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Synthesis of Novel Pyridotriazepinones as Antisecretory Agents

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In connection with the known antisecretory activity of the benzotriazepinone (**1**) and the pyridylurea (**2**), novel pyridotriazepinones (**3** and **4**) have been synthesized. They were prepared from aminopyridinecarboxylic acids *via* several steps, and their structures were confirmed by X-ray crystallographic analysis. Attempts to synthesize the positional isomer (**24**) resulted in formation of the pyridotriazine (**25** or **26**). Some of these compounds showed moderate antisecretory activity in rats.

Keywords——pyrido[2,3-*f*]-1,2,4-triazepinone; pyrido[2,3-*e*]-1,2,4-triazepinone; X-ray analysis; 1,3,4-oxadiazole; pyridotriazine; antisecretory activity; ring contraction

Some antisecretory compounds have their origins in psychotropic agents.[1] Among such compounds, 1,4-dihydro-4-methyl-5*H*-benzo-1,2,4-triazepin-5-one (**1**) is known to have antisecretory activity with diminished central nervous system (CNS) activity.[2] On the other hand, a number of pyridine derivatives were recently reported to inhibit gastric acid secretion, as exemplified by the pyridylurea derivative (**2**).[3] In the course of our continuing studies on antisecretory agents, we were interested in the activities of 1,4-dihydro-4-methyl-5*H*-pyrido[2,3-*f*]-1,2,4-triazepin-5-one (**3**) and 1,4-dihydro-4-methyl-5*H*-pyrido[2,3-*e*]-1,2,4-triazepin-5-one (**4**), which are pyrido analogues of **1**. No reports have appeared on the synthesis and biological activity of pyridotriazepinones, in contrast with benzotriazepinone derivatives.[4] We describe here the syntheses of the new pyridotriazepinones (**3**, **4**) and the results of several attempts to synthesize the other positional isomer (**24**). Since structural assignment for benzotriazepinones has sometimes been erroneous and has been intensively discussed in recent papers,[5] the structures of the pyrido analogues (**3**, **4**) and related products in this study were confirmed by X-ray crystallographic analysis. The antisecretory activity of the resulting compounds determined in rats is also presented.

The pyrido[2,3-*f*]-1,2,4-triazepinone (**3**) was synthesized through the sequence of reactions outlined in Chart 1. 3-Aminopicolinic acid (**5a**) was converted to the N-carbobenzyloxy (CBZ) derivative (**5b**), which in turn was condensed with dimethyl methylaminomalonate by the use of 1*H*-benzotriazol-1-ol (HOBt) and dicyclohexylcarbodiimide (DCC) to give the amide (**6a**). Reductive removal of the CBZ group afforded the amino-amide (**6b**) as an unstable oil. On diazotization by the method of Bianchi *et al.*,[2] **6b** readily underwent cyclization, giving the 1,2,4-triazepinone (**7**) in 77% yield. Treatment of **7** with 2 molar equivalents of aqueous NaOH in MeOH gave the monocarboxylic acid (**8**) in 52% yield. Decarboxylation of **8** readily occurred in dioxane at 80 °C and gave the desired 1,2,4-triazepinone (**3**) in 94% yield. The structure of **3** was unequivocally confirmed by X-ray crystallographic analysis. A perspective drawing of **3** is shown in Fig. 1.

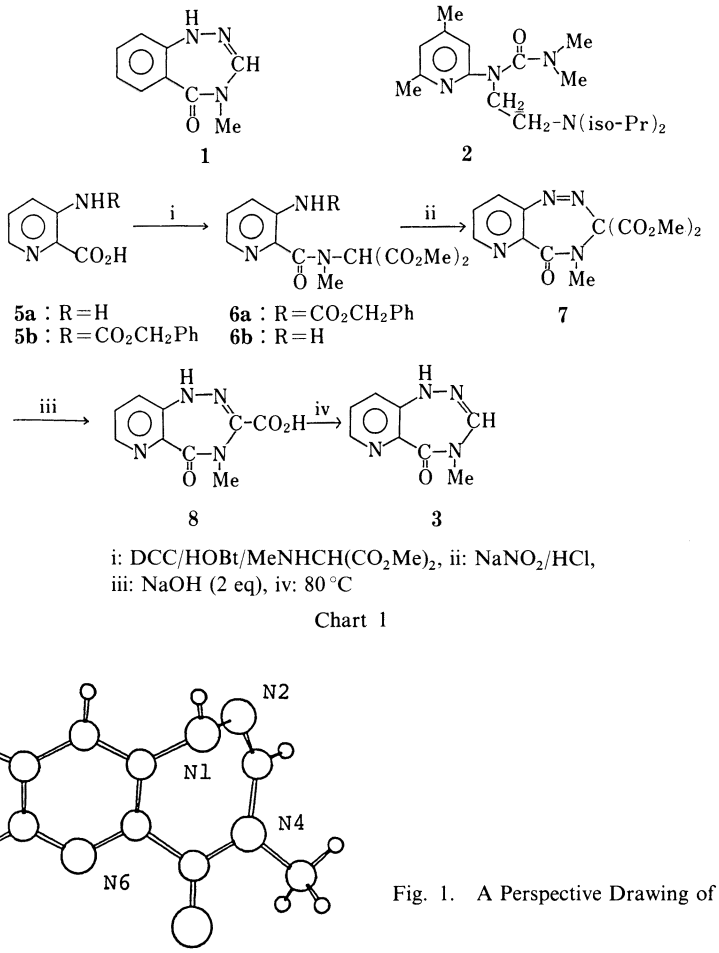
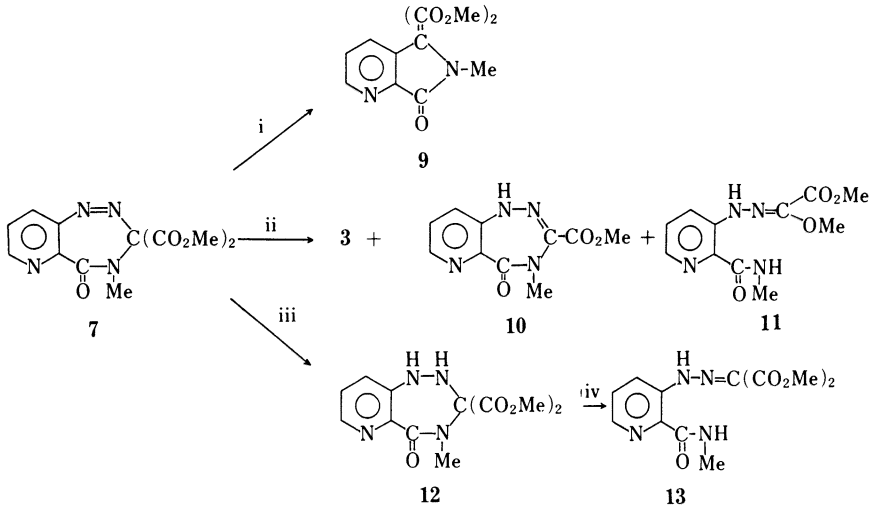


Chart 1

Fig. 1. A Perspective Drawing of **3**

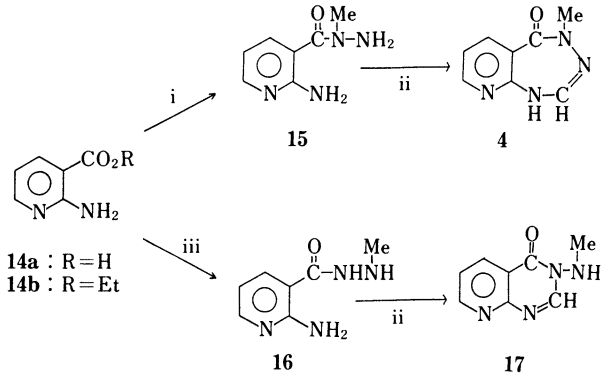
The results of other unsuccessful attempts to obtain **3** from **7** are summarized in Chart 2. On heating at 110 °C in dimethylsulfoxide (DMSO) in the presence of NaCl,[6] **7** gave only the ring-contracted product (**9**) in 26% yield. In the mass spectrum (MS), **9** showed the molecular ion peak at *m/e* 264 indicating loss of a nitrogen molecule from **7**. The proton nuclear magnetic resonance (^{1}H-NMR) spectrum of **9** showed signals due to the geminal methoxycarbonyl groups at δ 3.82 (6H, s) and the N-methyl group at δ 3.29 (3H, s) together with three aromatic protons at δ 7.46—8.82. In the infrared spectrum (IR), a five-membered lactam carbonyl band appeared at 1725 cm^{-1} together with ester carbonyl bands at 1740 cm^{-1}.

On treatment with 1 molar equivalent of NaOH in MeOH, **7** gave a mixture of the monoester (**10**), the ring-fissioned product (**11**), and the triazepinone (**3**) in yields of 6, 4.3, and 13%, respectively. The spectral data and elemental analysis of **10** were compatible with the assigned structure and are given in the experimental section. The ^{1}H-NMR spectrum of **11** showed, in addition to two OMe signals (δ 4.06 and 4.10), the signal due to the NMe group in the secondary amide at δ 2.95 as a doublet, which collapsed to a singlet on addition of D_2O. In its IR spectrum, **11** showed strong carbonyl bands at 1675 and 1720 cm^{-1} assignable to amide and ester groups. Compound **11** was correctly analyzed for $C_{11}H_{14}N_4O_4$ and showed the molecular ion peak at *m/e* 266. On the basis of these data, we tentatively assigned the ring-fissioned structure (**11**) to this compound. Susceptibility to cleavage of the C_3–N_4 bond of



i: 110 °C, NaCl/DMSO, ii: NaOH (1 eq)/MeOH,
iii: H_2 (1 eq)/Pd–C, iv: heat/EtOH

Chart 2



i: DCC/HOBt/$MeNHNH_2$, ii: $HC(OEt)_3$, iii: $MeNHNH_2$/150 °C

Chart 3

1,2,4-triazepinones was also observed for the dihydro derivative (**12**), obtained by catalytic hydrogenation of **7**. When heated in boiling EtOH for 7 h, **12** readily gave the ring-fissioned product (**13**) in 89% yield. Compound **13** showed spectroscopic data similar to those of **11** (see Experimental).

The pyrido[2,3-*e*]-1,2,4-triazepinone (**4**), a positional isomer of **3**, was synthesized from 2-aminonicotinic acid (**14a**) (Chart 3). Treatment of **14a** with methylhydrazine by the use of HOBt and DCC yielded the amide (**15**). Reaction of **15** with triethyl orthoformate ($HC(OEt)_3$) in boiling EtOH gave the desired product (**4**) in 52% yield. Since the pyridopyrimidone (**17**) is also a possible product of this sequence of reactions,[7] **17** was synthesized independently. Heating of ethyl 2-aminonicotinate (**14b**) with methylhydrazine yielded the secondary amide (**16**), which is isomeric with **15**. The ^{1}H-NMR spectrum of **16** showed the NMe signal at δ 2.71 as a doublet, which collapsed to a singlet on addition of D_2O. On the other hand, the NMe signal of **15** appeared at δ 3.25 as a singlet.[8] Cyclization of **16** with

$HC(OEt)_3$ gave **17** in 79% yield. The difference between the ^{1}H-NMR spectra of **4** and **17** is consistent with their assigned structures. While the signal due to the NMe group of **4** appeared at δ 3.17 as a singlet, that of **17** appeared at δ 2.92 as a doublet and collapsed to a singlet on addition of D_2O. The vinyl proton signal of **4** was observed at δ 6.92 as a doublet, which changed to a singlet on addition of D_2O. On the other hand, the vinyl proton of **17** appeared at δ 8.49 as a singlet. Further structural confirmation of **4**, including the position of the double bond, was obtained by X-ray crystallographic analysis (Fig. 2).

We next planned to prepare pyrido-1,2,4-triazepinones (**19a**, **b**) having an amino group at C_2 by the cyclodesulfurization[9] of the thiosemicarbazide (**18a**, **b**). However, treatment of **18a**, **b**[10] with DCC in pyridine only yielded the 1,3,4-oxadiazole (**20a**, **b**) (Chart 4). Similar formation of oxadiazole derivatives was reported for the corresponding benzo analogues by Peet *et al.*[11] The structural assignments of **20a**, **b** were based on the presence of signals due to a primary amino group in the ^{1}H-NMR spectra and the characteristic MS fragmentation pattern. These spectral data are quite similar to those reported for 2-(2-aminophenyl)-1,3,4-oxadiazole derivatives.[11]

Synthesis of the 3-substituted pyrido-1,2,5-triazepinone (**24**) was also attempted (Chart 5). Condensation of 3-nitro-2-pyridylhydrazines (**21a**, **b**)[12] with ethyl pyruvate or ethyl phenylglyoxylate gave the corresponding nitro-hydrazones (**22a**—**d**).[13] Catalytic hydrogenation of the nitro-hydrazones (**22a**, **b**) afforded a mixture of the corresponding amino-

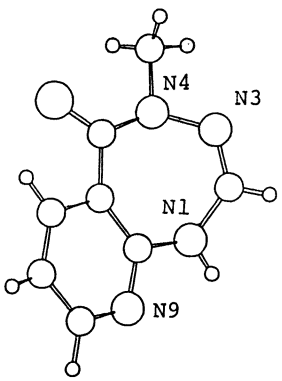


Fig. 2. A Perspective Drawing of **4**

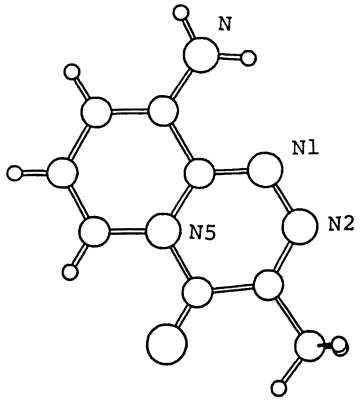
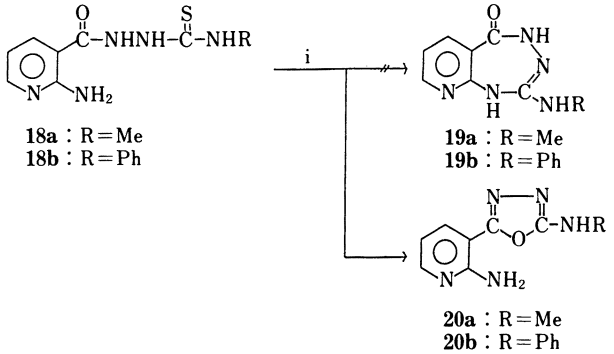


Fig. 3. A Perspective Drawing of **25a**



18a : R=Me
18b : R=Ph

19a : R=Me
19b : R=Ph

20a : R=Me
20b : R=Ph

i: DCC/60—80 °C

Chart 4

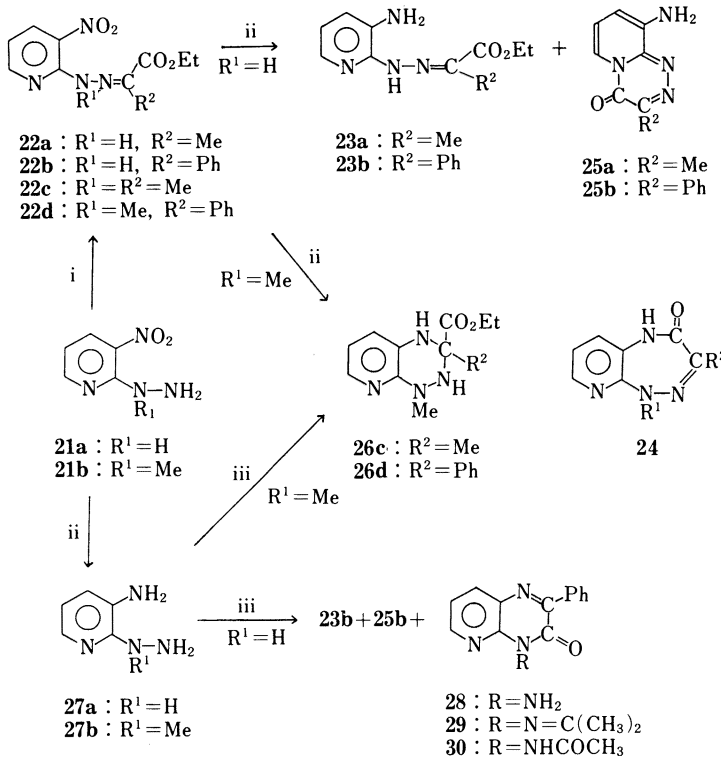


Chart 5

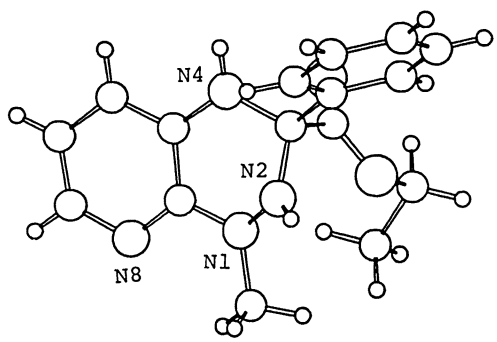


Fig. 4. A Perspective Drawing of **26d**

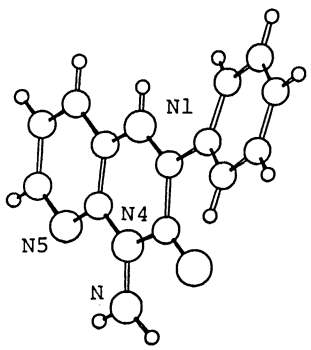


Fig. 5. A Perspective Drawing of **28**

hydrazones (**23a, b**) and pyrido[2,1-*c*]triazines (**25a, b**) instead of the desired triazepinone (**24**). Since the formation of **25a, b** from **23a, b** might be due to a tautomeric contribution of the hydrogen on the hydrazone group, catalytic hydrogenation of the corresponding N-methyl derivative (**22c**) was attempted. In this case, however, the aminal (**26c**) was obtained in 87% yield. Several attempts to convert **26c** to **24** ($R^1=R^2=Me$) under acidic or alkaline conditions were unsuccessful. Similarly, catalytic hydrogenation of **22d** gave **26d** in 59% yield. Alternatively, **26d** could be obtained by the reaction of 1-(3-amino-2-pyridyl)-1-methylhydrazine (**27b**)[12] with ethyl phenylglyoxylate in 68% yield.

TABLE I. The Antisecretory Activity of Pyridotriazepinones

Compound No.	Antisecretory activity % inhibition rat i.p. at 30 mg/kg	at 100 mg/kg
3	31	59
4	51	59
7		15
8		44
10		0
12		−16
1	48	

TABLE II. Crystal Data

	3	**4**	**25a**	**26d**	**28**
Crystal system	Monoclinic	Monoclinic	Orthorhombic	Monoclinic	Orthorhombic
Space group	$P2_1/c$	$P2_1/a$	*Pbca*	*Cc*	$P2_12_12_1$
a (Å)	11.190 (1)	14.183 (3)	14.446 (4)	8.735 (1)	12.810 (2)
b (Å)	7.210 (4)	14.967 (3)	12.881 (3)	22.005 (5)	14.686 (3)
c (Å)	10.677 (7)	3.788 (1)	8.674 (2)	9.136 (1)	5.889 (1)
β (°)	101.128 (4)	99.58 (1)	—	118.99 (1)	—
Volume (Å^3)	845.2 (1)	792.9 (3)	1614.0 (4)	1536.0 (3)	1107.9 (2)
Z	4	4	8	4	4
D_c (g cm^{-3})	1.384	1.476	1.450	1.290	1.428
No. of unique reflections	1448	1351	1071	1109	1119
No. of reliable reflections $\lvert F_o\rvert \geq 3\sigma(\lvert F_o\rvert)$	1187	1047	1068	1086	1099
Final *R*	0.051	0.073	0.063	0.049	0.073

As an alternative route to **24** ($R^1=H$, $R^2=Ph$), condensation of the aminohydrazine (**27a**)[12] with ethyl phenylglyoxylate was also attempted. The major product (51%) in this reaction, however, was the pyrido[2,3-*b*]pyrazine (**28**), compounds **23b** and **25b** being also isolated in low yields. The presence of the primary amino group in **28** was demonstrated by its conversion to the isopropylidene derivative (**29**) and the N-acetate (**30**). The structures of the pyridotriazines (**25a** and **26d**) and the pyridopyrazine (**28**) were unequivocally confirmed by X-ray crystallographic analysis, and perspective drawings are shown in Figs. 3, 4, and 5, respectively.

Pharmacology

The pyridotriazepinone derivatives and related compounds obtained in this study were tested for antisecretory activity in rats after intraperitoneal (i.p.) administration by the method reported previously.[14] The results are summarized in Table I together with comparative data for the benzotriazepinone (**1**). The antisecretory activity of the pyridotriazepinones (**3** and **4**) is of the same order as that of the benzo analogue (**1**).

Experimental

All melting points are uncorrected. IR spectra were recorded in Nujol mulls on a Hitachi IR-215 spectrometer.

^{1}H-NMR spectra were taken in $CDCl_3$ or DMSO-d_6 at 60 MHz on a JEOL PMX-60 spectrometer with tetramethylsilane (TMS) as an internal reference. The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and br = broad. MS were measured with a Hitachi RMU-6M instrument. Ultraviolet (UV) spectra were measured with a Hitachi 323 spectrometer. X-Ray crystallographic analyses were performed on a Rigaku AFC-5 diffractometer.

3-Benzyloxycarbonylaminopicolinic Acid (5b)——A solution of benzyl chloroformate (1.30 g, 7.71 mmol) in tetrahydrofuran (THF, 2 ml) and an aqueous (aq.) solution of LiOH (0.9 N, 9 ml) were added alternately to an ice-cooled mixture of 3-aminopicolinic acid (**5a**, 0.691 g, 5 mmol), aq. LiOH (0.9 N, 6 ml), and THF (8 ml) over a period of 30 min. After being stirred at 0—5 °C for 1 h and then at room temperature for 4 h, the mixture was diluted with H_2O and washed with Et_2O. The aq. solution was then acidified (pH 2—3) with dil. HCl and extracted with $CHCl_3$. The $CHCl_3$ extracts were dried over Na_2SO_4 and concentrated. The residue was recrystallized from benzene to give **5b** (1.137 g, 83%), mp 174—177 °C. IR (Nujol): 1730, 1660 cm^{-1}. MS *m/e*: 272 (M^+), 228, 166. *Anal.* Calcd for $C_{14}H_{12}N_2O_4$: C, 61.76; H, 4.44; N, 10.29. Found: C, 61.66; H, 4.26; N, 10.41.

Dimethyl [3-(Benzyloxycarbonylamino)-*N*-methylpicolinamido]malonate (6a)——DCC (21.95 g, 106.38 mmol) and HOBt (16.3 g, 106.4 mmol) were added to an ice-cold solution of **5b** (28.95 g, 106.3 mmol) in dimethylformamide (DMF, 250 ml), and the mixture was stirred at 0 °C for 30 min. A soltuion of dimethyl methylaminomalonate (20.6 g, 127.8 mmol) in DMF (30 ml) was then added dropwise. After the mixture had been stirred at room temperature for 62 h, insoluble materials were filtered off, and the filtrate was concentrated *in vacuo*. The residue was diluted with H_2O and extracted with EtOAc. The EtOAc extracts were dried over $MgSO_4$, and concentrated. The residue was purified by chromatography (SiO_2, hexane : EtOAc = 1 : 1) and recrystallized from Et_2O to give **6a** (33.9 g, 76.7%), mp 95—96 °C. IR (Nujol): 3300, 1740, 1635 cm^{-1}. MS *m/e*: 415 (M^+), 384, 356, 165. ^{1}H-NMR ($CDCl_3$) δ: 3.17 (3H, s, N-Me), 3.81 (6H, s, OMe). *Anal.* Calcd for $C_{20}H_{21}N_3O_7$: C, 57.83; H, 5.10; N, 10.12. Found: C, 57.81; H, 5.05; N, 9.91.

Dimethyl (3-Amino-*N*-methylpicolinamido)malonate (6b)——A mixture of **6a** (0.89 g, 2.14 mmol), 10% Pd–C (0.1 g), and MeOH (20 ml) was stirred for 2 h at room temperature under a stream of hydrogen. After removal of Pd–C, the mixture was evaporated *in vacuo* below 40 °C to give **6b** (0.69 g) as an oil. IR (liq.): 3460—3230, 1740, 1635 cm^{-1}. MS *m/e*: 281 (M^+).

Dimethyl 4,5-Dihydro-4-methyl-5-oxo-3*H*-pyrido[2,3-*f*]-1,2,4-triazepine-3,3-dicarboxylate (7)——A solution of $NaNO_2$ (0.15 g, 2.17 mmol) in H_2O (2 ml) was added dropwise to a mixture of conc. HCl (4.2 ml) and ice-sticks (17 g). Next, a solution of **6b** (0.6 g, 2.12 mmol) in MeOH (6 ml) was added dropwise at −10 °C. After being stirred at 0 °C for 2 h and then at room temperature for 2 h, the mixture was made alkaline (pH 9) with conc. NH_4OH and extracted with $CHCl_3$. The $CHCl_3$ extracts were dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by chromatography (SiO_2, $CHCl_3$) and recrystallized from hexane–benzene to give **7** (0.48 g, 77%), mp 138—140 °C (dec.). IR (Nujol): 1750, 1680 cm^{-1}. MS *m/e*: 294 ($M^+ + 2$), 264. *Anal.* Calcd for $C_{12}H_{12}N_4O_5$: C, 49.31; H, 4.14; N, 19.17. Found: C, 49.61; H, 4.05; N, 18.95.

4,5-Dihydro-4-methyl-5-oxo-1*H*-pyrido[2,3-*f*]-1,2,4-triazepine-3-carboxylic Acid (8)——Aqueous NaOH solution (10%, 1.7 ml, 4.25 mmol) was added to a solution of **7** (0.64 g, 2.19 mmol) in MeOH (7 ml) under ice-cooling (below 8 °C). The solvent was removed (below 18 °C), then the residue was diluted with H_2O and acidified with cold aq. 10% HCl (pH 2). The yellow crystalline precipitate was collected by filtration, washed with H_2O, and dried to give **8** (0.3 g, 52%), mp 100—102 °C (dec.). IR (Nujol): 3500—3280, 1710, 1665 cm^{-1}. MS *m/e*: 176 ($M^+ - CO_2$), 135, 107. ^{1}H-NMR ($CDCl_3$) δ: 3.08 (3H, s), 9.16 (1H, s, NH). *Anal.* Calcd for $C_9H_8N_4O_3 \cdot 2H_2O$: C, 42.19; H, 4.72; N, 21.87. Found: C, 42.28; H, 4.49; N, 21.56.

1,4-Dihydro-4-methyl-5*H*-pyrido[2,3-*f*]-1,2,4-triazepin-5-one (3)——Compound **8** (0.2 g, 0.91 mmol) was suspended in dioxane (10 ml), and the mixture was heated at 80 °C for 20 min. The solvent was removed and the residue was recrystallized from EtOAc to give **3** (0.15 g, 94%) as yellow needles, mp 179 °C (dec.). IR (Nujol): 3275, 1650 cm^{-1}. MS *m/e*: 176 (M^+), 135, 107. ^{1}H-NMR ($CDCl_3$ + DMSO-d_6) δ: 3.25 (3H, s), 6.71 (1H, s), 7.48 (1H, br s). UV λ_{max}^{EtOH} nm (ε): 247 (6300), 288 (4100). *Anal.* Calcd for $C_8H_8N_4O$: C, 54.54; H, 4.58; N, 31.80. Found: C, 54.42; H, 4.47; N, 31.79.

Dimethyl 6,7-Dihydro-6-methyl-7-oxo-5*H*-pyrrolo[3,4-*b*]pyridine-5,5-dicarboxylate (9)——A mixture of **7** (0.292 g, 1 mmol), NaCl (0.117 g, 2 mmol), and DMSO (3 ml) was heated at 110 °C for 10 min. After cooling, the mixture was diluted with H_2O (10 ml) and extracted with EtOAc. The EtOAc extracts were dried over $MgSO_4$ and evaporated. The residue was purified by chromatography (SiO_2, hexane : EtOAc = 1 : 1) and digested with hexane–Et_2O to give **9** (0.07 g, 26%), mp 105 °C (dec.). IR (Nujol): 1740, 1725 cm^{-1}. MS *m/e*: 264 (M^+), 220, 205, 177. ^{1}H-NMR ($CDCl_3$) δ: 3.29 (3H, s), 3.82 (6H, s), 7.46 (1H, dd, J_1 = 4.6 Hz, J_2 = 7.6 Hz), 8.05 (1H, dd, J_1 = 1.5 Hz, J_2 = 7.6 Hz), 8.82 (1H, dd, J_1 = 1.5 Hz, J_2 = 4.6 Hz). *Anal.* Calcd for $C_{12}H_{12}N_2O_5$: C, 54.54; H, 4.58; N, 10.60. Found: C, 54.21; H, 4.47; N, 11.04.

Treatment of 7 with NaOH (1 eq)——Aqueous NaOH (10%, 1.95 ml, 4.87 mmol) was added dropwise to a solution of **7** (1.47 g, 5.03 mmol) in MeOH (20 ml) under ice-cooling (below 8 °C). The solvent was removed, and the residue was acidified with 10% aq. HCl and then made alkaline with conc. NH_4OH. The aqueous layer was extracted with $CHCl_3$, and the $CHCl_3$ extracts were dried over $MgSO_4$ and concentrated. The residue was purified by chromatography (SiO_2, $CHCl_3$: MeOH = 50 : 1) to yield methyl 4,5-dihydro-4-methyl-5-oxo-1*H*-pyrido[2,3-*f*]-1,2,4-

triazepine-3-carboxylate (**10**, 0.071 g, 6%) and methyl 2-methoxy-2-(2-methylcarbamoyl-3-pyridylhydrazono)acetate (**11**, 0.058 g, 4.3%).

Physical data for **10**, mp 168 °C (dec.) (from MeOH–Et_2O–hexane): IR (Nujol): 3200, 1730, 1670, 1650 cm^{-1}. MS *m/e*: 234 (M^+), 219, 206, 203, 175. ^{1}H-NMR (DMSO-d_6) δ: 3.07 (3H, s), 3.82 (3H, s), 9.32 (1H, s, NH). *Anal.* Calcd for $C_{10}H_{10}N_4O_3$: C, 51.28; H, 4.30; N, 23.92. Found: C, 53.20; H, 5.23; N, 21.73.

Physical data for **11**, mp 147—148 °C (from benzene–hexane): IR (Nujol): 3450, 3300, 1720, 1675 cm^{-1}. MS *m/e*: 266 (M^+), 234, 207, 193, 175, 152, 148. ^{1}H-NMR ($CDCl_3$) δ: 2.95 (3H, d, J=5 Hz; s, in D_2O, NH–Me), 4.06 (3H, s), 4.10 (3H, s), 4.79 (1H, br s, NH). UV λ_{max}^{EtOH} nm (ε): 262 (6400), 367 (15400). *Anal.* Calcd for $C_{11}H_{14}N_4O_4$: C, 49.62; H, 5.30; N, 21.04. Found: C, 49.26; H, 5.14; N, 20.81.

The aqueous layer described above was evaporated to dryness and extracted with a mixture of boilding EtOH–Me_2CO. The EtOH–Me_2CO extracts were concentrated, and the residue was purified by chromatography (SiO_2, $CHCl_3$) to give **3** (0.117 g, 13%).

Dimethyl 1,2,4,5-Tetrahydro-4-methyl-5-oxo-3*H*-pyrido[2,3-*f*]-1,2,4-triazepine-3,3-dicarboxylate (12)——Compound **7** (2.92 g, 10 mmol) was hydrogenated in MeOH (160 ml) in the presence of 10% Pd–C (0.2 g) under ordinary pressure and temperature. After 1 molar equivalent of hydrogen had been absorbed, Pd–C and the solvent were removed. The residue was recrystallized from Et_2O–MeOH to give **12** (2.5 g, 85%), mp 176 °C (dec.). IR (Nujol): 3260, 1750, 1610 cm^{-1}. MS *m/e*: 294 (M^+), 263, 235, 204. ^{1}H-NMR ($CDCl_3$ + DMSO-d_6) δ: 3.10 (3H, s), 3.85 (6H, s), 5.02 (1H, s, NH), 7.19 (1H, s, NH). *Anal.* Calcd for $C_{12}H_{14}N_4O_5$: C, 48.98; H, 4.80; N, 19.04. Found: C, 49.08; H, 4.82; N, 19.08.

Dimethyl 2-[2-(Methylcarbamoyl)-3-pyridylhydrazono]malonate (13)——A solution of **12** (0.81 g, 2.75 mmol) in EtOH (20 ml) was heated under reflux for 7 h. The solvent was removed, and the residue was purified by chromatography (SiO_2, $CHCl_3$) and recrystallized from $CHCl_3$–MeOH to yield **13** (0.723 g, 89%) as needles, mp 200—203 °C. IR (Nujol): 3350, 3120, 1740, 1650 cm^{-1}. MS *m/e*: 294, 263, 234, 204, 175, 150, 149, 136, 121. ^{1}H-NMR ($CDCl_3$) δ: 3.0 (3H, d, J=5.1 Hz; s in D_2O), 3.87, 3.96 (each 3H, s). UV λ_{max}^{EtOH} nm (ε): 342 (26000). *Anal.* Calcd for $C_{12}H_{14}N_4O_5$: C, 48.98; H, 4.80; N, 19.04. Found: C, 49.03; H, 4.81; N, 19.07.

2-Aminonicotino-*N*-methylhydrazide (15)——2-Aminonicotinic acid (**14a**, 2.76 g, 20 mmol) was condensed with methylhydrazine (1.11 g, 24 mmol) using HOBt (3.37 g, 22 mmol), DCC (4.54 g, 22 mmol), Et_3N (4.05 g, 40 mmol), and DMF (30 ml) in the same manner as described for **6a** to yield **15** (0.72 g, 22%) as an oil. IR (liq.): 3450—3200, 1610, 1570 cm^{-1}. MS *m/e*: 166 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 3.25 (3H, s).

1,4-Dihydro-4-methyl-5*H*-pyrido[2,3-*e*]-1,2,4-triazepin-5-one (4)——A solution of **15** (0.64 g, 3.85 mmol), and $HC(OEt)_3$ (1.72 g, 11.61 mmol) in EtOH (30 ml) was refluxed for 2 h. After cooling, separated crystals were collected by filtration to give **4** (0.351 g, 52%) as yellow needles, mp 229—231 °C (from EtOH). IR (Nujol): 3220—3075, 1675 (w), 1630, 1610 cm^{-1}. MS *m/e*: 176 (M^+), 148, 133. ^{1}H-NMR (DMSO-d_6) δ: 3.17 (3H, s), 6.92 (1H, d, J=4.8 Hz; s in D_2O), 6.99 (1H, dd, J_1=4.8 Hz, J_2=7.6 Hz), 8.08 (1H, dd, J_1=1.9 Hz, J_2=7.8 Hz), 8.23 (1H, dd, J_1=1.9 Hz, J_2=4.8 Hz), 9.21 (1H, br s, NH). UV λ_{max}^{EtOH} nm (ε): 251 (6700), 285 (3700). *Anal.* Calcd for $C_8H_8N_4O$: C, 54.54; H, 4.58; N, 31.80. Found: C, 54.05; H, 4.50; N, 31.67.

2-Aminonicotino-*N'*-methylhydrazide (16)——A mixture of ethyl 2-aminonicotinate (2.36 g, 14.2 mmol) and methylhydrazine (1.3 g, 28 mmol) was heated at 150 °C for 4 h and then at 120 °C for 16 h. Volatile materials were removed by evaporation, and the residue was purified by chromatography (SiO_2, $CHCl_3$: MeOH = 20 : 1) and recrystallized from hexane–EtOAc to give **16** (0.753 g, 32%), mp 122—124 °C. IR (Nujol): 3280, 1630, 1575 cm^{-1}. MS *m/e*: 166 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 2.71 (3H, d; s in D_2O). *Anal.* Calcd for $C_7H_{10}N_4O$: C, 50.59; H, 6.07; N, 33.72. Found: 50.62; H, 6.02; N, 33.73.

3-Methylamino-pyrido[2,3-*d*]pyrimidin-4(3*H*)-one (17)——A solution of **16** (0.68 g, 4.09 mmol) and $HC(OEt)_3$ (1.82 g, 12.28 mmol) in EtOH (15 ml) was refluxed for 19 h. After cooling, the solution was treated with charcoal and concentrated to yield **17** (0.57 g, 79%), mp 187 °C (from EtOH). IR (Nujol): 3250, 1680, 1590 cm^{-1}. MS *m/e*: 176 (M^+), 147, 133. ^{1}H-NMR ($CDCl_3$) δ: 2.92 (3H, d, J=5.3 Hz; s in D_2O), 5.73 (1H, d, J=5.3 Hz, NH), 8.49 (1H, s). *Anal.* Calcd for $C_8H_8N_4O$: C, 54.54; H, 4.58; N, 31.80. Found: C, 54.29; H, 4.51; N, 31.66.

3-(5-Methylamino-1,3,4-oxadiazol-2-yl)-2-pyridinamine (20a)——A mixture of **18a** (2.65 g, 11.76 mmol), DCC (3.64 g, 17.64 mmol), and pyridine (200 ml) was heated at 80 °C for 29 h. After cooling, the separated solid was collected by filtration and extracted with MeOH. The MeOH was removed by evaporation, and the residue was crystallized from benzene to yield **20a** (0.757 g, 33%), mp 197—199 °C. IR (Nujol): 3420, 3220, 1680, 1640 cm^{-1}. MS *m/e*: 191 (M^+), 175, 134, 121, 119, 105. ^{1}H-NMR (DMSO-d_6) δ: 2.88 (3H, d, J=4.6 Hz; s in D_2O), 7.05 (2H, br s, NH_2). *Anal.* Calcd for $C_8H_9N_5O$: C, 50.25; H, 4.74; N, 36.63. Found: C, 50.27; H, 4.75; N, 36.64.

3-(5-Phenylamino-1,3,4-oxadiazol-2-yl)-2-pyridinamine (20b)——A mixture of **18b** (2.94 g, 10.23 mmol), DCC (3.17 g, 15.36 mmol), and pyridine (50 ml) was heated at 60 °C for 1 h. The pyridine was evaporated off, and the residue was recrystallized from benzene, and then from MeOH to give **20b** (2.15 g, 83%), mp 237—239 °C (dec.). IR (Nujol): 3460, 3360, 1670, 1630 cm^{-1}. MS *m/e*: 253 (M^+), 237, 211, 196, 169, 161, 134, 121, 119. ^{1}H-NMR (DMSO-d_6) δ: 7.20 (2H, br s, NH_2), 10.70 (1H, s, NH). *Anal.* Calcd for $C_{13}H_{11}N_5O$: C, 61.65; H, 4.38; N, 27.66. Found: C, 61.48; H, 4.25; N, 27.60.

Ethyl 2-(3-Nitro-2-pyridylhydrazono)propionate (22a)——A solution of 3-nitro-2-pyridylhydrazine[12] (**21a**, 6.17 g,

40 mmol), ethyl pyruvate (4.75 g, 40 mmol), H_3PO_4 (85%, 4 ml), and EtOH (60 ml) was heated for 2 h under reflux. After cooling, the separated crystalline solid was collected by filtration and recrystallized from EtOH to yield **22a** (7.56 g, 75%), mp 121—127 °C. IR (Nujol): 3225, 3080, 1690, 1600 cm^{-1}. MS *m/e*: 253 ($M^+ + 1$), 207. *Anal.* Calcd for $C_{10}H_{12}N_4O_4$: C, 47.62; H, 4.80; N, 22.22. Found: C, 47.41; H, 4.76; N, 22.21.

Ethyl 2-(3-Nitro-2-pyridylhydrazono)phenylacetate (22b)——This compound was prepared by the reaction of **21a** and ethyl phenylglyoxylate in the same manner as described above to give **22b** (68%), mp 135—137 °C (from EtOH). IR (Nujol): 3220, 1725, 1705, 1680, 1590 cm^{-1}. MS *m/e*: 315 ($M^+ + 1$), 269, 241. *Anal.* Calcd for $C_{15}H_{14}N_4O_4$: C, 57.32; H, 4.49; N, 17.83. Found: C, 57.03; H, 4.42; N, 17.80.

Ethyl 2-[Methyl(3-nitro-2-pyridyl)hydrazono]propionate (22c)——A mixture of **21b**[12] (3.37 g, 20 mmol), ethyl pyruvate (2.37 g, 20 mmol), H_3PO_4 (85%, 2 ml), and EtOH (30 ml) was stirred at room temperature for 15 h and then poured onto ice-sticks. The mixture was extracted with $CHCl_3$. The $CHCl_3$ extracts were washed with aq. NaCl and dried over Na_2SO_4. The solvent was evaporated, and the residue was recrystallized from aq. EtOH to give **22c** (4.14 g, 78%), mp 76—82 °C. IR (Nujol): 1700, 1580, 1560 cm^{-1}. MS *m/e*: 267 ($M^+ + 1$), 251, 236. ^{1}H-NMR ($CDCl_3$) δ: 2.31 (3H, s), 3.58 (3H, s). *Anal.* Calcd for $C_{11}H_{14}N_4O_4$: C, 49.62; H, 5.30; N, 21.04. Found: C, 49.66; H, 5.34; N, 21.27.

Ethyl 2-[Methyl(3-nitro-2-pyridyl)hydrazono]phenylacetate (22d)[13]——Compound **21b** (2,53 g, 15 mmol) and H_3PO_4 (85%, 1.5 ml) were added to a solution of ethyl phenylglyoxylate (2.68 g, 15 mmol) in EtOH (25 ml). After being stirred for 3.5 h at room temperature and then heated for 50 min under reflux, the mixture was poured onto H_2O and extracted with $CHCl_3$. The $CHCl_3$ extracts were washed with aq. NaCl and dried over Na_2SO_4. The solvent was evaporated off, and the residue was chromatographed (SiO_2, benzene : $CHCl_3$ = 1 : 1) repeatedly to yield **22d** (α isomer, 1.76 g, 36%) and **22d** (β isomer, 1.45 g, 29%). Physical data for **22d**-α, mp 75—78 °C (recrystallized from hexane–iso-Pr_2O): IR (Nujol): 1720, 1595, 1560 cm^{-1}. MS *m/e*: 329 ($M^+ + 1$), 298, 283, 255. ^{1}H-NMR ($CDCl_3$) δ: 1.45 (3H, t, J = 7.1 Hz), 3.75 (3H, s), 4.50 (2H, q, J = 7.1 Hz), 7.30—7.47 (5H, m), 6.99 (1H, dd, J_1 = 4.8 Hz, J_2 = 8.1 Hz), 7.85 (1H, dd, J_1 = 1.7 Hz, J_2 = 8.1 Hz), 8.40 (1H, dd, J_1 = 1.7 Hz, J_2 = 4.8 Hz). *Anal.* Calcd for $C_{16}H_{16}N_4O_4$: C, 58.53; H, 4.91; N, 17.07. Found: C, 58.49; H, 4.93; N, 17.00.

Physical data for **22d**-β, mp 134—135 °C (recrystallized from aq. EtOH): IR (Nujol): 1700, 1590, 1560 cm^{-1}. MS *m/e*: 329 ($M^+ + 1$), 298, 283, 255. ^{1}H-NMR ($CDCl_3$) δ: 1.36 (3H, t, J = 7.2 Hz), 3.16 (3H, s), 4.29 (2H, q, J = 7.2 Hz), 7.45 (5H, s-like), 7.02 (1H, dd, J_1 = 4.8 Hz, J_2 = 7.8 Hz), 8.0 (1H, dd, J_1 = 1.8 Hz, J_2 = 8.0 Hz), 8.38 (1H, dd, J_1 = 1.8 Hz, J_2 = 4.8 Hz).

Ethyl 2-(3-Amino-2-pyridylhydrazono)propionate (23a) and 9-Amino-3-methyl-4*H*-pyrido[2,1-*c*]-1,2,4-triazin-4-one (25a)——Compound **22a** (1.88 g, 7.45 mmol) was hydrogenated in EtOH (50 ml) in the presence of 10% Pd–C (0.15 g) under 2.5 atm pressure. After 50 min, Pd–C and the solvent were removed. The residue was purified by chromatography (SiO_2, $CHCl_3$: MeOH = 100 : 1) to yield **23a** (0.312 g, 19%) and **25a** (0.304 g, 23%).

Physical data for **23a**, mp 93 °C (from benzene–hexane): IR (Nujol): 3460—3255, 1700 cm^{-1}. MS *m/e*: 222 (M^+), 207, 177, 176. NMR ($CDCl_3$) δ: 2.13 (3H, s). *Anal.* Calcd for $C_{10}H_{14}N_4O_2$: C, 54.04; H, 6.35; N, 25.21. Found: C, 53.95; H, 6.34; N, 25.18.

Physical data for **25a**, mp 193—195 °C (from benzene): IR (Nujol): 3480, 3340, 1670, 1620, 1600 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.67 (3H, s), 5.78 (2H, br s, NH_2), 6.82—7.19 (2H, m), 8.20 (1H, dd, J_1 = 1.6 Hz, J_2 = 6.4 Hz). UV λ_{max}^{EtOH} nm (ε): 286 (3300), 342 (8900), 400 (10000). *Anal.* Calcd for $C_8H_8N_4O$: C, 54.54; H, 4.58; N, 31.80. Found: C, 54.37; H, 4.50; N, 31.59.

Ethyl 2-(3-Amino-2-pyridylhydrazono)phenylacetate (23b) and 9-Amino-3-phenyl-4*H*-pyrido[2,1-*c*]-1,2,4-triazin-4-one (25b)——These compounds were prepared from **22b** (0.3 g, 0.96 mmol) in the same manner as described above to give **23b** (0.08 g, 30%) and **25b** (0.08 g, 30%).

Physical data for **23b**, mp 151—153 °C (from benzene–hexane): IR (Nujol): 3400—3150, 1700 cm^{-1}. MS *m/e*: 284 (M^+), 238, 212, 211. *Anal.* Calcd for $C_{15}H_{16}N_4O_2$: C, 63.36; H, 5.67; N, 19.71. Found: C, 63.56; H, 5.58; N, 19.65.

Physical data for **25b**, mp 181—182 °C (from benzene): IR (Nujol): 3430—3200, 1670, 1630 cm^{-1}. MS *m/e*: 238 (M^+), 210, 181. ^{1}H-NMR ($CDCl_3$ + DMSO-d_6) δ: 5.77 (2H, br s, NH_2), 6.8—7.7 (5H, aromatic H), 8.20—8.46 (3H). UV λ_{max}^{EtOH} nm (ε): 222 sh. (13100), 250 (8500), 309 (6800), 352 (9600), 427 (17200). *Anal.* Calcd for $C_{13}H_{10}N_4O$: C, 65.53; H, 4.23; N, 23.52. Found: C, 65.31; H, 4.02; N, 23.54.

Ethyl 1,2,3,4-Tetrahydro-1,3-dimethylpyrido[3,2-*e*]-1,2,4-triazine-3-carboxylate (26c)——This compound was prepared by hydrogenation of **22c** (3.52 g, 13.32 mmol) in the same manner as described for **25a** to give **26c** (2.7 g, 87%), mp 115—117 °C (from benzene–hexane). IR (Nujol): 3370, 3160, 1720 cm^{-1}. MS *m/e*: 236 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 1.28 (3H, t, J = 7.1 Hz), 1.52 (3H, s), 3.22 (3H, s), 4.24 (2H, q, J = 7.1 Hz). UV λ_{max}^{EtOH} nm (ε): 266 (6500), 326 (9700). *Anal.* Calcd for $C_{11}H_{16}N_4O_2$: C, 55.91; H, 6.83; N, 23.72. Found: C, 56.03; H, 6.88; N, 23.74.

Ethyl 1,2,3,4-Tetrahydro-1-methyl-3-phenylpyrido[3,2-*e*]-1,2,4-triazine-3-carboxylate (26d)——This compound was prepared by hydrogenation of **22d**-α (3.28 g, 10 mmol) in the same manner as described for **25a** to give **26d** (1.76 g, 59%), mp 113—116 °C (from iso-Pr_2O). IR (Nujol): 3380, 3140, 1720 cm^{-1}. MS *m/e*: 298 (M^+), 225, 122. ^{1}H-NMR ($CDCl_3$) δ: 1.22 (3H, t, J = 7 Hz), 3.21 (3H, s), 4.20 (2H, dd, J = 7 Hz), 4.20, 5.10 (each 1H, br s, NH_2), 6.56 (1H, dd, J_1 = 5 Hz, J_2 = 8 Hz), 6.87 (1H, dd, J_1 = 2 Hz, J_2 = 8 Hz), 7.28—7.75 (6H, m). UV λ_{max}^{EtOH} nm (ε): 262 (5400), 328 (8000). *Anal.* Calcd for $C_{16}H_{18}N_4O_2$: C, 64.41; H, 6.08; N, 18.78. Found: C, 64.26; H, 6.03; N, 18.78.

Hydrogenation of **22d**-α also gave **26d** in comparable yield.

Compound **26d** was also prepared as follows. Ethyl phenylglyoxylate (1.53 g, 8.59 mmol) and AcOH (0.3 ml) were added to a cold solution of 1-(3-amino-2-pyridyl)-1-methylhydrazine (**27b**, 1.18 g, 8.54 mmol) in EtOH (15 ml). The mixture was stirred at room temperature for 4 d under an argon atmosphere, then the solvent was removed. The residue was dissolved in iso-Pr_2O, treated with charcoal, and concentrated to give **26d** (1.73 g, 68%), which has physical data identical with those described above.

4-Amino-2-phenylpyrido[2,3-*b*]pyrazin-3(4*H*)-one (28)——3-Amino-2-pyridylhydrazine[12] (**27a**, 3.73 g, 30 mmol) and AcOH (0.5 ml) were added to a solution of ethyl phenylglyoxylate (5.35 g, 30 mmol) in EtOH (5 ml). After being heated at 50 °C for 3 min, the mixture was concentrated. The residue was diluted with H_2O and extracted with $CHCl_3$. The $CHCl_3$ extracts were washed with aq. $NaHCO_3$ and aq. NaCl successively and dried over Na_2SO_4. Evaporation of the solvent and purification of the residue by chromatography (SiO_2, $CHCl_3$: MeOH = 100 : 1) gave **23b** (0.716 g, 8.4%), **25b** (0.86 g, 12%), and **28** (3.65 g, 51%), mp 155—156 °C (from benzene). IR (Nujol): 3300, 3230, 1640 cm^{-1}. MS *m/e*: 238 (M^+). UV λ_{max}^{EtOH} nm (ε): 230 (12200), 265 sh, (4300), 303 (4200), 372 (7800). *Anal.* Calcd for $C_{13}H_{10}N_4O$: C, 65.53; H, 4.23; N, 23.52. Found: C, 65.42; H, 4.15; N, 23.71.

4-Isopropylidenamino-2-phenylpyrido[2,3-*b*]pyrazin-3(4*H*)-one (29)——A mixture of **28** (0.1 g, 0.42 mmol), Me_2CO (5 ml), and AcOH (0.5 ml) was heated for 2 h under reflux. After cooling, the mixture was concentrated, and the residue was recrystallized from Me_2CO–hexane to give **29** (0.07 g, 60%) as pale yellow needles, mp 151—152 °C. IR (Nujol): 1650, 1580 cm^{-1}. MS *m/e*: 278 (M^+), 235. *Anal.* Calcd for $C_{16}H_{14}N_4O$: C, 69.05; H, 5.07; N, 20.13. Found: C, 68.70; H, 4.98; N, 20.22.

4-Acetamido-2-phenylpyrido[2,3-*b*]pyrazin-3(4*H*)-one (30)——Compound **28** (0.784 g, 3.29 mmol) was dissolved in Ac_2O (30 ml), and the mixture was stirred at room temperature overnight. Ac_2O was evaporated, and the residue was recrystallized from a mixture of AcOEt and hexane to yield **30** (0.732 g, 79%), mp 176—178 °C. IR (Nujol): 3250, 1690, 1645 cm^{-1}. MS *m/e*: 280 (M^+), 238. *Anal.* Calcd for $C_{15}H_{12}N_4O_2$: C, 64.27; H, 4.32; N, 19.99. Found: C, 64.20; H, 4.31; N, 19.77.

X-Ray Crystallographic Analysis——The structures of compounds **3**, **4**, **25a**, **26d** and **28** were solved by the direct method using MULTAN and refined by the block-diagonal least-squares method. The crystal data are summarized in Table II.

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