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### Hydrogen Fluoride Mediated Alkylation and Dimerization of the Base Moiety of the *cis* Diastereoisomers of 5,6-Dihydroxy-5,6-dihydrothymidine

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**HYDROGEN FLUORIDE MEDIATED ALKYLATION AND DIMERIZATION OF THE  
BASE MOIETY OF THE *CIS* DIASTEREOMERS OF 5,6-DIHYDROXY-5,6-  
DIHYDROTHYMIDINE.**

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**Abstract :** Hydrolysis of the *cis* diastereoisomers of 5,6-dihydroxy-5,6-dihydrothymidine by hydrogen fluoride stabilized in pyridine in the presence of ethanol gives rise to the *cis* thymine glycol and the *cis* 6-ethoxy-5-hydroxy-5,6-dihydrothymine enantiomers.

In the search of a mild and efficient chemical hydrolytic agent of DNA, hydrogen fluoride stabilized in pyridine appears to be a suitable alternative to concentrated formic acid or hydrochloric acid for hydrolyzing purine and pyrimidine bases from DNA (1). HF-pyridine was found to be particularly useful to obtain a quantitative release of pyrimidine photoproducts i.e. *cis-syn* cyclobutadithymine and 5-hydroxy-6-4'-(5'-methylpyridin-2'-one)-5,6-dihydrothymine from far UV-irradiated DNA (2).

HF-pyridine mediates hydrolysis of the N-glycosidic bond of the (5R, 6S) and (5S, 6R) diastereoisomers of 5,6-dihydroxy-5,6-dihydrothymine, the two main hydroxyl radical induced-decomposition of thymidine (3) was found to be completed within 15 minutes at 37°C. Two side products may also be formed, depending on the conditions of neutralization which are used.

**Materials and methods**

The chemically synthesized (5S,6R) diastereoisomer of the 5,6-dihydroxy-5,6-dihydrothymidine (5 mg) was brought to dryness and hydrolysed in polypropylene tubes at 37°C with HF-pyridine (0.1 ml) (Aldrich) for 15 minutes.

The reaction was conveniently quenched with 0.1 ml of 3 M sodium acetate and (or) mixture of 3 M sodium acetate (0.1 ml) and ethanol (0.8 ml) at -20°C overnight. Once centrifuged (8 min, 12000 g), the supernatant was brought to dryness and the

remaining pyridine was eliminated by two successive evaporations. The products were dissolved in water and separated by high performance liquid chromatography on a semi-preparative octadecylsilyl silicagel column and monitored by refractometric index detection. The separation was carried out with water as the eluting solvent at a flow-rate of 2 ml/min.

### Results and discussions

*Cis* thymine glycol was formed quantitatively and without any detectable decomposition upon hydrolysis of the (5S,6R) diastereoisomer of the 5,6-dihydroxy-5,6-dihydrothymidine with HF-pyridine (15 min., 37° C). If the acidic hydrolysis is carried out in the presence of ethanol, two side-products are formed i.e. 6-ethoxy-5-hydroxy-5,6-dihydrothymine and a dimeric product arising from an intermolecular etherification of the *cis* thymine glycol.

The *cis* orientation of the ethoxy group with respect to the vicinal hydroxyl function in the former compound was established from the results of NOE experiments. The molecular weight of the dimer was found to be 284 as inferred from exact mass measurement of FAB mass spectrometric analysis. A likely structure for this compound involves covalent attachment between 5-hydroxy-5,6-dihydrothymine-6-yl and 2,3,4,5-tetrahydro-2,4-dioxy-5-methylpyrimidine-5-yl moieties through an oxygen bridge. The relative importance to the two side-products is governed mainly by the concentration of thymidine glycol in HF-pyridine : the dimeric product is obtained with a high concentration of starting material (>100 mM), whereas the ethoxy adduct is predominant in more diluted solution (< 1 mM.).

The formation of the 6-ethoxy-5-hydroxy-5,6-dihydrothymine, the main derivatized product of the *cis*-thymine glycol offers an interesting perspective for the development of assays for measuring thymine glycols within DNA after acid hydrolysis with HF-pyridine.

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