanilide (53), N-diethylamino acetyl-4-substituted 2,6-xylidine dioxalate (16), a-diethylamino-4-amino-2,6-dimethyl acetanilide 2,4,6-Me, NH_2, Me-\(\text{C}_6\text{H}_2\text{NHOCCH}_2\text{NEt}_2\) (31), basically substituted acid amides of the type 2,6,-Cl,\(\text{NH}_2\text{C}_6\text{H}_3\text{NHOCCH}_2\text{NR}_2\) (14), a-diethylamino acetanilide derivatives 2,4,6-Me,R,Me,\(\text{C}_6\text{H}_2\text{NHOCCH}_2\text{NEt}_2\) (17), basic acetyl mesidines 2,4,6-Me_3\(\text{C}_6\text{H}_2\text{NHOCCH}_2\text{NR}_1\text{R}_2\) (32), amino acylanilides 2,4,6-Me, R,Me\(\text{C}_6\text{H}_2\text{NHOCCH}_2\text{NEt}_2\) (R=H or Me) (81), substituted-a-diethylamino acetanilides containing alkoxy, arloxy, aralkoxy groups (73), a-diethylamino-2-methyl-6-ethyl acetanilide, 2,6-Me, Et\(\text{C}_6\text{H}_3\text{NHOCCH}_2\text{NEt}_2\) (39), amides of N-substituted amino acids and 2,6-dichloroaniline -2,6-C\(\text{C}_6\text{H}_3\text{NHOCCH}_2\text{RIP}\) (R=H or Me)(65), 2-methyl acetanilide 2-Me \(\text{C}_6\text{H}_4\text{NHOCCH}_2\text{NR}_2\) (58), diphenyl-acrylic acid dialkylaminoethylamides (43), a-(diethylamino) ar-phenoxy acetanilide \(\text{RC}_6\text{H}_4\text{NHOCCH}_2\text{NEt}_2\) (R= -\(\text{C}_6\text{H}_5\), -\(\text{OCH}_2\text{C}_6\text{H}_5\), -\(\text{OC}_2\text{H}_2\text{C}_6\text{H}_3\)) (75), N-(a-cycloalkylbenzyl) acylamides (49), 1-acetylamino anthraquinone with basic substituents(67),

181
9-aminoacetamido-9,10-dihydro-9,10-ethanoanthracenes (11), 5-diethylamino acetamido-2-arylimino-3-aryl-4-thiazolidinones (7), 2-amino-N-(phenylalkyl)alkanamides (50), 2-(2-aminoalkanamido)-3-phenylnorbornanes (62), 2-(diethylamino)-N-naphthyl (1,2-d)-thiazol-2-yl (8), 2-(2-pyridylamino)-acetamido- and 2-(α-anilino acetamido) benzothiazoles (80), 2-(diethylamino)-N-(α,α-dimethylbenzyl) acetamide (51), dialkyaminooacetamides, pyrroles (69), 1,α,α-trimethyl-2-piperidyl carbinol diphenyl acetate (6), 4,N,N-disubstituted aminoacetamido-3,5-dimethyl-1,2,4-triazaoles (25), 2,6-Me₂-C₆H₄NHOCOCHNR²(1), p-N₂C₆H₄CO(CH₃)₂₄N₂Et₂(21), 2-(2-aminoacetamido)thiazoles (79), N-(2,3-dihydrobenzofurfurylalkyl)-2-(dialkyaminooacetamides (64), 3-methyl/phenyl-4-(dialkyaminooacyl)aminofurazans (3), p-acetamido-N-[2(diethylamino)] benzamide (74), 2-[2-(disubstituted amino)acetamido benzothiazol (9), m-(aminoacetamido)benzoates (66) and 5-acetamido-3-aryl-2-arylimino-4-thiazolidinone (24) were found to exhibit local anesthetic activity.

Basic amides with variation in the side chain including some amides having only secondary amino group in place of tertiary amino group have also been prepared and shown to be active. Some of these are summarised below:

α-Diethylamino-N-(α,α-methyl, carbalkoxy-benzyl) acetamide PhGRR'NHQ0CH₂NET₂ (R=CH₃, R'=COOEt) and α-(N,N-ethyl
carbalkoxy methyl amino) 2,6-substituted acetanilides
2,6-Me₃C₆H₄NHOC₂H₂NEt-CH₂COOEt (56), β-(dialky lamino)-
-butyranilide derivatives RR'C₆H₅NHOC₂H₂CH(Me)NR''R" (13),
β-isopropylamino-N-(2,6-dimethyl) propioanilide 2,6-Me₂C₆H₃-
-NHOC₂H₂CH₂NHCH₃Me₂ (55), diacetylamo acylamides
R''(CH₂)nCH(R)COCH₂NR" (10), diethylamino ethoxy-p-cyclohexyl
acetanilide p-R₆H₄NHOC₂H₂O(CH₂)nEt₂(R=cyclohexyl) (41),
a-(2-methyl-1-piperidyl) acylanilides (53), β-dimethylamino-
p-chlorobutyranilide p-G₆C₆H₄NHOC₂H₂CH₃ (92), derivatives
of 2,6-diethyl-4-methyl-α-butyramino acylanilides 2,6,4-
-Et₂Me₆C₆H₂NHOC₂H₂NH(C₄H₉) (54), l-(butyramino acetamino)-
-2-nitro-6-chlorobenzene 2,6-NO₂G₆C₆H₄NHOC₂H₂NH₂G₆H₄ (38),
2-methyl-6-carbalkoxy-N-(aminoalkyl) acylanilides 2,6-Me(QOR)-
-G₆C₆H₄NHOC₆H₄NR'R" (R=Me or Et; X=CH₂, (CH₂)n, CHMe₂,CH₂; R'=
lower alkyl; R''=H or lower alkyl) (42), 4-[(W-alkylamino
cyclamino) salicylates 3,₄-(OH)(NOOOC₆C₆H₄NHOC₂H₂)nNR'R" (R=CH₃,n-G₆C₆H₄etc., n=1; NR'R"=diethylamino, isopropylamino,
piperidino) (37), β-propylamino-2-methyl propioanilide
o-Me₆C₆H₄NHOC₂H₂CH₂NH(C₃H₇) (91), α-propylamino propiono-o-
toluidide and α-isopropylamino propiono-o-toluidide (90),
1-(α,N,N-diethylamino propionylamino)-2 or 4-alkoxynaphthalene
derivatives (95), 2-diethylamino propionanilide derivatives
(46) and 2-amino-2-methyl propionanilide (45).
A large number of amides, some of them containing phenoxy group, has been found to show local anesthetic activity. Dialkylamino amides $R_1R_2N(CH_2)_nCHR_3CONHR_4$ (60), 2-phenoxy acetamide derivatives (15), basic amides of acids acting as plant growth regulators $ROCH_2CONHCH_2CH_2N$Et$_2$ (R=aryl) (86), N,N-disubstituted amides of arylacetic acids (18), 2-phenoxy acetamides, amides of 4,2-CH$_2$=CHCH$_2$(MeO)-C$_6$H$_3$OCH$_2$OOH (87), 2-methoxy-4-butyryl phenoxyacetic acid diethylamide (83), N,N-disubstituted mono (aminoalkyl) amides $RCONHR'R''$ (R=halophenoxy methyl, naphthylmethyl or naphthoxymethyl; A=straight or branched chain hydrocarbon radical; R' and R'' each=saturated or unsaturated aliphatic or aromatic monovalent radical together with the N atom comprise a heterocyclic ring) (20), $\alpha$-benzyl-$\alpha$-(2-morpholinoethyl)-N-propyl-N-benzyl phenylacetic acid amides (2), amides of the type p-Ch$_6$H$_4$OCH$_2$CONHCH$_2$CH$_2$NMe$_2$ (or -NET$_2$) and C$_{10}$H$_7$CH$_2$CONHCH$_2$-CH$_2$NET$_2$ (23), 2-(4-allyl-2-methoxy phenoxy)-N,N'-diethylacetamides (94), 2-methoxy-4-allyl phenoxyacetic acid diethylamide (82), 2-(2,4-dichlorophenoxy)-N-(piperidino-methyl)-acetamides (35), aryloxyacetamides 2,4-MeO, EtCH(OH)-C$_6$H$_3$OCH$_2$CONEt$_2$ (19), 2-4(0Et)(CH$_2$=CHCH$_2$)$_2$C$_6$H$_3$OCH$_2$-CONR$_2$(R=Pr, Et and NR$_2$=piperidino) (84), alkoxybenzamides $ROC_7H_4CONH(C_7H_4)NGH_2$ (78), amides of 2-methoxy-4-allylphenoxy-$\alpha$-isobutyric acid (22), phenoxydialkylamino acylanilides (44), N,N-diethyl-2--4-(hydroxyalkyl)-2-methoxyphenoxy acetamides (52) and 2-diethylamino-ar'-phenoxy acetanilide $ROC_6H_4NOCH_2$-NET$_2$ (R=o,m,p-$OC_5H_5$, -OCH$_2$C$_6H$_5$, -OCH$_2$C$_2$H$_5$) (29).
PRESENT WORK

Several basic amides from a variety of amines have been synthesized in this laboratory and some of these have been shown to exhibit significant local anesthetic activity (28, 30, 63, 76, 77).

Some members of p-diaminodiphenoxylalkane exhibit anthelminitic activity and are several times more effective than Miracil D, (68a). Quaternary salt of p,p'-diaminodiphenoxylalkane inhibit acetyl cholinesterase and have only feeble action on serum cholinesterase (36a).

It was thought of interest to prepare basic amides of the following types,

(i) \[ 4,4'-\text{Di}(\alpha,\alpha\text{-diethylamino/morpholino/piperidino-acetamido}) \text{ diphenoxylalkane.} \]

\[ R^2R^1N-H_2C.OCHN-C_6H_4-O(\text{CH}_2)_nO-C_6H_4-NHCO.CH_2-NR^1R^2 \]

Where: \( n=2,3,4,5,6 \).

\( NR^1R^2=\text{Diethylamino/morpholino/piperidino.} \)

(ii) \[ 4,4'-\text{Di}(\alpha,\alpha\text{-diethylamino/morpholino/piperidino-acetamido}) \text{ diphenylmethane.} \]

\[ R^2R^1N-H_2C.OCHN-C_6H_4-CH_2-C_6H_4-NHCO.CH_2-NR^1R^2 \]

Where: \( NR^1R^2=\text{Diethylamino/morpholino/piperidino.} \)
PART IV
THEORETICAL
DI B R O M O A L K A N E S:

The dibromoalkanes can be prepared by the following methods.

(i) The dibromides of aliphatic glycols are best prepared by mixing the glycol with a cold hydrobromic acid-sulphuric acid mixture, allowing to stand for twenty four hours, and heating on a steam bath for three hours.

\[
\text{HO-} \left( CH_2 \right)_n \text{OH} + 2\text{HBr} \xrightarrow{\text{H}_2\text{SO}_4} \text{Br-} \left( CH_2 \right)_n \text{Br} + 2\text{H}_2\text{O}
\]

(ii) By the addition of liquid bromine to a warm mixture of the alcohol and purified red phosphorus.

\[
5\text{HO-} \left( CH_2 \right)_n \text{OH} + 2\text{P} + 5\text{Br}_2 \rightarrow 5\text{Br-} \left( CH_2 \right)_n \text{Br} + 2\text{H}_3\text{PO}_4 + 2\text{H}_2\text{O}
\]

Following dibromoalkanes were prepared by using the above methods.

<table>
<thead>
<tr>
<th>No.</th>
<th>n</th>
<th>B.P.</th>
<th>Reference</th>
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</table>
4,4'-Diacetamidodiphenylalkanes can be prepared by the condensation of p-acetaminol and dibromoalkane in presence of sodium ethoxide.

\[
\begin{align*}
&\text{\text{H}_3\text{C.CCHN} - \text{OH} + \text{Br-(CH}_2\text{)}_n\text{-Br} + \text{HO-} - \text{NHOOCH}_3

\downarrow \text{NaOEt}

&\text{\text{H}_3\text{C.OCHN} - \text{O-(CH}_2\text{)}_n\text{-O-} - \text{NHOOCH}_3}
\end{align*}
\]

Following 4,4'-diacetamidodiphenylalkanes were prepared.

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<tr>
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<td>5.</td>
<td>6</td>
<td>176-177</td>
<td>P. 671 (1968)</td>
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</table>
4,4'-DIAMINODIPHENOXYALKANES:

The 4,4'-diaminodiphenoxalkanes were prepared by hydrolysing 4,4'-diaacetamiddiphenoxalkanes. The amine dihydrochlorides so obtained were basified by alkali to get amines.

Following 4,4'-diaminodiphenoxalkanes were prepared.

<table>
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<th>No.</th>
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<td>2</td>
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<td>140-141</td>
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</table>
4,4'-DIAMINODIPHENYL METHANE:

The 4,4'-diaminodiphenylmethane was prepared by mixing aniline, concentrated hydrochloric acid and 40 per cent formaldehyde solution. The amine dihydrochloride so obtained was fractionally precipitated with dilute ammonium hydroxide (Scanlan, J.T., J. Am. Chem. Soc., 57, 890, 1935). M.P. 85-89 yield-57 per cent.

\[
\begin{align*}
\text{H}_2\text{N-} & \quad + \quad \text{HCHO} + \quad \text{NH}_2 \\
\text{H}_2\text{N-} & \quad \text{CH}_2 \quad \text{NH}_2 + \text{H}_2\text{O}
\end{align*}
\]

PREPARATION OF HALOACYLAMIDES:

These have been prepared mainly by two methods.

(1) Condensation of amine with haloacyl halide in presence of alkali (Nargund, K.S., J. Karnatak, Univ. 2,(1), 19, 1957).


Method (2)(i) was used in the present work.

\[ \text{RNH}_2 + \text{ClCOCH}_2\text{Cl} \rightarrow \text{RNCOCH}_2\text{Cl} + \text{HCl} \]

Following haloamides were prepared.

(A) TABLE -1-

<table>
<thead>
<tr>
<th>No.</th>
<th>n</th>
<th>M.P. (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>2</td>
<td>228-229</td>
</tr>
<tr>
<td>2.</td>
<td>3</td>
<td>192-193</td>
</tr>
<tr>
<td>3.</td>
<td>4</td>
<td>193-194</td>
</tr>
<tr>
<td>4.</td>
<td>5</td>
<td>149-150</td>
</tr>
<tr>
<td>5.</td>
<td>6</td>
<td>162-163</td>
</tr>
</tbody>
</table>

(B) \[ 4,4'-\text{DI-(a-CHLOROACETAMIDO)}\] Diphenylmethane:

\[ \text{ClH}_2\text{C.OCHN} \begin{array}{c} \text{CH}_2 \\ \text{O} \end{array} \text{O-(CH}_2)_n \text{O} \begin{array}{c} \text{NHCO.CH}_2\text{Cl} \\ \text{O} \end{array} \]

M.P. 226-227

In all the above methods replacement of halogen is carried out by heating the $\alpha$-halo acylamide with excess of secondary amine. Excess of secondary amine serves to bind the acid generated in the reaction. Hydrochloride or hydrobromide salt of secondary amine is removed by filtration.

Method (i) was used in the present work.

\[
(\text{i}) \quad \text{RNHOCOCH}_2\text{Cl} + \text{NH}(\text{C}_2\text{H}_5)_2 \rightarrow \text{RNHOCOCH}_2\text{N}((\text{C}_2\text{H}_5)_2 + \text{HCl}
\]
Compounds prepared are shown in the tables.
**TABLE 4.2**

\[
\text{[4,4'-DI-(\alpha-SECONDARYAMINOACETAMIDO)] DIPHENOXYALKANE:}
\]

\[
x \cdot H_2C_6OCHN - O-(CH_2)_n - O - NH\text{OO.C}_2H_2 \cdot x
\]

(i) \(x = -N\left(C_2H_5\right)_2\)

<table>
<thead>
<tr>
<th>No.</th>
<th>(n)</th>
<th>M.P. (\degree C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>2</td>
<td>95-96</td>
</tr>
<tr>
<td>2.</td>
<td>3</td>
<td>120-121</td>
</tr>
<tr>
<td>3.</td>
<td>4</td>
<td>112-113</td>
</tr>
<tr>
<td>4.</td>
<td>5</td>
<td>102-103</td>
</tr>
<tr>
<td>5.</td>
<td>6</td>
<td>106-107</td>
</tr>
</tbody>
</table>

(ii) \(x = -N\left(CH_2\right)_2\)

<table>
<thead>
<tr>
<th>No.</th>
<th>(n)</th>
<th>M.P. (\degree C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>2</td>
<td>205-206</td>
</tr>
<tr>
<td>2.</td>
<td>3</td>
<td>110-111</td>
</tr>
<tr>
<td>3.</td>
<td>4</td>
<td>130-131</td>
</tr>
<tr>
<td>4.</td>
<td>5</td>
<td>140-141</td>
</tr>
<tr>
<td>5.</td>
<td>6</td>
<td>160-161</td>
</tr>
</tbody>
</table>
(iii) \( x = \text{N} \)

![Chemical Structure](image)

<table>
<thead>
<tr>
<th>No.</th>
<th>X</th>
<th>M.P. °C</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Diethylamino</td>
<td>105-106</td>
</tr>
<tr>
<td>2.</td>
<td>Morpholino</td>
<td>165-166</td>
</tr>
<tr>
<td>3.</td>
<td>Piperidino</td>
<td>135-136</td>
</tr>
</tbody>
</table>

\[ 4,4'-\text{DI-(a-SECONDARYAMINOACETAMIDO)} \text{DIPHENYL METHANE} : \]

<table>
<thead>
<tr>
<th>No.</th>
<th>X</th>
<th>M.P. °C</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Diethylamino</td>
<td>105-106</td>
</tr>
<tr>
<td>2.</td>
<td>Morpholino</td>
<td>165-166</td>
</tr>
<tr>
<td>3.</td>
<td>Piperidino</td>
<td>135-136</td>
</tr>
</tbody>
</table>
***************
P A R T - IV
E X P E R I M E N T A L
***************
EXPERIMENTAL

GENERAL METHOD FOR THE PREPARATION OF DIBROMOALKANES:

METHOD-I: - (HYDROBROMIC-SULPHURIC ACID METHOD)

In a 500 ml. three-necked round bottomed flask, fitted with a separatory funnel and a reflux condenser, was placed 48 per cent hydrobromic acid (154 g., 1.9 moles). To this, concentrated sulphuric acid (130 g.) was added dropwise through the separatory funnel with shaking. The flask was cooled in an ice bath. To this cooled solution alkanediol (0.33 mole) was added dropwise through the separatory funnel. After addition of alkanediol, the reaction mixture was kept for twenty-four hours and then heated for three hours on a water bath. The reaction mixture was separated into two layers. The lower layer was separated, washed with water, 10 per cent sodium carbonate solution and water, and then dried over anhydrous magnesium sulphate. The crude dibromoalkanes were purified by distillation under reduced pressure (Vogel, I., Practical Organic Chemistry, 3rd Edition, Longmans, Green & Co. Ltd., p. 280, 1968).
METHOD-II: (RED PHOSPHORUS AND BROMINE METHOD)

In a dry 500 ml. three-necked round bottomed flask, fitted with an efficient mercury sealed stirrer, a separatory funnel and a reflux condenser attached to a gas absorption device, were placed alkanediol (0.5 mole) and purified red phosphorus (6.84 g.). The reaction mixture was heated at 100-150°C and bromine (80 g., 26 ml., 0.5 mole) was added dropwise through the separatory funnel. The reaction mixture was stirred and heated for one hour on a wire guaze at 100-150°C. It was allowed to cool, diluted with water and the excess of red phosphorus removed by filtration. The dibromoalkane was extracted with ether. The ether extract was washed successively with 10 per cent sodium thiosulphate solution and water and dried over anhydrous potassium carbonate. The crude dibromoalkane obtained after removal of ether, was purified by distillation under reduced pressure (Vogel, I., Practical Organic Chemistry, 3rd Edition, Longmans, Green & Co. Ltd., p. 283, 1968).

1,4-DIBROMOBUTANE:

This was prepared by using method-I, from tetrahydrofuran (18.1 g., 20.5 ml.), 48 per cent hydrobromic acid (250 g., 3.08 moles) and concentrated sulphuric acid (75 g.).
Following dibromoalkanes were prepared by these methods in 80-85 per cent yield.

<table>
<thead>
<tr>
<th>No.</th>
<th>Name</th>
<th>B.P.</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>1,5-Dibromopentane</td>
<td>221</td>
<td>Andrus, D.W., Org. Synthesis, 23, 67 (1943).</td>
</tr>
</tbody>
</table>

* 1,2-Dibromoethane was of Eastman Practical grade.
GENERAL METHOD FOR THE PREPARATION OF 4,4'-DIACETAMIDO-

DIPHENOXYALKANES:

Into a dry one litre round bottomed flask provided with a water condenser, was placed ethyl alcohol (131 g., 166 ml., 2.85 moles). To this flask, sodium pieces (8 g., 0.348 mole) were added from the top of the condenser. To control the vigorous reaction the round bottomed flask was immersed in a water bath. Para-acetamol (50 g., 0.33 mole) in 40 ml. of absolute alcohol was added to the reaction mixture.

Into a small separatory funnel supported by grooved cork on the top of the condenser, dibromoalkane (0.24 mole) was placed and this was added with shaking to the reaction mixture. The reaction mixture was heated for about half an hour and was poured into water, washed with 10 per cent sodium hydroxide and again with water and dried thoroughly

Following diacetamidodiphenoxylalkanes were prepared by this method in 85-90 per cent yield.

\[
\text{H}_3\text{COCHN-} \quad \text{O-(CH}_2\text{)}_n\text{O-} \quad \text{NHOOC-CH}_3
\]

<table>
<thead>
<tr>
<th>No.</th>
<th>n</th>
<th>M.P. °C</th>
<th>Molecular formula</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>235-236</td>
<td>C\textsubscript{18}H\textsubscript{20}N\textsubscript{2}O\textsubscript{4}</td>
<td>8.4 8.5</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>144-145</td>
<td>C\textsubscript{19}H\textsubscript{22}N\textsubscript{2}O\textsubscript{4}</td>
<td>8.0 8.2</td>
</tr>
<tr>
<td>4</td>
<td>5</td>
<td>181-182</td>
<td>C\textsubscript{21}H\textsubscript{26}O\textsubscript{4}N\textsubscript{2}</td>
<td>7.5 7.6</td>
</tr>
<tr>
<td>5</td>
<td>6</td>
<td>176-177</td>
<td>C\textsubscript{22}H\textsubscript{28}N\textsubscript{2}O\textsubscript{4}</td>
<td>7.2 7.3</td>
</tr>
</tbody>
</table>
GENERAL METHOD FOR THE PREPARATION OF 4,4'-DIAMINODIPHENOXY-ALKANES FROM 4,4'-DIACETAMIDODIPHENOXYALKANES BY HYDROLYSIS:

In a round bottomed flask 4,4'-diacetamidodiphenoxalkane (25g.) was dissolved in required quantity of alcohol. Concentrated hydrochloric acid (60 ml.) was added to this mixture in the flask and refluxed for five hours or until test sample remained clear upon dilution with two to three times its volume of water. The hot solution was poured into 500 ml. of cold water and neutralised with liquor ammonia. The solid amine which separated was filtered and dried. The yield was about 20 g.

Following 4,4'-diaminodiphenoxalkanes were prepared by this method in 85-90 per cent yield.

![Chemical Structure](image-url)

<table>
<thead>
<tr>
<th>No.</th>
<th>n</th>
<th>M.P. °C</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Per cent Nitrogen</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Found : Required</td>
</tr>
<tr>
<td>2.</td>
<td>3</td>
<td>105-106</td>
<td>10.7 : 10.85</td>
</tr>
<tr>
<td>3.</td>
<td>4</td>
<td>215-216</td>
<td>10.1 : 10.3</td>
</tr>
<tr>
<td>5.</td>
<td>6</td>
<td>140-141</td>
<td>9.2 : 9.33</td>
</tr>
</tbody>
</table>
PREPARATION OF 4,4'-DIAMINODIPHENYL METHANE:

Into a dry two litre round bottomed flask, were placed concentrated hydrochloric acid (188 ml., 2 moles), water (400 ml.) and aniline (186 g., 2 moles). The mixture was cooled to 15°C. To this, 40 per cent formaldehyde solution (76 g., 1 mole) was added and the mixture was heated to 55-60°C for four hours. During the heating the yellow precipitate, which formed when the formaldehyde was added, gradually dissolved. The reaction mixture was made alkaline with sodium carbonate and steam distilled until the distillate gave no test for aniline. The precipitate was then redissolved by the addition of a slight excess of concentrated hydrochloric acid, and the solution was chilled in an ice bath and fractionally precipitated with dilute ammonium hydroxide. Three fractions were obtained, each of which was redissolved by the addition of excess hydrochloric acid. To each of these three solutions, ammonium hydroxide was added slowly. At first resinous material was precipitated but as the addition of ammonium hydroxide continued, white crystalline material began to separate. At this point the addition of ammonium hydroxide was stopped and the resinous material was filtered off. An excess of ammonium hydroxide was added to each of the three filtrates and the precipitates thus obtained were combined. The product was white but turned brown upon standing. Total yield 112 g., 57 per cent of theoretical. M.P. 85-89°C, recrystallised from alcohol, it melted at 90-91°C (Scanlan, J.T., J.Am.Chem. Soc., 57, 890, 1935).
PREPARATION OF CHLOROACETYL CHLORIDE:

In a round bottomed flask fitted with a fractionating column were placed monochloroacetic acid (0.25 mole) and benzoyl chloride (0.325 mole). The mixture was heated to boiling. The acid chloride was distilled off the reaction mixture as rapidly as was consistent with good separation from the other constituents in the flask. Yield of chloroacetyl chloride was 71 per cent, B.P. 105-107 °C (Brown, H.C., J. Am. Chem. Soc., 60, 1325, 1938).

GENERAL METHOD FOR THE PREPARATION OF \(\text{4,4'-DI-(\alpha\text{-CHLORO-ACETAMIDO}) DIPHENOXYALKANES}\):

In a round bottomed flask, surrounded by an ice-bath was placed a mixture of the appropriate amine (0.05 mole), acetone (30 ml.), sodium acetate (0.5 mole) and water (30 ml.). To this, chloroacetyl chloride (0.3 mole) was added dropwise with vigorous shaking. After the addition of chloroacetyl chloride the reaction mixture was allowed to attain room temperature and more water was added to the reaction mixture. The precipitates were filtered, washed with cold water, sodium carbonate (10 per cent) solution, and finally with water. The chloroamides were crystallized from dilute alcohol or petroleum ether.

The compounds prepared are shown in the tables.
## Table 4.4

### 4,4'-DI-(α-CHLOROACETAMIDO) DIPHENOXYALKANES:

![Chemical Structure](https://via.placeholder.com/150)

<table>
<thead>
<tr>
<th>No.</th>
<th>n</th>
<th>M.P. (°C)</th>
<th>M.F.</th>
<th>Molecular formula</th>
<th>Percent Nitrogen</th>
<th>Percent Chlorine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Found: Required</td>
<td>Found: Required</td>
</tr>
<tr>
<td>1.</td>
<td>2</td>
<td>228-229</td>
<td>C\textsubscript{18}H\textsubscript{18}Cl\textsubscript{2}N\textsubscript{2}O\textsubscript{4}</td>
<td>6.9:7.0</td>
<td>17.8:17.9</td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td>3</td>
<td>192-193</td>
<td>C\textsubscript{19}H\textsubscript{20}Cl\textsubscript{2}N\textsubscript{2}O\textsubscript{4}</td>
<td>6.7:6.8</td>
<td>17.1:17.28</td>
<td></td>
</tr>
<tr>
<td>3.</td>
<td>4</td>
<td>193-194</td>
<td>C\textsubscript{20}H\textsubscript{22}Cl\textsubscript{2}N\textsubscript{2}O\textsubscript{4}</td>
<td>6.4:6.6</td>
<td>16.6:16.7</td>
<td></td>
</tr>
<tr>
<td>4.</td>
<td>5</td>
<td>149-150</td>
<td>C\textsubscript{21}H\textsubscript{24}Cl\textsubscript{2}N\textsubscript{2}O\textsubscript{4}</td>
<td>6.3:6.4</td>
<td>16.0:16.28</td>
<td></td>
</tr>
<tr>
<td>5.</td>
<td>6</td>
<td>162-163</td>
<td>C\textsubscript{22}H\textsubscript{26}Cl\textsubscript{2}N\textsubscript{2}O\textsubscript{4}</td>
<td>6.1:6.2</td>
<td>15.5:15.67</td>
<td></td>
</tr>
</tbody>
</table>
### TABLE 4.5

4,4'-DI-(α-CHLOROACETAMIDO) DIPHENYL METHANE:

![](image)

<table>
<thead>
<tr>
<th>No.</th>
<th>M.P. (°C)</th>
<th>Molecular formula</th>
<th>Per cent Nitrogen Found</th>
<th>Per cent Nitrogen Required</th>
<th>Per cent Chlorine Found</th>
<th>Per cent Chlorine Required</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>226-227</td>
<td>C₁₇H₁₆Cl₂N₂O₂</td>
<td>7.8</td>
<td>7.97</td>
<td>20.14</td>
<td>20.23</td>
</tr>
</tbody>
</table>
GENERAL METHOD FOR THE PREPARATION OF \(4,4'\)-DI-(\(\alpha\)-SECONDARY AMINOACETAMIDO) DIPHENOXYALKANES:

\[\begin{align*}
4,4'\text{-Di-(\(\alpha\)-chloroacetamido)} & \text{diphenoxalkane (1.0 mole)} \\
\end{align*}\]

in dry benzene (500 ml.) was refluxed for five hours with secondary amine (5.12 moles). The precipitated secondary amine hydrochloride was filtered off and washed with a small quantity of benzene. The filtrate was now treated with a little more than the calculated quantity of cold hydrochloric acid (3N, 680 ml.), the aqueous layer was separated, washed with ether, and made alkaline with ice cold ammonia. The liberated base was filtered, washed with water and dried. It was crystallized from aqueous alcohol or petroleum ether. If the base was liberated as an oil, it was taken up in ether and the ether extract was dried over anhydrous potassium carbonate or magnesium sulphate. To this dry ethereal extract of base, dry hydrogen chloride gas was passed, when the hydrochloride salt of basic amide was precipitated. It crystallized in colourless needles from dry acetone or a mixture of ether-ethanol (Lofgren, N., J. Sc. Ind. Re., 9, 63, 1950).

The compounds prepared are shown in the tables.
<table>
<thead>
<tr>
<th>No.</th>
<th>M.P.</th>
<th>Molecular formula</th>
<th>Found</th>
<th>Required</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>95-96</td>
<td>C_{26}H_{38}N_{4}O_{4}</td>
<td>11.7</td>
<td>11.92</td>
</tr>
<tr>
<td>2.</td>
<td>120-121</td>
<td>C_{27}H_{40}N_{4}O_{4}</td>
<td>11.4</td>
<td>11.57</td>
</tr>
<tr>
<td>3.</td>
<td>112-113</td>
<td>C_{28}H_{42}N_{4}O_{4}</td>
<td>11.1</td>
<td>10.94</td>
</tr>
<tr>
<td>4.</td>
<td>102-103</td>
<td>C_{29}H_{44}N_{4}O_{4}</td>
<td>10.8</td>
<td></td>
</tr>
<tr>
<td>5.</td>
<td>106-107</td>
<td>C_{30}H_{46}N_{4}O_{4}</td>
<td>10.5</td>
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</tr>
</tbody>
</table>
**TABLE 4.17**

<table>
<thead>
<tr>
<th>No.</th>
<th>M.P. °C</th>
<th>Molecular formula</th>
<th>Per cent Nitrogen</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Found</td>
</tr>
<tr>
<td>1.</td>
<td>205-206</td>
<td>C_{26}H_{34}N_{4}O_{6}</td>
<td>11.15</td>
</tr>
<tr>
<td>2.</td>
<td>110-111</td>
<td>C_{27}H_{36}N_{4}O_{6}</td>
<td>10.8</td>
</tr>
<tr>
<td>3.</td>
<td>130-131</td>
<td>C_{28}H_{38}N_{4}O_{6}</td>
<td>10.53</td>
</tr>
<tr>
<td>4.</td>
<td>140-141</td>
<td>C_{29}H_{40}N_{4}O_{6}</td>
<td>10.2</td>
</tr>
<tr>
<td>5.</td>
<td>160-161</td>
<td>C_{30}H_{42}N_{4}O_{6}</td>
<td>10.0</td>
</tr>
</tbody>
</table>

Where \( X = \begin{array}{c}
\text{CH}_2 \\
\text{NH}_2 \\
\text{CH}_2
\end{array} \)
TABLE 4.8

4,4'-Di-(α-Piperidinoacetamido) Diphenoxylalkane:

\[
x\cdot H_2C\cdot O\cdot CHN\cdot \left(O\cdot (CH_2)_n\cdot O\right)\cdot \left(NHCO\cdot CH_2\cdot X\right)
\]

Where \( X = \)

<table>
<thead>
<tr>
<th>No.</th>
<th>( n )</th>
<th>( \degree C )</th>
<th>Molecular formula</th>
<th>Per cent Nitrogen</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>( C_{28}H_{38}N_4O_4 )</td>
<td>Found : Required</td>
</tr>
<tr>
<td>1.</td>
<td>2</td>
<td>190-191</td>
<td>11.25</td>
<td>11.34</td>
</tr>
<tr>
<td>2.</td>
<td>3</td>
<td>100-101</td>
<td>10.9</td>
<td>11.00</td>
</tr>
<tr>
<td>3.</td>
<td>4</td>
<td>121-122</td>
<td>10.5</td>
<td>10.7</td>
</tr>
<tr>
<td>4.</td>
<td>5</td>
<td>132-133</td>
<td>10.3</td>
<td>10.45</td>
</tr>
<tr>
<td>5.</td>
<td>6</td>
<td>120-121</td>
<td>10.0</td>
<td>10.18</td>
</tr>
<tr>
<td>No.</td>
<td>Name</td>
<td>M.P.</td>
<td>M.C.</td>
<td>Molecular formula</td>
</tr>
<tr>
<td>-----</td>
<td>-----------------------</td>
<td>------------</td>
<td>------</td>
<td>-------------------</td>
</tr>
<tr>
<td>1.</td>
<td>Diethylamino</td>
<td>105-106</td>
<td></td>
<td>C&lt;sub&gt;25&lt;/sub&gt;H&lt;sub&gt;36&lt;/sub&gt;N&lt;sub&gt;4&lt;/sub&gt;O&lt;sub&gt;2&lt;/sub&gt;</td>
</tr>
<tr>
<td>2.</td>
<td>Morpholino</td>
<td>165-166</td>
<td></td>
<td>C&lt;sub&gt;25&lt;/sub&gt;H&lt;sub&gt;32&lt;/sub&gt;N&lt;sub&gt;4&lt;/sub&gt;O&lt;sub&gt;4&lt;/sub&gt;</td>
</tr>
<tr>
<td>3.</td>
<td>Piperidino</td>
<td>135-136</td>
<td></td>
<td>C&lt;sub&gt;27&lt;/sub&gt;H&lt;sub&gt;36&lt;/sub&gt;N&lt;sub&gt;4&lt;/sub&gt;O&lt;sub&gt;2&lt;/sub&gt;</td>
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