The Synthesis of β-Amino Mercaptans and β-Amino Thiosulfates *via* Ethylenimine Intermediates[1]

DAVID ROSENTHAL, GALINA BRANDRUP, KENNETH H. DAVIS, JR., AND MONROE E. WALL

The Natural Products Laboratory, Research Triangle Institute, Durham, North Carolina

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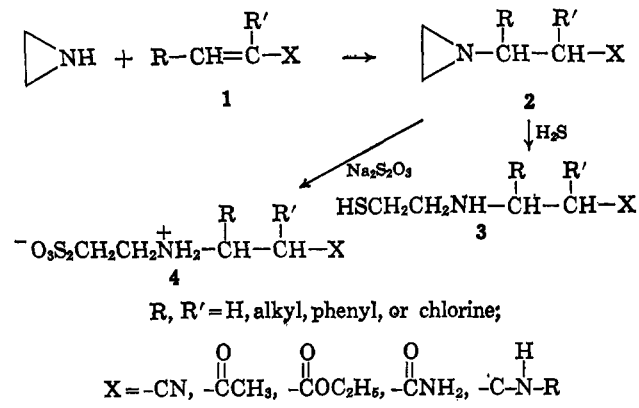
Novel syntheses of functionalized derivatives of β-mercaptoethylamine and of β-aminothiosulfuric acid are described. The general approach is *via* a two-step procedure involving the addition of ethylenimine to electrophilic olefins, and subsequent cleavage of the adducts with either hydrogen sulfide or sodium thiosulfate. The difference in the reactivity of ethylenimine with various electrophiles is discussed. The synthetic route to β-amino thiols and thiosulfates involving aziridines is compared with other methods of synthesis and the scope and limitations of these reactions are analyzed.

In recent years, interest in the radiation-protective action of β-amino mercaptans and some of their derivatives (sulfur-containing amines) has prompted many new synthetic investigations in this field.[2] We wish to report here on some of our investigations which have led to the synthesis of a number of functionalized derivatives of N-substituted β-amino mercaptans and β-amino thiosulfates.

A number of methods for the synthesis of compounds of type $R_2NCH_2CH_2SH$ have been reported. Among them are the displacement of chloride ion from a β-aminoethyl chloride with sodium hydrosulfide,[3] direct alkylation of S-benzylcysteamine followed by reduction with sodium in liquid ammonia,[4] reduction of a Schiff base,[5] hydride reduction of thiazolidines and mercaptoamides,[6] and the reaction of primary amines with a variety of electrophiles, such as S-benzyl-2-chloroethanetriol,[7] ethylene monothiol carbonate,[8] and ethylene sulfide.[9]

Recently our laboratory has reported the preparation of a series of carboxylic acid derivatives substituted in the β-position with the β-mercaptoethylamino grouping, prepared by the addition of S-tritylcysteamine to a series of acrylic acid derivatives and subsequent removal of the sulfur-protecting group.[10]

Since this approach was limited to the more reactive olefins we turned to alternative synthetic approaches which might be more general. Specifically, we investigated the reaction of ethylenimine with a variety of electrophilic olefins **1** to form the intermediate aziridines **2**, which were cleaved with hydrogen sulfide to form the amino mercaptans **3**. Alternatively, other nucleophiles, such as sodium thiosulfate, were used to convert **2** to the β-aminothiosulfuric acids **4**.



The general synthetic utility of ethylenimine in substitution and addition reactions was first demonstrated by Bestian,[11] who prepared a wide variety of N-substituted aziridines by a number of methods. Specific application to acrylic systems was further elaborated by two other groups.[12]

In our work, ethylenimine was reacted in a systematic fashion with several related series of acrylate derivatives in an effort to define further the scope and limitations of this reaction.

The Addition of Ethylenimine to α,β-Unsaturated Ketones and Acid Derivatives.—The reaction of ethylenimine with a large number of α,β-unsaturated compounds was carried out and it was concluded that this reaction is *nearly general*. However, there is a remarkable difference in the ease with which a variety of substrates enter into the addition reaction. Fortunately, both ethylenimine and the adducts were quite stable under all of the reaction conditions employed. The most reactive compound, α-chloroacrylonitrile, formed an adduct exothermically at −20° with solvent dilution, while N,N-dimethylacrylamide reacted only slowly at 120° in a sealed tube with alkaline catalysis. A selected list of reactants in order of decreasing reactivity with ethylenimine is as follows: $CH_2{=}CCl{-}CN > CH_2{=}CHCN \sim CH_2{=}CHCOCH_3 > CH_2{=}CH{-}COOC_2H_5 > CH_2{=}CH{-}CONH_2 > CH_2{=}CHCONH{-}CH(CH_3)_2 > CH_2{=}CH{-}CON(CH_3)_2$. This series of relative reactivity is in accord with the expected ability of the substrate to accommodate a transient partial negative charge in the transition state.

(1) (a) This investigation was supported by the Department of the Army and the U. S. Army Medical Research and Development Command, Contract No. DA-49-193-MD-2164. (b) Presented in part at the 148th National Meeting of the American Chemical Society, Chicago, Ill., Sept. 1964.

(2) Some recent work in this area was reported at the Symposium on Radiation-Protective Agents, 141st National Meeting of the American Chemical Society, Washington, D. C., March 1962.

(3) N. F. Albertson and R. O. Clinton, *J. Am. Chem. Soc.*, **67**, 1222 (1945).

(4) S.-H. Chu and H. G. Mautner, *J. Org. Chem.*, **26**, 4498 (1961).

(5) T. P. Johnston and A. Gallagher, *ibid.*, **27**, 2452 (1962).

(6) E. L. Eliel, E. W. Della, and M. M. Rogić, *ibid.*, **27**, 4712 (1962); C. W. Schimelpfenig, *ibid.*, **27**, 3323 (1962).

(7) G. Cavallini and F. Ravenna, *Farmaco* (Pavia), *Ed. sci.*, **12**, 151 (1957); *Chem. Abstr.*, **51**, 11245 (1957).

(8) D. D. Reynolds, M. K. Massad, D. L. Fields, and D. L. Johnson, *J. Org. Chem.*, **26**, 5109 (1961), and following papers.

(9) R. J. Wineman, M. H. Gollis, J. C. James, and A. M. Pomponi, *ibid.*, **27**, 4222 (1962).

(10) F. I. Carroll, H. M. Dickson, and M. E. Wall, *ibid.*, **30**, 33 (1965).

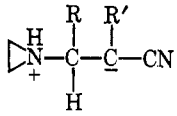
(11) H. Bestian, *Ann.*, **566**, 210 (1950).

(12) (a) T. Yoshida and K. Naito, *Kogyo Kagaku Zasshi*, **55**, 455 (1952); (b) K. C. Tsou, K. Hoegerle, and H. C. F. Su, *J. Med. Chem.*, **6**, 435 (1963).

The addition can be catalyzed with base. In our study sodium methoxide was used for this purpose.[13] Basic catalysts were not always compatible with certain substrates which were subject to base-catalyzed side reactions. For example, in the case of crotononitrile, the addition of even traces of sodium methoxide caused the self-condensation of the nitrile, and none of the desired adduct was formed. This substrate reacted normally, however, in the absence of catalyst.

The reaction of ethylenimine with unsaturated esters and amides is subject to steric influences of more than one type. Bestian noted that substituents on the acrylic double bond slowed the reaction. We have confirmed these findings. However, the deactivating effect of alkyl substituents depends on their placement. We have compared the reactivities of acrylonitrile, methacrylonitrile, and crotononitrile with ethylenimine under controlled conditions. Acrylonitrile is the most reactive, the reaction proceeding rapidly and exothermically at 35°. At 55°, in parallel experiments, crotononitrile reacted slowly to *ca.* 90% completion in 24 hr., while methacrylonitrile reacted less than 2% in the same time interval.[14]

These results are not readily rationalized by electronic considerations and the only explanations we can offer is that in intermediate **5a** there are no serious vicinal interactions between the substituents on the α- and β-carbon atoms while in **5b** there is a possible interaction between the heterocyclic ring and the methyl group on the neighboring carbon atom. Results similar to these have been observed previously.[15]



5a, R = CH_3; R′ = H
b, R = H; R′ = CH_3

Another important steric influence on this reaction is exemplified by the difference in reactivity between methyl and ethyl crotonate. The former reacts quantitatively with ethylenimine at 75° in 40 hr., while the latter is 2% reacted after this time. This difference in reactivity, however, was not noted in the acrylate series. Under suitable conditions (see Experimental Section) it was found that methyl acrylate reacts only about two times as fast as ethyl acrylate. In a competition experiment using a limited amount of ethylenimine in the presence of both esters the product ratio was 1.6:1 favoring the methyl ester.[16]

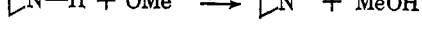
Similar effects were noted in the amide series. At 120°, N,N-dimethylacrylamide reacted slowly with ethylenimine to give a 60:40 ratio of adduct to starting amide after 2 days. This ratio was not altered after an additional 2 days of heating. By increasing the ratio of ethylenimine to amide, the product to starting material ratio was increased to 70:30. We believe that this is evidence for assuming an equilibrium between the reactants. At lower temperatures we always found the reactions to proceed to greater than 90% completion. However, at the elevated temperature of 120° the reverse reaction rate increases noticeably.

By way of comparison, N,N-diethylacrylamide (**6**) was completely inert under these conditions. In fact, this substance and two other amides, N,N-dibutyl- (**7**) and N-phenylacrylamide, were the only compounds which we studied which failed to give adducts with ethylenimine. N-Phenylacrylamide polymerized under the reaction conditions at 120° while **6** and **7** were totally inert. These results we also attribute to steric interference at the reaction site.

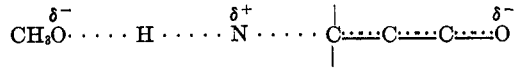
The aziridines which we have synthesized, along with experimental conditions and physical constants, are listed in Table I.

Cleavage of Aziridine Adducts with Hydrogen Sulfide to Form 2-Mercaptoethylamines.—Ethylenimine

(13) The function of the base is most likely that of proton abstraction from nitrogen. The strength of the N–H bond is progressively weakened as the addition reaction proceeds. With ethylenimine itself the equilibrium with methoxide ion to form ethylenimide ion and methanol is highly unfavorable, K_{equil} being estimated at 10^{-20}: H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, Inc., New York, N. Y., 1965, p. 164.



After the N–C bond is fully formed, proton removal from nitrogen would be very fast and not helped by base. A referee has suggested that the methoxide ion is involved at a point where partial N–C bond formation has

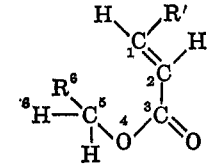


occurred and the N–H bond is considerably weakened, and we concur with this view.

(14) Similar differences in the relative reactivities of acrylonitrile and the methylacrylonitriles with amines have been observed previously: C. B. Pollard, E. G. Rietz, and R. Robbins, *J. Am. Chem. Soc.*, **75**, 2989 (1953).

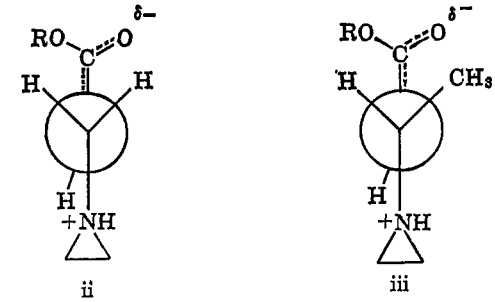
(15) H. A. Bruson, *Org. Reactions*, **5**, 108 (1949).

(16) In order to rationalize the difference between the acrylate and crotonate methyl and ethyl esters, we assume that the ethyl group contributes significantly more to the steric crowding in the region of the β-carbon atom than the methyl group. Newman has formulated the "rule of six" to correlate observed rates with variations in the steric environment of a reaction site. [M. S. Newman, in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, p. 203 ff]. In applying this rule to the case at hand one would predict equal hindrance for all the four esters i (six number = 3). However, in these



i, R = H, CH_3; R′ = H or CH_3

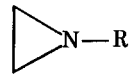
compounds it might be expected that the steric effects would be exerted at a distance somewhat *greater* than six atoms from the reaction site because of the lack of flexibility of the unsaturated acrylate moiety, thereby accounting for the greater hindrance of the ethyl over the methyl ester. If one pictures



ii iii

the transition states of the acrylates and crotonates by the Newman projections ii and iii, it can be seen that in the acrylates ii, the entering ethylenimino group can orient itself so that there are only ester–hydrogen interactions between the α- and β-carbon atoms so that the steric retardation of the ethyl ester is minimized, whereas in the crotonates, iii, either a methyl group or an ethylenimine moiety must always interact with the ester, thus explaining the difference observed between methyl and ethyl in this case.

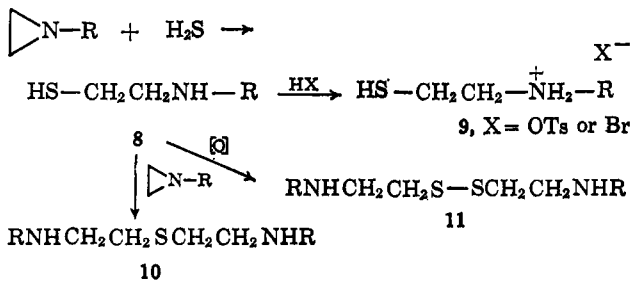
TABLE I. AZIRIDINES 2



Compd.	R	Method of synthesis[a]	Temp., °C.	Reactn. time	B.p. (mm.) or m.p. (solvent), °C.	$n^{25}D$	Yield,[b] %	Formula	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
2a	$-CH_2CH_2CONH_2$	A[c]	25	16 hr.	104–108[d] (EtOAc)	...	55	$C_5H_{10}N_2O$	52.61	8.83	...	52.35	8.83	...
2b	$-CH(CH_3)CH_2CN$	A	62[e]	18 hr.	111–112 (50)	1.4421	83	$C_6H_{10}N_2$	65.42	9.15	25.43	65.59	9.24	25.13
2c	$-CH_2CH(CH_3)CN$	D	100	21 hr.	107–109 (50)	1.4401	73	$C_6H_{10}N_2$	65.42	9.15	25.43	65.64	9.26	25.64
2d	$-CH_2CH_2COCH_3$	A[f]	15	48 hr.	67–68 (15)	1.4450	80	$C_6H_{11}NO$	63.66	9.80	12.37	63.77	9.67	12.49
2e	$-CH_2C(=O)OC_2H_5$	*g*	0	40 hr.	98–100 (53)	1.4324	53	$C_6H_{11}NO_2$	55.79	8.58	10.85	55.85	8.73	10.93
2f	$-CH_2CH(CH_3)C(=O)NH_2$	B[h]	Room temp.	123 days	101–102 (benzene)	...	21	$C_6H_{12}N_2O$	56.22	9.44	21.86	56.46	9.61	21.81
2g	$-CH_2CH_2COOC_2H_5$	A	70[e]	6 hr.	65–66 (7)	1.4324	90	$C_7H_{13}NO_2$	*i*					
2h	$-CH_2CH(CH_3)COOCH_3$	B	25	60 hr.	75–77 (16)	1.4336	30[j]	$C_7H_{13}NO_2$	58.72	9.15	9.78	58.69	9.12	9.64
2i	$-CH(CH_3)CH_2C(=O)OCH_3$	B	75	40 hr.	74–75 (14)	1.4315	84	$C_7H_{13}NO_2$	58.72	9.15	9.78	58.66	9.24	9.69
2j	$-CHCH_2COOC_2H_5$ (CH$_2$)	C	95	44 hr.	84–85 (16)	1.4306	69	$C_8H_{15}NO_2$	61.12	9.62	...	61.22	9.89	...
2k	$-CH_2CH(CH_3)C(=O)OCH_2CH_2OH_2$	A[k]	Room temp.	3 days	90–91 (15)	1.4607	36	$C_8H_{15}NO_3$	55.47	8.73	8.09	54.80	8.87	8.39
2l	$-CH_2CH_2CONHCH(CH_3)_2$	B	70	9 hr.	54–57 (benzene–hexane)	...	90	$C_8H_{16}N_2O$	61.50	10.32	17.93	61.53	10.36	17.72
2m	$-CH_2CH_2CONHC(CH_3)_3$	C	80	50 hr.	53–56 (hexane)	...	51	$C_9H_{18}N_2O$	63.49	10.65	16.46	63.82	10.76	16.29
2n	$-CH_2CH(CH_3)COO(CH_2)_2N(CH_3)_2$	B	65	21 hr.	95–97 (3.5)	1.4471	75	$C_{10}H_{20}N_2O_2$	59.97	10.07	13.99	58.92	10.06	13.78
2o	$-CH_2CH(CH_3)C(=O)OCH_2CH(CH_3)_2$	B	75	47 hr.	94–95 (8)	1.4316	40	$C_{10}H_{19}NO_2$	64.83	10.34	7.56	65.05	10.24	7.59
2p	$-CH(C_6H_5)CH_2CN$	B	65	7.5 hr.	99–102 (0.2)	1.5373	57	$C_{11}H_{12}N_2$	76.71	7.02	16.27	76.63	6.89	16.29
2q	$-CH_2CH(CH_3)COO(CH_2)_2NHC(CH_3)_3$	B	75	24 hr.	84–85 (0.1)	1.4485	74	$C_{12}H_{24}N_2O_2$	63.12	10.60	...	62.99	10.62	...
2r	$-CH_2CH_2COOC_{10}H_{21}$	A	70[e]	16 hr.	111–116 (1)	1.4483	78	$C_{15}H_{29}NO_2$	70.54	11.45	5.48	70.80	11.28	5.34

[a] See Experimental Section. [b] Yields are not maximal. Significant improvements may well be possible. [c] Run in ethyl acetate. [d] Bestian[11] reported m.p. 104–106°. [e] After original reaction at 0° had subsided. [f] Prepared according to the procedure of Bestian.[11] [g] This compound was prepared by the addition of ethylenimine to ethyl chloroacetate in the presence of triethylamine analogously to a published procedure.[11] It is a nor homolog of this series and is included since it also reacts smoothly with thiosulfate to form a Bunte salt. [h] See Experimental Section. [i] This is a known compound.[12a] [j] Because of extensive anionic polymerization the adduct was extracted from the polymeric product with hexane prior to distillation. [k] This reaction was carried out with ethanol as a solvent.

has been reported to react with hydrogen sulfide[11] and mercaptans[17] to form β-mercaptoethylamines, and it was expected that our aziridine intermediates should react with hydrogen sulfide to form functionalized N-substituted cysteamines. When the aziridines which we had prepared were treated with hydrogen sulfide, the reaction proceeded rapidly and the starting material was consumed in several hours at room temperature to form the amino mercaptans **8**. The products were not uniformly isolable. In our early work the initially formed amino mercaptan was converted into a salt and was purified by recrystallization. This approach was not always successful since the initial reaction product was always more or less contaminated with higher molecular weight and less soluble by-products, as shown by low sulfhydryl analyses. The by-products were most likely sulfides **10** and disulfides **11** arising from the reaction of the initially formed amino mercaptan **8** with starting material or with air, respectively.

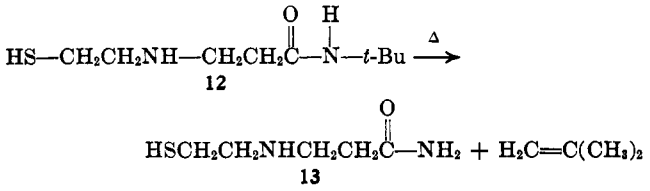


Substantial improvement of the initial procedure was achieved when it was noted that certain of the 1-mercapto-2-amino derivatives thus produced could be distilled *in vacuo* to give pure, water-white liquids, free of sulfides and disulfides.

These free mercaptans were relatively stable under nitrogen at −10° and gave excellent analyses. Their sulfhydryl content was invariably greater than 95%. The free mercaptans were then readily converted to salts **9** with excellent physical properties and analyses. The amino mercaptans synthesized and their salts are listed in Tables II and III, respectively.

This procedure is therefore mainly limited to the preparation of mercaptans of sufficiently low molecular weight that distillation is possible. In some cases moderately pure salts (70–90% -SH) could be obtained by direct crystallization. Our best results using distillation were achieved with esters.

Difficulty was experienced with amides, mainly because of their lack of volatility. In the case of the N-*t*-butylacrylamide derivative **12**, we noted that on attempted distillation, pyrolysis occurred to form the unsubstituted amide **13** and presumably isobutene.



(17) R. Kuhn and G. Quadbeck, *Ber.*, **84**, 844 (1951); G. Meguerian and L. B. Clapp, *J. Am. Chem. Soc.*, **73**, 2121 (1951).

TABLE II. AMINO MERCAPTANS 8 (HSCH₂CH₂R)

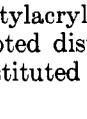
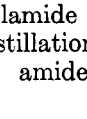
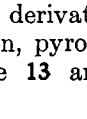
Compd.	R	B.p. (mm.), °C.	$n^{25}D$	Yield, %	Formula	Calcd., % C	H	N	S	Found, % C	H	N	S
8a		65–67 (0.04)	1.4760	76	$C_7H_{15}NO_2S$	47.44	8.53	7.91	18.06	47.22	8.36	7.95	18.29
8b		63–65 (0.15)	1.4759	83	$C_7H_{15}NO_2S$	47.44	8.53	7.91	18.06	47.62	8.29	7.84	17.97
8c		52–53 (0.03)	1.4697	76	$C_8H_{17}NO_2S$	50.25	8.96	7.33	16.74	50.37	8.83	7.03	16.52
8d		75–78 (0.025)	1.4650	71	$C_{10}H_{21}NO_2S$	54.77	9.65	6.39	14.60	55.05	9.82	6.20	14.81
8e		100–103 (0.2)	1.4785	54	$C_{10}H_{22}N_2O_2S$	51.24	9.46	11.96	13.68	51.75	9.00	11.81	13.48
8f		130–131 (0.05)	1.4759	80	$C_{12}H_{26}N_2O_2S$	54.96	9.92	10.69	12.21	54.76	9.73	10.69	12.32

TABLE III. SALTS OF AMINO MERCAPTANS 9 ($HSCH_2CH_2NH_2R$)

Compd.	R	M.p. (solvent), °C.	Yield, %	Formula	Calcd., % C	H	Cl	N	S	Found,[a] % C	H	Cl	N	S
9a	$-CH_2-\underset{CH_3}{CH}-\overset{O}{\overset{\|}{C}}OCH_2CH_2-\overset{+}{N}H(CH_3)_2\ 2Cl^-$	117–125 (2-propanol)	60	$C_{10}H_{24}Cl_2N_2O_2S$	39.08	7.87	23.08	9.12	10.44	39.14	7.71	22.98	9.15	10.26[b]
9b	$-CH_2-\underset{CH_3}{CH}-\overset{O}{\overset{\|}{C}}O-CH_2CH_2\overset{+}{N}H_2-C(CH_3)_3\ 2Cl^-$	180–181 (ethanol)	68	$C_{12}H_{28}Cl_2N_2O_2S$	42.98	8.36	21.19	8.36	9.55	42.97	8.33	21.02	8.26	9.53
9c	$-CH_2-\underset{CH_3}{CH}-\overset{O}{\overset{\|}{C}}-OCH_3\ OTs^-$	89–90 (ethanol)	53	$C_{14}H_{23}NO_5S_2$	48.11	6.63		4.01	18.35	48.65	6.75		3.89	18.45
9d	$-\underset{CH_3}{CH}-CH_2-\overset{O}{\overset{\|}{C}}-OCH_3\ OTs^-$	59–62 (ether–ethanol)	55	$C_{14}H_{23}NO_5S_2$	48.11	6.63		4.01	18.35	48.29	6.72		3.93	18.58
9e	$-CH_2CH_2-\overset{O}{\overset{\|}{C}}-OC_2H_5\ OTs^-$	63–64 (ether–benzene)	55	$C_{14}H_{23}NO_5S_2$	48.11	6.63		4.01	18.35	48.27	6.83		3.98	18.21
9f	$-\underset{CH_3}{CH}-CH_2-\overset{O}{\overset{\|}{C}}-OC_2H_5\ OTs^-$	59–61 (ether–ethanol)	62	$C_{15}H_{25}NO_5S_2$	49.58	6.94		3.86	17.61	49.93	6.78		3.87	18.23
9g	$-CH_2-\underset{CH_3}{CH}-\overset{O}{\overset{\|}{C}}-OCH_2CH(CH_3)_2\ OTs^-$	56–60 (ether–ethanol)	72	$C_{17}H_{29}NO_5S_2$	52.24	7.48		3.58	16.38	52.23	7.45		3.59	16.24

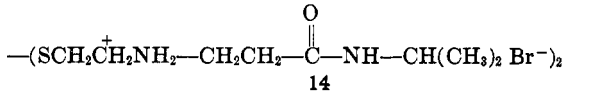
[a] In addition to elemental analysis all of the salts were analyzed for –SH content and gave values greater than 96%. [b] This compound was prepared without distillation of the intermediate free amine and gave an –SH analysis of 84.6%.

TABLE IV. AMINOTHIOSULFURIC ACIDS 16 ($^-O_3S_2CH_2CH_2\overset{+}{N}H_2R$)

Compd.	R	Method[a]	M.p. (solvent), °C.	Yield, %	Formula	Calcd., % C	H	N	S	Found, % C	H	N	S
16a	$-CH_2CH_2\overset{O}{\overset{\|}{C}}-NH_2$	B	178–179[b] (methanol–water)	60	$C_5H_{12}N_2O_4S_2$	26.25	5.29	12.27	28.10	26.49	5.30	12.03	28.07
16b	$-\underset{CH_3}{CH}-CH_2-CN$	A[c]	163–166 (acetonitrile)	20	$C_6H_{12}N_2O_2S_2$	32.13	5.39	12.49	28.59	31.87	5.52	12.20	28.60
16c	$-CH_2-\overset{O}{\overset{\|}{C}}-OC_2H_5$	B	118–119 (ethanol)	69	$C_6H_{12}NO_5S_2$	29.62	5.38	5.76	26.36	29.79	5.44	5.74	26.53
16d	$-CH_2-\underset{CH_3}{CH}-\overset{O}{\overset{\|}{C}}-NH_2$	A[d]	194–197 dec. (water)	73	$C_6H_{14}N_2O_4S_2$	29.74	5.82	11.56	26.46	29.75	5.80	11.78	26.49
16e	$-CH_2\underset{CH_3}{CH}-\overset{O}{\overset{\|}{C}}-OCH_3$	A	141–142 (methanol–ethanol)	22	$C_7H_{15}NO_5S_2$	32.68	5.88	5.46	24.98	32.70	5.82	5.44	25.01
16f	$-CH_2CH_2CO-NH-CH(CH_3)_2$	C	128–130 (ether–acetonitrile)	52	$C_8H_{18}N_2O_4S_2$	35.55	6.71	10.37	23.68	35.69	6.50	10.28	23.46
16g	$-CH_2CH_2\overset{O}{\overset{\|}{C}}-NH-C(CH_3)_3$	A[e]	126–129 (acetonitrile)	57	$C_9H_{20}N_2O_4S_2$	38.01	7.09	9.85	22.55	37.85	7.22	9.68	22.82
16h	$-CH(C_6H_5)-CH_2-CN$	A[f]	184–185 dec. (water)	44	$C_{11}H_{14}N_2O_3S_2$	46.15	4.93	9.79	22.36	45.98	5.00	9.97	22.58

[a] Method of isolation. See Experimental Section. [b] Isoelectric point was determined to be 5.3. [c] Freeze-dried crude material was extracted with hot ethanol. [d] Extracted with *n*-butyl alcohol, backwashed three times with water. [e] Extracted with hot ethanol. Additional purification through silica gel chromatography. [f] Total crude material was crystallized from hot water.

N-Isopropylacrylamide formed an adduct, which on cleavage and conversion to its salt, oxidized rapidly on attempted recrystallization and only the disulfide **14** (0.0%-SH) was isolated.

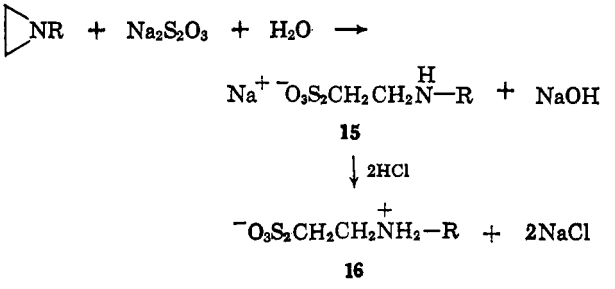


14

Cleavage of Aziridines with Sodium Thiosulfate.—Since the cleavage of aziridines with hydrogen sulfide was of limited applicability, we have also considered other ways in which aziridines could be cleaved to form possibly useful derivatives of β-amino mercaptans. We therefore investigated the reaction of aziridines with sodium thiosulfate, since the resulting amino Bunte salts and aminothiosulfuric acids were also known to possess antiradiation properties.

The literature on the subject of the cleavage of aziridines with thiosulfate is mainly concerned with the analysis of substituted aziridines,[18] and very little emphasis was placed on the isolation or physical properties of the products. We found it necessary to alter the procedure for this reaction in order to allow for the isolation and purification of the product.

The general reaction is shown below.



15

16

The initial reaction of the substituted aziridines with sodium thiosulfate formed the amino Bunte salts **15** and subsequent acidification yielded the zwitterionic aminothiosulfuric acids **16**.

The reaction undoubtedly occurs by the initial protonation of the aziridine followed by subsequent nucleophilic attack of thiosulfate ion. Since hydroxide ion is the product of the ring opening, the reaction is self-quenching and proceeds only to a trace extent. We found that on addition of a single mole of hydrochloric acid, reaction occurred at pH near 8.9 to form the Bunte salt **15**. At this stage the product was isolated by one of three methods: (1) ion exchange of the Bunte salt, or further acidification to the amino acid **16** and isolation (2) by extraction and crystallization, or (3) by countercurrent distribution. The yields in most cases were good (>50%) with the major losses due to mechanical manipulations and crystallization. We did not note any side products and the yield based on the moles of acid needed to bring the products to their isoelectric point (*ca.* 3.5) was essentially quantitative. No special attempts were made to maximize yields and improvements may be possible.

In contrast to the amino mercaptans, the aminothiosulfuric acids were all white, crystalline solids. The compounds were stable to mild oxidants such as air, and could be crystallized and filtered in a conventional manner. They were highly water soluble, readily purified, and gave excellent analytical values. The compounds synthesized are listed in Table IV.

Scope and Limitations.—In view of the fact that the approach described in this paper to synthesize amino mercaptans of type **12** is an alternative to the procedure described by Carroll, *et al.*,[10] some comparison of the two methods is in order. The two procedures are in many respects complementary.

The S-trityl route, when applicable, yields stable crystalline intermediates which are readily purified, and can be used in multistep syntheses involving reagents which are not compatible with aziridines.

The ethylenimine procedure is more generally applicable to less reactive electrophiles. It is more direct, involves less expensive reagents, and can be easily scaled up if need be.

Experimental Section

Materials and Analytical Methods.—Ethylenimine was obtained in commercial grade from the Dow Chemical Co. and stored at 5° over sodium hydroxide pellets. It was not necessary to distil this product before use. The acrylic substrates were obtained from normal commercial sources, primarily Monomer-Polymer Laboratories, Philadelphia, Pa.; Rohm and Haas Chemical Co., Philadelphia, Pa.; and American Cyanamid Co., Wayne, N. J. They were invariably stabilized with a variety of hydroquinones. The substrates were used without any prior purification.

The reactions involving aziridines either as starting materials or products were followed routinely by vapor phase chromatography (v.p.c.) using an F & M Model 300 vapor phase chromatograph with a 6 ft. × 0.25 in. aluminum column packed with 2% Silicone XE-60 on Anakrom 70/80 Type ABS. Adsorbents such as SE-30 or Apiezon L were not satisfactory for the chromatography of aziridines. The column had to be pretreated with several large injections of an aziridine and then baked off at 250° before reproducible results could be obtained.

Thin layer chromatography (t.l.c.) was carried out on silica gel G covered microscope slides, and the spots were developed with iodine. In some cases (mercaptans) the products appeared light on dark backgrounds.

Sulfhydryl determinations were made either by the N-ethylmaleimide method of Alexander[19] or more simply by direct iodimetric titration in dilute aqueous mineral acid with standard iodine solution.

Synthesis of Aziridines.—The aziridines listed in Table I were synthesized by four general methods, depending on the reactivity of the acrylic compound.

Method A was applied to highly reactive substrates. In this case it was sometimes necessary to add a solvent to moderate the reaction. No catalysts were used. The reaction mixture was cooled at first until the initial reaction had subsided and sometimes was brought to reflux to complete the addition reaction.

Method B was the most commonly employed. Ethylenimine was used as a solvent and catalytic amounts of sodium methoxide were added. Reaction temperatures at reflux could be controlled from about 60 to 85° by varying the ratio of ethylenimine to acrylic compound.

Method C was used for more unreactive substrates. In this case the acrylic compound containing catalyst was heated to 90–100°, and then ethylenimine was added until refluxing occurred at the selected temperature. More ethylenimine was added as it was consumed or evaporated. This method was often time consuming and required constant attention in order to maintain the temperature exactly. Too little ethylenimine caused a slow reaction because of the low concentration of reagent. Too much caused a slowing down due to temperature drop.

Method D involved placing the reactants in a sealed glass ampoule and heating to 100° or higher. In one instance an explosion occurred due to the increased pressure; however, later reactions carried out within an autoclave (tested at 10,000 p.s.i.) proceeded without incident.

(18) E. Allen and W. Seaman, *Anal. Chem.*, **27**, 540 (1955).

(19) N. M. Alexander, *ibid.*, **30**, 1292 (1958).

Typical examples follow.

Method A. No Catalyst. 3-(1′-Aziridinyl)butyronitrile (2b).—Crotononitrile (commercial, mixture of *cis* and *trans*, 50 ml., 41.3 g., 0.62 mole) was added slowly to 100 ml. of ethylenimine (83.3 g., 1.93 moles) which had been cooled to 0°. On completion of addition the reaction was slowly brought to room temperature and finally heated under reflux overnight. Distillation of the product gave 56.4 g. (83.2%) of 3-(1′-aziridinyl)butyronitrile (2b), b.p. 110–114° (50 mm.).

Method B. Base Catalyst. 3-(1′-Aziridinyl)-N-isopropylpropionamide (2i).—A solution of 10 g. (88.5 moles) of N-isopropylacrylamide containing a trace of hydroquinone and sodium methoxide (100 mg.) in 60 ml. of ethylenimine was heated to reflux. Formation of the adduct was followed by v.p.c. and the reaction was essentially complete in 9 hr. After removal of the excess ethylenimine on a rotary evaporator the product was distilled at 0.03 mm. A fraction weighing 12.5 g. (90%) distilled between 70 and 85°. On cooling, the product crystallized and melted at 46–56°. Subsequent runs gave 70–90% yield.

The product, 2i, was highly hygroscopic and was crystallized only with difficulty in a drybox from hexane–benzene. The analytical sample melted at 54–57° (sealed tube).

Method C. Slow Addition to Maintain Elevated Temperature. Ethyl 3-(1′-Aziridinyl)butyrate (2j).—To a flask fitted to measure the reaction temperature under reflux was added 22.4 g. of ethyl crotonate (0.20 mole). Five drops of saturated sodium methoxide in methanol were added along with a few crystals of toluhydroquinone. The ester was then heated to 90° and ethylenimine was added very slowly until refluxing began. The reaction temperature was maintained at 87–95° by the slow addition of ethylenimine as necessary. The reaction was followed by v.p.c. and terminated after 44 hr. By this time 97% of the original starting ester had disappeared. A total of 20 ml. of ethylenimine was added during the course of the reaction. The product was stripped of volatile materials and distilled at 16 mm.; 20.3 g. of ethyl 3-(1′-aziridinyl)butyrate (2j, 69%) was collected, b.p. 84–85°.

Method D. Sealed Tube Reaction. 1-(1′-Aziridinyl)-2-cyanopropane (2c).—A mixture of 17 ml. of methacrylonitrile (13.6 g., 0.203 mole), ethylenimine (33 ml.), 0.2 ml. of 1 *M* sodium methoxide in methanol, and 20 mg. of toluhydroquinone was sealed in a glass tube and heated in an oven to 100°. The reaction was followed by removing representative samples from the oven and analyzing the reaction products by v.p.c. After 21 hr., the reaction had proceeded to completion and the product was worked up.

The reaction products from two such identical runs were combined, and after removal of the ethylenimine at room temperature the product was distilled at 50 mm. The major fraction (26.0 g.) distilled at 107–109°; however, the fractions boiling 90–107° had essentially identical n_D values. The total yield of 1-(1′-aziridinyl)-2-cyanopropane (2c) was 32.4 g. (73%).

3-(1′-Aziridinyl)-2-methylpropionamide (2b).—Initial experiments with methacrylamide indicated that this substance polymerized rapidly at 60° in the presence of ethylenimine and base. Consequently the following procedure was adopted to prepare the adduct. Methacrylamide (100 g., 1.17 moles), 100 ml. of ethylenimine, 100 mg. of hydroquinone, and 0.5 ml. of a saturated solution of sodium methoxide in methanol were added to 300 ml. of methanol. The solution was allowed to stand at ambient temperature for 123 days. At this time the methacrylamide was about 50% reacted (t.l.c.). The reaction was then worked up as follows. After removal of methanol and ethylenimine under reduced pressure, the starting material was removed by distillation (sublimation) at 100 μ (recovered starting material, 15.3 g., b.p. 114°). Further distillation of the residue at 50 μ yielded 67.1 g. of a white solid which was a crude mixture of methacrylamide and adduct. Two recrystallizations from benzene yielded 29.2 g. of adduct, m.p. 90–101°, yield (accounting for recovered starting material) 23%.[20] The infrared spectrum of this sample was practically identical with that of the analytical sample, m.p. 100.5–102.5°, which was obtained by three further crystallizations from benzene.

Experiment with α-Chloroacrylonitrile.—α-Chloroacrylonitrile (10 g.) in 10 ml. of ethanol reacted vigorously with ethylenimine (10 ml.) at 3–5°. After the initial reaction had subsided the product was brought to room temperature. After 2 hr. the reaction was complete (as judged by v.p.c.). However, on attempted distillation at 20 mm. with a bath of 90°, the total reaction mixture decomposed violently leaving only a carbonized residue.

Qualitative Comparative Kinetic Studies. a. Crotononitrile *vs.* Methacrylonitrile.[21]—A solution of 5.0 ml. of crotononitrile in 10.0 ml. of ethylenimine was placed in a constant-temperature bath at 55°. A similar reaction was set up with methacrylonitrile. Aliquots were taken at various times and analyzed by v.p.c. The crotononitrile reacted at a demonstrable rate, the first half being consumed in 6 hr. After 28 hr. the reaction was 95% complete. At this time there was no detectable adduct from the methacrylonitrile. The sensitivity of the analysis was such that 5% reaction could be readily detected.

b. Methyl Acrylate *vs.* Ethyl Acrylate.—These esters, when prepared in 1.0 *M* concentration in ethylenimine at 0° were both completely converted to their adducts in less than 1 min., no starting ester being visible after that time (v.p.c.). Satisfactory conditions for observing the relative rates were achieved by running the reactions at the concentration of 1.0 *M* in ester and 5.0 *M* in ethylenimine in hexane solvent at 24°. The reaction was followed by the disappearance of acrylic ester using v.p.c. The kinetics was approximately pseudo first order with K_1 = 0.054 min.$^{-1}$ for ethyl acrylate and K_1 = 0.103 min.$^{-1}$ for methyl acrylate. In a competition experiment a solution 1.0 *M* in each acrylate and 1.0 *M* in ethylenimine in pentane was allowed to stand at room temperature for 20 hr. After this time the reaction products were examined by v.p.c. and it was shown that the two adducts, methyl and ethyl 3-(1′-aziridinyl)propanoate, had formed in the ratio of 1.6:1.

Cleavage of Aziridines with Hydrogen Sulfide.—The aziridines were cleaved with hydrogen sulfide to form the amino mercaptans 8 by a procedure of which the following example is representative. A solution of 10.54 g. of hydrogen sulfide in 50 ml. of ethanol at −40° was added to 15.98 g. (0.111 mole) of methyl 3-(1′-aziridinyl)butyrate (2i). The solution was allowed to come to room temperature slowly, then allowed to stand for 2 hr. After this time the starting material had disappeared completely (v.p.c.). The solvent was removed *in vacuo* and the product was distilled at 0.04 mm. The major fraction (11.90 g.) boiled at 65–67°. Additional slightly less pure fractions were collected (3.07 g.), the total yield of methyl β-(β-mercaptoethylamino)-butyrate (8a) amounting to 14.92 g. (76%).

The mercaptan was immediately converted into its *p*-toluenesulfonate salt as follows. A solution of 8.77 g. of the free mercaptan 8a in 50 ml. of benzene was mixed with 9.3 g. of toluenesulfonic acid hydrate which had been dehydrated by azeotropic distillation from benzene (final volume, 50 ml.). The solvent was removed and the residual oil was triturated with ether and allowed to crystallize slowly at −40°.

The product was then recrystallized once from ether–ethanol at −5° and yielded 9.67 g. (55%) of crystals: m.p. 54–62°; –SH analysis: 96.1, 100.8%. Recrystallization from ether–ethanol gave methyl β-(β-mercaptoethylamino)butyrate, toluenesulfonic acid salt (9d): 4.60 g.; analytically pure; m.p. 58.5–62°; –SH analysis 95.8, 98.9%.

Disulfide of N-Isopropyl-β-(β-mercaptoethylamino)propionamide, Dihydrobromide (14).—To a solution of 9.2 g. of N-isopropyl-3-(1′-aziridinyl)propionamide (2i) in 25 ml. of alcohol was added 38 g. of hydrogen sulfide in 40 ml. of alcohol (−40°). After standing for 2 hr. at 25°, 5 g. of hydrogen bromide in 20 ml. of ethanol was added. The solution was then evaporated to near dryness *in vacuo* and the solid residue was crystallized from methanol–ethanol. The initial crop of crystals melted in a mixed range 136–137° and again at 165–175°. Analysis showed 60% free –SH. The solid, on recrystallization in air, oxidized spontaneously and yielded 9.48 g. of crystals, m.p. 210–215°. From the mother liquors, an additional 1.0 g. was isolated, m.p. 216–219°.

The high-melting compound showed 0% –SH. The analytical sample of compound 14 melted at 217–219° (MeOH–EtOH). The combined yield was 29%.

Anal. Calcd. for $C_{16}H_{36}Br_2N_4O_2S_2$: C, 35.56; H, 6.71; Br, 29.58; N, 10.37; S, 11.87. Found: C, 35.77; H, 6.77; Br, 29.37; N, 10.09; S, 11.75; –SH, 0.0.

Cleavage of Aziridines with Sodium Thiosulfate.—The general method for carrying out the cleavage was the same in all cases.

(20) Yoshida and Naito[12a] report this compound to have m.p. 87–88°, 60% yield.

(21) This experiment was carried out by Mr. Jerry D. White.

After the reaction was completed we used three procedures to isolate the product. One example of each method is described.

Method A. Isolation by Extraction. Methyl β-(β-Mercaptoethylamino)isobutyrate, S-Sulfonic Acid (16e).—To a solution of 70 g. (0.28 mole) of sodium thiosulfate pentahydrate in 280 ml. of water was added 20.0 g. (0.14 mole) of methyl 3-(1′-aziridinyl)-2-methylpropanoate. The pH rose to 9.8. Then 232 ml. of 1.0 *M* hydrochloric acid was added, which brought the pH to 7.2. The product was extracted thoroughly with ether. The aqueous phase was then further acidified to pH 3.4 and the solution was freeze dried. The solid residue was extracted twice with hot ethanol. The ethanol solution was evaporated to dryness *in vacuo*, and the resulting oil was crystallized slowly at room temperature from 500 ml. of a hot 1:4 (v./v.) methanol–ethanol mixture, yielding 7.82 g. (22%) of **16e**, m.p. 137–143°. Three further recrystallizations gave 2.84 g. of analytical material, m.p. 142–145.5°.

On paper in a BuOH–HOAc–water system (4:1:5) the product moved as a single spot with an R_f of 0.5. The isoelectric point was 5.2.

Method B. Isolation by Ion-Exchange Chromatography. Ethyl β-Mercaptoethylaminoacetate, S-Sulfonic Acid (16c).—The pure liquid adduct, ethyl N-ethyleniminoacetate (**2e**, 15.0 g., 0.117 mole) was added to 32.02 g. of sodium thiosulfate pentahydrate, in 129 ml. of water. The pH rose to 9.4. Then 113.6 ml. of 1.03 *M* hydrochloric acid (0.118 mole) was added, bringing the pH down to 7.1. The total crude reaction mixture was then charged directly onto a 75-mm. o.d. ion-exchange column packed with 1.75 l. of Rohm and Haas resin IRA-400 pretreated as follows. The column (originally in the chloride form) was washed with 4 l. of 4% sodium hydroxide solution, followed by 8 l. of a 29% aqueous solution of sodium acetate trihydrate. The column finally was washed with distilled water (*ca.* 1 l.) until the effluent pH was 9.5. The column was eluted with 25 l. of a continuous gradient of acetic acid. The first 5 l. was 0.001 *M* acetic acid which verged to 15 l. of 0.05 *M* and finally shifted to 5 l. of 0.1 *M* acetic acid. T.l.c. was used to monitor the 285 fractions of 100 ml. each. Fractions 132–278 contained chromatographically pure product with an approximate maximum concentration in tube 203.

The product was obtained virtually pure on the freeze drying of the fractions in the range indicated. A representative aliquot from the combined fractions showed the presence of 19.6 g. (69%) of ethyl β-mercaptoethylaminoacetate, S-sulfonic acid (**16c**). Fractions 218–250 were freeze dried *in toto* and yielded 6.35 g. of crystals, infrared spectrum identical with the once-recrystallized (from ethanol) analytical sample, m.p. 119.5–120.5° (5.67 g.).

Method C. Isolation by Countercurrent Distribution. N-Isopropyl-β-(β-mercaptoethylamino)propionamide, S-Sulfonic Acid (16f).—A solution of 5.0 g. (32.1 mmoles) of N-isopropyl-3-(1′-aziridinyl)propionamide (**2l**) in water (10 ml.) was treated with 32.1 ml. of 1 *M* sodium thiosulfate solution. The product was then acidified to pH 5.2 with 6 *M* hydrochloric acid. From paper chromatography it was seen that the product had an R_f of somewhat less than 0.5 in a 1:1 butanol–water system, therefore this system was used for the countercurrent distribution. The total reaction product was diluted to 100 ml. with butanol-saturated water and placed in a 30-tube countercurrent apparatus which accommodated 100 ml. in each phase. The distribution was terminated after 55 transfers. The maximum concentration of amino acid was in tube 13 (K = 0.32). The product was isolated from tubes 8–18. The lower phases were freeze dried directly and the upper phases were combined with an equal volume of ether and extracted with water, and the aqueous fractions were freeze-dried. The total yield of crystalline product, m.p. 110–115°, was 4.5 g. (52%). Recrystallization was accomplished from acetonitrile–ether to yield 3.8 g. of analytically pure N-isopropyl-β-(β-mercaptoethylamino)propionamide, S-sulfonic acid (**16f**), m.p. 128–130°.

Sterically Crowded Amines. VI. Quaternary Salts from the Alkylation of Trimethylamine with *t*-Propargylic Chlorides[1]

G. F. HENNION AND C. V. DIGIOVANNA

Chemical Laboratories of the University of Notre Dame, Notre Dame, Indiana 46556

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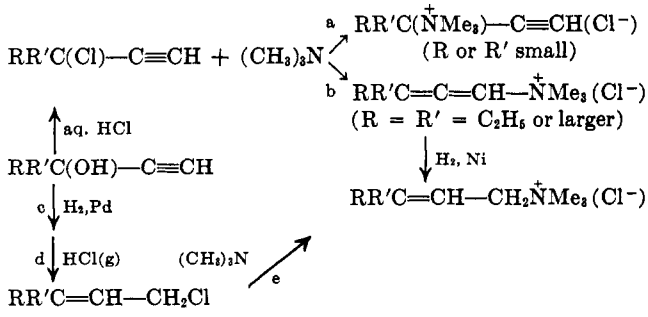
The reaction of trimethylamine with *t*-propargylic chlorides, RR′C(Cl)—C≡CH, produces quaternary ammonium chlorides; these have the propargylic structure when R *or* R′ is CH_3 and when RR′C comprise the cyclohexane ring. When R *and* R′ are larger than CH_3 (*e.g.*, R = R′ = C_2H_5), the products are allenic. The propargylic and the allenic products are believed to arise from intermediate zwitterion carbenes, (RR′$\overset{+}{C}$—C≡C$^-$ ⟷ RR′C=C=C:).

The alkylation of ammonia[2] and primary and secondary amines[3,4] with *t*-propargylic chlorides leads to the corresponding propargylic amines, and such reactions may be used to prepare amines characterized by a remarkably high degree of steric crowding about the nitrogen atom.[5] The products are believed to arise from stable zwitterion carbenes (RR′$\overset{+}{C}$—C≡C$^-$ ⟷ RR′C=C=C:), resistant to proton elimination from R or R′ and notably electrophilic at the tertiary carbon atom. Attempts to find halide–substrate combinations in which steric effects of necessity produce allenic amines have failed.[6] Several instances of steric control of this type have now been found, however, during a study of the reaction of *t*-propargylic chlorides with trimethylamine.



When R *or* R′ is small (one of them CH_3) or are parts of a cyclohexane ring, the products are quaternary *t*-propargylic ammonium salts (reaction a); when R *and* R′ are ethyl or larger, the isomeric allenic salts are formed (reaction b). In the original experiments the reactions were carried out with aqueous trimethyl-

(1) Paper No. 81 on substituted acetylenes; previous paper, G. F. Hennion and A. C. Hazy, *J. Org. Chem.*, **30**, 2650 (1965).
(2) G. F. Hennion and E. G. Teach, *J. Am. Chem. Soc.*, **75**, 1653 (1953).
(3) G. F. Hennion and K. W. Nelson, *ibid.*, **79**, 2142 (1957).
(4) G. F. Hennion and R. S. Hanzel, *ibid.*, **82**, 4908 (1960).
(5) G. F. Hennion and C. V. DiGiovanna, *J. Org. Chem.*, **30**, 2645 (1965).
(6) See, however, N. R. Easton, R. D. Dillard, W. J. Doran, M. Livezey, and D. E. Morrison, *ibid.*, **26**, 3772 (1961).