(20) W. H. Mueller and K. Griesbaum, *J. Org. Chem.*, **32,** 856 (1967).
(21) J. W. Timberlake, A. W. Garner, and M. L. Hodges, *Tetrahedron Lett.*, 309 (1973).
(22) H. Meerwein, K. F. Zenner, and R. Gipp, *Justus Liebigs Ann. Chem.*, **688,** 67 (1965).
(23) H. Noth and G. Mikulaschek, *Chem. Ber.*, **94,** 634 (1961).
(24) W. A. Smit, M. Z. Krimer, and E. A. Vorobeva, *Tetrahedron Lett.*, 2451 (1975).
(25) J. M. Lalancette, Y. Beauregard, and M. Bhéreur, *Can. J. Chem.*, **49,** 2983 (1971).

Notes

Alkyloxycarbonyl Thiosulfate, a New Family of Water-Soluble Acylating Agents: Amidation and Hydrolysis Reactions[1a]

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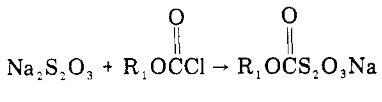
Many times it is necessary or convenient to perform acylation reactions of amines in aqueous media. Accordingly, a water-soluble acylating agent which undergoes hydrolysis slowly would be highly desirable whenever the presence of water is required or cannot be excluded from a reaction medium. Ito[2] prepared the water-soluble, but easily hydrolyzed, sodium benzoyl thiosulfate which reacts with amines and phenols in aqueous media to yield the corresponding benzoyl derivatives.[3] Caldwell, Ledger, and Milligan[4] carried out the reaction of benzyl chloroformate with sodium thiosulfate to yield the water-soluble sodium benzyloxycarbonyl thiosulfate which readily underwent reaction with amines and amino acids in aqueous media, and Lindemann and Wolfram[5] have reported the preparation and reaction of the bifunctional arymethyloxycarbonyl thiosulfate, disodium 1,4-xylylenebis(oxycarbonyl thiosulfate). To date, however, the preparation of alkali or alkaline earth alkyloxycarbonyl thiosulfates has not been reported. Green and Hudson[6] have described the reaction of ethyl chloroformate with sodium thiosulfate, but there is no indication that they isolated or identified the reaction product.

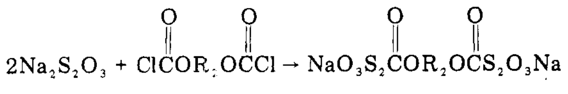
Results

We have now prepared, by the reaction of the appropriate chloroformate and sodium thiosulfate, several monofunctional (1) and difunctional (2)[7] sodium alkyloxycarbonyl thiosulfates.



$$Na_2S_2O_3 + R_1OC(=O)Cl \rightarrow R_1OC(=O)S_2O_3Na \qquad (1)$$

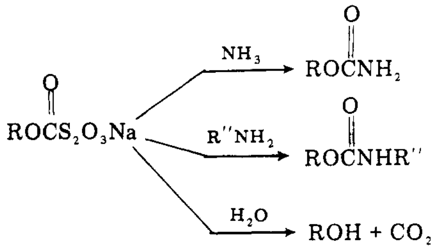
$R_1 = n\text{-}C_4H_9,\ n\text{-}C_6H_{13},\ n\text{-}C_8H_{17}$



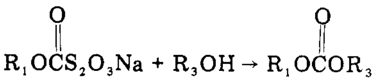
$$2Na_2S_2O_3 + ClC(=O)OR_2OC(=O)Cl \rightarrow NaO_3S_2C(=O)OR_2OC(=O)S_2O_3Na \qquad (2)$$

$R_2 = (CH_2)_4,\ (CH_2)_6,\ (CH_2)_8$

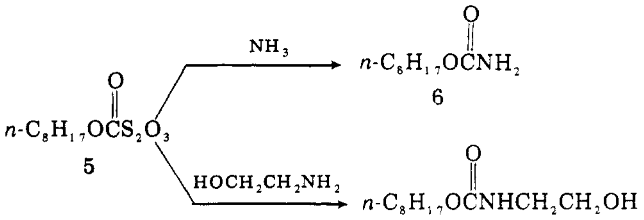
These compounds exhibit some degree of water solubility and react with ammonia and amines, both in the presence and absence of water, to form the corresponding carbamates and with water to liberate the parent alcohol (3). Alkyloxycarbonyl thiosulfates would be expected to react with alcohols to form the corresponding carbonate (4); however, this reaction was not examined in this study. Specifically, sodium *n*-octyloxycarbonyl thiosulfate (5) reacts with ammonia and 2-aminoethanol to yield *O*-(*n*-octyl) carbamate (6) and *O*-(*n*-octyl) 2-hydroxyethylcarbamate (7), respectively. The possibility exists, of course, of an initial acylation of the hydroxyl group followed by an *O*-*N*-acyl migration reaction.



(3)



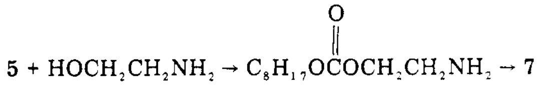
$$R_1OC(=O)S_2O_3Na + R_3OH \rightarrow R_1OC(=O)OR_3 \qquad (4)$$



5

6

7



$$5 + HOCH_2CH_2NH_2 \rightarrow C_8H_{17}OC(=O)OCH_2CH_2NH_2 \rightarrow 7$$

A review of the literature yielded no information concerning the relative rates of acylation of the hydroxyl and amino groups in 2-aminoethanol. Acylation reactions of 2-aminoethanol with acid chlorides[8,9] and 3-aminopropanol with ethyl chloroformate[10] under mild conditions resulted in high yields of amides and carbamate respectively with no report of ester or carbamate formation. In the absence of evidence to the contrary, and considering that water reacts more slowly with the acyloxycarbonyl thiosulfate than does the amino group, we suggest that N-acylation occurs with little or no O-acylation in the reaction of **5** with 2-aminoethanol.

A brief kinetic study of the reaction of the mono- and bifunctional alkyloxycarbonyl thiosulfates with 2-aminoethanol or water at pH 8.0 resulted in the relative rates for amidation and hydrolysis noted in Table I.

These data indicate that, for a given monofunctional alkyloxycarboxyl thiosulfate, the rate of carbamate formation is approximately an order of magnitude greater than the corresponding rate of hydrolysis and suggest that the rate of either reaction increases with decreasing carbon chain length. Similarly, for various bifunctional alkyloxycarbonyl thiosulfates the rate of amidation was found to be between five and ten times greater than the rate of hydrolysis, and again the reaction rate of these compounds is seen to increase with decreasing chain length. It is interesting to note that the monofunctional compounds appear to be somewhat more reactive

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Table I. Relative Rates of Amidation and Hydrolysis of Mono- and Bifunctional Alkyloxycarbonyl Thiosulfates[a]

compd	registry no.	rel rate of amidation	rel rate of hydrolysis	ratio of $K_{\text{amidation}}/K_{\text{hydrolysis}}$
disodium 1,8-octamethylenebis(oxycarbonyl thiosulfate)	69352-14-3	8.7	1.0	8.7
disodium 1,6-hexamethylenebis(oxycarbonyl thiosulfate)	69352-15-4	15.0	2.8	5.4
disodium 1,4-tetramethylenebis(oxycarbonyl thiosulfate)	69381-37-9	48.9	4.9	10.0
sodium hexyloxycarbonyl thiosulfate	69352-16-5	94.5	6.9	13.7
sodium butyloxycarbonyl thiosulfate	69352-17-6	123.3	11.9	10.4

[a] Reaction conditions were pH 8 and 42 °C, 0.01 M in the respective oxycarbonyl thiosulfate.

than bifunctional compounds of comparable chain length. These data recommend the utility of these compounds as acylating agents for amines in aqueous media.

Experimental Section

Carbon, hydrogen, nitrogen, and sulfur analyses were performed by Galbraith Laboratories, Knoxville, Tenn. Infrared spectra were obtained on a Perkin-Elmer Model 221 spectrophotometer. Melting point data were determined on a Perkin-Elmer Model DSC-1B differential scanning calorimeter. Kinetic data for determination of rates of hydrolysis and amidation were obtained with the aid of a Brinkman Automatic Titrator.

The rates of amidation of the various alkyloxycarbonyl thiosulfates were determined in the following manner. Exactly 0.0010 mol of the appropriate alkyloxycarbonyl thiosulfate was quickly dissolved with stirring in 100 mL of distilled water maintained at 42 °C with a Lauda Model K-2/RD constant temperature bath. The pH of the solution was then adjusted to 8.0 (self pH ranged between 4.4 and 5.5 for 0.01 M solutions of the various alkyloxycarbonyl thiosulfates) by the addition of a small amount of 0.2 M 2-aminoethanol. Amidation of the alkyloxycarbonyl thiosulfate was then carried out with the acid of a Brinkman Automatic Titrator which maintained the pH at 8.0 by dispensing additional 2-aminoethanol during the course of the study. The concentration of unreacted alkyloxycarbonyl thiosulfate was calculated at any time by observing the amount of 0.2 M 2-aminoethanol used and subsctracting this from the starting concentration. The titration was usually continued until 30–50% of the alkyloxycarbonyl thiosulfate had been converted to the carbamate. A plot of $\ln S_0/S$ against time (where S_0 is the initial concentration of the alkyloxycarbonyl thiosulfate and S is its concentration at any subsequent time) afforded a straight line, the slope of which was taken to be K, the rate constant for the amidation at pH 8 and 42 °C.

The rates of hydrolysis of the various alkyloxycarbonyl thiosulfates were determined in the same general manner as the rates of amidation except that in these studies 0.02 M solutions of the appropriate alkyloxycarbonyl thiosulfate were titrated at pH 8 with 0.1 N sodium hydroxide. A plot of $\ln S_0/S$ against time indicated that in this case too the reaction obeyed first-order kinetics.

Sodium *n*-Octyloxycarbonyl Thiosulfate. *n*-Octyl chloroformate,[11] 451.4 g (3.0 mol), was added to a flask containing 2000 mL of ethanol, followed immediately by 745 g (3.0 mol) of sodium thiosulfate pentahydrate in 755 g of water. The mixture was stirred overnight at room temperature after which most of the ethanol was removed under reduced pressure at room temperature. Upon cooling the aqueous solution to 4 °C, a white crystalline precipitate formed which was isolated by suction filtration. Recrystallization from absolute ethanol yielded platelike crystals (65%) which melted with decomposition at 254–256 °C: IR (pellet) 2925 (m), 1720 (s), 1267 (s), 1218 (s), 1145 (s), 1040 cm^{-1} (s). Under these preparative and purification procedures, competing alcoholysis or hydrolysis reactions did not present any problems.

Anal. Calcd for $C_9H_{17}O_5S_2Na$: C, 36.98; H, 5.86; S, 21.93. Found: C, 36.91; H, 6.00; S, 21.80.

The procedure described above when applied to *n*-butyl chloroformate and *n*-hexyl chloroformate resulted in sodium *n*-butyloxycarbonyl thiosulfate (mp 198–200 °C dec; IR (pellet) 2955 (m), 1710 (s), 1260 (s), 1225 (s), 1135 (s), and 1035 cm^{-1} (s)) and sodium *n*-hexyloxycarbonyl thiosulfate (mp 240–242 °C dec; IR (pellet) 2935 (m), 1725 (s), 1260 (s), 1225 (s), 1140 (s), and 1040 cm^{-1} (s)) with yields of 40 and 55%, respectively.

***O*-(*n*-Octyl) carbamate** was prepared by the reaction of sodium *n*-octyl oxycarbonyl thiosulfate with aqueous ammonia using a small scale derivatization procedure. The product was collected via suction filtration and, after recrystallization from absolute ethanol, yielded a white crystalline solid, mp 62–63 °C (lit.[12] mp 63 °C).

Anal. Calcd for $C_9H_{19}O_2N$: C, 62.43; H, 10.98; N, 8.09. Found: C, 62.51; H, 10.85; N, 8.10.

***O*-(*n*-Octyl) 2-hydroxyethylcarbamate** was prepared by the reaction of 2-aminoethanol with sodium *n*-octyloxycarbonyl thiosulfate in water in a small scale derivatization procedure. The aqueous solution was then extracted with diethyl ether, the ether extracts were evaporated, and a crude crystalline product was obtained. Recrystallization from petroleum ether yielded a white crystalline product, mp 39–42 °C.

Anal. Calcd for $C_{11}H_{23}O_3N$: C, 60.80; H, 10.66; N, 6.45. Found: C, 60.82; H, 10.51; N, 6.39.

Disodium 1,6-Hexamethylenebis(oxycarbonyl thiosulfate). The bis(chloroformate) of hexanediol was prepared as described by Iwakura et al.[13] The bis(chloroformate), 243 g (1.0 mol), was added to a flask contianing 2000 mL of ethanol, followed by 496 g (2.0 mol) of sodium thiosulfate pentahydrate in 755 g of water. The mixture was stirred at room temperature for 48 h whereupon the ethanol was removed, the mixture cooled to approximately 4 °C, and the white crystalline product collected by suction filtration. After recrystallization in ethanol, a crystalline product was obtained (70%) which melted with decomposition at 245–247 °C; IR (pellet) 2935 (m), 1737 (s), 1227 (s), 1125 (s), and 1030 cm^{-1} (s).

Anal. Calcd for $C_8H_{12}O_{10}S_4Na_2$: C, 21.72; H, 2.71; S, 28.96. Found: C, 21.92; H, 2.93; S, 29.18.

The procedure described above when applied to the bis(chloroformates) of butanediol and octanediol resulted in disodium 1,4-tetramethylenebis(oxycarbonyl thiosulfate) (mp 210–214 °C dec; IR (pellet) 1710 (s), 1230 (s), 1150 (s), and 1035 cm^{-1} (s)) and disodium 1,8-octamethylenebis(oxycarbonyl thiosulfate) (mp 250–252 °C dec; IR (pellet) 2935 (m), 1738 (s), 1225 (s), 1125 (s), and 1030 cm^{-1} (s)) with yields of 45 and 70%, respectively.

Registry No.—Sodium *n*-octyloxycarbonyl thiosulfate, 69352-18-7; *O*-(*n*-octyl) carbamate, 2029-64-3; *O*-(*n*-octyl) 2-hydroxyethylcarbamate, 69352-19-8; *n*-octyl chloroformate, 7452-59-7; *n*-butyl chloroformate, 592-34-7; *n*-hexyl chloroformate, 6092-54-2; hexanediol bis(chloroformate), 2916-20-3; butanediol bis(chloroformate), 2157-16-6; octanediol bis(chloroformate), 51772-87-3; sodium thiosulfate, 7772-98-7.

References and Notes

(1) (a) Presented in part at the 9th Central Regional Meeting of the American Chemical Society, Charleston, W.Va., October 1977; (b) Deceased October 31, 1978.

(2) A. Ito, *Yakugaku Zasshi*, **82**, 866 (1962); *Chem. Abstr.*, **58**, 6731 (1963).

(3) A. Ito, *Yakugaku Zasshi*, **82**, 875 (1962); *Chem. Abstr.*, **58**, 6731 (1963).

(4) J. B. Caldwell, R. Ledger, and B. Milligan, *Aust. J. Chem.*, **19**, 1297 (1966).

(5) M. K. O. Lindemann and L. J. Wolfram, *Proc. Int. Wolltextil Forschungskonferenz 5th*, **3**, 170 (1975).

(6) M. Green and R. F. Hudson, *Proc. Chem. Soc., London*, 149 (1959).

(7) M. K. O. Lindemann, U.S. Patent 3 906 021 (Sept. 16, 1975).

(8) M. Rona and D. Ben Ishai, *J. Org. Chem.*, **26**, 1446 (1961).

(9) S. Frankel and M. Cornelius, **51**, 1657 (1918).

(10) H. Najer, P. Chabrier, and R. Guidicelli, *Bull. Soc. Chim. Fr.*, 611, (1959).

(11) J. H. Saunders, R. J. Slocombe, and E. E. Hardy, *J. Am. Chem. Soc.*, **73**, 3796 (1951).

(12) P. Carre and H. Passedouet, *C. R. Hebd. Seances Acad. Sci.*, **204**, 347 (1937).

(13) Y. Iwakura, M. Sakamoto, and H. Yasuda, *Nippon Kagaku Zasshi*, **82**, 606 (1961); *Chem. Abstr.*, **56**, 8534 (1962).