Table I. Interaction Energy in kcal/mol and Energy Decomposition Analyses of the Complexes $(CH_3)_2O$-BH_3 and H_3N-BH_3 Using a 4-31G Basis Set

	$(CH_3)_2O$-BH_3 r(OB)=1.654 Å ∠XOY=27.0°	H_3N-BH_3 r (NB)=1.654 Å[a]	H_3N-BH_3 r (NB)=1.68351 Å[a,b]
ΔE	−34.2	−44.6(−9.1)[c]	−44.7(0)[c]
ES	−69.8	−104.4(238.9)	−97.6(223.9)
EX	72.3	103.0(−341.7)	93.4(−312.1)
PL	−19.8	−21.6(97.2)	−18.9(83.8)
CT		−32.3(114.2)	−29.1(99.3)
CT+MIX	−16.9	−21.8	−21.7
MIX		10.5	7.4

a) Values obtained from reference 7a) by using polynominal fits.
b) The optimized distance using a polynominal fit.
c) Numbers in parentheses show the interaction force in kcal/mol • Å and the results of force decomposition analysis.

and the energy decomposition analyses are also shown in Table I. The interaction energy of the $(CH_3)_2O$-BH_3 complex was smaller than that of the H_3N-BH_3 complex due to a difference between the ES terms. Accordingly, nitrogen in the complex is more active as a donor atom than oxygen.

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Syntheses of 9-Deazatheophyllines and 6-Deoxy-9-deazatheophyllines

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The reaction of 1,3-dimethyl-5-nitro-6-styryluracils (IIa—e) with sodium dithionite in formic acid afforded the corresponding 8-aryl-9-deazatheophyllines (IVa—e). The reaction of IVa with phosphorus oxychloride gave 6-chloro-6-deoxy-8-phenyl-9-deazatheophylline (XIII), while the reaction of IVa with phosphorus oxychloride in the presence of arylamines provided the corresponding 6-arylamino-6-deoxy-8-phenyl-9-deazatheophyllines (XIV—XVI) in a single step.

Keywords——1,3-dimethyl-5-nitro-6-styryluracils; sodium dithionite-formic acid; reductive cyclization; 8-aryl-9-deazatheophyllines; phosphorus oxychloride; 6-chloro-6-deoxy-8-phenyl-9-deazatheophylline; 6-arylamino-6-deoxy-8-phenyl-9-deazatheophyllines

The pyrrolo[3,2-*d*]pyrimidine (9-deazapurine) ring system has aroused considerable interest recently because of its close structural resemblance to purine as well as to other biologically important heterocycles, *e.g.*, pyrrolo[2,3-*d*]pyrimidine, pyrazolo[4,5-*d*]pyrimidine, and indole.[2] We report here the syntheses of two types of pyrrolo[3,2-*d*]pyrimidine related to theophylline,

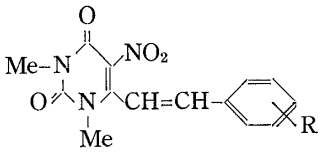
1) Location: *35, Shinanomachi, Shinjuku-ku, Tokyo 160, Japan*; *a*) To whom inquiries should be addressed.
2) V. Amarnath and R. Madhav, *Synthesis*, **1974**, 837; H. Fenner and H. Motschall, *Tetrahedron Lett.*, **1971**, 4185; T. Murata and K. Ukawa, *Chem. Pharm. Bull.*, **22**, 240 (1974); S. Senda and K. Hirota, *Chem. Pharm. Bull.*, **22**, 2593 (1974); Y. Okamoto and T. Ueda, *Chem. Pharm. Bull.*, **24**, 547 (1976); Y. Okamoto and T. Ueda, *Tetrahedron Lett.*, **1976**, 2317; S. Senda, K. Hirota, and M. Takahashi, *Heterocycles*, **4**, 461 (1976); M.T. Garcia-López, F.G. de las Heras, and M. Stud, *J. Chem. Soc. Perkin I*, **1978**, 483; R.S. Klein, Mu-ill Lim, S.Y.-K. Tam, and J.J. Fox, *J. Org. Chem.*, **43**, 2536 (1978); K. Senga, M. Ichiba, and S. Nishigaki, *Heterocycles*, **9**, 793 (1978).

i.e., 1,3-dimethylpyrrolo[3,2-*d*]pyrimidine-2,4(1H, 3H)-diones (referred to hereafter as 9-deazatheophyllines) and 1,3-dimethylpyrrolo[3,2-*d*]pyrimidine-2(1H, 3H)-ones (referred to hereafter as 6-deoxy-9-deazatheophyllines). The latter type belongs to a new class of pyrrolo [3,2-*d*]pyrimidine which has not hitherto been reported.

9-Deazatheophyllines

The requisite key intermediates, 1,3-dimethyl-5-nitro-6-styryluracils (IIa—e), were prepared in 48—77% yields by the condensation of 1,3,6-trimethyl-5-nitrouracil (I)[3] with the appropriate arylaldehydes in refluxing ethanol containing piperidine according to the reported procedure[4] (Table I).

Table I. 1,3-Dimethyl-5-nitro-6-styryluracils



Compd.	R	mp(°C)	Yield (%)	Formula	Analysis (%) Calcd (Found) C	H	N	IR(Nujol) cm^{-1} (CO)	
IIa	H	190—192[a]	77	$C_{14}H_{13}N_3O_4$	58.53 (58.49	4.56 4.56	14.63 14.59)	1710	1655
IIb	4-Br	208—211[b]	60	$C_{14}H_{12}BrN_3O_4$	45.90 (46.03	3.30 3.28	11.48 11.59)	1710	1650
IIc	4-Cl	203—204[a]	68	$C_{14}H_{12}ClN_3O_4$	52.24 (52.20	3.76 3.78	13.07 13.15)	1710	1655
IId	3,4-Cl_2	180—182[a]	48	$C_{14}H_{11}Cl_2N_3O_4$	47.19 (47.07	3.11 3.07	11.80 11.91)	1710	1640
IIe	4-OMe	185—186[a,c]	67	$C_{15}H_{15}N_3O_5$	56.78 (56.63	4.77 4.70	13.24 13.26)	1710	1650

a) Recrystallization from EtOH–DMF.
b) Recrystallization from *n*-BuOH.
c) Lit.[4] mp 186—187°.

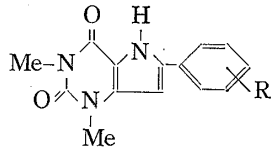
Treatment of the appropriate IIa—e with excess sodium dithionite in formic acid under reflux gave the corresponding 8-aryl-9-deazatheophyllines (IVa[4,5]—e) in 35—65% yields. The structures of IVa—e were readily confirmed by elemental analyses and satisfactory spectral data, particularly by the presence of the characteristic secondary amino absorption bands at 3160—3180 cm^{-1} in the infrared (IR) spectra (Table II).

The reductive cyclization of II into IV presumably proceeds through the intermediacy of 5-hydroxyamino-1,3-dimethyl-6-styryluracil (III) and subsequent cyclization by dehydration (Chart 1).

In contrast to the above result, the catalytic reduction of IIa with palladium-carbon in ethanol resulted in the formation of 5-amino-1,3-dimethyl-6-phenethyluracil (V), which was isolated as 5-benzylideneamino-1,3-dimethyl-6-phenethyluracil (VI) in 40% overall yield (Chart 2). The structure of VI was established by the presence of ethylenic protons in the nuclear magnetic resonance (NMR) spectrum (see "Experimental").

3) S. Senda, A. Suzui, M. Honda, and H. Fujimura, *Chem. Pharm. Bull.*, **6**, 482 (1958).
4) E.C. Taylor and E.E. Garcia, *J. Org. Chem.*, **30**, 655 (1965).
5) K. Senga, M. Ichiba, and S. Nishigaki, *J. Org. Chem.*, **44**, 3830 (1979).

Table II. 8-Aryl-9-deazatheophyllines



Compd.	R	mp(°C)[a]	Yield (%)	Formula	Analysis (%) Calcd (Formula) C	H	N	IR(Nujol) cm^{-1} (CO)	(NH)
IVa	H	>300	35	$C_{14}H_{13}N_3O_2$	65.87 (65.65	5.13 5.16	16.46 16.26)	1690 1635	3160
IVb	4-Br	>300	36	$C_{14}H_{12}BrN_3O_2$	50.30 (50.12	3.62 3.79	12.58 12.44)	1690 1630	3160
IVc	4-Cl	>300	65	$C_{14}H_{12}ClN_3O_2$	58.02 (57.82	4.18 3.96	14.51 14.42)	1695 1650	3180
IVd	3,4-Cl_2	>300	50	$C_{14}H_{11}Cl_2N_3O_2$	51.85 (51.68	3.42 3.49	12.97 12.81)	1695 1640	3180
IVe	4-OMe	>300[b]	35	$C_{15}H_{15}N_3O_3$	63.15 (63.17	5.30 5.29	14.73 14.79)	1705 1635	3180

a) All compounds were recrystallized from EtOH.
b) Lit.[4] mp 304—306° (dec.).

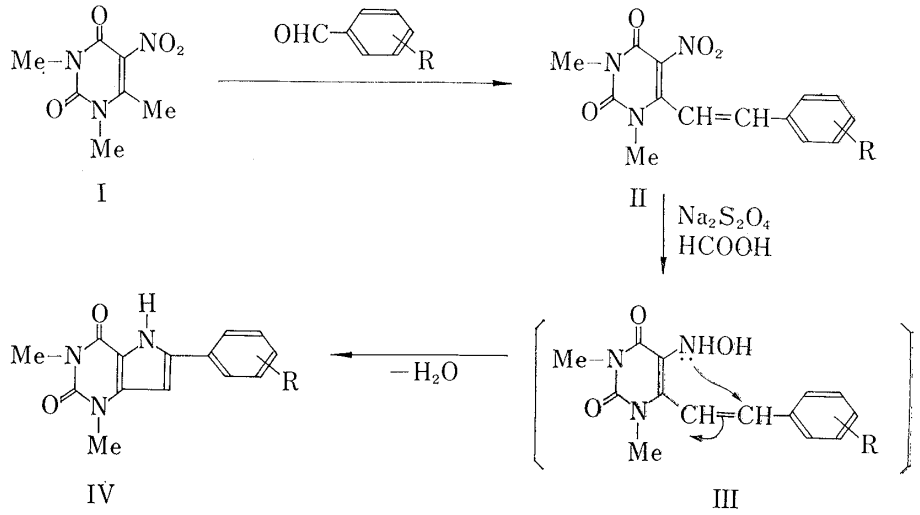


Chart 1

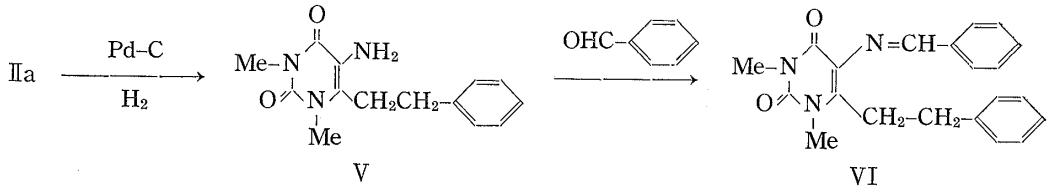


Chart 2

6-Deoxy-9-deazatheophyllines

We have previously reported that the reaction of 6-amino-1,3-dimethyluracil (VII),8-phenyl-7-deazatheophylline (VIII) or 8-phenyltheophylline (IX) with phosphorus oxychloride gives 6-chloro-1,3-dimethylcytosine (X), 6-chloro-6-deoxy-8-phenyl-7-deazatheophylline (XI)

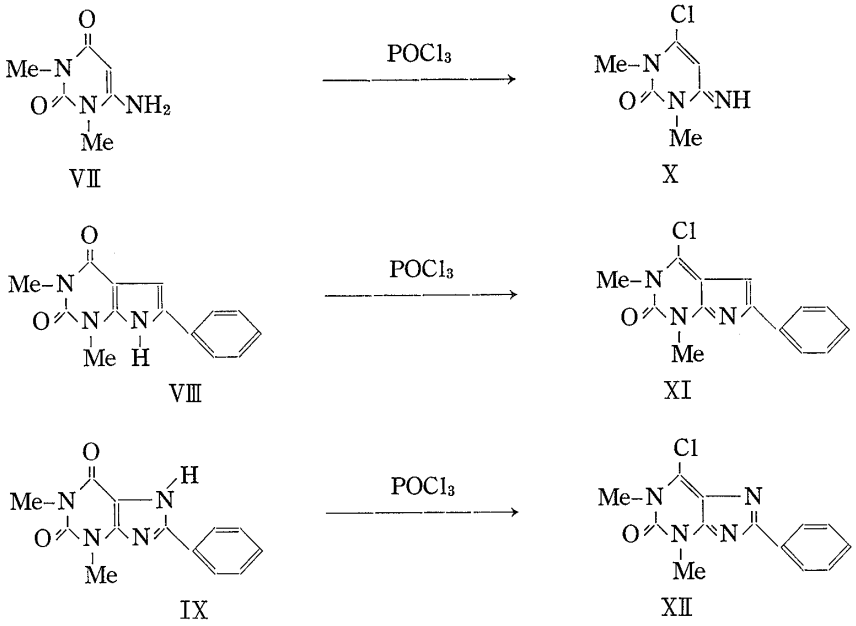


Chart 3

or 6-chloro-6-deoxy-8-phenyltheophylline (XII), respectively[6] (Chart 3). On the basis of these findings, we investigated the reaction of IVa with phosphorus oxychloride.

Refluxing of IVa with phosphorus oxychloride containing sulfolane[7] at 250° for 5 hr gave 6-chloro-6-deoxy-8-phenyl-9-deazathephylline (XIII) in quantitative yield (Chart 4). The structural assignment of XIII was based on the following evidence. Thus, the characteristic secondary amino absorption band at 3160 cm^{-1} observed for IVa was lost and a single new

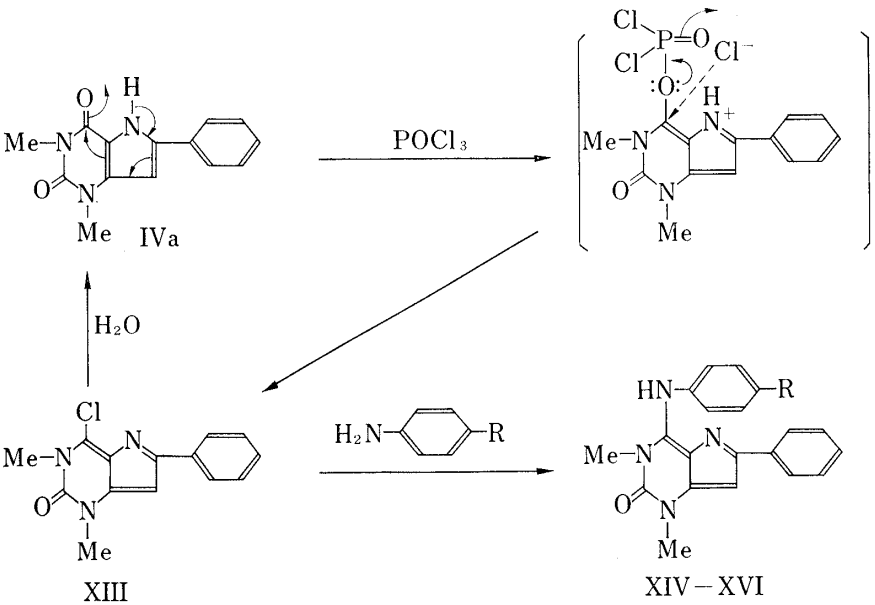


Chart 4

6) K. Senga, F. Yoneda, and S. Nishigaki, *J. Org. Chem.*, **36**, 1829 (1971); S. Nishigaki, K. Senga, and F. Yoneda, *Chem. Pharm. Bull.*, **19**, 2259 (1971); K. Senga, S. Nishigaki, M. Higuchi, and F. Yoneda, *Chem. Pharm. Bull.*, **20**, 1473 (1972); S. Nishigaki, Y. Kanamori, J. Sato, and K. Senga, *Chem. Pharm. Bull.*, **26**, 3237 (1978).

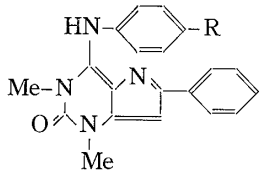
7) Sulfolane was used as an inert, high boiling solvent.

carbonyl absorption band appeared at 1675 cm^{-1}. Mass spectrometry revealed a parent ion (*m/e* 273) and an M+2 ion in the ratio of 3:1, which suggests that one chlorine atom is contained in the molecule.

Compound XIII is rather unstable and undergoes ready hydrolysis even by moisture in the air at elevated temperature to give IVa, so attempts at purification were unsuccessful. Furthermore, in several nucleophilic reactions, compound XIII underwent hydrolysis predominantly to give IVa. The marked instability of XIII might arise from the pyrrole nucleus which possesses an azafulvene-type structure.

In order to avoid such hydrolysis, the reaction of IVa with phosphorus oxychloride in the presence of nucleophiles was carried out, providing the expected 6-substituted derivatives. Namely, refluxing of a mixture of IVa, phosphorus oxychloride, and sulfolane in the presence of an appropriate excess of arylamine gave the corresponding 6-arylamino-6-deoxy-8-phenyl-9-deazatheophylline (XIV—XVI) in 86—92% yields (Table III). This procedure offers a convenient synthetic method for the preparation of 6-substituted amino derivatives since the chlorination and subsequent nucleophilic displacement could be achieved in a single operation.

Table III. 6-Arylamino-6-deoxy-8-phenyl-9-deazatheophyllines



Compd.	R	mp(°C)[a]	Yield (%)	Formula	Analysis (%) Calcd (Found) C	H	N	IR(Nujol) cm^{-1} (CO)	(NH)
XIV	H	202—203	86	$C_{20}H_{18}N_4O$	72.70 (72.58	5.49 5.46	16.96 16.91)	1655	3380
XV	Br	260—262	92	$C_{20}H_{17}BrN_4O$	58.67 (58.51	4.19 4.20	13.70 13.47)	1655	3390
XVI	OMe	244—247	89	$C_{21}H_{20}N_4O_2$	69.98 (69.89	5.59 5.59	15.55 15.52)	1645	3370

a) All compounds were recrystallized from EtOH.

Experimental[8]

1,3-Dimethyl-5-nitro-6-styryluracils (IIa—e) (Table I)——A suspension of 1,3,6-trimethyl-5-nitrouracil (I)[3] (0.995 g, 0.005 mol) and an appropriate arylaldehyde (0.005 mol) in EtOH (25 ml) containing piperidine (0.5 ml) was refluxed for 5 hr. The reaction mixture was concentrated *in vacuo* and the residue was triturated with EtOH. The insoluble material was filtered off, washed with EtOH, and recrystallized to give the corresponding IIa—e.

8-Aryl-9-deazatheophyllines (IVa—e) (Table II)——A mixture of the appropriate IIa—e (0.0005 mol) and sodium dithionite (0.435 g, 0.0025 mol) in formic acid (5 ml) was refluxed for 5—10 hr. The reaction mixture was concentrated *in vacuo* and the residue was covered with boiling H_2O. The insoluble material was filtered off, washed with H_2O, and recrystallized to give the corresponding IVa—e.

8) Melting points were taken on a YANACO micro hot-stage melting point apparatus and are uncorrected. IR spectra were recorded on a JASCO IR-E spectrophotometer from samples mulled in Nujol. NMR spectra were determined at 60 MHz with a Varian T-60 spectrometer, using tetramethylsilane as an internal standard. Mass spectra were obtained on a JEOL JMS-D 300 spectrometer with a direct inlet system at 70 eV.

5-Benzylideneamino-1,3-dimethyl-6-phenethyluracil (VI)——A solution of IIa (0.43 g, 0.0015 mol) in EtOH (300 ml) containing 10% palladium-carbon (0.2 g) was hydrogenated at room temperature and atmospheric pressure. After the consumption of hydrogen (135 ml) had stopped, the solution was filtered. Benzaldehyde (0.16 g, 0.0015 mol) was added to the filtrate and the mixture was refluxed for 2 hr. After cooling, the precipitates were filtered off and recrystallized from EtOH to give VI (0.21 g, 40%[9]), mp 121—122°, *Anal.* Calcd for $C_{21}H_{21}N_3O_2$: C, 72.60; H, 6.09; N, 12.10. Found: C, 72.34; H, 6.01; N, 11.99. IR cm^{-1}: 1685, 1643 (CO). NMR (DMSO-d_6): δ 2.60—3.43 (m, 4H, $-CH_2-CH_2-$), 3,27 (s, 3H, N–Me), 3.50 (s, 3H, N–Me), 7.25 (s, 5H, Ph), 7.37—8.00 (m, 5H, Ph), 9.33 (s, 1H, =CH–). MS *m/e*: 347.

6-Chloro-6-deoxy-8-phenyl-9-deazatheophylline (XIII)——A mixture of IVa (0.51 g, 0.002 mol), phosphorus oxychloride (10 ml), and sulfolane (1 ml) was refluxed for 5 hr at 250°. The reaction mixture was concentrated *in vacuo* and the residue was triturated with chilled 5% NH_3. The insoluble material was filtered off, washed with chilled H_2O, and dried in a desiccator (P_2O_5) *in vacuo* to give XIII (0.54 g, 100%). IR cm^{-1}: 1675 (CO). MS *m/e*: 273, 275.

6-Arylamino-6-deoxy-8-phenyl-9-deazatheophyllines (XIV—XVI) (Table III)——A mixture of IVa (0.255 g, 0.001 mol), phosphorus oxychloride (3 ml), sulfolane (1 ml), and an appropriate arylamine (0.003 mol) was refluxed for 3 hr at 250°. The reaction mixture was concentrated *in vacuo* and the residue was triturated with chilled 5% NH_3. The insoluble material was filtered off, washed with H_2O, dried, and recrystallized to give the corresponding XIV—XVI.

Acknowledgement The authors are grateful to Mr. Katsuhiko Nagahara of Kitasato University for NMR spectroscopy and elemental analyses, and to Dr. Kenji Ishii and Mr. Takafumi Harada of Keio University for determining mass spectra.

9) Calculated on the basis of IIa.

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Direct Fractionation Procedure for Hydrogen Peroxide-Acetic Acid Oxidation Products from Aromatic Amines by Reversed-Phase Liquid Chromatography

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In order to eliminate the tedious, multi-step isolation process commonly used in the synthesis of aromatic amine oxides employing hydrogen peroxide and acetic acid, a direct chromatographic fractionation procedure was developed. The polar reagents were found to be flushed out, while the N-oxide was retained by a reversed-phase column packed with styrene-divinylbenzene copolymer gel or octadecylsilanized silica gel as the stationary phase, and using methanol-water as the mobile phase. By stepwise elution, clean-up of the reagents and direct fractionation of the N-oxide from the crude reaction mixture were simultaneously accomplished.

Keywords——hydrogen peroxide-acetic acid N-oxidation; aromatic amine oxide; pyridine 1-oxide and homologs; pyrazine 1-oxide and homologs; pyrazine 1,4-dioxide and homologs; reversed-phase liquid chromatography

Ochiai and his co-workers developed a new procedure for the N-oxidation of heteroaromatic compounds such as pyridine, quinoline and their homologs by heating with hydrogen

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