TABLE II

PRODUCTS FROM THE REACTION OF SUBSTITUTED RHODANINES WITH GRIGNARD REAGENTS

Compound Number	Solvent of Crystallization	M.P.	Yield,[c] %	Formula[d]	Carbon, %		Hydrogen, %		Nitrogen, %		Sulfur, %	
					Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
IIa	B	88–89	38	$C_{23}H_{19}ONS_2$	70.92	71.07	4.8	4.78	3.5	3.49	16.4	16.31
IIb	B	164–165	40	$C_{27}H_{21}ONS_2$	73.8	74.12	4.78	4.66	3.1	3.07	14.5	14.43
IIc	B	187–188	45	$C_{21}H_{17}ONS_2$	69.4	70.03	4.6	4.64	3.8	3.51	17.6	16.71
IId	A	163–164	75	$C_{16}H_{13}ONS_2$	64.2	64.49	4.3	4.36	4.69	4.8	21.4	21.4
IIe	A	140–141	50	$C_{11}H_{11}ONS_2$	55.69	55.44	4.63	4.55	5.90	5.76	27.0	26.06

[a] Solvent, petroleum ether (b.p. 70–80°). [b] Solvent, benzene–methyl alcohol mixture. [c] Calculated for the pure product. [d] All crystals were colorless.

reagent (3 moles), was added a solution of the substance (Ia or Ib) (1 mole) in benzene. The reaction mixture was refluxed for 2 hr. and left overnight. It was then hydrolyzed with saturated ammonium chloride solution, dried over anhydrous sodium sulfate, and evaporated on a water bath nearly to dryness. The oily residue thus obtained was triturated with petroleum ether (b.p. 40–60°) and allowed to cool. The product was filtered off and recrystallized from a suitable solvent (*cf.* Table II).

Preparation of N-benzylrhodanine.[10] The procedure adopted here is similar to that described for rhodanine,[7] using benzylamine instead of ammonia. The yield is almost quantitative, m.p. 94–96°.

Anal. Calcd. for $C_{10}H_9ONS_2$: N, 6.27; S, 27.8. Found: N, 6.28; S, 28.52.

Preparation of benzylidene-N-benzylrhodanine (Ia).[11] N-Benzylrhodanine (2 g.) was dissolved in hot alcohol (80 ml.), then benzaldehyde (4 ml.) and pyridine (2.5 ml.) were added. The reaction mixture was left at room temperature for 0.5 hr. and then cooled in ice. Water was then added until the solution became turbid. After a short time, the solid so obtained was recrystallized from benzene. The yield was almost quantitative, m.p. 158–159°.

This compound was also prepared according to Andreasch[12] and the melting point was the same as described here and not 219° as stated in the reference.

Anal. Calcd. for $C_{17}H_{13}ONS_2$: C, 65.6; H, 4.18; N, 4.5; S, 20.57. Found: C, 65.99; H, 3.97; N, 4.23; S, 20.27.

Preparation of N-methylrhodanine.[13] The procedure adopted for this compound was similar to that described for rhodanine,[7] using methylamine gas instead of ammonia. The yield was almost quantitative and the product was recrystallized from benzene-petroleum ether (b.p. 40–60°), m.p. 69–70°.

Anal. Calcd. for $C_4H_5ONS_2$: C, 32.69; H, 3.40; N, 9.52; S, 43.5. Found: C, 33.36; H, 3.5; N, 9.05; S, 40.92.

Preparation of benzylidene-N-methylrhodanine (Ib).[14] The procedure was similar to that described for Ia. It was recrystallized from benzene in an almost quantitative yield as yellow crystals, m.p. 167–168°.

Anal. Calcd. for $C_{11}H_9ONS_2$: C, 56.18; H, 3.83; N, 5.95; S, 27.14. Found: C, 56.92; H, 3.71; N, 5.81; S, 26.39.

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(10) Andreasch, *Beil*, **27**, 244 (1937).
(11) Andreasch, *Beil*, **27**, 273 (1937).
(12) Andreasch, *Beil*, **27**, 273 (1937).
(13) Andreasch, *Beil*, **27**, 243 (1937).
(14) Andreasch, *Beil*, **27**, 277 (1937).

4-[*N*,*N*-Bis(2-haloethyl)amino]benzaldehyde Derivatives

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N-Phenyldiethanolamine has been converted to 4-[*N*,*N*-bis(2-chloroethyl)-amino]benzaldehyde in one step in 58% yield by reaction with phosphorus oxychloride in dimethylformamide. This synthesis offers advantages over that previously described[1]

(1) R. C. Elderfield, I. S. Covey, J. B. Geiduschek, W. L. Meyer, A. B. Ross, and J. H. Ross, *J. Org. Chem.*, **23**, 1749 (1958).

TABLE I

4-[*N*,*N*-BIS(2-HALOETHYL)AMINO]BENZALDEHYDE DERIVATIVES

Compound	Yield, %	M.P.[a]	Nitrogen, % Calcd.	Nitrogen, % Found
4-[*N*,*N*-Bis(2-chloroethyl)amino]benzaldehyde	58	85–88 E	—	—
anilide	61	62–65 BP	8.72	8.86
azine	84	162–164 E	11.45	11.59
dimethylhydrazone methiodide	47	167[b] W	9.77	9.28
2,4-dinitrophenylhydrazone	93	253–255[b] AP	16.41	16.48
isonicotinoylhydrazone	68	200–203[b] E	15.34	15.35
4-nitrophenylhydrazone	50	215–217 AM	14.68	14.52
semicarbazone	81	162–166 EW	18.48	18.46
4-[*N*,*N*-Bis(2-chloroethyl)amino]cinnamic acid	39	183–186 BP	[c]	[c]
4-{4′-[*N*,*N*-Bis(2-chloroethyl)amino]benzylidine}-aminomorpholine	97	97–99 MW	12.73	12.88
4-[*N*,*N*-Bis(2-iodoethyl)amino]benzaldehyde	59	105–107 MW	[d]	[d]
azine	72	175 TP	6.56	6.82
isonicotonoylhydrazone	76	205[b] T	10.22	10.48
4-nitrophenylhydrazone	76	202 EW	9.93	10.09
semicarbazone	76	156–158 EW	11.53	12.99
5-{4′-[*N*,*N*-Bis(2-iodoethyl)amino]benzylidine}-barbituric acid	87	230[b]	7.80	8.06

[a] Solvent for recrystallization: E, ethanol; A, acetone; M, methanol; W, water; B, benzene; P, petroleum ether (b.p. 66–75°); T, toluene. [b] Melts with decomposition. [c] Calcd. for $C_{13}H_{15}Cl_2NO_2$: C, 54.18; H, 5.24; neutr. equiv. 288. Found: C 55.10; H, 5.46; neutr. equiv. 298. [d] Calcd. for $C_{11}H_{13}I_2NO$: C, 30.79; H, 3.05. Found: C, 31.27; H, 3.14.

and has made possible the preparation of the derivatives listed in the Table. All of these derivatives are light sensitive. The pale purple aminomorpholine derivative is thermotropic. Its colorless solution in benzene turns deep violet when heated. It gives a deep violet solution in ethanol at room temperature. This may be due to a trace impurity which, however, was not removed by careful recrystallization. The chlorine atoms of the aldehyde were replaced by iodine on refluxing with sodium iodide in 2-butanone. These iodo compounds may have undergone inter- or intramolecular quaternization.

Screening data[2] have shown that 5-(4′-[*N*,*N*-bis(2-iodoethyl)amino]benzylidene)-barbituric acid has a rating of ±,— at a dose level of 63 mg./kg.; — at 16, 32, and 125 mg./kg.; and is toxic at 125 mg./kg. and that *p*,*p*′-[*N*,*N*bis(2′-chloroethyl)-amino]-benzaldehyde anil has a rating of — at 125 mg./kg. and ±, toxic at 500 mg./kg. in Sarcoma 180 Tumor retardation studies. These results do not establish either strong or consistent activity in these compounds.

EXPERIMENTAL[3]

4-[N,N-Bis(2-chloroethyl)amino]benzaldehyde. (I) One hundred and forty-six grams (2 moles) of dimethylformamide was placed in a 1-l. flask equipped with a mechanical stirrer and cooled to 0–5° as 153 g. (1 mole) of phosphorus oxychloride was added slowly over approximately 0.5 hr. A solution containing 60.5 g. (0.33 mole) of *N*,*N*-bis(2-hydroxyethyl) aniline in 150 ml. of dimethylformamide was then added with stirring and cooling. After heating at 85–90° for 2.5 hr., the mixture was cooled and poured into 2 l. of an ice water mixture. Concentrated ammonium hydroxide was then added with vigorous stirring until the solution was strongly basic and the crude yellow product had solidified. The solid was then collected and recrystallized from ethanol-water to give 47.4 g., 58%, of the cream-colored needles melting at 85–88°. Recrystallization from ethanol with decolorizing charcoal gave colorless needles of the same melting point.

4-[N,N-Bis(2-chloroethyl)amino]benzaldehyde 4-nitrophenylhydrazone. A hot solution containing 1.53 g. of 4-nitrophenylhydrazine in 40 ml. of methanol was added to a hot solution of 2.46 g. (0.01 mole) of the aldehyde in 40 ml. of methanol. This mixture was warmed for 15 min. and diluted with an equal volume of water. On cooling the red crystalline product separated. Recrystallization from acetone-methanol gave 1.89 g., 49.7%, of the reddish-brown crystals, m.p. 215–217°.

4-[N,N-Bis(2-chloroethyl)amino]benzaldehyde azine. 95% Hydrazine, 0.015 g., was added to 2.46 g. (0.01 mole) of the aldehyde in 30 ml. of hot ethanol and the mixture heated to boiling for 10 min. On cooling, 1.84 g. of the bright yellow azine, m.p. 162–164%, separated. Recrystallization from ethanol gave the analytical sample of the same melting point.

4-{4′-[N,N-Bis(2-chloroethyl)amino]benzylidine/aminomorpholine. An aqueous solution of 4-aminomorpholine, prepared from 0.113 moles of morpholine,[4] was adjusted to *p*H 5 with concentrated hydrochloric acid and diluted with 50 ml. of methanol. The mixture was then warmed to just under boiling and a solution containing 2.46 g. (0.01 mole) of the aldehyde in 50 ml. of methanol was added at once. This solution was heated to reflux and cooled. Five grams of sodium acetate was added. The pale purple crystals which separated after standing overnight were collected and recrystallized from methanol-water to give 3.2 g., 97%, of

(2) The authors are indebted to Drs. C. C. Stock, D. A. Clarke, and R. K. Barclay, Sloan-Kettering Institute, for conducting these tests. The procedure and rating scales are given in Cancer Research, Suppl. No. 1, p. 91 (1953) and Suppl. No. 2, p. 179 (1955).

(3) Analyses by Micro Tech Laboratories.

(4) Richard H. Wiley, H. K. White, and G. Irick, *J. Org. Chem.*, 24, 1784 (1959).

the product, m.p. 97–99°. Additional recrystallizations failed to remove the purple coloration.

4-[N,N-Bis(2-chloroethyl)amino]benzaldehyde semicarbazone. The aldehyde, 0.0123 g. (0.005 mole), was dissolved in 30 ml. of ethanol and water added to just the turbidity point. Five milliliters of ethanol, 0.6 g. of semicarbazide hydrochloride, and 0.8 g. of finely powdered sodium acetate were added. After heating and cooling, the solution set to a solid mass. The crystals were collected and dried to give 1.23 g., 81.4%, of the product, m.p. 161–166°. Recrystallization from ethanol-water gave the analytical sample, m.p. 162–166°.

4-[N,N-Bis(2-chloroethyl)amino]benzaldehyde dimethylhydrazone methiodide. Unsymmetrical dimethylhydrazine, 0.065 g., was added to a solution of 2.46 g. (0.01 mole) of the aldehyde in 50 ml. of ethanol. This mixture was heated to reflux for 1 hr. and allowed to stand at room temperature and then at 0°. The oil which separated was taken up in 75 ml. of ether, dried over magnesium sulfate. Addition of 2.5 g. of methyl iodide precipitated crystals which were collected and dried to yield 2.03 g., 47.2%, of the product, m.p. 167° dec. Recrystallization from water gave the analytical sample of the same melting point.

4-[N,N-Bis(2-chloroethyl)amino]benzaldehyde anilide. A solution containing 50 ml. of ethanol, 2.46 g. (0.01 mole) of the aldehyde, and 1.1 g. of aniline was refluxed for 1.5 hr. Upon cooling to room temperature 25 ml. of water was slowly added and the mixture cooled to 0° to precipitate 1.96 g., 61%, of the product. Two recrystallizations from benzene–petroleum ether (b.p. 00–00°) gave the analytical sample melting at 62–65°.

4-[N,N-Bis(2-chloroethyl)amino]cinnamic acid. A mixture composed of 6.15 g. (0.025 mole) of the aldehyde, 45 ml. of pyridine, 1 ml. of piperidine, and 2.7 g. (0.026 mole) of malonic acid was heated to 95° for 3 hr. The dark solution was then poured into cold water. The oil which separated solidified upon further stirring to give the crude, orange product. Recrystallization from benzene–petroleum ether gave 2.80 g., 38.8%, of the pale tan product, m.p. 183–186°.

4-[N,N-Bis(2-iodoethyl)amino]benzaldehyde. Nine grams of sodium iodide was dissolved in 250 ml. of 2-butanone and to this was added 6.15 g. (0.025) of the aldehyde. This mixture was then heated to reflux for 6 hr. During this time the sodium chloride liberated by the reaction precipitated and and the solution became a bright yellow. After cooling to 5°, the sodium chloride was removed by filtration and the solution evaporated to dryness to give the crude product. Recrystallization from methanol-water gave 6.36 g., 59.2%, of the product. Two recrystallizations from benzene–petroleum ether gave the analytical sample melting at 105–107°. Care had to be taken during the recrystallizations not to heat the solvents too rapidly or decomposition of the unstable aldehyde resulted.

5-{4'-[N,N-Bis(2-iodoethyl)amino]benzylidine}barbituric acid. A solution containing 1.07 g. (0.0025 mole) of the aldehyde in 25 ml. of ethanol was added to 6 ml. of warm water containing 0.32 g. (0.0025 mole) of barbituric acid. This mixture was warmed at 75° for 2 min. and cooled. The precipitate was collected, washed with distilled water, and dried to give 1.18 g., 87.5%, of the crude product decomposing at 230°. This compound had little or no solubility in the common organic solvents and was washed with hot distilled water followed by hot methanol to give the analytical sample.

4-[N,N-Bis(2-iodoethyl)amino]benzaldehyde isonicotinoylhydrazone. A solution consisting of 2.14 g. (0.005 mole) of the aldehyde in 175 ml. of hot methanol was added to 20 ml. of hot methanol containing 0.75 g. of isonicotinoylhydrazine. The resulting mixture was heated and cooled. The crystals which separated were collected to give 2.08 g., 75.9%, of the yellow product decomposing at 205°. Recrystallization from toluene gave the analytical sample which also decomposed without melting.

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2,6-Dimethyl-4-(3'-pyridyl)pyridine-3,5-dicarboxylic Acid and Products Derived Therefrom

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The aldehyde–acetoacetic ester–ammonia synthesis, which has been successfully used with pyridine-2 and 4-aldehydes,[1] has now been extended to pyridine-3-carboxaldehyde. The condensation gives 80% of the 1,4-dihydro derivative which has been oxidized in 90% yield to diethyl 2,6-dimethyl-4-(3'-pyridyl)pyridine-3,5-dicarboxylate.[2] This ester is readily hydrolyzed by alcoholic potassium hydroxide to give the mono ester in 60% yield. Saponification of the second carbethoxy group is unusually difficult. Furthermore, the monocarbethoxy compound, obtained by decarboxylation of the ester-acid, gave only very low yields (*ca.* 1%) of the mono carboxylic acid under conditions which readily saponified the diester. Attempts to convert the diester directly to the mono acid gave the mono ester or, after decarboxylation, low (*ca.* 5%) yields of 2,6-dimethyl-4-(3'-pyridyl)pyridine.[3] Because the first of the two ester groups, both of which are in sterically comparable environments, is readily saponified, it does not appear that steric hindrance provides a logical explanation for the low yields encountered in saponification of the second carbethoxy group. Alternative conditions used for the ester hydrolysis were less effective. Thus, the use of diethylene glycol for the saponification gave similar results but the presence of the glycol complicates the isolation. Longer reaction times failed to improve the yield. The ester is recovered unchanged when its solution in concentrated sulfuric acid is poured into water. The over-all conversion of the ester to the dimethylbipyridyl is much less satisfactory than the corresponding reaction[1] with the 2- and 4-pyridyl isomers.

(1) R. F. Homer, *J. Chem. Soc.*, 1574 (1958).

(2) This nomenclature is currently used in Chemical Abstracts indexes. These acids have been named as derivatives of 2,6-dimethyl-dinicotinic acid and of 2,6-lutidine-3,5-dicarboxylic acid. They can also be named as bipyridines.

(3) This compound may be named 3',4-(2,6-dimethyl)-bipyridine.