to give 36 g. (79%) of 3,5-difluoroiodobenzene, b.p. 58–60° (17 mm.).

Anal. Calcd. for $C_6H_3F_2I$: C, 30.03; H, 1.26; F, 15.83; I, 52.88. Found: C, 30.23; H, 1.17; F, 15.61; I, 52.68.

This substance was reported[27] as obtained from Dr. G. C. Finger.[15] The structure was confirmed by nitration with fuming nitric acid (d. 1.50) and sulfuric acid at −5°. After pouring onto ice and filtering, a 96.5% yield of 3,5-difluoro-2-nitroiodobenzene was obtained, m.p. 66.5–67.5°. An analytical sample was obtained upon recrystallization from petroleum ether (b.p. 40–60°), m.p. 66.5–67.5°.

Anal. Calcd. for $C_6H_2F_2INO_2$: N, 4.92. Found: N, 5.06.

The amine group of 3,5-difluoro-2-nitroaniline[15] was replaced in the usual way with iodine. This was identical with the sample obtained above (melting point and mixture melting point).

1,3-Difluorofluorenone. A mixture of 8 g. of 1,3-difluoro-5-iodobenzene, 11 g. of methyl *o*-bromobenzoate, and 11 g. of methyl *o*-chlorobenzoate was treated (rapid stirring) with 50 g. of activated copper (added gradually) at a temperature of 200–210° over a period of 1.5 hr. Stirring was continued after the addition, for 0.5 hr., at a bath temperature of 215–218°. The product was obtained from the reaction mixture in the usual way with the cyclodehydration step carried out in polyphosphoric acid. A crude yield of 1.65 g. of the ketone was obtained. Chromatography of 0.2 g. of this material through alumina (benzene) gave two zones. From the faster moving band, light yellow leaflets were obtained. Recrystallization from methanol gave 0.09 g., m.p. 188–189°. The same material was also obtained by subliming the crude product at 130–145° (bath) at 1 mm.

Anal. Calcd. for $C_{13}H_6F_2O$: C, 72.22; H, 2.80; F, 17.58. Found: C, 72.44; H, 2.94; F, 17.61.

From the slower-moving band there was obtained 0.03 g. of a yellow compound, m.p. 224.5–225.5°, which did not sublime at 145° (1 mm.).

Anal. Found: F, 10.46.

Further characterization has not been attempted.

SEATTLE 5, WASH.

---

[27] H. S. Gutowsky, D. W. McCall, B. R. McGarvey, and L. H. Meyer, *J. Am. Chem. Soc.*, **74**, 4809 (1952).

[CONTRIBUTION FROM THE CHEMISTRY RESEARCH LABORATORY OF THE DEPARTMENT OF SURGERY, UNIVERSITY OF WASHINGTON SCHOOL OF MEDICINE]

Derivatives of Fluorene. XI. New Nitrogen Mustards[1]

T. LLOYD FLETCHER AND WILLIAM H. WETZEL

Received January 27, 1960

Some *N*-fluorenyl nitrogen mustards postulated to give more or less tendency for ethylenimmonium ion formation have been designed. The ultraviolet spectra of these and related compounds have been determined, in both neutral and acidic solutions, with a view to studying quaternization (ethylenimmonium ion formation) and in order to correlate these data with possible biological activity. No ethylenimmonium ion formation occurs in most of the compounds reported and protonation of the amine nitrogen is achieved more readily with the amino, dimethylamino, or diethylamino groups than with the mustard group. It is tentatively concluded that a fluorene nitrogen mustard, properly substituted with strong electron donor groups, might exist, at least partially, in the ethylenimmonium ion form.

Prior to this work,[2] only two nitrogen mustard derivatives of fluorene have been reported in the literature, 2-*N*,*N*-di-(β-chloroethyl)aminofluorene[3] and its bromo analogue.

In view of the interesting biological effects of many nitrogen mustards, the variety of biological effects of many substituted fluorenes and the fact that 2-aminofluorene and a number of its derivatives are carcinogenic, we have synthesized a group of *N*,*N*-di-(β-chloroethyl)aminofluorenes and related substances for their own chemical and biological interest and as a background for further specifically tailored nitrogen mustards to be reported on shortly. We were interested in learning the effects of certain changes in the availability of the extra electron pair of the nitrogen atom of the mustard moiety, chemically, spectrally, and ultimately biologically. It was recently suggested[4] that certain structural devices—for example, hydrogen bonding with the electron pair of this nitrogen—would tend to stabilize the β-chloroethylamine form, thus retarding formation of the ethylenimmonium ion and prolonging or potentiating physiological activity of the compound *in vivo*. We felt that this same general purpose could be effected in a series of compounds with the fluorene nucleus properly substituted with electron attracting or electron donating groups. For example, in the case of 2- *N*,*N*-di(β-chloroethyl)amino-7-nitrofluorene the electronegative nitro group would lower the availability of the electron pair on the amine nitrogen and thus inhibit quaternization.

Some of the di-β-hydroxy compounds (See Table I) were prepared by the reaction of ethylene oxide in dilute acetic acid at elevated temperatures and pressures in a bomb. As poor yields resulted with certain amines, the method of bis-β-hydroxyethylation at room temperature[5] was adopted.

---

[1] This work was supported in part by a research grant (C-1744) from the National Cancer Institute, National Institutes of Health, U. S. Public Health Service.

[2] Some of the material was presented at the meeting of the American Chemical Society, New York, September 1957.

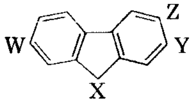
[3] W. Davis, J. L. Everett, and W. C. J. Ross, *J. Chem. Soc.* 1331 (1950).

[4] C. Weatherbee, R. Temple, and W. J. Burke, *J. Org. Chem.* **21**, 1138 (1956).

[5] F. Bergel and J. A. Stock, *J. Chem. Soc.*, 2409 (1954).

TABLE I

Preparation of Nitrogen Mustards



N,N-Di-β-hydroxyethylaminofluorenes																	
Substituents				Method			Yield, %	Recryst. solvent	M.P.° [b]	G. (Di-β-hydroxy Compound)	Mole Ratio: Chlorinating Agent/Amine		N,N-Di-β-chloroethylaminofluorenes				
W	X	Y	Z		Time hr.	Temp.[a]					PCl_5	$POCl_3$	Solvent, ml.	Time, min.	Yield, %	Recryst. solvent	M.P.° [b]
H[c]	H_2	NH_2	H	A[n]	2.8	132	52										
H	H_2	NH_2	H	B[n]	48	—[a]	99	Aq. ethanol	139.5–[d] 141	2	1.2		50	60	49	Abs. ethanol	136–137.5[e]
H[f]	OH, H	NH_2	H	B	48		69	Benzene/ acetone	158–159	0.5	2.4		27	60	34	Abs. ethanol	118.5–121.5[g]
NO_2	H_2	NH_2	H	B[h]	48		80	Abs. ethanol	181–182	0.5		4.8	—	60	36	Toluene	177–180
H[c]	H_2	$N(CH_3)_2$	NH_2	B	70		49	Ether	112–114		1.2		60	90	27	—[i]	195–196.5 (dec. 180)
$NHCOCF_3$[c]	H_2	NH_2	H	B	48		62	Chlorobenzene	191.5–193.5	11.4		4.4	—	90	95	Abs. ethanol	159–160.5
NH_2[c]	H_2	NH_2	H	B	60		50	Acetone/abs. ethanol	201.5–204	1.8		5.4	—	60	65	Abs. ethanol	111–113
H[c]	=O	NH_2	H	A	5	156	78	—[j]	gum	22	1.3		100	120	40		247–249[k]
H[l]	=O	NH_2	Br	A	3	130		Ethanol	127.5[m]–130	0.35	1.3		15	60		Ligroin	135–137[g]

[a] Room temperature unless noted. [b] M.p.'s are corrected to standards. [c] Prepared by the method of T. L. Fletcher and M. J. Namkung, *J. Org. Chem.*, **23,** 680 (1958). [d] Lit. m.p. 137°; J. L. Everett and W. C. J. Ross, *J. Chem. Soc.*, 1972 (1949). [e] Chromatographed before recrystallization, lit. m.p. 138°; see reference in preceding footnote. [f] Prepared by the method of H. L. Pan and T. L. Fletcher, *J. Org. Chem.*, **23,** 799 (1958). [g] Chromatographed before recrystallization. [h] To dissolve the amine (1 g.) it was warmed in a mixture of 40 ml. of acetone, 30 ml. of glacial acetic acid, and 12 ml. of water. Ethylene oxide (8 ml.) was added in portions during a 2-hr. period (40°), then the solution stood at room temperature. Otherwise the procedure is the same as method B. [i] The cooled reaction mixture was shaken with 600 ml. of chloroform and 80 ml. of 2N sodium bicarbonate. The chloroform layer was dried and evaporated to yield white crystals which were recrystallized from absolute ethanol and a chloroform–carbon tetrachloride mixture. [j] After the bomb reaction the crude red gum was washed with water, dried, taken up in chloroform, and the filtered solution used directly in the chlorinating step. [k] The cooled reaction mixture was stirred with ice and the chloroform solution separated and dried, after which it was chromatographed (chloroform) and the fractions evaporated to give a red oil which was characterized analytically as the 2,4-dinitrophenylhydrazone. The latter was recrystallized from a chlorobenzene-xylene mixture. [l] Reported by T. L. Fletcher, M. J. Namkung, and H. L. Pan, *Chem. and Ind.*, 660 (1957). [m] The amine (2.5 g.) gave a crude product which was recrystallized from 95% ethanol to give 0.67 g. of starting material. The filtrate was chromatographed (benzene-methanol), and purple crystals (0.35 g.) of the dihydroxy compound (not analyzed) were obtained. [n] For methods A and B see Experimental.

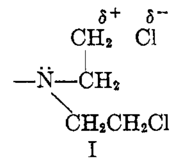
In cases where the amine was insoluble we added acetone to the mixture to effect solution. The yield and quality of the product was in general much better with the latter method. The 9-*N*,*N*-di-(β-hydroxyethyl)aminofluorene was prepared by reaction of 9-bromofluorene with diethanolamine.

In general, if the intermediate hydroxy compound was soluble in chloroform, we chlorinated with phosphorus pentachloride; otherwise, this step was carried out with phosphoryl chloride (see Table I).

Ultraviolet data for these nitrogen mustards and related substances are presented in Table III. It was first found that the spectrum of 2-*N*,*N*-di(β-chloroethyl)aminofluorene was very similar to that of 2-*N*,*N*-diethylaminofluorene and that the spectra in dilute alcoholic hydrochloric acid were changed, and again quite similar to each other. The spectrum of the methiodide of 2-*N*,*N*-diethylaminofluorene was also almost identical with that of the hydrochloride. The change in the spectrum of *N*,*N*-diethylaminofluorene, in going from neutral alcohol to 0.1*N* acidic alcohol (protonized nitrogen), or to the neutral solution of the methiodide (quaternized nitrogen) involved 1) a slight hypsochromic shift (309 mμ to 301 mμ) and 2) the appearance of new peaks (289, 266 mμ in the former case; 289, 267 mμ in the latter).

The spectrum of the analogous nitrogen mustard (Table III; No. 4,4a,5) in neutral solution had a maximum at 300 mμ. In acidic alcohol (0.1*N* concd. hydrochloric acid was added to absolute ethanol) there was no hypsochromic shift, but there was a new peak at 268 mμ and a pronounced shoulder. In more strongly acid solution (0.2*N*) the three characteristic peaks, at 301, 295, and 268 mμ, were observed. Apparently the β-chloroethyl group itself has the same effect in this molecule on the unshared pair of electrons as protonization in the *N*,*N*-diethylamino compound with respect to the small hypsochromic shift.

In the case of the nitrogen mustard, the slight tendency to ionize and the spatial orientation (I) would appear to have altered electronic oscillation enough so that protonization causes no further shift in the 300 mμ band. There is little, if any, ethylenimmonium ion formation, however, as the extra peaks which occur in the spectra of the $N(:H)(C_2H_5)_2^+$ and the $N(:CH_3)(C_2H_5)_2^+$ derivatives are not present in neutral solution. The steric or other effect is sufficient to require stronger (0.2*N*) acid to protonize fully the $—\ddot{N}R_2$ of the mustard.

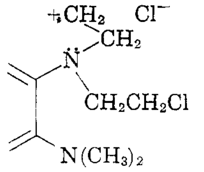


I

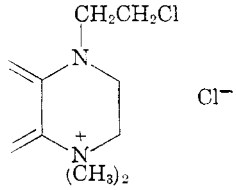
A similar series of spectra of the 7-nitro analogs of the foregoing compounds was studied. It had been observed[6] that the 400 mμ band of the 2-amino-7-nitrofluorene spectrum was hypsochromically displaced to 323 mμ in 0.1*N* alcoholic hydrochloric acid. Presumably, in neutral solution, the unshared electron pair contributed to extended conjugation and a more planar structure; protonization, even in 0.1*N* acid, was sufficient to render the electron pair unavailable for conjugation and the solution became colorless. We obtained the spectrum of this weak amine in more strongly acidic (3*N*) alcohol (Table III; No. 10): no further shift resulted but two shoulders appeared (301, 270 mμ) which were suggestive of the extra peaks found in the spectrum of protonized diethylaminofluorene (and the methiodide). However, in 6*N* acidic alcohol the main absorption (327 mμ) smoothly decreased to a minimum, about 250 mμ, with no hint of shoulders.

With 2-*N*,*N*-di(β-chloroethyl)amino-7-nitrofluorene (Table III; No. 16–19) a more strongly acidic solution (3*N* to 4*N*) was required to show band displacement from the visible part of the spectrum than with the 2-amino-7-nitro- or 2-dimethylamino-7-nitro derivatives. However, spectra of the 7-nitro mustard run at several different acid strengths showed no hint of the complexity observed, even at 0.2*N* acidity, with 2-*N*,*N*-di(β-chloroethyl) aminofluorene.

Thus far 7-*N*,*N*-dimethylamino-2-*N*′,*N*′-di(β-chloroethyl)aminofluorene has been obtained only as a crude oil and we have made no spectral observations. It is of interest, in this connection, that the spectrum of 2-*N*,*N*-dimethylamino-3-*N*′,*N*′-di(β-chloroethyl)aminofluorene (Table III; No. 20,21) is complex, showing four peaks even in neutral alcohol. Solution in acid does not change the absorption appreciably. At first we assumed that this resulted from the strong electron releasing influence of the $—\ddot{N}(CH_3)_2$ group making the unshared electron pair on the mustard group nitrogen sufficiently available for completion of ethylenimmonium ion formation (II). In the absence of sufficient present evidence, including a study of fluorene-3-nitrogen mustard and 3-*N*,*N*-diethylaminofluorene, it seems more likely that the multiple peaks, similar to those observed in the quaternary compounds above, resulted from quaternization of the $—\ddot{N}(CH_3)_2$ nitrogen (III).



II



III

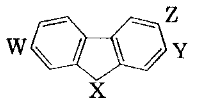
Corresponding data for 7-trifluoroacetamido-2-*N*,*N*-di(β-chloroethyl)aminofluorene is also pre-

---

[6] R. B. Sandin, R. Melby, A. S. Hay, R. N. Jones, E. C. Miller, and J. A. Miller, *J. Am. Chem. Soc.*, **74**, 5073 (1952).

TABLE II[a]

ANALYTICAL VALUES OF NITROGEN-MUSTARDS AND RELATED COMPOUNDS

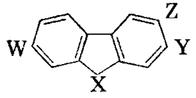


W	X	Y	Z	C Calcd.	C Found	H Calcd.	H Found	Cl Calcd.	Cl Found	N Calcd.	N Found
H	H_2	$N(CH_2CH_2OH)_2$	H	75.81	75.65	7.11	7.08			5.20	5.17
H	H_2	$N(CH_2CH_2Cl)_2$	H	66.67	66.51	5.60	5.41	23.15	23.38	4.58	4.52
H	—OH,—H	$N(CH_2CH_2OH)_2$	H	71.56	71.57	6.71	6.59			4.91	4.98
H	—Cl,—H	$N(CH_2CH_2Cl)_2$	H					31.22	30.92	4.11	3.94
NO_2	H_2	$N(CH_2CH_2OH)_2$	H	64.95	64.92	5.77	5.71			8.91	9.10
NO_2	H_2	$N(CH_2CH_2Cl)_2$	H	58.13	57.90	4.59	4.65	20.19	19.99	7.98	7.70
H	H_2	$N(CH_3)_2$	$N(CH_2CH_2OH)_2$	73.04	73.47	7.74	7.76			8.97	9.09
H	H_2	$N(CH_3)_2$	$N(CH_2CH_2Cl)_2$	65.33	65.56	6.35	6.53	20.30	20.32	8.02	7.73
$NHCOCF_3$	H_2	$N(CH_2CH_2OH)_2$	H			5.04	5.16			7.37	7.47
$NHCOCF_3$	H_2	$N(CH_2CH_2Cl)_2$	H	54.69	54.82	4.10	4.39	16.99	16.95	6.71	6.42
H	=O[b]	$N(CH_2CH_2Cl)_2$	H	55.21	55.14	3.82	3.96	14.18	14.31	14.00[b]	14.12[b]
H	=O	$N(CH_2CH_2Cl)_2$	Br	51.16	51.32	3.54	3.52	17.76[c]	17.43[c]	3.51	3.65
$N(CH_2CH_2OH)_2$	H_2	$N(CH_2CH_2OH)_2$	H	67.72	67.98	7.58	7.49			7.52	7.24
$N(CH_2CH_2Cl)_2$	H_2	$N(CH_2CH_2Cl)_2$	H	56.44	56.11	5.42	5.41	31.78	32.02	6.28	6.52
H	H_2	$N(C_2H_5)_2(CH_3)^+I^-$	H	57.00	57.10	5.85	5.87	33.46[d]	32.97[d]	3.69	3.69

[a] Analyses were made by the Schwarzkopf Microanalytical Laboratories, Woodside, N. Y. Melting points are corrected. [b] Analyzed as its 2,4-dinitrophenylhydrazone derivative. [c] Bromine analysis. [d] Iodine analysis.

TABLE III

ULTRAVIOLET SPECTRAL DATA[a] FOR REPORTED NITROGEN-MUSTARDS AND RELATED COMPOUNDS



No.	W	X	Y	Z	Concentration[b]	λ_{max}, mμ	ϵ_{max}[c]	$\lambda_{(shoulders)}$, mμ
1	H	H_2	$N(CH_2CH_3)_2$	H	3.33	309	3.46	
						301	1.31	293
2	H	H_2	$N(CH_2CH_3)_2$	H	3.68	289	1.06	226
					(0.1*N* HCl)	266	2.87	219
3	H	H_2	$N(C_2H_5)_2CH_3I$	H	2.5	301	1.29	270
						289	1.10	257
						267	2.53	
4	H	H_2	$N(CH_2CH_2Cl)_2$	H	2.5	300	2.95	340
								340
4a	H	H_2	$N(CH_2CH_2Cl)_2$	H	2.5	301	2.20	290
					(0.1*N* HCl)	268	1.36	279
								273
								220
					2.5	301	2.10	278
5	H	H_2	$N(CH_2CH_2Cl)_2$	H	(0.2*N* HCl)	295	1.87	273
						268	1.82	390
		H				307	0.38	
6	H	$N(CH_2CH_2Cl)_2$	H	H	3.33	297	0.42	285
						260	1.77	254
		·HCl				257	1.74	221
						227	1.10	
7	H	OH	$N(CH_2CH_2OH)_2$	H	2.25	318	2.88	254
		H				322	3.19	241
8	NO_2	H_2	NH_2	H	[e]	400		
						261		
9	NO_2	H_2	NH_2	H	(0.1*N* HCl)[e]	323	2.51	
						234		
10	NO_2	H_2	NH_2	H	3.41	325	2.08	270
					(3*N* HCl)	239	1.11	301
11	NO_2	H_2	NH_2	H	3.41	327	1.96	
					(6*N* HCl)	240	1.01	
12	NO_2	H_2	$—N(CH_3)_2$	H	3.28	492	2.44	
						272	1.65	
13	NO_2	H_2	$N(CH_3)_2$	H	3.28	317	2.53	
					(0.1*N* HCl)	238	1.17	
					3.28	321	2.30	
14	NO_2	H_2	$N(CH_3)_2$	H	(4N HCl)	241	0.98	
15[d]	NO_2	H_2	$—N(CH_3)_2$			491	0.97	
			.MeI[d]	H	0.983	314[d]	0.84	247
						279	0.95	

TABLE III *Continued*

No.	W	X	Y	Z	Concentration[b]	λ_{max}, mμ	ϵ_{max}[c]	$\lambda_{(shoulders)}$, mμ
16	NO_2	H_2	$N(CH_2CH_2Cl)_2$	H	3.44	400	2.56	
						269	1.52	
					3.3	404	2.17	
17	NO_2	H_2	$N(CH_2CH_2Cl)_2$	H	(0.2*N* HCl)	271	1.44	
					3.44	321	2.24	
18	NO_2	H_2	$N(CH_2CH_2Cl)_2$	H	(4N HCl)	244	0.88	
					2.064	323	1.94	
19	NO_2	H_2	$N(CH_2CH_2Cl)_2$	H	(6*N* HCl)	245	0.79	
						339	0.64	284
20	H	H_2	$N(CH_3)_2$	$N(CH_2CH_2Cl)_2$	2.5	295	1.20	274
						287	1.00	248
						254	4.14	
					2.5	340	0.64	284
21	H	H_2	$N(CH_3)_2$	$N(CH_2CH_2Cl)_2$	(0.2*N* HCl)	295	1.23	274
						287	1.03	248
						254	4.22	
22	CF_3CONH	H_2	$N(CH_2CH_2Cl)_2$	H	2.5	320	3.39	341
								240
					2.5			345
23	CF_3CONH	H_2	$N(CH_2CH_2Cl)_2$	H	(0.2*N* HCl)	316	2.98	393
								220
					2.5			
24	CH_3CONH	H_2	$N(CH_2CH_2Cl)_2$	H	(4*N* HCl)	312	2.79	283
						293	3.16	220
25	$N(CH_2CH_2Cl)_2$	H_2	$N(CH_2CH_2Cl)_2$	H	2.0	312	3.66	347
								323
					2.5	315	2.31	301
26	$N(CH_2CH_2Cl)_2$	H_2	$N(CH_2CH_2Cl)_2$	H	(0.2*N* HCl)			281
								270
								334
27	$N(CH_2CH_2OH)_2$	H_2	$N(CH_2CH_2OH)_2$	H	1.25	317	4.35	354
						300	1.79	292
					1.25	288	1.53	278
28	$N(CH_2CH_2OH)_2$	H_2	$N(CH_2CH_2OH)_2$	H	(0.1*N* HCl)	267	3.24	272
						262	3.05	252
						258	2.82	227
						220	3.49	
						209	5.45	

---

[a] These spectra were run on a Beckman DK-1 in 1 cm. silica cells. [b] Expressed as concentration in moles times 10^5, in absolute ethanol. [c] Expressed as ϵ max. times 10^{-4}. [d] The data seem to indicate that this is a mixture containing the unchanged $—N(CH_3)_2$ compound (491 mμ) and possibly the $—N(CH_3)^+{}_3I^-$ molecule (314 mμ). The latter band is observed in the spectrum of the hydrochloride as displaced hypsochromically from 492 mμ.

sented (Table III; No. 22,23,24). There is a slight hypsochromic shift in going from neutral to acid solution, and in strongly acidic alcohol a new peak and shoulders are apparent.

The case of the 2,7-bis(nitrogen mustard) (No. 25,26) is noteworthy and merits further study. When first dissolved in neutral alcohol the solution is colorless. Upon standing, especially in light, a yellow color appears which can be discharged with strong acid. Addition of a solution of this compound, which has been standing in light for a short time, to a solution of diphenylpicrylhydrazyl in alcohol discharges the color of the latter.[7] It is conceivable that, under the influence of light (and free radicals) and the electron releasing influence of the nitrogen mustard group, an equilibrium results which includes some of the compound having an ethylenimmonium ion on one of the rings. This form of the molecule would be stabilized like 2-amino-7-nitrofluorene by a contribution of the quinonoid structure containing the $=\overset{+}{N}<$ group on the other ring.[6]

We hope to make further studies with this 2,7-dimustard compound and with 2-*N*,*N*-di-β-chloroethylaminofluorene having strong electron donating groups at the 7-position. If we can obtain multiple absorption bands, as discussed above, but in neutral solution, we will then presumably have a molecule at least partially in the ethylenimmonium ion state.

EXPERIMENTAL

General preparation of di(β-hydroxyethyl)aminofluorenes. Method A.[3] A ratio of 4 to 9 moles of ethylene oxide to 1 mole of the amine was heated in a stainless steel bomb at 130–156° with 2*N* acetic acid (1 g. of amine to 1 ml. of acetic acid solution) for 2.5–13 hr.; the mole ratios and time depended on the nature of the amine. The bomb pressures ranged from 110–130 p.s.i. The crude product was ground in a mortar with warm water, neutralized with sodium carbonate or ammonium hydroxide solution, filtered, washed well with water, and dried. Usually the di(β-hydroxyethyl)-amino product was recrystallized from ethanol (Darco).

Method B.[5] One gram of the amine and 12 ml. of water were mixed and sufficient warm glacial acetic acid added to effect solution. Ethylene oxide (15 to 20 moles) was added to the cooled solution (30 to 40°). The higher ratio of oxide was used with weak amines and the solution was permitted to stand from 48–70 hr. The resulting mixture was neutralized and the product filtered and recrystallized, usually from 95% ethanol. In general, better yields and purer products resulted from method B.

General procedure for chlorinating di(β-hydroxyethyl)aminofluorenes. Method A. When the amine was soluble in chloroform it was chlorinated in this solvent with a slight molar excess of phosphorus pentachloride in a round bottom flask under reflux (drying tube) for 1 hr. The cooled solution was poured over ice and stirred and the chloroform layer separated, dried, and evaporated on the steam bath. The residue was purified by recrystallization from absolute ethanol or by dissolving in benzene and passing through a short column of alumina and then recrystallizing from absolute ethanol.

Method B. The di(β-hydroxyethyl)amine compound was dissolved in an excess of phosphoryl chloride (1 g. of amine to 2.5 ml. of phosphoryl chloride) in a round bottom flask and the mixture was heated on the hot water bath for 1 hr. under reflux (drying tube). The excess phosphoryl chloride was then distilled under vacuum on the steam bath. The resulting solid was dissolved in acetone and the solution poured over ice, with stirring and subsequent neutralization, to yield the fluorenyl mustard. This was recrystallized, after filtering and drying, usually from absolute ethanol.

9-N,N-Di(β-hydroxyethyl)aminofluorene. To 45 g. (0.184 mole) of 9-bromofluorene was added 37 g. (0.352 mole) of diethanolamine in 20 ml. of absolute ethanol; the mixture was heated for 1 hr. on the steam bath in a 300-ml. flask. This was then boiled on a hot plate for 10 min. with addition of 50 ml. of 95% ethanol. Darco was then added, boiling was continued for a few minutes, and the solution was filtered hot. Boiling water was added to the point of precipitation. A yield of 29 g. of white crystals resulted, m.p. 95–98.5°. Second and third crops gave an additional 16.6 g., m.p. 95–98°, giving a total yield of 91.5%.

An analytical sample was obtained after four recrystallizations from ether, m.p. 97.5–98° (cor.)

Anal. Calcd. for $C_{17}H_{19}O_2N$: C, 75.81; H, 7.11; N, 5.20. Found: C, 75.92; H, 7.24; N, 5.42.

9-N,N-Di(β-chloroethyl)aminofluorene hydrochloride. To a suspension of phosphorus pentachloride, 1.93 g (0.0093 mole), in 20 ml. of dry chloroform in a 100 ml. flask equipped with a reflux condenser and a drying tube, 2.1 g. (0.0078 mole) of 9-*N*,*N*-di(β-hydroxyethyl)aminofluorene was gradually added in a few minutes. After refluxing for 1 hr. and cooling, the mixture was poured over ice and stirred. The chloroform solution was separated and evaporated yielding 2.65 g. (quant.) as the hydrochloride salt of the nitrogen mustard. Upon neutralization of a small sample, the amine came out as an oil. After heating the hydrochloride with a little 2*N* hydrochloric acid, the dried product was recrystallized from a chloroform-ether solution four times and once from ethanol to yield a white salt, melting over a range to 138°.

Anal. Calcd. for $C_{17}H_{18}Cl_3N$: Cl, 31.04; N, 4.09. Found: Cl, 31.77; N, 4.27.

2-N,N-Diethylaminofluorene methiodide. This was prepared in the usual way, the analytical sample being obtained after two recrystallizations from absolute ethanol, m.p. 183–184° (see Table II for analyses).

7-Dimethylamino-2-N,N-di-(β-chloroethyl)aminofluorene. Thus far, this has been obtained, as above, only as an oil.

SEATTLE 5, WASH.

---

[7] C. E. H. Bawn and S. F. Mellish, *Trans. Faraday Soc.*, **47**, 1216 (1951).