2′,3′-Anhydrouridine

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The previously unreported title compound 4 is readily obtained by treating 2,2′-anhydro-1-β-D-arabinofuranosyluracil 1 with sodium hydride in dry dimethyl sulfoxide at room temperature.

In the course of their early and pioneering studies on the chemistry of pyrimidine anhydronucleosides, Brown, Todd and co-workers reported[1] that when 2,2′-anhydro-1-β-d-arabinofuranosyluracil **1** washeated at 100 °C in *N*,*N*-dimethylformamide (DMF) solution with a very large excess of sodium ethanethiolate, the 3′-ethylsulfanyl derivative **2** was obtained and isolated as a colourless glass in *ca*. 55% yield. We subsequently showed that when the anhydronucleoside **1** was heated in DMF solution at 60 °C with an excess both of ethanethiol and N^1, N^1, N^3, N^3-tetramethylguanidine (TMG), 2′-deoxy-2′-(ethylsulfanyl)uridine **3** was obtained and isolated as a crystalline solid in 93% yield.

Brown *et al*.[1] rationalized their observations by suggesting that, under their reaction conditions, the 2,2′-anhydronucleoside **1** first isomerized to 2′,3′-anhydrouridine **4** which then underwent nucleophilic attack at C-3′ to give the observed product **2**. At the time of our earlier study,[2] we were unable to explain why the sodium and N^1, N^1, N^3, N^3-tetramethylguanidinium salts of ethanethiol should react in a different manner with the 2,2′-anhydronucleoside **1**, and previous attempts[3] to prepare 2′,3′-anhydrouridine **4** have been unsuccessful. We now report that when 2,2′-anhydro-1-β-d-arabinofuranosyluracil[4] **1** was treated with 1.5 equiv. of sodium hydride in dry dimethyl sulfoxide (DMSO) at room temperature for 20 min, it was virtually quantitatively converted into 2′,3′-anhydrouridine **4** which was isolated as a colourless crystalline solid† in 69% yield. The characterization of this epoxy compound **4** is based on microanalytical data (found: C, 47.63; H, 4.34; N, 12.36. $C_9H_{10}N_2O_5$ requires: C, 47.79; H, 4.46; N, 12.38%) and on ^{1}H and ^{13}C NMR spectroscopic evidence. It can be seen from Fig. 1 that the ^{13}C NMR spectra [$(CD_3)_2SO$] of 2′,3′-anhydrouridine **4** [Fig. 1(*a*)] and the previously reported[5] and much more stable 2′,3′-anhydro-1-β-d-lyxofuranosyluracil **5** [Fig. 1(*b*)] are closely similar. The comparatively high field C-2′ and C-3′ resonance signals (δ 59.5 and 58.9 for the *ribo*-compound **4**; δ 55.9 and 55.6 for the *lyxo*-compound **5**) in the ^{13}C NMR spectra of these compounds are particularly noteworthy.

When 2′,3′-anhydrouridine **4** was allowed to stand in triethylamine–methanol (1 : 9 v/v) solution at room temperature, it was quantitatively converted back into the 2,2′-anhydronucleoside **1** within 1 h. The interconversion of compounds **1** and **4** is reminiscent of the previously reported interconversion[6] of 2′,3′-anhydro-7,8-dihydro-8-oxoadenosine **6** and the isomeric 8,2′-anhydronucleoside **7**. Perhaps the reason why the preparation of 2′,3′-anhydrouridine **4** has eluded previous workers is that stringently anhydrous conditions are required if the irreversible conversion of **1** into 1-β-d-arabinofuranosyluracil **8** is to be avoided. It should be added that the preparation of 2′,3′-anhydro-3-*N*-methyluridine **9** has been reported.[7]

When 2,2′-anhydro-1-β-d-arabinofuranosyluracil **1** (1.0 mmol) was allowed to react with sodium ethanethiolate [prepared from ethanethiol (4.0 mmol) and sodium hydride (2.0 mmol)] in dry DMF (10 cm^3) solution at room temperature for

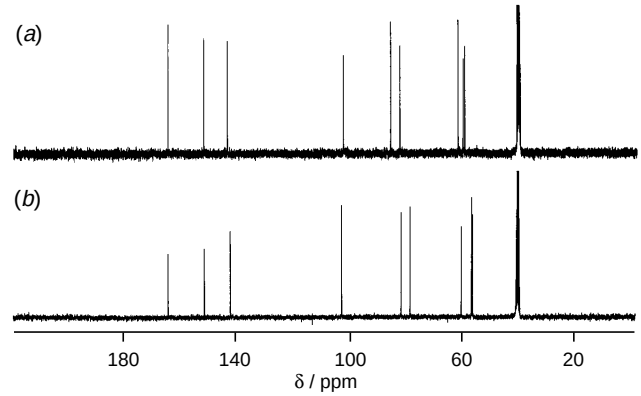
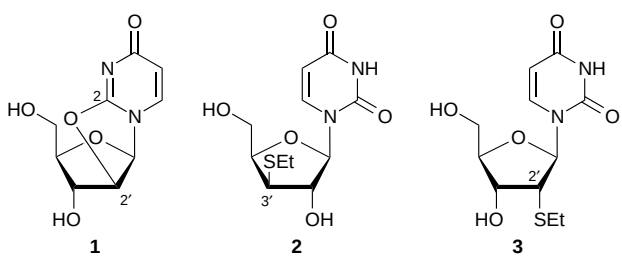
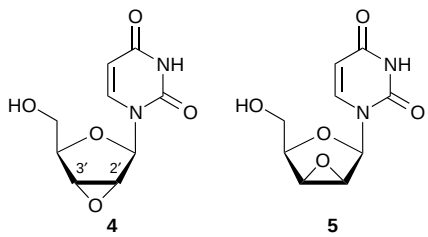
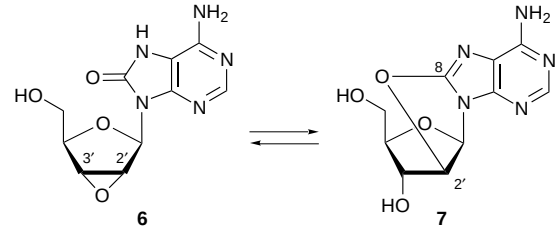
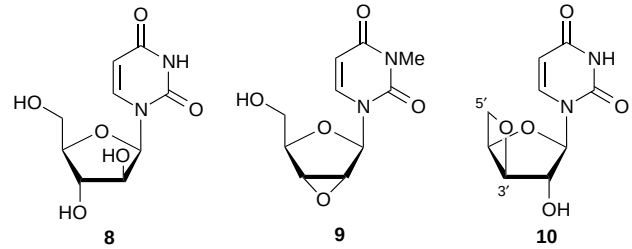


Fig. 1 ^{13}C NMR spectra in $(CD_3)_2SO$ of (*a*) 2′,3′-anhydrouridine **4** and (*b*) 2′,3′-anhydro-1-β-d-lyxofuranosyluracil **5**









18 h, 2′-deoxy-2′-(ethylsulfanyl)uridine **3** (mp 184–185 °C, lit.,[2] mp 183.5 °C) was obtained as the sole nucleoside product in 92% isolated yield. The course of this reaction corresponds with that of the previously reported[2] reaction between compound **1**, ethanethiol and TMG. However, when the 2,2′-anhydronucleoside **1** (1.0 mmol) was first treated with sodium hydride (4.0 mmol) in DMF (10 cm^3) for 2 h at room temperature and then, following the addition of ethanethiol (2.0 mmol), the reactants were stirred at room temperature for a further period of 18 h, the 3′-ethylsulfanyl derivative **2** (mp 130–132 °C)‡ was obtained in 90% isolated yield. It would therefore seem likely that the discrepancy between the results obtained by us in our previous study[2] and by Brown *et al*.[1] was due to the latter workers' sodium ethanethiolate being contaminated with a strong base (*e.g*. sodium methoxide). Finally, when the 2,2′-anhydronucleoside **1** was heated at 60 °C for 18 h with a five-fold excess of sodium hydride in dry *N*,*N*-dimethylacetamide in the absence of an additional nucleophile, 3′,5′-anhydro-1-β-d-xylofuranosyluracil **10** [mp 214–217 °C (decomp.), lit.,[8] mp 214–216 °C] was obtained and isolated in 62% yield. The fact that 2,2′-anhydro-1-β-d-arabinofuranosyluracil **1** can so easily be converted *in situ* into the isomeric 2′,3′-epoxide **4** makes it a particularly versatile synthetic intermediate.

Footnotes

† It was not possible to determine the melting point of 2′,3′-anhydrouridine **4** as, on heating, it isomerized back to 2,2′-anhydro-1-β-d-arabinofuranosyluracil **1** before it melted. Compounds **1** and **4** have R_f = 0.12 and 0.44, respectively, in chloroform–methanol (85 : 15 v/v).

‡ Found: C, 45.80; H, 5.58; N, 9.65. Calc. for $C_{11}H_{16}N_2O_5S$: C, 45.82; H, 5.59; N, 9.72%; δ_H [$(CD_3)_2SO$] 1.19 (3 H, t, *J* 7.4 Hz), 2.60 (2 H, quart, *J* 7.4 Hz), 3.36 (1 H, m), 3.64 (2 H, m), 4.11 (1 H, m), 4.29 (1 H, m), 5.06 (1 H, t, *J* 4.4 Hz), 5.69 (2 H, m), 5.82 (1 H, d, *J* 5.6 Hz), 7.93 (1 H, d, *J* 8.1 Hz), 11.34 (1 H, br s); δ_C [$(CD_3)_2SO$] 15.2, 26.1, 50.4, 61.4, 78.5, 80.3, 87.8, 101.9, 140.9, 150.9, 163.1; R_f 0.50 in chloroform–methanol (85 : 15 v/v) (the R_f of the 2′-ethylsulfanyl isomer **3** is 0.43 in the same solvent system).

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