New Chemical Modification of the Ribosyl Moiety in Uridines, Synthesis of Novel Types of 3',5'-Epithio Uridine Derivatives

Kosaku Hirota,* Yukio Kitade, Tetsuo Tomishi, and Yoshifumi Maki

Gifu Pharmaceutical University, 5–6–1 Mitahora-higashi, Gifu 502, Japan

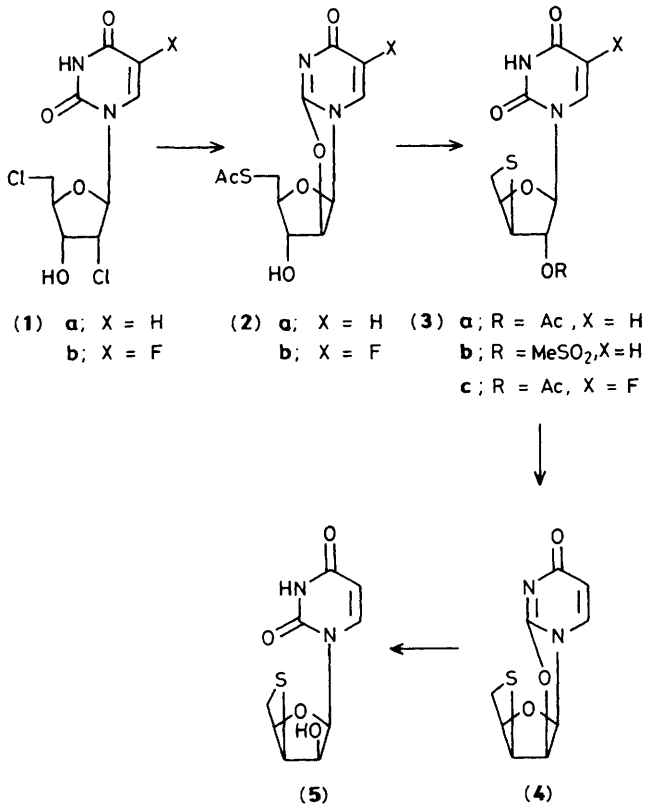
Treatment of 5-substituted 5'-*S*-acetyl-2,2'-anhydro-5'-thio-1-β-D-arabinofuranosyluracils (**2**), prepared with ease from 5-substituted 2',5'-dichloro-2',5'-dideoxyuridines (**1**), with methanolic sodium methoxide gave the corresponding 3',5'-epithio-3',5'-dideoxy-1-β-D-xylofuranosyluracils (**3**) fused with a thietane ring in the sugar moiety.

Previously we reported a convenient method for synthesis of 2',5'-dideoxy-2',5'-dihalogenouridines (**1**) from uridines.[1] In the course of our studies on the reactivity of the 2',5'-dihalogenouridines (**1**) towards various nucleophiles,[2,3] we found a simple procedure for their conversion into hitherto unknown 3',5'-epithio-3',5'-dideoxy-1-β-D-xylofuranosyluracil derivatives (**3**),† which possess a thietane ring[4] in the sugar moiety. The present result provides a new methodology for the chemical modifications of uridine derivatives.

Reaction of 2',5'-dichloro-2',5'-dideoxyuridine (**1a**) with thioacetic acid in the presence of triethylamine in *N*,*N*-dimethylformamide at 100 °C for 4 h gave the 5'-acetylthio-derivative (**2a**) in 66% yield. Compound (**2a**) was refluxed in methanolic sodium methoxide for 1 h and the resulting clear solution was neutralised with Amberlite CG-50 (H^+). After removal of the solvent under reduced pressure, the residue was treated with acetic anhydride in pyridine to give 2'-*O*-acetyl-3',5'-dideoxy-3',5'-epithio-1-β-D-xylofuranosyluracil (**3a**) in 67% yield. The structure of (**3a**) was deduced from its microanalytical and spectral (i.r., ^1H n.m.r., u.v., and mass) data.‡ Conclusive structural proof of (**3**) rests upon the following chemical conversions. Treatment of (**2a**) with

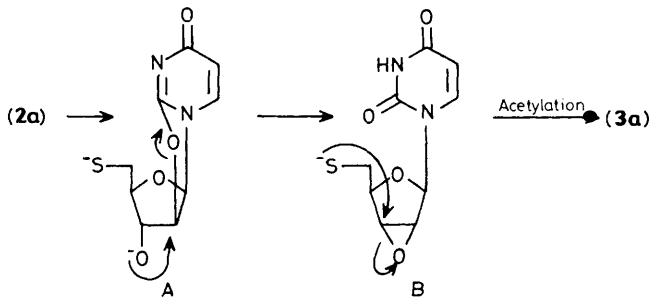
† The formation of this type of compound has been proposed as a transient intermediate (*cf.* I. Wempen and J. J. Fox, *J. Org. Chem.*, 1969, **34**, 1020).

‡ Characterization of (**3a**): m.p. 192—193 °C; u.v. λ_{max} (EtOH) 260 nm (log ε 4.00); mass *m/z* 284 (M^+); ^1H n.m.r. (270 MHz, $CDCl_3$) δ 8.34 (1H, br, HN^3), 8.15 (1H, d, *J* 8.12 Hz, 6-H), 6.29 (1H, d, *J* 3.42 Hz, 1'-H), 5.90 (1H, dd, *J* 2.14 and 8.12 Hz, 5-H), 5.26—5.21 (2H, m, 2'- and 4'-H), 4.03 (1H, d, *J* 5.56 Hz, 3'-H), 3.58 (1H, dd, *J* 4.70 and 10.69 Hz, 5'-H), 2.90 (1H, d, *J* 10.69 Hz, 5'-H), 2.09 (3H, s, COMe). Decoupling the 2H multiplet at δ 5.26—5.21 causes the two doublets at δ 6.29 and 4.03 to collapse to two sharp singlets and the double doublet at δ 3.58 to collapse to a doublet. Decoupling the two doublets at δ 6.29 and 4.03 partially collapses the multiplet at δ 5.26—5.21; ^{13}C n.m.r. [25 MHz, $(CD_3)_2SO$] δ 169.78 (s), 163.28 (s), 150.41 (s), 140.27 (d), 102.44 (d), 91.03 (d), 83.02 (d), 82.55 (d), 45.05 (d), 29.60 (t), 20.30 (q); i.r. (KBr) 1745, 1695, 1235, 1060 cm^{-1}. All compounds described herein gave satisfactory microanalytical results and spectral data consistent with their structures.



Scheme 1

sodium methoxide followed by reaction with methanesulphonyl chloride instead of acetic anhydride in the above reaction afforded the corresponding 2′-methylsulphonyl derivative (**3b**) in 72% yield. Compound (**3b**) was smoothly converted upon treatment with 1 equiv. of sodium methoxide in methanol under reflux for 30 min into the 2,2′-anhydro compound (**4**) quantitatively. This result clearly indicates that compound (**3a**) has the 3′,5′-*S*-cyclo structure rather than the alternative 2′,5′-*S*-cyclo structure because in the latter structure, formation of the 2,3′-anhydrocyclic bond is prevented by severe steric hindrance. Hydrolysis of (**4**) with sodium hydroxide at room temperature for 1.5 h led to the formation of (**5**) in 65% yield.



Scheme 2

A plausible reaction sequence for the formation of (**3a**) is outlined in Scheme 2. Deacetylation of the 5′-acetylthio group and deprotonation of the 3′-hydroxy group by base generate the dianion (A). The epoxide intermediate (B) could then be formed *via* the attack of the 3′-*O*-anionic site on the 2′-position and concurrent cleavage of the 2,2′-anhydro bond. Fission of the epoxide ring by the attack of the 5′-thiolate anion on the 3-position could produce the 3′,5′-epithio derivative (**3a**).

The above reaction was successfully applied to the 5-fluorouridine derivative (**1b**). The acetylthio compound (**2b**) was prepared by the reaction of (**1b**) with thioacetic acid in 92% yield, and was heated under reflux in methanolic sodium methoxide. Treatment with acetic anhydride gave the corresponding 3′,5′-epithio-5-fluoro derivative (**3c**) in 80% yield.

Thus, the 5′-acetylthio-2,2′-anhydro compounds (**2**) serve as versatile intermediates for the preparation of novel 3′,5′-epithio-pyrimidine nucleosides (**3**)—(**5**).

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