GENERAL INTRODUCTION - I
The term anesthesia is derived from Greek and means "without perception". One can define anesthetics as the drugs which depress vital functions of all types of cells, but especially those of nervous tissue. Pain is mankind's oldest enemy and it is also mankind's oldest friend. 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 the living creatures of danger. Pain saves the organism by informing it in time of disordered condition. Pain is cruel but life saving guardian of protoplasm. In general, it may be said that pain is a sensation produced by some external agents which may menace the integrity of the normal animal tissue.

The two principal types of pain are (i) superficial pain and (ii) 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.

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. Anesthetics can be classified into two parts
according to the site of application. General anesthetics are those which depress the central nervous system to such an extent that all sensitivity to pain is lost while definite local regions may be anesthetized without affecting other parts of nervous system by local anesthetics. It is worthwhile to note that the above definition of different types of anesthetics serves the usual surgical purpose. It is difficult to obtain their clear-cut definition since their effects may overlap. Moreover, analgesics and hypnotics partly cause the insensibility to pain and loss of consciousness. Vice versa a minor dose of a certain anesthetic causes analgesic and hypnotic effects.

From primitive times, men sought the separation of pain from the advancing knife of the surgeon. 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 was 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 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 the 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 extracted 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.

Some substances which are used or were used once as general anesthetics are shown below:

**VOLATILE ANESTHETICS:**

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

**INTRAVENTOUS ANESTHETICS:**

14. Thiopental
   \[ \text{HN} \quad \text{O} \quad \text{C}_2\text{H}_5 \]
   \[ \text{CH(CH}_3)(\text{CH}_2)_2\text{CH}_3 \]

15. Brevital
   \[ \text{CH}_3\text{N}--\text{O} \quad \text{CH}_2\text{CH} = \text{CH}_2 \]
   \[ \text{CH}(\text{CH}_3)(\text{CH}_2)\text{C} = \text{CC}_2\text{H}_5 \]
16. Hydroxydione

17. Propanidid

MISCELLANEOUS COMPOUNDS:

18. 1-Phenyl-1-piperidino-cyclohexane

19. 2(-2-Chlorophenyl)-2-methylamino-cyclohexanone.

20. Diazepam
21. Droperidol

\[
\text{\begin{tikzpicture}
\filldraw[fill=white] (0,0) circle (0.5cm);
\draw (0,0) -- (1,0);
\draw (0,0) -- (0,1);
\draw (0,1) -- (-1,0);
\draw (-1,0) -- (-1,-1);
\draw (1,0) -- (1,-1);
\draw (1,-1) -- (0,0);
\end{tikzpicture}}
\]

22. Fentanyl

\[
\text{\begin{tikzpicture}
\filldraw[fill=white] (0,0) circle (0.5cm);
\draw (0,0) -- (1,0);
\draw (0,0) -- (0,1);
\draw (0,1) -- (-1,0);
\draw (-1,0) -- (-1,-1);
\draw (1,0) -- (1,-1);
\draw (1,-1) -- (0,0);
\end{tikzpicture}}
\]

LOCAL ANESTHETICS:

(1) HISTORY AND DEVELOPMENT:

In common with many other therapeutic groups, the local anesthetics themselves found their start in a natural product which was observed to exhibit a certain biological effect. The first local anesthetic to be discovered was cocaine. Cocaine is the principle alkaloid from the leaves of \textit{Erythroxylon coca}. The pure alkaloid was first isolated by Niemann, a pupil of Wohler in 1860, who stated that it had bitter taste and produced a peculiar effect on the tongue, making it numb and almost devoid of sensation.
However, the credit for the introduction of cocaine into clinical use as a local anesthetic is usually given to Freud and Koller. Koller introduced cocaine in ophthalmological practice in 1884 and it was accepted immediately as a local anesthetic.

Eventhough cocaine was accepted as a local anesthetic without resistance, the configurational assignment of the molecule offered some formidable problems. Its structure was determined by Willstatter and Muller in 1898 and after about 60 years, the absolute configuration of cocaine was elucidated. Cocaine is a powerful cortical stimulant and both addiction and toerance can result from the continued use of cocaine. Cocaine shows excellent anesthetic effects on topical applications, infiltration and injection, but it unfortunately also exhibits undesirable side effect such as, for example, a relatively high toxicity, the risk of habituation or addiction.

A chemical search for synthetic substitutes for cocaine started in 1892 with the work of Einhorn and his colleagues. This resulted in 1905 in the synthesis of procaine, which today is still very widely employed. Chemical investigation still continues, however, because no available local anesthetic is free from undesirable properties. As a result, an unnecessarily large number of compounds are marketed for the clinical use. Most of these differ little in therapeutic efficiency and only a few have distinctive features to recommend their
preferential use. Ehrlich and Einhorn stated that the ability to induce anesthesia is a common property residing in widely differing organic compounds. The term "anesthesiophore" has since been used widely to indicate the structural fragments of a molecule to which it was believed, the local anesthetic effect could be ascribed.

The "anesthesiophore" group in cocaine may serve as the starting point for the systematization of the synthetic agents introduced during the last few years.

\[
\begin{align*}
\text{RNH-CO-alk-N} & \quad \text{RNH-CO-NH-alk-N} \quad \text{RNH-CO}_2\text{-alk-N} \\
aminoacylamides & \quad \text{aminoalkyl ureas} \quad \text{aminoalkylurethans} \\
\end{align*}
\]

\[
\begin{align*}
\text{MeO}_2\text{C.} & \quad \text{CH} \quad \text{CH} \quad \text{CH} \\
\text{C}_6\text{H}_5\text{CO}_2\text{-CH} & \quad \text{N-Me} \\
\text{CH}_2 & \quad \text{CH} \quad \text{CH}_2 \\
\text{R-CO-NH-alk-N} & \quad \text{R-CO}_2\text{-alk-N} \quad \text{R-CO-alk-N} \quad \text{R-O-alk-N} \\
aminoalkyl & \quad \text{aminoalkyl} \quad \text{aminoalkyl} \quad \text{aminoalkyl} \\
amides & \quad \text{esters} \quad \text{ketones} \quad \text{ethers}
\end{align*}
\]
where,

\[ R = \text{aryl, aralkyl, straight or branched alkyl}, \]
\[ \text{alk} = \text{alkylene}, \text{N}^* = \text{mono or disubstituted amino residue}. \]

The various types of local anesthetics differ only in so far as the ester linkage, \(-\text{CO}_2\)\,- in the intermediate chain between the benzene nucleus and the amino residue in cocaine has been exchanged for \(-\text{NHCO}_2\), \(-\text{NHCO}_2\), \(-\text{NH-CO-NH}_2\), \(-\text{CONH}_2\), \(-\text{CO-} \text{ or } -\text{O-}, \text{that is aminoaoclamides, urethanes, ureas, aminoalkylamides, aminoketones and aminoethers respectively.} \]

(A) AMINOACYL AMIDES:

Aminoacylamide type of compounds contain a \(-\text{NH-CO-}\) linkage in the intermediate chain between the benzene nucleus and the amino group. Xylocaine-Lidocaine-Lignocaine is the best known example of the aminoaoclamide group of local anesthetics. Xylocaine was synthesized by Dofgren\(^5,6\) and it shows all the characteristic properties of aminoacylamide group. This type of compound is more stable in solution, a particular advantage for heat sterilization.\(^7\) In contrast to procaine and its derivatives, this type of compound has quite broad usage, including topical and infiltration anesthesia and various nerve blocks. This type of compounds are also used as antiarrhythmic and analgesic agents.
The investigations of recent years have been largely concerned with variation in the aromatic moiety of xylocaine. The benzene nucleus of xylocaine may be an aliphatic radical but for anesthetic activity the radical has to contain a tertiary carbon atom.$^{8-10}$

The following compounds of this type have found clinical usage:

Mesocaine (Trimecaine)  Hostacaine

(II)  (III)
A large number of aminoacylamides have been synthesized in recent years. Some of these along with relevant references are summarised below.

Kopacova et al.\textsuperscript{11} observed better local anesthetic activity in basic 4-aryloxy or 4-aralkoxy-2,6-dimethyl anilides as compared to cocaine and procaine. The most potent surface anesthetic 2-(1-piperidinyl)-2',6'-dimethyl-4'-(2-phenyl ethoxy acetanilide) (VI) was 80 times as effective as cocaine.
Bhargava and Tiwari\textsuperscript{12} prepared benzothiazole derivatives. The local anesthetic activity of (VII) was greater than that of procaine-HCl.

\[
\begin{align*}
\text{R' - } & \text{NH-CO-CH}_2-\text{NR}_2 \\
\text{(VII) }
\end{align*}
\]

Lukas et al\textsuperscript{13} synthesized phenoxy and benzyloxy acyltoluidines (VIII) (\(R = \text{PhCH}_2\), \(R^1 = \text{Me}; R^2 = R^3 = \text{Et}\)) which were 10 times more active than cocaine in surface anesthesia and 4 times more active than procaine in infiltration anesthesia.

\[
\begin{align*}
\text{NHCOCHR}^1_{R^1}R^2_{R^2}R^3_{R^3} \\
\text{CH}_3 \\
\text{OR} \\
\text{(VIII) }
\end{align*}
\]

Singh and Ram\textsuperscript{14} prepared sixteen 2-(2-aminoacetamido) thiazole (IX) - hydrochlorides which were found inferior to procaine hydrochloride in local anesthetic activity.
where, $R = H, Me, alkoxy$ carbonyl.
$R^1 = Me, Ph, substituted$ phenyl.
$R^2 = Bu, Me_2CH-(CH_2)_2$.

(B) URETHANS AND UREAS:

Soehring and Rautmann\textsuperscript{15} have reviewed the work with
this group of compounds. Only two urethans, Diperodon
(diperoceaine, diothane)-(X) and carbacaine\textsuperscript{16,17}(XI) have
so far been clinically introduced as local anesthetics.

Diperodone \hspace{1cm} Carbacaine

(X) \hspace{1cm} (XI)
Recently Benes et al.\textsuperscript{18} synthesized 1-methyl-2-pyrrolidinoethyl-3-hexyloxycarbanilate - HCl (XII) which was 107-fold more active than cocaine as a surface anesthetic and 45-fold more active than procaine as an infiltration anesthetic.

\[
\text{NHC}O\text{OCHMeCH}_2\text{NR}_2
\]

( XII )

Benes and Borovansky\textsuperscript{19} also synthesized some basic trans and cis cyclohexyl esters of substituted alkoxycarbanilic acid. The compound (XIII) showed higher local anesthetic activity such as surface and infiltration anesthesia as compared to cocaine and procaine.

\[
\text{NHC}O\quad \text{NR}_1\text{R}_2
\]

( XIII )

where, \( R = H; R_1 = R_2 = \text{Et} \) or \( \text{NR}_1\text{R}_2 = 1\text{-Pyrrolidinyl or piperidino} \).
Relatively few aminoaalkylamides have been synthesized and cinchocaine (dibueaine, nupercaine, percaaine-L)-(XIV) was prepared by Miescher.  

![Chemical Structure](image)

Dibucaaine  

(XIV)

The toxicity of cinchocaine is considerable, yet it has been used because of its extraordinary potency, which permits its use at low concentrations. These amides are less satisfactory anesthetics than the corresponding esters and produce greater irritation. Buchi and Parlia synthesized some cinchocaine homologues and investigated their physical properties in details. Sieger, Klein and Sekel studied the diethylaminoalkylamides of 3-hydro and 3-alkoxy naphthalene-2-carboxylic acid and compared them with the corresponding esters.
Though more stable, the amides were generally more toxic as well. A few cinchocaine compounds, in which the butoxy group had been exchanged for a methoxy, ethoxy or an ethoxyl group showed reduced toxicity, but this modification also impaired other essential properties. \(^{24}\)

Haring and Stille\(^{25}\) studied, in cinchocaine molecule, the effect of (1) substitution of pyrrolidino for the diethylamino group, and (2) transposition of the butoxy group to -3-position (-ortho-to-amide group). They found that the pyrrolidino substitution failed to alter the activity, but lowered toxicity. The ortho-substitution reduced the surface effect.

Of the aminocalkylanides, those derived from substituted benzoic acids have received the greatest attention in the last few years.\(^{26-29}\)

The effect of a number of methylated benzamides on the rabbit cornea has been compared with that of xylocaine. In general, the new compounds were less active than the reference drugs, a few were more active but also more toxic.
Honkanen noted the following generalisation between structure and activity for amides of the type (XV).

(1) With variations in the amino component, -NR₂, local anesthesia was intensified with increasing length of R₁ but the solubility of the compounds decreased and they possessed a higher toxicity and exerted greater irritation.

(2) An increase in the number of methylene groups in the intermediate chain from two to three, reduced both the local anesthetic activity and toxicity of the compounds.

(3) Di-o-substitution in the benzoic acid moiety generally served to augment the activity. The superiority of 2,6-dimethyl substitution, as observed in the xylocaine series, was not found in the amides investigated.

(4) p-Alkoxy substitution enhanced the local anesthetic effect but increased the toxicity.
A maximum effect was recorded with pentoxy derivatives. An amino group in meta position in the acid moiety reduced both toxicity and local anesthetic effect, whereas para-substitution had the opposite effect. When p-amino group was alkylated the activity increased, but the irritation was also increased. Acylation of the amino group gave an inactive compound.

Another comparative study on compounds of the type (XVI) also showed that activity was generally lower than that of the corresponding ester, while the irritation effect and toxicity were unchanged. Many of the higher homologs had an antifibrillatory action.

![Chemical Structure](image)

(XVI)

o-Alkoxyl benzoic acid amides (XVII) exhibited local anesthetic properties but the compounds were more toxic and produced greater irritation than did xylocaine. The compound of structure (XVII) in which R is butyl, NR<sub>1</sub>R<sub>2</sub> is pyrrolidino and n is 2, has properties similar to xylocaine.
Recently Yung et al.\textsuperscript{34} have synthesized 4-amino-N-2-(substituted amino) ethyl-2,6-dimethyl benzamides (XVIII) which showed antiarrhythmic activity and local anesthetic activity in the corneal reflex test in rabbits.

\[
\text{CONH(CH}_2\text{)}_n \text{-NR}^1 \text{R}^2
\]

\[
\text{(XVII)}
\]

where \( R = \text{Morpholino,} \)

\( = \text{Piperidino,} \)

\( = 4-\text{Ph-I-Piperazinyl.} \)
(D) AMINOALKYL ESTERS:

An intensive study has been carried out on esters of various ring-substituted benzoic acids and esters of other acids with side chain variations, after the introduction of procaine (XIX) by Einhorn.35

![Chemical Structure](image)

(XIX)

The success of procaine led to an enormous effort to find an even better compound. Hundreds of aminoalcohol esters were prepared36,37 and some showed improvements over procaine in certain aspects such as potency, long duration of anesthesia or better surface anesthetic properties but none that could compete on an overall basis. Procaine is still employed in clinical practice. Other compounds of this type that have found clinical use are as follows:
**Chloroprocaine**  
(XX)

**Butethamine**  
(XXI)

**Meprylocaine**  
(XXII)
A large number of aminoalkyl esters have been synthesized in recent years. Some of these along with relevant references are summarised below:

Robinson and Rama\textsuperscript{38} found 6-(N,N-diethylamino)n-hexyl 3,4,5-trimethoxybenzoate (XXIV) as active as cocaine and three times as active as procaine as a surface anesthetic on the rabbit cornea.

Quinazolinylethyl esters (XXV) are also useful as local anesthetics and muscle relaxants according to Enein and Eid.\textsuperscript{39}
Griner et al.\textsuperscript{40} found ethyl-4-chloro-6-(dimethylamino) methyl)-5-hydroxy-2-methyl-3-benzofurancarboxylate (XXVI) useful as a local anesthetic and an antiarrhythmic compound.

Zahavevskii et al.\textsuperscript{41} synthesized 3,5-dimethyl-4-amino-benzoic acid N,N-diethylaminoethyl ester (XXVII) which had greater anesthetic effect than novocaine when applied in 5\% solution to the rabbit cornea and lower toxicity than benzocaine.
(E) AMINOKETONES (Aminoalkylketones):–

Only two drugs of this type have found some clinical use. They are Palicaine (XXVIII)\(^{42-44}\) and Dyclonine (XXIX).\(^{43-45}\)

Replacement of the benzene nucleus of Palicaine by thiophene\(^{46}\) produced a substantial decrease in the topical effect. A few thio analogues of morpholino propiophenones have also been synthesized.\(^{47}\) The introduction of sulphur into the molecule reduced the toxicity and increased the anesthetic effect.
Recently Asratyan et al. synthesized $\alpha$-phenyl-$\gamma$-(1-piperidyl) butyrophenone (XXX) and found it more active than Novocaine.

Recently Asratyan et al. synthesized $\alpha$-phenyl-$\gamma$-(1-piperidyl) butyrophenone (XXX) and found it more active than Novocaine.

$\text{COCH(Ph)CH}_2\text{CH}_2\text{R}^1$

(XXX)

Profft et al. prepared four piperidino-propiophenone salts. The local anesthetic activity of (XXXI) was 10-12 times as that of Cocaine or Novocaine.

$\text{CO(CH}_2\text{)}_2\text{N}^+\cdot\text{HCl}$

(XXXI)

where $R = \text{Pr, Bu, Pentyl, Hexyl}; \ n = 2, 4.$
AMINOALKYL ETHERS:

Quite early different authors reported that even the simple dialkylaminoalkyl ethers possessed outstanding local anesthetic effects. A small number of amino ethers have been investigated in comparison with other groups resulting in two clinically useful drugs; dimethisoquin (XXXII), and promoxine (XXXIII).

Their structures resemble specifically cinchocaine and the common pattern of xylocaine type agents respectively. Both are recommended only for topical use.
Recently Palekar et al\textsuperscript{53}, synthesized substituted amino-(benzyloxy) propiophenones - $\text{PhCH}_2\text{O}_6\text{H}_4\text{COCH}_2\text{CH}_2\text{NRR}^1$, which were useful as local anesthetics.

(2) \textbf{PROPERTIES DESIRABLE IN A LOCAL ANESTHETIC:—}

A good local anesthetic should possess certain fundamental characteristics which must include the following pharmacological properties:—

(1) It should not be irritating upon application.
(2) It should produce anesthesia without causing damage to nerve structure.
(3) Its toxicity should be low because the compounds are absorbed from their site of application.
(4) It should be soluble in water and stable in solution, and it should be possible to sterilize it by autoclaving without causing deterioration.
(5) The ideal local anesthetic must be effective regardless of whether it is injected into the tissue or whether it is applied locally to mucous membranes. The time required for the onset of anesthesia is an important factor and should be as short as possible. Further more the action must last long enough to allow time for the contemplated surgery.

There are excellent laboratory procedures available for testing these properties and determining which agents are suitable for clinical trial. In general, clinicians require
three types of anesthesia:

(1) Surface anesthesia, as on the mucous membrane of the eye or tongue.

(2) Conduction or regional anesthesia i.e. anesthesia of nerve trunks either peripherally or in spinal canal.

(3) Infiltration anesthesia or anesthesia of nerve fibers or endings.

(3) CHEMISTRY AND STRUCTURE ACTIVITY RELATIONSHIP:

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. The first effort to correlate structure to activity was made after three years of the introduction of cocaine as local anesthetic. Filehne\textsuperscript{54} suggested that the effect was associated with the benzoic acid moiety of cocaine and that the cocaine portion was of slight importance only. The benzoic acid hypothesis was soon criticized.\textsuperscript{55} It was pointed out that benzoyl ecgonine was inactive\textsuperscript{56} and that many analogues of cocaine with other organic acids possessed considerable anesthetic potency.

The toxicological profiles of several compounds related to cocaine were found to be practically identical by Ehrlich,\textsuperscript{57} whereas only a few of them were potent local anesthetics. These few were esters of acids closely related to benzoic acid.
In a homologous series local anesthetic parameters such as duration of potency usually increases with increasing molecular weight for the lower members until a maximum is reached, thereafter the anesthetic effect decreases with further increase of the number of carbon atoms. Studies of this phenomenon have most often been performed in vivo.58-60 The lipid water distribution coefficients for members of a homologous series increase with molecular weight. If the coefficient is low, the lipid membranes and body compartments limit the penetration or rate of penetration to the site of action, if the coefficient is high, water compartments become the limiting factor. This tends to optimize the chance for some intermediate members of the series to reach the active site on the nerve in sufficient concentration to achieve block.61 Another explanation is based on the assumption that aggregate or micelle formation begins to play a role as the molecular weight increases in a homologous series, thus the concentration of active member may actually decrease rather sharply with increasing molecular weight.62

Lofgren5,6 observed that almost all useful local anesthetic molecules could be arranged according to the following scheme:-

Lipophilic part - Intermediate chain - Hydrophilic part,
which can be expressed as,
Aromatic portion - Intermediate chain - amine portion.
There are exceptions; for example, phenacaine (XXXIV) and acoin (XXXV) are not easily arranged in agreement with this scheme, neither do all structures built after this pattern necessarily possess local anesthetic properties.

The lipophilic centre usually consists of an aromatic or heterocyclic nucleus, but it may be exchanged for an aralkyl or an alkyl group. In all anesthetics a secondary or a tertiary amino group acts as the hydrophilic centre, even though an
alkoxy or a hydroxy group may replace the amino group, as for instance in alcohols such as chlorobutol, benzyl alcohol and hydroxypolyethoxy dodecaine. The mode of action of these later compounds, however, usually differ from that of "true" local anesthetics. The intermediate chain consists in part of a hydrocarbon bridge attached to the hydrophilic centre and in part, of an atom or group of atoms such as \(-\text{CO}_2-, -\text{CONH}-, -\text{NHCO}, -\text{NHCO}_2-, \) or \(-\text{O}-\) attached to the lipophilic centre. Anesthetics in which the intermediate chain consists solely of a hydrocarbon bridge are also known.

Quevauviller\(^{64}\) pointed out that a balance between the lipophilic and hydrophilic parts of the molecule is essential. If the later attribute dominates, the anesthetic effect is lost. If, on the other hand, the lipophilic character is unduly marked, the compounds is not readily soluble. This intramolecular balance is, therefore, very essential for an anesthetic. It is, moreover, a key factor not merely in the solubility, for just as is the case with wetting agents - some properties of which may be characterized by an HLB value (hydrophile - lipophile balance) it determines the behaviour of molecule at interfaces, as for instance cell membranes. The inter relationship of these factors assumes a more complex pattern, however, when the anesthetic actions of different compounds are considered with special respect to the molecular structure. Buchi and Perlia\(^{22}\) have pointed out that, this
complexity is largely attributable to the fact that the structural formula of the compound does not adequately indicate the form, size, nor steric structure, nor the physical properties associated with the pharmacological action. Nor do structural formulae lend themselves to definition of the electron distribution within the molecule. Buchi and Perlia emphasize the importance of those aspects of anesthetic's which implicate electronic theory. Lofgren, and later Perkow pointed out that the carbonyl group in all active anesthetics of ester and amide type, is activated by lower electron density at the carbon atom. The electron distribution within the molecule is in turn responsible for those forces (e.g. Van der Waal's, dipole-dipole, hydrogen and ionic bonds) which modify not only the behaviour of the molecule at interfaces, but also association to form larger, anesthetically inactive aggregates. The fact than an apparently insignificant modification of the molecular structure of a local anesthetic substantially alters its anesthetic activity, may frequently be accounted for in terms of electron theory.

(4) MODE OF ACTION OF LOCAL ANESTHETICS:

Most of our knowledge about the mode of action of local anesthetics has come from experiments on isolated nerves. Local anesthetics prevent both the generation and conduction of the nerve impulse. Their main site of action is the cell
membrane. Until recently, little was known of the physiological events involved in conduction and hence little could be said of their mechanism of action. After the work of Hodgkin and Huxley and their colleagues, it is easy to explain, at least partially, the action of local anesthetics within the framework of the ionic theory of nervous activity.

Local anesthetics block conduction by interfering with the process fundamental to the generation of the nerve action potential, the large transient increase in the permeability of the membrane to sodium ions that is produced by a slight depolarization of the membrane. As the anesthetic action progressively develops in a nerve, the threshold for electrical excitability generally increases and the safety factor for conduction decreases. When this action is sufficiently well developed, block of conduction is produced.

The local anesthetics also reduce the resting permeability of nerves to potassium as well as to sodium ions. Bennett and Chinburg have extended the original observation of Bishop that local anesthetics block conduction without depolarizing the nerve. The local anesthetics generally reduced the permeability of the resting nerve membrane to sodium, potassium and other ions.

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 the monomolecular films of lipids.  

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 permeability and would also limit the increase in sodium permeability, the fundamental change necessary for the generation of the action potential.

**EFFECT OF pH:**

The local anesthetics in the form of the free base tend to be slightly soluble and unstable in solution, therefore, they are generally used in the form of their water-soluble salts, usually the hydrochlorides.

As the local anesthetics are weak bases, these salt solutions are quite acidic and increase the solubility of local anesthetics. There is abundant evidence to show that the acid salt must be neutralized in the tissue and the free base liberated before the drugs can penetrate the tissue and produce an anesthetic action. It has been shown that the addition of alkali to local anesthetic solutions will potentiate activity. This is also true when anesthetics are applied to isolated nerve trunks or to the cornea, where the buffering capacity of the tissue-fluids is
limited. It has, therefore, been predicted that previous alkalinization of an anesthetic solution or the use of a salt of a weak acid such as borate salt of the local anesthetic, will increase the clinical efficiency. However objective tests have failed to substantiate this point and more alkaline preparations have the disadvantage of being relatively unstable. The explanation probably is that under conditions usually encountered in clinical use, the pH of the local anesthetics is rapidly brought to that of the extracellular fluids, regardless of the pH of the solution in which it is injected.

Generally all the commonly used local anesthetics contain a tertiary (or secondary) nitrogen atom and therefore can exist either as the unchanged tertiary (or secondary) amine or as the positively charged substituted ammonium cation, depending on the dissociation constant (pKa) of the compound and pH of the solution. The ionization of a typical local anesthetic may be depicted as follows:-

\[
R : N + HCl \rightleftharpoons R : NH^+ + OH^-
\]

The pKa of any typical local anesthetic in common use lies between 8.0 and 9.0, so that only 10 to 20% will be in the form of the free base at the pH of the tissues. This fraction is important because the drug usually has to diffuse through connective tissue and other cellular membranes to get to its site of action and it is generally agreed that it can do so
only in the form of the unchanged amine. There has been a
difference of opinion as to which form is active, once the
anesthetic has reached the nerve cell. Krahl and his co-workers\textsuperscript{72}
pointed out that the intracellular presence of the cationic
form was responsible for the inhibition. Largely on the basis
of their experiment, it was suggested that the form of the
molecule active in nerve fibres is the cation. The conclusion
has been supported by the results of experiments on "anesthetized"
mammalian nonmyelinated fibres\textsuperscript{73} in which conduction could be
blocked or unblocked merely by setting the pH of the bathing medium
at pH 7.0 or pH 9.5, respectively without altering the medium
of anesthetic present. When the pH is low and the conduction
is blocked, most of the anesthetic must be in its cationic
form. This seems to indicate that the cation is the molecular
form that combines with some receptor in the membrane to
prevent the generation of an action potential.\textsuperscript{74}

(5) PHARMACOLOGICAL ACTION OF LOCAL ANESTHETICS:

In addition to blocking conduction in nerve aseous
in the peripheral nervous system, local anesthetics interfere
with the function of all organs in which conduction or transmission
of impulses occurs. Thus they have important effects on the
central nervous system and the heart. Local anesthetics depress
the central nervous system. However, if the rate of delivery
to the brain is not too fast, general excitation occurs, the
excitatory action of cocaine being unique in this regard. However, higher doses produce convulsions in both animal and man. The mechanism underlying this cortical excitation appears to involve a preferential block of inhibitory neurons in the brain with the subsequent unmasking of central excitation, higher doses of local anesthetics cause central nervous system depression and finally respiratory failure.

Cardiovascular collapse due to local anesthetics may be a greater potential hazard clinically since it may occur without any warning. With low doses of xylocaine a transitory increase in systemic blood pressure and an increase in cardiac output may occur. However, higher doses produce a fall in blood pressure predominantly due to a decrease in peripheral resistance. This tendency varies with the agents and is more marked for procaine than for lignocaine. Finally, as toxicity proceeds the force of contraction of the heart decreases and hypotension becomes severe. This toxicity is related to the potency of local anesthetic. Thus the mechanism of cardiac depression appears to be related to the local anesthetic action on excitable tissue generally. Only the myocardium is severely depressed, reversibility may be delayed or it may never occur and fatal cardiovascular collapse may result.
Certain principles of drug metabolism are general for all types of drugs administered by all routes. The plasma levels of cocaine depend on the route of administration, with both peak values and the rate of clearance being influenced. The metabolism of cocaine involves breakdown of the molecule into benzoate and ecgonine fractions by esterase activity. Studies of procaine and other synthetic esters indicate that bloodserum-esterase activity is responsible for their hydrolytic breakdown. The amides are more resistant to breakdown, with none of the metabolism occurring in the blood. Xylocaine is converted to secondary monoethyl derivatives by oxidative deethylation in the rat liver, after which hydrolytic cleavage of the amide bond takes place. Dealkylation to the monoethylglycine-xylidine product is also a major metabolic pathway for xylocaine breakdown in man. Since prilocaine is a secondary amine, more rapid breakdown by amidase activity in the liver can occur than in the case of xylocaine, for which the initial deethylation step is rate limiting. Mepivacaine is also relatively rapidly metabolized by the liver. Metabolites of local anesthetics are then excreted in the urine; local anesthetics themselves are excreted in only small amounts in the urine, by both animals and men. The pH of urine influences the renal excretion of local anesthetics in man.
The uptake from the site of injection and therefore the blocking efficiency, blood levels, and toxicity of local anesthetic can be influenced markedly by vasoconstrictors. The quantitative effect of vasoconstrictors on absorption varies with the local anesthetic. Generally vasoconstrictors slow down the absorption of local anesthetics from the site of injection in both animals and in men, thus providing better block. However, the systemic toxicity of plain solutions versus solution with vasoconstrictors, and probably the size of the animal, is probably the size of the animal. In clinical use the addition of vasoconstrictors improves local anesthesia, reduces blood levels of local anesthetics, and lowers systemic toxicity.

Once the local anesthetic is absorbed into the bloodstream, it is rapidly distributed to the various tissues. Autoradiographic, chemical, and radioactive measurement techniques all show substantial accumulation of local anesthetics in brain, lung and kidney tissues. Eventually the drug is cleared, metabolized and excreted in the urine.

It is clear that the disposition of the local anesthetic is complex. Moreover, it is very unlikely that the various equilibria depicted ever achieve a steady state. Thus the dynamics of the system are difficult to determine. When an injection is made in the vicinity of a nerve the drug immediately starts to enter nerves, other tissues, extracellular fluid and the circulating blood after injection. Since the blood carries
the drug to more remote areas, the resulting gradient favours movement of the drug out of the tissues and local extracellular space into the blood, thus decreasing the probability of good block in the nerve and increasing the probability of toxic effects in the heart and the central nervous system. It is here that the vasoconstrictor is of value in helping to achieve a better block and usually less toxicity. Meanwhile the circulating drug is being metabolized by the blood, the tissues, and especially the liver. Finally the metabolites and, to a lesser extent, the drug itself, are excreted by the kidneys. This decreases the gradient further, so that the drug leaves the tissues generally and is in turn metabolized and excreted. Ultimately the drug is cleared from all tissues and eliminated.
METABOLISM OF XYLOCAINE:

Metabolism of xylocaine according to Hullunger is as follows:

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

\[
\text{Xylocaine} \quad \downarrow \quad \text{Oxidation} \quad \downarrow \quad \text{Hydrolysis}
\]

\[
\text{CH}_3\quad \text{NH}_2\quad \text{CH}_3\quad \text{NH}_2\quad \text{COOH}
\]

\[
\text{2,6-Xyldidine} \quad \text{N-Ethylglycine} \quad \text{4-Hydroxy-2,6-xyldidine} \quad \text{2-Amino-3-methylbenzoic acid.}
\]
(7) CLINICAL APPLICATION OF LOCAL ANESTHETICS:

The synthetic local anesthetic agents may be divided into two groups (i) the soluble compounds and (ii) slightly soluble compounds. Only soluble compounds of relatively low toxicity should be injected.

Today local anesthetic agents have wide clinical applications in dentistry, medicine and veterinary medicine. Local anesthetics can be used as (A) surface anesthesia (B) infiltration anesthesia (C) block anesthesia and spinal anesthesia.

The insoluble local anesthetics (as well as many soluble agents) are used for surface (topical) application, since their slow absorption renders them safe for use on ulcers, wounds and mucous surface.

(8) MISCELLANEOUS APPLICATIONS:

Local anesthetics have also been employed for a number of other clinical indications. For example, (a) in the treatment of cardiac arrhythmias (b) as intravenous analgesic (c) as a supplementation of general anesthesia and (d) as an anticonvulsant.

(a) IN THE TREATMENT OF CARDIAC ARRHYTHMIAS:

Hitchcock and Keowan were among the first to show that intravenous xylocaine (0.3 to 2.0 mg/kg) was effective in
treatment of bigeminal rhythm during intracardiac surgery. The drugs have achieved widespread acceptance in the management of ventricular arrhythmias arising during anesthesia and operation. Xylocaine (1 to 2 mg/kg) is superior to procaine amide (2 to 4 mg/kg) because it decreases ventricular contractile force (Harrison et al., 96). Xylocaine also reduces the incidence of ventricular fibrillation during hypothermia.

(b) AS AN INTRAVENOUS ANALGESIC:

Intravenous procaine has been used with success by some workers as an analgesic. However, the side effect of tachycardia, dyspnea, anxiety and disorientation are considered by some to preclude its use. Keats and co-workers 99 have concluded that unless intravenous procaine can be demonstrated to produce significant beneficial effect on the specific disease processes, it has no place in the treatment of pain. At the same time Gilbert and co-workers 100 have had some success in treating the pain of malignancy by the use of 0.5% xylocaine solution given as an intravenous drip. In some patients pain relief persisted for 1 to 10 hours after stopping drug administration.
(c) AS A SUPPLEMENTATION OF GENERAL ANESTHESIA:

Xylocaine has been shown to suppress coughing in response to an endotracheal tube, before it produces respiratory depression. In contrast, thiopental and meperidine will produce respiratory depression or apnea before coughing is stopped. Steinhaus and Gaskin, 101 Declive-Lowe and associates, 102 are claiming the following advantages: (i) less succinyl choline is required to produce muscular relaxation and (ii) decreased requirements for postoperative sedation and narcotic analgesic.

(d) AS AN ANTICONVULSANT:

Bohm and coworkers 103 have shown that xylocaine in doses of 2 to 4 mg/kg is effective in rapidly controlling status epilepticus. This dose of xylocaine has the seizure protective effect of 10 mg/kg of pentobarbital. In addition, small dose of xylocaine acts synergistically with a barbiturate, so that seizure prophylaxis without undue sedation may be accomplished. Mepivacaine and xylocaine have similar action to those of diphenyl hydantoin in standard mouse screening test.

(9) CURRENTLY USED COMPOUNDS:

The first local anesthetic, cocaine is still used as a drug and that a few of the early synthetic agents such as benzocaine butyl-p-amino-benzoate-and procaine are still
used widely for more than 50 years after their introduction.

The table below is a compilation of agents that are listed in commonly used American handbook and a few other compounds that are often mentioned, especially in the European literature.

<table>
<thead>
<tr>
<th>No.</th>
<th>Name</th>
<th>Formula</th>
<th>Type of Application</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Benzocaine</td>
<td>4-NH₂-C₆H₄-COO-C₂H₅</td>
<td>Topical</td>
</tr>
<tr>
<td>2.</td>
<td>Bupivacaine</td>
<td>2,6(C₂H₅)₂-C₆H₅-NH-CO-</td>
<td>Parenteral</td>
</tr>
<tr>
<td>3.</td>
<td>Butacaine</td>
<td>4-NH₂-C₆H₄-CO₀(CH₂)₃₂N(C₄H₉)₂</td>
<td>Topical</td>
</tr>
<tr>
<td>4.</td>
<td>Chloroprocaine</td>
<td>2,4-ClNH₂-C₆H₅-CO₀(CH₂)₂₂N(C₂H₅)₂</td>
<td>Parenteral</td>
</tr>
<tr>
<td>5.</td>
<td>Cocaine</td>
<td>C₆H₅-CO₀-CH  NMe</td>
<td>Topical</td>
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<tr>
<td>6</td>
<td>Cyclomethycaine</td>
<td>C₆H₁₁-OC₆H₄-COO(CH₂)₃-NH</td>
<td>Topical</td>
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<tr>
<td>7</td>
<td>Dibucaine</td>
<td>O₈H₉</td>
<td>Topical, Parenteral</td>
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<tr>
<td>8</td>
<td>Falicaine</td>
<td>C₃H₇-C₆H₄-COCH₂-CH₂NG₅H₁₀</td>
<td>Topical, Parenteral</td>
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<tr>
<td>9</td>
<td>Hexylcaine</td>
<td>C₆H₅-COOCH-CH₂NHNC₆H₁₁</td>
<td>Topical, Parenteral</td>
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<tr>
<td>10</td>
<td>Hostacaine</td>
<td>2,6-Cl-C₆H₃-NH-COCH₂NH-C₄H₉</td>
<td>Topical, Parenteral</td>
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<tr>
<td>11</td>
<td>Isobucaine</td>
<td>C₆H₅-COOCH₂-C-NHCH₂CH(CH₃)₂</td>
<td>Parenteral</td>
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<td></td>
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</tr>
</tbody>
</table>
12. Xylocaine
2,6-(CH$_3$)$_2$-C$_6$H$_3$.NHCOCH$_2$N(C$_2$H$_5$)$_2$ Topical, Parenteral.

13. Mepivacaine
2,6-(CH$_3$)$_2$-C$_6$H$_3$-NH-GO
Topical, Parenteral.

14. Oxathazaine
C$_6$H$_5$-CH$_2$C(CH$_3$)$_2$N(CH$_3$)$_2$COCH$_2$N(CH$_2$)$_2$OH Parenteral.

15. Pilocarinate
C$_6$H$_5$CO(CH$_2$)$_3$-N(CH$_3$) Parentical, Parenteral.

16. Prilocaine
2-CH$_3$-C$_6$H$_4$-NHCOCHNHOCH$_3$H$_7$ Parenteral.

17. Procaine
4-NH$_2$-C$_6$H$_4$-COO(CH$_2$)$_2$N(C$_2$H$_5$)$_2$ Parenteral.

18. Tetracaine
4-C$_4$H$_9$NH-C$_6$H$_4$-COO(CH$_2$)$_2$N(CH$_3$)$_2$ Topical, Parenteral.
<table>
<thead>
<tr>
<th>(1)</th>
<th>(2)</th>
<th>(3)</th>
<th>(4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>19.</td>
<td><strong>Trimecaine</strong> 2,4,6-(CH$_2$)$_3$-C$_6$H$_2$-NHCOCH$_2$N(C$_2$H$_5$)$_2$</td>
<td>Topical, Parenteral.</td>
<td></td>
</tr>
<tr>
<td>20.</td>
<td>Benzyl alcohol C$_6$H$_5$CH$_2$OH</td>
<td>Topical.</td>
<td></td>
</tr>
<tr>
<td>21.</td>
<td><strong>Chlorobutanol</strong> CCl$_2$C(CH$_3$)$_2$OH</td>
<td>Topical.</td>
<td></td>
</tr>
</tbody>
</table>
PRESENT WORK:-

In an attempt to modify xylocaine molecule a variety of basic amides have been synthesized in this laboratory.

Following compounds were found more potent and less toxic:

1. O-Piperidino-N-(2-4-dimethylbenzyl-propionamide). \(^{10^4}\)
2. O-Diethylamino-N-(2-chlorobenzyl)-acetamide. \(^{10^4}\)
3. O-Morpholino-N-benzyl-p-methyl-acetanilide. \(^{10^5}\)
4. O-Diethylamino-N-(4-ethoxyphenyl)-2-phenylethyl acetamide. \(^{10^5}\)
5. O-Secondaryamino-N-(1,3, diarylethyl) acetamide. \(^{10^5}\)
6. O-Secondaryamino-N-(3-aryloxyethyl) acetanilide. \(^{10^6}\)
7. O-Secondaryamino-N-(substituted benzyl) acetanilide. \(^{10^7}\)
8. O-Secondaryamino-N-(arsalkyl) acetamides. \(^{10^6}\)

In all these compounds secondary amino groups were diethylamino, morpholino and piperidino.

Some of these compounds exhibited analgesic, anticonvulsant, antiarrhythmic and hypnotic effects in addition to the significant local anesthetic activity. The encouraging results obtained so far induced us to investigate further variations in the acid part of the molecule.
The following,

$$\text{C}_6\text{H}_5\text{-CH-CH}_2\text{-CO-NHR}$$

where

$$R = \text{C}_6\text{H}_5.$$ 

$$\text{NR}_1\text{R}_2 = \text{Morpholino and piperidino.}$$

amides show interesting pharmacological properties. It was of considerable interest to synthesize some $\alpha$ and $\beta$ substituted basic amides of these types, using some of the amines and examine their various types of pharmacological activities.

With this in view, the following types of compounds have been prepared and described in this part. The method followed is indicated by equations.

(a) $\alpha$-SUBSTITUTED BASIC AMIDES:

(i) $$R'\text{-C}_6\text{H}_4\text{-CH}_2\text{-CH-COCI} + \text{RNH}_2 \xrightarrow{\text{ether, low temp.}} \text{Br}$$

$$\text{R'}\text{-C}_6\text{H}_4\text{-CH}_2\text{-OH-CONER.}$$

$$\text{Br}$$
(ii) $R' \text{C}_6\text{H}_4\text{-CH}_2\text{-CH-CONHR} + \text{Br}$

$\text{Benzene}$

$R' \text{C}_6\text{H}_4\text{-CH}_2\text{-CH-CONHR}$

$\text{NR}_1\text{R}_2$

where

$R' = 4\text{-H, 4-CH}_3, 4\text{-OCH}_3, 4\text{-Cl}$.

$R = \text{C}_6\text{H}_5, 4\text{-CH}_3\text{-C}_6\text{H}_4, 4\text{-Cl-C}_6\text{H}_4, 4\text{-OCH}_3\text{-C}_6\text{H}_4, \text{C}_6\text{H}_5\text{CH}_2,$

$\text{C}_6\text{H}_5\text{-CH, 4-CH}_3\text{-C}_6\text{H}_4\text{-CH, 4-Cl-C}_6\text{H}_4\text{-CH, 1-C}_{10}\text{H}_7}.$

$\text{NR}_1\text{R}_2 = \text{Diethylamino, Morpholino and Piperidino}$.

(b) $\beta$-SUBSTITUTED BASIC AMIDES:

$\text{C}_6\text{H}_5\text{-CH-CH}_2\text{-COCl} - \text{RNH}_2 \text{ether low temp.}$

$\text{C}_6\text{H}_5\text{-CH-CH}_2\text{-CO-NHR}$

$\text{C}_6\text{H}_5\text{-CH-CH}_2\text{-CONHR} - \text{HNR}_1\text{R}_2 \text{Benzene}$

$\text{C}_6\text{H}_5\text{-CH-CH}_2\text{-CONHR} \text{NR}_1\text{R}_2$
where

\[ R = \text{C}_6\text{H}_5, 4-\text{CH}_3-\text{C}_6\text{H}_4, 4-\text{Cl}-\text{C}_6\text{H}_4, 4-\text{OCH}_3-\text{C}_6\text{H}_4, \]
\[ \text{C}_6\text{H}_5-\text{CH}_2, 1-\text{C}_6\text{H}_5-\text{CH} \],
\[ 4-\text{CH}_3-\text{C}_6\text{H}_4-\text{CH}, \]
\[ 4-\text{Cl}-\text{C}_6\text{H}_4-\text{CH}, 2-\text{C}_{10}\text{H}_7. \]

\[ \text{NR}_1\text{R}_2 = \text{Diethylamino, Morpholinio and Piperidino.} \]

(c) **-** **DISUBSTITUTED BASIC AMIDES**:

In this laboratory Shah and Trivedi have synthesized several phenylacetamides and benzylamides with a view to studying their physiological activities. Some of these compounds exhibited significant local anesthetic activity.

These encouraging results prompted us to explore further variations in the fundamental structure to prepare basic amides containing two phenyl rings.

With this in view, the following types of compounds have been prepared and described in this part. The method followed is indicated by equations.

![Chemical equations](image-url)
\[ \text{C}_6\text{H}_5\text{CONHR} + \text{HNR}_1\text{R}_2 \xrightarrow{\text{Benzene}} \text{C}_6\text{H}_5\text{CONHR} \cdot \text{NR}_1\text{R}_2 \]

where

\[ R = \text{C}_6\text{H}_5, \text{4-CH}_3\text{C}_6\text{H}_4, \text{4-COOH}_3\text{C}_6\text{H}_4, \text{4-Cl-C}_6\text{H}_4, \]
\[ \text{C}_6\text{H}_5\text{CH}_2, \text{C}_6\text{H}_5\text{CH}, \text{4-CH}_3\text{C}_6\text{H}_4\text{CH}, \text{4-Cl-C}_6\text{H}_4\text{CH}, \]
\[ \text{1-C}_{10}\text{H}_7, \text{2-C}_{10}\text{H}_7. \]

\[ \text{NR}_1\text{R}_2 = \text{Diethylamino, Morpholino and Piperidino}. \]
THEORETICAL - I
THEORETICAL

ACIDS:

Some important methods for the preparation of acids required in the present work are discussed below. These methods fall into seven main groups:

(A) Hydrolysis.
(B) Oxidation.
(C) Carbonation and carboxymethylation of organo-metallic compounds.
(D) Condensation.
(E) Alkali cleavage.
(F) Substitution and Addition.
(G) Rearrangements.

(A) HYDROLYSIS:

The acid derivatives may be arranged in a decreasing order of reactivity as shown:

Acid halide \( \rightarrow \) Acid anhydride \( \rightarrow \) Ester \( \rightarrow \) Amide \( \rightarrow \) Salt.

Only the first two are hydrolyzed spontaneously and completely in the majority of cases, depending on the aqueous medium. The rest of the derivatives react slowly
with water and approach an equilibrium state. For complete reaction it is best to saponify to the sodium salts and recover the free acid by acidification. Perhaps the most powerful reagent to split recalcitrant esters and other acid derivatives is potassium-t-butoxide. In converting one derivative into another it is more feasible to proceed from the more reactive to the less reactive.

(1) FROM ACID HALIDES OR ANHYDRIDES:

\[
\begin{align*}
R\text{COX} & \quad \xrightarrow{H_2O} \quad R\text{COOH} \\
R-C=O & \quad \xrightarrow{H_2O} \quad 2R\text{COOH}
\end{align*}
\]

Although these methods are very satisfactory, they are not widely used because the acid halide or anhydride is usually prepared from the acid. The mechanism in both cases usually consists of an SN₂ attack on the positively polarized carbon of the carbonyl group:
The acid halide hydrolysis is involved in the Hell-Volhard-Zelinsky synthesis in which the acid chlorides of \( \omega \)-halogenated acids are hydrolyzed to free acids. Anhydrides are sometimes found in nature and are thus likely starting materials for the preparation of acids. It is of interest to note that the hydrolysis of the anhydrides is catalyzed by tertiary amine bases.\(^{110}\)

Best examples of above method for the preparation of acids are shown below:

(a) \( 5\)-\( 5\)-Diphenyl acrylic acid (95\% from the acid chloride).\(^{111}\)

(b) Citraconic acid (94\% from the anhydride).\(^{112}\)

(c) I taconic acid (24-39\% from the anhydride).\(^{113}\)

(d) Mesaconic acid (43-52\% from citraconic anhydride).\(^{114}\)
Esters may be hydrolyzed in the presence of a base or an acid, although the use of the former is the more common procedure. In acidic hydrolysis, protonation of the carbonyl oxygen makes the carbonyl carbon more susceptible to nucleophilic attack by water.

Because the hydrogen ion plays such a predominant role or because compensating factors cancel each other (i.e., electron-releasing groups increase the extent of protonation but decrease the tendency of the carbonyl group to be attacked by water), substituent effects in acid hydrolysis by the SN₂ mechanism are negligible. Steric
effects of coarse still play a very important role in specific cases.

The basic hydrolysis mechanism is simpler in that the attack is made by the strong nucleophilic reagent OH.

\[
\begin{align*}
R-C & \quad \text{OH} \quad \longrightarrow \quad R-C \quad \text{OR} \quad \longrightarrow \quad R-C \quad \text{OH} \quad + \quad R'\text{OH}
\end{align*}
\]

This reaction appears to be largely irreversible because of the formation of the resonance-stabilized carboxylate anion. Substituent effects are important, i.e., electron-withdrawing groups accelerate saponification, and the steric effect is still a factor to be contended with as it was in acid hydrolysis.

Acids with groups sensitive to water may be prepared from the corresponding pyrrole and lithium aluminium hydride. 115

\[
\begin{align*}
\text{CH}_3 & \quad (1) \text{LiAlH}_4, \text{THF} \\
& \quad 0-10^\circ \quad \longrightarrow \quad \text{CH}_3\text{CH} = \text{CH-C} = \text{CHCO}_2\text{H} \\
\text{H}_3\text{C} & \quad (2) \text{H}_2\text{O}^+ \\
& \quad 3-\text{Methylhexa}-2,4-dienoic \text{ acid.}
\end{align*}
\]

The ring oxygen of the pyrrole in this reaction is displaced by hydride, perhaps via an alkyl fission, second order reaction.
Other examples of above method for the preparation of acids are shown below:-

(a) m-Nitrobenzoic acid (93-96% from the methyl ester).\textsuperscript{116}
(b) Myristic acid (89-95% from trimyristin).\textsuperscript{117}
(c) Linoleic acid (90% from the ethyl ester).\textsuperscript{118}
(d) Cyclopentan-2-one oxalic acid (81-92% from the ethyl ester and potassium hydroxide in alcohol water below 5° followed by acidification).\textsuperscript{119}
(e) o-Hydroxy hydro cinnamic acid (90% from dihydro coumarin and 40% aqueous sodium hydroxide).\textsuperscript{120}
(f) Nicotinic acid (76% from methyl nicotinate).\textsuperscript{121}

(3) AMIDES:–

\[
\begin{array}{c}
\text{RCONH}_2 + \text{H}^+ \\
or \text{OH}^-
\end{array} \rightarrow \text{RCOOH}
\]

This synthesis occurs in good yield in acidic or alkaline medium, although the latter appears to be the more widely used. The mechanism of these reactions are essentially the same as in the hydrolysis of esters. In acidic medium, hydrolysis again involves the attack by water on the protonated amide whereas, in basic medium, the powerful nucleophilic hydroxide ion attacks the free amide.\textsuperscript{122}

When the carboxyl group is produced from the cyanide group, the amide group is an intermediate which
may or may not be isolated. Difficultly hydrolyzable amides have been converted into acids successfully by the use of 100% phosphoric acid$^{123}$ or nitrous acid.$^{124}$ Hindered amides have been converted into the acid by 75% sulphuric acid and solid sodium nitrite.$^{125}$ In addition nitrosonium tetrafluoroborate, $\text{NOBF}_4^+$, in acetonitrile$^{126}$ and nitrosyl chloride in chloroform (in the sugar series)$^{127}$ have been used for the same purpose.

The phenyl hydrazide group can be removed by mild oxidation to yield acids.$^{123}$

(4) NITRILES:

\[
\text{RCN} \rightarrow \text{RCOOH}
\]

The hydrolysis may be carried out in acidic or alkaline medium. Either a proton and water or a hydroxide ion and water produce the intermediate acid amide, the mechanism of which has been discussed in amides. It has been found that alkali either in ethylene glycol$^{129}$ or in glycerol$^{130}$ is more effective in promoting hydrolysis than are other reagents.

The hydrolysis of cyanides has found rather wide use in the synthesis of $\alpha$-aminocarboxylic acids since the appropriate cyanide may be obtained from aldehyde or ketone
by the addition of hydrogen cyanide alone or in the presence of ammonia.

\[
\begin{align*}
RCHOHCN & \xrightarrow{H_2O} RCHOHCOOH \\
C &= O \\
H & \quad \xrightarrow{NH_3 + HCN} \quad \text{(Streeter Synthesis.)}
\end{align*}
\]

In the Strecker synthesis the nitrile anion probably adds to the iminoaldehyde \((RCH = NH)\) which is in equilibrium with the aldehyde and ammonia. The two essential reagents may be produced from ammonium cyanide generated from a mixture of sodium cyanide and ammonium chloride. As a rule the yields are more satisfactory for the simple than for the substituted carboxylic acids e.g.:-

(a) Preparation of 3-benzyl-3-methyl pentanoic acid (91-93\% from the nitrile and base in ethylene glycol).\(^{131}\)

(b) Other examples:

1. Mesitylacetic acid (87\% from the nitrile and sulphuric acid).\(^{132}\)

2. o-Toluic acid (30-89\% from the nitrile and 75\% aqueous sulphuric acid).\(^{133}\)

3. Nicotinic acid (87\% yield of nicotinamide)\(^{134}\) in the presence of sodium peroxide.
(5) ALDOXIMES:

\[ RCH_2CH = NOH \xrightarrow{KOH} RCH_2COOH \]

This reaction was first reported in 1936.\(^{135}\) It is applicable to aliphatic and aromatic aldoximes, the most frequently employed solvent being diethylene glycol at 170–190\(^\circ\).\(^{136}\) The reaction appears to proceed through the cyanide which under the conditions employed is hydrolyzed to the amide and finally to the acid.

(B) OXIDATION:

The oxidizing agents most commonly employed are potassium permanganate, potassium dichromate (or chromic anhydride), and dilute nitric acid. The advantages of potassium permanganate are that it is powerful as an oxidizer, and forms the insoluble manganese dioxide which is removed easily from the potassium salt of the acid dissolved in the aqueous medium. Its disadvantages are that it can not be dissolved well in non-aqueous media and it is unstable and releases oxygen in boiling water or refluxing pyridine-water solutions. Alkalinity increases this tendency.\(^{137}\)

Chromic acid oxidations invariably are conducted in acetic acid solution which occasionally creates isolation
problems. Other oxidizing agents are N-halo succinimides give low yields of esters in the reaction with alcohols.

\[ RCH_2OH \xrightarrow{(0)} RCHO \xrightarrow{(0)} RCO_2H \]

The mechanism of the oxidation, depends on the oxidizing agent used and the nature of medium. To cite one case, a primary alcohol in acidic solution with potassium dichromate forms the alkyl chromate which on acid catalysis yields the aldehyde.

\[ H_2O \xrightarrow{+} \text{H} \]
\[ \text{RCOOCR}_2 \xrightarrow{\text{H}_2\text{O}} \text{RC} = \text{O} + \text{O} = \text{Cr(OH)}_2 + \text{H}^+ \]

The aldehyde is then oxidized further in a similar manner perhaps via the hydrate. In the case of benzaldehyde in neutral or acidic solution of potassium permanganate, the steps appear to be :-
The following acids are the best examples of above method:

(a) Lauric acid (66% from dodecyl alcohol with platinum oxide and air).\(^ {141}\)

(b) Adipic acid (72% from cyclo hexanol and nitric acid).\(^ {142}\)

(c) \(\beta\)-Chloro propionic acid (78-79% from trimethylene chloro hydrin by means of nitric acid).\(^ {143}\)

(d) n-Heptanoic acid (85-90% from the aldehyde and acidic potassium permanganate).\(^ {144}\)

(e) Piperonylic acid (78-84% from piperonal and alkaline potassium permanganate).\(^ {145}\)

(2) ALDEHYDE (Cannizzaro):-

\[
\begin{align*}
2\text{RCHO} + \text{NaOH} & \rightarrow \text{RCH}_2\text{OH} + \text{RCOONa} \\
\end{align*}
\]

It involves the reaction of aldehyde having no \(\omega\)-hydrogen atoms with alkali to give a primary alcohol and
as to \( \alpha \)-keto-aldehydes and related types. The mechanism may be represented as follows:

\[
\begin{align*}
\text{Ar} & \quad \cdot \quad \text{C} \quad \cdot \quad \text{C} \quad \cdot \quad \text{Ar} \\
\text{OH} & \quad \rightarrow \\
\text{Ar} & \quad \cdot \quad \text{C} \quad \cdot \quad \text{C} \quad \cdot \quad \text{OH} \\
\end{align*}
\]

(1,2-Shift)

\[
\begin{align*}
\text{Ar} & \quad \cdot \quad \text{C} \quad \cdot \quad \text{C} \quad \cdot \quad \text{OH} \\
\rightarrow & \\
\text{Ar} & \quad \cdot \quad \text{C} \quad \cdot \quad \text{C} \quad \cdot \quad \text{OH} \\
\end{align*}
\]

This method was used for the preparation of benzilic acid as described in the experimental part-I, page 138.

(A) METHYL KETONES AND \( \beta \)-DIKETONES:

(a) TREATMENT WITH HALOGEN AND ALKALI (HALOFORM REACTION):

\[
\begin{align*}
\text{RCOCH}_3 & \quad \xrightarrow{\text{X}_2} \quad \text{RCOX}_3 \\
\text{NaOH} & \quad \rightarrow \\
\text{RCOONa} & \quad \xrightarrow{\text{NaOH}} \quad \text{CH}_3
\end{align*}
\]

In many cases this synthesis gives a satisfactory conversion of the acetyl into the carboxyl group. The mechanism of this multistep reaction consists first of the removal of an \( \alpha \)-hydrogen atom by the hydroxyl ion followed by an electrophilic attack of the positive halogen ion of the hypohalite.
The electronegative character of the halogen makes the $\alpha$-hydrogens which remain more readily replaceable, and thus substitution of halogen on the same carbon atom occurs until,

$$R - C - CH_3 \xrightarrow{\text{O\text{OH}}} R - C - CH_2 \xrightarrow{\text{X}^*} R - C - CH_2 X$$

is obtained. The product is then subject to a nucleophilic attack of the hydroxylion to form an anion which cleaves to give the anion of acid and the haloform:

$$R - C - CX_3 \xrightarrow{\text{OH}} R - C - CX_3 \xrightarrow{\text{OH}} \xrightarrow{\text{OH}} R - C + CHX_3$$

Not only are methyl ketones converted into acids by hypohalites, but also those compounds which split to form
methyl ketones. \( \beta \)-Diketones form such a class of compounds. Under typical hypohalite conditions they react as follows:

\[
\begin{align*}
\text{R-C-CH}_2-\text{C-R} & \xrightarrow{\text{NaOH, NaOCl}} 2\text{RCO}_2\text{Na} + \text{CHCl}_3 \\
\end{align*}
\]

(b) BY TREATMENT WITH IODINE - PYRIDINE AND ALKALI:

\[
\begin{align*}
\text{ArCOCH}_3 \xrightarrow{\text{I}_2, \text{C}_5\text{H}_5\text{N}} (\text{ArCOCH}_2\text{N}\text{C}_5\text{H}_5)_-^+ \xrightarrow{\text{NaOH}} \text{ArCOONa}
\end{align*}
\]

This method, devised by King,\(^{151}\) represents a second way for converting the acetyl into the carboxyl group. It has been employed giving a high yield, to a limited extent in cases in which the haloform reaction is unsatisfactory.\(^{52,153}\)

The mechanism of this synthesis appears to bear some resemblance to that of the haloform reaction. Iodine in the presence of the bases pyridine substitutes for an \( \omega \)-hydrogen atom to produce \( \text{ArCOCH}_2\text{N}\text{C}_5\text{H}_5\text{I}^- \) which is attacked by the hydroxyl ion to give an anion which cleaves to produce the carboxylic acid:\(~\)
Organometallic compounds are widely used to give high yields in the synthesis of carboxylic acids. The Grignard reagent is the most common, but in recent years the use of organolithium compounds has been on the increase, probably in part because of the availability from suppliers of the simpler ones used in the metalation. The mechanism of the reaction, as shown with the Grignard probably consists first of rapid coordination of the
magnesium atom with the oxygen atom of carbon dioxide followed by rate-determining nucleophilic attack of the R group:-

\[
\begin{align*}
\text{C}_2\text{H}_5\text{OC}_2\text{H}_5
\end{align*}
\]

\[
\begin{align*}
\text{R-Mg-X} + \text{CO}_2 & \quad \text{Rapid} \quad \rightarrow \quad \text{X-Mg-O} = \text{C} = \text{O} \\
\text{C}_2\text{H}_5\text{OC}_2\text{H}_5
\end{align*}
\]

\[
\begin{align*}
\text{Slow} \quad \rightarrow \quad \text{X-MgO-C-R} + \text{C}_2\text{H}_5\text{OC}_2\text{H}_5
\end{align*}
\]

The examples of carbonation for the preparation of acids are shown below:

(a) Mesitoic acid (86-87% from bromo mesitylene).\textsuperscript{154}

(b) Pentachloro benzoic acid (77% crude from pentachlorophenyl magnesium chloride).\textsuperscript{155}

(c) 2,5-Diphenyl adipic acid (meso-racemic mixture, 40% from dimerization of styrene with metallic sodium followed by carbonation).\textsuperscript{156}

(d) 3-Carboxy-5-methoxy-2-tetralone (45% from 5-methoxy-2-tetrolone and magnesium methyl carbonate).\textsuperscript{157}
Ketones with active hydrogen atoms may be carboxymethylated by treating the lithium enolate with the lithium salt of halo acetic acid. The first step is the usual method for active hydrogen replacement, while the second step follows the $SN_2$ mechanism. The lithium salt of the acid is prepared in situ by adding 2 equivalents of the ketone to more than 3 equivalents of lithium amide in liquid ammonia and, after replacing ammonia by ether, 1 equivalent of the halo acid in ether is added. Yields in five syntheses vary from 48% to 76%. Preparation of 1-keto-1,2,3,4-tetrahydro-naphthalene-2-acetic acid, is an example of carboxymethylation reaction.

(3) CARBONATION OF PHENOL SALTS (KOLBE):

The Kolbe synthesis involves the reaction of an alkali salt of a phenol with carbon dioxide to form a hydroxy benzoic acid. Schmitt's modification using relatively low temperature and longer reaction times allows for the
complete formation of sodium phenyl carbonate which then can be converted more or less completely into the hydroxy acid.\[C_6H_5Na + CO_2 \rightarrow C_6H_5CO_2Na \rightarrow C_6H_5CO_2Na^+\]

At low temperature the intramolecular route seems predominant, although it is the more reversible route. At high
temperature (and usually with potassium salts) the para isomer can be formed almost quantitatively. In this case intermolecular route is favoured.

Preparation of 2,4-dihydroxy benzoic (β-resorcyclic) acid is best example of Kolbe syntheses. 160

(4) REARRANGEMENT OF DICARBOXYLIC ACID SALTS (HENKEL):

Like the alkali salts of salicylic acids, which may be rearranged to those of p-hydroxy benzoic acids, the salts of dicarboxylic acids may be rearranged to more symmetrical isomers. 161, 162 The tautomeric transformation of this reaction is obscure but, from the possible course of the reaction, one can see why high temperatures are necessary.
Best results are obtained at a temperature of 400-420° in the absence of moisture at 10 atm. pressure (the reaction also occurs at atmospheric pressure) in the presence of cadmium or zinc or their compounds.

Preparation of terephthalic acid\textsuperscript{163} and naphthalene-2,6-dicarboxylic acid\textsuperscript{164} are well known examples of Henkel synthesis.

(D) \textbf{CONDENSATION:-}

\(\alpha,\beta\)- Unsaturated acids, \(\beta\)-hydroxy acids, and \(\beta\)-keto acids are available from aldol-type and Claisen-type condensation reactions.

(1) \textbf{AROMATIC ALDEHYDES AND ANHYDRIDES (PERKIN):-}

\[
\text{ArCHO} + (\text{CH}_2\text{CO})_2\text{O} \quad \xrightarrow{\text{1. CH}_3\text{COOK}} \quad \text{ArCH} = \text{CH}_2\text{COOH} + \text{CH}_3\text{COOK}
\]

This synthesis, which has been reviewed,\textsuperscript{165} is one of the oldest methods for preparing \(\alpha,\beta\)-unsaturated acids. The carboxylate anion of the salt reacts with the anhydride to form the anion of the anhydride, i.e.,

\[
\text{CH}_2 - \overset{0}{\text{C}} - \overset{0}{\text{C}} - \text{CH}_3
\]
which attacks the carbon of the aldehyde to produce an aldol anion, i.e.,

\[
\text{Ar} - \text{CH} - \text{CH}_2 - \text{C} - \text{O} - \text{C} - \text{CH}_3
\]

The latter in the presence of acid is converted into the aldol which in turn loses water and hydrolyzes to produce the \(\alpha,\beta\)-unsaturated acid. The synthesis is essentially applicable only to aromatic aldehydes, aliphatic aldehydes with no active hydrogen atoms, and to acetic or mono-substituted acetic acids.

Preparation of benzalpthalides,\textsuperscript{166} 2-furyl acrylic acid\textsuperscript{167} and trans-\(\alpha\)-nitro-\(\alpha\)-phenyl-cinnamic acid\textsuperscript{168} are well known examples of above method.

(2) AROMATIC ALDEHYDE AND MALONIC ACID (DOEBNER):

\[
\text{ArCHO} + \text{CH}_2(\text{COOH})_2 \xrightarrow{\text{Pyridine}} \text{Ar-CH} = \text{CH-COOH}
\]

This synthesis, which also occurs by the aldol mechanism,\textsuperscript{169} offers a second method for preparing \(\alpha,\beta\)-unsaturated acids. Recently the procedure has been modified by using a small amount of pyridine as a catalyst and by warming the reactants on a steam bath in the absence of alcohol.\textsuperscript{170} The yields for a series of substituted
cinnamic acids vary from 31% to 82%.

Preparation of 2-Puryl acrylic acid, \( \text{171} \) \( \alpha \)-Nitro cinnamic acid, \( \text{170} \) cyclohexylidene cyano acetic acid \( \text{173} \) and arylidene malonic acid \( \text{172} \) are examples of above method.

(3) CONDENSATION OF AROMATIC ALDEHYDE AND \( \alpha \)-HALOESTERS
(REFORMATSKII):

\[
\begin{align*}
C_6H_5CHO + Br-CH_2CO_2C_2H_5 & \quad \xrightarrow{\text{Zn}} \quad O\text{ZnBr} \\
C_6H_5-CH-CH_2-CO_2C_2H_5 + H_2SO_4 & \quad \xrightarrow{\text{Saponification}} \\
C_6H_5-CH-CH_2-COOH & \quad \xrightarrow{\text{KOH/C}_2\text{H}_5\text{OH}} \\
C_6H_5-CH-CH_2-COOH & \quad \xrightarrow{\text{HBr/Solvent}} \\
C_6H_5-CH-CH_2-COOH & \quad \xrightarrow{\text{Br}} \\
\end{align*}
\]

\( \beta \)-Bromo-hydrocinnamic acid.

The Reformatskii reaction involves the reaction of the product of an \( \alpha \)-halo ester and activated zinc in the presence of an anhydrous organic solvent, with a carbonyl compound, followed by hydrolysis. The reaction
is very similar in nature to the Grignard reaction except the carbonyl reagent is added at the start. It has been suggested that Grignard reactions might be conducted in a similar manner.  

Magnesium has been used in some reactions in place of zinc but poor yields resulted since the more reactive organo magnesium reagents attack the ester group. With zinc this latter reaction is not appreciable and the organozinc reagent attacks the cabonyl group of aldehydes and ketones to give the $\beta$-hydroxy ester.

$\alpha$-Bromo ester reacts satisfactorily but $\beta$- and $\gamma$-derivatives of saturated esters give poor yields unless activated by an unsaturated group in such a manner as to yield allylic bromide.  

$\beta$-Hydroxy ester undergoes saponification and bromination to yield $\beta$-bromo-hydro cinnamic acid.

This method was used for the preparation of $\beta$-bromo-hydro cinnamic acid as described in the experimental part-I, page 128.

(E) ALKALI CLEAVAGE:

Some of these methods are relatively new and useful routes to the preparation of acids of unique structure, particularly those cited in E. 3. Essentially they are reverse Claisen or aldol condensations.
(1) 5-KETO ESTERS (ACETOACETIC ESTER SYNTHESIS):

\[
\begin{align*}
\text{CH}_2\text{COCH}_2\text{COOC}_2\text{H}_5 & \xrightarrow{\text{RX}} \text{CH}_2\text{COCH COOC}_2\text{H}_5 \quad \text{NaOCH}_2\text{H}_5 \\
\text{NaOH} & \xrightarrow{\text{H}^+} \text{F.CH}_2\text{COOH}
\end{align*}
\]

In the first step of this synthesis the anion of sodium salt of acetoacetic ester, a resonance hybrid, and the alkyl halide produces C-alkylation. In the last step the mechanism is essentially the reverse of that of the Claisen ester condensation in that cleavage occurs to give two acid anions (retrograde claisen).

\[
\begin{align*}
\text{CH}_2\text{COCH- COOC}_2\text{H}_5 & \xrightarrow{(20H)} \text{CH}_2\text{COOH} + (\text{RCHCOOH}) + (\text{OC}_2\text{H}_5^-) \\
\text{CH}_2\text{COO}^- + \text{RCH}_2\text{COO}^- + \text{HOCH}_2\text{H}_5
\end{align*}
\]
The final alkaline hydrolysis gives ketones as well even though strong alkali is used, and thus the yields are often unsatisfactory. However, a procedure is now available which mitigates ketone formation by using only traces of sodium ethoxide as the catalyst in an excess of absolute ethanol and by removing ethyl acetate continuously as it is formed.\(^\text{176}\)

\[
\text{CH}_3\text{COOH} + \text{C}_2\text{H}_5\text{OH} \xrightarrow{\text{NaOC}_2\text{H}_5} \text{R-CH}_2\text{COOC}_2\text{H}_5 + \text{CH}_3\text{COOC}_2\text{H}_5
\]

6-Chloro-2,4-dinitro phenyl acetic acid\(^\text{177}\) and methylethyl acetic acid\(^\text{178}\) are other examples of above method.

(2) UNSATURATED ACIDS (VARENTRAPPP):-

\[
\text{CH}_3(\text{CH}_2)_n \text{CH} = \text{CH} \cdot \text{COOH} \xrightarrow{\text{KOH}} \text{CH}_3(\text{CH}_2)_n\text{COOH} + \text{CH}_3\text{COCH}.
\]

In this synthesis, yields are quite satisfactory in an inert atmosphere despite the high-temperature conditions. In fact, the method is employed as an isotopic assay method in which an acid is degraded by two carbon atoms.\(^\text{179}\)
This cleavage occurs not only with \( \omega,\beta \)-unsaturated acids but with almost any unsaturated acid. The phenomenon is due to the fact that the double bond migrates reversibly in both directions along the chain, but the irreversible fission occurs with the \( \omega,\beta \)-unsaturated isomer.\(^{180}\) Brassyl acid\(^{181}\) and pivalic acid\(^{182}\) are examples of above method.
(3) KETONES:

\[
\begin{align*}
0 & : \text{Ar} - \text{C} - \text{Ar} + \text{H}_2\text{O} \xrightarrow{\text{(CH}_3\text{)}_3\text{COK}} \text{ArCOOH} + \text{ArH} \\
0 & : \text{C}_6\text{H}_{12} + \text{H}_2\text{O} \xrightarrow{\text{(CH}_3\text{)}_3\text{COK}} \text{CH}_3(\text{CH}_2)_4\text{COOH}
\end{align*}
\]

This synthesis involves the cleavage of unenolizable aromatic or cyclic ketones with potassium hydroxide,\(^{183}\) with barium hydroxide or constant-boiling hydrochloric acid,\(^{184}\) with sulphuric acid,\(^{185}\) or with potassium t-butoxide-dimethyl sulfoxide.\(^{186,187}\) The potassium t-butoxide-dimethyl sulfoxide is the preferred reagent because it is effective at room temperature. It is thought that the reaction in alkaline solution involves an attack of the negative hydroxyl (or t-butoxide) on the positive carbonyl carbon to produce an anion capable of undergoing cleavage to carboxylic acid.
This synthesis has found its greatest value among cyclic ketones, as is shown by the exploitation of stetter in splitting the dihydro resorcinols. Dihydro resorcinol is a good source of acids because it can be alkylated, dimerized with aldehyde, or condensed with unsaturated compounds.

Other examples of above method are:

(a) (6-methyl-3-keto-7-cyclohexan-1-yl)-butyric acid.
(b) 3-Cyclopentenyl acetic acid.
(c) 2-Carboxy diphenyl.
(d) 5-Oxononanoic acid.
(e) Brassylic acid.

(F) SUBSTITUTION AND ADDITION (MAINLY ELECTROPHILIC):

(1) AROMATIC COMPOUNDS BY ACYLIATION OR CARBOXYLIATION

(FRIEDEL-CRAFTS):

\[
\begin{align*}
(1) \quad & \text{C}_6\text{H}_6 \xrightarrow[\text{AlCl}_3]{\text{COCl}_2} \quad \text{C}_6\text{H}_5\text{COCl} \xrightarrow[H_2\text{O}]{\text{H}_2\text{O}} \quad \text{C}_6\text{H}_5\text{COOH} \\
(2) \quad & \text{C}_6\text{H}_6 \xrightarrow[\text{AlCl}_3]{(\text{CH}_2)_n\text{CO}} \quad \text{C}_6\text{H}_5\text{CO}(\text{CH}_2)_n\text{COOH}
\end{align*}
\]

Carbonyl chloride (phosgene) or oxalyl chloride in the presence of a catalyst often introduces into aromatic
ring systems an acid-chloride group which is hydrolyzed readily to the acid. One must be aware of the possibility of the acid chloride further reacting to form a symmetrical ketone. The catalyst, such as aluminium chloride, forms the acylium ion (COCl) or a precursor where the carbon of the carbonyl is partially charged. In any form the acylium ion or its precursor is a weak attacking agent since resonance stabilization can delocalize the positive charge.

\[
\begin{align*}
\text{C-Cl} & \quad \text{C-Cl} \\
\text{+} & \quad \text{+} \\
\text{C = Cl} & \quad \text{C = Cl}
\end{align*}
\]

Therefore substitution is usually restricted to benzenoid compounds having substituents which increase the electron density of the ring or to other aromatic compounds in which substitution occurs more easily than in benzene.

Preparation of 1-azylene carboxylic acid,\textsuperscript{193}, anthracene-9-carboxylic acid,\textsuperscript{194} $\beta,\beta$-di(p-chlorophenyl) acrylic acid,\textsuperscript{195} cyclohexane carbonyl chloride,\textsuperscript{196} $\beta$-(p-methoxy benzoyl) proionic acid,\textsuperscript{197} and $\alpha$-benzoyl-pelargonic acid\textsuperscript{198} are well known examples of above method.
(2) ADDITION OF OLEFIN WITH DIAZONIUM SALTS IN THE PRESENCE OF CUPRIC SALTS (MEERWEIN ARYLATION):

\[
p-\text{CH}_2\text{COC}_6\text{H}_4\text{NH}_2 + \text{NaNC}_2 \xrightarrow{\text{HBr}} p-\text{CH}_2\text{COC}_6\text{H}_4^+ + \text{NBr}^- \]

\[
p-\text{CH}_2\text{COC}_6\text{H}_4^+ \xrightarrow{\text{CuBr}} p-\text{CH}_2\text{COC}_6\text{H}_4\text{CH}_2\text{CH}-\text{CO}_2\text{H} \]

This procedure has been used to prepare a variety of substituted $\alpha$-bromo-hydrocinnamic acids. $p$-acetyl-$\alpha$-bromo hydrocinnamic acid was prepared for the first time by this method. The method illustrates a typical application of the Meerwein reaction for the arylation of unsaturated substrates. In this reaction, a catalytic amount of a copper (I) salt is used to reduce an aryl diazonium salt forming an aryl radical and a copper (II) halide. Addition of the aryl radical to an unsaturated substrate forms an alkyl radical that is reoxidized by the copper (II) halide present forming an alkyl halide and regenerating the copper (I) salt catalyst. In this preparation, the product, an $\alpha$-bromo acid, is formed in an acidic reaction mixture and dehydrohalogenation does not occur. However, dehydrohalogenation
of the intermediate halide is often observed in analogous reactions performed under neutral or basic reaction conditions. The use of the Meerwein reaction to form ultimately 1-(p-nitrophenyl)-1,3-butadiene by the addition of an intermediate aryl radical to 1,3-butadiene followed by dehydrohalogenation of the initially formed alkyl halide is illustrated in organic syntheses. This method was used for the preparation of substituted α-bromo hydrocinnamic acids as described in the experimental part-I, page 111.

(3) ALCOHOLS, ALKENES, ALKYL HALIDES, OR ESTERS AND FORMIC-SULPHURIC ACID, OR 1,1-DICHLOORETHYLENE IN THE PRESENCE OF BORON TRIFLUORIDE-SULPHURIC ACID (KOCH-HAPF):

\[
\begin{align*}
(1) & & \text{C} = \text{O} & & \xrightarrow{\text{HCOOH}} & & \text{C} - \text{C} \\
& & & & \xrightarrow{\text{H}_2\text{SO}_4} & & \text{H} \quad \text{COOH}
\end{align*}
\]

\[
\begin{align*}
(2) & & \text{C} = \text{O} + \text{CH}_2 = \text{CCl}_2 & & \xrightarrow{\text{BF}_3 \cdot \text{H}_2\text{SO}_4} & & \text{C} - \text{C} - \text{CH}_2\text{COOH}
\end{align*}
\]

These syntheses resemble the OXO process but are more suitable for the laboratory. In the first case a carboxylic acid with one more carbon atom, and in second, a carboxylic acid with two more carbon atoms, is produced.
Alkenes are probably always intermediates, and under the acid conditions prevailing they probably form carbonium ions first. Isomerization of the carbonium ion tends to give the more stable tertiary carbonium ion, and thus the methods are of more value in preparing branched rather than straight-chain acids. The procedures are not difficult, but separation from the other acids formed is essential. Yields may be as high as 90%.

Preparation of 1-methylcyclohexane carboxylic acid \(^{206}\) (addition of one carbon atom) and 5-5-dimethylbutyric acid \(^{207}\) (addition of two carbon atoms) are examples of above method.

\(\text{(G) REARRANGEMENTS:—}\)

The preparation of acids by rearrangement comprises a rather heterogeneous collection of reactions.

\(\text{(1) ACID CHLORIDES VIA DIAZOKETONES (ARNDT-BISTERT AND WOLFF REARRANGEMENT):—}\)

\[
\begin{align*}
\text{RCOCl} & \quad \xrightarrow{\text{CH}_2\text{N}_2} \quad \text{RCOCHN}_2 \\
 & \quad \xrightarrow{\text{Ag}_2\text{O}} \quad \xrightarrow{\text{H}_2\text{O}} \quad \text{R-CH}_2\text{-COOH}
\end{align*}
\]

This synthesis, reviewed in detail, \(^{208}\) transforms a carboxylic acid to the next higher homolog via the diazoketone.
The three steps involved generally can be accomplished in one day with overall yields of 50-80%. The reaction requires anhydrous materials, and the usual precautions must be observed in working with diazomethane. Agents such as silver oxide, sodium thiosulfate, potassium hydroxide in methanol-water, a tertiary amine in benzyl alcohol, or simply irradiation have been used to catalyze the decomposition of the diazoketone:

\[
\text{RCOCH} = \overset{+} {\overset{-}{N}} = \overset{+} {\overset{-}{N}} \xrightarrow{-N_2} (\text{RCOCH}) \rightarrow \overset{0=c=CHR} {\overset{0=c=CHR} {\rightarrow}} \rightarrow \text{RC} \underset{2}{\overset{2}{\rightarrow}} \text{COOH}.
\]

but the most reliable, homogeneous catalyst is silver benzoate in triethylamine and t-butyl alcohol. Optically active diazoketones retain their configuration through the Wolff rearrangement.

Preparation of \(\alpha\)-naphthylacetic acid, indole-3-carboxylic acid, and other various acids are examples of Wolff rearrangement.

(2) FROM CYCLIC \(\alpha\)-HALOKE TONES (FAVORSKII):
This synthesis has been reviewed.\textsuperscript{214} It is applicable to both acyclic and cyclic types, although with the former the products of the reaction are not so predictable as in the case of the latter. For this reason the synthesis has found wider application in the cyclic series. In the alicyclic series in which the halogen is \( \omega \) and in which the keto group is a part of the ring system, rearrangement occurs in the presence of alkali to give carboxylic acids with ring contraction.

The mechanism of this reaction is variable, but in most reactions of \( \omega \)-chloro ketones with bases the unstable cyclopropanone derivative 13-III is accepted as the intermediate.\textsuperscript{215} According to this interpretation the ketone 13-I loses an \( \omega \)-hydrogen to form the anion 13-II which loses a negative chlorine ion to form the cyclopropane intermediate 13-III. The latter, on being attacked by the hydroxyl ion of the base, cleaves with ring contraction to give the carboxylic acid 13-IV:
Preparation of cyclohexane carboxylic acid, Diphenyl-4-carboxylic acid, and 5-Nonenoic acid are examples of Favorskii reaction.
Amides are prepared by a large number of methods. Some of the important methods for the preparation of amides required in the present work are described below. These fall into following main groups:-

(A) Solvolysis.
(B) Reduction.
(C) Oxidation.
(D) Electrophilic - Type Syntheses.
(E) Nucleophilic - Type Syntheses.
(F) Free Radical Reaction.
(G) Replacement Reaction of Halo-acyl-amide.

(A) SOLVOLYSIS:-

(1) FROM CARBOXYLIC ACIDS AND THEIR AMMONIUM SALTS:-

\[
\text{RCOOH} + \text{R}'\text{NH}_2 \xrightleftharpoons{\text{RCOONH}_2\text{R'}} \rightarrow \text{RCONHR'} + \text{H}_2\text{O}.
\]

Since an equilibrium is involved in this reaction, an excess of either amine or acid is desirable, the choice depending on which component is less costly. The most elegant
synthesis of amides from acids and amines is the carbodi-imide method:

\[
\text{R-COOH} \xrightarrow{\text{C}_6\text{H}_{11}N=\text{MC}_6\text{H}_{11}} \text{R-C-O-C} \rightleftharpoons \text{NHC}_6\text{H}_{11} \]

Yields of amides are almost quantitative. The method is particularly useful for the preparation of peptides. The reaction has been carried out in a number of ways. With less volatile substances the components can be heated together, nitrogen may be passed through to remove water, or water of reaction may be removed as an azeotrope with toluene (or other solvent). A recent example of the above reaction is preparation of N-ethyl-N'-3-dimethylaminopropyl carbodiimide at Ca.PH 4.7, and N,N-Bis(-2-chloroethyl)-2-((dichloro acetamido) acetamide. Free carboxylic acids may also be converted to amides by heating the acids with ureas as a source of the amino function.
This synthesis represents perhaps the best method for preparing amides. Yields are usually in the 80-90% range, and purification of the product is rarely difficult. Ammonia, ammonium salt, and primary or secondary amines are the customary amidating agents. The reaction with concentrated aqueous ammonia usually is quite exothermic. One equivalent of amine is lost as hydrochloride,

$$\text{RCOCl} + 2\text{R'NH}_2 \rightarrow \text{RCONHR'} + \text{R'NH}_2\text{Cl}$$

a circumstance which is of no concern in most cases, but which can be mitigated for water-insoluble (or less reactive) acid chlorides by shaking the acid-chloride with amine in aqueous base solution. Another method of utilizing a valuable amine completely is to add the acid-chloride to a mixture of the amine and a tertiary-amine such as triethylamine. Organic solvents such as ethylene dichloride, ether, benzene, carbon tetrachloride, chloroform, and toluene have been used to mitigate the exothermicity of amidation. Superior yields of benzoylated amino acids are obtained by treating 1 mole of the acid with 1 mole of benzoyl chloride
in the presence of 2 moles of aqueous sodium hydroxide at 1°C. Preparation of amides by the reaction of an amine and acyl chloride in the presence of aqueous alkali is known as "Schotten Baumann" reaction. This method was used for the preparation of α and β-Halo-alkanamides as described in the experimental part-I.

\[
\begin{align*}
\text{RCOOR'} & \xrightarrow{\text{NH}_3} \text{RCONH}_2 + \text{R'O}H \\
\end{align*}
\]

This synthesis has been accomplished with ammonia or unhindered amines as the amidating agent, although the use of the former is much more common. The ammonia has been employed in aqueous solution in alcoholic solution and as liquid ammonia. The reaction of esters with ammonia is catalyzed by water, glycols, and related compounds, while salts, such as ammonium chloride, promote a similar reaction with amines. Isoprophenyl acetate is a reactive ester quite suitable for preparing acetamides. In some cases, such as in the conversion of a triethyl ester into triamide, pressure is applied to promote the reaction. α,α-Disubstituted malonic esters may also be converted into diamides by heating with formamide in the presence of sodium methoxide.
(A) FROM NITRILES:-

\[
\text{RCN} + \text{H}_2\text{O} \xrightarrow{\text{Raney Ni}} \text{RCONH}_2
\]

The reagent of choice in this synthesis is aqueous sodium hydroxide containing about 6-12% hydrogen peroxide. The hydro-peroxide anion \((\text{HOO}^-)\) is several thousand times more reactive than the hydroxyl anion. Other acids reagents which have been employed are concentrated hydrochloric, concentrated sulphuric, poly phosphoric, hydrogen halides in glacial acetic, boron trifluoride in acetic and water, and a mixture of concentrated hydrochloric and concentrated sulphuric acids. Aqueous sodium hydroxide, potassium hydroxide in aqueous ethylene glycol mono ethyl ether, are some of the alkaline reagents which have been utilized in the hydrolysis.

(B) REDUCTION:-

(1) FROM HYDROXAMIC ACIDS:-

\[
\text{RCONHOH} + \text{H}_2 \xrightarrow{\text{Raney Ni}} \text{RCONH}_2
\]

Although hydroxamic acids would not ordinarily be considered as starting materials for the synthesis of amides,
it has been found that they may be reduced in yields of 76-97% by hydrogen in the presence of Raney nickel.

(C) OXIDATION:

(1) FROM KETONES (Willgerodt):

(i) \[ \text{ArCOCH}_3 \xrightarrow{(\text{NH}_4)_2\text{Sx}} \text{ArCH}_2\text{CONH}_2 \]

(ii) \[ \text{ArCO.CH}_2\text{CH}_3 \xrightarrow{(\text{NH}_4)_2\text{Sx}} \text{ArCH}_2\cdot\text{CH}_2\text{CONH}_2 \]

This remarkable rearrangement has been reviewed, strangely enough, the carbon skeleton remains unchanged in the reaction and the terminal methyl is always converted into carbamide group. As a synthetic method, the rearrangement has enjoyed its greatest success with aromatic-aliphatic ketones. Strictly aliphatic ketones also respond, but usually with lower yields. Other types which form amides with ammonium polysulphide are alkanes, alkynes, mercaptants, and cyclic oxides, but in these cases the return is also usually low.
(D) ELECTROPHILIC - TYPE SYNTHESSES:-

(1) FROM OXIMES (BECKMANN REARRANGEMENT) AND RELATED TYPES:-

\[
\text{Ar} - C - R \quad \xrightarrow{\text{PCl}_5} \quad O = C - R
\]

\[
\text{NH}_{\text{OH}} \quad \xrightarrow{} \quad \text{NH}_{\text{Ar}}
\]

The most common reagents used in the rearrangement of ketoximes are concentrated sulphuric acid, phosphorus pentachloride in ether and hydrogen chloride in a mixture of acetic acid and acetic anhydride (Beckmann's mixture\textsuperscript{267}), although recently it has been shown that poly phosphoric acid gives superior yields and more definitive products.\textsuperscript{268-270} In addition, tri-fluoro-acetic anhydride offers advantages in cases in which water-soluble amides are formed.\textsuperscript{271} The benzene sulfonyl esters (and other esters) of oximes re-arrange in neutral or aqueous alkaline solution, conditions which occasionally offer advantages.\textsuperscript{272,273}

The first step in the rearrangement appears to be reversible protonation of the oxime by the acid reagent to give 18-XII, which on the loss of water brings about the rearrangement as follows:-
As is well-known, the electron-deficient nitrogen atom attacks the group anti to the hydroxyl group originally present. Thus the syn and anti forms of a specific oxime potentially are capable of producing two different amides.

(B) NUCLEOPHILIC - TYPE SYNTHESSES:-

(1) FROM AMIDES BY ALCYLATION:-

\[
\text{RCONH}AR \xrightarrow{\text{Na}} \xrightarrow{\text{R'I}} \text{R'-CONAR}
\]

Amides are obtained from N-mono substituted amides by treatment of the sodium salt with methyl iodide or dimethyl
sulphate\(^{274,275}\). The sodium salt may be obtained with the use of sodium metal or sodium hydride. Yields for a series of N-mono substituted amides vary from 53 to 89\%.

(2) **FROM AMIDES BY HYDROXY ALKYLIATION:**

\[
\text{ArCONH}_2 + \text{CH}_2\text{O} \overset{\text{K}_2\text{CO}_3}{\longrightarrow} \text{ArCONHCH}_2\text{OH}
\]

Under mild conditions in neutral or alkaline medium, formaldehyde condenses with amides or imides to give N-hydroxymethyl derivatives\(^{276,277}\) in good yields but most higher aldehydes condense further to yield alkylidenediacylamides, RCH(NHCOR')\(_2\)\(^{278}\). A considerable number of hydroxy-methyl derivatives have been described by Einhorn,\(^{279}\) on of which has been oxidized to a formamide.

(W) **FREE RADICAL REACTIONS:**

The discovery that free radicals of the nature CONH\(_2\) or CH\(_2\)CONH\(_2\) can be generated photochemically or from free radical sources has led to some interesting syntheses of amides. These free radicals add to olefins in particular, but can be induced to substitute in hydrocarbons. With di-t-butyl peroxide as catalyst, the reaction is complicated by the intrusion of more than one free radical.\(^{280}\)
ECH = CH? + H-C-N(CH?)_2 -> Di-t-butyl peroxide.

ECH_2.CH_2CON(CH_3)_2 + R-CH_2-CH_2CL-N-C-H

52% 35% and higher telomers.

N-t-Butyl formamide yields only the product,
R-CH_2-CH_2-CONHC(CH_3)_2, while N,N-dimethyl acetamide yields
R-CH_2CH_2CH_2N(CH_3)_2CO-CH_3. Thus, either amidation or amino
alkylation can be carried out selectively by choice of
N-t-butyl formamide or N,N-dimethyl acetamide, respectively.
However, amidation has been accomplished with acetamide. 231

C_6H_13CH = CH_2 + CH_3CONH_2 -> Di-t-butyl peroxide

C_6H_13-CH_2-CH_2CHOCONH_2.
Decanamaide, 31%

(G) REPLACEMENT REACTION OF HALO-ACYLAMIDE:-

A large number of methods are known for the preparation of α-secondaryamino-acylamides. One of the important methods for the preparation of α-secondaryamino acylamides required in present work is discussed below.
A large number of \( \alpha \)-secondary amino-acyl-amides have been prepared by replacement reactions. In the preparation of \( \alpha \)-secondary amino acyl-amides, the halogen group of the \( \alpha \)-haloacylamides is replaced by the secondary amino group. The reaction of \( \alpha \)-haloacylamides and secondary amine is exothermic reaction hence it is carried out at low temperature.

The reaction itself is usually carried out in the presence of base and solvent. This base serves to neutralize hydrogen chloride, hydrogen bromide or hydrogen iodide formed as a co-product, which may form a solid amine hydrochloride, hydrobromide or hydriodide that could be discarded with other solid co-products by filtration.

Generally excess amine is used as a base to neutralize the acidic gas evolved during the reaction as a co-product. In other, particularly when the amine is only available in limited quantities, the anhydrous sodium carbonate\(^{282}\) is used as a base. In this reaction many solvents are used such as benzene\(^{283,284}\), toluene\(^{285}\), acetone\(^{286}\), and absolute alcohol\(^{287,283,282}\).

This method was used for the preparation of \( \alpha \)-secondary amino acylamide as described in the experimental part-I.
EXPERIMENTAL - I
GENERAL METHOD FOR THE PREPARATION OF PARA SUBSTITUTED ACETOPHENONE:-

In a 1-litre three necked flask, fitted with an efficient mercury sealed stirrer, a separatory funnel and a reflux condenser attached to a gas absorption device were placed finely powdered anhydrous aluminium chloride (140 gms) freshly distilled aromatic hydrocarbon (0.5 mole) and 200 ml of dry carbon disulphide. To this freshly distilled acetic anhydride (0.55 mole) was added dropwise through the separatory funnel within two hours. During the addition of acetic anhydride, the reaction mixture was stirred vigorously. After the completion of addition of acetic anhydride, the reaction mixture was stirred and heated for one hour on a water bath. The reaction mixture was decomposed with a mixture of 500 gm. of crushed ice and 30 ml of concentrated hydrochloric acid, and the ketone was extracted with ether. The ether extract was washed twice with water and dried over anhydrous magnesium sulphate or calcium chloride. The crude ketone obtained after removal of ether was purified by distillation under reduced pressure.


Following para-substituted acetophenones were prepared by this method.
### TABLE - 1.

![Chemical Structure](image)

<table>
<thead>
<tr>
<th>No.</th>
<th>R</th>
<th>B.P. °C.</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>(2)</td>
<td>p-Cl</td>
<td>236</td>
<td>- do -</td>
</tr>
</tbody>
</table>


GENERAL METHOD FOR THE PREPARATION OF $\omega$-ARALKYLAMINES:

Formic acid (21 ml) was slowly added to ammonium carbonate (21.5 gm), 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. Para substituted acetophenone (0.05 mole) was added in one lot to this reaction mixture and heating 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 form derivative was hydrolyzed with 12 per cent hydrochloric acid. In some cases, the amine was isolated as the hydrochloride, but where the hydrochloride was not obtained with ease, the hydrolyzed solution was basified and the liberated base was extracted with ether.


Following $\omega$-aralkylamines were prepared by this method.


<table>
<thead>
<tr>
<th>No.</th>
<th>R</th>
<th>B.P. °C.</th>
<th>Reference</th>
</tr>
</thead>
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<tr>
<td>2.</td>
<td>p-CH₃</td>
<td>204-05</td>
<td>- do -</td>
</tr>
<tr>
<td>3.</td>
<td>p-Cl</td>
<td>105-10/20 mm</td>
<td>- do -</td>
</tr>
</tbody>
</table>
GENERAL METHOD FOR THE PREPARATION OF α-BROMOHYDROCINNAMIC ACIDS:–

The aromatic amine (0.05 mole) was dissolved in acetone (100 ml), concentrated hydrobromic acid (16 ml of 48%) and the mixture was cooled to 3-5°C and stirred while diazotized beneath the surface with fused sodium nitrite (100 ml of 5.0 g). To this acrylic acid (50 ml) was added, and the mixture was cooled to 0.5°, cuprous bromide was added, the solution was stirred, and the temperature was regulated so that nitrogen was evolved at a reasonable rate. When nitrogen evolution ceased the mixture was concentrated in vacuo on steam to remove acetone and the bulk of acrylic acid and water. The residue was treated with water (200 ml) and stored at 0° for 24 hours. An organic residue, oil or solid was separated, washed twice with water (50 ml portions), dissolved in water (100 ml) by addition of a slight excess of sodium hydrogen carbonate, filtered if necessary, extracted with chloroform (50 ml) and ether (50 ml), stirred with carbon (2 gm), filtered, and acidified with concentrated hydrobromic acid. The mixture was extracted with benzene (300 ml), and the benzene layer was washed with water (25 ml), boiled to 100 ml, and concentrated in vacuo. The crude product was recrystallized from 40 ml of a 2:3 (V/V) formic acid-water mixture. The resulting crystals are collected on a filter, washed with 200 ml of cold mixture of formic acid and water (2:3 V/V) and dried in the air.
The following acids have been prepared by the above method, table-I.
<table>
<thead>
<tr>
<th>No.</th>
<th>Substituent on aniline R</th>
<th>M. P. °C.</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.</td>
<td>p-OCH₃</td>
<td>122-23</td>
<td>- do -</td>
</tr>
</tbody>
</table>
GENERAL METHOD FOR THE PREPARATION OF ACID CHLORIDES:

Finely powdered acid (1.00 mole) and freshly redistilled thionyl chloride (1.10 mole) were placed in a 500 ml. round bottomed flask fitted with a double surface reflux condenser carrying an anhydrous calcium chloride (or cotton wool) guard tube connected to gas absorption device for disposing off the evolved hydrogen chloride and sulphur dioxide gas. The flask was heated on a water bath with occasional shaking for one hour or until the evolution of hydrogen chloride and sulphur dioxide almost ceased. The reaction mixture was cooled and transferred to a claisen flask connected with a water reflux condenser and a receiver. The excess of thionyl chloride (B.P. 77°C.) was distilled slowly until the temperature rose up to 120°C., this assured that all the thionyl chloride was removed. The residual acid chloride was distilled under diminished pressure.


The following acid chlorides have been prepared by the above method. They were directly used for the preparation of α-halo alkanamides.
GENERAL METHOD FOR THE PREPARATION OF \( \alpha \)-HALO ALKANAMIDES:

To substituted aromatic amine \((8.1 \text{ gm, } 0.756 \text{ mole})\)
in ether \((125 \text{ ml})\) was added over a period of five minutes
\(\alpha\)-halo substituted hydrocinnamoyl chloride \((10 \text{ gm, } 0.0377 \text{ mole})\)
in ether \((100 \text{ ml})\). The reaction mixture was allowed to stand
three hours at room temperature and then filtered. The
precipitate was washed with ether and the filtrate and
combined ether washings were concentrated until a thick
mass of crystals remained. The solid was filtered and washed
with petroleum ether \((\text{b.p. } 50-60^\circ)\) to give 81 per cent of the
\(\alpha\)-halo substituted alkanamides \((10.3 \text{ gm})\). A recrystallization
from a petroleum ether-ether mixture gave needles.

Ref: Calvin L. Stevens and James C. French, J. Am. Chem.
Soc. 75, 657-660(1953).

The following \(\alpha\)-halo alkanamides have been prepared
by the above method, tables II, III, IV and V.
TABLE - II.

\[ \text{C}_6\text{H}_5-\text{CH}_2-\text{CH}-\text{CO}-\text{NHR} \]
\[ \text{Br} \]

N-Substituted-2-bromo-3-phenyl propionamide.

<table>
<thead>
<tr>
<th>R</th>
<th>Molecular Formula</th>
<th>M.P. °C.</th>
<th>% of Nitrogen Found</th>
<th>% of Halogen Found</th>
<th>Claded</th>
</tr>
</thead>
<tbody>
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<td>(1)</td>
<td>(2)</td>
<td>(3)</td>
<td>(4)</td>
<td>(5)</td>
<td>(6)</td>
</tr>
<tr>
<td>( \text{C}_6\text{H}_5 )</td>
<td>( \text{C}<em>{15}\text{H}</em>{14}\text{BrNO} )</td>
<td>68-69</td>
<td>4.69</td>
<td>4.60</td>
<td>26.18</td>
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<tr>
<td>4-( \text{CH}_3 ) - ( \text{C}_6\text{H}_4 )</td>
<td>( \text{C}<em>{16}\text{H}</em>{16}\text{BrNO} )</td>
<td>75-76</td>
<td>4.26</td>
<td>4.40</td>
<td>25.02</td>
</tr>
<tr>
<td>4-O( \text{CH}_3 ) - ( \text{C}_6\text{H}_4 )</td>
<td>( \text{C}<em>{16}\text{H}</em>{16}\text{BrNO}_2 )</td>
<td>98-99</td>
<td>4.07</td>
<td>4.19</td>
<td>23.83</td>
</tr>
<tr>
<td>4-Cl - ( \text{C}_6\text{H}_4 )</td>
<td>( \text{C}<em>{19}\text{H}</em>{15}\text{BrClNO} )</td>
<td>110-11</td>
<td>4.21</td>
<td>4.13</td>
<td>34.00</td>
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<tr>
<td>( \text{C}_6\text{H}_5 ) - ( \text{CH}_2 )</td>
<td>( \text{C}<em>{16}\text{H}</em>{16}\text{BrNO} )</td>
<td>134-35</td>
<td>4.28</td>
<td>4.40</td>
<td>25.03</td>
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<tr>
<td>1-( \text{C}_6\text{H}_5 ) - ( \text{CH} )</td>
<td>( \text{C}<em>{17}\text{H}</em>{18}\text{BrNO} )</td>
<td>73-74</td>
<td>4.09</td>
<td>4.22</td>
<td>24.19</td>
</tr>
<tr>
<td>4-( \text{CH}_3 ) - ( \text{C}_6\text{H}_4 ) - ( \text{CH} )</td>
<td>( \text{C}<em>{18}\text{H}</em>{20}\text{BrNO} )</td>
<td>115-16</td>
<td>4.16</td>
<td>4.05</td>
<td>23.01</td>
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<tr>
<td>4-Cl - ( \text{C}_6\text{H}_4 ) - ( \text{CH} )</td>
<td>( \text{C}<em>{17}\text{H}</em>{17}\text{BrClNO} )</td>
<td>180-81</td>
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<td>1-( \text{C}_{10}\text{H}_7 )</td>
<td>( \text{C}<em>{19}\text{H}</em>{16}\text{BrNO} )</td>
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<td>% Of Nitrogen Calcd.</td>
<td>% Of Halogen Calcd.</td>
</tr>
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<td>(1)</td>
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<tr>
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<td>C₁₆H₁₆BrNO</td>
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<td>4-OCH₃-C₆H₄</td>
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<td>C₆H₅-CH₂</td>
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<td>1-C₆H₅-CH</td>
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<td>CH₃</td>
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<td>CH₃</td>
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<tr>
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<td>3.80</td>
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<td>% Of Nitrogen Calcd.</td>
<td>% Of Halogen Found</td>
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<td>(2)</td>
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<td>(4)</td>
<td>(5)</td>
<td>(6)</td>
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<tr>
<td>$\text{C}_6\text{H}_5$</td>
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<td>3.80</td>
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<td>$\text{C}_6\text{H}_5-\text{CH}_2$</td>
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GENERAL METHOD FOR THE PREPARATION OF α-SECONDARY AMINOALKANAMIDES:

α-Halo alkanamide (1.0 mole) in dry benzene (500 ml) was refluxed for five hours with secondary amine (2.5 moles). The precipitated secondary amine hydrochloride was filtered off and washed with a small quantity of benzene. The filtrate was now treated with a little more than the calculated quantity of cold hydrochloric acid (3N, 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 crystallized 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 α-secondary amino alkanamides, dry hydrogen chloride gas was passed, when the hydrochloride salt precipitated. It crystallized in colourless needles from dry acetone or a mixture of ether-ethanol. If the hydrochloride separated as an oil on passing dry hydrogen chloride gas into the dry ethereal extract, the oxalates were prepared. The oxalates were prepared by addition of a saturated solution of anhydrous oxalic acid in dry ether into the dry ethereal extract. The precipitate was filtered off, and washed with dry ether and dried, it was crystallized.
from dry acetone or a mixture of ether-ethanol.

\[ \text{Ref: Lofgren, N. M., and Lundquist, B. J., Swed. 130, 729, Feb. 6, 1951., Chem. Abstr. 45, 8561(1951).} \]

The compounds prepared are shown in the following tables - VI, VII, VIII and IX.
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### TABLE VIII.

\[
\text{H}_2\text{CO-C}_6\text{H}_4\text{-CH}_2\text{-CH-CONHR} \\
\text{NR}_1\text{R}_2\cdot\text{A}
\]

**N-Substituted-2-secondaryamino-3-(p-methoxyphenyl)-propionamide.**

<table>
<thead>
<tr>
<th>R</th>
<th>NR(_1)R(_2)</th>
<th>A</th>
<th>Molecular Formula</th>
<th>M.P.(^\circ)C.</th>
<th>% Of Nitrogen Found</th>
<th>% Of Nitrogen Caled.</th>
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<td>C(_6)H(_5)</td>
<td>Diethylamino HCl</td>
<td>C(<em>20)H(</em>{26})N(_2)O(_2)HCl</td>
<td>134-35</td>
<td>7.89</td>
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<tr>
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<td>C(<em>20)H(</em>{24})N(_2)O(_3)HCl</td>
<td>155-56</td>
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<tr>
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<td>Piperidino HCl</td>
<td>C(<em>21)H(</em>{26})N(_2)O(_2)HCl</td>
<td>185-86</td>
<td>7.36</td>
<td>7.48</td>
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<tr>
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<td>Diethylamino HCl</td>
<td>C(<em>21)H(</em>{28})N(_2)O(_2)HCl</td>
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<td>Piperidino HCl</td>
<td>C(<em>22)H(</em>{28})N(_2)O(_3)HCl</td>
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<td>( \text{C}_6\text{H}_5-\text{CH} )</td>
<td>Morpholino HCl</td>
<td>( \text{C}<em>{22}\text{H}</em>{28}\text{N}_2\text{O}_3\cdot\text{HCl} )</td>
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<td>6.80</td>
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<td>( \text{C}<em>{23}\text{H}</em>{30}\text{N}_2\text{O}_2\cdot\text{HCl} )</td>
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<td>6.80</td>
<td>6.96</td>
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<tr>
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<td>( \text{C}<em>{22}\text{H}</em>{32}\text{N}_2\text{O}_2\cdot\text{HCl} )</td>
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<td>Morpholino HCl</td>
<td>( \text{C}<em>{23}\text{H}</em>{30}\text{N}_2\text{O}_3\cdot\text{HCl} )</td>
<td>176-77</td>
<td>6.80</td>
<td>6.92</td>
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<tr>
<td></td>
<td>Piperidino HCl</td>
<td>( \text{C}<em>{24}\text{H}</em>{32}\text{N}_2\text{O}_2\cdot\text{HCl} )</td>
<td>185-86</td>
<td>6.80</td>
<td>6.96</td>
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<td>4-\text{Cl}-\text{C}_6\text{H}_4-\text{CH}</td>
<td>Diethylamino HCl</td>
<td>( \text{C}<em>{22}\text{H}</em>{29}\text{ClN}_2\text{O}_2 \cdot \text{HCl} )</td>
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<td>( \text{C}_6\text{H}_5-\text{CH} )</td>
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<td>6.32</td>
<td>6.41</td>
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*Note: All compounds are listed with their molecular formulas and melting points.*
### TABLE IX

\[
\text{Cl-C}_6\text{H}_4-\text{CH}_2-\text{CH-CONHR} \quad \text{NR}_1\text{R}_2\text{A}
\]

\text{N-Substituted-2-secondaryamino-3-(p-chlorophenyl)-propionamide.}

<table>
<thead>
<tr>
<th>R</th>
<th>NR\text{I}\text{R}_2</th>
<th>A</th>
<th>Molecular Formula</th>
<th>M.P.°C.</th>
<th>% Of Nitrogen Found</th>
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<td>C\text{H}_5</td>
<td>Diethylamino</td>
<td>Oxalate</td>
<td>(\text{C}<em>{19}\text{H}</em>{25}\text{ClN}_2\text{O}_4)</td>
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<td>(\text{C}<em>{19}\text{H}</em>{21}\text{ClN}_2\text{O}_2)</td>
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<td>(\text{C}<em>{20}\text{H}</em>{23}\text{ClN}_2\text{O}_2)</td>
<td>106-07</td>
<td>8.05</td>
<td>8.17</td>
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<td>Oxalate</td>
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<td>Oxalate</td>
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<tr>
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<td>C₂₁H₂₅ClN₂O₂</td>
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<td>5.80</td>
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<tr>
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<td>C₂₁H₂₄Cl₂·N₂O₂</td>
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GENERAL METHOD FOR THE PREPARATION OF β-BROMO-β-PHENYL-
PROPIONIC ACID:

(a) PREPARATION OF ETHYL-β-PHENYL-β-HYDROXYPROPIONATE:

In a clean, dry, 500 ml. three-necked flask, fitted with a mechanical stirrer, a 250 ml. separatory funnel, and reflux condenser, the upper end of which was protected by calcium chloride drying tube, was placed finely powdered zinc 40 gm. (0.62 gm atom).

A solution of ethyl bromoacetate (53.5 gm, 0.50 mole) and of benzaldehyde (65.0 gm, 0.61 mole) in dry benzene (80 ml) and absolute ether (20 ml) was placed in separatory funnel. About 10 ml. of this solution was added to the zinc, and the flask was warmed until the reaction started. The mixture was then stirred and the rest of the solution added at such a rate that the reaction mixture refluxed. The reaction mixture was refluxed for 30 minutes on a water bath after the addition of the solution was complete.

The flask was then cooled in an ice-bath and the reaction mixture hydrolyzed by the addition of 200 ml. of cold 10% sulphuric acid with vigorous stirring during the addition. The acid layer was drawn off and the benzene solution extracted twice with 50 ml portions of 5% sulphuric acid. The benzene solution was washed once with 25.0 ml of 10% sodium
carbonate solution, then with 25 ml. of 5% sulphuric acid, and finally with two 25 ml. portions of water. The combined acid solutions were extracted with two 50 ml. portions of ether, and the combined ether and benzene solutions were dried with 5.0 gm of magnesium sulphate. The solution was filtered, the solvent removed by distillation at atmospheric pressure from a steam bath, and the ester was collected at 151-154/11-12 mm. The total yield was 59-62 gm.


(b) PREPARATION OF β-PHENYL-β-HYDROXYPROPIONIC ACID:

Ester (25.0 gm) was dissolved in ethanol (50 ml) containing potassium hydroxide (4.0 gm) and allowed to stand 48 hours. Some salt usually precipitated. The alcohol was evaporated completely and the salt was dissolved in the minimum of ice-water and acidified dropwise with 6N acid to give β-phenyl-β-hydroxypropionic acid, M.P. 115-16°C.

(c) PREPARATION OF $\beta$-BROMO-$\beta$-PHENYLPROPIONIC ACID:

The $\beta$-hydroxy-$\beta$-phenylpropionic acid (5.0 gm) was dissolved in formic acid (100 ml) previously saturated with hydrogen bromide. The acid passed slowly into the solution, and after 1/2 hours, $\beta$-bromo-$\beta$-phenylpropionic acid was isolated. The residual bromo acid was washed with cold water and dried over concentrated sulphuric acid in a vacuum desiccator. The yield of the product was 88%, M.P. 137°C.

GENERAL METHOD FOR THE PREPARATION OF $\beta$-HALO ALKANAMIDES:

In a 100 ml. round bottomed flask fitted with a reflux condenser was placed $\beta$-bromo hydrocinnamic acid (20 gm) to which thionyl chloride (30 ml) was added in one portion. The mixture was heated gently on a water bath held at 50-60°C. After about two to three 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 in a water bath to remove the excess of thionyl chloride. The residual $\beta$-chloro hydrocinnamoyl chloride (86% yield) b. 141°C. was used directly for the preparation of $\beta$-halo alkamides.

To substituted aromatic amines (1.0 mole) in dry ether (125 ml) was added over a period of five minutes $\beta$-chloro hydrocinnamoyl chloride (0.5 mole) in dry ether (100 ml). The reaction mixture was allowed to stand three hours at room temperature and then filtered. The precipitate was washed with ether and the filtrate and combined ether washings were concentrated until a thick mass of crystals remained. The solid was filtered and washed with petroleum ether (b.p. 30-60°C) to give $\beta$-halo alkanamides (80%). A recrystallization from petroleum ether-ether mixture gave needles.

The following β-halo alkanamides have been prepared by the above method, table-X.
### TABLE - X.

\[
C_6H_5-\text{CH-CH}_2-\text{CONHR} \quad \text{Cl}
\]

N-Substituted-3-chloro-3-phenyl propionamide.

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<th>R</th>
<th>Molecular Formula</th>
<th>M.P. °C</th>
<th>% Of Nitrogen Found</th>
<th>% Of Halogen Found</th>
<th>Reference</th>
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<tr>
<td>C\textsubscript{6}H\textsubscript{5}</td>
<td>C\textsubscript{15}H\textsubscript{14}ClNO</td>
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<td>12.86</td>
<td>12.93</td>
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<tr>
<td>4-\text{CH.}3-C\textsubscript{6}H\textsubscript{4}</td>
<td>C\textsubscript{16}H\textsubscript{16}ClNO</td>
<td>131-32</td>
<td>4.92</td>
<td>12.12</td>
<td>12.26</td>
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<td>4-\text{OCH.}2-C\textsubscript{6}H\textsubscript{4}</td>
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<td>125-26</td>
<td>4.64</td>
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<td>24.15</td>
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<td>4-\text{Cl-C}\textsubscript{6}H\textsubscript{4}</td>
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<td>128-29</td>
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<tr>
<td>C\textsubscript{6}H\textsubscript{5}-\text{CH}_2</td>
<td>C\textsubscript{16}H\textsubscript{16}ClNO</td>
<td>116-17</td>
<td>5.12</td>
<td>12.36</td>
<td>12.93</td>
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</table>

<table>
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<td>C₁₇H₁₈ClNO</td>
<td>97-98</td>
<td>4.99</td>
<td>4.87</td>
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<td>12.35</td>
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<td>C₁₈H₂₀ClNO</td>
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<td>4.64</td>
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<td>11.77</td>
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GENERAL METHOD FOR THE PREPARATION OF \( \beta \)-SECONDARY AMINO-ALKANAMIDES:

\( \beta \)-Halo alkanamides (1.0 mole) in dry benzene (500 ml) were refluxed for five hours with secondary amine (2.5 moles). The precipitated secondary amine hydrochloride was filtered off and washed with a small quantity of benzene. The filtrate was now treated with a little more than the calculated quantity of cold hydrochloric acid (3N, 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 crystallized from aqueous alcohol or petroleum ether.


The compounds prepared are shown in the following table-XI.
### TABLE - XI.

\[ C_6H_5-CH-CH_2-CO-NHR \]
\[ NR_2 \]

N-Substituted-3-secondaryamino-3-phenyl-propionamide.

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<td>Piperidino C₂₄H₂₆N₂O</td>
<td>75-76</td>
<td>7.96</td>
<td>7.82</td>
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</table>
GENERAL METHOD FOR THE PREPARATION OF BENZILIC ACID:

Rectified spirit (65 ml), benzaldehyde (50 gm, 47.5 ml) and a solution of sodium cyanide (59 gm, 96-98 per cent) in water (50 ml) were placed in 500 ml. round bottomed flask with a up right double surface condenser and gently boiled for half an hour. The contents of the flask were cooled, filtered, washed with cold water and dried. The yield of crude benzoin was 45 gm.

The crude benzoin was used directly for the preparation of the benzil.

Crude benzoin (20 gm) and concentrated nitric acid were placed in a 250 ml. round bottomed flask. The flask was heated on a water bath (in the fume cupboard) with occasional shaking until the evolution of oxides of nitrogen almost ceased (about 1.5 hours). The reaction mixture was then poured into 300-400 ml. of cold water in a beaker, stirred well until the oil crystallized completely as a yellow solid. The crude benzil was filtered at the pump, and washed thoroughly with water to remove the nitric acid. The crude benzil was recrystallized from alcohol or methylated spirit.

Potassium hydroxide (35.0 gm) in water (70 ml), then add rectified spirit (70.0 gm, 87 ml) and recrystallized benzil (35.0 gm) were placed in 500 ml. round bottomed flask. A deep bluish-black solution is produced. Boiled the mixture
on a water bath for 10-15 minutes. Pour the contents of the flask into a porcelain dish and allow to cool, preferably overnight. The potassium salt of benzilic acid crystallises out. Filter off the crystals of the pump and wash with a little ice-cold alcohol. Dissolve the potassium salt in about 350 ml of water, and add concentrated hydrochloric acid with stirring until the solution is acid to congo red paper. Filter off the benzilic acid with suction, wash thoroughly with cold water until free from chlorides, and allow to dry. The yield of crude benzilic acid, which is usually light pink or yellow in colour, is 30 gm. The crude benzilic acid was recrystallized from hot benzene or hot water, M.P. 150°C.

GENERAL METHOD FOR THE PREPARATION OF \(\alpha\)-CHLORODIPHENYL-ACETYL CHLORIDE:

After the initial vigorous interaction of phosphorus pentachloride (40 gm, 0.192 mole) and benzilic acid (20 gm, 0.088 mole) had subsided, the resulting oil, protected from moisture by a calcium chloride tube, was heated for one hour on a steam bath. Distillation under reduced pressure removed phosphorus oxychloride and gave \(\alpha\)-chlorodiphenylacetyl chloride (20.55 gm, 57\%) B. P. 125-128\(^\circ\) (0.5 mm), M.P. 45-49\(^\circ\)C.

GENERAL METHOD FOR THE PREPARATION OF N-SUBSTITUTED-\(\alpha\)-CHLORODIPHENYLACETAMIDES:

Substituted aromatic amine (8.1 gm, 0.0756 mole) in ether (125 ml) was added over a period of five minutes \(\alpha\)-chlorodiphenylacetyl chloride (10.0 gm, 0.0377 mole) in ether (100 ml). The reaction mixture was allowed to stand three hours at room temperature and then filtered. The precipitate was washed with ether and the filtrate and combined ether washings were concentrated until a thick mass of crystals remained. The solid was filtered and washed with petroleum ether (B.P. 50-60\(^\circ\)) to give \(\alpha\)-chloroamides (10.3 gm, 81%). A recrystallization from a petroleum ether-ether mixture gave needles.


Following N-substituted-\(\alpha\)-chlorodiphenylacetamides have been prepared by the above method, table-XII.
TABLE - XII.

\[
\begin{align*}
\text{N-Substituted-} \alpha \text{-chloro-} \alpha, \alpha \text{-diphenylacetamide.}
\end{align*}
\]

<table>
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<tr>
<th>R</th>
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<th>% Of Nitrogen Found</th>
<th>% Of Nitrogen Calcd.</th>
<th>% Of Halogen Found</th>
<th>% Of Halogen Calcd.</th>
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<td>(4)</td>
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<td>(6)</td>
<td>(7)</td>
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<td>( \text{C}<em>{22}\text{H}</em>{20}\text{ClNO} )</td>
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<td>4.00</td>
<td>10.04</td>
<td>10.16</td>
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<tr>
<td>( \text{C}_6\text{H}_4 \text{-CH} \quad \text{CH}_3 )</td>
<td>( \text{C}<em>{23}\text{H}</em>{22}\text{ClNO} )</td>
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<td>3.80</td>
<td>3.85</td>
<td>9.89</td>
<td>9.77</td>
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<td>( \text{C}_6\text{H}_4 \text{-CH} \quad \text{CH}_3 )</td>
<td>( \text{C}<em>{22}\text{H}</em>{19}\text{Cl}_2\text{NO} )</td>
<td>144-45</td>
<td>3.52</td>
<td>3.64</td>
<td>18.36</td>
<td>18.49</td>
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</table>
GENERAL METHOD FOR THE PREPARATION OF N-SUBSTITUTED
α-SECONDARYAMINO DIPHENYLA CETAMIDES:—

N-Substituted-α-chorodiphenylacetamide (1.0 mole) in dry benzene (500 ml) was refluxed for five hours with secondary amine (2.5 moles). The precipitated secondary amine hydrochloride was filtered off and washed with a small quantity of benzene. The filtrate was now treated with a little more than the calculated quantity of cold hydrochloric acid (3N, 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 crystallized 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 basic amides, dry hydrogen chloride gas was passed, when the hydrochloride salt precipitated. It crystallized in colourless needles from dry acetone or a mixture of ether-ethanol. If the hydrochloride separated as an oil on passing dry hydrogen chloride gas into the dry ethereal extract, the oxalates were prepared. The oxalates were prepared by addition of a saturated solution of anhydrous oxalic acid in dry ether into the dry ethereal extract. The precipitate was filtered off, and washed with dry ether and dried, it was crystallized from acetone or absolute alcohol or a mixture of ether-ethanol.
The compounds prepared are shown in the following table XIII.
TABLE XIII.

N-Substituted-α--secondaryamino-α,α-diphenylacetamide.

<table>
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<th>NR₁R₂</th>
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<th>Molecular Formula</th>
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<th>% Of Nitrogen Found</th>
<th>% Of Nitrogen Calcd.</th>
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<td>C₂₄H₂₆N₂O</td>
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<td>Morpholino</td>
<td>-</td>
<td>C₂₄H₂₄N₂O₂</td>
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<td>7.69</td>
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<td>-</td>
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<td>74-75</td>
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<td>109-10</td>
<td>6.54</td>
<td>6.67</td>
</tr>
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</table>
(A) SURFACE ANESTHESIA ON RABBIT CORNEA:

Solution of the test compounds prepared in phosphate buffer (pH 7.3) was dropped into an eye of a 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 the local anesthetic effect was observed from the complete absence of the partial hindrance in the blinking of the eye subjected to stimuli with brush. Partial recovery was observed after half an hour with some of the compounds.

(B) INTRADERMAL ANESTHESIA IN GUINEA PIG:

Groups of six adult guinea-pigs were selected. Hair from two circular patches was removed from the thigh region. The drug solution (0.2 ml) in phosphate buffer (pH 7.4) was
injected intradermally in the shaved area. The wheal formed was marked with a dye. Reference drug in phosphate buffer was administered on the other side. Bipolar electrode giving twenty impulses for a period of ten seconds at 60 ml was employed as electrical stimulus. The degree of anesthesia was expressed as number of times animals failed to respond to the stimuli. The local anesthetic activity was observed for a period of thirty minutes.

REFERENCES:


The compounds listed in the following table were studied for local anesthetic, C.N.S. and anticonvulsant activity on preliminary scale.
<table>
<thead>
<tr>
<th>No.</th>
<th>$R'$</th>
<th>$R$</th>
<th>$NR_1R_2$</th>
<th>Surface Anesthesia</th>
<th>Intradermal Anesthesia</th>
<th>C.N.S. activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>4-OCH$_3$-$C_6$H$_4$</td>
<td>Diethylamino</td>
<td>++</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>H</td>
<td>$C_6$H$_5$-CH$_2$</td>
<td>Piperidino</td>
<td>+</td>
<td>Nil</td>
<td>-</td>
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<tr>
<td>3</td>
<td>H</td>
<td>1-$C_6$H$_5$-CH</td>
<td>Morpholino</td>
<td>irritation</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>H</td>
<td>4-CH$_2$-$C_6$H$_4$-CH</td>
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<td>+</td>
<td>+</td>
<td>-</td>
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<td>5</td>
<td>4-CH$_3$</td>
<td>$C_6$H$_5$</td>
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<tr>
<td>6</td>
<td>4-CH$_4$</td>
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<td>++</td>
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<td>7</td>
<td>4-CH$_3$</td>
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<td>-</td>
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<td>4-CH$_3$</td>
<td>$C_6$H$_5$-CH$_2$</td>
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<td>irritation</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>4-OCH$_3$</td>
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<td>Diethylamino</td>
<td>+</td>
<td>++</td>
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<td>10</td>
<td>4-OCH$_3$</td>
<td>4-Cl-$C_6$H$_4$</td>
<td>Diethylamino</td>
<td>++</td>
<td>+</td>
<td>++</td>
</tr>
</tbody>
</table>
Drug concentration is 2%.

+ = Mild activity.
** = Moderate activity.
*** = Significant activity.
**** = Marked activity.

Compounds 6, 9, 10, 13 and 15 were tested for C.N.S. activity. Compounds 6, 10 and 15 showed moderate C.N.S. effect including anticonvulsive effect when tested at 200 mg/kg P.O. dose level.

<table>
<thead>
<tr>
<th></th>
<th>(1)</th>
<th>(2)</th>
<th>(3)</th>
<th>(4)</th>
<th>(5)</th>
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<tr>
<td>11</td>
<td>4-OC\textsubscript{H}\textsubscript{3}</td>
<td>4-CH\textsubscript{3}-C\textsubscript{6}H\textsubscript{4}-\textsubscript{CH}</td>
<td>Piperidino</td>
<td>irritation</td>
<td>-</td>
<td>-</td>
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<tr>
<td>12</td>
<td>4-OC\textsubscript{H}\textsubscript{3}</td>
<td>4-Cl-C\textsubscript{6}H\textsubscript{4}-\textsubscript{CH}</td>
<td>Piperidino</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>4-Cl</td>
<td>C\textsubscript{6}H\textsubscript{5}</td>
<td>Morpholino</td>
<td>+</td>
<td>++</td>
<td>+</td>
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<tr>
<td>14</td>
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<td>++</td>
<td>+</td>
<td>-</td>
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<tr>
<td>15</td>
<td>4-Cl</td>
<td>1-C\textsubscript{6}H\textsubscript{5}-\textsubscript{CH}</td>
<td>Diethylamino</td>
<td>+</td>
<td>++</td>
<td>++</td>
<td></td>
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<tr>
<td>16</td>
<td>4-Cl</td>
<td>4-CH\textsubscript{3}-C\textsubscript{6}H\textsubscript{4}-\textsubscript{CH}</td>
<td>Piperidino</td>
<td>irritation irritation</td>
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LOCAL ANESTHETIC ACTIVITY:

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<th>Intradermal C.N.S. Anesthesia Activity</th>
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<td>(1)</td>
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<td>Morpholino</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>2</td>
<td>4-CH&lt;sub&gt;3&lt;/sub&gt;-C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>Morpholino</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>3</td>
<td>4-OCH&lt;sub&gt;3&lt;/sub&gt;-C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>Piperidino</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>4-Cl-C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>Morpholino</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>5</td>
<td>C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;-CH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Piperidino</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>6</td>
<td>1-C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;-CH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Piperidino</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>7</td>
<td>4-CH&lt;sub&gt;3&lt;/sub&gt;-C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;-CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>Morpholino</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>8</td>
<td>2-C&lt;sub&gt;10&lt;/sub&gt;H&lt;sub&gt;7&lt;/sub&gt;</td>
<td>Diethylamino irritation</td>
<td>irritation</td>
<td>Mil</td>
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</table>

Drug concentration is 2%.

+ = Mild activity.
++ = Moderate activity.
+++ = Significant activity.
++++ = Marked activity.

All the compounds were tested for C.N.S. activity.

Compounds 1, 2, 5 and 7 showed moderate C.N.S. effect, including significant antispasmodic effect when tested at 200 mg/kg P.O. dose level.
### LOCAL ANESTHETIC ACTIVITY:

<table>
<thead>
<tr>
<th>No.</th>
<th>R</th>
<th>NR₁R₂</th>
<th>Surface Anesthesia</th>
<th>Intradermal C.N.S. Activity</th>
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<tbody>
<tr>
<td>1</td>
<td>4-CH₃-C₆H₄</td>
<td>Morpholino</td>
<td>+</td>
<td>Nil</td>
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<tr>
<td>2</td>
<td>4-OCH₂-C₆H₄</td>
<td>Morpholino</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>3</td>
<td>C₆H₅-CH₂</td>
<td>Piperidino</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>4</td>
<td>1-C₆H₅-CH₃</td>
<td>Diethylamo</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>4-CH₃-C₆H₄-CH</td>
<td>Piperidino</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>6</td>
<td>4-Cl-C₆H₄-CH₃</td>
<td>Morpholino</td>
<td>++</td>
<td>++</td>
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<td>1-C₁₀H₇</td>
<td>Morpholino</td>
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<td>++</td>
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<tr>
<td>8</td>
<td>2-C₁₀H₇</td>
<td>Diethylamo irritation</td>
<td>irritation</td>
<td>Nil</td>
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</tbody>
</table>

Drug concentration is 2%.

* = Mild activity.
++ = Moderate activity.
+++ = Significant activity.
++++ = Marked activity.

Compounds 1, 3, 5, 6 and 7 were tested for C.N.S. activity. Compounds 3, 5, 6 and 7 showed moderate C.N.S. effect, including significant, antispasmodic effect when tested at 200 mg/kg P.O. dose level.
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<table>
<thead>
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<th>Reference</th>
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