Syntheses of Some Tricyclic Heterocycles from 5,6-Diamino-1,3-dimethyluracil

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5-Amino-6-mercapto-1,3-dimethyluracil (2) was prepared by the treatment of 5,6-diamino-1,3-dimethyluracil (1) with liquid H_2S and pyridine in a sealed steel tube at 60 °C for 20 h. Thiazolo[5,4-*d*]pyrimidinediones 3a, b were obtained from 2 by cyclization with HCO_2H and AcOH.

Under stringent conditions, however, 1 was converted into the 5,9-dihydrodipyrimido[4,5-*b*:5′,4′-*e*][1,4]thiazine derivtive 4a.

The structure of 4a was confirmed by spectral (nuclear magnetic resonance and mass spectra) data and by comparison with a sample which was prepared from 2 and 5-hydroxy-1,3-dimethyluracil.

Benzylation of 4a gave 1,3,7,9-tetramethyl-5-benzyl (or *p*-bromobenzyl)-5,9-dihydrodipyrimido[4,5-*b*:5′,4′-*e*][1,4]thiazine-2,4,6,8-(1*H*,3*H*,7*H*)-tetrone (4b, c) and 1,3,7,9-tetramethyl-5-benzyl (or *p*-bromobenzyl)-5,9-dihydropyrrolo[3,2-*d*:4,5-*d*′]dipyrimidine-2,4,6,8-(1*H*,3*H*,7*H*)-tetrone (6a, b).

Keywords fused uracil; 5-amino-6-mercaptouracil; 5,9-dihydropyrrolo[3,2-*d*:4,5-*d*′]dipyrimidine-2,4,6,8(1*H*,3*H*,7*H*)tetrone; 5,9-dihydrodipyrimido[4,5-*b*:4′,5′-*e*][1,4]thiazine-2,4,6,8(1*H*,3*H*,7*H*)-tetrone; benzylation; thiazolo[5,4-*d*]pyrimidinedione; H-intra, H-extra configuration

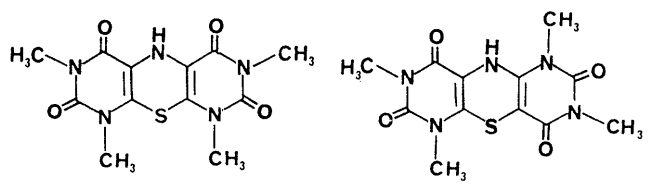
It is well known that 5,6-diamino-1,3-dimethyluracil (**1**) is a useful intermediate for the preparation of purines[1] and pteridines.[1] 5-Amino-6-mercapto-1,3-dimethyluracil[2] (**2**) could be a more useful starting material for the preparation of fused uracils if a facile synthesis of **2** was available, because the reported synthesis[2] of **2** is quite tedious.

We report herein a convenient synthesis of **2** from **1** by adaptation of the method developed by Inoue *et al.*[3] for conversion of cytidine into 4-thiouridine. We also describe the isolation and structure confirmation of an unusual tricyclic product which formed under certain conditions.

5-Amino-6-mercapto-1,3-dimethyluracil (**2**) was prepared by treatment of 5,6-diamino-1,3-dimethyluracil (**1**) with liquid H_2S and pyridine at 60 °C for 20 h in a sealed tube.[3] Compound **2** was further converted into 1,3,8-trialkyl-2,6-thiazolo[5,4-*d*]pyrimidinediones[2] (**3a, b**) upon treatment with formic or acetic acid, thus establishing the 5-amino-6-thio structure of **2**.

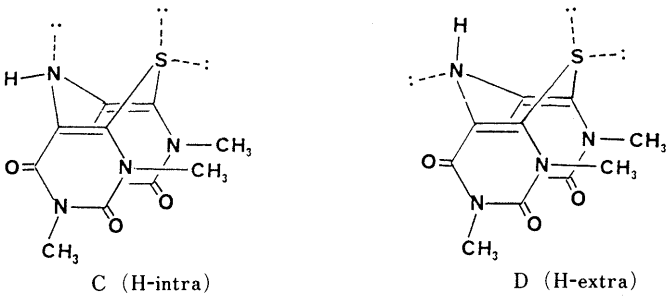
Surprisingly, the reaction of **1** with liquid H_2S in pyridine at 90 °C for 48 h in a sealed steel tube afforded a dimer [MS *m/z*: 323 (M^+)] of **2**. We have no reasonable explanation for the temperature dependence of the reaction. Two structures, A and B (Fig. 1), are possible for the dimer: A would be formed *via* a head-to-head reaction, whereas B by a head-to-tail reaction between two molecules of **2**.

In order to establish the correct structure of the product (A or B), we synthesized structure A from **2** by condensation with 5-hydroxy-1,3-dimethyluracil[4] in the presence of *N*-bromosuccinimide (NBS). Greenish yellow crystals (A) obtained in 58% yield had proton nuclear magnetic resonance (^{1}H-NMR) and mass spectra (MS) characteristics identical with those of the dimeric product **4a**.



A B

Fig. 1



C (H-intra) D (H-extra)

Fig. 2

Regarding the ^{1}H-NMR spectrum of **4a** it is noteworthy that signals due to two pairs of apparently equivalent methyl groups appeared as four (not two) separate peaks. This observation may be explained by the existence of two configurations, "H-intra (C) and H-extra (D),"[5] with respect to the proton on the bridge nitrogen (see Fig. 2) in which the two methyl groups are situated in nonequivalent magnetic environments. A similar case has been reported by Malrieu and Pullman[5b] for a phenothiazine.

In order to clarify the configuration (H-intra and H-extra), NH of **4a** was substituted by a benzyl group (*p*-bromo- or unsubstituted benzyl). Interestingly, however, the reaction afforded **4b, c** together with **6a, b** containing a five-membered ring.

It is thought that the benzyl group was bound in the extra mode at the nitrogen at position 5 on the basis of equivalent NMe × 2 and equivalent protons in the methylene moiety of the benzyl group in the ^{1}H-NMR spectrum of **4b, c**, and **4b, c** of type D might presumably be formed by approach of the benzyl group from the less crowded region around the nitrogen atom in a kinetically controlled reaction.

On the other hand, **6a, b** were produced by desulfurization of 5,9-dihydrodipyrimido[4,5-*b*:5′,4′-*e*][1,4]thiazine derivatives during the reaction. The tricycle **5** was also prepared to demonstrate the utility of the above-mentioned

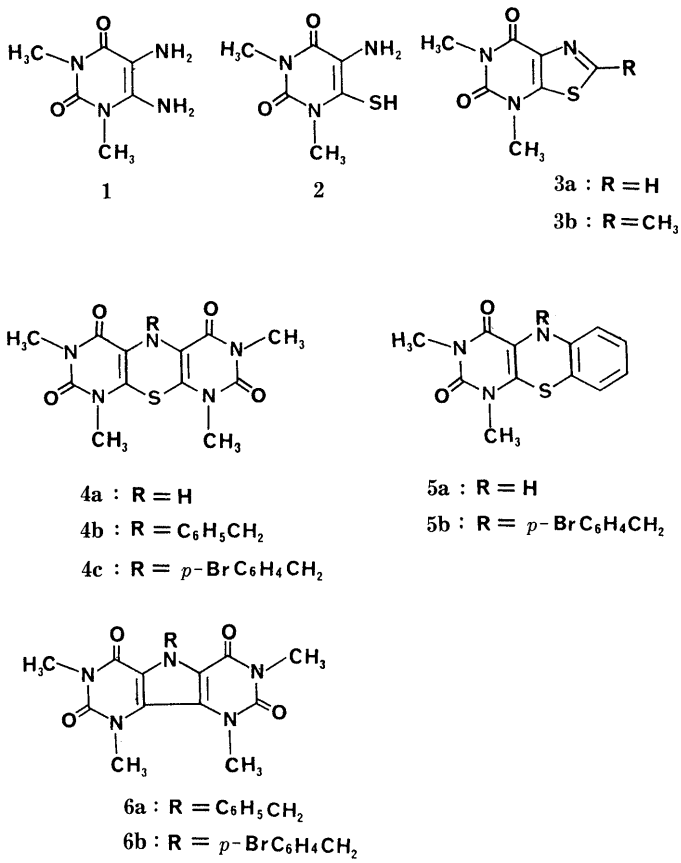


Fig. 3

reaction (see Experimental).

In summary, we have developed a facile method for the synthesis of 5-amino-6-mercapto-1,3-dimethyluracil (**2**) and **4a** from 5,6-diamino-1,3-dimethyluracil (**1**). The structure of **4a** was confirmed by an alternative synthesis. Compound **2** could be a useful starting material for the synthesis of various heterocyclic compounds.

Experimental

General Methods Melting points were determined in a capillary tube and are uncorrected. Mass spectra (MS) were recorded on a JEOL D-100 instrument. ^{1}H-NMR spectra were recorded on a Varian EM-390 NMR spectrometer with Me_4Si (TMS) as an internal standard in $CDCl_3$ or in DMSO-d_6. Microanalyses were performed by the staff in the Microanalytical Laboratory of this school. Column chromatography was performed on Wakogel C-200. Thin-layer chromatography (TLC) was performed on Kieselgel 60 GF_{254} (Merck) and spots were detected under UV light.

5-Amino-6-mercapto-1,3-dimethyluracil (2) 5,6-Diamino-1,3-dimethyluracil (**1**) (1.77 g, 10 mmol) was added to a pyridine solution (40 ml) into which hydrogen sulfide[2] (5 ml) had been introduced below −60 °C, and the mixture was stirred at 60 °C for 20 h in a sealed steel tube.

After removal of the pyridine, the residue was washed with carbon disulfide (15 ml × 2) and crystallized from CH_3CN–H_2O (2 : 1) to give yellow needles (**2**) (1.520 g, 81%), mp 278—280 °C (lit.,[2] mp 280—282 °C). MS *m/z*: 187 (M^+). ^{1}H-NMR (DMSO-d_6) δ: 3.17, 3.57 (3H each, s, N–CH_3), 3.27 (1H, s, –SH), 8.87 (2H, br, $-NH_2$). When D_2O was added, the spectrum showed only signals at 3.15 and 3.53 (3H each, s, N–CH_3).

4,6-Dimethyl-5,7-thiazolo[5,4-*d*]pyrimidinedione (3a) Treatment of 5-amino-1,3-dimethyl-6-mercaptouracil (187 mg, 1 mmol) in 90% formic acid (2 ml) in a manner similar to that described by Hager and Kaiser[2] gave **3a** (179 mg, 91%), mp 285—286 °C (lit.,[2] mp 286—286.5 °C). MS *m/z*: 211 (M^+). ^{1}H-NMR (DMSO-d_6) δ: 3.23, 3.46 (3H each, s, NCH_3 × 2), 8.74 (1H, s, =CH).

2,4,6-Trimethyl-5,7-thiazolo[5,4-*d*]pyrimidinedione (3b) A solution of **2** (178 mg, 1 mmol) in AcOH (2 ml) and Ac_2O (1.5 ml) was refluxed for 30 min, and the reaction mixture was cooled. The precipitate that formed was collected and recrystallized from MeOH to give yellow needles **3b** (194 mg, 92%), mp 196—197 °C (lit.,[2] mp 197—198 °C). MS *m/z*: 211 (M^+). ^{1}H-NMR (DMSO-d_6) δ: 2.67 (3H, s, CCH_3), 3.26, 3.46 (3H each, s, NCH_3).

1,3,7,9-Tetramethyl-5,9-dihydrodipyrimido[4,5-*b*:5′,4′-*e*][1,4]thiazine-2,4,6,8(1*H*,3*H*,7*H*)-tetrone (4a) 1) The reaction of **1** (850 mg, 5 mmol) with liquid H_2S (3 ml) in pyridine (10 ml) at 90 °C for 48 h and work-up of the reaction mixture were carried out as described above for **2** to give **4a** (444 mg, 55%) as a solid, mp 237—238 °C (from DMSO). MS *m/z*: 323.0698 (M^+). Calcd for $C_{12}H_{13}N_5O_4S$ (323.0687). ^{1}H-NMR (DMSO-d_6) δ: 3.20, 3.27, 3.41, 3.44 (3H each, s, NCH_3), 8.82 (1H, s, NH, exchangeable with D_2O).

ii) *N*-Bromosuccinimide (NBS) (178 mg, 1.1 mmol) was added to a solution of 5-hydroxy-1,3-dimethyluracil[6] (156 mg, 1 mmol) in EtOH (5 ml), and after stirring for 30 min at room temperature, 47% aqueous HBr (0.22 ml, 1 mmol) and **2** (625 mg, 5 mmol) were added to the solution, and the mixture was refluxed for 1 h. The precipitated crystalline mass was filtered off and recrystallized from MeOH to give **4a** as yellow greenish crystals (187 mg, 58%). mp 237—238 °C. MS *m/z*: 323.0694 (M^+). Calcd for $C_{12}H_{13}N_5O_4S$ (323.0687). ^{1}H-NMR (DMSO-d_6) δ: 3.20, 3.27, 3.41, 3.44 (3H each, s, NCH_3), 8.82 (1H, br, NH).

1,3-Dimethyl-1,5-dihydropyrimido[4,5-*b*][1,4]benzothiazine-2,4(3*H*)-dione (5a) NBS (979 mg, 5.5 mmol) was added to a solution of 5-hydroxy-1,3-dimethyluracil[6] (780 mg, 5 mmol) in EtOH (10 ml), and after stirring for 30 min at room temperature, 47% aqueous HBr (0.66 ml, 5 mmol) and 2-aminothiophenol (625 mg, 5 mol) were added. The reaction mixture was refluxed for 1 h.

The precipitate that formed was collected and recrystallized from MeOH to give orange columns (**5a**) (1.28 g, 98%), mp 225—227 °C. MS *m/z*: 261.0572 (M^+). *Anal.* Calcd for $C_{12}H_{11}N_3O_2S$: C, 55.17; H, 4.27; N, 16.09; S, 12.27. Found: C, 54.99; H, 4.17; N, 16.02; S, 11.98. ^{1}H-NMR (DMSO-d_6) δ: 3.20, 3.35 (3H each, s, NCH_3), 6.67—7.06 (4H, m, aromatic), 7.60 (1H, br, NH).

1,3-Dimethyl-5-*p*-bromobenzyl-1,5-dihydropyrimido[4,5-*b*][1,4]benzothiazine-2,4(3*H*)-dione (5b) A suspension of **5a** (261 mg, 1 mmol), *p*-bromobenzyl bromide (300 mg, 1.2 mmol), and K_2CO_3 (700 mg) in acetone (25 ml) was refluxed for 20 h. The filtered solution was concentrated under reduced pressure and the residual solid was subjected to preparative TLC (precoated TLC plates, Silica gel 60F-254, Merck) using benzene as the eluent to give yellow prisms (**5b**), mp 214—215 °C (from MeOH), (46%). MS *m/z*: 429, 431 (M^+). *Anal.* Calcd for $C_{19}H_{16}BrN_3O_2S$: C, 53.03; H, 3.74; N, 9.76. Found: C, 52.85; H, 3.67; N, 9.73. ^{1}H-NMR ($CDCl_3$) δ: 3.17, 3.50 (3H each, s, NCH_3), 5.08 (2H, s, $-CH_2-$), 6.90—7.46 (8H, br, aromatic).

1,3,7,9-Tetramethyl-5-benzyl-5,9-dihydrodipyrimido[4,5-*b*:5′,4′-*e*][1,4]-thiazine-2,4,6,8(1*H*,3*H*,7*H*)-tetrone (4b) and 1,3,7,9-Tetramethyl-5-benzyl-5,9-dihydropyrrolo[3,2-*d*:4,5-*d*′]dipyrimidine-2,4,6,8(1*H*,3*H*,7*H*)-tetrone (6a) Compound **4a** (488 mg, 1.5 mmol) and benzyl bromide (567 mg, 4.5 mmol) were added to a solution of NaH (180 mg, 45 mmol) in *N*,*N*-dimethylformamide (DMF) (5 ml). The solution was heated at 60 °C for 3 h, and then water (20 ml) was added. The precipitate that resulted was filtered off and recrystallized from MeOH to give yellow crystals (**4b**) (182 mg, 29%). mp 231—232 °C (dec.). MS *m/z*: 413 (M^+). *Anal.* Calcd for $C_{19}H_{19}N_5O_4S$: C, 55.20; H, 4.63; N, 16.94. Found: C, 55.05; H, 4.63; N, 16.78. ^{1}H-NMR ($CDCl_3$) δ: 3.36, 3.45 (6H each, s, $2NCH_3 \times 2$), 4.92 (2H, s, $-CH_2-$), 7.20—7.40 (5H, br, aromatic).

On the other hand, the aqueous filtrate was extracted with ether (5 ml × 3) to give colorless prisms (**6a**) (40 mg, 7%), mp 172 °C (sintering at 138 °C) (from MeOH). MS *m/z*: 381 (M^+). *Anal.* Calcd for $C_{19}H_{19}N_5O_4$: C, 59.83; H, 5.02; N, 18.36. Found: C, 59.53; H, 5.12; N, 18.21. ^{1}H-NMR ($CDCl_3$) δ: 3.39, 3.57 (6H each, s, $2NCH_3 \times 2$), 6.18 (2H, s, $-CH_2-$), 7.18—7.38 (5H, br, aromatic).

1,3,7,9-Tetramethyl-5-*p*-bromobenzyl-5,9-dihydrodipyrimido[4,5-*b*:5′,4′-*e*][1,4]thiazine-2,4,6,8(1*H*,3*H*,7*H*)-tetrone (4c) and 1,3,7,9-Tetramethyl-5-*p*-bromobenzyl-5,9-dihydropyrrolo[3,2-*d*:4,5-*d*′]dipyrimidine-2,4,6,8-(1*H*,3*H*,7*H*)-tetrone (6b) A suspension of **4a** (420 mg, 1.30 mmol), *p*-bromobenzyl bromide (1.125 g, 4.5 mmol) and K_2CO_3 (1.20 g) in acetone (30 ml) was refluxed for 20 h. The filtered solution was concentrated under reduced pressure and the residual solid was subjected to preparative TLC using a mixture of benzene–acetone (10 : 1) as the eluent to give **4c** and **6b**.

4c: Yellow prisms, (120 mg, 14%). mp 259—260 °C (from MeOH). MS *m/z*: 493, 491 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 3.35, 3.45 (6H each, s, $2NCH_3 \times 2$), 4.90 (2H, s, $-CH_2-$). 7.12 (2H, d, J = 7.5 Hz, aromatic), 7.40 (2H, d, J = 7.5 Hz, aromatic). *Anal.* Calcd for $C_{19}H_{18}BrN_5O_4S$: C, 46.35; H, 3.68; N, 14.22. Found: C, 46.13; H, 3.47; N, 14.08.

6b: White needles, (354 mg, 46%). mp 210—211 °C [from $CHCl_3$–MeOH

(1 : 1)]. *Anal.* Calcd for $C_{19}H_{18}BrN_5O_4$: C, 49.57; H, 3.94; N, 15.21. Found: C, 49.42; H, 3.88; N, 15.16. MS *m/z*: 459.461 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 3.42, 3.59 (6H each, s, $2NCH_3 \times 2$), 6.15 (2H, s, $-CH_2-$), 7.23 (2H, d, $J=6$ Hz, aromatic), 7.39 (2H, d, $J=6$ Hz, aromatic).

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