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Synthesis and Covalent Hydration of 4*H*-Pyrimido[1,6-*a*]pyrimidines

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Ethyl 4-oxypyrimido[1,6-*a*]pyrimidine-3-carboxylates (**4**) were prepared by the thermal cyclization of diethyl *N*-(4-pyrimidinyl)aminomethylenemalonates (**3**) in which no substituent was present at position 2. Some of the compounds **4** readily afforded stable covalent hydrates which proved to be ethyl 6,7-dihydro-6-hydroxy-4-oxypyrimido[1,6-*a*]pyrimidine-3-carboxylates (**9**) formed by the addition of a molecule of water across the 6,7 C=N bond in **4**. This hydration was affected by the electronic character of the substituent at position 8 in the 4*H*-pyrimido[1,6-*a*]pyrimidine ring.

Keywords—4*H*-pyrimido[1,6-*a*]pyrimidine; pyrido[2,3-*d*]pyrimidine; *N*-(4-pyrimidinyl)aminomethylenemalonate; thermal cyclization; orientation of cyclization; covalent hydration

In earlier studies on the pyrido[2,3-*d*]pyrimidine antibacterials,²⁻⁴⁾ thermal cyclization of diethyl *N*-(2-substituted 4-pyrimidinyl)aminomethylenemalonates (**3**) proved to be a fruitful source for the synthesis of the pyrido[2,3-*d*]pyrimidine ring system (**5**) and led to the finding of piromidic acid (**1a**)^{2a)} and pipemidic acid (**1b**)³⁾ as antibacterial agents. However, cyclization of the malonate (**3**: R₁=H) bearing no substituent at position 2 in the pyrimidine ring has not been much studied so far. The only reported reaction involves the cyclization of diethyl *N*-(4-acetamido-6-pyrimidinyl)aminomethylenemalonate (**3**: R₁=H, R₂=NHCOCH₃) to give ethyl 8-acetamido-4-oxypyrimido[1,6-*a*]pyrimidine-3-carboxylate (**4**: R₁=H, R₂=NHCOCH₃).⁵⁾ Our interest in the cyclization of **3** where R₁ is hydrogen and in the chemistry of the little known 4*H*-pyrimido[1,6-*a*]pyrimidine (**4**) has led us to carry out an additional work in this area.

The requisite diethyl *N*-(4-pyrimidinyl)aminomethylenemalonates (**3a—d**) were readily prepared by condensation of the corresponding 4-aminopyrimidines (**2a—d**) with diethyl ethoxymethylenemalonate. The structures of **3** were supported by the nuclear magnetic resonance (NMR) spectra which showed, in common, a pair of doublets around δ 11.0 and 9.1 with the same coupling constant ($J=12$ Hz); upon D₂O exchange the signals at δ 11.0 disappeared and a doublet at δ 9.1 collapsed to a sharp singlet, permitting assignment of the former to the NH proton and the latter to the adjacent olefinic proton.

When the malonates (**3a—d**) were heated in Dowtherm A at 253—255°, cyclization occurred always at the ring nitrogen atom to give the corresponding ethyl 4-oxypyrimido[1,6-*a*]pyrimidine-3-carboxylates (**4a—d**) in preference to the isomeric ethyl 5,8-dihydro-5-oxopyrido[2,3-*d*]pyrimidine-6-carboxylates (**5**). This is consistent with the result obtained by Rizkalla *et al.*⁵⁾ Proof of the structure of **4** was based on the appearance of three 1-proton singlets due to aromatic-type protons in the NMR spectra. Only two such protons would be expected if **5** had been afforded. Based on this finding, together with previous results,^{2,4,5)}

1) Location: Enoki-cho 33-94, Suita, Osaka 564, Japan.

2) a) S. Minami, T. Shono, and J. Matsumoto, *Chem. Pharm. Bull.*, **19**, 1426 (1971); b) *Idem, ibid.*, **19**, 1482 (1971).

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Chart 1

it is concluded that the orientation of thermal cyclization of **3** depends upon whether or not a substituent is present at position 2 in the pyrimidine ring; if $\text{R}_1 \neq \text{H}$, the pyrido[2,3-*d*]pyrimidine (**5**) is produced, and if $\text{R}_1 = \text{H}$, the pyrimido[1,6-*a*]pyrimidine (**4**) is produced. It is known that the same situation prevails in the cyclization of diethyl *N*-(2-pyridinyl)aminomethylene-malonates (**6**) under the same conditions.⁶⁾ Recently Hermecz *et al.*⁷⁾ demonstrated that the initial products of the thermal cyclization of **6** are pyrido[1,2-*a*]pyrimidines (**7**), which

Chart 2

- 6) J.T. Adams, C.K. Bradsher, D.S. Breslow, S.T. Amore, and C.R. Hauser, *J. Am. Chem. Soc.*, **68**, 1317 (1946); G.R. Lappin, *ibid.*, **70**, 3348 (1948); R. Adams and I.J. Pachter, *ibid.*, **74**, 5491 (1952).
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then, if R_1 is not hydrogen, isomerize thermally into 1,8-naphthyridines (8). At present, we have no basis for judging whether or not the cyclization of the *N*-(2-substituted 4-pyrimidinyl)aminomethylenemalonate (3: $R_1 \neq H$), which has previously been studied,^{2,4} always proceeds through 4 ($R_1 \neq H$) as an intermediate by analogy with 6 ($R_1 \neq H$). Attempts to isomerize 4a—d into the corresponding pyrido[2,3-*d*]pyrimidines (5: $R_1 = H$) failed.

The pyrimido[1,6-*a*]pyrimidines (4) have lower melting points and are more soluble in organic solvents as compared with the corresponding pyrido[2,3-*d*]pyrimidines (5).² The 8-unsubstituted (4a) and 8-methylpyrimido[1,6-*a*]pyrimidines (4b) were stable in the absence of water, but were susceptible to moisture in air or solvents, readily giving the covalent hydrates 9a and 9b, respectively. In contrast, the 8-methoxy- (4c) and 8-(1-pyrrolidinyl)pyrimido[1,6-*a*]pyrimidines (4d) remained essentially unchanged even when exposed to water.

TABLE I. NMR Spectral Data for Ethyl 4-Oxopyrimido[1,6-*a*]pyrimidine-3-carboxylates (4) and Their Covalent Hydrates (9) in DMSO-*d*₆ at 100 MHz

Compd.	Chemical shifts (ppm)						Coupling constants (Hz)			
	C ₂ -H	C ₆ -H	C ₈ -H [C ₈ -CH ₃]	C ₉ -H	N ₇ -H	C ₆ -OH	$J_{6,9}$	$J_{8,9}$	$J_{6,NH}$	$J_{8,NH}$
4a	8.85(s)	9.75(d)	8.62(d)	7.68(d-d)	—	—	1	6	—	—
4b	8.81(s)	9.63(d)	[2.58(s)]	7.56(d)	—	—	1	—	—	—
9a	8.52(s)	8.45(d)	7.55(d-d)	5.47(d)	11.56(br. s) ^{a)}	12.74(br. s) ^{b)}	—	9	4	11
9b	8.51(s)	8.76(d)	[2.33(s)]	5.26(s)	12.10(d)	12.75(very br. s)	—	—	9	—

Abbreviations: s, singlet; d, doublet; d-d, doublet of doublets; br. s, broad singlet.

a) Half-height width $W_{1/2}$ = 12 Hz.

b) Half-height width $W_{1/2}$ = 8 Hz.

The assigned structure 9 for the hydrate was supported by the following evidence. The molecular ion peaks in the mass (MS) spectra of 9a and 9b appeared at m/e 237 and 251, respectively, corresponding to the empirical formulas C₁₀H₁₁N₃O₄ (9a) and C₁₁H₁₃N₃O₄ (9b), which are consistent with the addition of H₂O to 4a and 4b, respectively. The NMR spectrum of 9a (Table I) showed double doublets at δ 7.55 (1H, J = 9 and 11 Hz) which, on irradiation at δ 5.47, changed to a doublet (J = 11 Hz) and further, on irradiation at δ 11.56, changed to a doublet (J = 9 Hz) with a concomitant change of a doublet at δ 8.45 (J = 4 Hz) into a broad singlet ($W_{1/2}$ = 3 Hz). On addition of D₂O the signal at δ 7.55 appeared again as a doublet (J = 9 Hz) and the doublet at δ 8.45 collapsed to a singlet, together with the disappearance of the two broad singlets at δ 11.56 (N₇-H) and 12.74 (C₆-OH). Similarly, in the NMR spectrum of 9b, irradiation of a singlet at δ 2.33 (3H, C₈-CH₃) enhanced the sharpness of a singlet at δ 5.26 (1H, C₉-H), indicating the presence of a long-range coupling between them and confirming the assignment. Upon either irradiation at δ 12.10 (N₇-H) or addition of D₂O, a doublet at δ 8.76 (1H, J = 9 Hz) collapsed to a singlet, thus being assignable to C₆-H. These data were fully in accord with the assigned structure 9 for the hydrate, corresponding to the covalent addition of a molecule of water across the 6,7 C=N bond in the pyrimido[1,6-*a*]pyrimidine (4).

Further confirmation of the structure was provided by chemical transformations. Thus, mild hydrolysis of 9 with aqueous 4% sodium hydroxide followed by careful neutralization with acetic acid gave enamines (10), which on treatment with 5% hydrochloric acid afforded the corresponding carbonyl compounds (11). Treatment of 9 with dilute hydrochloric acid also gave 11. Structural assignments for 10 and 11 were based on their IR, NMR, and MS spectral data and elemental analyses. Dehydration of 9b into 4b was accomplished effectively by refluxing a suspension of 9b in dry chloroform. However, attempts to dehydrate 9a

under various conditions including sublimation under high vacuum were unsuccessful, always resulting in recovery of the unchanged hydrate (**9a**).

The easy formation of the covalent hydrate (**9**) in the neutral species of **4** is probably due to the electron-attracting effect of the 3-ethoxycarbonyl and 4-oxo groups which causes an increase in the positive character of the carbon atom at position 6. Stabilization of **9** may occur through an intramolecular hydrogen-bonding between the 4-oxo and 6-hydroxyl groups. However, the presence of a methoxyl or pyrrolidinyl group at position 8 as in **4c** or **4d**, respectively, inhibits the hydration of the 6,7 C=N bond, probably because such electron-donating groups oppose the electronic influence of the ethoxycarbonyl and oxo functions on C₆; this is in good agreement with the upfield shift of the C₆-H resonances of **4c** and **4d** compared with those of **4a** and **4b** in the NMR spectra (Table IV).

Although covalent hydration of a C=N bond has been found in many nitrogen-containing heterocycles,⁸⁾ the only reported example in a fused-ring system with a bridgehead nitrogen atom is the irreversible formation of 5,6-dihydro-5-hydroxytetrazolo[1,5-*c*]pyrimidine (**13**) from tetrazolo[1,5-*c*]pyrimidine (**12**).⁹⁾ Our present work provides an example of a new type of covalent hydration in such heterocyclic ring systems.

Experimental

All melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were recorded on a Hitachi model 215 spectrophotometer and UV spectra were taken with a Shimadzu MPS-5000 spectrophotometer. NMR spectra were recorded on a Varian HA-100D or A-60 spectrometer with Me₄Si as an internal standard. Mass spectra were recorded on a Hitachi RMU-6 mass spectrometer using the direct inlet system at 70 eV ionization potential.

4-Aminopyrimidines (2a—d)—The following compounds were prepared by the procedures described in the literature; 4-amino- (**2a**),¹⁰⁾ 4-amino-6-methyl- (**2b**),¹¹⁾ 4-amino-6-methoxy- (**2c**),¹²⁾ and 4-amino-6-(1-pyrrolidinyl)-pyrimidine (**2d**).¹³⁾

General Procedure for the Preparation of Diethyl N-(4-pyrimidinyl)aminomethylenemalonates (3a—d)—An equimolar mixture of the 4-aminopyrimidine (**2a—d**) and diethyl ethoxymethylenemalonate was heated

TABLE II. Diethyl N-(4-Pyrimidinyl)aminomethylenemalonates

Compd.	R ₂	mp (°C)	Recrystn. solvent	Yield (%)	Formula	Analysis (%)		
						Calcd (Found)		
						C	H	N
3a	H	83—84	EtOH-H ₂ O	95	C ₁₂ H ₁₅ N ₃ O ₄	54.33 (54.22)	5.70 5.63	15.84 15.87
3b	CH ₃	101—102	EtOH	87	C ₁₃ H ₁₇ N ₃ O ₄	55.90 (56.04)	6.14 6.14	15.05 14.72
3c	CH ₃ O	109—111	EtOH	80	C ₁₃ H ₁₇ N ₃ O ₅	52.87 (52.67)	5.80 5.90	14.23 14.29
3d	N-	107—108	EtOH	96	C ₁₆ H ₂₂ N ₄ O ₄	57.47 (57.20)	6.63 6.54	16.76 16.57

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at 120—140° with stirring for 3 hr, during which period the EtOH formed was removed by distillation. After cooling the mixture, the resulting solid was collected and recrystallized from an appropriate solvent to give the corresponding malonate (3a—d). Analytical and physical data are given in Table II.

Ethyl 4-Oxopyrimido[1,6-*a*]pyrimidine-3-carboxylate (4a) and Ethyl 8-Methyl-4-oxopyrimido[1,6-*a*]pyrimidine-3-carboxylate (4b)—The malonate 3a or 3b (3.0 g) was added to 25 ml of Dowtherm A at 253—255°, then the mixture was kept at the same temperature for 40 or 15 min, respectively. The solvent was evaporated off under reduced pressure to leave the crude product, which, upon recrystallization from an appropriate dry solvent, gave 4a (1.27 g) or 4b (2.03 g). Analytical and physical data are given in Table III. NMR, IR, and UV spectral data are listed in Table IV; see also Table I for NMR spectral data.

Ethyl 8-Methoxy-4-oxopyrimido[1,6-*a*]pyrimidine-3-carboxylate (4c) and Ethyl 8-(1-Pyrrolidinyl)-4-oxopyrimido[1,6-*a*]pyrimidine-3-carboxylate (4d)—The malonate 3c or 3d (1.0 g) was added to 10 ml of Dowtherm A at 253—255°, then the mixture was kept at the same temperature for 10 min, cooled to about 50°, and diluted with 10 ml of *n*-hexane. The precipitate was collected and recrystallized from an appropriate solvent, giving 4c (0.66 g) or 4d (0.21 g), respectively. Analytical and physical data are given in Table III. NMR, IR, and UV spectral data are listed in Table IV.

TABLE III. Ethyl 4-Oxopyrimido[1,6-*a*]pyrimidine-3-carboxylates

Compd.	R ₂	mp (°C)	Recrystn. solvent	Yield (%)	Formula	Analysis (%)		
						Calcd	Found	
						C	H	N
4a	H	99—100	AcOEt	69	C ₁₀ H ₉ N ₃ O ₃	54.79 (55.06)	4.14 3.97	19.17 19.41
4b	CH ₃	154—156 (dec.)	AcOEt	81	C ₁₁ H ₁₁ N ₃ O ₃	56.65 (56.95)	4.75 4.63	18.02 18.10
4c	CH ₃ O	156—157	MeOH	75	C ₁₁ H ₁₁ N ₃ O ₄	53.01 (52.86)	4.45 4.44	16.86 17.14
4d	N-	234—236	EtOH	82	C ₁₄ H ₁₆ N ₄ O ₃	58.32 (58.48)	5.59 5.75	19.44 19.23

TABLE IV. Spectral Data for Ethyl 4-Oxopyrimido[1,6-*a*]pyrimidine-3-carboxylates

Compd.	NMR (CDCl ₃ , 60 MHz) ppm (<i>J</i> in Hz)				IR (KBr) ν cm ⁻¹ (CO)	UV $\lambda_{\text{max}}^{\text{CHCl}_3}$ nm (log ϵ)
	C ₂ -H	C ₆ -H	C ₉ -H	C ₈ -H		
4a	9.07 (s)	9.93 (d, <i>J</i> =1)	7.54 (d-d, <i>J</i> =1, 6)	8.56 (d, <i>J</i> =6)	1730, 1710, 1695	246(3.27), 353(4.17), 364 _{sh} (4.08)
4b	9.03 (s)	9.98 (d, <i>J</i> =1)	7.36 (d, <i>J</i> =1)	—	1740, 1710, 1680	351(4.23), 362(4.22)
4c	8.95 (s)	9.81 (d, <i>J</i> =1)	6.85 (d, <i>J</i> =1)	—	1720, 1700, 1680	356(4.39), 364(4.38)
4d	8.81 (s)	9.55 (s)	6.18 (s)	—	1740, 1705, 1670	254(3.88), 339 _{sh} (4.29), 368(4.44), 384(4.36)

Abbreviations: s, singlet; d, doublet; d-d, doublet of doublets; sh, shoulder.

Ethyl 6,7-Dihydro-6-hydroxy-4-oxopyrimido[1,6-*a*]pyrimidine-3-carboxylate (9a)—Compound 4a (1.0 g) was heated until it dissolved in 10 ml of 95% EtOH; the resulting precipitate was collected and recrystallized from EtOH to give 0.97 g (89.6%) of 9a, mp 231—232°, as colorless fine needles. IR $\nu_{\text{max}}^{\text{Nujol}}$ cm⁻¹: 3350—3200 (NH), 2750—2350 (chelated OH), 1735, 1660 (C=O). NMR spectral data are given in Table I. MS *m/e*: 237 (M⁺), 219 (M⁺—H₂O). Anal. Calcd for C₁₀H₁₁N₃O₄: C, 50.63; H, 4.67; N, 17.72. Found: C, 50.66; H, 4.68; N, 17.76.

Ethyl 6,7-Dihydro-6-hydroxy-8-methyl-4-oxopyrimido[1,6-*a*]pyrimidine-3-carboxylate (9b)—a) Using the procedure described for 9a, 1.0 g of 4b provided 0.98 g (90.6%) of 9b, mp 198—199°, as colorless fine needles. IR $\nu_{\text{max}}^{\text{Nujol}}$ cm⁻¹: 3200—3100 (NH), 2750—2350 (chelated OH), 1710—1675 (C=O). NMR spectral

data are given in Table I. MS m/e : 251 (M^+), 233 ($M^+ - H_2O$). Anal. Calcd for $C_{11}H_{13}N_3O_4$: C, 52.58; H, 5.22; N, 16.73. Found: C, 52.65; H, 5.09; N, 16.54.

b) At room temperature 1.0 g of **4b** was dissolved in 15 ml of aqueous 1% NaOH. The solution was stirred for 10 min, during which period a precipitate resulted, then the mixture was adjusted to pH 6.5 with AcOH. The precipitate was collected and washed with EtOH to give 0.96 g (88.7%) of **9b**.

Conversion of 9b into 4b—A suspension of 200 mg of **9b** in 80 ml of dry $CHCl_3$ was heated under reflux, gradually becoming a clear solution; the course of the reaction was monitored by TLC [solvent system: $CHCl_3$ -EtOH (10:1 v/v)]. After refluxing for 7 hr, the mixture was filtered to remove insoluble material and the filtrate was concentrated to dryness under reduced pressure. The residual solid was recrystallized from AcOEt to give 140 mg (65.3%) of **4b**.

Ethyl 2-(2-Aminovinyl)-1,4-dihydro-4-oxopyrimidine-5-carboxylate (10a)—A solution of 200 mg of **9a** in 12 ml of aqueous 4% NaOH was allowed to stand for 15 min at room temperature and then adjusted to pH 6.5 with AcOH to give a yellow precipitate, which, upon recrystallization from EtOH, gave 40 mg (22.7%) of **10a**, mp 199–201° (dec.), as greenish-yellow prisms. IR ν_{max}^{KBr} cm^{-1} : 3400–3300 (NH), 1725, 1715sh (C=O). The NMR spectrum could not be determined because of the poor solubility of this compound in organic solvents. MS m/e : 209 (M^+). Anal. Calcd for $C_9H_{11}N_3O_3$: C, 51.67; H, 5.30; N, 20.09. Found: C, 51.51; H, 5.28; N, 19.79.

Ethyl 2-(2-Aminopropenyl)-1,4-dihydro-4-oxopyrimidine-5-carboxylate (10b)—Using the procedure described for **10a**, 400 mg of **9b** provided 270 mg (76%) of **10b**, mp 257–261°, as greenish-yellow plates. IR ν_{max}^{KBr} cm^{-1} : 3350 (NH), 1710sh, 1680 (C=O). NMR (DMSO- d_6) δ : 11.54 (1H, br.s, NH), 9.20, 7.90 (each 1H, very br., NH), 8.40 (1H, s, C_6 -H), 4.68 (1H, s, =CH-), 1.98 (3H, s, = $\overset{|}{C}$ -CH₃), 4.15 (2H, q, $J=7$ Hz, OCH₂-CH₃), 1.22 (3H, t, $J=7$ Hz, OCH₂CH₃). MS m/e : 223 (M^+). Anal. Calcd for $C_{10}H_{13}N_3O_3$: C, 53.80; H, 5.87; N, 18.83. Found: C, 53.56; H, 5.71; N, 18.43.

Ethyl 1,2,3,4-Tetrahydro-4-oxo-2-(2-oxoethylidene)pyrimidine-5-carboxylate (11a)—Compound **9a** (100 mg) was dissolved in 2 ml of 10% HCl with heating, then the solution was cooled quickly to about 10° and adjusted to pH 6.0 with saturated aqueous NaHCO₃. The precipitate was collected, washed with water, and recrystallized from EtOH to give 45 mg (50.8%) of **11a** as prisms, mp ca. 193° (dec.). IR ν_{max}^{KBr} cm^{-1} : 1720sh, 1710, 1665 (C=O). NMR (DMSO- d_6) δ : ca. 12.0 (2H, very br., $2 \times$ NH), 8.85 (1H, br.s, $W_{1/2}=8$ Hz; on irradiation at δ 5.13, s, CHO), 8.31 (1H, s, C_6 -H), 5.13 (1H, d, $J=3.8$ Hz, =CH-), 4.18 (2H, q, $J=7$ Hz, OCH₂CH₃), 1.33 (3H, t, $J=7$ Hz, OCH₂CH₃). MS m/e : 210 (M^+). Anal. Calcd for $C_9H_{10}N_2O_4$: C, 51.42; H, 4.80; N, 13.31. Found: C, 51.53; H, 4.85; N, 13.14.

Ethyl 1,2,3,4-Tetrahydro-4-oxo-2-(2-oxopropylidene)pyrimidine-5-carboxylate (11b)—a) Compound **9b** (200 mg) was dissolved in 2 ml of 5% HCl with heating for several minutes; it immediately formed a precipitate which was collected, washed with water, and recrystallized from DMF-H₂O to give 95 mg (53.2%) of **11b** as prisms, mp ca. 255° (dec.). IR ν_{max}^{KBr} cm^{-1} : 1710sh, 1700sh, 1690sh, 1675sh, 1655 (C=O). NMR (DMSO- d_6) δ : ca. 13.0 (1H, br. s, NH), ca. 11.0 (1H, br.s, NH), 8.32 (1H, br.s, C_6 -H), 5.11 (1H, s, =CH- $\overset{|}{C}$ =O), 1.99 (3H, s, COCH₃), 4.16 (2H, q, $J=7$ Hz, OCH₂CH₃), 1.22 (3H, t, $J=7$ Hz, OCH₂CH₃). MS m/e : 224 (M^+), 43 ($CH_3C\equiv O^+$). Anal. Calcd for $C_{10}H_{12}N_2O_4$: C, 53.57; H, 5.39; N, 12.50. Found: C, 53.58; H, 5.52; N, 12.43.

b) A mixture of 120 mg of **10b** in 5 ml of 5% HCl and 1 ml of EtOH was stirred at room temperature for 5 min. The resulting precipitate was collected, washed successively with water and EtOH, and recrystallized from DMF to give 80 mg (66.4%) of **11b**.

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