A One-step Preparation of Pyrido[3,4-*d*]pyrimidine Ring System by Reaction of 5-Formyl-1,3,6-trimethylpyrimidine-2,4(1*H*,3*H*)-dione with Primary Amines [1]

Michihiko Noguchi*, Kazushige Sakamoto,
Seiji Nagata and Shoji Kajigaeshi

Department of Industrial Chemistry, Faculty of Engineering, Yamaguchi University,
Tokiwadai, Ube 755, Japan

Received July 16, 1987

6,7-Dihydropyrido[3,4-*d*]pyrimidine-2,4(1*H*,3*H*)-diones were obtained in high yields from the reaction of 5-formyl-1,3,6-trimethylpyrimidine-2,4(1*H*,3*H*)-dione (**1**) and primary amines. For this pyridopyrimidine synthesis the following reaction pathway is proposed; the [1,5]-hydrogen shift of **1** gives a 5,6-dihydro-5,6-dimethylenepyrimidine-2,4(1*H*,3*H*)-dione intermediate. The cycloaddition reaction of the intermediate with aldimines from **1** and the primary amines affords 5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidine-2,4(1*H*,3*H*)-diones, which are dehydrated to the final products.

J. Heterocyclic Chem., **25**, 205 (1988).

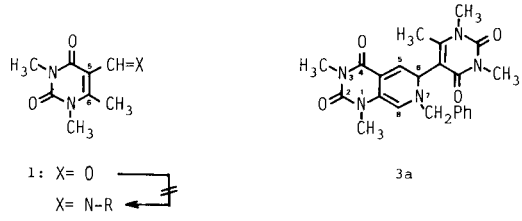
Although much attention has been focused on the pharmacological potentialities of pyrido[3,4-*d*]pyrimidine derivatives [2], their preparations *via* the pyrimidine ring construction onto pyridine ones seem to be considerably limited [3].

In a previous paper [4], we reported a facile preparation of the fused pyrido[2,3-*d*]pyrimidine derivatives *via* the pyridine ring construction onto pyrimidine ones, in which the intramolecular 1,3-dipolar addition of nitrile imines in a pyrimidine system was involved. In a series of our investigations on the preparation of pyridopyrimidines, we wish to report here a novel synthesis of pyrido[3,4-*d*]pyrimidine derivatives. For this pyridopyrimidine synthesis the cycloaddition reaction of 5,6-dihydro-5,6-dimethylenepyrimidine-2,4(1*H*,3*H*)-dione intermediate, from 5-formyl-1,3,6-trimethylpyrimidine-2,4(1*H*,3*H*)-dione, with aldimines will be described.

Results and Discussion.

In order to prepare the imines of 5-formyl-1,3,6-trimethylpyrimidine-2,4(1*H*,3*H*)-dione (**1**), the reaction of **1** with primary amines in some refluxing solvents under dehydrating conditions were surveyed to afford only disappointing results. However, the examination of the reaction by thin-layer chromatography (tlc) showed that a simple reaction took place at room temperature [5]; on standing of an equimolar mixture of **1** and benzylamine (**2a**) in dry tetrahydrofuran (THF) for 5 days gave yellow crystalline product **3a** in 74% yield as a sole product.

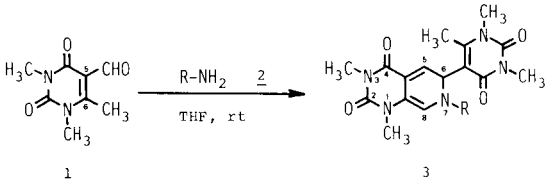
The results of its elemental analysis and mass spectrum indicated that the molecular formula of **3a** was consistent with those of the product extruding two molar water from the 2:1 adduct of **1** and **2a**. The structure of **3a** was deduced to be 7-benzyl-6,7-dihydro-6-(1′,2′,3′,4′-tetrahydro-1′,3′,6′-trimethyl-2′,4′-dioxopyrimidin-5′-yl)-1,3-dimethylpyrido-[3,4-*d*]pyrimidine-2,4-(1*H*,3*H*)-dione on the basis of



the following spectral data; in ^{1}H nmr spectrum an olefin proton signal at δ 7.66 as singlet and two vicinal proton signals at δ 3.80 and 6.40 as AB quartet (J_{AB} = 4 Hz) were found together with methyl (3H x 5), methylene (2H), and phenyl proton signals (5H). The ^{13}C nmr spectrum showed seven sp^3-carbon signals at δ 16.5 (q), 27.4 (q), 28.5 (q), 29.7 (q), 31.8 (q), 56.2 (d) and 58.7 (t), in which the latter two signals were assignable to the carbons at the 6-position and at the benzyl methylene, respectively.

Table 1

Reaction of **1** with Primary Amines **2**.

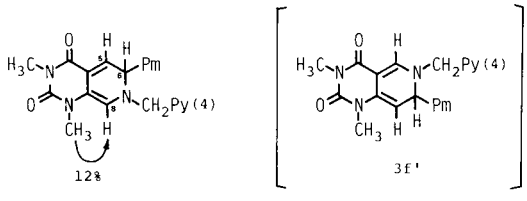


Reactant	R	R. conditions Time/day	product	Yield/% [a]
2a	CH_2Ph	5	**3a**	74
2b	Ph	7	**3b**	74
2c	*n*-Bu	5	**3c**	96
2d	CH_2-CH=CH_2	5	**3d**	78
2e	CH_2-Py(3)	5	**3e**	81
2f	CH_2-Py(4)	7	**3f**	63
2g	$CH_2CO_2C_2H_5$	5	**3g**	95
2h	CH_2CN	7	**3h**	56

[a] All isolated yields.

Similarly, the reaction of **1** with aniline (**2b**), butylamine (**2c**), allylamine (**2d**), 3-aminomethylpyridine (**2e**), and 4-aminomethylpyridine (**2f**) gave the corresponding pyrido[3,4-*d*]pyrimidine derivatives **3b-3f** in high yields. Fuctionalized amines such as ethyl glycinate (**2g**) and glycinonitrile (**2h**) also reacted with **1** to give the same type of products, **3g** and **3h**. These results are summarized in Table 1.

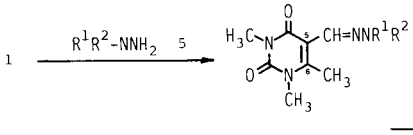
The regiochemistry of the fusing pyridine ring was confirmed by considerations using molecular models and the measurement of nuclear Overhauser effect (nOe) of **3f**. Among its four methyl proton signals at δ 3.1 to 3.5 due to *N*-methyl ones, the irradiation of the signal at δ 3.13 only resulted in *ca.* 12% nOe enhancement of the olefin proton signal at δ 7.88 (8-H, singlet), but no nOe enhancement of the signals at δ 4.05 and 6.34 (6- and 5-H, each doublet) (Figure 1). This means that another possible structure for **3**, pyrido[4,3-*d*]pyrimidine derivative **3′**, was ruled out.



Pm: 1,2,3,4-tetrahydro-1,3,6-trimethyl-2,4-dioxopyrimidin-5-yl

Figure 1. NOE Results for **3f**. %: Enhancement of signal area.

On the other hand, the reaction of **1** with secondary amines such as diethylamine and piperidine gave the same product **4** [6] including none of the amine moieties. The reaction of *N*,*N*-dimethylhydrazine (**5a**) and phenylhydrazine (**5b**) expecting the formation of 7-amino-substituted pyrido[3,4-*d*]pyrimidines gave the corresponding hydrazones, **6a** and **6b**. This indicates that the pyridopyrimidine synthesis from **1** is characteristic of the reaction with primary amines.



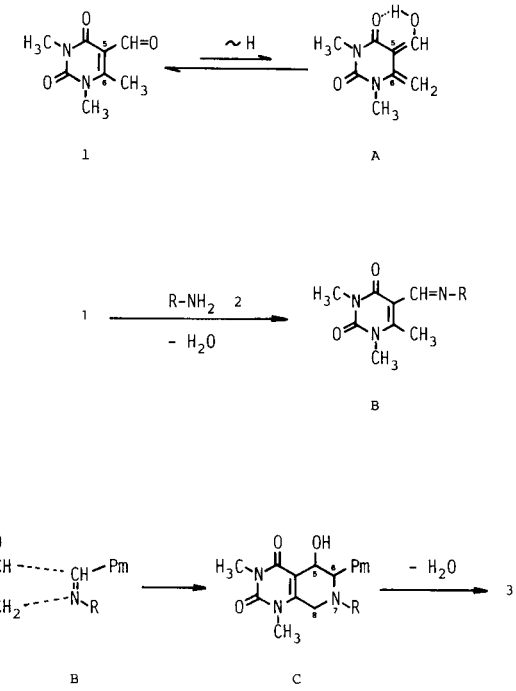
	R^1	R^2
a:	Me	Me
b:	Ph	H

6

A pathway for this pyridopyrimidine synthesis can be explained by assuming the equilibrium between the 5-formyl-6-methylpyrimidine-2,4(1*H*,3*H*)-dione (**1**) and the 5,6-dihydro-5,6-dimethylenepyrimidine-2,4(1*H*,3*H*)-dione **A** [7], which is formed *via* a [1,5]-sigmatropic hydrogen shift of **1** and can be stabilized by the formation of an intramolecular hydrogen bond between the hydroxyl hydrogen atom and the carbonyl oxygen atom at the 4-position. The cycloaddition reaction between the diene moiety of **A** and the aldimines **B** is a key reaction to afford the 5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidine-2,4(1*H*,3*H*)-dione **C**, which is converted to **3** by the successive dehydration as shown in Scheme 1.

As well-know, simple imines are unreactive in intermolecular [4+2] cycloaddition reactions [8] and only few examples of the Diels-Alder reaction have been found in the reaction with exceptionally reactive dienes such as *ortho*-quinone methides [9,10]. The formation of the pyrido[3,4-*d*]pyrimidine system indicated the intermediacy of a preformed 5,6-dihydro-5,6-dimethylenepyrimidine-2,4(1*H*,3*H*)-dione derivative. However, the regiochemistry

Scheme 1



on the cycloaddition reaction of **A** and **B** was different from that of an *ortho*-quinodimethane, derived from 1-hydroxybenzocyclobutene, and 3,4-dihydroisoquinoline [9]. Therein, the regiochemistry was controlled by the electron-donating hydroxyl group on the methylene moiety. Further investigations on this respect are under progress.

In conclusion, the generation of quinodimethane-like intermediate **A** from **1** was performed smoothly at room temperature in the presence of imines and the cycloaddition reaction of **A** with the imines turned out to be available to preparation of pyrido[3,4-*d*]pyrimidine derivatives.

EXPERIMENTAL

General.

All melting points are uncorrected. The ir spectra were recorded on a JASCO IRA-1 spectrometer as potassium bromide pellets. The pmr spectra were measured on a JEOL-MH-100 or Hitachi R-600 spectrometer for *ca.* 5-10% solution with tetramethylsilane as an internal standard; chemical shifts are expressed in δ values. The cmr spectra and nOe measurements were obtained by a JEOL FX-100 spectrometer. The mass spectra were determined with a JEOL JMS-D mass spectrometer equipped with a direct inlet and at an ionization energy of 75 eV. The elemental analyses were performed on a Hitachi 026 CHN analyzer. The tlc was accomplished on 0.2 mm precoated plates on silica gel 60 F-254 (Merck). Visualization was made with ultraviolet light (254 and 365 nm). For the preparative column chromatography, Wakogel C-300 (Wako Pure Chemical Industries LTD) was used.

General Procedure for the Reaction of 5-Formyluracil **1** with Primary Amine **2**.

An equimolar (3 mmoles) mixture of **1** [11] and benzylamine (**2a**) in dry THF (30 ml) was stirred at room temperature for 5 days. The solvent was evaporated to dryness and the residue was subjected to column chromatography over silica gel to give 0.48 g (74% yield based on **1**) of **3a** as an eluent of chloroform-ethyl acetate (4:1).

7-Benzyl-1,3-dimethyl-6-(1′,2′,3′,4′-tetrahydro-1′,3′,6′-trimethyl-2′,4′-dioxopyrimidin-5′-yl)pyrido[3,4-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (**3a**).

This compound was obtained as yellow needles (benzene-ethanol); mp 198-200°; ir: 1620 (CO) cm^{-1}; pmr (deuteriochloroform): δ 2.12 (s, 3H, $-CH_3$), 3.00, 3.14, 3.20, 3.24 (4s, 3H each, $>N-CH_3$), 3.80 (d, 1H, 6-H, J = 4 Hz), 4.08, 4.32 (2d, 1H each, $-CH_2-Ph$, J = 15 Hz), 6.40 (d, 1H, 5-H, J = 4 Hz), 7.2-7.4 (m, 5H, phenyl), 7.66 (s, 1H, 8-H); cmr (deuteriochloroform): δ (off resonance) 16.5 (q), 27.4 (q), 28.5 (q), 29.7 (q), 31.8 (q), 56.2 (d), 58.7 (t), 86.1 (d), 90.3 (s), 114.9 (s), 127.9 (d), 128.6 (d), 128.8 (d), 132.4 (s), 135.8 (s), 147.7 (d), 151.5 (s), 151.9 (s), 155.3 (s), 161.6 (s), 162.3 (s); ms: m/z (relative intensity) 435 (M^+, 16), 344 ($M^+ - CH_2Ph$, base peak), 285 (5), 217.5.

Anal. Calcd. for $C_{23}H_{25}N_5O_4$: C, 63.43; H, 5.79; N, 16.08. M, 435. Found: C, 63.49; H, 5.83; N, 15.96.

The results of the reaction of **1** with primary amines **2** are listed in Table 1.

1,3-Dimethyl-7-phenyl-6-(1′,2′,3′,4′-tetrahydro-1′,3′,6′-trimethyl-2′,4′-dioxopyrimidin-5′-yl)pyrido[3,4-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (**3b**).

This compound was obtained as yellow needles (benzene-ethanol); mp 194-195°; ir: 1620 (CO) cm^{-1}; pmr (deuteriochloroform): δ 2.40 (s, 3H, $-CH_3$), 3.16, 3.28, 3.30, 3.36 (4s, 3H each, $>N-CH_3$), 4.14 (d, 1H, 6-H, J = 4 Hz), 7.18 (d, 1H, 5-H, J = 4 Hz), 7.2-7.4 (m, 5H, phenyl), 7.84 (s, 1H, 8-H); cmr (deuteriochloroform): δ (off resonance) 16.1 (q), 27.5 (q), 28.5 (q), 29.8 (q), 31.9 (q), 55.4 (d), 87.7 (d), 93.2 (s), 115.2 (s), 119.8 (d), 126.6 (d), 129.8 (d), 131.5 (s), 143.1 (s), 114.1 (d), 151.7 (s), 153.5 (s), 162.0 (s); ms: m/z (relative intensity) 421 (M^+, 91), 344 ($M^+ - Ph$, base peak), 268 (60).

Anal. Calcd. for $C_{22}H_{23}N_5O_4$: C, 62.69; H, 5.50; N, 16.62. M, 421. Found: C, 62.66; H, 5.49; N, 16.59.

7-Butyl-1,3-dimethyl-6-(1′,2′,3′,4′-tetrahydro-1′,3′,6′-trimethyl-2′,4′-dioxopyrimidin-5′-yl)pyrido[3,4-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (**3c**).

This compound was obtained as yellow needles (benzene), mp 170-171°; ir: 1630 (CO) cm^{-1}; pmr (deuteriochloroform): δ 0.92 (t, 3H, $-CH_3$, J = 7 Hz), 1.2-1.8 (m, 6H, $-CH_2-$), 2.40 (s, 3H, $-CH_3$), 3.08, 3.18, 3.32, 3.48 (4s, 3H each, $>N-CH_3$), 3.92 (d, 1H, 6-H, J = 4 Hz), 6.44 (d, 1H, 5-H, J = 4 Hz), 7.42 (s, 1H, 8-H); cmr (deuteriochloroform): δ 13.6, 16.5, 19.7, 27.4, 28.6, 29.7, 32.1, 53.5, 54.8, 85.4, 89.5, 115.0, 132.7, 147.4, 152.0, 154.7, 162.0, 162.5; ms: m/z (relative intensity) 401 (M^+, 22), 344 ($M^+ - C_4H_9$, base peak), 248 (22), 200.5.

Anal. Calcd. for $C_{20}H_{27}N_5O_4$: C, 59.83; H, 6.78; N, 17.45. M, 401. Found: C, 59.86; H, 6.85; N, 17.33.

7-Allyl-1,3-dimethyl-6-(1′,2′,3′,4′-tetrahydro-1′,3′,6′-trimethyl-2′,4′-dioxopyrimidin-5′-yl)pyrido[3,4-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (**3d**).

This compound was obtained as yellow needles (benzene-ethanol), mp 182-183°; ir: 1630 (CO) cm^{-1}; pmr (deuteriochloroform): δ 2.50 (3H, s, $-CH_3$), 3.12, 3.20, 3.36, 3.56 (4s, 3H each, $>N-CH_3$), 3.76 (d, 2H, $-CH_2-CH=$, J = 6 Hz), 4.04 (d, 1H, 6-H, J = 4 Hz), 5.0-5.4 (m, 2H, $=CH_2$), 5.6-6.0 (m, 1H, $-CH=$), 6.44 (d, 1H, 5-H, J = 4 Hz), 7.58 (s, 1H, 8-H); ms: m/z (relative intensity) 385 (M^+, 9), 344 ($M^+ - C_3H_5$, 7), 232 (7), 248 (11), 192 (9), 41 ($C_3H_5^+$, base peak).

Anal. Calcd. for $C_{19}H_{23}N_5O_4$: C, 59.21; H, 6.02; N, 18.17. M, 385. Found: C, 59.16; H, 6.04; N, 18.39.

1,3-Dimethyl-6-(1′,2′,3′,4′-tetrahydro-1′,3′,6′-trimethyl-2′,4′-dioxopyrimidin-5′-yl)-7-(3′-pyridylmethyl)pyrido[3,4-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (**3e**).

This compound was obtained as yellow needles (benzene); mp 197-198°; ir: 1630 (CO) cm^{-1}; pmr (deuteriochloroform): δ 2.30 (s, 3H, $-CH_3$), 3.08, 3.22, 3.35, 3.38 (4s, 3H each, $>N-CH_3$), 3.90 (d, 1H, 6-H, J = 4 Hz), 4.20 (s, 2H, $-CH_2-Py$), 6.32 (d, 1H, 5-H, J = 4 Hz), 7.1-7.3, 7.5-7.6 (m, 1H each, pyridyl), 7.62 (s, 1H, 8-H), 8.4-8.6 (m, 2H, pyridyl); ms: m/z (relative intensity) 436 (M^+, 8), 344 ($M^+ - CH_2Py$, base peak), 283 (13), 230 (8).

Anal. Calcd. for $C_{22}H_{24}N_6O_4$: C, 60.54; H, 5.54; N, 19.26. M, 436. Found: C, 60.48; H, 5.50; N, 19.33.

1,3-Dimethyl-6-(1′,2′,3′,4′-tetrahydro-1′,3′,6′-trimethyl-2′,4′-dioxopyrimidin-5′-yl)-7-(4′-pyridylmethyl)pyrido[3,4-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (**3f**).

This compound was obtained as yellow needles (benzene), mp 195-197°; ir: 1630 (CO) cm^{-1}; pmr (deuteriochloroform): δ 2.40 (s, 3H, $-CH_3$), 3.13, 3.24, 3.32, 3.48 (4s, 3H each, $>N-CH_3$), 4.04 (d, 1H, 6-H, J = 4 Hz), 4.36 (s, 2H, $-CH_2-Py$), 6.34 (d, 1H, 5-H, J = 4 Hz), 7.4 (d, 2H, pyridyl, J = 5 Hz), 7.88 (s, 1H, 8-H), 8.68 (d, 2H, pyridyl, J = 5 Hz); ms: m/z (relative intensity) 436 (M^+, 7), 344 ($M^+ - CH_2Py$, base peak), 283 (8), 230 (11).

Anal. Calcd. for $C_{22}H_{24}N_6O_4$: C, 60.54; H, 5.54; N, 19.26. M, 436. Found: C, 60.55; H, 5.68; N, 19.38.

7-Ethoxycalbonylmethyl-1,3,-dimethyl-6-(1′,2′,3′,4′-tetrahydro-1′,3′,6′-trimethyl-2′,4′-dioxopyrimidin-5′-yl)pyrido[3,4-*d*]pyrimidine-2,4-(1*H*,3*H*)-dione (**3g**).

This compound was obtained as yellow needles (benzene), mp 187-189°; ir: 1750 (ester CO), 1630 (CO) cm^{-1}; pmr (deuteriochloroform): δ 1.16 (t, 3H, $-CH_3$, J = 7 Hz), 2.24 (s, 3H, $-CH_3$), 3.11, 3.22, 3.34, 3.48 (4s, 3H each, $>N-CH_3$), 3.70, 3.88 (2d, 1H each, $-CH_2-$, J = 14 Hz), 3.96 (d, 1H, 6-H, J = 4 Hz), 4.16 (t, 2H, $-CH_2-$, J = 7 Hz), 6.46 (d, 1H, 5-H, J = 4 Hz), 7.50 (s, 1H, 8-H); ms: m/z (relative intensity) 431 (M^+, 11), 344 ($M^+ - CO_2C_2H_5$, base peak), 278 (24), 250 (24), 193 (14).

Anal. Calcd. for $C_{20}H_{25}N_5O_6$: C, 55.67; H, 5.84; N, 16.23. M, 431. Found: C, 55.52; H, 5.83; N, 16.17.

7-Cyanomethyl-1,3-dimethyl-6-(1′,2′,3′,4′-tetrahydro-1′,3′,6′-trimethyl-2′,4′-dioxopyrimidin-5′-yl)pyrido[3,4-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (**3h**).

This compound was obtained as yellow needles (benzene), mp 223-225°; ir: 2230 (CN), 1620 (CO) cm^{-1}; pmr (deuteriochloroform): δ 2.50 (s, 3H, $-CH_3$), 3.16, 3.26, 3.40, 3.56 (4s, 3H each, $>N-CH_3$), 4.12 (s, 2H, $-CH_2-CN$), 4.24 (d, 1H, 6-H, J = 4 Hz), 6.54 (d, 1H, 5-H, J = 4 Hz), 7.70 (s, 1H, 8-H); ms: m/z (relative intensity) 384 (M^+, 41), 358 ($M^+ - CN$, 11), 344 ($M^+ - CH_2CN$, base peak), 231 (21), 202 (11), 139 (10).

Anal. Calcd. for $C_{18}H_{20}N_6O_4$: C, 56.24; H, 5.24; N, 21.87. M, 384. Found: C, 56.15; H, 5.25; N, 21.71.

General Procedure for the Reaction of 5-Formyluracil **1** with Hydrazine **5**.

An equimolar (5 mmoles) mixture of **1** and *N,N*-dimethylhydrazine (**5a**) in dry THF (40 ml) was stirred at room temperature for 4 days. The solvent was evaporated to dryness and the residue was recrystallized from benzene to give 0.90 g (80%) of the hydrazone **6a**.

1,2,3,4-Tetrahydro-1,3,6-trimethyl-2,4-dioxo-5-pyrimidinecarbaldehyde Dimethylhydrazone (**6a**).

This compound was obtained as colorless needles, mp 131-132°; ir: 1685, 1660 (CO and >C=N-) cm^{-1}; pmr (deuteriochloroform): δ 2.60 (s, 3H, $-CH_3$), 2.90 (s, 6H, $-N(CH_3)_2$), 3.36, 3.48 (2s, 3H each, >N-CH_3), 7.32 (s, 1H, -CH=N-).

Anal. Calcd. for $C_{10}H_{16}N_4O_2$: C, 53.55; H, 7.19; N, 24.99. M, 224. Found: C, 53.31; H, 7.15; N, 24.76.

1,2,3,4-Tetrahydro-1,3,6-trimethyl-2,4-dioxo-5-pyrimidinecarbaldehyde Phenylhydrazone (**6b**).

This compound was obtained as pale yellow prisms (benzene) in 81% yield, mp 227-229°; ir: 3260 (NH), 1680, 1620 (CO and >C=N-) cm^{-1}; pmr (deuteriochloroform and dimethyl sulfoxide-d_6): δ 2.76 (s, 3H, $-CH_3$), 3.32, 3.48 (2s, 3H each, >N-CH_3), 6.6-7.3 (m, 6H, phenyl and >NH), 8.02 (s, 1H, -CH=N-).

Anal. Calcd. for $C_{14}H_{16}N_4O_2$: C, 61.75; H, 5.92; N, 20.58. M, 272. Found: C, 61.81; H, 5.90; N, 20.50.

Acknowledgment.

The authors wish to thank Professors Masashi Tashiro and Hitoshi Takeshita, Institute of Advanced Material Study, Kyushu University, for the elemental analyses and the measurement of nOe.

REFERENCES AND NOTES

[1] Studies on Pyridopyrimidines. **III**. Part **II** of this series: M. Noguchi, S. Nagata, and S. Kajigaeshi, *Heterocycles*, **26**, 2355 (1987).

[2a] R. L. Jacobs, U. S. Patent 3,635,973; *Chem. Abstr.*, **76**, 113254y (1972); [b] S. Yurugi and A. Miyake, Japanese Kokai 74 36,700; *Chem. Abstr.*, **81**, 120689a (1974); [c] A. L. J. Beckwith, U. S. Patent 3,887,552; *Chem. Abstr.*, **83**, 147504q (1975); [d] Z. Ozdowska and B. Szczycinski, *Rocz. Chem.*, **50**, 1771 (1976); *Chem. Abstr.*, **86**, 155590s (1977); [e] J. Heider, German Offen. DE 3,220,898; *Chem. Abstr.*, **100**, 103384r (1984).

[3] D. J. Berry, J. D. Cook, and B. J. Wakefield, *J. Chem. Soc., Perkin Trans. 1*, 2190 (1972); K-Y. Tserng and L. Bauer, *J. Heterocyclic Chem.*, **9**, 1433 (1972); J. H. Maguire and R. L. McKee, *J. Org. Chem.*, **39**, 3434 (1974); M. Debeljak-Suster, B. Stanovnik, M. Tišler, and Z. Zrimsek, *J. Org. Chem.*, **43**, 393 (1978); J. H. Maguire and R. L. McKee, *J. Heterocyclic Chem.*, **16**, 133 (1979). Also see refs [2a], [2c], and [2e].

[4] M. Noguchi, S. Nagata, and S. Kajigaeshi, *Chem. Pharm. Bull.*, **34**, 3994 (1986).

[5] The reaction was carried out cleanly at room temperature (below 18°), but elevated room temperatures (above 25°) provided undesirable results; a lowering of the yields of **3** and an appearance of other side reactions.

[6] This compound was obtained as precipitates in these reactions (above 82% yield).

4: Colorless crystals, mp 184-185° dec; ir: 3300 (OH), 1705, 1690, 1635 (CO) cm^{-1}; ms: m/z (relative intensity) 364 (M^+), 346 ($M^+ - H_2O$, 43), 331 (10), 328 (8), 320, 246 (8), 183 (19), 182 (22), 154 (base peak).

Anal. Calcd. for $C_{16}H_{20}N_4O_6$: C, 52.74; H, 5.53; N, 15.38. M, 364. Found: C, 52.67; H, 5.51; N, 15.20.

This compound **4** was corresponded to a dimer of **1**. However, its structural confirmation was not accomplished because of its insolubility for most solvents.

[7] Recently, Senda *et al.* [12] reported the preparation of lithium dienolate of **A**, which cycloadded to electron-deficient olefins and acetylenes to yield quinazoline derivatives.

[8] For reviews: S. M. Weinreb and J. I. Levin, *Heterocycles*, **12**, 949 (1979); S. M. Weinreb and R. S. Staib, *Tetrahedron*, **21**, 3087 (1982).

[9] T. Kametani, Y. Katoh, K. Fukumoto, *J. Chem. Soc., Perkin Trans. 1*, 1712 (1974); T. Kametani, T. Takahashi, and K. Fukumoto, *ibid.*, 737 (1975).

[10] W. Oppolzer, *Angew. Chem., Int. Ed. Engl.*, **11**, 1031 (1972).

[11] S. Senda, K. Hirota, G-N. Yang, and M. Shiraishi, *Yakugaku Zasshi*, **91**, 1372 (1971).

[12] S. Senda, T. Abe, I. Sugiyama, and K. Hirota, *Tetrahedron Letters*, **21**, 531 (1980).