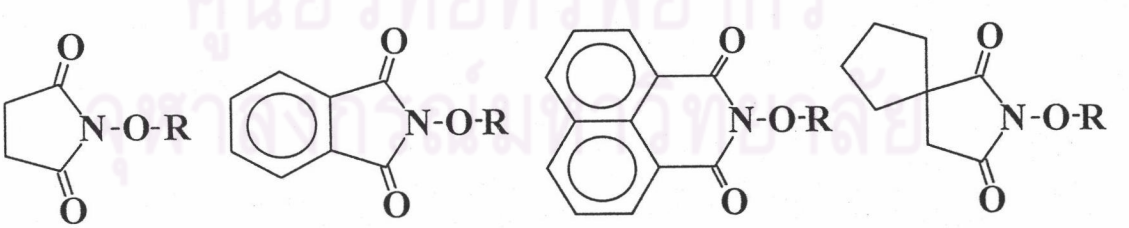
CHAPTER II

HISTORY

Aminooxyacetic acid (AOAA) was found to be a potent anticonvulsant by the inhibition of GABA-T (Wallach, 1961; Edafiogho, et al., 1992). AOAA was active in low doses against electrically-, chemically-, and kindling-induced seizures (Kuriyama, et al., 1966). The major disadvantage of AOAA is its ability to induce convulsions at higher doses (Loscher, 1979). It was thus hypothesized that molecular modification of the perent structure, AOAA, was necessary to determine which portion of the structure was responsible for this lethal effect and to separate it from the anticonvulsant action.

To design of prodrugs that would be hydrolysed to obtain sufficient quantities of AOAA, see figure 10, to elicit only anticonvulsant activity in the brain. The prodrugs, AOAA related to; the succinimidooxy (Type 1) (Owoyale, et al., 1981), the phthalimidooxy (Type 2), the naphthalimidooxy (Type 3), and the spirosuccinimidooxy (Type 4), were synthesized. The amino function of AOAA was converted into an imido group and the acid group was esterified (Edafiogho, et al., 1991).



After that several imidooxy compounds (1-21) were synthesized (See figure 11). A variety of *N*-hydroxy imides (22-29) and sodium salt (30-32) were employed in the synthesis of compounds (1-21) and (33-39) (See figure 12). Figure 13 shows imidooxy compounds (40-55)

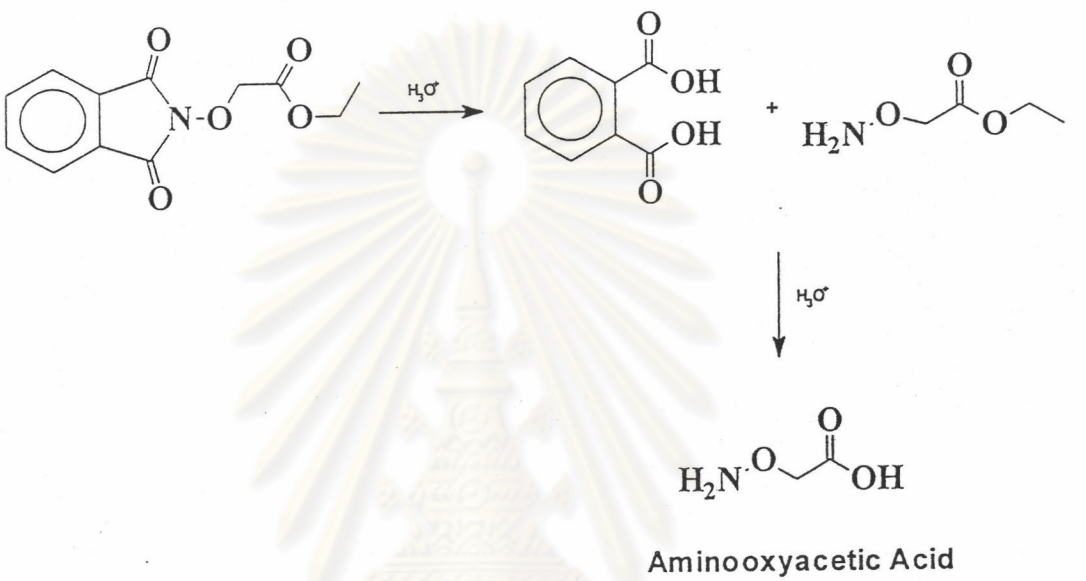


Figure 10. Possible hydrolysis of imidooxyethylacetate (11).

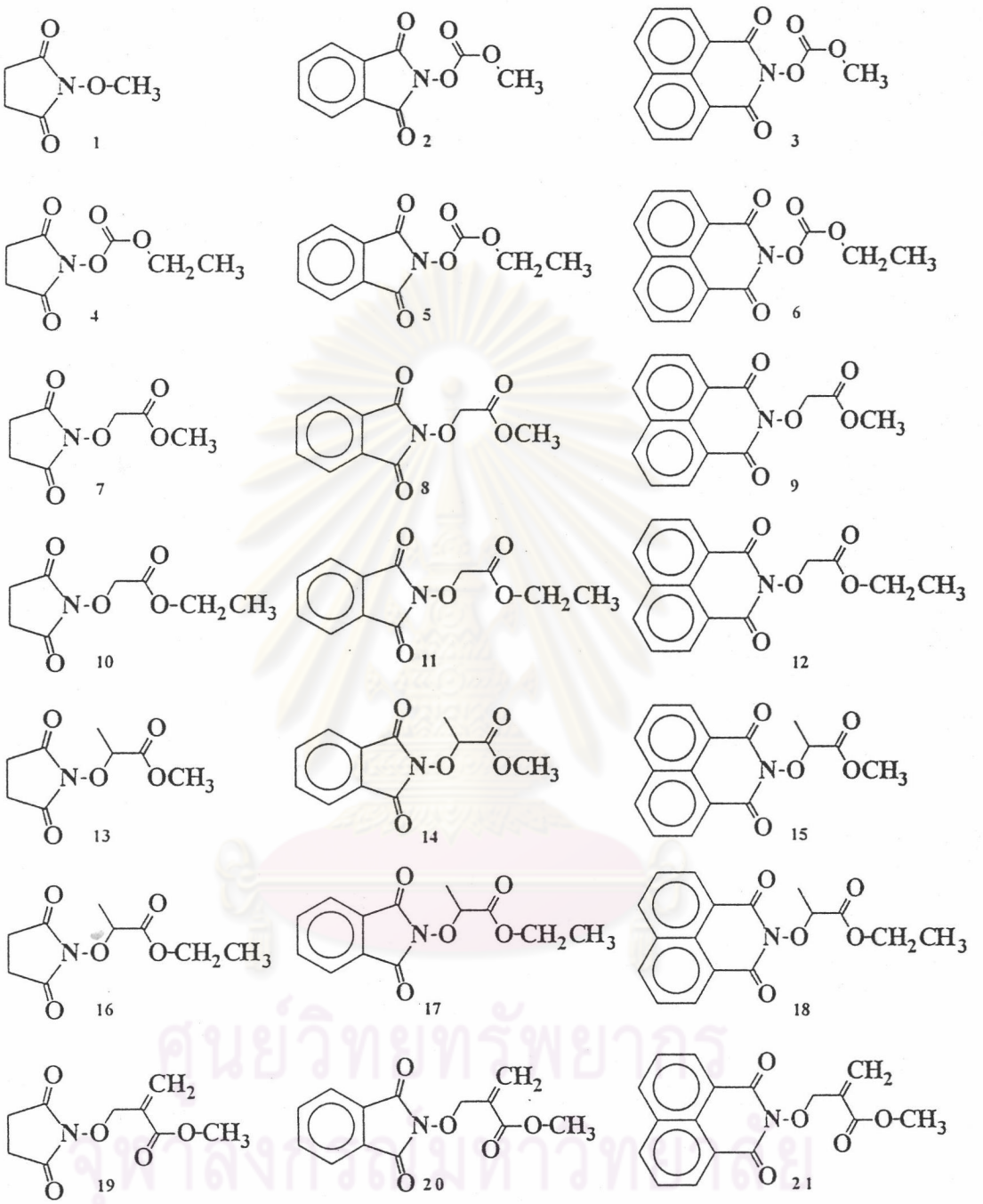


Figure 11. The chemical structure of imidooxy carboxylate derivatives.

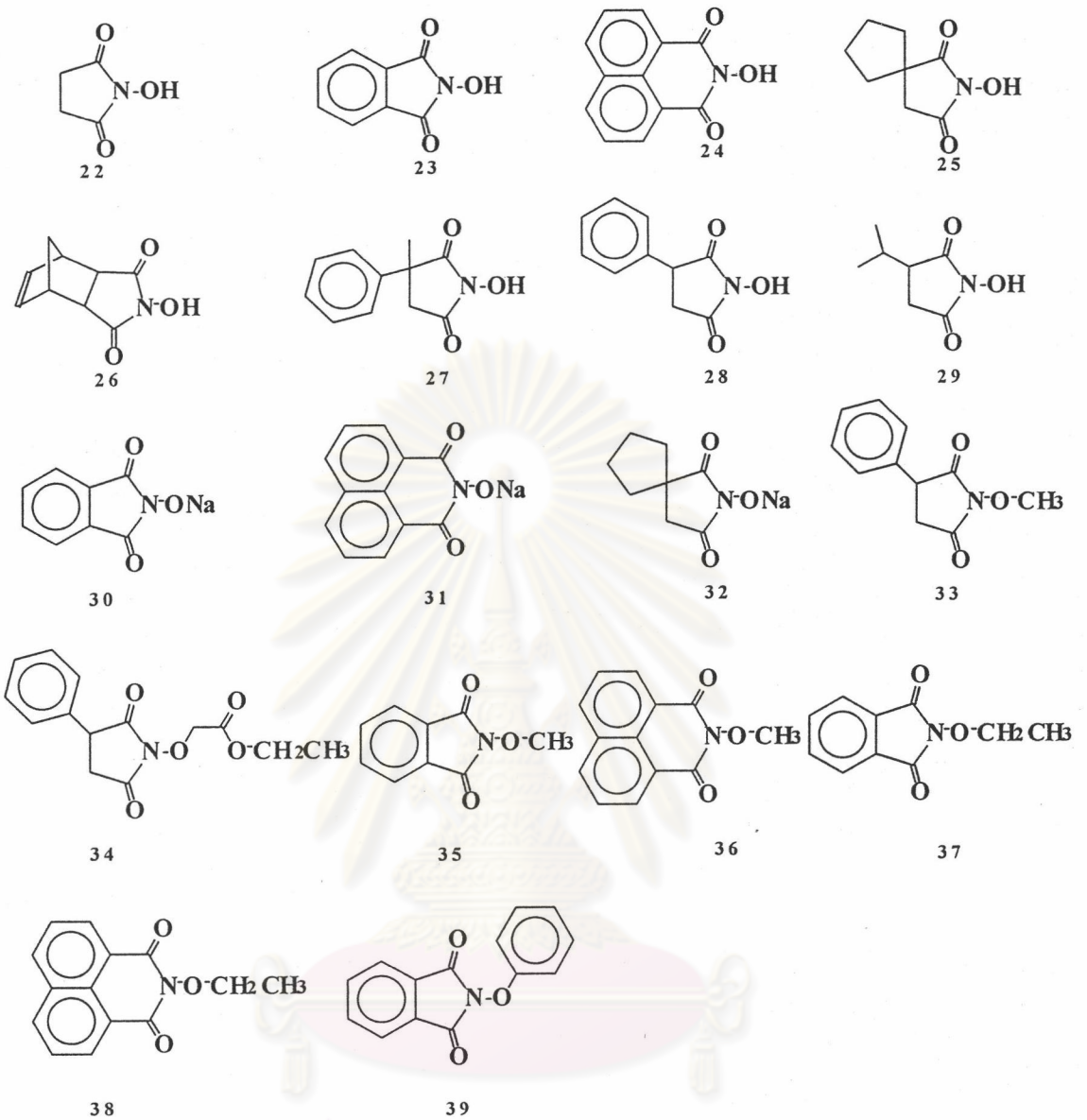


Figure 12. The chemical structures of *N*-Hydroxyimides and some sodium, alkyl or aryl derivatives.

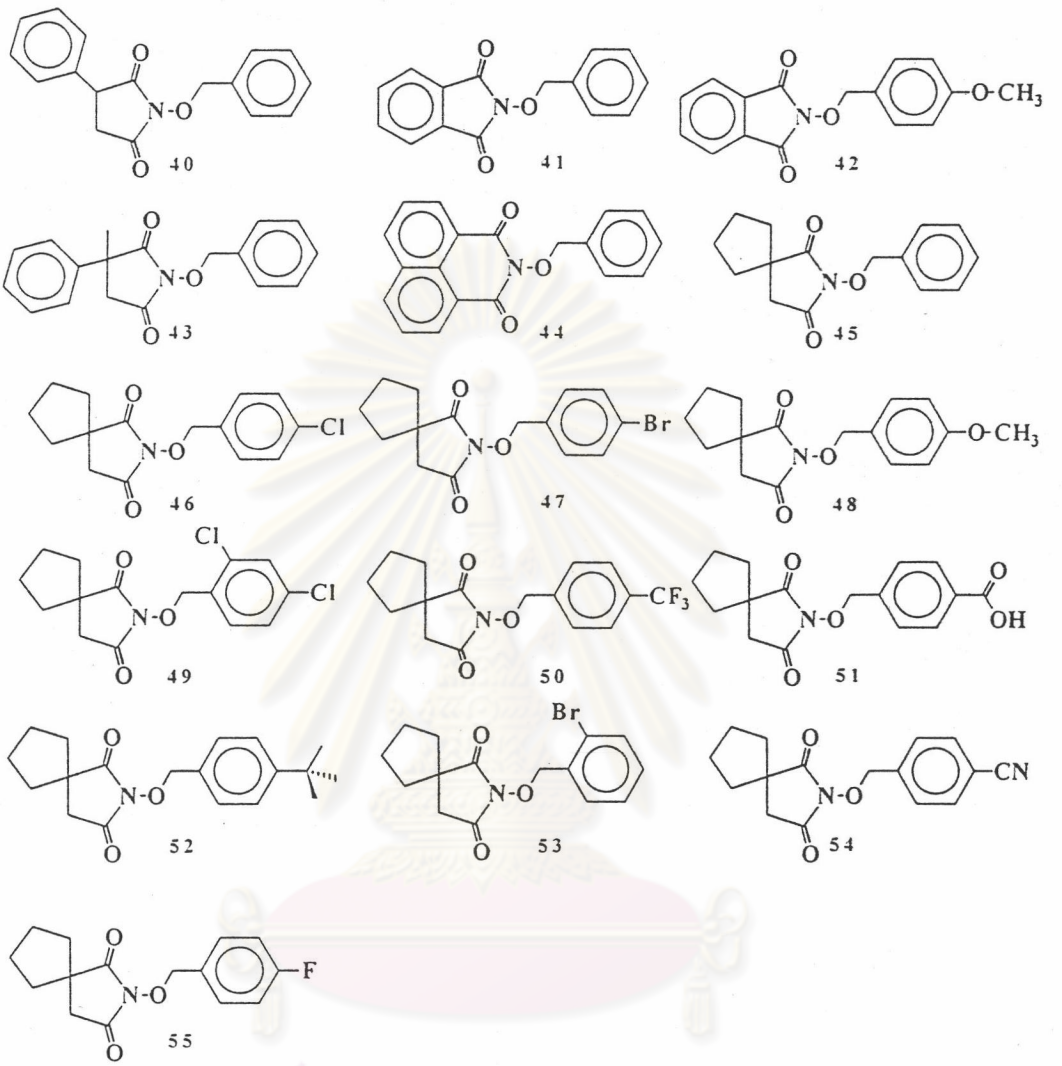


Figure 13. The chemical structures of imidooxy compounds containing the benzyloxy moiety.

containing the benzyloxy moiety. Some imidooxy carboxylates (7, 8, 10, 11, 17) were synthesized.

The compounds (7, 8, 10, 11, 17) gave the first series of imidooxy carboxylates which were screen by subjecting pretreated young chick to electrically- and chemically-induced seizures. The five compounds possessed anticonvulsant activity in young chick (Lahan, et al., 1979; Owoyale, et al., 1981; Edafiogho, et al., 1992).

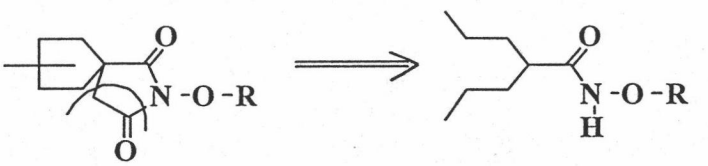
For the hydroxyimides, sodium, and methoxy derivatives, compounds 23, 31, 35, 36, gave anticonvulsant activity but also toxic while the methoxy derivative, compound 33, exhibited anticonvulsant activity against electroshock and chemical seizures with a remarkable lack of toxicity.

The imidooxy carboxylates derivatives, compound 4, displayed potency against chemical seizures but was found to be toxic after administration.

The benzyloxy series, compound 50, and 53, displayed seizure protection against electroshock and chemical seizures, but exhibited neurotoxicity. In contrast, compound 45, and 49, were effective against MES and scMET and devoid of any toxicity.

To increase anticonvulsant activity of these derivatives, the modification of the best compounds, that represented to the spirosuccinimidooxy derivatives, may afford the compounds with higher anticonvulsant activity. Because the chemical structure of 2-propyl pentamidooxy imitate to the spirosuccinimidooxy, when a cyclopentane ring of the spirosuccinimidooxy moiety was opened with elimination of $-CH_2-(C=O)-$. So that the 2-propylpentamidooxy derivatives were formed as novel imidooxy liked derivatives.

It had been reported that the variation of subtituent at *O*-position of imidooxy derivatives affected to anticonvulsant activity of compouds. Thus, the variation of substitutent at *O*-position of 2-propyl



pentamidooxy with alkyl or acyl groups may increase the anticonvulsant properties and decrease the neurotoxicity of compounds.

The anticonvulsant activity of *O*-alkyl or *O*-acyl-2-propylpentano hydroxamate may resulted from :

1. These compounds represented to derivatives of 2-propyl pentanoic acid (valproic acid).

2. The chemical structure of these compounds similar to other imidooxy derivatives, that found to be potent anticonvulsants.

3. The compound, ethyl-α-(2-propylpentamidooxy) acetate (CU-763-1203), could be hydrolyzed to obtain 2-propylpentanoic acid and aminooxyacetic acid (AOAA). Both were anticonvulsant drugs.

The synthesis of these compounds, the intermediates and end products of *O*-alkyl and *O*-acyl of 2-propylpentanohydroxamic acid, based on many general methods of synthesis including the synthesis of alkyl halides, acyl halides, esters, amines, hydroxamic acid. General methods for the synthesis were described as below (Solomons, 1984; Morrison and Boyd, 1987; Furniss et al., 1991)

1. The synthesis of aliphatic halide.

A. The displacement of the hydroxyl group in an alcohol by halogen chloride, bromide and iodide.

A.1. The preperation of alkyl chloride from alcohol.

The hydroxyl group in tertiary alcohol is most readily replaced, this is effected by simply allowing the alcohol to react with concentrated hydrochloric acid at room temperature (See figure 14-A.1.1).

Secondary, and to a greater extent primary, alcohols require more vigorous conditions to effect the substitution reaction, which is usually achieved by heating the alcohol-acid mixture with anhydrous zinc chloride (See figure 14-A.1.2). Or using thionyl

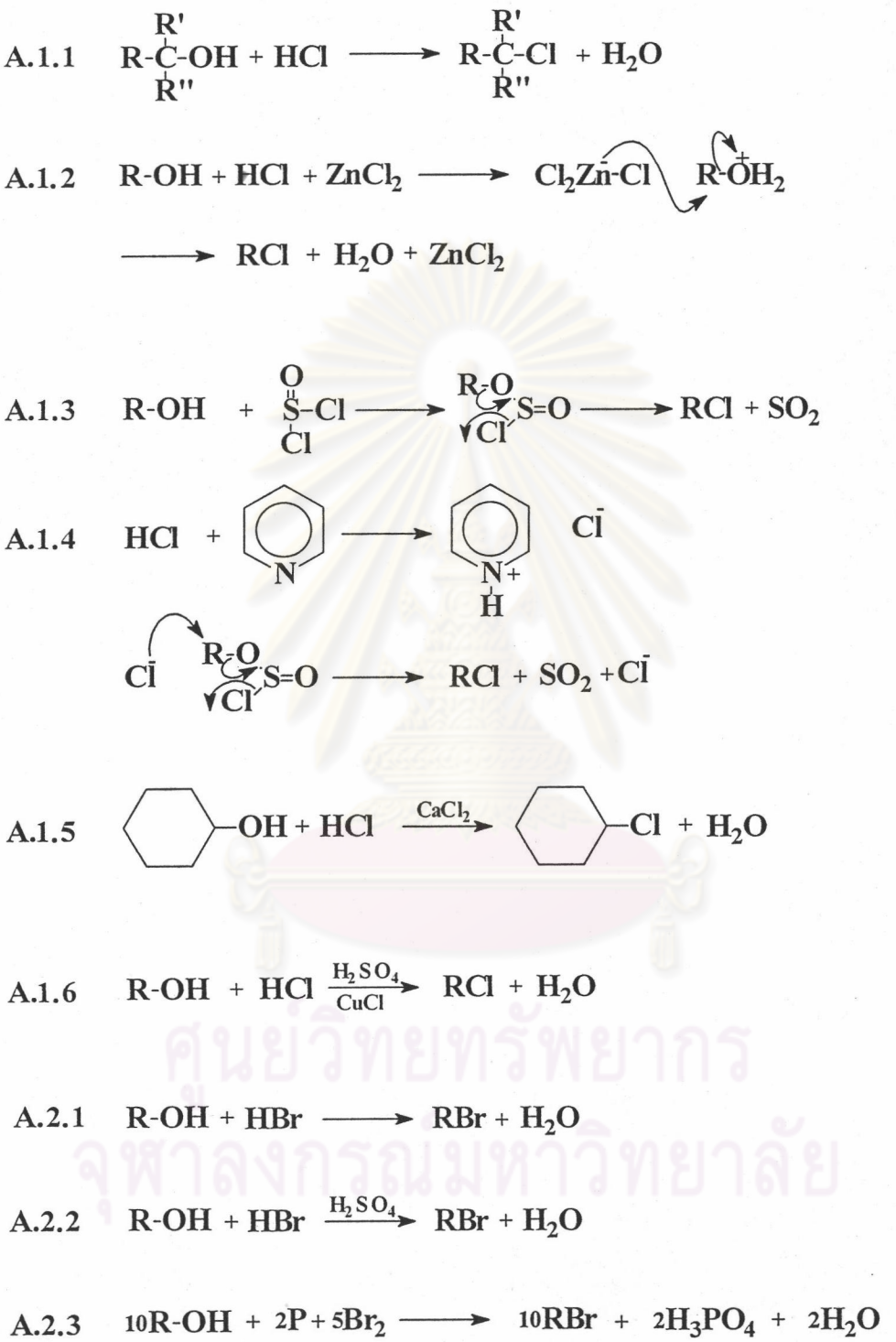
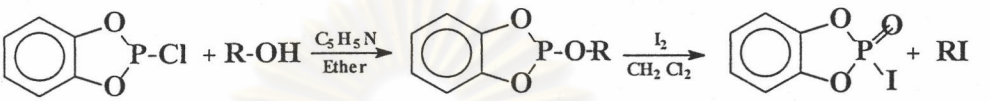


Figure 14. The synthesis of aliphatic halides.
A. The displacement of the hydroxyl group in an alcohol by halogen chloride, bromide, and iodide.

A.3.1 $R\text{-}OH + HI \longrightarrow RI + H_2O$

A.3.2 $R\text{-}OH + KI + H_3PO_4 \longrightarrow RI + KH_2PO_4 + H_2O$

A.3.3 $10R\text{-}OH + 2P + 5I_2 \longrightarrow 10RBr + 2H_3PO_4 + 2H_2O$

A.3.4 

B.1 $RBr + KF \longrightarrow RF + KBr$

B.2 $RCl + NaI \rightleftharpoons RI + NaCl$

$RBr + NaI \rightleftharpoons RI + NaBr$

C.1 $H_2C{=}CH_2 + H\text{-}X \longrightarrow CH_3\text{-}CH_2\text{-}X + H_2O$

C.2 $R\text{-}CH_2\text{-}CH{=}CH_2 \xrightarrow{H\text{-}X} R\text{-}CH_2\text{-}\overset{+}{C}H\text{-}CH_3 + X^- \longrightarrow R\text{-}CH_2\text{-}CHX\text{-}CH_3$

C.3 $R\text{-}CH_2\text{-}CH{=}CH_2 + HBr \xrightarrow{Peroxide} R\text{-}CH_2\text{-}CH_2\text{-}Br$

C.4 $R\text{-}CH{=}CH_2 + X_2 \longrightarrow R\text{-}CHX\text{-}CH_2X$

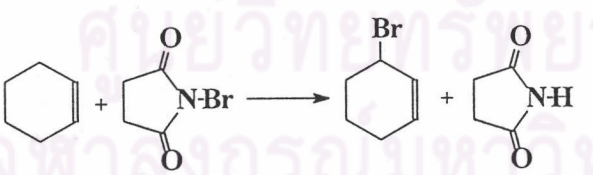
D 

Figure 14. (Continued). The synthesis of aliphatic halides.

A. (Continued). The displacement of the hydroxyl group in an alcohol by halogen chloride, bromide, and iodide.
B. Halogen exchange reactions.
C. Addition of hydrogen halide or halogen to alkenes.
D. Allylic halogenation.

chloride alone (See figure 14-A.1.3) or in the presence of pyridine, which may be present either in catalytic amounts or in an equimolar proportion (See figure 14-A.1.4).

Alicyclic secondary alcohol, anhydrous calcium chloride is recommended as an alternative (See figure 14-A.1.5).

Unsaturated alcohol, allyl alcohol, gives a poor yield by the HCl-$ZnCl_2$ method. However, an alternative procedure using copper(I)chloride as catalyst gives an excellent yield (See figure 14-A.1.6).

A.2. Preparation of alkyl bromide from alcohol.

The formation of allyl bromide is more ready than that of alkyl chlorides, and hence secondary as well as tertiary bromide can be obtained directly from the corresponding alcohols by heating with constant boiling point hydrobromic acid (See figure 14-A.2.1).

In case of primary alcohols the presence of sulfuric acid results in a more rapid reaction and in impaired yields (Also see figure 14-A.2.2).

Alkyl bromides may also be readily obtained by the addition of liquid bromine to a warm suspension of purified red phosphorus in the appropriate alcohol (See figure 14-A.2.3).

A.3. Preparation of alkyl iodides from alcohols.

Alkyl iodides are the most easily formed of the alkyl halides and the slow distillation of the alcohol with constant boiling point hydriodic acid is a general method of preparation (See figure 14-A.3.1).

React an alcohol with the mixture of potassium iodide and 95% orthophosphoric acid (See figure 14-A.3.2) or the addition of iodine to a gently boiling suspension of purified red phosphorus in the corresponding alcohol (See figure 14-A.3.3) was used as an alternative method.

Reaction of an alcohol with the reagent *O*-phenylene phosphorochloridite followed by treatment of the alkyl *O*-phenylene phosphite so obtained with iodine in methylene chloride at room temperature (See figure 14-A.3.4).

B. Halogen exchange reactions.

Alkyl fluorides may be prepared by interaction of an alkyl bromide with anhydrous potassium fluoride in the presence of dry ethylene glycol (See figure 14-B.1) and alkyl iodides were synthesized by interaction of alkyl chlorides or bromides with sodium iodide (See figure 14-B.2).

C. Addition of hydrogen halides or halogen to alkene.

Direct addition of hydrogen halide to an alkene gives rise to a alkyl halide (See figure 14-C.1). Unsymmetrical alkene, addition proceeds in the Markonikoff's manner via that positively charged intermediate which is stabilized to the greatest extent by charge disposal (See figure 14-C.2) while the addition of hydrogen bromide (not the iodide or chloride) in the presence of an added peroxide catalyst giving rise to the anti-Markonikoff mode of addition (See figure 14-C.3).

Halogens add to alkene to give vicinal dihalide (See figure 14-C.4).

D. Allylic halogenation.

The direct introduction of bromine into the allylic position of an alkene using *N*-bromosuccinimide is known as the Wohl-Ziegler reaction. The specific substitution into the allylic position is the result of a radical process which requires the generation of a low concentration of molecular bromine, probably by way of the action of traces of hydrogen bromide on the bromimide (See figure 14-D).

2. Synthesis of aromatic halide.

A. Direct halogenation.

A.1. Nuclear substitution.

Benzene react appreciably with chlorine and bromine in the presence of catalysts, such as aluminium amalgam, pyridine or iron, reaction takes place readily, affording in the first instance the mono-halogenated derivative as the main product. Disubstituted products are obtained if the proportion of the halogen is increased (See figure 15-A.1).

A.2. Side-chain halogenation.

In the absence of catalysts, treatment of toluene with chloride or bromine at the boiling point, preferably with exposure to sunlight or other bright light source, results in halogenation in the side chain (See figure 15-A.2.1). The rapid side chain chlorination of toluene proceeds in the dark with sulfuryl chloride in the presence of benzoyl peroxide as catalyst (See figure 15-A.2.2).

B. Chloromethylation.

This is the replacment of a hydrogen atom in an aromatic compound by a chloromethyl (CH_2Cl) group in a single operation. The reaction consists essentially of the interaction of formaldehyde and hydrochloride with an aromatic system (Blanc chloromethylation reaction) (See figure 15-B).

C. The replacement of a diazo group by a halogen.

Primary aromatic amines are diazotised in the presence of hydrochloric acid with sodium nitrite, and a solution of an equimolar quantity of copper(I)chloride in hydrochloric acid is added. Springly soluble complex of copper(I)chloride and the diazonium salt is formed, and decomposition ensures accompanied by the evolution of nitrogen. the aryl chloride is formed when the diazonium-copper(I) chloride complex decomposes (See figure 15-C).

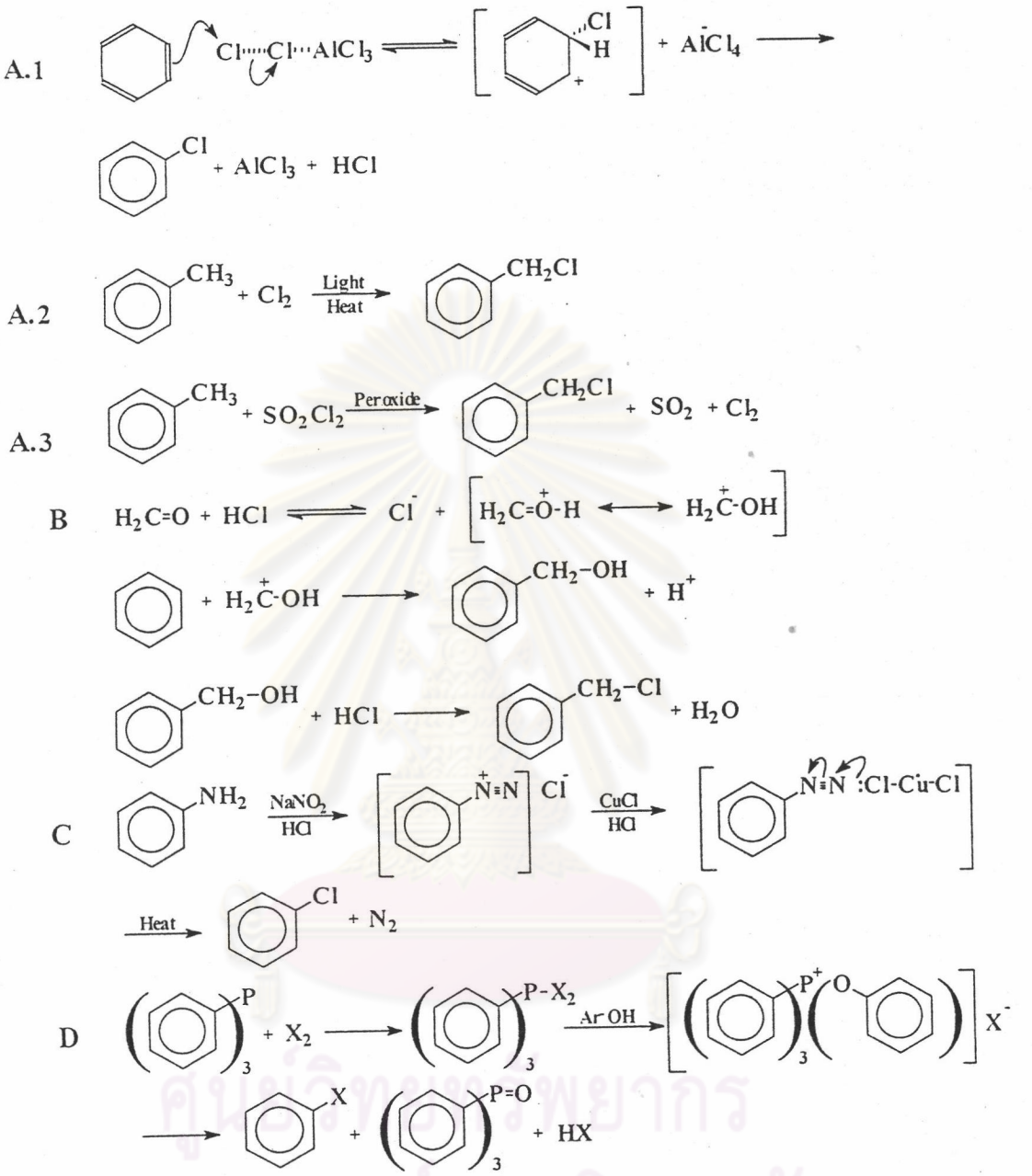


Figure 15. The synthesis of arimatic halides.
A. Direct halogenation.
B. Chloromethylation.
C. The replacement of a diazo group by a halogen.
D. The replacement of a hydroxyl group by a halogen.

D. The replacement of a hydroxyl group by a halogen.

Replacement of the hydroxyl group in a phenol by treated with the complex formed from triphenylphosphine and a halogen in acetonitrile solution, an aryloxytriphenylphosphonium halide is formed which on thermal decomposition yield the aryl halide (See figure 15-D).

3. Synthesis of acyl halide.

A.1. The use of carboxylic acid.

The conversion of carboxylic acid into the corresponding acyl chloride is usually achieved by heating the acid with phosphorus trichloride, or phosphorus pentachloride, or thionyl chloride (See figure 16-A.1.1, A.1.2, A.1.3). The acid chloride was formed in good yield. However, the use of phosphorus pentachloride is the prefered chlorinating agent for aromatic acid which contain electron-withdrawing substituents, and which do not react readily with thionyl chloride (See figure 16-A.1.4).

A.2. The use of anhydrous sodium salt of the acid.

When the anhydrous sodium salt of acid was heated with phosphorus oxychloride, the acid chloride will form as very pure product (See figure 16-B).

4. Synthesis of hydroxamic acid.

A. The preparations from esters compounds.

The reaction between an ester and hydroxylamine in absolute alcohol proceed rapidly at room temperature, particularly in the presence of an equimolar quantity of sodium alkoxide. In the absence of the alkaline reagent longer peroids of time are required. The reaction may be carried out in water, sodium carbonate replacing the sodium alkoxide (Yale, 1943), see figure 17-A.

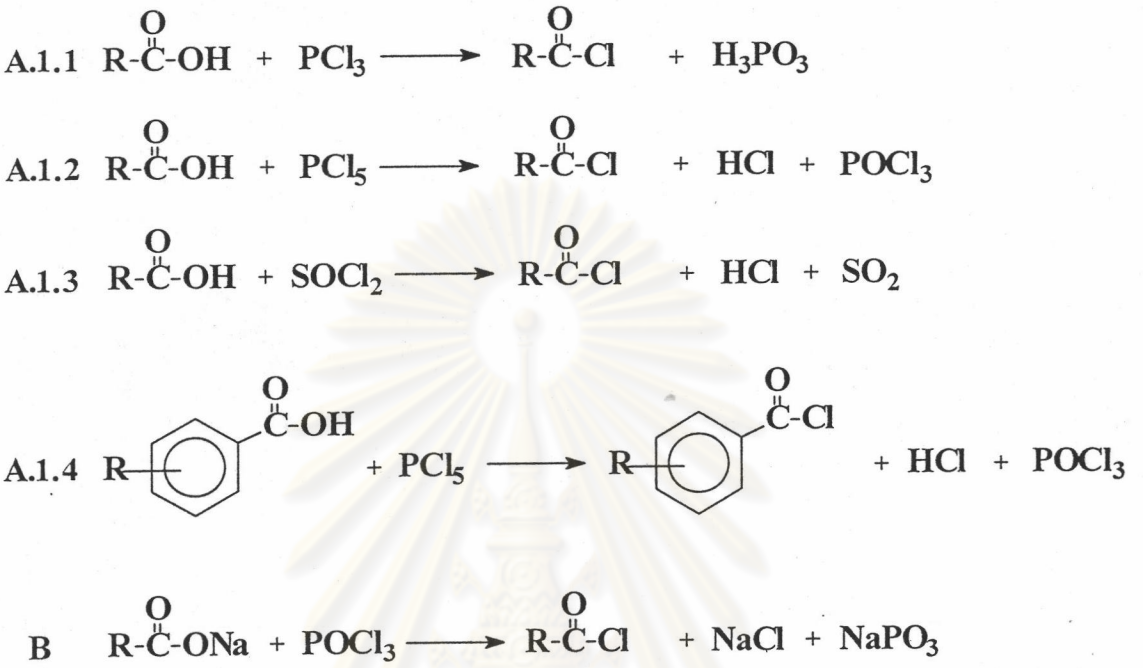


Figure 16. The synthesis of acyl halides.
A. The used of carboxylic acids.
B. The used of anhydrous sodium salt of the acid.

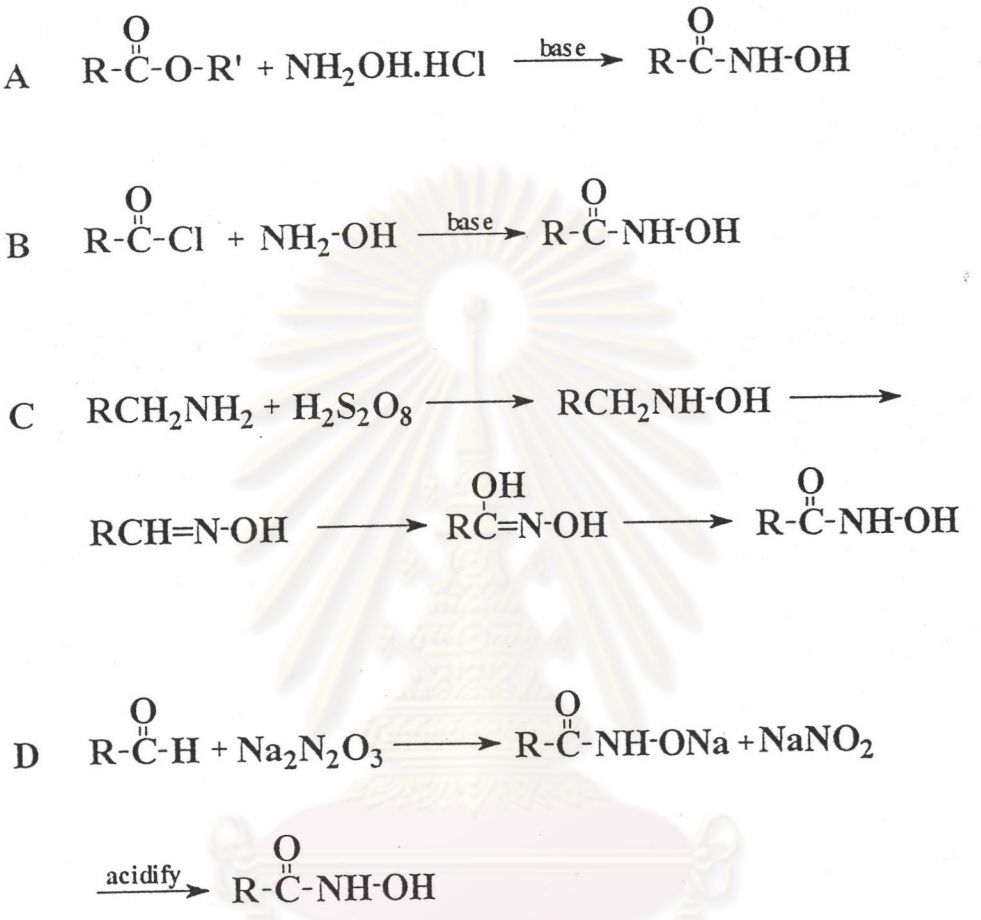


Figure 17. The synthesis of hydroxamic acids.
A. The used of esters.
B. The used of acid halides.
C. Oxidation of primary or secondary amines.
D. The used of aldehydes.

B. The use of acid halides.

The acid halide compounds were reacted with free hydroxylamine, prepared by neutralized with sodium carbonate in 25% aqueous tetrahydrofuran or with sodium ethoxide in methanol (Jones and Root, 1926), to form hydroxamic acid compounds (See figure 17-B).

C. Oxidation of primary or secondary amine.

The oxidation of amine by persulfuric acid yielded hydroxylamic acids. Amines of the general formulars RCH_2NH_2 and R_2CHNH_2 were successfully oxidized. The reaction probably proceed through several intermediate (Yale, 1943) (See figure 17-C).

D. The reaction between an aldehyde and compounds capable of yielding free nitrosyl.

In the course of an investigation into new methods for the preparation of monohydroxamic acids, Angeli prepared sodium nitrohydroxamate, $Na_2N_2O_3$. With certain aldehydes, this salt yielded the sodium salt of monohydroxamic acids. In practice, the sodium nitrohydroxamate, in aqueous solution, was added to the aqueous or alcoholic solution of aldehyde. An exothermic reaction ensured, and following this, acidification yielded the monohydroxamic acid (Yale, 1943) (See figure 17-D).

5. Synthesis of esters.

A. Direct esterification for aliphatic and aromatic carboxylic acid.

The interaction between a carboxylic acid and an alcohol is a reversible process and proceeds very slowly. Equilibrium is only attained after refluxing for several days. If, however, about 3 percent of either concentrated sulfuric acid or dry hydrogen chloride is added to the mixture, the same point of equilibrium can be reached after a few hours. When equimolecular quantities of the acid and alcohol are employed, only about two-thirds of the theoretically possible yield of ester is obtained (See figure 18-A.1).

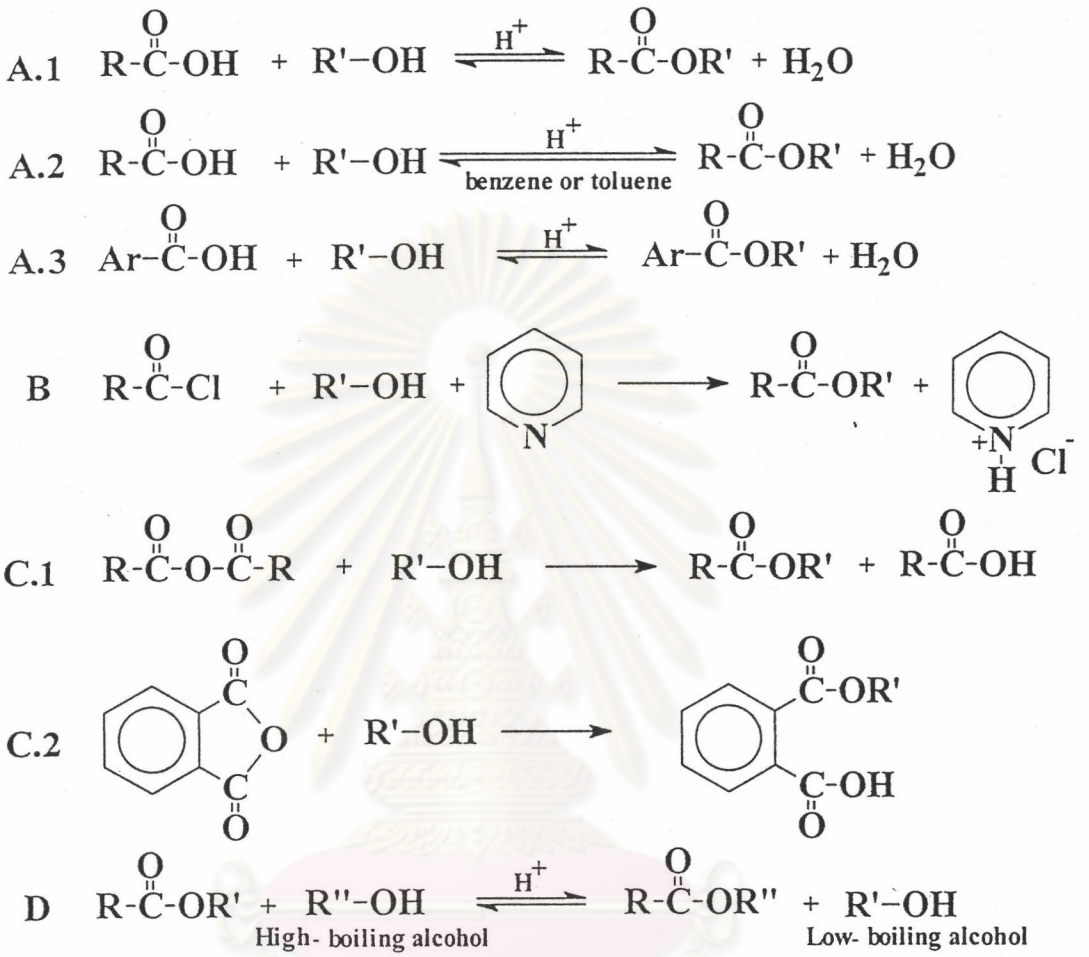


Figure 18. The synthesis of esters.
A. Direct esterification for aliphatic and aromatic carboxylic acids.
B. Esters from acid chlorides.
C. Esters from acid anhydrides.
D. Tranesterification.

Esterification with alicyclic alcohols proceeds best when the alcohol saturated with hydrogen chloride and treated with an excess of the carboxylic acid (the Fischer-Speier method); a very impure ester results if sulfuric acid is used as the catalyst.

The process of acid-catalysed esterification in the presence of benzene, or, better, of toluene, is greatly facilitated if the water produced in the reaction is removed by distillation as an azeotrope (See figure 18-A.2).

Aromatic esters may be prepared by direct esterification method similar to those already decribed for aliphatic esters (See figure 18-A.3).

B. Esters from acid chlorides.

Esters can also be synthesized by the reaction of acid chlorides with alcohols. Since acid cholrides are much more reactive toward nucleophilic substitution than carboxylic acids, the reaction of an acid chloride and an alcohol occurs rapidly and does not require an acid catalyst. Pyridine is usually added to the reaction mixture to react with the hydrogen chloride that formed (See figure 18-B).

C. Esters from acid anhydrides.

Acid anhydrides also react with alcohol to form esters in the absence of an acid catalyst (See figure 18-C.1). Cyclic anhydrides react with one mole of an alcohol to form a compound that is both an esters and an acid (See figure 18-C.2).

D. Transesterification.

Esters can also be synthesized by tranesterification. The mechanism for tranesterification is similar to that for an acid-catalyzed (or an acid-catalyzed ester hydrolysis) (See figure 18-D). In this procedure the equilibrium of the reaction was shifted to the right by allowing the low-boiling alcohol to distill from the reaction mixture.

6. Synthesis of amine.

A. The nucleophilic substitution reactions.

A.1. The use of ammonia.

Salts of primary amines can be prepared from ammonia and alkyl halides by nucleophilic substitution reaction. Subsequent treatment of the resulting ammonium salts with base gives primary amines. This method is very limited synthetic application because multiple alkylations occur. When alkyl halide react with ammonia the alkylammonium halide that is produced initially can react with ammonia to liberate alkylamine. Alkylamine can then compete with ammonia and react with alkyl halide to give dialkylammonium halide. Repetitions of acid-base and alkylation reaction ultimately produce some tertiary amines and even some quaternary ammonium salts if alkyl halide is present in excess (See figure 19-A.1). Multiple alkylations can be minimized by using a large excess of ammonia.

A.2. The use of azide.

A much better method for preparing a primary amine from an alkyl halide is first to convert thr alkyl halide to an alkyl azide by a nucleophilic substitution reaction. Then the alkyl azide can be reduced to a primary amine with sodium and alcohol or with lithium aluminum hydride (See figure 19-A.2).

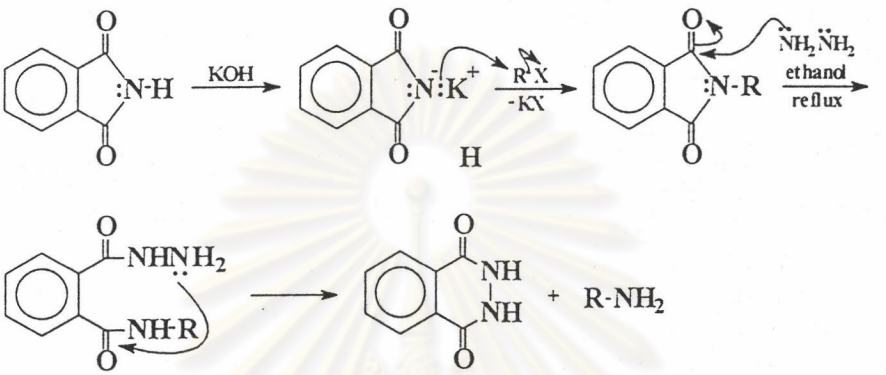
A.3. The use of phthalimide.

Potassium phthalimide can also be used to prepare primary amines by a method known as the Gabriel synthesis. Phthalimide can be converted to potassium phthalimide by potassium hydroxide. The phthalimide anion is a strong nucleophile and it reacts with an alkyl halide to give an *N*-alkylphthalimide. Treating the *N*-alkylphthalimide with hydrazine gives a primary amine (See figure 19-A.3). This synthesis also avoids the complications of multiple alkylations that occur when alkyl halides are treated with ammonia.

A.1 $NH_3 + R\text{-}X \longrightarrow R\text{-}NH_3^+ X^- \xrightarrow{OH^-} R\text{-}NH_2$

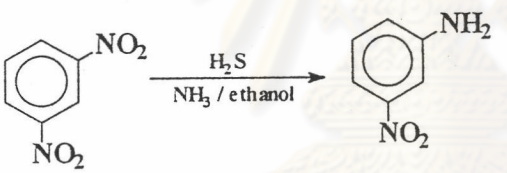
A.2 $R\text{-}X + N_3^- \xrightarrow{X^-} R\text{-}N{=}\overset{+}{N}{=}\overset{-}{N} \xrightarrow[\text{or } LiAlH_4]{Na/alcohol} R\text{-}NH_2$

A.3

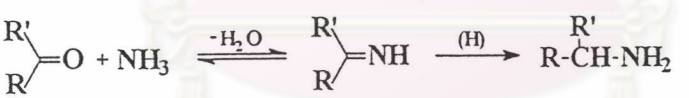


B.1 $Ar\text{-}H \xrightarrow[H_2SO_4]{HNO_3} Ar\text{-}NO_2 \xrightarrow{(H)} Ar\text{-}NH_2$

B.2



C.1



C.2

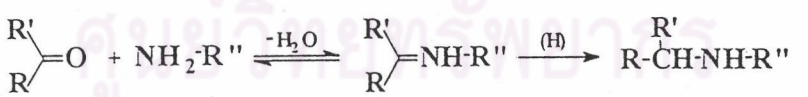


Figure 19. The synthesis of amines.
A. The nucleophilic substitution reaction.
B. The reaction of nitro compounds.
C. The reductive amination.

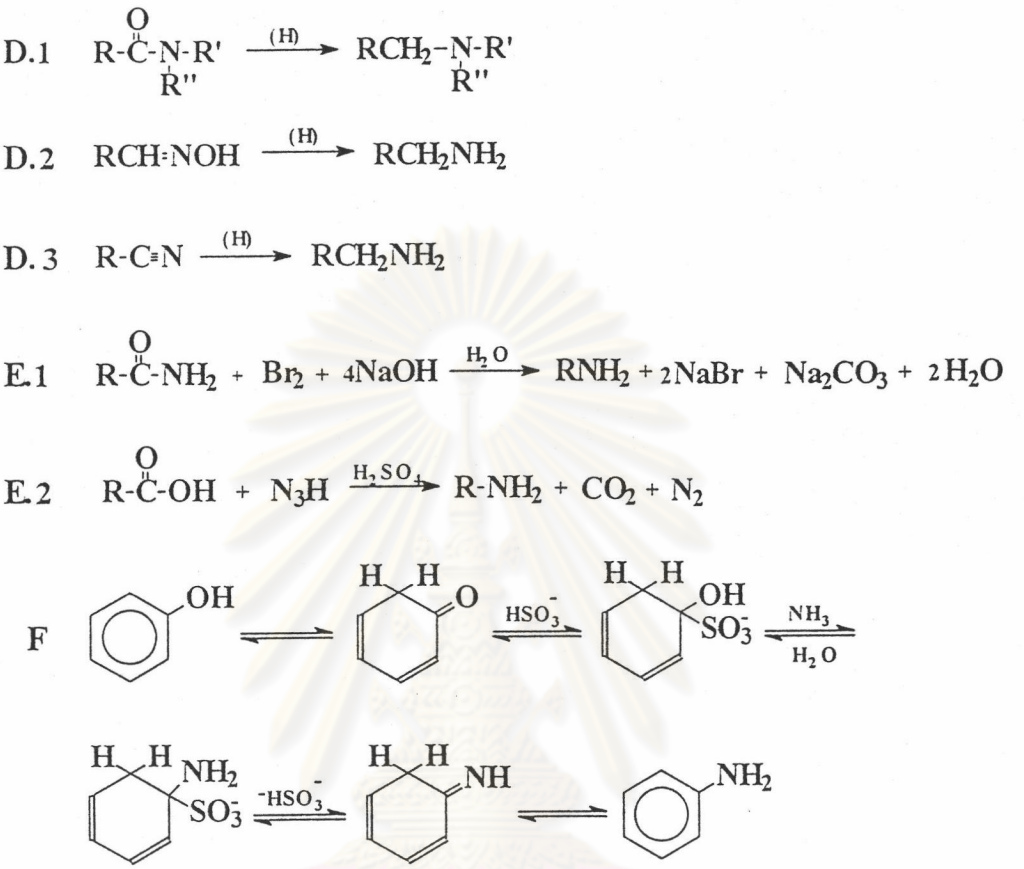


Figure 19. (Continued). The synthesis of amines.
D. The reduction of amides, oximes, and nitriles.
E. The Hoffmann degradation of amides.
F. The replacement of an aromatic hydroxyl group by amino group.

B. The Reduction of nitro compounds.

Reduction of the nitro group can also be carried out in a number of ways. The most frequently used methods are base on catalytic hydrogenation, or treatment of the nitro compound with acid and iron, zinc, or tin, or a metal salt such as $SnCl_2$ (See figure 19-B.1).

Selective reduction of one nitro group of a dinitro compound can often be achieved through the use of hydrogen sulfide in aqueous (or alcoholic) ammonia (See figure 19-B.2). When this method is used, the amount of the hydrogen sulfide must be carefully measured because the use of an excess may result in the reduction of more than one nitro group.

C. The reductive amination.

Aldehydes and ketones can be converted to primary amines through catalytic or chemical reduction in the presence of ammonia. This process, called reductive amination, proceeds through the formation of an imine (See figure 19-C.1).

Secondary amines can be prepared through reductive amination of an aldehyde or ketone in the presence of a primary amine (See figure 19-C.2).

D. The reduction of amides, oximes, and nitriles.

Amides, oximes, and nitriles can be reduced to amines (See figure 19-D.1, D.2, D.3). Reduction of a nitrile or an oxime yield a primary amine; reduction of an amide can yield a primary, secondary or tertiary amine. All of these reductions can be carried out with hydrogen and a catalyst or with lithium aluminium hydride. Oximes are also conveniently reduced with sodium in alcohol.

E. The Hofmann degradation of amides.

Amides react with solutions of bromine or chloride in sodium hydroxide to yield amines through a reaction known as the Hofmann degradation (See figure 19-E.1): The carbonyl carbon of amide

is lost (as carbonate) and the R group of the amide becomes attached to the nitrogen of the amine. Primary amines made this way are not contaminated by secondary or tertiary amines. The mechanism for this interesting reaction involves the following steps. In step 1, the amide undergoes a base-promoted N-bromination. In step 2, the N-bromo amide reacts with base to yield an anion which in step 3 simutaneously rearranges and lose a bromide ion to give an isocyanate. Finally, in step 4, the isocyanate undergoes hydrolysis to yield an amine and carbonate ion.

The conversion of a carboxylic acid into an amine by treatment with hydrazoic acid in concentrated sulfuric acid is termed the Schmidt reaction or rearrangement, which often gives higher yields than the related Hofmann rearrangement procedure (See figure 19-E.2).

F. The replacement of an aromatic hydroxyl group by an amino group.

The direct replacement of the hydroxyl group in simple phenols by an amino or substituted amino group requires drastic conditions and the method is not suitable for laboratory preparations. The reaction (the Bucherer reaction) depends upon the addition of the hydrogen sulphite ion to the keto form of the compound and the subsequent reaction with ammonia (See figure 19-F).