Reductive Debromination and Coupling Reaction in the Thermolysis of 5-Bromouracils in *N,N*-Dialkylamides. Cleavage of the C(5)–Bromine Bond by an Initial Electron-transfer Process

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Thermolysis of various 5-bromouracils (1) in *N,N*-dialkylamides results in the formation of methylenebisuracils (2) and reductive debrominated products (3) *via* cleavage of the C(5)–Br bond; the latter involves a one-electron transfer process. The product distribution between (2) and (3) depends upon the nature of substituents in the uracil ring.

THERE have been ample precedents for the photochemical C(5)–halogen bond cleavage of 5-halogenouracils implying generation of a uracil radical.[1,2] These observations have become of interest in recent years from a photobiological viewpoint.

Despite a number of studies of the photochemical reductive dehalogenation of 5-halogenouracils, the thermal homolytic process has not been documented.†

Here, we describe the first demonstration of the thermal cleavage of the C(5)–Br bond in 5-bromouracils *via* a one-electron transfer process, resulting in reductive debromination and a subsequent coupling reaction.

5-Bromouracils (1) were heated in *N,N*-dimethylacetamide (DMA) at 160 or 180 °C until disappearance of starting material (1—9 h, monitored by t.l.c.). After evaporation of the solvent, the residue was chromatographed over silica gel to isolate the methylenebisuracil (2) and debrominated uracils (3). Analogous results were obtained in the dark. The structure of (2a) was confirmed by spectral comparison with a sample prepared by the reaction of (3a) with paraformaldehyde.[3] The debrominated uracils (3) were identical in every respect with authentic samples. Thin layer chromatographic analysis of the reaction mixture showed traces of unidentified products.

The results of above reactions are summarized in the Table. It is clear that the product distribution of the reaction depends largely upon the nature of substituents at positions 1, 3, and 6 of the uracil ring.

Further experiments (i—iv) were carried out using 5-bromo-3-methyl-6-phenylthiouracil (1a) as a reactant.

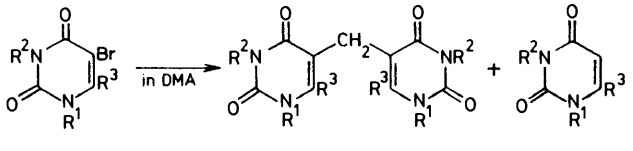
(i) When (1a) was heated in anhydrous DMA at 160 °C in the presence of *N,N,N′,N′*-tetramethyl-*p*-phenylenediamine, the solution turned blue after 30 s.‡ The u.v. spectrum of the reaction mixture diluted with methanol–0.05M-acetic acid (4 : 1) showed absorption at 568 and 612 nm, which is characteristic of the *N,N,N′,N′*-tetramethyl-*p*-phenylenediamine cation-radical.[4] §

TABLE

Thermolysis of 5-bromouracils (1a—h) in *N,N*-dimethylacetamide

	Compounds (1)			Reaction conditions Temp. (°C)	Time (h)	% Yield of products [a] (m.p. °C) [lit. m.p.] (2)	(3)
	R^1	R^2	R^3				
a	H	Me	PhS	160	1	93.7 (285)	Trace (223) [218 [b]]
b	H	Me	PhO	160	1	88.5 (313)	Trace (247) [243 [c]]
c	H	Me	*p*-BrC_6H_4NMe	160	1	92.3 (323)	Trace (268) [*d*]
d	H	H	PhS	160	1	92.5 (315)	Trace (278) [272 [e]]
e	Me	Me	PhS	160	1	31.2 (223)	63.9 (136) [137 [f]]
f [g]	H	H	H	180	7		93.8 (>300) [>300 [g]]
g [h]	H	Me	H	180	6	37.0 (330)	50.4 (187) [175 [h]]
h [i]	Me	Me	H	180	9	37.5 (285)	50.0 (125) [122 [i]]

[a] Isolated yields. [b] F. Yoneda, M. Kawazoe, and Y. Sakuma, *Tetrahedron Lett.*, 1978, 2803. [c] F. Yoneda, R. Hirayama, and M. Yamashita, *Chem. Lett.*, 1980, 1157. [d] F. Yoneda, K. Shinozuka, Y. Sakuma, and K. Senga, *Heterocycles*, 1977, **6**, 1179. [e] B. R. Baker and W. Rzeszotarski, *J. Med. Chem.*, 1967, **10**, 1109. [f] S. Senda, K. Hirota, and M. Takahashi, *J.C.S. Perkin I*, 1975, 503. [g] H. L. Wheeler and T. B. Johnson, *Am. Chem. J.*, 1904, **31**, 603. [h] T. B. Johnson and F. W. Heyl, *Am. Chem. J.*, 1907, **37**, 628. [i] T. B. Johnson and S. H. Clapp, *J. Biol. Chem.*, 1909, **5**, 49.



(1) (2) (3)

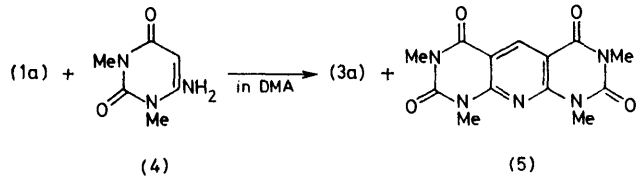
SCHEME 1

(ii) Upon heating (1a) in *N,N*-dimethylformamide, the

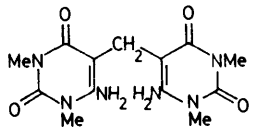
† Dehalogenation of 5-halogenouracils *via* an addition-elimination pathway has been extensively studied. (For a review, see E. G. Sander, in 'Bioorganic Chemistry,' ed. E. E. Tamelen, Academic Press, New York, 1978, vol. II, p. 273). Debromination of 5-bromouracils by ethylene glycol has been reported without detailed description of the mechanism [V. I. Gunar, I. A. Mikhailopulo, and S. I. Zav'yalov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1966, 1496 (*Chem. Abstr.*, 1967, **66**, 85749].

‡ In the absence of (1a), there was no colour development.

§ Thermolysis of (1a) in DMA leading to the methylenebisuracil (2a) was significantly accelerated by addition of a small amount of *N,N,N′,N′*-tetramethyl-*p*-phenylenediamine and almost completely suppressed in the presence of *p*-dinitrobenzene.



(4) (5)



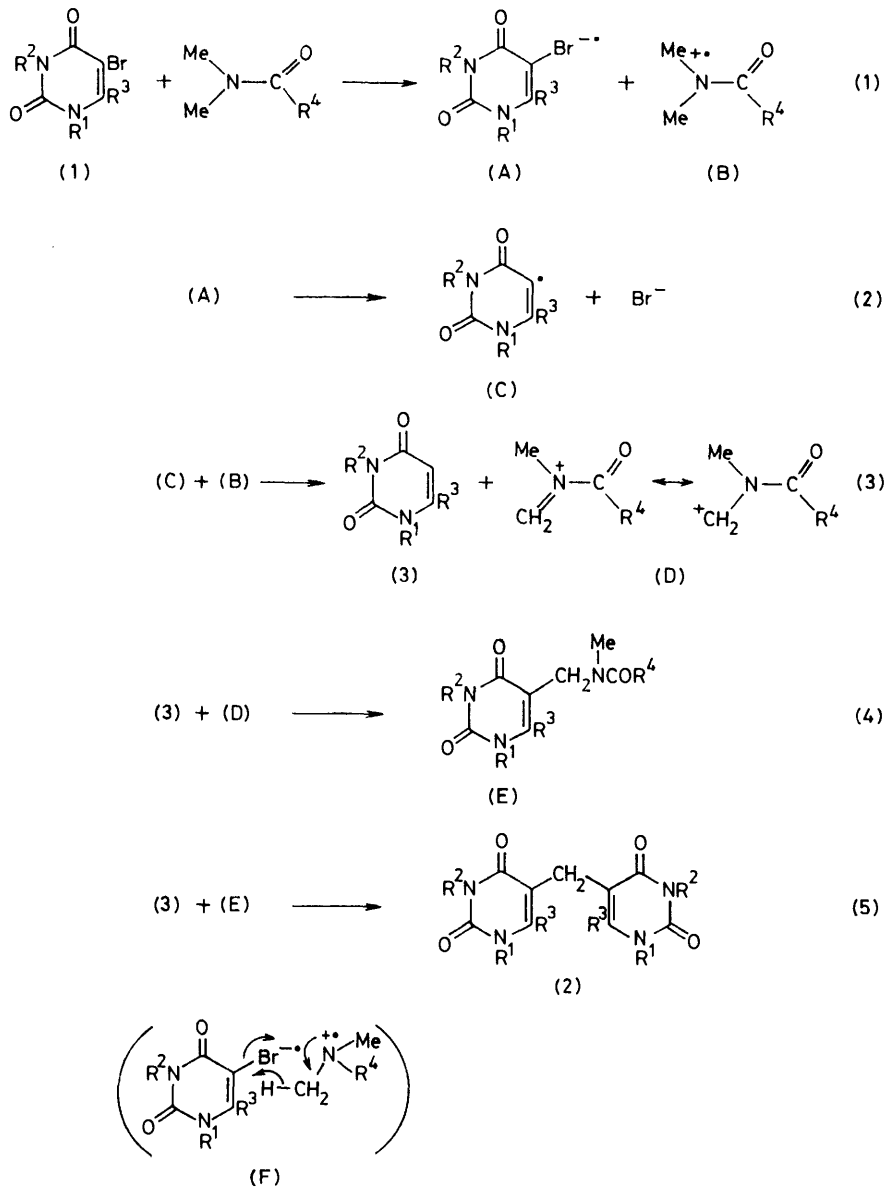
(6)

SCHEME 2

methylenebisuracil (2a) was obtained in 90% yield. Use of *N,N*-diethylacetamide as a solvent, however, gave only the debrominated product (3a).* In nonpolar solvents such as decalin and xylene, (1a) was recovered unchanged even after prolonged heating.

(iii) The reaction of (1a) with DMA at 160 °C was followed by n.m.r. spectroscopy. The result indicated accumulation and then decay of (3a) as the reaction proceeded. The yield of (3a) increased in the reaction (13.2% after 20 min) and then declined (2.1% after 1 h).

(iv) An equivalent mixture of (1a) and 6-amino-1,3-dimethyluracil (4) in DMA was heated at 160 °C for 4 h. After evaporation of the solvent, the residue was sub-



SCHEME 3

* Analogously, the formation of (2a) (yield 92%) was observed when hexamethylphosphoramide was employed as a solvent. The reaction of (1a) with *N,N*-dimethylaniline under the analogous conditions gave the debrominated product (3a) and 3-methyl-5-(*p*-dimethylaminophenylmethyl)-6-phenylthiouracil in 60% and 11% yields, respectively. Thioanisole also reacted with (1a) to give (3a) in 70% yield together with a trace amount of (2a).

jected to silica-gel chromatography to isolate (3a) and the pyridodipyrimidine (5) [5] in 96% [based on (1a)] and 39% [based on (4)] yields, respectively. The formation of compound (5) is explained in terms of intermediacy of the methylenebisuracil (6). In this reaction, no formation of (2a) was confirmed by t.l.c.

On the basis of the above experiments (i)—(iv), we present the reaction sequence for the formation of (2) and (3) from (1) as depicted in Scheme 3.

N,N,N',N'-Tetramethyl-*p*-phenylenediamine afforded a stable cation-radical (Wurster's blue) [4] by the action of bromine. Experiment (i) showed clearly the occurrence of a one-electron transfer from *N,N,N',N'*-tetramethyl-*p*-phenylenediamine to the 5-bromouracils (1). Thus, the initiation step of the reaction can be rationalised in terms of the donation of an electron from *N,N*-dialkylamide to (1) to give a radical-anion (A), which is then converted into a σ uracil radical (C) *via* subsequent elimination of bromide ion, and a cation radical (B) (steps 1 and 2 in Scheme 3).

Hydrogen abstraction by the uracil radical (C) from the cation radical (B) could give the dehalogenated product (3) and a carbonium ion (D) [6] which is highly reactive to nucleophiles (step 3 in Scheme 3).

Alternatively, formation of the debrominated uracils (3) and the carbonium ion (D) may occur *via* the reaction of the radical-anion (A) with the radical-cation (B) in a solvent cage as shown in (F) of Scheme 3.

Reductive dehalogenation of heteroaryl halides prompted by alkoxide ion has been shown to involve a one-electron transfer process followed by a chain reaction.[7] Some examples of thermal reductive dehalogenation of aryl halides by *N,N*-dimethylformamide under Ullmann's conditions have been reported without any detailed description of the mechanism.[8]

Electrophilic substitutions of uracils usually occur predominantly at position 5,[9] the ease of which depends upon the nature of substituents particularly at position 6.

Experiment (iii) suggests an intermediacy of the dehalogenated product (3) in the formation of (2). The former could undergo attack by the carbonium ion (D) to produce the 5-substituted methyluracil (E), which is transient under the reaction conditions (step 4 in Scheme 3).

The results obtained in experiment (ii) clearly show that the origin of the methylene carbon of (2) must be a methyl group of the dimethylamino-moiety in the amides employed.

As shown in the Table, the formation of the methylenebisuracil (2) is almost exclusive when a substituent is located at position 6 of compound (3). The result parallels the increased electron density at position 5 of (3) as a result of the influence of the 6-substituents,* 5-bromo-1,3-dimethyl-6-phenylthiouracil (1e) being an exception.

Further reaction of the 5-substituted methyluracils (E) with the dehalogenated products (3) gives the methylenebisuracils (2) under the conditions employed. Susceptibility of the substituents on the methyl group of thymines to nucleophilic displacement has been extensively studied.[10]

Trapping of the carbonium ion (D) was achieved by experiment (iv). Position 5 of 6-amino-1,3-dimethyluracil (4) is more susceptible to nucleophilic attack than that in (3a). Accordingly, step 4 in Scheme 3 is efficiently interrupted due to the presence of the 6-aminouracil (4) which reacts with the carbonium ion (D) to give the pyridodipyrimidine (5) *via* the methylenebisuracil (6).

* The chemical shifts of the C(5)-position in n.m.r. spectra of (3a—h) are in accord with this aspect.

EXPERIMENTAL

All melting points were determined on a Yanagimoto micro hot-stage apparatus and are uncorrected. Microanalytical results were obtained from the microanalytical laboratory of this College. I.r. spectra were recorded on a Hitachi 215 spectrometer for potassium bromide discs. ^{1}H N.m.r. spectra were obtained on a Hitachi R-24 B (60 MHz) spectrometer for solutions in deuteriodimethyl sulphoxide containing tetramethylsilane as internal standard. Mass spectra were measured at 75 eV with a JEOL JMS-OISG spectrometer and u.v. spectra with a Hitachi 323 spectrophotometer. Column chromatography was performed on silica gel (Wako gel C-300) using chloroform–acetone or chloroform–methanol as eluant.

Preparation of 5-Bromouracils (1a—e).—To a suspension of 3-methyl-6-phenylthiouracil (3a) (2.35 g) in methanol (10 ml), bromine (0.60 ml) was added and the mixture stirred for 1 h at room temperature. The crystalline mass was collected and recrystallised from methanol to give *5-bromo-3-methyl-6-phenylthiouracil* (1a) (3.06 g), m.p. 214—215 °C (Found: C, 42.45; H, 2.95; N, 9.0. $C_{11}H_9BrN_2O_2S$ requires C, 42.19; H, 2.90; N, 8.95%), *m/e* 313 (M^+), $\nu_{max.}$ 1 700 (CO) and 1 640 cm^{-1} (CO); δ 3.30 (3 H, s, NMe), 7.40 (1 H, b, NH, deuterium exchangeable), and 7.57 (5 H, s, ArH).

Analogously, 5-bromouracils (1b—e) were prepared. *5-Bromo-3-methyl-6-phenoxyuracil* (1b) (66.78%), m.p. 253—255 °C (ethanol) (Found: C, 44.5; H, 2.9; N, 9.5. $C_{11}H_9BrN_2O_3$ requires C, 44.47; H, 3.05; N, 9.43%), *m/e* 297 (M^+), $\nu_{max.}$ 1 700 (CO) and 1 640 cm^{-1} (CO); δ 3.26 (3 H, s, NMe) and 7.00—7.60 (6 H, m, ArH and deuterium exchangeable NH). *5-Bromo-6-(N-p-bromophenyl-N-methylamino)-3-methyluracil* (1c) (74.84%), m.p. 198—199 °C (methanol) (Found: C, 37.25; H, 2.9; N, 10.75. $C_{12}H_{11}Br_2N_3O_2$ requires C, 37.05; H, 2.85; N, 10.80%), *m/e* 389 (M^+), $\nu_{max.}$ 3 200 (NH), 1 700 (CO), and 1630 cm^{-1} (CO); δ 3.29 (6 H, s, NMe), 6.88 (2 H, d, *J* 11 Hz, ArH), 7.45 (2 H, d, *J* 11 Hz, ArH), and 11.84 (1 H, b, NH, deuterium exchangeable). *5-Bromo-6-phenylthiouracil* (1d) (82.86%), m.p. 310—317 °C (methanol) (Found: C, 40.15; H, 2.25; N, 9.4. $C_{10}H_7BrN_2O_2S$ requires C, 40.16; H, 2.36; N, 9.37%) *m/e* 299 (M^+), $\nu_{max.}$ 3 200 (NH), 1 710 (CO), and 1 660 cm^{-1}, (CO); δ 7.48 (5 H, s, ArH), 11.10 (1 H, b, NH, deuterium exchangeable), and 11.60 (1 H, b, NH, deuterium exchangeable). *5-Bromo-1,3-dimethyl-6-phenylthiouracil* (1e) (73.17%), m.p. 138—139 °C (methanol) (Found: C, 44.2; H, 3.4; N, 8.6. $C_{12}H_{11}BrN_2O_2S$ requires C, 44.06; H, 3.39; N, 8.56%), *m/e* 327 (M^+), $\nu_{max.}$ 1 690 (CO) and 1 640 cm^{-1} (CO); δ 3.30 (3 H, s, NMe), 3.47 (3 H, s, NMe), and 7.45 (5 H, s, ArH).

Thermolysis of 5-Bromouracils (1a—h) *in* N,N-*Dimethyl-*

acetamide (*DMA*).—A solution of the 5-bromouracil (1a) (0.32 g) in DMA (2 ml) was heated at 160 °C for 1 h. After removal of the solvent under reduced pressure, the residue was triturated with chloroform to give 5,5′-*methylene-bis*(3-*methyl*-6-*phenylthiouracil*) (2a) (0.23 g), m.p. 284—285 °C (methanol) (Found: C, 57.55; H, 4.1; N, 11.7. $C_{23}H_{20}N_4O_4S_2$ requires C, 57.50; H, 4.20; N, 11.66%), *m/e* 480 (M^+), $\nu_{max.}$ 1 700 (CO) and 1 640 cm^{-1} (CO); δ 3.12 (6 H, s, NMe), 3.94 (2 H, br s, CH_2), 7.37 (10 H, s, ArH), and 11.17 (2 H, b, NH, deuterium exchangeable). The mother liquor was chromatographed (eluant: chloroform–acetone, 20 : 1) to isolate the debrominated uracil (3a) (0.02 g).

Thermolysis of compounds (1b—h) was carried out under analogous conditions. The methylenebisuracils (2b—h) and the debrominated uracils (3b—h) were isolated in a manner similar to that described for (2a) and (3a) (see Table): 5,5′-*methylenebis*(3-*methyl*-6-*phenoxyuracil*) (2b), m.p. 308—313 °C (methanol) (Found: C, 61.7; H, 4.6; N, 12.6. $C_{23}H_{20}N_4O_6$ requires C, 61.60; H, 4.50; N, 12.50%), *m/e* 448 (M^+), $\nu_{max.}$ 1 700 (CO) and 1 640 cm^{-1} (CO); δ 3.07 (6 H, s, NMe), 3.12 (2 H, br s, CH_2), 6.70—7.50 (10 H, m ArH), and 11.60 (2 H, b, NH, deuterium exchangeable). 5,5′-*Methylbenebis*[6-(N-p-*bromophenyl*-N-*methylamino*)-3-*methyluracil*] (2c), m.p. 320—323 °C (methanol) (Found: C, 47.75; H, 3.9; N, 13.55. $C_{25}H_{24}Br_2N_6O_4$ requires C, 47.49; H, 3.83; N, 13.29%), *m/e* 632 (M^+), $\nu_{max.}$ 1 680 (CO) and 1 620 cm^{-1} (CO); δ 2.98 (6 H, s, NMe), 3.00 (2 H, b, CH_2), 3.08 (6 H, s, NMe), 6.53 (4 H, d, *J* 11 Hz, ArH), 7.32 4 H, d, *J* 11 Hz, ArH), and 11.00 (2 H, b, NH, deuterium exchangeable). 5,5′-*Methylenebis*(6-*phenylthiouracil*) (2d), m.p. 312—315 °C (methanol) (Found: C, 53.6; H, 3.55; N, 11.95. $C_{21}H_{16}N_4O_4S_2{\cdot}H_2O$ requires C, 53.62; H, 3.86; N, 11.91%), *m/e* 452 (M^+), $\nu_{max.}$ 3 150 (NH), 1 700 (CO), and 1 650 cm^{-1} (CO); δ 3.83 (2 H, br s, CH_2), 7.39 (10 H, s, ArH, 10.88 (2 H, b, NH, deuterium exchangeable), and 11.20 (2 H, b, NH, deuterium exchangeable). 5,5′-*Methylenebis*(1,3-*dimethyl*-6-*phenylthiouracil*) (2e), m.p. 222—223 °C (ethanol) (Found: C, 58.85; H, 4.7; N, 10.9. $C_{25}H_{24}N_4O_4S_2$ requires C, 59.05; H, 4.76; N, 11.02%), *m/e* 508 (M^+), $\nu_{max.}$ 1 700 (CO) and 1 640 cm^{-1} (CO); δ 3.17 (6 H, s, NMe), 3.23 (6 H, s, NMe), 4.07 (2 H, br s, CH_2), and 7.00—7.50 (10 H, m, ArH). 5,5′-*Methylenebis*(3-*methyluracil*) (2g), m.p. > 300 °C (methanol) (Found: C, 49.85; H, 4.55; N, 21.15. $C_{11}H_{12}N_4O_4$ requires C, 50.00; H, 4.58; N, 21.20%), *m/e* 264 (M^+), $\nu_{max.}$ 3 225 (NH), 1 710 (CO), 1 660 (CO), and 1 630 cm^{-1} (CO); δ 3.15 (6 H, s, NMe), 3.20 (2 H, br s, CH_2), 7.32 (2 H, broad s, 6 H), and 11.00 (2 H, b, NH, deuterium exchangeable). 5,5′-*Methylenebis*(1,3-*dimethyluracil*) (2h), m.p. 284—285 °C (methanol) (Found: C, 53.3; H, 5.5; N, 19.15. $C_{13}H_{16}N_4O_4$ requires C, 53.42; H, 5.52; N, 19.17%), *m/e* 292 (M^+), $\nu_{max.}$ 1 690 (CO), 1 660 (CO), and 1 630 cm^{-1} (CO); δ 3.20 (6 H, s, NMe), 3.25 (2 H, br s, CH_2), 3.31 (6 H, s, NMe), and 7.51 (2 H, br s, 6-H).

Thermolysis of 5-*Bromo*-3-*methyl*-6-*phenylthiouracil* (1a).—(a) *In* N,N-*dimethylformamide*. A solution of (1a) (313.2 mg) in *N,N*-dimethylformamide (2.0 ml) was heated at 160 °C for 1 h. After removal of the solvent under reduced pressure, the residue was triturated with chloroform to afford the methylenebisuracil (2a) (215.7 mg). The mother liquor was chromatographed to isolate the debrominated uracil (3a) (5.2 mg).

(b) *In* N,N-*diethylacetamide*. Treatment of (1a) (0.32 g) in *N,N*-diethylacetamide (2.0 ml) at 160 °C for 1 h gave only the debrominated uracil (3a) (0.23 g). No formation of other products was detected by t.l.c. of the reaction mixture.

Thermolysis of 5-*Bromo*-3-*methyl*-6-*phenylthiouracil* (1a) *in DMA in the Presence of* 6-*Amino*-1,3-*dimethyluracil* (4).—A mixture of (1a) (0.32 g) and 6-amino-1,3-dimethyluracil (4) (0.16 g) in DMA (3.0 ml) was heated at 160 °C for 4 h. After removal of the solvent under reduced pressure, the residue was chromatographed (eluant: chloroform–methanol, 50 : 1) to isolate the debrominated uracil (3a) (0.23 g) and 1,3,7,9-tetramethylpyrido[2,3-*d*; 6,5-*d*′]dipyrimidine-2,4,6,8(1*H*,3*H*,7*H*,9*H*)-tetraone (5) (0.06 g). The latter compound was identical with an authentic sample prepared by the thermal reaction of (3a) in dimethyl sulphoxide.[5] In this reaction, there was no formation of the methylenebisuracil (2a) as confirmed by t.l.c.

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