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Rearrangement of 5-Cyanouracils into 6-Aminouracils by Reaction with Amines and Hydroxide Ion[1]

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Treatment of 5-cyano-1-phenyluracil derivatives (1) with ammonia and alkylamines afforded 6-amino-5-iminomethyluracils (2) *via* rearrangement involving ring-opening and ring-closure processes. Upon reaction of 3-unsubstituted 5-cyano-1-phenyluracil (1d) with ammonia and methylamine, ring-opening products, 3-acryloyl-1-phenylureas (5a and 5b) were isolated and recyclized with ease to 6-aminouracils (2j and 2k). Employment of sodium hydroxide instead of amines caused analogous rearrangement to give 6-amino-5-formyluracils (7a—c).

Keywords rearrangement; ring transformation; 5-cyanouracil; 6-aminouracil; nucleophile; alkylamine

Our previous studies[2] have demonstrated that the reaction of 1,3-disubstituted uracil derivatives possessing an electron-withdrawing group such as a nitro or carbamoyl group at the 5-position with ammonia and alkylamines induced the exchange of N_1-moiety of the uracil ring for the employed amine. This type of exchange reaction proceeds *via* ring-opening and ring-closure processes as shown in Chart 1, and was accelerated by the presence of a phenyl group rather than an alkyl group at the N_1-position of the uracil ring (Chart 1).

During the course of our study on the application of this N_1-exchange reaction to 5-cyano-1-phenyluracil derivatives (**1**), we have encountered the rearrangement of **1** leading to 6-aminouracil derivatives (**2**). The present paper describes a further example of pyrimidine-to-pyrimidine ring transformation[3] involving ring-opening and ring-closure processes.

Treatment of 5-cyano-3-methyl-1-phenyluracil (**1a**)[4] with ammonia and methylamine in ethanol at room temperature afforded 6-amino-5-iminomethyluracil (**2a**) and 6-amino-5-(N-methyliminomethyl)uracil (**2b**) in 93% and 76% yields, respectively. The expected N_1-exchanged products, 5-cyano-3-methyluracil and 5-cyano-1,3-dimethyluracil, were not detected by thin layer chromatographic (TLC) analysis of the reaction mixture. The structures of **2a** and **2b** were determined on the basis of the microanalytical results and spectral data. The ultimate proof of the structures was provided by an alternate synthesis of **2a** and **2b** from 6-amino-3-methyl-1-phenyluracil (**3**) according to Bredereck *et al.*'s method.[5] The Vilsmeier–Haack reaction of **3** using a mixture of phosphorus oxychloride ($POCl_3$) and dimethylformamide (DMF) followed by addition of ammonia and methylamine to the reaction solution without isolation of the intermediate (**4**) gave 6-amino-5-iminomethyluracil derivatives, which were identical with the rearrangement products (**2a** and **2b**) obtained above (Chart 2).

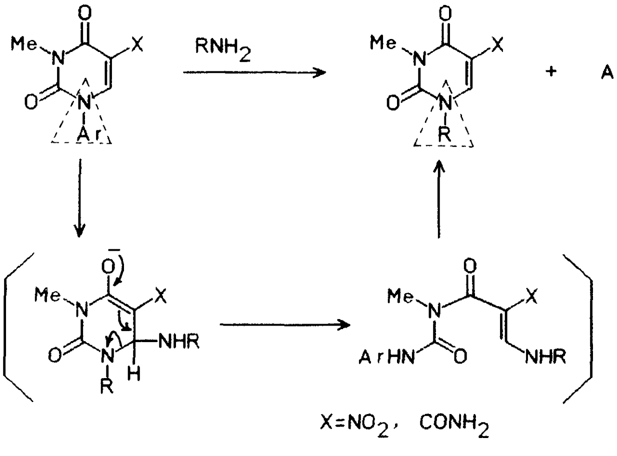


Chart 1

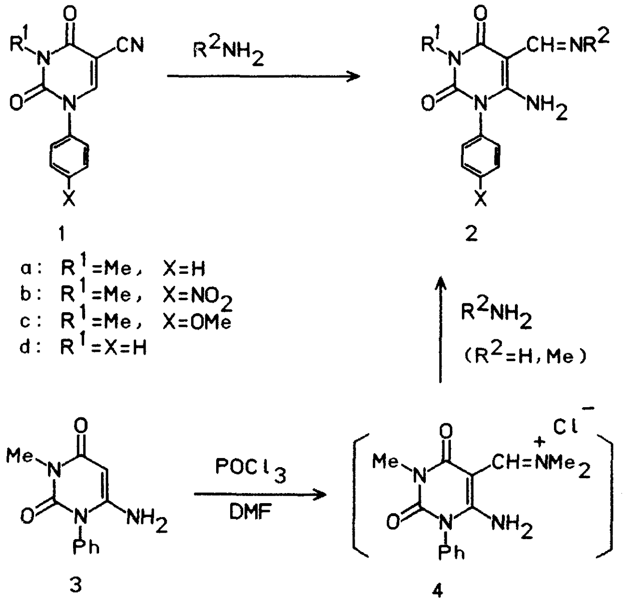
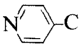
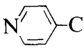
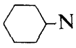
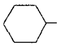
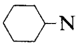
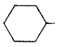


Chart 2

Analogous reactions of 1-phenyl-, 1-(p-nitrophenyl)-, and 1-(p-methoxyphenyl)-5-cyano-3-methyluracil derivatives (**1a**—**c**) with ammonia and alkylamines gave the corresponding rearrangement products (**2c**—**i**), as shown in Table I. The use of an acylhydrazine, isonicotinic acid hydrazide (isoniazid) instead of alkylamines also resulted in the formation of the corresponding 6-aminouracil (**2d**), although more drastic conditions were required (reflux in the presence of sodium ethoxide).

When 3-unsubstituted 5-cyano-1-phenyluracil (**1d**)[4] was allowed to react with ammonia and methylamine at room temperature, ring-opened products (**5a** and **5b**) were isolated in high yields. The infrared (IR) spectra of both **5a** and **5b** exhibited a sharp absorption at 2240 and 2220 cm^{-1}, respectively, assignable to a cyano group. Recrystallization of **5a** from ethanol caused rapid ring closure to give 6-amino-5-iminomethyluracil (**2j**). In contrast to **5a**, the other ring-opened product (**5b**) was stable enough to purify by recrystallization. The proton magnetic resonance (^1H-

Table I. Formation of 6-Amino-5-(iminomethyl)uracil Derivatives (**2a**—**n**)

Starting compound	Amines	Reaction temperature (°C)	Reaction time (h)	Product No.	R^1	R^2	X	mp (°C) (Recrystn. solvent$^{a)}$)	Yield (%)
1a	$NH_3$$^{b)}$	r.t.	48	**2a**	Me	H	H	227—228 (E)	93
1a	$MeNH_2$	r.t.	16	**2b**	Me	Me	H	248 (E)	76
1a	$PrNH_2$	r.t.	16	**2c**	Me	Pr	H	155—156 (E)	95
1a	-CONHNH$_2$	Reflux$^{c)}$	5 min	**2d**	Me	-CONH	H	292—293 (N)	77
1b	$NH_3$$^{b)}$	r.t.	3	**2e**	Me	H	NO_2	223—225 (E)	77
1b	$MeNH_2$	r.t.	3	**2f**	Me	Me	NO_2	249—250 (A)	59
1c	$NH_3$$^{b)}$	r.t.	16	**2g**	Me	H	MeO	235—237 (E)	69
1c	$MeNH_2$	r.t.	16	**2h**	Me	Me	MeO	252—254 (M)	87
1c	-NH$_2$	r.t.	16	**2i**	Me		MeO	167—168 (H)	81
1d	$NH_3$$^{b)}$	$^{d)}$	d	**2j**	H	H	H	285—287 (E)	70
1d	$MeNH_2$	100$^{e)}$	8	**2k**	H	Me	H	230 (E)	66
1d	$EtNH_2$	r.t.	24	**2l**	H	Et	H	287—289 (E)	66
1d	$BuNH_2$	r.t.	24	**2m**	H	Bu	H	198 (A)	77
1d	-NH$_2$	r.t.	2	**2n**	H		H	143—145 (E)	79

a) Recrystallization solvent: E, EtOH; N, acetonitrile; A, AcOEt; M, MeOH; H, H_2O–acetone. *b*) In absolute ethanol saturated with ammonia. *c*) In the presence of NaOEt. *d*) After reaction at room temperature for 11 h, the resulting intermediate (**5a**) was recrystallized from EtOH. *e*) In a sealed tube. r.t. = room temperature.

Table II. ^{1}H-NMR Spectral Data and Microanalytical Results of 6-Aminouracil Derivatives (**2a**—**n**)

Compound No.	^{1}H-NMR (DMSO-d_6) δ (J, Hz)	Formula	Analysis (%) Calcd (Found) C	H	N
2a	3.17 (3H, s, NMe), 5.94—6.53 (1H, br, NH), 7.18—7.77 (5H, m, Ph), 8.10—8.57 (1H, br, –CH=N–), 8.60—9.42 and 10.37—10.95 (each 1H, each br, NH)	$C_{12}H_{12}N_4O_2$	59.01 (59.14	4.95 5.01	22.94 22.99)
2b	3.17 and 3.30 (each 3H, each s, NMe), 6.45 (1H, br, NH), 7.15—7.74 (5H, m, Ph), 8.46 (1H, br s, –CH=N–), 11.05 (1H, br, NH)	$C_{13}H_{14}N_4O_2$	60.45 (60.31	5.46 5.41	21.70 21.76)
2c	0.20—1.81 (5H, m, NCH$_2\underline{Et}$), 3.17 (3H, s, NMe), 3.42 (2H, t, J=6.5, NCH$_2$), 6.47 (1H, br, NH), 7.05—7.74 (5H, m, Ph), 8.47 (1H, br s, –CH=N–), 11.05 (1H, br, NH)	$C_{15}H_{18}N_4O_2$	62.92 (62.91	6.34 6.52	19.57 19.56)
2d	3.24 (3H, s, NMe), 7.32—7.85 (5H, m, Ph), 7.96 and 8.89 (each 2H, each dd, each J= 4.5, 1.5, pyridyl), 8.96 (1H, s, –CH=N–)	$C_{18}H_{16}N_6O_3 \cdot H_2O$	56.54 (56.65	4.75 4.70	21.98 22.07)
2e	3.18 (3H, s, NMe), 6.34—7.13 (1H, br, NH), 7.78 and 8.52 (each 2H, each d, each J=9, C_6H_4), 8.44 (1H, br, –CH=N–), 8.75—9.80 and 10.18—11.33 (each 1H, each br, NH)	$C_{12}H_{11}N_5O_4$	49.83 (49.66	3.83 3.79	24.21 24.21)
2f	3.16 and 3.27 (each 3H, each s, NMe), 6.36—7.21 (1H, br, NH), 7.70 and 8.37 (each 2H, each d, each J=8.5, C_6H_4), 8.44 (1H, s, –CH=N–), 10.20—11.35 (1H, br, NH)	$C_{13}H_{13}N_5O_4$	51.48 (51.56	4.32 4.24	23.09 23.23)
2g	3.17 (3H, s, NMe), 3.86 (3H, s, OMe), 5.88—6.60 (1H, br, NH), 7.13 and 7.35 (each 2H, each d, each J=9, C_6H_4), 7.88—8.90 (2H, br, –CH=N– and NH), 10.18—11.43 (1H, br, NH)	$C_{13}H_{14}N_4O_3$	56.93 (56.80	5.15 5.06	20.43 20.24)
2h	3.18, 3.32 (each 3H, each s, NMe), 3.87 (3H, s, OMe), 6.63 (1H, br, NH), 7.17 and 7.41 (each 2H, each d, each J=9, C_6H_4), 8.57 (1H, br, –CH=N–), 10.86 (1H, br, NH)	$C_{14}H_{16}N_4O_2$	58.32 (58.37	5.59 5.54	19.44 19.39)
2i	0.78—2.24 (10H, m, cyclohexyl), 3.18 (4H, s and br, NMe and cyclohexyl), 3.87 (3H, s, OMe), 6.62 (1H, br, NH), 7.16 and 7.42 (each 2H, each d, each J=9, C_6H_4), 8.62 (1H, br s, –CH=N–), 11.16 (1H, br, NH)	$C_{19}H_{24}N_3O_4$	64.02 (63.80	6.79 6.80	15.72 15.74)
2j	6.31 (1H, br, NH), 7.18—7.82 (5H, m, Ph), 8.27 (1H, br, –CH=N–), 9.00 and 10.45 (each 2H, each br, NH)	$C_{11}H_{10}N_4O_2$	57.38 (57.19	4.38 4.28	24.34 24.10)
2k	3.28 (3H, s, J=7, NMe), 7.08—7.87 (5H, m, Ph), 8.50 (1H, br s, –CH=N–), 10.96 (2H, br, NH)	$C_{12}H_{12}N_4O_2$	59.01 (58.86	4.95 5.16	22.94 22.85)
2l	1.14 (3H, t, J=7, CMe), 3.45 (2H, q, J=7, NCH$_2$), 6.44 (1H, br, NH), 7.16—7.78 (5H, m, Ph), 8.42 (1H, br s, –CH=N–), 10.90 (2H, br, NH)	$C_{13}H_{14}N_4O_2$	60.45 (60.27	5.46 5.60	21.70 21.65)
2m	0.70—1.95 (7H, m, NCH$_2\underline{Pr}$), 3.20—3.64 (2H, m, NCH$_2$), 6.47 (1H, br, NH), 7.27—7.77 (5H, m, Ph), 8.39 (1H, br s, –CH=N–), 10.76 and 11.05 (each 1H, each Br, NH)	$C_{15}H_{18}N_4O_2$	62.92 (62.99	6.34 6.27	19.57 19.52)
2n	0.90—2.10 (10H, m, cyclohexyl), 2.89—3.40 (1H, m, cyclohexyl), 6.45 (1H, br, NH), 7.10—7.73 (5H, m, Ph), 8.43 (1H, br s, –CH=N–), 10.74 and 11.17 (each 1H, each br, NH)	$C_{17}H_{20}N_4O_2$	65.36 (65.37	6.45 6.45	17.94 17.91)

NMR) spectrum of **5b** indicated the presence of an olefinic proton (δ 8.27). Upon heating of **5b** in ethanol in the presence of triethylamine, 6-amino-5-(N-methyliminomethyl)uracil (**2k**) was produced smoothly in high yield. The 6-aminouracil (**2k**) was also prepared by heating of **1d** with methylamine in a sealed tube at 100 °C. The employment of ethylamine, butylamine, and cyclohexylamine in the reaction of the 3-unsubstituted uracil (**1d**) at room temperature led to the direct formation of 6-aminouracils (**2l**—**n**) without isolation of ring-opened intermediates (Table II).

Treatment of 5-cyano-1,3-dimethyluracil (**6**), which possesses no phenyl group at the N_1-position, with methylamine under various conditions resulted in the recovery of the starting material. This fact indicates that the presence of the phenyl group at the N_1-position plays an significant role in inducing the rearrangement of 5-cyanouracils (**1**) to 6-aminouracils (**2**) using ammonia and alkylamines as nucleophiles. It has often been observed that the N_1-substituted phenyl groups of uracils facilitate the cleavage of the N_1–C_6 bond by attack of nucleophiles on the 6-position.[2,6]

On the basis of these results, a plausible reaction sequence for the rearrangement of 5-cyanouracils (**1**) to 6-aminouracils (**2**) is outlined in Chart 4. An initial nucleophilic attack of amines on the 6-position of the uracil ring could form the 1,4-adduct (A), which should be converted more readily into the ring-opening intermediate (B), since the 1-phenyl group facilitates cleavage of the 1,6-bond in the uracil ring. Subsequent attack of the *N*-anion on the cyano group in B could afford 6-aminouracils (**2**) *via* the exo-methylene tautomer (C). Protonation of B could lead to the formation of the ring-opened product (**5**). This reaction mode is mechanistically similar to the pyrido[2,3-*d*]pyrimidine synthesis reported by Su and Watanabe.[7]

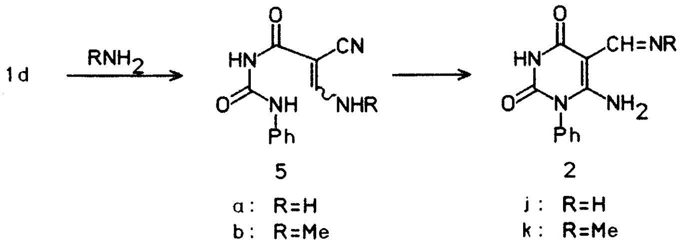


Chart 3

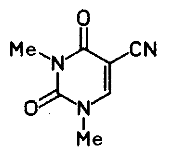


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Fig. 1

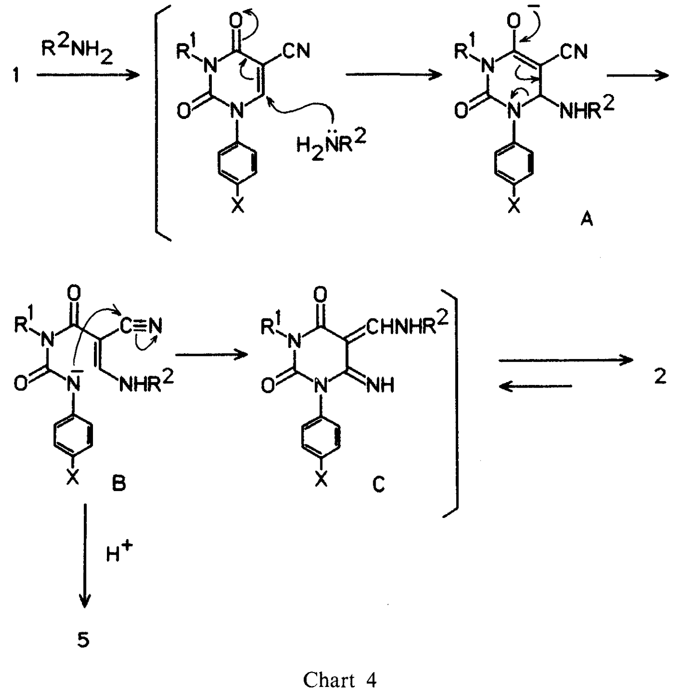

Chart 4

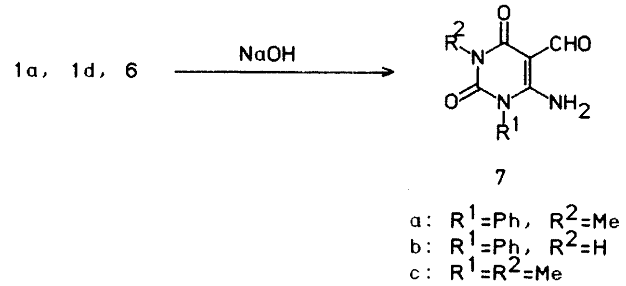

Chart 5

When amines such as aniline and diethylamine were used as nucleophiles in the reaction of **1a**, no appreciable reaction occurred. On the basis of the above findings, the rearrangement of 5-cyanouracil derivatives using sodium hydroxide instead of amines was examined. Treatment of **1a** and **1d** with sodium hydroxide in ethanol under reflux gave, as expected, the 6-amino-5-formyluracils (**7a** and **7b**) in 82% and 69% yields, respectively. Even when 5-cyano-1,3-dimethyluracil (**6**) was employed, the corresponding rearrangement product, 6-amino-5-formyl-1,3-dimethyluracil (**7c**), was obtained. The 6-amino-5-formyluracils (**7a** and **7c**) were alternatively prepared by the Vilsmeier–Haack reaction[8] of **3** and 6-amino-1,3-dimethyluracil. An analogous type of rearrangement has been observed in the reactions of 5-cyano-2-iminopyrimidine,[9] 3-cyano-4-oxo-4*H*-chromene,[10] 6-cyano-5-oxopyrido[2,3-*d*]pyrimidine[11] and ethyl 2,4-dioxopyrido[2,3-*d*]pyrimidine-6-carboxylate[12] with sodium hydroxide.

Experimental

All melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. Elemental analyses were carried out at the Microanalytical Laboratory of our University. IR spectra were taken on a Hitachi 215 instrument from KBr pellets. ^{1}H-NMR were recorded on a Hitachi Perkin-Elmer R-20B spectrometer for solutions in $(CD_3)_2SO$ unless otherwise stated, with sodium 2,2-dimethyl-2-silapentane-5-sulfonate as an internal reference. Chemical shifts are quoted in parts per million (s = singlet, d = doublet, t = triplet, m = multiplet, q = quartet, br = broad, br s = broad singlet, dd = double doublet). Mass spectra (MS) were mesured at 70 eV with a JEOL JMS-D300 spectrometer.

5-Cyano-3-methyl-1-(*p*-nitrophenyl)uracil (1b) Fuming nitric acid (15 ml) was added dropwise to a stirred suspension of 5-cyano-3-methyl-1-phenyluracil (**1a**)[4] (5.0 g, 22 mmol) in sulfuric acid (30 ml), keeping the temperature between −5 and 5 °C. The mixture was stirred at 10 °C for 30 min and then poured into ice water. The resulting precipitate was collected, washed with water and then hot MeOH, and dried to give **1b** (3.9 g, 65%). An analytical sample was obtained by recrystallization from MeOH, mp 201—203 °C. *Anal.* Calcd for $C_{12}H_8N_4O_4$: C, 52.94; H, 2.96; N, 20.58. Found: C, 52.82; H, 2.89; N, 20.37. MS *m/z*: 272 (M^+). ^{1}H-NMR δ: 3.25 (3H, s, NMe), 7.81 and 8.42 (each 2H, each d, each $J=8.5$ Hz, C_6H_4), 8.93 (1H, s, C_6-H).

5-Cyano-1-(*p*-methoxyphenyl)-3-methyluracil (1c) *p*-Anisidine (12.39 g, 100 mmol) was added dropwise to a stirred suspension of α-cyano-β-ethoxy-*N*-ethoxycarbonylacrylamide[4] (20 g, 94 mmol) in EtOH (70 ml). After cooling, the resulting precipitate was collected, washed with EtOH and dried to give α-cyano-β-(*p*-anisidino)-*N*-ethoxycarbonylacrylamide (26.1 g, 96%). An analytical sample was obtained by recrystallization from EtOH, mp 175 °C. *Anal.* Calcd for $C_{14}H_{15}N_3O_4$: C, 58.12; H, 5.23; N, 14.53. Found: C, 58.09; H, 5.22; N, 14.57. MS *m/z*: 289 (M^+). ^{1}H-NMR δ: 1.24 (3H, t, $J=7$ Hz, $CH_2C\underline{H}_3$), 3.74 (3H, s, OMe), 4.14 (2H, q, $J=7$ Hz, OCH_2), 6.96 and 7.42 (each 2H, each d, each $J=9$ Hz, C_6H_4), 8.38 (1H, br d, $J=14$ Hz, CH), 10.08—10.62 (2H, br, NH).

A suspension of α-cyano-β-(p-anisidino)-N-ethoxycarbonylacrylamide (25.03 g, 87 mmol) in tetralin was heated at 185—200 °C and the EtOH formed was continuously distilled off during *ca.* 30 min. After cooling, the resulting precipitate was collected, washed with ether, and dried to give 5-cyano-1-(p-methoxyphenyl)uracil (19.92 g, 94%). An analytical sample was obtained by recrystallization from AcOH, mp >300 °C. *Anal.* Calcd for $C_{12}H_9N_3O_3$: C, 59.26; H, 3.73; N, 17.28. Found: C, 59.51; H, 3.73; N, 17.28. MS *m/z*: 243 (M^+). ^{1}H-NMR δ: 3.82 (3H, s, OMe), 7.05 and 7.42 (each 2H, each d, each J=9 Hz, C_6H_4), 8.73 (1H, s, C_6-H), 12.70 (1H, br, NH).

Dimethyl sulfate (10.49 g, 83 mmol) was added dropwise to a stirred solution of 5-cyano-1-(p-methoxyphenyl)uracil (18.60 g, 76 mmol) and NaOH (4.3 g, 107 mmol) in water (88 ml). The resulting precipitate was collected by filtration and recrystallized from AcOH to give 5-cyano-1-(p-methoxyphenyl)-3-methyluracil (**1c**) (11.03 g, 56%), mp 243 °C. *Anal.* Calcd for $C_{13}H_{11}N_3O_3$: C, 60.69; H, 4.31; N, 16.34. Found: C, 60.71; H, 4.36; N, 16.32. MS *m/z*: 257 (M^+). ^{1}H-NMR δ: 3.25 (3H, s, NMe), 3.85 (3H, s, OMe), 7.14 and 7.50 (each 2H, each d, each J=9 Hz, C_6H_4), 8.87 (1H, s, C_6-H).

6-Amino-5-iminomethyluracil Derivatives (2a—n) Typical Procedure: A solution of 5-cyano-3-methyl-1-phenyluracil (**1a**)[4] (0.3 g, 1.32 mmol) and methylamine (40%, in water) (1.0 g, 13.2 mmol) in EtOH (15 ml) was stirred at room tempeature for 16 h. The resulting precipitate was collected by filtration and recrystallized from EtOH to give **2b** (0.26 g, 76%), mp 248 °C. MS *m/z*: 258 (M^+).

6-Aminouracils (**2a** and **2c—n**) were prepared according to the procedure described above. The reaction conditions and the physical data of **2a—n** are summarized in Tables I and II.

Alternate Synthesis of 6-Amino-5-iminomethyl-3-methyl-1-phenyluracil (2a) $POCl_3$ (0.50 g) was added dropwise to a stirred suspension of 6-amino-3-methyl-1-phenyluracil (**3**) (0.65 g, 3 mmol) in DMF (20 ml) at 20 °C. The mixture was stirred at 50 °C for 1 h. After cooling, absolute EtOH saturated with ammonia (3 ml) was added dropwise to the stirred reaction mixture at 5 °C and the whole was stirred at room temperature for 30 min. Water (30 ml) was added to the reaction mixture and the resulting precipitate was collected, washed with water and dried to give **2a** (0.45 g, 62%), which was identical with the product obtained by the reaction of **1a** with ammonia.

Alternate Synthesis of 6-Amino-3-methyl-5-(*N*-methyliminomethyl)-1-phenyluracil (2b) $POCl_3$ (0.77 g) was added dropwise to a stirred suspension of 6-amino-3-methyl-1-phenyluracil (**3**) (1.0 g, 4.6 mmol) in DMF (20 ml) at 20 °C. The mixture was stirred at 50 °C for 50 min, then allowed to cool. Methylamine (40% in MeOH) (2.0 g, 26 mmol) was added dropwise to the stirred reaction mixture at 5 °C and the whole was stirred at room temperature for 30 min. The solvent was evaporated off under reduced pressure and the residue was triturated with a small amount of water. The resulting precipitate was collected, washed with water, and dried to give **2b** (0.74 g, 62%), which was identical with the product obtained by the reaction of **1a** with methylamine.

Formation of 6-Amino-5-(*N*-methyliminomethyl)-1-phenyluracil (2j) *via* 3-(2-Cyano-3-aminoacryloyl)-1-phenylurea (5a) A suspension of 5-cyano-1-phenyluracil (**1d**)[4] (0.64 g, 3 mmol) in absolute EtOH saturated with ammonia (30 ml) was stirred at room temperature for 11 h. The resulting precipitate was collected by filtration to give **5a** (0.62 g, 90%). IR (KBr): 2240 (CN) cm^{-1}. Recrystallization of **5a** from EtOH gave **2j** (0.60 g, 87%) (see Tables I and II).

6-Amino-5-(*N*-methyliminomethyl)-1-phenyluracil (2k) A mixture of 3-(2-cyano-3-methylaminoacryloyl)-1-phenylurea (**5b**) (0.73 g, 3 mmol) and triethylamine (3.04 g, 30 mmol) in EtOH (30 ml) was refluxed for 3 h, then allowed to cool. The resulting precipitate was filtered off and washed with EtOH to give **2k** (0.56 g, 77%), which was identical with the product obtained by the reaction of **1a** with methylamine.

6-Amino-3-methyl-1-phenyluracil (3) A mixture of cyanoacetic acid (4.25 g), 1-methyl-3-phenylurea (7.5 g), acetic anhydride (10 ml), and AcOH (12 ml) was subjected to the procedure[13] for preparation of 6-aminouracils to give **3** (9.2 g, 85%), mp 289—290 °C (recrystallized from EtOH). *Anal.* Calcd for $C_{11}H_{11}N_3O_2$: C, 60.82; H, 5.10; N, 19.35. Found: C, 61.07; H, 5.28; N, 19.54.

3-(2-Cyano-3-methylaminoacryloyl)-1-phenylurea (5b) A suspension of 5-cyano-1-phenyluracil (**1d**)[4] (1.28 g, 6 mmol) and methylamine (40% in water) (4.70 g, 60 ml) in EtOH (50 ml) was stirred at room temperature for 30 min. The resulting precipitate was collected by filtration and recrystallized from EtOH to give **5b** (1.42 g, 97%), mp 170—172 °C. *Anal.* Calcd for $C_{12}H_{12}N_4O_2$: C, 59.01; H, 4.95; N, 22.94. Found: C, 59.23; H, 4.82; N, 22.75. MS *m/z*: 244 (M^+). IR (KBr): 2220 cm^{-1}. ^{1}H-NMR δ: 3.04 (3H, s, NMe), 6.68—7.65 (5H, m, Ph), 8.27 (1H, br s, CH), 10.77 (1H, br, NH).

6-Amino-5-formyl-3-methyl-1-phenyluracil (7a) a) A mixture of 5-cyano-3-methyl-1-phenyluracil (**1a**)[4] (0.68 g, 3 mmol) and NaOH (0.36 g, 9 mmol) in EtOH (30 ml) was refluxed for 15 min. The solvent was removed under reduced pressure and the residue was dissolved in water. The solution was neutralized with AcOH and the resulting precipitate was filtered off and recrystallized from MeOH to give **7a** (0.60 g, 82%), mp 248—250 °C. *Anal.* Calcd for $C_{12}H_{11}N_3O_3$: C, 58.77; H, 4.52; N, 17.14. Found: C, 58.85; H, 4.43; N, 17.12. MS *m/z*: 245 (M^+). ^{1}H-NMR δ: 3.19 (3H, s, NMe), 7.28—7.63 (6H, m, Ph and NH), 9.82 (1H, s, CHO), 9.86 (1H, s, NH).

b) $POCl_3$ (0.92 g, 6 mmol) was dissolved in dry DMF(20 ml) below 5 °C and 6-amino-3-methyl-1-phenyluracil (**3**) (1.09 g, 5 mmol) was added thereto. The mixture was heated at 60 °C for 2 h. The reaction solution was poured into cold water. The resulting precipitate was collected by filtration to give **7a** (0.714 g, 66%), which was identical with the sample prepared above.

6-Amino-5-formyl-1-phenyluracil (7b) A mixture of 5-cyano-1-phenyluracil (**1d**)[4] (0.64 g, 3 mmol) and NaOH (0.36 g, 9 mmol) in EtOH (30 ml) was refluxed for 25 h. The solvent was removed under reduced pressure and the residue was dissolved in water (15 ml). The solution was neutralized with AcOH and the resulting precipitate was filtered off and recrystallized from MeOH to give **7b** (0.48 g, 69%), mp >300 °C. *Anal.* Calcd for $C_{11}H_9N_3O_3$: C, 57.14; H, 3.92; N, 18.18. Found: C, 57.37; H, 3.94; N, 18.38. MS *m/z*: 231 (M^+). ^{1}H-NMR δ: 7.50 (6H, m, Ph and NH), 9.81 (1H, s, C_6-H), 9.96 (1H, br, NH), 10.70—11.65 (1H, br, NH).

6-Amino-5-formyl-1,3-dimethyluracil (7c) A mixture of 5-cyano-1,3-dimethyluracil (**6**)[4] (0.50 g, 3 mmol) and NaOH (0.36 g, 9 mmol) in EtOH (30 ml) was refluxed for 7 h. The solvent was removed under reduced pressure and the residue was dissolved in water. The solution was neutralized with AcOH and extracted with $CHCl_3$. The extract was dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was treated with ether. The resulting precipitate was filtered off to give **7c** (0.32 g, 58%), which was identical with an authentic sample.[8]

References

1) This paper is part 62 of a series entitled "Pyrimidines." For Part 61: see, K. Hirota, Y. Abe, T. Asao, S. Senda, Y. Kitade and Y. Maki, *J. Heterocycl. Chem.*, **25**, 985 (1988).
2) K. Hirota, Y. Kitade, H. Sajiki and Y. Maki, *Tetrahedron Lett.*, **27**, 3263 (1986).
3) K. Hirota, K. A. Watanabe and J. J. Fox, *J. Heterocycl. Chem.*, **14**, 537 (1977); *idem*, *J. Org. Chem.*, **43**, 1193 (1978); K. Hirota, Y. Kitade and S. Senda, *Tetrahedron Lett.*, **22**, 2409 (1981); *idem*, *J. Chem. Soc., Perkin Trans. 1*, **1984**, 1859; K. Hirota, Y. Kitade, H. Sajiki and Y. Maki, *Heterocycles*, **22**, 2259 (1984).
4) S. Senda, K. Hirota and J. Notani, *Chem. Pharm. Bull.*, **20**, 1380 (1972).
5) H. Bredereck, G. Simchen, R. Wahl and F. Effenberger, *Chem. Ber.*, **101**, 512 (1968).
6) S. Senda, K. Hirota and K. Banno, *Tetrahedron Lett.*, **1974**, 3087; K. Hirota, Y. Yamada, J. Haruta and S. Senda, *Heterocycles*, **19**, 2309 (1982); K. Hirota, K. Banno, Y. Yamada and S. Senda, *J. Chem. Soc., Perkin Trans. 1*, **1985**, 1137.
7) T.-L. Su and K. A. Watanabe, *J. Heterocycl. Chem.*, **19**, 1261 (1982).
8) K. Hirota, Y. Kitade, H. Sajiki and Y. Maki, *Synthesis*, **1984**, 589.
9) D. J. Brown and M. N. Paddon-Row, *J. Chem. Soc. (C)*, **1966**, 164.
10) U. Petersen and H. Heitzer, *Justus Liebigs Ann. Chem.*, **1976**, 1659.
11) J. Matsumoto, S. Mishio and S. Minami, *J. Heterocycl. Chem.*, **16**, 1169 (1979).
12) T. Nagamatsu, M. Koga and F. Yoneda, *Chem. Pharm. Bull.*, **32**, 1699 (1984).
13) V. Papesch and E. F. Schroeder, *J. Org. Chem.*, **16**, 1879 (1951).