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REACTION OF ACETYL BROMIDE AND ACETYL CHLORIDE WITH URETHANS

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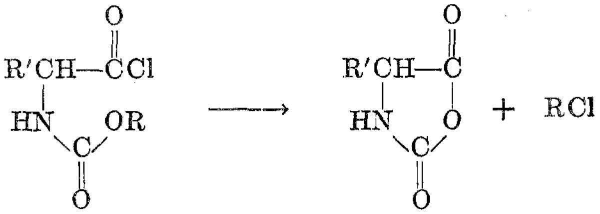
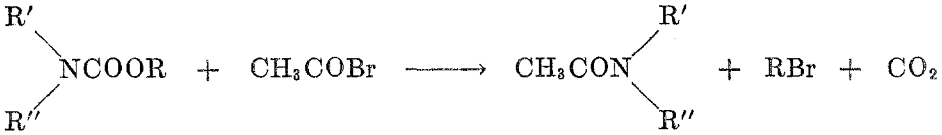
The observed cyclization of N-carbalkoxy-α-amino acid chlorides (I) to yield N-carboxy-α-amino acid anhydrides (II) (1), which may be interpreted as an *intra*molecular reaction between a urethan and an acyl halide, led to an investigation of the question whether *inter*molecular reactions of this type are possible, *e.g.* between acetyl bromide and acetyl chloride and urethans.



I II

Urethans (III, R = alkyl or aralkyl) react with acetyl bromide to form N-substituted acetamides (IV), alkyl or aralkyl bromides, and carbon dioxide (Table I):



III IV

$R = C_2H_5,\ CH_2C_6H_5;$
$R',\ R'' = H,\ CH_3,\ C_6H_5$

Only in the case of ethyl carbamate (III, $R = C_2H_5$, $R' = R'' = H$) was the acetamide accompanied by an appreciable amount of N-acetyl ethyl carbamate. Acetyl chloride did not react with the N,N-disubstituted- and N-phenylurethans under the experimental conditions used. The urethans themselves ($R' = R'' = H$) and their N-monomethyl derivatives underwent N-acetylation with evolution of hydrogen chloride (Table II).

In order to explain the reaction between urethans and acetyl bromide the possible formation of an intermediate ammonium (V or VI) or oxonium (VIII) salt should be considered. The formation of such a salt is supported by the observation that in the exothermic reaction of acetyl bromide with N-methylurethans and N,N-dimethylurethans, respectively, a crystalline salt-like mass is formed which disappears as the reaction progresses. The hygroscopic intermediate, which is insoluble in ether, readily dissolves in water and its aqueous solution contains bromide ions.

TABLE I

REACTION OF ACETYL BROMIDE WITH URETHANS

URETHAN	REACTION TEMP. (°C.)	REACTION TIME (HOURS)	PRODUCTS ISOLATED			
			Amide	Yield, %	Halide[f]	Yield, %
$(CH_3)_2NCOOC_2H_5$	120–130	18	$CH_3CON(CH_3)_2$[a]	80	C_2H_5Br	60
$(C_6H_5)_2NCOOC_2H_5$	96–98	48	$CH_3CON(C_6H_5)_2$[b]	50	C_2H_5Br	55
$CH_3NHCOOC_2H_5$	120–130	12	$CH_3CONHCH_3$[c]	82	C_2H_5Br	63
$C_6H_5NHCOOC_2H_5$	110–120	4	$CH_3CONHC_6H_5$[d]	74	C_2H_5Br	50
$NH_2COOC_2H_5$	100	1	$(CH_3CONH_2)_2 \cdot HBr$[e]	20	C_2H_5Br	40
$(CH_3)_2NCOOCH_2C_6H_5$	120–130	2	$CH_3CON(CH_3)_2$[a]	70	$C_6H_5CH_2Br$	80
$(C_6H_5)_2NCOOCH_2C_6H_5$	110–120	6	$CH_3CON(C_6H_5)_2$[b]	78	$C_6H_5CH_2Br$	70
$CH_3NHCOOCH_2C_6H_5$	120–130	2	$CH_3CONHCH_3$[c]	70	$C_6H_5CH_2Br$	90
$C_6H_5NHCOOCH_2C_6H_5$	100	1	$CH_3CONHC_6H_5$[d]	67	$C_6H_5CH_2Br$	65
$NH_2COOCH_2C_6H_5$	100	1	$(CH_3CONH_2)_2 \cdot HBr$[e]	16	$C_6H_5CH_2Br$	—
			$(CH_3CO)_2NH$	30		

[a] B.p. 166–167° (760 mm.), n_D^{30} 1.4304. Ref. (17) gives b.p. 165.5° (754 mm.), $n_D^{22.5}$ 1.4370. *Anal.* Calc'd: N, 16.1. Found: N, 16.3.

[b] Crystallized from aqueous ethanol and recrystallized from petroleum ether, m.p. 100–101°. Ref. (18) gives m.p. 100°. *Anal.* Calc'd: N, 6.6. Found: N, 6.8; 6.9.

[c] B.p. 97–100° (28 mm.); m.p. 27°, n_D^{30} 1.4272. Ref. (19) gives m.p. 27–28°, b.p. 202–204° (726 mm.). *Anal.* Calc'd: N, 19.1. Found: N, 18.8; 18.9.

[d] Crystallized from aqueous ethanol, m.p. 113°. Ref. (20) gives m.p. 113–114°. *Anal.* Calc'd: N, 10.3. Found: N, 10.1; 10.4. No *sym*-diphenyl-urea (*cf.* 21) could be detected in the reaction mixture.

[e] See experimental section.

[f] No attempt was made to collect the ethyl bromide quantitatively.

TABLE II

REACTION OF ACETYL CHLORIDE WITH URETHANS

URETHAN	REACTION TEMP., (°C.)	REACTION TIME (HOURS)	PRODUCT	YIELD, %
$CH_3NHCOOC_2H_5$	100	1	$CH_3N(COCH_3)COOC_2H_5$[a]	79
$CH_3NHCOOCH_2C_6H_5$	90	2.5	$CH_3N(COCH_3)COOGH_2C_6H_5$[b]	78
$NH_2COOC_2H_5$	100	1	$CH_3CONHCOOC_2H_5$[c]	85
$NH_2COOCH_2C_6H_5$	100	1	$CH_3CONHCOOCH_2C_6H_5$[d]	82

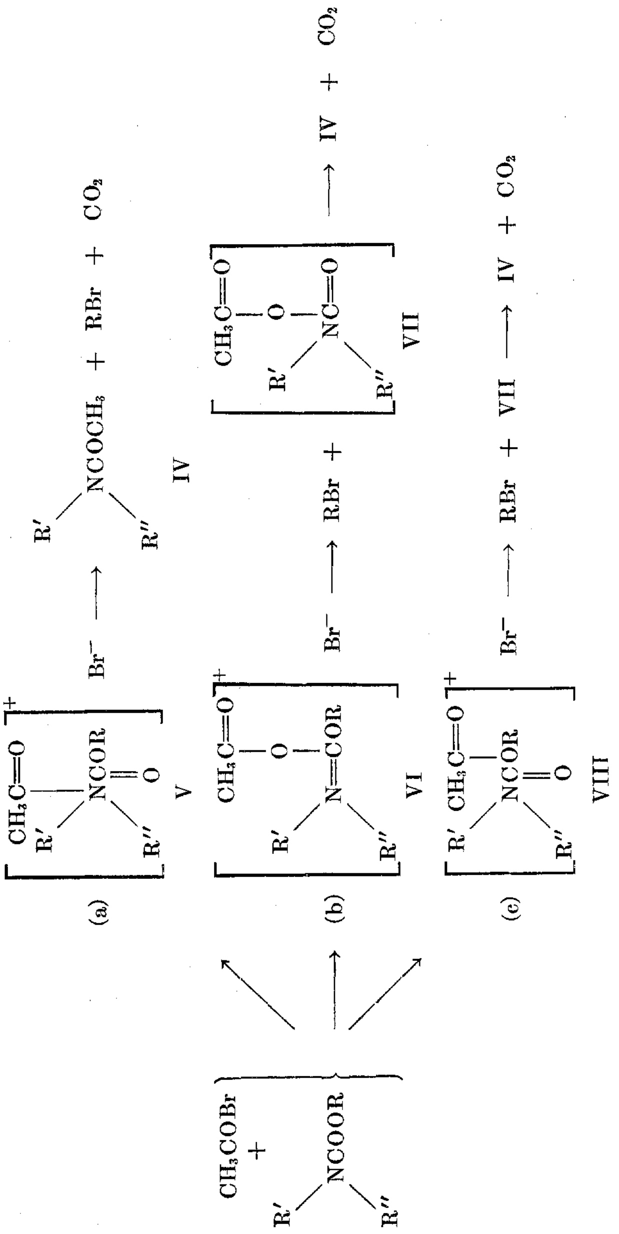
[a] B.p. 182° (760 mm.), n_D^{30} 1.4268; d_4^{30} 1.051. Ref. (25) gives b.p. 189° (corr.) (768.5 mm.), d_4^{15} 1.083. *Anal.* Calc'd: N, 9.6. Found: N, 9.6.

[b] B.p. 172° (30 mm.), n_D^{30} 1.5183; d_4^{30} 1.1257. *Anal.* Calc'd: C, 63.8; H, 6.3; N, 6.8. Found: C, 64.2; H, 6.5; N, 6.5.

[c] Recrystallized from petroleum-ether, m.p. 76–77°. Ref. (23) gives m.p. 76–77°. *Anal.* Calc'd: N, 10.7. Found: N, 10.5.

[d] Recrystallized from benzene-petroleum ether, m.p. 105°. *Anal.* Calc'd: N, 7.2. Found: N, 7.1.

At present no conclusive evidence is available concerning the mechanism of this reaction. Three different schemes: (a), (b), and (c) may be applied to describe the mode of interaction.


CH₃COBr + R′R″NCOOR
(a) [CH₃C=O—NCOR(=O) R′ R″]⁺ Br⁻ → R′R″NCOCH₃ + RBr + CO₂
V
IV
(b) [CH₃C=O—O—N=COR R′ R″]⁺ Br⁻ → RBr + [CH₃C=O—O—NC=O R′ R″] → IV + CO₂
VI
VII
(c) [CH₃C=O—NCOR(=O) R′ R″]⁺ Br⁻ → RBr + VII → IV + CO₂
VIII

N-carbalkoxytrimethylammonium chlorides, similar in structure to (V), normally decompose on heating to yield methyl chloride and dimethylurethans (2), *i.e.*, not in accordance with scheme (a). Furthermore, this mechanism does not explain the intramolecular cyclization of (I) to yield (II), which is the cyclic analog of our reaction.

The possibility of (VI) being formed from urethans and acetyl bromide is in accordance with the formation of oxazolonium halides and oxazolinium halides from N-acyl-α-amino acid chlorides (3) and from N-acyl-β-haloalkylamines (4), respectively. It must be noted, however, that the cyclization of N-carbalkoxy-α-amino acid chlorides (1, 3) and of N-carbalkoxy-β-haloalkylamines (5) differs from that of the corresponding N-acyl derivatives; no oxazolonium salts or free oxazolones were detected during cyclization of the former nor oxazolinium salts or oxazolines during cyclization of the latter. The cyclization mechanism as well as the differing behavior of N-carbalkoxy derivatives has been explained [(5), *cf.* also (6)] on the assumption that a reaction occurs between the alkoxy oxygen of the urethan group and the electrophilic halogen-bearing carbon. The analogy between the above mentioned *intra*molecular cyclization and our *inter*molecular reaction, as well as the following reasonings lead us to prefer mechanism (c) for the reaction between urethans and acetyl bromide.

The suggested formation and subsequent decomposition of the mixed anhydride (VII) is in keeping with the fact that such anhydrides decompose on heating into carbon dioxide and acetylated amides (7). It also recalls polyamide formation from substances of type II which is equally accompanied by carbon dioxide evolution (8).

The observed difference in behavior of acetyl chloride and acetyl bromide towards disubstituted urethans is not unusual; ethers, *e.g.*, react with acetyl chloride only sluggishly—in the absence of catalyst (9)—whilst acetyl bromide converts them into the corresponding esters with liberation of alkyl bromide (10). It thus seems plausible to assume that the urethan alkoxy-oxygen resembles to some degree an ethereal oxygen in its nucleophilic character.

The acetylation of ethylurethan (III, $R = C_2H_5$, $R' = R'' = H$) by acetyl bromide as well as the acetylation of unsubstituted (III, $R' = R'' = H$) and N-monomethylurethans (III, $R' = CH_3$, $R'' = H$) with acetyl chloride may be satisfactorily explained by the assumption of the intermediate ammonium salt (V, $R' = H$, $R'' = H$ or CH_3) yielding the corresponding acetyl urethans, with elimination of HBr or HCl.

EXPERIMENTAL

Preparation of urethans. Commercial ethyl carbamate and ethyl N-phenylcarbamate were used without further purification. Ethyl N-methylcarbamate was prepared from methylamine and ethyl chlorocarbonate (11), and ethyl N,N-dimethyl- and N,N-diphenylcarbamate were made analogously from dimethylamine (12) and diphenylamine (13), respectively. Benzyl carbamate was synthesized from benzyl chlorocarbonate and ammonia (14), and benzyl N,N-diphenylcarbamate from diphenylcarbamyl chloride and benzyl alcohol (15). The following new substances were prepared.

Benzyl N-methylcarbamate. Equimolar amounts of methylamine and benzyl chlorocarbonate were coupled in the usual way (Schotten-Baumann) (11). The product was extracted with ether, the ether removed, and the residue distilled in *vacuo*. B.p. 143° (8 mm.), n_D^{30} 1.5227, d_4^{30} 1.1078. Yield, 60%.

Anal. Calc'd for $C_9H_{11}NO_2$: C, 65.4; H, 6.7; N, 8.5.
Found: C, 65.4; H, 6.7; N, 8.7.

Benzyl N,N-dimethylcarbamate was prepared analogously, using dimethylamine. B.p. 151–152° (21 mm.); or 117° (6 mm.); n_D^{30} 1.5095, d_4^{30} 1.0707, yield 75%.

Anal. Calc'd for $C_{10}H_{13}NO_2$: C, 67.0; H, 7.3; N, 7.8.
Found: C, 67.5; H, 7.5; N, 7.8.

Benzyl N-phenylcarbamate. A mixture of 50 g. of isopropyl N-phenylcarbamate and 50 ml. of benzyl alcohol was refluxed for one hour and the isopropanol liberated removed continuously through a short column. The product was triturated with toluene-petroleum ether and recrystallized from petroleum ether, m.p. 77–78°. Ref. (16) gives m.p. 78°.

Anal. Calc'd for $C_{14}H_{13}NO_2$: N, 6.1. Found: N, 5.8.

Reaction of acetyl bromide with urethans. General procedure. A mixture of 0.1 mole each of the urethan and acetyl bromide was refluxed, until carbon dioxide evolution ceased. The temperatures and the times of reaction are recorded in Table I. At the completion of the reaction, the mixture was cooled to room temperature and treated as follows:

a. In the case of ethyl carbamates, the ethyl bromide formed was distilled directly from the reaction mixture at atmospheric pressure, and the amide purified by fractional distillation or crystallization (*cf.* Table I).

b. In the case of benzyl carbamates, the product was shaken with petroleum ether, the dissolved benzyl bromide was separated, and the amide was isolated as above from the residue.

Action of acetyl bromide on ethyl carbamate. When 8.9 g. (0.1 mole) of ethyl carbamate and 13 g. (0.105 mole) of acetyl bromide were mixed at room temperature an exothermic reaction set in after a short induction period. The reaction was accompanied by gas evolution (carbon dioxide and hydrogen bromide). Heating was continued under reflux (water-bath) for about one hour. Ethyl bromide was removed at atmospheric pressure and the solid residue treated with a boiling mixture of 25 ml. of acetone and 25 ml. of benzene. The solid remaining on the filter (0.75 g.) was identified as ammonium bromide. From the hot filtrate, crystals of $(CH_3CONH_2)_2 \cdot HBr$, m.p. 140°, separated on cooling (2 g.). Ref. (22) gives m.p. 138–139.5°.

Anal. Calc'd for $C_4H_{11}BrN_2O_2$: N, 14.0; Br, 40.2.
Found: N, 13.5; Br, 39.6.

The filtrate was concentrated to a volume of 10 ml. and boiling petroleum ether (40 ml.) added to the hot solution. The needle-like crystals which separated on cooling were filtered and identified as ethyl N-acetylcarbamate (2.5 g.), m.p. 76°. Ref. (23) gives m.p. 76–77°.

Anal. Calc'd for $C_5H_9NO_3$: N, 10.5. Found: N, 10.7.

Action of acetyl bromide on benzyl carbamate. When the above reaction was repeated, using 15.1 g. (0.1 mole) of benzyl carbamate, the following products were obtained: ammonium bromide (2 g.), acetamide hydrobromide (1.5 g.), and needle-like crystals of diacetamide, m.p. 76–77° (3 g.) (upon concentration of the petroleum ether solution). Ref. (24) gives m.p. 78°.

Anal. Calc'd for $C_4H_7NO_2$: N, 13.8. Found: N, 13.6.

The presence of benzyl bromide made itself felt during the operation (lachrymator); it could be isolated from the mother liquors by fractionation.

Reaction of acetyl chloride with urethans. General procedure: A mixture of 0.1 mole of the urethan and 0.11 mole of acetyl chloride was refluxed until hydrogen chloride evolution ceased; the temperatures and times of reaction are recorded in Table II. The mixture was cooled to room temperature and the products were isolated by fractionation or crystallization.

When no hydrogen chloride evolution was observed, the original urethans were usually recovered in 90–95% yield. No reaction was observed during 12 hours between acetyl chloride and the following urethans at the temperatures indicated (in brackets): ethyl N,N-dimethylcarbamate (80–90°), benzyl N,N-dimethylcarbamate (90–100°), ethyl N,N-diphenylcarbamate (63–66°), benzyl N,N-diphenylcarbamate (52–55°), ethyl N-phenylcarbamate (water-bath), benzyl N-phenylcarbamate (water-bath).

SUMMARY

Acetyl bromide reacts with N,N-disubstituted, N-monosubstituted, and N-unsubstituted ethyl and benzyl carbamates, to yield ethyl or benzyl bromide and the corresponding acetamides, with carbon dioxide evolution. A reaction mechanism is proposed.

Acetyl chloride causes N-acetylation of N-methyl and N-unsubstituted ethyl and benzyl carbamates. It does not react with N-phenyl and N,N-disubstituted carbamates.

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