Synthesis of 2-(2,3-Dihydro-2-oxo-1,3,4-oxadiazol-5-yl) Benzo Heterocycles. A Novel Series of Orally Active Antiallergic Agents

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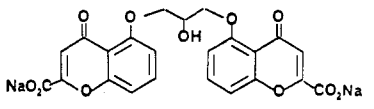
A series of new 2-(2,3-dihydro-2-oxo-1,3,4-oxadiazol-5-yl) benzo heterocycles has been prepared. These compounds were tested as inhibitors of antigen-induced release of histamine (AIR) in vitro from rat peritoneal mast cells (RMC) and as inhibitors of IgE-mediated rat passive cutaneous anaphylaxis in the rat (PCA). Most of this new class of antiallergic agents showed good activity in the RMC assay. The most potent compound, 3-chloro-2-(2,3-dihydro-2-oxo-1,3,4-oxadiazol-5-yl)benzo[*b*]thiophene (**6t**), with an I_{50} value of 0.2 μM, is 15 times more potent than disodium cromoglycate (DSCG) in the RMC assay. Many compounds were orally active in the PCA test, and several of these compounds showed higher potency when given in this way to that shown by DSCG when given intraperitoneally.

Since the introduction of disodium cromoglycate (DSCG, 1) for the treatment of asthma and allergy disease,[1] numerous compounds have been reported to be orally active antiallergic agents.[2] Most of these compounds are carboxylic acids or derivatives thereof, such as esters[3] or tetrazoles.[4] There are, however, several exceptions, such as nivimedone (2),[5] the pyran enamines 3,[6] the tetracyclic pyrazole 4,[7] and the benzoxepines 5.[8]



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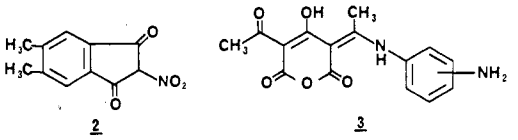

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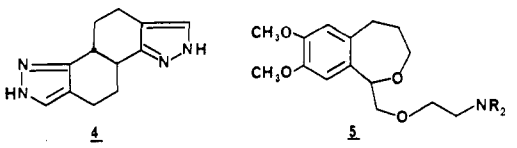

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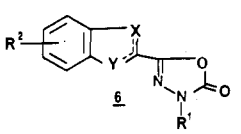
In this report, we describe a new series of structurally novel, orally active antiallergic agents, the 2-(2,3-dihydro-2-oxo-1,3,4-oxadiazol-5-yl) benzo heterocycles **6**.



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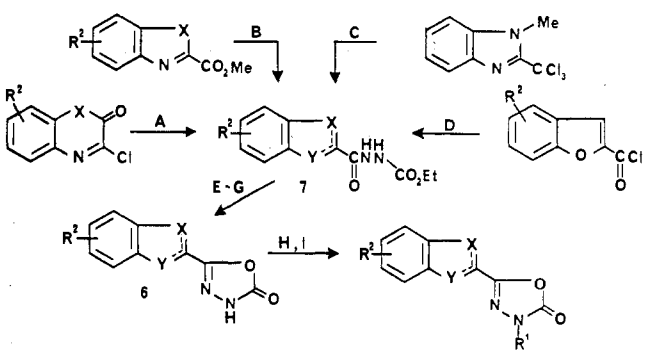
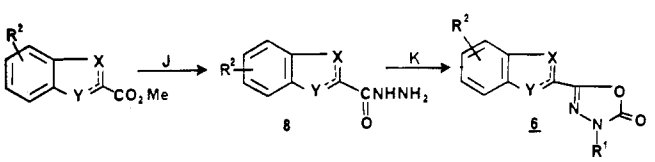
These compounds are potent inhibitors of the anaphylactically induced histamine release from rat peritoneal mast cells (RMC) and are orally active as inhibitors of IgE-mediated passive cutaneous anaphylaxis in the rat (PCA).

Chemistry. Several 2,3-dihydro-2-oxo-1,3,4-oxadiazole-substituted heterocycles are known. For example, pyridyl-, quinolyl-, furyl-, thienyl-,[9] pyridazyl,[10] and indolyloxadiazolones[11] have been described. In addition, nitroimidazolyloxadiazolones[12] and methyl isoxazolyloxadiazolone[13] have been reported active as antibacterial and antilepral agents, respectively. However, as far as we are able to determine, the benzo heterocyclic oxadiazolones (**6**) are new.[14]

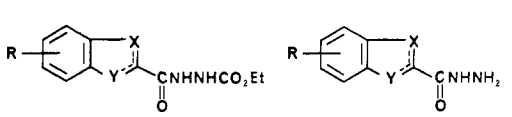
Scheme I



Scheme II



The oxadiazolones (**6**) herein described were prepared either by the thermal cyclization of acylcarbazates (**7**) or



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(1) Cox, J. S. G.; Beach, J. E.; Blair, A. M. J. N.; Clarke, A. J.; King, J.; Lee, T. B.; Loveday, D. E. E.; Moss, G. F.; Orr, T. S. C.; Ritchie, J. T.; Sheard, P. *Adv. Drug. Res.* **1970**, *5*, 115.

(2) Giles, R. E.; Herzig, D. *Annu. Rep. Med. Chem.* **1975**, *10*, 80. Oronsky, A. L.; Wasley, J. F. *Ibid.* 1975, *11*, 51. Oronsky, A. L.; Wasley, J. F. *Ibid.* **1977**, *12*, 70. Bell, S. C.; Capetola, R. J. *Ibid.* **1978**, *13*, 51. Bell, S. C.; Capetola, R. J. *Ibid.* **1979**, *14*, 51. Devlin, J. P. *Ibid.* **1980**, *15*, 59. Devlin, J. P. *Ibid.* **1981**, *16*, 61.

(3) For recent examples, see: Althuis, T. H.; Moore, P. F.; Hess, H. J. *J. Med. Chem.* **1979**, *22*, 44. Schwender, C. F.; Sunday, B. R.; Herzig, D. J. *Ibid.* **1979**, *22*, 114. Judy, P. E.; Hudyma, T. W.; Brown, M.; Essery, J. M.; Partyka, R. A. *Ibid.* **1979**, 163. Temple, D. L.; Yevich, J. P.; Cocington, R. R.; Hanning, C. A.; Seidehamel, R. J.; Mackey, H. K.; Bartek, M. J. *Ibid.* **1979**, *22*, 505. Schwender, C. F.; Sunday, B. R.; Herzig, D. J.; Kusner, E. K.; Schumann, P. R.; Gawlak, D. L. *Ibid.* **1979**, *22*, 748. Philipp, A.; Jirkousky, I.; Martel, R. R. *Ibid.* **1980**, *23*, 1372. Schwender, C. F.; Sunday, B. R.; Kerbleski, J. J.; Herzig, D. J. *Ibid.* **1980**, *23*, 964. Pfister, J. R.; Wymann, W. E.; Mahoney, J. M.; Waterbury, L. D. *Ibid.* **1980**, *23*, 1264. Klaubort, D. H.; Sellstedt, J. H.; Guinosso, C. J.; Capetola, R. J.; Bell, S. C. *Ibid.* **1981**, *24*, 742. Sirean, J. C.; Capiris, T.; Kesten, S. J.; Herzig, D. J. *Ibid.* **1981**, *24*, 735.

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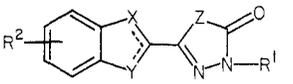
Table I. Inhibition of RMC and Rat PCA by 2-(2-Oxo-1,3,4-oxadiazol-5-yl) Benzo Heterocycles

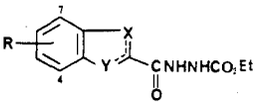


compd[e]	X	Y	Z	R^1	R^2	method	mp, °C	RMC:[a] I_{50}, μM	PCA,[b-d] po: % I at 25 mg/kg	PCA,[b-d] po: ED_{50}, mg/kg
6a	O	N	O	H	H	E	220-223	1.2		3 (7)
6b	O	N	O	H	5-Cl	E	263-266	0.35		16
6c	O	N	O	H	5-CO_2Me, 7-OMe	E	247-248	0.3		9 (2)
6d	O	N	O	H	6-Me	E	245-248	5.0		2 (4)
6e	O	N	O	H	5-CO_2Et	E	218-219	1.0	41	
6f	O	N	O	H	4-Me	E	247-251	1.0	43	
6g	O	N	O	H	5-Me	E	207-210	0.4		2 (4)
6h	S	N	O	H	H	E	235-236		43	
6i	O	N	O	Ac	H	H	231-232	1.4		
6j	O	N	O	CO_2Et	H	H	189-190	*f*		
6k	O	N	O	CO_2Et	6-Me	H	164-166	*f*		
6l	O	N	O	COCH=CHC_6H_5	H	H	229-232	15		13
6m	O	N	O	CH_2CO_2Et	H	I	125-126	*f*	2	
6n	O	N	O	Me	H	I	203-205	*f*		
6o	N Me	N	O	H	H	F, K	292-294	0.9		1 (6)
6p	N-Me	N	O	CO_2Et	H	H	179-181	*f*		
6q	N-Me	N	O	Ac	H	H	220-222	0.5		0.6 (3)
6r	N-Me	N	O	H	5-Me	K	>300	6.0		5
6s	N-Me	N	O	CO_2Et	5-Me	H	197-200	*f*		8 (2)
6t	C-Cl	S	O	H	H	K	218-220	0.2	31	>125
6u	C-Me	CH_2	O	H	H	K	229-230	*f*	30[g]	>100
6v	C-H	NH	O	H	H	K	226-270	33	18[h]	
6w	C-H	NH	O	H	6-Cl	K	265-268	*i*		9
6x	C-H	O	O	H	H	G	202-203	1.5		2
6y	N-Me	N	NH	H	H	K	293-296	*f*		
6z	O	N	NH	H	H	L	>300	60	29	
DSCG								3		6 (ip)

[a] For all compounds, inhibition of AIR was concentration dependent, and inhibition at <10 μM was significant at the 0.05 level. [b] Unless noted otherwise, results represent a single trial and are statistically significant using student's *t* test. ($p \leq 0.05$). [c] Total number of trials shown in parentheses. [d] Compounds that caused the stimulation of AIR were not tested in PCA. [e] All compounds, except 6a,g,o,v, had elemental analyses within ±0.4% of theory. For 6g: Anal. ($C_{10}H_7N_3O_3$) C, H; N: calcd, 19.35; found, 19.81. For 6v: Anal. ($C_{10}H_7N_3O_2$) C, H; N; calcd, 20.89; found, 21.30. [f] Stimulation of AIR. [g] Inhibition at 10 mg/kg. [h] Not statistically significant. [i] 46% inhibition at 100 μM.

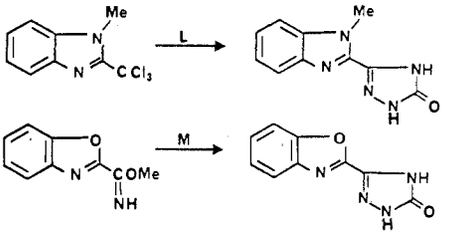
by the treatment of hydrazides (**8**) with phosgene. For example, 2-(2,3-dihydro-2-oxo-1,3,4-oxadiazol-5-yl)benzoxazole (**6a**) (Table I) was synthesized by heating ethyl 3-(2-benzoxazolyl)hydrazinecarboxylate (**7a**) (Table II) in

Table II. Substituted 3-(2-Benzo heterocyclic) Ethyl Hydrazinecarboxylates



compd	R	X	Y	method	mp, °C
7a	H	O	N	A, B	175-176
7b	5-Cl	O	N	A	189-190
7c	5-CO_2Me, 7-OMe	O	N	A	171-173
7d	6-Me	O	N	A	138-140
7e	5-CO_2Et	O	N	A	144-145
7f	4-Me	O	N	A	126-128
7g	5-Me	O	N	B	131-133
7h	H	S	N	B	168-169
7i	H	N-Me	N	C	190-193
7j	H	O	C	D	237-238

Scheme III



(4) For recent examples, see: Erickson, E. H.; Hainline, C. F.; Lenon, L. S.; Matson, C. J.; Rice, T. K.; Swingle, K. F.; Van Winkle, M. *J. Med. Chem.* **1979**, *22*, 816. Unangst, P. C.; Brown, R. E.; Herzig, D. J. *Ibid.* **1980**, *23*, 1251. Sircar, J. C.; Capiris, T.; Kesten, S. J. Herzig, D. J. *Ibid.* **1981**, *24*, 735. Kalubert, D. H.; Sellstedt, J. H.; Ginosso, C. J.; Bell, S. C.; Capetola, R. J. *Ibid.* **1981**, *24*, 748. Tinney, F. J.; Cetenko, W. A.; Kerbleski, J. J.; Connor, D. T.; Sorenson, R. J.; Herzig, D. J. *Ibid.* **1981**, *24*, 878.
(5) Buckle, D. R.; Cantello, B. C. C.; Smith, H.; Spicer, B. A. *J. Med. Chem.* **1977**, *20*, 265.
(6) Snader, K. M.; Chakrin, L. W.; Cramer, R. D.; Gelernt, Y. M.; Miao, C. K.; Shah, D. H.; Uenslausky, J. E.; Willis, C. R.; Sutton, B. M. *J. Med. Chem.* **1977**, *22*, 706.
(7) Vitolo, M. J.; Marquez, V. E.; Hurtado, I. *J. Med. Chem.* **1978**, *21*, 692.
(8) Tenbrink, R. E.; McCall, J. M.; Johnson, H. G. *J. Med. Chem.* **1980**, *23*, 1058.
(9) Yale, H. L.; Losee, K. A.; Perry, F. M.; Berstein, J. *J. Am. Chem. Soc.* **1954**, *76*, 2208.
(10) Akhrem, A. A. *Khim. Geterosilk. Svedin.* **1973**, 556.
(11) Robba, M.; Maume, D.; Lancelot, J. C. *Tetrahedron Lett.* **1973**, 3235.
(12) German Specification 2045789, 1971.
(13) Gardner, T. S.; Wenis, E.; Lee, J. *J. Org. Chem.* **1961**, *26*, 1514.
(14) The exception is compound **6v**; see ref 11.

Dowtherm A at 230 °C for 1 h (Scheme I). Intermediate **7a** was prepared by treating 3-chloro-1,4-benzoxazin-2-one[15] with ethyl carbazate in dioxane and triethylamine at room temperature for 4 h. In a like manner, compounds **6b–h** were prepared.

1-Methyl-2-(2,3-dihydro-2-oxo-1,3,4-oxadiazol-5-yl)-benzimidazole (**6o**) was also synthesized from intermediate **7i** via Scheme I; however, the route via Scheme II was preferable in the benzimidazole series. Thus, treatment of intermediate **8a** with excess phosgene in methylene chloride at room temperature gave compound **6o** as the hydrochloride salt. Intermediate **8a** was made by adding an aqueous solution of hydrazine to a solution of methyl 1-methyl-2-benzimidazolecarboxylate[16] in 2-propanol and heating the reaction at 60 °C for 1 h. The thiophene and indene derivatives (**6t** and **6u**) were also prepared via Scheme II. Triazolone derivatives of benzimidazole and benzoxazole (**6y** and **6z**) were synthesized for biological comparison with the active oxadiazolones (see Scheme III).

Biological Results and Discussion

The results obtained for the 2-(2,3-dihydro-2-oxo-1,3,4-oxadiazol-5-yl) benzoheterocycles in the antigen-induced release of histamine (AIR) from passively sensitized rat peritoneal mast cells (RMC) and in the IgE-mediated rat passive cutaneous anaphylaxis (PCA) assays are listed in Table I.

In general, oxadiazolones substituted in the 5-position with 2-benzoxazoles or 2-benzimidazoles are potent, relative to DSCG, inhibitors of AIR in vitro from RMC. The most potent compound, 3-chloro-2-(2,3-dihydro-2-oxo-1,3,4-oxadiazol-5-yl)benzo[*b*]thiophene (**6t**), with an I_{50} value of 0.2 μM, is 15 times more potent than DSCG as an inhibitor of AIR.

Substitution on the aromatic ring in the benzoxazole series resulted in increased activity (**6b,c,g**) or retention of the same level of potency (**6d,e,f**) relative to the unsubstituted compound (**6a**). Substitution on the 3-position (R^1) of the oxadiazolones resulted, in general, in stimulation of the spontaneous release of histamine from RMC.

The triazolone derivative of benzimidazole (**6y**) and benzoxazole (**6z**) were also prepared, and they displayed less activity as inhibitors of AIR than their corresponding oxadiazolones, **6o** and **6a**, respectively.

Twelve oxadiazolones (**6a–d,g,l,o,q–s,w,x**) in Table I showed good oral activity as inhibitors of the IgE-mediated passive cutaneous anaphylaxis reaction in the rat. When tested intraperitoneally, 1-methyl-2-(2,3-dihydro-2-oxo-1,3,4-oxadiazol-5-yl)benzimidazole (**6o**) is 4–5 times as potent as DSCG (dose–response curve not shown; see Figure 1 for a single dose study). There is no clear correlation between the in vitro and in vivo (oral) activity for the oxadiazolones listed in Table I.

Compound **6a** has been investigated in detail and was found to have an activity profile similar to that of DSCG as an inhibitor of AIR in vitro from RMC.[17] Secondary studies in the rat PCA demonstrated that **6o** has an intraperitoneal time course of activity similar to that of DSCG (Figure 1); inhibition of PCA was greatest when either compound was given 5–15 min prior to antigen challenge, and inhibitory activity diminished rapidly as the interval between administration of compound and antigen

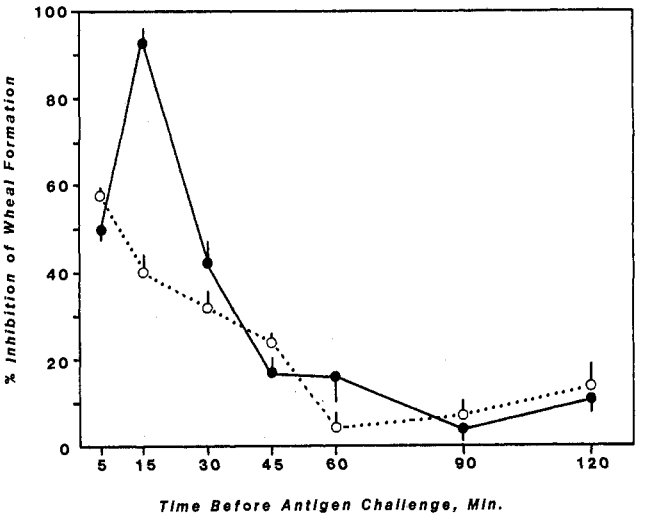


Figure 1. Effect of varying the time of intraperitoneal administration of compound on the inhibition of passive cutaneous anaphylaxis in the rat. Compound **6o** (●) was given at 1.5 mg/kg and DSCG (○) was given at 6 mg/kg. The values shown represent the mean percent inhibition plus or minus the standard error for each group of four to eight rats.

challenge was lengthened. These results taken together suggested that a DSCG-like inhibition of mediator release may be operative for the oxadiazolones described in this report.

We have described the preparation of a new series of benzo heterocyclic oxadiazolones. Most of these compounds possess significant antiallergic activity with a mechanism of action similar to that of DSCG. Both compounds **6a** and **6o**, which are of high interest as potential antiallergic agents for the prophylaxis of asthma, have been extensively studied.[17,18]

Experimental Section

Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. Spectra were recorded for all compounds and were consistent with assigned structures. NMR were recorded onna Varian EM-390 spectrometer at 90 MHz. IR spectra were recorded on a Perkin-Elmer Moodel 298 spectrophotometer. All compounds, unless otherwise indicated, had elemental analyses within ±0.4% of theoretical values.

Typical Procedures for Scheme I. Ethyl 3-(2-Benzoxazolyl)hydrazinecarboxylate (7a) Method A. A mixture of 15 g (82.4 mmol) of 3-chloro-1,4-benzoxazin-2-one[15] and 8.4 g (80 mmol) of ethyl carbazate in 80 mL of dioxane and 12 mL of triethylamine was stirred for 4 h at room temperature. The organic solvent was evaporated, and water (100 mL) was added to the residue with stirring. The resulting solid was filtered and dried. Recrystallization from acetonitrile gave 12.5 g (63%) of white crystals, mp 175–176 °C.

Method B. A mixture of methyl 2-benzoxazolecarboxylate (106 mg, 0.6 mmol) and ethyl carbazate (68.5 mg, 0.65 mmol) in dioxane was refluxed overnight. The organic solvent was evaporated, and the residue was extracted with hot hexane and ether to remove unreacted ester. Recyrstallization from acetonitrile gave 73.2 mg (49%) of pure material, mp 175–176 °C. Intermediates **7b–h** were prepared by the method indicated in Table II.

Ethyl 3-(1-methyl-2-benzimidazolyl)hydrazinecarboxylate (7i). Method C. A mixture of 1-methyl-2-(trichloromethyl)-benzimidazole[16] (24.9 g, 0.1 mol), ethyl carbazate (10.4 g, 0.1 mol), acetonitrile (100 mL), water (100 mL), and sodium bicarbonate

(15) Dickore, K.; Sasse, K.; Bode, K. *Liebigs Ann. Chem.* **1971**, *733*, 70–87.

(16) Methyl 1-methylbenzimidazole-2-carboxylate was made form 1-methyl-2-(trichloromethyl)benzimidazole by a modification of a procedure developed by: Nolan, G.; Samuel, E. L.; Ennis, B. C.; Hinde, R. W. *J. Chem. Soc. C* **1967**, 30.

(17) Khandwala, A.; Coutts, S. M.; Dally-Meade, V.; Jariwala, N.; Huang, F. C. *Int. Arch. Allergy Appl. Immunol.* **1983**, *70*, 311.

(18) Khandwala, A.; Coutts, S. M.; Dally-Meade, V.; Jariwala, N.; Musser, J.; Jones, H.; Loev, B.; Weinyrb, I. *Biochem. Pharmacol.*, in press.

(33.6 g, 0.8 mol) was refluxed for 1 h. After cooling, the reaction was diluted with methylene chloride (200 mL). The organic phase was separated, washed with water, dried ($MgSO_4$), and concentrated to give 12.8 g (49%) of solid, mp 190–193 °C.

Ethyl 3-(2-Benzofuranyl)hydrazinecarboxylate (7j). Method D. To a solution of 2-(chlorocarbonyl)benzofuran (45 g, 0.25 mol) in acetonitrile (500 mL) was added ethyl carbazate (27 g, 0.26 mol). After heating at reflux for 1 h, the reaction was cooled to 0 °C for 18 h. The precipitate was filtered, washed (ether), and dried. Recrystallization from ethanol gave 37.2 g (60%) of product, mp 137–138 °C.

2-(2,3-Dihydro-1,3,4-oxadiazol-5-yl)benzoxazole (6a). Method E. Twelve grams (0.048 mol) of intermediate **7a** was added with stirring to Dowtherm A (250 mL) at 230–240 °C. After heating for 1 h, the reaction mixture was cooled and filtered, and the solid product was washed with hexane. Recrystallization from acetonitrile gave 7.5 g (77%) of **6a**, mp 220–223 °C. Anal. ($C_9H_5N_3O_3$) C, H; N: calcd, 20.68; found, 21.10.

1-Methyl-2-(2,3-dihydro-2-oxo-1,3,4-oxadiazol-5-yl)benzimidazole (6o). Method F. A suspension of 10 g (0.038 mol) of the intermediate **7i** in Dowtherm A (30 mL) was heated at 180 °C for 30 min. The reaction was filtered hot. After coolng, the precipitate was washed with ether and recrystallized from acetone to give 1.69 g (22%) of **6o**, mp >300 °C. Anal. ($C_{10}H_8N_4O_2$) H; C, N: calcd, 55.55, 25.92; found, 55.06, 25.42.

2-(2,3-Dihydro-2-oxo-1,3,4-oxadiazol-5-yl)benzofuran (6x). Method G. Four grams (16 mmol) of intermediate **7i** in Dowtherm was heated at 240 °C for 4 h. After cooling, the reaction was filtered. The product was purified by HPLC, using 3:1 hexane/acetone, to give 2.8 g (88%) of white powder, mp 202–203 °C.

2-(2,3-Dihydro-2-oxo-3-acetyl-1,3,4-oxadiazol-5-yl)benzoxazole (6i). Method H. Five grams (24 mmol) of 2-(2,3-dihydro-2-oxo-1,3,4-oxadiazol-5-yl)benzoxazole in 50 mL of acetic acid containing 5 mL of acetic anhydride was heated for 1 h at 100 °C. The mixture was poured into water, and the crystalline product was filtered. Recrystallization from acetonitirle gave 3.9 g (64%) of **6i**, mp 231–232 °C. In a manner similar to the above general procedures and with appropriate starting materials and reagents, compounds **6j–6,p,q,s** were prepared (Table I).

2-[2,3-Dihydro-2-oxo-3-(methylenecarbethoxy)-1,3,4-oxadiazol-5-yl]benzoxazole (6m). Method I. To a degreased suspension of sodium hydride (7.7 g) in DMF was added 6.9 g (34 mmol) of compound **6a**. The mixture was stirred at room temperature for 5 min. Ethyl bromoacetate (10 g) was added slowly. The reaction was stirred overnight at room temperature. Water was added, and the resulting precipitate was collected and dried. Recrystallization from acetone gave the desired product (6.18 g, 63%), mp 125–126 °C. Compound **6n** was prepared in a similar manner.

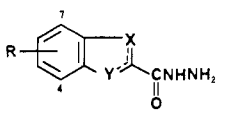
Typical Procedures for Scheme II. Methyl 1-Methyl-2-benzimidazolecarboxylate.[16] A solution of 1-methyl-2-(trichloromethyl)benzimidazole (249.5 g, 1 mol) in methanol (1 L) was refluxed for 2 days. The mixture was concentrated in vacuo, and water (200 mL) was added. The resulting suspension was neutralized with $NaHCO_3$ (250 g) and extracted with chloroform (3 × 200 mL). The organic phase was separated, dried ($MgSO_4$), and concentrated to give 117.8 g (62%) of solid, mp 99–99.5 °C.

2-(1-Methyl-2-benzimidazolyl)hydrazine (8a). Method J. To a solution of methyl 1-methyl-2-benzimidazolecarboxylate (95 g, 0.5 mol) in 2-propanol (500 mL) was added an aqueous solution (85%) of hydrazine (190 mL). The reaction was heated at 60 °C for 1 h and then cooled to 0 °C. The resulting precipitate was filtered, washed (ether), and dried to give 86.5 g (91%) of **8a**, mp 156–159 °C.

Intermediates **8b–f** were prepared by using appropriate starting materials in the same manner as above (see Table III).

1-Methyl-2-(2,3-dihydro-2-oxo-1,3,4-oxadiazol-5-yl)benzimidazole (6o). Method K. Phosgene gas was slowly dispersed through a suspension of 2-(1-methyl-2-benzimidazolyl)hydrazine (95 g, 0.5 mol) in methylene chloride (300 mL) until saturated. After the solution was stirred for 1 h, the precipitate was filtered, washed (CH_2Cl_2), and dried. The solid thus obtained is the hydrochloride salt (mp 253–261 °C dec), which can be converted to the free base (mp >300 °C) by treatment with aqueous sodium bicarbonate to give 92.9 g (92%) of **6o**. In a like manner as above, compounds **6r,t–w** were prepared with appropriate starting materials.

Table III. Substituted Benzo Heterocyclic Hydrazide



compd	R	X	Y	method	mp, °C
8a	H	N-Me	N	J	157–159
8b	5-Me	N-Me	N	J	185–186
8c	H	C-Cl	S	J	178–180
8d	H	C-CH_3	CH_2	J	64–65
8e	H	CH	NH	J	177–179
8f	5-Cl	CH	NH	J	263–267

Typical Procedures for Scheme III. 1-Methyl-2-(2,3-dihydro-2-oxo-1*H*-1,3,4-triazol-5-yl)benzimidazole (6y). Method L. A mixture of 1-methyl-2-(trichloromethyl)benzimidazole (23.7 g, 0.1 mol), semicarbazide (7.5 g, 0.1 mol), triethylamine (50 mL), water (100 mL), and acetonitrile (200 mL) was refluxed for 5 h. The reaction was filtered hot, giving 4.1 g of crude product. This material was purified by treating it with methanol at reflux for 0.5 and then filtering it hot to give a white solid (3.87 g, 18%), mp 293–296 °C.

2-(2,3-Dihydro-2-oxo-1*H*-1,3,4-triazol-5-yl)benzoxazole (6z). Method M. Methyl 2-benzoxazolimidate (8.0 g, 342 mmol) and ethyl carbazate (5.2 g, 50 mmol) in 60 mL of dioxane was heated at 110 °C overnight. After evaporation of solvent, the residue was suspended in 45 mL of Dow Therm and heated at 220 °C for 15 min. The precipitated product was filtered, washed with CH_2Cl_2 and CH_3OH, and dried to give 3.6 g (56%) of solid, mp >300 °C.

Rat Mast Cell (RMC) Test.[17,19] RMC were passively sensitized in vitro with rat anti-ovalbumin serum. Spontaneous histamine release (SR in the absence of antigen) and AIR (in the presence of antigen) from these passively sensitized RMC were measured after 15-min incubation. Both the histmaine released into the incubation medium and the residual histamine extracted from the RMC were measured fluorometrically with a Technicon Auto-Analyzer. Both SR and AIR are expressed as percent of total extractable histamine released in the presence of antigen. The effect of the test compound on both SR and AIR was determined. Test compounds were added simultaneously with antigen. The activity of the test compound is expressed as percent inhibition of AIR or as the I_{50} value (concentration of the test compound required to inhibit AIR by 50%). Test compounds were dissolved in Me_2SO (final concentration of Me_2SO was 0.17% and did not affect AIR).

Passive Cutaneous Anaphylaxis in the Rat (PCA). The effect of compounds on IgE-mediated cultaneous wheal formation in the rat was determined by a modification of the method of Watanabe and Ovary.[20] Antiserum for these studies was prepared according to the following immunization protocol. Male Sprague–Dawley rats (approximately 250 g) were injected intramuscularly on days 0, 2, and 4 with 10 μg of ovalbumin and 20 mg of aluminum hydroxide (Mphojel) in 1 mL of saline. On day 0 each rat also was given 10^9 *Bordatella pertussis* organisms by the intraperitoneal route. Rats were exsanguinated on day 8, and serum was collected by the usual methods. The method for passive cutaneous anaphylaxis was as follows. Naive rats were sensitized at dorsal sites by intradermal injection of the syngenetic IgE anti-ovalbumin antiserum (1:20 dilution). After a latency period of 48 h to allow cytophilic antibodies to bind to the cutaneous mast cells, groups of four rats were given either vehicle (1% methylcellulose, 3 mL) or graded doses of compound (1 dose/rat). Rats were challenged intravenously with antigen (4 mg of ovalbumin) in 1% Evans blue dye 10 min after oral administration of test compound. Thirty minutes after antigen challenge, the rats were sacrificed by cervical dislocation, the dorsal

(19) Kusner, E.; Dubnick, B.; Herzig, D. J. *J. Pharm. Exp. Ther.* **1973**, *184*, 41.
(20) Watanabe, N.; Ovary, A. *J. Immunol. Methods* **1977**, *14*, 381.

skins were reflected, and blued wheal areas were measured. Mean values, plus or minus the standard error, for wheal areas in control and drug-treated groups were determined and compared statistically by Student's t test. A comparative time-course study was carried out for one of the 2-(2,3-dihydro-2-oxo-1,3,4-oxadiazol-5-yl) benzo heterocycles (**6o**) and disodium cromoglycate. These studies were carried out by the same general passive cutaneous anaphylaxis (PCA) protocol, except that 1.5 mg/kg of compound **6o** or 6 mg/kg of DSCG was given intraperitoneally at intervals ranging from 5 to 120 min prior to antigen challenge.

Acknowledgment. We thank Dr. C. Rehm and his staff in the Department of Analytical Chemistry for the analyses.

Registry No. **6a**, 78620-37-8; **6b**, 78620-15-2; **6c**, 78620-16-3; **6d**, 78620-17-4; **6e**, 78620-18-5; **6f**, 78620-19-6; **6g**, 78620-20-9; **6h**, 78620-21-0; **6i**, 78620-22-1; **6j**, 78620-23-2; **6k**, 78620-24-3; **6l**, 87802-12-8; **6m**, 87802-13-9; **6n**, 87802-14-0; **6o**, 78620-28-7; **6p**, 78620-25-4; **6q**, 78620-26-5; **6r**, 87802-15-1; **6s**, 87802-16-2; **6t**, 78620-31-2; **6u**, 87802-17-3; **6v**, 37574-86-0; **6w**, 87802-18-4; **6x**, 78620-33-4; **6y**, 78620-32-3; **6z**, 78620-35-6; **7a**, 78620-14-1; **7b**, 78620-38-9; **7c**, 78620-39-0; **7d**, 78620-40-3; **7e**, 78620-41-4; **7f**, 78620-42-5; **7g**, 78620-43-6; **7h**, 78620-44-7; **7i**, 78620-27-6; **7j**, 78620-34-5; **8a**, 78620-29-8; **8b**, 87802-08-2; **8c**, 62524-21-4; **8d**, 87802-09-3; **8e**, 5055-39-0; **8f**, 20948-67-8; 3-chloro-1,4-benzoxazin-2-one, 27383-81-9; 3,6-dichloro-1,4-benzoxazin-2-one, 27507-86-4; 3-chloro-8-methoxy-6-(methoxycarbonyl)-1,4-benzoxazin-2-one, 87802-04-8; 3-chloro-7-methyl-1,4-benzoxazin-2-one, 79129-36-5; 3-chloro-6-(ethoxycarbonyl)-1,4-benzoxazin-2-one, 87802-05-9; 3-chloro-5-methyl-1,4-benzoxazin-2-one, 87802-06-0; ethyl carbazate, 4114-31-2; methyl 2-benzoxazolecarboxylate, 27383-86-4; methyl 5-methyl-2-benzoxazolecarboxylate, 27383-91-1; methyl 2-benzothiazolecarboxylate, 87802-07-1; 1-methyl-2-(trichloromethyl)benzimidazole, 14468-46-3; 2-(chlorocarbonyl)-benzofuran, 41717-28-6; ethyl bromoacetate, 105-36-2; methyl 1-methyl-2-benzimidazolecarboxylate, 2849-92-5; hydrazine, 302-01-2; methyl 1,5-dimethyl-2-benzimidazolecarboxylate, 87802-10-6; methyl 3-chloro-2-benzo[b]thiophenecarboxylate, 21211-07-4; methyl 3-methyl-1H-indene-2-carboxylate, 7316-64-5; methyl 2-indolecarboxylate, 1202-04-6; methyl 5-chloro-2-indolecarboxylate, 87802-11-7; phosgene, 75-44-5; semicarbazide, 57-56-7; methyl 2-benzoxazoleimidate, 33652-92-5.

Antiallergic Agents. 3.[1] N-(1H-Tetrazol-5-yl)-2-pyridinecarboxamides

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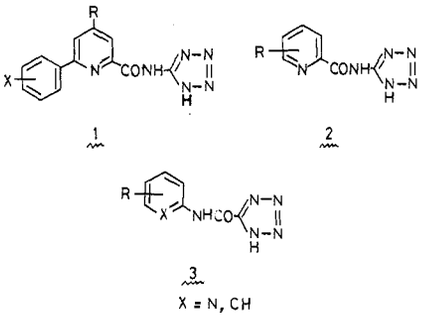
A series of N-tetrazolylpyridinecarboxamides was prepared and evaluated for antiallergic activity by the passive cutaneous anaphylaxis (PCA) assay. From the structure–activity relationships (SAR) of this class of compounds, it was revealed that the N-tetrazolylcarbamoyl group as an acidic functionality is required to be at the 2-position of the pyridine nucleus and that the phenyl group as a subtituent is not necessarily required for activity. 6-Methyl-N-(1H-tetrazol-5-yl)-2-pyridinecarboxamide (**36**) showed good oral activity and low toxicity.

Since the discovery of disodium cromoglycate (DSCG),[2] a large number of chemical series[3] have been disclosed as orally effective antiallergic agents. As part of a program aimed at seeking new series of antiallergic agents, we have previously reported[1a] that N-(1H-tetrazol-5-yl)-6-phenyl-2-pyridinecarboxamide, obtained by molecular modification of chromone-2-carboxylic acid, showed potent antiallergic activity on oral administration. After extensive study on this structure, **1** (R = Me; X = 4-NHMe) was



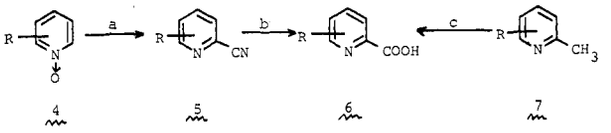
1 **2**

3

X = N, CH

found to be a potential candidate for a clinically useful antiallergic agent.[1b] While it appeared that the effect of substitution on the benzene ring of **1** was apparent,[1b] it was of interest to gain further insight into the structure–activity relationships (SAR) of this class of compounds. A larger number of derivatives (**2**), without a phenyl substituent, were prepared in view of this principle, and they were substantially potent inhibitors of the passive cutaneous anaphylaxis (PCA) reactions in rats. A recent publication[4] reporting the antiallergic activity of **3**, a reversed amide structure of **2**, prompted us to report our results obtained with **2**.

Scheme I[a]



4 **5** **6** **7**

[a] a = (1) Me_2SO_4, (2) NaCN; b = HCl; c = SeO_2, pyridine.

Chemistry. The N-tetrazolylpyridinecarboxamides listed in Tables I and II were prepared by condensation of 5-aminotetrazole with a carboxylic acid as described previously.[1] The choice of the condensation method (Experimental Section) was arbitrary. Most of the alkyl-substituted pyridinecarboxylic acids were prepared via a Reissert–Kaufman-type reaction,[5,1b] with the exception of 3- and 5-methyl-2-pyridinecarboxylic acids,[6] which were

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(1) (a) Part 1 of this series: Honma, Y.; Sekine, Y.; Hashiyama, T.; Takeda, M.; Ono, Y.; Tsuzurahara, K. *Chem. Pharm. Bull.* **1982**, *30*, 4314. (b) Part 2 of this series: Honma, Y.; Oda, K.; Hashiyama, T.; Hanamoto, K.; Nakai, H.; Inoue, H.; Ishida, A.; Takeda, M.; Ono, Y.; Tsuzurahara, K. *J. Med. Chem.* **1983**, *26*, 1499.
(2) (a) Speight, R. N.; Aery, G. S. *Drugs* **1974**, *7*, 164. (b) Cox, J. S. G. *Nature (London)* **1967**, *216*, 1328.
(3) Johnson, P. C.; Gillespie, E.; Temple, D. L., Jr. *Annu. Rep. Med. Chem.* **1982**, *17*, 51, and earlier volumes.
(4) (a) Klaubert, D. H.; Sellstedt, J. H.; Guinosso, C. J.; Bell, S. C.; Capetola, R. J. *J. Med. Chem.* **1981**, *24*, 748. (b) Klaubert, D. H.; Sellstedt, J. H.; Guinosso, C. J.; Capetola, R. J.; Bell, S. C. *J. Med. Chem.* **1981**, *24*, 742.
(5) Feely, W. E.; Evanega, G.; Beavers, E. M. In "Organic Syntheses"; Wiley: New York, 1973; Collect. Vol. V, p 269.
(6) Auterhoff, H. A.; Stecher, K. *Arch. Pharm. (Weinheim, Ger.)* **1963**, *296*, 660.

0022-2623/84/1827-0125$01.50/0