Sympathomimetic Amines Having a Carbostyril Nucleus

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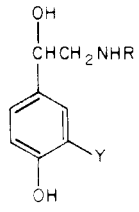
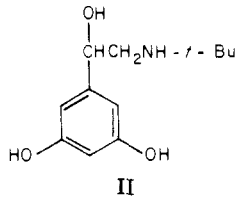
A series of new sympathomimetic amines containing an 8-hydroxycarbostyril moiety was synthesized. These compounds probably exist as resonance hybrids having two acidic hydrogen atoms in locations approximating to those of the hydroxyl groups of catechol-containing adrenergic agents. In an in vitro test, many of these compounds showed potent activity for relaxation of guinea pig tracheal smooth muscle. One of the compounds was 24 000 times more potent than isoproterenol. Their actions on cardiac muscle were also examined in vitro by measuring increase in the beating rate of the right atria of guinea pigs. Several of the compounds appeared to be β-selective. Some of the compounds seem suitable for use as bronchodilators. The structure-activity relationships of these compounds were discussed in comparison with those of catecholamines.

β-Adrenergic stimulants, such as isoproterenol (Ia),[1] are widely used clinically as therapeutic agents for asthma. However, isoproterenol has various β actions, causing palpitation and hypotension besides bronchodilation, so that between 1965 and 1969 correlations were reported between the dosage of isoproterenol aerosol and mortality of asthmatic patients from asphyxia or circulatory disturbances.[2-4]

Lands and his associates[5] classified β-receptors into two groups: β_1-receptors which mediate stimulation of cardiac muscle and release of fatty acids and β_2-receptors which mediate bronchodilation and hypotensive effects. In support of this, many β-selective sympathomimetic amines have been reported. These include soterenol (Ib), in which the *m*-OH group of catecholamines is replaced by a methanesulfonamido group,[6-8] salbutamol (Ic), which is a saligenin analogue of adrenergic catecholamines,[9-12] and terbutaline (II), which has a resorcinol skeleton.[13] The importance of sympathomimetic amines as bronchodilators is also supported by the β-adrenergic blockade theory[14] and the facts that these amines inhibit the release of histamine derived from antigen-antibody reactions in sensitized tissue.[15-17]

To develop sympathomimetic amines with potent bronchodilatory activity, high β-selectivity, and prolonged effectiveness, we synthesized a series of β-adrenergic stimulants with a carbostyril nucleus and examined their pharmacological effects.



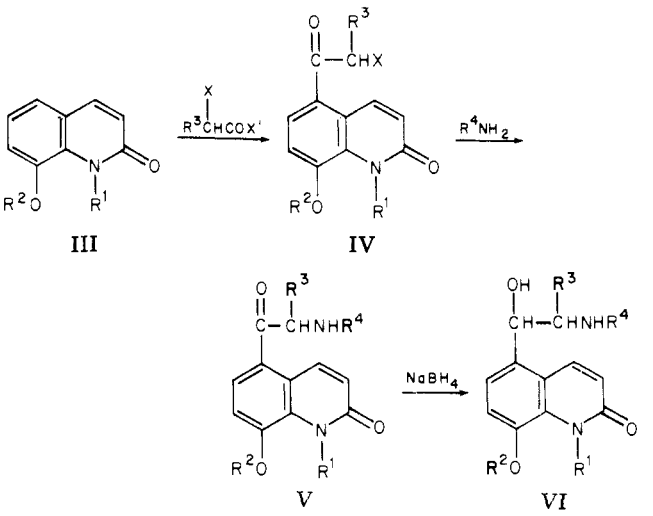


II

Ia, Y = OH; R = *i*-Pr
b, Y = $NHSO_2Me$; R = *i*-Pr
c, Y = CH_2OH; R = *t*-Bu

Chemistry. A series of sympathomimetic amines with an 8-hydroxycarbostyril moiety was synthesized as outlined in Scheme I. Friedel-Crafts reactions between 8-hydroxycarbostyrils (III) and α-haloalkanoyl halides gave 5-(α-haloalkanoyl)-8-hydroxycarbostyrils (IV) listed in Table I. The 5-(α-substituted aminoalkanoyl)-8-hydroxycarbostyrils (V) shown in Table II were obtained by condensation of α-halo ketones with amines. Reduction of amino ketones with $NaBH_4$ gave the 5-[(2-substituted amino-1-hydroxy)alkyl]-8-hydroxycarbostyrils (VI) listed in Table III. It was usually difficult to reduce only the ketone group in the side chains of amino ketones without reducing the 3,4 positions in the carbostyril skeleton by catalytic reduction. The 8-methoxycarbostyril derivative

Scheme I



32 was also synthesized as outlined in Scheme I to examine its structure-activity relationship.

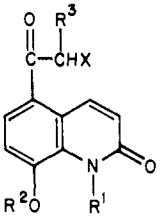
The sympathomimetic amines obtained were converted to free bases in aqueous alkali solution and then to the required acid salts. The β-adrenergic stimulants **26-30** probably existed as erythro isomers[7,18] as they were synthesized by hydride reduction[19,20] of secondary amino ketones. In agreement of this assignment, the NMR spectrum (D_2O) of compound **29** showed a doublet (J = 4.2 Hz)[18] at 5.77 ppm.

Results and Discussion

The potential bronchodilatory and cardiac-stimulating activities of the new sympathomimetic amines were examined in vitro on tracheal smooth muscle and right atria, respectively, from guinea pigs. The results are shown in Table IV.

From studies on catecholamines, Larsen and Lish[6] reported that the *m*-OH group of catecholamines can be replaced by a methanesulfonamido group without affecting bronchodilatory activity. Other groups, such as a CH_2OH,[9] or a ureido[21,22] group, or the aromatic N atom of 8-hydroxyquinoline,[23] may also be substituted for the *m*-OH group with retention of a high degree of β-adrenergic agonist activity. Sympathomimetic amines with an 8-hydroxycarbostyril moiety exist as resonance hybrids and possess two weakly acidic hydrogen atoms in about the same general vicinity as those in catecholamines, as shown in Scheme II. Replacement of either of these active hydrogen atoms by a Me group to give the *N*-Me derivative **31** and the ether **32** gave inactive or weakly active compounds, respectively, in agreement with the findings on other β-stimulants.[12,24] These results indicate the

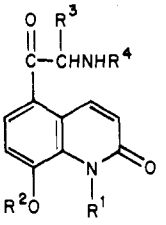
Table I. 5-(α-Haloalkanoyl)-8-hydroxycarbostyrils[a]



Compd	R¹	R²	R³	X	Formula	Mp,[b] °C	Recrystn solvent[c]
1	H	H	H	Cl	$C_{11}H_8ClNO_3$	285-287	A
2	H	H	Me	Br	$C_{12}H_{10}BrNO_3$	229-231	A
3	H	H	Et	Br	$C_{13}H_{12}BrNO_3$	221-222	A
4	Me	H	H	Cl	$C_{12}H_{10}ClNO_3$[d]	287-289	B
5	H	Me	H	Cl	$C_{12}H_{10}ClNO_3$	243-244	A

[a] Usually, these compounds were not purified before following procedures, but for identification, pure samples were obtained by recrystallization. [b] Decomposition. [c] A, MeOH; B, EtOH. [d] Not analyzed.

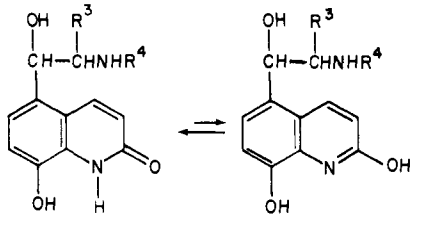
Table II. 5-(α-Substituted aminoalkanoyl)-8-hydroxycarbostyrils



Compd	R¹	R²	R³	R⁴	Formula[a]	Mp,[b] °C	Recrystn solvent[c]	Yield,[d] %
6	H	H	H	*i*-Pr	$C_{14}H_{16}N_2O_3 \cdot HCl \cdot H_2O$	288	A-C	49
7	H	H	H	*s*-Bu	$C_{15}H_{18}N_2O_3 \cdot HCl$	289-291	B	26
8	H	H	H	*t*-Bu	$C_{15}H_{18}N_2O_3 \cdot HCl$	291-293	A	45
9	H	H	H	CH_2Ph	$C_{18}H_{16}N_2O_3 \cdot HCl$	278-279	A-D	46
10	H	H	H	CMe_2CH_2Ph	$C_{21}H_{22}N_2O_3 \cdot HCl \cdot 0.5H_2O$	246-247	A-D	28
11	H	H	H	Cyclohexyl	$C_{17}H_{20}N_2O_3 \cdot HCl \cdot H_2O$	294-296	B	25
12	H	H	Me	*i*-Pr	$C_{15}H_{18}N_2O_3 \cdot HCl \cdot H_2O$	227-228	A-D	41
13	H	H	Me	*t*-Bu	$C_{16}H_{20}N_2O_3 \cdot HCl \cdot 0.5H_2O$	264-265	A-D	25
14	H	H	Et	Et	$C_{15}H_{18}N_2O_3 \cdot HCl \cdot H_2O$	232-234	A-D	37
15	H	H	Et	*i*-Pr	$C_{16}H_{20}N_2O_3 \cdot HCl \cdot 0.5H_2O$	245-247	A-D	55
16	H	H	Et	*s*-Bu	$C_{17}H_{20}N_2O_3 \cdot HCl \cdot 1.5H_2O$	212-214	B	35
17	Me	H	H	*i*-Pr	$C_{15}H_{18}N_2O_3 \cdot 2H_2O$	136-138	*e*	33
18	H	Me	H	*i*-Pr	$C_{15}H_{18}N_2O_3 \cdot HCl \cdot H_2O$	230-231	A-D	49

[a] Salts and/or degrees of hydration are shown with the formulas. [b] Decomposition. [c] A, MeOH; B, EtOH; C, acetone; D, Et_2O. [d] Total yield from 8-hydroxycarbostyrils. [e] Crystallized from aqueous alkali solution.

Scheme II



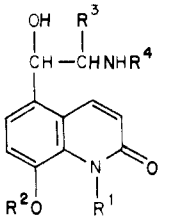
VIa VIb

availability of the 8-hydroxycarbostyril nucleus as a substitute for catechol. The delocalized hydrogen atom at the 1 and 2 positions is probably substituted for the *m*-OH group of catecholamines. The weak bronchorelaxing activity of compound **32** is probably explained by the hydrogen bonding capacities to β-receptors of the O atom of the 8-MeO group and the NH group at the 1 position.

In sympathomimetic amines VI, the substituents R^3 and R^4 had a great influence on bronchorelaxing activities. The effects of substituents R^4 on bronchorelaxing potency in the ethanolamine series (R^3 = H) decreased in the following order: *t*-Bu > *i*-Pr > CMe_2CH_2Ph > *s*-Bu >> CH_2Ph > cyclohexyl > isoproterenol > H. Surprisingly, the *t*-Bu derivative **22** was 24000 times more potent than isoproterenol. In the propanolamine (R^3 = Me) and butanolamine (R^3 = Et) series, respectively, the potencies decreased in the following orders: *t*-Bu > *i*-Pr > isoproterenol and *i*-Pr > *s*-Bu > isoproterenol > Et. The potencies of *i*-Pr derivatives varied from about the same to half those of *t*-Bu homologues, **20** vs. **22** and **26** vs. **27**, respectively, and 5–6 times those of *s*-Bu homologues, **20** vs. **21** and **29** vs. **30**. The structure–activity relationships follow a similar pattern to that observed by Lands[5] on catecholamines. The substituents R^3 also showed large effects on bronchorelaxing activities and the potency decreased in the following order: H > Me > Et. Among *i*-Pr derivatives, compound **20** (R^3 = H) was 700 times more potent than compound **26** (R^3 = Me) and 2800 times more potent than compound **29** (R^3 = Et). Similar differences in potencies were observed between *t*-Bu or *s*-Bu homologues.

The cardiac-stimulating activities of the ethanolamine series, as estimated in an in vitro assay utilizing guinea pig right atrial tissue, were all 0.06–0.003 times less than that of isoproterenol, except for that of compound **24**. The

Table III. 5-[(2-Substituted amino-1-hydroxy)alkyl]-8-hydroxycarbostyrils



Compd	R^1	R^2	R^3	R^4	Formula[a]	Mp,[b] °C	Recrystn solvent[c]	Yield, %
19[d]	H	H	H	H	$C_{11}H_{12}N_2O_3 \cdot HCl$[e]	261-262	A	90
20	H	H	H	*i*-Pr	$C_{14}H_{18}N_2O_3 \cdot HCl$	210-212	A-D	88
21	H	H	H	*s*-Bu	$C_{15}H_{20}N_2O_3 \cdot 2HCl \cdot H_2O$	187-188	B-C	94
22	H	H	H	*t*-Bu	$C_{15}H_{20}N_2O_3 \cdot HCl \cdot 0.5H_2O$	244-246	B-C	80
23	H	H	H	CH_2Ph	$C_{18}H_{18}N_2O_3 \cdot HCl \cdot 3H_2O$	131-132	A-C	72
24	H	H	H	CMe_2CH_2Ph	$C_{21}H_{24}N_2O_3 \cdot HCl \cdot H_2O$	167-168	A-C	96
25	H	H	H	Cyclohexyl	$C_{17}H_{22}N_2O_3 \cdot HCl \cdot H_2O$	115-117	B-C	40
26	H	H	Me	*i*-Pr	$C_{15}H_{20}N_2O_3 \cdot H_2O$	164-166	*f*	81
27	H	H	Me	*t*-Bu	$C_{16}H_{22}N_2O_3 \cdot HCl \cdot H_2O$	200-201	A-D	59
28	H	H	Et	Et	$C_{15}H_{20}N_2O_3 \cdot HCl \cdot H_2O$	182-184	A-D	43
29	H	H	Et	*i*-Pr	$C_{16}H_{22}N_2O_3 \cdot HCl \cdot H_2O$	213-215	A-D	73
30	H	H	Et	*s*-Bu	$C_{17}H_{24}N_2O_3 \cdot HCl \cdot 1.5H_2O$	182-183	B-C	67
31	Me	H	H	*i*-Pr	$C_{15}H_{20}N_2O_3 \cdot HCl$	202-204	B	30
32	H	Me	H	*i*-Pr	$C_{15}H_{20}N_2O_3 \cdot HCl \cdot 0.5H_2O$	235-237	B	40

[a] Salts and/or degrees of hydration are shown with the formulas. [b] Decomposition. [c] A, MeOH; B, EtOH; C, acetone; D, Et_2O. [d] Obtained by catalytic debenzylation of 23 over 10% Pd/C. [e] N: calcd, 10.91; found, 10.28. [f] Crystallized from aqueous alkali solution.

Table IV. Pharmacological Results

Compd	Guinea pig tracheal test: ED_{50}[a] with SE	Guinea pig tracheal test: Intrinsic act.	Guinea pig atrial test: ED_{25}[a] with SE	Guinea pig atrial test: Intrinsic act.
19	$(3.00 \pm 1.80) \times 10^{-7}$	0.97	$(4.53 \pm 2.08) \times 10^{-8}$	1.06
20	$(3.79 \pm 2.90) \times 10^{-12}$	0.92	$(2.01 \pm 0.55) \times 10^{-9}$	0.85
21	$(2.37 \pm 1.02) \times 10^{-11}$	0.87	$(3.92 \pm 2.29) \times 10^{-10}$	1.07
22	$(3.53 \pm 1.67) \times 10^{-12}$	1.06	$(5.62 \pm 3.89) \times 10^{-10}$	1.19
23	$(5.85 \pm 4.15) \times 10^{-9}$	0.85	$(8.60 \pm 4.90) \times 10^{-8}$	0.74
24	$(1.16 \pm 0.39) \times 10^{-11}$	1.08	$(3.05 \pm 1.35) \times 10^{-14}$	1.01
25	$(5.88 \pm 1.20) \times 10^{-8}$	1.19	$(8.10 \pm 3.90) \times 10^{-9}$	0.72
26	$(2.66 \pm 1.34) \times 10^{-9}$	1.06	$(1.99 \pm 1.17) \times 10^{-8}$	0.66
27	$(1.39 \pm 0.69) \times 10^{-9}$	1.01	$(7.00 \pm 2.65) \times 10^{-7}$	0.38
28	$(9.12 \pm 2.51) \times 10^{-8}$	0.96	$(2.27 \pm 1.44) \times 10^{-8}$	0.56
29	$(1.05 \pm 0.25) \times 10^{-8}$	1.01	$(4.55 \pm 1.30) \times 10^{-9}$	0.58
30	$(5.60 \pm 2.24) \times 10^{-8}$	1.13	$(5.95 \pm 1.75) \times 10^{-6}$	0.47
31	*b*	0.31	*c*	0.15
32	$(2.64 \pm 1.07) \times 10^{-7}$	0.66	$(9.53 \pm 5.37) \times 10^{-7}$	0.33
Isoproterenol	$(8.35 \pm 4.83) \times 10^{-8}$	1.00	$(2.48 \pm 1.52) \times 10^{-11}$	1.00
Salbutamol	$(4.19 \pm 1.65) \times 10^{-7}$	0.93	$(1.01 \pm 0.42) \times 10^{-7}$	0.65

[a] Molar concentration. [b] Maximum potency was observed at 3×10^{-6} mol. [c] Maximal activity was obtained at 3×10^{-8} mol.

propanolamine and butanolamine series was 0.0055–0.000035 times as potent as isoproterenol. The effect of substituents in the secondary amino group was not clarified.

Many of these sympathomimetic amines with a carbostyril nucleus seem suitable for use as bronchodilators because they showed more potent bronchorelaxing activities than isoproterenol and better selectivity for β_2-receptors than salbutamol. Further pharmacological tests are being performed to establish the value of these compounds as β_2-selective bronchodilators.

Experimental Section

Chemistry. Melting points were determined by the capillary method using a thermometer with an immersion line as described in the Pharmacopoeia of Japan. Melting points are given as uncorrected values. Elemental microanalyses were done in a Yanagimoto MT-2 CHN recorder and analytical values were within ±0.4% of the calculated ones unless otherwise stated. NMR spectra were recorded with a Hitachi R-20B spectrometer.

General Procedures. A. 5-(α-Haloalkanoyl)-8-hydroxycarbostyrils (IV). To a suspension of 0.1 mol of 8-hydroxycarbostyril[25] and 0.25 mol of α-haloalkanoyl halide in 150–350 ml of CS_2 was added 0.33 mol of $AlCl_3$ in small portions with stirring and cooling with ice–water. The mixture was refluxed for 6–15 h and the CS_2 layer was decanted after cooling. The residual solid was mixed with chipped ice and the resulting crystalline solid, crude α-halo ketone, was collected and washed with water and MeOH. Crude α-halo ketones were used without recrystallization because of their low heat stability and poor solubility in solvents. *Caution* must be taken to avoid contact with α-halo ketones since they sometimes cause skin irritation. Compound 1: NMR (Me_2SO-d_6) δ 8.65 and 6.67 (d, 1, J = 9.6 Hz, C_4H and C_3H), 7.79 and 7.03 [d, 1, J = 8.4 Hz, CH(Ar)], and 5.10 (s, 2, CH_2).

B. 5-(α-Substituted aminoalkanoyl)-8-hydroxycarbostyrils (V). A large excess of an appropriate amine was added to the α-halo ketone in *i*-PrOH or in the absence of solvent, and the mixture was warmed for 5–10 h at 30–50°. The solvent and

excess amine were evaporated at below 40° (in the case of aralkylamine, the excess amine was extracted with petroleum ether), and the residue was dissolved in a minimum volume of EtOH or *i*-PrOH, acidified with concentrated HCl to pH 1–2, and cooled. The precipitate was filtered, suspended in water or MeOH, and made alkaline with dilute KOH to give the free base of the amino ketone. When necessary, the amino ketone was converted to a suitable acid salt by adding the corresponding acid to the free base in water or MeOH and then recrystallizing the acid salt from the solvent, as shown in Table II. The free bases and acid salts of the amino ketones were generally hygroscopic and many of them were hydrated. Compound **6**: NMR (Me_2SO-d_6) δ 9.16 and 6.59 (d, 1, J = 9.6 Hz, C_4H and C_3H), 7.73 and 6.48 [d, 1, J = 9.0 Hz, CH(Ar)], 4.42 (s, 2, CH_2), 3.2 (m, 1, CH), and 1.29 (d, 6, J = 6.0 Hz, CMe_2).

C. 5-[(2-Substituted amino-1-hydroxy)alkyl]-8-hydroxycarbostyrils (VI). To a suspension of 0.01 mol of the appropriate amino ketone in 50–100 ml of MeOH (made alkaline with methanolic KOH when the starting material was an acid salt) was added 0.003–0.015 mol of $NaBH_4$ in small portions with stirring and cooling with ice–water. The reaction mixture was acidified to pH 1 with concentrated HCl. The resulting white precipitate was removed by filtration and the filtrate was evaporated to dryness. Then 50–100 ml of MeOH was added to the residue and evaporated off to remove boron as methyl borate. The residue was washed with acetone, suspended in a small volume of water, and made alkaline with aqueous KOH solution to give the alkanolamine. When necessary, this was purified by recrystallization after conversion to the acid salt. The free bases and acid salts of alkanolamines were usually hygroscopic and many of them were hydrated. Compound **29**: NMR (Me_2SO-d_6–D_2O) δ 8.19 and 6.71 (d, 1, J = 9.6 Hz, C_4H and C_3H), 7.36 and 7.14 [d, 1, J = 7.8 Hz, CH(Ar)], 5.63 [d (br), 1, CHO], 1.2–1.9 [m (br), 2, CH_2], 1.42 (q, 6, CMe_2), and (t, 3, CH_3).

8-Hydroxy-1-methylcarbostyril. To a solution of 60 g (0.37 mol) of 8-hydroxycarbostyril in 300 ml of 5 N NaOH was added dropwise 270 g (2.14 mol) of dimethyl sulfate with stirring and refluxing over a period of 3 h, and then refluxing was continued for 5 h. The reaction mixture was cooled and extracted with $CHCl_3$. The $CHCl_3$ layer was washed successively with dilute NaOH, dilute HCl, and water and evaporated to dryness. The residue was crystallized from petroleum ether to give crude 8-methoxy-1-methylcarbostyril. The crystalline material was mixed with 450 ml of 48% hydrobromic acid and refluxed for 8 h at 140°. Then the mixture was cooled and the precipitate was collected and washed with water, yielding 31 g (48%) of 8-hydroxy-1-methylcarbostyril, mp 275–276°. Anal. ($C_{10}H_9NO_2$) C, H, N.

8-Methoxycarbostyril. To a suspension of 32 g (0.20 mol) of 8-hydroxycarbostyril in a solution of 15.2 g (0.11 mol) of K_2CO_3 in 50 ml of water and 250 ml of acetone was added dropwise 25.2 g (0.20 mol) of dimethyl sulfate with stirring and refluxing. Then refluxing was continued for 1 h. The reaction mixture was evaporated and extracted with $CHCl_3$. The $CHCl_3$ layer was evaporated to dryness and the residue was recrystallized from petroleum ether to give 31 g (89%) of 8-methoxycarbostyril, mp[26] 108–109°. Anal. ($C_{10}H_9NO_2$) C, H, N.

Pharmacology. Methods. A. Guinea Pig Tracheal Test. The trachea was excised from male Hartley strain guinea pigs weighing from 450–600 g. A spiral section of the trachea was prepared as described by Constantine[27] and suspended in a 30-ml tissue bath containing Locke solution (NaCl, 154 mmol; KCl, 5.6 mmol; $CaCl_2$, 2.2 mmol; $NaHCO_3$, 2.4 mmol; and dextrose, 5.6 mmol) maintained at 36° and aerated with 95% O_2–5% CO_2. The resting tension was maintained at 2 g during experiments. The condition of the tracheal muscle was monitored by isometric recordings using force transducers (San-ei Sokki, Type 45072). Phentolamine (3×10^{-6} g/ml) was added to the bath fluid 15 min before induction of contraction with acetylcholine (1×10^{-5} g/ml) to block α-adrenergic receptors, and the relaxation produced by test compounds was studied after inducing muscle contraction with acetylcholine. The test compound was added to the bath fluid using the cumulative method of drug administration described by Van Rossum.[28] Responses were expressed as percentages of the maximum response of each tissue obtained on addition of a dose of isoproterenol which induced maximal relaxation of the tracheal muscle. ED_{50} values (n = 4–5) of the test compounds were determined from dose–response curves and compared with that of isoproterenol. The intrinsic activities of these compounds were calculated as multiples of their mean maximal responses to that of isoproterenol. Two representative compounds, **22** and **29**, did not show atropine-like competitive antagonism for contraction of guinea pig ileum induced with acetylcholine.[28,29] The log shifts of the dose–response curves (n = 5), which were determined at ED_{50}, were as follows for concentrations of 1×10^{-6}, 1×10^{-5}, and 1×10^{-4} mol, respectively, of these compounds: compound **22**, 0.17, 0.30, and 0.30; compound **29**, 0.33, 0.90, and 1.10; isoproterenol, 0.67, 0.93, and 1.00.

B. Guinea Pig Atrial Test. The atria were excised from male Hartley strain guinea pigs, weighing 450–600 g, and suspended in a 30-ml tissue bath containing Locke solution maintained at 36° and aerated with 95% O_2–5% CO_2. The spontaneous contraction rate was determined from isometric recordings using force transducers (San-ei Sokki, Type 45072). The resting tension was maintained at 1.0 g for each atrium. The test compound was added at increasing doses to the bath fluid, using the single dose technique to measure each response. The preparation was washed at least five times between doses to regain equilibration. The ED_{25} values (n = 4–5) of the test compounds (inducing 25 beats/min increase in contractile rate) were determined and compared with that of isoproterenol. The intrinsic activity was determined in the same manner as described for the guinea pig tracheal test.

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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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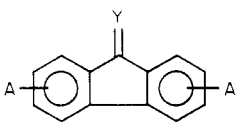
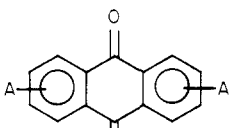
3,6-Bis[2-(dimethylamino)ethoxy]-9*H*-xanthen-9-one dihydrochloride (**4**, RMI 10874DA) and 1,1′-(9*H*-xanthene-2,7-diyl)bis[2-(dimethylamino)ethanone] dihydrochloride (**16**, RMI 11513DA) were found to prolong survival of mice infected with lethal challenges of encephalomyocarditis (EMC) virus. They 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.

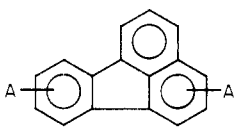
The discovery of antiviral activity of bisalkamine esters of fluorenone Ia[3] led to the development of tilorone hydrochloride and related bis-basic ethers of fluorenone Ib[4–7]



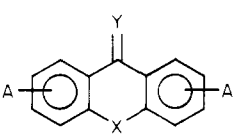
I, Y = O
II, Y = H, H



III



IV

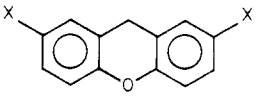


V, X, Y = O
VI, X = O; Y = H, H
VII, X = S; Y = H, H

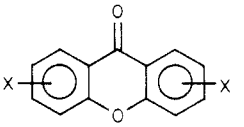
a, A = $-CO_2(CH_2)_nNR_2$
b, A = $-O(CH_2)_nNR_2$
c, A = $-CO(CH_2)_nNR_2$

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.

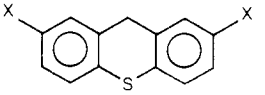
Chemistry. Bisalkamine esters of 9-oxo-9*H*-xanthene-2,7-dicarboxylic acid **1** and **2** and the -dicarboxamide **3** were prepared from the bisacid chloride of IX.[10] Compound IX was obtained from 2,7-diacetyl-9*H*-xanthene (VIII).[11] The bisalkamine ester of 9*H*-xanthene-2,7-dicarboxylic acid **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]