N-(Arylmercaptoalkyl) Amides by Reaction of Thiols with Amino Alcohols and Carboxylic Acids

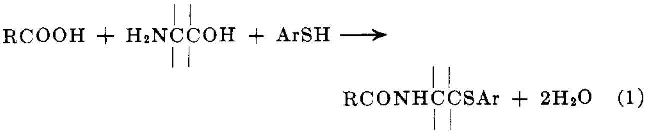
H. L. WEHRMEISTER

Research Department, Commercial Solvents Corporation, Terre Haute, Indiana

Received April 4, 1963

N-(Arylmercaptoalkyl) amides are obtained by reaction of aromatic thiols with amino alcohols and carboxylic acids. Structural requirements for the amino alcohol have in part been established. A reaction scheme involving the formation of cyclic intermediates is proposed. Arylmercaptoalkylamines are obtained on hydrolysis of the amides.

In a previous publication from this laboratory[1] it was reported that N-(arylmercaptoalkyl) amides are obtained on reaction of aromatic thiols with oxazolines. It has now been found that this type of product also is obtained by reaction of an aromatic thiol with a β-amino alcohol and a carboxylic acid (equation 1). Based on the previous work, the oxazoline is an assumed intermediate. This new route to these amides is generally preferable to that using the oxazoline since it eliminates the need for the preparation and isolation of the oxazoline and materially increases the over-all yield. This is especially significant, for example, with ethanolamine. Yields of less than 30% have been reported[2] for the preparation of an oxazoline by reaction of ethanolamine with an acid. Yields to the phenylmercaptoalkyl amide could not exceed this if the oxazoline has to be isolated. The one-step reaction of ethanolamine with benzenethiol and propionic acid, however, resulted in an 88% yield of N-(2-phenylmercaptoethyl)propionamide.



$$\mathrm{RCOOH + H_2N\overset{|}{\underset{|}{C}}\overset{|}{\underset{|}{C}}OH + ArSH \longrightarrow RCONH\overset{|}{\underset{|}{C}}\overset{|}{\underset{|}{C}}SAr + 2H_2O} \quad (1)$$

A variety of β-amino alcohols has been used. Included are those with the amino group on primary, secondary, and tertiary carbon atoms, and with the hydroxyl group on primary and secondary carbon atoms.

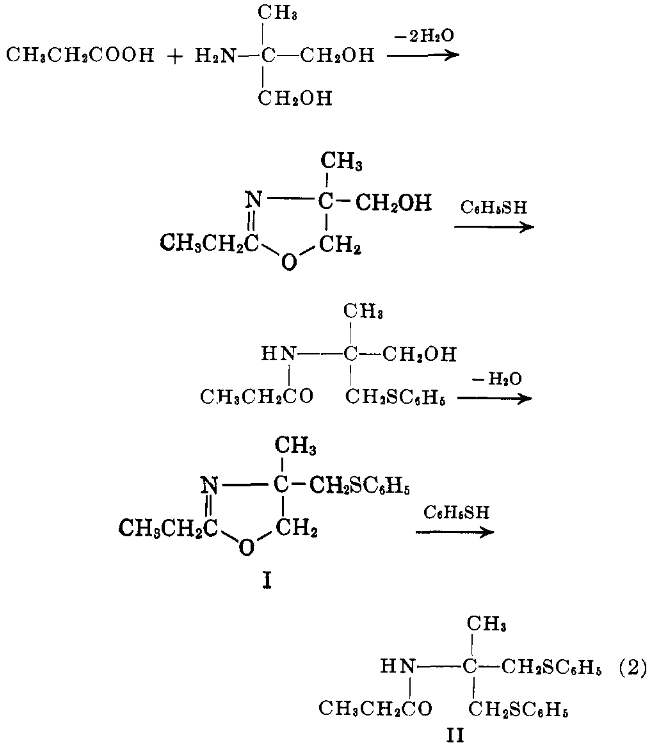
This reaction has been extended to an amino diol and an amino triol. A mixture of products is obtained on reaction of equimolar quantities of benzenethiol, propionic acid, and 2-amino-2-methyl-1,3-propanediol. This mixture contains both 2-ethyl-4-methyl-4-phenylmercaptomethyl-2-oxazoline (I) and N-[1,1-bis(phenylmercaptomethyl)ethyl]propionamide (II). Product II is the predominant one at a 2:1 molar ratio of thiol to diol.

N-[Tris(phenylmercaptomethyl)methyl]propionamide (III) is obtained on reaction of benzenethiol with propionic acid and tris(hydroxymethyl)aminomethane.

$$\mathrm{CH_3CH_2CONHC(CH_2SC_6H_5)_3}$$

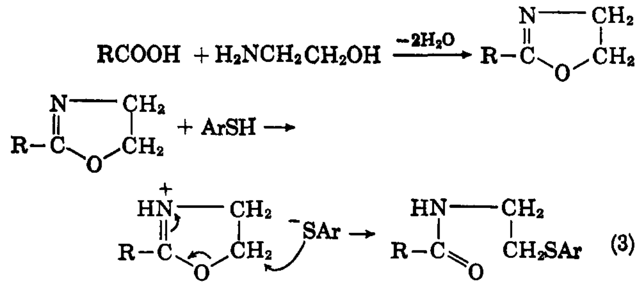
III

In these reactions of diols and triols it is assumed that an oxazoline is first formed, which then reacts with the thiol to yield an intermediate which can again form an oxazoline and again react with more of the thiol, until all of the thiol is consumed or all of the hydroxyl groups are replaced by phenylmercapto groups. This scheme is outlined for the amino diol (equation 2).



The reaction of benzenethiol with 3-amino-1-propanol and propionic acid gave N-(3-phenylmercaptopropyl)-propionamide. Here, oxazoline formation is precluded. The intermediate formation of a dihydrooxazine is a likely possibility. Benzenethiol failed to react with 4-amino-1-butanol and propionic acid, supporting the premise that a cyclic intermediate (oxazoline or dihydrooxazine) is involved.

As a possible mechanism for these reactions, it is proposed that the carboxylic acid first reacts with the amino alcohol to yield an oxazoline or dihydrooxazine. The oxazoline or dihydrooxazine can then react further by attack of mercaptide ion (equation 3).



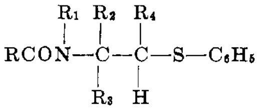
An alternative mechanism involving rearrangement of the oxazoline to an acylated aziridine, followed with ring opening by the thiol, is excluded since isomeric

---

[1] H. L. Wehrmeister, *J. Org. Chem.*, **28**, 2587 (1963).

[2] H. Wenker, *J. Am. Chem. Soc.*, **57**, 1079 (1935).

TABLE I

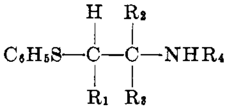


$$\mathrm{RCON(R_1)\text{—}C(R_2)(R_3)\text{—}C(R_4)(H)\text{—}S\text{—}C_6H_5}$$

No.	R	R_1	R_2	R_3	R_4	Yield,[a] %	B.p.,[a] °C. (mm.)	M.p.,[b] °C.	N, %[b] Calcd.	N, %[b] Found	S, %[b] Calcd.	S, %[b] Found
1	C_2H_5	H	H	H	H	88	125–173 (0.3)	76–77	6.69	6.34	15.32	15.20
2	CH_3	H	H	H	CH_3	80[c]	150 (0.25)–140 (0.22)	45–46	6.69	6.45	15.32	16.45
						50	152–153.5 (0.08)					
3	CH_3	H	CH_3	H	H	80	140–150 (0.2)	88.5–89.5	6.69	6.36	15.32	15.84
4	C_2H_5	H	CH_3	CH_3	H	80	145–153 (0.3)	47.5–48.5[d]	5.90	5.47	13.50	12.85
5	C_6H_5	H	CH_3	CH_3	H	57[e]		76–77[f]	4.91	4.78		
6	C_2H_5	H	C_2H_5	H	CH_3	91	144–150 (0.1)	53–54	5.57	5.45	12.75	13.29
7	C_2H_5	CH_3	H	H	H	88	137–148 (0.2)[g]		6.27	6.15	14.35	14.71
							154–158 (0.05)					

[a] Of distilled material. [b] Of recrystallized material. [c] Of crude material which could not be crystallized. Redistillation yielded material which could be recrystallized. [d] Lit.[1] m.p. 48–49°. [e] The reaction mixture was crystallized directly from hexane. [f] Lit.[1] m.p. 80.5–81°. [g] An oil which could not be crystallized. Redistillation through a packed column also yielded an oil. The analyses are of the redistilled oil.

TABLE II



$$\mathrm{C_6H_5S\text{—}C(H)(R_1)\text{—}C(R_2)(R_3)\text{—}NHR_4}$$

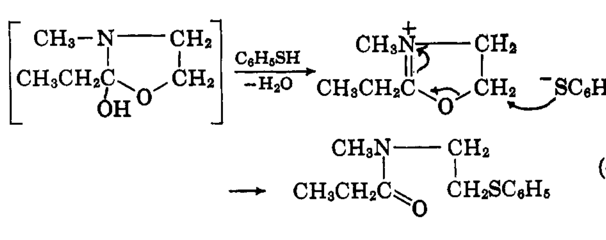
Amide no.	R_1	R_2	R_3	R_4	Yield, %	B.p., °C. (mm.)	N, % Calcd.	N, % Found	S, % Calcd.	S, % Found	Neut. equiv. Calcd.	Neut. equiv. Found
1	H	H	H	H	83	84–86(0.2)[d]	9.14	9.05	20.93	20.29 19.91	153.2	154.6
2	CH_3	H	H	H	78	111–113(4.0)[a]	8.37	8.89	19.16	19.73	167.3	168.3
3	H	CH_3	H	H	86	112–114(4.0)[b]	8.37	8.77	19.16	19.64	167.3	168.1
6	CH_3	H	C_2H_5	H	22[c]	124–127(4.0)	7.17	7.17 7.26	16.42	16.88	195.3	196.3
7	H	H	H	CH_3	82	112–112.5(4.0)	8.37	8.56	19.16	19.76	167.3	168.4

[a] Benzamide derivative, m.p. 86–87°. Calcd. for $C_{16}H_{17}NOS$: N, 5.16; S, 11.81. Found: N, 5.03; S, 11.73. [b] Benzamide derivative, m.p. 128–129°. Calcd. for $C_{16}H_{17}NOS$: N, 5.16; S, 11.81. Found: N, 4.88; S, 11.72. [c] Approximately 60% of the amide was recovered. [d] Lit. b.p. 90–95° (0.2 mm.); A. E. Senear, M. M. Rapport, and J. B. Koepfl, *J. Biol. Chem.*, **167**, 229 (1947).

products are obtained on reaction of the isomeric amino alcohols, 2-amino-1-propanol and 1-amino-2-propanol, with benzenethiol and acetic acid. Identical products or product mixtures would be expected if a common intermediate were involved.

2-(Methylamino)ethanol reacts with benzenethiol and propionic acid to yield N-methyl-N-(2-phenylmercaptoethyl)propionamide. In this case oxazoline formation is not possible. A mechanism involving the transient formation of a quaternized oxazoline derivative is suggested to account for the results obtained (equation 4).

$$\mathrm{CH_3CH_2COOH + CH_3NHCH_2CH_2OH \xrightarrow{-H_2O}}$$
$$\mathrm{CH_3CH_2CON(CH_3)CH_2CH_2OH \longrightarrow}$$



(4)

N,N-Bis(2-phenylmercaptoethyl)propionamide was obtained on reaction of benzenethiol with diethanolamine and propionic acid.

As expected, benzenethiol failed to react with propionic acid and the tertiary amino compound, 2-(dimethylamino)ethanol.

A relatively poor yield (35%) of N-methyl-N-(2-dodecylmercaptoethyl)acetamide was obtained on reaction of dodecanethiol with 2-(methylamino)ethanol and acetic acid. The reaction of aliphatic thiols with amino alcohols and acids is receiving further study.

The structures of the various products were established by analysis and infrared spectra, in some instances by comparison with previously prepared materials, and in most instances by hydrolysis to phenylmercaptoalkylamines.

Experimental[3]

Starting Materials.—Acetic acid,[4] propionic acid,[5] benzoic acid,[6] benzenethiol,[7] dodecanethiol,[8] 2-aminoethanol,[9] 2-amino-2-methyl-1-propanol,[5] 3-amino-1-propanol,[10] 4-amino-1-butanol,[11] 2-amino-2-methyl-1,3-propanediol,[5] tris(hydroxymethyl)aminomethane,[5] 2-(methylamino)ethanol,[8] diethanolamine,[12] and 2-(dimethylamino)ethanol[7] were used as received.

The following amino alcohols were prepared in these laboratories by reduction of the corresponding nitro alcohols, obtained in turn from the appropriate nitroparaffin and aldehyde: 1-amino-2-propanol [neut. equiv., 75.1 (calcd.), 75.6 (found)];

---

(3) Boiling points and melting points are uncorrected. All melting points were taken on a Fisher-Johns apparatus.

(4) Reagent grade, Allied Chemical Co.

(5) Commercial Solvents Corp.

(6) Analytical reagent grade, Mallinckrodt Chemical Works.

(7) Matheson Coleman and Bell.

(8) Distillation Products Industries.

(9) Purified grade, Fisher Scientific Co.

(10) American Cyanamid Co.

(11) Calbiochem Co.

(12) Union Carbide Chemicals Corp.

2-amino-1-propanol [neut. equiv., 75.1 (calcd.), 76.7 (found)]; and 3-amino-2-pentanol [neut. equiv., 103.2 (calcd.), 101.5 (found)].

N-(Phenylmercaptoalkyl) Amides. General Procedure.—A mixture of molar quantities of benzenethiol, an amino alcohol, and a carboxylic acid in 50 ml. of benzene was heated at reflux under an 18-in. Vigreux column with azeotropic removal of water. Reflux periods ranged from 6 to 14 hr. at pot temperatures of 134 to 202°.[13] After the reactions were essentially complete, the mixtures were distilled through an 18-in. Vigreux column. The distilled products, generally of better than 90% purity, were recrystallized to a constant melting point from either hexane, hexane–benzene, or ether.

Results are given in Table I and elsewhere in this report.

Phenylmercaptoalkylamines.—The phenylmercaptoalkyl amides can be hydrolyzed by the following general procedure.

A mixture of 0.3 mole of the amide in 100 ml. of concentrated hydrochloric acid is heated at reflux for 3–48 hr. Aqueous 50% sodium hydroxide solution (50 ml.) is added to the cooled hydrolysate and the alkaline mixture is extracted with three 100-ml. portions of benzene. The dried (sodium carbonate or sodium sulfate) extract is distilled finally at reduced pressure to yield the phenylmercaptoalkyamine. The results are given in Table II and elsewhere.

N-(3-Phenylmercaptopropyl)propionamide.—Molar quantities of 3-amino-1-propanol, benzenethiol, and propionic acid in 50 ml. of benzene were heated together with azeotropic removal of water as in the general procedure. There was obtained 35.8 ml. of water in 16 hr. at pot temperatures of 122–216°. Distillation through an 18-in. Vigreux column yielded 199 g. of product, b.p. 139 (0.1 mm.)–178° (0.2 mm.).

Anal. Calcd. for $C_{12}H_{17}NOS$: N, 6.27; S, 14.35. Found: N, 6.52.

The distilled product was crystallized from a mixture of hexane and benzene to a constant melting point of 66–67°.

Anal. Found: N, 5.76, 6.19; S, 15.06, 14.18.

3-Phenylmercaptopropylamine.—Hydrolysis of 44.7 g. of N-(3-phenylmercaptopropyl)propionamide by the general procedure yielded 25.5 g. of product, b.p. 125–126° (4.0 mm.).

Anal. Calcd. for $C_9H_{13}NS$: N, 8.37; S, 19.16; neut. equiv., 167.3. Found: N, 8.53; S, 19.37, 19.34; neut. equiv., 169.9.

2-Ethyl-4-methyl-4-phenylmercaptomethyl-2-oxazoline (I) and N-[1,1-Bis(phenylmercaptomethyl)ethyl]propionamide (II).—A stirred mixture of half-molar quantities of 2-amino-2-methyl-1,3-propanediol, benzenethiol, and propionic acid in 100 ml. of benzene was heated at reflux for 4 hr., pot temperature 134–203°, with azeotropic removal of 24 ml. of water. Distillation of the residue yielded the results shown in Table III.

Table III

Cut	Boiling range, °C. (mm.)	Wt., g.	Neut. equiv.	% N	% S
1	99–110 (10)	17.6	167.8	8.27	1.18
2	104–114 (0.2)	15.4			
3	114–116 (0.2)	26.0	233.7	6.09	13.28
4	116–207 (0.2)	11.8			
5	207–221 (0.1)	47.8	>6500	4.25	18.16

Anal. Calcd. for 2-ethyl-4-methyl-4-hydroxymethyl-2-oxazoline (a), $C_7H_{13}NO_2$: N, 9.78; S, 0.0; neut. equiv., 143.2.

Anal. Calcd. for I, $C_{13}H_{17}NOS$: N, 5.95; S, 13.63; neut. equiv., 235.3.

Anal. Calcd. for II, $C_{19}H_{22}NOS_2$: N, 4.07; S, 18.61; neut. equiv., nonbasic.

On the basis of these analyses and some supporting hydrolysis studies (described subsequently), cut 1 is believed to be mainly a with some I. Cut 3 is I and cut 5 is II.

Product II, b.p. 215–224° (0.1 mm.), was obtained in a 48% yield in a comparable run but using a 2:1:1 ratio of benzenethiol, 2-amino-2-methyl-1,3-propanediol, and propionic acid.

Anal. Found: N, 4.25; S, 18.23; neut. equiv., >11,500.

Product I also was obtained in approximately 15% yield as a crude distillate.

Anal. Found for cut 1, b.p. 118–125° (0.2 mm.): N, 5.61; S, 14.47; neut. equiv., 248.6. Found for cut 2, b.p. 125–130° (0.2 mm.): N, 6.24; S, 15.26; neut. equiv., 228.4.

3-Phenylmercapto-2-amino-2-methyl-1-propanol.—2-Ethyl-4-methyl-4-phenylmercaptomethyl-2-oxazoline was hydrolyzed by heating 20.3 g. with 40 ml. of 6 *N* hydrochloric acid at reflux for 3 hr. To the cooled hydrolysate was added 25 ml. of 50% sodium hydroxide solution, and the resulting mixture was extracted with two 50-ml. portions of benzene. Distillation yielded 14.3 g. (84%) of product, b.p. 125–127° (0.2 mm.).

Anal. Calcd. for $C_{10}H_{15}NOS$: N, 7.10; S, 16.25; neut. equiv., 197.3. Found: N, 6.99; S, 15.70; neut. equiv., 200.5.

N-[Tris(phenylmercaptomethyl)methyl]propionamide (III).—A mixture of 30.3 g. (0.25 mole) of tris(hydroxymethyl)aminomethane, 90 g. (0.82 mole) of benzenethiol, and 20 g. (0.27 mole) of propionic acid in 50 ml. of xylene was heated at 150–173° for 5 hr. with azeotropic removal of 16.2 ml. of water. The residue was crystallized from a hot mixture of 2300 ml. of hexane and 500 ml. of benzene. Several crops of crystals were obtained: (1) 52.9 g., m.p. 97–99°; (2) 5.0 g., m.p. 104–107°; (3) 4.5 g., m.p. 104–107°. The total yield of crystallized product is 55%. Material for analysis was recrystallized from ethanol to a constant melting point of 122–123°.

Anal. Calcd. for $C_{25}H_{27}NOS_3$: N, 3.09; S, 21.20. Found: N, 2.93; S, 20.49, 20.51.

N,N-Bis(2-phenylmercaptoethyl)propionamide.—A mixture of 52.5 g. (0.5 mole) of diethanolamine, 110 g. (1.0 mole) of benzenethiol, and 37 g. (0.5 mole) of propionic acid in 50 ml. of benzene was heated at 142–174° for 7 hr. with azeotropic removal of 27.4 ml. of water. Distillation yielded 154.6 g. (89%) of product, b.p. 218 (0.4 mm.)–239° (0.5 mm.).

Anal. Calcd. for $C_{19}H_{23}NOS_2$: N, 4.05; S, 18.56. Found: N, 4.26; S, 19.35.

Bis(2-phenylmercaptoethyl)amine.—A mixture of 35 g. of N,N-bis(2-phenylmercaptoethyl)propionamide and 100 ml. of concentrated hydrochloric acid was heated at reflux for 34 hr. To the cooled hydrolysate was added 100 ml. of water and 100 ml. of 50% sodium hydroxide. The mixture was extracted with three 100-ml. portions of benzene, and the extract was distilled.

There was obtained 20.2 g. (70%) of product, b.p. 187–193° (0.05 mm.).

Anal. Calcd. for $C_{16}H_{19}NS_2$: N, 4.84; S, 22.16; neut. equiv., 289.4. Found: N, 5.03; S, 21.98; neut. equiv., 290.9.

N-Methyl-N-(2-dodecylmercaptoethyl)acetamide.—A stirred mixture of half-molar quantities of dodecanethiol, 2-(methylamino)ethanol, and acetic acid in 50 ml. of benzene was heated at 166–197° for 8 hr. with azeotropic removal of 16 ml. of water. Distillation through an 18-in. Vigreux column yielded 63 g. of crude material, b.p., 118–205° (0.5 mm.). Redistillation yielded 53.4 g. (35%) of material, b.p., 165–174° (0.1 mm.).

Anal. Calcd. for $C_{17}H_{35}NOS$: N, 4.65; S, 10.63. Found: N, 5.16; S, 10.09.

Reaction of 4-Amino-1-butanol with Benzenethiol and Propionic Acid.—A mixture of 22.5 g. (0.25 mole) of 4-amino-1-butanol, 27.5 g. (0.25 mole) of benzenethiol, and 18.5 g. (0.25 mole) of propionic acid was heated at 147–181° for 7 hr. with azeotropic removal of 4.7 ml. of water. Distillation yielded 25.1 g. of a, b.p. 65–115° (20 mm.), and 31.0 g. of b, b.p. 130–150° (0.08 mm.). Product a was mostly unchanged thiol, while product b is probably impure N-(4-hydroxybutyl)propionamide.

Anal. Calcd. for $C_7H_{15}NO_2$: N, 8.91; S, 0.0. Found for b: N, 9.47; S, 2.41.

About 87.5% of unchanged thiol was accounted for. Very little if any reaction took place that involved the thiol.

Reaction of Dimethylaminoethanol with Benzenethiol and Propionic Acid.—A mixture of half-molar quantities of dimethylaminoethanol, benzenethiol, and propionic acid in 50 ml. of benzene was heated at 120–145° for 8 hr. with azeotropic removal of 13 ml. of water. At least 90% of the thiol was recovered by distillation. Some alkaline material, presumably dimethylaminoethyl propionate, was obtained in good yield but was not purified sufficiently for analysis.

Very little, if any, reaction took place involving the thiol.

Infrared Spectra.—The infrared spectra of the N-(arylmercaptoalkyl) amides appear consistent with the assigned structures. All had bands at about 6.05 μ (C=O), and all but those derived from secondary amino alcohols had bands at about 3.05 μ (NH).

---

(13) Removal of part of the benzene from the separator was necessary to obtain the higher pot temperatures indicated.