The following compounds were evaluated for effects on reproduction in the Japanese quail but were without effect at dietary levels as high as 400 p.p.m.: N,N'-diethyl-N,N'-bis(dichloroacetyl)-1,4-xylylenediamine, N,N'-bis(dichloroacetyl)-1,8-octamethylenediamine, **7**, **8**, and **10**.

Discussion of Biological Results

In the series of alkylene and xylylenediamines used as carriers for alkylating groups all active compounds in the fly reproduction experiments had the aziridinylacetyl grouping as the alkylating function. Even with that grouping in the case of the N-ethyl derivative (**3**) no activity was noted. The octamethylene derivative (**12**) was clearly the most effective while the *m*-xylylene derivative (**9**) showed some effect. The lack of activity of the benzyl derivative (**20**) would indicate the need for at least two alkylating groups per mole.

The lack of activity of the N-ethyl derivative (**3**) and the nitrogen mustards (**6** and **15**) emphasizes the specificity of activity toward inhibiting reproduction both with regard to the carrier moiety and the alkylating function. Current work in these laboratories is concerned with defining these parameters in greater detail and, in addition, investigating species specificity in the Japanese quail and in the rat.

Acknowledgment. This work was supported by United States Public Health Service Grant GM-11491 and by Stanford Research Institute's Research and Development Program. We wish to thank J. Barbaccia and S. Hawkins for assistance with the biological studies and R. M. Parkhurst for assistance with the chemical studies. The two dichloroacetyl derivatives were kindly supplied by Sterling-Winthrop Research Institute, Rensselaer, N. Y.

Some Amino and Ammonio Nitrogen Mustard Analogs

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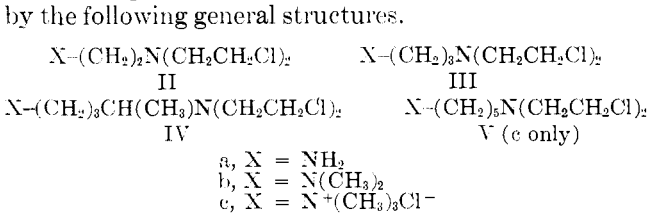
Procedures have been developed for the preparation of nitrogen mustard derivatives containing amino, dimethylamino, and trimethylammonio groups separated from the mustard group by two-, three-, four-, and five-carbon chains. A β-trimethylammonio group diminished the reactivity of an amino group so that it was possible to introduce only one hydroxyethyl group by reaction with ethylene oxide. Biological tests indicated the amino mustards to have toxic and antitumor properties similar to HN-2. The ammonio mustards were devoid of antitumor activity and were much less toxic.

Earlier reports have indicated interesting biological properties for a variety of basic heterocyclic compounds with bis(β-chloroethyl)aminoalkylamino side chains,[2-4] related to nitrogen mustard [HN-2, I, $CH_3N(CH_2CH_2Cl)_2$]. Furthermore, it is likely that analogs of such compounds might be formed *in vivo* through alkylation of primary, secondary, or tertiary nitrogens in proteins, DNA, RNA, or other basic constituents of cells. It, therefore, seemed desirable to study simple amino- and ammonio-substituted mustards, especially since one of the simplest possible analogs, β-aminoethylbis(β-chloroethyl)amine, has shown very promising activity at least comparable to HN-2 in our laboratories and elsewhere.[3]

The compounds selected for study may be represented by the following general structures.



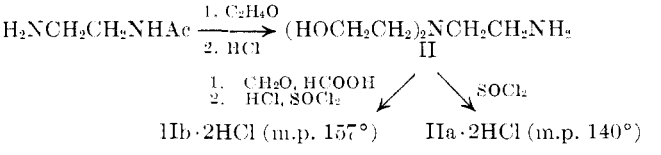
a, X = NH_2
b, X = $N(CH_3)_2$
c, X = $N^+(CH_3)_3Cl^-$

Since the ethylenediamine derivatives (II) showed the most interesting biological activities, a more extensive series was prepared for biological testing.

The required diols were prepared by either of two methods: (1) N,N-dialkylethylenediamine, prepared by the method of Turner,[5] was converted to the corresponding diol by reaction with ethylene oxide, or (2) N,N-dialkylaminoethyl chloride was treated with diethanolamine.[6]

Since it may be assumed that nitrogen mustards related to ethylenediamine could cyclize to piperazine derivatives, a related series of N-2-chloroethylpiperazines was also prepared.

The conversion of ethylenediamine to the mustard derivatives IIa and IIb was accomplished by the reactions outlined below.[7]



The conversion of the methylated diol II to IIb was not successful unless it was first converted to the hydrochloride. Reaction of the free base gave an entirely different product, m.p. 257° dec., which may have been the cyclized piperazinium isomer, although

(1) Supported in part by U. S. Public Health Service Grant No. Cy-2714. Abstracted from the doctoral dissertation of G. Kabas, June 1960.

(2) R. Jones, Jr., C. C. Price, and A. K. Sen, *J. Org. Chem.*, **22**, 783 (1957).

(3) H. J. Creech, R. M. Peck, and R. K. Preston, *J. Am. Chem. Soc.*, **81**, 3984 (1959).

(4) H. H. Lin and C. C. Price, *J. Org. Chem.*, **26**, 108, 264, 266 (1961).

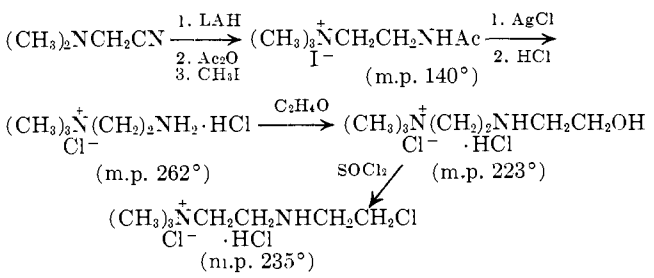
(5) R. Turner, *J. Am. Chem. Soc.*, **68**, 1607 (1946).

(6) G. Drefahl and K. H. König, *Chem. Ber.*, **87**, 1632 (1954).

(7) After we had prepared IIa, it was reported by Creech, Peck, and Preston.[3]

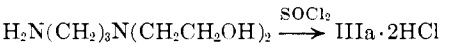
analysis indicated the presence of an extra half equivalent of HCl.

We were unsuccessful in efforts to prepare the quaternary mustard IIc, but the mono-2-chloroethyl analog IIc′ was prepared by the following sequence. Evi-



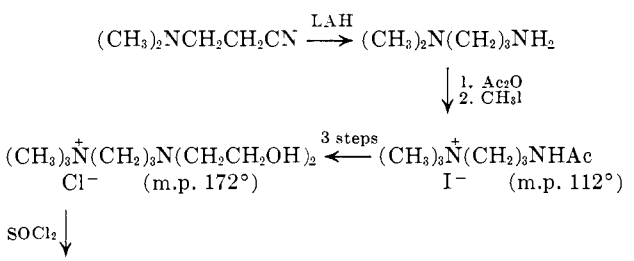
dently the positive charge on the quaternary nitrogen diminishes the nucleophilicity of the amino group and/or increases the steric hindrance at it enough to prevent reaction with ethylene oxide even at temperatures of 50–60°.

The preparation of IIIa was readily accomplished from the known diol[8] III. In this case, conversion of



III to IIIa was successful with the free base as well as with the dihydrochloride. Evidently cyclization to a seven-membered ring did not occur as readily as the formation of the piperazinium ring.

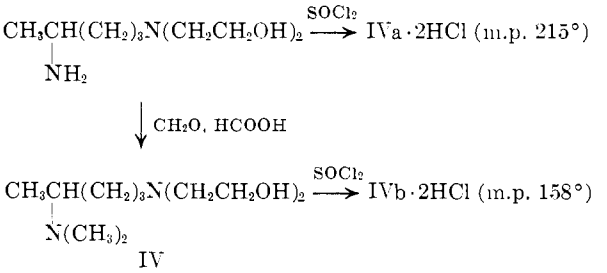
The preparation of IIIc was accomplished by the following sequence. With the trimethylammonio



group removed by one additional methylene group the primary amino group reacted normally with ethylene oxide.

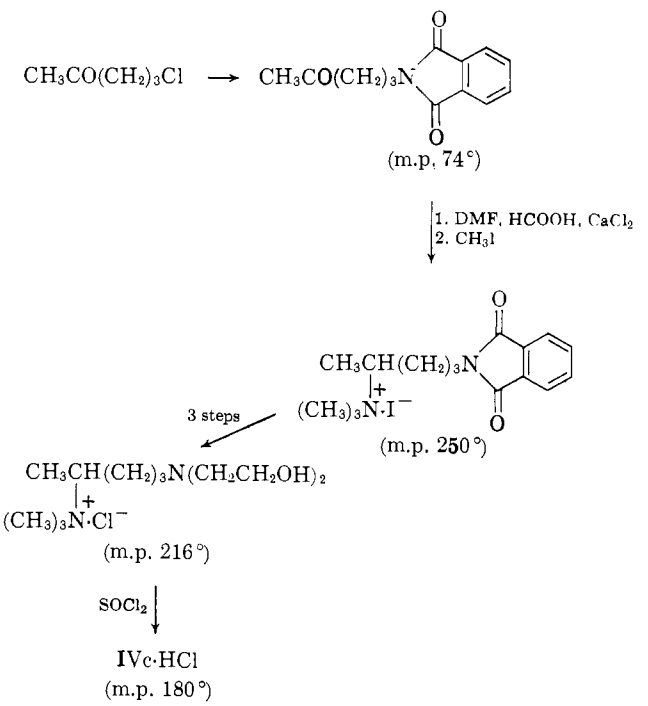
Our efforts to convert 3-dimethylaminopropylamine to the diol with ethylene oxide gave a viscous oil boiling over a wide range. While our work was in progress, we learned of an alternate synthesis and received a sample of IIIb for biological testing.[9]

The mustards IVa and IVb were prepared by the following scheme.[10] If the isolation procedure from the methylation above does not include a vigorous acid hydrolysis, the main product is the cyclic carbonate,



$(CH_3)_2NCH(CH_3)(CH_2)_3N(CH_2CH_2O)_2CO$, b.p. 210–215° (3.5 mm.).

Numerous efforts to prepare IVc by reaction of methyl iodide with IVb gave no pure, crystalline products. Similar efforts with the diol IV gave similar results. It thus appeared necessary to protect one amine group during quaternization, and the following scheme was developed. In the reductive



amination of the ketone to the dimethylamino compound with dimethylformamide and formic acid, the use of magnesium chloride[11] was unsuccessful, but the use of calcium chloride gave a 98% yield of the desired product.

Biological data on these compounds were reported in detail elsewhere.[12] The amino mustards were found to have a single LD_{50} of 3–8 mg./kg. compared to 3 mg./kg. for HN-2. In suppression of Ehrlich ascites tumor, IIa was the most active compound, being slightly superior to HN-2. However, it is of interest to note that in the primary amine series IIa is the most active and IVa is the least active while in the less active tertiary amine series, the order is reversed. This suggested to us the possible importance of a piperazine intermediate from IIa, a possibility further

(8) F. C. Whitmore, H. S. Mosher, R. R. Adams, R. B. Taylor, E. C. Chapin, C. Weisel, and W. Yanko, *J. Am. Chem. Soc.*, **66**, 725 (1944).

(9) We are indebted to Dr. Koert Gerzon, Eli Lilly and Co., Indianapolis, Ind., for this sample.

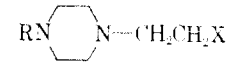
(10) We are grateful to Dr. B. F. Tullar, Sterling-Winthrop Research Institute, for the starting material.

(11) J. F. Bunnett, J. L. Marks, and H. Moe, *J. Am. Chem. Soc.*, **75**, 985 (1953).

(12) R. J. Rutman, F. S. Lewis, S. Buckner, C. C. Price, F. Llewellyn, and E. Owen, *Cancer Res.*, **22**, 559 (1962).

TABLE I

PIPERAZINE DERIVATIVES



	X = OH·2HCl							X = Cl·2HCl					
				Found, %[a]						Found, %[a]			
R	Yield, %	B.p., °C. (mm.)	M.p., °C. dec.	C	H	Cl	N	Yield, %	M.p., °C. dec.	C	H	Cl	N
Et	59	112 (10)[b]	237	41.14	8.50	31.08	12.06	82	234	38.57	7.64	42.86	11.37
n-Pr	72	114 (9)	225	43.93	8.90	29.01	11.13	77	234	40.83	7.75	40.53	10.83
n-Bu	70	85 (1)	219	46.31	9.33	27.50	11.05	84	235	43.48	8.21	38.18	10.15
n-Am	68	97 (1.5)	240	48.10	9.31	25.80	10.44	86	229	45.41	8.48	36.71	9.42
Benzyl	68	128 (1)[c]	238[c]	53.36	7.45	24.03	9.61	95	280	50.05	6.61	34.00	9.01

[a] Calculated values have been deleted upon special request by the senior author, since in a homologous series the changes are easily calculated. [b] R. S. Ide, E. Lorz, and R. Baltzly [*J. Am. Chem. Soc.*, **76**, 1122 (1954)] report b.p. 128° (21 mm.). [c] R. Baltzly, J. S. Buck, E. Lorz, and W. Schön [*ibid.*, **66**, 263 (1944)] report b.p. 143° (2 mm.) and m.p. (·2HCl) 225°.

explored by the compounds reported in Table I, but which did not show superior activity. The quaternary ammonium compounds were much less toxic (LD_{50} > 100 mg./kg.) and also were ineffective against Ehrlich tumors as compared to the free amines.

Experimental[13]

2-Bis(2-hydroxyethyl)aminoethylamine[3] was prepared in 65.8% over-all yield by reaction of monoacetylethylenediamine[14] with ethylene oxide in ethanol followed by hydrochloric acid hydrolysis; b.p. 131–132° (0.25 mm.) or 125–126° (0.15 mm.), $n^{20}D$ 1.4944 [lit.[3] b.p. 110° (0.02 mm.), $n^{20}D$ 1.4943]. **A dipicrate,** m.p. 185–186°, was obtained from ethanol.

Anal. Calcd. for $C_{18}H_{22}N_8O_{16}$: C, 35.65; H, 3.66; N, 18.48. Found: C, 35.49; H, 3.43; N, 18.64.

The diol was converted to **1-bis(2-chloroethyl)aminoethylamine dihydrochloride (IIa)** by reaction in excess thionyl chloride at 0 and 25°. It was recrystallized from absolute ethanol as large plates (60%), m.p. 139–140° (lit.[3] 138.5°).

1-Bis(2-hydroxyethyl)amino-2-dimethylaminoethane.—To 16 g. (0.108 mole) of 1-bis(2-hydroxyethyl)amino-2-aminoethane cooled with an ice–salt bath, 27.5 g. (0.54 mole) of 95% formic acid was slowly added with stirring. After complete addition, 28 g. (0.3 mole) of 35% formaldehyde and some boiling chips were added. The flask was then placed in an oil bath at 95–100° for 9 hr. Carbon dioxide was soon evolved. The flask was removed from the oil bath and after cooling, 32 g. of concentrated HCl was added, and the pale brown solution was refluxed for 3 hr. The low-boiling material was removed and the residue was dissolved in the minimum required amount of water. This water solution was saturated with Na_2CO_3 and the separated organic layer was removed. The remaining water solution was continuously extracted for 24 hr. with $CHCl_3$. The combined extract was dried (K_2CO_3) and distilled; b.p. 120–121° (3 mm.), yield 12.5 g. (66%), $n^{20}D$ 1.4727.

Anal. Calcd. for $C_8H_{20}N_2O_2$: N, 15.89. Found: N, 15.42.

It formed a **dipicrate** from ethanol, m.p. 214°, with softening at 209°.

Anal. Calcd. for $C_{20}H_{26}N_8O_{16}$: C, 37.86; H, 4.13; N, 17.66. Found: C, 37.65; H, 4.06; N, 17.62.

1-Bis(2-chloroethyl)amino-2-dimethylaminoethane Dihydrochloride (IIb).—A solution of 3 g. (0.017 mole) of the above diol in 20 ml. of dry $CHCl_3$ was saturated with anhydrous HCl whereupon the solution turned cloudy and a very viscous oil separated. This heterogeneous mixture was heated to reflux. Over a period of 20 min., 5.1 g. (0.042 mole) of $SOCl_2$ in 10 ml. of dry $CHCl_3$ was added. Reflux was continued for 1 hr. The chloroform was removed and the residue was dissolved in ethanol. Half of the ethanol used was distilled and the remaining ethanol was diluted up to 70–80 ml. with absolute ethanol, decolorized with charcoal, and ether was added until cloudiness appeared. After storing overnight in the freezer, the white precipitate was collected by filtration and recrystallized from the same solvent mixture to yield 3.6 g. (74%) of a white crystalline compound melting at 156–157°.

Anal. Calcd. for $C_8H_{20}Cl_4N_2$: C, 33.59; H, 7.05; Cl, 49.58; N, 9.79. Found: C, 33.65; H, 7.40; Cl, 47.12; N, 9.00; Cl^- (conductimetrically) before alkali treatment, 26.51; after alkali treatment, 49.31.

N,N-Dimethylethylenediamine,[5] b.p. 98–102° (lit.[5] 107°), was prepared in 89% yield by $LiAlH_4$ reduction of dimethylaminoacetonitrile. It formed a **dipicrate** from ethanol which could be recrystallized from water; m.p. 234–235° (lit.[15] 210°).

Anal. Calcd. for $C_{18}H_{18}N_8O_{14}$: C, 35.17; H, 3.23; N, 20.51. Found: C, 35.38; H, 3.52; N, 20.49.

N,N-Dimethyl-N′-acetylethylenediamine.—To a solution of 15 g. (0.175 mole) of N,N-dimethylethylenediamine in 100 ml. of toluene, 18 g. (0.175 mole) of acetic anhydride was carefully added. The solution was refluxed for 90 min., the low-boiling material was removed by distillation, and the oily residue was dissolved in water. The water solution was saturated with K_2CO_3 and continuously extracted for 48 hr. with $CHCl_3$. The chloroform extract was dried ($MgSO_4$) overnight and distilled, b.p. 82.5–83° (0.7 mm.), yield 18.5 g. (83.5%).

Anal. Calcd. for $C_6H_{14}N_2O$: C, 55.35; H, 10.84; N, 21.57. Found: C, 55.33; H, 10.29; N, 21.16.

2-Acetaminoethyltrimethylammonium Iodide.—To a chilled solution of 13 g. (0.1 mole) of N,N-dimethyl-N′-acetylethylenediamine in 100 ml. of absolute ethanol, 31.3 g. (0.15 mole) of methyl iodide was slowly added. The solution was refluxed for 30 min., half of the alcohol was removed by distillation, and ether was added until cloudiness appeared. Upon standing in the freezer overnight, 25.4 g. of a pale yellow crystalline compound separated; m.p. 139–140° unchanged on recrystallization from ethanol–hexane.

Anal. Calcd. for $C_7H_{17}IN_2O$: C, 30.89; H, 6.30; N, 10.29. Found: C, 30.77; H, 6.26; N, 10.19.

2-Trimethylammonioethylammonium dichloride was prepared from the iodide with freshly prepared silver chloride in 5% HCl solution. Filtration, refluxing in concentrated HCl, and evaporation left a white residue, only sparingly soluble in ethanol, but recrystallizable from methanol; yield 6.3 g. (89%), m.p. 262° dec.

Anal. Calcd. for $C_5H_{16}Cl_2N_2$: C, 34.29; H, 9.21; Cl, 40.49; N, 16.00. Found: C, 34.02; H, 9.41; Cl, 40.30; N, 16.02.

1-(2-Hydroxyethyl)ammonio-2-trimethylammonioethane Dichloride.—2-Trimethylammonioethylammonium dichloride (3.5 g., 0.02 mole) in 100 ml. of methanol was exactly neutralized with sodium ethoxide in ethanol. After 3 hr. the precipitated NaCl was removed and 2.2 g. (0.05 mole) of ethylene oxide in 20 ml. of methanol was added over a period of 20 min. with ice cooling. The reaction flask was allowed to reach room temperature overnight. The solution was then refluxed on a water bath at 40–50° using a Dry Ice–acetone cooling system to condense the ethylene oxide. After having refluxed the reaction mixture for 2 hr., a stream of anhydrous HCl was bubbled through until saturation. The flask was then stored at 0° for 3 days and 3.5 g. of a white crystalline powder separated. Upon adding ether to the mother liquor, an additional gram was obtained. The combined product was crystallized twice from a methanol–ether or an ethanol–methanol mixture yielding 3.5 g. (80%) of a white powder, m.p. 222–223° dec.

(13) Elementary analyses by Midwest Microlab, Inc., Indianapolis, Ind., and by Galbraith Laboratories, Knoxville, Tenn. All melting points are uncorrected.

(14) S. B. Aspinall and A. J. Hill, *J. Am. Chem. Soc.*, **61**, 822 (1939).

(15) Z. Welvart, *Bull. soc. chim. France*, 218 (1955).

Anal. Calcd. for $C_7H_{20}Cl_2N_2O$: C, 38.36; H, 9.20; Cl, 32.36; N, 12.78. Found: C, 38.26; H, 9.42; Cl, 32.10; N, 12.68.

1-(2-Chloroethyl)ammonio-2-trimethylammonioethane Dichloride (IIc′).—1-(2-Hydroxyethyl)ammonio-2-trimethylammonioethane dichloride (1.1 g., 5 mmoles) was suspended in 10 ml. of $SOCl_2$, and the mixture was refluxed for 2 hr. Excess $SOCl_2$ was removed by distillation under vacuum, and the almost white residue was recrystallized from ethanol–ether by cooling to −8°, yielding 0.910 g. (76%) of small pale yellow plates, m.p. 234–235° dec.

Anal. Calcd. for $C_7H_{19}Cl_3N_2 \cdot 0.3H_2O$: C, 34.51; H, 8.11; Cl, 43.77; N, 11.50. Found: C, 34.38; H, 7.97; Cl, 43.77; N, 11.76.

1-Bis(2-chloroethyl)amino-3-aminopropane Dihydrochloride (IIIa).—To 25 ml. of $SOCl_2$ chilled to 0°, 1.6 g. (0.01 mole) of 3-bis(2-hydroxyethyl)aminopropylamine[8] was carefully added with stirring over a period of 20 min. The stirring was continued for 2 hr. at 0°. The flask, fitted with a $CaCl_2$ tube, was stored at −8° for 48 hr. After an additional 48 hr. at room temperature, excess $SOCl_2$ was removed, and the brown residue was recrystallized from ethanol (charcoal), yielding 2.6 g. (96%) of a pale brown powder, m.p. 150–152° dec. It was recrystallized from ethanol with addition of anhydrous ether saturated with anhydrous HCl; m.p. 153–154° dec.

Anal. Calcd. for $C_7H_8Cl_4N_2$: C, 30.90; H, 6.67; Cl, 52.13; N, 10.30. Found: C, 30.90; H, 6.92; Cl, 52.10; N, 10.39; Cl^- (Volhard) before alkali treatment, 26.30; after alkali treatment, 52.20.

The same product in the same yield was obtained when the diol was converted to the hydrochloride before treatment with $SOCl_2$.

3-Dimethylaminopropionitrile,[15] b.p. 171–172°, $n^{20}D$ 1.4284 [lit.[15] b.p. 68° (18 mm.), $n^{20}D$ 1.4282], formed a **picrate** in alcohol; m.p. 157–158°.

Anal. Calcd. for $C_{11}H_{13}N_5O_7$: C, 40.37; H, 4.05; N, 21.40. Found: C, 40.67; H, 4.17; N, 21.51.

3-Dimethylamino-1-aminopropane[16] was prepared from the nitrile by $LiAlH_4$ reduction (44%), b.p. 130–134° (lit.[16] 131–134°). A **dipicrate** formed in alcohol decomposed at 224–225°.

Anal. Calcd. for $C_{17}H_{20}N_8O_{14}$: C, 37.36; H, 3.69; N, 18.36. Found: C, 37.19; H, 3.85; N, 18.63.

The **phenylthiourea** derivative melted at 117–118° after recrystallization from benzene–petroleum ether.

Anal. Calcd. for $C_{12}H_{19}N_3S$: C, 60.72; H, 8.07; N, 17.70; S, 13.51. Found: C, 60.87; H, 8.02; N, 17.90; S, 13.62.

3-Dimethylamino-1-N-acetylaminopropane.—To a solution of 20 g. (0.196 mole) of 3-dimethylamino-1-aminopropane in 100 ml. of toluene, 20 g. (0.196 mole) of acetic anhydride was slowly added with outside cooling. The mixture was refluxed for 3 hr. and evaporated, and the oily residue was dissolved in water. After saturation with K_2CO_3, it was continuously extracted for 24 hr. with $CHCl_3$. The product was obtained as a colorless oil, b.p. 120–121° (3 mm.) or 79–80° (0.3 mm.), yield 23.2 g. (82%).

Anal. Calcd. for $C_7H_{16}N_2O$: C, 58.30; H, 11.18; N, 19.43. Found: C, 57.99; H, 11.11; N, 19.47.

It formed a **picrate** from alcohol; m.p. 96–97°.

Anal. Calcd. for $C_{13}H_{19}N_5O_8$: C, 41.71; H, 5.06; N, 18.70. Found: C, 41.65; H, 4.98; N, 18.63.

3-Trimethylammonio-1-propylammonium dichloride was prepared by treatment of the above acetyl compound with methyl iodide in absolute ethanol. After precipitating from ether and recrystallization from an ethanol–ether mixture, the melting point was 111–111.5°. It was converted to the dichloride in 5% aqueous HCl by freshly precipitated AgCl. After filtration, addition of concentrated HCl, and evaporation to dryness, the white residue was crystallized from a mixture of absolute ethanol and ether to yield 6.1 g. (81%) of a white fluffy compound. A sample recrystallized from ethanol–hexane turned to a glass-like material at 202° and decomposed around 260°.

Anal. Calcd. for $C_6H_{18}Cl_2N_2$: C, 38.11; H, 9.60; Cl, 37.51; N, 14.81. Found: C, 37.94; H, 9.89; Cl, 37.51; N, 14.78.

1-Bis(2-hydroxyethyl)ammonio-3-trimethylammoniopropane Dichloride.—3-Trimethylammonio-1-propylammonium dichloride (3.78 g., 0.02 mole) in 75 ml. of absolute ethanol was exactly neutralized with 14.4 ml. of a sodium ethoxide solution in ethanol. After 3 hr., the precipitate of NaCl was removed by filtration, using a very fine filter paper, and to the filtrate 2.2 g. (0.05 mole) of ethylene oxide in 15 ml. of absolute ethanol was added over a period of 20 min., with ice cooling. The ice bath with the immersed reaction flask was allowed to reach room temperature overnight. The solution was then refluxed on a water bath at 40–50° using a Dry Ice–acetone cooling system to condense the ethylene oxide. After refluxing for 2 hr. the solvent was partially concentrated to about 70 ml. and a stream of anhydrous HCl was bubbled through for a period of 30 min. Some ether was added on warming until cloudiness appeared. On cooling to −8°, 4.3 g. (75%) of small white prisms separated; m.p. 153–159°. After four crystallizations from the minimum required amount of absolute ethanol, 2.7 g. (48.5%) of long crystals was obtained; m.p. 171–171.5° with softening at 163°.

Anal. Calcd. for $C_{10}H_{26}Cl_2N_2O_2$: C, 43.32; H, 9.46; Cl, 25.58; N, 10.11. Found: C, 42.91; H, 9.49; Cl, 25.69; N, 10.23.

1-Bis(2-chloroethyl)ammonio-3-trimethylammoniopropane Dichloride (IIIc).—The above diol (0.550 g., 0.002 mole) was suspended in 5 ml. of $SOCl_2$, and the solution was refluxed for 2 hr. After cooling, the $SOCl_2$ was removed under vacuum, and the residue was crystallized from a mixture of absolute ethanol and absolute ether. The yield of crude product was 0.540 g., m.p. 173–174° dec. (sintering at 168°). Two more crystallizations gave 0.410 g. (66%), m.p. 168–168.5° dec.

Anal. Calcd. for $C_{10}H_{24}Cl_4N_2 \cdot 1.5H_2O$: C, 35.21; H, 7.97; Cl, 41.58; N, 8.21. Found: C, 35.62; H, 7.91; Cl, 42.40; N, 8.51; Cl^- (Volhard) before alkali treatment, 21.20; after alkali treatment, 42.80.

1-Bis(2-chloroethyl)amino-4-aminopentane Dihydrochloride (IVa).—A stream of anhydrous HCl was passed through a solution of 4 g. (21 mmoles) of 1-bis(2-hydroxyethyl)amino-4-aminopentane[10] in 20 ml. of dry $CHCl_3$, until the weight of the solution had increased by 1.4 g. During this operation a white oily product separated. After heating to reflux, 6.3 g. (0.05 mole) of $SOCl_2$ in 15 ml. of dry $CHCl_3$ was added during 1 hr. The mixture was refluxed for another hour and kept overnight at room temperature. The residue from vacuum distillation was dissolved in absolute ethanol, decolorized with charcoal, and precipitated with ether. Another recrystallization from the same solvent mixture gave 4 g. (63.5%) of IVa, m.p. 214–215° dec.

Anal. Calcd. for $C_9H_{22}Cl_4N_2$: C, 36.00; H, 7.56; Cl, 47.26; N, 9.33. Found: C, 36.46; H, 7.87; Cl, 45.74; N, 9.56; Cl^- (conductimetric) before alkali treatment, 26.85; after alkali treatment, 46.17.

1-Bis(2-hydroxymethyl)amino-4-dimethylaminopentane.—While cooling with an ice–salt bath, 30 g. (0.158 mole) of 1-bis(2-hydroxyethyl)amino-4-aminopentane was carefully added to 43 g. (0.78 mole) of 98–100% formic acid. After addition was complete, 35 g. (0.348 mole) of 30% formaldehyde was added, and the flask, fitted with a reflux condenser, was placed in an oil bath at 90°. After a few minutes, vigorous gas evolution started; the flask was removed from the oil bath until evolution of gas had subsided (about 1 hr.). The flask was then returned to the oil bath at 95–100° for 18 hr. About 35 g. (0.35 mole) of concentrated HCl was added, and the solution was gently refluxed for 4 hr. Low-boiling material was removed, and the oily residue was dissolved in water. The water solution was saturated with K_2CO_3, the organic layer was removed, and the remaining solution continuously was extracted with chloroform for 16 hr. The product, b.p. 147–148° (3 mm.), was redistilled twice, yielding 19.4 g. (70%) of an almost colorless oil, $n^{20}D$ 1.4774.

Anal. Calcd. for $C_{11}H_{26}N_2O_2$: C, 60.51; H, 12.06; N, 12.83. Found: C, 59.45; H, 11.97; N, 12.74.

It formed a **dipicrate** from alcohol; m.p. 135–136°.

Anal. Calcd. for $C_{23}H_{32}N_8O_{16}$: C, 40.83; H, 4.77; N, 16.56. Found: C, 40.54; H, 4.79; N, 16.54.

1-Bis(2-chloroethyl)amino-4-dimethylaminopentane Dihydrochloride (IVb).—A solution of 5.5 g. (0.046 mole) of $SOCl_2$ in 10 ml. of dry $CHCl_3$ was added over a period of 20 min. to a boiling solution of 4 g. (0.0184 mole) of the above diol in 20 ml. of dry $CHCl_3$. The mixture was refluxed and stirred for another hour. After removal of the chloroform and the unreacted thionyl chloride, the oily residue was dissolved in warm ethanol, decolorized with charcoal, and half of the ethanol was removed by distillation. To the remaining ethanol solution, ether was added, and on scratching, a white crystalline compound precipitated. Two more crystallizations from an ethanol–ether

(16) I. N. Nazarov and G. A. Shvekhgeimer, *Zh. Obshch. Khim.*, **24**, 163 (1954); *Chem. Abstr.*, **49**, 3034c (1955).

mixture gave 5.7 g. (95%) of a white crystalline compound, m.p. 157–158° dec.

Anal. Calcd. for $C_{11}H_{26}Cl_4N_2$: C, 40.26; H, 7.99; Cl, 43.24; N, 8.54. Found: C, 39.93; H, 8.25; Cl, 41.47; N, 8.12; Cl^- (conductimetric) before alkali treatment, 22.55; after alkali treatment, 41.47.

1-N-Phthalimido-4-pentanone.—To a solution of 24 g. (0.2 mole) of 1-chloro-4-pentanone[17] in 160 ml. of dimethylformamide, 40.8 g. (0.22 mole) of potassium phthalimide[18] was added. The flask was placed in an oil bath at 100–105° and was vigorously stirred for 2 hr. After cooling, 200 ml. of $CHCl_3$ was added, and the mixture was poured into 300 ml. of water. The aqueous layer was separated and extracted three times with 50-ml. portions of chloroform. After washing, the $CHCl_3$ was removed, and the residue was crystallized from dilute ethanol to give 24–26 g. (52–56%) of a white crystalline compound, m.p. 73–74°.

Anal. Calcd. for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67; N, 6.06. Found: C, 67.55; H, 5.71; N, 6.04.

The **oxime**, prepared in ethanol and twice recrystallized from benzene–petroleum ether (b.p. 30–60°), formed silky needles, m.p. 135–135.5° (83%).

Anal. Calcd. for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.73; N, 11.38. Found: C, 63.63; H, 5.74; N, 11.39.

1-N-Phthalimido-4-dimethylaminopentane.—A mixture of 23 g. (0.1 mole) of 1-N-phthalimido-4-pentanone, 30 g. (0.4 mole) of dimethylformamide (DMF), 6.5 g. (0.14 mole) of 98–100% formic acid, 2.5 g. (0.017 mole) of $CaCl_2 \cdot 2H_2O$, and 12 ml. of water was heated in an oil bath. The bath temperature was gradually increased during 10 hr. from 160 to 195°. During this heating process, the reaction mixture temperature increased from 110 to 174°, and water and unreacted DMF distilled. After cooling, the reaction mixture was poured into 60 ml. of water, acidified with HCl, and then saturated with Na_2CO_3. The organic layer was separated and the alkaline water solution was filtered from $CaCO_3$ and extracted four times with 50-ml. portions of ether. The ether extracts were combined with the organic layer and dried (K_2CO_3). After removal of the ether, the product (25 g., 97%) distilled as a pale yellow oil at 150–151° (0.35 mm.), $n^{20}D$ 1.5378.

Anal. Calcd. for $C_{15}H_{20}N_2O_2$: C, 69.20; H, 7.74; N, 10.76. Found: C, 69.08; H, 7.50; N, 10.78.

1,4-Phthalimido-4-trimethylammoniopentane Iodide.—To a solution of 15.6 g. (0.06 mole) of 1-N-phthalimido-4-dimethylaminopentane in 200 ml. of absolute ethanol, 10 g. (0.07 mole) of methyl iodide was slowly added with cooling. After a few minutes, a voluminous precipitate was formed. The mixture was refluxed for 30 min. and, upon standing overnight at 0°, 22.5 g. (93.5%) of a pale yellow precipitate was obtained; m.p. 249–250° dec.

Anal. Calcd. for $C_{16}H_{23}IN_2O_2$: I, 31.55; N, 6.96. Found: I, 31.35; N, 6.75.

1-N-Phthalimido-4-trimethylammoniopentane Chloride.—A solution of 22.5 g. (0.056 mole) of the above iodide in 200 ml. of a 5% HCl solution diluted with 70 ml. of 95% ethanol was decolorized with 1 ml. of a 0.1 *N* sodium thiosulfate solution, and 33 g. (0.23 mole) of freshly precipitated AgCl was added. After stirring for 3 hr., the filtrate was concentrated to dryness; the white crystalline residue weighed 17 g. (98%). It recrystallized from ethanol–ether as small white plates decomposing at 230°.

Anal. Calcd. for $C_{16}H_{23}ClN_2O_2$: Cl, 11.48; N, 9.01. Found: Cl, 11.68; N, 8.92.

1-Ammonio-4-trimethylammoniopentane Dichloride.—A solution of 17.4 g. (0.056 mole) of 1-N-phthalimido-4-trimethylammoniopentane chloride in 80 ml. of concentrated HCl, diluted with 20 ml. of distilled water, was refluxed for 24 hr. The mixture was cooled and the phthalic acid was removed by filtration. The filtrate was vacuum dried, dissolved in absolute ethanol, and saturated with anhydrous HCl, and ether was added until cloudiness. Upon standing overnight at 0°, 10.5 g. of a white microcrystalline powder, decomposing at 253°, was obtained. With two more crystallizations from an ethanol–ether mixture, 8.3 g. (69%) of a white microcrystalline powder, decomposing sharply at 254°, was obtained.

Anal. Calcd. for $C_8H_{22}Cl_2N_2$: C, 44.24; H, 10.21; Cl, 32.65; N, 12.90. Found: C, 43.87; H, 10.50; Cl, 32.24; N, 12.74.

1-Bis(2-hydroxyethyl)ammonio-4-trimethylammoniopentane Dichloride.—1-Ammonio-4-trimethylammoniopentane dichloride (3.26 g., 0.015 mole) in 80 ml. of absolute ethanol was exactly neutralized by 19.8 ml. of a sodium ethoxide solution in ethanol. After 3 hr. at room temperature, the precipitated NaCl was removed by filtration and to the filtrate 2 g. (0.045 mole) of ethylene oxide in 15 ml. of absolute ethanol was added over a period of 15 min. with ice cooling. After warming to room temperature overnight, the solution was refluxed for 2 hr. on a water bath using a Dry Ice–acetone cooling system. The solvent was partially distilled and the residue was saturated with anhydrous HCl. Some ether was added with warming until cloudiness appeared, and the flask was stored at −8° for 24 hr. The white precipitate was collected and recrystallized three times from the minimum amount of absolute ethanol, yielding 2.6 g. (58%) of a white microcrystalline powder, m.p. 215–216° dec.

Anal. Calcd. for $C_{12}H_{30}Cl_2N_2O_2$: C, 47.21; H, 9.90; Cl, 23.23; N, 9.18. Found: C, 47.56; H, 9.99; Cl, 23.23; N, 8.81.

1-Bis(2-chloroethyl)ammonio-4-trimethylammoniopentane Dichloride (IVc).—The above diol (1.22 g., 4 mmoles) was suspended in 10 ml. of $SOCl_2$, and the mixture was refluxed for 2 hr. After cooling, the $SOCl_2$ was removed under vacuum and the white crystalline residue was crystallized from an ethanol–ether mixture. The crystallization was repeated yielding 0.8 g. (58.5%) of a white microcrystalline powder, m.p. 178–179° dec.

Anal. Calcd. for $C_{12}H_{28}Cl_4N_2$: C, 42.12; H, 8.25; Cl, 41.45; N, 8.19. Found: C, 41.94; H, 8.40; Cl, 41.19; N, 7.96.

1-Dimethylamino-4-cyanobutane.—1-Chloro-4-cyanobutane[19] (47.4 g.) was added to 25% aqueous dimethylamine (200 g.) and left standing for 5 days at room temperature. The mixture became an almost clear solution. The excess dimethylamine was driven off by means of a water pump without heating. With cooling, 80 ml. of 20% NaOH solution and powdered K_2CO_3 were added in succession to effect two layers. The organic layer was extracted with ether and dried (K_2CO_3). The ethereal solution was filtered, ether was removed by distillation, and the residue was fractionated to give 31.8 g. of product boiling at 106–108° (30 mm.), $n^{20}D$ 1.4330.

1-Dimethylamino-5-aminopentane.—Lithium aluminum hydride (12 g.) was dissolved in 400 ml. of anhydrous ether and cooled. To this was added dropwise a solution of 30 g. of 1-dimethylamino-4-cyanobutane in 100 ml. of anhydrous ether over 30 min. with stirring and cooling. After stirring for 24 hr. at room temperature, 20 ml. of water, 30 ml. of 20% NaOH, and 35 ml. of water were added cautiously in succession. The ether solution was decanted and the residue was washed with ether three times. The combined ether extract was dried overnight (NaOH). Ether was removed, and the residue was fractionated to give 19.3 g. of product, b.p. 88–89° (30 mm.), $n^{20}D$ 1.4436.

Anal. Calcd. for $C_7H_{18}N_2$: C, 64.56; H, 13.93; N, 21.51. Found: C, 64.63; H, 13.97; N, 21.41.

5-Acetamidopentyltrimethylammonium Iodide.—To a mixture of 9.1 g. of 1-dimethylamino-5-aminopentane and 20 ml. of toluene, 8 g. of acetic anhydride was added cautiously. After heating on a water bath for 3 hr., toluene was removed by vacuum distillation. After addition of 20 ml. of a 20% NaOH solution and powdered K_2CO_3, the organic layer was dried and the $CHCl_3$ was removed by distillation. The residue was dissolved in 20 ml. of absolute ethanol, and to this was added 14.2 g. of methyl iodide dropwise. After refluxing for 3 hr. and cooling, anhydrous ether was added to precipitate the ammonium salt. It was reprecipitated from ethanol by ether; yield 18.0 g., m.p. 142–143°.

Anal. Calcd. for $C_{10}H_{23}IN_2O$: C, 38.22; H, 7.38; I, 40.39; N, 8.92. Found: C, 38.05; H, 7.11; I, 40.13; N, 8.72.

1-Ammonio-5-trimethylammoniopentane Dichloride.—To a solution of 13.56 g. of the above iodide in 200 ml. of 5% HCl was added 23 g. of freshly prepared AgCl. The mixture was stirred for 3 hr. at room temperature, whereupon the conversion of the iodide into the chloride was completed. After removal of the silver halides by filtration, the solution was concentrated to about 100 ml. Then 20 ml. of concentrated HCl was added and the solution was vigorously refluxed for 3 hr. The solution was concentrated to dryness by vacuum distillation, and the white residue was dissolved in a small amount of methanol and

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(18) P. L. Salzberg and J. V. Supniewski, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 119.

(19) N. J. Leonard and E. Barthel, Jr., *J. Am. Chem. Soc.*, **71**, 3098 (1949).

TABLE II

DIALKYLAMINOETHYLDIETHANOLAMINES AND RELATED MUSTARDS

$$\begin{matrix} R' \\ R \end{matrix}\!>\!NCH_2CH_2N(CH_2CH_2X)_2$$

		X = OH						X = Cl, ·2HCl					
			B.p., °C.		Found, %[a]				M.p.,	Found, %[a]			
R	R'	Yield, %	(mm.)	$n^{20}D$	C	H	N	Yield, %	°C.	C	H	Cl	N
Et	Et	35.8[b]	108 (0.2)[c]	...	...	...	...	51	146[c]	...	..	...	...
n-Pr	*n*-Pr	55[d]	140 (0.3)[e]	1.4703	61.89	12.26	12.24	52	141	42.29	8.12	41.60	8.20
n-Bu	*n*-Bu	58[b]	148 (0.15)	...	64.62	12.80	10.79	79	126	45.71	8.83	38.36	7.48
CH_3	Benzyl	64[d]	178 (0.15)	1.5252	66.73	9.47	11.03	84	154	46.63	6.60	39.38	7.91
Et	Benzyl	44[d]	188 (0.3)	1.5253	67.89	9.92	10.48	91	178	47.86	6.83	37.93	7.35

[a] See Table I, footnote *a*. [b] By procedure A. [c] G. Prefahl and K. H. König [*Chem. Ber.*, **87**, 1632 (1954)] report b.p. 141° (0.15 mm.) and m.p. 147°. [d] By procedure B. [e] Picrate: m.p. 127–128°.

reprecipitated with ether. Finally, the compound was recrystallized from ethanol; yield 8.50 g., m.p. 234–235°.

Anal. Calcd. for $C_8H_{22}Cl_2N_2$: C, 44.24; H, 10.21; Cl, 32.65; N, 12.90. Found: C, 44.50; H, 10.02; Cl, 32.53; N, 12.80.

1-Bis(2-hydroxyethyl)ammonio-5-trimethylammoniopentane Dichloride.—A solution of 6.51 g. of the preceding compound in 75 ml. of absolute ethanol was neutralized with 20 ml. of sodium ethoxide in 20 ml. of absolute ethanol. Sodium chloride was removed by filtration, and a solution of 5 g. of ethylene oxide in 15 ml. of absolute ethanol was added dropwise with stirring and ice cooling. The mixture was left standing for 2 days at room temperature. After the solvent was partially removed without heating, it was saturated with dry HCl. Ether was added to cloudiness. After cooling, the white precipitate was collected by filtration and recrystallized from ethanol–2-propanol mixture three times yielding 6.30 g., m.p. *ca.* 175° (sintered at 140° and solidified again).

Anal. Calcd. for $C_{12}H_{30}Cl_2N_2O_2$: C, 47.21; H, 9.90; Cl, 23.23; N, 9.18. Found: C, 47.01; H, 10.01; Cl, 22.96; N, 9.11.

1-Bis(2-chloroethyl)ammonio-5-trimethylammoniopentane Dichloride.—The compound above was suspended in 10 ml. of $SOCl_2$ and gently refluxed for 2 hr. The excess $SOCl_2$ was distilled *in vacuo*, and the residue was dissolved in 2-propanol and precipitated with ether. The precipitate was collected by filtration and purified by reprecipitation with absolute alcohol and ether; yield 1.80 g., m.p. 192–193° dec.

Anal. Calcd. for $C_{12}H_{28}Cl_4N_2$: C, 42.12; H, 8.25; Cl, 41.45; N, 8.19. Found: C, 41.91; H, 8.39; Cl, 41.28; N, 8.28.

N,N-Dialkylaminoethyl Chloride Hydrochlorides.—Dialkylaminoethanol hydrochloride (0.1 mole) was added in small portions to 30 ml. of precooled $SOCl_2$ with stirring and cooling. The reaction mixture was then gently refluxed for 3 hr. Excess $SOCl_2$ was removed by distillation under diminished pressure, and the residue was recrystallized from an appropriate solvent.

N,N-Benzylmethylaminoethyl chloride hydrochloride was obtained in 80% yield, m.p. 142–143°.

Anal. Calcd. for $C_{10}H_{15}Cl_2N$: C, 54.54; H, 6.87; Cl, 32.21; N, 6.36. Found: C, 54.35; H, 6.83; Cl, 32.21; N, 6.37.

N,N-Benzylethylaminoethyl chloride hydrochloride was obtained in 63% yield, m.p. 154–155°.

Anal. Calcd. for $C_{11}H_{17}Cl_2N$: C, 56.42; H, 7.32; Cl, 30.28; N, 5.98. Found: C, 56.67; H, 7.06; Cl, 30.36; N, 6.21.

1-Bis(2-hydroxyethyl)amino-2-dialkylaminoethanes (Table II). A.—A solution of 0.05 mole of N,N-dialkylethylenediamine in 50 ml. of absolute ethanol was cooled in an ice bath. To this was added dropwise with stirring and cooling a solution of 0.2 mole of ethylene oxide in 50 ml. of absolute ethanol. After standing for 4 days at room temperature, the reaction mixture was gently refluxed on a water bath for 2 hr. Solvent was removed by distillation, and the residue was fractionated under diminished pressure.

B.—N,N-Dialkylaminoethyl chloride hydrochloride was treated with NaOH solution; the free base thus formed was extracted with ether and dried (K_2CO_3). The ethereal solution was filtered and ether was removed by evaporation under diminished pressure without heating. The residual dialkylaminoethyl chloride was used for the following reaction without further purification. Free aminoethyl chloride (0.1 mole) was added dropwise with stirring to a mixture of 0.2 mole of diethanolamine and 14 g. of finely pulverized anhydrous K_2CO_3, the temperature being held at 60–70°. The reaction mixture was stirred on a steam bath for 5 hr. After cooling, 20 ml. of 20% NaOH solution was added to the mixture, and solid material was removed by filtration. The filtrate was extracted with benzene or chloroform and dried (K_2CO_3 or $MgSO_4$). The solution was filtered, solvent was removed by distillation, and the residue was fractionated under diminished pressure.

1-Bis(2-chloroethyl)amino-2-dialkylaminoethane Dihydrochlorides (Table II).—The diols prepared above were converted to the dihydrochlorides. The diol dihydrochloride (10 moles) was mixed with 5 ml. of $SOCl_2$ and gently refluxed for 3 hr. The excess of thionyl chloride was removed by distillation, and the residue was purified by recrystallization from acetone or reprecipitation from methanol by diethyl ether.

1-(2-Hydroxyethyl)-4-alkylpiperazines (Table I).—The appropriate alkyl halide (0.1 mole) was added dropwise with stirring to a solution of 0.1 mole of piperazineethanol in ethanol, and the mixture was heated on a water bath for several hours. Solvent was removed by distillation (aspirator), and to the residue was added 25 ml. of 20% NaOH. The free base was extracted with $CHCl_3$ three times, dried (K_2CO_3), and fractionated under diminished pressure.

1-(2-Chloroethyl)-4-alkylpiperazine Dihydrochlorides (Table I).—Into 15 ml. of $SOCl_2$ was added, in small portions, 0.02 mole of 1-(2-hydroxyethyl)-4-alkylpiperazine dihydrochloride, and the mixture was gently refluxed for 3 hr. The excess thionyl chloride was removed by distillation (aspirator), and the residue was dissolved in methanol containing a small amount of water and reprecipitated by adding ether.