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# THE REACTIONS OF CARBAMATES WITH ALCOHOLS

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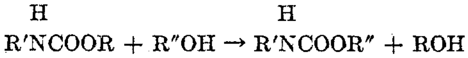
The preparation of esters of carbamic acid has been accomplished in many ways. Among the more important methods for the synthesis of unsubstituted carbamates are the reaction of carbamyl chloride with an alcohol (1) or metal alkoxide (2), and the reaction of cyanogen chloride (3, 4) or gaseous cyanic acid (5, 6) with an alcohol. Other well known methods include the reaction of a chloroformate (7, 8) or a dialkyl carbonate (4, 9) with ammonia, and the reaction of urea (10) or urea nitrate (11, 12) with an alcohol. N-Substituted carbamates are usually prepared by the reaction of the appropriate isocyanate and alcohol (13) or the reaction of a chloroformate and an amine (14). The latter method (15) as well as the reaction of a substituted carbamyl chloride with an alcohol (16) is utilized for the synthesis of N,N-disubstituted carbamates.

Carbamates have been reported to undergo a reaction with an alcohol to yield a new carbamate in which the ester residue is derived from the reacting alcohol.



$$R'\overset{H}{N}COOR + R''OH \rightarrow R'\overset{H}{N}COOR'' + ROH$$

R′ = H, alkyl or aryl group

Thus, it has been reported that high-boiling alcohols such as diethylaminoethanol (17) and bornyl, methylcyclohexyl, octadecyl, and benzyl alcohols (18) react with ethyl carbamate to form the corresponding carbamates. Ben-Ishai and Katchalski (19) recently reported a similar reaction of isopropyl N-phenylcarbamate and benzyl alcohol.

No work has been previously reported on reactions in which the alcohol is a low-boiling material, or in which the carbamate is N,N-disubstituted. This report is concerned with a study of the action of low- and high-boiling alcohols on N-unsubstituted, N-monosubstituted, and N,N-disubstituted carbamates. The results are indicated in Table I.

The reaction of isobutyl alcohol, b.p. 108°, with the unsubstituted ethyl carbamate was successful only in the presence of catalytic quantities of sulfuric acid. Under no circumstances would the reaction proceed at these low temperatures in the absence of an acidic catalyst. Isobutyl alcohol, under sulfuric acid catalysis, gave good yields of the corresponding carbamate. In the case of the secondary alcohol only fair yields were obtained while *tert*-butyl alcohol dehydrated to isobutylene without any carbamate being obtained. The reaction was carried out by refluxing ethyl carbamate with a large excess of the reacting alcohol, and the formation of high-melting by-products, *i.e.* allophanate and cyanuric acid, was limited to trace quantities with these low-boiling alcohols.

The sulfuric acid catalyst was found to be replaceable with *p*-toluenesulfonic acid while the use of toluene as a solvent did not change the course of the reaction or the yields of product.

# TABLE I

## REACTION OF CARBAMATES AND ALCOHOLS

| CARBAMATE | ALCOHOL | MOLAR RATIO C: A[a] | CATALYST | REACTION Temp. °C. | REACTION Time, hrs.[b] | YIELD, % |  | M.P., °C.[d] | ANALYSES, N |  | REMARKS |
|---|---|---|---|---|---|---|---|---|---|---|---|
|  |  |  |  |  |  | Crude | Purified[c] |  | Calc'd | Found |  |
| Ethyl carbamate | Isobutyl | 1:6 | None | 110–120 | 103 |  |  |  |  |  | e |
|  |  | 1:6 | $H_2SO_4$ | 110–120 | 19 | 87[f] | 56 | 63–64 | 11.96 | 11.95 | g |
|  |  | 1:6 | $(n\text{-}C_4H_9)_3N$[h] | 110–120 | 8 |  |  |  |  |  | e |
|  | *sec*-Butyl | 1:6 | $H_2SO_4$ | 105–110 | 16 | 37 |  | 92–93 | 11.96 | 12.15 | i |
|  | *tert*-Butyl | 1:6 | $H_2SO_4$ | 85–90 | 10 |  |  |  |  |  | j, k |
|  | Benzyl | 1:1.5 | None | 190–230 | 19 | 70 | 53 | 85–86 | 9.21 | 9.15 | l |
|  |  | 1:1.5 | $H_2SO_4$ | 140–240 | 5 | 9 |  | 82–84 | 9.21 | 9.35 | m, n, o |
| Ethyl N-ethylcarbamate | Isobutyl | 1:6 | $H_2SO_4$ | 110–114 | 147 |  |  |  |  |  | e, m |
| Ethyl N-phenylcarbamate | Isobutyl | 1:6 | $H_2SO_4$ | 112–115 | 120 |  |  |  |  |  | e, m |
|  | Benzyl | 1:1.5 | None | 220–255 | 1 | 76 | 64 | 75–76 | 6.17 | 6.07 | i |
|  |  | 1:1.5 | $H_2SO_4$ | 130–250 | 0.7 |  |  |  |  |  | m, p |
| Ethyl N,N-diethyl carbamate | Isobutyl | 1:6 | $H_2SO_4$ | 110–112 | 41 |  |  |  |  |  | e |
|  | Benzyl | 1:3 | None | 180–200 | 120 |  |  |  |  |  | e |
| Ethyl N,N-dibutyl carbamate | Benzyl | 1:3 | None | 210–215 | 120 |  |  |  |  |  | e |
| Ethyl N,N-diphenylcarbamate | Isobutyl | 1:6 | $H_2SO_4$ | 110–120 | 80 |  |  |  |  |  | e |
|  | Benzyl | 1:3 | None | 210–230 | 79 |  |  |  |  |  | e |
|  |  | 1:1.5 | $H_2SO_4$ | 135–320 | 3 |  |  |  |  |  | m, q |

[a] Carbamate: alcohol molar ratio. [b] Time to collect theoretical ethanol unless otherwise indicated. [c] Recrystallized or distilled. [d] Uncorrected. [e] No ethanol collected. [f] Including cyanuric acid. [g] Small amount of cyanuric acid recovered. [h] Catalytic or equivalent amounts. [i] Crude product had indicated m.p. and satisfactory analyses. [j] Ethyl carbamate recovered as sole product from reaction mixture. [k] Isobutylene generated. [l] 8% of cyanuric acid recovered, m.p. > 300°; Calc'd for $C_3H_3N_3O_3$: N, 32.56; Found, N, 32.58. [m] Water collected. [n] 32% of cyanuric acid and 52% of dibenzyl ether recovered. [o] In another run using one-half quantities 20% of benzyl carbamate, 26% of cyanuric acid, and 23% of dibenzyl ether were recovered. [p] Dibenzyl ether recovered. [q] Reaction mixture was a tarry material.

No reaction of isobutyl alcohol with N-monosubstituted or N,N-disubstituted carbamates took place even under the conditions effective for the unsubstituted carbamates, *i.e.* acid catalysis.

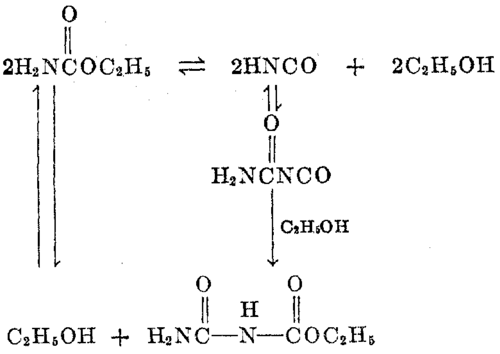
In the absence of catalysis benzyl alcohol, b.p. 205°, reacted with ethyl carbamate and ethyl N-phenylcarbamate to give high yields of the corresponding benzyl carbamate. In the case of the unsubstituted carbamate cyanuric acid was also obtained. No successful reaction took place with ethyl N,N-diethyl-, N,N-dibutyl-, or N,N-diphenyl-carbamates.

When sulfuric acid was included in the reaction mixtures, the course of the reaction was altered. The addition of acid in these high-boiling reactions resulted in the formation of dibenzyl ether and considerable quantities of tars and, in the case of the unsubstituted carbamate, increased the amount of cyanuric acid recovered. The yield of the desired carbamate was drastically reduced.

When the reaction of benzyl alcohol with ethyl carbamate was carried out in toluene at 115°, no ethanol was obtained in the absence of sulfuric acid. In the presence of acid, an exceedingly slow reaction occurred and the small yield of carbamate was accompanied by cyanuric acid or allophanate.

It is of interest to consider the data in Table I in the light of previous ideas on the mechanism of carbamate reaction.

The prevailing view has been that the reaction proceeded by an initial decomposition of the starting carbamate into cyanic acid, or an isocyanate, and an alcohol. The reacting alcohol would then form the new carbamate by reaction with cyanic acid, or the isocyanate, while the displaced alcohol would be distilled out of the reaction mixture. This idea has been advanced by Davis and Blanchard (6) to explain the formation of a small quantity of allophanate when ethyl carbamate is heated with ethanol in a *sealed tube* at 100°, although no allophanate was isolated in the absence of a closed system. Also the fact that allophanates can be converted to carbamates by heating with an excess of the alcohol (20) implies the existence of an equilibrium between allophanates on the one hand and cyanic acid and an alcohol on the other.



$$2H_2N\overset{O}{\overset{\|}{C}}OC_2H_5 \rightleftharpoons 2HNCO + 2C_2H_5OH$$

$$2HNCO \rightleftharpoons H_2N\overset{O}{\overset{\|}{C}}NCO \xrightarrow{C_2H_5OH}$$

$$C_2H_5OH + H_2N\overset{O}{\overset{\|}{C}}-\overset{H}{N}-\overset{O}{\overset{\|}{C}}OC_2H_5$$

It is our opinion, however, that this view does not adequately explain the facts reported here. When ethyl carbamate alone in toluene solution was heated at 115° in the presence of catalytic quantities of sulfuric acid, at the end of 20 hours only a minute quantity of cyanuric acid was obtained. The implication is that the decomposition proceeds to a much smaller extent than heretofore presumed, or that some cyanic acid might be lost by volatilization and be unavailable for formation of cyanuric acid.

Additional evidence for the stability of carbamates was shown in a recent publication of Metayer (21). It was demonstrated that low molecular weight N-unsubstituted carbamates are stable up to their boiling points, and can be distilled without decomposition. However, carbamates of higher molecular weight and boiling point, such as benzyl carbamate, decomposed to the alcohol and allophanate at elevated temperatures. Monosubstituted carbamates of high molecular weight decomposed at elevated temperatures to the isocyanate and alcohol. The N,N-disubstituted carbamates were uniformly very stable and distilled without decomposition.

These results help to explain the high yield of cyanuric acid which was obtained in the reaction of ethyl carbamate and benzyl alcohol. The benzyl carbamate most likely, upon formation, partially decomposed to cyanic acid which trimerized to cyanuric acid.

The minute amount of decomposition at low temperature of ethyl carbamate in the presence of sulfuric acid leads us to believe that the low temperature reactions proceed by ester exchange, almost to the exclusion of the decomposition reaction. In view of Metayer's report regarding thermal stability of unsubstituted and disubstituted carbamates, the high temperature reaction reported here also would proceed by an exchange mechanism. The monosubstituted carbamate decomposition on distillation indicates that only in this case as applied to the alcohol reaction does isocyanate formation proceed to any reasonable degree. This appears to be borne out by the rapidity of the reaction of benzyl alcohol and ethyl N-phenyl-carbamate as compared with the other reactions.

It is our proposal that two methods of reaction exist, one based on decomposition followed by reaction with the alcohol to yield the product carbamate, and the second based on a displacement reaction by ester exchange. The body of evidence is in favor of the second as the principal reaction mechanism with the unsubstituted carbamates while the first mechanism may occur to a considerable extent with the monosubstituted carbamates.

## EXPERIMENTAL

### REACTIONS WITH ETHYL CARBAMATE

*Reaction with isobutyl alcohol.* A mixture containing 44.5 g. (0.5 mole) of ethyl carbamate, 222 g. (3.0 moles) of isobutyl alcohol, and 2 ml. of concentrated sulfuric acid was heated under total reflux for 30 minutes and then distilled, with partial take-off, through an air-jacketed fractionating column (35 cm. effective length, 25 mm. i.d.) packed with 3⁄16″ glass helices, topped by a partial take-off distilling head. The homogeneous distillate contained water-soluble and water-insoluble fractions. After 19 hours a total of 96 ml. of distillate containing 33 ml. (26 g.) of water-soluble material had been collected and the reflux temperature rose to 104°. The reaction mixture was cooled and the excess isobutyl alcohol was evaporated by standing at 35–40° or by passing a current of air over the mixture at room temperature. The crude product, 51 g., was extracted with ligroin (b.p. 60–90°) and 3.9 g. of an insoluble material, m.p. 104–118°, was isolated. On recrystallization from water, the m.p. was raised to > 300° and analysis indicated the material to be cyanuric acid. The ligroin extract yielded 32.6 g. of isobutyl carbamate (56%), m.p. 57–59°. Recrystallization from water raised the melting point to 63–64° (reported at many different temperatures within the range 55° to 67°)[1] and a mixture m.p. with authentic isobutyl carbamate, m.p. 64–65°, prepared by ammonolysis of the chloroformate, showed no depression.

Attempts to carry out the reaction in the absence of sulfuric acid or in the presence of catalytic or equivalent amounts of tri-*n*-butylamine failed to produce any recoverable ethanol.

*Reaction with 2-butanol.* In a similar manner, 21.5 g. (37%) of *sec*-butyl carbamate, m.p. 92–93° [reported (26) 94°], was obtained from 222 g. of 2-butanol, 44.5 g. of ethyl carbamate, and 2 ml. of concentrated sulfuric acid.

*Reaction with tert-butyl alcohol.* Attempts to prepare *tert*-butyl carbamate by the reaction of *tert*-butyl alcohol with ethyl carbamate in the presence of sulfuric acid were unsuccessful. Isobutylene was generated and, although material boiling at 78–80° was collected, the recovery of unreacted urethan as the sole product from the reaction mixture indicated that the distillate was probably *tert*-butyl alcohol, b.p. 83°.

*Reaction with benzyl alcohol. A. In the absence of sulfuric acid.* A mixture of 89 g. (1.0 mole) of ethyl carbamate and 162 g. (1.5 moles) of benzyl alcohol was heated for 30 minutes and then distilled, with partial take-off, through a Vigreux column. After 19 hours the theoretical amount of ethanol had been collected and a white precipitate had formed. The reaction mixture was filtered at 150° and 2.5 g. of cyanuric acid was collected. The filtrate, on refrigeration, yielded 105 g. of crude product. On recrystallization from toluene an additional 0.8 g. of cyanuric acid (total yield 8%) and 80 g. (53%) of benzyl carbamate, m.p. 85–86° [reported (18) 86°], were obtained.

*B. In the presence of sulfuric acid.* When the above reaction was carried out in the presence of 2 ml. of concentrated sulfuric acid, the theoretical amount of distillate containing water was collected in five hours. Filtration of the reaction mixture gave 13.8 g. (32%) of cyanuric acid. The filtrate was neutralized with solid anhydrous sodium carbonate and then distilled. The distillate contained benzyl carbamate and dibenzyl ether which had co-distilled. The various fractions collected were extracted with hot water and the benzyl carbamate, 13 g. (9%), was recovered from the aqueous extracts. The organic layer from the aqueous extractions was dried and redistilled to yield 77 g. (52%) of dibenzyl ether.

When this reaction was carried out with one-half of the indicated quantities of reactants, 5.6 g. (26%) of cyanuric acid, 15.0 g. (20%) of benzyl carbamate, and 17.2 g. (23%) of dibenzyl ether were recovered.

*C. Reaction below reflux temperature of benzyl alcohol.* When 0.5 mole of ethyl carbamate, 0.75 mole of benzyl alcohol, and 100 g. of toluene were maintained at 115° for 52 hours no ethanol was obtained.

When this reaction at 115° was carried out in the presence of 2 ml. of sulfuric acid, after 56 hours the distillate contained 4 g. of water and 20 g. of a mixture of toluene and ethanol. Work-up of the reaction mixture gave 1.6 g. of cyanuric acid and 27 g. of benzyl carbamate. When the reaction was stopped after 24 hours and the reaction temperature was permitted to rise to 140° the products included 16.5 g. of benzyl carbamate and 4 g. of a product whose analysis and melting point corresponded to ethyl allophanate.

## REACTIONS WITH MONO-SUBSTITUTED CARBAMATES

The attempted *reactions of isobutyl alcohol with ethyl N-ethyl- and N-phenylcarbamates* in the presence of sulfuric acid, gave a small quantity of water but failed to yield any ethanol, after 147 and 120 hours of reflux, respectively.

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[1] The melting point of isobutyl carbamate has been reported as 55° (22), 59.5° (5), 61° (7), 64° (23), 64.4° (24), 65° (10), and 67° (25). In our investigation crude material, melting at 52–54°, gave perfectly satisfactory nitrogen analyses.

*Reactions with benzyl alcohol. A. In the absence of sulfuric acid.* Benzyl alcohol, 51 g., and ethyl N-phenylcarbamate, 51 g., yielded the theoretical amount of alcohol in one hour. On refrigeration, 53 g. (76%) of crude benzyl carbamate was obtained. This material gave satisfactory nitrogen analyses. On recrystallization from ligroin and toluene 45 g. (64%) of benzyl N-phenylcarbamate, m.p. 76° [reported (27) 78°] was obtained.

*B. In the presence of sulfuric acid.* When the reaction between the carbamate and benzyl alcohol was carried out in the presence of 1 ml. of sulfuric acid, the total reaction time was 0.7 hour and a considerable quantity of water was collected. On working up the reaction mixture a small quantity of high-melting material, m.p. > 300°, was recovered and a multitude of liquid fractions which appeared to be a mixture of dibenzyl ether and nitrogen-containing material was collected on distillation. Due to the heterogeneity of these products and the successful completion of the reaction in the absence of sulfuric acid further work with these fractions was discontinued.

### REACTIONS WITH DISUBSTITUTED CARBAMATES

The attempted *reactions of isobutyl alcohol with ethyl N,N-diethyl- and N,N-diphenylcarbamates*, in the presence of sulfuric acid, of *benzyl alcohol with ethyl N,N-diethyl-, N,N-dibutyl-, and N,N-diphenylcarbamates*, in the absence of sulfuric acid, and of *benzyl alcohol with ethyl N,N-diphenylcarbamate*, in the presence of sulfuric acid, failed to yield any isolatable ethanol.

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