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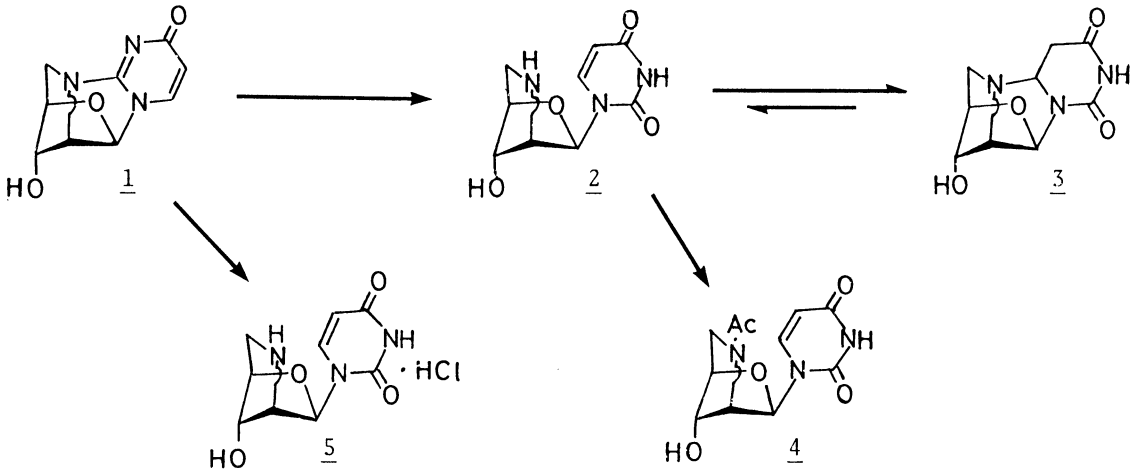
Strain-Assisted, Unusually Facile Hydrolysis of the Nitrogen-Bridge of a Tricyclic Uracil N-Cyclonucleoside

Katsumaro MINAMOTO,* Kishiko AZUMA, Yorihisa HOSHINO, and Shoji EGUCHI*
Institute of Applied Organic Chemistry, Faculty of Engineering,
Nagoya University, Furo-cho, Chikusa-ku, Nagoya 464

With respect to "up" amination of the sugar part of nucleosides through an appropriate N-cyclonucleoside, 5',N-anhydro-2,2'-imino-1-(2'-deoxy-β-D-arabinofuranosyl)uracil proved to be easily hydrolyzed to 1-(2',5'-N-anhydro-5'-amino-2',5'-dideoxy-β-D-arabinofuranosyl)-uracil (2) in dilute alkaline or acidic medium. 2 was characterized as its acetylimino analogue or hydrochloride, and proved to transform to 5',N-anhydro-6,2'-imino-1-(2'-deoxy-β-D-arabinofuranosyl)-5,6-dihydrouracil spontaneously.

As part of our program to exploit the chemistry of nitrogen-bridged nucleosides, we have reported the first alkali-catalyzed, hydrolytic cleavage of the nitrogen bridge of some 2,3'-arylimino[1] and 2,2'-arylimino uracil nucleosides[2,3] to realize "up" arylamination of the sugar part, while hydrolytic fission of the imino or alkyl-substituted-imino bridge in similar 2,3'- or 2,2'-imino or alkyl-substituted-imino nucleosides has not yet been achieved. Hence, the above stated arylamination through an appropriate N-bridged nucleoside has been interpreted by the "aryl-promoted resonance stabilization of an intervening nitrogen anion" formed under the alkaline conditions used.[1]

At this stage, our attention has been partially directed to probably strained, multi-cyclic N-bridged nucleosides as substrates for this type of hydrolysis: the imino bridge of this class of compounds may be sensitive to hydrolysis. Moreover, this simple working hypothesis lets us visuallize a new scope for chemical transformations of nitrogen-bridged nucleosides. This paper describes an example of unusually facile, hydrolytic bridge fission of such a multi-cyclic system of pyrimid-



ine series.

Immediately after treatment of 5',N-anhydro-2,2'-imino-1-(2'-deoxy-β-D-arabinofuranosyl)uracil (1)[2] with a 1:1 mixture of 1 M NaOH and MeOH at room temperature, extensive TLC-monitoring was initiated with the use of silica gel plates and $CHCl_3$/MeOH (9:1) as a developer to reveal that a single UV-absorbing, more polar product (A) was formed with a trace of UV-transparent product (B) having a mobility similar to that of 1 and that the starting material was consumed after 3 min. Furthermore, subsequent TLC-monitoring showed that the product A changed rather rapidly to B to attain finally an equilibrium between both, in favor of the latter. Repeated attempts to isolate the seemingly non-crystallizable product A failed, while the product B was isolated from the mixture as a highly crystalline substance of mp 200-202 °C (dec) (MeOH) in over 30% yields and characterized as 5',N-anhydro-6,2'-imino-1-(2'-deoxy-β-D-arabinofuranosyl)-5,6-dihydro-uracil (3).[4-6] Similar results were obtained when 1 was treated with 1 M Et_3N/H_2O-MeOH (1:1) (5 °C, 14 h; room temperature, 1.5 h).

In order to characterize the product A, we chose to block the imino group to evade the Michael type addition. Thus, after hydrolysis of 1 in 1 M Et_3N/H_2O-MeOH (1:1) followed by quick evaporation and drying, the residue was treated with Ac_2O in pyridine at room temperature to afford a 75% yield of 1-(2',5'-N-anhydro-5'-acetylamino-2',5'-dideoxy-β-D-arabinofuranosyl)uracil (4), which was shown to be homogeneous in terms of TLC using several solvent systems and to have a normal UV-absorption pattern of the uridine type.[7] However, ^1H NMR measurement at 500 MHz gave a pair of closely resembling spectra for a 1:1.2 mixture of two isomers which might depend upon a slight conformational difference in the puckering of the

sugar moiety or the base-sugar tortion angle.[8,9] The structure of the product A was thus identified as 1-(2',5'-N-anhydro-5'-amino-2',5'-dideoxy-β-D-arabino-furanosyl)uracil (2).

On the other hand, in situ trap of the nucleophilic nitrogen lone pair of the imino bridge appeared to be more economical for an unambiguous synthesis of 2. Thus, treatment of 1 with 1 M HCl-MeOH (1:1) at room temperature for a moment and rapid elimination of the hydrolysis medium allowed direct isolation of hydrochloride of 2 as crystals in a nearly quantitative yield.[10]

The results described here represent the first hydrolytic cleavage of the formally alkyl-substituted imino bridge of a N-cyclonucleoside and also the first successful acidic fission of this type. This concept of strain-assisted hydrolysis of the base-sugar nitrogen bridge has led to a promising result even in the purine series.[11] It must be noted that the condensed aliphatic nitrogen heterocycle newly formed may be amenable to a variety of further transformations involving the C-N fission by the methods commonly used in general organic chemistry.

References

1) K. Minamoto, T. Tanaka, K. Azuma, N. Suzuki, S. Eguchi, S. Kadoya, and T. Hirota, J. Org. Chem., 51, 4417 (1986).

2) K. Minamoto, K. Azuma, T. Tanaka, H. Iwasaki, S. Eguchi, S. Kadoya, and R. Moroi, J. Chem. Soc., Perkin Trans. 1, 1988, 2955.

3) Similar transformations have also been achieved in thymidine series in this laboratory.

4) Elemental analysis values for all new compounds are satisfactory.

5) ^{1}H NMR (DMSO-d_6) (500 MHz) δ= 2.82 (1H, d, J_{gem}=11.9 Hz, $H_{5'a}$), 2.98 (1H, d, J_{gem} =11.9 Hz, $H_{5'b}$), 4.04 (1H, s, $H_{4'}$), 4.27 (1H, s, $H_{3'}$), 3.49 (1H, s, $H_{2'}$), 5.59 (1H, s, $H_{1'}$), 2.50 (1H, dd, J_{gem}=15.9 Hz, $J_{5a,6}$=4.4 Hz, H_{5a}), 2.95 (1H, dd, J_{gem} =15.9 Hz, $J_{5b,6}$=13.1 Hz, H_{5b}), 4.61 (1H, dd, $J_{6,5a}$=4.4 Hz, $J_{6,5b}$=13.1 Hz, H_6), 5.38 (1H, br s, D_2O-exchangeable, 3'-OH), 10.25 (1H, s, D_2O-exchangeable, 3-NH).

6) A similar Michael type of 5,6-addition of the 5'-amino group in 5'-amino-5'-deoxy-2',3'-isopropylideneuridine was reported: K. Isono and T. Azuma, Chem. Pharm. Bull., 20, 193 (1972).

7) 4 decomposed between 267 and 280 °C; UV (MeOH) 207 (ε 10700) and 264 (7000) nm.

8) ^{1}H NMR (DMSO-d_6) (500 MHz): 4a (one isomer) δ= 1.77 (3H, s, CH_3CO), 3.63 (1H, d

J_{gem}=10.7 Hz, $H_{5'a}$), 3.80 (1H, d, J_{gem}=10.7 Hz, $H_{5'b}$), 4.34-4.54 (3H, m, $H_{2'}$, $H_{3'}$ and $H_{4'}$), 5.49 (1H, dd, $J_{5,6}$=7.95 Hz, $J_{5,3\text{-NH}}$=2.38 Hz, H_5), 6.08 (1H, br s, D_2O-exchangeable, 3'-OH), 6.16 (1H, s, $H_{1'}$), 7.66 (1H, d, $J_{6,5}$=7.95 Hz, H_6), 11.2 (1H, br s, D_2O-exchangeable, 3-NH). 4b (another isomer): δ= 1.67 (1H, s, CH_3CO), 3.40 (1H, d, J_{gem}=12.0 Hz, $H_{5'a}$), 3.52 (1H, d, J_{gem}=12.0 Hz, $H_{5'b}$), 4.35-4.54 (3H, m, $H_{2'}$, $H_{3'}$ and $H_{4'}$), 5.56 (1H, dd, $J_{5,6}$=7.95 Hz, $J_{5,3\text{-NH}}$=2.39 Hz, H_5), 6.16 (1H, br s, D_2O-exchangeable, 3'-OH), 6.12 (1H, s, $H_{1'}$), 7.58 (1H, d, $J_{6,5}$=7.95 Hz, H_6), 11.5 (1H, br s, D_2O-exchangeable, 3-NH).

9) The possibility that either of 4a and 4b is a 3'-O-acetylated analogue is precluded by the presence of normal 6.08 and 6.16 ppm signals for 3'-OH's and the absence of any signals corresponding to aliphatic imine protons which should resonate usually at 0.4-3.5 ppm. Moreover, the signal of the $H_{5'a}$ as well as $H_{5'b}$ of each isomer is a clear-cut doublet, no vic-coupling being observed.

10) mp above 300 °C; UV (MeOH) 214 (ε 23500) and 266 (12400) nm; ^1H NMR (DMSO-d_6) (500 MHz) δ= 3.40 (1H, d, J_{gem}=11.1 Hz, $H_{5'a}$), 3.43 (1H, d, J_{gem}=11.1 Hz, $H_{5'b}$), 4.33 (1H, t, $J_{2',3'}$=2.38 Hz, $J_{2',1'}$=1.59 Hz, $H_{2'}$), 4.50 (1H, d, $J_{3',2'}$=2.38 Hz, $H_{3'}$), 4.57 (1H, s, $H_{4'}$), 5.62 (1H, d, $J_{5,6}$=8.0 Hz, H_5), 5.90 (1H, d, $J_{1',2'}$= 1.59 Hz, $H_{1'}$), 6.51 (1H, br s, D_2O-exchangeable, 3'-OH), 7.83 (1H, d, $J_{6,5}$= 8.0 Hz, H_6), 8.92 (1H, br s, D_2O-exchangeable, NHa), 10.73 (1H, br s, D_2O-exchangeable, NHb), 11.40 (1H, s, D_2O-exchangeable, 3-NH).

11) Unpublished.

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