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A NOVEL CYCLIZATION REACTION OF A C-6 SUBSTITUTED URIDINE ANALOG: AN ENTRY TO 5,6-DIALKYLATED URIDINE DERIVATIVES

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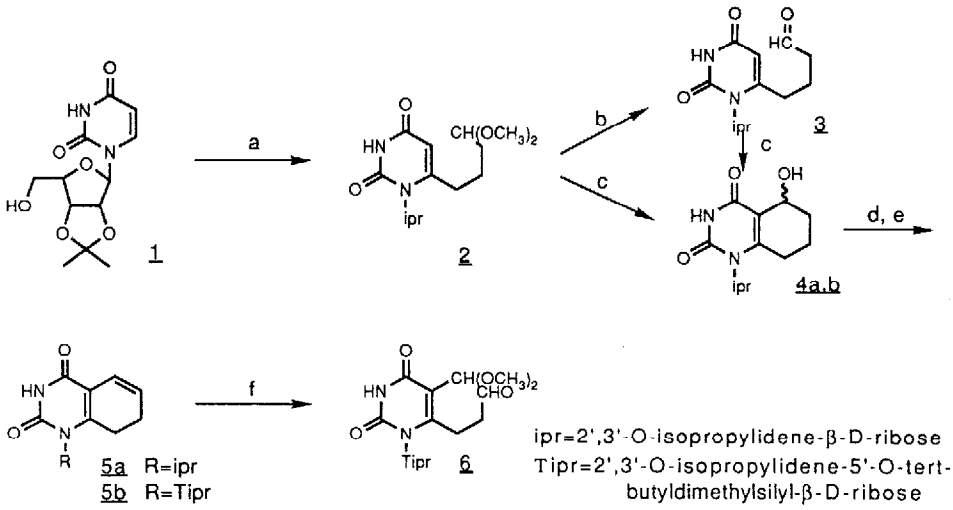
Summary: 5,6-Dialkylated uridine derivatives were conveniently synthesized in 5 steps starting from 2',3'-O-isopropylideneuridine (1) in a 43% overall yield. The key reaction is a novel acid catalyzed cyclization reaction of 6-(4-butanal)-2',3'-O-isopropylideneuridine.

It has been demonstrated in the past few decades that both C-5 or C-6 monosubstituted and C-5 , C-6 dialkylated uridine derivatives have exhibited various biological activities.[2-5] The availability of a reasonable synthetic procedure for the synthesis of 5,6-dialkylated pyrimidine nucleosides could prove useful in the development of new chemotherapeutic agents for the control of viral diseases and cancer. Although methods for alkylation at either the C-5 or C-6 position of the uracil ring of uridine analogs have been reported,[6] a general method for the preparation of the C-5, C-6 dialkyluridine derivatives has not appeared. Previously C-5 and C-6 dialkylated compounds have been prepared through lengthy syntheses[7] by methods which do not allow for easy variation of the side chains. In our studies, in investigating the chemical mechanism of thymidylate synthase, several 5, 6-dialkylated uridine derivatives were required. A convenient method for the synthesis of this type of compounds is reported herein.

In efforts to prepare 5, 6-dialkylated uridine derivatives, attempts were made to utilize literature methods for the preparation of C-5 or C-6 monoalkylated uridine derivatives. However, methylhydroxylation at the C-5 position of the C-6 alkylated compounds under either acidic or basic conditions was not successful, nor were alkylations at the C-6 position of C-5 alkylated compounds. The successful approach taken in this study utilized the dipolar nature of the 5, 6-double bond of the uracil ring, the key reaction being acid catalyzed nucleophilic addition of the C-5 of uridine to an appended aldehyde for the ring closure reaction. The only reported reactions that are analogous to this hydroxyalkylation are those of uridine with electron deficient aromatic aldehydes and formaldehyde.[8] Thus alkylation of 1 with γ-bromobutanal dimethyl acetal gave the C-6 alkylated product 2 , which on cyclization with CF_3COOH (TFA) in acetone gave a mixture of isomeric cyclized alcohols 4a and 4b. The mixture of these alcohols was subjected to dehydration in the presence of p-toluenesulfonic acid to afford the olefin. The 5'-hydroxyl group was then protected as the t-butyldimethylsilyl (TBDMS) ether to give 5b.

Ozonolysis of the protected olefin gave the dialdehyde, which offers the opportunity for further modifications. Furthermore, due to its benzylic-like nature, the aldehyde at the C-5 position can be selectively protected as dimethyl acetal 6, which makes it readily accessible for transformation of both the C-5 and C-6 positions into different functional groups.



a). i). LDA/THF, ii). $Br(CH_2)_3CH(OCH_3)_2$ b).$HOAc/H_2O$ (8:2)/silica gel c). Acetone:H_2O:TFA (85:10:5), RT, 36 hr d). p-toluenesulfonic acid/acetone, reflux e). TBDMSCl, DMAP, Et_3N f). i). O_3/CH_2Cl_2, -78 °C, ii). CH_3SCH_3, iii). NH_4Cl/CH_3OH

The first step in the sequence is the alkylation of the lithium anion of C-6 of 2',3'-O-isopropylideneuridine (1). In this reaction 2', 3'-O-isopropylideneuridine was first treated with 5 equivalents of LDA in THF for two hours at -78 °C. This was followed by the addition of 3 equivalents of γ-bromobutanal dimethylacetal.[9] After 90 hours at -78 °C, the reaction was quenched with acetic acid and the product purified by silica gel chromatography to afford 80% of compound 2.[10]

Deprotection of 2 and the subsequent cyclization of 3 were accomplished by stirring the acetal 2 in acetone containing 10% water and 5% trifluoroacetic acid at room temperature for 36 hours with a 75% yield. Shorter reaction time results in three major products: the aldehyde 3 and the two cyclized alcohols, 4a and 4b.[11] Studies with pure aldehyde 3, prepared by the hydrolysis of the acetal with acetic acid-water (8:2) solution mixed with silica gel, show that the aldehyde is converted to the cyclized alcohols 4a and 4b under the same conditions. Dehydration of the two isomeric alcohols was accomplished by refluxing in acetone with a catalytic amount of p-

toluenesulfonic acid overnight to give 5a in 82% yield.[12] After dehydration, the 5'-hydroxy group was protected as the TBDMS ether upon treatment with TBDMS chloride in the presence of triethylamine and a catalytic amount of 4-dimethylaminopyridine (DMAP) to give compound 5b in 93% yield. The ozonolysis was carried out at -78 °C in methylene chloride. After reductive workup with dimethylsulfide and solvent evaporation, the dialdehyde formed, without purification, was transformed directly into its 5-dimethylacetal form 6[13] by stirring in methanol with ammonium chloride giving an 88% overall yield. Thus this method can give the 5, 6-dialkylated uridine derivative in five steps with a 43% overall yield starting with isopropylideneuridine(1). The dimethylacetal 6 can be transformed into a variety of 5,6-dialkylated uridine derivatives.

The mechanism of the cyclization reaction of compound 3 was examined by monitoring the ultraviolet spectrum of the reaction mixture over a period of several hours. An initial decrease in the absorption maximum at 260 nm (reaching minimum at about 15 min) was followed by a gradual increase with formation of the product. The decrease indicates a loss of conjugation and the formation of a discrete intermediate in the conversion of the aldehyde 3 to the cyclized alcohols 4a and 4b. The role of catalysts in the reaction was also examined and it was found that acetic acid, sodium acetate, or methylthiolglycolate (over the pH range of 4 to 9) were ineffective in the cyclization. Acetic acid was effective, however, in the equilibration of the two alcohols 4a and b. These results suggest that the equilibration must proceed via a solvolysis reaction, not through the ring-opened aldehyde 3 since acetic acid under equilibrium conditions did not lead to the cyclization of the latter. The entropic advantage gained in this intramolecular cyclization reaction may account for the fact that simple aldehydes do not undergo a similar hydroxyalkylation reaction with uracil or uracil nucleosides.

References and notes

1. Correspondence can be addressed to Professor Kristin B. Mertes, Department of Chemistry, University of Kansas, Lawrence, Kansas, 66045, U.S.A.. This work was supported by a Biomedical Research Support Grant (RR 5606) and a Training Grant (GM 7775) from the National Institutes of Health and a grant from the Wesley Foundation. The authors thank Professors Jeffery Aube and Thomas Engler for helpful discussions and advice.

2). For recent review see: De Clercq, E. Nucleosides and Nucleotides **1987**, 6, 197-207, and references therein.

3). a). Tanaka, H.; Matsuda, A.; Iijima, S.; Hayakawa, H.; Miyasaka, T.; *Chem. Pharm. Bull.* **1983**, 31, 2164-2167. b). Kapuler, A. M.; Reich, E. *Biochemistry* **1971**, 10, 4050-4061. c). Schroeder, A. C.; Bloch, A.; Perman, J. L.; Bobek, M. *J. Med. Chem.* **1982**, 25, 1255-1258.

4). a).Diwan, A. R.; Robins, R. K.; Prusoff, W. H. *Experientia* **1969**, 25, 98-100. b). Krajewska, E.; Shugar, D. *Biochemical Pharmacology* **1982**, 31, 1097-1102. c). Kapuler, A. M.; Reich, E. *Biochemistry* **1971**, 10, 4050-4061.

5). a). Argoudelis, A. D.; Herr, R. R. *Antimicrob. Agents Chemother.* **1962**, 505. b). Goldberg, I. H. *Cancer Chemoth. Rep., Part I* **1974**, 58, 479.

6). a). Tanaka, H.; Nasu, I.; Miyasaka, T. *Tetrahedron Lett.* **1979**, 4755-4758. b). Scheit, K. H. *Chem. Ber.* **1966**, 99, 3884.

7). a).Basnak, I.; Farkas, J. *Tetrahedron Lett.* **1976**, 4379-4380. b). Frass, E.; Draminski, M.; Fiszer, B. *Ann. Soc. Chim. Polonorum* **1974**, 48, 971-979. c). Saito, I.; Shimozono, K.; Matsuura, T. *J. Am. Chem. Soc.* **1980**, 102, 3948-3950. d). Winkley, M. W.; Robins, R. K. *J. Org. Chem. 1968*, 33, 2822-2827.

8). a). Lam, B. L.; Pridgen, L. N. *J. Org. Chem.* **1986**, 51, 2592-2594. b). Brown, D. J. in *The Pyrimidines*; Weisburger, A. Ed.; Wiley; New York. **1962.**

9). 4-Bromobutanal dimethyl acetal was prepared in two steps from 4-bromobutyronitrile by 1) reduction at 0 °C in THF with 1.2 equivalent of DIBAL, and 2) reaction of the intermediate aldehyde with methyl orthoformate in methanol containing a trace of ammonium chloride.

10). Compound 2 6-(4-Butanal dimethyl acetal)-2',3'-O-isopropylideneuridine UV(MeOH): λ_{max} 260 nm (ε=9822); IR (CH_2Cl_2): 3450, 2930, 1689, 1450, 1385 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 5.60 (d,1 H, 1'-H), 5.53 (s, 1 H, 5-H), 5.17 (q, 1 H, 2'-H), 4.95 (q, 1 H, 3'-H), 4.35 (b, 1 H, CH(OCH_3)$_2$), 4.14 (d, 1 H, 4'-H), 3.77 (m, 2 H, CH_2OH), 3.26 (s, 6 H, OCH_3), 2.52 (b, 2 H, CH_2), 1.64 (b, 4 H, -(CH_2)$_2$CH(OCH_3)$_2$), 1.49 (s, 3 H, CH_3), 1.28 ppm (s, 3 H, CH_3); ^{13}C-NMR ($CDCl_3$): 162.8 (C-4), 156.2 (C-2), 151.8 (C-6), 114.0 (C(CH_3)$_2$), 103.7 (C-5), 102.9 (-C(OCH_3)$_2$), 91.6 (C-1'), 87.7 (C-4'), 83.4 (C-2'), 80.4 (C-3'), 62.5 (CH_2OH), 52.7 (OCH_3), 32.9, 31.9, 27.1 (CH_3), 25.4 (CH_3), 22.6 ppm; CIMS (NH_3) m/e (relative intensity) 401 (M+1, 0.9), 385 (M-Me, 5.9), 369 (0.7), 229 (58.4), 197 (100). Anal. Calcd for $C_{18}H_{28}N_2O_8$: C, 53.99; H, 7.05; N, 7.00. Found: C, 54.38; H, 7.24; N, 7.38.

11). Compound 4a , b [1H,3H]-5-Hydroxyl-1-(2',3'-O-isopropylidene-β-D-ribofuranosyl)-5,6,7,8,-tetrahydroquinazoline-2,4-dione Isomer A (with higher Rf value): UV(MeOH): λ_{max}=260 nm; ^{1}H-NMR ($CDCl_3$): 5.71 (d, 1 H, 1'-H), 5.25 (q, 1 H, 2'-H), 5.02 (q, 1 H, 3'-H), 4.78 (t, 1 H, CHOH), 4.19 (q, 1 H, 4'-H), 3.84 (m, 2 H, CH_2OH), 2.62 (b, 2 H, CH_2-uridine), 2.05-1.80 (m, 4 H, (CH_2)$_2$CHOH), 1.54 (s, 3 H, CH_3), 1.34 ppm (s, 3 H, CH_3); ^{13}C-NMR ($CDCl_3$): 163.98 (C-4), 151.77 (C-2), 150.66 (C-6), 114.10 (-(O)$_2$C(CH_3)$_2$), 112.89 (C-5), 91.17 (C-1'), 87.87 (C-4'), 83.64 (C-2'), 80.51 (C-3'), 62.56 (CH_2OH), 62.34 (CHOH), 28.51, 27.20 (CH_3), 26.87, 25.16 (CH_3), 17.80 ppm; EIMS m/e (relative intensity): 355 (16.8, M+1), 399 (17.3, M-CH_3), 181 (83.3, M-sugar), 165 (100, M-sugar-H2O); Isomer B (lower Rf): UV (MeOH): λmax=261 nm; ^{1}H-NMR (CDCl3): 5.70 (s, 1 H, 1'-H), 5.23 (t, 1 H, 2'-H), 5.01 (t, 1 H, 3'-H), 4.75 (b, 1 H, CHOH), 4.20 (d, 1 H, 4'-H), 3.86 (b, 2 H, CH_2OH), 2.8-1.8 (m, 6 H, CH_2), 1.52 (s, 3 H, CH_3), 1.32 ppm (s, 3 H, CH_3); ^{13}C-NMR ($CDCl_3$): 163.91 (C-4), 152.20 (C-2), 150.48 (C-6), 113.97 (C(CH_3)$_2$), 112.57 (C-5), 90.90 (C-1'), 88.30 (C-4'), 83.82 (C-2'), 80.57 (C-3'), 62.51 (-CH_2OH), 61.18 (-CHOH), 28.47, 27.27 (CH_3), 26.95, 25.30 (CH_3), 17.23 ppm; EIMS m/e 355 (M+1, 1.5), 339 (M-Me, 5.1), 181 (M-sugar, 56), 165 (M-sugar-H2O, 100); Anal. Cald for $C_{16}H_{22}N_2O_7.CH_3OH$ C, 52.84; H, 6.78; N,7.25; Found: C, 53.00; H, 6.48; N, 7.10.

12). Compound 5a [1H,3H]-1-(2',3'-O-isopropylidene-β-D-ribofuranosyl)-7,8-dihydroquinazoline-2,4-dione: UV (H_2O): λ_{max} 309 nm (ε 5500), 249 nm (ε 13,000); ^{1}H-NMR ($CDCl_3$): 10.12 (bs, 1 H NH), 6.40 (d, 1 H, C5-H), 5.71 (d, 1 H, C1'-H), 5.69 (m, 1 H, C6-H), 5.20 (dd, 1 H, C2'-H), 4.95 (m, 1 H, C3'-H), 4.16 (dd, 1 H, C4'-H), 3.80 (dd, 1 H, C5'-H_a), 3.75 (dd, 1 H, C5'-H_b), 2.78 (m, 1 H, C7-H_a), 2.67 (m, 1 H, C7-H_b), 2.38 (m, 2 H, C8-H_2), 1.49 (s, 3 H, CH_3), 1.28 ppm (s, 3 H, CH_3); ^{13}C-NMR ($CDCl_3$): 160.99 (C-4), 150.62 (C-2), 148.30 (C-8_a), 122.00 (C-6), 118.94 (C-5), 113.99 (C(CH_3)$_2$), 108.89 (C-4_a), 90.90 (C-1'), 88.09 (C-4'), 83.69 (C-2'), 80.61 (C-3'), 62.56 (C-5'), 27.12 (CH_3), 25.10 (CH_3), 23.59 (C-8), 22.09 ppm (C-7); CIMS (NH_3), m/e (Rel. Intens.): 337 (M^++1, 6), 220 (7), 165 (100). Anal. Calcd for $C_{16}H_{20}N_2O_6$: C, 57.13; H, 5.99; N, 8.33. Found: C, 57.24; H, 6.30; N, 8.10.

13). Compound 6 1-(2',3'-O-iospropylidene-5'-O-tert-butyldimethylsilyl)-5-(formyl-dimethylacetal)-6-(3-propanal)-uridine: UV (CH_3OH): λ_{max} 268 nm; ^{1}H-NMR ($CDCl_3$): 9.76 (s,1 H, CHO), 9.73 (bs, 1 H, NH), 5.60 (s, 1 H, C1'-H), 5.55 (s, 1 H, CH(OCH_3)$_2$, 5.16 (d, 1 H, C2'-H), 4.78 (dd, 1 H, C3'-H), 4.10 (dd, 1 H, C4'-H), 3.81 (m, 2 H, C5'-H), 3.40 (s, 3 H, OCH_3), 3.38 (s, 3 H, OCH_3), 3.31 (m, 2 H, C6-CH_2), 2.90 (m, 1 H, CH_a-CHO), 2.77 (m, 1 H, CH_b-CHO), 1.51 (s, 3 H, CH_3), 1.31 (s, 3 H, CH_3), 0.87 (s, 9 H, C(CH_3)$_3$), 0.04 ppm (s, 6 H, Si(CH_3)$_2$); ^{13}C-NMR ($CDCl_3$): 198.93 (CHO), 162.70 (C-4), 156.69 (C-2), 149.88 (C-6), 113.95 (C(CH_3)$_2$), 111.22 (C5), 100.68 (C(OCH_3)$_2$), 91.94 (C-1'), 89.93 (C-4'), 84.14 (C-2'), 81.99 (C-3'), 64.06 (C-5'), 56.21 (OCH_3), 56.02 (OCH_3), 42.07 (C6-CH_2), 27.15 (C(CH_3)$_2$), 25.87 (C(CH_3)$_3$), 25.32 (C(CH_3)$_2$), 18.38 C(CH_3)$_3$), -5.28 ppm(Si(CH_3)$_2$). Anal. Calcd for $C_{24}H_{40}N2Si$: C, 54.52; H, 7.64; N, 5.30. Found: C, 54.20; H, 7.95; N, 5.29.

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