to give ethyl 9-(methylphenylamino)-6-methyl-4-oxo-6,7-dihydro-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylate (**46**; 2.9 g, 58%), mp 140–142 °C. Anal. ($C_{19}H_{21}N_3O_3$) C, H, N.

The ethyl 9-(methylphenylamino)dihydropyridopyrimidine-3-carboxylate **46** (2 g, 5.9 mmol) was stirred in 1% sodium hydroxide solution (100 mL) at 60–70 °C for 4 h. The pH of the solution was adjusted to 2 with 10% hydrochloric acid, and the precipitated 9-(methylphenylamino)dihydropyridopyrimidine-3-carboxylic acid **28** was filtered off, washed with water, dried, and crystallized.

Registry No. **2**, 70999-20-1; **3**, 70999-31-4; **4**, 32092-24-3; **5**, 70998-87-7; **6**, 86610-83-5; **7**, 32092-14-1; **8**, 86610-84-6; **9**, 86610-85-7; **10**, 86610-86-8; **11**, 64399-30-0; **12**, 86610-87-9; **13**, 86610-88-0; **14**, 71165-25-8; **15**, 71165-95-2; **16**, 86610-89-1; **17**, 86610-90-4; **18**, 82074-89-3; **19**, 86610-91-5; **20**, 86610-92-6; **21**, 86610-93-7; **22**, 70943-70-3; **23**, 77020-26-9; **24**, 71222-75-8; **25**, 70993-81-6; **26**, 71222-67-8; **27**, 77020-32-7; **28**, 77020-28-1; **29**, 71222-64-5; **30**, 86610-94-8; **31**, 86610-95-9; **32**, 86610-96-0; **33**, 86610-97-1; **34**, 77020-40-7; **35**, 86610-98-2; **36**, 86610-99-3; **37**, 86611-00-9; **38**, 86611-01-0; **39**, 77020-37-2; **40**, 86611-02-1; **41**, 77020-41-8; **42**, 86611-03-2; **43**, 70943-64-5; **44**, 38326-49-7; **45**, 71222-72-5; **46**, 71222-65-6; aniline, 62-53-3; *N*-methylaniline, 100-61-8; 2-methylaniline, 95-53-4; 3-methylaniline, 108-44-1; 3-fluoroaniline, 372-19-0; 4-fluoroaniline, 371-40-4; 2-bromoaniline, 615-36-1; 3-bromoaniline, 591-19-5; 3-iodoaniline, 626-01-7; 4-hydroxyaniline, 123-30-8; 2-aminobenzoic acid, 118-92-3; 3-aminobenzoic acid, 99-05-8; 4-aminobenzoic acid, 150-13-0; 3-acetylaniline, 99-03-6; 1-naphthylamine, 134-32-7; 2-naphthylamine, 91-59-8.

Supplementary Material Available: Yields and melting points of 12 9-(arylamino)-6-methyl-4-oxo-6,7-dihydro-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylic acids, which were inactive when administered orally, are collected in Table III (1 page). Ordering information is given on any current masthead page.

Antiallergic Agents. 2.[1] *N*-(1*H*-Tetrazol-5-yl)-6-phenyl-2-pyridinecarboxamides

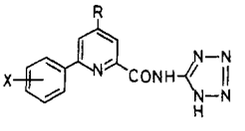
Yasushi Honma,*[†] Kuniyuki Oda,[†] Tomiki Hashiyama,[†] Kyoji Hanamoto,[†] Hideo Nakai,[†] Hirozumi Inoue,[†] Akihiko Ishida,[†] Mikio Takeda,[†] Yasutoshi Ono,[‡] and Kei Tsuzurahara[‡]

Organic Chemistry Research Laboratory and Pharmacological Research Laboratory, Tanabe Seiyaku Co., Ltd., 2-2-50, Kawagishi, Toda-shi, Saitama 335, Japan. *Received February 8, 1983*

A new series of *N*-(1*H*-tetrazol-5-yl)-6-phenyl-2-pyridinecarboxamides was prepared to determine the effects of substituents on the benzene and pyridine rings on antiallergic activity in the rat passive cutaneous anaphylaxis (PCA) assay after oral administration. One member of this series, *N*-(1*H*-tetrazol-5-yl)-4-methyl-6-[4-(methylamino)-phenyl]-2-pyridinecarboxamide (**23l**), has an ED_{50} value of 0.8 mg/kg po and is 85 times more potent than disodium cromoglycate (DSCG) on intravenous administration. Further evaluation of **23l** as a clinically useful antiallergic agent is in progress.

Extensive efforts[2] have been made to find an orally active and more potent antiallergic agent possessing pharmacological properties similar to those of disodium cromoglycate (DSCG).[3]

We have previously reported that some *N*-(1*H*-tetrazol-5-yl)-6-phenyl-2-pyridinecarboxamides (**1**, X = H; R



1

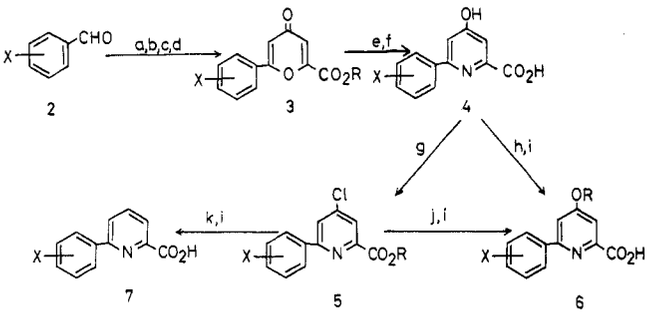
= H, OMe, Cl) displayed remarkably high potencies in the rat PCA test on oral administration.[1] Our attention was next focused on exploring this lead in an effort to enhance the activity. In this paper we describe the synthesis and antiallergic activity of this new series of *N*-tetrazolylpyridinecarboxamides represented by general structure **1**, which bears various substituents on the benzene and pyridine rings.

Chemistry. Most of the *N*-(1*H*-tetrazol-5-yl)-6-phenyl-2-pyridinecarboxamides listed in table I were prepared by condensation of the corresponding carboxylic acid chloride with 5-aminotetrazole (method A).[4]

The route for the preparation of the carboxylic acids[5] (**5–7**) is illustrated in Scheme I and is analogous to that described previously.[1]

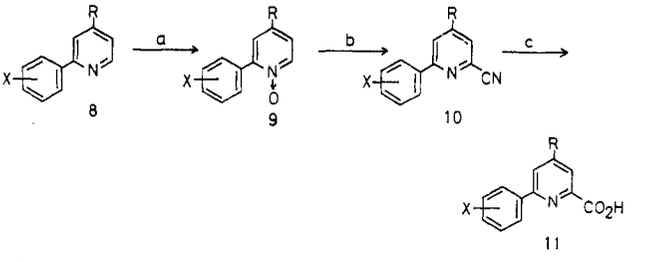
The 6-phenyl-4-alkyl-2-pyridinecarboxylic acids[5] (**11**) were synthesized from the appropriate 2-phenylpyridine

Scheme I[a]



[a] a = CH_3COCH_3, NaOH; b = $(CO_2Et)_2$/NaH; c = Br_2/CS_2; d = KOAc/ROH or DMF. e = NH_3/EtOH, 100–110 °C; f = concentrated HCl; g = (1) $POCl_3$ or $SOCl_2$, (2) MeOH. h = RX, K_2CO_3/DMF; i = KOH/MeOH; j = MeONa/MeOH; k = H_2, Pd/C.

Scheme II[a]



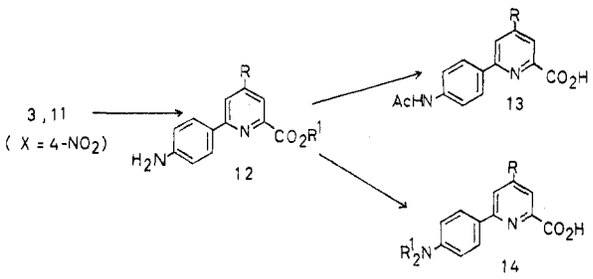
[a] a = 30% H_2O_2/AcOH; b = (1) Me_2SO_4; (2) = NaCN; c = concentrated HCl, reflux.

(**8**)[7] via a Reissert–Kaufman-type reaction[8] (Scheme II). The derivatives possessing amino functions on the benzene

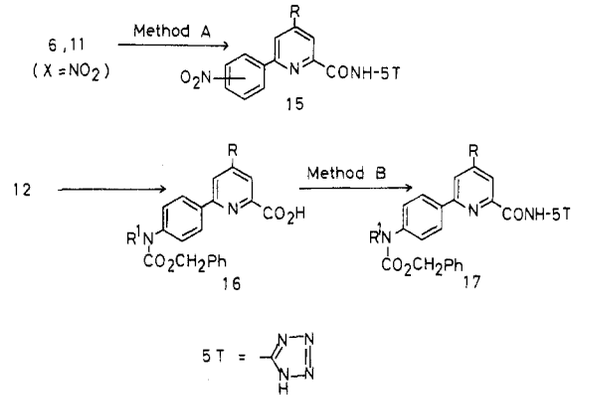
[†] Organic Chemistry Research Laboratory.
[‡] Pharmacological Research Laboratory.

0022-2623/83/1826-1499$01.50/0

Scheme III



Scheme IV



ring were prepared by the route shown in Schemes III and IV. Compound **12** (R = OH) was prepared by hydrogenation of **3** (X = 4-NO_2), followed by ammonolysis and hydrolysis. Acetylation of **12** (R = OH) with Ac_2O/pyridine, hydrolytic workup, and subsequent methylation with MeI/K_2CO_3 in DMF afforded **13** (R = OMe) after alkaline hydrolysis.

Coupling of **13** and **14** with 5-aminotetrazole was achieved in the presence of *N,N'*-carbonyldiimidazole (method B).[4] The amino and alkylamino derivatives were prepared by catalytic hydrogenation (method C) of **15** and **17**, respectively, the route to which is shown in Scheme IV. Treatment with HBr–AcOH was the method of choice for the removal of the *N*-benzyloxycarbonyl group in the case of **17** (R = Cl; R^1 = H).

Results and Discussion

The *N*-(1*H*-tetrazol-5-yl)-6-phenyl-2-pyridinecarboxamides were evaluated for their antiallergic activity in the rat PCA reaction after oral administration, as described previously.[1]

Effects of the substituents on the benzene ring on antiallergic activity were first examined in an attempt to maximize the potency. In the 4-chloropyridine series (**18**), a marked enhancement of activity was observed by methyl (**18g**) and amino (**18n**) substitution at the para position of the benzene ring. This effect was generally observed in the other 4-substituted and unsubstituted pyridine series. Transposition of the methyl or amino group to the meta or ortho position from the para position caused a marked decrease of the activity (**18f**, **19q**, **22h**, **23d**, and **23j**), even to the extent as to be less active than the respective parent.

Introduction of a chloro, methoxy, nitro, or acetamido group onto the benzene ring also lowered the activity in most cases. An unfavorable effect of the meta or ortho substitution was generally observed regardless of the nature of the substituent (**19b**, **19c**, and **22b**). Therefore, some minor modifications of the methyl or amino substituent at the para position were examined further. These analogues, however, did not show any further significant improvement over the parent compounds in each series.

While it is difficult to draw any firm conclusion from these results, it is interesting that the activity of this series of compounds is mainly affected by the substituent on the benzene ring but only slightly, if at all, but that of the 4-substituent on the pyridine nucleus.[9]

After pharmacological evaluation of the most active compounds, *N*-(1*H*-tetrazol-5-yl)-4-methyl-6-[4-(methylamino)phenyl]-2-pyridinecarboxamide (**23l**) was selected for further study as a candidate of clinically useful antiallergic agents. Its ID_{50} value in the rat PCA system is 0.8 mg/kg, po. On intravenous administration, it is approximately 85 times more potent than DSCG (ID_{50} = 0.95 mg/kg). Details of pharmacological studies on **23l** will be the subject of our forthcoming publications.

Experimental Section

Melting points were determined on a Yamato capillary melting point apparatus and are uncorrected. IR spectra were taken on a Hitachi IR-215 spectrometer, and NMR spectra were taken at 60 MHz on a JEOL PMX-60 spectrometer as a solution in $CDCl_3$ or Me_2SO-d_6 with tetramethylsilane as an internal standard. Mass spectra were obtained on a Hitachi RMU-6M instrument. All spectra were consistent with the expected structure.

6-Phenyl-4-oxo-1*H*-pyran-2-carboxylates (3). These compounds were prepared from benzaldehyde (**2**) according to Soliman's procedure.[10]

6-(4-Ethylphenyl)-4-hydroxy-2-pyridinecarboxylic Acid (4, X = 4-Et). A mixture of 10.0 g (0.0367 mol) of **3** (X = 4-Et; R = Et) and 17% NH_3–EtOH (70 mL) was heated at 100–110 °C in a sealed tube for 18 h. The reaction mixture was cooled, and the preceipitate was filtered. A mixture of the precipitate and 150 mL of concentrated HCl was heated under reflux for 18 h. The resulting solution was concentrated to dryness in vacuo. The residue was triturated with H_2O, filtered, washed with EtOH, and dried to give 6.1 g (89%) of **4** (X = 4-Et), mp 227–229 °C, which was used directly for subsequent reaction.

4-Chloro-6-(4-ethylphenyl)-2-pyridinecarboxylic Acid (5, R = H; X = 4-Et). Compound **4** (X = 4-Et) (6.5 g, 0.0267 mol) and $SOCl_2$ (50 mL) were heated at reflux temperature for 5 h. The mixture was concentrated to dryness in vacuo. MeOH (50 mL) was added, and the solution was warmed on a water bath. Evaporation of the solvent gave an oily residue, which was

(1) For Part 1 of this series, see Honma, Y.; Sekine, Y.; Hashiyama, T.; Takeda, M.; Ono, Y.; Tsuzurahara, K. *Chem. Pharm. Bull.* **1982**, *30*, 4314.
(2) Delvin, J. P. *Annu. Rep. Med. Chem.* **1981**, *16*, 61, and earlier volumes.
(3) Speight, R. N.; Aery, G. S. *Drugs* **1974**, *7*, 164.
(4) Ellis, G. P.; Becket, G. T. P.; Shaw, D.; Wilson, H. K.; Vardey, C. J.; Skidmore, I. F. *J. Med. Chem.* **1978**, *21*, 1120.
(5) None of the requisite carboxylic acids have been disclosed in the literature, to the best of our knowledge, except for 6-phenyl-2-pyridinecarboxylic acid.[6]
(6) Haring, M.; Prijs, B.; Erlenmeyer, H. *Helv. Chim. Acta* **1954**, *37*, 147.
(7) (a) Evans, J. C. W.; Allen, C. F. In "Organic Syntheses"; Wiley: New York, 1943; Collect. Vol. II, p 517. (b) van Bergen, T. J.; Kellog, R. M. *J. Org. Chem.* **1971**, *36*, 1705. (c) Osuch, C.; Levine, R. *J. Am. Chem. Soc.* **1956**, *78*, 1723.
(8) (a) Feely, W. E.; Beavers, E. M. *J. Am. Chem. Soc.* **1959**, *81*, 4004. (b) Feely, W. E.; Evanega, G.; Beavers, E. M. In "Organic Syntheses", Wiley: New York, 1973; Collect. Vol. V, p 269.
(9) This was inferred from the preliminary study of the quantitative structure–activity relationships of this series of compounds. Miyagishima, T.; Uchiyama, H., unpublished results. To them, acknowledgment should be addressed.
(10) Soliman, G.; Rateb, L. *J. Chem. Soc.* **1956**, 3663.

crystallized from aqueous MeOH to give 6.85 g (93%) of **5** (R = Me, X = 4-Et), mp 87–90 °C. This compound (1.90 g) was dissolved in 5% KOH–MeOH (40 mL) on a water bath and allowed to stand at room temperature for 1 h. The solution was evaporated in vacuo, and the residue was dissolved in H_2O. The aqueous solution was made acidic with 10% HCl to precipitate **5** (R = H; X = 4-Et) (2.54 g, 98%), mp 159–162 °C.

6-(4-Ethylphenyl)-4-methoxy-2-pyridinecarboxylic Acid (6, R = Me; X = 4-Et). A mixture of 4.0 g (0.0165 mol) of **4** (X = 4-Et), 4.5 mL (0.072 mol) of MeI, 6.8 g (0.049 mol) of K_2CO_3, and 30 mL of DMF was heated at 80 °C for 2 h with stirring. The solvent was evaporated in vacuo. H_2O (60 mL) was added, and the crystalline solid was filtered, washed with H_2O, and dried. The crude product was recrystallized from EtOH to give 3.0 g (67%) of **6** (R = Me; X = 4-Et), mp 79–83 °C. This compound (2.60 g) was treated with 5% KOH–MeOH, as described for the preparation of **5**, to give 2.40 g (97%) of **6** (R = Me; X = 4-Et), mp 130–133 °C dec.

6-(4-Ethylphenyl)-2-pyridinecarboxylic Acid (7, X = 4-Et). A solution of 3.0 g (0.011 mol) of **5** (R = Me; X = 4-Et) in 60 mL of MeOH and 5 mL of 10% HCl was hydrogenated at ambient pressure in the presence of 10% Pd/C (0.3 g) for 22 h, during which time 1 equiv of H_2 was taken up. The catalyst was filtered off, and the filtrate was evaporated in vacuo. The oily residue (3 g) was treated with 5% KOH–MeOH (80 mL), as described for the preparation of **5**, to give 2.68 g (81%) of **7** (X = 4-Et), mp 125–128 °C.

4-Methyl-6-phenyl-2-pyridinecarboxylic Acid (11, R = Me; X = H). A mixture of 3.3 g (0.0195 mol) of **8** (R = Me; X = H),[7c] 4.53 mL (0.038 mol) of 30% H_2O_2, and 11 mL of AcOH was heated at 80 °C for 4 h. Additional 30% H_2O_2 (2.3 mL, 0.02 mol) was added, and heating was continued for an additional 16 h. The solvent was removed in vacuo, and the residue was diluted with H_2O, made basic with K_2CO_3, and extracted with $CHCl_3$. The extracts were washed with H_2O, dried (Na_2SO_4), and evaporated in vacuo to give 3.14 g (85%) of the *N*-oxide **9** (R = Me; X = H), mp 116–118 °C (isopropyl ether). Anal. ($C_{12}H_{11}NO$) C, H, N. A mixture of 2.16 g (0.0117 mol) of this compound and 1.49 g (0.0118 mol) of Me_2SO_4 was heated at 80–90 °C for 2 h with stirring. After cooling, the mixture was dissolved in dioxane (6 mL) and H_2O (2.5 mL), and then a solution of 1.75 g (0.0357 mol) of NaCN in 15 mL of H_2O was added slowly at 5–10 °C with vigorous stirring. After being stirred at room temperature for 30 min, the whole mixture was extracted with ether. The organic extracts were washed with brine, dried (Na_2SO_4), and evaporated in vacuo to give the nitrile **10** (R = Me; X = H), which was used directly for subsequent hydrolysis. A mixture of the nitrile and 5 M HCl (40 mL) was refluxed for 11 h. The resulting solution was evaporated in vacuo, and the residue was dissolved in H_2O (20 mL), brought to pH 3–4 with 10% NaOH, and extracted with $CHCl_3$. The extracts were washed with brine, dried (Na_2SO_4), and evaporated in vacuo to give a syrup, which was crystallized from ether–hexane to give 2.3 g (81%) of **11** (R = Me; X = H). Recrystallization (ether–hexane) gave an analytical sample, mp 109–111 °C. Anal. ($C_{13}H_{11}NO_2$) C, H, N.

Methyl 6-(4-Aminophenyl)-4-hydroxy-2-pyridinecarboxylate (12, R = OH; R¹ = Me). A mixture of 59 g (0.23 mol) of **3** (R = Et; X = 4-NO_2), 10 g of AcONa, and 400 mL of DMF was shaken with H_2 in the presence of 10% Pd/C (6 g). After the theroretical amount of H_2 had been absorbed, the catalyst was filtered off. H_2O (400 mL) was added to the filtrate, and the resulting solid was collected by filtration to give 30 g (57.6%) of **3** (R = Et; X = 4-NH_2), mp 175–180 °C. This compound (24 g, 0.0988 mol) was treated as described for the preparation of **4** to afford **12** (R = OH; R¹ = H), which was heated under reflux with 400 mL of saturated HCl–MeOH for 14 h. The solvent was evaporated in vacuo, and the residue was taken up in H_2O (100 mL). The solution was neutralized with $NaHCO_3$. The precipitate was filtered, washed with H_2O, and dried to obtain 11.4 g (48.5%) of **12** (R = OH; R¹ = Me), mp 188–190 °C.

Ethyl 6-(4-Aminophenyl)-4-methyl-2-pyridinecarboxylate (12, R = Me, R¹ = Et). To a cooled solution of **12** (R = Me; R¹ = H), prepared from 19.1 g (0.74 mol) of **11** (R = Me; X = 4-NO_2) by catalytic hydrogenation, in 800 mL of EtOH was added 40 mL of $SOCl_2$ carefully. The resulting solution was refluxed for 4 h and then treated with charcoal. Evaporation of the solvent gave crystals, which was recrystallized from EtOH–Et_2O to give 19.4 g (89.6%) of **12**·HCl (R = Me; R¹ = Et), mp 210–213 °C.

6-(4-Acetamidophenyl)-4-methoxy-2-pyridinecarboxylic Acid (13, R = OMe). A mixture of 1.03 g (4.33 mmol) of **12**·HCl (R = OH; R¹ = Me), 15 mL of Ac_2O, 0.5 mL of pyridine, and 20 mL of THF was heated under reflux for 3 h. The solvent was evaporated in vacuo, and the residual solid was triturated with H_2O and collected by filtration. A solution of the solid in 10 mL of 10% NaOH and 30 mL of MeOH was allowed to stir at room termperature for 4.5 h. The solution was acidified with 10% HCl to give a solid, which was collected by filtration. 6-(4-Acetamidophenyl)-4-hydroxy-2-pyridinecarboxylic acid thus obtained was converted to 0.47 g (38%) of **13** (R = OMe), mp 234–235 °C dec, as described for the preparation of **6**.

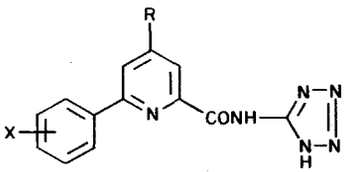
6-[4-(Diethylamino)phenyl]-4-methyl-2-pyridinecarboxylic Acid (14, R = Me; R¹ = Et). A mixture of 3.50 g (0.012 mol) of **12**·HCl (R = Me; R¹ = Et), 10 mL (0.133 mol) of EtBr, 8.8 g (0.0638 mol) of K_2CO_3, and 30 mL of DMF was stirred at 50 °C for 0.5 h. The bath temperature was raised to 100 °C, and heating was continued for an additional 3 h. The insoluble materials were removed by filtration, and the filtrate was evaporated in vacuo. H_2O was added, and the liberated oil was extracted with ethyl acetate. The extracts were washed with brine, dried (Na_2SO_4), and decolorized with charcoal. Evaporation of the solvent gave a pale yellow oil (3.4 g), which was subjected to column chromatography on silica gel eluting with $CHCl_3$–ethyl acetate (10:1) to afford 2.6 g (69.6%) of the ethyl ester of **14** (R = Me; R¹ = Et), mp 68–69 °C. The ester (2.5 g) and 8% HCl (40 mL) were heated at 80 °C for 5 h. The resulting solution was concentrated to dryness in vacuo to give 2.6 g (100%) of **14**·HCl (R = Me; R¹ = Et), mp 223–235 °C dec.

6-[4-[(Benzyloxycarbonyl)methylamino]phenyl-4-methyl-2-pyridinecarboxylic Acid (16, R = R¹ = Me). Benzyloxycarbonyl chloride (4.2 g, 0.0246 mol) was added dropwise to a cooled mixture of 6.0 g (0.0205 mol) of **12**·HCl (R = Me; R¹ = Et), 6.0 g of $NaHCO_3$, 150 mL of H_2O, and 150 mL of ethyl acetate. After being stirred for 45 min, the mixture was made acidic with 10% HCl. The resulting solid was filtered, washed with H_2O, and dried. The organic layer of the filtrate was washed with brine, dried (Na_2SO_4), and evaporated in vacuo, and the residue was crystallized from ethyl acetate. Filtration gave a solid, which was combined with the above solid and recrystallized from EtOH to give 6.0 g (75%) of the ethyl ester of **16** (R = Me; R¹ = H), mp 184–185 °C. A mixture of the ester, 15 mL (0.162 mol) of MeI, 18 g (0.13 mol) of K_2CO_3, and 50 mL of DMF was stirred at room temperature for 18 h. The insoluble materials were removed by filtration. The filtrate was concentrated in vacuo. The residue was diluted with H_2O and extracted with ethyl acetate. The extracts were washed with brine, dried (Na_2SO_4), and evaporated in vacuo. The residue was chilled in ethyl acetate, and insoluble materials were filtered off. The filtrate was evaporated in vacuo, and the residue was chromatographed on silica gel eluting with $CHCl_3$–ethyl acetate (10:1) to give 2.7 g (43.4%) of the ethyl ester of **16** (R = R¹ = Me) as a syrup. The ester was treated with 5% KOH–MeOH as described for the preparation of **5** to give 2.4 g (95.5%) of **16** (R = R¹ = Me) as a light yellow oil.

Method A. *N*-(1*H*-Tetrazol-5-yl)-6-(4-ethylphenyl)-4-methoxy-2-pyridinecarboxamide (19j). A mixture of 2.38 g (9.25 mmol) of **6** (R = Me; X = 4-Et) and 20 mL of $SOCl_2$ was refluxed for 1 h. The resulting solution was evaporated in vacuo to give a syrup, which was dissolved in 25 mL of DMF and treated with a solution of 0.87 g (10.1 mmol) of 5-aminotetrazole, 2.8 g of NEt_3, and 10 mL of DMF under ice cooling. After being heated at 80 °C for 2 h, the mixture was evaporated in vacuo and dissolved in H_2O. The solution was brought to pH 2–3 with 10% HCl, and the resulting solid was filtered, washed with H_2O, and dried. Recrystallization from DMF–EtOH gave 1.56 g (52%) of **19j**.

Method B. *N*-(1*H*-Tetrazol-5-yl)-6-[4-(diethylamino)-phenyl]-4-ethoxy-2-pyridinecarboxamide (20d). Carbonyldiimidazole (0.32 g, 1.98 mmol) was added to a solution of 0.56 g (1.78 mmol) of **14** (R = OEt; R¹ = Et) in 8 mL of DMF, and the mixture was stirred at room temperature for 1 h. After the addition of 0.17 g (2.0 mmol) of 5-aminotetrazole, the mixture was heated at 60–70 °C for 2 h. Workup as described above afforded 0.52 g (77%) of **20d**.

Table I. *N*-(5-Tetrazolyl)-6-phenyl-2-pyridinecarboxamides



no.	R	X	method[a]	yield,[b] %	dec pt, °C	recrystn solvent[c]	formula[d]	rat PCA: % inhibin[e] at the following po dose			
								0.3 mg/kg	1.0 mg/kg	3.0 mg/kg	10.0 mg/kg
18a[f]	Cl	H							40		
18b	Cl	4-Cl	A	74	280–281	D-E	$C_{13}H_8Cl_2N_6O$			11[t]	63[s]
18c	Cl	3-OMe	A	72	255–263	D-E-H	$C_{14}H_{11}ClN_6O_2$	32	51	95	
18d	Cl	4-OMe	A	80	250–251	E*	$C_{14}H_{11}ClN_6O_2$	40	43	100	
18e	Cl	3,4-$(OMe)_2$	A	48	250–251	E*	$C_{15}H_{13}ClN_6O_3 \cdot 0.5H_2O$		15[t]	30[t]	
18f	Cl	2-Me	A	78	~160 darken	E*	$C_{14}H_{11}ClN_6O$[g]				24[t]
18g	Cl	4-Me	A	79	259–262	D-E	$C_{14}H_{11}ClN_6O$	10[t]	86		
18h	Cl	4-Et	B	60	261–264	D-E	$C_{15}H_{13}ClN_6O$	13[s]	49	100	
18i	Cl	4-*n*-Pr_2	A	81	251–253	E*	$C_{16}H_{15}ClN_6O$	42	78		
18j	Cl	4-*i*-Pr	A	66	249–252	D-E	$C_{16}H_{15}ClN_6O$		14[t]	68	90
18k	Cl	4-*n*-Bu	A	46	245–250	D-E	$C_{17}H_{17}ClN_6O_3$[h]		0	83	
18l	Cl	3,4-Me_2	A	35	252–255	D-H	$C_{15}H_{13}ClN_6O$			32[t]	58[s]
18m	Cl	4-NO_2	A	70	289–290	D-E	$C_{13}H_8ClN_7O_3$			23[t]	48[t]
18n	Cl	4-NH_2	D	64	200	E*	$C_{13}H_{10}ClN_7O \cdot 0.25H_2O$	39	100	100	
19a[f]	OMe	H							62	97	100
19b	OMe	2-Cl	A	64	251–254	D-E-H	$C_{14}H_{11}ClN_6O_2$				17[t]
19c	OMe	3-Cl	A	62	253–255	E*	$C_{14}H_{11}ClN_6O_2$			34	64
19d	OMe	4-Cl	A	56	269–270	D-E	$C_{14}H_{11}ClN_6O_2$		0	12[t]	55
19e	OMe	2-OMe	A	27	266–267	E	$C_{15}H_{14}N_6O_3$	35[s]	41[t]	68	
19f	OMe	4-OMe	A	61	264–265	D-E	$C_{15}H_{14}N_6O_3$		25[t]	60	
19g	OMe	3,4-$(OMe)_2$	A	59	246–247	D-E	$C_{16}H_{16}N_6O_4 \cdot 0.5DMF$		18[t]	62[s]	51
19h	OMe	3,4,5-$(OMe)_3$	B	58	244–245	M	$C_{17}H_{18}N_6O_5$			0	25[t]
19i	OMe	4-Me	A	65	269–273	E*	$C_{15}H_{14}N_6O_2$	16[t]	42		
19j	OMe	4-Et	A	52	254–256	D-E	$C_{15}H_{14}N_6O$	23	43		
19k	OMe	4-*n*-Pr	A	57	251–252	D	$C_{17}H_{18}N_6O_2$	32[t]	73	93	
19l	OMe	4-*i*-Pr	B	58	229.5–230.5	E*	$C_{17}H_{18}N_6O_2$	29[t]	54		
19m	OMe	4-*n*-Bu	A	58	233–238	D-E	$C_{18}H_{20}N_6O_2$		29[t]	61	92
19n	OMe	4-*t*-Bu	A	58	257–259	D-H	$C_{18}H_{20}N_6O_2$[i]		29[t]	68[s]	
19o	OMe	3,4-Me_2	A	58	242–245	D-H	$C_{16}H_{16}N_6O$		21[t]	82	
19p	OMe	4-NO_2	A	82	279–281	D	$C_{14}H_{11}N_7O_4$				6[t]
19q	OMe	3-NH_2	C	63	259–260	D	$C_{14}H_{13}N_7O_2$		27[s]	41	58[s]
19r	OMe	4-NH_2	C	25	251–253	E*	$C_{14}H_{13}N_7O_2$	12[s]	50[s]		
19s	OMe	4-NHMe	C	87	251–252	D-E	$C_{15}H_{15}N_7O_2 \cdot 0.5H_2O$		35[t]	79	
19t	OMe	4-NMe_2	B	50	261–263	D-E	$C_{16}H_{17}N_7O_2$	29	64	100	
19u	OMe	4-NHAc	B	85	286–288	D-E	$C_{16}H_{15}N_7O_3$		0	27[t]	100
20a	OEt	H	A	63	262–263	D-E	$C_{15}H_{14}N_6O_2$[j]		29[t]	51[s]	
20b	OEt	4-Me	A	50	261–262	D-E	$C_{16}H_{16}N_6O_2$	26[t]	65		
20c	OEt	4-NH_2	C	74	263–265	E*	$C_{15}H_{15}N_7O_2 \cdot 0.5EtOH$	19[t]	52	62	
20d	OEt	4-NEt_2	B	77	228–230	D-E	$C_{19}H_{23}N_7O_2$	44	66		
21a	O-*n*-Pr	H	A	32	234–236	E	$C_{16}H_{11}N_6O_2$[k]	0	27[s]	100	
21b	O-*n*-Pr	4-NH_2	C	35	237–240	I*	$C_{16}H_{17}N_7O_2 \cdot 0.5H_2O$	7[t]	64	68	
22a[f]	H	H							36[s]	74	81
22b	H	2-OMe	A	68	246–247	D-E	$C_{14}H_{12}N_6O_2$				0

22c	H	4-OMe	A	76	268–271	E*	$C_{14}H_{12}N_6O_2$	4[t]	12[t]	36	
22d	H	3,4,5-$(OMe)_3$	B	64	260–264	M	$C_{17}H_{18}N_6O_5$			15[t]	45[t]
22e	H	4-Me	A	70	280–281	D–E	$C_{14}H_{12}N_6O$	21[t]	67		
22f	H	4-Et	A	52	272–278	D–E	$C_{15}H_{14}N_6O$[l]	14[s]	39[t]		
22g	H	3,4-Me_2	A	62	268–270	D–H	$C_{15}H_{14}N_6O$			28[t]	39[s]
22h	H	3-NH_2	C	85	274–275	D–E	$C_{13}H_{11}N_7O$			0	57[s]
22i	H	4-NH_2	C	84	268–273	D–E	$C_{13}H_{11}N_7O$[m]	11[t]	62	81	
22j	H	4-NHMe	C	89	264–266	D–E	$C_{14}H_{13}N_7O$[n]	29[t]	71[t]	83[t]	
23a	Me	H	A	87	263–263.5	D–E	$C_{14}H_{12}N_6O$		23[t]	50	88
23b	Me	3-OMe	A	62	214	D–M	$C_{15}H_{14}N_6O_2$		25[t]	65	
23c	Me	4-OMe	A	46	254–256	D–M	$C_{15}H_{14}N_6O_2$			43	52[s]
23d	Me	3-Me	A	66	250–251	D–E	$C_{15}H_{14}N_6O$		51	61	
23e	Me	4-Me	A	61	262.5–263	D–H	$C_{15}H_{14}N_6O$	51	80	100	
23f	Me	4-Et	A	78	252–253	D–E	$C_{16}H_{16}N_6O$			35[s]	100
23g	Me	4-*n*-Pr	A	63	240–241.5	D–E	$C_{17}H_{18}N_6O$	19[t]	65[t]		
23h	Me	4-*i*-Pr	A	74	260–261.5	D–E	$C_{17}H_{18}N_6O$		34	100	
23i	Me	4-*n*-Bu	A	87	238–239.5	D–E	$C_{18}H_{20}N_6O$	17[t]	42[s]	67	
23j	Me	3-NH_2	C	93	266–272	E*	$C_{14}H_{13}N_7O$[o]		29[t]	50[s]	
23k	Me	4-NH_2	C	78	259.5–260.5	D–E	$C_{14}H_{13}N_7O$	54[s]	75	100	
23l	Me	4-NHMe	C	96	272–273	D–E	$C_{15}H_{15}N_7O \cdot 0.5EtOH$	36[t]	89		
23m	Me	4-NMe_2	B	22	265–269	D–E	$C_{16}H_{17}N_7O$			24[t]	
23n	Me	4-NEt_2	B	74	254–256	D–E	$C_{18}H_{21}N_7O$	19[t]			
23o	Me	4-NHAc	B	72	309–310	D–E	$C_{16}H_{16}N_7O_2 \cdot 0.5EtOH$			32[t]	
24a	Et	H	A	56	246–247	E	$C_{15}H_{14}N_6O$			53	85
24b	Et	4-Me	A	50	238.5–239.5	E*	$C_{16}H_{16}N_6O$	33[t]			
24c	Et	4-*n*-Bu	A	39	181–183	D–E	$C_{19}H_{22}N_6O$		20[t]	70	
25a	*n*-Pr	H	A	50	234–235	A	$C_{16}H_{16}N_6O$			22[s]	85
25b	*n*-Pr	4-Me	A	34	243.5–244.5	D–E	$C_{17}H_{18}N_6O$			50	84
26a	*i*-Pr	4-Me	A	31	257–258	D–E	$C_{17}H_{18}N_6O$[p]		20[t]	42[s]	
26b	*i*-Pr	4-NH_2	C	71	268–270	D–E	$C_{16}H_{17}N_7O$	22[t]	29[t]	43[t]	
27a	*n*-Bu	H	A	65	242–243	A	$C_{17}H_{18}N_6O$		56	71	100
27b	*n*-Bu	3-Me	A	66	242–244	D–E–H	$C_{18}H_{20}N_6O$[q]		36	82	100
27c	*n*-Bu	4-Et	A	16	217–217.5	D–H	$C_{19}H_{22}N_6O$		19[t]	25[t]	
27d	*n*-Bu	4-NH_2	C	60	>300	D–E	$C_{17}H_{19}N_7O$[r]	41	81		
28a	*i*-Bu	H	A	55	266–268	D–H	$C_{17}H_{18}N_6O$				11[t]
28b	*i*-Bu	4-Me	A	56	256–257	D–E	$C_{18}H_{20}N_6O$		9[t]	52	
28c	*i*-Bu	4-*n*-Bu	A	34	236–238	D–E	$C_{21}H_{26}N_6O \cdot 0.25H_2O$			3[t]	13[t]

[a] See the Experimental Section. [b] For the purified product. [c] A = AcOH; D = DMF; E = EtOH; H = H_2O; I = *i*-PrOH; M = MeOH; * = washed with the indicated solvent. [d] Elemental analyses for C, H, N, and Cl gave results within 0.4% of the theoretical values, unless otherwise indicated. [e] $p < 0.05$ using Student's *t* test, unless otherwise indicated. [f] See ref 1. [g] N: calcd, 26.70; found, 26.10. [h] Cl: calcd, 9.94; found, 9.04. [i] N: calcd, 23.85; found, 23.41. [j] C: calcd, 58.05; found, 58.51. [k] N: calcd, 25.91; found, 26.41. [l] N: calcd, 28.56; found, 29.60. [m] N: calcd, 34.86; found, 34.15. [n] N: calcd, 33.20; found, 32.59. [o] N: calcd, 29.56; found, 29.14. [p] C: calcd, 63.34; found, 62.61. [q] C: calcd, 64.26; found, 63.76. [r] C: calcd, 60.52; found, 59.94. [s] $p < 0.1$. [t] Not statistically significant.

Method C. *N*-(1*H*-Tetrazol-5-yl)-4-methyl-6-[4-(methylamino)phenyl]-2-pyridinecarboxamide (23l). A solution of 0.48 g (1.08 mmol) of **17** (R = R^1 = Me) in 2 mL of 10% NaOH, 20 mL of H_2O, and 20 mL of EtOH was hydrogenated over 10% Pd/C (0.1 g). After the theoretical amount of H_2 had been absorbed, the catalyst was filtered off. The filtrate was acidified with 10% HCl, and the resulting solid was collected, washed with EtOH, and recrystallized from DMF–EtOH to give 0.32 g (96%) of **23l**.

Method D. *N*-(1*H*-Tetrazol-5-yl)-6-(4-aminophenyl)-4-chloro-2-pyridinecarboxamide (18n). A mixture of 0.43 g (0.937 mmol) of **17** (R = Cl; R^1 = H) and 4 mL of 25% HBr–AcOH was stirred at room temperature for 4 h. H_2O was added, and the resulting precipitate was filtered and washed with H_2O and EtOH, successively, to afford 0.19 g (64%) of **18n**.

Passive Cutaneous Anaphylaxis. Male Sprague–Dawley rats (ca. 200 g in body weight) were immunized with an extract of *Ascaris suum* according to the method of Strejan and Campbell,[11] except for the antigen doses (2 and 0.2 mg of protein for the first and second immunizations, respectively). The sensitized rats were bled 2 weeks after the second immunization, and the sera were assayed for IgE in the rat PCA. IgE was confirmed by its heat lability and long-lasting fixation on the rat skin.

Rats were passively sensitized by injecting intracutaneously on the back 0.05 mL of the diluted antiserum. Twenty-four hours later, they were challenged by injecting intravenously 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 (centimeters) and its perpendicular diameter of the blueing area. Control PCA reactions were 1.27 ± 0.03 cm^2 in this definition. Test compounds (as a sodium salt) were dissolved or suspended in saline containing 0.5% carboxymethylcellulose and administered orally to the sensitized rats (N = 2 to 4, mostly 3) 15 min before challenge.

The antiallergic activity of the compounds was expressed as percent inhibition of the PCA reaction compared with control rats.

Acknowledgment. The authors are indebted to Dr. S. Takeyama for preparing the manuscript for publication and helpful discussions. The authors thank Drs. S. Saito, A. Kiyomoto, and H. Nakajima for their encouragement and many suggestions during this work. Thanks are also due to T. Murata and A. Watanabe for their technical assistance and to the staff of the Analytical Center of Tanabe Seiyaku Co. Ltd., for spectral measurements and elemental analyses.

Registry No. **3** (R = Et; X = 4-Et), 86696-35-7; **3** (R = Et; X = 4-NO_2), 76781-89-0; **3** (R = Et; X = 4-NH_2), 80021-86-9; **4** (X = 4-Et), 86696-36-8; **5** (R = H; X = 4-Et), 86696-37-9; **6** (R = Me; X = 4-Et), 86696-38-0; **6** (R = Me; X = 2-Cl), 86696-53-9; **6** (R = Me; X = 3-Cl), 86696-54-0; **6** (R = Me; X = 4-Cl), 86696-55-1; **6** (R = Me; X = 2-OMe), 86696-56-2; **6** (R = Me; X = 4-OMe), 86696-57-3; **6** (R = Me; X = 3,4-$(OMe)_2$), 86696-58-4; **6** (R = Me; X = 3,4,5-$(OMe)_3$), 86696-59-5; **6** (R = Me; X = 4-Me), 86696-60-8; **6** (R = Me; X = 4-*n*-Pr), 86696-61-9; **6** (R = Me; X = 4-*i*-Pr), 86696-62-0; **6** (R = Me; X = 4-*n*-Bu), 86696-63-1; **6** (R = Me; X = 4-*t*-Bu), 86696-64-2; **6** (R = Me; X = 3,4-Me_2), 86696-65-3; **6** (R = Me; X = 4-NO_2), 80021-52-9; **6** (R = Et; X = H), 86696-66-4; **6** (R = Et; X = 4-Me), 86696-67-5; **6** (R = *n*-Pr; X = H), 86696-68-6; **7** (X = 4-Et), 86696-39-1; **7** (X = 2-OMe), 86696-69-7; **7** (X = 4-OMe), 86696-70-0; **7** [X = 3,4,5-$(OMe)_3$], 86696-71-1; **7** (X = 4-Me), 86696-72-2; **7** (X = 3,4-Me_2), 86696-73-3; **8** (R = Me; X = H), 3475-21-6; **9** (R = Me; X = H), 80635-42-3; **10** (R = Me; X = H), 80635-45-6; **11** (R = Me; X = H), 80635-46-7; **11** (R = Me; X = 4-NO_2), 80021-38-1; **11** (R = Cl; X = 4-Cl), 86696-42-6; **11** (R = Cl; X = 3-OMe), 86696-43-7; **11** (R = Cl; X = 4-OMe), 86696-44-8; **11** [R = Cl; X = 3,4-$(OMe)_2$], 86696-45-9; **11** (R = Cl; X = 2-Me), 86696-46-0; **11** (R = Cl; X = 4-Me), 86696-47-1; **11** (R = Cl; X = 4-*n*-Pr), 86696-48-2; **11** (R = Cl; X = 4-*i*-Pr), 86696-49-3; **11** (R = Cl; X = 4-*n*-Bu), 86696-50-6; **11** (R = Cl; X = 3,4-Me_2), 86696-51-7; **11** (R = Cl; X = 4-NO_2), 86696-52-8; **11** (R = Me; X = 3-OMe), 80636-14-2; **11** (R = *n*-Pr; X = H), 80636-11-9; **11** (R = *n*-Pr; X = 4-Me), 80636-20-0; **11** (R = *i*-Pr; X = 4-Me), 80636-21-1; **11** (R = *n*-Bu; X = H), 80636-12-0; **11** (R = *n*-Bu; X = 3-Me), 80636-17-5; **11** (R = *n*-Bu; X = 4-Et), 86696-74-4; **11** (R = *i*-Bu; X = H), 80636-13-1; **11** (R = *i*-Bu; X = 4-Me), 80636-22-2; **11** (R = *i*-Bu; X = 4-*n*-Bu), 80636-29-9; **12** (R = OH; R^1 = Me), 80021-88-1; **12**·HCl (R = Me; R^1 = Et), 80021-71-2; **12** (R = Me; R^1 = H), 86696-41-5; **13** (R = OMe), 80020-95-7; **13**·HCl (R = Me; R^1 = Et), 80021-75-6; **14** (R = OMe; R^1 = Me), 80020-86-6; **14** (R = OEt; R^1 = Et), 80020-97-9; **16** (R = R^1 = Me), 80021-10-9; **17** (R = Cl; R^1 = H), 86696-75-5; **17** (R = OMe; R^1 = H), 86696-77-7; **17** (R = OMe; R^1 = Me), 86696-78-8; **17** (R = OEt; R^1 = H), 86696-79-9; **17** (R = O-*n*-Pr; R^1 = H), 86696-80-2; **17** (R = R^1 = H), 86696-82-4; **17** (R = H; R^1 = Me), 86696-83-5; **17** (R = *i*-Pr; R^1 = H), 86696-84-6; **17** (R = *n*-Bu; R^1 = H), 86696-85-7; **18a**, 78296-74-9; **18b**, 78296-75-0; **18c**, 78296-77-2; **18d**, 78296-78-3; **18e**, 78296-80-7; **18f**, 78296-76-1; **18g**, 78296-73-8; **18h**, 78296-72-7; **18i**, 78312-70-6; **18j**, 78296-62-5; **18k**, 78296-64-7; **18l**, 78296-66-9; **18m**, 78296-81-8; **18n**, 80021-57-4; **19a**, 78296-45-4; **19b**, 78296-46-5; **19c**, 78296-47-6; **19d**, 78296-48-7; **19e**, 78296-50-1; **19f**, 78296-83-0; **19g**, 78296-52-3; **19h**, 78296-71-6; **19i**, 78296-49-8; **19j**, 78296-59-0; **19k**, 78296-61-4; **19l**, 78296-70-5; **19m**, 78296-63-6; **19n**, 78296-65-8; **19o**, 78296-67-0; **19p**, 78296-53-4; **19q**, 80021-32-5; **19r**, 80021-53-0; **19s**, 80021-16-5; **19t**, 80020-87-7; **19u**, 80020-96-8; **20a**, 78296-54-5; **20b**, 78296-55-6; **20c**, 80021-20-1; **20d**, 80021-69-8; **21a**, 78296-56-7; **21b**, 80021-24-5; **22a**, 78296-84-1; **22b**, 78296-43-2; **22c**, 78296-44-3; **22d**, 78296-69-2; **22e**, 78296-42-1; **22f**, 78296-60-3; **22g**, 78296-68-1; **22h**, 80021-36-9; **22i**, 80021-28-9; **22j**, 80021-08-5; **23a**, 80635-48-9; **23b**, 80635-54-7; **23c**, 80635-55-8; **23d**, 80635-56-9; **23e**, 80635-58-1; **23f**, 80635-63-8; **23g**, 80635-65-0; **23h**, 80635-66-1; **23i**, 80635-67-2; **23j**, 86696-40-4; **23k**, 80021-40-5; **23l**, 80021-12-1; **23m**, 80020-90-2; **23n**, 80020-93-5; **23o**, 80021-04-1; **24a**, 80635-50-3; **24b**, 80635-59-2; **24c**, 80635-68-3; **25a**, 80635-51-4; **25b**, 80635-60-5; **26a**, 80635-61-6; **26b**, 80021-47-2; **27a**, 80635-52-5; **27b**, 80635-57-0; **27c**, 80635-64-9; **27d**, 80021-51-8; **28a**, 80635-53-6; **28b**, 80635-62-7; **28c**, 80635-69-4; 4-methoxy-6-[3-[*N*-(benzyloxycarbonyl)-*N*-methylamino]phenyl]-*N*-(1*H*-tetrazol-5-yl)-2-pyridinecarboxamide, 86696-76-6; 6-[3-[*N*-(benzyloxycarbonyl)-*N*-methylamino]phenyl]-*N*-(1*H*-tetrazol-5-yl)-2-pyridinecarboxamide, 86696-81-3.

(11) Strejan, G.; Campbell, D. H. *J. Immunol.* **1968**, *101*, 628.