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Preliminary communication

Nucleoside transformations. Anhydro- and halo-nucleosides by treatment of nucleoside 2′,3′-ortho esters with halotrimethylsilanes

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There has been considerable interest in selective transformations of the vicinal diol portion of ribonucleosides[1–5]. Recent reports on the conversion of cyclic ortho acetates of 1,2-diols into acetates of chlorohydrins by treatment with chlorotriphenylmethane[6] and chlorotrimethylsilane[7] led us to apply this procedure to ribonucleosides. The conversion of uridine *via* a 2′,3′-ortho ester* into the corresponding 3′-*O*-acyl-2,2′-anhydrouridine and 3′-*O*-acyl-2′-deoxy-2′-halouridine (both of which are versatile intermediates for further modification of the nucleoside, *e.g.*, *ribo* to *arabino* configuration[8], and 2′-deoxy-2′-halo- to 2′-deoxynucleosides[2,4]) is now reported.

Treatment of 2′,3′-*O*-(methoxyethylidene)uridine[9] (1) with chlorotrimethylsilane in boiling acetonitrile for 10 min under reflux afforded** 2,2′-anhydro-1-(3-*O*-acetyl-β-D-arabinofuranosyl)uracil hydrochloride[2] (3a) in 72% yield***; n.m.r. data† (D_2O): δ 2.10 (s, 3, $COCH_3$), 3.51 (d, 2, J 4 Hz, H-5′), 5.28 (d, 1, J 2 Hz, H-3′), 5.48 (d, 1, J 6 Hz, H-2′), 6.00 (d, 1, J 7.5 Hz, H-5), 6.35 (d, 1, J 6 Hz, H-1′), and 7.68 (d, 1, J 7.5 Hz, H-6), whereas treatment of 1 with chlorotrimethylsilane in boiling nitromethane for 1.5 h under reflux gave 3′-*O*-acetyl-2′-chloro-2′-deoxyuridine[2] (4a) in 48% yield***; n.m.r. data [$(CD_3)_2SO$, Me_4Si]: δ 2.08 (s, 3, $COCH_3$), 3.52 (d, 2, J 3 Hz, H-5′), 4.10 (q, 1, J 3 Hz, H-4′), 4.64 (d of d, 1, $J_{2',1'}$ 7 Hz, $J_{2',3'}$ 5 Hz, H-2′), 5.18 (d of d, 1, $J_{3',2'}$ 5 Hz, $J_{3',4'}$ 3 Hz, H-3′), 5.55 (d of d, 1, $J_{5,6}$ 7 Hz, $J_{5,3}$ 2 Hz, H-5), 5.86 (d, 1, J 7 Hz, H-1′), 7.60 (d, 1, J 7.5 Hz, H-6), and 11.15 (br s, 1, H-3). Similarly, treatment of 1 with bromotrimethylsilane in boiling dichloromethane (for 1.5 h) and acetonitrile (for 10 min) under

*By treatment of their 2′,3′-ortho esters with pivaloyl chloride, purine ribonucleosides have been converted[1] into the corresponding 3′-deoxy-3′-halo-*xylo* esters.

**Ortho ester 1 was used as obtained from the crude reaction-mixture, without further purification; therefore, the yields given are based on the weight of uridine used.

***Other spectral data and physical properties were comparable to the values given in the literature.

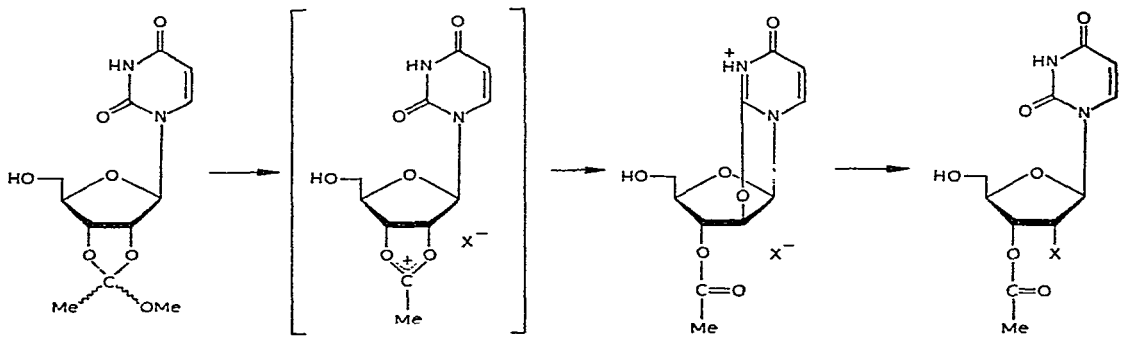
†All data from n.m.r. spectra taken in D_2O are in reference to sodium 2,2-dimethyl-2-silapentane-5-sulfonate as the internal standard.

reflux gave, respectively: (*a*) 2,2′-anhydro-1-(3-*O*-acetyl-β-D-arabinofuranosyl)uracil hydrobromide (**3b**) in 75% yield; m.p. 125° (dec.): λ_{max}^{MeOH} 250 (ϵ_{mM} 7.76) and 223 nm (ϵ_{mM} 8.69); n.m.r. data (D_2O): δ 2.10 (s, 3, $COCH_3$), 3.51 (d, 2, *J* 4 Hz, H-5′), 5.28 (d, 1, *J* 2 Hz, H-3′), 5.50 (d, 1, *J* 6 Hz, H-2′), 6.02 (d, 1, *J* 7.5 Hz, H-5), 6.37 (d, 1, *J* 6 Hz, H-1′), and 7.70 (d, 1, *J* 7.5 Hz, H-6), and (*b*) 3′-*O*-acetyl-2′-bromo-2′-deoxyuridine† (**4b**) in 59% yield; m.p. 150–151°; λ_{max}^{MeOH} 258.5 nm (ϵ_{mM} 9.25); n.m.r. data [$(CD_3)_2SO$, Me_4Si]: δ 2.15 (s, 3, $COCH_3$), 3.51 (br d, 2, *J* 3 Hz, H-5′), 4.00 (q, 1, *J* 3 Hz, H-4′), 4.60 (d of d, 1, $J_{2',1'}$ 7 Hz, $J_{2',3'}$ 5 Hz, H-2′), 5.10 (d of d, 1, $J_{3',2'}$ 5 Hz, $J_{3',4'}$ 3 Hz, H-3′), 5.52 (d of d, 1, $J_{5,6}$ 7.5 Hz, $J_{5,3}$ 2 Hz, H-5), 5.94 (d, 1, $J_{1',2'}$ 7 Hz, H-1′), 7.56 (d, 1, *J* 7.5 Hz, H-6), and 11.15 (br s, 1, H-3).

Both **3a** and **3b** were converted in 90% yield into 2,2′-anhydro-1-(3-*O*-acetyl-β-D-arabinofuranosyl)uracil[2] upon treatment* with Amberlite IR-45 (OH^-) ion-exchange resin in methanol.

Other selective transformations of vicinal diols[1–7,10] have been explained by invoking the intermediate formation of acetoxonium ions, and the present results can likewise be explained by intermediate formation of acetoxonium ion 2. Ion 2 is then trapped by an intramolecular participation of the carbonyl group at C-2 of the uracil ring, giving **3** at low temperatures. Under more forcing conditions, the halide ion attacks C-2′ of 3 to give the ring-opened product **4** having the D-*ribo* configuration. This type of ring opening of 2,2′-anhydrouridine is well documented[8].

The presented transformation procedure is appealing, in that (*1*) the reagents needed are readily available and preparation of 2-acetoxyisobutyryl chloride or bromide is obviated[2,3], (*2*) the excess of halotrimethylsilane and the methyl trimethylsilyl ether that is generated are very volatile and are readily removed with the solvent, leaving only the



†Compound **4b** was converted into the known[10] 3′,5′-di-*O*-acetyl-2′-bromo-2′-deoxyuridine by treatment with acetic anhydride in pyridine.

*Other spectral data and physical properties were comparable to the values given in the literature.

products, and (*3*) products **3** and **4** are formed in two simple steps from uridine, the hydroxyl group on C-3′ being protected as the acetate, and the hydroxyl group on C-5′ being left free for further modifications. The pivaloyl chloride[1], acetoxyisobutyryl chloride[2], and acetyl bromide[10] procedures give deoxyhalonucleosides in which the hydroxyl groups on C-3′ and C-5′ are both protected, thus requiring an extra step for the generation of the free hydroxyl group on C-5′.

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