E_1. Acylation as in method E of the corresponding 17′-hydroxy derivative.

F. 17β-[17′β-(1″-Ethoxyethoxy)-19′-nor-17′α-pregna-3′,5′-dien-20′-yn-3′-yloxy]estra-1,3,5(10)-trien-3-ol Acetate (39). A solution of **25** (1 g) in anhydrous THF (10 ml) was treated with Py TsOH (10 mg) and ethyl vinyl ether (2 ml) and kept at room temperature for 15 h. After addition of a few drops of Py, the mixture was percolated through an Al_2O_3 (10 g) column. The solvent was then removed under reduced pressure and the residue crystallized from EtOH.

G. 17β-(17′β-Propionoxy-5′α-androstan-3′ξ-yloxy)estra-1,3,5(10)-trien-3-ol Benzoate (47). To a solution of **44** (5 g) in anhydrous THF (300 ml), 10% Pd/C (5 g) was added and the resulting suspension was charged in an autoclave with 50 atm of H_2 and shaken for 24 h at room temperature. After removal of the catalyst by filtration, the mixture was percolated through an Al_2O_3 (20 g) column. The solvent was removed under reduced pressure and the residue crystallized from C_6H_6.

Intermediates. All enol ethers and acetals of 3-keto steroids, 3-esters, and 3-ethers of 17α- and 17β-estradiol required for preparation of compounds in Table I and II were obtained according to known procedures.[12] Among these, the following compounds appeared not yet described: 3,3-dimethoxy-5α-androstan-17β-ol propionate (**50**) [mp 135–138 °C; [α]D +9.5°. Anal. ($C_{24}H_{40}O_4$) C, H]; 3,3-dimethoxy-5β-androstan-17-ol propionate (**51**) [mp 100–102 °C; [α]D +17.3°. Anal. ($C_{24}H_{40}O_4$) C, H]; 3-ethoxyestra-3,5-dien-17β-ol benzoate (**52**) [mp 170–172 °C; [α]D −74°. Anal. ($C_{27}H_{34}O_3$) C, H]; and estra-1,3,5(10)-trien-3,17α-diol 3-benzoate (**53**) [mp 157–159 °C; [α]D +40°. Anal. ($C_{25}H_{28}O_3$) C, H].

The ethyl enol ether of norethindrone enanthate was not fully isolated and characterized.

Pharmacological Testing. Immature Wistar female rats, 23–25 days old, weighing 40–50 g, were spayed. On the day following surgery, the animals were gavaged by a single treatment. The autopsies were scheduled 1 and 2 weeks later. The uteri were separated from the vagina by cutting through the cervix and weighed fresh, on a torsion balance, after pressing out the intrauterine fluid.

Acknowledgment. The authors are indebted to Dr. C. Pedrali for the spectral determinations and to Mr. A. Valagussa, Mr. C. Pirovano, and Mr. A. Biffi for chemical assistance.

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Bis-Basic-Substituted Polycyclic Aromatic Compounds. A New Class of Antiviral Agents.[1-3] 8. Bis-Basic Derivatives of Carbazole, Dibenzofuran, and Dibenzothiophene

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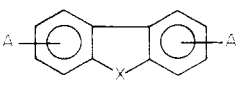
A series of bisalkamine esters, bis-basic ethers, and bis-basic ketones of carbazole, *N*-ethylcarbazole, dibenzofuran, and dibenzothiophene was synthesized and evaluated for antiviral activity. The series also included two bis-basic alkanes of *N*-ethylcarbazole and one bis-basic carboxamide of dibenzofuran. Structure–activity relationships indicated that within the carbazole and *N*-ethylcarbazole series the bisalkamine esters gave the most active derivatives while the bis-basic ketone derivatives of dibenzofuran and dibenzothiophene afforded the more potent compounds within the respective series. The [6,5,6] heterocyclic nuclei were compared with the [6,5,6] aromatic nuclei (fluorene and fluoren-9-one) including tilorone with respect to antiviral activity against encephalomyocarditis (EMC) virus. Maximum activity was associated with the bis-basic ketone side chain and fluoren-9-one nucleus.

Reports describing the antiviral activity of bisalkamine esters Ia,[4] bis-basic ethers Ib,[5] and bis-basic ketones Ic[6] of fluorene and fluorenone (IIa–c) led to the investigation of a variety of other bis-basic-substituted derivatives of various aromatic nuclei including anthraquinone,[7] fluoranthene,[8] and xanthene.[3] We now wish to report the synthesis and antiviral properties of a series of bis-basic derivatives of carbazole (III), *N*-ethylcarbazole (IV), dibenzofuran (V), and dibenzothiophene (VI).

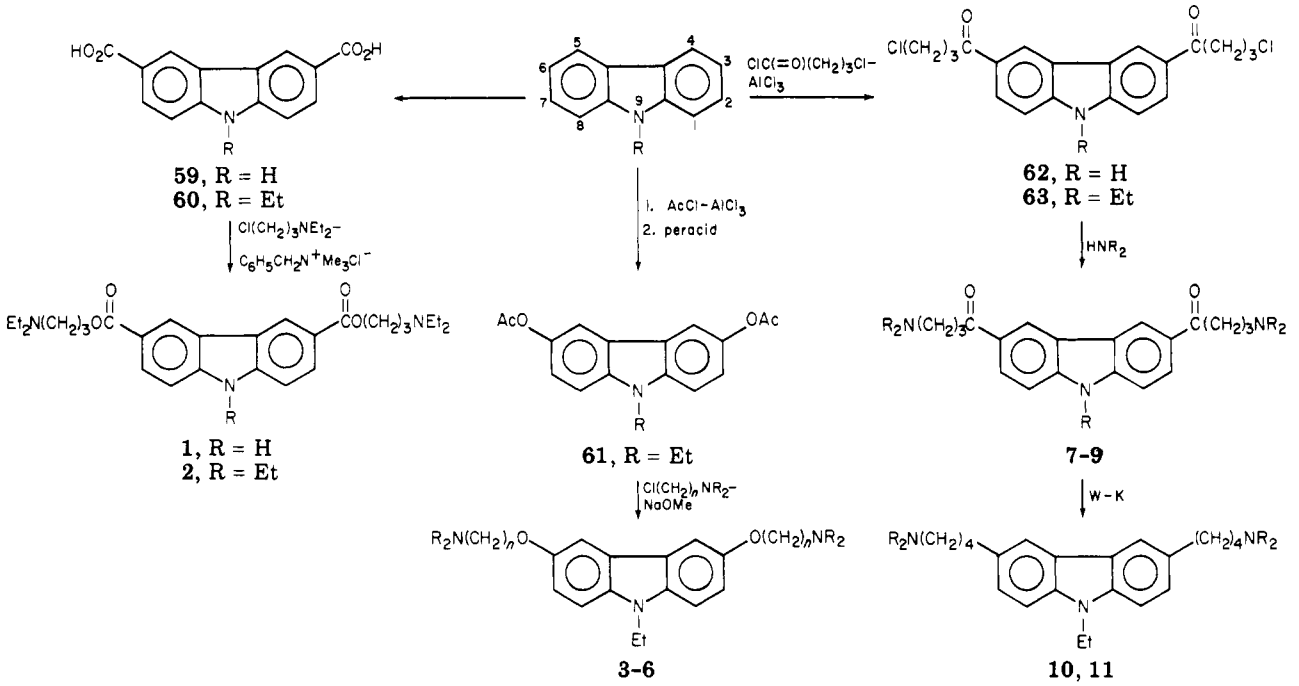


I, X = CH_2
II, X = C=O
III, X = NH
IV, X = NEt
V, X = O
VI, X = S

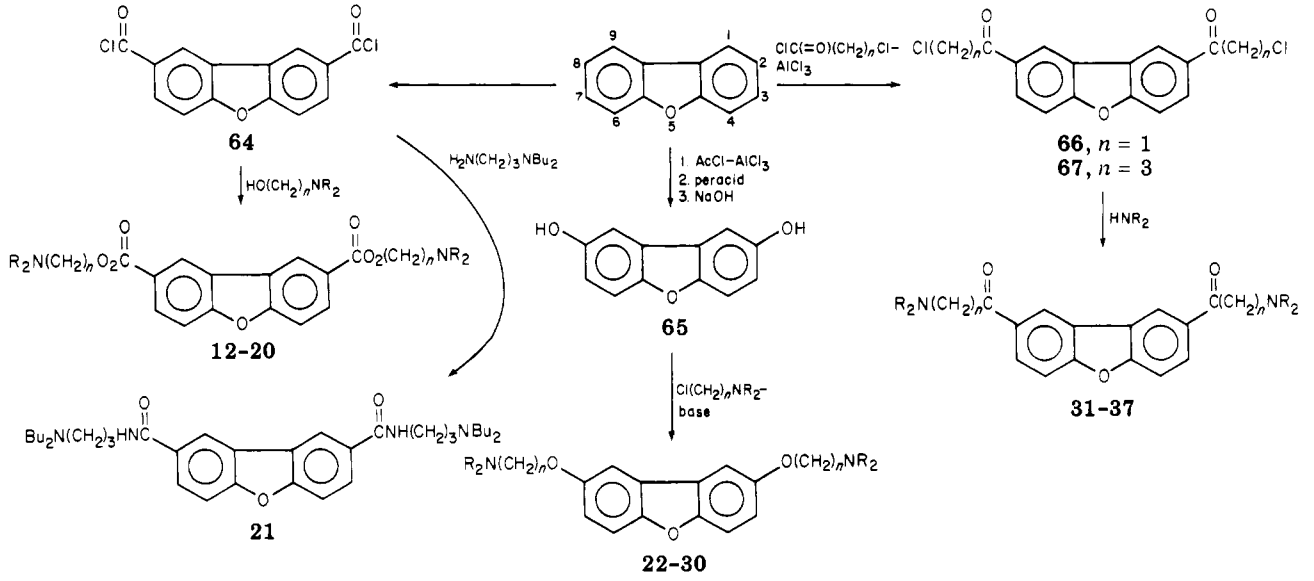
a, A = $CO_2(CH_2)_nNR_2$
b, A = $O(CH_2)_nNR_2$
c, A = $CO(CH_2)_nNR_2$
d, A = $(CH_2)_nNR_2$

Chemistry. The synthesis of bis-basic-substituted carbazoles is outlined in Scheme I. Carbazole-3,6-dicarboxylic acid prepared by the method of Preston et al.[9] and *N*-ethylcarbazole-3,6-dicarboxylic acid prepared by the method of Gilman and Spatz[10] were treated with 3-diethylaminopropyl chloride in the presence of a catalytic amount of benzyltrimethylammonium chloride to give the bisalkamine esters (Table I) **1** and **2**, respectively. The bis-basic ethers **3–6** (Table I) were prepared by the direct alkylation of *N*-ethylcarbazole-3,6-diol diacetate derived from 3,6-diacetyl-*N*-ethylcarbazole[11] via the Baeyer–Villiger oxidation reaction with *m*-chloroperbenzoic acid. This procedure, previously described for the synthesis of bis-basic ethers of fluoranthene,[8] was the method of choice since all attempts to isolate *N*-ethylcarbazole-3,6-diol

Scheme I



Scheme II



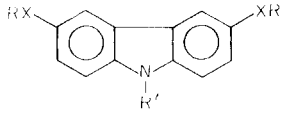
resulted in black polymeric material. The Friedel–Crafts diacetylation reaction of carbazole and *N*-ethylcarbazole with 4-chlorobutyryl chloride gave the respective 3,6-bis(4-chlorobutyryl) intermediates that were treated with a secondary amine to give the bis-basic ketones **7–9** (Table I). The bis-basic alkanes **10** and **11** (Table I) were prepared from the corresponding bis-basic ketones via the Wolff–Kishner reduction.

Scheme II illustrates the syntheses of bis-basic-substituted dibenzofurans. The bisalkamine esters **12–20** (Table II) were obtained by the esterification of dibenzofuran-2,8-dicarbonyl chloride[12] with the appropriate amino alcohol. The bis-basic carboxamide **21** (Table II) was also derived from the acid chloride upon reaction with *N*,*N*-dibutylaminopropylamine. The Baeyer–Villiger oxidation of 2,8-diacetyldibenzofuran[12] with *m*-chloroperbenzoic acid followed by alkaline hydrolysis of the intermediate diacetate gave 2,8-dihydroxydibenzofuran. This diol, when treated with various aminoalkyl chlorides, gave the bis-basic ethers **22–30** (Table II). The bis(aminoacyl)dibenzofurans **31–37** (Table II) were prepared by procedures analogous to those described above for the synthesis of bis(aminoacyl)carbazoles.

Several modifications of the above procedures were required for the synthesis of bis-basic-substituted dibenzothiophenes (Scheme III). Two problems were encountered in the chemistry of dibenzothiophene that was not prevalent with the other two heterocycles. First, substitution with electrophiles having electron-withdrawing effects gave rise to isomeric mixtures of bis-substituted products. Secondly, oxidative procedures gave rise to sulfoxides and sulfones of the dibenzothiophenes.

Friedel–Crafts reaction of dibenzothiophene with oxalyl chloride and subsequent reaction of the diacid with thionyl chloride gave dibenzothiophene-2,6- (and 2,8-) dicarbonyl chloride. The bisalkamine esters **38–43** were prepared by reacting the various amino alcohols with the isomeric mixture of the acid chlorides. The isomeric ratios of the bisalkamine esters were determined by GLC analysis as described in the Experimental Section.

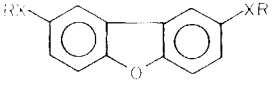
Table I. Bisalkamine Esters, Bis-Basic Ethers, and Bis(aminoacyl)- and Bis(alkamine)carbazoles



No.	X	R	R′	Mp, °C	Yield, %	Recrystn solvent	Formula[a]	STR[b] vs. EMC virus (mg/kg) sc admin 10	sc admin 50	sc admin 250	Oral admin 50	Oral admin 250
1	CO_2	$(CH_2)_3N(C_2H_5)_2$	H	230-233 dec	12	MeOH-MeCOEt	$C_{28}H_{39}N_3O_4 \cdot 2HCl \cdot 0.5H_2O$	1.04	1.69	1.47	1.10	1.17
2	CO_2	$(CH_2)_3N(C_2H_5)_2$	C_2H_5	233-234	20	MeOH-Me_2CO	$C_{30}H_{43}N_3O_4 \cdot 2HCl$	1.33	1.74	1.87		0.75
3	O	$(CH_2)_3N(C_2H_5)_2$	C_2H_5	208-210	23	MeOH-EtOAc	$C_{26}H_{39}N_3O_2 \cdot 2HCl$[c]	1.05	1.13	0.85[d]	0.87	0.92
4	O	$(CH_2)_2$-c-NC_5H_{10}	C_2H_5	248-250	39	MeOH-EtOAc	$C_{28}H_{39}N_3O_2 \cdot 2HCl$	1.16	1.32	1.25	1.09	1.09
5	O	$(CH_2)_2$-c-$N(CH_2CH_2)_2O$	C_2H_5	146-147	16	CH_2Cl_2-pentane	$C_{26}H_{35}N_3O_4$	0.92	1.08	1.02	0.86	0.88
6	O	$(CH_2)_3N(CH_3)_2$	C_2H_5	239-240	26	MeOH-EtOAc	$C_{24}H_{35}N_3O_2 \cdot 2HCl$	0.92	1.10	0.52[d]	0.90	0.88
7	C=O	$(CH_2)_3N(CH_3)_2$	C_2H_5	94-98	18	MeOH-EtOAc	$C_{26}H_{35}N_3N_2 \cdot 2C_4H_4O_4$[e]	1.42	1.63	1.44	0.94	1.06
8	C=O	$(CH_2)_3$-c-NC_5H_{10}	H	171-173	17	Me_2CO	$C_{30}H_{39}N_3O_2$	1.22	0.96	1.00	0.86	0.88
9	C=O	$(CH_2)_3$-c-NC_5H_{10}	C_2H_5	138-142	23	MeOH-EtOAc	$C_{32}H_{43}N_3O_2 \cdot 2HCl \cdot 0.5H_2O$[f]	1.68	1.58	0.56[d]	1.09	1.20
10	CH_2	$(CH_2)_3N(C_2H_5)_2$	C_2H_5	172-174	10	CH_2Cl_2-Me_2CO	$C_{30}H_{47}N_3 \cdot 2HCl$[g]	1.22	1.22		0.98	1.17
11	CH_2	$(CH_2)_3$-c-NC_5H_{10}	C_2H_5	260-262	62	MeOH-EtOAc	$C_{30}H_{47}N_3 \cdot 2HCl$	1.28	1.45	0.57[d]		

[a] 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. [b] STR defined in Experimental Section. [c] C: calcd, 62.63; found, 62.15. [d] Early deaths observed at specific dose. [e] $2C_4H_4O_4$ = bis acid fumarate salt. [f] C: calcd, 65.84; found, 65.34. [g] C: calcd, 68.94; found, 68.42.

Table II. Bisalkamine Esters, Bisalkamine Carboxamides, Bis-Basic Ethers, and Bis(aminoacyl)dibenzofurans

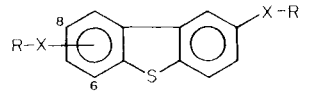


No.	X	R	Mp, °C	Yield, %	Recrystn solvent	Formula[a]	STR[b] vs. EMC virus (mg/kg) sc admin 10	sc admin 50	sc admin 250	Oral admin 50	Oral admin 250
12	CO_2	$(CH_2)_2N(C_2H_5)_2$	260-264[c]	43	MeOH-EtOAc	$C_{26}H_{34}N_2O_5 \cdot 2HCl$	1.00	1.02	1.09	1.02	0.98
13	CO_2	$(CH_2)_3N(CH_3)_2$	251-253	55	MeOH-MeCOEt	$C_{24}H_{30}N_2O_5 \cdot 2HCl \cdot 0.5H_2O$	1.19	1.26	1.36	1.07	1.07
14	CO_2	$(CH_2)_3N(C_2H_5)_2$	258-259.5	52	*i*-PrOH	$C_{28}H_{38}N_2O_5 \cdot 2HCl \cdot 0.5H_2O$		1.19	1.22		
15	CO_2	$(CH_2)_3N(n\text{-}C_3H_7)_2$	222.5-224	45	MeOH-MeCOEt	$C_{32}H_{46}N_2O_5 \cdot 2HCl \cdot 0.5H_2O$	0.96	1.21	1.88		
16	CO_2	$(CH_2)_3N(n\text{-}C_4H_9)_2$	200-202	28	EtOH	$C_{36}H_{54}N_2O_5 \cdot 2HCl \cdot 0.5H_2O$	1.06	1.40	1.60[d]		
17	CO_2	$(CH_2)_3N[(CH_2)_2CH(CH_3)_2]_2$	Oil	41	*e*	$C_{40}H_{62}N_2O_5$	0.91	1.07	1.11		
18	CO_2	$(CH_2)_3N(CH_2CH{=}CH_2)_2$	223-225 dec	80	MeOH-MeCOEt	$C_{32}H_{38}N_2O_5 \cdot 2HCl$	1.11	1.20	1.33		
19	CO_2	$(CH_2)_3$-c-NC_5H_{10}	252-253 dec	48	MeOH-Me_2CO	$C_{30}H_{38}N_2O_5 \cdot 2HCl \cdot H_2O$	1.11	1.22	0.91[d]	0.96	1.02
20	CO_2	3-CH_2-c-C_5H_9N-CH_3	274-283 dec	56	H_2O-MeOH-MeCOEt	$C_{28}H_{34}N_2O_5 \cdot 2HCl \cdot 2H_2O$[f]	1.07	1.07	1.05[d]	1.03	1.00
21	CONH	$(CH_2)_3N(n\text{-}C_4H_9)_2$	56-59	21	MeOH-MeCOEt	$C_{36}H_{56}N_4O_3 \cdot 2C_6H_8O_7$[g]	1.17	1.24[d]	0.85[d]		
22	O	$(CH_2)_2N(C_2H_5)_2$	236.5-238.5	52	MeOH-EtOAc	$C_{24}H_{34}N_2O_3 \cdot 2HCl$	1.21	1.31	0.91[d]	1.17	1.02
23	O	$(CH_2)_2N(i\text{-}C_3H_7)_2$	47-49	36	*e*	$C_{28}H_{42}N_2O_3$	0.88	1.24	1.14[d]	0.96	0.88
24	O	$(CH_2)_2$-c-NC_4H_8	257-259	29	MeOH-Me_2CO	$C_{24}H_{30}N_2O_3 \cdot 2HCl$	1.08	1.04	0.88[d]	0.98	1.00

25	O	$(CH_2)_2$-c-NC_5H_{10}	288-289	60	MeOH-EtOAc	$C_{26}H_{34}N_2O_3 \cdot 2HCl$	0.94	1.25	1.02	0.85	1.04
26	O	$CH(CH_3)CH_2N(CH_3)_2$	120-122	10	MeOH-Me_2CO	$C_{22}H_{30}N_2O_3 \cdot 2C_6H_8O_7$[g]	0.94	1.08	0.90[d]	0.84	0.84
27	O	$(CH_2)_3N(CH_3)_2$	257-258	32	MeOH-EtOAc	$C_{22}H_{30}N_2O_3 \cdot 2HCl$	0.92	1.24	0.66[d]	0.92	0.88
28	O	$(CH_2)_3N(C_2H_5)_2$	Oil	30	[e]	$C_{26}H_{38}N_2O_3$	0.98	0.88[d]	1.47[h]	0.98	0.92
29	O	$(CH_2)_3$-c-NC_5H_{10}	245-246.5	33	H_2O-Me_2CO	$C_{28}H_{38}N_2O_3 \cdot 2HCl$	1.46	1.44	0.63[d]	1.02	1.02
30	O	$CH_2CH(CH_3)CH_2N(CH_3)_2$	126-128	40	MeOH-Me_2CO	$C_{24}H_{34}N_2O_3 \cdot 2HCl$	1.20	1.14	0.57[d]	0.90	0.92
31	C=O	$CH_2N(CH_3)_2$	>330	44	EtOH-MeCOEt	$C_{20}H_{22}N_2O_3 \cdot 2HCl \cdot 2H_2O$	1.13	1.64	2.00	1.80	2.20
32	C=O	$CH_2N(C_2H_5)_2$	225-227 dec	21	EtOH-MeCOEt	$C_{24}H_{30}N_2O_3 \cdot 2HCl \cdot 0.5H_2O$	0.96	1.35	2.17	0.96	1.65
33	C=O	CH_2-c-NC_5H_{10}	306-308 dec[i]	11	MeOH-MeCOEt	$C_{26}H_{30}N_2O_3 \cdot 2HCl \cdot 1^1/_3H_2O$	1.11	1.12	2.41	0.87[d]	1.41
34	C=O	$(CH_2)_3$-c-NC_5H_{10}	70-71	24	Pentane	$C_{30}H_{38}N_2O_3$		1.49	1.81	1.06	1.19
35	C=O	$(CH_2)_3$-c-NC_5H_9-4-CH_3	72-73	12	Pentane	$C_{32}H_{42}N_2O_3$	1.23	2.13	2.04	1.11	1.19
36	C=O	$(CH_2)_3$-c-NC_5H_9-4-$CH_2C_6H_5$	252-253	10	EtOH	$C_{44}H_{50}N_2O_3 \cdot 2HCl$	1.27	1.70	1.82[h]	1.07	0.98
37	C=O	$(CH_2)_3$-c-$N(CH_2CH_2)_2O$	98-99	33	Pentane	$C_{28}H_{34}N_2O_5$	1.00	1.39	1.96	1.08	1.08

[a] See footnote *a*, Table I. [b] See footnote *b*, Table I. [c] Reported mp 251-253 °C (ref 21). [d] See footnote *d*, Table I. [e] Compound purified by column chromatography on Merck neutral alumina with $CHCl_3$ as eluting solvent. [f] H: calcd, 6.83; found, 7.25. [g] $2C_6H_8O_7$ = bis-dihydrogen citrate salt. [h] Activity determined from single dose administered 22 h before infection. [i] Reported mp >350 °C (ref 20) and >300 °C (ref 22).

Table III. Bisalkamine Esters, Bis-Basic Ethers, and Bis(aminoacyl)dibenzothiophenes



			Isomer ratio, %			Yield,			STR[b] vs. EMC virus (mg/kg)				
									sc admin			Oral admin	
No.	X	R	2,6	2,8	Mp, °C	%	Recrystn solvent	Formula[a]	10	50	250	50	250
38	CO_2	$(CH_2)_2N(C_2H_5)_2$	74	26	219-225	47	MeOH-Me_2CO	$C_{26}H_{34}N_2O_4S \cdot 2HCl$	1.14	1.04	1.20		
39	CO_2	$(CH_2)_3N(C_2H_5)_2$		100	243-245	45	MeOH-*i*-PrOH	$C_{28}H_{38}N_2O_4S \cdot 2HCl$		1.77	1.30[c]		
40	CO_2	$(CH_2)_3N(n\text{-}C_4H_9)_2$	40	60	143-146	44	MeOH-EtOAc	$C_{36}H_{54}N_2O_4S \cdot 2HCl \cdot 0.5H_2O$[d]	1.29	1.48	2.43	0.93	0.93
41	CO_2	$(CH_2)_3N[(CH_2)_2CH(CH_3)_2]_2$	69	31	110-118	19	EtOH-MeCOEt	$C_{40}H_{62}N_2O_4S \cdot 2HCl$	0.96	0.98	1.11		
42	CO_2	$(CH_2)_3$-c-NC_5H_{10}	75	25	248-256	36	MeOH-EtOAc	$C_{30}H_{38}N_2O_4S \cdot 2HCl \cdot H_2O$	1.40	1.36	1.55		
43	CO_2	$CH_2C(CH_3)_2(CH_2)_3N(CH_3)_2$	89	11	245-251	47	MeOH-Me_2CO	$C_{32}H_{46}N_2O_4S \cdot 2HCl$	1.07	1.42	1.11[c]		
44	O	$(CH_3)_2N(CH_3)_2$		100	248-250 dec	32	MeOH-MeCOEt	$C_{20}H_{26}N_2O_2S \cdot 2HCl$	1.09	1.13	0.91[c]	0.98	1.06
45	O	$(CH_2)_2N(C_2H_5)_2$		100	150-152	49	H_2O-MeOH-MeCOEt	$C_{24}H_{34}N_2O_2S \cdot 2C_6H_8O_7$[e]	0.96	1.12	1.32[c]	0.88	0.86
46	O	$(CH_2)_2N(i\text{-}C_3H_7)_2$		100	223-225	11	$CHCl_3$-Me_2CO	$C_{28}H_{42}N_2O_2S \cdot 2HCl$	1.24	1.30[c]	1.20[c]	1.18	1.00
47	O	$(CH_2)_2$-c-NC_5H_{10}		100	281-283	21	MeOH-Me_2CO	$C_{26}H_{34}N_2O_2S \cdot 2HCl$	1.09	1.57	1.30	0.98	1.02
48	O	$(CH_2)_3N(n\text{-}C_3H_9)_2$		100	155-157	16	$CHCl_3$-Me_2CO	$C_{34}H_{54}N_2O_2S \cdot 2HCl$	0.88	1.14	0.96[c]	0.90	0.88
49	O	$(CH_2)_3$-c-NC_5H_{10}		100	240-242	26	MeOH-MeCOEt	$C_{28}H_{38}N_2O_2S \cdot 2HCl$	1.34	1.94	0.77[c]	0.98	1.06
50	O	$CH_2CH(CH_3)CH_2N(CH_3)_2$		100	120-122	30	MeOH-MeCOEt	$C_{24}H_{34}N_2O_2S \cdot 2HCl \cdot H_2O$[f]	0.96	1.08	0.84[c]	1.04	0.94
51	C=O	$CH_2N(CH_3)_2$		100[g]	>340	47	MeOH-Et_2O	$C_{20}H_{22}N_2O_2S \cdot 2HCl \cdot H_2O$	1.10	2.29	2.29	1.75	2.29
52	C=O	$CH_2N(CH_3)_2$		*h*	215-217 dec	45	EtOH-MeCOEt	$C_{20}H_{22}N_2O_2S \cdot 2HCl \cdot 2H_2O$[i]	1.02	1.51	1.94	2.02	2.24
53	C=O	$CH_2N(C_2H_5)_2$		*h*	203-207	27	MeOH-EtOAc	$C_{24}H_{30}N_2O_2S \cdot 2HCl \cdot 2H_2O$	1.02	1.20	2.27	1.22	2.22
54	C=O	$(CH_2)_3N(CH_3)_2$		100	276-277.5 dec	7	MeOH-Me_2CO	$C_{24}H_{30}N_2O_2S \cdot 2HCl$	1.09	1.66	1.09[c]	1.00	0.95
55	C=O	$(CH_2)_3$-c-NC_5H_{10}	100		106-108	45	$CHCl_3$-Me_2CO	$C_{30}H_{38}N_2O_2S$	1.21	1.71	2.08	1.10	1.23
56	C=O	$(CH_2)_3$-c-NC_5H_{10}		100	93-95	86	Me_2CO	$C_{30}H_{38}N_2O_2S$	1.10	1.90	0.61[c]	1.16	1.22
57	C=O	$(CH_2)_3$-c-NC_5H_9-4-CH_3		100	136-137.5	53	$CHCl_3$-Me_2CO	$C_{32}H_{42}N_2O_2S$	1.22	1.84	1.69	1.06	1.10
58	C=O	$(CH_2)_3$-c-$N(CH_2CH_2)_2O$	100		241-242 dec	11	MeOH-EtOAc	$C_{28}H_{34}N_2O_4S \cdot 2HCl$	1.13	1.33	1.98	0.90	0.94

[a] See footnote *a*, Table I. [b] See footnote *b*, Table I. [c] See footnote *d*, Table I. [d] Degree of hydration not determined. [e] See footnote *g*, Table II. [f] C: calcd, 57.02; found, 56.48. [g] This isomer was prepared from 2,8-bis(bromoacetyl)dibenzothiophene (**73**). [h] Isomer composition not determined. [i] Cl: calcd, 15.30; found, 15.74.

The Baeyer–Villiger reaction of 2,8-diacetyldibenzothiophene failed to give the desired dibenzothiophene-2,8-diol diacetate but instead gave the sulfone. The use of 4 equiv of per acid did not yield the sulfonediol diacetate nor did reflux effect the Baeyer–Villiger product. The required 2,8-dihydroxydibenzothiophene was prepared by the method of Richter and Fuller.[13] The disodium salt was alkylated with the appropriate aminoalkyl chloride to give the bis-basic ethers **44–50** (Table III).

The Friedel–Crafts acylation reaction was complicated by the presence of a second isomer in addition to the desired 2,8 isomer. Acetylation of dibenzothiophene with 2 equiv of chloroacetyl chloride gave a mixture of the 2,6 and 2,8 isomers. This mixture was not readily separable by recrystallization and was aminated as such to give **52** and **53** (Table III). As we have previously reported, acetylation of dibenzothiophene with 2 equiv of acetyl chloride results in a mixture of 2,6 and 2,8 isomers that can be separated by fractional crystallization.[14] The pure 2,8 isomer was converted to 2,8-bis(bromoacetyl)dibenzothiophene and aminated with dimethylamine to give **51** (Table III). Acetylation with 4-chlorobutyryl chloride gave an isomeric mixture that could also be separated by crystallization. The pure 2,8 isomer was aminated to give **54**, **57**, and **58** while the pure 2,6 isomer gave **55** and **58** (Table III) under similar reaction conditions.

Antiviral Activity. The antiviral activity 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 antiviral activity for carbazole derivatives is presented in Table I. Although the two bisalkamine esters **1** and **2** differed from one another only by the presence of an ethyl group attached to the carbazole nitrogen in the latter compound, it was evident that this moiety imparted superior activity to the bisalkamine ester. Only one bis-basic ether, **4**, had high activity (STR > 1.30) subcutaneously. Under these test conditions, the other ethers were either inactive, **5**, or weakly active, **3** and **6**. Compounds **7** and **9** were more potent than **8** within the bis(aminoacyl) series. It was again noted that the ethyl group in the carbazole nucleus increased antiviral activity (cf. **9** to **8**). The bisalkamines **10** and **11** were less active than the bis-basic ketones from which they were derived. The bis-basic-substituted carbazole derivatives were either inactive or only weakly active when administered orally to mice at the specified doses.

The antiviral results obtained for dibenzofuran derivatives are tabulated in Table II. The most active bisalkamine esters were **15** and **16**. The SAR of these esters paralleled that reported for the bisalkamine esters of fluorenone;[4] however, compounds in the latter series were generally more potent. The bis-basic carboxamide **21**, which was a preferred aminoalkyl side chain [$-(CH_2)_3-N(C_4H_9)_2$] found in the ester series, was less active and more toxic than the corresponding bisalkamine ester **16**. The bis-basic ethers of dibenzofuran (**22–30**) had rather weak antiviral activity when administered either subcutaneously or orally. Only three compounds (**22**, **28**, and **29**) had STR values of >1.30. All of the bis(aminoacyl)dibenzofurans were potent antiviral agents at the highest subcutaneous dose (STR > 1.80). The activity was independent of the alkylene chain length (methylene–propylene) separating the carbonyl function from the terminal amino group and was also invariant with respect to the terminal amine group. The nature of the side chain, however, did have a significant effect on oral activity with only the aminoacetyl compounds (**31–33**) having high oral activity. Compound **31** was the most potent compound by the oral route.

Table IV. Comparison of STR Values[a] of Bis-Basic Derivatives

Ring	Side chain: Ester $-CO_2-(CH_2)_3-N(C_2H_5)_2$	Side chain: Ether $-O(CH_2)_2-N(C_2H_5)_2$	Side chain: Ketone $-CO-(CH_2)_3-$c-NC_5H_{10}
Fluorene	1.09[b]	1.22[c]	2.08[d]
Fluorenone	1.63[b]	1.95[c]	2.19[d]
N-Ethylcarbazole	1.74[e]	1.13[e]	1.58[e]
Dibenzofuran	1.19[e]	1.31[e]	1.49[e]
Dibenzothiophene	1.77[e]	1.12[e]	1.90[e]

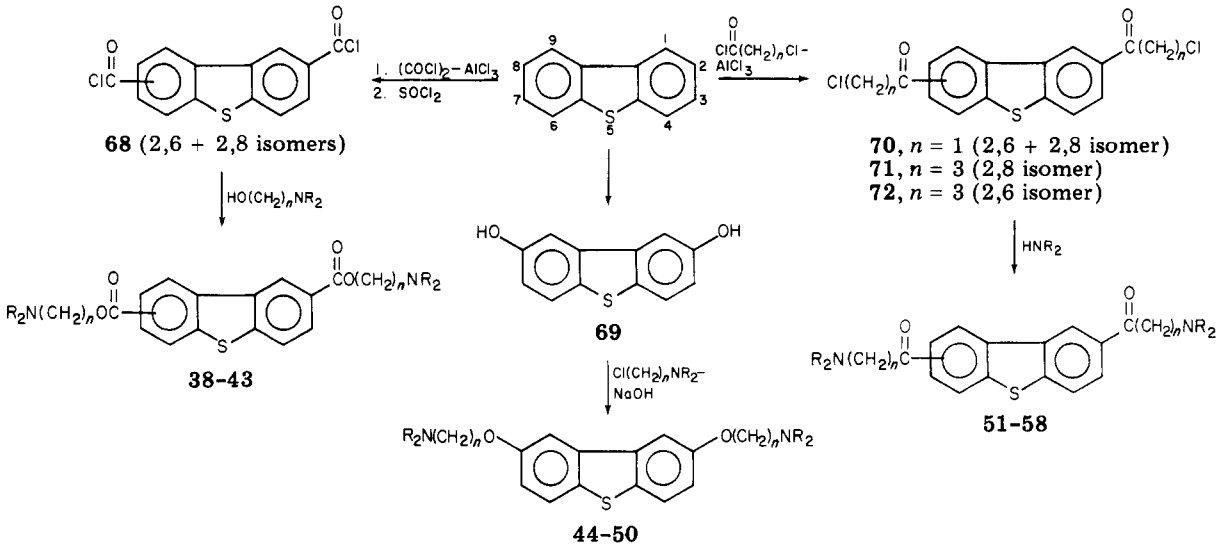
[a] STR values derived from 50 mg/kg of test compounds administered subcutaneously given 28, 22, and 2 h before and 2 h after inoculation with EMC virus. [b] Data taken from ref 4. [c] Data taken from ref 5. [d] Data taken from ref 6. [e] Data taken from Tables I–III, this paper.

The antiviral activity for the bis-basic-substituted dibenzothiophenes is presented in Table III. Activity for the bisalkamine esters **38–43** was determined on mixtures of the 2,6 and 2,8 isomers with the exception of **39**, which was the pure 2,8 isomer. The SAR for these esters was found to be similar to that observed within the bisalkamine ester series of fluorenone.[4] Maximum activity was observed for compounds **39** and **40**, in which the alkylene chain consisted of three carbon atoms and the terminal amine group was diethylamino or dibutylamino. Compound **49** was the most potent member of the bis-basic ether series (**44–50**) as seen by the STR value of 1.94 at 50 mg/kg sc. The dibenzothiophene bis-basic ethers were generally lethal at the higher subcutaneous dose. This effect was also observed in the tilorone series.[5] The dibenzothiophene ethers were not orally effective at the doses tested, in contrast to tilorone and other bis-basic ethers of fluorenone.[5] The bis(aminoacyl) derivatives **51–58** were the most potent antiviral agents within the dibenzothiophene series. Compounds **51–53** were also potent antiviral agents via the oral route. A comparison of antiviral activity of the 2,6 and 2,8 isomer (compounds **55** and **56**, respectively) indicated they were equipotent at all doses tested whether administered subcutaneously or orally except at the 250 mg/kg sc dose. Lethality as measured by early death in the treated animals was associated with the 2,8 isomer but not observed for the 2,6 isomer.

It was now possible to compare the antiviral activity of bis-basic-substituted derivatives of the polycyclic ([6,5,6] ring system) aromatic and heteroaromatic nuclei. Two striking results were seen when the STR's at 50 mg/kg sc were compared for the 15 compounds in Table IV. First, the fluorenone nucleus contributed most to the potency of the compound when the five ring systems were considered. Secondly, the basic ketone side chain had the greatest positive influence on antiviral activity relative to the basic ester and ether side chains. The most potent compound (STR = 2.19) in Table IV was obtained by the combination of these two fragments.

Two compounds selected on the basis of potency, one each from the bis-basic-substituted dibenzofurans (**31**, RMI 11 567DA) and dibenzothiophenes (**51**, RMI 11 877DA), were evaluated against *Herpesvirus hominis* (HVH), type 1, in vitro and in vivo. (See Experimental Section.) Both compounds reduced virus titer by at least 2.5 logs. The virus titer in the control group was log = 5.0.

Scheme III



Raised, blister-like lesions, brought about by the cutaneous inoculation of HVH type 1 into the base of the tails of white mice, could not be prevented by the oral administration of either compound **31** or **51**. Prophylactic systemic administration of either compound did not suppress the development of ulcerated zoster-like lesions provoked by cutaneous inoculation of HVH type 1 onto the backs of hairless mice; however, the in vitro results showing direct inactivation prompted the testing of these compounds topically in hairless mice. Comparison of the average lesion score for the treated groups with that of the control group revealed that both compounds were active. The most potent compound was **31** with a score of 0.33 while **51** gave a score of 1.00 as compared to the control value of 2.83.

Compounds **31** and **51**, given orally or subcutaneously to mice, induced significant amounts of serum interferon.[15,16] Besides the activity demonstrated against EMC virus and *Herpesvirus hominis* type 1, compound **31** was reported to be active in mice against Semliki Forest virus and vaccinia virus.[17] Compound **51**, in addition to the activity observed against EMC virus and *Herpesvirus hominis*, type 1, was also reported to be active in mice against Semliki Forest virus, influenza virus A_2 (Jap/305), influenza virus A_0 (Pr_8), and vaccinia virus.[17] Both compounds given orally to monkeys caused a significant reduction of Venezuelan equine encephalitis viremia.[18]

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

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 h before and 2 h after inoculation with virus. In oral evaluations, the 250 mg/kg dose was a single dose administered 22–28 h prior to virus infection.

The EMC virus was administered subcutaneously in the groin at effective doses in the range of 4–62 LD_{50}. (See 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 group, was calculated for each dose level.

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

In vitro evaluation against *Herpesvirus hominis* (HVH) was performed by preparing 10% solutions of the compounds in distilled water. These solutions were combined with equal volumes of virus suspensions (HVH, type 1) to provide final 5% concentrations of the compounds. The mixtures were left at room temperature for 1 h after which time they were dialyzed against distilled water at 4 °C for 24 h. Log dilutions of each dialyzed sample were made and the remaining viable virus was titrated by CPE (cytopathologic) assay in monkey viro cell cultures.

In the in vivo evaluation, the lower backs of the hairless mice were scarified with a sterile needle and were then inoculated with HVH, type 1, by application with a cotton swab. A viral-induced lesion developed unilaterally or bilaterally reaching maximum within 6–8 days. Solutions (5%) of the compounds were prepared in 0.1 M phosphate buffer (pH 7.5). The buffered formulations were swabbed onto the backs of the mice at 2, 4, and 6 h after virus inoculation and treatment was continued daily for 4 days, four times a day, at 2-h intervals. Fresh solutions of both compounds were prepared daily. On the eighth day after infection, the degree of lesion severity on each mouse was scored (3 = maximum severity, 2 = moderate, 1 = pinpoint, 0 = no lesions). The scores of each mouse within a group were totaled and averaged (six mice/treated group and 12 mice/control group).

Isomer Ratio Determination for Bisalkamine Esters of Dibenzothiophene. Compounds **38–42** were transesterified to the corresponding dimethyl esters with methanolic KOH. The isomeric mixture of the dimethyl esters was analyzed on a Model 1200-1 Varian aerograph gas chromatograph with a $^1/_8$ in. × 6 ft column, 2% Versamid, H.P. Chromosorb W (DMCS-AW),

100–120 mesh. The resulting chromatograms were compared to a standard curve, obtained from known mixtures of the 2,6- and 2,8-dimethyl esters, to give the isomer ratio. (See Table III for results.)

Bisalkamine Esters of Carbazole and *N*-Ethylcarbazole (1, 2). A mixture of 0.035 mol of the appropriate dicarboxylic acid, 10.5 g (0.07 mol) of 3-diethylaminopropyl chloride, and 0.5 ml of 60% aqueous benzyltrimethylammonium chloride was stirred and refluxed in 250 ml of 2-propanol for 2 h. On cooling, the product either crystallized or the reaction solvent was removed in vacuo and the resulting solid was recrystallized from the solvent system indicated in Table I.

Bisalkamine Esters of Dibenzofuran and Dibenzothiophene (12–20 and 38–43). A mixture of the diacid chloride (0.03 mol) and the dialkylaminoalkanol (0.06 mol) in 400 ml of hydrocarbon-stabilized $CHCl_3$ was stirred at reflux for 16 h. The reaction mixture was washed with saturated $NaHCO_3$ solution and water, dried ($MgSO_4$), and made acidic with ethereal HCl. The dihydrochloride salt that precipitated was recrystallized from the appropriate solvent.

***N,N'*-Bis(3-dibutylaminopropyl)dibenzofuran-2,8-dicarboxamide Dicitrate (21).** Following the procedure for the preparation of bisalkamine esters of dibenzofuran but replacing the dialkylaminoalkanol with 3-dibutylaminopropylamine and refluxing for 4 h gave the dihydrochloride salt that would not crystallize. The dihydrochloride salt was converted to the free base, treated with 2 equiv of citric acid, and recrystallized from MeOH–butanone.

Bis-Basic Ethers of *N*-Ethylcarbazole (3–6). A mixture of 15.5 g (0.05 mol) of 9-ethyl-3,6-carbazolediol diacetate, 0.1 mol of the dialkylaminoalkyl chloride hydrochloride, and 10.8 g (0.2 mol) of $NaOCH_3$ in 400 ml of chlorobenzene was stirred and refluxed for 24 h. After cooling, the reaction mixture was washed with water and dried ($MgSO_4$). The dihydrochloride salts were obtained by acidification of the chlorobenzene solution with ethereal HCl and recrystallized from MeOH–EtOAc. Compound **5** was reconverted to the free base and recrystallized from CH_2Cl_2–pentane.

Also prepared by this method were the bis-basic ethers of dibenzofuran **23–25, 27,** and **30** by replacing 9-ethylcarbazole-3,6-diol diacetate with dibenzofuran-2,8-diol diacetate.

Bis-Basic Ethers of Dibenzofuran and Dibenzothiophene (22, 26, 28, 29, 44–50). A mixture of 0.06 mol of 2,8-dihydroxydibenzofuran (or 2,8-dihydroxydibenzothiophene), 0.45 mol of NaOH, 0.15 mol of the dialkylaminoalkyl chloride hydrochloride, 200 ml of toluene, and 200 ml of water was stirred and refluxed for 24 h. The toluene layer was separated, washed with water, and dried ($MgSO_4$). The solvent was removed in vacuo and the residue chromatographed on alumina; $CHCl_3$ was used as the eluent. The product collected was either analyzed as the free base or converted to the salt form with citric acid in MeOH or ethereal HCl. Purification of the the salts was effected by recrystallization from the appropriate solvent.

Bis(aminoacyl)carbazoles, -*N*-ethylcarbazoles, -dibenzofurans, and -dibenzothiophenes. Method A (9, 32–37, 53, 55, 58). A mixture of 0.03 mol of the appropriate bis(ω-halo ketone), the secondary amine (0.24 mol), KI (10 g, 0.06 mol), and 200 ml of butanone was stirred at reflux for 3 days, cooled, and poured into water. If a solid free base precipitated, it was filtered, washed with water, and purified by recrystallization from the appropriate solvent. If 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 ($MgSO_4$), and acidified with ethereal HCl. The precipitated dihydrochloride salt was recrystallized from the appropriate solvent.

Method B. (7, 8, 31, 51, 52, 54, 56, 57). A mixture of the bis(ω-halo ketone) (0.05 mol), 50 ml of the secondary amine, 2 g of KI, and 250 ml of THF was stirred and heated in a stainless steel Parr bomb at approximately 110 °C for 24 h. The reaction mixture was evaporated in vacuo to semidryness, diluted with H_2O, and extracted with ether. The ether extract was washed with H_2O, dried ($MgSO_4$), and acidified with ethereal HCl. The resulting dihydrochloride salt was recrystallized from the appropriate solvent.

Bis-Basic Alkanes of Carbazole (10, 11). A mixture of the appropriate bis(aminoacyl)-*N*-ethylcarbazole (0.02 mol) and 15 ml of 85% hydrazine hydrate (0.2 mol) in 150 ml of ethylene glycol was heated at 100–120 °C for 3 h in an open flask, followed by the cautious addition of 10 g (0.25 mol) of NaOH, and allowed to reflux for 16 h. The cooled reaction mixture was poured into ice water and extracted with ether. The ether layer was dried ($MgSO_4$) and acidified with ethereal HCl. The resulting precipitate was recrystallized from the appropriate solvent.

Carbazole-3,6-dicarboxylic Acid (59). The compound was prepared according to the procedure of Preston et al.[9] in which carbazole was treated with trichloroacetonitrile in the presence of $AlCl_3$ to yield 3,6-bis(trichloroacetyl)carbazole. Subsequent boiling in dilute KOH followed by acidification gave **59**, mp >300 °C.

***N*-Ethylcarbazole-3,6-dicarboxylic Acid (60).** The procedure of Gilman and Spatz[10] was used whereby 3,6-dibromo-*N*-ethylcarbazole (5-ethyl-2,8-dibromocarbazole) was treated with *n*-BuLi and CO_2 to give **60**, mp >300 °C.

***N*-Ethyl-3,6-carbazolediol Diacetate (61).** A solution of 104 g (0.37 mol) of 3,6-diacetyl-*N*-ethylcarbazole[11] in 1.7 l. of $CHCl_3$ was cooled at ice-bath temperature while 153 g (0.8 mol) of 90% *m*-chloroperbenzoic acid was added portionwise over a period of 0.5 h. The mixture was stirred for 4 days in a flask protected from light and filtered to remove *m*-chlorobenzoic acid and the filtrate was washed with saturated $NaHCO_3$ and H_2O and dried ($MgSO_4$). The solvent was removed in vacuo and the residue recrystallized from acetone–methanol to give 80 g (70%) of **61**, mp 138–139 °C. Anal. ($C_{18}H_{17}NO_4$) C, H, N.

3,6-Bis(4-chlorobutyryl)carbazole (62). A mixture of 50.0 g (0.3 mol) of carbazole and 98.5 g (0.66 mol) of 4-chlorobutyryl chloride in 400 ml of CH_2Cl_2 was chilled to −20 °C and 93 g (0.66 mol) of $AlCl_3$ was added with rapid stirring over a period of 20 min. Stirring was continued overnight at room temperature. The reaction mixture was poured onto a mixture of ice–concentrated HCl. The organic solvent was boiled off on a steam bath. The crude product was removed by filtration, washed with water, and recrystallized from $CHCl_3$–Me_2CO to yield 23 g (20%), mp 195–198 °C.

3,6-Bis(4-chlorobutyryl)-*N*-ethylcarbazole (63). By replacing carbazole with *N*-ethylcarbazole and following the procedure for the preparation of **63**, the product was obtained: 79 g (65%) (Me_2CO–MeOH); mp 106–108 °C. Anal. ($C_{22}H_{23}NO_2Cl_2$) C, H, Cl.

Dibenzofuran-2,8-dicarbonyl Chloride (64). The compound was prepared by the method of Watson: mp 230–235 °C (lit.[12] mp 232 °C).

2,8-Dihydroxydibenzofuran (65). 2,8-Diacetyldibenzofuran[12] was oxidized by the procedure described for the preparation of **61**. The product, dibenzofuran-2,8-diol diacetate, was recrystallized from MeOH to yield 65 g (88%), mp 149–151 °C. This compound, 10.4 g (0.037 mol), was hydrolyzed by treatment with 5% NaOH (250 ml) at reflux for 1 h. The resulting solution was acidified (dilute HCl) and the precipitate recrystallized from Et_2O–pentane to give **65**: 6.9 g (93%); mp 232–235 °C (lit.[19] mp 230–235 °C).

2,8-Bis(chloroacetyl)dibenzofuran (66). The compound was prepared by the method of Whaley and White: mp 210–212 °C (lit.[20] mp 213–214 °C).

2,8-Bis(4-chlorobutyryl)dibenzofuran (67). A solution of 30 g (0.178 mol) of dibenzofuran and 62.7 g (0.445 mol) of 4-chlorobutyryl chloride in 1000 ml of CH_2Cl_2 was chilled to −20 °C and 49.9 g (0.374 mol) of $AlCl_3$ was added with rapid stirring. Stirring was maintained for 16 h at room temperature. The reaction mixture was poured onto a mixture of ice–concentrated HCl. Organic solvent was removed by boiling. The crude product was filtered and recrystallized from *i*-PrOH to yield 36.9 g (55.1%), mp 102–104 °C. Anal. ($C_{20}H_{18}O_3Cl_2$) C, H, Cl.

Dibenzothiophene-2,6- (or 2,8-) dicarbonyl Chloride (68). To 2400 ml of CS_2 cooled at −20 °C was added 168 g (1.26 mol) of $AlCl_3$, followed by 110.4 g (0.6 mol) of dibenzothiophene. The mixture was vigorously stirred while 303.0 g (2.4 mol) of oxalyl chloride in 300 ml of CS_2 was added dropwise at such a rate that the temperature remained below −10 °C. The mixture was stirred at room temperature for 2 days and then was slowly poured onto a mixture of ice-concentrated HCl. Solvent was removed by boiling. The solid residue was filtered, washed with H_2O, and then purified by treatment with 10% NaOH solution, followed

by slow acidification with dilute HCl. The yield of product was 93.8 g (57.4%), mp >300 °C. A mixture of 79.5 g (0.29 mol) of dibenzothiophenedicarboxylic acids, 1000 ml of $SOCl_2$, and 1 ml of pyridine was stirred and refluxed for 16 h. Excess $SOCl_2$ was removed by distillation, the last traces being removed by azeotropic distillation with dry toluene. The crude material was recrystallized from dry toluene to yield 62.3 g (69.7%), mp 194–207 °C.

2,8-Dihydroxybenzothiophene (69). The compound was prepared by the method of Richter and Fuller: mp 274–277 °C (lit.[13] 278–279 °C).

2,6- (and 2,8-) Bis(chloroacetyl)dibenzothiophene (70). A solution of 50.0 g (0.27 mol) of dibenzothiophene and 77.0 g (0.68 mol) of chloroacetyl chloride in 400 ml of CH_2Cl_2 was chilled to −20 °C and 76.5 g (0.572 mol) of $AlCl_3$ was added with rapid stirring. Stirring at room temperature was continued for 16 h and then the reaction was poured onto ice–concentrated HCl. Solvent was removed by boiling. Crude product was filtered and recrystallized from DMF–MeOH. The yield was 72.3 g (37.6%); mp 209–213 °C. Anal. ($C_{16}H_{10}O_2SCl_2$) C, H, Cl.

2,8-Bis(4-chlorobutyryl)dibenzothiophene (71). The procedure used for the preparation of this compound was analogous to that described for the preparation of **70**. Recrystallization of crude product from $CHCl_3$–Me_2CO gave the 2,8 isomer: 57.1 g (53.5%); mp 131–133 °C. Anal. ($C_{20}H_{18}O_2SCl_2$) C, H, Cl.

2,6-Bis(4-chlorobutyryl)dibenzothiophene (72). Repeating the reaction on the same scale and recrystallizing from $CHCl_3$ yielded the 2,6 isomer: 12.1 g (11.4%); mp 147–148.5 °C. Anal. ($C_{20}H_{18}O_2SCl_2$) C, H, Cl.

2,6-Bis(bromoacetyl)dibenzothiophene (73). A solution of 5.0 g (0.019 mol) of 2,8-diacetyldibenzothiophene[14] in 200 ml of $CHCl_3$ was stirred and refluxed while a solution of 6.1 g (0.038 mol) of bromine in 25 ml of $CHCl_3$ was added dropwise. After complete addition, the mixture was stirred and refluxed an additional hour. Upon cooling to room temperature, product was filtered and recrystallized from acetic acid. The yield was 3.2 g (39.5%); mp 187–189 °C dec. Anal. ($C_{16}H_{10}O_2SBr_2$) C, H, Br.

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Antagonists of Slow Reacting Substance of Anaphylaxis. Synthesis of a Series of Chromone-2-carboxylic Acids

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A series of substituted chromone-2-carboxylic acids was synthesized and tested as antagonists of SRS-A induced contractions of isolated guinea pig ileum. This work led to the discovery of sodium 7-[3-(4-acetyl-3-hydroxy-2-propylphenoxy)-2-hydroxypropoxy]-4-oxo-8-propyl-4*H*-1-benzopyran-2-carboxylate (FPL 55712) which is the first reported specific antagonist of SRS-A. Some structural requirements for biological activity within this series are discussed.

It is well established that anaphylaxis in the lung of the guinea pig involves the release of the mediators histamine and slow reacting substance of anaphylaxis (SRS-A).[1] In this species the inhibitory action of antihistamines[2] demonstrates that histamine plays the major role. In man, while both histamine and SRS-A have been shown to be