Novel Ring Transformations of 5-Cyanouracils into 2-Thiocytosines, 2,4-Diaminopyrimidines, and Pyrimido[4,5-*d*]pyrimidines by the Reaction with Thioureas and Guanidines[1,2]

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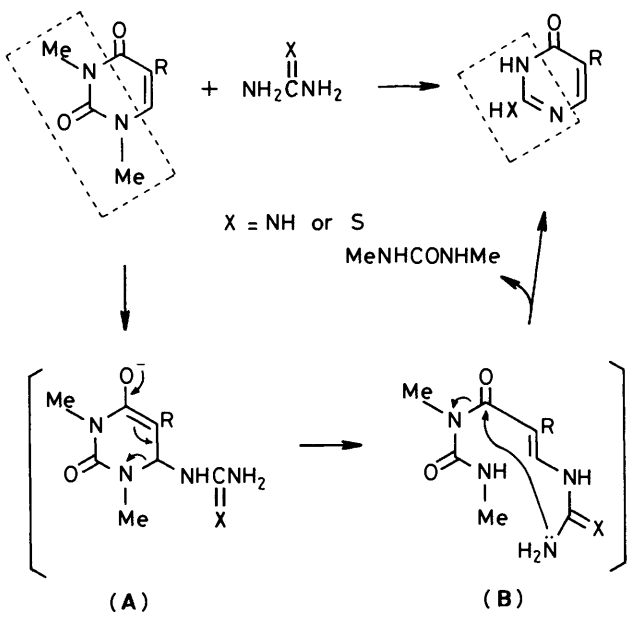
The reaction of 5-cyanouracils with thioureas and guanidines causes novel pyrimidine-to-pyrimidine ring transformations. Thus, 1,3-disubstituted 5-cyanouracils (**1**) react with thiourea and guanidines to give the corresponding 5-carbamoyl-2-thiocytosines (**2**) and 2,4-diamino-5-carbamoylpyrimidines (**5**), respectively. On the other hand, 5-cyanouracils (**8**) possessing a phenyl group at the 1-position react with thioureas to give 7-aminopyrimido[4,5-*d*]pyrimidine-2,4-diones (**9**).

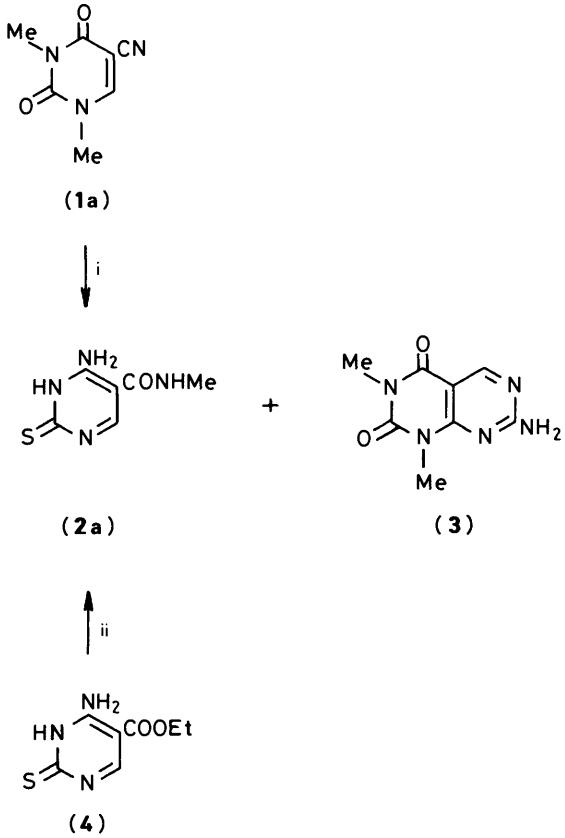
The reaction of 1,3-disubstituted uracil derivatives with 1,3-ambident nucleophiles causes various ring transformations involving the apparent displacement of an appropriate fragment of the uracil ring by the employed nucleophiles.[3–6] For example, treatment of 1,3-dimethyluracil with guanidine and thiourea afforded the corresponding isocytosine and 2-thiouracil, respectively.[3] These ring transformations resulted in the displacement of the dimethylurea portion of the uracil by guanidine or thiourea *via* a Michael adduct (**A**) and a ring-opening intermediate (**B**) (Scheme 1). During our attempts to extend the above ring transformation to 5-cyanouracils (**1**), we have encountered novel ring transformations in the reaction of compounds (**1**) with thioureas and guanidines, which lead to 2-thiocytosines (**2**), 2,4-diaminopyrimidines (**5**), and pyrimido[4,5-*d*]pyrimidine-2,4-diones (**9**).



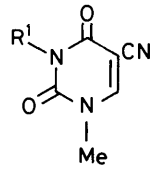
Scheme 1.

5-Cyano-1,3-dimethyluracil (**1a**) was allowed to react with thiourea under the reaction conditions employed previously for the pyrimidine-to-pyrimidine ring transformation (see Scheme 1), that is, under reflux with 3 molar equivalents each of thiourea and sodium ethoxide in absolute ethanol. Contrary to our expectation, 5-(*N*-methylcarbamoyl)-2-thiocytosine (**2a**) and 7-amino-1,3-dimethylpyrimido[4,5-*d*]pyrimidine-2,4-dione (**3**) were obtained in 48 and 20% yield, respectively, in place of the expected 5-cyano-2-thiouracil derivative (Scheme 2). The structures of compounds (**2a**) and (**3**) were supported by the spectral data and microanalytical results, and confirmed by comparison of their spectral data with those of authentic samples obtained by independent syntheses; *i.e.*, the 2-thiocytosine (**2a**) was prepared by the reaction of 5-ethoxycarbonyl-2-thiocytosine (**4**)[7,8] with methylamine and the pyrimido[4,5-*d*]pyrimidine (**3**) was fortunately available in our laboratory.[9]

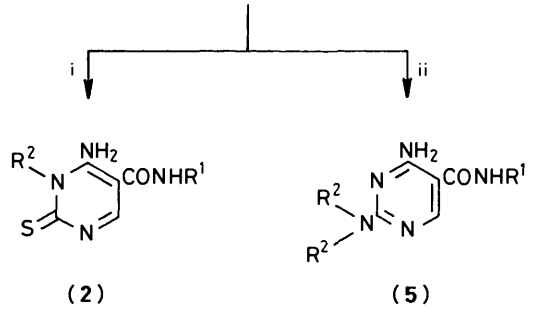
Various reaction conditions were examined with the purpose of selective synthesis of compound (**2a**) or (**3**). As a result, employment of sodium hydroxide as a base led to the exclusive formation of the 2-thiocytosine (**2a**), *i.e.*, treatment of the 5-cyanouracil (**1a**) with 3 molar equivalents each of thiourea and



Scheme 2. *Reagents:* i, NH_2CSNH_2; ii, $MeNH_2$

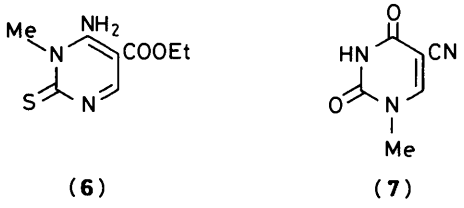


(1) a; R^1 = Me
b; R^1 = c-C_6H_{11}
c; R^1 = Ph



(2) (5)

Scheme 3. *Reagents:* i, $R^2NHCSNH_2$; ii, $(R^2)_2NC(=NH)NH_2$



(6) (7)

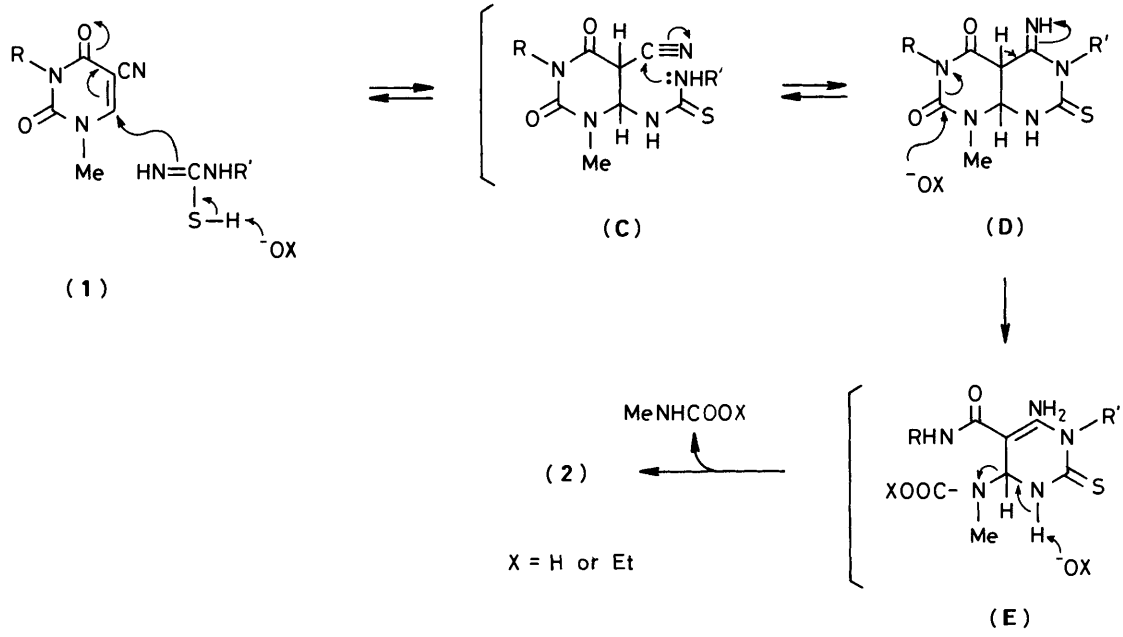
Table) are superimposable on that of 5-ethoxycarbonyl-3-methyl-2-thio-3*H*-cytosine (**6**) [$\lambda_{max.}$(EtOH) 221 (ε10 500 dm^3 mol^{-1} cm^{-1}), 299 (12 300), and 351 nm (21 200)].[7] This fact showed that the 2-thiocytosines (**2b—d**) adopt a 3-substituted structure rather than the isomeric 1-substituted one.

In order to determine a source of the 5-(*N*-methylcarbamoyl) group, the reactions of 5-cyano-3-cyclohexyl-1-methyluracil (**1b**), possessing different substituents at the N(1)- and N(3)-position with thiourea and *N*-methylthiourea were carried out. Both reactions afforded the corresponding 5-(*N*-cyclohexylcarbamoyl)-2-thiocytosines (**2e**) and (**2f**), respectively (Scheme 3). This result clearly shows that the *N*-substituent of the 5-carbamoyl group of compounds (**2**) originates from the *N*(3)-substituent of the parent 5-cyanouracils (**1**).

No formation of the expected 2-thiocytosine was observed in the reaction of 3-unsubstituted 5-cyano-1-methyluracil (**7**) with thiourea and the starting material (**7**) was recovered unchanged. This is ascribed to the presence of an acidic proton in the 5-cyanouracil (**7**). The formation of anionic species of (**7**) in the presence of a base seems to prevent the ring transformation *via* the uracil-ring cleavage on attack by nucleophiles.

On the basis of the above results, a reaction sequence for the present ring transformation is proposed as depicted in Scheme 4. An initial nucleophilic attack at the 6-position by thiourea could give rise to an adduct (**C**). Cyclization between the 5-cyano group and the terminal amino group of the thiourea moiety in (**C**) gives rise to a bicyclic intermediate (**D**), which subsequently undergoes cleavage of the C^2–N^3 bond by attack of the base (hydroxide ion or ethoxide ion) on the 2-position to give an intermediate (**E**). Elimination of the urethane moiety in (**E**) results in the formation of the 2-thiocytosine (**2**).

The present ring tranformation is applicable to the preparation of 2,4-diaminopyrimidine derivatives (**5**). Treatment of the 5-cyanouracil (**1a**) with guanidine (4 mol equiv.) in refluxing



(1) (C) (D) (E)

X = H or Et

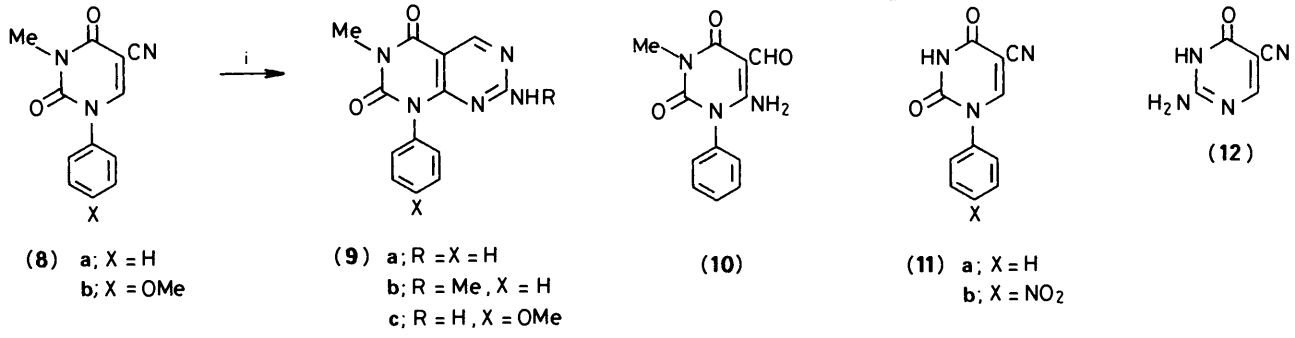
Scheme 4.

sodium hydroxide in absolute ethanol under reflux for 10 minutes afforded the 2-thiocytosine (**2a**) in 75% yield. Under analogous conditions, the reactions of compound (**1a**) with methyl-, butyl-, and phenyl-thioureas gave the corresponding 3-substituted 5-(*N*-methylcarbamoyl)-2-thiocytosines (**2b—d**), respectively, in good yields (Table). The u.v. spectra of products (**2b—d**) (see

ethanol gave 2,4-diamino-5-(*N*-methylcarbamoyl)pyrimidine (**5a**) in 75% yield. Analogous reactions of (**1a**) with *N*,*N*-dimethylguanidine and of 5-cyano-1-methyl-3-phenyluracil (**1c**) with guanidine led to the formation of the corresponding 2,4-diaminopyrimidine derivatives (**5b**) and (**5c**), respectively (see Table).

Table. Formation of 2-thiocytosines (**2**) and 2,4-diaminopyrimidines (**5**)

Starting compound	Reaction time (min)	Product	R^1	R^2	Yield (%)	M.p. (°C) (recryst. solv.)	U.v. spectra ($\lambda_{max.}^{EtOH}$, nm, ε)
(**1a**) + NH_2CSNH_2	10	(**2a**)	Me	H	75	276.5—277.5 (MeOH)	241 (14 700) 299 (23 600)
$NH_2CSNHMe$	10	(**2b**)	Me	Me	88	264.5—265 (EtOH)	224 (11 200) 291 (13 000) 355 (17 500)
$NH_2CSNHBu$	30	(**2c**)	Me	Bu	41	224—225 (water)	226 (11 100) 293 (13 100) 358 (17 100)
$NH_2CSNHPh$	30	(**2d**)	Me	Ph	75	227—228 (MeOH)	225 (15 900) 293 (13 500) 363 (14 800)
(**1b**) + NH_2CSNH_2	30	(**2e**)	c-C_6H_{11}	H	81	>300 (AcOH)	241 (15 800) 299 (26 000)
$NH_2CSNHMe$	150	(**2f**)	c-C_6H_{11}	Me	59	256—258 (MeOH)	227 (9 600) 291 (13 400) 355 (18 300)
(**1a**) + $NH_2C(NH)NH_2$	30	(**5a**)	Me	H	75	275 (MeCN)	213 (25 000) 252 (15 200) 295 (9 900)
$NH_2C(NH)NMe_2$	10	(**5b**)	Me	Me	24	245—246 (PhH)	222 (20 900) 261 (19 200) 305 (12 500)
(**1c**) + $NH_2C(NH)NH_2$	20	(**5c**)	Ph	H	64	267—269 (aq. acetone)	213 (28 300) 262 (19 700) 303 (18 800)



(**8**) **a**; X = H
b; X = OMe

(**9**) **a**; R = X = H
b; R = Me, X = H
c; R = H, X = OMe

(**10**)

(**11**) **a**; X = H
b; X = NO_2

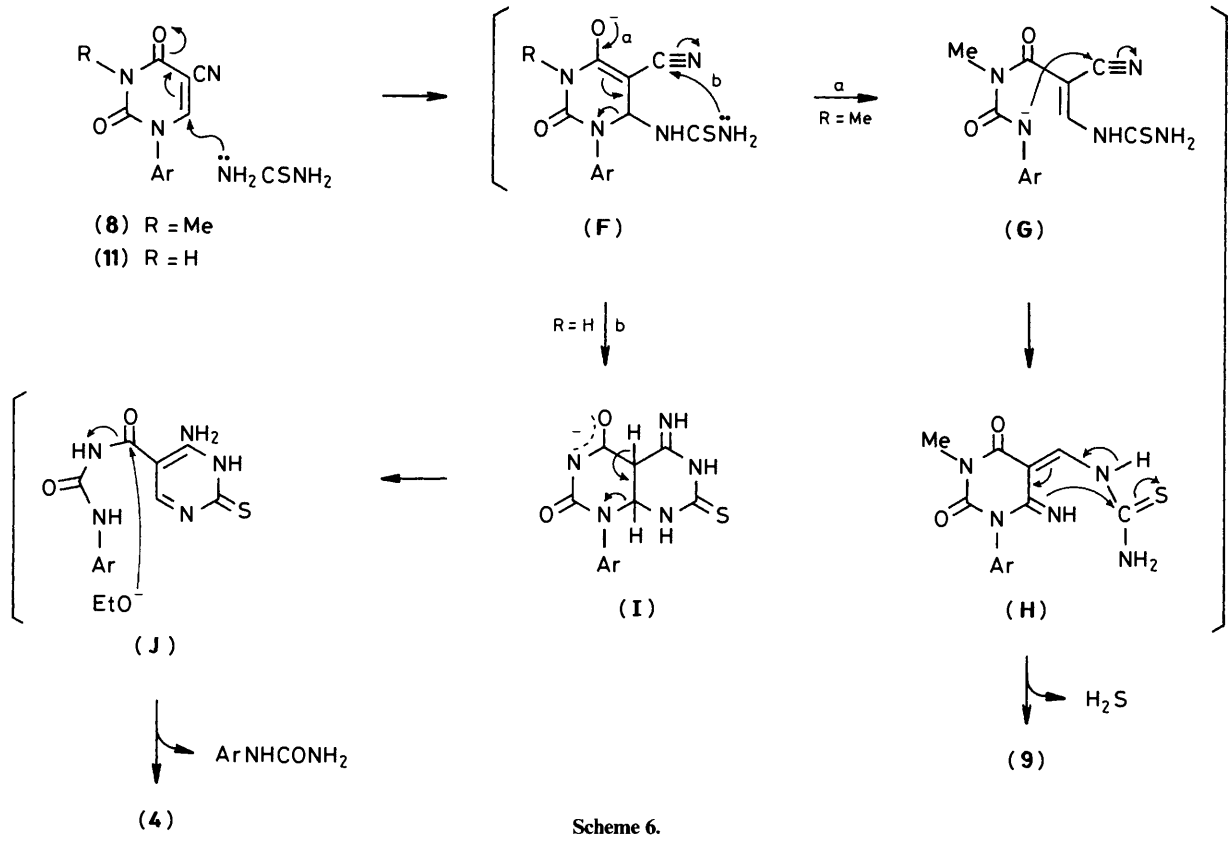
Scheme 5. *Reagents:* i, NH_2CSNHR, NaOEt

On the other hand, in the reaction of the 5-cyanouracil (**1a**) with thiourea (Scheme 2), the reaction conditions for the selective formation of the pyrimido[4,5-*d*]-pyrimidine (**3**) could not be found in spite of much effort. Both products (**2a**) and (**3**) were always obtained. However, when 5-cyano-3-methyl-1-phenyluracil (**8a**) was employed instead of (**1a**) in the reaction with thiourea in the presence of sodium ethoxide, the ring transformation of 5-cyanouracil into pyrimido[4,5-*d*]pyrimidine exclusively occurred to give the desired product (**9a**) in 66% yield (Scheme 5). The pyrimido[4,5-*d*]pyrimidine (**9a**) was alternatively prepared by the reaction of 6-amino-5-formyl-3-methyl-1-phenyluracil (**10**) with guanidine in high yield. Analogous reactions of the 1-phenyluracil (**8a**) with *N*-methylthiourea and of the 1-(*p*-methoxyphenyl)uracil (**8b**) with thiourea gave rise to the corresponding pyrimido[4,5-*d*]pyrimidines (**9b**) and (**9c**), respectively.

Upon treatment of 3-unsubstituted 5-cyano-1-phenyluracil (**11a**) with thiourea under the same conditions an unexpected product, 5-ethoxycarbonyl-2-thiocytosine (**4**), was obtained in 87% yield. 5-Cyano-1-(*p*-nitrophenyl)uracil (**11b**) was also converted into the same product (**4**) by the reaction with thiourea. The structure of compound (**4**) was confirmed by comparison with an authentic sample.[8]

The reaction sequence for the formation of products (**9**) and (**4**) is outlined in Scheme 6 on the basis of the fact that the substitution of phenyl groups at the N^1-position on the uracil ring remarkably facilitates the cleavage of the N^1–C^6 bond by attack of nucleophiles at the 6-position.[1,10–13] A Michael adduct (**F**) produced by the reaction of the 1,3-disubstituted 5-cyanouracil (**8**) with thiourea can be converted smoothly into an open-chain intermediate (**G**) because of the influence of the 1-phenyl group (pathway a). The intermediate (**G**) could be recyclized to the 6-aminouracil (**H**) as described previously.[1,14] Subsequent cyclization of (**H**) with elimination of hydrogen sulphide affords the pyrimido[4,5-*d*]pyrimidine (**9**). In the case of the 3-unsubstituted uracils (**11**), however, the bicyclic intermediate (**I**) could be formed initially *via* the Michael adduct (**F**) in a similar manner to the formation of the 2-thiocytosines (**2**) (see Scheme 4) (pathway b). A subsequent cleavage of the N^1–C^6 bond in (**I**) preferentially occurs due to the difficulty of the attack of an ethoxide anion at the 2-position to give the acylurea (**J**), the amide bond of which undergoes easy alcoholysis[15,16] by sodium ethoxide to produce the cytosine (**4**) and arylurea.

When guanidine was employed instead of thiourea in the reaction with 5-cyano-3-methyl-1-phenyluracil (**8a**), 5-cyano-isocytosine (**12**) was obtained in 68% yield together with the



Scheme 6.

pyrimido[4,5-*d*]pyrimidine (**9a**). The isocytosine (**12**) appears to be formed according to the reaction sequence depicted in Scheme 1.

Experimental

M.p.s were determined on a Yanagimoto melting-point apparatus and are uncorrected. I.r. spectra were recorded with a Hitachi Model 215 spectrophotometer using KBr pellets. U.v. spectra were obtained from ethanol solutions on a Shimadzu UV-260 spectrophotometer. ^{1}H N.m.r. spectra were determined with a Hitachi Perkin-Elmer R-20B (60 MHz) instrument for solutions in $(CD_3)_2SO$ unless otherwise stated, using DSS (3-trimethylsilylpropane-1-sulphonic acid, sodium salt) as internal standard. Chemical shifts are reported in p.p.m. (δ) and *J*-values are first order. 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.

General Procedure for the Preparation of 5-*Carbamoyl*-2-*thiocytosines* (**2a**—**f**).—A mixture of the 5-cyano-1-methyluracil derivatives[17] (**1a** and **b**) (3 mmol), thiourea derivative (9 mmol), and sodium hydroxide (0.36 g, 9 mmol) in absolute ethanol (30 ml) was refluxed for the time given in the Table. The solvent was removed under reduced pressure and the residue was dissolved in water. The insoluble material (excess of thiourea derivative) was filtered off. The filtrate was neutralized with acetic acid. The resulting precipitate was collected by filtration and recrystallized from an appropriate solvent (see Table) to give the corresponding 2-*thiocytosines* (**2a**—**f**).

5-(N-*Methylcarbamoyl*)-2-*thiocytosine* (**2a**). δ_H 2.68 (3 H, d, *J* 4.5 Hz, NMe, collapsed to singlet by deuterium exchange), 7.97 (1 H, s, 6-H), 8.45 (3 H, br, NH, deuterium exchangeable), and 12.41 (1 H, br, NH, deuterium exchangeable) (Found: C, 39.3; H, 4.35; N, 30.55. $C_6H_8N_4OS$ requires C, 39.12; H, 4.38; N, 30.41%).

3-*Methyl*-5-(N-*methylcarbamoyl*)-2-*thiocytosine* (**2b**). δ_H 2.73 (3 H, d, *J* 4.5 Hz, NMe, collapsed to singlet by deuterium exchange), 3.82 (3 H, s, NMe), 8.23 (1 H, s, 6-H), 8.45 (2 H, br, NH, deuterium exchangeable), and 9.15 (1 H, br, NH, deuterium exchangeable) (Found: C, 42.15; H, 5.0; N, 28.0 $C_7H_{10}N_4OS$ requires C, 42.42; H, 5.09; N, 28.29%).

3-*Butyl*-5-(N-*methylcarbamoyl*)-2-*thiocytosine* (**2c**). δ_H 0.70—1.14 (3 H, br, CMe), 1.14—2.00 (4 H, m, $NCH_2CH_2CH_2Me$), 2.73 (3 H, br s, NMe, collapsed to singlet by deuterium exchange), 4.20—4.84 (2 H, m, NCH_2), 8.16 (1 H, s, 6-H), and 8.47 (1 H, br, NH, deuterium exchangeable), the signal due to the NH_2 protons could not be observed (Found: C, 49.9; H, 6.85; N, 23.1. $C_{10}H_{16}N_4OS$ requires C, 49.99; H, 6.71; N, 23.32%).

5-(N-*Methylcarbamoyl*)-3-*phenyl*-2-*thiocytosine* (**2d**). δ_H 2.74 (3 H, d, *J* 4.5 Hz, NMe, collapsed to singlet by deuterium exchange), 7.10—7.84 (5 H, m, Ph), 8.35 (1 H, s, 6-H), and 8.54 (1 H, br, NH, deuterium exchangeable), the signal due to the NH_2 protons could not be observed (Found: M^+, 260.0739. $C_{12}H_{12}N_4OS$ requires *M*, 260.0732).

5-(N-*Cyclohexylcarbamoyl*)-2-*thiocytosine* (**2e**). δ_H 0.81—2.14 (10 H, m, c-C_6H_{11}), 3.08—4.00 (1 H, br, c-C_6H_{11}), 8.04 (1 H, s, 6-H), 8.21 (3 H, br, NH, deuterium exchangeable), and 12.39 (1 H, br, NH, deuterium exchangeable) (Found: C, 52.6; H, 6.4; N, 22.3. $C_{11}H_{16}N_4OS$ requires C, 52.35; H, 6.39; N, 22.21%).

5-(N-*Cyclohexylcarbamoyl*)-3-*methyl*-2-*thiocytosine* (**2f**). δ_H 1.04—2.13 (10 H, m, c-C_6H_{11}), 2.96—4.06 (1 H, br, c-C_6H_{11}), 3.83 (3 H, s, NMe), 8.25 (2 H, s and br, 6-H and NH), and 8.60—10.00 (2 H, br, NH_2) (Found: C, 53.9; H, 6.9; N, 20.8. $C_{12}H_{18}N_4OS$ requires C, 54.12; H, 6.81; N, 21.04%).

Alternative Synthesis of 5-(N-*Methylcarbamoyl*)-2-*thiocytosine* (**2a**)—A suspension of 5-ethoxycarbonyl-2-thiocytosine

(**4**)[7,8] (0.50 g, 2.5 mmol) in aqueous methylamine (40%) (20 ml) was heated in a sealed tube at 100 °C for 5 h. The reaction mixture was evaporated under reduced pressure and water was added to the residue. The resulting precipitate was collected by filtration and recrystallized from methanol to give the 2-*thiocytosine* (**2a**) (0.32 g, 69%), which was identical with the sample prepared above.

Formation of 5-(N-*Methylcarbamoyl*)-2-*thiocytosine* (**2a**) *and* 7-*Amino*-1,3-*dimethylpyrimido*[4,5-d]*pyrimidine*-2,4-*dione* (**3**).—A mixture of the 5-cyanouracil (**1a**)[17] (0.83 g, 5 mmol) and thiourea (1.14 g, 15 mmol) in ethanolic sodium ethoxide [prepared from Na (0.34 g, 15 mg-atom) in absolute ethanol (30 ml)] was heated under reflux for 3 h. The solvent was removed under reduced pressure and the residue was treated with cold water (10 ml). The insoluble material was collected by filtration and recrystallized from methanol to give the pyrimido[4,5-*d*]pyrimidine (**3**) (0.21 g, 20%), m.p. >300 °C, which was identical with an authentic sample.[9]

The filtrate was neutralized with acetic acid and the resulting precipitate was collected by filtration and recrystallized from methanol to give the 2-*thiocytosine* (**2a**) (0.44 g, 48%), m.p. 276.5—277.5 °C, which was identical with the sample prepared above.

5-*Ethoxycarbonyl*-2-*thiocytosine* (**4**).—(*a*) A mixture of 5-cyano-1-phenyluracil (**11a**)[17] (0.64 g, 3 mmol) and thiourea (0.69 g, 9 mmol) in ethanolic sodium ethoxide [prepared from Na (0.21 g, 9 mg-atom) in absolute ethanol (30 ml)] was refluxed for 6 h. The solvent was removed under reduced pressure and the residue was dissolved in water. The solution was neutralized with acetic acid and the precipitate was filtered off. Recrystallization from *N*,*N*-dimethylformamide (DMF) gave the 2-thiocytosine (**4**) (0.52 g, 87%); m.p. 281.5 °C (lit.,[7] 273 °C;[8] 260—262 °C); this product was identical with an authentic sample.[8]

(*b*) A mixture of 5-cyano-1-(*p*-nitrophenyl)uracil (**11b**) (1.29 g, 5 mmol) and thiourea (1.15 g, 15 mmol) in ethanolic sodium ethoxide [prepared from Na (0.34 g, 15 mg-atom) in absolute ethanol (50 ml)] was refluxed for 2 h. The solvent was removed under reduced pressure and the residue was treated with water (25 ml). The resulting precipitate was collected by filtration and recrystallized from water to give *p*-nitrophenylurea (0.13 g, 16%); m.p. 223 °C (lit.,[18] 237—238 °C); *m*/*z* 181 (M^+); $\lambda_{max.}$(EtOH) 327 (14 600 dm^3 mol^{-1} cm^{-1}) and 221 nm (9 200); δ_H 6.31 (2 H, br, NH, deuterium exchangeable), 7.72 and 8.23 (each 2 H, each d, each *J* 8.5 Hz, $C_6H_4NO_2$) and 9.40 (1 H, br, NH, deuterium exchangeable) (Found: C, 46.6; H, 3.8; N, 23.3. Calc. for $C_7H_7N_3O_3$: C, 46.41; H, 3.90; N, 23.20%).

The filtrate obtained above was neutralized with conc. hydrochloric acid. The resulting precipitate was collected by filtration and recrystallized from DMF to give the 2-thiocytosine (**4**) (0.30 g, 30%), which was identical with an authentic sample[8] and with the product obtained from the reaction of compound (**11a**) with thiourea.

2,4-*Diamino*-5-(N-*methylcarbamoyl*)*pyrimidine* (**5a**).—A mixture of guanidine hydrochloride (0.96 g, 10 mmol) and sodium hydroxide (0.32 g, 8 mmol) in absolute ethanol (30 ml) was stirred for 10 min and insoluble NaCl was removed by filtration. To the filtrate was added the 5-cyanouracil (**1a**)[17] (0.33 g, 2 mmol). The mixture was refluxed for 30 min. The solvent was removed under reduced pressure and a small amount of water was added to the residue. The insoluble material was collected by filtration and the filtrate was neutralized with acetic acid. The resulting precipitate was filtered off and recrystallized from acetonitrile to give the 5-(N-*methylcarbamoyl*)*pyrimidine* (**5a**) (see Table); δ_H 2.66 (3 H, d, *J* 4.0 Hz, NMe, collapsed to singlet by deuterium exchange), 6.47 (2 H, br s, NH_2, deuterium exchangeable), 7.47 (2 H, br, NH_2, deuterium exchangeable), 7.88—8.26 (1 **H**, br, NH, deuterium exchangeable), and 8.32 (1 H, s, 6-**H**) (Found: C, 43.4; H, 5.3; N, 42.05. $C_6H_9N_5O$ requires C, 43.11; H, 5.43; N, 41.90%).

4-*Amino*-2-*dimethylamino*-5-(N-*methylcarbamoyl*)*pyrimidine* (**5b**).—A mixture of 1,1-dimethylguanidine hydrochloride (1.85 g, 15 mmol) and sodium hydroxide (0.48 g, 12 mmol) in absolute ethanol (30 ml) was stirred for 10 min and insoluble NaCl was removed by filtration. To the filtrate was added the 5-cyanouracil (**1a**)[17] (0.50 g, 3 mmol) and the mixture was refluxed for 10 min. The solvent was removed under reduced pressure and the residue was dissolved in water. The solution was neutralized with acetic acid and extracted with chloroform. The extract was dried over $MgSO_4$ and evaporated to dryness under reduced pressure. The residue was subjected to silica gel column chromatography. Elution with chloroform–methanol (50:1) and then with chloroform–methanol (20:1) gave the 5-(N-*methylcarbamoyl*)*pyrimidine* (**5b**) (0.14 g, 24%) (see Table); δ_H 2.67 (3 H, d, *J* 4.5 Hz, NMe, collapsed to singlet by deuterium exchange), 3.08 (6 H, s, NMe), 7.20—7.70 (2 H, br, NH_2, deuterium exchangeable), 7.80—8.30 (1 H, br, NH, deuterium exchangeable), and 8.38 (1 H, s, 6-H) (Found: C, 49.35; H, 6.85; N, 35.9. $C_8H_{13}N_5O$ requires C, 49.22; H, 6.71; N, 35.88%).

2,4-*Diamino*-5-(N-*phenylcarbamoyl*)*pyrimidine* (**5c**).—A mixture of 5-cyano-1-methyl-3-phenyluracil (**1c**)[17] (0.68 g, 3 mmol), guanidine hydrochloride (0.34 g, 3.6 mmol), and sodium hydroxide (0.13 g, 3.25 mmol) in butan-1-ol (20 ml) was refluxed for 20 min. The solvent was removed under reduced pressure. The residue was triturated with water and the resulting precipitate was collected by filtration. The crude product was recrystallized from acetone–water to give the 5-(N-*phenylcarbamoyl*)*pyrimidine* (**5c**) (0.44 g, 64%) (see Table); δ_H 6.62 (2 H, br s, NH_2, deuterium exchangeable), 7.03—7.89 (7 H, m, Ph and NH_2, collapsed to 5 H by deuterium exchange), 8.57 (1 H, s, 6-H), and 9.80 (1 H, br, NH) (Found: C, 57.65; H, 4.85; N, 30.45. $C_{11}H_{11}N_5O$ requires C, 57.63; H, 4.84; N, 30.55%).

7-*Amino*-3-*methyl*-1-*phenylpyrimido*[4,5-d]*pyrimidine*-2,4-*dione* (**9a**).—(*a*) A mixture of the cyanouracil (**8a**)[17] (0.68 g, 3 mmol) and thiourea (0.69 g, 9 mmol) in ethanolic sodium ethoxide [prepared from Na (0.21 g, 9 mg-atom) in absolute ethanol (30 ml)] was refluxed for 1 h. The solvent was removed under reduced pressure and the residue was triturated with a small amount of water. The resulting precipitate was collected by filtration, washed with water, and dried to give the *pyrimido*[4,5-d]*pyrimidine* (**9a**) (0.53 g, 66%). An analytical sample was obtained by recrystallization from acetonitrile, m.p. >300 °C; *m*/*z* 269 (M^+); $\lambda_{max.}$(EtOH) 301 (11 100 dm^3 mol^{-1} cm^{-1}) and 264 nm (13 500); δ_H 3.29 (3 H, s, NMe), 7.14—7.76 (7 H, m, Ph and NH_2), and 8.76 (1 H, s, 5-H) (Found: C, 58.2; H, 4.0; N, 26.1. $C_{13}H_{11}N_5O_2$ requires C, 57.98; H, 4.12; N, 26.01%).

(*b*) A mixture of guanidine nitrate (0.73 g, 6 mmol) in ethanolic sodium ethoxide [prepared from Na (0.10 g, 4.35 mg-atom) in absolute ethanol (15 ml)] was stirred at room temperature for 5 min. To the solution was added 6-amino-5-formyl-3-methyl-1-phenyluracil (**10**)[1] (0.37 g, 1.5 mmol) and then the mixture was stirred at room temperature for 16 h. After the same procedure as described above, the pyrimido[4,5-*d*]pyrimidine (**9a**) (0.39 g, 96%) was obtained. This product was identical with the sample obtained by procedure (*a*).

3-*Methyl*-7-*methylamino*-1-*phenylpyrimido*[4,5-d]*pyrimidine*-2,4-*dione* (**9b**).—A mixture of the cyanouracil (**8a**)[17] (0.68 g, 3 mmol) and *N*-methylthiourea (0.81 g, 9 mmol) in ethanolic

sodium ethoxide [prepared from Na (0.21 g, 9 mg-atom) in absolute ethanol (30 ml)] was refluxed for 24 h. The solvent was removed under reduced pressure and the residue was triturated with a small amount of water. The resulting precipitate was collected by filtration, washed with water, and recrystallized from acetone–water to give the *pyrimido*[4,5-d]*pyrimidine* (**9b**) (0.60 g, 71%); m.p. 283.5—284 °C; *m/z* 283 (M^+); $\lambda_{max.}$(EtOH) 308 (10 400 dm^3 mol^{-1} cm^{-1}) and 271 nm (16 100); δ_H 3.10 (3 H, d, *J* 7.5 Hz, NMe), 3.26 (3 H, s, NMe), 7.15—7.76 (5 H, m, Ph), 7.95 (1 H, br, NH, deuterium exchangeable), and 8.85 (1 H, br s, 5-H) (Found: C, 59.6; H, 4.55; N, 24.8. $C_{14}H_{13}N_5O_2$ requires C, 59.35; H, 4.63; N, 24.72%).

7-*Amino*-1-(p-*methoxyphenyl*)-3-*methylpyrimido*[4,5-d]*pyrimidine*-2,4-*dione* (**9c**).—This compound was prepared from 5-cyano-1-(*p*-methoxyphenyl)-3-methyluracil (**8b**)[1] (0.77 g, 3 mmol) and thiourea (0.69 g, 9 mmol) in the same manner as described above for (**9b**): yield 70%, m.p. >300 °C (from EtOH); *m/z* 299 (M^+); $\lambda_{max.}$(EtOH) 299 (11 200 dm^3 mol^{-1} cm^{-1}), 260 (13 700) and 223 nm (31 900); δ_H 3.29 (3 H, s, NMe), 3.87 (3 H, s, OMe), 7.05 and 7.30 (each 2 H, each d, each *J* 9.0 Hz, C_6H_4), 7.47 (2 H, br, NH_2, deuterium exchangeable), and 8.87 (1 H, s, 5-H) (Found: C, 55.9; H, 4.3; N, 23.2. $C_{14}H_{13}N_5O_3$ requires C, 56.18; H, 4.38; N, 23.40%).

5-*Cyano*-1-(p-*nitrophenyl*)*uracil* (**11b**).—White fuming nitric acid (15 ml) was added dropwise to a stirred suspension of 5-cyano-1-phenyluracil (**11a**)[17] (5.0 g, 23.5 mmol) in sulphuric acid (30 ml) while the temperature was kept between −5 and 5 °C. The mixture was stirred at 10 °C for 30 min and then poured onto ice. The resulting precipitate was collected by filtration, washed successively with water and then hot MeOH, and dried to give the *title compound* (**11b**) (3.9 g, 65%). An analytical sample was obtained by recrystallization from methanol, m.p. 273—275 °C; *m/z* 278 (M^+); δ_H 7.93 and 8.50 (each 2 H, each d, each *J* 9 Hz, $C_6H_4NO_2$), 9.31 (1 H, s, 6-H), and 12.38 (1 H, br, NH, deuterium exchangeable) (Found: C, 43.4; H, 2.3; N, 19.9. $C_{10}H_6N_4O_6$ requires C, 43.17; H, 2.17; N, 20.14%).

Reaction of 5-*Cyano*-3-*methyl*-1-*phenyluracil* (**8a**) *with Guanidine*.—A mixture of guanidine nitrate (2.44 g, 20 mmol) in ethanolic sodium ethoxide [prepared from Na (0.35 g, 15 mg-atom) in absolute ethanol (50 ml)] was stirred for 10 min and insoluble $NaNO_3$ was removed by filtration. To the filtrate was added the uracil (**8a**)[17] (1.14 g, 5 mmol) and the mixture was then refluxed for 5 h under argon. The solvent was removed under reduced pressure and the residue was triturated with a small amount of water. The resulting precipitate was collected by filtration, washed with water, and dried to give 7-amino-3-methyl-1-phenylpyrimido[4,5-*d*]pyrimidine-2,4-dione (**9a**) (0.35 g, 26%), which was identical with the product obtained by the reaction of compound (**8a**) with thiourea.

The filtrate was neutralized with Amberlite CG-50 (H^+), and the neutral solution was evaporated to dryness under reduced pressure. The residue was recrystallized from water to give 5-*cyanoisocytosine* (**12**) (0.45 g, 68%); m.p. >300 °C; *m/z* 136 (M^+); $\lambda_{max.}$(EtOH) 302 (14 200 dm^3 mol^{-1} cm^{-1}) and 232 nm (10 300); $\nu_{max.}$ 2 220 cm^{-1} (CN); δ_H 7.58 (2 H, br, NH, deuterium exchangeable), 8.22 (1 H, s, 6-H), and 10.52—12.51 (1 H, br, NH, deuterium exchangeable) (Found: C, 44.4; H, 3.0; N, 40.9. $C_5H_4N_4O$ requires C, 44.12; H, 2.96; N, 41.17%).

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