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

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

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

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

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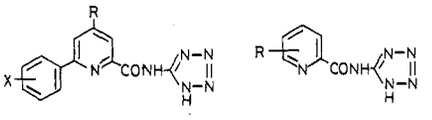
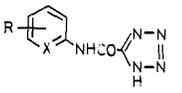
A series of N-tetrazolylpyridinecarboxamides was prepared and evaluated for antiallergic activity by the passive cutaneous anaphylaxis (PCA) assay. From the structure–activity relationships (SAR) of this class of compounds, it was revealed that the N-tetrazolylcarbamoyl group as an acidic functionality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

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



1

2

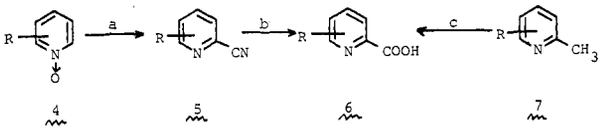


3

X = N, CH

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

Scheme I[a]



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

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

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

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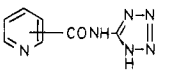
[‡] Pharmacological Research Laboratory.

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

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

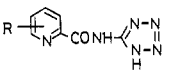
Table I. *N*-(1*H*-Tetrazol-5-yl)pyridinecarboxamides



no.	position	dec pt,[a] °C	yield,[b] %	formula	PCA:[c] % inhibn[d] at the following po doses 1 mg/kg	3 mg/kg	10 mg/kg	30 mg/kg
15	2	268–269	55	$C_7H_6N_6O$	0	29	35	100
16	3	277–278[e]	40	$C_7H_6N_6O$		4	3	18
17	4	253–254	26	$C_7H_6N_6O \cdot 0.25H_2O$				57

[a] All compounds were recrystallized from DMF–EtOAc. [b] Prepared by method A (Experimental Section). [c] As described in ref 1 with a 15-min pretreatment time. [d] Not statistically significant. [e] Literature mp 268–269 °C: Ettel, V.; Nosek, *J. Czech. Chem. Commun.* **1950**, *15*, 335.

Table II. Substituted *N*-(1*H*-Tetrazol-5-yl)-2-pyridinecarboxamides



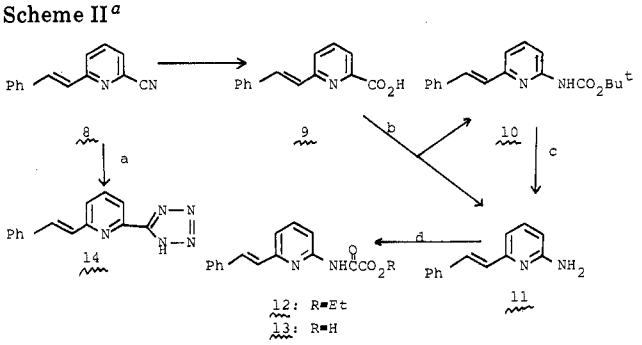
no.	R	method[a]	yield, %	dec pt, °C	recrystn solvent[b]	formula	PCA:[c] % inhibn[d] at the following po doses 1 mg/kg	3 mg/kg	10 mg/kg
18	3-Cl	A	37	252–254	D, E, H	$C_7H_5ClN_6O$			22[n]
19	3-OMe	A	21	213.5–215.5	D, H	$C_8H_8N_6O_2$			0
20	3-Me	B	9	227–230	D, E	$C_8H_8N_6O$			69
21	4-Cl	A	60	240–250[e]	D, E	$C_7H_5ClN_6O$[g]	38	72	100
22	4-Br	B	59	250–280[e]	D, E	$C_7H_5BrN_6O$[h]	9[o]	34[o]	100
23	4-OMe	A	56	235–250	E	$C_8H_8N_6O_2$			88
24	4-Me	B	33	241.5–242.5	D, H	$C_8H_8N_6O$	28[n]	42	
25	4-Et	B	24	217–218	D, H	$C_9H_{10}N_6O$	32[n]	29[o]	
26	4-*i*-Pr	B	29	198–203	D, E	$C_{10}H_{12}N_6O$	36[n]	34	
27	4-*n*-Bu	B	63	218–219	D, E, H	$C_{11}H_{14}N_6O$		33[o]	54
28	4-NO_2	B	56	250–270[e]	E*	*f*			38[n]
29	5-Me	A	36	275–277	D	$C_8H_8N_6O$			42[n]
30	5-SMe	A	34	275–276	D, E	$C_8H_8N_6OS$			29[o]
31	6-Cl	A	26	240–242	D, H	$C_7H_5ClN_6O$[i]		18[o]	13[o]
32	6-Br	B	57	250–280[e]	D, E	$C_7H_5BrN_6O$[j]		38	48
33	6-OMe	B	46	252–253	D, E, H	$C_8H_8N_6O_2$		36[o]	58[n]
34	6-O-*n*-Bu	A	61	203–204	D, E, H	$C_{11}H_{14}N_6O_2$		18[o]	8[o]
35	6-OPh	B	40	212–218	E	$C_{13}H_{10}N_6O_2$			0
36	6-Me	A	49	248–249	D, E	$C_8H_8N_6O$	40	46[n]	
37	6-*n*-Pr	A	10	218–220	D, H	$C_{10}H_{12}N_6O$			38[o]
38	6-*n*-Bu	A	29	194–197	D, E	$C_{11}H_{14}N_6O$			18[n]
39	6-CH=CHPh	A	58	261.5–262	D, E	$C_{15}H_{12}N_6O$[k]	53	73	
40	6-CH_2CH_2Ph	*a*	67	220–221	D, E	$C_{15}H_{14}N_6O$			45
41	4-Cl, 6-Me	B	69	240–250[e]	D, E	$C_8H_7ClN_6O$	66		100
42	4-OMe, 6-Me	B	73	252–258	D, E	$C_9H_{10}N_6O_2$			20[o]
43	4-NO_2, 6-Me	A	61	>300	E*	$C_8H_7N_7O_3$[l]			6[o]
44	3,6-Me_2	B	62	247–248	D, E	$C_9H_{10}N_6O$	37[o]	65	
45	4,6-Me_2	B	40	269–272	D, E	$C_9H_{10}N_6O$		44	
46	5,6-Me_2	B	55	240–242	D, E	$C_9H_{10}N_6O$[m]			42[n]
1 (R = Me; X = NHMe)								89	

[a] See Experimental Section. [b] D = DMF; E = EtOH: H = H_2O; * = washed with the indicated solvent. [c] See corresponding footnote to Table I. [d] $p < 0.05$ using student's *t* test, except as noted. [e] Gradually darken in this range of temperature. [f] Not obtained in an analytically pure state. [g] H: calcd, 2.25; found, 2.70. [h] N: calcd, 31.23; found, 31.80. [i] C: calcd, 37.43; found, 37.88. [j] N: calcd, 31.23; found, 30.51. [k] C: calcd, 61.63; found, 61.09. [l] N: calcd, 39.35; found, 38.02. [m] N: calcd, 38.52; found, 39.06. [n] $p < 0.1$. [o] Not statistically significant.

obtained by SeO_2 oxidation of 2,3- and 2,5-dimethylpyridines, respectively (Scheme I).

The 6-methoxy, 6-butoxy, and 6-phenoxy acids were obtained from 6-bromo-2-pyridinecarboxylic acid[7] by the action of the corresponding alkoxide. The preparation of the 5-methylthio derivative was patterned after the method reported by Finch et al.[8] Other 2-pyridinecarboxylic acids bearing chloro,[9,10] bromo,[11] methoxy,[9,12] and nitro[9] sub-

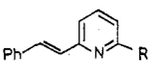
Scheme II[a]



[a] a = NaN_3, NH_4Cl/DMF; b = $(PhO)_2P(=O)N_3$, *t*-BuOH; (c) dilute HCl/EtOH; d = $ClCOCO_2Et$/pyridine.

(7) Gilman, H.; Spatz, S. M. *J. Org. Chem.* **1951**, *16*, 1485.
(8) Finch, N.; Campbell, T. R.; Gemenden, C. W.; Antonaccio, M. J.; Povalski, H. J. *J. Med. Chem.* **1978**, *21*, 1269.
(9) Matsumura, E.; Ariga, M.; Ohfugi, T. *Bull. Chem. Soc. Jpn.* **1970**, *43*, 3210.

Table III. 6-Styrylpyridines Bearing an Acidic Functionality



no.	R	yield,[a] %	mp, °C	formula	PCA test[b] (10 mg/kg, po)
9	CO_2H	100	200–203 dec	$C_{14}H_{11}NO_2 \cdot 0.5H_2O$	IA
12	$NHCOCO_2Et$	86	127–129	$C_{17}H_{16}N_2O_3$	IA
13	$NHCOCO_2H$	48	203–204 dec	$C_{15}H_{12}N_2O_3 \cdot 0.25H_2O$	IA
14	5-tetrazolyl	59	173–177 dec	$C_{14}H_{11}N_5$	IA

[a] Described under Experimental Section. [b] See footnote c in Table I. IA = inactive.

stituents were prepared by known procedures.

The 2-(1*H*-tetrazol-5-yl)pyridine **14** was obtained by reaction of the nitrile **8** with sodium azide and ammonium chloride in DMF. Treatment of the acid **9** with diphenyl phosphorazidate[13] in refluxing *tert*-butyl alcohol afforded **10** with concomitant formation of the amine **11** (Scheme II). The carbamate **10** was hydrolyzed with dilute acid to give **11**. Acylation of **11** with ethyl chloroglyoxalate in pyridine gave **12**, which provided the oxamic acid **13** by the literature method.[4b]

Results and Discussion

The compounds listed in Tables I–IV were tested in the rat PCA assay by the oral route of administration as described previously.[1] Among the three positional isomers (**15–17**) of *N*-(1*H*-tetrazol-5-yl)pyridinecarboxamide, the simplest member of this series, the 2-carbamoyl derivative **15**, exhibited substantial oral efficacy (Table I).

This result is consistent with our earlier finding[1a] in the 6-phenyl-2-pyridinecarboxamides, where the transposition of the tetrazolylcarbamoyl group to the 3-position resulted in a marked fall in activity. Since it appeared that the presence of a phenyl group is not essential for activity, effect of substitution on **15** was examined next (Table II).

Although no SAR is obvious, alkyl substitution tends to enhance activity, regardless of the position on the pyridine ring. On the other hand, the effect of chloro and methoxy groups on activity depends on the position of their substitution (**18**, **21**, and **31**; **19**, **23**, and **33**). The highest activity was observed with **41**, which bears both 4-chloro and 6-methyl substituents, while the other disubstituted derivatives, **42–46**, showed no improvement of the activity of the respective monosubstituted derivatives. As anticipated, compound **39**, a vinylogous analogue of the 6-phenyl derivative, also displayed significant activity.

Table III lists the 6-styrylpyridines bearing various acidic functionalities, which are often included in antiallergic agents, at the 2-position. They were all devoid of activity at a 10-mg/kg oral dose. On the basis of these results, it was concluded that the *N*-tetrazolylcarbamoyl group is required to be at the 2-position of the pyridine ring and that the phenyl group is not necessarily required for the antiallergic activity of this class of compounds.

Table IV gives the PCA results of the most active compounds in this series when administered at their optimal time[14] (5 min) before antigen challenge. Recently, the Wyeth group reported the antiallergic activity of **3**, a reversed amide structure of **2**. Therefore, the activities of the 6-methyl derivatives **36** and **3** (X = N; R = 6-Me) were compared, and it was revealed that **36** is approximately 2.5 times as potent as **3** in our test system. Compound **36** has ED_{50} value of 0.7 mg/kg po (95% confidence limit 0.5–09 mg/kg, N = 18) and low toxicity (LD_{50} = 1000 mg/kg po, rat).[14]

Table IV. PCA Results with a 5-min Pretreatment Time

no.	PCA:[a] % inhibn[b] at 3 mg/kg po
21	71
24	51
25	54 ($p < 0.01$)
36	73 ($p < 0.01$)
39	75
41	85
44	72
45	37 ($p < 0.05$)

[a] See footnote c in Table I, except for pretreatment time. [b] $p < 0.001$, unless otherwise noted (N = 4).

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. While most of the intermediates were not obtained in an analytically pure form, their spectra were consistent with the assigned structures. Where represented by elemental symbols, the analyses of these elements fell within ±0.4% of the theoretical values, unless otherwise indicated.

Method A. *N*-(1*H*-Tetrazol-5-yl)-6-methyl-2-pyridinecarboxamide (36). A mixture of 2.29 g (13.2 mmol) of **6**·HCl (R = 6-Me) and 20 mL of $SOCl_2$ was heated at reflux temperature for 2 h. Evaporation gave an oily residue, which was dissolved in DMF (10 mL) and added to a cooled solution of 1.33 g (15.6 mmol) of 5-aminotetrazole and 2.67 g (26.7 mmol) of triethylamine in DMF (10 mL). After being heated at 80 °C for 2 h, the mixture was diluted with H_2O and brought to pH 3 with 10% HCl. The precipitate was filtered off, washed with H_2O, and dried. The crude product was decolorized with charcoal and recrystallized from DMF–EtOH to give 1.31 g (49%) of **36**.

Method B. *N*-(1*H*-Tetrazol-5-yl)-4-chloro-6-methyl-2-pyridinecarboxamide (41). Carbonyldiimidazole (0.67 g, 4.14 mmol) was added to a solution of 0.68 g (3.96 mmol) of **6** (R = 4-Cl; 6-Me)[9] in DMF (5 mL) and THF (10 mL), and the mixture was stirred at room temperature for 1.5 h. 5-Aminotetrazole (0.37 g, 4.35 mmol) was added, and then the whole mixture was heated at 70 °C for 2 h. Evaporation of the solvent left an oily residue, which was dissolved in H_2O and made acidic with 10% HCl. The precipitate was collected by filtration, and recrystallized from DMF–EtOH to give 0.65 g (69%) of 41.

***N*-(1*H*-Tetrazol-5-yl)-6-(2-phenylethyl)-2-pyridinecarboxamide** (40). A solution of 2.0 g of **39** in 10% NaOH (5 mL), H_2O (30 mL), and EtOH (15 mL) was hydrogenated over 10% Pd/C (0.18 g). After the theoretical amount of H_2 had been absorbed, the catalyst was removed by filtration. Upon acidi-

(10) Takahashi, K.; Kimura, I.; Takei, Y.; Zaima, T.; Mitsuhashi, K. *Nippon Kagaku Kaishi.* **1975**, 1530.
(11) Deaky, L. W.; Shanks, R. A.; Campbell, A. D.; Chooi, S. Y. *Aust. J. Chem.* **1971**, *24*, 385.
(12) Brown, E. V.; Shambhu, M. B. *J. Org. Chem.* **1971**, *36*, 2002.
(13) Ninomiya, K.; Shioiri, T.; Yamada, S. *Tetrahedron* **1974**, *30*, 2151.
(14) The antiallergic activity of **36**, including the effect of the time of administration, will be published in detail later.

fication of the filtrate, a crystalline solid was precipitated. The solid was collected and recrystallized from DMF–EtOH to give 1.34 g (67%) of **40**.

2-Cyano-6-styrylpyridine (8). A mixture of 5.0 g (0.0254 mol) of 2-styrylpyridine *N*-oxide (**4**, R = 2-styryl),[15] 3.2 g (0.0254 mol) of Me_2SO_4, 20 mL of dioxane, and 10 mL of THF was heated at 50 °C for 1 h. The mixture was cooled (−5 °C) and treated with a solution of 1.5 g (0.03 mol) of NaCN in H_2O (13.5 mL). After being allowed to stand at room temperature overnight, the whole mixture was extracted with EtOAc. The extracts were washed with brine, dried (Na_2SO_4), and evaporated to give a crystalline residue. Recrystallization from *i*-PrOH gave 3.12 g (60%) of **8**, mp 90–92 °C. Anal. ($C_{14}H_{10}N_2$) C, H, N.

6-Styryl-2-pyridinecarboxylic Acid (9). A mixture of **8** (17 g) and concentrated HCl (400 mL) was heated under reflux overnight. Evaporation gave a crystalline solid, which was triturated with H_2O, filtered, and dried to afford 19.4 g (100%) of **9**, mp 191–197 °C dec. This compound was used directly for subsequent reaction without further purification. Recrystallization from EtOH gave a sample for analysis and biological testing, mp 200.5–202.5 °C dec.

2-[(*tert*-Butoxycarbonyl)amino]-6-styrylpyridine (10). A mixture of 12.3 g (0.0547 mol) of **9**, 5.59 g (0.0558 mol) of triethylamine, 16.56 g (0.06 mol) of diphenyl phosphorazidate, and *tert*-butyl alcohol (156 mL) was heated under reflux overnight. The solvent was evaporated, and the residue was dissolved in $CHCl_3$ and then washed with 5% aqueous citric acid, brine, and aqueous $NaHCO_3$ successively. The organic layer was dried (Na_2SO_4) and evaporated to give an oily residue, which was subjected to column chromatography on silica gel. The first eluate fraction with EtOAc–hexane (3:7) afforded 6.72 g (42%) of **10**, mp 100–101 °C (hexane). Anal. ($C_{18}H_{20}N_2O_2$) C, H, N.

The second eluate fraction gave 1.77 g (26%) of **11**, mp 106–108 °C (ether).

Acid Hydrolysis of Compound 10. A mixture of **10** (12.41 g), 10% HCl (17 mL), and EtOH (170 mL) was refluxed for 3 h. Evaporation of the solvent gave a solid, which was recrystallized from EtOH to give 8.55 g (88%) of **11**·HCl, mp 248–250 °C dec. Anal. ($C_{13}H_{12}N_2$·HCl) C, H, N, Cl.

Ethyl [[2-(6-styryl)pyridyl]amino]oxoacetate (12). To a cooled solution of 1.0 g (5.1 mmol) of **11** in pyridine (6.5 mL) was added 1.1 g (8.2 mmol) of ethyl chloroglyoxalate. After the mixture was stirred at room temperature overnight, there was added excess H_2O. The precipitate was collected by filtration and recrystallized from EtOH to afford 1.30 g (86%) of **12**.

[[2-(6-Styryl)pyridyl]amino]oxoacetic Acid (13). Compound **12** (0.58 g, 1.95 mmol) was dissolved in CH_2Cl_2 (34 mL); then 1 N NaOH (3.4 mL) and H_2O (14 mL) were added, and the mixture was stirred overnight at room temperature. After the aqueous layer was brought to pH 3 with 10% HCl, the organic phase was separated. The aqueous phase was extracted with CH_2Cl_2. The combined organic layer was dried (Na_2SO_4) and evaporated. The residue was recrystallized from EtOH to give 0.25 g (48%) of **13**.

6-Styryl-2-(1*H*-tetrazol-5-yl)pyridine (14). A mixture of 2.0 g (9.7 mmol) of **8**, 0.69 g (10.6 mmol) of NaN_3, and 0.57 g (10.7 mmol) of NH_4Cl in DMF (30 mL) was heated at 120 °C for 4.5 h. The mixture was cooled, diluted with H_2O, and then made acidic with 10% HCl. The precipitate was collected by filtration, washed with H_2O, and dried. Recrystallization from DMF–EtOH afforded 1.42 g (59%) of **14**.

***N*-(6-Methyl-2-pyridinyl)-1*H*-tetrazole-5-carboxamide (3, R = 6-Me; X = N).** This compound was prepared according to ref 4a, mp 261–262 °C dec (DMF). Anal. ($C_8H_7N_6O$) C, H, N.

Acknowledgment. The authors thank Drs. S. Saito, A. Kiyomoto, H. Nakajima, and S. Takeyama for their encouragement throughout this work. Thanks are also due to T. Murata for his 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 = 6-Me; X = N), 69407-31-4; **4** (R = 2-styryl), 13244-19-4; **6**·HCl (R = 6-Me), 87884-49-9; **6** (R = 4-Cl; 6-Me), 30235-19-9; **8**, 87884-41-1; **9**, 83282-01-3; **10**, 87884-42-2; **11**, 87884-43-3; **11**·HCl, 87884-50-2; **12**, 87884-44-4; **13**, 87884-45-5; **14**, 87884-46-6; **15**, 83281-97-4; **16**, 87884-47-7; **17**, 87884-48-8; **18**, 83282-18-2; **19**, 83282-22-8; **20**, 83282-42-2; **21**, 83282-16-0; **22**, 83282-52-4; **23**, 83282-24-0; **24**, 83281-99-6; **25**, 83282-34-2; **26**, 83282-37-5; **27**, 83282-40-0; **28**, 83282-60-4; **29**, 83282-06-8; **30**, 83282-29-5; **31**, 83282-20-6; **32**, 83282-54-6; **33**, 83282-56-8; **34**, 83282-27-3; **35**, 83282-58-0; **36**, 83282-08-0; **37**, 83282-11-5; **38**, 83282-14-8; **39**, 83282-02-4; **40**, 83282-04-6; **41**, 83282-62-6; **42**, 83282-65-9; **43**, 83282-32-0; **44**, 83282-47-7; **45**, 83282-44-4; **46**, 83282-50-2; 5-aminotetrazole, 4418-61-5; diphenyl phosphorazidate, 26386-88-9; ethyl chloroglyoxalate, 4755-77-5.

(15) Somani, R.; Sway, B. *Indian J. Chem.* **1978**, *15*, 927.