Pharmacology. First Investigation. The purpose of this first test was to preselect compounds with the same criteria for further investigation. Variation of serum cholesterol, triglycerides, and lipoprotein α-cholesterol were assessed in Sprague–Dawley male rats (185-g mean bodyweight), fed a normal diet and given orally, for 4 consecutive days, the investigational drugs at the dose of 50 mg/kg with **1d** or **1e** as standard or at the dose of 200 mg/kg with **2** as standard. Serum cholesterol,[28] lipoprotein α-cholesterol,[29] and triglycerides[30] were assayed on the blood taken. Blood was taken from the abdominal aorta 24 h after the last drug administration: the animals were fasted 18 h before the sacrifice.

The data obtained with the investigational drugs were compared with the data of the controls and the data of the standard (Student's *t* test for independent paired data).

Second Investigation. Sprague–Dawley male rats, 200-g mean bodyweight, were freely fed for 15 days a Nath's diet with the following composition: sucrose 49%, cocoa-nut oil 24%, casein 18%, vitamin mixture 2%, maize oil 1%, mineral salts 4%, cholic acid 1%, cholesterol 1%. The drugs, given daily for 15 days orally, were suspended in 10% gum arabic. After an 18-h fast, the animals were killed on the 16th day. Twenty-four hours after the last administration, serum total cholesterol[28] and triglycerides[30] were assayed, and the weight of the liver was measured; the percent variations from the liver weight values were calculated on the basis of 100 g of animal bodyweight. The data of the animals given the investigational drugs were compared with that of the controls fed the Nath's diet and with the data of the standard (Student's *t* test for independent paired data). Compound **18b** was tested at three doses, i.e., 6.25, 12.5, and 25 mg/kg os, using a Nath's diet containing cholesterol and cholic acid in a 0.5% concentration.

Investigations on Liver Enzymes and Peroxisomes. The investigation was carried out by J. K. Reddy.[26] F 344 rats were given the investigational compounds at the dose of 20 mg/kg by gastric incubation: **14b** for 6 weeks; **8**, **17b**, and **18b** for 7 weeks; and **24c** for 10 weeks. The methods used for the measurement of liver enzymes are reported in the literature.[19] The following explanations are given for the values reported in Table IV. A unit of catalase activity is defined as the amount that liberates half the peroxide hydrogen from a hydrogen peroxide solution at any concentration in 100 s at 25 °C and is, therefore, related to the half-time of the first-order reaction.[31] The carnitine acetyltransferase unit is expressed as nanomoles of CoA-SH (2-nitrobenzoic acid) with E_{412nm} = 13 600 M^{-1} cm^{-1}.[32] Enoyl-CoA hydratase activity[33] and palmitoyl-CoA oxidizing activity[34] are expressed as μmol min^{-1} (mg of protein)$^{-1}$. Peroxisomal proliferation was investigated by electron microscopy with a semiquantitative assessment based on the number of peroxisomes observed in the photogram.[19] The peptide, M_r 80 000, was examined by partial enzymatic proteolysis using *S. aureus* V-8 protease according to the method of Cleveland et al.[35]

Registry No. **1a**, 86627-43-2; **1b**, 91759-31-8; **1c**, 86627-39-6; **1d**, 50892-23-4; **1e**, 65089-17-0; **3**, 91759-32-9; **4a**, 50892-49-4; **4b**, 16953-21-2; **4c**, 1979-98-2; **4d**, 86627-13-6; **5a**, 50892-12-1; **5b**, 86627-07-8; **5c**, 6299-25-8; **5d**, 86627-14-7; **6a**, 86627-42-1; **6b**, 91759-33-0; **6c**, 86627-38-5; **6d**, 54061-62-0; **7**, 86627-11-4; **8**, 86627-49-8; **9**, 91759-34-1; **10a**, 86627-08-9; **10b**, 86627-09-0; **11a**, 86627-46-5; **11b**, 86627-48-7; **12a**, 91759-35-2; **12b**, 86626-95-1; **12c**, 86626-96-2; **12d**, 86627-47-6; **13a**, 91759-36-3; **13b**, 86627-00-1; **13c**, 86627-01-2; **14a**, 91759-37-4; **14b**, 86627-50-1; **14c**, 86627-51-2; **15a**, 91759-38-5; **15b**, 86627-26-1; **15c**, 86627-31-8; **16b**, 86627-16-9; **16c**, 86627-20-5; **17a**, 91759-39-6; **17b**, 86627-27-2; **17c**, 86627-32-9; **18b**, 86627-15-8; **18c**, 86627-19-2; **19**, 3764-01-0; **20**, 86627-10-3; **21**, 108-77-0; **22**, 61018-62-0; **23a**, 86627-52-3; **23b**, 86627-56-7; **23c**, 86627-54-5; **23d**, 86627-58-9; **24a**, 86627-53-4; **24b**, 86627-57-8; **24c**, 61018-63-1; **25**, 3140-74-7; **26**, 32998-04-2; **27**, 1202-22-8; **28**, 1075-39-4; 1-(chloromethyl)-4-methoxybenzene, 824-94-2; 1-iodooctane, 629-27-6; 2,3-dimethylphenol, 526-75-0; ethanolamine, 141-43-5; aziridine, 151-56-4; 2,3-dimethylaniline, 87-59-2; ethyl glycolate, 623-50-7; ethyl thioglycolate, 623-51-8; 2,4-dichloro-6-amino-1,3,5-triazine, 933-20-0; 4,6-dichloro-2-(dimethylamino)-pyrimidine, 5734-68-9.

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Acidic Furo[3,2-*b*]indoles. A New Series of Potent Antiallergy Agents

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A series of furo[3,2-*b*]indole carboxylic acids, tetrazoles, and carbamoyltetrazoles was prepared and tested in vitro with use of a model of active pulmonary anaphylaxis, the modified Schultz–Dale Test (SDT). In this model, isolated guinea pig lung strips are repeatedly challenged with antigen in the presence of an antihistamine (H_1). Most of the acidic furo[3,2-*b*]indoles tested inhibited the leukotriene-mediated lung contraction in a dose-related manner. Compounds with an *N*-phenyl substituent were more potent ($IC_{50} \leq 5.0$ μM) inhibitors of SDT than the *N*-methyl analogues ($IC_{50} \geq 22.0$ μM). Most of the *N*-phenyl analogues were more potent in SDT than Fisons' mediator-release inhibitor proxicromil (FPL-57,787; IC_{50} = 6.3 μM). The most potent furo[3,2-*b*]indoles were those unsubstituted at C-7 and with *N*-phenyl, 2-carbamoyltetrazole, and 3-alkoxy substituents. All of the carboxylic acid ester analogues tested were weak or inactive at concentrations of 10–30 μM.

Since the introduction of disodium cromoglycate (DSCG) in 1967, the international pharmaceutical industry has attempted to develop a more effective, orally active antiallergic drug.[1] Excessive reliance on passive cutaneous anaphylaxis (PCA) in the rat as a model of allergy may be one reason for the failure of this effort to date.[2] Inhibition of histamine release from passively sensitized, antigen-challenged isolated human lung has similarly been disappointing in predicting clinical efficacy in allergic asthma.[3]

We chose a modification of the classic Schultz–Dale test (SDT)[4] as an in vitro model of active anaphylaxis in the

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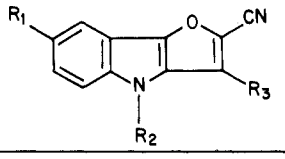
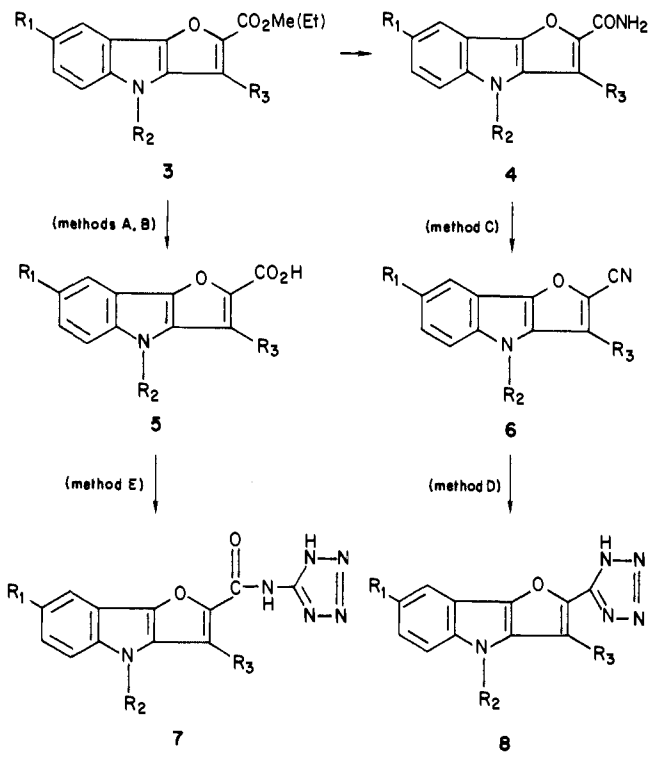
Table I. Furo[3,2-*b*]indole-2-carbonitrile Intermediates



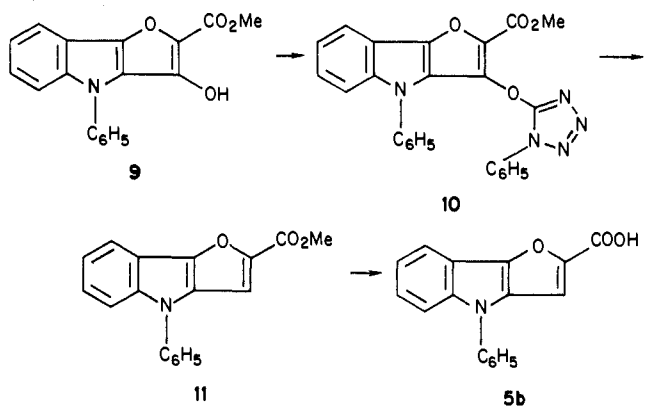
compd	R_1	R_2	R_3	formula	mp, °C	method	yield, %	crystn solvent	anal.
6a	H	CH_3	OCH_3	$C_{13}H_{10}N_2O_2$	144–146	C	88	EtOH	C, H, N
6c	H	C_6H_5	OCH_3	$C_{18}H_{12}N_2O_2$	182–184	C	82	EtOH/DMF	C, H, N
6d	H	C_6H_5	OC_2H_5	$C_{19}H_{14}N_2O_2$	121–122	C	90[a]	MeOH	C, H, N
6g	OCH_3	C_6H_5	OCH_3	$C_{19}H_{14}N_2O_3$	137–139	C	73	EtOH	C, H, N
6h	OCH_3	C_6H_5	OC_2H_5	$C_{20}H_{16}N_2O_3$	154–156	C	80	EtOH/DMF	C, H, N

[a] Crude yield before recrystallization.

Scheme I

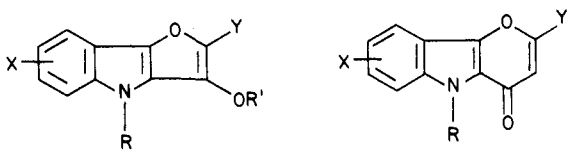


Scheme II



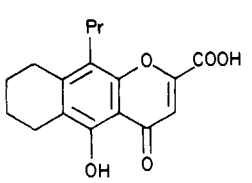
relevant target organ. This guinea pig model of allergy was selected because respiratory functional changes in vivo indicate that the site of action of some drugs or of immunologically released pharmacological mediators is mainly the terminal airways.[5] The use of isolated lung parenchyma to measure the effect of drugs on terminal airways is an established procedure.[4,6,7] Our model, which uses antigen contracted guinea pig lung strips in the presence of mepyramine (an H_1 antihistamine), has been pharmacologically characterized as leukotriene mediated.[8,9] Potential antiallergy compounds operating by a variety of biological mechanisms exhibit inhibition of SDT. Isoproterenol and procaterol (β-adrenergic stimulants), FPL-55,712 (a leukotriene antagonist), and nordihydroguaiaretic acid (a leukotriene biosynthesis inhibitor) are examples of the diversity of compound types active in SDT.[8,10,11] Proxicromil (FPL-57,787) is one of the few "PCA-active" antiallergic agents showing efficacy and potency in SDT.[12]

Previously, we reported[13] the antiallergic activity of acidic 4-oxopyrano[3,2-*b*]indoles **2**. We have now prepared and tested a series of related acidic furo[3,2-*b*]indoles **1**.



Y = acidic function

The described furo[3,2-*b*]indoles were potent inhibitors of SDT when compared to the mediator-release inhibitor, proxicromil, a clinically effective but toxic compound.[14,15]



proxicromil

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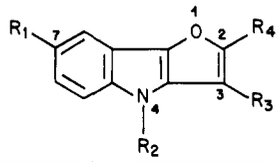
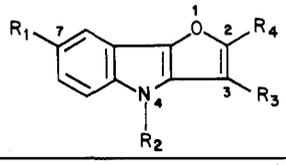
Table II. Physical Data and SDT Results for Acidic Furo[3,2-*b*]indoles (R_1 = H)



no.	R_2	R_3	R_4	formula	mp, °C	method	yield, %	crystn solvent	anal.	Schultz–Dale test: IC_{50},[a] μM
5a	CH_3	OCH_3	COOH	$C_{13}H_{11}NO_4$	141 dec	A	72[b]	DMF/H_2O	C, H, N	*c*
5b	C_6H_5	H	COOH	$C_{17}H_{11}NO_3$	211–212	*d*	16	MeOH	C, H, N	*e*
5c	C_6H_5	OCH_3	COOH	$C_{18}H_{13}NO_4$	154–155	B	45	MeOH	C, H, N	4.6 (2.7–7.1)
5d	C_6H_5	OC_2H_5	COOH	$C_{19}H_{15}NO_4$	146–147	B	59	EtOH	C, H, N[f]	3.2 (1.7–5.0)
5e	C_6H_5	$OCH(CH_3)_2$	COOH	$C_{20}H_{17}NO_4$	151 dec	A	34	EtOH	C, H, N	3.7 (1.4–4.3)
7a	CH_3	OCH_3	CONHtet[g]	$C_{14}H_{12}N_6O_3$	235 dec	*d*	38	DMF/H_2O	C, H, N[h]	21.6 (15.7–27.8)
7c	C_6H_5	OCH_3	CONHtet	$C_{19}H_{14}N_6O_3$	270 dec	E	59	DMF/H_2O	C, H, N	0.5 (0.3–0.8)
7d	C_6H_5	OC_2H_5	CONHtet	$C_{20}H_{16}N_6O_3$	244–247	E	50	DMF/H_2O	C, H, N[h]	0.2 (0.1–0.2)
7e	C_6H_5	$OCH(CH_3)_2$	CONHtet	$C_{21}H_{18}N_6O_3$	240–241	E	64	EtOAc	C, H, N	0.06 (0.04–0.09)
7f	C_6H_5	O(*n*-C_9H_{19})	CONHtet	$C_{27}H_{30}N_6O_3$	185 dec	E	3	DMF/H_2O	C, H, N	*i*
8a	CH_3	OCH_3	tet	$C_{13}H_{11}N_5O_2$	173 dec	D	56	2-methoxyethanol/H_2O	C, H, N[f]	*c*
8c	C_6H_5	OCH_3	tet	$C_{18}H_{13}N_5O_2$	212 dec	D	29	CH_2Cl_2/MeOH/hexane	C, H, N	2.9 (2.2–3.7)
8d	C_6H_5	OC_2H_5	tet	$C_{19}H_{15}N_5O_2$	189–192	D	20	EtOH	C, H, N[f]	3.2 (2.2–4.8)

[a] Concentration of drug (μM) inhibiting response 50% of control (95% confidence limits are in parentheses). [b] Crude yield before recrystallization. [c] No activity at 30 μM. [d] See Experimental Section. [e] 33% inhibition at 10 μM. [f] Calculated as ·0.25 H_2O. [g] tet = (1*H*-tetrazol-5-yl). [h] Calculated as ·1.0 DMF. [i] No significant activity at 1.0 μM (maximum solubility).

Table III. Physical Data and SDT Results for Acidic Furo[3,2-*b*]indoles (R_1 = OCH_3)



no.	R_2	R_3	R_4	formula	mp, °C	method	yield, %	crystn solvent	anal.	Schultz–Dale test: IC_{50},[a] μM
5g	C_6H_5	OCH_3	COOH	$C_{19}H_{15}NO_5$	148 dec	A	85[b]	acetone/H_2O	C, H, N	2.8 (1.6–4.2)
5h	C_6H_5	OC_2H_5	COOH	$C_{20}H_{17}NO_5$	166–167	A	85[b]	2-methoxyethanol	C, H, N	4.3 (0.7–10.2)
7g	C_6H_5	OCH_3	CONHtet[c]	$C_{20}H_{16}N_6O_4$	231 dec	E	61	DMF/H_2O	C, H, N[d]	0.9 (0.7–1.2)
7h	C_6H_5	OC_2H_5	CONHtet	$C_{21}H_{18}N_6O_4$	248–249	E	64	DMF/H_2O	C, H, N[e]	2.2 (1.7–2.8)
7i	C_6H_5	$OCH(CH_3)_2$	CONHtet	$C_{22}N_{20}N_6O_4$	225 dec	E	31	MeCN/DMF/H_2O	C, H, N[f]	2.8 (2.2–3.6)
8g	C_6H_5	OCH_3	tet	$C_{19}H_{15}N_5O_3$	191–192	D	40	acetone/H_2O	C, H, N[g]	1.5 (0.8–2.2)
8h	C_6H_5	OC_2H_5	tet	$C_{20}H_{17}N_5O_3$	183 dec	D	66	EtOH DMF	C, H, N[g]	1.7 (1.1–2.4)
proxicromil										6.3 (5.2–7.3)
FPL-55, 712										2.4 (1.4–3.9)
isoproterenol										0.15 (0.08–0.27)[h]

[a] Concentration of drug (μM) inhibiting response 50% of control (95% confidence limits are in parentheses). [b] Crude yield before recrystallization. [c] tet = (1*H*-tetrazol-5-yl). [d] Calculated as ·0.50 DMF. [e] Calculated as ·1.0 DMF. [f] Calculated as ·0.25 H_2O. [g] Calculated as ·0.50 H_2O. [h] IC_{50} value in nanomoles.

Chemistry. A series of furo[3,2-*b*]indole esters **3** and amides **4** were prepared as described[16] in detail elsewhere (Scheme I). The esters were hydrolyzed to the carboxylic acids **5** under basic conditions. Carbamoyltetrazoles **7** were obtained from the corresponding carboxylic acids and 1*H*-tetrazol-5-amine monohydrate by the use of the coupling reagent 1,1-carbonylbis(1*H*-imidazole). Intermediate nitriles **6** (Table I) were obtained by dehydration of the corresponding amides with tosyl chloride and pyridine in DMF. Tetrazoles **8** were then prepared from the corresponding nitriles and NaN_3/NH_4Cl in DMF.

The above preparative procedures are described as general methods A–E in the Experimental Section.

In order to prepare an acidic furo[3,2-*b*]indole with no substituent in the furan ring 3-position,[17] enol ester **9**[16] was reacted with 5-chloro-1-phenyl-1*H*-tetrazole to obtain the tetrazole ether **10** (Scheme II). Catalytic hydrogenation[18] of **10** effected cleavage of the ether to yield ester **11**, which was saponified to yield the target carboxylic acid **5b**.

Table IV. Inhibition of Modified Schultz–Dale Test by Furo[3,2-*b*]indole Esters

no.	R_1	R_2	R_3	R_4	method	% inhibn
3c	H	C_6H_5	OCH_3	$COOCH_3$	*a*	*b*
3g	OCH_3	C_6H_5	OCH_3	$COOCH_3$	*a*	23[c]
3h	OCH_3	C_6H_5	OC_2H_5	$COOCH_3$	*a*	24[c]

[a] Preparation and physical data described in *J. Heterocycl. Chem.* **1984**, *21*, 709. [b] No activity at 30 μM. [c] At 10 μM.

Biological Results

Acidic furo[3,2-*b*]indoles synthesized with R_1, R_2, R_3, and R_4 substituents are described in Tables II and III. Most of the acidic furo[3,2-*b*]indoles (R_4 = carboxylic acid, tetrazolylcarbamoyl, or tetrazolyl) inhibited SDT in a dose-related manner. Several carboxylic acid esters (**3c**, **3g**, **3h**, Table IV) were found to be weak or inactive at

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screening doses of 10–30 μM. The mediator-release inhibitor proxicromil also inhibited SDT in a dose-related manner (IC_{50} = 6.3 μM) but was less potent than many of the furo[3,2-*b*]indoles. DSCG, at a concentration of 100 μM, had no significant effect.[12]

Structure–Activity Relationships. Furo[3,2-*b*]indoles with R_1 = Hydrogen (Tables II). Two compounds with R_2 = methyl, R_3 = methoxy, and R_4 = carboxylic acid (compound **5a**) or tetrazolyl (compound **8a**) had no significant effect on SDT at 30 μM. The corresponding analogue with R_4 = tetrazolylcarbamoyl (**7a**) inhibited SDT in a dose-related manner (IC_{50} = 22 μM).

A compound (**5b**) with R_2 = phenyl, R_3 = hydrogen, and R_4 = carboxylic acid was a weak inhibitor of SDT (33 ± 10% inhibition at 10 μM).

Furo[3,2-*b*]indoles with R_2 = phenyl, R_3 = methoxy, and R_4 = carboxylic acid (**5c**), tetrazolyl (**8c**), or tetrazolylcarbamoyl (**7c**) all inhibited SDT in a dose-related manner. The tetrazolylcarbamoyl analogue **7c** was the most potent inhibitor of the group (IC_{50} = 0.5 μM).

A comparison of the three classes of acidic furo[3,2-*b*]indoles with R_2 = phenyl and R_3 = methoxy, ethoxy, or 1-methylethoxy ("isopropoxy") showed the compounds to be generally equipotent, with the exception of the tetrazolylcarboxamides. These compounds (**7c–e**) were increasingly potent as the R_3 substituent increased in size (IC_{50}'s = 0.5, 0.2, and 0.06 μM, respectively). However, increasing the number of carbon atoms in the R_3 substituent to nine resulted in a loss of SDT inhibitory activity (**7f**).

Furo[3,2-*b*]indoles with R_1 = Methoxy (Table III). The seven acidic furo[3,2-*b*]indoles with R_1 = methoxy and R_2 = phenyl were not significantly different in potency, in contrast to the compounds with R_1 = hydrogen. A comparison of Table II (R_1 = hydrogen) with Table III (R_1 = methoxy) permitted the effect of the R_1 substituent to be determined. Of the three classes of acidic compounds, only the tetrazolylcarboxamides showed a notable difference in potency when R_1 alone was varied. Three furo[3,2-*b*]indoles with R_1 = hydrogen (**7c–e**) were more potent inhibitors than the three analogues (**7g–i**) with R_1 = methoxy.

Conclusions

A new series of antiallergic compounds, acidic furo[3,2-*b*]indoles, has been prepared. The compounds usually inhibited SDT in a dose-related manner and were quite potent. Most had potency greater than the known mediator-release inhibitor, proxicromil.

A structure–activity relationship study indicated that compounds with an *N*-phenyl substituent were generally more potent than those with an *N*-methyl substituent. In some instances, potency increased with increasing bulkiness of the R_3 substituent. The most potent compounds had R_1 = hydrogen, R_2 = phenyl, R_3 = alkoxy, and R_4 = tetrazolylcarbamoyl. The carboxylic acid methyl esters were weak or inactive. Additional structure–activity relationships in other allergy models are being developed[19] and will further define the antiallergy drug potential of this series.

Experimental Section

Chemistry. General Procedures. Melting points were determined in a Mel-Temp capillary apparatus and are uncorrected. The NMR spectra were recorded at 90 MHz on a Varian EM-390 spectrometer, with tetramethylsilane as an internal standard. Infrared spectra were recorded on a Digilab FTS-14 pulsed Fourier-transform spectrophotometer as KBr disks. All new compounds yielded spectral data consistent with the proposed structure and microanalyses within 0.4% of theory unless indicated otherwise. Methods A–E, reported below, may be considered as general methods. Yields were not maximized.

Method A. 3,7-Dimethoxy-4-phenyl-4*H*-furo[3,2-*b*]indole-2-carboxylic Acid (5g). A suspension of 11.5 g (0.033 mol) of **3g**, the methyl ester[16] of the title compound, in 200 mL of 50% aqueous EtOH was treated with 25 mL of 10% aqueous NaOH. After stirring at reflux for 1.5 h, the reaction mixture was cooled and distributed between 750 mL of H_2O and 250 mL of CH_2Cl_2. The insoluble material (primarily the Na^+ salt of the product) was removed by filtration. The filtrate layers were separated, and the organic layer was discarded. The aqueous layer was washed several times with fresh CH_2Cl_2, cooled in ice, and acidified with 4 N HCl. The precipitated crude product was filtered and washed with H_2O. The original insoluble Na^+ salt was stirred in 400 mL of cold 1 N HCl, and the product acid was filtered, washed with H_2O, and combined with the material obtained from acidification of the original aqueous layer. The crude yield of acid **5g** was 9.4 g (85%). A sample recrystallized from acetone/H_2O yielded analytically pure **5g**: mp 148 °C dec; IR (KBr) 2620, 1670, 1461, 1221 cm^{-1}; NMR (Me_2SO-d_6) δ 3.70 (s, 3 H, OCH_3), 3.85 (s, 3 H, OCH_3), 6.81–7.12 (m, 1 H, 6-position H), 7.26–7.81 (m, 7 H, Ar H), 12.88 (br s, 1 H, CO_2H). Anal. ($C_{19}H_{15}NO_5$) C, H, N.

Method B. 3-Ethoxy-4-phenyl-4*H*-furo[3,2-*b*]indole-2-carboxylic Acid (5d). A suspension of 12.0 g (0.036 mol) of **3d**, the methyl ester[16] of the title compound, in 100 mL of MeOH was treated with 60 mL of 1 N NaOH. After stirring at reflux for 20 h, the cooled reaction mixture was added to 1.2 kg of ice/H_2O, and the mixture was acidified with HOAc. The crude product was filtered, washed with H_2O, and recrystallized from EtOH to yield 6.8 g (59% yield) of analytically pure acid **5d** containing 0.25 H_2O: mp 146–147 °C; IR (KBr) 2620, 1671, 1452, 1321 cm^{-1}; NMR (Me_2SO-d_6) δ 1.07 (t, 3 H, J = 7.5 Hz, CH_2CH_3), 3.88 (q, 2 H, J = 7.5 Hz, CH_2CH_3), 7.03–8.03 (m, 9 H, Ar H), 12.83 (br s, 1 H, CO_2H). Anal. ($C_{19}H_{15}NO_4 \cdot 0.25H_2O$) C, H, N.

Method C. 3-Methoxy-4-methyl-4*H*-furo[3,2-*b*]indole-2-carbonitrile (6a). A mixture of 11.7 g (0.048 mol) of 3-methoxy-4-methyl-4*H*-furo[3,2-*b*]indole-2-carboxamide (**4a**),[16] 11.7 mL (11.5 g, 0.15 mol) of pyridine, and 14.0 g (0.073 mol) of *p*-toluenesulfonyl chloride in 70 mL of DMF was heated on the steam bath under a N_2 atmosphere for 4 h. The mixture was cooled and added to 500 g of ice/H_2O, and the crude nitrile **6a** was filtered and washed with H_2O. Recrystallization from EtOH yielded 9.5 g (88% yield) of analytically pure **6a**: mp 144–146 °C; IR (KBr) 2218, 1579, 1323, 1117 cm^{-1}; NMR ($CDCl_3$) δ 3.75 (s, 3 H, CH_3), 4.18 (s, 3 H, CH_3), 6.96–7.38 (m, 3 H, Ar H), 7.57–7.78 (m, 1 H, 8-position H). Anal. ($C_{13}H_{10}N_2O_2$) C, H, N.

Method D. 3-Methoxy-4-methyl-2-(1*H*-tetrazol-5-yl)-4*H*-furo[3,2-*b*]indole (8a). A mixture of 11.3 g (0.05 mol) of nitrile **6a**, 10.0 g (0.15 mol) of NaN_3, and 8.5 g (0.16 mol) of NH_4Cl in 225 mL of DMF was heated on the steam bath under a N_2 atmosphere for 90 h. The mixture was cooled, added to 1.5 kg of ice/H_2O, and maintained at 0–5 °C while being acidified with 6 N HCl (**caution**: HN_3 is evolved).

The crude tetrazole product was filtered and washed with water. Recrystallization from 2-methoxyethanol/H_2O yielded 7.5 g (56% yield) of tetrazole **8a**. Several additional recrystallizations from acetone/H_2O yielded analytically pure **8a** containing 0.25 H_2O: mp 173 °C dec; IR (KBr) 1630, 1543, 1283, 742 cm^{-1}; NMR (Me_2SO-d_6) δ 3.90 (s, 3 H, CH_3), 4.13 (s, 3 H, CH_3), 6.94–7.81 (m, 4 H, Ar H). Anal. ($C_{13}H_{11}N_5O_2 \cdot 0.25H_2O$) C, H, N.

In some instances the initial heating time was reduced to 19 h.

Method E. 3,7-Dimethoxy-4-phenyl-*N*-(1*H*-tetrazol-5-yl)-4*H*-furo[3,2-*b*]indole-2-carboxamide (7g). A mixture of 7.5 g (0.022 mol) of acid **5g** and 7.5 g (0.046 mol) of 1,1′-carbonylbis(1*H*-imidazole) in 50 mL of DMF was stirred and heated on the steam bath for 30 min. The mixture was cooled, 2.6 g (0.026 mol) of 5-aminotetrazole hydrate was added, and heating was continued for an additional 30 min. The cooled reaction mixture was added to 350 g of ice/H_2O and acidified with 4 N HCl. The precipitated product was filtered, washed with H_2O,

(19) A preliminary account of the antiallergic activity of **7g** has been presented. See ref 11.

and recrystallized from DMF/H_2O (charcoal) to yield 6.0 g (61% yield) of tetrazole amide **7g** as a complex containing 0.50 DMF. An additional recrystallization as above yielded analytically pure **7g**: mp 231 °C dec; IR (KBr) 3418, 1678, 1442, 1033 cm^{-1}; NMR (Me_2SO-d_6) δ 3.85 (s, 3 H, OCH_3), 3.90 (s, 3 H, OCH_3), 6.93–7.20 (m, 1 H, 6-position H), 7.24–7.88 (m, 7 H, Ar H), 11.90 (s, 1 H, CONH). Anal. ($C_{20}H_{16}N_6O_4$·0.50DMF) C, H, N.

3-Methoxy-4-methyl-*N*-(1*H*-tetrazol-5-yl)-4*H*-furo[3,2-*b*]indole-2-carboxamide (7a). A mixture of 1.9 g (0.0078 mol) of acid **5a** and 1.4 g (0.0086 mol) of 1,1'-carbonylbis(1*H*-imidazole) in 20 mL of DMF was stirred and heated on the steam bath for 20 min. The mixture was cooled, 0.85 g (0.0083 mol) of 5-aminotetrazole hydrate was added, and heating was continued for an additional 20 min. Upon cooling, the tetrazole **7a** precipitated, and the product was filtered and washed with H_2O. Recrystallization from DMF/H_2O yielded 1.1 g (38% yield) of the product, mp 235 °C dec. An additional recrystallization as above yielded an analytically pure sample of **7a** as a complex containing 1.0 DMF: mp 235 °C dec; IR (KBr) 1655, 1568, 1318, 738 cm^{-1}; NMR (Me_2SO-d_6) δ 3.93 (s, 3 H, CH_3), 4.22 (s, 3 H, CH_3), 7.01–7.85 (m, 4 H, Ar H), 11.91 (br s, 1 H, CONH). Anal. ($C_{14}H_{12}N_6O_3$·1DMF) C, H, N.

Methyl 4-Phenyl-3-[(1-phenyl-1*H*-tetrazol-5-yl)oxy]-4*H*-furo[3,2-*b*]indole-2-carboxylate (10). A mixture of 7.0 g (0.023 mol) of ester **9**, 14.0 g (0.10 mol) of K_2CO_3, and 4.2 g (0.023 mol) of 5-chloro-1-phenyl-1*H*-tetrazole in 110 mL of DMF was stirred on the steam bath for 22 h. The cooled reaction mixture was added to 600 g of ice/H_2O and extracted with EtOAc (3 × 600 mL). Evaporation of the combined organic layers yielded an oil. The oil was stirred with 600 mL of H_2O for several days to precipitate a brown solid. Recrystallization from MeOH/H_2O yielded brown crystals of tetrazole ether **10** (2.0 g; 20% yield) in analytical purity as a complex containing 0.20 H_2O: mp 165–166 °C; IR (KBr) 1710, 1539, 1332, 752 cm^{-1}; NMR ($CDCl_3$) δ 3.83 (s, 3 H, OCH_3), 7.01–7.97 (m, 14 H, Ar H). Anal. ($C_{25}H_{17}N_5O_4$·0.20H_2O) C, H, N.

Methyl 4-Phenyl-4*H*-furo[3,2-*b*]indole-2-carboxylate (11). A mixture of 4.0 g (0.009 mol) of tetrazole ether **10** and 1.0 g of 20% Pd/C catalyst in 100 mL of HOAc was hydrogenated at room temperature for 3 h. The catalyst was filtered and the filtrate evaporated. Recrystallization of the residue from MeOH yielded 1.4 g (53% yield) of ester **11**: mp 140–142 °C; IR (KBr) 1723, 1460, 1195, 752 cm^{-1}; NMR ($CDCl_3$) δ 3.90 (s, 3 H, OCH_3), 7.00–7.90 (m, 10 H, Ar H + 3-position H). Anal. ($C_{18}H_{13}NO_3$·0.15H_2O) C, H; N: calcd, 4.76; found, 5.26.

4-Phenyl-4*H*-furo[3,2-*b*]indole-2-carboxylic Acid (5b). A suspension of 1.3 g (0.0045 mol) of ester **11** in 10 mL of MeOH was treated with 7.5 mL of 1 N NaOH, and the mixture was stirred at reflux for 3.5 h. The cooled reaction mixture was added to 150 g of ice/H_2O and acidified with HOAc. The crude product was filtered and recrystallized from MeOH to yield 0.20 g (16% yield) of analytically pure acid **5b**: mp 211–212 °C; IR (KBr) 2580, 1675, 1462, 1197 cm^{-1}; NMR (Me_2SO-d_6) δ 7.12–8.05 (m, 10 H, Ar H + 3-position H). Anal. ($C_{17}H_{11}NO_3$) C, H, N.

Biological Methods. Modified Schultz–Dale Test. Male Hartley guinea pigs, 250–300 g body weight, were injected intraperitoneally with 1 mg of ovalbumin in 1 mL of equal parts saline and complete Freund's adjuvant. Nineteen to 23 days later, animals were killed by cervical dislocation and exsanguinated. The heart, lungs, and trachea were removed as a unit and placed in Tyrode's solution, pH 7.4, at 37 °C. The solution was continually gassed with 95% O_2 and 5% CO_2. The heart beat for several minutes and spontaneously perfused the lung with buffer. Distal strips of lung, approximately 0.3 cm wide and 3 cm long, were cut from the diaphragmatic lobe. One end of the parenchymal strip was fixed to a support in the bottom of the 50-mL bath and the other end was attached by a thread to a force transducer (Grass Instruments, FT.03C). The antihistamine (H_1) mepyramine, at a concentration of 1 μM, was added to the perfusing Tyrode's solution. Lung strips were washed by rapidly emptying and filling the bath with buffer. After a period of equilibration, tissue base-line tension was adjusted to 300 mg. A ≤1 mL bolus injection of antigen was introduced into the bath and was rapidly dispersed by gas bubbles. The final concentration of ovalbumin in the bath was ≤5 ng/mL. The isometric force of contraction was quantitated in milligrams 15 min after antigen addition. Tissues were then washed repeatedly, and the initial base-line tension was reestablished. A rigid, hourly schedule of challenge gave reproducible contractions. This allowed each tissue to be used as its own control when testing drug effects.

The effect of drug on the response is reported as the percent inhibition of the response with drug compared to the previous control contraction. When applicable, linear regression analysis (least-squares fit) of the dose response was used to calculate the drug concentration inhibiting the response by 50% (IC_{50}).

Preparation and Administration of Drugs. Stock solutions of buffer-soluble drugs were made in 0.2% $NaHCO_3$. Drugs that were not soluble in buffer were partially dissolved in 5 mL of 0.2% $NaHCO_3$ and placed in a water bath at 37 °C with constant stirring. If necessary, ≤4 drops of 1 N NaOH was added to facilitate solubilization. Ethanol, ≤0.3 mL, was also added to compounds **5b**, **7c**, **7d**, and **7h**. Water to 10 mL total volume was added. Stock solutions of drug were added in a volume of ≤1 mL to the 50-mL tissue bath 15 min before the addition of ovalbumin. Tissues were treated only once. Usually, each drug concentration was tested on a minimum of four tissues. Final concentrations of NaOH and ethanol used to solubilize drugs did not exceed 0.0004 M and 0.06%, respectively, and had no effect on SDT.

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Registry No. **3c**, 89224-60-2; **3d**, 89224-61-3; **3g**, 89224-54-4; **3g** (sodium salt), 92671-24-4; **3h**, 89224-57-7; **4a**, 89236-91-9; **4c**, 89224-80-6; **4d**, 89224-85-1; **4g**, 89224-73-7; **4h**, 92671-25-5; **5a**, 89224-64-6; **5b**, 92671-18-6; **5c**, 89224-62-4; **5d**, 89224-83-9; **5e**, 92671-19-7; **5f**, 92671-28-8; **5g**, 89224-55-5; **5h**, 89224-69-1; **5i**, 92671-29-9; **6a**, 89224-71-5; **6c**, 89224-81-7; **6d**, 89224-86-2; **6g**, 89224-74-8; **6h**, 92671-17-5; **7a**, 89224-65-7; **7c**, 89224-63-5; **7d**, 89224-84-0; **7e**, 92671-20-0; **7f**, 92671-21-1; **7g**, 89224-56-6; **7h**, 89224-70-4; **7i**, 92671-22-2; **8a**, 89224-72-6; **8c**, 89224-82-8; **8d**, 89224-87-3; **8g**, 89224-75-9; **8h**, 92671-23-3; **9**, 89224-59-9; **10**, 92671-26-6; 11, 92671-27-7; 5-aminotetrazole, 4418-61-5; 5-chloro-1-phenyl-1*H*-tetrazole, 14210-25-4.