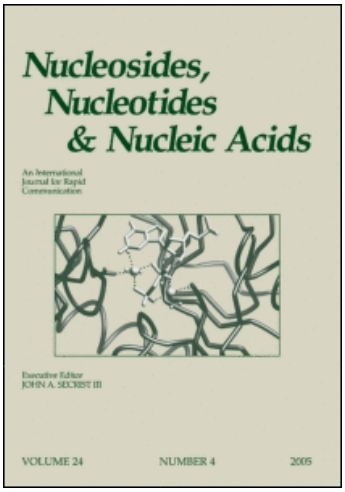

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Synthesis of 2,2'-Anhydro-1 - (3' -deoxy -3' -iodo-β-D-arabino-furanosyl) thymine and Its Derivatives as Versatile Synthetic Intermediates

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SYNTHESIS OF 2,2'-ANHYDRO-1-(3'-DEOXY-3'-IODO-β-D-ARABINO-FURANOSYL)THYMINE AND ITS DERIVATIVES AS VERSATILE SYNTHETIC INTERMEDIATES#

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Abstract

2,2'-Anhydro-1-(3'-deoxy-3'-iodo-5'-O-trityl-β-D-arabinofuranosyl)-thymine (2) was synthesized from 2',3'-didehydro-3'-deoxythymidine (DHT) (1). Compound 2 was readily converted into 2',3'-anhydro-lyxofuranosyl derivatives 4-6. Reaction of 4a with some nucleophiles (N_3^-, OMe^-, Cl^-) gave the corresponding 3'-substituted arabinonucleosides (7b,d,f) together with the minor xylosyl isomers (8a,c). Compounds 7b,d,f and 8a were deprotected to 7c,e,g and 8b, respectively.

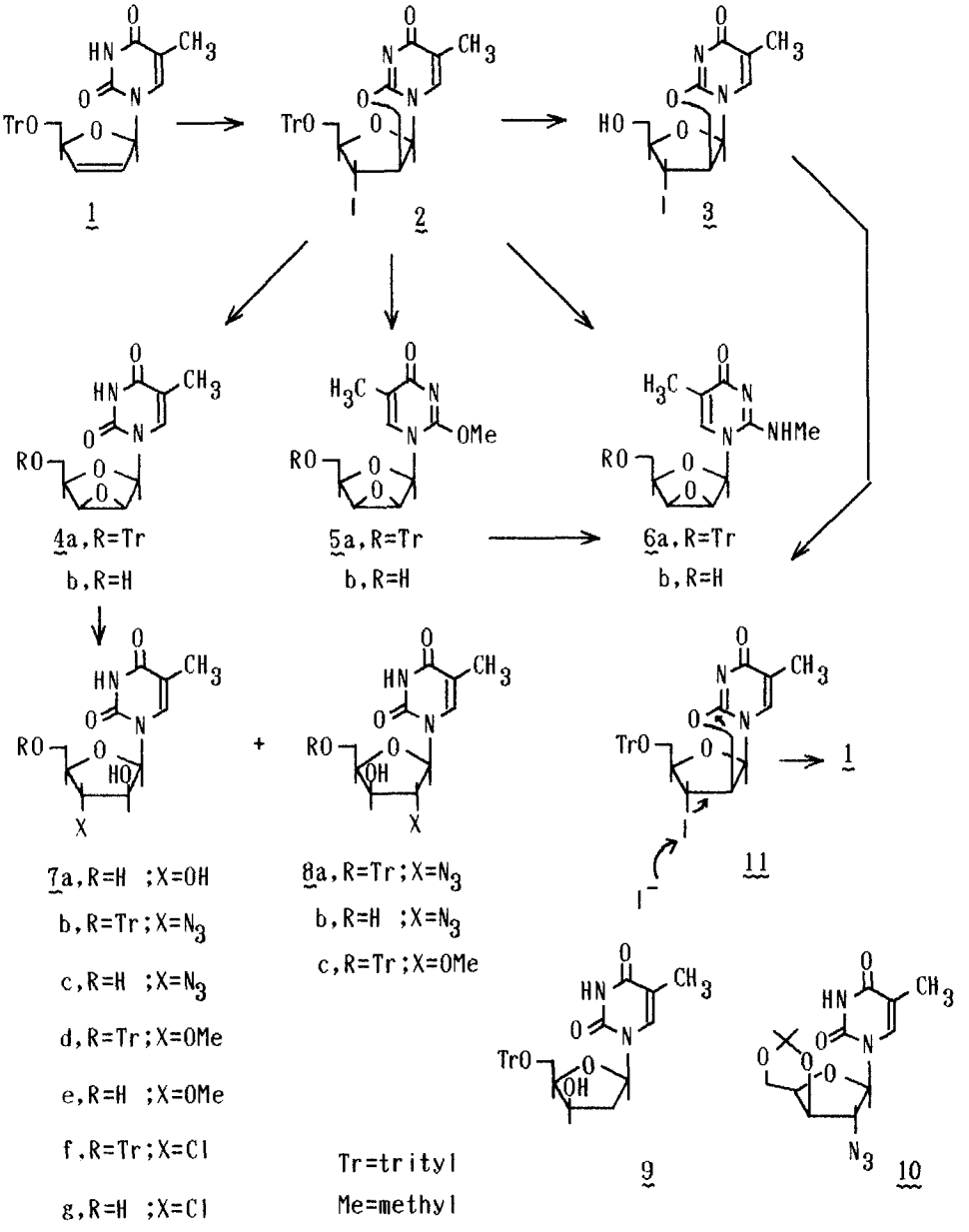
Among the many nucleoside analogues hitherto synthesized to obtain new drugs for treatment of AIDS, thymine analogues involving 3'-azido-3'-deoxythymidine (AZT), 3'-deoxythymidine, 2',3'-didehydro-3'-deoxythymidine (DHT) and others have attracted much concern. In fact, much recent research has aimed at effective deoxygenation of natural nucleosides to 2',3'-dideoxynucleosides.[1-11] On the other hand, continuing efforts have been and are being devoted to the synthesis of thymidine analogues carrying a sugar part modified in a

This paper is dedicated to the late Professor T. Ueda.

variety of ways. However, the range of sugar modification of thymidine lacking a 2'-hydroxy group appears to be notably limited as compared to that of a pyrimidine ribo- or arabinoside. In view of these situations, it seems to be important to establish an appropriate approach to analogues of a 2,2'-anhydro thymine nucleoside starting from thymidine which is much more easily available than the other thymine furanosides.[12] We report herein the synthesis of 2,2'-anhydro-1-(3'-deoxy-3'-iodo-5'-O-trityl-β-D-arabinofuranosyl)thymine (2), a conceptually versatile intermediate, from DHT and some of its chemical properties.[13]

We treated the didehydrothymidine 1[14] with a variety of electrophiles under various reaction conditions, from which a combination of an excess amount of iodine and silver acetate in chloroform was chosen to obtain 2 in 55-65% yield.[15] The structure of 2 is based upon the hypsochromic shift of the UV absorptions and the ^{1}H NMR data lacking an N^3-H signal (see Experimental Section). The abnormally deshielded $H_{2'}$-signal (5.45 ppm) and the large $J_{1',2'}$ (5.40 Hz) confirmed the arabinosyl structure, which was further reinforced by the small $J_{2',3'}$ (1.8 Hz) showing a trans $H_{2'}$-$H_{3'}$ geometry. Compound 2 decomposes in solvents containing any protonic acid, regenerating the starting material 1 and iodine,[16] but can be safely deprotected to 2,2'-anhydro-1-(3'-deoxy-3'-iodo-β-D-arabinofuranosyl)thymine (3) with the use of boron trifluoride etherate. The structure 3 is evident from the general spectroscopic data (see Experimental Section).

Treatment of 2 with a dilute alkali-solution gave a good yield of 1-(2 ,3 -anhydro-5 -O-trityl-β-D-lyxofuranosyl)-thymine (4a). Although this compound has been synthesized and utilized in several laboratories, the reported physical data are rather ambiguous, probably due to its non-crystalline nature.[17-19] Compound 4a was de-O-tritylated to 1-(2 ,3 -anhydro-β-D-lyxofuranosyl)thymine (4b).[19] Treatment of 2 with sodium methoxide gave 1-(2 ,3 -anhydro-5 -O-trityl-β-D-lyxofuranosyl)-2-O-methylthymine (5a) as a foam in an excellent yield. This was directly deprotected to crystalline 1-(2',3'-



anhydro-β-D-lyxofuranosyl)-2-O-methylthymine (5b), whose ^{1}H NMR spectral pattern is quite similar to that of 4b. The attack by methoxide ion on the C_2 of pyrimidine 2-anhydronucleosides is well established.[20-22] Treatment of 2 with 2 N aqueous methylamine gave a high yield of 1-(2 ,3 -anhydro-5 -O-trityl-β-D-lyxofuranosyl)-5-methyl-N^2-methylisocytosine (6a) which was also obtainable from 5a and 1 N aqueous methylamine as judged by TLC in a small scale trial experiment. Boron trifluoride catalyzed deprotection of 6a gave 1-(2 ,3 -anhydro-β-D-lyxofuranosyl)-5-methyl-N^2-methylisocytosine (6b), which was also obtained from 3 and methylamine. The structures of 6a,b are consistent with the whole spectral data. Rather curiously, treatment of 2 with 0.5 N aqueous methylamine gave a good yield of 1-(2 -deoxy-5 -O-trityl-β-D-threo-pentofuranosyl)thymine (9).[23] Although mechanistic details for the formation of 9 are unclear at present, the "up" configuration of the 3'-OH in 9 would invoke formation and cleavage of a 2,3'-anhydro bond.

At the initial stage of this series of work, we suffered from a rather perplexing situation caused by the physical data described for compounds 4a,b.[24] Accordingly, we decided to conduct some nucleophilic reactions with 4a,b for the purpose of their structural confirmation and further biological evaluation of some new compounds. Acidic hydrolysis of 4b in 0.1 N aqueous sulfuric acid[26] under reaction conditions milder than those described gave 1-β-D-arabinofuranosylthymine (spongothymidine) as a single product. Reaction of 4a with azide ion gave 1-(3 -azido-3 -deoxy-5 -O-trityl-β-D-arabinofuranosyl)thymine (7b)[18] and 1-(2 -azido-2 -deoxy-5 -O- trityl-β-D-xylofuranosyl)thymine (8a)[18] in 83% and 16% yields, respectively, both as a foam.[27] Deprotection of 7b gave 1-(3 -azido-3 -deoxy-β-D-arabinofuranosyl)thymine (7c)[19] as crystals, while the xylofuranosyl structure of 8a was confirmed by 3',5'-O,O-isopropylidenation of the deprotected form (8b) to 10. For the initial purpose of examining the regioselectivity of basic hydrolysis of the epoxide ring in

4a, this compound was treated with 1 N NaOH/H_2O-MeOH to yield, unexpectedly, merely methanolysis products, 1-(3 -O-methyl-5 -O-trityl-β-D-arabinofuranosyl)thymine (7d) (55%) and its xylosyl isomer (8c) (17%). Compound 7d was deprotected to crystalline 1-(3 -O-methyl-β-D-arabinofuranosyl)thymine (7e), while further manipulation of 8c was abandoned because of its material paucity. On treating 4a with pyridinium hydrochloride,[28] 1-(3 -chloro-3 -deoxy-5 -O-trityl-β-D-arabinofuranosyl)thymine (7f) (74%) was obtained together with a small amount of a less polar product (probably xylo-isomer). The former was deprotected to crystalline 1-(3 -chloro-3 -deoxy-β-D-arabinofuranosyl)thymine (7g). The arabinofuranosyl structures of 7 were in accord with the large $J_{1',2'}$ values (4.77-6.36 Hz) in their ^{1}H NMR spectra. It was also noted that the 5'-protected arabino isomers (7b,d,f) are more polar than the corresponding xylosyl counterparts in terms of TLC (see Experimental Section).

Finally, it must be noted that compound 2 represents a unique intramolecular *trans* elimination system (11) in which the 3'-iodo group would easily accept various nucleophiles to regenerate 1. For example, 2 smoothly regenerate 1 on being treated with 1-2 equivalent amounts of NaI in acetone at room temperature.[29] Despite this, compound 2 has led to the potentially useful intermediates 4, 5, and 6 in good to excellent yields.

Experimental Section

Mps were recorded on a Yanagimoto micro melting point apparatus and are uncorrected. UV spectra were measured on a Hitachi Model 200-10 spectrophotometer. The 200 MHz ^{1}H NMR spectra of compounds 2, 3, 4a,b, 6a,b, 7b and 7f were recorded on a GEMINI-200 FT NMR spectrometer, and the 500 MHz ^{1}H NMR spectra of compounds 5b, 7c,d,e,g, 9 and 10 on a JEOL-JNM-GSX500 FT NMR spectrometer, in the laboratory of the Daiichi Seiyaku Co., Ltd. Elemental analyses were conducted using a Perkin-Elmer 240B elemental analyser. For preparative-scale thick-layer chromatography, glass plates coated with a 2-mm thickness of Wakogel B-5F silica gel were used after

activation at 100°C for 10-12 h. All evaporations were carried out under reduced pressure at or below 40°C.

2,2'-Anhydro-1-(3'-deoxy-3'-iodo-5'-O-trityl-β-D-arabinofuranosyl)thymine (2). To a stirred solution of 1 (2.001 g, 4.29 mmol) in dry $CHCl_3$ (8 ml) was added iodine (1.017 g, 4.0 mmol). After 5 min, AgOAc (1.003 g, 6.0 mmol) was added and the mixture stirred at room temperature for 1 h. After addition of further iodine (908 mg, 3.56 mmol) followed by addition of AgOAc (867 mg, 5.19 mmol) after 5 min, the mixture was stirred for additional 2 h. The mixture was filtered through a celite pad and the filter-cake washed with $CHCl_3$ (2 x 5 ml). The filtrate was transferred into a separatory funnel and decolorized by gentle shaking with saturated sodium thiosulfate solution. The separated organic layer was quickly dried over Na_2SO_4 and evaporated, and the residue recrystallized from EtOAc at room temperature, evading room light as far as possible, to give TLC-homogeneous crystals of 2 (943 mg). Further crops (360 mg) were obtained on concentrating the filtrate. The final filtrate containing 2 and two minor by-products which were less polar than 1 was fractionated on a silica plate (20 x 20 cm; $CHCl_3$/MeOH, 9:1, twice developed) to give further 200 mg of 2 (Total: 1.50 g, 60%): mp 203-204°C (EtOAc); λmac (MeOH) nm (ε) 227 (4900, inflection), 253 (4970); ^{1}H NMR ($CDCl_3$) δ 1.92 (3H, d, J = 1.2, 5-Me), 2.97 (1H, dd, J_{gem} = 10.4, $J_{5'a,4'}$ = 6.4, $H_{5'a}$), 3.19 (1H, dd, J_{gem} = 10.4, $J_{5'b,4'}$ = 6.0, $H_{5'}$b), 4.60 (1H, ddd, $J_{4',5'a}$ = 6.4, $J_{4',5'b}$ = 6.0, $J_{4',3'}$ = 3.0, $H_{4'}$), 4.51 (1H, dd, $J_{3',4'}$ = 3.0, $J_{3',2'}$ = 1.7, $H_{3'}$), 5.45 (1H, dd, $J_{2',3'}$ = 1.7, $J_{2',1'}$ = 5.4, $H_{2'}$), 6.19 (1H, d, $J_{1',2'}$ = 5.4, $H_{1'}$), 7.16 (1H, d, J = 1.2, H_6), 7.24-7.35 (15H, m, Ar-H). Anal. ($C_{29}H_{25}IN_2O_4$) Calcd: C, 57.79; H, 4.25; N, 4.73. Found: C, 58.07; H, 4.28; N, 4.82.

2,2'-Anhydro-1-(3'-deoxy-3'-iodo-β-D-arabinofuranosyl)thymine (3). Boron trifluoride etherate (0.1 ml, 0.8 mmol) was added to a solution of 2 (1.0 g, 1.7 mmol) in $CHCl_3$ (50 ml) and the mixture stirred at room temperature for 1 h. The precipitating solid was collected by suction, washed with a small volume of $CHCl_3$, and dried under high vacuum. Recrystallization of the solid from MeOH at room temperature gave 548 mg (93%) of 3 as crystals of mp 182-183°C: λmax (MeOH) nm (ε) 228 (8830), 252 (10120); ^{1}H NMR (Me_2SO-d_6) δ 1.82 (3H, d, J = 1.2, 5-Me), 3.25 (2H, d, J = 5.4, 5'-CH_2), 4.49 (1H, dt, $J_{4',5'}$ = 5.4, $J_{4',3'}$ = 3.0, $H_{4'}$), 4.60 (1H, t, J =

7.2, 5'-OH), 4.66 (1H, dd, $J_{3',4'}$ = 3.0, $J_{3',2'}$ = 1.6, $H_{3'}$), 5.76 (1H, dd, $J_{2',3'}$ = 1.6, $J_{2',1'}$ = 5.6, $H_{2'}$), 6.43 (1H, d, $J_{1',2'}$ = 5.6, $H_{1'}$), 7.83 (1H, d, J = 1.2, H_6). Anal. ($C_{10}H_{11}IN_2O_4$) Calcd: C, 34.30; H, 3.17; N, 8.00. Found: C, 34.24; H, 3.04; N, 7.94.

1-(2 ,3 -Anhydro-5 -O-trityl-β-D-lyxofuranosyl)thymine (4a). To a stirred suspension of 2 (3.00 g, 5.06 mmol) in acetone (26 ml) was added 1 N aqueous NaOH (10 ml). The mixture became a solution in 15 min. Then, more 1 N aqueous NaOH (2 ml) was added, and the mixture stirred for additional 1.5 h, during which time 2 disappeared and a major, less polar product formed together with a far minor faster-running one in terms of TLC (silica; $CHCl_3$/EtOAc, 1:1). The mixture was neutralized with AcOH and the solvent evaporated. The residue was partitioned between $CHCl_3$ (50 ml) and water (10 ml). The separated organic layer was dried over Na_2SO_4 and evaporated to a paste, which gave crystals (1.33 g) on trituration with EtOAc. The mother liquor separated from the crystals was fractionated on silica gel plates (20 x 20 cm, 2 sheets; $CHCl_3$/EtOAc, 3:1, developed 3 times). The major bands were eluted with acetone and the combined acetone eluates thoroughly evaporated. Crystallization of the residual paste from EtOAc gave further 660 mg of the product as several crops (totally 1.99 g, 69%). For analysis a part was recrystallized from EtOAc at room temperature to give star-like congregated, massive needles which effervesced at 110-115°C and melted at 160-161°C: ^{1}H NMR ($CDCl_3$) δ 1.83 (3H, d, J = 1.2, 5-Me), 3.35 (1H, dd, J_{gem} = 9.8, $J_{5\,a,4}$ = 5.6, $H_{5\,a}$), 3.50 (1H, dd, J_{gem} = 9.8, $J_{5\,b,4}$ = 5.8, $H_{5\,b}$),4.16 (1H, ddd, $J_{4,5\,a}$ = 5.6, $J_{4,5\,b}$ = 5.8, $J_{4,3}$ = 0.6, H_4), 3.87 and 3.91 (each 1H, dd, $J_{2,1}$ = 0.6, $J_{2,3}$ = 3.0, $J_{3,4}$ = 0.6, H_2 and H_3), 6.19 (1H, d, $J_{1,2}$ = 0.6, H_1), 7.40 (1H, q, J = 1.2, H_6), 7.25-7.51 (15H, m, Ar-H), 11.47 (1H, br s, N^3-H). Anal. ($C_{29}H_{26}N_2O_5$·EtOAc) Calcd; C, 69.46; H, 6.01; N, 4.91. Found: C, 69.42; H, 5.93; N, 5.03.

1-(2 ,3 -Anhydro-β-D-lyxofuranosyl)thymine (4b). A solution of 4a (100 mg, 0.175 mmol) in 80% aqueous AcOH (10 ml) was left at room temperature for 2 days. TLC-Monitoring (silica, $CHCl_3$/MeOH, 9:1) of aliquots showed that a single, polar product formed. The mixture was evaporated and repeatedly co-evaporated with MeOH, and the residue fractionated on a silica plate (20 x 20 cm; $CHCl_3$/MeOH, 9:1, developed 3 times). The UV-absorbing band was eluted with MeOH and the combined eluates evaporated to give an amorphous solid, which resisted crystallization. For analysis,

the total in a small volume of MeOH was treated with Norit and the solution evaporated to give 38 mg (90%) of 4b as an amorphous solid after drying over silica gel in vacuo at 60°C for 5 h: ^{1}H NMR (CD_3OD) δ 1.87 (3H, d, J = 1.2, 5-Me), 3.79 (2H, d, $J_{5',4'}$ = 5.8, 5'-CH_2), 4.07 (1H, dt, $J_{4',5'}$ = 5.8, $J_{4',3'}$ = 0.8, $H_{4'}$), 3.93 and 3.98 (each 1H, dd, $J_{1',2'}$ = 0.8, $J_{2',3'}$ = 3.1, $J_{3',4'}$ = 0.8, $H_{2'}$ and $H_{3'}$), 6.13 (1H, d, $J_{1',2'}$ = 0.8, $H_{1'}$), 7.59 (1H, q, J = 1.2, H_6). Anal. ($C_{10}H_{12}N_2O_5$) Calcd: C, 50.00; H, 5.04; N, 11.66. Found: C, 50.02; H, 4.96; N, 11.51.

1-(2',3'-Anhydro-5'-O-trityl-β-D-lyxofuranosyl)-2-O-methylthymine (5a) and 1-(2',3'-Anhydro-β-D-lyxofuranosyl)-2-O-methylthymine (5b). To a suspension of 2 (200 mg, 0.34 mmol) in MeOH (1 ml) was added sodium methoxide (21.60 mg, 0.40 mmol) and the mixture was stirred at room temperature for 1.5 h. The basicity of the resulting solution was weakened with dry ice and the solution directly charged on a silica plate (20 x 20 cm). After development with $CHCl_3$/MeOH (9:1) 3 times, the major band was eluted with acetone to give 5a as a homogeneous foam (144 mg, 86%). Anal. ($C_{30}H_{28}N_2O_5$) Calcd: C, 72.56; H, 5.68; N, 5.64. Found: C, 72.33; H, 5.82; N, 5.74.

The total in 80% aqueous AcOH (19 ml) was stirred at room temperature for 25 h and the solution evaporated. The residue was repeatedly co-evaporated with MeOH and left with a small volume of MeOH to afford crystals of trityl alcohol, which were filtered off. The filtrate was fractionated on a silica plate (20 x 20 cm; $CHCl_3$/MeOH, 9:1, developed 3 times) and the major fraction eluted with MeOH to give a crystalline solid which was collected and recrystallized from EtOH at room temperature to give 52 mg (70% based upon 5a) of 5b, mp 172-174°C (dec): ^{1}H NMR (Me_2SO-d_6) δ 1.81 (3H, s, 5-Me), 5.00-5.01 (1H, br, 5'-OH, D_2O-exchangeable), 3.90 (3H, s, OMe), 3.59-3.66 (2H, m, 5'-CH_2, partially overlapped H_2O signal), 4.02 (1H, d, $J_{2',3'}$ = 3.18, $H_{3'}$ or $H_{2'}$), 4.07 (1H, t, $J_{4',5'a}$ = 6.0, $H_{4'}$), 4.14 (1H, d, $J_{2',3'}$ = 3.18, $H_{2'}$ or $H_{3'}$), 6.01 (1H, s, $H_{1'}$), 7.56 (1H, s, H_6). Anal. ($C_{11}H_{14}N_2O_5$) Calcd: C, 51.96; H, 5.55; N, 11.02. Found: C, 51.92; H, 5.56; N, 11.05.

1-(2',3'-Anhydro-5'-O-trityl-β-D-lyxofuranosyl)-5-methyl-N^2-methylisocytosine (6a). A mixture of 2 (592 mg, 1 mmol), 40% aqueous CH_3NH_2 (1.72 ml, ca. 20 mmol) and DMF (8.28 ml) (ca. 2 N solution with regard to CH_3NH_2) in an argon-filled pressure tube was stirred at 45°C for 2.5 h.

After thorough evaporation, the residue in a small volume of $CHCl_3$ was directly applied on a silica plate (20 x 20 cm) and developed with $CHCl_3$/MeOH (9:1). The major fraction was eluted with MeOH. The combined eluates were concentrated, treated with Norit, and poured into ice water (100 ml) to give an amorphous solid (6a), which was collected and dried over silica in vacuo at 60°C for 6 h (435 mg, 88%): λmax (MeOH) nm (ε) 222 (31400, shoulder), 260 (6380); ^{1}H NMR ($CDCl_3$) δ 1.87 (3H, s, 5-Me), 2.83 (3H, s, N^2-Me), 3.37 (1H, dd, J_{gem} = 9.6, $J_{5\,a,4}$ = 6.2, $H_{5\,a}$), 3.44 (1H, dd, J_{gem} = 9.6, $J_{5\,b,4}$ = 5.6, $H_{5\,b}$), 4.15-4.20 (2H, m, H_2 and H_4, overlapped each other), 3.96 (1H, dd, $J_{3,4}$ = 0.4, $J_{3,2}$ = 3.0, H_3), 5.79 (1H, s, H_1), 6.55 (1H, br, N^3-H, D_2O-exchangeable), 7.23-7.48 (16H, Ar-H and H_6). Anal. ($C_{30}H_{29}N_3O_4$) Calcd: C, 72.71; H, 5.90; N, 8.48. Found: C, 72.70; H, 5.87; N, 8.47.

1-(2,3-Anhydro-β-D-lyxofuranosyl)-5-methyl-N^2-methylisocytosine (6b). Method 1. Boron trifluoride etherate (0.10 ml, 0.81 mmol) was added to a solution of 6a (400 mg, 0.81 mmol) in $CHCl_3$ (4 ml) and the mixture stirred at room temperature for 4 h. The resulting precipitate was collected by suction and chromatographed on a TLC plate (20 x 20 cm; $CHCl_3$/MeOH, 7:3). The major fraction was eluted with MeOH and the concentrated methanolic solution was left at room temperature to give 146 mg (71%) of crystals of 6b, mp 197-200°C: λmax (MeOH) nm (ε) 263 (16330); ^{1}H NMR (Me_2SO-d_6) δ 1.74 (3H, d, J = 1.2, 5-Me), 2.74 (3H, d, J = 4.2, N^2-Me), 3.59 (2H, t, $J_{5,4}$ = 6.2, 5-CH_2), 3.99 (1H, dt, $J_{4,5}$ = 6.2, $J_{4,3}$ = 0.8, H_4), 4.06 (1H, dd, $J_{3,4}$ = 0.8, $J_{3,2}$ = 3.2, H_3), 4.20 (1H, d, $J_{2,3}$ = 3.2, H_2), 5.67 (1H, s, H_1), 5.08 (1H, t, J = 5.8, 5-OH), 7.01 (1H, q, J = 4.2, N^2-H), 7.34 (1H, d, J = 1.2, H_6). Anal. ($C_{11}H_{15}N_3O_4$) Calcd: C, 52.17; H, 5.97; N, 16.59. Found: C, 52.31; H, 5.87; N, 16.41.

Method 2. A mixture of 3 (38 mg, 0.11 mmol), DMF (0.91 ml) and 40% aqueous CH_3NH_2 (0.17 ml, ca. 2 mmol) was stirred under argon overnight at room temperature. The mixture was evaporated and the residue left with a small volume of MeOH to give 15 mg (54%) of crystals, identical with the above product 6b in terms of IR, UV, and NMR spectroscopy.

Conversion of 4b into 1-β-D-Arabinofuranosylthymine (7a). A mixture of 4b (90 mg, 0.37 mmol) and 0.1 N aqueous H_2SO_4 (4 ml) in a sealed vessel was heated at 85°C for 72.5 h, during which time 4b gradually disappeared and a single polar substance formed as judged by TLC. The cooled mixture was

neutralized with 1 N NH_4OH and evaporated. The residue was extracted with MeOH and the MeOH-extract chromatographed on a silica plate (20 x 20 cm; $CHCl_3$/MeOH, 85:15, developed 4 times) to remove inorganic material. Elution of the UV-absorbing band with MeOH gave 60 mg (63%) of 7a after recrystallization from MeOH, mp 228-230°C (lit.[26] 238-242°C), identical with a commercial authentic sample in terms of IR and UV spectroscopy.

1-(3 -Azido-3 -deoxy-5 -O-trityl-β-D-arabinofuranosyl)thymine (7b) and 1-(2 -Azido-2 -deoxy-5 -O-trityl-β-D-xylofuranosyl)thymine (8a). A mixture of sodium azide (910 mg, 14 mmol) and tetraethylammonium chloride (2.32 g, 14 mmol) and DMF (40 ml) in an argon-filled pressure tube was stirred at room temperature for 2 h. Then, the EtOAc-solvate of 4a (800 mg, 1.4 mmol) was added and the mixture stirred at 90°C for 4 h and 10 min. TLC-Monitoring confirmed the complete consumption of the starting material and formation of two substances. The mixture was evaporated and the residue partitioned between EtOAc (30 ml) and water (20 ml). The separated H_2O-layer was again extracted with EtOAc (20 ml). The combined EtOAc solutions were dried over Na_2SO_4, evaporated and the residue fractionated on silica plates (20 x 20 cm, 4 sheets; $CHCl_3$/EtOAc, 1;1, developed 3 times) to give 609 mg (83%) of 7b as a pure foam from the slower-moving band: IR (KBr) ν 2125 cm^{-1}; λmax nm (ε) 266.4 (9830); ^1H NMR ($CDCl_3$) δ 1.58 (3H, d, J = 1.0, 5-Me), 3.37 (1H, dd, J_{gem} = 10.8, $J_{5\,a,4}$ = 3.8, $H_{5\,a}$), 3.58 (1H, dd, J_{gem} = 10.8, $J_{5\,b,4}$ = 3.2, $H_{5\,b}$), 3.86 (1H, ddd, $J_{4,5\,a}$ = 3.8, $J_{4,5\,b}$ = 3.2, $J_{4,3}$ = 6.6, H_4), 4.15 (1H, dd, $J_{3,4}$ = 6.6, $J_{3,2}$ = 5.0, H_3), 4.60 (1H, dd, $J_{2,3}$ = 5.0, $J_{2,1}$ = 5.0, H_2), 4.80 (1H, br s, 2 -OH), 6.10 (1H, d, $J_{1,2}$ = 5.0, H_1), 7.26-7.49 (15H, m, Ar-H), 7.60 (1H, q, J = 1.0, H_6), 11.36 (3H, s, N^3-H). Anal. ($C_{29}H_{27}N_5O_5$) Calcd: C, 66.27; H, 5.18; N, 13.33. Found: C, 66.40; H, 5.37; N, 13.10.

Elution of the less polar band with EtOAc gave 120 mg (16%) of 8a as a foam, whose structure was confirmed after deprotection and further derivatization (vide infra).

1-(3-Azido-3 -deoxy-β-D-arabinofuranosyl)thymine (7c), 1-(2 -Azido-2 -deoxy-β-D-xylofuranosyl)thymine (8b), and 1-(2 -Azido-2 -deoxy-3 ,5 -O,O-isopropylidene-β-D-xylofuranosyl)thymine (10). The above obtained 7b (600 mg, 1.14 mmol) in 80% aqueous AcOH (25 ml) was stirred at room temperature for 2 days and the mixture evaporated. The residue was repeatedly

co-evaporated with MeOH and partitioned between H_2O (20 ml) and $CHCl_3$ (20 ml). The separated H_2O-layer was again washed with $CHCl_3$ (10 ml) and evaporated to give crystals, which were recrystallized from a mixture of MeOH and EtOH at room temperature to afford 228 mg (71%) of 7c, mp 159-160°C (ref.[25] 169.5-170.5°C): IR (KBr) ν 2115 cm^{-1} (N_3); Mass m/z 283 (M^+); ^1H NMR (Me_2SO-d_6) δ 1.78 (3H, s, 5-Me), 3.63 (1H, m, $H_{5\,a}$), 3.72 (2H, m, $H_{5\,b}$ and H_4), 4.03 (1H, t, $J_{3,2}$ = 6.35, $J_{3,4}$ = 7.5, H_3), 4.35 (1H, t-like dd, $J_{2,1}$ = 6.36, $J_{2,3}$ = 6.35, H_2), 5.28 (1H, t, J = 5.56, 5 -OH), 6.03 (1H, d, $J_{1,2}$ = 6.36, H_1), 6.06 (1H, d, J = 5.56, 2 -OH), 7.63 (1H, s, H_6), 11.26 (1H, s, N^3-H). Anal. ($C_{10}H_{13}N_5O_5$) Calcd: C, 42.40; H, 4.63; N, 24.73. Found: C, 42.33; H, 4.38; N, 24.92.

The above obtained 8a (120 mg, 0.23 mmol) in 80% aqueous AcOH (8 ml) was stirred at room temperature for 2 days and evaporated. The residue was repeatedly co-evaporated with MeOH and fractionated on a silica plate (20 x 20cm; $CHCl_3$/MeOH, 9:1) to give 41 mg (61%) of 8b as a foam: IR (KBr) ν 2130 cm^{-1} (N_3).

A mixture of 8b (40 mg, 0.14 mmol), DMF (0.5 ml), acetone (0.2 ml), 2,2-dimethoxypropane (0.1 ml), and a saturated solution of HCl in dioxane (2 drops) was stirred at room temperature for 1.5 h. The mixture was neutralized with solid $NaHCO_3$, filtered, and the filtrate evaporated to give crystals, which were recrystallized from MeOH to give 32 mg (71%) of 10, mp 202-204°C (dec): ^1H NMR (Me_2SO-d_6) δ 1.27 (3H, s, isopropylidene Me), 1.45 (3H, s, isopropylidene Me), 1.78 (3H, s, 5-Me), 4.03 (1H, s, H_4), 4.07 (1H, d, J_{gem} = 13.51, $H_{5\,a}$), 4.18 (1H, d, J_{gem} = 13.51, $H_{5\,b}$), 4.32 (1H, s, H_2), 4.38 (1H, s, H_3), 5.77 (1H, s, H_1), 7.78 (1H, s, H_6), 11.42 (1H, s, N^3-H). Anal. ($C_{13}H_{17}N_5O_5$) Calcd: C, 48.29; H, 5.30; N, 21.66. Found: C, 48.23; H, 5.37; N, 21.65.

1-(3 -O-Methyl-5 -O-trityl-β-D-arabinofuranosyl)thymine (7d) and 1-(2 -O-Methyl-5 -O-trityl-β-D-xylofuranosyl)thymine (8c). A mixture of 4a (EtOAc-solvate) (100 mg, 0.175 mmol), MeOH (6 ml), and 4 N aqueous NaOH (2 ml) (1 N NaOH/H_2O-MeOH) was stirred at 45-50°C for 7.5 h and then at 50-55°C for 19 h. The mixture was neutralized with AcOH and evaporated. The residue was partitioned between EtOAc (30 ml) and H_2O (10 ml). The separated EtOAc layer was evaporated and the residue fractionated on a silica plate (20 x 20 cm; $CHCl_3$/EtOAc, 1:1). The more polar band gave 50 mg (55%) of 7d as a foam: λmax (MeOH) nm (ε) 267 (9800); ^1H NMR

(Me_2SO-d_6) δ 1.62 (3H, s, 5-Me), 3.32 (3H, s, OMe), 3.27 (2H, d, $J_{5',4'}$ = 4.77, 5'-CH_2), 3.72 (1H, t-like dd, $J_{3',4'}$ = 9.3, $J_{3',2'}$ = 2.38, $H_{3'}$), 3.94 (1H, dd, $J_{4',3'}$ = 9.3, $J_{4',5'}$ = 4.77, $H_{4'}$), 4.17 (1H, dd, $J_{2',1'}$ = 4.77, $J_{2',3'}$ = 2.38, $H_{2'}$), 5.96 (1H, d, $J_{1',2'}$ = 4.77, $H_{1'}$), 7.28-7.43 (16H, Ar-H and H_6), 11.32 (1H, s, N^3-H). Anal. ($C_{30}H_{30}N_2O_6$) Calcd: C, 70.02; H, 5.88; N, 5.44. Found: C, 69.90; H, 5.98; N, 5.46.

The less polar TLC-fraction gave 15 mg (17%) of 8c as a foam. Anal. ($C_{30}H_{30}N_2O_6$) Calcd: C, 70.02; H, 5.88; N, 5.45. Found: C, 70.22; H, 5.65; N, 5.35.

1-(3'-O-Methyl-β-D-arabinofuranosyl)thymine (7e). A mixture of 7d (140 mg, 0.27 mmol) and 80% aqueous AcOH (6 ml) was stirred at room temperature for 2 days. After the usual work up (vide supra), the mixture was fractionated on a silica plate (20 x 20 cm; $CHCl_3$/MeOH, 85:15) and the obtained solid recrystallized from a mixture of MeOH and EtOH to give 60 mg (82%) of 7e, mp 169-170°C: λmax nm (ε) 268 (10100): ^{1}H NMR (Me_2SO-d_6) δ 1.78 (3H, s, 5-Me), 3.36 (3H, s, OMe), 3.62 (2H, dd, J_{gem} = 9.5, $J_{5',4'}$ = 4.77, 5'-CH_2), 3.69 (1H, t, J = 3.18, $H_{3'}$), 3.81 (1H, dd, $J_{4',3'}$ = 8.74, $J_{4',5'}$ = 4.77, $H_{4'}$), 4.15 (1H, dd, $J_{2',1'}$ = 4.77, $J_{2',3'}$ = 2.38, $H_{2'}$), 5.12 (1H, t, J = 5.56, 5'-OH), 5.64 (1H, d, J = 4.77, 2'-OH), 5.90 (1H, d, $J_{1',2'}$ = 4.77, $H_{1'}$), 7.51 (1H, s, H_6), 11.27 (1H, s, N^3-H). Anal. ($C_{11}H_{16}N_2O_6$) Calcd: C, 48.52; H, 5.92; N, 10.29. Found: C, 48.58; H; 5.89; N, 10.26.

1-(3'-Chloro-3'-deoxy-5'-O-trityl-β-D-arabinofuranosyl)thymine (7f). A mixture of 4a (EtOAc-solvate) (100 mg, 0.21 mmol) and pyridinium hydrochloride (121 mg, 1.05 mmol) in pyridine (5 ml) in an argon-filled pressure tube was stirred at 100-105°C for 4 h. TLC at this stage showed a major product and a less polar minor one. The mixture was evaporated and the residue partitioned between EtOAc (30 ml) and water (10 ml). The separated organic layer was evaporated to give the more polar product as crystals, which were collected by suction. The filtrate was fractionated on a silica plate (20 x 20 cm; $CHCl_3$/EtOAc, 1:1, twice developed) to afford another crop. The combined product was recrystallized from MeOH to give 80 mg (74%) of 7f, mp 205-207°C: λmax nm (ε) 266 (10500); ^{1}H NMR ($CDCl_3$) δ 1.58 (3H, d, J = 1.0, 5-Me), 3.45 (1H, dd, J_{gem} = 11.0, $J_{5'a,4'}$ = 3.6, $H_{5'a}$), 3.57 (1H, dd, J_{gem} = 11.0, $J_{5'b,4'}$ = 3.0, $H_{5'b}$), 4.14 (1H, ddd, $J_{4',5'a}$ = 3.6, $J_{4',5'b}$ = 3.0, $J_{4',3'}$ = 7.0, $H_{4'}$), 4.32 (1H, dd, $J_{3',4'}$ = 7.0, $J_{3',2'}$ = 5.2, $H_{3'}$), 4.39 (1H, br s, 2'-OH), 4.36

(1H, dd, $J_{2',3'}$ = 5.2, $J_{2',1'}$ = 5.0, $H_{2'}$), 6.20 (1H, d, $J_{1',2'}$ =5.0, $H_{1'}$), 7.27-7.48 (15H, m, Ar-H), 7.60 (1H, q, J = 1.0, H_6), 9.63 (1H, br s, N^3-H). Anal. ($C_{29}H_{27}ClN_2O_2$) Calcd: C, 67.11; H, 5.24; N, 5.40. Found: C, 67.21; H, 5.28; N, 5.27.

The less polar fraction was neglected.

1-(3 -Chloro-3 -deoxy-β-D-arabinofuranosyl)thymine (7g). A mixture of 7f (181 mg, 0.35 mmol) and 80% aqueous AcOH (15 ml) was stirred for 2 days. After thorough evaporation, the solid of trityl alcohol was filtered off and the filtrate fractionated on a silica plate (20 x 20 cm; $CHCl_3$/MeOH, 9:1, twice developed) to afford 72 mg (75%) of 7g after recrystallization from MeOH, mp 176-178°C: ^{1}H NMR (Me_2SO-d_6) δ 1.78 (3H, s, 5-Me), 3.63 (1H, dd, J_{gem} = 11.92, $H_{5'a,4'}$ = 3.18, $H_{5'a}$), 3.73 (1H, dd, J_{gem} = 11.92, $J_{5'b,4'}$ = 2.38, $H_{5'b}$), 3.98 (1H, m, $H_{4'}$), 4.20 (1H, t, J = 7.15, $H_{3'}$), 4.45 (1H, t, $J_{2',1'}$ = 6.36, $H_{2'}$), 5.30 (1H, br s, 5 -OH), 6.13 (1H, d, $J_{1',2'}$ = 6.36, $H_{1'}$), 6.19 (1H, br s, 2 -OH), 7.61 (1H, s, H_6), 11.29 (1H, br s, N^3-H). Anal. ($C_{10}H_{13}ClN_2O_5$) Calcd: C, 43.41; H, 4.74; N, 10.13. Found: C, 43.50; H, 4.71; N, 10.06.

1-(2 -Deoxy-5 -O-trityl-β-D-threo-pentofuranosyl)thymine (9).[23] A mixture of 2 (305.2 mg, 0.52 mmol), DMF (9.6 ml) and 40% aqueous CH_3NH_2 (0.43 ml, 5 mmol) (ca. 0.5 N solution with regard to CH_3NH_2) in an argon-filled pressure tube was stirred at room temperature for 14 h. After evaporation, the residue was fractionated on a silica plate (20 x 20 cm; $CHCl_3$/EtOAc, 1:1) and the major fraction was eluted with MeOH to give crystals, which were recrystallized from MeOH to afford 190 mg (76%) of 9, mp 229-230°C (lit.[23] 240-241°C), identical with an authentic sample[23] in terms of IR and ^{1}H NMR spectroscopy: ^{1}H NMR (Me_2SO-d_6) δ 1.65 (3H, s, 5-Me), 1.85 (1H, dd, J_{gem} = 14.30, $J_{2'a,1'}$ = 2.38, $H_{2'a}$), 2.54 (1H, m, $H_{2'b}$), 3.20 (1H, dd, J_{gem} = 10.33, $J_{5'a,4'}$ = 3.18, $H_{5'a}$), 3.39 (1H, dd, J_{gem} = 10.33, $J_{5'b,4'}$ = 7.95, $H_{5'b}$), 4.09 (1H, m, $H_{4'}$), 4.19 (1H, dd, J = 7.94 and 3.97, $H_{3'}$), 5.19 (1H, d, J = 3.18, 3 -OH), 6.13 (1H, dd, $J_{1',2'a}$ = 2.38, $J_{1',2'b}$ = 8.75, $H_{1'}$), 7.25-7.43 (15H, Ar-H), 7.57 (1H, s, H_6), 11.26 (1H, s, N^3-H). Anal. ($C_{29}H_{28}N_2O_5$) Calcd: C, 71.88; H, 5.83; N, 5.78. Found: C, 71.90; H, 5.89; N, 5.71.

REFERENCES

1. K. E. Pfitzner and J. G. Moffatt, J. Org. Chem., 29, 1508 (1964).
2. M. J. Robins and J. S. Wilson, J. Am. Chem. Soc., 103, 932 (1981).

3. R. A. Lessor and N. J. Leonard, J. Org. Chem., 46, 4300 (1981).
4. D. G. Norman and C. B. Reese, Synthesis, 304 (1983).
5. M. J. Robins, J. S. Wilson, and F. Hansske, J. Am. Chem. Soc., 105, 4059 (1983).
6. B. Doboszewski, C. K. Chu, and H. V. Halbeek, J. Org. Chem., 53, 2777 (1988).
7. V. Nair and G. S. Buenger, J. Am. Chem. Soc., 111, 8502 (1989).
8. H. Rosemeyer and F. Seela, Helv. Chim. Acta, 72, 1084 (1989).
9. P. Serafinowski, Synthesis, 411 (1990).
10. M. Sekine and T. Nakanishi, J. Org. Chem., 55, 924 (1990)
11. S. Czernecki and J.-M. Valéry, Synthesis, 239 (1991).
12. Arabinosyl or ribosyl thymine is several tens of times more expensive than thymidine.
13. An unsuccessful attempt to convert 1 into a cis-β-glycol by the I_2/AgOAc method is described: V. Škarić and J. Matulić-Adamić, Helv. Chim. Acta, 63, 2179 (1980).
14. J. P. Horwitz, J. Chua, M. A. Da Rooge, M. Noel, and I. L. Klundt, J. Org. Chem., 31, 205 (1966).
15. Although DMF can also be used, chloroform is recommended in order to avoid decomposition of the product during lengthy evaporation.
16. Compound 2 is also rather unstable even in neutral solutions, especially under light, giving 1 as one of the decomposition products.
17. Our attempts to crystallize 4a in non-solvated form have been unsuccessful. However, a very recent publication[18] has attributed mp 130-134°C (EtOH) to this compound, while we obtained 4a as a highly crystallizable mono-ethyl acetate solvate (see Experimental Section).
18. J.-T. Huang, L.-C. Chen, L. Wang, M.-H. Kim, J. A. Warshaw, D. Armstrong, Q.-Y. Zhu, T.-C. Chou, K. A. Watanabe, J. Matulić-Adamić, T.-L. Su, J. J. Fox, B. Polsky, P. A. Barton, J. W. M. Gold, W. D. Hardy, and E. Zuckerman, J. Med. Chem., 34, 1640 (1991).
19. For the corresponding 5'-O-(4,4'-dimethoxytrityl)derivatives, see: T. R. Webb, H. Mitsuya, and S, Broder, J. Med. Chem., 31, 1475 (1988).
20. D. M. Brown, A. R. Todd, and S. Varadarajan, J. Chem. Soc., 868 (1957).
21. I. L. Doerr and J. J. Fox, J. Org. Chem., 32, 1462 (1967).

22. I. L. Doerr, R. J. Cushley, and J. J. Fox, J. Org. Chem., 33, 1592 (1968).

23. J. P. Horwitz, J. Chua, J. A. Urbanski, and M. Noel, J. Org. Chem., 28, 942 (1963).

24. In our experiments, both 4a and 4b were not crystalline in non-solvated form, the former being a foam and the latter an amorphous powder (The mono-ethyl acetate of 4a is crystalline[17]). However, mps of non-solvated 4a[17,18] and 4b[25] are described. Moreover, no convincing information for comparison with our compounds are available from the ill-resolved ^{1}H NMR data[18,25] and the erroneous chemical formula of 4a.[18]

25. JP (Japan Patent) 1-151595: mp of 4b, 144-146°C.

26. J. J. Fox, N. Young, and A. Bendich, J. Am. Chem. Soc., 79, 2775 (1957).

27. Lit[18] has attributed mp 128-133°C to 7b and mp 125-130°C to 8a.

28. T. Sasaki, K. Minamoto, and N. Kidokoro, O. P. P. International, 5, (2) 75 (1973).

29. We have encountered other similar results in the reactions of 2 with various nucleophiles.

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