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.[12]

Experimental Section

Methods and Materials. Compounds. The pure 2,2′-anhydro-aThy and aThy were synthesized and characterized as described by Schinazi et al.[3] 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.[18] The toxicity of the drugs was quantitated by measuring their effect on rapidly dividing Vero cells for 3 days as described previously.[18] (The number of cells in control on day 3 was 1.96×10^6/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 Kα radiation. Fifteen reflections whose Bragg angles varied from $2\theta = 12.73°$ to 29.86° 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^3. ω scans of several low 2θ reflections gave peak widths at half-height of less than 0.3°, indicating a satisfactory mosaic spread for the crystals. The crystals' density determined by flotation in benzene/CCl_4 was $\rho_{exp} = 1.496$ (5) g cm^{-3} in agreement with the value $\rho_{calcd} = 1.508$ g cm^{-3}, calculated for four $C_{10}H_{12}N_2O_5$ 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 $P2_12_12_1$.[19] Intensity data were collected by the $\theta - 2\theta$ scan technique, with a scan rate ranging from 5.91 to 29.3° min^{-1}. A scan width of 2° 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 2θ equal to 4–110° (869 total) were corrected for Lorentz and polarization effects and for absorption by an empirical correction,[20] where the minimum transmission factor was $I(\Phi)/I_{max} = 0.91$. 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.[21] Stereo drawings were produced by ORTEP,[22] and distance and angle calculation were carried out with ORFFE.[23] 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 μL) 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_2SO_4, 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_∞ 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.

(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.
(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.

Additions and Corrections

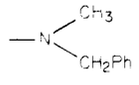
1981, Volume 24

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 Cathechol *O*-Methyltransferase.

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



Page 1275. The last three entries in Table V should read as follows:

compd	K_i,[b] mM
5'-deoxy-5'-(methylthio)-adenosine	>5.4[c]
methionine	stimulates enzyme[c]
5'-deoxy-5'-(dimethylsulfonio)adenosine	6.0

Kuo-Chang Tang, Roy Mariuzza, and James K. Coward*: Synthesis and Evaluation of Some Stable Multisubstrate Adducts as Specific Inhibitors of Spermidine Synthase.

Page 1277. In the abstract, **2b** should read **2c**, and **3b** should read **3c** in all cases.

Page 1278. In line 28, left column, **2b** and **3b** should read **2c** and **3c**.

Page 1278. In line 1, right column, **2a** and **3a** should read **2b** and **3b**. Line 5, right column, should read "... from rat prostate reveal that **2c** and **3c** are potent and ...".

Page 1282. Analysis for **6g** should read $C_8H_{20}N_2O\cdot 2HCl$.

Page 1283. In line 3, right column, sentence should read as follows: "The iodide thus obtained was converted to the perchlorate salt by use of an AG-1X8 column ...".

1982, Volume 25

Yoko Yasuda,* Kunio Tochikubo, Yoetsu Hachisuka, Hisao Tomida, and Ken Ikeda: Quantitative Structure–Inhibitory Activity Relationships of Phenols and Fatty Acids for *Bacillus subtillis* Spore Germination.

Page 318. The phenol substituent for compound **27** should be 2,4-$(NO_2)_2$ instead of 2,5-$(NO_2)_2$.

Staff Review: Amino Acids, Peptides and Proteins. Volume 11. Specialist Periodical Reports.

Page 749. The correct price for Volume 11 is $104.00. Volume 10 is priced at $86.00, and Volume 6 is priced at $52.00.

Book Reviews

Steroids: Keys to Life. By Rupert F. Witzmann. Translated by Rosemarie Peter. Van Nostrand Reinhold, New York. 1981. xiii + 256 pp. 17 × 23 cm. $28.50.

Africa 1859. Livingston and his botanist John Kirk are in the bush collecting samples of arrow poisons. "Kirk was rather careless in (their) handling, carrying them in the same pocket into which he occasionally tucked his toothbrush. One morning, a little of the poison must have stuck to the bristles, and after brushing his teeth, Kirk suddenly noticed that his pulse was slowing down... Fortunately, nothing further happened. An intact mucous membrane save Kirk's life." The physiological effects of the steroid glycoside strophanthidin had been discovered.

The scene shifts to Mexico, 1941. "Marker found what he had been looking for: the (*Carbenza de negro*) root was full of steroids that could be converted into progesterone. This was the moment when Parke-Davis missed the boat. They declined to set up a small laboratory... Angrily, Marker moved to Mexico to start out on his own: a loner, a stubborn individualist, a genius who was going to take on the world's mightiest steroid producer all by himself. On top of everything, he did not have a penny to his name... One has to hand it to the two owners of the insignificant Laboratorios Hormona. When a nondescript man plunked $160,000 worth of progesterone down on the table and asked, 'Are you interested?' they gave the correct answer." Syntex was formed.

Rupert Witzman is a superb storyteller, a practicing physician and previous European Medical Director for two U.S. drug companies. His new book, *Steroids: Keys To Life*, is one of the very best books ever written for a mixed audience of drug scientists and for the lay public. Drawings of cardiac genins' A/B-cis ring junctures and 5α-androstane are as expertly drawn and described as EKG changes caused by digitoxin. The stories of Kirk, Livingston, and Russell Marker are blended with those of Butenandt, Windaus, Bloch, Huggins, and many other distinguished workers in the steroid field. They make for great reading.

The drama and politics of steroid product development are also well described. Although the world's first oral contraceptive product Enovid (with the steroid progestin norethynodrel) was marketed in 1956, it was not until 1959 that Searle actually dared to include contraception as one of the drug's indications for use. Witzman writes, "The opposition was armed and ready for such a product. There were even reports that the President of the United States had personally ruled out allocation of public funds for family planning... The FDA was furious, and refused to accept the claim. A three-hour, heated debate ensued, for which Searle had called in Professor (John) Rock, a Catholic (and co-developer of 'the pill')... Rock reportedly yelled at the FDA's departmental expert, 'what would *you* know about cancer? You talk about religion! What would you know about *my* religion?"

Illustrations in the book are well done. They include biochemical and physiological pathways (e.g., regulatory mechanisms for progestins including LH-RH, aldosterone and the sodium pump, estrone fitted into a hypothetical receptor, human chromosomes, and gene activation by steroids), as well as the structures of all major natural steroids. Photographs of the Nobel Laureates in steroid research are included, as well as drawings showing past contributors, such as Arnold Berthold (1803–1861). A collection of fine color photographs is included in the middle of the volume. Although a few have at best a distant connection to steroids, most do show the diversity of effects of steroids in nature—a deer (velvet on antlers from the effects of testosterone), a child with steroid excess (Cushing's syndrome), and catepillars (under the influence of steroids) being transformed into colorful moths.

Steroids: Keys to Life was written for the layman, but in the process, Witzman and his gifted translator Rosemarie Peter have also written a fine reference for drug experts—both chemists and nonchemists alike. Many of the historical narratives exist in no other place, assembled by good historical research and by interviews with mordern-day workers. Although the great accomplishments of some outstanding steroid chemists are omitted (e.g., Carl Djerassi, Josef Fried, and George Rosenkranz), this is generally a fine book which will be as enjoyable to the layman as to the medicinal chemist.

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Hormonal Proteins and Peptides. Volume 10. β-Endorphin. Edited by C. H. Li. Academic Press, New York. xvii + 359 pp. 16 × 23.5 cm. ISBN 0-12-447210-9. $44.50.

This book is the 10th in a series of volumes that are dedicated to the extensive review of a particular aspect of hormones and peptides. This volume deals with β-endorphin.

The first chapter by C. H. Li mentions briefly the synthesis of β-endorphin and describes extensively the synthesis of a large number of β-endorphin analogues. Biological activity of the analogues is also included.

The second chapter reviews the work reported on the trypsin-like proteinases that are involved in the generation of opioid peptides, while the third chapter discusses the biosynthesis of β-endorphin from proopiomelanocortin. Many timely references are given.