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The Synthesis of N-Substituted Choline Carbamates and Trimethyl-β-phenylaminoethylammonium Chloride

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Since the demonstration by Hunt of the remarkable activity of acetyl choline in lowering the blood pressure, esters of choline have been extensively studied pharmacologically. Of these, choline chloride carbamate has been shown to be exceedingly active (about 40% of the activity of acetyl choline) and much more stable than acetyl choline.[3] Since only very few N-substituted choline carbamates have been reported,[4] it was thought desirable to synthesize compounds of this type for pharmacological investigation. Because of the similarity in structure it was expected that N substitution in this series would produce changes in pharmacological activity parallel to those observed in the betaine amides.[5] In the latter series, the N-methyl derivative was not only ten times as active in lowering blood pressure as the simple amide but also the most active compound of the group. The piperidino compound had a marked muscarine but no stimulating nicotine action, whereas the phenyl betaine amide showed only a stimulating nicotine action. Preliminary investigation by Dr. M. B. Bender[6] has shown, however, that N substitution practically abolishes the muscarine activity of choline carbamate but that the stimulating nicotine action remains of the same order.

The number of aminocholines reported in the literature is very small.[7] With the exception of the trimethyl-β-diethylaminoethylammonium bromide[7b] they were isolated only as metallic complexes. The pharmacological activity of trimethyl-β-phenylaminoethylammonium chloride, the synthesis of which is reported in this paper, may be expected to resemble that of the N-phenylamide of betaine and the phenyl ether of choline.[5b]

β-Halogeno-ethyl-N-substituted Carbamates.—The chloroethyl compounds were prepared by treating β-chloroethyl chlorocarbonate with 2 moles of the appropriate amine in benzene solution[8] or 1 mole of amine hydrochloride in aqueous sodium carbonate solution[9]

$$ClCH_2CH_2—O—CO—Cl + 2RNH_2 \longrightarrow ClCH_2CH_2—O—CO—NHR + RNH_2\cdot HCl$$

$$ClCH_2CH_2—O—CO—Cl + RNH_2\cdot HCl + Na_2CO_3 \longrightarrow ClCH_2CH_2—O—CO—NHR + 2NaCl + H_2O + CO_2$$

The yields were better in the first procedure, usually approaching the theoretical.

The β-iodoethyl carbamates, of which only the parent urethan is reported in the literature,[4a] were prepared from the corresponding chloroderivatives by refluxing with sodium iodide in acetone solution.

N-Substituted Choline Halide Carbamates.—Condensation of the halogeno-ethyl carbamates with trimethylamine gave rise to the corresponding onium compounds. The iodoethyl carbamates reacted much more smoothly and gave better yields than the chloroethyl derivatives.

The β-iodoethyl N-diethyl, N-phenyl and piperidino derivatives were also condensed with triethylamine. With the di-N-substituted carbamates, onium compounds were formed readily, but in the case of the β-iodoethylphenyl carbamate the only products isolated were 3-phenyloxazolidone-2 and triethylammonium iodide. The reaction ran the same course even at −10 to −5°. In view of the observations of Schotte[8a] and Pierce[9b] that the β-chloroethyl alkyl carbamates lose halogen acid more readily than the corresponding aryl derivatives, it may be expected that the alkyl mono-substituted carbamates would react similarly with triethylamine. Condensation with trimethylamine even at elevated temperatures, however, resulted in good

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(3) (a) Kreitmair, *Arch. exptl. Path. Pharmakol.*, **164**, 346 (1932); (b) Nöll, *ibid.*, **167**, 158 (1932); (c) Velten, *ibid.*, **168**, 223 (1933); (d) Feldberg, *ibid.*, **168**, 287 (1932); (e) Chang and Gaddum, *J. Physiol.*, **79**, 255 (1933).

(4) (a) Dalmer and Diehl, German Patents 539,329 and 590,311, U. S. Patent 1,894,162; (b) Ercoli, *Ann. chim. applicata*, **25**, 263 (1935).

(5) (a) Renshaw and Hotchkiss, *J. Biol. Chem.*, **103**, 183 (1933); (b) Hunt and Renshaw, *J. Pharmacol.*, **35**, 99 (1929).

(6) Personal communication.

(7) (a) Ewins, *Biochem. J.*, **8**, 369 (1914); (b) Meyer and Hopff, *Ber.*, **54**, 2280 (1921); (c) Fränkel and Nussbaum, *Biochem. Z.*, **182**, 424 (1927).

(8) (a) Schotte, *et al.*, *Z. physiol. Chem.*, **174**, 142 (1928); (b) Adams and Segur, THIS JOURNAL, **45**, 785 (1923).

(9) (a) Pierce with Adams, *ibid.*, **45**, 792 (1923); (b) Pierce, *ibid.*, **50**, 242 (1928).

TABLE I

β-CHLOROETHYL CARBAMATES

Carbamate	Yield, %	B. range °C.	Mm.	Nitrogen, % Calcd.	Found
$CH_3NH—CO—O—CH_2CH_2Cl$[a]	70	100–102	11		
$(CH_3)_2N—CO—O—CH_2CH_2Cl$	89	80–81	9	9.2	8.8
$C_2H_5NH—CO—O—CH_2CH_2Cl$	88	102–104[b]	11	9.2	8.8
$(C_2H_5)_2N—CO—O—CH_2CH_2Cl$	87	66–68[c]	1	7.8	7.3
$n\text{-}C_3H_7NH—CO—O—CH_2CH_2Cl$[d]	95	83–85	1		
$n\text{-}C_4H_9NH—CO—O—CH_2CH_2Cl$	92	97–99	1	7.8	7.3
$C_5H_{10}>N—CO—O—CH_2CH_2Cl$	93	91–93	2	7.3	7.0
$C_6H_5NH—CO—O—CH_2CH_2Cl$	82	133–135[e]	2		

[a] Prepared from methylamine hydrochloride and chloroethyl chlorocarbonate in sodium carbonate solution. Schotte, *et al.*,[8a] give 110–112° at 15 mm.; German Patent 539,329 gives 92–93° at 6 mm. [b] Schotte, *et al.*,[8a] give 94–95° at 10 mm.; and German Patent 442,413 gives 110–111° at 12 mm. [c] B. p. at 9 mm. is 93°. [d] Analyzed as iodoethyl derivative and choline carbamate. [e] Nemirowsky, *J. prakt. Chem.*, **31**, 175 (1885).

TABLE II

β-IODOETHYL CARBAMATES

Carbamate	Yield, %	B. p. °C.	Mm.	Analysis, % Calcd.	Found	
$(C_2H_5)_2N—CO—O—CH_2CH_2I$	66	109–110[a]	4	I 46.9	46.2	47.1
$n\text{-}C_3H_7NH—CO—O—CH_2CH_2I$[b]	84	98	0.07	I 49.4	49.4	49.8
$n\text{-}C_4H_9NH—CO—O—CH_2CH_2I$[c]	84	106–108	0.07	I 46.8	46.6	46.2
$C_5H_{10}>N—CO—O—CH_2CH_2I$[d]	56	115–117	2	N 4.95	4.85	4.90
$C_6H_5NH—CO—O—CH_2CH_2I$[e]	77			N 4.8	5.2	

[a] B. p. at 9 mm. is 122–123°. [b] Rectangular plates, from hexane; m. p. 50°. [c] Slender plates from hexane; m. p. 46°. [d] Obtained as an orange colored liquid. [e] Thin rectangular prisms from hexane containing a little benzene or from cyclohexane; m. p. 77–79°.

yields of onium compound. Renshaw and McGreal[10] have also reported splitting of hydrohalide in condensations with higher homologs of trimethylamine.

The ammonium compounds described are being studied pharmacologically.

Experimental

β-Chloroethyl Carbamates. Method 1.—Two moles of anhydrous amine in benzene was added slowly with shaking to a solution of 1 mole of β-chloroethyl chlorocarbonate in benzene surrounded by an ice-bath. After standing overnight in the refrigerator, the amine hydrochloride was filtered off, the solvent evaporated and the residue fractionated *in vacuo*.

Method 2.—One mole of amine hydrochloride was added to 1.05 moles of sodium carbonate (as a 10% aqueous solution) and chilled in a freezing mixture. One mole of β-chloroethyl chlorocarbonate was added slowly with stirring. Stirring was continued for one and one-half hours. After standing overnight, the mixture was neutralized, extracted eight times with chloroform, and the extract dried over anhydrous sodium sulfate. The solvent was then evaporated and the residue fractionated *in vacuo*.

The yields and boiling points of the β-chloroethyl carbamates are given in Table I. The disubstituted carbamates are characterized by lower boiling points than their monosubstituted homologs or isomers.

β-Iodoethyl Carbamates.—The β-iodoethyl carbamates were prepared from the corresponding chloro derivatives by refluxing for ten to fifteen hours with a large excess (3–5 times the theoretical requirement) of dry sodium iodide in anhydrous acetone or methyl alcohol. After standing overnight in the icebox the bulk of the solvent was evaporated and the residue extracted with water. The water extract was washed with ether and the ether solution added to the residue. This was washed with dilute sodium bisulfite solution, dried over anhydrous sodium sulfate, the solvent evaporated and the residue fractionated or recrystallized. The data for the β-iodoethyl carbamates are given in Table II.

N-Substituted Choline Halide Carbamates.—The halogeno-ethyl carbamates were condensed with equimolecular quantities of tertiary amine in a pressure bottle. Acetone was the solvent most often used, although occasionally methyl ethyl ketone or ethyl alcohol proved satisfactory. In the case of the chloro derivatives, heating at 50–70° for a few hours was necessary, but the iodo compounds reacted in good yield when allowed to stand overnight at room temperature. The onium derivatives are listed in Table III.

Attempted Condensation of β-Iodoethyl Phenyl Carbamate with Triethylamine.—Equimolecular quantities of the reactants in anhydrous acetone were allowed to stand at −10 to −5° for about two weeks. The solvent was evaporated and the residue crystallized from hot acetone–ether (4:1). The product, evidently still crude, melted at 168°[11] and had 57.0% I instead of the required 55.4% for triethylammonium iodide.

(10) Renshaw and McGreal, THIS JOURNAL, **54**, 1473 (1932).

(11) Dehn, *ibid.*, **34**, 293 (1912) gives 173°.

TABLE III

N-SUBSTITUTED CHOLINE HALIDE CARBAMATES

Choline halide carbamates	Crystal form	Yield, %	M. p., °C. (corr.)	Halogen, % Calcd.	Found	
$CH_3NHCO_2C_2H_4NMe_3Cl$[a]	Rectangular plates	55	178–180	18.03	18.00	18.10
$(CH_3)_2NCO_2C_2H_4NMe_3Cl$[a]	Rectangular prisms	50	185–187	16.83	16.62	16.57
$C_2H_5NHCO_2C_2H_4NMe_3Cl$[b]	Rectangular prisms	50	198–200	16.83	16.78	16.53
$(C_2H_5)_2NCO_2C_2H_4NMe_3Cl$[c]	Rectangular prisms	68	131–133	14.85	14.80	14.93
$(C_2H_5)_2NCO_2C_2H_4NMe_3I$[d]	Rectangular plates	69	121–123	38.43	38.45	38.35
n-$C_3H_7NHCO_2C_2H_4NMe_3I$[d]	Slender rect. plates	79	87–99[f]	40.10	40.12	40.40
n-$C_4H_9NHCO_2C_2H_4NMe_3I$[d]	Slender rect. plates	72	101–103	38.43	38.35	38.30
$C_5H_{10}>NCO_2C_2H_4NMe_3I$[g]	Rectangular plates	58	200–201	37.08	37.11	37.23
$C_6H_5NHCO_2C_2H_4NMe_3I$[h]	Irregular prisms	50	131–132	36.24	36.26	36.21
$(C_2H_5)_2NCO_2C_2H_4NEt_3I$[i]	Sheaths of needles	68	99–101	34.09	34.13	34.22
$C_5H_{10}>NCO_2C_2H_4NEt_3I$[j]	Minute prisms	65	95–97	33.02	33.08	32.90

[a] Moderately hygroscopic; crystallized from anhydrous ethyl alcohol–acetone mixtures; German Patent 539,329 gives m. p. 171–173° (uncorr.) for the N-methyl compound. [b] Calcd. for $C_8H_{19}O_2N_2Cl$: N, 13.3. Found: N, 13.1. Moderately hygroscopic; crystallized from anhydrous ethyl alcohol–acetone mixture. [c] Very hygroscopic; crystallized from a small volume of anhydrous acetone or acetone–ethyl acetate mixture. [d] Crystallized from methyl ethyl ketone. [e] Often with a square nick out of a corner. [f] Softening at 85–88°. [g] Crystallized from absolute alcohol. [h] Crystallized from anhydrous n-propyl alcohol. [i] Crystallized from a methyl ethyl ketone–ether mixture; moderately hygroscopic. [j] Crystallized from an acetone–isopropyl ether, or methyl ethyl ketone-ethyl acetate mixture; moderately hygroscopic.

The mother liquor was evaporated and the residue recrystallized from aqueous alcohol. The product melted at 121–122° and gave a mixed m. p. of 122–3° with an authentic specimen of 3-phenyloxazolidone-2.[12]

N-β-Chloroethylaniline.—The hydrochloride was prepared in good yield by the method of Clemo and Perkin.[13] Attempts to prepare this compound by chlorination of β-hydroxyethylaniline with thionyl chloride failed; m. p. 157–159°.

Anal. Calcd. for $C_8H_{10}NCl\cdot HCl$: N, 7.30. Found: N, 7.37.

Trimethyl-β-Phenylaminoethylammonium Chloride Hydrochloride.—Ten grams of β-chloroethylaniline hydrochloride (1 mole) was condensed in a pressure bottle with 6.2 g. of trimethylamine (2 moles) in 35 cc. of anhydrous acetone and allowed to stand overnight at room temperature. Next day the mixture was heated at 70–75° for seven hours. After cooling, the acetone solution was poured off from the crystalline, oily mass and the latter extracted with anhydrous n-propyl alcohol. The acetone solution was evaporated and its residue combined with the propyl alcohol extract. After thorough chilling a small amount of trimethylamine hydrochloride was filtered off. Dry hydrogen chloride was then passed into the solution, and the crystalline precipitate that formed was filtered off and recrystallized twice from anhydrous n-propyl or ethyl alcohol; yield, 8 g. of very fine needles, mostly in clusters; m. p. 221–222 (corr.) with decomposition.

Anal. Calcd. for $C_{11}H_{19}N_2Cl\cdot HCl$: N, 11.1; Cl, 28.2. Found: N, 11.0, 10.9; Cl, 28.1, 28.1. *Titration* with 0.1 N NaOH: Calcd. for $C_{11}H_{19}N_2Cl\cdot HCl$:HCl, 14.5. Found: HCl, 14.5.

(12) Otto, *J. prakt. Chem.*, **44**, 17 (1891), gives m. p. 122°.

(13) Clemo and Perkin, *J. Chem. Soc.*, **121**, 644 (1922); **125**, 1808 (1924).

Summary

1. A number of β-chloroethyl-N-substituted carbamates have been synthesized, and some of these have been converted to the corresponding iodo derivatives.

2. The halogeno-ethyl carbamates were converted to N-substituted choline halide carbamates by condensation with tertiary amines.

3. Condensation of β-iodoethylphenyl carbamate with triethylamine gave the 3-phenyloxazolidone-2 and triethylammonium iodide.

4. Trimethyl-β-phenylaminoethylammonium chloride hydrochloride was synthesized.

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