Thirty minutes later, 0.1 mL of 1% carrageenan was injected subcutaneously into the plantar surface of the hind paw. Three hours later, paw volume was measured again. The increase in paw volume of the drug-treated rat was compared with that of the control group for calculation of the percent inhibition.

Analgesic Activity.[11] Six male STD-ddY mice were used for each group. The test compound was administered orally as a suspension in 0.5% CMC. Thrity minutes later, 0.1 mL/10 g of 0.6% AcOH was injected into the peritoneal cavity, and then the frequency of the repeated characteristic writhing movements was measured for 20 min. The response of the drug-treated mouse was compared with the response using AcOH alone.

Acute toxicity, expressed as a LD_{50} value calculated by the method of Weil,[23] was determined 168 h after a single ip injection to groups of four male ddY mice.

Supplementary Material Available: Synthetic routes to intermediates **6**, **7a,b**, **8a–f**, **9–11**, **13**, **15**, **17–24**, **25a,b**, **26a,b**, and **2a–h** (Schemes I–IV) and NMR spectral data for all new compounds described in this paper (Tables IV–VIII) (8 pages). Ordering information is given on any current masthead page.

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Gastric Antisecretory Agents. 2. Antisecretory Activity of 9-[(Aminoalkyl)thio]-9*H*-xanthenes and 5-[(Aminoalkyl)thio]-5*H*-[1]benzopyrano[2,3-*b*]pyridines

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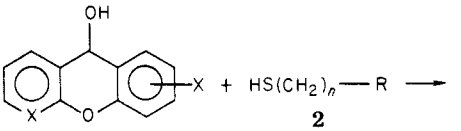
A series of 9-[(aminoalkyl)thio]-9*H*-xanthenes (**3–6**) and 5-[(aminoalkyl)thio]-5*H*-[1]benzopyrano[2,3-*b*]pyridines (**7–10**) possessing gastric antisecretory activity in the rat and dog is described. Many of the compounds possessed good activity in the pylorus-ligated rat and several inhibited histamine-stimulated gastric acid secretion in the dog. The mechanism of acid secretion inhibition is not related to anticholinergic or histamine (H_2) receptor antagonism.

As part of our efforts to identify novel compounds which inhibit gastric acid secretion,[2] we are reporting a series of 9-[(aminoalkyl)thio]-9*H*-xanthenes (**3–6**) and 5-[(aminoalkyl)thio]-5*H*-[1]benzopyrano[2,3-*b*]pyridines (azaxanthenes) (**7–10**) which represent a new class of gastric antisecretory agents. The present compounds are potent inhibitors of gastric acid secretion in the pylorus-ligated rat, and several inhibit histamine-stimulated gastric acid secretion in dogs.

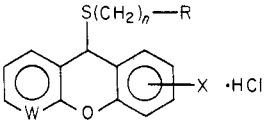
Chemistry. The [(aminoalkyl)thio]xanthenes and azaxanthenes were synthesized as shown in Scheme I from the alcohol **1** and the requisite (aminoalkyl)mercaptan hydrochloride, **2**, in CH_3CN. The alcohols **1a** were prepared by $LiAlH_4$ reduction of a 9*H*-xanthen-9-one, while **1b** was prepared by $NaBH_4$ reduction of 5*H*-[1]benzopyrano[2,3-*b*]pyridin-5-one[3] in CH_3OH at 20–25 °C.

Biological Test Methods. The compounds were evaluated for antisecretory activity in two animal models (Tables I and II). The pylorus-ligated rat[4] was used as the primary screen to assess antisecretory activity and to identify potentially toxic compounds. Compounds were administered at 40 mg/kg intraperitoneally at the time of ligation, and reduction in acid output was measured after 4 h. The secondary model was inhibition of histamine-stimulated gastric acid secretion in adult mongrel dogs[5] with surgically prepared Heidenhain pouches. Compounds were first administered at 5 mg/kg intravenously, and reduction in acid output, relative to the non-drug-treated control value in the same animal, was measured. Selected compounds were also tested at 8 mg/kg orally in the dog.

Scheme I



1a, W = CH
b, W = N



3, W = CH; R = NH_2
4, W = CH; R = $N(CH_3)_2$
5, W = CH; R = c-$N(CH_2CH_2)_2O$
6, W = CH; R = c-NC_5H_{10}
7, W = N; R = NH_2
8, W = N; R = $N(CH_3)_2$
9, W = N; R = c-$N(CH_2CH_2)_2O$
10, W = N; R = c-NC_5H_{10}

Results and Discussion

The antisecretory results for the xanthenes and benzopyrano[2,3-*b*]pyridines are shown in Tables I and II, re-

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0022-2623/81/1824-1010$01.25/0

Table I. Gastric Antisecretory Activity of 9*H*-9-[(Aminoalkyl)thio]xanthenes

compd	R	*n*	X	mp, °C	formula[a]	recrystn solvent	% yield	% reduction in gastric acid secretion: rat, 40 mg/kg ip	dog: 5 mg/kg iv	dog: 8 mg/kg po
cimetidine								74	84	86
3a	NH_2	2	H	189–191	$C_{15}H_{15}NOS\cdot HCl$	EtOH	52	35	<30	
3b	NH_2	2	2-Cl	215–218	$C_{15}H_{14}ClNOS\cdot HCl$	EtOH	63	74	<30	
3c	NH_2	3	H	191–193	$C_{16}H_{17}NOS\cdot HCl$	2-PrOH	62	44	68[b]	*f*
3d	NH_2	3	2-Cl	187–189	$C_{16}H_{16}ClNOS\cdot HCl$	MeOH/CH_3CN	40	89	39	
3e	NH_2	3	3-Cl	193–195	$C_{16}H_{16}ClNOS\cdot HCl$	EtOH	51	79	<30	
3f	NH_2	3	4-Cl	125–127	$C_{16}H_{16}ClNOS\cdot HCl$	EtOH/CH_3CN	41	99	33	
3g	NH_2	3	2-CH_3	155–157	$C_{17}H_{19}NOS\cdot HCl$	EtOH	35	100	80[c]	<50[f]
3h	NH_2	3	4-CH_3	188–192	$C_{17}H_{19}NOS\cdot HCl$	EtOH	20	71	87[c]	*f*
4a	$N(CH_3)_2$	2	H	139–142	$C_{17}H_{19}NOS\cdot HCl$	2-PrOH	86	65	<30	
4b	$N(CH_3)_2$	2	2-Cl	161–162	$C_{17}H_{18}ClNOS\cdot HCl$	CH_3CN	64	55	<30	
4c	$N(CH_3)_2$	2	2-CH_3O	153–156	$C_{18}H_{21}NO_2S\cdot HCl$	EtOH	38	63	<30[c]	
5a	1-morpholinyl	2	H	201–204	$C_{19}H_{21}NO_2S\cdot HCl$	CH_3CN	74	93	56[d]	<30
5b	1-morpholinyl	2	3-Cl	181–184	$C_{19}H_{20}ClNO_2S\cdot HCl$	CH_3CN	45	70	39[c]	
5c	1-morpholinyl	2	4-Cl	186–188	$C_{19}H_{20}NO_2S\cdot HCl$	CH_3CN	62	86	42	
5d	1-morpholinyl	2	2-CH_3	207–207	$C_{20}H_{23}NO_2S\cdot HCl$	CH_3CN	34	93	50[c]	
5e	1-morpholinyl	2	4-CH_3	178–180	$C_{20}H_{23}NO_2S\cdot HCl$	CH_3CN	62	71	<30	
5f	1-morpholinyl	2	2-CH_3O	204–206	$C_{20}H_{23}NO_3S\cdot HCl$	EtOH	71	94	*e*	
5g	1-morpholinyl	2	3-CH_3O	184–192	$C_{20}H_{23}NO_3S\cdot HCl$	CH_3CN	48	44	77	<30
5h	1-morpholinyl	3	H	166–168	$C_{20}H_{23}NO_2S\cdot HCl$	EtOH	35	98	47	
6a	1-piperidinyl	2	H	181–183	$C_{20}H_{23}NOS\cdot HCl$	CH_3CN	75	98	<30[d]	
6b	1-piperidinyl	2	3-Cl	175–177	$C_{20}H_{22}ClNOS\cdot HCl$	CH_3CN	71	80	<30	
6c	1-piperidinyl	2	4-Cl	198–200	$C_{20}H_{22}ClNOS\cdot HCl$	CH_3CN	82	87	44	
6d	1-piperidinyl	2	2-CH_3	209–210	$C_{21}H_{25}NOS\cdot HCl$	EtOH	51	88	<30	
6e	1-piperidinyl	2	4-CH_3	194–196	$C_{21}H_{25}NOS\cdot HCl$	CH_3CN	78	85	<30	
6f	1-piperidinyl	2	2-CH_3O	199–201	$C_{21}H_{25}NO_2S\cdot HCl$	CH_3CN	39	73	<30	
6g	1-piperidinyl	2	3-CH_3O	101–105	$C_{21}H_{25}NO_2S\cdot HCl$	Me_2CO	14	47	<58	<30
6h	1-piperidinyl	3	H	178–180	$C_{21}H_{25}NOS\cdot HCl$	CH_3CN	85	88	30	

[a] All new compounds had C, H, and N microanalyses within 0.4% of theory, except **3d** (C: calcd, 56.14; found, 55.71), **5b** (C: calcd, 57.28; found, 57.70), **5h** (H: calcd, 6.41; found, 6.88), **6f** (C: calcd, 64.35; found, 64.88), and **6g** (H: calcd, 6.69; found, 7.45). [b] Mean value from four determinations. [c] Mean value from two determinations. [d] Mean value from three determinations. [e] Stimulated gastric acid secretion. [f] Animal vomited upon compound administration.

Table II. Gastric Antisecretory Activity of 5*H*-5-[(Aminoalkyl)thio]benzopyrano[2,3-*b*]pyridines

compd	R	*n*	X	mp, °C	formula[a]	recrystn solvent	% yield	% reduction in gastric acid secretion: rat, 40 mg/kg ip	dog: 5 mg/kg iv	dog: 8 mg/kg po
7	NH_2	2	H	224–226	$C_{14}H_{14}N_2OS\cdot HCl$	CH_3CN	48	<30	<30	
8	$N(CH_3)_2$	2	H	241–243	$C_{16}H_{18}N_2OS\cdot HCl$	EtOH	67	79	<30	
9a	1-morpholinyl	2	H	205–207	$C_{18}H_{20}N_2O_2S\cdot HCl\cdot CH_3CN$	CH_3CN	60	64	66[b]	*d*
9b	1-morpholinyl	2	7-CH_3O	189–191	$C_{19}H_{22}N_2O_3S\cdot HCl$	CH_3CN	62	96	51	<30[d]
9c	1-morpholinyl	2	8-CH_3O	213–215	$C_{19}H_{22}N_2O_3S\cdot HCl$	CH_3CN	48	80	<30	
9d	1-morpholinyl	3	H	163–167	$C_{19}H_{22}N_2O_2S\cdot HCl$	CH_3CN	64	62		
10	1-piperidinyl	2	H	213–215	$C_{19}H_{22}NOS\cdot HCl$	CH_3CN	52	61	63[c]	<30

[a] All compounds had C, H, and N microanalyses within 0.4% of theory, except **7** (H: calcd, 5.13; found, 4.65). [b] Mean value from five determinations. [c] Mean value from four determinations. [d] Animal vomited upon compound administration.

spectively. Most of the compounds are highly potent antisecretory agents in the rat, many with potencies greater than cimetidine. Compounds active in the rat were tested at 5 mg/kg intravenously against histamine-stimulated gastric acid secretion in the dog. As seen in the tables, there is poor correlation between potency in the rat and dog, probably due to nonspecificity of the rat model.[6] In general, the most potent (>50% reduction in acid secretion) subgroups of compounds in the dog were those with a primary amino group separated from the sulfur by three methylene groups (**3c,g,h**) and several morpholine derivatives (**5a,d,g** and **9a,b**). In the piperidine subgroup, only **6g** and **10** were active in the dog. None of the dimethylamine derivatives were active in the dog nor were any of the ring-chlorinated derivatives. Apart from these qualitative observations, no clear structure–activity relationships (SAR) can be demonstrated.

When selected compounds showing greater than 50% inhibition at 5 mg/kg intravenously were tested at 8 mg/kg orally, no antisecretory activity was observed (Tables I and II). This was complicated by vomiting in dogs dosed orally with **3c,g,h** and **9a,b**. Vomiting did not occur, however, in dogs when these compounds were administered intravenously.

The antisecretory mechanism of the present class of compounds has not been established. Nevertheless, some mechanisms have been ruled out. At the testing dose of 40 mg/kg in the rat, none of the compounds caused mydriasis, suggesting that antisecretory activity is probably not the result of an anticholinergic mechanism. Similarly, compounds active (iv) in the dog against histamine (**3g,h**, **5b–d,g,h**, **6c**, and **10**) did not inhibit the histamine-stimulated chronotropic response in isolated guinea pig right atria, which is a standard assay for histamine (H_2) receptor antagonists.[7] Interestingly, none of the compounds reported here showed any effects in animal tests for neuroleptic or antidepressant agents, despite their resemblance to phenothiazines and other tricyclic compounds with basic three-atom side chains.[8] Thus, when representative compounds (**3a,h**, **4a–c**, **5a**, **6a,f,h**, **7**, **8**, **9a**, and **10**) were tested for antagonism of methamphetamine aggregate toxicity[9] and antagonism of tetrabenazine-induced ptosis,[9] no activity was apparent when the compounds were administered at 30 mg/kg orally to mice. The compounds of this series were not tested for histamine (H_1) receptor antagonism.

In conclusion, we have described a new class of gastric antisecretory agents, several of which possess good activity (iv) in a dog model. Vomiting in the dog upon oral dosing prevented a determination of relative oral potency in this series.

Experimental Section

General. Melting points were determined with a Thomas-Hoover melting point apparatus and are uncorrected. All new compounds gave satisfactory microanalyses. IR, ^1H NMR, and mass spectra were recorded for all new compounds, and the spectra support the structural assignments for these compounds. Distillation, concentration, or removal of organic solvents was done on a rotary evaporator under reduced pressure.

Chemistry. Alcohols. 9*H*-Xanthene-9-ols were freshly prepared by $LiAlH_4$ reduction in THF at 20 °C of the appropriate 9*H*-xanthen-9-ones.[10] The reaction mixtures were quenched (H_2O) and filtered, and the filtrate was evaporated to leave the crude alcohols, which were used directly. 5*H*-[1]Benzopyrano-[2,3-*b*]pyridin-5-ols were freshly prepared by $NaBH_4$ reductions of the appropriate ketones in CH_3OH at 20–25 °C.[3] The reaction mixtures were poured into cold brine and extracted with $CHCl_3$, and the $CHCl_3$ was evaporated to leave the crude alcohols, which were used directly.

(Dialkylamino)alkylthiols. 2-(1-Piperidinyl)ethanethiol,[11] 2-(4-morpholinyl)ethanethiol,[11] and 2-(1-pyrrolidinyl)ethanethiol were prepared by modification of a literature procedure.[12] 3-(1-Piperidinyl)propanethiol[13a] and 3-(4-morpholinyl)propanethiol were prepared by the general procedure of Clinton[13b] from the corresponding alcohols.[14]

[(Aminoalkyl)thio]xanthenes. General Procedure. The preparation of 9-[[2-(dimethylamino)ethyl]thio]-9*H*-xanthene is representative. A mixture of 10.0 g (0.055 mol) 9*H*-xanthen-9-ol, 7.4 g (0.055 mol) of (dimethylamino)ethanethiol hydrochloride, and 250 mL of CH_3CN was heated at reflux for 1.25 h. The solution was allowed to cool and then concentrated in vacuo, and the resulting residue was crystallized from 100 mL of 2-propanol to give 14.0 g (86%) 9-[[2-(dimethylamino)ethyl]thio]-9*H*-xanthene hydrochloride (**4a**).

Biology. Heidenhain Pouch Dog. Mongrel dogs, weighing between 12 and 18 kg, were surgically prepared with Heidenhain pouches. Any one dog that fasted for 18 h was used for experimentation 1 day a week. Compounds were dissolved in 3 mL of 0.4% methylcellulose/saline solutions for intravenous studies and in 5 mL for oral studies. A dose of histamine of 0.4 (μg/kg)/min was found to produce 50–60% maximal acid output, and this dose of histamine was selected as the most appropriate stimulant. The gastric secretions were collected at 30-min intervals for 0.5 to 1 h before the start of the infusion of histamine and for 4 and 5 h thereafter. The volume of each 30-min collection was recorded, and an aliquot was used for titration to determine the acid concentration. The AO was calculated by multiplying the volume times the acid concentration. One hour after the start of the histamine infusion, the test compound was given either intravenously or orally by gavage. The respective 30-min acid outputs were summated for 3 h after drug administration. The AO collected over the 3-h period after drug administration was divided by the 3-h AO collected in control experiments. This value times 100 yields the percentage of control AO. Percent inhibition = 100 − percent of control. Unless otherwise noted in Tables I and II, each compound was tested in a single dog. Each animal served as its own control because the response to a set dose of histamine depends upon the size of the pouch, and the pouch size is not constant across animals. In our laboratories, the mean plus or minus SE for acid output in control studies was 10.56 ± 1.15 mequiv/3 h. Cimetidine, iv, had an ID_{50} of 0.66 mg/kg with 95% confidence limits of 0.16–2.60. Cimetidine, po, had an ID_{50} value of 1.25 mg/kg with 95% confidence limits of 0.58–2.52.

Pylorus-Ligated Rat. Charles River CD (outbred albino) male rats, 150 to 200 g of body weight, were employed for gastric secretion studies using the pylorus-ligation technique. Rats that fasted for 24 h were anesthetized with a short-acting barbiturate anesthetic, Brevital. While under surgical level anesthesia, the abdomen was opened and a ligature was securely tied around the pylorus. The stomach was returned to the abdomen and the

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incision was closed with auto-clips. Test compounds were dissolved in a 2.5% Tween 80 solution and were administered intraperitoneally at a dose of 0.5 mL/200 g of body weight. Four hours after drug administration, the animals were killed and the stomachs removed. The contents of the stomach were collected and the volume was recorded. An aliquot was removed and the acid concentration was determined by automatic titration against 0.1 N NaOH to a pH end point of 7.0. The AO was calculated by multiplying the volume of gastric content in liters times the acid concentration in milliequivalents per liter, yielding AO values in milliequivalents/4 h. Six rats were used for each test compound and eight rats for the control. Percent inhibition was calculated as follows: 100 − [100 × (mean test AO/mean control AO)]. Results were statistically analyzed by Student's t test. The mean plus or minus SE acid output in our control studies using this procedure was 0.61 ± 0.04 mequiv/4 h.

Acknowledgment. We thank Dr. Frank Villani for providing us with the intermediate 5*H*-[1]benzopyrano-[2,3-*b*]pyridin-5-one. We also thank Christopher Casciano, Carolyn Jones, Mark Policelli, Susan Sehring, and Glen Tetzloff for expert technical assistance.

Dopamine Agonist Properties of *N*-Alkyl-4-(3,4-dihydroxyphenyl)-1,2,3,4-tetrahydroisoquinolines

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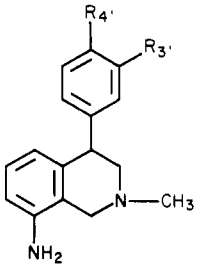
A series of homologous *N*-alkyl-4-(3,4-dihydroxyphenyl)-1,2,3,4-tetrahydroisoquinolines was synthesized and examined for a dopamine-like ability to dilate the renal artery. The *N*-methyl derivative was equipotent to the 3′,4′-dihydroxy derivative of the antidepressant agent nomifensine, indicating that the 8-amino group of the latter is not essential for dopamine-like activity. The *N*-ethyl homologue was reduced in potency when compared to the *N*-methyl, and the *N*-*n*-propyl, surprisingly, was essentially devoid of activity. This was unexpected in view of the fact that in all series of dopamine-like agents reported to date, *N*-alkylation, when one of the alkyls was an *n*-propyl group, either allowed retention or enhancement of potency.

Recently a number of reports have appeared which describe the dopamine agonist properties of the dihydroxy derivative **1** and of nomifensine (**2**).[1-3] Nomifensine itself

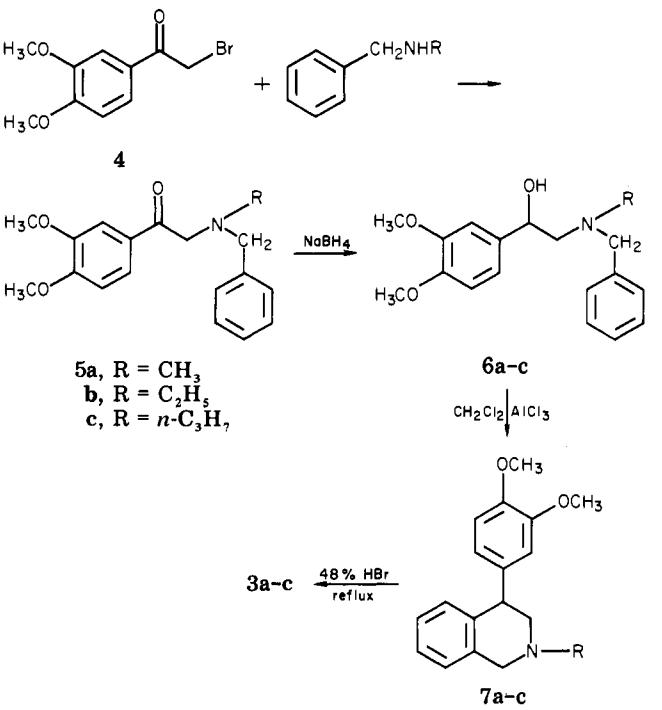


1, $R_{3'} = R_{4'} = OH$
2, $R_{3'} = R_{4'} = H$

possesses clinical utility as an antidepressant.[4] The further modification of adding hydroxy groups was apparently prompted by identification of the 4′-hydroxy metabolite, as well as by the observation that systemic administration of nomifensine produced modifications of motor behavior in rats characteristic of dopamine-like agents.[5,6]

In view of the currently accepted structure–activity relationships for dopamine agonists, it seemed that the presence of the 8-amino group on the isoquinoline nucleus might be superfluous to such an action. It was therefore decided to prepare derivatives of **1** which lacked this functionality. In particular, compounds **3a–c** were of interest. It was also speculated that extension of the *N*-alkyl to an *N*-propyl (**3c**) might result in enhanced activity, in parallel with other series of dopamine agonists.[7-11]

Scheme I



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