

CHAPTER II

HISTORY

The review reported herein focuses on structure-activity relationships of acylureas and evaluation of the anticonvulsant activities of these compounds. The pharmacology and toxicology of phenacemide, which is an acylurea antiepileptic drug used nowadays, is also reported. Furthermore, the general methods for the preparations of unsaturated N-(2-propylpentanoyl) urea analogues are described.

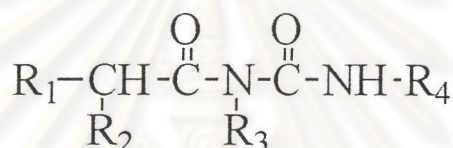
Structure-Activity Relationships of Acylureas.

Certain open chain ureids have already been employed therapeutically as hypnotics, but until 1952 none had revealed anticonvulsant properties worthy of therapeutic application. At this time Everett and Richards (1952) discovered such properties in phenacetylurea (phenacemide).

Subsequently, in studying a certain number of substituted acylureas, they defined structure-activity relationships in this series.

In the aliphatic series it is the acids possessing about 7 carbon atoms which confer the maximum anticonvulsant activity. The anticonvulsant activity is reduced progressively as the molecular weight is increased, while conversely, hypnotic activity develops. The most active compound is 2-ethyl-isovalerylurea (Spielman, 1948).

In the aromatic series the type of substituted radicals modified its properties in the following way:



Consideration of the structural formula of acetylurea indicates four positions at least which can be classified by different radicals.

If $\text{R}_1 = \text{C}_6\text{H}_5$, $\text{R}_2 = \text{R}_3 = \text{R}_4 = \text{H}$, phenacetylurea (phenacemide) is obtained which possesses maximum activity towards all types of experimental epileptic seizures—electrically or chemically induced.

If $\text{R}_1 = \text{C}_6\text{H}_5$, $\text{R}_2 = \text{R}_4 = \text{H}$, $\text{R}_3 = \text{CH}_3$, antipentetazol activity is increased.

If $\text{R}_1 = \text{C}_6\text{H}_5$, $\text{R}_2 = \text{CH}_3$, $\text{R}_3 = \text{R}_4 = \text{H}$, sedative properties are increased, but not anticonvulsant activity.

If $R_1 = C_6H_5$, $R_2 = R_3 = H$, $R_4 = CH_3$, anticonvulsant activity is reduced.

If $R_1 = C_6H_5$, $R_2 = H$, $R_3 = R_4 = CH_3$, antipentetrazol activity disappears.

If $R_1 = C_6H_5$, $R_2 = C_2H_5$, $R_3 = R_4 = H$, (ethylphenacemide), sedative activity increases, the compound is active in relation to electrical seizures but is less active with respect to pentetrazol.

If $R_1 = R_2 = C_6H_5$, $R_3 = R_4 = H$, (theoretically formed by opening of the phenytoin ring between positions 1 and 5), all activity disappears. This demonstrates that phenytoin does not undergo a transformation into diphenylacetylurea.

On the other hand, it is not conceivable that a cyclization of phenacetylurea into monophenylhydantoin takes place; for phenacetylurea does not possess the spectrum of anticonvulsant activity of the hydantoins, and mono-phenyl-5-hydantoin is almost free from activity.

If the phenyl group in position R_1 is substituted by CH_3 or Cl , or if it is replaced by a cyclohexane or a thienyl group, then activity again disappears.

The two compounds endowed with the greatest activity, experimentally and clinically, are phenacetylurea (phencemide, Phenurone[®]) and phenylethylacetylurea, ethylphenacemide, Pheneturide[®])

Pharmacology of Phenacemide.

Introduced in 1949, phenacemide is the straight-chain analog of 5-phenylhydantoin, the chemical structure is an acylurea anticonvulsant.

Pharmacokinetics.

1. Drug concentration levels.

Steady-state trough levels of 15 to 75 mcg/mL have been reported effective in controlling complex partial. It has been suggested that trough plasma levels of 50 mcg/mL or greater correlate best with good seizure control.

2. Absorption.

Phenacemide is almost completely absorbed from the gastrointestinal tract. Peak plasma levels occur 1 to 2 hours following administration.

3. Distribution.

The volume of distribution in a single subject was calculated as 1.51 L/kg

4. Metabolism.

Phenacemide is extensively hepatically metabolized with virtually no unchanged drug eliminated in the urine. Biotransformation includes para-hydroxylation of the phenyl substituent by hepatic microsomal enzymes. Although a metabolite of phenacemide has been detected in patients receiving the drug, the identity of the metabolite and its contribution to efficacy have not been established. Studies in rabbits have shown hydroxylation of the benzene nucleus of phenacemide followed by methylation of the 3-hydroxyl group and hydrolysis of the ureide group. Arene oxide intermediates have been proposed as responsible for the serious toxicities of phenacemide since they bind covalently to macromolecules.

5. Excretion.

In limited numbers of patients, the half-life of phenacemide has been calculated as 22 to 25 hours. Minimal amounts of unchanged drug are eliminated by the kidney. It is unknown whether or not phenacemide is excreted in breast milk. Because of the potential for serious toxicity to the infant, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Clinical Applications.

Phenacemide is used only in the treatment of severe epilepsy previously unresponsive to safer anticonvulsants. It is particularly useful in mixed forms of complex partial seizures. Because of its potential for toxicity, its use is restricted to patients unresponsive to other anticonvulsants.

Mechanism of Action.

In laboratory animals, phenacemide has been shown to elevate the seizure threshold for electroshock-induced convulsions and to abolish the tonic phase of electroshock-induced seizures. Phenacemide prevents or mitigates pentylenetetrazol-induced seizures. In comparative tests, phenacemide is as effective or more effective than other anticonvulsants in the treatment of complex partial seizures induced by low frequency stimulation of the cerebral cortex in mice.

Dosing Information.

The usual initial dosage of phenacemide for adults is 500 mg 3 times daily. The dosage may be increased by 500 mg weekly until seizure control is obtained. Although most patients respond to total daily doses of 2 to 3 grams, some patients have required as much as 5 grams daily. Pediatric doses for children 5 to 10 years of age are approximately one-half the adult dosage at similar intervals. Because phenacemide has the

potential for serious toxicity, it is recommended that the dosage be held to the minimal amount required to produce a therapeutic effect.

Cautions.

Psychic changes including personality disorders and psychosis have been associated with the use of phenacemide. The drug also causes blood dyscrasias, primarily leukopenia in up to 2% of patients. Other side effects include gastrointestinal disturbances including anorexia, skin rash, dizziness, drowsiness, hepatitis, elevations in serum creatinine and muscle pain. Reactions of an idiosyncratic nature including hepatitis, nephritis, and aplastic anemia, appear to be more frequent than with other antiepileptic drugs.

General Methods for the Preparations of Intermediates and the Final Product (Unsaturated N-(2-Propylpentanoyl) urea Analogues).

For the synthesis of unsaturated N-(2-propylpentanoyl) urea analogues, there are many compounds used as intermediates. These compounds represent many types of organic compounds i.e. monoalkyl diethylmalonate, dialkyl diethylmalonate, aliphatic ester, aliphatic carboxylic acid, acyl halides and acylureas. General methods for synthesis of these types of organic compounds are described as below (Morrison and Boyd, 1987).

1. Synthesis of acylureas.

Acylureas are synthesized by acylating urea with acid chloride. There are two methods which are used interchangeably with little difference in yield. In the first method, dry urea method, an acid chloride are allowed to react with urea in the absence of solvent. Reaction begin spontaneously or upon brief warming and is completed by heating on the steam-bath. In the second method, benzene method, the acid chloride is added to urea in refluxing benzene with a little conc. sulfuric acid as catalyst (Stugon et al., 1938). In contrast, Spielman et al. (1948) found that it is not necessary to use the trace of sulfuric acid as catalyst in this method. In 1992, Janwitayanuchit synthesized N-(2-propylpentanoyl) urea using benzene method in the present of potassium carbonate.



2. Synthesis of acyl chloride.

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.

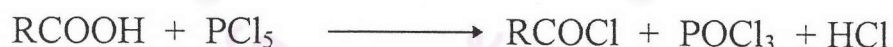


This reagent is particularly convenient as the by-products of the reaction do not contaminate the product, and excess thionyl chloride is usually separable by fractional distillation. If the boiling point of the acyl chloride is too near to that of thionyl chloride, the excess of the latter can be destroyed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



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.



3. Synthesis of Carboxylic acid.

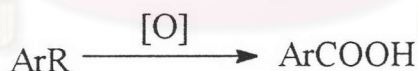
A. Oxidative methods.

Saturated primary alcohols are readily oxidised to aldehydes, which in turn are further oxidised to monocarboxylic acids having the same number of carbon atoms.



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

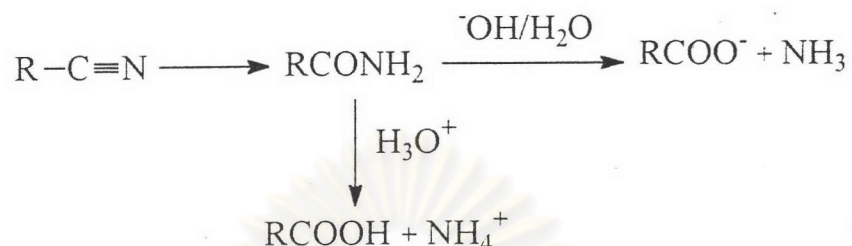
The oxidation of an alkyl group attached to an aromatic system is a frequently used method for the preparation of the corresponding carboxylic acid. The conversion can be accomplished most readily in the laboratory by using either a solution of sodium dichromate in concentrated sulphuric acid or aqueous potassium permanganate. the method is applicable to those case where activating groups are attached to the aromatic system, since these render the ring susceptible to oxidative cleavage.



B. The hydrolysis of nitriles.

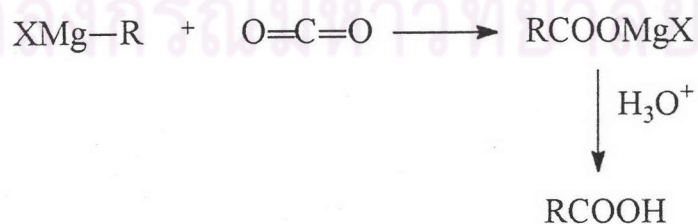
Since nitriles are readily available from the interaction of alkyl halides with sodium or potassium cyanide in aqueous alcoholic solution, or from the Sandmeyer reaction, their hydrolysis to carboxylic acids is a valuable synthetic method. Aqueous alkaline or acidic conditions may be used. the reaction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

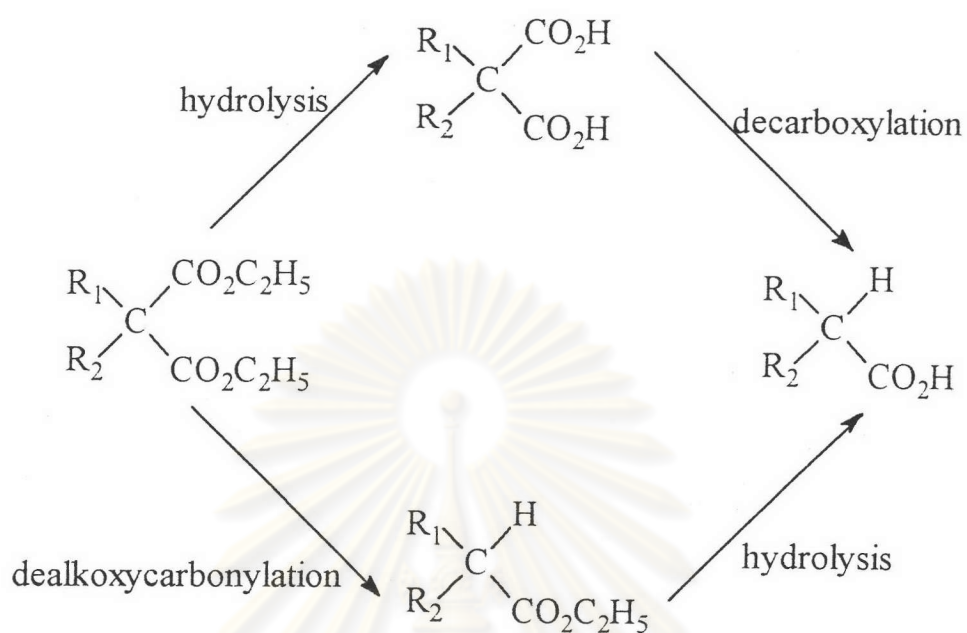
formation of an amide. Experimental conditions may be selected to interrupt the hydrolysis at the amide stage.



C. The carboxylation of Grignard reagents

The addition of a Grignard reagent to the carbon dioxide gives the salts of the corresponding carboxylic acid, which on acidification yields the free carboxylic acid. The reaction is best carried out by pouring the ethereal solution of the Grignard reagent directly onto 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.

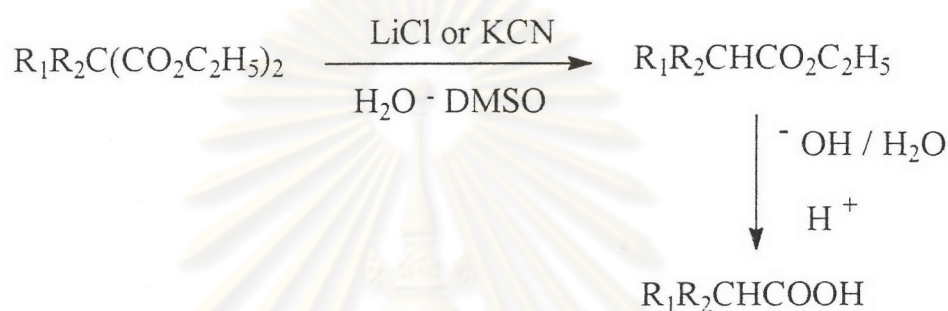




2.1. Alkaline hydrolysis of an alkylmalonic ester followed by careful acidification at 0 °C gives the alkylmalonic acid. The alkylmalonic acids undergo decarboxylation on heating under acid condition thus providing a convenient synthesis of mono or disubstituted acetic acids.

The decarboxylation step is responsible for the non-quantitative yields generally observed and for the presence of many by-products, since it is most frequently carried out at high temperature (150-250 °C). Toussaint et al., (1986) have recently reported a novel catalytic decarboxylation of malonic acids under mild conditions. This simple copper (I) catalyzed reaction affords the corresponding monocarboxylic acids in good purity and nearly quantitative yields.

2.2. The decarbalkoxylation of geminal diesters by heating with water-dimethylsulfoxide (DMSO) and/or water-DMSO with added salts such as NaCN, NaCl and LiCl is a convenient preparative route, leading to esters. The esters undergo hydrolysis or refluxing under alkaline condition to give carboxylic acid.



The decarbalkoxylation mechanism is a blend of $B_{AL}2$ (Figure 8) and $B_{AC}2$ (Figure 9) pathways which are dependent on substrates structure and nucleophile type. The formation of $\text{CH}_3\text{CH}_2\text{CN}$ can only arise from $B_{AL}2$ cleavage as depicted in Figure 8. A concerted decarbalkoxylation to directly yield carbanion must also be considered. However, the isolation of ethanol indicates that the $B_{AC}2$ mechanism is competitive. Figure 9 presents the mechanism for this route. Intermediates such as ethyl cyanoformate would be expected to undergo rapid hydrolysis in H_2O -DMSO (Krapcho et al., 1978)

Most monosubstituted malonic esters hydrolyze with acyl-oxygen cleavages ($B_{AC}2$) via presumed tetrahedral intermediates. However, in disubstituted malonic esters the $B_{AL}2$ route can eclipse the usual $B_{AC}2$ pathways.

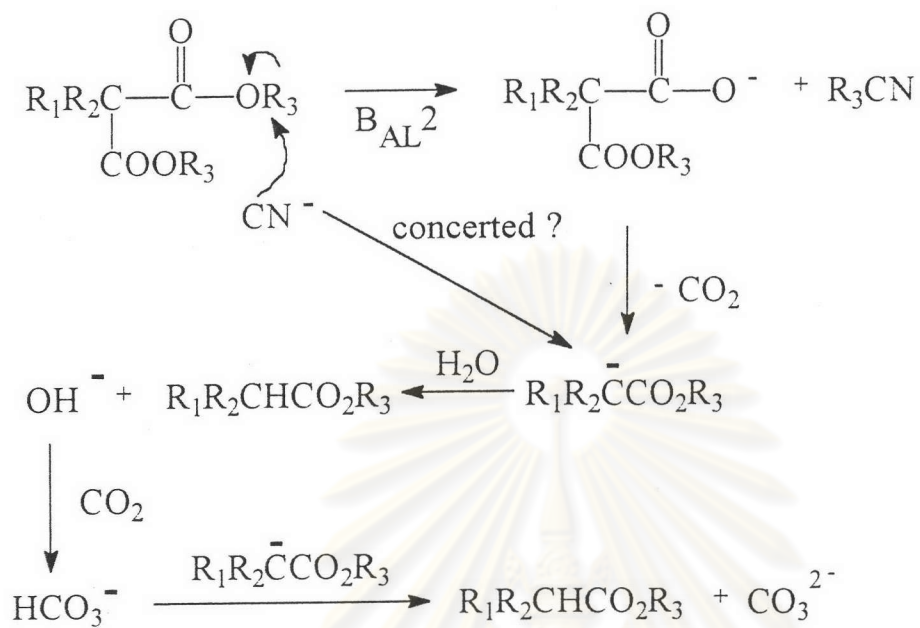


Figure 8. The mechanism pathway of ester hydrolysis with alkoxy-oxygen cleavage.

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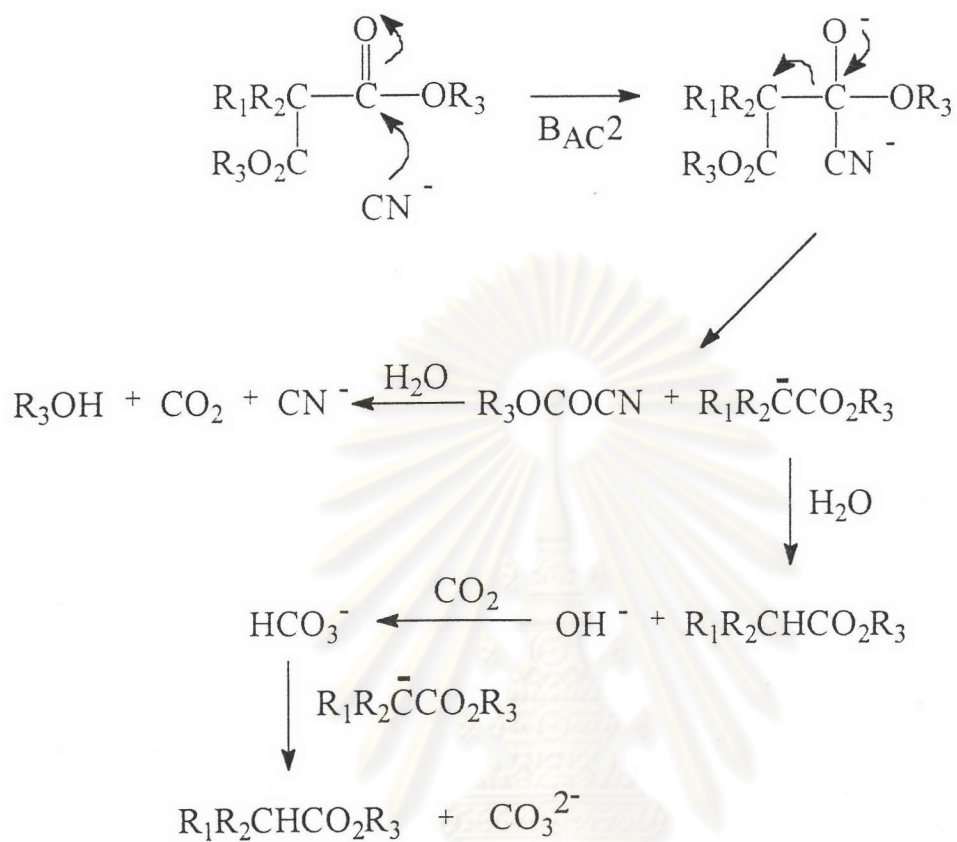


Figure 9. The mechanism pathway of ester hydrolysis with acyl-oxygen cleavage.

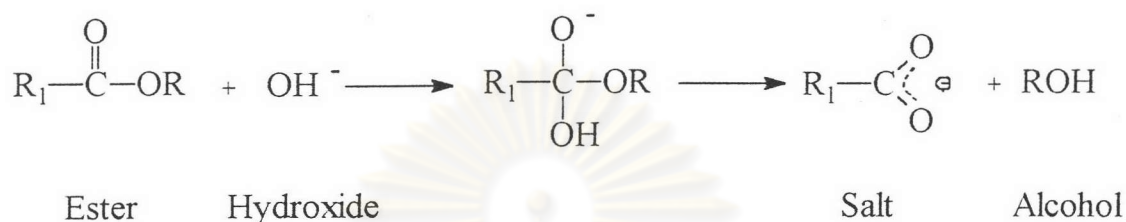
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Krapcho et al., (1978) have been reported the synthetic applications and mechanism studies of the decarboxylations of geminal diesters effected in DMSO by water and/or by water with added salts. The certain activated esters such as $C_6H_5CH(CO_2C_2H_5)_2$ decarboxylate on being refluxed in wet-DMSO. Monosubstituted diesters such as $CH_3CH_2CH(CO_2C_2H_5)_2$ undergo a much slower decarboxylation in refluxing water-DMSO while substrates such as $(CH_3)_2CHCH(CO_2C_2H_5)_2$ and the disubstituted diesters $(C_2H_5)_2C(CO_2C_2H_5)_2$ undergo no decarboxylations on being heated for long periods in water-DMSO. The addition of salts such as KCN, NaCl or LiCl to water-DMSO dramatically enhances the decarboxylation esters of these substrates. The decarboxylation of diethylphenylmalonate with DMF-NaCl-water proceeds in an excellent yield. However, in less reactive substrates such as diethyldiethylmalonate longer heating must be employed because of the lower boiling point of DMF to that of DMSO (Krapcho et al., 1973)

A monocarboxylic ester is hydrolyzed to a carboxylic acid and an alcohol or phenol when heated with aqueous acid or aqueous base. Under alkaline conditions, of course, the carboxylic acid is obtained as its salt, from which it can be liberated by addition of mineral acid.

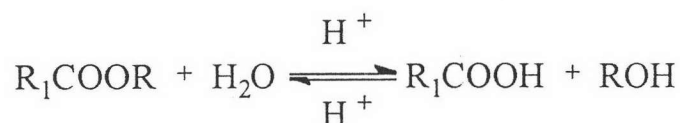
Base promotes hydrolysis of esters by providing the strongly nucleophilic reagent OH^- . This reaction is essentially irreversibly,

since a resonance-stabilized carboxylate anion shows little tendency to react with an alcohol.

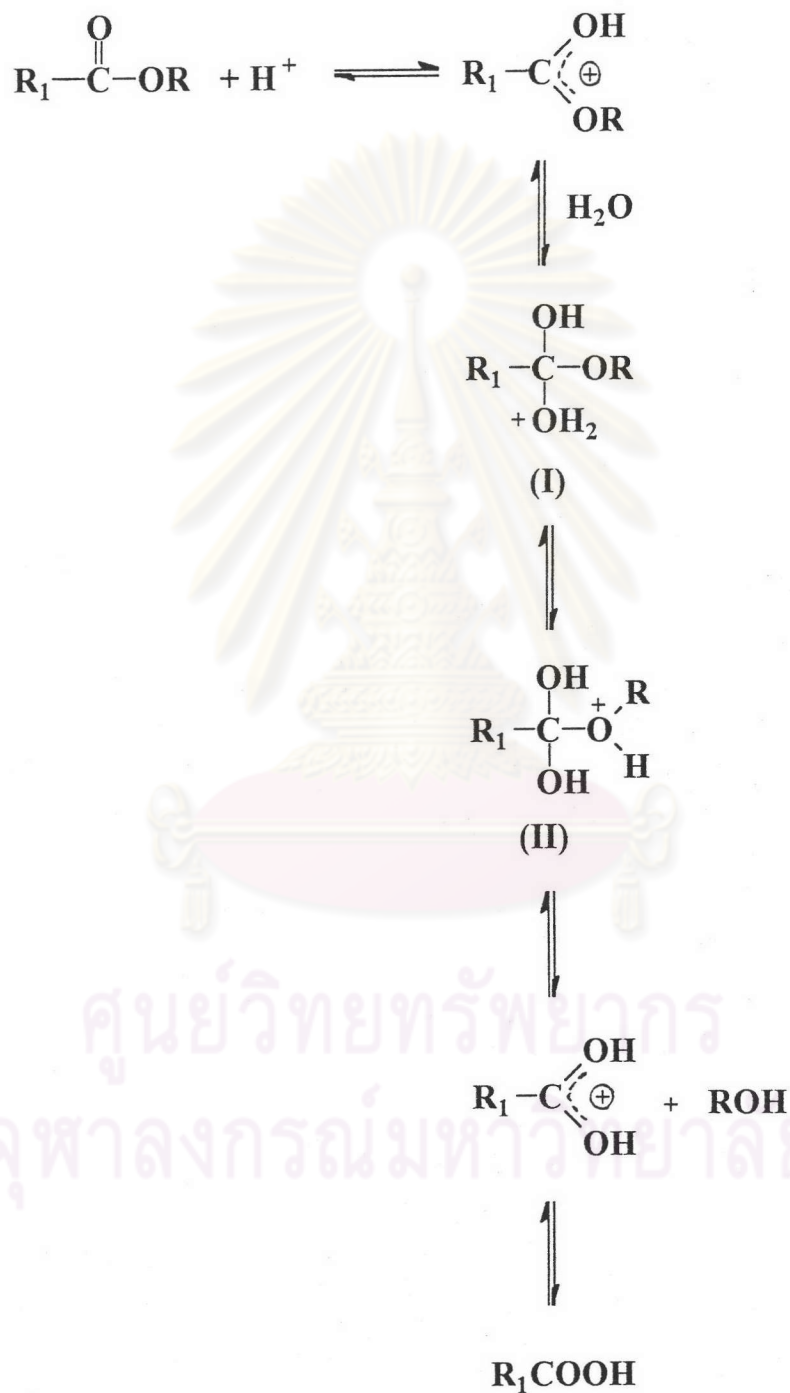


The reaction mechanism of the hydrolysis of an ester is described as followed. First, hydroxide ion attacks at the carbonyl carbon and displaces alkoxide ion. That is to say, reaction involves cleavage of the bond between oxygen and the acyl group, RCO-OR'. Attack by hydroxide ion on carbonyl carbon does not displace alkoxide ion in one step, but rather in two steps with the intermediate formation of a tetrahedral compound. Finally, there is a portion transfer from carboxylic acid to the alkoxide ion; the resulting products are carboxylate anion and alcohol.

Hydrolysis of esters is promoted not only by base but also by acid. Acidic hydrolysis is reversible and hence the mechanism for hydrolysis is also-taken in the opposite direction-the mechanism for esterification. Any evidence about one reaction must apply to both.



The mechanism for acid-catalyzed hydrolysis and esterification is contained in the following equilibria :



Mineral acid speeds up both protonating carbonyl oxygen and thus rendering carbonyl carbon more susceptible to nucleophilic attack. In hydrolysis, the nucleophile is a water molecule and the leaving group is an alcohol ; in esterification, the roles are exactly reversed.

These reactions are beneficial in the search for the synthetic pathway of unsaturated N-(2-propylpentanoyl) urea analogues. 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.



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