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Reactions of 5-Bromouracils as Electron Acceptors. Reductive Debromination Involving an Initial Electron Transfer Process

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Thermal reactions of 5-bromouracils **1** with a well-known one-electron donor such as *N*-methylindole (**2**) or *N*-methylphenothiazine (**13**) result in easy reductive debromination, presumably involving an initial electron transfer process which appears to depend largely upon the nature of the substituents at the N(1)- and C(6)-positions of the uracil ring.

Keywords——5-bromouracil; electron acceptor; electron transfer mechanism; reductive debromination; *N*-methylindole; *N*-methylphenothiazine

The dehalogenation of 5-halogenouracils by nucleophiles has been extensively investigated.[1] The frequently observed dehalogenation of 5-bromo- or 5-iodouracils can reasonably be explained in terms of an addition-elimination mechanism, involving the initial attack of nucleophiles on the C(6)-position of the uracil ring, as shown in Chart 1.

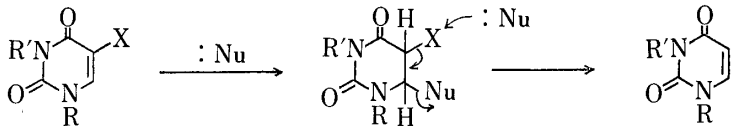


Chart 1

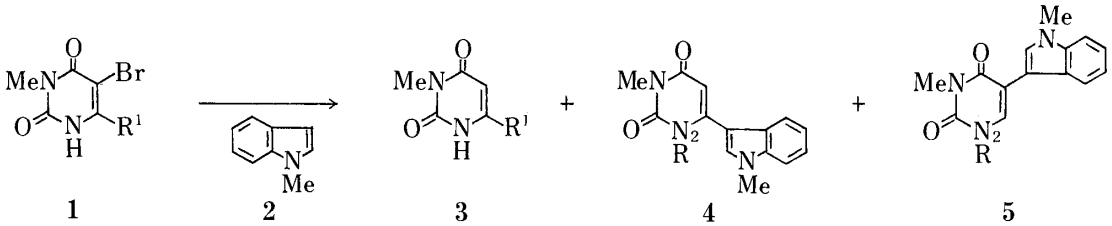
On the other hand, uracils are the strongest electron acceptors among nucleic acid bases.[2] This property can be further enhanced by the introduction of a halogen atom at the C(5)-position of the uracil ring. Thus, 5-bromodeoxyuridine (broxuridine) has been applied clinically as a radiation sensitizer.[3] The electron-accepting nature of 5-bromouracils has also been found in electrochemical reduction[4] and γ-ray[5] or ultraviolet[6] irradiation under certain conditions, resulting in debromination. The behavior of 5-bromouracils in the presence of electron donors under thermal conditions, however, has been little documented.

Our previous work[7] provided the first example of reductive debromination initiated by a one-electron transfer when the thermolysis of 5-bromouracils was carried out in *N*,*N*-dialkylamides. The present paper describes the thermolysis of 5-bromouracils **1** in the presence of a well-known one-electron donor, *N*-methylindole (**2**)[8] or *N*-methylphenothiazine (**13**),[9] which also results in reductive debromination. These findings provide further evidence that 5-bromouracils **1** undergo reductive debromination *via* an electron transfer process in the presence of a one-electron donor.

Results and Discussion

(1) Reactions of 5-Bromouracils 1 with *N*-Methylindole (2)

A mixture of 5-bromo-3-methyl-6-(*N*-methyl-*p*-bromoanilino)uracil (**1a**)[7] and excess **2** was heated at 90 °C[10] without any solvent under an argon atmosphere for 0.5 h. Silica gel column chromatography of the reaction mixture provided 3-methyl-6-(*N*-methyl-*p*-



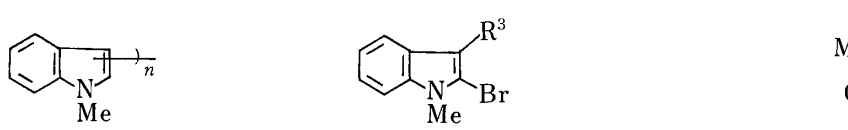
1 2 3 4 5

a : R^1=NMePh (*p*-Br)
b : R^1=OPh
c : R^1=SPh
d : R^1=H

a : R^1=NMePh (*p*-Br)
b : R^1=OPh
c : R^1=SPh
d : R^1=H

a : R^2=H
b : R^2=Me

a : R^2=H
b : R^2=Me



6 7 8

a : n=2
b : n=3

a : R^3=H
b : R^3=Br

Chart 2

bromoanilino)uracil (**3a**)[11] in excellent yield, together with significant amounts of an indole dimer, 1-methyl-2-(1-methylindol-3-yl)indole (**6a**)[12] and a trimer **6b**. No other products were detected by thin layer chromatography (TLC) analysis and nuclear magnetic resonance (NMR) spectroscopy of the reaction mixture. Experiments in total darkness gave analogous results, indicating that the reaction was not affected by sunlight.

Treatment of 5-bromo-3-methyl-6-phenoxyuracil (**1b**)[7] with **2** at 140 °C[10] gave 3-methyl-6-phenoxyuracil (**3b**, 68%)[13] and 3-methyl-6-(1-methylindol-3-yl)uracil (**4a**, 25%). The presence of the indole oligomers **6a,b** and phenol in the reaction mixture was shown by TLC analysis. Under similar conditions, 5-bromo-3-methyl-6-phenylthiouracil (**1c**)[7] gave 3-methyl-6-phenylthiouracil (**3c**, 75%)[14] and **4a** (16%) along with **6a,b** and thiophenol.

Thermolysis of 5-bromo-3-methyluracil (**1d**)[15] in **2** at 170 °C[10] resulted in the formation of 3-methyluracil (**3d**, 55%),[15] **4a** (9%), and 3-methyl-5-(1-methylindol-3-yl)uracil (**5a**, 18%). TLC analysis of the reaction mixture showed the presence of **6a,b**.

The debrominated uracils **3a**—**d** and the indole dimer **6a** obtained above were identical with authentic samples.[11-15] The precise structure of the indole trimer **6b** could not be determined on the basis of the available spectral data. The structures of the indolyluracil derivatives (**4a** and **5a**) were supported by microanalytical and spectral data, and by their conversion into the methyl derivatives (**4b** and **5b**). The structure of **4a** was easily distinguished from that of **5a** on the basis of the NMR spectra, *i.e.*, a uracil ring proton of **4a** is observed at higher field than that of **5a**. (δ 6.00 for **4a** and δ 7.67 for **5a**.)

The results of these thermal reactions show that the ease of the debromination of **1** depends largely upon the nature of the substituents at the C(6)-position of the uracil ring.[10]

In contrast to N(1)-unsubstituted 5-bromouracils **1** described above, 1,3-disubstituted 5-bromouracils, *e.g.*, 5-bromo-1,3-dimethyl-6-phenylthiouracil[7] and 5-bromo-1,3-dimethyluracil,[16] were inert upon treatment with **2** under analogous conditions.[17] Thus, non-substitution at the N(1)-position of the uracil ring was shown to be requisite for this type of debromination. The significant substituent effect on the reductive debromination can be rationalized in terms of the involvement of a tautomeric form **8** in the reaction.[18] The C(5)-bromine of **8** is activated by adjacent carbonyl and acylimino groups. Reductive de-

halogenation of activated halides, *e.g.*, α-haloketones, in the presence of electron donors has already been observed.[19]

The debrominated uracils **3a—d** do not react with **2** even under more drastic conditions; the starting materials are recovered. This fact indicates that **3** is not an intermediate in the formation of the indolyluracils **4a** and **5a**. Accordingly, the formation of **4a** seems to proceed *via* the nucleophilic addition of **2** at the C(6)-position of 5-bromouracils **1b—d** followed by debromination (addition-elimination mechanism), since the C(6)-position of **1b—d** is susceptible to attack by nucleophiles and the C(3)-position of the indole ring is the most nucleophilic site.[8] Formation of **5a** during thermolysis of **1d** in the presence of **2** can be explained in terms of nucleophilic substitution by **2** at the C(5)-position of the tautomeric form **8**.

As mentioned above, the thermal reactions of **1** with **2** yielded a significant amount of indole oligomers **6a,b** besides the uracil derivatives **3**, **4a**, and **5a**. Formation of **6a,b** seems to provide a clue concerning the mechanism of the debromination of **1**.

Further experiments were carried out with **1a** as a reactant.

When a solution of **1a** and an equimolar amount of **2** in acetonitrile was refluxed for 0.5 h under an argon atmosphere, 2-bromo-1-methylindole (**7a**, 72%) and 2,3-dibromo-1-methylindole (**7b**, 10%) were obtained as fairly stable oily products together with **3a** (86%) and **6a,b** (trace). Thus, employment of acetonitrile as a solvent for the reaction of **1a** with **2** allowed isolation of **7a,b**, the structures of which were assigned on the basis of their spectral data. The NMR spectrum of **7a** showed a singlet signal at δ 6.94, which was assigned to the C_3-proton of the indole ring. Treatment of **7a** with refluxing methanol afforded 1-methyl-2-oxindole[20] almost quantitatively. Heating of **7a** with **2** without any solvent at 90 °C for 0.5 h under an argon atmosphere gave **6a** in a good yield.

These results apparently indicate that the indole dimer **6a** is produced from **7a** initially formed in the thermal reaction of **1** with **2**. The formation of **7a** is accounted for by substitution of the bromide ion eliminated from **1** at the C(2)-position of **2**. Such a preferential substitution at the C(2)-position of the indole ring has been observed in the reactions of an indolyl cation radical with nucleophiles.[21] Thus, the formation of **7a** points to the occurrence of the reaction of the indolyl cation radical with bromide ion, supporting the view that the electron transfer process is involved in the debromination of **1** by **2**.

Taking into consideration the above results and the capacity of indoles as one-electron

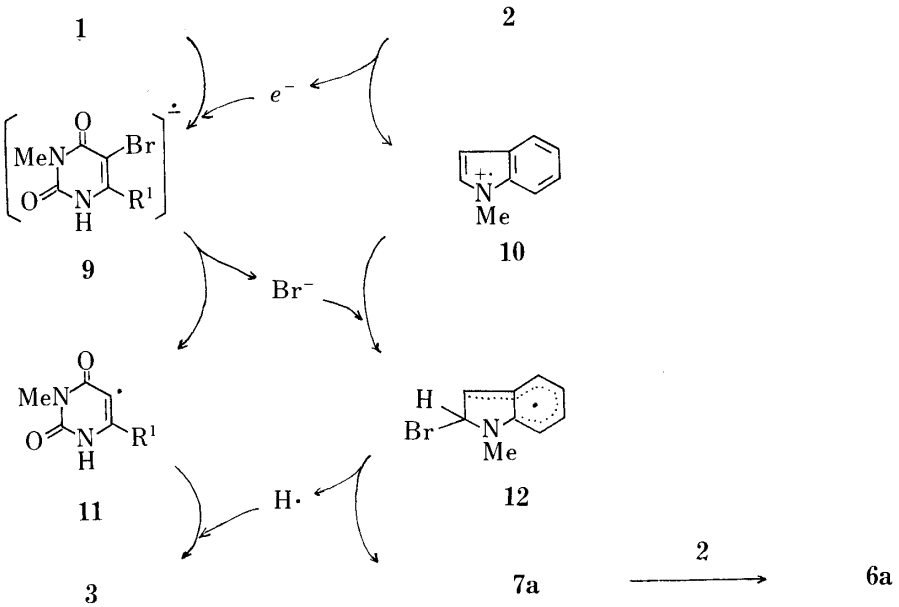
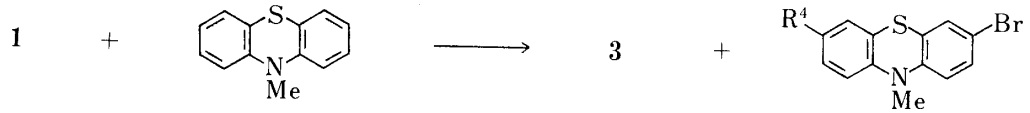


Chart 3

donors, we propose the reaction sequence depicted in Chart 3 for the thermal debromination of **1** by **2**, which occurs in competition with nucleophilic substitution.

The initiation step of the reaction can be rationalized by the donation of an electron from **2** to **1**[22] to give a uracilyl anion radical **9**, which is converted to a σ radical **11** by subsequent elimination of a bromide ion,[5] and an indolyl cation radical **10**. The cation radical **10** then captures the eliminated bromide ion at its C(2)-position to afford a radical **12**. Hydrogen abstraction by the σ radical **11** from the radical **12** results in the formation of the debrominated uracils **3** and 2-bromo-1-methylindole (**7a**) as final products. Subsequently, compound **7a** could react with **2** to give the indole dimer **6a** under the conditions employed.

(2) Reactions of 5-Bromouracils 1 with *N*-Methylphenothiazine (13)



a : R^4 = H
b : R^4 = Br

Chart 4

A mixture of **1a** and **13** (0.5 eq) was heated at 100 °C[10] without any solvent under an argon atmosphere for 0.5 h. The reaction mixture was subjected to sillica gel column chromatography to isolate **3a**, 3-bromo-10-methylphenothiazine (**14a**), and 3,7-dibromo-10-methylphenothiazine (**14b**) in 85, 50, and 46% yields, respectively. No other products were found by TLC analysis and NMR spectroscopy of the reaction mixture. The bromophenothiazines **14a,b** were identical with authentic samples[23] prepared by the reaction of **13** with bromine. Thermal reaction of an equivalent mixture of **1a** and **13** under analogous conditions resulted in an increase in the yield of **14a** rather than **14b**.

Under analogous conditions, other 5-bromouracils **1b—d** were also debrominated by **13**

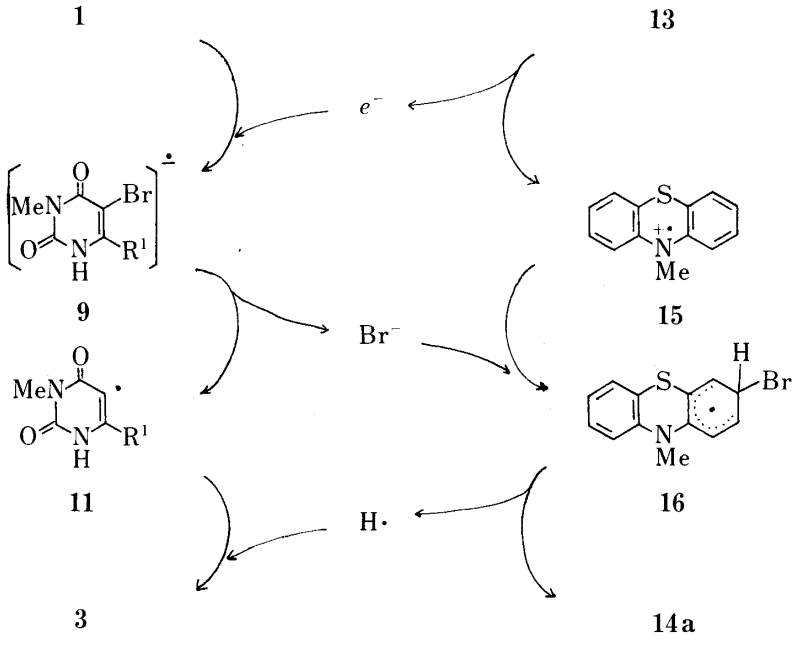


Chart 5

almost quantitatively. TLC analysis of these reaction mixtures showed the presence of **14a,b**.

The debromination of **1a** by **13** occurred even at room temperature. When **13** was added to a solution of **1a** in acetonitrile at room temperature, the color of the solution immediately turned reddish-orange and then faded gradually. The ultraviolet (UV) spectrum of the reaction mixture showed absorptions at 440 and 510 nm, which are characteristic of the phenothiazine cation radical.[24] TLC analysis of the reaction mixtures showed the presence of **3a** and **14a,b**. This observation supports the occurrence of a one-electron transfer from **13** to **1**. Thus, the debromination of **1** by **13** could also proceed *via* an electron transfer process as outlined in Chart 5.

Conclusion

The character of 5-bromouracils **1** as one-electron acceptors was substantiated under thermal conditions; the reaction of **1** with one-electron donors such as **2** and **13** results in reductive debromination, presumably *via* an initial electron transfer process, although the ease of the debromination depends largely upon the nature of substituents at the N(1)- and C(6)-positions of the uracil ring. The substituent dependence of the debromination in **1** presented in this paper has interesting mechanistic implications.

Experimental

All melting points were determined on a Yanagimoto micro hot stage apparatus and are uncorrected. Elemental analyses were performed at the Analytical Center in our college. Infrared (IR) spectra were recorded on a Hitachi 215 spectrometer in potassium bromide discs. ^{1}H-NMR spectra were obtained on a Hitachi R-24 B (60 Hz) spectrometer in deuteriodimethyl sulfoxide or deuteriochloroform containing tetramethylsilane as an internal standard. Mass spectra were measured at 75 eV with a JEOL JMS-OISG spectrometer and UV spectra with a Hitachi 323 spectrophotometer. Column chromatography was performed on silica gel (Wako gel C-300) using *n*-hexane–ethyl acetate, chloroform–acetone or chloroform–methanol as the eluant. TLC analyses were carried out by using silica gel plates (Merck pre-coated plates silica gel 60 F-254 and mixed solvents (*n*-hexane–ethyl acetate and chloroform–acetone).

Thermal Reactions of 5-Bromouracils 1 with *N*-Methylindole (2)——(1) 5-Bromo-3-methyl-6-(*N*-methyl-*p*-bromoanilino)uracil (**1a**): a) Without Solvent: A mixture of **1a** (389 mg, 1.0 mmol) and **2** (0.4 ml, 3.1 mmol) was heated at 90 °C under an argon atmosphere for 0.5 h. The reaction mixture was chromatographed over silica gel with chloroform–acetone (20 : 1) to afford **3a** (270 mg, 87%). Careful column chromatography of the first eluate with *n*-hexane–ethyl acetate (20 : 1) as the eluant yielded **6a**; mp 129—130 °C (lit.,[12] 137—138 °C); ^{1}H-NMR (in $CDCl_3$) δ: 3.69 (3H, s, NMe), 3.79 (3H, s, NMe), 6.65 (1H, s, C_3–H) 7.00—7.80 (9H, m, ArH); MS *m/e*: 260 (M^+), and an indole trimer **6b**; mp 175—176 °C (from *n*-hexane–ethyl acetate); *Anal.* Calcd for $C_{27}H_{23}N_3$: C, 83.26; H, 5.95; N, 10.79. Found: C, 82.91; H, 5.97; N, 10.60; ^{1}H-NMR (in $CDCl_3$) δ: 2.69 (3H, s, NMe), 3.44 (3H, s, NMe), 4.43 (3H, s, NMe), 6.76 (2H, br dd, J=8 Hz, ArH), 7.00—7.60 (9H, m, ArH), 7.94 (1H, s, ArH), 7.98 (1H, br d, J=8 Hz, ArH), 8.57 (1H, br d, J=8 Hz, ArH); MS *m/e*: 389 (M^+).

b) In Acetonitrile: A solution of **1a** (389 mg, 1.0 mmol) and **2** (0.13 ml, 1.0 mmol) in acetonitrile (10 ml) was refluxed for 0.5 h under an argon atmosphere. After removal of the solvent under reduced pressure, the residue was chromatographed over silica gel with *n*-hexane–ethyl acetate (20 : 1) and chloroform–acetone (20 : 1) to yield **3a** (268 mg, 86%), 2-bromo-1-methylindole (**7a**) (152 mg, 72%); ^{1}H-NMR (in $CDCl_3$) δ: 3.65 (3H, s, NMe), 6.94 (1H, s, ArH), 7.00—7.60 (4H, M, ArH); MS *m/e*: 210 (M^+), 130 ($M^+ - Br$), and 2,3-dibromo-1-methylindole (**7b**) (30 mg, 10%); ^{1}H-NMR (in $CDCl_3$) δ: 3.68 (3H, s, NMe), 6.90—7.60 (4H, m, ArH); MS *m/e*: 289 (M^+).

A solution of **7a** (50 mg, 0.2 mmol) in methanol (5 ml) was refluxed for 1 h. After removal of the solvent under reduced pressure, the residue was purified by silica gel chromatography with chloroform to give 1-methyl-2-oxindole (29 mg, 83%); mp 92 °C (lit.,[20] 86—88 °C).

A mixture of **7a** (105 mg, 0.5 mmol) and **2** (0.13 ml, 1.0 mmol) was heated at 90 °C without solvent under an argon atmosphere for 0.5 h. Purification of the reaction mixture by silica gel column chromatography with *n*-hexane–ethyl acetate (20 : 1) gave the indole dimer **6a** (49 mg, 75%).

(2) 5-Bromo-3-methyl-6-phenoxyuracil (**1b**): A mixture of **1b** (298 mg, 1.0 mmol) and **2** (1.0 ml, 7.8 mmol) was heated at 140 °C for 0.5 h under an argon atmosphere. Silica gel chromatography with chloroform–acetone (20 : 1) provided **3b** (214 mg, 68%) and 3-methyl-6-(1-methylindol-3-yl)uracil (**4a**) (65 mg, 25%); mp 295—297 °C (from

methanol); *Anal.* Calcd for $C_{14}H_{13}N_3O_2$: C, 65.87; H, 5.13; N, 16.46. Found: C, 66.11; H, 5.09; N, 16.61; IR ν_{max}^{KBr} cm^{-1}: 3220 (NH), 1705 (C=O), 1635 (C=O); UV λ_{max}^{MeCN} nm (ε): 222.5 (3.0×10^4), 262 (9.6×10^3), 320 (2.1×10^4); ^{1}H-NMR (in DMSO-d_6) δ:3.22 (3H, s, NMe), 3.89 (3H, s, NMe), 6.00 (1H, s, C_5–H), 7.0—8.00 (4H, m, ArH), 8.23 (1H, s, indole ring proton), 11.14 (1H, br, NH); MS *m/e*: 255 (M^+). Formation of **6a,b** and a trace amount of phenol was confirmed by TLC analysis of the reaction mixture.

(3) 5-Bromo-3-methyl-6-phenylthiouracil (**1c**): Under conditions similar to those used for **1b**, **1c** (314 mg, 1.0 mmol) afforded **3c** (176 mg, 75%) and **4a** (40 mg, 16%). Compounds **6a,b** and a trace amount of thiophenol were detected by TLC analysis of the reaction mixture.

(4) 5-Bromo-3-methyluracil (**1d**): A mixture of **1d** (206 mg, 1.0 mmol) and **2** (0.5 ml, 4.0 mmol) was heated at 170 °C for 0.5 h under an argon atmosphere. The reaction mixture was chromatographed over silica gel with chloroform–acetone (10:1) and chloroform–methanol (10:1) to afford **3d** (69 mg, 55%), **4a** (24 mg, 9%) and 3-methyl-5-(1-methylindol-3-yl)uracil (**5a**) (45 mg, 18%); mp 281—282 °C (from methanol); *Anal.* Calcd for $C_{14}H_{13}N_3O_2$: C, 65.87; H, 5.13; N 16.46. Found: C, 65.84; H, 5.10; N, 16.59; IR ν_{max}^{KBr} cm^{-1}: 3230 (NH), 1720 (C=O), 1640 (C=O); UV λ_{max}^{MeCN} nm (ε): 231 (3×10^4), 305 (9.5×10^3); ^{1}H-NMR (in DMSO-d_6) δ: 3.27 (3H, s, NMe), 3.83 (3H, s, NMe), 7.00—7.80 (4H, m, ArH), 7.67 (1H, s, C_6–H), 7.71 (1H, s, indole ring proton); MS *m/e*: 255 (M^+). TLC analysis of the reaction mixture showed the presence **6a,b**.

(5) 5-Bromo-1,3-disubstituted Uracils: Thermal reaction of 5-bromo-1,3-dimethyl-6-phenylthiouracil (1.0 mmol) in **2** (4 mmol) at 140 °C gave only unchanged starting material even after 2 h.

Treatment of 5-bromo-1,3-dimethyluracil (220 mg, 1.0 mmol) with **2** (0.5 ml, 4.0 mmol) at 180 °C for 1 h under an argon atmosphere gave only recovered starting material.

Methylation of the Indolyluracil Derivatives 4a and 5a—— (1) Methylation of **4a**: A mixture of **4a** (56 mg, 0.2 mmol), methyl iodide (1.0 ml), and anhydrous potassium carbonate (91 mg, 0.6 mmol) in acetone (4 ml) was stirred at room temperature for 2 h. After removal of the precipitate by filtration, the filtrate was evaporated to dryness under reduced pressure and purified by silica gel chromatography with chloroform to afford 1,3-dimethyl-6-(1-methylindol-3-yl)uracil (**4b**) (50 mg, 85%) mp 163—164 °C (from ethanol); *Anal.* Calcd for $C_{15}H_{15}N_3O_2$: C, 66.90; H, 5.61; N, 15.61. Found: C, 66.63; H, 5.57; N, 15.44; UV λ_{max}^{MeCN} nm (ε): 221 (3×10^4), 275 (1.1×10^4), 305 (1.1×10^4); ^{1}H-NMR (in $CDCl_3$) δ: 3.37 (3H, s, NMe), 3.40 (3H, s, NMe), 3.86 (1H, s, NMe), 5.82 (1H, s, C_5–H), 7.24 (1H, s, indole ring proton), 7.10—7.60 (4H, m, ArH); MS *m/e*: 269 (M^+).

(2) Methylation of **5a**: In a similar manner, **5a** (30 mg, 0.1 mmol) gave 1,3-dimethyl-5-(1-methylindol-3-yl)uracil (**5b**) (28 mg, 89%); mp 226—227 °C (from ethanol); *Anal.* Calcd for $C_{15}H_{15}N_3O_2$: C, 66.90; H, 5.61; N, 15.61. Found: C, 66.65; H, 5.61; N, 15.52; IR ν_{max}^{KBr} cm^{-1}: 1690 (C=O), 1660, 1635; UV λ_{max}^{MeCN} nm (ε): 231 (3×10^4), 310 (9.7×10^3); ^{1}H-NMR (in $CDCl_3$) δ: 3.40 (6H, s, NMe), 3.74 (3H, s, NMe), 7.00—7.70 (4H, m, ArH), 7.48 (1H, s, C_6–H), 7.66 (1H, s, indole ring proton); MS *m/e*: 269 (M^+).

Thermal Reactions of 5-Bromouracils 1 with *N*-Methylphenothiazine (13)——(1) 5-Bromo-3-methyl-6-(*N*-methyl-*p*-bromoanilino)uracil (**1a**): A mixture of **1a** (389 mg, 1.0 mmol) and **13** (107 mg, 0.5 mmol) was heated without solvent at 100 °C for 0.5 h under an argon atmosphere. The reaction mixture was chromatographed over silica gel with chloroform–acetone (20:1) to isolate **3a** (263 mg, 85%). silica gel column chromatography of the first eluate with *n*-hexane–ethyl acetate (30:1) as the eluant gave 3-bromo-10-methylphenothiazine (**14a**) (73 mg, 50%); mp 120—121 °C (lit.,[23] 108—112 °C), and 3,7-dibromo-10-methylphenothiazine (**14b**) (85 mg, 46%); mp 150—151 °C (lit.,[23] 144—145 °C). No other products were detected by TLC analysis or NMR spectroscopy of the reaction mixture.

(2) 5-Bromo-3-methyl-6-phenoxyuracil (**1b**): A mixture of **1b** (298 mg, 1.0 mmol) and **13** (214 mg, 1.0 mmol) was heated at 140 °C for 0.5 h under an argon atmosphere. Compound **3b** (210 mg, 96%) was isolated by column chromatography over silica gel with chloroform–acetone (20:1). Formation of **14a,b** was demonstrated by TLC analysis of the reaction mixture.

(3) 5-Bromo-3-methyl-6-phenylthiouracil (**1c**): Under conditions similar to those used for **1b**, **1c** (314 mg, 1.0 mmol) gave **3c** (206 mg, 88%) and **14a,b**.

(4) 5-Bromo-3-methyluracil (**1d**): Thermolysis of **1d** (206 mg, 1.0 mmol) in the presence of **13** (214 mg, 1.0 mmol) at 170 °C for 0.5 h resulted in the formation of **3d** (110 mg, 87%) and **14a,b**.

References and Notes

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