

hydrogen and O4 (HO3'-O4; 1.81 Å) is observed and may relate to the difference in sugar conformation in anhydro-aThy and the corresponding cytosine and uracil analogues. The conformation along the C4'-C5' bond appears trans-gauche, i.e., the O5' is trans to O1' and gauche to C3' (Figure 4). This conformation, coupled with the O1' pucker, does not permit the formation of a dimer linked by hydrogen bonds as seen in the structure of the uracil analogue.<sup>12</sup>

### Experimental Section

**Methods and Materials. Compounds.** The pure 2,2'-anhydro-aThy and aThy were synthesized and characterized as described by Schinazi et al.<sup>3</sup> For biological evaluations, the filter-sterilized drug stock solutions were prepared immediately before use in distilled sterile water.

**Biological Evaluation.** aThy and 2,2'-anhydro-aThy were tested simultaneously for antiviral activity against strain F of herpes simplex virus type 1 by a plaque reduction assay in Vero cells as described previously.<sup>18</sup> The toxicity of the drugs was quantitated by measuring their effect on rapidly dividing Vero cells for 3 days as described previously.<sup>18</sup> (The number of cells in control on day 3 was  $1.96 \times 10^6$ /flask.)

**X-ray Crystallography.** Colorless crystals of anhydro-aThy were grown from aqueous ethanol solution. A crystal with dimensions  $0.4 \times 0.3 \times 0.2$  mm was mounted on a quartz fiber with the long axis parallel to the fiber axis. Unit cell dimensions and the orientation matrix were determined at room temperature on a Nicolet R3 four-circle diffractometer (Cupertino, CA) using Ni-filtered Cu K $\alpha$  radiation. Fifteen reflections whose Bragg angles varied from  $2\theta = 12.73^\circ$  to  $29.86^\circ$  were centered by machine and used in an unconstrained least-squares refinement of the lattice parameters and orientation matrix;  $a = 7.825$  (1),  $b = 9.752$  (2),  $c = 13.924$  (3) Å;  $V = 1062.4$  (3) Å<sup>3</sup>.  $\omega$  scans of several low  $2\theta$  reflections gave peak widths at half-height of less than  $0.3^\circ$ , indicating a satisfactory mosaic spread for the crystals. The crystals' density determined by flotation in benzene/CCl<sub>4</sub> was  $\rho_{\text{exp}} = 1.496$  (5) g cm<sup>-3</sup> in agreement with the value  $\rho_{\text{calcd}} = 1.508$  g cm<sup>-3</sup>, calculated for four C<sub>10</sub>H<sub>12</sub>N<sub>2</sub>O<sub>5</sub> molecules per unit cell. Axial photographs indicated the crystals were orthorhombic. The absence of  $h00$  reflections with  $h = 2n + 1$ ,  $0k0$  with  $k = 2n + 1$ , and  $00l$  with  $l = 2n + 1$  was consistent only with the space group  $P2_12_12_1$ .<sup>19</sup> Intensity data were collected by the  $\theta - 2\theta$  scan technique, with a scan rate ranging from 5.91 to  $29.3^\circ$  min<sup>-1</sup>. A scan width of  $2^\circ$  was sufficient to collect all of the peak intensity. Stationary background counts were measured at the beginning and at the end of each scan with a total background to scan time

ratio of 1. No significant fluctuations were observed in the intensities of three standard reflections monitored every 82 reflections. Data with  $2\theta$  equal to  $4-110^\circ$  (869 total) were corrected for Lorentz and polarization effects and for absorption by an empirical correction,<sup>20</sup> where the minimum transmission factor was  $I(\Phi)/I_{\text{max}} = 0.91$ . The standard deviation for each reflection was calculated on the basis of counting statistics.

**X-ray Analysis.** The structure was solved by direct methods and refined with SHELX76.<sup>21</sup> Stereo drawings were produced by ORTEP<sup>22</sup> and distance and angle calculation were carried out with ORFFE.<sup>23</sup> After anisotropic refinement of non-hydrogen atoms, a difference Fourier synthesis revealed the positions of 5 of the 12 hydrogens. The remaining hydrogens were placed in their calculated positions. Refinement cycles of all positional parameters with anisotropic thermal parameters and isotropic thermal parameters for the hydrogen atoms were obtained by using the 851 reflections with  $F_{hkl} > \sigma_{hkl}$  until the shift/ESD for each parameter was less than 1. Final  $R$  and  $R_w = \sum w^{1/2}\Delta / \sum w^{1/2}F_0$  were 0.0441 and 0.0384, respectively.

**Hydrolysis Studies.** Stock solutions (1 mM) of anhydro-aThy were prepared immediately before use in phosphate-buffered saline (pH 7.2). A portion of that solution (100  $\mu$ L) was transferred to two UV quartz cuvettes containing PBS or cell culture medium (0.9 mL). The cuvettes were kept either at 22 or 38 °C for 8 weeks, and absorption spectra were obtained every 24 h on a Beckman Model 25 spectrophotometer. Similar experiments were carried out in acid or base (HCl, H<sub>2</sub>SO<sub>4</sub>, or NaOH; 0.1 M), and the spectral absorbance was monitored in situ every 10 min at 22 °C for 2 h and daily thereafter. The apparent first-order rate constant ( $k$ ) was derived from the expression:

$$\log_{10} (A_\infty - A_t) = -kt/2.303 + \log_{10} A_\infty$$

where  $A_t$  is the absorbance at time  $t$ , and  $A_\infty$  is the final absorbance.

**Acknowledgment.** This investigation was supported in part by Grants GM 26905, GM 27907, AI 18600, and DE 07074 from the National Institutes of Health.

**Supplementary Material Available:** Anisotropic thermal parameters, list of observed and calculated structure factors, and a tabulation of mean planes (2 pages). Ordering information is given on any current masthead page.

(20) A. C. T. North, D. C. Phillips, and F. S. Mathews, *Acta Crystallogr., Sect. B*, **B24**, 351 (1968).

(21) G. Sherdwick, "SHELX 76. A Program for Crystal Structure Determination", University of Cambridge, Cambridge, England, 1977.

(22) C. K. Johnson, "ORTEP II Report ORNL-3794, Oak Ridge National Laboratory, Oak Ridge, TN, 1971.

(23) W. R. Busing, K. O. Martin, and H. A. Levy. "ORFFE Report TM-306", Oak Ridge National Laboratory, Oak Ridge, TN, 1964.

(18) R. F. Schinazi and A. J. Nahmias, *Am. J. Med.*, **73**, 40 (1982).

(19) "International Tables for X-ray Crystallography", Vol. 1, Kynoch Press, Birmingham, 1962.

## Additions and Corrections

1981, Volume 24

Joseph W. Epstein,\* Herbert J. Brabander, William J. Fanshawe, Corris M. Hofmann, Thomas C. McKenzie, Sidney R. Safir, Arnold C. Osterberg, D. B. Cosulich, and F. M. Lovell: 1-Aryl-3-azabicyclo-[3.1.0]hexanes, a New Series of Nonnarcotic Analgesic Agents.

Page 481. In Table IX, the sign of the Z coordinate of atom C-8 is incorrect. The correct value is +0.152590.

Gary L. Anderson, Donald L. Bussolotti, and James K. Coward\*: Synthesis and Evaluation of Some Stable Multisubstrate Adducts as Inhibitors of Catechol O-Methyltransferase.

Page 1274. In Scheme I, structures 10, 11, 13, and 5e should read:

