GENERAL INTRODUCTION

PART I
GENERAL INTRODUCTION

Pain is mankind's oldest enemy and it is also mankind's oldest friend. From the beginning, man has thought of disease and affliction primarily in terms of the pain which results. Nature gives pain to life for its protection. Pain is the instinctive cry at the onset of injury and disease. Pain rings a sleepless alarm, warning all living creatures of danger. Pain saves the organism by informing it in time of disordered conditions. Pain is the cruel but life saving guardian of protoplasm. Man has struggled to avoid pain, and to alleviate or control it when pain came in connection with physical illness. The rebellion against pain of course was delayed far longer than the fight against disease. The development of scientific medicine and surgery, along with growing understanding of the nature of pain, and the means to relieve it mark the crowning achievements of mankind. In spite of this, satisfactory definition of the sensation of pain is lacking and it is very difficult to formulate one. 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 animal tissue.

The two principal types of pain are:
(a) Superficial pain and (b) Deep pain.

The superficial or cutaneous pain is sharp intense and sudden such as due to pin pricks, burns etc. The deep or visceral pain is denoted by a pulling, deep aching quality such as colic, cardiac, root pain etc.

Pain is conducted over two major paths, somatic and sympathetic. Pain is a sensation and hence it possesses two components, peripheral and central. Peripheral component comprises the purely anatomical sensory paths viz. along nerve fibers to the spinal cord and up into the thalamous. Part of the pain perception takes place here. The central component comprises the cortical or the integrative psychic element. It involves perception of the stimulus and the emotional overtones. It is here that the appreciation of the pleasantness or otherwise of a sensory impulse occurs and the appropriate pattern of reaction determined. This dichotomy of pain has been designated simply as pain perception and pain appreciation. Thus there can be two positive approaches, central and peripheral for abolishing pain.
Science has shown that we have minimum and maximum pain points, the minimum is known as the "pain perception threshold". It is at this point that we begin to feel pain. Somewhere above this threshold, the "pain ceiling" is reached. Here pain has increased to the point where it becomes unbearable. Adding to the intensity of the stimulus beyond this point does not increase the amount of pain because the sensory nerve fibres have reached the limit of their capacity to transmit pain impulses. This pain ceiling depends on psychological, neurological and constitutional factors like age, sex, temperament, race, culture and fatigue.

If we can prevent the pain message from reaching the brain or if we temporarily "knock out" the perception mechanism, there will be no feeling of pain. This is what anesthesia does. A similar result can be achieved by eliminating the central component, viz, pain appreciation. This is achieved by the use of analgesic agents which raise the pain threshold. The same result is achieved by cutting off pain fibres, coursing from thalamus to the frontal lobe.
From primitive times man sought the separation of pain from the advancing knife. To the surgeon, pain was the barrier, he was forced to penetrate before his terrible instrument became the healing knife. The pain of the patient often denied access to his body, the sick often preferred to die rather than submit to an operation. Thus the only way a surgeon could relieve the torture was to put speed above everything else and finish his work as quickly as possible. Beating a person on the head and pressing the carotid arteries to stop the supply of blood to the brain, were some of the cruel methods used to make the patient unconscious. Hemp, Scopolis atropoides, mandrake, opium and large doses of alcohol have been used for relieving pain but these never attained wide use as they were very weak in mild doses, while they were dangerous in high doses.

The first gaseous anesthetic to be discovered was nitrous oxide, by Priestly in 1776. In 1799, Humphry Davy announced that this gas had ability to destroy pain and suggested its use during surgical operations. In 1818 Faraday showed that ether possessed analgesic activity.
Hickman in 1824 performed surgical operation on an animal depressed by carbon dioxide. Long in 1842, used ether for removing a small tumor from the neck. As Long, never told this to anyone, his findings remained unknown until ether anesthesia was rediscovered by Morton. Wells in America had one of his teeth extraced painlessly under nitrous oxide but his demonstration of its effect in a Boston Hospital unfortunately failed (1845). Simpson introduced chloroform as an anesthetic in 1847.

Painless surgery has also been carried out under the effect of low temperature (refrigeration anesthesia) and also under the effect of hypnosis.

Formulae of some substances which are used, or were used once as general anesthetics are shown below.

**Volatile Anesthetics:**

1. Diethylether \( \text{C}_2\text{H}_5\text{O}-\text{C}_2\text{H}_5 \)
2. Divinylether \( \text{(CH}_2 = \text{CH}_2)_2\text{O} \)
3. Fluoroxene \( \text{CF}_3\text{CH}_2\text{OCH} = \text{CH}_2 \)
4. Methoxyflurane \( \text{Cl}_2\text{CHCF}_2\text{OCH}_3 \)
5. Chloroform \( \text{CHCl}_3 \)
6. Ethylchloride \( \text{C}_2\text{H}_5\text{Cl} \)
7. Trichloroethylene \( \text{Cl}_2\text{C} = \text{CH} \cdot \text{Cl} \)
8. Halopropane \( \text{F}_2\text{CHOF}_2\text{CH}_2\text{Br} \)
9. Teflurane \( \text{F}_3\text{CCHFBr} \)
10. Halothane \( \text{CF}_3\text{CHBrCl} \)
11. Ethylene \( \text{CH}_2 = \text{CH}_2 \)
12. Cyclopropane
\[
\text{CH}_2 \quad \text{CH}\quad \text{CH}_2
\]
13. Nitrous Oxide \( \text{N}_2\text{O} \)

**Intravenous Anesthetics**

14. Thiopental
\[
\text{O} \\
\text{HN} \\
\text{N} \\
\text{C}_2\text{H}_5 \\
\text{CH(CH)}(\text{CH}_2)\text{CH}
\]

15. Brevital
\[
\text{CH}_3 - \text{N} \\
\text{CH}_2\text{CH} = \text{CH}_2 \\
\text{CH(CH)}(\text{CH} \cdot \text{C} = \text{C}_2\text{H}_5
\]

\[
\text{HO}
\]
16. Hydroxydione

17. Propanidid

Miscellaneous Compounds

18. 1-Phenyl-1-piperidino-cyclohexane

19. 2(-2-chlorophenyl)-2-methylamino-cyclohexanone
20. Diazepam

21. Droperidol

22. Fentanyl
LOCAL ANESTHETICS

The local anesthetic drugs are capable of blocking nerve conduction when applied locally to nerve tissue in effective 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 anesthetized without affecting other parts 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 to nerve fibres or cells.

The history of the discovery of local anesthetics is no less interesting. Richardson produced local insensibility by freezing the part with ether spray,
which he devised in 1867, a method which remained in
general use for many years. The first local anesthetic
discovered was cocaine from the Divine plant of Incas,
Erythroxylon coca. Visitors in the early days, returning
from Peru, related exotic tales of a coca plant. Scherzer,
an Austrian naturalist returning from a scientific
expedition around the globe brought back from Peru the
sun-dried leaves of its shrubs. Niemann, Wohler's
assistant isolated the active principle from these leaves
in 1860. Wohler noted that cocaine was bitter to the
taste and had a peculiar effect on the tongue, making
it numb and almost devoid of sensation. Von Anrep in
1879 studied the pharmacological action of cocaine and
observed that after subcutaneous injection the skin
overlying the infiltrated area became insensitive to the
prick of a pin. He recommended that the alkaloids might
be useful clinically as a local anesthetic. Its power
of producing anesthetic state in animals and man was
demonstrated by Shroff (1862); Maiz (1868) and Anrep
(1880) the latter pointed out the possibility of cocaine's
becoming a useful local anesthetic. Freud who founded
psychoanalysis and Koller an interne in Vienna's general Hospital were the first to start work on cocaine. Freud, though familiar with the local anesthetising power of cocaine was primarily interested in the general action of the drug on the body. Koller was in search of a local anesthetic for the eye and had failed with chloral, bromide, morphine and ether spray of Richardson. In 1884, Koller demonstrated the local anesthetic activity of cocaine on the human eye before the Congress of Ophthalmology at Heidelberg. This was the most significant gift to ophthalmologists since Helmholtz had brought them the ophthalmoscope. The era of operating on the eye of a writhing and screaming patient belonged to the past, the era of local anesthesia had dawned. The invention of hypodermic syringe in 1853 by Wood of Scotland and Pravez of France helped introducing local anesthetic in dentistry and surgery. Corning (1885) produced spinal anesthesia in dogs. As cocaine was found to be habit-forming, an intensive search has been launched to devise cocaine substitutes not possessing this bad effect.
The following are the local anesthetics in common use. The type of application is indicated in the brackets.

1. Benoxinate, \(3,4-\text{OC}_4\text{H}_9-\text{NH}_2-\text{C}_6\text{H}_3-\text{CO}_2\text{CH}_2\text{CH}_2\text{N(C}_2\text{H}_5)_2\) (Topical)

2. Benzocaine \(4-\text{NH}_2-\text{C}_6\text{H}_4-\text{COOC}_2\text{H}_5\) (Topical)

3. Benzylalcohol \(\text{C}_6\text{H}_5\text{CH}_2\text{OH}\) (Topical)

4. Bupivacaine \(2,6(\text{CH}_3)_2-\text{C}_6\text{H}_3-\text{NH-CO}\) (Parenteral)

5. Butacaine, \(4-\text{NH}_2-\text{C}_6\text{H}_4-\text{COO(CH}_2)_3\text{N(C}_4\text{H}_9)_2\) (Topical)

6. Butethamine, \(4-\text{NH}_2-\text{C}_6\text{H}_4\text{COOC}_2\text{CH}_2\text{NHCH}_2\text{CH(CH}_3)_2\) (Parenteral)
7. Butyl-4-amino-benzoate \[4\text{-NH}_2\text{-C}_6\text{H}_4\text{COOC}_4\text{H}_9\] (Topical)

8. Chlorobutanol \[\text{CCl}_3\text{C(CH}_3\text{)}_2\text{OH}\] (Topical)

9. Chloroprocaine

Nesacaine \[2,4\text{-ClNH}_2\text{-C}_6\text{H}_3\text{-COOCH}_2\text{CH}_2\text{N(C}_2\text{H}_5\text{)}_2\]
(Parenteral)

10. Cocaine

\[\text{CH}_2\text{-CH} - \text{COOCH}_3\]
\[\text{N-CH}_3\text{-CH} - \text{O} - \text{CO} - \text{C}_6\text{H}_5\]
(Topical)

11. Cyclomethycaine \[\text{C}_6\text{H}_11\text{-O-}\text{C}_6\text{H}_4\text{-COO(CH}_2\text{)}_3\text{N}\]
CH$_3$
(Topical)

12. Dibucaine, Nupercaine, Percaine

\[\text{CONHCH}_2\text{CH}_2\text{N(C}_2\text{H}_5\text{)}_2\]
(Topical, Parenteral)
13. Dimethisoquin, Quotane

\[
\text{CHgCHgN (CH}_3\text{)}_2
\]

(Topical)

14. Diperodon (Diothene)

\[
\begin{align*}
\text{C}_6\text{H}_5-\text{NHCOOCH}_2 \\
\text{C}_6\text{H}_5-\text{NHCOOCH} \\
\text{CH}_2\text{NC}_5\text{H}_10
\end{align*}
\]

(Topical)

15. Dyclonine

\[
\begin{align*}
\text{OC}_4\text{H}_9-\text{C}_6\text{H}_4-\text{COCH}_2\text{CH}_2\text{NC}_5\text{H}_10
\end{align*}
\]

(Topical)

16. Ealicain

\[
\begin{align*}
\text{OC}_3\text{H}_7-\text{C}_6\text{H}_4-\text{COCH}_2\text{CH}_2\text{NC}_5\text{H}_10
\end{align*}
\]

(Topical, Parenteral)

17. Hexylcaine, Cyclaine

\[
\begin{align*}
\text{C}_6\text{H}_5-\text{COOCH-CH}_2\text{NHCH}_3\text{H}_11 \\
\text{CH}_3
\end{align*}
\]

(Topical, Parenteral)
18. Hostacaine  \(2,6-\text{Cl-CH}_3-\text{C}_6\text{H}_3-\text{NH-COCH}_2\text{NHCH}_4\text{H}_9\)  
(Topical, Parenteral)

19. Isobucaine  \(\text{C}_6\text{H}_5\text{COOCH}_2\text{C}-\text{NHCH}_2\text{CH(CH}_3)_2\)  
(Parenteral)

20. Lidocaine  \(2,6-(\text{CH}_3)_2-\text{C}_6\text{H}_3-\text{NHCOCH}_2\text{NH}(\text{C}_2\text{H}_5)_2\)  
(Topical, Parenteral)

21. Mepivacaine, Carbocaine  \(2,6-(\text{CH}_3)_2-\text{C}_6\text{H}_3-\text{NH-CO}\)  
(Parenteral)

22. Meprylcaine  \(\text{C}_6\text{H}_5\text{COOCH}_2\text{C}-\text{NHCH}_3\text{H}_7\)  
(Parenteral)

23. Meta-butethamine  \(2-\text{NH}_2-\text{C}_6\text{H}_4-\text{COOCH}_2\text{CH}_2\text{NHCH}_2\text{CH(CH}_3)_2\)  
(Parenteral)
24. Meta-butoxycaaine
   \[2,3-\text{OC}_3\text{H}_7,\text{NH}_2\text{C}_6\text{H}_3-\text{COOCH}_2\text{CH}_2\text{N(C}_2\text{H}_5)_2\]
   (Parenteral)

25. Naepaine (amylsine)
   \[4-\text{NH}_2\text{C}_6\text{H}_4\text{COOCH}_2\text{CH}_2\text{NH}_2\text{H}_5\_11\]
   (Topical)

26. Oxethiazaine
   \[\text{C}_6\text{H}_5-\text{CH}_2\text{C}((\text{CH}_3)_2\text{N(\text{CH}_3)}\text{COCH}_2\text{N(\text{CH}_2)}_2\text{OH}\]

27. Piperocaine
   Metycaine
   \[\text{C}_6\text{H}_5-\text{COO(CH}_2)_3\text{N}\]
   (Topical, Parenteral)

28. Phenacaine
   \[4-\text{OC}_2\text{H}_5-\text{C}_6\text{H}_4\text{NH}\]
   \[4-\text{OC}_2\text{H}_5-\text{C}_6\text{H}_4-\text{N}\]

29. Pramoxine
   Tronothane
   \[4-\text{OC}_4\text{H}_9-\text{C}_6\text{H}_4-\text{O-(CH}_2)_3-\text{N}\]
   (Topical)

30. Prilocaine
   \[2,\text{CH}_3-\text{C}_6\text{H}_4-\text{NHCOCHNH}_3\text{H}_7\]
   \[\text{CH}_3\]
   (Topical, Parenteral)
<table>
<thead>
<tr>
<th>No.</th>
<th>Substance</th>
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<tbody>
<tr>
<td>31.</td>
<td>Procaine, Novocaine</td>
<td>$4\text{-NH}_2\text{-C}_6\text{H}_4\text{-COO(CH}_2\text{)_2N(C}_2\text{H}_5\text{)_2}$</td>
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<td>(Parenteral)</td>
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<tr>
<td>32.</td>
<td>Proparacaine, Opthacaine</td>
<td>$3\text{-NH}_2\text{OC}_3\text{H}_7\text{C}_6\text{H}_3\text{-COOCH}_2\text{CH}_2\text{N(C}_2\text{H}_5\text{)_2}$</td>
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<td>(Topical)</td>
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<tr>
<td>33.</td>
<td>Propoxycaine</td>
<td>$2\text{-C}_3\text{H}_7\text{NH}_2\text{-C}_6\text{H}_3\text{-COOCH}_2\text{CH}_2\text{N(C}_2\text{H}_5\text{)_2}$</td>
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<tr>
<td>34.</td>
<td>Pyrrocaine</td>
<td>$2\text{-CH}_3\text{C}_6\text{H}_5\text{NHCOCH}_2\text{N}$</td>
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<td>(Parenteral)</td>
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<tr>
<td>35.</td>
<td>Tetracaine, Pentocaine</td>
<td>$4\text{-C}_4\text{H}_9\text{NH-C}_6\text{H}_4\text{-COO(CH}_2\text{)_2N(CH}_3\text{)_2}$</td>
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<td>36.</td>
<td>Thesit</td>
<td>$C\text{12}<em>2\text{H}</em>{25}(\text{OCH}_2\text{CH}_2)_9\text{OH}$</td>
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<td>(Topical)</td>
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<td>37.</td>
<td>Trimecaine</td>
<td>$2\text{-CH}_3\text{C}_6\text{H}_2\text{-NHCOCH}_2\text{N(C}_2\text{H}_5\text{)_2}$</td>
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MECHANISM OF ACTION OF LOCAL ANESTHETICS

Most of our knowledge about the mode of action of local anesthetics has come from experiments on isolated nerves. It is very unlikely that individual nerve fibres exist as 'naked' fibres. They are generally surrounded by other cells, connective tissues, collagen and matrix. Thus, it is not always safe to translate results obtained on isolated fibres to the fibres as existing in living organism.

Nerves function by conducting bioelectrical impulses along the nerve fibres, thus signalling the arrival of coded information. The precise mechanism by which charged ions play a role in the excitation phenomena is still unknown, although one ionic hypothesis (120) has received the widest acceptance. Essentially this hypothesis states that the resting potential of a nerve cell represents a steady state, with differential accumulation of sodium ions outside the cell and potassium ions inside the cell. During the dynamic changes of the action potential sodium ion enters the cell and potassium ion leaves the cell.
These changes occur in about a millisecond, after which a cell is ready to fire again. Of course, there are some nerve cells which can function in the absence of sodium ion (256,257).

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. A nerve impulse can be described in terms of a predictable pattern of electrical disturbance in the nerve cell. Local anesthetics are said to block conduction in nerve fibres through interference with electrical depolarisation. Acetyl choline seems to alter the permeability of the cell membrane and to trigger the migration of sodium ions across the membrane. Local anesthetics block conduction by interfering with this process fundamental to the generation of the nerve action (275). As the anesthetic action progressively develops in a nerve, the threshold for electrical excitability gradually increases and the safety factor for conduction decreases, when this action is sufficiently well developed, block of conduction is produced.
Local anesthetics also reduce the resting permeability of nerve to potassium as well as to sodium ions. This accounts for the observation that the block in conduction is not accompanied by any large or consistent change in the resting potential. A similar reduction in permeability also occurs in the membrane of skeletal muscle both in the resting state (255) and during the generation of an action potential (128). For example, Shanes showed that the swelling of muscle in a solution of high potassium content, a property dependent on the entry of potassium chloride, is inhibited by cocaine.

The exact mechanism whereby a local anesthetic influences the permeability of the membrane is at present unknown, but it is interesting that the relative anesthetic potency of a series of compounds exactly parallels their effectiveness in increasing the surface pressure of monomolecular films of lipid (263).

Shanes suggested that local anesthetics achieve block by increasing the surface pressure of the lipid layer that constitutes the nerve membrane thereby closing the pores through which ions move. This would
cause a general decrease in the resting permeability and would also limit the increase in sodium permeability, the fundamental change necessary for the generation of the action potential. As a general rule, small nerve fibers are more susceptible to the action of local anesthetics than are large fibers.

It is known that calcium ion is important in the proper functioning of excitable tissues (256, 257). Calcium antagonises the action of procaine on the spinal ganglion cells of the frog (2). Procaine and tetracaine inhibit the efflux of calcium ion from nerve and muscle. The action of local anesthetics may be related to the displacement of calcium ion from the excitable membrane (148).

The majority of the local anesthetics are basic compounds. They are used in the form of salts, more commonly as their soluble hydrochloride or sulfates. In presence of alkaline fluid of the animal tissue, the free base, the active constituent is liberated. Experiments indicate that the base may be four to eight times as potent as hydrochloride salts. This does not mean that
introduction of the anesthetic in the form of a salt into a strongly alkaline solution will ensure higher activity. On the contrary the free base in this concentration has been found to be inactive. The more alkaline properties have also the disadvantage of being relatively unstable. It has been demonstrated by Ritchie and Greengard (224) that the action is due to the molecular form that combines with some receptor in the membrane to prevent the generation of an action potential

\[
\begin{align*}
R &= N^+ \text{ HOH} \quad \rightarrow \quad R;^+ \text{ NH} + \text{ OH} \\
\end{align*}
\]

Löfgren (169) observed that almost all useful local anesthetic molecules can be arranged according to the following scheme.

Lipophilic part - intermediate chain - hydrophilic part, which usually can be expressed as

Aromatic portion - intermediate chain - amine portion.

There are exceptions to this, e.g. phenacaine and acoine. All structures built on this pattern do not always exhibit local anesthetic activity (308).
Evidence for the receptor sites being involved in local anesthesia has been presented recently. In biochemical studies binding affinities of local anesthetics to isolated 'receptor protein' and relative blocking potencies parallel one another (117). It has been suggested that the action of local anesthetic reacts with structural phospholipid compounds found in excitable membrane (76). Pairs of optical antipodes have been observed to exhibit difference in local anesthetic activity supporting the hypothesis regarding binding of local anesthetics with receptor sites (34, 245, 246).
Willstatter elucidated the structure of Cocaine in 1898 (300) and its absolute configuration was established after about sixty years. It has been assigned the structure of 2 (R)-carbomethoxy-3-(S)-(−) -benzoxyl-1 (R)-tropaine (78).

$$\text{CH}_2 - \text{CH} - \text{C} - \text{R} \quad \text{N-CH}_3 \quad \text{C} - \text{O-COC}_6\text{H}_5$$

(−) Cocaine $R = -\text{COOCH}_3$ ; $R' = H$

(+) Pseudo cocaine $R = H$ ; $R' = -\text{COOCH}_3$

Truxillines (e.g. α-truxiline), cinnamoyl cocaine, tropacocaine (benzoyl-γ-tropane) and (+) pseudococaine were found in Erythroxylon species.
and exhibited local anesthetic activity (39, 66, 161, 162, 163, 164, 213).

Mays (186) compared cocaine to brucine in man and found both active as local anesthetic. High concentrations of brucine were used by him in toothaches and against itching. Another natural product, the β-resin fraction from kavakava, shows local anesthetic activity (160). Some kava-kava constituents, such as pyrones (185, 195) have been identified more recently as compounds with some intradermal local anesthetic effect.
The following generalisations have been arrived at regarding structure activity relationship in cocaine derivatives:

1. Free carboxylic acids, benzoyl ecgonine and ecgonine have no local anesthetic activity.

\[
\begin{align*}
\text{Free carboxylic acids} & : \\
\text{CH}_2\text{--CH--CH-COOH} & \quad \text{CH}_2\text{--CH--CH-COOH} \\
\text{Benzoyl ecgonine} & : \\
\text{CH}_2\text{--CH--CH-COOH} & \quad \text{CH}_2\text{--CH--CH-COOH} \\
\text{Ecgonine} & : \\
\text{CH}_2\text{--CH--CH-COOH} & \quad \text{CH}_2\text{--CH--CH-COOH}
\end{align*}
\]

2. Pseudo tropine and ecgonidine are inactive.

\[
\begin{align*}
\text{Pseudo tropine} & : \\
\text{CH}_2\text{--CH--CH--CH}_2 & \quad \text{CH}_2\text{--CH--CH--CH}_2 \\
\text{Ecgonidine} & : \\
\text{CH}_2\text{--CH--CH--CH}_2 & \quad \text{CH}_2\text{--CH--CH--CH}_2
\end{align*}
\]
while tropacocaine containing the benzoyl group (differing from cocaine by a carbomethoxy group) is active.

\[
\text{CH}_2\text{CH—CH—CH}_2 \\
\text{N-CH}_3 \quad \text{CHO-CO-C}_6\text{H}_5 \\
\text{CH}_2\text{CH—CH—CH}_2
\]

Tropacocaine

Absence of local anesthetic in ekgonine and benzoyl ekgonine may be due to the fact that their sodium salts are insoluble in lipoids.

3. Esters other than methyl are active.

4. oo-cocaine, which differs from cocaine in having the carbomethoxy and benzoyl groups both attached to the same carbon atom is quite inactive. This shows that tropane ring system is not the only structural feature essential for local anesthetic property. In a general study of the influence on physiological activity of displacing some group from one position to another in the molecule of an active drug, Von Braun (284) undertook the
study of compounds containing an acylated hydroxyl group in the \( \gamma \) -position with regard to the basic nitrogen, as it is in cocaine. Compound I, II and III are prepared.

(I)

(II)

(III)

Eccaine
Compound I is as effective as atropine as a mydriatic, and compound II is as powerful a local anesthetic as cocaine. Compound III, called eccaine, is more active than cocaine and has been studied rather extensively.

5. Nor-cocaine (demethylated cocaine) has marked anesthetic properties, but nor-ecgonine and benzoyl nor-ecgonine are inactive.

Nor-cocaine

Nor-ecgonine

Benzoyl nor-ecgonine
It appears that there is some connection between the local anesthetic activity and the presence of an acylated hydroxy group in position 3 to the nitrogen atom.

6. McElvain (189) investigated the effect of a change in the bicyclic ring on anesthetic activity. He made ethylbenzoylisogranatoline-carboxylate (IV), an isomer of homococaine.

The relationship between (IV) and homococaine is more apparent if (IV) is written in the following way:
The carbon atoms numbered 1, 2, 3 in homococaine are still present in the new compound, but are attached in a slightly different manner.

The compound IV is found to be more toxic than cocaine.

7. When pseudopelletierine is reduced and acylated, the resulting esters are less potent than cocaine. For example, benzoyl-N-methylgranatolone (V), cinnamyl-N-methylgranatolone (VI) and p-aminobenzoyl-N-methylgranatolone (VII), have been prepared (274). Compound V showed the highest anesthetic potency and VII the lowest.

\[
\begin{align*}
\text{CH}_2 & \quad \text{CH} \quad \text{CH}_2 \quad \text{O} \\
\text{CH}_2 & \quad \text{N-CH}_3 \quad \text{HCO} \quad - \quad \text{C} \quad - \quad \text{R} \\
\text{CH}_2 & \quad \text{CH} \quad \text{CH}_2 \\
\end{align*}
\]

(V) \( R = -\text{C}_6\text{H}_5 \); (VI) \( R = \text{C}_6\text{H}_5\text{CH} = \text{CH}^- \); (VII) \( R = \text{NH}_2\text{C}_6\text{H}_4^- \)

The fact that simple basic esters like stovaine, show local anesthetic activity, indicates that heterocyclic six-membered nitrogen ring is not essential for the development of anesthetic properties.
The curiosity and interest aroused by the various pharmacological properties of cocaine led to manipulation of the molecule even before its complete structure had been ascertained. Thus alcohols other than methyl and acids other than benzoic were used to prepare analogues from the hydrolysis products of cocaine as soon as the presence of ester function was established in its molecule. Such attempts helped development of ideas regarding structure activity relationship. The part of the molecule under the dotted rectangle has been considered as the anesthesiophore. This can be looked upon in the simplest form as a basic ester of an aromatic acid. Basic esters and a variety of ether types of molecules which can be considered as related to this anesthesiophore have
been studied quite intensively and several useful products have been developed which are sometimes more potent and less toxic as compared to natural substance cocaine or which have some specific use superiority over cocaine. The synthetic substance in use are more or less free from euphoric effects of cocaine. A short survey of this work is presented in the following pages.

**EUCAINES**

In order to prove the significance of the tropane ring system for the local anesthetic effects of cocaine several simple derivatives of piperidine have been tested. \( \alpha \)- and \( \beta \)-eucaines were found to be active. \( \beta \)- being free from the irritating effects of \( \alpha \) (108). This shows that the tropane ring system is not needed for local anesthetic activity. It is strange that \( \alpha \)-cocaine which resembles \( \alpha \)-eucaine in the relative position of its functional group is inactive.
BENZOCAINÉ PROCAÏNE AND RELATED COMPOUNDS

R. Ritsert (225) in 1890 drew attention to the local anesthetic property of ethyl-4-aminobenzoate (Benzocaine, \( \text{C}_6\text{H}_4\text{N}-\text{C}_6\text{H}_4\text{COOC}_2\text{H}_5 \)) but it took about ten years...
to reach the clinic (225). It is a useful surface anesthetic still widely used.

Einhorn and Heinz prepared the following esters and found, contrary to their expectation that the unbenzoylated parent compound was more active than the benzoylated ester (65).

\[
\text{Benzoyl derivative of methylester of 4-hydroxy-3-amo benzoic acid.}
\]

\[
\text{Methylester of 4-hydroxy 3-amino benzoic acid.}
\]

From the above observation, two new local anesthetics orthoform old and orthoform new were introduced (63).

Orthoform old \( R = \text{OH} ; R' = \text{NH}_2 \)

Orthoform new \( R = \text{NH}_2 ; R' = \text{OH} \)
Pornean (81) introduced stovaine, the first recorded aminoalkyl benzoate. It was less potent than cocaine and was also irritating but it was superior to cocaine (29) as a spinal anesthesia.

The combined knowledge obtained from the degradation of cocaine and the activity of the alkyl p-aminobenzoates led to the development of procaine, a synthetic agent superior to cocaine. Procaine is 2-diethylaminoethyl-4-amino benzoate.

\[ 4-\text{NH}_2-C_6H_4-COOC_2H_5C_2H_2N(C_2H_5)_2 \]

The toxicity of the compound is low and it is unusually well tolerated by tissue though in activity and duration of action it is inferior to cocaine. It is in use since more than half a century.

Since the introduction of procaine, basic esters have been the subject of intensive study. In order to obtain esters possessing a lower hydrolysis rate, esters of sterically hindered alkyl substituted benzoic acids were prepared. \( \beta \)-Diethylaminoethyl 2,3,5,6 tetramethyl benzoic acid was more active and showed a longer duration of action as compared to procaine (217), 2,6-Dimethylamino-
benzoates exhibit a longer duration of activity as compared to benzocaine (60). Honkanen (123) also studied the steric effect. He observed in compounds of the following type that as regards alkoxy group in paraposition, propoxy and isobutoxy groups were the most effective groups in the relevant series. Majority of the compounds were, however irritating.

It was observed that an increase of the aminoalkyl group and the intermediate alkylene chain favoured the duration of anesthesia and activity. Thus alkyl-p-amino-benzoate showed increased activity with a lengthening of the alkyl chain (3).

In a series of monoalkoxybenzoic acid esters of morpholinoethanol,
lengthening of the alkyl group R first increased the activity and then declined probably because of solubility factors (202). Di-isopropyl homologue of procaine, isocaine was about as effective as cocaine on rabbit cornea (64, 243). Butacaine, 3-dibutyl-aminopropyl-4-aminobenzoate in which both chain length and N-alkyl groups were enlarged, was found to be about as active as cocaine as a surface active local anesthetic (27, 32, 132).

\[
4-\text{NH}_2-\text{C}_6\text{H}_4-\text{CO}_2(\text{CH}_2)_n\text{NR}
\]

Isocaine: \( n = 2 \); \( R = \text{CH(CH}_3)_2 \)

Butacaine: \( n = 3 \); \( R = (\text{C}_4\text{H}_9)_2 \)

Tutocaine which has greater duration of activity has two methyl groups on nitrogen while the chain has increased length and bulk (249, 248).

\[
\text{NH}_2-\text{C}_6\text{H}_4-\text{CO}_2\text{CH}_2\text{CH}-\text{CH-N(CH}_3)_2
\]

\[
\text{CH}_3\text{CH}_3
\]

Tutocaine
Secondary amines like butethamine, 2-isobutylaminoalkyl-4-aminobenzoate and naopaine 2-n-pentylaminoethyl-4-aminobenzoate are also good local anesthetics (93,91,126).

\[ \text{NH}_2\text{-C}_6\text{H}_4\text{-COCCH}_2\text{CH}_2\text{NHR} \]

Butethamine: \( R = \text{CH}_2\text{CH(\text{CH}_3)_2} \)
Naopaine: \( R = \text{C}_{13}\text{H}_{27} \)

Introduction of alkyl groups into the 4-amino group of the procaine type compounds increases the duration of activity. Tetracaine, 2-dimethylaminoethyl-4-butyramino benzoate is the best among such compounds.

\[ \text{C}_4\text{H}_9\text{-NH-\text{C}_6\text{H}_4\text{-CO}_2(\text{CH}_2)_2N(\text{CH}_3)_2} \]

Stovaine analogues with variation in the basic alcohol chain have been synthesised. Piperocaine, 3-(2-methylpiperidino) propylbenzoate is somewhat more potent and toxic than procaine (19,188).

\[ \text{C}_6\text{H}_5\text{-CO}_2(\text{CH}_2)_3\text{NH-N} \]

Piperocaine
Hexylcaine, (l-cyclohexylamino-2-propylbenzoate) is even more potent (19,103) and has found use especially in caudal and epidural anesthesia.

\[
C_6H_4CO_2CH - CH_2-NH-C_6H_{11}
\]

Hexylcaine

Various atoms or groups have been introduced in the benzene nucleus. The majority of the clinically useful substances contain amino group preferably in the para position. Introduction of an alkoxy group into the benzene nucleus was the most successful procedure for obtaining clinically acceptable drug of this type. In the case of basic esters from p-alkoxy benzoic acids an increase in the size of the alkyl group in the ether part led to an increase in the activity. Dialkylaminoalkyl-p-alkoxy benzoates are more active than alkyl-p-dialkyl aminoalkoxy benzoates indicating thereby the importance of basic function in the ester part of the molecule(226).
Diethylamino ethyl ester of amylsalicylic acid, prepared by Szadowska and Ciborska exhibited an anesthetic effect equal to that of procaine and toxicity only one half of procaine. On the introduction of two alkoxy groups, an increase of the the anesthetic effect was observed. Activity, frequently of a lower order has been observed in the case of esters of trialkoxy benzoic acid (214).

\[ 3,4,5 \text{ (OR)-C}_6\text{H}_2\text{COOCH}_2\text{CH}_2\text{N(Et)}_2 \]

Combination of alkoxy and or halogen groups with amino group in the benzoic acid moiety has led to the development of numerous clinically serviceable drugs (72, 191).

Benoxinate, 2-diethylaminoethyl-4-amino-3-n-butoxy-benzoate (239,286), propoxycaine, 2-diethylaminoethyl, 4-amino-2-proproxy benzoate (44, 47) and Ambucaine, (2-diethylaminoethyl-4-amino-2-n-butoxybenzoate) (44,177) are three closely related compounds that have been put to use. Hydroxyprocaine (diethylaminoethyl-4-amino-2-hydroxy benzoate) (116,287) is an agent that has been tested clinically and is of moderate activity (137,139).
(1) Benoxinate \[ R = \text{OC}_4\text{H}_9 \]
(ii) Propoxicaire \[ H \]
(iii) Ambucaine \[ H \]
(iv) Hydroxyprocaine \[ H \]

2-Dimethylaminoethyl-4-butylamino-2-hydroxybenzoate (98,138) and 2-diethylaminoethyl homolog possess longer duration of action.

Three, 3-aminobenzoic esters merit mentioning, namely, 2-isobutylaminoethyl-3-aminobenzoate (meta butethamine) (187,218) 2-diethylaminoethyl-3-amino-2-butoxybenzoate (metabutoxycaine) (72,143) and 2-diethylaminoethyl-3-amino-4-propoxybenzoate (proparacaine) (44,192).
The former two are relatively short acting, proparacaine is more potent than cocaine but is also of considerable toxicity.

\[
\text{R}^1\text{NH}_2\text{R}^2\text{CO}_2\text{CH}_2\text{CH}_2\text{R}^3
\]

(i) Metabutethylamine\[
\begin{array}{ccc}
\text{H} & \text{H} & \text{NHCH}_2\text{CH(CH}_3)_2 \\
\end{array}
\]
(ii) Metabutoxycai\[
\begin{array}{ccc}
\text{H} & \text{OC}_4\text{H}_9 & \text{N(C}_2\text{H}_5)_2 \\
\end{array}
\]
(iii) Proparacaine\[
\begin{array}{ccc}
\text{OC}_3\text{H}_7 & \text{H} & \text{N(C}_2\text{H}_5)_2 \\
\end{array}
\]

Piridocaine, 2-(2-piperidyl)-ethyl-2-amino-benzoate) (290) seems to be the only 2-aminobenzoic acid derivative that has passed preliminary pharmacological testing into the clinic (125).

The anesthetic effect of dimethyl, dialkyl and piperidino ethyl esters of \(\text{o-}, \text{m-}, \text{p-}\)fluorosubstituted benzoic acids and phenyl acetic acids, was proved to be less than that of procaine and they were irritating (208). A study of procaine derivative containing halogen, alkoxy groups and alkyl thio groups in 2- and 3-position in the
aromatic nucleus, revealed that methylmercapto and ethylmercapto derivatives were one and half times as active as cocaine (150). Chloroprocaine, (2-dialkylaminoethyl-4-amino-2-chloro benzoate) is close to procaine in anesthetic properties but probably is one of the systematically less toxic agents in use (79), a fact that is due to its fast metabolic hydrolysis (80).

The presence of a 4-substituted ether moiety is the common feature among the following examples:

Parethoxycaine (2-diethylaminoethyl)-4-ethoxybenzoate, and its homolog, stadacaine (191,227,237) and cyclomethycaine (190).

\[
\begin{align*}
4-\text{OC}_2\text{H}_5-\text{C}_6\text{H}_4-\text{CO}_2(\text{CH}_2)_2\text{N(C}_2\text{H}_5)_2 \\
Parethoxycaine \\
4-\text{OC}_4\text{H}_9-\text{C}_6\text{H}_4-\text{CO}_2(\text{CH}_2)_2\text{N(C}_2\text{H}_5)_2 \\
Stadacaine \\
\text{C}_6\text{H}_{11}\text{OC}_6\text{H}_4-\text{COO(CH}_2)_3\text{N(CH}_3)
\end{align*}
\]
Cyclomethycaine gives the longest anesthetic effect. It has certain use as a topical agent (229). The piperonylic acid derivative 2-diethylaminoethyl-3, 4-methyl enedioxybenzoate (153,214) has no particular use.

Local anesthetic action has also been observed in the 4-piperidyl esters of phenoxyacetic acids, cinnamic acid, and dihydrocinnamic acid (203). In these compounds the carboxylic acid group is not directly attached to the benzene ring.

Kucheruk reported that $\text{PhOCH}_2\text{COOC(Ph)(Et)}-\text{CH}_2\text{CH}_2\text{NMe}_2$ was three to four times as toxic as procaine but approximately eight times as active (145). Basic esters from furan, thiophene, pyrrole, pyridine, thiazole, quinoline, carbazole, dibenzofuran, and dibenzothiophene carboxylic acids have been prepared (201). The order of activity increases generally from furan through thiophene and pyrrole.
to benzene (262), but 2-furoates have been found more active than the corresponding benzoates in some cases (46). Basic esters of napthoic acid (23,77,111,232) anthracene carboxylic acid (157) and biphenyl carboxylic acids (42) possess local anesthetic properties and the effect of substitution in these carboxylic ring systems by imino, alkoxy and other groups follow largely the pattern laid down in the benzene series.

Of a large number of diesters of the following type studied those derived from aromatic acids

\[
\text{CO}_2\text{CHPhCH}_2\text{NR}_2 \\
/X \\
\text{CO}_2\text{CHPhCH}_2\text{NR}_2
\]

where \( X = -\text{CH}_2\text{CH}_2, -\text{OC}_6\text{H}_4, p-\text{C}_6\text{H}_4 \) and \( R = \text{lower alkyl or NR}_2 = \text{heterocycle} \). showed only slight anesthetic activity whereas the succinic acid esters were more active than lignocaine.
AMIDES:

Replacement of oxygen by imino group leads to isosteric compounds of similar properties, hence if oxygen of a basic ester is replaced by NH, a basic amide would be obtained.

\[ \text{RCOOR'} \quad \text{RCONHR'} \]

Ester Amide

NON-ANILIDE AMIDES:

Meisner (196) in an attempt to prepare antipyretics in the acetanilide series examined closely related heterocyclic compound and its ring homologue dihydrocarbostyril.

\[ \text{Oxindole} \quad \text{Dihydrocarbostyril} \]
As dihydrocarbostyril derivatiges exhibited narcotic properties, corresponding carboxylic acids in which the acidic function is weakened by amidation were studied. It was discovered that etherfification of the 2-hydroxyl group and substitution of amide group by basic radicals gave substances possessing local anesthetic properties. Dibucaine which is a 2-butoxy quinoline derivative, having a basic amide group, is active in a dilution of 1:120,000 as compared with 1:1000 of cocaine and 1:200 of procaine. In dialkylaminoalkyl esters of alkoxycinchoninic acids corresponding to dibucaine, maximum activity was noted again in 2-butoxy derivatiges but the position of the alkoxy group was of little consequence (304). 2-Butoxy-4-(3-diethylaminopropionamide)
quinoline a 'reversed' dibucaine is much less active and more toxic than dibucaine (30).

Shilov and Konf (240) have shown that hydrochloride salts of diethylaminoethylamide of 1-alkoxyisoquinoline-3-carboxylic acid possess local anesthetic activity. Amides of 3-substituted cinchoninic acid (106) do not show strong anesthetic activity. Local anesthetic activity of 2-methyl-4-benzyloxy decahydroquinoline derivatives has been compared with novocaine and cocaine (40).

Sieger (261) studied diethylaminoalkylamides of 3-hydroxy and 3-alkoxynaphthalene-2-carboxylic acid and found them more stable but more toxic as well, as compared to the corresponding esters of the aminoalkylamides derived from benzoic acids which have received the greatest
attention. In general these were less active and sometimes more toxic than lignocaine (171,178,179,176,269).

Honkanen (123) studied sterically hindered amides of aromatic acids. He found that (i) increasing the length of R in NR₂ intensified local anesthetic activity as well as toxicity and irritation, (ii) increase of 'n' from two to three reduced both activity and toxicity, (iii) di-o-substitution in benzoic acid part augmented the activity, (iv) p-alkoxy substitution enhanced local anesthetic effect but increased the toxicity. A maximum effect was obtained in the case of pentoxy derivative.

o-Alkoxybenzoic acid amides exhibited local anesthetic properties but the compounds were more toxic and produced greater irritation than did lignocaine (107).

Oxethazaine is about 2000 times as active as lidocaine but because of certain undesirable effects it has only limited application (14, 82,90).
ANILIDE AMIDES:

Einhorn (67) found that Nirvanine an acetanilide derivative showed local anesthetic properties along with many serious side effects. In a chemical study of the structure of Gramene, 3-(dimethylaminomethyl) indole, to determine the position of the side chain (285), it was found that 2-dimethylaminomethyl derivative as well as the
Gramine intermediate in its synthesis, 2-dimethylamino-2'-aceto-
toluidide, produced the typical local anesthetic response when tested on the tongue.

\[
2-\text{CH}_3-\text{C}_6\text{H}_4-\text{NHOCH}_2\text{N} \left(\text{CH}_3\right)_2
\]

2-Dimethylamino-2'-acetotoluidide

On investigation of related anilides Löfgren was able to develop lidocaine which can be considered as the nearest approach to an ideal local anesthetic. It is stable in solution and is more potent and faster in onset (296). The stability of lidocaine towards hydrolysis and hence prolonged activity, can be attributed to the presence of sterically hindered amide group. Lidocaine's toxicity is somewhat higher than that of procaine, the drug is nonetheless, relatively nontoxic, in contrast to most other local
anesthetics. Furthermore, it is well tolerated by the tissues.

\[ 2,6-(\text{CH}_3)\text{C}_6\text{H}_3\text{KHC0CH}_2\text{NET}_2 \]

The success of lidocaine started a surge of investigations of anilide derivatives. Löfgren prepared at the same time the qnalog trimecaine (2-diethylaminoacetomesidine) (92,169).

\[ 2,4,6-(\text{CH}_3)\text{C}_6\text{H}_2\text{NHOCH}_2\text{N}(\text{C}_2\text{H}_5)_2 \]

Trimecaine which has become one of the more commonly used agents in Eastern Europe (297) and somewhat later prilocaine, 2-propyl-amino-2'-propionotoluidide (173,294).

\[ 2-\text{CH}_3\text{C}_6\text{H}_4\text{NHOCH-NHC}_3\text{H}_7 \]

Ekenstam and co-workers had prepared two important clinically acceptable local anesthetics (68,114, 236,281).

Mepivacaine and Bupivacaine.
Mepivacaine possesses clinical properties of the lidocaine type, whereas bupivacaine is characterised by longer duration but also higher general toxicity and liability to cause irritation.

A large number of basic amides have been synthesised in recent years. Some of these along with relevant references are summarised below.

Alkylamino acyl anilides $\text{Ar-NCOR} \_ \text{NR}_3 \_ \text{R}_4$ (69);

N-aryl $\alpha$-diethylamino acetamides $\text{RC}_{6}^{\text{H}} \text{HCOCH}_{2} \text{NET}_2$ (18),

$\text{Ar-NHCOCH}_{2} \text{NET}_2$ ($\text{Ar} = \text{p-ClC}_{6}^{\text{H}}$; $\text{p-Br-C}_{6}^{\text{H}}$; $\text{2,5-Cl}_{2} \text{C}_{6}^{\text{H}}$ etc. (271), piperidino alkanoic acid anilides $\text{2,6-Me}_{2} \text{R-C}_{6}^{2} \text{H}_{2} \text{NHCO-Z-N pip R}_1 \_ \text{R}_2$ ($\text{R} = \text{H}$; $\text{R}_1 = \text{H}$ or $\text{2,5-Me}_2$; $\text{R}_2 = \text{4-OH}$ or $\text{4-(CH}_2)_3 \text{OH}$. $\text{Z} = \text{CH}_2$ or $\text{-CH}_2 \text{-CH}_2$ etc. (307),
aromatic acylamides substituted in both ortho positions
4,2,6-R, Me₂-C₆H₄-CNH(CH₂)_nNR₂ (R = H or alkoxy; R* = alkyl with 1 - 4 carbon atoms; n = 2 or 3) (154),
2,4-dimethyl-6-bromo-α-dieethylamino acetanilide 2,4,6-Me₂, Br-C₆H₂NHCCH₂NEt₂ (158), 2,5,6-tri-isopropyl-α-dieethyl-
amino (or other tert. base) acetanilide 2,4,6-(Me₂CH)₃
C₆H₂NHCCH₂X (X = tert. base as hydrochloride salt);
4-amino-α-dieethylamino acetanilide 4-H₂NRCOH₂NEt₂ (272),
α-(2-methyl-1-piperidyl)-acylanilide (174); N-dieethyl-
amino acetyl-4-substituted 2,6-xylidine dioxalate (204),
α-dieethylamino-4-amino-2,6-dimethyl acetanilide 2,4,6-Me₂, NH₂, Me-C₆H₂NHCCH₂NEt₂ (52), basically substituted acid
amides of the type 2,6-Cl, NH₂-C₆H₃NHCCH₂NRR' (73);
α-dieethylamino acetanilide derivatives 2,4,6-Me₂, R, Me,
C₆H₂NHCCH₂NEt₂ (7); basic acetyl mesidines 2,4,6-Me₃C₅H₂-
NHCCH₂NRR₂ (60 A), amino acylanilides 2,4,6-Me₂, R,
Me-C₆H₂NHCCH₂NEt₂ (R = H or Me) (6); substituted α-
diethylamino acylanilide containing alkoxy, aryloxy, aralkoxy
groups (238); α-diethylamino-2-methyl-6-ethyl acetanilide
2,6 Me, Et-C₆H₃NHCCH₂NEt₂ (74,75), amides of N-substituted
amino acids and 2,6-dichloroaniline 2,6-Cl₂C₆H₄NHCCHR=pip
(R = H; or Me) (200); 2-methyl acetanilide 2-Me-C₆H₄-
NHCOCH₂NR₁R₂ (180), diphenylacrylic acid dialkylaminoethyl
amides (135) and Ω-(diethylamino) Ar-phenoxy acetanilide
RC₆H₄-NHCOCH₂NEt₂ (R = OC₆H₅; O-CH₂C₆H₅; -OCH₂CH₂C₆H₅)
(251) were found to exhibit local anesthetic activity.

A series of aliphatic basic amides
R₁R₂N(CH₂)ₙCHR₃CONHR₄ (R₁ and R₂ are alkyl or heterocyclic
constituents, R₃ is alkyl, tert. alkyl and n = zero or
integral) have been prepared (25) by Ritter reaction. All
the compounds were tested and found active as local anesthetic,
spasmodics and hypertensive. Some basic amides of the
type R₁R₂N(CH₂)ₙCHR₃CONHR₄ (where R = Me, or Et and n = 0
to 12) and CMe₂(CH₂)ₙR (when R = alkyl or methyl substi-
tuted alicyclic) have been prepared. The compounds have
local anesthetics, analgesics and antispasmodic activity (26).
N-acyl-phenylcyclohexylamines was prepared and found its use
as a local anesthetic (273). Basic amides RCHNR₂CONHBU-tert.
were prepared by Girand (95), 9-(Aminoacetamido)-9,10-dihydro-
9, 10-ethanoanthracenes (265), dialkyl aminoacetamidopyrroles
(221), 6-(aminoacetamido) dihydro-1,3-benzoxazine-2,4-diones
(152), basic N-(Ω-cycloalkylbenzyl) acylamides and their
related compounds (165), 1-acetylaminoanthraquinone with basic substituents (209), 9-aminoacetamido-9, 10-dihydro-9, 10-ethanoanthracenes and their salts (129), 5-diethylamino acetamido-2-arylimino-2-aryl-4-thiazolidinones (20), 2-amino-N-(phenylalkyl) alkanamides (167), 2-(diethylamino)-N-napthol (1,2-)thiazol-2-yl (21), 2-\textsubscript{∞}-(2-pyridyl-amino) acetamido and 2-(\textsubscript{∞} anilinoacetamido) benzothiazoles (267), (\textsubscript{∞}, \textsubscript{∞}-p-trimethylbenzyl) acylamides (166) methoxylated derivatives of N-N-secondaryamino (\textsubscript{∞}-aminoacyl-1-2-di phenyl ethyl) acetamide (13), 5-acetamido-3-aryl-2-arylimino-4- thiazolidinone (43), 3-methyl/phenyl-4-(dialkylaminoacetyl) amifurazans (10).

Some 2-2-(disubstituted amino) acetamido benzothiazole hydrochloride (22) and m-(aminoacetamido) benzoates (205) show local anesthetic activity. 2-(2-amino- alkanamido)-3-phenylnorbornanes show analgesic activity (198), p-acetamido-N-2-(diethylamino) ethyl benzamide hydrochloride exhibits antiarrhythmic activity (247).

Dalal and Trivedi prepared N-benzylacetamides (53,54), N-(\textsubscript{∞}-alkyl/aryl/benzyl) acylamides (55), N-(\textsubscript{3}-phenylalkyl)-acylamides (56). Shah and Trivedi
prepared N-(substituted benzyl) phenyl acetamides (252), Shah, Trivedi and Patnaik prepared N-(substituted benzyl) acylamides (253). Patel and Trivedi prepared \( \alpha \)-secondary-amino-N-(substituted 1,2-diarylethyl) acetamide (211), secondary-N-(substituted benzyl), acetanilides (212), secondaryamino-N-(phenoxyalkyl)-acetamides (210), Shroff and Trivedi prepared N-(2-4-alkoxybenzyl) and 4-methoxybenzyl) acetamides and \( \alpha \)-benzylamino/dibenzylamino N-benzyl acetamides (259), Miyajiwala and Trivedi prepared N-aralkyl acetamides and N-(\( \beta \)-aryloxyethyl) acetamides (199). Shah and Trivedi prepared \( \alpha \)/\( \beta \)-secondaryamino-N-(1,2-diarylethyl)-propionamides, \( \alpha \)-secondaryamino-N-(\( \alpha \)/\( \beta \)-phenylalkyl) acetanilide and \( \alpha \)-secondaryamino-N-benzal-2,6-dimethyl acetanilide (254), Shah and Trivedi prepared \( \alpha \)-secondaryamino-N-(diaryl alkyl)-acetamides and \( \alpha \)-secondaryamino-N-(cyclohexyl aryl alkyl) acetamides (254A). These compounds 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 them are summarized below:

\[ \alpha \text{-Diethylamino-N-(} \alpha \text{-methyl, carbalkoxy benzyl) acetamide } \text{PhCRR'} \text{NHCOCH}_2 \text{NET}_2 \ (R = CH}_3, R' = \text{COOBt}) \]

and \( \alpha \)-(N, N-ethyl carbalkoxymethylamino) 2: 6-substituted acetanilides 2, 6-\( \text{Me}_2C\text{C}_6\text{H}_3\text{NHCOCH}_2\text{NET}-\text{CH}_2\text{COOBt} \) (172),
/β-(dialkylamino)-butyranilide derivatives RR'C₆H₅NHCOCH-
CH(Me)NR'R" (88). /β-isopropyl amino-N-(2,6-dimethyl)propi-
anilide 2,6-Me₂C₆H₅NHCOCH₂NHMe₂ (170), diacetylamo acyl-
amides R"(CH₂)n CH(R)CONHR' (26), diethylamine ethoxy-p-cyclo-
hexyl acetonilide p-RC₆H₄NHCOCH₂O(CH₂)₂NEt₂ (R = cyclohexyl)
(101), 1-(2-methyl-1-piperidyl) acylanilides (174), /β -
dimethylamino-p-chlorobutyranilide p-CI₂C₆H₄NHCO-CH₂CH=CH-
(CH₃)₂ (298) derivatives of 2,6-diethyl 4-methyl-o-butylamino acyl-
anilides, 2,6,4-Et₂MeC₆H₂NHCOCH₂NH(C₄H₉) (8) 1-(butylamino-
acetamido)-2-nitro-6-chlorobenzene 2,6-NO₂,C₁-C₆H₃NHCOCH₂
NH₄H₉ (61), 2-methyl-6-carbalkoxy-N-(amino alkyl) acylanilides
2,6-Me(COOR)-C₆H₃NHCOXR'R" (R' = Me or Et; X = CH₂ ;
(CH₂)n ; CHMe; CHMe₂ ; R' = lower alkyl ; R" = H or lower
alkyl (118); 4-(α)-alkylamino acylamido) salicylates 3,4(OH)
(ROOC)-C H NHCO-(CH₂)n NR'R" (R = CH₃ , n-C₆H₁₃ ; etc. n = 1 ;
nR'R" = diethylamino, isopropylamino, piperidion) (39), /β-isop-
propylamino-2-methyl propionanilide OMeC₆H₄NHCOCH₂CH₂-NH(C₃H₇)
(295), α-propylamino propiono-o-toluidide and α-isopropyl-
amino propiono-o-toluidide (175), 1-(α-N,N-diethylamino pro-
pionylamino)-2 or 4-alkoxy napthalene derivatives (306),2-di-
ethylamino propionanilide derivatives (146,147), and 2-amino-2-
methyl propionanilide (268).

A large number of amides, some of them
containing phenoxy group has been found to show local
anesthetic activity : Dialkylamino amides R₁R₂N(CH₃)n-
CHR₃CONHR₄ (25), 2-phenoxy acetamide derivatives (85 ),
basic amides of acids acting as plant growth regulators

ROCH₂CONHCH₂CH₂NET₂ (R = aryl) (277), N,N-disubstituted

amides of arylacetic acids (9), 2-phenoxy acetamides-

amides of 4,2 CH₂ = CHCH₂(MeO)-C₆H₃OCH₂-COOH (278)

2-methoxy-4-butyrylphenoxy acetic acid diethylamide (6),

N, N-disubstituted mono (aminoalkyl) amides RCONHNR'=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 (38), ω-benzyl-ω-(2-morpholinoethyl)−

N-propyl-N-benzyl phenylacetic acid amides (9), amides of

the type P-C₆H₄-6-CH₂CONHCH₂CH₂NW₂ or -NB₂ and

C₁₀H₇CH₂CONHCH₂CH₂NB₂ (37), 2-(4-allyl-2-methoxy phenoxy)

-N, N'-diethyl acetamide (305), aryloxy acetamides 2,4-MeO-

4CH(OH)C₆H₃OCH₂CONB₂ (86), 2,4-(OEt) (CH = CHCH₂)-C₆H₃-

OCH₂CONR₂ (R = Pr, Et and NR₂ = piperidino) (87), alkoxy-

benzamides ROC₆H₄-CNH(CH₂)n-N-C₄H₈ (260), amides of 2-metho-

xy-4-allyl phenoxy - ω-isobutyric acid (35), phenoxy dia-

kylamino acylanilides (136), N, N-diethyl-2-4-(hydroxy

alkyl) -2-methoxyphenoxy acetamides (168), 2-diethyldiamino −

Ar-phenoxy acetalanile R-C₆H₂NHCOCH₂NET₂ (R = o,m,p-C₆H₅;
-OCH₂C₆H₅; OCH₂CH₂C₆H₅ (251), α-butyryl-amino-/β-
chloro-propionalilides and 4-chlorobutyranilides (182),
N,N-dialkyl (2-alkoxy-4-acyloxy alkyl) phenoxy acetamides
(84), 2-Methoxy-4-allyl phenoxyacetic acid diethylamide
(262) and 2-(2-4-dichlorophenoxy)-N-(piperidinomethyl-
acetamide) (184).

MISCELLANEOUS AMIDES:

p-Aminothio-α-dimethylamino acetanilide (149), piperidino acylanilides XG₆H₄SCH₂CH₂NPhCO(CH₂)₄N-G-C₆H₆ (131), derivatives of diphenyl ether carboxylic acids of
the type, diphenylether-4-carboxylic acid diethylaminoethyl
amide hydrochloride XG₆H₄-O-C₆H₄-CONH(CH₂)₂R-HCl (X = p-Me,
NEt) (151), N-benzyl-N-(α-dimethylamino ethyl) cinnamide
(282); amides like

\[
\begin{align*}
\text{HCl-R'H}_2\text{C} & \\
\text{4-R-C}_6\text{H}_4\text{CONH} & \\
\end{align*}
\]

(R = BuO, -OC₅H₁₁, -OCH₂Ph, R' = piperidino, NMe₂) (276),
o-N-diisopropylamino ethoxybutyrophenone (57); and o-(2-
diisopropylaminoethoxy) butyrophenone(219) show significant
local anesthetic activity. Many heterocyclic basic amides are powerful local anesthetics. 10- (γ-amino) butyryl derivative of phenothiazine exhibits local anesthetic activity (50).

![Chemical structure of phenothiazine](image1)

Even properly hindered aliphatic amides like N-(α,α-dimethyl-octyl)-piperidino acetamides are active (17).

Dalal and Trivedi (53,54,55,56,170) showed that basic amides from substituted benzylamines show local anesthetic activity. This led Collins and Large (45) to synthesise related compounds which were found to be active.

**AMIDINES**

Phenacaine (Holocaine) (104) is the best known local anesthetic agent among the amidines tested.

![Chemical structure of Phenacaine](image2)
GUANIDINES:

Acoin is a guanidine derivative used as infiltration anesthetic drug (124).

URETHANES AND UREAS:

Phenyl urethane \( \text{C}_6\text{H}_5\text{NHCOOC}_2\text{H}_5 \) was found to exert effects on isolated systems similar to those observed with local anesthetic (182). Following this lead several useful urethanes possessing local anesthetic activity have been synthesised. Esterification of a series of dialkylaminoalcohols with phenyl carbamic acid gave compounds of the type

\[ \text{C}_2\text{H}_5\text{O} - \text{N} = \text{C} - \text{OCH}_3 \]

\[ \text{NH} - \text{NH} - \text{OCH}_3 \]
which showed local anesthetic activity but were also irritant. The rise in toxicity followed the order, morpholino \( \mathrm{NMe}_2 \) \( \mathrm{NET}_2 \) \( \mathrm{NBu}_2 \) \( \mathrm{NPr}_2 \) \( \mathrm{N}(\text{isopropyl})_2 \) (231). Compounds of the type PhNHCOOCHPhCH\(_2\)CH\(_2\)NMe\(_2\) were also active though slightly irritating (230). The compound

\[
2\text{-Cl-}C_6H_4\text{-NHCOOC}_2\text{H}_2\text{NEt}_2
\]

has only one-third activity of cocaine on the rabbit cornea (71). 3-Piperidinopropylenedicarbanilate (diporodan) has been accepted as a local anesthetic (193, 222, 223). Phenyl urethanes of diacylaminoalcohols \( C_6H_5\text{NHCOO}(\text{CH}_2)_n\mathrm{NR}_2 \) showed considerable activity (26).

Lengthening of alkyl chain was associated with more rapid induction but increasing toxicity. Urethane from 2,6-dimethyl aniline was more active as compared to lidocaine while the corresponding urea derivative was inactive.
Diaryl carbamates of the following type were also highly active as local anesthetic.

\[ R_1 - C_6H_4 - N - C_6H_4 - R_2 \]
\[ \text{COOCH}_2\text{CH}_2\text{NET}_2 \]

The compound with \( R_1 = H \), \( R_2 = \text{3-BuO} \) was 75 times as active as cocaine and 40 times as active as procaine.

**AMINO KETONES**

Beani and Fowst (15) studied propiophenone type of compounds:

\[ 4-R-C_6H_4-\text{COCH}_2\text{CH}_2-N-C_5H_10 \]

(a) \( R = OC_3H_7 \); Falicain

(b) \( R = OC_4H_9 \); Dyclonine

and also studied compounds in which ketonic group was replaced by CHOH, CH\(_2\), CH = CH and showed that local
anesthetic activity resided in ketones. The ketones of course were irritant. Falicaine and Dyclonine were two important local anesthetics which belong to this type (215).

Replacement of benzene ring in falicaine by thiophene reduces the activity (1, 216).

**AMINO ETHERS**

When it was recognised that amino alkyl amides owe their prolonged local anesthetic action to the much lower rate of hydrolysis as compared with that of the older aminoalkyl esters, it became apparent that aminoalkylethers might be even longer lasting because ether linkages are more resistant to hydrolysis than the amide link. Two compounds belonging to this class that have been introduced are dimethisoquin, 3-buty1-1-(2-dimethyl-aminoethoxy)-isoquinoline and pramoxine, 4-[3-(4-butoxyphenoxy) propyl] morpholine. Both are recommended only for topical use (242, 301).

![Dimethisoquin](image1)

![Pramoxine](image2)
MISCELLANEOUS SUBSTANCES CONTAINING NITROGEN:

Simple amines like 2-2'-diamino 1,1'-binapthyl, 2-2'-diaminobiphenyl and 9-aminofluorene show local anesthetic activity (41).

Several N-N-dialkyl substituted dimethylamino ethylamines have been found to exhibit local anesthetic activity (25). Simple amino alcohols with sufficiently high molecular weight produce local anesthesia. Thus 3-amino-6-methyl heptanol-4-(CH₃)₂CHCH₂CHOH.CH(CH₃)₂.NH₂ and 1-phenyl-2-amino pentanol-1, (C₆H₅-CHOH.CH(NH₂).CH₂CH₂CH₃ show definite activity (133). Low molecular weight alcohols when acylated also show local anesthetic activity. The powerful poison tetrodotoxin found in certain species of the family Tetraodontidae (e.g. puffer fish) block nerves reversibly at concentration that are lower than those of other known compounds (0.01 μg/ml).

\[
\begin{align*}
&\text{OH} &\text{OH} &\text{OH} \\
&\text{HN} &\text{OH} &\text{OH} \\
&\text{H₂N} &\text{NH} &\text{OH} \\
&\text{OH} &\text{OH} &\text{OH}
\end{align*}
\]
Whereas at least a reasonable lipid solubility has been a common feature of all local anesthesia, tetrodotoxin is a highly hydrophilic substance and its structure is unrelated to any local anesthetic (94, 181, 279).

**NITROGEN FREE LOCAL ANESTHESIA**

Phenol, guaiacol, eugenol, benzylalcohol, phenylethyl alcohol, benzoyl carbinol and chloretone $(\text{CH}_3)_2\text{C(OH)CCl}_3$ show local anesthetic activity (181).

Soehring (266) showed that certain polyglycol ethers [e.g. thesit $\text{C}_{12}\text{H}_{15}(\text{OCH}_2\text{CH}_2)_9\text{OH}$] are active as local anesthetic. All these compounds also show irritating activity.
PRESENT WORK

A large number of basic amides have been synthesised in this laboratory from a variety of aralkyl amines and some of these have shown significant local anesthetic and antifibrillatory properties. This has been summarised earlier in this part of the thesis. The encouraging results obtained so far induced us to investigate further variations in the amine part of the molecule.

We thought of studying basic amides containing two basic centers in the same molecule. The fundamental structure of such compounds would be as shown below:

\[
\text{R} - \text{CH} - \left( \text{CH}_2 \right)_n - \text{CH} - \text{R}
\]

\[
\text{NHCOCH}_2^+ \text{NR}_1 \text{R}_2 \quad \text{NHCOCH}_2^+ \text{NR}_1 \text{R}_2
\]

Such a compound is likely to have a different mode of attachment, to the receptor centers of the nerve fibre as compared to simple basic amides studied so far.
d-Tubocuraine possess two quaternary nitrogen atoms in its molecule and this feature of the molecule is considered essential for the curare-form activity.

Many bis-onium salts synthesised on the pattern of d-tubocurarine also possess two quaternary nitrogen atoms per molecule. These compounds can be represented as follows.

\[ \text{R}_3\text{N} (\text{CH}_2)_n \text{N(CH}_3)_3 \]
Decamethonium \((n = 10, R = \text{CH}_3)\) is one of the most potent curare-like agents known. Pentamethonium \((n = 5, R = \text{CH}_3)\) and Hexamethonium \((n = 6, R = \text{CH}_3)\) are important ganglionic blocking agents.

The desired compounds have been prepared as per scheme shown below.

\[
\begin{align*}
&\text{COCl} \\
&\left(\text{CH}_2\right)_n \text{COCl} + 2 \text{CO} \\
&\text{F.C. AlCl}_3 \\
&\text{Leuckart Reaction} \\
&\text{ClCOCH}_2\text{Cl}
\end{align*}
\]
where $R = H, 4-\text{CH}_3, 4-\text{Cl}, 4-\text{OCH}_3, 2,4-(\text{CH}_3)_2, 2,5-(\text{CH}_3)_2, 3,4-(\text{CH}_3)_2$

$NR_1R_2 = \text{diethylamino/morpholino/piperidino}$
THEORETICAL

Some important methods for the preparation of primary amines required in the present work are discussed below. These methods fall into four main groups.

1. Ammonolysis of halogen compounds.
2. Reduction of various types of nitrogen compounds.
3. Degradation methods.
4. Miscellaneous methods.

1. AMMONOLYSIS OF HALOGEN COMPOUNDS:

(A) \[ R \text{--Cl} + \text{NH}_3 \rightarrow R\text{NH}_2\text{HCl} \]

In general, the reaction between ammonia and an alkyl halide is effected by heating the reactants in alcoholic solution in a sealed tube, or in an autoclave or by keeping the mixture of ammonia and alkyl halide at room temperature (121).

The reaction of ammonia with alkyl halides generally forms a mixture of primary, secondary and tertiary amines and even a certain amount of quaternary ammonium halide.
(B) **Gabriel Synthesis.**

The primary amines are conveniently synthesised by the facile alkylation of phthalimide and subsequent hydrolysis of **N**-substituted derivatives. Substituted phthalimide was originally prepared by heating a mixture of phthalimide, potassium carbonate, and organic halide in a non-polar solvent for 2 to 24 hours at 100 to 150° (127). Substituted phthalimide is also prepared by an improved procedure which consists in performing this step in polar solvent in which potassium phthalimide is appreciably soluble, the reaction occurs at room temperature within 10 minutes (258). Hydrolysis may be carried out directly by refluxing the alkylated phthalimide in basic or acidic solution or by the action of hydrazine hydrate followed by acidification (127).

![Chemical Reaction](image)
Primary amines are obtained by interaction of alkyl halides with hexamine in chloroform or alcohol solution. The quaternary ammonium salts formed are converted to primary amines by heating with hydrochloric acid (59, 83, 97, 115).

\[
RCH_2Cl + C_6H_{12}N_4 \rightarrow (CH_2)_6N_4RCH_2Cl
\]

\[
6(CH_2)_6N_4RCH_2Cl + 8NH_3 \rightarrow 3(RCH_2N = CH_2) + 5(CH_2)_6N_4 + 6NH_4Cl
\]

\[
3(RCH_2N = CH_2) + 6HCl + 6H_2O \rightarrow 6RCH_2NH_2HCl + 6CH_2O
\]

Benzylamines have been prepared by this method (96, 97), certain haloketones (183) halo acids (24, 290)
and halo esters (24) are converted into corresponding amines by this method.

Benzyl amines have also been prepared by reaction with formamide, acetamide and urea and hydrolysing the resulting products formed (12, 141, 144).

2. REDUCTION OF VARIOUS TYPES OF NITROGEN COMPOUNDS

(A) NITRO COMPOUNDS

Reduction with a metal acid combination like granulated iron and small quantity of acid is an excellent method for the conversion of nitro compounds to primary amines (113, 293).

(B) REDUCTION OF AMIDES

Reduction of amides with sodium and alcohol results in the formation of both alcohols and amines (28, 99, 112). As convenient and efficient laboratory method, lithium-aluminium hydride was used in a suitable solvent for reduction of amides to amines. Here secondary and tertiary amines are not formed (62, 102, 119, 134, 140, 207, 270, 280, 299).
\[ 4R-\text{CONH}_2 + 4\text{LiAlH}_4 \rightarrow 2(R\text{CH}_2N = )_2\text{LiAl} + 2\text{LiAlO}_2 + 8\text{H}_2 \]

\[ (R\text{CH}_2N = )_2\text{LiAl} + 4\text{H}_2\text{O} \rightarrow R\text{CH}_2\text{NH}_2 + \text{LiOH} + \text{Al(OH)}_3 \]

\[ \text{CH}_3\text{CH}:\text{C(CH}_2)_2\text{CONH}_2 \rightarrow (\text{C}_2\text{H}_5)_2\text{CHCH}_2\text{NH}_2 \]

**C** REDUCTION OF OXIMES, PHENYHYDRAZONES AND ALDIMINES.

This may be accomplished by a wide variety of methods (4,228,303).

\[ (\text{CH}_3)_2\text{CH}-\text{CH} = \text{NOH} \quad 4\text{H} \rightarrow (\text{CH}_3)_2\text{CHCH}_2\text{NH}_2 + \text{H}_2\text{O} \]

\[ (\text{CH}_3)\cdot(\text{C}_3\text{H}_7)\text{C} = \text{NNHC}_6\text{H}_5 \quad 4\text{H} \rightarrow (\text{CH}_3)\cdot(\text{C}_3\text{H}_7)\cdot\text{CHNH}_2 + \text{C}_6\text{H}_5\text{NH}_2 \]

\[ \text{C}_3\text{H}_7\text{CH} = \text{NCH}_3 \quad 2(\text{H}) \rightarrow \text{C}_3\text{H}_7\text{CH}_2\text{NHCH}_3 \]

Oximes can also be reduced by lithium aluminium hydride to yield primary amines free from secondary amines (31).
The reduction of nitriles to amines may be effected with sodium and alcohol (100,155,156,233,234,283) and by catalytic methods. Catalytic hydrogenation of nitriles yields a mixture of primary and secondary amines (5,235,302). Reduction proceeds in two stages, aldimine formed in the first stage undergoing reduction to primary amine.

\[
\text{RCN} \rightarrow \text{RCH=NH} \rightarrow \text{RCH}_2\text{NH}_2
\]
The primary amine may react with the aldimine to give an azo-methine (\(-\text{CH} = \text{N-}\)) compound, and the reaction of the latter accounts for the formation of secondary amine.

\[
\text{RCH} = \text{NH} + \text{RCH}_2\text{NH}_2 \rightarrow \text{RCH} = \text{NCH}_2\text{R} + \text{NH}_3
\]

\[
\text{RCH} = \text{NCH}_2\text{R} \rightarrow (\text{RCH}_2)_2\text{NH}
\]

The yield of primary amine is increased at the expense of side reaction by using alcohol as solvent containing an equivalent of hydrochloric acid (110).

Raney nickel and also Raney cobalt have been found to be very effective for these reductions, generally using a high pressure of hydrogen with alcoholic ammonia, as solvent (142,194,220,244,250). An alternative method consists in carrying out the hydrogenation (platinum oxide catalyst) in acetic anhydride when the amine undergoes acetylation as it is formed and hence formation of secondary amines is suppressed (36,58).

A general method consists in using lithium aluminium hydride in ether. It has been used not only with
simple nitriles but also for the reduction of cyanohydrine to /3-hydroxy amines. In these methods secondary amines are not formed (207).

\[ 4RC \equiv N + 2\text{LiAlH}_4 \rightarrow 2(RCH_2\equiv N)\text{LiAl} \]
\[ (RCH_2\equiv N)\text{LiAl} + 4\text{H}_2\text{O} \rightarrow 2RCH_2\text{NH}_2 + \text{LiOH} + \text{Al(OH)}_3 \]

3. DEGRADATION METHODS

(A) HOFMANN REACTION

In Hofmann reaction carboxylic acid amides are converted to primary amines containing one carbon atom less, by the action of bromine or chlorine and alkali (122,289). The reaction proceeds through the following four steps.

(i) \[ \text{C}_2\text{H}_5\text{CONH}_2 + \text{Br}_2 + \text{OH} \rightarrow \text{C}_2\text{H}_5\text{CONHBr} + \text{Br}^- + \text{H}_2\text{O} \]

(ii) \[ \text{C}_2\text{H}_5\text{CONHBr} + \text{OH} \rightarrow \text{C}_2\text{H}_5\text{C(OH)NBr} + \text{H}_2\text{O} \]
The intermediate formation of isocyanates in the above reaction accounts for the formation of ureas and urethanes which are formed in the case of higher acids.

\[
\text{RNCH} + \text{OHR} \xrightleftharpoons{} \text{RNHCONHR} + \text{CO}_2
\]

\[
\text{RNCO} + \text{H}_2\text{O} \xrightarrow{\text{Hydrolysis}} \text{RNHCONHR} + \text{CO}_2
\]

(B) **Schmidt Reaction**

Carboxylic acids react with hydrazoic acid in presence of strong mineral acids to give primary amines with loss of carbon dioxide (241).

\[
\text{RCOOH} + \text{N}_3\text{H} \xrightarrow{} \text{RNH}_2 + \text{CO}_2 + \text{N}_2
\]
This method generally gives better yields of primary amines than Hofmann and Curtius reactions, but it is somewhat dangerous because of explosive and poisonous character of hydrazoic acid.

(C) CURTIUS DEGRADATION.

Acid azides formed from hydrazide under the action of nitrous acid are unstable and decompose on heating to give isocyanates. When the reaction is carried out in alcoholic solution, the isocyanate first formed reacts with an alcohol and a urethan is formed, from which a primary amine may be obtained by hydrolysis (49, 264).

\[
\begin{align*}
\text{RCONH} - \text{NH}_2 & \quad \rightarrow \quad \text{RCON}_3 + \text{RN} = \text{C} = \text{O} \\
\text{RN} = \text{C} = \text{O} & \quad \xrightarrow{\text{EtOH}} \quad \text{RNCOOEt} \quad \xrightarrow{\text{HCl}} \quad \text{RNH}_2
\end{align*}
\]

(D) BECKMANN TRANSFORMATION.

When ketoximes are treated with certain reagents, such as phosphorus pentachloride, and the products
are treated with water, substituted amides are formed, which may be hydrolysed to the corresponding primary amines (16). With mixed ketones isomeric products are obtained.

\[ 2RR'C = NOH \xrightarrow{} RCONHR' + R'CONHR \]

(E) FROM AMINO ACIDS.

Amino acids are decarboxylated when they are heated with diphenylamine (130).

\[ RCH(NH_2)COCH \xrightarrow{} RCH_2NH_2 + CO_2 \]

4. MISCELLANEOUS METHODS

(A) FROM ALDEHYDES AND KETONES BY LEUCKART REACTION.

Aldehydes and ketones are converted to the formyl derivatives of amines when they are heated with ammonium formate (159). This method appears best for aromatic aldehydes and water insoluble ketones boiling at about 100° or higher. Higher aliphatic ketones, aromatic aldehydes and ketones and certain terpenoid ketones, have
been used successfully. Application of this reaction to aliphatic aldehydes and ketones of lower molecular weight has been very limited. The method is superior to that involving the formation and reduction of aldoximes and ketoximes and succeeds where the reduction of oximes is unsatisfactory, particularly with compounds in which functional groups are present that are readily attacked by many reducing agents. The reduction of oximes of halogen substituted acetophenones with sodium and ethanol, sodium amalgam and acetic acid or by catalytic means proceeds with extensive removal of the nuclear halogen group(11,9). In addition to primary amines, secondary amines and tertiary amines are formed in small amounts. Primary and secondary amines in the presence of formic acid react in an analogous manner (288,291).

\[
RR'C = O + HCOONH_4 \rightarrow RR'CHNHCHO \rightarrow RR'CHNH_2
\]

This reaction is not limited to ammonium formate or formamide. Methyl formate has been used with a few primary amines. Substituted ammonium formates, such as monomethyl or dimethylammonium formate, react satisfactorily
and lead to the formation of secondary and tertiary amines of mixed type that cannot be obtained easily by other methods (33, 206).

(B) FROM ALDEHYDES AND KETONES BY REDUCTIVE AMINATION.

A versatile method for the preparation of amines consists in hydrogenating aldehydes or ketones in alcoholic ammonia in the presence of nickel catalyst (70, 197). A wide range of experimental conditions is available and the method, sometimes known as reductive alkylation, is applicable to primary and secondary amines with the production of secondary and tertiary amines. For obvious reasons, the method can only be used to attach primary or secondary alkyl groups to nitrogen.

\[
\begin{align*}
\text{C}_6\text{H}_3\text{COCH}_3 & \xrightarrow{\text{Ni/H}_2} \text{C}_6\text{H}_3\text{CHNH}_2\text{CH}_3 \\
\text{C}_3\text{H}_7\text{CHO} + \text{C}_3\text{H}_7\text{NH}_2 & \rightarrow \text{C}_4\text{H}_3\text{NHC}_3\text{H}_7 \\
2\text{CH}_3\text{CHO} + \text{NH}_3 & \rightarrow (\text{C}_2\text{H}_5)_2\text{NH}
\end{align*}
\]
I have used Friedal Crafts Reaction for the preparation of \( \omega,\omega' \)-diacyl alkanes in the present work.

\[
R \quad \text{CO} - (\text{CH}_2)_n - \text{CO} \quad R
\]

<table>
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<th>( n )</th>
<th>( R )</th>
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<td>27.</td>
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<td>4-Cl</td>
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<tr>
<td>28.</td>
<td>8</td>
<td>4-OCH$_3$</td>
<td>130</td>
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</table>
I have used Leuckart Reaction for the preparation of \(\alpha,\omega\)-diaryl, \(\alpha,\omega\)-diamino alkanes in the present work.

\[
\begin{align*}
\text{R} & \quad \text{CH} \quad \text{(CH}_2\text{n} \quad \text{CH} \quad \text{R} \\
\text{NH}_2 & \quad \ldots \quad \text{NH}_2
\end{align*}
\]

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<thead>
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<th>B.P.</th>
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<td>180-82/0.3 mm.</td>
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<tr>
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<td>210-225/1 mm.</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>2,4(CH(_3))(_2)</td>
<td>235-245/1.5 - 2 mm.</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>2,5(CH(_3))(_2)</td>
<td>205-225/1 - 1.5 mm.</td>
</tr>
<tr>
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<td>4</td>
<td>4-OCH(_3)</td>
<td>220-235/2 mm.</td>
</tr>
<tr>
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<td>5</td>
<td>H</td>
<td>210-220/1.5 mm.</td>
</tr>
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<td>4-CH(_3)</td>
<td>235-245/1.5 mm.</td>
</tr>
<tr>
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<td>5</td>
<td>3,4(CH(_3))(_2)</td>
<td>215-230/2 mm.</td>
</tr>
<tr>
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<td>5</td>
<td>4-Cl</td>
<td>245-255/3 mm.</td>
</tr>
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<td>208-220/2 mm.</td>
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<td>H</td>
<td>192-220/2 mm.</td>
</tr>
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<td>4-CH(_3)</td>
<td>232-256/1.5 mm.</td>
</tr>
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<td>6</td>
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<td>215-225/0.5 mm.</td>
</tr>
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<td>212-228/0.4 mm.</td>
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<td>210-225/0.3 mm.</td>
</tr>
<tr>
<td>16</td>
<td>6</td>
<td>4-OCH(_3)</td>
<td>230-242/2.5 mm.</td>
</tr>
<tr>
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<td>n</td>
<td>R</td>
<td>B.P. °C</td>
</tr>
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<td>---</td>
<td>---------------</td>
<td>-----------</td>
</tr>
<tr>
<td>17</td>
<td>7</td>
<td>H</td>
<td>205-228/1.0-1.5 mm.</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>4-CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>255-266/3.0-3.5 mm.</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>3,4(CH&lt;sub&gt;3&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>225-240/4 mm.</td>
</tr>
<tr>
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<td>4-Cl</td>
<td>225-240/5 mm.</td>
</tr>
<tr>
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<td>4-OCH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>262-280/5 mm.</td>
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<tr>
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<td>H</td>
<td>215-225/0.6 mm.</td>
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<tr>
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<td>2,4(CH&lt;sub&gt;3&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>210-220/1.0-1.5 mm.</td>
</tr>
<tr>
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<td>8</td>
<td>2,5(CH&lt;sub&gt;3&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>230-250/1 mm.</td>
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<td>8</td>
<td>3,4(CH&lt;sub&gt;3&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>235-246/3 mm.</td>
</tr>
<tr>
<td>27.</td>
<td>8</td>
<td>4-Cl</td>
<td>270-282/3.0-3.5 mm.</td>
</tr>
<tr>
<td>28.</td>
<td>8</td>
<td>4-OCH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>252-264/4 mm.</td>
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</table>
METHOD OF PREPARATION OF HALOACYLAMIDES

These have been prepared mainly by two methods:


(2) Condensation of amines with haloacetylhalide in presence of:
   (ii) sodium acetate and glacial acetic acid [Samdahl, Gerstad and Rydstorm, Ann. Pharm. France 12, 125-32 (1954)]
   and
   (iv) in benzene [Bespegnol, Neodeme and Aurosseau, Bull Soc. Pharm. Lille, No. 1, 81-85 (1955)] or
   (v) in ether [Toyozo Takada, Japan, 6879 (1955), Chem. Abstr., 52, 1257 (1958)].

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

\[ R-\text{NH}_2 + \text{ClCOCH}_2\text{Cl} \rightarrow \text{RNHCOCH}_2\text{Cl} + \text{HCl} \]

Following haloacylamides were prepared.
**1,4-DIARYL, 1,4-DI(CHLOROACETAMIDO) ALKANES**

![Chemical Structure](image)

<table>
<thead>
<tr>
<th>No.</th>
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<th>M.P. °C</th>
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</thead>
<tbody>
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<td>1.</td>
<td>4</td>
<td>H</td>
<td>187</td>
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<tr>
<td>2.</td>
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<td>4-CH₃</td>
<td>198</td>
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<tr>
<td>3.</td>
<td>4</td>
<td>4-OCH₃</td>
<td>162</td>
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<tr>
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<td>4</td>
<td>2,4(CH₃)₂</td>
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<td>5</td>
<td>H</td>
<td>92</td>
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<td>4-CH₃</td>
<td>76</td>
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<td>122</td>
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<td>116</td>
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<td>3,4(CH₃)₂</td>
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<td>11.</td>
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<td>H</td>
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<td>4-CH₃</td>
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<td>19.</td>
<td>7</td>
<td>4-OCH₃</td>
<td>106</td>
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<td>H</td>
<td>95</td>
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METHOD FOR THE PREPARATION OF \( \alpha \)-SECONDARY AMINOACYLAMIDES

\( \alpha \)-Secondaryamino N-aralkyl acylamides have been prepared by condensing N-aralkyl haloacylamides with excess of secondary amine in presence of:

(i) dry benzene \([\text{Lofgren, J. Sci. Ind. Res. 2, 63 (1950)}]\).

(ii) toluene \([\text{Ette and Neumann, Chem. Listy, 51, 1906-3 (1957)}]\).

(iii) alcohol \([\text{Sen Gupta, Shah and Gaind, J. Ind. Chem. Soc. 31, 845-847 (1954)}]\), or

(iv) acetone \([\text{Lespegnol, Neodeme and Aurousseau loc. cit.}]\).

In all the above methods replacement is carried out by heating the \( \alpha \)-haloacylamide with excess of secondary amine. Excess of secondary amine serves to bind the acid generated in the reaction. Hydrochloride salt of secondary amine is removed by filtration.

In the present work dry benzene was used as solvent and the use of 5-2 mol of secondary amine was found suitable.
\[ \text{(i) } \text{RNHCOCH}_2\text{Cl} + \text{HNR'}R'' \rightarrow \text{RNHCOCH}_2\text{NR'}R'' + \text{HCl} \]

where \( R'R'' = \) diethylamino

\( = \) morpholino

\( = \) piperidino

The basic amides were converted into hydrochloride, picrates or oxalates for characterisation.

Compounds prepared are shown in the table.
**α,α'-DIARYL, α,α'-DI (DIETHYLAMINO/MORPHOLINO/PIPERIDINO)-ALKANES**

![Structure Diagram]

<table>
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<tr>
<th>No.</th>
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<th>Morpholino</th>
<th>Piperidino</th>
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<td>M.P. A</td>
<td>M.P. A</td>
</tr>
<tr>
<td>1</td>
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<td>H</td>
<td>HCl 182</td>
<td>- 173</td>
<td>- 152</td>
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<tr>
<td>2</td>
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<td>- 134</td>
<td>HCl 161</td>
<td>HCl 138</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>4-OCH₃</td>
<td>HCl 178</td>
<td>HCl 126</td>
<td>HCl 168</td>
</tr>
<tr>
<td>4</td>
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<td>HCl 212</td>
<td>HCl 209</td>
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<td>5</td>
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<td>HCl 165</td>
<td>HCl 115</td>
<td>HCl 122</td>
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<td>6</td>
<td>5</td>
<td>H</td>
<td>HCl 118</td>
<td>HCl 220</td>
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<td>4-CH₃</td>
<td>HCl 148</td>
<td>HCl 92</td>
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<td>HCl 154</td>
<td>HCl 169</td>
<td>HCl 144</td>
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<td>HCl 142</td>
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<td>-</td>
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<td>(HCl 226)</td>
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<td>Piperidino</td>
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<td>26</td>
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<td>2,4(CH₃)₂</td>
<td>HCl</td>
<td>128</td>
<td>HCl</td>
</tr>
<tr>
<td>27</td>
<td>8</td>
<td>2,5(CH₃)₂</td>
<td>HCl</td>
<td>168</td>
<td>HCl</td>
</tr>
<tr>
<td>28</td>
<td>8</td>
<td>3,4(CH₃)₂</td>
<td>HCl</td>
<td>182</td>
<td>HCl</td>
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</table>
METHODS OF PHARMACOLOGICAL STUDY

Following table gives the structures of the compounds tested.

![Diagram](image)

<table>
<thead>
<tr>
<th>Compound</th>
<th>n</th>
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<th>$R_1R_2$</th>
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</thead>
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<td>H</td>
<td>Morpholino</td>
</tr>
<tr>
<td>C₃</td>
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<td>H</td>
<td>Morpholino</td>
</tr>
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<td>H</td>
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</tr>
<tr>
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<td>H</td>
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</tr>
<tr>
<td>C₆</td>
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<td>C₇</td>
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<td>4-Cl</td>
<td>Morpholino</td>
</tr>
<tr>
<td>C₁₁</td>
<td>8</td>
<td>H</td>
<td>Piperidino</td>
</tr>
<tr>
<td>C₁₂</td>
<td>8</td>
<td>H</td>
<td>Diethylamino</td>
</tr>
<tr>
<td>C₁₃</td>
<td>8</td>
<td>4-OCH₃</td>
<td>Morpholino</td>
</tr>
</tbody>
</table>
ANTICONVULSANT ACTIVITY

Compounds were tested for their effect on electrically induced convulsions (maximum electro-shock, M.E.S. test) and chemically induced convulsions (Pentylene tetrazol convulsions). These tests were carried out as described below.

(i) M.E.S. TEST

Mice of either sex weighing between 15 to 20 gm. were fed the compounds orally in the form of either solution or suspension in 1% C.M.C., in a Vol. of 10 cc/kg. One hour after feeding, they were subjected to electrical shock through corneal electrodes and rectangular pulses of 50 m.a. for 0.2 seconds. They were observed for protection against tonic seizures of hind legs.

(ii) PENTYLENE TETRAZOLE CONVULSION

Mice of either sex, weighing between 15 to 20 gm., were fed orally in the form of either solution or suspension in 1% C.M.C. in a volume of 10 cc/kg. One hour after feeding pentylene tetrazol was injected subcutaneously at a dose of 100 mg/kg. They were observed for protection against clonic and tonic convulsions.

Compounds C_1, C_2, C_3, C_5, C_6, C_7, C_8, C_9, C_11 did not show any significant C.N.S. effect, including anticonvulsive effect when tested at 200 mg/kg P.O. dose level.
Compounds $C_4$ and $C_{10}$ gave 50% protection against Metrazol convulsion at 200 mg/kg P.O. dose level.

SURFACE ANESTHESIA ON RABBIT CORNEA (1)

Compounds were studied for surface anesthesia on rabbit cornea and the activity was compared with xylocaine as a reference drug.

One percent solutions of the test compounds were prepared in phosphate buffer ($pH$ 7.3). Sufficient volume of test solution was dropped into one eye of the rabbit so that a thin film of the solution was formed in the eye and the other eye was kept as control. The conjunctival sac of the eye was kept apart so that the test compound may come into the biophase with the cornea.

Test for the local anesthetic activity was started thirty seconds after the instillation into the eye. A camel hair fine brush was used to test the activity. The test was carried out for half an hour after instillation of the test compounds testing at every thirty seconds interval. The degree of local anesthetic effect was observed from the complete absence of the partial hindrance in the blinking of the eye subjected to stimuli with the brush. Partial recovery was observed after half an hour with some of the compounds.
Compounds $C_1$, $C_2$, $C_3$, $C_4$, $C_5$, ..., $C_{13}$ were tested for local anesthetic activity for surface anesthesia.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Concentration</th>
<th>Local anesthetic effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_1$ &amp; $C_2$ not soluble</td>
<td>Not tested</td>
<td></td>
</tr>
<tr>
<td>$C_5$</td>
<td>2%</td>
<td>2 minutes</td>
</tr>
<tr>
<td>$C_7$</td>
<td>2%</td>
<td>2 minutes</td>
</tr>
<tr>
<td>$C_8$</td>
<td>2%</td>
<td>3 minutes</td>
</tr>
<tr>
<td>Xylocaine</td>
<td>2%</td>
<td>16 minutes</td>
</tr>
<tr>
<td>$C_3$, $C_4$, $C_6$, $C_9$, $C_{10}$, all 2%</td>
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<td></td>
</tr>
<tr>
<td>$C_{11}$, $C_{12}$, $C_{13}$</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

It is not possible to draw any definite conclusion from the above. The following trends may be noted.

(1) Compounds with $n = 8$ are more active as compared to those with $n = 4$, $5$, $6$, $7$.

(2) Introduction of two $\text{CH}_3$ groups in 2,5 positions makes the compound more active, compare $C_8$ with $C_5$, $C_7$.

References:

GENERAL METHOD FOR THE PREPARATION OF
ω,ω'-DIARYL ALKANES

In a 100 ml. round bottomed flask, fitted with a reflux condenser was placed (0.1 mole) dibasic acid to which (0.3 mole) thionyl chloride was added in one portion. The mixture was heated gently on a waterbath held at 50-60°C. After about four hours, the evolution of hydrogen chloride ceased and the solution became clear. The flask was then connected to a downward condenser and heated under diminished pressure on a waterbath to remove any excess of thionyl chloride. The residue of diacidchloride was used directly for the preparation of diketones by Friedel Craft reaction.

In three necked flask equipped with a stirrer, reflux condenser and a dropping funnel was placed a mixture of 30 gm. (0.225 mole) of anhydrous aluminium chloride, and 150 ml. (1.7 mole) of benzene. The reaction mixture was cooled in an ice bath, and with rapid stirring the diacidchloride was added through the dropping funnel at an even rate during the course of forty five minutes. After the addition of diacidchloride the ice bath was removed and stirring was continued for two hours at room temperature.
The solution was then poured slowly with constant stirring, into a mixture of 100 gm. of ice and 25 ml. of concentrated hydrochloric acid in a one litre beaker. The solid which separated was taken into benzene and dissolved by shaking and gentle warming on the steam bath. The benzene layer was separated and washed, first with an equal volume of dilute sodium carbonate solution and then with water. The benzene solution was placed in a 500 ml. flask and most of the benzene was removed by distillation. The residual liquid was set aside and allowed to cool. The diketone which crystallised after several hours was filtered. The diketone was recrystallised from hot 95 % ethyl alcohol. The yield was about 70 to 75 percent.

0.S. Coll. Vol. II. p. 169 (1946)

Following \( \omega, \omega \)-diaryl alkanes have been prepared in 70-75 percent yield by the above method.

\[
\begin{align*}
R & - \text{CO} - (\text{CH}_2)_n - \text{CO} - \text{R} \\
\end{align*}
\]

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<tr>
<th>No.</th>
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<th>( R )</th>
<th>M.P. ( ^\circ C )</th>
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<td>$2,5(CH_3)_2$</td>
<td>118</td>
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| 26.| 8   | $3,4(CH_3)_2$| 141 | Chakravarti, D., Saha, M.  
| 27.| 8   | 4-Cl         | 135 | -do-      |
| 28.| 8   | 4-0CH$_3$    | 130 | Chakravarti, D., and Chakravarti, A., J. Ind.  

Percent Carbon  

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Percent Hydrogen  

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GENERAL METHOD FOR THE PREPARATION OF

SUBSTITUTED $\alpha,\omega$-DIARYL $\alpha,\omega$-DIAMINOALKANES

Formic acid (21 ml) was slowly added to ammonium carbonate (21.5 g.), placed in a three-necked round bottomed flask, fitted with a thermometer and a distillation bend attached to a condenser, for simultaneous distillation. After complete addition of formic acid, the temperature was raised gradually to 165°C, and heating continued till the removal of water from the reaction mixture was complete. $\alpha,\omega$-Diaryl alkane (0.05 mole) was added in one lot to this reaction mixture and heating once again resumed. The temperature was slowly raised to 185°C and maintained at that temperature for four hours. The reaction mixture was then poured in water and the resulting solid formyl derivative was hydrolysed with 12 percent hydrochloric acid. In some cases, the amine was isolated as the hydrochloride, but where the hydrochloride was not obtained with ease, the hydrolysed solution was basified and the liberated base was extracted with ether.

Following substituted $\alpha,\omega$-diaryl $\alpha,\omega$-diamino-
alkanes were prepared by this method in about 25 percent yield.

![Chemical structure](image)

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</tr>
<tr>
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</tr>
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<td>2,5(CH₃)₂</td>
<td>205-225/1 mm</td>
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<tr>
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<td>4-OCH₃</td>
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</tr>
<tr>
<td>6</td>
<td>H</td>
<td>210-220/1.5 mm</td>
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</tr>
<tr>
<td>7</td>
<td>4-CH₃</td>
<td>235-245/1.5 mm</td>
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</tr>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
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<tr>
<td>8.</td>
<td>5</td>
<td>$3,4(CH_3)_2$</td>
<td>215-230/ 8.2</td>
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<td>208-220/ 8.0</td>
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<td>11.</td>
<td>6</td>
<td>H</td>
<td>192-220/ Miroslav, P. Milos, B., and Jiri, P., Chem. Listy, 49, 1802-7 (1955); Chem. Abst. 50, 9317 (1956)</td>
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<td>4-CH$_3$</td>
<td>232-256/ 8.6</td>
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<td>215-225/ 7.8</td>
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<td>14.</td>
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<td>$3,4(CH_3)_2$</td>
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<td>7</td>
<td>H</td>
<td>205-228/ 9.1</td>
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<td>1.0-1.5 mm.</td>
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<td>255-266/ 8.3</td>
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<td>225-240/ 7.6</td>
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<td>7</td>
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<td>225-240/</td>
</tr>
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<td>215-225/</td>
</tr>
<tr>
<td>23.</td>
<td>8</td>
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<td>225-245/</td>
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<td>24.</td>
<td>8</td>
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<tr>
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<td>270-282/</td>
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<td>28.</td>
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<td>4-OCH₃</td>
<td>252-264/</td>
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</tbody>
</table>
PREPARATION OF CHLOROACETYLCHLORIDE:

In a round bottomed flask fitted with a fractionating column was placed monochloroacetic acid (0.25 mole) and benzoyl chloride (0.325 mole). The mixture was heated to boiling and then the acid chloride was distilled off the reaction mixture at 105-107°C as rapidly as was consistent with good separation from the other constituents in the flask: Yield 71 percent. (Brown, J. Am. Chem. Soc., 1938, 60, 1325 quoted from Experimental Chemistry by Fieser, Third Edition, page 309).

GENERAL METHOD FOR THE PREPARATION OF \( \alpha, \omega \)-DIARYL \( \alpha, \omega \)-DI (CHLOROACETAMIDO) ALKANES

In a round bottomed flask, surrounded by an ice-bath was placed a mixture of the appropriate amine (1.4 mole), acetone (5 mole), sodium acetate (4.0 mole) and water (6.0 mole). To this, chloroacetyl chloride (2.82 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 precipitate was filtered, washed with cold water, sodium carbonate (10 percent) solution and finally with water. The chloroamides were crystallised from dilute alcohol or petroleum ether.

The compounds prepared are shown in the following tables.
### $\alpha,\alpha'$-DIARYL, $\alpha,\alpha'$-DI-(CHLOROACETAMIDO) ALKANES

![Diagram of the molecular structure](attachment:molecular_structure.png)

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<th>M.P. °C</th>
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<th>Percent Nitrogen Found</th>
<th>Percent Nitrogen Required</th>
<th>Percent Halogen Found</th>
<th>Percent Halogen Required</th>
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GENERAL METHOD FOR THE PREPARATION OF $\omega,\omega'$-DIARYL $\omega,\omega'$-DI(ETHYLAMINO/MORPHOLINO/PIPERIDINO ACETAMIDO) ALKANES:

$\omega,\omega'$-Diaryl $\omega,\omega'$-di(chloroacetamido) alkane (1.0 mole) in dry benzene (500 ml) was refluxed for five hours with secondary amine (5.2 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 (3 N, 340 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 crystallised from aqueous alcohol or petroleum ether. If the base liberated as an oil, it was then taken up in ether and the ether extract was dried over anhydrous potassium carbonate. To this dry ethereal extract of $\omega,\omega'$-diaryl $\omega,\omega'$-di(diethylamino acetamido) alkanes, dry hydrogen chloride gas was passed, when the hydrochloride salt precipitated. It crystallised in colourless needles from dry acetone or a mixture of ether-ethanol.

The compounds prepared are shown in the following tables.
**oc,oc-DIARYL, oc,oc-DI(DIETHYLAMINO ACETAMIDO) ALKANES**

![Chemical Structure](image)

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### DIARYL ACETAMIDO ALKANES

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\[ \text{iso,iso- DIARYL, iso,iso DI-(PIPERIDINO ACETAMIDO) ALKANES} \]

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