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C-Glycosyl Nucleoside. XI.[1] Interaction of Schiff Bases with Metal Halides in Dimethyl Sulfoxide

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In connection with studies of nucleoside analogs, the interactions of Schiff bases with $HgCl_2$, $PdCl_2$, and other metal halides ($MgCl_2$, $CaCl_2$, $BaCl_2$, $SrCl_2$, $ZnCl_2$, and $CdCl_2$) in dimethyl sulfoxide were examined at room temperature using time-dependent electron spin resonance and nuclear magnetic resonance spectroscopy.

Pteridine or theophylline derivatives were obtained from the reaction of Schiff bases with $HgCl_2$ or $PdCl_2$ *via* radical or ionic intermediates. On the other hand, in the cases of other metal halides, the products could not be isolated.

This reaction may be a useful tool for the preparation of nucleoside analogs.

Keywords——$HgCl_2$; Schiff base; NMR; ESR; chemical shift; nucleoside analog; pteridine; theophylline; pyrazine

The nucleoside-binding metal ions are of major biological importance, and nuclear magnetic resonance (NMR) studies on such binding have been reported by Li *et al.*[3] and Shimokawa *et al.*[4] Recently, we reported the interactions of $HgCl_2$ and $CdCl_2$ with several naturally occurring nucleosides, studied by means of NMR.[5]

This paper describes the interactions of Schiff bases with $HgCl_2$ $CdCl_2$, $ZnCl_2$, $CaCl_2$, $BaCl_2$, $SrCl_2$, $MgCl_2$ and $PdCl_2$ in dimethyl sulfoxide (DMSO) at room temperature. The metals used in this study are contained in natural products, especially RNA, as reported by Wacker *et al.*[6] Schiff bases were prepared from diamines (5,6-diamino-1,3-dimethyluracil and diaminomaleonitrile (DAMN)) and aldehydes (D-glucose, D-arabinose, L-arabinose, (±)-glyceraldehyde, glycolaldehyde and benzaldehyde).

Each Schiff base was treated with one equivalent of metal halide in DMSO at room temperature, and the reactions were studied by means of NMR and electron spin resonance (ESR) spectroscopy.

Results and Discussion

(A) $HgCl_2$—Schiff Base (1) of 5,6-Diamino-1,3-dimethyluracil with D-Glucose (a), D-Arabinose (b) and L-Arabinose (c)

The Schiff base (**1a**, **b**, **c**) of 5,6-diamino-1,3-dimethyluracil with D-glucose, D-arabinose and L-arabinose was treated with one equivalent of $HgCl_2$ in DMSO at room temperature to

1) *a*) Part X: H. Ogura, H. Takahashi, and E. Kudo, *J. Carbohydr. Nucleosides Nucleotides*, **5**, 329 (1978); *b*) This constituted Part XXV of a series entitled "Studies on Heterocyclic Compounds."
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3) S.M. Wang and N.C.Li, *J. Am. Chem. Soc.*, **90**, 5069 (1968); L.S. Kan and N.C. Li, *J. Am. Chem. Soc.*, **92**, 281, 4823 (1970); W.R. Walker, J.M. Guo, and N.C. Li, *Aust. J. Chem.*, **26**, 2391 (1973).
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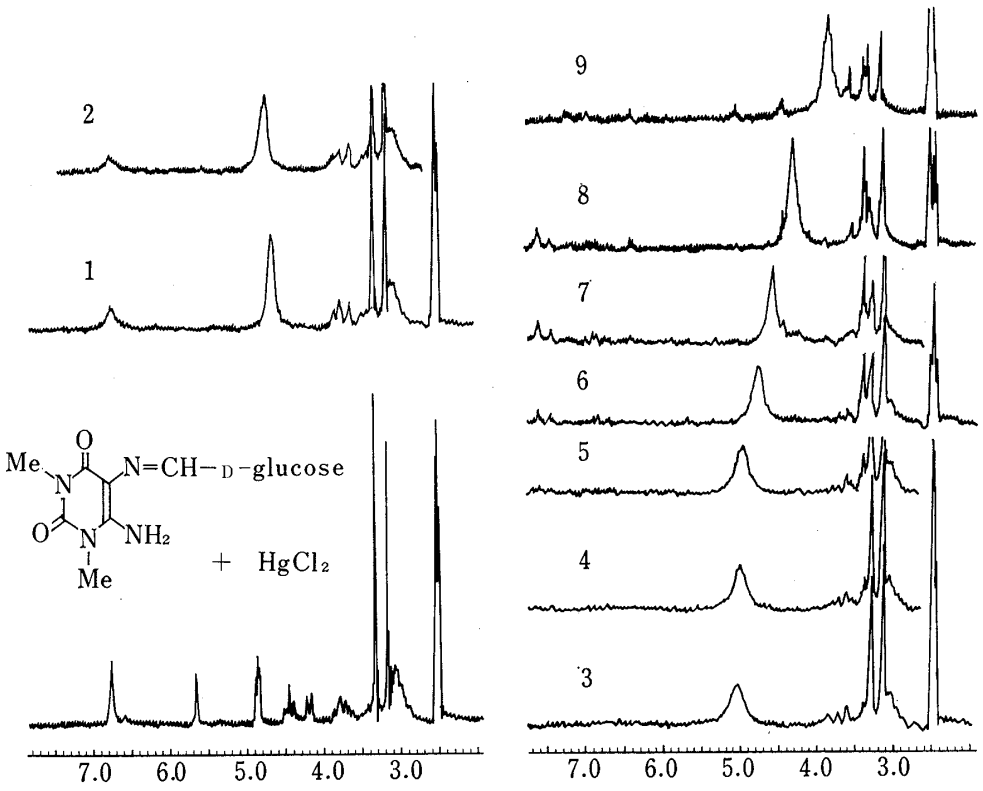

Fig. 1. Time-dependent NMR Spectra of Schiff Base (**1a**) with $HgCl_2$ in Dimethyl Sulfoxide

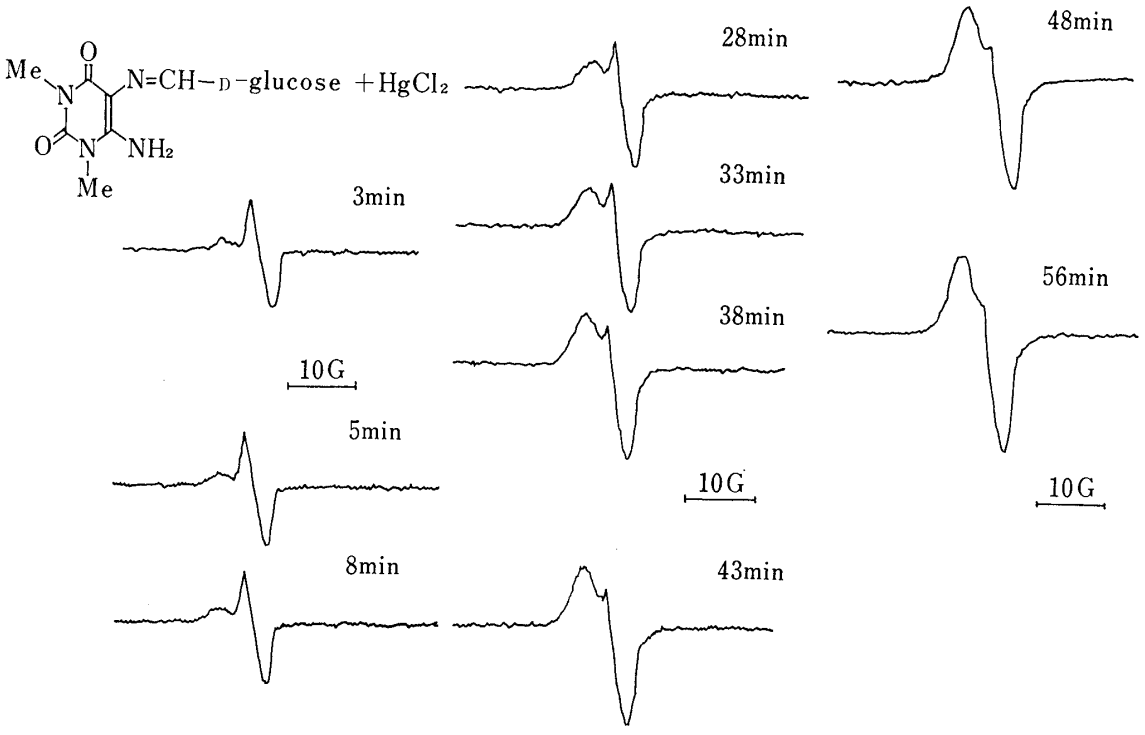

Fig. 2. Time-dependent ESR Spectra of Schiff Base (**1a**) with $HgCl_2$ in Dimethyl Sulfoxide

yield a 1,3,7,9-tetramethyl-2,4,6,8-(1H,3H,7H,9H)pyrimido[5,4-*g*]pteridinetetrone (**6**)[7] quantitatively with separation of metallic mercury.

Figure 1 shows the time-dependent NMR spectra of Schiff base (**1a**) with $HgCl_2$ in DMSO. The imino proton is not observed in the original spectra (generally, it is observed at 8.80—9.50 ppm), and this suggests that the structure of Schiff base (**1a**) is converted to **2** in DMSO. Signals of NH_2 disappeared at once upon the addition of $HgCl_2$, which suggests that this is the binding site of $HgCl_2$.

In the time-dependent ESR spectra, two signals were observed initially; one increased gradually and the other signal decreased, as shown in Fig. 2. In Fig. 2, the signal intensities at 28—56 min are twice as strong as the signal intensities at 3—8 min. The signal decrease corresponded to formation of the intermediate **4**, and the yield of product **6**, which separated as a yellow crystalline powder, was proportional to the decrement of the sharp signal.

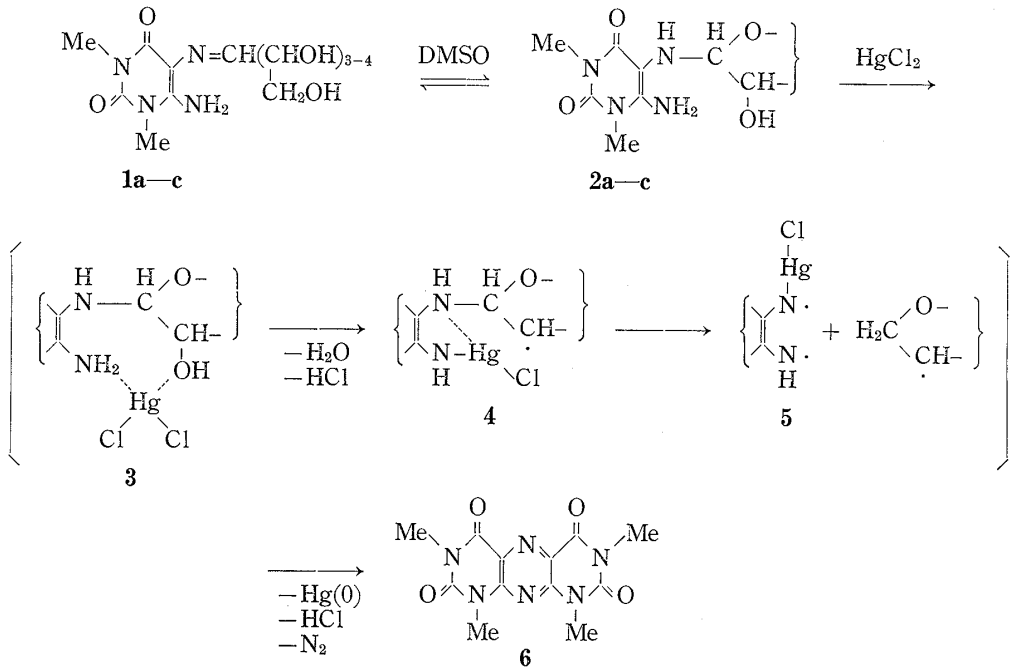

Chart 1

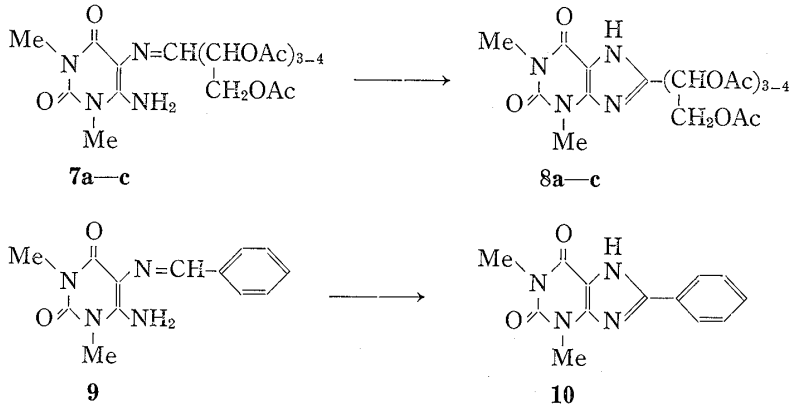

Chart 2

7) *a*) E.C. Taylor, Jr., H.M. Loux, E.A. Falco, and G.H. Hitchings, *J. Am. Chem. Soc.*, **77**, 2243 (1955); *b*) F. Yoneda and S. Nishigaki, *Chem. Pharm. Bull.* (Tokyo), **19**, 1060 (1971).

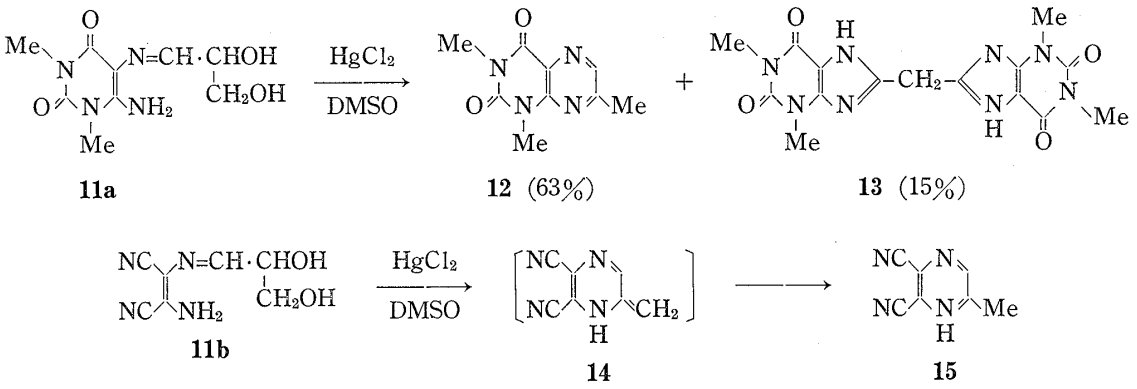

Chart 3

Fatiadi[8] assigned similar radicals from phenylhydrazones and osazones in DMSO with potassium *tert*-butoxide by using ESR spectra.

(B) $HgCl_2$—Schiff Base Acetate (7) of 5,6-Diamino-1,3-dimethyluracil with D-Glucose (a), D-Arabinose (b), and L-Arabinose (c)

The reaction required about 3 to 7 days at room temperature, and corresponding theophylline nucleoside analogs (**8a—c**) were formed in 35—40% yield by oxidative cyclization. In this reaction no ESR spectrum could be observed.

(C) $HgCl_2$—Schiff Base (9) of 5,6-Diamino-1,3-dimethyluracil with Benzaldehyde

In this reaction no ESR spectrum was observed and 8-phenyltheophylline (**10**)[9] was obtained quantitatively.

(D) $HgCl_2$—Schiff Base (11) of 5,6-Diamino-1,3-dimethyluracil (a) or DAMN (b) with (±)-Glyceraldehyde

1,3,7-Trimethylpteridine-2,4-dione (**12**) and bis(theophyllin-8-yl)methane (**13**)[10] were obtained from the reaction of **11** and $HgCl_2$. Similarly, 2,3-dicyano-5-methylpyrazine (**15**) was obtained from the reaction of **11b** and $HgCl_2$.

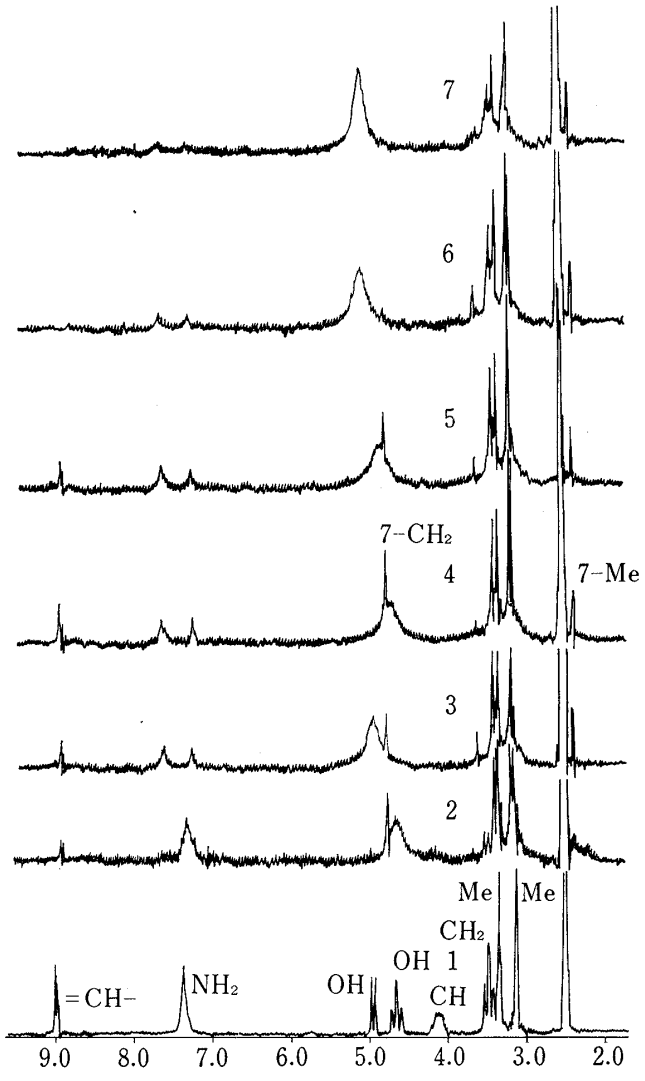

Fig. 3. Time-dependent NMR Spectra of Schiff Base (**11a**) with $HgCl_2$ in Dimethyl Sulfoxide

8) A.J. Fatiadi, "Carbohydrate in Solution," ed. by R.F. Gould, American Chemical Society, Washington, 1973, p. 88.
9) E.C. Taylor and E.E. Garcia, *J. Am. Chem. Soc.*, **86**, 4721 (1964).
10) H. Fuchs, M. Gottlieb, and W. Pfleiderer, *Chem. Ber.*, **111**, 982 (1978).

Figure 3 shows the time-dependent NMR spectra of **11a** with $HgCl_2$ in DMSO. Intermediate **16** was confirmed by the detection of methylene protons (4.73 ppm).

While ESR spectra were observed in this reaction, we confirmed that the main reaction was not involved by the spin trapping method.[11] Thus, the main reaction mechanism was estimated to be the ionic cyclodehydration reaction shown in Chart 4.

In addition, **13** was probably obtained by the oxidative dehydration reaction of **11a** with decomposed diamine.

Although cyclization to a pteridine from diaminopyrimidine with (±)glyceraldehyde has been reported by Karrer *et al.*,[12] Angier *et al.*[13] and Baugh *et al.*,[14] they did not show whether the intermediate was a Schiff base or compound **16**.

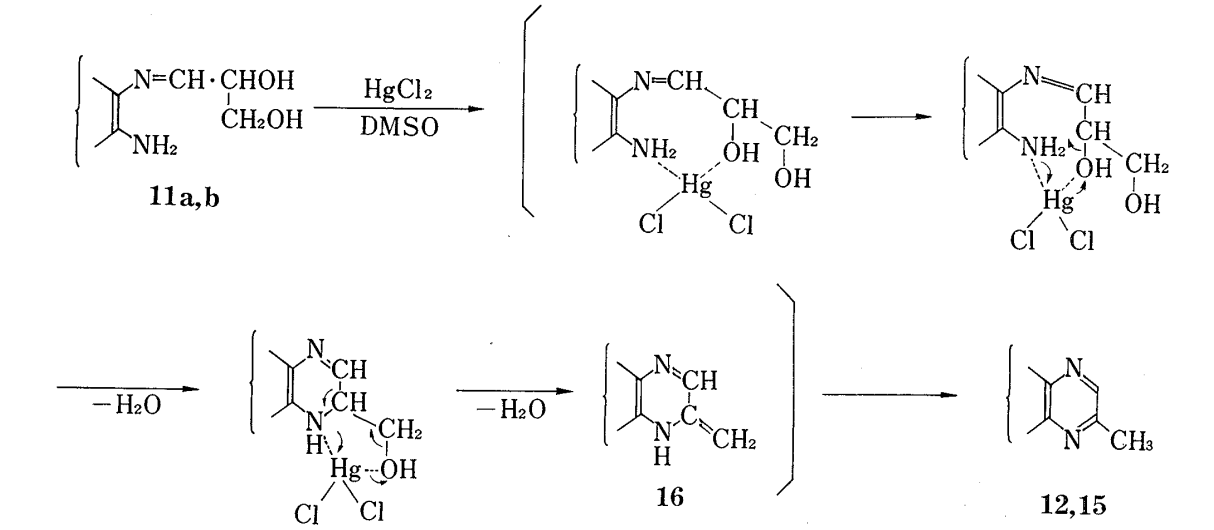

Chart 4

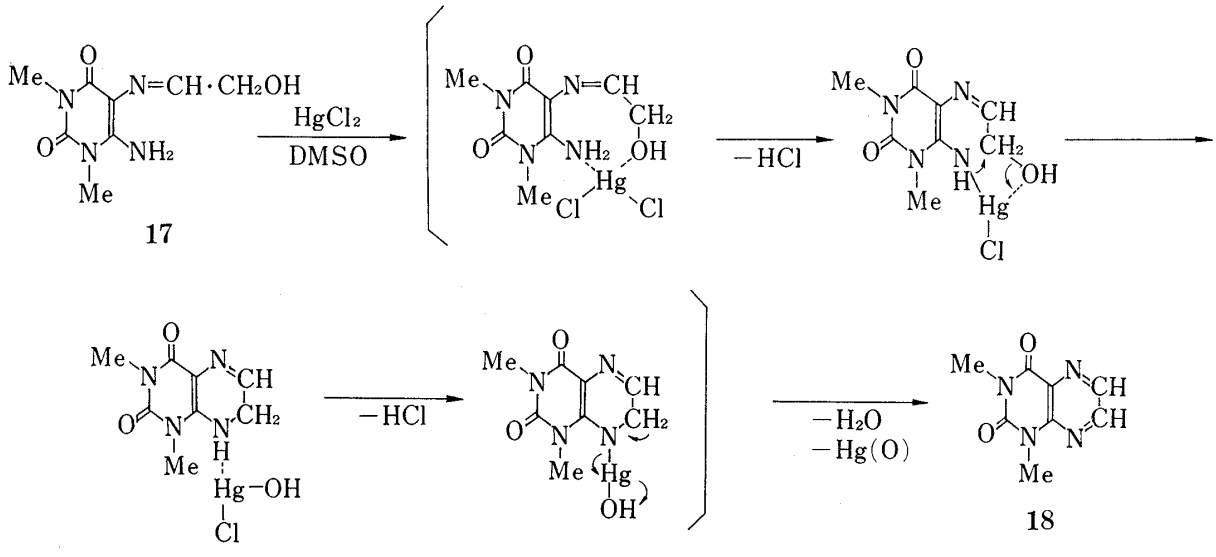

Chart 5

11) *a*) Though the ESR spectra changed entirely on adding trapping reagents, phenyl N-*tert*-butylnitrone or *tert*-nitrosobutane, to the reaction mixture, we could not detect any clear change of product yield compared with the original reaction; *b*) B.C. Gilbert and R.C. Sealy, *Electron Spin Resonance*, **3**, 231 (1974).

12) P. Karrer and R. Schwyzer, *Helv. Chim. Acta*, **31**, 777 (1948).

13) R.B. Angier, C.W. Waller, J.H. Boothe, J.H. Mowat, J. Semb, B.L. Hutchings, E.L.R. Stokstad, and Y. SubbaRow, *J. Am. Chem. Soc.*, **70**, 3029 (1948).

14) C.M. Baugh and E. Shaw, *J. Org. Chem.*, **29**, 3610 (1964).

(E) $HgCl_2$—Schiff Base (17) of 5,6-Diamino-1,3-dimethyluracil with Glycolaldehyde

1,3-Dimethylpteridine-2,4-dione (**18**) was obtained in 62% yield, probably by the oxidative cyclodehydration reaction shown in Chart 5.

While ESR spectra were observed in this reaction, the radical reaction did not influence the main reaction as determined by the spin trapping method.[11]

(F) Other Metal Halides ($PdCl_2$, $MgCl_2$, $CaCl_2$, $BaCl_2$, $SrCl_2$, $ZnCl_2$, and $CdCl_2$)—Schiff Base

The time-dependent NMR spectra of the reactions of $PdCl_2$–Schiff bases are similar to those of the reactions of $HgCl_2$–Schiff bases, and the products obtained by the reactions of $PdCl_2$–Schiff bases were the same as in the case of $HgCl_2$–Schiff bases. On the other hand, in the time-dependent NMR spectra, the signals of the Schiff base protons are only slightly shifted by adding other metal halides.

Experimental

All melting points were determined with a Yamato melting point apparatus, type MP-1. and are uncorrected. NMR spectra were measured in DMSO-d_6 or $CDCl_3$ with a JNM-4H-160 or a JNM-PS-100 spectrometer, and Me_4Si was used as an internal standard. Infrared (IR) spectra were recorded with a JASCO IR-A2 spectrophotometer. Mass spectra (MS) were taken with a JEOL-01S spectrometer using a direct inlet system at 75 eV.

1,3,7,9-Tetramethyl-2,4,6,8-(1H,3H,7H,9H)pyrimido[5,4-*g*]pteridinetetrone (6)——A mixture of $HgCl_2$ (2.72 g, 0.01 mol) and Schiff base (**1**) of 5,6-diamino-1,3-dimethyluracil with D-glucose (**a**), D-arabinose (**b**) or L-arabinose (**c**) (0.01 mol) in DMSO (15 ml) was stirred under N_2 at room temperature for 15 min. The separated solid was collected and recrystallized from DMF to give **6** quantitatively as pale yellow crystals. mp>300°.[15] MS *m/e*: 304 (M^+). *Anal.* Calcd. for $C_{12}H_{12}N_6O_4$: C, 47.37; H, 3.98; N, 27.62. Found: C, 47.38; H, 4.02; N, 27.47. IR ν_{max}^{KBr} cm^{-1}: 1710, 1660 (C=O). NMR (in DMSO-d_6) δ: 3.60 (6H, s, Me×2), 3.55 (6H, s, Me×2).

8-(D-Gluco-pentaacetoxypentyl)theophylline (8a)——A mixture of $HgCl_2$ (2.72 g, 0.01 mol) with Schiff base acetate (**7a**) (5.42 g, 0.01 mol) in DMSO (20 ml) was allowed to stand under N_2 at room temperature for 5 to 7 days. The separated metallic Hg was filtered off, and the solution was poured into H_2O (200 ml) then extracted with $CHCl_3$. The crude product was purified on a silica gel column (CCl_4, $CHCl_3$), and recrystallized from 90% EtOH to give 2.16 g (40%) of **8a** as pale yellow needles, mp 65°. MS *m/e*: 540 (M^+). *Anal.* Calcd. for $C_{22}H_{28}N_4O_{12}$: C, 48.89; H, 5.22; N, 10.37. Found: C, 48.90; H, 5.20; N, 10.30. IR ν_{max}^{KBr} cm^{-1}: 1740 (–OAc), 1700, 1660 (C=O). NMR (in $CDCl_3$) δ: 11.13 (1H, bs, NH), 6.00—4.15 (6H, m, sugar-H), 3.60 (3H, s, Me), 3.50 (3H, s, Me), 2.10 (15H, s×5, Ac×5).

8-(D-Arabino-tetraacetoxybutyl)theophylline (8b)——Using a procedure similar to that described for the synthesis of **8a**, **7b** (4.70 g, 0.01 mol) was treated with $HgCl_2$ (2.72 g, 0.01 mol) in DMSO (20 ml) to give 1.78 g (38%) of **8b** as pale yellow needles, mp 60°. MS *m/e*: 468 (M^+). *Anal.* Calcd. for $C_{19}H_{24}N_4O_{10}$: C, 48.72; H, 5.16; N, 11.96. Found: C, 48.68; H, 5.08; N, 12.20. IR ν_{max}^{KBr} cm^{-1}: 1740 (Ac), 1700, 1665 (C=O). NMR (in $CDCl_3$) δ: 12.66 (1H, bs, NH), 6.25—4.25 (5H, m, sugar-H), 3.60 (3H, s, Me), 3.46 (3H, s, Me), 2.10 (12H, s×4, Ac×4).

8-(L-Arabino-tetraacetoxybutyl)theophylline (8c)——Using a procedure similar to that described for the synthesis of **8a**, **7c** (4.70 g, 0.01 mol) was treated with $HgCl_2$ (2.72 g, 0.01 mol) in DMSO (20 ml) to give 1.75 g (37%) of **8c** as pale yellow needles, mp 60°. MS *m/e*: 468 (M^+). *Anal.* Calcd. for $C_{19}H_{24}N_4O_{10}$: C, 48.72; H, 5.16; N, 11.96. Found: C, 48.65; H, 5.19; N, 12.17. IR ν_{max}^{KBr} cm^{-1}: 1740 (Ac), 1700, 1665 (C=O). NMR (in $CDCl_3$) δ: 12.65 (3H, bs, NH), 6.23–4.20 (5H, m, sugar-H), 3.60 (3H, s, Me), 3.45 (3H, s, Me), 2.10 (12H, s×4, Ac×4).

8-Phenyltheophylline (10)——A mixture of $HgCl_2$ (1.36 g, 0.005 mol) and Schiff base (**9**) (1.29 g, 0.005 mol) in DMSO (20 ml) was stirred under N_2 at room temperature for 5 days. Separated crystals were collected by filtration, and washed with EtOH to give **10** (1.22 g, 95%) as colorless prisms, mp >300°. MS *m/e*: 256 (M^+). *Anal.* Calcd. for $C_{13}H_{12}N_4O_2$: C, 60.93; H, 4.72; N, 21.86. Found: C, 60.87; H, 4.59; N, 22.03. IR ν_{max}^{KBr} cm^{-1}: 3150 (NH), 1690 (C=O), 1603 (aromatic). NMR (in DMSO-d_6) δ: 10.00 (1H, s, NH), 7.60 (5H, m, aromatic-H), 3.50 (3H, s, Me), 3.33 (3H, s, Me).

1,3,7-Trimethylpteridine (12), Bis(theophyllin-8-yl)methane (13)——A mixture of $HgCl_2$ (1.36 g, 0.005 mol) and Schiff base (**11a**) (1.21 g, 0.005 mol) in DMSO (15 ml) was stirred under N_2 at room temperature for 3 hr. Separated crystals were collected by filtration and washed with DMSO and EtOH to give **13** (0.14 g, 15.1%) as a yellow crystalline powder, mp>300°. MS *m/e*: 372 (M^+). *Anal.* Calcd. for $C_{15}H_{16}N_8O_4$:

15) mp 374° (measured with a Perkin-Elmer DSC-1B analyser).

C, 48.39; H, 4.33; N, 30.09. Found: C, 48.66; H, 4.63; N, 30.16. IR ν_{max}^{KBr} cm^{-1}: 1690 (C=O). The DMSO solution was poured into H_2O (200 ml) then extracted with $CHCl_3$. The crude product was purified on a silica gel column (CCl_4, $CHCl_3$) and recrystallization from EtOH gave **12** (0.65 g, 63.1%) as colorless prisms, mp 159°. MS *m/e*: 206 (M^+). *Anal.* Calcd. for $C_9H_{10}N_4O_2$: C, 52.42; H, 4.89; N, 27.17. Found: C, 52.40; H, 4.87; N, 27.18. IR ν_{max}^{KBr} cm^{-1}: 1705, 1660 (C=O). NMR (in $CDCl_3$) δ: 8.40 (1H, s, 6-H), 3.75 (3H, s, N–Me), 3.55 (3H, s, N–Me), 2.70 (3H, s, 7-Me).

2,3-Dicyano-5-methylpyrazine (15)——A mixture of $HgCl_2$ (2.72 g, 0.01 mol) and Schiff base (**11b**) (1.80 g, 0.01 mol) in DMSO (15 ml) was stirred under N_2 at room temperature for 3 hr. The solution was poured into H_2O (200 ml) and then extracted with $CHCl_3$. The crude product was purified on a silica gel column (CCl_4, $CHCl_3$) and recrystallization from EtOH gave **15** (0.87 g, 60.4%) as a yellow crystalline powder, mp 95°. MS *m/e*: 144 (M^+). *Anal.* Calcd. for $C_7H_4N_4$: C, 58.33; H, 2.80; N, 38.87. Found: C, 58.60; H, 2.71; N, 38.80. IR ν_{max}^{KBr} cm^{-1}: 2250 (CN). NMR (in $CDCl_3$) δ: 8.77 (1H, s, 5-H), 2.85 (3H, s, Me).

1,3-Dimethylpteridine (18)——A mixture of $HgCl_2$ (1.36 g, 0.005 mol) and Schiff base (**17**) (1.06 g, 0.005 mol) in DMSO (15 ml) was stirred under N_2 at room temperature for 3 hr. The solution was poured into H_2O (200 ml) and then extracted with $CHCl_3$. The crude product was purified on a silica gel column (CCl_4, $CHCl_3$) and recrystallization from EtOH gave **18** (0.59 g, 61.5%) as colorless prisms, mp 198°. MS *m/e*: 192 (M^+). *Anal.* Calcd. for $C_8H_8O_2N_4$: C, 50.00; H, 4.20; N, 29.15. Found: C, 49.87; H, 4.22; N, 29.08. IR ν_{max}^{KBr} cm^{-1}: 1705, 1660 (C=O). NMR (in DMSO-d_6) δ: 8.73 (2H, dd, 6,7-H), 3.60 (3H, s, Me), 3.40 (3H, s, Me).

Reaction of Other Metal Halides ($PdCl_2$, $MgCl_2$, $CaCl_2$, $BaCl_2$, $SrCl_2$, $ZnCl_2$, and $CdCl_2$) with Schiff Base——Using a procedure similar to that described for the synthesis of the above compounds, Schiff bases (0.01 mol) were treated with $PdCl_2$ (0.01 mol) in DMSO (20 ml) to give corresponding products, but in low yields. On the other hand, Schiff bases were recovered quantitatively from the reaction mixtures of Schiff bases with other metal halides ($MgCl_2$, $CaCl_2$, $BaCl_2$, $SrCl_2$, $ZnCl_2$, and $CdCl_2$).