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Stable Thioaldehydes: Synthesis, Structure Assignment, and Stability of 6-Amino-5-thioformyluracils

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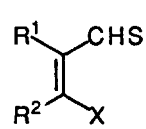
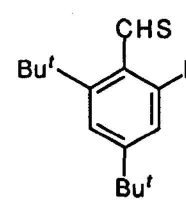
Abstract: Stable 6-amino-5-thioformyluracils **3a-e** were synthesized starting from 6-amino-1,3-disubstituted uracils **1a-e** in 23-98 % yields. According to the x-ray crystal structure, although the thioaldehyde **3c** possesses reasonable double-bond character of the C=S bond, the length of C=S bond of the thioaldehyde **3c** is longer than those of the kinetically stabilized thioaldehydes due to the mesomeric effect of the 6-amino group. Copyright © 1996 Elsevier Science Ltd

While thioaldehydes are usually unstable to be isolated as monomeric form because of their tendency to polymerize (*e.g.* cyclic trimers),[1] two types of stable monomeric thioaldehydes are known in literatures. One is stabilized by the mesomeric effect through hetero atoms (thermodynamic stabilization, **A**)[2] and the other is stabilized by the steric protection (kinetic stabilization, *e.g.* **B**).[3] A few reports on the synthesis of the thermodynamically stabilized thioaldehyde using Vilsmeier salts and sodium hydrogen sulfide (NaSH) have appeared.[2a,2l] We have previously reported the isolation of 6-imino-1,3-dimethyl-5-[(dimethylamino)methylene]-5,6-dihydrouracil hydrochloride **2**[4] (Vilsmeier salt) as a stable amorphous. This stability of the Vilsmeier salt **2** prompted us to convert it into the corresponding thioaldehyde **3** by the treatment with NaSH. We report here the one-pot synthesis, structure assignment, and stability of 6-amino-5-thioformyluracils **3a-e**.

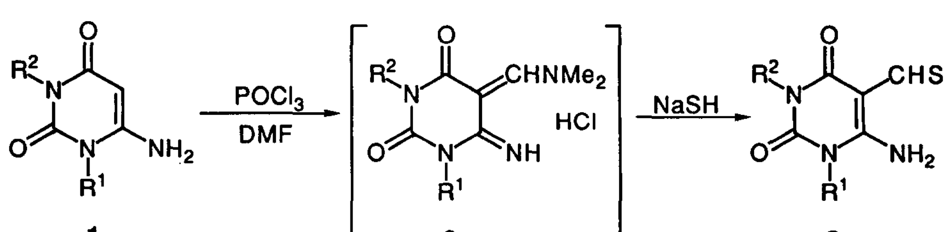


A



B

Scheme 1



1,3-Disubstituted 6-aminouracil derivatives **1a-e** were treated with DMF-$POCl_3$ to afford the corresponding Vilsmeier salts **2**, which were converted into the thioaldehydes **3a-e** *in situ* with sodium hydrogen sulfide without isolation of **2** (Scheme 1 and Table 1). The thioaldehydes **3** were orange crystalline compounds and the spectral data and the x-ray crystal structure of **3c** are in full agreement with thioaldehyde structures.

Table 1. Preparation of Thioformyluracils 3.

Substrate	R^1	R^2	Product	Yield (%)
1a	Me	Me	**3a**	60
1b	Bu	Me	**3b**	42
1c	Ph	Me	**3c**	98
1d	*p*-Br-C_6H_4	Me	**3d**	96
1e	Pr	Pr	**3e**	23

The ^1H NMR signals of thioformyl protons, which were observed at δ 10.61 - 10.78 in DMSO-d_6, are comparable to that of thermodynamically stabilized thioaldehydes in the previous reports[2] although they apper in the higher chemical shifts than that of the kinetically stabilized thioformyl protons (δ 11.45 – 13.02)[3]. The formyl signal of compound **4**[4] was appeared at δ 9.68, approximately one ppm higher than thioformyl signals (Table 2). The signals of 6-amino protons were observed as two separate peaks (see Table 2), indicating the presence of intramolecular hydrogen bonding between thioformyl group and amino group in DMSO-d_6 solution. Thioformyl ^{13}C NMR signals of **3a** and **3c** occur at lower field (δ 201.6 and 202.2 in DMSO-d_6, respectively) than those of the corresponding 5-formyl compound **4** (186.9 ppm in DMSO-d_6) and at higher field than that of the kinetically stabilized thioformyl ^{13}C NMR signals (δ 229.8 – 255.6). The distinctions are due to the presence of the conjugation between the thioformyl group and the 6-amino group.

Also, from the x-ray structural analysis[5] of **3c** the structure would be eventually determined as monomeric form (Figure 1). With our best knowledge, this is the first published crystal structure data of thermodynamically stabilized thioaldehydes. The C(7)-S bond distance (1.660 Å) of crystal structure **3c** is longer than those of thioformaldehyde (1.614 Å)[6] and kinetically stabilized (2,4,6-tri-*t*-butyl)thiobenzaldehyde **B** (1.602 Å)[3a,i] because of the mesomeric effect of 6-amino group of uracil ring system like the through conjugation between the C=S bond and the phenolic groups of *p,p'*-dihydroxythiobenzophenone (1.647 Å)[7] (see Table 3).

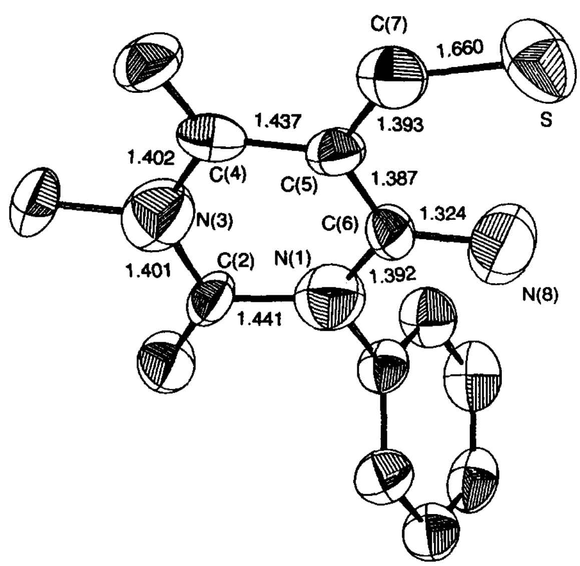
Thioaldehydes **3a-e** can be recrystalized from EtOH or benzene under the atmospher and stored stably in the solid state at room temperature under the atmosphere (in a vial) over several years. When **3a** was heated in refluxing in MeCN under oxygen atmosphere in the absence of water for 24 h (Table 4), it still remained unchanged (Okazaki *et al.* reported[3a,i] that the kinetically stabilized thioaldehyde **B** was unstable toward oxygen). These high stability of thioaldehydes **3** toward oxygen can be ascribed to reduction of the reactivity of thioformyl group by the mesomeric effect of 6-amino group (exsistence of hydrogen bonding between thioformyl group and amino group, see Table 2).

Table 2. ^{1}H-NMR Data (δ ppm) in DMSO-d_6 of Compounds 3 and 4.

Compound	CHS or CHO	NH$_2$[a]	
3a	10.61	9.16	12.30
3b	10.71	9.19	12.59
3c	10.74	7.88	12.11
3d	10.78	8.16	12.17
3e	10.73	9.24	12.51
4	9.68	8.45	10.07

[a]Deuterium exchangeable.

Figure 1. ORTEP Drawing of 3c with Selected Bond Distances (Å).



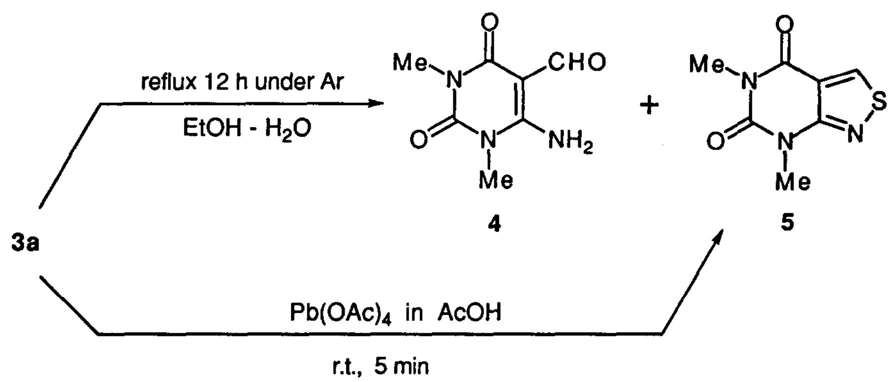
Thermal ellipsoids are drawn at the 50 % probability level; H atoms are not shown.

Addition of water caused the hydrolysis of thioformyl group to formyl group. When the reaction was carried out in the 50 % EtOH, the corresponding aldehyde **4** (70 % yield) and isothiazolo[3,4-*d*]pyrimidine derivative **5** was isolated (17 % yield) together with recovery of the starting material **3a** (4 % yield). The structure of **5** was confirmed by alternative synthesis according to Muraoka's method[21]. Thus, the oxidation of **3a** with $Pb(OAc)_4$ in AcOH gave the corresponding isothiazolopyrimidine **5** in good yield.

Table 3. C-S Bond Distance (Å) for 3c and Selected Compounds.

Compound	C-S Bond Distance (Å)
3c	1.660
B	1.602[3a,i]
$H_2C{=}S$	1.614[6]
$(p\text{-HO-}C_6H_4)_2C{=}S$	1.647[7]
MeSH	1.819[8]

Scheme 2



Hydrolysis of the thioaldehyde **3a** was carried out under aqueous basic and acidic conditions. Thus, when **3a** in EtOH was stirred in the presence of 10 eq. of *c*.HCl at r.t., the corresponding aldehyde **4** was obtained in 27 % yield, accompanied by 6-amino-1,3-dimethyluracil **6** (39 % yield) which would be produced by further hydrolytic decarbonylation of **4** (Table 4).

Scheme 3

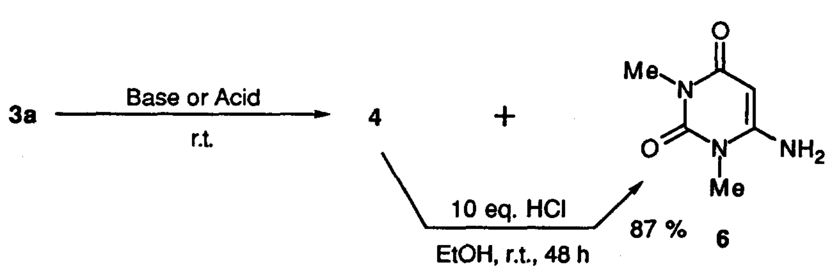


Table 4. Reaction of Thioaldehyde 3a under Various Conditions.

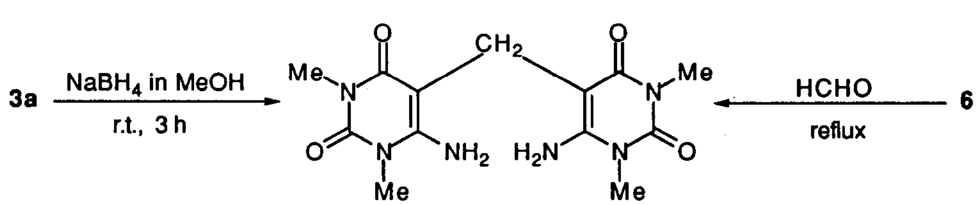
Entry	Reagents	Solvents	Reaction Temp.	Reaction Time	Other Conditions	Yield (%) 3a	4	5	6	7
1	—	dry MeCN	reflux	24 h	under O_2	100[b]	0	0	0	0
2	—	dry MeCN	reflux	24 h	under Ar	100[b]	0	0	0	0
3	—	EtOH - H_2O	reflux	12 h	under Ar	4	70	17	0	0
4	$Pb(OAc)_2$	AcOH	r.t.	5 min	—	0	0	81	0	0
5	NaOEt	dry EtOH	r.t.	48 h	—	85	0	0	0	0
6	KOH	dry EtOH	r.t.	96 h	—	80	0	0	0	0
7	KOH	EtOH - H_2O	r.t.	96 h	—	0	55	0	26	0
8	*c*.HCl	EtOH	r.t.	48 h	—	0	27	0	39	0
9	$NaBH_4$	MeOH	r.t.	3 h	—	0	0	0	0	93

[a]Recovery. [b]No reaction was observed on TLC.

Indeed, treatment of **4** with 10 eq. of *c*.HCl in EtOH at r.t. for 48 h afforded the 6-aminouracil **6**[4] in 87 % yield. Similarly the reaction of **3a** in aqueous 50 % EtOH in the presence of 3 eq. of KOH at r.t. gave **4** in 55 % yield together with **6** in 26 % yield. On the other hand, the reaction of the thioaldehyde **3a** with NaOEt (10 eq.) or KOH (3 eq.) in dry EtOH under Ar atmosphere resulted in the recovery of the starting material as shown in Table 4. Therefore, the thioaldehydes **3** are highly stable under anhydrous conditions but susceptible to convert of thioformyl group into formyl group under hydrolysis conditions.[21]

The reduction of **3a** with $NaBH_4$ in MeOH at r.t. resulted in the formation of the compound **7** in 93 % yield (Scheme 4). The ultimate proof of the structure was provided by an alternative synthesis; reaction of 6-amino-1.3-dimethyluracil **6** with formaldehyde gave **7** in 74 % yield. At present, however, the data rationalizing the mechanism for this reduction is not available.

Scheme 4



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In conclusion, we have demonstrated the synthesis of extremely stable thioaldehydes **3a-e** stabilized by mesomeric effect of an amino group. The reasonable double-bond character of the C=S bond of the thioaldehydes **3a-e** was evidenced by means of spectrum and analytical data especially x-ray crystal analysis. These products **3a-e** can be good starting materials for fused pyrimidine synthesis by the use of condensation reactions with various active methylene compounds or acid amides in analogy with 6-amino-5-formyluracil **4**.[4,9]

EXPERIMENTAL

M.p.s were determined on Yanagimoto melting point apparatus and are uncorrected. U.v. spectra were measured in EtOH with Simadzu UV-260 spectrophotometer. ^{1}H and ^{13}C NMR spectra were determined with a JEOL GX-270, a JEOL JNM FX-100 and/or a Hitachi-Perkin Elmer R-20B with sodium 2,2-dimethyl-2-silapentane-5-sulfonate (DSS) as the internal standard. 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.

6-Amino-1,3-dimethyl-5-thioformyluracil (3a). To a suspension of 6-amino-1,3-dimethyluracil **1a** (4.65 g, 30 mmol) in dry DMF (120 ml) below 20 ℃ was added phosphoryl chloride (5.06g, 33 mmol) dropwise. The mixture was stirred at room temperature for 30 min. To the resulting reaction mixture was added 70 % NaSH (7.20 g, 90 mmol) in dry DMF (50 ml) at 0 ℃ and it was allowed to reach room temperature. The solvent was removed under reduced pressure and the residue was triturated with water (10 ml). The resulting precipitate was collected on a suction filter and washed with ether (25 ml x 5) to give 6-amino-1,3-dimethyl-5-thioformyluracil **3a** (3.59 g, 60 %). An analytical sample was obtained by recrystallization from EtOH. m.p. 243-245 ℃; MS *m/z* 199 (M^+). UV/vis (EtOH) 355 (ε 28500), 239 nm (ε 11500). ^{1}H NMR (DMSO-d_6) δ 3.19 (s, 3H), 3.36 (s, 3H), 9.16 (br, 1H), 10.61 (s, 1H), 12.30 (br, 1H). ^{13}C NMR (DMSO-d_6) δ 28.0 (q), 29.5 (q), 106.1 (s), 149.4 (s), 157.0 (s), 160.2 (s), 201.6 (s). Anal. Calcd. for $C_7H_9N_3O_2S$: C, 42.20; H, 4.55; N, 21.09. Found: C, 42.37; H, 4.53; N, 21.22.

6-Amino-1-butyl-3-methyl-5-thioformyluracil (3b). To a suspension of 6-amino-1-butyl-3-methyluracil **1b** (1.97 g, 10 mmol) in dry DMF (50 ml) below 20 ℃ was added phosphoryl chloride (1.69 g, 11 mmol) dropwise. The mixture was heated at 50 ℃ for 1 h. To the resulting reaction mixture was added 70 % NaSH (2.40 g, 30 mmol) in dry DMF (20 ml) at 0 ℃ and it was allowed to reach room temperature. The solvent was removed under reduced pressure and the residue was treated as described above to give 6-amino-1-butyl-3-methyl-5-thioformyluracil **3b** (1.01 g, 42 %). An analytical sample was obtained by recrystallization from benzene. m.p. 147-148 ℃; MS *m/z* 241(M^+). UV/vis (EtOH) 355 (ε 29700), 241 nm (ε 14000). ^{1}H NMR (DMSO-d_6) δ 0.72-1.20 (m, 3H), 1.50 (m, 4H), 3.21 (s, 3H), 3.97 (m, 2H), 9.19 (br, 1H), 10.71 (s, 1H), 12.59 (br, 1H). Anal. Calcd. for $C_{10}H_{15}N_3O_2S$: C, 49.77; H, 6.27; N, 17.41. Found: C, 49.86; H, 6.30; N, 17.55.

6-Amino-3-methyl-1-phenyl-5-thioformyluracil (3c). To a suspension of 6-amino-3-methyl-1-phenyluracil **1c** (2.17 g, 10 mmol) in dry DMF (50 ml) below 20 ℃ was added phosphoryl chloride (1.69 g, 11 mmol) dropwise. The mixture was stirred at room temperature for 30 min. The resulting reaction mixture was treated as described above to give 6-amino-1-butyl-3-methyl-5-thioformyluracil **3c** (2.57 g, 98 %). An analytical sample was obtained by recrystallization from EtOH. m.p. 235-236 ℃; MS *m/z* 261(M^+). UV/vis (EtOH) (ε 21800). ^{1}H NMR (DMSO-d_6) δ 3.21 (s, 3H), 7.56 (br s, 5H), 7.88 (br, 1H), 10.74 (s, 1H), 12.11 (br, 1H). ^{13}C NMR (DMSO-d_6) δ 27.9, 106.3, 129.1, 130.1, 130.2, 133,0, 149.4, 157.1, 160.7, 202.2. Anal. Calcd. for $C_{12}H_{11}N_3O_2S \cdot 0.25\ H_2O$: C, 54.31; H, 4.33; N, 15.83. Found: C, 54.06; H, 4.21; N, 15.70.

6-Amino-1-butyl-3-methyl-1-(*p*-bromophenyl)-5-thioformyluracil (3d). To a suspension of 6-amino-3-methyl-1-(*p*-bromophenyl)uracil **1d** (1.48 g, 5 mmol) in dry DMF (50 ml) below 20 ℃ was added phosphoryl chloride (0.84 g, 5.5 mmol) dropwise. The mixture was stirred at room temperature for 1 h. To the resulting reaction mixture was added 70 % NaSH (1.20 g, 15 mmol) in dry DMF (20 ml) at 0 ℃ and it was treated in the same manner as described with **3a** to give 6-amino-1-butyl-3-methyl-1-(*p*-bromophenyl)-5-thioformyluracil **3d** (1.63 g, 96 %). An analytical samples obtained by recrystallization from EtOH. m.p. 229-230 ℃; MS *m/z* 339(M^+-1) 341(M^++1). UV/vis (EtOH) (ε 31100), 224 nm (ε 21200). ^{1}H NMR (DMSO-d_6) δ 3.23 (s, 3H), 7.49 (d, *J* = 8.0 Hz, 2H), 7.86 (d, *J* = 8.0 Hz, 2H), 8.16 (br, 1H), 10.78 (s, 1H), 12.17 (br, 1H). Anal. Calcd. for $C_{12}H_{10}N_3O_2SBr$: C, 42.37; H, 2.96; N, 12.35. Found: C, 42.64; H, 3.01; N, 12.16.

6-Amino-1,3-dipropyl-5-thioformyluracil (3e). To a suspension of 6-amino-1,3-dipropyluracil **1e** 0.8 g, 4 mmol) in dry DMF (25 ml) below 20 ℃ was added phosphoryl chloride (0.84 g, 5.5 mmol) dropwise. The mixture was stirred at room temperature for 30 min. To the resulting reaction mixture was added 70 % NaSH (1.20 g, 15 mmol) in dry DMF (10 ml) at 0 ℃ and it was treated in the same manner as described with **3a** to give 6-amino-1,3-dipropyl-5-thioformyluracil **3e** (0.23 g, 23 %). An analytical samples obtained by recrystallization from benzene. m.p. 177-179 ℃; MS *m/z* 255(M^+). UV/vis (EtOH) 355 (ε 29900), 242 nm (ε 13600). ^{1}H NMR (DMSO-d_6) δ 0.89 (m, 6H), 1.62 (m. 4H), 3.88 (br q, J = 7.0 Hz, 3H), 9.24 (br, 1H), 10.73 (s, 1H), 12.51 (br, 1H). Anal. Calcd. for $C_{11}H_{17}N_3O_2S$: C, 51.75; H, 6.71; N, 16.46. Found: C, 51.82; H, 6.75; N, 16.48.

Thermal stability of 3a in the presence of water. A suspension of 6-amino-1,3-dimethyl-5-thioformyluracil **3a** (199 mg, 1 mmol) in water (5 ml) and EtOH (5 ml) was refluxed under Ar atmosphere for 12 h. The solvents were removed under reduced pressure and the residue was purified by elution from silica gel column with a 100 : 1 (v/v) mixture of $CHCl_3$ and MeOH to yield 34 mg of isothiazolo[3,4-*d*]pyrimidine **5** (17 %), 8 mg of **3a** (recovery, 4 %) and 128 mg of **4** (70 %) in this order. Compound **4** thus obtained was identical with an authentic sample.[4] **5**: m.p. 175-176 ℃; MS *m/z* 197 (M^+). UV/vis (EtOH) 296 (ε 9860), 246 nm (ε 7100). ^{1}H NMR (DMSO-d_6) δ 3.24 (s, 3H), 3.49 (s, 3H), 9.84 (s, 1H). Anal. Calcd. for $C_7H_7N_3O_2S$: C, 42.64; H, 3.58; N,21.32. Found: C, 42.88; H, 3.45; N, 21.30.

Oxidation of 3a with Pb(OAc)$_4$. A mixture of 6-amino-1,3-dimethyl-5-thioformyluracil **3a** (199 mg, 1 mmol) and 90 % $Pb(OAc)_4$ (591 mg, 1.2 mmol) in AcOH (5 ml) was stirred at room temperature for 5 min. The resulting reaction mixture was diluted with water (30 ml) and it was extracted with AcOEt (30 ml). The organic layer was washed with water (25 ml) and brine (25 ml), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was triturated with ether (20 ml) and the resulting solid product was collected on a suction filter to give 160 mg of isothiazolo[3,4-*d*]pyrimidine **5** (81 %), which was identical with the product obtained above.

Reaction of 3a with NaOEt. A mixture of 6-amino-1,3-dimethyl-5-thioformyluracil **3a** (199 mg, 1 mmol) in ethanolic sodium ethoxide[prepared from Na (230 mg, 10 mmol) and absolute EtOH (10 ml)] was stirred at room temperature under Ar atmosphere for 48 h. EtOH was removed under reduced pressure and the residue was dissolved in water. The aqueous solution was neutralized with *c*.HCl and extracted with $CHCl_3$ (25 ml). The organic layer was washed with water (10 ml) and brine (10 ml), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was triturated in ether and resulting solid product was collected on a suction filter to give 169 mg of the starting material **3a** (85 %).

Reaction of 3a with KOH in abs. EtOH. A mixture of 6-amino-1,3-dimethyl-5-thioformyluracil **3a** (100 mg, 0.5 mmol) and KOH (84 mg, 1.5 mmol) in absolute EtOH was stirred at room temperature under Ar atmosphere for 96 h and it was treated as described above to give 80 m g of the starting material **3a** (80 %).

Reaction of 3a with KOH in EtOH-water. A mixture of 6-amino-1,3-dimethyl-5-thioformyluracil **3a** (100 mg, 0.5 mmol) and KOH (84 mg, 1.5 mmol) in EtOH (5 ml) and water (5 ml) was stirred at room temperature for 96 h. The solvents were removed under reduced pressure and the residue was dissolved in water. The aqueous solution was neutralized with *c*.HCl and extracted with $CHCl_3$ (25 ml). The organic layer was washed with water (10 ml) and brine (10 ml), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by elution from silica gel column with a 100 : 1 (v/v) mixture of $CHCl_3$ and MeOH to yield 51 mg of 6-amino-1,3-dimethyl-5-formyluracil **4** (55 %) and 20 mg of 6-amino-1,3-dimethyluracil **6** (26 %), which were identical with authentic samples.[4]

Reaction of 3a with *c*.HCl. A mixture of 6-amino-1,3-dimethyl-5-thioformyluracil **3a** (199 mg, 1 mmol) and *c*.HCl (0.8 ml, 10 mmol) in EtOH (10 ml) was stirred at room temperature for 96 h. The solvents were removed under reduced pressure and the residue was dissolved in water. The aqueous solution was neutralized with $NaHCO_3$ and extracted with $CHCl_3$ (25 ml). The organic layer was washed with water (10 ml) and brine (10 ml), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by elution from silica gel column with a 100 : 1 (v/v) mixture of $CHCl_3$ and MeOH to yield 49 mg of 6-amino-1,3-dimethyl-5-formyluracil **4** (27 %) and 60 mg of 6-amino-1,3-dimethyluracil **6** (39 %).

Reaction of 4 with *c*.HCl. A mixture of 6-amino-1,3-dimethyl-5-formyluracil **4** (366 mg, 2 mmol) and *c*.HCl (1.6 ml, 20 mmol) in EtOH (20 ml) was stirred at room temperature for 48 h. The mixture was treated as described above to give 18 mg of 6-amino-1,3-dimethyl-5-formyluracil **4** (recovery, 5 %) and 270 mg of 6-amino-1,3-dimethyluracil **6** (87 %).

Reduction of 3a with $NaBH_4$. A mixture of 6-amino-1,3-dimethyl-5-thioformyluracil **3a** (199 mg, 1 mmol) and $NaBH_4$ (57 mg, 1.5 mmol) in absolute MeOH (20 ml) was stirred at room temperature under Ar atmosphere for 3 h. MeOH was removed under reduced pressure and the residue was dissolved in water. The aqueous solution was neutralized with AcOH and resulting solid product was collected on a suction filter. Recrystallization from AcOH gave150 mg of the product **7** (93 %). m.p. >300 °C; MS *m/z* 322 (M^+). UV/vis (EtOH) 267 nm (ε 13500). ^1H NMR (CF_3COOH) δ 3.48 (s, 6H), 3.59 (s, 6H). Anal. Calcd. for $C_{13}H_{18}N_6O_4$: C, 48.44; H, 5.63; N, 26.08. Found: C,48.34; H, 5.66; N, 25.84.

Alternate synthesis of compound 7. A mixture of 6-amino-1,3-dimethyluracil **6** (0.465 mg, 3 mmol) and 37 wt. % formaldehyde solution (5 ml) in EtOH (5 ml) was refluxed for 5 h. The solvent was removed under reduced pressure and the residue was triturated with water (5 ml). The resulting precipitate was collected on a suction filter and washed with ether (5 ml x 3) to give the product **7** (357 mg, 74 %)., which were identical with the product obtained above.

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5 Crystal data of **3c**: $C_{12}H_{11}N_3O_2S$, monoclinic, space group $P2_1/C$, a = 8.493(3), b = 10.831(4), c = 13.140(5) Å, β = 93.71(3) °, Dx = 1.44 g/cm^3, Z = 4 and μ(MoKa) = 2.7 cm^{-1}. The cell dimensions and intensities were measured on a Syntex R3 four-circle diffractometer with graphite-monochromated Mo Ka radiation with w-scan mode within 2q less than 45 °. A total of 1575 independent reflections were collected, among which 1044 reflections [I ≥ 1.96 σ (I)] were stored as observed. The structure was solved by the direct method using the MULTAN program. All of atoms, except hydrogen atoms, were revealed on the first E-map. After several cycles of refinement, all hydrogen atoms were found on the different Fourier map. The R value finally obtained by the block-diagonal least-squares refinement was 0.071. The authors have deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Center. The coordinates can be obtained on request from The Director, Cambridge Crystallographic Data Center, University Chemical Laboratory, Lensfield Road, Cambridge CB12 1EW, UK.

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