accompanied by decarboxylation, esters of 2,3,4,5-tetrachlorobenzoic acid being obtained. This decarboxylation appears to be catalyzed by the addition of alkaline materials.

3. Several new esters of tetrachlorophthalic acid and 2,3,4,5-tetrachlorobenzoic acid have been prepared and improved syntheses have been developed for 2,3,4,5-tetrachlorobenzoic acid and 1,2,3,4-tetrachlorobenzene.

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[CONTRIBUTION FROM THE RESEARCH LABORATORY OF ENDO PRODUCTS, INC.]

N-Arylamides of Mercaptoacetic Acid. I. Analogs of α-Carbamylmercaptoacetanilide

BY ULRICH WEISS

The carbamyl compounds I have been prepared

$$Ar—N(R)—CO—CH_2—S—X$$
$$I,\ X = —CONH_2$$
$$II,\ X = —H$$

as intermediates for making the desired N-arylmercaptoacetamides II.[1]

The known compounds of this type[2] have been obtained by interaction of an aromatic amine with thiocyanoacetic acid: $Ar—NH_2 + COOH—CH_2—SCN = Ar—NH—CO—CH_2—S—CONH_2$, this acid being usually generated during the reaction from chloroacetic acid and an alkali thiocyanate.[3] In a few instances, however, interaction of the base with the free acid in ether,[4] or, in the case of aniline, of the hydrochloride with sodium thiocyanoacetate in aqueous solution[5] has been used. This latter modification was found to be the most satisfactory one in our experiments.

In slightly acidic aqueous solution of molar equivalents of aromatic amine hydrochloride and sodium thiocyanoacetate, crystallization of compounds of type I usually starts at room temperature within a short time and gives in many cases (after about two days) yields up to 85–90% of the nearly pure compound.[6] Where results are less satisfactory, reaction of the base with thiocyanoacetate in dilute acetic acid may be advantageous.

The reaction seems quite general and characteristic for aromatic amines, only a small number of those tested proving unreactive,[7a] while none of a wide variety of non-aromatic amino-compounds gave a water-insoluble compound of type I.[7b]

As postulated by Rizzo,[8] the reaction appears to proceed through formation and subsequent isomerization of the thiocyanoacetate of the base. Such salts have actually been isolated from reaction of hydrazine and derivatives with free thiocyanoacetic acid in ether[4c] and found to rearrange readily to compounds of type I. In the experiments reported here, four such salts have been obtained from aqueous solutions. Three of them, derived from "unreactive" amines (cyclohexylamine, α-aminopyridine, 2-aminothiazole), failed to rearrange to compounds of type I. The salt of 2,6-dimethylaniline (*vic.-m*-xylidine) crystallized from an aqueous solution of the components, due to its low solubility. It rearranges to I ($Ar—N(R) = 2,6\text{-}(CH_3)_2—C_6H_3—NH—$) either in the dry state, or upon warming of its aqueous or alcoholic solutions, or if it is brought back into solution by dilution of the original reaction mixture. Solutions of the pure salt in water or organic solvents are stable at room temperature; the rapid formation of I in the original reaction mixture must therefore be due to some catalytic influence. No other salts of "reactive" amines were observed; attempts to prepare the aniline salt yielded only I ($Ar—N(R)— = C_6H_5—NH—$).

Experimental

Preparation of Carbamyl Compounds II, General Procedure.—A. In Aqueous Solution.—One-tenth mole of the base is suspended in 100 cc. of water, and brought into solution with the minimum amount of dilute hydrochloric acid; 0.1 mole = 15.7 g. of sodium thiocyanoacetate, $NaOCO—CH_2—SCN\cdot H_2O$,[9] in about 10% aqueous solution is added. If the mixture is not acidic enough to give a slight bluish-gray color to congo paper, dilute hydrochloric acid is added; if the free base precipitates from the solution of its hydrochloride upon addition of the thiocyanoacetate, it is redissolved rapidly by addition of dilute hydrochloric acid (1:1), avoiding an excess. Crystalliza-

(1) Paper II, Weiss, THIS JOURNAL, **69**, 2684 (1947).

(2) $Ar—N(R)— = C_6H_5—NH—$, $C_6H_5—N(CH_3)—$, *p*-$Cl—C_6H_4—NH—$, *o,m,p*-$CH_3—C_6H_4—NH—$, 2,4,5-$(CH_3)_3—C_6H_2—NH—$, α,β-$C_{10}H_7—NH—$, *p*-$CH_3—O—C_6H_4—NH—$, *p*-$C_2H_5—O—C_6H_4—NH—$, $C_6H_5—NH—NH—$, $C_6H_5—N(CH_3)—NH—$, *p*-$CH_3—C_6H_4—NH—NH—$. *Cf.* (a) Jaeger, *J. prakt. Chem.*, [2] **16**, 17 (1877); (b) Beckurts and Frerichs, *ibid.*, **66**, 172 ff (1902), and later papers by Frerichs, *et al.*; (c) Rheinboldt, Tappermann and Kleu, *ibid.*, **153**, 65 (1939).

(3) α-Halogenopropionic and butyric acids undergo analogous reactions.

(4) (a) Claesson, *Ber.*, **14**, 732 (1881); (b) Harries and Klamt, *ibid.*, **33**, 1154 (1900); (c) Frerichs and Foerster, *Ann.*, **371**, 229 ff. (1909).

(5) Ref. 2b, p. 173; *cf.* the analogous reaction of α-thiocyanopropionic acid: Fredga, *J. prakt. Chem.*, [2] **123**, 110 (1929).

(6) The smooth formation of a —CO—NH— bond under such mild conditions is certainly remarkable.

(7) (a) Unreactive aromatic amines: *o*-nitraniline, 2-aminoresorcinol, diphenylamine, sulfanilic acid; (b) non-aromatic amino compounds tested: hydroxylamine, urea, thiourea, acetamidine, glycine, glycine ethyl ester, glutamic acid, cyclohexylamine, α-amino-pyridine, 2-amino-thiazole. The unidentified product obtained from semicarbazide is not of type I; see experimental part. It may be of interest that all reactive compounds are aromatic amines (or hydrazines) with pK-values between about 10^{-9} and 10^{-12}. The unreactive *o*-nitraniline, *e. g.*, differs from its reactive isomers by $pK \approx 10^{-14}$ against $\approx 10^{-12}$.

(8) Rizzo, *Gazz. chim. ital.*, **28**, I, 360 (1893).

(9) Prepared by the method of Claesson, *Ber.*, **10**, 1347 (1877).

TABLE I

N-Aryl-α-carbamylmercaptoacetamides, Ar—N(R)—CO—CH_2—S—$CONH_2$

Ar—N(R)—	Yield, proced. A	M. p., °C.[13]	—Analyses,[14] % N— Calcd.	Found
C_6H_5—N—(CH_3)—	82	147[a]		
C_6H_5—N(—CH_2—C_6H_5)—[b,c]		144	9.33	9.40
o-CH_3—C_6H_4—NH—[d]	77	133[e]		
p-CH_3—C_6H_4—NH—[d]	82	187[f]	12.49	12.47
3,4-$(CH_3)_2$—C_6H_3—NH—[g]	63	157	11.76	11.91
2,6-$(CH_3)_2$—C_6H_3—NH—[h]	64	160	11.76	11.49
o-C_6H_5—C_6H_4—NH—[h,i]	Very small	159	9.78	9.67
α-$C_{10}H_7$—NH—[j]	50	171–173[w]		
β-$C_{10}H_7$—NH—[k,l]	53	197[m]		
p-CH_3—CO—C_6H_4—NH—[n]	57	196	11.10	10.88
m-NO_2—C_6H_4—NH—[o]		156	16.47	16.57
p-NO_2—C_6H_4—NH—[p]	20	197[q]	16.47	16.46
o-OH—C_6H_4—NH—	83	184	12.39	12.41
m-OH—C_6H_4—NH—	85	176	12.39	12.46
p-OH—C_6H_4—NH—	84	190	12.39	12.50
o-CH_3—O—C_6H_4—NH—	90	172	11.66	11.45
p-CH_3—O—C_6H_4—NH—[d]	77	172[r]		
o-COOH—C_6H_4—NH—	71	188–190	11.02	10.83
p-COOH—C_6H_4—NH—[s]	67	215	11.02	11.18
p-C_2H_5—O—CO—C_6H_4—NH—[b]	48	146	9.92	9.78
2-OH,5—$COOCH_3$—C_6H_3—NH—[d]	70	205	9.85	9.66
p-COOH—CH_2—C_6H_4—NH—[t]	73	194	10.44	10.26
p-ASO_3H_2—C_6H_4—NH—	43		8.38	8.24
p-NH_2—SO_2—C_6H_4—NH—	61	215–217.5	14.53	14.49
p-C_5H_4N—NH—SO_2—C_6H_4—NH— (sulfapyridine)	40	190	15.29	15.09
p-C_3H_2NS—NH—SO_2—C_6H_4—NH— (sulfathiazole)[b]	48	192–194	15.20	15.05
p-$C_4H_3N_2$—NH—SO_2—C_6H_4—NH— (sulfadiazine)	13[l]	203–205[q]	19.06	18.78
C_6H_5NH—NH—[u]	Very small	157[v]		

[a] Ref. 2b, page 181: 147°; ref. 2c, page 68: 142–143°. [b] Recrystallized from ethanol, acidified with a few drops of aqueous hydrochloric acid. [c] Procedure B, yield 8%. Compound forms very slowly (two to three weeks). [d] Recrystallized from methanol, acidified as in [b]. [e] Beckurts, Frerichs and Beyer, *J. prakt. Chem.*, [2] **74**, 38 (1906): 123–124°. [f] Ref. 2a, p. 22: 176–182°; ref. *e*, p. 47: 196°. [g] Procedure B, yield 76%. Product is impure. [h] Recrystallized from methanol acidified as in[b], or hydrochloric acid. [i] Procedure B, yield 50%. [j] Procedure B, yield 78%. [k] Procedure B, yield 77%. Product is impure. [l] Recrystallized from ethanol or acetic acid, acidified as in [b]. [m] Frerichs and Wildt, *Ann.*, **360**, 116 (1908): 185–186°; ref. 2c, p. 73: 180–181°. [n] Procedure B, yield 64%. Product is impure. [o] Procedure B, yield 42%. [p] Procedure B, yield 46%. Product is impure. [q] Light yellow crystals; all attempts to secure a colorless, product unsuccessful. [r] Beckurts and Frerichs, *Arch. d. Pharm.*, **253**, 137 (1915): 160–161°. [s] Recrystallized from acetic acid, acidified as in [b]. [t] Compound forms very slowly (two to three weeks). [u] Procedure B, yield 35%. [v] Harries and Klamt, *Ber.*, **33**, 1154 (1900): m. p. 149°; ref. 2b, p. 193: 149°; ref. 4c, p. 246: 149°. [w] Ref. *m*, m. p., 65°.

tion of the carbamyl compound usually starts within a short time. In case of delay, seed-material can be obtained by heating a small sample of the solution on the steam-bath for a few minutes, and chilling. After two or three days, the product is filtered by suction, washed with dilute hydrochloric acid, followed by water, and dried. In the mother-liquors, addition of another 15.7 g. of thiocyanoacetate often brings about crystallization of an additional crop. The products obtained are generally very pure.

B. In Dilute Acetic Acid.—The base is dissolved, at room temperature, in the minimum amount of acetic acid, and the aqueous solution of a stoichiometric quantity of sodium thiocyanoacetate is added. The mixture is diluted with water; any precipitate of the base is brought back into solution by addition of a small quantity of acetic acid, and the mixture is worked up after one to two days, as in A. Products prepared by this modification are sometimes contaminated with an impurity which is hard to remove. For this reason, procedure A has been followed wherever possible.

The compounds are generally well crystallized, insoluble in cold water, more or less soluble in hot methanol, ethanol, acetic acid or 0.1 *N* hydrochloric acid. This last solvent often affords particularly fine recrystallization and has been used for preparation of many of the analytical samples, but only few of the compounds (derivatives of *p*-aminophenol, phenylhydrazine) are sufficiently soluble in the boiling acid to permit use of this solvent for preparative purposes.

The products are very sensitive to alkalies, and are decomposed by boiling water[8] and to a small extent even by boiling methanol or ethanol. This decomposition is suppressed in acidic medium[10]; crystallizations from methanol or ethanol should therefore be carried out with addition of a few drops of hydrochloric acid. It may be due to failure to recognize this sensitivity to boiling alcohols, that the melting points of compounds described in the literature have been reported as much as 12° below those observed by the author.[11]

Characteristic decomposition, with formation of cyanuric acid, occurs also at about 170–200°, and can be observed in the melting point apparatus in those compounds which melt without decomposition below approximately 200°.[12]

(10) *Cf.* Battegay and Krebs, *Compt. rend.*, **206**, 1262 (1938), who found a *p*H of approximately 3 optimal for the stability of the closely related thiourethan, C_2H_5—S—CO—NH_2.

(11) The m. p. of the *p*-toluidide, found about 9° below the literature value (see Table I), is an unexplained exception.

(12) Reported for the anilide by Beckurts and Frerichs (ref. 2b, p. 181), by Pinner, *Ber.*, **14**, 1083 (1881), for thiourethan.

The compounds give fairly stable, brownish-red colors with sodium nitroprusside and alcoholic alkali, in contrast to the transient purple given by the salts of thiocyanoacetic acid.

Alkaline lead solutions give yellow precipitates upon gentle warming[10]; in case of compounds with acidic substituents, the precipitate appears upon acidification.

Selenium oxychloride in concentrated sulfuric acid gives intense colorations, identical with those of the corresponding mercapto-compounds, except for transient differing shades sometimes developing in the first few seconds (see the following paper for details).

The individual compounds and their properties are listed in Table I. The A procedure was in general followed in their preparation; where this was not the case, this is indicated by a footnote. The yields in every case are those obtained upon interaction of stoichiometric quantities of the reactants. Higher yields may be attained by use of excess thiocyanoacetate. The recrystallization was in general carried out in water, acidified with a few drops of approximately 0.1 *N* hydrochloric acid. Where other solvents were employed, these are indicated by footnotes.

Samples of the three aminophenol derivatives were first prepared by Mr. M. J. Lewenstein, of these laboratories, who is applying for U. S. patents. The author, who continued the work on them is much indebted to Mr. Lewenstein for his permission to include those compounds in this report.

Reaction of Semicarbazide with Sodium Thiocyanoacetate.—One-tenth molar quantities of semicarbazide hydrochloride (11.1 g.) and sodium thiocyanoacetate (15.7 g.) were dissolved together in 200 cc. of water. The solution was adjusted to a *p*H of approximately 3 and seeded. The product was worked up after four days, as described in A. Yield was 14.3 g., m. p. 185–186° (dec.),[13] 187° (dec.), after crystallization from 0.1 *N* hydrochloric acid. The nitroprusside reaction was purple, and the color rather more stable than the one given by salts of thiocyanoacetic acid. Selenium oxychloride in concentrated sulfuric acid gives a cloudy, yellowish solution with gas developing.

(13) All m. p.'s are corrected.

Anal. Calcd. for $C_4H_3N_4O_3S$: N, 33.31. Found: N, 15.05.[14]

Salts of Thiocyanoacetic Acid. A.—Three and five-tenths grams of α-aminopyridine hydrochloride and 4.2 g. of sodium thiocyanoacetate were dissolved together in 25 cc. of water at 45°. The solution was filtered, and chilled in ice–salt mixture. The salt crystallizes within a short time in well-formed flat needles.

Yield was 3.0 g.; m. p. 112° dec. With sodium nitroprusside it gives an intense, transient purple color, with a solution of cupric chloride a deep purplish black precipitate[9] is formed after about fifteen minutes. Alkali liberates α-amino-pyridine. Corresponding salts of cyclohexylamine (m. p. 110.5–111.5°) and α-aminothiazole (m. p. 127–128° dec.) were obtained in a similar way.

B. 2,6-Dimethylaniline (2.42 g., b. p. 212–216°) was suspended in 20 cc. of water, and brought into solution by addition of the minimum quantity of dilute hydrochloric acid (1:1). A solution of 3.14 g. of sodium thiocyanoacetate in 20 cc. of water was added. Crystallization of platelets started within a few minutes. The product was filtered within five minutes, by suction, washed with some ice-cold water, and dried *in vacuo* over phosphorus pentoxide. It melts incompletely about 85°, becoming clear at about 140°. No cyanuric acid appears upon further heating. It is moderately soluble in water, very soluble in methanol, chloroform, ether, benzene and pyridine. (Other reactions as described under A.)

Acknowledgment.—The author is much indebted to Drs. S. M. Gordon and N. Weiner for their interest, to Mr. S. Sokol for assistance in part of the experiments.

Summary

A number of N-aryl-α-carbamylmercaptoacetamides has been prepared from the corresponding amines and sodium thiocyanoacetate in aqueous solution at room temperature.

(14) Analyses by Dr. I. A. Kaye, Brooklyn College; method of Pepkowitz and Shive, *Ind. Eng. Chem., Anal. Ed.*, **14**, 280 (1942); *cf.* Kaye and Weiner, *ibid.*, **17**, 397 (1945).

RICHMOND HILL, N. Y. RECEIVED JANUARY 31, 1947

[CONTRIBUTION FROM THE RESEARCH LABORATORY OF ENDO PRODUCTS, INC.]

N-Arylamides of Mercaptoacetic Acid. II. Analogs of α-Mercaptoacetanilide and Corresponding Gold Mercaptides

BY ULRICH WEISS

N-Arylamides of mercaptoacetic acid, I, were prepared by treatment of their carbamyl derivatives, II,[1] with hot dilute ammonia,[2] other methods used occasionally for this reaction being less favorable.[3]

$$\mathrm{Ar{-}N(R){-}CO{-}CH_2{-}S{-}X}$$

I, X = —H
II, X = —$CONH_2$
III, X = —Au

Purification of the compounds obtained (checked by iodometric assay) was achieved with some difficulty in many instances, owing to ease of autoxidation; in a few cases, no entirely satisfactory preparations were obtained.

The compounds were further converted to the gold mercaptides by the method already de-

(1) Paper I, Weiss, THIS JOURNAL, **69**, 2682 (1947).

(2) Beckurts and Frerichs, *J. prakt. Chem.*, [2] **66**, 181 (1902), and subsequent papers by Frerichs, *et al.*

(3) (a) Thermal decomposition: ref. 2; Rheinboldt, Tappermann, Kleu, *J. prakt. Chem.*, [2] **153**, 69 (1939); (b) boiling water: Rizzo, *Gazz. chim. ital.*, **28**, I, 360 (1898); (c) alcoholic alkali, Frerichs and Foerster, *Ann.*, **371**, 293 (1909); the claim that the grouping—$CONH_2$—is converted into cyanate rather than carbamate was confirmed by identification of NaCNO from II, Ar—N(R=) C_6H_5—NH—. Related cases of formation of cyanates: Arth, *Bull. Soc. Chim.* [2] **41**, 334 (1884), *Ann. Chim.*, [6] **8**, 430 (1886); Mulder, *Rec. trav. chim.*, **6**, 170 (1887); *cf.* also Dox and Yoder, THIS JOURNAL, **45**, 726 (1923).