The 5-lipoxygenase reaction (arachidonic acid → 5-hydroperoxy-6,8,11,14-eicosatetraenoic acid) was performed at 30 °C for 5 min in a 200-μL mixture containing 50 mM potassium phosphate buffer at pH 7.4, 2 mM ATP, 2 mM $CaCl_2$, 25 μM [1-^{14}C]arachidonic acid (50 000 cpm), and enzyme. The 12-lipoxygenase reaction (arachidonic acid → 12-hydroperoxy-5,8,10,14-eicosatetraenoic acid) was performed at 30 °C for 5 min in a 200-μL mixture containing 50 mM Tris·HCl buffer at pH 7.4, 25 μM [1-^{14}C]arachidonic acid (50 000 cpm), and enzyme. The prostaglandin endoperoxide synthase reaction (arachidonic acid → prostaglandin H_2) was performed at 24 °C for 2 min in a 200-μL mixture containing 0.1 M Tris·HCl buffer at pH 8.0, 2 μM hematin, 5 mM L-tryptophan, 25 μM [1-^{14}C]arachidonic acid (50 000 cpm), and enzyme. Termination of these enzyme reactions, extraction from the reaction mixtures, separation of substrates and products by thin-layer chromatography, and determination of radioactivity were described in individual papers.[25-27] The enzyme reaction was started by the addition of [1-^{14}C]arachidonic acid dissolved in 5 μL of ethanol. Each flavone compound at varying concentrations was dissolved in 4 μL of ethanol and added to the reaction mixture for 5-min preincubation with enzyme. Under the standard conditions the coefficient of intraassay variation was about 5.2% (n = 10). The intraassay variation of inhibitory effect of flavone compounds was determined with cirsiliol (**1a**) as a representative inhibitor. The coefficient of intraassay variation was 4.2% (n = 7) with 30 nM cirsiliol and 8.0% (n = 8) at 100 nM.

Registry No. **1a**, 34334-69-5; **1b**, 103776-90-5; **1c**, 102508-37-2; **1d**, 103776-91-6; **1e**, 103776-92-7; **1f**, 103776-93-8; **1g**, 103776-94-9; **1h**, 98892-90-1; **1i**, 103776-95-0; **1j**, 103776-96-1; **1k**, 102508-39-4; **2h**, 102508-35-0; **3a**, 10568-41-9; **3h**, 102508-36-1; **4h**, 102508-38-3; **5b**, 103776-66-5; **5c**, 103776-67-6; **5d**, 103776-68-7; **5e**, 103776-69-8; **5f**, 103776-70-1; **5g**, 103776-71-2; **5h**, 103776-72-3; **5i**, 103776-73-4; **5j**, 103776-74-5; **5k**, 103776-75-6; **6a**, 51145-79-0; **6b**, 103776-58-5; **6c**, 103776-59-6; **6d**, 103776-60-9; **6e**, 98892-88-7; **6f**, 103776-61-0; **6g**, 103776-62-1; **6h**, 98892-89-8; **6i**, 103776-63-2; **6j**, 103776-64-3; **6k**, 103776-65-4; **7a**, 97389-88-3; **7b**, 103776-80-3; **7c**, 103776-81-4; **7d**, 103776-82-5; **7e**, 98892-91-2; **7f**, 103776-83-6; **7g**, 103776-84-7; **7h**, 103776-85-8; **7i**, 103776-86-9; **7j**, 103776-87-0; **7k**, 103776-88-1; **8h**, 103776-76-7; **9a**, 90126-12-8; **9h**, 103776-77-8; **10h**, 103776-78-9; **11h**, 103776-79-0; **12**, 6962-57-8; **13a**, 22248-14-2; **13b**, 103777-33-9; **13c**, 103777-34-0; **13d**, 103777-35-1; **13e**, 98892-84-3; **13f**, 103777-36-2; **13g**, 103777-37-3; **13h**, 103777-38-4; **13i**, 103777-39-5; **13j**, 103777-40-8; **13k**, 103777-41-9; **14a**, 55274-37-8; **14a** (benzoate), 103777-48-6; **14b**, 103776-97-2; **14b** (benzoate), 103777-49-7; **14c**, 103776-98-3; **14c** (benzoate), 103777-50-0; **14e**, 98892-86-5; **14e** (benzoate), 103793-61-9; **14f**, 103776-99-4; **14f** (benzoate), 103777-51-1; **14g**, 103777-00-0; **14g** (benzoate), 103777-52-2; **14h**, 103777-01-1; **14h** (benzoate), 103777-53-3; **14i**, 103777-02-2; **14i** (benzoate), 103793-62-0; **14j**, 103777-03-3; **14j** (benzoate), 103777-54-4; **14k**, 103777-04-4; **14k** (benzoate), 103777-55-5; **15a**, 51145-78-9; **15b**, 103777-09-9; **15c**, 103777-10-2; **15d**, 103777-11-3; **15e**, 98892-87-6; **15f**, 103777-12-4; **15g**, 103777-13-5; **15h**, 103777-14-6; **15i**, 103777-15-7; **15j**, 103777-16-8; **15k**, 103777-17-9; **16**, 27181-96-0; **17**, 103777-42-0; **18h**, 103777-43-1; **19h**, 103777-05-5; **19h** (benzoate), 103777-56-6; **20h**, 103777-28-2; **21h**, 103776-89-2; **22**, 103777-60-2; **23b**, 103777-18-0; **23c**, 103777-19-1; **23d**, 103777-20-4; **23e**, 103777-21-5; **23f**, 103777-22-6; **23g**, 103777-23-7; **23h**, 103777-24-8; **23i**, 103777-25-9; **23j**, 103777-26-0; **23k**, 103777-27-1; **24a**, 103777-29-3; **24h**, 103777-30-6; **25**, 103777-61-3; **26**, 7499-99-2; **27a**, 7507-98-4; **27h**, 103777-44-2; **28a**, 103777-06-6; **28a** (benzoate), 103777-57-7; **28h**, 103777-07-7; **28h** (benzoate), 103777-58-8; **29h**, 103777-31-7; **30**, 103777-45-3; **31h**, 103777-46-4; **32h**, 103777-47-5; **33h**, 103777-08-8; **33h** (benzoate), 103777-59-9; **34h**, 103777-32-8; $H_3C(CH_2)_4I$, 628-17-1; $ICH_2CH_2CH(CH_3)_2$, 541-28-6; $H_3C(CH_2)_5I$, 638-45-9; $H_3C(CH_2)_7I$, 629-27-6; $H_3C(CH_2)_9I$, 2050-77-3; $H_3C(CH_2)_{11}I$, 4292-19-7; $H_3C(CH_2)_{13}I$, 19218-94-1; $H_3C(CH_2)_{15}I$, 544-77-4; $H_3C(CH_2)_{17}I$, 629-93-6; 4-(benzyloxy)-6-hydroxy-2,3-dimethoxyacetophenone, 25892-95-9; 3,4-bis(benzyloxy)benzoyl chloride, 1486-54-0; arachidonate 5-lipoxygenase, 80619-02-9.

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Studies on 1,2,3-Triazoles.[1] 13. (Piperazinylalkoxy)[1]benzopyrano[2,3-*d*]-1,2,3-triazol-9(1*H*)-ones with Combined H_1-Antihistamine and Mast Cell Stabilizing Properties

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Received March 18, 1986

Several *N*-benzylpiperazino derivatives of [1]benzopyrano[2,3-*d*]-1,2,3-triazol-9(1*H*)-one and its 5-methyl homologue have been prepared and evaluated for H_1-antihistamine activity on guinea pig ileum. The most potent compounds were also evaluated for their ability to stabilize mast cells in the rat passive peritoneal anaphylaxis (PPA) system and were shown to inhibit histamine release at concentrations below those required to inhibit extravasation, suggesting that this might be relevant to their antianaphylactic activity in this system. The compound tested with the most potent H_1-antihistamine activity was 6-[3-[4-(4-chlorobenzyl)-1-piperazinyl]propoxy][1]benzopyrano[2,3-*d*]-1,2,3-triazol-9(1*H*)-one, **28**, which had a pA_2 of 9.1 against histamine on guinea pig ileum, comparable to that of mepyramine, and inhibited histamine release in the rat PPA system with an IC_{50} value of 5.4×10^{-6} M.

In an earlier publication,[2] we reported the synthesis and biological evaluation of a small range-finding series of nitrocoumarin derivatives that combined potent H_1-antihistamine activity with mast cell stabilization. From this series, compound **1** was the most potent of the compounds studied. Subsequently, we have identified other potent mast cell stabilizing compounds based on [1]-benzopyrano[2,3-*d*]-1,2,3-triazol-9(1*H*)-one (**2**)[3,4] and the related naphtho[2,3-*d*]-1,2,3-triazole **3**,[5] and we have now

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(2) Buckle, D. R.; Outred, D. J.; Smith, H.; Spicer, B. A. *J. Med. Chem.* **1984**, *27*, 1452.
(3) Buckle, D. R.; Outred, D. J.; Rockell, C. J. M. *J. Heterocycl. Chem.* **1981**, *18*, 1117.
(4) Buckle, D. R.; Outred, D. J.; Rockell, C. J. M.; Smith, H.; Spicer, B. A. *J. Med. Chem.* **1983**, *26*, 251.
(5) Buckle, D. R.; Smith, H.; Spicer, B. A.; Tedder, J. M. *J. Med. Chem.* **1983**, *26*, 714.

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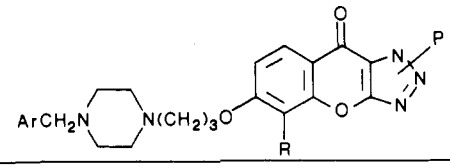
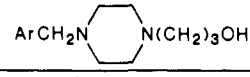
Table I. (Piperazinylalkoxy)[1]benzopyrano[2,3-*d*]-1,2,3-triazol-9-ones



no.	Ar	R	P	mp, °C	formula	recrystn solvent	anal.	yield, %	method[a]
15a	4-MePh	Me	1-(4-MeOPhCH$_2$)	150–152	$C_{33}H_{37}N_5O_4$	MeOH	C, H, N	83	A
15b	4-MePh	Me	2-(4-MeOPhCH$_2$)	125–127	$C_{33}H_{37}N_5O_4$	MeOH	C, H, N		A
16a	4-MeOPh	Me	1-(4-MeOPhCH$_2$)	157–158	$C_{33}H_{37}N_5O_5$	MeOH–$CHCl_3$	C, H, N	97	A
16b	4-MeOPh	Me	2-(4-MeOPhCH$_2$)	138–139	$C_{33}H_{37}N_5O_5$	MeOH–$CHCl_3$	C, H, N		A
17a	4-ClPh	Me	1-(4-MeOPhCH$_2$)	152–155	$C_{32}H_{34}ClN_5O_4$	MeOH–$CHCl_3$	C, H, N	89	A
17b	4-ClPh	Me	2-(4-MeOPhCH$_2$)	142–143	$C_{32}H_{34}ClN_5O_4$	MeOH–$CHCl_3$	C, H, N		A
18a	3-ClPh	Me	1-(4-MeOPhCH$_2$)	150–151	$C_{32}H_{34}ClN_5O_4 \cdot H_2O$	EtOH–$CHCl_3$	C, H, N, Cl	57	A
18b	3-ClPh	Me	2-(4-MeOPhCH$_2$)	144–150	$C_{32}H_{34}ClN_5O_4 \cdot 0.5H_2O$	EtOH–$CHCl_3$	C, H, N, Cl		A
19a	2-ClPh	Me	1-(4-MeOPhCH$_2$)	163–166	$C_{32}H_{34}ClN_5O_4$	EtOH–$CHCl_3$	C, H, N	90	A
19b	2-ClPh	Me	2-(4-MeOPhCH$_2$)	83–85	$C_{32}H_{34}ClN_5O_4$	EtOH	C, H, N		A
20a	2-pyr	Me	1-(4-MeOPhCH$_2$)	145–152 dec	$C_{31}H_{34}N_6O_4$		M^+ 554.2652	95	A
20b	2-pyr	Me	2-(4-MeOPhCH$_2$)	*b*	$C_{31}H_{34}N_6O_4$				A
21a	4-ClPh	H	1-(4-MeOPhCH$_2$)	151–152	$C_{31}H_{32}ClN_5O_4$	EtOH	C, H, N	65	A
21b	4-ClPh	H	2-(4-MeOPhCH$_2$)	130–131	$C_{31}H_{32}ClN_5O_4 \cdot 0.5H_2O$	EtOH	H, N, C[c]		A
22	4-MePh	Me	H	224–226 dec	$C_{25}H_{29}N_5O_3 \cdot 0.5H_2O$	*d*	C, H, N	70	B
23	4-MeOPh	Me	H	234–237 dec	$C_{25}H_{29}N_5O_4 \cdot H_2O$	*d*	C, H, N	92	B
24	4-ClPh	Me	H	ca. 134[e]	$C_{24}H_{26}ClN_5O_3 \cdot CF_3CO_2H \cdot 0.5H_2O$	MeOH	C, H, N	75[f]	B
25	3-ClPh	Me	H	130–135 dec	$C_{24}H_{26}ClN_5O_3 \cdot H_2O$	EtOH–H_2O	C, H, N	68	B
26	2-ClPh	Me	H	ca. 134[g]	$C_{24}H_{26}ClN_5O_3 \cdot CF_3CO_2H \cdot 0.5H_2O$	MeOH	C, H, N	67	B
27	2-pyr	Me	H	236–237	$C_{23}H_{26}N_6O_3$	MeOH	C, H, N	45	B
28	4-ClPh	H	H	215–216 dec	$C_{23}H_{24}ClN_5O_3$	EtOH–DMF	C, H, Cl, N	38[h]	B
32	4-ClPh	H	2-(Ph_3C)	182	$C_{42}H_{38}ClN_5O_3 \cdot 0.5H_2O$	EtOH–$CHCl_3$	C, H, N	63	A
33	4-ClPh	Me	2-(Ph_3C)	foam	$C_{43}H_{40}ClN_5O_3 \cdot 0.5H_2O$		C, H, N	65	A

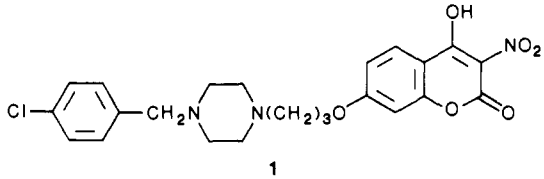
[a] See text and Experimental Section. [b] Obtained only as an isomeric mixture containing 16% of the N-1 isomer. [c] C: calcd, 63.85; found, 63.4. [d] Triturated with hot AcOEt. [e] Free base mp 232–235 °C dec. [f] 75% from **33**. [g] Free base mp 248–250 °C dec. [h] 94% from **32**.

Table II. Piperazinylpropanol Intermediates

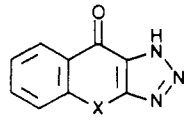


no.	Ar	mp, °C	recrystn solvent	formula	anal.	yield, %
5	4-MePh	62–63	petroleum ether (bp 40–60 °C)	$C_{15}H_{24}N_2O$	C, H, N	94
6	4-MeOPh	58–59	petroleum ether (bp 40–60 °C)	$C_{15}H_{24}N_2O_2$	C, H, N	100
7	4-ClPh	251–253	EtOH	$C_{14}H_{21}ClN_2O \cdot 2HCl$	C, H, Cl, N	75
8	3-ClPh	254–255	EtOH	$C_{14}H_{21}ClN_2O \cdot 2HCl$	C, H, N	88
9	2-ClPh	245–246	EtOH	$C_{14}H_{21}ClN_2O \cdot 2HCl$	C, H, Cl, N	37
10	2-pyr	oil		$C_{13}H_{21}N_3O$		47

extended the initial range-finding exercise to the benzopyranotriazolones **2**, which are the more accessible of the two aforementioned triazolic systems.



1



2: X = O
3: X = CO

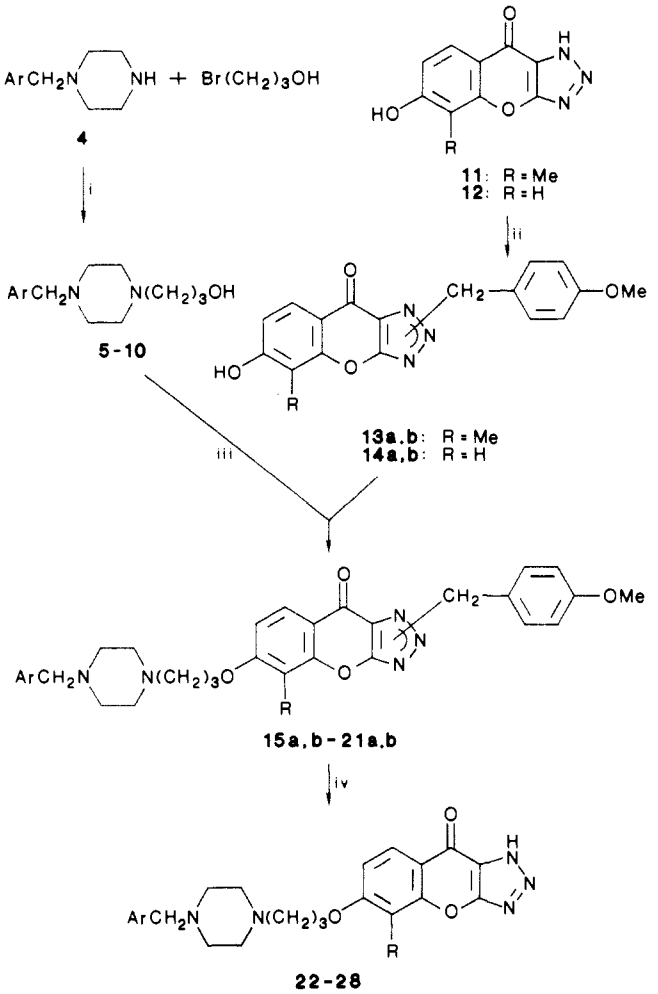
Chemistry

The [(piperazinopropyl)oxy]benzopyranotriazolones **22–28** (Table I) required in this work were readily prepared from the two general key intemediates **4** and **11** or **12** by using the twofold convergent synthesis outlined in Scheme I. The appropriate monobenzylated piperazines **4** were conveniently obtained by use of essentially the same procedure as that previously described by Protiva et al.[6,7] and were alkylated with 3-bromopropan-1-ol to give the corresponding piperazinopropanols **5–10** of Table II.

General routes to simple benzopyranotriazolones **2** have been previously described,[3,4] and these lend themselves to the facile synthesis of suitably hydroxylated derivatives **11** and **12** by the dealkylation of their methyl ethers.[4] Direct alkylation of **11** or **12**, however, leads exclusively to the *N*-substituted derivatives, a finding that parallels

(6) Protiva, M.; Rajsner, M.; Trcka, V.; Vanecek, M.; Nemec, J.; Sedivy, Z. *Collect. Czech. Chem. Commun.* **1975**, *40*, 3904.
(7) Vejdelek, Z. J.; Nemec, J.; Sedivy, Z.; Tuma, L.; Protiva, M. *Collect. Czech. Chem. Commun.* **1974**, *39*, 2276.

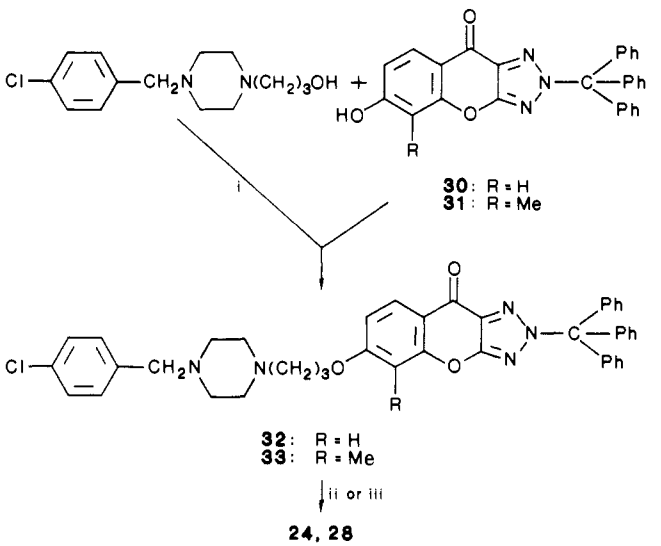
Scheme I[a]



[a] a, N-1 substituted; b, N-2 substituted. Reagents: i, K_2CO_3, butanone; ii, K_2CO_3, 4-MeOPhCH$_2$Cl, DMF; iii, $EtO_2CN{=}NCO_2Et$, Ph_3P, THF; iv, CF_3CO_2H, Δ.

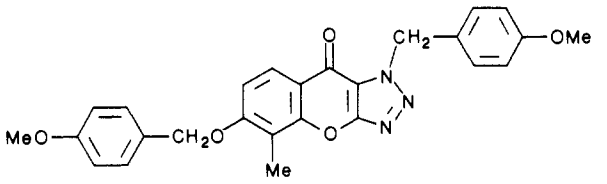
that with monocyclic triazoles of a similar type,[8] thus necessitating protection of the triazole ring prior to alkylation at the phenolic group. Earlier work[9] immediately suggested protection with the 4-methoxybenzyl group, which can be readily cleaved, after coupling, under relatively mild conditions. Thus, alkylation of **11** or **12** with 4-methoxybenzyl chloride under alkaline conditions afforded essentially a 1:1 mixture of the N-1 isomer and a second isomer, believed to be the N-2 derivative from its ^{1}H NMR spectrum and by comparison with similar monocyclic systems.[8] Small amounts of the N-1 and N-2 O,N-disubstituted compounds and trace quantities of the supposed N-3 isomer were also isolated. Unambiguous assignment of the N-1 isomer is possible from the low-field benzylic proton signals (δ 5.89) in its ^{1}H NMR spectrum, induced by the deshielding effect of the neighboring carbonyl group. The N-2 and N-3 isomers, however, have indistinguishable benzylic signals (δ 5.70). That one or other of these isomers is not an *O*-benzyl derivative is evident from the lower chemical shift (δ 5.13) typical for these derivatives (cf. **34**). Furthermore, methoxybenzylation of the *O*-mesylate[4] of compound **11** and subsequent alkaline hydrolysis results in compounds identical

Scheme II[a]



[a] Reagents: i, $EtO_2CN{=}NCO_2Et$, Ph_3P, THF; ii, CF_3CO_2H, Δ; iii, AcOH, HCl, Δ.

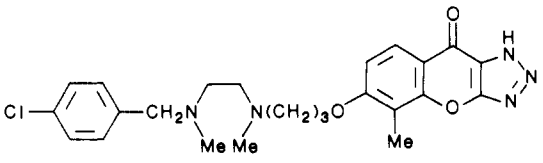
with those obtained from the direct methoxybenzylation of **11** itself.[10]



34

The major N-1 and N-2 isomers of both **12** and **14** were easily separable chromatographically from O,N-dialkylated products and from the trace impurities of the N-3 isomer but were less readily separable from each other. Small quantities were separated for characterization purposes, however, although the coupling reaction with the piperazinopropanols **5–10** was generally effected on the mixed isomers. The coupling itself was accomplished in good yield by using diethyl azodicarboxylate and triphenylphosphine[11] (method A) and led to the mixed isomers **15–21** (Table I), which were usually separated by taking advantage of the greater solubility of the N-2 isomers in ethanol. Deprotection of either isomer with refluxing trifluoroacetic acid (method B) furnished reasonable yields of the required N-unsubstituted triazoles **22–28** of Table I.

The ring-opened derivative **29** was prepared from the appropriate diaminopropanol precursor by using the same procedure as that shown in Scheme I.



29

It has previously been demonstrated that tritylation of a monocyclic triazole gave essentially the N-2 substituted derivative along with only trace quantities of the N-1 isomer,[8] and we have applied the same concept to the tricyclic precursors **11** and **12**. In this way only a single

(8) Buckle, D. R.; Rockell, C. J. M.; Oliver, R. S. *J. Heterocycl. Chem.* **1982**, *19*, 1147.
(9) Buckle, D. R.; Rockell, C. J. M. *J. Chem. Soc., Perkin Trans. 1* **1982**, 627.
(10) Unpublished results.
(11) Mitzunobu, O. *Synthesis*, **1981**, 1.

Table III. Rat Passive Peritoneal Anaphylaxis Data and H_1-Antihistamine Activities

compound	H_1-antihistamine act.: pA_2 on guinea pig ileum[a]	rat PPA, inhibn of release of histamine and extravasation: IC_{50}, M (95% confidence limits)[b]	
		histamine	extravasation
mepyramine	9.1	$>2 \times 10^{-4}$	2.9×10^{-5} (1.6×10^{-5} to 6.1×10^{-5})
ketotifen	9.5	$>2 \times 10^{-4}$	9.1×10^{-6} (4.0×10^{-6} to 2.3×10^{-5})
DSCG	inactive	7.4×10^{-7} (4.0×10^{-7} to 1.2×10^{-6})	5.8×10^{-6} (2.5×10^{-6} to 2.6×10^{-5})
22	7.8	8.9×10^{-7} (1.0×10^{-8} to 2.5×10^{-6})	$>2 \times 10^{-5}$
23	7.2		
24	8.8	8.4×10^{-7} (5.3×10^{-8} to 2.1×10^{-6})	5.5×10^{-5} (estimated)
25	8.4	1.0×10^{-6} (estimated)	$>2 \times 10^{-5}$
26	8.4	2.3×10^{-6} (9.9×10^{-7} to 4.5×10^{-6})	1.0×10^{-5} (3.9×10^{-6} to 6.6×10^{-5})
27	7.8	1.0×10^{-7} (estimated)	$>2 \times 10^{-5}$
28	9.1	5.4×10^{-6} (1.9×10^{-6} to 1.2×10^{-5})	3.1×10^{-5} (1.7×10^{-5} to 6.2×10^{-5})
29	7.1		

[a] The pA_2 value is the negative logarithm of the concentration of the compound producing a twofold shift to the right of the histamine dose–response curve as measured on the guinea pig ileum. [b] This is the concentration of the compound in 6 mL of fluid injected intraperitoneally that would reduce the concentrations of histamine and extravasated dye in the peritoneal fluids, 5 min later, by 50%.

N-2 isomer, **30** or **31** (Scheme II), was isolated in each case, which considerably facilitated the isolation and characterization of the subsequent coupled products **32** and **33**. Deprotection of these tritylated intermediates was rapidly effected with hot trifluoroacetic acid but could also be conveniently carried out by heating in glacial acetic acid containing small quantities of concentrated hydrochloric acid. In general this repesents a better alternative to the 4-methoxybenzyl procedure, in this instance because of the absence of the isomer problem and the more ready cleavage of the trityl protecting group. As a general triazole protecting group, however, the 4-methoxybenzyl moiety is still to be preferred because of the greater number of transformations that can be performed in its presence.[9]

Results and Discussion

Having demonstrated the feasibility of synthesizing compounds having both mast cell stabilizing and H_1-antihistamine activity in a series of 3-nitro-4-hydroxycoumarins,[2] we were interested in extending this study to similar compounds in which the mast cell stabilization was imparted by the [1]benzopyrano[2,3-*d*]-1,2,3-triazol-9-(1*H*)-one nucleus. As a basis for this extension, we selected the optimal four-atom chain length (three carbon atoms and one oxygen atom) separating the piperazine ring from the mast cell stabilizing fragment found in the earlier study,[2] and concentrated our modifications on the substituents of the benzyl group of the piperazine moiety.

All compounds were assayed first for their H_1-antihistamine activity (Table III), and the most potent compounds were then screened for their ability to stabilize mast cells by using rat passive peritoneal anaphylaxis (PPA). With the exception of the 4-methoxy derivative **23** and the ring-opened compound **29**, all compounds were H_1-antihistamines with potencies similar to or approaching that of mepyramine. The most potent in this respect were the two 4-chloro derivatives, **24** and its nor-methyl homologue **28**. Indeed, the chlorinated derivatives in general (**24–26**, **28**) were more potent than those containing either a methyl or a methoxyl group or where the benzenoid ring was replaced by 2-pyridyl (compounds **22**, **23**, and **27**, respectively). Compound **29**, the ring-opened analogue of **24**, the second most potent compound, was noticeably less potent although still an antihistamine.

Those compounds that were evaluated in the rat PPA screen (Table III) were all inhibitors of histamine release with potencies approaching that of disodium cromoglycate (DSCG). Since the inhibition of histamine release occurs at lower concentrations than those affecting extravasation, it is likely that mast cell stabilization is relevant to the antianaphylactic activity of these compounds in vivo, in this system.

Compound **28**, BRL 28390, has been selected for further pharmacological study, the results of which will be published elsewhere.

Experimental Section

Melting points were determined with a Büchi melting point apparatus and are recorded uncorrected. The structures of all compounds were consistent with their IR and ^1H NMR spectra, which were determined with a Perkin-Elmer 197 spectrophotometer and a Varian EM 390 90-MHz spectrometer, respectively. Mass spectral data was obtained from a VG-micromass 70-70F with use of electron impact ionization techniques. Where represented by elemental symbols, the analyses of these elements fall within ±0.4% of the calculated values.

1-(Arylmethyl)piperazines. These were prepared by the procedure of Protiva et al.[6,7] and where known had physical characteristics in agreement with the literature values. The 2-pyridylmethyl derivative was isolated as an oil by this procedure and was used without further purification.

3-[4-(Arylmethyl)piperazin-1-yl]propan-1-ols (5–10). General Procedure. Anhydrous K_2CO_3 (20.7 g, 0.15 mol) was added to a solution of the 1-(arylmethyl)piperazine (0.1 mol) and 3-bromopropan-1-ol (13.8 g, 0.1 mol) in dry butanone (200 mL), and the mixture was stirred at reflux for 3–5 h. Filtration of the cooled mixture and evaporation of the filtrate in vacuo gave the crude product as an oil, which was purified by chromatography on silica gel with $CHCl_3$ as the eluant. Recrystallization of the isolated material or of its dihydrochloride gave the data shown in Table II.

1-Chloro-3-(4-chlorobenzyl)-3-azabutane. A mixture of 2-(methylamino)ethanol (21.2 g, 0.283 mol), 4-chlorobenzyl chloride (45.5 g, 0.283 mol), and xylene (100 mL) was stirred at reflux for 7 h and allowed to cool overnight when the mass crystallized. Water and Et_2O were added, the phases were separated, and the aqueous phase was washed with Et_2O before being made strongly alkaline with NaOH solution. The product was extracted into ether, and the extracts were washed with H_2O and then dried ($MgSO_4$) and evaporated to a pale orange oil. Distillation then gave 30.9 g (55%) of 3-(4-chlorobenzyl)-3-azabutan-1-ol, bp 125–126 °C (0.3 mm) as a colorless oil, which was used without further purification.

A solution of this alcohol (20.0 g, 0.1 mol) in $CHCl_3$ (50 mL) was treated with $SOCl_2$ (25 g, 15.2 mL, 0.21 mol) with ice cooling such that $T \leq 23$ °C, and the mixture was stirred overnight at ambient temperature and then gently refluxed for 2 h. The bulk of the $CHCl_3$ was removed in vacuo, dry Et_2O (50 mL) was added, and the white crystalline solid was filtered off and washed well with Et_2O to give 24.15 g (95%) of the hydrochloride of the title compound of mp 177–178 °C. Recrystallization from EtOH raised the melting point to 181–182 °C. Anal. ($C_{10}H_{13}Cl_2N$·HCl) C, H, N, Cl.

7-(4-Chlorobenzyl)-4-methyl-4,7-diazaoctan-1-ol. 1-Chloro-3-(4-chlorobenzyl)-3-azabutane hydrochloride (24.0 g, 94 mmol) was added to a 40% solution of $MeNH_2$ (36 g, 0.47 mol),

and the mixture was stirred at room temperature for 1 h and then at 82 °C for 4 h. Solid NaOH (15.3 g) was added to the cooled mixture, and the product was extracted into Et_2O, dried, ($MgSO_4$), and evaporated to give a clear oil. Distillation afforded 8.16 g (41%) of 2-(4-chlorobenzyl)-2,5-diazahexane of bp 123 °C (0.3 mm), which was not further purified.

Alkylation of this amine (8.16 g, 38.4 mmol) with 3-bromopropan-1-ol (5.35 g, 38.4 mmol) as described in the general method for piperazines above gave 5.95 g (57%) of the title compound after chromatography on silica gel eluting with $CHCl_3$–MeOH (95:5). The dihydrochloride had mp (EtOH) 206–208 °C. Anal. ($C_{14}H_{23}ClN_2O\cdot 2HCl$) C, H, N, Cl.

4-Methoxybenzylation of 6-Hydroxy-5-methyl[1]benzopyrano[2,3-*d*]-1,2,3-triazol-9(1*H*)-one (11). Anhydrous K_2CO_3 (2.70 g, 19 mmol) was added to a solution of the triazole **11**[4] (2.80 g, 13 mmol) and 4-methoxybenzyl chloride (2.00 g, 13 mmol) in dry DMF (20 mL), and the mixture was stirred for 24 h at room temperature. The solvent was removed in vacuo and the residue partitioned between H_2O and AcOEt. After separation of the phases, the organic phase was washed with H_2O, dried ($MgSO_4$), and evaporated to give a crude yellow solid. Chromatography on silica gel eluting with $CHCl_3$ gave a small quantity of fast-running material (O,N-dialkylated material) from which pure 1-(4-methoxybenzyl)-6-(4-methoxybenzyloxy)-5-methyl[1]-benzopyrano[2,3-*d*]-1,2,3-triazol-9(1*H*)-one (**34**) could be isolated: mp ($CHCl_3$) 226–228 °C; IR ν_{max} (mull) 1510, 1530, 1610, 1665 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.40 (3 H, s, aromatic CH_3), 3.72 (3 H, s, OCH_3), 3.78 (3 H, s, OCH_3), 5.13 (2 H, s, OCH_2), 5.88 (2 H, s, NCH_2), 6.81 (2 H, d, J = 9 Hz), 7.03 (1 H, d, J = 9 Hz), 7.35 (2 H, d, J = 9 Hz), 7.48 (2 H, d, J = 9 Hz), 8.13 (1 H, d, J = 9 Hz); M^+ ($C_{26}H_{23}N_3O_5$) 457.1653. Anal. ($C_{26}H_{23}N_3O_5$) C, H, N.

Further chromatography gave 3.38 g (77%) of a 1:1 mixture of the N-1 and N-2 isomers **13a** and **13b**, respectively, a small sample of which was separated by further chromatography to give **13a**: mp (EtOH) 257–258 °C dec; IR ν_{max} (mull) 1615, 1660, 3100 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.30 (3 H, s, aromatic CH_3), 3.75 (3 H, s, OCH_3), 5.89 (2 H, s, CH_2), 7.03 (1 H, d, J = 9 Hz, C-7 H), 7.13 (4 H, AB q, J = 9 Hz, $\Delta\nu$ = 42 Hz), 7.92 (1 H, d, J = 9 Hz, C-8 H), 11.0 (1 H, br exchangeable, OH). Anal. ($C_{18}H_{15}N_3O_4$) C, H, N. The separation gave also **13b**: mp (EtOH) 264–265 °C dec; IR ν_{max} (mull) 1605, 1670, 3215 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.25 (3 H, s, aromatic CH_3), 3.74 (3 H, s, OCH_3), 5.70 (2 H, s, CH_2), 6.94 (1 H, d, J = 9 Hz, C-7 H), 7.13 (4 H, AB q, J = 9 Hz, $\Delta\nu$ = 40 Hz), 7.88 (1 H, d, J = 9 Hz, C-8 H), 10.90 (1 H, exchangeable s, OH). Anal. ($C_{18}H_{15}N_3O_4$) C, H, N.

Continued elution with $CHCl_3$ then afforded the N-3 isomer: 0.13 g (3%), mp (EtOH) 224–227 °C; IR ν_{max} (mull) 1515, 1540, 1580, 1612, 1660, 1675 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.25 (3 H, s, aromatic CH_3), 3.73 (3 H, s, OCH_3), 5.70 (2 H, s, CH_2), 6.92 (1 H, d, J = 9 Hz, C-7 H), 7.70 (4 H, AB q, J = 9 Hz, $\Delta\nu$ = 37 Hz), 7.92 (1 H, d, J = 9 Hz, C-8 H), 10.9 (1 H, br exchangeable, OH); M^+ ($C_{18}H_{15}N_3O_4$) 337.1034. Anal. ($C_{18}H_{15}N_3O_4$) C, H, N.

4-Methoxybenzylation of 6-Hydroxy[1]benzopyrano[2,3-*d*]-1,2,3-triazol-9(1*H*)-one (12). A similar alkylation of **12**[4] gave 89% of a 1:1 mixture of N-1 and N-2 isomers **14a** and **14b**, respectively, from which a small sample of pure **14a** was isolated by further chromatography on silica gel eluting with $CHCl_3$ to give material of mp (EtOH) 230–231 °C: IR ν_{max} (mull) 1605, 1640, 1660 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 3.74 (3 H, s, OCH_3), 5.90 (2 H, s, CH_2), 6.93 (2 H, m, C-5 H and C-7 H), 7.13 (4 H, AB q, J = 9 Hz, $\Delta\nu$ = 33 Hz), 8.05 (1 H, d, J = 9 Hz, C-8 H), 11.14 (1 H, br exchangeable s, OH). Anal. ($C_{17}H_{13}N_3O_4$) C, H, N.

6-Hydroxy-2-(triphenylmethyl)[1]benzopyrano[2,3-*d*]-1,2,3-triazol-9(2*H*)-one (30). Alkylation of **12**[4] (0.865 g, 42.5 mmol) with triphenylmethyl chloride (1.23 g, 44 mmol) in a manner similar to that described above, except that a further 0.62 g of the chloride was added after 24 h, gave 1.17 g (62%) of pure **30** after chromatography on silica eluting with $CHCl_3$. The pure material had mp 259–260 °C dec: IR ν_{max} (mull) 1550, 1615, 1665, 2600–3400 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 7.07 (17 H, m, C-5 H, C-7 H and Ph groups), 8.02 (1 H, d, J = 9 Hz, C-8 H), 11.06 (1 H, br exchangeable s, OH). Anal. ($C_{28}H_{19}N_3O_3$) C, H, N.

6-Hydroxy-5-methyl-2-(triphenylmethyl)[1]benzopyrano[2,3-*d*]-1,2,3-triazol-9(2*H*)-one (31). This compound was prepared in 59% yield from compound **11**[4] in a manner analogous to that described above, and after chromatography and recrystallization it had mp ($MeOH$–$CHCl_3$) 282 °C dec: IR ν_{max} (mull) 1545, 1590, 1598, 1650, 3260 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.25 (3 H, s, CH_3), 6.97 (1 H, d, J = 9 Hz, C-7 H), 7.22 (15 H, m, Ph groups), 7.90 (1 H, d, J = 9 Hz, C-8 H), 11.00 (1 H, sharp exchangeable s, OH). Anal. ($C_{29}H_{21}N_3O_3$) C, H, N.

6-[3-[4-(2-Chlorobenzyl)-1-piperazinyl]propoxy]-*N*-(4-methoxybenzyl)-5-methyl[1]benzopyrano[2,3-*d*]-1,2,3-triazol-9-ones (19a,b). Method A. Triphenylphosphine (0.79 g, 3 mmol) was added to a stirred solution of the triazole **13** (0.67 g, 2 mmol of a 1:1 mixture of the N-1 and N-2 isomers) and 1-chloro-3-[4-(2-chlorobenzyl)piperazin-1-yl]propane **9** (0.54 g, slight excess) in dry tetrahydrofuran (THF, 30 mL) followed by a solution of diethyl azodicarboxylate (0.72 g, 3.5 mmol of 85% pure material) in dry THF (5 mL). The resulting mixture was stirred for 1.5 h at ambient temperature after which time HPLC analysis showed the absence of **13**. The solvent was removed in vacuo, and the residue was briefly boiled with EtOH (25–50 mL) and then cooled. Filtration gave 0.525 g (44%) of the insoluble N-1 isomer **19a**: mp ($EtOH$–$CHCl_3$) 163–166 °C; IR ν_{max} (mull) 1245, 1265, 1510, 1525, 1605, 1665 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.02 (2 H, quintet, J = 6 Hz, $CH_2CH_2CH_2$), 2.38 (3 H, s, Ar CH_3), 2.53 (10 H, m, piperazine NCH_2), 3.61 (2 H, s, piperazine NCH_2 Ar), 3.72 (3 H, s, OCH_3), 4.15 (2 H, t, J = 6 Hz, OCH_2), 5.88 (2 H, s, triazole NCH_2 Ar), 6.98 (1 H, d, J = 9 Hz, C-7 H), 7.10–7.48 (4 H, complex m, ClPh), 7.20 (4 H, AB q, J = 9 Hz, $\Delta\nu$ = 59 Hz, CH_3OPh), 8.12 (1 H, d, J = 9 Hz, C-8 H). Anal. ($C_{32}H_{34}ClN_5O_4$) C, H, N.

Chromatography of the evaporated EtOH mother liquors on silica gel eluting with $CHCl_3$ afforded 0.29 g (25%) of pure N-2 isomer **19b**, mp (EtOH) 83–85 °C: IR ν_{max} (mull) 1515, 1545, 1605, 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.00 (2 H, quintet, J = 6 Hz, $CH_2CH_2CH_2$), 2.31 (3 H, s, Ar CH_3), 2.52 (10 H, m, piperazine NCH_2), 3.60 (2 H, s, piperazine NCH_2 Ar), 3.76 (3 H, s, OCH_3), 4.13 (2 H, t, J = 6 Hz, OCH_2), 5.60 (2 H, s, triazole NCH_2 Ar), 6.93 (1 H, d, J = 9 Hz, C-7 H), 7.09–7.50 (4 H, complex m, ClPh), 7.12 (4 H, AB q, J = 9 Hz, $\Delta\nu$ = 48 Hz, CH_3OPh), 8.20 (1 H, d, J = 9 Hz, C-8 H). Anal. ($C_{32}H_{34}ClN_5O_4$) C, H, N.

6-[3-[4-(4-Methoxybenzyl)-1-piperazinyl]propoxy]-5-methyl[1]benzopyrano[2,3-*d*]-1,2,3-triazol-9(1*H*)-one (23). Method B. A solution of the N-1 (4-methoxybenzyl) derivative **16a** (300 mg) in CF_3CO_2H (15 mL) was heated to 65 °C with stirring until no further material remained (3 h, HPLC monitoring), and the excess CF_3CO_2H was then evaporated in vacuo. Water was added to the residue and the suspension made alkaline with excess NaOH solution before acidification to pH 4.5 with glacial AcOH. The solid material was filtered off, washed well with water, and dried to give crude **23**. Chromatography on silica gel gradient eluting from $CHCl_3$ to $CHCl_3$–MeOH (4:1) gave 0.220 g (92%) of pure **23** after trituration with hot AcOEt with mp 234–237 °C dec: IR ν_{max} (mull) 1270, 1485, 1513, 1605, 1650 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.00 (2 H, quintet, $CH_2CH_2CH_2$), 2.20 (3 H, s, Ar CH_3), 2.78 (10 H, m, piperazine NCH_2), 3.60 (2 H, s, NCH_2 Ar), 3.66 (3 H, s, OCH_3), 4.06 (2 H, unresolved t, OCH_2), 6.92 (1 H, d, J = 9 Hz, C-7 H), 6.97 (4 H, AB q, J = 9 Hz, $\Delta\nu$ = 34 Hz, CH_3O Ar), 7.88 (1 H, d, J = 9 Hz, C-8 H), 8.39 (2 H, br exchangeable peak, NH + H_2O). Anal. ($C_{25}H_{29}N_5O_4$) C, H, N.

The N-2 isomer **16b** could be similarly deprotected to give **23** in the same yield.

6-[[7-(4-Chlorobenzyl)-4-methyl-4,7-diazaoctan-1-yl]-oxy]-5-methyl[1]benzopyrano[2,3-*d*]-1,2,3-triazol-9(1*H*)-one (29). Reaction of the mixed isomers **13** (0.67 g, 2 mmol) with (4-chlorobenzyl)-4-methyl-4,7-diazaoctan-1-ol (0.54 g, 2 mmol) according to method A gave 1.06 g (90%) of the N-1 and N-2 (4-methoxybenzyl) isomers of **29**, which were incompletely separated by the isolation procedure used for the piperazine analogues. Treatment of 0.65 g of the partially purified N-2 isomer with CF_3CO_2H (30 mL) as described in method B gave 0.43 g (68%) of **29** monotrifluoroacetic acid salt as a foam after chromatography on silica gel, gradient eluting with $CHCl_3$ to $CHCl_3$–MeOH (9:1). Boiling with Et_2O containing a little MeOH resulted in crystalline material: mp 164–166 °C dec; IR ν_{max} (mull) 1540, 1610, 1660 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.30 (8 H, m), 2.77 (3 H, s, Ar CH_3), 2.82 (2 H, m), 3.27 (4 H, m), 3.76 (2 H, s, Ar CH_2N), 4.22 (2 H, t, OCH_2), 7.19 (1 H, d, J = 10 Hz, C-7 H), 7.39 (4 H, s, ClPh), 8.08 (1 H, d, J = 10 Hz, C-8 H). Anal. ($C_{24}H_{28}ClN_5O_3\cdot CF_3CO_2H$) C, H, N.

6-[3-[4-(4-Chlorobenzyl)-1-piperazinyl]propoxy][1]benzopyrano[2,3-*d*]-1,2,3-triazol-9(1*H*)-one (28) by Detriphenylmethylation of 32. Concentrated HCl (5 mL) was added to a stirred solution of **32** (6.20 g) in glacial AcOH (200 mL), and the mixture was stirred for 3 h at 70 °C. After cooling, the solvent was removed in vacuo and the residue was suspended in water and the pH brought to 6.5 with dilute NaOH. The resulting white solid was filtered off, boiled with EtOH to remove triphenylmethyl alcohol, and refiltered to give 3.81 g (94%) of **28** spectroscopically identical with that prepared from **21b** (see Table I).

H_1-Antihistamine Activity: Determination of pA_2 Values. The terminal portion of guinea pig ileum was removed and suspended in a 4-mL organ bath and bathed in Tyrode solution, aerated and maintained at 35 °C. The tissue was washed by upward displacement of the bathing fluid. A tension of ca. 1 g was applied to the ileum, and the contractions were recorded by using a Devices isotonic photoelectric transducer and a Servoscribe flat bed recorder.

A dose–response curve was obtained for histamine, with use of a 3 × 3 Latin square design for dosing.

Method A. Increasing concentrations of antagonists were added to Tyrode solution, and the dose–response curves for histamine were repeated at each concentration of the antagonists.

The results were calculated from the dose–response lines for histamine at each drug concentration. These were parallel. The doses of histamine required to produce the same size contraction of the gut in the presence of each concentration of the antagonists were obtained from the graph.

The dose ratio of histamine at a given concentration of the antagonist was the dose of histamine required to produce the same, less than maximal, response in the presence of this concentration of the compound over that in its absence. The log of the dose ratios minus one (DR − 1) was plotted against the negative log of molar concentration of the compound. The pA_2 value was read from where this line intersected the abscissa.[12]

Method B. A dose–response curve to histamine was obtained as before. A dose of histamine was chosen that produced about 50% of the maximum response, and this dose was added to the organ bath at least three times to confirm that the same size contraction was obtained. The antagonist was then added to the organ bath, and after 10 min, twice the selected dose of histamine was added to the bath and the response recorded. The tissue was washed until the response to the selected dose of histamine was reestablished. Three doses of the antagonist were evaluated in this way, the doses being chosen so that twice the selected dose of histamine produced less than a maximum response. Each dose of the compound was tested three times, with use of a Latin square design. A graph was plotted of the log dose of the antagonist against the ratio of the response to a double dose of histamine in the presence of the antagonist over the mean response to a single dose of histamine in the absence of the antagonist. The dose producing a ratio of 1 was obtained from the graph, and the pA_2 value was the negative logarithm of the molar concentration of the antagonist at this dose.

For compounds evaluated by the different methods, little difference in the measured pA_2 values was obtained.

Passive Peritoneal Anaphylaxis (PPA). PPA was carried out and the antiserum was raised as previously described.[13] Briefly, rats were given intraperitoneal injections of 2 mL of a 1:5 dilution of the rat antiserum in isotonic saline. Two hours later, 0.3 mL of a 5% solution of Pontamine Sky Blue (Raymond A. Lamb, London) in isotonic saline was injected intravenously, followed 30 s later by an intraperitoneal injection of 5 mL of Tyrode solution containing 50 μg/mL of heparin and 0.4 mg/mL of ovalbumin. Exactly 5 min after challenge, the rats were stunned and bled and their peritoneal fluids were collected. Animals in control groups received a dilution of normal rat serum instead of antiserum at the time of sensitization (not sensitized) or were given Tyrode solution free of antigen at the time of challenge (not challenged). Compounds were given intraperitoneally in 1 mL of saline, 30 s before the antigen in 5 mL of Tyrode solution. Doses of the compounds are quoted as their concentrations in the the 6 mL of fluid injected intraperitoneally.

Assay of Peritoneal Fluids. Collected peritoneal fluids were immediately cooled to 0 °C and centrifuged, and the supernatant fluids were assayed for dye within 2 h. The supernatant (0.5 mL) was added to 1 mL of 12% trichloroacetic acid and stored at −20 °C and used to assay for histamine.

Dye Assay. The optical densities (OD) at 625 nm of the supernatants were determined.

Histamine Assay. Histamine was assayed by using an automated spectrofluorimetric system (Technicon Autoanalyzer) as described.[13] At the concentrations used, the compounds tested did not interfere with the assay.

The concentrations of histamine and extravasated dye in the peritoneal fluids collected from nondrug-treated control rats were similar to those described;[13] i.e., the mean values obtained ± SEM (n = 19–36) were, for passively sensitized and challenged rats, 2.03 ± 0.08 μg/mL of histamine and 0.88 ± 0.06 OD (625 nm) for dye. For negative control rats, passively sensitized and not challenged or not sensitized and challenged, the mean values were up to 0.2 μg/mL for histamine and 0.12 OD for dye. For each drug studied, each dose was given to five to seven animals, and at least two doses were given that produced some, but less than maximum, inhibition. The percentage inhibition was calculated from the concentration in that animal × 100 over the mean concentration in five to seven positive control animals treated at the same time from the same group. Negative controls were not taken into account. Regression lines were fitted to each data set plotted against the log of the dose. The median effective dose and associated confidence limits were then estimated as the doses corresponding to an inhibition of 50%, as calculated from the equations of the regression line and the 95% confidence limits of the line at 50% inhibition.

Registry No. **5**, 79837-40-4; **6**, 79837-50-6; **7**, 104131-26-2; **8**, 104131-27-3; **9**, 104131-28-4; **10**, 79837-55-1; **11**, 79572-25-1; **12**, 79572-30-8; **13a**, 79837-32-4; **13b**, 79837-37-9; **14a**, 79837-59-5; **14b**, 79837-58-4; **15a**, 79837-41-5; **15b**, 79837-42-6; **16a**, 79837-51-7; **16b**, 79837-52-8; **17a**, 79837-33-5; **17b**, 79837-38-0; **18a**, 104131-29-5; **18b**, 104131-30-8; **19a**, 79837-45-9; **19b**, 79837-46-0; **20a**, 79837-54-0; **20b**, 79837-56-2; **21a**, 79837-60-8; **21b**, 79851-07-3; **22**, 79837-43-7; **23**, 79837-53-9; **24**, 79837-39-1; **25**, 104131-31-9; **26**, 79837-48-2; **27**, 79837-57-3; **28**, 79837-61-9; **29a**, 104131-37-5; **29b**, 104131-38-6; **29**·CF_3CO_2H, 104155-47-7; **30**, 86223-15-6; **31**, 86223-12-3; **32**, 86223-16-7; **33**, 104131-32-0; **34**, 104131-36-4; $Br(CH_2)_3OH$, 627-18-9; $MeNH(CH_2)_2OH$, 109-83-1; 4-$ClC_6H_4CH_2Cl$, 104-83-6; 4-$ClC_6H_4CH_2N(Me)(CH_2)_2OH$, 35113-60-1; 4-$ClC_6H_4CH_2N(Me)(CH_2)_2Cl$·HCl, 23510-20-5; 4-$ClC_6H_4CH_2N(Me)(CH_2)_2NHMe$, 104131-33-1; 4-$ClC_6H_4CH_2N(Me)(CH_2)_2N(Me)(CH_2)_3OH$, 104131-34-2; 4-$ClC_6H_4CH_2N(Me)(CH_2)_2N(Me)(CH_2)_3OH$·2HCl, 104131-35-3; (4-methylbenzyl)piperazine, 23173-57-1; (4-methoxybenzyl)piperazine, 21867-69-6; (4-chlorobenzyl)piperazine, 23145-88-2; (3-chlorobenzyl)piperazine, 23145-91-7; (2-chlorobenzyl)piperazine, 17532-19-3; (2-pyridylmethyl)piperazine, 55579-01-6; 4-(4-chlorobenzyl)-piperidine-1-propanol, 79837-34-6.

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