Syntheses of β-D-Arabinofurano[1′,2′:4,5]oxa(thia)zolidines

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Treatment of 2,2′-anhydro-1-(3,5-diacetoxy-β-D-arabinofuranosyl)-5,6-dihydrouracil (**13**) and its 2-thio analogue (**17**) with refluxing 80% AcOH gives 3-propionamido-(3,5-diacetoxy-1,2-dideoxy-β-D-arabinofurano)[1′,2′:4,5]oxazolidin-2-one (**15**) and 3-carboxyethyl-(3,5-diacetoxy-1,2-dideoxy-β-D-arabinofurano)[1′,2′:4,5]thiazolidin-2-imine (**24**), respectively. While the appearance of compound (**15**) indicates the occurrence of an unusual C(2)–N(3) bond cleavage of (**13**) the 2-thio analogue (**17**) yields compound (**24**), the product of an N(3)–C(4) ring opening. The latter product gives first methoxycarbonylethyl(3,5-diacetoxy-1,2-dideoxy-β-D-arabinofurano)[1′,2′:4,5]thiazolidin-2-imine hydrochloride (**26**) by reaction with methanolic HCl and subsequently the corresponding thiazolidine-2-thione (**27**) on reaction with H_2S in DMF.

The synthesis of the 1-(3,5-diacetoxy-2-acetylthio-β-D-arabinofuranosyl) derivative of 2-*O*-methyl-5,6-dihydrouracil (**22**) and 5,6-dihydroisocytosine (**23**) is also described.

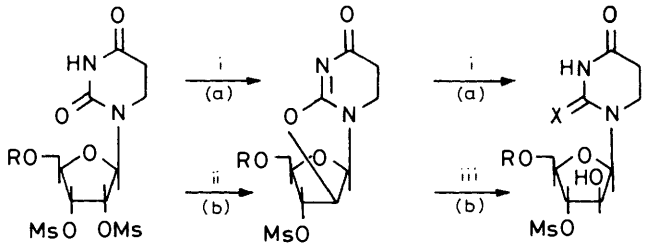
Anhydro pyrimidine nucleosides are unique intermediates for the configurational modification of sugar moieties, the introduction of various functional groups, and the rearrangement of aglycones.[1] Moreover, the 2,2′-anhydro structure, containing an intramolecularly protected 2′-hydroxy group, can be incorporated into diarabinonucleoside phosphates[2] and oligoarabinonucleotides[3] by the procedures described for the syntheses of deoxyoligonucleotides.[4]

In a recent communication[5] we showed that 5′-benzamido-5′-deoxy-2′,3′-dimesyloxy-5,6-dihydrouridine (**1**), on being heated under reflux in water, was converted into the corresponding intermediate 2,2′-anhydro compound (**2**) and then into the final product 1-(3-mesyloxy-β-D-arabinofuranosyl)-5,6-dihydrouracil (**3**) [Scheme 1(a)]. In contrast to this finding, the intramolecular reactions of the corresponding 2′,3′-dimesyloxy derivative in the uridine series,[5,6] under the same conditions, gave 1-(5-benzamido-5-deoxy-β-D-lyxofuranosyl)uracil *via* 1-(3-mesyloxy-β-D-arabinofuranosyl)uracil and the 2,3′-anhydro compound.

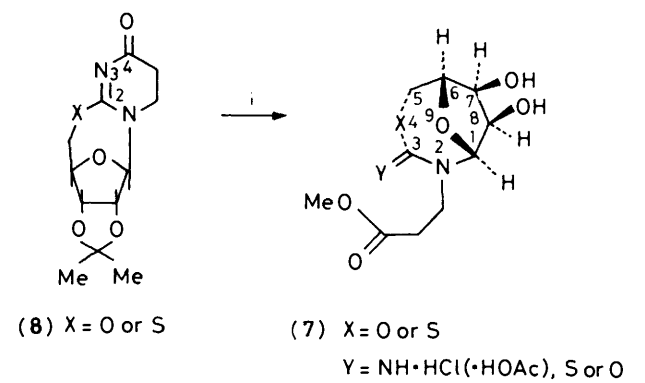
In conjunction with studies of the reluctance of 5,6-dihydrouridine analogues to undergo 2,3′-intramolecular cyclisations and isomerisations to give β-D-lyxofuranosyl derivatives, the synthesis of 1-(3,5-dimesyloxy-β-D-arabinofuranosyl)-2-thio-5,6-dihydrouracil (**4**) [Scheme 1(b)] was investigated. For the preparation of this activated precursor, containing a C(2) sulphur atom, 2′,3′,5′-trimesyloxy-5,6-dihydrouridine (**5**), was first converted into 2,2′-anhydro-1-(3,5-dimesyloxy-β-D-arabinofuranosyl)-5,6-dihydrouracil (**6**) by a regioselective cyclisation with NaOH in EtOH and then reopened by treatment with H_2S in DMF–Et_3N. However, all our attempts to convert compound (**4**) into the respective 2,3′-anhydro structure by refluxing in water were unsuccessful. On the other hand, a typical cyclisation reaction of compound (**4**) took place with NaOMe in MeOH, giving a mixture of undefined products.

We have already reported the syntheses of the 4-oxa(thia)-9-oxa-2-azabicyclo[4.2.1]nonan-3-one(thione) derivatives[7] (**8**) (Scheme 2). These oxygen-bridged, eight-membered cyclic compounds, however, were obtained in acidic media (AcOH–MeOH or HCl–MeOH) as a result of the cleavage of the N(3)–C(4) bonds of 2′,3′-*O*-isopropylidene-2,5′-anhydro-5,6-dihydrouridine (**8**; X = O) and its 2-thio analogue[8] (**8**; X = S).

Rosenthal and Dodd[9] described the transformations of 2,2′-anhydro-5,6-dihydrouridine derivatives (**9**) into the corresponding 3-propionamido-(1,2-dideoxy-β-D-arabinofurano)-[1′,2′:4,5]oxazolidin-2-ones (**10**) by treatment for 10 min with



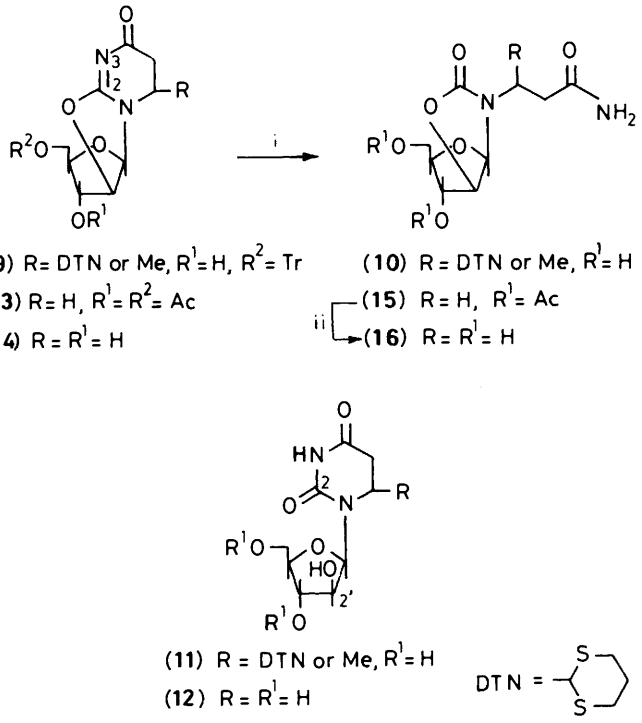
Scheme 1. *Reagents:* i, H_2O, heat; ii, NaOH, EtOH; iii, H_2S, DMF–Et_3N



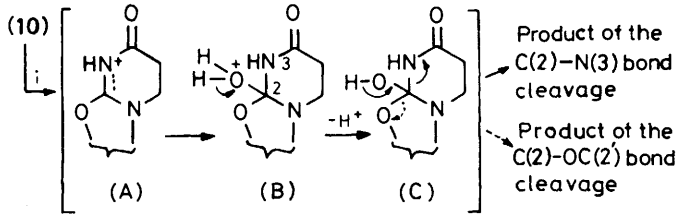
Scheme 2. *Reagents:* i, AcOH–MeOH or HCl–MeOH

boiling 80% AcOH (Scheme 3). This C(2)–N(3) rather than N(3)–C(4) bond cleavage was interpreted as a 2,2′-anhydro ring opening of compound (**9**), followed by attack of the *syn*-oriented C(2′)-hydroxy group[10] at the C(2) position of the intermediate substituted 1-(β-D-arabinofuranosyl)-5,6-dihydrouracil (**11**). If this is the case, an intramolecular cyclisation of 1-(β-D-arabinofuranosyl)-5,6-dihydrouracil (**12**) would be expected on treatment for 10 min with boiling 80% AcOH; however, this did not take place, even after prolonged (24 h) treatment.

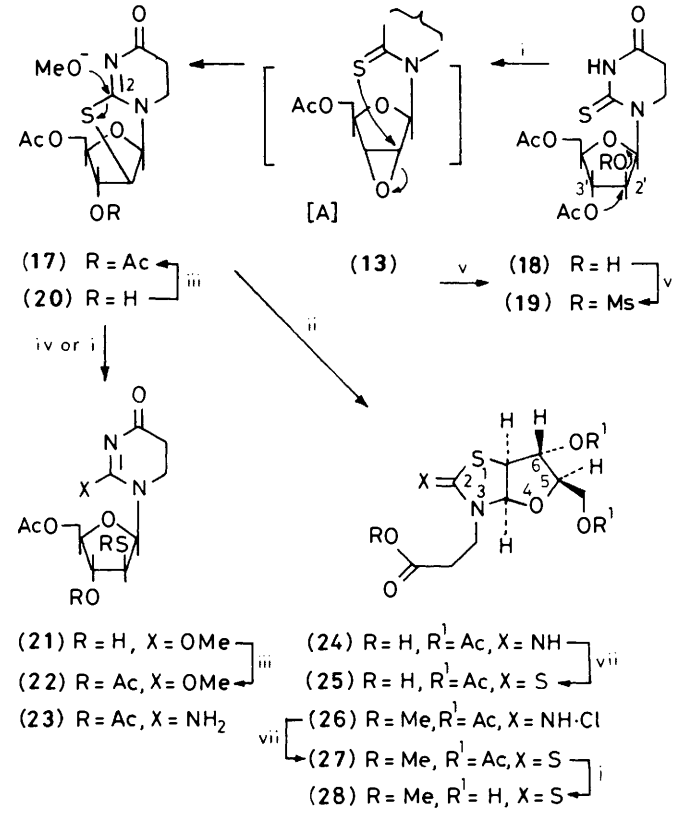
In an attempt to apply the transformations described by Rosenthal and Dodd[9] to an intramolecular process, we



Scheme 3. *Reagents:* i, 80% AcOH, heat, 10 min; ii, NaOMe, MeOH



Scheme 4. *Reagents:* i, 80% AcOH



Scheme 5. *Reagents:* i, NaOMe, MeOH; ii, 80% AcOH, heat or HCl, MeOH; iii, Ac_2O, pyridine; iv, NH_3, MeOH then Ac_2O, pyridine; v, H_2S, pyridine; vi, MsCl, pyridine; vii, H_2S, DMF, Et_3N

investigated the synsthesis of 2,2′-anhydro-1-(3,5-diacetoxy-β-D-arabinofuranosyl)-5,6-dihydrouracil (**13**) (Scheme 3) by hydrogenation, with Raney nickel[11] or 5% Rh–C of 2,2′-anhydro-1-(β-D-arabinofuranosyl)uracil[12] and acetylation of the 2,2′-anhydro-1-(β-D-arabinofuranosyl)-5,6-dihydrouracil (**14**) thus obtained. Compound (**13**) was also obtained by hydrogenation with 5% Rh–C of 2,2′-anhydro-1-(3,5-diacetoxy-β-D-arabinofuranosyl)uracil.[13] Hall *et al.*[14] reported the synthesis of compound (**14**) as a cyclo-condensation of (1,2-dideoxy-β-D-arabinofurano)[1′,2′:4,5]oxazolidin-2-amine with methyl acrylate.

Summing up our results,[5,7,8,15] the conversion of the 2,2′-anhydro-5,6-dihydronucleoside (**13**) into 3-propionamido-3,5-diacetoxy-1,2-dideoxy-β-D-arabinofurano[1′,2′:4,5]oxazolidin-2-one (**15**) (Scheme 3), by treatment for 10 min with boiling 80% AcOH, can be interpreted as N(3) protonation followed by the formation of the carbocation (A) and the oxonium ion (B) (Scheme 4). These intermediate stages, including the saturation of the C(2)–N(3) double bond, could result in the intermediate 2,2′-anhydro structure (C) leading to a C(2)–N(3) rather than a C(2)–OC(2′) ring cleavage. Deacetylation of the product thus obtained afforded β-propionamido-(1,2-dideoxy-β-D-arabinofurano)[1′,2′:4,5]oxazolidin-2-one (**16**) by treatment with NaOMe in MeOH.

The synthesis of 2,2′-anhydro-1-(3,5-diacetoxy-β-D-arabinofuranosyl)-2-thio-5,6-dihydrouracil (**17**) was then undertaken to study the influence of the 2-thio group on the 5,6-dihydropyrimidine ring opening. The thio analogue (**17**) was prepared from the 2,2′-anhydro compound (**13**) as shown in Scheme 5. The mesylation of 1-(3,5-diacetoxy-β-D-arabinofuranosyl)-2-thio-5,6-dihydrouracil (**18**), derived from compound (**13**) by treatment with H_2S in dry pyridine, afforded 1-(3,5-diacetoxy-2-mesyloxy-β-D-arabinofuranosyl)-2-thio-5,6-dihydrouracil (**19**). This compound was then converted into 2,2′-anhydro-1-(5-*O*-acetyl-β-D-arabinofuranosyl)-2-thio-5,6-dihydrouracil (**20**) by treatment with NaOMe in MeOH, and finally acetylated to give the desired compound (**17**). The intramolecular transformation of the β-D-arabinofuranosyl structure (**19**) into the 2,2′-anhydro compound (**20**) probably proceeded *via* the intermediate 2′,3′-epoxide (A), formed *via* NaOMe–MeOH deacetylation at the 3′-OAc group followed by the nucleophilic attack of the C(3′) alkoxide formed at the C(2′) position.

It is worth noting that in the above NaOMe–MeOH reactions to give compound (**20**) (Scheme 5), 1-(5-*O*-acetyl-2-deoxy-2-mercapto-β-D-arabinofuranosyl)-2-*O*-methyl-5,6-dihydrouracil (**21**) was also formed as a by-product, indicating that concomitant nucleophilic attack of methoxide ion at the C(2) position of the first-formed compound (**20**) had taken place. The acetylation of compound (**21**) yielded 1-(3,5-diacetoxy-2-deoxy-2-acetylthio-β-D-arabinofuranosyl)-2-*O*-methyl-5,6-dihydrouracil (**22**), which showed in the ^1H n.m.r. spectrum a singlet at δ 2.21 for the SAc–C(2′) moiety. The feasibility of the ring opening of the 2,2′-anhydro-2-thio-5,6-dihydrouracil nucleoside (**20**) to give the 2′-mercapto analogue (**21**) gained support from the preparation of 1-(3,5-diacetoxy-2-deoxy-2-acetylthio-β-D-arabinofuranosyl)-5,6-dihydroisocytosine (**23**) from the reaction of compound (**20**) with methanolic ammonia followed by acetic anhydride in pyridine.

Whereas the above 2,2′-anhydro compound (**13**), on being heated under reflux in 80% AcOH, afforded compound (**15**) (Scheme 3) as a result of C(2)–N(3) bond cleavage, the corresponding 2-thio analogue (**17**) was converted into 3-carboxyethyl-(3,5-diacetoxy-1,2-dideoxy-β-D-arabinofurano)-[1′,2′:4,5]thiazolidin-2-imine (**24**) (Scheme 5) under the same reaction conditions, indicating that a N(3)–C(4) bond cleavage had taken place. This *cis*-fused bicycle was obtained as the insoluble and remarkably stable internal salt (imino acid), which showed in its ^{1}H n.m.r. spectrum a broad singlet at δ 7.10 attributable to the protonated imino group. Treatment of compound (**24**) with H_2S in DMF–Et_3N afforded 3-carboxyethyl-(3,5-diacetoxy-1,2-dideoxy-β-D-arabinofurano)-[1′,2′:4,5]thiazolidine-2-thione (**25**) which showed in the ^{1}H n.m.r. spectrum a broad CO_2H singlet at δ 8.29. In good agreement with previously reported N(3)–C(4) bond cleavages of 2,5′-anhydro-5,6-dihydrouridine derivatives,[7,16–18] 3-methoxycarbonylethyl-(3,5-diacetoxy-1,2-dideoxy-β-D-arabinofurano)-[1′,2′:4,5]thiazolidin-2-imine hydrochloride (**26**) was prepared by allowing the 2,2′-anhydro-2-thio compound (**17**) to react with methanolic HCl. The imino hydrochloride (**26**) was easily converted into 3-methoxycarbonylethyl-(3,5-diacetoxy-1,2-dideoxy-β-D-arabinofurano)[1′,2′:4,5]thiazolidine-2-thione (**27**) by treatment with H_2S in DMF–Et_3N. The deacetylation of the latter product into 3-methoxycarbonylethyl-(1,2-dideoxy-β-D-arabinofurano)[1′,2′:4,5]thiazolidine-2-thione (**28**) was carried out with NaOMe–MeOH.

Experimental

The same techniques and apparatus were used as described previously.[19] In addition ^{13}C n.m.r. spectra were recorded in $(CD_3)_2SO$ on a JEOL FX 90 Q spectrometer (with tetramethylsilane as the internal standard) and optical rotations were measured in acetone, unless otherwise stated, using a Zeiss-Winkel 179707 apparatus. Ether refers to diethyl ether.

2′,3′,5′-*Trimesyloxy*-5,6-*dihydrouridine* (**5**).—To a cooled (0 °C) solution of 5,6-dihydrouridine[20] (180 mg, 0.82 mmol) in freshly distilled dry pyridine (1.6 ml), mesyl chloride (0.21 ml, 2.7 mmol) was added. The mixture was set aside at 0 °C for 16 h and then poured into cooled water (50 ml). The amorphous product separated by suction and then dissolved in acetone. It crystallized on addition of ether to give the *product* (**5**) (245 mg, 70%), m.p. 110 °C (extended), $[\alpha]_D^{24}$ −24° (*c* 1, Me_2SO) (Found: C, 30.2; H, 4.45; N, 5.8. $C_{12}H_{20}N_2O_{12}S_3$ requires C, 30.0; H, 4.2; N, 5.85%); $\nu_{max.}$ 3 448, 3 226sh, 3 030, 2 941, 1 706 br, 1 621sh, 1 565, 1 176, 1 046, 1 033, and 1 015 cm^{-1}; δ 9.22br (1 H, s, 3-NH), 6.04 (1 H, m, 1′-H), 5.56—5.38 (2 H, m, 2′-H and 3′-H), 4.68—4.45 (3 H, m, 4′-H and 5′-H_2), 3.67 (2 H, t, 6-H_2, $J_{6,5}$ 6.5 Hz), 3.31 and 3.29 (2 × Me, 2 × s, 2′-O- and 3′-O-MsMe), 3.20 (3 H, s, 5′-O-MsMe), and 2.70 (2 H, t, 5-H_2, $J_{5,6}$ 6.5 Hz).

2,2′-*Anhydro*-1-(3,5-*dimesyloxy*-β-D-*arabinofuranosyl*)-5,6-*dihydrouracil* (**6**).—To a solution of compound (**5**) (240.2 mg, 0.5 mmol) in acetone (5 ml) and EtOH (2.5 ml), NaOH (0.2M dm^{-3}) in EtOH (2.5 ml) was added dropwise and the mixture stirred at room temperature for an additional 30 min. The crystalline *product* (**5**) was separated from the cooled mixture by filtration (175 mg, 91%), m.p. 193—196 °C (from EtOH), $[\alpha]_D^{25}$ −70.5° (*c* 1, Me_2SO) (Found: C, 34.65; H, 4.45; N, 7.05. $C_{11}H_{16}N_2O_9S_2$ requires C, 34.35; H, 4.2; N, 7.3%); $\lambda_{max.}$ 234 nm (log ε 4.17); $\nu_{max.}$ 3 497, 3 030, 2 950, 1 686, 1 618, 1 592, 1 181, 1 171, 1 140, 1 096, 1 075, 1 040, and 1 027 cm^{-1}; δ 6.06 (1 H, d, 1′-H, $J_{1',2'}$ 6.0 Hz), 5.56 (1 H, d, 2′-H, $J_{2',1'}$ 6.0 Hz), 5.42 (1 H, m, 3′-H), 4.82—4.45 (1 H, m, 4′-H), 4.42—4.02 (2 H, m, 5′-H_2), 3.59 (2 H, t, 6-H_2. $J_{6,5}$ 7.4 Hz), 3.40 (3 H, s, 3′-OMsMe), 3.21 (3 H, s, 5′-OMsMe), and 2.49 (2 H, t, 5-H_2, $J_{5,6}$ 7.4 Hz).

1-(3,5-*Dimesyloxy*-β-D-*arabinofuranosyl*)-2-*thio*-5,6-*dihydrouracil* (**4**).—Into a solution of 2,2′-anhydro-1-(3,5-dimesyloxy-β-D-arabinofuranosyl)-5,6-dihydrouracil (**6**) (300 mg, 0.78 mmol) in DMF (8 ml) and Et_3N (0.2 ml) was bubbled H_2S for 1.5 h. The solvent was then removed under reduced pressure and the residue subjected to preparative t.l.c. (CH_2Cl_2–MeOH, 10:1, three developments, recovery with MeOH) to afford the *product* (**4**) (130 mg, 40%), m.p. 94—96 °C (from MeOH), $[\alpha]_D^{23}$ −11° (*c* 1 MeOH), and an unidentified product (20 mg) with lower R_F (Found: C, 31.4; H, 4.1; N, 7.0; S, 23.2. $C_{11}H_{18}N_2O_9S_3$ requires C, 31.55; H, 4.35; N, 6.7; S, 23.0%); $\lambda_{max.}$ 234 and 277 nm (log ε 4.00 and 4.08); $\lambda_{min.}$ 252 nm (log ε 3.58); $\nu_{max.}$ 3 435br, 3 380, 3 010, 2 930, 1 725br, 1 695sh, 1 625br, 1 179, and 1 170 cm^{-1}; δ 10.46 (1 H, s, 3-NH), 6.62 (1 H, d, 1′-H, $J_{1',2'}$ 4.5 Hz), 6.28 (1 H, d, 2′-H, $J_{2',1'}$ 4.5 Hz), 4.83 (1 H, m, 4′-H), 4.64—4.20 (4 H, m, 2′-OH, 3′-H, and 5′-H_2), 3.65 (2 H, t, 6-H_2, $J_{6,5}$ 6.5 Hz), 3.32 and 3.23 (3 H and 3 H, 2 × s, 2 × MsMe), and 2.67 (2 H, m, 5-H_2).

1-(β-D-*Arabinofuranosyl*)-5,6-*dihydrouracil* (**12**).—To a solution of 1-(β-D-arabinofuranosyl)uracil[10] (220 mg, 0.9 mmol) in H_2O (12 ml) was added 5% Rh/C (200 mg). The mixture was stirred under H_2 (0.32 MPa) at room temperature for 16 h. The catalyst was filtered off and the filtrate evaporated to dryness. The crystalline residue was recrystallized from EtOH to give the *product* (**12**) (200 mg, 90%), m.p. 191—192 °C, R_F *ca.* 0.28 ($CHCl_3$–MeOH, 3:1), $[\alpha]_D^{22}$ −4.5° (*c* 2, H_2O) (Found: C, 44.15; H, 5.8; N, 11.15. $C_9H_{14}N_2O_5$ requires C, 43.9; H, 5.75; N, 11.4%); $\nu_{max.}$ 3 502, 3 390, 3 237br, 2 945, 2 890, 1 709br, 1 667, 1 622sh, 1 141, 1 103, and 1 065 cm^{-1}; δ 10.14br (1 H, s, 3-NH), 5.85 (1 H, d, 1′-H, $J_{1',2'}$ 5.9 Hz), 5.47 and 5.29 (2 H, 2 × d, 2′-OH and 3′-OH, $J_{OH,2'}$ 4.7 and $J_{OH,3'}$ 4.4 Hz), 4.83 (1 H, m, 5′-OH), 4.09—3.62 (3 H, m, 2′-H, 3′-H, 4′-H), and 3.62—3.18 (4 H, m, 5′-H_2 and 6-H_2); 5-H_2 signal obscured by those of Me_2SO.

2,2′-*Anhydro*-1-(3,5-*diacetoxy*-β-D-*arabinofuranosyl*)-5,6-*dihydrouracil* (**13**).—(*a*) To a solution of 2,2-anhydro-1-(β-D-arabinofuranosyl)uracil[12] (200 mg, 0.88 mmol) in MeOH (9 ml) was added 5% Rh/C (160 mg). The mixture was stirred under H_2 (0.44 MPa) at room temperature for 18 h. The catalyst was filtered off and the filtrate evaporated to dryness. The 2,2′-anhydro-1-(β-D-arabinofuranosyl)-5,6-dihydrouracil (**14**) thus obtained was treated with acetic anhydride (0.19 ml, 2.01 mmol) in dry pyridine (6 ml) and left at room temperature for 16 h. The solvent was then removed azeotropically with MeOH under reduced pressure. The preparative t.l.c. ($CHCl_3$–MeOH, 9:2) afforded the *product* (**13**) as a foam (127 mg, 46%), R_F *ca.* 0.35 (CH_2Cl_2–MeOH, 10:1), $[\alpha]_D^{23}$ −154.5° (*c* 1, acetone) (Found: C, 50.05; H, 5.15; N, 9.15. $C_{13}H_{16}N_2O_7$ requires C, 50.0; H, 5.15; N, 8.95%); $\lambda_{max.}$ 238 nm (log ε 4.08); $\nu_{max.}$ 3 471br, 2 983, 2 952, 2 880, 1 739br, 1 691, 1 600br, and 1 482 cm^{-1}; δ 5.91 (1 H, d, 1′-H, $J_{1',2'}$ 5.7 Hz), 5.31 (1 H, m, 3′-H), 5.27 (1 H, d, 2′-H, $J_{2',1'}$ 5.7 Hz), 4.41br (1 H, s, 4′-H), 4.31—3.99 (2 H, m, 5′-H_2), 3.67 (2 H, t, 6-H_2, $J_{6,5}$ 7.6 Hz), 2.65 (2 H, t, 5-H_2, $J_{5,6}$ 7.6 Hz), and 2.15 and 2.10 (2 × Me, 2 × s, 2 × O-Ac).

(*b*) To a solution of 2,2′-anhydro-1-(3,5-diacetoxy-β-D-arabinofuranosyl)uracil[13] (91 mg, 0.29 mmol) in 50% EtOH (25 ml) was added Raney nickel (W-2, 0.4 ml). The mixture was stirred under H_2 (0.05 MPa) at room temperature for 3.5 h. The catalyst was filtered off and the filtrate evaporated to dryness. Preparative t.l.c., R_F *ca.* 0.35 (CH_2Cl_2–MeOH, 10:1, recovery with acetone), $[\alpha]_D^{22}$ −153.9° (*c* 1), gave compound (**13**) (48 mg, 53%), identical (i.r. and ^{1}H n.m.r. spectra) with that obtained in section (*a*).

(*c*) To a solution of 2,2′-anhydro-1-(3,5-diacetoxy-β-D-arabinofuranosyl)uracil[13] (100 mg, 0.33 mmol) in MeOH (4.5 ml) was added 5% Rh/C (80 mg). The mixture was stirred under H_2(0.36 MPa) for 8 h and worked up as described in section (*a*).

The product (**13**) (56 mg, 56%) thus obtained R_F *ca.* 0.35, $[\alpha]_D^{22}$ −154.1° (*c* 2), was identical (i.r. and ^{1}H n.m.r. spectra) with that obtained in section (*a*).

3-*Propionamido*-(3,5-*diacetoxy*-1,2-*dideoxy*-β-D-*arabino-furano*)[1′,2′:4,5]*oxazolidin*-2-*one* (**15**).—A solution of 2,2′-anhydro-1-(3,5-diacetoxy-β-D-arabinofuranosyl)-5,6-dihydro-uridine (**13**) (310 mg, 0.99 mmol) in 80% AcOH (7.2 ml) was heated under reflux for 10 min. The solvent was then removed azeotropically with EtOH under reduced pressure. Preparative t.l.c. (CH_2Cl_2–MeOH, 10:1, recovery with acetone) afforded the *product* (**15**) as a foam (170 mg, 52%), R_F *ca.* 0.50 (CH_2Cl_2–MeOH, 10:1), $[\alpha]_D^{24}$ −49.5° (*c* 1), and an unidentified by-product (37 mg) with a lower R_F value (Found: C, 47.3; H, 5.75; N, 8.2. $C_{13}H_{18}N_2O_8$ requires C, 47.25; H, 5.5; N, 8.5%); $\nu_{max.}$ 3 448br, 3 358br, 3 210, 2 953, 1 753br, 1 676br, 1 617br, and 1 048br cm^{-1}; δ 5.99br and 5.78br (2 H, 2 × s, $CONH_2$, disappearing in D_2O), 5.82 (1 H, d, 1′-H, $J_{1',2'}$ 5.9 Hz), 5.24br (1 H, s, 3′-H), 4.89 (1 H, d, 2′-H, $J_{2',1}$ 5.9 Hz), 4.32—4.12 (3 H, m, 4′-H and 5′-H_2), 3.73—3.44 (2 H, m, NCH_2), 2.77—2.38 (2 H, m, CH_2CO), and 2.11br (6 H, s, 2 × COMe).

3-*Propionamido*-(1,2-*dideoxy*-β-D-*arabinofurano*)-[1′,2′:4,5]*oxazolidin*-2-*one* (**16**).—To a solution of compound (**15**) (110 mg, 0.33 mmol) in anhydrous MeOH (2 ml) NaOMe (0.5 dm^{-3}) in MeOH (2 ml) was added and left aside at room temperature for 15 min. The mixture was then treated with silica gel (10 g) in EtOH (40 ml), filtered and the filtrate evaporated to dryness. Preparative t.l.c. ($CHCl_3$–MeOH, 3:1, recovery with MeOH) afforded the *product* (**16**) as a syrup (76 mg, 93%), R_F *ca.* 0.23, $[\alpha]_D^{25}$ −39° (*c* 1, MeOH) (Found: C, 43.95; H, 5.6; N, 11.25. $C_9H_{14}N_2O_6$ requires C, 43.9; H, 5.75; N, 11.4%); $\nu_{max.}$ 3 395br, 3 205sh, 2 945, 1 745br, 1 664br, and 1 605br cm^{-1}; δ 7.41br and 6.88br (2 H, 2 s, $CONH_2$), 5.68 (1 H, d, 1′-H, $J_{1',2'}$ 5.7 Hz), 4.69 (1 H, d, 2′-H, $J_{2',1'}$ 5.7 Hz), 4.16 (1 H, m, 3′-H), 3.88 (1 H, m, 4′-H), 3.64—3.16 (2 H, m, NCH_2), and 2.35 (2 H, t, CH_2CO, J_{CH_2,CH_2} 7.1 Hz).

1-(3,5-*Diacetoxy*-β-D-*arabinofuranosyl*)-2-*thio*-5,6-*dihydro-uracil* (**18**).—Into a cooled (0 °C) solution of 2,2′-anhydro-1-(3,5-diacetoxy-β-D-arabinofuranosyl)-5,6-dihydrouracil (**13**) (1 g, 3.2 mmol) in dry pyridine (75 ml) was bubbled H_2S for 1 h. The mixture was then kept at room temperature for 6 days in a sealed vessel and evaporated to dryness under reduced pressure. Preparative t.l.c. (CH_2Cl_2–MeOH, 20:1, recovery with acetone) afforded the *product* (**18**) as a foam (700 mg, 63%), R_F *ca.* 0.2 (CH_2Cl_2–MeOH, 30:1), $[\alpha]_D^{28}$ +4.9° (*c* 0.72) (Found: C, 44.85; H, 5.4; N, 8.0. $C_{13}H_{18}N_2O_7S$ requires C, 45.1; H, 5.25; N, 8.1%); $\lambda_{max.}$ 233 and 275 nm (log ε 4.10 and 4.19); $\lambda_{min.}$ 251 nm (log ε 3.72); $\nu_{max.}$ 3 448br, 3 263sh, 3 020, 2 958, 2 935, 1 735, 1 728, and 1 700sh cm^{-1}; δ 9.04br (1 H, s, 3-NH), 6.61 (1 H, d, 1′-H, $J_{1',2'}$ 4.9 Hz), 4.92 (1 H, d × d, 3′-H, $J_{3',4'}$ 4.5 and $J_{3',2'}$ 2.7 Hz), 4.62 (1 H, d × d, 2′-H, $J_{2',1'}$ 4.9 and $J_{2',3'}$ 2.7 Hz), 4.37 (2 H, m, 5′-H_2), 4.21—3.99 (2 H, m, 4′-OH and 4′-H), 3.91—3.49 (2 H, m, 6-H_2), 2.78—2.62 (2 H, m, 5-H_2), and 2.15 and 2.11 (6 H, 2 × s, 2 × OAc).

1-(3,5-*Diacetoxy*-2-O-*mesyl*-β-D-*arabinofuranosyl*)-2-*thio*-5,6-*dihydrouracil* (**19**).—To a cooled solution of compound (**18**) (630 mg, 1.82 mmol) in dry pyridine (13 ml) was added mesyl chloride (0.286 ml, 3.64 mmol) dropwise. The mixture was then kept at room temperature for 16 h and evaporated to dryness under reduced pressure. Preparative t.l.c. (CH_2Cl_2–MeOH, 30:1, recovery with acetone) afforded the product as a foam (550 mg, 76%), R_F *ca.* 0.36, $[\alpha]_D^{28}$ +60° (*c* 1) (Found: C, 39.55; H, 4.9; N, 6.7. $C_{14}H_{20}N_2O_9S_2$ requires C, 39.6; H, 4.75; N, 6.6%); $\lambda_{max.}$ 232 and 274.5 nm (log ε 4.05 and 4.15), $\lambda_{min.}$ 249.5 nm (log ε 3.62); $\nu_{max.}$ 3 317, 3 254br, 3 019, 2 932, 1 740br, 1 645br, and 1 117 cm^{-1}; δ 8.94 (1 H, s, 3-NH), 6.69 (1 H, d, 1′-H, $J_{1',2'}$ 3.9 Hz), 5.31 (1 H, d × d, 3′-H, $J_{3',4'}$ 4.2 and $J_{3',2'}$ 1.5 Hz), 5.21 (1 H, d × d, 2′-H, $J_{2',1'}$ 3.9 and $J_{2',3'}$ 1.5 Hz), 4.49—4.35 (2 H, m, 5′-H_2), 4.26—4.13 (1 H, m, 4′-H), 3.92—3.71 (2 H, m, 6-H_2), 3.17 (3 H, s, MsMe), 2.84—2.65 (2 H, m, 5-H_2), and 2.18 and 2.17 (3 H and 3 H, 2 × s, 2 × OAc).

2,2′-*Anhydro*-1-(3,5-*diacetoxy*-β-D-*arabinofuranosyl*)-2-*thio*-5,6-*dihydrouracil* (**17**) *and* 1-(3,5-*Diacetoxy*-2-*deoxy*-2-*aceytyl-thio*-β-D-*arabinofuranosyl*)-2-O-*methyl*-5,6-*dihydrouracil* (**22**).—A solution of 1-(3,5-diacetoxy-2-*O*-mesyl-β-D-arabino-furanosyl)-2-thio-5,6-dihydrouracil (**19**) (3 g, 7.07 mmol) in anhydrous MeOH (360 ml) was treated with NaOMe (2.5 mol dm^{-3}) in MeOH (15 ml) and then stirred at room temperature for an additional 2 h. The solution was filtered through a short silica-gel column and eluted with EtOH. The filtrate was evaporated to dryness. 1-(5-*O*-Acetyl-2-deoxy-2-mercapto-β-D-arabinofuranosyl)-2-*O*-methyl-5,6-dihydrouracil (**21**) thus obtained was dissolved in dry and freshly distilled pyridine (47 ml), treated with acetic anhydride (9 ml), and left at room temperature for 18 h. The solvent was then removed azeotropically with EtOH under reduced pressure. The residue was chromatographed on a silica-gel (80 g) column. Methylene dichloride and methanol (30:1 and 50:1) eluted the *acetylated by-product* (**22**) as an oil (460 mg, 16%), R_F *ca.* 0.60 (acetone–CH_2Cl_2; 10:1), $[\alpha]_D^{22}$ −34° (*c* 1) (Found: C, 47.9; H, 5.8; N, 7.15. $C_{16}H_{22}N_2O_8S$ requires C, 47.75; H, 5.5; N, 6.95%); $\lambda_{max.}$ 256 nm (log ε 3.88); $\nu_{max.}$ 3 465br, 3 003sh, 2 955, 2 925, 1 738, 1 641, 1 521, and 1 178 cm^{-1}; δ 5.93 (1 H, d, 1′-H, $J_{1',2'}$ 7.1 Hz), 5.16br (1 H, s, 3′-H), 4.34—413 (4 H, m, 2′-H, 4′-H, and 5′-H_2), 4.04—3.78 (2 H, m, 6-H_2), 3.70 (3 H, s, 2-OMe), 2.99 (1 H, d × d, 5-H_a, $J_{a,b}$ 16.8 and $J_{a,6}$ 7.0 Hz), 2.65 (1 H, d × d, 5-H_b, $J_{b,a}$ 16.8 and $J_{b,6}$ 5.9 Hz), 2.21 (3 H, s, SAc), and 2.11 and 2.05 (3 H, and 3 H, 2 × s, 2 × OAc).

Elution with CH_2Cl_2–MeOH (20:1) afforded the *product* (**17**) (1.2 g, 52%), R_F *ca.* 0.60 (CH_2Cl_2–MeOH; 20:1), m.p. 181—182 °C (from CH_2Cl_2–ether, $[\alpha]_D^{20}$ −156° (*c* 1, MeOH) (Found: C, 47.6; H, 4.9; N, 8.7. $C_{13}H_{16}N_2O_6S$ requires C, 47.55; H, 4.9; N, 8.55%); $\lambda_{max.}$ 254 nm (log ε 4.33); $\nu_{max.}$ 3 445br, 2 961, 2 935, 2 905, 1 730, 1 670, 1 560, 1 247, and 1 051 cm^{-1}; δ 5.87 (1 H, d, 1′-H, $J_{1',2'}$ 7.1 Hz), 5.16 (1 H, m, 3′-H, 4.42—4.12 (4 H, m, 2′-H, 4′-H, and 5′-H_2), 3.85—3.52 (2 H, m, 6-H_2), 2.64 (2 H, t, 5-H_2, $J_{5,6}$ 7.7 Hz), and 2.13 and 2.11 (3 H and 3 H, 2 × s, 2 × OAc).

1-(3,5-*Diacetoxy*-2-*deoxy*-2-*acetylthio*-β-D-*arabinofuranosyl*)-5,6-*dihydroisocytosine* (**23**).—A solution of 2,2′-anhydro-2-thio compound (**17**) (50 mg, 0.15 mmol) in MeOH (20 ml) was saturated with ammonia at room temperature. The mixture was left at room temperature for 48 h in a sealed vessel and then evaporated to dryness under reduced pressure. The residue was treated with acetic anhydride (0.5 ml) in pyridine (1.5 ml) under the above described conditions. Preparative t.l.c. (CH_2Cl_2–MeOH, 20:1, recovery with acetone) afforded the product (**23**) (40 mg, 68%), R_F *ca.* 0.15, m.p. 111—112 °C (from CH_2Cl_2–hexane), $[\alpha]_D^{24}$ −24° (*c* 1) (Found: C, 46.65; H, 5.45; N, 10.95. $C_{15}H_{20}N_3O_7S$ requires C, 46.6; H, 5.2; N, 10.9%); $\lambda_{max.}$ 256 nm (log ε 4.22); $\nu_{max.}$ 3 425, 3 351, 3 336, 3 213, 2 960, 1 734, 1 661, 1 647sh, 1 623, and 1 521 cm^{-1}; δ 6.10br and 5.50br (2 H, 2 × s, 2 × NH), 5.91 (1 H, d, 1′-H, $J_{1',2'}$ 7.7 Hz), 5.17 (1 H, m, 3′-H), 4.34—3.79 (6 H, m, 2′-H, 4′-H, 5′-H_2, and 6-H_2), 3.16—2.56 (2 H, m, 5′-H_2), 2.21 (3 H, s, SAc), and 2.11 and 2.04 (3 H, and 3 H, 2 × s, 2 × COMe).

3-*Carboxyethyl*-(3,5-*diacetoxy*-1,2-*dideoxy*-β-D-*arabino-furano*)[1′,2′:4,5]*thiazolidine*-2-*thione* (**25**).—A solution of 2,2′-anhydro-2-thio-5,6-dihydrouracil (**17**) (120 mg, 0.365 mmol) in 80% AcOH (3 ml) was heated under reflux for 10 min and then evaporated to dryness under reduced pressure. The residue was purified by preparative t.l.c. ($CHCl_3$–MeOH, 3:1, recovery

with acetone) to give an amorphous, but stable product which was identified as 3-carboxyethyl-(3,5-diacetoxy-1,2-dideoxy-β-D-arabinofurano)[1′,2′:4,5]thiazolidin-2-imine (**24**) (100 mg, 79%); $\nu_{max.}$ 3 428br, 2 935br, 1 738, 1 607br, and 1 570br cm^{-1}; δ 7.10br (2 H, s, $^{+}NH_2$), 5.97 (1 H, d, 1′-H, $J_{1',2'}$ 6.9 Hz), 5.04 (1 H, m, 3′-H), 4.38—4.07 (4 H, m, 2′-H, 4′-H and 5′-H_2), 3.86—3.55 (2 H, m, 6-H_2), 2.66—2.40 (2 H, m, 5-H_2), and 2.10 and 2.09 (3 H and 3 H, 2 × s, 2 × COMe).

Into a cooled (0 °C) solution of the imino acid (**24**) in DMF (6 ml) and Et_3N (0.3 ml) was bubbled H_2S for 1 h. The mixture was then kept at room temperature for 48 h in a sealed vessel and evaporated to dryness under greatly reduced pressure. Preparative t.l.c. ($CHCl_3$–MeOH 3:1, recovery with acetone) afforded the starting material (15 mg) and the oily *product* (**25**) [60 mg, 57% based on (**17**)], R_F *ca.* 0.14 ($CHCl_3$–MeOH 30:1), $[\alpha]_D^{20}$ −83.5° (*c* 2) (Found: C, 43.2; H, 5.0; N, 3.9. $C_{13}H_{17}NO_7S_2$ requires C, 42.95; H, 4.7; N, 3.85%); $\lambda_{max.}$ 248 and 275 nm (log ε 3.62 and 3.84), $\lambda_{min.}$ 219 and 258 nm (log ε 3.06 and 3.58); $\nu_{max.}$ 3 465br, 3 280br, 2 950br, 2 580br, 1 740br, 1 710br, and 1 650sh cm^{-1}; δ_C 195.4 (CO_2H), 176.4 (C=S), 170.7 (COAc), 170.1 (COAc), 101.2 (C-1′), 82.7 (C-2′), 80.8(C-3′), 63.2 (C-5′), 50.9 (C-4′), 43.3 (CN), 31.5 (CCO_2), 20.7 (2 × CMe); δ 8.29br (1 H, s, CO_2H), 6.20 (1 H, d, 1′-H, $J_{1',2'}$ 7.3 Hz), 5.15 (1 H, m, 3′-H), 4.43—3.82 (6 H, m, 2′-H, 4′-H, 5′-H_2, and 6-H_2), 3.27—2.55 (1 H, m, 5-H_2), and 2.12 and 2.11 (3 H and 2 H, 2 × s, 2 × COMe).

3-*Methoxycarbonylethyl*-(3,5-*diacetoxy*-1,2-*dideoxy*-β-D-*arabinofurano*)[1′,2′:4,5]*thiazolidine*-2-*thione* (**27**).—To a solution of 2,2′-anhydro-2-thio-5,6-dihydrouracil (**17**) (120 mg, 0.365 mmol) in anhydrous MeOH (41 ml) methanolic HCl (0.85 mol dm^{-3}; 0.62 ml) was added and kept at room temperature for 1 h. The solvent was removed under reduced pressure and evaporated to dryness. The 3-methoxycarbonylethyl-(3,5-diacetoxy-1,2-dideoxy-β-D-arabinofurano)[1′,2′:4,5]thiazolidine-2-thione (**26**) thus obtained was dissolved in DMF (8 ml) and Et_3N (0.40 ml) and cooled to 0 °C. H_2S was bubbled through the solution for 45 min, and it was then left at room temperature in a sealed vessel for 48 h. The solvent was removed under reduced pressure and the residue purified on preparative t.l.c. plates (CH_2Cl_2–MeOH, 99:1, recovery with acetone). The *product* (**27**) separated as an oil (80 mg, 60%), R_F *ca.* 0.53 (CH_2Cl_2–MeOH, 30:1), $[\alpha]_D^{20}$ −85° (*c* 2) (Found: C, 44.3; H, 5.1; N, 3.4. $C_{14}H_{19}NO_7S_2$ requires C, 44.55; H, 5.05; N, 3.7%); $\lambda_{max.}$ 249 and 276 nm (log ε 3.66 and 3.91); $\lambda_{min.}$ 221 and 257 nm (log ε 3.16 and 3.62); $\nu_{max.}$ 3 468, 2 990sh, 2 955, 1 740br, and 1 656 cm^{-1}; δ_C($CDCl_3$) 195.2 (CO_2Me), 172.0 (C=S), 170.4 (COAc), 170.0 (COAc), 101.3 (C-1′), 82.7 (C-2′). 80.8 (C-3′), 63.2 (C-5′), 51.9 (OMe), 50.9 (C-4′), 43.5 (CN), 31.4 (CCO_2), and 20.7 (2 × CMe); δ 6.23 (1 H, d, 1′-H, $J_{1',2'}$ 7.3 Hz), 5.15 (1 H, m, 3′-H), 4.47—3.97 (6 H, m, 2′-H, 4′-H, 5′-H_2, and NCH_2), 3.70 (3 H, s, OMe), 3.20—2.47 (2 H, m, CH_2CO_2), and 2.12 and 2.11 (3 H and 3 H, 2 × s, 2 × COMe).

3-*Methoxycarbonylethyl*-(1,2-*dideoxy*-β-D-*arabinofurano*)-[1′,2′:4,5]*thiazolidine*-2-*thione* (**28**).—A solution of thiazolidine-2-thione and the diacetoxy derivative (**27**) (40 mg, 0.106 mmol) in NaOMe–MeOH (0.1 mol dm^{-3}; 1.5 ml) was kept at room temperature for 30 min. The mixture was filtered through a short silica-gel (1 g) column and eluted with MeOH. The eluate was evaporated to dryness and the residue subjected to preparative t.l.c. (CH_2Cl_2–MeOH 30:1, two developments, recovery with acetone). The *product* (**28**) separated as a colourless oil (28 mg, 90%), R_F *ca.* 0.47 (CH_2Cl_2–MeOH 10:1), $[\alpha]_D^{23}$ −109° (*c* 2) (Found: C, 40.7; H, 5.25; N, 5.0. $C_{10}H_{15}NO_5S_2$ requires C, 40.95; H, 5.15; N, 4.8%); $\lambda_{max.}$ 253 and 276.5 nm (log ε 3.87 and 4.12); $\lambda_{min.}$ 259.5 nm (log ε 3.85); $\nu_{max.}$ 3 400br, 3 000, 2 953, 2 930sh, 2 885, 2 880, 1 725br, and 1 630br cm^{-1}; δ 6.13 (1 H, d, 1′-H, $J_{1',2'}$ 7.3 Hz), 4.46 (1 H, m, 3′-H), 4.30—3.63 (6 H, m, 2′-H, 4′-H, 5′-H_2, and NCH_2), 3.71 (3 H, s, OMe), and 3.14—2.54 (1 H, m, CH_2CO_2).

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