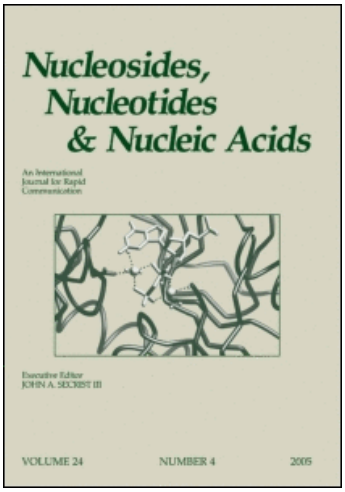

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Synthesis of 5-Benzyl and 5-Benzyloxybenzyl 2,2'-Anhydrouridines and Related Nucleoside Analogs as Inhibitors of Uridine Phosphorylase

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SYNTHESIS OF 5-BENZYL AND 5-BENZYLOXYBENZYL 2,2'-ANHYDROURIDINES AND RELATED NUCLEOSIDE ANALOGS AS INHIBITORS OF URIDINE PHOSPHORYLASE

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Abstract: Furanosyl analogs of BAU (5-benzylacyclouridine) and BBAU (5-benzyloxybenzylacyclouridine), two potent inhibitors of uridine phosphorylase, were synthesized and evaluated as potential cancer chemotherapeutic agents. The analogs included ribosides, 2,2'-anhydro nucleosides, arabinosides and deoxyribosides. The anhydrouridine intermediates were potent inhibitors of uridine phosphorylase and good potentiators of FdUrd activity in human tumor cells in culture.

Abbreviations:

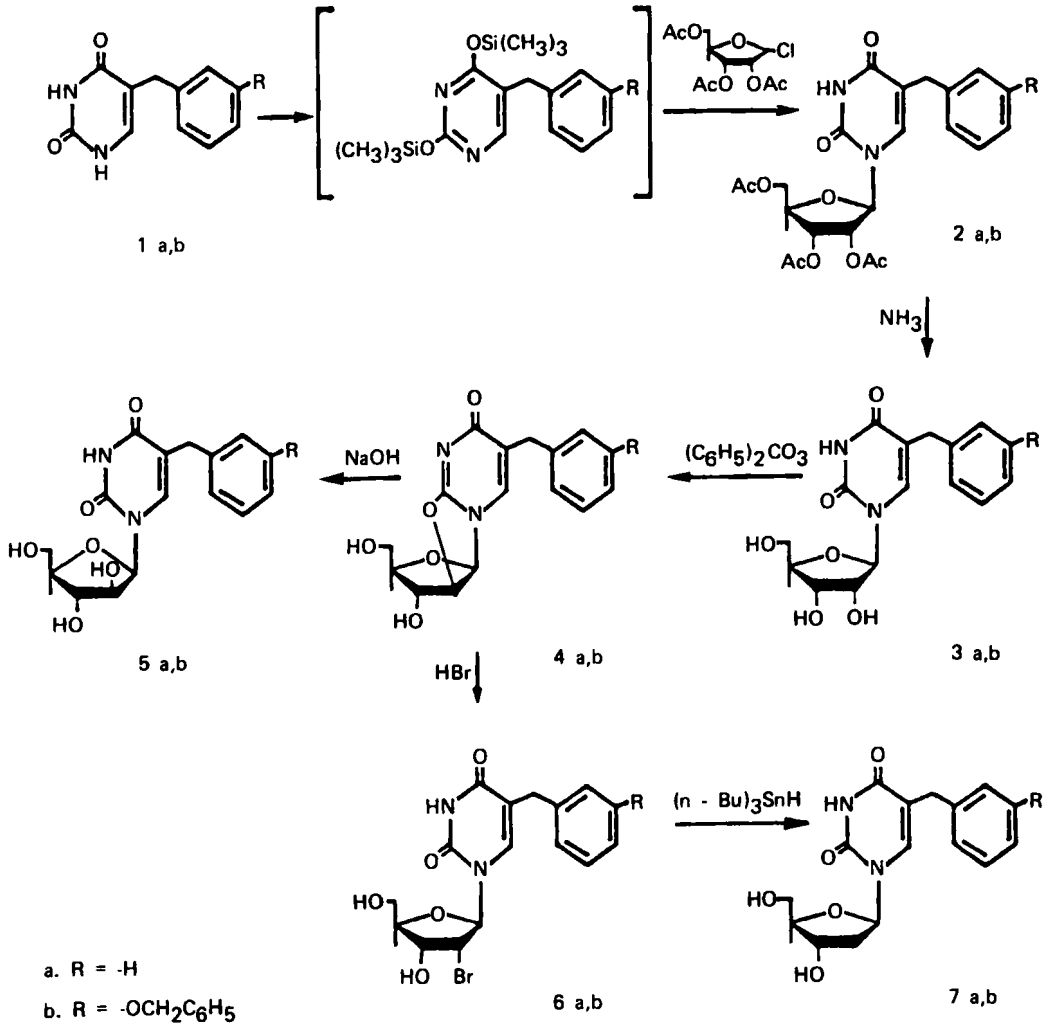
Acyclo-:	2'-Hydroxyethoxymethyl-
BAU:	5-Benzylacyclouridine
BBAU:	5-(m-Benzyloxybenzyl)acyclouridine
BU:	5-Benzyluracil
BBU:	5-Benzyloxybenzyluracil
FdUrd:	5-Fluoro-2'-deoxyuridine
FUra:	5-Fluorouracil
ABU:	2,2'-Anhydro-5-benzyluridine
ABBU:	2,2'-Anhydro-5-benzyloxybenzyluridine
AEU:	2,2'-Anhydro-5-ethyluridine
HM-acyclo-:	1'-Hydroxymethyl-2'-hydroxyethoxymethyl-

The benzylacyclouridines BAU (5-benzyl-1-(2'-hydroxyethoxymethyl) uracil) and BBAU (5-benzyloxybenzyl-(2'-hydroxyethoxymethyl)uracil)[1,2] and their HM- (1'-hydroxymethyl-)[3] and AM- (1'-aminomethyl-)[4] analogs are potent inhibitors of uridine phosphorylase, an enzyme important in the salvage pathway of uridine metabolism. The acyclo moiety consists

of a linear side chain equivalent to the $C_{1'}$-O-$C_{4'}$-$C_{5'}$ portion of ribose or deoxyribose. Since inhibitors of this enzyme can also inhibit the phosphorolysis of uridine nucleoside analogs used in cancer chemotherapy, they may have clinical use as potentiators of the cytotoxic effect of the drug FdUrd against human solid tumor cells in vitro and in vivo[5]. By inhibiting the intracellular phosphorolysis of FdUrd to the less selectively toxic FUra, a uridine phosphorylase inhibitor would extend the action of a given dose of FdUrd over a longer period of time and thus be of potential clinical benefit[1,6,7]. In the course of our study of potent uridine phosphorylase inhibitors related to BAU and BBAU, we now report the synthesis of a series of BAU and BBAU analogs containing three common furanosyl groups as the sugar moieties. In addition, we have found the anhydrobenzyluridines, prepared as synthetic intermediates, to be active both as inhibitors of uridine phosphorylase and as potentiators of FdUrd cytotoxicity. Ribosyl-, arabinosyl-, and deoxyribofuranosides are currently under biological testing.

5-Benzyl and 5-benzyloxybenzyl ribonucleosides were synthesized by a modified Hilbert-Johnson[8] procedure from triacetylribosyl-1-chloride and bis-silylated derivatives of the respective uracil bases, using mercuric cyanide as a catalyst (as shown in the Scheme). UV and NMR data confirmed to site of glycosidation to be at N-1, and the configuration to be β, as is usual with this procedure. The 2,2'-anhydronucleosides of BU and BBU were synthesized from the corresponding ribonucleosides by the direct and convenient method of Hampton and Nichol[9], using diphenyl carbonate as shown in Scheme I. The shift of the ultraviolet absorption maxima of the benzyluridines from 268 to 255 nm during this reaction was taken to be indicative of the formation of anhydronucleoside, and is consistent with the shift observed by Brown, Todd and Varadarajan[10]. The ultraviolet absorption maxima returned to 268 nm for all of the compounds obtained subsequently.

Ring opening of the anhydronucleosides could then be accomplished with aqueous alkali to yield the respective arabinosides; or with hydrobromic acid in DMF to give 2'-substituted bromides. The bromides were reduced with tributyltin hydride in DMF in the presence of AIBN (2,2'-azobis-2-methylpropionitrile) to deoxyribonucleosides by the method of Hřebabecký and Beránek[11].



SCHEME 1

2,2'-Anhydronucleosides have been reported by Veres et al[12] to be potent inhibitors of uridine phosphorylase. They found the most active of several substituted 2,2'-anhydrouridines to be the 5-ethyl derivative. The anhydrouridines were therefore prepared for biological evaluation as well as for use as synthetic intermediates. The finding of increased binding activity associated with hydrocarbon substituents at the 5-position of the pyrimidine ring is consistent with the hypothesis of a hydrophobic binding region adjacent to the active site of the enzyme[1,2,6,7].

Biological Studies

Apparent inhibition constants of anhydrobenzyl and anhydrobenzyloxybenzyl uridines **4a** and **4b** and a sample of 2,2'-anhydro-5-ethyl uridine[12] prepared by the same procedure were determined, using uridine phosphorylase from the 105,000 x g supernatant of human liver homogenates by the procedure of Naguib et al[13]; and assayed as previously described[1]. With competitive inhibition, generally the case with these analogs, apparent K_i is equal to $K_i(1 + [S]/K_m)$, with true K_i values being lower than apparent K_i values by a factor of $1 + [S]/K_m$. Apparent K_i values for samples of AEU, ABU and ABBU, obtained with uridine phosphorylase prepared from human liver are shown in Table 1 in com-parison with apparent K_i values of some benzylacyclouridines measured similarly. The anhydrouridines were approximately as potent inhibitors of uridine phosphorylase as the corresponding HM-acyclouridines, with the potency of the benzylanhydrouridines of the same order of magnitude, if a little less than the potency of the ethyl derivative.

Potentiation of the growth inhibiting effect of FdUrd by the two benzylanhydrouridines **4a** and **4b** in comparison with ethylanhydrouridine was evaluated against the cell lines DAN (human pancreatic carcinoma) and LX-1 (human lung carcinoma) in culture (Table 2) as previously described[5].

All three 2,2'-anhydrouridines potentiated the cytotoxic action of FdUrd against DAN and LX-1 cells in culture (Table 2). Although the two anhydrobenzyluridines were a little less potent as uridine phosphorylase inhibitors than the 5-ethyl analog, they were generally

Table 1. Apparent Inhibition Constants for Uridine Phosphorylase prepared from Cytosol of Human Liver.

Compound	App. K_i (μM)[a]
BAU[b]	3.97 ± 0.30
BBAU[b]	1.95 ± 0.23
HM-BAU[b]	2.53 ± 0.33
HM-BBAU[b]	0.65 ± 0.07
AEU	0.47 ± 0.03
ABU	2.40 ± 0.10
ABBU	0.74 ± 0.05

a. Values ± standard error of at least three determinations.
b. From Reference 13.

Table 2. % Inhibition[a] of DAN and LX-1 Cells in Culture

FdUrd (μM)	Potentiator: None	AEU[b] 50 μM	ABU[b] 50 μM	ABBU[b] 50 μM
DAN				
1.0	63.1 ± 2.2[c]	81.0 ± 5.9[b,d]	90.2 ± 2.4[b,d]	91.2 ± 1.9[b,d]
0.1	15.3 ± 2.2	27.5 ± 1.7	31.1 ± 8.5	39.9 ± 3.7
LX-1				
1.0	52.0 ± 3.2[a]	65.5 ± 5.7[b]	69.5 ± 3.7[b]	98.0 ± 1.3[b]
0.1	11.6 ± 5.1	22.1 ± 1.5	37.1 ± 8.5	47.4 ± 3.1

a. Growth inhibition was calculated as the reduction in the number of cell doublings after 72 hr incubation as determined by the trypan blue exclusion method. Cells were pretreated with potentiator for 5 minutes before the addition of FdUrd. In each experiment the non-treated controls reached at least 3 doublings.

b. Neither cell line was inhibited by AEU, ABU or ABBU alone at 50 μm concentration in the absence of FdUrd.

c. Mean ± S.E.

d. The values with potentiator are significantly different at $P < 0.05$ from control value.

more effective as potentiators of the action of FdUrd. ABBU was the more effective of the two anhydrobenzyluridines, as to be expected from potentiation data obtained with other 5-benzylacyclouridine analogs[3-5]. The observation of better potentiation in DAN than in LX-1 could be due to the lower ratio of thymidine phosphorylase to uridine phosphorylase in this cell line, in accordance with previous studies with benzylacyclouridines[5].

Chemical Synthesis

Melting points were determined on a Gallenkamp apparatus and are uncorrected. Ultraviolet absorption maxima and extinction coefficients were determined using a Perkin-Elmer Model 402 recording spectrophotometer and ^1H NMR spectra were run on a Bruker WM-250 or WM-400 instrument in DMSO-d_6 or deuteropyridine, using trimethylsilane as an internal standard. Analytical TLC was run on Merck silica gel 60 F-254 plates using methylene chloride-ethanol solvent systems; and preparative TLC on Analtech silica gel GF plates (2 mm). All removal of solvents was done under vacuum on a rotary evaporator unless otherwise noted. Analyses were performed by the Baron Consulting Co. of Orange, Conn., and the Galbraith Laboratories of Knoxville, Tenn.

5-benzyl-1-(2',3',5'-triacetyl-B-D-ribofuranosyl)uracil (2a).

A suspension of dry, powdered 5-benzyluracil (Ia, 20.0 g, 0.1 mole) and 0.5 g of $(NH_4)_2SO_4$ in 160 ml of hexamethyldisilazane was heated under reflux for 4 hours with the exclusion of moisture and stored at room temperature overnight. The reaction mixture was evaporated to dryness under diminished pressure. The residue was dissolved in xylene (150 ml) and evaporated again to remove any remaining hexamethyldisilazane.

Dry hydrogen chloride gas was bubbled into a solution of 1,2,3,5-tetra-O-acetyl-B-D-ribofuranose (40.0 g, 136 mmoles) in 150 ml of CH_2Cl_2 at 0-5°C for 2.5 hrs. After standing in the refrigerator overnight, the solvent and excess HCl were removed under vacuum. The residue was dissolved in toluene (150 ml) and reevaporated.

The residue was then redissolved in dry toluene (150 ml) and added to the bis-trimethylsilyl derivative of **1a**. After the addition of

1.5 g of $Hg(CN)_2$, the reaction mixture was stirred at 60-70°C for 6 hrs under anhydrous conditions and again allowed to stand at room temperature overnight.

The mixture was then washed with water, dried over anhydrous $MgSO_4$, filtered and evaporated. The residual oil was passed through a silica gel column. Elution using CH_2Cl_2-MeOH (30:1) gave 19.5 g of **2a** (43%). NMR(DMSO-d_6): δ 2.01, 2.06, 2.09 (3s, 9H, CH_3 of Acetate), 3.55 (s, 2H, CH_2 at C_5), 4.17-4.35 (m, 3H, C_4'-H and C_5'-H), 5.34 (dd, 1H, C_3'-H, $J_{2',3'}$=5 Hz, $J_{3',4'}$=5 Hz), 5.48 (dd, 1H, C_2'-H, $J_{1',2'}$=6 Hz, $J_{2',3'}$=6 Hz), 5.90 (d, 1H, C_1'-H, $J_{1'2'}$=6 Hz), 7.15-7.31 (m, 5H, ArH), 7.68 (s, 1H, C_6-H), 11.50 (br.s, 1H, N_3-H).
Anal. Calc'd for $C_{22}H_{24}N_2O_9 \cdot 0.75\ H_2O$: C, 55.75; H, 5.42; N, 5.91. Found: C, 55.92; H, 5.46; N, 5.51.

5-(m-Benzyloxybenzyl)-1-(2',3',5'-triacetyl-β-D-ribofuranosyl)uracil (2b).

Compound 1b (10 g, 32 mmoles) was converted in a similar manner to its 2,4-bis-trimethylsilyl derivative and treated with excess triacetylribosyl chloride prepared as above, in dry toluene in the presence of $Hg(CN)_2$ to yield 6.8 g of **2b** (37%), m.p. 67-70°C. NMR(DMSO-d_6): δ 1.99, 2.05, 2.08 (3s, 9H, CH_3 of Acetate, 3.52 (s, 2H, CH_2 at C_5), 4.14-4.35 (m, 3H, C_4'-H and C_5'-H), 5.07 (s, 2H, CH_2 of term. Bzl), 5.34 (dd, 1H, C_3'-H, $J_{2',3'}$=5 Hz, $J_{3',4'}$=5 Hz), 5.49 (dd, 1H, CH_2'-H, $J_{1',2'}$=5 Hz, $J_{2',3'}$=6 Hz), 5.91 (d, 1H, C_1'-H, $J_{1',2'}$=5 Hz), 6.79-6.91 (m, 3H, o and p-H of inner Bzl), 7.18 (t(dd), 1H, m-H of inner Bzl, J=8 Hz), 7.29-7.47 (m, 5H, ArH of term. Bzl), 7.70 (s, 1H, C_6-H), 11.50 (br.s, 1H, N_3-H).
Anal. Calc'd for $C_{29}H_{30}N_2O_{10} \cdot H_2O$: C, 59.58; H, 5.52; N, 4.79. Found: C, 59.52; H, 5.66; N, 4.83.

5-Benzyl-1-β-D-ribofuranosyluracil (3a).

A solution of 24 g of the triacetate **2a** (52 mmoles) in 200 ml of MeOH was saturated with gaseous NH_3 with cooling in an ice bath until the volume had increased by 40 ml (20%). The reaction mixture was refrigerated for 12 hours at 4°C (overnight) and then allowed to stand for 4 hours at room temperature. After removing the solvent, the residue was dissolved in hot water, filtered and cooled to yield 12.0 g

of **3a** (69%). M.p. 182-183°C. UV (pH 1): λ_{max} 268 nm (9300), (pH 11): λ_{max} 268 nm (7400); NMR(DMSO-d_6): δ 3.48-3.67 (m, 4H, C_5'-H and CH_2 at C_5), 3.84 (dd, 1H, C_4'-H, J_a and J_b=3 Hz), 3.97 (dd, 1H, C_3'-H, J_a and J_b=4 Hz), 4.03 (dd, 1H, C_2'-H, J_a and J_b=4 Hz), 5.03-5.14 (m, 2H, C_2'-OH and C_5'-OH, D_2O-labile), 5.40 (m, 1H, C_3'-OH, D_2O-labile), 5.75 (d, 1H, C_1'-H, $J_{1',2'}$=6 Hz), 7.15-7.30 (m, 5H, ArH), 7.85 (s, 1H, C_6-H), 11.33 (s, 1H, N_3-H).

Anal. Calc'd for $C_{16}H_{18}N_2O_6$: C, 57.48; H, 5.43; N, 8.38.
Found: C, 57.86; H, 5.51; N, 8.30

5-(m-Benzyloxybenzyl)-1-β-D-ribofuranosyl)uracil (**3b**).

Compound **2b** (20.0 g, 35.3 mmoles) was similarly deblocked to yield 9.5 g (61%) of the ribofuranosyl analog **3b**. M.p. 161-164°C, UV(pH 1): λ_{max} 270nm (10,300; (pH 11): λ_{max} 270 nm (10,000). NMR(DMSO-d_6): δ 3.53-3.68 (m, 4H, C_5'-H and CH_2 at C_5), 3.85 (dd, 1H, C_4'-H, J_a and J_b=3 Hz), 3.98 (dd, 1H, C_3'-H, J_a, J_b=3 Hz), 4.05 (dd, 1H, C_2'-H, J_a and J_b=3 Hz), 5.06 (m, 4H, CH_2 of term. Bzl(2), C_2'-OH and C_5'-OH, 2H are D_2O-labile), 5.40 (d, 1H, C_3'-OH, J=3 Hz, D_2O-labile), 5.80 (d, 1H, C_1'-H, $J_{1',2'}$=3 Hz), 6.78-6.92 (m, 3H, o and p-H of inner Bzl), 7.19 (t, 1H, m-H of inner Bzl, J=5 Hz), 7.36-7.48 (m, 5H, ArH of term. Bzl), 7.90 (s, 1H, C_6-H), 11.34 (s, 1H, N_3-H).

Anal. Calc'd for $C_{23}H_{24}N_2O_7$: C, 62.72; H, 5.50; N, 6.36.
Found: C, 62.75; H, 5.55; N, 6.28.

5-Benzyl-1-(2,2'-anhydro-β-D-arabinofuranosyl)uracil (**4a**).

According to the procedure of Hampton and Nichol[9], a mixture of the ribofuranosyl analog **3a** (5.0 g, 15 mmole), diphenyl carbonate (5.0 g, 23 mmole), and $NaHCO_3$ (0.10 g) in dimethyl formamide (10.0 ml) was heated at 150°C for 30 minutes under nitrogen. The DMF was removed by spin evaporation and the residue washed with Et_2O by decantation and then stirred to induce crystallization. Recrystallization from EtOH and drying yielded 3.55 g (75%), m.p. 227-228°C. UV(EtOH): λ_{max} 254 nm (8300). NMR(pyr-d_5): δ3.68 (d, 1H, C_5'-H, J=15 Hz), 3.85-3.94 (m, 2H, CH_2 at C_5), 3.97 (d, 1H, C_5'-H, J=15 Hz), 4.79 (dt, 1H, C_4'-H, $J_{3',4'}$=2 Hz, $J_{4',5'}$=5 Hz), 4.96 (s, >2H, H_2O and OH), 5.16 (m, 1H, C_3'-H), 5.67 (d, 1H, C_2'-H, J=6 Hz), 6.59 (d, 1H, C_1'-H, J=6 Hz), 7.00-8.10 (m, 7H, ArH and C_6-H). No peak at 11.3 (N_3-H).

Anal. Calc'd for $C_{16}H_{16}N_2O_5$: C, 60.75; H, 5.10; N, 8.85.
Found: C, 60.45; H, 5.16; N, 9.14.

5-(m-Benzyloxybenzyl)-1-(2,2'-anhydro-β-D-arabinofuranosyl)uracil (4b).

The same procedure was used to prepare the anhydro derivative **4b** from 1.0 g (2.3 mmoles) of the corresponding ribonucleoside **3b**, to yield 0.55 g (57%), m.p. 84-90°C. UV(EtOH): λ_{max} 255 nm (9400). NMR(pyr-d_5): δ3.70 (d, 1H, C_5'-H, J=15 Hz), 3.90 (m, 1H, C_4'-H), 4.02 (d, 1H, C_5'-H, J=15 Hz), 4.79 (dt, 1H, C_4'-H, $J_{3',4'}$=5 Hz, $J_{4',5'}$2 Hz), 4.96 (s, >2H, H_2O and 2 OH), 5.06, (s, 2H, CH_2 of term. Bzl), 5.18 (m, 1H, C_3'-H), 5.67 (d, 1H, C_2'-H, J=6 Hz), 6.60 (d, 1H, C_1'-H, J=6 Hz), 6.93-7.06 (m, 3H, o and p-H of inner Bzl), 7.30-8.11 (m, 7H, rest of ArH and C_6-H). No peak at 11.3 (N_3-H).
Anal. Calc'd for $C_{23}H_{22}N_2O_6 \cdot H_2O$: C, 62.72; H, 5.49; N, 6.36.
Found: C, 62.49; H, 5.61; N, 6.31.

5-Benzyl-1-(β-D-arabinofuranosyl)uracil (5a).

A solution of 500 mg (1.58 mmoles) of the anhydronucleoside **4a** in 20 ml of 0.1 M NaOH was stirred at room temperature for 1.5 hours and then neutralized with Rexyn 101 (H^+). The resin was filtered off and washed with water. The combined filtrates were evaporated under vacuum. The residue was chromatographed on a silica gel preparative plate, and the appropriate band scraped off and eluted with CH_2Cl_2-MeOH (20:1) to give 350 mg of the arabinoside **5a** (66%), m.p. 211-212°C. UV(pH 1): λ_{max} 269 (9000); (pH 11): λ_{max} 269 nm (7690). NMR(DMSO-d_6): δ 3.45-3.60 (m, 4H, CH_2 at C_5 and C_5'-H). 3.70 (dd, 1H, C_4'-H, $J_{3',4'}$=4 Hz, $J_{4',5'}$=4 Hz), 3.89 (dd, 1H, C_3'-H, $J_{2',3'}$=3 Hz, $J_{3',4'}$=3 Hz), 4.01 (br.s, 1H, C_2'-H), 5.03 (br.s, 1H, C_5'-OH), 5.45 (d, 1H, C_3'-OH, J=3 Hz), 5.57 (br.s, 1H, C_2'-OH), 5.99 (d, 1H, C_1'-H, J=4 Hz), 7.14-7.32 (m, 5H, ArH), 7.54 (s, 1H, C_6-H), 11.30 (s, 1H, N_3-H).
Anal. Calc'd for $C_{16}H_{18}N_2O_6$: C, 57.48; H, 5.43; N, 8.38.
Found: C, 57.49; H, 5.73; N, 8.36.

5-(m-Benzyloxybenzyl)-1-(β-D-arabinofuranosyl)uracil (5b).

A suspension of 1.0 g (2.37 mmoles) of the anhydronucleoside **4b** in a mixture of 40 ml of 0.1 M sodium hydroxide and 20 ml of methanol was stirred at room temperature overnight and then neutralized with Rexyn 101 (H^+). The resin was filtered off and washed with water. The combined filtrates were evaporated under vacuum. The residue was applied to a preparative chromatography plate and the band containing

5b eluted with CH_2Cl_2-MeOH (20:1) to give 0.80 mg of **5b** (77%). UV(pH 1): λ_{max} 270 nm (12,000); (pH 11): λ_{max} 270 nm (12,000). After recrystallization from EtOH-Acetone it melted at 195-6°C. NMR(DMSO-d_6): δ 3.47-3.62 (m, 4H, CH_2 at C_5 and C_5'-H), 3.72 (dd, 1H, C_4'-H, $J_{3',4'}$=4 Hz, $J_{4',5'}$=4 Hz), 3.91 (dd, 1H, C_3'-H, $J_{2',3'}$=4 Hz, $J_{3',4'}$=4 Hz), 4.01 (dd, 1H, C_2'-H, $J_{1',2'}$=4 Hz, $J_{2',3'}$=4 Hz), 5.05 (s, 3H, CH_2 of term.Bzl and C_5'-OH), 5.44 (d, 1H, C_2'-OH, J=4 Hz), 5.59 (d, 1H, C_3'-OH, J=5 Hz), 6.00 (d, 1H, C_1'-H, J=5 Hz), 6.77-6.87 (m, 3H, o- and p-H of inner Bzl), 7.18 (t, 1H, m-H of inner Bzl, J=8 Hz), 7.31-7.47 (m, 5H, ArH of term.Bzl), 7.56 (s, 1H, C_6-H), 11.30 (s, 1H, N_3-H).
Anal. Calc'd for $C_{23}H_{24}N_2O_7$: C, 62.72; H, 5.50; N, 6.36.
Found: C, 62.70; H, 5.56; N, 6.29.

5-Benzyl-2'-bromo-2'-deoxyuridine (**6a**).

A solution of 1.6 g (5.1 mmoles) of anhydronucleoside in a mixture of 18 ml of 8% HBr in DMF was heated at 100°C for 15 minutes. After evaporation of the solvent under vacuum, the residue was chromatographed on a preparative silica gel plate and eluted with CH_2Cl_2-MeOH (20:1) to give 1.4 g of the bromide **6a** (70%). M.p. 88-92°C; UV(EtOH): λ_{max} 264 nm (9100); NMR(DMSO-d_6): δ 2.09 (s, <2H, C_2'-H), 3.52 (s, 2H, CH_2 at C_5), 3.55-3.72 (m, 2H, C_5'-H), 3.95 (dd, 1H, C_4'-H, J_a,J_b=3 Hz), 4.11 (t, 1H, C_3'-H, J=5 Hz), 4.62 (t, 1H, C_2'-H, J=6 Hz), 6.13 (d, 1H, C_1'-H, J=6 Hz), 7.15-7.29 (m, 5H, ArH), 7.98 (s, 1H, C_6-H), 11.42 (s, 1H, N_3-H).
Anal. Calc'd for $C_{16}H_{17}N_2O_5Br \cdot 0.25\ H_2O$: C, 47.84; H, 4.39; N, 6.97.
Found: C, 47.60; H, 4.43; N, 7.08.

5-(m-Benzyloxybenzyl)-2'-bromo-2'-deoxyuridine **6b**.

The anhydro compound **4b** (1.6 g, 5.8 mmoles) was brominated in a similar manner to yield 1.5 g (79%) of the corresponding bromide **6b**. The compound was isolated as an oil and used without further purification. NMR(DMSO-d_6): δ 2.09 (s, <1/2H, C_2'-H), 3.50 (s, 2H, CH_2 at C_5), 3.67-3.80 (m, >6H, C_5'-H), 3.91 (m, <1H, C_4'-H), 4.12 (m, <1H, C_3'-H), 4.64 (t, <1H, C_5'-OH, J=5 Hz), 5.05 (s, 2H, CH_2 of term.Bzl), 6.14 (d, <1H, C_1'-H, J=6 Hz), 6.76-7.91 (m, <3H, o and p-H of inner Bzl), 7.15-7.22 (m, 1H, m-H of inner Bzl), 7.27-7.46 (m, 5H, ArH of term.Bzl), 7.99 (s, <1H, C_6-H), 11.46 (s, <1H, N_3-H).

Anal. Calc'd for $C_{23}H_{23}N_2O_6Br \cdot 0.75\ H_2O$: C, 53.45; H, 4.78; N, 5.42. Found: C, 53.39; H, 4.50; N, 5.16.

5-Benzyl-deoxyuridine (7a).

The brominated compound **6a** (1.2 g, 3 mmoles) was dissolved in a mixture of 16 ml of benzene and 5 ml of MeOH and reduced by the procedure of Hřebabecký and Beránek[11], with tributyltin hydride (3 g in 3 ml of benzene) in the presence of 100 mg of 2,2'-azobis-2-methylpropionitrile (AIBN). The mixture was refluxed for 30 minutes, evaporated under vacuum, and the residue treated with 50 ml of light petroleum ether. It was then chromatographed on preparative silica gel plates and eluted with CH_2Cl_2-MeOH (20:1) to give 0.7 g of the deoxyribosyl analog **7a** (73%). M.p. 123-125°C; UV (pH 1): λ_{max} 268 nm (9800); (pH 11): λ_{max} 268 nm (9500). NMR(DMSO-d_6): δ 2.08 (br.s, 2H, $C_{2'}$-H), 3.44-3.60 (m, 4H, CH_2 at C_5 and $C_{5'}$-H), 3.76 (d, 1H, $C_{4'}$-H, J=3 Hz), 4.22 (br.s, 1H, $C_{3'}$-H), 5.02 (br.s, 1H, $C_{5'}$-OH), 5.25 (d, 1H, $C_{3'}$-OH, J=4 Hz), 6.16 (t, 1H, $C_{1'}$-H, J=7 Hz), 7.15-7.30 (m, 5H, ArH), 7.78 (s, 1H, C_6-H), 11.31 (s, 1H, N_3-H).
Anal. Calc'd for $C_{16}H_{18}N_2O_5 \cdot 0.5\ H_2O$: C, 60.38; H, 5.66; N, 8.80. Found: C, 60.37; H, 5.70; N, 8.80

5-(m-Benzyloxybenzyl)-deoxyuridine (7b).

The bromo analog **6b** (1.0 g, 2 mmoles) in a mixture of 14 ml of benzene and 2 ml of MeOH was reduced using 1.5 g of tributyltin hydride in 3 ml of benzene and 70 mg of AIBN. The mixture was heated to reflux for 30 minutes and worked up as above to give 0.65 g of the corresponding deoxyribosyl analog **7b** (77%). M.p. 157-161°C; UV(pH 1): λ_{max} 268 nm (9800); (pH 11): λ_{max} 269 nm (8800). NMR(DMSO-d_6): δ 2.07-2.12 (m, 2H, $C_{2'}$-H), 3.46-3.58 (m, 4H, CH_2 at C_5 and $C_{5'}$-H), 3.77 (dd, 1H, $C_{4'}$-H, $J_{3',4'}$=6 Hz, $J_{4',5'}$=4Hz), 4.23 (br.s, 1H, $C_{3'}$-H), 5.03 (t, 1H, $C_{5'}$-OH, J=5 Hz), 5.05 (s, 2H, CH_2 of term.Bzl), 5.25 (d, 1H, $C_{3'}$-OH, J=4 Hz), 6.16 (t, 1H, $C_{1'}$-H, J=7 Hz), 6.78-6.89 (m, 3H, o and p-H of inner Bzl), 7.18 (t, 1H, m-H of inner Bzl, J=8 Hz), 7.29-7.47 (m, 5H, ArH of term.Bzl), 7.80 (s, 1H, C_6-H), 11.32 (s, 1H, N_3-H).
Anal. Calc'd for $C_{23}H_{24}N_2O_6$: C, 65.09; H, 5.66; N, 6.60.
Found: C, 64.92; H, 5.84; N, 6.40.

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