4-(1,2,4-Triazol-1-yl)- and 4-(3-Nitro-1,2,4-triazol-1-yl)-1-(β-D-2,3,5-tri-*O*-acetylarabinofuranosyl)pyrimidin-2(1*H*)-ones. Valuable Intermediates in the Synthesis of Derivatives of 1-(β-D-Arabinofuranosyl)cytosine (Ara-C)

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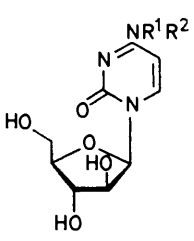
Treatment of the acetylated derivative (3b), which was prepared from uridine in 86% overall yield, with tri(1*H*-1,2,4-triazol-1-yl)phosphine oxide gave compound (6a) in high yield, and with 3-nitro-1,2,4-triazole and diphenyl phosphorochloridate it gave compound (6b) in high yield. When the former product (6a) was allowed to react with ammonia, methylamine, dimethylamine, and morpholine at room temperature, and the products further deacetylated if necessary, ara-C (1; $R^1 = R^2 = H$) and its corresponding 4-*N*-alkyl derivatives (1; $R^1 = H$, R^2 =Me), (1; $R^1 = R^2 = Me$), and [1; $R^1,R^2 = -(CH_2)_2O(CH_2)_2-$] were obtained in very high yields. 4-*N*-Phenyl-ara-C (1; $R^1 = H$, $R^2 = Ph$) was obtained in high yield when compound (6a) or (6b) was heated with aniline in pyridine solution and the products then deacetylated. The nitro-compound (6b) was converted into the ara-C derivative (1; $R^1 = H$, $R^2 = CH_2CO_2Me$), and the sulphide (7) was obtained following the deacetylation of the products of the reaction between the 1,2,4-triazolyl derivative (6a), toluene-*p*-thiol, and triethylamine.

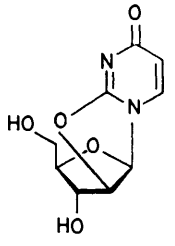
By virtue of its anti-leukaemic activity [1] 1-(β-D-arabinofuranosyl)cytosine (ara-C) (1) is a compound of considerable importance. The possibility clearly exists that some of its simple analogues will also find use in chemotherapy. Our recent interest in the development of new methods for the synthesis of purine arabinosides [especially 1-(β-D-arabinofuranosyl)adenine (ara-A),[2,3] 1-(β-D-arabinofuranosyl)guanine (ara-G) [4] and some of their derivatives] has led us to search for a convenient general method for the synthesis of pyrimidine arabinosides and especially of ara-C (1; $R^1 = R^2 = H$) and its 4-*N*-alkyl and aryl derivatives [represented generally by (1)]. It was apparent to us that this problem could be tackled by adopting one of two possible approaches: in the first approach, modified cytidine derivatives would be prepared and then converted into the corresponding arabinosides by inversion at C-2′; in the second approach, a suitable 1-(β-D-arabinofuranosyl)pyrimidine derivative with a good leaving group at C-4 would be prepared and then treated with appropriate nitrogen nucleophiles. We decided to follow the second approach.

We required 1-(β-D-2,3,5-tri-*O*-acetylarabinofuranosyl)uracil [5] (3b) as our key starting material. When uridine was heated with diphenyl carbonate in the presence of a small quantity of sodium hydrogen carbonate in hexamethylphosphoric triamide at 150 °C, according to the procedure of Moffatt and his co-workers,[6] 2,2′-anhydro-1-(β-D-arabinofuranosyl)uracil (2) was obtained in virtually quantitative yield; it was not isolated but was hydrolysed by heating with an excess of triethylamine in aqueous solution at 70 °C for 5 h. The 1-(β-D-arabinofuranosyl)uracil (ara-U) (3a) so obtained was again not isolated but was treated with an excess of acetic anhydride in pyridine solution to give the required starting material (3b) as a crystalline solid in 86% overall yield for the three steps based on uridine. It was quite convenient to carry out this preparation starting from relatively large quantities (*i.e.* 0.1 mol or more, see Experimental section) of uridine.

Uracil nucleosides have been converted into the corresponding cytosine and 4-*N*-substituted cytosine nucleosides in several ways. Vorbrüggen's trimethylsilyl procedure,[7] by which it should be possible to convert unprotected ara-U (3a) directly into ara-C derivatives (1),



(1)



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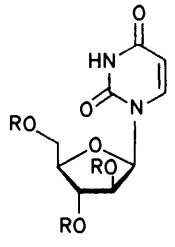
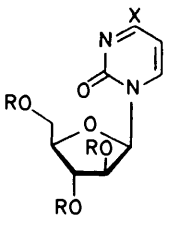


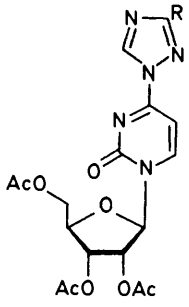
(3) a; R = H
b; R = Ac

would appear to be the most straightforward way. However, the reaction conditions are relatively drastic and an autoclave is required [7] when volatile amines are used. Furthermore, the procedure cannot be used [7] in the preparation of 4-*N*-aryl cytosine nucleosides. 4-Chloro-1-(β-D-2,3,5-tri-*O*-acetylarabinofuranosyl)pyrimidin-2(1*H*)-one [8] (4a; R = Ac), which may be prepared directly from ara-U (3a), reacts readily [8] with ammonia to give ara-C (1; $R^1 = R^2 = H$) and would also presumably react with other nitrogen nucleophiles. However, it has been isolated [8] as a moisture-sensitive syrup which cannot

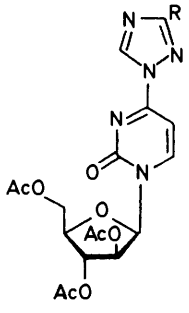
be induced to crystallize. 4-Thiouracil nucleosides such as (4b; R = H or acyl), presumably present mainly in the thiolactam tautomeric form, are also potentially suitable intermediates for the present purpose. Thus Fox and his co-workers have prepared cytidine [9] and 4-*N*,4-*N*-dimethylcytidine [10] in high yields by treating 2′,3′,5′-tri-*O*-benzoyl-4-thiouridine [9] with ammonia and dimethylamine, respectively, but had to carry out the



(4) a; X = Cl
b; X = SH
c; X = SMe



(5) a; R = H
b; R = NO_2



(6) a; R = H
b; R = NO_2

reactions at 100 °C in sealed tubes. Not surprisingly, the corresponding 4-methylmercapto-derivatives [*e.g.* (4c)] have proved [11] to be more reactive intermediates. Indeed, Fox and his co-workers found [12] that, when the sulphide (4c; R = H) was allowed to react with neat methylamine for 20 h in a sealed vessel at room temperature, the 4-*N*-methyl derivative of ara-C (1; R^1 = H, R^2 = Me) was obtained in very high yield.

While both the chloro-compound (4a; R = Ac) and the methylmercapto-compound (4c; R = H) appeared to be potentially useful general intermediates in the synthesis of 4-*N*-alkyl and -aryl derivatives of ara-C (1), it seemed to us that a stable crystalline compound which was less reactive than compound (4a; R = Ac) and more reactive than the sulphide (4c; R = H) would be the synthetic intermediate of choice. Fortunately, some studies which we had recently carried out,[13] with the intention of elucidating the nature of the side-reactions involving uracil residues in oligoribonucleotide synthesis,[14] suggested two intermediates to us which seemed likely to meet the above requirements.

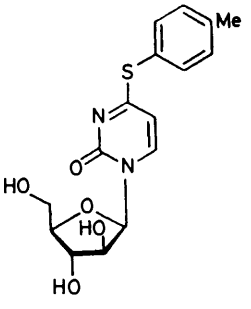
When 2′,3′,5′-tri-*O*-acetyluridine was allowed to react with an excess of 1-(mesitylene-2-sulphonyl)-3-nitro-1,2,4-triazole,[14,15] in the presence of a catalytic amount of diphenyl hydrogen phosphate in pyridine solution, 4-(3-nitro-1,2,4-triazol-1-yl)-1-(β-D-2,3,5-tri-*O*-acetylribofuranosyl)pyrimidin-2(1*H*)-one (5b) was obtained [13] and could be isolated as a stable crystalline solid in good yield. This compound (5b), which was subsequently prepared [16] more conveniently by treating 2′,3′,5′-tri-*O*-acetyluridine with diphenyl phosphorochloridate and 3-nitro-1,2,4-triazole, was found [13] to react readily with ammonia in wet dioxan solution. Following the removal of the acetyl groups by treatment with methanolic ammonia, cytidine was obtained [13] as the sole product. When the nitro-derivative (5b) was treated with 1,2,4-triazole and triethylamine in acetonitrile solution, compound (5a) was obtained [16] as a crystalline solid in high yield. It was later found that this derivative (5a) could be more conveniently obtained by treating 2′,3′,5′-tri-*O*-acetyluridine with *o*-chlorophenyldi(1*H*-1,2,4-triazol-1-yl)phosphine oxide [17] or with the even more readily accessible tri(1*H*-1,2,4-triazol-1-yl)phosphine oxide [18] [prepared [19] *in situ* by treating phosphoryl chloride with at least 3 mol equiv. each of 1,2,4-triazole and triethylamine] in acetonitrile solution. It was anticipated that both compounds (5a) and (5b) would be valuable intermediates in the syntheses of 4-*N*-alkyl and -aryl derivatives of cytidine and that the corresponding arabinosides (6a) and (6b), respectively, would similarly be of value in the syntheses of the corresponding derivatives (1) of ara-C.

4-(1,2,4-Triazol-1-yl)-1-(β-D-2,3,5-tri-*O*-acetylarabinofuranosyl)pyrimidin-2(1*H*)-one (6a) was prepared by treating 1-(β-D-2,3,5-tri-*O*-acetylarabinofuranosyl)uracil (3b) with a *ca.* two-fold excess of the putative tri(1*H*-1,2,4-triazol-1-yl)phosphine oxide [19] in the presence of additional 1,2,4-triazole and triethylamine in acetonitrile at room temperature. The reaction was complete after 90 min and the desired intermediate (6a) was isolated from the products as a crystalline solid, m.p. 160 °C, in 89% yield. The proportions of the reactants required have not yet been optimized. However, the reaction conditions are suitable for relatively large-scale preparations (see Experimental section). When compound (3b) was treated with diphenyl phosphorochloridate (*ca.* 2.1 mol equiv.) and 3-nitro-1,2,4-triazole (*ca.* 2.5 mol equiv.) in pyridine solution at room temperature 4-(3-nitro-1,2,4-triazol-1-yl)-1-(β-D-2,3,5-tri-*O*-acetylarabinofuranosyl)pyrimidin-2(1*H*)-one (6b) was obtained and was isolated from the products as a crystalline solid, m.p. 89 °C, in 87% yield.

The results obtained by treating compounds (6a) and (6b) with ammonia and a selected group of amino-compounds are summarized in the Table. The 1,2,4-triazolyl-compound (6a) readily underwent nucleophilic substitution at C-4 with some apparent (by t.l.c.) concomitant deacetylation when it was treated with aqueous ammonia, ethanolic dimethylamine, and morpholine in dioxan solution at room temperature (experiments nos.

1, 3 and 4, respectively, in Table). Treatment of these initial reaction products with methanolic ammonia at room temperature gave the desired ara-C derivatives (1; $R^1 = R^2 = H$), (1; $R^1 = R^2 = Me$), and [1; R^1,-$R^2 = -(CH_2)_2O(CH_2)_2-$] which were isolated as crystalline solids in yields of 92, 96, and 96%, respectively. The 4-*N*-methyl derivative of ara-C (1; $R^1 = H$, $R^2 = Me$) was even more readily prepared (experiment no. 2 in Table) from the 1,2,4-triazolyl compound (6a) by treating it with a relatively large excess of methylamine in ethanol solution at room temperature for 2 h; it was isolated as a crystalline solid in 93% yield. Not unexpectedly, the reaction between compound (6a) and aniline (experiment no. 5 in Table) proceeded much less readily and was best carried out in boiling pyridine solution. Under these conditions the reaction was complete in 4.5 h and, following the removal of the acetyl groups by treatment with ammonia in methanol solution at room temperature, the 4-*N*-phenyl derivative of ara-C (1; $R^1 = H$, $R^2 = Ph$) was obtained and isolated as a crystalline solid in 91% yield. The 4-*N*-phenyl derivative (1; $R = H$, $R^2 = Ph$) was also prepared (experiment no. 6 in Table) from 4-(3-nitro-1,2,4-triazol-1-yl)-1-(β-D-2,3,5-tri-*O*-acetylarabinofuranosyl)pyrimidin-2(1*H*)-one (6b). The reaction between the latter compound (6b) and aniline in boiling pyridine solution was complete in 25 min and, after deacetylation of the products, the 4-*N*-phenyl derivative of ara-C (1; $R^1 = H$, $R^2 = Ph$) was isolated in 96% yield. Finally, when the nitro-compound (6b) was allowed to react with glycine methyl ester (generated *in situ* from its hydrochloride and triethylamine) in acetonitrile at room temperature for 1 h (experiment no. 7 in Table), and the products treated with sodium methoxide in methanol solution, the 4-*N*-methoxycarbonylmethyl derivative of ara-C (1; $R^1 = H$, $R^2 = CH_2CO_2Me$) was obtained and isolated as a crystalline solid in 91% yield.

It is clear from the above results that both compounds (6a) and (6b) are valuable intermediates * in the synthesis of ara-C (1; $R^1 = R^2 = H$) and its 4-*N*-alkyl and -aryl derivatives (1). In each experiment (see Table) high yields of crystalline products were obtained and the reactive intermediates (6a) and (6b) themselves were both obtained in overall yields of *ca.* 75% for the four steps starting from uridine. The final products (1) were characterized on the basis of microanalytical and spectroscopic evidence. Their n.m.r. spectra are of particular interest: the anomeric protons of ara-C and its five derivatives (see Table) all resonate in the range δ 6.02—6.07 p.p.m. with $J_{1',2'}$ *ca.* 4 Hz in each case. The chemical shifts of their C-2′ and C-3′ resonance signals are perhaps even more significant. We have previously found [2,4] that, in the case of purine arabinosides, the C-2′ and C-3′ resonance signals usually both occur in the region of δ 74—77 p.p.m. and the difference between them is rarely greater than 2 p.p.m. This generalization appears also to hold for pyrimidine arabinosides.



(7)

The synthetic intermediates (6a) and (6b) would clearly be expected to react with nucleophiles other than ammonia and primary and secondary amines. Indeed, when the 1,2,4-triazolyl compound (6a) was allowed to react with toluene-*p*-thiol and triethylamine in dioxan solution and the products were then treated with ammonia in methanol solution, the 4-*p*-tolylthio-derivative (7) was obtained and isolated as a crystalline solid in 88% yield. In this initial study, we have not attempted to investigate the full synthetic potential of the intermediates (6a) and (6b) or indeed of the corresponding ribonucleoside derivatives [13,16-18] (5a) and (5b); we have

TABLE

Products obtained from reactions of compounds (6a) and (6b) with amino-compounds

Expt. no.	Substrate	Amino-compound	Isolated product (1) [a] R^1	R^2	Yield [b] (%)	M.p. (°C)	N.m.r. [$(CD_3)_2SO$] (δ p.p.m.) [c] H-1′ ($J_{1',2'}$ Hz)	C-5′	C-2′, C-3′	C-1′, C-4′
1	(6a)	NH_3	H	H	92	212—213	6.04(4.1)	61.20	74.80, 76.38	84.83, 85.88
2	(6a)	$MeNH_2$	H	Me	93	256 (decomp.)	6.04(4.0)	61.25	74.92, 76.44	84.88, 85.94
3	(6a)	Me_2NH	Me	Me	96	226 (decomp.)	6.05(4.0)	61.20	74.86, 76.38	85.00, 86.00
4	(6a)	Morpholine	$-(CH_2)_2O(CH_2)_2-$		96	211.5	6.04(4.0)	61.20	74.86, 76.32	85.12, 86.12
5	(6a)	$PhNH_2$	H	Ph	91	263	6.07(4.1)	61.25	74.86, 76.44	84.24, 86.41
6	(6b)	$PhNH_2$	H	Ph	96					
7	(6b)	$MeO_2CCH_2NH_2$	H	CH_2CO_2Me	91	188—189	6.02(3.7)	61.10	74.70, 76.29	84.91, 85.90

[a] Except in the case of experiment no. 2, the initial products are deacetylated by treatment with ammonia (experiments nos. 1, 3, 4, 5, and 6) or sodium methoxide (experiment no. 7). [b] These percentages represent isolated yields of products following crystallization. [c] No attempt has been made to assign chemical shifts (a) in the region of δ 74—76 p.p.m., specifically to the resonances of C-2′ and C-3′ or (b) in the region of δ 84—86 p.p.m., specifically to the resonances of C-1′ and C-4′.

* As indicated above compounds (6a) and (6b) can both be readily prepared in high yields from the acetylated compound (3b). In choosing between the triazolyl derivatives (6a) and (6b) it should be noted that while the nitro-compound (6b) is the more reactive, compound (6a) is somewhat more accessible in that 1,2,4-triazole is commercially available at a moderate price.

also not yet investigated the reactions between other hetero-aromatic lactam systems [*i.e.* systems other than 1-alkyluracil derivatives such as (3b) or 2′,3′,5′-tri-*O*-acetyluridine] and tri(1*H*-1,2,4-triazol-1-yl)phosphine oxide [19] or diphenyl phosphorochloridate–3-nitro-1,2,4-triazole. We nevertheless believe that the novel activation methods described in this paper will find more widespread application in heterocyclic chemistry.

EXPERIMENTAL

^{1}H N.m.r. spectra were measured at 250 MHz with a Bruker WH 250 spectrometer. ^{13}C N.m.r. spectra were measured at 22.63 MHz with a Bruker HFX 90 spectrometer. Tetramethylsilane was used as an internal standard. U.v. spectra were measured with a Cary 17 recording spectrophotometer. Merck silica gel 60 F_{254} plates [developed in chloroform–methanol (19 : 1 v/v) (system A)] and DC-Alufolien cellulose F_{254} sheets [developed in butan-1-ol–acetic acid–water (5 : 2 : 3 v/v) (system B)] were used for t.l.c. Merck silica gel H was used for short-column chromatography. Acetonitrile, triethylamine and pyridine were dried by heating, under reflux, with calcium hydride for 3—5 h; the solvents were than distilled at atmospheric pressure. Acetonitrile and pyridine were stored over molecular sieves (no. 4A).

1-(β-D-2,3,5-*Tri*-O-*acetylarabinofuranosyl*)*uracil* (3b).—Uridine (26.5 g, 0.109 mol), diphenyl carbonate (30.96 g, 0.145 mol; recrystallised from ethanol), anhydrous sodium hydrogen carbonate (0.697 g, 8.3 mmol) and redistilled hexamethylphosphoric triamide (105 ml) were stirred together with the exclusion of moisture at 150 °C. After 20 min the products were cooled and poured into cold water (850 ml), the resulting mixture extracted with chloroform (3 × 100 ml) and the extracts discarded. Triethylamine (50 ml, 0.36 mol) was added to the remaining aqueous layer which was then heated at 70 °C for 5 h. The products were then cooled and evaporated to dryness under reduced pressure. The residue was dissolved in pyridine (100 ml) and the resulting solution was evaporated under reduced pressure. After this process had been repeated three times more, the residue was dissolved in pyridine (280 ml) and acetic anhydride (48.8 ml, 0.52 mol) was added. The reactants were stirred at room temperature for 5 h, then treated with methanol (50 ml) and, after a further period of 30 min, concentrated under reduced pressure. The residue was evaporated with ethanol (3 × 100 ml) and toluene (50 ml) and then crystallized from ethanol (500 ml) to give 1-(β-D-2,3,5-tri-*O*-acetylarabinofuranosyl)uracil (Found: C, 48.4; H, 4.8; N, 7.5. Calc. for $C_{15}H_{18}N_2O_9$: C, 48.65; H, 4.9; N, 7.6%), m.p. 129 °C (lit.,[5] 129—130 °C); yield (in 2 crops) 34.7 g (86% based on uridine); R_F (system A) 0.53; $\lambda_{max.}$ (95% EtOH) 258 (ε 9 600), $\lambda_{min.}$ 236 nm (3 200); δ_H [$(CD_3)_2SO$] 1.98 (3 H, s), 2.07 (3 H, s), 2.10 (3 H, s), 4.2—4.4 (3 H, m), 5.22 (1 H, m), 5.36 (1 H, dd, *J* 3.2 and 5.0 Hz), 5.67 (1 H, d, *J* 7.8 Hz), 6.23 (1 H, d, *J* 5.1 Hz), 7.59 (1 H, d, *J* 8.3 Hz), and 11.44br (1 H, s); δ_C [$(CD_3)_2SO$] 20.15, 20.50, 62.78, 74.33, 75.33, 78.32, 83.07, 101.30, 141.06, 149.91, 162.81, 168.80, 169.62, and 170.14 p.p.m.

4-(1,2,4-*Triazol*-1-*yl*)-1-(β-D-2,3,5-*tri*-O-*acetylarabinofuranosyl*)*pyrimidin*-2(1H)-*one* (6a).—Triethylamine (64.8 ml, 0.465 mol) was added dropwise to a stirred, cooled (ice–water bath) mixture of 1,2,4-triazole (33.56 g, 486 mmol), phosphoryl chloride (9.7 ml, 104 mmol) and acetonitrile (280 ml). To the resulting products was added a solution of (3b) (20.0 g, 54 mmol) in acetonitrile (170 ml) and the reaction mixture was stirred at room temperature for 90 min. Triethylamine (45 ml, 320 mmol) and water (11.6 ml, 650 mmol) were then added and, after 10 min, the solvent was evaporated under reduced pressure. The residue was partitioned between chloroform (250 ml) and saturated aqueous sodium hydrogen carbonate (200 ml). The organic layer was separated off and the aqueous layer was extracted with chloroform (2 × 75 ml). The combined organic layers were dried ($MgSO_4$) and the residue crystallized from ethanol to give 4-(1,2,4-*triazol*-1-*yl*)-1-(β-D-2,3,5-*tri*-O-*acetylarabinofuranosyl*)*pyrimidin*-2(1H)-*one* (Found: C, 48.8; H, 4.6; N, 16.65. $C_{17}H_{19}N_5O_8$ requires C, 48.5; H, 4.5; N, 16.6%), m.p. 160 °C; yield (in 3 crops) 20.4 g (89%); R_F (system A) 0.56; $\lambda_{max.}$ (95% EtOH) 313, 250 (ε 7 550, 13 300), $\lambda_{min.}$ 279, 233 nm (ε 2 430, 5 840); δ_H [$(CD_3)_2SO$] 1.92 (3 H, s), 2.10 (3 H, s), 2.14 (3 H, s), 4.38 (3 H, m), 5.21 (1 H, m), 5.50 (1 H, dd, *J* 2.3 and 4.6 Hz), 6.31 (1 H, d, *J* 4.6 Hz), 7.08 (1 H, d, *J* 7.3 Hz), 8.39 (1 H, d, *J* 7.3 Hz), 8.43 (1 H, s), and 9.47 (1 H, s); δ_C [$(CD_3)_2SO$] 20.15, 20.50, 62.78, 73.45, 75.74, 79.96, 85.41, 93.97, 143.82, 148.68, 153.08, 154.14, 159.00, 168.50, 169.56, and 170.26 p.p.m.

4-(3-*Nitro*-1,2,4-*triazol*-1-*yl*)-1-(β-D-2,3,5-*tri*-O-*acetylarabinofuranosyl*)*pyrimidin*-2(1H)-*one* (6b).—1-(β-D-2,3,5-Tri-*O*-acetylarabinofuranosyl)uracil (3.70 g, 10.0 mmol), 3-nitro-1,2,4-triazole (2.85 g, 25 mmol), diphenyl phosphorochloridate (4.35 ml, 21 mmol) and pyridine (150 ml) were stirred together at room temperature. After 3 h water (4.5 ml) was added and, after a further period of 10 min, the products were concentrated under reduced pressure. The residue was partitioned between chloroform (100 ml) and saturated aqueous sodium hydrogen carbonate (100 ml). The organic layer was separated, washed with saturated aqueous sodium hydrogen carbonate (2 × 100 ml) and water (100 ml) and dried ($MgSO_4$). It was then concentrated under reduced pressure. When propan-2-ol (90 ml) was added to a solution of the resulting glass in ethyl acetate (15 ml), crystals of 4-(3-*nitro*-1,2,4-*triazol*-1-*yl*)-1-(β-D-2,3,5-*tri*-O-*acetylarabinofuranosyl*)*pyrimidin*-2(1H)-*one* were obtained (Found: C, 44.0; H, 4.05; N, 17.8. $C_{17}H_{18}N_6O_{10}$ requires C, 43.8; H, 3.9; N, 18.0%), m.p. 89 °C; yield 4.05 g (87%) (after chromatography of the mother liquors and recrystallization from propan-2-ol); R_F (system A) 0.57; $\lambda_{max.}$ (95% EtOH) 323, 248 (ε 6 100, 15 000), $\lambda_{min.}$ 290, 232 nm (3 300, 11 600); δ_H [$(CD_3)_2SO$] 1.91 (3 H, s), 2.10 (3 H, s), 2.14 (3 H, s), 4.3—4.5 (3 H, m), 5.22 (1 H, m), 5.53 (1 H, dd, *J* 2.3 and 4.6 Hz), 6.33 (1 H, d, *J* 4.6 Hz), 7.12 (1 H, d, *J* 6.9 Hz), 8.48 (1 H, d, *J* 7.3 Hz), and 9.79 (1 H, s).

1-(β-D-*Arabinofuranosyl*)*cytosine* (1; $R^1 = R^2 = H$).—Aqueous ammonia (*d* 0.88) (1.6 ml, 30 mmol) was added to a solution of compound (6a) (1.054 g, 2.5 mmol) in dioxan (10 ml) at room temperature. After 6 h the products were concentrated under reduced pressure and the residue was dissolved in methanolic ammonia (half-saturated at 0 °C, 16.5 ml). After 16 h the products were evaporated to dryness. Crystallization of the residue from aqueous ethanol gave 1-(β-D-*arabinofuranosyl*)*cytosine* (Found: C, 44.2; H, 5.3; N, 17.0. Calc. for $C_9H_{13}N_3O_5$: C, 44.4; H, 5.4; N, 17.3%), m.p. 212—213 °C (lit.,[8] 212—213 °C); yield 0.562 g (92%); R_F (system B) 0.58; $\lambda_{max.}$ (H_2O) 272 (ε 9 700), $\lambda_{min.}$ 250 nm (6 100); δ_H [$(CD_3)_2SO$] 3.60 (2 H, m), 3.74 (1 H, m), 3.89 (1 H, m), 3.95 (1 H, m), 5.02 (1 H, m), 5.40 (2 H, m), 5.67 (1 H, d, *J* 7.3 Hz), 6.04 (1 H, d, *J* 4.1 Hz), 7.08 (2 H, m), 7.58 (1 H, d, *J* 7.3 Hz); δ_C [$(CD_3)_2$-

SO] 61.20, 74.80, 76.38, 84.83, 85.88, 92.45, 142.94, 155.25, and 165.63 p.p.m.

4-*Methylamino*-1-(β-D-*arabinofuranosyl*)*pyridin*-2(1H)-*one* (1; R^1 = H, R^2 = Me).—A solution of (6a) (2.50 g, 5.9 mmol) in ethanolic methylamine (33% w/w; 11.1 ml) was stirred at room temperature. After 2 h the resulting suspension was concentrated under reduced pressure. Crystallization of the residue from ethanol–water (9 : 1 v/v) gave 4-*methylamino*-1-(β-D-*arabinofuranosyl*)*pyrimidin*-2(1H)-*one* (Found: C, 46.4; H, 5.8; N, 16.65. $C_{10}H_{15}N_3O_5$ requires C, 46.7; H, 5.9; N, 16.3%), m.p. 256 °C (decomp.) [lit.,[12] 264—265 °C (decomp.)]; yield 1.42 g (93%); R_F (system B) 0.60; $\lambda_{max.}$ (95% EtOH) 271, 234 (ε 11 500, 8 800), $\lambda_{min.}$ 249, 229 nm (7 700, 8 600); δ_H [$(CD_3)_2SO$–D_2O] 2.76 (3 H, s), 3.55—3.70 (2 H, m), 3.76 (1 H, m), 3.89 (1 H, m), 3.97 (1 H, dd, *J* 2.6 and 4.0 Hz), 5.71 (1 H, d, *J* 7.7 Hz), 6.04 (1 H, d, *J* 4.0 Hz), and 7.54 (1 H, d, *J* 7.4 Hz); δ_C [$(CD_3)_2SO$] 26.95, 61.25, 74.92, 76.44, 84.88, 85.94, 93.21, 141.59, 155.37, and 163.93 p.p.m.

4-*Dimethylamino*-1-(β-D-*arabinofuranosyl*)*pyrimidin*-2-(1H)-*one* (1; R^1 = R^2 = Me).—Ethanolic dimethylamine (33% w/w; 3.25 ml, *ca.* 18 mmol) was added to a solution of compound (6a) (2.0 g, 4.7 mmol) in dioxan (40 ml) at room temperature. After 90 min the products were concentrated under reduced pressure and the residue was dissolved in methanolic ammonia (half-saturated at 0 °C; 25 ml) at room temperature. After 16 h the products were evaporated to dryness. Crystallization of the residue from methanol gave 4-*dimethylamino*-1-(β-D-*arabinofuranosyl*)*pyrimidin*-2(1H)-*one* (Found: C, 48.4; H, 6.4; N, 15.3. $C_{11}H_{17}N_3O_5$ requires C, 48.7; H, 6.3; N, 15.5%), m.p. 226 °C (decomp.); yield 1.24 g (96%); R_F (system B) 0.62; $\lambda_{max.}$ (95% EtOH) 278 (ε 14 600), $\lambda_{min.}$ 239 nm (7 000); δ_H [$(CD_3)_2SO$] 3.03 (6 H, s), 3.60 (2 H, m), 3.76 (1 H, m), 3.91 (1 H, m), 3.97 (1 H, m), 5.06 (1 H, t, *J* 5.3 Hz), 5.41 (2 H, m), 6.00 (1 H, d, *J* 7.7 Hz), 6.05 (1 H, d, *J* 4.0 Hz), and 7.66 (1 H, d, *J* 7.7 Hz); δ_C[$(CD_3)_2SO$] 36.86, 61.20, 74.86, 76.38, 85.00, 86.00, 89.93, 142.89, 154.37, and 163.17 p.p.m.

4-*Morpholino*-1-(β-D-*arabinofuranosyl*)*pyrimidin*-2(1H)-*one* [1; R^1,R^2 = $-(CH_2)_2O(CH_2)_2-$].—Morpholine (1.45 ml, 16.6 mmol) was added to a solution of compound (6a) (2.0 g, 4.7 mmol) in dioxan at room temperature. After 2 h the products were concentrated under reduced pressure and the residue was dissolved in methanolic ammonia (half-saturated at 0 °C; 25 ml) at room temperature and, after a further period of 16 h, the products were concentrated to dryness. Crystallization of the residue from ethanol gave 4-*morpholino*-1-(β-D-*arabinofuranosyl*)*pyrimidin*-2(1H)-*one* (Found: C, 49.7; H, 5.8; N, 13.4. $C_{13}H_{19}N_3O_6$ requires C, 49.8; H, 6.1; N, 13.4%), m.p. 211.5 °C; yield 1.43 g (96%); R_F (system B) 0.58; $\lambda_{max.}$ (95% EtOH) 283 (ε 16 500), $\lambda_{min.}$ 238 nm (7 060); δ_H [$(CD_3)_2SO$] 3.62 (10 H, m), 3.77 (1 H, m), 3.90 (1 H, m), 3.98 (1 H, m), 5.07 (1 H, t, *J* 5.5 Hz), 5.42 (2 H, d, *J* 4.4 Hz), 6.04 (1 H, d, *J* 4.0 Hz), 6.12 (1 H, d, *J* 7.7 Hz), and 7.71 (1 H, d, *J* 7.7 Hz); δ_C [$(CD_3)_2SO$] 44.13, 61.20, 66.00, 74.86, 76.32, 85.12, 86.12, 89.81, 143.58, 154.61, and 162.70 p.p.m.

4-*Anilino*-1(β-D-*arabinofuranosyl*)*pyrimidin*-2(1H)-*one* (1; R^1 = H, R^2 = Ph).—(a) A solution of compound (6a) (2.5 g, 5.9 mmol) and freshly distilled aniline (4.42 ml, 48.5 mmol) in anhydrous pyridine (25 ml) was heated, under reflux, for 4.5 h. The cooled products were evaporated under reduced pressure and then triturated with diethyl ether to remove the remaining aniline. The residue was dissolved in methanolic ammonia (half-saturated at 0 °C; 30 ml) at room temperature and, after 16 h, the products were evaporated under reduced pressure. Crystallization of the residue from ethanol–water (1 : 4 v/v) gave 4-*anilino*-1-(β-D-*arabinofuranosyl*)*pyrimidin*-2(1H)-*one* (Found: C, 56.7; H, 5.55; N, 13.1. $C_{15}H_{17}N_3O_5$ requires C, 56.4; H, 5.4; N, 13.2%), m.p. 263 °C; yield 1.73 g (91%); R_F (system B) 0.81; $\lambda_{max.}$ (95% EtOH) 294 (ε 18 500), $\lambda_{min.}$ 249 nm (5 900); δ_H [$(CD_3)_2SO$] 3.61 (2 H, m), 3.79 (1 H, m), 3.92 (1 H, m), 4.02 (1 H, m), 5.04 (1 H, t, *J* 5.3 Hz), 5.44 (2 H, m), 5.97 (1 H, d, *J* 8.3 Hz), 6.07 (1 H, d, *J* 4.1 Hz), 7.04 (1 H, m), 7.32 (2 H, m), 7.76 (3 H, m), and 9.67 (1 H, s); δ_C [$(CD_3)_2SO$] 61.25, 74.86, 76.44, 85.24, 86.41, 94.09, 120.42, 123.06, 128.63, 139.36, 143.00, 154.96, and 162.05 p.p.m.

(b) A solution of 4-(3-nitro-1,2,4-triazol-1-yl)-1-(β-D-2,3,5-tri-*O*-acetylarabinofuranosyl)pyrimidin-2(1H)-one (6b) (0.233 g, 0.5 mmol) and freshly distilled aniline (0.45 ml, 4.9 mmol) in pyridine (2 ml) was heated, under reflux, for 25 min. The products were then worked-up and treated with ammonia in methanol solution, as above, to give 4-*anilino*-1-(β-D-*arabinofuranosyl*)*pyrimidin*-2(1H)-*one* (0.153 g, 96%).

4-*Methoxycarbonylmethylamino*-1-(β-D-*arabinofuranosyl*)-*pyrimidin*-2(1H)-*one* (1; R^1 = H, R^2 = CH_2CO_2Me).—4-(3-Nitro-1,2,4-triazol-1-yl)-1-(β-D-2,3,5-tri-*O*-acetylarabinofuranosyl)pyrimidin-2(1*H*)-one (6b) (1.85 g, 3.97 mmol), glycine methyl ester hydrochloride (0.87 g, 6.9 mmol), triethylamine (1.1 ml, 7.9 mmol), and acetonitrile (30 ml) were stirred together at room temperature. After 1 h the products were concentrated under reduced pressure to give a thick syrup which was dissolved in chloroform (50 ml), and the solution extracted with water (3 × 25 ml). The dried ($MgSO_4$) organic layer was concentrated under reduced pressure to give a glass which was dissolved in methanol (30 ml) and the solution was treated with 25% methanolic sodium methoxide (3.0 ml, *ca.* 13 mmol) at room temperature. After 15 min, the products were neutralized with acetic acid and evaporated under reduced pressure. Crystallization of the residue from propan-2-ol gave 4-*methoxycarbonylmethylamino*-1-(β-D-*arabinofuranosyl*)*pyrimidin*-2(1H)-*one* (Found: C, 45.7; H, 5.5; N, 13.6. $C_{12}H_{17}N_3O_7$ requires C, 45.7; H, 5.4; N, 13.3%), m.p. 188—189 °C; yield 1.15 g (91%); R_F (system B) 0.64; $\lambda_{max.}$ (95% EtOH) 273 (ε 6 850), $\lambda_{min.}$ 250 (4 650), $\lambda_{infl.}$ 230 nm 5 600); δ_H [$(CD_3)_2SO$] 3.59 (2 H, m), 3.65 (3 H, s), 3.75 (1 H, m), 3.90 (1 H, m), 3.95 (1 H, m), 4.06 (2 H, d, *J* 6.0 Hz), 5.04 (1 H, m), 5.43 (2 H, m), 5.82 (1 H, d, *J* 7.3 Hz), 6.02 (1 H, d, *J* 3.7 Hz), 7.61 (1 H, d, *J* 7.3 Hz), and 8.04 (1 H, t, *J* 6.0 Hz); δ_C [$(CD_3)_2SO$] 41.34, 51.66, 61.10, 74.70, 76.29, 84.91, 85.90, 92.82, 142.37, 154.86, 163.54, and 170.34 p.p.m.

4-(p-*Tolylthio*)-1-(β-D-*arabinofuranosyl*)*pyrimidin*-2(1H)-*one* (7).—4-(1,2,4-Triazol-1-yl)-1-(β-D-2,3,5-tri-*O*-acetylarabinofuranosyl)pyrimidin-2(1*H*)-one (6a) (2.0 g, 4.7 mmol), toluene-*p*-thiol (3.0 g, 24 mmol), triethylamine (6.75 ml, 48 mmol) and dioxan (40 ml) were heated at 70 °C for 3 h. The cooled products were concentrated under reduced pressure and then triturated several times with cyclohexane. The solid residue thereby obtained was dissolved in methanolic ammonia (half-saturated at 0 °C; 35 ml) at room temperature. After 16 h, the products were evaporated to dryness. Crystallization of the residue from ethyl acetate–methanol gave 4-(p-*tolylthio*)-1-(β-D-*arabinofuranosyl*)*pyrimidin*-2(1H)-*one* (Found: C, 54.9; H, 5.3; N, 8.05. $C_{16}H_{18}N_2O_5S$ requires C, 54.8; H, 5.2; N, 8.0%), m.p. 173 °C; yield 1.47 g (88%); R_F (system B) 0.91; $\lambda_{max.}$ (95% EtOH) 307, 274 (ε 11 600, 8 700), $\lambda_{min.}$ 278, 243 nm (8 600, 4 100); δ_H [$(CD_3)_2SO$] 2.38 (3 H, s), 3.58 (2 H, m), 3.83 (1 H, m),

3.92 (1 H, m), 4.07 (1 H, m), 5.03 (1 H, t, *J* 5.5 Hz), 5.45—5.55 (2 H, m), 5.98 (1 H, d, *J* 4.0 Hz), 6.02 (1 H, d, *J* 7.4 Hz), 7.34 (2 H, d, *J* 8.1 Hz), 7.49 (2 H, d, *J* 8.1 Hz), and 7.92 (1 H, d, *J* 7.4 Hz); δ_C [$(CD_3)_2SO$] 20.91, 60.96, 74.57, 67.09, 86.00, 87.29, 99.90, 123.64, 130.51, 135.55, 140.30, 152.61, and 178.00 p.p.m.

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REFERENCES

[1] R. J. Suhadolnik, ' Nucleoside Antibiotics,' Wiley–Interscience, New York, 1970, pp. 156 *et. seq.*
[2] J. B. Chattopadhyaya and C. B. Reese, *J. Chem. Soc., Chem. Commun.*, 1977, **414**.
[3] K. J. Divakar and C. B. Reese, *J. Chem. Soc., Chem. Commun.*, 1980, 1191.
[4] J. B. Chattopadhyaya and C. B. Reese, *Synthesis*, 1978, 908.
[5] D. M. Brown, A. Todd, and S. Varadarajan, *J. Chem. Soc.*, 1956, 2388.
[6] J. P. H. Verheyden, D. Wagner, and J. G. Moffatt, *J. Org. Chem.*, 1971, **36**, 250.
[7] H. Vorbrüggen, K. Krolikiewicz, and U. Neidballa, *Liebigs Ann. Chem.*, 1975, 988.
[8] M. Kaneko and B. Shimizu, *Chem. Pharm. Bull.*, 1972, **20**, 1050.
[9] J. J. Fox, D. Van Praag, I. Wempen, I. L. Doerr, L. Cheong, J. E. Knoll, M. L. Eidinoff, A. Bendich, and G. B. Brown, *J. Am. Chem. Soc.*, 1959, **81**, 179.
[10] I. Wempen, R. Duschinsky, L. Kaplan, and J. J. Fox, *J. Am. Chem. Soc.*, 1961, **83**, 4755.
[11] J. J. Fox, N. Miller, and I. Wempen, *J. Med. Chem.*, 1966, **9**, 101.
[12] I. Wempen, N. Miller, E. A. Falco, and J. J. Fox, *J. Med. Chem.*, 1968, **11**, 144.
[13] C. B. Reese and A. Ubasawa, *Tetrahedron Lett.*, 1980, **21**, 2265; *Nucleic Acids Res. Symposium Series No. 7*, 1980, 5.
[14] S. S. Jones, B. Rayner, C. B. Reese, A. Ubasawa, and M. Ubasawa, *Tetrahedron*, 1980, **36**, 3075.
[15] C. B. Reese, R. C. Titmas, and L. Yau, *Tetrahedron Lett.*, 1978, 2727.
[16] C. B. Reese and A. Ubasawa, unpublished observations.
[17] C. B. Reese and M. Ubasawa, unpublished observations.
[18] G. R. Grierson and C. B. Reese, unpublished observations.
[19] A. Kraszewski and J. Stawinski, *Tetrahedron Lett.*, 1980, **21**, 2935.