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

N-Arylamides of Mercaptoacetic Acid. III

BY ULRICH WEISS AND SAUL SOKOL[1]

The general reaction of hydrochlorides of aromatic amines with sodium thiocyanoacetate in water at room temperature, to give α-carbamylmercaptoacetyl derivatives of the amine[2]: $Ar–NH_2 + COOH–CH_2–SCN \rightarrow Ar–NH–CO–CH_2–S–CO–NH_2$ (I) has been extended to 6- and 8-aminoquinoline. From the latter amine the sparingly water-soluble thiocyanoacetate was obtained first; this salt isomerized to the amide [I, Ar = 8-C_9H_7N] with much greater ease than the analogous salt of 2,6-dimethylaniline described earlier.[2]

It had been found (ref. 2, footnote 7) that 2-aminoresorcinol is one of the few aromatic amines that do not undergo the above reaction. Its isomer, phloramine, 5-aminoresorcinol, was now found to react smoothly.

For comparison with the α-auromercaptoacetanilides described in paper II,[3] anilides of a few homologs of auromercaptoacetic acid were prepared. α-Auromercaptopropionanilide (II, X = Au) was made from the known[4] α-mercaptopropionanilide (II, X = H) by the method given earlier[5] for the preparation of α-auromercaptoacetanilide.

II, $C_6H_5—NH—CO—CH(SX)—CH_3$
$C_6H_5—NH—CO—(CH_2)_n—SX$
III, a, $n = 1$; b, $n = 2$; c, $n = 10$

While α-mercaptoacyl derivatives of aromatic amines are conveniently prepared from their carbamyl derivatives (I), which themselves are readily accessible according to the equation given above or its extension to other α-thiocyano-acids,[6] one would hardly expect such acids with the –SCN– group in a position other than α to react in the same way with amines.

Compounds of type III (X = H) were therefore prepared from the corresponding halo-acylamines. Among the methods for replacement of halogen by SH, which we tested in the case of IIIb, we found reaction with sodium thiosulfate to the Bunte salt (IIIb, X = $–SO_3Na$) and subsequent acid hydrolysis to the thiol preferable to reaction with thiourea to give the intermediate IIIb [X = $–C{=}(NH)–NH_2{\cdot}HCl$], which yields the thiol upon treatment with alkali. The former method was also found to be applicable for the preparation of α-mercaptoacetanilide from the chloro-compound, while thiourea in this case yields N^2-phenyl-pseudothiohydantoin (2-phenylimino-4-thiazolidone).[7]

We observed that the Bunte salt (IIIb, X = SO_3Na) readily gave the corresponding thiol (IIIb, X = H) upon hydrolysis with a mixture of ethanol and concd. hydrochloric acid. With dilute aqueous hydrochloric acid, a well crystallized compound, m. p. 198–200°, was obtained in moderate yields. This could be recrystallized with good recovery from boiling 0.1 *N* hydrochloric acid, but upon heating with ethanol–concd. hydrochloric acid mixture gave the thiol IIIb (X = H), m. p. 87.5–89.5°. Analysis showed this compound to be the aniline salt of the thiosulfuric acid (IIIb, X = $–SO_3H$), aniline obviously being formed through hydrolysis of the CO–NH–bond of part of the Bunte salt. The stability to aqueous acid of the thiosulfate group is remarkable. The same aniline salt was also obtained directly from aqueous solutions of aniline hydrochloride and the Bunte salt. The formation of the aniline salt with aqueous hydrochloric acid seems restricted to the Bunte salt IIIb (X = $–SO_3Na$); both the lower (IIIa) and higher (IIIc) homolog failed to yield crystalline solids under identical conditions, although their aqueous solutions gave crystalline precipitates with aniline hydrochloride and a variety of other amine salts, especially those of primary aromatic amines. Among other Bunte salts, $C_6H_5–CH_2–S–SO_3Na$ showed the same tendency to form water-insoluble amine salts, while this was not the case to the same extent with the aliphatic compounds, n-$C_5H_{11}S–SO_3Na$ and $C_3H_5S–SO_3Na$.

The compound IIIc (X = H) was prepared via the Bunte salt (IIIc, X = $–SO_3Na$). Both compounds were remarkable for their low solubility in water. The thiols IIIb and IIIc (X = H) were converted to the corresponding auro-mercaptides and disulfides.

Experimental

α-Carbamylmercaptoacetyl Compounds (I).—These compounds were prepared by the method described earlier,[2]

TABLE I

ARYL-α-CARBAMYLMERCAPTOACETAMIDES, $Ar—NH—CO—CH_2—S—CO—NH_2$

Ar =	Yield, %	M. p., °C.[8]	Color with $SeOCl_2/H_2SO_4$[3]	N Analyses, %[9] Calcd.	Found
6-C_9H_6N–	85	190	Yellow	16.09	15.53
8-C_9H_6N–	91	200 dec.	Yellow	16.09	16.06
3,5-$(OH)_2C_6H_3$–	70	217 dec.	Blue	11.56	11.44

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[1] Deceased February 5, 1948.

[2] Weiss, THIS JOURNAL, **69**, 2682 (1947), and older literature.

[3] Weiss, *ibid.*, **69**, 2684 (1947).

[4] Beckurts and Frerichs, *J. prakt. Chem.*, [2], **66**, 189 (1902).

[5] Weiss, THIS JOURNAL, **67**, 1424 (1945).

[6] Beckurts and Frerichs, ref. 4, and *Arch. Pharm.*, **253**, 155 (1915); Fredga, *J. prakt. Chem.*, [2] **123**, 110 (1929).

[7] P. J. Meyer, *Ber.*, **10**, 1965 (1877).

[8] All m. p.s' are corrected.

[9] Analyses by Mr. W. Saschek, Columbia University, and Oakwold Laboratories, Alexandria, Va.

TABLE II

COMPOUNDS $C_6H_5NH—CO—CH(SX)—CH_3$ (II), $C_6H_5NH—CO—(CH_2)_n—SX$ (IIIa,b,c,), AND DISULFIDES $[C_6H_5NH—CO—(CH_2)_n—S—]_2$

Compound	X = —SO_3Na, % Na		X = H				X = —Au			Disulfides		
	Calcd.[a]	Found	M. p., °C.	SH,[b] % Calcd.	Found	Color with $SeOCl_2/H_2SO_4$	Dec., °C.	Gold, % Calcd.	Found	M. p., °C.	Nitrogen, % Calcd.	Found
II	..		91[c]	18.24	18.24	Brownish red	246	52.3	51.7	..	..	
IIIa	8.0	8.1	...	...	...	......	...	..	..	..	..	
IIIb	7.63	7.64	89	18.24	18.08	Orange	253	52.3	51.6	161[d]	7.77	7.60
IIIc	5.56	5.71	73	11.27	11.07	Yellow	203	40.3	39.5	115	4.79	4.61

[a] Values calculated for mono-hydrates; for IIIc (X = —SO_3Na), analysis does not permit decision between the anhydrous compound (5.81% Na) and the monohydrate. [b] Analysis by titration of the alcohol solution with 0.1 *N* iodine; *cf.* ref. 3, footnote 8. [c] Ref. 4, m. p. 91°. [d] The compound resolidifies and melts again at 172°.

but using 100% excess of sodium thiocyanoacetate. The aminoquinoline derivatives were recrystallized from acetone, the phloramine derivative from 0.1 *N* hydrochloric acid.

When equimolecular quantities of 8-aminoquinoline (28.8 g.) and sodium thiocyanoacetate (31.4 g.) were brought to reaction in a total volume of 250 ml., a light red precipitate was first obtained. This was assumed to be the thiocyano-acetate of 8-aminoquinoline, as it was comparatively soluble in water, gave with sodium nitroprusside a transient purple color similar to that given by sodium thiocyanoacetate rather than to the more stable brownish red of the carbamylmercaptoacetyl compound, and changed to the compound of the latter type with such ease that no further characterization was possible. This change took place upon attempted drying *in vacuo*, when a m. p. was taken, or when either a solution in water or the original reaction mixture was allowed to stand for a short time. In the latter case, the water-insoluble carbamyl compound was obtained in 73% yield.

Bunte Salts, III, (X = —SO_3Na).—The compounds IIIa and b, (X = —SO_3Na) were prepared by several hours of refluxing of the corresponding haloacyl-anilide with one mole of sodium thiosulfate in 50% ethanol. Dilution with water precipitated a small quantity of the corresponding disulfide, which was filtered. The clear filtrate was evaporated to dryness *in vacuo* and the dried residue was extracted several times with boiling ethanol. The Bunte salt crystallized on cooling; additional quantities were obtained upon concentrating the mother liquors. The total yields were nearly quantitative. The compounds contain one mole of water of crystallization.

The compound IIIc (X = —SO_3Na) was prepared from commercial ω-bromoundecylenic acid,[10] which was converted to the chloride with thionyl chloride. ω-Bromohendecanilide was obtained from the chloride with two moles of aniline in benzene; yield, 86%; m. p. 71° (from heptane). *Anal.* Calcd. for $C_{17}H_{26}NOBr$: N, 4.12. Found: N, 3.98.

The **Bunte salt,** IIIc (X = —SO_3Na), was prepared by four and one-half hours of refluxing of 34.0 g. of this compound with 24.8 g. of sodium thiosulfate pentahydrate in 500 ml. of 50% ethanol. After cooling and removal of a small amount of precipitate, 1000 ml. of water was added. Upon chilling, the water-insoluble Bunte salt crystallized in 89% yield.

For analysis, samples of the Bunte salts were recrystallized from ethanol. Analyses are listed in Table II.

Mercapto-acylanilides. (1) **α-Mercaptopropionanilide** II, (X = H) was prepared by the method described in the literature.[4]

(2) **β-Mercaptopropionanilide.** (a) **with Thiourea.**—β-Chloropropionanilide,[11] 36.7 g. (0.2 mole), was refluxed for 24 hr. with 15.2 g. (0.2 mole) thiourea and 300 ml. of ethanol. The resulting clear solution was diluted with 250 ml. of water and concentrated *in vacuo* to strong crystallization. After cooling, 6.5 g. (17.7%) unchanged starting material was removed by filtration. Concentration *in vacuo* of the mother liquors nearly to dryness gave 33.3 g. (64%) of the desired isothiouronium chloride; m. p. 179° after recrystallization from ethanol. *Anal.* Calcd. for $C_{10}H_{14}N_3OSCl$: HCl, 14.04. Found: HCl, 14.10, 14.18. Hydrolysis of this compound with alcoholic alkali gave only unsatisfactory yields of the corresponding thiol.

(b) **From the Bunte Salt,** IIIb (X = —SO_3Na).—Twenty-seven grams of this salt was refluxed for one hour with 350 ml. of ethanol and 25 ml. of concd. hydrochloric acid. The mixture was next cooled and diluted with 750 ml. water, when the solid originally present ($NaHSO_4$) went into solution, and a milky liquid resulted. This was extracted four times with chloroform. The clear aqueous phase did not react with sodium nitroprusside any more, and was discarded. The dried chloroform extracts were evaporated to dryness in a stream of nitrogen. The oily residue, which solidified soon, weighed 13.6 g. (84%). This crude β-mercaptopropionanilide was strongly contaminated with the corresponding disulfide, from which it was separated by repeated extraction with boiling 0.1 *N* hydrochloric acid. The pure thiol crystallized from the extracts in aggregates of fine needles (for analysis see Table II).

(3) **ω-Mercaptohendecanilide.**—Twelve grams of the Bunte salt IIIc (X = —SO_3Na) was refluxed for one hour with a mixture of 150 ml. of ethanol and 12 ml. of concd. hydrochloric acid. On dilution with water and chilling, the crude thiol separated; yield, 8.20 g. (96%). Two extractions with boiling pentane removed small amounts of an impurity which gave a positive reaction with nitroprusside and aqueous ammonia. The insoluble residue was recrystallized from ethanol, yielding the pure thiol. The compound was entirely insoluble in boiling water, and in aqueous ammonia and alkali; it failed to react with nitroprusside in aqueous medium, but did so readily in presence of alcoholic alkali. For analysis see Table II.

Disulfides, $[C_6H_5\text{-}NH\text{-}CO\text{-}(CH_2)_n\text{-}S\text{-}]_2$.—These compounds were prepared by titration of an alcoholic solution of the thiol with 0.1 *N* iodine.[3] They were recrystallized from ethanol. Their properties are listed in Table II.

Auromercapto-acylanilides (II and IIIa-c, X = Au).—These compounds were prepared from the corresponding thiols by the method described earlier.[5] They form off-white to yellowish, non-crystalline powders. Their properties are listed in Table II.

Aniline Salt of β-Propionanilide-thiosulfuric Acid.—When hydrolysis of the Bunte salt [III b, X = —SO_3Na] was attempted with dilute (1:1) hydrochloric acid, complete decomposition seemed to take place. However, when 6 g. of the salt was heated for ten minutes on the steam-cone with a mixture of 45 ml. of water and 15 ml. of concd. hydrochloric acid, it dissolved rapidly, soon giving a yellowish, milky liquid. Addition of charcoal and filtration gave a clear, colorless solution in which crystallization of platelets of the aniline salt started within a short time; yield, 1.8 g. (25.7%); m.p. 197°, not changed upon recrystallization from boiling 0.1 *N* hydrochloric acid: recovery 80%. *Anal.* Calcd. for $C_{15}H_{18}N_2O_4S_2$: C, 50.83; H, 5.11; N, 7.90; S, 18.09. Found: C, 50.95; H, 5.09; N, 8.36; S, 18.04. The same compound was obtained in 81% yield from a mixture of aqueous solutions of the Bunte salt and of aniline hydrochloride; m. p. and

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(10) Farchan Laboratories, Cleveland, Ohio.

(11) F. Mayer, van Zütphen and Phillips, *Ber.*, **60**, 858 (1927).

mixed m. p. 198°. A sample of the compound obtained by acid-treatment of the Bunte salt, warmed with alcohol and hydrochloric acid, gave 84% of the theory of the thiol, only little contaminated with disulfide.

Summary

1. The α-carbamylmercaptoacetyl derivatives of 5-aminoresorcinol and 6- and 8-aminoquinoline have been prepared.

2. β-Mercaptopropionanilide and ω-mercaptohendecanilide, the corresponding disulfides and auro-mercaptides have been prepared. The two thiols were obtained from the corresponding thiosulfates (Bunte salts) with a mixture of ethanol and concd. hydrochloric acid; treatment of sodium propionanilide β-thiosulfate with dilute aqueous hydrochloric acid unexpectedly led to the aniline salt of propionanilide-β-thiosulfuric acid.

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The Reaction of *n*-Butyllithium with Some Organosilicon Compounds

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It has been shown that when triphenylcarbinol,[2a] triphenylamine,[2b] triphenylphosphorus[2c] or triphenylarsenic[2d] is refluxed with *n*-butyllithium in ether, metalation of the aromatic nucleus occurs; whereas, in triphenylbismuth[3a] and tetraphenyltin[3b] the carbon-to-metal bond is cleaved by *n*-butyllithium. The present investigation was undertaken in order to ascertain the effect of *n*-butyllithium on some organosilicon compounds of related structure.

Accordingly, triphenylsilanol was treated with two equivalents of *n*-butyllithium by the method used for triphenylcarbinol.[2a] Upon carbonation of the reaction mixture, benzoic acid and diphenyl-*n*-butylsilanol were isolated. It is apparent, therefore, that *n*-butyllithium attacks the carbon-to-silicon bond in triphenylsilanol rather than the carbon-to-hydrogen bond as is the case with the analogous triphenylcarbinol. Results with some other silanols are shown in Table I. The over-all reaction may be represented by the general equations

$$R_3SiOH + R'Li \longrightarrow R_3SiOLi + R'H \qquad (1)$$

$$R_3SiOLi + R'Li \longrightarrow R_2R'SiOLi + RLi \qquad (2)$$

where R is an aryl and R′ an alkyl group. In the case of symmetrical silanols, the R_3SiOLi formed in reaction (1) is precipitated immediately upon the addition of the R′Li, and slowly redissolves as reaction (2) proceeds. If R and R′ are both aryl groups, or if alkyl Grignard reagents are used instead of alkyllithium compounds, reaction (2) does not take place to a detectable extent. Neither the nature of the products nor the yields is appreciably altered if the amount of R′Li is increased to as much as four moles to one of silanol.

TABLE I

CLEAVAGE OF SILANOLS BY ORGANOMETALLIC COMPOUNDS

Silanol	Cleaving agent	Acid formed	Yield, %
Triphenyl	*n*-BuLi	Benzoic	76
Triphenyl	*n*-BuMgBr	None	0
Triphenyl	*p*-$CH_3C_6H_4Li$	None	0
Tri-*p*-tolyl	*n*-BuLi	*p*-Toluic	61
Tri-*p*-tolyl	C_6H_5Li	None	0
Diphenyl-*p*-tolyl	*n*-BuLi	*p*-Toluic	18
		Benzoic	6
Tri-1-naphthyl[a]	*n*-BuLi	None	0

[a] This compound was first prepared by Mr. C. G. Brannen, and the procedure will be reported in a forthcoming paper.

When hexaphenyldisiloxane was treated with *n*-butyllithium both the carbon-to-silicon and silicon-to-oxygen bonds were attacked, since triphenyl-*n*-butylsilane and benzoic acid were obtained on carbonation and hydrolysis. It is known that phenyllithium reacts with hexaphenyldisiloxane according to the equation[4]

$$(C_6H_5)_3SiOSi(C_6H_5)_3 + C_6H_5Li \longrightarrow (C_6H_5)_4Si + (C_6H_5)_3SiOLi$$

in which the group $-OSi(C_6H_5)_3$ behaves like the ethoxy group in triphenylethoxysilane. This suggests that the reaction between hexaphenyldisiloxane and *n*-butyllithium should be formulated as follows

$$(C_6H_5)_3SiOSi(C_6H_5)_3 + C_4H_9Li \longrightarrow (C_6H_5)_3SiC_4H_9 + (C_6H_5)_3SiOLi$$

$$(C_6H_5)_3SiOLi + C_4H_9Li \longrightarrow (C_6H_5)_2C_4H_9SiOLi + C_6H_5Li$$

The fact that no diphenyldi-*n*-butylsilane was isolated, as might be expected if the carbon-to-silicon bond were attacked prior to the silicon-to-oxygen bond, tends to support the assumption that the reaction takes place in the manner shown.

Attempts were made to extend the reaction to compounds in which all four valences of silicon are attached to carbon. Table II shows the results obtained when a number of silanes were treated with *n*-butyllithium under the conditions used with the silanols. It is seen that only in the case of trimethyl-9-fluorenylsilane was an acid

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[1] Assistant Professor of Chemistry, Purdue University.

[2] (a) Gilman, Brown, Webb and Spatz, THIS JOURNAL, **62**, 977 (1940); (b) Gilman and Brown, *ibid.*, **62**, 3208 (1940); (c) Gilman and Brown, *ibid.*, **67**, 824 (1945); (d) Gilman and Stuckwisch, *ibid.*, **63**, 3532 (1941).

[3] (a) Gilman, Yablunky and Svigoon, *ibid.*, **61**, 1170 (1939); (b) Gilman, Moore and Jones, *ibid.*, **63**, 2482 (1941).

[4] Unpublished studies by H. N. Benedict.