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 diseases¹⁻⁷ 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 $n-C_4H_9NH_2 + 2BrCH_2CH_2F = \frac{1. K_2CO_3-C_6F}{2. HC1}$

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 = CH₃).¹⁻⁶ Formula II represents the generalized structure of a nitrogen

$$\begin{array}{ccc} R - N - (CH_2CH_2Cl)_2 & R - N(CH_2CH(X)Y)_2 \\ I & II \end{array}$$

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 = CH₃) 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' - diffuorodiethylamine hydrochloride,

- (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).

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

$$\xrightarrow{\text{D}_3-\text{C}_8\text{H}_6} \xrightarrow{n-\text{C}_4\text{H}_8\text{NHCH}_2\text{CH}_2\text{F}\cdot\text{HCl}} (\text{XLV})$$

$$+ n-\text{C}_4\text{H}_8\text{N(CH}_2\text{CH}_2\text{F})_2\cdot\text{HCl} (\text{XXXI})$$

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

$$RX + NH(CH_{2}CHOHY)_{2} \xrightarrow{EtOH}_{K_{2}CO_{2}}$$

$$R - N(CH_{2}CHOHY)_{2} \xrightarrow{SOX_{2}} RN(CH_{2}CHY)_{2} \cdot HX$$

$$\downarrow X$$

$$X = Cl, Br \qquad Y = H, CH_{3}$$

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).

00	00											Е	VE.	LYI	N I	<i>N</i> 1	LS	OP	N E	IN	D	IVI	AX	(1	ISHLI	ER									VC	DI. 73	٢
	10	Caled. Found 53.58 53.50	53.65 48.20	37.79	72.20	30.62	46.00	42.50	40.40				35.80		01 02	00.00 77	00.00	46.80	33.81	55.48	48.40	67.58	40.64								10.41	42.74	13.76		37.86		
			48.22	37.64	г 72.24	30.67	46.02	42.79	40.49				35.85		20 05	00.00 77	20.02	46.79	33.92	55.54	48.56	Br 67.73	40.82								10.04	42.96	l 13.40		38.04		
	10	7.06 6.64			Br											0.00				7.43		Bı									Ionic Cl 10.04		Ionic CI 13.40				
															10 10	0.0				7.32																	
	70 uono.	Caled. Found 6.09 5.88	6.50	6.65		9.79	7.29	8.18			10.59	10.59		5 7 2 7 2 7 2 7 2 7 2 7 2 7 2 7 2 7 2 7	04.0 16. 1	17.0				5.92	6.97			9.30			10.20	5.07 5.07	0.0	5.78		7.76	7.38				
	Hwd	Caled. 6.09	7.31	6.42		9.88	7.20	8.11			10.22	10.50		67 O	н. 1 1 1 1 1 1	111			:	5.79	6.90			9.04			10.37	5.69 5.14	11.0	5.93		7.73	7.62				
	20 U.	Caled. Found 33.27 33.39	38.39	50.83		55.32	39.01	43.28			57.75	59.78		50 10 10	90 00	67.00				31.90	37.00			57.40		00	08.80 20	30.04 30.61	10.00	33.25		43.96	40.18				
	Carl	Caled. 33.27	38.11	51.00		55.41	38.98	43.48			57.68	59.62		20 00	20.00 00.00	00.07				31.35	37.00			57.22		00	00.00 	20.03 30.36	00.00	32.97		43.66	40.85				
	$K - N(CH_2CH(X)Y)_2 \cdot HX$	Formula C ₁₁ H24Cl6N2	C ₇ H ₁₆ Cl ₈ N	C ₁₂ H ₁₈ Cl ₃ N	C ₁₁ H ₂₄ Br ₆ N ₂	C ₁₆ H ₃₄ Cl ₃ N	C16H32Cl6N2.1/2H2O	C,H20Cl3N	$C_{10}H_{22}Cl_3N$		C ₁₈ H ₃₈ Cl ₃ N	C20H42Cl3N	solve C13H20Cl3N	C.HCLNO.	C.H.CI.N	C.H.C.N				Ci0H22CI6N2	C ₉ H ₁₀ Cl ₄ N·1/ ₂ H ₂ O	C ₇ H ₁₆ Br ₃ N	C10H20Cl3N	C ₁₇ H ₃₂ Cl ₃ N				CIGH 18 CI3N C.H., CI, NS		C ₁₇ H ₁₅ Cl ₄ N	C ₁₄ H ₂₉ Cl ₄ N	C ₁₈ H ₄₈ Cl ₆ N ₂	C ₉ H ₂₀ Cl ₃ NO		C24H30Cl6N2		
	NITROGEN MUSTARDS, K-N(C) Yield.	Crystusolvent CH2OH-CHCl3	C ₆ H ₆ -CHCl ₃	C ₆ H ₆ -CHCl ₃	CH ₃ OH	CHCl ₃ -pet. ether	CHCl ₈ -CH ₃ OH	C ₆ H ₆ -pet. ether	CHCl ₃ -diethyl cel-	losolve	CHCl ₁ -pet. ether	CHCl _s -pet. ether	Acetone-diethyl cellosolve C13H20Cl3N	Acetone ether	Acetone-FtOH	CHCI-FIOH	Anatomo			Acetone-CH ₃ UH		Acetone	Acetone-CH ₁ OH	C ₆ H ₆ -pet. ether			CIICI2-pet. etner	ELUII CeHa-CHCI.		Acetone-diethyl	cellosolve Acetone-ether	Acetone-EtOH	Acetone-ether		EtOH		
	SEN N Vield.	% 42 ^b	28°	50°	19°	72^{b}	38	17c	546		64^{b}		52%	950	476	966	119	1.20		27.0	10^{6}	17.5^{b}	88 88	52°		467	6.00	126		64^{b}		26^{b}	62				
NT-00-1	NITROC	M.p., °C.ª 138-139	120-121	110-111	170–173 dec.	67.6 - 69	177-178 dec.	79.8 - 80.6	82.2-82.8		73-74.4	76.4 - 77.2	99.2 - 100	100-112	131-132 2	78-70 4	140-141	141_011		10.8			62	128-130		79 6 75 0	100 100	102-104		84-86	61-63		75-78		200–205 dec.		
		ЧΗ	Η	Н	Н	Н	CH3	Н	Н		Н	Н	Η	н	H	н	: ¤	1 1	1 2	z ; ;	H	CH,	Н	H		þ	# E	H		Н	Н	Н	Н		н		
		× IJ	ũ	ฮ	Br	บ	Ū	Ũ	อ		ฮ	Ũ	Ũ	Ð	Ū	5	5 2	5 5	5 8	53			Ū	Ũ		ξ	5 2	50		C		ฮ	ū		บ		
		Method X D-2 Cl	D	Q	A	D-2	D-2	Ω	D	l	D-2	D-2	Q		1-CI	<u>1-9</u>			A F	ם נ	A	Ω	D	D		6 (1	i A A	A A		D	ਸ਼	Q	D		E		
		R- (CICH ₂ CH ₂) ₂ NCH ₂ CH ₂ CH ₂ -	n-C ₃ H _r ^d	C,H,CH2CH2-	(BrCH ₂ CH ₂) ₂ NCH ₂ CH ₂ CH ₂ -	n-C ₁₂ H ₂₆ -	(CH ₃ CHCICH ₂) ₂ N(CH ₂) ₃ -	**-C ₆ H ₁₁ -	3-C6H13-	;	n-CitHar-	n-C16H33-	CaH,CH2CH2CH2-CH2-CH2-CH2-CH2-CH2-CH2-CH2-CH	OCH, CH, OCH, CH, CH, -	CICH, CH,-	CH.CHCICH.J	-CHCHCI				CHICHCICH2-	CHr	C ₆ H ₁₁ -	$\sim \sim (^{(CH_2)r})$	\sum	*.C.H			CHr-CHr-	CICH2CH2CH2-	CI(CH ₂) ₁₀ -		C2H6OCH2CH2CH2- CH2N(CH2CH2CI)2			\leftarrow	
		had	IJ	311	IV	Λ	ΝI	IΙΛ	IIIA	;	X	X	XIX XIX		XIII	XIV	ХV	XVI			TITAX	XIX	XX		IXX	1188	IIIAA		1144	ХХУ	ΙΛΧΧ	ΙΙΛΧΧ	IIIVXX	XIXX			

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4 1	Method X Y	M.p.	M.p., °C.¢	Yield, C C	TABLE I (Continued) Crystnsolvent	ed) Formula	Carbon, % Calcd. Found	Hyerogen, % Calcd. Found	, % Nid ound Cale	Nitrogen, % Chi Calcd. Found Calco	Chlorine, % Calcd. Found
NCH ₂ CH ₂ -	E CI H		179–182 dec.	51 ⁴ CH ₄	CH,OH	C ₁₀ H22Cl4N2O				Ionic Cl 21.61	21.43
r CH ₂ OCH	F F H	66-68	8	6° Ace	Acetone-ether	C ₈ H ₁₈ CIF ₂ N				17.57	17.80
CH ₂	ВСІН	173-	176 dec. 47 ⁶		BtOH-acetone	C13H22N2O2C14.2H2O 37.51	20 37.51 37.69	6.30 5.	5.85	Ionic Cl 17.04	16.90
-CH ₂	E CI H		201–240 dec. 41 ⁶		CH ₃ OH	C12H20N2OCI4	41.17 41.50	5.76 5.	5.90	Ionic Cl 20.20	20.12
tts are uncorrec oride salt. " Fi d by Childs, et	• All melting points are uncorrected. ⁶ Yield in halogenation reaction. ^e Over-all yield. ⁴ Free base described by Hanby and Rydon, J. Chem. Soc., 513 (1947). ^e Dihydro- halide. ⁷ Hydrochloride salt. ^e Free base described by Jones and Wilson, J. Chem. Soc., 547 (1949). ^h Free base described by Ford, Moore, Lidstone and Waters, <i>ibid.</i> , 820 (1946). ^e Free base described by Childs, <i>et al.</i> , <i>ibid.</i> , 2174 (1948).	logenation y Jones ar 8).	ı reactic ıd Wilso	on. ^e Ovei on, J. Chem	all yield. ^d Fr t. <i>Soc.</i> , 547 (1949 	ee base described). ^h Free base des	by Hanby and Ry scribed by Ford, Ma	don, J. Chei oore, Lidstoi	m. Soc., 1 ne and W	513 (1947). •] /aters, ibid., 82)ihydro-) (1946).
c.1	TABLE IA INTERMEDIATES FOR NITROGEN MUSTARDS IN TABLE I, R—N—(CH2CHOHY), c.b. = crude base used in halogenation step; D.E.A. denotes diethanolamine; d.b. isolated as distilled free base.	RMEDIATE d in halo	ts FOR N genation	NITROGEN] a step; D.I	TABLE Ia MUSTARDS IN TA E.A. denotes diei	TABLE IA INTERMEDIATES FOR NITROGEN MUSTARDS IN TABLE I, R—N—(CH2CHOHY), se used in halogenation step; D.E.A. denotes diethanolamine; d.b. isolated as di	:H2CHOHY)A isolated as distilled	l free base.	;		
R− (HOCH₄CH₄)ѧNCH₂CH₄CH₂−	H2CH2-	Used as 2 HCl	х Н	М.р., °С." 92. –93.2	°C. ^{B.p.} Mm.		Prepared 1. Br(CH ₂) ₃ Br + 2D.E.A. 2. EtOH-HCI	ž Ž	50 CI	CH30H CH30H	Method A-2,3
n-C _a H ,- C ₆ H ₆ CH ₂ CH ₂ -	i	c.b.	нн			RBr + D.E.A.	3. A.				A
(HOCH2CH2)2NCH2CH2CH2-	H2CH2-	c.b.	H	i		Br(CH ₂) ₃ Br	$Br(CH_2)_3Br + 2D.E.A.$				A-2,3
n-Cl2H2- (CH3CH0HCH2)2NCH2CH2CH2-	H2CH2CH2-	HCI 2HCI	H CH i	75-76 232-234 dec.	3C.	ر 1. Br(CH ₂) ₃ Br + 2. CHCl ₅ -HCl	ь Br(CH ₂) ₃ Br + 2NH(CH ₂ CHOHCH ₃) ₂ 2. CHCl ₂ -HCl		60 ¥0	Acetone CH ₃ OH-acetone	A-2,3
<i>n</i> -C ₆ H ₁₁ -		c.b.	Н			RBr + D.E.A.	E.A.				A
n-C ₆ H ₁₃ -		d.b.	H		126–130	m	E.A.		87 50		A d
n-C14H29-		DH	H			1. RDT \mp U.E.A. 2. Acetone-concd	кыт † л.ь.а. Acetone-concd. HCl	J		Aducous accione	۹
<i>n</i> -C ₁₆ H ₃₃ -		нсі	Н				RBr + D.E.A. Rther-HCl	0	62		в
C ₆ H ₈ CH ₃ CH ₂ CH ₂ CH ₂ - (CH ₃) ₃ CCH ₃ (CH ₃) ₂ C	$-0CH_2CH_2$	c.b. d.b.	н		200-210	6 U	E.A. ^d	ω	85		A
HOCH1CH2- CH1CHOHCH2- -CH2-0-C4H1-C1	UCH1CH1-	d.b. HCI HCI	H H	132-135 100-107	162168		D.E.A.	1	75 87 Bł	BtOH-ether	A
−CH ₂ −∲−C ₆ H₄−NO₂ (HOCH2CH2)≥NCH2CH2−	$H_{2^{}}$	c.b. c.b.	н			Z. EUH-HU RBr + D.E.A.	E.A.				B-2

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Mathed	DOULATIN	C	B-1	B-1	B-2 B-2	A-1	A-5 A	I-A		¥	V	m Paragon , Ber , 74 , , $128-132^\circ$ d by a dif- escribed in
Crystn	soivent			CHCl ₃ -ether		Acetone-EtOH	Acetone	Aqueous EtOH	CH ₃ OH-EtOH	EtOH-CH1OH	EtOH-CH ₃ OH	 Purchased from Paragon 6° (0.2 mm.); cf., Ber., 74, is tribromide, b.p. 128–132° has been prepared by a dif- has been prepared by a dif- n of this halide described in
Yield,	%	60 80		53	54 38	50 60	52 42	87.5		49	46	70,111. 100–10 osphoru opound paratio
	Frepared b	CH ₃ I + NH(CH ₂ CHOHCH ₃) ^k RNH ₂ + $2CH_2$ -CH ₂ in CH ₃ OH; 57°	$RBr^{a} + D.E.A.$	1. RBr ^h + D.E.A. 2. HCl-ether	00	1. RCI + D.E.A.	Z. Accenterated Br(CH ₃) ₁₀ Br + 2D.E.A. RCl ⁱ + D.B.A. CH ₃ Cl ⁱ		2. EtOH 1. RNH 2. EtOH	RCI ⁿ + D.E.A.; EtOH-HCI	RCI ^a + D.E.A.; EtOH-HCI	• Supplied by Rohm & Haas Co. ^a U. S. Patent 2,170,111. roomine and silver salt of γ -decalylbutyric acid, b.p. 100–10 f. g. • Prepared from decamethylene glycol and phosphori thoxide in alcohol, b.p. 128–131° (38%). ^k This compound 1, 805 (1939). ^m Boiling point of free base. ⁿ Preparatio s and Wilson, J. Chem. Soc., 547 (1948).
(pent	Mm.	$0.8 \\ 10$			1.0 1.0	0.8	2.5		2.2m			pplied 1 ine and * Pre ide in a 05 (1930)
	Ċ,	88-96 170-175			198 156-158	160–161	124-130		170-184			Corp. ^e Su from brom i; <i>cf.</i> ref. <i>g.</i> dium ethox ok, <i>ibid.</i> , 80 [*] Jones and
TABLE Ia	M.p., 'C."			73-77		75-77			125–130 dec.	175–181 dec.	183–187	arbon Chem. (). ^e Prepared 156° (2.5 mm.) promide and so adger and Co , 486 (1940).
;	сн з	СН <u>,</u> Н	Н	Н	Н	н	н	Н	н	н	н	(de & C) (1946) p. 152- chlorol chlorol chlorol em., 32
-	Used as c.b.	d.b. d.b.	c.b.	HCI	d.b. d.b.	d.b. HCl	c.b. d.b.	2HCI	2HCI	2HCI	2HCI	n Carbi oc., 820 hylene 3 (1947 2ng. Ch
	R^- CH ₃ CHOHCH ₂ -	CH _I - C ₄ H ₁ -		n-C ₁₆ H ₃₁ -	α -C ₁₀ H ₇ CH ₂ - $\left[\begin{array}{c} \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\$	HOCH ₂ CH ₂ CH ₂ - HO(CH ₂) ₁₀ -	(HOCH ₂ CH ₂) ₁ N-(CH ₂) ₁₀ - a C ₃ H ₆ OCH ₂ CH ₂ CH ₂ - CH ₂ N(CH ₂ CH ₂ OH) ₃			HO HI-CHI-	HO CH _s -CH _s -	 All melting points are uncorrected. ^b Purchased from Carbide & Carbon Chem. Corp. ^e Supplied by Rohm & Haas Co. ^d U. S. Patent 2,170,111. ^e Purchased from Paragon Chem. J Ford-Moore, Lidstone and Waters, J. Chem. Soc., 820 (1946). ^e Prepared from bromine and silver salt of y-decalylbutyric acid, b.p. 100–106° (0.2 mm.); ef. Ber., 74, 1567 (1941). ^h Prepared from bromine and silver palmitate, b.p. 152–156° (2.5 mm.); ef. ref. g. ⁱ Prepared from decamethylene glycol and phosphorus tribromide, b.p. 128–132° (0.26 mm.), m.p. 24–26° (65%). ⁱ 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). ⁱ Badger and Cook, <i>ibid</i>, 805 (1939). ^m Boiling point of free base. ⁿ Preparation of this halide described in Table II (XLIX, L). ^e Padget and Degering, J. Ind. Eng. Chem., 32, 486 (1940). [*] Jones and Wilson, J. Chem. Soc., 547 (1948).
	XVIIIa	XIX a XXa	XXIa	XXIIa	XXIIIa XXIVa	XXVa XXVIa	XXVIIa XXVIIIa	XXIXa	XXXa	XXXIIa	XXXIIIa	 All Chem. 1567 (1 (0.25 n ferent Table

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						0000
Lethod D D-1° D	H O O O H	н Ц	ы	Е	н	E cribed
ound M	6.91 14.49 5.30 18.06 13.96 13.96	22.54 15.15		17.19	30.45 20.28	21.58 lesis des E.
N or Cl (I, ionic), % Caled. Found Method D G D-1 ⁶ D						Cl I 21.25 21.58 E * Alternate synthesis described :c., see Procedure E.
N or Calc	N 6.47 N 14.33 N 5.33 CI 117.72 CI 112.47 CI 112.47 CI 114.26	CI I 22.79 CI I 15.33		Cl I 17.04	CI 30.77 CI I 20.51	Cl I 21.25 ternate syn
en, % Found 6.77 6.16 6.25 7.40	5.43 6.70 8.36 9.48 11.09). ° Al dec., se
Hydrogen, % Calcd. Found 6.87 6.77 6.14 6.16 6.39 6.25 7.70 7.40						C ₁₂ H ₂₁ Cl ₃ N ₂ O·H ₂ O C ₁₂ H ₂₁ Cl ₃ N ₂ O·H ₂ O Picrate prepared by Ross, J. Chem. Soc., 183 (1949). ^e Alternate synthes are E. ^e For preparation of free base, m.p. 133-137° dec., see Procedure E.
n, % Found 57.67 33.73 38.27						<i>Soc.</i> , 18 , m.p. 1
Carbon, % Caled. Found 54.57 54.66 57.93 57.67 33.92 33.73 38.24 38.27						<i>Chem.</i> ce base
33 24 25 C	59 59 59 59 59 50 50 50 50 50 50 50 50 50 50 50 50 50	0				0 oss, J. 1 of fre
nula N V ₃ O ₄ N,		N N2:2H2	N	Q	N_2O_2	N2O·H2 d by R
LOGS Formula C10H1sC12N C13H2aC1NsOs C4H1sC14N CaH1sC14N	C,H12C14N C,H12C14N C,H13C14N C,H13C14N C,H13C14N C,H13C14N C,H2C14N C,H2C14N C,H2C14NO	Ctuburto CtubusCIFN CusHuCUNF-2H2O	C ₆ H ₁₂ Cl ₂ O2N	C ₃ H ₁₁ Cl ₃ NO	C ₁₃ H23Cl2N2O2	C ₁₂ H ₂₁ Cl ₃ N ₂ O·H ₂ O e prepared by Ros ⁹ For preparation (
ANALOC C C C		บ ขึ่ง	J	Ű		C ₁ , icrate 1 E. "F
TABLE II MUSTARD J Suysta- suysta- suysta- suysta- suysta- bue H-acetone	EtOH etone cellosol				CH3OE	d. ^d P edure]
TABLE II NITROGEN MUSTARD ANALOGS ield, Crystn- 25 ^b Acctone C1 ^a H EtOH-acctone 69 ^b CH ₄ OH C1 ^a H C1 ^b EtOH C1 ^a H	 8° Acetone-EtOH 8° Acetone-EtOH 68° CH₄0H 65⁰ EtOH-acetone 60° Acetone Acetone-diethyl cellosolve 45^b EtOH 	Acetone		EtOH	Acetone-CH ₃ OH	30° EtOH ° Over-all yield. 3-91°, see Proced
Vield, Vield, 25 ⁵⁶ Ac 25 ⁹ Ac 69 ⁶ CH	8° Ac 8° Ac 68° CU 65° Et 66° Ac 60° Ac 60° Ac 60° Ac		4		77 ⁶ Ac	60 ⁶ Et ° Over 8891°, s
P		+ 1	94	ec. 53		ec. 60 ion. '
M-p., °C.ª 131–132.2 192–194 dec. 250 dec. 159–160	145-148 145-148 163-167 78-80 226-229 dec. 220-205 dec. 67-70	195-200 100-101	138-140	–225 dec.	177-178 dec.	-214 dec. n reaction base, m.p.
$^{ m M}_{ m 131}$	145 163 163 226 226 226 200 226 154	195	138	220-	177	211- genation of free b
G	HCI	-2HCI) n halog ation o
ure Ji.HCl ^a HC ₆ H ₆) ₂ .HCl NCH ₂ CH ₂ Cl·HCl		cci -NCH2CH2CH2CH2			СН₄N—СН₄СН₂СН₄СІ.НСІ С₂Н₄	CH ₂ N—CH ₂ CH ₂ CH ₂ CI:2HCI C ₂ H ₆ uncorrected. ^b Yield on (1948). ^f For prepara
ure I.HCl ^d IC,H ₆), ICH ₂ Cl	H ₂ Cl H ₂ Cl H ₂ Cl HCl HCl HCl HCl HCl	C ^H ^t	5	ø	H2CH2	H ₂ CH ₄ (
Structure 2CH2CI-H CONHC, NCI NCH	CH4CH4CI CH4CH4CH4CH4CH4CH4CH4CH4CH4CH4CH4CH4CH4C	L12-L12-L12-L12-L12-L12-L12-L12-L12-L12-	СН₁СІ.НСІ	CH2CI-HCI	c ^h C ₁ H ₆	² N-C) C ₂ H ₆ C ₂ H ₆ 1948).
H ₆)CH I ₅ CH ₂ 0 1 ⁻ N	CH ₃ CCI= 2,CC1= 2,CC1= 2,CC1= 2,CC1= 1,CCH ₃) 1,(CH ₃) 1,(CH ₃) 1,(CH ₃) 1,(CH ₃) 1,(CH ₃)	N CURC NHCH,CH H,N-(CI C,H, CH,	-CH	CH2CH2CH2CH2CH2CH2CH2CH2CH2CH2CH2CH2CH2C		CH, CH, 2174 (
C ₄ H ₆ N(C ₂ H ₆)CH ₂ CH ₂ CI.HCl ⁴ CH ₄ N(CH ₂ CH ₂ CH ₂ CI.HCl ⁴ CH ₄ N(CH ₂ CH ₂ OCONHC ₆ H ₆) ₂ .HCl ClCH ₂ CH ₂ -N NCH ₂ CH ₂ Cl.	CH4CH4CI CH4CH4CI CH4CH4CI CH4CH4CI CH4CH4CH4CH4CH4CI CICH4CH4CH4CH4CH4CH4CH CCH4N(CH4CH4CH4CH4CH3CH4CI n-CH4N(CH4,CH4CH4CI)h-HCI n-CH4N(CH4,CH4CH4CI)HCI n-CH4N(CH2,CH4CH4CI)CH4CH4CI -CH4N(CH2,CH4CH4CI)CH4CH4CI+CI	n-CH2CH2CH2CH n-CH4NHCH2CH2FFHCI ClCH3CH3N-(CH2),0-D C3H3 CH3OCH3	\searrow	\rightarrow		points , ibid.,
	н	CIC	HO, H ₃ C	H ^O C H	HaC	• All melting points are uncorrected. ^b Yield on halogenation reaction. • Childs, <i>et al.</i> , <i>ibid.</i> , 2174 (1948). ^f For preparation of free base, m.p. E_{1}
UXXXX VXXX VXXXX VIXXXX	XXXIX IIIIX XXXIX XIII XXI XIII XXII XIIX XIIX		IIATX	XLVIII	XIIX	
XX X X	N XXXXXX X	s xx	X	×	×	H 5

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	J	INTERMEDIA: .b. is crude base;	res ror Ni d.b. denot	TABI TROGEN es distil	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.					
		M.p., °C.ª	B.p., °C.	Mm.		Yield, %	Crystnsolvent	Method Used as	Used as	
XXXIVa XXXVa	CHIN(CH2CH2CH2CH2UH CH1N(CH2CH2OCONHCh4)	74-76	118-122	1.0	$CH_{3}N(CH_{2}CH_{2}OH)_{2}^{b} + 2C_{6}H_{5}NCO$ (65°)		CHCl _s -pet. ether		a.b.	
XXXVIa	HOCHICHI-N NCHICHIOH				٩				c.b.	
XXXVIIa	C ₃ H ₆ N-CH ₂ CH ₂ -N-C ₂ H ₆		100-106	1.0	$Br(CH_2)_3Br + 2C_2H_5NHCH_2CH_2OH$	40		A	d.b.	
XXXVIIIa	снаснаон снаснаон снаснаон хххиша снам(снассесна)		78-80	40	$CH_3NH_2 + 2CH_2 = CCH_2CI$			q	d.b.	
XXXIXa X1.a	Ċl HOCH5CH5NHCH12CH2NH2-2HCl #-C.HaN(CH4CH4CH4OH)-	114-116	122-128	1.0	Ċl HOCH2CH2NHCH2CH3NH2 + BtOH-HCl n-C.Ha.NH3 + 2CICH4CH4.CH3.OH	99		e V	2HCI d.b.	
XLIa	n-C,H,NH(CH2),OH		84-90	1.0	$n-C_{4}H_{9}NH_{2} + Cl(CH_{2}),OH'$	35		V	d.b.	
XLIIa XLIIIa	"-C,H" NH(CH 3 ,I) 0 OH <i>n</i>-C,H" N(CH 3 ,CH 3 OH)CH 3 CH 2 CH 3 OH	85-94	112–118 122–128	14 1.0	<i>n</i> -C _t H ₈ NH ₂ + Cl(CH ₂) ₁₀ OH 1. <i>n</i> -C _t H ₈ NH ₂ + Cl(CH ₂) ₈ OH-ether, 25° 2. <i>n</i> -C _t H ₈ NH(CH ₂) ₅ OH + ClCH ₅ CH ₂ OH	$\frac{52}{18}$	Acetone	A-1 A	b.p. d.b. d.b.	
XLIVa	N-CH ₂ CH ₂ OH				0				p.b.	
XLVIa	_0 C₂H₄Ŋ(CH₂)₀-Ŋ-C₄H₁				$Br(CH_2)_{16}Br + 2C_2H_6NHCH_2CH_2OH$			A-4	c.b.	
	снаснаон снаснаон снаосна				CH2OCH4					
XLIXa	HO CH ₂ -N C ₂ H ₆ H ₁ C N	185-190 dec.			HO $(H_3CH_3CI^h + C_3H_5NHCH_3CH_5OH)$	16	CH ₃ OH- <i>i</i> -C ₃ H ₇ OH	A	2HCI	
LA	СН, НО, Д				CH_{3} HO \bigwedge					
	H ₁ C ^N CH ₁ NCCH ₂ CH ₂ OH	220–223 dec.			$H_{3}C M_{N} = CH_{2}CH_{2}CH_{1}OH_{2}O$	20	EtOH-CH ₃ OH	V	2HCI	
 All mel and Pollard preparation 	ting points are uncorrected. ⁶ Purchased 1 1, <i>J. Org. Chem.</i> , 8 , 342 (1943). ⁷ From to 1 of alkylating halide, see Table II, XLVI	rom Carbide & C. :trahydrofuran aı I, XLVIII.	arbon Corp 1d hydroge	, ^d Wi	• 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 K and Pollard, J. Org. Chem., 8 , 342 (1933). ^f From tetrahydrofuran and hydrogen chloride, "Org. Syntheses," Coll. Vol. II, p. 571 1943. ^g Knunjanz, Ber., 68 , 397 (1935). preparation of alkylating halide, see Table II, XLVIII, XLVIII.	(1947); ^ø Km	; <i>C. A.</i> , 41 , 4148 (194 Injanz, <i>Ber.</i> , 68 , 397	17). ° (1935)	 Kitchen ⁵). ^A For 	

preparation of alkylating halide, see Table II, XLVII, XLVIII.

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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 bromide⁹ is the halogenating agent.) Since water accelerates the cyclization of β , β' -dichlorodiethyl-amines, 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 The mixture was cooled, and 200 cc. of chloroform hours. 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 alkanol-(2) For any 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 con-centration 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 anhy-drous potassium carbonate. (5) The filtered and concen-trated 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 sul-fate 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% so-dium 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.

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

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.

was concentrated *in vacuo*, and the residual oil was distilled. Halogenation. D. N- γ -Phenylpropyl- β , β' -dichlorodi-ethylamine 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' -diffuorodiethylamine 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 etheracetone and chilled while hydrogen chloride gas was bubbled into the solution. The white granular solid was filtered and washed with ether (XXXV).

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