CHAPTER II

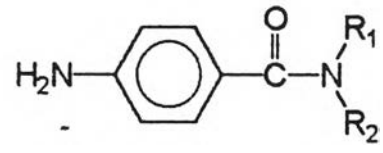
HISTORICAL

Recent reports have indicated a renewed interest in the pharmacological activity of substituted benzamides. Benzamide drugs, such as metoclopramide, and clebopride, produce neuroleptic activity through an antidopaminergic mechanism. Iwanami and co-workers have reported the neuroleptic activity of a group of benzamides, some of which exhibited greater potency than haloperidol (Clark et al.,1984). The review reported herein focuses on the synthesis of some simple aminobenzamides substituted at the amide nitrogen with alkyl- and arylalkyl groups and an evaluation of the anticonvulsant activities of these compounds.

Structure-Activity Relationships of 4-Aminobenzamides.

1. The effects of substitution with alkyl- and arylalkyl groups at the amide nitrogen. (See figure 10.)

The unsubstituted 4-aminobenzamide (1) shows some slight activity against subcutaneous metrazole (scMet) induced seizures and no activity against maximal electroshock (MES) induced seizures at 600 mg/kg. The N-methyl amide 2 exhibits anti-MES activity at 600 mg/kg, while compounds 3-8 are effective against MES at 100 mg/kg. These compounds are effective against



compound	R_1	R_2
1	H	H
2	CH_3	H
3	CH_2CH_3	H
4	$CH_2CH_2CH_3$	H
5	$CH_2CH_2CH_2CH_3$	H
6	$CH_2CH_2CH_2CH_2CH_3$	H
7	$CH_2CH_2CH_2CH_2CH_2CH_3$	H
8	cyclohexyl	H
9	$CH_2CH_2CH_3$	$CH_2CH_2CH_3$
10	C_6H_5	H
11	CH_2-C_6H_5	H
12	$CH(CH_3)$-C_6H_5	H
13	$CH_2CH_2C_6H_5$	H
14	$CH(CH_3)CH_2$-C_6H_5	H
15	$CH_2CH(CH_3)$-C_6H_5	H
16	CH_2-C_6H_5	CH_3
17	$CH(C_6H_5)_2$	H

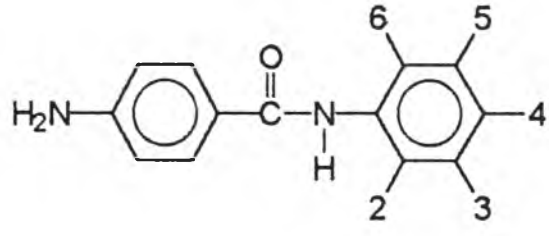
Figure 10. The chemical structures of 4-Amino-N-substituted benzamides.

scMet at less than toxic doses. The toxic effects of the N-*n*-alkylbenzamides 2-7 appear to increase with the chain length. This trend continues through the highest homologue, *n*-hexyl amide. The N-cyclohexylbenzamide 8 is more potent against MES and scMet than the *n*-hexyl amide 7 or the other *n*-alkyl amides.

The initial anticonvulsant evaluation was extended to the compounds containing an aromatic ring (10-16) in the amine component of the amides. These results indicate that one additional aromatic ring produced optimal activity. The N-benzyl amide 11 shows anti-MES activity with greater potency than any of the N-alkyl amides. However, the addition of a second phenyl group as in 17 drastically decreases the anticonvulsant effects. Compounds 10-12 display maximum anti-MES activity, with compound 12 appearing to be the most potent. A substantial drop in activity is observed when the N-α-methylbenzyl group of 12 is replaced by the isomeric β-phenylethyl group (13) or the N-benzyl-N-methyl derivative (Clark et al, 1984). However, because of untoward toxicological findings of 12, the development of this compound or either of its enantiomers was precluded (Leander et al., 1988).

2. The effects of substitution of additional groups on the N-phenyl ring. (See figure 11.)

Compound 1 possesses activity against MES- and scMet-induced convulsions in the 50 mg/kg dose range. Compound 1-13 all show activity against MES-induced convulsions at 300 mg/kg 30 min after administration with most compounds maintaining minimal anti-MES activity at least 4 hrs after administration. Several compounds show some activity against scMet-induced



compound	substituent position				
	2	3	4	5	6
1	H	H	H	H	H
2	CH_3	H	H	H	H
3	H	CH_3	H	H	H
4	H	H	CH_3	H	H
5	CH_3	CH_3	H	H	H
6	CH_3	H	CH_3	H	H
7	CH_3	H	H	CH_3	H
8	CH_3	H	H	H	CH_3
9	H	CH_3	CH_3	H	H
10	H	CH_3	H	CH_3	H
11	$CH(CH_3)_2$	H	H	H	H
12	$CH(CH_3)_2$	H	H	H	CH_3
13	$CH(CH_3)_2$	H	H	H	CH_2CH_3

Figure 11. The chemical structures of substituted 4-aminobenzanilides.

convulsions at 30 min; however, the activity has essentially disappeared at 4 hrs. Each of the monomethylated anilides 2-4 exhibited convulsant activity similar to 1.

Compound 5-10 represent all the possible dimethylated anilides, and these compounds continue to show good anti-MES activity with compound 8 being the most effective. The profile of anticonvulsant activity for 8 is characterized by marked ability to modify the maximal electroshock seizure pattern and inability to elevate the metrazole seizure threshold. The compounds 11-13 all possess an *o*-isopropyl group and represent diverse activity and toxicity profiles.

The screening results do not allow for any clearcut conclusions concerning structure-activity relationships; however, the anti-MES activity is observed in all compounds (Clark et al., 1985).

3. The effects of the ring substitution pattern of the amino group. (See figure 12.)

The pattern of substitution in the aminobenzoyl moiety is important for activity, with the 4-aminobenzanilides (1) showing the highest potency and the 2-aminobenzanilides (3) the least. In general, the anticonvulsant activity of the aminobenzanilides corresponds to the ring substitution pattern of 4-amino (1) > 3-amino (2) > 2-amino (3). Nevertheless, the 2,6-dimethylaniline derivative is still the most potent anti-MES agent in each series (Clark et al., 1986).

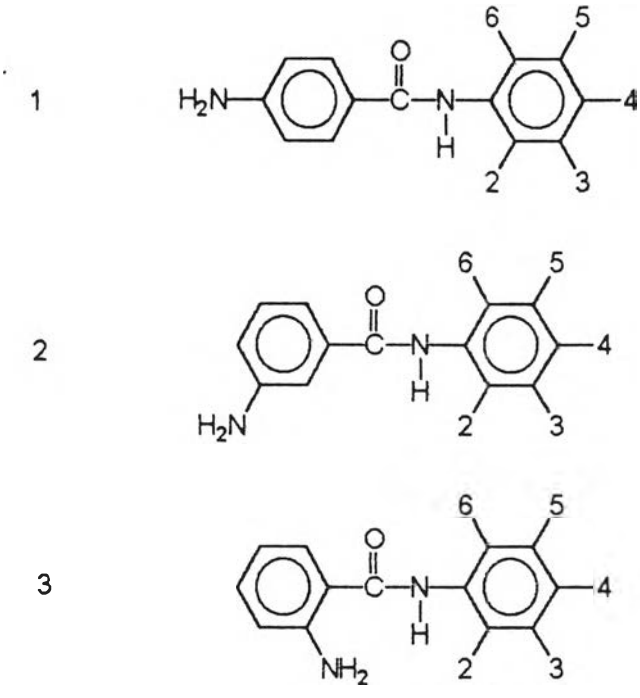


Figure 12. The chemical structures of aminobenzanilide derivatives.

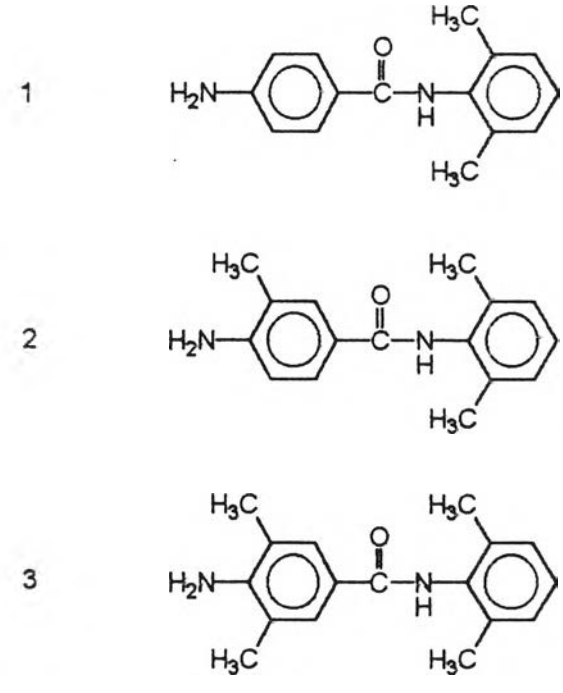


Figure 13. The chemical structures of 4-aminobenzamides with/without substituent(s) on the aminobenzoyl moiety.

4. The effects of substitution on the aminobenzoyl moiety of 4-amino-N-(2,6-dimethylphenyl)benzamide (ameltolide, LY201116). (See figure 13.)

In order to sterically preclude or diminish the rate of matabolic N-acetylation, analogues of ameltolide (1), possessing either one (2) or two (3) methyl groups ortho to the 4-amino substituent, were synthesized. Both compounds antagonize MES-induced seizures after administration to mice. Compound 2 is still rapidly metabolized by N-acetylation. However, compound 3 provides exceptionally high and long-lived plasma concentrations of parent drugs; no N-acetyl metablite can be detected. While 1 and 2 have no pharmacologically relevant effects on hexobarbital-induced sleeping time in mice, 3 is a potent, dose-dependent potentiator of sleeping time. Oral administration of 375 mg/kg led to a 61% increase in sleeping time relative to control values. Thus, 3 represents one of the most potent potentiators of hexobarbital-induced sleeping time described to date (Robertson et al., 1987; Robertson et al., 1988).

Metabolism, Disposition, and Pharmacokinetics of Ameltolide in Rats.

The metabolism, disposition, and pharmacokinetics of ameltolide have been studied in rats by Potts et al. (1989). ^{14}C-ameltolide was well absorbed (~94%) from the gastrointestinal tract following oral administration. Of the dose administered, 64.5% was excreted in the urine and 29% in the bile; with the majority being excreted during the first 24 hrs. Peak plasma levels of ameltolide were observed at 0.75 hr. Its biotransformation in rats was investigated by quantitating and isolating metabolites from urine and plasma. The major route of metabolism was N-acetylation to form 4-(Acetylamino)-N-(2,6-

dimethylphenyl)benzamide (ADMP), and subsequent hydroxylation to form 4-(Acetylamino)-N-(2-hydroxymethyl-6-methylphenyl)benzamide (HADMP). (See figure 14.) Pharmacological studies demonstrated that N-acetylation and hydroxylation of one of the methyl substituents leads to a substantial decline in the potency of ameltolide as an anticonvulsant (Robertson et al., 1991). However, in the step that ameltolide was inactivated by metabolism to its N-acetyl analogue (ADMP), this metabolic pathway appeared to be reversible to the parent compound in a veriety of species (Parli et al., 1987). Two hours after oral dosing with ^{14}C-ameltolide, ADMP and HADMP comprised 92% of the total radioactivity in the plasma. The major urinary metabolite, accounting for 63% of the radioactivity in the urine, was HADMP. The elimination of ameltolide from the systemic circulation following iv administration was monophasic, with a terminal half-life of 9.4 min. The volume of distribution was 911 ml/kg and the plasma clearance was 66.9 ml/min/kg.

Pharmacology of Ameltolide.

Ameltolide is a potent and selective anticonvulsant in the maximal electroshock test in mice. The ED50 values after oral and intravenous administration were 1.7 mg/kg and 0.51 mg/kg, respectively. For comparison, the oral and intravenous ED50 values for the anticonvulsant phenytoin which is selective for the maximal electroshock test were 9.1 and 8.5 mg/kg, respectively. After oral administration, ameltolide had a protective index (ED50 to produce neurological impairment, divided by ED50 on the maximal electroshock) of 13.5 (Leander et al., 1988). After i.p. administration to mice, therapeutic indices (LD50 /MES ED50) for ameltolide, phenytoin, and phenobarbital were 62, 24, and 12, respectively (Robertson et al., 1986). After

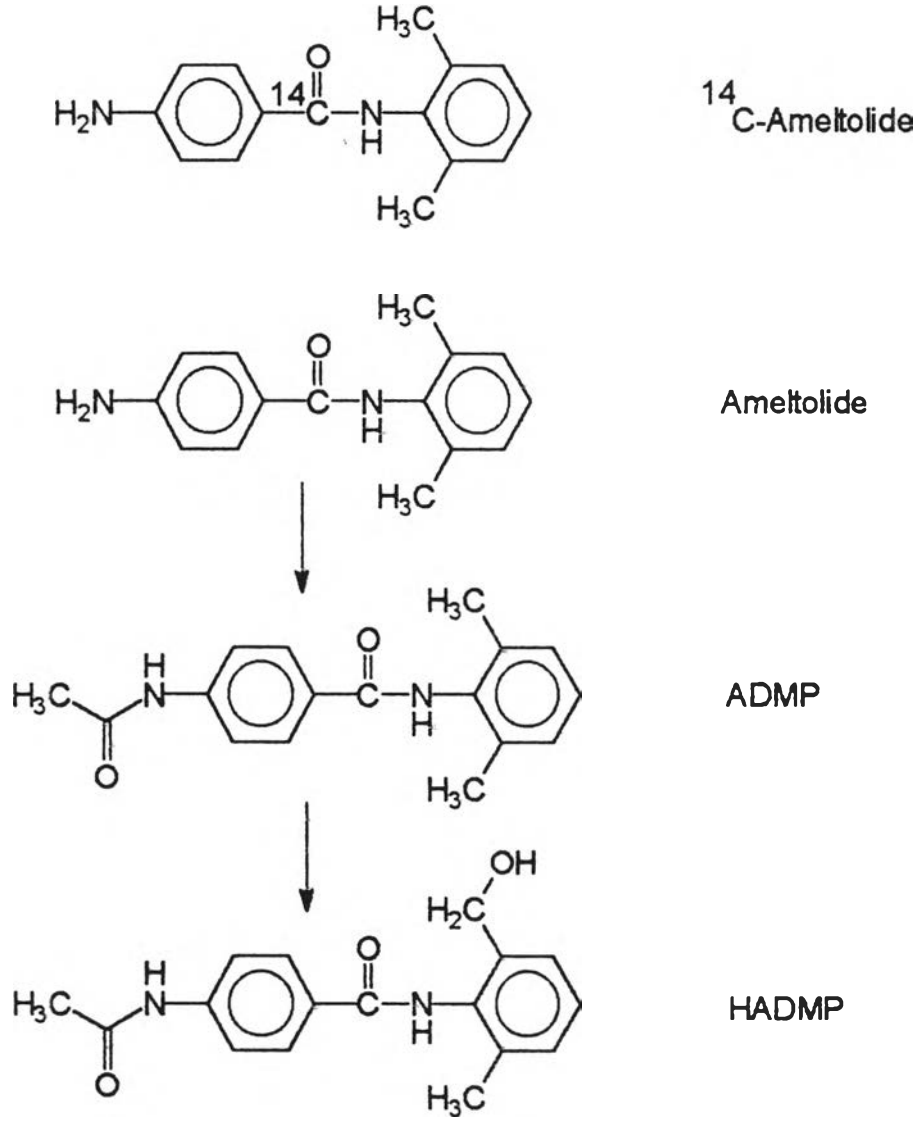


Figure 14. Metabolic pathway of ameltolide.

4 days of administration, there was no evidence of the development of tolerance to the anticonvulsant effects of ameltolide. The hexobarbital-induced sleeping time was not significantly affected by either acute of chronic administration of ameltolide for 4 days. In combination studies with the anticonvulsants, phenytoin and carbamazepine, which are selective for the maximal electroshock test, ameltolide produced dose-additive effects which suggest that it produces its anticonvulsant action through the same mechanism of action as these prototype anticonvulsants. In addition, ameltolide was unable to inhibit seizures induced by s.c. administration of pentylenetetrazole, bicuculline, picrotoxin, or strychnine to mice. This marked MES-selective profile resembles that of phenytoin.

The anticonvulsant and toxic properties of ameltolide were compared with phenytoin, phenbarbital, ethosuximide, and valproate by Clark (1988). The results indicate that ameltolide is the most potent anticonvulsant in the maximal electroshock seizure (MES) model. The protective indices of ameltolide compare favorably with prototype anticonvulsants, and there appears to be a good safety margin. The studies suggest that ameltolide will be an effective anticonvulsant in humans and support development of the compound for the treatment of epilepsy. Because of its efficacy in the maximal electroshock test, ameltolide can be predicted to be an effective anticonvulsant for the treatment of partial seizures and generalized tonic-clonic seizures.

Mechanism of Action of Ameltolide.

Because ameltolide produced dose-additive effects with the two prototype anticonvulsants, phenytoin and carbamazepine, which are selective for

the maximal electroshock test, these interactions suggest that ameltolide, phenytoin, and carbamazepine produce their selective anticonvulsant effects in the maximal electroshock test by the same mechanism of action. Perhaps ameltolide produces a membrane-stabilizing effect, as measured by the reduction of sustained repetitive firing, possibly by a use-dependent block of sodium conductance channels, as has been charactarized previously for phenytoin and carbamazepine. Because ameltolide is much more potent than phenytoin or carbamazepine by both the intravenous and oral routes, ameltolide may produce membrane-stabilizing effects at far smaller concentrations than are needed for phenytoin and carbamazepine. Thus, ameltolide may be useful for detailing further the molecular interactions responsible for the membrane-stabilizing effects of these anticonvulsants which are selective in the maximal electroshock test (Leander et al., 1988).

General Methods for the Preparations of Intermediates and the Final Product [N-(*p*-Aminobenzoyl)-1,2,3,4-tetrahydro-4,8-dimethyl quinoline].

For the synthesis of N-(*p*-Aminobenzoyl)-1,2,3,4-tetrahydro-4,8-dimethylquinoline, there are many compounds used as intermediates. These compounds represent many types of organic compounds i.e. esters, amides, alkyl halides, acyl halides, carboxylic acids, amines, and nitro compounds. General methods for the syntheses of these types of organic compounds are described as below (Furniss et al., 1991; Morrison and Boyd, 1987).

1. Syntheses of esters.

A. Direct esterification.

The interaction between a carboxylic acid and an alcohol is a reversible process and proceeds very slowly. (Figure 15-A.)

Equilibrium is only attained after refluxing for several days. If, however, about 3 percents (of the weight of the alcohol) of either concentrated sulphuric acid or of dry hydrogen chloride is added to the mixture, the same point of equlibrium 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. According to the law of mass action, the equilibrium may be displaced in favour of the ester by the use of an excess of the acid, but if the acid is expensive, a large excess of the alcohol is generally employed. This method of esterification, in general, gives good yields with primary alcohols and fairly good yields with secondary alcohols. The method is unsatisfactory for use with tertiary alcohols owing to competing alkene formation from an acid catalysed dehydration.

B. The use of acyl chlorides.

Acyl chlorides react readily with primary and secondary alcohols to give esters in very good yields. With tertiary alcohols the presence of base (e.g. dimethylaniline) is essential to prevent acid-catalysed side reactions, such as dehydration or formation of the alkyl chloride. (Figure 15-B.)

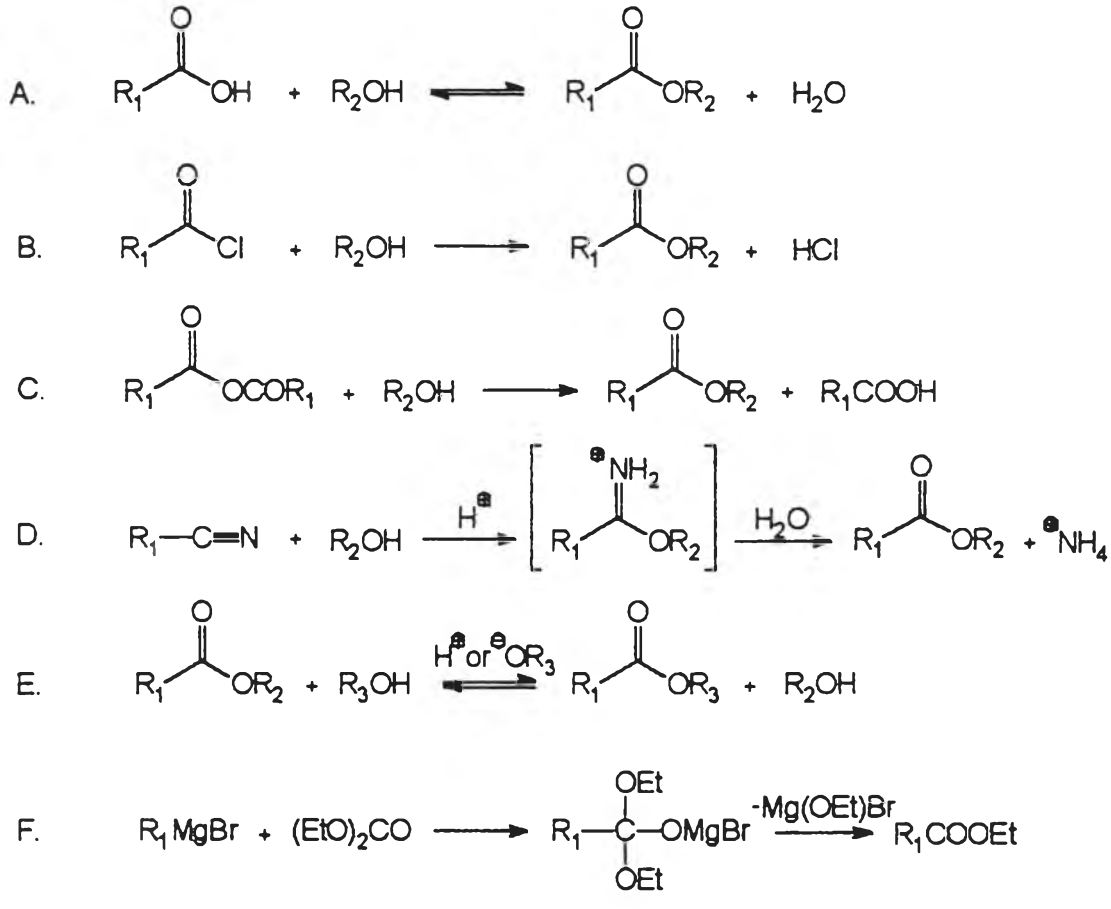


Figure 15. Syntheses of esters by

A. Direct esterification.

B. The use of acyl chlorides.

C. The use of acid anhydrides.

D. The alcoholysis of nitriles.

E. Transesterification.

F. The use of Grignard reagents.

C. The use of acid anhydrides.

Acylation may also be carried out with acid anhydrides in the presence of a suitable catalyst; either an acidic catalyst, such as sulphuric acid or zinc chloride, or a basic catalyst such as pyridine, may be used. (Figure 15-C.)

D. The alcoholysis of nitriles.

An ester is formed when a nirile is heated with an alcohol in the presence of concentrated sulphuric acid, thus providing a two-step synthesis of an ester from an alkyl halide. The reaction proceeds by way of an intermediate imino-ester which is not usually isolated, but may be if so required (Dox,1932). (Figure 15-D.)

E. Transesterification.

One alcohol is capable of displacing another alcohol from an ester. This alcoholysis (cleavage by an alcohol) of an ester is called transesterification. (Figure 15-E.) This reaction is an equilibrium reaction. To shift the equilibrium to the right, it is necessary to use a large excess of the alcohol whose ester wished to make, or else to remove one of the products from the reaction mixture. The second approach is the better one when feasible, since in this way the reaction can be driven to completion.

F. The use of Grignard reagents.

The preparation of a carboxylic ester by a variant of the Grignard carboxylation route has been described. The alkylmagnesium bromide is first prepared and added to an excess of diethyl carbonate, conditions which minimised the possibility of further reaction of the Grignard reagent with the ester initially produced to form the tertiary alcohol. (Figure 15-F.)

2. Syntheses of amides.

A. Heating the ammonium salts, or heating an acid with urea.

Primary aliphatic amides are formed on heating the ammonium salts of the corresponding carboxylic acids, or by heating an acid or its ammonium salt with urea. (Figure 16-A.)

B. The use of acyl chlorides.

The reaction of an acyl chloride with an excess of ammonia represents one of the best procedures for the preparation of primary amides. (Figure 16-B.) The acyl chloride (the crude material prepared by the thionyl chloride method is quite satisfactory) is added dropwise to well-stirred concentrated aqueous ammonia cooled in a freezing mixture. The amides of the higher carboxylic acids crystallise out on standing and need only to be filtered and recrystallised. Water-soluble amides are isolated by extraction with hot ethyl acetate following removal of water on a rotary evaporator.

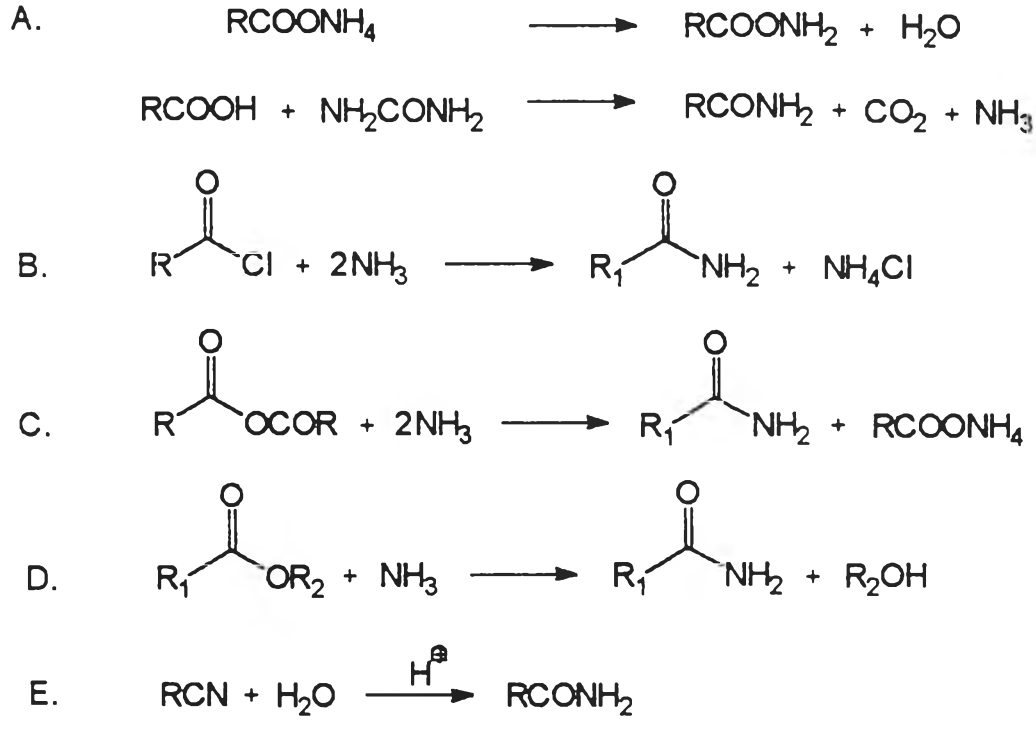


Figure 16. Syntheses of amides by

A. Heating the ammonium salts, or heating an acid with urea.

B. The use of acyl chlorides.

C. The use of acid anhydrides.

D. The use of esters.

E. The hydrolysis of nitriles.

The use of primary or secondary amines in place of ammonia yields the corresponding secondary or tertiary amides in reaction with an acyl chloride.

C. The use of acid anhydrides.

In the laboratory, amides are prepared by the reaction of ammonia with acid anhydrided. (Figure 16-C.) Acid anhydrides undergo the same reactions as acid chlorides, but a little more slowly; where acid chlorides yield a molecule of HCl, anhydrides yield a molecule of carboxylic acid.

D. The use of esters.

Amides are very easily prepared by the interaction of carboxylic esters with concentrated aqueous ammonia (ammonolysis). (Figure 16-D.) The reaction usually proceeds readily in the cold, particularly when the methyl esters of the lower molecular weight carboxylic acids are involved.

E. The hydrolysis of nitriles.

The interruption of the hydrolysis of a nitrile at the amide stage can often be achieved in a preparative manner, where the nitrile is dissolved in concentrated hydrochloric acid at 40^{o}C and subsequently poured into water. (Figure 16-E.) The use of hot polyphosphoric acid has also been recommended (Snyder and Elston, 1954).

Reaction conditions which are particularly applicable to aromatic nitriles involves the use of an aqueous solution of sodium hydroxide containing hydrogen peroxide, but alkyl cyanides do not always give good results.

3. Syntheses of acyl halides.

A. The use of thionyl chloride.

Acyl halides are invaluable acylating reagents and their preparation is therefore of great importance. The conversion of a carboxylic acid into the corresponding acyl chloride is usually achieved by heating the acid with thionyl chloride. (Figure 17-A.)

This reagent is particularly convenient as the by-products of the reaction do not contaminate the product, and excess thionyl chloride is usually separable by fractional distillation. If the boiling point of the acyl chloride is too near to that of thionyl chloride, the excess of the latter can be destroyed by the addition of pure formic acid. (Figure 18.)

B. The use of phosphorus pentachloride.

Phosphorus pentachloride is the preferred chlorinating agent for aromatic acids which contain electron-withdrawing substituents, and which do not react readily with thionyl chloride. (Figure 17-B.)

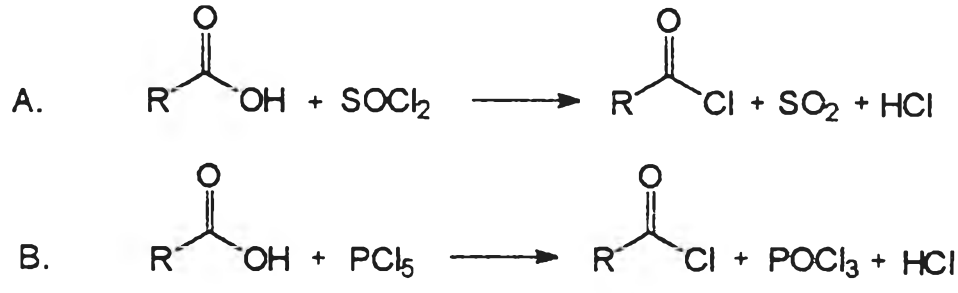


Figure 17. Syntheses of acyl halides by

A. The use of thionyl chloride.

B. The use of phosphorus pentachloride.

Figure 18. The reaction of formic acid with thionyl chloride.

4. Syntheses of alkyl halides.

A. The displacement of a hydroxyl group in an alcohol by halogen.

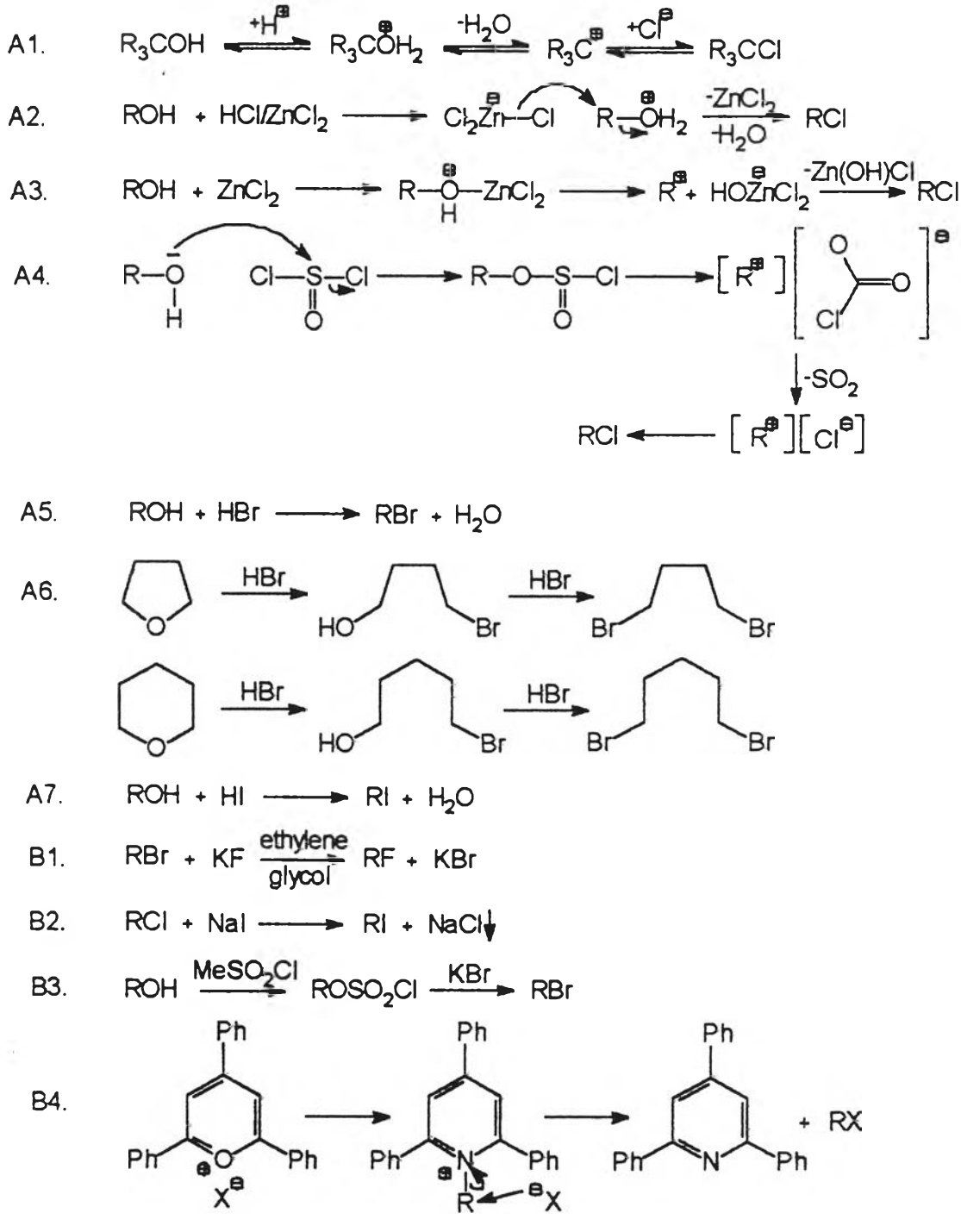
The hydroxyl group in teriary alcohols is most readily replaced, and this is effected by simply allowing the alcohol to react with concentrated hydrochloric acid at room temperature. The reaction is a nucleophilic displacement of the S_N1 type involving the formation of a relatively stable carbocation intermediate. (Figure 19-A1.)

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. In the case of alicyclic secondary alcohols, anhydrous calcium chloride is recommended. The unsaturated alcohol, allyl alcohol, gives a poor yield by the HCl-$ZnCl_2$ method, but an alternative procedure using copper (I) chloride as catalyst has proved to be more satisfactory.

The hydrochloric acid-zinc chloride reaction may be an S_N2 type displacement, particularly in the case of primary alcohols. (Figure 19-A2.)

An S_N1 mechanism is also possible, particularly in the case of secondary alcohols. (Figure 19-A3.)

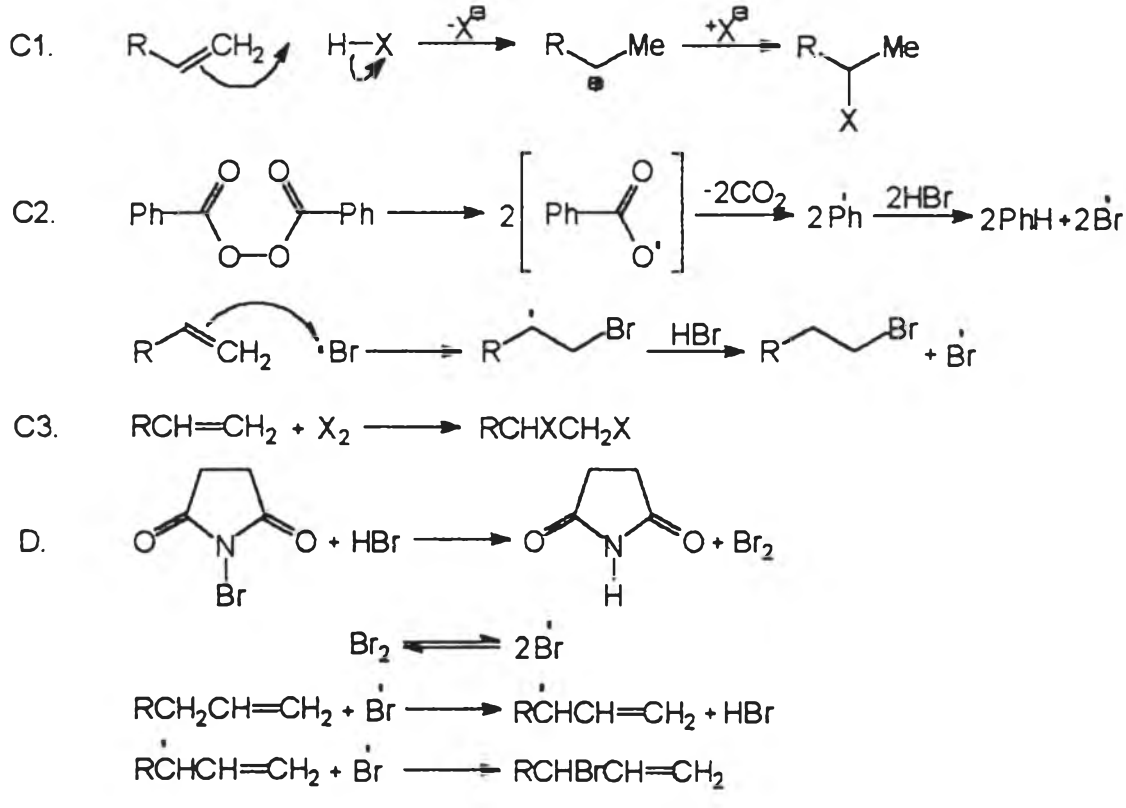
The regioselectivity of this latter reaction pathway may be diminished owing to the tendency of carbocations to rearrange, particularly when branching of the carbon chain occurs in the β-position. Hence the method



Figures 19. Syntheses of alkyl halides by

A. The displacement of a hydroxy group in an alcohol by halogen.

B. Displacement reactions involving a hydrogen atom, a methane-sulphonyloxy group, and an amino group.



Figures 19 (continued). Syntheses of alkyl halides by

C. The addition of hydrogen halides or halogen to alkenes.

D. The replacement of reactive allylic hydrogen atoms by bromine.

is preparatively useful only with secondary alcohols where one unique secondary carbocation is involved.

Rearrangement may be largely (but not entirely) suppressed by preparing the alkyl chloride from a reaction of the alcohol with thionyl chloride. (Figure 19-A4.)

The formation of alkyl bromides is more ready than that of alkyl chlorides. Hence secondary as well as tertiary bromides can be obtained diretly from the corresponding alcohols by heating with constant boiling hydrobromic acid, although, in the case of primary alcohols, the presence of sulphuric acid results, as a rule, in a more rapid reaction and in improved yields. (Figure 19-A5.)

The method is readily adapted for the preparation of dibromides from diols. The cyclic ethers tetrahydrofuran and tetrahydropyran are readily cleaved by the hydrobromic acid-sulphuric acid medium, and this provides an alternative and convenient preparation of the corresponding α,ω-dihalides. (Figure 19-A6.)

Alkyl iodides are the most easily formed of the alkyl halides and the slow distillation of the alcohol with constant boiling hydriodic acid is a general method of preparation. (Figure 19-A7.)

B. Displacement reactions involving a hydrogen atom, a methanesulphonyloxy group, and an amino group.

Alkyl fluorides may be prepared in moderate yield by interaction of an alkyl bromide with anhydrous potassium fluoride in the presence of dry ethylene glycol as a solvent for the inorganic fluoride. (Figure 19-B1.)

The most widely used example of halogen exchange is provided by the preparation of alkyl iodides from chlorides or bromides using sodium iodide in a solvent, such as acetone, in which sodium iodide is soluble but sodium chloride or bromide is relatively less so. (Figure 19-B2.)

Alcohols, as their derived methanesulphonates, may be readily converted into alkyl halides by reaction with inorganic halides. With chiral substrates, the reaction is often highly stereospecific in that inversion of configuration is obtained. (Figure 19-B3.)

The displacement of the amino group involves the initial reaction of the 2,4,6-triphenylpyrylium halide with the primary amine to yield the corresponding 2,4,6-triphenylpyridinium halide; this reaction proceeds either at room temperature in a suitable solvent, or more efficiently under reflux in benzene with azeotropic removal of water. Pyrolysis of the pyridinium halide under controlled conditions then yields the alkyl (or aralky) halide in good yield. (Figure 19-B4.)

C. The addition of hydrogen halides or halogens to alkenes.

Direct addition of a hydrogen halide to an alkene gives rise to an alkyl halide, the order of reactivity being HI>HBr>HCl. In the case of an unsymmetrical alkene, the regioselectivity of the reaction may be predicted from

the mechanism of the reaction. Thus, the carbocation which is the most stabilised by charge dispersal will be the one which is the most stabilised by charge dispersal will be the one which is formed preferentially. Classically the mode of addition is described as proceeding in the Markownikoff manner. (Figure 19-C1.)

The addition of hydrogen bromide (but not the iodide or chloride) in the presence of an added peroxide catalyst proceeds by a radical mechanism, giving rise to a regioselectivity which is opposite to that of the ionic mechanism (anti-Markownikoff). (Figure 19-C2.)

Halogens add to alkenes to give vicinal dihalides. (Figure 19-C3.) The addition of bromine usually proceeds the most smoothly, and is conveniently carried out in a solvent such as carbon tetrachloride.

D. The replacement of reactive allylic hydrogen atoms by bromine.

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. (Figure 19-D.)

5. Syntheses of carboxylic acids.

A. Oxidative methods.

Saturated primary alcohols are readily oxidised to aldehydes, which in turn are further oxidised to monocarboxylic acids having the same number of carbon atoms. (Figure 20-A1.)

The reaction is frequently effected using alkaline potassium permanganate solution. Aqueous sodium dichromate/ sulphuric acid mixtures may be used, but yields are not always satisfactory because of the attendant production of appreciable amount of esters.

The oxidation of an alkyl group attached to an aromatic system is a frequently used method for the preparation of the corresponding carboxylic acid. (Figure 20-A2.) The conversion can be accomplished most readily in the laboratory by using either a solution of sodium dichromate in concentrated sulphuric acid or aqueous potassium permanganate. The method is not applicable to those cases where activating groups are attached to the aromatic system, since these render the ring susceptible to oxidative cleavage.

B. The hydrolysis of nitriles.

Since nitriles are readily available from the interaction of alkyl halides with sodium or potassium cyanide in aqueous alcoholic solution, or from the Sandmeyer reaction, their hydrolysis to carboxylic acids is a valuable synthetic method. Aqueous alkaline or acidic conditions may be used. The

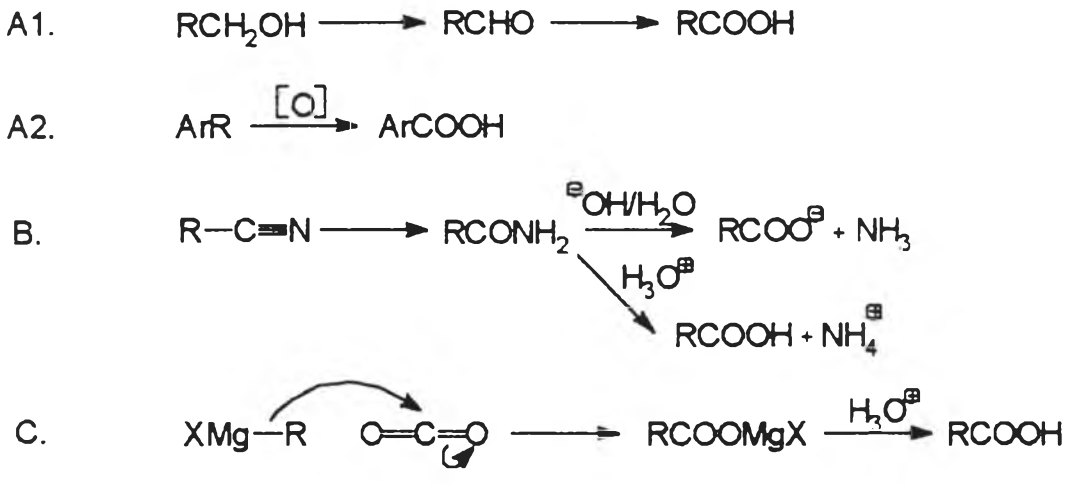


Figure 20. Syntheses of carboxylic acids by

A. Oxidative methods.

B. The hydrolysis of nitriles.

C. The carboxylation of Grignard reagents.

reaction proceeds via the intermediate formation of an amide. Experimental conditions may be selected to interrupt the hydrolysis at the amide stage. (Figure 20-B.)

C. The carboxylation of Grignard reagents.

The addition of a Grignard reagent to carbon dioxide gives the salts of the corresponding carboxylic acid, which on acidification yields the free carboxylic acid. (Figure 20-C.) The reaction is best carried out by pouring the ethereal solution of the Grignard reagent directly on to an excess of coarsely powdered solid carbon dioxide. The alternative procedure of passing dry carbon dioxide gas into the Grignard reagent solution may give rise to the formation of ketonic by-products by further reaction of the Grignard reagent with the carboxylate salt.

6. Syntheses of amines.

A. The reduction of alkyl azides, alkyl cyanides, and amides.

As these compounds all possess a nitrogen-containing functional feature, it is worth pointing out that they arise from alkyl halides (or methanesulphonates) in the case of azides and cyanides, or from carboxylic acid chlorides in the case of amides.

The reduction of the azide is effected by the addition of sodium borohydride to a reaction mixture arising from the displacement reaction of an alkyl halide with sodium azide. (Figure 21-A1.) The reaction appears to be

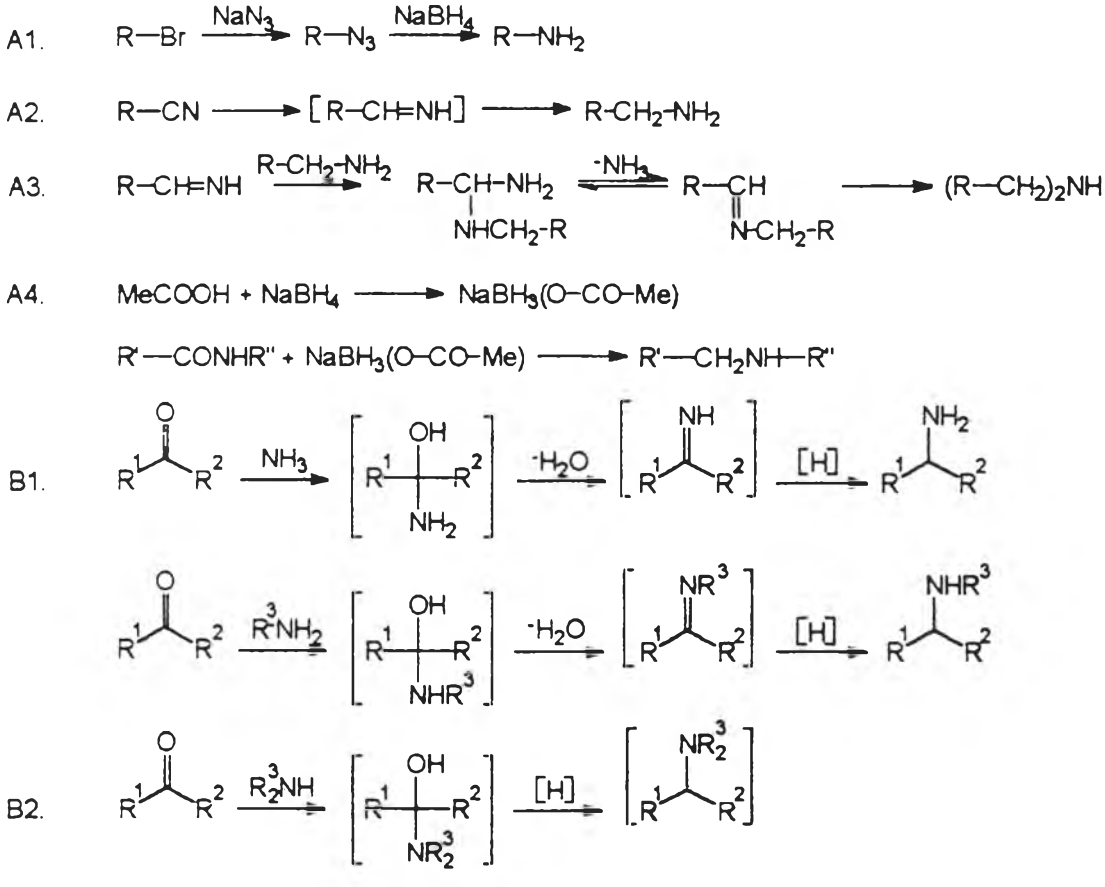


Figure 21. Syntheses of amines by

A. The reduction of alkyl azides, alkyl cyanides, and amides.

B. Reductive alkylation of ammonia or amine.

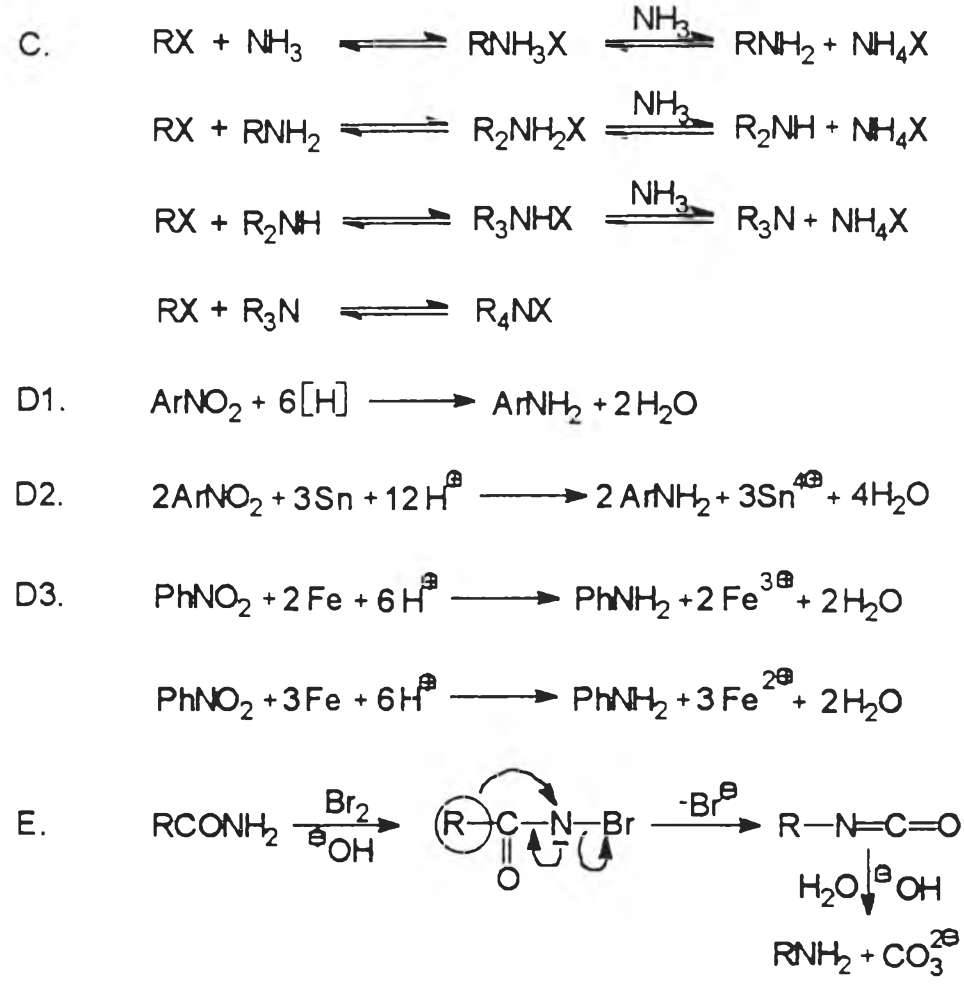


Figure 21 (continued). Syntheses of amines by

C. The alkylation of ammonia and its derivatives.

D. The reduction of nitro compounds and oximes.

E. Molecular rearrangements of the Hofmann type.

applicable to primary and secondary alkyl halides, alkyl methanesulphonates and benzylic halides.

Alkyl cyanides in general are smoothly reduced to primary amines (giving a product having one carbon atom more than the alkyl halide starting material) by the action of sodium and ethanol. (Figure 21-A2.) The use of a metal-acid reducing medium is unsatisfactory since extensive hydrolysis of the cyano group occurs. Catalytic hydrogenation over a Raney-nickel catalyst, in the presence of excess ammonia to suppress secondary amine formation, is possible. The secondary amine may be formed as in figure 21-A3.

Lithium aluminium hydride has also been used for the reduction of nitriles to amines. In addition, the reduction of nitriles is also effected by the use of sodium trifluoroacetoxy borohydride (from sodium borohydride and trifluoroacetic acid) in tetrahydrofuran solution.

Amides may be reduced to the corresponding primary, secondary and tertiary amines with lithium aluminium hydride with a varying degree of success. The reagent sodium acetoxyborohydride has been used to reduce a wide range of aliphatic and aromatic primary and secondary amides to the corresponding primary and secondary amines (figure 21-A4); in the case of tertiary amides ($RCONR_2$), sodium trifluoroacetoxy-borohydride is the reagent of choice. In addition, sodium borohydride with methanesulphonic acid is also a convenient and effective reductant for amides.

B. Reductive alkylation of ammonia or amines.

The process of reductive alkylation involves the treatment of ammonia or primary or secondary amines with an aldehyde or ketone under reducing conditions. The conversion in the case of ammonia or primary amines and a carbonyl compound probably involves the stages showed in figure 21-B1. When secondary amines are used the intermediated aminol cannot give rise to an imine and the tertiary amine product is formed by a hydrogenolytic pathway. (Figure 21-B2.)

C. The alkylation of ammonia and its derivatives.

It might be predicted that treatment of an alkyl halide with ammonia under pressure would constitute a suitable synthesis of a primary amine. In practice, however, the yield is poor since a mixture of all three classes of amines, together with some of the quarternary ammonium salt, is obtained, owing to move ready further alkylation of the sequentially formed products. (Figure 21-C.)

D. The reduction of nitro compounds and oximes.

Primary arylamines are generally prepared by the reduction of nitro compouds. (Figure 21-D1.) When only small quantities are to be reduced and cost is a secondary consideration, tin and hydrochloric acid may be employed. Theoretically 1.5 mol of tin are needed for the reduction of the nitro group, the metal being oxidised to the tin (IV) state. (Figure 21-D2.) Other metal-acid reducing systems may be used; reduction with iron and hydrochloric

acid is employed on the technical scale for the manufacture of aniline. (Figure 21-D3.)

Aromatic and heterocyclic nitro compounds are readily reduced in good yield to the corresponding amines by sodium borohydride in aqueous methanol solution in the presence of a palladium-on-carbon catalyst.

Another method of reduction includes catalytic hydrogenation over Raney-nickel or palladium-on-charcoal.

E. Molecular rearrangements of the Hofmann type.

By treatment of an amide with sodium hypobromite or sodium hypochlorite solution (or with halogen admixed with aqueous alkali), a primary amine having one less carbon atom is produced. Good yields are obtained when the reaction is applied to most aliphatic and aromatic amides.

The conversion of an amide in this way is termed the Hofmann reaction or the Hofmann rearrangement. The mechanism of the reaction involves an intramolecular 1,2-carbon-to-nitrogen nucleophilic shift of the alkyl (or aryl) group in the bromo amide anion to form an isocyanate, which is hydrolysed to the primary amine by the aqueous base present. (Figure 21-E.)

7. Syntheses of aromatic nitro compounds.

A. Direct nitration.

Aromatic hydrocarbons may be nitrated, i.e. the hydrogen atoms replaced by nitro (NO_2) groups, with concentrated nitric acid in the presence of concentrated sulphuric acid ('mixed acid reagent'). (Figure 22-A1.)

The function of the sulphuric acid is to convert the nitric acid into the highly reactive, electrophilic, nitronium ion which is the effective nitrating agent. (Figure 22-A2.)

The mechanism of aromatic nitration, which is illustrated in the case of bezene, is a two-step process involving electrophilic attack of the nitronium ion on the benzene molecule to form the intermediate mesomeric ion, followed by removal of a proton by the hydrogen sulphate ion, which is the most basic species in the reaction mixture. (Figure 22-A3.)

Nitration of aromatic hydrocarbons is usually carried out with the above mixed acid reagent at comparatively low temperatures (e.g. about $50^{\circ}C$). Unnecessarily high temperatures should be avoided since polynitration is then more likely and oxidative breakdown of the aromatic ring system may occur.

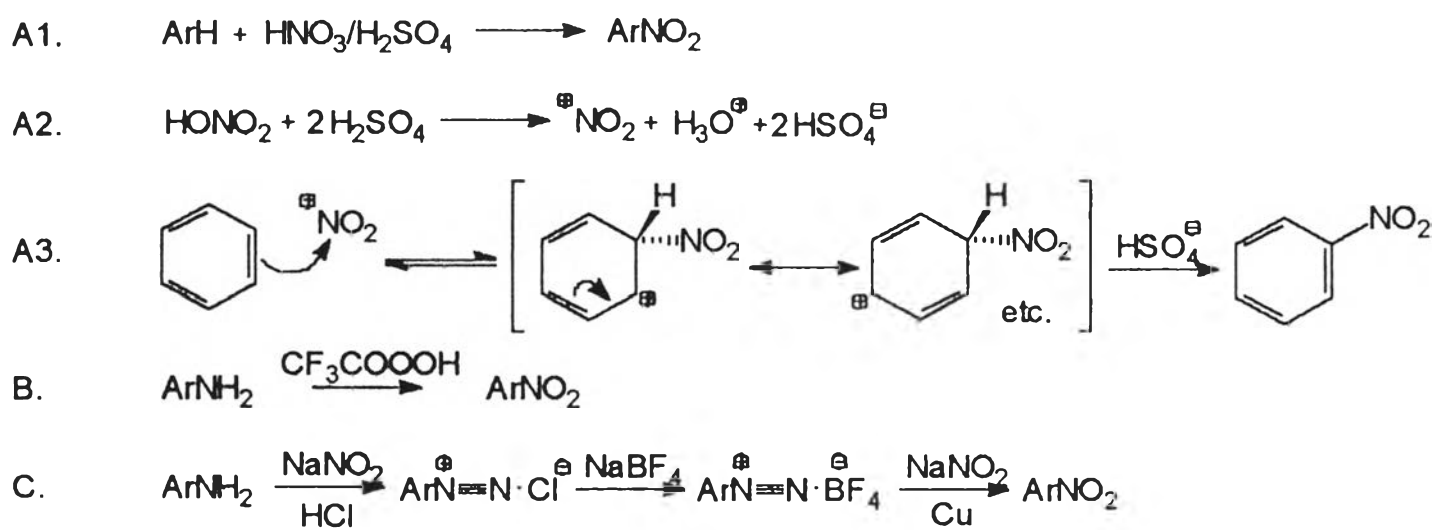


Figure 22. Syntheses of aromatic nitro compounds by

A. Direct nitration.

B. The oxidation of amines.

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

B. The oxidation of amines.

Various reagents are available for the oxidation of an aromatic amine to the corresponding nitro compound. For example, peroxymonosulphuric acid and other peroxyacids have been quite widely used in the past, although the yields of nitro compounds are rather variable owing to the concomitant formation of azoxycompounds. Pertrifluoroacetic acid is the reagent of choice since it generally gives improved yields of purer products. (Figure 22-B.)

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

This replacement is achieved by the decomposition of the aryldiazonium fluoroborate with aqueous sodium nitrite in the presence of copper powder. (Figure 22-C.) This procedure gives better yields and thus replaces the former method of reacting an acidic aryldiazonium salt solution with nitrous acid in the presence of copper (I) oxide.

These reactions are beneficial in the search for the synthetic pathway of N-(*p*-Aminobenzoyl)-1,2,3,4-tetrahydro-4,8-dimethylquinoline. Nevertheless, most of them require some adaptations in order to acquire an appropriate condition for each reaction. The details for experimental methods are described in the next chapter.