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Synthesis of 1,3-Dialkylcytosine Derivatives

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The reaction of 1,3-dialkyl-6-amino-uracils with phosphorus oxybromide gave 1,3-dialkyl-6-bromo-cytosines in good yields. The latter served as starting materials for several nucleophilic reactions.

The imino-type pyrimidines have customarily been prepared by alkylation of the parent aminopyrimidines,[2] however the yields were generally recorded as low. As a part of the exploitation of the synthetic methods of iminopyrimidines, we have recently developed a new synthesis of 1,3-dimethylcytosine derivatives.[3] Our procedure consisted of treatment of 6-amino-1,3-dimethyluracil with phosphorus oxychloride as a key step to give 6-chloro-1, 3-dimethylcytosine, which undergoes several transformation reactions. We describe in this paper the synthesis of 6-bromo-1,3-dialkylcytosines and further derivatives derived from them.

Heating of 6-amino-1,3-dimethyluracil (I) with phosphorus oxybromide at 205° for 5 min, under much milder conditions than those in the chlorination of I,[3] afforded 6-bromo-1, 3-dimethylcytosine (Ia) in 70% yield. Satisfactory analytical and spectral data were obtained for Ia: The infrared spectra of Ia were quite similar with those of 6-chloro-1,3-dimethylcytosine. The nuclear magnetic resonance spectrum (CF_3COOH) showed singlets at 3.68 (CH_3), 3.85 (CH_3) and 6.78 ppm (C_5 H in pyrimidine), and two broad bands at 7.75 and 7.99 ppm ($=N^+H_2$).

Similarly, treatment of several 1,3-dimethyl-6–secondaryaminouracils with phosphorus oxybromide gave the corresponding 6-bromo-1,3-dimethylcytosines in good yields (Table I). 6-(2-Hydroxyethylamino)-1,3-dimethyluracil (II) as one exception gave 6-bromo-4-N-(β-bromoethyl)-1,3-dimethylcytosine (IIa).

These 6-bromo-1,3-dimethylcytosines could be obtained by bromination of the corresponding 6-chloro-derivatives. For example, treatment of 6-chloro-1,3-dimethylcytosine with phosphorus oxybromide at 210° for 15 min gave Ia in 61% yield.

Some nucleophilic reactions were carried out to get further derivatives in addition to previously reported 6-substituted-1,3-dimethylcytosines.[3] The reaction of Ia with 2 equivalents of benzylamine yielded 4-N-benzyl-6-benzylamino-1,3-dimethylcytosine (VII). Reaction of Ia with sodium ethoxide, ethyl mercaptan and benzenethiol gave 6-ethoxy-1,3-dimethyl-cytosine (VIII), 6-ethylthio-1,3-dimethyl-cytosine (IX) and 1,3-dimethyl-6-phenylthiocytosine (X), the latter two of which yielded 1,3-dimethyl-6-thiocytosine (XI)[3] in excellent yields on reaction with sodium hydrosulfide. Although the imino group of the 1, 3-dimethylcytosines described above was generally stable against acid hydrolysis, IX and X were sensitive to hydrolysis and they were converted into the corresponding uracils even on recrystallization from water.

Reaction of 6-amino-1,3-diethyluracil with phosphorus oxychloride and phosphorus oxybromide gave 6-chloro- (XIV) and 6-bromo-1,3-diethylcytosine (VIa), which was converted into 1,3-diethyl-6-thiocytosine (XII) and 6-anilino-1,3-diethylcytosine (XIII).

1) Location: *35, Shinanomachi, Shinjuku-ku, Tokyo.*

2) D.J. Brown, "The Chemistry of Heterocyclic Compounds, The Pyrimidines," Interscience Publishers, A. Weissberger, ed., 1962, p. 356.

3) K. Senga, F. Yoneda and S. Nishigaki, *J. Org. Chem.*, **36**, 1829 (1971).

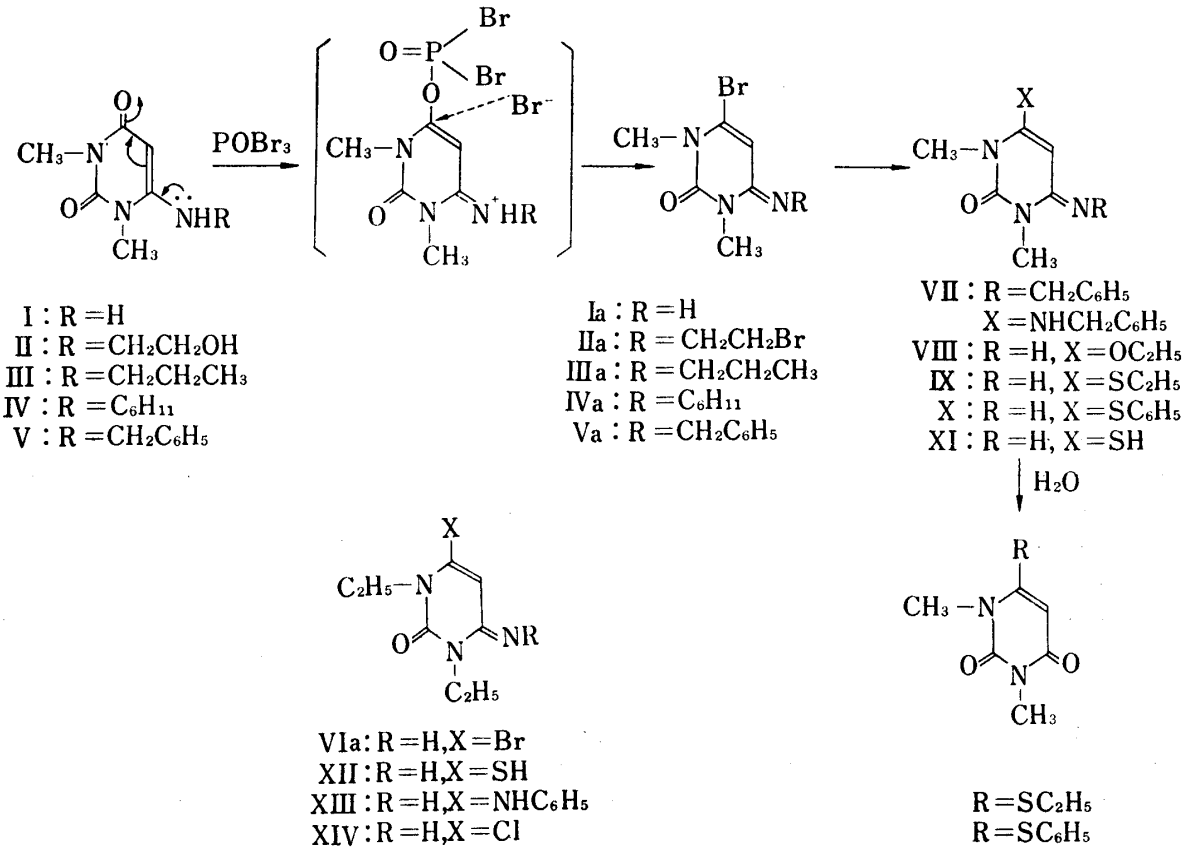
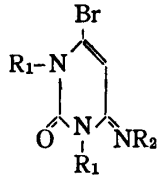


Chart 1

TABLE I. 6-Bromo-1,3-dialkylcytosines



Compound No.	Substituent R_1	Substituent R_2	Yield (%)	mp (°C)	Recrystn. solvent	Formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
Ia	CH_3	H	70	190 (dec.)	benzene	$C_6H_8ON_3Br$	33.05	3.69	19.27	33.22	3.65	19.29
IIa	CH_3	CH_2CH_2Br	63	121—122	EtOH	$C_8H_{11}ON_3Br_2$	29.56	3.41	12.93	29.58	3.46	12.95
IIIa	CH_3	$CH_2CH_2CH_3$	48	68	CH_3CN–ether	$C_9H_{14}ON_3Br$	41.56	5.42	16.15	41.32	5.58	15.97
IVa	CH_3	C_6H_{11}	67	128—129	CH_3CN	$C_{12}H_{18}ON_3Br$	48.01	6.04	14.00	48.16	6.31	14.14
Va	CH_3	$CH_2C_6H_5$	85	90— 92	—a)	$C_{13}H_{14}ON_3Br$	50.66	4.58	13.64	50.68	4.63	13.83
VIa	C_2H_5	H	93	97— 98	ether	$C_8H_{12}ON_3Br$	39.04	4.87	17.07	39.21	4.78	17.28

a) purification by sublimation; 200—210° at 1 mm Hg

Experimental[4]

General Procedure for Synthesis of 1,3-Dialkyl-6-bromo-cytosines (Ia—VIa)——A mixture of 0.002—0.003 mole of 6-amino-1,3-dialkyluracil and 3—5 g of $POBr_3$ was heated at 190—210° for 5—15 min. The reaction mixture was poured into 5 ml of 2N HCl under cooling, and the precipitates were filtered off. The filtrate was made alkaline with 5% aq. NH_3, extracted with $CHCl_3$, dried over Na_2SO_4, and concentrated to dryness. The residue was recrystallized from an appropriate solvent.

4) All melting points are uncorrected.

When crystals were separated from the alkaline solution, they were collected by filtration, washed with H_2O, dried and recrystallized from an appropriate solvent.

Preparation of 6-Bromo-1,3-dimethylcytosine (Ia) from 6-Chloro-1,3-dimethylcytosine——A mixture of 0.52 g (0.003 mole) of 6-chloro-1,3-dimethylcytosine and 5.2 g of $POBr_3$ was heated at 210° for 15 min and treated in the same manner as described above to give 0.4 g (61%) of pale yellow plates.

4-N-Benzyl-6-benzylamino-1,3-dimethylcytosine (VII)——A mixture of 1.09 g (0.005 mole) of Ia and 1.07 g (0.01 mole) of benzylamine was heated at 190° for 2 hr. After cooling, the reaction mixture was crushed in 30 ml of H_2O. The precipitates were collected by filtration, washed with H_2O and dried to give 0.75 g (45%) of pale brown crystals. Recrystallization from EtOH–H_2O gave colorless needles, mp 110—112°. *Anal.* Calcd. for $C_{20}H_{22}ON_4$: C, 71.83; H, 6.63; N, 16.76. Found: C, 71.63; H, 6.46; N, 16.81.

6-Ethoxy-1,3-dimethyl-cytosine (VIII)——A mixture of 0.87 g (0.004 mole) of Ia in 10 ml of EtOH containing 0.092 g (0.004 mole) of NaOEt was refluxed for 2 hr. After the reaction mixture was evaporated to dryness, the residue was extracted with $CHCl_3$. The extracts were dried over Na_2SO_4, evaporated to dryness and the residue was recrystallized from benzene to give 0.6 g (82%) of colorless needles, mp 141—142°. *Anal.* Calcd. for $C_8H_{13}O_2N_3$: C, 52.44; H, 7.15; N, 22.94. Found: C, 52.46; H, 7.33; N, 23.19.

6-Ethyl-1,3-dimethyl-thiocytosine (IX)——A mixture of 1.09 g (0.005 mole) of Ia and 0.62 g (0.01 mole) of ethylmercaptan was maintained for 2 hr at room temperature under stirring. The resulting clear solution was made alkaline with 5% aq. NH_3 and extracted with $CHCl_3$. The extracts were dried over Na_2SO_4, evaporated to dryness and recrystallized from $CHCl_3$ to give 1 g (100%) of a pale yellow powder, mp 66°. *Anal.* Calcd. for $C_8H_{13}ON_3S$: C, 48.23; H, 6.58; N, 21.10. Found: C, 47.97; H, 6.53; N, 20.82.

Its infrared (IR) spectrum shows a secondary amino stretching absorption band at 3260 cm^{-1}. The mass spectrometry reveals a parent ion (*m/e* 199). This compound is very sensitive to hydrolysis; recrystallization from H_2O gave 6-ethyl-1,3-dimethyl-thiouracil, mp 127—128°. *Anal.* Calcd. for $C_8H_{12}O_2N_2S$: C, 47.50; H, 5.98; N, 13.86. Found: C, 47.40; H, 6.00; N, 13.89.

1,3-Dimethyl-6-phenylthiocytosine (X)——A mixture of 1.09 g (0.005 mole) of Ia and 0.55 g (0.005 mole) of thiophenol in 10 ml of EtOH was maintained under stirring at room temperature for 4 hr. The reaction mixture was evaporated under reduced pressure to dryness, and the resulting residue was dissolved in 10 ml of 2N HCl with warming and neutralized with 5% aq. NH_3. The separated crystals were collected by filtration, washed with H_2O and dried to give 0.9 g (73%) of a yellow powder. Recrystallization from $CHCl_3$ gave a yellow powder, mp 96°. *Anal.* Calcd. for $C_{12}H_{13}ON_3S$: C, 58.29; H, 5.30; N, 17.00. Found: C, 58.17; H, 5.23; N, 16.79.

This compound is also very sensitive to hydrolysis; recrystallization from EtOH–H_2O gave 1,3-dimethyl-6-phenylthiouracil, mp 131°. *Anal.* Calcd. for $C_{12}H_{12}O_2N_2S$: C, 58.04; H, 4.83; N, 11.28. Found: C, 58.12; H, 4.82; N, 11.26.

1,3-Dimethyl-6-thiocytosine (XI) Method A——A mixture of 0.36 g (0.0018 mole) of IX and 0.28 g (0.0018 mole) of 40% aq. NaSH in 10 ml of EtOH was refluxed at 95° for 4 hr. The reaction mixture was evaporated to dryness and 30 ml of H_2O was added to the residue. The separated crystals were collected by filtration, washed with H_2O and dried to yield 0.29 g (94%) of a pale yellow powder. Recrystallization from DMF–H_2O (1:1) gave pale yellow crystals, mp 260° (dec.). *Anal.* Calcd. for $C_6H_9ON_3S$: C, 42.09; H, 5.30; N, 24.54. Found: C, 41.87; H, 5.24; N, 24.61.

A comparison of its IR spectrum with that of an authentic sample of 1,3-dimethyl-6-thiocytosine[3] showed the two materials to be identical.

Method B——A mixture of 0.25 g (0.001 mole) of X and 0.14 g (0.001 mole) of 40% aq. NaSH in 5 ml of EtOH was refluxed for 3 hr at 95°. The reaction mixture was treated as described in Method A to give 0.17 g (100%) of a yellow powder.

1,3-Diethyl-6-thiocytosine (XII)——A mixture of 0.74 g (0.003 mole) of VIa and 0.42 g (0.003 mole) of 40% aq. NaSH in 10 ml of H_2O was heated at 80° for 3 hr. After cooling, the precipitates were collected by filtration, washed with H_2O and dried to give 0.84 g (95%) of a yellow powder. Recrystallization from DMF–H_2O gave pale brown plates, mp 174—175°. *Anal.* Calcd. for $C_8H_{13}ON_3S$: C, 48.21; H, 6.57; N, 21.09. Found: C, 48.19; H, 6.77; N, 21.13.

6-Anilino-1,3-diethylcytosine (XIII)——A mixture of 0.74 g (0.003 mole) of VIa, 0.28 g (0.003 mole) of aniline and 2 drops of conc. aq. HCl was heated for 1 hr at 170°. After cooling, the reaction mixture was suspended in 10 ml of 2N HCl and made alkaline with 5% aq. NH_3. The alkaline solution was maintained on steam bath for 5 min, and allowed to stand overnight at room temperature. Crystals which separated were collected by filtration, dried and recrystallized from EtOH–H_2O to give colorless needles, mp 203—204°. *Anal.* Calcd. for $C_{14}H_{18}ON_4$: C, 65.09; H, 7.02; N, 21.69. Found: C, 64.79; H, 7.10; N, 21.99.

6-Chloro-1,3-diethylcytosine (XIV)——A mixture of 5.5 g (0.03 mole) of 6-amino-1,3-diethyluracil and 55 ml of $POCl_3$ was refluxed for 5 hr at 240°. After excess $POCl_3$ was removed *in vacuo*, the resulting residue was dissolved in 50 ml of H_2O and made alkaline with 5% aq. NH_3 and allowed to stand overnight at room temperature. The separated crystals were filtered, washed with H_2O and dried to give 2.72 g (45%) of pale yellow crystals, mp 105—106°. *Anal.* Calcd. for $C_8H_{12}ON_3Cl$: C, 47.65; H, 6.00; N, 20.83. Found: C, 47.52; H, 6.05; N, 20.90.