Synthesis of some Piperidine Sugar Uracil Nucleosides with a 2,3'-Substituted-imino Bridge

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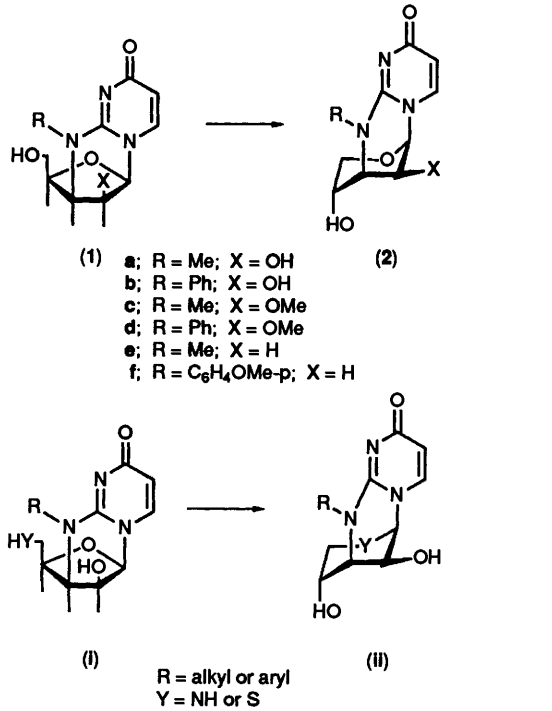
Base-catalysed isomerization of 2,3'-(substituted-imino)-1-(3'-deoxy-β-D-lyxofuranosyl)uracils (**1**) to the corresponding pyranosyl analogues (**2**) was extended to the synthesis of analogous 2,3'-imino nucleosides having a piperidine sugar moiety. Trimesyluridine (**3**) with methylamine gave the 2,3'-methylimino-5'-*O*-mesyl-lyxofuranosyluracil (**5**). Compound (**5**) with ammonia, methylamine, or benzylamine gave the corresponding 5'-amino (**6a**), 5'-methylamino (**6b**), or 5'-benzylamino analogue (**6c**), while the 3',5'-di-*O*-mesyl derivative (**4**) of 2,2'-anhydrouridine with aniline gave the 2,3'-phenylimino analogues (**6d**), (**7**), and (**8**). Alkaline hydrolysis of compounds (**6b** and **c**) with 3M-NaOH–EtOH gave the corresponding piperidine sugar nucleosides (**9a** and **b**), while similar treatment of compound (**6d**) gave the piperidine (**9c**) and the dianilinolyxofuranosyluracil (**10**). On the other hand, the same reaction with compound (**6a**) yielded 3-hydroxypyridine (**12**) and N^2-methylisocytosine (**13**) *via* the furanosyl-to-piperidinyl isomerization, anomeric bond fission, and elimination of compound (**13**) by [1,2]-hydride shift. 2'-*O*-Methyl analogue of (**6a**), compound (**18b**), with alkali gave N^2-methyl-N^2-(4-pyridino)isocytosine (**19**) exclusively, confirming the above mechanism for the formation of compounds (**12**) and (**13**) from (**6a**).

Previously, we reported that 2,3'-(substituted-imino)-1-(3'-deoxy-β-D-lyxofuranosyl)uracils like (**1a** and **b**) (Scheme 1) are convertible into their pyranosyl isomers, such as (**2a** and **b**), under strongly alkaline conditions[1] and that cleavage of the 2,3'-imino[1] or 2,2'-imino bridge[2] can also occur when the imino-bridge substituent R is an aryl group. More recently, some closer studies of the reaction conditions and mechanistic details for these transformations have been conducted using compounds (**1a–f**) as substrates for comparison purposes.[3]

At this stage, we were interested in the synthesis and biological evaluation of some 2,3'-substituted-imino uracil nucleosides having a piperidine- or tetrahydrothiopyran-type sugar moiety [(**ii**), Scheme 1], which seemed to be accessible from 2,3'-(substituted-imino)-lyxofuranosyluracils with a 5'-amino (or 5'-substituted amino) or 5'-thiol group (**i**) by similar isomerization reactions. In view of previous efforts to form nucleosides[4] or other glycosides[5] containing pyrrolidine sugars, the synthesis of compounds (**ii**; Y = NH or NR) appeared to be most attractive and the results of our synthetic work along these lines are described herein.

Substrate Synthesis.—On the basis of our previous experience,[1] 2',3',5'-tri-*O*-mesyluridine (**3**)[6] was treated with an excess of methylamine in dimethylformamide (DMF) under mild conditions to give a reasonable yield of (3'-deoxy-5'-*O*-mesyl-β-D-lyxofuranosyl)-2,3'-methyliminouracil (**5**), which should have been formed through 2,2'-anhydro-1-(3',5'-di-*O*-mesyl-β-D-arabinofuranosyl)uracil (**4**)[6] (Scheme 2). The 2,3'-cyclic nature of compound (**5**) was evident from the major UV absorption at 224 nm (Table 1), while the location of the remaining mesyloxy group at the C-5' was also clear from the highly deshielded signals of the 5'-methylene protons (δ 4.20 and 4.22, Table 2). Treatment of compound (**5**) with a large excess of ammonia gave 1-(5'-amino-3',5'-dideoxy-β-D-lyxofuranosyl)-2,3'-methylimino uracil (**6a**) as a crystalline methanesulphonate. Attempted isolation of compound (**6a**) as a free amine was unsuccessful.



Scheme 1.

Similarly, reaction of compound (**5**) with an excess of methylamine afforded a good yield of 1-(3',5'-dideoxy-5'-methylamino-β-D-lyxofuranosyl)-2,3'-methylaminouracil (**6b**). In the hope that an *N*-benzyl group would ultimately be removed by hydrogenolysis, 1-(5'-benzylamino-3',5'-dideoxy-β-D-lyxofuranosyl)-2,3'-methyliminouracil (**6c**) was also synthesized. The

Table 1. UV absorptions of compounds (**5**), (**6a–d**), (**7**), (**9a–c**), (**10**), (**17**), and (**18a** and **b**) in methanol.

Compound	λ_{max}/nm (ε)
(**5**)	218 (24 400), 224 (21 900)[a], 263 (3 100)[b]
(**6a**)	219 (23 000), 228 (19 200)[a], 264 (2 200)[b]
(**6b**)	218 (21 100), 227 (17 700)[a], 263 (2 400)[b]
(**6c**)	216 (26 300), 227 (19 000)[a], 264 (3 500)[b]
(**6d**)	205 (35 100), 242 (28 200), 295 (2 400)[a]
(**7**)	212 (30 000), 234 (28 800), 266 (20 500)[a]
(**9a**)	217 (23 700), 226 (20 200)[a], 263 (3 100)[b]
(**9b**)	214 (30 200), 227 (22 200)[a], 257 (4 400)[b]
(**9c**)	204 (40 800), 237 (25 200), 280 (5 900)[a]
(**10**)	203 (48 300), 246 (27 100), 267 (12 500)[a] 293 (3 800)[b]
(**17**)	219.5 (26 100), 228 (20 900)[a], 265 (2 700)[b]
(**18a**)	219.2 (22 900), 228 (18 700)[a], 265 (2 700)[b]
(**18b**)	218 (29 000), 229 (22 600)[a], 265 (3 600)[b]

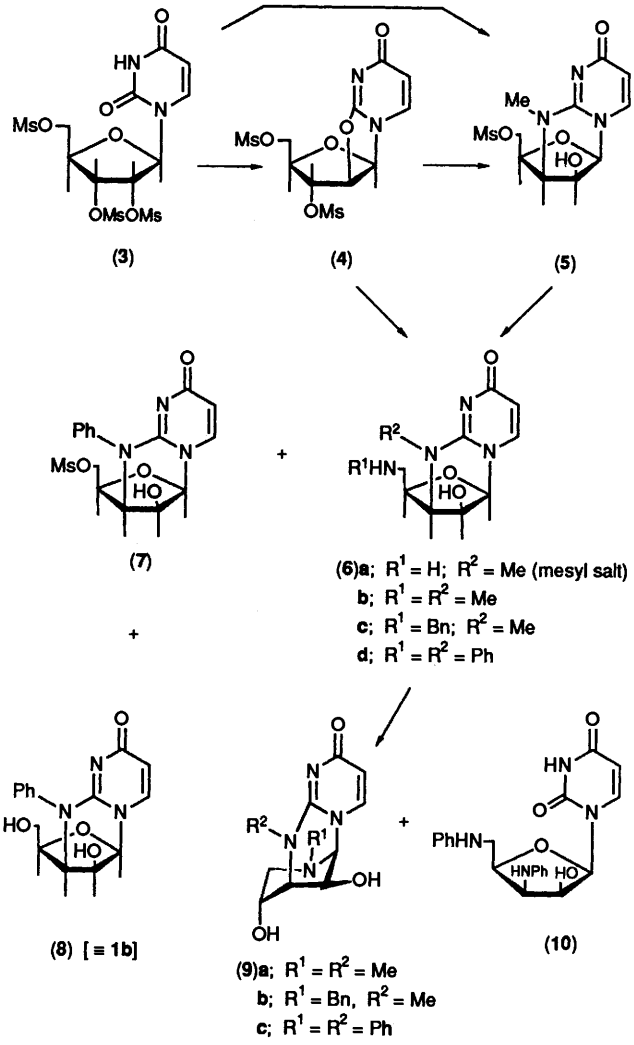
[a] Inflection. [b] Shoulder.

structure of compound (**6a–c**) is consistent with the general spectroscopic data (Tables 1 and 2): the rather shielded chemical shift (δ 2.33) for the mesyloxy anion in compound (**6a**), as compared with that of a mesyl ester, parallels our earlier finding,[7] and the reasonable resonances for the 5′-NHs in compounds (**6b** and **c**) confirm that the furanose ring has survived the rather drastic basic reaction conditions needed in both cases. On the other hand, displacement of the mesyloxy group in compound (**5**) with the less electrophilic aniline proved to be extremely difficult, while reaction of compound (**4**) with aniline under forcing conditions gave 1-(5′-anilino-3′,5′-dideoxy-β-D-lyxofuranosyl)-2,3′-phenyliminouracil (**6d**) (37%) together with the minor products 1-(3′-deoxy-5′-*O*-mesyl-β-D-lyxofuranosyl)-2,3′-phenyliminouracil (**7**) and 1-(3′-deoxy-β-D-lyxofuranosyl)-2,3′-phenyliminouracil (**8**) [≡(**1b**)].[1] Since a model study had shown that the 2,3′-phenylimino group in compound (**6d**) sterically hinders C-5′, the compound seems to have formed *via* C-5′-displacement prior to 2,3′-bridge formation.

Alkaline Hydrolysis of Compounds (**6**).—Alkaline hydrolysis of compound (**6b**) in a 1:1 mixture of 6M-NaOH and EtOH gave a mixture of two products, from which crystalline 1-(3′,5′-dideoxy-5′-methylamino-β-D-lyxopyranosyl)-2,3′-methyliminouracil (**9a**) was isolated in 24% yield. The UV spectrum of the product (**9a**) resembled that of compound (**6b**). The pyranosyl nature of its sugar moiety followed from the doublet signals for the two hydroxy protons, the well separated signals for the two 5′-methylene protons (Δ δ 0.5 ppm) as compared with the signals for the furanosyl precursor,[1,3] and also the significant upfield shifts of the anomeric as well as the 5′-methylene protons [> 1 ppm upfield shift when compared with the corresponding signals of the oxygen isostere (**2a**)[1]]. Except for these chemical-shift differences, the overall proton resonance pattern of compound (**9a**) was quite similar to that of compound (**2a**). The β configuration of the aglycone was evident from the small $J_{1',2'}$ value (~4 Hz).[8]

Since some TLC-controlled, small-scale experiments had shown that compound (**9a**) is rather less stable than its isostere (**2a**) under strongly alkaline conditions, compound (**6c**) was treated with 3M-NaOH in neat EtOH[3] for a limited period (4 h) to give 1-(5′-benzylamino-3′,5′-dideoxy-β-D-lyxopyranosyl)-2,3′-methyliminouracil (**9b**) as a single product [33% based on consumed (**6c**)] (see Experimental section). The spectroscopic features of compound (**9b**) parallel those of its methyl analogue (**9a**) (Tables 1 and 2). Despite others' previously unsuccessful attempts to obtain nucleosides containing an *N*-unsubstituted pyrrolidine sugar (a nitrogen hemiacetal),[4] formation of (**9**) having an N-unsubstituted piperidine sugar seemed to be probable under mild conditions in view of the generally known high stability of bicyclo[3.3.1] systems. Hence, compound (**9b**) was subjected to catalytic hydrogenolysis under atmospheric pressure to give very gradually, two more polar products, whose isolation has not yet been achieved. Similar alkaline hydrolysis of compound (**6d**) gave 1-(5′-anilino-3′,5′-dideoxy-β-D-lyxopyranosyl)-2,3′-phenyliminouracil (**9c**) and 1-(3′,5′-dianilino-3′,5′-dideoxy-β-D-lyxofuranosyl)uracil (**10**) in 26 and 10.4% yield, respectively. Although the resonance patterns of the 5′-H_2 and 1′-H in compound (**9c**) are rather different from those of (**9a** and **b**), perhaps owing to anisotropy by the phenyl groups, the doublet signals for the two hydroxy groups confirm the structure assigned to compound (**9c**). The formation of compound (**10**) was not unexpected from our earlier findings[1–3] and its structure was confirmed by the δ 11.29 signal normal for the 3-NH of a 1-substituted uracil, D_2O-exchangeable triplet signal of the 5′-NHPh group, 6.01 signal normal for the 1′-H of a furanosyl uracil, and other ^1H NMR and UV spectral features.

Compound (**6a**) was similarly treated with 3M-NaOH in neat EtOH with TLC monitoring until the starting material disappeared to give, unexpectedly, 3-hydroxypyridine (**12**) and N^2-methylisocytosine (**13**)[9] in comparable yields (Scheme 3). The latter was identical with an authentic sample obtainable together with 1-methylisocytosine (**16**) from 1,3-dimethyluracil



Scheme 2.

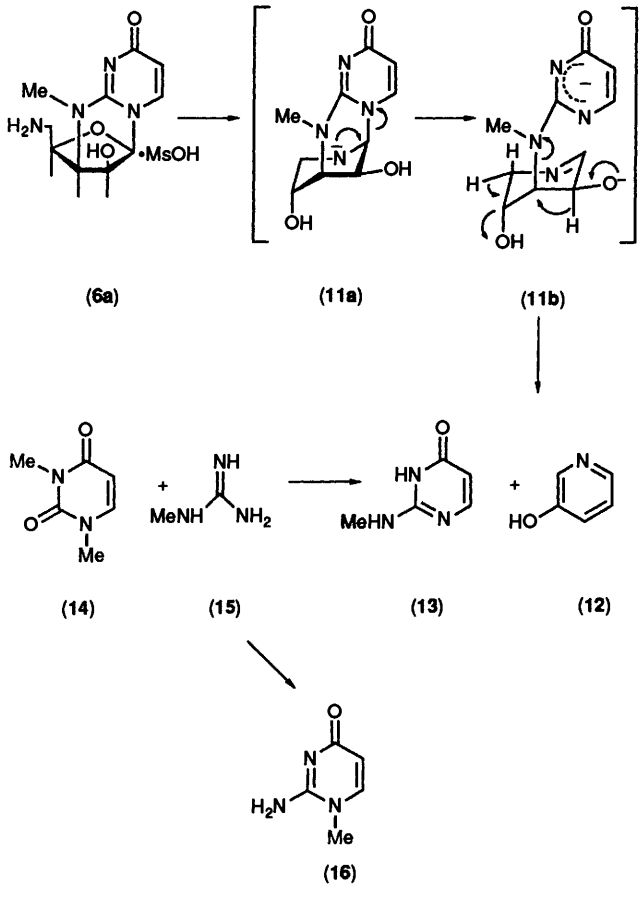
Table 2. ^{1}H NMR resonances of compounds (**5**), (**6a–d**), (**7**), (**9a–c**), (**10**), (**17**), and (**18a** and **b**) in [$^2H_6$]Me_2SO.[a]

Compound	5′-H	4′-H	3′-H	2′-H	1′-H	5-H	6-H	others
(**5**)	4.20 (1 H, dd, J_{gem} 10.8, $J_{5',4'}$ 7.2, 5′-H[a]) 4.22 (1 H, dd, J_{gem} 10.8, $J_{5'b,4'}$ 4.8, 5′-H[b]	4.52 (m,over-lapped 2′-H),	4.00 (t, $J_{3',2'}$ = $J_{3',4'}$ = 2.0)	overlapped 4′-H	4.52 (d, $J_{1',2'}$ 4.0)	5.53 (d, $J_{5,6}$ 8.0)	7.48 (d, $J_{6,5}$ 8.0)	3.04 (3 H, s, NMe), 3.24 (3 H, s, Ms), 6.27 (1 H, d, *J* 3.6, 2′-OH)
(**6a**)	2.81 (1 H, dd, J_{gem} 13.1 $J_{5'a,4'}$ 10.3, 5′-H[a], 3.25 (1 H, dd, J_{gem} 13.1, $J_{5'b,4'}$ 3.0,5′-H[b])	4.39 (dt, $J_{4',3'}$ = $J_{4',5'b}$ = 3.0, $J_{4',5'a}$ 10.3)	3.97 (t, $J_{3',2'}$ = $J_{3',4'}$ = 3.0)	4.55 (dd, $J_{2',1'}$ 4.0, $J_{2',3'}$ 3.0)	5.46 (d, $J_{1',2'}$ 4.0)	5.50 (d, $J_{5,6}$ 7.5)	7.45 (d, $J_{6,5}$ 7.5)	2.33 (3 H, s, Ms), 3.03 (3 H, s, NMe), 6.27 (1 H, d, *J* 2.8, 2′-OH), 8.02 (3 H, br s, NH_3^+)
(**6b**)	2.57 (1 H, br d, J_{gem} 12.8, 5′-H[a]), 2.65 (1 H, br d, J_{gem} 12.8, $J_{5'a,4'}$ = $J_{5'b,4'}$ = 6.0, 5′-H[b]),	4.34 (dt, $J_{4',3'}$ 3.2, $J_{4',5'a}$ = $J_{4',5'b}$ = 6.0)	3.94 (br s)	4.48 (t, $J_{2',1'}$ = $J_{2',3'}$ = 4.0)	5.33 (d, $J_{1',2'}$ 4.0)	5.49 (d, $J_{5,6}$ 8.0)	7.44 (d, $J_{6,5}$ 8.0)	2.30 (3 H, s, NH*Me*) 3.07 (3 H, s, NMe), 3.20 (1 H, br s, N*H*Me), 6.20 (1 H, br s, 2′-OH)
(**6c**)	2.57 (1 H, dd, J_{gem} 11.6, $J_{5'a,4'}$ 7.6, 5′-H[a]), 2.63 (1 H, dd, J_{gem} 11.6, $J_{5'b,4'}$ 6.1, 5′-H[b]),	4.29 (m)	3.88 (t, $J_{3',2'}$ = $J_{3',4'}$ = 3.4)	4.44 (q; t after D_2O-addition, $J_{2',1'}$ 4.3, $J_{2',3'}$ 3.4)	5.28 (d, $J_{1',2'}$ 4.3)	5.44 (d, $J_{5,6}$ 7.3)	7.39 (d, $J_{6,5}$ 7.3)	2.25 (1 H, br s, N*H*Bn), 3.01 (3 H, s, NMe), 3.65 (1 H, d, *J* 13.4, CH_2Ph), 3.71 (1 H, d, *J* 13.4, CH_2Ph), 3.71 (1 H, d, *J* 13.4, CH_2Ph), 6.14 (1 H, d, *J* 3.36, 2′-OH), 7.20–7.30 (5 H, m, ArH)
(**6d**)	3.38 (2 H, m)	4.50 (m, $J_{4',3'}$ 4.0)	4.37 (t, $J_{3',2'}$ = $J_{3',4'}$ = 4.0)	4.65 (q; t after D_2O-addition, $J_{2',1'}$ = $J_{2',3'}$ = 4.0)	5.55 (d, $J_{1',2'}$ 4.0)	5.64 (d, $J_{5,6}$ 8.0)	7.62 (d, $J_{6,5}$ 8.0)	5.65 (1 H, overlapped 5-H N*H*Ph), 6.52 (1 H, d, 2′-OH), 6.56–7.48 (10 H, m, ArH)
(**7**)	4.52 (2 H, d $J_{5',4'}$ 6.4)	4.58 (m)	4.39 (t, $J_{3',2'}$ = $J_{3',4'}$ = 4.0)	4.71 (q; t after D_2O-addition, $J_{2',1'}$ = $J_{2',3'}$ = 4.0)	5.60 (d, $J_{1',2'}$ 4.0)	5.72 (d, $J_{5,6}$ 8.0)	7.62 (d, $J_{6,5}$ 8.0)	3.18 (3 H, s, Ms), 6.58 (1 H, d, *J* 3.6, 2′-OH), 7.36–7.56 (5 H, m, ArH)
(**9a**)	2.03 (1 H, dd, J_{gem} 14.0, $J_{5'a,4'}$ 2.8, 5′-H[a]), 2.53 (1 H, d, J_{gem} 14.0, 5′-H[b]),	3.97 (m)	3.44 (t, $J_{3',2'}$ = $J_{3',4'}$ = 2.4)	4.28 (q; t after D_2O-addition, $J_{2',1'}$ = $J_{2',3'}$ = 2.4)	4.62 (br s)	5.53 (d, $J_{5,6}$ 8.0)	7.41 (d, $J_{6,5}$ 8.0)	2.29 (3 H, s, sugar-NMe), 3.04 (3 H, s, bridge-NMe), 5.35 (1 H, d, *J* 4.0, OH), 5.64 (1 H, d, *J* 4.0, OH)
(**9b**)	2.03 (1 H, dd, J_{gem} 12.7, $J_{5'a,4'}$ 2.4, 5′-H[a]), 2.45 (1 H, d, J_{gem} 12.7, 5′-H[b]),	3.91 (br s)	3.47 (br s)	4.36 (q; t after D_2O-addition, $J_{2',1'}$ = $J_{2',3'}$ = 3.2)	4.75 (br s)	5.56 (d, $J_{5,6}$ 7.1)	7.37 (d, $J_{6,5}$ 7.1)	3.02 (3 H, s, NMe), 3.34 (1 H, d, *J* 13.5, CH_2Ph), 4.12 (1 H, d, *J* 13.5, CH_2Ph), 5.24 (1 H, d, *J* 3.2, OH), 5.63 (1 H, d, *J* 4.76, OH), 7.24–7.34 (5 H, m, ArH)
(**9c**)	3.12 (1 H, d J_{gem} 13.4, 5′-H[a]), 3.26 (1 H, dd, J_{gem} 13.4, $J_{5'b,4'}$ 2.5, 5′-H[b]),	4.07 (m)	3.87 (br s)	4.62 (q; t after D_2O-addition, $J_{2',1'}$ = $J_{2',3'}$ = 3.4)	5.84 (br s)	5.36 (d, $J_{5,6}$ 7.3)	6.70 (d, $J_{6,5}$ 7.3)	5.45 (1 H, d, *J* 4.0, OH), 5.99 (1 H, d, *J* 3.7, OH), 6.95–7.50 (10 H, m, ArH)
(**10**)	3.14 (2 H, m)	4.53 (2 H, overlapped 3′-H)		4.21 (dd, $J_{2',1'}$ = $J_{2',3'}$ = 3.1)	6.01 (d, $J_{1',2'}$ 3.1)	5.53 (d, $J_{5,6}$ 8.0)	7.63 (d, $J_{6,5}$ 8.0)	5.38 (1 H, d, *J* 5.4, OH or NH), 5.58 (1 H, t, *J* 5.8, 5′-N*H*Ph), 5.99 (1 H, d, *J* 4.9, OH or NH), 11.29 (1 H, s, 3-NH)
(**17**)	4.23 (1 H, dd, J_{gem} 11.12, $J_{5'a,4'}$ 11.12, 5′-H[a]), 4.39–4.44, (1 H, m, 5′-H[b])	4.51–4.53 (complex m)	4.31 (d, $J_{3',4'}$ = 3.18)	4.40 (d, $J_{2',1'}$ 3.18)	5.64 (d, $J_{1',2'}$ 3.18)	5.57 (d, $J_{5,6}$ 7.2)	7.46 (d, $J_{6,5}$ 7.2)	3.06 (3 H, s, NMe), 3.18 (3 H, s, OMe), 3.38 (3 H, s, Ms)

Table 2 (*continued*).

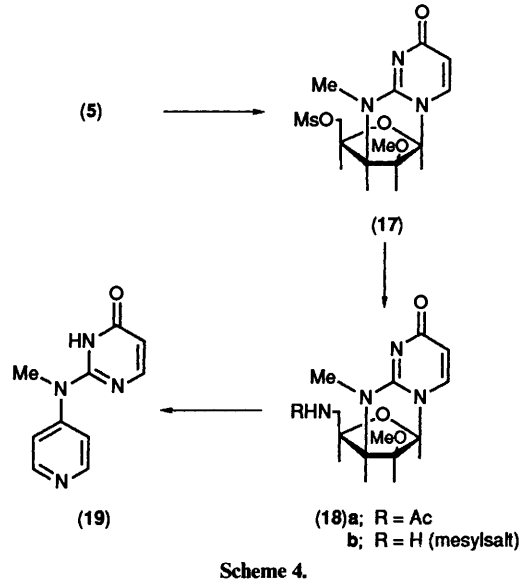
Compound	5′-H	4′-H	3′-H	2′-H	1′-H	5-H	6-H	others
(18a)	2.99 (1 H, dd, J_{gem} 14.3, $J_{5'a,4'}$ 7.9, 5′-H[a]), 3.38 (dd, J_{gem} 14.3, $J_{5'b,4'}$ 5.6, 5′-H[b])	4.27 (ddd, $J_{4',3'}$ 2.4, $J_{4',5'a}$ 7.9 $J_{4',5'b}$ 5.6)	4.22 (dd, $J_{3',2'}$ 3.2 $J_{3',4'}$ 2.4)	4.34 (dd, $J_{2',1'}$ 4.0 $J_{2',3'}$ 3.2)	5.57 (d, $J_{1',2'}$ 4.0)	5.47 (d, $J_{5,6}$ 7.1)	7.42 (d, $J_{6,5}$ 7.1)	1.81 (3 H, s, NHCO*Me*), 3.05 (3 H, s, NMe), 3.36 (3 H, s, OMe), 8.06 (1 H, t, *J* 4.8, N*H*COMe)
(18b)	2.83 (1 H, dd, J_{gem} 13.50, $J_{5'a,4'}$ 10.31, 5′-H[a]), 3.29 (1 H, dd, J_{gem} 13.50, $J_{5'b,4'}$ 2.38, 5′-H[b])	4.42–4.44 (complex m, overlapped 2′-H),	4.29 (t, *J* 3.18)	overlapped 4′-H	5.69 (d, $J_{1',2'}$ 3.17)	5.59 (d, $J_{5,6}$ 7.2)	7.48 (d, $J_{6,5}$ 7.2)	2.40 (3 H, s, $MeSO_3^-$), 3.06 (3 H, s, NMe), 3.39 (3 H, s, OMe), 8.03 (3 H, br s, NH_3^+)

[a] All the chemical shifts are recorded from the spectra before D_2O addition, and all the coupling constants, except those for the labile protons, are from spin-decoupling experiments after D_2O addition.



Scheme 3.

(**14**) and 1-methylguanidine (**15**).[9] This reaction is unusual in that a sugar C–N bond was easily cleaved as judged by TLC at the earlier stages of the reaction and may be explicable in terms of elimination of the heterocyclic base from the sugar moiety: the transiently formed nitrogen anion of the piperidine sugar nucleoside (**11a**) would form anion (**11b**). In ion (**11b**), the drive toward delocalization of the 2′-hydroxy anion would trigger a suprafacial [1,2]-hydride shift of the 2′-H to C-3′ to remove the pyrimidine moiety (**13**).[10] This elimination and the accompanying dehydration of the glycone (before or after the elimination of the base) should be accelerated by a trend to aromatization to afford compound (**12**).



Scheme 4.

To check this hypothesis, we prepared another substrate in which the 2′-hydroxy group is blocked (Scheme 4). Thus, compound (**5**) was methylated to afford 1-(3′-deoxy-5′-*O*-mesyl-2′-*O*-methyl-β-D-lyxofuranosyl)-2,3′-methyliminouracil (**17**) in high yield, which was then aminated as in the case of compound (**6a**). At the initial stage of this experiment, isolation of the product either as a crystalline mesylsalt or as a foamy free amine was unsuccessful (see Experimental section). Accordinlgly, the crude free amine was acetylated to give 1-(5′-acetamido-3′,5′-dideoxy-2′-*O*-methyl-β-D-lyxofuranosyl)-2,3′-methyliminouracil (**18a**) (hydroscopic foam). In another attempt to obtain the free amine, however, the crystalline mesyl derivative of 1-(5′-amino-3′,5′-dideoxy-2′-*O*-methyl-β-D-lyxofuranosyl)-2,3′-methyliminouracil (**18b**) was obtained in reasonable yield (see Experimental section). The structure of products (**17**) and (**18a** and **b**) is in accord with the general spectroscopic data. Compound (**18b**) was then similarly treated with 3M-NaOH in neat EtOH, when the reaction proceeded extremely fast as expected from the absence of a 2′-hydroxy anion which screens the anomeric carbon against the external hydroxy ions,[3] and gave N^2-methyl-N^2-(4-pyridino) isocytosine (**19**), the structure of which followed from its mass, ^{1}H NMR (see Experimental section), and UV spectra (Figure 1). It is interesting to note that the UV spectrum of compound (**19**) resembles that resulting from summation of the absorptions of compounds (**13**) and 4-

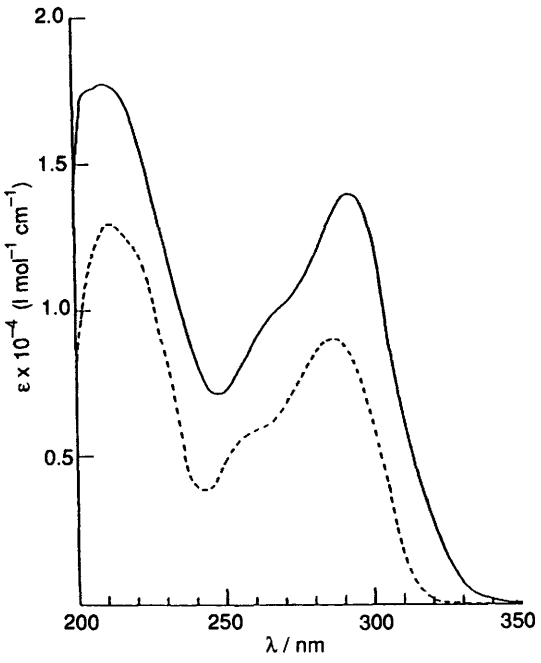


Figure 1. UV absorption of compound (**19**) (—) and summation of the absorptions (εs) of compound (**13**) and 4-dimethylamino pyridine (– –) in methanol.

dimethylaminopyridine even in neutral medium. This suggests that in compound (**19**) conjugation between both heterocycles through the nitrogen bridge is suppressed to a minimum by the rings twisting away from mutual coplanarity. The formation of product (**19**) is explicable by aromatization of the sugar moiety through simple dehydration and elimination of methanol after fission of the anomeric bond of a transient piperidine sugar nucleoside such as (**11a**). It must be added that no evidence for the formation of compound (**13**) was found in this reaction and hence the above stated elimination process through intermediate (**11b**) seems to be reasonable.

Experimental

M.p.s were recorded on a Yanagimoto micro melting point apparatus and are uncorrected. UV spectra were measured on a Hitachi Model 200-10 spectrophotometer, and mass spectra on a ESCO Model EMD-05B spectrometer at this faculty. The 200 MHz ^{1}H NMR spectra of compounds (**5**), (**6b**), (**6d**), (**7**), and (**9a**) were recorded on a Varian XL-200 FT NMR spectrometer, and the 500 MHz ^{1}H NMR spectra of compounds (**6a**), (**6c**), (**9b**), (**9c**), (**10**), (**17**), (**18a** and **b**), and (**19**) on a JEOL-JNM-GX500 FT NMR spectrometer at room temperature, using $SiMe_4$ as internal standard, in the laboratory of the Daiichi Seiyaku Co., Ltd. Elemental analyses were conducted using a Perkin-Elmer 240B elemental analyser. For preparative-scale thick-layer chromatography, glass plates coated with a 2-mm thickness of Wakogel B-5F silica gel were used after activation at 110 °C for 10–12 h. All evaporations were carried out under reduced pressure at or below 40 °C.

1-(3′-*Deoxy*-5′-O-*mesyl*-β-D-*lyxofuranosyl*)-2,3′-*methyliminouracil* (**5**).—A mixture of methylamine hydrochloride (1.7 g, 25 mmol) and triethylamine (3.53 ml, 25 mmol) in dry DMF (35 ml) in an argon-filled pressure tube was stirred at room temperature for 2 h and was then cooled to *ca.* 0 °C. Compound (**3**) (2 g, 4.18 mmol) and additional DMF (5 ml) were added, and the mixture was stirred at 45–50 °C for 18 h. After cooling to room temperature, the solid precipitate was filtered off and the filtrate was evaporated to *ca.* 1/3 volume. The new precipitate solid was again filtered off and the filtrate was evaporated under reduced pressure. Trituration of the residue with EtOH (15 ml) gave a solid, which was collected and recrystallized from water to give compound (**5**) (794 mg, 60%), m.p. 214–215 °C (Found: C, 41.85; H, 4.7; N, 13.3. $C_{11}H_{15}N_3O_6S$ requires C, 41.64; H, 4.7; N, 13.25%).

1-(5′-*Amino*-3′,5′-*dideoxy*-β-D-*lyxofuranosyl*)-2,3′-*methyliminouracil Methanesulphonate* (**6a**).—A mixture of compound (**5**) (300 mg, 0.95 mmol) and conc. NH_4OH (9 ml) in an argon-filled pressure tube was stirred at 95 °C for 17 h, and was then cooled. The mixture was evaporated and repeatedly co-evaporated with EtOH to give a powdery solid, which was collected with a small volume of EtOH, again dissolved in EtOH, and treated with Norite. Concentration of the solution under reduced pressure at room temperature gave compound (**6a**) (247 mg, 78%) as a powder, m.p. 240–241 °C (Found: C, 39.5; H, 5.5; N, 16.7. $C_{11}H_{18}N_4O_6S$ requires C, 39.5; H, 5.4; N, 16.8%).

1-(3′,5′-*Dideoxy*-5′-*methylamino*-β-D-*lyxofuranosyl*)-2,3′-*methyliminouracil* (**6b**).—A mixture of compound (**5**) (350 mg, 1.10 mmol), 40% aq. methylamine (1.90 ml, 22 mmol), and EtOH (8 ml) in an argon-filled pressure tube was stirred at 90–95 °C for 20 h, and was then cooled. After evaporation of the solvent, the residue, in a small volume of MeOH was subjected to flash chromatography on a silica gel column (2 × 25 cm) and MeOH–$PrNH_2$ (100:1, v/v) as eluant to give compound (**6b**) (222 mg, 80%), m.p. 208.5–209.5 °C, after recrystallization of the main fraction from MeOH (Found: C, 52.6; H, 6.5; N, 22.0. $C_{11}H_{16}N_4O_3$ requires C, 52.4; H, 6.4; N, 22.2%).

1-(5′-*Benzylamino*-3′,5′-*dideoxy*-β-D-*lyxofuranosyl*)-2,3′-*methyliminouracil* (**6c**).—A mixture of compound (**5**) (800 mg, 2.52 mmol), benzylamine (4.4 ml, 40 mmol), EtOH (16 ml), and water (2.4 ml) in an argon-filled pressure tube was stirred at 95 °C for 20 h, and was then cooled. After thorough evaporation of the solvent, the residue was triturated with diethyl ether (20 ml) and the organic layer decanted off. The residue was again washed with diethyl ether (10 ml) and was then triturated with MeOH (5 ml) to give crystals, which were collected and recrystallized from MeOH (5 ml) to give crystals, which were collected and recrystallized from MeOH to afford compound (**6c**) (642 mg, 78%), m.p. 204–206 °C (Found: C, 60.2; H, 6.6; N, 15.5. $C_{17}H_{20}N_4O_3$·MeOH requires C, 60.0; H, 6.7; N, 15.6%).

Reaction of compound (**4**) *with Aniline. Formation of* 1-(5′-*anilino*-3′,5′-*dideoxy*-β-D-*lyxofuranosyl*)-2,3′-*phenyliminouracil* (**6d**), *as well as compounds* (**7**) *and* (**8**).—A mixture of (**4**) (600 mg, 1.57 mmol), aniline (2.2 ml, 24 mmol), and DMF (10 ml) in an argon-filled pressure tube was stirred at 100 °C for 73 h and then at 115 °C for 25 h. TLC of an aliquot of the reaction mixture revealed two less polar products and one more polar product together with a negligible amount of the starting material. After evaporation under reduced pressure, the residue was triturated with diethyl ether (10 ml) and the organic layer was decanted off. This procedure was repeated until the mixture became a semi-solid. This was taken up into a small volume of MeOH and fractionated on a silica plate (20 × 20 cm; $CHCl_3$–MeOH 85:15; developed twice). Recrystallization of the least polar fraction from MeOH containing a small volume of water gave *title compound* (**6d**) (218 mg, 37%), m.p. 143–145 °C (Found: C, 67.1; H, 5.5; N, 14.6. $C_{21}H_{20}N_4O_3$ requires C, 67.0; H, 5.4; N, 14.88%).

The second less polar fraction was recrystallized from MeOH to afford compound (**7**) (24 mg, 4%), m.p. 186–187 °C (Found: C, 50.7; H, 4.6; N, 10.9. $C_{16}H_{17}N_3O_6S$ requires C, 50.7; H, 4.5; N, 11.1%).

Recrystallization of the most polar fraction from EtOH gave compound (**8**) [≡ (**1b**)] (16 mg, 3%), identifical with an authentic sample[1] by IR spectroscopy, ^{1}H NMR spectrometry, and mixed m.p. determination.

1-(3′,5′-*Dideoxy*-5′-*methylamino*-β-D-*lyxopyranosyl*)-2,3′-*methyliminouracil* (**9a**).—A mixture of compound (**6b**) (200 mg, 0.79 mmol), 6M-NaOH (2 ml), and EtOH (2 ml) in an argon-filled pressure tube was stirred at 75–80 °C for 50 h, during which time most of the starting material disappeared and two major, less polar products were formed. The mixture was neutralized with 1M-HCl and thoroughly evaporated. The residue, dissolved in MeOH (20 ml), was heated to reflux for 15 min, cooled to room temperature, and filtered to remove the inorganic salt. The filtrate was concentrated and subjected to preparative TLC (silica, 20 × 20 cm; $CHCl_3$–MeOH 8:2; developed 3 times). Elution and recrystallization of the least polar fraction with MeOH gave compound (**9a**) (48 mg, 24%), m.p. 202–203 °C (Found: C, 52.4; H, 6.5; N, 22.1. $C_{11}H_{16}N_4O_3$ requires C, 52.4; H, 6.4; N, 22.2%).

Characterization of another non-crystalline product was abandoned.

1-(5′-*Benzylamino*-3′,5′-*dideoxy*-β-D-*lyxopyranosyl*)-2,3′-*methyliminouracil* (**9b**).—A mixture of compound (**6c**) (690 mg, 2.1 mmol), EtOH (14 ml), and NaOH (1.68 g, 42 mmol) (*ca.* 3M-NaOH–EtOH) in an argon-filled pressure tube was stirred at 75–80 °C for 4 h. TLC (silica; $CHCl_3$–MeOH 8:2) at this stage showed the presence of the starting material and a single, faster running product in comparable amounts. After neutralization with AcOH, the mixture was evaporated and repeatedly co-evaporated with MeOH. The residue dissolved in EtOH (30 ml), was heated to reflux and cooled. After the UV-transparent solid was filtered off, the filtrate was concentrated to half-volume to give a further precipitate of AcONa, which was filtered off. This concentration–filtration procedure was repeated several times and each filter cake was checked by TLC for its UV transparency. The mixture finally obtained was fractionated on two silica plates (20 × 20 cm; $CHCl_3$–MeOH 8:2; twice developed). The slower moving fraction gave the starting material (**6c**) (269 mg, 39% recovery) (identical with an authentic sample by IR spectroscopy and mixed m.p.), while the faster moving band gave compound (**9b**) (137 mg, 33% based on the consumed starting material), m.p. 183–185 °C (Found: C, 62.3; H, 6.2; N, 16.9. $C_{17}H_{20}N_4O_3$ requires C, 62.2; H, 6.1; N, 17.1%).

1-(5′-*Anilino*-3′,5′-*dideoxy*-β-D-*lyxopyranosyl*)-2,3′-*phenyliminouracil* (**9c**) *and* 1-(3′,5′-*Dianilino*-3′,5′-*dideoxy*-β-D-*lyxofuranosyl*)*uracil* (**10**).—A mixture of compound (**6d**) (200 mg, 0.53 mmol), EtOH (8 ml), and NaOH (1 g, 25 mmol) in an argon-filled pressure tube was stirred at 75–80 °C under careful TLC control for 4 h. TLC (silica; $CHCl_3$–MeOH–$PrNH_2$ 85:15:1) at this stage showed the absence of the starting material and the presence of two major, less polar products together with a negligible amount of a third product. The mixture was neutralized with AcOH, then evaporated, and the residue was dissolved in MeOH (15 ml) and heated to reflux for 10 min. After cooling, the UV-transparent solid was filtered off and the filtrate was evaporated. The residue was similarly treated with EtOH (10 ml) to remove a further crop of AcONa. This processing was followed several times, using successively smaller volumes of EtOH, under TLC control for each filter cake. The finally obtained gum was fractionated on a TLC plate (20 × 20 cm; $CHCl_3$–MeOH 85:15; developed 3 times) to give compound (**9c**) (50 mg, 26%) from the more polar fraction, m.p. 225–228 °C after recrystallization from MeOH (Found: C, 66.9; H, 5.5; N, 14.6. $C_{21}H_{20}N_4O_3$ requires C, 67.0; H, 5.4; N, 14.88%).

The far less polar fraction gave compound (**10**) (22 mg, 10.4%), m.p. 185–186 °C after recrystallization from EtOH (Found: C, 62.7; H, 6.3; N, 12.6. $C_{21}H_{22}N_4O_4 \cdot C_2H_5OH$ requires C, 62.7; H, 6.4; N, 12.7%).

Alkaline Hydrolysis of Compound (**6a**).—A mixture of (**6a**) (450 mg, 1.35 mmol), EtOH (9 ml), and NaOH (1.10 g, 28 mmol) was heated under the same conditions as above for 5 h. TLC monitoring (silica; $CHCl_3$–MeOH 8:2) showed spots for two less polar, major products and a very minor product. The mixture was neutralized with AcOH, thoroughly evaporated, and the residue was digested with hot EtOH (15 ml). After cooling, the UV-transparent solid was filtered off and the filtrate was concentrated to remove an additional UV-transparent solid. This process was repeated 4 times as above to remove most of the AcONa. The gum finally obtained was fractionated on a silica plate (20 × 20 cm; $CHCl_3$–MeOH 85:15; developed 3 times). Elution of the most mobile band with MeOH gave a solid, which was recrystallized from EtOAc–acetone to afford compound (**12**) (48 mg, 38%), m.p. 124–125 °C, identical with a commercially available specimen in terms of UV, IR, and ^{1}H NMR spectra.

The less mobile fraction gave compound (**13**) (57 mg, 34%), m.p. 214–217 °C (lit.,[9] 214–215 °C), identical with an authentic sample in all respects.

1-(3′-*Deoxy*-5′-O-*mesyl*-2′-O-*methyl*-β-D-*lyxofuranosyl*)-2,3′-*methyliminouracil* (**17**).—To a stirred suspension of compound (**5**) (718 mg, 2.26 mmol) in DMF (32 ml) at 0 °C was added 60% oil-immersed NaH (99.6 mg, 2.49 mmol). The mixture became roughly clear in 10 min. MeI (0.15 ml, 2.49 mmol) was added and the mixture was stirred at 0 °C for 2 h and then at room temperature for 6 h under exclusion of moisture. The mixture was evaporated and the residue was directly fractionated on two silica plates (20 × 20 cm; $CHCl_3$–MeOH 8:2; developed 3 times) to give compound (**17**) (681 mg, 91%) as a TLC-homogeneous foam, which was rather hygroscopic and which resisted crystallization (Found: C, 43.8; H, 5.1; N, 12.5. $C_{12}H_{17}N_3O_6S$ requires C, 43.5; H, 5.2; N, 12.7%).

1-(5′-*Acetamido*-3′,5′-*dideoxy*-2′-O-*methyl*-β-D-*lyxofuranosyl*)-2,3′-*methyliminouracil* (**18a**).—A mixture of compound (**17**) (580 mg, 1.75 mmol) and conc. NH_4OH (16 ml) in an argon-filled pressure tube was stirred at 80 °C for 27 h, during which time the starting material disappeared and a highly polar substance was formed, together with a negligible amount of a far less polar product. The mixture was evaporated, then repeatedly co-evaporated with MeOH, and the residue was fractionated on a silica plate (20 × 20 cm; $CHCl_3$–MeOH 7:3; developed 4 times) to give a foam (470 mg), which resisted crystallization and complete purification by silica gel or alumina chromatography. Hence, the total residue was dissolved in pyridine (6 ml) and treated with Ac_2O (0.66 ml, 7.0 mmol) and Et_3N (0.98 ml, 7.0 mmol) overnight. The mixture was treated with MeOH (2 ml) at room temperature for 30 min, then thoroughly evaporated, and the residue was fractionated on 2 silica plates (20 × 20 cm; $CHCl_3$–MeOH 7:3; developed 3 times). The recovered major fraction was again chromatographed on two silica plates (20 × 20 cm; $CHCl_3$–MeOH 8:2; developed 4 times) to give compound (**18a**) (320 mg, 62%) as a rather hygroscopic, pure foam (Found: C, 53.2; H, 6.1; N, 18.9. $C_{13}H_{18}N_4O_4$ requires C, 53.1; H, 6.2; N, 19.0%).

1-(5′-*Amino*-3′,5′-*dideoxy*-2′-O-*methyl*-β-D-*lyxofuranosyl*)-2,3′-*methyliminouracil Methanesulphonate* (**18b**).—A mixture of compound (**17**) (1.19 g, 3.59 mmol) and conc. NH_4OH (33 ml) in an argon-filled pressure tube was stirred at 55–60 °C for 39 h. TLC at this stage showed that *ca.* half of the starting material remained unchanged. After further heating at 80 °C for 22 h and

cooling to room temperature, the mixture was evaporated, repeatedly co-evaporated with dry MeOH, and finally dried under high vacuum. A solution of the residue in DMF (15 ml) was stirred at room temperature for a few min to give crystals. After evaporation of the solvent, the solid was collected with a small volume of MeOH (TLC-pure; 891 mg, 71%). For analysis, an aliquot was recrystallized from MeOH to give sandy crystals of compound (**18b**), m.p. 258–259 °C (decomp.) (Found: C, 41.6; H, 5.8; N, 15.9. $C_{12}H_{20}N_4O_6S$ requires C, 41.4; H, 5.8; N, 16.1%).

Alkaline Hydrolysis of Compound (**18b**).—A mixture of NaOH (685 mg, 17.1 mmol) and dry EtOH (5.76 ml) in an argon-filled pressure tube was stirred at 75–80 °C for 25 min to give a solution (*ca.* 3M-NaOH in EtOH). After the solution had cooled, compound (**18b**) (300 mg, 0.86 mmol) was added and the tube was refilled with argon. TLC monitoring of the reaction at 75–80 °C showed that substrate (**18b**) disappeared during 1 h and a less polar, major product had formed together with a minor product. There were no TLC spots corresponding to uracil, N^2-methylisocytosine (**13**) or/and 3-hydroxypyridine (**12**). The mixture was neutralized with AcOH after addition of EtOH (5 ml), and was then evaporated. The residue was triturated with EtOH (6 ml) and the UV-transparent solid was filtered off. The filtrate was concentrated to half-volume and a further precipitate of AcONa was filtered off. The filtrate was evaporated, taken up in MeOH (2 ml), and fractionated on a silica plate (20 × 20 cm; $CHCl_3$–MeOH 85:15; developed 3 times). The MeOH eluate from the major band gave TLC-pure crystals of compound (**19**) (30 mg) after filtration with a small volume of EtOH. The filtrate was again chromatographed similarly as above to afford an additional crop (15 mg) (total 45 mg, 26%). For analysis, the total crop was recrystallized from a small volume of MeOH at room temperature to afford *needles*, which gradually changed into massive prisms above 173 °C and which then melted at 197 °C after being dried at 50 °C; *m/z* 202.2 (M^+); δ[$(CD_3)_2SO$] 3.47 (3 H, s, NMe), 6.08 (1 H, d, $J_{5,6}$ 5.56 Hz, pyrimidine 5-H), 7.41 (2 H, d, $J_{3',2'} = J_{5',6'} = 6.36$ Hz, 3'- and 5'-H), 7.96 (1 H, br d, $J_{6,5}$ 5.56 Hz, pyrimidine 6-H), 8.60 (2 H, d, $J_{2',3'} = J_{6',5'} = 6.36$ Hz, 2'- and 6'-H), 11.66 (1 H, br s, 3-NH, D_2O-exchangeable) (Found: C, 59.3; H, 5.0; N, 27.8. $C_{10}H_{10}N_4O$ requires C, 59.4; H, 5.0; N, 27.7%).

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