Pergamon

Bioorganic & Medicinal Chemistry, Vol. 3, No. 7, pp. 891–897, 1995

0968-0896/95 $9.50 + .00

0968-0896(95)00085-2

Reactions of Diazines with Nucleophiles—IV.[1] The Reactivity of 5-Bromo-1,3,6-trimethyluracil with Thiolate ions—Substitution Versus X-Philic Versus Single Electron Transfer Reactions

Subodh Kumar, Swapandeep Singh Chimni, Deepika Cannoo and Jasbir Singh Arora
Department of Chemistry, Guru Nanak Dev University, Amritsar-143 005, India

Abstract—Reaction of 5-Bromo-1,3,6-trimethyluracil (1) with alkylthiolate (propane-1-, toluene-α-, allyl-, etc.) ions under phase transfer catalytic conditions follows nucleophilic substitution and X-philic (Br and S) elimination to give 5-alkylthio-1,3,6-trimethyluracils, 6-alkylthiomethyl-1,3-dimethyluracils and 1,3,6-trimethyluracil. Reaction of compound 1 with heteroarylthiolate ions (pyridine-2-, quinazoline-4-. uracil-2- and 4,6-dimethylpyrimidine-2-thiolate) gives only nucleophilic substitution products. However, arylthiolate (phenyl-, 4-chlorophenyl-, 2-aminophenyl-) ions follow a single electron transfer (SET) mechanism to give 5-arylthio-6-arylthiomethyl-1,3-dimethyluracils along with normal substitution products. 1,3,6-Trimethyluracil does not react with alkyl- or heteroaryl-thiolate ions but reacts with arylthiolate ions (SET) providing mainly 5-arylthio-1,3,6-trimethyluracils.

Introduction

The initial addition of enzyme bound thiolate ion at C-6 of dUMP, in its thymidylate synthetase catalysed conversion to dTMP[2] and the mutagenic activities of various substituted uracils[3] have prompted the study of reactions of various uracil derivatives towards nucleophiles. As a result, the nucleophilic substitutions in the presence of a good leaving group at C-5 or at C-6 of uracil have been meticulously used for the synthesis of various functionalised uracils.[4] 6-Methyluracil and its 5-bromo derivatives have been relatively less studied[5] due to lower reactivity towards nucleophiles.[6] Further, unlike in the case of reactions of 5-bromouracils, the reaction of 5-bromo-1,3,6-trimethyluracil (**1**) with alkyl amines (at < 100 °C) gives normal 5-alkylamino-1,3,6-trimethyluracils but with aryl amines and alkylamines (at 150 °C) provides 6-(aryl-/alkyl-aminomethyl)-1,3-dimethyluracils.[6a,6b] The reactivity of **1** towards thiolate ions is not reported. Here, we report that under phase transfer catalytic conditions, reaction of **1** with alkylthiolate ions follows a nucleophilic addition–elimination and X-philic (Br-/S-philic) route to provide mono(alkylthio)uracils **4** and **5** and debrominated product **3** and with the heteroarylthiolate ions follows only nucleophilic substitution to give mono-(heteroarylthio)uracils **13e–g**. The reaction of **1** with arylthiolate ions causes oxidative addition, through a SET mechanism, to provide bis(arylthio)uracils **12a–d** along with **13a–d**. 1,3,6-Trimethyluracil (**3**) does not react with alkyl- or heteroaryl-thiolate ions, but with arylthiolate ions undergoes oxidative addition to form arylthiouracils.

Results and Discussion

Reaction of compound **1** with propane-1-thiolate ion under phase transfer catalytic (PTC) conditions in DMF at 30–40 °C, gave two isomeric products, m/z 228 (M^+); **4a** (35%) and **5a** (6%), [R_f 0.5 and 0.4 (chloroform:ethyl acetate, 10:1)] along with **3** (13%). Similarly, reaction of **1** with allyl- (generated from **6a**), toluene-α- (generated from **6b**) and ethoxy carbonylmethane- (generated from **6c**) thiolate ions gave **4b** (35%), **5b** (7%); **4c** (26%), **5c** (15%) and **4d** (40%), **5d** (6%), respectively. In each case 10 ± 4% of **3** was also isolated. Therefore, in contrast with reactions of **1** with amines, where participation of tautomers **1** and **1a** was temperature dependent, here the participation of both the tautomers is evident even at room temperature. All attempts at forming **4** or **5** selectively by varying the reaction temperature failed.

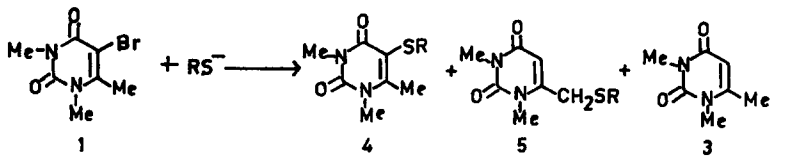
In the reactions of **1** with arylthiolate ions, a unique substitution pattern which is at variance with the above results was observed. Reaction of **1** with phenyl thiolate ion (**7a**) under PTC conditions gave three components. The first component (30%), m/z 370 (M^+), was assigned the structure **12a** as it showed the absence of both 6-CH_3 and C-5H and the presence of two aryl units in its ^1H NMR. Also, in its off resonance proton decoupled ^{13}C NMR spectrum it showed two quartets due to 2 × NCH_3 and one triplet due to -CH_2S in the aliphatic region and twelve signals (six singlets due to 2 × C=O, C=C, 2 × ArC and six doublets due to ArCH) in the aromatic region. The second (38%), m/z 262 (M^+), and third (< 1%), m/z 262 (M^+), components

were found to be **13a** and **14a**, respectively. Similarly, reaction of **1** with 4-chlorophenylthiolate and 2-aminophenylthiolate and pyridine-2-thiolate (**8**) ions gave compounds **12b–d**, **13b–d** and **14b–d** respectively. However reaction of **1** with heteroarylthiolate ions **9–11** gave exclusively the respective 5-heteroarylthio-1,3,6-trimethyluracils **13e–g**. In these reactions corresponding compounds **12** and **14** could not be isolated.

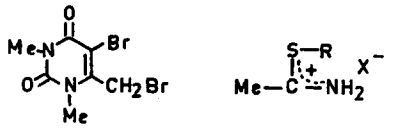
Therefore, reaction of **1** with alkylthiolate ions provides 5-alkylthio- and 6-alkylthiomethyl-uracils and with heteroarylthiols gives only 5-heteroarylthiouracils (**13**) but with arylthiols, bis(arylthio)uracils (**12**) are formed along with compounds **13** and **14**. Evidently, in the formation of compounds **12** from **1** and arylthiolate ions the two hydrogens, one from uracil and one from arylthiol, have been removed to give oxidative addition products. When the reaction was carried out in the absence of phase transfer catalyst or K_2CO_3, such C–H substitution reactions did not occur.

Further, we envisaged that 5-bromo-6-bromomethyl-1,3-dimethyluracil (**2**) with thiolate ions would first undergo nucleophilic substitution at allylic C_6–CH_2Br and then would follow the usual nucleophilic substitution to give compounds **15** and **16** (Scheme 1). Reaction of compound **2** with propane-1-thiolate ion gave compound **15** (R = $CH_2CH_2CH_3$) in only 3% amounts along with **4a** (26%), **5a** (29%) and **1** (9%). Therefore, reaction of **2** with propane-1-thiolate ions gave mainly mono-(alkylthio)uracil derivatives (**4a** and **5a** = 55%), the expected compound **15** is formed in 3% amounts and **16** is not formed. Reaction of **2** with phenyl thiolate ion gave bis(arylthio)uracil **12a** (60%) as the major product along with **13a** (12%), but with heteroarylthiolate ions **9** and **11** gave **12e** and **12g**, respectively.

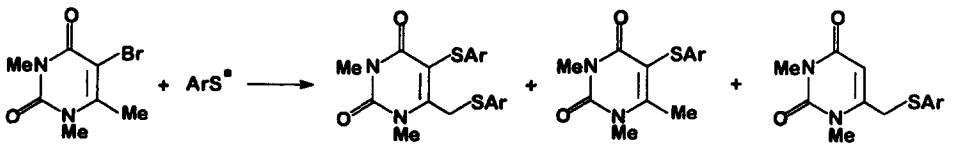
In view of these observations, we argued that 1,3,6-trimethyluracil (**3**) might undergo similar oxidative arylthiolation at C-5. Reaction of **3** with phenylthiolate ion under PTC conditions gave **12a** (4%) and **13a** (37%). Even after 48 h of stirring this reaction is not completed and unreacted **3** (18%) was isolated. Similarly, reaction of **3** with 4-chlorophenylthiolate ion gave **12b** (3%), **13b** (35%) and **14b** (4%), and with 2-aminophenylthiolate ion gave **12c** (4%) and **13c** (30%).

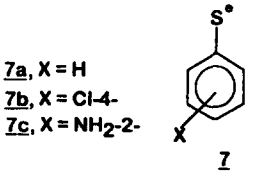


for 4 and 5 a, R = $CH_2CH_2CH_3$; b, R = $CH_2CH{=}CH_2$
c, R = CH_2Ph; d, R = CH_2CO_2Et



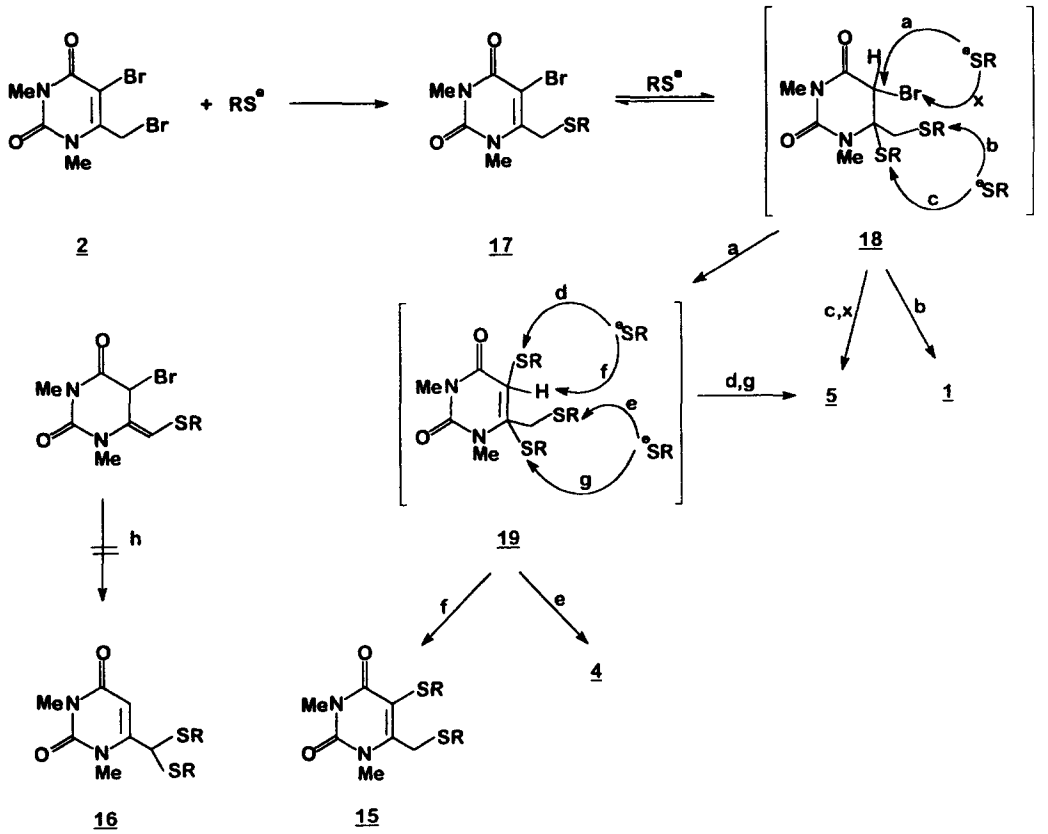
a, R = $CH_2CH{=}CH_2$, X = Br
b, R = CH_2Ph, X = Cl
c, R = CH_2CO_2Et





7a, X = H
7b, X = Cl-4-
7c, X = NH_2-2-

for 12-14
a, Ar = Ph
b, Ar = 4-Cl-C_6H_4
c, Ar = 2-NH_2-C_6H_4
d, Ar = Py-2-
e, Ar = quinazolinyl-4-
f, Ar = thiouracil-2-
g, Ar = 4,6-dimethyl-pyrimidine-2-



Scheme 1.

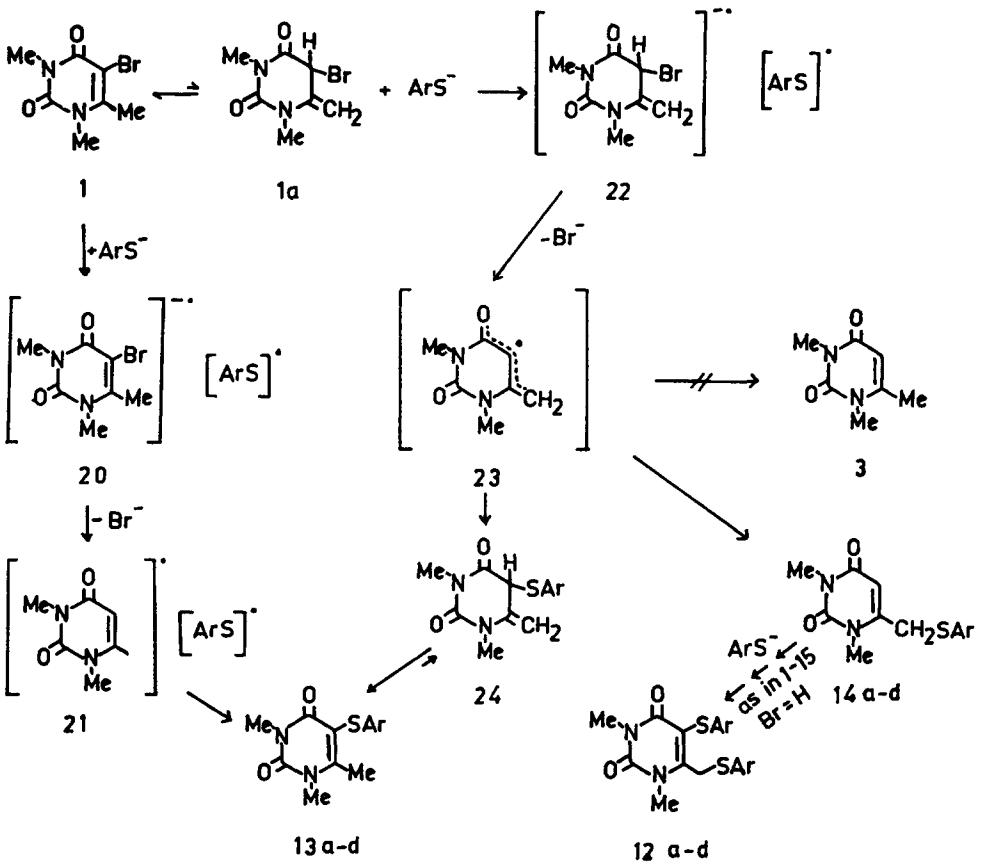
In these reactions unreacted **3** (37% and 10%, respectively) could also be isolated. Reaction of **3** with pyridine-2-thiol gave **12d** (1%) and **13d** (2%) and 60% of unreacted **3** was isolated. Therefore, **3** which does not react with alkyl- and heteroaryl-thiolate ions, reacts with arylthiolate ions to give arylthiouracil derivatives. On performing the reaction of **3** with phenyl thiolate ion in the presence of *m*-dinitrobenzene (a radical trap), the reaction remains unaffected and in the presence of *N,N,N',N'*-tetramethyl-*p*-phenylenediamine (TMPDA, a radical anion trap), the reaction turned blue and the formation of products failed. Since TMPDA is a better electron donor than phenylthiolate, the radical ion pair formation between **3** and phenylthiolate is inhibited. These observations point towards the participation of a single electron transfer mechanism in the reactions of arylthiols with compounds **1–3**. This constitutes the first example of single electron transfer from arylthiolate ions to 5-bromo-6-methyluracil or 6-methyluracil derivatives.[8]

Therefore, compounds **1–3** with alkylthiolate and heteroarylthiolate ions give normal substitution products along with reductive debrominated product but with arylthiolate ions give oxidative addition products along with normal substitution products. This difference in distribution of products could be rationalised through the following two mechanisms.

In the case of reactions with alkyl thiolate ions, intermediate **17*** is initially formed, which undergoes nucleophilic addition of the thiol at C-6 to give intermediate **18**, but the thiolate ion does not attack the 6-CH_2 carbon which already bears the thiol unit (path h) and restricts the formation of compound **16**. Compound **18** could follow various elimination routes (paths b, c and x) to give **5a** (paths c and x) and **1** (path b) or could undergo substitution to give **19** (path a) (Scheme 1). The S-philic nature of alkylthiol facilitates its attack on the thioether -S- of **19** to form products **4** (path e) and **5** (paths d and g) and restricts the nucleophilic attack on carbons on abstraction of hydrogen and thus inhibits the formation of bis(alkylthio)uracil derivatives **15** and **16**. However, heteroaryl thiols due to their poor S-philic character do not attack -S- and prefer C–H abstraction to give compounds **15**. Similar arguments explain the formation of compounds **4** and **5** in the case of reactions of **1** with alkyl thiolate ions and compounds **12** only with heteroaryl thiolate ions.

In the case of reactions of **1–3** with arylthiolate ions, the mechanism has been explained by considering the reaction of **1** with arylthiolate ions (Scheme 2) and would also be true for compounds **2** and **3**. The initial step of the reaction could be rationalised in terms of the

*The formation of 5-bromo-6-(ethoxycarbonylmethanethio)-1,3-dimethyluracil (**17**, R = CH_2CO_2Et) as the only product in the reaction of **2** with **6c** under PTC conditions (CH_2Cl_2–TEBA–K_2CO_3) supports the formation of intermediate **17** (Scheme 1) in the reactions of **2**



Scheme 2.

donation of an electron from arylthiolate ion to **1** to give a radical anion **20** which on subsequent elimination of Br^- is converted into a uracil radical **21**. Compound **21** collapses with the thiol radical in the solvent cage to give the 5-arylthio-1,3,6-trimethyluracil (**13a–d**). Similarly, electron transfer could occur on the tautomer **1a** and subsequent elimination of Br^- to give intermediate **23** which collapses with the arylthio-radical to provide compounds **13a–d** and **14a–d**. The presence of an electron donating group at the 6-position facilitates the electron transfer[8,9] and the observation that compounds **14** undergo facile oxidative arylthiolation but compounds **13** do not undergo such reactions, supports the intermediacy of **14a–d** in the formation of compounds **12a–d**. Similarly, in the reaction of **3** with arylthiolate ions, the participation of intermediates **21** and **23** could lead to the respective arylthiouracil derivatives.[8]

Thus, both alkylthiolate and heteroarylthiolate ions in their reactions with **1** and **2** follow an addition–elimination mechanism. Alkylthiolate ions which are highly X- and S-philic, cause debromination along with the formation of substituted products, whereas poorly X- and S-philic heteroarylthiolate ions give only substitution products. In the case of arylthiolate ions, a single electron transfer process leads to oxidative arylthiolation.

Experimental[4d]

Reactions of 1[5a] with alkylthiolate and arylthiolate ions

General procedure. A solution of **1** (0.7 g, 3 mmol), alkane thiol/arylthiol/thioiminium salts (**6a–c**) (6 mmol) in DMF (25 mL) containing anhydrous potassium carbonate (1.1 g, 8 mmol) and tetrabutylammonium hydrogensulphate (TBA HSO_4) (15–20 mg) was stirred under nitrogen at 30–35 °C. The reaction was monitored by TLC and after its completion (4–6 h), the suspended solid was filtered off and washed with ethyl acetate. The combined filtrate was distilled under vacuum and the residue was chromatographed over silica gel to isolate the pure compounds.

Reaction of 1 with propane-1-thiolate ion

5-(Propane-1-thio)-1,3,6-trimethyluracil (4a). (35%); liquid; m/z 228 (M^+), ^1H NMR ($CDCl_3$): 0.97 (*t*, *J* = 7 Hz, 3H, CH_3), 1.53 (sext, *J* = 7 Hz, 2H, CH_2), 2.57 (*t*, *J* = 7 Hz, 2H, SCH_2), 2.65 (*s*, 3H, 6-CH_3), 3.35 (*s*, 3H, NCH_3), 3.50 (*s*, 3H, NCH_3); IR ν_{max} ($CHCl_3$)/cm^{-1} 1700 (C=O), 1650 (C=O).

1,3-Dimethyl-6-[(propane-1-thio]methyl]uracil(5a). (6%); liquid; m/z 228 (M^+); ^1H NMR ($CDCl_3$): 0.95 (*t*, *J* = 7 Hz, 3H, CH_3), 1.63 (sext, *J* = 7 Hz, 2H, CH_2), 2.49 (*t*, *J* = 7 Hz, 2H, SCH_2), 3.28 (*s*, 3H, NCH_3), 3.40

(*s*, 2H, 6-CH_2), 3.44 (*s*, 3H, CH_3), 5.51 (*s*, 1H, 5-H); IR ν_{max} ($CHCl_3$)/cm^{-1} 1700 (C=O), 1655 (C=O), 1615 (C=C).

Reaction of ***1*** *with* ***6a****.*

5-Allylthio-1,3,6-trimethyluracil ***(4b)****.* (35%); liquid; m/z 226 (M^+); ^1H NMR ($CDCl_3$): 2.56 (*s*, 3H, CH_3), 3.30 (*d*, *J* = 7 Hz, 2H, SCH_2), 3.33 (*s*, 3H, NCH_3), 3.44 (*s*, 3H, NCH_3), 4.50–6.10 (*m*, 3H, $CH{=}CH_2$); IR ν_{max} ($CHCl_3$)/cm^{-1} 1690 (C=O), 1640 (C=O), 1590 (C=C).

6-[(Allylthio)methyl]-1,3-dimethyluracil ***(5b)****.* (7%); liquid; m/z 226 (M^+); ^1H NMR ($CDCl_3$): 3.17 (*s*, 3H, NCH_3), 3.23 (*d*, *J* = 10 Hz, 2H, SCH_2), 3.34 (*s*, 2H, 6-CH_2S), 3.37 (*s*, 3H, NCH_3), 4.85–6.06 (*m*, 4H, $CH{=}CH_2$ with a sharp singlet at 5.41 due to 5-H); IR ν_{max} ($CHCl_3$)/cm^{-1} 1695 (C=O), 1655 (C=O).

Reaction of ***1*** *with* ***6b****.*

5-Benzylthio-1,3,6-trimethyluracil ***(4c)****.* (26%); mp 77–78 °C; m/z 276 (M^+), ^1H NMR ($CDCl_3$): 2.06 (*s*, 3H, 6-CH_3), 3.26 (*s*, 3H, NCH_3), 3.36 (*s*, 3H, NCH_3), 3.87 (*s*, 2H, SCH_2), 7.03 (*s*, 5H, ArH); IR ν_{max} ($CHCl_3$)/cm^{-1} 1695 (C=O), 1640 (C=O), 1590 (C=C). Found: C, 60.58; H, 5.61; N, 10.04; $C_{14}H_{16}N_2O_2S$ requires C, 60.87; H, 5.80; N, 10.15%.

6-[(Benzylthio)methyl]-1,3-dimethyluracil ***(5c)****.* (15%); mp 114–115 °C; m/z 276 (M^+); ^1H NMR ($CDCl_3$): 3.23 (embedded singlets, 5H, CH_2S and NCH_3), 3.33 (*s*, 3H, NCH_3), 3.67 (*s*, 2H, SCH_2), 5.43 (*s*, 1H, 5-H), 7.16 (*s*, 5H, ArH); IR ν_{max} ($CHCl_3$)/cm^{-1} 1695 (C=O), 1660 (C=O), 1620 (C=C). Found: C, 60.76; H, 5.51; N, 9.98; $C_{14}H_{16}N_2O_2S$ requires C, 60.87; H, 5.80; N, 10.15%.

Reaction of ***1*** *with* ***6c***

5-[(Ethoxycarbonylmethane)thio]-1,3,6-trimethyluracil ***(4d)****.* (40%): mp 108–109 °C; m/z 272 (M^+); ^1H NMR ($CDCl_3$): 1.23 (*t*, *J* = 7 Hz, 3H, CH_3); 2.63 (*s*, 3H, 6-CH_3), 3.33 (*s*, 3H, NCH_3), 3.46 (*s*, 5H, NCH_3 and SCH_2), 4.06 (*q*, *J* = 7 Hz, 2H, OCH_2); IR ν_{max} ($CHCl_3$)/cm^{-1} 1735 (C=O), 1710 (C=O), 1645 (C=O). Found: C, 48.63; H, 5.69; N, 9.87; $C_{11}H_{16}N_2O_4S$ requires C, 48.53; H, 5.88; N, 10.29%.

6-[(Ethoxycarbonylmethanethio)methyl]-1,3-dimethyluracil ***(5d)****.* (6%); liquid; m/z 272 (M^+); ^1H NMR ($CDCl_3$): 1.30 (*t*, *J* = 7 Hz, 3H, CH_3), 3.22 (*s*, 2H, 6-CH_2S), 3.33 (*s*, 3H, NCH_3), 3.46 (*s*, 3H, NCH_3), 3.63 (*s*, 2H, SCH_2), 4.16 (*q*, *J* = 7 Hz, 2H, OCH_2), 5.64 (*s*, 1H, 5-H); IR ν_{max} ($CHCl_3$)/cm^{-1} 1730 (C=O), 1700 (C=O), 1655 (C=O).

Reactions of ***1*** *with phenyl thiol*

1,3-Dimethyl-5-phenylthio-6-[(phenylthio)methyl]uracil ***(12a)****.* (30%); liquid; m/z 370 (M^+); ^1H NMR ($CDCl_3$): 3.34 (*s*, 3H, NCH_3), 3.62 (*s*, 3H, NCH_3), 4.42 (*s*, 2H, CH_2), 7.10 (*s*, 5H, ArH), 7.23–7.55 (*m*, 5H, ArH); ^{13}C NMR ($CDCl_3$): 28.95 (*q*, NCH_3), 33.10 (*q*, NCH_3), 35.75 (*t*, CH_2), 105.67 (*s*, C-5), 127.07 (*d*, ArCH), 128.38 (*d*, ArCH), 128.78 (*d*, ArCH), 129.28 (*d*, ArCH), 132.55 (*d*, ArCH), 132.42 (*s*, ArC), 135.87 (*s*, ArC), 151.46 (*s*, C=O), 155.82 (*s*, C-6), 160.67 (*s*, C_4=O); IR ν_{max} ($CHCl_3$)/cm^{-1} 1700 (C=O), 1650 (C=O).

5-Phenylthio-1,3,6-trimethyluracil ***(13a)****.* (38%); mp 98–99 °C; m/z 262 (M^+); ^1H NMR ($CDCl_3$): 2.63 (*s*, 3H, 6-CH_3), 3.36 (*s*, 3H, NCH_3), 3.50 (*s*, 3H, NCH_3), 7.15 (*s*, 5H, ArH); ^{13}C NMR ($CDCl_3$): 19.26 (*q*, 6-CH_3), 28.99 (*q*, NCH_3), 33.38 (*q*, NCH_3), 104.03 (*s*, C-5), 128.32 (*d*, ArCH), 128.78 (*d*, ArCH), 129.28 (*d*, ArCH), 136.13 (*s*, ArC), 151.49 (*s*, C=O), 158.18 (*s*, C_6), 161.13 (*s*, C_4=O); IR ν_{max} ($CHCl_3$)/cm^{-1} 1690 (C=O), 1640 (C=O). Found: C, 59.65; H, 5.26; N, 10.50; $C_{13}H_{14}N_2O_2S$ requires C, 59.54; H, 5.34; N, 10.69%.

1,3-Dimethyl-6-[(phenylthio)methyl]uracil ***(14a)****.* (1%); liquid; ^1H NMR ($CDCl_3$): 3.28 (*s*, 3H, NCH_3), 3.50 (*s*, 3H, NCH_3), 3.77 (*s*, 3H, CH_2), 5.34 (*s*, 1H, 5-H), 7.33 (*s*, 5H, SPh).

Reaction of ***1*** *with 4-chlorophenyl thiol*

5-(4-Chlorophenylthio)-6-[(4-chlorophenylthio)methyl]-1,3-dimethyluracil ***(12b)****.* (12%); liquid; m/z 438, 440, 442 (M^+); ^1H NMR ($CDCl_3$): 3.35 (*s*, 3H, NCH_3), 3.63 (*s*, 3H, NCH_3), 4.47 (*s*, 2H, CH_2), 6.96–7.33 (*m*, 8H, ArH).

5-(4-Chlorophenylthio)-1,3,6-trimethyluracil ***(13b)****.* (38%); mp 111–112 °C; m/z 296/298 (3:1) (M^+); ^1H NMR ($CDCl_3$): 2.64 (*s*, 3H, 6-CH_3), 3.34 (*s*, 3H, NCH_3), 3.50 (*s*, 3H, NCH_3), 7.07 (*s*, 4H, ArH); ^{13}C NMR ($CDCl_3$): 19.26 (*q*, CH_3), 28.99 (*q*, NCH_3), 33.38 (*q*, NCH_3), 104.50 (*s*, C-5), 128.32 (*d*, ArCH), 129.01 (*d*, ArCH), 131.74 (*s*, ArCS), 134.85 (*s*, ArCCl), 151.50 (*s*, C), 158.18 (*s*, C=O), 161.13 (*s*, C=O); IR ν_{max} ($CHCl_3$)/cm^{-1} 1700 (C=O), 1640 (C=O). Found: C, 52.42; H, 4.34; N, 9.24; $C_{13}H_{13}N_2O_2SCl$ requires C, 52.61; H, 4.38; N, 9.44%.

6-[(4-Chlorophenylthio)methyl]-1,3-dimethyluracil ***(14b)****.* (4%); mp 123–124 °C; m/z 296/298 (3:1) (M^+); ^1H NMR ($CDCl_3$): 3.28 (*s*, 3H, NCH_3), 3.47 (*s*, 3H, NCH_3), 3.71 (*s*, 2H, 6-CH_2S), 5.30 (*s*, 1H, 5H), 7.22 (*s*, 4H, ArH); IR ν_{max} ($CHCl_3$)/cm^{-1} 1700 (C=O), 1650 (C=O). Found: C, 52.35; H, 4.31; N, 9.32; $C_{13}H_{13}N_2O_2SCl$ requires C, 52.61; H, 4.38; N, 9.44%.

Reaction of ***1*** *with 2-aminophenyl thiol*

5-(2-Aminophenylthio)-6-[(2-aminophenylthio)methyl]-1,3-dimethyluracil ***(12c)****.* (20%); mp 208–210 °C; m/z 400 (M^+); ^1H NMR 3.53 (*s*, 3H, NCH_3), 3.75 (*s*, 3H, NCH_3), 4.66 (*s*, 2H, CH_2), 5.03 (*br*, 4H, NH_2), 6.26–7.40 (*m*, 8H, ArH); ^{13}C NMR ($CDCl_3$): 27.02 (*t*, CH_2), 31.12 (*q*, CH_3), 31.97 (*q*, CH_3), 104.69 (*s*, C-5), 110.68 (*d*, ArCH), 112.92 (*d*, ArCH), 113.20 (*d*, ArCH), 114.84 (*d*, ArCH), 115.11 (*s*, ArC), 115.57 (*s*, ArC), 126.95 (*d*, ArCH), 129.23 (*d*, ArCH), 131.18 (*d*, ArCH), 135.03 (*d*,

ArCH), 146.73 (*s*, ArC), 148.93 (*s*, ArC), 149.25 (*s*, C_6), 154.44 (*s*, C=O), 159.54 (*s*, C=O); IR ν_{max} (KBr)/cm^{-1} 3420, 3330 (NH_2), 1690 (C=O), 1640 (C=O). Found: C, 57.11; H, 5.13; N, 13.89; $C_{19}H_{20}N_4O_2S_2$ requires C, 57.00; H, 5.00; N, 14.00%.

5-(2-Aminophenylthio)-1,3,6-trimethyluracil (13c). (28%) mp 148–150 °C; m/z 277 (M^+); ^{1}H NMR ($CDCl_3$): 2.70 (*s*, 3H, $6CH_3$), 3.33, (*s*, 3H, NCH_3), 3.43 (*s*, 3H, NCH_3), 4.27 (*s*, 2H, NH_2 exchanges with D_2O), 6.47–7.43 (*m*, 4H, ArH); ^{13}C NMR 19.49 (*q*, CH_3), 29.10 (*q*, NCH_3), 33.35 (*q*, NCH_3), 106.67 (*s*, C-5), 115.47 (*d*, ArCH), 117.43 (*s*, ArC), 117.63 (*d*, ArCH), 129.96 (*d*, ArCH), 134.97 (*d*, ArCH), 149.20 (*s*, ArC), 151.33 (*s*, 6H) 158.08 (*s*, C=O), 162.59 (*s*, C=O); IR ν_{max} (KBr)/cm^{-1} 3420, 3330 (NH_2), 1695 (C=O), 1645 (C=O). Found: C, 56.07; H, 5.34; 15.24; $C_{13}H_{15}N_3O_2S$ requires C, 56.32; H, 5.42; N, 15.16%.

6-[(2-Aminophenylthio)methyl]-1,3-dimethyluracil (14c). (3%); m/z 277 (M^+); ^{1}H NMR ($CDCl_3$): 3.37 (*s*, 3H, NCH_3), 3.50 (*s*, 3H, NCH_3), 3.70 (*s*, 2H, SCH_2), 4.13 (*s*, 2H, NH_2, exchanges with D_2O) and 5.30 (*s*, 1H, 5H).

Reaction of 1 with pyridine-2-thiol

5-(Pyridine-2-thio)-6-(pyridine-2-thio)methyl-1,3-dimethyluracil (12d). (12%); liquid; m/z 372 (M^+); ^{1}H NMR ($CDCl_3$): 3.38 (*s*, 3H, NCH_3), 3.63 (*s*, 3H, NCH_3), 4.88 (*s*, 2H, SCH_2), 6.63–8.44 (*m*, 8H, ArH); ^{13}C NMR ($CDCl_3$): 28.91 (*q*, CH_3), 33.19 (*q*, CH_3), 77.26 (*t*, CH_2), 140.27 (*s*, C_5), 120.00 (*d*, ArCH), 120.24 (*d*, ArCH), 122.17 (*d*, ArCH), 136.20 (*d*, ArCH), 149.39 (*d*, ArCH), 155.30 (*s*, C_6), 157.19 (*s*, C=N), 157.91 (*s*, C=O), 160.75 (*s*, C=O); IR ν_{max} ($CHCl_3$)/cm^{-1} 1710 (C=O), 1670 (C=O).

5-(Pyridine-2-thio)-1,3,6-trimethyluracil (13d). (44%); mp 133–137 °C; m/z 263 (M^+); ^{1}H NMR ($CDCl_3$): 2.73 (*s*, 3H, $6CH_3$), 3.33 (*s*, 3H, NCH_3), 3.66 (*s*, 3H, NCH_3), 6.60–8.41 (*m*, 4H, ArH); ^{13}C NMR ($CDCl_3$): 19.1 (*q*, CH_3), 28.59 (*q*, NCH_3), 33.09 (*q*, NCH_3), 101.82 (*s*, C_5), 119.67 (*d*, ArCH), 120.48 (*d*, ArCH), 136.22 (*d*, ArCH), 149.25 (*d*, ArCH), 151.33 (*s*, C_6), 158.05 (*s*, C=N), 160.57 (*s*, C=O), 160.8 (*s*, C=O); IR ν_{max} ($CHCl_3$)/cm^{-1} 1660 (C=O), 1620 (C=O). Found: C, 54.42; H, 4.74; N, 15.77; $C_{12}H_{13}N_3O_2S$ requires C, 54.75; H, 4.94; N, 15.97%.

6-[(Pyridine-2-thio)methyl-1,3-dimethyluracil (14d). (5%); liquid; ^{1}H NMR ($CDCl_3$): 3.36 (*s*, 3H, NCH_3), 3.56 (*s*, 3H, NCH_3), 4.40 (*s*, 2H, CH_2), 5.88 (*s*, 1H, 5-H), 6.73–8.70 (*m*, 4H, ArH).

5-Bromo-6-[(ethoxycarbonylmethanethio)methyl]-1,3-dimethyluracil (17) (R = CH_2COOEt). A solution of **2** (0.7 g, 2.0 mmol) in CH_2Cl_2 containing **6c** (6 mmol), TBA HSO_4 (15–20 mg) and K_2CO_3 (anhyd.) (0.8 g, 6 mmol) was stirred at 30 °C. After completion of the reaction (6 h), the solid was filtered off and the residue was chromatographed to isolate **17** (R = CH_2COOEt) (52%); liquid; m/z 350, 352 (1:1) (M^+); ^{1}H NMR ($CDCl_3$): 1.26 (*t*, *J* = 7 Hz, 3H, CH_3), 3.37 (embedded singlets, 5H, NCH_3 and CH_2S), 3.58 (*s*, 3H, NCH_3), 4.06 (*s*, 2H, SCH_2CO), 4.17 (*q*, *J* = 7 Hz, 2H, OCH_2); IR ν_{max} ($CHCl_3$)/cm^{-1} 1735 (C=O), 1650 (C=O).

Reaction of 2 with propane-1-thiol: formation of 4a (26%), 5a (29%), 1 (9%) and 15 (3%)

1,3 -Dimethyl-5-propylthio-6-[(propylthio)methyl]uracil (15). (R = $CH_2CH_2CH_3$) (3%); liquid, m/z 302 (M^+); ^{1}H NMR ($CDCl_3$): 0.94 (*t*, *J* = 7 Hz, 6H, 2 × CH_3), 1.54 (sext, *J* = 7 Hz, 4H, 2 × CH_2), 2.63 (*t*, *J* = 7 Hz, 4H, 2 × SCH_2), 3.37 (*s*, 3H, NCH_3), 3.57 (*s*, 3H, NCH_3), 4.16 (*s*, 2H, 6-CH_2S); IR ν_{max}/cm^{-1} 1710 (C=O), 1650 (C=O).

The spectral data for **4a** and **5a** are given above.

Reactions of compounds 1 and 2 with heteroaryl thiols 9–11

A solution of **1** (0.7 g, 3.0 mmol)/**2** (0.7 g, 2.0 mmol) and 4-mercaptoquinazolone (1.0 g, 6 mmol)/2-thiouracil (0.8 g, 6 mmol)/4,6-dimethyl-2-mercaptopyrimidine hydrochloride (1.1 g, 6 mmol) in DMF containing K_2CO_3(anhyd.) (1.24 g, 9 mmol) and TBA HSO_4 (15–20 mg) was stirred at 60 °C. After completion of the reaction (8–10 h, TLC), the suspended solid was filtered off and washed with ethyl acetate. The solid was dissolved in water, neutralised with dil. HCl and extracted with ethyl acetate. The combined filtrate and extract were distilled under vacuum and the residue column chromatographed to isolate the respective pure compounds **12e–g**, **13e** and **14g**.

5-(Quinazolin-4-thio)-6-[(quinazolin-4-thio)methyl]-1,3-dimethyluracil (12e). (60%); mp 175–177 °C; ^{1}H NMR (TFA + $CDCl_3$): 3.48 (*s*, 3H, NCH_3), 3.69 (*s*, 3H, NCH_3), 5.00 (*s*, 2H, CH_2), 7.82–8.24 (*m*, 8H, ArH), 8.88 (*s*, 2H, quinazoline 2-H); ^{13}C NMR (TFA + $CDCl_3$): 29.35 (*t*, CH_2), 29.92 (*q*, NCH_3), 33.57 (*q*, NCH_3), 102.64 (*s*, C-5), 123.97 (*d*, ArCH), 124.25 (*d*, ArCH), 127.66 (*s*, ArC), 127.96 (*s*, ArC), 128.83 (*d*, ArCH), 128.99 (*d*, ArCH), 134.08 (*d*, ArCH), 134.35 (*d*, ArCH), 148.26 (*s*, ArC), 148.54 (*s*, ArC), 151.78 (*s*, ArC), 152.90 (*s*, ArC), 152.91 (*d*, ArCH), 153.65 (*d*, ArCH), 156.97 (*s*, C_6=O), 160.59 (*s*, C), 167.75 (*s*, C), 169.37 (*s*, C); IR ν_{max} (KBr)/cm^{-1} 1700 (C=O), 1655 (C=O). Found: C, 58.12; H, 3.73; N, 17.50; $C_{23}H_{18}N_6O_2S_2$ requires C, 58.28; H, 3.80; N, 17.72%.

5-(4-Hydroxypyrimidine-2-thio)-6-[(4-hydroxypyrimidine-2-thio)methyl]-1,3-dimethyluracil (12f). (25%); mp 205–207 °C; m/z 406 (M^+); ^{1}H NMR 2.60 (*s*, 3H, 6-CH_3), 3.42 (*s*, 3H, NCH_3), 3.68 (*s*, 3H, N-CH_3), 4.68 (*s*, 2H, CH_2), 6.14 (*d*, *J* = 6 Hz, 2H, 5-H), 7.62–7.71 (*d*, *J* = 6 Hz, 2H, 6-H); IR ν_{max} (KBr)/cm^{-1} 3240 (OH), 1700 (C=O), 1640 (C=O). Found: C, 44.42; H, 3.42; N, 20.57; $C_{15}H_{14}N_6O_4S_2$ requires C, 44.33; H, 3.45; N, 20.69%.

5-(4,6-Dimethylpyrimidine-2-thio)-6-[(4,6-dimethylpyrimidine-2-thio)methyl]-1,3-dimethyluracil (12g). (45%); mp 180–182 °C; m/z 430 (M^+); ^{1}H NMR ($CDCl_3$): 2.34

(*s*, 6H, Py-CH_3), 2.41 (*s*, 6H, Py-CH_3), 3.42 (*s*, 3H, NCH_3), 3.64 (*s*, 3H, NCH_3), 4.67 (*s*, 2H, CH_2), 6.67 (s, 1H, Py 5-H), 6.74 (*s*, 1H, Py 5-H); ^{13}C NMR ($CDCl_3$) 23.84 (*q*, Py CH_3), 29.02 (*t*, CH_2), 31.45 (*q*, NCH_3), 33.25 (*q*, NCH_3), 105.15 (*s*, C-5), 116.35 (*d*, Py 5-CH), 116.46 (*d*, Py 5-CH), 151.93 (*s*, Py C-2), 156.06 (*s*, C), 161.00 (*s*, C_6), 167.29 (*s*, C), 167.42 (*s*, C), 168.34 (*s*, C), 169.45 (*s*, C); IR ν_{max} (KBr)/cm^{-1} 1700 (C=O), 1640 (C=O). Found: C, 52.95; H, 4.95; N, 18.47; $C_{19}H_{22}N_6O_2S_2$ requires C, 53.00; H, 5.11; N, 18.87%.

5-(Quinazolin-4-thio)-1,3,6-trimethyluracil (13e). (65%); mp 238 °C; m/z 314 (M^+); ^1H NMR (TFA + $CDCl_3$): 2.37 (*s*, 3H, 6-CH_3), 3.57 (*s*, 3H, NCH_3), 3.76 (*s*, 3H, NCH_3), 8.13–8.62 (*m*, 4H, ArH), 9.14 (*s*, 1H, quinazoline 2-H); ^{13}C NMR (TFA + $CDCl_3$): 19.48 (*q*, 6-CH_3), 30.20 (*q*, NCH_3), 34.51 (*q*, NCH_3), 98.12 (*s*, C-5), 120.81 (*d*, ArCH), 123.149 (*s*, ArC), 125.46 (*d*, ArCH), 132.60 (*d*, ArCH), 136.44 (*s*, ArC), 140.86 (*d*, ArCH), 148.23 (*s*, ArC), 152.90 (*s*, C-6), 163.99 (*s*, C_2=O), 165.36 (*s*, C_4=O); IR ν_{max} (KBr)/cm^{-1} 1700 (C=O), 1640 (C=O). Found: C, 56.91; H. 4.07: N 17.56; $C_{15}H_{14}N_4O_2S$ requires C, 57.32; H, 4.45; N, 17.83%.

5-(4-Hydroxypyrimidine-2-thio)-1,3,6-trimethyluracil (13f). (27%); mp 245–247 °C; m/z 280 (M^+); ^1H NMR (DMSO + $CDCl_3$): 2.59 (*s*, 3H, 6-CH_3), 3.30 (*s*, 3H, NCH_3), 3.52 (*s*, 3H, NCH_3), 6.07–6.04 (*d*, J = 6 Hz, 1H, C_5'-H), 7.60–7.69 (*d*, J = 6 Hz, 1H, C_6'-H); ^{13}C NMR (DMSO + $CDCl_3$): 17.66 (*q*, 6-CH_3), 26.99 (*q*, NCH_3), 31.57 (*q*, NCH_3), 96.17 (*s*, C_5), 108.55 (*d*, C_6'-H), 149.69 (*s*, C), 152.03 (*d*, C'6-H), 156.97 (*s*, C'-6), 159.24 (*s*, C), 160.57 (*s*, C=O), 161.90 (*s*, C=O); IR ν_{max} (KBr)/cm^{-1} 3240 (OH), 1700 (C=O), 1640 (C=O). Found: C, 47.23; H, 4.39; N, 19.49; $C_{11}H_{12}N_4O_3S$ requires C, 47.14; H, 4.29; N, 20.0%.

5-(4,6-Dimethylpyrimidine-2-thio)-1,3,6-trimethyluracil (13g). (30%); mp 178–180 °C; m/z 292 (M^+); ^1H NMR ($CDCl_3$): 2.34 (*s*, 6H, Py-CH_3), 2.59 (*s*, 3H, 6-CH_3), 3.41 (*s*, 1H, N-CH_3), 3.56 (*s*, 3H, N-CH_3), 6.70 (*s*, 1H, Py5-H); ^{13}C NMR ($CDCl_3$): 19.39 (*q*, Py-CH_3), 23.75 (*q*, 6-CH_3), 29.01 (*q*, NCH_3), 33.32 (*q*, NCH_3), 103.01 (*s*, C_5), 116.50 (*d*, PyC-5), 151.99 (*s*, PyC-4, C-6), 157.73 (*s*, C-6), 161.25 (*s*, C-2), 167.44 (*s*, C-4), 169.55 (*s*, PyC-2); IR ν_{max} (KBr)/cm^{-1} 1700 (C=O), 1640 (C=O). Found: C, 53.36; H, 5.40; N, 18.87; $C_{13}H_{16}N_4O_2S$ requires C, 53.36; H, 5.48; N, 19.18%.

Acknowledgements

We thank UGC for financial assistance under COSIST and Special Assistance programmes.

References and Notes

1. Preliminary communication: Kumar, S.; Chimni, S. S.; Cannoo, D. *Heterocycles* **1992**, *34*, 425.

2. Pogolotti, Jr, A. L.; Santi, D. V. *Bioorganic Chemistry*, Vol. 1, p. 279, van Tamelen, E. E., Ed.; Academic Press; New York, 1977.

3. (a) Bergstrom, D.; Deal, P.; Husain, A.; Lind, R.; Jenson, J. *J. Am. Chem. Soc.* **1989**, *111*, 374; (b) Lee, C. H.; Kim, J. Y.; Kim, W. J.; Kim, Y. H. *Heterocycles* **1990**, *31*, 211; (c) Rao, T. S.; Reese, C. B. *J. Chem. Soc., Chem. Commun.* **1989**, 997; (d) Ashwell, M.; Jones, S. A.; Kumar, A.; Sayers, R. J.; Walker, T. R.; Sukuma, T.; De clercq, E. *Tetrahedron* **1987**, *43*, 4601.

4. (a) Hirota, K.; Kitade, Y.; Sajiki, H.; Maki, Y. *J. Chem. Soc. Perkin Trans. 1* **1990**, *367* and references therein; (b) van der Plas, H. C. *Tetrahedron* **1985**, *41*, 237; (c) van der Meij, P. F. C.; Pandit, U. K. *Tetrahedron Lett.* **1988**, *29*, 5445; (d) Kumar, S.; Chimni, S. S. *J. Chem. Soc. Perkin Trans. 1* **1992**, 449; (e) Kumar, S.; Chimni, S. S. *J. Chem. Res.* **1992**, (S)18, (M)0343.

5. (a) Senda, S.; Hirota, K.; Banno, K. *J. Med. Chem.* **1972**, *15*, 471; (b) Hirota, K.; Yamada, Y.; Kitade, Y.; Senda, S. *J. Chem. Soc. Perkin Trans. 1* **1981**, 2943 and references therein; (c) Hirota, K.; Banno, K.; Yamada, Y.; Senda, S. *J. Chem. Soc. Perkin Trans. 1* **1985**, 1137.

6. Hirota, K.; Watanabe, K. A.; Fox, J. J. *J. Org. Chem.* **1978**, *43*, 1193.

7. Pal, B. C. *J. Am. Chem. Soc.* **1978**, *100*, 5170.

8. Similar, single electron transfers from the electron donors 1-methylindole, 4-methylphenothiazine and *N,N*-dimethylacetamides to 6-phenylthio-, 6-phenoxy-, and 6-(*N*-methyl-*p*-bromoanilino)-5-bromouracils are well documented.[9]

9. (a) Sako, T.; Suzuki, M.; Tanabe, M.; Maki, Y. *J. Chem. Soc. Perkin Trans. 1* **1981**, 3114; (b) Sako, M.; Hirota, K.; Maki, Y. *Chem. Pharm. Bull.* **1983**, *31*, 3496.

(*Received in Japan* 8 *November* 1994; *accepted* 27 *March* 1995)