concentration dependence in the concentration range 5×10^{-1}–1.25×10^{-2}. The chemical shift values are expressed in parts per million (ppm) downfield (Me$_4$Si).

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Antiallergic Activity of Some 9*H*-Xanthen-9-one-2-carboxylic Acids

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The synthesis and antiallergic activity of a new series of 9*H*-xanthen-9-one-2-carboxylic acids are described. Antiallergic activity was evaluated in the rat passive cutaneous anaphylaxis (PCA) screen. Biological results were analyzed using regression analysis techniques, and the antiallergic activity of the compounds in the series was found to be highly correlated with substituent size.
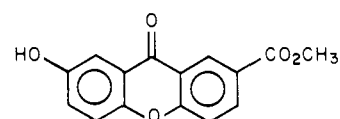
Following the discovery,[1] in 1967, of the novel antiallergic properties of disodium cromoglycate (**1**), research
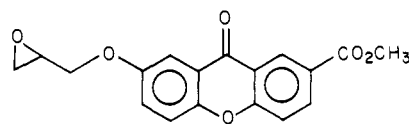

1

2

3, X = S
4, X = O
5, X = S$^+$-O$^-$

6

7
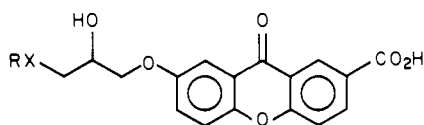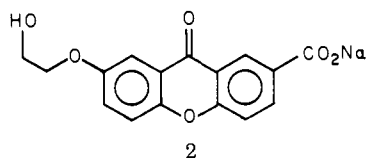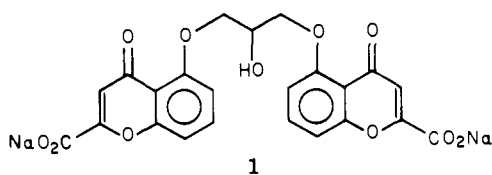
on prophylactic inhibitors of the release of mediators of immediate hypersensitivity has expanded rapidly. Many different classes of chemical compounds have been claimed to exhibit varying degrees of antiallergic activity.[2] Included among these are three reports of the antiallergic activity of 9*H*-xanthen-9-onecarboxylic acids.[3–5] AH7725 (**2**) was the first 9*H*-xanthen-9-one-2-carboxylic acid to undergo clinical investigation.[6] We report the preparation and antiallergic activity of a new series of 9*H*-xanthen-9-one-2-carboxylic acids of general structures **3–5** which have thiomethyl, oxomethyl, and sulfinylmethyl substituents appended to the terminal methylene group of **2**.

Chemistry. Alkylation of methyl 7-hydroxy-9*H*-xanthen-9-one-2-carboxylate (**6**)[3] with epichlorohydrin gave the epoxide **7** which served as a common intermediate to the target compounds **3–5**. Under basic conditions, reaction of the requisite nucleophile (mercaptide or alkoxide) at the terminus of the epoxide, followed by saponification of the ester, provided **3** and **4**. NaIO$_4$ oxidation of the thioether **3** gave the sulfoxide **5**.

Results and Discussion

The antiallergic activity of the 9*H*-xanthen-9-one-2-carboxylic acids reported herein was assessed in the standard rat PCA screen (see Experimental Section for test details). Compounds were initially screened by intraperitoneal (ip) administration at 5 or 10 mg/kg. Representative compounds which provided greater than 50% inhibition of the rat PCA reaction by ip dosing were subsequently tested by oral administration.

The biological results described in Table I present no obvious structure–activity relationships. In order to provide further insight into the factors influencing the antiallergic activity of this series of compounds, the biological data were studied by regression analysis. Biological activities were expressed as log (percent inhibition) instead of the usual molar scale, since antiallergic activity was measured only at a single dose. Expression of the biological activity as log (molecular weight × percent inhibition) was not warranted since a high correlation ($r = 0.99$) existed between this and log (percent inhibition).

Table I. Physical Properties, Yields, Analyses, and Biological Data of Various 9*H*-Xanthen-9-one-2-carboxylic Acids

compd	RX	emp formula	analyses[a]	% yield[b]	recrystn solvent[c]	mp, °C	% inhibn of PCA 5 mg/kg ip	10 mg/kg ip	25 mg/kg po
1								89	
2							100	100	100
3a	C_6H_5S-	$C_{23}H_{18}O_6S$	C, H, S	32	C	193-195	88	100	22
3b	$4-FC_6H_4S-$	$C_{23}H_{17}FO_6S$	C, H, S	52	C	201-203	38		
3c	$4-ClC_6H_4S-$	$C_{23}H_{17}ClO_6S$	C, H, S	70	D	196-199	37		
3d	$3,4-Cl_2C_6H_3S-$	$C_{23}H_{16}Cl_2O_6S$	C, H	52	C	205-210	7		
3e	$4-BrC_6H_4S-$	$C_{23}H_{17}BrO_6S$	C, H, Br	52	C	197-199	14		
3f	$4-CH_3OC_6H_4S-$	$C_{24}H_{20}O_7S$	C, H, S	21	D	183-186	51		
3g	CH_3S-	$C_{18}H_{16}O_6S$	C, H, S	41	C	224-227		71	48
3h	$HOCH_2CH_2S-$	$C_{19}H_{18}O_7S$	C, H	48	E	199-202		100	0
3i	$(CH_3)_2CHS-$	$C_{20}H_{20}O_6S$	C, H, S	51	E	218-222		38	
3j	$(CH_3)_3CS-$	$C_{21}H_{22}O_6S$	C, H, S	49	D, E	228-230		83	
3k	$C_6H_{11}S-$	$C_{23}H_{24}O_6S$	C, H, S	47	E	225-226		39	
3l	1-adamantyl-S-	$C_{27}H_{28}O_6S$	C, H, S	32	E	245-248		16	
3m	$n-C_7H_{15}S-$	$C_{24}H_{28}O_6S$	C, H, S	50	E	226-228		17	
4a	HO-	$C_{17}H_{14}O_7$	C, H	30	B	272-273		78	19
4b	CH_3O-	$C_{18}H_{16}O_7$	C, H	63	A	211-214		29	
4c	$HOCH_2CH_2O-$	$C_{19}H_{18}O_8$	C, H	39	C	207-211		77	
4d	$CH_3OCH_2CH_2O-$	$C_{20}H_{20}O_8$	C, H	35	B	189-191		99	15
4e	CF_3CH_2O-	$C_{19}H_{15}F_3O_7$	C, H, F	53	A	221-223		100	0
5a	C_6H_5SO-	$C_{23}H_{18}O_7S$	C, H, S	32	C	208-215	42		
5b	CH_3SO-	$C_{18}H_{16}O_7S$	C, H, S	58	A	263-265		100	0

[a] All microanalyses are within 0.4% of theoretical values. [b] Percent yields are calculated from 7. [c] A = $CH_3OCH_2CH_2OH$, B = $(CH_3)_2CHOH$, C = C_2H_5OH, D = CH_3CN, E = CH_3OH.

Table II. Parameters Studied by Regression Analyses

	log PCT				
compd	obsd[a]	calcd[b]	dev	log P^c	E_S-R^d	MR-$R^{e,f}$
3a	2.00	1.82	0.18	3.80	-3.82	2.54
3g	1.85	1.88	0.03	2.81	-1.24	0.57
3h	2.00	1.92	0.08	2.32	-2.14	1.21
3i	1.54	1.82	0.28	3.06	-1.71	1.50
3j	1.92	1.85	0.07	2.83	-2.78	1.96
3k	1.59	1.54	0.05	2.95	-2.03	2.67
3l	1.20	1.33	0.13	2.58	-5.04	4.06
3m	1.23	1.22	0.01	2.81	-1.56	3.35
4a	1.89	1.74	0.15	2.33	0.00	0.10
4b	1.46	1.88	0.42	2.13	-1.24	0.57
4c	1.89	1.92	0.03	2.31	-2.14	1.21
4d	2.00	1.76	0.24	2.08	-2.01	1.92
4e	2.00	2.03	0.03	3.14	-2.71	0.96
5b	2.00	1.88	0.12	1.36	-1.24	0.57

[a] Log (percent inhibition of PCA reaction). [b] Equation 1. [c] Octanol-pH 4.0 citrate buffer; $pK_a = 6.1 \pm 0.1$. [d] E_S-R values taken from ref 7 were estimated as follows: E_S for 3l was assumed to be equal to E_S for $(CH_3CH_2)_3C-$; E_S for 3m was assumed to be midway between E_S for $n-C_6H_{13}-$ and $n-C_8H_{17}-$; E_S for 4e was assumed to be approximately equal to E_S for $-CH_2NO_2$. [e] MR-R values were taken from ref 8 or were estimated by additivity rules; for example, MR for $n-C_7H_{15} = MR_{C_2H_5} - MR_H + MR_{n-C_5H_{11}}$. [f] MR-R values scaled by 0.1.

The biological data and physiochemical parameters used in the analysis are given in Table II. Only the alkyl or aryl portion of the side chain was considered, and initially an indicator variable was used to distinguish between R–S, R–O, and R–S(O) (compounds 3–5). It became evident during the course of the analysis that use of the indicator variable was unnecessary.

The "best" equation (eq 1) defining the biological activity has two terms: E_S-R^7 and $(MR-R)^{2.8}$ Both terms are significant at the $F = 0.05$ level. The data set for

$$\log (\% \text{ inhibn}) = 1.74(\pm 0.24) - 0.13(\pm 0.13)E_S-R - 0.064(0.034)(MR-R)^2 \quad (1)$$

$$n = 14; \quad r = 0.795; \quad s = 0.193$$

purposes of analysis was limited to 14 of the 20 compounds reported since compounds 3b–f and 5a were tested at 5 mg/kg ip and it was not possible to accurately extrapolate these results to 10 mg/kg in order to be consistent with the remaining members of the set.

A number of equations were studied (Table III) and, in all cases, the compound where RX = CH_3O (4b) was an outlier (Table II). There is no apparent reason for this compound to behave differently since the CH_3S derivative 3g is well predicted. Inclusion of a third term, MR-R (eq 7), does not improve the correlation. The squared correlation matrix for the terms in the equations is given in Table IV.

Equation 1 suggests that the bulk of the substituent R plays a dominant role in determining the inhibitory ac-

Table III. Equations Developed by Regression Analyses[a]

eq	intercept	log P	$(\log P)^2$	MR-R	$(MR-R)^2$	E_S-R	r	s
1	1.74 (0.24)				-0.064 (0.034)	-0.13 (0.13)	0.795	0.193
2	1.85 (0.36)					0.047 (0.148)	0.195	0.300
3	2.00 (0.26)			0.15 (0.13)			0.594	0.245
4	1.92 (0.17)				-0.42 (0.027)		0.692	0.220
5	1.90 (0.28)			-0.24 (0.18)		-0.12 (0.17)	0.690	0.231
6[b]	1.75 (0.35)			-0.24 (0.41)	-0.097 (0.098)		0.739	0.215
7	1.66 (0.34)			0.13 (0.41)	-0.092 (0.092)	-1.1 (0.15)	0.807	0.198
8	1.88 (0.84)	-0.05 (0.31)					0.093	0.304
9	3.33 (2.38)	-1.23 (1.84)	0.23 (0.35)				0.406	0.291

[a] $n = 14$; numbers in parentheses are 95% confidence limits. [b] Equation 1 statistically better than eq 6.

Table IV. Squared Correlation Matrix

	log P	MR-R	E_S-R
log P	1.0	0.16	0.19
MR-R		1.0	0.53
E_S-R			1.0

tivity. This is indicated by the negative coefficient of the (MR-R)^2 term.[9] The negative sign of the E_S-R term in eq 1 may indicate that an ideal size for R exists.

Although a poor correlation exists between the biological activity and log P (eq 8 and 9), care must be exercised in disposing of this parameter from any future analyses involving antiallergic activity of 9H-xanthen-9-one-carboxylic acids. The measured log P values (Table II) do not adhere to the additive rules developed by Hansch[8] (i.e., there is a small range in measured log P for the series where additivity rules predict a much larger range).

While many of the compounds in this series were reasonably potent by ip dosing, only that compound in which RX = methylthio (**3g**) was orally active. Substitution on the phenyl ring, as in compounds **3b–f**, resulted in reduced activity vs. the unsubstituted derivative **3a**. None of the compounds was more active than **2**.

Experimental Section

General. Melting points were determined with a Thomas-Hoover melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Varian A-60A spectrometer, IR spectra were recorded on a Perkin-Elmer 221 spectrophotometer, and mass spectra were determined with a Varian MAT CH5. The spectral data of all intermediates and final products are in agreement with their structures and are not reported herein. All distillative concentration of solvents was carried out using a rotary evaporator under reduced pressure. 1-Octanol–pH 4.0 buffer partition coefficients were measured by the usual methodology, both phases being analyzed by UV spectrometry.

Methyl 7-(Oxiranylmethoxy)-9H-xanthen-9-one-2-carboxylate (7). A mixture of 20.0 g (0.074 mol) of **6**,[3] 20.5 g (0.15 mol) of anhydrous K_2CO_3, and 100 mL of epichlorohydrin in 500 mL of 2-butanone was heated under reflux for 16 h. The cooled mixture was concentrated and the residue was triturated with petroleum ether (bp 30–60 °C) to remove the remaining solvent and epichlorohydrin. The solid residue was partitioned between an equal volume of $CHCl_3$ and H_2O, and the organic layer was washed with saturated NaCl, dried (MgSO$_4$), and concentrated to give 20.5 g (85%) of **7** which was sufficiently pure to be used in the subsequent steps. A 2.0-g sample was recrystallized from 215 mL of CH_3CN to give an analytically pure sample of **7**: mp 148 °C sinters, melts 159–161 °C. Anal. ($C_{18}H_{14}O_6$) C, H.

7-[[2-Hydroxy-3-(phenylthio)propyl]oxy]-9H-xanthen-9-one-2-carboxylic Acid (3a). To a solution of thiophenol (3.0 mL, 0.029 mol) and commercial NaOCH$_3$ (3.24 g, 0.06 mol) in 200 mL of CH_3OH was added 9.0 g (0.028 mol) of **7**, and the resultant mixture was heated under reflux with magnetic stirring for 0.75 h. Upon cooling, the solid product was collected and washed with CH_3OH to afford 9.0 g of the methyl ester of **3a**: mp 109–115 °C. A sample was recrystallized from CH_3CN to give the analytical sample: mp 112–115 °C. Anal. ($C_{24}H_{20}O_6S$) C, H, S. A solution of the methyl ester (1.0 g, 0.0023 mol) in 5 mL of 10% NaOH and 20 mL of CH_3OH was heated under reflux for 3 h. Upon cooling, a solid separated and the mixture was concentrated to remove most of the CH_3OH. The residue was diluted with 100 mL of H_2O and then with 10 mL of 10% HCl, and the solid product was collected and dried to give 0.86 g of **3a** which was recrystallized from 145 mL of C_2H_5OH to afford 0.42 g of **3a**. Anal. ($C_{23}H_{18}O_6S$) C, H, S. In the same manner, compounds **3b–m** were prepared.

7-[(2,3-Dihydroxypropyl)oxy]-9H-xanthen-9-one-2-carboxylic Acid (4a). A mixture of **7** (6.0 g, 0.018 mol) and KOAc (7.0 g) was heated under reflux in an oil bath for 29 h with magnetic stirring under N$_2$. H_2O (35 mL) was added and the reaction mixture was heated under reflux for 4 days. The resulting solution was cooled, poured onto ice–water, and extracted with EtOAc. The organic layer was washed with 10% NaOH and then

H_2O and dried (MgSO$_4$). Concentration gave 2.58 g (47%) of the methyl ester of **4a**. A solution of this material in 80 mL of CH_3OH and 20 mL of 10% NaOH was heated under reflux for 1 h; upon cooling, the solution was acidified with concentrated HCl, and the product which separated was collected, washed with CH_3OH, and then recrystallized from 350 mL of $(CH_3)_2CHOH$ to give 1.78 g (82%) of **4a**: mp 270–273 °C. Anal. ($C_{17}H_{14}O_7$) C, H.

7-[(2-Hydroxy-3-methoxypropyl)oxy]-9H-xanthen-9-one-2-carboxylic Acid (4b). A solution of 2.5 g (0.0077 mol) of **7** in 10 mL of 10% NaOH and 40 mL of CH_3OH was heated under reflux for 4 h. Concentration of the CH_3OH and dilution of the residual liquid with cold H_2O, followed by the addition of 25 mL of 10% HCl, gave 2.24 g of **4b**. This was recrystallized from 20 mL of $CH_3O(CH_2)_2OH$ to give 1.68 g (63%) of **4b**: mp 211–214 °C. Anal. ($C_{18}H_{16}O_7$) C, H. In a similar manner, **4c** and **4d** were prepared.

7-[[2-Hydroxy-3-(2,2,2-trifluoroethoxy)propyl]oxy]-9H-xanthen-9-one-2-carboxylic Acid (4e). To a mixture of **7** (3.26 g, 0.01 mol) in 20 mL of CF_3CH_2OH and 85 mL of C_6H_6 was added 1.44 g (0.03 mol) of 50% NaH (mineral oil dispersion), and the resultant solution was heated under reflux in a N$_2$ atomsphere for 23 h. Since there was no reaction by TLC, the reaction mixture was concentrated and the residue was treated with 25 mL of CF_3CH_2OH, followed by 1.4 g (0.03 mol) of 50% NaH. This mixture was heated under reflux for 1.5 h, then 7 mL of H_2O was added, and heating was continued for 1.5 h. The reaction mixture was concentrated, the residue was diluted with 75 mL of H_2O and filtered, and the aqueous layer was filtered again and acidified with 20 mL of 10% HCl. The solid product which separated was collected and dried to give 3.32 g of **4e**. Recrystallization from 600 mL of CH_3CN gave 2.19 g (53%) of **4e**: mp 221–223 °C. Anal. ($C_{19}H_{15}F_3O_7$) C, H, F.

7-[[2-Hydroxy-3-(phenylsulfinyl)propyl]oxy]-9H-xanthen-9-one-2-carboxylic Acid (5a). A mixture of the methyl ester of **3a** (5.0 g, 0.011 mol) and NaIO$_4$ (2.58 g, 0.012 mol) in 150 mL of CH_3OH was stirred at ambient temperature for 5 days. An additional 10.0 g (0.046 mol) of NaIO$_4$ was added, and the reaction mixture was allowed to stir for 3 days and then concentrated. The solid residue was treated with a mixture of 200 mL of CH_2Cl_2 and 200 mL of H_2O, and the organic layer was filtered. The filtrate was washed with saturated NaCl solution, dried (MgSO$_4$), and concentrated to give 3.56 g of the methyl ester of **5a** as a mixture of two diastereomers (TLC, 1:1 C_6H_6–EtOAc on silica gel). A solution of 0.95 g (0.0021 mol) of the diastereomeric mixture in 5 mL of 10% NaOH and 25 mL of CH_3OH was heated under reflux for 1 h and, upon cooling, the solution was concentrated to give 0.86 g of a mixture of two diastereomers. Fractional crystallization from 25 mL of CH_3CH_2OH yielded two crops: 0.31 g of a lower melting diastereomer (mp 130 °C dec) and 0.28 g of a higher melting diastereomer (mp 208–215 °C dec), **5a**. Anal. ($C_{23}H_{18}O_7S$) C, H, S.

Biological Methods. Male Sprague–Dawley rats, 150–200 g, were injected subcutaneously with 3000 larvae of *Nippostrongylus brasiliensis* (NB) and 28 days later were reinfected with 3000 larvae. Serum was collected 7–12 days following reinfection and frozen in small aliquots at –40 °C. Adult worms were harvested from the small intestine of rats 8–11 days after infection with larvae. A homogenate was prepared from a suspension of worms in 0.15 M saline. The homogenate was centrifuged at 3000g for 15 min, and the supernatant was carefully removed and frozen at –40 °C. Just prior to use as antigen, the supernatant was adjusted to a concentration of 5 mg of protein per milliliter.

Passive Cutaneous Anaphylaxis (PCA). Five male, Sprague–Dawley rats weighing 250–300 g were used for PCA reactions for each test compound. Nine twofold dilutions of antisera containing homocytotropic antibodies against NB were made 0.15 M saline. Each dilution was injected intradermally at separate sites onto the shaved backs of normal rats, and 48 h later the animals were challenged intravenously with 0.1 mL of antigen (worm extract) mixed with 0.9 mL of a 1% solution of Evans blue dye. The test compounds were administered 15 min ip and 8 min po prior to antigen challenge. The animals were sacrificed 45 min following antigen challenge and skinned, and the area of blueing was measured. The diameter of the sites of reaction was measured in millimeters. The percent inhibition of the PCA reaction was calculated as follows: [(mean diameter

of control) – (mean diameter of experimental)]/(mean diameter of control) × 100. The average mean score of the control animals for 72 experiments was 17.7 mm. Statistical analysis by Student's *t* test showed an inhibition of the PCA reaction of greater than 35% to be statistically significant at $p \leq 0.05$.

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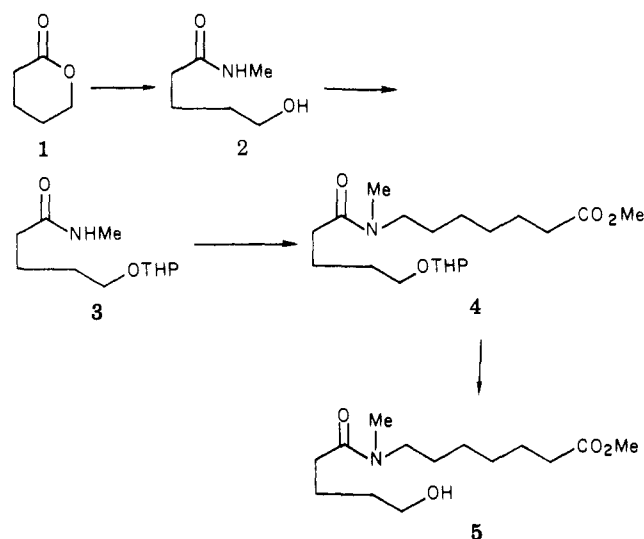(9) W. J. Dunn, III, *Eur. J. Med. Chem.*, **12**, 109 (1977).

Synthesis and Gastric Antisecretory Properties of an 8-Aza- and a 10-Oxa-8,12-secoprostaglandin

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The synthesis and gastric antisecretory properties of two novel 8,12-secoprostaglandin analogues, 8-aza-8,12-secoprostaglandin E_1 and methyl 10-oxa-8,12-secoprostaglandin E_1, are reported.

Recently the synthesis of 11,12-secoprostaglandins[2] and the synthesis of eicosatrienoic acid analogues[3] have been reported. Herein we describe the synthesis and the gastric antisecretory properties of two novel 8,12-secoprostaglandin analogues, 8-aza-8,12-secoprostaglandin E_1 (9) and methyl 10-oxa-8,12-secoprostaglandin E_1 (14).

Chemistry. Reaction of δ-valerolactone 1 with methylamine (Scheme I) afforded the alcohol amide 2. Treatment of 2 with dihydropyran in the presence of an acid yielded the tetrahydropyranylamide 3. Alkylation of the sodium salt of 3 with methyl 7-bromoheptanoate gave the tetrahydropyranyl ester 4. Cleavage of the protecting group of 4 was smoothly accomplished with methanol in the presence of a catalytic amount of *p*-toluenesulfonic acid, affording the alcohol ester 5. Oxidation of 5 with Collins reagent[4] (Scheme II) gave the aldehyde 6. Reaction of 6 with the lithium salt of dimethyl (2-oxoheptyl)-phosphonate afforded the enone 7. Hydride reduction of 7 and subsequent hydrolysis of the alcohol ester 8 yielded the alcohol acid 9.

Reaction of 1,3-propanediol (10) with 8-(methoxy-carbonyloctanoyl) chloride (Scheme III) in the presence of pyridine gave the ester alcohol 11. Oxidation of 11 with Collins reagent[4] afforded the aldehyde 12. Reaction of 12 with the lithium salt of dimethyl (2-oxoheptyl)phosphonate yielded the enone 13. Reduction of 13 with a methanolic sodium borohydride solution afforded the alcohol ester 14.

Biological Activity. Compounds 8, 9, and 14 were found to be active in inhibiting gastric acid secretion. The procedure based on that of Lippmann[5] was used to assess the influence of the seco analogues on gastric acid secretion. These results are summarized in Table I.

Experimental Section

NMR spectra were recorded on a Joelco Model C6OHL spectrometer at 60 MHz with Me$_4$Si as an internal standard. IR spectra were recorded on a Perkin-Elmer Model 337 spectrometer. Where the analyses are represented by symbols only, the values were found within ±0.4% of the theoretical values.

Scheme I

Table I. Effect on Gastric Acid Secretion in Rats^a

	% change	
	volume	total acid
8	−21	−32
9	−25	−25
14	−25	−34
$PGF_{2\alpha}$	−37	−42
PGE_1	−74	−96

^{a} Test dose, 3 mg/kg sc.

N-Methyl-5-hydroxypentanamide (2). Methylamine gas was passed slowly into δ-valerolactone (15 g, 0.15 mol) in 60 mL of dry THF under N$_2$ at 20 °C. After a pH of 9 was obtained, the reaction mixture was stirred at room temperature for 1 h. The solvent was removed in vacuo and the resulting oil was heated [40 °C (0.1 mm)] for 1.5 h to afford 20 g (100%) of 2: bp 130–135