(s, 3 H, CH_3), 0.87 (s, 9 H, $C(CH_3)_3$), 0.17 (s, 3 H, $SiCH_3$), 0.15 (s, 3 H, $SiCH_3$); ^{13}C NMR ($CDCl_3$) ppm 173.9, 78.1, 68.5, 38.1, 36.9, 36.4, 35.1, 25.8, 25.0, 18.2, -4.9, -5.5; IR (neat) 2956, 2929, 2857, 1710, 1352, 1060, 835 cm^{-1}; MS for $C_{14}H_{27}NO_2Si$, m/z (relative intensity) 254 (6), 213 (17), 212 (100), 154 (2), 138 (20), 75 (21). Anal. Calcd for $C_{14}H_{27}NO_2Si$: C, 62.40; H, 10.10; N, 5.20. Found: C, 62.35; H, 10.40; N, 5.13. Corrected for 0.23% H_2O.

Hexahydro-5-methoxy-7a-methyl-3*H*-pyrrolin-3-one (15). Lactam alcohol **8b** (4.38 g, 28 mmol), dissolved in MeOH (50 mL), was added to MeOH (200 mL, brought to pH = 3 with concentrated HCl) at 0 °C. After 1.5 h the mixture was concentrated in vacuo to 4.8 g. This was chromatographed on a Waters' Prep-500 [SiO_2, CH_2Cl_2/MeOH (3%)] to yield 4.35 g (92%) of **15**: ^1H NMR ($CDCl_3$, 300 MHz) δ 5.13-5.10 (m, 1 H, NCHO), 3.37 (s, 3 H, OCH_3), 2.84-2.72 (m, 1 H), 2.45-2.22 (m, 2 H), 2.14-1.84 (m, 4 H), 1.72-1.58 (m, 1 H), 1.38 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) ppm 176.5, 86.6, 67.6, 56.0, 38.3, 35.1, 34.0, 33.4, 27.1; IR (neat) 3570 (H_2O), 2966, 1702, 1459, 1376, 1364, 1335, 1196, 1179, 1093 cm^{-1}; MS for $C_9H_{15}NO_2$, m/z (relative intensity) 169, (M^+, 24), 154 (91), 139 (83), 138 (91), 122 (11), 98 (100). Anal. Calcd for $C_9H_{15}NO_2$: C, 63.88; H, 8.93; N, 8.28. Found: C, 63.75; H, 8.93; N, 8.19. Corrected for 0.98% H_2O. TLC (SiO_2) R_f = 0.39, EtOAc.

Bis(hexahydro-7a-methyl-3-oxo-3*H*-pyrrolizin-5-yl) Ether (16). Lactam **8b** (4.11 g, 26.5 mmol) and acidic H_2O (80 mL, pH = 1 from a few drops of 10% HCl) were combined. The mixture was evaporated in vacuo to 4.0 g. This material was chromatographed on a Waters' Prep-500 [SiO_2, CH_2Cl_2/MeOH (3%)] to yield **15** (430 mg, 10%), a fraction containing a 3:2 mixture of starting material to ether **16** (510 mg), and ether **16** (1.86 g, 47%) as a mixture of diastereomers. Data for **16**: ^1H NMR ($CDCl_3$) δ 1.20-3.00 (m, 16 H), 1.40 (s, 3.75 H, CH_3), 1.46 (s, 2.25 H, CH_3), 5.30-5.50 (m, 0.66 H, NCHO), 5.50-5.80 (m, 1.33 H, NCHO); ^{13}C NMR ($CDCl_3$) ppm (peaks of major diastereomer) 175.1, 84.8, 67.5, 38.4, 35.4, 34.5, 33.7, 26.5 (peaks of minor diastereomer) 175.7, 81.7, 67.7, 38.4, 35.5, 33.9, 26.6; IR (mineral oil mull) 2926, 1698, 1056, 1047 cm^{-1}; MS for $C_{16}H_{24}N_2O_3$, m/z (relative intensity) 292 (M^+, 0.3), 264 (0.1), 213 (0.2), 170 (1), 154 (15), 140 (10), 139 (100), 138 (62), 111 (6), 95 (15). Anal. Calcd for $C_{16}H_{24}N_2O_3$: C, 65.73; H, 8.27; N, 9.58. Found: C, 65.39; H, 8.25; N, 9.55. Corrected for 0.81% H_2O.

6-Hydroxy-1-methyl-2-piperidinone (19). Lithium triethylborohydride (220 mL, 1.0 M in THF) was added dropwise to a solution of *N*-methylglutarimide (**18**) (25.4 g, 0.2 mol) in CH_2Cl_2 (650 mL) at -78 °C. Saturated NH_4Cl (150 mL) was added to the reaction 15 min following the addition. The solution was allowed to warm to room temperature. The organic layer was removed, and the aqueous layer was extracted with CH_2Cl_2 (3 × 200 mL). The organic layers were combined, dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was chromatographed on an SiO_2 PrepPAK eluting with 5% CH_3OH/CH_2Cl_2. The appropriate fractions were combined and concentrated in vacuo. The residue was dissolved in Et_2O and allowed to crystallize. The product was collected by filtration and dried under vacuum to give **19** as an extremely deliquescent white solid (13.4 g, 52.8%): mp 36-38 °C; ^1H NMR ($CDCl_3$) δ 1.68-1.74 (m, 1 H, CH_2), 1.89-2.16 (m, 1 H, CH_2), 2.25-2.45 (m, 2 H, CH_2), 2.98 (s, 3 H, NCH_3), 4.31 (d, 1 H, J = 9.0 Hz, OH), 4.91 (dt, 1 H, J = 4.6, 8.9 Hz, NCH); IR (mineral oil mull) 3212, 2952, 1623, 1491, 1084, 987 cm^{-1}; HRMS for $C_6H_{11}NO_2$ calcd 129.0790, found 129.0789, m/z (relative intensity) 129 (M^+, 57), 101 (30), 73 (50), 60 (82), 42 (100). Anal. Calcd for $C_6H_{11}NO_2$: C, 55.80; H, 8.58; N, 10.84. Found: C, 54.97; H, 8.74; N, 10.73. TLC (SiO_2) R_f = 0.22, 5% CH_3OH/CH_2Cl_2.

Acknowledgment. We wish to thank the Upjohn Company's Physical and Analytical Chemistry Department for elemental analyses, mass spectra, and IR spectroscopy. We appreciate the stimulating discussions and helpful suggestions from Professors Philip Magnus and Edwin Vedejs.

Synthesis and Alkali-Hydrolysis Reactions of Some 2,3′-(Substituted imino)pyrimidine Nucleosides Lacking a 2′-Hydroxyl Group

Katsumaro Minamoto,* Kishiko Azuma, Norio Fujiwara, and Shoji Eguchi*

Institute of Applied Organic Chemistry, Faculty of Engineering, Nagoya University, Furo-cho, Chikusa-ku, Nagoya, Japan

Toyohiko Hirota and Shizuo Kadoya

Research Institute, Daiichi Seiyaku Co., Ltd., 16-13, Kita-kasai 1-Chome, Edogawa-ku, Tokyo, Japan

Received January 26, 1989

2,3′-(Methylimino)- (**6a**) and 2,3′-(phenylimino)-1-(3′-deoxy-2′-*O*-methyl-β-D-lyxofuranosyl)uracil (**6b**) and 2,3′-(methylimino)- (**11a**), 2,3′-(phenylimino)- (**11b**), and 2,3′-[(*p*-methoxyphenyl)imino]-1-(2′-deoxy-β-D-*threo*-pentofuranosyl)uracil (**11c**) were synthesized. Alkaline hydrolysis of **6a**, **6b**, **11a**, and **11c** gave the corresponding pyranosyl isomers **13a-d**, while the 2,3′-(phenylimino)-bridged thymidine analogue **15** gave exclusively the C_2-N fission product **17**. Some mechanistic corroboration and difference of reactivity between 2,3′-N-bridged uracil and thymine nucleosides are described. 3′,5′-Anhydro nucleosides **12** and **16** were also isolated with **11c** and **15**.

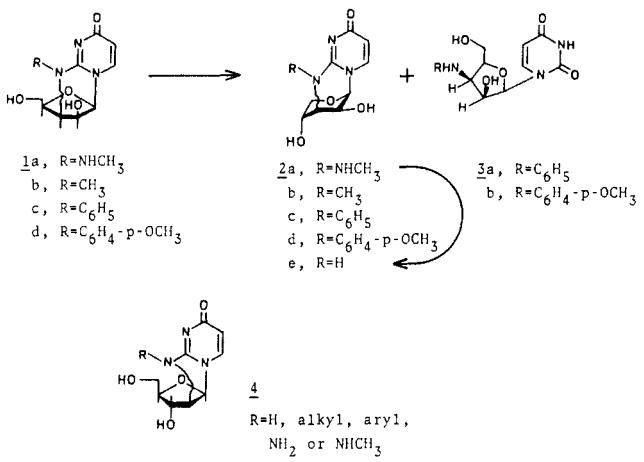
In a recent publication,[1] we have reported that 2,3′-(substituted imino)-1-(3′-deoxy-β-D-lyxofuranosyl)uracils (**1a-d**) are convertible into their pyranosyl isomers **2a-d** under strongly alkaline conditions and that cleavage of the 2,3′-imino bridge also occurs to a similar extent to give a 3′-(arylamino)-3′-deoxy-β-D-lyxofuranosyluracil (**3a** or **3b**) when R is an aryl group (Scheme I). The results of similar hydrolysis studies on 2,2′-imino and 2,2′-(substituted imino)uracil nucleosides (**4**) have also been reported.[2] For this furanosyl-to-pyranosyl isomerization, we have proposed a general reaction mechanism involving fission of the anomeric as well as $C_{1'}$-O bond by the initial attack of a hydroxide ion on the anomeric carbon, followed by molecular reorganization with retention of chirality at the

(1) Minamoto, K.; Tanaka, T.; Azuma, K.; Suzuki, N.; Eguchi, S.; Kadoya, S.; Hirota, T. *J. Org. Chem.* **1986**, *51*, 4417.

(2) Minamoto, K.; Azuma, K.; Tanaka, T.; Iwasaki, H.; Eguchi, S.; Kadoya, S.; Moroi, R. *J. Chem. Soc., Perkin Trans 1* **1988**, 2955.

0022-3263/89/1954-4543$01.50/0

Scheme I



$C_{2'}$, $C_{3'}$, and $C_{4'}$. However, this furanosyl-to-pyranosyl isomerization is generally a rather sluggish, low-yield reaction [20–34% yield after 21–63-h treatment with 6 N NaOH/EtOH (1:1), depending upon the substituent on the nitrogen bridge] unacceptable for further transformations. Because the 2′-hydroxyl in common nucleosides is known to possess higher acidity under the influence of the rather electronegative heterocyclic base, it seemed important to gain an insight into the role of a 2′-hydroxyl anion, which may be formed under the strongly alkaline conditions used. This paper deals with the results of similar hydrolysis reactions with some 2′-deoxy- and 2′-methoxy-2,3′-(substituted imino)uracil nucleosides as well as a thymine analogue.

Substrate Synthesis

2,3′-(Methylimino)-1-(3′-deoxy-2′-*O*-methyl-β-D-lyxofuranosyl)uracil (**6a**) and its *N*-phenyl analogue (**6b**) were prepared from the 5′-*O*-benzoylated precursors of **1b,c** (**5a,b**)[1] by treatment with CH_3I/NaH in DMF followed by debenzoylation with methanolic ammonia (Scheme II).[3] We also wanted 2,3′-(methylimino)-1-(2′-deoxy-β-D-*threo*-pentofuranosyl)uracil (**11a**) and its N-aryl analogues (**11b,c**) as substrates for comparative studies. After several unsuccessful attempts to introduce a leaving group into the $C_{2'}$ of **5** for the purpose of successive reductive elimination or displacement,[4] 2′-deoxyuridine (**7**) was used as starting material for 11.[5] According to the described procedure for a series of thymine analogues,[6] 5′-deoxy-5′-iodo-3′-*O*-mesyl-2′-deoxyuridine (**9**) was obtained in 78% yield from **7** after dimesylation and iodination (NaI/acetone) of noncrystalline crude **8**. Treatment of **9** with silver acetate in methanol gave a 72% yield of the 2,5′-anhydrodeoxyuridine **10**, which was then converted into 2,3′-(methylimino)-1-(2′-deoxy-β-D-*threo*-pentofuranosyl)uracil (**11a**) in over 85% isolated yields by treating with excess 40% CH_3NH_2/DMF. The reaction of **10** with excess aniline required more forcing conditions to give, from a rather complex mixture, a low yield of 2,3′-(phenylimino) analogue (**11b**). Another less polar product was also obtained and tentatively assigned as

Scheme II

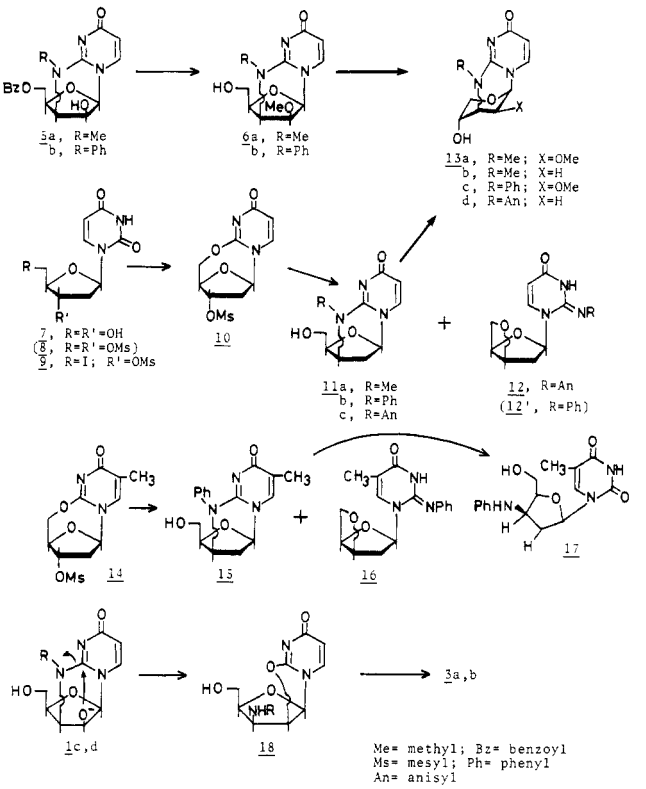


Table I. UV Absorptions of 11a–c, 12, 13a–d, 15–17, and S in Methanol

compd	λ_{max}, nm (ε)
6a	218 (25 200), 228 (20 700),[a] 258 (3 400)[b]
6b	214 (21 200), 234 (19 600), 252.5 (12 400),[a] 264 (8400)[a]
11a	219 (26 900), 227 (22 300), 259 (3 800)[b]
11b	202.5 (32 900), 243 (19 600), 292 (1 800)
11c	202 (24 700), 215.5 (27 600), 230 (21 800)[b]
12	203 (31 400), 240 (20 200), 309 (2 300)
13a	217 (35 500), 263 (4200)[a]
13b	219 (30 700), 259 (4100)[a]
13c	212 (25 800), 229.5 (21 100)
13d	217 (28 000), 233 (23 200)
15	204 (33 400), 245 (20 300), 292 (2 000)
16	210 (28 200), 253 (18 700), 272 (9 800)[b]
17	203 (30 500), 248 (15 600), 265 (8 700),[b] 296 (2100)[a]
S[c]	203 (35 400), 247 (19 000), 267 (10 700)[b] 300 (2300)[a]

[a] Inflection. [b] Shoulder. [c] Summation of the absorptions (ε's) of thymidine and *N*-methylaniline.

1-(3′,5′-*O*-anhydro-2′-deoxy-β-D-*threo*-pentofuranosyl)-N^2-phenylisocytosine (**12′**). Reaction of **10** with *p*-anisidine also gave a similar product distribution; in this case both the desired 2,3′-[(*p*-methoxyphenyl)imino] nucleoside **11c** and less polar major product, 1-(3′,5′-*O*-anhydro-2′-deoxy-β-D-*threo*-pentofuranosyl)-N^2-(*p*-methoxyphenyl)-isocytosine (**12**), were isolated and fully characterized. The structures of the above stated new compounds (**6, 7, 9, 10, 11,** and **12**) are in accord with the UV (Table I) and ^1H NMR data (Table II). The furanosyl nature of the sugar part in **6** and **11** are based upon the ^1H NMR triplet signal for the 5′-hydroxyl. The extremely bathochromic shift of the UV-absorption and the normal 11.37 ppm ^1H NMR signal for the 3-NH shown by **12** characterized the structure of the aglycon and accordingly of the sugar moiety.[7,8]

(3) TLC monitoring showed that the reaction was complete and homogeneous but the 5′-*O*-benzoyl group was partially lost during preparative TLC in repeated experiments. Hence, **6** was isolated after complete deprotection by using methanolic ammonia.

(4) In the repeated reaction of **5** with mesyl chloride, a crystalline 2′-*O*-mesyl derivative was isolated in low yields, which was not acceptable for further transformations.

(5) The authors are indebted to the Nippon Ajinomoto Co., Ltd., for a generous gift of 2′-deoxyuridine.

(6) Doerr, I. L.; Cushley, R. J.; Fox, J. J. *J. Org. Chem.* **1968**, *33*, 1592.

(7) The signal of 3-NH in a wide variety of uridine derivatives resonate usually at 11–12 ppm.

(8) This type of 3′,5′-epoxy nucleosides was already synthesized: Doerr, I. L.; Codington, J. F.; Fox, J. J. *J. Org. Chem.* **1965**, *30*, 467.

The known 2,5′-anhydro-1-(2-deoxy-3-*O*-mesyl-β-D-pentofuranosyl)thymine (**14**)[6] was treated with excess aniline to afford 2,3′-(phenylimino)-1-(2-deoxy-β-D-*threo*-pentofuranosyl)thymine (**15**) and 1-(3′,5′-*O*-anhydro-2′-deoxy-β-D-*threo*-pentofuranosyl)-N^2-phenyl-5-methylisocytosine (**16**) in low yields. The general spectroscopic data for **15** and **16** are in good agreement with the assigned structures.

Alkaline Hydrolysis of 6, 11, and 15. Alkaline hydrolysis experiments were first conducted with **6a** and **11a** under the same conditions as in the case of **1b**,[1] using a one-to-one mixture of 6 N NaOH and EtOH in an argon-filled pressure tube at 75–80 °C until the starting material was consumed. Repeated TLC monitoring confirmed a single, slightly less polar UV-absorbing product in the case of **6a**, while as for **11a** negligible amounts of extremely mobile impurities were observed with a single major product. In each case, similar workup processing gave highly crystalline 2,3′-(methylimino)-1-(3′-deoxy-2′-*O*-methyl-β-D-lyxopyranosyl)uracil (**13a**) and 2,3′-(methylimino)-1-(2′-deoxy-β-D-*threo*-pentopyranosyl)uracil (**13b**) in 45 and 51% yields, respectively. The structures of **13a,b** directly followed from spectral comparison with **2a,b**:[1] the ^{1}H NMR spectroscopic features of major structural significance are the large chemical shift difference between the two 5′-methylene protons of **13a,b** as compared to the corresponding furanosyl precursors (**6a**, **11a**) and the doublet signal shown by the 4′-OH.

Similar alkaline hydrolysis with **6b** and **11c** proceeded much faster (3–4 h) to give 35 and 64% yields of **13c** and **13d**, respectively, as single UV-absorbing products (vide infra).[9] The structures of **13c,d** are clear from the general spectroscopic data, especially from the doublet 4′-OH signals (the $J_{1',2'}$ value, 3.7 Hz, for **13c** is comparable with that for **2c**, 3.2 Hz).[1] Also, it is interesting to note the slightly less polar nature of **13c,d** as compared to each furanosyl precursor. This sort of mobility order on TLC covers all the pairs of furanosyl and pyranosyl isomers hitherto synthesized by us, when appropriate mixtures of chloroforms (or methylene chloride) and methanol are used as developers. The reaction times and yields for **13a–d** are given together in Table III with those for **2b,c**.

It can be seen that the reaction rate of **6a** and **11a** increased, together with a significant increase in the respective product yields, and that the increasing order of the rates roughly parallels that of the yields. This may imply, as already mentioned,[1,10] that shortening of the reaction time reduces the alkali-catalyzed decomposition of the heterocyclic base in the starting material (**6a**, **11a**) and/or the products (**13a,b**) to UV-transparent products. The noted small difference of the reaction time between **6a** and **11a** may reflect a steric effect by the 2′-methoxyl in **6a**. The abnormally lengthy reaction of **1b** suggests that an entirely different factor controlled, at least in part, that situation. An influence may reasonably be attributed to an electronic effect by a 2′-hydroxyl anion, which would screen, to a certain extent, the nearby anomeric carbon against the external hydroxide ions.

In the case of thymine analogue **15**, the hitherto utilized hydrolysis medium, 6 N NaOH/EtOH (1:1), proved to be unfruitful, causing extensive tailing of the TLC spots. After preliminary experimentation, 3 N NaOH in neat EtOH was chosen as a hydrolysis medium for the thymine series. Treatment of **15** in this medium at 90 °C gave, rather surprisingly, a nearly quantitative yield of 1-(3′-anilino-2′-deoxy-β-D-*threo*-pentofuranosyl)thymine (**17**) as a monohydrate but no isomerzation product. The structure of **17** followed from the UV absorptions closely corresponding to those resulting from simple summation of the absorptions of spongouridine and *N*-methylaniline (Table I)[11] and the 500-MHz ^{1}H NMR spectrum (Table II), in which a normal N^2H signal appeared at 11.25 ppm. Although the labile proton signals for the 5′-OH and PhNH appeared as two broad singlets (5.41 and 5.59 ppm), the chemical shift difference between the two 5′-methylene protons ($\Delta\delta$ 0.12) is small enough to substantiate the furanosyl structure of **17**.[1]

For comparison, **6b** was subjected to the same hydrolysis with 3 N ethanolic sodium hydroxide (3 N NaOH/EtOH) on a similar scale. The reaction proceeded extremely faster than in the hitherto utilized hydrolysis medium containing water to give a better yield (55%) of **13c** as a single major product. This finding spurred us to apply the same hydrolysis conditions also to **1c** to give **2c** and **3a** in 51 and 28% yields, respectively, in a far shorter reaction time: the yield of the intermolecular reaction product **2c** was raised to 51 from 34%,[1] while the yield of **3a** (28%) was similar to that previously reported (31%,[1] see Table III). On the basis of this observation, **1c** was treated with a more dilute ethanolic solution of NaOH (1 N NaOH/EtOH) to give **3a** almost exclusively (80%), suggesting an intramolecular mechanism for the formation of **3a**.

Thus, this piece of work has corroborated the evidence that some of the basic nucleophiles such as hydroxide or methoxide ion[12] can directly attack the anomeric carbon in pyrimidine nucleosides. We have also disclosed that the conversion of **6b** or **11c** to **13c** or **13d** is not accompanied by any C_2–N fission to give an "up" arylamino nucleoside like **3a,b**, and hence the reported formation of **3a,b**[1] must have occurred through a 2,2′-anhydro nucleoside (**18**) formed by entropically favorable, intramolecular attack of 2′-hydroxyl anion on the C_2 in **1c,d**. In contrast, the thymine analogue **15** underwent the C_2–N fission exclusively by direct attack of an external hydroxide ion. This subtle difference of reactivity between the uracil and thymine analogues may have stemmed from inductive effect by the 5-methyl, which would make the anomeric carbon less electrophilic, thus precluding the nucleophilic $C_{1'}$ attack of a hydroxide ion.

Experimental Section[13]

2,3′-(Methylimino)-1-(3′-deoxy-2′-*O*-methyl-β-D-lyxofuranosyl)uracil (6a). To a stirred solution of **5a** (686 mg, 2 mmol) in DMF (26 mL) was added at −10 °C 60% oil-immersed NaH (2.4 mmol). After 10 min, methyl iodide (0.149 mL, 2.4 mmol) was added, and the total allowed to warm to room temperature. After stirring overnight, the mixture was evaporated, and the residue fractionated on a silica plate (20 × 20 cm; $CHCl_3$/MeOH, 9:1, developed several times). The pasty product recovered from the major band was treated with a mixture, concentrated NH_4OH/MeOH (1:3 v/v, 28 mL), at room temperature overnight. After evaporation, the residue was stirred in Et_2O/acetone (4:1, 25 mL) for 1 h, and the sparingly soluble solid collected. Recrystallization from MeOH gave 375 mg (74.1%) of **6a**, mp 235–236 °C.

Anal. Calcd for $C_{11}H_{15}O_4N_3$: C, 52.17; H, 5.97; N, 16.59. Found: C, 52.36; H, 5.91; N, 16.46.

2,3′-(Phenylimino)-1-(3′-deoxy-2′-*O*-methyl-β-D-lyxofuranosyl)uracil (6b). Similarly with the above, **5b** (438 mg,

(9) Experimentation with **11b** was abandoned owing to material shortage.

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

(11) This method was used for characterization of **3a** also.[1]

(12) **1a** proved to react with 1.5 N CH_3ONa/MeOH at 100 °C to give a 33% yield of **2a** after 40 h of reaction. A similar observation was made when **1a** was treated with 1.5 N aqueous CH_3SNa/pyridine under similar conditions (orally published).

(13) The general methods used are similar to those described earlier.[1]

Table II. ^{1}H NMR Resonances of 6a,b, 9, 10, 11a–c, 12, 13a–d, 15, 16, and 17 in Me_2SO-d_6[a,b]

compd	5′-H	4′-H	3′-H	2′-H	1′-H	5-H	6-H	others
6a	3.49 (2 H, m, J_{gem} = 6.4)	4.25 (2 H, m, overlapped $H_{3'}$)		4.35 (t, $J_{2',1'}$ = 4.0, $J_{2',3'}$ = 2.4)	5.58 (d, $J_{1',2'}$ = 4.0)	5.50 (d, $J_{5,6}$ = 8.0)	7.45 (d, $J_{6,5}$ = 8.0)	3.07 (3 H, s, Me), 3.39 (3 H, s, OMe), 5.07 (t, $J_{5'\text{-OH},5'}$ = 4.8, 5′-OH)
6b	3.62–3.71 (2 H, m)	4.26 (dt, $J_{4',3'}$ = 3.18, $J_{4',5'}$ = 6.36 and 7.16)	4.45 (dd, $J_{3',2'}$ = 3.97, $J_{3',4'}$ = 3.18)	4.41 (t-like dd, $J_{2',1'}$ = 3.18, $J_{2',3'}$ = 3.97)	5.71 (d, $J_{1',2'}$ = 3.18)	5.57 (d, $J_{5,6}$ = 7.15)	7.55 (d, $J_{6,5}$ = 7.15)	3.45 (3 H, s, OMe), 5.05 (1 H, t, $J_{5'\text{-OH},5'}$ = 5.0, 5′-OH), 7.27–7.32 (3 H, m, Ar H), 7.40–7.43 (2 H, t, Ar H)
9	3.47 (dd, J_{gem} = 10.4, $J_{5'a,4'}$ = 7.2, $H_{5'a}$), 3.60 (dd, J_{gem} = 10.4, $J_{5'b,4'}$ = 6.0, $H_{5'b}$)	4.24 (m, $J_{4',3'}$ = 2.4, $J_{4',5'a}$ = 6.0, $J_{4',5'b}$ = 7.2)	5.20 (m)	2.46–2.78 (2 H, m)	6.24 (t, $J_{1',2'}$ = 7.0)	5.76 (d, $J_{5,6}$ = 8.0)	7.77 (d, $J_{6,5}$ = 8.0)	3.35 (3 H, s, Ms), 11.48 (br s, 3-NH)
10	4.21 (dd, J_{gem} = 12.0, $J_{5'a,4'}$ = 1.6, $H_{5'a}$), 4.68 (dd, J_{gem} = 12.0, $J_{5'b,4'}$ = 1.6, $H_{5'b}$)	4.83 (d, $J_{4',5'a,b}$ = 1.6)	5.58 (dd, $J_{3',2'b}$ = 7.2, $J_{3',4'}$ = 2.0)	2.66 (dd, J_{gem} = 16.0, $J_{2'a,1'}$ = 8.0, $H_{2'a}$) 2.85 (ddd, J_{gem} = 16.0, $J_{2'b,1'}$ = 2.0, $J_{2'b,3'}$ = 7.2, $H_{2'b}$)	6.21 (dd, $J_{1',2'a}$ = 8.0, $J_{1',2'b}$ = 2.0)	5.96 (d, $J_{5,6}$ = 8.0)	7.92 (d, $J_{6,5}$ = 8.0)	3.33 (3 H, s, Ms)
11a	3.42 (dd, J_{gem} = 10.0, $J_{5'a,4'}$ = 8.0, $H_{5'a}$), 3.61 (dd, J_{gem} = 10.0, $J_{5'b,4'}$ = 6.0, $H_{5'b}$)	4.15 (2 H, m, overlapped $H_{3'}$)		2.33 (2 H, br s)	5.70 (br s)	5.46 (d, $J_{5,6}$ = 8.0)	7.46 (d, $J_{6,5}$ = 8.0)	3.06 (3 H, s, Me), 5.04 (t, $J_{5'\text{-OH},5'}$) = 5.0, 5′-OH)
11b	3.20 (m, J_{gem} = 14.0, $J_{5'a,4'}$ = 7.2, $H_{5'a}$), 3.33 (m, J_{gem} = 14.0, $J_{5'b,4'}$ = 6.0, $H_{5'b}$)	4.42 (t, $J_{4',5'a}$ = 7.2, $J_{4',5'b}$ = 6.0)	5.40 (s)	2.54 (m, J_{gem} = 13.2, $J_{2'a,1'}$ = 3.2, $H_{2'a}$) 2.67 (d, J_{gem} = 13.2, $H_{2'b}$)	5.97 (d, $J_{1',2'a}$ = 3.2)	5.84 (d, $J_{5,6}$ = 8.0)	7.74 (d, $J_{6,5}$ = 8.0)	5.84 (overlaid on H_5, 5′-OH), 6.60 (3 H, m, Ar H), 7.12 (2 H, m, Ar H)
11c	3.64 (m, J_{gem} = 10.0, $J_{5'a,4'}$ = 7.2, $H_{5'a}$), 3.73 (m, J_{gem} = 10.0, $J_{5'b,4'}$ = 7.2, $H_{5'b}$)	4.15 (m, $J_{4',5'}$ = 7.2)	4.38 (br s)	2.41 (dt, J_{gem} = 12.0, $J_{2'a,1'}$ = 4.0, $J_{2'a,3'}$ = 2.4, $H_{2'a}$) 2.65 (d, J_{gem} = 12.0, $H_{2'b}$)	5.84 (d, $J_{1',2'a}$ = 4.0)	5.55 (d, $J_{5,6}$ = 8.0)	7.59 (d, $J_{6,5}$ = 8.0)	3.80 (3 H, s, OMe), 5.01 (t, $J_{5'\text{-OH},5'}$ = 4.0, 5′-OH), 6.69 (2 H, d, J = 8.0, Ar H), 7.34 (2 H, d, J = 8.0, Ar H)
12	3.69 (2 H, br s)	4.84 (br s)	4.58 (t, $J_{3',2'b}$ = 6.0, $J_{3',4'}$ = 6.0)	2.39 (dd, J_{gem} = 16.0, $J_{2'a,1'}$ = 2.0, $H_{2'a}$) 2.64 (m, J_{gem} = 16.0, $J_{2'b,1'}$ = 8.0, $J_{2'b,3'}$ = 6.0, $H_{2'b}$)	6.53 (m, overlapped Ar H)	5.66 (d, $J_{5,6}$ = 8.0)	8.14 (d, $J_{6,5}$ = 8.0)	3.69 (3 H, br s, overlaid on $H_{5'}$, OMe), 6.53 (2 H, d, J= 8.8, overlaid on $H_{1'}$, Ar H), 6.86 (2 H, d, J = 8.8, Ar H), 11.37 (br s, 3-NH)
13a	3.29 (d, J_{gem} = 13.2, $H_{5'a}$), 3.61 (d, J_{gem} = 13.2, $H_{5'a}$), 3.61 (d, J_{gem} = 13.2, $H_{5'b}$)	4.86 (br s)	4.01 (2 H, m, overlapped $H_{2'}$)		5.59 (br s)	5.65 (d, $J_{5,6}$ = 8.0)	7.51 (d, $J_{6,5}$ = 8.0)	3.10 (3 H, s, Me), 3.32 (3 H, s, OMe), 5.67 (d, $J_{4'\text{-OH},4'}$ = 2.4, 4′-OH)
13b	3.39 (dd, J_{gem} = 12.0, $J_{5'a,4'}$ = 2.0, $H_{5'a}$), 3.65 (d, J_{gem} = 12.0, $H_{5'b}$)	3.74 (br s)	3.65 (overlaid on $H_{5'b}$)	1.78 (dd, J_{gem} = 12.0, $J_{2'a,3'}$ = 4.0, $H_{2'a}$), 2.50 (ddd, J_{gem} = 12.0, $J_{2'b,1'}$ = 2.0, $J_{2'b,3'}$ = 2.4, $H_{2'b}$)	5.50 (br s)	5.61 (d, $J_{5,6}$ = 8.0)	7.48 (d, $J_{6,5}$ = 8.0)	3.11 (3 H, s, Me), 5.50 (overlaid on $H_{1'}$, 4′-OH)
13c	3.67 (2 H, t, J_{gem} = 13.7)	4.01 (m)	3.95 (br s)	4.11 (m)	5.59 (d, $J_{1',2'}$ = 3.7)	5.68 (d, $J_{5,6}$ = 7.6)	7.58 (d, $J_{6,5}$ = 7.6)	3.45 (3 H, s, OMe), 5.70 (d, $J_{4'\text{-OH},4'}$ = 2.4, 4′-OH), 7.26 (2 H, d, J = 7.0, Ar H), 7.37 (t, Ar H), 7.47 (2 H, t, J = 7, Ar H)
13d	3.68 (d, J_{gem} = 13.51, $H_{5'a}$) 3.74 (dd, J_{gem} = 13.51, $J_{5'b,4'}$ = 1.59, $H_{5'b}$)	3.65 (m)	3.78 (m)	2.08 (br d, J_{gem} = 13.49, $H_{2'a}$), 2.59 (ddd, J_{gem} = 13.49, $J_{2'b,1'}$ = 2.29, $J_{2'b,3'}$ = 3.17, $H_{2'b}$)	5.57 (br s)	5.62 (d, $J_{5,6}$ = 7.15)	7.53 (d, $J_{6,5}$ = 7.15)	3.78 (3 H, s, OMe), 5.41 (d, $J_{4'\text{-OH},4'}$ = 3.98, 4′-OH), 6.98 (2 H, d, Ar H), 7.27 (2 H, d, Ar H)
15[c]	3.31 (dd, J_{gem} = 13.5, $J_{5'a,4'}$ = 7.2, $H_{5'a}$) 3.16 (dd, J_{gem} = 13.5, $J_{5'b,4'}$ = 6.4)	4.41 (ddd, $J_{4',5'a}$ = 7.2, $J_{4',5'b}$ = 6.4, $J_{4',3'}$ = 2.4)	5.35 (br s)	2.52 (dt?, J_{gem} = 12.7, $J_{2'a,1'}$ = $J_{2'a,3'}$ = 4.0), 2.61 (d, J_{gem} = 12.7, $J_{2'b,1'}$ = $J_{2'b,3'}$ = 0)	5.85 (d, $J_{1',2'a}$ = 4.0)		7.57 (s)	1.80 (3 H, s, Me), 5.78 (t, $J_{5'\text{-OH},5'}$ = 6.4, 5′-OH), 6.53–6.60 (3 H, m, Ar H), 7.05–7.08 (2 H, t, Ar H)

16	3.69 (d, J_{gem} = 8.7, H_{5a}), 3.77 (dd, J_{gem} = 8.7, $J_{5'b,4'}$ = 4.8, H_{5b})	4.84 (t, $J_{4',5'b}$ = $J_{4',3'}$ = 4.8)	4.71 (dd, $J_{3',4'}$ = 4.8, $J_{3',2'b}$ = 6.0)	2.41 (dd, J_{gem} = 15.1, $J_{2'a,1'}$ = 2.4, $H_{2'a}$), 2.60 (ddd, J_{gem} = 15.1, $J_{2'b,1'}$ = 8.0, $J_{2'b,3'}$ = 6.0, $H_{2'b}$)	6.51 (dd, $J_{1',2'a}$ = 2.4, $J_{1',2'b}$ = 8.0)	7.80 (s)	1.57 (3 H, s, Me), 11.31 (1 H, s, 3-NH), 6.55 (2 H, d, Ar H), 6.76 (1 H, t, Ar H), 7.23 (2 H, t, Ar H)
17	3.31 (dd, J_{gem} = 13.51, $J_{5'a,4'}$ = 7.15, $H_{5'a}$), 3.43 (dd, J_{gem} = 13.51, $J_{5'b,4'}$ = 4.77, $H_{5'b}$)	3.95 (m)	4.28 (dd, $J_{3',2'b}$ = 4.77, $J_{3',4'}$ = 3.18)	1.88 (dd, J_{gem} = 14.31, $J_{2'a,1'}$ = 2.38, $H_{2'a}$), 2.60 (ddd, J_{gem} = 14.31, $J_{2'b,1'}$ = 8.74, $J_{2'b,3'}$ = 4.77, $H_{2'b}$)	6.09 (dd, $J_{1',2'a}$ = 2.38, $J_{1',2'b}$ = 8.74)	7.83 (s)	1.77 (3 H, s, 5-Me), 5.41 (1 H, br s, 5′-OH or PhNH), 5.59 (1 H, br s, PhNH or 5′-OH), 11.25 (1 H, s, N^3H), 6.51–7.09 (5 H, m, Ph)

[a] s = singlet, d = doublet, dd = doublet of doublets, ddd = doublet of doublets of doublets, dt = doublet of triplets, t = triplet, 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 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. The spectra of **6b**, **13d**, and **17** were measured at 500 MHz and the others at 200 MHz. [c] The 2.52 ppm signal partially merged into the signal of dimethyl sulfoxide.

1.08 mmol) in DMF (8.8 mL) was treated with 60% oil-immersed NaH (52 mg, 1.30 mmol) and then with MeI (0.082 mL, 1.30 mmol). The residue after evaporation of the solvent was dissolved in a small volume of MeOH and subjected to preparative TLC (silica, 20 × 20 cm; $CHCl_3$/MeOH, 8:2). The product obtained from the major band was treated with concentrated NH_4OH/MeOH (1:3, 10 mL) at room temperature overnight. After evaporation, the residue was digested with a small volume of MeOH to give a crystalline precipitate, which was collected and recrystallized from MeOH to afford 205 mg (60.2%) of **6b**, mp 286 °C (dec).

Anal. Calcd for $C_{16}H_{17}O_4N_3$: C, 60.94; H, 5.43; N, 13.33. Found: C, 60.78; H, 5.33; N, 13.45.

2,5′-Dideoxy-5′-iodo-3′-*O*-(methylsulfonyl)uridine (9). To a stirred ice-cold solution of **7** (1.5 g, 6.57 mmol) in pyridine (7.23 mL) was added dropwise mesyl chloride (1.27 mL, 16.4 mmol), and the mixture kept at 0 °C for 4 h. The mixture was then treated with MeOH (3 mL) at room temperature for 30 min, evaporated to ca. one-half volume, and dropped into stirred ice water (27 mL). The gummy precipitate was rapidly collected by suction, and the filtrate extracted with EtOAc (7 × 50 mL). The EtOAc extract was combined with the filter cake and repeatedly coevaporated with a mixture of MeOH and acetone to give a foam (**8**), which resisted crystallization.

A mixture of the total of crude **8**, NaI (1.68 g, 11.2 mmol), and acetone (30 mL) was stirred in a pressure tube at 80–85 °C for 10 h, and the filtrate evaporated. The residue was partitioned between EtOAc (80 mL) and water (10 mL). The EtOAc layer was dried, treated with Norit and concentrated in vacuo to give 1.99 g of TLC-pure crystals, which were collected by suction. A further crop obtained by preparative TLC (silica, 20 × 20 cm; $CHCl_3$/MeOH, 9:1) with the filtrate was combined with the above product and recrystallized from MeOH to give 2.143 g (78.3%) of **9**, mp 148–149 °C.

Anal. Calcd for $C_{10}H_{13}O_6N_2SI$: C, 28.86; H, 3.15; N, 6.73. Found: C, 28.88; H, 3.07; N, 6.79.

2,5′-Anhydro-2′-deoxy-3′-*O*-(methylsulfonyl)uridine (10). A mixture of **9** (1.993 g, 4.79 mmol) and AgOAc (800 mg, 4.79 mmol) in MeOH (206 mL) was heated to reflux for 7 h in the dark (the vessel was wrapped with aluminum foil) and filtered through a Celite pad while hot. Upon being cooled to room temperature, the filtrate gave crude crystals, which were collected by suction and immediately dried in vacuo. The filtrate was evaporated and repeatedly coevaporated with MeOH to remove the acetic acid released from the AgOAc. The residue was taken into a minimum amount of MeOH and neutralized with Et_3N to give further crystals.

The above Celite filter cake was extracted with hot DMF (5 × 30 mL) to afford another substantial crop of product. Repeated recrystallization of the combined products from a large volume of MeOH using Norit and Celite pads gave 983 mg (71.2%) of **10**, mp 159–160 °C.

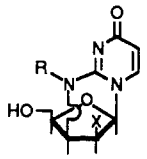
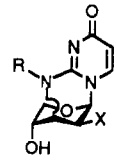
Anal. Calcd for $C_{10}H_{12}O_6N_2S$: C, 41.66; H, 4.20; N, 9.72. Found: C, 41.97; H, 4.20; N, 9.68.

2,3′-(Methylimino)-1-(2′-deoxy-β-D-*threo*-pentofuranosyl)uracil (11a). A mixture of **10** (682 mg, 2.37 mmol), 40% aqueous CH_3NH_2 (1.9 mL, 22.1 mmol), and DMF (11.5 mL) in an argon-filled pressure tube was stirred at room temperature for 4 h and then at 50 °C for 5 h. A single, more polar product was detected by TLC. After thorough evaporation, the residue was digested with a small volume of EtOH to give crystals, which were collected by suction and recrystallized from MeOH to afford 450 mg (85.2%) of **11a**, mp 280–282 °C.

Anal. Calcd for $C_{10}H_{13}O_3N_3$: C, 53.80; H, 5.87; N, 18.82. Found: C, 53.77; H, 5.98; N, 18.75.

2,3′-(Phenylimino)-1-(2′-deoxy-β-D-*threo*-pentofuranosyl)uracil (11b). A mixture of **10** (200 mg, 0.69 mmol), aniline (0.63 mL, 6.93 mmol), and DMF (2 mL) in an argon-filled pressure tube was stirred at 75–80 °C for 35 h, at 95 °C for 18 h, and then at 110 °C for 6 h. The resulting complex mixture containing two major products more polar and two other major ones less polar than **10** was evaporated in vacuo, the residue repeatedly was digested with ether, and the ether layers were decanted off, until the residue became a semisolid. This residue was then fractionated on a silica plate (20 × 20 cm; CH_2Cl_2/MeOH, 9:1), and the impure major fraction was eluted with

Table III. Reaction Times and Yields in the Furanosyl to Pyranosyl Isomerization[a]

substrate	R	X	product	time, h	yield, %
 **1b**[b]	Me	OH	 **2b**	48	30
6a	Me	OMe	**13a**	16	45
11a	Me	H	**13b**	12.5	51
6b	Ph	OMe	**13c**	5.5	53
11c	An	H	**13d**	3	64.2
1c[b]	Ph	OH	**2c**	21	34[c]

[a] The hydrolysis reactions were conducted at 75–80 °C under argon atmosphere until the starting material disappeared in terms of TLC. [b] Cited from ref 1. [c] The C_2–N fission product (**3a**): 31% yield.

MeOH. The combined eluants were concentrated in vacuo to give TLC-homogeneous crystals, which were collected and recrystallized from MeOH to afford 14 mg (7.1%) of **11b**, mp 193–196 °C.

Anal. Calcd for $C_{15}H_{15}O_3N_3$: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.03; H, 5.58; N, 14.57.

The ether extract was discarded.

2,3′-[(*p*-Methoxyphenyl)imino]-1-(2′-deoxy-β-D-*threo*-pentofuranosyl)uracil (11c) and 1-(3′,5′-*O*-Anhydro-2′-deoxy-β-D-*threo*-pentofuranosyl)-N^2-(*p*-methoxyphenyl)-isocytosine (12). A mixture of **10** (300 mg, 1.04 mmol), *p*-anisidine (1.28 g, 10.4 mmol), and DMF (5 mL) in an argon-filled pressure tube was stirred at 115–120 °C for 38 h. TLC monitoring at this stage using a silica plate and $CHCl_3$/MeOH (85:15) showed consumption of the starting material and formation of two more polar and two less polar products. After evaporation, the residue was repeatedly digested with ether, and the ether layers were decanted off, until the mixture became a semisolid. This residue containing mainly the two less polar products was fractionated on two sheets of silica plates (20 × 20 cm; CH_2Cl_2/MeOH, 9:1, twice developed) to give, from the major band, 40 mg (12.2%) of **11c**, mp 238–240 °C, after recrystallization from MeOH.

Anal. Calcd for $C_{16}H_{17}O_4N_3$: C, 60.94; H, 5.43; N, 13.33. Found: C, 60.66; H, 5.59; N, 13.45.

The above ether extract was fractionated on two sheets of silica plates (20 × 20 cm; $CHCl_3$/EtOAc, 5:1, developed three times) to give, from the minor UV-absorbing band, 65 mg (20.2%) of **12** as leaflets, mp 181–183 °C (MeOH).

Anal. Calcd for $C_{16}H_{17}O_4N_3$: C, 60.94; H, 5.43; N, 13.33. Found: C, 60.92; H, 5.51; N, 13.26.

2,3′-(Methylimino)-1-(3′-deoxy-2′-*O*-methyl-β-D-lyxo-pyranosyl)uracil (13a). A mixture of **6a** (127 mg, 0.50 mmol), EtOH (1.9 mL), and 6 N NaOH (1.9 mL) in an argon-filled pressure tube was stirred at 75–80 °C for 16 h. TLC monitoring indicated a single, slightly less polar product and no **6a**. After cooling, the mixture was neutralized with AcOH and evaporated. The residue in MeOH/acetone (2:9, 11 mL) was heated to reflux for 15 min and filtered while hot. The filter cake was again extracted with hot acetone (2 × 10 mL). The combined extracts were fractionated on a silica plate (20 × 20 cm; $CHCl_3$/MeOH, 85:15, developed three times) to give, after recrystallization from MeOH, 57 mg (45%) of **13a**, which gradually softened above 290 °C and melted at 298 °C.

Anal. Calcd for $C_{11}H_{15}O_4N_3$: C, 52.17; H, 5.97; N, 16.59. Found: C, 52.10; H, 5.85; N, 16.49.

2,3′-(Methylimino)-1-(2′-deoxy-β-D-*threo*-pentopyranosyl)uracil (13b). A mixture of **11a** (223 mg, 1 mmol), EtOH (4.8 mL), and 6 N NaOH (4.8 mL) in an argon-filled pressure tube was stirred at 75–80 °C for 12.5 h. After cooling, the mixture was carefully neutralized by adding concentrated HCl (2 mL) and then 1 N HCl. The mixture was thoroughly evaporated, the residue heated to reflux in MeOH (20 mL), and the UV-transparent inorganic salt filtered off. The filtrate was evaporated, and the residue again extracted with hot EtOH (4 mL) to remove a further small amount of salt. The EtOH extract was then fractionated on a silica plate (20 × 20 cm; twice developed in $CHCl_3$/MeOH, 85:15, then three times in $CHCl_3$/MeOH, 8:2). The main fraction was eluted and recrystallized with MeOH to afford 114 mg (51.1%) of **13b**, mp above 300 °C.

Anal. Calcd for $C_{10}H_{13}O_3N_3$: C, 53.80; H, 5.87; N, 18.82. Found: C, 53.66; H, 5.79; N, 18.71.

2,3′-(Phenylimino)-1-(3′-deoxy-2′-*O*-methyl-β-D-lyxo-pyranosyl)uracil (13c). A mixture of **6b** (315.3 mg, 1 mmol), EtOH (4.8 mL), and 6 N NaOH (4.8 mL) in an argon-filled pressure tube was stirred at 75–80 °C for 5.5 h, during which time the starting material was consumed and a single less polar product formed as judged by TLC. The mixture was neutralized with AcOH and thoroughly evaporated, and the residue stirred in acetone (50 mL) for 15 min. The solid was collected by suction, again stirred in acetone (30 mL), and filtered (the filter cake was now UV-transparent). The combined acetone solutions were evaporated and the residue fractionated on a silica plate (20 × 20 cm; $CHCl_3$/MeOH, 9:1, developed three times) to give from the UV-absorbing band 167 mg (53%) of **13c**, mp 288–290 °C (dec), after recrystallization from a small volume of MeOH.

Anal. Calcd for $C_{16}H_{17}O_4N_3$: C, 60.94; H, 5.43; N, 13.33. Found: C, 60.71; H, 5.45; N, 13.12.

2,3′-[(*p*-Methoxyphenyl)imino]-1-(2′-deoxy-β-D-*threo*-pentopyranosyl)uracil (13d). A mixture of **11c** (120 mg, 0.38 mmol), EtOH (1.4 mL), and 6 N NaOH (1.4 mL) in an argon-filled pressure tube was stirred at 75–80 °C for 3 h, during which time **11c** disappeared and a single, UV-absorbing less polar product appeared. The mixture was neutralized with AcOH and evaporated, and the residue extracted with acetone (25 mL) at room temperature. The filter cake was again extracted with acetone (20 mL). The combined acetone solutions were evaporated, and the residue fractionated on a silica plate (20 × 20 cm; CH_2Cl_2/MeOH, 9:1, developed three times) to give 77 mg (64.2%) of **13d**, mp 256–258 °C (MeOH).

Anal. Calcd for $C_{16}H_{17}O_4N_3$: C, 60.94; H, 5.43; N, 13.33. Found: C, 60.71; H, 5.71; N, 13.20.

2,3′-(Phenylimino)-1-(2′-deoxy-β-D-*threo*-pentofuranosyl)thymine (15) and 1-(3′,5′-*O*-Anhydro-2′-deoxy-β-D-*threo*-pentofuranosyl)-N^2-phenyl-5-methylisocytosine (16). A mixture of **14** (200 mg, 0.66 mmol), aniline (0.6 mL, 6.6 mmol), and DMF (2.5 mL) in an argon-filled pressure tube was stirred at 85–90 °C for 65 h and thoroughly evaporated. The residue was repeatedly treated with ether as in the synthesis of **11c** and **12**. The ether-insoluble semisolid residue was fractionated on a silica plate (20 × 20 cm; CH_2Cl_2/MeOH, 9:1, developed four times) to afford, from the main band, 40 mg (20.2%) of **15**, mp 208–210 °C (MeOH).

Anal. Calcd for $C_{16}H_{17}O_3N_3$: C, 64.20; H, 5.72; N, 14.04. Found: C, 63.96; H, 5.93; N, 14.04.

The ether-soluble part was also fractionated on a silica plate (20 × 20 cm; $CHCl_3$/EtOAc, 5:1, developed three times) to give 36 mg (18%) of **16**, mp 214–216 °C (MeOH), from a major fraction more polar than aniline.

Anal. Calcd for $C_{16}H_{17}O_3N_3$: C, 64.20; H, 5.72; N, 14.04. Found: C, 64.44; H, 6.00; N, 13.79.

1-(3′-Anilino-2′-deoxy-β-D-*threo*-pentofuranosyl)thymine (17). A mixture of **15** (200 mg, 0.67 mmol), EtOH (4.5 mL), and NaOH (553 mg, 13.8 mmol) (3 N NaOH in EtOH) in an argon-filled pressure tube was stirred at 90 °C. The mixture became a solution within 15 min. Repeated TLC monitoring showed that the starting material disappeared during 24 h and at this point a major, less polar product formed together with a trace of a far less polar product. After neutralization with AcOH, the mixture was evaporated, the residue triturated with EtOH (20 mL), and the precipitate of AcONa filtered off. The filtrate was again evaporated, and the residue swirled with acetone (40 mL). The UV-transparent solid was filtered off, and the acetone extract fractionated on a silica plate (20 × 20 cm; CH_2Cl_2/MeOH, 9:1, twice developed). The major fraction was eluted with MeOH to give 202 mg (95%) of **17** after recrystallization from a small volume of MeOH, mp 187–190 °C.

Anal. Calcd for $C_{16}H_{17}O_3N_3 \cdot H_2O$: C, 60.55; H, 6.04; N, 13.24. Found: C, 60.52; H, 6.27; N, 13.33.

Hydrolysis of 6b with 3 N NaOH/EtOH. A mixture of **6b** (200 mg, 0.63 mmol), EtOH (4.3 mL), and NaOH (523 mg, 13.1 mmol) (3 N NaOH in EtOH) in an argon-filled pressure tube was stirred at 90 °C. The mixture became a solution in 25 min. Repeated TLC monitoring showed that **6b** disappeared during 110 min, and a single major product formed together with negligible amounts of two far less polar products. After neutralization with AcOH, the mixture was evaporated and repeatedly coevaporated with MeOH. The residue was stirred in acetone (25 mL) for 20 min, and the solid filtered by suction. After washing the filter cake with acetone (12 mL; the filter cake was UV-transparent at this stage), the combined filtrates were evaporated, and the residue subjected to preparative TLC (silica, 20 × 20 cm; $CHCl_3$/MeOH, 9:1, twice developed). The major fraction was eluted with MeOH and recrystallized from a small volume of MeOH to afford 110 mg (55%) of **13c**, identical with the above-obtained product.

Hydrolysis of 2,3′-(Phenylimino)-1-(3′-deoxy-β-D-lyxofuranosyl)uracil (1c) with 3 N NaOH/EtOH. A mixture of NaOH (553 mg, 13.8 mmol) and EtOH (4.5 mL) in an argon-filled pressure tube was stirred at 90 °C for 25 min to give a solution (ca. 3 N NaOH in EtOH). After cooling to room temperature, **1c** (202 mg, 0.67 mmol) was added, and the tube refilled with argon. TLC monitoring of the reaction at 90 °C showed that **1c** disappeared during 70 min and two products formed. The cooled mixture was diluted with MeOH (10 mL), neutralized with AcOH, and then evaporated. After repeated coevaporation with MeOH, the residue was stirred in acetone/MeOH (9:1, 45 mL) for 15 min, and the sparingly soluble solid (UV-transparent) filtered off. The filtrate was evaporated, and the residue heated to reflux in acetone (50 mL) for 10 min to give further UV-transparent solid, which was filtered off. The acetone solution was evaporated, and the residue in hot MeOH was allowed to cool to room temperature to give TLC-pure crystals of **2c**, which were collected by suction (56 mg). Fractionation of the filtrate on a silica plate (20 × 20 cm; $CHCl_3$/MeOH, 85:15, developed three times) gave from the slower moving band an additional crop of **2c**. The combined crops were recrystallized from MeOH to afford 113 mg (50.8%) of the methanolate of **2c**, identical with an authentic sample[1] in terms of IR spectroscopy and mixed melting point determination.

Elution of the less polar fraction with MeOH gave a solid, which was recrystallized from a small volume of MeOH to give 60 mg (28.1%) of **3a**, mp 224–226 °C.

Anal. Calcd for $C_{15}H_{17}N_3O_5$: C, 56.42; H, 5.37; N, 13.16. Found: C, 56.19; H, 5.58; N, 13.17.

The identity of **3a** with an authentic sample[1] was confirmed by IR spectroscopy and mixed melting point determination.

Hydrolysis of 1c with 1 N NaOH/EtOH. A mixture of NaOH (177 mg, 4.4 mmol) and EtOH (4.4 mL) in an argon-filled pressure tube was stirred at 90 °C for 10 min to obtain a ca. 1 N ethanolic solution of NaOH. After the solution cooled, **1c** (91 mg, 0.302 mmol) was added, and argon gas refilled. Under careful TLC control, the mixture was stirred at 90 °C for 3.5 h (at this point, a single major TLC spot for **3a** and two negligibly thin spots corresponding to **1c** and **2c** were observed). After cooling, the mixture was diluted with MeOH, neutralized with AcOH, and thoroughly evaporated. The residue in acetone (20 mL) was stirred at room temperature for 30 min, and the insoluble solid filtered by suction. The filter cake was washed with acetone (10 mL), and the combined acetone solutions evaporated after treatment with Norit. On leaving the residue with a small volume of MeOH, TLC-pure crystals of **3a** (60 mg) were obtained. Preparative TLC (silica, 10 × 20 cm; $CHCl_3$/MeOH, 85:15, developed three times) with the filtrate separated from the major crop gave another crop. The combined crops were recrystallized from a small volume of MeOH to afford 77 mg (79.5%) of **3a**, identical with the above-obtained product.

Secondary β-Aminobenzamide and Heteroatom Directed Lithiation in the Synthesis of 5,6-Dimethoxyanthranilamides and Related Compounds†

Stefan Bengtsson and Thomas Högberg*

Department of Medicinal Chemistry, CNS 2 Research and Development, Astra Research Centre AB, S-151 85 Södertälje, Sweden

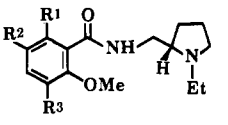
Received March 13, 1989

Directed ortho-lithiation strategies have been applied in the synthesis of the dopamine D-2 antagonist (*S*)-6-amino-5-bromo-2,3-dimethoxy-*N*-((1-ethyl-2-pyrrolidinyl)methyl)benzamide (NCQ 318). The secondary β-amino side chain was found to be a powerful ortho directing group which enabled the direct introduction of the amino group after dilithiation with *n*-BuLi. Alternatively, 3,4-dimethoxy-*N*-(*tert*-butoxycarbonyl)aniline was regioselectively metalated with 2 equiv of *n*-BuLi and reacted with carbon dioxide. The methods permit efficient syntheses of the therapeutically important substituted 2-methoxybenzamides also in technical scale. The lithiated secondary β-amino benzamides, e.g. $ArCONHCH_2CH_2NMe_2$, were found to react with various electrophiles with high regioselectivity in contrast to the corresponding ArCONHMe derivative.

The substituted 2-methoxybenzamides (orthopramides) constitute a recently developed class of antipsychotics, which selectively block dopamine D-2 receptors.[1,2] Especially, benzamides with 2-pyrrolidinylmethyl side chains, e.g. sulpiride, remoxipride, and raclopride, display promising features (Chart I).[3] As an extension of our investigations on 6-methoxysalicylamides[4] we required an efficient synthesis of a related anthranilamide NCQ 318 (1).[5]

The directed metalation strategy offers efficient routes for regiospecific synthesis of polysubstituted aromatics.[6,7]

Chart I



	R1	R2	R3
(S)-sulpiride	H	SO_2NH_2	H
remoxipride	OMe	Br	H
raclopride	OH	Cl	Cl
NCQ 318	NH_2	Br	OMe

In the case of NCQ 318, two possibilities are evident (eq 1). In one option, regiocontrol is ascertained by the co-

† Part of this work has been presented at the 194th National Meeting of the American Chemical Society, New Orleans, MEDI43, 1987, and the Xth International Symposium on Medicinal Chemistry, Budapest, B12, 1988.

0022-3263/89/1954-4549$01.50/0