2-Chloro-4-(benzoyloxy)phenol (32). To a suspension of 107.1 g (0.5 mol) of 4-(benzoyloxy)phenol[7] in 1500 mL of $CHCl_3$ was added dropwise 67.5 g (0.5 mol) of SO_2Cl_2 in 100 mL of $CHCl_3$ over a 30-min period. The suspension was then stirred overnight at room temperature. A small amount of undissolved material was separated by filtration and the filtrate was concentrated in vacuo to a white solid. The material was recrystallized from EtOAc: yield 73.5 g (59.2%); mp 123–124 °C. Anal. ($C_{13}H_9ClO_3$) C, H, Cl.

4-[6-(2-Chloro-4-hydroxyphenoxy)hexyl]-3,5-diethyl-1*H*-pyrazole (26). A mixture of 24.9 g (0.1 mol) of 2-chloro-4-(benzoyloxy)phenol (**32**), 29.1 g (0.1 mol) of 4-(6-bromohexyl)-3,5-heptanedione,[3] 27.6 g (0.2 mol) of anhydrous K_2CO_3, 6 g of KI, and 400 mL of CH_3COCH_3 was refluxed with stirring for 24 h. The insoluble material was removed by filtration. The filtrate was concentrated to ~100 mL and diluted with 500 mL of $(C_2H_5)_2O$, and then the organic layer was washed with H_2O and dried. Removal of the solvent gave an oil, 45.9 g, which would not solidify. To a solution of 14.2 g (0.1 mol) of the oil obtained above in 50 mL of absolute C_2H_5OH was added 10 mL (0.2 mol) of hydrazine hydrate. The solution was refluxed with stirring for 2 h and then the solvent was removed in vacuo. To the residual oil was added 20 mL of 6 N HCl and the mixture was stirred until a solid formed. The material was collected and recrystallized from CH_3CN: yield 12.2 g (31.79%); mp 109–111 °C. Anal. ($C_{19}H_{27}ClN_2O_2$) C, H, N.

(7) F. Kehrmann, M. Sandoz, and R. Monnier, *Helv. Chim. Acta*, 4 941 (1921).

4-[6-[2-Chloro-4-(methylthio)phenoxy]hexyl]-3,5-heptanedione (33). A mixture of 25.7 g (0.147 mol) of 2-chloro-4-(methylthio)phenol,[8] 48.6 g (0.15 mol) of 4-(6-bromohexyl)-3,5-heptanedione, 25 g (0.18 mol) of K_2CO_3, 2 g of KI, and 250 mL of $CH_3CH_2COCH_3$ was refluxed with stirring for 20 h. The solid was removed by filtration and the filtrate was concentrated to dryness. The residue was triturated with CH_2Cl_2 and the resulting suspension was filtered. The filtrate was again concentrated to an oil, which was distilled: bp 170 °C (0.4 mm); yield 46.9 g (82.3%). Anal. ($C_{20}H_{29}ClO_3S$) C, H, Cl.

4-[6-[2-Chloro-4-(methylsulfinyl)phenoxy]hexyl]-3,5-heptanedione (35). To a solution of 14 g (0.066 mol) of $NaIO_4$ in 250 mL of H_2O was added, with stirring, a solution of 23.5 g (0.0611 mol) of **33** in 250 mL of CH_3OH. The solution was stirred at room temperature for 18 h, during which time $NaIO_3$ precipitated. The mixture was concentrated in vacuo to a solid and then stirred with CH_2Cl_2 and filtered. The filtrate was concentrated to an oil, which was passed through a chromatographic column packed with 200 g of silica and eluted with ether to remove less polar impurities and then with MeOH. The material obtained by elution with MeOH was then passed through a high-pressure liquid chromatography column and eluted with a solution of 5% CH_3COCH_3–95% ether, and the product was obtained as an orange viscous oil: yield 11.5 g (81%). Anal. Calcd for $C_{20}H_{29}ClO_4S$: C, 59.91; H, 7.29; Cl, 8.84. Found: C, 58.93; H, 7.28; Cl, 8.50.

(8) S. L. Chein and K. T. Chow, *J. Chem. Soc.*, 7, 46 (1939).

Pyrazolo[5,1-*b*]quinazolin-9-ones: A New Series of Antiallergic Agents

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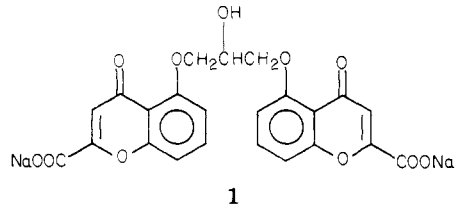
A new series of antiallergic agents, pyrazolo[5,1-*b*]quinazolin-9-ones, was synthesized and evaluated for inhibitory effects in the rat reaginic passive cutaneous anaphylaxis (PCA) screen. Several analogues were found to be more potent than cromolyn sodium intravenously. Structure–activity relationships are discussed. One of the compounds, 4,9-dihydro-5-methoxy-9-oxopyrazolo[5,1-*b*]quinazoline-2-carboxylic acid (**36**), was found to be approximately 250 times more potent than cromolyn sodium intravenously.

Cromolyn sodium (DSCG, 1) is a well-established drug



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for the treatment of asthma. Since its discovery, there have been intensive efforts in numerous laboratories to find additional DSCG-like antiallergic agents.[1] The dose (20 mg) of 1 is too large to be delivered by a metered-dose inhaler, so it has to be insufflated as a powder. This method of powder administration poses problems for young patients lacking coordination, and in some individuals the powder can cause irritation and bronchospasm. Moreover, recent studies[2] using ^{99m}Tc-labeled particles suggest that it is likely that there is considerable variation in the quantity and distribution of inhaled drug in patients with airway obstruction. This demonstrates the difficulty in delivering the right amount of drugs to the target organ via the inhalation route. The difficulty is further compounded when the drug must be delivered in high doses, as in the case of 1 (20 mg/dose). Hence, a compound which is at least 100–300 times more potent than 1 will reduce the dose (0.2–0.07 mg/dose) to a more acceptable range, thereby reducing the variability in the amount of drugs delivered to the target organ, and will probably increase the efficacy of the drug.

A desirable compound should share with cromolyn sodium[3] the capacity to inhibit allergen-induced mast-cell

(1) (a) E. H. Erickson, C. F. Hainline, L. S. Lenon, C. J. Matson, T. K. Rice, K. F. Swingle, and M. V. Winkle, *J. Med. Chem.*, **2?**, 816 (1979); (b) C. F. Schwender, B. R. Sunday, D. J. Herzig, E. K. Kusner, P. R. Schumann, and D. L. Gawlak, *J. Med. Chem.*, **22**, 748 (1979); (c) J. P. Devlin, *Annu. Rep. Med. Chem.*, **15**, 59 (1980); (d) M. K. Church, *Med. Actual.*, **14** (7), 281 (1978); (e) A. Philipp, I. Jirkovsky, and R. R. Martel, *J. Med. Chem.*, **23**, 1372 (1980).

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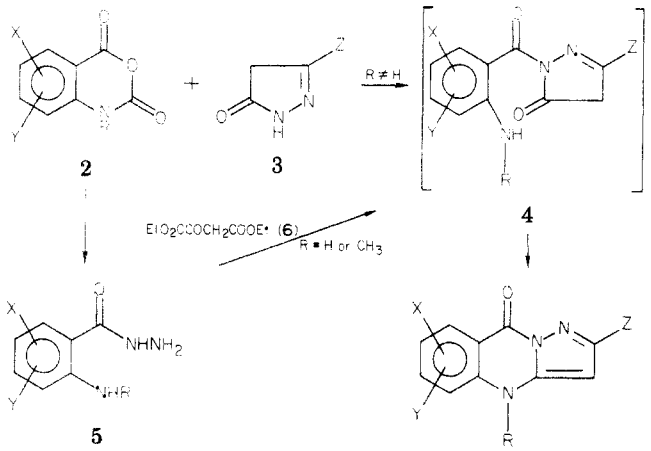
Scheme I



7a, Z = COOEt
b, Z = COOH
c, Z = $CONH_2$
d, Z = C≡N
e, Z = tetrazole
f, Z = CONH-tetrazole

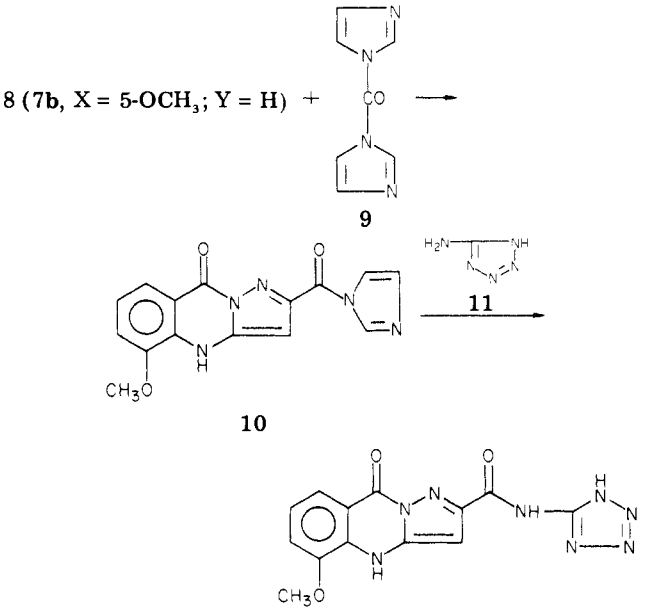
degranulation,[4] be active intravenously and inactive orally, and be administered by metered-dose aerosol. Aerosol administration has the advantage over oral administration of requiring lower doses, since the drug is delivered to the target organ; thus, one would expect possibly fewer systemic side effects. However, because the amount of drug that can be delivered by a metered-dose inhalation is limited, a drug must be relatively very potent to be used this way.

In this paper we report the synthesis and studies of the inhibitory effect of some pyrazolo[5,1-*b*]quinazolin-9-ones[5] on rat reaginic passive cutaneous anaphylaxis (PCA), a possible model of human atopy,[6] and compare their activities with cromolyn sodium (**1**). This series of antiallergic agents is much more potent than cromolyn sodium (**1**) intravenously. Thus, they are candidates for use as aerosol antiasthmatic agents.

Chemistry. The compounds were synthesized according to Scheme I. Anionic ring opening[8] of 2*H*-3,1-benzoxazine-2,4(1*H*)-diones [isatoic anhydrides (**2**)] with 3-substituted 1,4-dihydro-5*H*-pyrazol-5-ones (**3**) gave **7**, probably via **4**. The acids (**7b**; Z = COOH) were prepared by hydrolysis of the ester (**7a**). The acids (**7b**) were converted to the tetrazoles via the sequence of acid (**7b**; Table I) to amide (**7c**; Table IV) to nitrile (**7d**; Table V) to the tetrazoles (**7e**; Table II).

The *N*-1*H*-tetrazol-5-ylamides (**7f**; Table III) were made from the acids (**7b**) and 1*H*-tetrazol-5-amine (**11**) using 1,1′-carbonyldiimidazole (**9**) as a coupling agent[7] (Scheme II). Sometimes, the intermediates (**10**) were isolated and,

Scheme II



on treatment with 1*H*-tetrazol-5-amine (**11**) in DMF, gave the desired product, **12**.

The NH series (**7**, R = H) was mainly prepared from the acid hydrazide (**5**; Table VI) by reacting with sodium diethyloxalacetate (**6**). The compounds (**7**; R = H) were alkylated with alkyl halides and sodium carbonate in DMF to give **7** (R = alkyl), which were also synthesized by a ring-opening reaction of isatoic anhydrides (**2**) discussed below.

The acid hydrazides (**5**) were prepared either from the corresponding isatoic anhydrides (**2**) or anthranilate esters by reacting with hydrazine. Isatoic anhydrides (**2**) were prepared using the general methods reported earlier[8,9] except in a few cases (Table VII). 2-Amino-3,5-dimethoxybenzoic acid (**13**) was prepared by catalytic reduction of the corresponding 2-nitrobenzoic acid[10] methyl ester, followed by hydrolysis of the methyl anthranilate (**14**).

Biological Results and Discussion

The pyrazolo[5,1-*b*]quinazolin-9-ones synthesized as above were tested for their ability to inhibit the passive cutaneous anaphylaxis (PCA) reaction in rats (see Table I) as described under Experimental Section.[11] Those agents which showed an inhibition greater than 70% at 5 mg/kg ip were studied further for their iv and oral efficacy and compared with cromolyn sodium (**1**).

In the carboxylic acid series (Table I), substitution on the nitrogen in the 4 position showed methylated analogues to be similar in activity to those of the unsubstituted 4-NH series (**15** vs. **30**; **20** vs. **33**; **22** vs. **32**). In the case of the 7-chloro analogues (**16**, **31**, and **19**), N_4-methyl was more active than the NH compound, while N_4-benzyl was the least active. Aromatic substitution in the N_4-CH_3 series (Table I) indicated the following potency order preference at the 7 position: Cl, F, OCH_3 > CH_3 ≫ NH_2 > NHCO-

(3) P. J. Kingsley and J. S. G. Cox, *Allergy: Princ. Pract.*, **1**, 481-498 (1978).
(4) (a) D. Danoff, J. Shuster, and P. Gold, *J. Chronic Dis.*, **33**, 135 (1980); (b) M. H. M. Dykes, *J. Am. Med. Assoc.*, **227**, 1061 (1974); (c) N. Mazurek, G. Berger, and I Pecht, *Nature (London)*, **286**, 722 (1980).
(5) Recently, N. D. Heindel et al. have reported the synthesis of eight esters of the series but no biological activity: C. F. Beam, J. Brown, D. R. Dawkins, W. P. Fives, and N. D. Heindel, *J. Heterocycl. Chem.*, **16**, 957 (1979).
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(10) O. Eisleb, German Patent 501 609 (1927); *Chem. Abstr.*, **24**, 4792[9].
(11) D. J. Herzig, P. R. Schumann, E. J. Kusner, L. Robichaud, R. E. Giles, B. Dubnick, M. Von Strandtmann, S. Klutchko, M. P. Cohen, and J. Shavel, Jr., "Immunopharmacology", M. E. Rosenthale and H. C. Mansmann, Eds., Spectrum Publications, New York, 1975, pp 103-124.

CH_3 > $NHCOC_6H_5$. The 5-methoxy analogue (**26**) was similar in activity to the 7-methoxy analogue (**22**).

Aromatic substitution in the 4-NH series indicated a similar relationship, except for the 7-chloro analogue (**31**) which is less active than the unsubstituted analogue (**30**). The position of the methoxy substituent on the benzene ring does not seem to make a difference with intraperitoneal activity (**32** vs. **36** vs. **37**). Intravenously and orally, however, the 5-methoxy analogue (**36**) is the most active in the series.

In the cases of 5- or 7-hydroxy substitution, significant activity was retained as in the case of **39** and **40**. The dimethoxy analogues (**28** and **43**) were also very active. However, the activity of the 6,7-dichloro derivative (**42**) was absent at the screening dose (5 mg/kg).

Modification of the 2-carboxyl substitution led to interesting results (Table II and III). In the N_4-methyl series, carboxylic acid (**15**) and tetrazole analogues (**47**) were more active than the *N*-tetrazolylcarboxamide (**55**), while in the 4-NH series, carboxylic acid (**30** and **36**) and *N*-tetrazolylcarboxamide analogues (**57** and **59**) were more active than the corresponding tetrazoles (**51** and **53**).

The 7-carboxy-2-methyl analogue (**44**) was less active than the 2-carboxy-7-methyl derivative (**21**). Dicarboxy substitution as in the 2,7-analogue (**45**) led to reduced activity compared to the parent compound (**30**), but the 2,6-dicarboxylic acid (**46**) retained significant activity.

From the data presented here on the variations in structures around the pyrazoloquinazolinone nucleus, one cannot identify a specific factor, such as electronic vs. lipophilic *or* substitution on N_4, that is critical for biological activity. The biological activity of the compounds as inhibitors of rat reaginic PCA is dependent on the combination of factors, such as alkyl side chain (R), substitution (X and Y), and acidic group (Z), as a whole rather than any one single factor. Since the compounds of the series have significant potency intravenously, they may have utility for treating asthma prophylactically using a metered-dose inhaler.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus or on a Mel-Temp apparatus and are uncorrected. Each analytical sample was homogeneous by TLC and had IR, UV, and NMR spectra compatible with its structure. Combustion analysis for C, H, N, and halogen or sulfur gave results within 0.4% of theory unless otherwise indicated. The procedures for the preparation of the reported compounds are listed as methods A–T and may be considered as general methods of preparation. The reported yields for the products obtained were not maximized.

Biological Test Procedure. The PCA test[11] involved immunization of rats with 1 mg of ovalbumin intramuscularly and approximately 10^{10} *B. pertussis* organisms as pertussis vaccine intraperitoneally. Fourteen days later, the rats were bled and the serum was prepared. Suitable dilutions of antiserum were injected intradermally at various sites on the back of rats 48 h before an intravenous injection of 1 mg of ovalbumin in 1 mL of physiological saline and 0.25% Evans blue. Thirty minutes later, the animals were killed with ether, the dorsal skin was reflected, and the mean orthogonal diameter of the wheal was measured. For oral or intraperitoneal dosing, the drugs were suspended in 1% gum tragacanth in physiological saline and given 10–15 min before intravenous antigen challenge. For intravenous dosing, the compounds were dissolved in the saline/ovalbumin/Evans blue solution and given with the antigen. If necessary, the compounds were first dissolved in a slight molar excess of sodium bicarbonate and then diluted into the antigen solution. Groups of five animals were used for all dose levels and control groups.

To quantitate the PCA test, the mean diameter of each wheal spot was graphed as a function of the relative antiserum concentration. The line, fitted by the least-squares equation, was extrapolated to the value at "zero" antiserum concentration (base value). The following equation was then used to calculate the percent inhibition:

$$\% \text{ inhibn} = \left[1 - \left(\frac{\text{diameter of drug} - \text{base value}}{\text{diameter of control} - \text{base value}}\right)\right] \times 100$$

The statistical significance of the results was determined by Student's *t* test ($p \leq 0.05$). An inhibition of 15% was significant.

Method A. General Method for the Preparation of 4-Alkyl-4,9-dihydro-9-oxopyrazolo[5,1-*b*]quinazoline-2-carboxylate Derivatives (7a, R = Alkyl). To a suspension of NaH (50% mineral oil; 0.11 mol) in DMF (50 mL), cooled to −10 °C, was added slowly under N_2 atmosphere a solution of ethyl 4,5-dihydro-5-oxo-1*H*-pyrazole-3-carboxylate[12] (0.1 mol) in DMF (120 mL). When the evolution of hydrogen ceased, the solution was stirred for 2 h with the temperature gradually rising to 0 °C. The mixture was cooled back to −10 °C and a solution of the appropriate 1-substituted 2*H*-3,1-benzoxazine-2,4(1*H*)-dione (N-substituted isatoic anhydride; 0.1 mol) in DMF (250 mL) was added slowly to it. The resulting mixture was stirred overnight at room temperature and then heated at 90 °C for 2 h. Most of the solvent was removed under reduced pressure, and the residue poured into an ice–water mixture containing 1 equiv of concentrated HCl (pH ~5.0). The resulting precipitate was washed with water, dried, and recrystallized from an ethanol–methylene chloride mixture or DMF.

All the compounds (**7a** and **7b**) showed the characteristic bands in the IR (Nujol), 1730–1700 and 1600–1630 cm^{-1}, for the ester or acid and amide carbonyl group. In the NMR (Me_2SO-d_6), all of them showed a one-proton singlet at 6.40–6.90 ppm for the C_3 proton.

Method B. General Method for the Preparation of 4-Alkyl-4,9-dihydro-9-oxopyrazolo[5,1-*b*]quinazoline-2-carboxylic Acid Derivatives (7b, R = Alkyl). A mixture of the appropriate 4-alkyl-4,9-dihydro-9-oxopyrazolo[5,1-*b*]-quinazoline-2-carboxylate derivative (**7a**; 0.1 mol), 1 N NaOH solution (0.2 mol), and methanol (200 mL) was refluxed until a clear solution was formed (30 min). The methanol was distilled off, and the residual solution was diluted with water and acidified with dilute HCl or acetic acid. The precipitated acid was filtered, washed, dried, and recrystallized from methanol or DMF.

Method C. 4,9-Dihydro-5-methoxy-9-oxopyrazolo[5,1-*b*]-quinazoline-2-carboxylic Acid (36). A mixture of 2-amino-3-methoxybenzoic acid hydrazide (23.6 g, 0.13 mol) and 90% sodium diethyloxalacetate (**6**) (32.7 g, 0.14 mol) in water (400 mL) was heated under reflux for 1.5 h. Sodium carbonate (14.8 g, 0.14 mol) was added to the yellow solution and the mixture was refluxed for an additional hour. The cooled reaction mixture was cautiously treated with concentrated HCl (0.28 mol), and the precipitated solid was filtered off, washed with water, and recrystallized from methanol (1500 mL): yield 5.8 g; mp 271–272 °C dec.

Method D. 7-(Acetylamino)-4,9-dihydro-4-methyl-9-oxopyrazolo[5,1-*b*]quinazoline-2-carboxylic Acid (24). A mixture of 7-amino-4,9-dihydro-4-methyl-9-oxopyrazolo[5,1-*b*]-quinazoline-2-carboxylic acid (**23**; 2.6 g, 0.01 mol) and acetic anhydride (50 mL) was heated on a steam bath for 20 h and then refluxed for 2.0 h. After the reaction mixture cooled, some product crystallized out; this mixture was then poured onto ice, and the crude product was filtered off and recrystallized from a large volume of DMF: yield 2.1 g; mp 292–293 °C dec.

Method E. 4,9-Dihydro-5-methoxy-4-methyl-9-oxopyrazolo[5,1-*b*]quinazoline-2-carboxylic Acid (26). A mixture of 4,9-dihydro-5-methoxy-9-oxopyrazolo[5,1-*b*]quinazoline-2-carboxylic acid hydrate (1:0.25) (2.64 g, 0.01 mol), anhydrous

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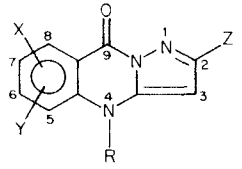
Table I. PCA Activity of 4,9-Dihydro-9-oxopyrazolo[5,1-*b*]quinazoline-2-carboxylic Acids and Ethyl Esters (7b and 7a)

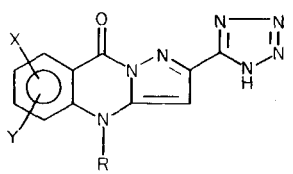


compd	X	Y	Z	R	mp, °C	formula	recrystn solvent	method	yield, %	anal.	PCA test: % inhibn, mg/kg ip	iv	po
15	H	H	COOH	CH_3	265	$C_{12}H_9N_3O_3$ [a]	DMF-MeOH	B	81	C, H, N	100 (5) [b] 59 (1) [b]	100 (0.5) [b]	40 (5) [b] 9 (2)
16	7-Cl	H	COOH	CH_3	280	$C_{12}H_8ClN_3O_3$	DMF-MeOH	B	92	C, H, Cl, N	100 (5) [b]	70 (0.5) [b] 8 (0.1)	25 (5) [b] 16 (2)
17	7-Cl	H	$COOC_2H_5$	CH_2CH_3	256-257	$C_{15}H_{14}ClN_3O_3$	DMF-MeOH	A	20	C, H, Cl, N	27 (5)		15 (5)
18	7-Cl	H	COOH	CH_2CH_3	267-268	$C_{13}H_{10}ClN_3O_3$	DMF-MeOH	B	31	C, H, Cl, N		16 (0.1) 21 (0.01)	23 (2) [b]
19	7-Cl	H	COOH	$CH_2C_6H_5$	239	$C_{18}H_{12}ClN_3O_3$	DMF	B	62	C, H, Cl, N	0 (5)		7 (5)
20	7-F	H	COOH	CH_3	295	$C_{12}H_8FN_3O_3$	DMF-MeOH	B	99	C, H, F, N	83 (5) [b]	84 (0.5) [b]	40 (2) [b]
21	7-CH_3	H	COOH	CH_3	269	$C_{13}H_{11}N_3O_3$	DMF-EtOH	B	72	C, H, N		55 (0.5) [b]	25 (2) [b]
22	7-OCH_3	H	COOH	CH_3	259	$C_{13}H_{11}N_3O_4$	DMF	B	81	C, H, N	81 (5) [b]	100 (0.5) [b] 41 (0.1) [b] 23 (0.01)	4 (5)
23	7-NH_2	H	COOH	CH_3	276-277	$C_{12}H_{10}N_4O_3$	DMF	C	75	H, N; C [c]	84 (5) [b]	16 (0.1) 12 (0.01) [b]	0 (5)
24	7-CH_3CONH	H	COOH	CH_3	292-293	$C_{14}H_{12}N_4O_4$	DMF	D	70	C, H, N	54 (5) [b]		0 (5)
25	7-C_6H_5CONH	H	COOH	CH_3	243-245	$C_{19}H_{14}N_4O_4 \cdot 0.5C_3H_7NO$	MeOH-H_2O	D	18	C, H, N	29 (5) [b]		1 (5)
26	5-OCH_3	H	COOH	CH_3	255	$C_{13}H_{11}N_3O_4$	MeOH	E	14	C, H, N	60 (5) [b]		
27	5-O-*n*-C_3H_7	H	COOH	*n*-C_3H_7	201-202	$C_{17}H_{19}N_3O_4$	MeOH-H_2O	E	13	C, H, N	72 (5) [b]		
28	7-OCH_3	6-OCH_3	COOH	CH_3	284-285	$C_{14}H_{13}N_3O_5$	DMF-MeOH	E	60	C, H, N	100 (5) [b]		6 (5)
29	H	H	$COOC_2H_5$	H	297-302	$C_{13}H_{11}N_3O_3$ [a]	EtOH	F	80	H, N; C [d]	74 (5) [b]		0 (5)
30	H	H	COOH	H	315-320	$C_{11}H_7N_3O_3$	DMF	C	30	C, H, N	100 (5) [b] 55 (1) [b]	54 (0.1) [b] 0 (0.01)	23 (1) 5 (5)
31	7-Cl	H	COOH	H	356-359	$C_{11}H_6ClN_3O_3$	DMF	C	33	C, H, Cl, N	45 (5) [b]		0 (5)
32	7-OCH_3	H	COOH	H	>300	$C_{12}H_9N_3O_4$	DMF	C	39	C, H, N	94 (5) [b]	40 (0.1) [b] 30 (0.01) [b]	0 (5)
33	7-F	H	COOH	H	>300	$C_{11}H_6FN_3O_3$	DMF	C	20	C, H, F, N	95 (5) [b]	62 (0.1) [b] 2 (0.01)	16 (5) [b]
34	7-CH_3	H	COOH	H	290-295	$C_{12}H_9N_3O_3$	DMF-Et_2O	C	10	C, H, N	100 (5) [b]		0 (5)
35	7-NH_2	H	COOH	H	>300	$C_{11}H_8N_4O_3 \cdot C_3H_7NO \cdot H_2O$	DMF-H_2O	C	21	C, H, N	38 (5) [b]		16 (5) [b]
36	5-OCH_3	H	COOH	H	271-272	$C_{12}H_9N_3O_4 \cdot 0.25H_2O$	MeOH-H_2O	C	17	C, H, N, H_2O	70 (5) [b]	100 (0.1) [b] 74 (0.01) [b] 31 (0.005) [b] 8 (0.001)	79 (5) [b] 62 (10) [b]
37	8-OCH_3	H	COOH	H	293-295	$C_{12}H_9N_3O_4$	DMF	C	56	C, H, N	62 (5) [b]		18 (5)
38	5-CH_3	H	COOH	H	268-274	$C_{12}H_9N_3O_3$	MeOH-H_2O	C	24	C, H, N	58 (5) [b]		0 (5)
39	7-OH	H	COOH	H	285-286	$C_{11}H_7N_3O_4$	DMF-Et_2O	G	58	C, H, N	100 (5) [b]		0 (5)
40	5-OH	H	COOH	H	326-330	$C_{11}H_7N_3O_4 \cdot 0.25H_2O$	*f*	G	75	C, H, N	100 (5) [b]	75 (0.1) [b]	
41	8-CF_3	H	COOH	H	298-302	$C_{12}H_6F_3N_3O_3$	DMF-MeOH	C	52	C, H, F, N	100 (5) [b]		10 (5) [b]
42	7-Cl	6-Cl	COOH	H	>300	$C_{11}H_5Cl_2N_3O_3 \cdot 0.85C_3H_7NO$	DMF	C	7	H, Cl, N; C [e]	9 (5)		0 (5)

43	7-CH_3O	6-CH_3O	COOH	H	305–308	$C_{13}H_{11}N_3O_5$	DMF	C	25	C, H, N	97 (5)[b]	100 (0.1)[b] 16 (0.01)	5 (5)
44	7-COOH	H	CH_3	CH_3	>360	$C_{13}H_{11}N_3O_3$	DMF	B	99	C, H, N		21 (0.5)	9 (2)
45	7-COOH	H	COOH	H	>380	$C_{12}H_7N_3O_5 \cdot 0.25C_3H_7NO$	DMF-Et_2O	C	5	C, H, N	21 (5)		7 (5)
46	6-COOH	H	COOH	H	375	$C_{12}H_7N_3O_5 \cdot C_5H_5N$	pyridine	C	19	C, H, N	74 (5)[b]	56 (0.1)[b]	
1 (cromolyn sodium)												50 (1.5)[b]	inactive

[a] Reference 3. Ethyl ester. [b] Significantly different from control ($p < 0.05$). [c] C: calcd, 55.81; found, 55.29. [d] C: calcd, 60.69; found, 60.25. [e] C: calcd, 45.18; found, 44.44, 44.32. [f] Not recrystallized.

Table II. PCA Activity of 2-(1*H*-Tetrazol-5-yl)pyrazolo[5,1-*b*]quinazolin-9(4*H*)-ones (7e)



compd	X	Y	R	mp, °C	formula	recrystn solvent	method	yield, %	anal.	PCA test: % inhibn, mg/kg ip	iv	po
47	H	H	CH_3	323	$C_9H_{12}N_7O$	DMF-EtOH	H	86	C, H, N	91 (5)[a]	84 (0.5)[a] 0 (0.1) 17 (0.01)	0 (5) 52 (2)[a]
48	7-Cl	H	CH_3	312	$C_{12}H_8ClN_7O$	DMF-EtOH	H	31	C, H, Cl, N	100 (5)[a]	100 (0.5)[a] 72 (0.1)[a] 9 (0.01)	39 (2)[a] 0 (5)
49	7-F	H	CH_3	350–360	$C_{12}H_8FN_7O$	DMF	H	52	C, H, F, N	100 (5)[a]	100 (0.1)[a] 10 (0.01) 36 (0.001)	8 (5) 27 (2)[a]
50	7-OCH_3	H	CH_3	287–288	$C_{13}H_{11}N_7O_2$	DMF-EtOH	H	29	C, H, N	100 (5)[a]	100 (0.5)[a] 72 (0.1)[a] 27 (0.01)[a]	0 (5)
51	H	H	H	342–345 dec	$C_{11}H_7N_7O$	DMF	H	10	C, H, N	26 (5)[a]		0 (5)
52	7-Cl	H	H	>300	$C_{11}H_6ClN_7O$	DMF-MeOH	H	22	C, H, N, Cl	25 (5)[a]		1 (5)
53	5-OCH_3	H	H	>300	$C_{12}H_9N_7O_2 \cdot 0.8C_3H_7NO$	DMF	H	10	C, H, N	27 (5)[a]		3 (5)
54	7-OCH_3	H	H	>300	$C_{12}H_9N_7O_2 \cdot 0.5H_2O$	DMF-Et_2O	H	11	C, H, N	87 (5)[a]		21 (1)[a]

[a] Statistically different from control ($p > 0.05$).

Table III. PCA Activity of 4,9-Dihydro-9-oxo-*N*-1*H*-tetrazol-5-ylpyrazolo[5,1-*b*]quinazoline-2-carboxamide (7f)

compd	X	Y	R	mp, °C	formula	recrystn solvent	meth- od	yield, %	anal.	PCA test: % inhibn, mg/kg ip	iv	po
55	H	H	CH_3	338–340	$C_{13}H_{10}N_8O_2$	DMF	I	99	C, N; H[a]	51 (5)[b]		0
56	7-Cl	H	$CH_2C_6H_5$	335–340	$C_{19}H_{13}ClN_8O_2$	DMF-MeOH	I	79	C, H, Cl, N	3 (5)		0 (5)
57	H	H	H	>300	$C_{12}H_8N_8O_2$	DMF-MeOH	I	44	C, H, N	100 (5)[b]		1 (5)
58	7-Cl	H	H	>360	$C_{12}H_7ClN_8O_2 \cdot {}^1/_{12}C_2H_4O_2$	DMF-AcOH	I	49	C, Cl, N; H[c]	22 (5)[b]		8 (5)
59	5-OCH_3	H	H	280–285	$C_{13}H_{10}N_8O_3$	DMF	I	11	H, N; C[d]	100 (5)[b]		14 (5)[b]
60	8-OCH_3	H	H	340–344	$C_{13}H_{10}N_8O_3$	DMF	I	67	C, N; H[e]	100 (5)[b]		18 (5)[b]
61	7-OCH_3	H	H	335	$C_{13}H_{10}N_8O_3$	DMF-MeOH	I	58	C, H, N	80 (5)[b]	90 (0.1)[b]	43 (10)[b]
62	5-CH_3	H	H	290–295	$C_{13}H_{10}N_8O_2 \cdot C_3H_4N_2$	DMF	I	48	C, H, N	100 (5)[b]		9 (5)
63	7-OCH_3	6-OCH_3	H	290–295	$C_{14}H_{12}N_8O_4 \cdot C_2H_4O_2$	DMF-AcOH	I	49	C, H, N	100 (5)[b]		0 (5)
64	7-OH	H	H	>295	$C_{12}H_8N_8O_3 \cdot C_3H_4N_2 \cdot 0.33H_2O$	DMF-MeOH-H_2O	I	29	C, N; H[f]	100 (5)[b]	90 (0.1)[b]	6 (10)
65	7-SCH_3	H	H	285	$C_{13}H_{10}N_8O_2S \cdot C_3H_4N_2 \cdot 1.25H_2O$	DMF-H_2O	I	35	C, H, N, S	90 (5)[b]		

[a] H: calcd, 3.25; found, 3.77. [b] Significantly different from control ($p < 0.05$). [c] H: calcd, 2.20; found, 2.66. [d] C: calcd, 47.86; found, 47.43. [e] H: calcd, 3.09; found, 3.64. [f] H: calcd, 3.31; found, 3.74.

potassium carbonate (5.52 g, 0.04 mol), and methyl iodide (15 mL) in DMF (75 mL) was stirred at room temperatures for 2 days. Water was added and the gray solid was filtered off and taken up in 2 N sodium hydroxide solution (50 mL) and methanol (50 mL). The mixture was heated under reflux for 2 h and the methanol was distilled off in vacuo. The aqueous solution was acidified with concentrated HCl and the yellow precipitate was collected and recrystallized from methanol (275 mL)–water (5 mL): yield 0.33 g; mp 255 °C dec.

Method F. Ethyl 4,9-Dihydro-9-oxopyrazolo[5,1-*b*]quinazoline-2-carboxylate (29). A mixture of 4,9-dihydro-9-oxopyrazolo[5,1-*b*]quinazoline-2-carboxylic acid (**30**; 1.0 g) and 2 drops of pyridine in thionyl chloride (50 mL) was stirred at room temperature overnight. The mixture was evaporated to dryness at 25–40 °C in vacuo, and the yellow solid residue was cooled and treated with cold absolute ethanol (50 mL). The mixture was heated at reflux for 45 min and allowed to crystallize: yield 0.9 g; mp 298–302 °C dec.

Method G. 4,9-Dihydro-7-hydroxy-9-oxopyrazolo[5,1-*b*]quinazoline-2-carboxylic Acid. A suspension of 4,9-dihydro-7-methoxy-9-oxopyrazolo[5,1-*b*]quinazoline-2-carboxylic acid (2.0 g, 0.0077 mol) in 48% hydrobromic acid (30 mL) and glacial acetic acid (50 mL) was refluxed for 23 h. The clear reaction mixture was cooled and then diluted with water (25 mL), after which a yellow solid precipitated out. It was filtered and recrystallized from DMF–ether (1:1) (90 mL): yield 1.1 g; mp 285–286 °C dec.

Method H. 5-Methoxy-2-(1*H*-tetrazol-5-yl)pyrazolo[5,1-*b*]quinazolin-9(4*H*)-one. To a warm solution of 4,9-dihydro-5-methoxy-9-oxopyrazolo[5,1-*b*]quinazoline-2-carbonitrile (2.98 g, 0.0124 mol) in DMF (150 mL) was added sodium azide (2.42 g, 0.0372 mol) and ammonium chloride (1.99 g, 0.0372 mol). The reaction mixture was heated at 100 °C for 22 h, concentrated to one-third volume, and then poured into an ice–water mixture. The mixture was acidified to pH 1.0 with 4 N hydrochloric acid (15 mL), and the product was filtered off. The crude product was stirred with 0.5 N sodium hydroxide solution (600 mL) for 1.0 h, the insoluble material was filtered off, and the filtrate was acidified with concentrated HCl (30 mL). The precipitated solid was filtered, washed with water, and dried. Analytical sample was recrystallized from DMF: mp >300 °C; yield 0.425 g.

Method I. 4,9-Dihydro-4-methyl-9-oxo-*N*-(1*H*-tetrazol-5-yl)pyrazolo[5,1-*b*]quinazoline-2-carboxamide. To a warm mixture of 4,9-dihydro-4-methyl-9-oxopyrazolo[5,1-*b*]-quinazoline-2-carboxylic acid (1.9 g, 0.0078 mol) and DMF (50 mL) was added 1,1′-carbonyldiimidazole[7] (2.78 g, 0.0172 mol), and the mixture was heated at 100 °C for 15 min. 1*H*-Tetrazol-5-amine monohydrate (0.88 g, 0.0086 mol) was then added to the hot solution, and the heating continued for another 2.5 h. The reaction mixture was cooled to 50 °C, and the solid was filtered, washed successively with methanol and ether, and dried: yield 2.4 g; mp 338–340 °C dec.

Some of the 4,9-dihydro-9-oxopyrazolo[5,1-*b*]quinazoline-2-carboxylic acids were reported in ref 8 and the rest are described in Table I.

Preparation of Intermediates. Method J. 7-Chloro-4,9-dihydro-4-methyl-9-oxopyrazolo[5,1-*b*]quinazoline-2-carboxamide. A mixture of 7-chloro-4,9-dihydro-4-methyl-9-oxopyrazolo[5,1-*b*]quinazoline-2-carboxylic acid (6 g, 0.0216 mol) and thionyl chloride (200 mL) was refluxed for 3 h. The solvent was distilled off under reduced pressure and the residue was cooled to −10 °C. Aqueous ammonium hydroxide (58%, 200 mL) was added to it in one lot and then the mixture was stirred at room temperature for 3 h. The precipitated yellow solid was filtered off, washed with water, and recrystallized from a DMF–EtOH mixture: yield 5.0 g (83%); mp >360 °C; IR (Nujol) 3460, 3300–3100, 1690, 1660, 1610, 1600 cm^{-1}; UV (EtOH) λ_{max} 241 nm (ϵ 33 400), 290 (7000), 297 (8500), 377 (4400); NMR (F_3AcOH) δ 4.15 (s, 3), 7.2 (s, 1), 7.75 (d, 1), 8.05 (d, 1), 8.55 (d, 1).

Method K. 4,9-Dihydro-5-methoxy-9-oxopyrazolo[5,1-*b*]quinazoline-2-carboxamide. A mixture of 4,9-dihydro-5-methoxy-9-oxopyrazolo[5,1-*b*]quinazoline-2-carboxylic acid (6.6 g, 0.025 mol) and phosphorus oxychloride (100 mL) was stirred at room temperature overnight. The solid was filtered off, washed with ether, dried, and treated with cold (0 °C) ammonium hydroxide solution (58%, 50 mL). After the solution was left standing overnight at room temperature, the product was filtered

Table IV. Substituted 4,9-Dihydro-9-oxopyrazolo[5,1-*b*]quinazoline-2-carboxamides (7c)

compd	X	Y	R	mp, °C	formula	recrystn solvent	method	yield, %
66	H	H	CH_3	327-330	$C_{12}H_{10}N_4O_2$	DMF-EtOH	J	94
67	7-Cl	H	CH_3	>360	$C_{12}H_9ClN_4O_2$	DMF-EtOH	J	83
68	7-F	H	CH_3	>350	$C_{12}H_9FN_4O_2$ [a]	c	J	96 [b]
69	7-OCH_3	H	CH_3	>300	$C_{13}H_{12}N_4O_2$ [a]	c	J	97 [b]
70	H	H	H	335-340	$C_{11}H_8N_4O_2$	DMF	J	64
71	7-Cl	H	H	350-360	$C_{11}H_7ClN_4O_2$ [a]	c	J	98 [b]
72	5-OCH_3	H	H	265-270	$C_{12}H_{10}N_4O_3$ [a]	c	K	78 [b]
73	7-OCH_3	H	H	340-355	$C_{12}H_{10}N_4O_3$ [a]	c	K	92 [b]
74	5-CH_3	H	H	340-345	$C_{12}H_{10}N_4O_2$ [a]	c	L	62 [b]

[a] Not analyzed. [b] Crude yield. [c] Not recrystallized.

Table V. Substituted 4,9-Dihydro-9-oxopyrazolo[5,1-*b*]quinazoline-2-carbonitrile (7d)

compd	X	Y	R	mp, °C	formula	recrystn solvent	method	yield, %
75	H	H	CH_3	307-310	$C_{12}H_8N_4O$	DMF-EtOH	M	97
76	7-Cl	H	CH_3	350	$C_{12}H_7ClN_4O$	DMF-EtOH	M	84
77	7-F	H	CH_3	331-340	$C_{12}H_7FN_4O$ [a]	DMF-EtOH	M	99 [b]
78	7-OCH_3	H	CH_3	316-320	$C_{13}H_{10}N_4O_2$ [c]	DMF-EtOH	M	68
79	H	H	H	365-375 dec	$C_{11}H_6N_4O$ [a]	DMF	N	96 [b]
80	7-Cl	H	H	400-405 dec	$C_{11}H_5ClN_4O$	DMF	N	40
81	5-OCH_3	H	H	292-297 dec	$C_{12}H_8N_4O_2$ [a]	d	N	64 [b]
82	7-OCH_3	H	H	343-346 dec	$C_{12}H_8N_4O_2$ [a]	d	N	52 [b]
83	5-CH_3	H	H	335-345 dec	$C_{12}H_8N_4O$ [a]	d	N	75 [b]

[a] Not analyzed. [b] Crude yield. [c] C: calcd, 61.41; found, 60.77. [d] Not recrystallized.

Table VI. Substituted 2-Aminobenzoic Acid Hydrazides (5)

compd	X	Y	R	mp, °C	formula	recrystn solvent	method	yield, %
84	3-CH_3	H	H	155-158	$C_8H_{11}N_3O$ [a]	d	O	97 [b]
85	3-OCH_3	H	H	142-147	$C_8H_{11}N_3O_2$	benzene	O	68
86	5-CH_3	H	H	137-139	$C_8H_{11}N_3O$ [a]	d	O	77 [b]
87	5-OCH_3	H	H	141-143	$C_8H_{11}N_3O_2$	water	O	50
88	5-Cl	H	H	133-136	$C_7H_8ClN_3O$	d	O	97
89	6-CF_3	H	H	120-125 dec	$C_8H_8F_3N_3O$	d	O	20
90	5-Cl	4-Cl	H	203-207	$C_7H_7Cl_2N_3O$	d	O	93
91	5-F	H	H	248-251	$C_7H_8FN_3O$ [a]	CH_2Cl_2-MeOH	O	58 [b]
92	5-NO_2	H	H	206-210	$C_7H_8N_4O_3$	d	O	71
93	6-OCH_3	H	H	151-155	$C_8H_{11}N_3O_2$	d	O	49
94	5-OCH_3	4-OCH_3	H	177-178	$C_9H_{13}N_3O_3$	d	O	69
95	5-NH_2	H	CH_3	120-122	$C_8H_{12}N_4O$	MeOH-CH_2Cl_2-*i*-Pr_2O	P	85
96	5-NH_2	H	H	138-140	$C_7H_{10}N_4O$	MeOH	P	70
97	5-NO_2	H	CH_3	232-236	$C_8H_{10}N_4O_3$ [c]	MeOH	O	75
98	5-OCH_3	3-OCH_3	H	137-141	$C_9H_{13}N_3O_3$	d	O	86

[a] Not analyzed. [b] Crude yield. [c] N: calcd, 26.66; found, 26.06. [d] Not recrystallized.

Table VII. Substituted Isatoic Anhydrides (2) [a]

compd	X	Y	R	mp, °C	formula	method	yield, %
99	3-CH_3	H	H	286-288 dec	$C_9H_7NO_3$	Q	96
100	5-CH_3	H	H	248-250 dec	$C_9H_7NO_3$	Q	76
101	5-OCH_3	H	H	244-246 dec	$C_9H_7NO_4$	Q	88
102	5-Cl	4-Cl	H	297-299 dec	$C_8H_3Cl_2NO_3$	Q	90 [b]
103	6-OCH_3	H	H	260-264 dec	$C_9H_7NO_4$	Q	93 [b]
104	5-COOH	H	H	>360	$C_9H_5NO_5$	R	91 [b]
105	5-OCH_3	3-OCH_3	H	263-265 dec	$C_{10}H_9NO_5$	R	97
106	5-F	H	H	270 dec	$C_8H_4FNO_3$ [c]	c	73
107	4-COOH	H	H	>300	$C_9H_5NO_5$	R	99
108	5-CH_3O	4-CH_3O	H	274-275	$C_{10}H_9NO_5$ [d]	d	
109	6-CF_3	H	H	245-247	$C_9H_4F_3NO_3$ [e]	e	
110	5-CH_3	H	CH_3	166-169	$C_{10}H_9NO_3$	S	92 [b]
111	5-F	H	CH_3	150-155	$C_9H_6FNO_3$	S	49 [b]
112	5-CH_3O_2C	H	CH_3	163-166	$C_{11}H_9NO_5$	T	75 [b]
113	5-Cl	H	CH_2CH_3	143-145	$C_{10}H_8ClNO_3$ [f]	S	37
114	5-Cl	H	$CH_2C_6H_5$	147-149	$C_{15}H_{10}ClNO_3$ [f]	S	42
115	5-CH_3O	H	CH_3	228-231	$C_{10}H_9NO_4$ [f]	S	60

[a] In general, isatoic anhydrides were not recrystallized. [b] Analyzed. [c] Reference 13. [d] Reference 14. [e] Reference 14. [f] Reference 9.

off, dried, and used in the next step without further purification: yield 5.06 g; mp 265–270 °C.

Method L. 4,9-Dihydro-5-methyl-9-oxopyrazolo[5,1-*b*]quinazoline-2-carboxamide. To a solution of 4,9-dihydro-5-methyl-9-oxopyrazolo[5,1-*b*]quinazoline-2-carboxylic acid (4.86 g, 0.02 mol) in DMF (50 mL) was added 1,1′-carbonyldiimidazole[7] (4.86 g, 0.03 mol). The reaction mixture was heated at 100 °C for 12 min and then cooled and diluted with ether (75 mL) and

dichloromethane (25 mL). The tan solid was filtered off and suspended in cold (0 °C) DMF (50 mL). Anhydrous ammonia was bubbled through for 10 min, and the resulting solution was allowed to stand at room temperature overnight. The DMF solution was evaporated to dryness under reduced pressure, and the residue was washed with CH_2Cl_2 and ether and dried: yield 3.0 g; mp 340–345 °C dec.

Method M. 7-Chloro-4,9-dihydro-4-methyl-9-oxopyrazolo[5,1-*b*]quinazoline-2-carbonitrile. 7-Chloro-4,9-dihydro-4-methyl-9-oxopyrazolo[5,1-*b*]quinazoline-2-carboxamide (3 g, 0.011 mol) was heated at 56 °C with thionyl chloride (1.6 mL, 0.022 mol) and DMF (35 mL) for 18 h. The resulting clear solution was evaporated to dryness, and the residue was treated with water (600 mL). After the solution was left standing for 1 h, the crude nitrile was filtered off, washed with water, and recrystallized from a DMF–EtOH mixture: yield 2.4 g (84%); mp 350 °C; IR (Nujol) 2240, 1705, 1695, 1600 cm^{-1}; UV (EtOH) λ_{max} 222 nm (ϵ 26 500), 239 (43 500), 252 (24 250), 288 (8250), 297 (11 500), 375 (6250); NMR (F_3AcOH) δ 4.1 (s, 3), 6.9 (s, 1), 7.7 (d, 1), 8.10 (d, 1), 8.6 (d, 1).

Method N. 4,9-Dihydro-5-methoxy-9-oxopyrazolo[5,1-*b*]quinazoline-2-carbonitrile. A suspension of 4,9-dihydro-5-methoxy-9-oxopyrazolo[5,1-*b*]quinazoline-2-carboxamide (5.05 g, 0.0195 mol) in phosphorus oxychloride (100 mL) was heated under reflux for 2 h. After the suspension was left standing for 2 days at room temperature, excess phosphorus oxychloride was removed under reduced pressure, and the residue was suspended in saturated sodium bicarbonate solution (100 mL). The solid was filtered off, washed with water, and dried: yield 3.0 g; mp 292–297 °C dec.

Method O. Substituted 2-Aminobenzoic Acid Hydrazide. The substituted 2*H*-3,1-benzoxazine-2,4(1*H*)-dione (substituted isatoic anhydride) (0.14 mol) was slowly added to a cold (5–10 °C) 18% aqueous solution of hydrazine (225 mL). During the exothermic reaction, a white solid was formed. After the solution was stirred at room temperature overnight, the product was filtered off and washed with water. The hydrazide was used as is *or* was purified, if necessary, via crystallization before use.

Compounds **95** and **96** were prepared by catalytic (5% Pd/C) reduction of **97** and **92**, respectively.

Method P. Methyl 2-Amino-3,5-dimethoxybenzoate (14). A mixture of methyl 3,5-dimethoxy-2-nitrobenzoate[10] (39.0 g, 0.162 mol), 5% Pd on charcoal (2.0 g), methanol (200 mL), and tetrahydrofuran (200 mL) was shaken in an atmosphere of hydrogen at 52 lb of pressure for 46 h when the theoretical amount of hydrogen was taken up. The catalyst was filtered off and the filtrate was evaporated to dryness. The residue was recrystallized from methanol: yield 28.6 g; mp 93–95 °C. Anal. ($C_{10}H_{13}NO_4$) C, H, N.

Method Q. 8-Methoxy-2*H*-3,1-benzoxazine-2,4(1*H*)-dione (3-Methoxyisatoic Anhydride). To a solution of 2-amino-3-methoxybenzoic acid (8.36 g, 0.05 mol) in dioxane (75 mL) and benzene (25 mL) was added a 12.5% solution of phosgene in benzene (46 g) with cooling in an ice bath. After the addition, the reaction mixture was stirred at room temperature overnight. The precipitated product was filtered off, washed with benzene and ether, dried, and used without further purification: yield 9.1 g (94%); mp 263–264 °C dec.

Method R. 6,8-Dimethoxy-2*H*-3,1-benzoxazine-2,4(1*H*)-dione (3,5-Dimethoxyisatoic Anhydride; 105). A mixture of methyl 2-amino-3,5-dimethoxybenzoate (14; 21.2 g, 0.1 mol) and 1 N sodium hydroxide solution (100 mL) was refluxed for 2.0 h, cooled, and buffered with dry ice. The solution was treated with 12.5% phosgene in benzene (110 mL) in an ice bath. The mixture was stirred for 4.0 h, and the product was filtered off and dried in vacuo: yield 22.0 g; mp 263–265 °C dec.

Method S. 1,6-Dimethyl-2*H*-3,1-benzoxazine-2,4(1*H*)-dione (*N*,5-Dimethylisatoic Anhydride; 109). A solution of 5-methylisatoic anhydride (**100**; 26.6 g, 0.15 mol) in DMF (150 mL) was treated with anhydrous sodium carbonate (17.5 g, 0.165 mol) and then with iodomethane (32 g), and the mixture was stirred at 20–25 °C for 18 h. The reaction mixture was poured into ice–water (1.25 L) and the resulting precipitate of *N*,5-dimethylisatoic anhydride was collected by filtration, washed with water, and dried: yield 26.3 g (92%); mp 166–169 °C.

Method T. 6-Carbomethoxy-1-methyl-2*H*-3,1-benzoxazine-2,4(1*H*)-dione (5-Carbomethoxy-*N*-methylisatoic Anhydride; 112). Diazomethane generated from Diazald (100 g, 0.467 mol) was slowly distilled with ether (1000 mL) into a stirring mixture of 5-carboxyisatoic anhydride (**104**; 27.8 g, 0.134 mol) in THF (650 mL) at 5 °C. After all the diazomethane had been distilled, the reaction mixture was stirred at room temperature for 1.0 h. It was cooled to 5 °C and decomposed with acetic acid, and the crystals were filtered off: yield 17.1 g (54%); mp 163–166 °C.

1-[(4,9-Dihydro-5-methoxy-9-oxopyrazolo[5,1-*b*]quinazolin-2-yl)carbonyl]-1*H*-imidazole (10). To a warm (75 °C) solution of 4,9-dihydro-5-methoxy-9-oxopyrazolo[5,1-*b*]quinazoline-2-carboxylic acid (0.52 g) in DMF (100 mL) was added 1,1′-carbonyldiimidazole (0.49 g) and the mixture was heated at 85 °C for 15 min, after which a yellow solid slowly crystallized out: yield 0.24 g; mp 296–300 °C. Anal. ($C_{15}H_{11}N_5O_3$) C, H, N.

Compound **10** was converted to **59** and **72** by reacting it with 1*H*-tetrazol-5-amine and ammonia, respectively, in DMF.

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N-(Aminophenyl)oxamic Acids and Esters as Potent, Orally Active Antiallergy Agents

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A series of *N*-(2-cyano-substituted-phenyl)oxamates was prepared by acylation of the appropriate anthranilonitrile with ethyloxalyl chloride. Hydrolysis with sodium hydroxide gave the corresponding oxamic acid sodium salts. These compounds were extremely potent when tested in the rat passive cutaneous anaphylaxis (PCA assay either by the ip or the po route of administration). One of the sodium salts, [[2-cyano-3-(methylamino)phenyl]oxoacetic acid sodium salt (**11a**, Wy-41 195), has an ED_{50} value of 0.07 mg/kg po and has been selected for further evaluation.

The search for compounds possessing antiallergic activity of the type displayed by disodium cromoglycate (**1**),[2] but orally active and more potent, has been undertaken by numerous laboratories.[3-5] This paper and an accom-

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