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Mercaptoethylation. III. Reactions of 2-Mercaptoethyl Carbamates

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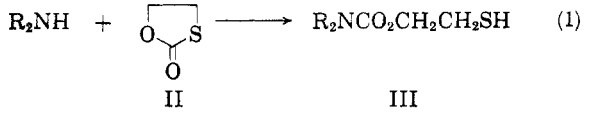
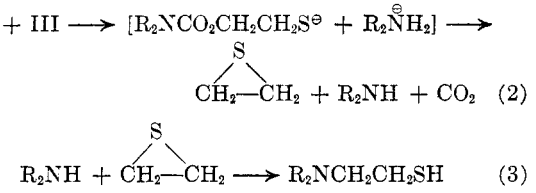
Three representative examples of 2-mercaptoethyl carbamates and four different types of *S*-substituted 2-mercaptoethyl carbamates are shown to be mercaptoethylating agents for moderately to strongly basic primary and secondary amines. Side reactions encountered in this preparation are discussed and an evaluation is made of 2-mercaptoethyl carbamates as intermediates in the synthesis of 2-aminoethanethiols.

In an earlier paper[1b] of this series[1] it was postulated that the formation of 2-aminoethanethiols (I) from the reaction of primary and secondary amines with ethylene monothiolcarbonate (II) involved a 2-mercaptoethyl carbamate (III) intermediate, as illustrated in Equations 1–3. This was substantiated to some extent by the preparation[1b] of a number of these carbamates, as depicted in Equation 1. If the proposed explanation for the



$$R_2NH + \text{II} \longrightarrow \text{III} \quad (1)$$



$$R_2NH + \text{III} \longrightarrow [R_2NCO_2CH_2CH_2S^{\ominus} + R_2\overset{\oplus}{N}H_2] \longrightarrow \text{(S)} + R_2NH + CO_2 \quad (2)$$

$$R_2NH + \text{(S)} \longrightarrow R_2NCH_2CH_2SH \quad (3)$$

mercaptoethylation is correct, it would follow that such carbamates would serve as mercaptoethylating agents. We shall report here the exploration of this possibility.

Three representative 2-mercaptoethyl carbamates (III), *i.e.*, R_2N— = (IV)  , (V) *n*-C_4H_9NH—, (VI), C_6H_5NH—, were each refluxed overnight with a two-fold excess of morpholine, benzylamine, and diethylamine, respectively, in toluene. As predicted, in each case carbon dioxide was evolved and the desired 2-aminoethanethiol was obtained upon distillation in the yield recorded in Table I.

The reason for the variations in yields observed for a given 2-aminoethanethiol derived from these three carbamates is quite apparent after consideration of the stoichiometry of the reaction, Equation 4. From this equation it is seen that an amine is generated from III as it decomposes to ethylene sulfide and carbon dioxide. If this amine differs from the amine introduced to be mercaptoethylated ($R_2N \neq R_2'N$—), it may act as a competing nucleophile for the ethylene sulfide, yielding an aminoethane thiol corresponding to the parent 2-mercaptoethyl carbamate. Thus, although an 87% yield of 2-morpholinoethanethiol was obtained when both R_2N— and $R_2'N$– = ; this yield was reduced to 74%, accompanied by a 7% crude yield of 2-*n*-butylaminoethanethiol when R_2N— = *n*-C_4H_9NH— and $R_2'N$– = . This side reaction was even more troublesome for R_2N– = and $R_2'N$— = $C_6H_5CH_2NH$—. From this experiment only a 33% yield of pure 2-benzylaminoethanethiol was isolated, and a considerable part of the yield was lost as a difficultly separable mixture of 2-benzyl- and 2-morpholinoethanethiols.

Thus, mercaptoethylation reactions with a 2-mercaptoethyl carbamate are often accompanied by a competing reaction that does not occur when ethylene monothiolcarbonate (II) is used, and one which can be avoided only if the amine liberated

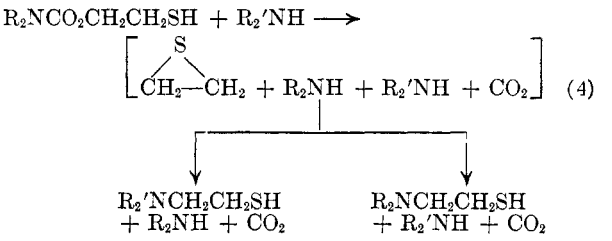
TABLE I

MERCAPTOETHYLATION WITH 2-MERCAPTOETHYL CARBAMATES

$R_2NCO_2CH_2CH_2SH + R_2'NH \longrightarrow R_2'NCH_2CH_2SH + R_2NH + CO_2$

		% Yield $R_2'N$—		
	R_2N—	[a]	$C_6H_5CH_2NH$—[a]	$(C_2H_5)_2N$—[a]
IV		87	33	36
V	*n*-C_4H_9NH—	74	51	43
VI	C_6H_5NH—	85	65	35

[a] The physical constants were in good agreement with those previously reported.[1a]



$$R_2NCO_2CH_2CH_2SH + R_2'NH \longrightarrow [\text{(S)} + R_2NH + R_2'NH + CO_2] \quad (4)$$

$$\downarrow \qquad\qquad \downarrow$$

$R_2'NCH_2CH_2SH + R_2NH + CO_2$ $\qquad$ $R_2NCH_2CH_2SH + R_2'NH + CO_2$

(1) (a) D. D. Reynolds, M. K. Massad, D. L. Fields, and D. L. Johnson, *J. Org. Chem.*, **26**, 5107 (1961), Part I of this series. (b) D. D. Reynolds, D. L. Fields, and D. L. Johnson, *J. Org. Chem.*, **26**, 5109 (1961), Part II of this series.

from the carbamate is either the same amine, or an amine which is much less nucleophilic than the amine introduced to be mercaptoethylated. Of the three carbamates investigated, only 2-mercaptoethyl phenylcarbamate (VI) would be expected to be of general use in mercaptoethylation reactions, since the aniline liberated during the reaction would not readily compete with an amine basic enough to promote the decomposition of the carbamate. From a preparative viewpoint, however, even this prospect is not believed to be very attractive, since, on a weight basis, about 70% of the starting material is evolved as useless by-products.

S-Substituted 2-mercaptoethyl carbamates. During the study of mercaptoethylations involving 2-mercaptoethyl carbamates, we examined the reaction of an amine with *S*-substituted 2-mercaptoethyl carbamates, in which the mercaptan was blocked by base-labile groups, such as —COR, $-CO_2R$, $-CONR_2$, and $-C(=NH)NH_2\cdot HX$, where R is alkyl. That these compounds under basic conditions would be precursors to ethylene sulfide and hence to aminoethanethiols we realized quite early in this study, when our attempt to prepare 2-mercaptoethyl *n*-butylcarbamate by the saponification of its isothiouronium salt resulted in the production of polyethylene sulfide to the complete exclusion of the desired carbamate. Therefore, in a more systematic investigation, compounds VII–X, Table II, were each refluxed with morpholine in toluene overnight, with a four-to-one (4:1) molar ratio of amine to mercaptoethylating agent. As shown in Table II, in each of these cases, the 2-morpholinoethanethiol was isolated in a high state of purity, and the major cleavage product identified. Since an excess of morpholine was employed, the cleavage product was expected to be primarily a morpholino derivative, *i.e.*, O(CH2CH2)2N—R. This was found to be the case when R = $=COC_3H_7$-*n*, $-CO_2C_6H_{13}$-*n* and $-C(=NH)-NH_2\cdot HCl$. However, unexpectedly, the major cleavage product from the *n*-butylcarbamoyl derivative (X) was found not to be 1-*n*-butyl-3-(3-oxapentamethylene)urea, but was instead 1,3-di-*n*-butylurea, as proved by elemental analysis, mixed melting point, and infrared spectra comparisons with an authentic sample. Therefore, from the selectivity of this particular reaction, it becomes apparent that the nucleophilic attack by amine, resulting in the carbon-sulfur bond cleavage, occurs much more slowly with morpholine than with *n*-butylamine, as illustrated in Fig. 1. Secondly, it represents evidence that the carbon-sulfur bond cleavage of the thiolcarbamate group of X under our experimental conditions occurs much more slowly than a similar cleavage involving the thiol ester (VII), thiolcarbonate (VIII), or the isothiourea (IX) of Table II.

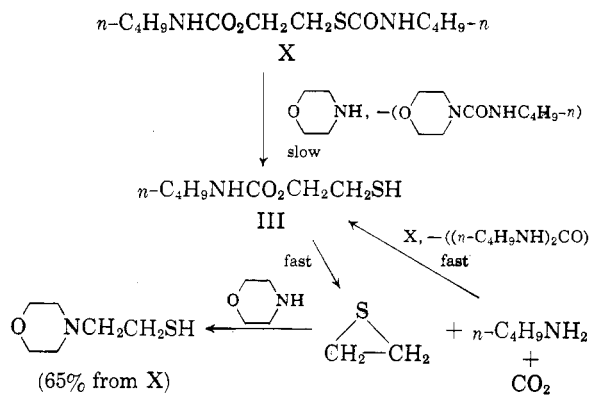


Figure 1

EXPERIMENTAL[2]

Preparation of 2-mercaptoethyl carbamates. (a) *2-Mercaptoethyl 3-oxapentamethylenecarbamate* (III. R_2N- = O(CH2CH2)2N–), n_D^{25} 1.5058 was prepared from ethylene monothiolcarbonate (II) and morpholine by a previously described procedure.[1b]

(b) *2-Mercaptoethyl n-butylcarbamate* (III. R_2N- = n-C_4H_9NH—), b.p. 103°/0.1 mm., n_D^{25} = 1.4782 (lit.[1b] b.p. 98°/0.5 mm., n_D^{25} = 1.4782) was prepared by the dropwise addition of *n*-butyl isocyanate (198 g., 2.0 moles) to 2-mercaptoethanol (174 g., 2.23 moles) with stirring over a 30-min. period. The ensuing exothermic reaction was moderated by a water bath to maintain a reaction temperature below 120°. The desired carbamate (254 g., 72%) was obtained after distillation through a 14-in. Vigreux column.

(c) *2-Mercaptoethyl phenylcarbamate* (III. R_2N- = C_6H_5NH—), was prepared in 81% yield (485 g.) from phenyl isocyanate (357 g., 3.0 moles) and 2-mercaptoethanol (234 g., 3.0 moles). After standing overnight, the reaction mixture completely crystallized and had a m.p. of 61–62° (lit.[3] m.p. 62°) after a single recrystallization from ethanol.

Mercaptoethylation with 2-mercaptoethyl carbamates. General procedure. A mixture of 0.5 mole of 2-mercaptoethyl carbamate (IV, V, or VI), 1.5 moles of amine and 250 ml. of toluene was refluxed overnight under an efficient condenser. The product was isolated by distillation under reduced pressure through a 14-in. Vigreux column equipped with a variable take-off head. The yields of the 2-aminoethanethiols thus obtained are listed in Table I. The physical constants of these aminomercaptans were in good agreement with those previously reported.[1a]

Preparation of S-substituted 2-mercaptoethyl n-butylcarbamates. (a) *2-(n-Butyrylmercapto)ethyl n-butylcarbamate* (VII). A mixture of 2-mercaptoethyl *n*-butylcarbamate (155 g., 0.88 mole), *n*-butyric anhydride (158 g., 1.17 moles) and 50 ml. of benzene was refluxed for 15 hr. The product (155 g., 72%), b.p. 152°/0.1 mm., n_D^{25} 1.4787, was obtained upon distillation.

Anal. Calcd. for $C_{11}H_{21}NO_3S$: C, 53.4; H, 8.5; N, 5.7. Found: C, 53.5; H, 8.7; N, 5.7.

(b) *n-Hexyl n-butylcarbamoyloxyethylthiolcarbonate* (VIII). *n*-Hexyl 2-hydroxyethylthiolcarbonate was prepared in 77% yield by reaction of sodium 2-hydroxyethyl mercaptide with *n*-hexyl chloroformate. This was, in turn, caused to react with *n*-butyl isocyanate to yield the desired thiolcarbonate.

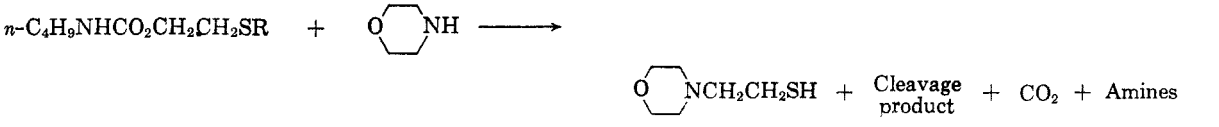
Thus, the mercaptide solution, consisting of 2-mercaptoethanol (390 g., 5.0 moles) and sodium hydroxide pellets (200 g., 5.0 moles) dissolved in 2 l. of water, was added,

(2) The melting points are uncorrected.

(3) J. F. Smith and E. C. Friedrich, *J. Am. Chem. Soc.*, **81**, 161 (1959).

TABLE II

MERCAPTOETHYLATION WITH 2-SUBSTITUTED 2-MERCAPTOETHYL CARBAMATES



	R	% Yield O(CH2)2NCH2CH2SH	% Purity[b]	Cleavage Product[c]
VII	—COC_3H_7-n[a]	68	98	O(CH2)2NCOC3H7-n
VIII	—$CO_2C_6H_{13}$-n[a]	72	97	O(CH2)2NCO2C6H13-n
IX	—C(=NH)NH_2·HCl	47	98	O(CH2)2NC(=NH)NH2·HCl
X	—$CONHC_4H_9$-n	65	99	(n-C_4H_9NH)$_2$CO

[a] The alkyl group was chosen so that the cleavage product could be easily separated by distillation from 2-morpholinoethanethiol. [b] Purity determined by iodometric titration. [c] See the Experimental section for characterization of the cleavage products.

TABLE III

CHARACTERIZATION OF CLEAVAGE PRODUCTS

	Cleavage Product	B.p./Mm. or M.P.	n_D^{25}		C, %	H, %	N, %
VII[a]	O(CH2)2NCOC3H7-n	75/0.07	1.4742	Calcd.	61.1	9.6	8.9
				Found	60.9	9.9	9.2
VIII[a]	O(CH2)2NCO2C6H13-n	95/0.05	1.4552	Calcd.	61.4	9.9	6.5
				Found	61.8	9.8	6.9
IX[a]	O(CH2)2NC(=NH)NH2·HCl[b]	162–164		Calcd.	36.3	7.3	25.4
				Found	36.5	7.4	25.8
X[a]	(n-C_4H_9NH)$_2$CO[c]	76–77		Calcd.	62.7	11.7	16.3
				Found	62.8	12.0	16.5

[a] Starting material. [b] Recrystallized twice from ethanol-ether. [c] Recrystallized twice from benzene-ligroin. Mixed melting point with authentic 1-n-butyl-3-(3-oxapentamethylene)urea was depressed to 48°. The mixed melting point was undepressed with authentic 1,3-di-n-butylurea.

with efficient, high-speed stirring, to n-hexyl chloroformate (823 g., 5.0 moles) in 2 l. of benzene over a 3-hr. period. The mixture was rapidly stirred for an additional 0.5 hr., acidified with 30 ml. of glacial acetic acid, and the organic layer separated and dried over mgnesium sulfate. After further stabilization of the organic phase with 30 g. of stearic acid, it was distilled through a 14-in. Vigreux column, yielding 796 g. of product, b.p. 109°/0.05 mm., n_D^{25} 1.4665.

Anal. Calcd. for $C_9H_{18}O_3S$: C, 52.5; H, 8.7; S, 15.5. Found: C, 52.3; H, 8.6; S, 15.1.

n-Hexyl 2-hydroxyethylthiolcarbonate (103 g., 0.50 mole) and n-butyl isocyanate (54.5 g., 0.55 mole) were mixed, allowed to stand for 0.5 hr. and then heated to 90° on a steam bath for an additional 0.5 hr. Volatile material boiling below 130°/0.07 mm. was removed by distillation, leaving 151 g. of undistilled product, n_D^{25} 1.4707.

Anal. Calcd. for $C_{14}H_{27}NO_4S$: C, 55.1; H, 8.9; N, 4.6. Found: C, 54.8; H, 9.0; N, 4.9.

(c) *n-Butylcarbamoyloxyethylisothiourea hydrochloride* (IX). 2-Chloroethyl n-butylcarbamate (188.5 g., 1.05 moles), b.p. 96–97°/0.7 mm., n_D^{25} 1.4548, prepared by the reaction of n-butyl isocyanate with an equimolar amount of 2-chloroethanol (88%), was refluxed overnight with thiourea (76 g., 1.0 mole) in 500 ml. of isopropyl alcohol. The resulting solution was concentrated to a viscous sirup which crystallized upon trituration with ether. Yield, 242 g. (95%); m.p. 77–79°.

Anal. Calcd. for $C_8H_{18}NO_2SCl$: C, 37.6; H, 7.1; N, 16.5; S, 12.5; Cl, 13.9. Found: C, 37.3; H, 7.4; N, 16.5; S, 12.9; Cl, 13.9.

(d) *2-n-Butylcarbamoyloxyethyl n-butylcarbamate* (X). n-Butyl isocyanate (198 g., 2.0 moles) and 2-mercaptoethanol (87 g., 1.0 mole) were mixed together and cooled to moderate the exothermic reaction. The reaction mixture solidified overnight and was recrystallized once from benzene; yield, 193 g. (68%); m.p. 94–97°.

Anal. Calcd. for $C_{12}H_{23}N_2O_3S$: C, 52.4; H, 8.4; N, 10.2; S, 11.6. Found: C, 52.4; H, 8.9; N, 9.9; S, 11.5.

Mercaptoethylation with S-substituted 2-mercaptoethyl n-butylcarbamates. General procedure. A mixture of 0.5 mole of the 2-mercaptoethyl n-butylcarbamate derivatives listed in Table II (VII, VIII, IX, or X), morpholine (174 g., 2.0 moles) and 250 ml. of toluene was refluxed overnight under an efficient reflux condenser. The 2-morpholinoethanethiol so produced was isolated in the yield tabulated in Table II by distillation through a 14-in. Vigreux column. The major cleavage products, as characterized in Table III, were left as pot residue in all cases and were then isolated either by further distillation or by crystallization.

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