Pyrimidines. LII [1]. Synthesis of Pyrido[2,3-*d*]pyrimidine-2,4-diones and Pyrido[2,3-*d*:6,5-*d'*]dipyrimidine-2,4,6,8-tetrones

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Reactivities of 5-dimethylaminomethylene-6-imino-1,3-dimethyluracil hydrochloride (**1**) toward a variety of active methylene compounds **2** and **5** were investigated. Treatment of **1** with active methylene compounds such as malononitrile and ethyl cyanoacetate in the presence of triethylamine gave pyrido[2,3-*d*]pyrimidine-2,4-dione derivatives **3**. Reaction of **1** with barbituric acids resulted in the formation of pyrido[2,3-*d*:6,5-*d'*]dipyrimidine-2,4,6,8-tetrone derivatives **6**.

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Synthetic studies on fused pyrimidines have been documented extensively in connection with the biologically important purines and pteridines. 6-Aminouracil derivatives have been employed as a convenient starting material for the preparation of not only purines [2] and pteridines [3] but also a variety of fused pyrimidines such as pyrrolo[2,3-*d*]pyrimidines [4,5], thiazolo[3,4-*d*]pyrimidines [6,7], pyrido[2,3-*d*]pyrimidines [5,8-10], pyrimido[4,5-*d*]pyrimidines [7,10-12], pyrimido[4,5-*b*][1,3]thiazines [12], pyrimido[4,5-*b*]indoles [13], pyrimido[5,4-*g*]pteridines [14], and pyrido[2,3-*d*:6,5-*d'*]dipyrimidines [15]. Recently, we found [16] that 5-dimethylaminomethylene-6-imino-1,3-dimethyluracil hydrochloride (**1**) (the Vilsmeier intermediate) obtained with ease by the Vilsmeier reaction of 6-amino-1,3-dimethyluracil was an useful intermediate for the preparation of pyrimido[4,5-*d*]pyrimidine derivatives. During our investigation on the synthesis of fused pyrimidines by use of the Vilsmeier intermediate **1**, we now found a versatile and convenient method for the preparation of pyrido[2,3-*d*]-pyrimidines **3** and pyrido[2,3-*d*:6,5-*d'*]dipyrimidines **6** by reaction of **1** with active methylene compounds.

Reaction of **1** with malononitrile (**2a**) and triethylamine in ethanol at room temperature for 2 hours afforded 7-amino-6-cyano-1,3-dimethylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (**3a**) in 82% yield. The structure of **3a** was presumed by microanalysis and spectral data. Further treatment of **3a** with sodium nitrite in aqueous solution of acetic acid easily led to the formation of 1,3-dimethylpyrido[2,3-*d*]pyrimidine-2,4,7(1*H*,3*H*,8*H*)-trione (**4**), which was identical with an authentic sample previously prepared [9]. Analo-

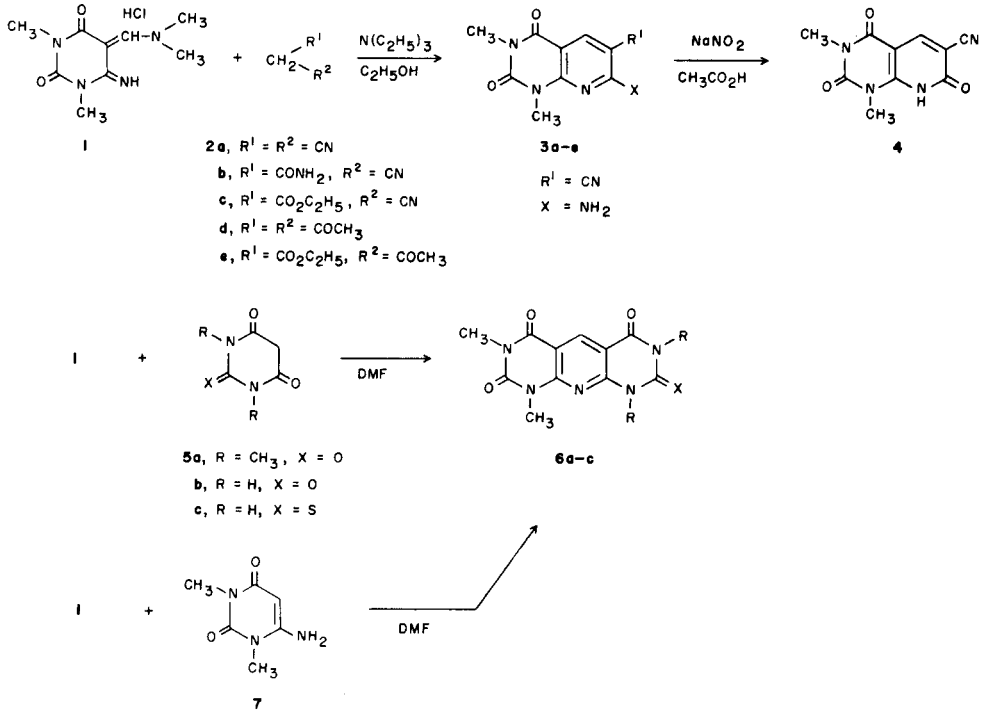

Table 1

Physical Data of Pyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione

Compound No.	R¹	X	Yield %	Mp, °C (Recryst Solvent)	Molecular Formula	Analysis % Calcd./(Found) C	H	N
3a	CN	NH_2	82	> 300 [a] (CH_3CO_2H)	$C_{10}H_9N_5O_2$	51.94 (51.72	3.92 3.95	30.29 30.36)
3b	$CONH_2$	NH_2	74	> 300 (DMF)	$C_{10}H_{11}N_5O_3$	48.19 (48.39	4.45 4.41	28.10 27.85)
3c	$CO_2C_2H_5$	NH_2	83	220 (C_2H_5OH)	$C_{12}H_{14}N_4O_4$	51.79 (51.99	5.07 5.11	20.14 20.20)
3d	$COCH_3$	CH_3	42	151 (C_2H_5OH)	$C_{12}H_{13}N_3O_3$	58.29 (58.42	5.30 5.41	17.00 17.07)
3e	$CO_2C_2H_5$	CH_3	58	123 (C_2H_5OH)	$C_{13}H_{15}N_3O_4$	56.31 (56.08	5.45 5.45	15.16 15.28)

[a] Lit mp 354° [10a].

Table 2

Physical Data of Pyrido[2,3-*d*:6,5-*d'*]dipyrimidine-2,4,6,8(1*H*,3*H*,7*H*,9*H*)-tetrone

Compound No.	R¹	X	Yield %	Mp, °C (Recryst Solvent)	Molecular Formula	Analysis % Calcd./(Found) C	H	N
6a	CH_3	O	91	> 300 (DMF)	$C_{13}H_{13}N_5O_4$	51.48 (51.69	4.32 4.23	23.09 23.04)
6b	H	O	76	> 300 (H_2O)	$C_{11}H_9N_5O_4$	48.00 (48.17	3.30 3.38	25.45 25.33)
6c	H	S	67	> 300 [a]	$C_{11}H_9N_5O_3S$	45.36 (45.28	3.11 3.20	24.04 24.08)

[a] Recrystallization not possible. Washed with boiling DMF.

gous reaction of **1** with active methylene compounds such as cyanoacetamide (**2b**), ethyl cyanoacetate (**2c**), acetylacetone (**2d**), and ethyl acetoacetate (**2e**) gave the corresponding pyrido[2,3-*d*]pyrimidines **3b-e**, respectively, in good yields (Table 1).

Subsequently, barbituric acid derivatives were employed as active methylenes. Heating of **1** with 1,3-dimethylbarbituric acid (**5a**) in dimethylformamide (DMF) at reflux temperature for 1 hour gave 1,3,7,9-tetramethylpyrido-[2,3-*d*:6,5-*d'*]dipyrimidine-2,4,6,8(1*H*,3*H*,7*H*,9*H*)-tetrone (**6a**) in 91% yield. Alternatively, **6a** could be obtained in 46% yield by the reaction of **1** with 6-amino-1,3-dimethyluracil (**7**) in refluxing DMF for 12 hours. Under the same conditions, reaction of **1** with barbituric acid (**5b**) and 2-thiobarbituric acid (**5c**) gave the corresponding pyridodipyrimidines **6b** and **6c** in 76% and 67% yield, respectively (Table 2).

EXPERIMENTAL

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. Nuclear magnetic resonance spectra were recorded on a Hitachi Perkin-Elmer R-20B spectrometer (60 MHz) using tetramethylsilane as an internal standard. Chemical shifts are reported as δ values in parts per million (ppm). Mass spectra were taken on a JEOL JMS-D300 machine operating at 70 eV. Elemental analyses were carried out at the Microanalytical Laboratory of our university.

General Procedure for 6,7-Disubstituted Pyrido[2,3-*d*]pyrimidine-2,4-(1*H*,3*H*)-diones **3a-e** (Table 1).

Triethylamine (490 mg, 4.9 mmoles) was added to a suspension of **1** (4.1 mmoles) [16] and an active methylene compound **2** (4.1 mmoles), such as malononitrile (**2a**), cyanoacetamide (**2b**), ethyl cyanoacetate (**2c**), acetyl acetone (**2d**), and ethyl acetoacetate (**2e**), in ethanol (30 ml) under ice-cooling with stirring. The mixture was stirred for 1-2 hours at room temperature and the resulting precipitate was collected by filtration to give the product **3**. Recrystallization from an appropriate solvent gave an analytically pure sample.

7-Amino-6-cyano-1,3-dimethylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (**3a**).

This compound had ^{1}H-nmr (trifluoroacetic acid): δ ppm 3.60 (3H, s), 3.80 (3H, s), and 8.73 (1H, s).

7-Amino-6-carbamoyl-1,3-dimethylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (**3b**).

This compound had ^{1}H-nmr (trifluoroacetic acid): δ ppm 3.60 (3H, s), 3.87 (3H, s), and 9.36 (1H, s).

7-Amino-6-ethoxycarboylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (**3c**).

This compound had ^{1}H-nmr (hexadeuteriodimethyl sulfoxide): δ ppm 1.35 (3H, t, J = 7 Hz), 3.18 (3H, s), 3.38 (3H, s), 4.27 (2H, q, J = 7 Hz), 7.93 (2H, br s), and 8.31 (1H, s).

6-Acetyl-1,3,7-trimethylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (**3d**).

This compound had ^{1}H-nmr (deuteriochloroform): δ ppm 2.67 (3H, s), 2.86 (3H, s), 3.50 (3H, s), 3.74 (3H, s), and 8.77 (1H, s).

6-Ethoxycarbonyl-1,3,7-trimethylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (**3e**).

This compound had ^{1}H-nmr (deuteriochloroform): δ ppm 1.42 (3H, t, J = 7 Hz), 2.92 (3H, s), 3.50 (3H, s), 3.75 (3H, s), 4.38 (2H, q, J = 7 Hz), and 8.93 (1H, s).

Hydrolysis of **3a**.

A mixture of **3a** (115 mg) and sodium nitrite (1.0 g) in acetic acid (170 ml) and water (10 ml) was stirred for 30 minutes at room temperature. The solvent was removed under reduced pressure. The residue was treated with water and the precipitate was collected by filtration to give **4** (80 mg) [9].

General Procedure for Pyrido[2,3-*d*:6,5-*d'*]dipyrimidine-2,4,6,8(1*H*,3*H*,7*H*,9*H*)-tetrone (**5a-c**) (Table 2).

A mixture of **1** (490 mg, 2 mmoles) and **5** (2 mmoles) in DMF (7 ml) was heated at 160-170° for 30-60 minutes. After cooling the reaction solution was diluted with ethanol and the resulting precipitate was collected by filtration. Recrystallization from an appropriate solvent gave an analytically pure sample.

1,3,7,9-Tetramethylpyrido[2,3-*d*:6,5-*d'*]dipyrimidine-2,4,6,8(1*H*,3*H*,7*H*,9*H*)-tetrone (**6a**).

This compound had ^{1}H-nmr (trifluoroacetic acid): δ ppm 3.60 (6H, s), 3.88 (6H, s), and 9.36 (1H, s); ms: m/e 303 M$^+$.

1,3-Dimethylpyrido[2,3-*d*:6,5-*d'*]dipyrimidine-2,4,6,8(1*H*,3*H*,7*H*,9*H*)-tetrone (**6b**).

This compound had ^{1}H-nmr (trifluoroacetic acid): δ ppm 3.59 (3H, s), 3.82 (3H, s), and 9.30 (1H, s); ms: m/e 275 M$^+$.

1,3-Dimethylpyrido[2,3-*d*:6,5-*d'*]dipyrimidine-2,4,6(1*H*,3*H*,7*H*)-trione-8(7*H*)-thione (**6c**).

This compound had ms: m/e 291 M$^+$.

Alternative Procedure for **6a**.

A mixture of **1** (490 mg, 2 mmoles) and **7** (372 mg, 2.4 mmoles) in DMF (7 ml) was heated at 160-170° for 12 hours. After cooling the reaction solution was diluted with ethanol and the resulting precipitate was collected by filtration to give **6a** (280 mg, 46%).

REFERENCES AND NOTES

[1] Part LI: M. Yogo, K. Hirota and S. Senda, *Chem. Pharm. Bull.*, **32**, 3695 (1984).

[2] J. H. Lister, "Fused Pyrimidines, Part II Purines", D. J. Brown, ed, Wiley-Interscience, New York, 1971, Chapter II.

[3] J. Weijlard, M. Tishler and A. E. Erickson, *J. Am. Chem. Soc.*, **67**, 802 (1945); V. F. Dallacker and G. Steiner, *Ann. Chem.*, **660**, 98 (1962).

[4] C. W. Noell and R. K. Robins, *J. Heterocyclic Chem.*, **1**, 34 (1964); E. C. Taylor and E. E. Garcia, *J. Org. Chem.*, **30**, 655 (1965); H. Ogura, M. Sakaguchi and K. Takeda, *Chem. Pharm. Bull.*, **20**, 404 (1972); S. Senda and K. Hirota, *Chem. Pharm. Bull.*, **22**, 1459 (1974).

[5] Y. Tamura, T. Sakaguchi, T. Kawasaki and Y. Kita, *Heterocycles*, **3**, 183 (1975).

[6] Y. Furukawa, O. Miyashita and S. Shima, *Chem. Pharm. Bull.*, **24**, 970 (1976); Y. Furukawa and S. Shima, *Chem. Pharm. Bull.*, **24**, 979 (1976).

[7] R. Niess and H. Eilingsfeld, *Ann. Chem.*, 2019 (1974).

[8] H. Ogura and M. Sakaguchi, *Chem. Pharm. Bull.*, **21**, 2014 (1973); A. D. Broom, J. L. Shim and G. L. Anderson, *J. Org. Chem.*, **41**, 1095 (1976); S. Wawzonek, *ibid.*, **41**, 3149 (1976); F. Yoneda, M. Koga and T. Nagamatsu, *Synthesis*, 75 (1983).

[9] K. Hirota, Y. Kitade, S. Senda, M. J. Halat, K. A. Watanabe and J. J. Fox, *J. Org. Chem.*, **46**, 846 (1981).

[10a] H. Bredereck, G. Simchen, R. Wahl and F. Effenberger, *Chem. Ber.*, **101**, 512 (1968); [b] Y. Tominaga, S. Kohra, H. Okuda, A. Ushirogochi, Y. Matsuda and G. Kobayashi, *Chem. Pharm. Bull.*, **32**, 122 (1984).

[11] F. Yoneda, T. Yano, M. Higuchi and A. Koshiro, *Chem. Letters*, 155 (1979).

[12] Y. Tominaga, T. Machida, H. Okuda, Y. Matsuda and G. Kobayashi, *Yakugaku Zasshi*, **99**, 515 (1979).

[13] J.-L. Bernier and J.-P. Henichart, *J. Org. Chem.*, **46**, 4197 (1981).

[14] T. Nagamatus, E. Matsumoto and F. Yoneda, *Chem. Letters*, 1127 (1982); T. Nagamatsu, H. Yamato, K. Takai and F. Yoneda, *Synthesis*, 563 (1983).

[15] H. Bredereck, R. Effenberger and G. Simchen, *Chem. Ber.*, **97**, 1403 (1964); F. Yoneda, K. Senga and S. Nishigaki, *Chem. Pharm. Bull.*, **21**, 260 (1973); T. Nagamatsu, Y. Sakuma and F. Yoneda, *Synthesis*, 923 (1983).

[16] K. Hirota, Y. Kitade, H. Sajiki and Y. Maki, *Synthesis*, 589 (1984).