# Syntheses and Hydrolysis Reactions of Some 2,3′-(Substituted-imino)-1-(3′-deoxy-β-D-lyxofuranosyl)uracils†

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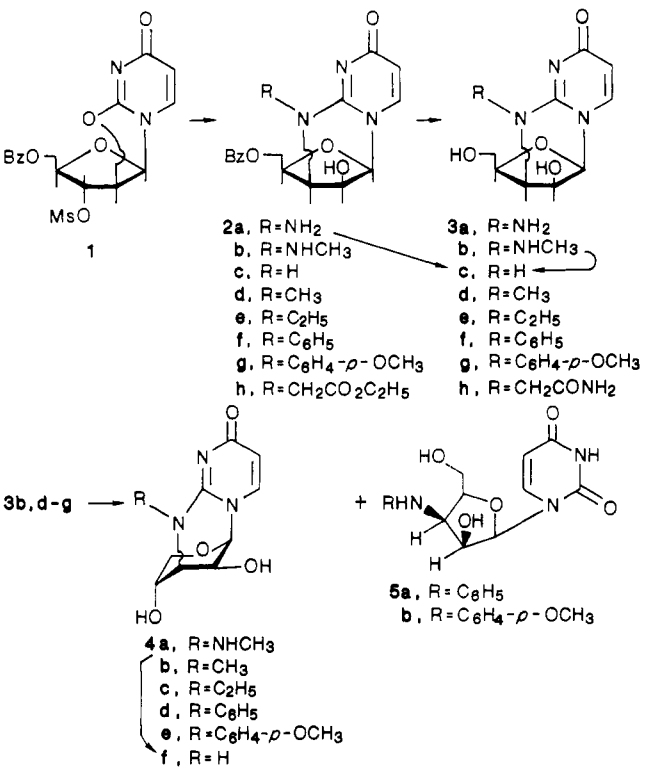
With a view to examining the possibility of "up" amination of the sugar moiety of pyrimidine furanosyl nucleosides through pyrimidine *N*-cyclonucleosides, variously N-substituted derivatives of 2,3′-imino-1-(3′-deoxy-β-D-lyxofuranosyl)uracil (**3c**)[3a] (**3a,b** and **3d–h**) were synthesized through their 5′-*O*-benzoyl precursors (**2a,b** and **2d–h**), which in turn were obtained from 2,2′-anhydro uracil nucleosides (**1**)[7] and excess amounts of various amines. **2a** and **3b** are oxidatively convertible into **3c**. Alkaline hydrolysis of **3b**, **3d**, and **3e** with 6 N NaOH/EtOH (1:1) gave the corresponding N-bridged lyxopyranosyl nucleosides **4a–c**, while the similar treatments of the *N*-aryl analogues **3f,g** gave the corresponding lyxopyranosyl isomers **4d,e** as well as the "up" arylamino nucleosides **5a,b** in similar yields in each case. The parent compound **4f** was prepared from **4a**. Some spectroscopic and mechanistic arguments on the formation and structures of the products are also given.

Despite the large number of publications on the chemistry of purine and pyrimidine cyclonucleosides,[1] information on nitrogen-bridged isosteres is rather limited.[2] As part of a program to exploit the chemistry of such compounds as biological and/or optical models,[3] we are interested in utilizing pyrimidine *N*-cyclonucleosides as possible synthetic intermediates for pyrimidine nucleosides carrying an "up" amino group.[2a,4] In addition, because of recent observations that the >CNH- or >C=N- bridge bond in some adenine *N*-cyclonucleosides is sufficiently stable under hydrolytic conditions to allow fission-recombination of the glycosidic bond,[3f,h] it may be feasible to transform these pyrimidine *N*-cyclonucleosides into pyranosyl nucleosides. We describe herein the synthesis of a series of variously N-substituted derivatives of 2,3′-imino-1-(3′-deoxy-β-D-lyxofuranosyl)uracil (**3c**)[3a,5] and the behavior of some of these compounds toward alkaline hydrolysis.

For the synthesis of 2,3′-(aminoimino)-1-(5′-*O*-benzoyl-3′-deoxy-β-D-lyxofuranosyl)uracil (**2a**), appropriately buffered conditions were first chosen to protect the base and ester parts of starting material as well as the product (Scheme I). Thus, 2,2′-anhydro-1-(5′-*O*-benzoyl-3′-*O*-methanesulfonyl-β-D-arabinofuranosyl)uracil (**1**)[7] with excess hydrazine in the presence of acetic acid in DMF (ca. 0.7 M solution of hydrazine) gave a 66% yield of **2a** after chromatography (see Experimental Section, method A). The use of milder reaction conditions (more dilute hydrazine solution, room temperature) improved the yield to over 85% without chromatography (method B). The structure **2a** followed not only from the UV (Table I) and $^1$H NMR data (Table II) (the NMR signal of *N*-amino group at 5.06 ppm excluded a 2,3′-hydrazo structure) but also from a chemical transformation: treatment of **2a** with isoamyl nitrite followed by a workup involving preparative TLC gave **3c** directly. This type of oxidative deamination of an aminoimino bridge has already been described by us,[3b] but the reason for the facile debenzoylation is unclear at present. Similarly, treatment of **1** with a dilute solution of methylhydrazine offered the (methylamino)imino analogue **2b** in moderate yield, clearly due to steric retardation and minor side reactions such as debenzoylation as judged by TLC. Although three isomeric structures containing a 2,3′-[(methylamino)imino]-, 2,3′-

**Scheme I**




$N^{\alpha}$-methylhydrazo- ($C_{3'}NHN(Me)C_2$) or 2,3′-$N^{\beta}$-methylhydrazo- ($C_{3'}N(Me)NHC_2$) were considered possible for

†This paper is dedicated to Professor Morio Ikehara on the occasion of his retirement from Osaka University in March, 1986.

(1) For reviews, see: (a) Ts'o, P. O. P., Ed. *Basic Principles in Nucleic Acid Chemistry*; Academic Press: New York, 1974; Vol. 1, p 170. (b) Ikehara, M. *Acc. Chem. Res.* **1969**, *2*, 47.

(2) (a) Doerr, I. L.; Cushly, R. J.; Fox, J. J. *J. Org. Chem.* **1968**, *33*, 1592. (b) Kaneko, M.; Shimizu, B.; Ikehara, M. *Tetrahedron Lett.* **1971**, 3113. (c) Ogilvie, K. K.; Slotin, L. A.; Westmore, J. B.; Lin, D. C. K. *J. Heterocycl. Chem.* **1972**, *9*, 1179.

(3) (a) Sasaki, T.; Minamoto, K.; Sugiura, T. *J. Org. Chem.* **1975**, *40*, 3498. (b) Sasaki, T.; Minamoto, K.; Itoh, H. *Ibid.* **1978**, *43*, 2320; (c) *Tetrahedron* **1980**, *36*, 3509. (d) Sasaki, T.; Minamoto, K.; Suzuki, T.; Sugiura, T. *J. Am. Chem. Soc.* **1978**, *100*, 2248; (e) *J. Org. Chem.* **1979**, *44*, 1424. (f) Sasaki, T.; Minamoto, K.; Yamashita, S.; Yamaguchi, K.; Miyake, K. *Ibid.* **1981**, *46*, 5176. (g) Sasaki, T.; Minamoto, K.; Yamashita, S.; Fujiki, Y. *Ibid.* **1982**, *47*, 4465. (h) Sasaki, T.; Minamoto, K.; Nakade, H. *Nucleic Acid Res., Symp. Ser. No. 11*, **1982**, 57. (i) Minamoto, K.; Fujiki, Y.; Shiomi, N.; Uda, Y.; Sasaki, T. *J. Chem. Soc., Perkin Trans 1* **1985**, 2337. (j) Minamoto, K.; Nakade, H.; Fujiki, Y.; Sasaki, T. *Ibid.* **1985**, 2347.

0022-3263/86/1951-4417$01.50/0 

**Table I. UV Absorptions of 2a,b, 2d–f, 3a–h, 4a–f, 5a,b, and S in Methanol**

| compd | $\lambda_{max}$, nm ($\epsilon$) |
|---|---|
| **2a** | 201 (17 400), 224 (31 400), 262 (4600)[a] |
| **b** | 200.5 (17 200), 226 (34 400), 263 (5400)[a] |
| **d** | 200 (13 300), 223 (23 600), 260 (4900)[a] |
| **e** | 200 (17 000), 224.5 (32 400), 266 (3100)[a] |
| **f** | 200 (28 400), 227 (32 900), 245.5 (18 700)[a] |
| **3a**[c] | 218 (21 100), 234 (17 000),[a] 270 (3600)[a] |
| **b** | 223 (22 500), 270 (3400)[a] |
| **d** | 217.5 (24 200), 228 (20 100), 258 (5400)[a] |
| **e** | 220 (22 900), 227 (21 100), 258 (5800)[a] |
| **f** | 214 (17 600), 233.5 (17 800)[b] |
| **g** | 215.5 (21 100)8 232.5 (17 800), 258,5 (9200)[b] |
| **h** | 219 (21 900), 229 (18 100),[a] 258.5 (3500)[b] |
| **4a** | 221.5 (21 500) |
| **b** | 217.5 (26 800) |
| **c** | 218.5 (28 700) |
| **d** | 208 (23 900), 228 (19 000) |
| **e** | 214.5 (17 300), 227 (16 300) |
| **f** | 212 (28 400) |
| **5a** | 202.5 (27 500), 246.5 (18 300), 262.5 (13 100)[a] 295 (1800)[c] |
| **b** | 201 (26 200), 247 (16 400), 305 (1600) |
| **S**[d] | 202 (26 300), 249 (16 300), 265 (10 700)[a] 293 (1400)[a] |

[a] Inflection. [b] Shoulder. [c] Monohydrochloride. [d] Summation of the absorptions ($\epsilon$'s) of spongouridine and *N*-methylaniline.

this product, structure **2b** became evident mainly on the basis of the $^1$H NMR spectrum, whose sugar proton resonance pattern resembles that of **2a** (Table II), and the chemical conversion of its deprotected form **3b** into **3c** (vide infra). This propensity to form a bicyclic system containing a six-membered ring coincides with the cases of purine 8,2′-$N^{\alpha}$-methylhydrazo[3f] and 8,3′-aminoimino cyclonucleosides.[3j] Analogously, treatment of **1** with excess methyl- and ethylamine at higher temperatures yielded the 2,3′-methylimino (**2d**) and 2,3′-ethylimino analogues (**2e**) in reasonable yields, while the reaction of **1** with aniline, *p*-anisidine, or ethyl glycinate required far more forcing conditions but gave reasonable yields of the 2,3′-phenylimino (**2f**), (p-methoxyphenyl)imino (**2g**), and (ethoxycarbonylmethylene)imino analogues (**2h**).

Some comments on the high reactivity of **1** with a wide variety of amines are in order. In this cyclized system, $C_2$ of the base seems to be particularly activated electrophilically by the electron-withdrawing 3′-mesyloxy group through three bonds ("through bond" inductive effect), since treatment of 2,2′-anhydro-1-(5′-*O*-trityl-β-D-arabinofuranosyl)uracil with methylhydrazine under similar conditions resulted in complete recovery of starting material even at 65 °C, while at 100 °C extensive degradation occurred. Similar observations were made when methylamine was used.

Treatment of **2a** with a mixture of ammonium hydroxide and methanol gave 2,3′-(aminoimino)-1-(3′-deoxy-β-D-lyxofuranosyl)uracil (**3a**), which resisted crystallization, while **2b** and **2d–g** were similarly deprotected to crystalline **3b** and **3d–g**. Compound **2h** gave exclusively the amidation product, 2,3′-[(carbamoylmethylene)imino]-1-(3′-deoxy-β-D-lyxofuranosyl)uracil (**3h**). A few of these transformations are described in the Experimental Section.

In the course of efforts to synthesize an *N*-oxide from the compounds of type **3**, we found that **3b** was quantitatively converted into **3c**, in terms of TLC, by treatment with *m*-chloroperbenzoic acid (MCPBA) in acetic acid. This oxidative de-methylamination is unprecedented and while mechanistically obscure may find some synthetic applications.

The structures assigned to **3** are consistent with the UV (Table I) and NMR data (Table II). It is interesting to note that each *N*-methylene proton in compounds **3e** and **3h** resonates at distinctly different magnetic field ($\Delta\delta$ 0.66 for **3e** and 0.90 ppm for **3h**). This suggests that hydrogen bonding exists between the lone pair of the bridge nitrogen and 2′-hydroxyl, thus rendering the configuration of the nitrogen rigid and asymmetric-like, whereas the corresponding $\Delta\delta$'s for the 5′-methylene protons of **2e**, **3e**, **2h**, and **3h** are small or unspecifiable, thus excluding such an interaction between the 5′-hydroxyl and the bridge nitrogen.

**Alkaline Hydrolysis of 3.** In 1968 Fox and co-workers[2a] reported that 2,3′-imino- and 2,3′-(substituted-imino)-1-(2′-deoxy-β-D-*threo*-pentofuranosyl)thymines were stable under acid and basic conditions which readily cause a 2,3′-anhydro uracil nucleoside to react, and that hence an "up" 3′-amino-3′-deoxy nucleoside could not be obtained from these imino nucleosides even under strongly alkaline conditions (7 N KOH, room temperature, 3 weeks). Appropriate reaction conditions have now been found to transform some of the compounds of type **3**. Thus, prolonged heating of **3b** with a 1:1 mixture (v/v) of 6 N NaOH and ethanol at 75–80 °C gave 2,3′-[(methylamino)imino]-1-(3′-deoxy-β-D-lyxopyranosyl)uracil (**4a**) as a single UV-absorbing product in 28% yield. The UV spectrum of this compound resembles that of **3b** except that the former has no inflection, indicating that the chromophore remains intact. In the 200-MHz $^1$H NMR spectrum of **4a**, the signals of the two hydroxyls appeared as sharp doublets with $J$ = 4.0 Hz in contrast with the triplet for the 5′-OH of **3b**. The chemical shift difference between the two 5′-methylene protons of **4a** ($\Delta\delta$ 0.32 ppm) is larger than that of **3b** ($\Delta\delta$ 0.15 ppm). These differences showed **4a** to be a pyranosyl isomer, with the higher resonating $H_{5'}$ in **4a** axial.[8] Its lyxopyranosyl nature follows from inspection of a molecular model, which shows that the obligatory intermediate ii, iii, or iv (or an equilibrium mixture of these) (see Scheme II, path a) formed by the attack of a hydroxide ion on the anomeric carbon can produce no structure other than **4a** as long as chirality at the $C_{2'}$, $C_{3'}$, and $C_{4'}$ is conserved. Although, as a referee has pointed out, the attack of hydroxide ion on the anomeric carbon may appear to be unlikely at first, this furanosyl to pyranosyl transformation absolutely requires cleavage of the anomeric as well as the $C_{1'}$–O bond and there is no other way for these cleavages to occur, since the 2′-hydroxyl cis to the base cannot trigger the fission of the anomeric bond in any sense. It should also be recognized that the N–$C_{1'}$–O partial structure is not that of a common acetal and that nucleic acid bases are rather weak leaving groups as demonstrated by the generally observed higher acidity of the 2′-hydroxyl and extremely low-field resonance of the anomeric proton in the $^1$H NMR spectra of nucleosides. Thus, the very slow reaction, as observed, with the external hydroxide ion would yield i or its ring-opened form (an aldehyde). The anion ii is a simple rotamer resulting from rotation of the $C_{3'}$, $C_{4'}$ bond. Ring closure to the ener-

(4) Sasaki, T.; Minamoto, K.; Niwa, M. *J. Org. Chem.* **1976**, *41*, 3138 and the literature cited therein.

(5) Compound **3c** is now easily available by simply heating a mixture of **1** and excess ammonium acetate in DMF after a mechanistic reexamination of our reaction by Robins et al.[6]

(6) Robins, M. J; Kanai, T. *J. Org. Chem.* **1976**, *41*, 1886.

(7) Codington, J. F.; Fecher, R.; Fox, J. J. *J. Am. Chem. Soc.* **1960**, *82*, 2794.

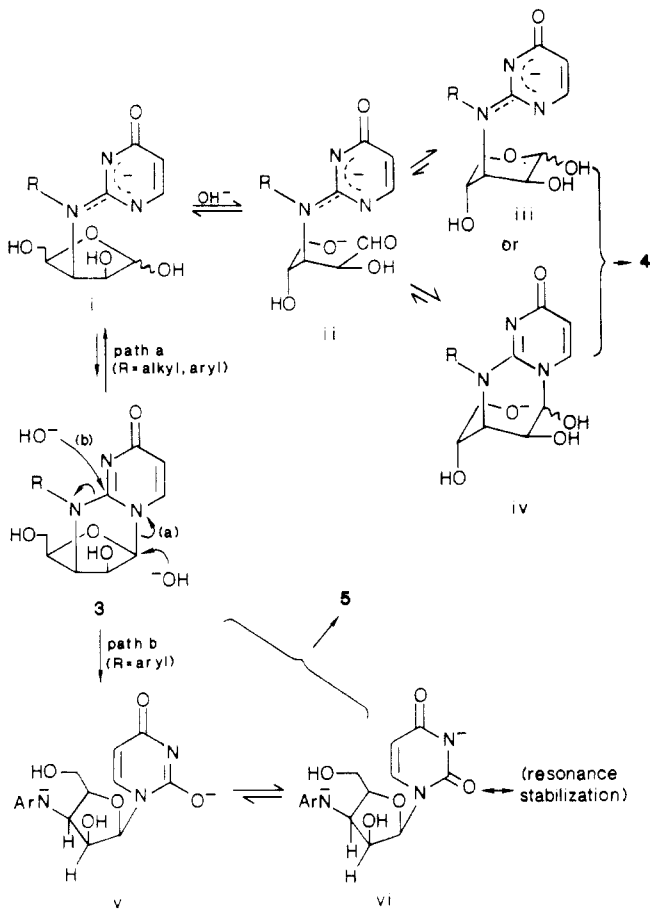
(8) Jackman, L. M.; Sternhell, S. *Application of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry*, 2nd ed.; Pergamon Press: New York, 1969; p 238.

Table II. $^1$H NMR Resonances of 2a, 2b, 2e, 3b, and 3d-h in $Me_2SO$-$d_6$ [a,b]

| compd | 5′-H | 4′-H | 3′-H | 2′-H | 1′-H | 5-H | 6-H | 2′-OH | 5′-OH | others |
|---|---|---|---|---|---|---|---|---|---|---|
| 2a | 4.36 (1 H, dd, $J_{5'a,4'}$ = 6.8, $J_{gem}$ = 12.0, $H_{5'a}$ | | 4.12 (br s) | | 5.43 (d, $J_{1',2'}$ = 4.0) | 5.52 (d, $J_{5,6}$ = 8.0) | 7.48 (d, $J_{6,5}$ = 8.0) | 6.19 (d, $J$ = 4.0) | | 5.06 (2 H, br s, $NH_2$)<br>7.56 (2 H, d, $J$ = 8.0, Ar-H)<br>7.69 (1 H, t, $J$ = 8.0, Ar-H)<br>7.98 (2 H, d, $J$ = 8.0, Ar-H) |
| | 4.46–4.68 (3 H, m, $H_{5'b}$, $H_{4'}$, $H_{2'}$ overlapped) | | | | | | | | | |
| 2b | 4.37 (1 H, dd, $J_{5'a,4'}$ = 6.8, $J_{gem}$ = 10.8, $H_{5'a}$) | | 4.12 (br s) | | 5.42 (d, $J_{1',2'}$ = 4.0) | 5.54 (d, $J_{5,6}$ = 8.0) | 7.52 (d, $J_{6,5}$ = 8.0) | 6.30 (d, $J$ = 3.2) | | 2.52 (3 H, s, $NHCH_3$)<br>5.63 (1 H, br s, $NHCH_3$)<br>7.56 (2 H, d, $J$ = 7.2, Ar-H)<br>7.70 (1 H, t, $J$ = 7.2, Ar-H)<br>7.96 (2 H, d, $J$ = 7.2, Ar-H) |
| | 4.44–4.70 (3 H, m, $H_{5'b}$, $H_{4'}$, $H_{2'}$ overlapped) | | | | | | | | | |
| 2e | 4.38 (1 H, dd, $J_{5'a,4'}$ = 6.4, $J_{gem}$ = 10.0, $H_{5'a}$)<br>4.42 (1 H, dd, $J_{5'b,4'}$ = 5.2, $J_{gem}$ = 10.0, $H_{5'b}$) | 4.63 (m) | 4.13 (t, $J_{3',2'}$ = $J_{3',4'}$ = 3.2) | 4.58 (m, $J_{2',1'}$ = 4.0, $J_{2',3'}$ = 3.2) | 5.43 (d, $J_{1',2'}$ = 4.0) | 5.64 (d, $J_{5,6}$ = 4.0) | 7.50 (d, $J_{6,5}$ = 8.0) | 6.24 (d, $J$ = 3.6) | | 1.08 (3 H, s, $CH_2CH_3$)<br>3.14 (1 H, m, $CH_2CH_3$)<br>3.96 (1 H, m, $CH_2CH_3$)<br>7.57 (2 H, d, $J$ = 6.8, Ar-H)<br>7.72 (1 H, t, $J$ = 6.8, Ar-H)<br>8.01 (2 H, d, $J$ = 6.8, Ar-H) |
| 3b | 3.46–3.61 (2 H, m[overlapped, $H_2O$], $J_{gem}$ = 12.0, $J_{5'a,4'}$ = 7.2, $J_{5'b,4'}$ = 5.6) | 4.22 (dt, $J_{4',3'}$ = 4.0) | 3.95 (t, $J_{3',2'}$ = $J_{3',4'}$ = 4.0) | 4.48 (q, $J_{2',1'}$ = $J_{2',3'}$ = 4.0) | 5.34 (d, $J_{1',2'}$ = 4.0) | 5.32 (d, $J_{5,6}$ = 8.0) | 7.49 (d, $J_{6,5}$ = 8.0) | 6.20 (d, $J$ = 4.0) | 4.86 (br s) | 2.53 (3 H, s, $CH_3$) |
| 3d | 3.30–3.60 (2 H, m, $J_{gem}$ = 10.0, $J_{5'a,4'}$ = $J_{5'b,4'}$ = 6.8) | 4.26 (dt, $J_{4',3'}$ = 3.2, $J_{4',5'a}$ = $J_{4',5'b}$ = 6.8) | 3.93 (t, $J_{3',2'}$ = 3.2, $J_{3',4'}$ = 3.2) | 4.48 (m, $J_{2',1'}$ = 4.0, $J_{2',3'}$ = 3.6) | 5.34 (d, $J_{1',2'}$ = 4.0) | 5.49 (d, $J_{5,6}$ = 8.0) | 7.43 (d, $J_{6,5}$ = 8.0) | 6.28 (d, $J$ = 4.0) | 5.04 (t, $J$ = 5.2) | 3.07 (3 H, s, $CH_3$) |
| 3e | 3.50 (2 H, m $J_{gem}$ = 2.0, $J_{5',4'}$ = 6.8) | 4.24 (dt, $J_{4',3'}$ = 2.0, $J_{4',5'}$ = 6.8) | 3.90 (t-like, $J_{3',2'}$ = 4.0, $J_{3',4'}$ = 2.0) | 4.68 (dd, $J_{2',1'}$ = 4.8, $J_{2',3'}$ = 4.0) | 5.32 (d, $J_{1',2'}$ = 4.8) | 5.50 (d, $J_{5,6}$ = 8.0) | 7.44 (d, $J_{6,5}$ = 8.0) | 6.13 (d, $J$ = 4.8) | 5.00 (d, $J$ = 4.8) | 1.06 (3 H, t, $J$ = 6.8, $CH_2CH_3$)<br>3.08 (1 H, q, $J$ = 6.8, $CH_2CH_3$)<br>3.96 (1 H, q, $J$ = 6.8, $CH_2CH_3$) |
| 3f | 3.69 (2 H, m $J_{gem}$ = 2.4, $J_{5',4'}$ = 6.4) | 4.30 (dt, $J_{4',3'}$ = 3.6, $J_{4',5'}$ = 6.4) | 4.19 (t, $J_{3',2'}$ = $J_{3',4'}$ = 3.6) | 4.64 (q, $J_{2',1'}$ = $J_{2',3'}$ = 3.6) | 5.50 (d, $J_{1',2'}$ = 3.6) | 5.61 (d, $J_{5,6}$ = 8.0) | 7.60 (d, $J_{6,5}$ = 8.0) | 6.48 (d, $J$ = 3.6) | 5.03 (t, $J$ = 4.8) | 7.30–7.50 (5 H, Ar-H) |
| 3h | 3.40 (1 H, m, $J_{gem}$ = 9.6, $J_{5'a,4'}$ = 7.2, $H_{5'a}$)<br>3.52 (1 H, m, $J_{gem}$ = 9.6, $J_{5'b,4'}$ = 6.4, $H_{5'b}$) | 4.28 (dt, $J_{4',3'}$ = 2.8) | 4.13 (t, $J_{3',2'}$ = 3.2, $J_{3',4'}$ = 2.8) | 4.56 (m, $J_{2',1'}$ = 4.0, $J_{2',3'}$ = 3.2) | 5.45 (d, $J_{1',2'}$ = 4.0) | 5.58 (d, $J_{5,6}$ = 8.0) | 7.52 (d, $J_{6,5}$ = 8.0) | 7.10 (d, $J$ = 4.0) | 5.08 (t, $J$ = 4.4) | 3.67 (1 H, d, $J$ = 18.0, $CH_2CONH_2$)<br>4.57 (1 H, d, $J$ = 18.0, $CH_2CONH_2$)<br>7.50 (1 H, s, $CH_2CONH_2$)<br>7.70 (1 H, s, $CH_2CONH_2$) |

[a] s = singlet, d = doublet, dd = doublet of doublets, t = triplet, dt = doublet of triplets, q = quartet, br s = broad singlet, and m = multiplet. Chemical shifts are given in parts per million and $J$ values in hertz. [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.

**Scheme II**



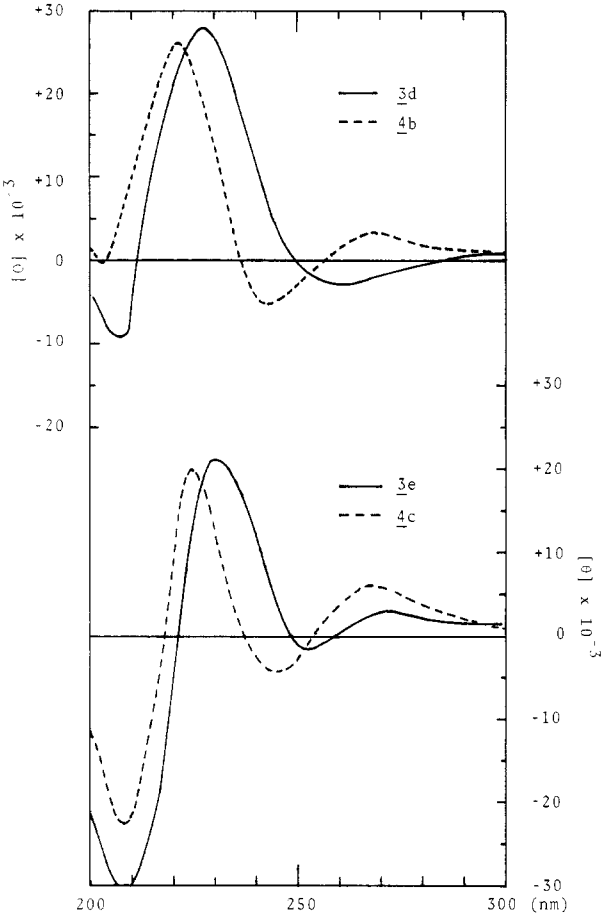




**Figure 1.** CD spectra of **3d**, **4b**, **3e**, and **4c** in methanol.

getically favored six-membered framework iii or iv (or their hydroxide anions) would be sufficiently fast not to allow generation of 1′,2′-enediol, which requires prior development of a 2′-carbanion. Anyway, no epimerization at $C_{2'}$ has been found under the reaction conditions used and this is sustained by retention of the optical activity as shown by the CD data of some analogues (vide infra). In addition, the axial orientation of the base, and accordingly the trans base-$H_{2'}$ geometry, is firmly grounded upon the small $J_{1',2'}$ value (3.6 Hz)[9] (Table III).

Similar alkaline hydrolysis of **3d** and **3e** gave the corresponding pyranosyl analogues **4b** and **4c** in 29% and 32% yield, respectively, while the products on similar treatments of **3a** and **3c** could not be isolated due to limited solubility in appropriate solvents and insufficient mobility on TLC plates. The parent imino compound **4f** was finally obtained by the MCPBA oxidation of **4a** referred to previously. Structures assigned to **4b,c** are based upon the almost complete coincidence of their UV and NMR spectra with those of **4a**. Characteristically, the UV spectra of **4a–c** and **4f** lack the shoulder or inflections observed for their precursors.

On the other hand, when compound **3f** was subjected to the same hydrolysis reaction, another extremely apolar substance, 1-(3′-anilino-3′-deoxy-β-D-lyxofuranosyl)uracil (**5a**, 31%), was obtained together with the expected 2,3′-(phenylimino)-1-(3′-deoxy-β-D-lyxopyranosyl)uracil (**4d**, 34%). The structural assignment of the latter was not straightforward on the basis of the $^1$H NMR spectroscopic features discussed previously. Compound **5a** showed UV absorptions at 202.5, 246.5, 262.5 (infl), and 295 nm (infl), which corresponded to the absorptions at 202, 249, 265 (infl), and 293 nm (infl), resulting from simple summation of the absorptions of spongouridine and *N*-methylaniline, the 265-nm absorption being caused principally by the 1-substituted uracil chromophore (Table I) (the NMR spectrum also shows a normal $N_3$H signal at 11.38 ppm, Table III). Hydrolysis of **3g** under slightly different conditions gave the 2,3′-(*p*-methoxyphenyl)imino- (**4e**, 21%) and the anisidino analogue of **5a** (**5b**, 23.3%).[10] General spectroscopic similarities were observed between **4d** and **4e** as well as between **5a** and **5b**. Although in the $^1$H NMR spectrum of **5a** the signal at 5.00 ppm for a labile proton was ill-resolved, the corresponding resonance at 5.02 ppm for **5b** appeared as a sharp triplet (5′-OH), underlining the aminofuranose structures of **5a** and **5b**.[11] It must be noted further that both secondary hydroxyls in **4** resonated at significantly lower field as compared to the primary ones in **3** or **5**, while the $H_{4'}$'s in **4** generally revealed a striking upfield shift, suggesting anisotropic influences by the nitrogen bridge owing to mutual proximity. These incidental observations seem to be of some diagnostic significance for the lyxopyranosyl structure of **4** also.

The CD spectra of **4b,c** are given in Figure 1 together with those of their precursors, and those of **3f**, **4d**, and **5a** in Figure 2.[12] The spectral patterns of **3** and **4** are similar

(9) For the $J_{1',2'}$'s in the NMR spectra of pyranosyl nucleosides, see: (a) Leutzinger, E. E.; Boweles, W. A.; Robins, R. K.; Townsend, L. B. *J. Am. Chem. Soc.* **1968**, *90*, 127. (b) Lichtenthaler, F. W.; Zinke, H. *J. Org. Chem.* **1972**, *37*, 1612. (c) Fisher, L. V.; Lee, W. W.; Goodman, L. *J. Heterocycl. Chem.* **1969**, *6*, 949. (d) Pan, Y. H.; Robins, R. K.; Townsend, L. B. *Ibid.* **1967**, *4*, 246. (e) Beránek, J.; Friedman, H. A.; Watanabe, K. A.; Fox, J. J. *Ibid.* **1965**, *2*, 188.

(10) The yields were not optimized.

(11) Compound **4d** resisted the alkali treatment similar to that of **3f**, only **4d** being recovered as a UV-absorbing substance even after 40-h reaction at 75–80 °C.

Table III. $^1$H NMR Resonances of 4a–e and 5a,b in $Me_2SO$-$d_6$ [a,b]

| compd | 5′-H | 4′-H | 3′-H | 2′-H | 1′-H | 5-H | 6-H | 2′-OH and 4′-OH | | others |
|---|---|---|---|---|---|---|---|---|---|---|
| 4a | 3.26 (1 H, dd, $J_{5'a,4'}$ = 1.6, $J_{gem}$ = 12.8, $H_{5'a}$)<br>3.58 (1 H, d, $J_{gem}$ = 12.8, $H_{5'b}$) | 3.92 (m) | 3.69 (m) | 4.25 (q, $J_{2',1'}$ = 3.6) | 5.27 (br s) | 5.66 (d, $J_{5,6}$ = 8.0) | 7.58 (d, $J_{6,5}$ = 8.0) | 5.82 (d, $J$ = 4.0) | 5.60 (d, $J$ = 4.0) | 2.53 (3 H, s NHC$H_3$)<br>5.55 (1 H, br s, NHC$H_3$) |
| 4b | 3.25 (1 H, d, $J_{gem}$ = 13.6, $H_{5'a}$)<br>3.56 (1 H, d, $J_{gem}$ = 13.6, $H_{5'b}$) | 3.95 (m) | 3.60 (m[overlapped $H_{5'b}$]) | 4.24 (dt, $J_{2',1'}$ = $J_{2',3'}$ = 2.4) | 5.28 (br s) | 5.64 (d, $J_{5,6}$ = 8.0) | 7.53 (d, $J_{6,5}$ = 8.0) | 5.79 (d, $J$ = 4.4) | 5.57 (d, $J$ = 4.0) | 3.09 (3 H, s, $CH_3$) |
| 4c | 3.26 (1 H, d, $J_{gem}$ = 12.8, $H_{5'a}$)<br>3.57 (1 H, d, $J_{gem}$ = 12.8, $H_{5'b}$) | 3.87 (m[overlapped $CH_2CH_3$]) | 3.60 (m[overlapped $H_{5'b}$]) | 4.25 (q, $J_{2',1'}$ = $J_{2',3'}$ = 3.2) | 5.27 (br s) | 5.64 (d, $J_{5,6}$ = 8.0) | 7.53 (d, $J_{6,5}$ = 8.0) | 5.75 (d, $J$ = 4.0) | 5.58 (d, $J$ = 4.0) | 1.10 (3 H, t, $CH_2CH_3$)<br>3.21 (1 H, q, $CH_2CH_3$)<br>3.87 (1 H, q, $CH_2CH_3$) |
| 4d | 3.20–4.00 (4 H, m, $H_{5'a,b}$,$H_{4'}$,$H_{3'}$ overlapped) | | | 4.36 (m, $J_{2',1'}$ = $J_{2',3'}$ = 3.2) | 5.43 (br s, $J_{1',2'}$ = 3.2) | 5.71 (d, $J_{5,6}$ = 8.0) | 7.64 (d, $J_{6,5}$ = 8.0) | 5.55 (d, $J$ = 4.0) | 6.05 (d, $J$ = 4.0) | 7.34–7.55 (5 H, Ar-H) |
| 4e | 3.64 (2 H, br s) | 3.91 (m) | 3.80 (m[overlapped $OCH_3$]) | 4.35 (t, $J_{2',1'}$ = $J_{2',3'}$ = 2.4) | 5.43 (br s) | 5.69 (d, $J_{5,6}$ = 8.0) | 7.63 (d, $J_{6,5}$ = 8.0) | 5.56 (br s) | 6.04 (br s) | 3.80 (3 H, s[overlapped $H_{3'}$], $OCH_3$)<br>7.04 (2 H, d, Ar-H)<br>7.24 (2 H, d, Ar-H) |

| compd | 5′-H | 4′-H | 3′H | 2′-H | 1′-H | 5-H | 6-H | 2′-OH | 5′-OH | others |
|---|---|---|---|---|---|---|---|---|---|---|
| 5a | 3.48 (1 H, dd, $J_{5'a,4'}$ = 2.4, $J_{gem}$ = 12.8, $H_{5'a}$)<br>3.62 (1 H, dd, $J_{5'b,4'}$ = 6.8, $J_{gem}$ = 12.8, $H_{5'b}$) | 4.40–4.60 (2 H, m, $H_{4'}$,$H_{3'}$ overlapped) | | 4.19 (q, $J_{2',1'}$ = $J_{2',3'}$ = 3.2) | 6.03 (d, $J_{1',2'}$ = 3.2) | 5.64 (d, $J_{5,6}$ = 8.0) | 7.80 (d, $J_{6,5}$ = 8.0) | 5.87 (d, $J$ = 6.8) | 5.00 (br s) | 5.20 (1 H, d, Ph-NH)<br>6.63 (1 H, t, Ar-H)<br>6.80 (2 H, d, Ar-H)<br>7.16 (1 H, t, Ar-H)<br>11.38 (1 H, s, uracil $N^3$-H) |
| 5b | 3.35 (2 H, s) | 4.32–4.50 (2 H, m $H_{4'}$,$H_{3'}$ overlapped) | | 4.18 (m, $J_{2',1'}$ = 3.2) | 6.02 (d, $J_{1',2'}$ = 3.2) | 5.65 (dd, $J_{5,6}$ = 8.0, $J_{5,N^3\text{-}H}$ = 2.0) | 7.81 (d, $J_{6,5}$ = 8.0) | 5.83 (d, $J$ = 6.4) | 5.02 (t, $J$ = 5.6) | 3.67 (3 H, s, $OCH_3$)<br>4.85 (1 H, d, Ar-NH)<br>6.78 (4 H, s, Ar-H)<br>11.36 (1 H, br s, uracil $N^3$-H) |

[a] s = singlet, d = doublet, dd = doublet of doublets, t = triplet, q = quartet, br s = broad singlet, and m = multiplet. Chemical shifts are given in parts per million and $J$ values in hertz. [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.

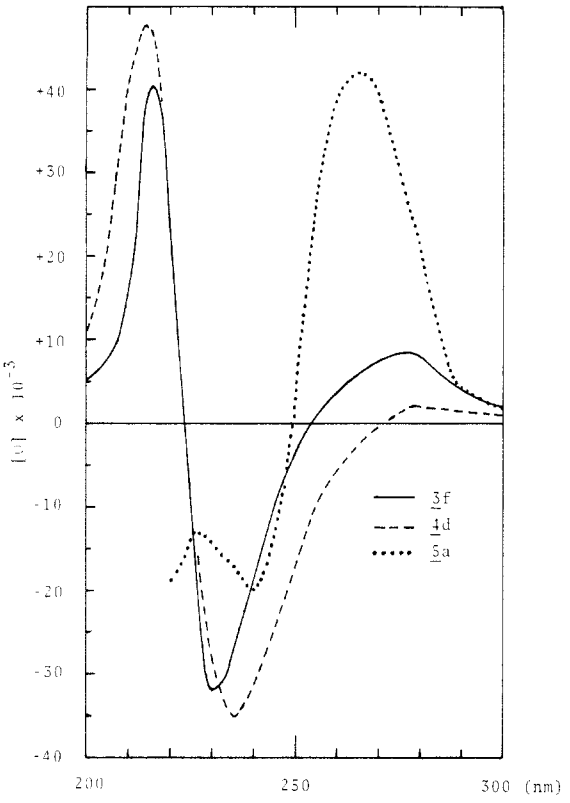



**Figure 2.** CD spectra of **3f**, **4d**, and **5a** in methanol.

in each pair, indicating the retention of chirality in **4b,c**. The negative Cotton effects[13] in the 243–262-nm region in Figure 1 coincide with the generally accepted notion of the syn conformation of pyrimidine nucleosides,[14] whereas specification of the Cotton effects of **3f** and **4d** is made difficult by presence of the phenyl group. On the other hand, the strong positive Cotton effect at 265 nm shown by **5a** corresponds to the known anti conformation of spongouridine or 5′,6-anhydro-6-hydroxyuridine.[14]

Thus, the present alkaline hydrolysis of **3** proceeded in two ways as summarized in Scheme II as far as the isolated products are concerned. When the nitrogen bridge is substituted with an aryl group, both $C_2$ and $C_{1'}$ are vulnerable to the attack of a hydroxide anion, giving rise to **4** and **5** in similar yields. Formation of **5** is explicable by the aryl-promoted resonance stabilization of the intervening nitrogen anion in v and/or vi (path b). The generally low yields of **4a–c** at the stage of consumption of starting material should be ascribed to concomitant degradation of the base moiety to a mixture of UV-transparent products as described,[15] although our attempts to isolate these byproducts in the hydrolysis of **3e** and some other analogues failed. In spite of these uncertainties, the aryl-promoted $C_2$–N fission suggests that a nitrogen bridge properly substituted with a conjugated or pro-conjugated protective group may be used to realize "up" amination.

## Experimental Section[16]

**2,3′-(Aminoimino)-1-(5′-*O*-benzoyl-3′-deoxy-β-D-lyxofuranosyl)uracil (2a). Method A.** A mixture of **1** (500 mg, 1.225 mmol), hydrazine hydrate (0.245 mL, 4 × 1.225 mmol), acetic acid (0.28 ml, 4 × 1.225 mmol), and DMF (7 mL) (ca. 0.7 M hydrazine solution) in an argon-filled pressure tube was stirred at 85 °C for 4 h. The mixture was thoroughly evaporated at 40–45 °C, dissolved in EtOH (3.5 mL), and left in a refrigerator after seeding overnight to give 127 mg of TLC-pure product. The filtrate was evaporated and heated to reflux in a 1:1 mixture of MeOH and acetone (10 mL) for 1 h. TLC at this stage revealed that the residual product and hydrazine changed into each faster moving hydrazone. The mixture was evaporated and chromatographed on a silica gel plate (20 × 20 cm; $CHCl_3$/MeOH, 8:2, twice developed). The slower running band was eluted with MeOH and the obtained solid proved to be identical with the above obtained product (but not a hydrazone!!). The combined crops were recrystallized from MeOH to give 280 mg (66%) of **2a**, mp 252–253 °C dec.

Anal. Calcd for $C_{16}H_{16}N_4O_5$: C, 55.81; H, 4.68; N, 16.27. Found: C, 55.69; H, 4.74; N, 16.33.

**Method B.** A mixture of **1** (3.0 g, 7.35 mmol) and hydrazine hydrate (1.47 mL, 4 × 7.35 mmol = 29.4 mmol) in DMF (90 mL) (ca. 0.32 M hydrazine solution) in an argon-filled pressure tube was stirred at room temperature for 6.5 h and thoroughly evaporated in vacuo below 40 °C. The residue in EtOH (8 mL), on being left in a refrigerator overnight after seeding, gave 2.183 g (86.26%) of TLC-homogeneous crystals (**2a**), identical with the product by method A in terms of TLC and IR spectroscopy.

**2,3′-[(Methylamino)imino]-1-(5′-*O*-benzoyl-3′-deoxy-β-D-lyxofuranosyl)uracil (2b).** A mixture of **1** (1.0 g, 2.45 mmol) and methylhydrazine (0.65 mL, 5 × 2.45 mmol) in DMF (30 mL) in an argon-filled pressure tube was stirred at 30–35 °C for 30 h and thoroughly evaporated. The residue was left with MeOH (5 mL) in a refrigerator to give crystals, which were collected by suction. The filtrate was chromatographed on a silica gel plate (20 × 20 cm, $CHCl_3$/MeOH, 85:15, developed several times) to give a further crop from the major fraction. Recrystallization of the combined crops from MeOH gave 467 mg (53%) of **2b**, mp 254–255 °C dec.

Anal. Calcd for $C_{17}H_{18}N_4O_5$: C, 56.98; H, 5.06; N, 15.64. Found: C, 56.91; H, 5.08; N, 15.69.

**Conversion of 2a into 3c.** To a solution of **2a** (150 mg, 0.436 mmol) in acetic acid (5 mL) was added isoamyl nitrite (0.064 mL, 1.1 × 0.436 mmol), and the mixture stirred at room temperature for 1 h and 45 min. TLC-monitoring at this stage using silica gel and $CHCl_3$/MeOH (8:2) showed no starting material and a single less polar product. The mixture was evaporated and directly chromatographed on a silica gel plate (20 × 20 cm; $CHCl_3$/MeOH, 8:2, twice developed). Elution of the major fraction with MeOH and recrystallization of the obtained solid from MeOH gave homogeneous crystals, which were, surprisingly, more polar than the starting material and proved to be **3c** in terms of TLC and IR spectroscopy; yield 74 mg (75%). The filtrate of **3c** gave an aromatic fragrance.

**2,3′-(Methylimino)-1-(5′-*O*-benzoyl-3′-deoxy-β-D-lyxofuranosyl)uracil (2d).** A mixture of methylamine hydrochloride (1.35 g, 20 mmol), $Et_3N$ (2.8 mL, 20 mmol), and DMF (40 mL) under argon in a pressure tube was stirred at 50 °C for 1 h. After cooling, compound **1** (1.438 g, 3.52 mmol) and further DMF (6 mL) were added to the mixture, and the total were stirred at 60–65 °C for 17 h under argon and then cooled. The inorganic salt was filtered off and the filtrate evaporated. Leaving the residue with EtOH (10 mL) in a refrigerator overnight gave voluminous crystals, which were collected and recrystallized from MeOH to afford 1.063 g (88%) of **2d**, mp 244–246 °C.

Anal. Calcd for $C_{17}H_{17}N_3O_5$: C, 59.47; H, 4.99; N, 12.24. Found: C, 59.50; H, 4.95; N, 12.25.

**2,3′-(Ethylimino)-1-(5′-*O*-benzoyl-3′-deoxy-β-D-lyxofuranosyl)uracil (2e).** A mixture of ethylamine hydrochloride (995 mg, 12.2 mmol) and $Et_3N$ (1.7 mL, 12.2 mmol) and DMF (15 mL) in an argon-filled pressure tube was stirred at room temperature for 5–6 h. After addition of **1** (1.0 g, 2.44 mmol) with further DMF (5 mL) and argon-bubbling, the sealed tube was stirred at 85–90 °C for 24 h. The mixture was worked up as for **2d** and the obtained residue partitioned between ethyl acetate (30 mL) and water (6–7 mL). The aqueous phase was repeatedly extracted with ethyl acetate (2 × 30 mL), when a homogeneous

(12) The CD spectra were recorded on a JASCO J-500 spectropolarimeter equipped with a JASCO DP-500 data processor for CD.

(13) The values for the major Cotton effects are as follows: nm ([θ] × $10^{-3}$): **3d**, 261.5 (−2.96); **4b**, 243 (−5.19); **3e**, 252.5 (−1.72); **4c**, 245 (−4.28); **3f**, 277 (+8.66); **4d**, 278 (+1.83); **5a**, 265 (+42).

(14) Zorbach, W. W., Tipson, R. S., Ed. *Synthetic Procedures in Nucleic Acid Chemistry*; Wiley Interscience: New York, 1973; Vol. 2, p 177.

(15) Jones, A. S.; Walker, R. T. *J. Chem. Soc. C* **1966**, 1784.

(16) The general method used are similar to those described earlier.[3e]

crystalline solid deposited. The collected solid and EtOAc extract were combined and recrystallized from MeOH to afford 480 mg (55%) of **2e**, mp 243–246 °C.

Anal. Calcd for $C_{18}H_{19}N_3O_5$: C, 60.49; H, 5.36; N, 11.76. Found: C, 60.49; H, 5.56; N, 11.54.

**2,3′-(Phenylimino)-1-(5′-*O*-benzoyl-3′-deoxy-β-D-lyxofuranosyl)uracil (2f).** Compound **1** (1.846 g, 4.52 mmol) was treated with freshly distilled aniline (6.15 mL, 67.6 mmol) in DMF (23 mL) similarly with the above at 125–130 °C for 77 h. After having removed the solvent, the residual paste was repeatedly digested with ether and the aniline-containing supernatant was decanted off, until the dark residue became a pulverizable solid. This was collected with ether by suction and then stirred in water (16 mL) for 10 min and again collected. The air-dried crude product was recrystallized from MeOH to give 1.084 g of **2f**. Preparative TLC with the filtrate (silica gel, 20 × 20 cm; $CHCl_3$/MeOH, 85:15, twice developed) gave 160 mg of a 2nd crop (total yield: 1.244 g, 68.2%); mp 268–270 °C.

Anal. Calcd for $C_{22}H_{19}N_3O_5$: C, 65.18; H, 4.72; N, 10.37. Found: C, 65.24; H, 4.73; N, 10.29.

**2,3′-[(*p*-Methoxyphenyl)imino]-1-(5′-*O*-benzoyl-3′-deoxy-β-D-lyxofuranosyl)uracil (2g).** Compound **1** (500 mg, 1.22 mmol) was treated with *p*-anisidine (1.18 g, 9.66 mmol) in DMF (7.4 mL) at 125–130 °C for 65 h and worked up similarly with the case of **2f**, and the crude product obtained after ether-washing was chromatographed on a silica gel plate (20 × 20 cm, 2 sheets; $CHCl_3$/MeOH, 8:2). The major band was eluted with MeOH and the obtained solid recrystallized from the same solvent to give 150 mg (28.7%) of **2g**, mp 251–253 °C.

Anal. Calcd for $C_{23}H_{21}N_3O_6$: C, 63.44; H, 4.86; N, 9.65. Found: C, 63.41; H, 4.89; N, 9.68.

The filtrate separated from the major part of **2g** gave 107 mg (27%) of the debenzoylated product **3g**.

**2,3′-[((Ethoxycarbonyl)methyl)imino]-1-(5′-*O*-benzoyl-3′-deoxy-β-D-lyxofuranoysl)uracil (2h).** A mixture of ethyl glycinate hydrochloride (851 mg, 6.12 mmol), $Et_3N$ (0.85 mL, 6.12 mmol), and DMF (6.1 mL) in an argon-filled pressure tube was stirred at room temperature overnight. Then, compound **1** (500 mg, 1.22 mmol) was added and the mixture stirred at 75–80 °C for 40 h. Further ethyl glycinate hydrochloride (6.12 mmol) and $Et_3N$ (6.12 mmol) were added and the reaction continued at the same temperature range for additional 9 h. After cooling, the inorganic salt was filtered off and the filtrate evaporated. The residue was partitioned between ethyl acetate (20 mL) and water (7 mL), and the separated EtOAc layer was chromatographed on a silica gel plate (20 × 20 cm; $CHCl_3$/MeOH, 85:15). Elution of the major band with a mixture of MeOH and acetone gave 481 mg (95%) of foam, which was directly debenzoylated (vide infra).

**General Procedures for Debenzoylation of 2.** A mixture of each of the compounds **2** and concentrated ammonium hydroxide/MeOH (1:3, v/v) (12–15 mL per mmol of **2**) was stirred in a closed vessel at room temperature for 5–30 h, until **2** disappeared completely. In every case, a single product was detected by TLC and excessive elongation of the hydrolysis time did not affect the product. After evaporation of the solvent and excess ammonia at below 40 °C in vacuo, the residue was digested with a small volume of EtOH or MeOH to give directly crystals. For optimization of the isolated yields, however, it is recommended to digest or stir the residue with neat ether or ether containing a small portion of EtOAc or acetone to remove the major part of the released benzoic acid and/or benzamide and then to recrystallize the collected solid from MeOH. In this way, **3b** and **3d–g** are obtainable in 80–90% isolated yields. All compounds involving **3a** and **3h** gave elemental values for C, H, N within acceptable limits (0.3%): mp (°C) **3a** (monohydrochloride), 210–217 dec; **3b**, 260–265 dec; **3d**, >290; **3e** >290; **3f**, 263–265; **3g**, 274–276 dec; **3h**, 225–228.

**Example 1. Preparation of 3a.** A mixture of **2a** (127 mg, 0.37 mmol) and concentrated $NH_4OH$/MeOH (1:3) (5 mL) was stirred at room temperature for 5 h, evaporated, and repeatedly coevaporated with MeOH. The residual glass was thoroughly digested with ether (5 mL) containing a small volume of EtOH. The collected hygroscopic solid was chromatographed on a silica gel plate (20 × 20 cm; $CHCl_3$/MeOH, 6:4) and the fraction concerned eluted with MeOH to give a foam, which resisted crystallization. The total in MeOH (3 mL) was acidified with saturated HCl in dioxane and the solution evaporated. Repeated coevaporation of the residue with MeOH gave crystals, which were recrystallized from dried MeOH to afford 73 mg (71%) of a monohydrochloride of **3a**.

**Example 2. Preparation of 3h.** A mixture of **2h** (370 mg, 0.89 mmol) and concentrated $NH_4OH$/MeOH (1:3) (30 mL) was stirred at room temperature overnight and evaporated. The residue was fractionated on a silica gel plate (20 × 20 cm; $CHCl_3$/MeOH, 7:3, developed 3 times) and the desired band eluted with MeOH. Recrystallization of the obtained solid gave 152 mg (61%) of **3h**.

**Conversion of 3b into 3c.** A solution of **3b** (100 mg, 0.39 mmol) and *m*-chloroperbenzoic acid (MCPBA) (102 mg, 0.59 mmol) in acetic acid (2 mL) was stirred at room temperature for 1 h. After having evaporated the solvent, the residue was repeatedly coevaporated with MeOH and then thoroughly digested with ether. The sparingly soluble solid was collected by suction and recrystallized from MeOH to give 69 mg (78%) of **3c**, identical with an authentic specimen[3a] in terms of TLC, IR spectroscopy, and mixture melting point.

**2,3′-[(Methylamino)imino]-1-(3′-deoxy-β-D-lyxopyranosyl)uracil (4a).** A mixture of **3b** (220 mg, 0.87 mmol), EtOH (4 mL), and 6 N NaOH (4 mL) in an argon-filled pressure tube was stirred at 75–80 °C. TLC-monitoring with an aliquot after neutralizatiosn at intervals of 1 or 2 h indicated slow formation of a slightly less polar, UV-absorbing substance at the expense of the starting material. After a total of 21.5 h, during which time **3b** was exhausted, the mixture was cooled, neutralized with 1 N HCl, evaporated, and coevaporated with MeOH a couple times. A repeat of TLC at this stage using silica gel and $CHCl_3$/MeOH (8:2) indicated again a single UV-absorbing, less polar product, but when the used plate was put in atmosphere of iodine vapor coloration occurred also near the starting spot. The residue was heated with EtOH (35 mL) to reflux for 10 min and then cooled to room temperature, and the precipitate of inorganic salt was filtered off. The filtrate was adjusted to pH 8 with $NH_4OH$/MeOH (1:3) and again evaporated. The residue was dissolved in EtOH, filtered with Norit, and evaporated. The residue in a small volume of MeOH was applied on a silica gel plate (20 × 20 cm) and developed with $CHCl_3$/MeOH (7:3) 3 times. The UV-absorbing band concerned gave, after elution with MeOH and recrystallization from EtOH, 62 mg (28.2%) of **4a**, mp 229–231 °C.

Anal. Calcd for $C_{10}H_{13}N_3O_4$: C, 50.20; H, 5.48; N, 17.57. Found: C, 50.26; H, 5.36; N, 17.62.

**2,3′-(Methylimino)-1-(3′-deoxy-β-D-lyxopranosyl)uracil (4b).** A mixture of **3d** (100 mg, 0.42 mmol), EtOH (2 mL), and 6 N NaOH (2 mL) was stirred at 75–80 °C in an argon atmosphere in the same way as in the case of **4a** under careful TLC control. After a total of 48 h, the mixture was neutralized with acetic acid and thoroughly evaporated. The residue was heated to reflux in acetone/MeOH (9:1) (ca. 50 mL), cooled up to room temperature, and the sparingly soluble solid filtered off. The filtrate was evaporated and the residue chromatographed on a silica gel plate (20 × 20 cm; $CHCl_3$/MeOH, 8:2, twice developed) to afford 29 mg (29.0%) of **4b** after elution with MeOH and one recrystallization from the same solvent, mp above 290 °C.

Anal. Calcd for $C_{10}H_{13}N_3O_4$: C, 50.20; H, 5.48; N, 17.57. Found: C, 50.37; H, 5.47; N, 17.41.

**2,3′-(Ethylimino)-1-(3′-deoxy-β-D-lyxopyranosyl)uracil (4c).** A mixture of **3e** (200 mg, 0.79 mmol), EtOH (3.7 mL), and 6 N NaOH (3.7 mL) in a pressure tube was stirred under the same reaction conditions as in the case of **4b**. Repeated TLC-monitoring using silica gel and $CHCl_3$/MeOH (8:2) indicated a mobility pattern similar to the above cases, a single UV-absorbing, less polar product being detected. After 63 h, the mixture was neutralized with acetic acid and thoroughly evaporated. The residue was digested with MeOH (ca. 10 mL) and the UV-transparent sparingly soluble solid filtered off. The filtrate containing the MeOH-soluble, UV-transparent solid was directly subjected to preparative TLC (silica gel, 20 × 20 cm, 2 sheets; $CHCl_3$/MeOH, 75:25), expecting also separation of the UV-transparent side products, which proved, after all, to be an uncharacterizable salt-like material or material mixture and were discarded. The UV-absorbing fraction gave 64 mg (32.0%) of **4c** as prisms of mp above 285 °C after recrystallization from MeOH.

Anal. Calcd for $C_{11}H_{15}N_3O_4$: C, 52.17; H, 5.97; N, 16.59. Found: C, 52.24; H, 5.93; N, 16.56.

**2,3′-(Phenylimino)-1-(3′-deoxy-β-D-lyxopyranosyl)uracil (4d) and 1-(3′-Anilino-3′-deoxy-β-D-lyxofuranosyl)uracil (5a).** A mixture of **3f** (300 mg, 1.0 mmol), 6 N NaOH (3.8 mL), and EtOH (3.8 mL) was heated at 75–80 °C strictly as for the above cases. TLC-monitoring showed that an extremely mobile substance was forming together with the anticipated, slightly less polar product. After 21 h, the reaction was quenched with acetic acid and the mixture thoroughly evaporated. The residual solid was pulverized, heated to reflux in hot acetone/MeOH (9:1) (60 mL), and filtered after being cooled to room temperature. The filter-cake was again extracted with hot acetone (30 mL). The combined solutions were evaporated and the residue chromatographed on a silica gel plate (20 × 20 cm; $CHCl_3$/MeOH, 85:15, developed 3 times). The slower moving band was eluted with MeOH and the obtained solid recrystallized from MeOH to afford 102 mg (34.0%) of **4d** as a methanolate after drying under high vacuum at 80 °C for 4 h, mp above 300 °C.

Anal. Calcd for $C_{15}H_{15}N_3O_4 \cdot CH_3OH$: C, 57.65; H, 5.75; N, 12.61. Found: C, 57.58; H, 5.67; N, 12.75.

On the other hand, elution of the faster moving fraction with acetone gave a solid, which was recrystallized from acetone to afford 98 mg (30.7%) of **5a** as a monohydrate, mp 225–226 °C.

Anal. Calcd for $C_{15}H_{15}N_3O_4 \cdot H_2O$: C, 56.42; H, 5.37; N, 13.16. Found: C, 56.54; H, 5.37; N, 13.05.

**2,3′-[(p-Methoxyphenyl)imino]-1-(3′-deoxy-β-D-lyxopyranosyl)uracil (4e) and 1-(3′-Anisidino-3′-deoxy-β-D-lyxofuranosyl)uracil (5b).** A mixture of **3g** (110 mg, 0.33 mmol), 5 N NaOH (1 mL) and MeOH (1 mL) in an argon-filled pressure tube was stirred at 75–80 °C for 45 h. After neutralization with 0.8 N HCl, MeOH (10 mL) was added and the inorganic salt filtered off. The filtrate was concentrated and chromatographed on a silica gel plate (20 × 20 cm, $CHCl_3$/MeOH, 8:2). The slower moving band gave 23 mg (20.9%) of **4e**, mp 253–255 °C, after recrystallization from MeOH.

Anal. Calcd for $C_{16}H_{17}N_3O_5$: C, 58.00; H, 5.17; N, 12.68. Found: C, 57.87; H, 5.35; N, 12.63.

Similar processing with the faster running fraction afforded 27 mg (23.3%) of **5b** as crystals of mp 194–195 °C (MeOH).

Anal. Calcd for $C_{16}H_{19}N_3O_6$: C, 55.01; H, 5.48; N, 12.03. Found: C, 55.27; H, 5.52; N, 11.83.

**2,3′-Imino-1-(3′-deoxy-β-D-lyxopyranosyl)uracil (4f).** A solution of **4a** (25 mg, 0.098 mmol) and MCPBA (26 mg, 0.15 mmol) in acetic acid (0.5 mL) was stirred at room temperature for 1 h and 10 min. After the solvent was evaporated off, the residue was repeatedly coevaporated with methanol and then thoroughly digested with dry ether. The sparingly soluble solid was collected and repeatedly recrystallized from methanol to give 12 mg (54.4%) of **4f** as powdery crystals, mp above 300 °C.

Anal. Calcd for $C_9H_{11}N_3O_4$: C, 48.00; H, 4.92; N, 18.66. Found: C, 48.21; H, 5.08; N, 18.40.

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**Registry No.** **1**, 56687-59-3; **2a**, 90597-04-9; **2b**, 90597-05-0; **2d**, 103251-64-5; **2e**, 103251-65-6; **2f**, 103251-66-7; **2g**, 104531-58-0; **2h**, 103251-67-8; **3a**·HCl, 104597-34-4; **3b**, 90597-07-2; **3c**, 56615-08-8; **3d**, 103251-68-9; **3e**, 103251-69-0; **3f**, 103251-70-3; **3g**, 104531-59-1; **3h**, 104531-60-4; **4a**, 103251-72-5; **4b**, 103251-73-6; **4c**, 103251-74-7; **4d**, 103251-75-8; **4e**, 104531-61-5; **4f**, 104548-71-2; **5a**, 104531-62-6; **5b**, 104531-63-7; methylhydrazine, 60-34-4; methylamine hydrochloride, 593-51-1; ethylamine hydrochloride, 557-66-4; aniline, 62-53-3; *p*-anisidine, 104-94-9; ethyl glycinate hydrochloride, 623-33-6.

# Photochemical Cyclization of 2-Alkyl-3-aryl-2-cyclohexenones and 2-Alkoxy-3-aryl-2-cyclohexenones

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Irradiation at 254 nm of 2-alkyl-3-aryl-2-cyclohexenones and 2-alkoxy-3-aryl-2-cyclohexenones leads to oxidative cyclization involving the aryl group and the 2-alkyl or the 2-alkoxy substituent. This cyclization cannot be sensitized by triplet sensitizers nor trapped by triplet quenchers. A solvent effect and a concentration dependence have been detected for 2-ethyl-3-phenyl-2-cyclohexenone and for 2-methoxy-3-phenyl-2-cyclohexenone, which are indicative of a complex reaction mechanism.

The photochemistry of conjugated enones and especially cyclohexenones has attracted the efforts of many photochemists, due to their numerous synthetic applications. Among the reactions available to excited cyclohexenones, photocycloadditions[1] and rearrangements to lumiproducts[2] have received particular attention. Hydrogen abstraction by conjugated cyclohexenones is far less important than for aromatic ketones, although it can sometimes become the major process in hydrogen-atom-donating solvents.[3] By contrast, intramolecular γ-hydrogen abstraction is a general process for α-substituted conjugated enones; depending on the nature of the substituent X, cyclobutyl,[4]

(1) (a) de Mayo, P. *Acc. Chem. Res.* **1971**, *4*, 41. (b) Baldwin, S. W. *Organic Photochemistry*; Padwa, A., Ed.; Marcel Dekker: New York, 1981; Vol. 5, p 123.

(2) (a) Schuster, D. I. *Pure Appl. Chem.* **1975**, *41*, 601. (b) Kropp, P. J. *Organic Photochemistry*; Chapman, O. L., Ed.; Marcel Dekker: New York, 1967; Vol. 1, p 1. (c) Chapman, O. L.; Weiss, D. S. *Organic Photochemistry*; Chapman, O. L., Ed.; Marcel Dekker: New York, 1973, Vol. 3, p 197.

(3) (a) Schaffner, K.; Jeger, O. *Tetrahedron* **1974**, *30*, 1891 and references cited therein. (b) Zimmerman, H. E.; Lewis, R. G.; McCullough, J. J.; Padwa, A.; Staley, S. W.; Semmelhack, M. *J. Am. Chem. Soc.* **1966**, *88*, 1965. (c) Dauben, W. G.; Shaffer, G. W.; Vietmeyer, N. D. *J. Org. Chem.* **1968**, *33*, 4060. (d) Koller, H.; Rabold, G. P.; Weiss, K.; Muhkerjee, T. K. *Proc. Chem. Soc.* **1964**, 232. (e) Schuster, D. I.; Nunez, I. M.; Chan, C. B. *Tetrahedron Lett.* **1980**, *21*, 1197.

(4) (a) Cormier, R. A.; Schreiber, W. L.; Agosta, W. C. *J. Am. Chem. Soc.* **1973**, *95*, 4873. (b) Cormier, R. A.; Schreiber, W. L.; Agosta, W. C. *J. Chem. Soc., Chem. Commun.* **1972**, 729. (c) Cormier, R. A.; Agosta, W. C. *J. Am. Chem. Soc.* **1974**, *96*, 618 and 1867.

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