Cyclization of 5-Chloro-2-(3-chlorophenoxy)benzoic Acid (16)——A mixture of **16** (0.85 g, 0.003 mol) and H_2SO_4 (5 ml) was heated in a boiling water bath for 30 min, and the solution was poured into ice-water (100 ml). The precipitate was collected and extracted with hot Na_2CO_3 solution, and the insoluble dichloroxanthone **B** (0.64 g, 80%) was collected. It had a melting point of 153—185°. The crude dichloroxanthone **B** and two compounds obtained by recrystallizations as described below were analyzed by gas chromatography using a glass column (2 m×3 mm) packed with 1.5% OV-1 on Chromosorb W (80—100 mesh). The conditions for gas chromatography were as follows: column temperature, 210°; injection temperature, 260°; carrier gas, N_2. Retention times: **14b**, 15.3 min; **19**, 11.8 min. The results indicated that the crude dichloroxanthone **B** was a mixture of **14b** (48%) and **19** (52%). Two compounds, mp 170—210° and mp 142—146°, obtained by two recrystallizations of the crude dichloroxanthone **B** from EtOH were mixtures of **14b** (15%) and **19** (85%), and **14b** (70%) and **19** (30%).

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Studies on Heterocyclic Compounds. XXXII.[1] Synthesis of 8-Substituted Theophyllines from 6-Amino-5-benzylideneamino-1,3-dimethyluracils with Nickel Peroxide

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Oxidation of 6-amino-5-benzylideneamino-1,3-dimethyluracils (Ia—e) with nickel peroxide (Ni–PO) in dimethylsulfoxide (DMSO) afforded 8-substituted theophyllines (IIa—e) and dimethylsulfone. Ni–PO oxidation of the Schiff base acetate (V) of 5,6-diamino-1,3-dimethyluracil with D-glucose did not give a nucleoside analog; in stead, 1,3,7,9-tetramethyl-2,4,6,8-(1H,3H,7H,9H)pyrimido[5,4-*g*]pteridinetetrone (VI) and penta-*O*-acetylgluconic acid were obtained. The reaction mechanisms of Ni–PO and the Schiff bases (Ia—e, V) are discussed.

Keywords——8-substituted theophyllines; 6-amino-5-benzylideneamino-1,3-dimethyluracils; Nickel peroxide; oxidative cyclization; 1,3,7,9-tetramethyl-2,4,6,8-(1H,3H,7H,9H)-pyrimido[5,4-*g*]pteridinetetrone; penta-*O*-acetylgluconic acid

In our previous paper, it was shown that Schiff bases of *o*-aminophenols with benzaldehydes were oxidized by nickel peroxide (Ni–PO) in an organic solvent to give the corresponding 2-substituted phenylbenzoxazoles.[3] Schiff bases of 5,6-diamino-1,3-dimethyluracil with benzaldehyde or aldoses were treated with N-bromosuccinimide[4a] or $HgCl_2$[4b] to give theophylline nucleoside analogs. As an extension of work on the synthesis of 8-substituted theophyllines from 4,5-diaminopyrimidine by oxidative cyclization,[5] we now report the synthesis of 8-

1) XXXI: H. Ogura, H. Takahashi, and O. Sato, *Nucleic Acid Research*, s **6**, 13 (1979).
2) Location: *a) Shirokane, Minato-ku, Tokyo 108, Japan*; *b) Yamashiro-cho, Tokushima-shi, Tokushima 770, Japan.*
3) K. Nakagawa, H. Onoue, and J. Sugita, *Chem. Pharm. Bull.*, **12**, 1135 (1964).
4) *a)* H. Ogura, H. Takahashi, and M. Sakaguchi, *Heterocycles*, **3**, 93 (1975); *b)* M. Sakaguchi, Y. Miyata, H. Ogura, K. Gonda, S. Koga, and T. Okamoto, *Chem. Pharm. Bull.*, **27**, 1094 (1979).
5) J.H. Lister, "Fused Pyrimidines, Part II, Purines," ed. by D.J. Brown, Wiley-Interscience, New York, 1971, pp. 69—71, and references cited therein.

substituted phenyltheophyllines (IIa—e) by Ni–PO oxidation of 6-amino-5-benzylideneamino-1,3-dimethyluracil (Ia—e). The oxidation of Ia—e was carried out as follows. Ni–PO was added to a dimethylsulfoxide (DMSO) solution of Ia—e and the heterogeneous mixture was stirred at 80° for 1.0—7.5 hr. The reaction were conducted with 1.2—2.0 times as much Ni–PO as the theoretical amount based on the available oxygen content (O*), which was determined by means of iodometry. After removal of Ni–PO, the filtrate was concentrated under reduced pressure. The residue was crystallized from acetic acid. The yields of IIa—e are shown in the table. Dimethylsulfone, which was an oxidized product of solvent DMSO, was obtained from the mother liquor of II (Chart 1). As regards the mechanism of the formation of IIa—e, it seemed reasonable that DMSO oxidized Ia—e. However, when Ia was treated as described previously but without the addition of Ni–PO, no IIa was obtained and the starting material (Ia) was recovered. No theophylline derivative was obtained by Ni–PO oxidation of the Schiff base acetate (V) of 5,6-diamino-1,3-dimethyluracil with D-glucose under reflux for 10 hr in benzene. The products were 1,3,7,9-tetramethyl-2,4,6,8-(1H, 3H, 7H, 9H)-pyrimido[5,4-*g*]pteridinetetrone (VI) and penta-*O*-acetylgluconic acid (Chart 2).

Konaka *et al.*[6] reported that Ni–PO could generate a hydroxy radical and abstracted a hydrogen radical from a target molecule. Presumably the mechanism of formation of

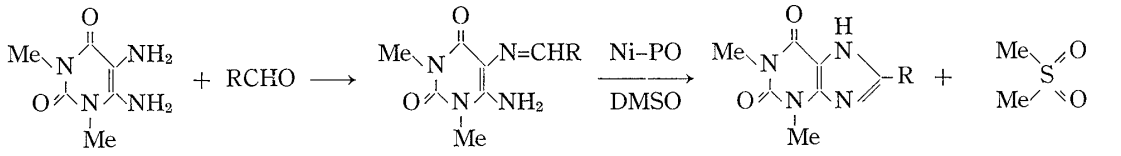
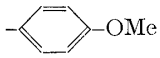
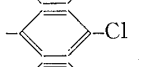
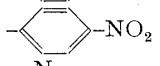


Chart 1

Table I. 8-Substituted Theophyllines

II	R	Yield (%)	mp (°C)	Reaction Time (hr)	Ni–PO (O*)
a		30	300<	3.0	1.5
b		31	300<	1.0	1.2
c		24	300<	7.0	1.5
d		65	300<	7.5	2.0
e		18	300<	6.0	1.2

II	IR ν_{max}^{KBr} cm^{-1} (C=O)	Formula	Analysis (%) Calcd C	Calcd H	Calcd N	Found C	Found H	Found N
a	1690, 1645	$C_{13}H_{12}N_4O_2$	60.93	4.72	21.87	60.71	4.72	21.66
b	1690, 1650	$C_{14}H_{14}N_4O_3$	58.73	4.93	19.57	59.04	5.05	19.27
c	1700, 1650	$C_{13}H_{11}ClN_4O_2$	53.71	3.81	19.27	53.69	3.84	19.38
d	1715, 1655	$C_{13}H_{11}N_5O_4$	51.83	3.68	23.25	51.53	3.66	23.08
e	1690, 1630	$C_{12}H_{11}N_5O_2$	56.02	4.31	27.23	55.86	4.26	27.39

6) R. Konaka, S. Terabe, and K. Kuruma, *J. Org. Chem.*, **34**, 1334 (1969).

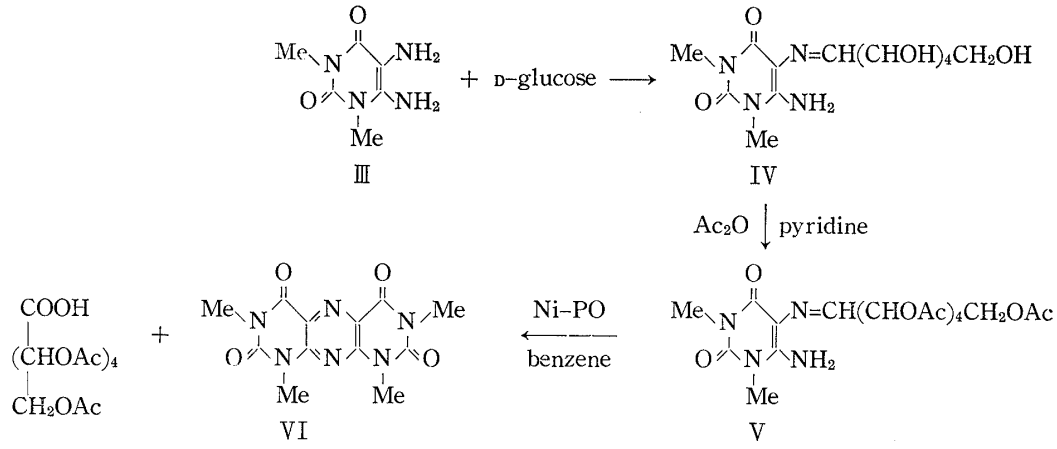


Chart 2

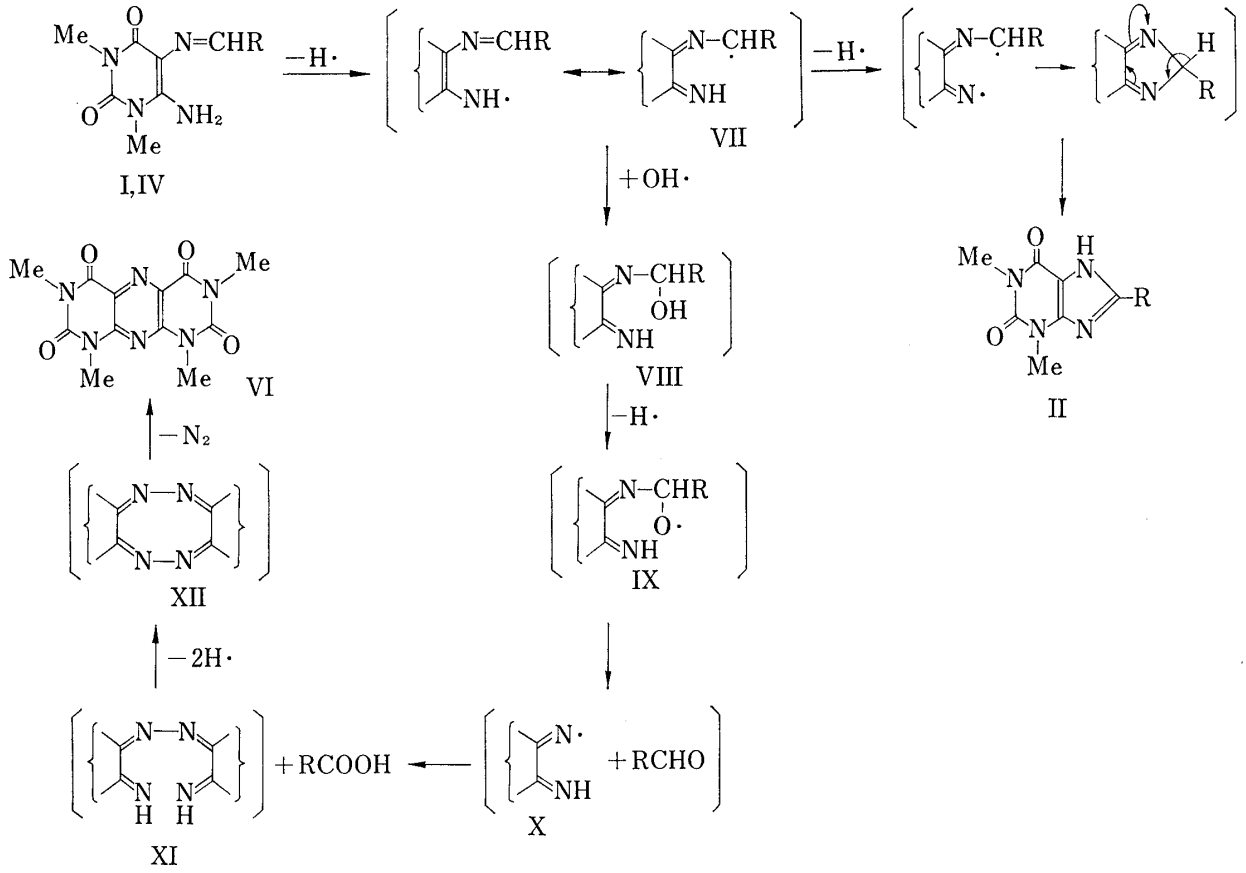


Chart 3

IIa—e or VI proceeds through initial abstraction of a hydrogen radical from the amino group. When R was phenyl, a hydrogen radical was abstracted from the intermediate (VII) and afforded II. When R was an acetylated polyhydroxyalkyl group, the hydroxy radical attacked VII and then a hydrogen radical was abstracted from the hydroxy group of VIII. The intermediate (IX) was cleaved, affording the aldehyde and intermediate (X). The aldehyde was oxidized with Ni–PO to form penta-*O*-acetylgluconic acid. Dimerization of X afforded XI, and VI was obtained from the cyclized intermediate (XII) by elimination of N_2 (Chart 3).

Experimental

Preparation of Schiff Bases (Ia—e)——The Schiff bases were prepared by the general method described below for 6-amino-5-benzylideneamino-1,3-dimethyluracil (Ia).

6-Amino-5-benzylideneamino-1,3-dimethyluracil (Ia)——Benzaldehyde (0.63 g) was added dropwise to a solution of 5,6-diamino-1,3-dimethyluracil (1.0 g) in MeOH (47 ml) and H_2O (20 ml). The mixture was stirred for 30 min at room temperature and the product was obtained by filtration. The pale yellow crystals were washed throughly with MeOH and Et_2O. Recrystallization from EtOH gave pale yellow needles (1.35 g, 89%), mp 234—237° of Ia (Lit.[7] mp 233—235°).

Preparation of 8-Substituted Theophyllines (IIa—e)——Unless otherwise stated, 8-substituted theophyllines (IIa—e) summarized in the table were obtained by the general method described below for the preparation of 8-phenyltheophylline (IIa).

8-Phenyltheophylline (IIa)——To a solution of Ia (1.29 g) in DMSO (30 ml), Ni–PO (3.57 g, 1.5 times the theoretical amount) was added gradually with stirring on a magnetic stirrer, and the heterogeneous solution was stirred at 80° for 3 hr. The reaction mixture was filtered through a glass filter (G-4), and washed repeatedly with DMSO. The combined filtrate was concentrated under reduced pressure to remove the solvent. The residue was crystallized from AcOH to give IIa (384 g, 30%). Two or three drops of MeOH were added to the mother liquor of IIa, and dimethylsulfone was obtained as white needles (815 mg), mp 107—109°. Its structure was determined by comparison with an authentic sample (mixed mp and IR).[8]

Schiff Base of 5,6-Diamino-1,3-dimethyluracil with D-Glucose (IV)——5,6-Diamino-1,3-dimethyluracil (6.80 g, 0.04 mol) was added to a solution of D-glucose (7.20 g, 0.04 mol) in hot MeOH (150 ml). The mixture was refluxed under N_2 for 5 hr. After cooling to room temperature, the precipitates were collected and recrystallized from 90% EtOH to give 12.35 g (93%) of IV, mp 203°. *Anal.* Calcd for $C_{12}H_{20}N_4O_7$: C, 43.37; H, 6.07; N, 16.86. Found: C, 43.37; H. 6.12; N, 17.07. UV λ_{max}^{EtOH} nm (log ε): 276 (4.12). IR ν_{max}^{KBr} cm^{-1}: 3420, 3350 (NH_2).

Schiff Base Acetate of 5,6-Diamino-1,3-dimethyluracil with D-Glucose (V)——A suspension of IV (8.30 g, 0.025 mol) in a mixture of dry pyridine (10 ml) and acetic anhydride (6 ml) was stirred at room temperature for 12 hr. The solvents were removed under reduced pressure and the residue was dissolved in a mixture of EtOH (70 ml) and toluene (70 ml). Once again the solvent were removed under reduced pressure. Crude crystals were recrystallized from EtOH to give 11.4 g (84%) of V, mp 172°. *Anal.* Calcd for $C_{22}H_{30}N_4O_{12}$: C, 48.71; H, 5.57; N, 10.33. Found: C, 48.70; H, 5.59; N, 10.35. UV λ_{max}^{EtOH} nm (log ε): 284 (4.27). IR ν_{max}^{KBr} cm^{-1}: 3470, 3350 (NH_2). MS *m/z*: 542 (M^+). NMR ($CDCl_3$) δ: 8.93 (1H, d, –N=CH–), 5.86 (2H, s, NH_2), 5.59—4.18 (6H, m, sugar-H), 3.48 (3H, s, Me), 3.32 (3H, s, Me), 2.08 (15H, s×5, Ac×5).

Oxidation of the Schiff Base Acetate (V) with Ni-PO——To a solution of V (1.084 g, 0.002 mol) in hot benzene (300 ml), Ni–PO (2.52 g, 4.0 times the theoretical amount) was added under stirring, and the heterogeneous solution was stirred under reflux for 10 hr. The reaction mixture was filtered through a glass filter (G-4), and washed repeatedly with hot benzene. The combined filtrate was concentrated under reduced pressure. The residue was subjected to column chromatography using SiO_2–AcOEt to give VI and penta-*O*-acetylgluconic acid monohydrate. VI (56 mg), mp 300°<. MS *m/z*: 304 (M^+). *Anal.* Calcd for $C_{12}H_{12}N_4O_6$: C, 47.34; H, 3.98; N, 27.62. Found: C, 47.41; H, 4.00; N, 27.65. IR ν_{max}^{KBr} cm^{-1}: 1710, 1660 (C=O). Penta-*O*-acetylgluconic acid monohydrate (10 mg), mp 100°. *Anal.* Calcd for $C_{16}H_{22}O_{12}\cdot H_2O$: C, 45.28; H, 5.70. Found: C, 45.57; H, 6.00. IR ν_{max}^{KBr} cm^{-1}: 3250, 1740. NMR ($CDCl_3$) δ: 9.13 (1H, s, COOH), 5.80—4.90 and 4.30—4.10 (6H, m, –CH×4 and CH_2), 3.85 and 3.78 (15H, s×2, Ac×5).

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8) D.T. McAllan, T.V. Cullum, R.A. Dean, and F.A. Fidler, *J. Am. Chem. Soc.*, **73**, 3627 (1951).