2,6-Dihydroxy-9*H*-fluoren-9-one. Following the procedure of Barker and Barker,[10] nitrosylsulfuric acid, prepared from 60.0 g (0.086 mol) of $NaNO_2$ and 120 ml of H_2SO_4, was added dropwise to a cooled (0–5°) H_2SO_4 solution of 9.0 g (0.043 mol) of 2,6-diamino-9*H*-fluoren-9-one, mp 203–204° (lit.[28] mp 202–203°), prepared by $SnCl_2$–HCl–AcOH reduction of 2,6-dinitro-9*H*-fluoren-9-one. The mixture was stirred at 0–5° for 45 min and then poured onto 600 g of ice. Excess HNO_2 was destroyed by addition of 8.4 g of sulfamic acid and the solution was warmed slowly to boiling. The solution was cooled and the precipitate that separated was collected. It was dissolved in aqueous alkali, filtered, and reprecipitated by addition of dilute HCl. The product was recrystallized from aqueous EtOH to give 6.5 g (71%) of 2,6-dihydroxy-9*H*-fluoren-9-one, mp 247–249°. *Anal.* Calcd for $C_{13}H_8O_3$: C, 73.58; H, 3.80. Found: C, 73.03; H, 3.79.

This sample was used to prepare **10**. 2,5-Dihydroxy-9*H*-fluoren-9-one was similarly prepared from 2,5-dinitro-9*H*-fluoren-9-one; the crude material, mp 299–301°, was used to prepare **9**.

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Bis-Basic-Substituted Polycyclic Aromatic Compounds. A New Class of Antiviral Agents.[1-4] 3. 2,7-Bis(aminoacyl)fluorenes and -fluorenones

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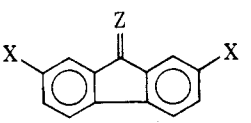
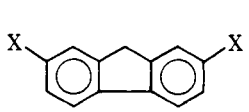
The synthesis and antiviral activity of a number of 2,7-bis(aminoacyl)fluorenes and -fluorenones are described. The structural features investigated include the alkylene chain, the terminal amine function of fluorene and fluorenone bis-basic ketones, and reduction of the carbonyl function in the side chain. Several compounds have broad spectrum antiviral activity, induce interferon, and are effective by oral as well as parenteral administration. 1,1′-(9*H*-Fluorene-2,7-diyl)bis[2-(diethylamino)ethanone]dihydrochloride (**2**, RMI 11002 DA) was selected for clinical trial.

It was previously reported from this laboratory that bisalkamine esters of fluorenone-, fluorenol-, and fluorenedicarboxylic acids I are potent antiviral agents.[1] In these compounds the two basic-substituted side chains are attached to the fluorene moiety by an ester linkage. To explore the importance of this linkage, analogous compounds were prepared in which the side chains are linked through ether bonds, as in II. This led to antiviral agents effective on oral as well as subcutaneous administration including tilorone hydrochloride, the first member of this class of antiviral agents to be reported.[5,6] This series is described in the preceding paper.[2] In this paper, we are reporting the synthesis and antiviral properties of a series of compounds III in which the basic-substituted side chains are linked to the fluorene moiety by carbon–carbon bonds. Of these, 2,7-bis(aminoacyl)fluorenes and -fluorenones (III, Y = O) showed favorable antiviral properties and several members were found to be active on oral administration.

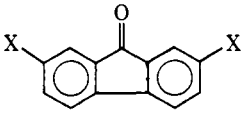


I, X = $-C(=O)O(CH_2)_nNR_2$ Z = O; H, OH; H, H
II, X = $-O(CH_2)_nNR_2$ Z = O; H, OH; H, H
III, X = $-C(=Y)(CH_2)_nNR_2$ Z = O; H, H
Y = O: H, OH; H, H; NOH

Chemistry. The 2,7-bis(aminoacyl)fluorene derivatives were prepared from 2,7-bis(ω-chloroalkanoyl)fluorenes IV–VI, obtained by Friedel–Crafts diacylation of fluorene with appropriate ω-chloroalkanoyl chlorides. These intermediates were subsequently aminated in the presence of excess amine to 2,7-bis(aminoacyl)fluorenes **1–3** and **5–17**. Two general procedures were used for the amination reaction. In method A the amination was conducted at atmospheric pressure in refluxing butanone, while in method B the amination was carried out in a sealed stainless steel reaction vessel at about 100° in tetrahydrofuran. Compound **4** was obtained by Mannich reaction from 2,7-diacetylfluorene (VII).



IV, X = $-COCH_2Cl$
V, X = $-CO(CH_2)_3Cl$
VI, X = $-CO(CH_2)_4Cl$
VII, X = $-COCH_3$



VIII, X = $-COCH_3$
IX, X = $-COCH_2Br$
X, X = $-CO(CH_2)_nCl$

The 2,7-bis(aminoacyl)fluoren-9-ones **19** and **21–28** were obtained by oxidation of the corresponding fluorenes. The method of Sprinzak[7] with molecular oxygen in 40% Triton B in pyridine gave satisfactory results. Compound **20** was obtained by sodium dichromate oxidation in acetic acid. Compound **18** was prepared from IX, obtained by bromination of 2,7-diacethylfluoren-9-one (VIII). Dichromate oxidation of 2,7-bis(ω-chloroalkanoyl)fluorenes IV–VI gave only moderate yields of the corresponding fluorenones X, which can serve as intermediates for the preparation of 2,7-bis(aminoacyl)fluoren-9-ones.

The 2,7-fluorenedimethanols **30** and **31** were obtained by sodium borohydride reduction and the 2,7-bis(aminoalkyl)fluorene **32** by Wolff–Kishner reduction of the corresponding 2,7-bis(aminoacyl)fluorene analogs, respectively. The 2,7-bis(aminoalkyl)fluoren-9-one **33** was obtained by oxidation of the corresponding 2,7-bis(aminoalkyl)fluorene with molecular oxygen in 40% Triton B in pyridine. Examples of these syntheses are given in the Experimental Section.

Biological Activity. The antiviral activity of compounds listed in Table I was determined in an *in vivo* model in mice inoculated with a lethal challenge of encephalomyocarditis (EMC) virus. A detailed description of the test method and expression of the data are given in the first two papers of this series.[1,2] Antiviral activity is expressed as the survival time ratio (STR). For example, an STR value of 1.00 indicates that a compound is inactive at the specified dose; that is, mice treated with compound remained alive no longer than untreated controls. Thus, at a specified dose, the greater the STR value, the more active the compound.

In this study, the effects of four structural variables on antiviral activity were investigated: the aromatic nucleus (fluorene and fluorenone), the terminal amine function, alkylene group of side chains, and reduction of the carbonyl function in side chains. A number of compounds in this series are active subcutaneously against EMC infection in mice, while a smaller number are active orally (Table I).

Of the orally active compounds, the aminoacetylfluorenes **1** and **2** are clearly the most effective (STR values greater than 1.80 at 250 mg/kg). The aminobutyrylfluorenes **5**, **6**, and **6a**† also have significant oral activity (STR values between 1.50 and 1.70 at one of two dose levels). These compounds all contain low molecular weight tertiary amine functions (Me_2N, Et_2N, piperidino, 4-methylpiperidino) of relatively strong basicity. Thus, in this series, optimum oral activity is obtained with fluorenes having aminoacetyl side chains. The dialkylaminoacetylfluorenes **1** and **2** are unique in having a high degree of antiviral activity whether administered subcutaneously or orally.

Subcutaneously, the most effective compounds are the fluorenes **1**, **2**, **5**, **6**, **6a**,† and **7** and the fluorenones **19**, **20**, **20a**,† **21**, **22**, **24**, and **26**. At one or more of the three dose levels, the STR value of each of these compounds is 1.80 or greater. These include the orally active compounds already discussed. In addition, several compounds with side chains of three and four alkylene carbon atoms (*e.g.*, **21** and **24**) and with higher molecular weight tertiary amine functions (*e.g.*, **22**) show high activity on subcutaneous administration.

Comparison of antiviral activity of 2,7-bis(aminoacyl)-fluorenes with the corresponding fluorenones (**5** *vs.* **19**, **6** *vs.* **20**, and **7** *vs.* **21**) indicated that there was little difference between the two groups. However, fluorenones with butylene side chains were generally more effective than the corresponding fluorenes (**24** *vs.* **11**, **26** *vs.* **15**). The oxime derivative **29** has activity comparable to that of the parent compound **6**. The 2,7-fluorenedimethanols **30** and **31** and the 2,7-bis(aminoalkyl)fluorene **32** were found to be less active than the corresponding 2,7-bis(aminoacyl)-fluorenes **2** and **6**. The 2,7-bis(aminoalkyl)fluorenone **33**, on the other hand, showed antiviral potency approaching that of **26**. These findings indicate that a carbonyl group at either the 9 position of the fluorene nucleus or at the point of attachment of the side chains is required for optimum antiviral activity. It is likely that the electron-withdrawing effect of the carbonyl group(s) imparts properties to the fluorene nucleus that are favorable to the interaction of the molecule with the biological receptor site. It is interesting to speculate that charge-transfer complex formation may be the nature of this interaction. This interpretation would be consistent with the reports of Chandra, *et al.*,[8,9] on interactions of tilorone hydrochloride with nucleic acids. An analogous binding model was proposed for the antimalarial acridines.[10,11]

Compounds **2**, **6**, and **20** were chosen for further biological evaluations. They showed broad spectrum antiviral activity in mice.[12] All three compounds were effective against infections by Semliki Forest virus, an RNA virus of the arbovirus group, and compounds **6** and **20** were also effective against influenza A_2 (Jap/305), an RNA virus of the myxovirus group, and vaccinia, a DNA virus. Interferon was detected in the serum of mice treated with **2**, **6**, or **20**, respectively. Maximum interferon levels in mice were found between 12 and 24 hr after treatment with 250 mg/kg po of **6** or **20**, and 12 hr after 250 mg/kg po or 100 mg/kg sc of **2**. Compound **2** (RMI 11,002 DA) was selected for clinical trial.

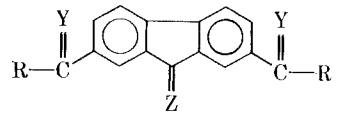
Experimental Section

Melting points were determined in open capillaries in a Thomas-Hoover apparatus and were uncorrected. The infrared and ultraviolet spectra were obtained with a Perkin-Elmer 521 and Perkin-Elmer 350 recording spectrophotometer, respectively. The nuclear magnetic resonance spectra were recorded on a Varian A-60A spectrometer. All spectra were consistent with the proposed structures. All compounds were analyzed for C, H, and either N or Cl and are within ±0.4% of the theoretical values except where indicated.

2,7-Bis(chloroacetyl)fluorene (IV). A mixture of 83.1 g (0.5 mol) of fluorene and 141.0 g (1.25 mol) of chloroacetyl chloride in 2000 ml of CH_2Cl_2 was cooled to −15° and 140.5 g (1.25 mol) of

†Compounds 6a and 20a are the dihydrochloride salts of 6 and 20, respectively.

Table I. 2,7-Bis(aminoacyl)fluorenes and -fluorenones



Compd	R	Y	Z	Preparative method[a]	Recrystn solvent	Mp, °C	Formula[b]	STR[c] *vs.* EMC virus: mg/kg sc 250	mg/kg sc 50	mg/kg sc 10	mg/kg po 250	mg/kg po 50
1	$(CH_3)_2NCH_2$	O	H_2	B	MeOH–MeCOEt	>330	$C_{21}H_{24}N_2O_2 \cdot 2HCl \cdot 3H_2O$[d]	2.34[e]	2.00[e]	1.32[e]	1.84[e,f]	1.91[e,f]
2	$(C_2H_5)_2NCH_2$	O	H_2	A	MeOH–EtOAc	225–228 dec	$C_{25}H_{32}N_2O_2 \cdot 2HCl$	2.28[e]	1.31[e]	1.09[e]	2.33[e,g]	1.23[e]
3	c-$C_5H_{10}NCH_2$	O	H_2	A	EtOH–MeCOEt	302–304	$C_{27}H_{32}N_2O_2 \cdot 2HCl \cdot H_2O$	1.20[e,f]	1.41[e]		1.54[e,g]	1.26[e,f]
4	c-$C_5H_{10}N(CH_2)_2$	O	H_2		MeOH–EtOAc	236–237 dec	$C_{29}H_{36}N_2O_2 \cdot 2HCl \cdot H_2O$[h,i]		1.23	1.04	1.24	1.37
5	$(C_2H_5)_2N(CH_2)_3$	O	H_2	B	Et_2O–pentane	79–81	$C_{29}H_{40}N_2O_2$	2.55	1.81	1.17	1.52	1.52
6	c-$C_5H_{10}N(CH_2)_3$	O	H_2	A	CH_2Cl_2–pentane	158–160	$C_{31}H_{40}N_2O_2$	2.31	2.08	1.28	1.65	1.39
6a					MeOH–MeCOEt	286–288 dec	$C_{31}H_{40}N_2O_2 \cdot 2HCl \cdot 2H_2O$	2.11	1.64	1.47	1.53	1.23
7	4-CH_3-c-$C_5H_9N(CH_2)_3$	O	H_2	A	$CHCl_3$–MeCOEt	180–181 dec	$C_{33}H_{44}N_2O_2$	1.90	1.71	1.71	1.20[g]	1.56
8	4-C_6H_5-c-$C_5H_9N(CH_2)_3$	O	H_2	A	$CHCl_3$–MeCOEt	190–192 dec	$C_{34}H_{48}N_2O_2$	1.17	1.15	1.28	0.96[g]	1.11
9	4-$C_6H_5CH_2$-c-$C_5H_9N(CH_2)_3$	O	H_2	A	$CHCl_3$–MeCOEt	135–137 dec	$C_{45}H_{52}N_2O_2$	1.34	1.44	1.41	1.02[g]	1.07
10	c-$O(CH_2CH_2)_2N(CH_2)_3$	O	H_2	A	CH_2Cl_2–MeCOEt	167–168	$C_{29}H_{36}N_2O_4$	1.41	1.20		1.09[g]	1.00[g]
11	$(CH_3)_2N(CH_2)_4$	O	H_2	B	$CHCl_3$–pentane	124–126	$C_{27}H_{36}N_2O_2$	1.41[f]	1.48[f]	1.09	1.04	0.98
12	$(C_2H_5)_2N(CH_2)_4$	O	H_2	B	Et_2O–pentane	78–80	$C_{31}H_{44}N_2O_2$	*f*	1.52	1.12	1.33[g]	1.14
13	$(n\text{-}C_4H_9)_2N(CH_2)_4$	O	H_2	B	*j*	48–50	$C_{39}H_{60}N_2O_2$	1.73	1.24	1.10	1.08	0.96
14	c-$C_5H_{10}N(CH_2)_4$	O	H_2	A	*j*	124–127	$C_{33}H_{44}N_2O_2$		1.77	1.25		
14a					MeOH–EtOAc	268–270 dec	$C_{33}H_{44}N_2O_2 \cdot 2HCl \cdot 2H_2O$	1.31[k]			1.20[g]	
15	4-CH_3-c-$C_5H_9N(CH_2)_4$	O	H_2	A	$CHCl_3$–MeCOEt	143–144	$C_{35}H_{48}N_2O_2$	1.07	1.67	1.26	1.35[g]	1.16
16	4-$C_6H_5CH_2$-c-$C_5H_9N(CH_2)_4$	O	H_2	A	$CHCl_3$–MeCOEt	147–149	$C_{47}H_{56}N_2O_2$	1.21		1.23	1.02[g]	1.02
17	c-$O(CH_2CH_2)_2N(CH_2)_4$	O	H_2	A	CH_2Cl_2–MeOH	134–136	$C_{31}H_{40}N_2O_4$	1.27	1.10	1.02	1.27[g]	1.14[g]
18	$(C_2H_5)_2NCH_2$	O	O		Dil HCl–Me_2O	225–228 dec	$C_{25}H_{30}N_2O_3 \cdot 2HCl \cdot H_2O$[l]					
19	$(C_2H_5)_2N(CH_2)_3$	O	O	C	MeOH–EtOAc	275 dec	$C_{29}H_{38}N_2O_3 \cdot 2HCl$	0.70[f]	1.87	1.32	1.34	1.15
20	c-$C_5H_{10}N(CH_2)_3$	O	O		$CHCl_3$–MeCOEt	168–170	$C_{31}H_{38}N_2O_3$	2.29	2.19	1.38	1.71[g]	1.60
20a					MeOH–EtOAc	322–323	$C_{31}H_{38}N_2O_3 \cdot 2HCl \cdot 1.5H_2O$	2.12[m]	2.50	1.35	1.65[g]	
21	4-CH_3-c-$C_5H_9N(CH_2)_3$	O	O	C	$CHCl_3$–MeCOEt	178–180 dec	$C_{33}H_{42}N_2O_3$	1.96	1.95	1.94	1.43	1.32
22	4-$C_6H_5CH_2$-c-$C_5H_9N(CH_2)_3$	O	O	C	$CHCl_3$–MeCOEt	141–143	$C_{45}H_{50}N_2O_3$	1.88	1.52	1.93	1.07	1.02
23	c-$O(CH_2CH_2)_2N(CH_2)_3$	O	O	C	$CHCl_3$–MeCOEt	174–175 dec	$C_{29}H_{34}N_2O_3$	1.48	1.69	1.09	1.12	1.21
24	$(CH_3)_2N(CH_2)_4$	O	O	C	$CHCl_3$–pentane	150–151	$C_{27}H_{34}N_2O_3$	1.21	1.79	1.81	1.26	1.17
25	$(C_2H_5)_2N(CH_2)_4$	O	O	C	$CHCl_3$–pentane	108–109	$C_{31}H_{42}N_2O_3$	*f*	1.26	1.56	1.24	0.96
26	CH_3-c-$C_5H_9N(CH_2)_4$	O	O	C	$CHCl_3$–MeCOEt	151–153	$C_{35}H_{46}N_2O_3$	2.17	2.10	1.95	1.31	1.40
27	4-$C_6H_5CH_2$-c-$C_5H_9N(CH_2)_4$	O	O	C	$CHCl_3$–MeCOEt	124–126 dec	$C_{47}H_{54}N_2O_3$	1.54	1.61		0.93	0.98
28	c-$C_5H_{10}N(CH_2)_4$	O	O	C	$CHCl_3$–MeCOEt	146–148	$C_{31}H_{38}N_2O_5$	1.48	1.59	1.19	1.07	1.17
29	c-$C_5H_{10}N(CH_2)_3$	NOH	H_2		$CHCl_3$	190–196 dec	$C_{31}H_{42}N_4O_2$	2.00	1.40	1.17	1.33	1.02
30	$(C_2H_5)_2NCH_2$	H, OH	H_2		EtOAc	89.5–91	$C_{25}H_{36}N_2O_2$					
31	c-$C_5H_{10}N(CH_2)_3$	H, OH	H_2		Benzene–Et_2O	181.5–184	$C_{31}H_{44}N_2O_2$	1.30	1.06	0.96	1.04	1.04
32	c-$C_5H_{10}N(CH_2)_3$	H_2	H_2		Me_2CO	108–110	$C_{31}H_{44}N_2$	1.43	1.18	1.08	1.24	1.12
33	4-CH_3-c-$C_5H_9N(CH_2)_4$	H_2	O		MeOH–MeCOEt	241–243	$C_{35}H_{50}N_2O \cdot 2HCl$	*f*	1.72	1.40	0.98	0.87
Tilorone								*f*	1.95	1.37	2.27[g]	1.83

[a] See Experimental Section for description of the methods. [b] Analyses for C, H, and either N or Cl were within ±0.4% of the theoretical values except where indicated. Degree of hydration was determined by the Karl Fischer method or by neutralization equivalent obtained from nonaqueous titration. [c] See ref 2. [d] Cl: calcd, 15.01; found, 14.03. [e] Activity determined in Cox male mice. [f] Early deaths observed at specified dose. [g] Activity determined from single dose administered either 22 or 24 hr before infection. [h] C: calcd, 65.23; found, 65.65. [i] Degree of hydration not determined. [j] Compound purified by column chromatography on Merck neutral alumina with $CHCl_3$ as eluting solvent. [k] Activity determined at 400 mg/kg with compound suspended in 10% Tween 80 and 5% $NaHCO_3$. [l] C: calcd, 60.35; found, 58.99. [m] Activity determined at 100 mg/kg.

$AlCl_3$ was added with rapid stirring. The mixture was stirred overnight at room temperature and then poured onto a mixture of ice–concentrated HCl. The organic solvent was removed by boiling. Crude product was purified by digestion with boiling DMF, in which the compound is insoluble. The yield was 94.5 g (57.3%), mp 292–296° (lit.[13] mp 280°). This method was also used to prepare **2,7-bis(4-chlorobutyryl)fluorene** (V) [yield 127.0 g (acetone) (72.0%); mp 172–175°. *Anal.* ($C_{21}H_{20}Cl_2O_2$) C, H, Cl] and **2,7-bis(5-chlorovaleryl)fluorene** (VI) [yield 93.0 g (EtOH) (46.3%), mp 124–125°. *Anal.* ($C_{23}H_{24}Cl_2O_2$) C, H, Cl].

Aminolysis of Bis(chloro ketones) by Method A. In a typical example, a mixture of 100 g (0.266 mol) of V, 180 g (2.1 mol) of piperidine, 10 g (0.06 mol) of KI, and 1 l. of butanone was stirred at reflux for 3 days. The reaction mixture was poured into 2 l. of H_2O. The precipitate was collected, washed with water, and crystallized from CH_2Cl_2–pentane to give 67 g (55%) of **6** (Table I).

The free base was converted to the dihydrochloride salt **6a** by standard methods.

Method B. In a typical example, a mixture of 30.0 g (0.074 mol) of VI, 100 ml of diethylamine, 2 g of KI, and 250 ml of THF was stirred and heated in a Parr bomb for 24 hr at approximately 100°. The reaction mixture was concentrated *in vacuo* to semidryness and then diluted with 1 l. of H_2O. The resulting solid was collected by filtration, washed with water, and crystallized twice from ether–pentane to give 23.9 g (68%) of **12** (Table I).

When the free base was isolated as an oil, it was converted to the dihydrochloride salt by standard methods.

Oxidation of Bis(aminoacyl)fluorenes to the Corresponding Bis(aminoacyl)fluorenones (Method C). In a typical example, a mixture of 10.0 g (0.019 mol) of **15**, 2.5 ml of a 40% solution of Triton B in pyridine, and 150 ml of dry pyridine was stirred while oxygen was bubbled through the reaction mixture at the rate of approximately 400 ml/min for 3 hr. Pyridine was removed *in vacuo*. The residue was dissolved in $CHCl_3$, washed well with water, and dried ($MgSO_4$). The resulting solution was chromatographed on alumina with $CHCl_3$ as the eluent. The eluent was partially concentrated and diluted with acetone to give 5.2 g (50%) of **26** (Table I).

2,7-Bis(3-piperidinopropionyl)fluorene Dihydrochloride (4). A solution of 25.0 g (0.1 mol) of 2,7-diacetylfluorene, prepared by the procedure of Dashevskii and Shamis,[14] 9.0 g (0.3 mol) of paraformaldehyde, and 25.5 g (0.21 mol) of piperidine hydrochloride in 200 ml of *n*-butyl alcohol was refluxed for 2 hr and then cooled to room temperature. Product that crystallized was filtered and recrystallized from MeOH–EtOAc to give 12 g (25%) of **4** (Table I).

2,7-Bis[2-(diethylamino)acetyl]fluoren-9-one Dihydrochloride Monohydrate (18). A mixture of 25.0 g (0.1 mol) of 2,7-diacetylfluorene[14] and 39.4 g (0.133 mol) of $Na_2Cr_2O_7 \cdot 2H_2O$ in 500 ml of HOAc was refluxed for 2 hr. On cooling, a yellow crystalline solid was obtained which was collected and recrystallized from CH_3CN to give 24 g (90%) of 2,7-diacetylfluoren-9-one (VIII), mp 251–253° (lit.[15] mp not given). *Anal.* ($C_{17}H_{12}O_3$) C, H.

This ketone VIII was treated with 2 equiv of Br_2 in 700 ml of $(CHCl_2)_2$ at reflux for 1 hr. On cooling, 26.0 g (46%) of 2,7-bis(2-bromoacetyl)fluoren-9-one (IX), mp 215–218°, was obtained. An analytical sample was prepared by recrystallization from HOAc: mp 222–225°. *Anal.* ($C_{17}H_{10}Br_2O_3$) C, H, Br.

To a suspension of IX (15.0 g, 0.035 mol) in 200 ml of Me_2CO at 0° was added 75 ml of diethylamine with constant stirring. The reaction mixture was stirred at room temperature for 1 hr and then diluted with 500 ml of Et_2O. The resulting precipitate ($Et_2NH \cdot HCl$) was separated and the filtrate evaporated *in vacuo* at 40–50°. The brown residue was dissolved in $CHCl_3$, extracted with saturated $NaHCO_3$ solution and water, and dried ($MgSO_4$). Addition of ethereal HCl gave a precipitate that was recrystallized from MeOH–EtOAc and from 3 *N* HCl–acetone to yield 3.8 g (22%) of 18 (Table I).

2,7-Bis(4-piperidinobutyryl)fluoren-9-one (20). A mixture of 9.0 g (0.019 mol) of 2,7-bis(4-piperidinobutyryl)fluorene, 7.54 g (0.0253 mol) of sodium dichromate dihydrate, and 300 ml of acetic acid was stirred and refluxed for 1 hr. Most of the acetic acid was removed *in vacuo* on a steam bath. The reacton mixture was made basic with concentrated NH_4OH. Crude product that precipitated was filtered, washed well with water, and purified by recrystallization from $CHCl_3$–MeCOEt to give 3.7 g (38%) of **20** (Table I).

2,7-Bis(4-piperidinobutyryl)fluorene Dioxime (29). A mixture of 10.0 g (0.021 mol) of **6** and 25 g (0.36 mol) of hydroxylamine hydrochloride in 250 ml of pyridine was stirred and heated just below reflux temperature for 6 hr. The reaction mixture was concentrated *in vacuo* and the residue was recrystallized twice from $CHCl_3$ to give 7.6 g (75%) of the product **29** (Table I).

2,7-Bis[(2-diethylamino-1-hydroxy)ethyl]fluorene (30). A mixture of 7.5 g (0.15 mol) of $NaBH_4$, 200 ml of MeOH, and 80 ml of 10% NaOH solution was added dropwise to a cold solution of 39.0 g (0.075 mol) of **2** in 200 ml of THF and stirred overnight at room temperature. The reaction mixture was poured into 1 l. of water and extracted with CH_2Cl_2. The CH_2Cl_2 extract was dried ($MgSO_4$) and evaporated to dryness *in vacuo*. The residue was crystallized from CH_2Cl_2–pentane and finally from EtOAc to give 11.5 g (39%) of product **30** (Table I).

Compound **31** was prepared from **6** by an analogous procedure.

2,7-Bis(4-piperidinobutyl)fluorene (32). A mixture of 23.6 g (0.05 mol) of **6**, 38.6 g (0.5 mol) of 85% hydrazine hydrate, and 200 ml of diethylene glycol was stirred and heated at 100–120° for 3 hr in an open flask, followed by the cautious addition of 28 g (0.5 mol) of KOH, and then refluxed overnight. The cooled reaction mixture was poured into ice water and extracted with $CHCl_3$. Evaporation of the solvent *in vacuo* gave 10.4 g of crude product which was purified by recrystallization from acetone to give 8.8 g (41%) of **32** (Table I).

2,7-Bis[5-(4-methylpiperidino)pentyl]fluoren-9-one Dihydrochloride (33). Compound **15**, 10.0 g (0.019 mol), was reduced by the Wolff–Kishner procedure described above to give 2,7-bis[5-(4-methylpiperidino)pentyl]fluorene. This intermediate was subsequently oxidized by the procedure of method C to give **33** in an overall yield of 17%.

Antiviral Evaluation Method. The antiviral activity was determined by the methods described in paper 2.[2]

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