XIII was 37%. When XII and N,N'-carbonyldiimidazole were allowed to react in N,N-dimethylformamide for 1 hr at room temperature, the yield of XIII was 11%. When the acid XII was treated with 1.05 equiv of $SOCl_2$ in N,N-dimethylformamide at room temperature for 15 min and then allowed to react with diethyl glutamate and triethylamine for 20 hr at room temperature, a very small amount of XIII was formed, as indicated by paper chromatography. The mixed anhydride method[9] was also tried. A mixture of XII and 1.1 equiv of triethylamine in N,N-dimethylformamide treated with 1.2 equiv of isobutyl chloroformate at room temperature for 45 min followed by 2.5 equiv of diethyl glutamate hydrochloride and 2.5 equiv of triethylamine at room temperature for 21 hr yielded 8% of XIII.

N-[*p*-(N-{3-[N-(2-Amino-4-hydroxy-5-pyrimidinyl)amino]-propyl}amino)benzoyl]-L-glutamic Acid (IV).—A solution of 1.00 g (1.74 mmoles) of the triformamido ester XIII in 25 ml of 12 *N* HCl was hydrolyzed at 37° for 1.5 hr under N_2 and evaporated to a syrup *in vacuo* at 25°. The syrup was dissolved in 25 ml of water, treated with charcoal, and filtered. The filtrate was adjusted to pH 2.5 with 1 *N* NaOH and decanted from a small amount of yellow gummy precipitate. The supernatant liquid was adjusted to pH 4 and cooled in ice for 30 min. The precipitate was collected, washed with H_2O and ethanol, and dried to yield 0.45 g (57% as IV·1.33H_2O) as a white powder, mp 164–168°, which gradually acquired a pink color during subsequent handling, perhaps because of air oxidation. Two recrystallizations from H_2O afforded IV as a pink powder: mp 165–167.5°; λ_{max}^{Nujol} (μ) 3.0 (NH, OH), 5.73, 5.88 (COOH); $\lambda_{max}^{pH\ 1}$ 222 mμ (ϵ 14,800), 257–260 plateau (11,000), 295 shoulder (7200); $\lambda_{max}^{pH\ 13}$ 295 mμ (ϵ 25,800); $[\alpha]^{22}D$ −9° (*c* 1.0, 1 *N* HCl); it moved as a single spot in solvents E, D, and C with R_{Ad} 1.86 (blue fluorescence), 1.05 (spot with fluorescent ring), and 0.95 (spot with fluorescent ring), respectively.

Anal. Calcd for $C_{19}H_{24}N_6O_6 \cdot 1.33H_2O$: C, 50.0; H, 5.89; N, 18.4. Found: C, 50.1, 50.1; H, 5.83, 6.02; N, 18.3, 18.4.

Comparison of Ease of Cyclic Methenyl Derivative Formation.—Compounds III, IV, and IX were each dissolved in 97–100% formic acid in the proportion of 0.25 mmole to 5 ml of acid and heated on the steam bath for 1 hr.[16] The solution was evaporated to dryness *in vacuo*. The gummy residue was triturated in $CHCl_3$ or ether and again evaporated to give a foam or powder. The spectrum of the product in 0.1 *N* HCl was measured at intervals. The results are given in Table III, and should be compared with the maximum (313 mμ) for the methenyl compound XIV.[4]

TABLE III
ULTRAVIOLET SPECTRA AT pH 1 AFTER FORMYLATION

	λ_{max}, mμ for product from		
Time	III	IV	IX
0.25 hr	317	268	269
1 day	313	268	270

Acknowledgments.—The authors thank Dr. Peter Lim for interpretation of the infrared spectra and his staff for the ultraviolet spectra and paper chromatography. The authors also thank Mr. O. P. Crews, Jr., and his staff for large-scale preparation of some intermediates.

(16) D. E. Wolf, R. C. Anderson, E. A. Kaczka, S. A. Harris, G. E. Arth, P. L. Southwick, R. Mozingo, and K. Folkers, *J. Am. Chem. Soc.*, **69**, 2753 (1947).

Derivatives of Fluorene. XXII.[1a,b] Nitrogen Mustards. II[1c]

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In a continuation of earlier work, synthesis of a number of new N-2-fluorenyl mustards and such analogs as bis-2-bromoethylamino- and bis-2-halopropylaminofluorenes with various substituents in the 7 position is reported. Dimethyl sulfoxide is found to be a good medium for di-2-hydroxy ethylation; higher yields were obtained in shorter times than in the usual media. Biological data are presented showing that some of these compounds, particularly with activating groups in the 7 position, inhibit some tumor systems and have relatively low toxicity. Synthesis of several new 7-amido-N-fluoren-2-ylamines is described. Ultraviolet spectral properties in neutral and acidic solutions are recorded.

Since the only N-2-fluorenyl mustard (reported earlier[1c]) that showed any tumor inhibitory effect, and that minimal, was the one with a 7-dimethylamino group,[2] we felt that other electron donor groups, particularly in the 7 position, might confer interesting biological properties on compounds in this series. Table I lists data concerning the new chloro and bromo mustards, the corresponding bis-2-halopropyl compounds, and their precursors.

Table II presents the results of biological testing for some of these compounds as supplied by the Cancer Chemotherapy National Service Center and by the Chester Beatty Research Institute. In particular, three of the compounds gave total inhibition of the Walker rat tumor 256.

(1) (a) Paper XXI in this series by H.-L. Pan and T. L. Fletcher appeared in *J. Med. Chem.*, **8**, 491 (1965). (b) Supported in part by a grant (CA-01744) from the National Cancer Institute, National Institutes of Health, and in part by Research Career Development Award 5-K3-GM- (now CA-) 14,991 (T. L. F.). (c) For part I, see T. L. Fletcher and W. H. Wetzel, *J. Org. Chem.*, **25**, 1348 (1960).

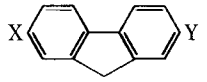
(2) This was obtained and tested only as an impure oil.

An improved method of di-2-hydroxyethylation in dimethyl sulfoxide (DMSO) was used in two cases as described below, and we suggest that such use of DMSO may be valuable with amines having low solubility in the usual media. In this work we found a simpler approach (A in the general chlorination procedure) with high yields, for chlorinating the more stable compounds. Syntheses of the new 7-nitro- and 7-amino-N-2-fluorenylformamides, -propionamides, -urethans, and -N'-*n*-propylureas are reported. All of these 7-amino derivatives (plus the previously reported 7-amino-N-2-fluorenylacetamide), except the formamide, gave analytically pure di-2-hydroxyethylated and di-2-chloroethylated derivatives.

We also have extended the ultraviolet spectral data recorded in our first paper with similar information about the new compounds, including the effect of various concentrations of acid in causing a characteristic increase in complexity of the spectra. The latter effect depends markedly on the nature of the substituents in the 7 position. Examination of the spectral

TABLE I

FLUORENYL NITROGEN MUSTARDS AND RELATED COMPOUNDS



No.	X	Y	Mp, °C	Yield, %	Formula	C, % Calcd	C, % Found	H, % Calcd	H, % Found	Br, % Calcd	Br, % Found	Cl, % Calcd	Cl, % Found	N, % Calcd	N, % Found
1	H	$N(CH_2CHOHCH_3)_2$	149.5–150.5	68[a]	$C_{19}H_{23}NO_2$	76.73	76.76	7.80	7.91					4.71	4.73
2	H	$N(CH_2CHClCH_3)_2$	119–120	95[b]	$C_{19}H_{21}Cl_2N$	68.26	68.14	6.33	6.36			21.21	20.90	4.19	4.18
3	H	$N(CH_2CHBrCH_3)_2$	106–108	31[c]	$C_{19}H_{21}Br_2N$	53.92	53.92	5.00	4.75	37.77	37.85			3.31	3.35
4	F	$N(CH_2CH_2OH)_2$	147–148	61.5[c,d]	$C_{17}H_{18}FNO_2$	71.06	71.30	6.31	6.31					4.88	4.92
										(Fluorine)					
5	F	$N(CH_2CH_2Cl)_2$	126–126.5	80[b]	$C_{17}H_{16}Cl_2FN$	62.97	63.08	4.97	5.35	5.86	6.18	21.88	21.80	4.32	4.09
6	F	$N(CH_2CHOHCH_3)_2$	165–166	55[c]	$C_{19}H_{22}FNO_2$	72.36	71.98	7.03	7.07					4.61	4.99
										(Fluorine)					
7	F	$N(CH_2CHClCH_3)_2$	126–127	95[b]	$C_{17}H_{20}Cl_2FN$	64.78	64.67	5.72	5.86	5.39	5.60	20.13	19.91	3.98	4.09
8	Cl	$N(CH_2CH_2OH)_2$	183–184	72[a,c]	$C_{17}H_{18}ClNO_2$	67.21	67.55	5.97	5.46					4.61	4.57
9	Cl	$N(CH_2CH_2Cl)_2$	155.5–156.5	86[b]	$C_{17}H_{16}Cl_3N$	59.93	59.97	4.73	4.79			31.22	31.57	4.11	4.10
10	Cl	$N(CH_2CH_2Br)_2$	159.5–160.5	87[c]	$C_{17}H_{16}Br_2ClN$	47.53	47.90	3.75	3.86	37.20	36.80	8.25	8.17	3.26	3.01
11	Br	$N(CH_2CH_2OH)_2$	192.5–193.5	85[a,c]	$C_{17}H_{18}BrNO_2$	58.63	58.89	5.21	5.10	22.90	23.30			4.02	4.08
12	Br	$N(CH_2CH_2Cl)_2$	164–165.5	90[b]	$C_{17}H_{16}BrCl_2N$	53.01	52.99	4.19	4.27	20.75	20.88	18.41	18.53	3.63	3.80
13	Br	$N(CH_2CH_2Br)_2$	172–173	96[c,d]	$C_{17}H_{16}Br_3N$	43.07	43.09	3.39	3.23	50.58	50.38			2.96	3.01
14	NO_2	$N(CH_2CH_2Br)_2$	154.5–156	47.5[c,d]	$C_{17}H_{16}Br_2N_2O_2$	46.39	46.61	3.66	3.87	36.31	36.25			6.37	6.62
15	NO_2	$N(CH_2CHOHCH_3)_2$	172–174	44[a]	$C_{19}H_{22}N_2O_4$	66.65	66.67	6.48	6.58					8.18	8.45
16	NO_2	$N(CH_2CHClCH_3)_2$	136.5–138	65[c]	$C_{19}H_{20}Cl_2N_2O_2$	60.16	60.42	5.32	5.25			18.69	18.35	7.39	7.35
17	NO_2	$N(CH_2CHBrCH_3)_2$	146–147.5	65[c]	$C_{19}H_{20}Br_2N_2O_2$	48.74	48.94	4.31	4.10	34.14	34.16				
18	$NHCOCH_3$	$N(CH_2CH_2OH)_2$	188–189	77[a,c]	$C_{19}H_{22}N_2O_3$	69.92	69.76	6.79	6.54					8.58	8.42
19	$NHCOCH_3$	$N(CH_2CH_2Cl)_2$	178 dec	55[b]	$C_{19}H_{20}Cl_2N_2O$							19.52	19.86	7.71	7.39
20	$NHCOCH_2CH_3$	$N(CH_2CH_2OH)_2$	193–194	93[a,c]	$C_{20}H_{24}N_2O_3$	70.56	70.77	7.11	6.88					8.23	8.16
21	$NHCOCH_2CH_3$	$N(CH_2CH_2Cl)_2$	169.5 dec	23[b]	$C_{20}H_{22}Cl_2N_2O$							18.79	18.10	7.43	7.22
22	$NHCOOCH_2CH_3$	$N(CH_2CH_2OH)_2$	159–161.5	79[a,c]	$C_{20}H_{24}N_2O_4$	70.56	70.77	7.11	6.88					8.23	8.16
23	$NHCOOCH_2CH_3$	$N(CH_2CH_2Cl)_2$	114–115.5	48[c]	$C_{20}H_{22}Cl_2N_2O_2$							18.03	17.93	7.13	7.18
24	$NHCONHCH_2CH_2CH_3$	$N(CH_2CH_2OH)_2$	182.5–186 dec	42.5[c,d]	$C_{21}H_{27}N_3O_3$	68.27	68.24	7.37	7.25					11.37	11.27
25	$NHCONHCH_2CH_2CH_3$	$N(CH_2CH_2Cl)_2$	115–117 dec	12.7[b]	$C_{21}H_{25}Cl_2N_3O$							17.45	17.16	10.34	10.26
26	OCH_3	$N(CH_2CH_2OH)_2$	158.5–159.5	86[a,b]	$C_{18}H_{21}NO_3$	72.21	72.14	7.07	7.21					4.68	4.69
27	OCH_3	$N(CH_2CH_2Cl)_2$	141.5–142.5	77[b]	$C_{18}H_{19}Cl_2NO$	64.29	64.45	5.70	5.60			21.09	21.02	4.17	4.20
28	2-OCH_3	3-$N(CH_2CH_2OH)_2$	135–136	92[a,b,e]	$C_{18}H_{21}NO_3$	72.21	72.01	7.07	7.24					4.68	4.69
29	2-OCH_3	3-$N(CH_2CH_2Cl)_2$	93–94	94[b]	$C_{18}H_{19}Cl_2NO$	64.29	64.82	5.70	5.62			21.09	20.41	4.17	4.31

[a] See general procedure (Experimental Section); all melting points are corrected.[9] [b] This was made by one of the three general chlorination procedures. Compounds are listed by number at the beginning of the procedure employed. [c] General bromination procedure. [d] This was also prepared using dimethyl sulfoxide as described in the Experimental Section. [e] See Experimental Section. [f] 7-Chlorofluoren-2-amine was kindly supplied by H.-L. Pan of this laboratory. [g] 2-Bromo-7-nitrofluorene was prepared by the method of N. Campbell and A. F. Temple, *J. Chem. Soc.*, 207 (1957). [h] HBr (48%) was used as in the preparation of N,N-bis(2-bromo-1-propyl)-7-nitrofluoren-2-amine described in the Experimental Section. The amine was added over a 0.5-hr period. [i] See footnote 4 for the reduction of N-2-(7-nitrofluorenyl)acetamide; however, the Pd–C catalyst[9] is better for this reduction. [j] See Experimental Section for preparation of the starting material. [k] 2-Methoxyfluoren-7- (and -5-) amines were prepared by reducing[5] the corresponding nitro compound. The latter was made by the method of N. Ishikawa and M. Okazaki, *Yuki Gosei Kagaku Kyokai Shi*, **16,** 467 (1958); however, we used a modified procedure for making 2-hydroxyfluorene [M. J. Namkung and T. L. Fletcher, *Org. Syn. Japan*, **15,** 74 (1964)]. [l] See footnote *k* for method; the bis-2-hydroxyethylated compound was recrystallized from ether.

TABLE II

ANTITUMOR ACTIVITY OF SOME N-2-FLUORENYL NITROGEN MUSTARDS

A. CCNSC[a]

No.[b]	Tumor system[c]	Daily dose, mg/kg	Survivors	Tumor wt, mg (or survival, days) T/C	% T/C
13	AA[d]	100	3/3		
	AA	33.0	3/3		
	AA	10.0	3/3		
	AA	3.0	3/3		
	WA[d]	500	4/6	0.0/6.1	0
	WA	250	6/6	1.0/6.1	16
	WA	125	5/6	6.0/6.1	98
	WA	62.5	6/6	(3.0/6.1)	49
21	LE	400	5/6	(8.2/8.6)	95
	AA[d]	100	3/3		
	AA	33.0	3/3		
	AA	10.0	3/3		
	AA	3.0	3/3		
	WA[d]	200	6/6	1.4/4.0	35
	WA	100	6/6	3.4/4.0	85
	WA	50.0	6/6	5.0/4.0	125
	WA	25.0	6/6	(3.7/4.0)	92
23	SA	500	0/6		
	SA	250	6/6	691/1057	65
	LL	250	2/6	185/548	
	LL	125	3/6	668/813	
	LL	100	1/6	275/736	
	LL	50.0	6/6	234/538	43
	LL	50.0	5/6	340/785	43
	LL	50.0	3/6	295/851	
	LL	50.0	4/6	28/495	5
	LL	50.0	5/6	293/494	59
	LL	50.0	5/6	768/1013	75
	LL	50.0	4/6	243/589	41
25	LE	100	6/6	(8.3/8.6)	96
2	D[e]				
3	D[f]				
14	D[g]				

B. CBRI[h]

No.[b]	C/T[i]	Dose, mg/kg	Toxic deaths
2	1.28	100	Toxic
3	1.2	100	None
7	0.8	100	None
10	7	200	*j*
12	1.1	100	*j*
14	1.02	100	*j*
17	0.9	100	None
19	1.6	125	*j*
	∞[k,l]	250	None
21	∞[l]	640	None
23	3	160	None
25	∞[l]	640	None

[a] The screening data in part A were kindly supplied by the Cancer Chemotherapy National Service Center, National Institutes of Health, Bethesda, Md. Assays on the first four compounds, still incomplete, are being performed according to specifications established by the CCNSC as reported in *Cancer Chemotherapy Rept.*, **25**, 1 (1962). [b] From Table I. [c] AA, toxicity test (tested in random-bred albino rats or in BCF_1 mice); WA, Walker carcinosarcoma 256 (tested as for AA); LE, L1210 lymphoid leukemia (in BALB/c or BCF_1 mice); SA, Sarcoma 180 (in Swiss mice); LL, Lewis lung carcinoma (in BALB/c mice); D, Dunning rat leukemia. [d] Incomplete; multiple-dose assay. [e] Compound reported as weakly active. [f] Tests incomplete; compound reported as active and toxic (6/6) at 500 mg/kg. [g] Tests incomplete; compound reported as active and nontoxic (0/3) at 500 mg/kg. [h] The screening data in part B were kindly supplied by the Chester Beatty Research Institute (Mr. J. L. Everett). [i] Average weight of control tumors over average weight of treated tumors; tested on Walker 256. [j] No apparent damage. [k] This compound, tested on the Crocker tumor (rats), gave a C/T of 2.4 with 1 death at 2000 mg/kg. [l] ∞ = total inhibition.

data for this limited series of compounds, based on the reasoning in the earlier paper,[1c] leads to the following observations. (1) Bromo mustards are more basic than the analogous chloro mustards; more acidic conditions are required to alter the spectra of the latter to the same degree. (2) Chloroethyl mustards are slightly more basic than the corresponding chloropropyl compounds although a nitro group in the 7 position makes this difference insignificant; in contrast, the 7-nitrofluorenyl-N-2-bromopropyl mustard is significantly *more* basic than its bromoethyl analog. (3) Bis(2-hydroxyalkyl)aminofluorenes are all more basic than the corresponding bis(2-haloalkyl)aminofluorenes. These data are presented in Table III.

Experimental Section[3]

General Procedures of N,N-Bis(2-hydroxyalkyl)aminofluorenes.—This method was essentially the same as method B in an earlier report.[1c] It appeared to improve yields and quality in many cases when 50% additional ethylene oxide (or propylene oxide) was added after the first day.

Di-2-hydroxyethylation in Dimethyl Sulfoxide. 2,2'-(Fluoren-2-ylimino)diethanol.—To a solution of 18.1 g (0.1 mole) of fluoren-2-amine in 100 ml of DMSO, 50 ml of ethylene oxide was added with thorough mixing. To this 10 ml of 1 *N* HCl was added and clear green solution was allowed to stand overnight. A white precipitate was filtered off and dried giving 25.2 g (94%) of the product, mp 138–139°.[1c] By diluting the filtrate with water, we recovered an additional 1.6 g (5%) of the product, mp 137–139°.

2,2'-(7-Fluorofluoren-2-ylimino)diethanol.—A similar procedure was followed with 7-fluorofluoren-2-amine. No precipitate formed and the solution was diluted with 3 vol of water. A crude yield of 93% was obtained which gave 80%, mp 147–148°. This is 20% better than by the usual method and was obtained in about one-fourth the time.

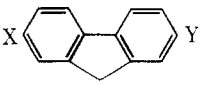
General Procedures of N,N-Bis(2-chloroalkyl)fluoren-2-amines. A.—The following procedure was used for compounds (Table I) **2**, **5**, **7**, **9**, and **12**. The same proportions of reactants were used as described in chlorination method B in the previous paper.[1c] However, a simplified procedure was used in the preparation of the more stable mustards; in general, these are compounds with halogen or nitro in the 7 position. The bis(2-hydroxyalkyl)amine was placed in a suction flask and freshly distilled $POCl_3$ was added with initial external cooling and thorough mixing. After the vigorous reaction subsided, the mixture was heated to 120° for 3 min. Excess $POCl_3$ was evaporated off on the steam bath under vacuum (water aspirator). The gummy product was taken up in absolute ethanol which was boiled briefly with Darco (~250 ml to 15 g of the starting amine). The filtered solution was boiled down to 100 ml or less and cooled with the addition of 20 ml of acetone to obtain the product.

B.—The following procedure was used in the synthesis of compounds **23**, **25**, **27**, and **29**. The bis(2-hydroxyalkyl)amine was dissolved in an excess of freshly distilled $POCl_3$ (1 g of amine to 2.5 ml) under reflux, and the mixture was heated on the steam bath for 1 hr with occasional stirring. Excess $POCl_3$ was then distilled *in vacuo* and the residue was poured over ice. This mixture was made slightly alkaline with concentrated NH_4OH to yield the crude mustard which was recrystallized (benzene, benzene–ligroin (bp 30–60°)). With some crude products subsequent purification was aided by filtering the warm benzene solution through a 2.5-cm layer of alumina in a Büchner funnel

(3) Melting points were taken on a Fisher-Johns block and are corrected to standards. Analyses were performed by Schwarzkopf Microanalytical Laboratories, Woodside, N. Y., and by A. Bernhardt, Mülheim (Ruhr).

Table III

Ultraviolet Spectral Data[a] for Fluorenyl Nitrogen Mustards and Related Compounds



No.[b]	X	Y	Concn, moles × 10^5	λ_{max}, mμ	$\epsilon_{max} \times 10^{-4}$	Sh, mμ
1	H	$N(CH_2CHOHCH_3)_2$	2.5	306	2.97	230, 343
			2.5 (0.1 *N* HCl)	301	1.22	293, 277, 272,
				289	0.97	262, 257,
				266	2.44	227, 219
2	H	$N(CH_2CHClCH_3)_2$	2.5	301	3.02	330
			2.5 (0.1 *N* HCl)	301	2.56	270, 330
			2.5 (0.2 *N* HCl)	301	0.61	330, 270
3	H	$N(CH_2CHBrCH_3)_2$	2.0	304	2.97	341
			2.0 (0.1 *N* HCl)	302	2.09	339, 292, 279,
				267	1.85	273, 221
4	F	$N(CH_2CH_2OH)_2$	2.5	303	3.14	335
			2.5 (0.1 *N* HCl)	304	1.02	298, 275, 260
				292	0.84	
				264	2.38	
5	F	$N(CH_2CH_2Cl)_2$	2.5	298	3.11	328
			2.5 (0.1 *N* HCl)	303	2.06	330, 271,
				297	2.08	
			2.5 (0.2 *N* HCl)	304	1.84	281, 275, 266,
				298	1.80	330
				269	1.57	
6	F	$N(CH_2CHOHCH_3)_2$	2.5	304	2.94	344
			2.5 (0.1 *N* HCl)	304	1.04	296, 275, 259
				292	0.84	
				264	2.36	
7	F	$N(CH_2CHClCH_3)_2$	2.5	299	3.07	330
			2.5 (0.1 *N* HCl)	298	2.75	330
			2.5 (0.2 *N* HCl)	298	2.66	330, 302
8	Cl	$N(CH_2CH_2OH)_2$	2.5	313	3.02	345, 232
			2.5 (0.1 *N* HCl)	306	1.43	282, 277, 268,
				294	1.18	263, 221
				272	2.83	
9	Cl	$N(CH_2CH_2Cl)_2$	2.5	307	3.22	340
			2.5 (0.1 *N* HCl)	306	2.69	228
10	Cl	$N(CH_2CH_2Br)_2$	2.5	308	3.24	343, 240
			2.5 (0.1 *N* HCl)	306	2.11	342, 289, 296,
				272	1.98	284, 278,
						267, 262, 221
11	Br	$N(CH_2CH_2OH)_2$	2.5	315	2.97	345, 233
			2.5 (0.1 *N* HCl)	306	1.24	232
				299	1.14	
				294	1.24	
				272	2.68	
				266	2.72	
12	Br	$N(CH_2CH_2Cl)_2$	2.5	307	3.49	342, 232
			2.5 (0.1 *N* HCl)	306	2.99	342
			2.5 (0.2 *N* HCl)	306	2.79	344, 300, 287,
						279, 275
14	NO_2	$N(CH_2CH_2Br)_2$	3.33	410	2.49	
				272	1.49	
			3.33 (0.1 *N* HCl)	410	2.19	250
				274	1.41	
			3.33 (0.2 *N* HCl)	410	2.07	250
				275	1.37	
			3.33 (2.0 *N* HCl)	420	0.78	296, 286
				319	1.61	
				246	0.92	
15	NO_2	$N(CH_2CHOHCH_3)_2$	3.33	430	2.35	
				275	1.48	
			3.33 (0.1 *N* HCl)	318	2.23	240
			3.33 (2.0 *N* HCl)	320	2.30	
				240	1.29	
16	NO_2	$N(CH_2CHClCH_3)_2$	3.33	410	2.30	
				270	1.49	
			3.33 (0.1 *N* HCl)	410	2.26	
				271	1.47	

TABLE III (*Continued*)

No.	X	Y	Concn, moles × 10^5	λ_{max}, mμ	$\epsilon_{max} \times 10^{-4}$	Sh, mμ
16	NO_2	$N(CH_2CHClCH_3)_2$	3.33 (0.2 *N* HCl)	410	2.22	
				271	1.50	
			3.33 (2.0 *N* HCl)	417	1.15	250
				323	0.86	
				276	1.23	
			3.33 (4.0 *N* HCl)	321	2.09	412
				244	0.92	
17	NO_2	$N(CH_2CHBrCH_3)_2$	3.33	422	2.28	
				276	1.52	
			3.33 (0.1 *N* HCl)	415	1.34	
				319	1.12	
				280	1.15	
				249	0.91	
			3.33 (0.2 *N* HCl)	413	1.24	
				319	1.17	
				281	1.13	
				249	0.91	
			3.33 (2.0 *N* HCl)	420	0.71	282
				320	1.55	
				246	0.90	
18	$NHCOCH_3$	$N(CH_2CH_2OH)_2$	2.5	318	3.44	255
			2.5 (0.1 *N* HCl)	317	2.44	304, 221
				293	2.96	
			2.5 (0.2 *N* HCl)	317	2.44	305, 222
				293	3.00	
19	$NHCOCH_3$	$N(CH_2CH_2Cl)_2$	2.5	314	2.79	343
			2.5 (0.1 *N* HCl)	314	2.27	342
			2.5 (0.2 *N* HCl)	312	2.16	242, 295
26	CH_3O	$N(CH_2CH_2OH)_2$	2.5	304	3.44	338
			2.5 (0.1 *N* HCl)	315	1.22	302, 220
				182	2.47	
			2.5 (0.2 *N* HCl)	315	1.19	302, 219
				283	2.44	
27	CH_3O	$N(CH_2CH_2Cl)_2$	2.5	334	0.88	348
				299	3.52	
			2.5 (0.1 *N* HCl)	285	2.53	314, 302, 219
			2.5 (0.2 *N* HCl)	284	2.71	313, 302, 253, 249, 220

[a] These spectra were run on a Beckman DK-1 in 1-cm silica cells in commercial absolute ethanol or, for **8, 9, 10, 26,** and **27**, in absolute ethanol redistilled from CaO. [b] From Table I.

C.—This method was used for some of the mustards with an activating group in the 7 position (see **19** and **21**, Table I). The bis(2-hydroxyalkyl)amine was added with swirling to an excess of ice-cold freshly distilled $POCl_3$ and the mixture was allowed to stand in ice for 0.75 hr. It was then cautiously heated in a water bath with occasional swirling, with the temperature rising to 95° in 15 min, and then further heated just under the boiling point of water with occasional swirling for 30 min or until the solid was in solution. The mixture was then poured on ice, with thorough stirring to destroy excess $POCl_3$, and made slightly basic with concentrated NH_4OH, filtered, and washed. The precipitate was spread thin and dried in a vacuum for a short time since overnight drying in air seemed to result in decomposition of these unstable mustards. The product was extracted once with benzene (50 ml to 10 g of starting amine) at room temperature and then three times with hot benzene. The combined filtrates were dried ($MgSO_4$) and filtered, and the solution was boiled down (30 ml for 10 g of starting amine) and, upon cooling, enough ligroin was added to precipitate the nitrogen mustard, usually pure enough for analysis or use. Further crystallization often gave progressively poorer material.

General Procedure of N,N-Bis(2-bromoalkyl)fluorenamines.—To the N,N-bis(2-hydroxyalkyl)fluoren-2-amine contained in a suction flask PBr_3 (20 g to 10 g of the amine) was added gradually with stirring (*Caution:* a violent reaction may ensue if the addition is too sudden!). Usually there was a strong exothermic reaction and the temperature rose to near 100° with the evolution of fumes. The gummy mixture was heated briefly to 120° and excess PBr_3 was evaporated off under vacuum. The gummy product was dissolved in acetone and poured over ice, and the mixture was made slightly alkaline with NH_4OH to give a white precipitate. This was filtered, washed with water, and finally with a few milliliters of acetone–absolute ethanol. The dried crude product was usually recrystallized as rapidly as possible from absolute ethanol, benzene, or ethyl acetate.

2,2′-(7-Fluorofluoren-2-ylimino)dipropanol.—To a solution of 10 g of 7-fluorofluoren-2-amine in 100 ml of acetic acid and 100 ml of water (warmed until homogeneous and then cooled to 35°) 55 ml of propylene oxide was added with swirling. After 1 day a further 25 ml of propylene oxide was added and the reaction was allowed to continue 2 more days. The mixture was worked up to give 13.2 g of crude product. After two recrystallizations from alcohol the white crystals (8.7 g, 55%) melted at 161–163°. A small amount of the compound was again recrystallized to give an analytical sample.

N,N-Bis(2-chloro-1-propyl)-7-nitrofluoren-2-amine.—2,2′-(7-Nitrofluoren-2-ylimino)dipropanol (10 g) was added cautiously to 50 ml of freshly distilled $POCl_3$ in a 200-ml round-bottomed flask with thorough swirling, and the mixture was heated on the steam bath under reflux for 1 hr. The excess $POCl_3$ was then evaporated off, and the cooled red oil was dissolved in dry acetone and poured over ice. The mixture was made barely alkaline with concentrated NH_4OH and ground in a mortar, giving a crude yellow-orange product, mp 120–125°, which was extracted with two 300-ml portions of boiling ligroin (*d* 0.72–0.74). The extracts were combined and boiled down to ~100 ml to give an 80% crude yield, mp 121.5–128.5° with softening. Recrystallizatoin twice from benzene gave a 65% yield (see Table I).

N,N-Bis(2-bromo-1-propyl)-7-nitrofluoren-2-amine.—To 70 ml of PBr_3 containing 10 drops of 48% HBr, in a 200-ml round-bottomed flask, 15 g of 2,2′-(7-nitrofluoren-2-ylimino)-

dipropanol was added cautiously with thorough swirling (to prevent an otherwise violent reaction) over a 0.5-hr period. An air condenser was attached and the mixture was heated on the steam bath for 1 hr. The flask was cooled in cracked ice and excess PBr_3 was poured from the readily friable solid which was then ground with ice. After neutralization with a slight excess of concentrated NH_4OH, the light red solid was collected by filtration and dried (19 g), mp 139.5–142°. The product was dissolved in acetone and recrystallized from a mixture of acetone and absolute ethanol to give 13.5 g (66%) of light orange crystals, mp 141.5–142.5°. The analytical sample was obtained by two recrystallizations from ethyl acetate.

N-2-(7-Nitrofluorenyl)propionamide.—After boiling 113 g of 7-nitrofluoren-2-amine[4] in 1 l. of toluene in a 2-l. flask under reflux it was cooled to 50° and 40 g of pyridine and, with continuous swirling, 48 g (0.52 mole) of propionyl chloride were added over a 10-min period. After refluxing for 4 hr the mixture was cooled and filtered and the precipitate washed thoroughly with water. The product was then boiled in 700 ml of acetone and filtered hot, thus removing a small amount of unreacted amine, and the residue was recrystallized from 1.5 l. of chlorobenzene to give 86.5 g (61%) of yellow crystals, mp 238–240°. An analytical sample was obtained by two further recrystallizations, mp 241–243.5°.

Anal. Calcd for $C_{16}H_{14}N_2O_3$: C, 68.07; H, 5.00; N, 9.92. Found: C, 68.20; H, 5.26; N, 9.92.

N-2-(7-Aminofluorenyl)propionamide.—Raney nickel-hydrazine hydrate reduction[5] of 86.5 g of 2-nitro-7-propionamidofluorene with 86 ml of 85% hydrazine hydrate in 1.5 l. of 95% ethanol and 200 ml of toluene, after filtration and evaporation to 60 ml, gave 70 g (91%), mp 182–183°. Recrystallization from ethanol gave an analytical sample, mp 182.5–184°.

Anal. Calcd for $C_{16}H_{16}N_2O$: C, 76.16; H, 6.39; N, 11.10. Found: C, 76.25; H, 6.55; N, 10.85.

Ethyl N-2-(7-Nitrofluorenyl)carbamate.—A mixture of 7-nitrofluoren-2-amine (40 g), 800 ml of toluene, and 40 g of pyridine was warmed with stirring in a 2-l. round-bottomed flask with a reflux condenser. Ethyl chloroformate (25 g) was added over a period of 10 min. The mixture was slowly brought to the boiling point and, with continued stirring, a further 25 g of ethyl chloroformate was added and refluxing was continued for another hour. The mixture was then cooled, filtered, and washed with a little toluene. The crude product, mp 197.5–202.5°, was ground in a mortar with 20 ml of concentrated NH_4OH, filtered, washed with water, and dried. It was then suspended in 400 ml of boiling acetone which was cooled and filtered to give a residue (50 g, 95%), mp 208.5–210.5°. An analytical sample was obtained by recrystallization from acetone and then chloroform: mp 209–211°.

Anal. Calcd for $C_{16}H_{14}N_2O_4$: C, 64.42; H, 4.73; N, 9.39. Found: C, 64.56; H, 4.85; N, 9.44.

Ethyl N-2-(7-Aminofluorenyl)carbamate.—Ethyl N-2-(7-nitrofluorenyl)carbamate (45 g) was reduced with 90 ml of 85% hydrazine hydrate and 5% Pd–C catalyst[5] in 1.5 l. of ethanol and 200 ml of toluene. The product (36 g, 89%) melted at 210–211° with sintering at 205°. An analytical sample with unchanged melting point was obtained by two recrystallizations from 95% ethanol.

Anal. Calcd for $C_{17}H_{16}N_2O_2$: C, 65.58; H, 5.50; N, 13.50. Found: C, 65.71; H, 5.61; N, 13.28.

N-2-(7-Aminofluorenyl)-N′-*n*-propylurea.—A mixture of 12 g of N-2-(7-nitrofluorenyl)-N′-*n*-propylurea,[6] 1.2 l. of 95% ethanol, 5.4 ml of 85% hydrazine hydrate, and two spoonfuls of 5% Pd–C[5] was refluxed for 2 hr. The hot mixture was filtered twice and boiled down until precipitation occurred giving 9 g (83%) of crude amine. This was recrystallized from 200 ml of 95% ethanol (Darco) to give 7.5 g, dec pt 227°. One more recrystallization gave an analytical sample.

Anal. Calcd for $C_{17}H_{19}N_3O$: C, 72.57; H, 6.81; H, 14.94. Found: C, 72.86; H, 7.08; N, 15.18.

N-2-(7-Nitrofluorenyl)formamide.—To 40 g of 7-nitrofluoren-2-amine[4] in 400 ml of hot f (~100°) toluene in a round-bottomed flask 32 ml of 98–100% formic acid was gradually added with thorough stirring. The mixture was boiled under reflux with a water trap for 2 hr and cooled to room temperature. The resulting yellow solid was filtered off and dried (45.5 g, 100%). Recrystallization from *o*-dichlorobenzene gave an analytically pure material, mp 221–222.5°.

Anal. Calcd for $C_{14}H_{10}N_2O_3$: C, 66.13; H, 3.96; N, 11.02. Found: C, 66.21; H, 3.97; N, 11.00.

N-2-(7-Aminofluorenyl)formamide.—The foregoing nitro compound was reduced[5] and the crude amine was crystallized from toluene–ethanol and then ethanol, mp 207–208.5°, to obtain an analytical sample.

Anal. Calcd for $C_{14}H_{12}N_2O$: C, 74.99; H, 5.38; N, 12.49. Found: C, 75.28; H, 5.71; N, 12.44.

Attempts to prepare the 7-bis(2-hydroxyethyl) derivative have failed; at best an apparent mixture of the mono- and dihydroxyethylated amine was obtained.

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(4) M. J. Namkung and T. L. Fletcher, *J. Org. Chem.*, **25**, 740 (1960). *Care* should be used in this and the following Raney nickel or Pd–C-catalyzed reductions to keep the catalyst wet with solvent. These are pyrophoric materials and can readily spark. See this and the following references.

(5) T. L. Fletcher and M. J. Namkung, *ibid.*, **23**, 680 (1958); see footnote 14 in M. J. Namkung, T. L. Fletcher, and W. H. Wetzel, *J. Med. Chem.*, **8**, 551 (1965).

(6) Made in 90% analytically pure yield by the reaction of *n*-propyl isocyanate with 7-nitro-2-fluorenamine in dimethylformamide. After filtration and washing the product was boiled in acetone and refiltered. *Anal.* Calcd for $C_{17}H_{17}N_3O_3$: C, 65.58; H, 5.50; N, 13.50. Found: C, 65.71; H, 5.61; N, 13.28.