Syntheses and Alkaline Hydrolyses of 2,2'-Imino- and 2,2'-(Substituted imino)-1-(2'-deoxy-β-D-arabinofuranosyl)uracils

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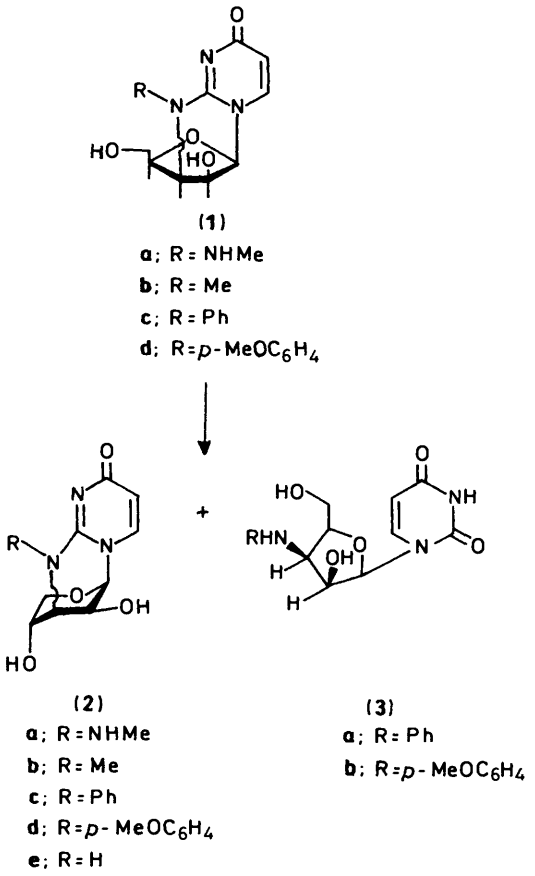
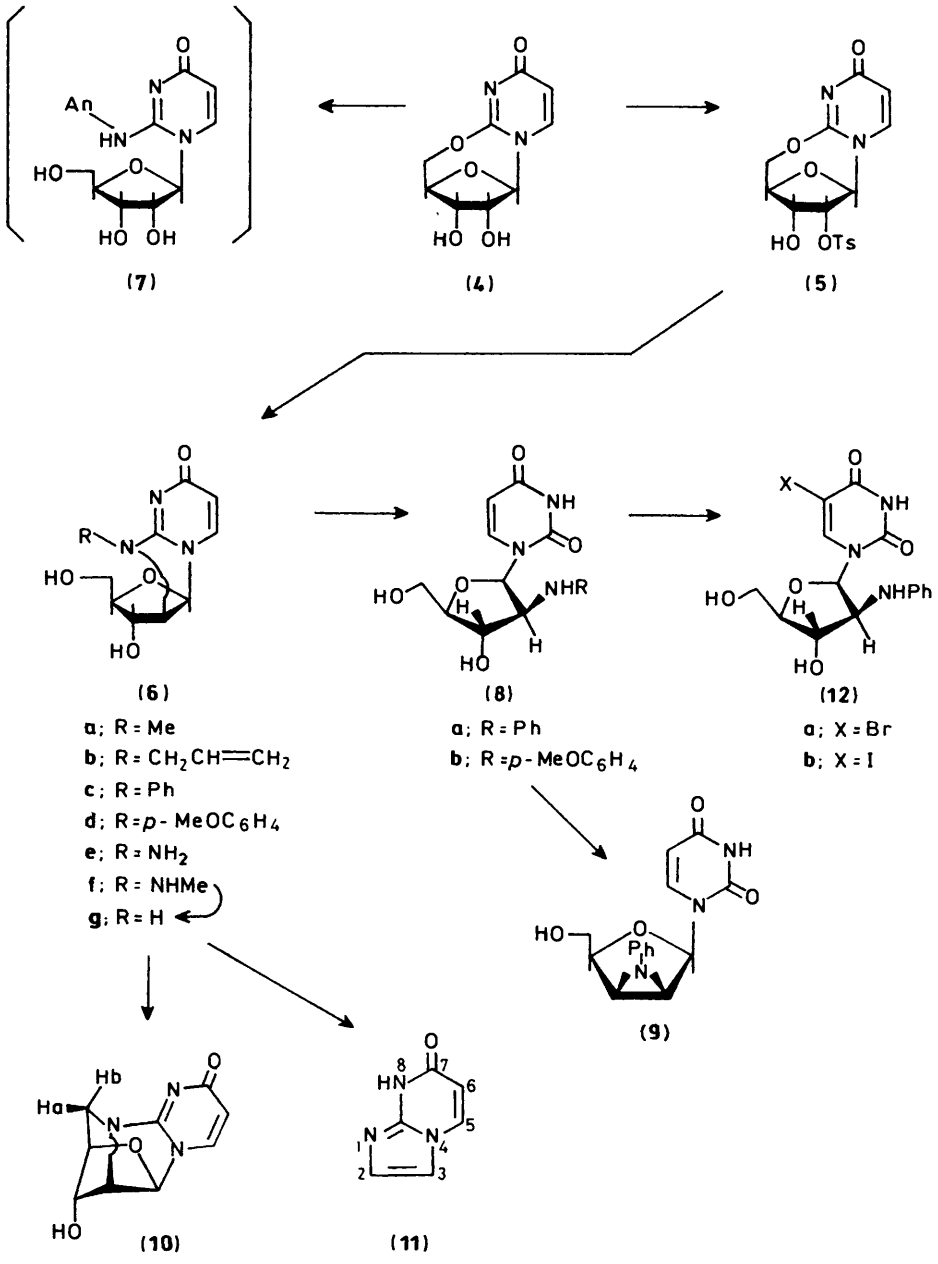
In order to examine the possiblity of 'up' amination of the sugar part of pyrimidine nucleosides through pyrimidine N-cyclonucleosides, 2,2'-imino-1-(2'-deoxy-β-D-arabinofuranosyl)uracil (**6g**) and various N-substituted derivatives of (**6g**), (**6a**—**f**) were synthesized by amination-cyclization reactions of 2'-*O*-tosyl-2,5'-anhydrouridine (**5**). The latter was synthesized from 2,5'-anhydrouridine (**4**) by 2',3'-*O*-dibutylstannylation followed by *in situ* tosylation. *N*-*p*-Methoxyphenylisocytidine (**7**) obtainable from (**4**) was also cyclized to (**6d**) by treatment with 1,1'-carbonyldi-imidazole. 2,2'-Arylimino analogues (**6c,d**) were hydrolysed with 2M NaOH–MeOH (1:1) extremely rapidly to give 2'-deoxy-2'-arylamino uracil-arabinosides (**8a,b**). The 2',3'-dideoxy-2',3'-(*N*-phenyl)imino analogue of arabinoside (**8a**), (**9**), was used for the purpose of structural corroboration of (**8a,b**). Similar dehydrative cyclization of (**6g**) gave the 5',*N*-anhydro derivative, compound (**10**), while alkali-treatment gave a fragmentation product, imidazo[1,2-*a*]pyrimidin-7(8*H*)-one (**11**). Spectroscopic arguments which support structures (**6**), (**10**), and (**11**) are also presented.

In contrast to oxygen and sulphur-bridged nucleosides, nitrogen-bridged isosteres have been little studied, a result perhaps of the rather limited scope for chemical modification of the latter. In this connection, hydrolytic cleavage of the bridge being of particular interest in order to effect the 'up' amination of the sugar part of nucleosides,[1] we have recently reported the alkali-catalyzed isomerization of 2,3'-(substituted-imino)-1-(3'-deoxy-β-D-lyxofuranosyl)uracils (**1a**—**d**) to their pyranosyl isomers (**2a**—**d**) with concomitant formation of 3'-arylamino-3'-deoxy-β-D-lyxofuranosyluracil (**3a**) or (**3b**) (R = Aryl)[2a,b] (Scheme 1). For this furanosyl to pyranosyl isomerization, we have proposed a general reaction mechanism involving fission of both the anomeric and the C-1'–O bonds by the initial attack of hydroxide ion on the anomeric carbon.

In this paper we describe the results of similar alkaline hydrolyses of a series of 2,2'-imino and substituted-imino uracil arabinosides (**6a**—**g**), which are readily accessible substrates starting from uridine. Although Ueda and co-workers have described the synthesis of 2,2'-imino-1-(2'-deoxy-β-D-arabino-furanosyl)uracil (**6g**)[3] (Scheme 2) and its 5-bromo analogue[1c] *via* isocytidine derivatives, we have chosen a pathway to a variety of N-substituted 2,2'-iminonucleosides from a single precursor. Thus, dibutylstannylation[4] of 2,5'-anhydrouridine (**4**)[5] followed by *in situ* tosylation gave a good yield of 2'-*O*-tosyl-2,5'-anhydrouridine (**5**). Although location of the tosyloxy group at C-2' could not be deduced directly from the ^{1}H n.m.r. resonance of 2'-H at δ 4.97 owing to the lack of a 1'-H—2'-H interaction and the ill resolved 3'-H resonance (Table 2), it was established after its derivatization. Thus, compound (**5**) gave a high yield of 2,2'-methylimino-1-(2'-deoxy-β-D-arabinofurano-syl)uracil (**6a**) with an excess of methylamine at ambient temperature. The structure of (**6a**) and hence that of (**5**), was now unambiguous on the basis of the ^{1}H n.m.r. spectrum of (**6a**): the δ 4.19 signal of the 2'-H interacting with the 1'-H (*J* 7.2 Hz) is reasonably separated from the 3'-H signal at δ 4.31. Similarly, 2,2'-allylimino (**6b**), 2,2'-phenylimino (**6c**), 2,2'-aminoimino (**6e**) and 2,2'-(methylamino)imino (**6f**) analogues were obtained under more forcing conditions in moderate to good yields, except in the case of (**6d**) (32%). Attempts to improve the yield of (**6d**) have failed despite the higher nucleophilicity of *p*-anisidine as compared to aniline. An arbitrary trial to aminate (**4**) directly with *p*-anisidine also gave a comparable yield of *N*-(*p*-methoxyphenyl)isocytidine (**7**) (38%) as a foam, which was, as such, cyclized to (**6d**) in 76% isolated yield. On the other hand,



Scheme 1.



Scheme 2.

the parent compound (**6g**) is obtained in almost quantitative yield by a known method.[6] Compound (**6g**) was also obtained from (**6f**) by oxidation with *m*-chloroperbenzoic acid (MCPBA).[2a] In the case of (**6c**) as well as (**6d**), a small amount of 2,2′-anhydrouridine[7] was formed as a by-product. The u.v. spectra of (**6a,b**) and (**6e,f**) are similar and akin to those of the corresponding 2,3′-substituted imino analogues [(**1a,b**) in Scheme 1 and others[2a]], while the arylimino analogues (**6c,d**) revealed an additional strong absorption at 242 nm in contrast with (**1c**).[2a] The ^{1}H n.m.r. spectra of (**6a,b**) and (**6e,f**) (Table 2) showed similar 1′-H and 2′-H chemical shifts with the same $J_{1',2'}$ values (7.2 Hz), whereas (**6c,d**) revealed significant downfield shifts of 3′-H, 2′-H, 1′-H, 5-H, and 6-H, among which that of 2′-H was the most striking, thus causing a reversion of the order of 2′-H and 3′-H. These anomalies can be explained by the anisotropic nature of the aromatic ring. A study with a Dreiding or HGS stereomodel* has shown that upside-orientation of the *N*-aryl group is excluded because of collision between the 3′-H and an *ortho*-aryl proton, and that the furanose part should take a ^{3}E envelope conformation as depicted in structures **A** and **B** (Figure 1), taking the sp^3 configuration of N-1 and N-2 (bridge-nitrogen) into account. The $J_{1',2'}$ values of 7.2 Hz for (**6a,b**) and (**6e,f**) are in good agreement with a maximum 1′-H–2′-H dihedral angle of *ca.* 30° allowed by the HGS model according to the standard Karplus rule,[8] while $J_{1',2'}$ 4.8 Hz for (**6c,d**) requiring a dihedral angle of 45° is abnormal, suggesting a fair degree of skeletal distortion.[9] A further interesting point is that the ^{1}H n.m.r. resonance of (**6g**) is suggestive of an upright

* An HGS flexible molecular model set is available from the Maruzen Co. Ltd., Tokyo.

Table 1. U.v. absorptions of (**5**), (**6a**—**g**), (**8a**,**b**), (**9**), (**10**), (**11**) and (**12a**,**b**) in methanol.

Compd.	$\lambda_{max.}$/nm(ε)
(**5**)	200 (15 500), 227.5 (21 400), 246.5 (10 700)[a]
(**6a**)	211 (23 800), 224 (18 700),[b] 263 (6 200)[b]
(**6b**)	216 (22 900), 224 (21 400),[a] 266 (3 300)[b]
(**6c**)	202 (25 200), 229 (13 500),[a] 242 (17 200), 290 (1 700)
(**6d**)	202 (27 300), 230 (17 000),[a] 242 (19 600), 305 (2 200)
(**6e**)	211 (21 800), 225 (18 600),[a] 264 (3 600)[b]
(**6f**)	213 (23 300), 225 (20 000),[a] 266 (3 300)[b]
(**6g**)	206.5 (28 600), 219 (16 000),[a] 259 (4 200)[b]
(**8a**)	202 (25 400), 245 (16 400), 260 (10 400),[a] 292 (1 100)[b]
(**8b**)	203 (23 200), 247 (16 000), 307 (1 700)
(**9**)	202.5 (29 000), 247 (18 500), 294 (1 700)[b]
(**10**)	225.5 (13 300), 253 (7 700)[b]
(**11**)	208 (9 600),[a] 215 (11 400), 246 (3 600), 283 (2 100)
(**12a**)	209.5 (26 800), 253 (15 700), 277 (7 900), 308 (2 200)[b]
(**12b**)	204 (30 300), 222 (30 200), 258 (20 000), 280 (8 300),[b] 316 (3 800)[b]

[a] Inflection. [b] Shoulder.

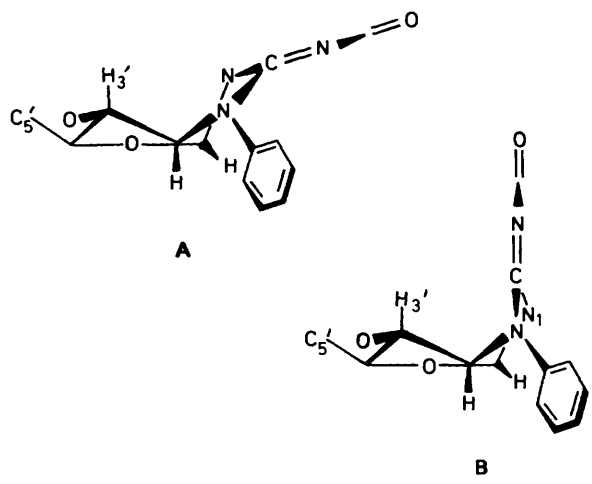


Figure 1.

orientation of the pyrimidine base (**B**), since (**6g**) showed a different order of $J_{1',2'}$ (6.4 Hz) as well as reversion of the order of the 2'-H and 3'-H chemical shifts. This reversion should be ascribed to the marked upfield shift of the 3'-H resonance, which can be easily rationalized from tight overlap of 3'-H on the shielding cone of the C-2, N-3 double bond. It must be added that when such an upright orientation is assumed, a C-3' *exo*-conformation is unfavourable owing to very considerable steric hindrance between the base and 5'-OH.

Alkaline hydrolyses, first conducted using (**6a**,**b**) and (**6f**) under a variety of reaction conditions, invariably resulted in recovery of starting material or complex decomposition: (**6b**) was used in the expectation that the known allyl to isopropenyl isomerization under strongly alkaline conditions[10] would occur to facilitate the hydrolysis of the resulting conjugated imino bridge.[2a] In the event, the arylimino bridge in (**6c**) and (**6d**) proved to be extraordinarily susceptible to alkaline hydrolysis [*cf.* the formation of (**3a**,**b**) from (**1c**,**d**)]. Thus, (**6c**) and (**6d**) can be quantitatively (t.l.c.) converted into 1-(2'-anilino-2'-deoxy-β-D-arabinofuranosyl)uracil (**8a**) and the 2'-anisidino analogue (**8b**) in 2 and 7 min respectively, at room temperature by treatment with 2M NaOH–MeOH (1:1): these reaction conditions are in sharp contrast with those applied to (**1c**,**d**), *i.e.*, 6M NaOH–EtOH (1:1); 75—80 °C; 21 h for (**1c**) and 45 h for (**1d**).[2a] In both cases, cleavage of the more electronegative phenylimino bridge is faster. This unusually fast hydrolysis may reflect abnormal molecular distortion of (**6c**,**d**) as suggested above, besides the proposed, aryl-promoted resonance stabilization of an intervening nitrogen anion.[2a] The u.v. spectrum of (**8a**) as well as (**8b**) is quite similar to that of (**3a**) and (**3b**), respectively. In the ^{1}H n.m.r. spectrum of (**8a**), the 5'-hydroxy resonated at δ 5.82 as a triplet, indicating retention of the furanose ring (Table 2). However, the assignment of the labile proton signals at δ 5.50—6.10 were somewhat uncertain and, moreover, there appeared to be no lactam NH signal which normally occurs at δ 11—12. Accordingly, the 1-[2',3'-dideoxy-2',3'-(*N*-phenyl)epimino-β-D-lyxofuranosyl]uracil derivative of (**8a**), (**9**), was formed using the Mitsunobu reaction.[11] On the basis of the ^{1}H n.m.r. spectrum of (**9**), the proton signals of which were all assigned, the structures of (**8a**,**b**) were established. The formation of (**9**), *i.e.* the first pyrimidine nucleoside having an 'up' epimino group,[12] led us to subject (**6g**) to a Mitsunobu reaction in the hope of preparing a (2',3'-dideoxy-2',3'-epimino)uracil nucleoside, some aziridine-containing purine nucleosides having been synthesized recently and shown to have potential as chemotherapeutic agents or synthetic intermediates.[13] However, in this reaction, (**6g**) yielded 5', *N*-anhydro-2,2'-imino-1-(2'-deoxy-β-D-arabinofuranosyl)uracil (**10**), the structure of which followed from its ^{1}H n.m.r. spectrum (see Experimental section), in which the 3'-OH signal appeared as a sharp doublet and that of 5'-CH_2 as two clearly separated pairs of doublets. The δ 3.47 signal is reasonably assignable to H_a and that at δ 2.99 to the remote hydrogen H_b which is shown, by a model study, to lie in the shielding zone of anisotropy of the C-2, N-3-double bond and near O-1. This compound contains a highly strained 3-ring system and may be an interesting intermediate.

Rather surprisingly, alkaline hydrolysis of (**6g**) gave solely, by an unknown mechanism, a good yield of blue-fluorescent imidazo[1,2-*a*]pyrimidin-7(8*H*)-one (**11**). Its ^{1}H n.m.r. spectrum (see Experimental section) displayed a set of alkene proton signals at δ 7.07 (2-H) and 7.41 (3-H) (*J* 2.0 Hz)* between the two far-separated doublets for 6-H and 5-H. Notably, the chemical shift for 6-H (δ 6.07) as well as 5-H (δ 6.35) roughly corresponds to that of 5-H and 6-H in uracil, respectively. The downfield shifts, as compared to the uracil protons, of 5-H and 6-H in (**11**) are explicable in terms of extended conjugation through N-4. Similarly, the δ 12.37 signal for the 8-NH compares favourably with those at δ 11—12 usually found for the 3-NH in a wide variety of uridine derivatives; the slight downfield shift may also be rationalized in similar terms. Moreover, the value of $J_{5,6}$ (8.0 Hz) and corresponding values normally found for the uracil base are in perfect agreement. This sort of comparative analysis by analogy also holds for the ^{13}C n.m.r. data of (**11**).† This

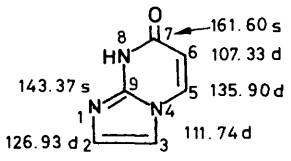
* These assignments are based on a comparison with the described ^{1}H n.m.r. data for 1-methylimidazole: the 4-H and 5-H resonate at δ 6.86 and 7.05 respectively (see ref. 9, p. 209). Furthermore, the small $J_{2,3}$ value (2.0 Hz) corresponds to the recorded $J_{4,5}$ (1.6 Hz) for imidazole (see ref. 9, p. 307).

† The ^{13}C n.m.r. data of (**11**) (measured in [$^2H_6$]Me_2SO) are given together with the recorded values for uridine (**13**),[14] 1-methylimidazole (**14**),[15] and imidazo[1,2-*a*]pyrimidine (**15**)[15] (Figure 2). The two downfield signals at δ 161.60s and 143.37s p.p.m. for (**11**) are assignable to C-7 and C-9, respectively, from inspection of the corresponding shifts for uridine (**13**). Also, the order of magnitude of chemical shifts of the C-6 and C-5 in (**11**) compares favourably with the C-5 and C-6 chemical shifts for (**13**). Interestingly, even for the parent imidazopyrimidine (**15**), the scale of magnitude and increasing order of the shifts for all carbon atoms parallel those for (**11**), irrespective of the absence of a substituent at the C-7. A similar situation is observed when the values for the imidazole carbons in compounds (**11**), (**15**), and (**14**) are compared.

Table 2. ^{1}H N.m.r. resonances of (**5**), (**6a—g**), (**8a,b**), (**9**), and (**12a,b**) in [$^2H_6$]Me_2SO[a,b]

Compd.	5′-H	4′-H	3′-H	2′-H	1′-H	5-H	6-H	3′-OH	5′-OH	Others
(**5**)	4.16 (d, J_{gem} 12.0, 5′a-H) 4.52 (3 H, m, $J_{3',2'}$ 6.8, 5′b-H, 4′-H, and 3′-H)			4.97 (d, $J_{2',3'}$ 6.8)	6.03(s)	5.95 (d, $J_{5,6}$ 8.0)	7.75 (d, $J_{6,5}$ 8.0)	5.86—6.10 (overlaid on the 1′-H, 5-H signals)		2.44 (3 H, s, CH_3) 7.50 (2 H, d, ArH) 7.87 (2 H, d, ArH)
(**6a**)	3.20 (2 H, m, J_{gem} 12.0, $J_{5',4'}$ 6.0)	4.02 (t, $J_{4',5'}$ 6.0)	4.31 (s)	4.19 (d, $J_{2',1'}$ 7.2)	6.15 (d, $J_{1',2'}$ 7.2)	5.54 (d, $J_{5,6}$ 8.0)	7.63 (d, $J_{6,5}$ 8.0)	5.72 (br s)	4.97 (br s)	2.94 (3 H, s, CH_3)
(**6b**)	3.22 (2 H, m, J_{gem} 13.6, $J_{5',4'}$ 2.0)	4.03 (t, $J_{4',5'}$ 6.8)	4.32 (s)	4.26 (d, $J_{2',1'}$ 7.2)	6.19 (d, $J_{1',2'}$ 7.2)	5.58 (d, $J_{5,6}$ 8.0)	7.66 (d, $J_{6,5}$ 8.0)	5.70 (d, J 4.0)	4.96 (t, J 5.2)	3.87 (1 H, dd, J_{gem} 16.0, $J_{Hd,Hx}$ 6.0, Hd) 4.19 (1 H, d, $H_{Hc,Hx}$ 5.2, Hc) 5.28 (1 H, d, $J_{Hb,Hx}$ 6.0, Hb) 5.35 (1 H, d, $J_{Ha,Hx}$ 13.2, Ha) 5.86 (1 H, m, Hx)
(**6c**)	2.97 (2 H, br s, J_{gem} 14.4, $J_{5'a,4'}$ 6.8, $J_{5'b,4'}$ 6.0)	4.23 (t)	4.45 (s)	5.29 (d, $J_{2',1'}$ 4.8)	6.38 (d, $J_{1',2'}$ 4.8)	5.90 (d, $J_{5,6}$ 8.0)	7.92 (d, $J_{6,5}$ 8.0)	6.00 (d, J 3.2)	5.77 (br s)	6.58 (3 H, m, ArH) 7.09 (2 H, t, ArH)
(**6d**)	2.90 (2 H, m, J_{gem} 14.0, $J_{5',4'}$ 7.2)	4.21 (t, $J_{4',5'}$ 7.2)	4.45 (br s)	5.28 (d, $J_{2',1'}$ 4.8)	6.38 (d, $J_{1',2'}$ 4.8)	5.90 (d, $J_{5,6}$ 8.0)	7.93 (d, $J_{6,5}$ 8.0)	5.98 (d, J 4.0)	5.30 (br s overlaid on the 2′-H signal)	3.64 (3 H, s, OCH_3) 6.51 (2 H, d, ArH) 6.74 (2 H, d, ArH)
(**6e**)	3.22 (2 H, t, $J_{5',4'}$ 5.6, $J_{5',5'\text{-OH}}$ 5.6)	4.04 (t, $J_{4',5'}$ 5.6)	4.4 (d, $J_{3',3'\text{-OH}}$ 4.8)	4.18 (d, $J_{2',1'}$ 7.2)	6.11 (d, $J_{1',2'}$ 7.2)	5.56 (d, $J_{5,6}$ 8.0)	7.63 (d, $J_{6,5}$ 8.0)	5.71 (d, J 4.8)	4.88 (t, J 5.6)	4.79 (2 H, br s, NH_2)
(**6f**)	3.26 (2 H, m, $J_{5',4'}$ 7.2)	4.05 (t, $J_{4',5'}$ 7.2)	4.37 (d, $J_{3',3'\text{-OH}}$ 4.0)	4.27 (d, $J_{2',1'}$ 7.2)	6.10 (d, $J_{1',2'}$ 7.2)	5.60 (d, $J_{5,6}$ 8.0)	7.66 (d, $J_{6,5}$ 8.0)	5.73 (d, J 4.0)	4.94 (t, J 5.2)	2.62 (3 H, s, CH_3) 5.38 (1 H, br s, NH)
(**6g**)	3.22 (2 H, m, J_{gem} 2.4, $J_{5',4'}$ 7.2)	4.02 (t, $J_{4',5'}$ 7.2)	4.16 (d, $J_{3',4'}$ 1.6)	4.24 (d, $J_{2',1'}$ 6.4)	6.18 (d, $J_{1',2'}$ 6.4)	5.56 (d, $J_{5,6}$ 8.0)	7.62 (d, $J_{6,5}$ 8.0)	5.67 (d, J 4.8)	4.96 (t, J 4.4)	8.53 (1 H, br s, NH)
(**8a**)	3.38 (2 H, m, J_{gem} 12.8, $J_{5'a,4'}$ 7.2, $J_{5'b,4'}$ 4.8)	3.95 (2 H, br s, 4′-H, 3′-H)		4.03 (m)	6.06 (d, $J_{1',2'}$ 3.6)	5.56 (d, $J_{5,6}$ 8.0)	7.60 (d, $J_{6,5}$ 8.0)		5.82 (t, J 5.6)	6.61 (3 H, m, ArH) 7.12 (2 H, t, ArH)
								5.50—6.10 (? H, br s, overlaid on the 5′-H signals, 3′-OH, 3-NH, NHPh)		1′-H, 5′-OH,
(**8b**)	3.32 (2 H, br s)	3.4—4.2 (? H, br s, overlaid on the 2′-H, 3′-H signals, 4′-H, OCH_3)	3.94 (br s)	4.03 (br s)	6.04 (br s)	5.58 (d, $J_{5,6}$ 8.0)	7.61 (d, $J_{6,5}$ 8.0)	D_2O-exchangeable, 3′-OH, 5′-OH, ArH)	5.4—5.8 (3 H, ArH)	6.47—6.92 (4 H, m, ArH) 11.34 (1 H, br s, 3-NH)
(**9**)	3.30 (m, J_{gem} 13.2, $J_{5'a,4'}$ 6.4, 5′a-H) 3.46 (m, J_{gem} 13.2, $J_{5'b,4'}$ 6.4, 5′b-H)	4.22 (t, $J_{4',5'}$ 6.4)	4.16 (d, $J_{3',2'}$ 3.6)	4.05 (d, $J_{2',3'}$ 3.6)	6.12(s)	5.74 (d, $J_{5,6}$ 8.0)	7.73 (d, $J_{6,5}$ 8.0)		5.85 (t, J 5.6)	6.64 (3 H, m, ArH) 7.14 (2 H, t, ArH) 11.49 (1 H, br s, 3NH)
(**12a**)	3.50 (2 H, m)	4.00 (3 H, m, 4′-H, 3′-H, 2′-H)			6.01 (d, $J_{1',2'}$ 3.2)		7.83 (s)	5.92 (d, J 4.0)	5.64 (2 H, D_2O-exchangeable, 5′-OH, N*H*Ph)	6.76 (2 H, d, ArH) 7.38 (2 H, dd, ArH) 7.64 (1 H, d, ArH) 11.92 (1 H, br s, 3-NH)
(**12b**)	3.48 (2 H, m)	3.98 (3 H, m, 4′-H, 3′-H, 2′-H)			6.04 (d, $J_{1',2'}$ 3.2)		7.85 (s)	5.88 (br s)	5.20 (t, J 3.2)	5.65 (1 H, br s, NHPh) 6.58 (2 H, d, ArH) 7.54 (2 H, dd, ArH) 7.92 (1 H, d, ArH) 11.78 (1 H, br s, 3-NH)

[a] Chemical shifts are given in p.p.m. and J values in Hz. [b] All the chemical shifts of the sugar protons are recorded from the spectra before D_2O addition and all the coupling constants except those for the labile protons from spin-decoupling experiments after D_2O addition. All the spectra were measured at 200 MHz.



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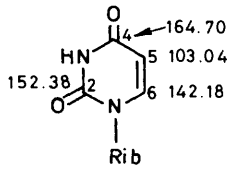

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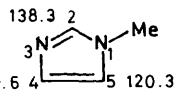

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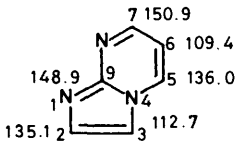

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Figure 2. ^{13}C N.m.r. data for (**11**), uridine (**13**),[14] 1-methylimidazole (**14**),[15] and imidazo[1,2-*a*]pyrimidine.[15] Multiplicities of the signals in the partially decoupled spectrum of (**11**) are given in parentheses. The shifts given for uridine are values obtained by converting the original benzene scale to the TMS scale.

cycloreversion-like fragmentation is unprecedented in cyclonucleoside chemistry, and needs a separate mechanistic study.

Finally, 1-(2′-anilino-2′-deoxy-β-D-arabinofuranosyl)-5-bromouracil (**12a**) and its iodo analogue (**12b**)[16] were prepared from a sample of (**8a**) for biological evaluation; they were of interest because they contain intact 5′- and 3′-hydroxy groups. These are a prerequisite for incorporation into a nucleic acid and other biological studies. The general physical data in Tables 1 and 2 are in accord with the structures of (**12a,b**).

Experimental

The general methods used are similar to those described earlier.[17]

The ^{13}C n.m.r. spectrum of (**11**) was recorded on a JEOL JNM-FX60 spectrometer in [$^2H_6$]Me_2SO, using TMS as an internal standard, and all the u.v. spectra on a Hitachi Model 200-10 spectrophotometer in the laboratory at this faculty, while the 200 MHz ^1H n.m.r. spectra were recorded on a Varian XL-200 FT n.m.r. spectrometer in the laboratory of the Daiichi Pharmaceutical Co. Ltd.

2′-O-*Tosyl*-2,5′-*anhydrouridine* (**5**).—A mixture of (**4**) (500 mg, 2.2 mmol) and dibutyltin oxide (550 mg, 2.2 mmol) in MeOH (110 ml) was heated at reflux for 30 min. The resulting solution was filtered whilst hot to remove any undissolved material. The filtrate was allowed to cool to room temperature, and then triethylamine (3.68 ml, 26.5 mmol) was added with stirring followed by a solution of tosyl chloride (5.06 g, 26.5 mmol) in acetone (8.8 ml). After 10 min, the solvent was removed, and the residue was collected with acetone and recrystallized from MeOH to give (**5**) (613 mg, 73%), m.p. >196 °C (decomp.) (Found: C, 50.55; H, 4.25; N, 7.2. $C_{16}H_{16}N_2O_7S$ requires C, 50.52; H, 4.24; N, 7.36%).

2,2′-*Methylimino*-1-(2′-*deoxy*-β-D-*arabinofuranosyl*)*uracil* (**6a**).—A mixture of (**5**) (100 mg, 0.26 mmol) and 40% aqueous methylamine (0.23 ml, 2.6 mmol) in DMF (1 ml) was stirred in an argon-filled pressure tube at room temperature for 3 h. The solvent was evaporated and the collected solid recrystallized from MeOH to afford (**6a**) (50 mg, 80%), m.p. 243—245 °C (Found: C, 50.45; H, 5.35; N, 17.45. $C_{10}H_{13}N_3O_4$ requires C, 50.21; H, 5.48; N, 17.56%).

2,2′-*Allylimino*-1-(2′-*deoxy*-β-D-*arabinofuranosyl*)*uracil* (**6b**).—A mixture of (**5**) (500 mg, 1.31 mmol) and allylamine (0.79 ml, 10.5 mmol) in DMF (5 ml) in an argon-filled pressure tube was stirred at room temperature for 3 days. The solvent was evaporated and the residual gum was triturated with a small volume of EtOH to give crystals, which were collected by suction. The filtrate was evaporated and the residue fractionated on a silica plate (20 × 20 cm; $CHCl_3$–MeOH, 8:2, twice developed) to afford a further crop. The combined product was recrystallized from EtOH to give (**6b**) (226 mg 65%), m.p. 199—202 °C (Found: C, 54.15; H, 5.75; N, 15.65. $C_{12}H_{15}N_3O_4$ requires C, 54.33; H, 5.70; N, 15.84%).

2,2′-*Phenylimino*-1-(2′-*deoxy*-β-D-*arabinofuranosyl*)*uracil* (**6c**).—Compound (**5**) (300 mg, 0.79 mmol) was treated in a similar way to that described above with freshly distilled aniline (0.72 ml, 7.9 mmol) in DMF (3 ml) at 75—80 °C for 44 h; t.l.c. monitoring showed the absence of starting material and the formation of two products. The mixture was evaporated and the residue was chromatographed on a silica plate (20 × 20 cm; $CHCl_3$–MeOH, 8:2, twice developed). Elution and recrystallization of the faster running major product using MeOH gave (**6c**) (135 mg, 56.8%), m.p. 243—246 °C (Found: C, 59.8; H, 5.05; N, 13.9. $C_{15}H_{15}N_3O_4$ requires C, 59.80; H, 5.02; N, 13.95%). The more polar fraction was recrystallized from MeOH to afford 2,2′-anhydrouridine (20 mg, 11.3%), identical by t.l.c. and i.r. with an authentic sample.[7]

2,2′-p-*Methoxyphenylimino*-1-(2′-*deoxy*-β-D-*arabinofuranosyl*)*uracil* (**6d**).—*Method A.* A mixture of (**5**) (500 mg, 1.31 mmol), *p*-anisidine (1.62 g, 13.1 mmol), and DMF (5 ml) was stirred in an argon-filled pressure tube at 100 °C for 4 days to give complete consumption of compound (**5**) and the formation of two major products. After evaporation, the resinous oil was triturated with ether (20 ml) and the ether decanted off: this procedure was repeated 4 times to remove the excess of anisidine and other apolar impurities. The semi-solid so obtained was then triturated with a small volume of MeOH to give the less polar product as an almost pure solid, which was collected. The filtrate was then fractionated on a silica plate (20 × 20 cm; $CHCl_3$–MeOH, 8:2, developed 3 times). The crop from the faster running band was combined with the above product and recrystallized from MeOH to afford (**6d**) (140 mg, 32%), m.p. 155—156 °C (Found: C, 58.05; H, 5.3; N, 12.6. $C_{16}H_{17}N_3O_5$ requires C, 58.00; H, 5.17; N, 12.68%). The polar fraction gave 2,2′-anhydrouridine (16 mg; 5.4%), identical with an authentic specimen.[7]

Method B. A mixture of (**4**) (400 mg, 1.77 mmol), *p*-anisidine (2.18 g, 17.7 mmol), and DMF (6.8 ml) was stirred under argon in a pressure tube at 100 °C for 4 days. After removal of the solvent, the residue was repeatedly washed with ether as above and fractionated on two silica plates (20 × 20 cm; CH_2Cl_2–MeOH, 9:1, developed 4 times) to give, from the major bands, (**7**) (234 mg, 37.9%) as a t.l.c.-homogeneous foam, which resisted crystallization.

A mixture of the total of crude (**7**) (234 mg, 0.67 mmol), 1,1′-carbonyl-di-imidazole (CDI) (162.2 mg, 1.0 mmol), and DMF (4 ml) was stirred under argon at 125—130 °C for 1.5 h. Evaporation and fractionation (silica, 20 × 20 cm; CH_2Cl_2–MeOH, 9:1, developed 3 times) of the mixture gave, from the major band, (**6d**) (170 mg, 76.1%) after recrystallization from MeOH, identical with the product obtained by Method A.

2,2′-*Aminoimino*-1-(2′-*deoxy*-β-D-*arabinofuranosyl*)*uracil* (**6e**).—A mixture of (**5**) (200 mg, 0.53 mmol), hydrazine hydrate (0.13 ml, 2.63 mmol), and DMF (4 ml) in an argon-filled pressure tube was stirred at room temperature for 7.5 h and then at 60—65 °C for 15.5 h. The mixture was thoroughly

evaporated, taken into EtOH, treated with Norit, and concentrated to *ca.* 2 ml. After being left in a refrigerator overnight, the crystalline deposit was collected and recrystallized from EtOH to afford (**6e**) (82 mg, 65%), m.p. above 252 °C (decomp.) (Found: C, 45.15; H, 5.1; N, 23.35. $C_9H_{12}N_4O_4$ requires C, 45.00; H, 5.03; N, 23.32%).

2,2′-*Methylaminoimino*-1-(2′-*deoxy*-β-D-*arabinofuranosyl*)-*uracil* (**6f**).—Compound (**5**) (200 mg, 0.53 mmol) in DMF (2.8 ml) was treated at room temperature for 23 h with methylhydrazine (0.22 ml, 4.2 mmol) in a similar way to that described above. After thorough evaporation, the residue was fractionated on a silica plate (20 × 20 cm; $CHCl_3$–MeOH, 85:15, developed 3 times). The major fraction was eluted with MeOH and the solid obtained recrystallized from the same solvent to give (**6f**) (81 mg, 56.6%) as a crystalline monohydrate, m.p. 132—135 °C (Found: C, 44.3; H, 5.9; N, 20.5. $C_{10}H_{14}N_4O_4{\cdot}H_2O$ requires C, 44.12; H, 5.92; N, 20.58%).

2,2′-*Imino*-1-(2′-*deoxy*-β-D-*arabinofuranosyl*)*uracil* (**6g**).—*Method A.* A mixture of (**5**) (500 mg, 1.31 mmol), anhydrous NH_4OAc (810 mg, 10.5 mmol), and DMF (5 ml) in a pressure tube was vigorously stirred at 80—85 °C for 2 h. After evaporation, the residue was dissolved in hot MeOH, treated with Norit and left at room temperature for several hours to give a voluminous solid precipitate, which was collected and recrystallized from MeOH to afford (**6g**) (278 mg, 94%), m.p. > 280 °C (decomp.) (Found: C, 48.0; H, 4.85; N, 18.75. $C_9H_{11}N_3O_4$ requires C, 48.00; H, 4.92; N, 18.66%).

Method B. A mixture of (**6f**) (35 mg, 0.138 mmol) and MCPBA (36 mg, 0.206 mmol) in AcOH (0.7 ml) was stirred at room temperature under an argon atmosphere. After 15 h, further MCPBA (36 mg, 0.206 mmol) was added and the mixture stirred for an additional 3.5 h. The total was neutralized with 5M NaOH and evaporated. After repeated co-evaporation with MeOH, the residue was swirled in a small volume of hot MeOH and the total cooled to room temperature. The u.v.-transparent solid was filtered off and the filtrate fractionated on a silica plate (20 × 20 cm; $CHCl_3$–MeOH, 7:3). The major band was eluted with MeOH, and the solid obtained recrystallized from MeOH to give (**6a**) (18 mg, 56%), identical with the product obtained above.

1-(2′-*Anilino*-2′-*deoxy*-β-D-*arabinofuranosyl*)*uracil* (**8a**).—2M NaOH (3 ml) was added to a stirred suspension of (**6c**) (200 mg, 0.66 mmol) in MeOH (3 ml) at ambient temperature (30 °C) to give, within 10 s, complete dissolution of the latter. After this, an aliquot was withdrawn every 1 min for a period of 5 min and poured into AcOH sufficient to quench the reaction. After removal of the AcOH from the sampling tubes, t.l.c. monitoring of the residue (silica; $CHCl_3$–MeOH, 85:15) showed that the reaction was complete within 2 min to yield a single, less polar product, which was unaffected by a prolonged reaction time of up to 2 h. Neutralization of the remaining reaction mixture with 2M HCl gave a crystalline solid, which was collected. Concentration of the filtrate gave further t.l.c.-pure crops (total: 191 mg, 90.6%). Recrystallization of the product from MeOH gave (**8a**) as needles, m.p. 230—232 °C (Found: C, 56.2; H, 5.35; N, 13.1. $C_{15}H_{17}N_3O_5$ requires C, 56.42; H, 5.37; N, 13.16%). The use of more concentrated alkaline solutions (5M NaOH–MeOH, 1:1; 6M NaOH–MeOH, 1:2) and of longer times ($\frac{1}{2}$, 1 and 2 h) gave similar results.

1-(2′-p-*Anisidino*-2′-*deoxy*-β-D-*arabinofuranosyl*)*uracil* (**8b**).—2M NaOH (1.5 ml) was added in one portion to a stirred suspension of (**6d**) (109 mg, 0.33 mmol) in MeOH (1.5 ml) at 25 °C to give instantaneously a clear solution. Extensive t.l.c. monitoring (silica; CH_2Cl_2–MeOH, 9:1) of aliquots withdrawn every 1 min and neutralized with AcOH indicated that the reaction was complete in 7 min to give a single, less polar product. The mixture was neutralized with 1M HCl and evaporated. The residue was digested with ice–water (*ca.* 2 ml) and the sparingly soluble, t.l.c.-pure solid collected by suction and dried (96 mg, 82%). A sample recrystallized from EtOH gradually decomposed > 139 °C (Found: C, 55.1; H, 5.55; N, 11.85. $C_{16}H_{19}N_3O_6$ requires C, 55.01; H, 5.48; N, 12.03%).

1-[2′,3′-*Dideoxy*-2′,3′-(N-*phenyl*)*epimino*-β-D-*lyxofuranosyl*]*uracil* (**9**).—Di-isopropyl azodiformate (DIAD) (0.08 ml, 0.42 mmol) was added by a syringe through a rubber stopper to a mixture of (**8a**) (46 mg, 0.14 mmol), triphenylphosphine (TPP) (107 mg, 0.42 mmol), and dry dioxane (0.6 ml) under argon. After 4.5 h, more TPP (54 mg, 0.21 mmol) and DIAD (0.04 ml, 0.21 mmol) were added. After a total of 38 h, t.l.c. monitoring showed the presence of a less polar product and (**8a**) (*ca.* 1:1 ratio) besides TPP and TPP oxide. After addition of a small volume of water, the mixture was evaporated and the residue fractionated on a silica plate (20 × 20 cm, $CHCl_3$–MeOH, 8:2). The product was eluted with MeOH and recrystallized from MeOH to give (**9**) (16 mg 36.8%), which decomposed > 179 °C (Found: C, 59.75; H, 5.1; N, 13.85. $C_{15}H_{15}N_3O_4$ requires C, 59.80; H, 5.02; N, 13.95%). The polar fraction gave (**8a**) (17 mg 40.0%) after similar processing.

5′,N-*Anhydro*-2,2′-*imino*-1-(2′-*deoxy*-β-D-*arabinofuranosyl*)-*uracil* (**10**).—DIAD (0.36 ml, 1.82 mmol) was added dropwise to a stirred mixture of (**6g**) (114 mg, 0.51 mmol), TPP (478 mg, 1.82 mmol), and dioxane (2.5 ml) under argon. After 24 h, the mixture was treated with water (1 ml), evaporated, and repeatedly co-evaporated with EtOH. The residue was heated to reflux in benzene (2 ml) for 10 min, and the sparingly soluble product collected and recrystallized from EtOH to give (**10**) (35 mg, 33.4%), m.p. 258—259 °C (decomp.); δ[$(CD_3)_2SO$] 2.99 (1 H, d, J_{gem} 12.0 Hz, 5′b-H), 3.47 (1 H, d, J_{gem} 12.0 Hz, 5′a-H), 4.50 (1 H, s, 4′-H), 4.56 (1 H, t, $J_{3',2'}$ 2.4 Hz, 3′-H), 4.14 (1 H, t, $J_{2',3'}$ 2.4 Hz, $J_{2',1'}$ 1.8 Hz, 2′-H), 5.95 (1 H, d, *J* 4.0 Hz, D_2O-exchangeable, 3′-OH), 6.02 (1 H, br s, 1′-H), 5.90 (1 H, d, $J_{5,6}$ 8.0 Hz, 5-H), 8.08 (1 H, d, $J_{6,5}$ 8.0 Hz, 6-H) (Found: C, 52.0; H, 4.5; N, 20.3. $C_9H_9N_3O_3$ requires C, 52.17; H, 4.38; N, 20.28%).

Imidazo[1,2-a]*pyrimidin*-7(8H)-*one* (**11**).—*Method A.* A mixture of (**6g**) (400 mg, 1.67 mmol), 3M NaOH (5 ml), and EtOH (5 ml) in an argon-filled pressure tube was stirred at 75—80 °C for 10 h. T.l.c. monitoring showed a single, faster-moving, blue-fluorescent product with a trace of (**6g**). The mixture was neutralized with AcOH, evaporated, and co-evaporated with MeOH. The residue was extracted with hot acetone (2 × 35 ml) and the combined acetone extracts were chromatographed on a silica plate (20 × 20 cm; $CHCl_3$–MeOH, 8:2) to give, from the fluorescent fraction, (**11**) (162 mg, 72%) after recrystallization from MeOH, m.p. 218—220 °C (decomp.); *m/z* 135 (M^+); δ[$(CD_3)_2SO$] 6.07 (1 H, d, $J_{6,5}$ 8.0 Hz, 6-H), 7.07 (1 H, d, $J_{2,3}$ 2.0 Hz, 2-H), 7.41 (1 H, d, $J_{3,2}$ 2.0 Hz, 3-H), 8.35 (1 H, d, $J_{5,6}$ 8.0 Hz, 5-H), 12.37 (1 H, br s, 8-NH, D_2O-exchangeable) (Found: C, 53.6; H, 3.75; N, 30.8. $C_6H_5N_3O$ requires C, 53.55; H, 3.73; N, 31.10%).

Method B. A mixture of (**6g**) (100 mg, 0.418 mmol), MeONa (203 mg, 9 × 0.418 mmol), and MeOH (1.7 ml) (*ca.* 2M MeONa–MeOH) was similarly heated at 95 °C for 3 days. Similar t.l.c. monitoring and work-up gave results similar to those in Method A.

1-(2′-*Anilino*-2′-*deoxy*-β-D-*arabinofuranosyl*)-5-*bromouracil* (**12a**).—*N*-Bromoacetamide (130 mg, 0.942 mmol) was added to a stirred suspension of (**8a**) (100 mg, 0.314 mmol) in dry THF (4 ml). After 5 min, the resulting solution was neutralized with 1M NH_4OH–MeOH and evaporated. The residue was partitioned

between EtOAc (60 ml) and water (15 ml). The separated organic layer was dried and evaporated. Fractionation of the residue on a silica plate (20 × 20 cm; CH_2Cl_2–MeOH, 9:1, twice developed) gave, from the major band, (**12a**) (55 mg, 44%) after recrystallization from MeOH, m.p. 197—199 °C (Found: C, 45.5; H, 3.8; N, 10.3. $C_{15}H_{16}BrN_3O_5$ requires C, 45.24; H, 4.05; N, 10.55%).

1-(2′-*Anilino*-2′-*deoxy*-β-D-*arabinofuranosyl*)-5-*iodouracil* (**12b**).—*N*-Iodosuccinimide (353 mg, 1.57 mmol) was added to a stirred solution of (**8a**) (100 mg, 0.314 mmol) and dibutyl disulphide (0.04 ml, 0.21 mmol) in DMF (3 ml). T.l.c. monitoring (silica; $CHCl_3$–MeOH, 85:15) after 20 h indicated the absence of starting material and the presence of two close running apolar substances, the less polar one being the major. After evaporation, the mixture was directly fractionated on a silica plate (20 × 20 cm; CH_2Cl_2–MeOH, 9:1, developed 3 times). The separation was incomplete but the recovered mixture, on being left at room temperature with a small volume of MeOH, gradually gave crystals (the less polar product), which were collected and recrystallized from MeOH to afford (**12b**) (42 mg, 32%) m.p. 165.5—168 °C (Found: C, 40.6; H, 3.45; N, 9.45. $C_{15}H_{16}IN_3O_5$ requires C, 40.46; H, 3.62; N, 9.44%).

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