ESTERS OF CARBAMIC ACID

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Received January 4, 1965

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I. INTRODUCTION

The adaptation to an industrial scale of one of the earliest preparations of the then new science of organic chemistry, Wohler's (210) preparation in 1840 of ethyl carbamate, $H_2NCOOC_2H_5$ (I), from urea and ethanol, has stimulated renewed interest in the properties of ethyl carbamate.

The esters of carbamic acid exhibit some of the characteristic properties of carboxylic esters and amides. Some of their reactions are those of esters, amides, enols, and apparently of cyanic acid. Carbamic acid itself has not been isolated.

The roster of chemists who have investigated carbamate esters through the years includes many notable organic chemists of their day.

II. SCOPE OF THE REVIEW

This review will be limited to a discussion of the properties of simple carbamate esters. Cyclic carbamates (*i.e.*, oxazolidones) have been discussed elsewhere (85). Polyurethans and isocyanates have been amply covered in other review articles (12). N-Substituted carbamates and thiocarbamate esters have not been stressed but are included only to maintain the continuity of the discussion of carbamates (215).

The literature, including *Chemical Abstracts* and readily available periodicals, has been reviewed through October 1964. Included in this work are unpublished contributions from our laboratory.

III. NOMENCLATURE

Chemical Abstracts nomenclature has been generally followed throughout this article. In the phrase, "alkyl carbamate," alkyl refers to the O-alkyl (or the alcohol-derived moiety). All nitrogen-substituted carbamates will bear the notation (N-alkyl) carbamate; thus, ethyl N-phenylcarbamate is $C_6H_5NHCOOC_2H_5$.

The historic term "urethan" has been pre-empted by

the class of polymers, "polyurethans." We have rarely used this term in reference to ethyl carbamate.

IV. Physical Properties

Ethyl carbamate (I), long known as "urethan," is a white solid, m.p. 48.19°, b.p. 185.25° (760 mm.), d^{48}_4 1.0599, $n^{52}D$ 1.41439. It sublimes, absorbs moisture, and is soluble in lower alcohols, ketones, ethers, esters, chlorinated hydrocarbons, and water. It is partially soluble in aromatic hydrocarbons and insoluble in aliphatic hydrocarbons.

Methyl carbamate (II), "urethylan," is a white solid which melts at 54.2° and boils at 177° (760 mm.), $d^{55.9}_4$ 1.1358, $n^{56.6}D$ 1.41253. Heats of formation (for I, 397.5 cal./mole) (290), latent heats of fusion, heats of solution (for I, −15.9° at 23°) (141), solvent characteristics (320), vapor pressures, and other physical properties of ethyl and methyl carbamate have been studied (180).

The solvent characteristics of ethyl carbamate are enhanced by the addition of methyl carbamate. A eutectic mixture of 52% ethyl carbamate–48% methyl carbamate, m.p. 13–17°, with a dielectric constant (ϵ = 20 at 25°) comparable to that of acetone or 1-propanol, dissolves most classes of organic liquids except aliphatic hydrocarbons (45). Table I lists various eutectic mixtures.

Table I

Eutectic Mixtures of Carbamates (46)

Carbamate	% in mixture	2nd (carbamate) component	Equil. f.p., °C.
Ethyl	64	Isopropyl	38
	61.1	2-Ethylbutyl	34
	62	*n*-Propyl	32
	35	2-Ethylhexyl	12
	47	2-Ethylhexyl	14
	68	*n*-Amyl	18.5
	57	*n*-Butyl	22.5
	46	*n*-Butyl	22
	76	Isobutyl	36
	88	Dodecyl	43
Methyl	94	Dodecyl	53
	60	Isopropyl	30
	36	2-Ethylhexyl	18
	65	2-Ethylbutyl	40
	45	*n*-Butyl	19
	51	Isobutyl	17
	49	*n*-Propyl	18
	28	*n*-Amyl	35
	62	*n*-Amyl	33
Isopropyl	24	2-Ethylhexyl	20
	30	*n*-Propyl	42
Isobutyl	36	*n*-Propyl	47
	39	2-Ethylhexyl	14
Propyl	33	2-Ethylhexyl	15
sec-Butyl	23	2-Ethylhexyl	21
n-Butyl	65	*sec*-Butyl	37
4-Methylpentyl	46	2-Ethylbutyl	47
n-Amyl	26	2-Methylpentyl	33
2-Ethylbutyl	22	2-Methylpentyl	35

Table II

Melting Points of N-Unsubstituted Carbamates

Carbamates	M.p. °C.
Allyl	22
Isoamyl	59
n-Amyl	55.5
Isobutyl	55
n-Butyl	53
sec-Butyl	94
$C_{22}H_{45}$	96–97
Ethyl	48.19
1-Ethylamyl	45–46
1-Ethylpropyl	110
2-Ethylbutyl	82–83
2-Ethylhexyl	42.5
n-Hexyl	59–61
Lauryl	81–82
Methyl	54.2
2-Methylbutyl	49–51
n-Octyl	67
Isopropyl	95
n-Propyl	60
n-Stearyl	94–95

Carbamates of higher alcohols are well-defined crystalline solids having melting ranges which are always higher than the corresponding acetates. As is the case of fatty esters, the higher fatty alcohol carbamates are waxy. Table II lists the carbamates with no substituent on the nitrogen atom.

Infrared Spectra of Carbamates. The major infrared absorption region of the carbamates is the carbonyl region. In absorption of infrared, the ester aspect predominates over the amide aspect of carbamate. The carbonyl band absorbs in the ester rather than the amide region, and many carbamates share with esters what appears to be a –C–O–C– stretching pattern in the 1050–1000-cm.$^{-1}$ region.

However, the amide II band is found in its normal position in monosubstituted and unsubstituted carbamates; *i.e.*, in ethyl carbamate it is 1618 cm.$^{-1}$. The N–H stretch absorption band for solid carbamates is in the same position as in open-chain amides, 3300–3250 cm.$^{-1}$. The carbonyl groups of N-unsubstituted carbamates absorb at 1725 ± 3 cm.$^{-1}$, monosubstituted carbamates at 1714 ± 4 cm.$^{-1}$ (both as solids and chloroform solutions) (268). Lower carbamates often exhibit skeletal bands between 850 and 900 cm.$^{-1}$.

V. Methods of Analysis

Unsubstituted carbamates can be assayed readily, but substituted carbamates defy simple chemical assay. Nonchemical approaches to the assay of substituted carbamates have thus received increased attention in recent years.

The titrimetric determination of unsubstituted carbamates involves, as a preliminary step, treatment with (a) acid or (b) alkali.

(*a*). Acid hydrolysis, with subsequent analysis for

ammonia, is preceded by complete destruction of organic matter or partial destruction with sulfuric acid (280) or by prolonged treatment with hydrochloric acid. The ammonia content is then determined by distillation or formal titration (U.S.P.). A recent procedure which uses excess perchloric acid in acetic acid as a hydrolytic medium, followed by a back-titration with an amine, could not be corroborated (119).

(*b*). Aqueous alkaline hydrolysis, followed by an analysis for ammonia gives inconsistent and inconclusive results (281). Earlier, Werner pointed out that when a carbamate is treated with aqueous alkali, a mixture of alkali cyanate and, subsequently, alkali carbonate results (354).

The rate of conversion of cyanate to carbonate is inhibited by excess alkali.

$$ROCONH_2 + KOH \rightarrow ROH + KOCN + H_2O \quad \text{(Eq. 1)}$$

$$KOCN + KOH + H_2O \rightarrow K_2CO_3 + NH_3 \quad \text{(Eq. 2)}$$

$$KOCN + 2H_2O \rightarrow KHCO_3 + NH_3 \quad \text{(Eq. 3)}$$

To avoid the inconsistent results of ammonia determination, alkaline treatment followed by a determination of the alcohol content rather than ammonia has been employed. The alcohols in such a procedure are usually separated by distillation and oxidized with potassium dichromate (11, 35, 287). This procedure is generally applicable to the carbamates derived from lower alcohols. Recently, by using sodium alkoxide in a nonaqueous medium, it was found possible to restrict the alkaline hydrolyses to the cyanate state (see Eq. 1) (352).

Thus, unsubstituted carbamates can be quantitatively converted to sodium cyanate by refluxing with sodium methoxide in the presence of pyridine. Titration of the cyanate with benzoic acid in anhydrous methanol–benzene to a thymol blue end point completes the procedure (74).

Equally good results are obtained by the use of 0.5 *N* anhydrous alcoholic potassium hydroxide as base. The small amounts of water present in the potassium hydroxide, or formed during the reaction, do not convert cyanate to carbonate in amounts sufficient to interfere. Under these conditions, the potassium cyanate precipitates as it forms, affording a convenient method of preparing pure potassium cyanate free from carbonate. Titration of the sodium cyanate to a phenolphthalein end point is conveniently accomplished with aqueous hydrochloric acid (352).

The assay of N-substituted carbamates is probably best accomplished by the Kjeldahl procedure, while some N-hydroxycarbamates require the use of a reductive Kjeldahl method.

A method of determining unsubstituted carbamates to within an error of ±0.5% consists of heating the carbamate in 5% aqueous sodium hydroxide in the presence of Raney nickel containing 3–4% aluminum. Ammonia thus liberated is titrated with acid. Substituted carbamates cannot be determined in this manner (329).

Recently a determination of a complex carbamate utilizing n.m.r. spectroscopy has been reported (303).

VI. SYNTHESIS OF CARBAMATES

Of all the preparative methods evolved during the long history of carbamate chemistry, only three have reached any commercial importance. They are: (a) the reaction of urea with an alcohol

$$H_2NCONH_2 + ROH \rightarrow H_2NCOOR + NH_3 \quad \text{(Eq. 4)}$$

(b) the amination of an alkyl chloroformate

$$ROCOCl + 2R'NH_2 \rightarrow ROCONHR' + R'NH_3Cl \quad \text{(Eq. 5)}$$

and (c) the transesterification of an alkyl carbamate with a higher boiling alcohol

$$ROCONH_2 + R'OH \rightarrow R'OCONH_2 + ROH \quad \text{(Eq. 6)}$$

A. REACTION OF ALCOHOLS WITH UREA

Although not the oldest, or most popular, from a laboratory standpoint, the urea method is the preferred commercial route to methyl or ethyl carbamate (67, 69, 172, 354).

Hofmann (172) and later workers studied the preparation of ethyl carbamate by heating ethanol with urea under pressure at 150°. Because a temperature of 150° was necessary for the optimum dissociation of urea to the reactive intermediates, cyanic acid and ammonia, only those alcohols boiling above 140–150° gave good yields of carbamate esters (185, 203, 229). For example, a 75% yield of butyl carbamate was obtained when urea and 4 moles of butanol were refluxed at 115–120° for 40 hr. (95).

Here matters stood until Paquin (260) in 1946 reported the catalytic effect of various metal salts upon the rate of reaction of an alcohol with urea. By using heavy metal salts of weak organic acids, or zinc and cobalt chlorides, alkyl carbamates were obtained in yields of 90% or better with much shorter heating cycles. Strong mineral acids gave completely different materials (viscous oils). In the absence of catalyst, 3 moles of isobutyl alcohol per mole of urea, when refluxed 150 hr. at 108–126°, gave a 49% yield of the carbamate. Lead acetate or cobalt chloride lowered the time of reaction of 75 hr. and raised the yield of 92%.

Butyl carbamate was produced on a commercial scale by using a much smaller excess of butanol and catalytic quantities of cupric acetate. This permitted the reaction to be run in a shorter time, at higher temperatures and atmospheric pressure (36).

From a commercial standpoint, however, the employment of butyl carbamate in transesterification reactions suffers from two drawbacks: the high molecular weight of the butyl group and the instability of butyl carbamate during distillation.

A reinvestigation of the reaction of methyl and ethyl alcohol with urea led to the finding that in order to obtain good yields, ammonia had to be separated from methanol by fractionation. Although anhydrous systems were used, the unanticipated formation and sublimation of ammonium carbamate led to clogged condensers and vent lines during the separation of ammonia from alcohol under pressure. Large-scale manufacture of methyl and ethyl carbamate from urea was successful only after it was found that by heating the condenser and exit lines just above the dissociation temperature of ammonium carbamate both NH_3 and CO_2 were successfully vented as gases (39). Temperatures above 140° had to be attained and the ammonia separated from the system. This could be accomplished by operating at 6–7 atm. pressure and by employing a fractionating column to separate the ammonia from the methanol or ethanol (39).

Urea and excess alcohol do not react further to form a dialkyl carbonate and 2 moles of ammonia under normal conditions (185).

$$H_2NCONH_2 + C_2H_5OH \rightarrow C_2H_5OCONH_2 + NH_3$$

$$C_2H_5OCONH_2 + C_2H_5OH \not\rightarrow (C_2H_5O)_2CO + NH_3$$

The use of BF_3 to capture the ammonia and remove it from the reaction zone has been patented by Sowa (313). Either ethyl carbamate or diethyl carbonate could be formed depending upon the mole ratio of BF_3 to urea. The cost of a full mole of BF_3 makes this method unattractive.

A urea–water system for the preparation of carbamates has also been described. This system is not practical owing to the formation of large amounts of ammonium carbamate from the hydrolysis of urea (278). The reaction of urea with alcohols to form carbamates fails when tertiary alcohols, phenols, or urea-reactive groups are present.

In the foregoing reactions of an alcohol with urea to form the alkyl carbamate and ammonia

$$ROH + H_2NCONH_2 \rightarrow H_2NCO_2R + NH_3$$

alkylation of the nitrogen atom of urea to form an alkylurea and water does not occur.

$$ROH + H_2NCONH_2 \not\rightarrow RNHCONH_2 + H_2O$$

However, in the presence of concentrated sulfuric acid, *t*-butyl alcohol forms a carbonium ion which does alkylate urea to give a 31–33% yield of *t*-butylurea (304a).

$$(CH_3)_3C\text{–}OH + H_2NCONH_2 \xrightarrow[20°]{H_2SO_4} (CH_3)_3CNHCONH_2$$

Carbamates are not formed under these acidic conditions since they would be immediately cleaved (section VIIIB2). The above *t*-butylurea may be hydrolyzed with alkali at 200° to give 71–78% yields of *t*-butylamine (264a).

$$(CH_3)_3CNHCONH_2 + 2NaOH \rightarrow (CH_3)_3CNH_2 + NH_3 + Na_2CO_3$$

N-Substituted ureas could react with alcohols to produce either an alkyl carbamate, an alkyl N-substituted carbamate, or a mixture of these.

$$CH_3NHCONH_2 + ROH \rightarrow \begin{cases} H_2NCO_2R + CH_3NH_2 \\ \text{or} \\ CH_3NHCO_2R + NH_3 \end{cases}$$

Apparently, no studies have been reported on the alcoholysis of mono-N-alkyl- or -N-arylureas. However, diphenylurea undergoes methanolysis to methyl N-phenylcarbamate in the presence of a tin catalyst (3).

B. AMMONOLYSIS OF ALKYL CHLOROFORMATES

The ammonolysis of an alkyl chloroformate is an excellent general laboratory method for the preparation of carbamate esters.

$$ROH + COCl_2 \rightarrow ROCOCl + HCl$$

$$ROCOCl + 2NH_3 \rightarrow ROCONH_2 + NH_4Cl \quad \text{(Eq. 5a)}$$

In the presence of a base, most alcohols react with phosgene to give the chloroformic ester which then can react with ammonia or amines to give the desired carbamate (15, 190, 201, 324). However, for ethyl or methyl carbamate, the urea method is economically more favorable, owing to more favorable weight relationship of urea as compared with phosgene. Thus, assuming 100% yields, 75 lb. of methyl carbamate may be obtained from 60 lb. of urea whereas 109 lb. of phosgene would be required. Moreover, isolation of the product and recycling of the ammonia (Eq. 4) is less costly than separating the carbamate from ammonium chloride (Eq. 5a) and recovering the ammonia.

C. TRANSESTERIFICATION

Prior to 1948, there were isolated examples in the literature which described the formation of novel carbamates by heating together ethyl carbamate with a higher boiling alcohol, with or without base catalysts (140, 166, 238).

Then in 1948, Kraft found that aluminum isopropoxide catalyzed the interchange reaction between ethyl carbamate and benzyl alcohol to give benzyl carbamate in good yields (200). This catalyst system has since been used to prepare a multitude of mono- and dicarbamates in excellent yields from primary and secondary alcohols and diols. N-Alkyl carbamates, as well as unsubstituted carbamates, can also be used as an interchange component (164).

The use of dibutyltin dilaurate (189) and dibutyltin oxide as an interchange catalyst (46) has been reported. Strong bases, however, such as alkali metal alkoxides are ineffective owing to their high reactivity with the starting carbamate ester to form alkali cyanates.

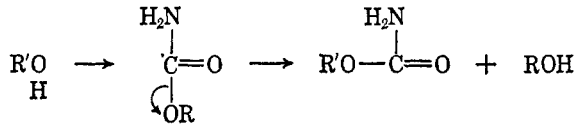
Removal of the ethanol by fractional distillation drives the reaction to completion. Tertiary alcohols and phenols do not react under these conditions. The potentially low cost of manufacture of methyl or ethyl carbamate and their ability to undergo ester interchange reactions have made economically feasible the preparation of mono- and dicarbamates.

Gaylord and Sroog (140) studied the acid-catalyzed reaction between ethyl carbamate and a higher alcohol. They proposed two mechanisms for the alcohol–alkyl carbamate interchange reaction. The first involved decomposition of the carbamate ester to cyanic acid and its subsequent reaction with the higher boiling alcohol.

$$ROCONH_2 \rightarrow ROH + \underset{\text{III}}{(HNCO)}$$

$$HNCO + R'OH \rightarrow R'OC(=O)NH_2$$

The second was based on a displacement reaction.



The authors felt that the body of evidence was in favor of the latter displacement reaction with unsubstituted carbamates, while the decomposition mechanism pertained to a certain extent to monosubstituted carbamates. In the presence of catalytic quantities of strong acid, ethyl carbamate reacted with an excess of isobutyl alcohol at 115° to form isobutyl carbamate in 50% yield.

$$C_4H_9OH + C_2H_5OCONH_2 \rightarrow C_2H_5OH + C_4H_9OCONH_2$$

D. MISCELLANEOUS METHODS

The following methods of preparation are important mainly from a historical perspective or for the preparation of special carbamates.

Cahours (68), in 1845, found that the ammonolysis of diethyl carbonate under pressure gave ethyl carbamate. This reaction will be discussed later in the section on diol monocarbamates.

$$(C_2H_5O)_2CO + NH_3 \rightarrow C_2H_5OCONH_2 + C_2H_5OH$$

Mixed phenyl alkyl carbonates are selectively ammonolyzed to form the alkyl carbamate and phenol. This route is one of the few methods used to prepare tertiary alkyl esters of carbamic acid (162, 228, 311).

Aminoethyl carbamates are formed by the reaction of urea and ethylene oxide (330).

$$H_2NCONH_2 + \underset{\diagdown\,O\,\diagup}{CH_2—CH_2} \rightarrow H_2NCOOCH_2CH_2NH_2$$

The reaction of carbamoyl chloride with alcohols is a general method for making carbamates (138). However, carbamoyl chloride is not readily available.

$$NH_2COCl + ROH \rightarrow NH_2COOR + HCl$$

The wide availability of alkyl and aryl isocyanates makes them quite important starting materials for the preparation of N-substituted carbamates (12). This phase of isocyanate chemistry is outside the scope of this review.

Liebig and Wohler (210) have prepared ethyl carbamate in a small yield by passing cyanic acid gas into a mixture of ethanol and ether. Amato (7) modified this procedure by using a mixture of potassium cyanate, dilute hydrochloric acid, and alcohol. Using this method, Folin (133) obtained a 60% yield of ethyl carbamate (31).

It must be noted at this point that passing cyanic acid gas (usually obtained by the thermal decomposition of cyanuric acid) into an alcohol gives not only the carbamate ester, but the allophanate (IV) as well (80).

Close and Spielman have shown that in spite of a large excess of alcohol, cyanic acid gas reacts to form considerably more allophanate than carbamate in a neutral system. In the presence of hydrogen chloride, carbamate formation is favored (80).

$$\underset{\text{III}}{HNCO} + ROH \rightarrow ROCONH_2 + \underset{\text{IV}}{ROCONHCONH_2}$$

Excellent yields of carbamates are obtained when sodium cyanate is added to a solution of an alcohol in trifluoroacetic acid (212).

The Hofmann degradation of amides by means of halogen and alkali has been used to prepare a wide variety of N-alkyl- (especially N-vinyl-) carbamates (342).

Carbamate esters are obtained from the interaction of bromine, sodium ethoxide, and an alkyl oxamate. This is an extension of the Hofmann degradation (239).

$$C_2H_5OCOCONH_2 + Br_2 + NaOC_2H_5 \rightarrow C_2H_5OCONH_2$$

The reaction of thiocyanogen trichloride (Cl_3S = NCl) with alcohols gave alkylcarbamate esters in 20–60% yields (17).

When a mixture of amine, alcohol, and urea is heated together, both N-alkylcarbamates and unsubstituted carbamates are formed (66, 294).

$$H_2NCONH_2 + RNH_2 + R'OH \rightarrow RNHCOOR' + NH_3 + H_2NCOOR,$$

By heating an alcohol with urea nitrate to 125–130°, the corresponding carbamate is formed (20, 79, 161). Recently, zinc chloride has been used as a catalyst (271).

Ethyl carbamate has been reportedly prepared by refluxing a solution of urea in ethanolic nitric acid (271).

Alkyl halides reacting upon silver carbamate afford carbamate esters (184).

$$RCl + AgOCONH_2 \rightarrow ROCONH_2 + AgCl$$

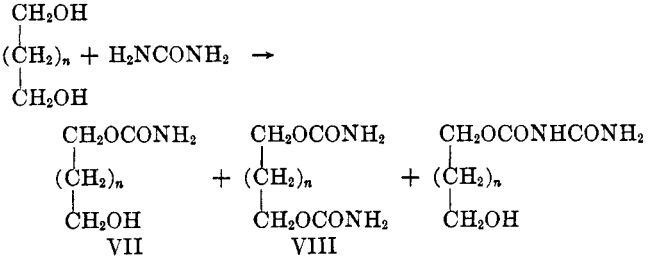
When phenyl cyanate was hydrolyzed with acid, phenyl carbamate was obtained (224).

$$C_6H_5OCN + H_2O \rightarrow C_6H_5OCONH_2$$

VII. SYNTHESIS OF CARBAMATES OF DIOLS

A. DIOL MONOCARBAMATES

When diols rather than monofunctional alcohols were treated with urea, ethyl carbamate, or phosgene, a wide variety of products resulted. With urea, mixtures of unreacted diol monocarbamate (VII), dicarbamate (VIII), and allophanate were obtained.

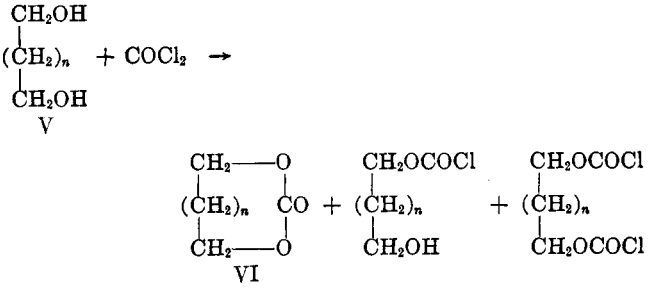


Paquin (262) found that when lower molecular weight diols (V) are heated with urea and a catalyst, either a monocarbamate or a dicarbamate is formed, depending upon mole ratios. Heat-stable monocarbamate can be separated from the mixture by fractional distillation under low pressure. Dicarbamates cannot be distilled.

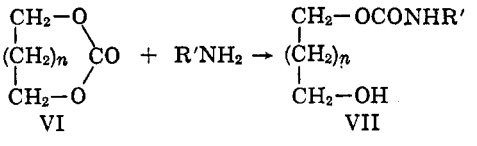
The recovery in good yields of pure monocarbamate by this method is quite tedious. Ammonolysis of cyclic carbonates leads to better yields of purer products.

When diols were treated with ethyl carbamate under ester interchange conditions, mixtures of mono- and dicarbamates could be obtained (23, 285, 363).

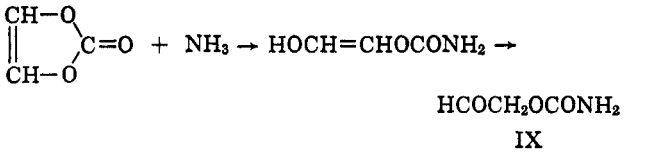
Phosgenation of diols with or without an organic base produced a mixture of cyclic carbonate VI, monochloroformate, and bischloroformate (44, 214).



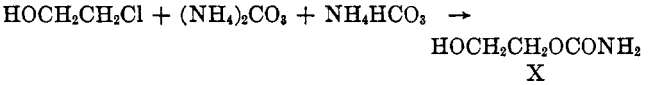
The diol monocarbamates (VII) are obtained in excellent yields by the reaction of substituted *m*-dioxanones ($n = 0$) and dioxalanones (VI, $n = 1$) (cyclic carbonates) with ammonia or amines (218, 338, 339).



The starting cyclic carbonates were prepared by the alkali-catalyzed exchange reaction between diethyl carbonate (or an *m*-dioxanone) with a diol (284, 285). Vinyl carbonate condensed with ammonia to form the carbamate of glycol aldehyde (IX) (110). This aldehyde then undergoes self-polymerization.



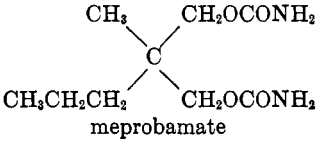
By heating together ammonium sesquicarbonate and ethylene chlorohydrin, the corresponding glycol monocarbamate (X) is formed in 87% yield (307).



Carbamyl chlorides were treated with epoxides to form the β-chloroethyl carbamates (57), and with diols to give the chlorocarbamates (349).

B. DIOL DICARBAMATES

The unique pharmacological activity of 2-methyl-2-*n*-propyl-1,3-propanediol dicarbamate (meprobamate) as a tranquilizer for control of anxiety, tension, and



meprobamate

muscle spasm has stimulated interest in the field of diol dicarbamates (VIII). Here the simplest method of preparation was the ester interchange of a diol with ethyl or methyl carbamate in the presence of aluminum isopropoxide with (65, 147, 148) or without a solvent (37), in yields of 80–90%.

The reaction of diols (V) with urea in the presence of a catalyst had been reported by Paquin to form diol dicarbamates (VIII) in good yields (260). In an attempt to prepare meprobamate by treating the corresponding diol with urea following Paquin's directions, low melting material in poor yields was obtained. The only area of Paquin's paper that could be repeated was the preparation of monocarbamates in the presence of catalysts (3). Ferrari (131) has also obtained dicarbamates from urea and diols in poor yields.

The reaction of diols and polyols with urea has been frequently reported in the patent literature, but attempts to prepare pure products in good yields have failed. Heating urea and triethanolamine together, for example, gives mixtures of tricarbamate and triallophanate, depending upon mole ratios (34).

When butanol in limited quantities is added to a mixture of urea and a diol with aluminum isopropoxide as catalyst, reasonable yields (50–60%) of pure dicarbamates are obtained (38). This reaction combines the alcoholysis of urea by butanol to form butyl carbamate *in situ* and its concurrent transesterification with the diol to form the desired product.

When an ethylene glycol is heated with urea in the presence of potassium fluoride, a 50% yield of the dicarbamate was claimed (136).

When 1,2-diols are heated with ethyl carbamate at 160° without a catalyst, cyclic carbonates are formed (84).

The conventional method for the preparation of diol dicarbamates by the reaction of diols with phosgene in the presence of organic bases (254) has been improved considerably by the discovery (142) that tetrahydrofuran could act as an HCl acceptor during the phosgenation and, subsequently, release the HCl at its boiling point. Removal of the tetrahydrofuran solvent followed by addition of the residue to either ammonia or amines gives excellent yields (85–90%) of dicarbamates.

When diol bischloroformates were treated with 1 mole of triethylamine and 2 moles of ammonia, only one of the chloro groups was replaced by NH_2. Using this technique, the preparations of diol monocarbamates and N-alkyl diol dicarbamates were claimed (257).

Propanediol bisthiocarbamates were obtained when thiophosgene was condensed with the diol and the product treated with ammonia (346).

When HCl gas was passed into a mixture of a diol and sodium cyanate in a solvent, mixtures of dicarbamates and allophanates were obtained (206, 212).

When a diol monocarbamate was heated with an ester-interchange catalyst, disproportionation occurred, and a mixture of diol and dicarbamate was obtained (40). Distillation of the diol at low pressure left a residue of the dicarbamate.

VIII. Reactions of Carbamates

A. Thermal Decomposition

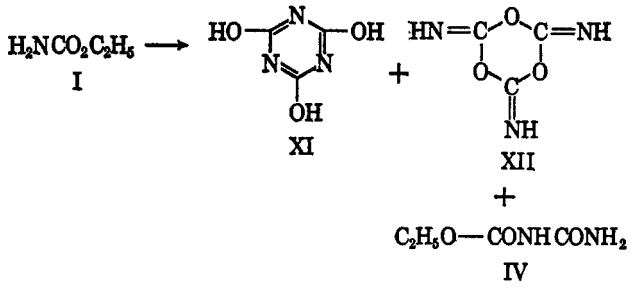
The thermal and hydrolytic stabilities of carbamates exhibit a striking dependence upon the degree of N-substitution. Disubstituted carbamates are quite resistant to thermal decomposition (as well as to hydrolysis); monosubstituted carbamates readily undergo thermal decomposition at elevated temperatures primarily to alkyl isocyanates, and unsubstituted carbamates decompose quite readily to derivatives of cyanic acid.

Unsubstituted carbamates decompose to allophanates (IV), cyanuric acid (XI), and alcohol, above 130°, the decomposition rate increasing with temperature.

The presence of even trace quantities of metal salts accelerates thermal decomposition appreciably and allows the formation of an additional decomposition product, cyamelide (XII) (13).

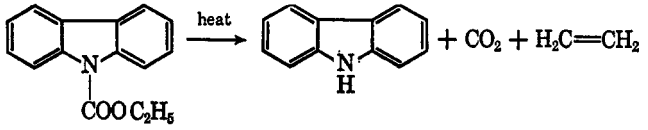
N-Monoalkylated carbamates are more stable, and N,N-dialkylated carbamates are the most stable. (Increasing N-substitution stabilizes carbamates toward base-catalyzed hydrolysis as well.)

Among the products of thermal decomposition of

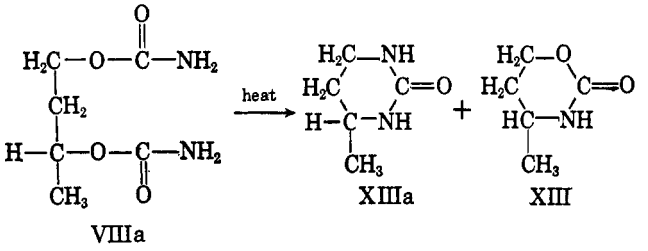


monosubstituted carbamates are isocyanates, alcohols, and, to a lesser extent, olefins, carbon dioxide, ureas, and carbodiimides (112, 238).

Disubstituted carbamates rarely decompose cleanly; ethyl carbazole-9-carboxylate is one example of clear-cut decomposition of a disubstituted carbamate to carbon dioxide, olefin (ethylene), and disubstituted amine (carbazole) (54).



Pyrolysis of the dicarbamate of 1,3-butylene glycol (VIIIa) reportedly afforded an oxazolidone (XIII) and a cyclic urea (XIIIa). No mechanism has yet been offered for this unusual reaction in which C–O bonds are replaced by C–N bonds (260).



Stability of Carbamates Heated in Acidic and Basic Solvents. Thermal decomposition of substituted carbamates in solution into isocyanates and alcohols has been studied (245).

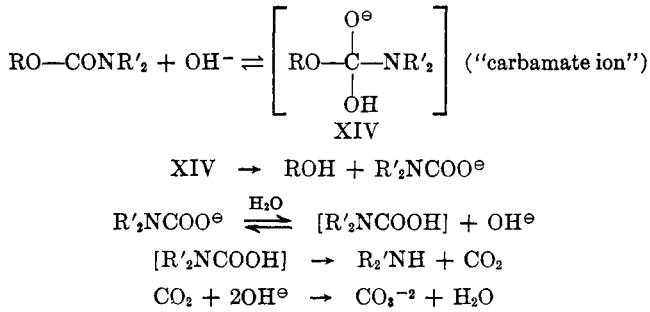
The rate of carbamate decomposition in fatty acid solvents, or in amine solvents, increased with the acidity of the fatty acid and with the basicity of the amine solvent. The reverse of thermal decomposition of carbamates, the exothermic formation of carbamates from isocyanate and alcohols, proceeds in solvents at a rate similarly dependent upon the pH of the solvent.

B. Hydrolysis

1. Alkaline

In alkaline solution, hydrolysis of all disubstituted carbamates and mono- and unsubstituted carbamates derived from aliphatic alcohols reportedly proceed (108) by the following path.

SCHEME A



XIV → ROH + $R'_2NCOO^{\ominus}$

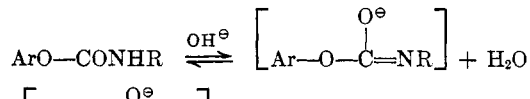
$R'_2NCOO^{\ominus} \xrightleftharpoons{H_2O} [R'_2NCOOH] + OH^{\ominus}$

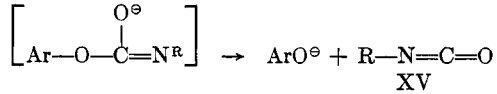
$[R'_2NCOOH] \rightarrow R_2'NH + CO_2$

$CO_2 + 2OH^{\ominus} \rightarrow CO_3^{-2} + H_2O$

Carbamates derived from phenols hydrolyze more rapidly than aliphatic carbamates and apparently by a different mechanism. The ease of departure of the phenoxide ion is a driving force of this fast reaction. The signal difference between Scheme B and Scheme A is the formation of an isocyanate intermediate (XV).

SCHEME B





XV

$XV \xrightarrow{H_2O} [R—NHCOOH]$

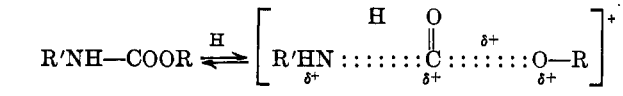
$[R—NHCOOH] \rightarrow CO_2 + RNH_2$

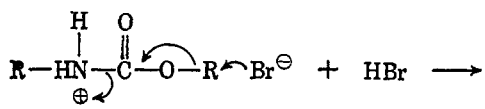
$CO_2 + 2OH^{\ominus} \rightarrow CO_3^{-2} + H_2O$

However, N-disubstituted aromatic carbamates cannot form an isocyanate intermediate (XV), and these carbamates hydrolyze rather slowly *via* the "carbamate ion" (XIV) intermediates (Scheme A).

2. *Acidic*

Treatment of carbamates in glacial acetic acid with either HCl or HBr leads to CO_2, ammonium halide, and alkyl halide. The carbamate molecule is initially protonated and its alkoxy group then attacked by halide ion (41).





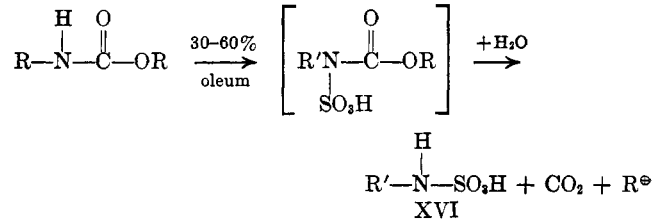
$R'NH_2 \cdot HBr + CO_2 + RBr$

However, carbamates are quite stable to acids under many other conditions. Anhydrous HCl or BF_3 do not decompose carbamates.

When heated in 5% oleum to 90°, carbamates undergo unimolecular alkyl–oxygen cleavage.

$RNHCOOR' \xrightarrow[90°]{5\%\ \text{oleum}} RNH_2 + HSO_4^{\ominus} + CO_2 + R^{\oplus}$

However, when 30–60% oleum is used, unsubstituted or monoalkylated carbamates become N-sulfonated prior to cleavage, affording sulfamic acids (XVI) (50).



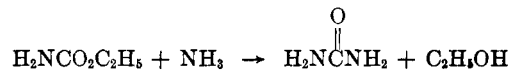
XVI

C. REACTIONS AT ESTER GROUP

1. *Reaction of Carbamates with Amines and Amine Derivatives*

The reaction between amines and carbamate esters has not been studied in depth. Interest in this area has been stimulated by the discovery (1) that tin compounds are catalysts in the formation of substituted ureas from the carbamate esters and aliphatic amines.

Werner has shown that upon heating ethyl carbamate (I) with ammonia at 150° in a sealed system urea was obtained in a 33% yield (354).



N,N′-Dialkylureas (XVII) were formed by heating N-alkyl carbamates with the corresponding amine at 230° (109) or by heating ethyl carbamate with an amine at 150° (99, 178).

$I + RNH_2 \rightarrow H_2NCONHR + C_2H_5OH$ (Eq. 7)

$H_2NCONHR + RNH_2 \rightarrow RNHCONHR + NH_3$ (Eq. 8)

$RNHCOOC_2H_5 + RNH_2 \rightarrow RNHCONHR + C_2H_5OH$ (Eq. 9)

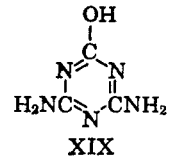
XVII

Diphenylurea was formed when aniline and ethyl carbamate were heated together (222, 359).

Until recently the only examples of the reaction of amines with carbamates to form monosubstituted urea derivatives were: (a) the reaction of ethyl carbamate (I) with dicyandiamide (XVIII) at 190° to form ammeline (XIX) (27), by way of the postulated cyanoguanylurea (XX)

$H_2NC(=NH)NHCN + I \rightarrow [H_2NCONHC(=NH)NHCN] \rightarrow$

XVIII XX

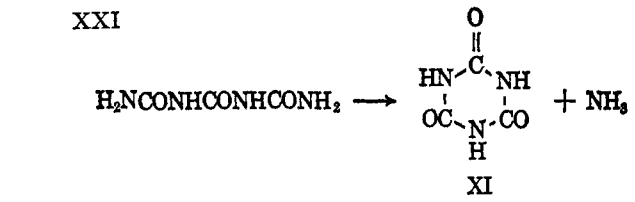


XIX

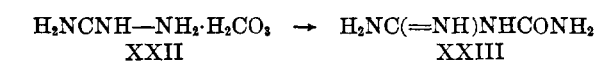
(b) with biuret (XXI) to form cyanuric acid (XI) (27), (c) with guanidine carbonate (XXII) to form guanylurea (XXIII) (27)

$H_2NCONHCONH_2$ + I →

XXI

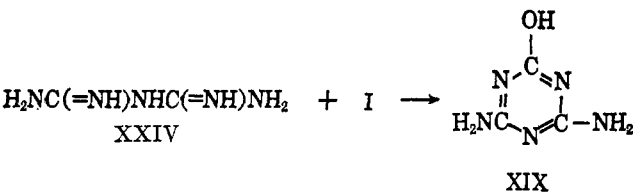


XI



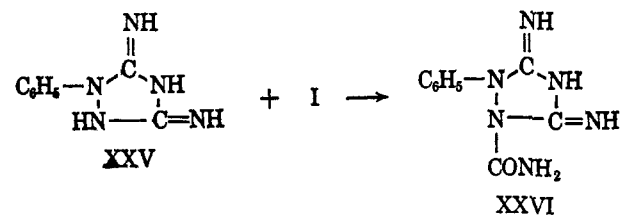
XXII XXIII

(d) and with biguanide (XXIV) to form ammeline (XIX) (305, 306).



XXIV XIX

Ethyl carbamate condenses with phenylguanazole (XXV) affording the corresponding 2-carbamyl derivative (XXVI) (259).



XXV XXVI

N-Alkylureas can be formed in excellent yields by the reaction of a primary or secondary alkylamine with an alkyl carbamate at 130° with the removal of the alcohol formed by fractional distillation (Eq. 4). Dibutyltin oxide and cuprous acetate were shown to be excellent catalysts (1).

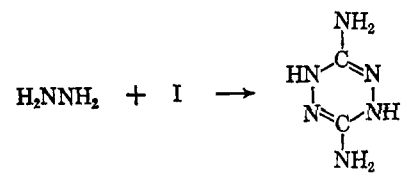
Brander (63) has shown that the reaction of an alkylamine with a carbamate leads to amine interchange in the presence of the hydrochloride salt.

$$I + RNH_2 \xrightarrow{RNH_3Cl} RNHCOOC_2H_5 + NH_4Cl$$

Crosby and Niemann (86) found that ethyl carbamate did not react with amines in boiling dioxane, although N,S-diphenyl thiocarbamates or N,O-diphenyl carbamates did.

Hydroxylamine has been shown to react with carbamate esters to form N-hydroxyureas (97).

Diaminotetrazine (XXVII) has been claimed as the reaction product of hydrazine hydrate with ethyl carbamate (343).



XXVII

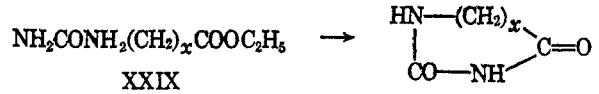
This interesting reaction and ring system have not been further investigated.

Phenylhydrazine behaves normally and forms N-phenylsemicarbazide upon heating with ethyl carbamate (187).

Amino esters react with ethyl N-sodiocarbamate (XXVIII) to form the corresponding ureido ester (XXIX) (104) which is then ring-closed to the hydantoin or the dihydropyrimidinedione.

$H_2N(CH_2)_xCOOC_2H_5$ + $NaHNCOOC_2H_5$ →

XXVIII

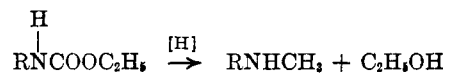


XXIX

x = 1, hydantoin; x = 2, dihydropyrimidinedione

2. Reduction

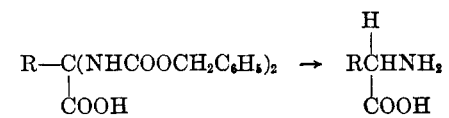
Chemical reduction of carbamates is accompanied by cleavage about the carboxy group. For example, carbamate esters have been reduced to the corresponding N-methylamine by lithium aluminum hydride (88, 196, 356).



The hydrogenation of phenyl alkylidene biscarbamates with hydrogen, and palladium catalyst led to the formation of benzylamines (223).

$$ArCH(NHCOOCH_2C_6H_5)_2 \rightarrow ArCH_2NH_2 + 2CH_3C_6H_5 + NH_3 + CO_2$$

When substituted pyruvic acid–carbamate condensates (XXXI) are hydrogenated, α-amino acids result.



XXXI

Metayer heated alkyl carbamates with Raney nickel at the boiling point and obtained cyanuric acid and alcohol or the corresponding allophanate ester, depending upon the molecular weight of the alkyl group. There was no indication of reduction taking place (238).

3. Transesterification

(See section VIC.)

D. REACTIONS AT AMIDO GROUP

1. Acylation

Carbamates can be acylated by various carboxylic esters, anhydrides, acid halides, as well as such reagents as ketenes. Certain carbamates are acylated by isocyanates. In general, carbamates are more readily acetylated than ordinary acid amides.

a. By Carboxylic Acid Derivatives

With Esters. N-Acylcarbamates (XXXIII) have been formed from the reaction of carboxylic acid esters with carbamates (104, 163) or N-sodiocarbamates (282). However, the keto carbonyl group, rather than the carbethoxy group, of ethyl acetoacetate reacted with ethyl carbamate (230) to give the substituted eneamine (LI).

$$CH_3—CO—CH_2—COOC_2H_5 + I \rightarrow \underset{\displaystyle NHCO_2C_2H_5}{CH_3C{=}CHCO_2C_2H_5}$$

LI

With ethyl glycinate (XXXIV), ethyl hydantoinate (XXXV) is produced from ethyl carbamate (104).

$$\underset{\text{XXIV}}{H_2NCH_2COOC_2H_5} + I \rightarrow \underset{\text{XXXV}}{H_2NCONHCH_2COOC_2H_5}$$

Acid Halides. Aliphatic and aromatic acyl chlorides acylate unsubstituted carbamates (32, 42). Diacid chlorides such as oxalyl chloride usually react with 2 moles of ethyl carbamate (I) affording biscarbamates (XXXVII) (332).

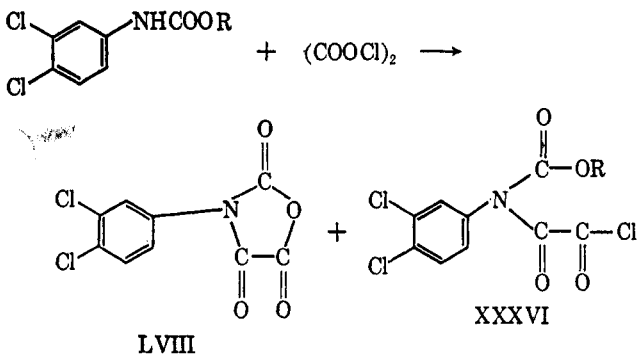
$$(COCl)_2 + 2I \rightarrow \underset{\text{XXXVII}}{(CONHCOOC_2H_5)_2}$$

When heated in benzene, oxalyl dicarbamate loses carbon monoxide. However, some aspects of this reaction are unresolved (245a).

$$\text{XXXVII} \xrightarrow{C_6H_6} CO + OC(NHCOOC_2H_5)_2$$

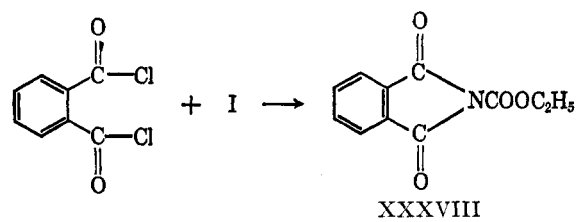
Other reactions of oxalyl dicarbamate have been investigated (149).

Both oxazolidinetriones (LVIII), a novel ring system, and oxanilyl chlorides (XXXVI) have been prepared by the action of oxalyl chloride on various aniline-derived carbamates (319a).



LVIII XXXVI

Phthaloyl chloride affords a cyclic-substituted imide (XXXVIII).



XXXVIII

N-Carbethoxyphthalimides (XXXVIII) have found wide use in the preparation of phthaloylamino acids (without racemization of the amino acid) which are then used in peptide synthesis (251). Phthalic anhydride, by contrast, reacts with N-substituted carbamates to form N-alkyl (or aryl) phthalimides (see section VIIID1b).

Substituted and unsubstituted carbamates react with acetyl bromide to form N-substituted acetamides, carbon dioxide, and alkyl halides.

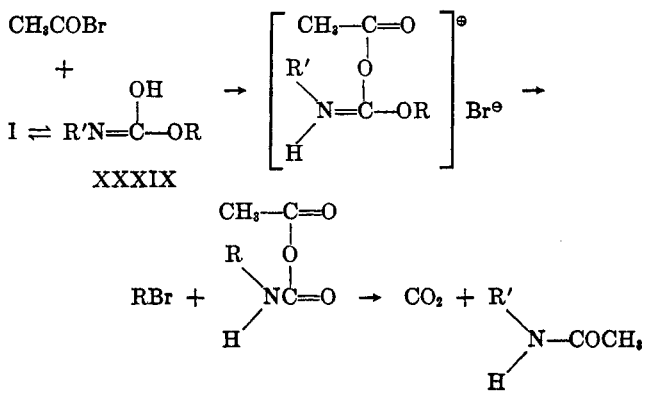
$$R'R''NCOOR + CH_3COBr \rightarrow CH_3CONR'R'' + RBr + CO_2$$

R = C_2H_5 or benzyl

R', R'' = H, CH_3, or C_6H_5

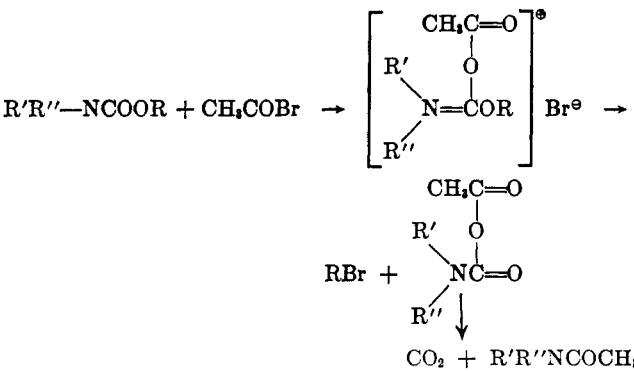
Only with ethyl carbamate is an appreciable amount of ethyl N-acetylcarbamate found (42).

A likely mechanism would involve displacement of the bromine by the OH group of the enolic form of the unsubstituted or monosubstituted carbamate (XXXIX). Such enolic forms of carbamates have been postulated (see section VIIID2b).



XXXIX

A mechanism encompassing the reaction of the disubstituted carbamates has been proposed (42).



Displacement of bromine by alkoxy oxygen, as proposed here, has been observed in the facile displacement of bromine from acetyl bromides by ethers.

Carboxylic acids generally fail to acylate carbamates, except in the presence of an agent such as $POCl_3$ or acetic anhydride (159). Malonic acid reacts to afford malonylbis(ethyl carbamate) (XL) in the presence of acetic anhydride (82).

$$H_2C(COOH)_2 + (CH_3CO)_2O + I \rightarrow \underset{XL}{H_2C(CONHCOOC_2H_5)_2}$$

Cyanoacetic acid and ethyl carbamate (I) react in the presence of acetic anhydride to give ethyl cyanacetylcarbamate (XLI).

$$HOCOCH_2CN + I + \xrightarrow{(CH_3CO)_2O} \underset{XLI}{C_2H_5OCONHCOCH_2CN}$$

If ethyl orthoformate is included in this last reaction mixture, then the more complex molecule, ethyl α-cyano-β-ethoxyacryloylcarbamate (XLII)

$$C_2H_5O-\underset{}{\overset{H}{C}}=\underset{CN}{C}-CONHCOOC_2H_5$$

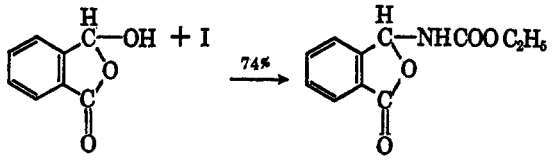
is formed (297).

Keto acids, like keto esters, react with carbamates, not by acylation, but rather by carbonyl condensation (CXVIII) (300).

$$CH_3COCOOH + I \rightarrow \underset{CXVIII}{CH_3-C(COOH)(NHCOOC_2H_5)_2}$$

b. By Other Acylating Agents

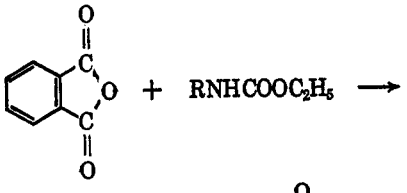
Ethyl 3-oxo-1-phthalancarbamate (XLIII) results when ethyl carbamate is refluxed in a 2-butanone solution with phthalaldehydic acid (357).

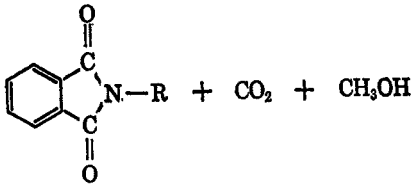


XLIII

Acetic anhydride acylates ethyl carbamate at 100° (227).

Phthalic anhydride reacts with monosubstituted carbamates to form N-substituted phthalimides (XLIV). (Unsubstituted carbamates afford phthalimide.) Under the conditions of the reaction, phthalic anhydride both decarbethoxylates the original carbamate and diacylates the carbamate's amino fragment (221).

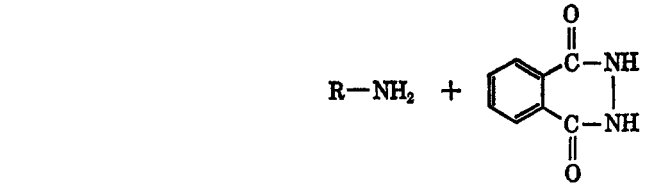




XLIV

Hydrolysis of the phthalimide affords the amine R-NH_2.

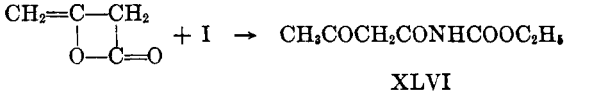
As a general method of hydrolysis of N-substituted carbamates where hydrolysis with acid or bases is detrimental, the carbamate is converted to a phthalimide (XLIV), and the phthalimide is then treated with hydrazine hydrate to release the desired amine (182).



Ethyl diacetylcarbamate (XLV) can be prepared from ketene and ethyl carbamate (304)

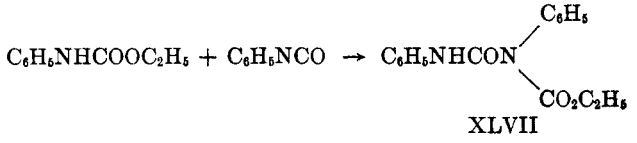
$$CH_2=C=O + I \rightarrow \underset{XLV}{(CH_3CO)_2NCOOC_2H_5}$$

while diketene affords ethyl acetoacetylcarbamate (XLVI) (275).



XLVI

The reaction of phenyl isocyanate with ethyl N-phenylcarbamate, an N-acylation reaction, affords ethyl N,N′-diphenylallophanate (XLVII). Only N-arylcarbamates undergo this reaction (197).



XLVII

Ethyl carbamate reacts with ethyl orthoformate in the presence of boron trifluoride (157) to give ethyl ethoxymethylenecarbamate.

$$I + (C_2H_5O)_3CH \xrightarrow{BF_3} \underset{XLVIII}{C_2H_5OCH=NCOOC_2H_5}$$

The ethoxy group of XLVIII can be easily replaced by various amines, affording XLIX, a polyfunctional intermediate.

$$XLVIII + RNH_2 \rightarrow \underset{XLIX}{R-NH-CH=NCOOC_2H_5}$$

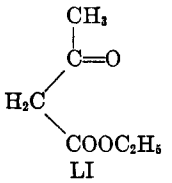
Ethyl formate reacts with ethyl N-sodiocarbamate (XXVIII) to afford ethyl N-formylcarbamate (LI) (282).

$$C_2H_5OCHO + XXVIII \rightarrow \underset{LI}{HCONHCOOC_2H_5}$$

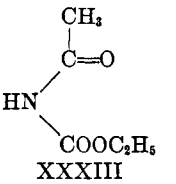
c. Reaction of Acetylcarbamates

Acetylcarbamates can react either solely at the carbalkoxy group, or at both that group and the acetyl carbonyl group simultaneously. In the latter case cyclic products are formed, as when reagents such as phenylhydrazine, urea, amines, or thiosemicarbazides are employed.

Acetoacetic esters (LI) and N-acetylcarbamates (XXXIII) can be considered isosteres, and their apparent similarity has prompted investigations of the reactions of acetylcarbamates under the same conditions in which acetoacetic esters are known to react. In general, it was found that acetylcarbamates react with the basic compounds (amines, etc.) but not with the "acidic compounds"; *i.e.*, phenols, etc., with which acetoacetic esters are known to react. N-Alkylation of the imido nitrogen of XXXIII does not occur as readily as C-alkylation of the methylene group of LI.



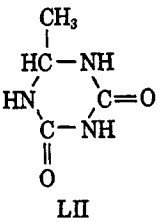
LI



XXXIII

Both ethyl N-acetylcarbamate and ethyl acetoacetate condense with urea, the acetoacetates affording methyluracil, and the acetylcarbamates forming 2-methyl-4,6-dioxohexahydro-*s*-triazine (LII) and acetylbiuret (LIII) (258).

XXXIII + H_2NCONH_2 ⟶

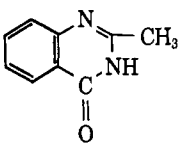


LII + $CH_3CONHCONHCONH_2$ LIII

Aniline and ethyl N-acetylcarbamate react in the presence of zinc chloride or phosphorus trichloride to form diphenylurea (29, 100). (Ethyl acetoacetate and aniline afford acetoacetanilide.)

$C_6H_5NH_2$ + XXXIII ⟶

$C_6H_5NHCONHC_6H_5$ +



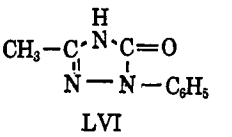
LIV

When the same two reagents are treated with excess phosphorus pentoxide, 4-quinalazone (LIV) is obtained (58). However, in the presence of smaller amounts of phosphorus pentoxide, a simple amide formation occurs; thus, when an aromatic amine such as *m*-toluidine is treated with acetylcarbamate and 1 mole of P_2O_5, acetyl-*m*-tolylurea (LV) is formed.

m-$CH_3C_6H_4NH_2$ + XXXIII $\xrightarrow{P_2O_5}$ *m*-$CH_3C_6H_4NHCONHCOCH_3$ LV

Phenylhydrazine and ethyl N-acetylcarbamate undergo an Einhorn–Brunner reaction affording 5-hydroxy-3-methyl-1-phenyl-4H-1,2,4-triazole (LVI) (8).

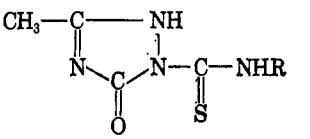
XXXIII + $C_6H_5NHNH_2$ ⟶



LVI

Thiosemicarbazides react at their hydrazine grouping, rather than thiocarbamide group with acetylcarbamates to afford 1-thiocarbamido-3-methyl-5-keto-1,2,4-triazole (LVII) (8).

XXXIII + $H_2NNHC(S)NHR$ ⟶



LVII

Hydroxylamine decomposes acetylcarbamates to hydroxamic acids (272).

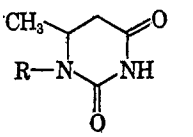
$CH_3CONHCOOC_2H_5 + H_2NOH \rightarrow CH_3—C(=NOH)OH$

Reactions of Functional-Bearing Acylcarbamates. Ethyl N-acetoacetylcarbamate (XLVI) reacts with primary amines, subsequently cyclizing to form substituted uracils (LIXa).

$CH_3—CO—CH_2—CONHCOOC_2H_5$ + RNH_2 ⟶

XLVI

$[CH_3—COCH_2CONHCONHR]$ $\xrightarrow{NaOH}$



LIXa

α,β-Unsaturated acylcarbamates, such as ethyl propiolylcarbamate (LX) or ethyl β-ethoxyacryloylcarbamate (LXI), react with primary amines and can be cyclized to uracils (LIXb) (275).

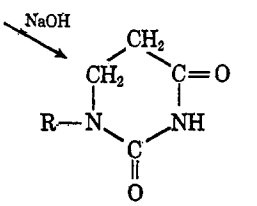
$HC\equiv CCONHCOOC_2H_5$

or

$C_2H_5OCH=CHCONHCOOC_2H_5$ $\xrightarrow{RNH_2}$

$R—NHCH=CHCONHCOOC_2H_5$

$\xrightarrow{NaOH}$



LIXb

2. Reaction with Inorganic Halides

a. General

Carbamates react with inorganic acid dichlorides to form either (a) allophanates (IV) or (b) N-substituted carbamate derivatives (LXII and LXIII). N-Sub-

stitution occurs only in the presence of acid acceptors. (In the absence of bases capable of removing acidic by-products, allophanates are formed instead.)

$$H_2NCOOR + (A)Cl_2 \xrightarrow{base} base\cdot HCl + \underset{LXII}{(A)(NHCOOR)_2} + \underset{LXIII}{Cl{-}(A){-}NHCOOR}$$

Reagents which react as indicated in the above equation are sulfuryl chloride (LXIIa, (A) = SO_2) (96, 120) and phosgene (LXIIb + LXIII, (A) = CO) (9, 133, 256). These reagents afford only allophanates in the absence of base (120, 211).

Allophanates (IV) are the sole product of the reaction of carbamates with phosphorus oxychloride (133), phosphoric anhydride (51), and thionyl chloride (292).

b. Thionyl Chloride

Ethyl carbamate (I) when treated with thionyl chloride affords exceptionally good yields of ethyl allophanate, accompanied by the evolution of sulfur dioxide, HCl, and ethyl chloride (292).

$$SOCl_2 + I \rightarrow SO_2 + HCl + C_2H_5Cl + H_2NCONHCOOC_2H_5$$

Under similar conditions, amides are usually dehydrated to nitriles. One explanation of the reaction is the following. An enolic form of ethyl carbamate (XXXIX) reacts with thionyl chloride in a manner similar to that reaction of propyl alcohol and thionyl chloride which affords the propyl ester of chlorosulfinic acid. The chlorosulfinate (LXIV) loses sulfur dioxide, ethyl chloride, and cyanic acid. Intact ethyl carbamate then reacts with the nascent cyanic acid (III), which in the presence of HCl forms intermediary carbamoyl chloride, to produce ethyl allophanate (IV) (274, 355).

$$H_2N{-}\overset{O}{\overset{\|}{C}}OC_2H_5 \rightleftharpoons \underset{XXXIX}{HN{=}\overset{OH}{\overset{|}{C}}OC_2H_5} \xrightarrow{SOCl_2} \underset{LXIV}{HN{=}\overset{OSOCl}{\overset{|}{C}}OC_2H_5} + HCL$$

$$LXIV \xrightarrow{-SO_2} HN{=}\overset{Cl}{\overset{|}{C}}OC_2H_5 \rightarrow C_2H_5Cl + HNCO$$

$$HCl + HCNO \rightarrow [H_2N{-}COCl] \xrightarrow{I} \underset{IV}{H_2N{-}CONHCOOC_2H_5}$$

The reaction of ethyl N-phenylcarbamate with excess thionyl chloride at room temperature is unique (as are many of the reactions of N-phenylcarbamates). The reaction proceeds with evolution of sulfur dioxide, HCl, and ethyl chloride, to give a 65–70% yield of 1,3-diphenyluretedione (LXV) (formerly known as diphenyl diisocyanate). Of all the N-arylcarbamates, only N-phenylcarbamates react in this manner (345).

The reaction of ethyl carbamate and thionyl chloride in the presence of dimethylformamide is discussed in section VIIIM.

$$C_6H_5NHCOOC_2H_5 + SOCl_2 \text{ (excess)} \rightarrow$$

$$SO_2 + HCl + C_2H_5Cl + C_6H_5{-}N\underset{\displaystyle C}{\overset{\displaystyle O}{\overset{\|}{<}}}N{-}C_6H_5 \quad \underset{\displaystyle O}{\overset{\displaystyle \|}{}}$$

LXV

c. Phosphorus Halides

Whereas amides such as benzamide react with phosphorus pentachloride to afford an intermediate (LXVI)

$$ArCONH_2 + PCl_5 \rightarrow \underset{LXVI}{[ArCCl_2NH_2]} \rightarrow ArCN + POCl_3$$

which breaks down into a nitrile and phosphorus oxychloride (341), the comparable organophosphorus intermediate (LXVII) from the reaction of phosphorus pentachloride and carbamates decomposes in a different manner. When ethyl carbamate reacts with phosphorus pentachloride at 0–10°, an intermediate product, ethyl trichlorophosphorylcarbamate (LXVII),

$$I + PCl_5 \xrightarrow{95\%} \underset{LXVII}{Cl_3P{=}NCOOC_2H_5} + 2HCl$$

is obtained initially. The trichlorophosphorylcarbamate decomposes at 60° to ethyl chloride and dichlorophosphorylisocyanate (LXVIII) (191).

$$LXVII \xrightarrow{90\%} \underset{LXVIII}{Cl_2PONCO} + C_2H_5Cl$$

Ethyl carbamate reacts with phosphorus pentachloride at higher temperature (70°) in an inert solvent to form dichlorophosphorylisocyanate (LXVIII) directly in 90% yield (192). In their reaction toward PCl_5, carbamates thus resemble sulfonamides.

When phenyl carbamate is used in place of ethyl carbamate, the intermediate formed (LXIX) has different characteristics. Since the aryl–oxygen bond cannot cleave to be replaced by an aryl–halide bond, a different mode of thermal cleavage is followed. The intermediate (LXIX) decomposes in the manner of amides, affording phosphorus oxychloride, polymers of the anticipated nitrile (LXX), and other fragments (192).

$$C_6H_5OCONH_2 + PCl_5 \rightarrow \underset{LXIX}{C_6H_5OCON{=}PCl_3}$$

$$C_6H_5OCON{=}PCl_3 \rightarrow POCl_3 + \underset{LXX}{(C_6H_5OCN)_3} + (CNCl)_3 + C_6H_5OPCl_2$$

Ethyl N-phenylcarbamate (which reacts uniquely with various reagents) is chlorinated by phosphorus pentachloride at 50–55°, to the "chloroformanilide" (LXXI) which, at 90°, decomposes into HCl and phenyl isocyanate (133).

$$C_6H_5{-}NHCOOC_2H_5 + PCl_5 \xrightarrow{55°} POCl_3 + \underset{LXXI}{[C_6H_5NHCOCl]} + C_2H_5Cl$$

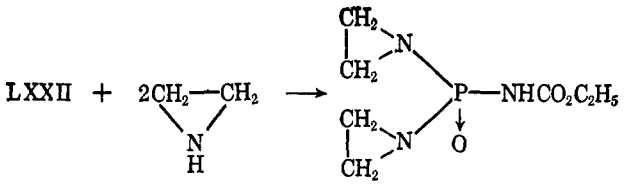
$$HCl + C_6H_5{-}NCO \xleftarrow{90°} [C_6H_5NHCOCl]$$

Reactions of Dichloro- and Trichlorophosphocarbamate Derivatives. Ethanol reacts with the isocyanato group of dichlorophosphorylisocyanate (LXVIII) under refrigeration to give 82% yield of ethyl N-dichlorophosphorylcarbamate (LXXII).

$$C_2H_5OH + \underset{\text{LXVIII}}{Cl_2PONCO} \rightarrow Cl_2PNHCOOC_2H_5 \quad (O)$$

LXXII

Alkyl N-dichlorophosphorylcarbamate (LXXII) reacts with ethylenimine to form bisaziridinylphosphorylcarbamates (LXXIII). These compounds have been studied extensively as antitumor agents (30).



LXXIII

In order for the chloro groups of LXVIII to react, strongly nucleophilic reagents must be employed; thus, only when sodium methoxide in methanol is used, can methyl dimethoxyphosphorylcarbamate (LXXIV) be obtained.

$$\underset{\text{LXVIII}}{Cl_2P(O)NCO} + CH_3OH + NaOCH_3 \rightarrow (CH_3O)_2P(O)NHCOOCH_3$$

LXXIV

Methyl dimethoxyphosphorylcarbamate reacts with amines to afford ureas (LXXV) (194).

$$\underset{\text{LXXIV}}{(CH_3O)_2P(O)NHCOOCH_3} + C_6H_5NH_2 \rightarrow (CH_3O)_2P(O)NHCONHC_6H_5$$

LXXV

Reaction with Phosphonium Halides. Phenyl trichlorophosphonium chloride (LXXVI) reacts with carbamates, affording phenylchlorophosphorylisocyanate (LXXVII) (193).

$$\underset{\text{LXXVI}}{C_6H_5PCl_3^{\oplus}Cl^{\ominus}} + II \xrightarrow{in\ vacuo} [C_6H_5P(Cl_2)=NCOOCH_3] \xrightarrow{in\ vacuo} C_6H_5P(O)(Cl)NCO + CH_3Cl$$

LXXVII

d. Silicon Derivatives

N-Silylcarbamates. Ethyl N-trimethylsilylcarbamate (LXXVIII) is formed when trimethylsilyl chloride is treated with ethyl carbamate in the presence of an organic base (353).

$$(CH_3)_3SiCl + I + R'_3N \rightarrow (CH_3)_3SiNHCOOC_2H_5 + R_3N\cdot HCl$$

LXXVIII

The free acid is formed upon hydrolysis of the carbamate with alkali. An alternate method for obtaining this same compound, although in poor yield, is the heating of ethyl carbamate with hexamethyldisilazane (LXXIX) (273).

$$\underset{\text{LXXIX}}{[(CH_3)_3Si]_2NH} + I \rightarrow LXXVIII$$

Still another method for preparing the same compound from ethyl carbamate utilizes N-(trimethylsilyl)-*t*-butylamine (LXXX) (43).

$$\underset{\text{LXXX}}{(CH_3)_3SiNHC(CH_3)_3} + I \rightarrow LXXVIII + H_2N{-}C(CH_3)_3$$

In an attempt to prepare N-triarylsilylcarbamates, a triarylsilyl chloride (LXXXI) was heated with ethyl N-sodiocarbamate (XXVIII). Triarylsilyl isocyanate (LXXXII) was the only product isolated (153).

$$\underset{\text{LXXXI}}{Ar_3SiCl} + \underset{\text{XXVIII}}{NaNHCOOC_2H_5} \rightarrow \underset{\text{LXXXII}}{Ar_3SiNCO} + NaCl + C_2H_5OH$$

E. HALOGENATION OF CARBAMATES

N-Halocarbamates are readily prepared by careful halogenation of carbamates, and their reactions parallel those of N-haloamides. In an attempted preparation of N-chlorocarbamates, Schmidt (291) passed chlorine gas through ethyl carbamate at 90–100° and obtained dichloroethylidenebiscarbamates (LXXXIII). The first reaction which occurs when ethyl carbamate is chlorinated at 90° is a decomposition affording ethanol. The ethanol is oxidized and chlorinated to dichloroacetaldehyde (LXXXIV), which then condenses with intact ethyl carbamate to afford the observed dichloroethylidenebiscarbamate (93, 321).

$$I + 3Cl_2 \rightarrow [C_2H_5OH] \rightarrow \underset{\text{LXXXIV}}{Cl_2CHCHO}$$

$$I + LXXXIV \rightarrow \underset{\text{LXXXIII}}{Cl_2CHCH(NHCOOC_2H_5)_2} + H_2O$$

1. *Preparation of Monochlorocarbamates (LXXXV)*

To prepare ethyl N-chlorocarbamate, chlorine gas is passed through a dilute aqueous solution of ethyl carbamate at 20° (91). Other methods of preparing N-monochlorocarbamates consist of passing a measured amount of chlorine gas into a carbamate solution (although the product is then often contaminated by N-dichlorocarbamates) or by treating various N-dichlorocarbamates (LXXXVI) with molar quantities of the parent unsubstituted carbamate (76, 92).

$$H_2NCOOR + \underset{\text{LXXXVI}}{Cl_2NCOOR} \rightarrow \underset{\text{LXXXV}}{2ClNHCOOR}$$

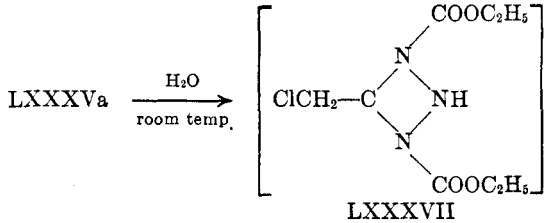
2. *Preparation of Dichlorocarbamates (LXXXVI)*

Dichlorocarbamates, especially of esters higher than ethyl, are prepared by chlorination in aqueous solution under controlled conditions, such as in the presence of calcium carbonate or sodium acetate (123). (Many carbamates do not form monochloro derivatives at all, but rather dichloro derivatives upon chlorination in

aqueous solution, *i.e.*, methyl, isoamyl, etc. (92).) Hypochlorous acid is capable of chlorinating carbamates to their dichloro derivatives (77).

3. *Reactions of Monochlorocarbamates*

Ethyl N-chlorocarbamate (LXXXVa), when in contact with water or ethanol at room temperature for several days, reportedly affords diethyl 4-chloromethylcyclomethylenehydrazinimide-1,3-dicarboxylate (LXXXVII) (93).



LXXXVII

However, recent work by Adams and Baron indicates that the product of the reaction is actually the β-chlorethylidene biscarbamate (LXXXVIII) (46).

Monochlorocarbamates are easily converted into β-chlorethylidenebiscarbamates (LXXXVIII) (321).

$$\text{LXXXVa} + (C_2H_5)_2O \rightarrow \underset{\text{LXXXVIII}}{Cl{-}CH_2CH(NHCOOC_2H_5)_2} + H_2O + C_2H_5OH + HCl$$

Monochlorocarbamates efficiently chlorinate the nitrogen atom of amines and amides, affording monochloramines or -amides (90, 265).

Ethyl N-chlorocarbamate (LXXXVa) is not merely alkylated by ethyl chloroformate, but rather abstracts a chlorine atom from the reaction intermediate (LXXXIX) and reacts further to afford ethyl N,N-dichlorocarbamate (LXXXVIa).

$$\text{LXXXVa} + Cl{-}COOC_2H_5 \rightarrow \underset{\text{LXXXIX}}{ClN(COOC_2H_5)_2}$$

$$\text{LXXXIX} \xrightarrow{ClNHCOOC_2H_5} \text{LXXXVIa} + HN(COOC_2H_5)_2$$

Ethyl N-chlorocarbamates, whose amino hydrogen is quite labile (acidic), are methylated with dimethyl sulfate to afford N-methyl-N-chlorocarbamates (321). Chlorination of N-methylated ethyl carbamate leads to the same compound. When treated with sodium in the presence of amides, N-chlorocarbamates afford allophanates (IV) (125).

$$ClNHCOOCH_3 + Na + RCONH_2 \xrightarrow{C_6H_6} \underset{\text{IV}}{RNHCONHCOOCH_3}$$

In this reaction, the starting amide ($RCONH_2$) appears to have undergone a Hofmann-type degradation, prior to its combination with the carbamate moiety.

Insecticides have been prepared from the thiophosphoric acid esters (XC) generated by the reaction of N-chlorocarbamates and acid salts of dithiophosphoric esters (XCI) (219).

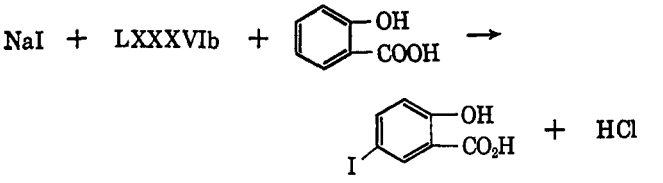
$$\underset{\text{XCI}}{(C_2H_5O)_2P(S)SNa} + \underset{\text{LXXXVa}}{ClNHCOOC_2H_5} \rightarrow \underset{\text{XC}}{(C_2H_5O)_2P(S)SNHCOOC_2H_5}$$

4. *Reactions of Dichlorocarbamates (LXXXVI)*

Ethyl N,N-dichlorocarbamate (LXXXVIa) (as well as ethyl N-chlorocarbamates) have been found to react with unsaturated hydrocarbons. Phenethylamine (XCII) has been prepared from styrene and ethyl N,N-dichlorocarbamate (77, 317).

$$\text{LXXXVIa} + C_6H_5CH{=}CH_2 \rightarrow C_6H_5CHClCH_2NClCOOC_2H_5 \xrightarrow[\text{2. hydrolysis}]{\text{1. reduction}} \underset{\text{XCII}}{C_6H_5CH_2CH_2NH_2}$$

Methyl N,N-dichlorocarbamate (LXXXVIb) reacts with salicylic acid in the presence of sodium iodide to iodinate the aromatic nucleus of salicylic acid affording XCIII (75).



XCIII

Methyl N,N-dichlorocarbamate which is 49% chlorine by weight has been patented as a means of transporting chlorine. The chlorine can be liberated from the carbamate by HCl gas (124).

$$\text{LXXXVIb} + 2HCl \rightarrow 2Cl_2 + \text{II}$$

Methyl triphenylphosphazocarboxylate (XCIV) is produced in 60% yield from the reaction of methyl N,N-dichlorocarbamate (LXXXVIb) with triphenylphosphine.

$$(C_6H_5)_3P + \text{LXXXVIb} \rightarrow \underset{\text{XCIV}}{(C_6H_5)_3P{=}NCOOCH_3}$$

The same product (XCIV) is obtained quantitatively if methyl N-sodio-N-chlorocarbamate (XCVa) ($NaNClCOOCH_3$) is used in place of the dichlorocarbamate. (Methyl N-sodio-N-chlorocarbamate (XCVa) is formed by caustic treatment of the acidic methyl N-chlorocarbamate.)

Ethyl N-sodio-N-chlorocarbamate (XCVb) reacts with phenylsulfinyl chloride (XCVI) to afford a N-carbethoxyarylimine sulfonyl chloride (XCVII) (198).

$$\underset{\text{XCVI}}{C_6H_5SOCl} + \text{XCVb} \rightarrow \underset{\text{XCVII}}{C_6H_5S(O)Cl{=}NCOOC_2H_5}$$

5. *Bromocarbamates*

Ethyl N,N-dibromocarbamate (XCVIII) results from the bromination of a caustic solution of ethyl carbamate. However, the first intermediate of this reaction, "ethyldibromoamide carboxylate sodium bromide," $[(NBr_2COOC_2H_5)_4]NaBr$ (IC), must be hy-

drolyzed with dilute sulfuric acid before XCVIII is realized (92).

$$Br_2 + I \xrightarrow{NaOH} \underset{IC}{[(NBr_2COOC_2H_5)_4]NaBr} \xrightarrow[H_2O]{H^+} \underset{XCVIII}{Br_2NCOOC_2H_5}$$

Treatment of IC with sodium amalgam and ether affords β-bromoethylidenebis(ethyl carbamate) (C) (106).

$$IC \xrightarrow[(C_2H_5)_2O]{Na\text{-}Hg} \underset{C}{Br—CH_2—CH\left[\overset{H}{|}NCOOC_2H_5\right]_2}$$

Reinvestigation of the structure of IC by modern methods may shed more light on its various reaction paths.

Bromocarbamates (as well as dichlorocarbamates) react with styrenes. The initially formed product (CI) affords pseudoephidrine (CII) upon hydrolysis (132).

$$CH_3NBrCOOC_2H_5 + C_6H_5CH{=}CHCH_3 \rightarrow \underset{CI}{C_6H_5CHBrC(CH_3)N(CH_3)COOC_2H_5}$$

$$CI \xrightarrow{H_2O} \underset{CII}{C_6H_5CH(OH)CH(CH_3)NCH_3}$$

F. REACTIONS OF CARBONYL COMPOUNDS WITH CARBAMATES

The reaction of amides with carbonyl compounds has been studied quite thoroughly in the 1950's. The advent of formaldehyde–urea condensates for coatings and of formaldehyde–fatty acid amides condensates for textile agents has greatly stimulated interest in this field.

Although carbamate esters react readily with aldehydes, commercial interest in this field has lagged owing to the high cost of ethyl carbamate. The production of carbamate esters from alcohols and urea on a commercial scale should stimulate interest in this area.

Reaction with Carbonyl Compounds. Summary. The type of product obtained when aldehydes are treated with carbamate esters depends on the pH of the reaction. Simple ketones do not react under any conditions, but ketals react in the presence of an amine hydrochloride.

$$RCHO + H_2NCOOR' \xrightarrow[alkali]{trace} \underset{CIII}{\underset{OH}{RCHNHCOOR'}} \quad (Eq. 10)$$

$$RCHO + 2H_2NCOOR' \xrightarrow[acid]{trace} \underset{CVI}{RCH(NHCOOR')_2} + H_2O \quad (Eq. 11)$$

$$RCHO + H_2NCOOR' \xrightarrow[acid]{strongly} \underset{CXXV}{(R\overset{|}{C}H—\overset{|}{N}COOR')_x} + H_2O \quad (Eq. 12)$$

Equations 10, 11, and 12 list the mode of reaction of the three primary condensation products between aldehydes and carbamate esters.

Only formaldehyde, chloral, bromal, glyoxals, and ene-als have been reported to undergo Eq. 10 type reactions. Equation 11 is a general reaction. Equation 12 seems to be general although, aside from mention of formaldehyde and chloral, the literature references are sparse.

1. Preparation of Alkyl N-Hydroxymethylcarbamates (CIII)

The reaction between formaldehyde and ethyl carbamate to form ethyl N-hydroxymethylcarbamate (CIIIa), Eq. 10, was first reported by Einhorn in 1908 (116).

$$CH_2O + I \rightarrow \underset{CIIIa}{HOCH_2NHCOOC_2H_5}$$

Trace amounts of barium hydroxide, K_2CO_3, or NaOH (127, 293) were used. To obtain sharply melting material, strict control of mole ratios and temperature are necessary. When paraformaldehyde is used, the product is obtained as a crystalline solid. As is the case of all hydroxymethyl compounds, heating causes dissociation of CIII to formaldehyde and carbamate esters.

Diol dicarbamates react with 2 moles of formaldehyde (173) and higher aldehydes (4) to form bis-N-hydroxymethyldicarbamates.

A solution containing "so-called" ethyl N,N-bishydroxymethylcarbamate (CIV), prepared by treating ethyl carbamate with 2 moles of formaldehyde, has been studied as a cotton cross linker (10).

The only extant derivative of a N,N-bishydroxymethylcarbamate was reported by Einhorn when he prepared the N,N-bischloromethylcarbamate from methyl salicylate O-carbamate, 2 moles of formalin, and 2 moles of HCl gas (118).

The reaction of acylamides with formaldehyde has been the subject of an extensive kinetic study in both acid and basic solutions (334). When equimolar quantities of chloral and ethyl carbamate are treated at a low pH, ethyl N-(2,2,2-trichloro-1-hydroxyethyl)-carbamate (CV) is formed (52, 231).

$$CCl_3CHO + I \rightarrow \underset{CV}{\underset{OH}{CCl_3CH—NHCOOC_2H_5}}$$

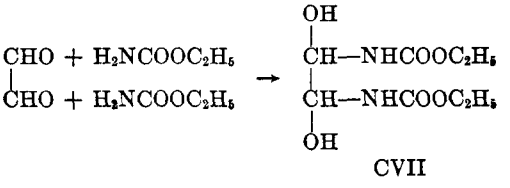
Vasilev described additional examples of aldehydes containing negative groups in the α-position reacting with carbamates to form α-hydroxyalkyl-substituted carbamates (CIIIb) (337).

$$RCHO + H_2NCOOC_2H_5 \rightarrow \underset{CIIIb}{R—\overset{H}{\underset{OH}{C}}—NHCOOC_2H_5}$$

$$R = CH_3CHClCCl_2,\ CBr_3,\ CCl_3$$

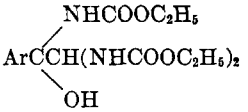
Attempts to prepare other simple N-(1-hydroxyalkyl)carbamates by heating equimolar quantities of aldehyde and carbamate on the acid side have failed. Only the N,N′-methylenebiscarbamates (CVI) were obtained (223).

Glyoxal has been shown to react with 2 moles of ethyl carbamate to form the corresponding bis-1-hydroxy compound (CVII) in the presence of base (19).



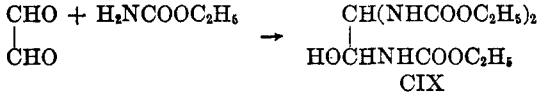
CVII

Trichlorophenylglyoxal reacts with 3 moles of ethyl carbamate to form the triester (CVIII).



CVIII

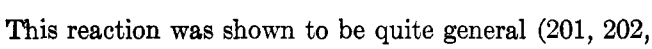
Glyoxal also reacts with 3 moles of ethyl carbamate in the presence of trace amounts of acids to form the 1,2,2-tris(carboxyethylamino)ethanol (CIX).



CIX

2. Preparation of Methylenebiscarbamates (CVI)

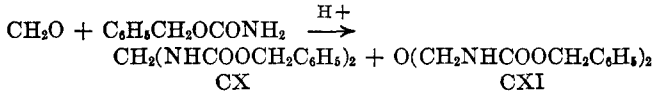
Conrad, in 1903 (81), described the preparation of methylenebis(ethyl carbamate) (CVI) by the reaction of 2 moles of ethyl carbamate and 1 mole of formaldehyde in the presence of trace amounts of mineral acids.



CVI

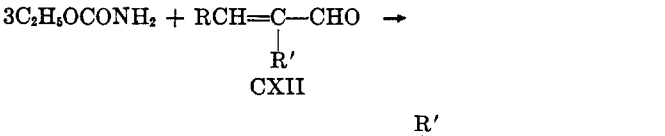
This reaction was shown to be quite general (201, 202, 209). Numerous examples of combinations of different carbamates and aldehydes are given.

The report by Wolfrom and co-workers (362) that neither formaldehyde nor butyraldehyde condensed with benzyl carbamate has been disputed. Formaldehyde has been shown to react with benzyl carbamate to form the methylenebis(benzyl carbamate) (CX) and N,N′-carboxybenzylaminodimethyl ether (CXI) (247).



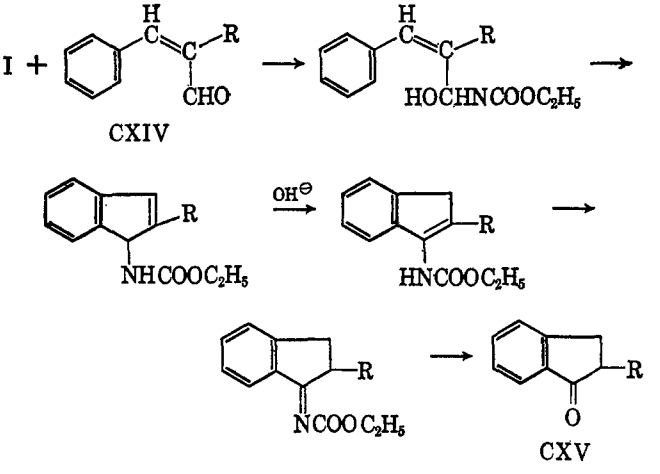
CX CXI

Substituted acroleins (CXII) have been treated with 3 moles of ethyl carbamate in a combination of Michael-type reaction and normal aldehyde condensation (CXIII) (201, 209).



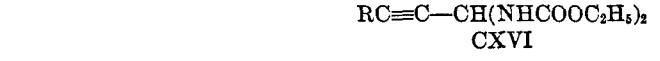
CXII CXIII

Cinnamaldehyde condensed with only 2 moles of ethyl carbamate to form the cinnamylidenebis(ethyl carbamate). No addition across the double bond was observed. On the other hand, the 2-alkylcinnamaldehyde (CXIV) added 1 mole of ethyl carbamate and cyclized to the substituted indanone (CXV) (200) in 48–55% yield.



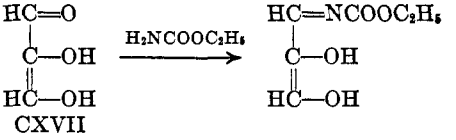
CXIV CXV

The analogous acetylenic aldehydes behaved normally in their reactions with ethyl carbamate and formed the alkylidenebiscarbamates (CXVI) (340).



CXVI

One mole of ethyl carbamate reacted with *aci*-reductones (CXVII) only at the aldehyde carbonyl group (122).



CXVII

Bischoff (52) reported that mono- or dichloroacetaldehyde (LXXXIV) condensed with ethyl carbamate in the presence of a trace of acid to form the corresponding alkylidenebiscarbamates (CVI) while chloral gave only the N-(2,2,2-trichloro-1-hydroxyethyl carbamate) (52).

These chlorinated carbamates can be formed *in situ* by the chlorination of a mixture of ethanol and ethyl carbamate. When methanol is used in place of ethanol, methylenebis(ethyl carbamate) is formed.

In the presence of traces of mineral acid, α-keto acids were treated with carbamate esters to form α,β-bis(carbethoxyimino) acids (CXVIII) (300). These compounds, on heating to 140°, lost 1 mole of ethyl carbamate (223) to form α-(N-carbethoxyimino)acrylic acid (CXIX).

$$2H_2NCOOC_2H_5 + CH_3COCOOH \rightarrow CH_3C(NHCOOC_2H_5)_2 \rightarrow CH_2{=}C(COOH){-}NHCOOC_2H_5$$

CXVIII CXIX

When the product of the condensation of phenylglyoxylic acid and benzyl carbamate, an imino acid (CXX), decarboxylates, a derivative of an imine (CXXI) is formed.

$$C_6H_5{-}C(=O){-}COOH + H_2NCOOCH_2C_6H_5 \rightarrow C_6H_5C(=NCOOCH_2C_6H_5){-}COOH \rightarrow C_6H_5CH{=}NCOOCH_2C_6H_5$$

CXX CXXI

Hydrogenolysis of the intermediate imino acid (CXX) formed the corresponding α-amino acids.

Acetals were condensed with carbamates in the presence of trace amounts of acids to form alkylidenebiscarbamates (CVI). Presumably, the aldehyde was formed from the acetal prior to reaction with the carbamates (201, 209).

When α,β-dibromoethyl acetate (CXXII) is heated with ethyl carbamate, replacement of the α-substituents occurred stepwise, *i.e.*, CXXIII and CXXIV (5).

$$H_2NCOOC_2H_5 + CH_2Br{-}CHBr(OAc) \rightarrow$$

CXXII

$$CH_2Br{-}CH(OAc){-}NHCOOC_2H_5 \rightarrow CH_2Br{-}CH(NHCOOC_2H_5)_2$$

CXXIII CXXIV

3. "Anhydro Methylene" Carbamates (C=N—) (CXXV)

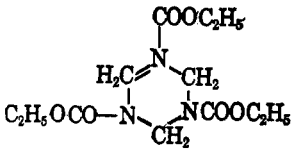
When formaldehyde and ethyl carbamate were heated with strong mineral acid, "anhydro methylene" carbamates (CXXV) were formed (81). Bischoff and Reinfeld (53) erroneously proposed the dimeric structure (pseudo-CXXV).

$$CH_2O + H_2NCOOC_2H_5 \rightarrow CH_2{=}NCOOC_2H_5 \text{ or } C_2H_5OC(=O){-}N(CH_2){-}COOC_2H_5$$

pseudo-CXXV

Giva and Raccin (153), and later Marvel and his coworkers (225), showed that this compound was actually a trimer and had the hexahydrotriazine ring structure (CXXV).

When acid-formed urethan–formaldehyde polymers were heated at 100°, depolymerization occurred and



CXXV

triscarbalkoxyhexahydrotriazines were formed (145). George and Tuemmler also prepared these compounds by acylation of hexahydrotriazine with alkyl chloroformates in the presence of an acid absorber (146).

Marvel could not replace the ester group of the formaldehyde carbamate trimer with an amide.

$$>NCOOR + NH_3 \not\rightarrow >NCONH_2$$

The reaction between allyl carbamate, concentrated hydrochloric acid, and either formaldehyde, citral, acetaldehyde, and glyoxal has been said to form the corresponding "anhydro derivatives" in 50–90% yield (154), although the reported assay values leave something to be desired.

The reaction of glyoxal with 2 moles of ethyl carbamate in the presence of strong hydrochloric acid was studied by Pauly (264). (For reaction in dilute hydrochloric acid see section VIIIF1.) He reported the formation of the glyoxal biscarbethoxyimine (CXXVI).

$$CHO{-}CHO + 2I \xrightarrow{HCl} CH(=NCOOC_2H_5){-}CH(=NCOOC_2H_5) + 2H_2O$$

CXXVI

Gaylord (139) used lithium aluminum hydride to reduce the glyoxal carbamate condensate to N,N′-dimethylethylenediamine. Heating the condensate to 200° in tetralin resulted in cleavage to form 2 moles of ethyl carbamate and 1 mole of acetylene.

The $CCl_3CH{=}NCOOC_2H_5$ formula proposed for "anhydro chloral urethan" prepared by heating chloral with ethyl carbamate was shown to be in error (129).

Although simple ketones do not react with carbamate esters, various fluoroketones do (see analogous chloral reaction, section VIIIF2).

When either tetrafluorodichloroacetone or perfluoroacetone was treated with isopropyl carbamate, the α-hydroxyalkylamide was obtained (248a).

$$(CF_3)_2CO + H_2NCOOC_3H_7 \rightarrow (CF_3)_2CHOHNHCOOC_3H_7$$

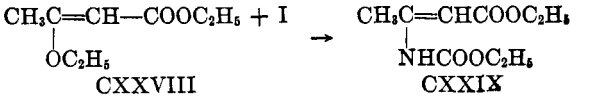
Hoch reported that the reaction between ketals (as contrasted to ketones) and carbamates is a general reaction. He stated that the product (CXXVII) of the reaction between ketals and carbamates in the presence of an acid catalyst contains the imino group (170).

$$R_2C(OC_2H_5)_2 + I \rightarrow R_2C{=}NCOOC_2H_5 + 2C_2H_5OH$$

CXXVII

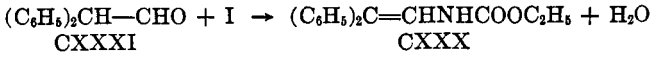
The low boiling points of these condensates seem to indicate that these compounds are monomeric and not

trimeric as contrasted to the trimeric aldehyde–carbamate condensates. Hoch also found that the ethoxy group of ethyl 3-ethoxycrotonate (CXXVIII) was replaced by the carbamate moiety upon treatment with ethyl carbamate to afford CXXIX.



CXXVIII CXXIX

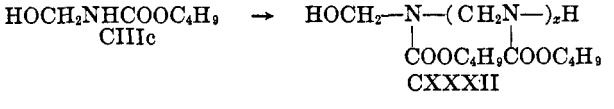
Acyl enamines (CXXX) have been prepared (113) by heating diphenylacetaldehyde (CXXXI) with ethyl carbamate in the presence of toluenesulfonic acid.



CXXXI CXXX

Miscellaneous. The copolymerization of cyanic acid with paraformaldehyde was reported in 1962 (208) to form $(-CH_2O-)_x(\underset{\displaystyle O}{\overset{\displaystyle \|}{C}}-NH-)_y$.

U-Resins (CXXXII) were formed (266) when N-hydroxymethylcarbamates (CIIIc) were heated to high temperatures.



CIIIc CXXXII

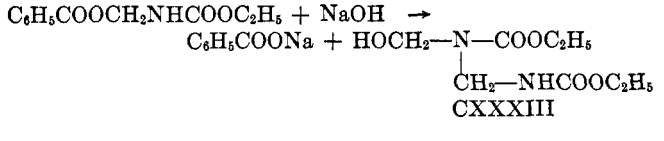
When the 1,1-di-(H)-perfluoroalkyl ester was used, compounds corresponding to $x = 1$, $x = 2$, were isolated and characterized (248).

4. *Reactions of N-Hydroxymethylcarbamates (CIII)*

a. General

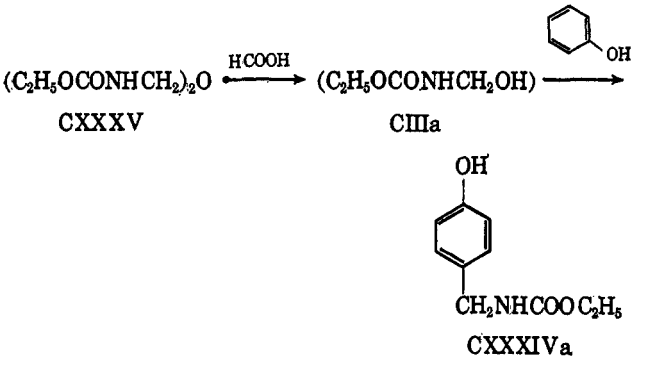
The reactions of hydroxymethylcarbamates and hydroxymethylamides are very similar. Although the literature has abundant references to the reactions of alkyl N-hydroxymethylcarbamates (CIII), it was not until the work of Zigeuner (365, 366), in 1951, that a systematic study of the chemical properties of these compounds was begun.

In the earlier work of Einhorn (115, 116) the treatment of ethyl N-benzoyloxymethylcarbamate with alkali gave a compound described as the N-hydroxymethylmethylenebisamide (CXXXIII).

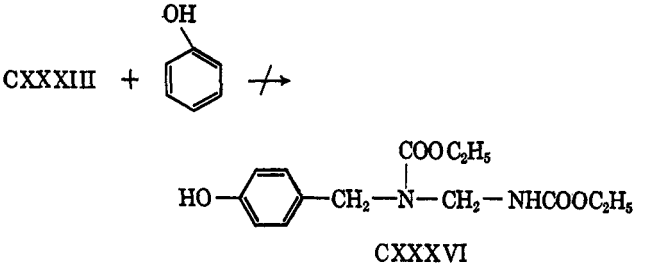


CXXXIII

Zigeuner proved the structure to be CXXXV by its reaction with phenol in formic acid at 50° to form 2 moles of compound CXXXIVa. Apparently in formic acid the acetal group $-O-CH_2-O-$ is hydrolyzed, affording 2 moles of an N-hydroxymethyl intermediate (CIIIa). The erroneously reported structure CXXXIII should have produced the N-(4-hydroxyphenylmethyl)-carbamate (CXXXVI) under these conditions.



CXXXV CIIIa CXXXIVa



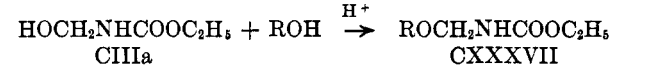
CXXXIII

CXXXVI

In his earlier investigation of N-hydroxymethylcarbamates (CIII) and methylenebiscarbamates (CVI), Zigeuner had shown that N-hydroxymethylcarbamates, but not methylenebiscarbamates, will alkylate phenols in the presence of formic acid to form carbethoxyaminomethylphenols (CXXXIV).

Zigeuner then concluded that above pH 4, the oxygen atom of hydroxymethylcarbamate was alkylated by another ethyl hydroxymethylcarbamate to form the bismethylene ether (CXXXV), and below pH 4 the nitrogen atom was alkylated to form the unstable hydroxymethyl compound (CXXXIII) which then dissociated to the stable methylenebisamide and formaldehyde.

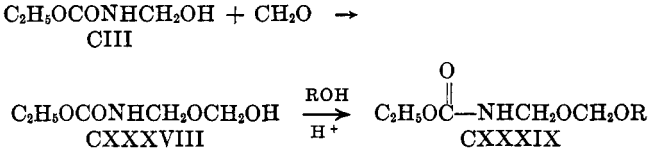
When ethyl N-hydroxymethylcarbamate (CIIIa) was refluxed for a short time with methanol (R = methyl) and a trace of hydrochloric acid, the methyl ether (CXXXVII) was formed (368).



CIIIa CXXXVII

This compound had been prepared previously by the Curtius degradation of methoxyacetylazide (56).

In the presence of acid, methyl N-hydroxymethylcarbamate condensed with another mole of formaldehyde to form the mixed acetal CXXXVIII; if methanol is used, the methyl N-methoxymethylcarbamate acetal is formed. Zigeuner showed that the structure was a linear acetal (CXXXIX).



CIII CXXXVIII CXXXIX

TABLE III

Acidic component = Z	Product (CXLI)	Ref.
	Formaldehyde	
H_2NCSNH_2	$H_2N-\underset{\underset{NH_2\cdot HCl}{\|}}{C}-SCH_2NHCOOC_2H_5$	159
$NH_4^{\oplus\ominus}OAc$	$RNHCH_2NHCOOC_2H_5$	283
$RNH_3^{\oplus\ominus}OAc$		
R_2NH	$R_2NCH_2NHCOOC_2H_5$	167, 283
H_2NSO_3Na	$Na^{\oplus\ominus}SO_3NHCH_2NHCOOC_2H_5$	24, 128
$(CH_3)_2NH + CS_2$	$(CH_3)_2NC-\underset{\underset{S}{\|}}{S}-CH_2NHCOOC_2H_5$	220
$HOCH_2SO_2Na$	$Na^{\oplus\ominus}SO_2CH_2NHCOOC_2H_5$	312
$(RO)_2PS_2H$	$(RO)_2PS_2CH_2NHCOOC_2H_5$	232
$(RO)_2PS_2H$	$[(RO)_2PS_2CH]_2NCOOC_2H_5$	269
$HOCH_2COOH$	$HOC\underset{\underset{O}{\|}}{C}H_2OCH_2NHCOOC_2H_5$	181
ROH	$ROCH_2NHCOOC_2H_5$	21
HCl	$ClCH_2NHCOOC_2H_5$	25, 111
$ArSO_2H$	$ArSO_2CH_2NHCOOC_2H_5$	119a
$ArSO_2Cl$	$ArSO_2CH_2NHCOOC_2H_5$	119a
$(RCO)_2O$	$RCOOCH_2NHCOOC_2H_5$	126
$(NO_2)_3CH$	$(NO_2)_3CHCH_2NHCOOC_2H_5$	252
	Acetaldehyde	
$(CH_3CO)_2CH_2$	$(CH_3CO)_2CH-\underset{\underset{CH_3}{\|}}{C}HNHCOOC_2H_5$	47
$CH_3COCH_2COOC_2H_5$	$CH_3COCH\underset{\underset{COOC_2H_5}{\|}}{C}HNHCOOC_2H_5$	48
	Benzaldehyde	
RSH or $HSCH_2COOH$	$RS\underset{\underset{COOC_2H_5}{\|}}{C}HNHCOOC_2H_5$	301
$CH_3COCH_2COOC_2H_5$	$CH_3COCH\underset{\underset{C_6H_5}{\|}}{C}HNHCOOC_2H_5$	48
$C_6H_5COCH_2COCH_3$	$C_6H_5COCH\underset{\underset{COCH_3}{\|}}{\overset{\overset{C_6H_5}{\|}}{C}}HNHCOOC_2H_5$	207
$CH_3COCH_2COCH_3$	$(CH_3CO)_2CH\underset{\underset{C_6H_5}{\|}}{C}HNHCOOC_2H_5$	207
$HCN(C_6H_5CHOH)$ (CN)	$C_6H_5-\underset{\underset{NHCOOC_2H_5}{\|}}{CH}-CN$	207

Arcenaux and co-workers reported the use of a solution of slightly over 2 moles of formaldehyde and 1 mole of ethyl carbamate as a textile coating agent (10). They postulate the formation of ethyl N,N′-bishydroxymethylcarbamate and its subsequent reaction with cellulose to give a cross-linked finish. They claim that the lack of an imino hydrogen gives the fiber good chlorine wash resistance. Considerable doubt has been expressed as to the correctness of their structure CIV in light of the work by Zigeuner.

A derivative (CXL) of ethyl N,N-bishydroxymethylcarbamate (CIV) has been synthesized by Zigeuner in 25% yield by heating 2 moles of phenol with 2 moles of formaldehyde and 1 mole of ethyl carbamate in the presence of formic acid at 50° (367).

$$2HOC_6H_5 + 2CH_2O + H_2NCOOC_2H_5 \rightarrow (HOC_6H_4CH_2)_2NCOOC_2H_5$$

CXL

N-Hydroxymethylcarbamates upon reaction with simple carboxylic acid amides formed mixed methylene bisamides (370).

b. Mannich Reactions

Carbamate esters can take part in the Mannich reaction as the amino component in the reaction of formaldehyde (R = H) with active hydrogen compounds. The use of preformed N-hydroxymethylcarbamate or its individual components have been found to be equivalent.

$$HZ + RCHO + H_2NCOOC_2H_5 \rightarrow RCH(Z)NHCOOC_2H_5 + H_2O$$

CXLI

In Table III are listed the components used in the Mannich reaction.

A comprehensive study of the products obtained from the reaction between formaldehyde and higher fatty acid amides has been published. The preparation and analysis of the infrared patterns of the various formaldehyde–amide condensates have been presented (62).

Weaver, Schuyten, Frick, and Reid (348) compared the properties of $RCONHCH_2OR$ with $ROCH_2OR$ (R = stearyl) and found the nitrogen analogs were more stable.

5. Reactions of Diol Carbamates with Aldehydes

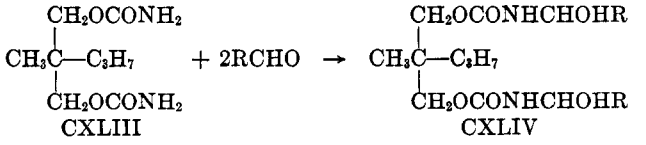
Diol monocarbamates (VII) can react with up to 3 moles of formaldehyde to give mono- and di(hydroxymethyl) compounds on the alkaline side and methylenebiscarbamates and mixed formals on the acid side (308). N-Hydroxymethyl diol monocarbamates have been treated with aryl diisocyanates to form polyurethan resins (310).

With equal molar ratios, diol monocarbamates (VII) were condensed with formaldehyde to form tetramers and polymers (CXLII) (309).

$$HO-\left[-CH_2-N(CO-O-C_2H_4OH)-\right]_4H$$

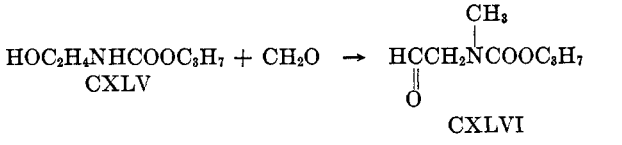
CXLII

On the acid side, dicarbamates react with formaldehyde to give methylenebiscarbamate polymers (261, 350). The preparation of crystalline bis-N,N′-hydroxymethyldiol dicarbamates has been claimed (327). The reaction of formaldehyde and higher aldehydes with meprobamate (CXLIII) has been described (4).



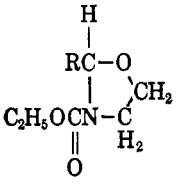
CXLIII CXLIV

Aldehydes were condensed with β-haloethyl carbamates in the normal manner to form β-haloethyl methylenebiscarbamates (59, 60, 98). N,N-Bishydroxymethylbutynediol dicarbamate, when treated with ammonium chloride, gave a hard resin (173). When propyl N-β-hydroxyethylcarbamate (CXLV) is heated with formaldehyde at 145°, simultaneous reductive alkylation on the nitrogen and oxidation of the alcohol to aldehyde CXLVI occurred (169).



CXLV CXLVI

With simple aldehydes on the other hand, N-β-hydroxyethylcarbamates form N-carboxyethyloxazolidones (CXLVII) (280).

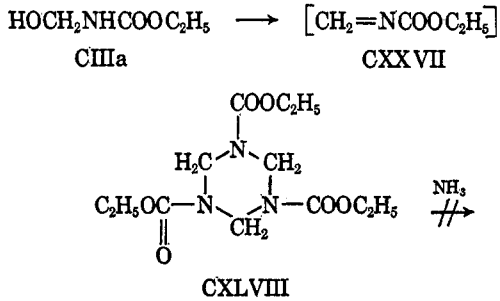


CXLVII

G. REACTIONS OF "ANHYDRO METHYLENE" CARBAMATES (CXXVII)

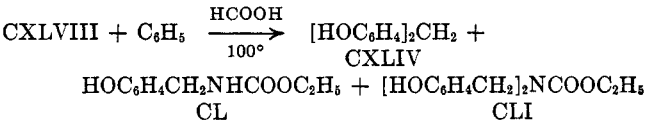
The dehydration of ethyl N-hydroxymethylcarbamate (CIIIa) *via* "methylene urethan" (CXLVII) to the triscarbethoxyhexahydrotriazine (CXLVIII) has been used by many workers to study this triazine ring system. Work by Merten and Muller has shown that the intermediate derived from methylenebiscarbamate can participate in both the Diels–Alder reaction and the Prins reaction.

Marvel and co-workers attempted to convert the N-carbethoxy group of the hexahydrotriazine (CXLVIII) (derived from the dehydration of ethyl N-hydroxymethylcarbamate) to the amide with ammonia but did not succeed (225).



CIIIa CXXVII CXLVIII

Zigeuner, in a continuation of his study of the reaction between formaldehyde–carbamate condensates and phenols, found that the triazine ring cleaved when the "methylene" carbamate was heated with a phenol in formic acid just below 100° (365, 366). Compounds were formed, according to the equation



CXLVIII CXLIV CL CLI

The same reaction, carried out at 50° for 48 hr., afforded equimolar quantities of CL and CLI only.

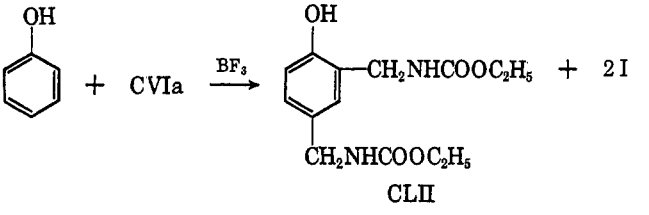
Higher alkyl esters have been prepared by the reaction of the corresponding chloroformate ester with hexahydrotriazine *in situ* (146). These authors claim that the ester grouping can undergo transesterification reactions, but no details were given.

H. REACTIONS OF METHYLENEBISCARBAMATES (CVI)

Zigeuner showed that the methylene bridge of methylenebiscarbamates (CVI) does not react with phenols in formic acid solution at 50° for 3 hr. (365). However, at 100°, the following Mannich-type reaction takes place in 95% yield.

CVIa

Merten, using BF_3 as a catalyst, alkylated phenols in 70–90% yields to CLII with methylenebis(ethyl carbamates) (235).

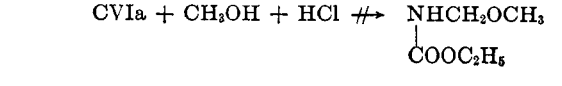


CLII

A Mannich reaction involving phenol, formaldehyde, and ethyl carbamate should undergo the same type of reaction.

Bianci used ethylidinebis(ethyl carbamate) (CVIb) as the amine-plus-aldehyde component in the Mannich reaction with acetylacetone (47).

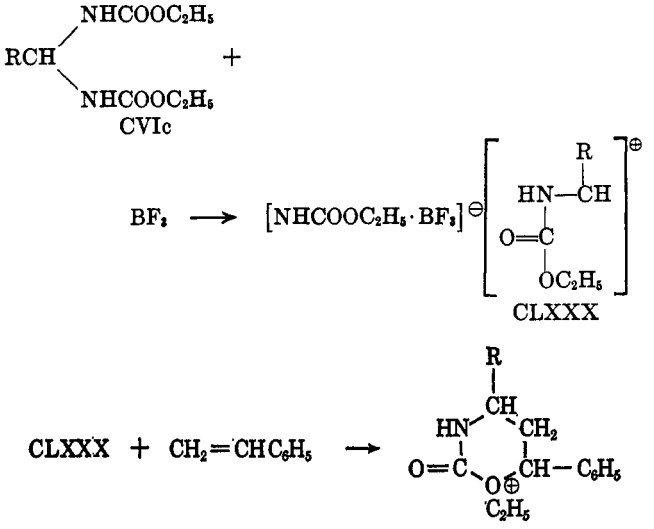
Methylenebiscarbamates do not react with methanol and HCl (368).



The work of Merten and co-workers using BF_3 catalysis has expanded the chemistry of methylenebiscarbamate esters to an exciting degree. They have

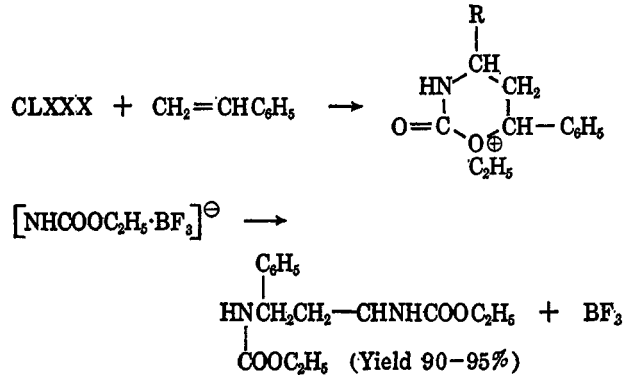
used these esters successfully as a component in the Prins reactions leading to new heterocyclics and new reaction paths (233, 234, 237).

Merten and Muller in 1962 showed that methylene-bis-carbamates can be used in the Prins reaction (14) by preparing N,N′-bisalkoxycarbonyl-1-phenylpropane-1,3-diamine (CLIII), by the reaction of styrene with the methylenebiscarbamates (CVIc), in the presence of 15–20 mole % BF_3 (237). Their mechanism is shown below.



CVIc

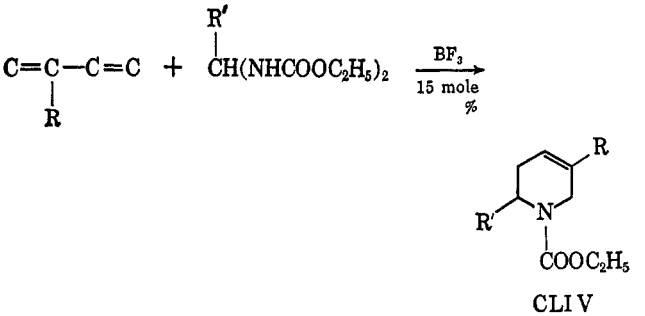
CLXXX



CLIII

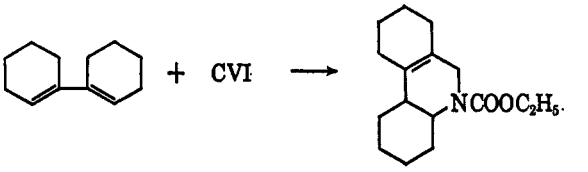
These products were hydrolyzed at high temperatures to the corresponding aryltrimethylenediureas and diamines. No telemers were observed.

Merten and Muller further expanded the "Prins"-type reactions of methylene biscarbamates, when they substituted dienes for olefins in their study. This led to a general method for the preparation of 2,(4,5)-dialkyl-Δ-2-piperidine-N-carboxylic esters (CLIV).

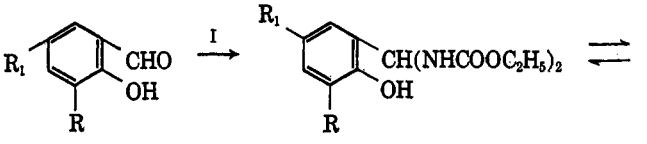


CLIV

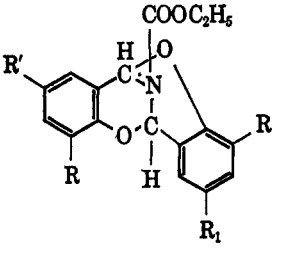
Of the butadienes, only substituted butadienes give good yields; for example



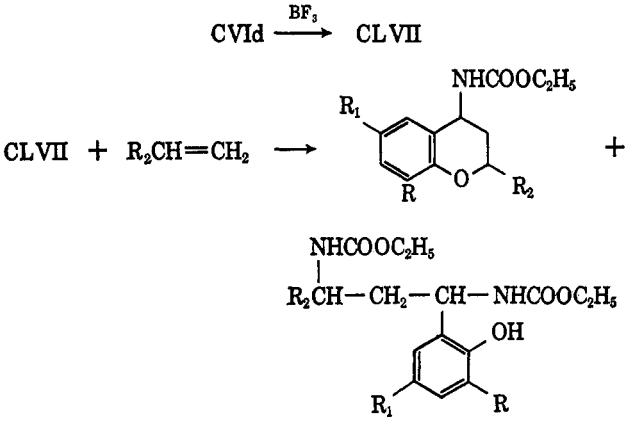
In a continuation of their studies with methylenebis-carbamates, Merten and Muller found that the bis-carbamates (CVId) from *o*-hydroxybenzaldehydes react with olefins to form chromans (CLV) (237). The intermediate (CLVII) is similar to CLXXX.



CVId

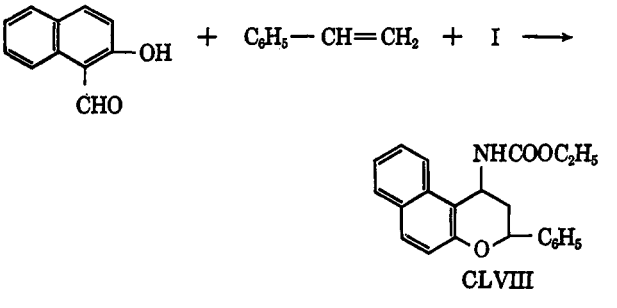


CLV



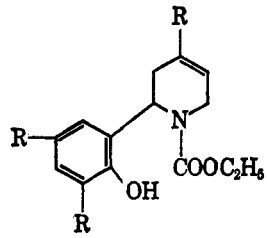
Aluminum chloride and concentrated hydrochloric acid also served as catalysts.

Benzoflavans (CLVIII) were obtained when 2-hydroxynaphthaldehyde was condensed with styrene and ethyl carbamate.



CLVIII

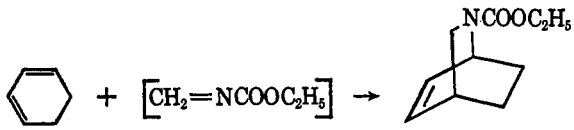
With dienes, CVId forms the 2-vinyl homolog along with lesser amounts of the tetrahydropyridine compounds (CLIX)



CLIX

Compound CLV was formed when 1 mole of salicylaldehyde and 2 moles of ethyl carbamate were heated with BF_3 under azeotropic conditions. The best yields were obtained when the aldehyde was in molar excess.

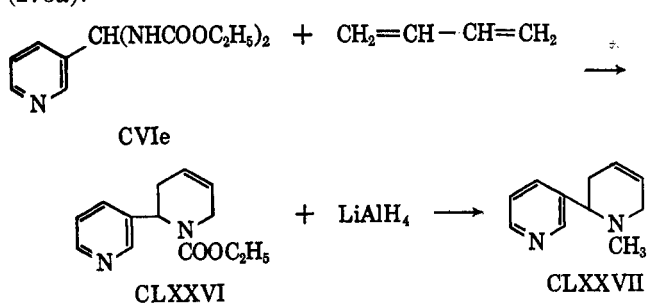
Cava and Wilkens (73a) applied the Merten method to the synthesis of isoquinuclidine. In the presence of BF_3, methylenebis(ethyl carbamate) condenses with cyclohexadiene-1,3 to form 2-carbethoxy-2-azabicyclo-[2.2.2]oct-5-ene (CLX).



CXXVII CLX

In contrast to Merten's contention that the reactive intermediate (arising from the treatment of a biscarbamate with BF_3) is a carbonium ion (CLXXX), $^{\oplus}CH_2$-$NHCOOC_2H_5$, Cava considers the intermediate to be an uncharged, reactive dienophile, $H_2C{=}N{-}COOC_2H_5$ (CXXVII).

The alkaloid anatabine (CLXXVII) was synthesized by the synthetic route developed by Merten and Muller. Quin and co-workers condensed the biscarbamate (CVIe) of 3-pyridinealdehyde with butadiene in the presence of a massive excess of BF_3 to form CLXXVI. Reduction of the ester group of CLXXVI with lithium aluminum hydride gave *d,l*-anatabine (CLXXVII) (273a).



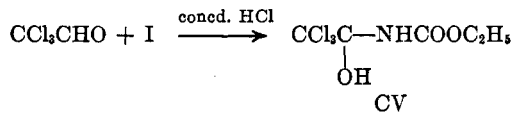
CVIe

CLXXVI CLXXVII

I. REACTIONS OF CHLORAL CARBAMATE CONDENSATES

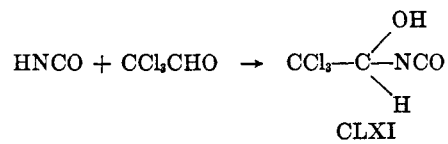
The stability of the trichloromethyl group leads to anomalous reactions of chloral "urethan." The chemistry of this intermediate needs to be studied in greater depth.

In his studies on the reaction of aldehydes with carbamates, Bischoff (52) reported the formation of alkylidenebiscarbamates (CVI) when catalytic quantities of concentrated hydrochloric acid were used. However, when chloral (trichloroacetaldehyde) is employed as the aldehyde, only the intermediate hydroxymethyl derivative (CV) was formed.



CV

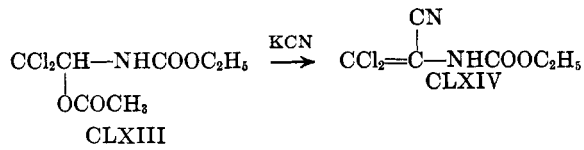
This is a nitrogen analog of a hemiacetal. It should be possible to prepare this compound by the reaction of 1-hydroxy-2,2,2-trichloroethyl isocyanate (CLXI) with methanol. This isocyanate (CLXI) is formed by the reaction of isocyanic acid with chloral at low temperatures (176).



CLXI

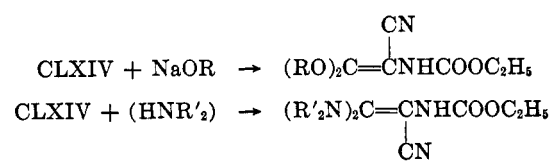
Among its reactions, chloral urethan (CV) reacts with dimethyl sulfate in the presence of alkali to form an ether. With phosphorus pentachloride, chloral bisurethan, $CCl_3CH(NHCOOC_2H_5)_2$ (CLXII), and pentachloroethane are formed.

Treatment of acetyl chloral urethan (CLXIII) with 2 moles of potassium cyanide resulted in the formation of N-(2,2-dichloro-1-cyanovinyl)carbamate (CLXIV).



CLXIII CLXIV

In this last reaction, the acetoxy group was replaced by the cyano group, and dehydrohalogenation occurred to form the olefin (CLXIV). The structure of CLXIV was confirmed by ozonolysis (103), affording phosgene and an oxalic acid derivative. The conjugated vinyl chlorine groups were easily replaced by ethoxy or amino groups.



Moscheles (241) studied the reactivity of the hydroxyl group of CV and converted it to the compound pseudo-CLXV by first esterifying the hydroxyl group *in situ* with benzoyl chloride and then splitting out benzoic acid by treatment with cold dilute alkali to afford "anhydro chloral urethan" (pseudo-CLXV).

$$CCl_3CHOH \quad + ArCOCl \rightarrow CCl_3CHOCOAr \rightarrow$$
$$NHCOOC_2H_5 \qquad\qquad NHCOOC_2H_5$$
$$CV$$
$$[CCl_3CH{=}NCOOC_2H_5]$$
$$\text{pseudo-CLXV}$$

The actual structure of "anhydro chloral urethan" was shown (129) to be an ether (CLXV) which can exist as a racemic form (m.p. 143°) and a *meso* form (m.p. 164°).

$$2CV \rightarrow CCl_3{-}CHNHCOOC_2H_5$$
$$O$$
$$CCl_3{-}CHNHCOOC_2H_5$$
$$\text{CLXV}$$

The ether CLXV can be distilled under vacuum, split with dilute alkali, but surprisingly is stable to fuming nitric acid. "Anhydro chloral urethan" (CLXV) does not react with dimethyl sulfate or phenyl isocyanate. Diels and Seib (107) studied the reactivity of "anhydro chloral urethan" with various anions (Z).

$$CLXV + NaZ \rightarrow CCl_3CHNHCOOC_2H_5$$
$$Z$$
$$\text{CLXVI}$$

With alcoholic sodium ethoxide, ethyl chloral urethan (CLXVI, Z = ethoxy) was formed. Hantzsch (163) had earlier prepared the same compound but assigned an incorrect formula to it.

When diethyl sodiomalonate (Z = $CH(COOC_2H_5)_2$) or ethyl N-sodiocarbamate (Z = $NHCOOC_2H_5$) were used, yields of CLXVI under 50% were obtained. The malonic ester intermediate (CLXVIa) was hydrolyzed by hydrogen bromide to 4,4,4-trichloro-3-aminobutyric acid.

$$CCl_3CHNHCOOC_2H_5 \xrightarrow{HBr} CCl_3CHNH_2$$
$$CH(COOC_2H_5)_2 \qquad\qquad CH_2COOH$$
$$\text{CLXVIa}$$

The poor yields obtained by Diels could be explained by the following equation (129).

$$CLXV + NaZ \rightarrow CCl_3CHNHCOOC_2H_5 + CLXVI$$
$$ONa$$

There is enough doubt remaining as to the structure of "anhydro chloral urethan" to warrant its re-examination in light of modern analytical techniques.

J. REACTIONS OF N-HYDROXYCARBAMATES (CLXVII)

Interest in alkyl N-hydroxycarbamates arises from their use as precursors for the preparation of nitrogen- and/or oxygen-substituted hydroxylamine derivatives. The reactions of the carbethoxy group *per se* have not been studied thoroughly.

The formation of ethyl N-hydroxycarbamate (CLXVIIa) by the reaction of ethyl chloroformate, hydroxylamine hydrochloride, and alkali was first described by Hantzsch (163).

N-Alkyl-N-hydroxylamines were condensed in a similar manner with ethyl chloroformate (369).

$$C_2H_5OCCl + H_2NOH\cdot HCl \xrightarrow{base} C_2H_5OCNHOH$$
$$O \qquad\qquad\qquad\qquad\qquad\qquad O$$
$$\text{CLXVIIa}$$

This compound could also be prepared by the condensation of diethyl carbonate and hydroxylamine hydrochloride in the presence of 2 equiv. of sodium ethoxide (163). Its properties were investigated in great detail by Jones (188), who improved the method of preparation and found ethyl N-hydroxycarbamate to be a viscous, water-soluble liquid giving the typical ferric chloride test for hydroxamic acids. Its decomposition at 180° to ethyl carbamate was also described. As this latter compound was at a lower reduction level than ethyl N-hydroxycarbamate, more deep-seated reactions must have occurred.

Nicolaus (250) reported that the ethyl N-hydroxycarbamate decomposed explosively upon large-scale distillation at 115–120° (0.2 mm.). The infrared spectra and melting points of various N-hydroxycarbamates have been reported (94). Ethyl N-hydroxycarbamate can be alkylated stepwise by reacting its sodium salt with alkyl iodides or alkyl sulfonates (250). The monoalkylated product obtained was the O-alkyl derivative (28, 195) which was soluble in alkali (83, 188). The dialkylated product was neutral. Treatment of these alkylated hydroxycarbamates with hydrochloric acid gave the corresponding alkylated hydroxylamine salt. With alkali, the free base was obtained (83). *o*-Alkyl-N-phenyl-N-hydroxycarbamates were not hydrolyzed by acids or bases.

Ethyl N-hydroxycarbamate was heated in a stepwise manner with ethyl chloroformate in the presence of base to form first diethyl N-hydroxyiminodicarboxylate (CLXVIII) and then O,N,N-hydroxyiminotricarboxylic esters (CLXIX) (369).

$$CLXVIIa + ClCOOC_2H_5 \rightarrow HON(COOC_2H_5)_2 \rightarrow$$
$$\text{CLXVIII}$$
$$O$$
$$C_2H_5OCON(COOC_2H_5)_2$$
$$\text{CLXIX}$$

Winternitz (361) reported the formation of ethyl O-(2-hydroxyethoxy)carbamate (CLXXI) by the treatment of the corresponding diester (CLXX) with lithium aluminum hydride at 0°.

$$HNCOOC_2H_5 \xrightarrow[0°]{LiAlH_4} HNCOOC_2H_5$$
$$OCH_2COOC_2H_5 \qquad\qquad OCH_2CH_2OH$$
$$\text{CLXX} \qquad\qquad \text{CLXXI}$$

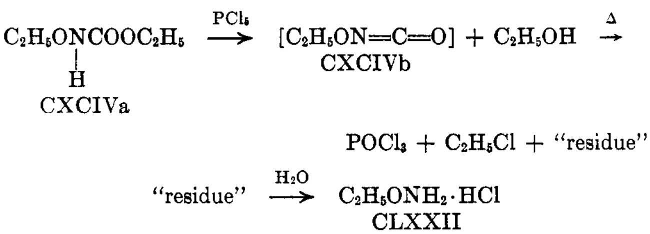
The chemistry of *t*-butyl N-hydroxycarbamates has been studied by Carpino (72). Benzoylation of ethyl N-hydroxycarbamate gave the corresponding O-benzoyl derivative (188), which when cleaved with hydrogen

chloride gave the unstable O-benzoylhydroxylamine hydrochloride salt. The O,N-dibenzoyl derivative of ethyl N-hydroxycarbamate was prepared by Jones (188).

The properties of N-phenoxycarbamates were studied by Steinberg and Bolger (319). They reported that these compounds behave as typical hydroxamic acids, except in phosphorylation or sulfation reaction, *i.e.*, conditions for the Lössen rearrangement. These compounds did not undergo the Lössen rearrangement owing to increased resonance stability of the starting material.

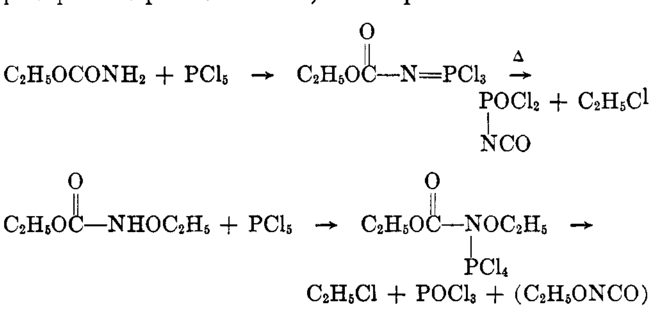
The different silver salts of N-hydroxycarbamates were studied by Oesper (253), who found the silver bound to the nitrogen instead of to oxygen. It was noted that these compounds are polychromic.

In an attempt to prepare the O-alkyl carbon dioxide monoxime (CXCIVb), Jones (188) treated CXCIVa with phosphorus pentachloride according to the following scheme.



Heating this mixture gave ethyl chloride, phosphorus oxychloride, and a heat-sensitive residue. When the reaction mixture was poured into water, a good yield of O-alkylhydroxylamine hydrochloride (CLXXII) was obtained.

It is interesting at this point to review Kirsanov's work with phosphorus pentachloride. (See section VIIID2c on the reaction of ethyl carbamate with phosphorus pentachloride.) The products were

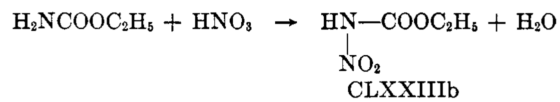


K. ALKYL-N-NITRO- AND N-NITROSOCARBAMATES

1. Preparation

The preparation of N-nitrocarbamates by nitration of carbamates in acetic anhydride has provided a convenient source of these materials. A restudy of the reaction of the nitrocarbamate anion $(N(NO_2)COOR)^{\ominus}$ should lead to fruitful results.

The ammonium salt of methyl N-nitrocarbamate (CLXXIIIa) was first prepared (324) by the reaction of ethyl nitrate with methyl carbamate and sulfuric acid. The resultant oil was treated with ammonia to form the salt. The use of 500% excess of fuming nitric acid (174) with N-alkylcarbamates gives the N-nitro-N-alkylcarbamate (CLXXVIII). By using a mixture of fuming nitric acid in excess acetic anhydride, N-nitro- (87, 174) and N-nitro-N-alkylcarbamates (87) were formed in excellent yields.



Thomas (325) claimed that equimolar quantities of 100% nitric acid and acetic anhydride can be used to prepare N-nitrocarbamates. The rate of nitration of ethyl carbamate with nitric acid in acetic anhydride–acetic acid mixtures has been studied by Holstead and co-workers (175).

Reduction of the ammonium salt of methyl N-nitrocarbamates with zinc and acetic acid gave methyl N-nitrosocarbamate (CLXXIVa) (324) as an unstable solid.

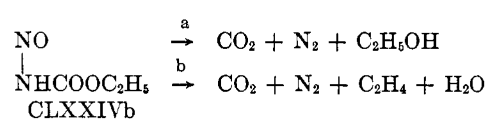
When sodium nitrite was added to a mixture of an alkyl carbamate and sulfuric acid, fragmentation resulted and nitrogen and a mixture of olefin and alcohol were obtained. The position of the double bond was not indicated.

$$H_2NCOOCH_2CHR + NaNO_2 + H_2SO_4 \rightarrow RCH{=}CH_2 + ROH + N_2 + CO_2$$

Only in the presence of a strong mineral acid will nitrous acid react with ethyl carbamate to form N_2 gas (179). Nitroxylboron tetrafluoride reacts (in liquid SO_2 or CCl_4) with ethyl carbamate to form nitrogen, NO, and N_2O (344).

2. Reactions of N-Nitrosocarbamates (CLXXIV)

Ethyl N-nitrosocarbamate (CLXXIVb) is a strong acid. Its alkali metal salt is neutral (134). When heated, the decomposition of ethyl N-nitrosocarbamate can go in two directions.



Hydrolysis of CLXXIVb regenerates nitrous acid and ethyl carbamate. With KOH, the dipotassium salt of N-nitrosocarbamic acid (O=C(OK)N=NOK) was formed. Franchimont found that methyl N-nitrosocarbamate did not couple with phenol (134).

3. Reactions of N-Nitrocarbamates (CLXXIII)

The N-nitrocarbamates are strong acids and form salts that are stable to hydrolysis. They act as nitrating agents in the presence of sulfuric acid (174,

323). The silver salt of N-nitrocarbamate was alkylated on the nitrogen by methyl iodide (323). Both sulfuric acid and sodium hydroxide decompose ethyl N-nitrocarbamate (CLXXIIIb) (121).

$$\text{CLXXIIIb} \xrightarrow[\text{or NaOH}]{H_2SO_4} N_2O + HOC_2H_5 + CO_2$$

The thermal decomposition of both N-nitroso- and N-nitro-N-alkylcarbamates has been studied (358). Ethyl N-nitrocarbamate was hydrolyzed with alcoholic potassium hydroxide to form potassium N-nitrocarbamate. Acidification of this salt forms nitramide (324).

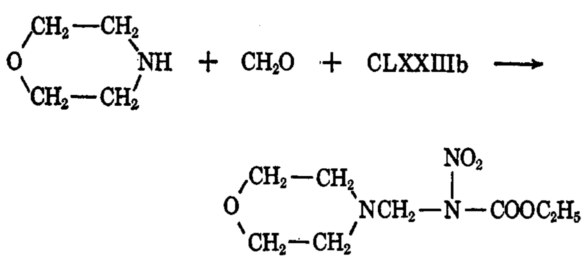
$$2KOH + \underset{\underset{\text{CLXXIIIb}}{NO_2}}{NHCOOC_2H_5} \rightarrow \underset{NO_2}{KNCOOK} + C_2H_5OH$$

$$\underset{NO_2}{KNCOOK} + H_2SO_4 \rightarrow H_2NNO_2$$

Aminolysis of N-nitro-N-alkylcarbamates (CLXXVIII) forms amine salts of alkyl-N-nitroamine (87).

$$\text{CLXXVIII} + R''NH_2 \rightarrow \underset{NO_2}{RN^{\ominus}}R''NH_3^{\oplus} + R''NHCOOR'$$

N-Nitrocarbamate CLXXIIIb was found to react as a Mannich reaction acid component (204) with formaldehyde and morpholine to form CLXXIX.



CLXXXIX

Reduction of N-nitrocarbamates with zinc and acetic acid forms N-carbethoxyhydrazine (ethyl carbazate), $H_2N–NHCOOC_2H_5$ (323). Ethyl N-nitrocarbamate (CLXXIIIb) has been treated with diazoalkanes to form the ethyl N-alkyl-N-nitrocarbamate (CLXXVIII). Subsequent ammonolysis forms the ammonium salts of N-alkyl-N-nitroamine (CLXXXI) (151).

$$R_2CN_2 + \text{CLXXIIIb} \rightarrow \text{CLXXVIII} \xrightarrow[H_2O]{(NH_3)}$$

$$\underset{\text{CLXXXI}}{R_2CH\overset{H}{N}—NO_2 \cdot NH_3} + H_2NCOOC_2H_5$$

When diphenyldiazomethane is used, some O-alkylation is observed; *i.e.*, $(C_6H_5)_2CH—O—\underset{\downarrow\\O}{N}{=}NCOOC_2H_5$.

Ethyl N-nitrocarbamate has been chlorinated with *t*-butyl hypochlorite or chlorine to form ethyl N-chloro-N-nitrocarbamate (326). The crude N-chloro-N-nitrocarbamate was then treated with ethylene at 0–25° under pressure to form ethyl N-nitro-N-(2-chloroethyl)carbamate. Examples of other olefins are given (see section VIIIN6).

When O-(2-hydroxyethyl) carbamate is treated with fuming nitric acid, the dinitro compound CLXXXII is obtained (101).

$$HOC_2H_4OCONH_2 \xrightarrow{HNO_3} \underset{\underset{\text{CLXXXII}}{NO_2}}{O}—C_2H_4OCONHNO_2$$

The nitration of methylenebis(ethyl carbamate) (CVI) gave the N-nitrocarbamate (CLXXIIIb) and an unidentified neutral oil when 98% HNO_3 was used (64). Frankel (135) has nitrated methylenebis(2,2,2-trinitroethyl carbamates) with acetic anhydride and 100% nitric acid and obtained the N,N′-dinitro compound.

L. REACTIONS OF N-ALKALI METAL CARBAMATES

Sodium derivatives of carbamate esters react with alkyl and acyl chlorides to form the corresponding N-substituted carbamates. Their reaction with reactive inorganic chlorides has barely been touched.

The reaction of ethyl carbamate (I) with sodium metal in an inert solvent (78, 105, 199, 302, 328) gave ethyl N-sodiocarbamate (XXVIII). The use of sodium amide has been shown to be advantageous in the formation of alkyl N-sodiocarbamates (89).

$$Na + I \rightarrow \underset{\text{XXVIII}}{NaNHCOOC_2H_5} \rightarrow NaCNO + C_2H_5OH$$

The formation of alkali cyanates by the reaction of ethyl carbamate with alkali amides (55) and with alkali alcoholates above 40° has been described (13).

The preparation of the disodium salt (CLXXXIII) of allophanic acid when ethyl N-sodiocarbamate was heated at 80° over a long period of time was noted by Ephraim (120).

$$2I + 2Na \rightarrow \underset{\text{CLXXXIII}}{H_2NCO\overset{Na}{N}COONa} + C_2H_5OH$$

In order to balance this equation, 1 mole of water is necessary. The stoichiometry and products of this reaction should be reinvestigated. The pK_a value of ethyl carbamate has not been measured.

Methyl benzyl ether was the only product isolated from the reaction of benzyl chloride with a mixture of sodium methoxide and methyl carbamate (46).

In liquid ammonia, ethyl N-sodiocarbamate reacts readily with alkyl halides to form ethyl N-alkylcarbamates in good yield (89). When ethyl carbamate was alkylated with methyl iodide in the presence of large amounts of silver oxide and a small yield of CLXXXIV,

the ethyl ether of the enolic form of ethyl carbamate was obtained.

$$Ag(NHCOOC_2H_5) + CH_3I \rightarrow CH_3OC(=HN)OC_2H_5$$

CLXXXIV

With acid chlorides and esters, ethyl N-sodiocarbamate forms the N-acylcarbamates (XXXIII) (199).

The preparation of bis(ethoxycarbonylamino) sulfide (LXIIc) by treating ethyl N-sodiocarbamate with sulfur dichloride has been described (162).

$$2XXVIII + SCl_2 \rightarrow S(NHCOOC_2H_5)_2$$

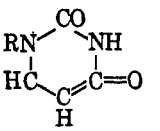
LXIIc

The condensation of ethyl propiolate with ethyl N-sodiocarbamate led to ethyl N-propiolylcarbamate (LX) which can be used in the preparation of uracils (LIX).

$$HC{\equiv}C{-}COOC_2H_5 + XXVIII \rightarrow HC{\equiv}C{-}CONHCOOC_2H_5$$

LX

$$LX + RNH_2 \longrightarrow RNHCH{=}CHCONHCOOC_2H_5 \longrightarrow$$



LIX

The reaction of ethyl chloroformate with XXVIII has been studied extensively (6, 105). When ethyl

$$XXVIII + ClCOOC_2H_5 \rightarrow NH(COOC_2H_5)_2 + NaCl$$

CLXXXV

$$XXVIII + NH(COOC_2H_5)_2 \rightarrow NaN(COOC_2H_5)_2 + NH_2COOC_2H_5$$

$$NaN(COOC_2H_5)_2 + ClCOOC_2H_5 \rightarrow N(COOC_2H_5)_3 + NaCl$$

CLXXXVI

chloroformate was used in excess, diethyl iminodicarboxylate (CLXXXV) was formed. As this material was more acidic than ethyl carbamate, it was converted into its sodium salt by N-sodiocarbamate. Therefore, 2 moles of the ethyl N-sodiocarbamate and 2 moles of ethyl chloroformate gave ethyl N-tricarboxylate (CLXXXVI) in 75% yield. Diels proved that disodiocarbamate (a hypothetical entity) was not an intermediate in this reaction (106).

The iminodicarboxylate anion, *i.e.*, $^{\ominus}N(COOC_4H_9)_2$, is quite an active nucleophilic agent. For example, it reacts with benzyl halides, as well as esters of hydroxylamine (72a), *i.e.*, a standard aminating agent.

$$NaN(COOC_4H_9)_2 + (CH_3)_3C_6H_2COONH_2 \rightarrow H_2N{-}N(COOC_4H_9)_2 + (CH_3)_3C_6H_2COONa$$

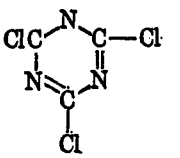
Ethyl chloroacetate behaved anomalously when treated with ethyl N-sodiocarbamate (199). In this case, the carbethoxy group reacted, and the N-chloroacetylcarbamic ester was obtained.

Sulfuryl chloride was condensed with 2 moles of ethyl sodiocarbamate to form diethyl N,N′-sulfonyldicarbamate (LXIIa) (96).

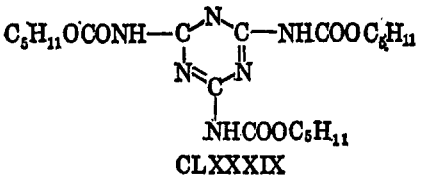
$$XXVII + SO_2Cl_2 \rightarrow SO_2(NHCOOC_2H_5)_2 + 2NaCl$$

LXIIa

Cyanuryl tris(*n*-amyl carbamate) (CLXXXIX) has been prepared by the reaction of amyl N-sodiocarbamate with cyanuric chloride (162a).



$$+ 3NaNHCOOC_5H_{11} \longrightarrow$$



CLXXXIX

The addition of ethyl N-sodiocarbamate across α,β-unsaturated systems has been reported (149, 150).

Substituted cinnamic esters were treated with ethyl N-sodiocarbamate to form β-carbethoxyaminohydrocinnamic esters (CLXXXVII), which when treated with water, regenerated the cinnamic ester (149).

$$C_6H_5CH{=}CHCOOC_2H_5 + XXVIII \rightarrow C_6H_5{-}CH(NHCOOC_2H_5){-}CH_2COOC_2H_5$$

CLXXXVII

Fumaric, citraconic, and mesaconic esters also underwent addition with ethyl N-sodiocarbamate to form the substituted amino diesters (CLXXXVIII) in poor yields.

$$C_2H_5OC(=O){-}CH{=}CHC(=O)OC_2H_5 + XXVIII \rightarrow C_2H_5OC(=O){-}C(H)(NHCOOC_2H_5){-}CH(COOC_2H_5)$$

CLXXXVIII

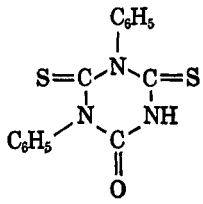
The reaction between phenyl isocyanate and ethyl N-sodiocarbamate gave the ethyl N-phenylallophanic ester (IVb).

$$C_6H_5NCO + XXVIII \rightarrow C_6H_5NHC(=O){-}NHCOOC_2H_5$$

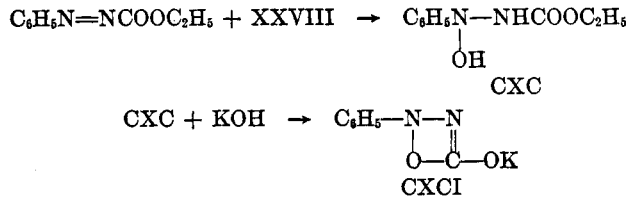
IVb

Phenyl isothiocyanate reacted anomalously to form 1,5-diphenyl-2,6-dithionotriazin-4-one. Allyl isothiocyanate behaved normally.

The reaction between phenylazocarbamate and ethyl sodiocarbamate resulted in the formation of ethyl carbamate and 2-hydroxy-2-phenylhydrazinecarboxylic ester (CXC). Reaction of the latter with potassium



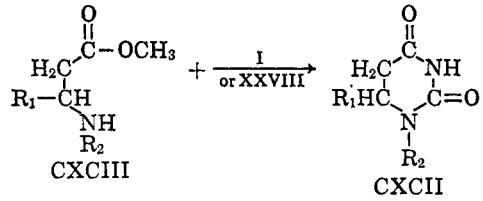
hydroxide gave an unusual heterocyclic compound (CXCI) (150).



This work may be worth reinvestigation, as the structures postulated are quite unusual.

The amino group of glycine ethyl ester (XXXIV) was condensed with ethyl N-sodiocarbamate (XXVIII) to give hydantoic acid ethyl ester (XXXV) (104). Winterfield and Gobel (360) prepared tetrahydropyrimidinediones (CXCII) by condensing ethyl N-sodiocarbamate with substituted β-aminopropionic esters in boiling ether.

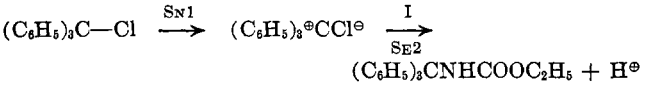
Adams and Juliano have shown that this ring system can be formed by the condensation of ethyl carbamate with β-aminopropionic acid esters (CXCIII) (2). The reaction was driven to completion by the removal of alcohol.



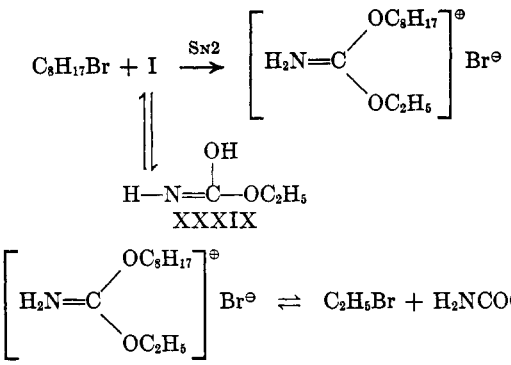
M. REACTIONS OF CARBAMATES WITH CARBONIUM IONS

Carbamates can be alkylated at either the nitrogen or (carbonyl) oxygen atom. Alkylation at the carbonyl oxygen is followed by loss of alkyl halide, and the net result of the process is exchange of the alkoxy group (155).

Active alkyl halides, such as triphenylmethyl chloride, which can undergo SN1 ionization in polar solvents, alkylate the nitrogen of carbamates.

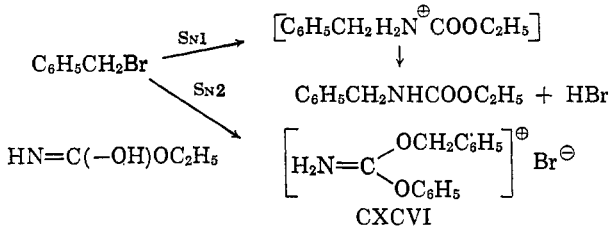


Less active alkyl halides, incapable of undergoing SN1 ionization, alkylate the carbonyl oxygen, or rather the hydroxyl group of the enolic form of the carbamate (XXXIX). The reaction may be considered an SN2 displacement of the halide ion from the alkyl halide by the enolic "hydroxy group" of the carbamate (XXXIX).

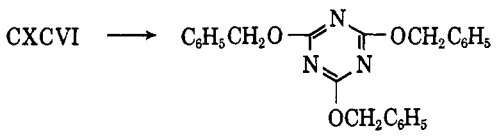


Somewhat more active alkyl halides, such as benzyl bromide, which are not quite active enough to undergo SN1 ionization, do not afford the anticipated mixture of benzyl carbamate and ethyl N-benzylcarbamate upon reaction with ethyl carbamate. Ethyl N-benzylcarbamate is formed, but in place of the anticipated benzylcarbamate, its trimer, tribenzyl cyanurate (CXCV), is formed. Cyanuric acid is also formed.

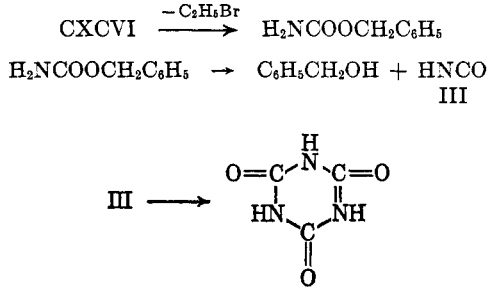
The reactions expected of an active alkyl halide and an inactive alkyl halide are both thought to occur, the former leading to ethyl N-benzylcarbamate, and the latter initially to an intermediate ion (CXCVI).



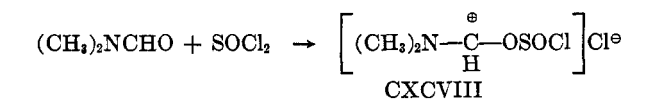
Trimerization of CXCVI affords tribenzyl cyanurate (CXCV).



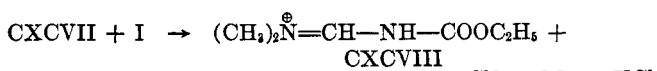
The explanation offered for the appearance of cyanuric acid is based on the facility of condensation of benzyl carbamates. The anticipated benzyl carbamate loses benzyl alcohol and forms the cyclic compound (XL) cyanuric acid under the reaction conditions (155).



Reactions with Other Carbonium Ions. Amidinium salts (CXCVIII) are formed from the reaction on ethyl carbamate of thionyl chloride and dimethylformamide. The reactive intermediate which attacks ethyl carbamate is believed to be a Vilsmeier-type carbonium ion (CXCVII) (114).



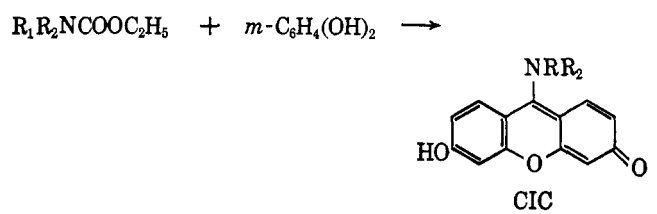
CXCVIII



N. MISCELLANEOUS REACTIONS

1. With Resorcinols

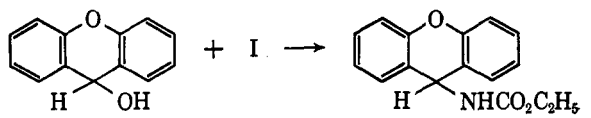
Two moles of resorcinol react with 1 mole of substituted or unsubstituted carbamates to afford 6-hydroxy-9-(substituted) aminofluorone (CIC) (296).



CIC

2. With Xanthydrols

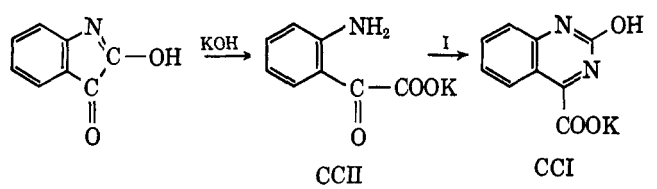
Xanthydrols, which are used as reagents for detecting amides, react with ethyl carbamate with loss of water to form N-xanthylcarbamates (CC) (333).



CC

3. With Isatinic Acid

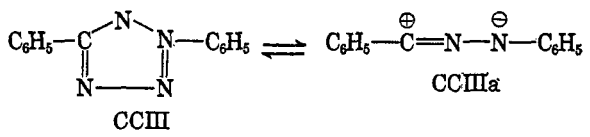
Quinazoline-4-carboxylic acids (CCI) are formed when unsubstituted carbamates react with salts of isatic acid (CCII) (derived from isatin by caustic treatment) (318).



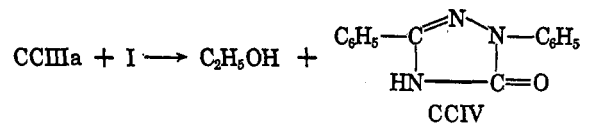
CCII CCI

4. 1,3-Dipolar Addition Reactions

Ethyl carbamate undergoes a 1,3-dipolar addition with diphenyltetrazole (CCIII), with loss of ethanol. The product is diphenyl-1,2,4-triazolone-5 (CCIV) (177).



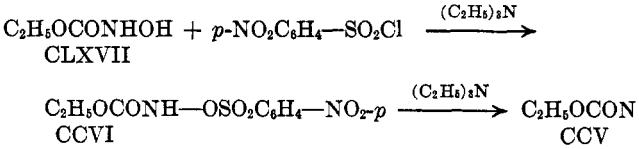
CCIII CCIIIa



CCIV

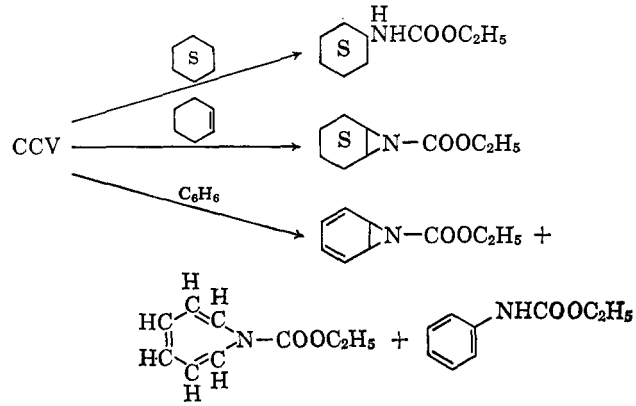
5. Carbethoxyimidogen, Generation and Reactions (CCV)

Carbethoxyimidogen (CCV), the imidyl radical of ethyl carbamate, has been generated from ethyl N-*p*-nitrobenzenesulfonoxycarbamate (CCVI), which is prepared from ethyl N-hydroxycarbamate (CLXVII) (216).



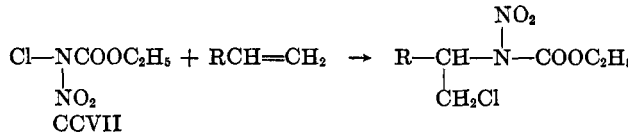
CLXVII CCVI CCV

The same imidyl radical can be prepared by decomposition of ethyl azidoformate, $C_2H_5OCON_3$ (217). Carbethoxyimidogen reacts with olefins and aliphatic and aromatic hydrocarbons, affording N-substituted ethyl carbamates.



6. Reactions with Hydrocarbons

Until the recent work by Merten and Muller (237) [for a late review, see G. Muller and R. Merten, *Chem. Ber.*, **98**, 1097 (1965)], only carbamates substituted on nitrogen with electron-withdrawing groups, *i.e.*, N-nitro and N-chloro esters, had been shown to react with olefins. For example, N-chloro-N-nitrocarbamate esters (CCVII) were condensed with olefins in the following manner (326).



CCVII

Ethyl N,N-dichlorocarbamate (LXXXVI) when treated with styrene yields the N-chloro-N-(2-chlorophenethyl)carbamate (CCVIII) (77).

$$C_6H_5CH{=}CH_2 + Cl_2NCOOC_2H_5 \rightarrow$$
LXXXVI

$$C_6H_5CH(Cl){-}CH_2NHCOOC_2H_5 \quad (Cl)$$
CCVIII

However, in 1963, Merten and Muller were able to alkylate carbamate esters with olefins in the presence of Lewis acid catalysts (233–236).

$$CH_2{=}CR_1R_2 + I \xrightarrow{BF_3} (R_1R_2)CNHCOOC_2H_5 \quad (CH_3)$$

R_1	R_2
CH_3	CH_3
H	C_6H_5
CH_3	C_6H_5
CH_3	$CH{=}CH_2$

With isoprene (237) as the alkylating agent, an N-allylic carbamate was obtained, along with smaller quantities of telemers.

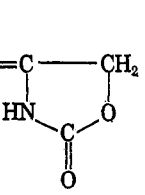
$$H_2C{=}C(CH_3){-}CH{=}CH_2 + I \rightarrow CH_3{-}C(CH_3){=}CH{-}CH_2NHCOOC_2H_5$$

N-Vinylcarbamates (CCIX) are formed from the reaction of simple carbamates with acetylene or methylacetylene, under the influence of a catalyst (102).

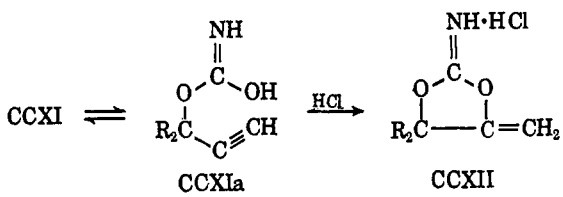
$$R{-}C{\equiv}CH + H_2N{-}COOC_2H_5 \rightarrow R{-}C(=CH_2){-}NHCOOC_2H_5$$
CCIX

4-Methylene-2-oxazolidinone (CCX) was formed when propargyl carbamate (CCXI) was refluxed in pyridine (70).

$$H{-}C{\equiv}CCH_2OC(=O)NH_2 \xrightarrow{\Delta}$$
CCXI


CCX

In the presence of anhydrous HCl, propargyl carbamates react in their enolic form, cyclizing to iminodioxolane hydrochlorides (CCXII). Apparently the enolic hydroxyl group added across the triple bond of the molecule (73).


CCXIa

CCXII

The reaction between ethyl N-chlorocarbamate and acetylene to form ethyl N-vinyl-N-chlorocarbamate has been described (316).

IX. Uses of Carbamates

A. Physiological Properties of Ethyl Carbamates

Ethyl carbamate inhibits mitosis, thus slowing cellular growth, especially of bone marrow cells (171), and inhibits enzymes such as cholinesterase. Its inhibition of cellular growth has prompted the use of ethyl carbamate as an antileukemic agent.

Ethyl carbamate depresses the nervous system and has thus found use as an antidote for poisoning by central nervous system stimulants such as strychnine, picrotoxin, etc. Large doses of ethyl carbamate depress respiration to such a degree that these same stimulants, or metrazole, are needed to relieve the condition.

Of all the carbamates, only ethyl carbamate has been found to have a significant carcinogenic effect on mammals. Ethyl carbamate is converted into and excreted as ethyl N-hydroxycarbamate (CLXVII) and ethyl N-acetyl-N-hydroxycarbamate by mammals. These hydroxycarbamates, formed *in vivo*, can act as alkylating agents towards mercaptoamino acids, giving rise to the observed radiomimetic effects. Ethyl N-hydroxycarbamate has been found to have a carcinogenic action comparable to that of ethyl carbamate (61). Methyl carbamate seems to lack most of the physiological effects of ethyl carbamate. The pharmacology of carbamates was reviewed in 1948 (165).

Simple carbamates have been employed medicinally as antiseptics (352), local anesthetics (277, 289, 299), anticonvulsants (226), and antipyretics, with little success.

Ethyl carbamate (U.S.P.) has been used in doses of up to 3 g. per day as an antileukemia agent (263) and in treatment of multiple myeloma. However, gastrointestinal irritation often results from oral ingestion (213).

As a hypnotic and diuretic, its action is weak and immunity towards it is rapidly acquired. However, simple carbamates, such as secondary amyl carbamate (hedonal) and trichloroethyl carbamate (voluntal), have been employed clinically as hypnotics and sedatives.

Although ethyl carbamate itself inactivates the enzyme cholinesterase only slightly (143), carbamates such as physostigmine (U.S.P.) and carbachol (U.S.P.) are much more active cholinesterase inhibitors and are used extensively as parasympathomimetic agents in disorders such as glaucoma, myasthenia gravis, etc.

A major therapeutic application of carbamate is the use of meprobamate (U.S.P.) and related dicarbamates of propanediols as muscle relaxants (tranquilizers) (44).

Other biological applications of various carbamates have been their uses as biocides such as herbicides, *i.e.*, isopropyl N-phenylcarbamate (I.P.C.) (144), insecticides (315), insect repellants (130, 267), and fungicides (242).

Ethyl carbamate has been used in purifications and compounding of medicinals such as purifications of tetracycline (255) and reserpine (286), and compounding of lindane (hexachlorocyclohexane) (331) and parenteral barbiturate solutions (336).

B. INDUSTRIAL USES OF CARBAMATES

The spectacular success of meprobamate as a tranquilizer in the 1950's brought forth a demand for the commercial production of the intermediates, methyl and ethyl carbamate. A major use of methyl and ethyl carbamate is for meprobamate manufacture.

The work of Arcenaux, *et al.* (10), has stimulated the use of ethyl carbamate with formaldehyde as a crease-resistant finish in the textile industry. This particular use is showing great industrial potential.

The discovery of a liquid eutectic mixture of methyl and ethyl carbamate has led to a study of its unique solvent properties (45). This solvent is competitive in price with other well-known high dielectric solvents.

Ethyl carbamate has been used in hair conditioners (168, 347), in the preparation of sulfamic acids (49), as an extractant of hydrocarbons from crude oil (85a), and as a food flavor enhancing agent (202). Other simple carbamates have been used as plasticizer (softener) for rubbers (71), plasticizer for melamine alkyd resins, (335), and as fuel additive (189a, 270).

ACKNOWLEDGMENTS.—We wish to thank S. Beinfest, J. Halpern, B. Juliano, G. Scinto, and M. Weiss at Millmaster Chemical Corporation for their contributions to the field of carbamate chemistry.

X. REFERENCES

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