[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE]

Sulfur-containing Amines. IV[1]

BY S. C. LASKOWSKI AND R. O. CLINTON

In previous communications[1,2,3] in this series there have been reported the preparation of certain sulfur-containing amines and various 4- and 8-substituted quinolines and 9-substituted acridines derived therefrom. Pharmacological evidence indicated the necessity of extending the investigation to further compounds of similar type before any generalization could be made about the effect of the sulfur on chemotherapeutic activity. The present work outlines the preparation of suitable additional side-chains to make possible such an investigation.

The list of side-chains previously reported[3,4] has been extended by increasing the number of carbons between the sulfur and the tertiary amino group and between the sulfur and the terminal reactive groups (alcohols, halides and primary amines), by branching of the carbon chain, *i. e.*, *i*-propyl, and by varying the type of tertiary amino group. The methods employed in some cases were similar to those previously reported,[3] and the yields were comparable except in the condensation of sodio-3-diethylaminopropanethiol with tetramethylene chlorohydrin, in which case the yield was lower due to cyclization of the chlorohydrin to tetrahydrofuran.

1-(2-Diethylaminoethylmercapto)-2-propanol was prepared both by the condensation of sodio-2-diethylaminoethanethiol and propylene chlorohydrin, and by the reduction of 1-(2-diethylaminoethylmercapto)-2-propanone with sodium and ethanol. The intermediate ketone, in the latter case, was obtained by condensing chloroacetone with 2-diethylaminoethanethiol in dry benzene at room temperature.

The chlorination of 1-(2-diethylaminoethyl)-2-propanol with thionyl chloride in dry chloroform was carried out at −30° in good yield; at higher temperatures (*e. g.*, 0°) decomposition was extensive.

The Blanc reaction[5] has been extended to the condensation of 2-diethylaminoethanethiol with paraformaldehyde in dry chloroform in the presence of dry hydrogen chloride. The yield of 2-chloromethylmercaptotriethylamine hydrochloride was poor, due to manipulative difficulties.

Contrary to the general type of salt formation of the monobasic side-chains, 3-(3-N-piperidylpropylmercapto)-propanol was unique in that it formed a dipicrate. In other cases where the length of the chain was comparable crystalline derivatives could not be obtained.

The majority of the compounds prepared and characterized by derivatives are described in Table I. Examples of the new procedures are given in the Experimental Part.

Experimental[6]

3-(3-Diethylaminopropylmercapto)-propylamine.—To a stirred solution of 29.4 g. (0.2 mole) of 3-diethylaminopropanethiol in 200 cc. of absolute ethanol was added a solution of 4.6 g. (0.2 mole) of sodium in 100 cc. of absolute ethanol under anhydrous conditions. To this stirred solution was added in a fine steam a warm solution of 53.4 g. (0.2 mole) of 3-bromopropylphthalimide in 200 cc. of absolute ethanol. After the addition was complete the resulting mixture was refluxed for twenty-four hours. The cooled mixture was filtered to remove the precipitated sodium bromide and the ethanol was removed by distillation under reduced pressure. The residue was triturated with 400 cc. of dry benzene and the benzene solution was filtered. The benzene was removed from the filtrate under reduced pressure, yielding 57 g. (85.3%) of **(3-(3-phthalimidopropylmercapto)-propyl)-diethylamine** as a straw-colored viscous oil. No crystalline derivative of this compound could be obtained.

To a stirred refluxing solution of 74 g. (0.22 mole) of the above phthalimido compound in 300 cc. of absolute ethanol was added slowly 13.5 g. (0.23 mole) of 85% hydrazine hydrate, and the resulting solution was refluxed for four hours. After cooling, the precipitated solid was removed by filtration and washed with ethanol. The filtrate and washings were combined and the ethanol was removed *in vacuo*. The yellow, semi-solid residue was combined with the above solid and was suspended in 500 cc. of hot water. The suspension was made acid to congo red paper with concentrated hydrochloric acid, mixed thoroughly, and the precipitated phthalhydrazide was filtered and washed with dilute (2%) hydrochloric acid. The acidic filtrate and washings were combined, made alkaline with 35% potassium hydroxide solution, saturated with sodium chloride, and extracted with chloroform–ether (1:1). The chloroform–ether extracts were dried over anhydrous potassium carbonate, the solvent was removed under reduced pressure, and the residue distilled *in vacuo* to give 30.5 g. of colorless distillate, which on redistillation yielded 29.5 g. (66%) of product, b. p. 86–87° at 0.04 mm., $n^{20}D$ 1.4880.

Anal. Calcd. for $C_{10}H_{24}N_2S$: N, 13.73; S, 15.69. Found: N, 13.70; S, 15.24.

The **dithiocarbamate** crystallized from absolute ethanol as fine white needles, m. p. 135–136°.

Anal. Calcd. for $C_{11}H_{24}N_2S_2$: N, 10.00. Found: N, 9.79.

2-Chloromethylmercaptotriethylamine Hydrochloride.—Dry hydrogen chloride was passed into a stirred, cooled mixture (−10°) of 13.5 g. (0.1 mole) of 2-diethylaminoethanethiol and 3 g. (0.33 mole) of paraformaldehyde in 50 cc. of dry chloroform for two hours. After the reaction was complete two layers were present. The mixture was diluted to 200 cc. with additional dry chloroform and dried with a large amount of anhydrous sodium sulfate. On addition of anhydrous ether to the dried chloroform solution, a small amount of finely divided white solid separated, m. p. 197–202°. Two recrystallizations from anhydrous ethanol–anhydrous ether raised the melting point to 210–214°.

(1) For the preceding paper in this series see: Huber, Bair, Laskowski, Jackman and Clinton, THIS JOURNAL, **68**, 322 (1946).

(2) Huber, Bair, Boehme, Laskowski, Jackman and Clinton, *ibid.*, **67**, 1849 (1945).

(3) Clinton, Suter, Laskowski, Jackman and Huber, *ibid.*, **67**, 594 (1945).

(4) Albertson and Clinton, *ibid.*, **67**, 1222 (1945).

(5) *Cf.*, Walter Goodson and Fosbinder, *ibid.*, **67**, 657 (1945).

(6) All melting points and boiling points are uncorrected.

TABLE I

SULFUR-CONTAINING AMINES

Amines												Salts					
								Analyses,[a] %						Analyses, %			
R	n	m	Method	Yield, %	B. p., °C.	Press., mm.	Bath temp., °C.	$n^{20}D$	Sulfur Calcd.	Sulfur Found	Nitrogen Calcd.	Nitrogen Found	Deriv.	M. p., °C.	Sulfur Calcd.	Sulfur Found	Nitrogen Calcd.	Nitrogen Found
$R(CH_2)_nS(CH_2)_mOH$																		
Et_2N—	2	4	B	57.2	109–110	0.03	145–150	1.4942		[b]			Cit.[c]	74–80	..	..	3.53	3.58
Et_2N—	3	2	C	85.8[d]	106–107[d]	.7	140	1.4945		[e]	7.33	7.31	Cit.	96–100	..	..	3.66	3.87
Et_2N—	3	3	B	74.3	108–110[f]	.2	145	1.4928		[g]	6.83	6.83	[h]					
Et_2N—	3	4	B	40.0[i]	109–110	.4	165	1.4919	...	...	6.39	6.44	Cit.	96–100	7.79	7.98	3.41	3.35
Me_2N—	2	2	C	59.0	70–71	.05	125–130	1.4992	21.48	21.61	9.40	9.38	Picr.[j]	127–128	7.75	7.61	...	...
Me_2N—	2	3	B	83.4	90	.05	130–140	1.4958	19.63	19.30	8.59	8.59	Cit.	63–66	..	..	3.94	3.92
$C_5H_{10}N$—[k]	3	2	C	91.5	113–115	.1	170–175	1.5188	15.76	15.68	6.90	6.79	Cit.	63–66	..	..	3.54	3.76
													Picr.	142–144	7.47	7.38	...	...
$C_5H_{10}N$—	3	3	B	77.4	115–120	.01	150–160	1.5148	14.75	14.83	7.45	6.64	Dipic.[l]	170–172	4.74	4.93	14.52	14.55
$R(CH_2)_nSCH_2CHOHCH_3$																		
Et_2N—	2	..	B	85.8	92–94	.15	130–135	1.4867		See text			Cit.	83–88	..	..	3.66	3.86
Et_2N—	3	..	B	25[m]	82–83	.03	135–145	1.4871	15.61	15.52	6.83	7.04	Cit.	76–78	..	..	3.53	3.53
Me_2N—	2	..	B	80.0	64–65	.05	108–110	1.4888	19.63	19.61	8.59	8.60	Picr.	129–130	7.47	7.43	...	...
$C_5H_{10}N$—	3	..	B	77.0	104–105	.05	140–155	1.5098	14.75	14.54	6.45	6.72	Cit.	72–76	..	..	3.42	3.33
$R(CH_2)_nSC(=NH)NH_2 \cdot 2HCl$																		
Et_2N—	3	..	..	96.0	123–125[n]	...	.....	.....		[o]	16.03	16.49	.....	.....	..	..	...	...
Et_2N—	4	..	..	90.0	[p]	...	.....	.....	...	...	...	...	Dipic.	166–167	4.84	4.85	...	...
$C_5H_{10}N$—	3	..	..	98.6	196–200[n]	...	.....	.....	11.64	11.64		[q]	.....	.....	..	..	...	...
$R(CH_2)_nSH$																		
Et_2N—	3[r]	..	..	35.3	80	15	95–100	1.4650[s]		[t]	9.52	9.19	Cit.	91–93	..	..	4.13	4.08
Et_2N—	4	..	..	53.4	95–96	15	110–115	1.4678	...	...	8.70	8.69	Cit.	92–96	..	..	3.97	3.93
$C_5H_{10}N$—	3	..	..	52.5	93	10	110–115	1.5000	20.09	20.11	...	...	Pic.[u]	109–110	8.25	8.17	...	...

[a] The authors are indebted to Mr. Morris E. Auerbach and his staff for the analyses. [b] This base could not be obtained analytically pure. [c] Citrate. [d] Gilman and Tolman, THIS JOURNAL, **67**, 1847 (1945), reported b. p. 100–102° at 0.1 mm., 77%. [e] Carbon, calcd. 56.52; found, 56.94. Hydrogen, calcd. 11.07; found, 10.83. [f] Ref. [d], reported b. p. 126–129° at 0.1 mm. [g] Carbon, calcd. 58.54; found, 58.63. Hydrogen, calcd. 11.22; found, 10.99. [h] No crystalline derivative could be obtained. [i] Low yield due to cyclization of tetramethylene chlorohydrin to tetrahydrofuran. [j] Picrolonate. [k] N-Piperidyl. [l] Dipicrate. [m] Used impure oily isothiouronium salt in this preparation. [n] Melting point. [o] Carbon, calcd. 36.64; found, 36.86. Hydrogen, calcd. 8.02; found, 7.81. [p] Viscous straw-colored oil. [q] Chlorine, calcd. 25.91; found, 26.01. [r] Gilman, Plunkett, Tolman and Broadbent, THIS JOURNAL, **67**, 1845 (1945), reported b. p. 76–77.5°, at 26 mm., $n^{20}D$ 1.4668; *cf.* U. S. Patent 2,401,234 (1946). [s] $n^{25}D$. [t] Carbon, calcd. 57.14; found, 57.01. Hydrogen calcd. 11.56; found, 11.32. [u] Picrate.

Anal. Calcd. for $C_7H_{16}ClNS \cdot HCl$: C, 38.53; H, 7.80; N, 6.42. Found: C, 38.62; H, 8.21; N, 6.50.

When recrystallized from warm anhydrous ethanol by the slow addition of anhydrous ether, the compound separated in long glass-like needles, m. p. 93–96°. This compound is probably an alcoholate. The low-melting compound was precipitated from anhydrous ethanol with anhydrous ether in the high-melting form when precipitation was rapid.

(2-Diethylaminoethylmercapto)-2-propanone.—To a stirred solution of 9.3 g. (0.1 mole) of chloroacetone in 50 cc. of dry benzene was added dropwise, at room temperature, a solution of 13.3 g. (0.1 mole) of 2-diethylaminoethanethiol in 50 cc. of dry benzene. After the addition was complete the mixture was warmed to 50° and maintained at that temperature for one-half hour, after which time the benzene was removed under reduced pressure leaving 21 g. (93%) of crude, straw-colored (2-diethylaminoethylmercapto)-2-propanone hydrochloride as a viscous oil.

Thirty-five grams of the above oily hydrochloride was dissolved in 300 cc. of water, the solution was made alkaline with 35% potassium hydroxide solution, saturated with sodium chloride, and exhaustively extracted with ether. The combined ethereal extracts were dried over anhydrous potassium carbonate, the ether was removed under reduced pressure and the residue distilled *in vacuo*. There was obtained in 80% yield a water-white product, b. p. 115–116° at 10 mm., $n^{20}D$ 1.4792.

Anal. Calcd. for $C_9H_{19}NOS$: C, 57.14; H, 10.05; N, 7.41. Found: C, 57.10; H, 10.12; N, 7.43.

The **picrolonate** crystallized from anhydrous ethanol in fine yellow needles, m. p. 101–102°.

Anal. Calcd. for $C_9H_{19}NOS \cdot C_{10}H_8N_4O_5$: S, 7.06. Found: S, 6.89.

1-(2-Diethylaminoethylmercapto)-2-propanol. Method A.—To a refluxing solution of 53.5 g. (0.28 mole) of (2-diethylaminoethylmercapto)-2-propanone in 1500 cc. of anhydrous ethanol was added, over a period of one hour, 65 g. (2.83 moles) of sodium. The resulting solution was cooled and neutralized with 2.83 moles of concentrated hydrochloric acid. The precipitated sodium chloride was removed by filtration, the alcohol removed under reduced pressure, and the residue distilled *in vacuo*. There was obtained 27 g. (50%) of colorless product, b. p. 62–64° at 0.3 mm.

Anal. Calcd. for $C_9H_{21}NOS$: C, 56.52; H, 11.07; N, 7.33. Found: C, 56.77; H, 11.19; N, 6.93.

The **picrate** formed yellow needles from anhydrous ethanol, m. p. 62–64°.

Anal. Calcd. for $C_9H_{21}NOS \cdot C_6H_7N_3O_7$: N, 13.33. Found: N, 13.73.

Method B.—To a stirred refluxing solution of 248 g. (1 mole) of 2-diethylaminoethylisothiouronium chloride hydrochloride[4] in 1000 cc. of anhydrous ethanol was added 94.5 g. (1 mole) of propylene chlorohydrin followed by a solution of 69 g. (3 moles) of sodium in a mixture of 750 cc. ethanol and 75 cc. of water, in a very fine stream. After the addition was complete the mixture was refluxed for twelve hours, cooled, and the sodium chloride was removed by filtration and washed with 2 × 50 cc. of ethanol.

The filtrate and washings were combined, the alcohol was removed under reduced pressure, and the residue distilled *in vacuo*. The product was colorless.

2-(3-Diethylaminopropylmercapto)-ethanol.[7] **Method C.**—To a stirred cooled solution (0°) of 11.5 g. (0.5 mole) of sodium in 500 cc. of ethanol was added 39 g. (0.5 mole) of 2-thiolethanol. To this solution was added dropwise at 0°, 74.8 g. (0.5 mole) of 3-diethylaminopropyl chloride during one-half hour. The mixture was stirred in the cold for 2 hours, refluxed four hours and then cooled. The sodium chloride was removed by filtration and washed with 2 × 50 cc. of ethanol. The filtrate and washings were combined, the alcohol was removed under reduced pressure and the residue was distilled *in vacuo*. The product was colorless.

N-(3-(3-Chloropropylmercapto)-propyl)-diethylamine.—To a stirred, cooled solution (0°) of 75 g. (0.366 mole) of 3-(3-diethylaminopropylmercapto)-propanol in 175 cc. of dry chloroform was added dropwise, in the absence of moisture, a solution of 43.5 g. (0.366 mole) of purified thionyl chloride in 175 cc. of dry chloroform, over a period of one hour. When the addition was complete the solution was stirred in the cold for one hour and refluxed for one hour. Most of the solvent was distilled off and to the cooled residue was added 90 cc. of ethyl acetate and 200 cc. of ether. A tan-colored, hygroscopic hydrochloride was obtained in quantitative yield.

The hydrochloride was dissolved in 500 cc. of water, the solution was made alkaline with 35% potassium hydroxide solution, saturated with sodium chloride and extracted with ether. The combined ethereal extracts were dried over anhydrous potassium carbonate, the solvent was removed under reduced pressure and the residue was distilled *in vacuo*. There was obtained 56.8 g. (69.4%) of water-white product, b. p. 80–82° at 0.025 mm., $n^{20}D$ 1.4875.

Anal. Calcd. for $C_{10}H_{22}ClNS$: C, 53.69; H, 9.84; N, 6.26. Found: C, 53.50; H, 10.01; N, 6.01.

The **citrate** crystallized as rosets of white needles from absolute ethanol, m. p. 85–89°.

Anal. Calcd. for $C_{10}H_{22}ClNS \cdot C_6H_8O_7$: N, 3.37. Found: N, 3.38.

2-(2-Chloropropylmercapto)-triethylamine Hydrochloride.—This compound was prepared by the above method, except that the initial temperature of the chlorination was −30°. The product was obtained as hygroscopic white platelets in 72% yield.

The free base was liberated in ice–water with 35% potassium hydroxide solution. The aqueous mixture was saturated with sodium chloride, extracted with ether, and the combined ethereal extracts were dried over anhydrous sodium sulfate. When this base was added to a solution of citric acid monohydrate in ether, the **citrate** separated as a fine white solid, m. p. 88–91°.

Anal. Calcd. for $C_9H_{20}ClNS$: C, 44.83; H, 6.97; N, 3.49. Found: C, 44.69; H, 6.55; N, 3.42.

Summary

The preparation of a series of dialkylaminoalkylmercaptoalkyl alcohols, chlorides, an amine and related compounds is described.

RENSSELAER, NEW YORK RECEIVED SEPTEMBER 26, 1946

(7) *Cf.* Gilman and Tolman, THIS JOURNAL, **67**, 1847 (1945).

[CONTRIBUTION FROM THE DEPARTMENT OF AGRICULTURAL CHEMISTRY, PURDUE UNIVERSITY AGRICULTURAL EXPERIMENT STATION]

Partial Characterization of a Compound Involved in the Blackening of White Potatoes[1]

BY W. R. LEWIS AND D. M. DOTY

The development during cooking of grey or black discolorations of white potatoes (*Solanum tuberosum* L.) is of considerable commercial importance as well as of academic interest. Spangler[2] reported that 25% of 1,165 Chicago retailers listed tendency to cook black as either the first or second most objectionable defect of potatoes. Similarly it was shown to be the most common complaint of 880 retailers in the cities of Cleveland and Rochester.

Several investigators have studied causes and means of preventing blackening. Much of their time has been devoted to studies of environmental conditions which cause blackening. Tottingham,[3] *et al.*, studied the effect of mineral nutrition, of various soil moisture levels, and of high temperatures. They found no consistant correlation between blackening and any of these factors. Smith and Kelly[4] state that potatoes maturing at temperatures below 60°F. darken to a greater extent than those maturing at higher temperatures. However, after noting the above statement, Rieman,[5] *et al.*, say ". . . it has not been possible thus far to induce blackening with certainty under controlled experimental conditions by varying any environmental factor." Although these studies have made valuable contributions to the knowledge of the nutritional requirements of the potato plant, it is obvious that little is known concerning the fundamental cause of blackening.

The purpose of this investigation was, therefore, to characterize chemically the precursor of the black pigment so that a practical means of preventing the discoloration might be devised.

The concentration of a pigment precursor was greatly facilitated by the discovery that it showed a characteristic blue fluorescence. Partial characterization was effected in the following manner. The colorless fluorescent precursor was extracted from the fresh tubers with acidified alcohol. The

(1) Journal Paper No. 271 of the Purdue University Agricultural Experiment Station.

(2) R. L. Spangler, "Retail Trade Practices and Preferences for Late-Corp Potatoes in Chicago and Suburbs and Quality Analysis of Potatoes Offered for Sale to Consumers, 1939–40," Agr. Marketing Service, U. S. D. A., 1940, 66 pages.

(3) W. E. Tottingham, R. Nagy and A. F. Ross, *Am. Potato J.*, **13**, 297 (1936).

(4) Ora Smith and W. C. Kelly, *Food Packer*, **25**, 32 (1944).

(5) G. H. Rieman, W. E. Tottingham and John S. McFarlane, *J. Agric. Research*, **69**, 21 (1944).