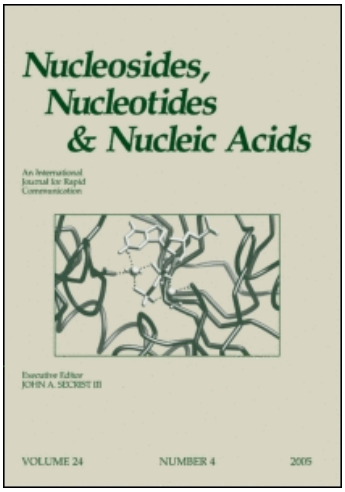

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Synthesis and Structure of 2',3'-Dideoxy-3'-fluoro-5-cyanouridine

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SYNTHESIS AND STRUCTURE OF 2',3'-DIDEOXY-3'-FLUORO-5-CYANOURIDINE

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ABSTRACT

The title compound was prepared by reaction of the 5-bromo congener with potassium cyanide in DMF. X-ray analysis revealed its solid state structure and the obtained conformation was compared to the conformation of 3'-azido-3'-deoxythymidine (AZT) and of 2',3'-dideoxy-3'-fluoro-5-chlorouridine, respectively, two very selective anti-HIV agents. They both show two separate molecules in their asymmetric unit, one of each fairly resembling the conformation of the title compound 4. The latter, however, displayed only very moderate activity.

INTRODUCTION

The advent of AIDS and the resulting need to develop strategies for the chemotherapy of this devastating disease has focussed attention mainly on dideoxynucleosides.[1] Recently, we reported on the very selective anti-HIV action of 2',3'-dideoxy-3'-fluoro-5-chlorouridine.[2] Introduction of chlorine at the C-5 position of the very potent but quite toxic 2',3'-dideoxy-3'-fluorouridine,[3] gave a 6-fold drop in activity in comparison to the parent compound, but a 500-fold reduction of cytotoxicity. This rendered the new analogue with a selectivity index of 1400, comparable to AZT.[4] Introduction of the halogen atoms chlorine, bromine and iodine at the C-5 position, yielded almost equally active compounds. Introduction of a 5-ethyl group on the other hand annihilated the activity.[3,5] A cyano group displays a total bond

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distance[6] [C(sp^2)-C≡N] and a molecular volume[7] in between the bond distances and the volumes of a chlorine and of an ethyl group, respectively. Therefore, keeping in mind that a 5-cyano group will have a greater electron withdrawing character,[6] it would be worthwhile to prepare and to evaluate 2',3'-dideoxy-3'-fluoro-5-cyanouridine as a potential anti-HIV compound, and to compare its solid state structure with the one of its 5-chloro analogue.

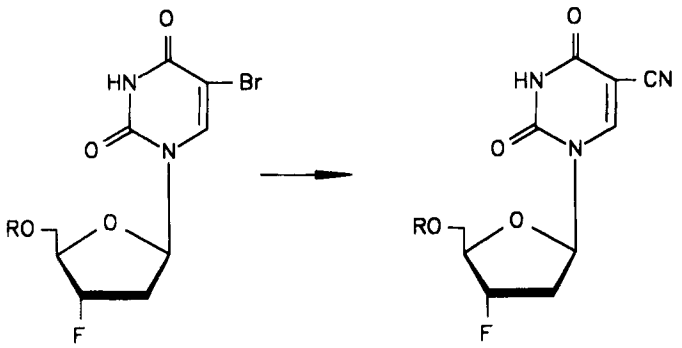
RESULTS AND DISCUSSION

Chemistry

Heat treatment of a protected 5-bromouridine derivative with cyanide affords the 5-cyanouridine analogue by a double addition-elimination reaction sequence as shown by Inoue and Ueda.[8] Repeating their reaction conditions using the alkaline labile acetyl group for protection of the ribose moiety, we found a seriously diminished yield due to considerable loss of the acetyl groups. We therefore decided to protect 2',3'-dideoxy-3'-fluoro-5-bromouridine (**1**) with the acid labile monomethoxytrityl group. Tritylation was straightforward affording **2** in 87% yield (FIG. 1). The obtained foam was converted in a one pot reaction to the 5-cyano derivative. Therefore, it was dissolved in anhydrous DMF, 6 equivalents of potassium cyanide were added under stirring, and the mixture was heated at 80°C. The intermediate 6-cyano derivative could be visualized by TLC analysis, but was not isolated. After 7 h, work-up and chromatographic purification afforded 68% of **3**. The presence of the cyano group at the 5-position was confirmed by ^{13}C NMR analysis. Treatment of this product with aqueous acetic acid for 3 h at room temperature afforded 80% of the final compound **4** after purification on silica gel (49% overall yield from **1**). After crystallization from acetone-hexane, the product was fully characterized and its solid state conformation was determined by X-ray analysis.

Conformational studies

2',3'-Dideoxy-3'-fluoro-5-cyanouridine: $C_{10}H_{10}N_3O_4F$, M_r=255.207, orthorhombic, $P2_12_12_1$, a=6.8173(2), b=10.1276(5), c=15.7968(9)Å, V=1090.65(9)Å^3, Z=4, D_m=1.56 , D_x=1.554 Mg m^{-3}, Ni-filtered Cu $K\alpha$ radiation, λ=1.54178Å, μ=1.1082 mm^{-1}, $F(000)$=528, T=298K. Final R=0.032 for 886 unique observed reflections. The N-glycosidic torsion angle χ



1 R=H
2 R=MMTr
3 R=MMTr
4 R=H

FIG. 1. Synthesis scheme.

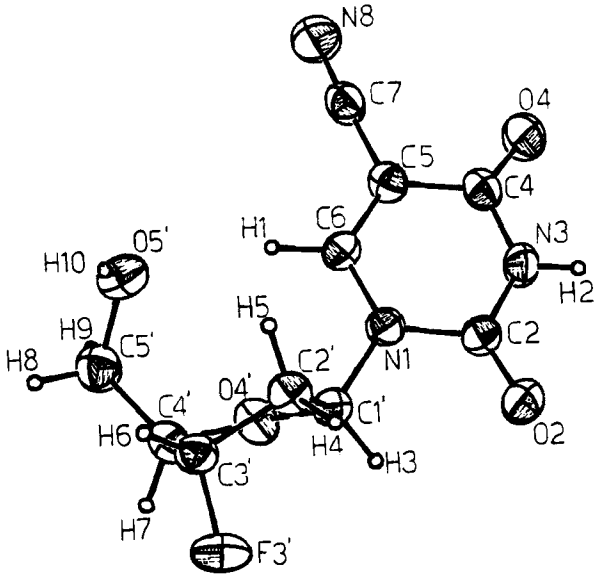


FIG. 2. An *ORTEP* view[10] showing the numbering scheme of the molecule.

TABLE 1. *Atomic coordinates*($x10^4$) *and equivalent isotropic thermal parameters with e.s.d.'s of the refined parameters in parentheses.*

				$B_{eq} = {}^4/_3 \Sigma_i\Sigma_j B_{ij}a_i.a_j$
Atom	x	y	z	B_{eq}(Å^2)
N1	4212(4)	1723(2)	3949(1)	2.57(4)
C2	5853(5)	1525(3)	4460(2)	2.66(5)
O2	7439(4)	1989(2)	4297(1)	3.54(4)
N3	5507(4)	755(3)	5157(1)	3.04(5)
C4	3798(5)	117(3)	5364(2)	2.96(6)
O4	3658(4)	-495(3)	6029(1)	4.55(5)
C5	2241(5)	288(3)	4769(2)	2.68(5)
C6	2480(5)	1101(3)	4091(2)	2.56(5)
C7	460(5)	-417(3)	4929(2)	3.28(6)
N8	-914(5)	-1021(3)	5074(2)	5.07(7)
C1'	4412(5)	2657(3)	3238(2)	2.68(5)
C2'	4490(5)	1997(3)	2371(2)	2.68(5)
C3'	3543(4)	3027(3)	1815(2)	2.65(5)
F3'	4970(3)	3988(1)	1620(1)	4.38(4)
C4'	2020(5)	3671(3)	2380(2)	2.83(6)
O4'	2733(3)	3487(2)	3232(1)	3.00(4)
C5'	-37(5)	3141(3)	2303(2)	3.60(7)
O5'	-179(4)	1747(2)	2420(1)	3.49(4)

has a value of -134.7(3)° in the *anti* range. The sugar pucker is $^2T_3$ with P=174(1)° and ψ_m=34(1)°. The C4'-C5' conformation is *+sc* with γ=54.3(4)°. The conformational parameters are in accordance with the IUPAC-IUB Joint Commission on Biochemical Nomenclature guidelines.[9] The molecules in the crystal structure are linked by an intensive network of hydrogen bonds, including three of the less common(C-)H...O types. An *ORTEP* view[10] with the atomic numbering is shown in FIG. 2. The final fractional atomic coordinates are given in Table 1. Fig. 3 shows the classical hydrogen bonds and the intramolecular hydrogen bond. Table 2

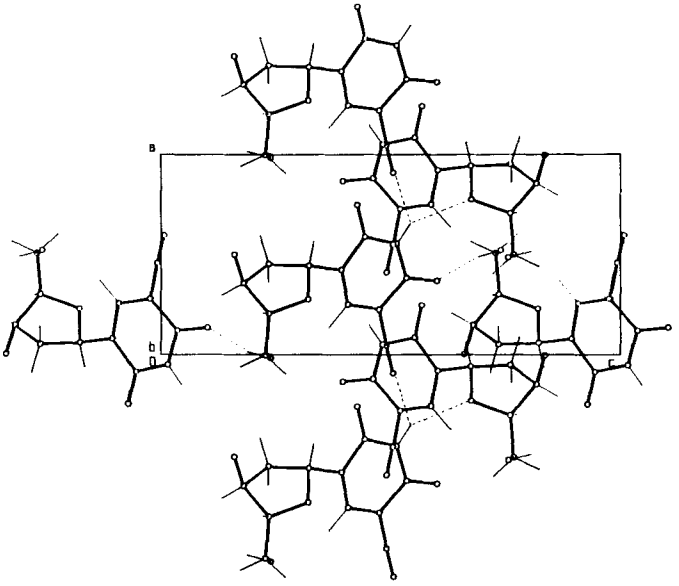


FIG. 3. A *PLUTO* plot[23] showing the intramolecular hydrogen bonds and the most important intermolecular hydrogen bonds in the crystal structure as indicated by dashed lines.

TABLE 2. *Geometry of intra- and intermolecular hydrogen bonds with e.s.d.'s in parentheses.(distances in Å, angles in°).*

A B C	AB	BC	AC	ABC
C6-H1....O5'(i)	1.03(3)	2.29(3)	3.269(4)	158(3)
N3-H2....N8(ii)	0.84(4)	2.47(4)	3.034(4)	125(3)
N3-H2....O4'(iii)	0.84(4)	2.43(3)	3.062(3)	132(3)
C2'-H4...O4(iv)	0.98(3)	2.73(3)	3.379(4)	124(2)
C3'-H6...O4(iv)	0.92(3)	2.52(3)	3.220(4)	133(2)
O5'-H10..O4(iv)	0.93(4)	1.82(3)	2.740(3)	168(3)
C4'-H7...O5'(v)	1.01(3)	2.55(3)	3.374(4)	139(2)

(i) x,y,z
(ii) x+1,y,z
(iii) x+1/2,-y+1/2,-z+1
(iv) -x+1/2,-y,z-1/2
(v) -x,y+1/2,-z+1/2

gives the geometry of all hydrogen bonds. The network of classical hydrogen bonds consists of one strong bond and two weaker bonds. The strong hydrogen bond involves O5', so that one molecule donates its O5'-H to the O4 of a symmetry related molecule (-x+1/2,-y, z-1/2). This bond creates a network of hydrogen bonds along the **c** crystallographic axis. The two weaker bonds both involve N3 (bifurcated or 'three-centered'-system[11]), so that the same molecule donates its N3-H to the N8 of one molecule only differing in a translation along the **a** crystallographic axis(x+1,y,z) and creating hereby a network of hydrogen bonds along the **a** crystallographic axis on one side and to the O4' of a symmetry related molecule(x+1/2,-y+1/2,-z+1) on the other side. Each molecule has also one intramolecular hydrogen bond: C6-H1...O5'. This non-classical hydrogen bond can reasonably be described as a hydrogen bond by satisfying the description established by Taylor and Kennard[12], *i.e.* this hydrogen bond favoures the *+sc* conformation with *anti*-oriented base moieties over the other two possible staggered forms(*-sc* and *ap*). Apart from the described hydrogen bonds there are three other (C-)H...O contacts present, which have also been interpreted as hydrogen bonds by Taylor and Kennard.[12] The conformation is almost identical with one of the two conformers of AZT.[13] This latter compound has two separate molecules in its asymmetric unit with χ = -125.9(5) and -172.0(5)° and sugar ring pucker P = 171(1) and 213(1)°, respectively, compared to χ = -134.7(3)° and P = 174(1)° for structure **4**. Although this compound has a high anti-structure and strong puckering believed to be necessary to display good anti-HIV activity,[14] it only proved marginally active [ED_{50} of 50 μM (for experimental conditions, see ref. 2) when evaluated *in vitro* in a MT-4 cell system].[15] On the other hand, 2',3'-dideoxy-3'-fluoro-5-chlorouridine, which has two separate molecules in its asymmetric unit with χ = -168.8(3)° and -131.3(3)°, and a sugar ring pucker P = 179(1)° and 163(1)°, respectively,[16] shows a high anti-HIV activity.[2] As in the case of 2',3'-dideoxy-3'-fluoro-5-ethyluridine, which also displays very moderate activity,[3] carrying a larger substituent at the 5-position (either a 5-ethyl or a 5-cyano group) might hamper the interaction with kinases necessary for the phosphorylation of these compounds.

EXPERIMENTAL SECTION

Methods

The melting point was determined with a Büchi-Tottoli apparatus and is uncorrected. Infrared spectra were recorded with a Perkin-Elmer 257 spectrophotometer on samples in potassium bromide disks at 1.5%. Ultraviolet spectra were recorded with a Beckman UV 5230 spectrophotometer. The ^{1}H NMR and ^{13}C NMR spectra were determined with a JEOL FX 90Q spectrometer with tetramethylsilane as internal standard (s=singlet; d=doublet; t=triplet; m=multiplet; br=broad signal). Electron impact mass spectra (70 eV) were recorded on a AEI-MS12 mass spectrometer. B: base, S: sugar. Elemental analyses were carried out by Dr. Rozdzinski at the Institut für Organische Chemie in Stuttgart. Precoated Merck silica gel F254 plates were used for TLC. Column chromatography was performed on Merck silica gel (0.063-0.200 mm). Anhydrous N,N-dimethylformamide was obtained by distillation with benzene followed by distillation *in vacuo*. Pyridine was dried by distillation after it had been refluxed on potassium hydroxide for 24 h.

5'-O-Monomethoxytrityl-2',3'-dideoxy-3'-fluoro-5-bromouridine (2). An amount of 370 mg (1.19 mmol) of **1**[2] was coevaporated twice with anhydrous pyridine. After dissolving the oily residue in 10 mL of pyridine, 0.6 g (1.95 mmol) monomethoxytrityl chloride was added and the mixture was stirred for 3 h at 40°C. The contents were diluted with 100 mL of $CHCl_3$ and the organic layer was washed twice with 50 mL of a 5% $NaHCO_3$ solution, dried (Na_2SO_4), evaporated and coevaporated with toluene. The residue was purified on silica gel [40 g, elution: 1) $CHCl_3$-hexane 1:1, 2) $CHCl_3$]. Evaporation of the combined fractions gave 600 mg (1.03 mmol, 87%) of a yellow foam.

UV (MeOH) λ_{max} 277 and 234 nm, λ_{min} 255 nm. ^{1}H NMR ($CDCl_3$) δ 2.3-3.0 (m, H-2', H-2"), 3.41 (m, H-5', H-5"), 3.77 (s, CH_3O), 4.34 (dt, $J_{4',F}$ = 27.7 Hz, H-4'), 5.27 (dd, J = 4.4 Hz, $J_{3',F}$ = 53.6 Hz, H-3'), 6.36 (dd, J = 5.5 and 9.2 Hz), 6.84 (d) and 7.15-7.45 (m) (trityl), 8.08 (s, H-6) ppm. ^{13}C NMR ($CDCl_3$) δ 39.3 (C-2', J = 20.8 Hz), 55.2 (CH_3O), 63.1 (C-5', J = 11 Hz), 84.5 (C-4', J = 25.6 Hz), 85.4 (C-1'), 87.6 (Ph_3C), 94.1 (C-3', J = 178.2 Hz), 97.4 (C-5), 138.8 (C-6), 149.5 (C-2), 158.8 (C-4) ppm + trityl signals.

5'-O-Monomethoxytrityl-2',3'-dideoxy-3'-fluoro-5-cyanouridine (3). The foam of the previous preparation was dissolved in 25 mL anhydrous

DMF and 400 mg (6 mmol) of potassium cyanide was added. The mixture was stirred under nitrogen at 80°C. TLC ($CHCl_3$-acetone 9:1) at first showed a trityl positive spot with slightly higher mobility than the reference compound, which gradually was converted to a more polar compound. After 7 h DMF was removed *in vacuo* and the residue was dissolved in $CHCl_3$ (100 mL). The organic layer was washed twice with a 5% $NaHCO_3$ solution, dried (Na_2SO_4) and evaporated. Purification on silica gel (hexane-$CHCl_3$ 1:1, followed by $CHCl_3$) afforded 370 mg (0.7 mmol, 68%) of a white foam. UV (MeOH) λ_{max} 230, 277, 281 (sh) nm, λ_{min} 253 nm. ^1H NMR ($CDCl_3$) δ 2.3-3.0 (m, H-2', H-2"), 3.42 (m, H-5', H-5"), 3.79 (s, CH_3O), 4.44 (dt, $J_{4',F}$ = 25 Hz, H-4'), 5.31 (dd, J = 5 Hz, $J_{3',F}$ = 53.6 Hz, H-3'), 6.19 (dd, J = 5.0 and 8.8 Hz, H-1'), 6.85 (d) and 7.15-7.45 (m) (trityl), 8.26 (s, H-6), 9.55 (brs, NH) ppm. ^{13}C NMR ($CDCl_3$) δ 40.1 (C-2', J = 23 Hz), 55.2 (CH_3O), 63.1 (C-5', J = 11 Hz), 85.3 (C-4', J = 25.6 Hz), 87.1 (C-1'), 87.8 (Ph_3C), 90.3 (C-5), 94.1 (C-3', J = 179.4 Hz), 113.1 (CN), 147.3, 148.2 (C-2, C-6), 162.6 (C-4) ppm + trityl signals.

2',3'-Dideoxy-3'-fluoro-5-cyanouridine (4). The foam **3** was treated with 30 mL of 80% aqueous acetic acid for 3 h at room temperature. After evaporation and coevaporation with toluene (2 x), the residue was dissolved in MeOH and adsorbed on about 4 g of silica gel, which was put on top of a small silica gel column (20 g). Elution with $CHCl_3$-MeOH (97:3) and crystallisation from acetone-hexane yielded 143 mg (0.56 mmol, 80%) of colorless needles. mp 178-180°C (dec); UV (MeOH) λ_{max} 278 nm (ε 12250), λ_{min} 237 nm; IR 2250 cm^{-1} (CN); MS (m/z) 255 (M), 138 (base + 2 H), 137 (base + H), 119 (sugar, 100%), 99 (sugar - HF); ^1H NMR (DMSO-d_6) δ 2.1-2.7 (m, H-2', H-2"), 3.65 (d, J = 3.5 Hz, H-5', H-5"), 4.25 (dt, $J_{4',F}$ = 26.4 Hz, H-4'), 5.30 (dd, $J_{3',F}$ = 54.5 Hz, H-3'), 6.10 (dd, J = 6.2 and 8.0 Hz, H-1'), 8.72 (s, H-6) ppm; ^{13}C NMR (DMSO-d_6) δ 38.7 (C-2', J = 19.5 Hz), 60.8 (J = 11.0 Hz), 86.1 (C-4', J = 23.2 Hz), 86.3 (C-1', s), 88.9 (C-5), 94.6 (C-3', 174.6 Hz), 114.6 (CN), 149.3 (C-2), 149.8 (C-6), 160.3 (C-4) ppm. Anal. calculated for $C_{10}H_{10}FN_3O_4$: C, 47.06; H, 3.95; N, 16.47. Found: C, 47.06; H, 4.03; N, 16.71.

Structure Determination

Colourless prismatic crystals from an acetone-hexane solution, the selected crystal had dimensions ~ 0.25 x 0.2 x 0.2 mm. Density measured

by flotation in n-heptane/CCl_4. Hilger & Watts computer-controlled four-circle diffractometer, Ni-filtered Cu $K\alpha$ radiation, $\omega/2\theta$ scan technique ($2\theta_{max}=130^{o}$, $-8\leq h\leq 0$, $0\leq k\leq 12$, $-19\leq l\leq 19$), cell dimensions by least-squares refinement of the setting angles of 24 reflections with $43<2\theta<48^{o}$, spacegroup $P2_12_12_1$ from systematic absences $h00$ for h odd, $0k0$ for k odd and $00l$ for l odd. Four standard reflections (105, 025, 124, 230) monitored after every 50 reflections showed no significant decrease in intensity per hour, 2054 reflections measured, 1063 unique reflections , 887 unique observed reflections [$F>6\sigma(F)$]. One reflection (002) badly affected by extinction was eliminated. Lorentz-polarisation corrections, absorption corrections by the method of North,[17] based on two reflections (-200, -400) with values between 0.9928 and 0.9533, scattering factors from Cromer[18] and Stewart[19] (for H). $R_{int}=0.019$. The structure was solved by *MULTAN 82*.[20] The *E*-map calculated from the solution with the best figure of merit revealed all of the 18 non-hydrogen atoms. A difference synthesis revealed the position of the hydrogen atom attached to atom O5'. All other hydrogen atoms were included at calculated positions (C-H and N-H distances 0.95Å). The hydrogen atoms were refined with given fixed isotropic temperature factors 1.3 times that of the parent atom. All other atoms were refined anisotropically on F by full-matrix least-squares; the refinement converged at $R=0.032$ (including unobserved reflections), $wR=0.046$, $S=5.056$, $w=(C_0+C_1*|F_o|+C_2*|F_o|^2+C_3*|F_o|^3)^{-1}$, where $C_0=4$, $C_1=0.0001$, $C_2=0.00005$, $C_3=1x10^{-8}$. 193 refined parameters, max. shift/e.s.d.=0.03; min. and max. electron density -0.219 and 0.148 e $Å^{-3}$. The number of reflections per refined variable was 886/193 = 4.6. All calculations were performed on a PDP-11/73 microcomputer using *SDP/PDP*[21] and *PARST*.[22]

Supplementary Material Available

All further information concerning the X-ray analysis is available on request at the authors' address.

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