[COMMUNICATION NO. 2175 FROM THE KODAK RESEARCH LABORATORIES, EASTMAN KODAK CO.]

Mercaptoethylation. IV. Preparation and Some Reactions of Alkyl 2-Hydroxyethylthiolcarbonates

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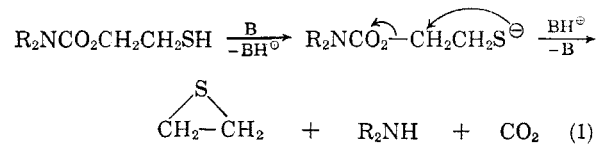
A convenient synthesis for alkyl 2-hydroxyethylthiolcarbonates in 85–92% yields is described. These thiolcarbonates are shown to be mercaptoethylating agents for moderately to strongly basic primary and secondary amines. An evaluation is made of their usefulness in the synthesis of 2-aminoethanethiols. Results of a brief examination of 2-mercaptoethyl acetate as a mercaptoethylating agent are also recorded.

In work described in the preceding paper of this series,[1] 2-mercaptoethyl carbamates were shown to decompose readily under basic conditions to ethylene sulfide, carbon dioxide, and amine, as depicted in Equation 1. It was also shown that if the decomposition of the carbamate to ethylene sulfide, and then would react with the ethylene sulfide to form a 2-aminoethanethiol (Ia), as shown in Equation 2. The preparative value of this reaction for the synthesis of 2-aminoethanethiols, however, was found to be questionable since mixtures of aminothiols (Ia and Ib) often resulted unless the amine liberated from the carbamate was of much weaker nucleophilic character than the amine introduced to be mercaptoethylated.



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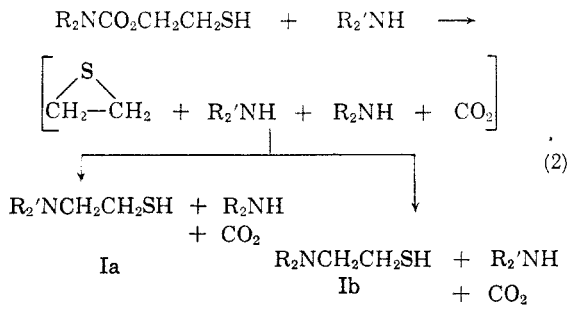
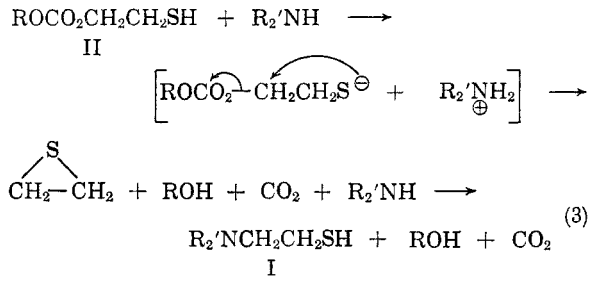


(2)

In seeking to avoid this type of side reaction, the possibility of employing a 2-mercaptoethyl carbonate (II) as a mercaptoethylating agent was suggested. The advantage in such use would be derived from the elimination of the type of competitive reaction just described, since an alcohol instead of an amine would be generated as a reaction by-product (Eq. 3).



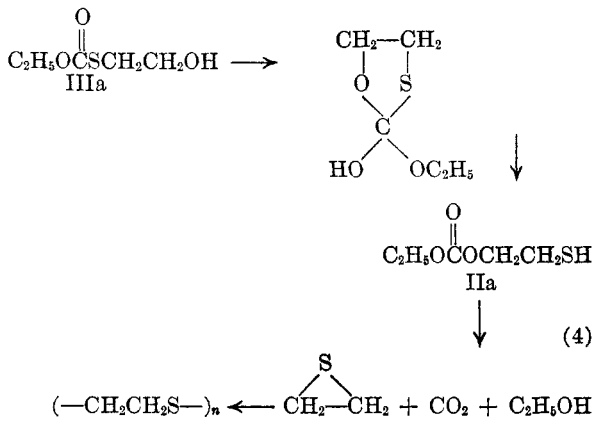
(3)

However, our preliminary efforts to prepare ethyl 2-mercaptoethylcarbonate (IIa) in a reasonable yield were not particularly successful since the synthesis necessarily had to be conducted under neutral or acidic conditions. The highest yield of IIa obtained in these exploratory experiments was 35%, obtained by refluxing 2-mercaptoethanol with ethyl chloroformate in the absence of base catalyst. In the light of our difficulty in obtaining IIa in good yield, attention was diverted to an indirect approach to IIa *via* the more readily prepared isomeric ethyl 2-hydroxyethylthiolcarbonate (IIIa). Culvenor and co-workers[2] first reported the preparation of IIIa in an impure state by reaction of 2-mercaptoethanol with ethyl chloroformate in pyridine. They also demonstrated that a polyethylene sulfide resulted when IIIa was treated with alkali. The reaction mechanism proposed for this transformation (Eq. 4) entailed the isomerization of IIIa to IIa through a 1,3-oxathiolane intermediate, the decomposition of IIa to ethylene sulfide, and then the polymerization of ethylene sulfide to polyethylene sulfide.

In order to determine the usefulness of this sequence in the preparation of 2-aminoethanethiols, a convenient synthesis of pure IIIa was developed. This was accomplished in 87–92% yield by the addition of an aqueous sodium 2-hydroxyethyl mercaptide solution to an efficiently stirred two-phase system of ethyl chloroformate in benzene and water, followed by distillation of the organic

(1) D. D. Reynolds, D. L. Fields, and D. L. Johnson, Part III, *J. Org. Chem.*, 26, 5116 (1961).

(2) C. C. Culvenor, W. Davies, and W. E. Savige, *J. Chem. Soc.*, 4480 (1952).



(4)

phase. This reaction occurs at a rate rapid enough to allow the preparation to be conducted in a continuous reactor (see Experimental section), in which 50 kg. of IIIa could be prepared in 92% yield in an eight-hour day. The only precaution taken against premature decomposition of IIIa by foreign basic materials was the addition of a high-boiling carboxylic acid, *i.e.*, stearic acid, to the stillpot prior to the distillation and isolation of the product. Once purified by distillation, thiolcarbonate IIIa was found to be indefinitely stable at room temperature.

Ethyl 2-hydroxyethylthiolcarbonate (IIIa) was evaluated as a mercaptoethylating agent by refluxing IIIa overnight in toluene with a twofold molar excess of each of the representative amines of Table I. In each case, carbon dioxide was smoothly evolved in the early stages of the reaction period, and the product was isolated by distillation. Unfortunately, in four of the six examples examined, the isolation of the desired 2-aminoethanethiol (I) by distillation was not possible, owing to the similarities of the boiling points of the mercaptoethylated amine and a contaminating ethyl carbamate by-product (IVa) arising from the side reaction (Path 2) shown in Chart I.

The assignments of composition of the mixtures of I and IVa were based on the determination of the per cent of 2-aminoethanethiol present by iodometric titration, supplemented by comparison of the infrared spectra of the mixture with those of a synthetic mixture of identical composition prepared from authentic materials. In each case, the pairs of infrared curves were identical in every respect.

Thus, although it would seem that reaction Path 2, Chart I, (where R = C_2H_5—) was probably not followed by greater than a 30% extent, this side reaction did materially reduce the anticipated high yields of 2-aminoethanethiols and often prevented their isolation in a pure condition by distillation.

In the hope of avoiding this problem, a few cursory experiments employing isobutyl 2-hydroxyethylthiolcarbonate (IIIb) as a mercaptoethylating agent were made. Two effects were sought in using a larger alkyl homolog of IIIa. First, it would allow the isolation of the pure aminoethanethiol since the boiling point of the isobutyl carbamate (IVb) would be sufficiently different from the aminoethanethiol to allow the two to be separated by distillation. Second, it was hoped the increased

TABLE I

MERCAPTOETHYLATION BY 2-HYDROXYETHYL ALKYLTHIOLCARBONATES

$$\underset{\text{III}}{ROCOSCH_2CH_2OH} + \underset{\text{excess}}{R_2'NH} \longrightarrow \underset{\text{I}}{R_2'NCH_2CH_2SH} + \underset{\text{IV}}{R_2'NCO_2R} + ROH + CO_2 + HOCH_2CH_2SH$$

$R_2'N$	B.P./Mm.	% Yield[a] I	% Purity[b]	n_D^{25}
IIIa. R = C_2H_5—				
	81–87/12	62	76	
	101–104/12	59	72	
	107–111/26	62	72	
$(C_2H_5)_2N$—	73–74/34	61	99	
$(n\text{-}C_4H_9)_2N$—	64/0.7	73	99	
$n\text{-}C_6H_{13}NH$—	114–130/15	46	81	
IIIb. R = $i\text{-}C_4H_9$—				
$R_2'N$				
	88–91/15	61	97	1.4985
	109–114/24	57	98	1.5014
$(n\text{-}C_4H_9)_2N$—	64/0.7	69	100	1.4619
$n\text{-}C_6H_{13}NH$—	63–65/0.7	46	99	1.4691

[a] The calculated yield of I is adjusted for the purity indicated. [b] Product purity was determined by iodometric titration. The impurity in each case was the alkyl carbamate, IV.

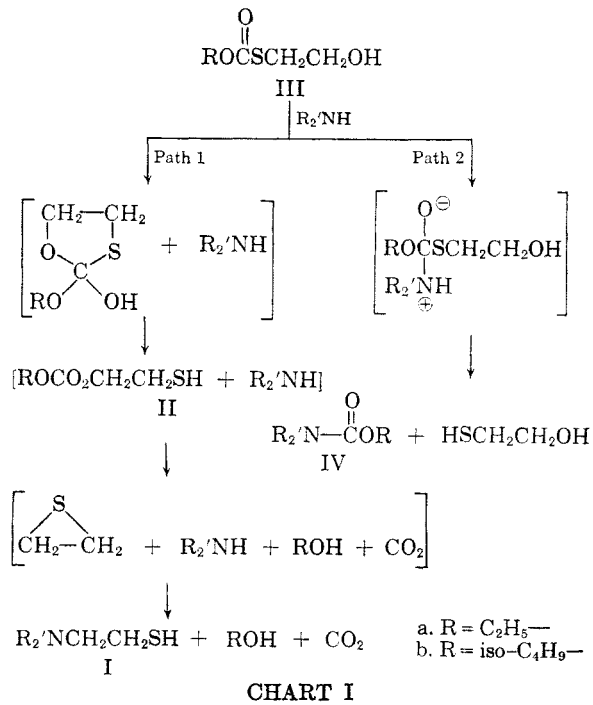
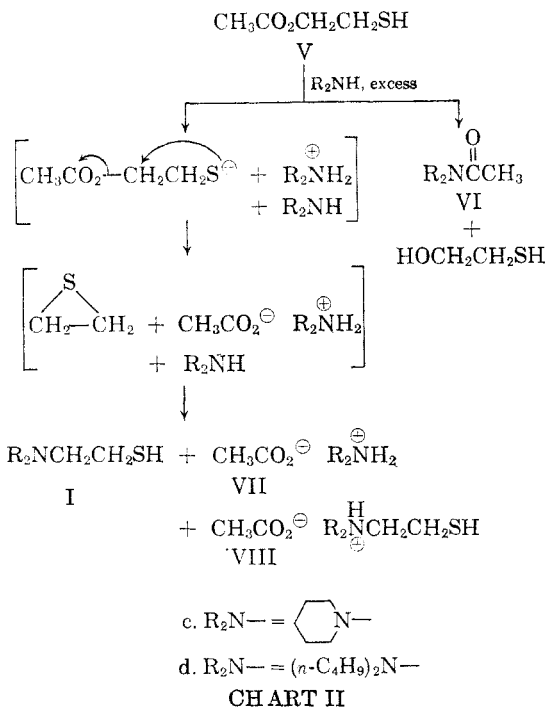


CHART I

steric requirements of the isobutyl group, compared with those of the ethyl group, would decrease the rate of amine attack on carbonyl (Path 2, Chart I), compared to the rate of isomerization (Path I) leading to the mercaptoethylation sequence.

From Table I, it is seen that only one of these objectives was realized. The four aminoethanethiols prepared in this manner were readily separated by distillation from the isobutyl carbamate (IVb), but the ratio of Path 1 to Path 2 followed by the reaction was not seriously affected by the change in alkylating agent.

As a supplement to the alkylation sequences just described, 2-mercaptoethyl acetate[3] (V) was also briefly examined as a mercaptoethylating agent for amines. In the two examples studied, approximately 60% and 42% yields of 2-di-*n*-butylaminoethanethiol (Id) and 2-piperidinoethanethiol (Ic), respectively, were formed when a two-molar excess of di-*n*-butylamine and piperidine were each refluxed overnight in toluene with 2-mercaptoethyl acetate. Again, a number of by-products (Chart II), including the acetamide VI and the amine acetates VII and VIII, prohibited the isolation of the pure aminoethanethiol (I) by simple distillation, making 2-mercaptoethyl acetate a less attractive mercaptoethylating agent than the previously discussed isobutyl 2-hydroxyethylthiolcarbonate (IIIb).



c. $R_2N- = \langle N- \rangle$

d. $R_2N- = (n\text{-}C_4H_9)_2N-$

CHART II

EXPERIMENTAL

Preparation of ethyl 2-mercaptoethylcarbonate (IIa). 2-Mercaptoethanol (156 g., 2.0 moles) and ethyl chloroformate (434 g., 4.0 moles) were heated on a steam bath under a reflux condenser for 7 hr. Crude ethyl 2-mercaptoethylcarbonate was collected by distillation, b.p. 74–80°/7.0 mm., n_D^{25} 1.4568; yield, 105 g. (35%).

Anal. Calcd. for $C_5H_{10}O_3S$: C, 40.0; H, 6.7; S, 21.3. Found: C, 40.2; H, 6.7; S, 21.3.

Preparation of alkyl 2-hydroxyethylthiolcarbonates. (*a*) *Ethyl 2-hydroxyethylthiolcarbonate* (IIIa). Ethyl chloroformate (1085 g., 10.0 moles), 3 l. of technical grade benzene, and 500 ml. of water were placed in a 12-l., three necked flask equipped with thermometer, high-speed, propeller-blade-type agitator and dropping funnel, and cooled to 0°.

A cooled sodium 2-hydroxyethyl mercaptide solution, prepared from sodium hydroxide pellets (400 g., 10 moles), practical grade 2-mercaptoethanol (782 g., 10 moles), and enough water to bring the total volume to 4 l., was then introduced to the rapidly stirred chloroformate mixture over a 30-min. period. The mildly exothermic reaction was moderated during this addition to maintain a reaction temperature below 30°.

The mixture was stirred for an additional 10 min., acidified with 10 ml. of concd. hydrochloric acid from a *p*H 8 → 3 (estimated by Universal Indicator paper) and the organic phase separated, dried over magnesium sulfate, and filtered. After the filtrate had been stabilized with 30 g. of stearic acid, the material was distilled under reduced pressure through an 18-in., glass-helices-packed column to yield 1365 g. (91.0%) of product (negative I_2–mercaptan test), with a b.p. of 108°/5 mm., n_D^{25} 1.4782.

Anal. Calcd. for $C_5H_{10}O_3S$: C, 40.0; H, 6.7; S, 21.3. Found: C, 40.3; H, 6.7; S, 21.1.

This synthesis was very conveniently conducted in a continuous reactor consisting of four 1-l. overflow reaction flasks arranged in a cascading sequence and equipped with air-driven stirrers to provide efficient agitation of the reactants. Equimolar quantities of ethyl chloroformate in benzene and sodium 2-hydroxyethyl mercaptide in water were simultaneously introduced into the top flask by means of two Lapp positive displacement proportionating pumps and thence cascaded with vigorous agitation through the remaining three reaction flasks. The products were collected at the bottom. The organic layer was separated, treated with stearic acid, and distilled to give 92% yields of IIIa.

(*b*) *Isobutyl 2-hydroxyethylthiolcarbonate* (IIIb) was prepared by an analogous procedure in 85% yield from isobutyl chloroformate and sodium 2-hydroxyethyl mercaptide on a 3.7-mole basis. The reaction was considerably more sluggish than in the preparation of IIIa, necessitating a 4-hr. mercaptide addition period at 40°. The product had a b.p. of 81°/0.1 mm., n_D^{25} 1.4696, and gave a negative I_2–mercaptan test.

Anal. Calcd. for $C_7H_{14}O_3S$: C, 47.2; H, 7.8; S, 18.0. Found: C, 47.0; H, 7.9; S, 17.8.

Mercaptoethylation with alkyl 2-hydroxyethylthiolcarbonates. General procedure. A. A mixture of 1.0 mole of ethyl 2-hydroxyethylthiolcarbonate (IIIa), 3.0 moles of amine, and 500 ml. of toluene was refluxed overnight under an efficient reflux condenser. The product was isolated by distillation under reduced pressure through a 14-in., glass-helices-packed column. The results are tabulated in Table I.

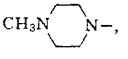
For use as authentic samples in the infrared comparisons, the following ethyl carbamates (IVa) were prepared by the reaction of ethyl chloroformate with an excess of the amine in benzene: IVa,

$R = \langle O \rangle N-$,

b.p. 54°/0.1 mm., n_D^{25} 1.4562;

(3) L. W. C. Miles and L. N. Owen [*J. Chem. Soc.*, 817 (1952)] have previously demonstrated that 2-mercaptoethyl acetate is readily hydrolyzed in the presence of cold dilute alkali to give ethylene sulfide and polymer.

b.p. 99°/14 mm., n_D^{25} 1.4571;



b.p. 116°/15 mm., n_D^{25} 1.4638; n-$C_6H_{13}NH$—, b.p. 129°/14 mm., n_D^{25} 1.4350. Correct elemental analyses were obtained for the four carbamates.

B. *Mercaptoethylation with isobutyl 2-hydroxyethylthiolcarbonate* (IIIb) was conducted on a 0.5-mole basis by a similar procedure.

Mercaptoethylation with 2-mercaptoethyl acetate (V). 2-Mercaptoethyl acetate (V) was prepared by the acid-catalyzed acetylation of 2-mercaptoethanol following Miles and Owen[3] and had a b.p. of 49°/8 mm., n_D^{25} 1.4582 (lit. b.p. 55°/13 mm., n_D^{17} 1.4658), with a purity of 98% by iodometric titration. The general mercaptoethylation procedure described for thiolcarbonates IIIa and IIIb was employed with V and piperidine, and with V and di-*n*-butylamine. The product compositions were analyzed as follows:

A. *Piperidine*. After the reactants had refluxed overnight, the reaction mixture was cooled and the acetate salts of piperidine (VIIc) and possibly some VIIIc separated from solution and were filtered. After removal of solvent and lower boiling fractions, distillation of the filtrate gave three fractions which were analyzed by iodometric titration, infrared spectroscopy, and in one instance by elemental analysis:

(1) B.p. 73–83°/8 mm., n_D^{25} 1.497 (39 g.) and consisted of 87% Ic and 13% VIc;

(2) B.p. 83–91°/8 mm., n_D^{25} 1.487 (11 g.) and consisted of 35% Ic and 65% VIc;

(3) B.p. 91–92°/8 mm., n_D^{25} 1.4801 (31.5 g.) and consisted of 6% Ic and 94% VIc.

Anal. of Fraction 3. Calcd. for pure VIc ($C_7H_{13}NO$): C, 66.1; H, 10.0; N, 11.0. Found: C, 66.2; H, 10.4; N, 10.9.

Fractions 1–3 were added to 800 ml. of ether and the 2-piperidinoethanethiol component (Ic) precipitated as its hydrochloride by bubbling in hydrogen chloride. The hydrochloride was filtered, washed with ether, and dried to yield a total of 77 g. (41.5%) of product of 96.6% purity by iodine titration.

B. *Di-n-butylamine*. Unlike the piperidine example, no acetate salts precipitated from solution after the reaction mixture had cooled. Four product fractions were collected upon distillation of this mixture; the analysis by titration and infrared indicated the following compositions: (1) B.p. 82–84°/8 mm., n_D^{25} 1.447 (185 g.) consisting of 43% Id and 57% VIId and VIIId; (2) B.p. 84–100°/8 mm., n_D^{25} 1.454 (9 g.) consisting of 59% Id and 41% VIId and VIIId; (3) B.p. 100–105°/8 mm., n_D^{25} 1.455 (35 g.) consisting of 61% Id and 39% VId; (4) B.p. 105–111°/8 mm., n_D^{25} 1.449 (18 g.) consisting of 21% Id and 79% VId.

From these data a calculated yield of 62% of 2-di-*n*-butylaminoethanethiol (Id) was obtained.

ROCHESTER, N. Y.

[COMMUNICATION NO. 2176 FROM THE KODAK RESEARCH LABORATORIES, EASTMAN KODAK CO.]

Mercaptoethylation. V. A New Synthesis of Ethylene Monothiolcarbonate

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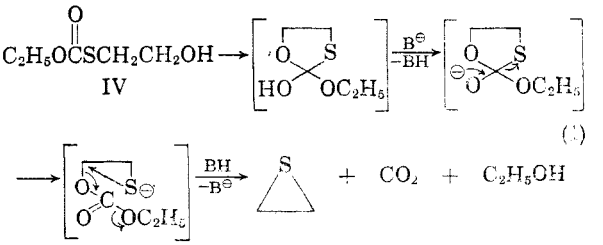
A new synthesis of ethylene monothiolcarbonate by the acid-catalyzed intramolecular transesterification of ethyl 2-hydroxyethylthiolcarbonate is described.

In a previous paper[1] one of the authors described the preparation of ethylene monothiolcarbonate (I) in a 48% yield by the reaction of phosgene with 2-mercaptoethanol in the presence of pyridine. Investigations of the chemistry of I have since led to several interesting and useful syntheses, as summarized in Chart I. To date, the pyrolysis of I to ethylene sulfide (II)[1] constitutes the most convenient synthesis of pure II, and the preparation of 2-mercaptoethyl carbamates (III) derived from secondary amines represents the only known route to this type of compound.[2]

In a recent investigation concerned with mercaptoethylation reactions, a synthesis of ethyl 2-hydroxyethylthiolcarbonate (IV) was developed in 87–92% yield, by the reaction of ethyl chloroformate with sodium 2-hydroxyethyl mercaptide.[3] Under basic conditions, this thiolcarbonate decomposes primarily to ethylene sulfide, ethanol, and carbon dioxide following the probable reaction path of Equation 1.[3,4]



(1)

We now wish to report that under the action of *p*-toluenesulfonic acid (PTSA) in refluxing benzene,

(1) D. D. Reynolds, *J. Am. Chem. Soc.*, 79, 4951 (1957).

(2) D. D. Reynolds, D. L. Fields, and D. L. Johnson, *J. Org. Chem.*, 26, 5111 (1961), Part II of this series; D. D. Reynolds, D. L. Fields, and D. L. Johnson, *J. Org. Chem.*, 26, 5109 (1961), Part I of this series.

(3) D. D. Reynolds, D. L. Fields, and D. L. Johnson, *J. Org. Chem.*, 26, 5119 (1961), Part IV of this series.

(4) C. C. Culvenor, W. Davies, and W. E. Savige, *J. Chem. Soc.*, 4480 (1952).