Synthesis of 4-Mono-and 2, 4-Disubstituted Derivatives of Pyrido-[3, 2-d]pyrimidine, Pyrido[2, 3-d]pyrimidine and Quinazoline

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Introduction

Since 4-substituted-amino derivatives of pyrido[3, 2-d]pyrimidine, pyrido[4, 3-d]pyrimidine, pyrido[3, 4-d]pyrimidine and pyrido[2, 3-d]pyrimidine, which are trivially named 1, 3, X-triazanaphthalene(X=5, 6, 7 and 8, respectively), are structurally related to N^6-adenine-type cytokinins, their biological activity is interesting in structure-activity study of cytokinins[1]. It has been previously shown in systematic studies on the relation between the structure and biological activity of the four kinds of the pyridopyrimidines that 4-substituted-aminopyrido[4, 3-d]pyrimidines have no cytokinin activity in lettuce seed germination and *Amaranthus* betacyanin tests; thus, the presence of nitrogen in the 6-position of the pyridopyrimidine ring is not favorable to the activity[2]. However, the effect of nitrogen in the other positions (X=5, 7 and 8) of the heteroaromatic ring on cytokinin activity has not been studied. Thus, this report deals with the synthesis of pyrido[3, 2-d]pyrimidine, pyrido[2, 3-d]pyrimidine and quinazoline analogs of N^6-adenine-type cytokinins by the usual two-step synthetic method and by a new, convenient one-step amination method in which most of the compounds are new. Additionally, their effects on lettuce seed germination and betacyanin biosynthesis of *Amaranthus* is described briefly.

Summary

Some 4- and 2, 4-substituted derivatives of pyrido[3, 2-d]pyrimidine and pyrido[2, 3-d]pyrimidine were synthesized from the corresponding 4(3H)-ones by the usual method comprised of chlorodehydroxylation and subsequent amination and by "one-pot" amination. The latter method was more convenient and efficient than the former one. Similarly, 4- and 2, 4-substituted quinazolines were prepared. All of the cytokinin analogs were inactive in lettuce seed germination and *Amaranthus* betacyanin tests.

Results and Discussion

Pyridopyrimidin-4(3H)-ones which can be prepared from anthranilic analogs of pyridine by cyclization with amides or by cyclization with acid anhydrides followed by treatment with ammonia are useful intermediates for synthesis of 4-substituted-aminopyridopyrimidines. The 4(3H)-ones are usually converted into the 4-aminated pyridopyrimidines via 4-chloropyridopyrimidines. In a process similar to preparing 4-chloroquinazolines **4a** and **4b** from quinazolin-4(3H)-ones **1a** and **1b**[3], pyrido[3, 2-d]pyrimidin-4(3H)-one(**2a**), pyrido[2, 3-d]pyrimidin-4(3H)-one(**3a**) and its 2-methyl derivative **3b** were chlorodehydroxylated with $POCl_3$ and triethylamine in refluxing benzene to give the 4-chlorides **6a**, **8a** and **8b** in 53%, 48% and 18% yields, respectively. However, chlorodehydroxylation of **2b** under the same conditions gave 2-methyl-4-diethylaminopyrido[3, 2-d]pyrimidine as a major product together with the chloride **6b**; the 4-diethylamino compound was presumably formed through nucleophilic substitution of **6a** with triethylamine followed by β-elimination. To avoid inevitable formation of the 4-diethylamino compound, *N*, *N*-di-

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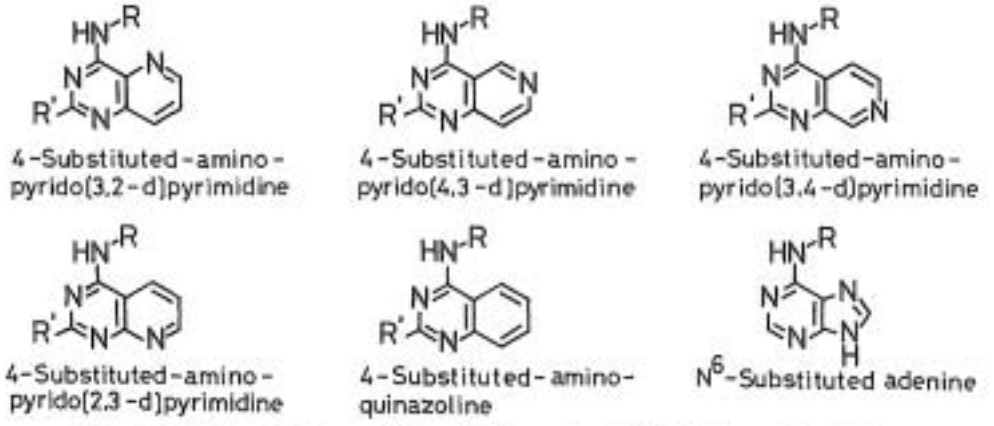

Fig. 1. Pyridopyrimidine and Quinazoline Anoalgs of N^6-Adenine-type Cytokinins.

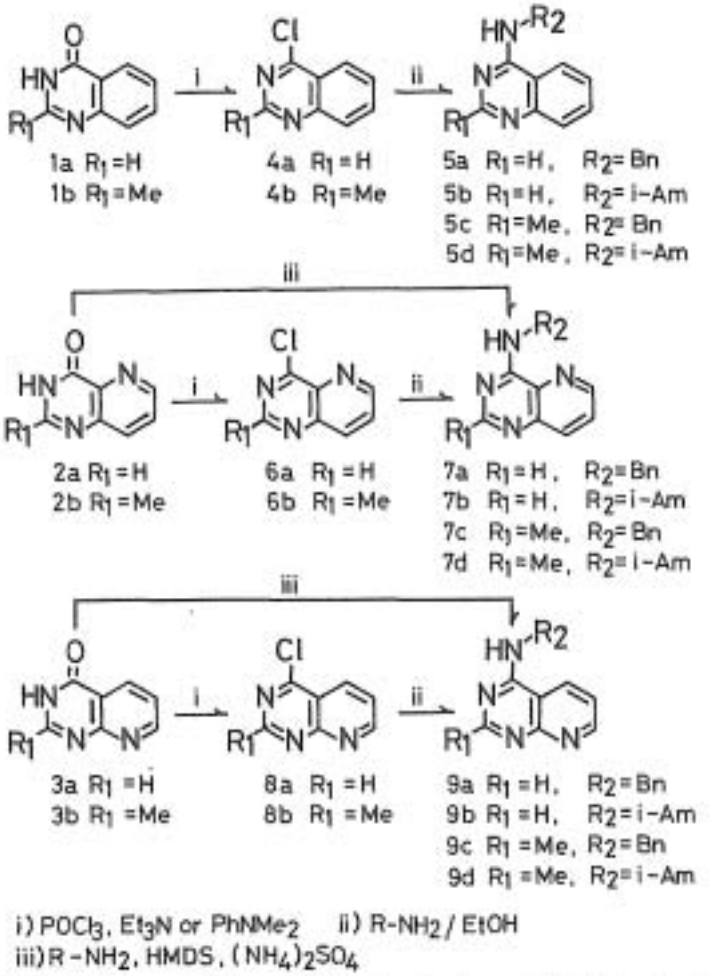

Fig. 2. Synthesis of Pyridopyrimidine and Quinazoline Analogs of N^6-Adenine-type Cytokinins.

methylaniline was used in place of triethylamine. Chlorodehydroxylation of **2b**, using the aromatic amine, afforded **6b** in a moderate yield (49%). Czuba and Kowalska[4] have already synthesized **6b** only in a low yield by refluxing **2b** in $POCl_3$ and triethylamine. The low yield may be related to the formation of 2-methyl-4-diethylaminopyrido[3, 2-d]pyrimidine. Since the 2-methyl-substituted chlorides **6b** and **8b** were more unstable than the 2-unsubstituted ones **6a** and **8a**, they were used for amination immediately after isolation.

Nucleophilic substitution of the 4-chlorides as well as **4a** and **4b** with benzylamine or isoamylamine gave the 4-substituted-amino derivatives **5**, **7** and **9** in high yields; the compounds **7b**, **7c** and **7d**, oily products, were crystallized as picrates respectively (see Table 1). Since the yields of **6b** and **8b** were low to moderate, the overall yields of the 4-substituted-amino derivatives **7c**, **7d**, **9c** and **9d** from the 4(3H)-ones **2b** and **3b** were not satisfactory. Therefore, a more efficient method of synthesizing the aminated derivatives was elucidated. In a previous study[2], some 4-substituted-aminopyrido-[4, 3-d]pyrimidines were successfully synthesized by "one-pot" amination using hexamethyldisilazane (HMDS)[5,6]. Similar "one-pot" amination of **2b** and **3b** with benzylamine or isoamylamine gave **7c**, **7d**, **9c** and **9d** in 65%–100% yields (Table 1). The results show that the 4-substituted-amino derivatives of pyrido[3, 2-d]pyrimidine and pyrido[2, 3-d]-pyrimidine can be synthesized directly from the 4(3H)-ones **2b** and **3b** in high yields. Therefore, "one-pot" method is more convenient and efficient for synthesis of the 4-aminated pyridopyrimidines than the usual two-step synthetic method described above.

Table 1. Synthesis of 4-Substituted-amino Derivatives of Pyrido[3, 2-d]pyrimidine, Pyrido[2, 3-d]-pyrimidine and Quinazoline.

product	time (hr)	method[s]	yield (%)	mp. (°C)	formula	analysis					
						calcd, %			found, %		
						C	H	N	C	H	N
5a	1.5	a	85	174	$C_{13}H_{13}N_3$	76.57	5.57	17.86	76.59	5.51	17.91
5b	1.5	a	92	136–137	$C_{13}H_{17}N_3$	72.52	7.96	19.52	72.24	7.91	19.34
5c	1.2	a	92	189	$C_{16}H_{13}N_3$	77.08	6.06	16.86	76.97	6.00	16.85
5d	1.2	a	82	127–128	$C_{16}H_{19}N_3$	73.32	8.35	18.33	73.37	8.48	18.29
7a	2	a	70	81	$C_{14}H_{12}N_4$	71.16	5.12	23.72	71.14	5.00	23.60
7b	2	a	70	oil (168–169*)	$C_{18}H_{16}N_4O_7$	48.54	4.30	22.01	48.66	4.22	21.78
7c	0.5	a	94	oil (210–216*)	$C_{21}H_{17}N_4O_7$	52.61	3.45	20.45	52.86	3.53	20.41
7c	5	b	65								
7d	1	a	92	oil (141–142*)	$C_{18}H_{21}N_4O_7$	49.67	4.61	21.34	49.56	4.54	21.37
7d	5	b	96								
9a	1	a	80	264–266 (Lit.[11] 249–252)	$C_{14}H_{12}N_4$	71.16	5.12	23.72	70.86	5.00	23.85
9b	1	a	83	197–198	$C_{12}H_{16}N_4$	60.04	7.46	25.91	66.37	7.50	25.85
9c	1	a	88	198–199	$C_{15}H_{14}N_4 \cdot 2H_2O$	62.92	6.34	19.57	63.31	6.21	19.28
9c	5	b	100								
9d	1	a	93	137–138	$C_{13}H_{18}N_4 \cdot 1.5H_2O$	60.08	8.23	21.75	60.84	8.21	21.57
9d	5	b	83								

[s]: a, nucleophilic substitution of the 4-chloride with amine; b, amination of the 4(3H)-one using amine and hexamethyl disilazane.

*: melting point of picrate

Cytokinin activities of the 4-substituted-amino derivatives of pyrido[3, 2-d]pyrimidine, pyrido[2, 3-d]-pyrimidine and quinazoline were assayed by both *Amaranthus* betacyanin test[7] and lettuce seed germination test[8]. In the two tests, all of the compounds were completely inactive at the concentrations

tested(1–400 μM). From these results, it was concluded that the presence of nitrogen in the 5- and 8-positions does not make the pyridopyrimidines cytokinin-active and that removal of nitrogen from the pyridine moiety of the pyridopyrimidines is also ineffective in giving rise to cytokinin activity.

In the present study as well as the previous one, we have synthesized cytokinin analogs of pyrido[3, 2-d]pyrimidine, pyrido[2, 3-d]pyrimidine, pyrido[4, 3-d]pyrimidine and quinazoline and have tested their biological activity. Efforts to synthesize the remaining pyrido[3, 4-d]pyrimidine analogs are continued.

Experimental

General method

All melting points are uncorrected. IR spectra were recorded on a JASCO IR-G spectrophotometer. ^{1}H NMR spectra were obtained with a Hitachi R-22 spectrometer, chemical shifts being expressed in δ values from tetramethylsilane as internal reference. E. I. mass spectra were recorded on a Hitachi M-50 spectrometer at 70 eV by direct inlet method. Elemental analyses were performed at Analytical Center of Kyoto University, Kyoto. Silica gel column chromatography was carried out on Wakogel C-200 (Wako Pure Chemical Industries Ltd.).

Bioassay

Amaranthus betacyanin test was made according to the method of Biddington and Thomas[7]. Lettuce seed germination test was made at 30(±1)°C for 3–4 days in the dark using seeds of Great Lakes 366 according to the method of Skinner et al.[8]

4-*Chloroquinazoline* (**4a**)

The compound, mp. 96–97°C(Lit.[2] 94.5–96°C) was prepared in 66% yield by chlorodehydroxylation of quinazolin-4(3H)-one(**1a**)[6] with $POCl_3$ and triethylamine[3]. IR(KBr) 1615, 1570, 1560 (C=N, C=C) cm^{-1} ^{1}H NMR ($CDCl_3$) 7.6–8.3 (4H, aromatic), 9.02 (1H, s, 2-H).

2-*Methyl*-4-*chloroquinazoline* (**4b**)

Similarly, the compound, mp. 83°C (Lit.[2] 81.5–83°C) was prepared in 47% yield from 2-methylquinazolin-4(3H)-one(**1b**)[10] IR (KBr) 1615, 1575, 1555 (C=N, C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$) 2.84 (3H, s, $-CH_3$), 7.5–8.4 (4H, aromatic).

4-*Chloropyrido*[3, 2-*d*]*pyrimidine* (**6a**)

Pyrido[3, 2-d]pyrimidin-4(3H)-one(**2a**) was prepared from quinolinic acid via quinoline imide[11] (64%) and 3-aminopicolinic acid[12] (63%) in an overall yield of 24% according to the known procedures[12]. The chloride was synthesized according to the method of Scarborough et al.[3] A mixture of powdered **2a** (2.00 g, 13.6 mmole), $POCl_3$ (1.39 g, 9.06 mmole), triethylamine (2.75 g, 27.2 mmole) and anhydrous benzene (50 m*l*) was refluxed for 2.2 hr. After removing the solvent under reduced pressure, the residue was extracted with hot n-hexane (50 m*l*×3) and the extracts were evaporated to afford yellow crystalline mass (1.27 g, 53%). Recrystallization from n-hexane gave needles, mp. 148–150°C (Lit.[13] 148–150°C). IR(KBR) 1570 (C=N) cm^{-1}; ^{1}H NMR ($CDCl_3$–CD_3OD) 8.17 (1H, dd, J=8.2, 4.2 Hz, 7-H), 8.95 (1H, dd, J=8.2, 4.2 Hz, 8-H), 9.26 (1H, dd, J=4.2, 2.0 Hz, 6-H), 9.33 (1H, s, 2-H).

2-*Methyl*-4-*chloropyrido*[3, 2-*d*]*pyrimidine* (**6b**)

2-Methylpyrido[3, 2-d]pyrimidin-4(3H)-one(**2b**) was prepared from 3-aminopicolinic acid via 2-methylpyrido[3, 2-d] [1, 3]oxazin-4-one (64%) and 3-acetamidopicolinamide (75%) in an overall yield of 20% according to the known procedures[4]. A mixture of powdered **2b** (3.45 g, 21.4 mmole), $POCl_3$ (2.41 g, 15.7 mmole), *N*, *N*-dimethylaniline (5.71 g, 47.1 mmole) and anhydrous benzene (150 m*l*) was refluxed for

5 hr. The mixture was filtered, concentrated to ca. 50 ml under reduced pressure and chromatographed on silica gel (20 g) eluting with benzene. After evaporating the eluting solvent, **6b** was obtained as yellow needles, mp. 125–126°C (decomp.) (Lit.[4] 86–87°C). IR (KBr) 1575 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$–CD_3OD) 3.10 (3H, s, $-CH_3$), 8.07 (1H, dd, J=8.2, 4.5 Hz, 7–H), 8.96 (1H, dd, J=8.2, 1.7 Hz, 8–H), 9.15 (1H, dd, J=4.5, 1.7 Hz, 6–H). Although the melting point was higher than that reported[4], IR and ^1H NMR spectra supported the structure. Chlorodehydroxylation using triethylamine in place of *N*, *N*-dimethylaniline afforded a 3: 1 mixture of 2-methyl-4-diethylaminopyrido[3, 2-d]pyrimidine and **6b**. The structure of the former was confirmed by the ^1H NMR spectrum. ^1H NMR ($CDCl_3$) 1.27 (6H, t, J=6 Hz, $-C-CH_3$), 2.53 (3H, s, $-CH_3$), 4.07 (4H, q, J=6 Hz, $N-CH_2$), 7.50 (1H, dd, J=8.4, 4.2 Hz, 7–H), 7.99 (1H, dd, J=8.4, 4.1 Hz, 8–H), 8.65 (1H, dd, J=4.2, 1.4 Hz, 6–H).

4-*Chloropyrido*[2, 3-*d*]*pyrimidine* (**8a**)

Pyrido[2, 3-d]pyrimidin-4(3H)-one(**3a**) was prepared from 2-amino-β-picoline via 2-aminonicotinic acid (83%) in an overall yield of 50% according to the known procedures[14]. A mixture of **3a** (2.00 g, 13.6 mmole), $POCl_3$ (1.39 g, 9.1 mmole), triethylamine (2.75 g, 27.2 mmole) and anhydrous benzene (50 ml) was refluxed for 2.4 hr. Tarry material was filtered off and the filtrate was evaporated under reduced pressure to give powder, which was extracted with hot n-heptane-benzene (5: 1) (50 ml×2). The extracts were concentrated and cooled to afford slightly yellow needles, mp. 134°C (1.08 g, 48%). Recrystallization from n-heptane gave **8a**, mp. 134–135°C (Lit.[14] 135°C). IR (KBr) 1610, 1580, 1555 (C=N, C=C) cm^{-1}; ^1H NMR ($CDCl_3$–CD_3OD) 8.06 (1H, dd, J=8.0, 4.6 Hz, 6–H), 8.98 (1H, dd, J=8.0, 2.0 Hz, 5–H), 8.06 (1H, dd, J=8.0, 4.6 Hz, 6–H), 8.98 (1H, dd, J=8.0, 2.0 Hz, 5–H), 9.37 (1H, s, 2–H), 9.45 (1H, dd, J=4.6, 2.0 Hz, 7–H).

2-*Methyl*-4-*chloropyrido*[2, 3-*d*]*pyrimidine* (**8b**)

2-Methylpyrido[2, 3-d]pyrimidin-4(3H)-one(**3b**) was prepared from 2-aminonicotinic acid via 2-methylpyrido[2, 3-d] [1, 3]oxazin-4-one[15] (95%) in an overall yield of 86% similar to the method of Irwin and Wibberley[16]. A mixture of powdered **3b** (3.00 g, 18.6 mmole), $POCl_3$ (2.05 g, 13.4 mmole), triethylamine (4.07 g, 40.2 mmole) and anhydrous benzene (125 ml) was refluxed for 6 hr. The mixture was dried and the residue was extracted with boiling n-hexane (50 ml×3). The extracts were filtered, concentrated and cooled to afford slightly yellow needles, mp. 96°C (0.609 g, 18%). IR (KBr) 1600, 1580, 1575 (C=N, C=C) cm^{-1}; ^1H NMR ($CDCl_3$) 2.88 (3H, s, $-CH_3$), 7.60 (1H, dd, J=8.2, 4.4 Hz, 6–H), 8.57 (1H, dd, J=4.3, 2.0 Hz, 5–H), 9.24 (1H, dd, J=8.2, 2.9 Hz, 7–H).

4-*Benzylaminoquinazoline* (**5a**)

A mixture of **4a** (329 mg, 2.0 mmole), benzylamine (459 mg, 4.28 mmole) and ethanol (10 ml) was refluxed for 1.5 hr. After removing the solvent under reduced pressure, crystalline residue was washed with water, filtered and dried. The crude material, mp. 174–175°C (457 mg) was recrystallized from aqueous methanol to afford colorless needles, mp. 174°C (398 mg, 85%). IR (KBr) 3230 (NH), 1620, 1580, 1575 (C=N, C=C), 1340 cm^{-1}; ^1H NMR (DMSO-d6) 4.81 (2H, m, $N-CH_2$), 7.2–8.4 (9H, m, phenyl and aromatic), 8.47 (1H, s, 2–H), 8.78 (1H, t, braod, NH); MS: m/z 235 (M^+).

4-*Isoamylaminoquinazoline* (**5b**)

A mixture of **4a** (329 mg, 2.0 mmole), isoamylamine (368 mg, 4.22 mmole) and ethanol (10 ml) was refluxed for 1.5 hr. After removing the solvent, the residue was chromatographed on silica gel (10 g) eluting with ethyl acetate to afford slightly yellow needles, mp. 136–137°C (198 mg, 92%). IR (KBr) 3230 (NH), 1620, 1580, 1575 (C=N, C=C), 1355 cm^{-1}; ^1H NMR (DMSO-d6) 0.93 (6H, d, J=6 Hz, $-CH_3$×2), 1.3–1.8 (3H, m, $-CH_2-CH=$), 3.53 (2H, m, $N-CH_2$), 7.4–8.3 (4H, aromatic), 8.16 (1H, t, broad, NH), 8.44 (1H, s, 2–H); MS: m/z 215 (M^+).

2-*Methyl*-4-*benzylaminoquinazoline* (**5c**)

A mixture of **4b** (309 mg, 1.73 mmole), benzylamine (386 mg, 3.60 mmole) and ethanol (10 m*l*) was refluxed for 1.2 hr. After workup above, the mixture gave slightly yellow needles, mp. 189°C (397 mg, 92%). IR (KBr) 3230 (NH), 1620, 1580, 1575 (C=N, C=C), 1340 cm^{-1}; ^1H NMR (DMSO-d6) 2.42 (3H, s, $-CH_3$), 4.78 (2H, m, N-CH_2), 7.2–8.3 (9H, m, phenyl and aromatic), 8.61 (1H, t, braod, NH); MS: m/z 249 (M^+).

2-*Methyl*-4-*isoamylaminoquinazoline* (**5d**)

A mixture of **4b** (357 mg, 2.0 mmole), isoamylamine (360 mg, 4.13 mmole) and ethanol (10 m*l*) was refluxed for 1.2 hr. The mixture was purified by the column chromatography to afford needles, mp. 127–128°C (374 mg, 82%), which were recrystallized from aqueous methanol to give colorless needles of the same melting point. IR (KBr) 3230 (NH), 1620, 1580, 1575 (C=N, C=C), 1360 cm^{-1}; ^1H NMR (DMSO-d6) 0.92 (6H, d, J=6 Hz, $-CH_3\times2$), 1.3–1.8 (3H, m, $-CH_2-CH=$), 2.42 (3H, s, $-CH_3$), 3.56 (2H, m, N-CH_2), 7.2–8.3 (4H, aromatic); MS: m/z 229 (M^+).

4-*Benzylaminopyrido*[3, 2-d]*pyrimidine* (**7a**)

A mixture of **6a** (183 mg, 1.11 mmole), benzylamine (250 mg, 2.33 mmole), and ethanol (10 m*l*) was refluxed for 2 hr. Purification by the column chromatography afforded an oil (183 mg, 70%), which was crystallized from benzene to give needles, mp. 81°C. IR (KBr) 3300 (NH), 1605, 1590, 1585 (C=N, C=C), 1350 cm^{-1}; ^1H NMR (DMSO-d6) 4.81 (2H, d, J=6 Hz, N-CH_2), 7.3–7.5 (5H, phenyl), 7.84 (1H, dd, J=8.4, 4.2 Hz, 7-H), 8.13 (1H, dd, J=8.4, 1.7 Hz, 8-H), 8.51 (1H, s, 2-H), 8.82 (1H, dd, J=4.2, 1.7 Hz, 6-H), 9.04 (1H, braod, NH); MS: m/z 236 (M^+).

4-*Isoamylaminopyrido*[3, 2-*d*]*pyrimidine* (**7b**)

A mixture of **6a** (183 mg, 1.11 mmole), isoamylamine (217 mg, 2.49 mmole) and ethanol (20 m*l*) was refluxed for 2 hr. Chromatographic separation on silica gel gave **7b** as an oil (167 mg, 70%). IR (neat) 3320 (NH), 1600, 1590 (C=N, C=C), 1365 cm^{-1}; ^1H NMR (DMSO-d6) 0.99 (6H, d, J=6 Hz, $-CH_3\times2$), 1.5–1.9 (3H, m, $-CH_2-CH=$), 3.59 (2H, m, N-CH_2), 7.83 (1H, dd, J=8.3, 4.2 Hz, 7-H), 8.11 (1H, dd, J=8.3, 1.7 Hz, 8-H), 8.46 (1H, braod, NH), 8.50 (1H, s, 2-H), 8.79 (1H, dd, J=4.2, 1.7 Hz, 6-H); MS: m/z 216 (M^+). The picrate was prepared as usual manner and recrystallized from ethanol, mp. 168–169°C.

2-*Methyl*-4-*benzylaminopyrido*[3, 2-*d*]*pyrimidine* (**7c**)

A mixture of **6b** (359 mg, 2.0 mmole), benzylamine (458 mg, 4.27 mmole) and ethanol (10 m*l*) was refluxed for 30 min. After purification by the column chromatography, **7c** was obtained as an oil (468 mg, 94%). IR (neat) 3430 (NH), 1605, 1590, 1585 (C=N, C=C), 1345 cm^{-1}; ^1H NMR (DMSO-d6) 0.93 (6H, d, J=6 Hz, $-CH_3\times2$), 1.3–1.8 (3H, m, $-CH_2-CH=$), 2.47 (3H, s, $-CH_3$), 3.57 (2H, m, N-CH_2), 7.73 (1H, dd, J=8.4, 4.2 Hz, 7-H), 7.97 (1H, dd, J=8.4, 1.4 Hz, 8-H), 8.21 (1H, t, braod, NH), 8.67 (1H, dd, J=4.2, 1.4 Hz, 6-H); MS: m/z 230 (M^+). Recrystallization of the picrate from aqueous methanol gave yellow crystalline mass, mp. 141–142°C.

4-*Benzylaminopyrido*[2, 3-*d*]*pyrimidine* (**9a**)

A mixture of **8a** (183 mg, 1.11 mmole), benzylamine (149 mg, 1.39 mmole), and ethanol (5 m*l*) was refluxed for 5 hr. After workup above, crystalline product (210 mg, 80%) was obtained. Recrystallization from aqueous ethanol gave **9a** as needles, mp. 264–266°C (Lit.[17] 249–252°C). IR (KBr) 3250 (NH), 1605, 1580, 1570 (C=N, C=C), 1335 cm^{-1}; ^1H NMR (DMSO-d6) 4.83 (2H, d, J=6 Hz, N-CH_2), 7.57 (1H, dd, J=8.2, 4.5 Hz, 6-H), 8.62 (1H, s, 2-H), 8.78 (1H, dd, J=8.2, 2.0 Hz, 5-H), 9.00 (1H, dd, J=4.5 Hz, 2.0 Hz, 7-H), 9.10 (1H, t, braod, NH); MS: m/z 236 (M^+).

4-Isoamylaminopyrido[2, 3-*d*]*pyrimidine* (**9b**)

A mixture of **8a** (183 mg, 1.11 mmole), isoamylamine (196 mg, 2.25 mmole) and ethanol (5 ml) was refluxed for 1 hr. After workup above, crystalline product (199 mg, 83%) was obtained. Recrystallization from aqueous ethanol gave colorless needles, mp. 197–198°C. IR (KBr) 3250 (NH), 1610, 1590, 1575 (C=N, C=C), 1340 cm^{-1}; ^1H NMR (DMSO-d6) 0.93 (6H, d, J=6Hz, $-CH_3 \times 2$), 1.3–1.8 (3H, m, $-CH_2-CH=$), 3.57 (2H, m, $N-CH_2$), 7.53 (1H, dd, J=8.2, 4.5 Hz, 6–H), 8.48 (1H, t, braod, NH), 8.58 (1H, s, 2–H), 8.68 (1H, dd, J=8.2, 2.0 Hz, 5–H), 8.94 (1H, dd, J=4.5, 2.0 Hz, 7–H); MS: m/z 216 (M^+).

2-Methyl-4-benzylaminopyrido[2, 3-*d*]*pyrimidine* (**9c**)

A mixture of 8b (300 mg, 1.67 mmole), benzylamine (381 mg, 3.56 mmole) and ethanol (10 ml) was refluxed for 1 hr. Similarly, crystalline mass, mp. 190°C (439 mg) was obtained. Recrystallization from aqueous methanol gave colorless needles, mp. 198–199°C (368 mg, 88%). IR (KBr) 3270 (NH), 1610, 1595, 1585 (C=N, C=C), 1345 cm^{-1}; ^1H NMR (DMSO-d6) 2.47 (3H, s, $-CH_3$), 4.82 (2H, m, $N-CH_2$), 7.2–7.5 (5H, phenyl), 7.47 (1H, dd, J=8.2, 4.5 Hz, 6–H), 8.70 (1H, dd, J=8.2, 2.0 Hz, 5–H), 8.94 (1H, dd, J=4.5, 2.0 Hz, 7–H), 8.94 (1H, braod, NH); MS: m/z 250 (M^+).

2-Methyl-4-isoamylaminopyrido[2, 3-*d*]*pyrimidine* (**9d**)

A mixture of **8b** (300 mg, 1.67 mmole), isoamylamine (305 mg, 3.50 mmole) and ethanol (10 ml) was refluxed for 1 hr. After workup above, crude product was recrystallized from aqueous methanol to give colorless needles, mp. 137–138°C (358 mg, 93%). IR (KBr) 3270 (NH), 1610, 1580, 1575 (C=N, C=C), 1340 cm^{-1}; ^1H NMR (DMSO-d6) 0.93 (6H, d, J=6 Hz, $-CH_3 \times 2$), 1.3–1.8 (3H, m, $-CH_2-CH=$), 2.46 (3H, s, $-CH_3$), 7.42 (1H, dd, J=8.2, 4.5 Hz, 6–H), 8.29 (1H, t, braod, NH), 8.64 (1H, dd, J=8.2, 2.0 Hz, 5–H), 8.87 (1H, dd, J=4.5, 2.0 Hz, 7–H); MS: m/z 230 (M^+).

General Procedure for amination using hexamethyldisilazane

Amination of 2-methylpyridopyrimidin-4(3H)-ones **2b** and **3b** by this method was made as reported[2,3,4]. A mixture of the 4(3H)-one (1.0 mmole), amine (3.0 mmole), hexamethyldisilazane (3.0 mmole) and ammonium sulfate (0.1 mmole) was refluxed for 5 hr. To the mixture was added ethanol (10 ml) and the solution was refluxed for 15–30 min. The solvent was evaporated and the residue was purified by the column chromatography as mentioned above (**7e** and **7d**) or by crystallization from water (**9c** and **9d**).

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摘　　要

4-置換及び2,4-二置換ピリド[3,2-d]ピリミジン，ピリド[2,3-d]-ピリミジン及びキナゾリン類の合成

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アデニン型サイトカイニン類縁体としての4-置換アミノピリド[3,2-d]ピリミジン，ピリド[2,3-d]ピリミジン及びキナゾリンを4-クロル体を経由する従来の2段階反応により行なった。4-クロル体とアミンとの反応は円滑に進行したが，4(3H)-オンのクロル化の収率が悪く，4-置換アミノ体の合成法として問題であった。そこで4(3H)-オンより1段階で4-置換アミノ体を得る合成法について検討した。ヘキサメチルジシラザンを用いるVorbrüggenらの方法により，簡便かつ高収率で目的物を合成できることが判った。

ひもげいとう色素形成テスト及びレタス発芽テストによりサイトカイニン活性を調べたが，いづれの化合物も活性を示さなかった。これらの結果よりピリドピリミジン環の5位及び8位の窒素は6位の窒素と同様，活性の発現に寄与しないことが明らかになった。