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Novel Intramolecular Rearrangement of 5-Carbamoyluracils into Barbituric Acids[1]

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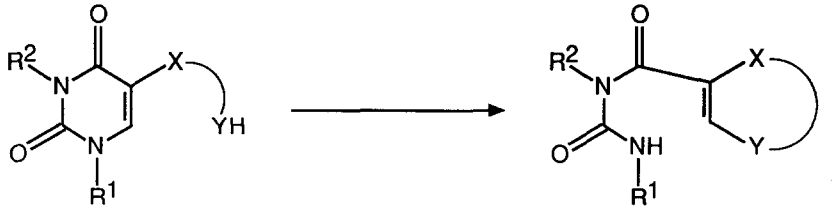
Abstract: Heating of 5-carbamoyl- (**1**) and 5-thiocarbamoyl-3-methyl-1-phenyluracil (**5**) derivatives in ethanolic sodium ethoxide causes a novel intramolecular rearrangement to give 5-anilinomethylenebarbituric acids (**2**) and 5-anilinomethylene-4-thiobarbituric acid (**6**), respectively.

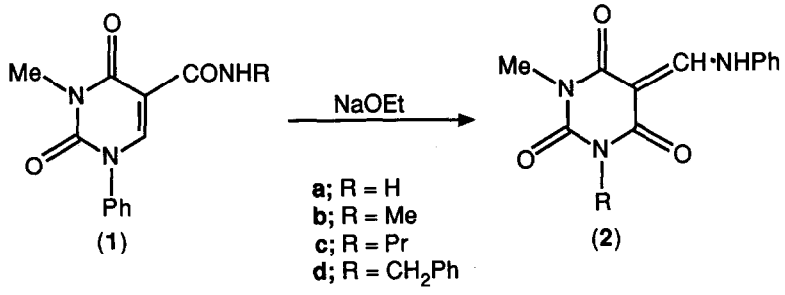
It is well known that the uracil ring system is susceptible to nucleophilic attack at the 6-position[3] and uracil derivatives react with various nucleophiles to undergo ring transformation reactions.[4-16] The presence of a terminal nucleophile in the side chain on uracil ring frequently made possible the ring transformation of uracil into other ring systems *via* an intramolecular rearrangement (Scheme 1).[17-21] For example, we have reported that uracil derivatives, possessing a terminal nucleophilic side chain [-CH=NNH$_2$, -CH=CHCONH$_2$, -CH=C(R)COCH$_3$] at the 5-position under acidic or basic conditions, undergo the ring transformation into pyrazole,[18] pyridine,[19] and benzene[20] ring systems, respectively, involving the N(1)–C(6) bond cleavage.



Scheme 1

During our investigation on the reaction of uracil derivatives bearing an electron-withdrawing group at the 5-position with nucleophiles under basic conditions,[11,14,16] we have found that the carbamoyl group of 5-carbamoyluracils (**1**) behaves as an intramolecular nucleophile in the presence of sodium ethoxide (NaOEt). This paper describes such a novel type of rearrangement of the uracils (**1**) into barbituric acids (**2**) involving the N(1)–C(2)-bond cleavage.

Treatment of 5-carbamoyl-3-methyl-1-phenyluracil (**1a**) with excess NaOEt in refluxing ethanol for 3 h resulted in the formation of 5-anilinomethylene-1-methylbarbituric acid (**2a**)[22] (61% yield), which was alternatively synthesized by condensation of 5-formyl-1-methylbarbituric acid with aniline.[23] Analogous reactions of 5-(*N*-substituted carbamoyl)uracil derivatives (**1b-d**), which were prepared by the reaction of 5-carboxy-3-methyl-1-phenyluracil with amines in the presence of diphenylphosphoryl azide, also gave the corresponding barbituric acids (**2b-d**). The structures of (**2b-d**)[22] were confirmed on the basis of their microanalytical results and comparison of their spectral data with those of (**1a**) (Table 1). The tautomeric structure (**B**) alternative to the barbituric acid (**2**) was ruled out by the absence of a signal due to the 5-methine proton in the ^{1}H n.m.r. spectrum.



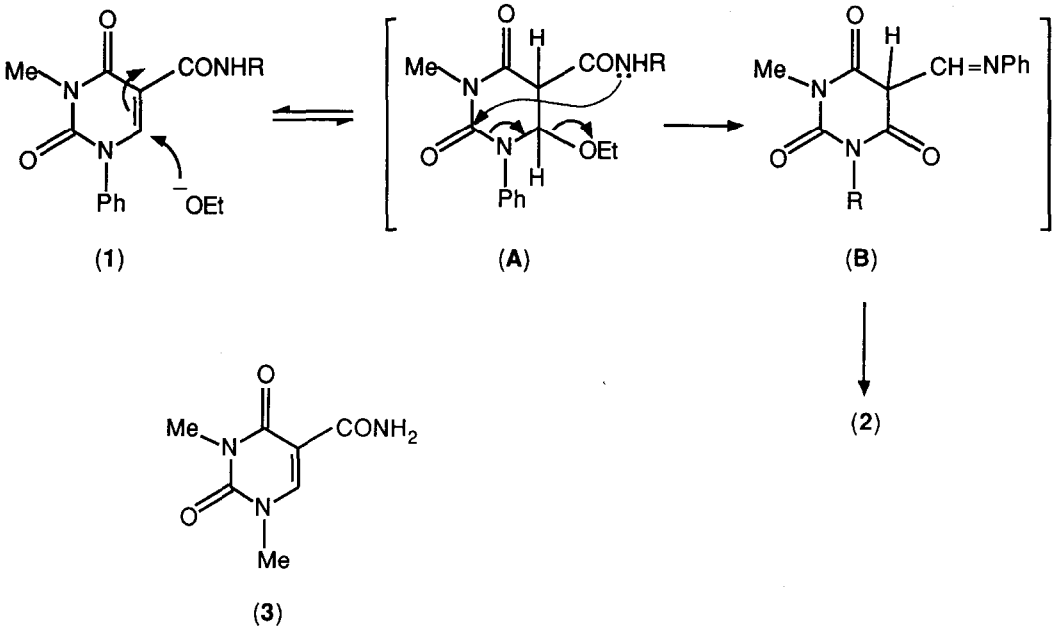
Scheme 2

Table 1. Formation of 5-Anilinomethylenebarbituric Acids (**2**) and (**6**)

Starting compound	Reaction time (h)	Product	Yield (%)	^{1}H n.m.r. (δ)[a] C_5=CH[b]	NHPh[c]	u.v. (EtOH) λ_{max} (ε)
(**1a**)	3	(**2a**)	61	8.54 (br)	11.84	341 (30800) 223 (20400)
(**1b**)	4	(**2b**)	71	8.64 (d, *J* 13.5 Hz)	12.17	339 (27400) 225 (18000)
(**1c**)	5	(**2c**)	39	8.68 (d, *J* 14.0 Hz)	12.05	342 (33100) 225 (22600)
(**1d**)	2	(**2d**)	68	8.68 (d, *J* 14.0 Hz)	12.03	342 (22100) 225 (15100)
(**5**)	6	(**6**)	92	9.17 (d, *J* 15.0 Hz)[d] 8.91 (d, *J* 15.0 Hz)[e]	12.42[d] 14.56[e]	338 (14400) 304 (10200) 266 (16700) 252 (9800)

[a]Measured in $CDCl_3$ except for (**2a**) and (**6**) [in $(CD_3)_2SO$]. [b]Collapsed to singlet by deuterium exchange. [c]Deuterium exchangeable. [d](*E*)-isomer (**6a**). [e](*Z*)-isomer (**6b**).

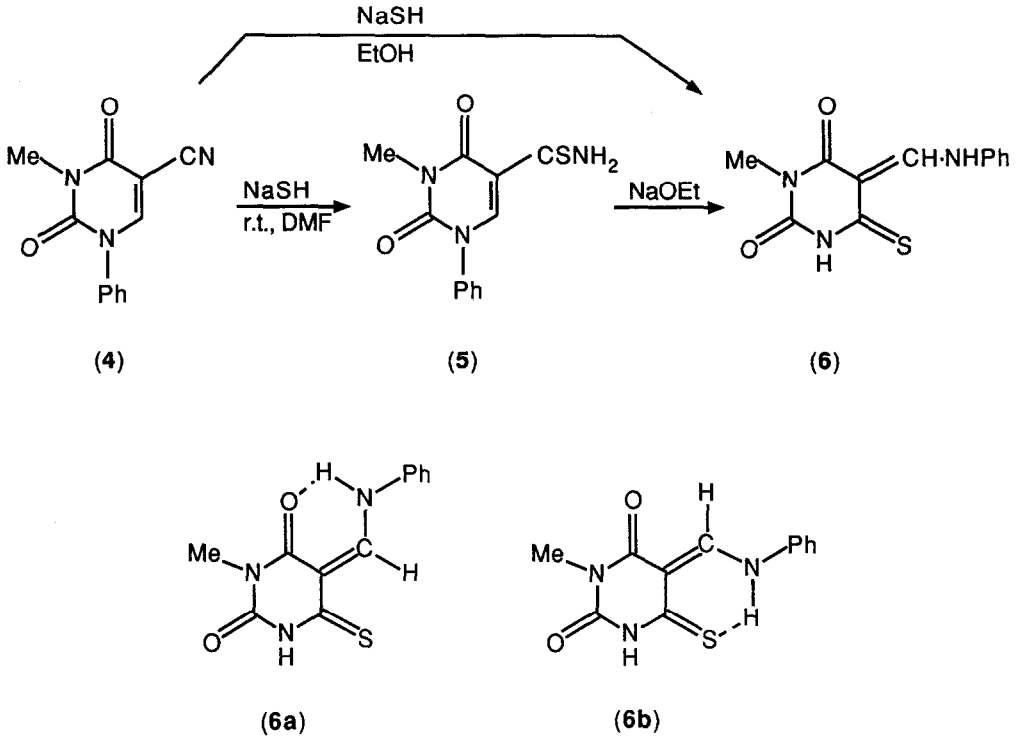
The reaction of 5-carbamoyl-1,3-dimethyluracil (**3**), which has no phenyl group at the 1-position, with NaOEt under similar conditions resulted in the recovery of the starting material. This fact suggests that the presence of the 1-phenyl group significantly facilitates the cleavage of the N(1)–C(2) bond by attack of the 5-carbamoyl group on the 2-position in the C(6)-addition intermediate (**A**) as shown in Scheme 3. Taking the above facts into consideration, a plausible reaction sequence for the present rearrangement is outlined in Scheme 3. An initial nucleophilic attack at the 6-position of the 5-carbamoyluracil (**1**) by ethoxide ion could give rise to an adduct (**A**) (Michael addition). The conversion of sp^2-carbon into sp^3-carbon at the 5-position allows an intramolecular nucleophilic attack of the 5-carbamoyl group on the 2-carbonyl group followed by cleavage of the N(1)-C(2) bond to give a barbituric acid (**B**), which can be tautomerize to much more stable product (**2**).



Scheme 3

In order to extend the rearrangement described above to a reaction of 5-thiocarbamoyluracil derivative, 3-methyl-1-phenyl-4-thiocarbamoyluracil (**5**) was prepared in high yield by the reaction of 5-cyano-1-methyl-1-phenyluracil (**4**) with sodium hydrosulfide (NaSH) in DMF at room temperature. Treatment of (**5**) with NaOEt under rearrangement conditions described above afforded 5-anilinomethylene-1-methyl-4-thiobarbituric acid (**6**) (92 % yield), which was also obtained in 78% yield directly upon treatment of the 5-cyanouracil (**4**) with NaSH in ethanol instead of DMF under reflux. The ^{1}H n.m.r. spectrum of (**6**) in a dimethyl sulfoxide (DMSO) solution at room temperature shows the presence of both (*E*)- and (*Z*)-isomers, (**6a**) and (**6b**), in the ratio 3:2. Each pair of peaks of the isomers

merges at 100 °C. This fact clearly indicates that (**6**) is a mixture of (*E*)- and (*Z*)-isomers in a DMSO solution. Attempt to separate the isomers was unsuccessful. Assignment of the structures (**6a**) and (**6b**) in their ^{1}H n.m.r. spectrum is possible by considering the effect on hydrogen bond and anisotropy effect on the methine proton induced by the 4-thiocarbonyl and 6-carbonyl groups, as shown in Table 1.



Scheme 4

The thermal rearrangement of uracils involving the cleavage of the N(1)-C(2) bond has been unprecedented except for the uracil-to-pyridine ring transformation reported recently.[21] Thus, the present reaction is most intriguing with respect to involvement of the rare N(1)–C(2) bond-cleavage.

Experimental

All melting points were determined on a Yanagimoto melting point apparatus and are uncorrected. Elemental analyses were carried out at the Microanalytical Laboratory of our university. Proton magnetic resonance spectra were recorded on a Hitachi Perkin-Elmer R-20B (60 MHz) or a JEOL TNM-GX270

(270 MHz) spectrometer using tetramethylsilane (TMS) in $CDCl_3$ or sodium 2,2-dimethyl-2-silapentane-5-sulfonate (DSS) in $(CD_3)_2SO$ as an internal standard. Chemical shifts are reported in parts per million (δ), the *J* values are given in hertz, and signals are quoted as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), or br (broad); *J* values are first order. Infrared spectra were taken on a Hitachi 215 instrument in KBr pellets. Mass spectra were obtained with a JEOL JMS-D300 machine operating at 70 eV. Ultraviolet spectra were obtained in ethanol on a Shimadzu UV-260 spectrophotometer. Column chromatography was carried out on a silica gel (Wakogel C-300).

3-Methyl-5-(*N*-methylcarbamoyl)-1-phenyluracil (1b).

Diphenylphosphoryl azide (DPPA) (0.68 g, 2.48 mmol) was added to a mixture of 5-carboxy-3-methyl-1-phenyluracil[24] (0.51 g, 2.07 mmol) and methylamine (40% in methanol) (0.91 g, 2.48 mmol) in dry DMF (10 ml) and dry dimethyl sulfoxide (DMSO) (5 ml), and the mixture was stirred at room temperature for 1 h. After evaporation of the solvent and addition of ice-water, the mixture was extracted with ethyl acetate. The extracts were washed with saturated aqueous $NaHCO_3$ solution and water and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was recrystallized from ethanol to give the uracil (**1b**) (0.46 g, 86%), m.p. 189–190 °C; *m/z* 259 (M^+); λ_{max} (EtOH) 282 nm (ε 8000); δ_H (60 MHz, $CDCl_3$) 2.95 (3 H, d, *J* = 5 Hz, NMe), 3.41 (3 H, s, NMe), 7.10-7.80 (5 H, m, Ph), 8.46 (1 H, s, C_6-H), and 8.72 (1 H, br, NH); (Found: C, 60,07; H, 4.97; N, 15.92. $C_{13}H_{13}N_3O_3$ requires C, 60.22; H, 5.05; N, 16.21%).

3-Methyl-1-phenyl-5-(*N*-propylcarbamoyl)uracil (1c).

DPPA (0.96 g, 3.50 mmol) was added to a mixture of 5-carboxy-3-methyl-1-phenyluracil[24] (0.72 g, 2.92 mmol) and propylamine (0.21 g, 3.50 mmol) in dry DMF (10 ml) and dry DMSO (5 ml). The mixture was treated as described above to give the uracil (**1c**) (0.36 g, 43%), m.p. 128-130 °C (from cyclohexane); *m/z* 287 (M^+); λ_{max} (EtOH) 283 nm (ε 9300); δ_H (60 MHz, $CDCl_3$) 0.98 (3 H, t, *J* = 7.5 Hz, CMe), 1.10-1.93 (2 H, m, CCH2C), 3.40 (2 H, q, *J* = 6.7 Hz, NCH_2), 3.43 (3 H, s, NMe), 7.09-7.67 (5 H, m, Ph), 8.50 (1 H, s, C_6-H), and 8.87 (1 H, br, NH); (Found: C, 62.40; H, 5.82; N, 14.83. $C_{15}H_{17}N_3O_3$ requires C, 62.70; H, 5.96; N, 14.63%).

5-(*N*-Benzylcarbamoyl)-3-methyl-1-phenyluracil (1d).

DPPA (0.96 g, 3.50 mmol) was added to a mixture of 5-carboxy-3-methyl-1-phenyluracil[24] (0.72 g, 2.92 mmol) and benzylamine (0.38 g, 3.50 mmol) in dry DNF (10 ml) and dry DMSO (5 ml). The mixture was treated as described above to give the uracil (**1d**) (0.85 g, 87%), m.p. 177–178 °C (from ethanol); *m/z* 335 (M^+); λ_{max} (EtOH) 283 nm (ε 11000); δ_H (60 MHz, $CDCl_3$) 3.42 (3 H, s, NMe), 4.61 (2 H, d, *J* = 6 Hz, NCH_2), 7.06-7.80 (10 H, m, Ph), 8.53 (1 H, s, C_6-H), and 9.20 (1 H, br, NH); (Found: C, 67.86; H, 5.11; N, 12.49. $C_{19}H_{17}N_3O_3$ requires C, 68.05; H, 5.11; N, 12.53%).

5-Anilinomethylenebarbituric Acid Derivatives (2). General Procedure (Table 1). A mixture of the 5-carbamoyluracils (**1a**[24]-**d**) (3 mmol) in ethanolic sodium ethoxide [prepared from Na (0.21 g, 9 mmol) and absolute ethanol (30 ml)] was refluxed for the reaction time specified in Table 1. The reaction mixture was treated as described below unless otherwise stated. The solvent was removed from the reaction mixture under reduced pressure and the residue was dissolved in water (50 ml). The aqueous solution was neutralized with concentrated hydrochloric acid (35%) and the resulting precipitate was filtered off and recrystallized from an appropriate solvent, giving the 5-anilinomethylenebarbituric acid derivatives (**2a-d**).

5-Anilinomethylene-1-methylbarbituric Acid (2a). m.p. 284–286 °C (from MeOH) (lit.,[23] 285–287 °C); *m/z* 245 (M^+); λ_{max} (EtOH) 341 (ε 30800), 223 (20400); δ_H [60 MHz, $(CD_3)_2SO$] 3.14 (3 H, s, NMe), 7.06-7.63 (5 H, m, Ph), 8.54 (1 H, br, =CH-N, collapsed to singlet by deuterium exchange), 11.07 (1 H, br, N_3-H, deuterium exchangeable), and 11.84 (1 H, br, NHPh, deuterium exchangeable). This product was identical with an authentic sample[23].

5-Anilinomethylene-1,3-dimethylbarbituric Acid (2b). m.p. 196–198 °C (from MeOH) (lit.,[23] 198–200 °C); *m/z* 259 (M^+); λ_{max} (EtOH) 339 (ε 27400), 225 nm (18000); δ_H (60 MHz, $CDCl_3$) 3.31 (6 H, s, NMe), 7.07-7.51 (5 H, m, Ph), 8.64 (1 H, d, J = 13.5 Hz, =CH-N, collapsed to singlet by deuterium exchange), and 12.17(1 H, br, NHPh, deuterium exchangeable); (Found: C, 60.16; H, 5.03; N, 16.10. $C_{13}H_{13}N_3O_3$ requires C, 60.22; H, 5.05; N, 16.21%).

5-Anilinomethylene-1-methyl-3-propylbarbituric Acid (2c). The neutralized solution was extracted with ethyl acetate and the extracts were evaporated *in vacuo*. The residue was chromatographed on a silica gel column eluting with chloroform and the crude product was recrystallized from cyclohexane-light petroleum to give the barbituric acid (**2c**), m.p. 108–111 °C; *m/z* 287 (M^+); λ_{max} (EtOH) 342 (ε 33100), 225 nm (22600); δ_H (60 MHz, $CDCl_3$) 0.97 (3 H, t, J = 7.5 Hz, CMe), 1.45-2.05 (2 H, m, CCH_2C), 3.34 (3 H, s, NMe), 3.91 (2 H, t, J = 7.5 Hz, NCH_2), 7.70-7.82 (5 H, m, Ph), 8.68 (1 H, d, J = 14 Hz, =CH-N, collapsed to singlet by deuterium exchange), and 12.05 (1 H, br, NHPh, deuterium exchangeable), (Found: C, 62.63; H, 5.96; N, 14.40. $C_{15}H_{17}N_3O_3$ requires C, 62.70; H, 5.96; N, 14.63%).

5-Anilinomethylene-1-benzyl-3-methylbarbituric Acid (2d). The neutralized solution was evaporated *in vacuo*. The residue was chromatographed on a silica gel column eluting with chloroform and the crude product was recrystallized from cyclohexane to give the barbituric acid (**2d**), m.p. 122–124 °C; *m/z* 335 (M^+); λ_{max} (EtOH) 342 (ε 22100), 225 nm (15100); δ_H (60 MHz, $CDCl_3$) 3.33 (3 H, s, NMe), 5.11 (2 H, s, NCH_2), 6.95-7.57 (10 H, m, Ph), 8.68 (1 H, d, J = 14 Hz, =CH-N, collapsed to singlet by deuterium exchange), and 12.03 (1 H, br, NHPh, deuterium exchangeable); (Found: C, 68.00; H, 5.11; N, 12.36. $C_{19}H_{17}N_3O_3$ requires C, 68.05; H, 5.11; N, 12.53%).

3-Methyl-1-phenyl-5-thiocarbamoyluracil (5).

A mixture of 5-cyano-3-methyl-1-phenyluracil (**4**)[25] (0.68 g, 3 mmol) and sodium hydrosulfide (NaSH) (70%) (0.72 g, 9 mmol) in dimethylformamide (DMF) (5 ml) was stirred at room temperature for 45 h. The solvent was removed under reduced pressure and the residue was triturated with water (20 ml). The resulting precipitate was filtered off and recrystallized from methanol to give the 5-thiocarbamoyluracil (**5**) (0.71 g, 91%), m.p. 227 °C; *m/z* 261 (M^+); λmax (EtOH) 337 nm, 273, 265; δ_H[60 MHz, $(CD_3)_2SO$] 3.32 (3 H, s, NMe), 7.60 (5 H, s, Ph), 9.00 (1 H, s, C_6-H), and 10.04 and 10.31 (each 1 H, each br, NH, deuterium exchangeable); (Found: C, 55.12; H, 4.21; N, 16.03. $C_{12}H_{11}N_3O_2S$ requires C, 55.16; H, 4.24; N, 16.08%).

5-Anilinomethylene-1-methyl-4-thiobarbituric Acid (6).

(a) A mixture of 3-methyl-1-phenyl-5-thiocarbamoyluracil (**5**) (0.13 g, 0.5 mmol) in ethanolic sodium ethoxide [prepared from Na (0.017 g, 0.74 mmol) and absolute ethanol (10 ml)] was refluxed for 6 h. The solvent was removed under reduced pressure and the residue was dissolved in water. The aqueous solution was neutralized with acetic acid and the resulting precipitate was filtered off and recrystallized from methanol to give the 4-thiobarbituric acid (**6**) (0.12 g, 92 %), m.p. >300 °C; *m/z* 261 (M^+); λ_{max} (EtOH) 388 (ε 14400), 304 (10200), 266 (16700), 252 nm (9800); δ_H [270 MHz, 22 °C, $(CD_3)_2SO$] 3.17 (3 H, s, NMe), 7.31-7.53 (5 H, m, ph), 8.91 (0.4 H, d, J = 15 Hz, =CH-N, collapsed to singlet by deuterium exchange), 9.17 (0.6 H, d, J = 15 Hz, =CH-N, collapsed to singlet by deuterium exchange), 12.18 (0.4 H, brs, N_3-H, deuterium exchangeable), 12.23 (0.6 H, brs, N_3-H, deuterium exchangeable), 12.42 (0.6 H, brd, J = 15 Hz, NHPh, deuterium exchangeable), and 14.56 (0.4 H, brd, J = 15 Hz, NHPh, deuterium exchangeable); [270 MHz, 100 °C, $(CD_3)_2SO$] 3.19 (3 H, s, NMe), 7.29-7.67 (5 H, m, ph), 9.05 (1 H, d, J = 12.8 Hz, =CH-N), and 11.76 (1 H, br, N_3-H), the signal due to the NHPh proton could not be observed; (Found: C, 54.99; H, 4.27; N, 15.93. $C_{12}H_{11}N_3O_2S$ requires C, 55,16; H, 4.24; N, 16.08%).

(b) A suspension of 5-cyano-3-methyl-1-phenyluracil (**4**)[25] (0.68 g, 3 mmol) and NaSH (70%) (0.72 g, 9 mmol) in ethanol (30 ml) was refluxed for 12 h and then treated as described above to give the 4-thiobarbituric acid (**6**) (0.61 g, 78%), which was identical with the product obtained above.

References and Notes

1 This paper is part 66 of a series entitled "Pyrimidines". For part 65, see Hirota, K.; Shirahashi, M.; Senda, S.; Yogo, M., *J. Heterocycl. Chem.*, in press.

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22 For convenient drawings, the rearrangement products are represented as the barbituric acid forms (**2**) and (**6**) rather than the 6-hydroxy- or 6-mercaptouracil form (**C**).

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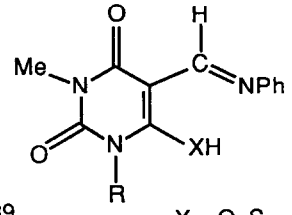

(**C**)