HETEROCYCLES, Vol.12, No. 3, 1979

C-GLYCOSYL NUCLEOSIDE XVII. A NOVEL REACTION OF SCHIFF BASES WITH MERCURIC CHLORIDE IN DIMETHYL SULFOXIDE[1]

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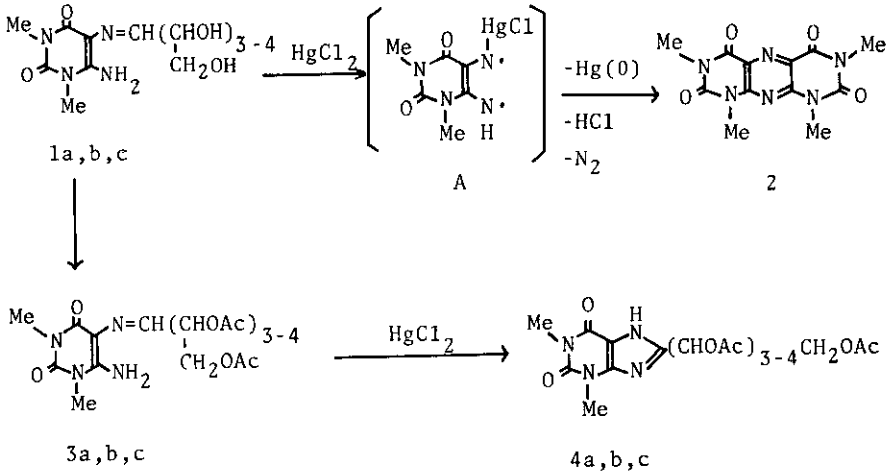
Pteridine or theophylline derivatives were obtained from the reaction of Schiff bases of 5,6-diamino-1,3-dimethyluracil with $HgCl_2$ in dimethylsulfoxide via radical or ionic mechanisms which were confirmed by the studies of time dependent ESR and NMR spectra. These reactions are useful for the preparation of nucleoside analogs.

In relation to synthetic studies of nucleoside analogs, cyclization of Schiff bases of 5,6-diamino-1,3-dimethyluracil with aldehydic sugars in the presence of NBS or DDQ afforded theophylline C-nucleoside or pteridine C-nucleoside analogs, respectively.[3] Karrer et al.,[4] Angier et al.,[5] and Baugh et al.[6] have been reported a reaction of diaminopyrimidine and (±)-glyceraldehyde to form pteridine derivatives without proof of the intermediate.

The nucleoside binding metal ions are of prime biological importance and NMR studies on the binding have been reported by Li et al.[7] and Shimokawa et al.[8] Recently, we reported the interactions of $HgCl_2$ and $CdCl_2$ with several naturally occurring nucleosides by means of NMR studies.[9]

In this report we would like to show the formation of pteridine or theophylline derivatives under mild conditions, from the reactions of Schiff bases and $HgCl_2$ in DMSO. In the course of the reactions, separation of metallic mercury was observed accompanied with pteridine or theophylline derivatives. Schiff bases used in this study 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) in methanol with introducing nitrogen. The reactions of Schiff bases with $HgCl_2$ in DMSO were studied by means of the time dependent NMR and ESR spectra.

In a typical experiment, Schiff base of 5,6-diamino-1,3-dimethyluracil with D-glucose (1a) was treated with an equivalent of $HgCl_2$ in DMSO at room temperature to yield a pyrimidopteridine (2)[10] quantitatively with separation of metallic mercury. The reaction mechanism suggests the formation of a bi-radical intermediate as shown in Chart 1.



a; Schiff base of D-glucose
b; Schiff base of D-arabinose
c; Schiff base of L-arabinose

Chart 1

This was estimated by the time dependent ESR spectra. Two signals were observed, and the broad signal increased gradually and another signal decreased as shown in Figure 1. Yielding of pyrimidopteridine (2) was in proportion to the decreased signal which estimated the intermediate (A). Fatiadi[11] reported a similar radical structure from osazones with potassium tert-butoxide in DMSO by using ESR spectra.

The reaction of acetates (3a,b,c) gave theophylline nucleoside analogs (4a,b,c) in 35-40% yields under the same reaction conditions, but radical peaks could not be observed under similar conditions in the ESR spectra. The structures of 4a,b,c agreed with the theophylline nucleoside analogs which were obtained by the reaction of Schiff base acetates with NBS.[3]

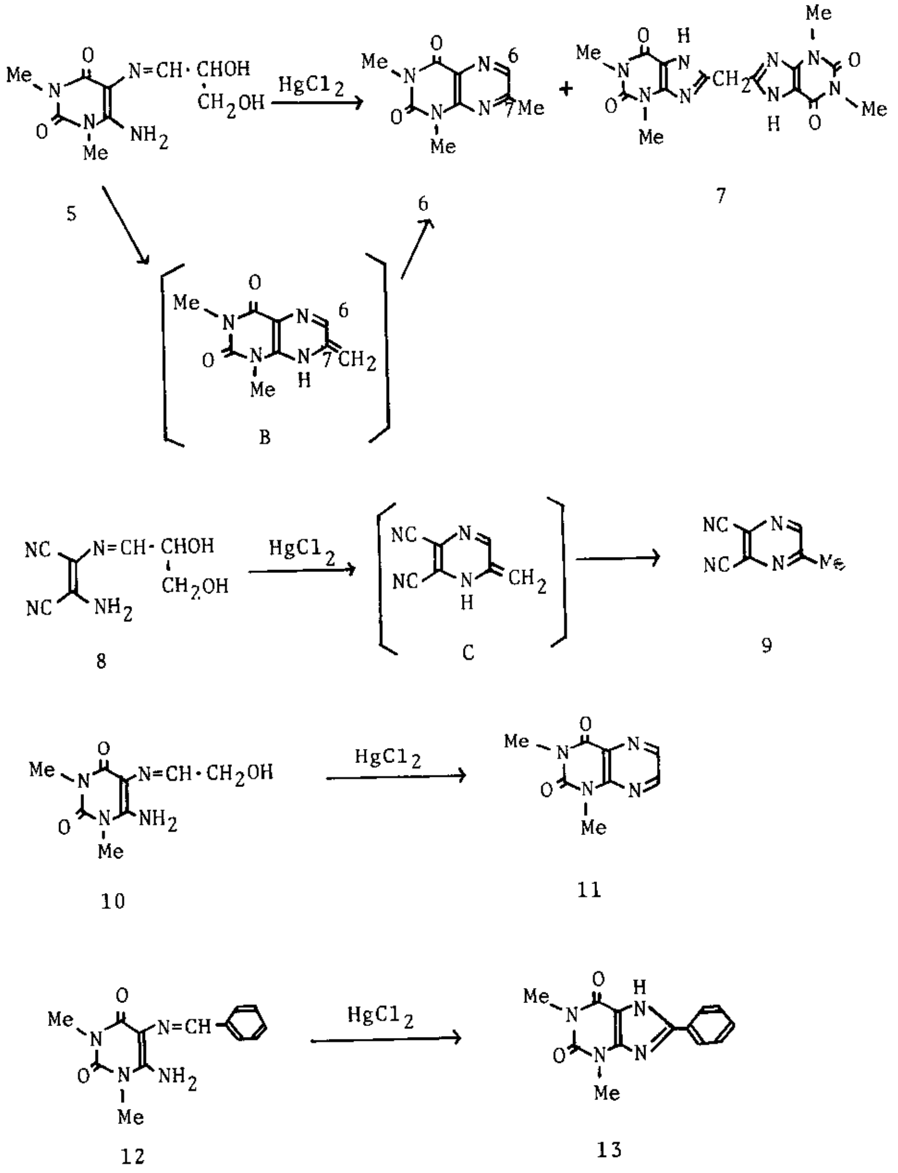


Chart 2

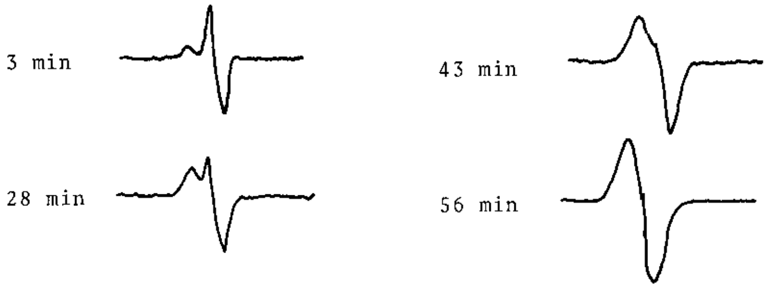


Figure 1

Schiff base of 5,6-diamino-1,3-dimethyluracil with (±)-glyceraldehyde (5) was treated with $HgCl_2$ under the same conditions to afford 1,3,7-trimethylpteridine-2,4-dione (6)[12] (63% yield) and 15% of bis-theophylline derivative (7).[13] The intermediate (B) was determined by the time dependent NMR spectra. Methylene protons at 7-position were estimated at 4.73 ppm (singlet), and methyl protons at 7-position of 6 were estimated at 2.45 ppm. (Chart 2)

A similar reaction occurred when Schiff base of DAMN with (±)-glyceraldehyde (8) was treated with $HgCl_2$ under the same conditions, and 2,3-dicyano-5-methylpyrazine (9) was obtained in 65% yield via ionic mechanism from the ESR spectra by using the spin trapping reagents. The reaction of Schiff base of 5,6-diamino-1,3-dimethyluracil with glycolaldehyde (10) under the same conditions formed 1,3-dimethylpteridine-2,4-dione (11)[14] in 62% yield.

Schiff base of 5,6-diamino-1,3-dimethyluracil with benzaldehyde (12) was treated in a similar manner, the reaction proceeded under an ionic mechanism (from ESR spectra by using the spin trapping reagents) and 8-phenyltheophylline (13)[15] was obtained quantitatively.

Acknowledgment This work was supported in part by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science and Culture (187147).

References and Notes

1. This constitutes Part XXXI of a series entitled "Studies on Heterocyclic Compounds."

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Received, 17th November, 1978