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Mercaptoethylation. II. Preparation of 2-Mercaptoethyl Carbamates and Oligoethylene Sulfides

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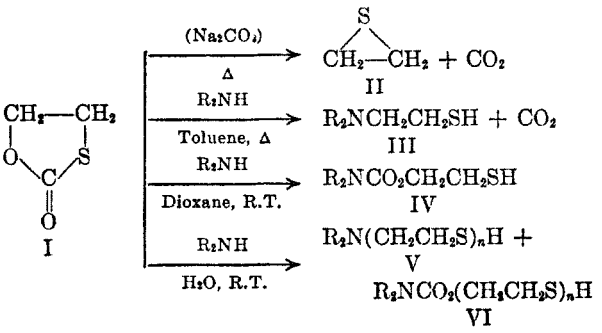
A series of 2-mercaptoethyl carbamates have been prepared in non-polar solvents by the reaction of primary and secondary amines with ethylene monothiolcarbonate. In the presence of an ionizing solvent, ethylene monothiolcarbonate and amine were found to react to produce low-molecular-weight polyethylene sulfides of the general formulas, $R_2N(CH_2CH_2S)_nH$ and $R_2NCO_2(CH_2CH_2S)_nH$. The 2-mercaptoethyl carbamates were further characterized by oxidation to their respective disulfides.

In a previous paper,[1] the preparation of ethylene monothiolcarbonate (I) was described. Its uses as a convenient precursor to ethylene sulfide (II), and more recently as a mercaptoethylating agent for primary and secondary amines (III)[2] were demonstrated. It was noted in this latter investigation that attempts to prepare a bis(2-mercaptoethyl)amine by the reaction of two molar equivalents of I with one equivalent of primary amine, in several instances, yielded a 2-mercaptoethyl carbamate (IV) instead of the desired bis-mercaptoethylated amine. As a continuation of the study of the chemistry of ethylene monothiolcarbonate, we shall describe here the preparation of a number of these 2-mercaptoethyl carbamates and some interesting low-molecular-weight polyethylene sulfides initiated by amine (V) and by carbamate (VI) groups.



The 2-mercaptoethyl carbamates were prepared by the reaction of a primary or secondary amine with I under mild, non-polar conditions unfavorable to mercaptoethylation side reactions. On substituting a polar solvent such as water or ethanol for dioxane, the reaction media used in this carbamate synthesis resulted in the production of the "oligomers"[3] V and VI to the complete exclusion of IV. The only previously reported 2-mercaptoethyl carbamates were prepared by the uncatalyzed reactions of phenyl, *p*-methoxyphenyl and 1-naphthyl isocyanates with 2-mercaptoethanol.[4] As the work described in this paper was being completed, Smith and Friedrich[4b] reported their observations on the base-catalyzed polymerization of 2-mercaptoethyl carbanilates to oligomers of structure VI.

2-Mercaptoethyl carbamates. The experimental conditions used in preparing the 2-mercaptoethyl carbamates (IV) were to allow a mixture of amine, a slight molar excess of ethylene monothiolcarbonate, and dioxane to stand at room temperature for a reaction period dependent upon the nucleophilicity of the amine. The product was isolated either by distillation or by crystallization after removal of solvent and unchanged starting materials. It should be pointed out that while a general procedure is proposed for the preparation of these carbamates, more vigorous conditions, and thus shorter reaction periods, may often be successfully employed for specific cases.

Table I demonstrates the generality of this preparation. Most of the carbamates were further characterized by oxidation to their respective disulfides, as listed in Table II. The oxidation of the bis-2-mercaptoethyl carbamates of piperazine and ethylenediamine led to interesting polymeric disulfides which will be reported in a subsequent paper.

As can be noted in Table I, in several cases the rates of ring opening of I by amine were quite slow, thus permitting some observation on the relative nucleophilicities of the amines toward ethylene monothiolcarbonate. When the yields of representative examples of 2-mercaptoethyl carbamates are plotted against reaction time (Fig. 1) these variations in reaction rates become more apparent. The orders of reactivity, *i.e.*, nucleophilicity, of the amines under these experimental conditions would appear to be as given here.

It is evident that the rates of reaction are greatly influenced by the steric requirements of the attacking amine as well as its basicity (see pK_a values, Table I). The decrease in rates observed for iso-

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

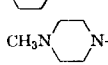
(2) D. D. Reynolds, M. K. Massad, D. L. Fields, and D. L. Johnson, *J. Org. Chem.*, 26, 5109 (1961), Part I of this series.

(3) This is a convenient name to be used to refer to low-molecular-weight polyethylene sulfides (oligoethylene sulfides) of D. P. ten or less.

(4) (a) G. M. Bennett and E. M. Whincop, *J. Chem. Soc.*, 119, 1861 (1921). (b) J. F. Smith and E. C. Friedrich, *J. Am. Chem. Soc.*, 81, 161 (1959).

TABLE I

2-MERCAPTOETHYL CARBAMATES
$RCO_2CH_2CH_2SH$

No.	R	pK_a of RH	% Yield for Reaction Time (Hr.) 15	60	90	170	B.P./Mm. or M.P.[f]	n_D^{25}	Calcd., % C	H	N	S	Found, % C	H	N	S
1	n-C_4H_9NH—	10.61[a]	80	—	—	—	98/0.5	1.4782	47.5	8.5	7.9	18.1	47.4	8.6	7.9	18.1
2	n-$C_6H_{13}NH$—	10.64[a]	83	—	—	—	134/0.3	1.4755	52.7	9.3	6.8	15.6	52.7	8.9	7.2	15.7
3	CH_2=$CHCH_2NH$—	9.76[b]	43	69	81	—	83/0.2	1.4978	44.7	6.8	8.7	19.9	43.9	6.9	8.4	20.1
4	$(CH_3)_2CHNH$—	10.72[b]	10	—	44	50	93/1.0	1.4792	44.2	8.0	8.6	19.6	44.6	8.4	8.8	19.6
5	$(CH_3)_3CNH$—	10.53[b]	0	—	—	0	—	—								
6	$(n$-$C_4H_9)_2N$—	11.31[c]	0	—	—	34	106/0.6	1.4660	56.7	9.9	6.0	13.7	57.2	10.2	6.2	14.0
7		8.70[d]	60	78	86	—	108/0.6	1.5058	44.0	6.8	7.3	16.8	44.2	6.9	7.0	16.5
8		11.28[d]	82	—	—	—	83/0.1	1.5038	50.8	7.9	7.4	16.9	50.5	8.3	7.9	16.9
9		—	82	—	—	—	118/1.0	1.5078	47.1	7.8	13.7	15.7	46.8	8.1	13.6	15.5
10	C_6H_5NH—	4.66[b]	0	—	—	0	—	—								
11	$C_6H_5CH_2NH$—	9.62[d]	56[e]	—	—	—	151/0.05	1.5531	56.8	6.2	6.6	15.2	57.6	6.6	7.6	15.2
12		9.81[b]	86	—	—	—	72–74	—	40.8	6.1	9.5	21.8	41.0	6.2	9.9	21.6
13	—$HNCH_2CH_2NH$—	9.93[b]	70	—	—	—	101–104	—	35.8	6.0	10.4	23.9	36.6	6.5	9.9	23.9

[a] C. W. Hoerr, M. R. McCorkle, and A. W. Ralston, *J. Am. Chem. Soc.*, **65**, 328 (1943). [b] I. Heilbron, "Dictionary of Organic Compounds," Oxford Press, New York, N. Y., 1946. [c] N. F. Hall and M. R. Sprinkle, *J. Am. Chem. Soc.*, **54**, 3469 (1932). [d] R. J. Bruehlman and F. H. Verhoek, *J. Am. Chem. Soc.*, **70**, 1401 (1948). [e] The crude yield was higher, but the high-boiling point of the product resulted in some thermal degradation during distillation. [f] Boiling points and melting points are uncorrected.

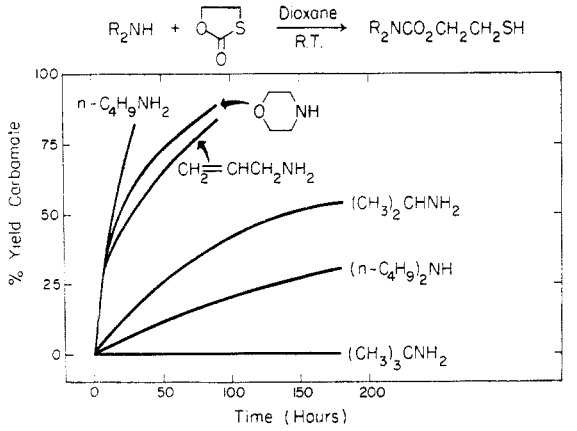
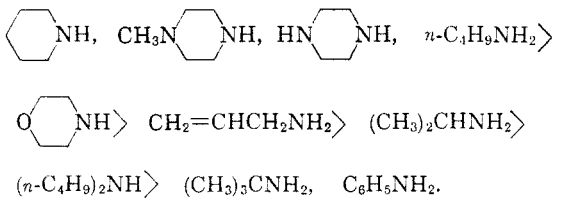


Fig. 1. Variations of yields of 2-mercaptoethyl carbamates with reaction time.



propyl-, di-*n*-butyl-, and *tert*-butylamines as compared with *n*-butylamine can best be attributed to a steric effect. In comparing amines with similar steric requirements such as piperidine and morpholine, piperidine was found to be the faster reactant. This would be predicted on the basis of their relative basicities. No reaction occurred with the weakly basic aniline or with the sterically bulky *tert*-butylamine.

Oligoethylene sulfides. The nonpolar, room-temperature reaction conditions used in preparing the 2-mercaptoethyl carbamates (IV) were found necessary owing to their instability, especially in polar solvents and at elevated temperatures, to catalytic amounts of organic or inorganic base. Attempted preparations of IV conducted in more polar solvents such as water or ethanol resulted in no isolable IV, but instead yielded oligomers of structure V and/or VI. The chain lengths of oligomers derived from a large variety of amines were found to vary between n = 2–10, depending on the nucleophilicity and concentration of the amine, the solvent, and the reaction temperature. Whether the structure of the oligomer is a multi-mercaptoethylated amine (V), a multi-mercaptoethylated carbamate (VI), or a mixture of the two, seems dependent only on the nucleophilicity of the starting amine.

Thus, when *n*-butylamine and I were refluxed together in a methanol-water solvent, a white solid shortly began to precipitate from solution. This material was assigned the structure VI ($n\simeq4$) based on elemental analysis, iodometric titration and infrared spectroscopy. It exhibited a strong carbonyl band, at 5.92 μ, and a weak—SH band, at 3.92 μ, in agreement with spectral data of higher mercaptoethylated carbamates reported by Smith and Friedrich.[4b]

In contrast, the reaction of *tert*-butylamine under identical reaction conditions also led to an oligomer, but of structure V ($n\simeq7$). The infrared spectra showed practically no carbonyl absorption. The proposed structure was again supported by elemental analysis and iodometric titration. Using the same methods of structure assignment, amines of intermediate reactivity such as isopropylamine and diethylamine were expected, and indeed were found to lead to mixtures of V and VI. Although varying the molar ratio of reactants did have an influence on the degree of polymerization of the oligomer, it did not appear to alter the general structure assigned.

DISCUSSION

To explain the experimental facts thus far observed for the reaction of an amine with ethylene monothiolcarbonate, a reaction sequence is suggested in Chart I. From this postulated mechanism one might expect at least five (III, IV, V, VI, and X) different types of isolable products. Indeed, four (III, IV, V, and VI) of the five possibilities have been obtained. Therefore, considering the complexity of this reaction, it is not surprising that a careful choice of reaction conditions was found necessary in order to obtain either 2-mercaptoethyl carbamates (IV) or 2-aminoethanethiols (III) in satisfactory yields. The 2-mercaptoethyl carbamates were isolated under such mild conditions that Step 2 was not in play. In this regard it was earlier found[2] that, in a few instances, 2-mercaptoethyl carbamates were produced by refluxing in toluene a two-fold excess of I with the very reactive amines such as *n*-butylamine and allylamine. Evidently this rather high reaction temperature was only possible because these amines were rapidly converted to their carbamates (Step 1), thus eliminating the base necessary to catalyze the decomposition of the carbamates to ethylene sulfide (Step 2).

The previously described synthesis of 2-aminoethanethiols[2] was effected in refluxing toluene by the reaction of amine with I in the presence of excess amine. The excess amine and higher reaction temperature promoted the breakdown (Step 2) of IV to ethylene sulfide while the use of non-polar toluene and excess amine usually favored the mercaptoethylation of amine over mercaptan, although products resulting from mercaptoethylation of mercaptan always occurred to some extent.

The emphasized importance of solvent polarity arises from the competitive reaction between the amine and the relatively weakly nucleophilic thiols formed during the reaction for the ethylene sulfide. An amine is highly competitive only in nonpolar, nonionizing solvents where the strongly

nucleophilic mercaptide ion is not favored. In solvents conducive to mercaptide-ion formation, mercaptoethylation of mercaptan, *i.e.*, oligomer formation, is the predominant, if not exclusive, course of reaction.

By considering the reaction scheme of Chart I, in which the initial attack of the amine (Step 1) is by far the slowest step in the over-all reaction. The carbamate IV (R_2N— = $(CH_3)_3CNH$—) is always in very low concentration since it is decomposing to ethylene sulfide (II) (Step 2) at a much faster rate than it is being formed, *i.e.*,

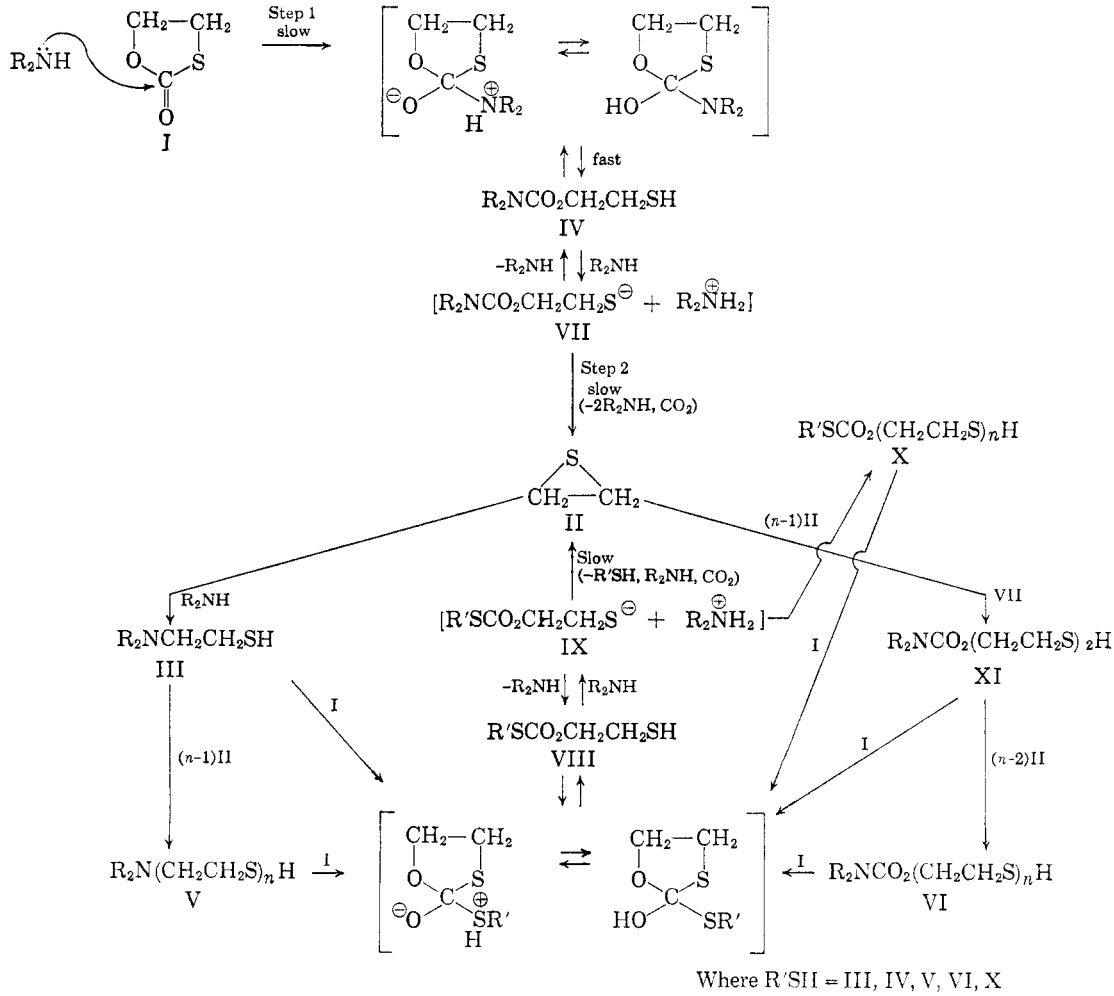


CHART I

explanations and predictions of the structures of the oligomers produced in polar solvents for a given amine may be made. The structure of these oligomers will either be V, VI, or a mixture of the two, depending on the relative rates of Step 1 to Step 2. *n*-Butylamine, for example, has already been established to react readily with I (Step 1) to form the 2-mercaptoethyl carbamate IV (R_2N— = *n*-C_4H_9NH—); IV, in turn, slowly decomposes, *via* its mercaptide (VII) (Step 2), to ethylene sulfide (II). As the ethylene sulfide is generated, it reacts preferentially with VII to yield XI, since VII is a much stronger nucleophile than the competing amine and is present in relatively high concentration. Subsequent mercaptoethylation of these newly produced thiols (as their mercaptides) by ethylene sulfide yields carbamate-type oligomers of structure VI.

tert-Butylamine, on the other hand, is an example of Step 1 << rate of Step 2. With no mercaptide available for reaction, the ethylene sulfide reacts, also probably slowly,[5] with *tert*-butylamine to yield III. At this point, the reaction picks up momentum, for, although the amine is only slowly reacting with I, the mercaptide of III is now available, and would be expected to attack I readily, forming the 2-mercaptoethyl thiolcarbonate (VIII). Again, ethylene sulfide is generated, this time from the decomposition of the mercaptide of VIII, thus continuing this mercaptoethylation process, ultimately leading to multimercaptoethylated amines of structure V.

Following this same type of explanation, an amine of intermediate reactivity gives mixtures of V and VI because the rate of Step 1 is more closely

(5) H. R. Snyder and co-workers [*J. Am. Chem. Soc.*, 69, 2672 (1947)] have noted steric retardations in the ring opening of episulfides by bulky amines.

TABLE II

DISULFIDES OF 2-MERCAPTOETHYL CARBAMATES
$(RCO_2CH_2CH_2S—)_2$

No.	R	M.P.[b]	Calcd., %				Found, %			
			C	H	N	S	C	H	N	S
1	n-C_4H_9NH—	101–103	47.8	7.9	7.9	18.4	47.9	8.0	7.6	18.1
2	n-$C_6H_{13}NH$—	102–103	52.9	8.8	6.8	15.7	53.0	8.9	6.7	15.4
3	CH_2=$CHCH_2NH$—	80–82	45.0	6.2	8.8	20.0	44.6	6.2	8.8	20.5
4	$(CH_3)_2CHNH$—	92–93	44.5	7.4	8.6	19.8	44.7	7.7	8.9	19.5
5	$C_6H_5CH_2NH$—	134–135	57.2	5.7	6.7	15.2	56.9	5.7	7.0	14.9
6		54–56	44.3	6.3	7.4	16.8	44.4	6.4	7.8	16.8
7		48–49	51.1	7.5	7.5	17.0	51.0	7.5	7.5	17.6
8		196–198	40.1	6.7	11.7	13.4	40.9	7.0	11.1	13.8

[a] As dihydrochloride. *Anal.* Calcd.: Cl, 14.8. Found, 15.0. [b] Melting points are uncorrected.

comparable to the rate of Step 2. The oligomer (VI) will predominate in the mixture if the amine approaches n-butylamine in reactivity, whereas V predominates if the amine is more closely related to *tert*-butylamine in reactivity.

EXPERIMENTAL

Materials. Ethylene monothiolcarbonate, n^{25}_D 1.5102, was purchased from Distillation Products Industries, Rochester, N. Y. The amines and solvents were dried by redistillation over calcium hydride. All distillations, unless otherwise noted, were effected through a 14-in. Vigreux column equipped with a variable reflux-ratio head.

2-Mercaptoethyl carbamates. (*a*) *Carbamates 1–11*, Table I, were prepared by allowing a mixture of 0.55 mole of ethylene monothiolcarbonate, 0.5 mole of amine and 500 ml. of dioxane to stand at 25°–30° for a reaction period indicated in Table I. The mixture was then subjected to distillation, initially under a water-pump vacuum to remove solvent and unchanged starting materials, and then by a vacuum pump to yield analytically pure product. Owing to its high boiling point, distillation of the carbamate from benzylamine (No. 11, Table I) was effected through a 3-in. unpacked column.

(*b*) *The biscarbamates of piperazine and ethylenediamine* (No. 12 and 13, Table I) were prepared by an analogous procedure except that 0.25 mole of starting amine was used. Both biscarbamates crystallized after removal of solvent, and were recrystallized twice from ethanol.

Disulfides. The disulfides 1–5 (Table II) were prepared by the dropwise addition of a 30% aqueous hydrogen peroxide solution to 10 g. of the 2-mercaptoethyl carbamate in 75 ml. of ethanol. The resulting disulfides crystallized directly from solution, were filtered, and recrystallized once from the same solvent. To eliminate the possibility of overoxidation, disulfides 6–9 were prepared by iodine rather than hydrogen peroxide oxidation, since these disulfides did not crystallize from solution during the oxidation. Thus, 100-ml. portions of iodine solution (200 g. of iodine, 200 g. of potassium iodide per 800 ml. of water) were added, with vigorous shaking, to a solution of 10 g. of 2-mercaptoethyl carbamate (IV, R =  ,  , ) and 300 ml. of benzene in a separatory funnel, until the iodine color persisted in the organic phase. The aqueous layer was periodically separated during this addition to the morpholino- and piperidino-derivatives to prevent a possible reversible reduction by the hydriodic acid formed. The organic layer was then back-titrated by the dropwise addition of the 2-mercaptoethyl carbamate until the iodine color just disappeared. After the organic phase had been washed with a dilute sodium hydroxide solution (4 g. of sodium hydroxide in 100 ml. of water), followed by two 100-ml. portions of water, the organic phase was separated, dried over magnesium sulfate and concentrated to a syrup on a rotary evaporator. Disulfides 6 and 7 crystallized after being reconcentrated twice from ether, and were recrystallized twice from warm ethanol-water. Disulfide 9 was obtained crystalline only as its bishydrochloride. 2-Mercaptoethyl di-n-butylcarbamate (No. 6, Table I) failed to give a crystalline disulfide.

Oligoethylene sulfides. A mixture of 0.5 mole (52 g.) of ethylene monothiolcarbonate and 1.5 moles of amine in 500 ml. of methanol and 500 ml. of water was refluxed under an efficient reflux condenser for 6 hr. After cooling, the precipitate was filtered off and dried *in vacuo* over calcium chloride. The molecular weights were determined by iodometric titration of the mercaptan. Examples of the types of oligomers obtained for a few amines under the experimental conditions given are as follows:

(*a*) *n-Butylamine;* yield, 34.5 g.

Anal. Calcd. for VI, n = 4; $C_{13}H_{23}NO_2S_4$: C, 44.2; H, 6.5; N, 4.0; S, 36.2; mol. wt., 353. Found: C, 44.0; H, 7.7; N, 4.1; S, 36.1; mol. wt., 422.

(*b*) *Isopropylamine;* yield, 31.0 g.

Anal. Calcd. for V, n = 8; $C_{19}H_{41}NS_8$: C, 42.2; H, 7.6; N, 2.6; S, 47.6; mol. wt., 540.

Anal. Calcd. for VI, n = 8; $C_{20}H_{41}NO_2S_8$: C, 41.1; H, 7.0; N, 2.4; S, 44.0; mol. wt., 584. Found: C, 41.2; H, 8.5; N, 2.5; S, 45.4; mol. wt., 562.

(*c*) *tert-Butylamine*, yield, 30.8 g.

Anal. Calcd. for V, n = 7; $C_{18}H_{39}NS_7$: C, 43.8; H, 7.9; N, 2.8; S, 45.4; mol. wt., 493. Found: C, 43.4; H, 7.9; N, 2.0; S, 45.1; mol. wt., 503.

(*d*) *Diethylamine*, yield, 31.5 g.

Anal. Calcd. for V, n = 7; $C_{18}H_{39}NS_7$: C, 43.8; H, 7.9; N, 2.8; S, 45.4; mol. wt., 493. Found: C, 43.7; H, 7.9; N, 2.6; S, 46.5; mol. wt., 518.

(*e*) *Morpholine.* Little precipitate was formed in this example even after the reaction mixture was cooled in an ice bath. Therefore, the solvents, residual morpholine and 15.8 g. (21.5% yield) of 2-morpholinoethanethiol (b.p. 90–91°/10 mm., n^{25}_D 1.5014; lit. b.p. 92°/10 mm., n^{25}_D 1.5025[2]), were removed by distillation, leaving 33.0 g. of residue boiling above 135°/0.05 mm.

Anal. Calcd. for VI, n = 3; $C_{11}H_{21}NO_3S_3$: C, 42.4; H, 6.7; N, 4.5; S, 30.8; mol. wt., 311.

Anal. Calcd. for V, n = 3; $C_{10}H_{21}NOS_3$: C, 45.0; H, 7.9; N, 5.2; S, 35.9; mol. wt., 267. Found: C, 44.7; H, 7.8; N, 5.8; S, 31.5; mol. wt., 286.

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