THE REACTIONS OF ALIPHATIC ACID CHLORIDES

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I. Introduction

The aliphatic carboxylic acid chlorides as a class are among the most versatile
and reactive of organic compounds. Some of the lower homologs, particularly
those containing from two to five carbon atoms, have long been used in the prep-
aration of a large variety of chemical compounds in a series of well-known and

well-understood reactions, such as the esterification of alcohols and the Friedel–Crafts acylation of aromatic hydrocarbons. Recent research has greatly extended the applicability of these materials in new and unprecedented ways. The straight-chain aliphatic acid chlorides containing from eight to eighteen carbon atoms, especially the even-numbered members, have achieved prominence as a consequence of recent developments in the field of fatty acid derivatives among which the esters, metallic salts, amides, nitriles, amines, and amine quaternaries have been noteworthy. These derivatives have assumed commercial importance over a period of years. The acid chlorides have received somewhat less attention, in general, than the other types of fatty acid derivatives, probably as a result of their relatively poorer stability and the difficulties encountered in handling them. In spite of these minor disadvantages more and more attention has been focused upon fatty acid chlorides as useful intermediates for the preparation of a huge number of products. The advent of newer synthetic routes to the aliphatic acids, particularly those utilizing inexpensive animal fats and vegetable oils, and the ease with which these acids can be converted into acid chlorides are further factors which enhance the importance of acid chlorides.

II. Scope of the Review

This review covers the chemical reactions of aliphatic carboxylic acid chlorides containing two or more carbon atoms. Straight- and branched-chain, saturated and unsaturated, and mono- and polyfunctional types have been included. The literature has been surveyed through December, 1951. In instances where certain portions of the material have been reviewed elsewhere within the last ten years the attempted coverage has been less complete, and an effort has been made, where feasible, to bring the previously reviewed material up to date. No attempt has been made to include the reactions of aromatic or aromatic-aliphatic acid chlorides, except for certain examples of the former type where differences in reaction behavior bring out the variation in general reactivity between these types and aliphatic acid chlorides. The reactions of alicyclic and heterocyclic acid chlorides have not been included, nor have those of amino-, alkoxy-, or mercapto-substituted aliphatic acid chlorides.

III. Nomenclature

The nomenclature of acid chlorides requires the names of acyl radicals in the several systems of nomenclature, since, regardless of the system, the name for an individual species is "acyl chloride." The acyl radicals in turn are derivable from the names of the acids; hence these should be considered first.

Four systems of nomenclature of acids represent current usage. First are the "common" names; since aliphatic acids include some of the oldest of known compounds, it is understandable that many of them have common names. The three derived systems include the simple nucleus plan, the Geneva and I.U.C. systems, and the additive plans. The selection of the preferred name among several possible synonyms depends primarily on relative simplicity and usage, but other considerations such as the showing of structural relationships may govern the choice

for a less-used synonym. The several systems are alike in that the names of acids in all of them are two-word names, the last word being "acid."

Many of the common names of acids require no prefix, since the name itself incorporates not only all the atoms but the structure and/or configuration as well, but another large group of common names does require the use of structural prefixes, letters, or numerals to distinguish among isomers. If substituting groups are present, these are indicated by directly attached prefixes. If numerals are used with open-chain compounds, the I.U.C. numbering is adopted, i.e., the carboxyl carbon atom is No. 1.

(a) Structural prefixes are not required in such names for acids as formic, acetic, butyric, oleic, and fumaric.

(b) Structural prefixes are required in some instances. The prefix n- for normal is usually omitted but may be used, as in n-valeric acid. Structural prefixes are encountered frequently in the trivial names of acids such as isovaleric acid, D-gluconic acid, L-mannosaccharic acid, mesotartaric acid, o-toluic acid, 3-thenoic acid, etc.

(c) The use of radicals as prefixes is illustrated in the names "dichloroacetic acid," "trimethylacetic acid," "2,3-dimethyllauric acid (or "α,β-dimethyllauric acid"), and "2-methylacrylic acid."

Formic acid would provide the simplest nucleus, but acetic acid is usually selected, since it has three identical replaceable hydrogen atoms rather than one. Thus the name "triethylacetic acid" is simple, whereas its equivalent, based on formic acid, would be complex. A few names necessarily use "formic acid" as the nucleus, examples being chloroformic and benzoylformic acids. Examples of the simple nucleus plan are the names "trimethylacetic," "allylacetic," etc. CH_3CH_2-$CH(C_2H_5)CH_2COOH$ might be called (1-ethylpropyl)acetic acid but most chemists prefer to avoid this type of situation, if possible, by selecting a larger nucleus and using the name "3-ethylvaleric acid."

The Geneva Congress of 1892 set up international rules for naming fatty acids. These rules involved selection of the longest chain containing the carboxyl group and numbering the latter as 1 unless a side chain or double bond were present, in which case the latter would take precedence (as in the name "2-methyl-4-butanoic acid" for isovaleric acid). Modernization of this rule by the International Union of Chemistry at Liége in 1930 gave the carboxyl carbon atom precedence as No. 1 and also ruled against avoidable multiple suffixes. This system is widely used for open-chain acids which have no common names. One attaches the ending "oic acid" (or "dioic acid" if two carboxyls are involved) to the name of the unbranched hydrocarbon with the same number of carbon atoms, includ-

ing the carboxyl carbon. The terminal "e" of an alkane or an alkyne is elided before "oic" but not before "dioic." (Δ is not used, as formerly, to denote the position of a double bond.)

$$CH_3(CH_2)_{11}COOH$$
Tridecanoic acid

$$CH_2{=}CHCH_2COOH$$
3-Butenoic acid

$$HOOC(CH_2)_8COOH$$
Decanedioic acid

$$CH_3CH_2CH_2CH(CH_3)CH_2COOH$$
3-Methylhexanoic acid
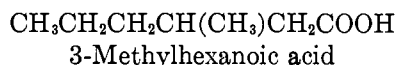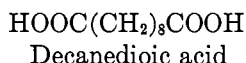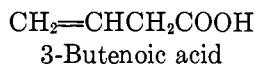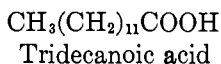
Although "methanoic," "ethanoic," "propanedioic," "butanedioic," etc. are correct Geneva or I.U.C. names, they have never supplanted the common names "formic", "acetic," "malonic," "succinic," etc. For this reason, Rule No. 1 of the *Definitive Report* of the International Union of Chemistry stated: "As few changes as possible will be made in terminology universally adopted." In this sense "formic acid," "acetic acid," and other widely used names belong not only to the common system but also come within the I.U.C. framework. At its 1951 session the International Union of Chemistry recommended the use of hexanoic, octanoic, and decanoic in place of caproic, caprylic, and capric, respectively, because of the ambiguity inherent in the use of the latter names.

The carboxyl carbon atom is assigned the No. 1 position, but this number is omitted in the name, since it is unnecessary. In naming a tricarboxylic acid, it is preferable to treat all carboxyl groups alike, if possible, rather than to designate one by a prefix. For example, $HOOCCH_2CH(COOH)COOH$ is better named by the additive system (see below) than as 2-carboxybutanedoic acid.

D. ADDITIVE SYSTEMS

Two additive plans are used in naming acids. In both an ending is attached to the name of the appropriate fundamental nucleus, not to the radical of that nucleus.

The first plan deals with the simple carboxylic ending (and also with such endings as arsonic, diazoic, phosphonic, seleninic, stibonic, sulfenic, sulfinic, and sulfonic). This ending is a principal function and thus determines the numbering, although the rule (I.U.C. Rule No. 29) is ambiguously worded in this regard, since it states that "the carboxyl group will be considered as a substituting group." Other "substituting groups" are prefixes and are therefore not principal functions.

$$\begin{array}{c} HOOCCH_2\,CHCH_2\,COOH \\ | \\ COOH \end{array}$$
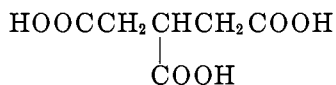
1, 2, 3-Propanetricarboxylic acid

$$\begin{array}{c} CH_3\,CH{=}C{-}CHCH_3 \\ |\quad| \\ HOOC\ \ COOH \end{array}$$
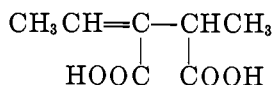
3-Pentene-2, 3-dicarboxylic acid
(not 2-pentene-3, 4-dicarboxylic acid)

The second plan for additive names uses such endings as the following: "acetic acid" or "ethanoic acid" for an attached —CH_2COOH group, "butyric acid"

or "butanoic acid" for an attached —$CH_2CH_2CH_2COOH$ group, "malonic acid" or "propanedioic acid" for an attached —$CH(COOH)_2$ group, and "succinic acid" or "butanedioic acid" for an attached —$CH(COOH)CH_2COOH$ group.

$$HOOCCH_2CH_2CH(CH_2COOH)_2 \qquad (HOOC)_2CHC{\equiv}CCH(COOH)_2$$

1,1,2-Ethanetriacetic acid   Acetylenedimalonic acid

The ending "formic acid" is not used in these names, since it would be the same as "carboxylic acid," but those derived from acetic, propionic, valeric, and higher homologs are applicable. The attachment must be at the terminal position. Therefore the compound having the structure

$$CH_2{=}CHC{=}CH_2$$
$$|$$
$$CH_3\overset{}{C}HCH_2COOH$$
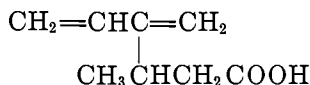
would have the additive name "1,3-butadiene-2-(β-methylpropionic) acid."

E. ACYL RADICALS

For naming acid chlorides, acyl radicals are required. Until 1949 this matter was handled simply by changing the "ic" of the name of the acid to "yl" (or the "oic" to "oyl"); in a few instances "yl" was expanded to "oyl" in order to avoid ambiguity. Acid radicals from the carboxylic additive names end in carbonyl, not carboxylyl. If the "ic acid" ending of a di- or polycarboxylic acid is changed to "yl chloride," this implies that all —COOH groups in the compound are changed to —COCl.

Regularly formed examples are such names as acetyl, butyryl, isovaleryl, triethylacetyl, tridecanoyl, decanedioyl [for —$CO(CH_2)_8CO$—], oxalyl (for —COCO—), malonyl (for —$COCH_2CO$—), 1,2,3-propanetricarbonyl [for —$COCH_2CH(CO—)CH_2CO$—], 1,1,2-ethanetriacetyl [for —$COCH_2CH_2CH$-$(CH_2CO—)_2$].

Typical expanded forms are lauroyl, myristoyl, palmitoyl, stearoyl, oleoyl. The necessity for the "oyl" endings for the acyl radicals arose when "yl" endings were used also for the corresponding alkyl radicals. The unfortunate name "stearyl alcohol" leads also to the name "stearyl chloride." Thus the latter name could mean either $C_{17}H_{35}CH_2Cl$ or $C_{17}H_{35}COCl$. The names "octadecyl chloride" and "stearoyl chloride" for these two substances completely eliminate the ambiguity. There are only about ten other instances in organic chemistry of similar ambiguity: namely, anisyl, camphoryl, chaulmoogryl, cinnamyl, cumyl, hydnocarpyl, phthalyl, vanillyl, and veratryl.

At its 1949 and 1951 meetings the International Union of Chemistry made a change and proposed to have the names of acyl radicals end in "oyl" whether or not the name of the acid ended in "oic acid." Thus, the names "palmitoyl," "stearoyl," and "oleoyl" became regularized, but here also many exceptions were stipulated: namely, formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, oxalyl, malonyl, succinyl, glutaryl, carbonyl, alkanecarbonyl (and alkanedicarbonyl, etc.), "the acid radicals derived from sulfonic and sulfinic

TABLE 1

Names of alkanoyl chlorides

(The preferred name is in italics; the word "chloride" is omitted)

FORMULA	COMMON NAME		GENEVA-I. U. C.
	Old	I. U. C. tentative	
(HCOCl)..............	*Formyl*	Formyl	Methanoyl
CH₃COCl.............	*Acetyl*	Acetyl	Ethanoyl
C₂H₅COCl............	*Propionyl*	Propionyl	Propanoyl
C₃H₇COCl............	*Butyryl*	Butyryl	Butanoyl
(CH₃)₂CHCOCl.......	*Isobutyryl*	Isobutyryl	Methylpropanoyl
C₄H₉COCl............	*Valeryl*	Valeryl	Pentanoyl
i-C₄H₉COCl..........	*Isovaleryl*	Isovaleryl	3-Methylbutanoyl
s-C₄H₉COCl..........	*2-Methylbutyryl*		2-Methylbutanoyl
t-C₄H₉COCl..........	*Trimethylacetyl (pivalyl)*	Pivaloyl	Dimethylpropanoyl
C₅H₁₁COCl...........	Caproyl		*Hexanoyl*
C₆H₁₃COCl...........	Enanthoyl (heptyloyl)	Enanthoyl	*Heptanoyl*
C₇H₁₅COCl...........	Caprylyl		*Octanoyl*
C₈H₁₇COCl...........	Pelargonyl	Pelargonoyl	*Nonanoyl*
C₉H₁₉COCl...........	Capryl		*Decanoyl*
C₁₀H₂₁COCl..........	Undecylyl		*Undecanoyl*
C₁₁H₂₃COCl..........	*Lauroyl*	Lauroyl	Dodecanoyl
C₁₂H₂₅COCl..........			*Tridecanoyl*
C₁₃H₂₇COCl..........	*Myristoyl*	Myristoyl	Tetradecanoyl
C₁₄H₂₉COCl..........			*Pentadecanoyl*
C₁₅H₃₁COCl..........	*Palmitoyl*	Palmitoyl	Hexadecanoyl
C₁₆H₃₃COCl..........	Margaryl	Margaroyl	*Heptadecanoyl*
C₁₇H₃₅COCl..........	*Stearoyl*	Stearoyl	Octadecanoyl
C₁₈H₃₇COCl..........			*Nonadecanoyl*
C₁₉H₃₉COCl..........	Arachidyl	Arachidoyl	*Eicosanoyl*
C₂₀H₄₁COCl..........			*Heneicosanoyl*
C₂₁H₄₃COCl..........	Behenyl		*Docosanoyl*
C₂₂H₄₅COCl..........			*Tricosanoyl*
C₂₃H₄₇COCl..........	Lignoceryl		*Tetracosanoyl*
C₂₄H₄₉COCl..........			*Pentacosanoyl*
C₂₅H₅₁COCl..........	Cerotyl		*Hexacosanoyl*
C₂₆H₅₃COCl..........			*Heptacosanoyl*
C₂₇H₅₅COCl..........	Montanyl		*Octacosanoyl*
C₂₈H₅₇COCl..........			*Nonacosanoyl*
C₂₉H₅₉COCl..........	Melissoyl		*Triacontanoyl*
C₃₀H₆₁COCl..........			*Hentriacontanoyl*
C₃₁H₆₃COCl..........	Lasseroyl		*Dotriacontanoyl*
C₃₂H₆₅COCl..........			*Tritriacontanoyl*
C₃₈H₇₇COCl..........			*Nonatriacontanoyl*
C₃₉H₇₉COCl..........			*Tetracontanoyl*

acids and the like" (such as benzenesulfonyl), and the amino acid radicals (such as aspartyl, glutamyl, glycyl, tyrosyl, etc.). This is a large list of exceptions. The proposal is tentative, but if made firm, it would seem that the net result is the introduction of a second system with many exceptions, whereas previously

there existed only one, with fewer exceptions. It may be assumed that the older common names which have been used as correct for so many decades will continue to be regarded as correct. Indeed, they conform to I.U.C. Rule No. 1, mentioned above.

TABLE 2
Names of alkenoyl and alkynoyl chlorides

FORMULA	COMMON NAME		GENEVA-I. U. C.
	Old	I. U. C. tentative	
CH_2=CHCOCl...............	*Acrylyl*	Acryloyl	Propenoyl
CH_3CH=CHCOCl............	*Crotonyl*	Crotonoyl	*trans*-2-Butenoyl
CH_2=CHCH$_2$COCl...........	*Vinylacetyl*		3-Butenoyl
CH_2=C(CH$_3$)COCl...........	*Methacrylyl* (2-methylacrylyl)	Methacryloyl	Methylpropenoyl
C_2H_5CH=CHCOCl...........	3-Ethylacrylyl (propylidene-acetyl)		*2-Pentenoyl*
CH_3CH=CHCH$_2$COCl........	3-Ethylidenepropionyl		*3-Pentenoyl*
CH_2=CHCH$_2$CH$_2$COCl........	*Allylacetyl*		*4-Pentenoyl*
CH_2=C(CH$_3$)CH$_2$COCl........			*3-Methyl-3-butenoyl*
$(CH_3)_2$C=CHCOCl...........	*3,3-Dimethyl-acrylyl*		*3-Methyl-2-butenoyl*
CH_2=C(C$_2$H$_5$)COCl...........	*2-Ethylacrylyl*		Ethylpropenoyl
CH_2=CHCH(CH$_3$)COCl.......	2-Vinylpropionyl		*2-Methyl-3-butenoyl*
CH_3CH=C(CH$_3$)COCl........	*Tiglyl*	Tigloyl	2-Methyl-*cis*-2-butenoyl
CH_3CH=C(CH$_3$)COCl........	*Angelyl*	Angeloyl	2-Methyl-*trans*-2-butenoyl
C_2H_5CH=CHCH$_2$COCl........	Hydrosorbyl		*3-Hexenoyl*
C_3H_7CH=CHCOCl............	Isohydrosorbyl or 3-propylacrylyl		*2-Hexenoyl*
$C_{17}H_{33}$COCl..................	*Oleoyl*	Oleoyl	*cis*-9-Octadecenoyl
$C_{17}H_{33}$COCl..................	*Elaidoyl*	Elaidoyl	*trans*-9-Octadecenoyl
$C_{17}H_{31}$COCl..................	*Linoleoyl*	Linoleoyl	*cis*-9, *cis*-12-Octadecadienoyl
$C_{17}H_{29}$COCl..................	*Linolenoyl*	Linolenoyl	*cis*-9, *cis*-12, *cis*-15-Octadecatrienoyl
HC≡CCOCl..................	*Propiolyl*	Propioloyl	Propynoyl
CH_3C≡CCOCl...............	*Tetrolyl*	Tetroloyl	2-Butynoyl
C_3H_7C≡CCOCl..............			*2-Hexynoyl*

Tables 1, 2, and 3 list the synonyms for various saturated and unsaturated acyl chlorides, the preferred name being set in italics. The preferred names will be used exclusively in this review.

F. ACID CHLORIDES WHICH ARE ALSO ACIDS

To name a structure such as $HOOC(CH_2)_4COCl$, it is best to select one function (COOH or COCl) as the principal function for the ending of the name and to include the other as a prefix. The two possible names for this compound would be 5-carboxyvaleryl chloride and 5-(chloroformyl)valeric acid.

IV. REDUCTION OF ALIPHATIC ACID CHLORIDES

The reduction of monobasic aliphatic acid chlorides with a variety of reducing agents leads to aldehydes, alcohols, hydrocarbons, and to a lesser extent to acids, ethers, esters, and anhydrides. Dibasic acid chlorides afford variable yields of

TABLE 3

Names of alkanedioyl and alkenedioyl chlorides

FORMULA	COMMON NAME		GENEVA-I. U. C.
	Old	I. U. C. tentative	
$(COCl)_2$	*Oxalyl*	Oxalyl	Ethanedioyl
$CH_2(COCl)_2$	*Malonyl*	Malonyl	Propanedioyl
$(CH_2COCl)_2$	*Succinyl*	Succinyl	Butanedioyl
$CH_3CH(COCl)_2$	*Methylmalonyl* (isosuccinyl)	Methylmalonyl	Methylpropane-dioyl
$CH_2(CH_2COCl)_2$	*Glutaryl*	Glutaryl	Pentanedioyl
$(CH_2CH_2COCl)_2$	*Adipyl*	Adipoyl	Hexanedioyl
$CH_2(CH_2CH_2COCl)_2$	*Pimelyl*	Pimeloyl	Heptanedioyl
$(=CHCOCl)_2$	*Maleyl*	Maleoyl	*cis*-Butenedioyl
$(=CHCOCl)_2$	*Fumaryl*	Fumaroyl	*trans*-Butenedioyl

dialdehydes, frequently together with considerable amounts of unpredictable reduction products. Under rigid conditions the reduction of aliphatic acid chlorides may yield essentially one type of product.

A. THE ROSENMUND REDUCTION

It is sometimes desirable to convert an aliphatic acid to the corresponding aldehyde, another organic type of considerable versatility and pronounced reactivity. The Rosenmund reduction (581) consists in the selective hydrogenation of an acid chloride to the corresponding aldehyde in the presence of a suitable catalyst, generally supported palladium. The technique for this reduction has been adequately reviewed by Mosettig and Mozingo (497), with examples from the literature tabulated for aliphatic, hydroaromatic, aliphatic-aromatic, and heterocyclic acid chlorides until November of 1947. Generally, the reduction is carried out by bubbling hydrogen gas through a hot solution of the acid chloride in which the catalyst is suspended. The reduction involves the elimination of hydrogen chloride and depends critically upon the resistance of the aldehyde to

$$RCOCl + H_2 \xrightarrow{Pd-BaSO_4} RCHO + HCl$$

further reduction, a situation which is maintained through the use of a catalyst poison or "regulator," generally quinoline-S, thiourea, or some other sulfur-containing material, which inactivates the catalyst for reduction of an aldehyde but not for reduction of an acid chloride. The mechanism for this catalytic phenomenon is obscure. In this instance, at least, the aliphatic acid chloride displays a greater activity than does the corresponding aldehyde.

Competing reactions which are of importance in instances where the catalyst regulator affords incomplete inhibition of aldehyde reduction are alcohol and hydrocarbon formation. If these occur, secondary formation of acid and anhydride are possible. In addition, the alcohol may give rise to ether formation, presumably by dehydration, the ester may be cleaved to the acid and the hy-

$$RCOCl \ + \ 2H_2 \ \xrightarrow{\text{catalyst}} \ RCH_2OH \ + \ HCl$$

$$RCH_2OH \ + \ H_2 \ \xrightarrow{\text{catalyst}} \ RCH_3 \ + \ H_2O$$

$$RCOCl \ + \ RCH_2OH \ \rightarrow \ RCOOCH_2R \ + \ HCl$$

$$RCOCl \ + \ H_2O \ \rightarrow \ RCOOH \ + \ HCl$$

$$RCOOH \ + \ RCOCl \ \rightarrow \ (RCO)_2O \ + \ HCl$$
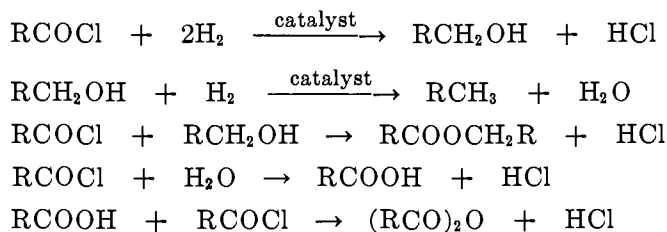
drocarbon, and the entire —COCl group may be removed to give a hydrocarbon containing one less carbon atom, a side-reaction occurring more frequently with aromatic types. Of considerable importance is the possibility of aldehyde polymerization, which necessitates operating at as low a temperature as is consistent with reduction. In practice, losses of aldehyde in working up the reaction

$$2RCH_2OH \ \rightarrow \ RCH_2OCH_2R \ + \ H_2O$$

$$RCO_2CH_2R \ + \ H_2 \ \rightarrow \ RCOOH \ + \ RCH_3$$

$$RCOCl \ + \ H_2 \ \rightarrow \ RH \ + \ CO \ + \ HCl$$
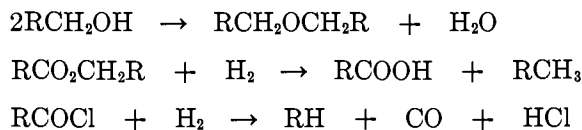
mixture may be reduced by immediate conversion to the oxime, semicarbazone, or other suitable derivatives (204, 581).

Data available indicate that catalyst poisons of other types may completely inhibit reduction of an acid chloride. The presence of a trace of phosphorus oxychloride in the acid chloride prohibits the reduction to aldehyde; indeed, phosphorus-containing materials in general cause this inhibition. Aliphatic acid chlorides prepared from the acid with phosphorus trichloride or pentachloride must be free of these contaminants to assure reduction to aldehyde by the Rosenmund method.

In the aromatic series other reducible groups such as nitro and chloro do not normally interfere (582), and Rosenmund reductions have been carried out with aliphatic acid chlorides in anhydrous acetone and ethyl acetate without reduction of the solvents (598). 4-Carbomethoxybutyryl chloride has been reduced to methyl 4-formylbutyrate without simultaneous reduction of the ester group (288). A recent report (641), in fact, claims the reduction of 7-, 11-, and 15-

carbethoxyalkanoyl chlorides to the corresponding ester-aldehydes by the usual Rosenmund technique in yields of 65, 89, and 95 per cent, respectively. Recently (191) xylene has been used as a solvent in which palmitoyl chloride was reduced by the usual Rosenmund technique to hexadecanal in 86 per cent yield.

Dibasic acid chlorides generally do not give good yields of dialdehydes in the Rosenmund reduction as a result of an increased tendency to polymerize. Succinyl chloride gave butyrolactone (238), and adipyl chloride has given the corresponding aldehyde acid and cyclopentanecarboxylic acid (238).

Considerably improved yields (80–90 per cent) of aliphatic aldehydes in the Rosenmund reduction have been claimed (598) through the use of a palladium hydroxide–barium sulfate catalyst regulated with dimethylaniline in anhydrous acetone or ethyl acetate as solvents. Acetyl, butyryl, nonanoyl, palmitoyl, and stearoyl chlorides were reduced in this manner, as was the unsaturated oleoyl chloride. Succinyl chloride could not be reduced in this way, however.

B. CATALYTIC HYDROGENATION

Efforts to obtain good yields of aliphatic aldehydes by the catalytic hydrogenation of aliphatic acid chlorides using unpoisoned catalysts other than supported palladium have met with little success. In all reported instances these reductions have given mixtures of products. The use of platinum on pumice at reduced pressures (196) for the even-numbered members of the straight-chain aliphatic acid chlorides containing from eight to fourteen carbon atoms yielded variable mixtures of the desired aldehydes along with hydrocarbons and secondary polymerized products. The highest yield reported in this series was 50 per cent for the conversion of octanoyl chloride to octanal. Only slightly better results have been reported with platinum oxide as catalyst (267). At atmospheric pressure valeryl and hexanoyl chlorides have given the corresponding aldehydes, but there were large attendant losses. The vapor-phase catalytic reduction of isovaleryl chloride with palladinized asbestos has been claimed (237) to give a nearly quantitative yield of isovaleraldehyde. Under the same conditions butyryl chloride gave principally butyraldehyde with a little 2-ethyl-2-hexenal. Raney nickel was observed to be useless for aldehyde formation, and in all cases the presence of phosphorus and sulfur compounds was detrimental to the reduction.

The catalytic hydrogenation of an aliphatic acid chloride to the corresponding alkyl chloride or the elimination of carbon monoxide and conversion to the alkyl chloride containing one less carbon atom is evidently not possible. Efforts to achieve the latter conversion using nickel catalyst at 400°C. have given unsaturated hydrocarbons, carbon monoxide, hydrogen chloride, and methane,

$$RCOCl \;+\; 2H_2 \;\rightarrow\; RCH_2Cl \;+\; H_2O$$

$$RCOCl \;\rightarrow\; RCl \;+\; CO$$
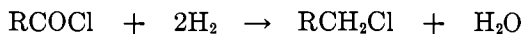
together with smaller amounts of carbon, hydrogen, and carbon dioxide (461, 462). Isovaleryl chloride gave isobutylene and propylene in addition to the other products; isobutyryl chloride gave propylene plus the other products; and pro-

pionyl chloride gave only ethylene, hydrogen chloride, carbon monoxide, methane, carbon, and hydrogen. Acetyl chloride decomposed violently under the same conditions to give ethylene, carbon monoxide, hydrogen, carbon dioxide, and hydrogen chloride. The formation of these products has been explained (462) by an initial decomposition to the alkyl chloride and carbon monoxide, the former immediately decomposing, in turn, to the ethylene derivative. The reduction and decomposition of isovaleryl chloride would then involve formation of isobutyl chloride, dehydrohalogenation to isobutylene, and the splitting of a small portion of this to propylene and —CH$_2$—, the latter becoming hydrogenated to methane at the expense of the hydrogen which originates from the decomposi-

$$(CH_3)_2CHCH_2COCl \rightarrow (CH_3)_2CHCH_2Cl + CO$$

$$(CH_3)_2CHCH_2Cl \rightarrow (CH_3)_2C{=}CH_2 + HCl$$
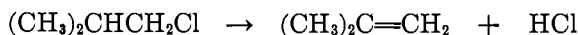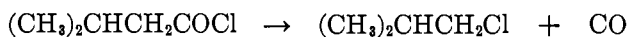
tion of a part of the CH$_3$CH=CH$_2$ into carbon and hydrogen. The traces of carbon dioxide were attributed to the reaction 2CO → C + CO$_2$. Whether the products arise as a result of the postulated sequences is problematical. It may also be considered that the isovaleryl chloride is hydrogenated to isovaleraldehyde with the liberation of hydrogen chloride, and the aldehyde further reduced to

$$(CH_3)_2CHCH_2COCl + H_2 \rightarrow (CH_3)_2CHCH_2CHO + HCl$$

$$(CH_3)_2CHCH_2CHO + H_2 \rightarrow (CH_3)_2CHCH_2OH$$

$$(CH_3)_2CHCH_2CH_2OH \rightarrow (CH_3)_2CH{=}CH_2 + H_2O$$
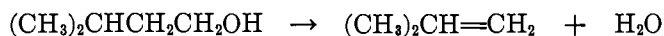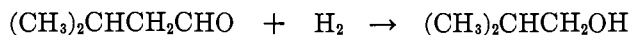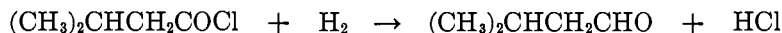
the alcohol, which is then thermally dehydrated to isobutylene. Aldehydes have also been observed to give carbon monoxide upon catalytic reduction (597). The data on hand indicate, at least, that the halogen in the acid chloride is always removed in catalytic reductions in the form of hydrogen chloride.

There have been no reported attempts to improve the yields in the reduction of aliphatic acid chlorides to esters. A patent (337) covering the hydrogenation of acid chlorides to wax-like materials containing larger proportions of saponifiable materials represents the only attempt to this end.

C. CHEMICAL METHODS OF REDUCTION

1. With sodium amalgam

The reaction of aliphatic acid chlorides with sodium leads to two types of products, depending upon the solvent used. The reaction of sodium in an inert solvent such as anhydrous ether affords the ester of an enediol (563),

$$4RCOCl + 4Na \rightarrow \underset{\underset{RCOO\ \ OCOR}{|\quad|}}{RC{=}CR} + 4NaCl$$
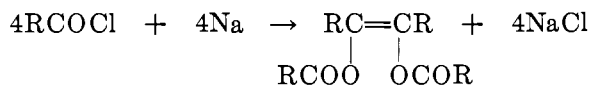
a reaction which will be dealt with later under Section XIX,A. A second type of reaction may occur in a solvent which enters into the reaction. By using sodium amalgam in methanol, palmitoyl chloride has been reduced continuously to

hexadecanol (628). This conversion can be conceived as an initial esterification with the solvent, followed by a Bouveault–Blanc type of ester reduction, thought now to proceed through a mechanism involving decomposition of a sodium ester

$$RCOCl \ + \ CH_3OH \ \rightarrow \ RCOOCH_3 \ + \ HCl$$
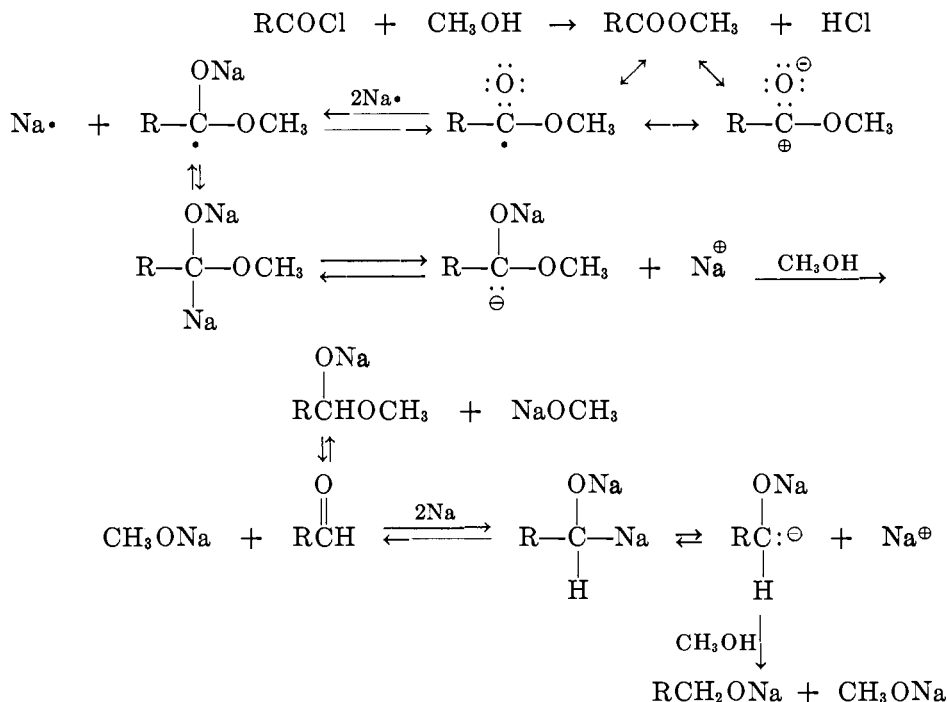
ketal with alcohol. The reaction of the acid chloride in this instance may be properly considered as an esterification, a type discussed later in Section IX,A. A reaction of similar character is apparently involved in the report (238) that succinyl chloride is converted to butyrolactone by treatment with sodium amalgam.

$$ClCOCH_2CH_2COCl \ + \ ROH \ \rightarrow \ ROOCCH_2CH_2COCl \ \xrightarrow{Na}$$

$$HOCH_2CH_2CH_2COCl \ \rightarrow \ CH_2CH_2CH_2CO \ + \ HCl$$
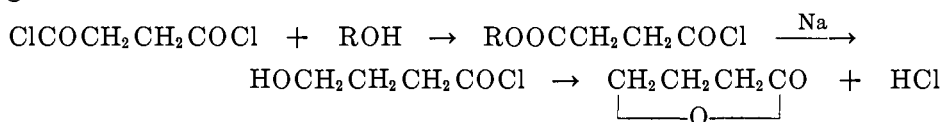
2. With metal hydrides

The metal hydrides have recently been applied to the reduction of carbonyl compounds. The technique applicable with lithium aluminum hydride, perhaps the most important hydride from the preparative standpoint, has been reviewed, together with examples, for carbonyl compounds including aliphatic acid chlorides by Brown (117). Excellent yields of the corresponding alcohols are obtainable from aliphatic acid chlorides by this method. Under forcing conditions (elevated temperatures for long times) the reduction may be carried beyond the alcohol stage, but this is not the normal mode of operation. The reduction prob-

ably involves a characteristic Grignard type of addition to the carbonyl group, and, like the latter, requires hydrolysis to liberate the reduced product. It has been assumed (691) that the reactive species is the aluminohydride ion, AlH_4^-, and that hydrogen is transferred as hydride in a bimolecular nucleophilic displacement. With an aliphatic acid chloride the reduction may be written as follows:

$$LiAlH_4 \rightarrow Li^\oplus + AlH_4^\ominus$$

$$R-\overset{\frown}{C}=O \quad \leftrightarrow \quad R-\overset{\oplus}{C}-\overset{\ominus}{O}: \quad + \quad AlH_4^\ominus \quad \rightarrow \quad R-\overset{\overset{\displaystyle H}{|}}{\underset{\underset{\displaystyle H}{|}}{C}}-\overset{\ominus}{O}AlH_2Cl$$
$$\underset{Cl}{|} \qquad\qquad \underset{Cl}{|}$$
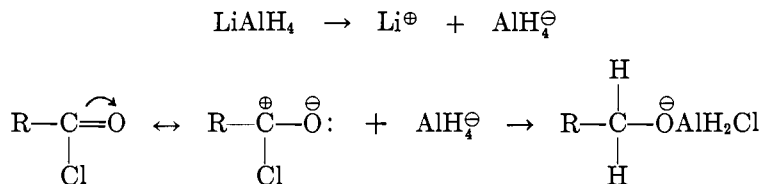
The alkoxide ion may by successive bimolecular reaction of a similar kind with additional acid chloride molecules be essentially converted to $AlCl_2(OR)_2^-$ ions while acting as a means of hydrogen transfer. In this manner only 0.5 mole of lithium aluminum hydride is theoretically required for the reduction of 1 mole of acid chloride.

Reductions with lithium aluminum hydride are usually carried out with an excess of the reagent, which decomposes upon hydrolysis with the evolution of hydrogen. Hydrogenation of the product may result unless the use of too large an excess of the reagent is avoided.

$$LiAlH_4 + 2H_2O \rightarrow LiAlO_2 + 4H_2$$
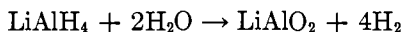
By using lithium hydride with aliphatic acid chlorides yields of the corresponding aldehydes in the range of 20–25 per cent have been reported (109). It is probable that hydride ion does not replace chlorine initially in the acid chloride, the aldehyde resulting through hydrolysis of a 1-chloroalkanol.

$$R-\overset{\overset{\displaystyle H}{|}}{\underset{\underset{\displaystyle Cl}{|}}{C}}=O \; + \; LiH \; \rightarrow \; R\overset{\overset{\displaystyle H}{|}}{\underset{\underset{\displaystyle Cl}{|}}{C}}OLi \; \xrightarrow{H_2O} \; \left[R-\overset{\overset{\displaystyle H}{|}}{\underset{\underset{\displaystyle Cl}{|}}{C}}-OH \; + \; LiOH \right] \rightarrow$$

$$RCHO \; + \; LiCl \; + \; H_2O$$
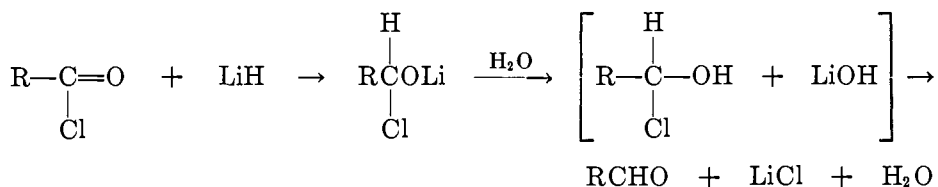
Calcium and sodium hydrides under the same conditions have yielded less than 1 per cent of the corresponding aldehydes, but sodium borohydride, like lithium aluminum hydride, has afforded reduction in excellent yield to the alcohol (142). Acetyl chloride, however, was not reduced by copper hydride (263), the acetic acid formed being attributed to hydrolysis alone.

The reduction of unsaturated aliphatic acid chlorides with metallic hydrides may lead to saturation of a conjugated double bond by analogy with the example of cinnamic acid (263), although no instances of this have as yet been reported.

3. With other reducing agents

Reactions of aliphatic acid chlorides with various other reducing agents have not been noteworthy and do not present any particular advantages. The reduction to alcohols with Grignard reagents is treated in Section XIX,C.

The Meerwein–Ponndorf–Verley reduction of carbonyl-containing compounds (69, 748), which generally involves the use of aluminum alkoxides in 2-propanol solution, cannot be applied to the reduction of aliphatic acid chlorides, owing to esterification with the alcohol. Our own experience (647) indicates that reduction with aluminum isopropoxide also cannot be achieved by employing dry toluene as a solvent because of the competing reaction of esterification, as described in detail in Section IX,A.

Reduction of certain aromatic and heterocyclic acid chlorides to alcohols has been reported with chromous hydroxide (263), but the reduction has not been reported for the aliphatic series. The most economical conversion of an aliphatic acid chloride to the alcohol is apparently the two-step process involving esterification and then reduction of the ester with sodium or by other means. A definite increase in overall yield for this conversion appears to be conversion to a thioester intermediate with methyl mercaptan or benzyl mercaptan and subsequent hydrogenation over Raney nickel.

$$\text{RCOCl} \xrightarrow{\text{R'SH}} \text{RCOSR'} \xrightarrow[\text{Raney nickel}]{\text{H}_2} \text{RCH}_2\text{OH}$$
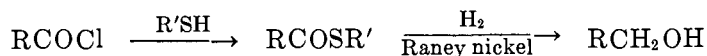
Palmitoyl chloride has been reduced to hexadecanol in yields up to 98 per cent of theory (359) by this method, which compares favorably with reductions through the ester. It appears doubtful, however, that the improvement in yield can warrant its successful economic application to an overall three-step conversion of an acid to an alcohol (I) *versus* the common route (II).

(I) $\text{RCOOH} \rightarrow \text{RCOCl} \rightarrow \text{RCOSR'} \rightarrow \text{RCH}_2\text{OH}$

(II) $\text{RCOOH} \rightarrow \text{RCOOR'} \rightarrow \text{RCH}_2\text{OH}$

In contrast to the above are reports that the hydrogenation of ethyl thiopropionate with Raney nickel has given propionaldehyde in 73 per cent yield (753, 754). Ethyl thiopropionate itself is said to have been prepared in 82 per cent yield from propionyl chloride and the lead salt of ethyl mercaptan in ether.

V. Hydrolysis of Aliphatic Acid Chlorides

Perhaps the most prominent chemical property of the aliphatic acid chlorides is their pronounced tendency to undergo hydrolysis to hydrogen chloride and the corresponding acid, a property which is in remarkable contrast to the behavior exhibited by the alkyl chlorides. The reaction demonstrates the ease with which

$$\text{RCOCl} + \text{H}_2\text{O} \rightarrow \text{RCOOH} + \text{HCl}$$
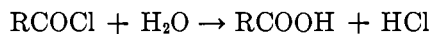
the carbon–chlorine bond in acid chlorides may be broken. The differences in the chemical properties of acid chlorides and alkyl halides are reflected in unique

differences in the physical properties of the carbon–chlorine bond in an alkyl chloride and the carbonyl carbon–chlorine bond in an acid chloride, and are a subject of considerable theoretical interest. A brief discussion of the structure and physical properties of acid chlorides which relate to these phenomena is appropriate here.

The presence of a carbonyl group in an aliphatic acid chloride gives rise to a number of possible resonance structures, each of which may be considered more or less important in its contribution to the resonance state. Structure II represents the type of carbonyl resonance usually postulated for aldehydes. Structures III

$$
\begin{array}{cc}
:\overset{..}{O}:^{\ominus} & :\overset{..}{O}: \\
R:\overset{..}{C}:\overset{..}{Cl}: & R:\overset{..}{C}^{\oplus} \quad :\overset{..}{Cl}:^{\ominus} \\
{}^{\oplus} & \\
II \qquad\qquad \searrow \quad :\overset{..}{O}: \quad \nearrow \qquad III \\
R:\overset{..}{C}:\overset{..}{Cl}: \\
:\overset{..}{O}:^{\ominus} \quad \nearrow \quad I \quad \searrow \quad {}^{\oplus}O: \\
R:\overset{..}{C}::\overset{..}{Cl}^{\oplus} \qquad\qquad R:\overset{..}{C} \quad :\overset{..}{Cl}:^{\ominus} \\
V \qquad\qquad\qquad\qquad IV
\end{array}
$$
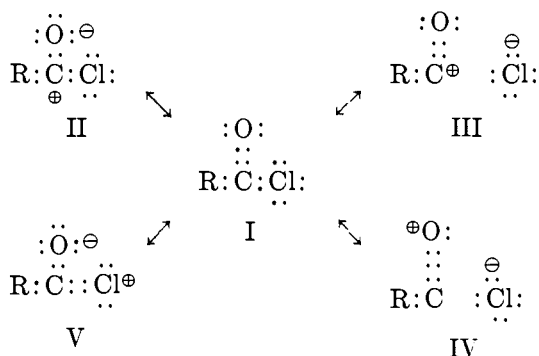
and IV are ionic in character, while structure V embodies a positive chlorine atom doubly bound to carbon. The concept of ionization in aliphatic acid chlorides is not a new one. It has been employed as a means of explaining halogen interchange reactions. Data which have been reported for the bond distances in aliphatic acid chlorides may be interpreted on the basis of these principal resonance structures.

Electron-diffraction measurements (12, 189) with organic halides have indicated that the carbon–chlorine bond in acetyl chloride is some 2 per cent longer than that in methyl chloride, while the carbon–oxygen bond in acetyl chloride is similarly less than that found in acetone, as shown in table 4.

The data in table 4 would seem to indicate that a significant contribution to the resonance state is made by structure IV, in which the carbon–oxygen bond distance is decreased by virtue of triple-bond formation and the carbon–chlorine bond distance is increased by no-bond resonance or ionization. It is generally empirically assumed that in a series of bonds between the same pair of atoms, the short bonds are stronger than the long ones. This theoretical picture agrees, in general, with the observed weakened carbon–chlorine bond in an acid chloride. However, the technique with which the carbon–chlorine bond distance was obtained in acetyl chloride by Allen and Sutton is subject to some question. The possible presence of phosphorus trichloride or acetoxyphosphorus dichloride in the acetyl chloride has not been fully ascertained. The sample measured was merely distilled once from a commercial product and had a boiling-point range of 0.5°. The magnitude of the possible error involved would of course depend upon

the amount of the contaminants present. In the light of the latter objection it would appear desirable to remeasure the bond distance in pure acetyl chloride to check the validity of the reported results.

TABLE 4

Measurements of bond distances in acetyl chloride, methyl chloride, and acetone

	ALLEN AND SUTTON (12)	DORNTE (189)
In acetyl chloride:		
(C—O)	1.17 ± 0.04 Å.	1.14 ± 0.05 Å.
(C—Cl)	1.82 ± 0.02 Å.	1.82 ± 0.1 Å.
$\angle$ O—C—Cl	$122.5 \pm 2.5°$	$125°$
$\angle$ O—C—Cl	$105 \pm 5°$	$110°$
In acetone:		
(C—O)	1.14 Å. (51)	1.19 ± 0.02 Å. (13)
In methyl chloride:		
(C—Cl)	1.779 Å. (51)	1.786 Å. (629)

TABLE 5

Molar refractivities of straight-chain aliphatic acid chlorides

FORMULA	$d_{4°}^{25°}$	$n_D^{25°}$	M_{D1}*	M_{D2}	$+\Delta M_D$
CH_3COCl	1.0982 (720)	1.3878 (401)	16.314	16.861	0.55
CH_3CH_2COCl	1.0508 (720)	1.4057 (401)	20.932	21.624	0.69
$CH_3(CH_2)_2COCl$	1.0154_{20}^{25} (401)	1.4115 (401)	25.550	26.053	0.50_{20}^{25}
$CH_3(CH_2)_3COCl$	1.004_4^{20} (229)	1.4207_D^{20} (229)	30.168	30.548	0.38_4^{20}
$CH_3(CH_2)_4COCl$	0.97042 (630)	1.42424 (630)	34.786	35.411	0.63
$CH_3(CH_2)_5COCl$	0.9565 (647)	1.4279 (647)	39.404	39.96	0.56
$CH_3(CH_2)_6COCl$	0.9446 (647)	1.4321 (647)	44.022	44.67	0.65
$CH_3(CH_2)_7COCl$	0.9378 (173)	1.4350 (647)	48.640	49.16	0.52
$CH_3(CH_2)_8COCl$	0.9293 (647)	1.4380 (647)	53.258	53.87	0.61
$CH_3(CH_2)_9COCl$	0.9245 (647)	1.4416 (647)	57.876	58.55	0.68
$CH_3(CH_2)_{10}COCl$	0.9169 (647)	1.4427 (647)	62.494	63.22	0.73
$CH_3(CH_2)_{11}COCl$	0.9123 (647)	1.4441 (647)	67.112	67.80	0.69
$CH_3(CH_2)_{12}COCl$	0.9078 (647)	1.4460 (647)	71.73	72.50	0.77
$CH_3(CH_2)_{13}COCl$	0.9041 (647)	1.4472 (647)	76.348	77.11	0.76
$CH_3(CH_2)_{14}COCl$	0.9016 (648)	1.4482 (648)	80.966	81.65	0.68
$CH_3(CH_2)_{16}COCl$	0.8969 (648)	1.4510 (648)	90.202	90.94	0.74

* M_{D1} = molar refraction obtained as summation of atomic refractions;

M_{D2} = molar refraction calculated from $d_{4°}^{25°}$ and $n_D^{25°}$ with the Lorentz–Lorenz formula;

$+\Delta M_D$ = positive exaltation of M_{D2} over M_{D1}.

Other physical data reveal the unusual character of the chlorine atom in aliphatic acid chlorides. The molar refractivities of straight-chain aliphatic acid chlorides calculated from the density and refractive indexes with the Lorentz–Lorenz equation as indicated in table 5 are uniformly greater than the values obtained from the summation of the atomic bond refractions using the accepted value of 5.967 for chlorine.

The relative constancy of the positive exaltations indicates that the value of the carbon–chlorine bond refraction in straight-chain aliphatic acid chlorides should be in the region 6.609 to 6.625 and not 5.967, the value obtained from alkyl chlorides.

The phenomenon of exaltation with acid chlorides was first noted by Bruhl for several lower homologs (6.336 as an average of five values varying from 6.321 to 6.600 compared to some chlorides (average 5.967)) and was confirmed by Eisenlohr. It was assumed by Eisenlohr that this exaltation in the acid chlorides was due to some kind of conjugation between the carbonyl group and the chlorine atom, and he excluded this "special" value of chlorine from his table of "normal" atomic refractions. In view of the facts that molar refractivities measured at finite wave lengths are not strictly additive and that the use of finite wave lengths of light in the Lorentz–Lorenz formula involves an obvious deviation from ideality (although it gives a satisfactory close approximation for practical purposes), the true theoretical basis for the observed exaltations is not yet apparent. At this point it may be considered only a further manifestation of the unusual character of the chlorine–carbon bond in acid chlorides.

The relative ease of hydrolysis of aliphatic acid chlorides is apparently related to the acid strengths of the corresponding acids and, indeed, may be correlated with the solubilities of the acids in water. It has long been observed that acetyl chloride is vigorously hydrolyzed by cold water and almost explosively by hot water, but that stearoyl chloride, lighter than water and immiscible with it, is only slowly hydrolyzed. With 10 per cent acetone–water mixture the rate of hydrolysis is increased. The rates of hydrolysis of acetyl and chloroacetyl chlorides have been measured by determination of the rate of diffusion of the reaction products into water from toluene at 25°C. (704). The relation between the reaction velocities of hydrolysis, k_1 and k_2, and the dissociation constants of the corresponding acids, K_1 and K_2, was given by the expression:

$$\frac{k_1}{k_2} = \sqrt{\frac{K_1}{K_2}}$$

A similar agreement was observed (705) for the hydrolysis of thionyl and sulfuryl chlorides (where K_1 and K_2 were the dissociation constants in seconds for sulfurous and sulfuric acids, respectively). Measurements of the velocities of hydrolysis of acetyl and chloroacetyl chlorides at several temperatures (706) have enabled a calculation of the energy of activation and a further deduction that substitution of chlorine in acetyl chloride has no steric effect upon the behavior of the —COCl group. This contention has been seriously criticized on both a theoretical basis (48) and on the basis of the uncertainty involved in the technique of measurement (49), in which, it is held, the process of hydrolysis is accompanied by one of diffusion. In view of this latter valid objection it is probable that the above equation is not strictly applicable and that the deductions of steric hindrance involved may indeed be invalidated.

The ease with which hydrolysis of aliphatic acid chlorides proceeds is further indicated by the observation that acetyl chloride undergoes a hydrolytic ex-

change reaction with solid crystallohydrates, such as those of $CoCl_2$, $BaCl_2$, and $FeCl_2$, and with many sulfates, phosphates, and alums (620).

The rate of hydrolysis of the straight-chain aliphatic acid chlorides is decreased with an increase in the length of the alkyl chain, at least for the lower members. Kinetic measurements with acetyl, propionyl, and butyryl chlorides in toluene at 25°C. and 45°C. (707) and with valeryl and hexanoyl chlorides in several solvents (708) have indicated a simple relationship between the velocity of hydrolysis (k) and the number of carbon atoms (n) for successive homologs as given by the expression:

$$\log \frac{k_2}{k_1} = 0.3 \times (n_2 - n_1)$$

Since a calculation of the activation energies for the lower three chlorides showed that they were almost identical, the differences in the reaction rates were logically ascribed to functional steric hindrance. Branching in the alkyl chain would be expected to decrease the rate of hydrolysis below that for the straight-chain isomer as a result of steric hindrance, although data to support this contention have not been reported.

A comprehensive study of the kinetics of the hydrolysis of octanoyl, decanoyl, lauroyl, myristoyl, palmitoyl, stearoyl, oleoyl, elaidoyl, and linoleoyl chlorides in water at 25°C. (54) by determination of the unchanged acid chloride remaining after shaking for different reaction periods has been extremely revealing. Surprisingly, the acid chlorides of the longer-chain fatty acids, palmitic and stearic, reacted at a more rapid rate than the acid chlorides of the shorter-chain fatty acids, and lauroyl chloride appeared to resist hydrolysis more than the acid chlorides of the lower-molecular-weight acids, octanoic and decanoic, or than those of the higher-molecular-weight acids, myristic to stearic. Furthermore, the acid chlorides of the unsaturated acids oleic, elaidic, and linoleic were hydrolyzed less rapidly than stearoyl chloride, with elaidoyl and myristoyl chlorides exhibiting the same relative rates of hydrolysis during the first 2 hr. Several hypotheses have been advanced to explain the differences in the rates of hydrolysis between the C_8–C_{12} and the C_{12}–C_{18} saturated acid chlorides and the observed apparent equilibrium reached in the case of the shorter-chain compounds. The decrease in the reaction rates of the fatty acid chlorides from C_8 to C_{12} may be attributed to decreasing activity of the acid chlorides with increasing chain length. The increasing reaction rates of the acid chlorides from C_{12} to C_{18} is probably due to the increase in the melting point and the decrease in the solubility of the fatty acids, liberated by hydrolysis, in the unhydrolyzed fatty acid chloride. This would result in a more complete withdrawal of the reaction products from the interface at which the reaction occurs. The fact that the hydrolysis of the shorter-chain compounds reached an apparent equilibrium before the acid chloride was completely hydrolyzed indicates the probable formation of a monomolecular layer of free fatty acid at the interface which inhibits contact between the unhydrolyzed acid chloride and water. Further experimental data would be required to substantiate these hypotheses. No marked differences in the velocities of hydrolysis have been observed for ordinary and heavy water,

using a unimolecular film of palmitoyl chloride in the method of surface potentials (326). In ordinary water at a pH of 7.4 this hydrolysis was complete in 20 min. at 20°C.

The hydrolysis of acid chlorides proceeds in an exothermic fashion. From measurements of the heat of hydrolysis of acetyl halides (70, 129) the heats of formation of the liquid forms have been calculated. These values, taken in conjunction with the probable value of the heat of formation of the acetyl radical, have given values for the dissociation energies of the carbon–halogen bond in the acetyl halides. The results are tabulated in table 6. The study has been ex-

TABLE 6

Some thermodynamic constants for acetyl halides (129)

$$D(CH_3COX) = Q_f(CH_3COX) - Q_f(CH_3CO-) - Q_f(X)$$
$$CH_3COX(liq) + H_2O(aq) = CH_3COOH(aq) + HX(liq) + Q$$
$$Q_f(CH_3COX, liq) = Q_f(CH_3COOH, aq) + Q_f(HX, aq) - Q_f(H_2O, liq) - Q$$
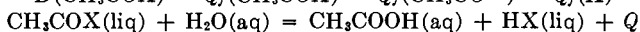
CH₃COX X =	HEAT OF FORMATION $Q_f(CH_3COX, liq.)$	HEAT OF FORMATION (LANDOLT-BÖRNSTEIN) $Q_f(CH_3COX, gas)$	HEAT OF HYDROLYSIS	BOND DISSOCIATION ENERGY $D(CH_3COX)$
	kcal./mole	*kcal./mole*	*kcal./mole*	*kcal./mole*
Cl.............	65.8	58.94	22.09	76.7
Br.............	53.9	46.6	23.03	62.0
I.............	39.95	31.8	21.59	46.0
F.............	110.6	104.6	42.8	110

TABLE 7

Heats of hydrolysis and formation of chloroacetyl chlorides (557)

ACID CHLORIDE	HEAT OF HYDROLYSIS	HEAT OF FORMATION	
	$Q(aq.), (-\Delta H)$	$Q_f(liquid)$	$Q_f(gas)$
	kcal./mole	*kcal./mole*	*kcal./mole*
CH₃COCl..........................	22.05	66.2	59.4
CH₂ClCOCl.......................	22.35	70.1	62.1
CHCl₂COCl.......................	25.73	68.7	60.7
CCl₃COCl.........................	28.12	68.8	60.5

* The heat of hydrolysis for higher homologous acid chlorides has apparently not been measured.

tended to the hydrolysis of the chloro-substituted acetyl chlorides in aqueous acetone (557) and, with corrections applied for the differences in the heats of solution of the corresponding chloro acids in aqueous acetone and in water, has given the values for pure water indicated in table 7.

The exact mechanism involved in the hydrolysis of aliphatic acid chlorides is obscure. That the mechanism is different from that of esters and amides is evident from the fact that the hydrolysis is not catalyzed by hydrogen ions (326, 706, 707) but is catalyzed by hydroxyl ions (73, 526). In most respects this mechanism must be similar to that involved in the hydrolysis of acetic, propionic, and butyric anhydrides, for here too hydrogen ions do not catalyze the hydrolysis (703), the reaction is apparently of the first order (255, 432) (although it has

been held to be truly of the second order (255)), and there is no change in the order of the reaction in the presence of pyridine (432). In the aromatic series the kinetics of the hydrolysis of substituted benzoyl chlorides (64) have been shown to follow the first-order reaction law, although it must be borne in mind that if the hydrolysis is carried out in such a manner that the water in such a bimolecular process is present in excess, the reaction becomes kinetically of the first order. Indeed, the hydrolysis of benzoyl chloride has been referred to as a nucleophilic attack by hydroxyl ion on carbon (S_N2) (570). Recent kinetic studies with benzoyl chloride indicate that it is hydrolyzed by an S_N1 mechanism in highly aqueous solvents (325). It was found that the ratio of the bimolecular reaction velocity constant with hydroxyl ions to the velocity constant of the pseudo-unimolecular reaction for the neutral hydrolysis is of the same order as for the hydrolysis of benzyl chloride. In addition, the activation energies for the neutral hydrolysis of benzoyl chloride and several para-substituted benzoyl chlorides were found to vary little with the nature of the substituent. This result contrasts with the alcoholysis in a solvent of low ionization power. These results with benzoyl chloride have been interpreted in terms of a dual mechanism involving bimolecular substitution and unimolecular ionization, a conclusion which is supported by alcoholysis studies. Further, measurements of the hydrolysis of benzoyl chloride in aqueous acetone containing from 5 to 75 per cent by volume of water (20) reveal that with increasing water content in the solvent the activation energy increases, an indication of a change in mechanism. This is supported by a positive temperature coefficient of activation energy and by the increasing effect of water on the rate in highly aqueous solutions. Under certain conditions the hydrolysis of an acid chloride may conform to a termolecular process. When the solvent is of very low ionization power compared to water, then apparently solvation of the transition state is involved. Acetyl chloride exhibits third-order kinetics upon hydrolysis in dioxane (20). In view of what has been said for aromatic acid chlorides, it seems probable that the actual mechanism for hydrolysis of an aliphatic acid chloride involves an S_N1 attack, at least in water, the rate-controlling step of which is the formation of the acyl ion, as in the following sequence:

$$
RCOCl \xrightarrow{\text{slow}} \begin{bmatrix} R\!-\!\overset{\oplus}{\underset{\underset{\displaystyle\updownarrow}{\overset{\|}{O}}}{C}}\ \overset{\ominus}{Cl} \\[2pt] R\!-\!\underset{\overset{\|}{O}^{\oplus}}{C}\ \overset{\ominus}{Cl} \end{bmatrix} + \overset{\displaystyle H}{\underset{}{O}}\!-\!H \xrightarrow{\text{fast}}
$$

$$
\underset{\overset{\|}{O}}{RC}\!-\!\overset{\oplus}{O}\overset{\diagup H}{\diagdown H} + \overset{\ominus}{Cl} \rightarrow \underset{\overset{\|}{O}}{RCOH} + HCl
$$
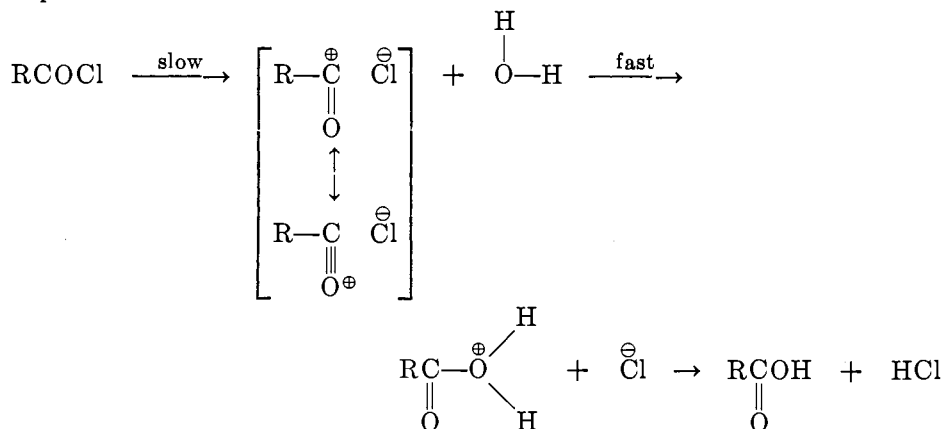
In anhydrous organic solvents the mechanism may be largely of the S_N2 type.

The relative degree of hydrolysis of aliphatic acid chlorides with aqueous alkaline solutions of alcohols or amines, as exemplified in the so-called Schotten–Baumann reaction, is discussed in Section VII,A.

There is little or no synthetic value for the hydrolysis of acid chlorides, since these compounds are almost exclusively prepared from the acids. In certain instances some utility may be achieved in the preparation of pure acids from a mixture of acids. The acid mixture is converted to acid chlorides with a suitable inorganic halide, the acid chlorides fractionally distilled, and the fractions hydrolyzed to afford the pure acids. The boiling points of the first ten straight-chain acid chlorides average 53.7° less than those of the corresponding acids. This is also the average value for the depression in the boiling points of the methyl esters, the derivatives commonly employed for separations of this sort. For the separation of mixtures of branched-chain acids which are difficult to esterify, the use of fractional distillation of acid chlorides and subsequent hydrolysis may well be considered. Acetyl chloride, further, finds some use in the volumetric determination of water in organic liquids (386, 639) and in organic reactions requiring the removal of water, such as condensations or ring closures.

From a practical point of view the hydrolysis of aliphatic acid chlorides has been one of the chief deterrents to the large-scale industrial use of these compounds as chemical intermediates. Problems due to decomposition during storage, corrosion (421), and improper handling in unsuitable materials of construction during chemical operations, however, do not appear to be insurmountable. Our own experience indicates that pure samples of higher aliphatic acid chlorides may be stored in glass under a dry nitrogen atmosphere for years without decomposition. Distillation under reduced pressure is satisfactory when moisture has been excluded. When certain fundamental conditions have been adhered to in the storage and handling of aliphatic acid chlorides, it appears that the objections occasioned by hydrolysis may be curtailed.

VI. Reactions of Aliphatic Acid Chlorides with Ammonia, Hydroxylamine, and Hydrazine

A. REACTION WITH AMMONIA

The reaction of aliphatic acid chlorides with ammonia leads to amides or to nitriles depending upon the temperature of the reaction.

1. At low temperatures

The rapid exothermic reaction of an aliphatic acid chloride with ammonia to produce an amide (ammonolysis) is among the oldest known organic chemical reactions. Apparently it was first applied to butyryl, valeryl, and octanoyl chlorides in 1869 (300) by modifying an older technique developed by Wöhler and Liebig in 1832 for benzoyl chloride (750), and thereafter the reaction was

$$RCOCl + 2NH_3 \rightarrow RCONH_2 + NH_4Cl$$
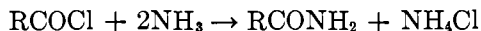
extended to other saturated and unsaturated homologs (28, 411) before the turn of the twentieth century. The reaction occurs readily in the gaseous phase, in liquid ammonia at very low temperatures, in organic solvents with dry gaseous ammonia, and in aqueous ammonia solutions with almost complete exclusion of the competing reaction of hydrolysis. All the lower aliphatic acid chlorides form amides by merely standing in aqueous ammonia solutions, the reactivity apparently decreasing as the homologous series is ascended. The preparation of amides from acids by treatment with thionyl chloride or phosphorus pentachloride to form acid chlorides and reaction of the latter with ammonia represents a simple and widely applicable method for the preparation of amides. Table 8 summarizes the amides which have been prepared directly from or through the corresponding acid chlorides by a variety of methods.

The modification of the technique of amide preparation in method f (table 8) requires further comment. This involves heating the acid with benzoyl chloride for 2–3 hr. and adding to the mixture an aqueous solution of sodium and ammonium hydroxides. Its success depends upon a shift in the equilibrium which obtains when an acid, $RCOOH$, and the acid chloride, C_6H_5COCl, are mixed together, such that halogen–hydroxyl interchange occurs to give $RCOCl$ and C_6H_5COOH.

$$2C_6H_5COCl + 2RCOOH \rightleftarrows 2HCl + 2C_6H_5COOCOR \rightleftarrows$$

$$(C_6H_5CO)_2O + (RCO)_2O + 2HCl \rightleftarrows 2C_6H_5COOH + 2RCOCl$$
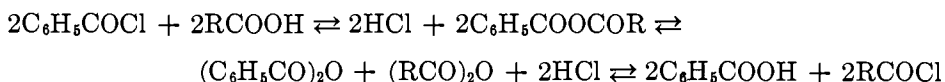
The theory underlying this interchange is discussed in detail in Section X,C,1. Ammonolysis of the mixture occurs almost exclusively rather than hydrolysis, even in the presence of considerable concentration of hydroxyl ion, in accord with the principle of the Schotten–Baumann reaction (see Section VII,A). Evidently, sodium hydroxide performs the function of combining with the hydrogen chloride liberated by the reaction. The modified technique fails, however, in the preparation of diamides from diacid chlorides (530).

Although conclusive data to support a mechanism for the ammonolysis of aliphatic acid chlorides are lacking, the course of the reaction can be assumed to be, in agreement with that of the hydrolysis, a slow rate-determining ionization followed by a rapid S_N1 reaction with ammonia.
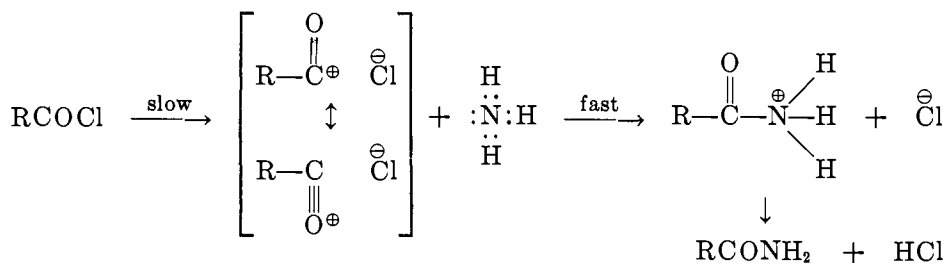
The further action of a second molecule of ammonia upon the amide to yield a substituted amide is not observed under usual conditions.

TABLE 8

Formation of amides by the ammonolysis of aliphatic acid chlorides

ACID CHLORIDE	METHOD*	MELTING POINT OF AMIDE	YIELD	REFERENCE
		Saturated acid chlorides		
		°C.	per cent	
Acetyl	a	81.5	70–88	(28)
	b			(260)
Propionyl	c	79–81	46	(28)
Butyryl	a			(300)
	c	212–216 (b.p.)	47	(28)
Isobutyryl	a	127–129	79–83	(388)
	d	215–220 (b.p.)	44	(28)
C₅ *chlorides:*				
Valeryl	a	104–105		(608)
	h	106		(574)
Isovaleryl	d	127–129	60	(28)
2-Methylbutyryl	a	112		(608)
Trimethylacetyl	a			(608)
	e (ether)†			(608)
C₆ *chlorides:*				
Hexanoyl	h	101		(574)
	e (ether)	98		(55)
2-Methylvaleryl	e (ether)	79		(318)
(+)-2-Methylvaleryl	a	78		(439)
3-Methylvaleryl	e (ether)	124.9		(318)
4-Methylvaleryl	e (ether)	118.8		(318)
	c		62	(28)
2,2-Dimethylbutyryl	a	100 (subl.)		?
	e (ether)	99.8		(318)
2,3-Dimethylbutyryl	e (ether)	130.9		(318)
3,3-Dimethylbutyryl	a	140–141	Good	(499)
	e (ether)	132.0		(318)
2-Ethylbutyryl	a	112	82	(512)
	e (ether)	111.8		(318)
C₇ *chlorides:*				
Heptanoyl	c	93–94	80	(28)
	h	96		(574)
2-Methylhexanoyl	e (benzene)	70–72.5		(566)
(+)-2-Methylhexanoyl	a	66		(439)
2-Ethylvaleryl	e (benzene)	102–103.5		(566)
5-Methylhexanoyl	a	102–103		(747)
3-Ethylvaleryl	a	127.5		(201)
2,4-Dimethylvaleryl	a	90		(122)
2-Ethyl-3-methylbutyryl	a	134–134.5		(164)
2,2-Dimethylvaleryl	e (ether)	95–96		(448)
2,2,3-Trimethylbutyryl	e (benzene)?	129		(448)

TABLE 8—*Continued*

ACID CHLORIDE	METHOD*	MELTING POINT OF AMIDE	YIELD	REFERENCE
Saturated acid chlorides—*Continued*				
		°C.	per cent	
C₈ *chlorides:*				
Octanoyl......................	a			(300)
	c	97–98	100	(28)
2-Ethylhexanoyl................	c	101–102		(564)
2,3-Dimethylhexanoyl..........	a	121		(406)
2,5-Dimethylhexanoyl..........	a?	99–100		(44)
	a	103		(644)
2,2,3,3-Tetramethylbutyryl....	e (ether)	200 (subl.)		(449)
2,2,3-Trimethylvaleryl.........	e (ligroin)	71		(430)
2,2-Dimethylhexanoyl..........	e (ether)	92		(430)
2-Ethyl-4-methylvaleryl.........	a	89		(687)
C₉ *chlorides:*				
Nonanoyl......................	h	99		(574)
2-Propylhexanoyl..............	a	125		(406)
	a	122–123		(644)
2-Isopropylhexanoyl............	a	93		(364)
2,2-Dimethylheptanoyl.........	e (ether)	101–102		(430)
2-Ethyl-5-methylhexanoyl......	a	106–108		(687)
2-Propyl-4-methylvaleryl.......	a	121		(644)
C₁₀ *chlorides:*				
Decanoyl......................	a			(630)
	h	99		(574)
5-Methyl-2-propylhexanoyl.....	a	117–118		(644)
	a	106–107		(687)
Diisobutylacetyl................	e (ether)	74–75		(232)
(+)-2-Methylnonanoyl..........	a	78		(439)
C₁₁ *chlorides:*				
Undecanoyl....................	h	99		(574)
4,8-Dimethylnonanoyl..........	a (aqueous alcohol)	80–81		(294)
C₁₂ *chlorides:*				
Lauroyl.......................	c	102	96–98	(411)
	h	100		(574)
2-Isopentyl-5-methylhexanoyl...	a	115		(218)
C₁₃ *chlorides*				
Tridecanoyl...................	h	100		(574)
(−)-2-Methyllauroyl............	a	77		(439)
C₁₄ *and higher chlorides:*				
Myristoyl.....................	a	105–107		(91)
	c	104–105	96–98	(411)
	h	103		(574)

TABLE 8—*Continued*

ACID CHLORIDE	METHOD*	MELTING POINT OF AMIDE	YIELD	REFERENCE
		Saturated acid chlorides—*Continued*		
		°C.	*per cent*	
Pentadecanoyl..................	a	102.5		(433)
Palmitoyl......................	a	105.3		(279)
	c	106–107	96–98	(411)
	h	106		(574)
Heptadecanoyl................	a	103		(445)
Stearoyl......................	a	108.4		(279)
	c		87	(28)
	c	108.5–109		(411)
	f	106–107		(530)
	h	109		(574)
Heneicosanoyl.................	e (ether)†	110		(435)
	a	108		(209)
Docosanoyl....................	c	111		(209)
	a	111		(209)
Hexacosanoyl.................	a	106		(470)
	a	109		(446)
Hentriacontanoyl..............	a	116		(470)
		Unsaturated acid chlorides		
Acrylyl.........................	c (benzene)	84–85	80	(498)
Crotonyl.......................	a	159.5–160	(Good)	(672, 756)
Ethacrylyl......................	e (ether)	83.5		(84)
2-Pentenoyl....................	e (ether)	148		(38)
3-Pentenoyl....................	e (ether)		69–70	(38)
3,3-Dimethylacrylyl............	g	65–66	60	(38)
	e	108?		(548)
C₆ *chlorides:*				
3-Hexenoyl...................	e (ether)	60	(Good)	(38)
	g			
2-Methyl-3-pentenoyl..........	e (benzene)	74		(256)
3-Methyl-3-pentenoyl..........	e (ether)	123–124		(404)
2-Methyl-2-pentenoyl..........	e (benzene)	80		(256)
4-Methyl-2-pentenoyl..........	e (ether)	82–86	62	(38)
2-Ethylcrotonyl...............	e (ether)	114–115		(38)
2,3-Dimethylcrotonyl..........	e (ether)	127–128	55	(38)
3-Methyl-2-pentenoyl..........	a	92–93		(404)
Vinyldimethylacetyl...........	a	93		(162)
C₇ *chlorides:*				
5-Methyl-3-hexenoyl...........	d	68–70		(722)
2,2-Dimethyl-3-pentenoyl.......	e (ether)	88		(162)
3,3-Dimethyl-4-pentenoyl.......	d	98		(89)
2,2,3-Trimethyl-3-butenoyl.....	e (ether)	107–108		(162)
3-Ethyl-2-pentenoyl............	a	89		(404)
3-Ethyl-3-pentenoyl............	e (ether)	113–114		(404)

TABLE 8—*Continued*

ACID CHLORIDE	METHOD*	MELTING POINT OF AMIDE	YIELD	REFERENCE
		°C.	per cent	

Unsaturated acid chlorides—*Continued*

ACID CHLORIDE	METHOD*	MELTING POINT OF AMIDE	YIELD	REFERENCE
C_8 *chlorides:*				
3-Methyl-2,4-hexadienoyl.......	a	147–148		(123)
C_9 *chlorides:*				
2-Nonenoyl....................	a	126–127		(287)
3-Propyl-2-hexenoyl............	a	72		(405)
C_{11} *chlorides:*				
3-Propyl-3-hexenoyl............	a	120–121		(405)
9-Undecenoyl..................	?	77–78.5		(360)
10-Undecenoyl.................	d	84.5–85.5	64	(28)
$CH_3C_9H_{16}COCl$ (?).............	a	78		(203, 686)
C_{14} *chlorides:*				
2-Methyl-12-tridecenoyl........	h?			(218)
C_{16} *chlorides:*				
2-Hexadecenoyl................	a			(550)
C_{18} *chlorides:*				
Oleoyl........................	c	75–76	82	(28)
C_{22} *chlorides:*				
13-Docosenoyl.................	a	94		(410, 568)
C_7 *chlorides:*				
2,4-Hexadienoyl...............	g			(314)
C_8 *chlorides:*				
2-Octynoyl....................	d	91–92		(499)
C_{17} *chlorides:*				
2-Heptadecynoyl...............	c	76–77		(408)
C_{22} *chlorides:*				
13-Docosynoyl.................	a	90		(280)

Polyfunctional and other types of acid chlorides

ACID CHLORIDE	METHOD*	MELTING POINT OF AMIDE	YIELD	REFERENCE
Methylcarboxyacetyl............	e (benzene)	68–69		(80)
Dimethylmalonyl................	a	261	71	(210)
Ethylmethylmalonyl.............	a (20°C.)		90	(102)
	a (50°C.)		50	(102)

TABLE 8—*Concluded*

ACID CHLORIDE	METHOD*	MELTING POINT OF AMIDE	YIELD	REFERENCE

Polyfunctional and other types of acid chlorides—*Continued*

ACID CHLORIDE	METHOD*	°C.	per cent	REFERENCE
Succinyl	a	Imide or amide		(34)
	a	260	5	(496)
	c	216–217	56	(28)
3-Methyladipyl	a	191		(621)
2,2-Dimethylglutaryl	a	169–172		(79)
Diethylmalonyl	a (20°C.)		90	(102)
	a (50°C.)		50	(102)
	g	224	55	(210)
Dipropylmalonyl	a	214	67	(210)
2-Isopropyl-5-methyladipyl	e (ether)†	90		(473)
Adipyl	a			(637)
	a		90	(110)
Methylsuccinyl	e (benzene)	225		(496)
Ethylfumaryl	a	203–204		(469)
Isopropylfumaryl	a	240 (d.)		(469)
Propylfumaryl	a	214–215		(469)
Isobutylfumaryl	a	250–252 (d.)		(469)
2,2-Dimethyladipyl	a	169–172		(79)
Butylmalonyl	e (ether)	195–196		(233)
3-Isopropyladipyl	a	169.5		(111)
4,4-Dimethylpimalyl	a	176		(403)
Dibutylmalonyl	e (ether)	280–281		(233)
1,9-Nonanedicarbonyl	h	173		(47)
1,10-Decanedicarbonyl	h	189		(47)
1-Octyl-1,8-octanedicarbonyl	e (ether)	167–168		(434)
Sebacyl	d	208	63	(28)
9-Carbomethoxynonanoyl	a	72–74	93–95	(75)
Carbethoxyethylacetyl	e (benzene)	90		(80)
1,11-Undecanedicarbonyl	d	171		(209)
9-Carbethoxynonanoyl	a	126.5		(214)
12-Carbethoxydodecanoyl	a	91–92		(596)
2-Methyl-1,13-tridecanedicarbonyl	a	145–150		(596)
2-Methyl-1,10-decanedicarbonyl	a	86–86.5		(149)

* a = RCOCl in NH₃(aq);
  b = RCOCl in NH₃(l);
  c = RCOOH + PCl₅ + NH₃(aq);
  d = RCOOH + PCl₃ + NH₃(aq);
  e = RCOCl in organic solvent + NH₃(g);
  f = RCOOH + C₆H₅COCl + NH₃(aq) + NaOH;
  g = RCOCl + (NH₄)₂CO₃(aq);
  h = RCOOH + SOCl₂ + NH₃(aq).
† Ether = ethyl ether.

The formation of amides from acid chlorides finds some utility in the characterization of both acids and acid chlorides (312, 626, 716). Although the amides melt uniformly higher than the acids from which they are derived, the relatively small differences in melting points between successive homologs seriously limit the applicability of the reaction for this purpose.

The aliphatic amides possess properties which render them useful for a great variety of purposes (560). They have been used as waterproofing agents, protective coatings, paper sizes, plasticizers, lubricant modifiers, and also as chemical intermediates for the preparation of other fatty acid derivatives such as the aliphatic nitriles. Industrially, the preparation of amides from fatty acid esters (327, 580) is more important than from the acid chlorides (52). In the ammonolysis of a monoester or a triglyceride, however, the corresponding alcohol is obtained besides the amide, and if this is not removed from the mixture the equilib-

$$RCOOR' + NH_3 \rightarrow RCONH_2 + R'OH$$
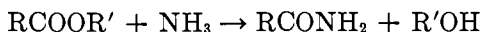
rium established enables only partial conversion from ester to amide. Furthermore, while the reaction of an aliphatic acid chloride proceeds to completion quickly in either aqueous ammoniacal solutions or liquid ammonia (50), ester ammonolysis in liquid ammonia does not occur at all except in the presence of a suitable catalyst such as ammonium chloride (33, 90, 202, 253, 544, 635) and is not nearly quantitative. Although the older preparative method of amides, involving the pyrolysis of ammonium salts of acids (315), is an economical one,

$$RCOONH_4 \rightarrow RCONH_2 + H_2O$$

the ammonolysis of an acid chloride is cleaner and proceeds with better yield. On the other hand, the preparation involving ammonolysis of a carboxylic acid anhydride suffers in that an amide is obtained which is contaminated with the

$$(RCO)_2O + NH_3 \rightarrow RCONH_2 + RCOOH$$

corresponding acid or its ammonium salt.

The formation of amides from aliphatic acid chlorides has also been applied in an analytical method for the determination of free fatty acid in crude fatty acid chloride mixtures (1).

2. At high temperatures

When the vapors of the lower aliphatic acid chlorides and gaseous ammonia are passed over alumina at a temperature of 490–500°C., nitriles are produced (459). The reaction undoubtedly involves the intermediate formation of the amide, which is then dehydrated at the elevated temperature, and takes the overall course of the equation:

$$RCOCl + NH_3 \rightarrow RCN + H_2O + HCl$$

Neither the course nor the mechanism of the dehydration of the intermediate amide is thoroughly understood. Such a dehydration apparently occurs readily in the presence of other dehydrating agents, in accord with the observation that

ammonolysis of acetic, propionic, and hexanoic acids at temperatures of 170–190°C. yields small amounts of nitriles, the amounts being increased in the presence of zinc chloride (491). It is a reversible process, for the lower nitriles are not only hydrolyzed back to amides with aqueous or alcoholic alkali hydroxides (2, 223) and with aqueous hydrochloric acid (416), but also catalytically at 420°C. with steam (460). Further, the course of the dehydration is not alone represented by $RCONH_2 \rightarrow RCN + H_2O$, as has been generally assumed as a result of studies of this dehydration under distillation (750), with phosphorus pentasulfide (299), with phosphorus pentoxide (411), and catalytically over aluminum oxide at 425°C. (98). It appears instead that in the decomposition 1 mole of the amide yields 1 mole of water, which can hydrolyze a second mole of amide to the acid, a contention which is supported by the fact that the distillation of stearamide has given vapors at 340°C. from which almost equal quanti-

$$2RCONH_2 \rightarrow RCOOH + RCN + NH_3$$

ties of stearonitrile and stearic acid were obtained (562). Any acid produced as a result of the above reaction would normally be expected to regenerate nitrile eventually by further reaction with ammonia. However, transformations involving the intermediate formation of ammonium salts appear unlikely, as these are never formed even at temperatures as low as 400°C.
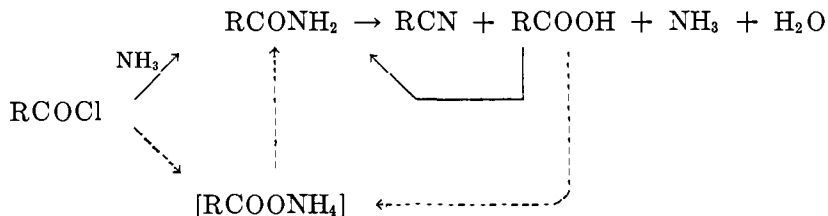
These facts indicate that satisfactory yields in the overall conversion can be achieved only by continuously removing water as it is formed. Only propionyl, isobutyryl, and isovaleryl chlorides have been reported converted to nitriles by this method (459). The overall yields achieved compare very favorably with synthetic routes involving dehydration of amides with phosphorus pentoxide (411), with phosphorus pentasulfide (299), with carbonyl chloride, catalytically (97, 98), or by heating (750).

B. REACTION WITH HYDROXYLAMINE AND HYDRAZINE

Reactions of aliphatic acid chlorides with inorganically substituted ammonias, such as hydrazine and hydroxylamine, do not appear to have received much attention. Monohydroxamic acids have been prepared by the reaction of aromatic, aromatic-aliphatic, and heterocyclic acid chlorides with hydroxylamine in both aqueous alkaline solution and organic solvents (97, 368, 369, 371, 451).
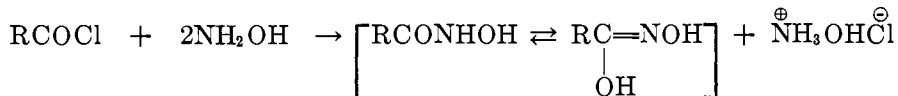
These acylations may proceed further to yield diacyl- or triacylhydroxyl-amines. The former (455) are classified as "dihydroxamic acids," RCO—NH—OCOR (317, 370, 373, 452, 454, 571), and the latter (451) as "trihydroxamic acids." When three different acyl radicals are involved, different trihydroxamic acids are formed (285) depending on the order of their introduction; hence there is evidence for the structures (RCO)$_2$N—O—COR and *syn* or *anti* forms of RCOOCR=NOCOR.

Dihydroxamic acids usually have been prepared in the past for the purpose of studying the Lossen rearrangement. Since the second acyl group to be introduced is the one lost in this process, it is usually acetyl or benzoyl (for convenience). Benzoyl is conventionally introduced by means of benzoyl chloride, and acetyl by means of acetic anhydride. Both of these reagents may be used in the presence of water in the Schotten–Baumann procedure. Acetyl chloride, on the other hand, reacts so readily with water that its use is avoided ordinarily; but van Raalte (559) has reported its use with a suspension of barium hydroxamate in benzene:

$$(C_6H_5CONHO)_2Ba + 2CH_3COCl \rightarrow 2C_6H_5CONHOCOCH_3 + BaCl_2$$

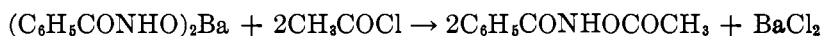The reaction was rapid. van Raalte (558) made the same compound by the action of acetyl chloride on sodium *aci*-phenylnitromethane, C$_6$H$_5$CH=N(=O)ONa, thus extending the reaction of *aci*-nitro salts and benzoyl chloride which was studied by L. W. Jones (367) and in similar cases by others (316, 398, 505, 558, 745).

Two homologs of acetyl chloride have been converted to hydroxamic acids by reaction with hydroxylamine: isobutyryl chloride (372) in benzene solution and diisobutylacetyl chloride (233) in the presence of zinc oxide. Zinc oxide is a base which permits the use of only 1 mole of hydroxylamine; otherwise 2 moles would be required. This is not unlike the Schotten–Baumann reaction.

As mentioned above, acetyl chloride is avoided in aqueous acetylations. It seems reasonable to believe that the higher and relatively insoluble acyl chlorides could be used effectively with aqueous hydroxylamine or hydroxamic acids in the Schotten–Baumann procedure. Examples are the formation of diphenylaceto-hydroxamic acid from diphenylacetyl chloride (368), triphenylacetohydroxamic acid from triphenylacetyl chloride (368), or diphenylcarbamohydroxamic acid from diphenylcarbamyl chloride, (C$_6$H$_5$)$_2$NCOCl (329). The last two reactions were performed in benzene solution with an excess of hydroxylamine to serve as the base, but the first made use of aqueous sodium carbonate as the base. The reaction of a mixture of stearo- and palmitohydroxamic acids with chloroacetyl chloride in dioxane to give a product mixture useful as a textile assistant has been patented (642):

$$RCONHOH + CH_2ClCOCl \rightarrow RCONHOCOCH_2Cl$$

Phosgene is another acyl chloride which has been allowed to react with hydroxylamine, in ice-cold aqueous solution (286). The unstable product was regarded as hydroxyformohydroxamic acid, HOCONHOH.

Ethyl chloroformate, C_2H_5OCOCl, has been used with hydroxylamine to yield N-hydroxyurethan (285) and with N-phenylhydroxylamine to yield N-phenyl-N-hydroxyurethan (41).

Hydroximyl chlorides, $RCCl\!\!=\!\!NOH$, also may be regarded as acyl chlorides. Reaction with amines bears out this viewpoint (333). Such compounds are never prepared from acyl chlorides and hydroxylamine, however. Instead, they arise from the chlorination of aldoximes (546, 744) or by reaction between ω-nitrostyrene, benzene, and aluminum chloride (333).

The reaction of aliphatic acid chlorides with hydrazine or hydrazine hydrate to produce aliphatic hydrazides does not appear to have been extensively in-

$$RCOCl + 2NH_2NH_2 \rightarrow RCONHNH_2 + N_2H_5Cl$$
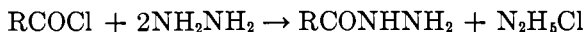
vestigated, the hydrazides having been reported almost exclusively as products of the reaction of hydrazine and esters (199, 200).

$$RCOOR' + NH_2NH_2 \rightarrow RCONHNH_2 + R'OH$$
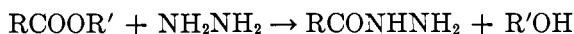
Apparently, dibromofumaryl chloride is the only aliphatic acid chloride to have been studied in this type of reaction. In ethereal solution the dihydrazide of dibromofumaric acid, $H_2NNHCOCBr\!\!=\!\!CBrCONHNH_2$, was obtained (588).

The aliphatic hydrazides have attracted but little attention in commercial applications. Stearic hydrazide has been treated first with glycidol and subsequently with ethylene oxide to give surface-active agents (262).

$$C_{17}H_{35}CONHNH_2 \quad + \quad CH_2\!\!-\!\!-\!\!-\!\!CHCH_2OH \quad \rightarrow$$

$$\underset{O}{\diagdown\diagup}$$

$$\underset{CH_2OH}{\overset{CH_2OH}{C_{17}H_{35}CONHNHCH}} \quad \xrightarrow{2nC_2H_4O} \quad \underset{CH_2O(C_2H_4O)_nH}{\overset{CH_2O(C_2H_4O)_nH}{C_{17}H_{35}CONHNHCH}}$$
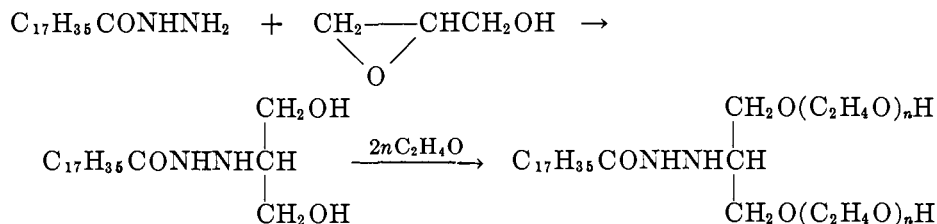
Two examples involving the use of aliphatic acid chlorides in the formation of diacylated hydrazines from hydrazine hydrate have been reported.

$$2RCOCl + 3NH_2NH_2\cdot H_2O \rightarrow RCONHNHCOR + 2N_2H_5Cl + 3H_2O$$

Trimethylacetyl chloride has given 1,2-bis(trimethylacetyl)hydrazine (746), and tiglyl chloride has given 1,2-ditiglylhydrazine (231). The Schotten–Baumann dibenzoylation of hydrazine sulfate has been reported (290).

VII. Reaction of Aliphatic Acid Chlorides with Amines, Substituted Amines, and Related Compounds

The acylation of primary and secondary amines, the formation of addition compounds with tertiary amines, and other reactions with tertiary amines and with imines are reactions of aliphatic acid chlorides which are not only the most numerous as a class but are of the utmost importance technically. Approximately 30 per cent of the literature concerned with aliphatic acid chlorides involves

reactions with these types of compounds under various conditions for the preparation of a large number of useful products.

A. REACTION WITH PRIMARY AMINES

The acylation of primary amines with aliphatic acid chlorides is, in general, a rapid exothermic reaction which proceeds well in organic solvents, in the liquid phase, in aqueous alkaline solutions (for the higher homologous members), and even, for isolated cases, in the gaseous phase.

$$RCOCl + 2R'NH_2 \rightarrow RCONHR' + R'NH_3Cl$$
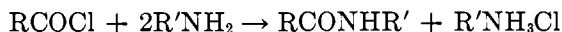
The initial mole of amine reacts to evolve hydrogen chloride, which if not removed combines with a second mole of amine to effectively reduce by one-half the amount of amine converted to a substituted amide. Two moles are always consumed unless some other base is available to accept the hydrogen chloride which must be detached. When the reaction is performed in benzene or ether it is the salt, RNH_3Cl, that precipitates, and the amide, $RCONHR$, is in the filtrate. In water perhaps the opposite situation is encountered. In order to conserve amine the reaction is usually run in the presence of a hydrogen chloride acceptor, a suitable base which reacts preferentially with hydrogen chloride and much less rapidly, if at all, with the aliphatic acid chloride than does the amine. The general conditions which are necessary to achieve this can be represented by expressions 1 and 2.

$$RCOCl + R'NH_2 \xrightarrow{k_1} RCONHR' + HCl \qquad (I)$$

$$:B + HCl \xrightarrow{k_2} H—B + :Cl \qquad (II)$$

$$R'NH_2 + HCl \xrightarrow{k_3} R'NH_2HCl \qquad (III)$$

$$RCOCl + :B \xrightarrow{k_4} RCOB + :Cl \qquad (IV)$$

$$(1) \quad k_2 > k_3 \quad (2) \quad k_4 \ll k_1; \text{ preferably } k_4 = 0$$
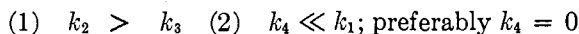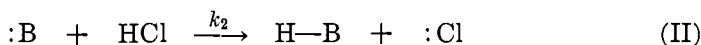
Condition 1 can usually be maintained by employing as a hydrogen chloride acceptor a base which is stronger in the usual sense than the base $R'NH_2$. This effectively eliminates reaction III from consideration. Thus, the acylation of an equimolar mixture of two amines usually gives the substituted amide of the weaker amine and the hydrochloride of the stronger in many solvents, as indicated in table 9 for two aliphatic acid chlorides and benzoyl chloride. Note that in certain instances this phenomenon is reversed. With ethylamine–ammonia, aniline–o-toluidine, and aniline–p-phenetidine mixtures the stronger amine is acylated. Apparently the selectivity of acylation in a mixture of bases is not wholly dependent upon the relative base strengths in water. In the case with o-toluidine steric hindrance or the ortho effect may be assumed to play a role.

The second condition cannot always be achieved with aliphatic acid chlorides as readily as desired. Through the use of a base which does not undergo reaction

TABLE 9

Acylation of equimolar amine mixtures with acid chlorides (166)

ACID CHLORIDE	STRONG AMINE	$K_b \times 10^{10}$ (25°C.)	WEAK AMINE	$K_b \times 10^{10}$ (25°C.)	SOLVENT	PRODUCTS
Acetyl....	Aniline	4.6	o-Toluidine	3.3	Benzene	$C_6H_5NHCOCH_3 + 2\text{-}CH_3C_6H_4NH_3\overset{\oplus}{}\overset{\ominus}{Cl}$
Succinyl..	Aniline	4.6	o-Toluidine	3.3	Water	Solid is $\begin{array}{l}CH_2CONHC_6H_5 \\ \mid \\ CH_2CONHC_6H_5\end{array}$
Acetyl....	p-Toluidine	20	Aniline	4.6	Benzene	$C_6H_5NHCOCH_3 + 4\text{-}CH_3C_6H_4NH_3\overset{\oplus}{}\overset{\ominus}{Cl}$
	Pseudo-cumidine	17.2	Aniline	4.6	Benzene	$C_6H_5NHCOCH_3 + $ $1,2,4\text{-}(CH_3)_3\text{-}5\text{-}(\overset{\oplus}{NH_3}\overset{\ominus}{Cl})C_6H_2$
	Aniline	4.6	α-Naphthylamine	0.99	Benzene	$\alpha\text{-}C_{10}H_7NHCOCH_3 + C_6H_5\overset{\oplus}{NH_3}\overset{\ominus}{Cl}$
	Aniline	4.6	β-Naphthylamine	2	Benzene	$\beta\text{-}C_{10}H_7NHCOCH_3 + C_6H_5\overset{\oplus}{NH_3}\overset{\ominus}{Cl} + $ $\beta\text{-}C_{10}H_7NH_2$
	p-Toluidine	20	o-Toluidine	3.3	Ethyl ether	$4\text{-}CH_3C_6H_4NHCOCH_3 + $ $2\text{-}CH_3C_6H_4NH_2(?)$
Benzoyl..	Ammonia	18×10^4	Aniline	4.6		$C_6H_5NHCOC_6H_5 + NH_4Cl$
	Ethylamine	56×10^5	Ammonia	18×10^4	Water	$C_6H_5CONHC_2H_5 + NH_4Cl$
	Ammonia	18×10^4	Phenylhydrazine	16	Water	$C_6H_5N(COC_6H_5)NHCOC_6H_5 + $ $NH_4Cl + C_6H_5NHNH_2$
	Aniline	4.6	Methylaniline	2.5 (18°C.)	Water	$C_6H_5CONHC_6H_5 + C_6H_5CON(CH_3)\text{-}$ $C_6H_5 + C_6H_5\overset{\oplus}{NH_3}\overset{\ominus}{Cl}$
	Ammonia	18×10^4	m-Bromo-p-toluidine	?	Water	$3\text{-}Br\text{-}4\text{-}CH_3C_6H_3NHCOC_6H_5 + NH_4Cl$
	Ammonia	18×10^4	o-Toluidine	3.3	Water	$2\text{-}CH_3C_6H_4NHCOC_6H_5 + NH_4Cl$
	Phenylhydrazine	16	Aniline	4.6	Water	$C_6H_5NHCOC_6H_5 + C_6H_5\overset{\oplus}{NHNH_3}\overset{\ominus}{Cl}$
	Aniline	4.6	m-Nitroaniline	0.04	Water	$2\text{-}O_2NC_6H_4NHCOC_6H_5 + C_6H_5\overset{\oplus}{NH_3}\overset{\ominus}{Cl}$ $+ 3\text{-}O_2NC_6H_4NH_2$

Aniline	4.6	3-Nitroaniline	0.04	Benzene	$3\text{-}O_2NC_6H_4NHCOC_6H_5 + C_6H_5\overset{\oplus}{N}H_3\overset{\ominus}{Cl}$ $+ 3\text{-}O_2NC_6H_4NH_2$
Aniline	4.6	p-Bromoaniline	0.88	Benzene	$4\text{-}BrC_6H_4NHCOC_6H_5 + C_6H_5\overset{\oplus}{N}H_3\overset{\ominus}{Cl}$
Aniline	4.6	o-Anisidine	1.9 (15°C.)	Benzene	$2\text{-}CH_3OC_6H_4NHCOC_6H_5 +$ $C_6H_5\overset{\oplus}{N}H_3\overset{\ominus}{Cl}$
p-Phenetidine	21.5 (15°C.)	Aniline	4.6	Benzene	Mixtures; $4\text{-}C_2H_5OC_6H_4NHCOC_6H_5$ mostly

IV (or I), such as a tertiary amine like pyridine, which is preferably a stronger base than the amine being acylated, successful results are usually obtained. Other hydrogen chloride acceptors have been employed in the reaction (21, 115).

Effects observed in the acylation of two different amines with one acyl chloride may be considered in the following way. Ionization of the acid chloride may be postulated first, followed by reversible addition of the carbonium ion to both amines (say with aniline and nitroaniline).

$$C_6H_5NH_2 \; + \; R\overset{\oplus}{C}O \; + \; \overset{\ominus}{Cl} \; \rightleftarrows \; C_6H_5\overset{\oplus}{N}H_2COR \; + \; \overset{\ominus}{Cl} \quad (1)$$

$$O_2NC_6H_4NH_2 \; + \; R\overset{\oplus}{C}O \; + \; \overset{\ominus}{Cl} \; \rightleftarrows \; O_2NC_6H_4\overset{\oplus}{N}H_2COR \; + \; \overset{\ominus}{Cl} \quad (2)$$
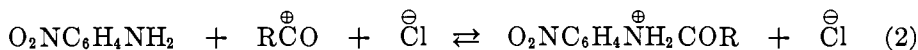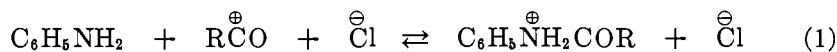
There will now be a reaction of the adduct with aniline, the stronger base, to pull a proton away.

$$O_2NC_6H_4\overset{\oplus}{N}H_2COR \; + \; \overset{\ominus}{Cl} \; + \; C_6H_5NH_2 \; \rightarrow$$

$$O_2NC_6H_4NHCOR \; + \; C_6H_5\overset{\oplus}{N}H_3 \; + \; \overset{\ominus}{Cl} \quad (3)$$
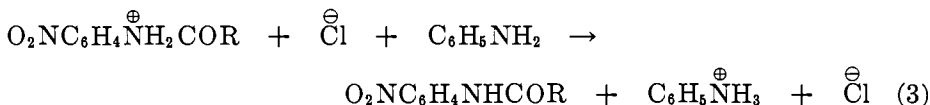
Since equations 1 and 2 are equilibrium reactions, this means that 1 is depleted by 3, making 2 the favored reaction. If a still stronger base than aniline were available for reaction 3, such as hydroxide ion (as in homogeneous Schotten–Baumann reactions but not heterogeneous ones), then both reactions 1 and 2 should progress equally.

Phenylhydrazine is a base containing both a strong and a weak basic nitrogen. The nitrogen atom in the NH_2 group is stronger by possibly a factor of 10^5 (cf. NH_3 vs. $C_6H_5NH_2$). If the weaker basic amine group were always acylated and the stronger always converted to a salt, one would predict that phenylhydrazine should react with RCOCl to yield $C_6H_5NH(COR)NH_3Cl$. This, however, is contrary to fact, for $C_6H_5NHNHCOR$ and $C_6H_5NHNH_3Cl$ are the products formed. The latter is what would be expected if it is assumed that the stronger basic position competes for the carbonium ion as well as the proton:

$$C_6H_5NHNH_2 \; + \; R\overset{\oplus}{C}O \; \rightarrow \; C_6H_5NH\overset{\oplus}{N}H_2COR \; \xrightarrow{\;C_6H_5NHNH_2\;}$$

$$C_6H_5NHNHCOR \; + \; C_6H_5NH\overset{\oplus}{N}H_3$$
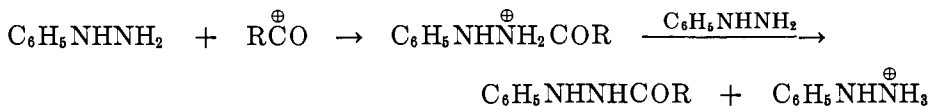
If the two amines are of not too different base strengths, anomalous effects may be expected; these have been noticed in mixtures of aniline with o-toluidine and with p-phenetidine.

The use of aqueous sodium hydroxide in the acylation of amines with benzoyl chloride is effective because the rate of hydrolysis of benzoyl chloride is extremely slow. This is an example of the Schotten–Baumann reaction (614, 615, 693). Because aliphatic acid chlorides hydrolyze in general much more rapidly than aromatic types, the Schotten–Baumann technique with aliphatic acid chlorides affords substituted amides contaminated with acids. Somewhat better purity of product is obtained with the C_{10} to C_{18} aliphatic acid chlorides than with the

C_2 to C_9 homologs. Lauroyl chloride, which hydrolyzes more slowly than either the lower or some of the higher homologs (54), would be expected to react most efficiently. With lower temperatures some decrease in the hydrolysis reaction can be achieved. Oleoyl chloride acylated leucine to give an 80.9 per cent yield of the substituted amide at 20°C. and only a 78.8 per cent yield at 40–65°C., the remainder in each case consisting of oleic acid and unchanged leucine (502). Occasionally, a purer product can be produced by adjusting the ratios of the reactants, as indicated for leucine and oleoyl chloride in table 10.

Schotten–Baumann acylations of primary amines usually give no diacylated derivatives and any such tendency is minimized by adding the acid chloride very slowly with rapid stirring to a cooled suspension of the amine in aqueous alkali. With amines containing other groups also capable of being acylated there is generally at least some formation of diacylated products in the reaction. In the Schotten–Baumann acylation of a series of bifunctionally substituted amino

TABLE 10

Reaction products in the Schotten–Baumann acylation of leucine (502)

STARTING MATERIALS		PRODUCTS		OLEIC ACID
Leucine	Oleoyl chloride	N-Oleoylleucine	Leucine uncombined	
moles	*moles*	*moles*	*moles*	*moles*
100	100	78.8	19.0	18.4
125	100	88.1	34.3	10.7
100	125	90.8	8.3	33.3

acids with oleoyl chloride (502), for example, a comparison of the relative degrees of reactivity of various other functional groups has been made. The results for both dilute and concentrated alkali are summarized in table 11.

The acylation of *o*- and *p*-aminophenols and of 8-amino-2-naphthol with a series of straight-chain aliphatic acid chlorides has been observed (207) to yield products consisting of variable mixtures of mono- and diacylated compounds. It has been found possible in certain instances to partially saponify the diacylated component (an ester amide) to the desired mono-*N*-acylated compound (an amide). On the other hand, in instances where either a primary amino group or a carbon atom with an easily replaceable hydrogen atom may be acylated in a molecule, little or no success is achieved in linking the acyl group to the central carbon atom (447).

$$H_2NCH(COOC_2H_5)_2 \ + \ RCOCl \ \xrightarrow{\ C_2H_5ONa\ }$$
$$RCONHCH(COOC_2H_5)_2 \ + \ HCl$$
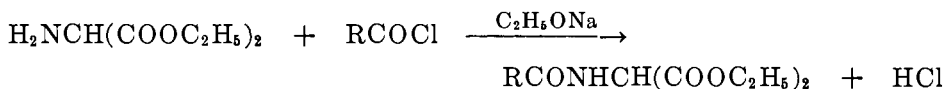
Various other techniques employed for the benzoylation of amines (43, 152, 224, 230) have been applied to aliphatic acid chlorides. Alcoholic sodium ethoxide has been rarely employed, but the acylation has been carried out in the presence of sodium bicarbonate in chloroform (115), with alkali carbonate in ether (647),

with pyridine (115, 207), which serves both as the base and as an excellent solvent, or with sodium acetate without a solvent (21). Many other organic solvents have been used. An innovation which eliminates the necessity of a hydrogen acceptor and appears promising for certain amines consists in the acylation of a suspension of the hydrochloride of the amine in hot benzene (224).

TABLE 11

A. *Products from the Schotten–Baumann acylation of amino acids with oleoyl chloride (502)*

AMINO ACID (100 MOLES USED)	ALKALI	OLEOYL CHLORIDE	AMIDE FORMED		OLEOYL CHLORIDE HYDROLYZED	AMINO ACID UNCOMBINED
			Mono-acylated	Di-acylated		
		moles	*moles*	*moles*	*moles*	*moles*
Leucine.............	Dilute	97.6	78.8	0.0	18.4	19.0
	Concentrated	96.5	68.1	0.0	27.7	29.9
Serine..............	Dilute	101.0	37.8	21.5	17.7	37.8
	Concentrated	101.0	79.0	0.0	28.9	29.8
Tyrosine...........	Dilute	102.8	32.9	23.8	18.7	41.3
	Concentrated	104.5	16.7	28.5	29.1	53.4
Lysine..............	Dilute	105.0	17.0	33.1	20.4	44.4
	Concentrated	103.0	14.2	27.4	31.0	58.6
Histidine...........	Dilute	101.0	43.4	14.0	24.9	37.9
	Concentrated	108.0	4.7	27.0	41.9	66.4
Arginine...........	Dilute	106.5	54.6	13.5	23.1	31.2
	Concentrated	102.1	34.4	20.1	28.2	44.1

B. *Relative affinities of amino acid groups for oleoyl chloride in Schotten–Baumann acylations (166)*

NaOH	α-NH₂	ALCOHOLIC OH	PHENOLIC OH	ε-NH₂	IMIDAZOLE NH	GUANIDINE NH₂
	moles	*moles*	*moles*	*moles*	*moles*	*moles*
Dilute...............	100	36	42	66	25	20
Concentrated.........	100	0	63	66	85	37

In the acylation of certain primary amines in anhydrous solvents a part of the acid chloride may add to the base to produce a salt-like material, either the hydrochloride of the amide or the acid chloride salt of the amine.

$$R'NH_2 \; + \; RCOCl \; \rightarrow \; R' : \overset{\overset{\textstyle H}{\cdot\cdot}}{\underset{\underset{\textstyle O}{\overset{\textstyle \|}{CR}}}{N}}^{\oplus} : H \quad : \overset{\ominus}{Cl}$$
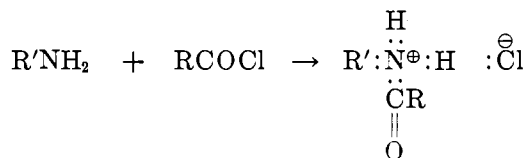
This is probably the course of the reaction of acetyl chloride with benzylamine in anhydrous ether (174). These salts have been compared to the salt-like addition products of tertiary amines and acetyl chloride (see Section VII,C). Like the latter they are hydrolyzed in the presence of water, but they afford the acy-

lated derivatives, while the tertiary amine salts, whose amines are much stronger bases than amides, give instead the hydrochloride of the amine and either the acid or the anhydride (7) corresponding to the acid chloride.

$$R':\overset{\overset{\displaystyle H}{\cdot\cdot}}{\underset{\underset{\displaystyle O}{\parallel}}{\underset{\displaystyle \overset{\cdot\cdot}{C}:R}{N}}}{}^{\oplus}:H \quad :\overset{\oplus}{C}l \ + \ H_2O \ \rightarrow \ RCONHR' \ + \ HCl \ + \ H_2O$$

$$R_3N \cdot CH_3COCl + H_2O \rightarrow R_3N \cdot HCl + CH_3COOH$$

$$2R_3N \cdot CH_3COCl + H_2O \rightarrow 2R_3N \cdot HCl + (CH_3CO)_2O$$
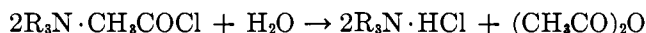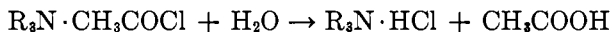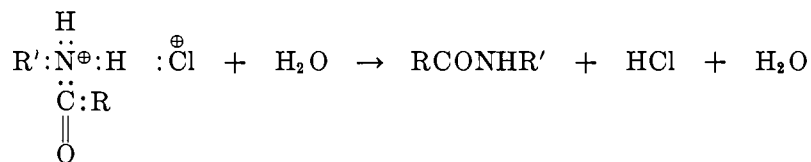
In the hydrolysis of the amide hydrochlorides apparently the reaction proceeds merely because of the energy of solvation of hydrogen chloride, indicating that the bond forces which hold the salt together are very weak ones. A certain few amides when dissolved in anhydrous ether and treated with hydrogen chloride can be induced to form hydrochlorides. On the basis of a series of acetylations in anhydrous ether (174) it has been assumed that the usual end products in acylations with acid chlorides in organic solvents are the result of decompositions brought about by the action of water or alkalies on such salts. This contention does not appear valid for the greater number of instances.

It is quite probable that the mechanism of the acylation of primary amines with aliphatic acid chlorides is determined, as is the mechanism of hydrolysis, by the conditions under which the reaction is carried out. Considering the S_N1 and S_N2 mechanisms in general, experience has shown that the nucleophilic power of an attacking reagent roughly parallels its basic strength.

$$Y: \ + \ H—Z \ \rightleftarrows \ Y—H \ + \ :Z \quad \text{(measure of base strength)}$$

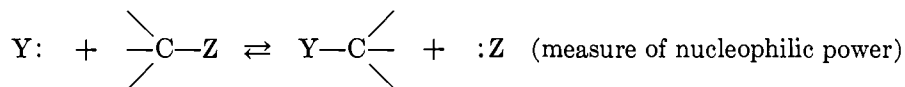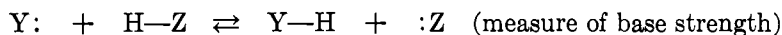$$Y: \ + \ \overset{\diagdown}{\underset{\diagup}{C}}—Z \ \rightleftarrows \ Y—\overset{\diagup}{\underset{\diagdown}{C}} \ + \ :Z \quad \text{(measure of nucleophilic power)}$$

Applying a series of increasingly strong bases in nucleophilic displacements results mainly in an increase in the importance of second-order reactions at the expense of the first-order reactions.

$$\overset{\ominus}{O}COCH_3, \quad \overset{\ominus}{O}C_6H_5, \quad \overset{\ominus}{O}H, \quad \overset{\ominus}{O}R$$
$$\xrightarrow{\hspace{6cm}}$$
$$\text{increasing base strength}$$
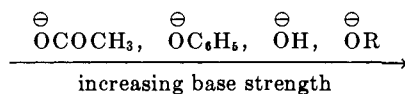
All other factors being held constant, the nucleophilic attack at the center of a positive carbon atom should be facilitated with greater base strength. However, the halogen atom of an aromatic or aliphatic acid chloride is displaced by an amine (or a phenol or alcohol) under various conditions in preference to hydroxide ion. This result points out that while strong bases are strong toward hydrogen atoms, weak bases appear to undergo displacements on carbon atoms more readily than their basicity would indicate. Conversely, it may be argued that

in the Schotten–Baumann reaction of an aliphatic acid chloride there is little
or no concentration of hydroxyl ion in the acid chloride–amine phase of the
heterogeneous system and consequently that reaction occurs with the available
weaker base therein. It is noteworthy that in the homogeneous system of ethyl-
amine and ammonia in water the stronger base is acylated heterogeneously with
benzoyl chloride (166). Further, there may be no direct correlation between the
relative strengths of a series of bases in water and in many organic solvents of
widely varying dielectric constants. Because of these several factors and in view
of the fact that kinetic data for this rapid reaction are difficult to obtain, par-
ticularly in the heterogeneous Schotten–Baumann technique, the mechanism
of acylation remains obscure. It can be tentatively assumed to be either S_N1
or S_N2 or dual, depending upon the exact conditions maintained.

Products produced by the acylation of primary amines with aliphatic acid
chlorides are of value as detergents, wetting and foaming agents, waterproofing
compounds, textile-processing agents, adhesives, dyeing assistants, dyes, and
for many other purposes. Acid chlorides have been employed to react with the
products of the reaction of 2 moles of diethanolamine and 1 mole of fatty acid
(417). The resulting Ninol-type detergent, which probably consists of the amide,
piperazine ester, ammonium-type soap, fatty acid, and excess diethanolamine,
has been found to be of value as a product for use in cosmetic creams, shaving
creams, textile, leather and hide treatments, and for ore separations. Fatty
polyamides useful as textile lubricants and softeners which do not yellow textile
material have been prepared (516) from polyamines such as ethylenediamine
and tetraethylenetriamine by first acylating one amino group with 1 mole of a
fatty acid containing from eight to twenty-two carbon atoms at 120–200°C., and
subsequently acylating with 1 mole of an acid chloride containing from two to
five carbon atoms. Increased water solubility of the product is achieved by the
addition of lactic acid. Fluorescent brightening agents for animal or vegetable
fibers have been prepared (245) by reacting monoacylated 4,4′-diaminostilbene-
disulfonic acid with a series of acid chlorides. The products are said to possess a
blue to greenish-blue fluorescence with good water solubility, excellent affinity
for wool as well as cellulose fibers, and good soap fastness. Coating materials
which may be applied as films for the preparation of varnishes, enamels, and the
like have been manufactured (374) from such amino hydroxy compounds as
diethanolamine through the use of acid chlorides. The products, which probably
result through acylation of hydroxyl and amino groups and also through ether
formation, exhibit improved rapid drying, hardness, resistance to water and
alkalies, and durability to exposure. The formation of anilides from aliphatic
acid chlorides with excess aniline in dry ether is the basis for an analytical method
for the determination of free acid in acid chlorides (53). Amide formation with
acetyl chloride has been less successfully applied to an analytical method for
the determination of active hydrogen in amines (528) than ester formation from
the same reagent with alcohols and phenols (638).

Heterocyclic compounds may be formed from certain types of primary amines.
The condensation of aliphatic acid chlorides with N-phenyl-N-aminocarbamo-
nitrile, $C_6H_5N(CN)NH_2$, in benzene solution has given a series of substituted

diazoles (537). The condensation apparently proceeds through acylation of the amino group and subsequent cyclization through the tautomeric form.

$$C_6H_5N \left(\begin{matrix} C{\equiv}N \\ NH_2 \end{matrix} \right. + \text{RCOCl} \rightarrow \text{HCl} +$$

$$\left[C_6H_5N \left(\begin{matrix} C{\equiv}N \\ NHCOR \end{matrix} \right. \rightleftharpoons C_6H_5N \left(\begin{matrix} C{\equiv}N \\ N{=}COHR \end{matrix} \right. \right] \rightarrow C_6H_5N \left\langle \begin{matrix} C{=}NH \\ | \quad \diagdown O \\ N \quad \diagup \\ {\parallel} \\ CR \end{matrix} \right.$$
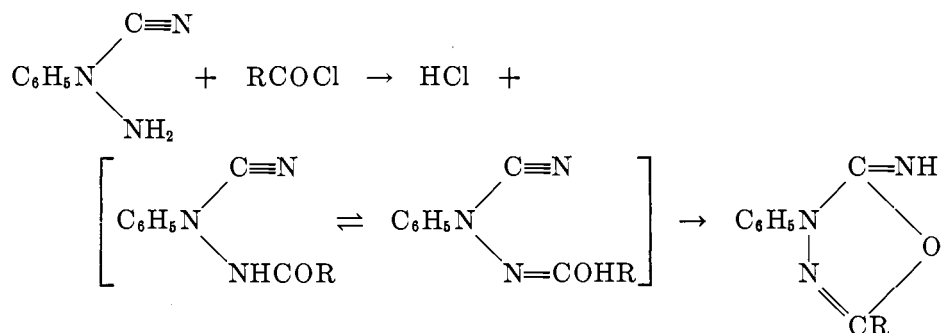
Under certain conditions the acylation of phenylenediamines has led to either diacylated diamines or benzimidazoles. In the Schotten–Baumann technique the former are produced exclusively (the benzimidazoles are cleaved in alkaline solution), while acylations in organic solvents (76) tend to give benzimidazoles at higher temperatures and diacylated diamines at lower temperatures.
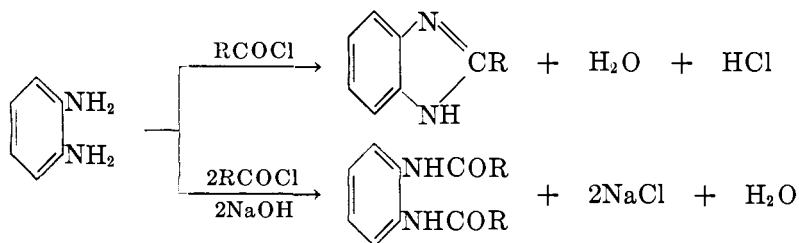
In order to facilitate the tabulation of the many individual reactions, table 12 has been designed to represent reactions of aliphatic acid chlorides with general amine types wherever possible. Organically substituted hydrazines and hydrazides are included.

B. REACTION WITH SECONDARY AMINES (SEE TABLE 13)

Although the primary amino group in bifunctional compounds is almost always preferentially acylated with aliphatic acid chlorides, the secondary amino group is, in general, less active in this respect. The acylation of p-hydroxyphenyl-β-naphthylamine with acetyl chloride in acetone with potassium carbonate to
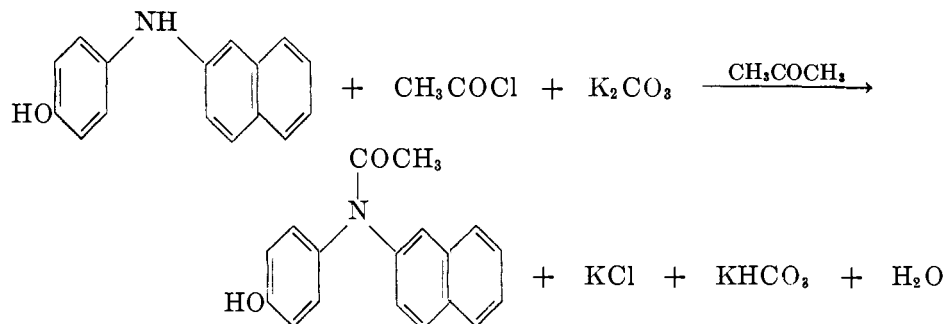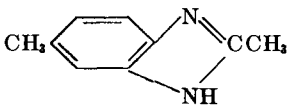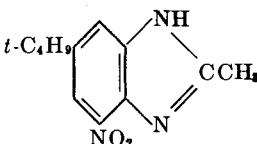
TABLE 12
Reactions of aliphatic acid chlorides with primary amines

ACID CHLORIDE	AMINE	METHOD*	BASE	PRODUCTS (YIELD)	REFERENCES
Acetyl.............	$C_2H_5NH_2$	b (ether)†		$\overset{\oplus}{C_2H_5NH_3}\overset{\ominus}{Cl}$, $C_2H_5N(COCH_3)_2$, $\overset{\oplus}{C_2H_5NH_2}(COCH_3)\overset{\ominus}{Cl}$, $\overset{\oplus}{C_2H_5NH}(COCH_3)_2\overset{\ominus}{Cl}$	(174)
	i-$C_5H_{11}NH_2$	b (ether)		i-$C_5H_{11}NHCOCH_3$	(174)
	$C_6H_5NH_2$	b (ether)		$\overset{\oplus}{C_6H_5NH_3}\overset{\ominus}{Cl}$, $C_6H_5NHCOCH_3$	(174)
	4-$CH_3C_6H_4NH_2$	b (ether)		$\overset{\oplus}{4\text{-}CH_3C_6H_4NH_3}\overset{\ominus}{Cl}$, 4-$CH_3C_6H_4$-$NHCOCH_3$, 4-$CH_3C_6H_4N(COCH_3)_2$	(174)
	$C_6H_5CH_2NH_2$	b (ether)		$\overset{\oplus}{C_6H_5CH_2NH_2}(COCH_3)\overset{\ominus}{Cl}$ + oil (?)	(174)
	α-$C_{10}H_7NH_2$	b (ether)		α-$\overset{\oplus}{C_{10}H_7NH_3}\overset{\ominus}{Cl}$, α-$C_{10}H_7NHCOCH_3$, + ?	(174)
	β-$C_{10}H_7NH_2$	b (ether)		β-$\overset{\oplus}{C_{10}H_7NH_3}\overset{\ominus}{Cl}$, β-$C_{10}H_7NHCOCH_3$	(174)
	$C_6H_5NH_2$	?		$C_6H_5NHCOCH_3$	(247, 714)
	$H_2NCOOCH_2CH_2OH$	b (acetyl chloride)		$CH_3CONHCOOCH_2CH_2OCOCH_3$	(175)
	4-$CH_3C_6H_3(NH_2)_2$-$1,2$	b (benzene; not cooled)			(76)
	4-$CH_3C_6H_3(NH_2)_2$-$1,2$	b (benzene; cooled)		4-$CH_3C_6H_3(NHCOCH_3)_2$-$1,2$	(76)
	3-NO_2-5-$(t\text{-}C_4H_9)C_6H_2(NH_2)_2$-$1,2$				(358)
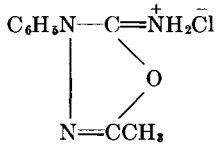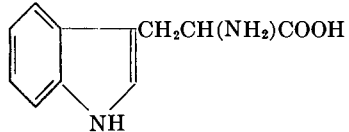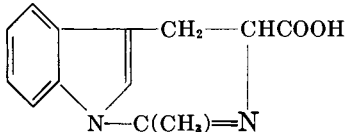
$C_6H_5N(CN)NH_2$	b (benzene)		$C_6H_5N\!-\!C\!=\!\overset{+}{N}H_2\bar{C}l$ with O, $N\!=\!CCH_3$ ring	(537)
indole-$CH_2CH(NH_2)COOH$	?		indole structure $CH_2\!-\!CHCOOH$, $N\!-\!C(CH_3)\!=\!N$	(755)
$H_2NCH(COOC_2H_5)_2$	c	Pyridine	$CH_3CONHCH(COOC_2H_5)_2$	(447)
$C_6H_5NH_2$ (and others)	d	Sodium acetate	$C_6H_5NHCOCH_3$ (96%)	(21)
dl-$C_6H_5CH_2CH(NH_2)COOH$	b (pyridine)	Pyridine	$C_6H_5CH_2CH(NHCOCH_3)COOH$ (40%)	(130, 131)
Propionyl .... $\;$ 3-CH_3O-4-$HOC_6H_3CH_2NH_2$	b (ether)		3-CH_3O-4-$HOC_6H_3CH_2NHCOC_2H_5$ (46%)	(507)
Butyryl .... $\;$ 3-CH_3O-4-$HOC_6H_3CH_2NH_2$	b (ether)		3-CH_3O-4-$HOC_6H_3CH_2NHCOC_3H_7$ (44%)	(507)
dl-$C_6H_5CH_2CH(NH_2)COOH$	b (pyridine)	Pyridine	$C_6H_5CH_2CH(NHCOC_3H_7)COOH$ (60%)	(130, 131)
Isobutyryl .... $\;$ $H_2NCH(COOC_2H_5)_2$	c	Pyridine	i-$C_3H_7CONHCH(COOC_2H_5)_2$	(447)
dl-$C_6H_5CH_2CH(NH_2)COOH$	b (pyridine)	Pyridine	$C_6H_5CH_2CH(NHCOC_3H_7\text{-}i)COOH$ (70%)	(130, 131)
Valeryl .... $\;$ 2-$HOC_6H_4NH_2$	c	Pyridine	2-$HOC_6H_4NHCOC_4H_9$, 2-$C_4H_9COOC_6H_4NHCOC_4H_9$	(207)
4-$HOC_6H_4NH_2$	c	Pyridine	4-$HOC_6H_4NHCOC_4H_9$, 4-$C_4H_9COOC_6H_4NHCOC_4H_9$	(207)
8-Amino-2-naphthol	c	Pyridine	8-$C_4H_9CONHC_{10}H_6OH$-2, 8-$C_4H_9CONHC_{10}H_6OCOC_4H_9$-$2$	(207)
dl-$C_6H_5CH_2CH(NH_2)COOH$	b (pyridine)	Pyridine	$C_6H_5CH_2CH(NHCOC_4H_9)COOH$ (60%)	(130, 131)

TABLE 12—*Continued*

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ACID CHLORIDE	AMINE	METHOD*	BASE	PRODUCTS (YIELD)	REFERENCES
Isovaleryl............	$H_2NCH(COOC_2H_5)_2$	c	Pyridine	$i\text{-}C_4H_9CONHCH(COOC_2H_5)_2$	(447)
Trimethylacetyl.....	$dl\text{-}C_6H_5CH_2CH(NH_2)COOH$	b (pyridine)	Pyridine	$C_6H_5CH_2CH(NHCOC_4H_9\text{-}t)COOH$ (55%)	(130, 131)
Hexanoyl...........	$H_2NCH(OC_2H_5)_2$	b	Pyridine	$C_5H_{11}CONHCH(OC_2H_5)_2$	(115)
	$2\text{-}HOC_6H_4NH_2$	c	Pyridine	$2\text{-}HOC_6H_4NHCOC_5H_{11},$ $2\text{-}C_5H_{11}COOC_6H_4NHCOC_5H_{11}$	(207)
	$4\text{-}HOC_6H_4NH_2$	c	Pyridine	$4\text{-}HOC_6H_4NHCOC_5H_{11},$ $4\text{-}C_5H_{11}COOC_6H_4NHCOC_5H_{11}$	(207)
	8-Amino-2-naphthol	c	Pyridine	$8\text{-}C_5H_{11}CONHC_{10}H_6OH\text{-}2,$ $8\text{-}C_5H_{11}CONHC_{10}H_6OCOC_5H_{11}\text{-}2$	(207)
	$3\text{-}CH_3O\text{-}4\text{-}HOC_6H_3CH_2NH_2$	b (ether)		$3\text{-}CH_3O\text{-}4\text{-}HOC_6H_3CH_2NHCOC_5H_{11}$ (poor yield)	(216, 507)
3-Methylvaleryl.....	$dl\text{-}C_6H_5CH_2CH(NH_2)COOH$	b (pyridine)	Pyridine	$C_6H_5CH_2CH[NHCOCH_2CH\text{-}(CH_3)C_2H_5]COOH$ (70%)	(130, 131)
4-Methylvaleryl.....	$H_2NCH(OC_2H_5)_2$	c	Pyridine	$i\text{-}C_5H_{11}CONHCH(OC_2H_5)_2$	(115)
Heptanoyl..........	$2\text{-}HOC_6H_4NH_2$	c	Pyridine	$2\text{-}HOC_6H_4NHCOC_6H_{13},$ $2\text{-}C_6H_{13}COOC_6H_4NHCOC_6H_{13}$	(207)
	$4\text{-}HOC_6H_4NH_2$	c	Pyridine	$4\text{-}HOC_6H_4NHCOC_6H_{13},$ $2\text{-}C_6H_{13}COOC_6H_4NHCOC_6H_{13}$	(207)
	8-Amino-2-naphthol	c	Pyridine	$8\text{-}C_6H_{13}CONHC_{10}H_6OH\text{-}2,$ $8\text{-}C_6H_{13}CONHC_{10}H_6OCOC_6H_{13}\text{-}2$	(207)
	$3\text{-}CH_3O\text{-}4\text{-}HOC_6H_3CH_2NH_2$	c (ether)		$3\text{-}CH_3O\text{-}4\text{-}HOC_6H_3CH_2NHCOC_6H_{13}$ (81%)	(216, 507)
Octanoyl...........	$(C_2H_5O)_2CHCH(NH_2)COOC_2H_5$	c	Pyridine	$(C_2H_5O)_2CHCH(NHCOC_7H_{15})\text{-}COOC_2H_5$	(115)
	$H_2NCH(OC_2H_5)_2$	b (benzene)		$C_7H_{15}CONHCH(OC_2H_5)_2$	(115)
	$2\text{-}HOC_6H_4NH_2$	c	Pyridine	$2\text{-}HOC_6H_4NHCOC_7H_{15},$ $2\text{-}C_7H_{15}COOC_6H_4NHCOC_7H_{15}$	(207)
	$4\text{-}HOC_6H_4NH_2$	c	Pyridine	$4\text{-}HOC_6H_4NHCOC_7H_{15},$ $4\text{-}C_7H_{15}COOC_6H_4NHCOC_7H_{15}$	(207)
	8-Amino-2-naphthol	c	Pyridine	$8\text{-}C_7H_{15}CONHC_{10}H_6OH\text{-}2$	(207)
	$3\text{-}NH_2C_6H_4SO_2NHCOC_6H_4NH_2\text{-}3$	a	NaOH	$3\text{-}C_7H_{15}CONHC_6H_4SO_2N(Na)\text{-}COC_6H_4(NHCOC_7H_{15})\text{-}3$	(305)

Nonanoyl..........	3-CH₃O-4-HOC₆H₃CH₂NH₂	b (ether)		3-CH₃O-4-HOC₆H₃CH₂NHCOC₇H₁₅	(216, 507)
	2-HOC₆H₄NH₂	c	Pyridine	2-C₈H₁₇CONHC₆H₄OH, 2-C₈H₁₇CONHC₆H₄OCOC₈H₁₇	(207)
	4-HOC₆H₄NH₂	c	Pyridine	4-C₈H₁₇CONHC₆H₄OH, 4-C₈H₁₇CONHC₆H₄OCOC₈H₁₇	(207)
	8-Amino-2-naphthol	c	Pyridine	8-C₈H₁₇CONHC₁₀H₆OH-2	(207)
	H₂NCH(COOC₂H₅)₂	c	Pyridine	C₈H₁₇CONHCH(COOC₂H₅)₂	(447)
	3-CH₃O-4-HOC₆H₃CH₂NH₂	b (ether)		3-CH₃O-4-HOC₆H₃CH₂NHCOC₈H₁₇ (76%)	(216, 507)
Decanoyl..........	2-HOC₆H₄NH₂	c	Pyridine	2-C₉H₁₉CONHC₆H₄OH, 2-C₉H₁₉CONHC₆H₄OCOC₉H₁₉	(207)
	4-HOC₆H₄NH₂	c	Pyridine	4-C₉H₁₉CONHC₆H₄OH, 4-C₉H₁₉CONHC₆H₄OCOC₉H₁₉	(207)
	8-Amino-2-naphthol	c	Pyridine	8-C₉H₁₉CONHC₁₀H₆OH-2	(207)
	3-CH₃O-4-HOC₆H₃CH₂NH₂	b (ether)		3-CH₃O-4-HOC₆H₃CH₂NHCOC₉H₁₉ (80%)	(216, 507)
Undecanoyl........	8-Amino-2-naphthol	c	Pyridine	8-C₁₀H₂₁CONHC₁₀H₆OH-2	(207)
	3-CH₃O-4-HOC₆H₃CH₂NH₂	b (ether)		3-CH₃O-4-HOC₆H₃CH₂NHCOC₁₀H₂₁ (96%)	(216, 507)
Lauroyl............	H₂NCH₂CH₂NH₂	a	NaOH	C₁₁H₂₃CONHCH₂CH₂NH₂	(384)
	H₂NCH₂OH	a	NaOH	C₁₁H₂₃CONHCH₂OH	(71)
	H₂NC₂H₄OSO₃Na	a	NaOH	C₁₁H₂₃CONHC₂H₄OSO₃Na	(274)
	3-SO₃H-4-CH₃OC₆H₃NH₂	a	NaOH	3-SO₃Na-4-CH₃OC₆H₃NHCOC₁₁H₂₃	(710)
	3-SO₃H-4-CH₃C₆H₃NH₂	a / c (acetone)	NaOH / Na₂CO₃	3-SO₃Na-4-CH₃C₆H₃NHCOC₁₁H₂₃	(711) (710)
	2-SO₃H-3-C₂H₅OC₆H₃NH₂	a	NaOH	2-SO₃Na-3-C₂H₅OC₆H₃NHCOC₁₁H₂₃	(710)
	2-HOC₆H₄NH₂	c	Pyridine	2-HOC₆H₄NHCOC₁₁H₂₃, 2-C₁₁H₂₃COOC₆H₄NHCOC₁₁H₂₃	(207)
	4-HOC₆H₄NH₂	c	Pyridine	4-HOC₆H₄NHCOC₁₁H₂₃, 4-C₁₁H₂₃COOC₆H₄NHCOC₁₁H₂₃	(207)
	8-Amino-2-naphthol	c	Pyridine	8-C₁₁H₂₃CONHC₁₀H₆OH-2	(207)
	4-C₆H₅C₆H₄NH₂	c	Pyridine (100–160°C.)	C₁₁H₂₃CONHC₆H₄C₆H₅-4	(215)

TABLE 12—*Continued*

ACID CHLORIDE	AMINE	METHOD*	BASE	PRODUCTS (YIELD)	REFERENCES
	4-(4'-NH$_2$C$_6$H$_4$)C$_6$H$_4$NH$_2$	c	Pyridine	4-(4'-C$_{11}$H$_{23}$CONHC$_6$H$_4$)C$_6$H$_4$-NHCOC$_{11}$H$_{23}$	(215)
	3-CH$_3$O-4-HOC$_6$H$_3$CH$_2$NH$_2$	b (ether)		3-CH$_3$O-4-HOC$_6$H$_3$CH$_2$NHCOC$_{11}$H$_{23}$ (70%)	(216, 507)
	4-NH$_2$C$_6$H$_4$COOH	c	Pyridine	4-C$_{11}$H$_{23}$CONHC$_6$H$_4$COOH	(215)
	4-NO$_2$C$_6$H$_4$NH$_2$	100–160°C.	No solvent	4-NO$_2$C$_6$H$_4$NHCOC$_{11}$H$_{23}$	(215)
	1-CH$_3$-4-(*i*-C$_3$H$_7$)C$_6$H$_3$NH$_2$	b (ether)		1-CH$_3$-4-(*i*-C$_3$H$_7$)C$_6$H$_3$NHCOC$_{11}$H$_{23}$	(284)
	3-CH$_3$SO$_2$NHSO$_2$C$_6$H$_4$NH$_2$	a	NaOH	3-CH$_3$SO$_2$NHSO$_2$C$_6$H$_4$NHCOC$_{11}$H$_{23}$	(303)
	4-C$_6$H$_5$CONHSO$_2$C$_6$H$_4$NH$_2$	c (methyl ether)	Pyridine	4-C$_6$H$_5$CONHSO$_2$C$_6$H$_4$NHCOC$_{11}$H$_{23}$	(305)
	2-SO$_3$H-4-ClC$_6$H$_3$NH$_2$	c	Pyridine	2-SO$_3$H-4-ClC$_6$H$_3$NHCOC$_{11}$H$_{23}$	(711)
	H$_2$NC$_2$H$_4$OC$_6$H$_{11}$O$_5$	a (ethanol)	Na$_2$CO$_3$	C$_{11}$H$_{23}$CONHC$_2$H$_4$OC$_6$H$_{11}$O$_5$	(150)
	H$_2$NC$_2$H$_4$NH$_2$	c	Pyridine	C$_{11}$H$_{23}$CONHC$_2$H$_4$NH$_2$	(194, 384)
	2,4-(NO$_2$)$_2$C$_6$H$_3$NHNH$_2$	b (benzene)		2,4-(NO$_2$)$_2$C$_6$H$_3$NHNHCOC$_{11}$H$_{23}$	(215)
	3-SO$_3$H-4-C$_2$H$_5$OC$_6$H$_3$NH$_2$	a	NaOH	3-SO$_3$Na-4-C$_2$H$_5$OC$_6$H$_3$NHCOC$_{11}$H$_{23}$	(710)
	4-CH$_3$OC$_6$H$_4$NH$_2$	a	NaOH	4-CH$_3$OC$_6$H$_4$NHCOC$_{11}$H$_{23}$	(343)
Lauroyl............	C$_4$H$_9$NHCH$_2$CH$_2$OSO$_3$Na	a	NaOH	C$_4$H$_9$N(COR)CH$_2$CH$_2$OSO$_3$Na	(274)
(Cocoyl)	NH$_2$CH$_2$CH$_2$SO$_3$Na	b (water)		RCONHCH$_2$CH$_2$SO$_3$Na	(274)
Tridecanoyl........	8-Amino-2-naphthol	c	Pyridine	8-C$_{12}$H$_{25}$CONHC$_{10}$H$_6$(OCOC$_{12}$H$_{25}$)-2	(207)
	3-CH$_3$O-4-HOC$_6$H$_3$CH$_2$NH$_2$	b (ether)		3-CH$_3$O-4-HOC$_6$H$_3$CH$_2$NHCOC$_{12}$H$_{25}$	(216)
Myristoyl..........	4-C$_6$H$_5$C$_6$H$_4$NH$_2$	100–160°C.	No solvent	4-C$_6$H$_5$C$_6$H$_4$NHCOC$_{13}$H$_{27}$	(215)
	4-(4'-NH$_2$C$_6$H$_4$)C$_6$H$_4$NH$_2$	c	Pyridine	4-(4'-C$_{13}$H$_{27}$CONHC$_6$H$_4$)C$_6$H$_4$NH-COC$_{13}$H$_{27}$	(215)
	2-HOC$_6$H$_4$NH$_2$	c	Pyridine	2-HOC$_6$H$_4$NHCOC$_{13}$H$_{27}$, 2-C$_{13}$H$_{27}$COOC$_6$H$_4$NHCOC$_{13}$H$_{27}$	(207)
	4-HOC$_6$H$_4$NH$_2$	c	Pyridine	4-HOC$_6$H$_4$NHCOC$_{13}$H$_{27}$, 4-C$_{13}$H$_{27}$COOC$_6$H$_4$NHCOC$_{13}$H$_{27}$	(207)

	3-CH₃O-4-HOC₆H₃CH₂NH₂	b (ether)		3-CH₃O-4-HOC₆H₂CH₂NHCOC₁₃H₂₇	(216)
	8-Amino-2-naphthol	c	Pyridine	8-C₁₃H₂₇CONHC₁₀H₆OH-2	(207)
	1-CH₃-4-(i-C₃H₇)C₆H₃NH₂	b (ether)		1-CH₃-4-(i-C₃H₇)C₆H₃NHCOC₁₃H₂₇	(284)
	4-NO₂C₆H₄NH₂	100–160°C.	No solvent	4-NO₂C₆H₄NHCOC₁₃H₂₇	(215)
	2-NO₂-4-CH₃C₆H₃NH₂	100–160°C.		2-NO₂-4-CH₃C₆H₃NHCOC₁₃H₂₇	(215)
	4-NH₂C₆H₄COOH	c	Pyridine	4-C₁₃H₂₇CONHC₆H₄COOH	(215)
	2,4-(NO₂)₂C₆H₃NHNH₂	b (benzene)		2,4-(NO₂)₂C₆H₃NHNHCOC₁₃H₂₇	(215)
Pentadecanoyl......	8-Amino-2-naphthol	c	Pyridine	8-C₁₄H₂₉CONHC₁₀H₆OH-2	(207)
	3-CH₃O-4-HOC₆H₃CH₂NH₂	b (ether)		3-CH₃O-4-HOC₆H₃CH₂NHCOC₁₄H₂₉	(216)
Palmitoyl.........	4-C₆H₅C₆H₄NH₂	100–160°C.		4-C₆H₅C₆H₄NHCOC₁₅H₃₁	(215)
	2-HOC₆H₄NH₂	c	Pyridine	2-HOC₆H₄NHCOC₁₅H₃₁	(207)
	4-HOC₆H₄NH₂	c	Pyridine	4-HOC₆H₄NHCOC₁₅H₃₁	(207)
	4-(4′-NH₂C₆H₄)C₆H₄NH₂	c	Pyridine	4-(4′-C₁₅H₃₁CONHC₆H₄)C₆H₄-NHCOC₁₅H₃₁	(215)
	8-Amino-2-naphthol	c	Pyridine	8-C₁₅H₃₁CONHC₁₀H₆OH-2	(207)
	2-Aminodibenzofuran	c		C₁₂H₇ONHCOC₁₅H₃₁	(215)
	3-CH₃O-4-HOC₆H₃CH₂NH₂	b (ether)		3-CH₃O-4-HOC₆H₃CH₂NHCOC₁₅H₃₁	(216)
	4-NO₂C₆H₄NH₂	100–160°C.		4-NO₂C₆H₄NHCOC₁₅H₃₁	(215)
	1-CH₃-4-(i-C₃H₇)C₆H₃NH₂	b (ether)		1-CH₃-4-(i-C₃H₇)C₆H₃NHCOC₁₅H₃₁	(284)
	2-NO₂-4-CH₃C₆H₃NH₂	d		2-NO₂-4-CH₃C₆H₃NHCOC₁₅H₃₁	(215)
	2-NH₂C₆H₄COOH	c (CHCl₃)		2-C₁₅H₃₁CONHC₆H₄COOH	(215)
	4-NH₂C₆H₄COOH	c	Pyridine	4-C₁₅H₃₁CONHC₆H₄COOH	(215)
	2,4-(NO₂)₂C₆H₃NHNH₂	b (benzene)		2,4-(NO₂)₂C₆H₃NHNHCOC₁₅H₃₁	(215)
	2-CH₃C₆H₄NHNH₂	b (benzene)		2-CH₃C₆H₄NHNHCOC₁₅H₃₁, 2-CH₃C₆H₄NHNH₂·HCl	(244)
	H₂NCH₂SO₃H	a	NaOH	C₁₅H₃₁CONHCH₂SO₃Na	(273)
Heptadecanoyl......	8-Amino-2-naphthol	c	Pyridine	8-C₁₆H₃₃CONHC₁₀H₆OH-2	(207)
Stearoyl...........	2-HOC₆H₄NH₂	c	Pyridine	2-C₁₇H₃₅COOC₆H₄NHCOC₁₇H₃₅, 2-HOC₆H₄NHCOC₁₇H₃₅	(207)
	4-HOC₆H₄NH₂	c	Pyridine	4-HOC₆H₄NHCOC₁₇H₃₅, 4-C₁₇H₃₅-COOC₆H₄NHCOC₁₇H₃₅	(207)
	4-(4′-NH₂C₆H₄)C₆H₄NH₂	c	Pyridine	4-(4′-C₁₇H₃₅CONHC₆H₄)C₆H₄-NHCOC₁₇H₃₅	(215)

TABLE 12—*Continued*

ACID CHLORIDE	AMINE	METHOD*	BASE	PRODUCTS (YIELD)	REFERENCES
	8-Amino-2-naphthol	c	Pyridine	8-$C_{17}H_{35}CONHC_{10}H_6OH$-2	(207)
	4-$NO_2C_6H_4NH_2$	100–160°C.		4-$NO_2C_6H_4NHCOC_{17}H_{35}$	(215)
	3-CH_3O-4-$HOC_6H_3CH_2NH_2$	b (ether)		3-CH_3O-4-$HOC_6H_3CH_2NHCOC_{17}H_{35}$	(216)
	2-NO_2-4-$CH_3C_6H_2NH_2$	100–160°C.		2-NO_2-4-$CH_3C_6H_2NHCOC_{17}H_{35}$	(215)
	4-$C_6H_5C_6H_4NH_2$	100–160°C.		4-$C_6H_5C_6H_4NHCOC_{17}H_{35}$	(215)
	2-Aminodibenzofuran	100–160°C.		$C_{12}H_7ONHCOC_{17}H_{35}$	(215)
	3-$NH_2C_6H_4COOH$	c	Pyridine	3-$C_{17}H_{35}CONHC_6H_4COOH$	(306)
	2-CH_3-4-$(i$-$C_3H_7)C_6H_2NH_2$	b (ether)		2-CH_3-4-$(i$-$C_3H_7)C_6H_3NHCOC_{17}H_{35}$	(284)
	2,4-$(NO_2)_2C_6H_3NHNH_2$	b (benzene)		2,4-$(NO_2)_2C_6H_3NHNHCOC_{17}H_{35}$	(215)
	$H_2NCH_2CH_2OSO_3Na$	a	NaOH	$C_{17}H_{35}CONHCH_2CH_2OSO_3Na$	(274)
	2-SO_3H-4-$CH_3C_6H_3NH_2$	a	NaOH	2-SO_3Na-4-$CH_3C_6H_3NHCOC_{17}H_{35}$	(343)
	2-$CH_3C_6H_4NH_2$	a	NaOH	2-$CH_3C_6H_4NHCOC_{17}H_{35}$	(343)
Nonadecanoyl........	8-Amino-2-naphthol	c	Pyridine	8-$C_{18}H_{37}CONHC_{10}H_6OH$-2	(207)
15-Methyloctadeca-noyl..............	2,4,6-$Br_3C_6H_2NH_2$	d		2,4,6-$Br_3C_6H_2NHCO(CH_2)_{13}$-$CH(CH_3)(CH_2)_2CH_3$	(137)
4-Carbomethoxy-butyryl..........	4-$NaHO_3AsC_6H_4NH_2$	a	NaOH (+HCl)	4-$H_2O_3AsC_6H_4NHCO(CH_2)_3COOCH_3$	(494)

Unsaturated acid chlorides

Crotonyl...........	3-CH_3O-4-$HOC_6H_3CH_2NH_2$	b (ether)		3-CH_3O-4-$HOC_6H_3CH_2NHCOCH$=$CHCH_3$ (50%)	(507)
2-Hexenoyl.........	$H_2NCH(OC_2H_5)_2$	c	Pyridine	C_3H_7CH=$CHCONHCH(OC_2H_5)_2$	(115)
	$H_2NCHCOOC_2H_5$ | $CH(OC_2H_5)_2$	c (CHCl₃)	NaHCO₃	C_3H_7CH=$CHCONHCHCOOC_2H_5$ | $CH(OC_2H_5)_2$	(115)
3-Hexenoyl.........	$H_2NCH(OC_2H_5)_2$	c	Pyridine	C_2H_5CH=$CHCH_2CONHCH$-$(OC_2H_5)_2$	(115)

	$H_2NCHCOOC_2H_5$ $\mid$ $CH(OC_2H_5)_2$	c (CHCl$_3$)	NaHCO$_3$	$C_2H_5CH{=}CHCH_2CO$-$NHCHCOOC_2H_5$ $\mid$ $CH(OC_2H_5)_2$	(115)
4-Hexenoyl..........	$H_2NCH(OC_2H_5)_2$	c	Pyridine	$CH_3CH{=}CHC_2H_4CONHCH$-$(OC_2H_5)_2$	(115)
	$H_2NCHCOOC_2H_5$ $\mid$ $CH(OC_2H_5)_2$	c	Pyridine	$CH_3CH{=}CHC_2H_4CO$-$NHCHCOOC_2H_5$ $\mid$ $CH(OC_2H_5)_2$	(115)
5-Hexenoyl..........	$H_2NCHCOOC_2H_5$ $\mid$ $CH(OC_2H_5)_2$	c (water–CHCl$_3$)	NaHCO$_3$	$CH_2{=}CH(CH_2)_3CONHCHCOOC_2H_5$ $\mid$ $CH(OC_2H_5)_2$	(115)
9-Undecenoyl.......	3-CH$_3$O-4-HOC$_6$H$_3$CH$_2$NH$_2$	b (ether)		3-CH$_3$O-4-HOC$_6$H$_3$CH$_2$NHCO-$(CH_2)_7CH{=}CHCH_3$	(507)
Oleoyl..............	Primary amines from protein hydrolysates	a	NaOH	Amide mixtures	(645)
	H$_2$NCH$_2$CH$_2$OSO$_3$Na	a	NaOH	C$_{17}$H$_{33}$CONHCH$_2$CH$_2$OSO$_3$Na	(274)
	H$_2$NC$_2$H$_4$OC$_6$H$_{11}$O$_5$	a (water–ethanol)	Na$_2$CO$_3$	C$_{17}$H$_{33}$CONHC$_2$H$_4$OC$_6$H$_{11}$O$_5$	(150)
	H$_2$NC$_2$H$_4$NH$_2$	a	NaOH	C$_{17}$H$_{33}$CONHC$_2$H$_4$NHCOC$_{17}$H$_{33}$	(274)
	4-NO$_2$C$_6$H$_4$NH$_2$	c (100–160°C.)		4-NO$_2$C$_6$H$_4$NHCOC$_{17}$H$_{33}$	(215)
	3-NH$_2$C$_6$H$_4$COOH	c	Pyridine	3-C$_{17}$H$_{33}$CONHC$_6$H$_4$COOH	(306)
	H$_2$NCH$_2$SO$_3$H	a	NaOH	C$_{17}$H$_{33}$CONHCH$_2$SO$_3$Na	(273)
	2-NO$_2$-4-CH$_3$C$_6$H$_3$NH$_2$	d (100–160°C.)		2-NO$_2$-4-CH$_3$C$_6$H$_3$NHCOC$_{17}$H$_{33}$	(215)
	4-(4'-NH$_2$C$_6$H$_4$)C$_6$H$_4$NH$_2$	d (100–160°C.)	Pyridine	4-(4'-C$_{17}$H$_{33}$CONHC$_6$H$_4$)C$_6$H$_4$-NHCOC$_{17}$H$_{33}$	(215)
	8-Amino-2-naphthol	c	Pyridine	8-C$_{17}$H$_{33}$CONHC$_{10}$H$_6$OH-2	(207)
	4-NH$_2$C$_6$H$_4$CH$_2$SO$_3$H	a	NaOH	4-C$_{17}$H$_{33}$CONHC$_6$H$_4$CH$_2$SO$_3$Na	(274)
	4-C$_6$H$_5$CONHSO$_2$C$_6$H$_4$NH$_2$	a	NaOH	4-C$_6$H$_5$CON(Na)SO$_2$C$_6$H$_4$-NHCOC$_{17}$H$_{33}$	(305)
	2,4-(NO$_2$)$_2$C$_6$H$_3$NHNH$_2$	b (benzene)		2,4-(NO$_2$)$_2$C$_6$H$_3$NHNHCOC$_{17}$H$_{33}$	(215)

TABLE 12—*Concluded*

ACID CHLORIDE	AMINE	METHOD*	BASE	PRODUCTS (YIELD)	REFERENCES
	$3\text{-}HOOC\text{-}4\text{-}HOC_6H_3NH_2$	a (acetone)	NaOH	$3\text{-}NaOOC\text{-}4\text{-}HOC_6H_3NHCOC_{17}H_{33}$	(306)
	$3\text{-}HO_3S\text{-}4\text{-}ROC_6H_3NH_2$	a	NaOH	$3\text{-}NaO_3S\text{-}4\text{-}ROC_6H_3NHCOC_{17}H_{33}$	(343, 344)
	$2\text{-}CH_3O\text{-}4\text{-}HSO_3C_6H_3NH_2$	a	NaOH	$2\text{-}CH_3O\text{-}4\text{-}NaSO_3C_6H_3NHCOC_{17}H_{33}$	(344)
	$H_2NC_2H_4N(C_2H_5)_2$	a	NaOH	$C_{17}H_{33}CONHC_2H_4N(C_2H_5)_2$	(619)
	$i\text{-}C_4H_9NH_2$	b (ether)		$C_{17}H_{33}CONH(i\text{-}C_4H_9)$	(351)
Elaidoyl............	$i\text{-}C_4H_9NH_2$	b (ether)		$C_{17}H_{33}CONH(i\text{-}C_4H_9)$	(351)
Linoleoyl...........	$i\text{-}C_4H_9NH_2$	b (ether)		$CH_3(CH_2)_4CH{=}CHCH_2CH{=}CH\text{-}$ $(CH_2)_7CONH(i\text{-}C_4H_9)$	(351)
Linolenoyl..........	$i\text{-}C_4H_9NH_2$	b (ether)		$CH_3CH_2CH{=}CHCH_2CH{=}CHCH_2\text{-}$ $CH{=}CH(CH_2)_7CONH(i\text{-}C_4H_9)$	(351)
$\beta\text{-}9,11,13\text{-}$Octadeca-trienoyl..........	$i\text{-}C_4H_9NH_2$	b (ether)		$CH_3(CH_2)_3CH{=}CHCH{=}CHCH{=}$ $CH(CH_2)_7CONH(i\text{-}C_4H_9)$	(351)
$10,12,14\text{-}$Octadeca-trienoyl...........	$i\text{-}C_4H_9NH_2$	b (ether)		$CH_3(CH_2)_2CH{=}CHCH{=}CHCH{=}$ $CH(CH_2)_8CONH(i\text{-}C_4H_9)$	(351)
$2,4\text{-}$Hexadienoyl.....	$H_2NCH(OC_2H_5)_2$			$CH_3CH{=}CHCH{=}CHCONHCH\text{-}$ $(OC_2H_5)_2$	(115)
	$(C_2H_5O)_2CHCH(NH_2)COOH$	c	Pyridine	$(C_2H_5O)_2CHCH(NHCOCH{=}$ $CHCH{=}CHCH_3)COOH$	(115)
$1,7\text{-}$Undecadiyne-1-carbonyl..........	$i\text{-}C_4H_9NH_2$	b (ether)		$C_3H_7C{\equiv}C(CH_2)_4C{\equiv}CCONH(i\text{-}C_4H_9)$	(565)
$1,7\text{-}$Undecadiene-1-carbonyl..........	$i\text{-}C_4H_9NH_2$	b (ether)		$C_3H_7CH{=}CH(CH_2)_4CH{=}CH\text{-}$ $CONH(i\text{-}C_4H_9)$	(565)
7-Undecen-1-yne-1-carbonyl..........	$i\text{-}C_4H_9NH_2$	b (ether)		$C_3H_7CH{=}CH(CH_2)_4C{\equiv}CCONH\text{-}$ $(i\text{-}C_4H_9)$	(565)
$1,5\text{-}$Nonadiyne-1-carbonyl..........	$i\text{-}C_4H_9NH_2$	b (benzene)		$C_3H_7C{\equiv}C(CH_2)_2C{\equiv}CCONH(i\text{-}C_4H_9)$	(565)

Dibasic chlorides and other types

Oxalyl.............	[2-NH$_2$C$_6$H$_4$S]$_2$Zn	d (60–80°C.)	(100)
Carboxyacetyl	C$_6$H$_5$NH$_2$	?	HOOCCH$_2$CONHC$_6$H$_5$ (661)
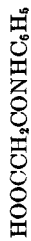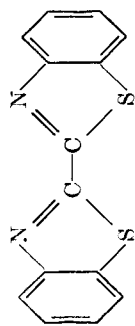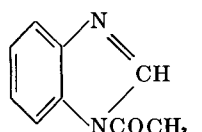
* a = Schotten–Baumann reaction;
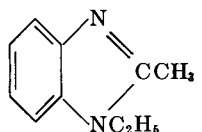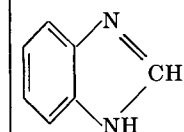 b = amine in organic solvent + RCOCl;
 c = amine in organic solvent + base + RCOCl;
 d = no solvent.
† Ether = ethyl ether.
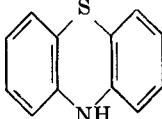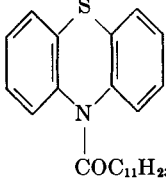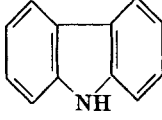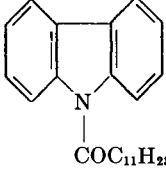
TABLE 13
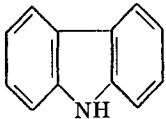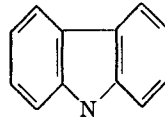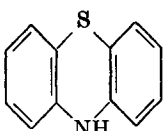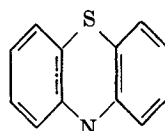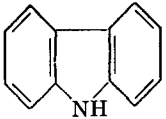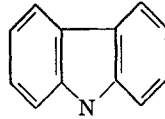
Reaction of aliphatic acid chlorides with secondary amines

ACID CHLORIDE	AMINE	METHOD*	BASE	PRODUCTS	REFERENCE
		Saturated acid chlorides			
Acetyl.............	$(C_2H_5)_2NH$	b (ether)†		$\overset{\oplus}{(C_2H_5)_2NH_2}\overset{\ominus}{Cl}$, $(C_2H_5)_2\overset{\oplus}{N}(COCH_3)$- $\overset{\ominus}{HCl}$, oil (?)	(174)
	$(C_5H_{11})_2NH$	b (ether)†		$\overset{\oplus}{(C_5H_{11})_2NH_2}\overset{\ominus}{Cl}$, $(C_5H_{11})_2\overset{\oplus}{N}(COCH_3)$- $\overset{\ominus}{HCl}$(?), $(C_5H_{11})_2NCOCH_3$(?)	(174)
	$C_6H_5NHCH_3$	b (ether)†		$C_6H_5\overset{\oplus}{NH_2}(CH_3)\overset{\ominus}{Cl}$, $C_6H_5N(CH_3)COCH_3$	(174)
	$C_6H_5NHC_2H_5$	b (ether)†		$C_6H_5\overset{\oplus}{NH_2}(C_2H_5)\overset{\ominus}{Cl}$, $C_6H_5N(C_2H_5)$- $COCH_3$, $C_2H_5\overset{\oplus}{NH_2}(COCH_3)\overset{\ominus}{Cl}$(?)	(174)
	$(C_5H_{11})_2NH$	b (ether)†		$C_5H_{11}\overset{\oplus}{NH_2}\overset{\ominus}{Cl}$, $(C_5H_{11})_2NCOCH_3$(?)	(174)
	$2\text{-}NH_2C_6H_4NHC_2H_5$	b or d			(298)
		b(?) dry			(42)

	C_6H_4 ring with N, CH, NH ‡	d		C_6H_4 ring with N, CH, $NCOCH_3$	(524)
	$2\text{-}NO_2NHC_5H_4N$	d		$2\text{-}HO\text{-}5\text{-}ClC_6H_4N(?) + N_2$	(375)
	$\beta\text{-}C_{10}H_7NHC_6H_4OH\text{-}4$	c (acetone)	K_2CO_3	$\beta\text{-}C_{10}H_7NC_6H_4OH\text{-}4$ | $COCH_3$	(184)
Propionyl...........	C_6H_4 ring with N, CH, NH ‡	d		C_6H_4 ring with N, CH, $NCOC_2H_5$	(524)
Butyryl............	$NHCH_2CH_2OH$ | $C_3H_7CHCOOH$	a	NaOH	$C_3H_7CONCH_2CH_2OH$ | $C_3H_7CHCOONa$	(695)
Octanoyl...........	$C_8H_{17}NH(CH_2)_2SO_3Na$	a (water)	NaOH– pyridine	$C_8H_{17}N(CH_2)_2SO_3Na$ | COC_7H_{15}	(246)
Decanoyl..........	$RNH(CH_2)_2SO_3Na$ $(R = C_2H_5C_6H_{10},$ $C_8H_{17})$	a	NaOH– pyridine	$RN(CH_2)_2SO_3Na$ | COC_9H_{19}	(246)
Undecanoyl........	$C_8H_{17}NH(CH_2)_2SO_3Na$	a	NaOH– pyridine	$C_8H_{17}N(CH_2)_2SO_3Na$ | $COC_{10}H_{21}$	(246)
Lauroyl............	$RNH(CH_2)_2SO_3Na$ $(R = {}_5H_{11},$ $i\text{-}C_6H_{11}, C_5H_{11}, C_7H_{15})$	a	NaOH– pyridine	$RN(CH_2)_2SO_3Na$ | $COC_{11}H_{23}$	(246)

TABLE 13—*Continued*

ACID CHLORIDE	AMINE	METHOD*	BASE	PRODUCTS	REFERENCE
	α-C$_{10}$H$_7$NHCH$_2$C$_6$H$_5$	d (100°C.)		α-C$_{10}$H$_7$NCH$_2$C$_6$H$_5$ COC$_{11}$H$_{23}$	(274)
	phenothiazine (NH)	d (100–160°C.)		phenothiazine (NCOC$_{11}$H$_{23}$)	(215)
	carbazole (NH)	d (100–160°C.)		carbazole (NCOC$_{11}$H$_{23}$)	(215)
	CH$_2$ClCH—CH O NH CHC$_6$H$_5$	c (CHCl$_3$)	Pyridine	CH$_2$ClCH—CH O NCOC$_{11}$H$_{23}$ CHC$_6$H$_5$	(68)
Cocoyl§............	C$_4$H$_9$NH(CH$_2$)$_2$SO$_3$Na	a	NaOH	C$_4$H$_9$N(CH$_2$)$_2$SO$_3$Na COR	(274)
	CH$_3$NH(CH$_2$)$_2$SO$_3$H	a	NaOH	CH$_3$N(CH$_2$)$_2$SO$_3$Na COR	(274)

	$CH_2NHCH_2SO_3H$	a	NaOH	$CH_2NCH_2SO_3Na$ │ COR	(273)
Myristoyl...........	$C_5H_{11}NH(CH_2)_2SO_4Na$	a	NaOH	$C_5H_{11}N(CH_2)_2SO_3Na$ │ $COC_{13}H_{27}$	(246)
	(carbazole, NH)	d (100–160°C.)		*(carbazole, N–$COC_{13}H_{27}$)*	(215)
	(phenothiazine, NH)	d (100–160°C.)		*(phenothiazine, N–$COC_{13}H_{27}$)*	(215)
Palmitoyl...........	$(CH_2{=}CHCH_2)_2NH \cdot \tfrac{1}{2}H_2SO_4$	a	NaOH	$(CH_2{=}CHCH_2)_2NCOC_{15}H_{31}$	(274)
	(carbazole, NH)	d (100–160°C.)		*(carbazole, N–$COC_{15}H_{31}$)*	(215)

	CH$_2$ClCH——CH
	  O NH
	    CHC$_6$H$_5$
		c (CCl$_4$)	Pyridine	CH$_2$ClCH——CH
				  O NCOC$_{17}$H$_{35}$
				    CHC$_6$H$_5$
					(68)

<div align="center">Unsaturated acid chlorides</div>

3,3-Dimethylacrylyl.	(C$_2$H$_5$)$_2$NH	e (ether)		(C$_2$H$_5$)$_2$NCOCH=C(CH$_3$)$_2$	(548)
Oleoyl...............	CH$_3$NHCH$_2$CH$_2$SO$_3$Na	a (acetone)	NaOH	CH$_3$NCH$_2$CH$_2$SO$_3$Na COC$_{17}$H$_{33}$	(274)
	C$_6$H$_{11}$NHCH$_2$CH$_2$SO$_3$Na	a	NaOH	C$_6$H$_{11}$NCH$_2$CH$_2$SO$_3$Na COC$_{17}$H$_{33}$	(274)
	(C$_6$H$_5$)$_2$NH	d		(C$_6$H$_5$)$_2$NCOC$_{17}$H$_{33}$	(338)
	CH$_2$=CHCH$_2$NHC$_6$H$_4$CH$_3$-2(or 4)	a	NaOH	CH$_2$=CHCH$_2$NC$_6$H$_4$CH$_3$-2(or 4) COC$_{17}$H$_{33}$	(274)
	RNHC$_2$H$_4$SO$_3$H (R = CH$_3$, C$_6$H$_{11}$)	a	NaOH	RNC$_2$H$_4$SO$_3$Na COC$_{17}$H$_{33}$	(274)
	C$_2$H$_5$NHC$_6$H$_4$SO$_3$H-3	a	NaOH	C$_2$H$_5$NC$_6$H$_4$SO$_3$Na-3 COC$_{17}$H$_{33}$	(274, 603)
	CH$_3$NHC$_2$H$_4$OC$_6$H$_{11}$O$_5$	c (benzene)	Na$_2$CO$_3$	CH$_3$NC$_2$H$_4$OC$_6$H$_{11}$O$_5$ COC$_{17}$H$_{33}$	(150)
	⟨carbazole⟩ NH	d (100–160°C.)		⟨carbazole⟩ N—COC$_{17}$H$_{33}$	(215)

* a = Schotten–Baumann reaction;
  b = amine in organic solvent + RCOCl;
  c = amine in organic solvent + base + RCOCl;
  d = no solvent.

† Ether = ethyl ether.
‡ Magnesium derivative.
§ Cocoyl chloride from the fatty acids of coconut oil contains saturated C$_{10}$ to C$_{18}$ and oleyl chlorides in varying proportions.

give the N-acylated derivative exclusively (184) is indicative of the strong tendency for N-acylation despite the influence of steric factors. In the general case, secondary amines are more basic than primary amines but are more sterically hindered. The reactivity towards acyl chlorides is a weighted mean of both factors.

The industrial technique involved in a typical Schotten–Baumann acylation of a secondary amine is illustrated by the preparation of Igepon T, a detergent made from sodium methyltaurine with oleoyl chloride in sodium hydroxide solution. The process was carried out during the Second World War by the I. G.

$$C_{17}H_{33}COCl + HN(CH_3)CH_2CH_2SO_3Na$$

$$+ NaOH \rightarrow C_{17}H_{33}CON(CH_3)CH_2CH_2SO_3Na + NaCl + H_2O$$
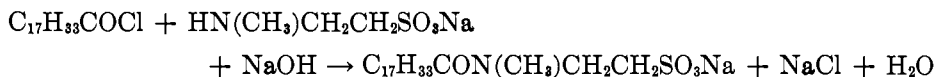
Farbenindustrie at Hoechst, Germany, for the production of a very high-grade alkali-resistant product (114):

"2,224 kg of sodium methyltaurine solution of 25% strength were run into the steel phenol-formaldehyde resin-lined 15 cubic meter reaction vessel, together with 320 kg of sodium chloride and 3,896 kg condenser water; the solution then contained about 10% sodium methyltaurine. 400 kg of 33% sodium hydroxide solution were added with stirring (wooden stirrer, at 28 RPM) and cooling (heating-cooling coil of stainless steel) to 25–30°. 1,252 kg of oleoyl chloride were then run in under the surface of the solution, together with another 400 kg of 33% sodium hydroxide solution so that the mixture was always alkaline to triazene paper; the addition took 2-3 hours. The mixture was then stirred for a further 30 minutes to make certain that the product was permanently alkaline. The product was then heated to 50° during the course of an hour, and neutralized with 125 kg of 19-20° Bé hydrochloric acid to a pH of 7.2-7.5. The mixture was then diluted with condensate water to 35% active detergent content and fed into a drum drier where it was dried at about 13 atmospheres steam pressure to a yellowish white powder. The powder was then milled to give "Igepon T Pulver Hoch Konz", the total fat content of which was 46% (active detergent content 66%); the yield 2,440 kg. Commercial Igepon T powder was obtained by diluting this with sodium sulfate."

The formation of N-substituted benzimidazoles has been observed (298) from secondary phenylenediamines in a manner analogous to the formation of benzimidazoles from o-phenylenediamine itself (76).
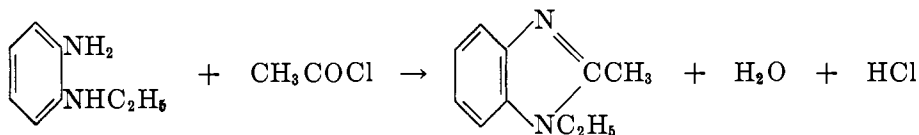
C. REACTION WITH TERTIARY AMINES

The reaction of aliphatic acid chlorides with tertiary amines (see table 14) may conform to two general types. In the first of these a salt-type adduct is formed; in the second the tertiary amine induces a dehydrochlorination of the acid chloride to a ketene. In both reactions the products are unstable and are

Type I: $RCOCl + R_3N \rightarrow R_3\overset{\oplus}{N}(COR)\overset{\ominus}{Cl}$

Type II: $RCH_2COCl + R_3N \rightarrow RCH{=}C{=}O + R_3\overset{\oplus}{N}H\overset{\ominus}{Cl}$
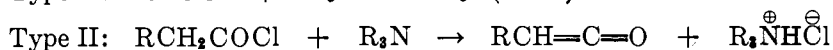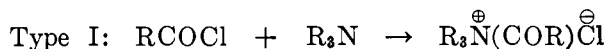
prone to react further to afford a variety of compounds.

The stability of the salts formed in the type I reaction varies widely with the individual compounds concerned. The tetraacetyl chloride adduct of tetrakis-p-dimethylaminophenylethylene, $[(CH_3)_2NC_6H_5)_2C=]_2$, appears to be particularly stable (458), while, on the other hand, early attempts to prepare the adduct of acetyl chloride and pyridine (174, 228) have been unsuccessful. These chlorides have always been prepared in anhydrous organic solvents and have only been preserved in the absence of moisture. With water either acids or anhydrides may be formed from them depending upon the quantity of water employed (7, 174):

$$R_3\overset{\oplus}{N}(COR)\overset{\ominus}{Cl} \; + \; H_2O \; \rightarrow \; RCOOH \; + \; R_3\overset{\oplus}{N}H\overset{\ominus}{Cl}$$

$$2R_3\overset{\oplus}{N}\cdot RCO\overset{\ominus}{Cl} \; + \; H_2O \; \rightarrow \; (RCO)_2O \; + \; 2R_3\overset{\oplus}{N}H\overset{\ominus}{Cl}$$
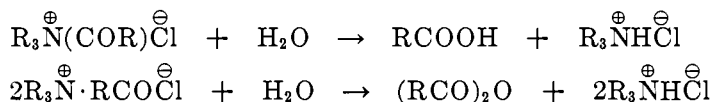
The formation of benzoic anhydride from benzoylpyridinium chloride with water was recorded in 1892 (490), and the products of the general reaction have been assumed (349) to result through the action of the acid chloride with acid present in the mixture as a contaminant or arising through hydrolysis.

$$RCOCl + RCOOH \rightarrow (RCO)_2O + HCl$$
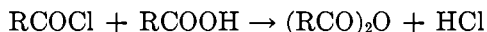
This view is not consistent with the fact that it is only through the use of acid-free acid chlorides and the addition of a minimum of water that good yields are obtained (7). It is also noteworthy that the formation of a ketene polymer before the addition of water, as in the case of 9-undecenoyl chloride and pyridine, prevents the formation of anhydride. Pyridine is most satisfactory for anhydride formation. Apparently it possesses sufficient basicity to form an adduct with the acid chloride while not aiding in the dehydrochlorination process.

Acetylpyridinium chloride, prepared from a toluene solution of acetyl chloride and pyridine, has been used as an analytical reagent for the determination of active hydrogen in the hydroxyl group of various alcohols and phenols (638). The method consists in pipetting a known excess of 1.5 M acetyl chloride and pyridine into a reaction flask to give a paste of the adduct, adding the weighed portion of alcohol or phenol, allowing reaction to occur for 20 min. at 60°C., adding excess water to give a two-phase system, and titrating the liberated acid with standard alkali.

$$CH_3COCl \; + \; C_5H_5N \; \rightarrow \; C_5H_5\overset{\oplus}{N}(CH_3CO)\overset{\ominus}{Cl}$$

$$C_5H_5\overset{\oplus}{N}(CH_3CO)\overset{\ominus}{Cl} \; + \; ROH \; \rightarrow \; CH_3COOR \; + \; C_5H_5\overset{\oplus}{N}H\overset{\ominus}{Cl}$$

$$C_5H_5\overset{\oplus}{N}(CH_3CO)\overset{\ominus}{Cl} \; + \; H_2O \; \rightarrow \; CH_3COOH \; + \; C_5H_5\overset{\oplus}{N}H\overset{\ominus}{Cl}$$
$$\text{excess}$$
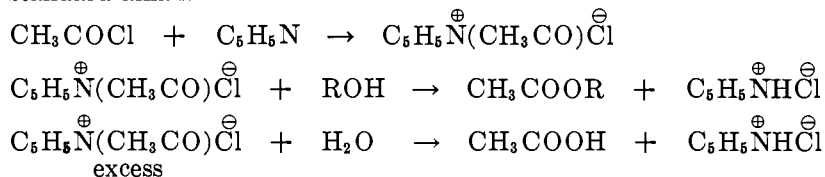
In addition to promoting anhydride formation (diacylation of water) these quaternary adducts of bases and acid chlorides have been observed to be capable of acylating hydrogen sulfide to diacyl sulfides (7) and, in addition, of monoacylating aliphatic and aromatic carboxylic amides (685) (see Section VIII,B).

Dehydrochlorination reactions of acid chlorides with tertiary amines which afford ketenes and their further reaction products were reviewed in 1946 (283) and examples were tabulated. Since preparations of disubstituted ketenes (602) afford a dehydrochlorination which is accomplished by treatment with slightly

TABLE 14

Reactions of aliphatic acid chlorides with tertiary amines

ACID CHLORIDE	AMINE	SOLVENT	PRODUCTS (YIELD)	REFERENCE
			A. Reactions involving the formation of quaternary ammonium salts	
Acetyl............	$(C_2H_5)_3N$	Ether*	$\overset{\oplus}{(C_2H_5)_3}\overset{\ominus}{N}HCl$ (?)	(174)
	$(C_3H_7)_3N$	Ether	$\overset{\oplus}{(C_3H_7)_3}\overset{\ominus}{N}HCl$, $\overset{\oplus}{(C_3N_7)_3}N\overset{\ominus}{(COCH_3)Cl}$ (?)	(174)
	$C_6H_5N(C_2H_5)_2$	Ether	$C_6H_5\overset{\oplus}{N}(C_2H_5)_2\overset{\ominus}{H}Cl$, $C_6H_5\overset{\oplus}{N}(C_2H_5)_2\overset{\ominus}{(COCH_3)Cl}$	(174)
	$C_6H_5N(CH_3)_2$	Ether	$C_6H_5\overset{\oplus}{N}(CH_3)_2\overset{\ominus}{(COCH_3)Cl}$	(174)
	$4\text{-}CH_3C_6H_4N(C_2H_5)_2$	Ether	$4\text{-}CH_3C_6H_4\overset{\oplus}{N}(C_2H_5)_2\overset{\ominus}{H}Cl$ (?), $4\text{-}CH_3C_6H_4\overset{\oplus}{N}(C_2H_5)_2\overset{\ominus}{(COCH_3)Cl}$	(174)
	C_5H_5N	Ether	$C_5H_5\overset{\oplus}{N}\overset{\ominus}{(COCH_3)Cl}$ (unstable)	(174, 228, 555)
	C_9H_7N	Ether	$C_9H_7\overset{\oplus}{N}\overset{\ominus}{(COCH_3)Cl}$, $C_9H_7\overset{\oplus}{N}\overset{\ominus}{H}Cl$	(174)
	$2\text{-}CH_3C_9H_6N$	Ether	$2\text{-}CH_3C_9H_6\overset{\oplus}{N}\overset{\ominus}{H}Cl$, $2\text{-}CH_3C_9H_6\overset{\oplus}{N}\overset{\ominus}{(COCH_3)Cl}$	(174)
	$C_{12}H_8N$	Ether	$C_{12}H_8\overset{\oplus}{N}\overset{\ominus}{(COCH_3)Cl}$	(174)
	$([(CH_3)_2NC_6H_4]_2C=)_2$	Ether	$([(CH_3)_2NC_6H_4]_2C=)_2 \cdot 4CH_3COCl$	(458)
	$(C_2H_5)_3N$	Ether (+ H_2O)	$(CH_3CO)_2O$	(7)
	C_5H_5N	Ether (+ H_2O)	$(CH_3CO)_2O$	(7)
Propionyl........	$(C_2H_5)_3N$	Ether (+ H_2O)	$(C_2H_5CO)_2O$	(7)
	(C_5H_5N)	Ether (+ H_2O)	$(C_2H_5CO)_2O$	(7)

2-Ethylhexanoyl..	(C_5H_5N)	Benzene (+ H_2O)	$(C_4H_9CHCO)_2O$
			    |
			    C_2H_5
				(7)

Propionyl.........	$(C_3H_7)_3N$	Ligroin	$CH_3CHCOCCH_3$ (?)
			    | |
			  $C-O-CC_2H_5$
				(725, 727)

Hexanoyl.........	$(C_2H_5)_3N$	Ether ($+ H_2O$)	$C_5H_{11}COC_5H_{11}$	(603)
Lauroyl..........	$(C_2H_5)_3N$	Ether ($+ H_2O$)	$C_{11}H_{21}COC_{11}H_{21}$	(603)
2,3-Dichloro- butyryl.........	$(C_2H_5)_3N$		2-Chlorocrotonyl chloride	(450)
3-Chloroacrylyl...	$(C_2H_5)_3N$		Acrylyl chloride	(450)
Suberyl..........	$(C_2H_5)_3N$	Benzene ($+$ KOH)	1,8-Cyclotetradecanedione (10%)	(95)
Sebacyl..........	$(C_2H_5)_3N$	Ether ($+$ KOH)	1,10-Cyclotriadecanedione (16%)	(95)
Thapsyl..........	$(C_2H_5)_3N$	Ether ($+$ KOH)	1,16-Cyclotriacontanedione (5.3%)	(95)
9-Octadecanedi- oyl.............	$(C_2H_5)_3N$	Ether ($+$ KOH)	Civetone (33%)	(94)
3-Methylhexa- decanedioyl.....	$(C_2H_5)_3N$	Ether ($+$ KOH)	dl-Muscone	(94)

* Ether = ethyl ether.

more than equivalent amounts of tertiary amine, it is probable that the mechanism of the process consists of an elimination reaction which is catalyzed by base, but requires equivalent quantities of amine, owing to subsequent removal of amine as hydrochloride.

$$R_2CHCOCl \ + \ :NR_3 \ \rightarrow \ R_2\overset{\ominus}{\overset{..}{C}}COCl \ + \ R_3\overset{\oplus}{NH}$$

$$R_2\overset{\ominus}{C}\overset{\curvearrowleft}{-}\overset{\overset{O}{\|}}{C}-Cl \ \rightarrow \ R_2C{=}C{=}O \ + \ \overset{\ominus}{Cl}$$
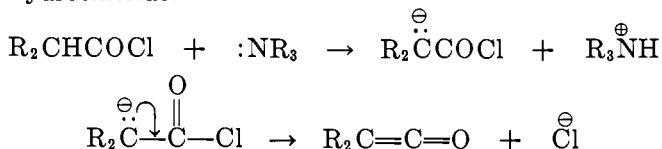
Reactions of aliphatic acid chlorides involving dehydrochlorination with tertiary amines have led to other compounds in addition to ketenes. A series of valuable higher-membered cyclic ketones, including civetone and *dl*-muscone, have been prepared from the appropriate bis(carbonyl chlorides) with triethylamine in ether (94, 95). The general reaction pattern may be illustrated by the following:

$$\begin{array}{c} O{=}CCl \\ | \\ (CH_2)_n \\ | \\ O{=}CCl \end{array} \rightarrow \begin{bmatrix} CH{=}C{=}O \\ | \\ (CH_2)_{n-2} \\ | \\ CH{=}C{=}O \end{bmatrix} \rightarrow \begin{bmatrix} (CH_2)_{n-2}{-}CH{-}CO \\ | \qquad\qquad | \\ CH{=\!=\!=}C{-}O \end{bmatrix} \rightarrow$$

$$\begin{bmatrix} (CH_2)_{n-2}{-}CHCOOH \\ | \qquad\qquad | \\ CH{=\!=\!=}COH \end{bmatrix} \rightarrow (CH_2)_n \overset{CO}{\underset{CO}{\diagup\,\diagdown}} (CH_2)_n \ +$$

$$(CH_2)_nC{=}O \ + \ HOOC(CH_2)_n[CO(CH_2)_n]_xCOOH$$
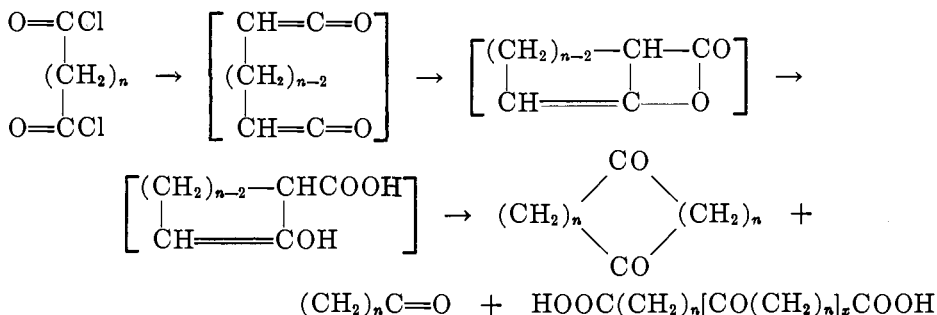
Satisfactory conversion to the cyclic monoketones has been achieved in certain cases by application of the dilution principle. Thus, civetone has been prepared (94) in 33 per cent yield from 9-octadecendioyl chloride after hydrolysis and decarboxylation of the initially formed intermediate.

Dehydrochlorination reactions of acid chlorides frequently have led to ketene dimers, intermediates from which valuable derivatives have been obtained. Laurone has been synthesized (603) in 46–55 per cent overall yield from lauroyl chloride by a hydrolytic decarboxylation of the ketene dimer, best represented as follows:

$$2C_{11}H_{23}COCl \ + \ 2(C_2H_5)_3N \ \xrightarrow{(C_2H_5)_2O} \ C_{11}H_{23}COC{=}C{=}O \ \xrightarrow{H_2O}$$
$$\underset{\overset{|}{C_{10}H_{21}}}{}$$
$$C_{11}H_{23}COC_{11}H_{23} \ + \ CO_2$$
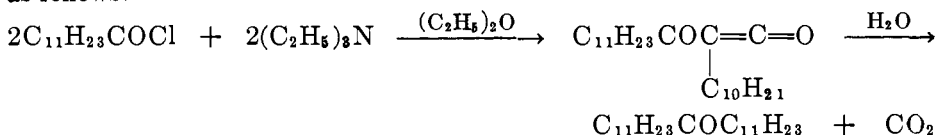
An attractive synthetic route to derivatives of β-keto acids—for example, esters of the type $RCH_2COCHRCO_2C_2H_5$—consists in allowing a ketene dimer to react with ethanol.

$$RCH_2COC{=}C{=}O \ + \ C_2H_5OH \ \xrightarrow{H^{\oplus}} \ RCH_2COCHCOOC_2H_5$$
$$\qquad\quad \underset{R}{|} \qquad\qquad\qquad\qquad\qquad\qquad \underset{R}{|}$$
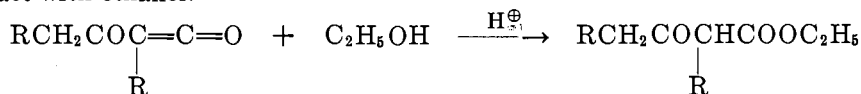
The latter series of reactions has not been extensively reported.

D. REACTION WITH COMPOUNDS CONTAINING A CARBON–NITROGEN DOUBLE BOND

Reactions of aliphatic acid chlorides with the carbon–nitrogen double bond have not been extensively reported (see table 15). One case of this type appears to be the reaction of butyryl chloride with indolenine (436). The real action is

$$\text{(indolenine structure)} \quad + \quad C_3H_7COCl \quad \rightarrow \quad \text{(acylated product structure)}$$
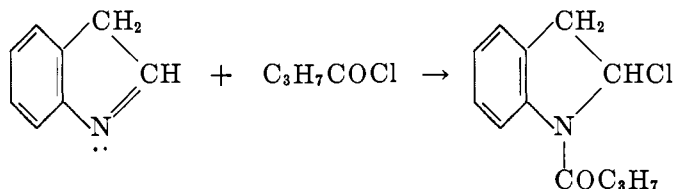
one of addition. Other attempts to accomplish this type of reaction have been unsuccessful (680).

A series of patents (429, 594, 595) covering the manufacture of quaternary compounds for use as softening agents, water repellants, etc., from tertiary amines, aliphatic nitriles, formaldehyde, and aliphatic acid chlorides is apparently the only other significant example of this reaction. Evidently the products in these reactions are mixtures consisting of some proportion of quaternized material derived from the following sequence:

$$R'C{\equiv}N \ + \ HCHO \ \rightarrow \ R'CH{=}NCHO \ \xrightarrow{\text{RCOCl}}$$
$$\text{(and polymers)}$$

$$R'CHClN(COR)CHO \ \xrightarrow{R_3N:} \ \overset{\oplus}{R}NCHR'N(COR)CHO \ \overset{\ominus}{Cl}$$
$$\text{(and polymers)} \qquad\qquad \text{(and polymers)}$$
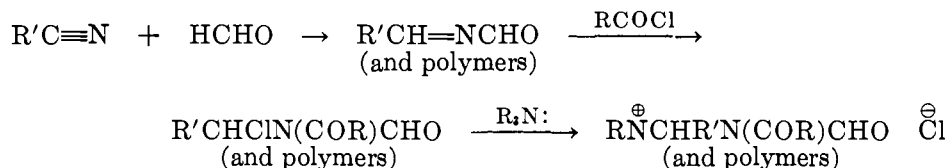
A series of fatty acid chlorides have been treated with the diamidine "Biguanide" in toluene in the presence of sodium carbonate to yield a series of alkylguanamines (2-alkyl-4,6-diamino-s-triazines) (269).

$$\text{(Biguanide structure)} \quad + \quad \begin{array}{c} Cl \\ | \\ CR \\ \| \\ O \end{array} \quad \rightarrow \quad H_2O \ + \ HCl \ +$$

$$\left[\text{(triazine structure)} \rightleftharpoons \text{(triazine tautomer structure)} \right]$$
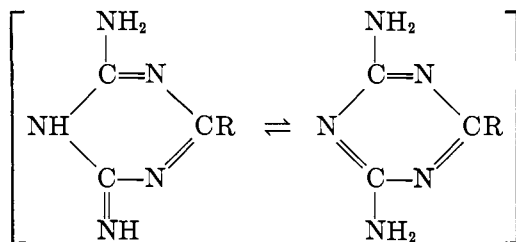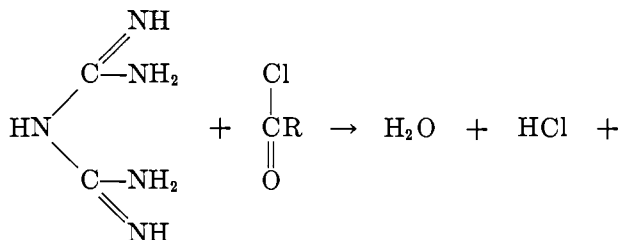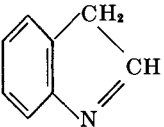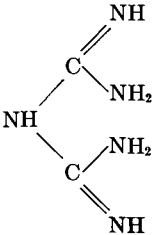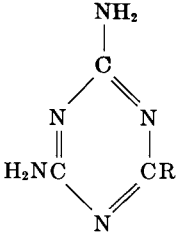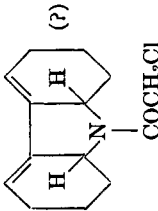
TABLE 15

Reactions of aliphatic acid chlorides with compounds containing a carbon–nitrogen double bond

ACID CHLORIDE	COMPOUND	SOLVENT, METHOD	PRODUCTS	REFERENCES
Acetyl..........	C_6H_5NC $C_6H_5CH=NC_6H_5$		$C_6H_5N=CClCOCH_3$ $C_6H_5CHClN(COCH_3)C_6H_5$	(503) (241)
Butyryl........				(436)
Palmitoyl......	Nitrile + HCHO	Heated, then RCOCl, then C_5H_5N		(594, 595)
Stearoyl........	Nitrile + HCHO			(594, 595)
Adipyl.........	Nitrile + HCHO			(429)
Glutaryl........	Nitrile + HCHO			(429)
Decanoyl Lauroyl Myristoyl }..... Palmitoyl Stearoyl		$C_6H_5CH_3$, Na_2CO_3	 $R = C_9H_{19}$, $C_{11}H_{23}$, $C_{13}H_{27}$, $C_{15}H_{31}$, $C_{17}H_{33}$	(269)

Chloroacetyl....	$C_6H_5CH=N-N=CHC_6H_5$	C_6H_5CHO, $C_6H_5CH=NNHCOCH_2Cl$ (60)
	$C_6H_{11}=N-N=C_6H_{11}$	NH_4Cl, (60)

(?)

$COCH_2Cl$

The compounds have proven of value as intermediates for the manufacture of therapeutic agents and medicinals.

Other instances of addition of acetyl chloride to compounds containing the —C=N— grouping are with isocyanides. Thus, phenyl isocyanide and acetyl chloride yield the adduct $C_6H_5N=CCl(COCH_3)$ (503). Schiff bases provide other comparable examples. Benzylideneaniline and acetyl chloride have also given an adduct (241).

VIII. REACTION OF ALIPHATIC ACID CHLORIDES WITH AMIDES AND IMIDES

Included among the variety of products that may be obtained from aliphatic acid chlorides and amides and imides are amide hydrochlorides, amidines, mono- and diacylated amides, various heterocyclic derivatives, and acylated imides. From other amide types may be obtained acylated saccharins, barbituric acid derivatives, mono- and diureides, thiadiazoles, and other compounds.

A. REACTION WITH AROMATIC CARBOXYLIC AMIDES

Aliphatic acid chlorides have been caused to react with aromatic carboxylic amides to yield products that vary widely with the conditions employed.

The formation of salts from aromatic carbonamides and aliphatic acid chlorides at room temperature has been observed in a number of instances. Acetyl chloride and benzamide in anhydrous ether have given *N*-acetylbenzamide hydrochloride (174) and possibly *N*-acetylbenzamide.

$$CH_3COCl \quad + \quad C_6H_5CONH_2 \quad \rightarrow \quad C_6H_5CO\overset{\oplus}{N}H_2\overset{\ominus}{Cl}COCH_3$$
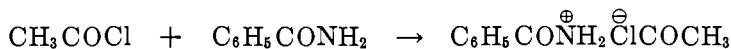
Comparable salts of aliphatic amides have rarely been reported, but several derived from aromatic amides are sufficiently stable to be isolated. In the usual aliphatic amide, such as acetamide, structure III contributes predominantly to the resonance state, with the result that the nitrogen atom in the molecule is essentially neutral in character and salt formation with acids is not possible.

$$CH_3-\overset{\overset{\textstyle O}{\|}}{C}-\overset{..}{N}H_2 \leftrightarrow CH_3-\underset{\oplus}{\overset{\overset{\textstyle \ominus}{\overset{\textstyle O}{|}}}{C}}-\overset{..}{N}H_2 \leftrightarrow CH_3-\overset{\overset{\textstyle \ominus}{\overset{\textstyle O}{|}}}{C}=\overset{\oplus}{N}H_2 \leftrightarrow \overset{\oplus}{H}CH_2=\overset{\overset{\textstyle \ominus}{\overset{\textstyle O}{|}}}{C}-\overset{..}{N}H_2$$

$$\quad\quad\quad I \quad\quad\quad\quad\quad\quad II \quad\quad\quad\quad\quad\quad III \quad\quad\quad\quad\quad\quad IV$$
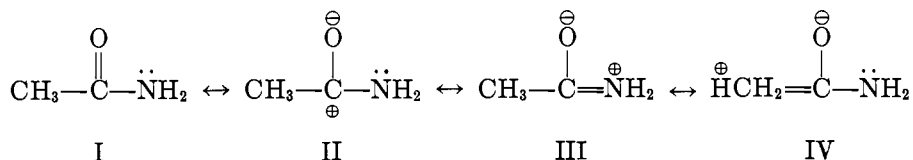
With benzamide, however, apparently the benzene ring, through the equivalent resonance structures IV and V, and also VI, contributes significantly to the

resonance state to confer some degree of basicity upon the nitrogen atom,
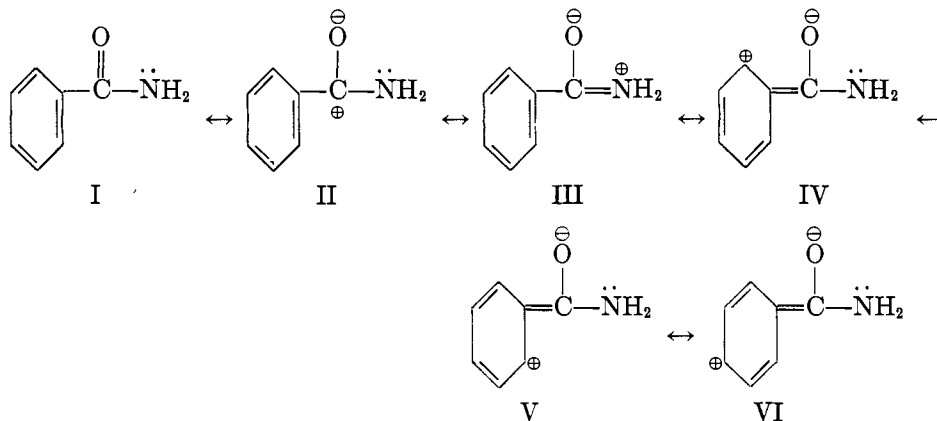
enabling salt formation. Only a few instances of the formation of such salts have been reported in the literature. They are included in table 16.

Aliphatic acid chlorides have been observed to induce the formation of amidines from formanilide, acetanilide, or benzanilide.

$$2RCONHC_6H_5 \xrightarrow[R = H, CH_3, C_6H_5]{R'COCl} \begin{array}{c} RC{=}NC_6H_5 \\ | \\ NHC_6H_5 \end{array} + R'COOH$$
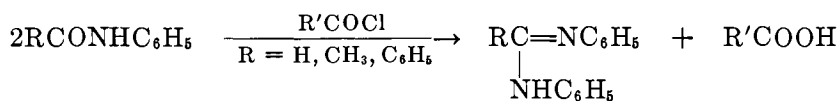
The reaction has also been incorrectly reported (322, 533) as a conversion in which either hydrazobenzene or bases were formed. N,N-Diphenylformamidine, N,N-diphenylacetamidine, and N,N-diphenylbenzamidine have been obtained from formanilide, acetanilide, and benzanilide, respectively, with several aliphatic acid chlorides (236, 322, 533). This reaction may be assumed to occur through the sequence

$$C_6H_5NHCOR + RC(OH){=}NC_6H_5 \xrightarrow{-H_2O}$$

$$RCONC_6H_5CR{=}NC_6H_5 \xrightarrow{H_2O} C_6H_5NHCR{=}NC_6H_5 + RCOOH$$
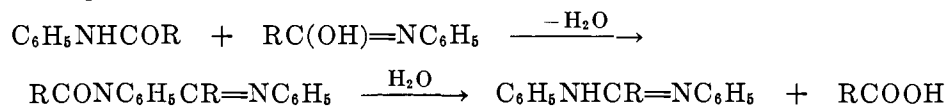
with hydrogen chloride aiding in the condensation step.

Interchange reactions between aromatic carbonamides and aliphatic acid chlorides have been observed in a number of instances.

$$RCOCl + C_6H_5CONHC_6H_5 \rightarrow C_6H_5COCl + RCONHC_6H_5$$
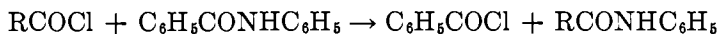
Succinyl chloride and benzanilide have given a little benzoyl chloride, propionyl chloride and benzanilide gave benzoyl chloride and propionanilide, and acetyl chloride and benzanilide have interacted to give benzoyl chloride and a compound which apparently was acetylbenzanilide and not acetanilide (236). It is noteworthy that the interchange reaction tends to supplant amidine formation with an increase in the chain length of the aliphatic acid chloride employed.
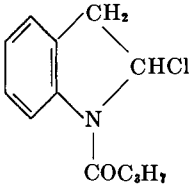
TABLE 16

Reaction of aliphatic acid chlorides with amides and imides

ACID CHLORIDE	AMIDE	CONDITIONS	PRODUCTS (YIELD)	REFERENCES
A. Aromatic carboxylic amides				
Acetyl.............	$C_6H_5CONH_2$		$C_6H_5CONH_2(\overset{\oplus}{COCH_3})\overset{\ominus}{Cl}$, $C_6H_5CONHCOCH_3(?)$	(174)
	$C_6H_5CONH_2$	Boiled	$C_6H_5CONHCOCH_3$, C_6H_5COOH, C_6H_5COCl	(689)
	$HCONHC_6H_5$	100°C., reflux	$HC(=NC_6H_5)NHC_6H_5$	(236)
	$CH_3CONHC_6H_5$		$(CH_3\overset{\oplus}{CONHC_6H_5})_2 \cdot \overset{\ominus}{HCl}$, ?, $(CH_3CO)_2$-NC_6H_5, $CH_3CONHC_6H_5$	(174)
	$CH_3CONHC_6H_5$	Reflux	$CH_3C(=NC_6H_5)NHC_6H_5$, $CH_3CONHC_6H_5$	(236)
	$CH_3CONHC_6H_5$ (sodium derivative)		$(C_6H_5NH)_2$ (?) (amidine)	(236, 533)
	$C_6H_5CONHC_6H_5$	180°C., 1 hr.	$C_6H_5CON(COCH_3)C_6H_5$, C_6H_5COCl, $C_6H_5CONHC_6H_5$	(236)
	$C_6H_5CONHC_6H_5$	Reflux, 20 hr.	$C_6H_5C(=NC_6H_5)NHC_6H_5$, $C_6H_5CONHC_6H_5$	(236)
	$C_6H_5CONHC_6H_5$	200°C.	$C_6H_5CON(COCH_3)C_6H_5$	(387)
	C_6H_5NHOH (sodium derivative)		$(C_6H_5NH)_2$ (?) (amidine)	(236, 533)
Propionyl..........	$HCONHC_6H_5$	Reflux	$HC(=NC_6H_5)NHC_6H_5$	(236)
	$CH_3CONHC_6H_5$	Reflux	$CH_3C(=NC_6H_5)NHC_6H_5$	(236)
Succinyl............	$CH_3CONHC_6H_5$	Reflux	$C_{29}H_{29}N_4$ (?) (amidine)	(236, 322)
	$CH_3CONHC_6H_5$	$CHCl_3$, reflux 7 hr.	$CH_3C(=NC_6H_5)NHC_6H_5$, $CH_3CONHC_6H_5$	(236)
	$C_6H_5CONHC_6H_5$	Reflux	$C_{42}H_{36}N_4$ (?) (amidine)	(236, 322)
B. Aliphatic carboxylic amides				
Acetyl.............	CH_3CONH_2		$(CH_3\overset{\oplus}{CONH_2})_2 \cdot \overset{\ominus}{HCl}$, ?, $(CH_3CO)_2NH$	(174)
	$C_6H_5CH_2CONHCH_2COOC_2H_5$ (sodium salt)	Ethyl ether	$C_6H_5CH_2CON(COCH_3)$ $\mid$ $CH_2COOC_2H_5$	(115)

Propionyl...........	CH_3CONH_2	RCOCl + C_5H_5N in $CHCl_3$; $-60°C$.	$C_2H_5CONHCOCH_3$ (24%)	(685)
	$C_2H_5CONH_2$	RCOCl + C_5H_5N in $CHCl_3$; $-70°C$.	$(C_2H_5CO)_2NH$ (60%)	(685)
4-Methylvaleryl.....	$(CH_3)_2CHCH_2CH_2CONH_2$	RCOCl + C_5H_5N in $CHCl_3$; $-60°C$.	$[(CH_3)_2CHCH_2CH_2CO]_2NH$	(685)
	CH_3CONH_2	RCOCl + C_5H_5N in $CHCl_3$; $-65°C$.	$(CH_3)_2CHCH_2CH_2CONHCOCH_3$ (38%)	(685)
Dipropylmalonyl....	$CH_2(CONH_2)_2$		$(C_3H_7)_2C(CONHCOCH_2CONH_2)_2$	(569)

<center>C. Sulfonamides</center>
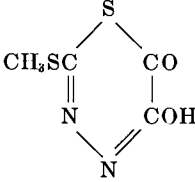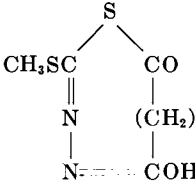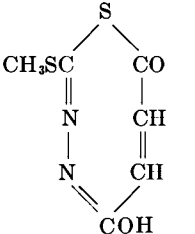
Acetyl...............	x,y-$(i$-$C_4H_9)_2C_{10}H_5SO_2NH_2$	Toluene	x,y-$(i$-$C_4H_9)_2C_{10}H_5SO_2NHCOCH_3$	(304)
Octanoyl............	4-$C_7H_{15}CONHC_6H_4SO_2NH_2$	Water–acetone (NaOH)	4-$C_7H_{15}CONHC_6H_4SO_2NHCOC_7H_{15}$	(304)
Decanoyl............	4-$C_7H_{15}CONHC_6H_4SO_2NH_2$	Xylene	4-$C_7H_{15}CONHC_6H_4SO_2NHCOC_9H_{19}$	(304)
Lauroyl.............	$1,2$-$C_6H_4(SO_2NH_2)_2$	$C_2H_4Cl_2$	$1,2$-$C_6H_4(SO_2NHCOC_{11}H_{23})_2$	(8)
	4-$CH_3C_6H_4SO_2NH_2$	No solvent	4-$CH_3C_6H_4SO_2NHCOC_{11}H_{23}$	(215)
Myristoyl...........	4-$CH_3C_6H_4SO_2NH_2$	No solvent	4-$CH_3C_6H_4SO_2NHCOC_{13}H_{27}$	(215)
Palmitoyl...........	$1,2$-$C_6H_4(SO_2NH_2)_2$	CCl_4	$1,2$-$C_6H_4(SO_2NHCOC_{15}H_{31})_2$	(8)
	4-$CH_3C_6H_4SO_2NH_2$	No solvent	4-$CH_3C_6H_4SO_2NHCOC_{15}H_{31}$	(215)
Stearoyl............	4-$CH_3C_6H_4SO_2NH_2$	No solvent	4-$CH_3C_6H_4SO_2NHCOC_{17}H_{35}$	(215)
Oleoyl..............	4-$CH_3C_6H_4SO_2NH_2$	No solvent	4-$CH_3C_6H_4SO_2NHCOC_{17}H_{33}$	(215)

<center>D. Ureas and urethans</center>
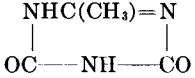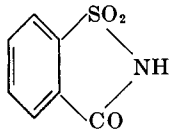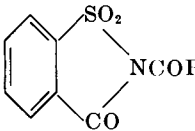
Acetyl...............	$CO(NH_2)_2$	Benzene (H_2SO_4)	$CH_3CONHCONH_2$	(673)
	$RCONHCONH_2$ (R = CH_3, C_2H_5, C_3H_7, C_5H_{11}, C_6H_{13}, C_7H_{15}, etc.)	Benzene (H_2SO_4)	$RCONHCONHCOCH_3$	(673)
	$R'R''NCOOR$ (R' = H)		$CH_3CON(R')COOR$	(61)
Chloroacetyl........	$CH_3NHCONH_2$ or $CH_3CONHCO$-$NHCH_3$		$CH_2ClCONHCONHCH_3$	(32)

TABLE 16—*Continued*

ACID CHLORIDE	AMIDE	CONDITIONS	PRODUCTS (YIELD)	REFERENCES
		D. Ureas and urethans—*Continued*		
Propionyl...........	$CO(NH_2)_2$	Benzene (H_2SO_4)	$C_2H_5CONHCONH_2$	(673)
	$RCONHCONH_2$ (R = C_3H_7, C_4H_9, C_5H_{11}, C_6H_{13}, C_7H_{15})	Benzene (H_2SO_4)	$RCONHCONHCOC_2H_5$	(673)
Butyryl............	$CO(NH_2)_2$	Benzene (H_2SO_4)	$C_3H_7CONHCONH_2$	(673)
	$RCONHCONH_2$ (R = C_4H_9, C_5H_{11}, C_8H_{17})	Benzene (H_2SO_4)	$RCONHCONHCOC_3H_7$	(673)
Valeryl.............	$CO(NH_2)_2$	Benzene (H_2SO_4)	$C_4H_9CONHCONH_2$	(673)
	$RCONHCONH_2$ (R = C_5H_{11}, C_6H_{15})	Benzene (H_2SO_4)	$RCONHCONHCOC_4H_9$	(673)
Hexanoyl..........	$CO(NH_2)_2$	Benzene (H_2SO_4)	$C_5H_{11}CONHCONH_2$	(673)
	$RCONHCONH_2$ (R = C_6H_{13})	Benzene (H_2SO_4)	$RCONHCONHCOC_5H_{11}$	(673)
Heptanoyl..........	$CO(NH_2)_2$	Benzene (H_2SO_4)	$C_6H_{13}CONHCONH_2$	(673)
	$RCONHCONH_2$ (R = C_7H_{15})	Benzene (H_2SO_4)	$RCONHCONHCOC_6H_{13}$	(673)
Octanoyl...........	$CO(NH_2)_2$	Benzene (H_2SO_4)	$C_7H_{15}CONHCONH_2$	(673)
3,3-Dimethylacrylyl.	$CO(NH_2)_2$	Benzene	$(CH_3)_2C{=}CHCONHCONH_2$	(548)
		E. Miscellaneous amide types		

Acetyl............	$NH_2CSNHNH_2$	S_2Cl_2	I: R = CH_3	(663)
Propionyl..........	$NH_2CSNHNH_2$	PCl_3	I: R = C_2H_5	(663)
Butyryl............	$NH_2CSNHNH_2$	S_2Br_2	I: R = C_3H_7	(663)
Valeryl............	$NH_2CSNHNH_2$	$ClSO_3H$	I: R = C_4H_9	(663)
2-Butenoyl.........	$NH_2CSNHNH_2$	$SOCl_2$	I: R = C_3H_5	(663)
3-Chloropropionyl...	$NH_2CSNHNH_2$	PCl_3	I: R = $CH_2{=}CH{-}$	(663)
2-Chlorobutyryl.....	$NH_2CSNHNH_2$	$SOBr_2$	I: R = $CH_3CH{=}CH{-}$	(663)

| Oxalyl............. | CH₃SCSNHNH₂ | | | (276) |

Oxalyl............. $CH_3SCSNHNH_2$

$$\begin{array}{c}S\\ CH_3SC \quad CO\\ \| \qquad \\ N \qquad COH\\ \| \\ N \end{array}$$

(276)

Succinyl............ $CH_3SCSNHNH_2$

$$\begin{array}{c}S\\ CH_3SC \quad CO\\ \| \qquad \\ N \qquad (CH_2)_2\\ N\text{------}COH \end{array}$$

(276)

Fumaryl............ $CH_3SCSNHNH_2$

$$\begin{array}{c}S\\ CH_3SC \quad CO\\ \| \qquad \|\\ N \qquad CH\\ \| \qquad \|\\ N \qquad CH\\ COH \end{array}$$

(276)

F. Imides

Acetyl............. $H_2NCONHCONH_2$ $\quad$ CH₃COCl (excess)

$$\begin{array}{c}NHC(CH_3)=N\\ OC\text{---}NH\text{---}CO\end{array}$$

(532)

Lauroyl
Myristoyl
Palmitoyl
Stearoyl
Oleoyl

(benzisothiazolone sulfonyl NH structure) $\quad$ CHCl₃ (NaOH)

(N-acyl structure NCOR)

R = $C_{11}H_{22}$
R = $C_{13}H_{27}$
R = $C_{15}H_{31}$
R = $C_{17}H_{35}$
R = $C_{17}H_{33}$

(215)

Under more vigorous conditions the formation of acylated derivatives of amides is possible.

$$CH_3COCl + C_6H_5NHCOC_6H_5 \rightarrow C_6H_5N(COCH_3)COC_6H_5 + HCl$$
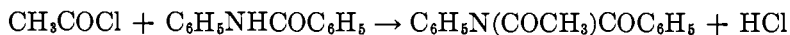
Usually treatment near 200°C. for extended times results in formation of acylated amide, although the overall yields cannot be considered as uniformly good (236, 387). The technique of acylation through the use of the (acid chloride)–pyridine complexes (see Section VIII,B) is of value in this connection.

B. REACTION WITH ALIPHATIC CARBOXYLIC AMIDES

Although acetamide is reported to have been acylated with acetyl chloride (174), reactions of this type with aliphatic amides are not easily carried out and except for certain isolated cases (569) are particularly unattractive. The acylation of aliphatic amides with the addition products of pyridine and acid chlorides, however, appears promising. These addition compounds have smoothly mono-acylated primary amides in non-aqueous solvents at very low temperatures. Propionyl and 4-methylvaleryl chlorides have monoacylated acetamide at $-60°C$. in chloroform in 24 and 38 per cent yields, respectively (685). Somewhat better conversion has been achieved with the amide corresponding to the acid chloride used.

$$C_5H_5\overset{\oplus}{N}(COR)\overset{\ominus}{Cl} \quad + \quad R'CONH_2 \quad \rightarrow \quad R'CONHCOR \quad + \quad C_5H_5\overset{\oplus}{N}H\overset{\ominus}{Cl}$$
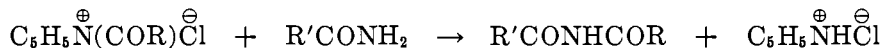
The theoretical reason why the alkanoylpyridinium chlorides are able to acylate amides while the free acid chloride is ineffective is not quite clear. Perhaps it is due to greater positivity of the acyl carbon atom in the complex in anhydrous organic solvents owing to possible resonance contribution of non-ionic structure II, or to an induction caused by the electronegative oxygen and the positively charged nitrogen atom in I, which renders the acyl carbon relatively more positive and thus capable of reacting more readily with the only very slightly negative nitrogen center of the almost neutral amide.

$$\underset{\underset{\text{R'CONH}_2}{\overset{|}{\underset{\oplus}{\text{R—C—O}^{\ominus}}}}}{\overset{\oplus}{\underset{\text{Cl}^{\ominus}}{\text{N}}}} \qquad \rightarrow \quad \text{R'CONHCOR} \quad + \quad \underset{\underset{\text{H}}{\overset{|}{\underset{\oplus}{\text{N}}}}}{\text{Cl}^{\ominus}}$$

Transition
state
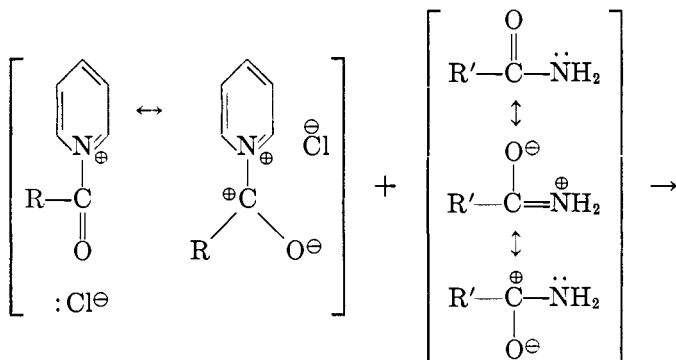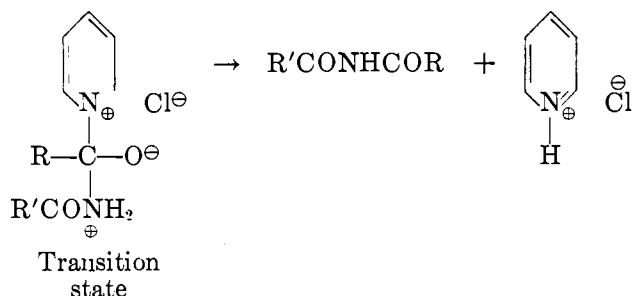
It has been observed that aromatic acid chlorides give diacylation of amides or even dehydration to nitriles through their pyridine addition compounds.

In the presence of certain aliphatic acid chlorides α-acylamino acids have been caused to undergo cyclization to azlactones, apparently through the enol form.

$$\text{RCHNHCOR'COOH} \quad \rightleftharpoons \quad \begin{bmatrix} \text{RCHCOOH} \\ | \\ \text{N=C(OH)R'} \end{bmatrix} \xrightarrow{\text{RCOCl}}$$

$$\underset{\underset{\text{CR'}}{\overset{\diagdown\diagup}{\underset{}{\text{N} \qquad \text{O}}}}}{\text{RCH—C=O}} \quad + \quad \text{H}_2\text{O}$$
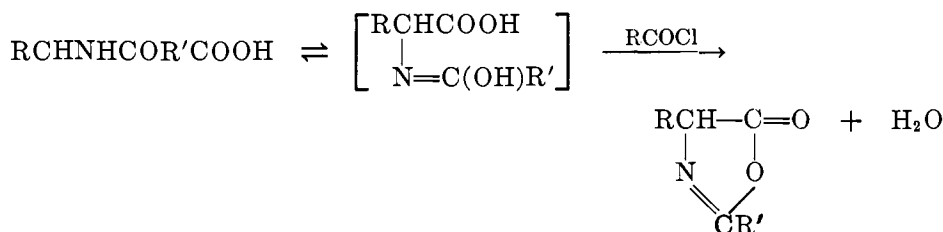
A similar reaction has also been encountered with ketones capable of enolization (Section X,A), in which the acyl chloride apparently acts as a dehydrating agent. The azlactone reaction has been applied to syntheses of peptides directly from amino acids with lower aliphatic acid chlorides (130, 131) in yields of from 20 to 70 per cent.

$$\text{RCH(NH}_2\text{)COOH} \xrightarrow{\text{RCOCl}} \text{RCH(NHCOR)COOH} \xrightarrow{\text{RCOCl}}$$

$$\underset{\underset{\text{CR'}}{\overset{\diagdown\diagup}{\underset{}{\text{N} \qquad \text{O}}}}}{\text{RCH—CO}} \xrightarrow{\text{R'NH}_2} \underset{\underset{\text{NHCOR}}{\overset{|}{}}}{\text{RCHCONHR'}}$$
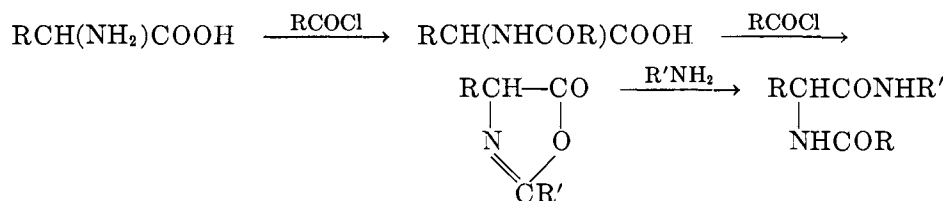
C. REACTION WITH SULFONAMIDES

It has been noticed that aliphatic acid chlorides acylate the amino group of a sulfonamide more readily than that of a carbonamide (8, 304), apparently as a consequence of the stabilization afforded to the resonance state of a sulfonamide by structures I and II, which maintain a degree of negativity at the nitrogen

$$\underset{\underset{\text{O}}{\overset{\text{O}}{\overset{\|}{\text{R—S—}}}}}{\underset{}{\overset{}{}}}\overset{\text{H}}{\underset{\text{H}}{\overset{\diagup}{\text{N}}}} \quad \leftrightarrow \quad \underset{\underset{\text{O}}{\overset{\text{O}}{\overset{\oplus|}{\text{R—S—}}}}}{}\overset{\overset{\ominus}{}\text{H}}{\underset{\text{H}}{\overset{\diagup}{\text{N}}}} \quad \leftrightarrow \quad \underset{\underset{\underset{\ominus}{\text{O}}}{\overset{\text{O}}{\overset{\oplus\|}{\text{R—S—}}}}}{}\overset{\text{H}}{\underset{\text{H}}{\overset{\diagup}{\text{N}}}} \quad \leftrightarrow \quad \underset{\underset{\text{O}}{\overset{\overset{\ominus}{\text{O}}}{\overset{|}{\text{R—S=}}}}}{}\overset{\text{H}}{\underset{\text{H}}{\overset{\oplus\diagup}{\text{N}}}}$$
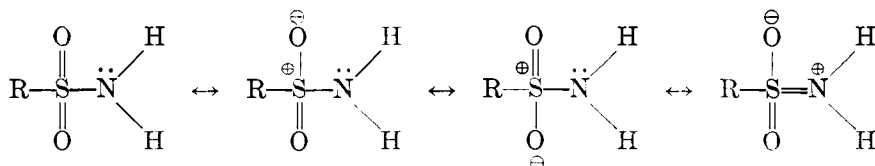
atom sufficient for attack. Acylations have been reported only for aromatic sulfon-amides by the Schotten–Baumann technique (304) or with aliphatic acid chlorides in organic solvents with or without the use of bases (8, 304).

$$C_6H_5SO_2NH_2 + RCOCl \rightarrow C_6H_5SO_2NHCOR + HCl$$
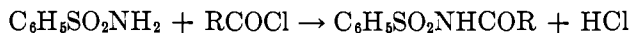
Aromatic sulfonamides would be expected to undergo acylation more easily than aliphatic types as a consequence of resonance involving the benzene ring
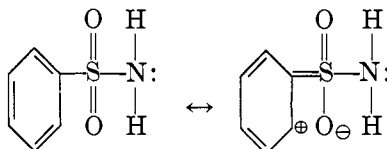
(indicated for one resonance form) which permits the nitrogen atom to retain its activity. This is true and parallels the case of benzamide and acetamide (Section VIII,A).

D. REACTION WITH UREAS AND URETHANS

The acylation of urea with aliphatic acid chlorides has been accomplished in

$$RCOCl + H_2NCONH_2 \rightarrow RCONHCONH_2 + HCl$$
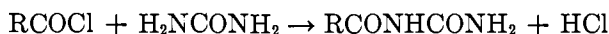
organic solvents to give principally the monoacylated ureas (32, 548, 673). Yields of monoureides ranging from 75 to 85 per cent of the theoretical have been obtained from urea and straight-chain aliphatic acid chlorides containing from two to eight carbon atoms, using a little sulfuric acid as a catalyst in benzene solution (673). Use of the acid as a catalyst produces a resonating ionic intermediate which is relatively more easily acylated than the urea molecule, evidently as a consequence of the stabilization contributed by structures I and
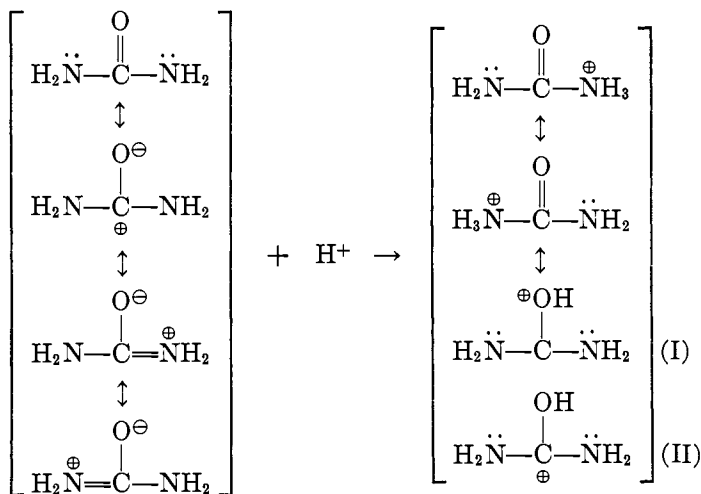
II to the resonance state. The monacylated ureas produced in this fashion have been found to be smoothly acylated to the diureides under similar conditions in 75–85 per cent overall yield.

$$RCOCl + R'CONHCONH_2 \rightarrow R'CONHCONHCOR + HCl$$
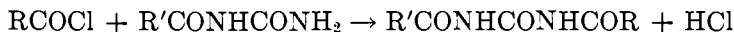
It has been suggested that the diacylated ureas are pseudo-ureido esters (729) in which the second acyl group is attached to the oxygen atom, $RCONHC=NHCOOCH_3$, but this contention has been proven incorrect by the observation (673) that the same diacylated urea is obtained from the reaction of acetylurea and butyryl chloride as is obtained from the reaction of butyrylurea and acetyl chloride. Slightly better yields for the mixed diacylated ureas result when the monoureide of the acid of higher molecular weight is prepared first and is acylated with the acid chloride of lower molecular weight. Monoacylated ureas have also been obtained from stearoyl and oleoyl chlorides by reaction of the sodium derivative of urea in liquid ammonia (352).

An interesting comparison of the interchange reactions of acetyl bromide and the acetylations of acetyl chloride has recently been observed (61) with urethans of the general type $RR'NCOOR$. The former afforded the substituted acetamides and an alkyl bromide, while acetyl chloride gave only acetylation for monosubstituted urethans and no reaction for disubstituted urethans ($R = R' = CH_3$, C_6H_5, etc.).

$$CH_3COBr + RR'NCOOR \rightarrow CH_3CONRR' + RBr + CO_2$$

$$CH_3COCl + RR'NCOOR \rightarrow CH_3CON(R')COOR + RCl$$
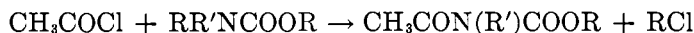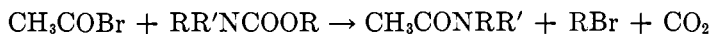
$R' = H$, CH_3; $R = H$.

E. REACTION WITH MISCELLANEOUS AMIDE TYPES

Condensations of aliphatic acid chlorides with thiosemicarbazide, $NH_2CSNHNH_2$, in the presence of a suitable condensing agent have led to substituted 1,3,4-thiadizoles, compounds of interest as antibacterial agents (663). The condensation probably proceeds through the tautomeric thienol form with the condensing agent aiding in the removal of water.

2-Amino-5-R-1,3,4-
thiadiazole
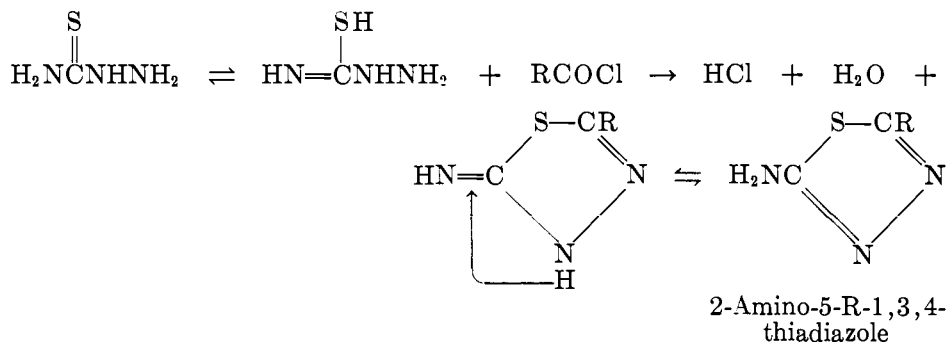
Dibasic aliphatic acid chlorides have been condensed with methyl N-aminodi-thiocarbamate, $CH_3S_2CNHNH_2$, to give a series of substituted 1,3,4-thiadi-azines (276).

$$
\begin{bmatrix}
\overset{S}{\overset{\|}{CH_3SCNHNH_2}} & \rightleftharpoons & \overset{SH}{\overset{|}{CH_3SCNNH_2}}
\end{bmatrix} + (COCl)_2 \rightarrow
$$
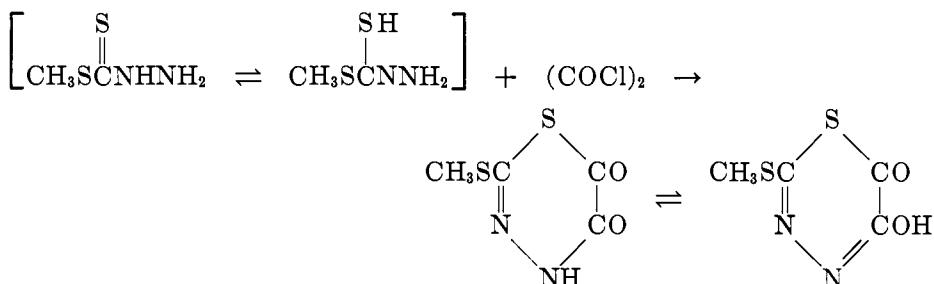
Oxalyl, succinyl, and fumaryl chlorides have been used; the last two chlorides yielded octathiadiazines.

IX. Reaction of Aliphatic Acid Chlorides with Hydroxy-containing Compounds (Esterification Reactions)

Second in importance only to the reactions with amines are the esterification reactions of aliphatic acid chlorides with a host of hydroxy-containing compounds. Roughly ten per cent of the literature concerned with the reactions of aliphatic acid chlorides deals with the esterification of primary and secondary (occasionally tertiary) alcohols, phenols, glycols, glycerol, higher polyhydroxy compounds, and hydroperoxides. A pronounced tendency to apply acid chlorides instead of acids in the esterification of some hydroxy-containing compounds has manifested itself in recent years.

A. REACTION WITH ALCOHOLS (SEE TABLE 17)

Primary and secondary alcohols may be readily esterified with aliphatic acid chlorides in organic solvents, under Schotten–Baumann conditions (see Section VIII,A), or even for certain isolated cases in the gaseous phase.

$$RCOCl + R'OH \rightarrow RCOOR' + HCl$$
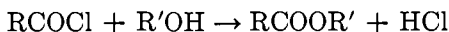
The reaction is usually quite rapid, is somewhat exothermic, and proceeds well at low temperatures, but the rate of esterification is less rapid than for esterification with the corresponding aliphatic acid bromide. With methanol and ethanol acetyl chloride produces less ester than either benzenesulfonyl chloride or benzoyl chloride in the Schotten–Baumann technique (481), owing to its greater tendency to hydrolyze under these conditions. Esterifications have been carried out in ether (108), dioxane (534), carbon tetrachloride (561), in the presence of excess alcohol, or in the absence of a solvent altogether.

Unlike the acylation of amines (see Section VIII,A) the removal of the hydrogen chloride produced in the reaction is not always required. With a primary alcohol there is no formation of alkyl chloride or olefin with the hydrogen chloride formed in the reaction. However, the ester may be hydrolyzed back to the alcohol and the acid if the hydrogen chloride is permitted to accumulate and re-

main in the solvent, particularly at higher temperatures for aqueous or alcoholic solutions and, in fact, may react in other ways, so that excellent yields are achieved only when it is removed. Frequently pyridine has been applied as an efficient hydrogen chloride acceptor (561). An interesting illustration of the deleterious effect of hydrogen chloride is given by the reaction of crotonyl chloride with ethanol (301), in which it has been found to add to the double bond of the acid chloride in good yield to give ethyl β-chlorobutyrate.

$$CH_3CH{=}CHCOCl + C_2H_5OH \rightarrow CH_3CHClCH_2COOC_2H_5$$
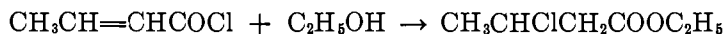
Secondary alcohols generally require removal of the hydrogen chloride produced for satisfactory acylation. With tertiary alcohols, however, acylation does not normally occur; the reaction affords instead tertiary chlorides (156) or olefins.

$$CH_3COCl + R_3COH \rightarrow R_3CCl + CH_3COOH$$

$$CH_3COCl + (CH_3)_3COH + C_5H_5N \rightarrow (CH_3)_3COOCH_3 + C_5H_5N \cdot HCl$$
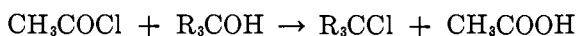
The Schotten–Baumann acylation of alcohols has been submitted to extensive practical study (481). In general, the same conditions prevail that are applicable for amines. The yield of ester is uniformly greater the lower the temperature, as hydrolysis of the acid chloride is inhibited. The acid chloride should be added in small portions to prevent local overheating. Potassium hydroxide has functioned best as the hydrogen chloride acceptor, although sodium hydroxide is good. Best results have been obtained when the alkali is as concentrated as possible, as the amount of ester formed generally decreases with increasing excess of alkali used. In order to prevent hydrolysis of the ester it is preferably removed from the solution as rapidly as possible. Generally from 120 to 150 per cent of the theoretical amount of acid chloride assures a reasonable yield. Acetylations of aqueous methanol and ethanol solutions by this technique are ineffective, but the substitution of higher homologous acid chlorides reduces the importance of the competing hydrolysis reaction. The use of acetone as a solvent for acylations with the lower acid chloride homologs is efficient. The esterification of bifunctional compounds such as aminoalcohols, which are usually prone to react preferentially at the amino group (see Section VII) can be accomplished by conducting the reaction in acid solution, under which conditions the salt of the amine is inert and the hydroxyl group is readily acylated. This is the case in the preparation of several effective cationic surface-active agents (356, 361).

$$RCOCl + \overset{\ominus}{Cl}\overset{\oplus}{N}H_3C_2H_4OH \rightarrow RCOOC_2H_4\overset{\oplus}{N}H_3\overset{\ominus}{Cl}$$

$$RCOCl + \overset{\ominus}{Cl}\overset{\oplus}{N}H_2(C_2H_4OH)_2 \rightarrow [RCOOC_2H_4\overset{\oplus}{N}H_2C_2H_4OH]\overset{\ominus}{Cl}$$
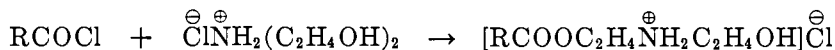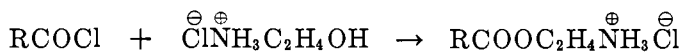
From a theoretical point of view the acylation of alcohols is more suitable for study than the acylation of amines. A large number of homogeneous systems are available, and in some of them the rate of reaction is sufficiently slow to enable measurement of the kinetics involved. This has been accomplished with acetyl, propionyl, butyryl, and chloroacetyl chlorides with ethylene chlorohydrin in dioxane solution at 5°, 15°, 25°, and 35°C. (534); with the isomeric acid chlorides

TABLE 17

Reaction of aliphatic acid chlorides with alcohols

ACID	ALCOHOL	METHOD*	BASE	PRODUCTS (YIELD)	REFERENCES
		Primary and secondary alcohols			
Acetyl...............	C_2H_5OH	b (ether)†		$CH_3COOC_2H_5$	(108)
	ROH (R = $CH_3, C_2H_5, C_3H_7, C_4H_9,$ C_5H_{11})	d		CH_3COOR	(591)
	ROH (R = CH_3, C_2H_5)	a	NaOH	CH_3COOR	(481)
	$C_6H_{11}OH$	b (dioxane)		$CH_3COOC_6H_{11}$	(534)
	$C_6H_5CH_2OH$	b (dioxane)		$CH_3COOCH_2C_6H_5$	(431)
	$HOCH_2CH_2Cl$	b (dioxane)		$CH_3COOCH_2CH_2Cl$	(431, 534)
	$HOCH_2NHCOR$	?		CH_3COOCH_2NHCOR	(190)
	$HO(CH_2)_3Cl$	b (dioxane)		$CH_3COO(CH_2)_3Cl$	(176)
	$HOC_2H_4OC_2H_4N(CH_2CH_2)_2NC_2H_4\text{-}$ OC_2H_4OH	?		Corresponding diester	(465)
	$C_6H_5CHOHCOOH$	d		$C_6H_5CH(OCOCH_3)COOH$	(683)
	$RR'NCOOCH_2CH_2OH$	?		$RR'NCOOCH_2CH_2OCOCH_3$	(175)
Propionyl..........	ROH (R = $CH_3, C_2H_5, C_3H_7, C_4H_9,$ C_5H_{11})	d		C_2H_5COOR	(591)
	$C_6H_5CH_2OH$	b (dioxane)		$C_2H_5COOCH_2C_6H_5$	(431)
	$HOCH_2CH_2Cl$	b (dioxane)		$C_2H_5COOCH_2CH_2Cl$	(431, 534)
	$HOCH_2NHCOR$			$C_2H_5COOCH_2NHCOR$	(190)
	$C_6H_{11}OH$	b (dioxane)		$C_2H_5COOC_6H_{11}$	(534)
Butyryl.............	ROH (R = $CH_3, C_2H_5, C_3H_7, C_4H_9,$ C_5H_{11})	d		C_3H_7COOR	(534)
	$C_6H_5CH_2OH$	b (dioxane)		$C_3H_7COOCH_2C_6H_5$	(591, 592)
	$HOCH_2CH_2Cl$	b (dioxane)		$C_3H_7COOCH_2CH_2Cl$	(534)
	$HOCH_2NHCOR$			$C_3H_7COOCH_2NHCOR$	(431, 534)
	$C_6H_{11}OH$	b (dioxane)		$C_3H_7COOC_6H_{11}$	(190)
Isobutyryl.........	$C_6H_5CH_2OH$	b (dioxane)		$(CH_3)_2CHCOOCH_2C_6H_5$	(534)
	$HOCH_2CH_2Cl$	b (dioxane)		$(CH_3)_2CHCOOCH_2CH_2Cl$	(534)

	$C_6H_{11}OH$	b (dioxane)		$(CH_3)_2CHCOOC_6H_{11}$	(431)
	$HOCH_2NHCOR$			$(CH_3)_2CHCOOCH_2NHCOR$	(190)
Trimethylacetyl.....	CH_3OH	?		$(CH_3)_3CCOOCH_3$	(735)
Isovaleryl..........	$HOCH_2CH_2Cl$	b (dioxane)		$i\text{-}C_4H_9COOCH_2CH_2Cl$	(431)
	$C_6H_5CH_2OH$	b (dioxane)		$i\text{-}C_4H_9COOCH_2C_6H_5$	(534)
	$C_6H_{11}OH$	b (dioxane)		$i\text{-}C_4H_9COOC_6H_{11}$	(534)
Heptanoyl..........	ROH	c (CHCl$_3$)	Pyridine	$C_6H_{13}COOR$	(583)
	$\quad C_6H_5CH_2OH$				
	$\quad C_6H_5CH_2CH_2OH$				
	$\quad C_6H_5(CH_2)_3OH$				
	$\quad$ Geraniol				
	$\quad$ Terpineol				
5-Methylhexanoyl...	ROH (as for heptanoyl)	c (CHCl$_3$)	Pyridine	$i\text{-}C_6H_{13}COOR$	(583)
Lauroyl.............	ROH (R = CH_3, C_2H_5)	?		$C_{11}H_{23}COOR$	(328)
	$C_6H_5CH_2OH$	b(dioxane)		$C_{11}H_{23}COOCH_2C_6H_5$	(625)
	Menthol	?		Menthyl laurate	(112)
	$HOC_2H_4OC_2H_4N(CH_2CH_2)_2NC_2H_4\text{-}$	?		Corresponding diester	(465)
	$\quad OC_2H_4OH$				
Myristoyl...........	ROH (R = CH_3, C_2H_5)	?		$C_{13}H_{27}COOR$	(328)
	$C_6H_5CH_2OH$	b (dioxane)		$C_{13}H_{27}COOCH_2C_6H_5$	(625)
	Menthol	?		Menthyl myristate	(112)
Palmitoyl..........	ROH (R = CH_3, C_2H_5)	?		$C_{15}H_{31}COOR$	(328)
	$C_6H_5CH_2OH$	b (dioxane)		$C_{15}H_{31}COOCH_2C_6H_5$	(625)
	Menthol	?		Menthyl palmitate	(112)
Stearoyl...........	ROH (R = CH_3, C_2H_5)	?		$C_{17}H_{35}COOR$	(328)
	$C_6H_5CH_2OH$	b (dioxane)		$C_{17}H_{35}COOCH_2C_6H_5$	(625)
	Menthol	?		Menthyl stearate	(112)
Oleoyl.............	$HOCH_2CH_2CN$	b (CCl$_4$)	Pyridine		
		b (ether)	Diethyl-aniline	$C_{17}H_{33}COOCH_2CH_2CN$	(561)
	$HOC_2H_4SO_3Na$	d	Na$_2$CO$_3$	$C_{17}H_{33}COOC_2H_4SO_3Na$	(340)
	$HOC_6H_{10}SO_3Na$	a	NaOH	$C_{17}H_{33}COOC_6H_{10}SO_3Na$	(340)
Sebacyl.............	CH_3OH (1 mole)	d		$(+H_2O)$ $CH_3OCO(CH_2)_8COOH$	(483)
	C_2H_5OH (absolute)	d		$C_2H_5OCO(CH_2)_8COCl$	(217)
Suberyl.............	CH_3OH(excess)	d		$CH_3COO(CH_2)_6COOCH_3$	(483)
Crotonyl............	C_2H_5OH	d		$CH_3CHClCH_2COOC_2H_5$	(301)

TABLE 17—*Concluded*

ACID	ALCOHOL	METHOD*	BASE	PRODUCTS (YIELD)	REFERENCES
			Tertiary alcohols		
Acetyl.............	t-C_4H_9OH	d		t-C_4H_9Cl	(156)
	t-C_4H_9OH	c	Pyridine	$CH_3COO(t$-$C_4H_9)$	(156)
	$(C_6H_5)_2C(OH)COCH_3$	d		$(C_6H_5)_2C(OCOCH_3)COCH_3,$ $C_6H_5COC(OCOCH_3)CH_3$	(682)
				$\mid$	
				C_6H_5	
	$(C_6H_5)_3COH$	d		$(C_6H_5)_3CCl$	(649)
	$(C_6H_5CH_2)_3COH$	d		$CH_3COOC(CH_2C_6H_5)_3$	(649)
	t-C_4H_9OH	c (ether)†	Dimethyl-aniline	$CH_3COO(t$-$C_4H_9)$ (63–68%)	(291)
Chloroacetyl........	t-C_4H_9OH	c (ether)	Dimethyl-aniline	$CH_2ClCOO(t$-$C_4H_9)$ (63%)	(291)
Propionyl...........	t-C_4H_9OH	c (ether)	Dimethyl-aniline	$C_2H_5COO(t$-$C_4H_9)$ (61.4%)	(291)
Isobutyryl.........	t-C_4H_9OH	c (ether)	Dimethyl-aniline	$(CH_3)_2CHCOO(t$-$C_4H_9)$ (71%)	(291)
Isovaleryl..........	t-C_4H_9OH	c (ether)	Dimethyl-aniline	i-$C_4H_9COO(t$-$C_4H_9)$ (26%)	(291)

* a = Schotten–Baumann type of reaction;
  b = alcohol in organic solvent + RCOCl;
  c = alcohol in organic solvent + base + RCOCl;
  d = no solvent.
† Ether = ethyl ether.

containing up to six carbon atoms for ethylene chlorohydrin, benzyl alcohol, and cyclohexanol in dioxane at 15°, 25° and 35°C. (431); with butyryl chloride for the first five normal alcohols at 2°, 15°, and 28°C. (591, 592); and for acetyl, some substituted benzoyl, and three chloroacetyl chlorides with ethanol in ether (108). The data obtained in these researches indicate that the rate of reaction for a given alcohol decreases with an increase in the chain length of the acid chloride, with propionyl chloride peculiarly out of line with the regular order of the series. Further, acetyl chloride and other homologous acyl chlorides react much more rapidly with a given alcohol than benzoyl chloride or substituted benzoyl chlorides (similar to the comparative rate in the hydrolysis reaction) but less rapidly than the chlorosubstituted acetyl chlorides. This has been usually explained on the basis that the positive potential of the carbonyl carbon atom in benzoyl chloride is lowered considerably by the adjacent phenyl group through the contributions of resonance forms I to III (or I' to III'), whereas in acetyl chloride the carbonyl unsaturation has no aromatic nucleus in conjugation with which to promote strong resonance.

$$CH_3COCl \;\leftrightarrow\; CH_3\overset{\oplus}{\underset{}{C}}{-}Cl \;\leftrightarrow\; \overset{\oplus}{H}\;\; CH_2{=}\overset{\overset{\ominus}{O}}{C}{-}Cl$$

(three forms)

$$CH_3CO^{\oplus}\;\;\overset{\ominus}{Cl} \;\leftrightarrow\; \overset{\ominus}{Cl}\;\; \overset{\oplus}{H}\;\; CH_2{=}C{=}O$$

(three forms)
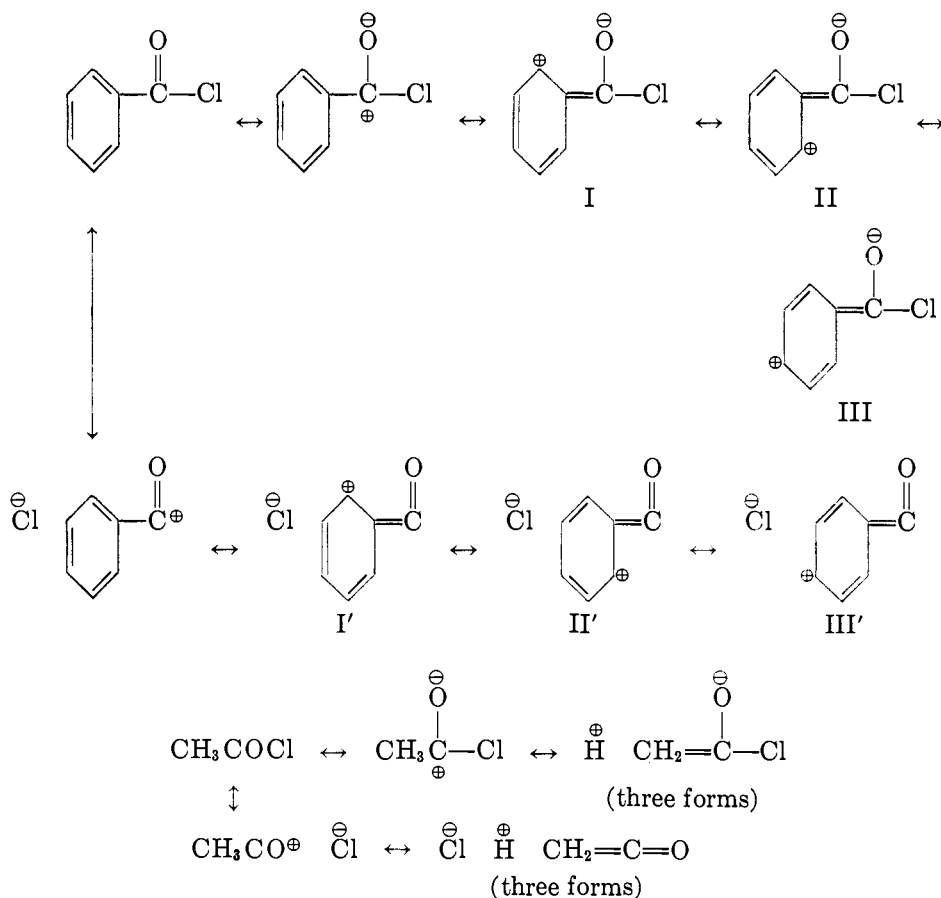
In chloroacetyl chloride, however, the enhanced rate of alcoholysis or hydrolysis may be attributed to an increased positivity of the carbonyl carbon atom induced by the electronegative chlorine atom. Branching of the chain in an aliphatic acid chloride has been observed to lower the velocity of the acylation, probably as a consequence of steric hindrance. The kinetics of alcoholysis of both aromatic (518, 519, 521) and aliphatic acid chlorides conform to a first-order reaction and in dilute solution the reaction has shown the characteristics of both a unimolecular and a pseudo-unimolecular reaction. Plotting the logarithm of the concentration *versus* time has given a straight line for the earliest points with a sharp transition point to a straight line of greater slope for the latter points. This observation has been explained by a mechanism which may operate through two simultaneous paths.

$$(1) \quad RCOCl + C_2H_5OH \underset{k_2}{\overset{k_1}{\rightleftarrows}} \overset{\overset{OH}{|}}{R\overset{|}{C}OC_2H_5} \overset{k_3}{\longrightarrow} RCOOC_2H_5 + H^{\oplus} + Cl^{\ominus}$$
$$\underset{Cl}{|}$$

$$(2) \qquad RCOCl \underset{k_2'}{\overset{k_1'}{\rightleftarrows}} (RC{=}O)^{\oplus} + Cl^{\ominus}$$

$$(RC{=}O)^{\oplus} + C_2H_5OH \overset{k_3'}{\longrightarrow} RCOOC_2H_5 + H^{\oplus}$$
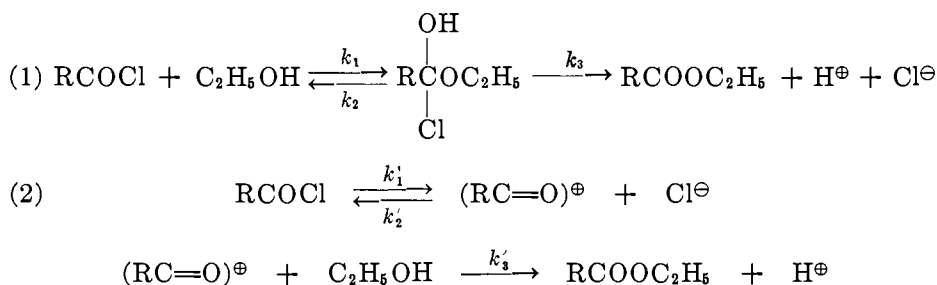
Evidently, the exact mechanism of alcoholysis in any instance is determined by the nature of the reactants and the medium in which the reaction is carried out.

When the esterification of secondary and tertiary alcohols with aliphatic acid chlorides is conducted in ether in the presence of certain metals, good yields of the corresponding esters are produced. Magnesium, aluminum, zinc, and the alkali metals have been studied for this purpose under a variety of conditions (649, 651). Generally best results are obtained using 0.2–0.3 M alcohol in ether with magnesium, adding the acid chloride in slight excess with cooling, letting stand for 1 hr., heating, and then isolating. Primary and secondary alcohols reacted very rapidly, although use of the metal gave no increase in the yield of ester with the primary alcohols. The dehydrating action of acetyl chloride on tertiary alcohols was inhibited, and in most instances reasonable conversions to the esters of tertiary alcohols could be obtained. It has been inferred (649) that the metal functions in these reactions as a hydrogen chloride acceptor, a contention supported by the fact that hydrogen gas is also evolved, except with aluminum. The possibility that esterification occurs through the metal alkoxide, formed directly from the alcohol and the metal, is more probable, at least with sodium metal, in agreement with the general observation that acid chlorides react very readily with metal alkoxides to give esters.

$$2R'OH + 2M \rightarrow 2R'OM + H_2$$
$$R'OM + RCOCl \rightarrow RCOOR' + MCl$$
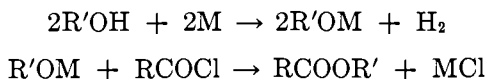
From a commercial point of view the application of acid chlorides instead of acids for esterifications involves several advantages. Since the reaction is not a reversible equilibrium, it would be expected to proceed to completion. No acidic catalyst is required to initiate it. Reaction occurs faster and at much lower temperatures and therefore the products are exposed to heat for far less time with consequent improvement in the color of the product. For many purposes such advantages are sufficient to justify the choice of the more expensive acid chloride over the acid. A typical commercial esterification of a primary alcohol with an aliphatic acid chloride is the acylation of dry sodium isethionate with oleoyl chloride, a process applied in Germany (114) for the preparation of the valuable detergent Igepon AP.

$$C_{17}H_{33}COCl + HO(CH_2)_2SO_3Na \rightarrow C_{17}H_{33}COO(CH_2)_2SO_3Na + HCl$$
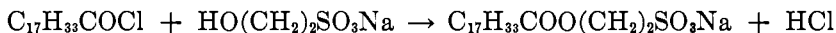
"The preparation is carried out in a 2 cu. ft. leadlined condensation vessel fitted with a low pressure heating and cooling jacket. The stirrer revolves at 15 RPM and is driven from a 25 KW shaft and is of specially heavy design, because the mixture becomes solid as the reaction proceeds; temperature control is electrical. 185 Kg of sodium 2-hydroxy-1-sulfonate (calculated as 98–99% purity, mol. wt. 118) are shoveled into the reaction vessel and three atmospheres steam pressure are applied. The manhole of the vessel is closed and 316 kg of oleoyl chloride are run in from a measuring tank with stirring. The temperature is raised to 100°C and after 15 minutes the reaction becomes vigorous with evolution of hydrogen chloride gas which is sucked into an absorption vessel. On continued heating and stirring to a temperature of 110° the thick pasty reaction mixture becomes a brittle solid and then breaks up into waxlike flakes. After cooling to 90–100° with continued stirring a gritty yellowish brown powder is formed. Sufficient solid sodium carbonate is then added to adjust the pH of a 5% solution of the product to 7.2–7.5. The product, which is known as Igepon A Konz is then emptied through the floor valve into barrels on the floor below. Yield— 460 Kg."

It is of interest that the lead-lined reaction vessels used in the above wear quite well, and that the lining requires renewing only every 2 or 3 years. Breaks in the lead lining are repaired immediately only if they occur at the liquid line. More recent practice involves heating a mixture of 1 M proportion of oleoyl chloride, 1.2 M proportion of dry sodium isethionate, and about 0.1 M proportion of soda ash with good agitation to 115°C. The gaseous hydrogen chloride evolved in either method apparently has little or no deleterious effect on the product. The Igepon has also been prepared from sodium isethionate and oleic acid, but this requires heating for an extended period at 180–200°C. and the product is considerably darker.

Esters produced in the acylation of alcohols with aliphatic acid chlorides are of value for many applications. Recent innovations have included the preparation of a series of β-cyanoethyl esters of fatty acids (561) suitable as softeners or plasticizers for elastomers, resins, and plastics which are held to overcome objectionable tendencies towards brittleness and which impart flexibility to the products. Stearoyl chloride dissolved in benzene or carbon tetrachloride has been used as an analytical reagent for the determination of the hydroxyl group "active hydrogen" (569). A similar application with acetyl chloride involves the use of pyridine (638) (see Section VII,C).

B. REACTION WITH PHENOLS

The esterification of phenols with aliphatic acid chlorides is only one of the modes in which these compounds may react (I). In the presence of suitable acidic catalysts or solvents the acid chloride may condense in Friedel–Crafts type acylations (II) to give phenolic ketones (Section XIII,A).

$$RCOCl + C_6H_5OH \longrightarrow RCOOC_6H_5 + HCl \qquad (I)$$

$$RCOCl + C_6H_5OH \xrightarrow{AlCl_3} HOC_6H_4COR(o/p) + HCl \quad (II)$$

In a few instances the hydrogen chloride eliminated in the esterification may function as the acid catalyst to induce Friedel–Crafts acylation of the phenol. This is particularly true where the phenolic aromatic ring is polyfunctional, the reaction usually occurring in the absence of added catalyst. Thus, resorcinol has been found to be readily acylated in good yield to phenolic ketones at 100°C. with acetyl, isobutyryl, isovaleryl, or 4-methylvaleryl chloride (163). The situation is further complicated by the more or less ready tendency of phenolic esters to undergo the Fries rearrangement to phenolic ketones, indicating that the two types of reactions are chemically similar in result if not in mechanism. It is probable that the phenolic ketones produced from resorcinol are derived through a

Friedel–Crafts type of acylation with hydrogen chloride catalyzing the condensation and not through esterification followed by a Fries rearrangement, since the latter type of rearrangement is not known to occur with hydrogen chloride. For these reasons the yields of esters of phenols by this method are in general somewhat or considerably smaller than those obtained in the esterification of alcohols.

A further indication that the formation of hydroxyketones in the Friedel–Crafts acylation of phenols does not occur through a Fries rearrangement is the fact that aluminum chloride and phenols yield molecular compounds having the formula $ArO \cdot AlCl_2$, which react with acyl chlorides to give hydroxyketones (601). This conversion has been considered (341) to pass through the following sequence:

$$C_6H_5OAlCl_2 + RCH_2COCl \rightarrow C_6H_5 \overset{\oplus}{O}COCH_2R \xrightarrow{-HCl}$$
$$\underset{\ominus AlCl_3}{\big|}$$

$$\underset{\overset{\|}{CHR}}{C_6H_5OCOAlCl_2} \rightarrow \underset{\overset{\|}{CHR}}{HOC_6H_4COAlCl_2} \xrightarrow[-(AlOHCl_2)]{+H_2O} HOC_6H_4COCH_2R$$

It could be assumed that substitution of the phenolic hydrogen by the $AlCl_2$ group renders the hydrogen atoms in the o- and p-positions still more reactive towards acid chlorides. The reaction

$$ArOCl_2 + RCH_2COCl \rightarrow RCH{=}C(OAlCl_2)Cl + ArOH$$

has been held to be less probable.

The Schotten–Baumann technique of acylation is not applicable to the esterification of phenols. Since phenols are solubilized by sodium hydroxide into the aqueous phase to phenoxide ions, generally less basic and less nucleophilic in water than hydroxyl ions, the stronger hydroxyl ions undergo selective reaction with the acid chloride instead (III) to afford a soap, and the desired esterification (reaction I) is thereby minimized.

$$RCOCl + NaOH \rightarrow RCOONa + NaCl \qquad\qquad (III)$$

Attempts to acylate aqueous sodium phenoxide solutions without excess base have not been particularly successful, in view of the simultaneous hydrolysis of the acid chloride to its corresponding acid and the hydrolysis of the ester with the hydrogen chloride produced in the reaction. In the presence of a suitable hydrogen chloride acceptor such as magnesium (5, 651) or in the absence of a solvent the maximum conversion to ester can usually be realized.

Table 18 includes the reported esterification reactions of phenols with aliphatic acid chlorides. Numerous examples of the Friedel–Crafts acylation reactions of phenols were given by Thomas (684) in 1941.

C. REACTION WITH POLYHYDROXY COMPOUNDS

Reactions of aliphatic acid chlorides with polyhydroxy compounds have lately come into commercial prominence as an efficient means of preparing a great many useful esters. Examples have been collected up to 1943 in a recent review (258) and need not be repeated. The usual technique has involved dissolving an anhydrous polyhydric alcohol in a large excess of a tertiary amine such as triethylamine, pyridine, or quinoline and adding the acid chloride, preferably in a solvent such as chloroform. After reaction the product is isolated by pouring into dilute mineral acid to remove the excess amine and its halide salt. The ester is recoverable as a supernatant layer or by extraction and is usually treated to remove acidity. Alternate techniques have involved mixing the acid chloride and alcohol and eliminating free hydrogen chloride gas by means of an inert gas (or by proposed initial reaction of a tertiary amine and acid chloride (Section VII,C)), filtration of the precipitate of the hydrochloride, and reaction of the filtrate with the polyhydric alcohol. Amines have occasionally been replaced by metallic halides, which help liberate hydrogen halide (257, 336). These various techniques are most suitable for the preparation of a fully esterified polyalcohol.

The preparation of pure partial esters of polyhydric alcohols with acid chlorides is a more complicated problem which requires special innovations. These

TABLE 18

Reactions of aliphatic acid chlorides with phenols

ACID CHLORIDE	PHENOL	METHOD*	BASE	PRODUCTS	REFERENCES
Acetyl......	C_6H_5OH	d		$CH_3COOC_6H_5$	(5, 313)
	C_6H_5OH	c (benzene)	Mg	$CH_3COOC_6H_5$	(5, 651)
Propionyl...	C_6H_5OH	d		$C_2H_5COOC_6H_5$	(291)
Undecanoyl.	$1,4\text{-}C_6H_4(OH)_2$	d		$1,4\text{-}C_6H_4(OCOC_{10}\text{-}H_{21})_2$	(26)
Lauroyl.....	C_6H_5OH	d		$C_{11}H_{23}COOC_6H_5$	(407)
	$4\text{-}CH_3C_6H_4OH$	d		$C_{11}H_{23}COOC_6H_4\text{-}CH_3\text{-}4$	(407)
	$1,2\text{-}C_6H_4(OH)_2$ $1,3\text{-}C_6H_4(OH)_2$ $1,4\text{-}C_6H_4(OH)_2$	d (110°C.)		Corresponding diesters	(468)
Myristoyl...	C_6H_5OH	d		$C_{13}H_{27}COOC_6H_5$	(407)
	$4\text{-}CH_3C_6H_4OH$	d		$C_{13}H_{27}COOC_6H_4\text{-}CH_3\text{-}4$	(407)
	$1,2\text{-}C_6H_4(OH)_2$ $1,3\text{-}C_6H_4(OH)_2$ $1,4\text{-}C_6H_4(OH)_2$	d		Corresponding diesters	(468)
Palmitoyl...	C_6H_5OH	d		$C_{15}H_{31}COOC_6H_5$	(407)
	$4\text{-}CH_3C_6H_4OH$	d		$C_{15}H_{31}COOC_6H_4\text{-}CH_3\text{-}4$	(407)
	$1,2\text{-}C_6H_4(OH)_2$ $1,3\text{-}C_6H_4(OH)_2$ $1,4\text{-}C_6H_4(OH)_2$	d d d		Corresponding diesters	(468)
Heptadec- anoyl.....	C_6H_5OH	d		$C_{16}H_{33}COOC_6H_5$	(634)
Stearoyl....	C_6H_5OH	d		$C_{17}H_{35}COOC_6H_5$	(407)
	$4\text{-}CH_3C_6H_4OH$	d		$C_{17}H_{35}COOC_6H_4\text{-}CH_3\text{-}4$	(407)
	$1,2\text{-}C_6H_4(OH)_2$ $1,3\text{-}C_6H_4(OH)_2$ $1,4\text{-}C_6H_4(OH)_2$	d		Corresponding diesters	(468)
Oleoyl......	C_6H_5OH	d		$C_{17}H_{33}COOC_6H_5$	(633)
Succinyl....	C_6H_5OH	d		$(CH_2COOC_6H_5)_2$	(730)
Dimethyl- malonyl...	C_6H_5OH	d		$(CH_3)_2C(COOC_6H_5)_2$	(652)
Diethyl- malonyl...	C_6H_5OH	d		$(C_2H_5)_2C(COOC_6\text{-}H_5)_2$	(652)
Butylethyl- malonyl...	C_6H_5OH	d		$(C_4H_9)(C_2H_5)C\text{-}(COOC_6H_5)_2$	(652)
Suberyl.....	C_6H_5OH	d		$(CH_2CH_2CH_2\text{-}COOC_6H_5)_2$	(103, 468)
Azelyl......	C_6H_5OH	d		$C_6H_5OCO(CH_2)_7\text{-}COOC_6H_5$	(468)

* b = phenol in organic solvent + RCOCl;
   c = phenol in organic solvent + base + RCOCl;
   d = no solvent.

have been based on the blocking of certain of the hydroxyl groups in the poly-alcohol before acylation with easily removed groups. Monoglycerides of the fatty acids have been prepared through the use of blocking groups such as iso-propylidene, benzylidene, carbobenzyloxy, and certain others. Other desired partial esters may be produced through similar processes, provided acyl migration is not a factor in the product. Halohydrins may be acylated and the halo ester treated to remove the halogen atom with silver nitrite (198) or silver oxide in ethanol (543). These techniques and examples have been reviewed elsewhere (258, 517).

A comprehensive study of the preparation and a survey of the numerous uses to which the polyesters of glycols, glycerol, and other polyhydroxy compounds are suited has been given (258).

Aliphatic acid chlorides have also been caused to react with many higher poly-hydroxy compounds such as sugars, cellulose, starch, and polysaccharides to afford polyesterified materials which are potentially valuable. Attempts to re-solve the structure of the glucose molecule have involved preparation of the pentaacetyl derivative with acetyl chloride at −15°C. (310) and other penta-esters of glucose with propionyl, butyryl, isobutyryl, valeryl, isovaleryl, palmitoyl, stearoyl, and oleoyl chlorides. The preparations have involved acyla-tion with pyridine in chloroform solution. In similar fashion sucrose octapalmitate (5.6 g. of polyester from 1.8 g. of sugar with 12 g. of palmitoyl chloride), sucrose octastearate, and raffinose hendecapalmitate (12.6 g. of polyester from 0.5623 g. of raffinose and 30.2 g. of palmitoyl chloride) have been prepared. Numerous examples of the esterification of glucosides with acetyl chloride have been re-ported (442).

Interesting and valuable polyesters of cellulose have been prepared, usually by adding the acid chloride to a suspension of cellulose in pyridine and chloro-form or toluene. The yield and composition of the final product depend upon the proportions of the reactants as well as the temperature. "Cellulose distearate," obtained from the reaction of six parts of stearoyl chloride with one part of cellu-lose in a mixture of pyridine and benzene (270), is said to melt with decomposition at 220°C. and is scarcely distinguishable from the original cellulose. It is insolu-ble in the usual solvents, and in CuO–NH₄OH, but dissolves in fatty acids and glycerides at 200°C. "Cellulose monostearate" is similarly prepared from one part each of cellulose and stearoyl chloride. The dilaurate of cellulose, obtained through a 6:1 ratio, melts at approximately 250°C. and is precipitated from solu-tion by acetone but not by ether. Cellulose tripalmitate (243) and hexapalmitate (381) have been claimed as pure materials. The preparation of chloroacetyl esters of cellulose from chloroacetyl chloride (46) appears to be accompanied by a resolution of the cellulose complex with partial hydration. The product con-tains little chlorine and this is easily split off by sodium hydroxide. Evidently cellulose chloroacetate is first formed but is hydrolyzed to a glycolic ester.

The esterifications of complex polyhydroxy compounds with aliphatic acid chlorides have not only afforded an insight into the structure of these materials but have provided a series of commercially valuable products. The preparations

of polyesters from polysaccharides with fatty acid halides (541) and of cellulose derivatives from octanoyl and decanoyl chlorides (643), for example, have been patented.

D. REACTION WITH HYDROPEROXIDES

The reaction of hydroperoxides with aliphatic acid chlorides is a relatively recent innovation. The stable tertiary-alkyl hydroperoxides have been smoothly acylated under Schotten–Baumann conditions to afford *tert*-alkyl acyl peroxides (489).

$$RCOCl + R_3'COOH \xrightarrow{KOH} R_3'COOCOR + KCl + H_2O$$
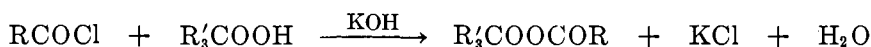
The tertiary alkyl peresters have been described as stable viscous liquids or solids used for pharmaceutical (germicidal, fungicidal) and therapeutic purposes, as catalysts in the production of polymeric products, as vulcanizing agents for various natural and synthetic resins and rubbers, as bleaching agents for flour and textiles, as accelerators for the combustion of diesel fuels, and, in general, for various other uses where a stable oxidizing agent is required.

X. REACTION OF ALIPHATIC ACID CHLORIDES WITH CARBONYL-CONTAINING COMPOUNDS

Reactions of aliphatic acid chlorides with carbonyl-containing compounds such as aldehydes, ketones, esters, carboxylic acids, their salts, anhydrides, lactones, ketenes, and quinones are characterized by considerable diversity in mode of reaction. Perhaps the best known of these reactions are the acylations of the "*sodio*" derivatives of esters (frequently applied to the syntheses of ketones and acids) and the preparation of anhydrides from salts of carboxylic acids. In addition, there are a number of unusual reactions between these various components.

A. REACTION WITH ALDEHYDES AND KETONES

Reactions between aliphatic acid chlorides and aliphatic aldehydes have not lent themselves to fruitful study. One of the few definite references to this reaction appears to consist in the preparation of certain alkanoylmethylpyridinium chlorides (593) in which the acid chloride is added to formaldehyde and the product added to a tertiary amine like pyridine to produce a relatively stable

$$RCOCl + HCHO \rightarrow ClCH_2COCR \xrightarrow{C_5H_5N} C_5H_5\overset{\oplus}{N}CH_2OCOR \quad \overset{\ominus}{Cl}$$

quaternary salt. The preparation of bromomethyl acetate from acetyl bromide and polyoxymethylene (180) and the reaction of benzoyl bromide and 4-bromobenzaldehyde, affording 80 per cent of the corresponding ester (4), are similar.

Aliphatic acid chlorides have been reported to undergo a reaction with benzaldehyde akin to the Perkin reaction, but drastic conditions render the yields rather low. Acetyl chloride, heated with benzaldehyde for 8.5 hr. in a sealed tube at 170–180°C. in the presence of triethylamine, has given an 11.8 per cent

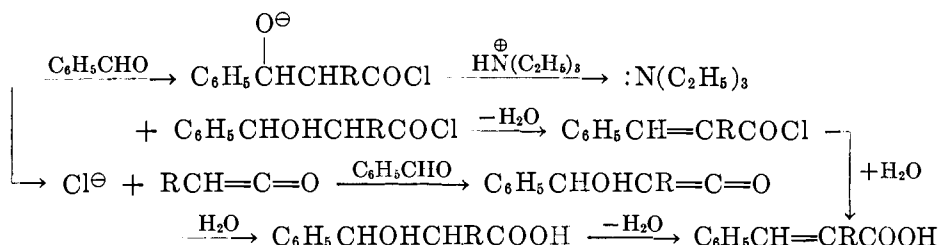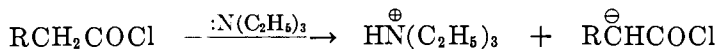yield of cinnamic acid (383); butyryl chloride treated similarly afforded a 6.6 per cent yield of α-ethylcinnamic acid; higher homologs are also reported to

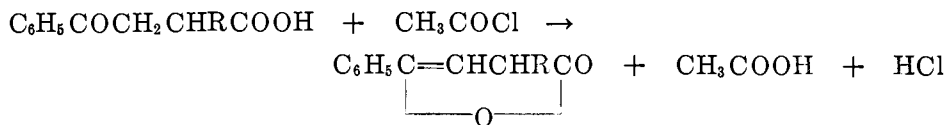$$RCH_2COCl + C_6H_5CHO \xrightarrow{N(C_2H_5)_3} C_6H_5CH{=}CRCOOH + HCl$$
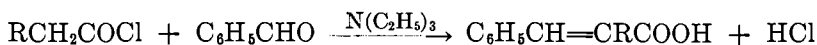
R = H or an alkyl group.

undergo the reaction. These cinnamic acids may be produced in the reaction through the Perkin mechanism (upper sequence), but in view of the ease with which acid chlorides undergo dehydrochlorination when heated with tertiary

$$RCH_2COCl \xrightarrow{:N(C_2H_5)_3} H\overset{\oplus}{N}(C_2H_5)_3 + R\overset{\ominus}{C}HCOCl$$

$$\overset{O^{\ominus}}{\underset{|}{}}$$

$$\xrightarrow{C_6H_5CHO} C_6H_5CHCHRCOCl \xrightarrow{H\overset{\oplus}{N}(C_2H_5)_3} :N(C_2H_5)_3$$

$$+ C_6H_5CHOHCHRCOCl \xrightarrow{-H_2O} C_6H_5CH{=}CRCOCl -\!\!\!\rceil$$

$$\rightarrow Cl^{\ominus} + RCH{=}C{=}O \xrightarrow{C_6H_5CHO} C_6H_5CHOHCR{=}C{=}O \quad\Big|{+}H_2O$$

$$\xrightarrow{H_2O} C_6H_5CHOHCHRCOOH \xrightarrow{-H_2O} C_6H_5CH{=}CRCOOH$$

amines (Section VII,C), it seems probable that the more likely mode of formation involves reaction through the ketene produced by dehydrochlorination (lower sequence). This appears to be the case, inasmuch as similar products were not reported produced from either acetic acid and benzaldehyde or from ethyl acetate and benzaldehyde (Knoevenagel reaction) under the same conditions. The latter reaction afforded only benzoic acid as a product. Additional evidence supports the above contention (334).
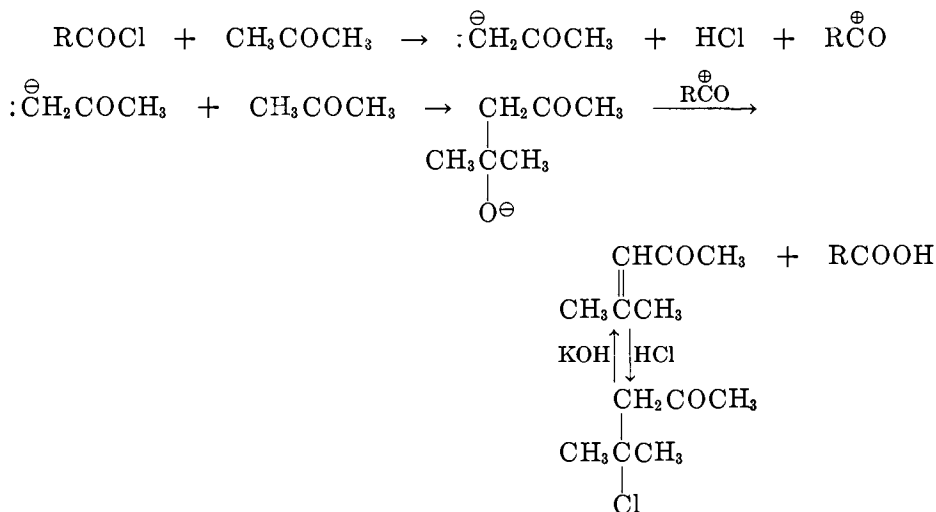
The reactions of aliphatic acid chlorides with ketones or their alkali enolates may conform to several patterns, but numerous examples of each type are not to be found in the literature. Reactions with simple ketones frequently proceed through the enol form to afford O-acylation. Under certain conditions acetyl chloride reacts with cyclohexanone to give the enol acetate (11). On the other hand, the somewhat analogous betaines of pyridine have been found to react with higher aliphatic acid chlorides such as palmitoyl chloride to afford acylation of the α-carbon atom of the betaine exclusively (181). Treatment of certain ketones with acetyl chloride has been observed to cause selective reaction of the ketone through its enol form. Thus, acetyl chloride reacts with β-aroyl-propionic acids to give the corresponding unsaturated lactones (11), apparently as a consequence of its dehydrating action.

$$C_6H_5COCH_2CHRCOOH + CH_3COCl \rightarrow$$

$$C_6H_5\underset{\underset{\displaystyle O}{\rule{0.5pt}{14pt}\quad\rule{0.5pt}{14pt}}}{C}{=}CHCHRCO + CH_3COOH + HCl$$

Acetone has been reported to react with phosgene on standing for half an hour to yield isopropenyl chloroformate (476), but the reaction has not been con-

firmed in the hands of other workers (332). Similarly, a mixture of phosgene, acetoacetic ester, and ligroin did not react at room temperature.

Reactions of simple ketones with acid chlorides in the presence of a dehydrating agent such as zinc chloride have been reported to give unsaturated ketones as final products. Two moles of acetone and one of acetyl chloride in the presence of 50 g. of anhydrous zinc chloride in the cold have given a mixture of chloro intermediates said to be $(CH_3)_2CClCH_2COCH_3$ and $(CH_3)_2CClCH_2COCH_2CCl$-$(CH_3)_2$, from which mesityl oxide and phorone were easily obtained with alcoholic potassium hydroxide (181). A more recent report (158) states that self-condensation of methyl ketones occurs to the extent of 40–50 per cent at 20°C. for 24 hr. in the presence of acetyl chloride, benzoyl chloride, or phosphorus oxychloride. These reactions are apparently self-condensations of ketones in which the carbonyl group of one molecule and the reactive methylene group of a second interact in similar fashion as in the Perkin (aldehyde–anhydride), Knoevenagel (aldehyde–ester (or acid)), Doebner, and aldol (aldehyde–aldehyde) condensations. The interest involves the apparent formation of the methylene anion without the presence of the usual base. This may be attributed to the acid chloride.

$$RCOCl \ + \ CH_3COCH_3 \ \rightarrow \ :\overset{\ominus}{C}H_2COCH_3 \ + \ HCl \ + \ R\overset{\oplus}{C}O$$

$$:\overset{\ominus}{C}H_2COCH_3 \ + \ CH_3COCH_3 \ \rightarrow \ \underset{\underset{\underset{O^{\ominus}}{|}}{CH_3\overset{|}{C}CH_3}}{CH_2COCH_3} \ \xrightarrow{\ R\overset{\oplus}{C}O\ }$$

$$\underset{\underset{CH_3\overset{|}{C}CH_3}{\|}}{CHCOCH_3} \ + \ RCOOH$$

$$KOH\uparrow\ \Big|HCl$$

$$\underset{\underset{Cl}{|}}{\underset{CH_3\overset{|}{C}CH_3}{CH_2COCH_3}}$$

The acylation of alkali derivatives of simple ketones with aliphatic acid chlorides to produce 1,3-diketones according to the following equation has not been reported; acetylacetone itself is commonly prepared from ethyl acetate and

$$RCOCl \ + \ CH_3COCH_3 \ \xrightarrow{\ NaOC_2H_5\ } \ RCOCH_2COCH_3 \ +$$
$$HCl \ + \ C_2H_5OH$$
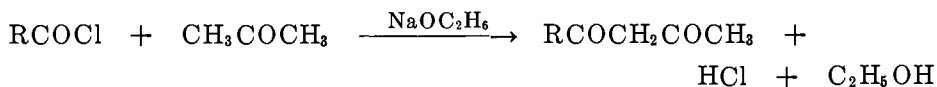
acetone (154) and not from acetyl chloride. Certain β-keto esters such as acetoacetic and related types (Section X,B) are easily acylated at the reactive methylene group, however.

The reaction of 1,3-diketone enolates with aliphatic acid chlorides has not

been reported, but the behavior may be inferred to be similar to that observed for aromatic and aromatic-aliphatic types. Phenylpropiolyl chloride with the sodium derivative of acetylacetone has given a compound said to be 3-acetyl-5-benzylidene-4-keto-2-methyl-4,5-dihydrofuran (590).
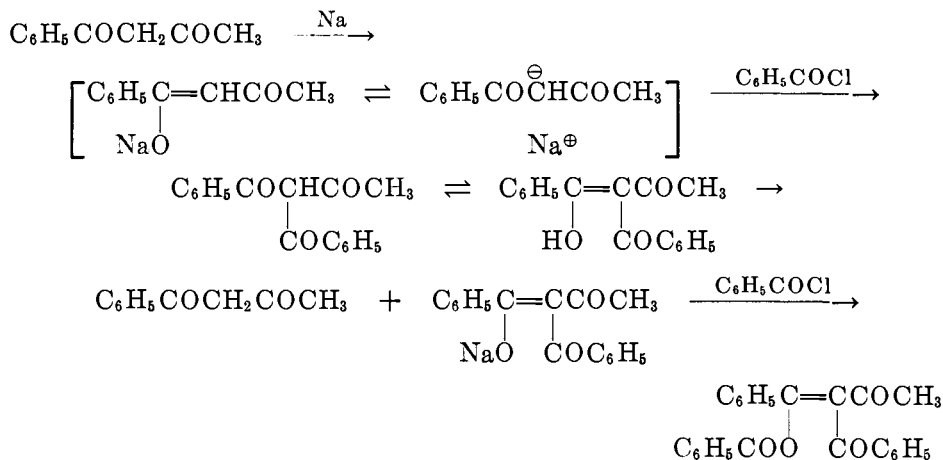
$$C_6H_5C{\equiv}CCOCl \ + \ \overset{\oplus}{Na}[CH_3CO\overset{\ominus}{C}HCOCH_3] \ \rightarrow \ NaCl \ +$$

$$\begin{bmatrix} CH_3COCHCOCH_3 \\ | \\ COC{\equiv}CC_6H_5 \end{bmatrix} \ \rightarrow$$
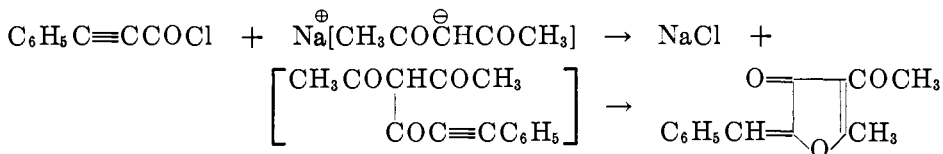
The experience gained through a study of the reaction of benzoyl chloride and the sodium salt of benzoylacetone may be profitably applied to an understanding of the acylation of sodium enolates with aliphatic acid chlorides. Attempts to prepare 1,1-dibenzoylacetone through this reaction afford instead principally the O-benzoylated derivative of its enol (151). An explanation of this behavior has involved the essential difference between the methods used for the alkylation and the acylation of sodium enolates, based upon the comparative acidity of the keto–enol intermediates. Compounds formed by the acylation of keto–enols are more acid than the starting materials. In this reaction the sodium salt of benzoylacetone and benzoyl chloride first form 1,1-dibenzoylacetone, but since this is a stronger acid than the sodium salt of benzoylacetone it reacts with it to liberate benzoylacetone and give its own sodium enolate. Further reaction of the latter with benzoyl chloride then affords the main reaction product:

$$C_6H_5COCH_2COCH_3 \quad \xrightarrow{\ \ Na\ \ }$$

$$\begin{bmatrix} C_6H_5C{=}CHCOCH_3 \\ | \\ NaO \end{bmatrix} \rightleftharpoons \ C_6H_5CO\overset{\ominus}{C}HCOCH_3 \ \Big] \ \xrightarrow{\ C_6H_5COCl\ }$$
$$Na^{\oplus}$$

$$C_6H_5COCHCOCH_3 \ \rightleftharpoons \ C_6H_5C{=}CCOCH_3 \ \rightarrow$$
$$| \qquad\qquad\qquad\quad | \quad\ |$$
$$COC_6H_5 \qquad\qquad\quad HO \ \ COC_6H_5$$

$$C_6H_5COCH_2COCH_3 \ + \ C_6H_5C{=}CCOCH_3 \ \xrightarrow{\ C_6H_5COCl\ }$$
$$| \quad\ \ |$$
$$NaO \ \ COC_6H_5$$

$$C_6H_5C{=}CCOCH_3$$
$$| \qquad\quad |$$
$$C_6H_5COO \ \ COC_6H_5$$

To improve the yield of 1,1-dibenzoylacetone as much as possible in this reaction it was reasoned that an excess of the sodium salt of benzoylacetone was to be avoided. By adding portions of measured amounts of sodium ethoxide to the alcoholic solution of the keto–enol being acylated and allowing the reaction to proceed with a portion of the acid chloride, continuing in this manner until the calculated amount was used up, the yield of 1,1-dibenzoylacetone was increased fivefold. Frequently these conditions are complicated by the changing acidity

and tendency towards enolization in the general case. During the acylation of keto-enols the acidity always increases but the tendency to enolize does not necessarily do so. Acylation becomes especially difficult if the tendency to enolize increases; conversely, as in the case of 1,1-dibenzoylacetone, which is more stable in the triketo form, acylation takes place more easily. The technique can be simplified in certain other cases.

Acylations of the copper salt of 1,3-diacetylacetone with malonyl chloride, oxalyl chloride, and phosgene have been reported (74), using acid chlorides in benzene with an ice-cold solution of the salt in benzene. The products were cyclic
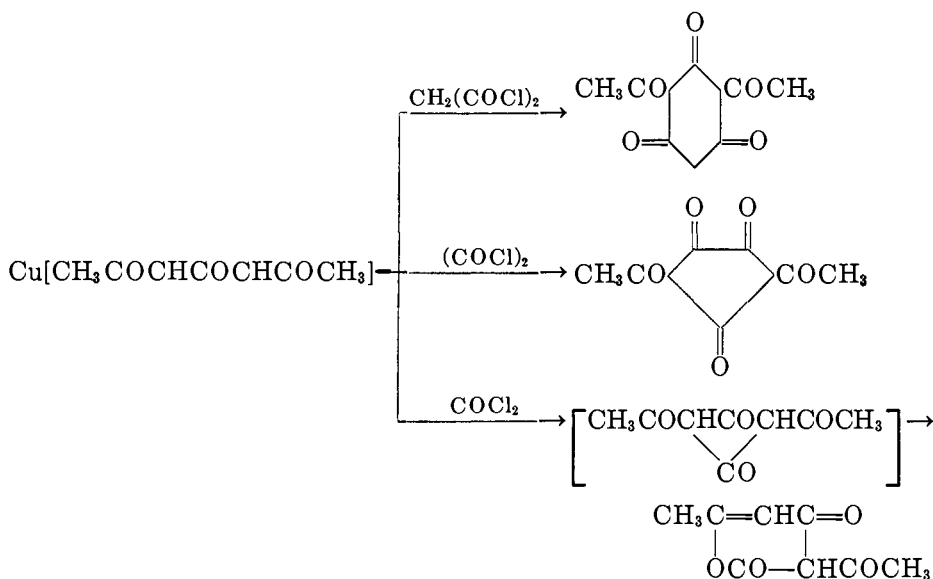
triketo derivatives and dehydroacetic acid, respectively; the latter was derived from phosgene apparently through rearrangement of the 2,4-diacetyl-1,3-cyclo-butanedione intermediate.

B. REACTION WITH ESTERS

Reactions of aliphatic acid chlorides with esters according to equations A and B are difficult to find in the literature, and any deductions made as to these

$$RCOCl + R'COOR'' \rightarrow RCOOCOR' + R''Cl \qquad (A)$$

$$RCOCl + R'COOR'' \rightarrow RCOOR'' + R'COCl \qquad (B)$$
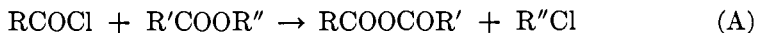
reactions must be based upon the behavior of analogous aromatic acid chlorides. The data here are both conflicting and uncertain. Benzoyl chloride and phenyl acetate in the presence of zinc chloride have been reported to give phenyl benzoate and acetyl chloride (187), apparently in accord with reaction B, while the

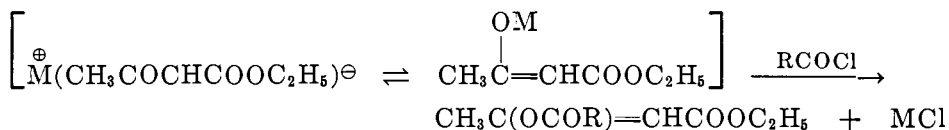reaction of benzoyl chloride and ethyl benzoate at moderate temperatures in the presence of zinc chloride is said to give benzoic anhydride and ethyl chloride (reaction A) (425). Further confusing the issue is the report (14) that the yield of alkyl chlorides from acid chlorides and esters is small or non-existent and is always accompanied by the coformation of unsaturated hydrocarbons.
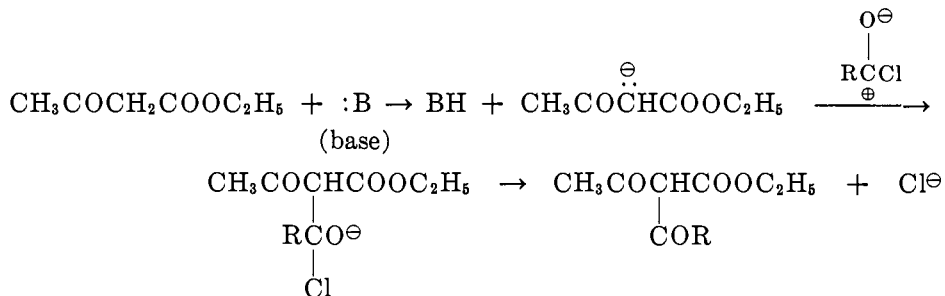
The acylation of metallic derivatives of esters to give ketones, acids, and keto acids or occasionally esters is an important synthetic route to many valuable compounds. Reactions of this type lead most frequently to formation of a carbon–carbon bond (I) and only rarely to the formation of a carbon–oxygen bond of an ester (II) (depending upon the structure of R′ in the ester), as illustrated by the unique case of acetoacetic ester.

$$M[CH_3COCHCOOC_2H_5] + RCOCl \xrightarrow{\text{I}} CH_3CO\overset{\displaystyle COR}{\overset{|}{C}}HCOOC_2H_5$$

$$+ MCl$$

$$M[R'CHCOOC_2H_5] \qquad \overset{\text{II}}{\searrow} \quad CH_3C{=}CHCOOC_2H_5$$
$$\text{general type} \qquad\qquad\qquad\qquad\qquad \underset{\displaystyle OCOR}{\overset{|}{}}$$
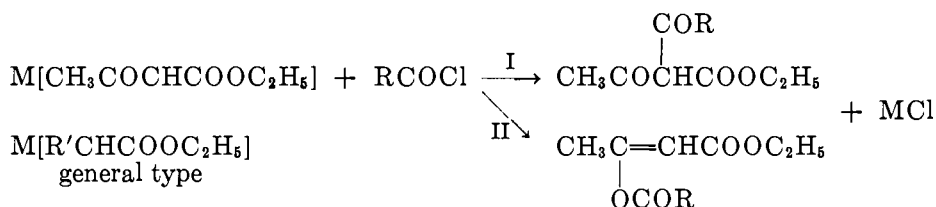
Several factors, such as the nature of the ester, the nature of the keto–enol, the solvent, and the proximity of other methylene-activating groups in the ester determine whether path I or II predominates in the reaction. The formation of an ester is generally considered to occur through the enol form, and is not observed for esters like ethyl acetate (R′ = H).
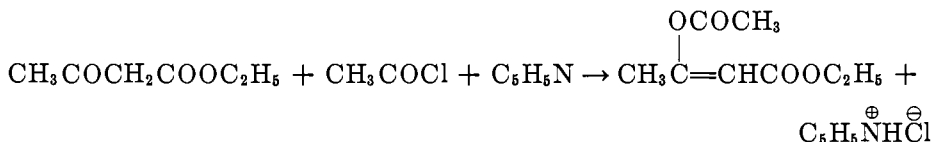
$$\left[\overset{\oplus}{M}(CH_3COCHCOOC_2H_5)^\ominus \ \rightleftharpoons \ CH_3\overset{\displaystyle OM}{\overset{|}{C}}{=}CHCOOC_2H_5\right] \xrightarrow{\text{RCOCl}}$$

$$CH_3C(OCOR){=}CHCOOC_2H_5 \ + \ MCl$$

The formation of a ketone is ascribed to a mechanism involving carbanion attack at the center of a positive carbonyl group.

$$CH_3COCH_2COOC_2H_5 \ + \ :B \ \rightarrow \ BH \ + \ CH_3CO\overset{\ominus}{C}HCOOC_2H_5 \xrightarrow[\oplus]{\overset{\displaystyle O^\ominus}{\overset{|}{R}\overset{|}{C}Cl}}$$

$$CH_3CO\underset{\displaystyle \underset{\displaystyle Cl}{\overset{|}{R\overset{|}{C}O^\ominus}}}{\overset{|}{C}}HCOOC_2H_5 \ \rightarrow \ CH_3CO\underset{\displaystyle COR}{\overset{|}{C}}HCOOC_2H_5 \ + \ Cl^\ominus$$

The acylation of esters like acetoacetic and malonic esters is usually carried out by mixing the alkaline alcoholic solution of the ester with the acyl chloride without the previous isolation of the alkali compound. In certain instances formation

of the carbanion is facilitated through the use of other bases, such as sodium amide (281) or potassium or sodium hydroxide. Acetone finds some use as an alternate solvent. What has been said here concerning the acylation of esters applies equally to the acylation of ketones (see Section X,A).

The acyl derivatives of the enol form of acetoacetic ester are most conveniently prepared by the reaction of the ester with the appropriate acid chloride in pyridine solution, as in the preparation of acetoxycrotonic ester (155).

$$CH_3COCH_2COOC_2H_5 + CH_3COCl + C_5H_5N \rightarrow CH_3\overset{\overset{\displaystyle OCOCH_3}{|}}{C}{=}CHCOOC_2H_5 +$$

$$C_5H_5\overset{\oplus}{N}H\overset{\ominus}{Cl}$$

Examples of both types of reactions have been collected and tabulated in table 19. Obviously there are other functional groups besides carbalkoxy or carbonyl which may activate an adjacent methylene group sufficiently to enable formation of alkali metal derivatives and permit C-acylation with acid chlorides. The nitrile group of benzyl cyanide offers an example. The sodium derivative of benzyl cyanide has been acylated with acetyl chloride to afford α-acetyl-α-tolunitrile in small yield (96).

$$CH_3COCl + Na[C_6H_5CHCN] \rightarrow C_6H_5CH(COCH_3)CN + NaCl$$
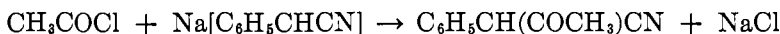
C. REACTION WITH ACIDS AND SALTS OF ACIDS

Aliphatic acid chlorides react with carboxylic acids to afford several products depending upon the conditions employed. The anhydride of the acid is produced by heating the acid chloride and its corresponding acid, at least for the lower homologs:

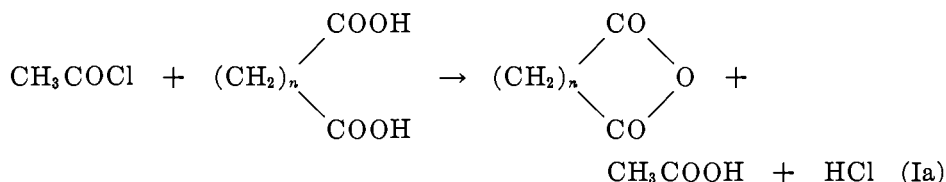$$RCOCl + RCOOH \rightarrow (RCO)_2O + HCl \qquad (I)$$
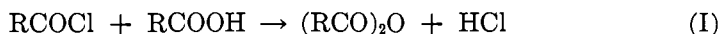
This reaction proceeds rather slowly to a 50 per cent overall yield with acetyl chloride and acetic acid (377), but is not general for higher members. Butyric anhydride is said to have been prepared in 86–90 per cent yield by means of it (444), but a contrary claim (16) infers that this reaction occurs only in the presence of a hydrogen chloride acceptor. There is little reported for higher homologs either with or without the use of a hydrogen chloride acceptor, aside from the preparation of heptanoic anhydride (10) through the use of pyridine. It does not seem probable that the copious evolution of hydrogen chloride observed in the preparation of an acid chloride from the corresponding acid and phosphorus trichloride at temperatures lower than 50°C. (113) can be due to anhydride formation according to equation I.

$$3RCOOH + PCl_3 \rightarrow 3RCOCl + P(OH)_3$$
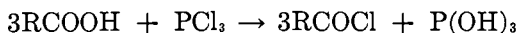
Acetyl chloride has been applied to the synthesis of dicarboxylic anhydrides such as glutaric anhydride and those of adipic to sebacic acids according to equa-

tion Ia (493, 715). A 97 per cent yield of 3,3-dimethylglutaric anhydride has been obtained from the acid and acetyl chloride (140).

$$CH_3COCl \ + \ (CH_2)_n \diagup{}^{COOH}_{COOH} \ \rightarrow \ (CH_2)_n \diagup{}^{CO}_{CO}\diagdown O \ +$$

$$CH_3COOH \ + \ HCl \quad (Ia)$$

The technique involves heating and removing the acetic acid formed and the excess acetyl chloride by vacuum distillation.

The possibility of obtaining both anhydrides simultaneously with a homologous acid, as in equation II, has been investigated (219) for acetyl chloride alone.

$$2CH_3COCl + 2RCOOH \rightarrow (CH_3CO)_2O + (RCO)_2O + 2HCl \quad (II)$$
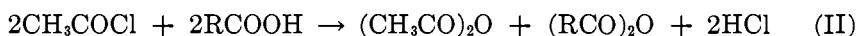
Yields of 55–75 per cent of fatty acid anhydrides have resulted from heating various acids to a temperature of 120–125°C. in an oil bath and adding excess acetyl chloride dropwise, heating to 180°C., and fractionating the products under vacuum. Whether the resulting products are produced directly according to equation II or indirectly through the mixed anhydrides followed by disproportionation under heating (equations III and IV) is problematical.

$$CH_3COCl + R'COOH \rightarrow CH_3COOCOR' + HCl \quad (III)$$

$$2CH_3COOCOR' \rightarrow (CH_3CO)_2O + (R'CO)_2O \quad (IV)$$
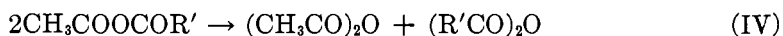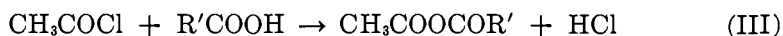
The formation of mixed acetic anhydrides by the method of equation III has not been reported in the literature, although they have been isolated by the careful interaction of lower acids and acetic anhydride (36, 57, 719) or *via* acids and ketene (330).

The reaction of acetyl chloride and anhydrous oxalic acid is also said to give acetic anhydride (17).

$$2CH_3COCl + HOOCCOOH \rightarrow (CH_3CO)_2O + 2HCl + CO_2 + CO$$
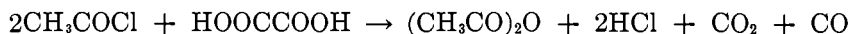
Interchange reactions between an aliphatic acid chloride and a homologous acid have not been reported for the higher-boiling aliphatics, although the reac-

$$RCOCl + R'COOH \rightarrow R'COCl + RCOOH \quad (V)$$
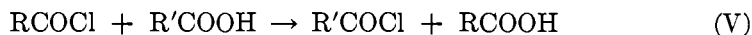
tion of oxalyl chloride and a carboxylic acid has been used as an efficient synthetic preparation for acid chlorides (3). In the aromatic series examples of

$$(COCl)_2 + 2RCOOH \rightarrow 2RCOCl + (COOH)_2 \quad (VI)$$

reaction V have included the reaction of benzoyl chloride with trichloroacetic, acetic, propionic, butyric, valeric, isovaleric, hexanoic, trimethylacetic, and aromatic acids (116) and of phthaloyl chloride with fumaric acid (424). The in-

TABLE 19

Reactions of aliphatic acid chlorides with esters

ACID CHLORIDE	ESTER	CATALYST	CONDITIONS*	PRODUCTS (YIELD)	REFERENCES
Acetyl..............	Acetoacetic	(Na)		$(CH_3CO)_2CHCOOC_2H_6$	(193, 353, 486)
	Acetoacetic	(Mg)		$(CH_3CO)_2CHCOOC_2H_5$	(525, 650)
	Acetoacetic	(C_5H_5N)		$CH_3C(OCOCH_3)=CHCOOC_2H_5$	(155)
	$(C_6H_5)_2CHCOO(t\text{-}C_4H_9)$	(K)		$(C_6H_5)_2C(COCH_3)COO(t\text{-}C_4H_9)$	(757)
Chloroacetyl........	Malonic	(Na)		$CH_2ClC(OH)=C(COOC_2H_5)_2,$	(59)
				$\begin{array}{c} CH_2OCOC_2H_5 \\ \vert \quad\quad \Vert \\ CO\text{---}CCOOC_2H_5 \end{array}$	
Propionyl...........	Malonic	(Mg)	$(+H_2O)$	$C_2H_5COCH_2COOC_2H_5$	(573)
3-Chloropropionyl....	Cyanoacetic	(Na)		$ClCH_2CH_2COCH(CN)COOC_2H_5$	(728)
2-Methylpentanoyl...	Acetoacetic	(Na)	CH_3ONa	$C_3H_7CH(CH_3)COCH_2COOCH_3$ (63.5%)	(668)
2-Methylhexanoyl....	Acetoacetic	(Na)	CH_3ONa	$C_4H_9CH(CH_3)COCH_2COOCH_3$ (61%)	(668)
Heptanoyl..........	Acetoacetic	(Na)	CH_3ONa	$C_6H_{13}COCH_2COOCH_3$	(667)
Octanoyl............	$C_6H_5CH_2OCOCH_2COOC_2H_5$	(Na)	(1) Ethyl ether (2) H_2, Pd $-CO_2$	$C_7H_{15}COCH_2COOC_2H_5$ (60–70%)	(105)
	Acetoacetic	(Na)	CH_3ONa	$C_7H_{15}COCH_2COOCH_3$	(667)
Nonanoyl...........	Acetoacetic	(Na)	CH_3ONa	$C_8H_{17}COCH_2COOCH_3$	(668)
	$RCH(COOCH_2C_6H_5)_2$	(Na)	H_2, $-CO_2$	$RCH_2COC_8H_{17}$ (R = C_4H_9, C_6H_{13})	(104)
	Acetoacetic	(Na)	$(+H_2O)$	$C_8H_{17}COCH_2COOC_2H_5$	(25)
	Acetoacetic	(Na)	$(+H_2O)$	$C_8H_{17}COCH_2COOC_2H_5$ (55%)	(667)
	$RCH(CN)COOCH_2C_6H_5$ (R = C_4H_9, $C_6H_{11}CH(CH_3)-$)	(Na)	(1) H_2, Pd (2) $-CO_2$	$C_8H_{17}COCHRCN$	(105)
Decanoyl...........	Acetoacetic	(Na)	CH_3ONa	$C_9H_{19}COCH_2COOCH_3$	(667)
Undecanoyl.........	$C_2H_5OCOCHCH_2COOC_2H_5$ $\vert$ $COCH_3$	(Na)	$(+H_2O)$	$C_{10}H_{21}COCH_2CH_2COOH$	(575)

	$CH_3COCH(COOC_2H_5)(CH_2)_{10}$-$COOC_2H_5$	(Na)	$(+H_2O)$	$C_{10}H_{21}CO(CH_2)_{11}COOH$	(31)
	Acetoacetic	(Na)	CH_3ONa	$C_{10}H_{21}COCH_2COOCH_3$	(667)
Lauroyl.............	$C_4H_9CH(CN)COOCH_2C_6H_5$	(Na)	(1) H_2, Pd (2) $-CO_2$	$C_4H_9CH(CN)COC_{11}H_{23}$	(105)
	$C_6H_5CH_2OCOCH_2COOC_2H_5$	(Na)	Ethyl ether (1) H_2, Pd (2) $-CO_2$	$C_{11}H_{23}COCH_2COOC_2H_5$ (60–70%)	(105)
	$NCCH_2CH_2CH(COOCH_2C_6H_5)_2$	(Na)	Benzene (1) H_2, Pd (2) $-CO_2$	$C_{11}H_{23}COCH_2CH_2CH_2CN$	(104)
	$(C_2H_5O)_2CHCH_2CH(COOCH_2$-$C_6H_5)_2$	(Na)	Benzene (1) H_2, Pd (2) $-CO_2$	$C_{11}H_{23}COCH_2CH_2CH(OC_2H_5)_2$	(104)
	$C_{16}H_{33}CH(COCH_3)COOC_2H_5$	(Na)	$(+H_2O)$	$C_{17}H_{35}COC_{11}H_{23}$	(547)
	$CH_3COCH(COOC_2H_5)(CH_2)_{10}$-$COOC_2H_5$	(Na)	$(+H_2O)$	$C_{11}H_{23}CO(CH_2)_{11}COOH$	(31)
	$C_6H_5CH_2OCOCH_2CH(COOCH_2$-$C_6H_5)_2$	(Na)	(1) H_2, Pd (2) $-CO_2$ (3) $(+H_2O)$	$C_{11}H_{23}COCH_2CH_2COOH$ (94%)	(104)
	Acetoacetic	(Na)	$(+H_2O)$	$C_{11}H_{23}COCH_2COOC_2H_5$	(25)
	Acetoacetic	(Na)	CH_3ONa	$C_{11}H_{23}COCH_2COOCH_3$	(667)
Tridecanoyl.........	Acetoacetic	(Na)	CH_3ONa	$C_{12}H_{25}COCH_2COOCH_3$	(667)
Myristoyl...........	Acetoacetic	(Na)	$(+H_2O)$	$C_{13}H_{27}COCH_2COOC_2H_5$	(27)
	Acetoacetic	(Na)	CH_3ONa	$C_{13}H_{27}COCH_2COOCH_3$	(667)
Pentadecanoyl.......	Acetoacetic	(Na)	CH_3ONa	$C_{14}H_{29}COCH_2COOCH_3$	(667)
2-Methyltetradeca- noyl..............	Acetoacetic	(Na)	CH_3ONa	$C_{12}H_{25}CH(CH_3)COCH_2COOCH_3$ (52%)	(668)
Palmitoyl...........	Acetoacetic	(Na)	$(+H_2O)$	$C_{15}H_{31}COCH_2COOC_2H_5$	(25, 296, 438)
	Acetoacetic	(Na)	CH_3ONa	$C_{15}H_{31}COCH_2COOCH_3$	(667)
Heptadecanoyl.......	Acetoacetic	(Na)	CH_3ONa	$C_{16}H_{33}COCH_2COOCH_3$	(667)

TABLE 19—*Concluded*

ACID CHLORIDE	ESTER	CATALYST	CONDITIONS*	PRODUCTS (YIELD)	REFERENCES
Stearoyl.............	$CH_3COCH(CH_2)_{10}COOC_2H_5$	(Na)	$(+H_2O)$	$C_{17}H_{35}CO(CH_2)_{11}COOH$	(576)
	Acetoacetic	(Na)	$(+H_2O)$	$CH_3COCH(COC_{17}H_{35})COOC_2H_5$, $C_{17}H_{35}COCH_2COOC_2H_5$	(63)
	Acetoacetic	(Na)	CH_3ONa	$C_{17}H_{35}COCH_2COOCH_3$	(667)
Nonadecanoyl........	Acetoacetic	(Na)	CH_3ONa	$C_{18}H_{37}COCH_2COOCH_3$	(667)
Eicosanoyl...........	Acetoacetic	(Na)	CH_3ONa	$C_{19}H_{39}COCH_2COOCH_3$	(667)
Heneicosanoyl........	Acetoacetic	(Na)	CH_3ONa	$C_{20}H_{41}COCH_2COOCH_3$	(667)
Docosanoyl..........	Acetoacetic	(Na)	CH_3ONa	$C_{21}H_{43}COCH_2COOCH_3$	(667)
	$(C_6H_5CH_2OCO)_2CH(CH_2)_{14}$- $CH_2COOCH_2C_6H_5$	(Na)	(1) H_2, Pd (2) $-CO_2$	$C_{21}H_{43}CO(CH_2)_{16}COOH$	(106)
	Acetoacetic	(Na)	CH_3ONa	$C_{21}H_{43}COCH_2COOCH_3$ (40%)	(655)
	$CH_3COCH(CH_2)_{10}(COOC_2H_5)_2$	(Na)	Ethyl ether, $(+H_2O)$	$C_{21}H_{43}CO(CH_2)_{11}COOH$	(222)
Tetratricontanoyl....	$CH_3COCH(CH_2)_{10}(COOC_2H_5)_2$	(Na)	$(+H_2O)$	$C_{33}H_{67}CO(CH_2)_{11}COOH$	(222)
Nonatricosanoyl.....	$(C_6H_5CH_2OCO)_2CH(CH_2)_{14}$- $CH_2COOCH_2C_6H_5$	(Na)	(1) H_2, Pd (2) $-CO_2$	$C_{38}H_{77}CO(CH_2)_{17}COOH$	(106)
10-Undecenoyl.......	$CH_3COCH[(CH_2)_5COOC_2H_5]$- $COOC_2H_5$	(Na)	$(+H_2O)$	$CH_2{=}CH(CH_2)_8CO(CH_2)_6COOH$	(378)
	Acetoacetic	(Na)	CH_3ONa	$CH_2{=}CH(CH_2)_8COCH_2COOCH_3$ (21%)	(669)
9-Undecenoyl........	$CH_3COCH[(CH_2)_5COOC_2H_5]$- $COOC_2H_5$	(Na)	$(+H_2O)$	$CH_3CH{=}CH(CH_2)_7CO(CH_2)_6$- $COOH$	(378)
16-Bromo-9-hexa-decenoyl...........	Acetoacetic	(Na)	$(+H_2O)$	$CH_2Br(CH_2)_7COCH_2COOC_2H_5$	(93)
3-Carbomethoxy-propionyl.........	Malonic	(Mg)	Ethyl ether, $(+H_2O)$	$(CH_2COOC_2H_5)_2$	(573)
	$C_{11}H_{23}CH(COCH_3)COOC_2H_5$	(Na)	$(+H_2O)$	$C_{12}H_{25}CO(CH_2)_2COOH$	(577)
	$C_9H_{19}CH(COCH_3)COOC_2H_5$	(Na)	$(+H_2O)$	$C_{10}H_{21}CO(CH_2)_2COOH$	(577)

	$CH_3CH(COCH_3)COOCH_3$	(Na)	($+H_2O$)	$C_2H_5CO(CH_2)_2COOH$	(578)
	$C_6H_5O(CH_2)_2CH(COCH_3)$-$COOC_2H_5$	(Na)	($+H_2O$)	$C_6H_5O(CH_2)_4COCH_3$	(45)
		(Na)	H_2O, H_2	$C_6H_5O(CH_2)_4COOC_2H_5$, C_6H_5O-$(CH_2)_7COOC_2H_5$	(45)
	$C_6H_5O(CH_2)_2CH(COCH_3)$-$COOC_2H_5$	(Na)	($+H_2O$)	$C_6H_5O(CH_2)_3COOH$	(579)
	Acetoacetic	(Na)	Ethyl ether, ($+H_2O$)	$CH_3COCH(COOC_2H_5)CO(CH_2)_2$-$COOH$	(579)
5-Carbethoxy-valeryl.............	$CH_3COCH(C_2H_5)COOC_2H_5$	(Na)	($+H_2O$)	$C_3H_7CO(CH_2)_2COOCH_3$	(589)
9-Carbethoxynon-anoyl..............	$C_{11}H_{23}CH(COCH_3)COOC_2H_5$	(Na)	($+H_2O$)	$C_{12}H_{25}CO(CH_2)_4COOH$	(577)
11-Cyanoundeca-noyl...............	$C_7H_{15}CH(COCH_3)COOC_2H_5$	(Na)	Ethyl ether, ($+H_2O$)	$C_8H_{17}CO(CH_2)_8COOH$	(577)
	Acetoacetic	(Na)		$NC(CH_2)_{10}COCH(COCH_3)$-$COOC_2H_5$	(538)
Succinyl.............	Malonic	(Na)	($+H_2O$)	$HOOC(CH_2)_2COCH(COOC_2H_5)_2$	(605)
	Acetoacetic	(Na)	Ethyl ether	$CH_3COCH(COOC_2H_5)CO(CH_2)_2$-$COOH$, $CH_3COCH(COOC_2H_5)$-$COCH_2CH_2COCH(COCH_3)$-$COOC_2H_5$	(606)
Glutaryl.............	Malonic	(Na)	($+H_2O$)	$(C_2H_5OCO)_2CHCO(CH_2)_3COCH$-$(COOC_2H_5)_2$	(605)
	Acetoacetic	(Na)		$CH_3COCH(COOC_2H_5)CO(CH_2)_3$-$COCH(COCH_3)COOC_2H_5$	(606)
Adipyl..............	Malonic	(Na)	($+H_2O$)	$(C_2H_5OCO)_2CHCO(CH_2)_4COCH$-$(COOC_2H_5)_2$	(605)
	Acetoacetic	(Na)		$CH_3COCH(COOC_2H_5)CO(CH_2)_4$-$COCH(COCH_3)COOC_2H_5$	(606)

* ($+H_2O$) indicates that the product was obtained by hydrolysis of the initial condensation product.

terchange reaction (VII) between 2 moles of an aliphatic acid chloride and 1 mole of a dibasic acid appears to be particularly difficult to achieve under any conditions.

$$2RCOCl + HOOC(CH_2)_nCOOH \rightarrow (CH_2)_n(COCl)_2 + 2RCOOH \quad (VII)$$
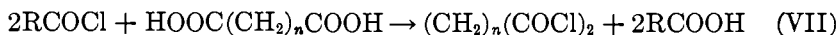
The products resulting from the reaction of an aliphatic acid chloride and an acid may be considered in the light of the reversible equilibria which maintain between the various species present, assuming that the acyl groups are capable of ionization. This explanation of the course of these reactions is subject to some

$$2RCOCl + 2R'COOH \rightleftarrows RCOCl + R'COOH + HCl + RCOOCOR'$$

$$\rightleftarrows R'COCl + RCOOH + HCl + RCOOCOR' \rightleftarrows 2RCOOCOR'$$

$$+ 2HCl \rightleftarrows (RCO)_2O + (R'CO)_2O + 2HCl \rightleftarrows 2R'COCl + 2RCOOH$$
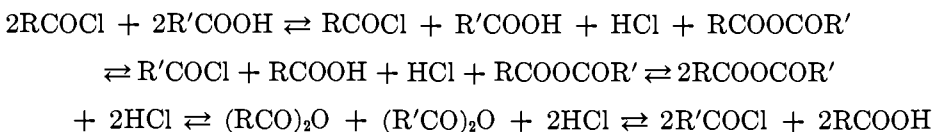
question. It has been pointed out (116) that the uniformly high yields obtained in the interchange conversion of benzoyl chloride and acetic acid, for example, seem quite unlikely upon the assumption that the splitting off of hydrogen chloride is a necessary step to the formation of acetyl chloride. If this were the case, in view of the relatively high temperature of the reaction mixture, the loss of hydrogen chloride from the system and consequent decrease in yield would be expected to be much greater than actually occurs. Therefore, it would appear likely that the formation of the acid chloride takes place either directly, as in reaction V, or through some intermediate product which does not involve the complete separation of hydrogen chloride. It follows that in attempts to carry out reaction V the observed evolution of hydrogen chloride can be largely attributed to the side reaction III. The improvement of yield of V with rapid distillation can be explained on the ground that the sooner the acid chloride is removed from the reaction mixture the less chance it has to participate in the side reaction. Indeed, in this reaction both anhydride and acid chloride formation may take place through the same intermediate

$$\begin{array}{ccc} Cl & & O \\ | & & \| \\ R-C-O-C-R \\ | \\ OH \end{array}$$
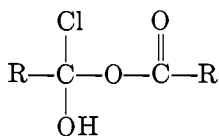
as the formation of stable addition products of both acids and acid chlorides to the carbonyl group has been reported (484, 610). The exact nature of the intermediate in these reactions is still obscure.

The most efficient conversion of an aliphatic acid chloride to the corresponding anhydride is apparently the reaction with a salt of the corresponding acid; the sodium salts have been most suitable (197, 409, 553), although the use of

$$RCOCl + RCOOM \rightarrow (RCO)_2O + MCl$$

silver salts is also recorded (719, 732). The usual technique involves treating a suspension of the salt in an anhydrous organic solvent such as ether with the

acid chloride involved, filtering from the inorganic salt, and evaporating the filtrate.

The formation of mixed anhydrides has been achieved through the use of acetyl chloride and the sodium salts of butyric, isovaleric, and lower acids (37). Although the acetyl alkanoyl anhydrides have been isolated in certain instances at low temperatures, attempts to distill them almost invariably result in disproportionation to the symmetrical anhydrides.

$$2RCOOCOCH_3 \rightarrow (RCO)_2O + (CH_3CO)_2O$$

D. REACTION WITH ACID ANHYDRIDES AND LACTONES

The interchange reaction between an aliphatic acid chloride and an anhydride differs from that with an acid, in that hydrogen chloride cannot be involved in the proposed equilibria. In order to prepare an anhydride from an aliphatic acid chloride by this interchange all that is necessary is that the boiling point

$$2RCOCl + (R'CO)_2O \rightleftarrows RCOCl + R'COCl + RCOOCOR'$$

$$\rightleftarrows 2R'COCl + (RCO)_2O$$

of R'COCl be lower than that of either RCOCl, $(RCO)_2O$, $(R'CO)_2O'$ or RCOOCOR', so that it will be capable of fractionation from the heated mixture. The reaction has not been previously reported for the higher aliphatic acid chlorides, but it has been reported with benzoyl chloride and acetic anhydride (760), with thionyl chloride and phthalic anhydride (423), and with phthaloyl chloride and maleic or succinic anhydride in the presence of zinc chloride (424).

Few reports are available concerning the reactions of acid chlorides and lactones. Propiolactone added over the course of 3 hr. to a slight excess of acetyl chloride at 0°C. with constant stirring has afforded β-acetoxypropionyl chloride,

$$H_2C—CH_2—CO + CH_3COCl \rightarrow CH_3COOCH_2CH_2COCl$$
$$\underset{\displaystyle O}{\underline{\qquad\qquad}}$$

and analogous acid chlorides and β-lactones are held to undergo a similar reaction (265, 266).

E. REACTION WITH KETENES

Although reports are sparse, some evidence is available indicating that aliphatic acid chlorides react with ketenes by addition to the carbon–carbon double bond. Diphenylketene and oxalyl chloride have been reported to react in 1 hr. in the cold to afford an 84 per cent yield of diphenylmalonyl chloride (659), and the same compound was also obtained through the use of phosgene after several hours at 130°C.

$$(C_6H_5)_2C{=}C{=}O + (COCl)_2 \rightarrow (C_6H_5)_2C(COCl)_2 + CO$$

$$(C_6H_5)_2C{=}C{=}O + COCl_2 \rightarrow (C_6H_5)_2C(COCl)_2$$

Diphenylketene and acetyl chloride, however, apparently undergo an interchange reaction to give diphenylacetyl chloride and ketene, and succinyl chloride is also reported to undergo this latter type of reaction.

$$(C_6H_5)_2C{=}C{=}O \ + \ CH_3COCl \ \rightarrow \ (C_6H_5)_2CHCOCl \ + \ CH_2{=}C{=}O$$

With ketene acetals, such as the diethyl acetal of ketene itself, acetyl chloride has given (477) a mixture of products, among which ethyl chloride, acetyl chloride, ethyl acetate, acetoacetic ester, $CH_3C(OC_2H_5){=}CHCOOC_2H_5$ (26 per cent), and $CH_3C(OCOCH_3){=}CHCOOC_2H_5$ (30 per cent) were identified. By increasing the relative proportion of acetyl chloride in the reaction the yield of the last-named compound could be increased to 52 per cent.

F. REACTION WITH QUINONES

Addition reactions of aliphatic acid chlorides and quinones have been restricted to those with acetyl chloride. With benzoquinone a mixture consisting predominantly of the chlorohydroquinone diacetate, together with smaller amounts of hydroquinone and dichlorohydroquinone diacetates, has resulted (124, 261, 607, 618).
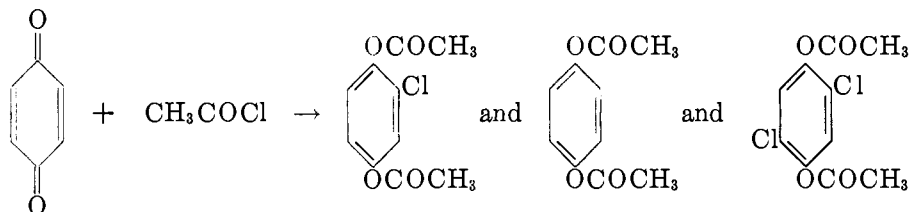

The reaction is apparently not general, for the 2,5-dimethoxy-, 2,6-dimethoxy-, 2,3-dichloro-, 2,5-dichloro-, and 2,6-dichlorobenzoquinones did not react with acetyl chloride, hot or cold (527), although the aluminum chloride-catalyzed reaction has been observed to afford some products. An interesting feature of this reaction is that under anhydrous conditions the reaction with benzoquinone is very slow unless hydrogen chloride is present (261). For example, only 17.5 per cent of converted material has been obtained after 4 hr. of refluxing, but on passage of dry hydrogen chloride for a short time, or on addition of a small drop of water, a vigorous reaction has been observed and this is then complete in 30 min. Methylbenzoquinone, which does not react with acetyl chloride alone after refluxing for 4 hr., reacts slowly on addition of a drop of water to give 5-chloro-2-methylhydroquinone diacetate and much uncrystallizable material which
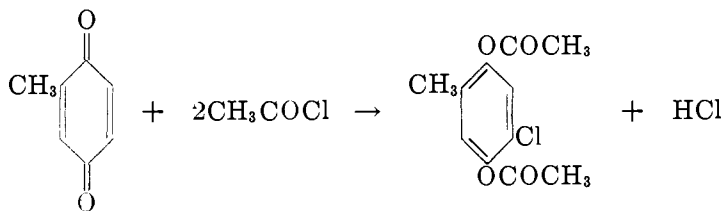

5-Chloro-2-methyl-
hydroquinone diacetate

contains unchanged methylbenzoquinone. 1,4-Naphthoquinone under similar conditions has given an almost black polymeric material (400).

A probable reaction course for the formation of diacetates of chlorohydroquinone, hydroquinone, and dichlorohydroquinone in the reaction of acetyl chloride with benzoquinone has been given (261) as the addition of hydrogen chloride followed by acetylation of the intermediate chlorohydroquinone, a contention supported by the observation that free chlorohydroquinone has been isolated from the reaction when an excess of acetyl chloride is avoided. Oxidation of chlorohydroquinone by benzoquinone could then afford chlorobenzoquinone, which could add hydrogen chloride to give dichlorohydroquinone. The latter would then be acetylated, together with the hydroquinone formed in the oxidation. The possibility of reaction occurring *via*
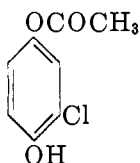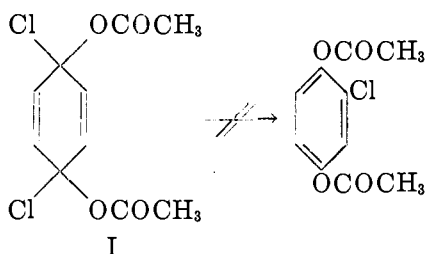

has evidently not been considered.
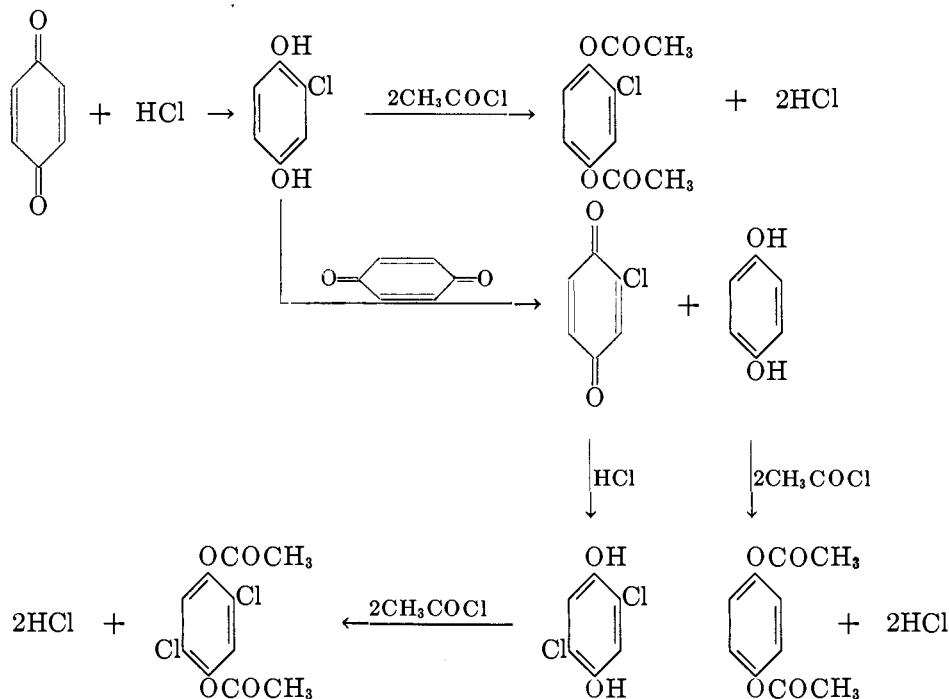
The course of the chlorination–acetylation has likewise been held to pass through an intermediate of type I, which with elimination of hydrogen chloride would

conceivably yield chlorohydroquinone diacetate. The latter course appears highly improbable.
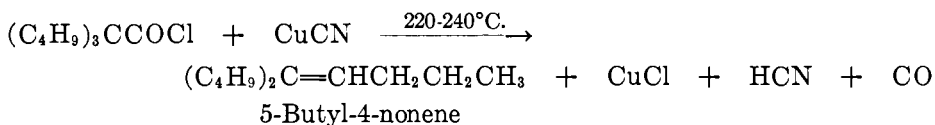

I

XI. Reaction of Aliphatic Acid Chlorides with Inorganic Compounds Involving Replacement of the Chlorine Atom

A. REPLACEMENT OF THE CHLORINE ATOM BY THE CYANO GROUP

The interchange of an acid chloride with metallic cyanides to afford an acyl cyanide has been reported for benzoyl chloride with cuprous cyanide (523) and

$$RCOCl + MCN \rightarrow RCOCN + MCl \qquad (I)$$

silver cyanide (504). The product, benzoyl cyanide, is a crystalline solid stable enough to be capable of purification by fractional distillation. It represents, like the acyl cyanides derived from aliphatic acid halides, a useful intermediate in the synthesis of α-keto acids (523). Apparently trimethylacetyl chloride is the only aliphatic acid chloride which has been reported as entering into this reaction. When refluxed for 20 hr. with anhydrous cuprous cyanide it afforded an 87 per cent yield of trimethylacetyl cyanide (653). On the other hand, tributyl-acetyl chloride when refluxed for 8 hr. at 220–240°C. gave instead an 81 per cent yield of 5-butyl-4-nonene. Presumably hydrogen cyanide and carbon monoxide were also formed.

$$(C_4H_9)_3CCOCl + CuCN \xrightarrow{\quad 220\text{-}240°C. \quad}$$

$$(C_4H_9)_2C{=}CHCH_2CH_2CH_3 + CuCl + HCN + CO$$
$$\text{5-Butyl-4-nonene}$$

At 100°C., however, the latter reaction apparently did not proceed. Although acetyl bromide and cuprous cyanide have afforded a 77 per cent yield of pyru-vonitrile (331), apparently acetyl chloride could not be induced to react with either cuprous or potassium cyanide under various conditions.

The reaction of acid chlorides with anhydrous hydrogen cyanide occurs in the presence of pyridine, probably with the separation of pyridinium chloride.

$$RCOCl + HCN + C_5H_5N \rightarrow RCOCN + C_5H_5\overset{\oplus}{N}H\overset{\ominus}{Cl} \qquad (II)$$
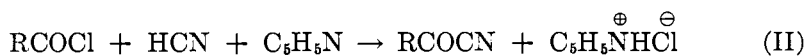
Benzoyl chloride reacts in this manner (153), a recent claim inferring that the yield is as high as 78 per cent (354). Acetyl chloride reacts to the extent of only

20 per cent, but a brown residue, presumably dimerized acetyl cyanide, obtained in the reaction could account for the reduction in the yield. It appears that reaction II is prone to proceed only if the pyridinium chloride is precipitated by the addition of absolute ether.

B. REPLACEMENT OF THE CHLORINE ATOM BY OTHER HALOGENS

Aliphatic acid chlorides provide the most economical means for the conversion of an acid to its acid fluoride, bromide, or iodide. It has been pointed out (475) that on the basis of available data on the heats of formation of halides and oxides of non-metals (silicon, boron, antimony, arsenic, phosphorus, and sulfur) further attempts to produce acyl fluorides directly from carboxylic acids and non-metallic fluorides or oxyfluorides should remain fruitless.

The conversion of aliphatic acid chlorides to acid fluorides has been reported through a variety of methods. Acetyl chloride, prepared from acetic acid with

$$RCOCl + MF \rightarrow RCOF + MCl$$
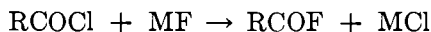
thionyl chloride followed by subsequent removal of hydrogen chloride and sulfur dioxide, has been converted to acetyl fluoride with potassium hydrogen fluoride, sodium hydrogen fluoride, potassium fluoride, sodium fluoride, ammonium fluoride, and lithium fluoride in yields ranging from 54.6 down to 4 per cent, respectively (475). Although each of the products contained acetyl chloride, a simple fractionation could separate the two components easily. It was significant that when phosphorus trichloride, phosphorus pentachloride, or sulfuryl chloride was used to prepare the acid chlorides, unsatisfactory results were obtained in conversion to the fluoride. Chloroacetyl chloride has given a 55.6 per cent yield of chloroacetyl fluoride with potassium fluoride at 170°C., while at 200°C. the same reaction gave a 33.2 per cent yield after 45 min. and a 45.2 per cent yield after 20 min. (604). Acetyl fluoride has been prepared by the action of potassium fluoride on a solution of benzoyl chloride in acetic acid (510).

$$CH_3COOH + C_6H_5COCl \rightarrow CH_3COCl + C_6H_5COOH$$

$$CH_3COCl + KF \rightarrow CH_3COF + KCl$$
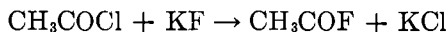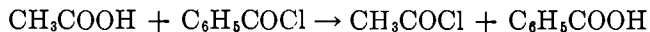
The most volatile component, acetyl fluoride, is removed by distillation as it is formed (compare Section X,C). Hydrogen fluoride has had limited use in the exchange reaction of aliphatic acid chlorides. The reaction has been claimed to proceed almost quantitatively when the acyl chloride is dissolved in anhydrous hydrogen fluoride, as a consequence of the fact that hydrogen chloride is completely insoluble in anhydrous hydrogen fluoride (170, 225). The method could

$$RCOCl + HF \rightarrow RCOF + HCl$$
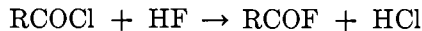
be important for the preparation of higher-boiling acyl fluorides which are easily separated from hydrogen fluoride by distillation. Acyl fluorides have also been prepared through the use of antimony trifluoride. The yield of acetyl fluoride

obtained by this method is poor—approximately 30 per cent, accompanied by some acetyl chloride—and this yield is decreased to 25 per cent in benzene solution with the formation of traces of acetophenone (718). Fluoroacetyl chloride, refluxed for 3 hr. with antimony trifluoride, afforded a 64.4 per cent yield of fluoroacetyl fluoride (604). Thallous fluoride has also proven to be a satisfactory fluorinating interchange reagent (272).

The conversion of aliphatic acid chlorides to acid bromides or iodides has been relatively unimportant, in view of the limited utility of the latter compounds compared to acid chlorides. Gaseous hydrogen bromide has been employed in the cold to convert chlorides to bromides, but acetyl and trichloroacetyl chlorides alone are reported (30, 631, 657).

$$RCOCl + HBr \rightarrow RCOBr + HCl$$
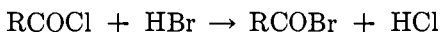
Conversion to acid iodides has been expeditiously achieved with either dry
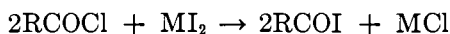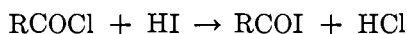
$$RCOCl + HI \rightarrow RCOI + HCl$$

$$2RCOCl + MI_2 \rightarrow 2RCOI + MCl$$

hydrogen iodide (277, 657) or calcium or magnesium iodide (654). Direct replacement through the use of potassium iodide with cinnamoyl or trichloroacetyl chloride has been unsuccessful, and the small amount of iodine liberated from potassium iodide by benzoyl chloride was attributed to an oxidation–reduction phenomenon (539).

C. REPLACEMENT OF THE CHLORINE ATOM BY OTHER GROUPS

The replacement of the chlorine atom of an aliphatic acid chloride by the isocyanate group has been accomplished for sebacyl chloride using silver isocyanate (443).

$$ClCO(CH_2)_8COCl + 2AgNCO \rightarrow O{=}CNCO(CH_2)_8CONC{=}O + 2AgCl$$
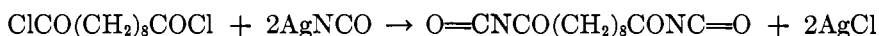
The unstable filtrate obtained from the reaction of acetyl chloride and silver perchlorate in acetic anhydride (457) apparently contained acetyl perchlorate.

$$CH_3COCl + AgClO_4 \rightarrow CH_3COClO_4 + AgCl$$
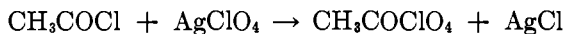
The acyl nitrates are probably also unstable, explaining the observation that most organic acid chlorides react explosively with concentrated nitric acid (553). Attempts to achieve reaction between acetyl or benzoyl chloride and silver nitrate have yielded, instead of the acyl nitrates, the corresponding carboxylic anhydrides (221, 428). Similar results obtained with acetyl and chloroacetyl chlorides and potassium nitrate (183) have been explained by a disproportionation of the initially formed acetyl nitrate. The formation of trimethylacetyl hydrogen sulfate

$$CH_3COCl + KNO_3 \rightarrow CH_3COONO_2 + KCl$$

$$2CH_3COONO_2 \rightarrow (CH_3CO)_2O + N_2O_5$$
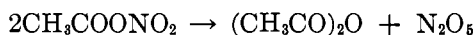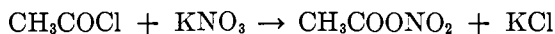
from trimethylacetyl chloride and sulfuric acid has been noted at ordinary temperatures (99). On warming the mixture carbon monoxide was set free and the

$$(CH_3)_3CCOCl + H_2SO_4 \rightarrow (CH_3)_3CCOOSO_3H + HCl$$
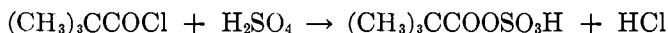
isobutylene formed reacted with the sulfuric acid to form isobutylenedisulfonic acid, $C_4H_6(SO_3H)_2$.

The reaction of an acid chloride and a metal oxide (478) written in the overall form may also be considered to occur stepwise through the formation and dis-

$$2RCOCl + M_2O(M'O) \rightarrow (RCO)_2O + 2MCl(M'Cl_2)$$
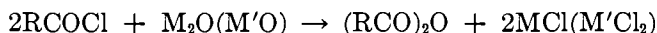
proportionation of two moles of a salt. This reaction is discussed under Section XII.

$$RCOCl + M_2O \rightarrow RCOOM + MCl$$

$$2RCOOM \rightarrow (RCO)_2O + M_2O$$
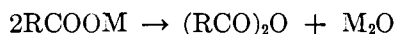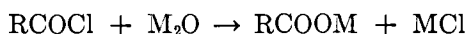
XII. Reaction of Aliphatic Acid Chlorides with Peroxides and Oxides

A. REACTION WITH PEROXIDES

Aliphatic acid chlorides react with inorganic peroxides to yield the acyl peroxides. The usual technique has involved dissolving the acid chloride in an inert

$$2RCOCl + M_2O_2 \rightarrow RCOOOCOR + 2MCl$$
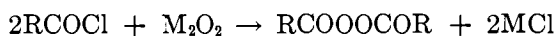
solvent like ligroin and adding this to a suspension of the alkali or alkaline earth peroxide in a mixture of cracked ice and a suitable solvent, stirring or shaking, and extracting the peroxide with ether or dioxane. Drying and evaporation of the solvent yield the peroxide as a solid. Under these conditions the corresponding peroxides were obtained from lauroyl, myristoyl, tridecanoyl, 13-docosenoyl, and 12-heneicosenoyl chlorides in from 40 to 85 per cent yields with sodium peroxide (205, 205, 671). Barium peroxide has also been used efficiently for this purpose (208). The application of hydrogen peroxide to this reaction has not been frequently reported with aliphatic acid chlorides but with p- and m-nitrobenzoyl chlorides in dry acetone solution in the presence of pyridine (or sodium hydroxide, sodium acetate) this reagent is also claimed to give acceptable yields (699). Thirty per cent hydrogen peroxide in ether with aqueous sodium hydroxide at 0°C. has been used efficiently (205).

The acyl peroxides, particularly the higher members, have attracted considerable attention as vinyl polymerization accelerators (474), as catalysts for drying oils (713), as bleaching agents for oils, fats, and waxes, as pharmaceuticals and cosmetic ingredients, and as raw materials for organic syntheses.

Reactions of aliphatic acid chlorides with organic peroxides are infrequently referred to in the literature. Among the products isolated and identified in the decomposition of acetyl peroxide in dimethylacetyl chloride were methane, carbon dioxide, methyl acetate, acetyl chloride, tetramethylsuccinyl chloride, and tetramethylsuccinic anhydride (394). The products were assumed to arise through

free-radical mechanisms through an attack of the methyl radical on the tertiary hydrogen in the acid chloride and subsequent dimerization of the resulting radical. Tetramethylsuccinic anhydride and acetyl chloride were apparently products of

$$(CH_3CO)_2O_2 \rightarrow CH_3COO\cdot + CO_2 + CH_3\cdot$$

$$(CH_3)_2CHCOCl + \cdot CH_3 \rightarrow (CH_3)_2\overset{\cdot}{C}COCl + CH_4$$

$$2(CH_3)_2\overset{\cdot}{C}COCl \rightarrow \begin{array}{c} (CH_3)_2CCOCl \\ | \\ (CH_3)_2CCOCl \end{array}$$
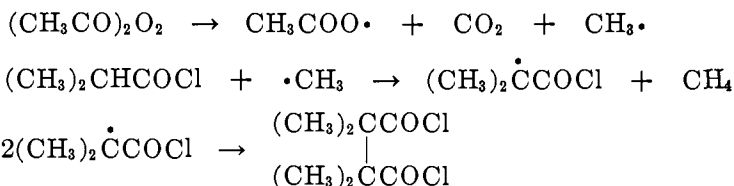
side reactions occurring during the isolation of the material. Similarly, the conversion of trichloroacetyl chloride to tetrachlorosuccinic acid with acetyl peroxide and subsequent hydrolysis (389) follows the same reaction pattern.

B. REACTION WITH OXIDES

Scattered references attest to the utility of acetyl chloride as a chlorinating agent for inorganic compounds, particularly oxides of non-metals and of heavier metals. Pervanadyl chloride has been prepared from vanadium pentoxide, the green tetrachloride of quadrivalent manganese from manganese dioxide, and uranyl dichloride from uranium trioxide (146). New and interesting organoarsenic compounds of the type $CH_2(AsCl_2)_2$ and $RCH(AsCl_2)_2$ have been produced by heating mixtures of either arsenic trioxide or arsenic pentoxide with aluminum chloride and acetyl or propionyl chloride at elevated temperatures (551). A recent attempt to prepare anhydrous beryllium chloride by heating beryllium oxide with acetyl chloride at 200–700°C. (72) failed, apparently because of decomposition of the acetyl chloride to carbon, hydrogen chloride, and acetic anhydride under these conditions.

Although aliphatic acid chlorides have thus far not been observed to react in this manner, silver and yellow mercuric oxides reacted with benzoyl and *p*-toluoyl chlorides to furnish anhydrides (478). A parallel may be pointed out in the similarity of this reaction to those involving disproportionation of mixed anhydrides

$$2RCOCl + M_2O(M'O) \rightarrow (RCO)_2O + 2MCl(M'Cl_2)$$

(see Section XI,C). When considered stepwise these reactions could conceivably involve initial formation and immediate disproportionation of two moles of the mercury or silver salt under heating.

$$RCOCl + M_2O \rightarrow RCOOM + MCl$$

$$2RCOOM \rightarrow (RCO)_2O + M_2O$$

Since the reaction is also observed to proceed with calcium oxide, although in considerably reduced yield, the parallelism is somewhat more evident.

$$RCOCl + MO \rightarrow RCOOMCl$$

$$2RCOOMCl \rightarrow (RCO)_2O + MO + MCl_2$$

XIII. REACTION OF ALIPHATIC ACID CHLORIDES WITH HYDROCARBONS (FRIEDEL–CRAFTS TYPE OF REACTION)

Aliphatic acid chlorides react with hydrocarbons in the presence of acidic catalysts like anhydrous aluminum chloride in a variety of ways. Aromatic hydrocarbons are acylated in the well-known Friedel–Crafts synthesis of aromatic ketones in the presence of anhydrous aluminum chloride (first applied in the aromatic series with phthaloyl chloride and benzene to give anthraquinone in 1878 (234) and in the aliphatic series with butyryl chloride and benzene to give butyrophenone in 1882 (121)).

$$C_6H_6 \; + \; RCOCl \; \xrightarrow{\text{AlCl}_3} \; C_6H_5COR \; + \; HCl$$

Similar reactions to which the name Friedel–Crafts is not generally applied occur in the presence of other catalysts, such as the chlorides of zinc, ferric iron, and tin and boron trifluoride as well as many others, and are referred to under the general treatment of reactions of the Friedel–Crafts type. With olefins and acetylenes addition reactions have been observed, although many other modes are also in evidence.

$$RCOCl \; + \; -CH{=}CH- \; \longrightarrow \; RCO\overset{|}{CH}-\overset{|}{CH}Cl$$

$$RCOCl \; + \; -C{\equiv}C- \; \longrightarrow \; RCO\overset{|}{C}{=}\overset{|}{C}Cl$$

Saturated hydrocarbons react by substitution, with rearrangement and ring cleavage sometimes exhibited.

The general scope of reactions of hydrocarbons with aliphatic acid chlorides in the presence of anhydrous aluminum chloride with particular respect to mechanisms of reaction, physical-chemical studies, reaction conditions, effect of heat, solvents, and stirring, reversibility of reaction, and the synthetic applications has been included in an exhaustive treatise in 1941 (684). Repetition of these facts is unnecessary and attention therefore will be directed now to newer material of a unique nature appearing subsequent to 1941.

A. REACTION WITH AROMATIC HYDROCARBONS

The Friedel–Crafts acylation of aromatic hydrocarbons provides a synthetic route, *via* the Clemmensen or Wolff–Kishner reduction of the ketone intermediates, to long-chain aromatic-aliphatic hydrocarbons. Similarly, the employment of carbalkoxy acid chlorides leads to aromatic-aliphatic keto esters, converted by reduction and hydrolysis to aromatic-aliphatic acids or by hydrolysis to keto acids.

$$RCOCl \; + \; C_6H_6 \; \xrightarrow{\text{AlCl}_3} \; C_6H_5COR \; \rightarrow \; C_6H_5CH_2R$$

$$ROOC(CH_2)_xCOCl \; + \; C_6H_6 \; \xrightarrow{\text{AlCl}_3}$$

$$C_6H_5CO(CH_2)_xCOOR \; \rightarrow \; C_6H_5(CH_2)_{x+1}COOR$$
$$\downarrow \qquad\qquad\qquad\qquad \downarrow$$
$$C_6H_5CO(CH_2)_xCOOH \qquad C_6H_5(CH_2)_{x+1}COOH$$

Friedel–Crafts reactions of the latter type in general have not achieved as uniformly high yields as the reactions of diarylcadmium with carbalkoxy acid chlorides (Section XIX,D,2), but Friedel–Crafts syntheses are generally favored economically when considerations of yield and the observed formation of mixtures of o- and p-isomers are not of paramount importance, or when methods are available for separating such mixtures. It is not surprising, therefore, that recent attention has been directed to the search for other acidic catalysts which will either increase the total yield of acylated products or increase the degree of specificity in substitution of benzene homologs. In the acetylation of toluene, for example, zirconium tetrachloride has given better but less consistent results than aluminum chloride. With a 1:1 ratio of catalyst to acetyl chloride, an 80 per cent yield of 4-tolyl methyl ketone has been obtained with zirconium tetrachloride and only a 68 per cent yield with aluminum chloride (295). In the same reaction a series of metal chlorides (177) and bromides (178) has been investigated.

Some recent attention has been focused on the exact function of the catalyst in Friedel–Crafts acylation reactions. There is a divergence of opinion as to whether the catalyst first forms a complex with the acid chloride or acts through an abstraction of chlorine from it with the formation of ions of the type $AlCl_4^-$ and acyl ions, the latter being generally assumed to attack the aromatic nucleus. Generally high yields produced in the Perrier modification of the Friedel–Crafts acylation (540), in which the acyl chloride and aluminum chloride are first combined in a solvent and then treated with the hydrocarbon, have pointed to the former view. One explanation has involved a postulation that the acid chloride reacts with the aluminum chloride through an enol form, in accordance with the observation that acetyl chloride and aluminum chloride react to evolve hydrogen chloride and give a complex which on further reaction with benzene gives a 65 per cent yield of acetophenone and additional hydrogen chloride (342).

$$H_2C=C(OH)Cl + AlCl_3 \rightarrow H_2C=C(OAlCl_2)Cl + HCl$$

$$H_2C=C(OAlCl_2)Cl + C_6H_6 \rightarrow H_2C=C(OAlCl_2)C_6H_5 + HCl$$

$$H_2C=C(OAlCl_2)C_6H_5 + H_2O \rightarrow C_6H_5COCH_3 + Al(OH)Cl_2$$
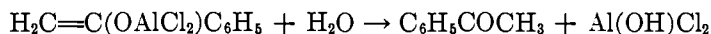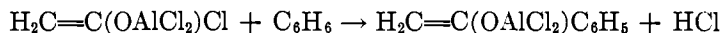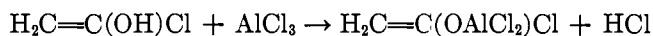
Although the enol form of an aliphatic acid chloride has been offered before as an intermediate to explain reactions of acid chlorides (refer to Section XVI,B), it must be pointed out that there is no physical evidence to indicate that acid chlorides are themselves capable of enolization.

One of the abnormal reactions encountered in the Friedel–Crafts acylation of hydrocarbons is that which occurs with acylating agents of the type of trialkylacetyl chloride. These acyl chlorides afford carbon monoxide and alkyl hydrocarbons under some conditions to the total exclusion of the normal ketone products. Products obtained under a variety of conditions with trimethylacetyl chloride and hydrocarbons and anisole have been tabulated in table 20.

Studies have been made of the kinetics of the isolated alkylation and acyla-

TABLE 20

Reaction products obtained from trimethylacetyl chloride in the Friedel–Crafts reaction (584)

AROMATIC COMPOUND	RELATIVE PROPORTION OF PRODUCTS		CARBON MONOXIDE	TOTAL PRODUCTS
	Hydrocarbon	Ketone		
An excess of the hydrocarbon and 1 mole of aluminum chloride used				
			per cent	*per cent*
$C_6H_5CH_3$........	$4\text{-}CH_3C_6H_4(t\text{-}C_4H_9)$ (41.4)	$t\text{-}C_4H_9COC_6H_4CH_3\text{-}4$ (58.6)	53	87
C_6H_6............	$t\text{-}C_4H_9C_6H_5$ (100)	(0)	87	67
$C_6H_5C_2H_5$......	$4\text{-}C_2H_5C_6H_4(t\text{-}C_4H_9)$ (37.1)	$4\text{-}C_2H_5C_6H_4CO(t\text{-}C_4H_9)$ (62.9)	50	78.5
$t\text{-}C_4H_9C_6H_5$......	$1,4\text{-}C_6H_4(t\text{-}C_4H_9)_2$	$4\text{-}(t\text{-}C_4H_9)C_6H_4CO(t\text{-}C_4H_9)$ (26.3)	65	
$CH_3OC_6H_5$.......	(0)	$4\text{-}CH_3OC_6H_4CO(t\text{-}C_4H_9)$ (100)	7	79.6
In carbon disulfide solution				
$C_2H_5C_6H_5$......	$4\text{-}C_2H_5C_6H_4(t\text{-}C_4H_9)$ (57.6)	$4\text{-}C_2H_5C_6H_4CO(t\text{-}C_4H_9)$ (42.4)		66
$t\text{-}C_4H_9C_6H_5$......	$1,4\text{-}C_6H_4(t\text{-}C_4H_9)_2$ (100)	(0)		71
$CH_3OC_6H_5$.......	(0)	$4\text{-}CH_3OC_6H_4CO(t\text{-}C_4H_9)$ (100)		45

tion reactions with trimethylacetyl chloride (585, 586). It has been assumed that the stability of the acyl ion determines whether acylation or alkylation predominates in the reaction. Thus, loss of carbon monoxide is facilitated with trialkylacetyl chlorides because the resulting tertiary carbonium ions are stable. In the presence of an aromatic hydrocarbon this ion produces the alkyl aromatic; where no aromatic is present it may actually rearrange to an olefin. The inability of straight-chain aliphatic acid chlorides to produce hydrocarbons is

$$RCOCl + AlCl_3 \rightarrow R\overset{\oplus}{C}O(Al\overset{\ominus}{Cl_4})$$

$$R\overset{\oplus}{C}O(Al\overset{\ominus}{Cl_4}) \rightarrow R^{\oplus} + Al\overset{\ominus}{Cl_4} + CO$$

(a) $\quad R^{\oplus} + HC_6H_5 \rightarrow RC_6H_5 + H^{\oplus}$

(b) $\quad R_2'CH\overset{\oplus}{C}R_2'' \rightarrow R_2'C=CR_2'' + H^{\oplus}$
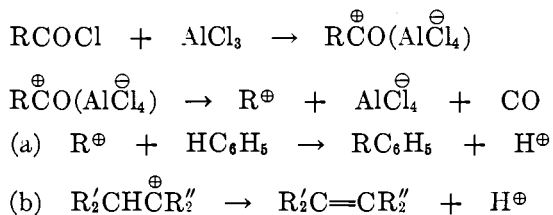
$R'' = H$ or alkyl; $R'' = $ alkyl.

evidently attributable to the relative instability of ions of the type $R'CH_2^{\oplus}$. Since secondary carbonium ions are generally intermediate in stability between primary and tertiary types, some alkylation would be expected in reactions with dialkylacetyl chlorides. The tendency is not especially pronounced however, as diethylacetyl chloride and benzene in the presence of anhydrous aluminum chloride have been observed to give only a 7 per cent yield of carbon monoxide and an 81 per cent yield of α-ethylbutyrophenone (587). Some recent acylations with trimethylacetyl chloride and polymethylbenzenes (514) have been reported to give yields of the order of 60 per cent of the corresponding pivalophenones, but the formation of hydrocarbons was not noted.

The relative reactivity of various acyl chlorides as acylating agents in the Friedel–Crafts reaction has been investigated with acetyl, benzoyl, and 2-ethylbutyryl chlorides (467). Using preformed equimolecular quantities of two acyl chloride–aluminum chloride complexes in competition for 1 mole of toluene it has been shown that the relative reactivities of these acid chlorides in the form of their complexes decreases in the order $CH_3COCl > C_6H_5COCl > CH_3CH_2-CH(C_2H_5)COCl$. Results have shown that not only is the coördination complex with acetyl chloride more reactive than that with benzoyl chloride but that the complex is apparently formed more readily with acetyl chloride.

B. REACTION WITH OLEFINS

Although the principal reaction of aliphatic acid chlorides with olefins in the presence of catalysts like anhydrous aluminum chloride is one of addition, many other modes of reaction are exhibited and frequently several kinds of reactions occur simultaneously. Phenomena like the rearrangement of the carbon skeleton of the olefin, addition of hydrogen chloride, addition of the acid chloride–aluminum chloride complex, dehydrogenation, polymerization, and cracking are not uncommon. The products are frequently determined by the order of addition of the reactants. Olefins have extraordinary affinity for aluminum chloride.

If a dilute solution of an olefin in an inert solvent like carbon disulfide is shaken with aluminum chloride, the entire olefin is immediately precipitated on the aluminum chloride and the resulting layer of carbon disulfide is free of olefin. The reaction is quantitative, but the olefin as such is not recoverable. In view of the complexity of such reactions and their adequate treatment and review elsewhere (684), attention has been focused upon more recent material which involves only the simple reaction of the addition of an acid chloride to olefins.

TABLE 21

Addition reactions of aliphatic acid chlorides with ethylene and its derivatives in the presence of anhydrous aluminum chloride (141)

| ACID CHLORIDE | OLEFIN | PRODUCT | |
		Formula	Yield
			per cent
Acetyl	$CH_2=CH_2$	$CH_2ClCH_2COCH_3$	40
	$CH_2=CHCl$	$CH_2ClCOCH_2CH_2Cl$	94
	$CHCl=CHCl$	$CH_2ClCOCHClCHCl_2$	75
Chloroacetyl	$CH_2=CH_2$	$CH_2ClCOCH_2CH_2Cl$	45
2-Chloropropionyl	$CH_2=CH_2$	$CH_2ClCH_2COCHClCH_3$	60
3-Chloropropionyl	$CH_2=CH_2$	$(ClCH_2CH_2)_2CO$	30
Trichloroacetyl	$CHCl=CCl_2$	$CCl_3COCCl_2CHCl_2$	(?)

The lower aliphatic acyl and α- and β-chloroacyl chlorides have reacted with ethylene and some of its derivatives to give variable yields of chloroketones. The technique has consisted in combining 1 mole of the acyl chloride with 1

$$RCOCl + CH_2=CH_2 \rightarrow RCOCH_2CH_2Cl$$
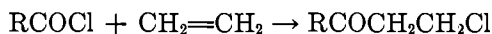
mole of aluminum chloride at the ice–salt temperature and then adding olefin slowly at room temperature to a maximum increase in weight, all in the absence of solvent. Several examples are given in table 21.

1,3-Diketones have been prepared in yields up to 38 per cent by the reaction of 2 moles of an aliphatic acid chloride with vinyl acetate in the presence of aluminum chloride (627). In certain instances the diketones derived from 1 mole

$$2RCOCl + CH_2=CHOCOCH_3 \xrightarrow{AlCl_3}$$
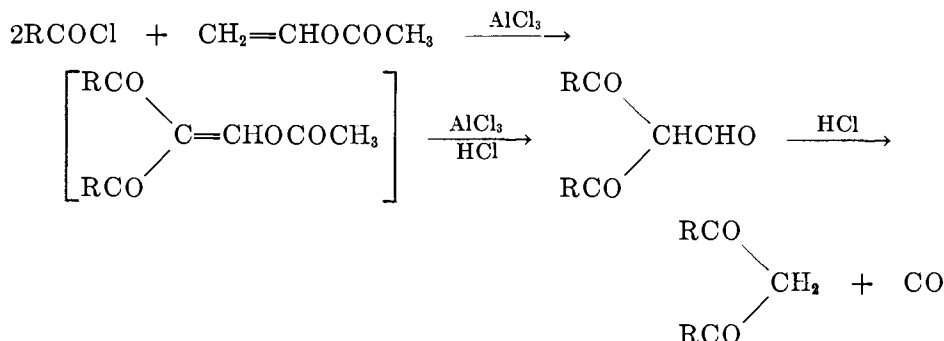
of acetyl chloride and 1 mole of another acyl chloride could be obtained in small yield, either through the direct reaction or by treating the symmetrical derivative with acetyl chloride. Examples are given in table 22.

RCOCl

$\qquad$ + CH$_2$=CHCOOCH$_3$ $\xrightarrow{\text{AlCl}_3}$

CH$_3$COCl

(RCO)$_2$CHCHO + CH$_3$COCl $\xrightarrow{\text{AlCl}_3}$

(RCO)$_2$CHCOCH$_3$ + HCl + CO
↓
RCOCH$_2$COCH$_3$ + RCOOH
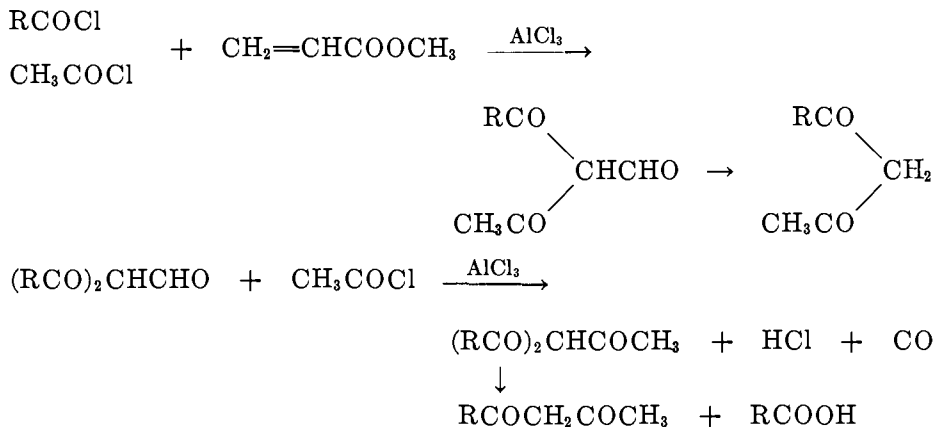
A remarkable reaction has been reported with acetyl chloride and cyclohexene in benzene solution (or in carbon disulfide with benzene added to the last) in the presence of anhydrous aluminum chloride. The product has consisted of 3-phenylhexahydroacetophenone together with a little of the 2-isomer in about 36 per cent total yield (278, 362, 578). The 4-isomer is evidently formed by addition of acetyl chloride to cyclohexene, migration of the chlorine from the 2- to the 4-position under the influence of aluminum chloride, and subsequent Friedel–Crafts reaction with benzene.
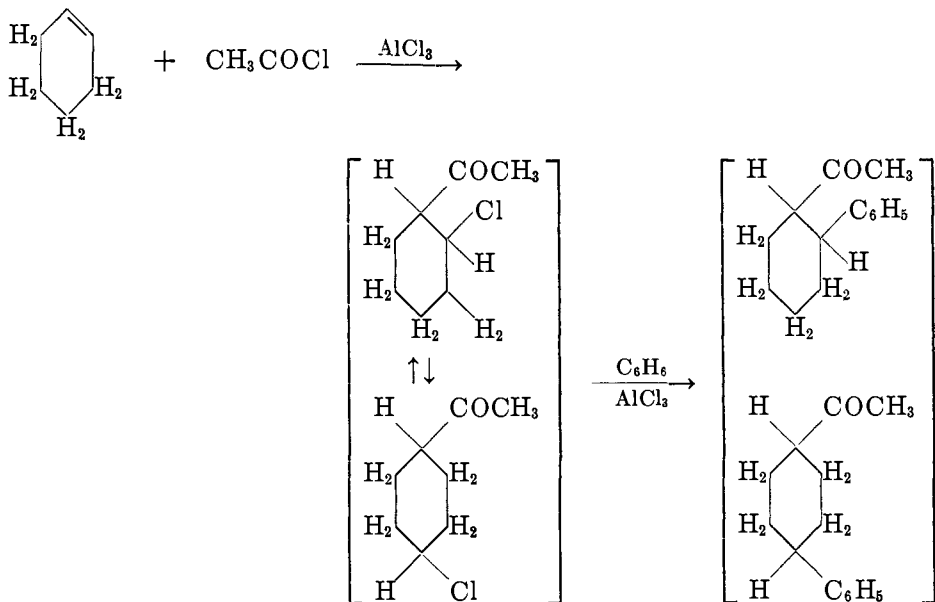
Recently the reaction of acetyl chloride and cyclohexene in carbon disulfide at $-5°$ to $0°$C. in the presence of aluminum chloride has given as the only defined product 1-acetyl-1-cyclohexene in 22 per cent yield (681). With stannic chloride as catalyst and without a solvent acetyl chloride and 4-methylcyclohexene have given a 60 per cent yield of crude ketones, from which methyl 5-methyl-2-cyclohexen-1-yl ketone and methyl 5-methyl-1-cyclohexen-1-yl ketone were isolated in the form of their semicarbazones (500).

TABLE 22

Reaction of aliphatic acid chlorides with vinyl acetate in the presence of anhydrous aluminum chloride (627)

| ACID CHLORIDE	SYMMETRICAL DIKETONE		UNSYMMETRICAL DIKETONE	
	Formula	Yield	Formula	Yield
		per cent		*per cent*
Acetyl........	$CH_3COCH_2COCH_3$	38		
Chloroacetyl..	$CH_2ClCOCH_2COCH_2Cl$	15		
Propionyl....	$(C_2H_5CO)_2CH_2$	25	$CH_3CH_2COCH_2COCH_3$	(?)
Butyryl......	$(C_3H_7CO)_2CH_2$	31		
Isovaleryl....	$(i\text{-}C_4H_9CO)_2CH_2$	6	$i\text{-}C_4H_9COCH_2COCH_3$	10
Lauroyl......	$(C_{11}H_{23}CO)_2CH_2$	20		

TABLE 23

Addition reactions of aliphatic acid chlorides with acetylene in the presence of anhydrous aluminum chloride

ACID CHLORIDE	PRODUCT		REFERENCE
	Formula	Yield	
		per cent	
Acetyl..........................	$CH_3COCH=CHCl$	62	(556)
Chloroacetyl.....................	$CH_2ClCOCH=CHCl$	40	(141)
3-Chloropropionyl................	$CH_2ClCH_2COCH=CHCl$	(?)	(141)
Isovaleryl.......................	$i\text{-}C_4H_9COCH=CHCl$	66	(556)
5-Methylhexanoyl................	$i\text{-}C_6H_{13}COCH=CHCl$	65	(556)
6-Methylheptanoyl...............	$i\text{-}C_4H_9(CH_2)_3COCH=CHCl$	80	(556)

C. REACTION WITH ACETYLENES

Aliphatic acid chlorides react with acetylene and its derivatives in the presence of aluminum chloride by addition to afford chlorovinyl ketones in yields of 60–80 per cent (see table 23). Best results have been obtained by conducting the reaction at $0°$C. in carbon tetrachloride, passing gaseous acetylene into the

$$RCOCl + HC \equiv CH \rightarrow RCOCH = CHCl$$
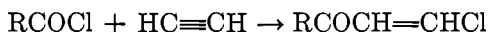
acyl chloride–aluminum chloride complex until no increase in weight is observed, and then pouring over an ice–salt mixture and extracting with ether. Methyl

β-chlorovinyl ketone is intensely lachrymatory, but the higher homologs apparently do not possess this disagreeable property.

An interesting example of addition-rearrangement in the conjugated system of vinylacetylene is provided by the reaction with acetyl chloride in the presence of cuprous and ammonium chlorides. When a mixture of the enyne and acetyl chloride is run into the catalyst at −40°C. and permitted to react for 1.5–2.5 hr. until the reaction temperature is about 28°C., hydrogen chloride is added peculiarly and the product is 75–80 per cent of 2-chloro-1,3-butadiene (chloroprene) (402). The formation of this product has been observed with the same catalyst from vinylacetylene and hydrogen chloride in 65 per cent yield (128), while in the absence of a catalyst 1,4-addition is preferred with the same reactants (127).

D. REACTION WITH SATURATED HYDROCARBONS

Aliphatic acyl chlorides react with saturated aliphatic hydrocarbons in the presence of aluminum chloride in reactions characterized by rearrangement of the carbon skeleton, dehydrogenation, polymerization, and occasionally by chlorination (by substitution) among other types of reaction. The subject is complicated by the fact that isomerizations occur between saturated hydrocarbons and aluminum chloride. Cyclohexane is converted into methylcyclopentane in the presence of aluminum chloride, and the latter is acylated with acetyl chloride to afford methyl 2-methylcyclopentyl ketone (509).
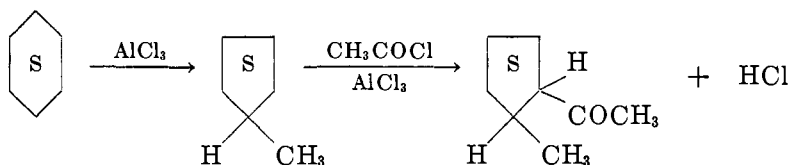
Butane, pentane, and hexane have been shown to react with acyl chlorides in the presence of aluminum chloride to give low yields of ketones. In view of the excellent treatment of these reactions elsewhere (684), further review will be dispensed with here.

Reactions of saturated hydrocarbons with acyl halides in the presence of aluminum chloride have previously been held to occur first through dehydrogenation, followed by reaction of the olefin with excess aluminum chloride. The older views have recently been contrasted with a mechanism involving a typical cationoid substitution reaction (309).

XIV. REACTION OF ALIPHATIC ACID CHLORIDES WITH HETEROCYCLIC COMPOUNDS (FRIEDEL–CRAFTS TYPE OF REACTION)

A. REACTION WITH FURANS

The Friedel–Crafts acylation of furans with acyl chlorides proceeds inefficiently with aluminum chloride, and recourse must be had to catalysts like stannic or ferric chloride. The details of such methods have already been completely reviewed (684).

B. REACTION WITH THIOPHENES

Thiophene itself is so readily acylated by acyl chlorides in the Friedel–Crafts reaction with aluminum chloride that care must be taken to mitigate the violence of the reaction. Low yields of ketone and much tar frequently result unless specific directions are rigidly adhered to. Excess of solvent, slow addition, low reaction temperature, and the use of less acidic catalysts have been useful. The reaction of alkylated thiophenes with acid chlorides in the presence of aluminum chloride proceeds quite regularly. The scope and techniques for these reactions have been reviewed frequently (289, 665, 684).

C. REACTION WITH PYRROLES

Acetyl chloride has been reported to react with pyrrole in ether in the absence of a catalyst to give 2-acetylpyrrole together with N-acetylpyrrole (309). Alkyl-pyrroles have generally given nearly quantitative yields of ketones with aluminum chloride. The ketones of pyrrole or its simple derivatives are generally obtained by the Friedel–Crafts reaction in carbon disulfide, but a newer route has consisted in the action of acid chlorides on pyrrylmagnesium halides (from pyrrole and a Grignard reagent), involving migration from the nitrogen atom to the α-carbon atom.
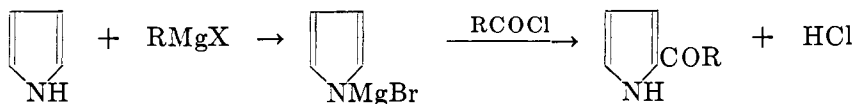
Tabulations of pyrrole–acid chloride reactions have been given in the more comprehensive reviews (212, 684).

D. REACTION WITH OTHER HETEROCYCLICS

The Friedel–Crafts acylation of pyridine, like that of nitrobenzene, is exceedingly difficult. Certain substituted pyridines containing highly activating groups are capable of slight reaction with acyl chlorides but the method is not efficient. Indeed, methyl pyridyl ketones are ordinarily prepared from the corresponding picolinic acid and calcium acetate and phenyl pyridyl ketones by the reaction of the picolinyl chloride and benzene with aluminum chloride. Other Friedel–Crafts reactions of various heterocyclic substances have been reviewed (684).

XV. REACTION OF ALIPHATIC ACID CHLORIDES WITH ETHERS AND EPOXIDES

Aliphatic acid chlorides undergo cleavage reactions with many types of ethers, generally in the presence of metals or metal salts as catalysts. These reactions become significant when it is realized that ethers are used as inert solvents for many of the reactions of acid chlorides. As preparative methods, however, the reactions have achieved little importance.

Early observations (179, 726) have indicated that esters could be formed by the reaction of ethyl and methyl isopentyl ethers with acetyl chloride in the

presence of anhydrous zinc or ferric chloride, and these observations have been made more recently (734, 743). With symmetrical aliphatic ethers and considerable amounts of anhydrous zinc chloride, esters and alkyl chlorides could be obtained from several aliphatic acid chlorides after 2–3 hr. refluxing at the

$$RCOCl \ + \ R'OR' \ \xrightarrow{\ ZnCl_2\ } \ RCOCR' \ + \ R'Cl$$
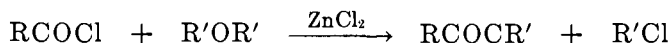
boiling point (696). Acetyl, chloroacetyl, propionyl, butyryl, and isovaleryl chlorides with ethyl ether gave respectively 40, 35, 15, 21, and 20 per cent of ester, but the amount of ethyl chloride isolated was considerably less than required by the equation. Since many ethers were observed to yield small amounts of alcohols and unsaturated hydrocarbons when heated with anhydrous zinc chloride (697), the following course of reaction was assumed:

$$CH_3CH_2OCH_2CH_3 \rightarrow CH_3CH_2OH + CH_2{=}CH_2$$

$$CH_3CH_2OH + CH_3COCl \rightarrow CH_3COOCH_2CH_3 + HCl$$

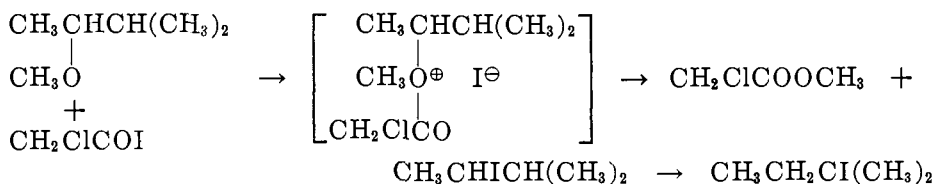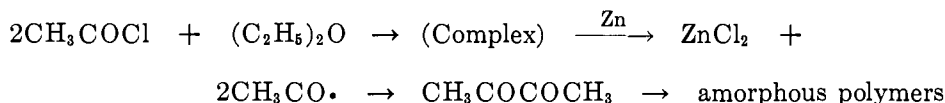$$CH_3CH_2OH + HCl \rightarrow CH_3CH_2Cl + H_2O$$
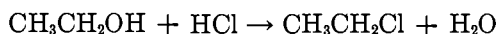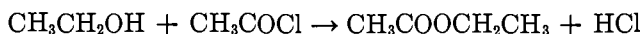
However, by dropping ether into lauroyl chloride at 140°C. in the presence of only a trace of anhydrous zinc chloride, ethyl laurate and ethyl chloride were obtained in nearly equimolar quantities (422), a result which the investigators interpreted as indicative of the direct reaction. Again, the cleavage with acid chlorides has been considered to occur through an oxonium salt intermediate. Esters of various types have been observed to form molecular compounds with boron trifluoride, antimony pentachloride, aluminum chloride, and other compounds (479), and the thesis has been advanced that the products in this reaction are formed by the decomposition of such complexes and their subsequent reaction with the acid chlorides. The formation of isobutyl and *tert*-butyl chlorides from methyl isobutyl ether and acetyl chloride in the presence of zinc chloride (520) and of a mixture of isomeric pentyl iodides from chloroacetyl iodide and methyl 1,2-dimethylpropyl ether (277) has also been explained through oxonium salts as intermediates.

$$\begin{array}{c} CH_3CHCH(CH_3)_2 \\ | \\ CH_3O \\ + \\ CH_2ClCOI \end{array} \rightarrow \left[\begin{array}{c} CH_3CHCH(CH_3)_2 \\ | \\ CH_3\overset{\oplus}{O} \quad I^{\ominus} \\ | \\ CH_2Cl\overset{|}{C}O \end{array} \right] \rightarrow CH_2ClCOOCH_3 \ +$$

$$CH_3CHICH(CH_3)_2 \ \rightarrow \ CH_3CH_2CI(CH_3)_2$$

It has been pointed out that both acid chlorides and acid iodides (277) react with unsymmetrical ethers in such a manner that most of the acyl group of the acid chloride combines with the smaller group of the ether to form the ester. A discussion of the mechanism of ether cleavages with acid chlorides and boron trifluoride or metal halides has been given (145).
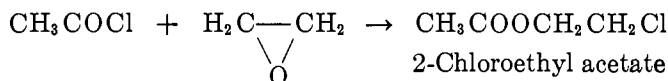
The reaction of acid chlorides and aliphatic ethers is catalyzed by zinc and iron (385, 700), but with these metals there is produced, in addition to the ester and alkyl chloride, much amorphous polymeric material. It has been proposed that under these conditions two reactions are possible: the first is the predominant aforementioned ester formation; the second involves reaction of the ether and acid chloride to form a complex which, on reaction with zinc (or iron), gives zinc chloride (or ferric chloride) and acyl residues, the latter combining to give diacyl compounds which polymerize and react in additional ways.
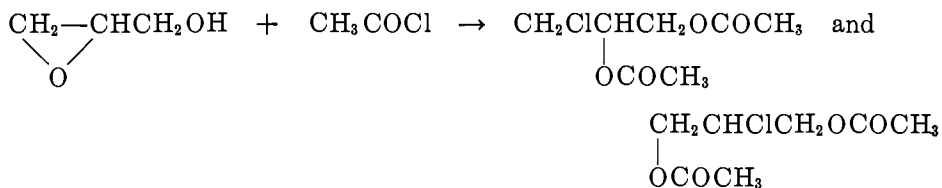
$$2CH_3COCl \; + \; (C_2H_5)_2O \; \rightarrow \; (Complex) \; \xrightarrow{\;Zn\;} \; ZnCl_2 \; +$$

$$2CH_3CO\cdot \; \rightarrow \; CH_3COCOCH_3 \; \rightarrow \; amorphous \; polymers$$

The reaction of 2,3-dibromopropionyl chloride with zinc in ether solution has given debromination and ester formation simultaneously (143).

$$CH_2BrCHBrCOCl + Zn + (C_2H_5)_2O \rightarrow CH_2{=}CHCOOC_2H_5 + ZnBr_2 + C_2H_5Cl$$
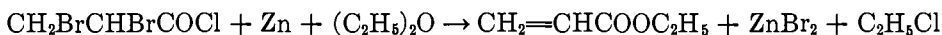
Aliphatic acid chlorides react with saturated cyclic ethers and cyclic acetals to cleave them in more or less ready fashion. The reaction of acetyl chloride and ethylene oxide at room temperature is slow, but apparently not exothermic.

$$CH_3COCl \; + \; H_2C\!\!-\!\!CH_2 \; \rightarrow \; CH_3COOCH_2CH_2Cl$$
$$\underset{O}{\diagdown\diagup} \qquad \text{2-Chloroethyl acetate}$$

After 45 days at 25°C. a 95.7 per cent yield of 2-chloroethyl acetate is obtained (277). Hydrogen chloride and iodine apparently catalyze the cleavage. Both modes of epoxide ring opening are evident in the reaction of acetyl chloride with oxiranes like glycidol. Heated for several hours with 2 moles of acetyl chloride, glycidol has been converted to a mixture of α- and β-monochlorohydrin diace-

$$CH_2\!\!-\!\!CHCH_2OH \; + \; CH_3COCl \; \rightarrow \; CH_2ClCHCH_2OCOCH_3 \; \text{ and}$$
$$\underset{O}{\diagdown\diagup} \qquad\qquad\qquad\qquad\quad \underset{OCOCH_3}{|}$$

$$CH_2CHClCH_2OCOCH_3$$
$$\underset{OCOCH_3}{|}$$

tates (572), with the α-isomer largely predominating. Similarly, both ring openings apparently occur in the reaction of acetyl chloride with glyceryl glycide, in which 37 per cent of monochlorohydrin diacetates were recovered consisting of 92 per cent of the α-monochlorohydrin diacetate (632), and also apparently in the cleavage of epichlorohydrin to 73 per cent of α,γ-dichlorohydrin acetate with acetyl chloride. The so-called "normal" cleavage of the oxirane (yielding a derivative of a secondary alcohol) seems to be largely preferred. Insufficient data are available to enable further generalizations as to these reactions. 1,4-Dioxane has been cleaved with acetyl chloride in the presence of zinc to produce ethylene

TABLE 24

Some recent Friedel–Crafts type reactions of aliphatic acid chlorides and aromatic ethers

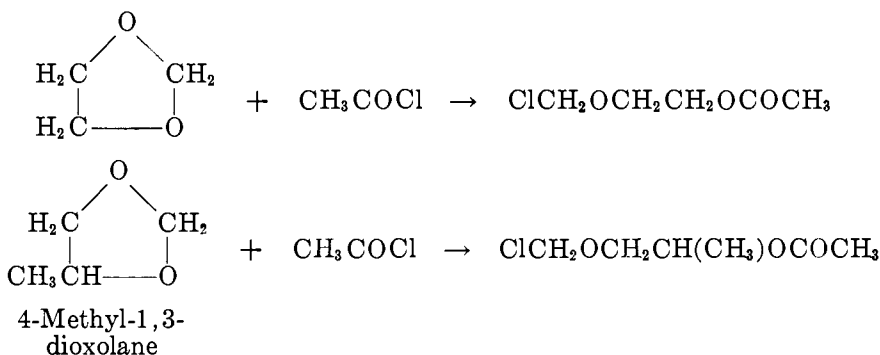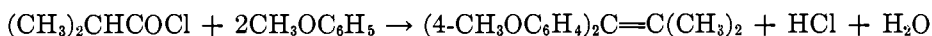| ACID CHLORIDE	ETHER	CATALYST	PRODUCTS (YIELD)	REFERENCE
Acetyl...............	$CH_3OC_6H_5$	$AlCl_3$	$(4\text{-}CH_3OC_6H_4)_2C\!\!=\!\!CH_2$	(676, 677)
	$1,2,3\text{-}(CH_3O)_3C_6H_3$	$HgCl_2$	$2\text{-}HO\text{-}3,4\text{-}(CH_3O)_2C_6H_2COCH_3,$ $2,3,4\text{-}(CH_3O)_3C_6H_2COCH_3$	(471)
	$1,3,5\text{-}(CH_3O)_3C_6H_3$	H_2SO_4	$2\text{-}HO\text{-}4,6\text{-}(CH_3O)_2C_6H_2COCH_3$	(58)
	$CH_3OC_6H_5$	H_2SO_4	$4\text{-}CH_3OC_6H_4COCH_3$ (2%)	(58)
	$1\text{-}CH_3OC_{10}H_7$	H_2SO_4	$1\text{-}CH_3O\text{-}4\text{-}(CH_3CO)C_{10}H_6$ (31%)	⎫(58)
	$1\text{-}CH_3OC_{10}H_7$	$AlCl_3$	$1\text{-}CH_3O\text{-}4\text{-}(CH_3CO)C_{10}H_6$ (47%)	⎭
	$1\text{-}C_2H_5OC_{10}H_7$	H_2SO_4	$1\text{-}C_2H_5O\text{-}4\text{-}(CH_3CO)C_{10}H_6$ (16%)	⎫(58)
	$1\text{-}C_2H_5OC_{10}H_7$	$AlCl_3$	$1\text{-}C_2H_5O\text{-}4\text{-}(CH_3CO)C_{10}H_6$ (48%)	⎭
	$2\text{-}CH_3OC_{10}H_7$	H_2SO_4	$1\text{-}(CH_3CO)C_{10}H_6OCH_3\text{-}2$ (10%)	(58)
	$2\text{-}C_2H_5OC_{10}H_7$	H_2SO_4	$1\text{-}(CH_3CO)C_{10}H_6OC_2H_5\text{-}2$ (14%)	(58)
Propionyl............	$1,2\text{-}(CH_3O)_2C_6H_4$	$AlCl_3$	$[3,4\text{-}(CH_3O)_2C_6H_4]_2C\!\!=\!\!CHCH_3$	(677)
	$1,2\text{-}(C_2H_5O)_2C_6H_4$	$AlCl_3$	$[3,4\text{-}(C_2H_5O)_2C_6H_4]_2C\!\!=\!\!CHCH_3$	(677)
	$CH_3OC_6H_5$	$AlCl_3$ (1–5°C.)	$(4\text{-}CH_3OC_6H_4)_2C\!\!=\!\!CHCH_3$	(676)
	$3\text{-}CH_3OC_6H_4CH_3$	$AlCl_3$	$(2\text{-}CH_3C_6H_3OCH_3\text{-}4)_2C\!\!=\!\!CHCH_3$	(482)
	$2\text{-}CH_3OC_6H_4CH_3$	$AlCl_3$	$(3\text{-}CH_3C_6H_3OCH_3\text{-}4)_2C\!\!=\!\!CHCH_3$	(482)
	$3\text{-}CH_3OC_6H_4OCH_3$	$AlCl_3$	$(2\text{-}CH_3OC_6H_3OCH_3\text{-}4)_2C\!\!=\!\!CHCH_3$	(482)
Isobutyryl............	$CH_3OC_6H_5$	$AlCl_3$	$(4\text{-}CH_3OC_6H_4)_2C\!\!=\!\!C(CH_3)_2$	(482)
Trimethylacetyl........	$1\text{-}CH_3C_6H_4OCH_3\text{-}3$ also $2\text{-}CH_3C_6H_4OCH_3\text{-}4$ $3\text{-}CH_3C_6H_4OCH_3\text{-}4$ $2\text{-}CH_3C_6H_4OCH_3\text{-}5$	$AlCl_3$	$4\text{-}CH_3O\text{-}2\text{-}CH_3C_6H_3COC(CH_3)_3$ (63%)	(514)
Chloroacetyl...........	$CH_3OC_6H_5$	$AlCl_3$	$(4\text{-}CH_3OC_6H_4)_2C\!\!=\!\!CHCl$	(482)

acetate (701). In this reaction the exact role of the zinc is uncertain, but the reaction can now be assumed to be represented as also producing s-dichloroethane.

$$
\begin{array}{c}
\text{O} \\
\diagup \quad \diagdown \\
\text{H}_2\text{C} \qquad \text{CH}_2 \\
| \qquad\quad | \\
\text{H}_2\text{C} \qquad \text{CH}_2 \\
\diagdown \quad \diagup \\
\text{O}
\end{array}
\quad + \quad 2\text{CH}_3\text{COCl} \quad \rightarrow \quad (\text{CH}_2\text{OCOCH}_3)_2 \quad + \quad \text{CH}_2\text{ClCH}_2\text{Cl}
$$

Ethylene acetate   s-Dichloroethane
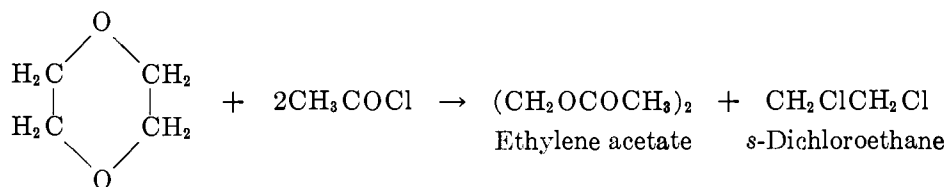
Acetyl chloride cleaves cyclic acetals exothermally (572). Apparently selectivity of the carbon–oxygen bond cleavage is manifested here, for 4-methyl-1,3-dioxolane has been claimed to give only one product.

$$
\begin{array}{c}
\text{O} \\
\diagup \quad \diagdown \\
\text{H}_2\text{C} \qquad \text{CH}_2 \\
| \qquad\quad | \\
\text{H}_2\text{C} \!-\!\!-\!\!- \text{O}
\end{array}
\quad + \quad \text{CH}_3\text{COCl} \quad \rightarrow \quad \text{ClCH}_2\text{OCH}_2\text{CH}_2\text{OCOCH}_3
$$

$$
\begin{array}{c}
\text{O} \\
\diagup \quad \diagdown \\
\text{H}_2\text{C} \qquad \text{CH}_2 \\
| \qquad\quad | \\
\text{CH}_3\text{CH} \!-\!\!-\!\!- \text{O}
\end{array}
\quad + \quad \text{CH}_3\text{COCl} \quad \rightarrow \quad \text{ClCH}_2\text{OCH}_2\text{CH(CH}_3)\text{OCOCH}_3
$$

4-Methyl-1,3-
dioxolane

Aromatic ethers (see table 24) may undergo Friedel–Crafts type acylations (Section XIII,A) with aliphatic acid chlorides in the presence of certain metal halide catalysts. Many examples have been given in a 1941 compilation (684) for anhydrous aluminum chloride. Examples have been noted in which unsymmetrical diarylolefins instead were products of such reactions (242), particularly in instances where an excess of phenolic ethers was employed. The reaction of 1 mole of isobutyryl chloride and 2.5 moles of anisole in the presence of 1 mole of anhydrous aluminum chloride has been observed to afford 1,1-bis(4-methoxyphenyl)-2-methylpropene in good yield (482). This has been attributed to an initial addition which yields an enol through loss of hydrogen chloride.

$$(\text{CH}_3)_2\text{CHCOCl} + 2\text{CH}_3\text{OC}_6\text{H}_5 \rightarrow (4\text{-CH}_3\text{OC}_6\text{H}_4)_2\text{C}\!\!=\!\!\text{C(CH}_3)_2 + \text{HCl} + \text{H}_2\text{O}$$

The enol is said to exist as an aluminum chloride complex which on irreversible tautomerization affords a ketone, or with 1 mole of aromatic ether forms the diarylolefin and water. The mechanism has been supported by the fact that only highly enolized ketones, such as cyclohexanone or biacetyl, condense with aromatic compounds in the presence of aluminum chloride, as in the formation of a 40–50 per cent yield of (4-methoxyphenyl)cyclohexane from cyclohexanone and anisole. Another view (677) explains the formation of olefins in the reaction

by virtue of the fact that the acid chloride complex cannot be formed in required amount (lack of dissolved aluminum chloride) and thus 1 mole of acid
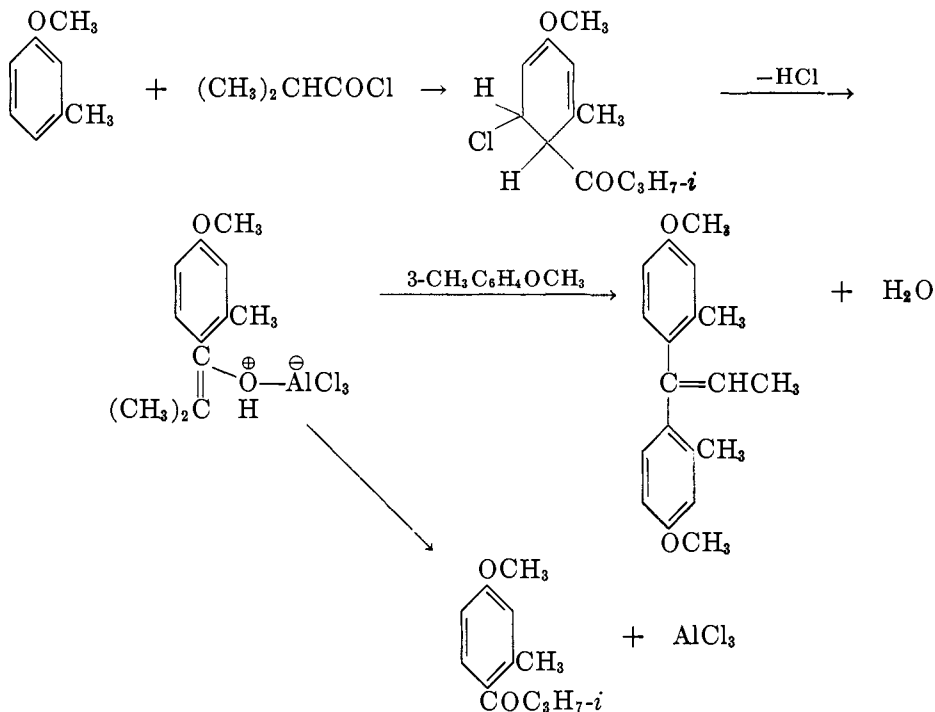
chloride reacts with 2 moles of aromatic ether with removal of water followed by loss of hydrogen chloride.
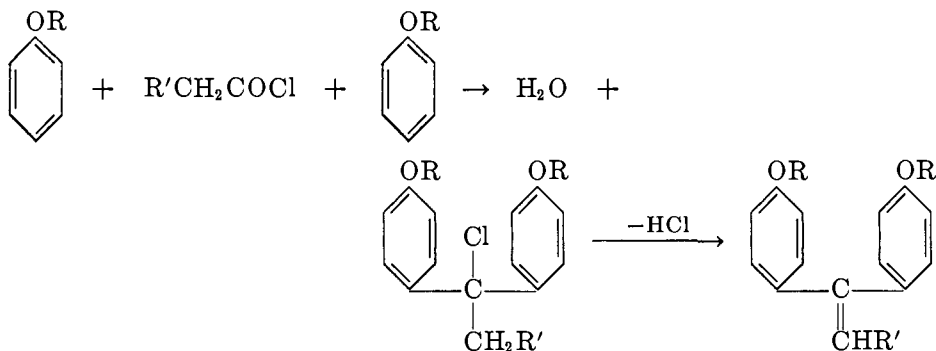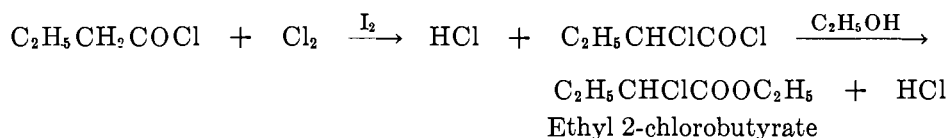

XVI. REACTION OF ALIPHATIC ACID CHLORIDES WITH HALOGENS AND HALOGENATING AGENTS

Brominations and chlorinations of aliphatic acid chlorides have both practical and theoretical aspects. The many divergent reports which are available make it certain that additional data are required before these types of reactions will

be thoroughly understood. Many of the investigations have been carried out without the knowledge that various conditions such as the solvent, the temperature, light, and the presence of catalysts critically influence the kind of product obtained, the rate of reaction, and even the rate and nature of the competing reactions. In spite of the degree of uncertainty concerning the exact mechanisms of these halogenations there is considerable utility for the products as reactive chemical intermediates for syntheses.
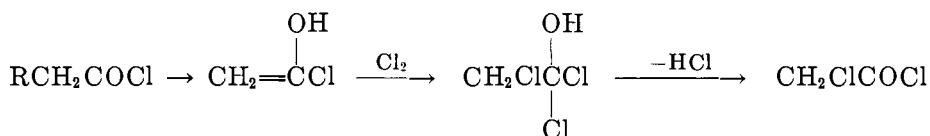
A. CHLORINATION

Early reports of the direct chlorination of aliphatic acid chlorides have indicated that the α-position undergoes replacement of hydrogen with chlorine if the chlorination is carried out in the presence of iodine. In 1870 this method was applied to an elegant synthesis of ethyl 2-chlorobutyrate from butyryl chloride (472) and later of diethyl 2-chloroadipate (346). Acetyl chloride,

$$C_2H_5CH_2COCl \;+\; Cl_2 \;\xrightarrow{\;I_2\;}\; HCl \;+\; C_2H_5CHClCOCl \;\xrightarrow{\;C_2H_5OH\;}$$

$$C_2H_5CHClCOOC_2H_5 \;+\; HCl$$
Ethyl 2-chlorobutyrate

chlorinated without the use of iodine (724), has shown an increase in the rate of disappearance of the chlorine as chlorination proceeded as a consequence of side reactions. Addition of a small amount of iodine was observed to catalyze the formation of chloroacetyl chloride so powerfully that the side reactions were rendered imperceptible (357) and the velocity of the reaction was observed to be proportional to the concentration of chlorine. Acetyl chloride, chlorinated with phosphorus trichloride at 190°C., has afforded not only chloroacetyl chloride (600) but dichloro- and trichloroacetyl chlorides as well (235, 321, 485), while at 200°C. this reagent is said to give hexachloroethane (323). Chlorinations of acid chlorides under the influence of light but without catalysts have been less straightforward. Acetyl chloride has been chlorinated only to the extent of 2 per cent (119), and higher homologs have given mixtures of various isomeric chlorinated products. Isobutyryl chloride has given a mixture of 31 per cent of the 2-chloro and 69 per cent of the 3-chloro derivatives, while butyryl and valeryl chlorides each gave a mixture consisting of 5 per cent of the 2-chloro, 65 per cent of the 3-chloro, and 30 per cent of the 4-chloro compounds (119). Propionyl and isobutyryl chlorides, chlorinated at $-10°$ to $+10°C.$, have given largely the 3-chloropropionyl and 3-chloroisobutyryl chlorides, respectively (613). Acid chlorides were also observed to be chlorinated in the absence of light (308). These various results have pointed to two separate modes of reaction in the chlorination of acid chlorides—the first resulting in α-substitution through the use of iodine or other non-metal halogen carriers and the second resulting predominantly in β- or γ-substitution, catalyzed by light.

The mechanism of the dark chlorination of acid chlorides has been held to consist of an addition to the enol form of the acid chloride followed by dehydro-

chlorination (308), and accounts only for products which have been chlorinated in the 2-position.

$$RCH_2COCl \rightarrow CH_2{=}\overset{\overset{\displaystyle OH}{|}}{C}Cl \xrightarrow{Cl_2} CH_2Cl\overset{\overset{\displaystyle OH}{|}}{\underset{\underset{\displaystyle Cl}{|}}{C}}Cl \xrightarrow{-HCl} CH_2ClCOCl$$
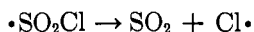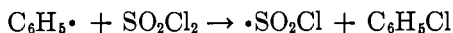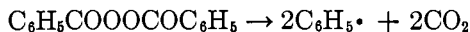
More recently it has been pointed out that the light-catalyzed reactions bear the characteristics of a chain reaction involving free radicals. Products obtained by the chlorination of aliphatic acid chlorides with sulfuryl chloride in the presence of peroxides have shown a similar predominance for β- or γ-substitution over α-substitution (391). Although sulfuryl chloride does not react with ali-
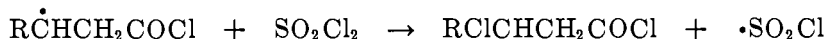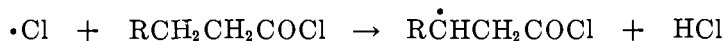
TABLE 25

Products from chlorination of acids and acid chlorides by sulfuryl chloride and peroxides (391)

ACID OR ACID CHLORIDE	PRODUCTS		
	α	β	γ
	per cent	*per cent*	*per cent*
Acetic acid..	50		
Acetyl chloride......................................			
Propionic acid.......................................	45	55	
Propionyl chloride...................................	40	60	
Isobutyric acid......................................	15	85	
Isobutyryl chloride..................................	20	80	
Butyric acid..	10	45	45
Butyryl chloride....................................	15	55	30

phatic acids or acid chlorides in the dark without catalysts at temperatures as high as the boiling point (70–90°C.), chlorination takes place readily in the presence of peroxides. Acetic acid and acetyl chloride react exceptionally slowly. The formation of chlorine atoms from sulfuryl chloride and benzoyl peroxide can be assumed to follow the course (390)

$$C_6H_5COOOCOC_6H_5 \rightarrow 2C_6H_5\cdot + 2CO_2$$

$$C_6H_5\cdot + SO_2Cl_2 \rightarrow \cdot SO_2Cl + C_6H_5Cl$$

$$\cdot SO_2Cl \rightarrow SO_2 + Cl\cdot$$

and the chlorination itself establishes the chain transfer involved.

$$\cdot Cl + RCH_2CH_2COCl \rightarrow R\overset{\displaystyle \cdot}{C}HCH_2COCl + HCl$$

$$R\overset{\displaystyle \cdot}{C}HCH_2COCl + SO_2Cl_2 \rightarrow RClCHCH_2COCl + \cdot SO_2Cl$$

Except for acetic acid, chlorination of acids by this technique is a vigorous reaction and it is desirable to add a small quantity of solvent, while acid chlorides

react much less rapidly and a diluent is unnecessary. Mixtures of sulfuryl chloride and peroxide react to give chloroacetic acid, although the yield is not greater than 50 per cent because of loss of sulfuryl chloride by dissociation. Acetyl chloride cannot be chlorinated by sulfuryl chloride with either benzoyl or lauroyl peroxide. Table 25 includes the results of chlorination of several acids and acid chlorides by this method. The yields indicate that the α-position of the chain is substituted with greater difficulty than the β- or γ-position. Significantly, however, the reaction of sulfuryl chloride and propionyl chloride at 70°C. in the presence of iodine gave only the α-chloropropionyl chloride. Evidently the iodine-catalyzed reaction is due to another form of active chlorine. Characteristic properties of the two kinds of chlorinations have been summarized in table 26

TABLE 26

Characteristics of two types of chlorinations of acid chlorides

TYPE	SPEED AS COMPARED WITH ACID CHLORINATION	POSITION PREFERENTIALLY ATTACKED	PROPOSED MECHANISM	EFFECT OF CHAIN INHIBITORS
Iodine-catalyzed......	RCOCl > RCOOH	α	(1) Enol addition (2) Loss of HCl	None
Light-catalyzed......	RCOOH > RCOCl	β and γ	Chain free radical	Stops reaction

A unique photochlorination technique applied to the chlorination of acetyl chloride takes advantage of the fact that illumination of carbon tetrachloride with radiation of 335 mμ evolves chlorine gas at the rate of 0.1 mole per hour.
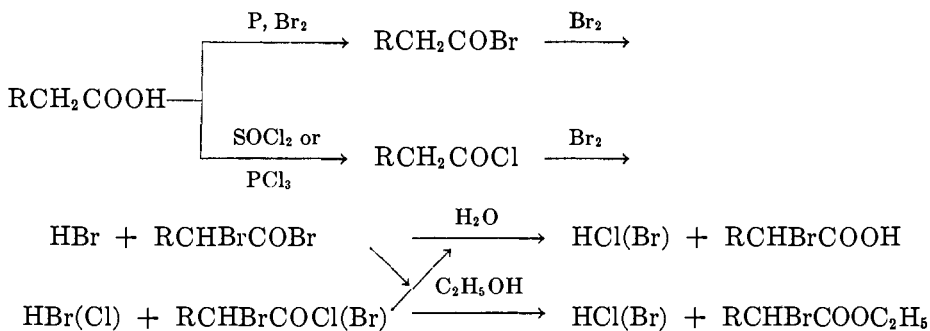
$$2CCl_4 + h\nu \rightarrow C_2Cl_6 + Cl_2$$
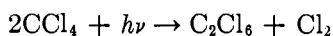
This unusual method, in which the solvent acts also as the chlorinating agent, hardly seems practical (62).

B. BROMINATION

By analogy two mechanisms would be expected to govern brominations of acid chlorides. It must again be realized that the existence of two distinct patterns of behavior in this respect was not realized in many of the investigations reported in the literature.
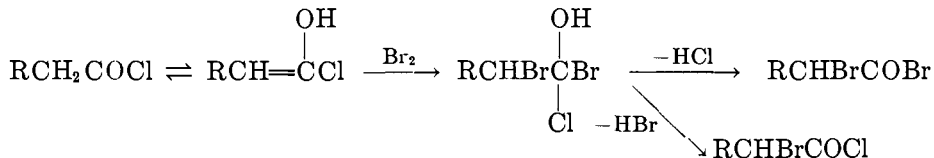
Early attempts to prepare α-bromo acids or esters were easily accomplished through the acid chloride or bromide with the aid of such halogen carriers as phosphorus or sulfur, followed by hydrolysis or alcoholysis. The Hell–Volhard bromination (297, 717) of carboxylic acids in the α-position was based upon the greater ease of bromination of the acid chloride or bromide over the acid itself, and has been applied frequently to the synthesis of α-bromo acids and esters. This synthesis is generally carried out with red phosphorus (free of phosphoric

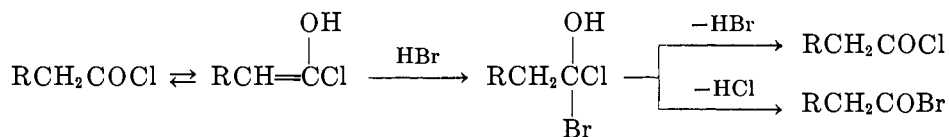acid) and bromine, or occasionally with phosphorus trichloride and bromine or thionyl chloride and bromine.

$$RCH_2COOH \begin{cases} \xrightarrow{P,\ Br_2} RCH_2COBr \xrightarrow{Br_2} \\ \xrightarrow[PCl_3]{SOCl_2\ or} RCH_2COCl \xrightarrow{Br_2} \end{cases}$$

$$HBr + RCHBrCOBr \quad \searrow \xrightarrow{H_2O} \nearrow \quad HCl(Br) + RCHBrCOOH$$

$$HBr(Cl) + RCHBrCOCl(Br) \nearrow \xrightarrow{C_2H_5OH} HCl(Br) + RCHBrCOOC_2H_5$$

Typical directions have been given for 2-bromobutyric acid (211) and for 2-bromohexanoic acid (248) through the acid bromide and for ethyl 2-bromo-glutarate, ethyl 2,4-dibromoglutarate (345), ethyl 2,5-dibromoadipate, ethyl 2-bromoadipate (346), and 2,7-dibromosuberic acid through the acid chloride intermediate. Apparently bromine reacts more slowly with acetyl chloride than with acetyl bromide (723) and similarly for the higher homologs, so that the acid bromide is generally the preferred intermediate in the synthesis, although the route through the acid chloride has the advantage of using less bromine.

Explanations of the mechanism of the Hell–Volhard reaction have been numerous. A study of the bromination of acetyl, propionyl, valeryl, stearoyl, and succinyl chlorides with the calculated amounts of bromine at room temperature, 100°C., and 135°C. (without the presence of a catalyst) has indicated that from 62 to 88 per cent of the chlorine was eliminated as hydrogen chloride (29). The products consisted of RCHBrCOBr and RCHBrCOCl, with the former in far greater amount. No RCHClCOCl in amount sufficient to be detected by the method used (conversion to ethyl ester) was formed, indicating that bromine in this reaction had not merely replaced chlorine in RCH_2COCl, for then chlorine would have been formed and would have given a 2-chloro derivative. (The alternate possibility of bromine reacting with the acid chloride to form bromine monochloride, followed by reaction of the latter with the acid to give the 2-bromo derivative and hydrogen chloride was not considered at this time.) This fact having apparently been established, the mechanism was postulated as the addition of bromine to the enol form of the acid chloride, followed by elimination of hydrogen chloride or bromide. To test this mechanism further, the addition

$$RCH_2COCl \rightleftharpoons RCH\!\!=\!\!\overset{\overset{\displaystyle OH}{|}}{C}Cl \xrightarrow{Br_2} RCHBr\overset{\overset{\displaystyle OH}{|}}{\underset{\underset{\displaystyle Cl}{|}}{C}}Br \xrightarrow[-HBr]{-HCl} \begin{array}{l} RCHBrCOBr \\ \\ RCHBrCOCl \end{array}$$
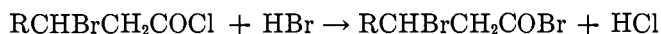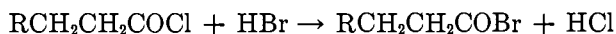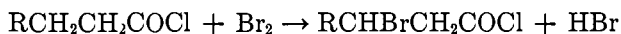
of hydrohalic acids to acid chlorides was studied (30), in order to ascertain the effects of halogen interchanges. Acetyl chloride was observed to form acetyl

$$RCH_2COCl \rightleftarrows RCH\!\!=\!\!\overset{\displaystyle OH}{\overset{|}{C}}Cl \xrightarrow{\text{HBr}} RCH_2\overset{\displaystyle OH}{\overset{|}{\underset{\underset{\displaystyle Br}{|}}{C}}}Cl \begin{array}{l} \xrightarrow{-\text{HBr}} RCH_2COCl \\ \xrightarrow{-\text{HCl}} RCH_2COBr \end{array}$$
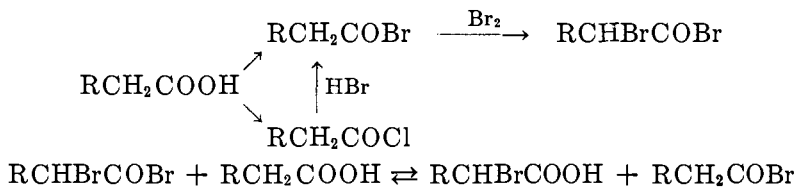
bromide with hydrogen bromide at room temperature in 2 hr.; the reaction was reversible, and acetyl bromide could be converted by hydrogen chloride to acetyl chloride to the extent of 6 per cent in 1 hr. and 42 per cent in 24 hr. at 18°C. The hydrohalogenation of haloacetyl chlorides afforded abnormal results, however. Chloroacetyl chloride and hydrogen bromide gave, upon analysis of the products, more chlorine at the beginning than was ascribable to one atom in $CH_2ClCOCl$ and, as the reaction proceeded, more bromine than was accounted for in $CH_2ClCOBr$. This result could be attributed to an enhanced stability of the hypothetical intermediate, $CH_2ClC(OH)XX'$ (X and X'=Cl, Br), over those where there is no 2-halo substituent, as in the case of CH_3COCl.

The formation of ethyl 3-bromobutyrate from butyryl chloride and bromine, followed by alcoholysis (488), established that in this instance the mechanism could not follow the path of addition to the enol followed by dehydrohalogenation. Rather, it was inferred that formation of hydrogen chloride in the reaction of bromine on acid chlorides, in general, was due to direct reaction between the acid chloride and the hydrogen bromide formed.

$$RCH_2CH_2COCl + Br_2 \rightarrow RCHBrCH_2COCl + HBr$$

$$RCH_2CH_2COCl + HBr \rightarrow RCH_2CH_2COBr + HCl$$

$$RCHBrCH_2COCl + HBr \rightarrow RCHBrCH_2COBr + HCl$$

The bromination of acid chlorides has been claimed to be similar to that of both acids and anhydrides and to occur through the same intermediate acid bromide (531, 723). The acid bromide has been assumed to form in this scheme through traces of hydrogen bromide present. (In the Hell–Volhard reaction this can be attributed to the phosphorus tribromide formed from phosphorus and bromine or to replacement of the acid chloride [formed from phosphorus trichloride] by bromine.) Bromination has been considered to occur by (a) direct bromination of the acid bromide or (b) reaction of the enol form of acid chloride with bromine and elimination of hydrogen chloride. In acid structures wherein the α-hydrogen atoms exhibit little tendency to enolize it has been assumed that the acid bromide is first brominated to a bromoacyl bromide, which then reacts with more acid to form the 2-bromo acid and regenerate acyl bromide, the latter acting as the bromine carrier in the presence of less than molar equivalents of phosphorus or hydrogen bromide.

$$RCH_2COBr \xrightarrow{\text{Br}_2} RCHBrCOBr$$

$$RCH_2COOH \overset{\nearrow}{\underset{\searrow}{}} \quad \uparrow HBr$$

$$RCH_2COCl$$

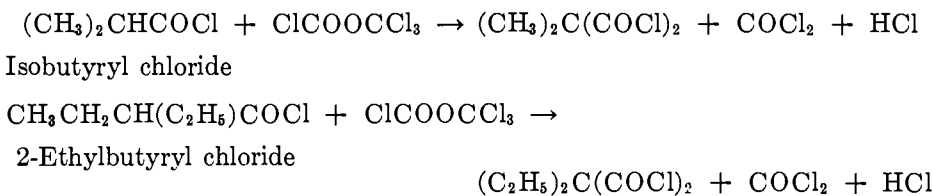$$RCHBrCOBr + RCH_2COOH \rightleftarrows RCHBrCOOH + RCH_2COBr$$

For acyl derivatives capable of enolization it is assumed that the process is accompanied by the enol-addition type of substitution.

Recent investigations have been of relatively greater value in elucidating the dual nature of the bromination of acids, anhydrides, and acyl halides. It is now rather generally believed that the bromination of propionic, butyric, and higher straight-chain aliphatic acids proceeds by a chain mechanism involving bromine atoms (393), but that the bromination of acetic acid does not go in this way. Light accelerates and oxygen inhibits the bromination of propionyl and butyryl chlorides, but the effects of light and of oxygen on the bromination of acetyl chloride, in comparison to those of higher homologs, are much smaller. Dark brominations of acetyl chloride are much faster than those of higher homologs. Additional data are required before these matters can be thoroughly understood.

C. CHLOROFORMYLATION

When certain aliphatic acid chlorides are heated with trichloromethyl chloroformate (diphosgene) in sealed tubes at 225°C. for periods of about 10 hr. the —COCl group easily replaces a tertiary hydrogen atom on the α-carbon atom of the acid chloride, less easily replaces a secondary hydrogen atom, and does not react with a primary hydrogen atom. Presumably phosgene and hydrogen chloride are also formed in the reaction (392). Isobutyryl chloride has afforded a 70 per cent yield of dimethylmalonyl chloride, 2-ethylbutyryl chloride gave a 90 per cent yield of diethylmalonyl chloride, 2-ethylhexanoyl chloride a 30 per cent yield of ethylbutylmalonyl chloride, and propionyl chloride only a 15 per cent yield of methylmalonic acid. Acetyl chloride gave no malonyl chloride.

$$(CH_3)_2CHCOCl + ClCOOCCl_3 \rightarrow (CH_3)_2C(COCl)_2 + COCl_2 + HCl$$
Isobutyryl chloride

$$CH_3CH_2CH(C_2H_5)COCl + ClCOOCCl_3 \rightarrow$$
2-Ethylbutyryl chloride
$$(C_2H_5)_2C(COCl)_2 + COCl_2 + HCl$$

D. OTHER HALOGENATIONS

Reactions of aliphatic acid chlorides with free iodine or fluorine have achieved no prominence and apparently have not been reported.

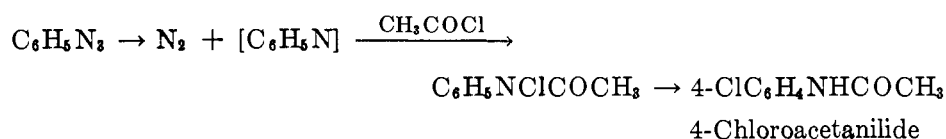### XVII. REACTION OF ALIPHATIC ACID CHLORIDES WITH AZIDES

Acid chlorides react with alkali metal azides to form so-called acid azides, compounds of value as intermediates for the preparation of isocyanates, ure-

$$RCOCl + MN_3 \rightarrow RCON_3 + MCl$$
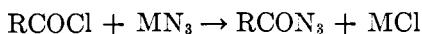
thans, ureas, amides, and amines through the Curtius rearrangement. The latter reaction has been reviewed in 1946 (640) with examples tabulated and need not be discussed further here.

Acid azides are usually prepared as intermediates for other syntheses, and the method of preparation is largely dependent upon the further treatment intended. The dry preparation, suitable for the lower homologous acid chlorides which are prone to undergo hydrolysis or for unstable azides, is most convenient for the multiple-step conversion $RCOOH \rightarrow RCOCl \rightarrow RCON_3 \rightarrow RNCO \rightarrow RNH_2$ in one flask, but suffers from the disadvantage that acid chlorides are inert to some samples of dry sodium azide, and that the heating which is required to form the azide sometimes causes rearrangement. In the dry method the acid chloride, dissolved in an inert solvent (benzene, toluene, xylene, nitrobenzene, pentyl ether, or bromobenzene) is stirred and/or heated with powdered sodium azide (occasionally ammonium azide). Heating frequently converts the azide formed entirely or partly to the isocyanate and this conversion is completed by refluxing. The alternate wet method of preparation, not suited for use with lower aliphatic acid chlorides, has involved adding the acid chloride, dissolved in a water-miscible solvent (acetone, methanol, ethanol, or dioxane), to a concentrated aqueous solution of sodium azide kept at or below room temperature. Dilution of the resulting solution with water precipitates the acid azide. The preparation of undecyl isocyanate from lauroyl chloride (9) has employed this method without isolation of the acid azide. Other examples of the dry preparative method have involved acetyl chloride (501, 616, 636), propionyl chloride (640), heptanoyl chloride (506), and palmitoyl and stearoyl chlorides (501). Trifluoroacetyl chloride has been converted to the isocyanate with sodium azide in benzene (324).

Reactions of aliphatic acid chlorides with organic azides have received little attention. Acetyl chloride in the presence of aluminum chloride and acetic anhydride has been reported to react with phenyl azide to give 4-chloroacetanilide (101). Evidently the N-chloroacetanilide intermediate rearranges during the reaction.

$$C_6H_5N_3 \rightarrow N_2 + [C_6H_5N] \xrightarrow{CH_3COCl}$$

$$C_6H_5NClCOCH_3 \rightarrow 4\text{-}ClC_6H_4NHCOCH_3$$
$$4\text{-Chloroacetanilide}$$

XVIII. Reaction of Aliphatic Acid Chlorides with Diazo Compounds

A. REACTION WITH DIAZOMETHANE

When aliphatic acid chlorides are added slowly to a cold solution of excess diazomethane the products are diazo ketones, compounds of value in the preparation of acids, esters, amides, or substituted amides through the Wolff re-

$$RCOCl + 2CH_2N_2 \rightarrow RCOCHN_2 + CH_3Cl + N_2$$

arrangement. Occasionally, when diazomethane is added to the acid chloride at temperatures near 35°C., the product of the reaction is an alkyl chloromethyl

ketone, assumed to form from the hydrogen chloride liberated in the formation
of the diazo ketone and additional diazo ketone. If hydrogen chloride is not

$$RCOCl + CH_2N_2 \rightarrow RCOCHN_2 + HCl \qquad (I)$$

$$HCl + CH_2N_2 \rightarrow CH_3Cl + N_2 \qquad (II)$$

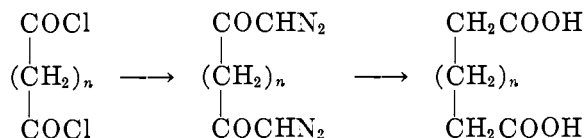$$RCOCHN_2 + HCl \rightarrow RCOCH_2Cl + N_2 \qquad (III)$$

consumed fast enough by excess diazomethane, as in equation II, it may react
as in equation III if there is excess acid chloride present (as when diazomethane
is added to the acid chloride). The use of tertiary amines in the diazo ketone
synthesis has been efficient in removing the hydrogen chloride and preventing
the destruction of a second mole of diazomethane. Thus, slow addition of an
ether solution of trimethylacetyl chloride to diazomethane and triethylamine in
ether affords a 98 per cent yield of the diazo ketone (513).

The reaction of an acid chloride and diazomethane to yield a diazo ketone
comprises one of the steps in the Arndt–Eistert synthesis, which is of value in
the conversion of an acid to its next higher homolog or its derivative. This

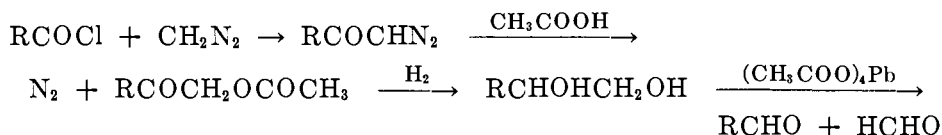$$RCOOH \rightarrow RCOCl \rightarrow RCOCHN_2 \rightarrow RCH_2COOH$$

reaction sequence has been reviewed (40) in 1942 for various types of acid
chlorides; hence repetition of details is unnecessary here. The technique in-
volved in preparing the diazo ketone is a standard one, in which a solution or
suspension of the acid chloride in ether or benzene is added slowly to a cold
(0–5°C.) solution of diazomethane in ether or benzene with stirring. At the con-
clusion of the brisk evolution of nitrogen the reaction is generally complete.
With procedures quite similar to that described, acetyl (24, 752) and 4-carbeth-
oxybutyryl chlorides (40) have been converted to propionamide and adipic acid
(69 per cent), respectively, in the Arndt–Eistert synthesis. Adipyl and sebacyl
chlorides have been converted in 75 and 55 per cent yields, respectively, to

$$
\begin{array}{ccc}
\text{COCl} & \text{COCHN}_2 & \text{CH}_2\text{COOH} \\
| & | & | \\
(\text{CH}_2)_n & \longrightarrow \quad (\text{CH}_2)_n & \longrightarrow \quad (\text{CH}_2)_n \\
| & | & | \\
\text{COCl} & \text{COCHN}_2 & \text{CH}_2\text{COOH}
\end{array}
$$

suberic acid and 1,10-decanedicarboxylic acid (721). Recent examples have in-
cluded stearoyl, nonadecanoyl, and eicosanoyl chlorides (to the corresponding
homologous acids) (698), linoleoyl and 10,13-nonadecadienoyl chlorides (to the
unsaturated homologous acids) (380), and 3,7,11-trimethyldodecanoyl chloride
(to the homologous ester) (379). Although diazoethane has been used with
aromatic acid chlorides (172), it has apparently not as yet been applied to the
aliphatic series.

An innovation not usually encountered has been applied to the synthesis of

aldehydes from acids containing the same number of carbon atoms. For this purpose the diazo ketone, rather than being decomposed and rearranged in the presence of a metal catalyst, is caused to react with acetic acid to give the acetoxymethyl ketone with elimination of nitrogen, and with subsequent treatment is converted to the aldehyde:

$$RCOCl + CH_2N_2 \rightarrow RCOCHN_2 \xrightarrow{CH_3COOH}$$

$$N_2 + RCOCH_2OCOCH_3 \xrightarrow{H_2} RCHOHCH_2OH \xrightarrow{(CH_3COO)_4Pb}$$

$$RCHO + HCHO$$

Under these conditions stearoyl and elaidoyl chlorides have given, respectively, 88.5 and 83 per cent yields of the isolable diazo ketones and then 89 and 94 per cent yields of the corresponding acetoxymethyl ketones (271). 10-Undecenoyl, 3-hexenoyl, and succinyl chlorides have also been given this overall treatment.

Although the formation of the chloromethyl ketones in the diazomethane reaction has been noted principally with aromatic acid chlorides (157, 440, 446), it has also been observed with a few aliphatic acid chlorides. If it is desired to have the reaction take this course, the diazomethane is added to the acid chloride, generally in ether, and after nitrogen has been completely eliminated hydrogen chloride is passed in. In this manner 2-methylbutyryl chloride has given *sec*-butyl chloromethyl ketone (56), 3-iodopropionyl chloride has afforded a 60–80 per cent yield of 2-iodoethyl chloromethyl ketone (382), and 5-carbethoxyvaleryl, 6-carbethoxyhexanoyl, 8-carbethoxyoctanoyl, and 9-carbethoxynonanoyl chlorides have given the corresponding ketones (185).

B. REACTION WITH DIAZOACETIC ESTER AND DIAZOACETONE

In a series of important papers on diazo compounds (658, 660) it was pointed out that acid chlorides react with monosubstituted diazo compounds containing a reactive α-hydrogen atom, such as diazoacetic ester, $N_2CHCOOC_2H_5$, according to equation I,
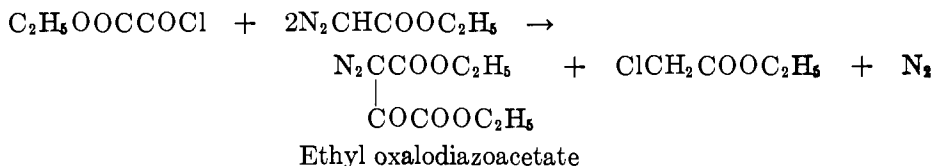
$$RCOCl + 2N_2CHCOOC_2H_5 \rightarrow RCOCN_2COOC_2H_5$$

$$+ CH_2ClCOOC_2H_5 + N_2 \quad (I)$$
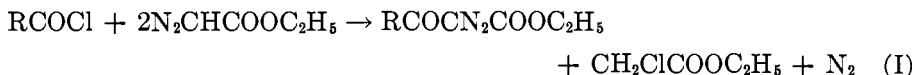
while non-carbonyl-substituted compounds, typified by diphenyldiazomethane, reacted as shown in equation II.

$$RCOCl + N_2C(C_6H_5)_2 \rightarrow RCOCCl(C_6H_5)_2 + N_2 \qquad (II)$$
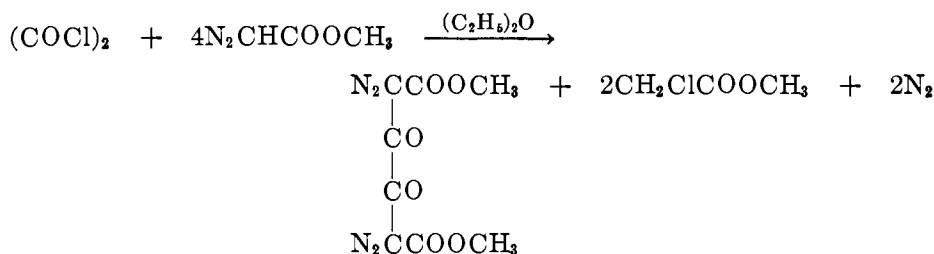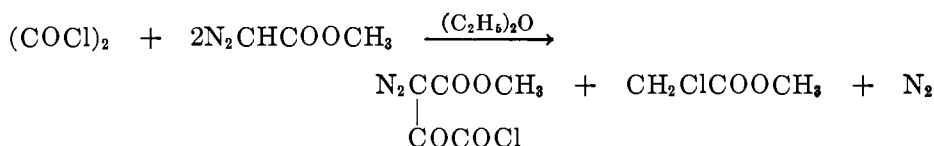
Examples of reaction I have included that of acetyl chloride without a solvent to give ethyl acetyldiazoacetate after 2 days, and of propionyl chloride at 60°C. to afford ethyl propionyldiazoacetate after 1 day (658). Crotonyl chloride with methyl diazoacetate in ether, however, gave methyl chloroacetate and an oil (precipitated from ether solution with methanol), presumably methyl crotonyldiazoacetate, which quickly decomposed. Similarly, a stable compound, ethyl
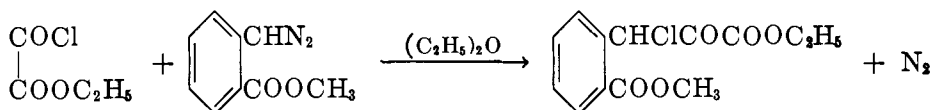
oxalodiazoacetate, is said to have been prepared from carbethoxyformyl chloride and diazoacetic ester in ether.

$$C_2H_5OOCCOCl \ + \ 2N_2CHCOOC_2H_5 \ \rightarrow$$

$$N_2\overset{|}{\underset{|}{C}}COOC_2H_5 \ + \ ClCH_2COOC_2H_5 \ + \ N_2$$
$$\underset{COCOOC_2H_5}{|}$$

Ethyl oxalodiazoacetate

The reaction of oxalyl chloride and methyl diazoacetate in ether is unique. The first product was said to be methyl (chloroglyoxylyl)diazoacetate but after several days the reaction proceeded further to yield dimethyl 2,5-bisdiazo-3,4-dioxoadipate.

$$(COCl)_2 \ + \ 2N_2CHCOOCH_3 \ \xrightarrow{(C_2H_5)_2O}$$

$$N_2\overset{|}{\underset{COCOCl}{C}}COOCH_3 \ + \ CH_2ClCOOCH_3 \ + \ N_2$$

$$(COCl)_2 \ + \ 4N_2CHCOOCH_3 \ \xrightarrow{(C_2H_5)_2O}$$

$$N_2CCOOCH_3 \ + \ 2CH_2ClCOOCH_3 \ + \ 2N_2$$
$$|$$
$$CO$$
$$|$$
$$CO$$
$$|$$
$$N_2CCOOCH_3$$

Examples similar to that given in equation II are not common. Carbethoxyformyl chloride and methyl 2-(diazomethyl)benzoate have reacted in ether to give ethyl (2-carbomethoxyphenyl)chloropyruvate (660).

$$\underset{COOC_2H_5}{\overset{COCl}{|}} \ + \ \left[\overset{CHN_2}{\underset{COOCH_3}{\bigcirc}}\right] \ \xrightarrow{(C_2H_5)_2O} \ \left[\overset{CHClCOCOOC_2H_5}{\underset{COOCH_3}{\bigcirc}}\right] \ + \ N_2$$

Similar reactions with acid chlorides could be expected with diazo compounds containing an α-hydrogen atom activated by an adjoining keto group, such as diazoacetone.

$$RCOCl \ + \ 2CH_2COCHN_2 \ \rightarrow \ CH_3COCN_2COR \ + \ CH_3COCH_2Cl \ + \ N_2$$

Such reactions are not in evidence in the literature. It is probable that molecules of diazo ketone are prone to rearrange or to react with hydrogen chloride more readily than they undergo reactions of this type. At any rate, in the preparation of diazoacetone from acetyl chloride and diazomethane in ether (22) there is
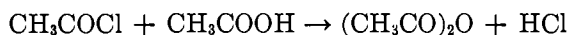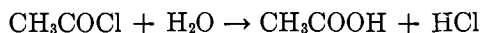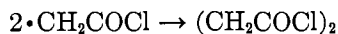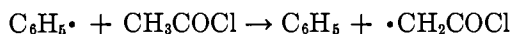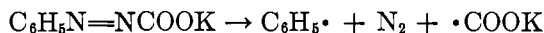
little tendency displayed for further reaction of the diazoacetone with additional acetyl chloride under the conditions maintained.

$$CH_3COCl + CH_2N_2 \rightarrow CH_3COCHN_2 + HCl$$
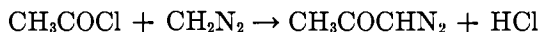
C. REACTION WITH OTHER DIAZO COMPOUNDS

Aliphatic acid chlorides have been observed to form stable adducts with many azo compounds in ether (213), particularly when an aromatic ring in the azo compound is substituted with a hydroxyl group in the p-position. The dark red adduct of acetyl chloride and 4-hydroxyazobenzene is a stable solid. Propionyl, isovaleryl, and oxalyl chlorides and phosgene have also been observed to form these addition products with many hydroxyazobenzenes.

Free-radical reactions of aliphatic acid chlorides and azo compounds are possible in instances where the latter can form or be induced to form radicals. The reaction of acetyl chloride and potassium azo-1-phenyl-2-carboxylate (511) to give benzene, succinyl chloride, and acetic anhydride may be explained on the basis of a free-radical mechanism.

$$C_6H_5N{=}NCOOK \rightarrow C_6H_5{\cdot} + N_2 + {\cdot}COOK$$

$$C_6H_5{\cdot} + CH_3COCl \rightarrow C_6H_6 + {\cdot}CH_2COCl$$

$$2{\cdot}CH_2COCl \rightarrow (CH_2COCl)_2$$

$$CH_3COCl + H_2O \rightarrow CH_3COOH + HCl$$

$$CH_3COCl + CH_3COOH \rightarrow (CH_3CO)_2O + HCl$$

XIX. REACTION OF ALIPHATIC ACID CHLORIDES WITH METALS AND ORGANOMETALLIC COMPOUNDS
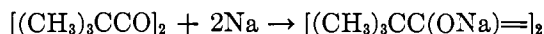
A. REACTION WITH ALKALI METALS

It appears that under certain conditions aliphatic acid chlorides may enter into Wurtz-type reactions with alkali metals, although reported yields of 1,2-

$$2RCOCl + M \rightarrow RCOCOR + MCl_2$$

diketones prepared through this route are quite small. Trimethylacetyl chloride and sodium in wet ether refluxed for 10–12 hr. have been reported (192) to give a total yield of isolable material of only 30–40 per cent with considerable formation of tar. The relative amounts of pure material isolated from the reaction were 70 per cent of the compound $(CH_3)_3CCOCH[OCOC(CH_3)_3]C(CH_3)_3$, and 15 per cent of a polymer of the diketone, $(C_{10}H_{18}O_2)_n$. It has been inferred that these products arise first through the initial reaction
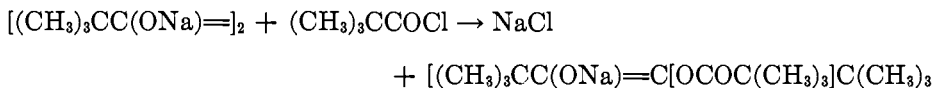
$$2(CH_3)_3CCOCl + Na \rightarrow [(CH_3)_3CCO]_2 + 2NaCl$$
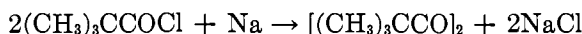
then through a portion of the diketone reacting with sodium

$$[(CH_3)_3CCO]_2 + 2Na \rightarrow [(CH_3)_3CC(ONa){=}]_2$$

to give the sodium salt of the enediol, which on decomposition with water affords the hydroxyketone,

$$[(CH_3)_3CC(ONa)=]_2 + 2H_2O \rightarrow (CH_3)_3CCOCHOHC(CH_3)_3 + 2NaOH$$

or which may react as follows:

$$[(CH_3)_3CC(ONa)=]_2 + (CH_3)_3CCOCl \rightarrow NaCl$$

$$+ [(CH_3)_3CC(ONa)=C[OCOC(CH_3)_3]C(CH_3)_3$$

The latter compound through the action of water gives $(CH_3)_3CCOCH[OCOC-(CH_3)_3]C(CH_3)_3$, the ester of the hydroxyketone. The formation of trimethyl-acetic acid from the diketone is explained by the reaction:

$$[(CH_3)_3CCO]_2 + NaOH \rightarrow (CH_3)_3CCOONa + (CH_3)_3CCHO$$

followed by

$$(CH_3)_3CCHO \rightarrow (CH_3)_3CCOOH$$
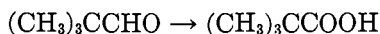
Treatment of higher aliphatic acid chlorides with sodium wire in dry ether has been reported to convert them in good yield to the esters of enediols (563). Lauroyl chloride after refluxing for 10 hr. afforded the dilaurate of 12-tetracosene-12,13-diol in 60 per cent yield and myristoyl, palmitoyl, and stearoyl chlorides gave respectively 64, 70, and 67 per cent yields of the analogous compounds. These enediol esters may be considered to result through the following sequence:
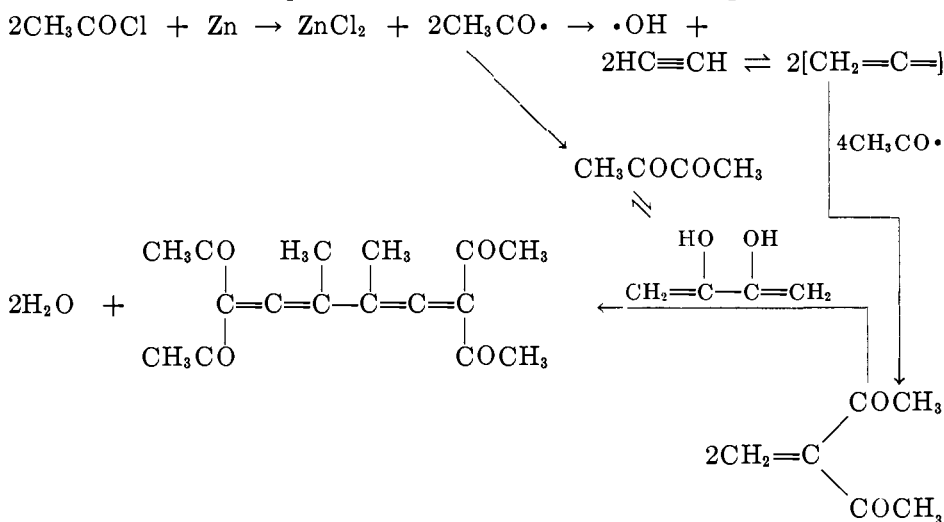
$$2RCOCl + 2Na \rightarrow \underset{\underset{O}{\|}}{RC}-\underset{\underset{O}{\|}}{CR} + 2Na \rightarrow \underset{\underset{NaO}{|}}{RC}=\underset{\underset{ONa}{|}}{CR} +$$

$$2RCOCl \rightarrow \underset{\underset{RCOO}{|}}{RC}=\underset{\underset{OCOR}{|}}{CR}$$
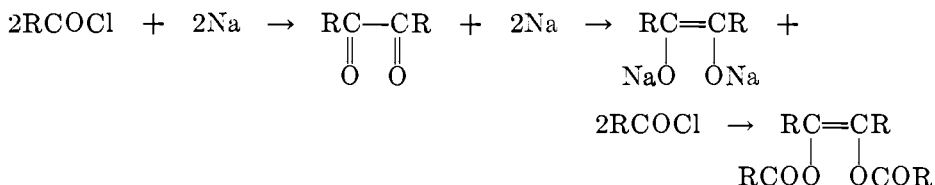
Succinyl chloride, when treated with either sodium or potassium in ether, however, has been converted to succinic anhydride (536).

B. REACTION WITH OTHER METALS

The behavior of other metals such as zinc and iron with aliphatic acid chlorides in ether solutions has already been mentioned (Section XV). It was apparent that in addition to the predominant reaction of ester formation a considerable amount of polymeric material was produced, presumably derived from the corresponding diketone obtained from acyl residues. Other reports have also pointed out that 1,2-diketones or their derivatives occur as products in the reaction of aliphatic acid chlorides with zinc, iron, and magnesium.

The reaction of acetyl chloride and zinc was studied in 1873 and was observed to yield zinc chloride and a resinous-like material for which the formula $C_{16}H_{18}O_4$ was given (690). The structure of the product has recently been given (552) as

that of the diallene 1,1,6,6-tetraacetyl-3,4-dimethyl-1,2,4,5-hexatetraene and its mode of formation represented in an unusual manner through the mechanism:

$$2CH_3COCl + Zn \rightarrow ZnCl_2 + 2CH_3CO\cdot \rightarrow \cdot OH +$$
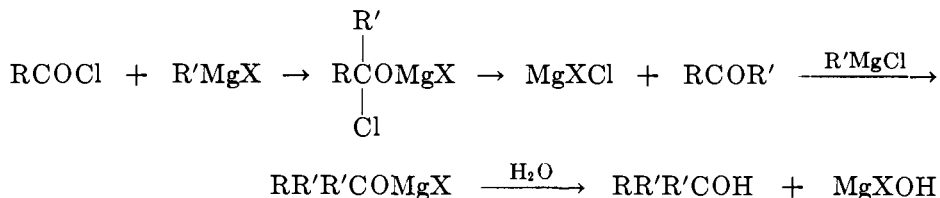
$$2HC\equiv CH \rightleftharpoons 2[CH_2=C=]$$

$$CH_3COCOCH_3$$

$$4CH_3CO\cdot$$

$$\underset{HO\quad OH}{CH_2=C-C=CH_2} \leftarrow$$

$$2H_2O + \underset{\underset{CH_3CO}{|}}{\overset{\overset{CH_3CO}{|}}{C}}=C=\underset{}{\overset{H_3C}{\underset{}{C}}}-\underset{}{\overset{CH_3}{\underset{}{C}}}=C=\underset{\underset{COCH_3}{|}}{\overset{\overset{COCH_3}{|}}{C}}$$

$$2CH_2=C\overset{COCH_3}{\underset{COCH_3}{}}$$

Reactions of aliphatic acid chlorides with the binary mixture magnesium iodide–iodine have provided interesting results. This reagent, developed and applied to the study of pinacol formation from aromatic ketones (259), wherein it is assumed to involve the existence of the magnesous state of valence, has been used to convert substituted aromatic chlorides to mixtures of the corresponding benzils and enediols. Thus, 3-methoxymesitoyl chloride has given cis-2,2',4,4',6,6'-hexamethyl-3,3'-methoxystilbenediol in 55 per cent yield and 26 per cent of the corresponding benzil (239). Similarly, from mesitoyl chloride (240) 35 per cent of the enediol and 34 per cent of the benzil were obtained. Efforts to apply this reagent to aliphatic acid chlorides have only been made with propionyl and butyryl chlorides in ether (347), in which small yields of the 1,2-diketones (isolated in the form of their bis-4-nitrophenylhydrazones) were the only products identified. Assuming that the reagent acts in the way originally inferred (259), the course of the mechanism is probably as follows:

$$2R\overset{\overset{Cl}{|}}{C}=O + 2MgI \rightarrow \underset{\underset{Cl}{|}}{\overset{\overset{Cl}{|}}{\underset{RCOMgI}{RCOMgI}}} \xrightarrow{H_2O}$$

$$\begin{bmatrix} \overset{Cl}{|} \\ R\overset{|}{C}OH \\ R\overset{|}{C}OH \\ \underset{Cl}{|} \end{bmatrix} \xrightarrow{-2HCl} \begin{matrix} RC=O \\ | \\ RC=O \end{matrix}$$

$$+2MgIOH$$
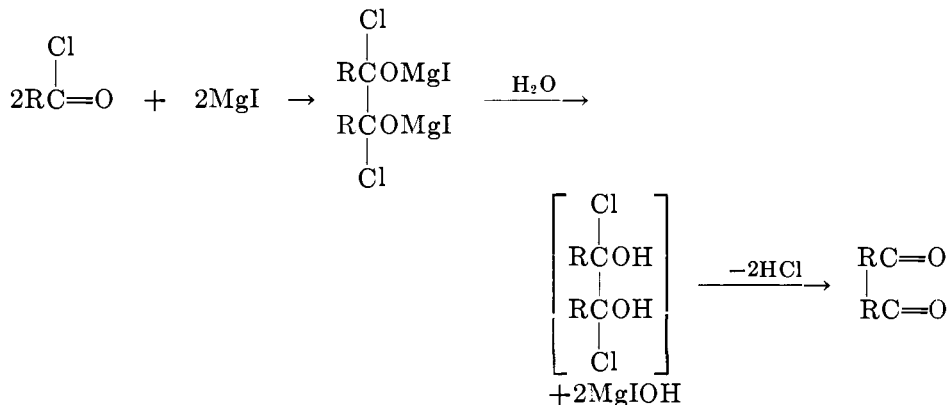
C. REACTION WITH GRIGNARD REAGENTS

Reactions of aliphatic acid chlorides with the Grignard reagent are characterized by normal and abnormal modes of reaction. The normal reaction consists of two additions; in the first of these a ketone is formed. Reaction of the secondary magnesium adduct or of the ketone with another mole of Grignard reagent affords a tertiary alcohol upon hydrolysis.

$$RCOCl + R'MgX \rightarrow \underset{\underset{Cl}{|}}{\overset{\overset{R'}{|}}{RCOMgX}} \rightarrow MgXCl + RCOR' \xrightarrow{R'MgCl}$$

$$RR'R'COMgX \xrightarrow{H_2O} RR'R'COH + MgXOH$$

Occasionally small quantities of esters derived from the tertiary magnesium adduct and the original acid chloride may contaminate the product.

$$RCOCl + RR'R'COMgX \rightarrow RCOOCRR'R' + MgClX$$
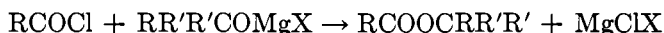
Typical of this simple synthesis is the preparation of *tert*-butyl alcohol from acetyl chloride and methylmagnesium iodide (688). The method is ill-suited for the synthesis of ketones, for yields of these products are rarely greater than 35 per cent even under the most ideal conditions. From 8 moles of trimethylacetyl chloride and 1.5 mole of *tert*-butylmagnesium chloride only a 32 per cent yield of di-*tert*-butyl ketone has been obtained together with abnormal reduction products (734). In many instances, depending on the particular acid chloride and Grignard reagent and other factors, neither the tertiary alcohol nor the ketone can be obtained. Instead, the reaction takes the abnormal course mentioned below. An innovation which has been employed to prepare the esters of tertiary (or secondary) alcohols involves treating a Grignard reagent, usually methylmagnesium iodide, with an alcohol and esterifying the resulting magnesium adduct with an acid chloride. Isopentyl acetate has been prepared from

$$CH_3MgI + R'OH \rightarrow R'OMgI + CH_4$$

$$R'OMgI + RCOCl \rightarrow R'OCOR + MgClI$$
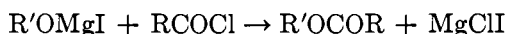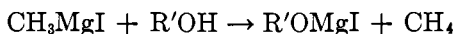
isopentyl alcohol and acetyl chloride through this route (165, 319). The method offers no especial advantages over the usual esterification techniques.

The abnormal reaction of acid chlorides and the Grignard reagent may proceed in one or more of several ways: (*1*) reduction of the acid chloride to a primary alcohol, (*2*) reduction to a secondary alcohol, and (*3*) reduction to an aldehyde. Formation of an olefin from the Grignard reagent accompanies each reduction. The reactions by which the Grignard reagent reduces acid chlorides have been extensively investigated (264, 702, 738, 741, 742) and reviewed (731). The various factors pertaining thereto which influence the course of the reaction in addition to the structures of the components include the presence of free magnesium, the concentration of the solutions, the order of addition, the kind of halogen, and to a minor degree the solvent, stirring, and the temperature.
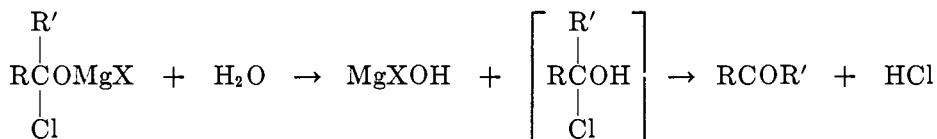
Typical results are illustrated in the reaction of 2-ethylbutyryl chloride and *tert*-butylmagnesium chloride, in which the acid chloride has been added gradually with vigorous stirring to 3 moles of 2 M Grignard solution. The products were 18–30 per cent of 2-ethyl-1-butanol and 43–68 per cent of 4-ethyl-2,2-dimethyl-3-hexanol (742). Increasing the concentration of the Grignard reagent slightly increased the yield of the primary alcohol at the expense of the secondary. The formation of these products may be considered in the light of the general pattern of reduction–addition reactions with the Grignard reagent.

General pattern of reduction–addition reactions of acid chlorides with Grignard reagents
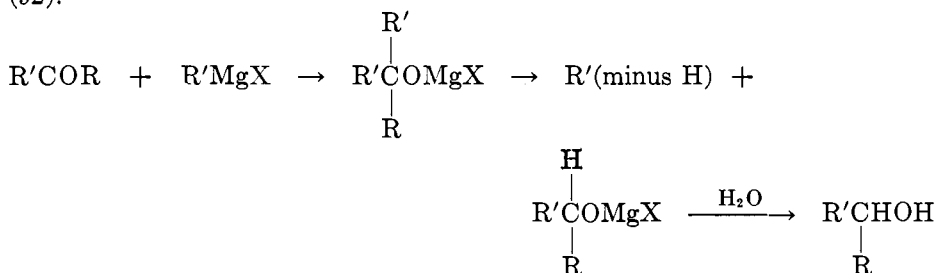
$$\tfrac{1}{2}R_2Mg \;+\; \tfrac{1}{2}MgX_2$$
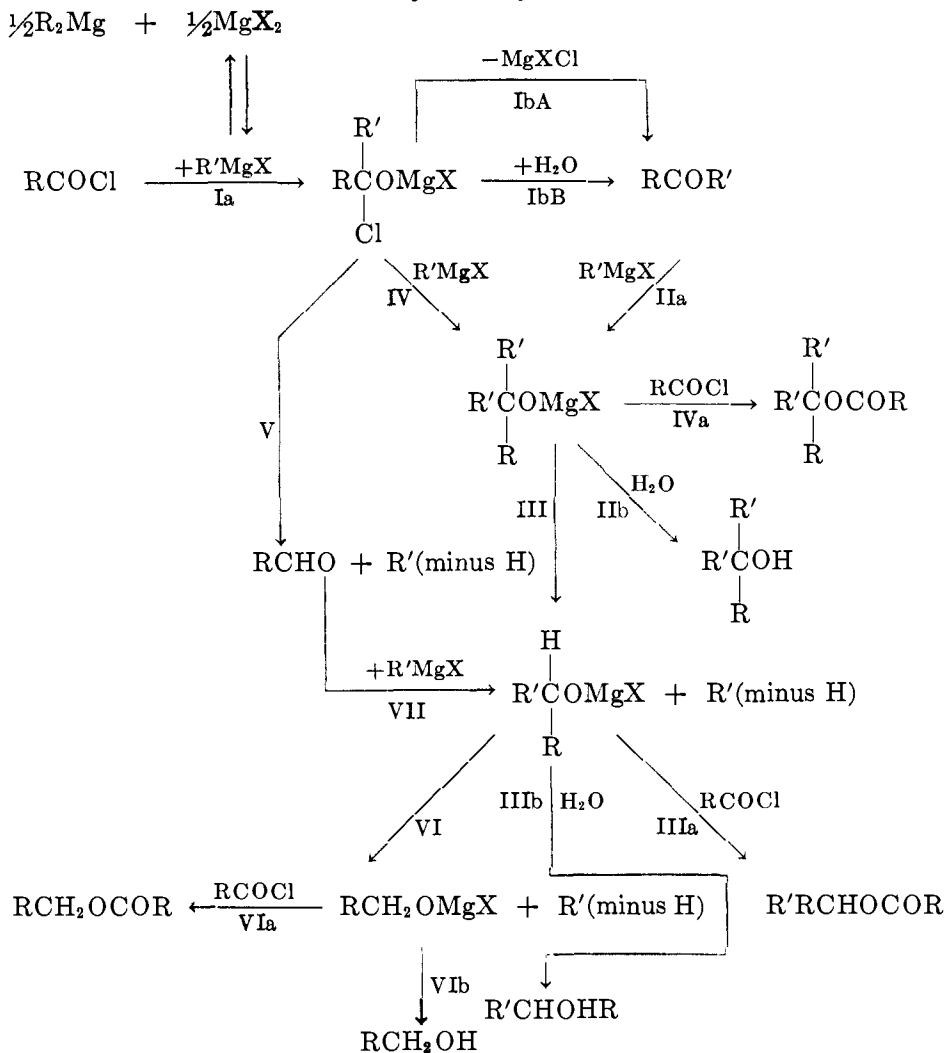
The addition of an acid chloride and 1 mole of Grignard reagent to give a ketone (Ia and Ib, first steps of the normal mode) has been observed with acetyl chloride
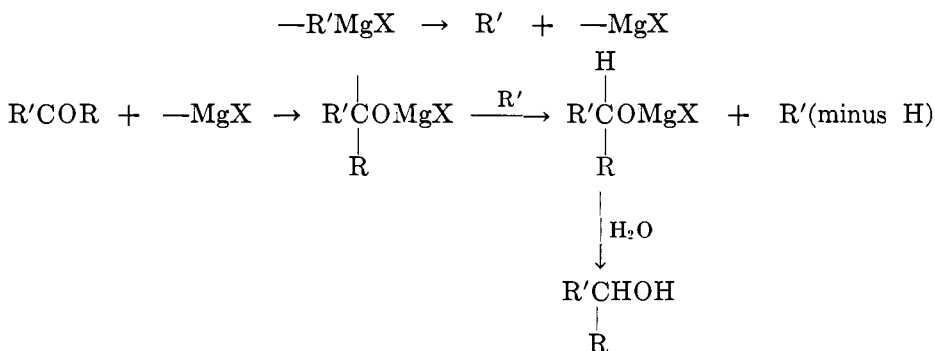
and *tert*-butylmagnesium chloride to give *tert*-butyl methyl ketone (736), also with primary Grignard reagents and primary acid chlorides (737), and, again, with the tertiary Grignard reagents and mono-, di-, and trialkylacetyl chlorides (264, 737). Conversion of the magnesium intermediate to the ketone is apparently achieved through splitting out of magnesium chlorohalide by reaction IbA or through hydrolysis (reaction IbB), as follows:

$$
\underset{\underset{Cl}{|}}{\overset{\overset{R'}{|}}{R\overset{}{C}OMgX}} + H_2O \rightarrow MgXOH + \left[\underset{\underset{Cl}{|}}{\overset{\overset{R'}{|}}{R\overset{}{C}OH}}\right] \rightarrow RCOR' + HCl
$$

The further addition of a Grignard reagent to the postulated ketone intermediate (third and fourth steps of the normal mode) is exemplified in the conversion of acetyl chloride to trimethylcarbinol with 2 moles of methylmagnesium iodide and only one hydrolysis step (Ia → IbA → IIa → IIb or alternatively Ia → IV → IIb) (688). The reduction phenomenon to a secondary alcohol by a Grignard reagent (III; abnormal mode after two normal additions) has in general been summarized (397) adequately. Briefly, two explanations for this reduction involve, respectively, a normal-type addition with abstraction of hydrogen from the Grignard alkyl group, as in A (311), and an assumption that the Grignard reagent dissociates to a free organic radical and magnesium subhalide, as in B (92).

$$
R'COR + R'MgX \rightarrow \underset{\underset{R}{|}}{\overset{\overset{R'}{|}}{R'\overset{}{C}OMgX}} \rightarrow R'(\text{minus } H) +
$$

$$
\underset{\underset{R}{|}}{\overset{\overset{H}{|}}{R'\overset{}{C}OMgX}} \xrightarrow{H_2O} \underset{\underset{R}{|}}{R'CHOH}
$$

Mechanism A

$$
-R'MgX \rightarrow R' + -MgX
$$

$$
R'COR + -MgX \rightarrow \underset{\underset{R}{|}}{R'\overset{}{C}OMgX} \xrightarrow{R'} \underset{\underset{R}{|}}{\overset{\overset{H}{|}}{R'\overset{}{C}OMgX}} + R'(\text{minus } H)
$$

$$
\downarrow H_2O
$$

$$
\underset{\underset{R}{|}}{R'CHOH}
$$

Mechanism B

The fact that yields of secondary alcohols are greater from acid chlorides than from ketones makes it probable that the overall transition RCOCl → RCHOHR′ proceeds not through the ketone by Ia → Ib → IIa → III → IIIb but through the aldehyde by an alternate path, Ia → V → VII → IIIb, or more probably by Ia → IV → III → IIIb.

On some occasions the secondary magnesium adduct which is formed by IV → III (Ia → IbA → IIa → III) may be esterified with the original acid chloride to afford an ester (IIIa), as in the formation of a 45 per cent yield of 1-*tert*-butyl-2-methylpropyl i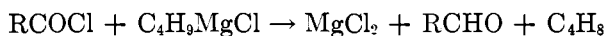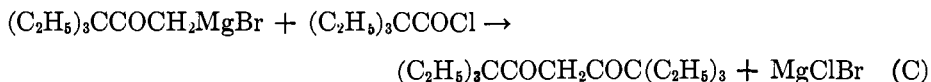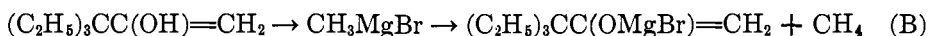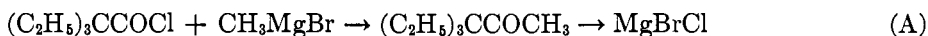sobutyrate in the reaction of isobutyryl chloride and *tert*-butylmagnesium chloride (742). The reduction of an acid chloride to aldehyde (Ia → V; abnormal mode after initial addition) has been observed in those instances in which the aldehyde is hindered at the carbonyl group and is not prone to undergo further addition (VII) or reduction (VI). In the reactions of trimethylacetyl and 3,3-dimethylbutyryl chlorides with *tert*-butylmagnesium chloride, traces of trimethylacetaldehyde and *tert*-butylacetaldehyde, respectively, have been detected (742). Similarly, the reactions of 2-*tert*-butyl-2,2,4-trimethylvaleryl chloride with *tert*-butyl and *tert*-amylmagnesium chlorides have given 70 per cent yields of the corresponding aldehydes (742), inert to both addition or reduction. Addition of the Grignard reagent to an aldehyde to give the secondary alcohol (VII; normal mode in the abnormal reaction) is generally observed except for highly branched reagents. The reduction of aldehyde to a primary alcohol with the Grignard reagent, VII → VI → VIb (abnormal), is also possible. Trimethylacetaldehyde and *tert*-butylmagnesium chloride have given a 65 per cent yield of neopentyl alcohol exclusively (159, 160). When Grignard reagents act as reducing agents 1 mole of olefin is formed for each mole of secondary alcohol formed, and 2 moles for each mole of primary alcohol.

$$RCOCl + C_4H_9MgCl \rightarrow MgCl_2 + RCHO + C_4H_8$$

$$RCHO + C_4H_9MgCl \rightarrow RCH_2OMgCl + C_4H_8$$
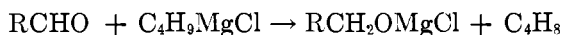
In rare instances the primary magnesium adduct formed through VI may be esterified with the original acid chloride to give an ester (VIa). Thus, in the reaction of isobutyryl chloride and *tert*-pentylmagnesium chloride, a 44 per cent yield of isobutyl isobutyrate has been formed (742). Occasionally by-products may be formed from the acid chloride, olefin, and anhydrous magnesium chloride which are present in the mixture. Acetyl chloride and *tert*-butylmagnesium chloride have given rise to mesityl oxide (743), and isobutyryl chloride and *tert*-pentylmagnesium chloride have yielded 3,4-dimethyl-3-penten-2-one (743). The formation of a 32 per cent yield of 3,3,7,7-tetraethyl-4,6-nonanedione from 2,2-diethylbutyryl chloride and methylmagnesium bromide (739) is an abnormal reaction that is especially unique in that reductions are probably not involved. In this example evidently a normal addition first occurs with formation of a ketone capable of enolization as in equation A, which reacts through its enol form with additional Grignard reagent to give an intermediate enol Grig-

nard reagent as in equation B, which reacts further with acid chloride through its keto form in normal fashion as in equation C.

$$(C_2H_5)_3CCOCl + CH_3MgBr \rightarrow (C_2H_5)_3CCOCH_3 \rightarrow MgBrCl \qquad (A)$$

$$(C_2H_5)_3CC(OH){=}CH_2 \rightarrow CH_3MgBr \rightarrow (C_2H_5)_3CC(OMgBr){=}CH_2 + CH_4 \quad (B)$$

$$(C_2H_5)_3CCOCH_2MgBr + (C_2H_5)_3CCOCl \rightarrow$$

$$(C_2H_5)_3CCOCH_2COC(C_2H_5)_3 + MgClBr \quad (C)$$

An exceedingly rare reaction that may occur in instances where the tertiary magnesium adduct produced through IIa or IV (containing at least one R or R′ group not tertiary) is heated for prolonged periods consists in formation of olefin, as in the case of the pyrolysis of the adduct of benzophenone and ethylmagnesium iodide (399).
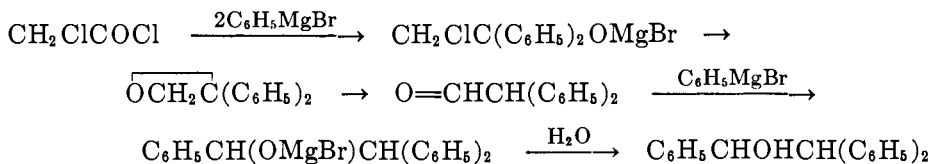
$$\begin{array}{c} \overset{\displaystyle C_6H_5}{\underset{\displaystyle CH_2CH_3}{C_6H_5\overset{|}{\underset{|}{C}}OMgX}} \rightarrow (C_6H_5)_2C{=}CHCH_3 + MgOHX \end{array}$$
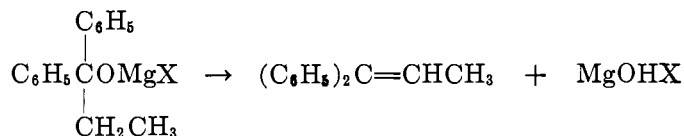
Such prolonged heating is not usual for acid chloride and Grignard reagent reactions and the reaction has not been reported.

Reactions of aliphatic acid chlorides with benzylmagnesium halides and their homologs deserve comment. The formation of o-tolyl methyl ketone from acetyl chloride and benzylmagnesium chloride (741) and also of abnormal products in the reactions of acetyl chloride with 1-naphthyl- and 2-naphthylmethylmagnesium chlorides (126) are indicative of the well-known benzylmagnesium halide type of rearrangement, which has been investigated and reviewed (35, 249) in detail.

The reactions of 2-haloacyl chlorides and the Grignard reagent are unique. Chloroacetyl chloride has given 48–51 per cent yields of 3-methyl-2-butanol from methylmagnesium bromide (335) and 1,2,2-triphenyl-1-ethanol from phenylmagnesium bromide (107). The latter conversion has been assumed to follow the path:

$$CH_2ClCOCl \xrightarrow{2C_6H_5MgBr} CH_2ClC(C_6H_5)_2OMgBr \rightarrow$$

$$\overline{OCH_2C}(C_6H_5)_2 \rightarrow O{=}CHCH(C_6H_5)_2 \xrightarrow{C_6H_5MgBr}$$

$$C_6H_5CH(OMgBr)CH(C_6H_5)_2 \xrightarrow{H_2O} C_6H_5CHOHCH(C_6H_5)_2$$

On this basis the formation of 3-methyl-2-butanol would be considered to pass through the intermediate 1,2-epoxy-2-methylpropane. Significantly, this intermediate has been shown to yield the homologous 2-methyl-3-pentanol with ethylmagnesium bromide, while with diethylmagnesium it has been shown to give 2-methyl-2-pentanol (302, 522).

Examples of reactions between acid chlorides and Grignard reagents which

TABLE 27
Reactions of aliphatic acid chlorides with the Grignard reagent

ACID CHLORIDE	GRIGNARD REAGENT	TYPE OF REACTION*	PRODUCTS (YIELD)	REFER-ENCE
Acetyl............	CH_3MgI	N	$(CH_3)_3COH$	(688)
	C_4H_9MgBr	A, N	C_4H_8, $C_4H_9CHOHCH_3$ (13%), C_2H_5OH (8%), C_4H_9OH, $CH_3(C_4H_9)_2COH$	(740)
	$1\text{-}C_{10}H_7CH_2MgBr$	S	$1\text{-}C_{10}H_7CH{=}C(CH_3)CH_2C_{10}\text{-}H_7\text{-}1$	(126)
	$2\text{-}C_{10}H_7CH_2MgBr$	S	$2\text{-}C_{10}H_7CH{=}C(CH_3)CH_2C_{10}\text{-}H_7\text{-}2$	(126)
	$[Mg(C_2H_5)_2]$	N	$(C_2H_5)_2C(CH_3)OH$	(251)
	$t\text{-}C_6H_{11}MgBr$	A, N	$t\text{-}C_6H_{11}COCH_3$ (9%), $(CH_3)_2\text{-}C{=}C(CH_3)COCH_3$ (9%)	(742)
	$C_6H_5CH_2MgCl$	S	$2\text{-}CH_3C_6H_4COCH_3$ (18%)	(741)
	$C_6H_5CH_2MgBr$	N	$C_6H_5CH_2COCH_3$ (27%)	(624)
	$t\text{-}C_4H_9MgCl$	A	$t\text{-}C_4H_9COCH_3$ (6.6%), $t\text{-}C_4H_9\text{-}CHOHCH_3$ (8%), $(CH_3)_3\text{-}CCH_2COOC_2H_5$ (9%), C_4H_8 (6.6%), C_4H_{10} (23.6%), mesityl oxide (6.6%)	(743)
	$t\text{-}C_4H_9MgCl$	A	$CH_3COOC_2H_5$ (9.5%), C_4H_8, pinacol (18%), pinacol acetate (8%), mesityl oxide (6.6%)	(734)
	$t\text{-}C_4H_9MgCl$	N	$t\text{-}C_4H_9COCH_3$ (40.7–54%)	(736)
	$t\text{-}C_4H_9MgCl$	A, N	$t\text{-}C_4H_9COCH_3$ (9%), $t\text{-}C_4H_9\text{-}CHO$ (?%), mesityl oxide (5%), $CH_3COOC_4H_9$ (2%), $CH_3COOCH(CH_3)(t\text{-}C_4H_9)$ (11%), C_4H_8, C_4H_{10}, CO	(742)
	$t\text{-}C_5H_{11}MgCl$ (0°C.)	N	$t\text{-}C_5H_{11}COCH_3$ (?%)	(736)
	$(C_2H_5)_2C(CH_3)MgCl$	N	$(C_2H_5)_2C(CH_3)COCH_3$ (18%)	(736)
	$C_4H_9C(CH_3)_2MgCl$	N	$C_4H_9C(CH_3)_2COCH_3$ (9%)	(736)
	C_4H_9MgBr	A	$C_4H_9CHOHCH_3$ (13%), C_2H_5OH (8%)	(734)
	$2\text{-}C_5H_4NCH_2MgBr$	N	$2\text{-}(CH_3COCH_2)C_5H_4N$ (11.4%), $CH_3C(OH)\text{-}[CH_2(2\text{-}C_5H_4N)]_2$	(252)
	$2\text{-}C_5H_5NCH_2MgI$	N	$2\text{-}(CH_3COCH_2)C_5H_4N$, $CH_3C(OH)[CH_2(2\text{-}C_5H_4N)]_2$	(252)
Propionyl........	$t\text{-}C_4H_9MgCl$	A, N	$C_2H_5COOCH(C_2H_5)(t\text{-}C_4H_9)$, $C_2H_5COOCH(C_2H_5)_2$?, $(C_2H_5)_2CO$?, C_2H_5COOH	(542)
Butyryl.........	$t\text{-}C_4H_9MgCl$	A	$t\text{-}C_4H_9CHOHC_3H_7$ (71%), C_4H_9OH (9%), C_4H_8	(734)
	$t\text{-}C_4H_9MgCl$	A, N	$C_3H_7COOCH(C_2H_5)(t\text{-}C_4H_9)$ (36%), $t\text{-}C_4H_9COC_3H_7$ (21%), $C_3H_7COO(t\text{-}C_4H_9)$ (11%)	(742)

TABLE 27—*Continued*

ACID CHLORIDE	GRIGNARD REAGENT	TYPE OF REACTION*	PRODUCTS (YIELD)	REFER-ENCE
Butyryl (0.98 mole)...........	t-C$_4$H$_9$MgCl (4 moles)	A	t-C$_4$H$_9$CHOHC$_3$H$_7$ (71%), C$_4$H$_9$OH (9%), C$_2$(CH$_3$)$_6$	(264)
Isobutyryl........	CH$_3$MgCl	N	i-C$_3$H$_7$COCH$_3$ (7.6%)	(702)
	C$_3$H$_7$MgCl	N	(i-C$_3$H$_7$)$_2$CO (12.7%)	(702)
	i-C$_3$H$_7$MgCl	N	(i-C$_3$H$_7$)$_2$CO (6%)	(702)
	t-C$_4$H$_9$MgCl	N	i-C$_3$H$_7$CO(t-C$_4$H$_9$) (35%)	(702)
	t-C$_4$H$_9$MgCl	A	i-C$_3$H$_7$CHOH(t-C$_4$H$_9$) (63%), C$_4$H$_9$OH (20%), C$_4$H$_8$	(734)
	t-C$_4$H$_9$MgCl	A	i-C$_3$H$_7$CHOH(t-C$_4$H$_9$) (63%), C$_4$H$_9$OH (20%), C$_2$(CH$_3$)$_6$	(264)
	t-C$_4$H$_9$MgCl	A, N	i-C$_3$H$_7$COOCH(i-C$_3$H$_7$)(t-C$_4$H$_9$) (45%), i-C$_3$H$_7$COO-(i-C$_4$H$_9$) (18%), i-C$_3$H$_7$CO-(t-C$_4$H$_9$) (17%)	(742)
	t-C$_5$H$_{11}$MgCl	A	i-C$_3$H$_7$COO(i-C$_4$H$_9$) (44%)	(742)
	C$_6$H$_5$MgBr	N	i-C$_3$H$_7$COC$_6$H$_5$ (21%)	(702)
	2-CH$_3$C$_6$H$_4$MgBr	N	2-CH$_3$C$_6$H$_4$CO(i-C$_3$H$_7$) (67%)	(702)
	2-CH$_3$OC$_6$H$_4$MgBr	N	2-CH$_3$OC$_6$H$_4$CO(i-C$_3$H$_7$) (63%)	(702)
	1-C$_{10}$H$_7$MgBr	N	1-C$_{10}$H$_7$CO(i-C$_3$H$_7$) (63%)	(702)
	9-C$_{14}$H$_9$MgBr	N	9-C$_{14}$H$_9$CO(i-C$_3$H$_7$) (61%)	(702)
Trimethylacetyl...	C$_2$H$_5$MgBr	A, N	t-C$_4$H$_9$CHOHC$_2$H$_5$ (60%), t-C$_4$H$_9$C(C$_2$H$_5$)$_2$OH (26.1%)	(738)
	t-C$_4$H$_9$MgCl (CuCl)	N	[(CH$_3$)$_3$C]$_2$CO (71.6%), (CH$_3$)$_3$CCOOC(CH$_3$)$_3$ (1.3%), (CH$_3$)$_3$CCH$_2$OH	(161)
	C$_3$H$_7$MgBr	A	t-C$_4$H$_9$CHOHC$_3$H$_7$ (70%), (CH$_3$)$_3$CCH$_2$OH (20%)	(738)
	i-C$_3$H$_7$MgBr	A	(CH$_3$)$_3$CCH$_2$OH (23%), t-C$_4$H$_9$CHOH(i-C$_3$H$_7$) (53%)	(738)
	C$_4$H$_9$MgBr	A	(CH$_3$)$_3$CCH$_2$OH (28%), t-C$_4$H$_9$CHOHC$_4$H$_9$ (71%)	(738)
	C$_4$H$_9$MgBr	A	(CH$_3$)$_3$CCH$_2$OH (27%), t-C$_4$H$_9$CHOHC$_4$H$_9$ (69%)	(740)
	i-C$_4$H$_9$MgBr	A	(CH$_3$)$_3$CCH$_2$OH (61%), t-C$_4$H$_9$CHOH(i-C$_4$H$_9$) (26%)	(738)
(1 mole)........	t-C$_4$H$_9$MgCl (4 moles)	A	(CH$_3$)$_3$CCH$_2$OH (94%), C$_4$H$_8$, (t-C$_4$H$_9$)$_2$CHOH	(734)
(0.22 mole).....	t-C$_4$H$_9$MgCl (1 mole)	A	(CH$_3$)$_3$CCH$_2$OH (45%), t-C$_4$H$_9$COOCH$_2$C(CH$_3$)$_3$, C$_4$H$_8$	(734)
(8 moles).......	t-C$_4$H$_9$MgCl (1.5 moles)	N	(t-C$_4$H$_9$)$_2$CO (32%), t-C$_4$H$_9$COOCH$_2$C(CH$_3$)$_3$ (8%), (CH$_3$)$_3$CCOOH	(734)
(1 mole)........	C$_4$H$_9$MgBr (4 moles)	A	t-C$_4$H$_9$CHOH(C$_4$H$_9$) (69%), (CH$_3$)$_3$CCH$_2$OH (27%)	(734)
(1.1 moles).....	t-C$_4$H$_9$MgCl (3.9 moles)	A	(CH$_3$)$_3$CCH$_2$OH (94%), (t-C$_4$H$_9$)$_2$CHOH (1.5%), C$_4$H$_8$ (55%), C$_2$(CH$_3$)$_6$ (5%)	(264)

TABLE 27—*Continued*

ACID CHLORIDE	GRIGNARD REAGENT	TYPE OF REACTION*	PRODUCTS (YIELD)	REFER-ENCE
Trimethylacetyl..	t-C$_5$H$_{11}$MgCl	A	(CH$_3$)$_3$CCH$_2$OH (97%)	(742)
	i-C$_4$H$_9$MgCl	A	(CH$_3$)$_3$CCH$_2$OH (61%), i-C$_4$H$_9$CHOH(t-C$_4$H$_9$) (26%)	(742)
2,2-Dimethyl-butyryl.........	i-C$_3$H$_7$MgBr	A	t-C$_5$H$_{11}$CHOH(i-C$_3$H$_7$) (49.3%), t-C$_5$H$_{11}$CH$_2$OH (24%)	(738)
3,3-Dimethyl-butyryl.........	C$_2$H$_5$MgBr	N	(CH$_3$)$_3$CCH$_2$C(C$_2$H$_5$)$_2$OH (57.6%)	(738)
	C$_3$H$_7$MgBr	N, A	(CH$_3$)$_3$CCH$_2$C(C$_3$H$_7$)OH (57%), (CH$_3$)$_3$CCH$_2$CH-OHC$_3$H$_7$ (24.4%)	(738)
	i-C$_3$H$_7$MgBr	N, A	(CH$_3$)$_3$CCH$_2$CHOH(i-C$_3$H$_7$) (26.7%), (CH$_3$)$_3$CCH$_2$CO-(i-C$_3$H$_7$) (32.7%)	(738)
	C$_4$H$_9$MgBr	A, N	(CH$_3$)$_3$CCH$_2$CHOHC$_4$H$_9$ (20.5%), (CH$_3$)$_3$CCH$_2$-(C$_4$H$_9$)$_2$COH (9.9%)	(738)
	i-C$_4$H$_9$MgBr	A, N	(CH$_3$)$_3$CCH$_2$CHOH(i-C$_4$H$_9$) (48.9%), (CH$_3$)$_3$CCH$_2$-C(i-C$_4$H$_9$)$_2$OH (13.8%)	(738)
	t-C$_4$H$_9$MgCl	A	(CH$_3$)$_3$CCH$_2$CHOH(t-C$_4$H$_9$) (48%), (CH$_3$)$_3$CCH$_2$CH$_2$-OH (5%), t-C$_4$H$_9$CH$_2$CHO (1%)	(742)
2-Ethylbutyryl...	t-C$_4$H$_9$MgCl	A	t-C$_4$H$_9$CHOHCH(C$_2$H$_5$)$_2$ (43–68%), (C$_2$H$_5$)$_2$CHCH$_2$OH (18–30%)	(742)
	t-C$_5$H$_{11}$MgCl	A	(C$_2$H$_5$)$_2$CHCH$_2$OH (74%), (C$_2$H$_5$)$_2$CHCHOH(t-C$_5$H$_{11}$) (7%)	(742)
4,4-Dimethyl-valeryl.........	t-C$_4$H$_9$MgCl	A	(CH$_3$)$_3$CCH$_2$CH$_2$CHOH(t-C$_4$H$_9$) (67%), (CH$_3$)$_3$CCH$_2$-CH$_2$OH (13.5%)	(742)
2-Ethylhexanoyl..	t-C$_4$H$_9$MgCl	A	C$_4$H$_9$CH(C$_2$H$_5$)CHOH(t-C$_4$H$_9$) (64%), C$_4$H$_9$CH-(C$_2$H$_5$)CH$_2$OH (29%)	(742)
	t-C$_5$H$_{11}$MgCl	A	C$_4$H$_9$CH(C$_2$H$_5$)CH$_2$OH (74%), C$_4$H$_9$CH(C$_2$H$_5$)CH-OH(t-C$_5$H$_{11}$) (15%)	(742)
2,2-Diethylbu-tyryl..........	CH$_3$MgBr	N	(C$_2$H$_5$)$_3$CCOOCH$_3$ (34%), CH$_2$[COC(C$_2$H$_5$)$_3$]$_2$ (32%), gas	(739)
	t-C$_4$H$_9$MgCl	A	(C$_2$H$_5$)$_3$CCH$_2$OH (89%)	(742)

TABLE 27—*Continued*

ACID CHLORIDE	GRIGNARD REAGENT	TYPE OF REACTION*	PRODUCTS (YIELD)	REFER-ENCE
2,4,4-Trimethyl-valeryl.........	t-C_4H_9MgCl	A	t-$C_4H_9CH_2CH(CH_3)CHOH$-(t-C_4H_9) (67%), t-C_4H_9-$CH_2CH(CH_3)CH_2OH$ (21%)	(742)
Lauroyl..........	t-C_4H_9MgCl	A	$C_{11}H_{23}CH_2OH$ (13%), $C_{11}H_{23}$-$CHOH(t$-$C_4H_9)$ (67%)	(742)
	t-$C_5H_{11}MgCl$	A	$C_{11}H_{23}CH_2OH$ (54%), $C_{11}H_{23}$-$CHOH(t$-$C_5H_{11})$ (17%)	(742)
4,4-Dimethyl-2-neopentylval-eryl............	t-C_4H_9MgCl	A	$[(CH_3)_3CCH_2]_2CHCH_2OH$ (60%), $[(CH_3)_3CCH_2]_2$-$CHCHOH(t$-$C_4H_9)$ (17%)	(742)
2,2,4-Trimethyl-2-*tert*-butylval-eryl............	t-C_4H_9MgCl	A	$[(CH_3)_3CCH_2]C(t$-$C_4H_9)(CH_3)$-CHO (62.5%), $[(CH_3)_3C$-$CH_2](C_4H_9)(CH_3)CCH_2OH$ (19%)	(742)
	t-$C_5H_{11}MgCl$	A	$[(CH_3)_3CCH_2]C(C_4H_9)(CH_3)$-$CHO$ (78%), $[(CH_3)_3C$-$CH_2]C(C_4H_9)(CH_3)CH_2OH$ (17%)	(742)
2,2-Dibutylhex-anoyl..........	t-C_4H_9MgCl	A	$(C_4H_9)_3CCH_2OH$ (88%)	(742)
2,2-Dibutylhex-anoyl (excess)..	t-C_4H_9MgCl	A	t-$C_4H_9CHOHCH_2C(CH_3)_3$ (71%), $(CH_3)_3CCH_2CH_2OH$ (1%)	(737)
2,2-Dibutylhex-anoyl..........	t-C_4H_9MgCl (excess)	N	t-$C_4H_9COCH_2C(CH_3)_3$(51%), $(CH_3)_3CCH_2COOCH(t$-$C_4H_9)CH_2C(CH_3)_3$ (17%)	(737)
Chloroacetyl......	CH_3MgBr	S	i-$C_3H_7CHOHCH_3$	(335)
Oxalyl...........	$C_6H_5CH(COONa)$-$MgCl$	S	$(C_6H_5CH_2CO)_2O$ (78.1%), $C_6H_5CH_2COOH$ (15.6%), CO_2, CO	(664)
Succinyl.........	$C_6H_5CH(COONa)$-$MgCl$	S	$(C_6H_5CH_2CO)_2O$, $(CH_2$-$CO)_2O$, $C_6H_5CH_2COOH$	(664)
Adipyl..........	$C_6H_5CH(COONa)$-$MgCl$	S	$(C_6H_5CH_2CO)_2O$ (16.6%), $C_6H_5CH_2COOH$ (58%), adipic acid	(664)
Sebacyl..........	$C_6H_5CH(COONa)$-$MgCl$	S	$(C_6H_5CH_2CO)_2O$ (15.8%), $C_6H_5CH_2COOH$ (60.2%), sebacic acid	(664)

TABLE 27—*Concluded*

ACID CHLORIDE	GRIGNARD REAGENT	TYPE OF REACTION*	PRODUCTS (YIELD)	REFERENCE
3-Carbomethoxy-propionyl.......	i-$C_5H_{11}MgBr$	N	i-$C_5H_{11}CO(CH_2)_2COOCH_3$ (10.5%)	(132)
9-Carbethoxyno-nanoyl.........	i-C_4H_9MgBr	N	i-$C_4H_9CO(CH_2)_8COOH$ (43–47%)	(217)
	5-Methyloctylmag-nesium bromide	N	$C_3H_7CH(CH_3)(CH_2)_4CO$-$(CH_2)_8COOC_2H_5$ (65%)	(135)
	i-$C_9H_{19}MgBr$	N	i-$C_8H_7(CH_2)_6CO(CH_2)_8$-$COOC_2H_5$ (20%)	(132)

* N = normal type of reaction; A = abnormal type of reaction; S = special type of reaction.

are collected in table 27 have been classified with respect to normal (addition), abnormal (reduction), or special (rearrangement, etc.) types of reaction.

D. REACTION WITH OTHER ORGANOMETALLIC COMPOUNDS (SEE TABLE 28)

Although reactions of aliphatic acid chlorides with the Grignard reagent have achieved little importance as preparative methods, owing to the variety of reaction modes possible, other organometallic compounds, particularly the zinc, cadmium, and lately the aluminum compounds, are, as a result of decreased general activity, considerably more specific in their reactions with acid chlorides. As a consequence these metal compounds have been more prominent in synthetic methods for the preparation of various types of ketones.

1. Dialkylzinc compounds

The inability of alkylzinc halides to add to the carbonyl group of either esters or ketones as illustrated in the Reformatsky synthesis has also been applied to elegant syntheses of keto acids and diketones from carbalkoxyacyl chlorides and dicarbonyl chlorides, respectively. Illustrative of the method is the formation in 80–95 per cent yield of 6-ketoheptanoic, 6-ketoöctanoic, 7-ketononanoic, 8-ketodecanoic, and 4-ketoöctanoic acids from 5-carbethoxyvaleryl, 5-carbethoxy-valeryl, 6-carbethoxyhexanoyl, 7-carbethoxyheptanoyl, and 3-carbethoxypro-pionyl chlorides, and of 3,8-decanedione, 3,9-undecanedione, 3,10-dodecanedi-one, 2,9-decanedione, and 2,10-undecanedione from adipyl, pimelyl, suberyl, suberyl, and azelyl chlorides, respectively (83).
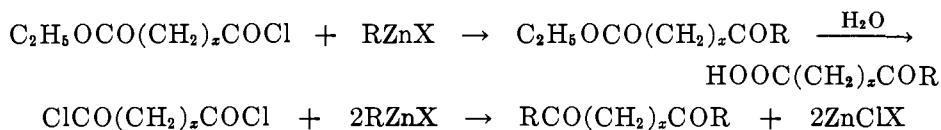
$$C_2H_5OCO(CH_2)_xCOCl + RZnX \rightarrow C_2H_5OCO(CH_2)_xCOR \xrightarrow{\ H_2O\ }$$
$$HOOC(CH_2)_xCOR$$

$$ClCO(CH_2)_xCOCl + 2RZnX \rightarrow RCO(CH_2)_xCOR + 2ZnClX$$

TABLE 28
Reaction of aliphatic acid chlorides with organometallic compounds

ACID CHLORIDE	ORGANOMETALLIC COMPOUND	PRODUCTS (YIELD)	REFERENCE
		Organozinc compounds	
Propionyl	$(C_2H_5)_2Zn$	$C_2H_5COC_2H_5$	(487)
Butyryl	$(C_2H_5)_2Zn$	$C_3H_7COC_2H_5$	(487)
Isobutyryl	$(C_2H_5)_2Zn$	$i\text{-}C_3H_7COC_2H_5$	(487)
	$(CH_3)_2Zn$	$i\text{-}C_3H_7COCH_3$	(487)
Valeryl	$(C_2H_5)_2Zn$	$C_4H_9COC_2H_5$	(487)
Isovaleryl	$ZnCH_3I$	$i\text{-}C_4H_9COCH_3$	(487)
3-Carbethoxypropionyl	C_4H_9ZnI $(+H_2O)$	$C_4H_9COCH_2CH_2COOH$ (80–95%)	(83)
5-Carbethoxyvaleryl	CH_3Zn/CuI	$CH_3CO(CH_2)_4COOC_2H_5$ (93%)	(549)
	CH_3ZnI $(+H_2O)$	$CH_3CO(CH_2)_4COOH$ (80–95%)	(83)
	C_2H_5ZnI $(+H_2O)$	$C_2H_5CO(CH_2)_4COOH$ (80–95%)	(83)
6-Carbethoxyhexanoyl	C_2H_5ZnI $(+H_2O)$	$C_2H_5CO(CH_2)_5COOH$ (80–95%)	(83)
7-Carbethoxyheptanoyl	C_2H_5ZnI $(+H_2O)$	$C_2H_5CO(CH_2)_6COOH$ (80–95%)	(83)
4-Chlorobutyryl	C_2H_5ZnI	$CH_2Cl(CH_2)_2COC_2H_5$	(751)
	$4\text{-}CH_3C_6H_4ZnI$	$CH_2Cl(CH_2)_2COC_6H_4CH_3\text{-}4$	(751)
4-Chlorovaleryl	C_2H_5ZnI	$CH_2ClCH_2COC_2H_5$	(751)
	C_6H_5ZnI	$CH_2Cl(CH_2)_3COC_6H_5$	(751)
4-Bromovaleryl	C_2H_5ZnI	$CH_2Br(CH_2)_3COC_2H_5$	(751)
Ethoxyacetyl	C_2H_5ZnI $(-18°C.)$	$C_2H_5OC_3H_7$ (50%), $C_2H_5OCH_2COC_2H_5$ (23%)	(87)
	C_2H_5ZnI $(32°C.)$	$C_2H_5OC_3H_7$ (74%), $C_2H_5OCH_2COC_2H_5$ (13%)	(87)
	C_4H_9ZnI	$C_2H_5OC_3H_7$, $C_2H_5OCH_2COC_4H_9$, $C_2H_5OCH_2COOC_2H_5$, $C_2H_5OCH_2COOC_4H_9$?	(87)
	$i\text{-}C_5H_{11}ZnI$	$i\text{-}C_5H_{11}CH_2OC_2H_5$ (30%), $i\text{-}C_5H_{11}COCH_2OC_2H_5$ (16%)	(87)
	$C_7H_{15}ZnI$	$C_8H_{17}OC_2H_5$, CO	(85)
	$C_7H_{15}ZnI$	$C_8H_{17}OC_2H_5$, $C_2H_5OCH_2COOC_2H_5$?	(87)
	$4\text{-}CH_3C_6H_4ZnBr$	$4\text{-}CH_3C_6H_4COCH_2OC_2H_5$	(85)
Butoxyacetyl	C_2H_5ZnI	$C_4H_9OCH_2COC_2H_5$, others	(88)
Isobutoxyacetyl	C_2H_5ZnI	$i\text{-}C_4H_9OCH_2COC_2H_5$ (50%), $i\text{-}C_4H_9OC_3H_7$ (10%)	(85)
2-Ethoxyhexanoyl	C_2H_5ZnI	$C_4H_9CH(OC_2H_5)C_2H_5$?, CO	(86, 88)
Adipyl	C_2H_5ZnI	$C_2H_5CO(CH_2)_4COC_2H_5$	(83)
Pimelyl	C_2H_5ZnI	$C_2H_5CO(CH_2)_5COC_2H_5$	(83)

Suberyl	CH_3ZnI	$CH_3CO(CH_2)_6COCH_3$	(83)
	C_2H_5ZnI	$C_2H_5CO(CH_2)_6COC_2H_5$	(83)
Azelyl	CH_3ZnI	$CH_3CO(CH_2)_7COCH_3$	(83)

Organocadmium compounds

Acetyl	$(C_2H_5)_2Cd$	$CH_3COC_2H_5$ (46%)	(250)
	C_2H_5CdBr	$CH_3COC_2H_5$ (50%)	(250)
	$(C_4H_9)_2Cd$	$C_4H_9COCH_3$	(250)
	$(t\text{-}C_4H_9)_2Cd$	$t\text{-}C_4H_9COCH_3$ (17%)	(250)
	$(C_6H_5CH_2)_2Cd$	$C_6H_5CH_2COCH_3$ (18%)	(250)
	$(C_6H_5)_2Cd$	$C_6H_5COCH_3$ (61–83%)	(250)
	C_6H_5CdBr	$C_6H_5COCH_3$ (83%)	(250)
Butyryl	$(i\text{-}C_3H_7)_2Cd$	$i\text{-}C_3H_7COC_3H_7$ (60%)	(250)
Stearoyl	$(C_2H_5)_2Cd$	$C_{17}H_{35}COC_2H_5$ (65%)	(250)
Hydromuconyl	$(CH_3)_2Cd$	$(=CHCH_2COCH_3)_2$ (15%)	(646)
Muconyl	$(CH_3)_2Cd$	$(-CH=CHCOCH_3)_2$ (2%)	(646)
3-Carbomethoxypropionyl	$(i\text{-}C_5H_{11})_2Cd$	$i\text{-}C_5H_{11}CO(CH_2)_2COOCH_3$ (44%), $CH_3OCO(CH_2)_2COOC_2H_5$	(132)
	$(i\text{-}C_3H_7)_2Cd$	$i\text{-}C_5H_{11}CO(CH_2)_2COOCH_3$ (73.5%)	(138)
	$(i\text{-}C_3H_7)_2Cd$	$i\text{-}C_5H_{11}CO(CH_2)_2COOCH_3$ (78.7%)	(133)
	$[C_3H_7(CH_3)CH]_2Cd$	$C_3H_7CH(CH_3)CO(CH_2)_2COOCH_3$ (10.4%)	(133)
	$(C_4H_9)_2Cd$ (from the bromide)	$C_4H_9CO(CH_2)_2COOCH_3$ (79.5%)	(133)
	$(C_4H_9)_2Cd$ (from the chloride)	$C_4H_9CO(CH_2)_2COOCH_3$ (63%)	(133)
	$(C_4H_9)_2Cd$ (from the iodide)	$C_4H_9CO(CH_2)_2COOCH_3$ (45%)	(133)
	$[C_3H_7CH(CH_3)_2]_2Cd$	$C_3H_7CH(CH_3)CO(CH_2)_2COOCH_3$ (21%)	(138)
	$[C_2H_5CH(CH_3)CH_2]_2Cd$	$C_2H_5CH(CH_3)CH_2CO(CH_2)_2COOCH_3$ (24–27%)	(138)
	$(i\text{-}C_5H_{11})_2Cd$	$i\text{-}C_5H_{11}CO(CH_2)_2COOCH_3$	(139)
2,3-Dimethyl-3-carbomethoxypropionyl	$(CH_3)_2Cd$	$CH_3COCH(CH_3)CH(CH_3)COOCH_3$ (54%)	(136)
5-Carbethoxyvaleryl	$(CH_3)_2Cd$	$CH_3CO(CH_2)_4COOC_2H_5$ (76%)	(138)
6-Carbethoxyhexanoyl	$[CH_2=CH(CH_2)_9]_2Cd$	$CH_2=CH(CH_2)_9CO(CH_2)_5COOC_2H_5$ (67.3%)	(320a)
9-Carbethoxynonanoyl	$(CH_3)_2Cd$	$CH_3CO(CH_2)_8COOC_2H_5$ (83.7%)	(133)
	$(CH_3)_2Cd$	$CH_3CO(CH_2)_8COOC_2H_5$ (83%)	(138)
	$(i\text{-}C_5H_{11})_2Cd$	$i\text{-}C_5H_{11}CO(CH_2)_8COOC_2H_5$ (85%)	(138)
	$[C_2H_5CH(CH_3)(CH_2)_5]_2Cd$	$C_2H_5CH(CH_3)(CH_2)_5CO(CH_2)_8COOC_2H_5$ (76.5%)	(139)
	$[(i\text{-}C_3H_7(CH_2)_6)]_2Cd$	$i\text{-}C_3H_7(CH_2)_6CO(CH_2)_8COOC_2H_5$ (46%)	(132)

TABLE 28—*Concluded*

ACID CHLORIDE	ORGANOMETALLIC COMPOUND	PRODUCTS (YIELD)	REFERENCE
4-Carbomethoxy-3,3-dimethyl-butyryl	$(C_{13}H_{27})_2Cd$	$C_{13}H_{27}COCH_2C(CH_3)_2CH_2COOCH_3$ (88%)	(140)
3-Carbomethoxy-2,3-dimethyl-propionyl	$(C_{14}H_{29})_2Cd$	$C_{14}H_{29}COCH(CH_3)CH(CH_3)COOCH_3$ (64.5%)	(140)
11-Carbethoxyundecanoyl	Di(3-methylhexyl)cadmium	$C_3H_7CH(CH_3)(CH_2)_2CO(CH_2)_{10}COOC_2H_5$ (54.6%)	(137)
Chloroacetyl	$(C_4H_9)_2Cd$	$C_4H_9COCH_2Cl$ (26%)	(120)
	$(C_5H_{11})_2Cd$	$C_5H_{11}COCH_2Cl$ (24%)	(120)
	$(C_{12}H_{25})_2Cd$	$C_{12}H_{25}COCH_2Cl$ (8–18%)	(120)
	$(C_{14}H_{29})_2Cd$	$C_{14}H_{29}COCH_2Cl$ (22%)	(120)
1-Chlorobutyryl	$(C_4H_9)_2Cd$	$CH_3CHClCOC_4H_9$ (42.7%)	(133)
	$(C_{12}H_{25})_2Cd$	$CH_3CHClCOC_{12}H_{25}$ (13%)	(120)
Oxalyl	$(C_2H_5)_2Cd$	$(C_2H_5)_2COHCOC_2H_5$ (27%)	(250)

Miscellaneous organometallic compounds

ACID CHLORIDE	ORGANOMETALLIC COMPOUND	PRODUCTS (YIELD)	REFERENCE
Acetyl	$RAlCl_2$	CH_3COR	(18)
	$[(C_6H_5)_4Al]Li$	$CH_3COC_6H_5$	(749)
	$(C_6H_5)_2Hg$	$C_6H_5COCH_3$, C_6H_5HgCl, $(C_6H_5)_2$?	(125)
	$(C_2H_5)_2Hg$	$C_2H_5COCH_3$, C_2H_5HgCl (low)	(480)
	$2\text{-}C_5H_4NCH_2Li$ ($-78°C.$)	$2\text{-}(CH_3COCH_2)C_5H_4N$, $CH_3C(OH)[CH_2(2\text{-}C_5H_4N)]_2$	(252)
Butyryl	CH_3AlCl_2	$C_3H_7COCH_3$ (70%)	(6)
	$(CH_3)_2AlCl$	$C_3H_7COCH_3$ (65%)	(6)
Isovaleryl	$(C_2H_5)_2Hg$	$i\text{-}C_4H_9COC_2H_5$, C_2H_5HgCl (small)	(480)
3-Carbomethoxypropionyl	CH_3AlCl_2	$CH_3CO(CH_2)_2COOCH_3$ (24%)	(6)
3-Carbethoxypropionyl	CH_3AlCl_2	$CH_3CO(CH_2)_2COOC_2H_5$ (36%)	(6)
5-Carbethoxyvaleryl	CH_3AlCl_2	$CH_3CO(CH_2)_4COOC_2H_5$ (92–95%)	(6)
	$CH_3AlCl_{sesq.}$	$CH_3CO(CH_2)_4COOC_2H_5$ (90%)	(6)
	$C_2H_5AlCl_2$	$C_2H_5CO(CH_2)_4COOC_2H_5$ (94%)	(6)
9-Carbethoxynonanoyl	CH_3AlCl_2	$CH_3CO(CH_2)_8COOC_2H_5$ (93%)	(6)
	$C_2H_5AlCl_2$	$C_2H_5CO(CH_2)_8COOC_2H_5$ (94%)	(6)
Adipyl	CH_3AlCl_2	$CH_3CO(CH_2)_4COCH_3$ (35%)	(6)
RCOCl	$C_6H_5AlCl_2$	C_6H_5COR, $AlCl_3$	(188)

The alkylzinc halides required in these reactions have been usually prepared from zinc and alkyl iodide in ethyl acetate and toluene, or from the Grignard reagent in a suitable solvent with anhydrous zinc chloride. An alternate method

$$Zn + RX \rightarrow RZnX$$
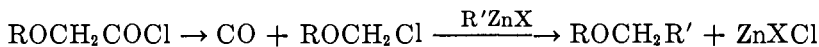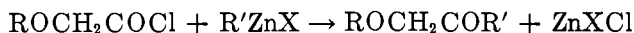
$$RMgX + ZnCl_2 \rightarrow RZnX + MgCl_2$$
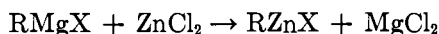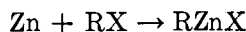
has consisted in the reaction of acid chlorides with dialkylzinc compounds (487), which are themselves prepared from alkyl iodides and zinc dust (427).

$$2RI + 2Zn \rightarrow R_2Zn + ZnI_2$$

$$RCOCl + R_2Zn \rightarrow RCOR + RZnCl$$
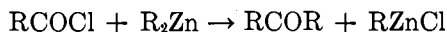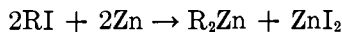
Although the majority of acyl chlorides yield ketones with zinc reagents, some unsaturated acid chlorides yield esters of tertiary alcohols as the products of condensation with alkylzinc halides (81).

Some attention has also been given the reactions of α-alkoxyacyl chlorides with alkylzinc halides. In some instances α-alkoxyacyl chlorides have reacted normally to give α-alkoxyketones, but usually carbon monoxide is evolved with the formation of an ether.

$$ROCH_2COCl + R'ZnX \rightarrow ROCH_2COR' + ZnXCl$$

$$ROCH_2COCl \rightarrow CO + ROCH_2Cl \xrightarrow{\ R'ZnX\ } ROCH_2R' + ZnXCl$$

Ether formation appears to be enhanced with an increase in the molecular weight of the R' group, with higher reaction temperatures, or with a decrease in the molecular weight of the R group. When either R or R' is cyclic in structure, the ketone is the only product. Ethoxyacetyl chloride and heptylzinc iodide have given only ethyl octyl ether (85), and isobutoxyacetyl chloride and ethylzinc iodide a 50 per cent yield of ethyl isobutoxymethyl ketone (85). At −18°C. the reaction of ethoxyacetyl chloride and ethylzinc iodide has afforded a 50 per cent yield of ethyl propyl ether and a 23 per cent yield of ethoxymethyl ethyl ketone, while at 32°C. the yields were 74 and 13 per cent, respectively. Ethoxyacetyl chloride and 4-tolylzinc bromide have given only ethoxymethyl 4-tolyl ketone (85).

The reactions of γ-haloacyl chlorides and the Grignard reagent are interesting. At temperatures of −20° to −5°C. good yields of the γ-chloroalkyl ketones have been obtained, but at temperatures near 0°C. mixtures of the ketone and esters of a tertiary alcohol have been obtained (751).

2. Dialkylcadmium compounds

The preparation of organocadmium compounds and their reactions with both acid chlorides and anhydrides have been reviewed (709). These metal compounds exhibit inertness to the carbonyl group of esters and ketones (except with ketones capable of enolization) and have been applied with success to elegant syntheses of keto esters and keto acids from carbalkoxy acid chlorides. In general, the

yields in this conversion are superior to those methods involving the Grignard reagent or zinc compounds and the procedure is convenient. With Grignard

$$ROOC(CH_2)_xCOCl \; + \; R_2Cd \; \rightarrow$$

$$RCdCl \; + \; ROOC(CH_2)_xCOR \; \xrightarrow{\; H_2O \;} \; HOOC(CH_2)_xCOR$$

reagents and 3-carbomethoxypropionyl and 9-carbethoxynonanoyl chlorides only 10.5 and 20 per cent yields of methyl 7-methyl-4-ketoöctanoate and ethyl 17-methyl-10-ketoöctadecanoate have been obtained, but from the same acyl chlorides and the corresponding dialkylcadmium the yields of keto esters have been increased to 44 and 46 per cent, respectively (132). Evidently dibutyl ether is not suitable as a solvent, but a benzene–ether mixture is claimed to be superior (133). In the procedure the organocadmium compound is never isolated but is prepared by the direct addition of anhydrous cadmium chloride to an ethereal solution of the Grignard reagent. Reaction is then completed by the addition of

$$2RMgX + CdCl_2 \rightarrow R_2Cd + 2MgXCl$$
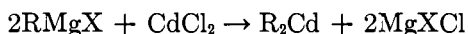
the acid chloride in ether–benzene. With di-*sec*-alkyl- or di-*tert*-alkylcadmium compounds the temperature must be maintained below 0°C., and even under these conditions results are none too good. Yields are at least 50 per cent if the cadmium reagent does not contain a secondary or tertiary alkyl group; usually they are 70–84 per cent.

3. Other organometallic compounds

The preparation, properties, and analyses of alkylaluminum halides have been reported (268). These compounds have been prepared from lower alkyl halides and metallic aluminum under pressure in an autoclave. Apparently aluminum sesquihalides are initially formed and may be converted to alkylaluminum dihalides with the appropriate aluminum trihalide.

$$3RX \; + \; 2Al \; \rightarrow \; (R_2Al \cdot RAlX_2) \; \xrightarrow{\; AlX_3 \;} \; 3RAlX_2$$

The preparation of ketones by the reaction of benzoyl or acetyl chloride with alkylaluminum halides has been reported (18). Recently, excellent yields of quite pure keto esters have been obtained through the use of ethyl- and methyl-aluminum dichlorides with carbethoxyacyl chlorides in benzene solution (6).

$$C_2H_5OOC(CH_2)_xCOCl + RAlCl_2 \rightarrow C_2H_5OOC(CH_2)_xCOR + AlCl_3$$
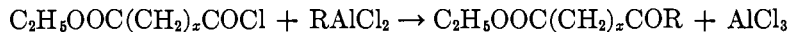
The synthesis has also been extended to the preparation of methyl ketones from butyryl chloride.

Organo mercury compounds offer little utility in reactions with acid chlorides, but the reactions of acetyl chloride with diphenyl- (125) and diethyl- (480) mercury have been reported. Addition of cuprous chloride to the Grignard reagent (161) and of copper to the zinc in the preparation of methylzinc iodide (549) has been claimed to increase the yields of ketone (normal mode) and keto ester, respectively.

XX. Reaction of Aliphatic Acid Chlorides with Mercaptans
(Thioesterification) and Other Sulfur, Arsenic, Silicon,
Phosphorus, and Selenium Compounds

In most respects the reactions of aliphatic acid chlorides with bivalent sulfur-containing compounds are similar to those of the oxygen-containing analogs, although there are minor differences worthy of mention in certain instances.

The thioesterification of acid chlorides with mercaptans evolves hydrogen chloride, which is usually not troublesome and need not be removed with ter-

$$RCOCl + R'SH \rightarrow RCOSR' + HCl$$
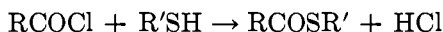
tiary amines or other hydrogen chloride acceptors. Oxalyl chloride has been reacted with 2 moles of methyl, ethyl, propyl, isopentyl, and phenyl mercaptans without a solvent in this way to give the dithio esters of oxalic acid (366). The diacylation of 2-hydroxyethyl mercaptan has been accomplished in benzene at the reflux temperature (492). Conversion to a thioester with methyl or benzyl

$$2CH_3COCl + HOCH_2CH_2SH \rightarrow CH_3COOCH_2CH_2SCOCH_3 + 2HCl$$
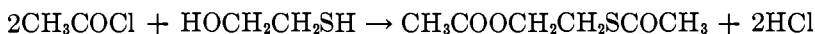
mercaptan is one of the steps in an efficient synthesis of an alcohol from an acid chloride (see Section IV,B,3). Palmitoyl chloride has given 1-hexadecanol in

$$RCOCl \xrightarrow{R'SH} RCOSR' \xrightarrow{H_2} RCH_2OH$$

98 per cent overall yield (359). The reaction of an aliphatic acid chloride with hydrogen sulfide to give a thio acid, however, appears to proceed best when the

$$RCOCl + H_2S \rightarrow RCOSH + HCl$$
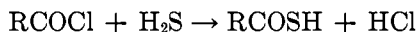
gas is passed into anhydrous pyridine and the mixture treated in the cold with the acid chloride. The method requires that external cooling be applied to avoid high temperatures. Yields of the order of 60–65 per cent are obtainable when the pyridine is anhydrous, the stream of hydrogen sulfide rapid, and the stirring vigorous. Adipyl chloride has given thioadipic acid when the reaction mixture is kept at 10°C. (675). An alternate route to thioacids from acid chlorides and hydrogen sulfide consists in the ice-temperature reaction in the presence of aluminum chloride. Although frequently applied in the aromatic series, the method has apparently only been used with acetyl and chloroacetyl chlorides (23).

The direct diacylation of hydrogen sulfide

$$2RCOCl + H_2S \rightarrow (RCO)_2S + 2HCl$$
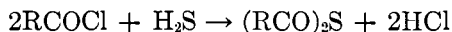
has evidently not been achieved, but like the analogous diacylation of water (Section VII,C) it can be accomplished indirectly through the acid chloride–pyridine adduct. Such a reaction has not been reported for aliphatic acid chlo-

$$RCOCl \cdot C_5H_5N + H_2S \rightarrow (RCO)_2S + C_5H_5NHCl$$

rides, but from benzoyl chloride, pyridine, and hydrogen sulfide at −20°C. in petroleum ether an 85 per cent yield of dibenzoyl sulfide has been obtained (7).

Analogous reactions with hydrogen selenide or telluride have apparently not been observed for aliphatic acid chlorides, but benzoyl chloride has afforded benzyl selenobenzoate after a 31-hr. reaction with hydrogen selenide at 45°C.

in xylene solution and a mixture of dibenzoyl selenide, dibenzoyl diselenide, and benzylidene diselenobenzoate when reacted at room temperature for 4 hr. in the presence of aluminum chloride (679). The latter conditions with phthaloyl chloride have been used to prepare phthaloyl selenide (678).

The reactions of acid chlorides with thiiranes have been characterized by ring cleavage. Acetyl chloride has cleaved ethylene sulfide to 2-chloroethyl thioacetate in chloroform in 82 per cent yield after 30 min. at the reflux temperature (492). With unsymmetrical analogs such as propylene sulfide, however, the so-called abnormal ring opening (yielding derivatives of primary mercaptans) is preferred in contrast to the normal cleavage usually exhibited by acetyl chloride with oxiranes (yielding derivatives of secondary alcohols) (Section XV). Acetyl chloride has rapidly cleaved propylene sulfide to afford 2-chloropropyl thioa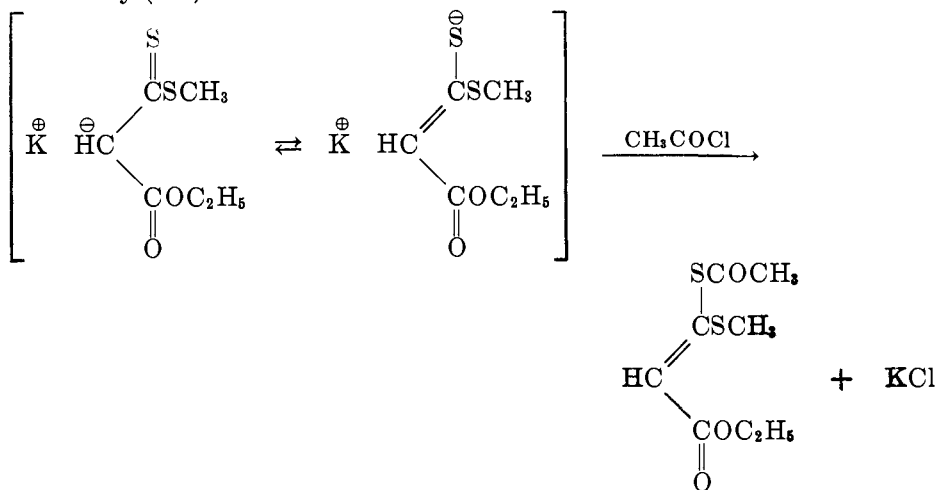cetate quantitatively (abnormal ring opening), whereas acetic anhydride and pyridine have yielded 2-(thiocarbomethoxy)propyl acetate (normal ring opening) (171).

$$
CH_3CH\!-\!CH_2 \underset{S}{\diagdown\diagup}
\quad
\begin{array}{l}
\xrightarrow{\ CH_3COCl\ } \quad CH_3CHClCH_2SCOCH_3 \\
\qquad\qquad\qquad\qquad \text{2-Chloropropyl thioacetate} \\[1em]
\xrightarrow[C_5H_5N]{(CH_3CO)_2O} \quad CH_3CHCH_2OCOCH_3 \\
\qquad\qquad\qquad\qquad\quad |\\
\qquad\qquad\qquad\qquad SCOCH_3 \\
\qquad\qquad\qquad \text{2-(Thiocarbomethoxy)-} \\
\qquad\qquad\qquad\qquad \text{propyl acetate}
\end{array}
$$
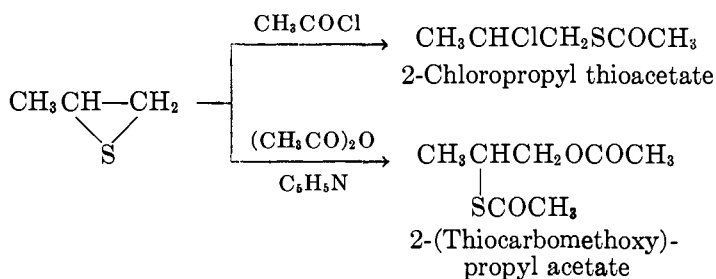
The abnormal ring opening has been attributed to the **tendency of thiiranes to** form onium ions more readily than oxiranes do.

Although numerous examples are not available to illustrate the point, the reaction of acid chlorides with alkali salts of thioesters apparently tends to afford *S*-acylation and not *C*-acylation as in the case with the oxygen analog, malonic ester. Acetyl chloride has been reported to react with *O*-ethyl *S*-methyl potassiodithiomalonate in ether to yield ethyl 3-acetyl-3-methylthiothioacrylate exclusively (426).

$$
\left[
\begin{array}{c}
\overset{\displaystyle S}{\underset{\displaystyle \|}{}}\\
\overset{\ominus}{K}\ \ \overset{\ominus}{HC}\!\diagup^{\!CSCH_3}\diagdown_{COC_2H_5}\\
\underset{O}{\|}
\end{array}
\ \rightleftarrows\
\begin{array}{c}
\overset{\ominus}{\underset{\displaystyle |}{S}}\\
\overset{\oplus}{K}\ \ \overset{\oplus}{HC}\!\diagdown^{\!CSCH_3}\diagdown_{COC_2H_5}\\
\underset{O}{\|}
\end{array}
\right]
\xrightarrow{\ CH_3COCl\ }
$$

$$
\begin{array}{c}
SCOCH_3\\
|\\
HC\!\diagup^{\!\overset{\displaystyle CSCH_3}{}}\diagdown_{COC_2H_5}\\
\underset{O}{\|}
\end{array}
\quad + \quad KCl
$$

The same reaction in benzene in the presence of magnesium, however, has given a product corresponding to the formula $C_{14}H_{16}O_6S_2$, for which the structure

$$CH_3CO \diagdown \quad S \quad \diagup COOC_2H_5$$
$$\quad\quad C \quad\quad C$$
$$C_2H_5OOC \diagup \quad S \quad \diagdown COCH_3$$

has been given.

With respect to reactions of aliphatic acid chlorides with tetracovalent sulfur compounds relatively little has been reported. Chlorosulfonic acid gives products which depend upon the chain length of the acid chloride and the temperature of the reaction. Acetyl chloride at 20° and 45°C. has given sulfoacetic acid; at 60° and 100°C. methionic acid; and at 140°C. 2-methyl-1,4-pyrone-6-acetic acid (412, 415). These products were assumed to be formed as follows:

$$CH_3COCl \;+\; ClSO_3H \;\rightarrow\; CH_3COOSO_2Cl \;+\; HCl$$

$$CH_3COOSO_2Cl \;\xrightarrow[\text{above 45°C.}]{\text{rearranges}}\; HO_3SCH_2COCl$$

$$HO_3SCH_2COCl \;+\; H_2O \;\rightarrow\; HO_3SCH_2COOH \;+\; HCl$$
$$\text{Sulfoacetic acid}$$

$$HO_3SCH_2COCl \;+\; ClSO_3H \;\xrightarrow{\text{above 60°C.}}$$
$$HO_3SCH_2SO_2Cl \;+\; CO_2 \;+\; HCl$$

$$HO_3SCH_2SO_2Cl \;+\; H_2O \;\rightarrow\; CH_2(SO_3H)_2 \;+\; HCl$$
$$\text{Methionic acid}$$

$$4CH_3COCl \;\xrightarrow[\text{temperature}]{\text{high}}$$

$$OC(CH_3)=CHC=O$$
$$\quad\quad C=CH \quad + \; 3HCl \;+\; H_2O$$
$$\quad\quad CH_2COCl$$

$$OC(CH_3)=CHC=O$$
$$\quad\quad C=CH \quad + \; 4HCl$$
$$\quad\quad CH_2COOH$$

2-Methyl-1,4-pyrone-6-acetic acid

Propionyl chloride has given with chlorosulfonic acid a mixture consisting of the δ-lactone of 5-hydroxy-2,4-dimethyl-3-ketoheptanoic acid (I) and a little 2-sulfo-
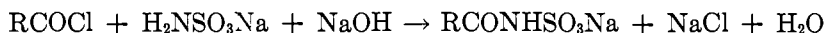
propionic acid after 5–10 days (413). The products were presumed to arise through the following reactions:

$$CH_3CH_2COCl + HO_3SCl \rightarrow CH_3CH_2COOSO_2Cl + HCl$$

$$CH_3CH_2COOSO_2Cl \rightarrow CH_3CH(SO_3H)COCl$$

$$CH_3CH(SO_3H)COCl + H_2O \rightarrow CH_3CH(SO_3H)COOH + HCl$$

<div align="right">2-Sulfopropionic acid</div>

$$3CH_3CH_2COCl + 2ClSO_3H \rightarrow 4HCl +$$

$$CH_3CH_2COOSO_2CH(CH_3)COOSO_2CH(CH_3)COCl \xrightarrow{\ -2SO_3\ }$$

$$CH_3CH_2COCH(CH_3)COCH(CH_3)COCl \rightleftarrows$$

$$CH_3CH_2C(OH){=}C(CH_3)COCH(CH_3)COCl \rightarrow$$

$$CH_3CH_2C{=}C(CH_3)COCHCH_3 + HCl$$

with the ring: O——CO

<div align="center">I</div>
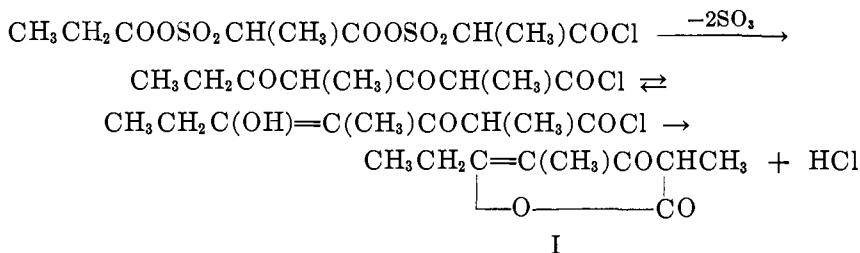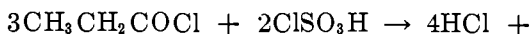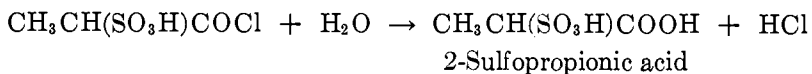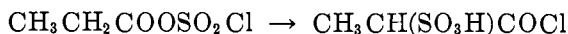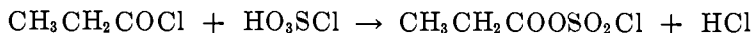
Butyryl chloride has given dipropyl ketone with chlorosulfonic acid with evolution of carbon monoxide and hydrogen chloride (414), but no 2-sulfobutyric acid could be obtained.

The acylation of aminosulfonic acid has been reported. Palmitoyl chloride has been used to acylate its amino group in pyridine solution to give a product whose sodium salt has been employed as a wetting agent (339). Evidently a Schotten–Baumann acylation of sodium aminosulfonate is also possible.

$$C_{15}H_{31}COCl + C_5H_5N + H_2NSO_3H \rightarrow C_{15}H_{31}CONHSO_3H + C_5H_5NHCl$$

$$RCOCl + H_2NSO_3Na + NaOH \rightarrow RCONHSO_3Na + NaCl + H_2O$$
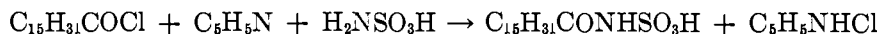
The formation of mixed sulfonic-carboxylic anhydrides from sulfonic acids or their salts and aliphatic acid chlorides does not seem to have been reported.

$$RCOCl + R'SO_3H \rightarrow RCOOSO_2R' + HCl$$

$$RCOCl + R'SO_3Na \rightarrow RCOOSO_2R' + NaCl$$
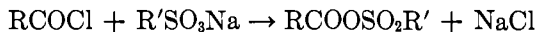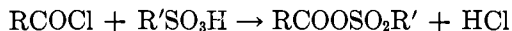
Unique reactions have been observed for acetyl and chloroacetyl chlorides with dimethyl sulfate and sulfuryl chloride. At 140–150°C. in the presence of zinc chloride a 20–25 per cent yield of dimethyl sulfoacetate has been claimed (437) from acetyl chloride and dimethyl sulfate. Fluoroacetyl chloride and a 100 per cent excess of sulfuryl chloride have reacted at 150–160°C. to afford a 50 per cent yield of methyl chlorofluoroacetate (272).

Reactions with organic arsenic compounds have been confined to aromatic arsines and chloroarsines of the types R_2AsH, $RAsCl_2$, R_2AsCl, R_2AsCN, and R_3As, and to one isolated type $RAsCl_4$ with acetyl and chloroacetyl chlorides, usually in the presence of anhydrous aluminum chloride. These reactions have been collected in table 29. Since CH_3CO- or CH_2ClCO- groups always replace

TABLE 29

Reaction of acetyl and chloroacetyl chlorides with various aromatic arsines

ARSENIC COMPOUND		REACTION PRODUCT OBTAINED FROM					
		Acetyl chloride			Chloroacetyl chloride		
		Formula	Yield	Reference	Formula	Yield	Reference
			per cent			*per cent*	
$(C_6H_5)_2AsH$		$(C_6H_5)_2AsCOCH_3$		(666)	$(C_6H_5)_2AsCl$		(666)
$C_6H_5AsCl_2$	$(AlCl_3)$	$C_6H_5COCH_3$	50	(464)	$C_6H_5COCH_2Cl$	55	(464)
$4\text{-}NO_2C_6H_4AsCl_2$	$(AlCl_3)$	$4\text{-}NO_2C_6H_4COCH_3$	65	(464)	$4\text{-}NO_2C_6H_4COCH_2Cl$	60	(464)
$4\text{-}ClC_6H_4AsCl_2$	$(AlCl_3)$	$4\text{-}ClC_6H_4COCH_3$		(464)			
$(C_6H_5)_2AsCl$	$(AlCl_3)$	$C_6H_5COCH_3$	63	(464)	$C_6H_5COCH_2Cl$		(464)
$(C_6H_5)_2AsCN$	$(AlCl_3)$	$C_6H_5COCH_3$	25	(464)			
		$CH_3COCOOH$					
$C_6H_5AsCl_4$	$(AlCl_3)$	$C_6H_5COCH_2Cl$	35	(464)			
$C_6H_5AsO(OH)_2$	$(AlCl_3)$	C_6H_5Cl, As_2O_3		(464)			
$(C_6H_5)_3As$	$(AlCl_3)$	$(C_6H_5)_2AsCOCH_3$		(666)	$(C_6H_5)_2AsCl$		(666)

arsenic in the arsine (except with benzenearsonic acid), it has been suggested that such decompositions be used for the identification of unknown substituted aromatic arsines (464).

Almost all that has been reported concerning the reaction of aliphatic acid chlorides with organic phosphorus compounds consists of reactions with phosphorous acid esters or their thio derivatives. With the former acid chlorides have been observed to undergo the Arbuzov reaction (19), affording the diesters of ketophosphonic acids at ordinary temperatures. It has been assumed that this reaction occurs through the rearrangement of a pentavalent phosphorus intermediate.

$$RCOCl + P(OR')_3 \rightarrow RCOP(OR')_3Cl \rightarrow RC\overset{O}{\overset{\|}{O}}P(OR')_2 + R'Cl$$

With unsaturated aliphatic acid chlorides products have been obtained which after polymerization with peroxides have been found useful as plasticizers, oil additives, or stabilizers (195). The phosphorous thioesters, however, do not

TABLE 30

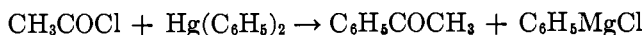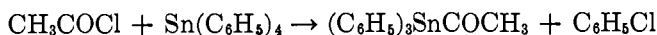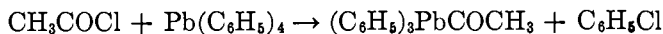*Reactions of aliphatic acid chlorides with organic phosphorus compounds*

ACID CHLORIDE	PHOSPHORUS COMPOUND	PRODUCTS (YIELD)	REFERENCES
Acetyl........	$P(OR)_3$ (R = CH_3, C_2H_5)	$CH_3COP(OR)_2$ (67%)	(19, 195)
	$(C_2H_5S)_3P$	$(C_2H_5S)_2PCl$, $CH_3COSC_2H_5$	(186)
	$(C_6H_5S)_3P$	$(C_6H_5S)_2PCl$, $CH_3COSC_6H_5$	(186)
	$(C_2H_5S)_2PCl$	$C_2H_5SPCl_2$, $CH_3COSC_2H_5$	(186)
	$C_2H_5SPCl_2$	$CH_3COSC_2H_5$, PCl_3	(186)
	$(C_2H_5S)_3PO$	$(C_2H_5S)_2POCl_2$ (40%), $CH_3COSC_2H_5$ (66%)	(186)
Methacrylyl...	$(C_2H_5O)_3P$	$[(C_2H_5O)_2POCOC(CH_3)=CH_2]_x$ (59%)	(195)

undergo a similar Arbuzov reaction. With these materials acid chlorides afford products of the type $(RS)_2PCl$ and RSCOR only. The general reaction may be written as

$$RCOCl + (R'S)_3P \rightarrow (R'S)_2PSR'COR(Cl) \rightarrow (R'S)_2PCl + R'SCOR$$
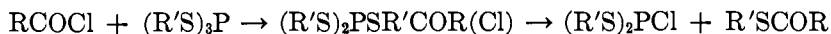
and the difference in mode of reaction may be attributed to the tendency of sulfur to form onium ions more readily than phosphorus does. Examples of reactions with phosphorous and thiophosphorous esters are given in table 30.

The reaction of triphenylphosphine and acetyl chloride in the presence of anhydrous aluminum chloride, unlike that of triphenylarsine, apparently does not split off a phenyl group, but tetraphenyllead and tetraphenyltin each lose one phenyl group, and diphenylmercury is converted to acetophenone smoothly (463).

$$CH_3COCl + Pb(C_6H_5)_4 \rightarrow (C_6H_5)_3PbCOCH_3 + C_6H_5Cl$$

$$CH_3COCl + Sn(C_6H_5)_4 \rightarrow (C_6H_5)_3SnCOCH_3 + C_6H_5Cl$$

$$CH_3COCl + Hg(C_6H_5)_2 \rightarrow C_6H_5COCH_3 + C_6H_5MgCl$$

Triethylphenylsilane, $C_6H_5Si(C_2H_5)_3$, exhibits a comparable behavior in the presence of anhydrous aluminum chloride. In the cold 72 and 62 per cent yields of acetophenone and butyrophenone, respectively, have been obtained from acetyl and butyryl chlorides (188).
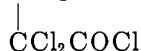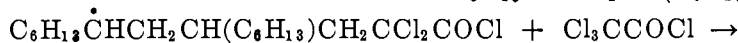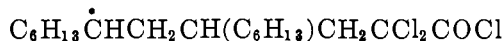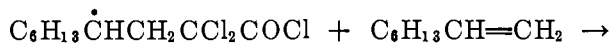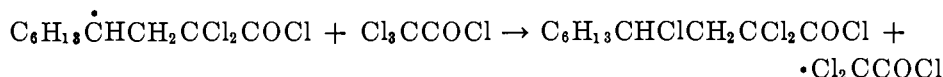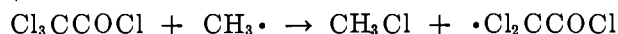
XXI. REACTIONS (NON-FRIEDEL–CRAFTS TYPE) OF ALIPHATIC ACID CHLORIDES WITH COMPOUNDS CONTAINING DOUBLE OR TRIPLE BONDS

In addition to reactions with aromatic hydrocarbons, olefins, acetylenes, and saturated hydrocarbons under Friedel–Crafts conditions (Section XIII), there have been reported reactions of aliphatic acid chlorides with unsaturated compounds which proceed without the presence of aluminum chloride or similar catalysts. One group of these are initiated by peroxides and proceed through free-radical mechanisms.
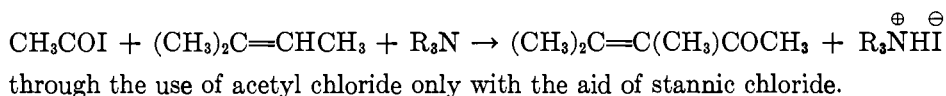
Although examples of peroxide-catalyzed reactions of aliphatic acid chlorides and olefins are not numerous, the reaction of 1-octene with trichloroacetyl chloride in the presence of acetyl peroxide to give an 81 per cent yield of 2,2,4-trichlorodecanoyl chloride (396) is typical of what can be accomplished.
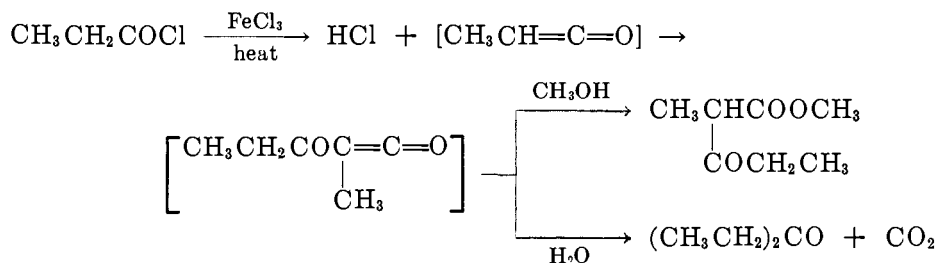
$$CCl_3COCl + C_6H_{13}CH{=}CH_2 \xrightarrow{(CH_3CO)_2O_2} C_6H_{13}CHClCH_2CCl_2COCl$$
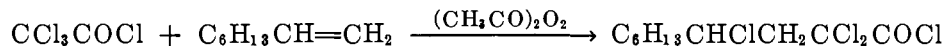
The monoaddition product and other compounds produced in this reaction can be ascribed to the following reaction mechanisms:

$$(CH_3CO)_2O_2 \rightarrow CH_3{\cdot} + CO_2 + CH_3COO{\cdot}$$

$$Cl_3CCOCl + CH_3{\cdot} \rightarrow CH_3Cl + {\cdot}Cl_2CCOCl$$

$$C_6H_{13}CH{=}CH_2 + {\cdot}Cl_2CCOCl \rightarrow C_6H_{13}\overset{\cdot}{C}HCH_2CCl_2COCl$$

$$C_6H_{13}\overset{\cdot}{C}HCH_2CCl_2COCl + Cl_3CCOCl \rightarrow C_6H_{13}CHClCH_2CCl_2COCl + {\cdot}Cl_2CCOCl$$

$$C_6H_{13}\overset{\cdot}{C}HCH_2CCl_2COCl + C_6H_{13}CH{=}CH_2 \rightarrow$$
$$C_6H_{13}\overset{\cdot}{C}HCH_2CH(C_6H_{13})CH_2CCl_2COCl$$

$$C_6H_{13}\overset{\cdot}{C}HCH_2CH(C_6H_{13})CH_2CCl_2COCl + Cl_3CCOCl \rightarrow$$
$$C_6H_{13}CHClCH_2CH(C_6H_{13})CH_2CCl_2COCl + {\cdot}Cl_2COCl$$

$${\cdot}Cl_2CCOCl + {\cdot}Cl_2CCOCl \rightarrow \underset{\underset{CCl_2COCl}{|}}{CCl_2COCl}$$

The direct addition of a saturated aliphatic acid chloride to an olefin without some kind of catalyst does not seem to have been accomplished. Acetyl iodide, however, has been reported to react at 25°C. after 26 days in the dark with 2-methyl-2-butene to give a red oil from which a tertiary amine could remove all the iodine, presumably as hydrogen iodide, and yield a small amount of a dimethylpentenone (670). The same compound could apparently be formed

$$CH_3COI + (CH_3)_2C{=}CHCH_3 + R_3N \rightarrow (CH_3)_2C{=}C(CH_3)COCH_3 + R_3\overset{\oplus}{N}H\overset{\ominus}{I}$$

through the use of acetyl chloride only with the aid of stannic chloride.

Certain strongly polar reagents have caused substitution at the β-carbon atom of 1,1-diarylethylenes: e.g., phosphorus pentachloride (65), oxalyl chloride (67, 395), and thionyl chloride (535) eliminate hydrogen chloride, giving $CR_2=$ $CH \cdot PCl_4$, $CR_2=CHCOCl$, and $CR_2=CHSOCl$, respectively. Certain acyl chlorides have recently been found to react similarly at high temperatures in the absence of a catalyst. Benzoyl, cinnamyl, and phenylacetyl chlorides have reacted in this manner (66), but saturated aliphatic acyl chlorides apparently are not sufficiently stable to react at the elevated temperatures required. Fumaryl chloride, however, when refluxed in dry xylene at 147–149°C. with 1,1-diphenylethylene has afforded a 22 per cent yield of 4-keto-6,6-diphenyl-2,5-hexadienoic acid.

$$ClCOCH=CHCOCl + (C_6H_5)_2C=CH_2 \rightarrow$$

$$(C_6H_5)_2C=CHCOCH=CHCOCl \xrightarrow[\text{(2) } H_2SO_4]{\text{(1) } Na_2CO_3}$$

$$(C_6H_5)_2C=CHCOCH=CHCOOH$$

The triple-bond nitrile group, like the carbonyl and carbalkoxy groups (Sections X, A and X, B), may activate an adjacent methylene group to permit formation of metal derivatives which may afford C-acylation with acid chlorides. The formation of α-acetyl-α-tolunitrile in small yield from benzyl cyanide (96) is illustrative. A similar type of activation can be attributed to the triple

$$CH_3COCl + Na(C_6H_5CHCN) \rightarrow C_6H_5CH(COCH_3)CN + NaCl$$

bond of phenylacetylene, whose potassium derivative has yielded phenylacetylacetylene in small yield (515) with acetyl chloride.

$$CH_3COCl + C_6H_5C\equiv CK \rightarrow C_6H_5C\equiv CCOCH_3 + KCl$$

Addition of a typical acid chloride (acetyl chloride) to the internally activated olefinic unsaturation of a typical acrylonitroalkane, 2-nitro-1-butene, has been accomplished in the absence of added catalyst at 36–43°C. (420). 3-Chloro-

$$RCOCl + CH_2=C(R)NO_2 \rightarrow RCOC(R)NO_2$$
$$\overset{|}{C}H_2Cl$$

methyl-3-nitro-4-pentanone has been obtained in 66 per cent yield after 24 hr.

XXII. Miscellaneous Reactions of Aliphatic Acid Chlorides

A. DEHYDROCHLORINATION

The dehydrochlorination of aliphatic acid chlorides to ketenes in the presence of tertiary amines has already been mentioned (Section VII). Ketenes can also be obtained through the use of other substances. Ferric chloride has afforded

dehydrochlorination of propionyl chloride to give a mixture of products from which propionylpropionic ester and diethyl ketone were obtained (282).

$$CH_3CH_2COCl \xrightarrow[\text{heat}]{FeCl_3} HCl + [CH_3CH=C=O] \rightarrow$$

$$\left[\begin{array}{c} CH_3CH_2COC=C=O \\ | \\ CH_3 \end{array}\right] \begin{array}{l} \xrightarrow{CH_3OH} \begin{array}{c} CH_3CHCOOCH_3 \\ | \\ COCH_2CH_3 \end{array} \\ \\ \xrightarrow[H_2O]{} (CH_3CH_2)_2CO + CO_2 \end{array}$$

Direct pyrolysis of acyl chlorides also results in some dehydrochlorination.

B. PYROLYSIS

The pyrolysis of acid chlorides may yield several types of products. Mixed aromatic-aliphatic acid chlorides frequently evolve carbon monoxide in almost quantitative yield (77), but this reaction is not usually observed with aliphatic types.

$$(C_6H_5)_3CCOCl \xrightarrow{\text{heat}} (C_6H_5)_3CCl + CO$$
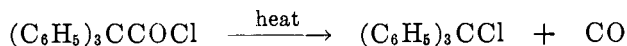
Diphenylacetyl chloride has been reported to give a low yield of diphenylketene upon distillation (656), but acyl chlorides, in general, are not generally used for the preparation of ketenes or their dimers (283).

$$(C_6H_5)_2CHCOCl \xrightarrow{\text{heat}} (C_6H_5)_2C=C=O + HCl$$
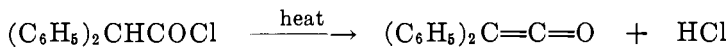
Acetyl chloride, heated at 700–850°C. on a platinum wire, has been reported to give a mixture of ethylene, hydrogen chloride, and carbon monoxide (363), but undoubtedly some ketene is formed simultaneously in this reaction.

$$2CH_3COCl \xrightarrow{700-850°C.} C_2H_4 + 2HCl + 2CO$$
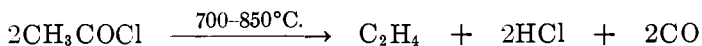
Trichloroacetyl chloride, on the other hand, has given a mixture when pyrolyzed at 600°C. in which carbon tetrachloride was a component (631).

The pyrolysis of higher aliphatic acid chlorides has been only briefly described in the literature. Elimination of hydrogen chloride during distillation has been frequently observed (254). At 250–275°C. palmitoyl chloride, in a current of dry carbon dioxide, has evolved hydrogen chloride and given a compound of the formula $(C_{16}H_{30}O)_3$, presumed to be tristetradecyl ketene on the basis of molecular-weight determination (78). Similarly, at 250–280°C. lauroyl chloride has given a compound said to be $C_{12}H_{22}O$, but in the absence of a molecular-weight determination it is more likely that the product was the dimer (603). Nonanoyl chloride has been dehydrochlorinated almost quantitatively on heating, although the organic products from the reaction were not thoroughly investigated.

The pyrolysis of carboxyacetyl chloride has afforded carbon monoxide, hydrogen chloride, acetyl chloride, and polymerized solid material assumed to have been derived from ketene through further reactions (661).

<div align="center">C. REARRANGEMENT</div>

The existence of ring–chain tautomerism in the diacyl chlorides of certain dibasic acids has been well established. The diacyl chlorides of phthalic and succinic acids, for example, exhibit typical tautomeric properties which are represented by the equilibrium between the two structures I and II, where A and B are Cl. The occurrence of similar tautomeric properties in the acid chlorides of the half-esters of dibasic acids, e.g., I ⇄ II, where A is OR and B is Cl, has not hitherto been generally recognized, although there is considerable experimental evidence which can only be interpreted satisfactorily on the basis of the existence of such tautomeric forms. Systems in which A and B are not identical differ from those of the diacid chlorides of dibasic acids in that, provided the molecule of the parent dicarboxylic acid is itself dissymmetric by the possession of some structural feature which will differentiate the atoms C^a and C^b, the cyclic tautomeride (II) now allows ring fission to occur with formation of a second open-chain form (III) and also a second ring form (IV).
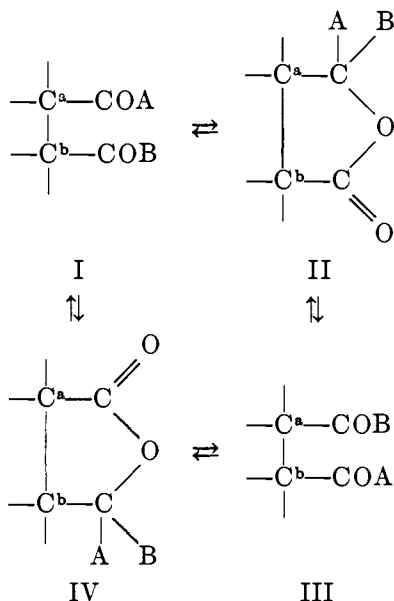
The experimental proof of existence of the two tautomers I and II in the acid chlorides of dibasic acids depends largely on evidence obtained from the chemical reactions of these two forms which lead to fundamentally different structures, but in the series of acid chlorides of the half-esters it is possible to utilize the reactions of the isomeric open-chain forms I and III. Failure to recognize the existence of this type of tautomerism has led in the past to much confusion,

and a number of reactions in which such half-ester acid chlorides have been used require reinvestigation. Any investigation of such reactions depends in the first instance upon unambiguous preparative methods both for the half-ester acid and for the half-ester acid chloride.

A typical example of such a rearrangement is involved in the report that 2-butyl-2-ethyl-4-carbomethoxybutyryl chloride and 4-ethyl-4-carbomethoxy-octanoyl chlorides both give poor yields of the same tribromoanilide with tri-bromoaniline, evidently that of the former (134). A considerable number of other examples of similar rearrangements of aliphatic, aromatic, and aliphatic-aromatic acid chlorides has been given (144).

The absence of evidence for the rearrangement of acid chlorides of the half-esters of substituted isophthalic acid and terephthalic acid suggests that the change is intramolecular rather than intermolecular and involves a cyclic inter-mediate. It is possible to visualize three types of intermediate: (a) the anhydride of the dicarboxylic acid, (b) an oxonium chloride, and (c) an alkoxychlorolactone. An oxonium salt has been suggested (554) as an intermediate in the closely

(a)   (b)   (c)
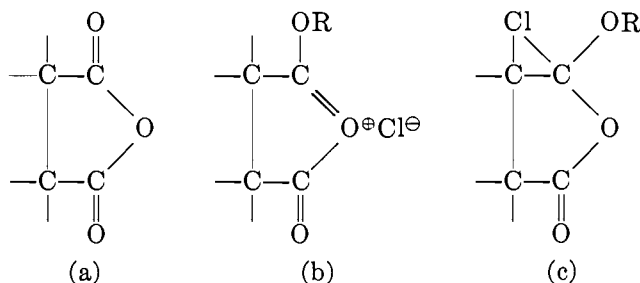
related isomerization of 4-ethoxybutyryl and 5-ethoxyvaleryl chlorides to ethyl 4-chlorobutyrate and ethyl 5-chlorovalerate, respectively. The lactone inter-mediate has been suggested for specific examples of interchange between half-ester and acid halide (292, 599) and appears more probable, however.

The acid chlorides of certain acetyl derivatives of α-hydroxy acids behave in some respects as though they were cyclic acetals (II) and not simple acid chlo-rides (I) (52), especially in reactions with organozinc derivatives and in those of the Friedel–Crafts type.
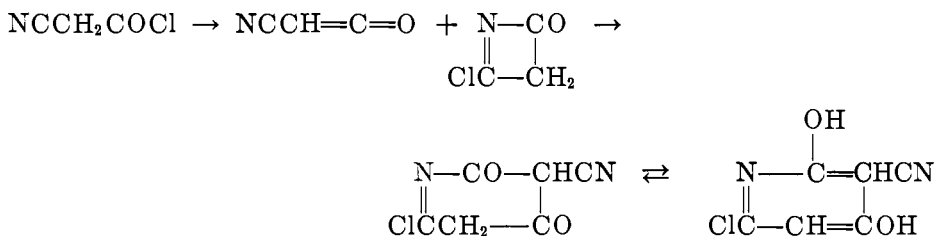

I   II
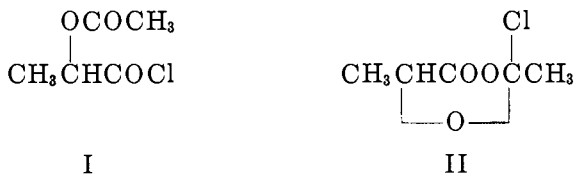
Halogen interchanges in haloacyl chlorides would appear to be possible, but examples of such rearrangements are not common. Fluoroacetyl chloride, pre-pared from sodium fluoroacetate and phosphorus pentachloride in 83 per cent yield (692), does not exhibit significant fluorine and chlorine interchange.

D. POLYMERIZATION

The acetyl peroxide-initiated free-radical polymerization of acid chlorides to succinyl chloride derivatives has already been mentioned (Section XII,A), as has the formation of polymeric material through the reaction of acid chlorides with tertiary amines (Section VII,C) or with zinc (Section XIX,B), the former through ketenes and the latter through diacyl intermediates.

The spontaneous polymerization of cyanoacetyl chloride has been shown to produce a yellow resin consisting chiefly of 6-chloro-2,4-dihydroxy-3-nicotino-nitrile (617), and has been assumed to follow the course:

$$NCCH_2COCl \rightarrow NCCH{=}C{=}O \ + \ \begin{array}{c} N{-}CO \\ \| \quad | \\ ClC{-}CH_2 \end{array} \rightarrow$$

$$\begin{array}{c} N{-}CO{-}CHCN \\ \| \qquad | \\ ClCCH_2{-}CO \end{array} \rightleftarrows \begin{array}{c} \qquad\ OH \\ \qquad\ | \\ N{-}\!\!-C{=}CHCN \\ \| \qquad | \\ ClC{-}CH{=}COH \end{array}$$

The product is an intermediate in the synthesis of the natural alkaloid ricinine.

"Pour depressants" for waxy mineral lubricating oils have been prepared by copolymerizing 3–5 moles of a fatty acid chloride such as stearoyl chloride and 1 mole of an aromatic acid chloride such as benzoyl chloride at 400–700°F. for 2.5–24 hr. to give products of average molecular weight 500–1200 (best 600–800) (441). After heating to eliminate all the hydrogen chloride evolved, extracting with tetrachloroethane, filtering, and vacuum distilling to remove a low-boiling fraction, the oil-soluble materials are applicable for this purpose in 0.1–5 per cent concentrations.

E. MISCELLANEOUS

Various other applications to which aliphatic acid chlorides, particularly acetyl chloride, have been put demonstrate the utility of these compounds as acidic reaction catalysts, esterification promoters, or dehydrating agents.

2,3,6-Trimethylglucose in methyl orthoformate and methanol has been converted to methyl glucoside even at 20°C. in the presence of acetyl chloride, while the use of hydrogen chloride instead of acetyl chloride affords a decrease in the yield of product (226). Acetyl, stearoyl, and thionyl chlorides have been used as catalysts in the esterification of veratric, p-nitrobenzoic, and stearic acids with methanol or ethanol at 20°C., with excellent results (227). With 2 g. of veratric acid in 40 ml. of methanol containing 0.3 g. of acetyl chloride the methyl ester could be obtained in good yield in 24 hr. at 20°C., whereas 0.3 g. of hydrogen chloride under the same conditions gave none at all. The general method has been applied to the esterification of acetic, lactic, glutacuronic, benzoyl-DL-alanine and certain proteins with various alcohols, using 30–50 equivalents of the catalyst per 10^4 g. of protein (220).

Several acyl chlorides have been studied as catalysts in the Beckmann rear-

rangement of oximes (418, 419). The rate of rearrangement in each instance has depended upon the strength of the acid from which the acid chloride was derived, the strong acid chloride causing more rapid rearrangement (judged by the per cent of substituted amide produced in equal time periods) in the order $C_6H_5SO_2Cl > CH_2ClCOCl > C_6H_5COCl > CH_3COCl$.

In the Friedel–Crafts alkylation of benzene with propylene some success has been achieved with the use of solid complexes of acetyl and aluminum chlorides as catalysts (612).

The nitration of acetanilide and dimethylaniline with nitric acid has been improved by the addition of acetyl chloride as a dehydrating agent (148). The yield of nitro derivatives is increased somewhat, and with the latter the yield of *o*-nitro compound is increased at the expense of the para derivative. In the nitration of thiophenes the yield of nitro derivatives has been claimed to be quadrupled if acetyl chloride is added to the nitrating mixture of acetic anhydride and nitric acid (147).

In view of what has been pointed out already (Section XVI) it is not surprising that the addition of acid chlorides to fatty acids greatly speeds up the direct chlorination of the latter even in the absence of a halogen-carrying catalyst (623).

Acetyl, propionyl, and fumaryl chlorides have been applied as polymerization inhibitors for organic isocyanates or diisocyanates when used in concentrations of 0.3–5 per cent (712).

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