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# NUCLEOSIDES CXI . 6,6'-ANHYDRO-HEXOFURANOSYLURACILS, A NEW CLASS OF PYRIMIDINE ANHYDRO NUCLEOSIDES[1]

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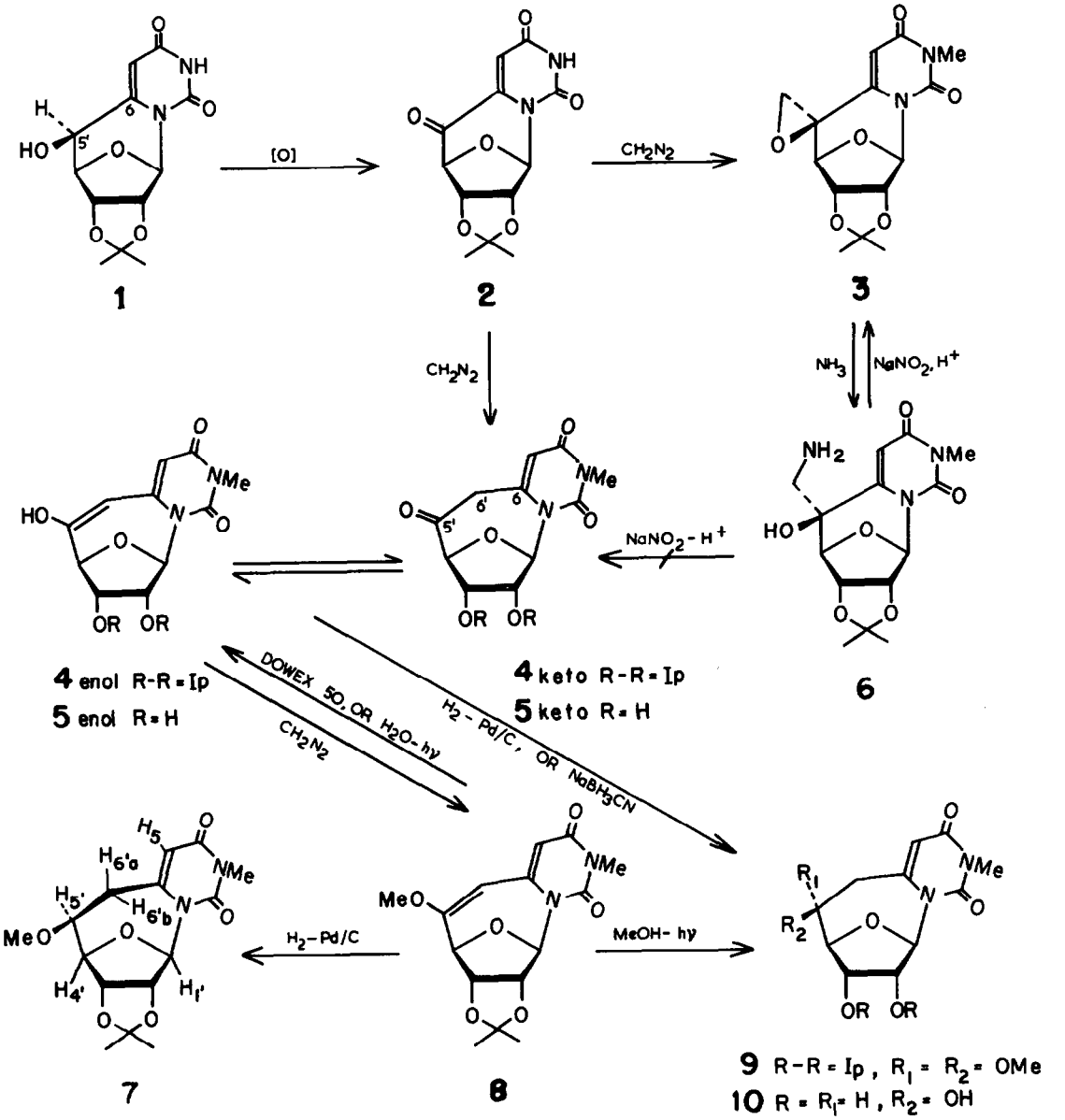
Recent studies from this laboratory have shown that 6,5'-cyclopyrimidine nucleosides[2], for example the isopropylideneuridine analogue 1, are very susceptible to oxidation at C-5'. Thus, autoxidation[3] of 1 with $O_2$-NaOH, or treatment with $MnO_2$ in methanol readily affords the 5'-ketonucleoside 2. These 5'-keto compounds are attractive starting materials for elaboration into a new class of pyrimidine cyclonucleosides, namely the 6'-deoxy-6,6'-anhydro-hexofuranosyluracils[4] represented by structures 7 and 10. The unsubstituted versions of 10 can be regarded as conformationally restricted models of ordinary pyrimidine nucleosides because they retain a full complement of hydrogen bonding sites, are restricted to the anti range by a carbon ratherthan an electronegative heteroatom bridge, and feature asymmetric 5'-hydroxy groups that simulate various degrees of rotation about the $C_{4'}$-$C_{5'}$ bond. Besides serving as models in physico-chemical studies of nucleoside conformation, such compounds are potentially useful for probing the conformational factors that affect the specificities of the enzymes involved in pyrimidine nucleotide metabolism.

We envisioned that 6,5'-cyclo-5'-keto-nucleosides such as 2 might undergo ring expansion to the desired ring system when treated with diazomethane[5]. Alternatively, the 5'-keto nucleosides would serve as sources of amino alcohols related to 6, which might undergo the Demjanov-Tiffeneau reaction[6] to give the same expanded ring system.

Preliminary studies using the 5'-keto nucleoside 2 as a model, without regard for N-methylation, show that diazomethane induced ring-expansion does indeed take place. Treatment of methanolic solutions of 2 with an excess of diazomethane affords the crystalline enol ether 8 (20% yield, prep. tlc)[7] together with the spiro-epoxide 3 (60% yield, prep. tlc)[8] and a host of unidentified, minor compounds. In principle the ring-expansion of 2 can lead to both the 5' and 6' homologous ketones. That enol ether 8 is substituted at C-5', and hence is derived by O-methylation of the initially formed 5'-ketone 4, follows from the appearance of H-4' as a singlet ($J_{3',4'} = 0$, allylic $J_{4',6'} < 0.5$Hz) in the nmr spectrum of 8. Had the methoxyl group of 8 been located at C-6' — as would occur if the ring expansion afforded the isomeric 6'-keto-nucleoside[9] — H-4' would appear as a doublet because of coupling to H-5'. Migration of the 5',6 bond of 2, leading to 4, in preference to migration of the 4',5' bond leading to the 6'-keto isomer, is consistent with the migratory aptitudes observed in previous studies [5b] of diazoalkane promoted ring-enlargements

of cyclic α,β unsaturated ketones. However, unlike previous examples, the ring - expansion 2→4 does not require Lewis acid catalysis. In the absence of such catalysis, α,β unsaturated ketones are usually unreactive or form pyrazolines[5]. Preliminary attempts to conduct the ring expansion reaction in the presence of $BF_3$, $AlCl_3$ or LiCl have not resulted in improved yields of 8.



Catalytic reduction of 8 affords the saturated methyl ether 7 in 75% yield, with hydrogen addition occuring from the less-hindered side to give the 5'S configuration. The various coupling constants observed in the nmr spectrum[10] of 7 are fully consistent with this assignment: moreover, the large value of $J_{5',6'b}$ (11.7 Hz, trans) and the presence of four-bond couplings between H-4'/H-6'a (1.5 Hz, W configuration) and H-5/H-6'b ($\sim$1 Hz, allylic) indicate that the methylene bridge projects over the furanose ring toward C-2' and C-3'. In this conformation, H-5 and H-1' are essentially coplanar, and the existence of a small $J_{1',5}$ can be demonstrated by decoupling experiments[11]. This, in turn, indicates a glycosyl torsion angle (O-1', C-1', N-1, C-6) of about 65°.

Compound 8, being an enol ether, is susceptible to acid hydrolysis and although the methoxyl group survives extended refluxing in 80% acetic acid, smooth conversion into ketone 5 (61% yield) occurs in boiling water containing a suspension of Dowex 50 ($H^+$). Compound 5 crystallizes in the keto form (5'-oxo at 1725 $cm^{-1}$, KBr), and a comparison of the uv spectrum ($H_2O$, $\lambda_{max}$ 262 nm) with that of enol ether 8 ($H_2O$, broad $\lambda_{max}$ 306-315 nm) indicates that the keto form (presumably hydrated) of 5 also predominates in neutral, aqueous solution. Compound 5 adopts the enol form in dimethyl sulfoxide solution as shown by the similarity of the uv spectrum (DMSO, broad $\lambda_{max}$ 310-320 nm) to that of enol ether 8 (see above), and by the nmr spectrum in DMSO-$d_6$ which shows singlets at $\delta$5.42 (H-6') and 10.86 (5'-hydroxyl). Addition of $D_2O$ to the DMSO-$d_6$ solution results in the almost instantaneous exchange of these signals, and is accompanied by the exchange of H-5 at a slower rate ($\sim$50% in five minutes). Exchange of H-5 is consistent with extensive delocalization in the anion derived from 5. Delocalization is also reflected in the uv spectrum of the anion (pH 9, $\lambda_{max}$ 355 nm). The 2',3'-O-isopropylidene ketone 4 can be regenerated from 8 by the photochemical addition of water to the 5',6'-double bond (low-pressure lamp, pyrex filter). This reaction presumably leads initially to a 5'-hemiacetal that decomposes spontaneously to give 4. However, ketone 4 is itself somewhat unstable during prolonged irradiation, making large scale photolysis unattractive. Irradiation of 8 in methanol affords the crystalline 5'-dimethyl acetal 9 in 30% yield. Similar photoadditions of alcohols to conjugated enol ethers have been observed in the steroid series.[12]

Reduction of aqueous solutions of 5 with $H_2$/Pd-C affords the crystalline 5'S alcohol 10 in 50% yield.[13] The same product was obtained in a similar yield by hydrolysis of acetal 9 with 80% acetic acid followed by in-situ reduction of the resulting 5 with sodium cyanoborohydride at pH $\sim$4. The pattern of coupling constants observed for 10 and its syrupy tri-O-acetate are similar to those found for the methyl ether 7, although the appearance of coupling between H-1'/H-2' (1.5 Hz) points to small changes in the conformation of the furanose ring. Studies on the solution conformation of 10 are in progress, as are modifications in the ring-enlargement procedure designed to avoid N-methylation.

The alternative approach to ring-expansion, namely the Demjanov-Tiffeneau reaction, proved to be unsuccessful. Ammonolysis of epoxide 3 readily affords the crystalline amino alcohol 6, but diazotization of 6 results in the re-formation of 3, with no uv spectral evidence for the formation of 4 or its 6'-keto isomer.

Acknowledgements. The authors are indebted to Dr. J. J. Fox for his continued interest, and to the American Cancer Society (grant CH-38) and the National Cancer Institute (grant 1PO1-CA-18856) for financial support.

## References and Footnotes

1. This paper is the third of a series entitled Conformationally Restricted Analogues of Pyrimidine Nucleosides. For part 2, see ref. 3.

2. B. A. Otter, E. A. Falco and J. J. Fox, J. Org. Chem., 41, 3133 (1976).

3. B. A. Otter, E. A. Falco and J. J. Fox, J. Org. Chem., 43, 481 (1978).

4. These compounds are more properly described as derivatives of 7, 10 Epoxypyrimido[1, 6a]azocine but for ease of comparison with ordinary nucleosides we prefer the trivial 6, 6'-anhydro designation with conventional nucleoside ring numbering.

5. a) C. D. Gutsche, Org. Reactions 8, 364 (1954).
   b) C. D. Gutsche, and D. Redmore, Carbocyclic Ring Expansion Reactions, Supplement 1 of Advances in Alicyclic Chemistry (H. Hart and G. J. Karabatsos, Eds.) Academic Press 1968.

6. P. A. S. Smith and D. R. Baer, Org. Reactions 11, 157 (1960).

7. All new compounds have been characterized by nmr and uv spectra, and (except for compound 4, which was not isolated), by elemental analysis.

8. Compound 3 was readily identified from a two proton quartet at $\delta$3.14 ($CDCl_3$) that exhibits the small splitting (5.5 Hz) characteristic of epoxide geminal couplings. We assume that diazomethane attacks from the less-hindered side to generate the stereochemistry indicated at C-5'.

9. The possibility that materials derived from the 6' keto isomer of 4 are present amongst the unidentified components cannot be excluded.

10. nmr, 100 MHz, pyridine-$d_5$; 7.17 (s, H-1'), 5.96 (broad s, H-5) 5.27 and 5.20 (ABq, H-2', H-3'), 4.88 (dd, H-4'), 3.63 (doublet of pseudo triplets, H-5'), 3.39 (s, $OCH_3$), 3.29 (s, $NCH_3$), 3.09 (eight lines, H-6'a), 2.65 (eight lines, H-6'b), 1.58 and 1.38 (s, isopropylidene methyls). $J_{1',2'}$ = $J_{3',4'}$ = O, $J_{2',3'}$ = 5.9, $J_{4',5'}$ = 3.7, $J_{5',6'a}$ = 3.9, $J_{5',6'b}$ = 11.7, $J_{6'a,6'b}$ = 15.5, $J_{4',6'a}$ = 1.5, $J_{5',6'b}$ ~ 1, $J_{5',6'a}$ ~ O Hz, $J_{1',5}$ detectable by decoupling.

11. The existence of a five bond $J_{1',5}$ has been observed previously for uridine and similar nucleosides, and used as evidence for the anti - conformation. F. E. Hruska, Can. J. Chem., 49, 2111 (1971).

12. G. Just and C. C. Leznoff, Can. J. Chem., 42, 79 (1964).

13. Reactions leading to 9 and 10 were conducted on a small scale (10-20mg) and it is likely that the yields are not optimum.

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