2′,3′-Anhydrouridine. A useful synthetic intermediate

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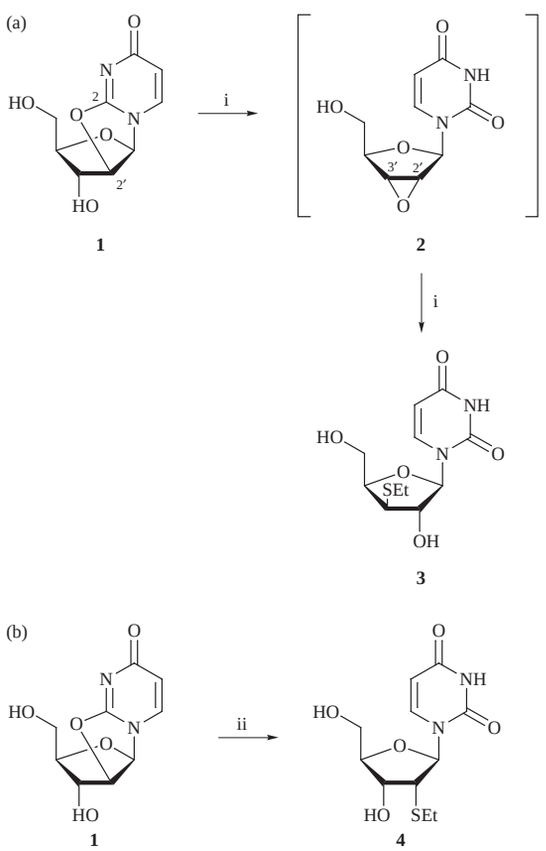
2,2′-Anhydro-1-(β-D-arabinofuranosyl)uracil **1** reacts with sodium hydride in dry DMSO to give 2′,3′-anhydrouridine **2**. When the latter compound **2** is heated below its melting point or treated with triethylamine in methanol, it isomerises back to the 2,2′-anhydronucleoside **1**. Treatment of compound **1** with sodium ethanethiolate or the sodium salt of benzyl mercaptan in the presence of an excess of the corresponding thiol in DMA gives 2′-*S*-ethyl- or 2′-*S*-benzyl-2′-thiouridine (**4** or **11**) in high yield; however, treatment of the 2,2′-anhydronucleoside **1** first with sodium hydride in DMA and then with a deficiency (with respect to sodium hydride) of ethanethiol or benzyl mercaptan gives the corresponding 3′-*S*-ethyl or 3′-*S*-benzyl derivative (**3** or **12**) in high yield. When the 2,2′-anhydronucleoside **1** is allowed to react with an excess of potassium *tert*-butoxide in DMSO, the 3′,5′-anhydronucleoside **13** is obtained in good yield. The latter compound **13** undergoes hydrolysis in aqueous trifluoroacetic acid to give 1-(β-D-xylofuranosyl)uracil **14** in high yield. The 3′-*S*-benzyl derivative **12** is converted by Raney nickel desulfurisation into 3′-deoxyuridine **15** which, in turn, is converted into 3′-deoxycytidine **17** in good yield. X-Ray crystallographic data relating to compounds **11** and **12** are also reported.

Introduction

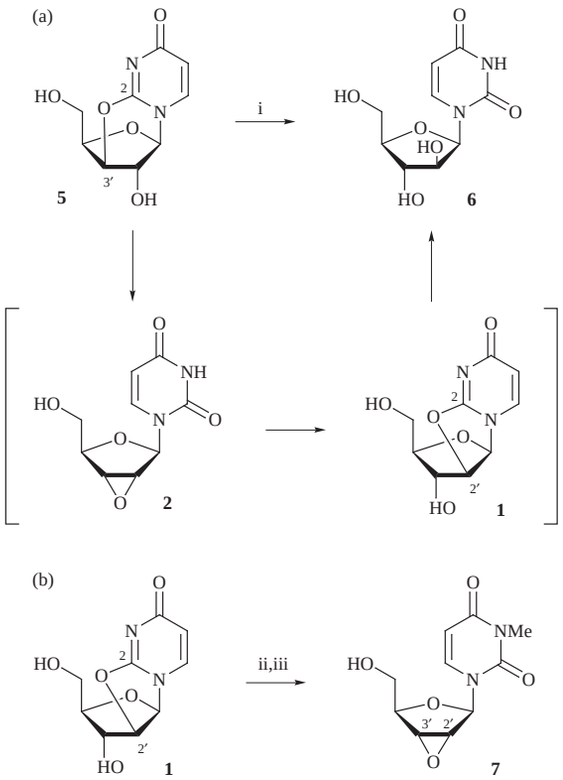
In the course of their early and pioneering studies on anhydronucleoside chemistry, Brown, Todd and their co-workers[1] reported that when 2,2′-anhydro-1-(β-D-arabinofuranosyl)-uracil **1** was heated with a large excess of sodium ethanethiolate in DMF solution at 100 °C, the 3′-ethylsulfanyl derivative **3** was obtained and isolated as a glass in 55% yield. Brown *et al.*[1] rationalised this observation by invoking the intermediacy of 2′,3′-anhydrouridine **2** (Scheme 1a). Many years later, we found[2] that when the 2,2′-anhydronucleoside **1** was heated with an excess of ethanethiol and N^1,N^1,N^3,N^3-tetramethylguanidine in DMF solution at 60 °C for 12 h (Scheme 1b), 2′-*S*-ethyl-2′-thiouridine **4** was obtained and was isolated as a crystalline solid in 93% yield.

At the time of our own study,[2] we were unable to explain why the products of the reactions between the N^1,N^1,N^3,N^3-tetramethylguanidinium and sodium salts of ethanethiol and the anhydronucleoside **1** should differ. Indeed, the earlier result[1] was surprising in that a 'soft' nucleophile such as the conjugate base of ethanethiol would be expected to attack the anhydronucleoside **1** at C-2′ (Scheme 1b), and furthermore ethanethiolate ion (pK_a 10.5) would be expected to be too weakly basic to remove a proton from the 3′-hydroxy function of the anhydronucleoside **1**, and thereby promote its conversion (Scheme 1a) into the isomeric epoxide **2**. However, further convincing evidence was obtained in support of the existence of 2′,3′-anhydrouridine **2** as a reaction intermediate.

In 1979, Buchanan and Clark reported[3] that when 2,3′-anhydro-1-(β-D-xylofuranosyl)uracil **5** was heated with an excess of sodium *tert*-butoxide in DMF, 1-(β-D-arabinofuranosyl)uracil **6** was obtained, amongst other products, in 45% isolated yield. This result can perhaps best be rationalised by invoking (Scheme 2a) the intermediacy both of 2′,3′-anhydrouridine **2** and 2,2′-anhydro-1-(β-D-arabinofuranosyl)-uracil **1**. A small quantity of the latter 2,2′-anhydronucleoside **1** was indeed also isolated from the products. In another study,[4] more direct evidence was obtained for the existence of 2′,3′-anhydrouridine **2** as a reaction intermediate. When the 2,2′-anhydronucleoside **1** was treated first with sodium methoxide in methanol and the residue obtained after evaporation of the products was allowed to react with methyl iodide in DMSO (Scheme 2b), 2′,3′-anhydro-3-methyluridine **7** was obtained[4] and isolated in 48% yield. We now report the preparation and isolation of 2′,3′-anhydrouridine **2**, and describe its use as a synthetic intermediate. This study has already been published in part, in a preliminary form.[5]



Scheme 1 *Reagents and conditions*: i, NaSEt, DMF, 100 °C, 22 h; ii, EtSH, $(Me_2N)_2C{=}NH$, DMF, 60 °C, 12 h.



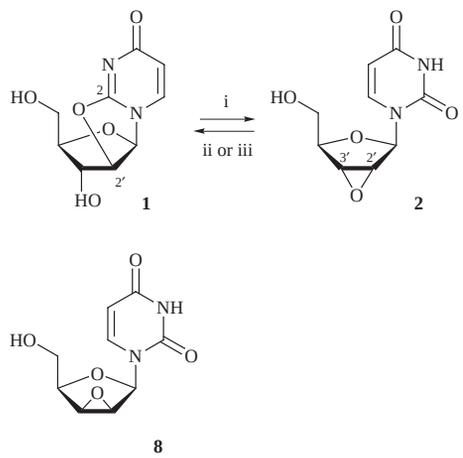
Scheme 2 *Reagents and conditions*: i, (a) NaOBu^t, DMF, 100 °C, 48 h; (b) Dowex 50 (NH_4^+), water; ii, NaOMe, MeOH, rt, 15 min; iii, MeI, DMSO, rt to 60 °C.

Results and discussion

2,2′-Anhydro-1-(β-D-arabinofuranosyl)uracil **1** may be prepared[6] in high yield by heating uridine with diphenyl carbonate in the presence of a catalytic quantity of sodium hydrogen carbonate in HMPA at 150 °C. As HMPA is expensive and possibly also carcinogenic, we have investigated the use of DMF as the solvent in this reaction. When uridine was heated with 1.1 mol equiv. of diphenyl carbonate and 5 mol% of sodium hydrogen carbonate in DMF (~1.0 cm^3 g^{-1} of uridine) at 100 °C for 4 h, it was quantitatively converted into the anhydronucleoside **1**. Hampton and Nichol[7] had previously reported that 2,2′-anhydro-1-(β-D-arabinofuranosyl)uracil **1** was obtained in only 59% yield when DMF was used as solvent.

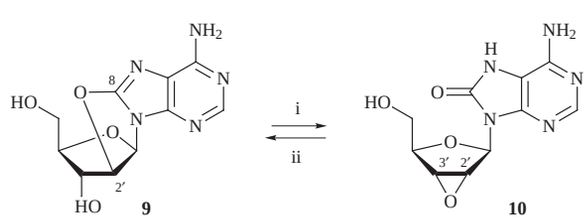
In a preliminary experiment, 2,2′-anhydro-1-(β-D-arabinofuranosyl)uracil **1** was treated with 1.5 mol equiv. of sodium hydride in [$^2H_6$]DMSO at rt in an NMR tube. After 10 min, the resonance signals assignable to the starting material **1** had completely disappeared, and it was clear from the resulting ^{13}C NMR spectrum (δ_C 59.1, 59.5, 61.4, 80.9, 85.3, 102.6, 139.6, 158.2 and 174.7) that a single product had been obtained. The relatively high-field resonance signals at δ_C 59.5 and 59.1, which were assigned to C-2′ and C-3′, suggested that the product was indeed 2′,3′-anhydrouridine **2**. It is particularly noteworthy that the signals assignable to the resonances of C-2′ and C-3′ in the ^{13}C NMR spectrum (in [$^2H_6$]DMSO) of the isomeric but much more stable 2′,3′-anhydro-1-(β-D-lyxofuranosyl)uracil[8] **8** are found[5] at δ_C 56.3 and 56.0. A preparative experiment (Scheme 3) was then carried out. 2,2′-Anhydro-1-(β-D-arabinofuranosyl)uracil **1** was treated with sodium hydride in very dry DMSO† at rt. After quenching the reaction with solid carbon dioxide, the products were fractionated by short-column chromatography on silica gel to give 2′,3′-anhydrouridine **2** as a solid in 69% isolated yield. The latter compound **2** was characterised by ^1H and ^{13}C NMR spectroscopy and, following recrystallisation from absolute ethanol, by elemental analysis. It is further noteworthy that the R_f-values [in chloroform–methanol (85:15 v/v), see Experimental section] of 2′,3′-anhydrouridine **2** and the corresponding *lyxo*-isomer[8] **8** are very closely similar.

† It is absolutely essential that the reaction solution should be strictly anhydrous. The presence of water leads to the irreversible conversion of the substrate **1** into 1-(β-D-arabinofuranosyl)uracil **6**.



Scheme 3 *Reagents and conditions*: i, (a) NaH, DMSO, rt, 20 min; (b) solid CO_2; ii, heat slowly to ~160 °C; iii, Et_3N–MeOH (1:9 v/v), rt, 1 h.

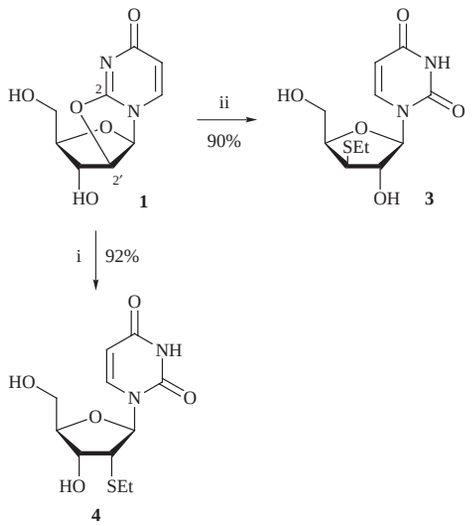
Although we have succeeded in isolating and characterising 2′,3′-anhydrouridine **2**, it is a relatively unstable compound. For example, it is not possible to determine its melting point; when it is heated slowly to ~160 °C, it is quantitatively converted (Scheme 3) in the solid state back into 2,2′-anhydro-1-(β-D-arabinofuranosyl)uracil **1** which subsequently melts at its normal melting point (*i.e.*, 234–237 °C). 2′,3′-Anhydrouridine **2** is also readily converted back into 2,2′-anhydro-1-(β-D-arabinofuranosyl)uracil **1** by treating it with triethylamine in methanol at rt (Scheme 3). The interconversion of isomers **1** and **2** is reminiscent of the previously reported[9] interconversion of 8,2′-anhydro-[9-(β-D-arabinofuranosyl)-8-hydroxyadenine] **9** and 2′,3′-anhydro-7,8-dihydro-8-oxoadenosine **10** (Scheme 4). Thus



Scheme 4 *Reagents and conditions*: i, 1.25 mol equiv. NaOH, aq. DMSO, rt, 12 min; ii, morpholine, DMSO, 78 °C, 19 h.

when the 8,2′-anhydronucleoside **9** is treated with a slight excess of sodium hydroxide in aq. DMSO at rt, the isomeric 2′,3′-epoxide **10** is obtained. However, when the epoxide **10** is heated with an excess of morpholine in dry DMSO, it is converted back into the 8,2′-anhydronucleoside **9**.

Now that we had succeeded in preparing and characterising 2′,3′-anhydrouridine **2**, we undertook a re-examination of the reaction between 2,2′-anhydro-1-(β-D-arabinofuranosyl)uracil **1** and sodium ethanethiolate. In the first experiment (Scheme 5, reaction i), ethanethiol (4.0 mmol) was allowed to react with a deficiency of sodium hydride (2.0 mmol) in *N*,*N*-dimethylacetamide (DMA) at rt. After 5 min, 2,2′-anhydro-1-(β-D-arabinofuranosyl)uracil **1** (1.0 mmol) was added, and the reaction was allowed to proceed at rt for 18 h. The products were worked up and fractionated by short-column chromatography on silica gel to give 2′-*S*-ethyl-2′-thiouridine[2] **4** as the sole nucleoside product in 92% isolated yield. Thus, not surprisingly, both the sodium and N^1,N^1,N^3,N^3-tetramethylguanidinium



Scheme 5 *Reagents and conditions*: i, [reagent prepared from EtSH (4 mol equiv.) and sodium hydride (2 mol equiv.), DMA, rt, 5 min], DMA, rt, 18 h; ii, (a) NaH (4 mol equiv.), DMA, rt, 2 h; (b) EtSH (2 mol equiv.), rt, 18 h.

salts of ethanethiol react with 2,2′-anhydro-1-(β-D-arabinofuranosyl)uracil **1** to give the same product. However, when the latter compound **1** (1.0 mmol) was allowed to react first with sodium hydride (4.0 mmol) in DMA at rt for 2 h and, after ethanethiol (2.0 mmol; a deficiency with respect to sodium hydride) had been added, the reaction was allowed to proceed at rt for a further period of 18 h, 1-(3-*S*-ethyl-3-thio-β-D-xylofuranosyl)uracil[1] **3** was obtained as the sole nucleoside product, and was isolated as a solid in 90% yield. Therefore, a possible explanation of the results reported[1] by Brown *et al.* is as follows. Ethanethiol (bp 35 °C) is extremely volatile. If its sodium salt were prepared first by adding ethanethiol to a solution of sodium alkoxide in the corresponding alcohol (*e.g.*, sodium methoxide in methanol or sodium ethoxide in ethanol) and then removing the solvent by evaporation, it is not improbable that the sodium ethanethiolate obtained would be contaminated with sodium alkoxide. Brown *et al.*[1] heated 2,2′-anhydro-1-(β-D-arabinofuranosyl)uracil **1** with a large excess of sodium ethanethiolate in DMF at 100 °C for a total period of 22 h. It is not unlikely that the substrate **1** reacted first with contaminating sodium alkoxide to give 2′,3′-anhydrouridine **2** which then reacted with sodium ethanethiolate to give the 3′-*S*-ethyl compound **3**.

Clearly, due to its volatility, ethanethiol is not a particularly convenient reagent to work with. We therefore undertook a corresponding study with benzyl mercaptan (bp 194–195 °C). When 2,2′-anhydro-1-(β-D-arabinofuranosyl)uracil **1** (1 mol equiv.) was treated at rt for 24 h with the reagent prepared from benzyl mercaptan (toluene-α-thiol) (4 mol equiv.) and sodium hydride (2 mol equiv.) (*cf.* Scheme 5, reaction i), 2′-*S*-benzyl-2′-thiouridine **11** was obtained in 93% isolated yield. However, when 2,2′-anhydro-1-(β-D-arabinofuranosyl)uracil **1** (1 mol equiv.) was treated, first, with sodium hydride (3 mol equiv.) in DMA at rt for 2 h and then with benzyl mercaptan (2 mol equiv.) in DMA at rt for 1.5 h (*cf.* Scheme 5, reaction ii), the isomeric 3′-*S*-benzyl derivative **12** was obtained in 88% isolated yield. The comparatively rapid reaction between the conjugate base of benzyl mercaptan and the intermediate 2′,3′-anhydrouridine **2** is particularly noteworthy. Compounds **11** and **12** were characterised by ^{1}H and ^{13}C NMR spectroscopy, and by elemental analysis. Their structures were further confirmed by X-ray crystal-structure analysis (Fig. 1). The structures of both compounds **11** and **12** were solved by the routine use of direct methods and were refined by full-matrix least-squares methods[10] using a riding model for hydrogen-atom positions. For compound **11**, the final *R*-factor was 0.0482 for

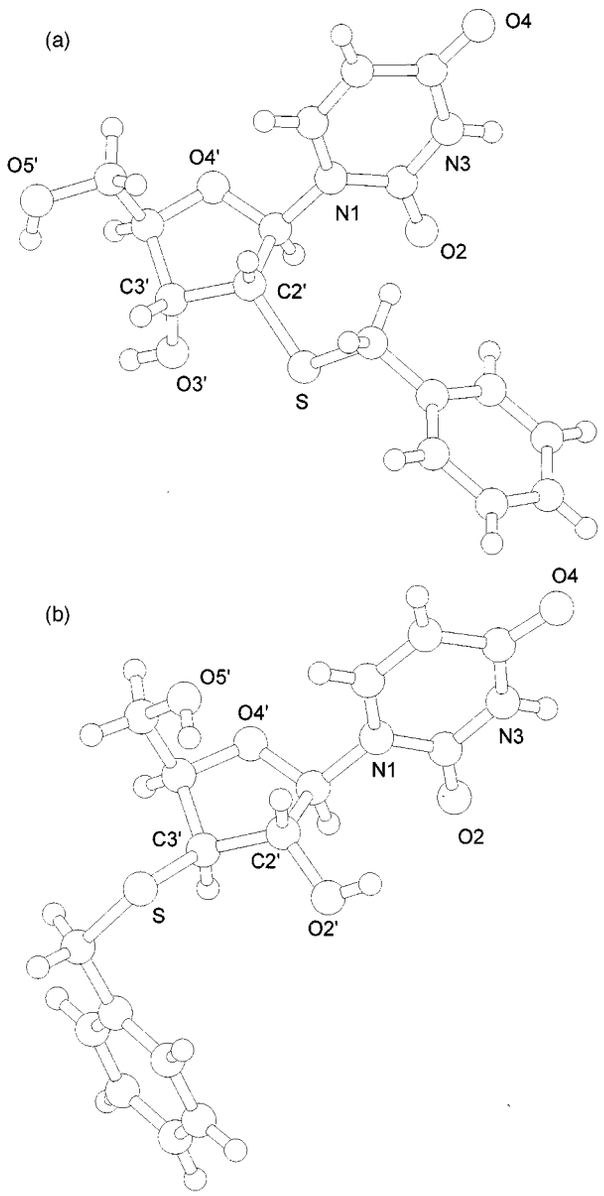
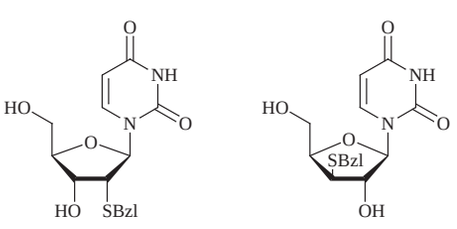


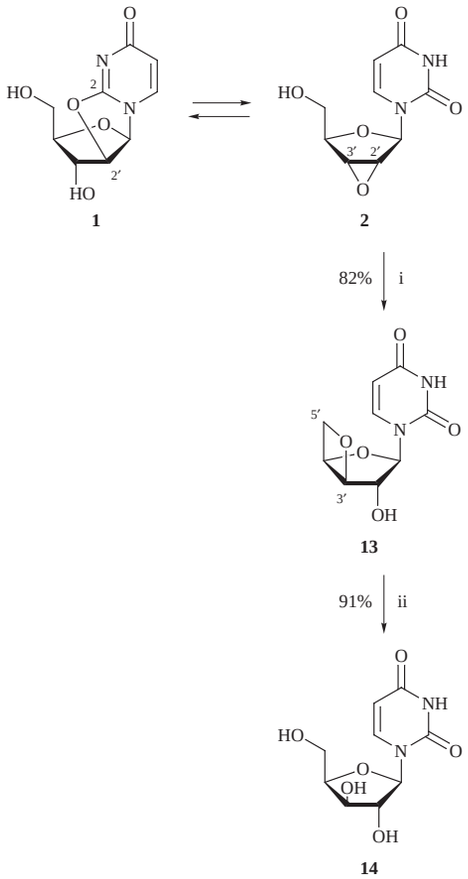
Fig. 1 Computer-drawn plots of the molecular structures of (a) 2′-*S*-benzyl-2′-thiouridine **11** and (b) 1-(3-*S*-benzyl-3-thio-β-D-xylofuranosyl)uracil **12**.



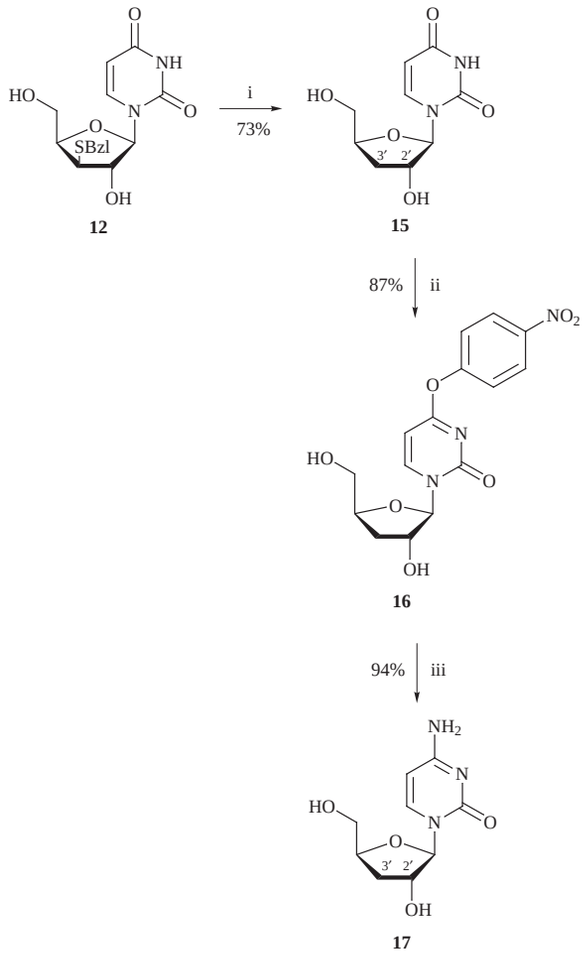
Bzl = CH_2Ph

1542 statistically significant reflections; for compound **12**, *R* was 0.0482 for 1672 significant reflections.

The value of 2′,3′-anhydrouridine **2** as a synthetic intermediate was further illustrated when it was generated in the absence of an external nucleophile. Thus, when the anhydro-arabinoside **1** was treated with a slightly greater than two-fold excess of potassium *tert*-butoxide in dry DMSO at rt for 48 h (Scheme 6), 3′,5′-anhydro-1-(β-D-xylofuranosyl)uracil **13** was obtained in 82% isolated yield. Although the preparation of the latter compound **13** has been reported in two previous publications,[11,12] the procedures described involved relatively inaccessible start-



Scheme 6 *Reagents and conditions*: i, KOBu^t, DMSO, rt, 48 h; ii, TFA–H_2O (1 : 4 v/v), 50 °C, 18 h.



Scheme 7 *Reagents and conditions*: i, Raney nickel, water, 75 °C, 1 h; ii, (a) Me_3SiCl, 1-methylpyrrolidine, rt, 1 h; (b) TFAA, 0 °C, 35 min; (c) 4-nitrophenol, 0 °C, 3 h; iii, conc. aq. NH_3 (*d* 0.88), 1,4-dioxane, 50 °C, 24 h.

ing materials and only milligram quantities of the 3′,5′-anhydro-xyloside **13** were obtained. Both groups of workers[11,12] obtained paper chromatographic and electrophoretic evidence which indicated that when the anhydro-xyloside **13** was heated in dil. aq. sulfuric acid, it was converted into 1-(β-D-xylofuranosyl)uracil **14**. We now report that when 3′,5′-anhydro-1-(β-D-xylofuranosyl)uracil **13** was heated in 20% aq. TFA at 50 °C for 18 h (Scheme 6), it was quantitatively converted into 1-(β-D-xylofuranosyl)uracil **14**. The latter compound **14**, identical with authentic material,[13] was isolated as a crystalline solid in 91% yield. Although the two-step conversion of uridine into 1-(β-D-arabinofuranosyl)uracil[14] **6** (*via* the 2,2′-anhydronucleoside **1**, Scheme 2) and the conversion of uridine into 1-(β-D-lyxofuranosyl)uracil[15] both involve straightforward procedures, we are unaware of any previously reported convenient and efficient method for the conversion[16] of uridine into the corresponding xyloside **14**. In our opinion, the fact that the very readily accessible anhydro-*arabinoside* **1** can be converted reversibly into the anhydro-*riboside* **2** (Schemes 3 and 6) and also irreversibly into the anhydro-*xyloside* (Scheme 6) is a particularly interesting aspect of nucleoside chemistry.

Finally, in order further to illustrate the value of 2′,3′-anhydrouridine **2** as a synthetic intermediate, we undertook the preparation of 3′-deoxyuridine **15** and 3′-deoxycytidine **17**. While 3′-deoxyuridine **15** had been prepared by Brown *et al.*[1] in very low (~3.3%) isolated yield from 1-(3-*S*-ethyl-3-thio-β-D-xylofuranosyl)uracil **3**, and then by Kowollik and Langen[17] by a much longer route involving the relatively inaccessible 2,3′-anhydro-1-(β-D-xylofuranosyl)uracil[16] **5**, 3′-deoxycytidine **17** had, to the best of our knowledge, been prepared previously[18] only by coupling together appropriate 3-deoxy-D-ribose and cytosine derivatives. We now report that when 1-(3-*S*-benzyl-3-thio-β-D-xylofuranosyl)uracil **12** was heated with Raney nickel in water at 75 °C for 1 h (Scheme 7), 3′-deoxyuridine **15** was obtained and isolated in 73% yield. This represents an overall yield of ~64% for the three steps starting from uridine. In a one-pot reaction (Scheme 7, reaction ii), 3′-deoxyuridine **15** was trimethylsilylated, the product activated with TFAA[19] and then treated with 4-nitrophenol[20] to give 1-(3-deoxy-β-D-*erythro*-pentofuranosyl)-4-(4-nitrophenoxy)pyrimidin-2(1*H*)-one **16** as a crystalline solid in 87% isolated yield. When the latter intermediate **16** was heated with ammonia in aq. 1,4-dioxane at 50 °C for 24 h, 3′-deoxycytidine **17** was obtained and isolated in 94% yield. It is anticipated that a variety of 3′-deoxynucleoside analogues could be prepared in high yield from the 4-*O*-(4-nitrophenyl) derivative **16**.

Experimental

Mps were measured with a Büchi melting point apparatus and are uncorrected. ^{1}H NMR spectra, unless otherwise stated, were measured at 360 MHz with a Bruker AM 360 spectrometer. ^{13}C NMR spectra were measured at 90.6 MHz with the same spectrometer. Tetramethylsilane was used as the internal standard, and *J*-values are given in Hz. Sonications were performed with a Kerry PUL S5 ultrasonic bath. Merck silica gel 60 F_{254} plates were developed in solvent system A [chloroform–methanol (85 : 15 v/v)]. Merck Kieselgel H (Art. 7729) was used for short-column chromatography. Diethyl ether was dried over sodium wire and was then distilled; acetonitrile and pyridine were dried by heating, under reflux, over calcium hydride and were then distilled; DMA, DMF and DMSO were dried by distillation over calcium hydride under reduced pressure. X-Ray crystallographic data on compounds **11** and **12** were collected by the EPSRC National Crystallographic Service. Both compounds crystallised in space group

$P2_12_12_1$ with cell dimensions for compound **11** of $a = 6.916(2)$, $b = 10.265(1)$ and $c = 23.124(5)$ Å, and for compound **12** of $a = 5.368(1)$, $b = 12.508(2)$ and $c = 24.903(8)$ Å. Intensity data for both structures were collected on an Enraf–Nonius FAST detector using Cu-Kα radiation from a rotating-anode source and an ω-scan technique. Data collection and processing used the MADNES program.[21] A total of 7062 reflections were measured for compound **11** which reduced to 2542 independent reflections, of which 1529 had $I > 2\sigma(I)$. A total of 7114 were measured for compound **12**, which reduced to 2533 independent reflections, of which 1672 had $I > 2\sigma(I)$.‡

2,2′-Anhydro-1-(β-D-arabinofuranosyl)uracil 1

Uridine (9.77 g, 40.0 mmol), diphenyl carbonate (9.43 g, 44.0 mmol), sodium hydrogen carbonate (0.17 g, 2.0 mmol) and DMF (10 cm^3) were heated together, with stirring, at 100 °C. After 4 h, the products were cooled to rt and diethyl ether (200 cm^3) was added, with stirring. After a further period of 2 h, the products were filtered and the residual 2,2′-anhydro-1-(β-D-arabinofuranosyl)uracil **1** was washed with diethyl ether (100 cm^3). The resulting off-white solid (9.35 g) had mp 234–237 °C (lit.,[7] 238–244 °C); R_f 0.12 (system A); $\delta_H[(CD_3)_2SO]$ 3.17 (1 H, m), 3.27 (1 H, m), 4.06 (1 H, m), 4.37 (1 H, s), 4.98 (1 H, t, *J* 5.0), 5.19 (1 H, d, *J* 5.7), 5.83 (1 H, d, *J* 7.5), 5.89 (1 H, br), 6.30 (1 H, d, *J* 5.7) and 7.83 (1 H, d, *J* 7.4); $\delta_C[(CD_3)_2SO]$ 60.9, 74.8, 88.8, 89.3, 90.1, 108.7, 137.0, 159.9 and 171.4.

2′,3′-Anhydrouridine 2

(a) An NMR tube containing 2,2′-anhydro-1-(β-D-arabinofuranosyl)uracil **1** (0.045 g, 0.2 mmol), sodium hydride (60% dispersion in mineral oil; 0.012 g, 0.3 mmol) and [$^2H_6$]DMSO (1.0 cm^3) was sonicated at rt. After 10 min, the ^{13}C NMR spectrum displayed the following resonance signals: δ_C 59.1, 59.5, 61.4, 80.9, 85.3, 102.6, 139.6, 158.2, 174.7. Except for the last three resonance signals this spectrum was closely similar to that of pure 2′,3′-anhydrouridine (see below). No remaining 2,2′-anhydro-1-(β-D-arabinofuranosyl)uracil **1** could be detected.

(b) 2,2′-Anhydro-1-(β-D-arabinofuranosyl)uracil **1** (0.45 g, 2.0 mmol), sodium hydride (60% dispersion in mineral oil; 0.12 g, ~3 mmol) and dry DMSO (5 cm^3) were stirred together at rt. After 20 min, solid carbon dioxide (~1 g) was added to the resulting clear solution. Stirring was continued for a further period of 10 min, and then toluene (25 cm^3) was added to the products. The mixture obtained was applied to a column of silica gel (3 cm × 5 cm diameter) which was then eluted with dichloromethane–methanol (95 : 5 to 90 : 10 v/v). Concentration of the appropriate fractions gave the *title compound* **2** as a solid (0.31 g, 69%) (Found, in material recrystallised from absolute ethanol: C, 47.6; H, 4.3; N, 12.4. $C_9H_{10}N_2O_5$ requires C, 47.79; H, 4.46; N, 12.38%), mp 234–237 °C [see conversion of 2′,3′-anhydrouridine **2** into 2,2′-anhydro-1-(β-D-arabinofuranosyl)-uracil **1** below]; R_f 0.44 (system A) [2′,3′-anhydro-1-(β-D-lyxofuranosyl)uracil **8** has R_f 0.43 (system A)]; $\delta_H[(CD_3)_2SO]$ 3.58 (2 H, d, *J* 4.5), 4.07 (1 H, d, *J* 2.6), 4.10 (1 H, t, *J* 5.4), 4.20 (1 H, d, *J* 2.6), 5.16 (1 H, br), 5.59 (1 H, d, *J* 8.0), 5.83 (1 H, s), 7.85 (1 H, d, *J* 8.1) and 11.38 (1 H, br); $\delta_C[(CD_3)_2SO]$ 58.9, 59.5, 61.2, 81.8, 85.0, 101.7, 142.6, 151.0 and 163.6. {2′,3′-Anhydro-1-(β-D-lyxofuranosyl)uracil **8** has $\delta_H[(CD_3)_2SO]$ 3.56 (2 H, m), 4.00 (2 H, m), 4.08 (1 H, m), 5.01 (1 H, br), 5.66 (1 H, d, *J* 8.1), 6.03 (1 H, s), 7.60 (1 H, d, *J* 8.2) and 11.42 (1 H, br); and $\delta_C[(CD_3)_2SO]$ 56.0, 56.3, 59.9, 78.1, 81.3, 102.4, 141.7, 150.8 and 163.4}.

‡ Full crystallographic details, excluding structure factor tables, have been deposited at the Cambridge Crystallographic Data Centre (CCDC). For details of the deposition scheme, see 'Instructions for Authors', *J. Chem. Soc.*, *Perkin Trans. 1*, available *via* the RSC Web page (http://www.rsc.org/authors). Any request to the CCDC for this material should quote the full literature citation and the reference number 207/250.

Conversion of 2′,3′-anhydrouridine 2 into 2,2′-anhydro-1-(β-D-arabinofuranosyl)uracil 1

(a) 2′,3′-Anhydrouridine **2** (~0.001 g), contained in a capillary tube, was slowly heated to ~160 °C. The resulting solid was allowed to cool to rt, and was found to have R_f 0.12 (system A). In a separate experiment, the material was found to have mp 234–237 °C.

(b) 2′,3′-Anhydrouridine **2** (0.045 g, 0.2 mmol) was added, with stirring, to a solution of triethylamine (1.0 cm^3) in methanol (9 cm^3) at rt. After 1 h, the products were evaporated under reduced pressure to give a solid (0.045 g, 100%) that was identical [^1H and ^{13}C NMR; TLC (system A)] with 2,2′-anhydro-1-(β-D-arabinofuranosyl)uracil **1**.

2′-*S*-Ethyl-2′-thiouridine 4

Ethanethiol (0.3 cm^3, 4.00 mmol), sodium hydride (60% dispersion in mineral oil; 0.08 g, 2.0 mmol) and dry DMA (10 cm^3) were stirred together at rt for 5 min. 2,2′-Anhydro-1-(β-D-arabinofuranosyl)uracil **1** (0.226 g, 1.0 mmol) was added to the resulting clear solution, and the reactants were stirred at rt. After 18 h, solid carbon dioxide (~0.5 g) was added, and the products were evaporated (bath temperature ~100 °C) under reduced pressure. The residue was fractionated by short-column chromatography on silica gel; the appropriate fractions, which were eluted with dichloromethane–methanol (96 : 4 to 92 : 8 v/v), were evaporated under reduced pressure to give the *title compound* **4** as a solid (0.265 g, 92%) (Found, in material recrystallised from absolute ethanol: C, 45.6; H, 5.6; N, 9.7. $C_{11}H_{16}N_2O_5S$ requires C, 45.82; H, 5.59; N, 9.72%), mp 184–185 °C (lit.,[2] 183.5 °C); R_f 0.43 (system A); $\delta_H[(CD_3)_2SO]$ 1.10 (3 H, t, *J* 7.4), 2.45 (2 H, m), 3.42 (1 H, dd, *J* 5.2 and 8.7), 3.57 (2 H, m), 3.87 (1 H, m), 4.17 (1 H, m), 5.15 (1 H, t, *J* 5.2), 5.61 (1 H, d, *J* 5.3), 5.71 (1 H, d, *J* 8.1), 6.01 (1 H, d, *J* 8.8), 7.89 (1 H, d, *J* 8.1) and 11.40 (1 H, br s); $\delta_C[(CD_3)_2SO]$ 15.1, 24.6, 51.6, 61.4, 72.1, 86.6, 87.5, 102.4, 140.4, 150.8 and 162.9.

1-(3-*S*-Ethyl-3-thio-β-D-xylofuranosyl)uracil 3

2,2′-Anhydro-1-(β-D-arabinofuranosyl)uracil **1** (0.226 g, 1.0 mmol), sodium hydride (60% dispersion in mineral oil; 0.16 g, 4.0 mmol) and dry DMA (10 cm^3) were stirred together at rt for 2 h. Ethanethiol (0.15 cm^3, 2.0 mmol) was then added, with continued stirring. After 18 h, solid carbon dioxide (~1 g) was added and the products were concentrated (bath temperature ~100 °C) under reduced pressure. The residue was fractionated by short-column chromatography on silica gel; the appropriate fractions, which were eluted with dichloromethane–methanol (96 : 4 to 92 : 8 v/v), were evaporated under reduced pressure to give the *title compound* **3** as a solid (0.260 g, 90%) (Found, in material recrystallised from ethyl acetate; C, 45.8; H, 5.6; N, 9.65. $C_{11}H_{16}N_2O_5S$ requires C, 45.82; H, 5.59; N, 9.72%), mp 130–132 °C; R_f 0.50 (system A); $\delta_H[(CD_3)_2SO]$ 1.19 (3 H, t, *J* 7.4), 2.60 (2 H, quart, *J* 7.4), 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), 5.69 (2 H, m), 5.82 (1 H, d, *J* 5.6), 7.93 (1 H, d, *J* 8.1) and 11.34 (1 H, br s); $\delta_C[(CD_3)_2SO]$ 15.2, 26.1, 50.4, 61.4, 78.5, 80.3, 87.8, 101.9, 140.9, 150.9 and 163.1.

2′-*S*-Benzyl-2′-thiouridine 11

Benzyl mercaptan (4.70 cm^3, 40 mmol), sodium hydride (60% dispersion in mineral oil; 0.80 g, 20 mmol) and dry DMA (25 cm^3) were stirred together at rt for 10 min. 2,2′-Anhydro-1-(β-D-arabinofuranosyl)uracil **1** (2.26 g, 10.0 mmol) was added to the resulting clear solution, and the reactants were stirred at rt. After 24 h, acetic acid (2.0 cm^3) was added, and the products were evaporated (bath temperature ~100 °C) under reduced pressure. The residue was fractionated by short-column chromatography on silica gel; the appropriate fractions, which were eluted with toluene, dichloromethane, and then with

dichloromethane–methanol (100:0 to 90:10 v/v), were evaporated under reduced pressure to give the *title compound* **11** as a glass (3.27 g, 93%) (Found, in material crystallised from ethyl acetate: C, 54.6; H, 5.1; N, 7.9. $C_{16}H_{18}N_2O_5S$ requires C, 54.85; H, 5.18; N, 7.99%), mp 186–189 °C; R_f 0.60 (system A); δ_H[$(CD_3)_2SO$] 3.37 (1 H, m), 3.56 (2 H, m), 3.71 (2 H, dd, *J* 13.1 and 17.0), 3.89 (1 H, m), 4.18 (1 H, m), 5.11 (1 H, br), 5.58 (1 H, d, *J* 8.1), 5.67 (1 H, d, *J* 5.3), 6.07 (1 H, d, *J* 8.5), 7.24 (5 H, m), 7.72 (1 H, d, *J* 8.1) and 11.35 (1 H, br s); δ_C[$(CD_3)_2SO$] 34.5, 51.8, 61.3, 71.8, 86.6, 87.5, 102.4, 126.9, 128.4, 128.6, 138.1, 140.0, 150.7 and 162.9.

1-(3-*S*-Benzyl-3-thio-β-D-xylofuranosyl)uracil 12

2,2′-Anhydro-1-(β-D-arabinofuranosyl)uracil **1** (2.26 g, 10.0 mmol), sodium hydride (60% dispersion in mineral oil; 1.20 g, 30 mmol) and dry DMA (25 cm^3) were stirred together at rt for 2 h. Benzyl mercaptan (2.35 cm^3, 20 mmol) was then added, with continued stirring. After 1.5 h, acetic acid (2.0 cm^3) was added, and the products were evaporated (bath temperature 100 °C) under reduced pressure. The residue was fractionated by short-column chromatography on silica gel: the appropriate fractions, which were eluted with toluene, dichloromethane, and then with dichloromethane–methanol (100:0 to 90:10 v/v), were evaporated under reduced pressure to give the *title compound* **12** as a glass (3.11 g, 88%) (Found, in material crystallised from ethyl acetate: C, 54.6; H, 5.1; N, 7.9. $C_{16}H_{18}N_2O_5S$ requires C, 54.85; H, 5.18; N, 7.99%), mp 153–154 °C; R_f 0.65 (system A); δ_H[$(CD_3)_3SO$] 3.34 (1 H, t, *J* 7.3), 3.58 (2 H, m), 3.86 (2 H, dd, *J* 13.0 and 20.0), 4.16 (2 H, m), 5.07 (1 H, m), 5.67 (1 H, d, *J* 8.1), 5.69 (1 H, d, *J* 5.6), 5.89 (1 H, d, *J* 5.2), 7.22–7.36 (5 H, m), 7.94 (1 H, d, *J* 8.1) and 11.34 (1 H, br s); δ_C[$(CD_3)_2SO$] 35.7, 50.0, 61.0, 78.0, 80.0, 87.8, 101.7, 126.9, 128.3, 128.8, 138.3, 140.7, 150.7 and 163.0.

3′,5′-Anhydro-1-(β-D-xylofuranosyl)uracil 13

2,2′-Anhydro-1-(β-D-arabinofuranosyl)uracil **1** (2.26 g, 10.0 mmol), potassium *tert*-butoxide (2.44 g, 21.7 mmol) and anhydrous DMSO (30 cm^3) were stirred together at rt. After 48 h, water (50 cm^3) and solid CO_2 (~5 g) were added and the resulting solution was continuously extracted with ethyl acetate for 15 h. The organic layer was separated, dried ($MgSO_4$) and evaporated (bath temperature ~60 °C) under reduced pressure. Crystallisation of the residue from absolute ethanol (50 cm^3) gave the title compound **13** as a crystalline solid (1.85 g, 82%) (Found: C, 47.9; H, 4.4; N, 12.2. Calc. for $C_9H_{10}N_2O_5$: C, 47.79; H, 4.46; N, 12.38%), mp 214 °C (decomp.) [lit.,[12] 214–216 °C (decomp.)]; R_f 0.59 (system A); δ_H[$(CD_3)_2SO$] 4.11 (1 H, dd, *J* 1.3 and 8.1), 4.52 (1 H, d, *J* 1.5), 4.70 (1 H, dd, *J* 3.9 and 8.1), 5.04 (1 H, m), 5.10 (1 H, m), 5.72 (1 H, d, *J* 8.1), 5.87 (1 H, br), 6.14 (1 H, d, *J* 1.8), 8.01 (1 H, d, *J* 8.1) and 11.43 (1 H, br); δ_C[$(CD_3)_2SO$] 75.8, 78.0, 79.9, 90.9, 95.3, 102.4, 141.1, 151.0 and 163.1.

1-(β-D-Xylofuranosyl)uracil 14

A solution of 3′,5′-anhydro-1-(β-D-xylofuranosyl)uracil **13** (1.13 g, 5.0 mmol) and TFA (4.0 cm^3) in water (16 cm^3) was stirred at 50 °C. After 18 h, the products were concentrated under reduced pressure and the residue was evaporated with absolute ethanol (2 × 20 cm^3). Crystallisation of the residual solid from acetonitrile gave the title compound **14** as crystals (1.10 g, 91%) (Found: C, 44.25; H, 4.9; N, 11.3. Calc. for $C_9H_{12}N_2O_6$: C, 44.27; H, 4.95; N, 11.47%), mp 154–155 °C (decomp.) (lit.,[13] mp 158–160 °C); R_f 0.21 (system A); δ_H[$(CD_3)_2SO$] 3.68 (2 H, m), 3.92 (1 H, m), 3.96 (1 H, m), 4.10 (1 H, m), 4.78 (1 H, t, *J* 5.6), 5.44 (1 H, d, *J* 3.4), 5.63 (1 H, d, *J* 8.1), 5.66 (1 H, d, *J* 1.0), 5.79 (1 H, d, *J* 4.2), 7.77 (1 H, d, *J* 8.1) and 11.32 (1 H, br s); δ_C[$(CD_3)_2SO$] 59.1, 74.5, 80.7, 83.8, 90.9, 100.9, 141.4, 150.6 and 163.4.

3′-Deoxyuridine 15

1-(3-*S*-Benzyl-3-thio-β-D-xylofuranosyl)uracil **12** (3.50 g, 10.0 mmol), Raney nickel (W-2, 10 cm^3) and water (100 cm^3) were stirred together at 75 °C. After 1 h, the products were filtered and the residue was washed with water (3 × 20 cm^3). The combined filtrate and washings were evaporated to dryness under reduced pressure. The residue was co-evaporated with absolute ethanol (2 × 20 cm^3) and then fractionated by short-column chromatography on silica gel: the appropriate fractions, which were eluted with dichloromethane–methanol (95:5 v/v), were evaporated under reduced pressure to give the title compound **15** as an off-white solid (1.68 g, 73%) (Found, in material crystallised from acetonitrile: C, 47.1; H, 5.2; N, 12.1. Calc. for $C_9H_{12}N_2O_5$: C, 47.37; H, 5.30; N, 12.28%), mp 175–177 °C (lit.,[17] 178–179 °C); R_f 0.36 (system A); δ_H[$(CD_3)_2SO$–D_2O] 1.77 (1 H, m), 1.96 (1 H, m), 3.52 (1 H, dd, *J* 3.4 and 12.3), 3.72 (1 H, dd, *J* 2.9 and 12.2), 4.19 (1 H, m), 4.27 (1 H, m), 5.57 (1 H, d, *J* 8.1), 5.63 (1 H, d, *J* 2.0) and 7.96 (1 H, d, *J* 8.1); δ_C[$(CD_3)_2SO$] 33.3, 61.6, 74.7, 80.7, 91.3, 101.0, 140.6, 150.5 and 163.3.

1-(3-Deoxy-β-D-*erythro*-pentofuranosyl)-4-(4-nitrophenoxy)-pyrimidin-2(1*H*)-one 16

3′-Deoxyuridine **15** (1.14 g, 5.0 mmol), dry 1-methylpyrrolidine (5.0 cm^3, 48 mmol), chlorotrimethylsilane (1.90 cm^3, 15 mmol) and dry acetonitrile (25 cm^3) were stirred together at rt. After 1 h, the reaction solution was cooled to 0 °C (ice–water-bath) and TFAA (2.1 cm^3, 14.9 mmol) was added dropwise during 5 min. After a further period of 30 min, 4-nitrophenol (2.09 g, 15 mmol) was added and the reactants were stirred at 0 °C. After 3 h, water (2.5 cm^3) was added. The products were stirred at rt for 30 min, and then concentrated under reduced pressure. The residue was partitioned between dichloromethane (50 cm^3) and saturated aq. sodium hydrogen carbonate (50 cm^3). The layers were separated and the aqueous layer was extracted with dichloromethane (3 × 25 cm^3). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure. Diethyl ether (25 cm^3) was added dropwise during 1 h to a solution of the above residue in absolute ethanol (5 cm^3). The resulting mixture was cooled to 0 °C, stirred for 5 h and then filtered. The residue was washed with diethyl ether (3 × 10 cm^3) to give the *title compound* **16** as a pale yellow crystalline solid (1.52 g, 87%) (Found, in colourless material obtained after recrystallisation from absolute ethanol: C, 51.75; H, 4.2; N, 11.8. $C_{15}H_{15}N_3O_7$ requires C, 51.58; H, 4.33; N, 12.03%), mp 223–224 °C; R_f 0.68 (system A); δ_H[$(CD_3)_2SO$] 1.70 (1 H, dd, *J* 5.2 and 13.1), 1.90 (1 H, m), 3.61 (1 H, m), 3.90 (1 H, m), 4.19 (1 H, m), 4.41 (1 H, m), 5.26 (1 H, t, *J* 5.0), 5.63 (1 H, s), 5.68 (1 H, d, *J* 3.9), 6.37 (1 H, d, *J* 7.3), 7.51 (2 H, m), 8.33 (2 H, m) and 8.69 (1 H, dd, *J* 1.2 and 7.4); δ_C[$(CD_3)_2SO$] 32.0, 60.7, 75.3, 82.1, 93.2, 93.6, 123.4, 125.3, 145.0, 146.2, 154.1, 156.6 and 170.3.

3′-Deoxycytidine 17

1-(3-Deoxy-β-D-*erythro*-pentofuranosyl)-4-(4-nitrophenoxy)-pyrimidin-2(1*H*)-one **16** (0.70 g, 2.0 mmol), conc. aq. ammonia (*d* 0.88, 5 cm^3) and 1,4-dioxane (25 cm^3) were heated together at 50 °C in a sealed flask. After 24 h, the products were concentrated to dryness under reduced pressure. The residue was coevaporated with absolute ethanol (3 × 10 cm^3) and then triturated with diethyl ether (10 cm^3) to give the title compound **17** (0.43 g, 94%) (Found, in colourless material obtained by crystallisation from methanol–diisopropyl ether: C, 47.6; H, 5.7; N, 18.2. Calc. for $C_9H_{13}N_3O_4$: C, 47.57; H, 5.77; N, 18.49%), mp 223 °C (decomp.) (lit.,[18] 222 °C); R_f 0.07 (system A); δ_H[$(CD_3)_2SO$] 1.70 (1 H, m), 1.87 (1 H, m), 3.53 (1 H, m), 3.74 (1 H, m), 4.10 (1 H, m), 4.28 (1 H, m), 5.07 (1 H, t, *J* 5.0), 5.50 (1 H, d, *J* 3.9), 5.65 (1 H, d, *J* 1.1), 5.67 (1 H, d, *J* 7.4), 7.05 (1 H, br), 7.12 (1 H, br) and 7.94 (1 H, d, *J* 7.4); δ_C[$(CD_3)_2SO$] 33.2, 61.6, 75.3, 80.8, 92.3, 93.1, 141.0, 155.3 and 165.7.

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References

1 D. M. Brown, D. B. Parihar, A. Todd and S. Varadarajan, *J. Chem. Soc.*, 1958, 3028.
2 K. J. Divakar and C. B. Reese, *J. Chem. Soc.*, *Perkin Trans. 1*, 1982, 1625.
3 J. G. Buchanan and D. R. Clark, *Carbohydr. Res.*, 1979, **68**, 331.
4 M. Màrton-Merész, J. Kuszmann, I. Pelczer, L. Pàrkànyi, T. Koritsànszky and A. Kàlmàn, *Tetrahedron*, 1983, **39**, 275.
5 A. Miah, C. B. Reese and Q. Song, *Chem. Commun.*, 1997, 407.
6 J. P. H. Verheyden, D. Wagner and J. G. Moffatt, *J. Org. Chem.*, 1971, **36**, 250.
7 A. Hampton and A. W. Nichol, *Biochemistry*, 1966, **5**, 2076.
8 J. F. Codington, R. Fecher and J. J. Fox, *J. Org. Chem.*, 1962, **27**, 163.
9 J. B. Chattopadhyaya and C. B. Reese, *J. Chem. Soc.*, *Chem. Commun.*, 1976, 860.
10 G. M. Sheldrick, SHELX-97, a crystallographic structure determination and refinement program, University of Göttingen, 1990.
11 I. L. Doerr, J. F. Codington and J. J. Fox, *J. Org. Chem.*, 1965, **30**, 467.
12 K. Kikugawa and T. Ukita, *Chem. Pharm. Bull.*, 1969, **17**, 775.
13 G. Gosselin, M.-C. Bergogne, J. de Rudder, E. DeClercq and J.-L. Imbach, *J. Med. Chem.*, 1986, **29**, 203.
14 K. J. Divakar and C. B. Reese, *J. Chem. Soc.*, *Perkin Trans. 1*, 1982, 1171.
15 R. Fecher, J. F. Codington and J. J. Fox, *J. Am. Chem. Soc.*, 1961, **83**, 1889.
16 N. C. Yung and J. J. Fox, *J. Am. Chem. Soc.*, 1961, **83**, 3060.
17 G. Kowollik and P. Langen, *Chem. Ber.*, 1968, **101**, 235.
18 J. J. K. Novák and F. Šorm, *Collect. Czech. Chem. Commun.*, 1973, **38**, 1173.
19 R. Fathi, B. Goswami, P.-P. Kung, B. L. Gaffney and R. A. Jones, *Tetrahedron Lett.*, 1990, **31**, 319.
20 A. Miah, C. B. Reese and Q. Song, *Nucleosides*, *Nucleotides*, 1997, **16**, 53.
21 J. W. Pflugrath and A. Messerschmidt, MADNES, Munich Area Detector Systems, Enraf-Nonius, Delft, 1990.

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