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O^6,5'-CYCLONUCLEOSIDES. REACTIONS OF 5-IODOPYRIMIDINE NUCLEOSIDES WITH BASE[1]

D. Lipkin, C. Cori, and M. Sano[2]

Chemistry Dept., Washington University, St. Louis, Mo. 63130

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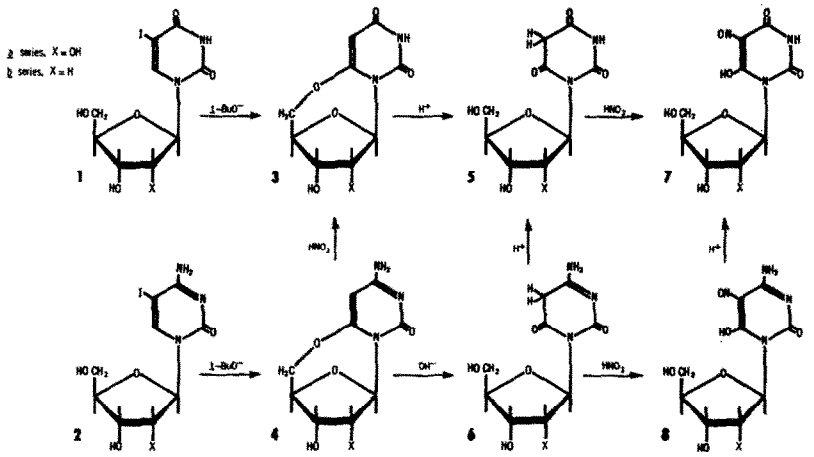
The recent note by Fox et al.,[3] prompts us to report the synthesis of four O^6,5'-cyclopyrimidine nucleosides[4] (3a, 3b, 4a, 4b) from the corresponding 5-iodopyrimidine nucleosides.[5] Such cyclonucleosides are of interest since they can be used as intermediates in the synthesis of 6-substituted pyrimidine nucleosides, a class of compounds that may prove to be of biological importance, but which to date have been little explored.[6,7,8] Thus, when 5-iodouridine (1a) was treated with an excess of potassium t-butoxide in a 1:1 (v/v) mixture of t-butyl alcohol and DMSO (60°, 24 hr), O^6,5'-cyclouridine[9] (3a) [mp 283-285° dec; $\lambda_{max}^{pH\ 7}$ 262 mμ (ε, 12,080)] was obtained. Analogously, starting with 5-iodocytidine (2a) and 5-iodo-2'-deoxycytidine (2b), O^6,5'-cyclocytidine·1/2H_2O (4a) [mp > 320°, $\lambda_{max}^{pH\ 7}$ 271.5 mμ (ε, 11,320)] and O^6,5'-cyclo-2'-deoxycytidine (4b) [mp > 300°, $\lambda_{max}^{pH\ 7}$ 272 mμ (ε, 10,400)], resp., were obtained. When 5-iodo-2'-



deoxyuridine (1b) replaced 1a in the above type of reaction, only a 19% yield of O^6,5'-cyclo-2'-deoxyuridine·1/2H_2O[10] (3b) [mp 209-210° dec; $\lambda_{max}^{pH\ 7}$ 262.5 mμ (ε, 12,600)] was isolated. The remainder of the reaction mixture was 40% unreacted 1b, 2% barbituric acid (13), and 27% 6-hydroxy-2'-deoxyuridine (5b). Preparatively it proved advantageous to obtain 3b by treating 4b with an excess of $LiNO_2$ and glacial acetic acid in DMSO.

The structures of 3a and 3b were confirmed by the following observations. Treatment of 3a and 3b with 60% HF[5,11] (25°, 15 hr) yielded 13 and ribose (14) or deoxyribose (15), resp. On the other hand, 0.1N H_2SO_4 converted 3a and 3b (70°, 1 hr) to 6-hydroxyuridine·H_2O (5a) [mp 114.5-115°; $\lambda_{max}^{pH\ 7}$ 264 mμ (ε, 21,890)] and 6-hydroxy-2'-deoxyuridine (5b) ($\lambda_{max}^{pH\ 7}$ 265 mμ), resp. This indicates that the position of attachment of the cyclo-linkage is at C_6 of the aglycon. It is possible to differentiate 5a from the isomeric 5-hydroxyuridine[12] (16) [$\lambda_{max}^{pH\ 7}$ 280 mμ (ε, 8,200)] by comparison of their UV spectra; the lack of blue color when 5a is treated with aqueous $FeCl_3$;[13,14] and the orange color produced when 5a or 13 are treated with Ehrlich's reagent.[15] No color is produced when 16 is treated with Ehrlich's reagent. NMR spectra of 3a and 3b in DMSO-d_6 showed a single vinylic proton at 5.32 δ and 5.19 δ, resp. These singlet resonances are assigned to the H_5 protons[16a] of 3a and 3b. The H_5' resonances of 3a and 3b, on the other hand, are pairs of doublets[16b] centered at 3.95 δ and 4.58 δ ($J_{H_5',H_5'}$ = 13 cps) and 3.89 δ and 4.51 δ ($J_{H_5',H_5'}$ = 12 cps), resp. Such a pattern has been reported[3,17] as typical of cyclonucleosides that have an oxygen cyclo-linkage to C_5'. Compound 3a rapidly consumed one mole of metaperiodate.[18] This is consistent with a ribofuranosyl structure and a cyclo-linkage which does not involve C_2' or C_3'.

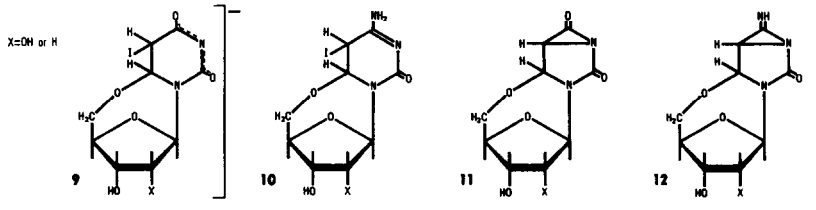
Similar methods were used to determine the structures of 4a and 4b. Using deaminating conditions analogous to those used for the conversion of 4b to 3b, it was possible to convert 4a to 3a. This indicates that the cyclo-linkage does not involve C_4 of the aglycon. It was possible, furthermore, to open the cyclo-linkage of 4a and 4b by refluxing (1 hr) in aqueous 0.2M $Ba(OH)_2$. 6-Hydroxycytidine·H_2O (6a) [mp 181-182° dec; $\lambda_{max}^{pH\ 7}$ 267 mμ (ε, 19,800)] and 6-hydroxy-2'-deoxycytidine·H_2O (6b) [mp 195-197° dec; $\lambda_{max}^{pH\ 7}$ 267 mμ (ε, 19,990)], resp., were obtained. The H_5 protons[16a] of 4a and 4b were single unsplit resonances at 5.40 δ and 5.33 δ resp., while the H_5' protons in each were again pairs of doublets centered at 4.50 δ and 3.87 δ ($J_{H_5',H_5'}$ = 14 cps) and 4.49 δ and 3.82 δ ($J_{H_5',H_5'}$ = 13 cps), resp. Compound 4a rapidly consumed one mole of metaperiodate. Once again, this is consistent with a ribofuranosyl structure and a cyclo-linkage that is to C_5' rather than to C_2' or C_3'.

By treatment of 2a and 2b with excess aqueous tetramethylammonium hydroxide in DMSO (25°, 3 days) it is possible to isolate 6a and 6b, resp. In all likelyhood 4a and 4b, resp., are intermediates. This supposition is supported by the observations that during the conversion of 2a to 6a a small amount of 4a always is present and that the cyclo-linkage in 4a and 4b is opened with $Ba(OH)_2$ to form 6a and 6b, resp. Compounds 6a and 6b can be deaminated to 5a and 5b, resp.,

by treatment with aqueous 0.1M H_2SO_4 (25°, 18 hr). The structures of 6a and 6b were further confirmed by cleavage with 60% HF (25°, 16 hr) to 6-hydroxycytosine (17) and 14 or 15, resp. It was possible also to distinguish 6a from the isomeric 5-hydroxycytidine[19] [$\lambda_{max}^{pH\ 7}$ 292 mμ (ε, 7837)] by comparison of their UV spectra and the lack of blue color when 6a was treated with aqueous $FeCl_3$.[13] Finally, it was possible to convert 5a to 5-nitroso-6-hydroxyuridine (7a) [mp 166-167° dec; $\lambda_{max}^{pH\ 7}$ 311 mμ (ε, 8000)] by treatment with excess HNO_2. This is further evidence that the cyclo-linkage in 3a does not involve C_5 of the aglycon. The structure of 7a was confirmed by comparison of its UV spectrum with violuric acid [$\lambda_{max}^{pH\ 7}$ 311 mμ]. Likewise, reaction of 6a with aqueous HNO_2 at pH > 4 yielded 5-nitroso-6-hydroxycytidine·1/2H_2O (8a) [mp 210-211° dec; $\lambda_{max}^{pH\ 7}$ 317 mμ (ε, 17,400)]. Compound 8a then was deaminated to 7a by treatment with aqueous 0.1M H_2SO_4 (25°, 15 hr).

Two plausible mechanisms can explain the conversion of 5-iodopyrimidine nucleosides to the corresponding O^6,5'-cyclopyrimidine nucleosides. The first is an addition-elimination mechanism. This would involve the anion 9 or the intermediate 10, which could either eliminate HI directly by the loss of H_6 and iodide[3] or it could form the α-lactam 11 or the α-iminolactam 12 by displacement of iodide at C_5 by N_3. H_6 could then be lost with concomitant lactam ring opening to form the observed product. Related mechanisms[20,21,22] have been proposed to explain reaction at C_6 in various other pyrimidine nucleosides and the conversion[23] of showdomycin to cycloshowdomycin. The second plausible mechanism involves a hetaryne. In this case the first step is abstraction of H_6 by base followed by loss of iodide and the attack of the C_5' oxygen on the hetaryne. Hetaryne intermediates have been observed with other 5-halopyrimidines.[24] Evidence obtained thus far in This Laboratory supports either mechanism. No matter which is operative, however, it need not function only intramolecularly, since treatment of 5-iodocytidine-5'-phosphate[25] with aqueous tetramethylammonium hydroxide in DMSO yields the 5'-phosphate of 4a.

Further work is in progress in order to elucidate mechanisms for these reactions and to determine the scope of ring-opening reactions of the cyclonucleosides with common nucleophiles.



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(2) Present address: Central Research Laboratory, Daiichi Seiyaku Co., Tokyo, Japan.

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