obtained as described for the dialkylamino aldehydes. The crude aldehyde was purified by column chromatography on 50 g of silica gel (SilicAR cc-7, Mallinckrodt), using EtOAc as eluent, and then characterized by ir (appearance of C=O, 1708 cm^{-1}), nmr (loss of CH_3, δ 3.18; appearance of singlet, δ 10.33, 1 H, CHO), and derivatization.

Thiosemicarbazones. A solution of thiosemicarbazide (0.091 g, 1 mmol) dissolved in hot H_2O (6–7 ml) plus AcOH (1 drop) was added to a solution of appropriate aldehyde (1 mmol) dissolved in EtOH (2 ml). The solution was stirred and refluxed for 1 hr and upon cooling the derivative precipitated. Purification was effected by recrystallizing or by dissolving in warm 10% HCl, treating with charcoal, and reprecipitating with $NaHCO_3$.

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Bis-Basic-Substituted Polycyclic Aromatic Compounds. A New Class of Antiviral Agents.[1,2] 6. Bis-Basic-Substituted Fluoranthenes

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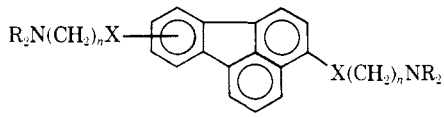
A series of bis-basic esters, ketones, ethers, and alkanes of fluoranthene was synthesized and evaluated for antiviral activity. Compounds from each group were found to have potent antiviral activity when administered subcutaneously to mice infected with encephalomyocarditis virus. Bis-basic ketones of fluoranthene were the most potent antiviral agents when administered orally. Structural modifications included variation of the alkylene chain and amine substituents within each group. Position of attachment of the basic side chain to the fluoranthene nucleus was varied for bis-basic esters of fluoranthene. 3,9-Fluoranthenedicarboxylic acid bis[3-(diethylamino)propyl]ester dihydrochloride (**9**, RMI 9563DA) and 1,1′-(3,9-fluoranthenediyl)bis[2-(dimethylamino)ethanone] dihydrochloride (**24**, RMI 11,645DA) were selected for further biological evaluation.

In this paper we will discuss results obtained from testing a series of bis-basic-substituted fluoranthene derivatives for antiviral activity. The fluoranthene nucleus, containing four fused rings, was the first example of an aromatic hydrocarbon that differed from the general structure for tricyclic aromatic hydrocarbons previously reported.[3-7] A number of esters I, ketones II, ethers III, and alkanes IV were synthesized for the purpose of comparing antiviral activity with the corresponding fluorene and fluorenone derivatives.[3-5] In general, the SAR pattern for the



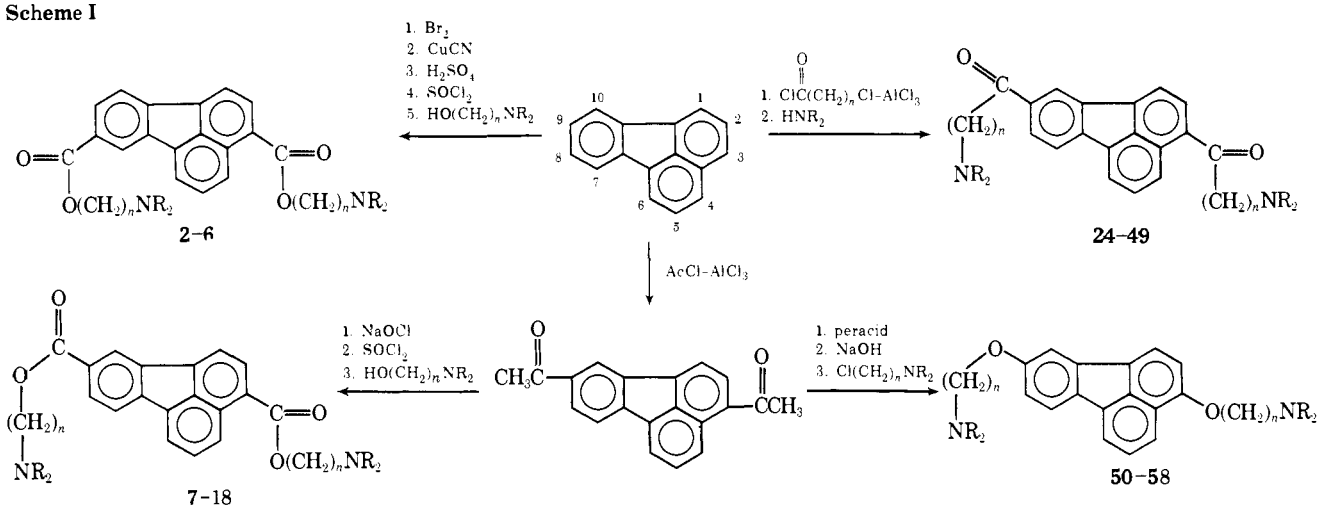
I, X = CO_2
II, X = CO
III, X = O
IV, X = CH_2

fluoranthene series corresponded to that previously reported for the fluorene(one) series. Representative fluoranthene derivatives were shown to induce interferon,[8-10] an activity consistent with the possible mode of action for tilorone and other fluorenone compounds.

Chemistry. The general method of synthesis of the bis-basic-substituted fluoranthenes is outlined in Scheme I. Bromination of fluoranthene with 2 equiv of bromine gave 3,8-dibromofluoranthene which was converted to the dinitrile followed by hydrolysis to the dicarboxylic acid.[11] The diacid chloride when treated with the appropriate aminoalkanols gave the 3,8-bis-basic esters **2–6** (Table I). The 3,9-bis-basic esters **7–18** (Table I) were synthesized from the diacid,[12] obtained by the haloform reaction on 3,9-diacetylfluoranthene.

The 3,9-bis-basic ketones **24–49** (Table II) were prepared by amination of 3,9-bis(ω-chloroalkanoyl)fluoranthenes obtained by Friedel–Crafts diacylation of fluoranthene. Two general procedures were used for the amination reaction. The amine was allowed to react with the appropri-

Scheme I



ate 3,9-bis(ω-chloroalkanoyl)fluoranthene at atmospheric pressure in refluxing butanone (method A) or the reaction was allowed to proceed in a sealed stainless steel reaction vessel at about 100° in tetrahydrofuran (method B).

To synthesize 3,9-bis-basic ethers **50–58** (Table III), 3,9-diacetylfluoranthene was allowed to react under the conditions of the Baeyer–Villiger reaction with *m*-chloroperbenzoic acid to yield fluoranthene-3,9-diol diacetate. The diol[13] obtained from alkaline hydrolysis of the diacetate was then allowed to react with the appropriate dialkylaminoalkyl chloride (method C). An alternative procedure that eliminates the necessity for isolating the diol was also used in the synthesis of the bis-basic ethers. In this procedure (method D), the diacetate was allowed to react directly with the dialkylaminoalkyl chloride in the presence of 4 equiv of NaOMe in chlorobenzene to yield the desired product.

The bis-basic alkanes **59–61** (Table IV) were prepared from the corresponding bis-basic ketones under the conditions of Wolff–Kishner reduction (method E).

Antiviral Activity. The antiviral activity of these compounds was determined *in vivo* against encephalomyocarditis (EMC) virus according to the procedure described in the Experimental Section. The activities are expressed as a survival time ratio (STR). STR is defined as the mean day of death of the treated group of mice divided by the mean day of death of the control group. The compounds were administered subcutaneously in multiple doses prior to and subsequent to virus challenge.

We considered four structural variables to provide information for the structure–activity relationships for these compounds. The first structural modification was the position of substitution of the basic side chain within the bis-basic ester series. The second modification was to vary the functional group attached directly to the aromatic nucleus; these were the carboxylic ester (Table I), carbonyl (Table II), ether (Table III), and methylene groups (Table IV). The third variable was the alkylene chain that separates the functional group from the terminal amine. Finally, a broad selection of compounds with different substituted amine groups was evaluated.

Within the bis-basic ester series (Table I) the more active compounds were **2**, **6**, **7**, **9**, **11**, **15**, **16**, and **18**. Little difference in activity was seen between the 3,8- and 3,9-position isomers (*cf.* **6** and **16**). The length of the alkylene chain separating the basic nitrogen and the ester function was not critical. Good activity was maintained when the alkylene chain was modified from ethylene **7** to the more complex 2,2-dimethylpentylene **18**. The nature of the terminal amine substituents had the greatest effect on activity. Large lipophilic groups such as *n*-pentyl **13** and isopentyl **5** and **14** reduced the activity. Optimum activity was seen with dimethyl, diethyl, and dipropyl substitution.

Within the bis-basic ketone series (Table II) many compounds were active. There was, however, an apparent limitation that was related to the size of the substituents in the 4 position of the piperidine ring as shown by the low activity of compounds **35–37**. The chain length of the alkylene group that separates the terminal amine from the carbonyl function had little effect on antiviral activity when the length was increased from one to four carbon atoms, with the one exception of the ethylene group. Our interpretation is that the low activity of **28** is related to the well-known instability of Mannich bases.

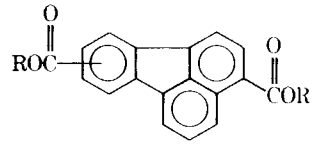
The bis-basic ethers (Table III) were highly active compounds with the exception of compounds **52** and **53**. A possible explanation for the low activity of **52** may be the lower basicity of the morpholino nitrogen as compared to the other amines in the series. There is no apparent reason for the activity of **53** to be so much lower than that of **54**. The bis-basic alkanes (Table IV) were potent antiviral agents having STR values similar to those of the corresponding bis-basic ketones.

Oral effectiveness was demonstrated for certain members of the bis-basic-substituted fluoranthenes. An STR of 1.80–2.00 was measured for compounds **24–26**, when administered orally at a dose of 250 mg/kg 22–24 hr prior to challenge with EMC virus. Other compounds that exhibited weaker oral activity under similar experimental conditions include **32a**,† **33**, **48**, and **58**.

Two representatives, **9** (RMI 9563DA) and **24** (RMI 11,645DA), were selected for further biological evaluation based on their potent antiviral activity against EMC virus. Significant levels of interferon were demonstrated for **9** when administered subcutaneously and for **24** when given orally to mice.[9] Compound **9** was evaluated subcutaneously for broad-spectrum antiviral activity and was found to be effective in controlling both RNA (Semliki Forest) and DNA (vaccinia) virus infections in mice.[10] Compound **24** given orally was also effective. The acute toxicity of the compounds administered *via* their respective routes of optimal activity was determined in mice. Single doses of the compounds were given to groups of ten mice and the LD_{50} (dose that killed 50% of the mice over

†Compund 32a is the dihydrochloride salt of compound 32.

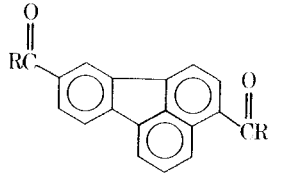
Table I. Fluoranthene Esters



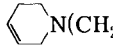
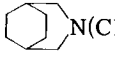
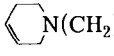
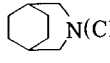
Compd[a]	Position	R	Recrystn solvent	Mp, °C	Formula[b]	STR,[c] mg/kg sc		
						10	50	250
1	3,8	CH_3	MeOH	169–170[d]	$C_{20}H_{14}O_4$	0.94	0.94	1.19
2	3,8	$(C_2H_5)_2N(CH_2)_3$	MeOH–EtOAc	259–261	$C_{32}H_{40}N_2O_4 \cdot 2HCl$	1.84	1.88	1.45
3	3,8	$(CH_2{=}CHCH_2)_2N(CH_2)_3$	MeOH–Me_2CO–Et_2O	216.5–219	$C_{36}H_{40}N_2O_4 \cdot 2HCl$	1.07	1.23	1.27
4	3,8	$(n\text{-}C_4H_9)_2N(CH_2)_3$	MeOH–MeCOEt–Et_2O	169–173	$C_{40}H_{56}N_2O_4 \cdot 2HCl$	1.20	1.59	1.64
5	3,8	$[(CH_3)_2CHCH_2CH_2]_2N(CH_2)_3$	MeCOEt	168–170	$C_{44}H_{64}N_2O_4 \cdot 2HCl$	1.04	1.07	1.14
6	3,8	c-$C_5H_{10}N(CH_2)_3$	MeOH–EtOAc	258–260	$C_{34}H_{40}N_2O_4 \cdot 2HCl$	1.39	2.06	1.61
7	3,9	$(C_2H_5)_2N(CH_2)_2$	*e*	Oil	$C_{30}H_{36}N_2O_4$	1.07	1.38	1.96[f]
8	3,9	$(CH_3)_2N(CH_2)_3$	MeOH–MeCOEt	242.5–244	$C_{28}H_{32}N_2O_4 \cdot 2HCl$	1.45	1.61	1.73
9	3,9	$(C_2H_5)_2N(CH_2)_3$	MeOH–EtOAc	258.5–260	$C_{32}H_{40}N_2O_4 \cdot 2HCl$	1.27	1.82	0.86
10	3,9	$(CH_2{=}CHCH_2)_2N(CH_2)_3$	*e*	Oil	$C_{36}N_{40}N_2O_4$	0.96	1.11	1.35[f]
11	3,9	$(n\text{-}C_3H_7)_2N(CH_2)_3$	MeOH–EtOAc	247–249	$C_{36}H_{48}N_2O_4 \cdot 2HCl$	1.31	1.86	2.19
12	3,9	$(n\text{-}C_4H_9)_2N(CH_2)_3$	*e*	Oil	$C_{40}H_{56}N_2O_4$	1.09	1.20	1.71[f]
13	3,9	$(n\text{-}C_5H_{11})_2N(CH_2)_3$	*e*	Oil	$C_{44}H_{64}N_2O_4$	1.07	1.24	1.52[f]
14	3,9	$[(CH_3)_2CHCH_2CH_2]N(CH_2)_3$	MeOH–MeCOEt	191.5–194	$C_{44}H_{64}N_2O_4 \cdot 2HCl$	1.28	1.16	1.23
15	3,9	c-$CH_3N(CH_2CH_2)_2CH$	MeCOEt	152–154	$C_{30}H_{32}N_2O_4$	1.24	1.80	2.20[f]
16	3,9	c-$C_5H_{10}N(CH_2)_3$	MeOH–EtOAc	247–250	$C_{34}H_{40}N_2O_4 \cdot 2HCl$	1.20	2.02	1.73
17	3,9	$(C_2H_5)_2N(CH_2)_4$	MeOH–EtOAc	205–209	$C_{34}H_{44}N_2O_4 \cdot 2HCl \cdot H_2O$[g]	1.26	1.63	1.80
18	3,9	$(CH_3)_2N(CH_2)_3C(CH_3)_2CH_2$	MeOH–MeCOEt	246–248.5	$C_{36}H_{48}N_2O_4 \cdot 2HCl$	1.82	2.18	0.47[h]

[a] Synthetic method described in Experimental Section. [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 neutralization equivalent obtained from nonaqueous titration or by the Karl Fischer method. [c] STR = survival time ratio. For experimental conditions see ref 4. [d] Reported mp 168–169° (ref 11). [e] Compound purified by column chromatography on Merck neutral alumina with $CHCl_3$ as eluting solvent. [f] 10% Tween 80 added to vehicle at all three dose levels. [g] C: calcd, 64.13; found, 64.66. [h] Early deaths observed at specific dose.

Table II. Fluoranthene Ketones

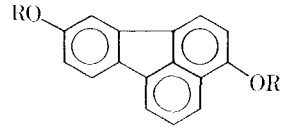


Compd	R	Prep method[a]	Recrystn solvent	Mp, °C	Formula[b]	STR,[c] mg/kg sc		
						10	50	250

19	CH_3			142–144[d]	$C_{20}H_{14}O_2$		0.99	0.99
20	$ClCH_2$			231–233 dec	$C_{20}H_{12}O_2Cl_2$	0.94	0.96	0.90
21	$Cl(CH_2)_3$			124–126	$C_{24}H_{20}O_2Cl_2$		1.05	1.16
22	$Cl(CH_2)_4$			142–144	$C_{26}H_{24}O_2Cl_2$		1.12	1.15
23	c-C_3H_5			156–158	$C_{24}H_{18}O_2$	1.10	1.10	1.22
24	$(CH_3)_2NCH_2$	B	$MeOH–Me_2CO$	285–288 dec	$C_{24}H_{24}N_2O_2\cdot 2HCl\cdot 2H_2O$	1.32	1.94	2.17
25	$(C_2H_5)_2NCH_2$	B	$MeOH–Me_2CO$	252–254 dec	$C_{28}H_{32}N_2O_2\cdot 2HCl\cdot 2H_2O$	1.04	1.11	2.00
26	c-$C_5H_{10}NCH_2$	B	$MeOH–Me_2CO$	263–265	$C_{30}H_{32}N_2O_2\cdot 2HCl\cdot 4H_2O$	1.32	2.23	2.50
27	4-CH_3-c-$C_5H_9NCH_2$	A	MeOH–MeCOEt	228–231 dec	$C_{32}H_{36}N_2O_2\cdot 2HCl\cdot 2H_2O$	1.49	1.33	1.23
28	c-$C_5H_{10}N(CH_2)_2$	A	$H_2O–Me_2CO$	206–210	$C_{32}H_{36}N_2O_2\cdot 2HCl\cdot H_2O$		1.11	1.52
29	$(CH_3)_2N(CH_2)_3$	B	$MeOH–Me_2COEt$	245–250 dec	$C_{28}H_{32}N_2O_2\cdot 2HCl$	1.19	1.81	0.66[e]
30	$(C_2H_5)_2N(CH_2)_3$	B	MeOH–EtOAc	236–239	$C_{32}H_{40}N_2O_2\cdot 2HCl$	1.96	2.00	
31	c-$C_4H_8N(CH_2)_3$	A	MeOH-EtOAc	230–234 dec	$C_{32}H_{36}N_2O_2\cdot 2HCl\cdot H_2O$	1.76	1.42	*e*
32	c-$C_5H_{10}N(CH_2)_3$	A	$CHCl_3–Me_2CO$	126–128	$C_{34}H_{40}N_2O_2$		1.42	
32a	c-$C_5H_{10}N(CH_2)_3$	A	MeOH–MeCOEt	271–274 dec	$C_{34}H_{40}N_2O_2\cdot 2HCl$	1.64	2.16	*e*
33	4-CH_3-c-$C_5H_9N(CH_2)_3$	A	MeOH–MeCOEt	254–256 dec	$C_{36}H_{44}N_2O_2\cdot 2HCl\cdot H_2O$	1.84	2.16	0.59[e]
34	4-*n*-C_3H_7-c-$C_5H_9N(CH_2)_3$	A	$CHCl_3–Me_2CO$	129–131.5	$C_{40}H_{52}N_2O_2$	1.90	1.60	1.60[f,g]
35	4-$(CH_3)_3C$-c-$C_5H_9N(CH_2)_3$	A	MeOH–MeCOEt	150–152	$C_{42}H_{56}N_2O_2$	1.17	1.17	1.14[g]
36	4-C_6H_5-c-$C_5H_9N(CH_2)_3$	A	$CHCl_3–Me_2CO$	153–155	$C_{46}H_{48}N_2O_2$	1.00	1.04	1.09[g]
37	4-$C_6H_5(CH_2)_3$-c-$C_5H_9N(CH_2)_3$	A	$CHCl_3–Me_2CO$	99–101	$C_{52}H_{60}N_2O_2$	1.07	1.11	1.13[g]
38	 $N(CH_2)_3$	A	MeOH	248–250 dec	$C_{34}H_{36}N_2O_2\cdot 2HCl\cdot 2H_2O$	1.60	2.19	1.72
39	c-$O(CH_2CH_2)_2N(CH_2)_3$	A	MeOH–MeCOEt	188–191	$C_{32}H_{36}N_2O_4\cdot 2HCl\cdot H_2O$	1.70	1.61	2.14
40	 $N(CH_2)_3$	A	$CHCl_3–Me_2CO$	146–148	$C_{40}H_{48}N_2O_2$	1.13	1.80	1.87[g]
41	$(CH_3)_2N(CH_2)_4$	B	MeOH–EtOAc	112–113	$C_{30}H_{36}N_2O_2$	1.24	1.66	*e*
42	$(C_2H_5)_2N(CH_2)_4$	B	Et_2O	84–85	$C_{34}H_{44}N_2O_2$	1.24	2.11	0.46[e,g]
43	$(n\text{-}C_4H_9)_2N(CH_2)_4$	B	Me_2CO	124–128	$C_{42}H_{60}N_2O_2\cdot 2HCl$	1.84	2.12	1.65
44	c-$C_5H_{10}N(CH_2)_4$	A	MeOH–EtOAc	241–243	$C_{36}H_{44}N_2O_2\cdot 2HCl\cdot 0.5H_2O$	2.10	1.95	0.86[g]
45	4-CH_3-c-$C_5H_9N(CH_2)_4$	A	$CHCl_3–Me_2CO$	141–142	$C_{38}H_{48}N_2O_2$[h]	1.88	1.59	0.93[g]
46	4-*n*-C_3H_7-c-$C_5H_9N(CH_2)_4$	A	$CHCl_3–Me_2CO$	146–148	$C_{42}H_{56}N_2O_2$	1.14	1.16	1.76[g]
47	4-$C_6H_5CH_2$-c-$C_5H_9N(CH_2)_4$	A	$CHCl_3–Me_2CO$	127–128	$C_{50}H_{56}N_2O_2$	1.18	1.47	1.60[g]
48	 $N(CH_2)_4$	A	MeOH–MeCOEt	214–216 dec	$C_{36}H_{40}N_2O_2\cdot 2HCl$	1.59	2.14	1.86
49	 $N(CH_2)_4$	A	$CHCl_3–Me_2CO$	142–143	$C_{42}H_{52}NO_2$	1.19	1.77	1.53[g]

[a]See footnote *a*, Table I. [b]See footnote *b*, Table I. [c]See footnote *c*, Table I. [d]Reported mp 138–142° (ref 12). [e]See footnote *h*, Table I. [f]Activity determined from single dose administered 22 hr before infection at each dose level. [g] See footnote *f*, Table I. [h] C: calcd, 80.80; found, 80.37.

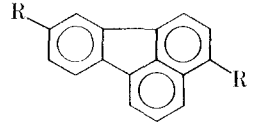
Table III. Fluoranthene Ethers



Compd	R	Prep method[a]	Recrystn solvent	Mp, °C	Formula[b]	STR,[c] mg/kg sc 10	50	250
50	$(C_2H_5)_2N(CH_2)_2$	C	MeOH–MeCOEt	220–222	$C_{28}H_{36}N_2O_2 \cdot 2HCl$	1.19	1.89	1.34
51	c-$C_5H_{10}N(CH_2)_2$	D	$CHCl_3$–pentane	122–123	$C_{30}H_{36}N_2O_2$	1.24	1.60	2.02
52	c-$O(CH_2CH_2)_2N(CH_2)_2$	D	MeOH–Me_2CO	284–286 dec	$C_{28}H_{32}N_2O_4 \cdot 2HCl$	1.31	1.02	1.16
53	$(CH_3)_2NCH_2CH(CH_3)$	D	*d*	Oil	$C_{26}H_{32}N_2O_2$	1.06	1.18	1.26
54	$(C_2H_5)_2NCH_2CH(CH_3)$	D	*d*	Oil	$C_{30}H_{40}N_2O_2$	1.45	1.73	2.06
55	$(CH_3)_2N(CH_2)_3$	D	CH_2Cl_2–pentane	80–82	$C_{26}H_{32}N_2O_2$			1.84[e]
56	$(C_2H_5)_2N(CH_2)_3$	C	MeOH–MeCOEt	235–236	$C_{30}H_{40}N_2O_2 \cdot 2HCl$	1.45	2.16	1.18[f]
57	$(n\text{-}C_4H_9)_2N(CH_2)_3$	C	MeOH–MeCOEt	170–172	$C_{38}H_{56}N_2O_2 \cdot 2HCl$	1.06	1.71	1.75
58	c-$C_5H_{10}N(CH_2)_3$	C	MeOH–EtOAc	92–93	$C_{32}H_{40}N_2O_2$	1.68	1.95[g]	*f*
Tilorone hydrochloride[h]						1.87	1.95	*f*

[a]See footnote *a*, Table II. [b]See footnote *b*, Table I. [c]See footnote *c*, Table I. [d]See footnote *e*, Table I. [e]See footnote *f*, Table II. [f]See footnote *h*, Table I. [g]See footnote *f*, Table I. [h]See ref 4.

Table IV. Fluoranthene Alkanes



Compd	R	Prep method[a]	Recrystn solvent	Mp, °C	Formula[b]	STR,[c] mg/kg sc 10	50	250
59	c-$C_5H_{10}N(CH_2)_3$	E	MeOH–MeCOEt	283–286 dec	$C_{34}H_{44}N_2 \cdot 2HCl$	1.29	2.20	1.38
60	c-$O(CH_2CH_2)_2N(CH_2)_4$	E	MeOH–MeCOEt	280–282 dec	$C_{32}H_{40}N_2O_4 \cdot 2HCl$	1.00	1.31	2.15
61	4-*n*-C_3H_7-c-$C_5H_{10}N(CH_2)_5$	E	MeOH–MeCOEt	211–213	$C_{42}H_{60}N_2 \cdot 2HCl$	1.35	1.55	1.67

[a]See footnote *a*, Table I. [b]See footnote *b*, Table I. [c]See footnote *c*, Table I.

a 7-day observation period) was calculated for each compound. The subcutaneous LD_{50} for **9** was 684 mg/kg and the oral LD_{50} for **24** was 2590 mg/kg. In addition to antiviral activity, **9** enhanced the antibody response to sheep red blood cell antigen as determined by an increase in the number of hemolytic plaque-forming cells in spleens of treated mice. Antitumor activity was shown against Ehrlich solid tumor.[14]

Experimental Section

Antiviral Evaluation Method. The anti-EMC virus activity of compounds in this study was determined in CF-1 male mice, 15–20 g each, at the several dose levels indicated in the tables. Ten mice were used for each dose level of a compound, and the control group for each compound included 20–30 untreated mice. The test compound was dissolved or suspended in 0.15% hydroxyethylcellulose in H_2O and injected subcutaneously in the nape of the neck or administered orally by gavage. In those instances in which compounds were tested as free bases, 10% Tween 80 was added to aid dispersion. For each dose level, the indicated dose was given 28, 22, and 2 hr before and 2 hr after inoculation with virus. In oral evaluations, the 250 mg/kg dose was a single dose administered 22–28 hr prior to virus infection.

The EMC virus was administered subcutaneously in the groin at effective doses in the range of 4–62 LD_{50} (*cf.* paper 2 for a discussion of the effect of variation of the strength of viral challenge on STR).[4] Simultaneously untreated control mice were infected with the same viral challenge. The mice were observed for 10 days after inoculation. Deaths were recorded twice daily and the mean day of death of the group was determined. A score of 11 was assigned to each survivor and used in determining the mean. A survival time ratio (STR), which is the mean day of death of the treated group divided by the mean day of the control groups, was calculated for each dose level.

Activity is interpreted on the basis of parameters derived from standard deviations of the mean of control groups. An STR of less than 0.90 indicates that early deaths were observed; a ratio of 0.90–1.09 indicates that there was no activity; a ratio of 1.10–1.19 indicates low or weak activity (p = 0.2–0.05 by Student's t test); a ratio of 1.20–1.29 indicates medium activity (p = 0.1–<0.001); and a ratio of 1.30 or greater indicates high activity (p = 0.05–<0.001).

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 were within ±0.4% of the theoretical values except where indicated. The degree of hydration was determined by neutralization equivalent derived by nonaqueous titration or by the Karl Fischer method.

Fluoranthene-3,8-dicarbonyl Chloride (62). A mixture of 250 ml of $SOCl_2$, 20.5 g (0.07 mol) of fluoranthene-3,8-dicarboxylic acid,[11] and 0.5 g of *N,N*-dimethylcyclohexylamine was stirred and refluxed for 4 hr. Excess $SOCl_2$ was removed by distillation and the last trace was removed by azotropic distillation with dry toluene. The product was recrystallized from dry toluene to yield 16.7 g (73.0%), mp 222–227°.

Fluoranthene-3,9-dicarbonyl Chloride (63). A mixture of 3 l. of $SOCl_2$, 200 g (0.69 mol) of fluoranthene-3,9-dicarboxylic acid,[12] and 10 ml of dry pyridine was stirred and refluxed for 16 hr. The product was purified exactly as described for the purification of **62**. The yield was 172.8 g (76.4%), mp 201–204°.

Preparation of Bis-Basic Esters. A mixture of the acid chloride (9.8 g, 0.03 mol) and the appropriate dialkylaminoalkanol (0.06 mol) in 400 ml of hydrocarbon-stabilized $CHCl_3$ was stirred and refluxed for 16 hr. The reaction mixture was washed with a saturated $NaHCO_3$ solution. The $CHCl_3$ solution was separated, washed with H_2O, and then dried over $MgSO_4$. Solvent was removed *in vacuo* on a steam bath. Compounds that were analyzed as free bases were purified by column chromatography. Dihydrochloride salts were obtained by dissolving the free base in butanone and acidifying to Congo Red end point with ethereal HCl.

3,9-Bis(2-chloroacetyl)fluoranthene (20). A solution of 28.7 g (0.142 mol) of fluoranthene and 40.0 g (0.354 mol) of 2-chloroacetyl chloride in 1.5 l. of CH_2Cl_2 was chilled to −20° and 39.8 g (0.298 mol) of $AlCl_3$ was added with rapid stirring. Stirring was continued for 16 hr at room temperature. The reaction mixture was poured onto a mixture of ice–concentrated HCl. The organic layer which separated was washed with a saturated $NaHCO_3$ solution, dried over $MgSO_4$, and filtered. The filtrate was evaporated to dryness, and the solid residue left was recrystallized once from DMF. The yield of product was 30.3 g (60.0%), mp 228–230°.

3,9-Bis(3-chloropropionyl)fluoranthene. The procedure used for the preparation of this compound was analogous to that described for the preparation of **20**. Crude product was recrystallized from $CHCl_3$ to give a 33.9% yield of desired material, mp 154–156°.

3,9-Bis(4-chlorobutyryl)fluoranthene (21). The procedure used for the preparation of this compound was analogous to that described for the preparation of **20**. Solid residue obtained on work-up was recrystallized from EtOAc to yield the desired product (52.6%), mp 124–127°.

3,9-Bis(5-chlorovaleryl)fluoranthene (22). The procedure used for the preparation of this compound was analogous to that described for the preparation of **20**. Crude product obtained on work-up was recrystallized from EtOAc to yield the desired product (49.7%), mp 142–144°.

3,9-Bis(cyclopropylcarbonyl)fluoranthene (23). A mixture of 10.0 g (0.024 mol) of **21**, 8.8 g (0.142 mol) of KOH, 50 ml of MeOH, and 25 ml of *p*-dioxane was stirred and refluxed for 2 hr. The reaction mixture was poured into 400 ml of H_2O. Product which precipitated was filtered, washed with H_2O, and recrystallized from $CHCl_3$–MeOH. The yield was 5.5 g (67.8%), mp 156.5–158.5°.

Bis-Basic Ketones. The bis-basic ketones were prepared by one of the following methods.

Method A. A mixture of the bis-chloro ketone (0.03 mol), the appropriate amine (0.24 mol), KI (10.0 g, 0.06 mol), and 200 ml of butanone was stirred and refluxed for 3 days. The reaction mixture was poured into 2 l. of H_2O. In those cases in which a solid precipitated, it was filtered, washed well with water, and purified by recrystallization. When the free base did not precipitate, the mixture was extracted with 500 ml of $CHCl_3$. The $CHCl_3$ solution was washed with H_2O, dried over $MgSO_4$, and then filtered. The resulting filtrate was acidified with ethereal HCl. The dihydrochloride salt which precipitated was recrystallized from the indicated solvent.

Method B. A mixture of the bis-chloro ketone (0.05 mol), 50 ml of the appropriate amine, 2 g of KI, and 250 ml of THF was stirred and heated in a Paar bomb for 24 hr at approximately 100°. The reaction mixture was evaporated *in vacuo* to semidryness and was then diluted with 1 l. of H_2O. If a solid formed at this point, it was filtered, washed with H_2O, and recrystallized. If an oil separated, it was dissolved in Et_2O. The resulting solution was washed with H_2O and saturated NaCl solution, dried over $MgSO_4$, and filtered; the filtrate was acidified with ethereal HCl. The resulting dihydrochloride salt was recrystallized from the appropriate solvent.

Fluoranthene-3,9-diol Diacetate (64).[13] A mixture of 96.0 g (0.34 mol) of 3,9-diacetylfluoranthene, 2 ml of CF_3COOH, and 1.7 l. of hydrocarbon-stabilized $CHCl_3$ was placed in a blackened flask cooled in an ice bath. To the stirred solution was added 144.0 g (0.75 mol) of 90% *m*-chloroperbenzoic acid in one portion. The reaction mixture was allowed to warm slowly to room temperature and was stirred for 3 days. The mixture was extracted with a saturated $NaHCO_3$ solution, washed with saturated NaCl solution, and then dried over $MgSO_4$. After filtration, the filtrate was evaporated to semidryness and the resulting residue recrystallized from $CHCl_3$–MeOH. The yield of product was 44.3 g (41.1%), mp 165–167°. *Anal.* ($C_{20}H_{14}O_4$) C, H.

Bis-Basic Ethers. The bis-basic ethers were prepared by one of the following methods.

Method C. A mixture of 15.7 g (0.067 mol) of 3,9-dihydroxyfluoranthene,[13] 16.0 g (0.4 mol) of NaOH, 0.4 mol of the dialkylaminoalkyl chloride, 200 ml of toluene, and 200 ml of H_2O was stirred and refluxed for 24 hr. The toluene layer was separated, washed with saturated NaCl solution, and then dried over $MgSO_4$. After filtration, solvent was removed *in vacuo* at steam bath temperature. The residue obtained was chromatographed on alumina, with $CHCl_3$ used as the eluent. The solvent was removed from the fraction collected. The free base was either purified by recrystallization or dissolved in butanone and converted to the dihydrochloride salt with ethereal HCl. Purification of the salts was effected by recrystallization from the indicated solvent.

Method D. A mixture of 10.6 g (0.033 mol) of **64**, 0.066 mol of the dialkylaminoalkyl chloride hydrochloride, 7.2 g (0.132 mol) of NaOMe, and 400 ml of chlorobenzene was stirred and refluxed for 24 hr. The reaction mixture was diluted with 1 l. of H_2O. The or-

ganic phase was separated, washed with H_2O, and then dried over $MgSO_4$. After filtration, solvent was removed *in vacuo* on a steam bath. The residue obtained was chromatographed on neutral alumina with $CHCl_3$ used as the eluent. Solvent was removed from the fraction collected. The free base was either analyzed at this point, purified by recrystallization, or dissolved in butanone and converted to the dihydrochloride salt with ethereal HCl.

Reduction of Bis-Basic Ketones to Bis-Basic Alkanes (Method E). In a typical example, a mixture of 16.8 g (0.033 mol) of **32** and 25 ml of 85% hydrazine hydrate (0.33 mol) in 200 ml of ethylene glycol was heated at 100–120° for 3 hr in an open flask followed by the cautious addition of 18.5 g (0.33 mol) of KOH and allowed to reflux for 16 hr. The cooled reaction mixture was poured into ice water and extracted with $CHCl_3$. The residue obtained after evaporation of the solvent *in vacuo* was dissolved in butanone and made acidic with ethereal HCl to give the crude product. Two recrystallizations from MeOH–butanone gave 6.6 g (36%) of **59** (Table IV).

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Agonist and Antagonist Relationships in 1- and 8-Substituted Analogs of Angiotensin II†

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[1-Pyroglutamic acid,8-alanine]-, [1-D-*allo*-*N*-methylisoleucine,8-isoleucine]-, prolyl[1-sarcosine,8-isoleucine]-, and [1-sarcosine,8-isoleucine]angiotensyl II proline and [8-tryptophan]-, [8-thienylalanine]-, and [1-sarcosine,8-threonine]angiotensin II, synthesized by Merrifield's solid-phase procedure, possess 0.2, 0.5, 0.0, 0.03, 22.2, 26.6, and 0.6% pressor activity of angiotensin II (vagotomized, ganglion-blocked rats) and pA_2 values (rabbit aortic strips) of 7.15, 8.33, 2.49, incalculable, 8.36, 9.36, and 8.79, respectively. The pressor activity of [1-dimethylglycine]angiotensin II was 171.8% of the parent hormone. These results suggest that (a) an increase in the basicity of the N-terminal nitrogen atom enhanced the pressor (or antagonistic) properties of angiotensin II analogs; (b) prolongation of the chain length at the N terminus in [1-sarcosine,8-isoleucine]angiotensin II with a proline residue reduced the antagonistic activity of the compound drastically without any increase in the duration of action (a similar change at the C terminus invoked noncompetitive antagonism); (c) substitution of position 8 with the aromatic groups, *e.g.*, thienylalanine and tryptophan, gave analogs with moderate pressor activity (however, [8-tryptophan]angiotensin II showed competitive type of antagonism to angiotensin II while [8-thienylalanine]angiotensin II, at concentrations over 100 ng/ml, showed noncompetitive antagonism); and (d) substitution of the aliphatic side chain in position 8 with a polar group (threonine) gave good antagonistic activity with the additional advantage that the initial transient pressor activity of [1-sarcosine,8-threonine]angiotensin II was 50% that of [1-sarcosine,8-isoleucine]angiotensin II.

Earlier work from our laboratories indicated that sarcosine in the 1 position of angiotensin II (Asp-Arg-Val-Tyr-Ile-His-Pro-Phe) enhanced the agonist potency of this hormone by (a) an increased binding affinity for the receptor site and (b) a decreased rate of breakdown due to angiotensinase A, which is the major enzyme responsible for the destruction of angiotensin II in plasma.[1,2] [1-Sarcosine]angiotensin II was found to be 1.5 times as active as angiotensin II as a pressor agent and 8–10 times as active as a myotropic agent.[1,2] To further investigate the factors responsible for protection of these peptides against aminopeptidase, we report the synthesis of [Me_2Gly[1]]angiotensin II.‡ We also modified the antagonists of angiotensin II, [Ala[8]]- and [Ile[8]]angiotensin II, by substituting position 1 in these peptides with pyroglutamic acid and D-*allo*-*N*-methylisoleucine, respectively. Similarly, the chain length of [Sar[1],Ile[8]]angiotensin II was extended with a proline residue either at the C or N terminus.

†Abbreviated designation of amino acid derivatives and peptides is according to the recommendation of IUPAC–IUB Commission (IUPAC Information Bulletin No. 26). In addition, the following abbreviations were used: Me_2Gly = dimethylglycine, Pyr = pyroglutamic acid, *a*Melle = *allo*-*N*-methylisoleucine, Sar = sarcosine, Tal = thienylalanine.

‡While this manuscript was under preparation Regoli, *et al.*,[3] also reported that [Sar[1]]angiotensin II is more potent and longer acting than angiotensin II on isolated intestinal and vascular smooth muslces but not *in vivo*. Although the *in vitro* results by these authors are qualitatively similar to our findings in isolated smooth muscle, the *in vivo* results (rat pressor assay) are quite different. Regoli, *et al.*,[3] and Rioux, *et al.*,[4] reported that [Sar[1]]- and [Me_2Gly[1]]angiotensin II possess 70 and 88% pressor activity of angiotensin II, respectively; we obtained 150 and 172% pressor activity for these compounds.