fones were isolated in the usual manner and, where solid, were crystallized to constant melting point from ethanol. The properties of the sulfones are given in Table II.

Acknowledgment.—The authors wish to thank Mr. J. A. Conyers for assistance in the synthetic work and also Mrs. D. Haresnape and Messrs. R. A. Lowry, D. G. Barnard-Smith, D. H. Desty and W. Crawford for carrying out the fractionations and the determinations of the physical constants which are quoted in this paper.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF MERCK & CO., INC.]

Nitrogen Mustards

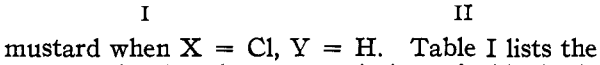
BY EVELYN WILSON AND MAX TISHLER

A number of new compounds belonging to the general class of nitrogen mustards have been synthesized for testing as chemotherapeutic agents against neoplastic diseases.

The discovery of nitrogen mustards (I) as chemotherapeutic agents in the treatment of certain neoplastic diseases[1-7] prompted a coöperative reasearch program with the Sloan–Kettering Institute for Cancer Research in order to explore further the potentialities of nitrogen mustards.

We have prepared a large number of nitrogen mustards and related compounds, which have been screened at the Sloan–Kettering Institute. Since the biological data of many of these compounds have been and are being reported,[8] the chemical data are now presented.

We have mainly been interested in synthesizing compounds that are structural variants of the effective nitrogen mustard N-methyl-β,β'-dichlorodiethylamine (I, R = CH_3).[1-6] Formula II represents the generalized structure of a nitrogen

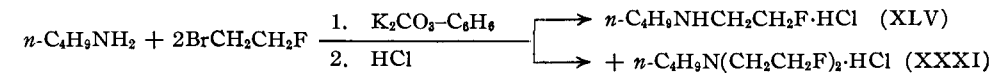


mustard when X = Cl, Y = H. Table I lists the compounds that have a variation of this basic structure. The variations in general were limited to: (1) a change in the nature of the R– group; (2) the introduction into the molecule of an additional β,β'-dichlorodiethylamino group; (3) substitution of the β-chloro-*n*-propyl group (X = Cl, Y = CH_3) for the usual β-chloroethyl group (X = Cl, Y = H); (4) introduction of an additional β,β'-dichlorodipropylamino group into the molecule; (5) substitution of bromine for chlorine; (6) substitution of fluorine for chlorine; and some of the compounds of course show a combination of these structural variations.

A number of other compounds (Table II) were also synthesized. These compounds, although they are not represented by the nitrogen mustard formula II, are related to that class of compounds.

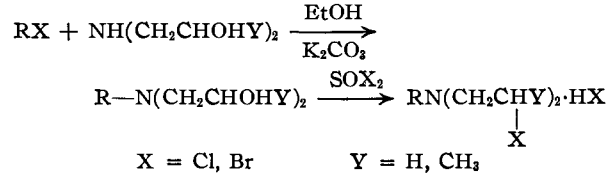
The compounds listed in Table I, except N-*n*-butyl-β,β'-difluorodiethylamine hydrochloride, were prepared by the action of a thionyl halide on the corresponding aminoalcohol or on its halogen acid salt (Table Ia).

N-*n*-Butyl-β,β'-difluorodiethylamine hydrochloride (XXXI) was prepared from the condensation of β-fluoroethyl bromide with *n*-butylamine. Both the mono- (XLV) and disubstituted (XXXI) product form. The two compounds can



be effectively separated however by fractional crystallization of their hydrochlorides from benzene.

The intermediate aminoalcohols that were not commercially available were generally obtained by the condensation of the appropriate alkyl halide and dialkanolamine. The intermediate aminoalcohol whenever possible was purified either by distillation or by conversion into its halogen acid



salt. Whenever either method of purification was not practicable, the crude condensation product was used for the halogenation reaction.

Experimental

The nitrogen mustard-free bases are strong vesicants and are therefore preferably isolated as salts. The salts, although their vesicant action is considerably less than that of the free bases, are sufficiently vesicant to make their handling somewhat hazardous. Handling of these compounds should always be done in a well-ventilated hood; and use of rubber gloves is also recommended. A 3% solution of sodium thiosulfate or potassium permanganate should be used immediately if any spilling or splashing does occur. Precautions should also always be taken to prevent any solid particles of the compound from coming in contact with the eyes.

Procedures for the preparation of specific compounds are described. These procedures however also illustrate the general methods used for the synthesis of the other compounds. The reagents needed, the amount of halogenating reagent required, and the solvent used for crystallization will of course vary for the particular compound being prepared. The tables provide this information. The precursors of the compounds shown in Tables I and II, and their mode of synthesis, are listed in Tables Ia and IIa,

(1) Gilman and Philips, *Science*, **103**, 409 (1946).
(2) Goodman, *et al.*, *J. Am. Med. Assoc.*, **132**, 126 (1946).
(3) Jacobson, *et al.*, *ibid.*, **132**, 263 (1946).
(4) Rhoads, *ibid.*, **131**, 656 (1946).
(5) Tafel, *Yale J. Biol. Med.*, **19**, 971 (1947).
(6) Ap Thomas and Cullumbine, *Lancet*, **1**, 899 (1947).
(7) *J. Am. Med. Assoc.*, **135**, 98 (1947).
(8) Burchenal, *et al.*, *Cancer Res.*, **8**, 385, 387 (1948); **9**, 553 (1949); *Cancer*, **1**, 399 (1948); **2**, 1 (1949); Burchenal, *Radiology*, **50**, 494 (1948); Stock, *Am. J. Med.*, **8**, 658 (1950).

TABLE I

NITROGEN MUSTARDS, R—N($CH_2CH(X)Y)_2$·HX

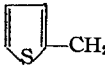
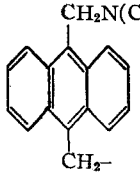
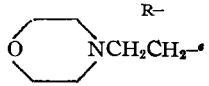
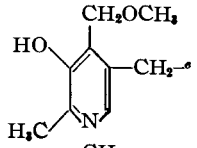
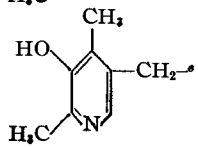
	R–	Method	X	Y	M.p., °C.[a]	Yield, %	Crystn.-solvent	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Chlorine, % Calcd.	Chlorine, % Found
I	$(ClCH_2CH_2)_2NCH_2CH_2CH_2$–[c]	D-2	Cl	H	138–139	42[b]	CH_3OH–$CHCl_3$	$C_{11}H_{24}Cl_6N_2$	33.27	33.39	6.09	5.88	7.06	6.64	53.58	53.50 53.65
II	*n*-C_3H_7–[d]	D	Cl	H	120–121	28[c]	C_6H_6–$CHCl_3$	$C_7H_{16}Cl_2N$	38.11	38.39	7.31	6.50			48.22	48.20
III	$C_6H_5CH_2CH_2$–	D	Cl	H	110–111	50[c]	C_6H_6–$CHCl_3$	$C_{12}H_{18}Cl_2N$	51.00	50.83	6.42	6.65			37.64	37.79
IV	$(BrCH_2CH_2)_2NCH_2CH_2CH_2$–[e]	D	Br	H	170–173 dec.	19[c]	CH_3OH	$C_{11}H_{24}Br_6N_2$							Br 72.24	72.20
V	*n*-$C_{12}H_{25}$–	D-2	Cl	H	67.6–69	72[b]	$CHCl_3$–pet. ether	$C_{16}H_{34}Cl_2N$	55.41	55.32	9.88	9.79			30.67	30.62
VI	$(CH_3CHClCH_2)_2N(CH_2)_3$–[e]	D-2	Cl	CH_3	177–178 dec.	38[b]	$CHCl_3$–CH_3OH	$C_{15}H_{32}Cl_6N_2 \cdot {}^1/_2H_2O$	38.98	39.01	7.20	7.29			46.02	46.00
VII	*n*-C_5H_{11}–	D	Cl	H	79.8–80.6	17[c]	C_6H_6–pet. ether	$C_9H_{20}Cl_2N$	43.48	43.28	8.11	8.18			42.79	42.50
VIII	*n*-C_6H_{13}–	D	Cl	H	82.2–82.8	54[b]	$CHCl_3$–diethyl cellosolve	$C_{10}H_{22}Cl_2N$							40.49	40.40
IX	*n*-$C_{14}H_{29}$–	D-2	Cl	H	73–74.4	64[b]	$CHCl_3$–pet. ether	$C_{18}H_{38}Cl_2N$	57.68	57.75	10.22	10.59				
X	*n*-$C_{16}H_{33}$–	D-2	Cl	H	76.4–77.2	40[b]	$CHCl_3$–pet. ether	$C_{20}H_{42}Cl_2N$	59.62	59.78	10.50	10.59				
XI	$C_6H_5CH_2CH_2CH_2$–	D	Cl	H	99.2–100	52[c]	Acetone–diethyl cellosolve	$C_{13}H_{20}Cl_2N$							35.85	35.80
XII	$(CH_3)_3CCH_2C(CH_3)_2$–C_6H_5–$OCH_2CH_2OCH_2CH_2$–	D	Cl	H	109–112	25[b]	Acetone–ether	$C_{22}H_{38}Cl_2NO_2$	58.08	58.19	8.42	8.45				
XIII	$ClCH_2CH_2$–	D-1	Cl	H	131–132.2	47[b]	Acetone–EtOH	$C_6H_{13}Cl_4N$	29.90	30.23	5.44	5.21	5.81	5.98	58.85	58.70
XIV	$CH_3CHClCH_2$–[h]	D-2	Cl	H	78–79.4	22[b]	$CHCl_3$–EtOH	$C_7H_{15}Cl_4N$							55.62	55.60
XV	$-CH_2-C_6H_4-o-Cl$	D-2	Cl	H	140–141	41[b]	Acetone	$C_{11}H_{15}Cl_4N$							46.79	46.80
XVI	$NO_2-C_6H_4-p-CH_2$–	D	Cl	H	144–146	16[c]	$CHCl_3$	$C_{11}H_{15}Cl_2N_2O$							33.92	33.81
XVII	$(ClCH_2CH_2)_2N(CH_2)_2$–[e,i]	D	Cl	H	109.6–110.8	27[b]	Acetone–CH_3OH	$C_{10}H_{22}Cl_6N_2$	31.35	31.90	5.79	5.92	7.32	7.43	55.54	55.48
XVIII	$CH_3CHClCH_2$–	D	Cl	H	112–113	10[b]	$CHCl_3$–pet. ether	$C_9H_{19}Cl_4N \cdot {}^1/_2H_2O$	37.00	37.00	6.90	6.97			48.56	48.40
XIX	CH_3–	D	Br	CH_3	135–138	17.5[b]	Acetone	$C_7H_{16}Br_3N$							Br 67.73	67.58
XX	C_6H_{11}–	D	Cl	H	178–179	88[b]	Acetone–CH_3OH	$C_{10}H_{20}Cl_2N$							40.82	40.64
XXI		D	Cl	H	128–130	52[c]	C_6H_6–pet. ether	$C_{17}H_{32}Cl_2N$	57.22	57.40	9.04	9.30				
XXII	*n*-$C_{15}H_{31}$–	D-2	Cl	H	73.6–75.8	73[b]	$CHCl_3$–pet. ether	$C_{19}H_{40}Cl_2N$	58.66	58.80	10.37	10.20				
XXIII	α-$C_{10}H_7CH_2$–	D	Cl	H	188–189	68[b]	EtOH	$C_{15}H_{18}Cl_2N$	56.53	56.04	5.69	5.51				
XXIV		D	Cl	H	102–104	12[b]	C_6H_6–$CHCl_3$	$C_9H_{14}Cl_2NS$	39.36	39.61	5.14	5.07				
XXV	$ClCH_2CH_2CH_2$–[g]	D	Cl	H	84–86	64[b]	Acetone–diethyl cellosolve	$C_{17}H_{15}Cl_4N$	32.97	33.25	5.93	5.78				
XXVI	$Cl(CH_2)_{10}$–	E	Cl	H	61–63		Acetone–ether	$C_{14}H_{29}Cl_4N$						Ionic Cl	10.04	10.41
XXVII	$(ClCH_2CH_2)_2N(CH_2)_{10}$–[e]	D	Cl	H	145–148	26[b]	Acetone–EtOH	$C_{18}H_{38}Cl_6N_2$	43.66	43.96	7.73	7.76			42.96	42.74
XXVIII	$C_2H_5OCH_2CH_2CH_2$–	D	Cl	H	75–78	62[b]	Acetone–ether	$C_9H_{20}Cl_2NO$	40.85	40.18	7.62	7.38		Ionic Cl	13.40	13.76
XXIX		E	Cl	H	200–205 dec.		EtOH	$C_{24}H_{30}Cl_6N_2$							38.04	37.86

TABLE I (*Continued*)

	R–	Method	X	Y	M.p., °C.[a]	Yield, %	Crystn.–solvent	Formula	Carbon, % Calcd.	Carbon, % Found	Hyerogen, % Calcd.	Hyerogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Chlorine, % Calcd.	Chlorine, % Found
XXX	 –[e]	E	Cl	H	179–182 dec.	51[b]	CH_3OH	$C_{10}H_{22}Cl_4N_2O$						Ionic Cl 21.61		21.43
XXXI	*n*-C_4H_9–[f]	F	F	H	66–68	6[c]	Acetone–ether	$C_8H_{18}ClF_2N$							17.57	17.80
XXXII		E	Cl	H	173–176 dec.	47[b]	EtOH–acetone	$C_{13}H_{22}N_2O_2Cl_4 \cdot 2H_2O$	37.51	37.69	6.30	5.85		Ionic Cl 17.04		16.90
XXXIII		E	Cl	H	201–240 dec.	41[b]	CH_3OH	$C_{12}H_{20}N_2OCl_4$	41.17	41.50	5.76	5.90		Ionic Cl 20.20		20.12

[a] All melting points are uncorrected. [b] Yield in halogenation reaction. [c] Over-all yield. [d] Free base described by Hanby and Rydon, *J. Chem. Soc.*, 513 (1947). [e] Dihydrohalide. [f] Hydrochloride salt. [g] Free base described by Jones and Wilson, *J. Chem. Soc.*, 547 (1949). [h] Free base described by Ford, Moore, Lidstone and Waters, *ibid.*, 820 (1946). [i] Free base described by Childs, *et al.*, *ibid.*, 2174 (1948).

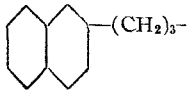
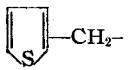
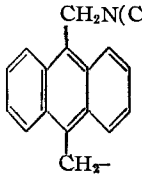
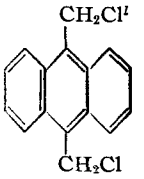
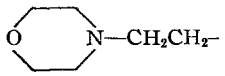
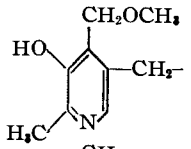
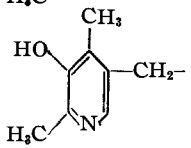
TABLE Ia

INTERMEDIATES FOR NITROGEN MUSTARDS IN TABLE I, R—N—$(CH_2CHOHY)_2$

c.b. = crude base used in halogenation step; D.E.A. denotes diethanolamine; d.b. isolated as distilled free base.

	R–		Used as	Y	M.p., °C.[a]	B.p. °C.	B.p. Mm.	Prepared	Yield, %	Crystn.–solvent	Method
Ia	$(HOCH_2CH_2)_2NCH_2CH_2CH_2$–		2 HCl	H	92.–93.2			1. $Br(CH_2)_3Br$ + 2D.E.A. 2. EtOH–HCl	50	CH_3OH	A-2,3
IIa	*n*-C_3H_7–		c.b.	H				[k]			
IIIa	$C_6H_5CH_2CH_2$–		c.b.	H				RBr + D.E.A.			A
IVa	$(HOCH_2CH_2)_2NCH_2CH_2CH_2$–		c.b.	H				$Br(CH_2)_3Br$ + 2D.E.A.			A-2,3
Va	*n*-$C_{12}H_{25}$–		HCl	H	75–76			[e]	68	Acetone	
VIa	$(CH_3CHOHCH_2)_2NCH_2CH_2CH_2$–		2HCl	CH_3	232–234 dec.			1. $Br(CH_2)_3Br$ + $2NH(CH_2CHOHCH_3)_2$ 2. $CHCl_3$–HCl	60	CH_3OH–acetone	A-2,3
VIIa	*n*-C_5H_{11}–		c.b.	H				RBr + D.E.A.			A
VIIIa	*n*-C_8H_{13}–		d.b.	H		126–130	1.0	RBr + D.E.A.	87		A
IXa	*n*-$C_{14}H_{29}$–		HCl	H				1. RBr + D.E.A. 2. Acetone–concd. HCl	50	Aqueous acetone	B
Xa	*n*-$C_{16}H_{33}$–		HCl	H				1. RBr + D.E.A. 2. Ether–HCl	62		B
XIa	$C_6H_5CH_2CH_2CH_2$–		c.b.	H				RBr + D.E.A.			A
XIIa	$(CH_3)_2CCH_2(CH_3)_2C$—	—OCH_2CH_2– OCH_2CH_2–	d.b.	H		200–210	0.5	RCl[e] + D.E.A.[d]	85		
XIIIa	$HOCH_2CH_2$–		d.b.	H		162–168	1.0	[e]			
XIVa	$CH_3CHOHCH_2$–		HCl	H	132–135			[f]	75		
XVa	–CH_2–*o*–C_6H_4–Cl		HCl	H	100–107			1. RCl + D.E.A. 2. EtOH–HCl	87	EtOH–ether	A
XVIa	–CH_2–*p*–C_6H_4–NO_2		c.b.	H				RBr + D.E.A.			B-2
XVIIa	$(HOCH_2CH_2)_2NCH_2CH_2$–		c.b.	H				[b]			

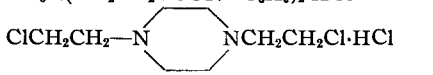
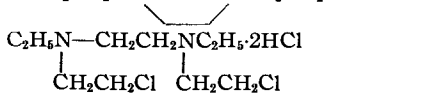
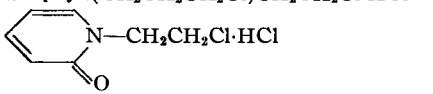
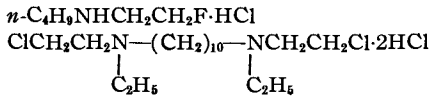
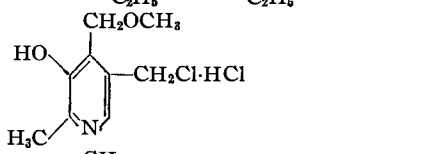
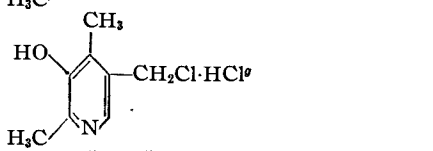
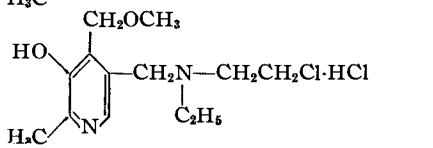
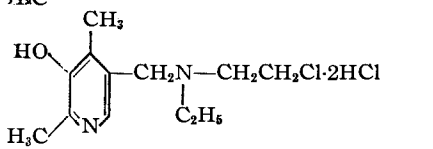
TABLE Ia (*Continued*)

	R–	Used as	Y	M.p., °C.[a]	B.p. °C.	Mm.	Prepared[b]	Yield, %	Crystn.-solvent	Method
XVIIIa	$CH_3CHOHCH_2$–	c.b.	CH_3							
XIXa	CH_3–	d.b.	CH_3		88–96	0.8	CH_3I + $NH(CH_2CHOHCH_3)_2$[k]	60		C
XXa	C_6H_{11}–	d.b.	H		170–175	10	RNH_2 + 2CH_2—CH_2 (O) in CH_3OH; 57°	80		
XXIa		c.b.	H				RBr[g] + D.E.A.			B-1
XXIIa	n-$C_{15}H_{31}$–	HCl	H	73–77			1. RBr[h] + D.E.A. 2. HCl–ether	53	$CHCl_3$–ether	B-1
XXIIIa	α-$C_{10}H_7CH_2$–	d.b.	H		198	1.0	RCl + D.E.A.	54		B-2
XXIVa		d.b.	H		156–158	1.0	RCl + D.E.A.	38		B-2
XXVa	$HOCH_2CH_2CH_2$–	d.b.	H		160–161	0.8	[p]	70		
XXVIa	$HO(CH_2)_{10}$–	HCl	H	75–77			1. RCl + D.E.A. 2. Acetone–HCl	60	Acetone–EtOH	A-1
XXVIIa	$(HOCH_2CH_2)_2N$-$(CH_2)_{10}$–	c.b.	H				$Br(CH_2)_{10}Br$ + 2D.E.A.	52	Acetone	A-5
XXVIIIa	$C_2H_5OCH_2CH_2CH_2$–	d.b.	H		124–130	2.5	RCl[i] + D.E.A.	42		A
XXIXa		2HCl	H				1.  2. EtOH–HCl	87.5	Aqueous EtOH	A-1
XXXa		2HCl	H	125–130 dec.	170–184	2.2[m]	1. RNH_2 + 2CH_2—CH_2 (O); EtOH; 0–15° 2. EtOH–HCl		CH_3OH–EtOH	
XXXIIa		2HCl	H	175–181 dec.			RCl[n] + D.E.A.; EtOH–HCl	49	EtOH–CH_3OH	A
XXXIIIa		2HCl	H	183–187			RCl[n] + D.E.A.; EtOH–HCl	46	EtOH–CH_3OH	A

[a] All melting points are uncorrected. [b] Purchased from Carbide & Carbon Chem. Corp. [c] Supplied by Rohm & Haas Co. [d] U. S. Patent 2,170,111. [e] Purchased from Paragon Chem. [f] Ford-Moore, Lidstone and Waters, *J. Chem. Soc.*, 820 (1946). [g] Prepared from bromine and silver salt of γ-decalylbutyric acid, b.p. 100–106° (0.2 mm.); *cf.*, *Ber.*, **74**, 1567 (1941). [h] Prepared from bromine and silver palmitate, b.p. 152–156° (2.5 mm.); *cf.* ref. *g*. [i] Prepared from decamethylene glycol and phosphorus tribromide, b.p. 128–132° (0.25 mm.), m.p. 24–26° (65%). [j] Prepared from trimethylene chlorobromide and sodium ethoxide in alcohol, b.p. 128–131° (38%). [k] This compound has been prepared by a different method by Hanby and Rydon, *J. Chem. Soc.*, 513 (1947). [l] Badger and Cook, *ibid.*, 805 (1939). [m] Boiling point of free base. [n] Preparation of this halide described in Table II (XLIX, L). [o] Padgett and Degering, *J. Ind. Eng. Chem.*, **32**, 486 (1940). [p] Jones and Wilson, *J. Chem. Soc.*, 547 (1948).

TABLE II

NITROGEN MUSTARD ANALOGS

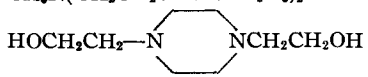
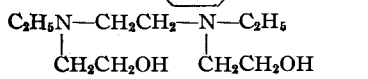
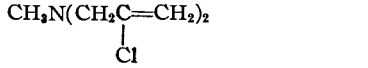
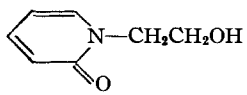
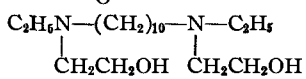
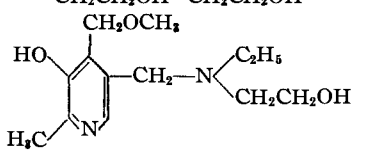
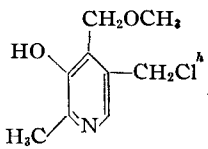
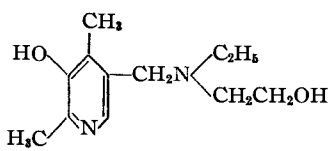
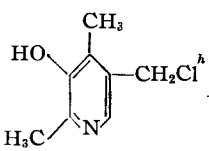
	Structure	M-p., °C.[a]	Yield, %	Crystn.-solvent	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	N or Cl (I, ionic), % Calcd.	N or Cl (I, ionic), % Found	Method
XXXIV	$C_6H_5N(C_2H_5)CH_2CH_2Cl\cdot HCl$[d]	131–132.2	25[b]	Acetone	$C_{10}H_{15}Cl_2N$	54.57	54.66	6.87	6.77			D
XXXV	$CH_3N(CH_2CH_2OCONHC_6H_5)_2\cdot HCl$	192–194 dec.		EtOH–acetone	$C_{19}H_{24}ClN_3O_4$	57.93	57.67	6.14	6.16			G
XXXVI		250 dec.	69[b]	CH_3OH	$C_8H_{18}Cl_4N$	33.92	33.73	6.39	6.25			D-1[e]
XXXVII		159–160	71[b]	EtOH	$C_{10}H_{24}Cl_4N_2$	38.24	38.27	7.70	7.40			D
XXXVIII	$CH_3N(CH_2CCl{=}CH_2)_2\cdot HCl$	145–148	8[c]	Acetone–EtOH	$C_7H_{12}Cl_3N$	38.83	38.99	5.59	5.43	N 6.47	6.91	
XXXIX	$ClCH_2CH_2NHCH_2CH_2NH_2\cdot 2HCl$	163–167	68[b]	CH_3OH	$C_4H_{13}Cl_3N_2$	24.57	25.31	6.90	6.70	N 14.33	14.49	E
XL	$n\text{-}C_4H_9N(CH_2CH_2CH_2Cl)_2\cdot HCl$	78–80		C_6H_6	$C_{10}H_{22}Cl_3N$	45.73	45.68	8.44	8.36	N 5.33	5.30	D
XLI	$n\text{-}C_4H_9NH(CH_2)_4Cl\cdot HCl$	226–229 dec.	65[b]	EtOH–acetone	$C_8H_{19}Cl_2N$	48.02	48.10	9.57	9.48	Cl I 17.72	18.06	D
XLII	$n\text{-}C_4H_9NH(CH_2)_{10}Cl\cdot HCl$	200–205 dec.	60[b]	Acetone	$C_{14}H_{31}Cl_2N$	59.14	59.34	11.00	11.09	Cl I 12.47	12.61	D
XLIII	$n\text{-}C_4H_9N(CH_2CH_2CH_2Cl)CH_2CH_2Cl\cdot HCl$	67–70		Acetone–diethyl cellosolve	$C_9H_{20}Cl_3N$					Cl I 14.26	13.96	E
XLIV		154–157	45[b]	EtOH	$C_7H_9Cl_2NO$					Cl I 18.26	18.14	
XLV	$n\text{-}C_4H_9NHCH_2CH_2F\cdot HCl$	195–200			$C_6H_{15}ClFN$					Cl I 22.79	22.54	F
XLVI		100–101	10[c]	Acetone	$C_{18}H_{40}Cl_4N_2\cdot 2H_2O$					Cl I 15.33	15.15	D
XLVII		138–140	94		$C_9H_{12}Cl_2O_2N$							E
XLVIII		220–225 dec.	53	EtOH	$C_8H_{11}Cl_2NO$					Cl I 17.04	17.19	E
XLIX		177–178 dec.	77[b]	Acetone–CH_3OH	$C_{13}H_{23}Cl_2N_2O_2$					Cl 30.77 Cl I 20.51	30.45 20.28	E
L		211–214 dec.	60[b]	EtOH	$C_{12}H_{21}Cl_3N_2O\cdot H_2O$					Cl I 21.25	21.58	E

[a] All melting points are uncorrected. [b] Yield on halogenation reaction. [c] Over-all yield. [d] Picrate prepared by Ross, *J. Chem. Soc.*, 183 (1949). [e] Alternate synthesis described by Childs, *et al.*, *ibid.*, 2174 (1948). [f] For preparation of free base, m.p. 88–91°, see Procedure E. [g] For preparation of free base, m.p. 133–137° dec., see Procedure E.

TABLE IIa

INTERMEDIATES FOR NITROGEN MUSTARD ANALOGS IN TABLE II

c.b. is crude base; d.b. denotes distilled base; p.b. is crystallized free base.

	Structure	M.p., °C.[a]	B.p., °C.	Mm.	Prepared	Yield, %	Crystn.-solvent	Method	Used as
XXXIVa	$C_6H_5N(C_2H_5)CH_2CH_2OH$		118–122	1.5	[b]				d.b.
XXXVa	$CH_3N(CH_2CH_2OCONHC_6H_5)_2$	74–76			$CH_3N(CH_2CH_2OH)_2$[b] + $2C_6H_5NCO$ (65°)		$CHCl_3$–pet. ether		p.b.
XXXVIa					[b]				c.b.
XXXVIIa			100–106	1.0	$Br(CH_2)_3Br$ + $2C_2H_5NHCH_2CH_2OH$	40		A	d.b.
XXXVIIIa			78–80	40	CH_3NH_2 + $2CH_2{=}CCH_2Cl$			*d*	d.b.
XXXIXa	$HOCH_2CH_2NHCH_2CH_2NH_2 \cdot 2HCl$	114–116			$HOCH_2CH_2NHCH_2CH_2NH_2$ + EtOH–HCl			*e*	2HCl
XLa	$n\text{-}C_4H_9N(CH_2CH_2CH_2OH)_2$		122–128	1.0	$n\text{-}C_4H_9NH_2$ + $2ClCH_2CH_2CH_2OH$	66		A	d.b.
XLIa	$n\text{-}C_4H_9NH(CH_2)_4OH$		84–90	1.0	$n\text{-}C_4H_9NH_2$ + $Cl(CH_2)_4OH$[f]	35		A	d.b.
XLIIa	$n\text{-}C_4H_9NH(CH_2)_{10}OH$	85–94			$n\text{-}C_4H_9NH_2$ + $Cl(CH_2)_{10}OH$	52	Acetone	A-1	b.p.
XLIIIa	$n\text{-}C_4H_9N(CH_2CH_2OH)CH_2CH_2CH_2OH$		112–118	14	1. $n\text{-}C_4H_9NH_2$ + $Cl(CH_2)_3OH$–ether, 25°	18			d.b.
			122–128	1.0	2. $n\text{-}C_4H_9NH(CH_2)_3OH$ + $ClCH_2CH_2OH$	42		A	d.b.
XLIVa					[g]				p.b.
XLVIa					$Br(CH_2)_{10}Br$ + $2C_2H_5NHCH_2CH_2OH$			A-4	c.b.
XLIXa		185–190 dec.			 + $C_2H_5NHCH_2CH_2OH$; $i\text{-}C_3H_7OH$—HCl	16	CH_3OH–$i\text{-}C_3H_7OH$	A	2HCl
LA		220–223 dec.			 + $C_2H_5NHCH_2CH_2OH$; $i\text{-}C_3H_7OH$—HCl	20	EtOH–CH_3OH	A	2HCl

[a] All melting points are uncorrected. [b] Purchased from Carbide & Carbon Corp. [d] Wichterle and Hudlicky, *Coll. Czech. Comm.*, **12**, 101 (1947); *C. A.*, 41, 4148 (1947). [e] Kitchen and Pollard, *J. Org. Chem.*, **8**, 342 (1943). [f] From tetrahydrofuran and hydrogen chloride, "Org. Syntheses," Coll. Vol. II, p. 571 1943. [g] Knunjanz, *Ber.*, **68**, 397 (1935). [h] For preparation of alkylating halide, see Table II, XLVII, XLVIII.

respectively. Tables Ia and IIa also indicate whether these intermediates were used crude, as distilled free bases, or as salts.

The presence of thionyl chloride or thionyl bromide in the reaction product enhances the solubility of the nitrogen mustard. All halogenating agent should therefore be removed before an attempt is made to crystallize the nitrogen mustard product. (It is particularly necessary to do this when thionyl bromide[9] is the halogenating agent.) Since water accelerates the cyclization of β,β'-dichlorodiethylamines, only anhydrous solvents should be used.

Alkylation. A. γ-Phenylpropyl Diethanolamine (XIA).—A mixture of 100 g. (0.5 mole) of γ-phenylpropyl bromide, 52.5 g. (0.5 mole) of diethanolamine and 35 g. (0.25 mole) of anhydrous potassium carbonate in 200 cc. of absolute ethanol was stirred and heated at reflux temperature for 48 hours. The mixture was cooled, and 200 cc. of chloroform was added. After several hours at room temperature the mixture was filtered; the solid was washed thoroughly with chloroform, and the combined filtrates were concentrated *in vacuo*. The residue was a colorless oil. (1) In the alkylation of diethanolamine with decamethylene chlorohydrin the solvent used for the reaction was xylene–ethanol (4:1); and the reaction time was extended to 72 hours. (2) For alkylation with dihalides two moles of the alkanolamine and one mole of potassium carbonate per mole of dihalide were used. (3) The alkylation with trimethylene bromide was carried out for 64 hours. (4) The reaction time used for the alkylation with decamethylene bromide of ethyl ethanolamine was 72 hours. After filtration and concentration of the reaction mixture water was added to the residue; and the undissolved oil was extracted with chloroform, which was washed with water and dried with anhydrous potassium carbonate. (5) The filtered and concentrated reaction product from the alkylation with decamethylene bromide of diethanolamine was dissolved in water. Solid sodium chloride was added until an oily layer appeared. The oil was separated, dissolved in isopropyl alcohol, and sodium hydroxide pellets were added. The solution was filtered, dried with anhydrous magnesium sulfate and again filtered. Removal of the solvent *in vacuo* left an oil that was dissolved in hot acetone. The acetone solution after being chilled deposited a hygroscopic solid, which was filtered and dried *in vacuo*.

B. *n*-Tetradecyl Diethanolamine Hydrochloride (IXa).—A solution of 138.5 g. (0.5 mole) of tetradecyl bromide, 105 g. (1 mole) of diethanolamine in 400 cc. of diethylcarbinol was heated at reflux temperature overnight. The solution was poured into ice-water, and the oily layer was extracted with ether. The ether layer was washed with water and then extracted three times with dilute hydrochloric acid. The combined acidic extracts were made alkaline with 30% sodium hydroxide solution. The oily layer was extracted with ether; and the ethereal solution was washed with water, brine and then dried with anhydrous potassium carbonate. The ether was evaporated from the filtered solution, and the residue was dissolved in a small amount of acetone. Concentrated hydrochloric acid was added, and the solution was chilled. The white solid was filtered and dried. (1) The alkylation with γ-(β′-decalyl)-propyl bromide was carried out similarly. The solvent used in the alkylation was *n*-butanol, and the reaction mixture was concentrated dry *in vacuo* before the water was added. The material was obtained as the crude free base. (2) The alkylation with *p*-nitrobenzyl bromide was carried out using absolute alcohol as the solvent. The reaction mixture, after removal of the solvent, was dissolved in dilute hydrochloric acid; and the acidic solution was extracted with ether. The acid layer was then treated as in example B. The material was used as the crude free base.

C. Methyldiisopropanolamine (XIXa).—A solution of 284 g. of methyl iodide, 296 g. of diisopropanolamine in 600 cc. of absolute ethanol was heated at reflux temperature for 48 hours. The solvent was removed *in vacuo*, and the residue was made alkaline with 30% sodium hydroxide solution. The mixture was extracted four times with chloroform, and the combined chloroform extracts were dried with anhydrous potassium carbonate. The solution was filtered; the filtrate was concentrated *in vacuo*, and the residual oil was distilled.

Halogenation. D. N-γ-Phenylpropyl-β,β′-dichlorodiethylamine Hydrochloride (XI).—A solution of 90 cc. of thionyl chloride in 100 cc. of chloroform was chilled to 0° in a four-necked, round-bottomed flask equipped with a mercury-sealed stirrer, thermometer, dropping funnel and a very efficient condenser. (The condenser and dropping funnel were fitted with calcium chloride tubes.) A solution of the aminoalcohol (from A) in 100 cc. of chloroform was added slowly to the stirred, chilled thionyl chloride solution at a rate that maintained the temperature of the reaction mixture at 0–10°. The mixture was kept overnight at room temperature and was then heated at reflux temperature a few hours. The mixture was concentrated *in vacuo*. The residue was dissolved in benzene and was again concentrated *in vacuo*. The residue was dissolved in chloroform, treated with Darco and filtered. Benzene was added to the filtrate until crystallization began. The mixture was chilled, filtered, and the solid was recrystallized from acetone–diethyl cellosolve. (1) In a few cases the thionyl chloride in chloroform was added to a chilled chloroform solution of the aminoalcohol. (2) When the alkylated product was isolated as the hydrochloride the halogenation reaction was carried out by adding the solid hydrochloride portionwise at room temperature to a stirred solution of thionyl chloride in chloroform. The reaction mixture was kept overnight at room temperature, heated at reflux temperature for two hours and worked up as in example D.

E. 3-Chloromethyl-4-methoxymethyl-5-hydroxy-6-methylpyridine Hydrochloride (XLVII).—A suspension of 127 g. (0.58 mole) of 3-hydroxymethyl-4-methoxymethyl-5-hydroxy-6-methylpyridine hydrochloride in 250 cc. of chloroform was stirred while 95 cc. of thionyl chloride was slowly added at room temperature. The mixture after remaining at room temperature overnight was heated at reflux temperature for two hours. The mixture was concentrated *in vacuo*, acetone–ether was added to the residue. A crystalline solid was deposited from the chilled solution. The solid was filtered and washed well with ether.

Free Base.—The salt was dissolved in a minimum quantity of water and treated with a saturated solution of sodium bicarbonate until the mixture was alkaline to litmus paper. The solid was filtered, washed well with water and then air-dried.

F. N-*n*-Butyl-β,β′-difluorodiethylamine Hydrochloride (XXXI) and N-*n*-Butyl-β-fluoroethylamine Hydrochloride (XLV).—A mixture of 30 g. (0.4 mole) of *n*-butylamine, 128 g. (1 mole) of β-fluoroethyl bromide, 55.2 g. of anhydrous potassium carbonate in 250 cc. of dry benzene was stirred and heated at reflux temperature 36 hours. The mixture was cooled, filtered, and hydrogen chloride gas was passed into the chilled filtrate. A small amount of ether was added, and the crystalline white solid was filtered and washed with benzene. (This material is *n*-butyl-β-fluoroethylamine hydrochloride, m.p. 185–190°.) The filtrate and benzene washes are combined, concentrated free of solvent *in vacuo*, and the residue was slurried with ether. The oily residue readily solidified to a white fluffy solid, which is N-*n*-butyl-β,β′-difluorodiethylamine hydrochloride, m.p. 66–68°.

Miscellaneous. G. Methyl Diethanolamine-bis-phenylcarbamate Hydrochloride (XXXV, XXXVA).—Phenyl isocyanate (131 g.) was added slowly to 59.5 g. (0.5 mole) of distilled methyl diethanolamine so that the temperature of the reaction mixture did not exceed 65° (an ice-bath was required). The mixture was warmed at 65° a few hours. The glassy mixture was dissolved in hot chloroform, and a small amount of petroleum ether was added. The precipitated white solid, m.p. 74–76° (XXXVA), was dissolved in ether–acetone and chilled while hydrogen chloride gas was bubbled into the solution. The white granular solid was filtered and washed with ether (XXXV).

(9) Elderfield, *et al.*, THIS JOURNAL, **68**, 1581 (1946).

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