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Medicinal Chemical Studies on Antiplasmin Drugs. VI.[1] Aza Analogs of 4-Aminomethylbenzoic Acid

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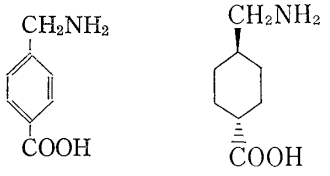
Four aza analogs of 4-aminomethylbenzoic acid (**1**) were prepared as part of a search for new antiplasmin drugs. 5-Aminomethylpyridine-2-carboxylic acid (**5**) was prepared by the hydrogenation of methyl 5-cyanopyridine-2-carboxylate (**4**), followed by alkaline hydrolysis. Similarly, 6-aminomethylpyridine-3-carboxylic acid (**7**) was prepared from ethyl 6-cyanopyridine-3-carboxylate (**6**). 5-Aminomethylpyrimidine-2-carboxylic acid (**12**) was obtained from methyl 5-methylpyrimidine-2-carboxylate (**8**) *via* the phthalimido derivative (**10**). 2-Aminomethylpyrimidine-5-carboxylic acid (**25**) was obtained by the reaction of benzyloxycarbonylaminoacetamidine (**22**) with ethoxycarbonylmalonaldehyde (**18**) in acetic acid, followed by deblocking of the protected groups. Treatment of benzoylaminoacetamidine (**14**) with acetylacetone (**15**) in acetic acid provided 2-benzoylaminomethyl-4,6-dimethylpyrimidine (**16**), whereas in the presence of K_2CO_3, 2-amino-3-benzoylamino-4,6-dimethylpyridine (**17**) was obtained together with a trace of **16**. No compound showed more potent antiplasmin activity than tranexamic acid (**2**), but **5** was more active than **1**.

Keywords——antiplasmin drug; 4-aminomethylbenzoic acid; tranexamic acid; bioisostere; aminomethylpyridinecarboxylic acid; aminomethylpyrimidinecarboxylic acid; pyridine ring closure; pyrimidine ring closure; benzoylaminoacetamidine; benzyloxycarbonylaminoacetamidine

4-Aminomethylbenzoic acid (PAMBA, **1**) is a potent synthetic inhibitor of plasmin, though it is less active than 4-aminomethylcyclohexanecarboxylic acid (AMCHA)[3]: the *trans* isomer (tranexamic acid, **2**) is more potent than the *cis* isomer.



1 **2**

Chart 1

From the viewpoint of the structure-activity relationship, it was of interest to replace the phenyl ring of **1** by a pyridine or a pyrimidine ring, which is often assumed to be a bioisostere. This paper describes the syntheses and antiplasmin activities of aza analogs of **1**.

Aminomethylpyridinecarboxylic Acid

As starting materials for synthesizing aminomethylpyridinecarboxylic acids, methyl 5-cyanopyridine-2-carboxylate (**4**) was prepared by dehydration of the 5-carbamoyl derivative (**3**)[4] with phosphorus oxychloride-pyridine, and ethyl 6-cyanopyridine-3-carboxylate (**6**) was prepared according to the procedure of Tani.[5] Hydrogenation of **4** and **6** over Pd-carbon in HCl–MeOH followed by hydrolysis under alkaline conditions afforded **5** and **7**, respectively. The infrared (IR) spectrum of **5** showed amino acid bands at 3000—2100 and 1550 cm^{-1}, and that of **7** showed such bands at 3000—2100 and 1520 cm^{-1}. Matsumoto

1) Part V: S. Isoda, *Chem. Pharm. Bull.*, **27**, 3039 (1979).
2) Location: *Minamifunabori-cho, Edogawa-ku, Tokyo 132, Japan.*
3) M. Mangyo, *Seikagaku*, **36**, 735 (1964).
4) L. Thunus and M.D. Duchene, *J. Pharm. Belg.*, **24**, 3 (1969) [*C.A.*, **71**, 81100 (1969)].
5) H. Tani, *Chem. Pharm. Bull.*, **7**, 930 (1959).

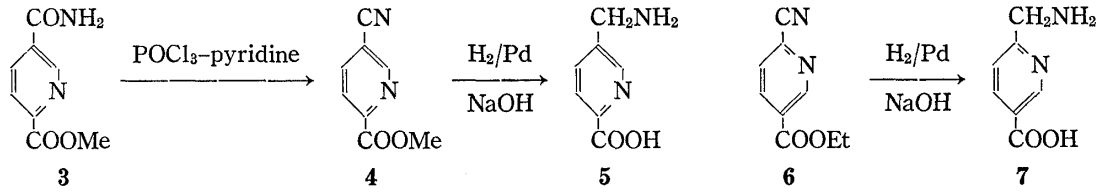


Chart 2

et al.[6] reported the synthesis of **5** by the hydrogenation of 5-cyanopyridine-2-carboxylic acid or its chloro derivative, but they did not mention its biological activity.

Aminomethylpyrimidinecarboxylic Acid

Methyl 5-methylpyrimidine-2-carboxylate (**8**)[7] in benzene was brominated with N-bromosuccinimide (NBS) in the presence of benzoylperoxide. Since the isolation of the

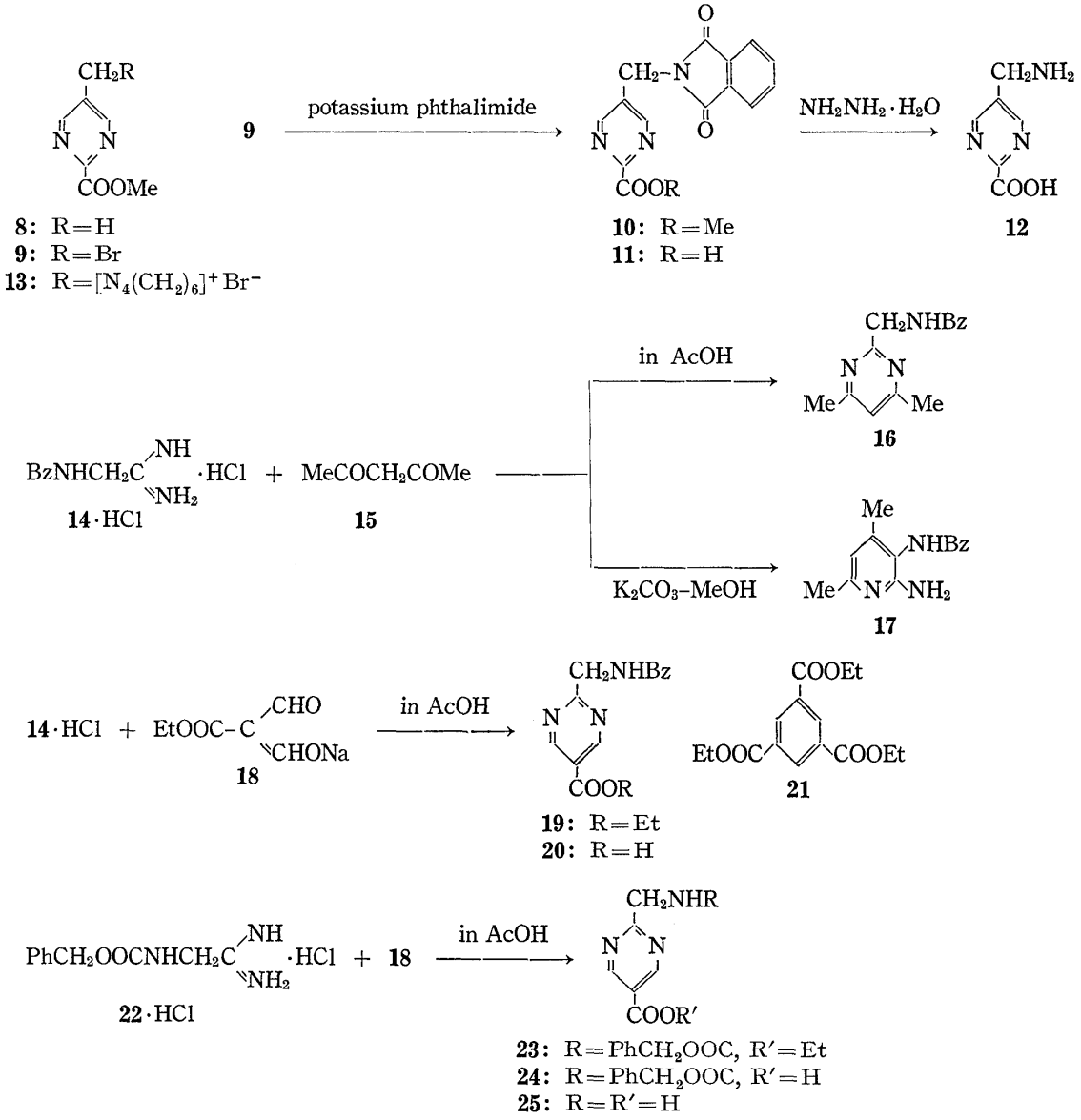


Chart 3

6) I. Matsumoto and K. Tomimoto, Japan Kokai 74-24969 (1974) [*C.A.*, **81**, 77810 (1974)].
7) A. Holland, Brit. Patent, 777465 (1957) [*C.A.*, **52**, 1285 (1958)].

monobromo derivative (**9**) from the resulting mixture (**8**, **9**, and the dibromo derivative) was troublesome, the reaction was stopped as soon as a trace of the dibromo derivative was detected on thin-layer chromatography (TLC). This resulted in a low yield of **9** with high recovery of **8**. Treatment of **9** with potassium phthalimide in dimethylformamide (DMF) at 50—60° afforded the phthalimidomethyl derivative (**10**), which was readily hydrolyzed in 0.5 N NaOH at room temperature to give 5-phthalimidomethylpyrimidine-2-carboxylic acid (**11**). Crystallization of **11** from MeOH afforded colorless needles, mp 145—146°, $C_{15}H_{15}N_3O_6$, containing one mol each of MeOH and H_2O. The crystals were recrystallized from H_2O to afford non-solvated **11**, mp 196—197°. Compound **11** was heated with hydrazine hydrate in MeOH for 40 hr according to the procedure of Rapp.[8] The precipitated mixture of 5-aminomethylpyrimidine-2-carboxylic acid (**12**) and phthalazinedione was fractionally recrystallized several times from H_2O to afford **12**, the structure of which was established from the following results: the IR spectrum showed amino acid bands at 3030—2050 and 1570 cm^{-1}, the nuclear magnetic resonance (NMR) spectrum in D_2O revealed only two singlet signals at 3.99 and 8.79 ppm in a ratio of 1:1, and the elemental analysis data were consistent with the molecular formula, $C_6H_7N_3O_2$. When the hexamethylenetetraminium compound (**13**) obtained by heating **9** with hexamethylenetetramine was heated with HCl-EtOH,[9] **12** was obtained in poor yield.

Uchida *et al.*[10a] reported that both benzoylaminoacetamidine (**14**)[11] and benzyloxycarbonylaminoacetamidine (**22**)[10a] could be treated with acetylacetone (**15**) in the presence of K_2CO_3 to afford 2-amino-3-benzoylamino-4,6-dimethylpyridine (**17**), which had been erroneously reported by Goldberg *et al.*[11] to be 2-benzoylaminomethyl-4,6-dimethylpyrimidine (**16**), and 2-amino-3-benzyloxycarbonylamino-4,6-dimethylpyridine, respectively. Uchida *et al.* also reported[10b] that the high reactivity of the methylene groups of **14** and **22** is responsible for the formation of the pyridine derivative; in contrast, the reaction of **15** with 2-benzoylamino-2-methylpropionamidine, which has no α-hydrogen, did not afford a pyridine derivative under similar conditions but gave 2-(1-benzoylamino-1-methylethyl)-4,6-dimethylpyrimidine, although the yield was only 17%.

In the NMR spectrum, the methylene signal of **14** HCl (4.33 ppm in CD_3OD) disappeared slowly on addition of K_2CO_3, while the spectrum was little affected by the presence of DCl. An AcOH solution of **14** HCl and **15** was refluxed for 5 hr to yield a product having the same empirical formula as **17** ($C_{14}H_{15}N_3O$) but with mp 115—117°, different from that of **17** (mp 197—198°).[10a] Its mass (MS) spectrum gave the molecular ion peak at *m/e* 241, and the IR spectrum showed absorptions at 3400 and 1650 cm^{-1} attributed to NH and an amide carbonyl group, respectively. The NMR spectrum showed a singlet peak at 2.47 ppm (6H) due to two equivalent methyl groups, a doublet at 4.78 ppm (2H), which turned into a singlet upon addition of D_2O, a singlet at 6.92 ppm (1H) and a multiplet due to protons of benzene and NH. Therefore the product was established to be 2-benzoylaminomethyl-4,6-dimethylpyrimidine (**16**). Further, **16** was isolated in 0.7% yield along with **17** from the reaction mixture of **14** with **15** under the reaction conditions described by Uchida *et al.*[10a] On the basis of these findings, it is presumed that **14a** is in equilibrium with **14b** in MeOH in the presence of K_2CO_3, and that **16** and **17** were produced through the routes shown in Chart 4.

Both **14** HCl and **22** HCl were allowed to react with the sodium salt of ethoxycarbonylmalonaldehyde (**18**)[12] in AcOH to afford ethyl 2-benzoylaminomethylpyrimidine-5-carboxylate (**19**) in 30% yield together with triethyl trimesate (**21**), and the 2-benzyloxycarbonylaminomethyl derivative (**23**) in 31% yield, respectively. Their structures were confirmed by their

8) R. Rapp, *Can. J. Chem.*, **49**, 2155 (1971).
9) J.H. Burckhalter, R.J. Seiwald, and H.C. Scarborough, *J. Am. Chem. Soc.*, **82**, 991 (1960).
10) *a*) H. Uchida, H. Iwasawa, and M. Ohta, *Bull. Chem. Soc. Jpn.*, **46**, 3277 (1973); *b*) H. Uchida, A. Chinone, and M. Ohta, *ibid.*, **47**, 1720 (1974).
11) A.A. Goldberg and W. Kelly, *J. Chem. Soc.*, **1947**, 1372.
12) E. Dyer and T.B. Johnson, *J. Am. Chem. Soc.*, **56**, 222 (1934).

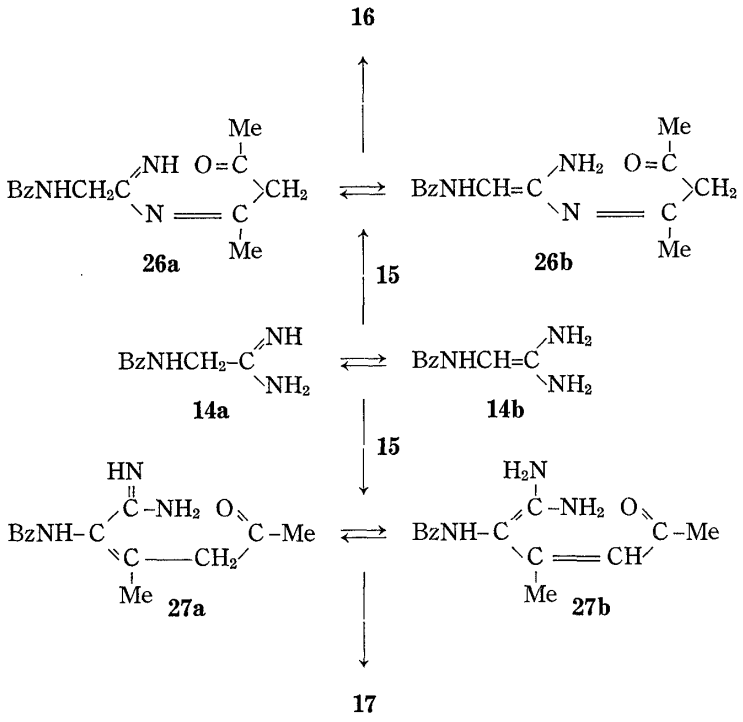


Chart 4

elemental analysis data and IR and NMR spectra. The by-product **21** may have arisen from ethyl formylacetate contaminating the starting material **18**. Hydrolysis of **19** in alkaline or acidic solution did not afford 2-aminomethylpyrimidine-5-carboxylic acid (**25**) but its benzoyl derivative (**20**), benzoic acid and glycine. The elimination of the benzoyl group occurred with accompanying rupture of the pyrimidine ring. Hydrogenolysis of 2-benzyloxycarbonylaminomethylpyrimidine-5-carboxylic acid (**24**), which was obtained by mild alkaline hydrolysis of **23**, over Pd-carbon afforded **25**, the structure of which was established from the following results: the IR spectrum showed amino acids bands at 3300—2000 and 1580 cm^{-1}, the NMR spectrum in D_2O revealed only two singlet signals at 4.56 and 9.16 ppm in a ratio of 1:1, and the elemental analysis data were consistent with the molecular formula $C_6H_7N_3O_2$.

Table I shows the antiplasmin activity of compounds obtained in this work. All the compounds were found to have lower antiplasmin activity than **2**. This is mainly because of their planar structure and the slightly greater distance between functional groups compared with **2**. The compounds having a carboxyl group near the ring nitrogen (s) (**5**, **12**) have more potent activity than those having a carboxyl group far from the ring nitrogen (s) (**7**, **25**).

Table I. Antifibrinolytic Activity[a] of Aza Analogs of PAMBA (**1**)

Compound No.	Relative activity[b]	Compound No.	Relative activity[b]
1	0.49	7	0.36
2	1.00	12	0.28
5	0.67	25	0.051

a) The inhibitory effects on fibrin clot lysis were determined according to the method of Okamoto.[13]
b) Relative activities are assigned on a molar basis with the activity of **2** assigned a value of 1.0.[14]

13) S. Okamoto and U. Okamoto, *Keio. J. Med.*, **11**, 105 (1962).
14) A. Okano, M. Inaoka, S. Funabashi, M. Iwamoto, S. Isoda, R. Moroi, Y. Abiko, and M. Hirata, *J. Med. Chem.*, **15**, 247 (1972).

The compounds having one nitrogen have more potent activity than those having two nitrogens (**5** and **12**, **7**, and **25**). It is noteworthy that the basic amino acid **5** has, in contrast to the relationship between lysine and 6-aminocaproic acid,[3] more potent activity than the neutral amino acid **1**.

Experimental

The following instruments were used: melting points, a Yanagimoto MP-1 melting point apparatus; IR spectra, a Hitachi 285 spectrometer; NMR spectra, a Hitachi Perkin-Elmer R-20B spectrometer with tetramethylsilane (TMS) as an internal standard (TMS in CCl_4 was used as an external standard when D_2O was used as a solvent); MS spectra, a Hitachi RMS-4 spectrometer. All melting points are uncorrected. For preparative TLC, silica gel (Merck GF_{254}) was used.

Methyl 5-Cyanopyridine-2-carboxylate (4)——$POCl_3$ (21.7 g, 0.14 mol) was added dropwise to a solution of **3**[4] (31.0 g, 0.17 mol) in pyridine (170 ml) over a 5 min period below 50°. After warming at 70° for 0.5 hr, the solution was poured into ice-water and extracted with $CHCl_3$. The extract was washed with H_2O, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was chromatographed over neutral alumina (300 g) and eluted with $CHCl_3$. The eluate was evaporated to dryness *in vacuo* and the residue was recrystallized from MeOH to give **4** (17.8 g, 64%) as a colorless powder, mp 146.5—147°. *Anal.* Calcd for $C_8H_6N_2O_2$: C, 59.25; H, 3.73; N, 17.28. Found: C, 59.31; H, 3.88; N, 17.41. IR ν_{max}^{KBr} cm^{-1}: 2230, 1720. NMR ($CDCl_3$) δ: 4.08 (3H, s), 8.22 (2H, m), 9.02 (1H, m).

5-Aminomethylpyridine-2-carboxylic Acid (5)——A solution of **4** (30.8 g, 0.19 mol) in a mixture of MeOH (600 ml) and c HCl (35 ml) was hydrogenated over 5% Pd-carbon (12.0 g) at room temperature and atmospheric pressure. The hydrogenation was completed in 10 hr. The catalyst was filtered off and the filtrate was concentrated *in vacuo*. The residue was treated with 4 N NaOH (100 ml) and the solution was refluxed for 2 hr. The solution was applied to a column of Amberlite IR-120B (H^+ type, 1.0 l) and the column was washed with H_2O. The amino acid was eluted with 3 N NH_4OH and the effluent was evaporated to dryness *in vacuo*. The residue was recrystallized from H_2O to give **5** (27.0 g, 93%) as colorless prisms, mp above 280° (reported[6] mp above 280°). *Anal.* Calcd for $C_7H_8N_2O_2$: C, 55.25; H, 5.30; N, 18.42. Found: C, 55.34; H, 5.40; N, 18.57. IR ν_{max}^{KBr} cm^{-1}: 3000—2100, 1640, 1550, 1380. NMR (CF_3COOD) δ: 4.95 (2H, s), 8.88 (1H, d, J=9), 9.25 (1H, dd, J=9, J=2), 9.53 (1H, d, J=2).

6-Aminomethylpyridine-3-carboxylic Acid (7)——Using the method described above, **6**[5] (15.7 g, 89 mmol) gave **7** (11.4 g, 84%) as colorless prisms, mp above 280°. *Anal.* Calcd for $C_7H_8N_2O_2$: C, 55.25; H, 5.30; N, 18.42. Found: C, 54.77; H, 5.55; N, 18.37. IR ν_{max}^{KBr} cm^{-1}: 3000—2100, 1600, 1520, 1380. NMR (D_2O) δ: 4.40 (2H, s), 7.53 (1H, d, J=8), 8.23 (1H, dd, J=8, J=2), 8.96 (1H, d, J=2).

Methyl 5-Bromomethylpyrimidine-2-carboxylate (9)——A solution of **8**[7] (24.5 g, 0.16 mol), NBS (29.0 g, 0.16 mol) and benzoyl peroxide (1.5 g, 6 mmol) in C_6H_6 (450 ml) was refluxed for 5 hr with stirring. The solvent was evaporated off *in vacuo* and the residue was chromatographed on silica gel (500 g) using C_6H_6 as a solvent. The initial eluate was evaporated to dryness *in vacuo* and the residue was recrystallized from C_6H_6–petroleum ether to give **9** (4.30 g, 12%) as colorless needles, mp 121—123°. *Anal.* Calcd for $C_7H_7BrN_2O_2$: C, 36.38; H, 3.06; Br, 34.58; N, 12.13. Found: C, 36.89; H, 3.13; Br, 34.84; N, 12.03. IR ν_{max}^{KBr} cm^{-1}: 1720, 1575, 1550, 1445, 1420. NMR ($CDCl_3$) δ: 4.09 (3H, s), 4.53 (2H, s), 9.00 (2H, s). From the later fraction **8** (17.5 g, 72%) was recovered.

Methyl 5-Phthalimidomethylpyrimidine-2-carboxylate (10)——A solution of **9** (0.81 g, 3.5 mmol) and potassium phthalimide (0.65 g, 3.5 mmol) in DMF (6 ml) was warmed at 50—60° for 4 hr with stirring. After cooling, H_2O was added to the reaction mixture and the solution was extracted with $CHCl_3$. The extract was washed with H_2O, dried over Na_2SO_4 and concentrated *in vacuo*. After washing with Et_2O, the residue was recrystallized from MeOH to give **10** (0.64 g, 64%) as colorless scales, mp 206—207°. *Anal.* Calcd for $C_{15}H_{11}N_3O_4$: C, 60.60; H, 3.73; N, 14.14. Found: C, 60.78; H, 3.83; N, 14.37. IR ν_{max}^{KBr} cm^{-1}: 1735, 1710, 1550. NMR ($CDCl_3$) δ: 4.04 (3H, s), 4.93 (2H, s), 7.82 (4H, m), 9.02 (2H, s).

5-Phthalimidomethylpyrimidine-2-carboxylic Acid (11)——A suspension of **10** (595 mg, 2 mmol) in 0.5 N NaOH (8.0 ml, 4 mmol) was stirred at room temperature for 1 hr, giving a clear solution. Next, 1 N HCl (4 ml) was added. The resulting precipitate was filtered and recrystallized from MeOH to give **11**·MeOH·H_2O (550 mg, 97%) as colorless needles, mp 145—146°. *Anal.* Calcd for $C_{14}H_9N_3O_4 \cdot CH_3OH \cdot H_2O$: C, 54.05; H, 4.54; N, 12.61. Found: C, 53.87; H, 4.62; N, 12.76. Recrystallization from H_2O gave **11** as colorless needles, mp 196—197°. *Anal.* Calcd for $C_{14}H_9N_3O_4$: C, 59.36; H, 3.20; N, 14.84. Found: C, 59.57; H, 3.52; N, 14.85. IR ν_{max}^{KBr} cm^{-1}: 1720, 1685, 1635, 1590, 1575, 1560. NMR (DMSO-d_6) δ: 4.54 (2H, bs), 7.60 (4H, m), 8.97 (2H, s).

N-(2-Methoxycarbonyl-5-pyrimidinyl)methyl Hexamethylenetetraminium Bromide (13)——A solution of **9** (0.40 g, 1.7 mmol) in $CHCl_3$ (20 ml) was added to a refluxing solution of hexamethylenetetramine (0.27 g, 1.9 mmol) in $CHCl_3$ (20 ml). The solution was refluxed for 2 hr. After cooling, the precipitate (0.45 g, 70%) was collected, mp 185—188°, and used without further purification.

5-Aminomethylpyrimidine-2-carboxylic Acid (12)——a) A solution of **11** (57 mg, 0.2 mmol) and 80% $NH_2NH_2 \cdot H_2O$ (12 mg, 0.2 mmol) in MeOH (2 ml) was refluxed for 40 hr with stirring. The precipitate was collected and fractionally recrystallized from H_2O to give **12** (8 mg, 25%) as colorless needles, mp 280—281° (dec.). *Anal.* Calcd for $C_6H_7N_3O_2$: C, 47.05; H, 4.61; N, 27.44. Found: C, 47.00; H, 4.60; N, 27.18. IR ν_{max}^{KBr} cm^{-1}: 3030—2050, 1620, 1570, 1535, 1370. NMR (D_2O) δ: 3.99 (2H, s), 8.79 (2H, s).

b) A solution of **13** (0.45 g) in c HCl–EtOH (1: 1, 30 ml) was refluxed for 2 hr. After concentration to one-third of its original volume *in vacuo* followed by addition of H_2O (10 ml), the solution was refluxed for 1 hr. The solution was applied to a column of Diaion SK#1 (H^+ type, 50 ml) and the column was washed with H_2O. The amino acid was eluted with 1.5 N NH_4OH and the effluent was concentrated *in vacuo*. After washing with H_2O, a trace amount of **12** was obtained as a yellow powder, which was identical with an authentic sample (IR spectrum and TLC).

Reaction of Benzoylaminoacetamidine Hydrochloride (14 HCl) and Acetylacetone (15)——a) A solution of **14** HCl[11] (1.50 g, 7 mmol) and **15** (0.90 g, 9 mmol) in AcOH (10 ml) was refluxed for 5 hr. The solvent was removed *in vacuo*, and H_2O was added to the residue. The mixture was extracted with $CHCl_3$. The extract was washed with H_2O, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was recrystallized from C_6H_6–petroleum ether to give **16** (95 mg, 6%) as pale yellow prisms, mp 115—117°. *Anal.* Calcd for $C_{14}H_{15}N_3O$: C, 70.07; H, 6.27; N, 17.01. Found: C, 69.69; H, 6.27; N, 17.41. IR ν_{max}^{KBr} cm^{-1}: 3400, 1650, 1595, 1510, 1480, 1440. NMR ($CDCl_3$) δ: 2.47 (6H, s), 4.78 (2H, d, J=4), 6.92 (1H, s), 7.35—7.6, 7.6—8.06 (total 6H, m). MS *m/e*: 241 (M^+), 164 ($M^+-C_6H_5$), 136 ($M^+-C_6H_5CO$).

b) A solution of **14** HCl (1.50 g, 7 mmol), **15** (0.90 g, 9 mmol) and K_2CO_3 (1.0 g, 7 mmol) in EtOH (7.5 ml) was refluxed for 4 hr. Next, 3 N HCl (7 ml) was added to the reaction mixture and the solution was allowed to stand at room temperature overnight. The precipitate was filtered and extracted with C_6H_6. The extract was concentrated *in vacuo* and the residue was subjected to preparative TLC using C_6H_6–Me_2CO (5: 1) as a developing solvent. The adsorption band of *Rf* 0.15 was eluted with $CHCl_3$. The eluted solution was concentrated *in vacuo* to give **16** (12 mg, 0.7%), which was identical with an authentic sample (TLC and NMR spectrum). The initial acidic filtrate was made alkaline with 2.5 N NaOH and allowed to stand at room temperature overnight. The precipitate was filtered and recrystallized from MeOH to give **17** (113 mg, 7%) as colorless needles, mp 199° (reported[10a] mp 197—198°). IR ν_{max}^{KBr} cm^{-1}: 3430, 3360, 3200, 3080, 1640, 1520. NMR ($CDCl_3$) δ: 2.13 (3H, s), 2.31 (3H, s), 4.56 (2H, bs), 6.43 (1H, s), 7.3—8.0 (6H, m).

Ethyl 2-Benzoylaminomethylpyrimidine-5-carboxylate (19)——A solution of **14** HCl (21.35 g, 0.10 mol) and **18**, which was prepared from Na powder (2.80 g, 0.12 mol), ethyl 3,3-diethoxypropionate[15] (19.0 g, 0.10 mol) and ethyl formate (7.40 g, 0.20 mol) in Et_2O (100 ml) according to the procedure of Dyer,[12] in AcOH (200 ml) was refluxed for 5 hr with stirring. The solution was neutralized with aqueous $NaHCO_3$ and extracted with $CHCl_3$. The extract was washed with H_2O, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was chromatographed over silica gel (180 g) using C_6H_6 and subsequently C_6H_6–Me_2CO (49: 1) as solvents. The former eluate was evaporated to dryness, and the residue was recrystallized from EtOH to give **21** (1.20 g, 4%) as colorless needles, mp 132—133° (reported[16] mp 129°). IR ν_{max}^{KBr} cm^{-1}: 1720. NMR ($CDCl_3$) δ: 1.39 (9H, t, J=6), 4.40 (6H, q, J=6), 8.80 (3H, s). The latter eluate was concentrated *in vacuo*, and the residue was recrystallized from C_6H_6–C_6H_{14} to give **19** (8.58 g, 30%) as colorless fine needles, mp 110—110.5°. *Anal.* Calcd for $C_{15}H_{15}N_3O_3$: C, 63.15; H, 5.30; N, 14.73. Found: C, 62.96; H, 5.45; N, 14.76. IR ν_{max}^{KBr} cm^{-1}: 3290, 1720, 1630, 1585, 1545. NMR ($CDCl_3$) δ: 1.40 (3H, t, J=7), 4.48 (2H, q, J=7), 4.93 (2H, d, J=5), 7.2—7.6, 7.7—8.0 (total 6H, m), 9.19 (2H, s).

2-Benzoylaminomethylpyrimidine-5-carboxylic Acid (20)——A suspension of **19** (1.14 g, 4 mmol) in 0.5 N NaOH (8 ml, 4 mmol) was stirred at room temperature for 15 min, giving a clear solution. Next, 0.5 N HCl (8 ml, 4 mmol) was added and the precipitate was filtered to give **20** (0.79 g, 77%). Recrystallization from H_2O gave colorless prisms, mp 187—189°. *Anal.* Calcd for $C_{13}H_{11}N_3O_3$: C, 60.70; H, 4.31; N, 16.33. Found: C, 60.45; H, 4.46; N, 16.22. IR ν_{max}^{KBr} cm^{-1}: 3400—2300, 1710, 1640, 1590, 1520. NMR (DMSO-d_6) δ: 4.78 (2H, d, J=6), 7.45—7.7, 7.85—8.05 (total 5H, m), 9.19 (2H, s).

Hydrolysis of 19——a) A suspension of **19** (285 mg, 1 mmol) in 2.5 N NaOH (3 ml, 7.5 mmol) was refluxed for 5 hr. The solution was concentrated *in vacuo*. After acidification with 1 N HCl, the residue was extracted with $CHCl_3$. The extract was washed with H_2O, dried over Na_2SO_4 and evaporated to dryness to give benzoic acid, which was identical with an authentic sample (mixed melting point and IR spectra). The aqueous solution was applied to a column of Amberlite IR-120B (H^+ type) and the column was washed with H_2O. The amino acid was eluted with 3 N NH_4OH and the effluent was evaporated to dryness *in vacuo* to give glycine, which was identified by comparison with an authentic sample (paper chromatography and NMR spectra).

b) A suspension of **19** (50 mg, 0.18 mmol) in 1 N HCl (1 ml) was refluxed for 3 hr. The solution was treated in the manner described above and benzoic acid and glycine were identified.

Ethyl 2-Benzyloxycarbonylaminomethylpyrimidine-5-carboxylate (23)——A solution of **22** HCl[10a]

15) S. Sugasawa, *Yakugaku Zasshi*, **54**, 551 (1927).
16) A. Bayer, *Chem. Ber.*, **19**, 2186 (1886).

(2.29 g, 9.4 mmol) and **18**, which was prepared from Na powder (0.27 g, 12 mmol), ethyl 3,3-diethoxypropionate (1.90 g, 10 mmol) and ethyl formate (1.50 g, 20 mmol) in Et_2O (20 ml), in AcOH (20 ml) was refluxed for 4 hr with stirring. The solvent was removed. H_2O was added to the residue and the solution was extracted with $CHCl_3$. The extract was washed with H_2O, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was chromatographed on silica gel (25 g) using C_6H_6–Me_2CO (49: 1) as a solvent. The eluate was evaporated to dryness *in vacuo*, and the residue was recrystallized from C_6H_6–C_6H_{14} to give **23** (905 mg, 31%) as colorless fine needles, mp 104—106°. *Anal.* Calcd for $C_{16}H_{17}N_3O_4$: C, 60.94; H, 5.43; N, 13.33. Found: C, 61.01; H, 5.52; N, 13.05. IR ν_{max}^{KBr} cm^{-1}: 3350, 1705, 1585, 1520. NMR ($CDCl_3$) δ: 1.45 (3H, t, $J=7$), 4.46 (2H, q, $J=7$), 4.76 (2H, d, $J=5$), 5.18 (2H, s), 5.8—6.4 (1H, bs), 7.36 (5H, s), 9.23 (2H, s).

2-Benzyloxycarbonylaminomethylpyrimidine-5-carboxylic Acid (24)——A suspension of **23** (630 mg, 2 mmol) in 0.5 N NaOH (4 ml, 2 mmol) was stirred at room temperature for 4 hr, giving a clear solution. Next, 0.5 N HCl (4 ml, 2 mmol) was added and the precipitate was filtered off to give **24** (425 mg, 74%) as a pale yellow powder, mp 135—137°. Recrystallization from EtOH–H_2O gave colorless fine needles, mp 139—140°. *Anal.* Calcd for $C_{14}H_{13}N_3O_4$: C, 58.53; H, 4.56; N, 14.63. Found: C, 58.62; H, 4.71; N, 14.40. IR ν_{max}^{KBr} cm^{-1}: 3250, 3100—2250, 1715, 1690, 1590, 1550. NMR (CD_3OD) δ: 4.61 (2H, s), 5.11 (2H, s), 7.33 (5H, s), 9.18 (2H, s).

2-Aminomethylpyrimidine-5-carboxylic Acid (25)——A suspension of **24** (340 mg, 1.2 mmol) in a mixture of EtOH (10 ml) and H_2O (20 ml) was hydrogenated over 10% Pd-carbon (50 mg) at room temperature and atmospheric pressure. The catalyst was filtered off and the filtrate was evaporated to dryness *in vacuo*. The residue was recrystallized from H_2O–EtOH to give **25** (50 mg, 28%) as colorless rods, mp 291—293° (dec.). *Anal.* Calcd for $C_6H_7N_3O_2$: C, 47.06; H, 4.61; N, 27.44. Found: C, 47.24; H, 4.60; N, 27.19. IR ν_{max}^{KBr} cm^{-1}: 3300—2000, 1580, 1500. NMR (D_2O) δ: 4.56 (2H, s), 9.16 (2H, s).

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