(23) A. Scriabine, P. F. Moore, L. C. Iorio, I. M. Goldman, W. K. McShane, and K. D. Booher, *J. Pharmacol. Exp. Ther.*, **162**, 60 (1968).
(24) J. Champagne, A. D'Iorio, and A. Beaulnes, *Science*, **132**, 419 (1960).
(25) G. R. Pettit, W. C. Fleming, and K. D. Paull, *J. Org. Chem.*, **33**, 1089 (1968).
(26) G. S. Sidhu, G. Thyagarajan, and S. Ansari, *Justus Liebigs Ann. Chem.*, **627**, 218 (1959).
(27) J. W. Constantine, *J. Pharm. Pharmacol.*, **17**, 384 (1965).
(28) J. M. Van Rossum, *Arch. Int. Pharmacodyn. Ther.*, **143**, 299 (1963).
(29) Staff of the Department of Pharmacology, University of Edinburgh, in "Pharmacological Experiments on Isolated Preparations", 2nd ed, E. and S. Livingstone, Edinburgh and London, 1970, p 58.

Bis-Basic-Substituted Polycyclic Aromatic Compounds. A New Class of Antiviral Agents.[1,2] 7. Bisalkamine Esters of 9-Oxoxanthene-2,7-dicarboxylic Acid, 3,6-Bis-Basic Ethers of Xanthen-9-one, and 2,7-Bis(aminoacyl)xanthen-9-ones, -xanthenes, and -thioxanthenes

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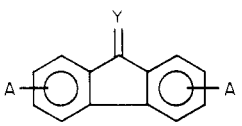
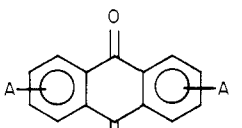
3,6-Bis[2-(dimethylamino)ethoxy]-9*H*-xanthen-9-one dihydrochloride (**4**, RMI 10874DA) and 1,1′-(9*H*-xanthene-2,7-diyl)bis[2-(dimethylamino)ethanone] dihydrochloride (**16**, RMI 11513DA) were found to prolong survival of mice infected with lethal challenges of encephalomyocarditis (EMC) virus. They were effective by oral as well as subcutaneous administration and showed broad-spectrum antiviral activity. They were selected for preclinical evaluation from the five series of compounds named in the title that were synthesized in analogy to tilorone and related fluorenone derivatives, described earlier. In addition to **4** and **16**, compounds **11**, **12**, **17**, and **18** showed high antiviral activity on oral as well as subcutaneous administration. High antiviral activity on subcutaneous administration was found in the bisalkamine esters **1**, **2**, and **14**, the bis(aminoacyl)xanthenes **23** and **26**, the bis(aminoalkylene)xanthene **31**, the bis(aminoacyl)thioxanthenes **34–40**, and the bis-basic ethers of 9-benzylidenexanthenes **41** and **42**. Structure–activity relationships showed a decrease of oral activity with increased length of side chains and increased molecular weight of dialkylamino substituents of 3,6-bis-basic ethers of xanthen-9-one and of 2,7-bis(aminoacyl)xanthenes and -xanthen-9-ones. At least one carbonyl or alkenyl function in conjugation to the xanthene nucleus either at the 9 position of the nucleus or in the side chains is required for high antiviral activity.

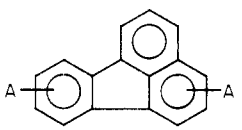
The discovery of antiviral activity of bisalkamine esters of fluorenone Ia[3] led to the development of tilorone hydrochloride and related bis-basic ethers of fluorenone Ib[4–7]



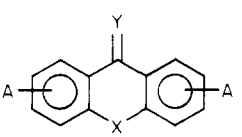
I, Y = O
II, Y = H, H



III



IV

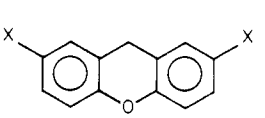


V, X, Y = O
VI, X = O; Y = H, H
VII, X = S; Y = H, H

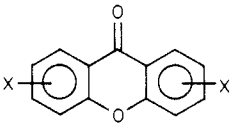
a, A = $-CO_2(CH_2)_nNR_2$
b, A = $-O(CH_2)_nNR_2$
c, A = $-CO(CH_2)_nNR_2$

and bis(aminoacyl)fluorenes IIc.[8] Analogous bis-basic-substituted anthraquinones IIIa,b[9] and fluoranthenes IVa–c were then prepared.[2] In this paper we are reporting the synthesis and antiviral evaluation of bisalkamine esters of 9-oxoxanthene- and xanthenedicarboxylic acids Va and VIa, bis-basic ethers of xanthenone Vb, and bis(aminoacyl)xanthenes and thioxanthenes VIc and VIIc.

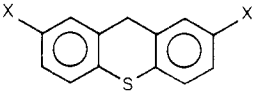
Chemistry. Bisalkamine esters of 9-oxo-9*H*-xanthene-2,7-dicarboxylic acid **1** and **2** and the -dicarboxamide **3** were prepared from the bisacid chloride of IX.[10] Compound IX was obtained from 2,7-diacetyl-9*H*-xanthene (VIII).[11] The bisalkamine ester of 9*H*-xanthene-2,7-dicarboxylic acid **14** was obtained from X.[12] Baeyer–Villiger oxidation of VIII gave XI, from which XII was obtained and used for the preparation of the 2,7-bis-basic ether **15**.



VIII, X = $COCH_3$
X, X = COOH
XI, X = $OCOCH_3$
XII, X = OH
XVI, X = $CO(CH_2)_nCl$



IX, X = 2,7-$(COOH)_2$
XIII, X = 3,6-$(OH)_2$
XIV, X = 3,6-$[OC(=S)NMe_2]_2$
XV, X = 3,6-$[SC(=O)NMe_2]_2$
XVII, X = $COCH_2Br$



XVIII, X = $CO(CH_2)_nCl$

XVIa and XVIIIa, $n = 1$
XVIb and XVIIIb, $n = 2$
XVIc and XVIIIc, $n = 3$
XVId and XVIIId, $n = 4$

The 3,6-bis-basic ethers of xanthenone **4–9** were prepared from XIII,[13] which was converted to the disodium salt with sodium methoxide in refluxing chlorobenzene and allowed to react with the appropriate aminoalkyl halide. Less vigorous conditions led to formation of monoethers analogous to reactions with dihydroxyanthraquinones.[9,14] The thioether **10** was prepared from 3,6-bis(dimethylcarbamoylthio)-9*H*-xanthen-9-one (XV), obtained by pyrolysis of the dimethylthiocarbamoyl derivative XIV by the method of Newman and Karnes.[15]

The 1,1'-(9*H*-xanthene-2,7-diyl)bis(ω-chloro-1-alkanones) XVIa–d and the corresponding thioxanthene analogues XVIIIa–d were obtained in good yields by Friedel–Crafts acylation with ω-chloroalkanoyl chlorides of xanthene and thioxanthene, respectively. Reaction of these intermediates with secondary amines in the presence of potassium iodide in tetrahydrofuran, preferably carried out in a pressure bottle or stainless steel bomb at temperatures of from 25 to 120°,[8] gave the bis(aminoacyl)xanthenes and thioxanthenes **16–27** and **32–40**, respectively. Bis(aminoacyl)xanthen-9-ones **12** and **13** were obtained by sodium dichromate oxidation in acetic acid of the corresponding bis(aminoacyl)xanthenes **23** and **26**, respectively. Bis(aminoacyl)xanthen-9-one **11** was obtained from XVII by the amine alkylation procedure at low temperature (–20°) and XVII was prepared by reaction of $CuBr_2$ with 2,7-diacetyl-9*H*-xanthenone which in turn was derived from VIII by sodium dichromate oxidation. Reduction of bis(aminoacyl)xanthenes **19**, **22**, and **23** with sodium borohydride in methanol gave the 9*H*-xanthene-2,7-dimethanols **28–30**. The latter was dehydrated to **31** with hydrochloric acid. Reaction of bis-basic ether **4** or the thioether **10** of xanthen-9-one with *p*-chlorobenzylmagnesium chloride gave the 9-benzylidene derivatives **41** and **42**; in one instance, the intermediate carbinol **43** was isolated.

Representative examples of these reactions are described in the Experimental Section. Physical properties and yield of the end products are given in Table I. No efforts were made to optimize yields, except for compounds **4** and **16**. Infrared and ultraviolet spectra were obtained for all compounds and absorptions were as expected.

Biological Evaluations and Structure–Activity Relationships. The compounds listed in Table I were evaluated for their effectiveness in protecting mice against encephalomyocarditis (EMC) virus infections. As defined in the Experimental Section, antiviral activity is expressed as the survival time ratio (STR). By our definition, an STR of 1.30 or greater indicates high activity.

Of the orally active compounds, the bis-basic ether of xanthenone **4** (RMI 10874DA) and the bis(aminoacyl)-xanthene **16** (RMI 11513DA) were clearly the most effective. Compounds **17** and **18** also showed good activity, as well as the bis(aminoacyl)xanthenones **11** and **12**. Within the group of bis-basic ethers of xanthenone (**4–9**) members other than **4** showed good activity, particularly **5** and **9**, but oral activity decreased with increasing molecular weight. The bis-basic thioether **10** was less effective than its O-ether analogue **4**. Similar relationships were found earlier in the series of bis-basic ethers of fluorenone[5] and of anthraquinone.[9] The bisalkamine esters of xanthene- and 9-oxoxanthene-2,7-dicarboxylic acid **1**, **2**, and **14** as well as the dicarboxamide **3** were much more effective on subcutaneous than on oral administration under present test conditions. Only compounds with side chains previously found optimal in the bisalkamine 9-oxofluorene-2,7-dicarboxylic acid[3] and dicarboxamide[16] series were prepared.

Of the bis(aminoacyl)xanthenones **11–13**, -xanthenes **16–27**, and -thioxanthenes **32–40**, **16** was the most effective antiviral agent. An increase in length of side chain and/or size of dialkylamino groups again caused a decrease in oral activity (**11** vs. **12** and **13**; **16** vs. **17–27**), while survival time ratios after subcutaneous administration reached a second maximum value with congeners of higher molecular weight (**26** vs. **18**; **38** vs. **32**).

The most interesting feature of structural requirement for high antiviral activity is the apparent need for at least one carbonyl group in conjugation with the tricyclic aromatic ring system at either the 9 position of the xanthene nucleus or in the side chains. Thus, compound **4** is much superior to **15**, and compounds **22** and **23** to **29** and **30**, respectively. A similar observation was made in the fluorene[5,8] and anthraquinone[9] series. It was postulated that the carbonyl group imparts properties to the tricyclic aromatic nucleus that are favorable to the interaction of the molecule with the biological receptor site, possibly by charge-transfer complex formation.[8] In the 9,10-dihydroanthracene series it was found that the carbonyl groups at the 9 and 10 positions can be replaced by alkylidene groups. In the present series, the carbonyl group of xanthen-9-one can similarly be replaced by a *p*-chlorobenzylidene group (**41**, **42**) while the side-chain carbonyl groups of bis(aminoacyl)xanthene derivatives can be replaced by alkylidene groups as in **31**.

The two compounds of the series that displayed the most prominent oral activity against EMC virus (**4** and **16**) were evaluated in mice against the RNA arbovirus Semliki Forest virus (SFV). Table II shows the optimal oral treatment times for these compounds. Maximal antiviral activity was achieved with compound **4** when the compound was administered 24 h before viral challenge. The best activity was observed with compound **16** when it was given 4 h before virus inoculation. The difference in results obtained with the 24- and 4-h preinfection doses of either compound was not significant, however.

Both compounds were effective in mice against a nonlethal challenge of vaccinia virus, a DNA virus. Compound **4** given orally at a 250 mg/kg dose 24 and 2 h before infection, and again 24 and 48 h after infection, reduced the severity of virus-induced tail lesions by 83%. Compound **16** was less active in a similar study in which it decreased lesion severity by 31%. Compound **4** was reported to induce high levels of circulating interferon after oral administration to mice.[17] Compound **16** induced comparable amounts of serum interferon under similar conditions.[18] Additional preclinical evaluations of **4** and **16** are being done.

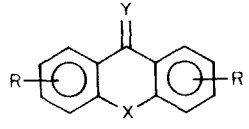
Experimental Section

Melting points were determined in open capillaries in a Thomas-Hoover apparatus and are uncorrected. Ir and uv spectra of all compounds in Table I were obtained and absorptions were as expected. Where analyses are indicated only by symbols of the elements, results obtained were within ±0.4% of theoretical values. Neutralization equivalents (NE) were determined by nonaqueous titration with $HClO_4$ in AcOH with $Hg(OAc)_2$ added and crystal violet or *p*-naphtholbenzein as indicator [USP XVIII, 836 (1970)].

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 Table I. 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 infective 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).[5] 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

Table I. Chemical and Antiviral Properties of Bisalkamine Esters of 9-Oxoxanthene-2,7-dicarboxylic Acid, 3,6-Bis-Basic Ethers of Xanthen-9-one, and 2,7-Bis(aminoacyl)xanthen-9-ones, -xanthenes, and -thioxanthenes



No.	X	Y	R	Mp, °C	Recrystn solvent[a]	Yield, %	Formula[b]	STR vs. EMC virus in mice at various doses (mg/kg)[c]				
								Sc admin			Oral admin	
								250	50	10	250[d]	50
1	O	O	2,7-$CO_2(CH_2)_3NEt_2$	270–271	A–C	30	$C_{29}H_{38}N_2O_6 \cdot 2HCl$	1.94		1.33	1.25	
2	O	O	2,7-$CO_2(CH_2)_3NBu_2$	223–224	C	13	$C_{37}H_{54}N_2O_6 \cdot 2HCl$	1.98	1.36			
3	O	O	2,7-$CONH(CH_2)_3NBu_2$	89–92	G	27	$C_{37}H_{54}N_4O_4$	0.98[e]	1.61[e]	1.20		
4[f]	O	O	3,6-$O(CH_2)_2NMe_2$	285–287	A–C	66	$C_{21}H_{26}N_2O_4 \cdot 2HCl$	2.18[d,e,g]	1.91[g]	1.11[g]	2.11[g]	1.68[g]
5	O	O	3,6-$O(CH_2)_2NEt_2$	71–72	K	59	$C_{25}H_{34}N_2O_4$	2.06[h]	1.22	1.18	1.27	1.06[e]
6	O	O	3,6-$O(CH_2)_2$piperidino	134–135	A	21	$C_{27}H_{34}N_2O_4$	1.50[e,i]	1.45[h]	1.07	1.11[e]	1.20
7	O	O	3,6-$O(CH_2)_2$morpholino	154–155	C	14	$C_{25}H_{30}N_2O_4$	1.00	0.93	1.11	1.00	0.98
8	O	O	3,6-$O(CH_2)_2N$-*i*-Pr_2	117–118	K	33	$C_{29}H_{42}N_2O_4$	1.64	1.27	1.05	1.07	0.95
9	O	O	3,6-$O(CH_2)_3NMe_2$	69–70	K	7	$C_{25}H_{30}N_2O_4$	2.23[i]	1.41[h]	1.16	1.23	1.23
10	O	O	3,6-$S(CH_2)_2NEt_2$	227–229	B	31	$C_{25}H_{34}N_2O_2S_2 \cdot 2HCl$	1.74	1.22	0.98	1.10	0.96
11	O	O	2,7-$COCH_2NEt_2$	220–221 dec	G	21	$C_{23}H_{30}N_2O_4 \cdot 2HCl \cdot 2.5H_2O$[j]	Lethal[g]	1.24[g]	1.04[g]	1.75[g]	1.10[g]
12	O	O	2,7-$CO(CH_2)_3$piperidino	93–95	L	24	$C_{31}H_{38}N_2O_4$	2.17	1.50	1.09	1.50	1.07
13	O	O	2,7-$CO(CH_2)_4$piperidino	109–110	J–L	47	$C_{33}H_{42}N_2O_4$	0.86[d,e]	1.56	1.35	1.05	1.05
14	O	H, H	2,7-$CO_2(CH_2)_3NBu_2$	188–190	C	30	$C_{37}H_{56}N_2O_5 \cdot 2HCl$	2.14	1.82	1.14		
15	O	H, H	2,7-$O(CH_2)_2NMe_2$	85–87	K	36	$C_{21}H_{28}N_2O_3$	Lethal	1.02[d,e]	0.93	1.33	1.02
16[k]	O	H, H	2,7-$COCH_2NMe_2$	285 dec	A–F	47	$C_{21}H_{24}N_2O_3 \cdot 2HCl$	2.39[i]	2.02	1.20	2.15	1.76
17	O	H, H	2,7-$COCH_2NEt_2$	164–167 dec	A–G	4	$C_{25}H_{32}N_2O_3 \cdot 2HCl \cdot 3.25H_2O$	2.33	1.37	1.05	2.16	1.05
18	O	H, H	2,7-$COCH_2$piperidino	261–262 dec	A–G	13	$C_{27}H_{32}N_2O_3 \cdot 2HCl \cdot 3.5H_2O$	0.70[d,e]	1.37	0.86	1.73	1.22
19	O	H, H	2,7-$COCH_2$morpholino	>350	A–G	6	$C_{25}H_{38}N_2O_3 \cdot 2HCl \cdot 3H_2O$	0.93	1.11	0.89[e]	1.00	1.35
20	O	H, H	2,7-$COCH_2N$(Me)cyclohexyl	203–206 dec	A–G	11	$C_{31}H_{40}N_2O_3 \cdot 2HCl \cdot 3.5H_2O$	1.54	1.39	1.15	1.00	1.22
21	O	H, H	2,7-$CO(CH_2)_2NEt_2$	185–186	A–G	37	$C_{27}H_{36}N_2O_3 \cdot 2HCl \cdot 2.5H_2O$	Lethal	1.14	1.00	1.17[e]	1.05
22	O	H, H	2,7-$CO(CH_2)_3NEt_2$	63–65 dec	L	5	$C_{29}H_{40}N_2O_3$	1.65[d]	1.40	1.28	1.00	1.36
23	O	H, H	2,7-$CO(CH_2)_3$piperidino	115–117	K	20	$C_{31}H_{40}N_2O_3$	2.29[e,i]	1.33	1.14	1.10	1.20
24	O	H, H	2,7-$CO(CH_2)_3$morpholino	110–112	J–L	46	$C_{29}H_{36}N_2O_5$	1.07	1.33	1.04	1.07	0.91
25	O	H, H	2,7-$CO(CH_2)_4NMe_2$	127–129	I–L	86	$C_{27}H_{36}N_2O_3$	1.30[d,e]	1.59[h]	1.16	1.00	1.02
26	O	H, H	2,7-$CO(CH_2)_4$piperidino	129–130	L	88	$C_{33}H_{44}N_2O_3$	1.68[i]	2.28	1.37	1.00	0.98
27	O	H, H	2,7-$CO(CH_2)_4N(CH_2CH{=}CH_2)_2$	54–55	L	52	$C_{35}H_{44}N_2O_3$	1.48	1.46	1.06	0.90	0.90
28	O	H, H	2,7-$CH(OH)CH_2$morpholino	170–171	H	55	$C_{25}H_{32}N_2O_5$	1.04[g]	1.12[g]	1.04[g]	1.08[g]	1.04[g]
29	O	H, H	2,7-$CH(OH)(CH_2)_3NEt_2$	98–99	G	53	$C_{29}H_{44}N_2O_3$	0.79[d,e]	0.98	0.95	0.95	0.93
30	O	H, H	2,7-$CH(OH)(CH_2)_3$piperidino	145–146	J	76	$C_{31}H_{44}N_2O_3$	1.26[h]	1.31	1.14	1.21	1.02[e]
31	O	H, H	2,7-$CH{=}CH(CH_2)_2$piperidino	159–161	C	71	$C_{31}H_{40}N_2O$	2.17	2.29	1.23	1.21[e]	1.00
32	S	H, H	2,7-$COCH_2NEt_2$	122–124	A–G	32	$C_{25}H_{32}N_2O_2S \cdot 2HCl \cdot 4.5H_2O$	1.34[h]	1.05	1.14	0.95	1.00
33	S	H, H	2,7-$CO(CH_2)_2NEt_2$	138–140	A–G	66	$C_{27}H_{36}N_2O_2S \cdot 2HCl \cdot 2H_2O$		1.09	1.07	1.09	1.05
34	S	H, H	2,7-$CO(CH_2)_3NEt_2$	188–191	A–D	21	$C_{29}H_{40}N_2O_2S \cdot 2HCl$[l]	1.18[d,e]	2.20[h]	1.59	1.09	1.07

35	S	H, H	2,7-CO(CH$_2$)$_3$piperidino	229–231 dec	B	23	$C_{31}H_{40}N_2O_2S\cdot 2HCl\cdot H_2O$	1.13[e,i]	2.13[h]	1.13	0.96	0.89
36	S	H, H	2,7-CO(CH$_2$)$_3$morpholino	91–92	J–L	15	$C_{29}H_{36}N_2O_4S$	2.12	1.24	1.02	1.05	1.00[e]
37	S	H, H	2,7-CO(CH$_2$)$_4$NMe$_2$	232–235	A–F	37	$C_{27}H_{36}N_2O_2S\cdot 2HCl$	Lethal	1.86[e,i]	1.70	1.02	1.05
38	S	H, H	2,7-CO(CH$_2$)$_4$NEt$_2$	198–200	A–F	75	$C_{31}H_{44}N_2O_2S\cdot 2HCl$	1.23[d,e]	1.81[i]	1.58	1.02	1.00
39	S	H, H	2,7-CO(CH$_2$)$_4$piperidino	99–100	L	60	$C_{33}H_{44}N_2O_2S$	0.67[e,i]	1.48[e,h]	1.76	0.98	1.15
40	S	H, H	2,7-CO(CH$_2$)$_4$N(CH$_2$CH=CH$_2$)$_2$	Oil		26	$C_{35}H_{44}N_2O_2S$	1.66	1.47	1.02	0.98	0.91
41	O	CHC$_6$H$_4$-*p*-Cl	3,6-O(CH$_2$)$_2$NMe$_2$	254–257 dec	A–F	15	$C_{28}H_{31}ClN_2O_3\cdot 2HCl$	1.03[e,i]	1.79	1.28	1.02	1.06
42	O	CHC$_6$H$_4$-*p*-Cl	3,6-S(CH$_2$)$_2$NEt$_2$	232–234 dec	A–F	48	$C_{32}H_{39}ClN_2OS_2\cdot 2HCl$	1.41[d,e]	1.70	1.14	1.25	1.02
43	O	OH, CH$_2$C$_6$H$_3$-*p*-Cl	3,6-S(CH$_2$)$_2$NEt$_2$	120–121	K	30	$C_{32}H_{41}ClN_2O_4$	1.65[c]	1.79	1.08	0.90	0.94
		Tilorone hydrochloride[m]						Lethal	1.95	1.37	2.27	1.83

[a] A = MeOH, B = EtOH, C = *i*-PrOH, D = Me_2CO, E = EtOAc, F = Et_2O, H = THF, I = CH_2Cl_2, J = C_6H_6, K = C_6H_{14}, L = C_7H_{16}. [b] All compounds were analyzed for the elements C, H, and Cl (or N). Unless otherwise indicated, microanalytical results were within ± 0.4%. Neutralization equivalents (NE) or Karl Fisher titrations were run on all hydrated compounds. All NE were within 1% of calculated values; all Karl Fisher titrations were within ± 0.4% of the calculated values, unless otherwise indicated. [c] STR, survival time ratio, is defined in the description of the test method in the Experimental Section. [d] Single dose administered 22–28 h before virus inoculation. [e] Early deaths were observed indicating toxicity at specified dose. [f] RMI 10 874DA. [g] Tested in 20-g mice. [h] Only first three doses of standard regimen given. [i] Only first two doses of standard regimen given. [j] Anal. Calcd: C, 55.06; H, 6.90; N, 5.19. Found: C, 55.14; H, 6.82; N, 4.81. NE: calcd, 540.5; found, 594.4. [k] RMI 11 513DA. [l] Anal. Cl: calcd, 12.81; found, 12.30. [m] Reference 5.

Table II. Activity of Compounds 4 and 16 against Semliki Forest Virus in Mice[a]

Time of treatment	% survivors 10 days after virus challenge	
	4[b]	16[c]
72-h prechallenge	70	20
48-h prechallenge	60	67
24-h prechallenge	100	80
4-h prechallenge	80	88
4-h postchallenge	40	20

[a] Each compound, in 0.15% hydroxyethylcellulose, administered orally to 20-g mice. Semliki Forest virus (28–32 LD_{50}) was inoculated subcutaneously. [b] RMI 10 874DA. [c] RMI 11 513DA.

group divided by the mean day of death of the untreated control groups, was calculated for each dose level. 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 to <0.001); and a ratio of 1.30 or greater indicates high activity (p = 0.05 to <0.001).

Bis(3-dibutylaminopropyl) 9-Oxo-9*H*-xanthene-2,7-dicarboxylate Dihydrochloride (2). To 272 g (2.02 mol) of $AlCl_3$ under 370 ml of cold (0°) $Cl_2CHCHCl_2$ was added dropwise 102 g (1.0 mol) of Ac_2O. The resulting complex was added to a cold (0°) solution of 45.5 g (0.25 mol) of 9*H*-xanthene in 100 ml of $Cl_2CHCHCl_2$. The mixture was stirred at 0° for 0.5 h, was allowed to warm to room temperature, and was then slowly heated to 100° for 1 h. The mixture was poured into 300 ml of concentrated HCl and ice, 1 l. of CH_2Cl_2 was added, and the organic phase was separated, washed (H_2O, 2 N Na_2CO_3), dried ($MgSO_4$), and evaporated to dryness. The residue was crystallized from 95% EtOH to give 51.8 g (78%) of 2,7-diacetyl-9*H*-xanthene (VIII): mp 168–169° (lit.[11] mp 168°).

A suspension of 15.3 g (0.0575 mol) of VIII in 1 l. (0.80 mol) of a 6% NaOCl solution was stirred at 90° for 4 h. A small amount of solid that remained was removed by filtration and excess reagent was destroyed by addition of sodium thiosulfate. Cautious acidification with concentrated HCl gave a precipitate that was recrystallized from DMF and gave 6.1 g of 9-oxo-9*H*-xanthene-2,7-dicarboxylic acid (IX), mp >360° (lit.[10] mp >300°). A second crop of 3.0 g (56% total yield) was recovered.

A solution of 28.4 g (0.1 mol) of IX and 150 ml of $SOCl_2$ in dry THF was refluxed for 3 h. Solvent and excess reagent were removed by evaporation under vacuum at 60° and by azeotroping with benzene under vacuum at 60°. The residue was dissolved in CH_2Cl_2 and was added to a solution of 38.0 g (0.203 mol) of 3-(di-*n*-butylamino)propanol in 1 l. of CH_2Cl_2. The solution was refluxed for 3 h and was washed with 2 N HCl, dried ($MgSO_4$), and evaporated to dryness. The residue was crystallized and recrystallized twice from CH_2Cl_2–$CH_3COCH_2CH_3$ and from *i*-PrOH to give 9.1 g of **2** (Table I).

A similar reaction of the diacid chloride from IX with 3-(diethylamino)propanol gave **1** (Table I).

***N*,*N*′-Bis(3-dibutylaminopropyl)-9-oxo-9*H*-xanthene-2,7-dicarboxamide (3).** A solution of 41.0 g (0.22 mol) of *N*,*N*-dibutyl-1,3-propanediamine in 100 ml of $CHCl_3$ was added to 9-oxo-9*H*-xanthene-2,7-dicarboxylic acid chloride, prepared from 28.4 g (0.1 mol) of IX in the manner described in the preceding example, and the mixture was refluxed for 2 h. The solution was washed (2 N NaOH, H_2O) and dried ($MgSO_4$) and the solvent was evaporated. The residue was crystallized and recrystallized from Et_2O to give 17.0 g of **3** (Table I).

Bis(3-dibutylaminopropyl) 9*H*-Xanthene-2,7-dicarboxylate Dihydrochloride (14). 9*H*-Xanthene-2,7-dicarboxylic acid (X) was prepared in poor yield by Friedel–Crafts acylation of 9*H*-xanthene with oxalyl chloride in $Cl_2CHCHCl_2$ in the presence of $AlCl_3$ as described by Liebermann and Zsuffa.[12] A solution of 17.35 g (0.0638 mol) of X and 100 ml of $SOCl_2$ in 100 ml of dry THF containing 3 drops of pyridine was refluxed for 4 h. Solvent and excess reagent were removed by evaporation under vacuum and by azeotroping with benzene. The residue and 24.0 g (0.128 mol) of 3-(di-*n*-butylamino)propanol in 600 ml of CH_2Cl_2 were

refluxed for 3 h and allowed to stand overnight. The solution was washed (2 N HCl) and dried ($MgSO_4$), and the solvent was evaporated. The residue was crystallized and recrystallized from *i*-PrOH and gave 12.9 g of 14 with the properties given in Table I.

2,7-Bis[2-(dimethylamino)ethoxy]-9*H*-xanthene (15). To a solution of 53.2 g (0.2 mol) of VIII in 1 l. of hydrocarbon-stabilized $CHCl_3$ containing 5 ml of CF_3COOH was added 84.4 g (0.44 mol) of 90% *m*-chloroperoxybenzoic acid in portions and the solution was stirred at room temperature overnight. The solution was filtered and the filtrate was washed (saturated $NaHCO_3$ solution, H_2O), dried ($MgSO_4$), and concentrated to give 54.0 g (90%) of crude 2,7-diacetoxy-9*H*-xanthene (XI), mp 180–186°. A sample was recrystallized from EtOAc: mp 194–195°. Anal. ($C_{17}H_{14}O_5$) C, H.

A suspension of 40.0 g of XI in 100 ml of 2 N NaOH was stirred at reflux temperature until homogeneous (3.5 h). The solution was acidified with 2 N HCl, and the precipitate was collected and recrystallized from MeOH–H_2O to give 23.0 g (80%) of 9*H*-xanthene-2,7-diol (XII), mp 220–224°.

To a solution of 20.0 g (0.094 mol) of XII in 350 ml of ClC_6H_5 was added 16.5 g (0.3 mol) of NaOMe and 50 ml of MeOH and the mixture was stirred for 2 h at 130° in an open vessel to allow MeOH to escape. The mixture was then cooled to 90°, 28.0 g (0.26 mol) of $Me_2NCH_2CH_2Cl$ was added, and the mixture was stirred at the reflux temperature for 4 h. The mixture was cooled, 100 ml of 1 N NaOH and 100 ml of $CHCl_3$ were added, the organic phase was washed (1 N NaOH, H_2O) and dried ($MgSO_4$), and the solvent was evaporated. The residue (26.0 g) was recrystallized twice from hexane to give 12.0 g (33%) of **15** (Table I).

3,6-Bis[2-(dimethylamino)ethoxy]-9*H*-xanthen-9-one Dihydrochloride (4). Following essentially the procedure of Meyer and Conzetti,[13] a magnetically stirred mixture of 50.0 g (0.203 mol) of 2,2′,4,4′-tetrahydroxybenzophenone and 300 ml of H_2O was heated to 170° in a stainless steel bomb for 4.5 h and was allowed to cool overnight. The solid product was collected, washed thoroughly with hot H_2O, and dried in a vacuum oven at 80° to give 44.4 g (95%) of 3,6-dihydroxy-9*H*-xanthen-9-one (XIII), mp >300° (lit.[13] mp >350°).

A solution of 46.0 g (0.2 mol) of XIII and 32.0 g (0.592 mol) of NaOMe in 700 ml of ClC_6H_5 and 120 ml of MeOH was heated to 130° in an open vessel to allow MeOH to escape. The solution was then cooled to 100°, 52.4 g (0.490 mol) of $Me_2NCH_2CH_2Cl$ was added, and the mixture was refluxed for 5 h. An additional 10.0 g (0.09 mol) of $Me_2NCH_2CH_2Cl$ was added after 2 h of refluxing. The solution was cooled to 100°, 600 ml of 0.5 N NaOH was added, and stirring was continued for 0.5 h. The aqueous layer was separated and extracted with Et_2O. The combined organic layers were dried ($MgSO_4$) and evaporated to dryness. The residue was recrystallized twice from hexane and gave 49.0 g (66%) of 4 (free base), mp 88–89°. A dihydrochloride salt was prepared and recrystallized from MeOH–*i*-PrOH to the material described in Table I.

In an analogous manner, XIII was allowed to react with appropriate tertiary aminoalkyl chlorides to give **5** to **9** (Table I).

3,6-Bis[[(dimethylamino)thioxomethyl]oxy]-9*H*-xanthen-9-one (XIV). By the general procedure of Newman and Karnes,[15] 32.0 g (0.80 mol) of a 60% dispersion of NaH in mineral oil was added in small portions to a cooled solution of 90.8 g (0.40 mol) of XIII in 450 ml of $HCONMe_2$ under N_2. After hydrogen evolution had ceased, 100.0 g (0.80 mol) of dimethylthiocarbamoyl chloride was added and the mixture was stirred at room temperature overnight and at 80° for 1.5 h. The mixture was then poured onto 1.5 l. of H_2O and the yellow precipitate that formed was collected and recrystallized from $HCONMe_2$. The product was dried overnight in a vacuum oven at 80° and gave 68.4 g (43%) of XIV; a sample was recrystallized again from $HCONMe_2$, mp 253–255°. Anal. ($C_{19}H_{18}N_2O_4S_2$) C, H, S.

3,6-Bis[[(dimethylamino)carbonyl]thio]-9*H*-xanthen-9-one (XV). The dimethylthiocarbamoyl derivative XIV (55.4 g) was pyrolyzed at 240–295° for 25 min. The melt was cooled, dissolved in $HCONMe_2$, and precipitated by addition of H_2O to give 41.4 g (83%) of XV. A sample was recrystallized from $HCONMe_2$ and from $CHCl_3$–hexane: mp 178–180°. Anal. Calcd: C, 56.69; H, 4.56; S, 15,93. Found: C, 57.68; H, 4.47; S, 15.35.

3,6-Bis[2-(diethylaminoethyl)thio]-9*H*-xanthen-9-one Dihydrochloride (10). A mixture of 34.0 g (0.0844 mol) of XV, 200 ml of MeOH, and 200 ml of 25% NaOH was refluxed under N_2 for 24 h. C_6H_5Cl (700 ml) was added and the mixture was heated and stirred in such a way as to allow MeOH and H_2O to distill off until the reaction mixture reached a temperature of 125°. The mixture was then cooled, 37.5 g (0.278 mol) of $Et_2NCH_2CH_2Cl$ was added, and refluxing under N_2 was resumed for 8 h. The mixture was cooled, 300 ml of 2 N NaOH was added, and the mixture was stirred for 0.5 h. The organic layer was separated, washed (H_2O), and dried ($MgSO_4$), and the solvent was evaporated. The residue was dissolved in 100 ml of Et_2O and acidified with ethereal HCl. The resulting precipitate was collected and recrystallized three times from 95% EtOH to give 9.4 g of **10** (Table I).

1,1′-(9*H*-Xanthene-2,7-diyl)bis(2-chloroethanone) (XVIa). To a cooled (−20°) solution of 91.1 g (0.5 mol) of xanthene and 141.2 g (1.25 mol) of $ClCOCH_2Cl$ in 3 l. of dry CH_2Cl_2 was slowly added 146.7 g (1.1 mol) of $AlCl_3$ in portions. The mixture was then allowed to warm to room temperature, was refluxed for 4 h, and was allowed to cool overnight. It was then cautiously poured into 2.5 l. of 0.5 N HCl. Solid product was collected and dissolved in 2 l. of CH_2Cl_2. This solution was combined with the organic phase of the filtrate, washed (2 N HCl, saturated NaCl solution), dried ($MgSO_4$), and evaporated to dryness. The residue was recrystallized from acetone and gave 121.1 g (72%) of XVIa, mp 199–200°.

1,1′-(9*H*-Xanthene-2,7-diyl)bis[2-(dimethylamino)-ethanone] Dihydrochloride (16). To a mixture of 50.0 g (0.15 mol) of XVIa in 350 ml of butanone was added dropwise 250 ml of a 40% aqueous dimethylamine solution and the mixture was stirred for 1 h. The reaction mixture was concentrated in vacuo to remove butanone and the residual aqueous mixture was stirred with $CHCl_3$ and a saturated solution of Na_2CO_3. The $CHCl_3$ phase was separated, dried ($MgSO_4$), concentrated to 50 ml, and acidified with methanolic HCl. The resulting precipitate was recrystallized from MeOH–EtOAc to give 30.0 g (47%) of **16** (Table I).

In a similar manner, XVIa was allowed to react with excess of the appropriate anhydrous amine in butanone or THF for 7 days at room temperature to give **17** to **20** (Table I).

1,1′-(9*H*-Xanthene-2,7-diyl)bis(3-chloro-1-propanone) (XVIb). To a cooled (−20°) solution of 91.1 g (0.5 mol) of xanthene and 158.5 g (1.25 mol) of $ClCOCH_2CH_2Cl$ in 2 l. of dry CH_2Cl_2 was slowly added 146.7 g (1.1 mol) of $AlCl_3$ in portions. The mixture was then allowed to warm to room temperature, was refluxed for 4 h, and was allowed to cool overnight. It was then poured into ice water and sufficient CH_2Cl_2 was added to dissolve solids. The solution was washed (2 N HCl, H_2O) and dried ($MgSO_4$) and the solvent was evaporated. The material was recrystallized from Me_2CO and twice from MeCOEt to give 100.0 g (55%) of XVIb, mp 180.5–181°. Anal. Calcd: C, 62.82; H, 4.44; Cl, 19.52. Found: C, 62.05, H, 4.38; Cl, 20.11.

1,1′-(9*H*-Xanthene-2,7-diyl)bis[3-(diethylamino)-1-propanone] Dihydrochloride Hydrate (21). A mixture of 18.2 g (0.05 mol) of XVIb, 2 g of KI, 100 ml of Et_2NH, and 100 ml of THF was allowed to stand at room temperature for 3 days. The mixture was filtered to remove a solid. The filtrate was evaporated to dryness, 2 N HCl was added, and the insoluble solid was removed by filtration. The filtrate was made basic with saturated $NaHCO_3$ solution and the product was extracted into CH_2Cl_2. The extract was washed (H_2O, saturated NaCl solution), dried ($MgSO_4$), and evaporated to dryness. The residue was dissolved in EtOH and acidified with ethereal HCl. The resulting precipitate was collected and recrystallized twice from MeOH–Et_2O to give 10.2 g (37%) of **21** (Table I).

1,1′-(9*H*-Xanthene-2,7-diyl)bis(4-chloro-1-butanone) (XVIc). To a cooled (−20°) solution of 91.1 g (0.05 mol) of xanthene and 176.3 g (1.25 mol) of $ClCOCH_2CH_2CH_2Cl$ in 3 l. of dry CH_2Cl_2 was added 146.7 g (1.1 mol) of $AlCl_3$ in portions over 30 min. The mixture was then allowed to warm to room temperature, was stirred at the reflux temperature for 4 h, and was allowed to cool overnight. It was then poured into 2 l. of ice–water. The CH_2Cl_2 phase was separated, washed (2 N HCl, H_2O), dried ($MgSO_4$), and concentrated to a volume of about 1 l. The product crystallized and was recrystallized from Me_2CO to give 155.3 g (79%) of XVIc, mp 131–132°; a second crop of 17.2

g (9%), mp 129–131°, was also obtained.

1,1′-(9*H*-Xanthene-2,7-diyl)bis[4-(1-piperidinyl)-1-butanone] (23). A mixture of 43.2 g (0.08 mol) of XVIc, 150 ml of piperidine, and 2.0 g of KI in 150 ml of THF was heated in a stainless steel bomb to 110° for 24 h. The solution was evaporated to dryness and the residue was refluxed for 1.5 h in 500 ml of 2 N HCl. The resulting solution was allowed to cool and was made basic by addition of 10 N NaOH. The resulting precipitate was collected, washed with H_2O, dried, and recrystallized from heptane to give 34.3 g (88%) of **23**, mp 114–116°. The material listed in Table I was obtained in low yield under somewhat different reaction conditions and was purified by chromatography on alumina and repeated recrystallization from hexane.

Reaction of XVIc with morpholine similarly gave **24**. Reaction of XVIc with $HNEt_2$ at 90–95° in a similar manner, but without solvent, gave **22** after purification from an alumina column (eluted with hexane–benzene) (Table I).

2,7-Bis[1-oxo-4-(1-piperidinyl)butyl]-9*H*-xanthen-9-one (12). To a solution of 9.8 g (0.025 mol) of **23** in 300 ml of AcOH was added 9.8 g (0.033 mol) of $Na_2Cr_2O_7 \cdot 2H_2O$ in portions over 0.5 h. The mixture was stirred at room temperature for 1.5 h, at reflux temperature for 1 h, and again at room temperature for 17 h. The mixture was then evaporated to dryness, the residue was dissolved in H_2O, and the solution was made basic with 28% NH_4OH. The resulting oil was separated by decantation, washed with H_2O, and dissolved in CH_2Cl_2. The solution was washed (H_2O), dried ($MgSO_4$), and chromatographed on alumina (50 g). Elution with CH_2Cl_2 (880 ml) gave a crystalline product that was recrystallized from heptane to give 3.0 g of **12** (Table I).

2,7-Bis[2-(diethylamino)acetyl]-9*H*-xanthen-9-one Dihydrochloride Hydrate (11). The oxidation procedure used to prepare **12** was carried out using VIII to give 2,7-diacetyl-9*H*-xanthen-9-one, mp 227.5–228.5°. Treatment of this latter compound with a threefold excess of $CuBr_2$ in ethyl acetate–chloroform (3:1) by 6-h reflux, after filtering and cooling, gave XVII, mp 207.5–208.5°. A mixture of 21.9 g (0.05 mol) of XVII and 200 ml of diethylamine in 500 ml of THF was kept at −20° for 24 h. The reaction mixture after treatment with water was filtered. The resulting precipitate was dissolved in CH_2Cl_2, dried ($MgSO_4$), treated with ethereal HCl, and concentrated to give a solid which, when recrystallized from MeOH and then MeOH–EtOAc, gave **11** (Table I).

By the method used to obtain **12**, compound **26** was oxidized to give **13** (Table I). Purification was effected by elution from an alumina column using CH_2Cl_2.

1,1′-(9*H*-Xanthene-2,7-diyl)bis(5-chloro-1-pentanone) (XVId). This material was prepared in 81% yield from xanthene and $ClCO(CH_2)_4Cl$ in the manner described for XVIa and was recrystallized from Me_2CO: mp 134–136°. Anal. ($C_{23}H_{24}Cl_2O_3$) C, H, Cl.

1,1′-(9*H*-Xanthene-2,7-diyl)bis[5-(dimethylamino)-1-pentanone] (25). A mixture of 20.0 g (0.048 mol) of XVId, 2.0 g of KI, 200 ml of 40% aqueous Me_2NH solution, and 100 ml of THF was heated to 100° for 3 days in a stainless steel bomb. The reaction mixture was allowed to cool and was transferred to a round-bottom flask, and THF and Me_2NH were evaporated under reduced pressure. The remaining precipitate was collected and recrystallized from CH_2Cl_2–heptane to give 16.0 g of **25** with the properties given in Table I.

Following the above general procedure, XVId was allowed to react with anhydrous piperidine or diallylamine for 24 h to give **26** and **27**, respectively (Table I).

α,α′-Bis[3-(1-piperidinyl)propyl]-9*H*-xanthene-2,7-dimethanol (30). A solution of 4.2 g (0.11 mol) of $NaBH_4$ in 100 ml of MeOH and 10 ml of 2 N NaOH was added dropwise over 30 min to a cooled (0°) solution of 25.6 g (0.053 mol) of **23** in 200 ml of MeOH. The mixture was allowed to warm to room temperature overnight. Water (500 ml) was added and the resulting precipitate was collected and dissolved in 2 N HCl to liberate any boron complex that may have formed. The solution was filtered, made alkaline, and was extracted with CH_2Cl_2. The extract was washed (H_2O, saturated NaCl solution), dried ($MgSO_4$), and evaporated to dryness. The residue was recrystallized twice from benzene to give 2.3 g of **30** (Table I); a second crop of 17.4 g (total yield 76%) was recovered from the mother liquors and was used for preparation of **31**.

By this general method, **19** and **22** (in THF) were allowed to react with $NaBH_4$ to give **28** and **29**, respectively (Table I).

1,1′-[(9*H*-Xanthene-2,7-diyl)bis(3-butene-4,1-diyl)]bispiperidine (31). A solution of 17.4 g (0.035 mol) of **30** in 25 ml of concentrated HCl and 25 ml of $CH_3CH_2OCH_2CH_2OH$ was heated on a steam bath for 5 min. Water was added and the solution was made alkaline with 5 N NaOH. The product was extracted into ether, and the extract was washed (H_2O, saturated NaCl solution), dried ($MgSO_4$), and evaporated to dryness. The residue was recrystallized twice from EtOH, further purified by suspension in anhydrous Et_2O, and again recrystallized from *i*-PrOH to give 1.1 g of **31** (Table I). A second crop of 10.3 g (total yield of 71%) was obtained. An NMR ($CDCl_3$) spectrum did not permit assignment of cis and/or *trans* configuration to the double bond.

1,1′-(9*H*-Thioxanthene-2,7-diyl)bis(2-chloroethanone) (XVIIIa). To a cooled (−20°) solution of 99.2 g (0.5 mol) of thioxanthene and 141.2 g (1.25 mol) of $ClCOCH_2Cl$ in 2 l. of dry CH_2Cl_2 was added 146.7 g (1.1 mol) of $AlCl_3$ in portions over 0.5 h. The mixture was then allowed to warm to room temperature, was refluxed for 4 h, and was allowed to cool overnight. It was then cautiously poured into 2.5 l. of H_2O. Sufficient CH_2Cl_2 was added to dissolve solids, and the solution was washed (H_2O), dried ($MgSO_4$), and evaporated to dryness. The residue was recrystallized from Me_2CO and gave 105.2 g (60%) of XVIIIa, mp 166–167° dec. Anal. Calcd: C, 58.00; H, 3.44; Cl, 20.14. Found: C, 58.27, H, 3.63; Cl, 18.98.

1,1′-(9*H*-Thioxanthene-2,7-diyl)bis[(2-diethylamino)-ethanone] Dihydrochloride Hydrate (32). A mixture of 35.1 g (0.10 mol) of XVIIIa, 2.0 g of KI, 200 ml of Et_2NH, and 500 ml of THF was allowed to stand for 7 days in a stoppered flask. The mixture was filtered to remove a solid. The filtrate was evaporated to dryness, the residue was dissolved in 2 N HCl, and insoluble material was removed by filtration. The filtrate was made alkaline and was extracted with CH_2Cl_2. The extract was washed (H_2O), dried ($MgSO_4$), and acidified with ethereal HCl. The resulting precipitate was collected, recrystallized twice from MeOH–Et_2O, dried, and allowed to stand in a constant humidity chamber for several days to give 18.9 g (33%) of **32** (Table I).

1,1′-(9*H*-Thioxanthene-2,7-diyl)bis(3-chloro-1-propanone) (XVIIIb). This material was obtained in 25% yield from thioxanthene and $ClCOCH_2CH_2Cl$ in the manner described for XVIIIa. The product was triturated with pentane and recrystallized twice from benzene–heptane: mp 105–107°.

1,1′-(9*H*-Thioxanthene-2,7-diyl)bis[3-(diethylamino)-1-propanone] Dihydrochloride Hydrate (33). A mixture of 13.0 g (0.034 mol) of XVIIIb, 1.0 g of KI, and 75 ml of Et_2NH in 75 ml of THF was allowed to stand at room temperature for 3 days. A solid was removed by filtration and washed with THF and the filtrate was evaporated to dryness. The residue was dissolved in EtOH, acidified with ethanolic HCl, and precipitated by addition of Et_2O. The precipitate was recrystallized twice from MeOH–Et_2O and gave 11.4 g (66%) of **33** (Table I).

1,1′-(9*H*-Thioxanthene-2,7-diyl)bis(4-chloro-1-butanone) (XVIIIc). This material was obtained in 76% yield from thioxanthene and $ClCO(CH_2)_3Cl$ in the manner described for XVIIIa. The product was crystallized from benzene–heptane: mp 115–116°.

1,1′-(9*H*-Thioxanthene-2,7-diyl)bis(5-chloro-1-pentanone) (XVIIId). This material was obtained in 75% yield from thioxanthene and $ClCO(CH_2)_4Cl$ in the manner described for XVIIIa. The product was crystallized from a small volume of CH_2Cl_2 and recrystallized from benzene–hexane: mp 85–86°. Anal. ($C_{23}H_{24}Cl_2O_2S$) C, H, Cl.

Reaction of XVIIIc with diethylamine, piperidine, or morpholine at 110° for 24 h, using dry THF as a solvent, by the general procedure used for the preparation of **33** gave **34–36**. Compounds **34** and **35** were purified as their salts as indicated in Table I. Compound **36** was chromatographically purified as the free base on silica gel using CH_2Cl_2 to elute **36** (Table I). Reaction of XVIIId with dimethylamine by the procedure used for the preparation of **33** gave **37** (Table I).

1,1′-(9*H*-Thioxanthene-2,7-diyl)bis[5-(diethylamino)-1-pentanone] Dihydrochloride (38). A mixture of 20.0 g (0.046 mol) of XVIIId, 2.0 g of KI, 150 ml of Et_2NH, and 200 ml of THF was stirred at 106° for 24 h in a stainless steel bomb. The reaction

mixture was evaporated to dryness, water was added, and the product was extracted into heptane. The extract was acidified with ethereal HCl, and the precipitate was collected and recrystallized twice from MeOH–EtOAc to give 20.0 g of **38** with the properties listed in Table I.

In the same manner, XVIIId was allowed to react with piperidine or diallylamine (reaction times 72 and 24 h, respectively) to give **39** and **40**, respectively. Compound **40** was chromatographically purified from an alumina column, eluted with CH_2Cl_2.

9-(4-Chlorobenzylidene)-3,6-bis[2-[diethylamino(ethyl)-thio]]-9*H*-xanthene Dihydrochloride (42). An ethereal solution of **10** [free base, prepared from 14.5 g (0.0273 mol) of the dihydrochloride salt] was added to *p*-chlorobenzylmagnesium chloride [prepared from 17.6 g (0.109 mol) of *p*-chlorobenzyl chloride] in Et_2O and the mixture was refluxed for 5 h. Ammonium chloride solution was added to decompose the Grignard complex and the ether phase was washed (H_2O), dried ($MgSO_4$), and evaporated to dryness. The residue could not be induced to crystallize. It was redissolved in Et_2O and extracted with 2 N HCl. The solution was made alkaline with 2 N NaOH and was extracted with Et_2O. The extract was dried ($MgSO_4$) and acidified with ethereal HCl. The precipitate was collected and was recrystallized twice from MeOH–EtOAc to give 8.3 g (48%) of **42** (Table I).

Reaction of **4** with 4-chlorobenzylmagnesium chloride followed by the same purification procedure as described for **42** gave **41** (Table I). Dehydration of the intermediate carbinols occurred under the conditions described. There was no evidence to indicate the presence of such intermediates in either **41** or **42**.

9-(4-Chlorobenzyl)-3,6-bis[2-(diethylamino)ethoxy]-9*H*-xanthen-9-ol (43). An ethereal solution of 10.7 g (0.025 mol) of **5** was added to 4-chlorobenzylmagnesium chloride [prepared from 16.1 g (0.1 mol) of 4-chlorobenzyl chloride] in Et_2O and the mixture was refluxed for 4 h. Ammonium chloride solution and some $CHCl_3$ were added and the organic phase was separated, dried ($MgSO_4$), and evaporated to dryness. The residue was recrystallized twice from hexane to give 4.2 g of **43** (Table I).

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References and Notes

(1) Presented in part at the 13th National Medicinal Chemistry Symposium, American Chemical Society, Iowa City, Iowa, June 1972.
(2) W. L. Albrecht, R. W. Fleming, S. W. Horgan, B. A. Deck, J. W. Hoffman, and G. D. Mayer, *J. Med. Chem.*, **17**, 1150 (1974) (paper 6).
(3) A. D. Sill, W. L. Albrecht, E. R. Andrews, R. W. Fleming, S. W. Horgan, E. M. Roberts, and F. W. Sweet, *J. Med. Chem.*, **16**, 240 (1973) (paper 1).
(4) W. L. Albrecht, E. R. Andrews, R. W. Fleming, J. M Grisar, S. W. Horgan, A. D. Sill, F. W. Sweet, and D. L. Wenstrup, Abstracts, 160th National Meeting of the Americal Chemical Society, Chicago, Ill., Sept 1970), MEDI 18.
(5) E. R. Andrews, R. W. Fleming, J. M. Grisar, J. C. Kihm, D. L. Wenstrup, and G. D. Mayer, *J. Med. Chem.*, **17**, 882 (1974) (paper 2).
(6) R. F. Krueger and G. D. Mayer, Science, **169**, 1213 (1970).
(7) G. D. Mayer and R. F. Krueger, *Science*, **169**, 1214 (1970).
(8) W. L. Albrecht, R. W. Fleming, S. W. Horgan, J. C. Kihm, and G. D. Mayer, *J. Med. Chem.*, **17**, 886 (1974) (paper 3).
(9) A. D. Sill, E. R. Andrews, F. W. Sweet, J. W. Hoffman, P. L. Tiernan, J. M. Grisar, R. W. Fleming, and G. D. Mayer, *J. Med. Chem.*, **17**, 965 (1974) (paper 5).
(10) T. Sengoku, *J. Pharm. Soc. Jpn.*, **53**, 962 (1933); *Chem. Abstr.*, **29**, 5445 (1935).
(11) Ng. D. Xuong and Ng. Ph. Buu-Hoi, *J. Chem. Soc.*, 3741 (1952).
(12) C. Liebermann and M. Zsuffa, *Ber.*, **44**, 852 (1911).
(13) R. Meyer and A. Conzetti, *Ber.*, **30**, 969 (1897); **32**, 2103 (1899).
(14) W. Wenner, *Justus Liebigs Ann. Chem.*, **607**, 121 (1957).
(15) M. S. Newman and H. A. Karnes, *J. Org. Chem.*, 31, 3980 (1966).
(16) R. W. Fleming, A. D. Sill, and F. W. Sweet, U.S. Patent 3 576 865 (1971); *Chem. Abstr.*, **73**, 3705 (1970).
(17) R. F. Krueger, G. D. Mayer, K. P. Camyre, and S. Yoshimura, paper presented at the 11th Interscience Conference on Antimicrobial Agents and Chemotherapy, Atlantic City, N.J., Oct 1971.
(18) G. D. Mayer, unpublished results, Merrell-National Laboratories, 1972.

Synthesis and Antimycotic Properties of 1-(2-Alkyl-2-phenylethyl)-1*H*-imidazoles

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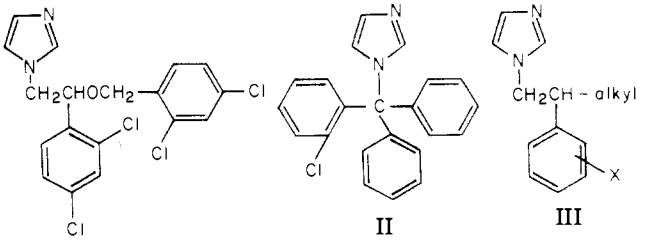
The synthesis of 1-(2-alkyl-2-phenylethyl)-1*H*-imidazoles was accomplished starting from the corresponding phenylacetonitriles. Via alkylation, esterification, and sodium borohydride reduction—in the presence of lithium iodide—β-phenylalcanols were obtained. Mesylation of these alcohols and refluxing with imidazole in dimethylformamide furnished title compounds, which were active in vitro against dermatophytes, yeasts, other fungi, and gram-positive bacteria and in vivo as well as in vitro against *Candida albicans*.

Substances containing the imidazole nucleus are known for their antimycotic activity. Miconazole[1] (I) and clotrimazole[2] (II) are among them, displaying a marked, broad-spectrum activity, not only against dermatophytes but also against yeasts (e.g., *Candida albicans*) and gram-positive bacteria. In the present paper we wish to report the synthesis and chemotherapeutic activity of a number of 1-(2-alkyl-2-phenylethyl)-1*H*-imidazoles (III).



I II III

Chemistry. The synthesis, starting from substituted phenylacetonitriles, is outlined in Scheme I. Monoalkylation of the phenylacetonitrile with an appropriate alkyl halide was performed via the carbanion, generated