[Chem. Pharm. Bull. 30(12)4314—4324(1982)]

Studies on Antiallergic Agents. I. Phenyl-substituted Heterocycles with a 5-Tetrazolyl or *N*-(5-Tetrazolyl)carbamoyl Group

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(Received June 11, 1982)

A series of phenyl-substituted pyrones, pyridines, and pyrimidines bearing a 5-tetrazolyl or *N*-(5-tetrazolyl)carbamoyl group as an acidic moiety was synthesized. The compounds were tested for antiallergic activity by passive cutaneous anaphylaxis (PCA) assay in rats after oral administration. Among the compounds synthesized, *N*-(5-tetrazolyl)-6-phenylpyridine-2-carboxamides (**53**, **54** and **55**) were found to display remarkably high potency.

Keywords——pyrones; pyridines; pyrimidines; *N*-(5-tetrazolyl)-6-phenylpyridine-2-carboxamides; PCA assay; antiallergic activity

Disodium cromoglycate (DSCG) is a clinically useful antiallergic agent, in particular for bronchial asthma, and it is thought to inhibit the release of mediators (histamine, leukotrienes, and several kinins) of the immediate hypersensitivity reactions.[1] The lack of intestinal absorption of this drug, however, has prevented its use by the oral route.

Over the past ten years, numerous efforts[2] have been made to find more potent and orally active compounds possessing a pharmacological profile similar to that of DSCG. Therefore, much of the research has centered around chemical structures resembling the chromone nucleus. While diverse types of compounds have been reported to display antiallergic activity to date, most of them bear an acidic moiety, *e.g*, carboxylic acid, on the aromatic or hetero rings in their structures. Furthermore, claims have been often made in the literature that a 5-tetrazolyl[3] or *N*-(5-tetrazolyl)carbamoyl group[4] is a good biological isostere for the carboxylic acid group in such compounds.

The reported modifications of the chromone structure mostly gave rise to many kinds of bi or tricyclic compounds, and little attention has been paid to monocyclic hetero ring structures.[5] As part of a program aimed at discovering new series of antiallergic agents, we were interested to determine whether a phenylpyrone and its aza-analog, phenylpyridine, could act as a substitute for the benzopyrone (chromone)nucleus. Phenylpyrimidine was also a framework of choice, because a quinazoline appeared to serve as a good substitute for chromone.[6] We describe here the synthesis of phenylpyrones, phenylpyridines, and phenylpyrimidines substituted with a 5-tetrazolyl or *N*-(5-tetrazolyl)carbamoyl group, and the results of evaluation of their antiallergic activity as determined by passive cutaneous anaphylaxis (PCA) assay in rats after oral administration of the compounds.

Synthesis

The *N*-(5-tetrazolyl)carboxamides listed in Tables I—III were synthesized by condensation of 5-aminotetrazole either with a carboxylic acid chloride (Method A), or with a carboxylic acid in the presence of *N*,*N*′-carbonyldiimidazole (Method B). All but **63** of the 5-tetrazole derivatives were prepared by the reaction of a carbonitrile with sodium azide and ammonium chloride in dimethylformamide (Method C). 4-Hydroxy-2-phenylpyrimidine derivatives (**62**) and (**63**) were obtained by demethylation of the corresponding 4-methoxy derivatives (**64**) and (**65**) with HBr–AcOH (Method D). Compound (**55**) was conveniently obtained by catalytic

hydrogenation of the 4-chloro derivative (**54**) (Method E). The requisite carboxylic acids and carbonitriles were prepared by either following the known procedure or using the standard synthetic methods described below.

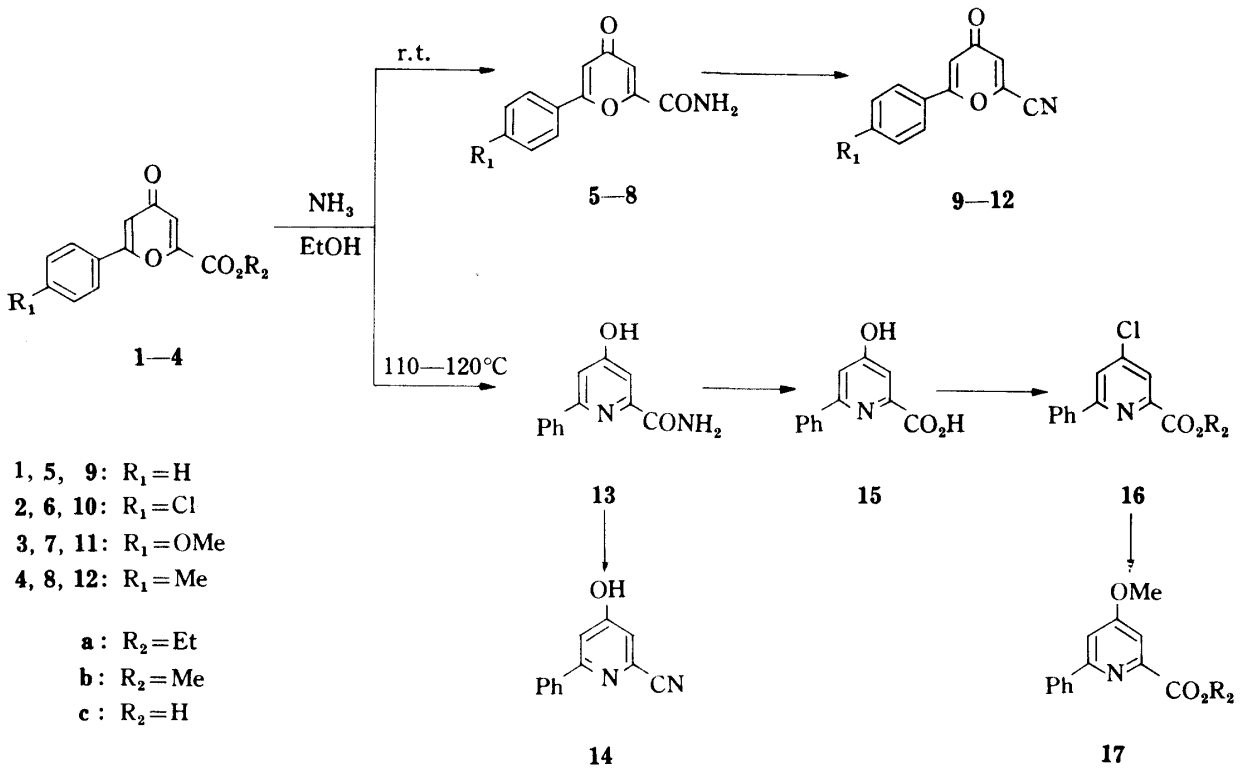


Chart 1

Ethyl 6-aryl-4-pyrone-2-carboxylates (**1a—4a**), which also served as intermediates for the pyridine derivatives (**14—17**) were prepared from ethyl 6-aryl-2,4-dioxohex-5-enoate following Soliman's procedure.[7]

Treatment of (**1a—4a**) with anhydrous ammonia in EtOH at room temperature gave exclusively the pyrone carboxamide (**5—8**). When the reaction was carried out at elevated temperature in a sealed tube, the pyridine carboxamide (**13**) was obtained as a sole product (Chart 1). Dehydration of (**5—8**) was effected successfully with trifluoroacetic anhydride in the presence of pyridine,[8] though several attempts under the usual reaction conditions, *e.g.* $POCl_3$, TsCl/pyridine, resulted in the formation of resinous material.

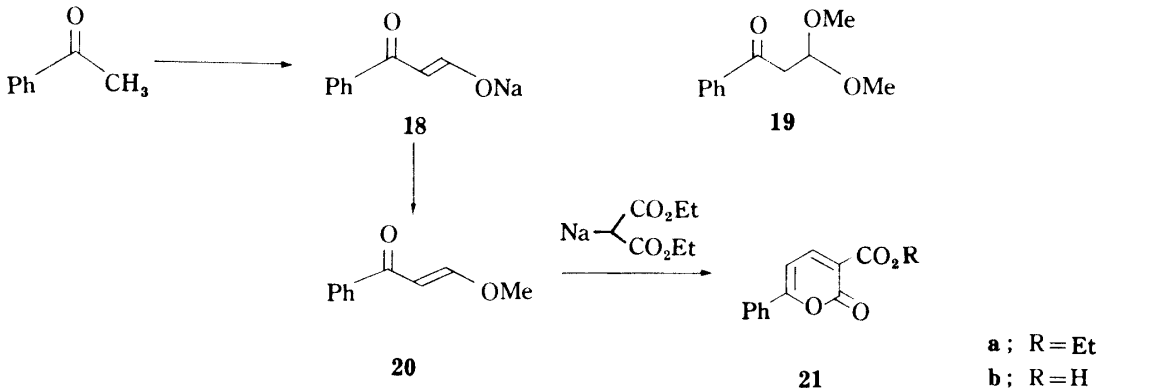
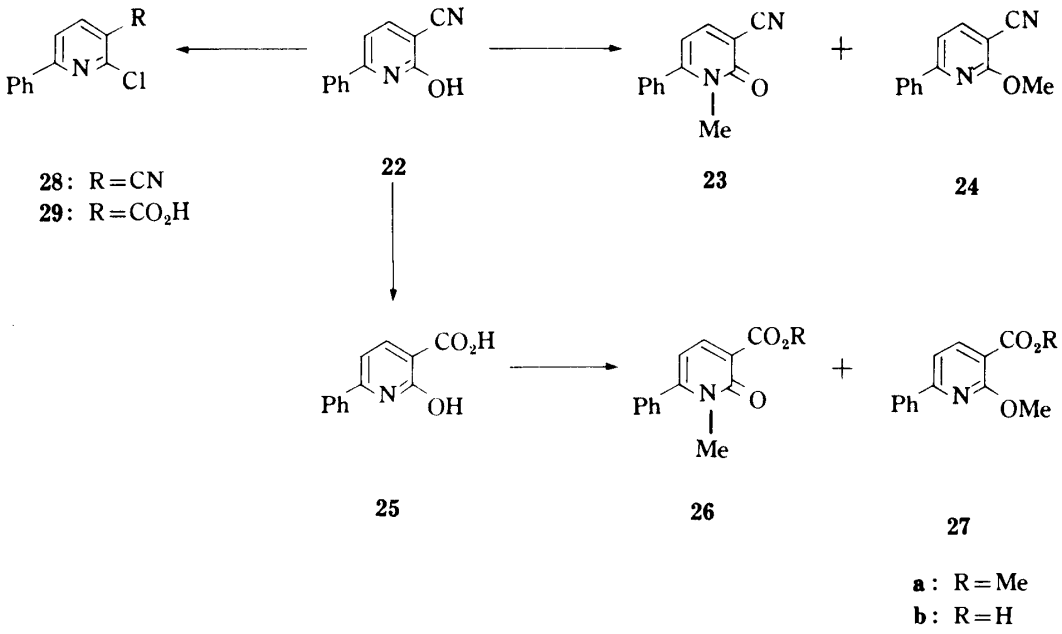
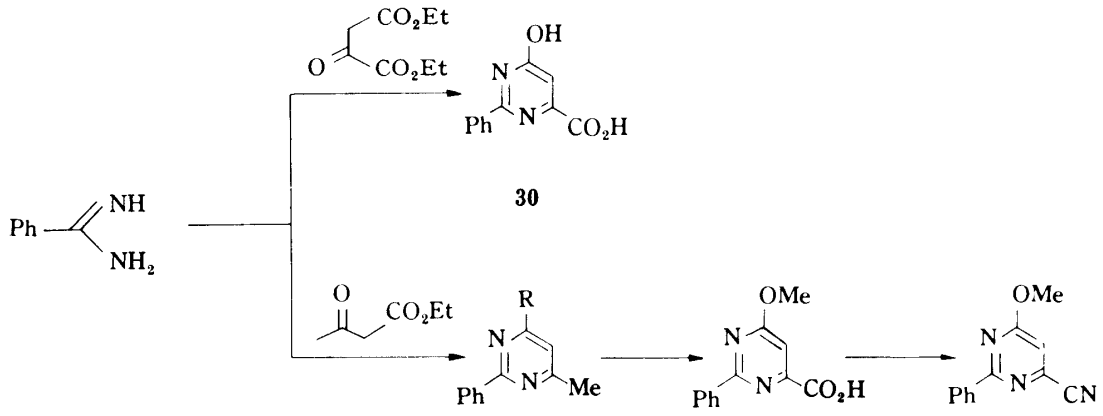


Chart 2



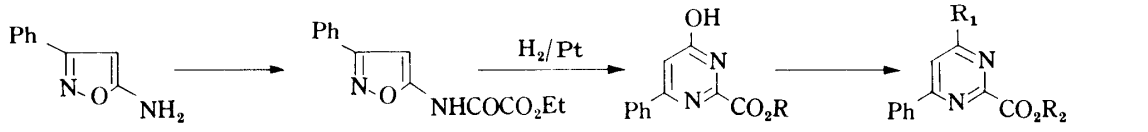
28: R=CN
29: R=CO_2H

Chart 3



31: R=OH
32: R=Cl
33: R=Me

Chart 4



38: R=Et
39: R=Na

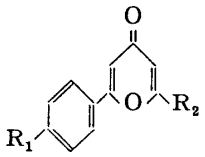
40: R_1=Cl, R_2=Et
41: R_1=OEt, R_2=H

Chart 5

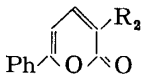
Ethyl 6-phenyl-2-pyrone-3-carboxylate (**21a**) was prepared by the method[9] outlined in Chart 2. Royals and Brannock[10] reported that treatment of the sodium salt of hydroxymethylene acetophenone (**18**) with methanolic hydrogen chloride gave the methoxymethylene derivative (**20**) instead of formylacetophenone dimethylacetal (**19**). However, we found that this method was unsatisfactory because of the predominant formation of (**19**). Methylation of **18** was achieved with dimethyl sulfate in dimethylformamide to afford **20** in rather good yield.

2-Hydroxy-6-phenylpyridine-3-carboxylic acid (**25**) and related compounds were synthesized in a straightforward manner as illustrated in Chart 3. Methylation of either **22** or **25** gave predominantly the *O*-Me product by using Ag_2O as a base. Alternativily, when sodium hydride was used instead of Ag_2O, the *N*-Me product could be obtained as a major product.

Table I.



42—49



50

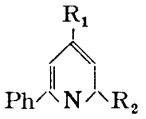
No.	R_1	R_2[a]	Method[b]	Yield (%)	mp (°C)	Analysis (%) Calcd (Found) C H N Cl	PCA % inhibition[c] *p.o.* at 10 mg/kg
						$C_{13}H_9N_5O_3$	
42	H	CONH5T	A[d]	36	257—258 (dec.)	55.12 3.20 24.73 (55.42 3.18 25.00)	0
						$C_{12}H_8N_4O_2$	
43	H	5T	C	82	257—258 (dec.)	60.00 3.36 23.32 (59.89 3.48 23.49)	0
						$C_{14}H_{11}N_5O_4$	
44	OCH_3	CONH5T	A[d]	39	260—261 (dec.)	53.67 3.54 22.36 (53.58 3.76 22.47)	24
						$C_{13}H_{10}N_4O_3$	
45	OCH_3	5T	C	91	245—246 (dec.)	57.77 3.73 20.73 (57.80 3.82 21.04)	10
						$C_{13}H_8ClN_5O_3$	
46	Cl	CONH5T	A[d]	42	255—257 (dec.)	49.15 2.54 22.05 11.16 (49.12 2.69 22.18 11.16)	0
						$C_{13}H_7ClN_4O_2$	
47	Cl	5T	C	74	251—252 (dec.)	52.47 2.57 20.40 12.91 (51.97 2.67 20.41 12.81)	0
						$C_{14}H_{11}N_5O_3$	
48	CH_3	CONH5T	A[d]	35	264—265 (dec.)	56.56 3.73 23.56 (56.32 3.78 23.67)	32
						$C_{13}H_{10}N_4O_2$	
49	CH_3	5T	C	70	262—263 (dec.)	61.41 3.96 22.04 (61.15 4.12 22.17)	36
						$C_{13}H_9N_5O_3$	
50	—	CONH5T	A	85	264—266 (dec.)	55.12 3.20 24.73 (55.02 3.33 24.73)	0

a) 5T denotes a 5-tetrazolyl group.
b) See the experimental section.
c) All compounds tested were administered as their sodium salts except for **50**, which was used as the tris (hydroxymethyl aminomethane salt.
d) Acid chlorides were prepared with a $PPh_3 \cdot CCl_4$ complex.[23]

Alkaline condensation of benzamidine and diethyl 2-oxosuccinate was first reported by Pinner[11] to give 4-hydroxy-2-phenylpyrimidine-6-carboxylic acid (**30**). This method, although reasonably straightforward, gave only a poor yield in our hands. Similar condensation of benzamidine with ethyl acetoacetate gave **31**[12] in 64% yield, and this was converted into **32** and **33** successively by standard techniques. Oxidation of **33** with selenium dioxide[13] in boiling pyridine afforded the acid (**34**), which was further led to the nitrile (**35**).

Synthesis of ethyl 4-hydroxy-6-phenylpyrimidine-2-carboxylate(**38**) from **37** was patterned after the preparation of 4-hydroxy-2-methyl-6-phenylpyrimidine from 5-acetylamino-3-phenylisoxazole reported by Shaw[14] (Chart 5). Since partial decarboxylation

Table II.



51—55

56—61

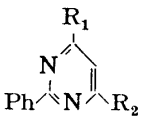
No.	R_1	R_2[a]	Method[b]	Yield (%)	mp (°C)	Analysis (%) Calcd (Found)				PCA % inhibition[c] *p.o.*, mg/kg			
						C	H	N	Cl	1	3	10	30
						$C_{13}H_{10}N_6O_2$							
51	OH	CONH5T	A[d]	43	280—281 (dec.)	55.31 (55.25	3.57 3.69	29.78 29.42)				20	
						$C_{12}H_9N_5O$							
52	OH	5T	C	73	183—185 (dec.)	60.24 (60.35	3.79 3.62	29.28 29.51)				13	
						$C_{14}H_{12}N_6O_2$							
53	OCH_3	CONH5T	A	56	266—267 (dec.)	56.75 (56.60	4.08 4.13	28.37 28.12)		62	97	100	
						$C_{13}H_9ClN_6O$							
54	Cl	CONH5T	A	84	*Ca.* 260 (darken)	51.92 (51.91	3.02 3.39	27.95 27.81	11.79 12.44)	90	100	100	
						$C_{13}H_{10}N_6O \cdot 1/2H_2O$							
55	H	CONH5T	E	78	275—277 (dec.)	56.72 (57.31	4.03 3.85	30.53 30.23)		10	33	52	
						$C_{13}H_{10}N_6O_2 \cdot 1/3H_2O$							
56	OH	CONH5T	B	47	>300	54.17 (53.73	3.62 3.71	29.15 28.93)					11
						$C_{12}H_9N_5O$							
57	OH	5T	C	97	>300	60.24 (60.16	3.79 3.97	29.28 28.96)					0
						$C_{14}H_{12}N_6O_2$							
58	OCH_3	CONH5T	A	70	269—273 (dec.)	56.75 (56.57	4.08 4.21	28.37 28.15)					13
						$C_{13}H_9ClN_6O$							
59	Cl	CONH5T	B	85	271—272 (dec.)	51.92 (51.74	3.02 3.23	27.95 27.91	11.79 11.60)				28
						$C_{14}H_{12}N_6O_2$							
60	=O (*N*-Me)	CONH5T	B	80	243—244 (dec.)	56.75 (56.54	4.08 4.26	28.37 28.47)					69
						$C_{13}H_{11}N_5O$							
61	=O (*N*-Me)	5T	C	12	280—281 (dec.)	61.65 (61.50	4.38 4.42	27.66 27.88)					35

a) 5T denotes a 5-tetrazolyl group.
b) See the experimental section.
c) All compounds tested were administered as their sodium salts.
d) The acid chloride was prepared with 5 eq. of $SOCl_2$ at room temperature in order to prevent chlorination of the 4-hydroxyl group.

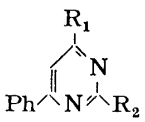
occurred on acidification of the sodium salt (**39**), **39** was directly used to prepare the *N*-(5-tetrazolyl)carboxamides (**66**) and (**67**).

4-Methyl-6-phenylpyrimidine-2-carboxylic acid was obtained by alkaline hydolysis of the known 2-cyano-4-methyl-6-phenylpyrimidine.[15]

TABLE III.



62—65



66—69

No.	R_1	R_2[a]	Method[b]	Yield (%)	mp (°C)	Analysis (%) Calcd (Found) C H N Cl	PCA % inhibition[c] *p.o.* at 30 mg/kg
						$C_{12}H_9N_7O_2$	
62	OH	CONH5T	D	96	>300	50.88 3.20 34.62 (51.02 3.31 34.32)	0
						$C_{11}H_8N_6O$	
63	OH	5T	D	85	>300	55.00 3.36 34.99 (55.12 3.33 35.18)	8
						$C_{13}H_{11}N_7O_2$	
64	OCH_3	CONH5T	A	73	263—265 (dec.)	52.52 3.73 32.99 (52.63 3.77 33.34)	31
						$C_{12}H_{10}N_6O$	
65	OCH_3	5T	C	66	207—209 (dec.)	56.68 3.96 33.06 (56.23 4.05 32.65)	8
						$C_{12}H_9N_7O_2 \cdot 3/4H_2O$	
66	OH	CONH5T	A[d]	25	298—300 (dec.)	43.57 3.57 33.10 (48.52 3.62 33.19)	0
						$C_{12}H_8ClN_7O$	
67	Cl	CONH5T	A[e]	25	270—275 (dec.)	47.78 2.67 32.50 11.75 (47.77 2.50 31.76 11.76)	7
						$C_{14}H_{13}N_7O_2$	
68	OC_2H_5	CONH5T	B	47	259—261 (dec.)	54.02 4.21 31.50 (54.39 4.23 31.89)	36
						$C_{13}H_{11}N_7O$	
69	CH_3	CONH5T	B	72	268—269 (dec.)	55.51 3.84 34.86 (55.43 3.83 34.71)	2

a) 5T denotes a 5-tetrazolyl group.
b) See the experimental section.
c) All compounds tested were administered as their sodium salts except for **63** and **65**, which were used as the tris (hydroxymethyl) aminomethane salt.
d) The acid chloride was prepared with 5 eq of $SOCl_2$ at room temperature in order to prevent chlorination of the 4-hydroxyl group.
e) Compound **39** was used as a starting material.

Results and Discussion

The compounds listed in Tables I—III were tested for their ability to inhibit the PCA reaction in rats on oral administration. Both the pyrone *N*-(5-tetrazolyl)carboxamide (**42**) and the 5-tetrazole (**43**) were found to be devoid of oral activity, though they exhibited significant activity on intravenous or intraperitoneal administration. Of the substituted phenyl derivatives (**44**—**49**) prepared in efforts to enhance the activity, the *p*-methoxy (**44**, **45**) and *p*-methyl (**48**, **49**) derivatives showed slightly superior oral activity (Table I).

In the pyridine series (Table II), high potency was observed with the *N*-(5-tetrazolyl)-carboxamides (**53**, **54** and **55**), which were active even at 1 mg/kg oral dose. Transposition of

the acidic moiety to the 3 position of the pyridine nucleus resulted in a marked decrease of the activity (**56**—**61**).

The pyrimidine derivatives (**62**—**69**), obtained by incorporation of an additional nitrogen atom at the 3 or 5 position of the pyridine ring, failed to show significant activity.[17] In both the pyridine and pyrimidine series it appears that the 4-alkoxy and 4-chloro derivatives tend to be more active than the 4-hydroxy relatives.

In the series of the compounds that we synthesized, the *N*-(5-tetrazolyl)carbamoyl group appeared to be superior to the 5-tetrazolyl group as an acidic function for antiallergic activity. Since the highest activity was observed for *N*-(5-tetrazolyl)-6-phenyl-2-pyridinecarboxamides (**53**—**55**), we are currently investigating the effects of substituents on the benzene and pyridine rings in efforts to enhance the activity. These results will be described in a later communication.

Experimental

All melting points are uncorrected. Infrared (IR) spectra were recorded on a Hitachi IR-215 spectrometer in Nujol mulls. Nuclear magnetic resonance (NMR) spectra were taken at 60 MHz on a JEOL PMX-60 spectrometer with TMS as an internal reference in $CDCl_3$ or DMSO-d_6. The following abbreviations are used: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, and br=broad. Mass spectra were measured with a Hitachi RMU-6M instrument.

Method A: ***N*-(5-Tetrazolyl)-4-chloro-6-phenylpyridine-2-carboxamide (54)**——A solution of **16c** (5.58 g, 2.39 mmol) in $SOCl_2$ (35 ml) was refluxed for 1 h. The solution was concentrated to dryness *in vacuo*, then 5-aminotetrazole (2.7 g, 3.18 mmol) was added to a solution of the residue in pyridine (30 ml). After being heated at 60—70°C with stirring overnight, the reaction mixture was concentrated *in vacuo* to leave a dark oil. H_2O was added thereto, and the mixture was acidified with 10% aq. HCl. The precipitate was collected by filtration washed with H_2O, dried, and recrystallized from DMF–EtOH to give **54**.

Method B: ***N*-(5-Tetrazolyl)-1-methyl-6-phenyl-2-pyridone-3-carboxamide (60)**——*N*,*N*′-Carbonyldiimidazole (0.948 g, 5.58 mmol) was added to a solution of **26b** (1.16 g, 5.07 mmol) in DMF (12 ml). The solution was stirred at room temperature for 1.5 h, then 5-aminotetrazole (0.566 g, 6.66 mmol) was added, and the mixture was heated at 80°C with stirring for 3 h. The reaction mixture was worked up as described in Method A to give **60**.

Method C: **2-Phenyl-6-(5-tetrazolyl)pyrone (43)**——A mixture of **9** (1.0 g, 5.08 mmol), NaN_3 (0.36 g, 5.58 mmol), NH_4Cl (0.30 g, 5.58 mmol), and DMF (15 ml) was heated at 120—130°C with stirring for 1 h. Work-up as described in Method A give **43**.

Method D: ***N*-(5-Tetrazolyl)-4-hydroxy-2-phenylpyrimidine-6-carboxamide (62)**——A mixture of **64** (0.80 g) and 25% HBr–AcOH (18.5 ml) was heated at 75—80°C for 40 min, then cooled. The precipitate was filtered off and recrystallized from EtOH–DMF (1: 1) to give **62**.

Method E: ***N*-(5-Tetrazolyl)-6-phenylpyridine-2-carboxamide (55)**——A solution of **54** (0.36 g) in DMF (10 ml), EtOH (10 ml) and 10% aq·HCl (1 ml) was hydrogenated over 10% Pd on charcoal (0.1 g) at room temperature. After the theoretical amount of H_2 had been absorbed, the catalyst was filtered off, and H_2O was added to the filtrate. The precipitate was collected and recrystallized from DMF–H_2O to give **55**.

6-Phenyl-4-pyrone-2-carboxamide (5)——Compound **1a** (0.70 g) was dissolved in 14% NH_3–EtOH (10 ml) on a water bath. The solution was allowed to stand at room temperature for 1.5 h, during which period a crystalline solid precipitated. The crystals were filtered off, washed with EtOH, and dried to give **5** (0.58 g, 94.5%) mp 247—250°C (lit.[18] 248°C). IR ν_{max}^{Nujol} cm^{-1}: 3420, 3130, 1710, 1640. MS *m/e*: 215 (M^+). NMR (DMSO-d_6) δ: 6.80 (1H, d, J=2 Hz), 6.95 (1H, d, J=2 Hz), 7.41—7.49 (3H, m), 8.16 (4H, m). Compounds **6**, **7** and **8** were prepared in a similar manner.

6-*p*-Chlorophenyl-4-pyrone-2-carboxamide (6)——mp >300°C, 91.5%. IR ν_{max}^{Nujol} cm^{-1}: 3405, 3250, 3180, 1710, 1640. MS *m/e*: 249 (M^+).

6-*p*-Methoxyphenyl-4-pyrone-2-carboxamide (7)——mp 290—293°C dec., 90.5%. IR ν_{max}^{Nujol} cm^{-1}: 3360, 3190, 1715, 1638. MS *m/e*: 244 (M^+).

6-*p*-Tolyl-4-pyrone-2-carboxamide (8)——mp 295—300°C dec., 96.7%. IR ν_{max}^{Nujol} cm^{-1}: 3350, 3200, 1715, 1640. MS *m/e*: 229 (M^+).

2-Cyano-6-phenyl-4-pyrone (9)——Pyridine (1.25 ml) and trifluoroacetic anhydride (1.55 ml) were added successively to a suspension of **5** (1.33 g, 6.19 mmol) in dioxane (12 ml) under ice-cooling. The mixture was stirred at room temperature for 0.5 h. After addition of H_2O, the precipitate was filtered off and recrystallized from iso-PrOH to give **9** (1.03 g, 85%) as plates, mp 148—149°C. IR ν_{max}^{Nujol} cm^{-1}: 2250, 1645. MS *m/e*: 197 (M^+). NMR ($CDCl_3$) δ: 6.53 (2H, s), 7.10—7.49 (m, 5H). *Anal.* Calcd for $C_{12}H_7NO_2$: C, 73.09; H, 3.58; N, 7.10. Found: C, 72.90; H, 3.97; N, 7.04.

Compounds **10**, **11**, and **12** were prepared in a similar manner.

2-Cyano-6-*p*-chlorophenyl-4-pyrone (10)——mp 143—145°C, 81.5%. IR ν_{max}^{Nujol} cm^{-1}: 2250, 1650. MS *m/e*: 231 (M^+). NMR ($CDCl_3$) δ: 6.53 (2H, s), 7.15—7.49 (5H, m). *Anal.* Calcd for $C_{12}H_6ClNO_2$: C, 62.22; H, 2.61; N, 6.05; Cl, 15.31. Found: C, 62.41; H, 2.79; N, 5.88; Cl, 15.28.

2-Cyano-6-*p*-methoxyphenyl-4-pyrone (11)——mp 145—147°C, 69.5%. IR ν_{max}^{Nujol} cm^{-1}: 2250, 1642. MS *m/e*: 227 (M^+). *Anal.* Calcd for $C_{13}H_9NO_3$: C, 68.72; H, 3.99; N, 6.17. Found: C, 68.80; H, 4.13; N, 6.01.

2-Cyano-*p*-tolyl-4-pyrone (12)——mp 175—177°C, 79.3%. IR ν_{max}^{Nujol} cm^{-1}: 2250, 1645. MS *m/e*: 211 (M^+). *Anal.* Calcd for $C_{13}H_9NO_2$: C, 73.92; H, 4.30; N, 6.63. Found: C, 73.77; H, 4.22; N, 6.60.

4-Hydroxy-6-phenylpyridine-2-carboxamide (13)——A mixture of **1a** (5.0 g) and 14% NH_3–EtOH (50 ml) was heated at 110—120°C in a sealed tube for 16 h. The mixture was concentrated *in vacuo* to leave a crystalline solid. Recrystallization from EtOH gave **13** (3.3 g, 75%) as plates, mp 225—226°C. IR ν_{max}^{Nujol} cm^{-1}: 3420, 3180(br), 1695. MS *m/e*: 214 (M^+). *Anal.* Calcd for $C_{12}H_{10}N_2O_2$: C, 67.28; H, 4.71; N, 13.08. Found: C, 67.13; H, 4.79; N, 13.07.

2-Cyano-4-hydroxy-6-phenylpyridine (14)——This compound was prepared from **13** in a manner similar to that described for **9**. mp 157—159°C, 71.5%. IR ν_{max}^{Nujol} cm^{-1}: 3260; 2270. MS *m/e*: 196 (M^+). NMR (DMSO-d_6) δ: 6.77 (1H, d, J=2 Hz), 6.98—7.12 (4H, m), 7.46—7.61 (2H, m), *ca.* 10 (1H, b). *Anal.* Calcd for $C_{12}H_8N_2O$: C, 73.46; H, 4.11; N, 14.28. Found: C, 73.22; H, 4.25; N, 14.35.

4-Hydroxy-6-phenylpyridine-2-carboxylic Acid (15)——A mixture of **13** (2.67 g), 5 N NaOH (60 ml), and EtOH (30 ml) was refluxed for 2 h. The reaction mixture was diluted with H_2O, and made acidic with conc.HCl to precipitate a solid. Filtration and washing with EtOH gave **15** (2.41 g, 90%), mp 241—242°C dec. (DMF). IR ν_{max}^{Nujol} cm^{-1}: 1720; 1660. MS *m/e*: 215 (M^+), 171 (M^+-CO_2). *Anal.* Calcd for $C_{12}H_9NO_3\cdot$DMF: C, 62.49; H, 5.59; N, 9.72. Found: C, 62.55; H, 5.67; N, 9.76.

Methyl 4-Chloro-6-phenylpyridine-2-carboxylate (16b)——A mixture of **15** (7.23 g) and $POCl_3$ (70 ml) was heated under reflux for 19 h. The solution was concentrated to dryness *in vacuo*. MeOH (70 ml) was added to the residue under ice-cooling and the solution was concentrated to half of its original volume. Addition of H_2O (100 ml) caused precipitation of a crystalline solid, which was filtered off and recrystallized from *n*-hexane to afford **16b** (5.63 g, 72%), mp 86—88°C. IR ν_{max}^{Nujol} cm^{-1}: 1722. MS *m/e*: 247 (M^+). NMR ($CDCl_3$) δ: 4.08 (3H, s), 7.45—7.66 (3H, m), 7.92—8.18 (4H, m). *Anal.* Calcd for $C_{13}H_{10}ClNO_2$: C, 63.04; H, 4.07; N, 5.66. Found: C, 63.41; H, 4.31; N, 5.92.

4-Chloro-6-phenylpyridine-2-carboxylic Acid (16c)——The ester **16b** (6.0 g) was dissolved in 5% KOH–MeOH (100 ml), and the solution was allowed to stand at room temperature overnight. After evaporation of the solvent, H_2O was added to the residue. The solution was brought to pH 2 with 10% aq.HCl, and extracted with $CHCl_3$. The extracts were washed with H_2O, dried over Na_2SO_4, and concentrated to give **16c** (5.58 g, 98.5%) as an oil, which was pure enough for subsequent reaction without further purification. Recrystallization from petroleum ether gave an analytical sample, as needles mp 82—84°C. *Anal.* Calcd for $C_{12}H_8ClNO_2$: C, 61.68; H, 3.45; N, 6.00, Cl, 15.18. Found: C, 61.81; H, 3.63; N, 6.01; Cl, 15.04.

Methyl 4-Methoxy-6-phenylpyridine-2-carboxylate (17b)——Compound **16b** (4.0 g, 0.016 mol) was added to a solution of NaOMe in MeOH (prepared by adding 1.85 g of Na in 100 ml of MeOH) and the mixture was refluxed for 16 h. The reaction mixture was concentrated to one-third of the initial volume and poured into a mixture of 10% aq.HCl (22 ml) and ice. The liberated oil was extracted with $CHCl_3$, and the extracts were washed successively with sat.aq.$NaHCO_3$ (twice) and H_2O. Evaporation of the solvent gave an oil, which was crystallized from *n*-hexane to afford **17b** (3.43 g, 87%), mp 57—59°C, IR ν_{max}^{Nujol} cm^{-1}: 1710. MS *m/e*: 243 (M^+). NMR ($CDCl_3$) δ: 3.93 (3H, s), 7.33—7.61 (5H, m), 7.92—8.10 (2H, m). *Anal.* Calcd for $C_{14}H_{13}NO_3$: C, 69.12; H, 5.39; N, 5.76. Found: C, 69.05; H, 5.47; N, 5.78.

4-Methoxy-6-phenylpyridine-2-carboxylic Acid (17c)——This compound was prepared from **17b** in a manner similar to that described for **16c**, mp 87—89°C (*n*-hexane). *Anal.* Calcd for $C_{13}H_{11}NO_3$: C, 68.11; H, 4.84; N, 6.11. Found: C, 68.07; H, 4.92; N, 6.13.

Methoxymethylene Acetophenone (20)——A mixture of acetophenone (48 g, 0.40 mol), methyl formate (29.4 g, 0.49 mol), and NaOMe (prepared from 9.2 g of Na and 200 ml of MeOH) in ether (500 ml) was refluxed for 1 h. The precipitate was filtered off, washed with ether, and dried to give **18** (60.5 g, 89%). Dimethyl sulfate (39 g, 0.31 mol) was added dropwise to a cooled solution of **18** in DMF (180 ml), and then the mixture was stirred at room temperature for 1.5 h. The reaction mixture was diluted with H_2O and extracted with ether. The extracts were washed with H_2O, 2% aq.NaOH, and H_2O successively, and dried over Na_2SO_4. Evaporation of the solvent left an oil which was distilled under reduced pressure to give **20** (38.8 g, 67.9%), bp 102—105°C (3 mmHg) [lit.[10] 112°C (1.8 mmHg)]. IR $\nu_{max}^{liq.}$ cm^{-1}: 1665. MS *m/e*: 162 (M^+). NMR ($CDCl_3$) δ: 3.83 (3H, s), 6.37 (1H, d, J=12 Hz), 7.45—8.03 (6H, m).

6-Phenyl-2-pyrone-3-carboxylic Acid (21b)——This compound was prepared from **20** according to the literature.[9] mp 169—170°C (lit.[9b] 166°C). IR ν_{max}^{Nujol} cm^{-1}: 1750, 1665. MS *m/e*: 216 (M^+). *Anal.* Calcd for $C_{12}H_8O_4$: C, 66.67; H, 3.73. Found: C, 66.56; H, 3.88.

6-Phenyl-2-hydroxypyridine-3-carboxylic Acid (25)——A solution of **22**[19] (3.4 g, 0.0173 mol) in a mixture of aq.KOH (5 g of KOH and 50 ml of H_2O) and ethylene glycol (50 ml) was heated at 120—130°C with stirring for 2 d. The reaction mixture was diluted with H_2O and acidified with conc.HCl. The precipitate was collected by filtration, washed with H_2O, and dried to give **25** (3.01 g, 88.8%), mp 300—302°C (lit.[19] 303—

305°C). IR ν_{max}^{Nujol} cm^{-1}: 1750, 1630. MS *m/e*: 215 (M$^+$). NMR (DMSO-d_6) δ: 7.04 (1H, d, J=8 Hz), 8.45 (1H, d, J=8 Hz), 7.5—8.0 (5H, m), 13.5—14.5 (1H, br s).

Methylation of 22——(a) A mixture of **22** (4.0 g, 0.0204 mol), CH_3I (5 ml, 0.0803 mol), and Ag_2O (10.0 g, 0.0432 mol) in DMF (20 ml) was stirred at 80°C for 0.5 h. The insoluble materials were removed by filteration, and the filtrate was concentrated *in vacuo*. The residue was subjected to column chromatography on silica gel. The first eluate with $CHCl_3$ afforded **24** (2.77 g, 64.6%). mp 169—171°C (EtOH). IR ν_{max}^{Nujol} cm^{-1}: 2230. MS *m/e*: 209 (M$^+$−1). NMR ($CDCl_3$) δ: 4.13 (3H, s), 7.2—8.2 (7H, m). *Anal.* Calcd for $C_{13}H_{10}N_2O$: C, 74.27; H, 4.79; N, 13.32. Found: C, 74.20; H, 4.60; N, 13.24. The second eluate provided **23** (0.35 g, 8.2%). mp 110—112°C (iso-Pr_2O). IR ν_{max}^{Nujol} cm^{-1}: 2230, 1645. MS *m/e*: 210 (M$^+$). NMR ($CDCl_3$) δ: 3.43 (3H, s), 6.18 and 7.78 each (1H, d, J=7 Hz), 7.20—7.60 (5H, m). *Anal.* Calcd for $C_{13}H_{10}N_2O$: C, 74.27; H, 4.79; N, 13.32. Found: C, 74.01; H, 4.59; N, 13.24.

(b) A solution of **22** (2.5 g, 0.0153 mol) in DMF (15 ml) was treated with NaH (0.735 g as 60% oil dispersion, 0.0184 mol), and the mixture was stirred at 80°C for 1 h. MeI (3.1 ml, 0.050 mol) was added thereto, and the whole was further heated at 80°C for 1 h. The reaction mixture was concentrated under reduced pressure. The residue was chromatographed on silica gel with $CHCl_3$ to give **23** (1.27 g, 47.4%) and **24** (0.91 g, 34%).

Methylation of 25——(a) **25** was methylated with MeI and Ag_2O in a manner similar to that described for **22**(a) to give **26a** (7.9%) and **27a** (52.5%). **26a**: mp 176—178°C (MeOH). IR ν_{max}^{Nujol} cm^{-1}: 1730, 1615. MS *m/e*: 242 (M$^+$). NMR ($CDCl_3$) δ: 3.42 (3H, s), 3.92 (3H, s), 6.19 (1H, d, J=7 Hz), 8.16 (1H, d, J=7 Hz), 7.20—7.65 (5H, m). *Anal.* Calcd for $C_{14}H_{13}NO_3$: C, 69.12; H, 5.39; N, 5.76. Found: C, 69.08; H, 5.32; N, 5.77. **27a**: mp 61—62°C (iso-Pr_2O). IR ν_{max}^{Nujol} cm^{-1}: 1705. MS *m/e*: 242 (M$^+$). NMR ($CDCl_3$) δ: 3.93 (3H, s), 4.17 (3H, s), 7.20—8.30 (7H, m). *Anal.* Calcd for $C_{14}H_{13}NO_3$: C, 69.12; H, 5.39; N, 5.76. Found: C, 69.32; H, 5.34; N, 5.73.

(b) **25** was methylated with MeI and NaH in a manner similar to that described for **22**(b) to give **26a** (60.1%) and **27a** (6.7%).

1-Methyl-6-phenyl-2-pyridone-3-carboxylic Acid (26b)——A solution of **26a** (1.5 g) in a mixture of EtOH (10 ml) and $CHCl_3$ (5 ml) was treated with 10% aq.NaOH (5 ml). After being stirred at room temperature, the solution was made acidic with AcOH. The precipitate was filtered off, washed with H_2O, dried, and recrystallized from EtOH to give **26b** (1.16 g, 82%), mp 206—207°C. IR ν_{max}^{Nujol} cm^{-1}: 1725, 1615. MS *m/e*: 229 (M$^+$). *Anal.* Calcd for $C_{13}H_{11}NO_3$: C, 68.11; H, 4.84; N, 6.11. Found: C, 68.04; H, 4.73; N, 6.09.

2-Methoxy-6-phenylpyridine-3-carboxylic Acid (27b)——A mixture of **24** (2.0 g), aq.KOH (6 g of KOH in 20 ml of H_2O), and ethylene glycol (20 ml) was heated overnight at 120—130°C with stirring. The reaction mixture was diluted with H_2O and acidified with aq.HCl to precipitate a crystalline solid. Filtration and recrystallization from EtOH gave **27b** (1.3 g, 68.8%). mp 143—145°C. IR ν_{max}^{Nujol} cm^{-1}: 1660. MS *m/e*: 229 (M$^+$). *Anal.* Calcd for $C_{13}H_{11}NO_3$: C, 68.11; H, 4.84; N, 6.11. Found: C, 68.07; H, 4.73; N, 6.11.

2-Chloro-3-cyano-6-phenylpyridine (28)——A mixture of **22** (3.4 g), PCl_5 (10 g), and $POCl_3$ (3.4 g) was heated at 150°C for 1 h. The mixture was concentrated *in vacuo*, and the residue was poured into ice water. The precipitate was collected, washed with H_2O, and dried. Recrystallization from benzene gave **28** (3.5 g, 93.8%), mp 144°C (lit.[20] 143—144°C). IR ν_{max}^{Nujol} cm^{-1}: 2225. MS *m/e*: 214 (M$^+$). *Anal.* Calcd for $C_{12}H_7ClN_2$: C, 67.15; H, 3.29; N, 13.05; Cl, 16.52. Found: C, 66.89; H, 13.13; N, 12.82; Cl, 16.19.

2-Chloro-6-phenylpyridine-3-carboxylic Acid (29)——A solution of **28** (1.7 g, 7.9 mmol) in 90% H_2SO_4 (10 ml) was heated at 120°C with stirring for 2 h. The reaction mixture was cooled below 10°C in an ice-water bath, and a solution of sodium nitrite (2.2 g, 31.9 mmol) in H_2O (4 ml) was carefully added dropwise thereto. After being heated at 80°C for 0.5 h, the mixture was poured into ice water. The precipitate was collected by filtration, washed with H_2O, and dried. Recrystallization from benzene gave **29** (1.34 g, 80.2%), mp 196—196.5°C (lit.[20] 184—185°C). IR ν_{max}^{Nujol} cm^{-1}: 1690. MS *m/e*: 233 (M$^+$). *Anal.* Calcd for $C_{12}H_8ClNO_2$: C, 61.69; H, 3.45; N, 6.00; Cl, 15.17. Found: C, 61.50; H, 3.33; N, 6.10; Cl, 15.26.

4-Chloro-6-methyl-2-phenylpyrimidine (32)——A mixture of **31**[12] (2.0 g) and $POCl_3$ (12 ml) was refluxed for 3.5 h, then concentrated to dryness *in vacuo*. Excess ice water was added to decompose the remaining $POCl_3$, and the liberated oil was extracted with AcOEt. The extracts were washed with H_2O, sat.aq.$NaHCO_3$, and H_2O successively and dried over Na_2SO_4. After removal of the solvent, the residual solid was recrystallized from hexane to give **32** (2.15 g, 97%). mp 72—74°C (lit.[21] 71°C). MS *m/e*: 206, 204 (M$^+$), 169, 104.

4-Methoxy-6-methyl-2-phenylpyrimidine (33)——A mixture of **32** (18.56 g, 0.091 mol) and NaOMe in MeOH (prepared by adding 4.9 g of Na to 250 ml of MeOH) was refluxed for 5 h. The mixture was concentrated under reduced pressure. The residue was dissolved in $CHCl_3$ and the solution was washed with H_2O, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was distilled under reduced pressure to give **33** (17.42 g, 95.7%). bp 114—116°C (3 mmHg). [lit.[21] 160°C (32 mmHg)]. MS *m/e*: 200 (M$^+$), 171, 104. NMR ($CDCl_3$) δ: 2.44 (3H, s), 3.98 (3H, s), 6.39 (1H, s), 7.33—7.47 (3H, m), 8.30—8.58 (2H, m).

4-Methoxy-2-phenylpyrimidine-6-carboxylic Acid (34)——A mixture of **33** (11.45 g, 0.0575 mol), SeO_2 (6.90 g, 0.062 mol), and pyridine (600 ml) was heated under reflux for 50 h. Insoluble material was filtered off and the filtrate was concentrated to dryness *in vacuo*. After addition of 10% aq. NaOH (30 ml) and ether (300 ml), the mixture was stirred for a while. The resulting solid was filtered off, and washed with ether. The filtered cake was dissolved in hot H_2O (250 ml), and the solution was brought to pH 2 with AcOH

then extracted with $CHCl_3$. The extracts were washed with H_2O, dried over Na_2SO_4, and concentrated. The residual solid was recrystallized from aq. EtOH to afford **34** (3.52 g, 26.7%) as needles, mp 149—151°C. IR ν_{max}^{Nujol} cm^{-1}: 1750. MS *m/e*: 230 (M^+). *Anal.* Calcd for $C_{12}H_{10}N_2O_3$: C, 62.60; H, 4.38; N, 12.17. Found: C, 62.83; H, 4.42; N, 12.20.

6-Cyano-2-methoxy-2-phenylpyrimidine (35)——A mixture of **34** (1.23 g) and $SOCl_2$ (25 ml) was refluxed for 2 h. The mixture was concentrated to dryness *in vacuo*. A solution of the residue in benzene (10 ml) was added dropwise to aq.NH_4OH (30 ml) under ice-cooling. After being stirred at room temperature for 2.5 h, the reaction mixture was concentrated *in vacuo*. H_2O was added to the residue, and the resulting solid was collected by filtration to give the carboxamide (1.18 g), mp 196—198°C. IR ν_{max}^{Nujol} cm^{-1}: 3440, 3270, 3200, 3120, 1702. MS *m/e*: 229 (M^+). A mixture of the carboxamide and $POCl_3$ (20 ml) was refluxed for 1 h, then concentrated to dryness *in vacuo*. Ice water was added to the residue, and the solution was made basic with K_2CO_3, then extracted with $CHCl_3$. The extracts were washed with H_2O, dried over Na_2SO_4, and concentrated. The residue was passed through a silica gel short column with $CHCl_3$ to afford **35** (1.04 g, 96%) which was pure enough for the subsequent reaction. Recrystallization from *n*-hexane–ether gave an analytical sample as needles. mp 124—127°C. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1565, 1550, 1362. MS *m/e*: 211 (M^+), 210 (M^+-1), 183, 182, 104. *Anal.* Calcd for $C_{12}H_9N_3O$: C, 68.23; H, 4.30; N, 19.90. Found: C, 68.41; H, 4.35; N, 19.73.

Ethyl (3-Phenylisoxazol-5-yl)aminooxoacetate (37)——Ethyl oxalylchloride (16.38 g, 0.12 mol) was added dropwise to a stirred solution of **36**[14] (16.0 g, 0.10 mol) in pyridine (100 ml) under ice-cooling. After being stirred for 2 h, the mixture was diluted with AcOEt, washed with H_2O, and dried over $MgSO_4$. The solvent was evaporated off *in vacuo* to leave a crystalline solid. Recrystallization from AcOEt–*n*-hexane gave **37** (22.88 g, 88%). mp 146.5—148°C. IR ν_{max}^{Nujol} cm^{-1}: 3280, 1730. NMR ($CDCl_3$) δ: 1.45 (3H, t, $J=7$ Hz), 4.43 (2H, q, $J=7$ Hz), 6.81 (1H, s), 7.40—7.55 (3H, m), 7.71—7.86 (2H, m), 9.86 (1H, br s, D_2O-exchangable). MS *m/e*: 260 (M^+). *Anal.* Calcd for $C_{13}H_{12}N_2O_4$: C, 60.00; H, 4.65; N, 17.76. Found: C, 59.80; H, 4.48; N, 10.77.

Ethyl 4-Hydroxy-6-phenylpyrimidine-2-carboxylate (38)——A mixture of **37** (4.3 g), PtO_2 (0.4 g), and EtOH (200 ml) was shaken with H_2 at 50°C. After the theoretical amount of H_2 had been absorbed, the catalyst was removed by filtration and the filtrate was concentrated *in vacuo*. The residue was dissolved in EtOH (50 ml) and the solution was refluxed for 0.5 h under argon. After removal of the solvent, the residue was recrystallized from EtOH to give **38** (3.14 g, 78%), mp 176—181°C. IR ν_{max}^{Nujol} cm^{-1}: 3150, 1750, 1650. MS *m/e*: 244 (M^+). NMR ($CDCl_3$) δ: 1.49 (3H, t, $J=7$ Hz), 4.56 (2H, q, $J=7$ Hz), 7.05 (1H, s), 7.43—7.54 (3H, m), 7.96—8.11 (2H, m). *Anal.* Calcd for $C_{13}H_{12}N_2O_3$: C, 63.93; H, 4.95; N, 11.47. Found: C, 63.66; H, 4.93; N, 11.19.

Sodium 4-Hydroxy-6-phenylpyrimidine-2-carboxylate (39)——A mixture of **38** (0.50 g, 2.05 mmol), NaOH (0.17 g, 4.30 mmol), H_2O (2 ml) and EtOH (10 ml) was stirred at room temperature overnight. After being heated under reflux for 1 h, the solution was evaporated to dryness. The residual solid was triturated with EtOH, collected by filtration and dried to give **39** (0.53 g). **39** thus obtained was directly used to prepare **66** and **67** without further purification.

Ethyl 4-Chloro-6-phenylpyrimidine-2-carboxylate (40)——A mixture of **38** (0.50 g, 2.05 mmol), dimethylaniline (0.298 g, 2.46 mmol) and $POCl_3$ (3 ml) was heated under reflux for 1 h. The reaction mixture was concentrated *in vacuo*, and the oily residue was washed with sat.aq.$NaHCO_3$ and water to afford a crystalline solid. The solid was suspended with H_2O containing a small amount of aq.HCl, filtered off, and washed with H_2O. Recrystallization from *n*-hexane gave **40** (0.47 g, 87.5%). mp 69—71°C. IR ν_{max}^{Nujol} cm^{-1}: 1730. MS *m/e*: 262 (M^+). NMR ($CDCl_3$) δ: 1.46 (3H, t, $J=7$ Hz), 4.51 (2H, q, $J=7$ Hz), 7.43—7.53 (3H, m), 7.80 (1H, s), 8.02—8.18 (2H, m). *Anal.* Calcd for $C_{13}H_{11}ClN_2O_2$: C, 59.44; H, 4.22; N, 10.67; Cl, 13.50. Found: C, 59.28; H, 4.05; N, 10.28; Cl, 13.77.

4-Ethoxy-6-phenylpyrimidine-2-carboxylic Acid (41)——Compound **40** (1.0 g, 3.81 mmol) was added to a cooled solution of NaOEt in EtOH (prepared by adding 0.22 g of 50% NaH to 20 ml of EtOH), and the mixture was stirred for 0.5 h. After addition of 1 N NaOH (5 ml), the mixture was refluxed for 1 h. The solution was made acidic with 10% aq.HCl, and diluted with AcOEt. The whole was washed with H_2O, dried over Na_2SO_4, and concentrated *in vacuo*. The residual solid was recrystallized from AcOEt–*n*-hexane to give **41** (0.6 g, 64.5%). mp 101—103°C. IR ν_{max}^{Nujol} cm^{-1}: 1710. MS *m/e*: 244 (M^+). *Anal.* Calcd for $C_{13}H_{12}N_2O_3$: C, 63.93; H, 4.95; N, 11.47. Found: C, 63.75; H, 4.89; N, 11.54.

4-Methyl-6-phenylpyrimidine-2-carboxylic Acid——A mixture of 2-cyano-4-methyl-6-phenylpyrimidine[15] (1.40 g) in 2 N NaOH (25 ml) and dioxane (25 ml) was heated under reflux for 1.5 h. The reaction mixture was concentrated *in vacuo*. The residue was dissolved in H_2O and washed with AcOEt. The aqueous layer was made acidic with 10% aq.HCl, and extracted with AcOEt. The extracts were dried over Na_2SO_4 and concentrated to leave a crystalline solid. Recrystallization from AcOEt–*n*-hexane gave 4-methyl-6-phenylpyrimidine-2-carboxylic acid (1.04 g, 67.7%). mp 124—126°C. IR ν_{max}^{Nujol} cm^{-1}: 1740. MS *m/e*: 214 (M^+), 170, 169. NMR ($CDCl_3$) δ: 2.73 (3H, s), 7.48—7.65 (3H, m), 7.79 (1H, s), 8.05—8.21 (2H, m), 10.30 (1H, s, D_2O exchangeable). *Anal.* Calcd for $C_{12}H_{10}N_2O_2$: C, 67.28; H, 4.71; N, 13.08. Found: C, 67.32; H, 4.66; N, 13.02.

Passive Cutaneous Anaphylaxis (PCA)——Male Sprague–Dawley rats (*ca.* 200 g in body weight) were

purchased from Shizuoka Laboratory Animal Center, and maintained on laboratory chow before use. Rat antiserum to the protein extracted from *Ascaris suum* was prepared as described previously.[22] Rats were passively sensitized by injecting *i.c.* on the back 0.05 ml of the antiserum diluted so as to give PCA reactions in the range of 1.0—1.5 cm^2 (see below) in control rats. Twenty-four hour later, they were challenged by injecting *i.v.* 1 ml of a solution containing 0.5 mg of *Ascaris* protein and 5 mg of Evans blue. PCA reactions were assayed 30 min after the challenge, and expressed as the product of the largest diameter (cm) and its perpendicular diamter of the blueing area. Test compounds (as sodium salts or tris(hydroxymethyl)aminomethane salts) were dissolved or suspended in saline containing 0.5% carboxymethylcellulose, and administered to sensitized rats ($N=2$ to 5) 15 min before challenge. The antiallergic activity of the compounds was expressed as per cent inhibition of the PCA reaction compared with control rats.

Acknowledgement The authors are indebted to Drs. S. Saito, S. Takeyama, A. Kiyomoto, and H. Nakajima for their encouragement throughout this work. Thanks are also due to Mr. T. Murata for his technical assistance, and to the members of analytical center of this company.

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