Pyrimidine Derivatives and Related Compounds. Part 37.[1] Novel Nucleophilic Substitutions of 5-Bromo-6-methyluracils or 5-Bromo-6-bromomethyluracils with Aromatic Amines [2]

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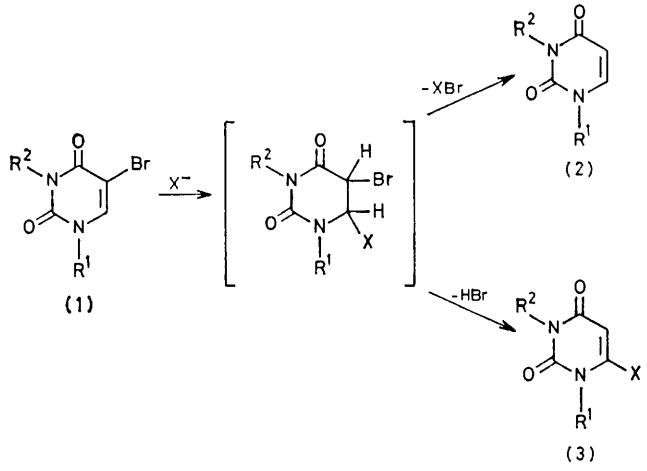
Condensation of 1-substituted or 1,3-disubstituted 5-bromo-6-methyluracils (4) and aromatic amines gave the corresponding 6-arylaminomethyluracil derivatives (5). Treatment of 5-bromo-6-bromomethyl-1,3-dimethyluracil (10) with primary aromatic amines gave the corresponding 6-arylidenemethyluracil derivatives (11). Reaction of (10) with *N*-methylaniline gave 5-bromo-1,3-dimethyl-6-(*N*-methylanilino)methyluracil (13a), which was further treated with primary aromatic amines to afford (11).

It is well known that 5-halogenouracil derivatives exhibit high reactivity towards soft [3] nucleophiles, such as SO_3^{2-}, cysteine, and CN^-, under mild conditions.[4] When 5-bromouracils (1) are used as a starting material, the reaction affords the debrominated products (2) or the 6-substituted products (3) *via* an initial attack of the nucleophile on the 6-position of the uracil ring. On the other hand, reaction with hard [3] nucleophiles, such as aliphatic and aromatic amines, proceeds only under more drastic reaction conditions, and gives the ordinary 5-substituted products.[5,6]

In contrast with 6-unsubstituted 5-bromouracils (1), reaction of 6-substituted 5-bromouracils with such hard nucleophiles has not been much investigated. Previously, we have reported [7] the synthesis of 5-alkylamino-6-methyluracil derivatives, useful analgesic agents, by

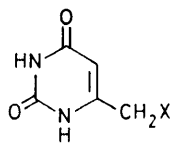


SCHEME 1

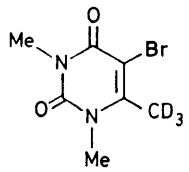
heating 5-bromo-6-methyluracils (4) with aliphatic amines in *NN*-dimethylformamide (DMF). We then investigated the reaction of (4) with aromatic amines in order to synthesize the corresponding 5-arylamino-6-methyluracils, and found a novel nucleophilic substitution reaction.[2] In this paper, we have extended this study and now report our results in detail.

RESULTS AND DISCUSSION

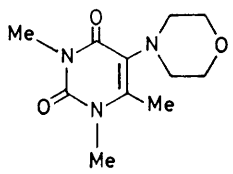
Hitchings *et al.* reported [6] the synthesis of 5-anilino-6-methyluracil by refluxing 5-bromo-6-methyluracil and aniline in ethylene glycol. Similar reaction of 5-bromo-1,3,6-trimethyluracil (4a) with aniline under such conditions was attempted, but resulted in recovery of the starting material. When the reaction was carried out in refluxing DMF, the expected 5-anilinouracil was not obtained, but instead 6-anilinomethyl-1,3-dimethyluracil (5a). This compound (5a) was identical with an authentic sample prepared by condensation of 6-chloromethyluracil (6) [8] with aniline followed by methylation of the resulting 6-anilinomethyluracil (7).



(6) X = Cl
(7) X = NHPh



(8)

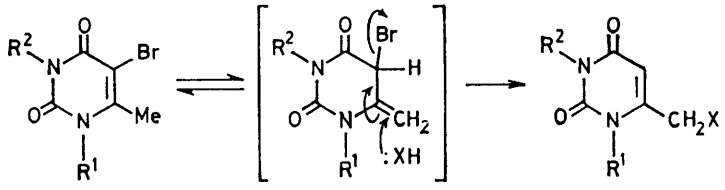


(9)

In order to clarify the mechanism for this nucleophilic substitution, (4a) was refluxed in deuterium oxide in the presence of NaOD to afford 5-bromo-6-trideuteriomethyl-1,3-dimethyluracil (8). The result suggests that 5-bromo-6-methyluracils (4) have a strong possibility of tautomerism into methylene intermediates in basic media. A plausible mechanism for the nucleophilic substitution of (4) into (5) is as follows; the key intermediate shown in Scheme 2 is a tautomer of (4) and initial attack of the nucleophile on the *exo*-methylene group of the intermediate would occur, followed by elimination of hydrogen bromide to give (5).

Similar treatment of 1-substituted or 1,3-disubstituted 5-bromo-6-methyluracils (4a—d) with aniline, *N*-methylaniline, *p*-toluidine, *p*-anisidine, and β-naphthylamine afforded the corresponding 6-arylaminomethyl derivatives (5b—h), whose structures were confirmed by

analytical and spectral data (Table 1). No reaction, however, occurred between 1-unsubstituted uracils (4e) and (4f) and aniline. This is because both (4e) and (4f) contain dissociable protons and in the presence of a base such as aniline, they are in the anionic form which inhibits their reaction with nucleophiles. Subsequently, (4a) reacted under the same conditions with sodium acetate and sodium benzoate, instead of aromatic amines, a 5-debrominated Schiff's base, 6-(phenyliminomethyl)-1,3-dimethyluracil (11a). The structure of (11a) was assigned on the basis of the ^{1}H n.m.r. spectrum. This Schiff's base (11a) was also easily prepared from 6-anilinomethyl)-5-bromo-1,3-dimethyluracil (12a). Thus, the reaction of (10) with aniline (2 equiv.) in ethyl acetate gave the postulated intermediate (12a) which was then treated with triethylamine in refluxing ethanol to give



(4) (5)

	R^1	R^2
a;	Me	Me
b;	Me	Ph
c;	Bu	H
d;	Ph	H
e;	H	H
f;	H	Me

SCHEME 2

to form the 6-acetoxymethyl and 6-benzoyloxymethyl derivatives (5i) and 5(j), respectively. Heating (4b) in formamide at 170 °C in the absence of other nucleophiles gave 6-formylaminomethyl-1-methyl-3-phenyluracil (5k). Alternatively (4a) was heated with morpholine in DMF at 100 °C to give 1,3,6-trimethyl-5-morpholinouracil (9) as described previously,[7] but the same reaction at 150 °C (*i.e.* in refluxing DMF) gave 1,3-dimethyl-6-morpholinomethyluracil (5l) besides (9). These results lead to the conclusion that this abnormal nucleophilic substitution requires more drastic conditions than the normal one.

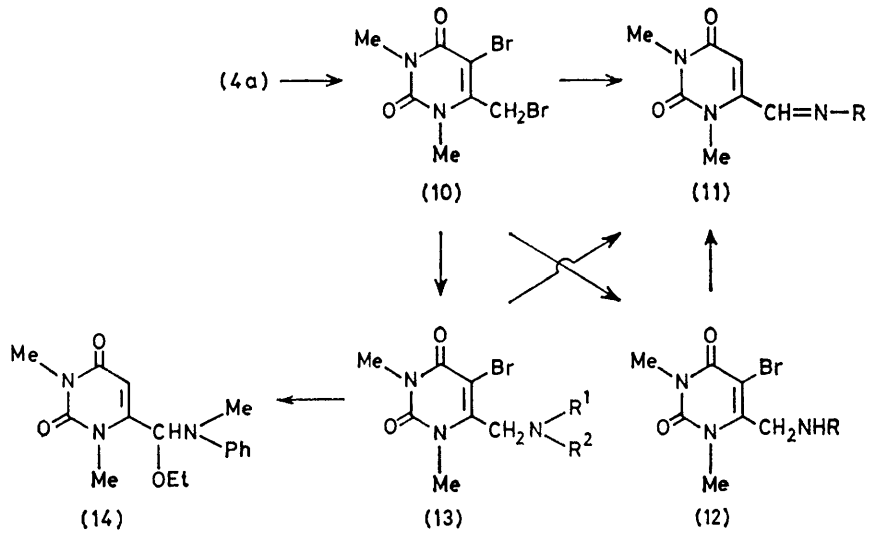
Furthermore, we have studied the reaction of 5-bromo-6-bromomethyl-1,3-dimethyluracil (10) [which is readily available from (4a)] with aromatic amines. Treatment of this dibromouracil derivative (10) with aniline in refluxing ethanol in the presence of triethylamine yielded (11a). Under the same conditions, the reaction of (10) with primary aromatic amines such as *p*-toluidine, *p*-anisidine, and β-naphthylamine afforded the corresponding 6-arylidenemethyluracil derivatives (11b—d). Similar treatment of (10) with phenylhydrazine instead of aromatic amines gave the corresponding hydrazone (11e) (Table 2).

TABLE 1

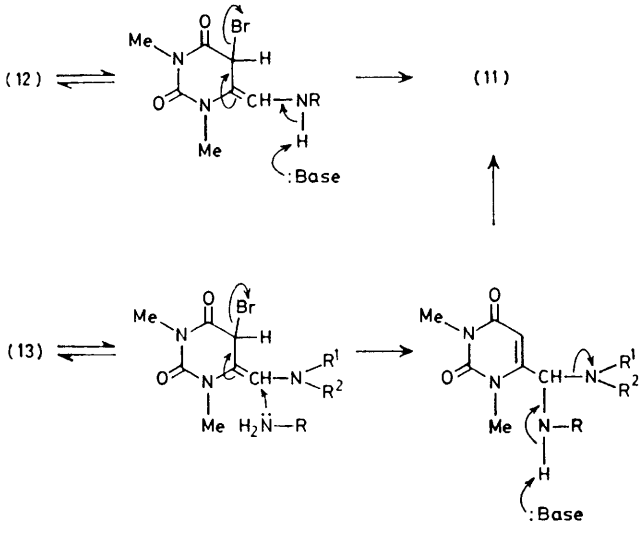
Formation of 6-(substituted methyl)uracils (5)

Compound	R^1	R^2	X	M.p. (°C)	Recrystallization solvent	Yield (%)	^{1}H N.m.r. data (δ from $SiMe_4$) 5-H	6-CH_2X	Solvent
(5a)	Me	Me	PhNH	192	AcOEt	85	5.91	4.17	$CDCl_3$
(5b)	Me	Me	PhNMe	159	Ligroin	13	5.72	4.28	$CDCl_3$
(5c)	Me	Me	*p*-MeC_6H_4NH	209	MeOH	64	5.90	4.19	$CDCl_3$
(5d)	Me	Me	*p*-$MeOC_6H_4NH$	202	MeOH	63	5.93	4.16	$CDCl_3$
(5e)	Me	Me	β-Naphthylamino	268	AcOH	54	6.52	5.09	CF_3CO_2H
(5f)	Me	Ph	PhNH	228	AcOH	73	5.75	4.33	[$^2H_6$]DMSO
(5g)	Bu	H	PhNH	156	Benzene	58	6.45	4.96	CF_3CO_2H
(5h)	Ph	H	PhNH	273	AcOEt	64	6.73	4.52	CF_3CO_2H
(5i)	Me	Me	AcO	128	H_2O	71	5.84	4.93	$CDCl_3$
(5j)	Me	Me	$PhCH_2O$	141	H_2O	73	5.97	5.20	$CDCl_3$
(5k)	Me	Ph	OHC·NH	238	MeOH	33	5.73	4.37	[$^2H_6$]DMSO
(5l)	Me	Me	Morpholino	126—128	Ligroin	27	5.73	3.29	$CDCl_3$

On the basis of the above conversion of (12a) into (11a) under the same conditions, and the mechanism for the abnormal nucleophilic substitution described above, the mechanism for these reactions is postulated in Scheme 4. 6-Arylaminomethyl-5-bromouracil derivatives (12) would be formed first and then tautomerised to a methylene intermediate. Abstraction of the proton from the amino-group accompanied by elimination of hydrogen bromide would give (11).



SCHEME 3



SCHEME 4

6-Arylaminomethyl-5-bromouracil derivatives (12b—d) were also prepared by the reaction of (10) with *p*-toluidine, *p*-anisidine, and β-naphthylamine. Subsequently, (10) reacted with *N*-methylaniline, morpholine, and methylhydrazine, instead of primary aromatic amines, under the same conditions to form the corresponding compounds (13a—c) (Table 3).

On the other hand, the reaction of 5-bromo-1,3-dimethyl-6-(*N*-methylanilino)methyluracil (13a) with primary aromatic amines led to nucleophilic substitution on the methylene carbon. Thus, compound (13a) was refluxed with aniline in ethanol in the presence of triethylamine to give 6-(*N*-phenyliminomethyl)-1,3-dimethyluracil (11a). Treatment of (13a) with triethylamine in the absence of aniline afforded the ethoxy-substituted product (14) in 30% yield. On the basis of these results, a plausible mechanism for the formation of (11a) is shown in Scheme 4.

Similar treatment of (13a) with *p*-toluidine, *p*-anisi-

TABLE 2

Formation of 6-arylidenemethyl-1,3-dimethyluracils (11)

Compound	R	M.p. (°C)	Recrystallization solvent	Yield (%) From (10)	Yield (%) From (13a)	^{1}H Nm.r. data (δ from SiMe$_4$) C-5—H	C-6—C*H*=	Solvent
(11a)	Ph	136—137	Ligroin	39	66	6.22	8.23	$CDCl_3$
(11b)	*p*-MeC_6H_4	172—173	EtOH	20	68	6.03	8.52	[$^2H_6$]DMSO
(11c)	*p*-$MeOC_6H_4$	173—174	EtOH	59	62	6.04	8.58	[$^2H_6$]DMSO
(11d)	β-Naphthyl	214	EtOH	77	34	6.32	8.70	[$^2H_6$]DMSO
(11e)	PhNH	240	EtOH	47	41	6.04	7.72	[$^2H_6$]DMSO

TABLE 3

Formation of 6-(substituted aminomethyl)-5-bromo-1,3-dimethyluracils (12) and (13)

Compound	RNH (or R^1R^2N)	M.p. (°C)	Recrystallization solvent	Yield (%)	^{15}N n.m.r. data (δ from SiMe$_4$) 6-CH_2N	Solvent
(12a)	PhNH	171—172	Pr^{i}OH	83	4.42	[$^2H_6$]DMSO
(12b)	*p*-MeC_6H_4NH	177—178	EtOH	80	4.38	[$^2H_6$]DMSO
(12c)	*p*-$MeOC_6H_4NH$	187—188	EtOH	65	4.35	[$^2H_6$]DMSO
(12d)	β-Naphthylamino	200—202	EtOH	33	4.51	[$^2H_6$]DMSO
(13a)	PhNMe	128—129	MeOH	79	4.57	($CDCl_3$)
(13b)	Morpholino	146—148	Ether	94	3.60	($CDCl_3$)
(13c)	H_2N·NMe	104—106	Ether	83	3.88	($CDCl_3$)

dine, β-naphthylamine, and phenylhydrazine gave the corresponding Schiff's bases (11b—d) and hydrazone (11e) (Table 2). However, the 6-morpholinomethyluracil (13b) did not react with aniline under the same conditions.

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 spectrometer using KBr pellets; ^{1}H n.m.r. spectra were determined with a Hitachi Perkin-Elmer R-20B 60-MHz instrument using tetramethylsilane as internal standard; 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 college.

1-Substituted or 1,3-Disubstituted 6-Arylaminomethyluracils (5a—h).—*General procedure.* 5-Bromo-6-methyluracils (4a—d) (0.02 mol) and aromatic amines (0.04 mol) were mixed with DMF (50 ml), and the mixture was refluxed for 5 h. The solvent was removed *in vacuo*, and the residue was dissolved in ether. The resulting precipitates were collected by filtration. Recrystallization from an appropriate solvent gave the corresponding 1-substituted or 1,3-disubstituted 6-arylaminomethyluracils (Table 1). Analytical data are in Table 4.

6-Acetoxymethyl-1,3-dimethyluracil (5i). A mixture of (4a) (4.6 g, 0.02 mol) and sodium acetate (1.64 g, 0.02 mol) was refluxed in DMF (30 ml) for 2 h. The solvent was removed *in vacuo*, and the residue was treated with water. The precipitate was filtered off and recrystallized from water (Table 1).

6-Benzoyloxymethyl-1,3-dimethyluracil (5j). A mixture of (4a) (4.6 g, 0.02 mol) and sodium benzoate (2.88 g, 0.02 mol) was treated as described above to give the product (Table 1).

6-Formylaminomethyl-1-methyl-3-phenyluracil (5k). A solution of (4b) (5.9 g, 0.02 mol) in formamide (30 ml) was heated at 170 °C for 5 h. The reaction mixture was allowed to stand overnight and the precipitate was filtered off (Table 1).

6-Anilinomethyluracil (7).—A mixture of 6-chloromethyluracil (6) [8] (3.2 g, 0.04 mol) and aniline (3.6 g, 0.04 mol) in DMF (10 ml) was heated on a steam-bath for 30 min. The solvent was removed *in vacuo* and the residue was treated with water to give a precipitate. Recrystallization from water gave *compound* (7) (1.15 g, 35%), m.p. 228 °C (Found: C, 60.75; H, 5.15; N, 19.1. $C_{11}H_{11}N_3O_2$ requires C, 60.82; H, 5.10; N, 19.35%).

Alternative Preparation of 6-Anilinomethyl-1,3-dimethyluracil (5a).—Compound (7) (0.8 g) was dissolved in aqueous NaOH [NaOH (0.45 g) dissolved in water (5 ml)], dimethyl sulphate (1.4 g) was added dropwise with stirring, and the precipitate was filtered off. Recrystallization from ethyl acetate gave needles (0.43 g), identical with the sample of (5a) prepared by reaction of (4a) with aniline.

5-Bromo-6-trideuteriomethyl-1,3-dimethyluracil (8).—5-Bromo-1,3,6-trimethyluracil (1a) (0.500 g, 0.002 mol) was dissolved in D_2O in the presence of a catalytic amount of NaOD, and the mixture was refluxed for 7 min. After cooling, the precipitates were filtered off (0.488 g, 98%), m.p. 137 °C; *m/e* 237 (M^+, 94%) and 235 (100); δ ($CDCl_3$) 3.50 (3 H, s) and 3.39 (3 H, s).

Reaction of (4a) *with Morpholine.—Method A.* A mixture of (4a) (1.17 g, 0.005 mol) and morpholine (2.175 g. 0,025 mol) in DMF (15 ml) was heated for 8 h at 100 °C. After evaporation of the solvent, the residue was treated with ice-cold water to give *1,3,6-trimethyl-5-morpholinouracil* (9) (0.788 g, 66%), m.p. 183—186 °C. Recrystallization from ethanol gave an analytically pure sample of (9), m.p. 184—187 °C (Found: C, 55.0; H, 7.15; N, 17.3. $C_{11}H_{17}O_3N_3$ requires C, 55.23; H, 7.11; N, 17.57%); δ ([$^2H_6$]DMSO) 3.70—3.20 (4 H, br), 3.32 (3 H, s), 3.15 (3 H, s), 2.80—2.00 (4 H, br), and 2.38 (3 H, s).

Method B. Compound (4a) (2.34 g, 0.010 mol) was dissolved in DMF (30 ml). Morpholine (1.74 g, 0.02 mol) was added dropwise to the mixture pre-heated at 150 °C for 1 h.

TABLE 4

Analytical data

	Found (%)				Required (%)		
	C	H	N	Formula	C	H	N
(5a)	63.56	6.12	17.10	$C_{13}H_{15}N_3O_2$	63.66	6.16	17.13
(5b)	64.74	6.54	16.44	$C_{14}H_{17}N_3O_2$	64.84	6.61	16.21
(5c)	65.11	6.44	16.06	$C_{14}H_{17}N_3O_2$	64.84	6.61	16.21
(5d)	60.88	5.72	15.28	$C_{14}H_{17}N_3O_2$	61.08	6.22	15.26
(5e)	69.10	5.74	14.16	$C_{17}H_{17}N_3O_2$	69.13	5.80	14.23
(5f)	70.28	5.61	13.58	$C_{18}H_{17}N_3O_2$	70.34	5.84	13.67
(5g)	65.91	6.91	15.11	$C_{15}H_{19}N_3O_2$	65.91	7.01	15.37
(5h)	69.40	5.15	14.34	$C_{17}H_{15}N_3O_2$	69.61	5.15	14.33
(5i)	51.00	5.84	12.94	$C_9H_{12}N_2O_4$	50.94	5.70	13.20
(5j)	61.24	5.12	10.16	$C_{14}H_{14}N_2O_4$	61.31	5.15	10.21
(5k)	60.14	4.78	15.99	$C_{13}H_{13}N_3O_3$	60.22	5.05	16.21
(11a)	63.88	5.25	17.13	$C_{13}H_{13}N_3O_2$	64.18	5.39	17.28
(11b)	65.12	5.91	16.22	$C_{14}H_{15}N_3O_2$	65.35	5.88	16.33
(11c)	61.32	5.46	15.40	$C_{14}H_{15}N_3O_3$	61.53	5.53	15.38
(11d)	69.41	5.09	14.21	$C_{17}H_{15}N_3O_2$	69.61	5.15	14.33
(11e)	60.37	5.49	21.53	$C_{13}H_{14}N_4O_2$	60.15	5.46	21.70
(12a)	48.19	4.32	12.91	$C_{13}H_{14}BrN_3O_2$	48.19	4.36	12.97
(12b)	49.69	4.65	12.34	$C_{14}H_{16}BrN_3O_2$	49.70	4.73	12.43
(12c)	47.36	4.39	11.91	$C_{14}H_{16}BrN_3O_3$	47.46	4.52	11.86
(12d)	54.72	4.34	11.09	$C_{17}H_{16}BrN_3O_2$	54.55	4.28	11.23
(13a)	49.78	4.65	12.56	$C_{14}H_{16}BrN_3O_2$	49.63	4.76	12.41
(13b)	41.68	5.13	13.21	$C_{11}H_{16}BrN_3O_3$	41.54	5.07	13.22
(13c)	34.50	4.66	20.14	$C_8H_{13}BrN_4O_2$	34.69	4.73	20.23

After evaporation of the solvent, the residue was treated with ice-cold water and the precipitate was collected. Recrystallization from ethanol gave a mixture (0.48 g) of (9) and (4a). The aqueous filtrate was extracted with chloroform and the extract was dried over $MgSO_4$. After evaporation of the solvent, the residue was subjected to column chromatography (silica gel, chloroform) to afford 1,3-*dimethyl*-6-*morpholinomethyluracil* (5l) (0.636 g, 27%), m.p. 120 °C, along with unreacted (4a) (0.262 g, 11%). Recrystallization from ligroin gave analytically pure (5l), m.p. 126—128 °C (Found: C, 55.25; H, 7.15; N, 17.6. $C_{11}H_{17}N_3O_3$ requires C, 55.23; H, 7.11; N, 17.57%); δ ($CDCl_3$) 5.73 (1 H, s), 3.85—3.62 (4 H, m), 3.51 (3 H, s), 3.33 (3 H, s), 3.29 (2 H, s), and 2.63—2.42 (4 H, m).

5-*Bromo*-6-*bromomethyl*-1,3-*dimethyluracil* (10).—A mixture of (4a) (1.2 g, 0.005 mol) and bromine (1.2 g, 0.0075 mol) in acetic acid (15 ml) was refluxed for 30 min. After evaporation of the solvent, the residue was treated with ice-cold water and recrystallized from Pr^iOH to give (10) (1.24 g, 80%), m.p. 160—162 °C (Found: C, 27.0; H, 2.6; N, 9.0. $C_7H_8Br_2N_2O_2$ requires C, 26.95; H, 2.58; N, 8.98%); δ ($CDCl_3$) 4.52 (2 H, s), 3.62 (3 H, s), and 3.41 (3 H, s).

6-*Arylidenemethyl*-1,3-*dimethyluracils* (11).—*General procedure A*. A mixture of (10) (0.624 g, 0.002 mol), an aromatic amine or phenylhydrazine (0.0022 mol), and triethylamine (1.5 ml) in ethanol (15 ml) was refluxed for 24 h. After evaporation of the solvent, the residue was treated with ether and recrystallized from an appropriate solvent to give the corresponding 6-arylidenemethyl-1,3-dimethyluracils (11) (Table 2).

General procedure B. A mixture of (13a) (0.680 g, 0.002 mol), an aromatic amine or phenylhydrazine (0.0022 mol), and triethylamine (1.5 ml) in ethanol (15 ml) was treated as described in General Procedure A (Table 2).

Treatment of 6-*anilinomethyl*-5-*bromo*-1,3-*dimethyluracil* (12a) *with triethylamine*. A mixture of (12a) (0.323 g, 0.001 mol) and triethylamine (1.5 ml) in ethanol (15 ml) was refluxed for 24 h. After evaporation of the solvent, the residue was treated with ether and recrystallized from ligroin to give 6-(*N*-phenyliminomethyl)-1,3-dimethyluracil (11a) (0.159 g, 65%).

6-(N-*Substituted-aminomethyl*)-5-*bromo*-1,3-*dimethyluracils* (12) *and* (13).—*General procedure*. To a solution of (10) (0.624 g, 0.002 mol) in ethyl acetate (15 ml) were added dropwise an amine or methylhydrazine (0.004 mol) with stirring in an ice-cold water bath. The solution was stirred at room temperature for 7 h and then evaporated *in vacuo*. The residue was treated with water, and the resulting precipitate was collected by filtration. Recrystallization from an appropriate solvent gave the corresponding (12) and (13) (Table 3).

6-[*Ethoxy*-(N-*methylanilino*)*methyl*]-1,3-*dimethyluracil* (14).—A mixture of (13a) (0.340 g, 0.001 mol) and triethylamine (2 ml) in ethanol (15 ml) was refluxed for 8 h. After evaporation of the solvent, the residue was treated with ether and recrystallized from Pr^iOH to give *compound* (14) (0.100 g, 33%), m.p. 136—138 °C (Found: C, 63.15; H, 6.85; N, 13.85. $C_{16}H_{21}N_3O_3$ requires C, 63.35; H, 6.98; N, 13.85%); δ ($CDCl_3$) 7.05 (5 H, m), 6.08 (1 H, s), 5.60 (1 H, s), 3.52 (2 H, q, *J* 7 Hz) 3.37 (3 H, s), 3.32 (3 H, s), 2.85 (3 H, s), and 1.23 (3 H, t, *J* 7 Hz).

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