Synthesis of 5-Ethylpyrimidine Nucleoside Analogs

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This paper describes the synthesis of acyclic, cyclic, and deoxy sugar nucleosides of 5-ethylpyrimidine, *i.e.*, i) 1-(2-hydroxyethoxymethyl), 1-(2-methoxyethoxymethyl), and 1-ethoxyethyl derivatives of 5-ethyluracil and 5-ethylcytosine, ii) 5-ethyl-1-(tetrahydro-2*H*-pyran-2-yl)- and -1-(tetrahydrofuran-2-yl)uracils, and iii) 5-ethyl-2'-deoxyuridine.

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In a series of reports on our work on the synthesis of pyrimidine and purine nucleosides [1-3], we have described that 5-ethyluracil ribonucleoside and gluconucleoside exerted inhibitory effects on both DNA and RNA containing viruses [1].

Swierkowska *et al.* reported that 5-ethyl-2'-deoxyuridine possesses inhibitory effects against vaccinia and herpes simplex viruses [4]. Its activity was comparable to that of 5-iodo-2'-deoxyuridine. 1-(2'-Deoxy-2'-fluoro-β-D-arabinofuranosyl)-5-ethyluracil also exhibited antiviral activity against herpes simplex virus [5].

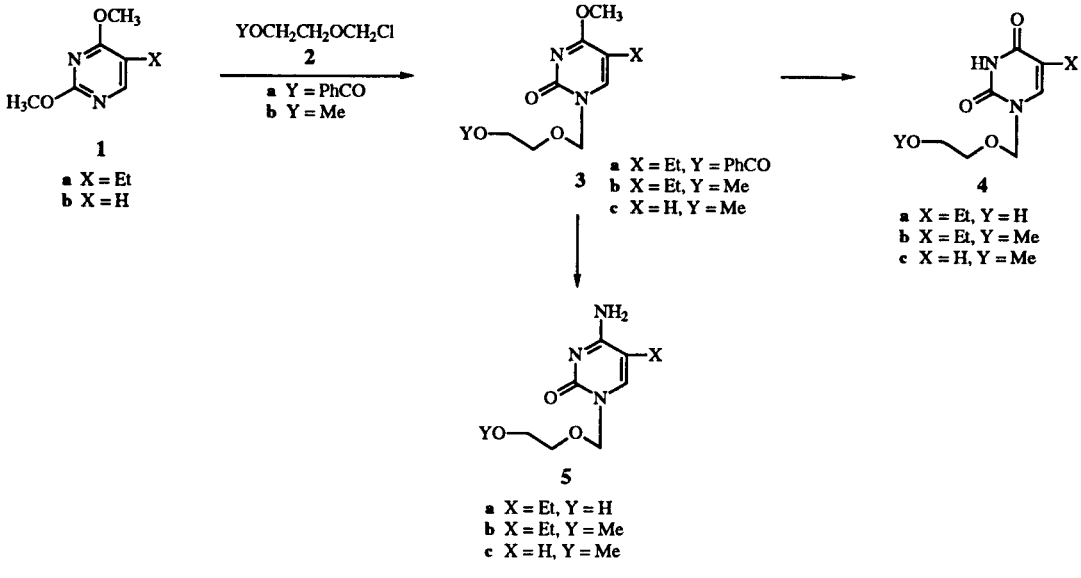
As a part of an investigation to find antiviral drugs, many modified nucleosides in which the furanose ring of pyrimidine and purine nucleosides was replaced by an acyclic group were synthesized. Among these compounds, 9-(2-hydroxyethoxymethyl)guanine was found to possess remarkable inhibitory effects on the growth of herpes simplex virus type 1 [6]. Furthermore, it was reported that 1-(2-hydroxyethoxymethyl)-5-methyluracil among the many derivatives of 5-substituted uracils, was an antagonist of uridine phosphorylase [7].

On the basis of these findings, it was of interest to prepare modified 5-ethylpyrimidine nucleosides to search for more effective agents. This paper describes the synthesis of 5-ethyluridine and -cytidine analogs possessing acyclic, cyclic, and deoxy sugars.

Trimethylsilylated uracil was usually employed for the synthesis of 1-(alkoxymethyl)uracils **4a-c** by the Hilbert-Johnson procedure [8]. We applied 2,4-dimethoxypyrimidine **1a-b** [9] for the synthesis of **4a-c** and the 1-(alkoxymethyl)cytosines **5a-c** *via* the common intermediates, the 1-(2-alkoxymethyl)-4-methoxy-2-oxopyrimidine derivatives **3a-c**. Thus, compounds **1a** and **1b** were converted to **3a-c** *via* alkylation using the alkoxymethyl chlorides **2a-b** in the presence of anhydrous sodium carbonate in dichloromethane. The subsequent hydrolysis of **3a-c** furnished the acyclic nucleosides of uracil **4a-c** (10-47% yields from **1**), while the ammonolysis afforded those of cytosine **5a-c** (5-54% yields from **1**).

The structures of **3-5** were determined by elementary analysis, and mass, ^{1}H nmr, and uv spectra. Namely, according to Fox and Shugar's method [10] in the uv spectra, the lack of a

Scheme 1

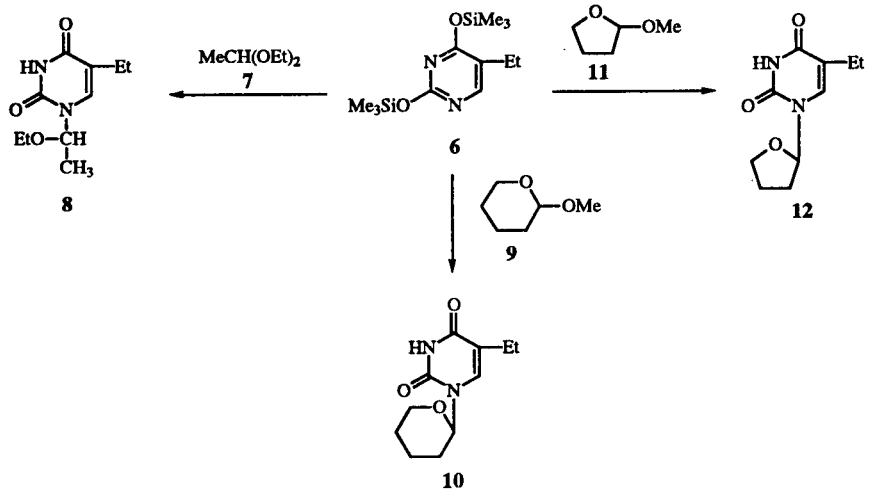


bathochromic effect of an *N*-alkylated uracil derivative in alkaline medium indicates *N*-1-alkylation.

We then prepared 1-(1-ethoxyethyl)-5-ethyluracil (**8**) by the reaction of trimethylsilylated uracil **6** [11] with 1,1-diethoxyethane **7** in the presence of anhydrous tin(IV) chloride in a 77% yield. Earl *et al.* prepared 1-(tetrahydro-2*H*-pyran-2-yl)- and 1-(tetrahydrofuran-2-yl)uracil by the treatment of **6** with the 2-chloro derivatives of tetrahydropyran and tetrahydrofuran, respectively [12]. We, on the other hand, synthesized these compounds by the use of a readily available cyclic acetal. Thus, we reacted **6** with either 2-methoxytetrahydropyran **9** or -furan **11**, in the presence of anhydrous tin(IV) chloride to obtain the 5-ethyl-1-(tetrahydro-2*H*-pyran-2-yl)- and -1-(tetrahydrofuran-2-yl)uracils **10** and **12** as enantiomeric mixtures, in yields of 57 and 72%, respectively.

Finally, we investigated the preparation of 5-ethyl-2'-deoxyuridine **16** [15] from 5-ethyl-2,2'-*O*-cyclouridine. 2,2'-Anhydro-1-β-D-arabinofuranosyl-5-ethyluracil **14** [13] has been successfully prepared from 5-ethyluridine **13** and diphenyl carbonate in *N,N*-dimethylformamide [16]. It was assumed that the exclusive formation of the β anomer of 2'-deoxyuridine would be realized by the nucleophilic attack of a bromide ion on 2,2'-*O*-cydouridine, followed by the hydrogenolysis of the resultant 2'-bromo-2'-deoxyuridine. For the reliable bromination of the 2'-position of uridine, the acetylation of the 3'- and 5'-hydroxy groups should be a prerequisite. We intended to use ethyl acetate-acetyl bromide by analogy with the ethyl acetate-phosphoryl chloride reagent for simultaneous acetylation and cyclization of uridine. 5-Ethyl-2,2'-*O*-cyclouridine **14** was reacted with ethyl acetate-acetyl bromide. Purification of the reaction product

Scheme 2



The structures of **8**, **10**, and **12** were confirmed by uv and ^{1}H nmr spectra. The uv spectra were essentially identical to that of 5-ethyluridine [1a, 13], thereby proving the site of alkylation at the *N*-1 position. The ^{1}H nmr spectra were assigned by tracing the crosspeaks of the two-dimensional COSY spectra. The value of the coupling constant, 10.6 Hz, at the 2'-position of **10** was comparable with that of 8-10 Hz, because of the diaxial proton coupling on the pyran ring [14], suggesting that the pyrimidine ring might possess an equatorial conformation.

afforded a colorless crystal in a 92% yield, which was identified as 5-ethyl-3'-*O*-acetyl-2'-bromo-2'-deoxyuridine **15** on the basis of elementary analysis, and ^{1}H nmr and uv spectra. The signal assignments of the ^{1}H nmr were confirmed by the COSY spectrum. The chemical shift of the 3'-H was downfield from those of **13** (5.30 ppm vs. 3.98 ppm). In addition, the signals of the 5'-hydroxy group and the three protons of the 3'-acetyl group appeared at 5.41 ppm and 2.14 ppm, respectively. These results suggest that the structure of **15** was 5-ethyl-3'-*O*-acetyl-2'-bromo-2'-deoxyuridine.

Scheme 3

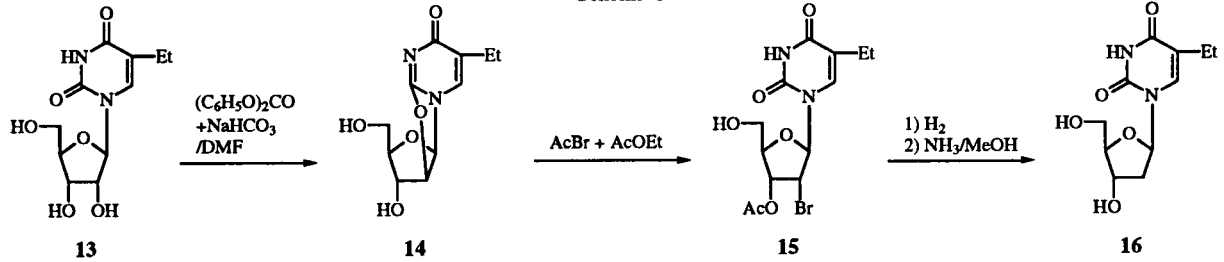


Table 1
Characteristics of 5-Ethyluridine Analogs

Compound	Mp,°C	Formula	Analysis, Calcd. (Found) %C	%H	%N	Solvent	UV λmax nm	ε
3a	94.5-95	$C_{17}H_{20}N_2O_5$	61.43 (61.50)	6.07 (6.22)	8.43 (8.32)	EtOH	278	5500
3b	(oil)	$C_{11}H_{18}N_2O_4$	54.53 (54.43)	7.49 (7.43)	11.56 (11.62)	EtOH	282	6300
3c	(oil)	$C_9H_{14}N_2O_4 \cdot 1/3CH_3OH$	49.84 (50.18)	6.87 (6.60)	12.46 (12.38)	EtOH	273	6100
4a	135.5-136 [a]	$C_9H_{14}N_2O_4$	50.46 (50.44)	6.59 (6.75)	13.08 (12.98)	EtOH	262 206	8700 9600
4b	57	$C_{10}H_{16}N_2O_4$	52.62 (52.66)	7.07 (7.25)	12.27 (12.36)	EtOH	262 208	7400 8000
4c	60-61	$C_8H_{12}N_2O_4$	47.99 (47.61)	6.04 (5.87)	13.99 (13.83)	EtOH	257 205	8400 8200
5a	165.5-167	$C_9H_{15}N_3O_3$	50.69 (50.61)	7.09 (7.03)	19.71 (19.65)	EtOH	276 240	4800 5700
5b	155-158.5	$C_{10}H_{17}N_3O_3$	52.85 (52.83)	7.54 (7.53)	18.49 (18.37)	EtOH	277 240	8900 10700
5c	200-201	$C_8H_{13}N_3O_3$	48.23 (48.15)	6.58 (6.40)	21.20 (20.94)	EtOH	267 240	6700 7400
8	114-115	$C_{10}H_{16}N_2O_3 \cdot H_2O$	52.16 (52.27)	7.88 (7.99)	12.17 (12.14)	H_2O	269	9100
10	144.5-145	$C_{11}H_{16}N_2O_3$	58.91 (58.51)	7.19 (7.11)	12.49 (12.24)	MeOH	265	8100
12	135.5-136.5	$C_{10}H_{14}N_2O_3$	57.13 (57.40)	6.71 (6.76)	13.33 (13.50)	EtOH	267 209	9200 9000
14	154-156	$C_{11}H_{14}N_2O_5$	51.96 (51.66)	5.55 (5.51)	11.02 (11.13)	H_2O	255	12100
15	73-76	$C_{13}H_{17}N_2O_6Br$	41.39 (41.33)	4.54 (4.53)	7.42 (7.33)	EtOH	262	9500

[a] Lit [8] mp 135-136°, Lit [17] 140-142°.

Furthermore, 5-ethyl-2'-deoxyuridine **16** was obtained in a 49% yield by hydrogenolysis of the acetylbromouracil derivative **15**, followed by deacetylation. The structures of **14** and **16** were confirmed by comparison mps and uv spectra with those of the authentic sample [13,15]. This method is the first synthesis of 5-ethyl-2'-deoxyuridine **16** from 5-ethyluridine **13**.

The mps, elementary analyses, and uv data of the new compounds are shown in Table 1.

In conclusion, the successful preparation of new modified 5-ethyluridines and 5-ethylcytidines has been performed.

EXPERIMENTAL

The uv spectra were recorded on a Hitachi 340 spectrometer. The ms spectra were recorded on a JEOL JMX-DX300 spectrometer. The ^1H nmr spectra were recorded on a Bruker AMX 400 spectrometer and a JEOL JNM PMX60 spectrometer. The ir spectra were recorded on a Hitachi 260-10 spectrometer. The melting points were determined on a Yazawa micromelting-point apparatus type BY-1 and were uncorrected. The tlc was performed on silica gel plates (Merck 60 F_{245}).

Procedure for the Preparation of 1-(2-Alkoxymethyl)-4-methoxy-2-oxopyrimidines **3**.

1-(2-Benzoyloxyethoxymethyl)-5-ethyl-4-methoxy-2-oxopyrimidine (**3a**).

A mixture of 5-ethyl-2,4-dimethoxypyrimidine [9] (**1a**, 3.1562 g, 0.188 mole), benzoyloxyethoxymethyl chloride [7] (**2a**, 4.0280 g, 0.188 mole), and anhydrous sodium carbonate (2.188 g) in dichloromethane (37.5 ml) was stirred for 24 hours at room temperature. After completion of the reaction, the mixture was filtered and the solvent was removed under reduced pressure. The residue was washed with petroleum ether, and was recrystallized from diisopropyl ether as colorless needles in a 91% yield; ^1H nmr (deuteriochloroform): δ 1.12 (t, 3H, 5-CH_3), 2.36 (q, 2H, 5-CH_2), 4.02 (s, 3H, 4-OCH_3), 4.51 (m, 2 x 2H, 4'- and 5'-H), 5.41 (s, 2H, 1'-H), 7.60 (t, 5H, ArH), 8.06 (d, 1H, 6-H); ms: m/z 332 (M^+).

5-Ethyl-4-methoxy-1-(2-methoxyethoxymethyl)-2-oxopyrimidine (**3b**).

This compound was prepared from **1a** (2.3845 g, 0.01418 mole) and β-methoxyethoxymethyl chloride (**2b**, 1.77 g, 0.01418 mole), by the method described for the preparation of **3a**. The residue was purified by silica gel column chromatography using methanol in dichloromethane (0-3%), as an oil in a 90% yield; ^1H nmr (deuteriochloroform): δ 1.19 (t, 3H, 5-CH_3), 2.31 (q, 2H, 5-CH_2), 3.43 (s, 3H, 5'-OCH_3), 3.73, (q, 2 x 2H, 4'- and 5'-H), 4.06 (s, 3H, 4-OCH_3), 5.38 (s, 2H, 1'-H), 7.41 (s,

1H, 6-H); high resolution ms: m/z 242.1271 (M^+ for $C_{11}H_{18}N_2O_4$: Calcd. 242.1265).

4-Methoxy-1-(2-methoxyethoxymethyl)-2-oxopyrimidine (**3c**).

This compound was prepared from 2,4-dimethoxypyrimidine (**1b**, 0.4880 g, 3.48 mmoles) and **2b** (0.4338 g, 3.48 mmoles), by the method described for the preparation of **3a**. The residue was purified by silica gel column chromatography using methanol in dichloromethane (0-3%), as an oil in an 80% yield; ^1H nmr (deuteriochloroform): δ 3.44 (s, 3H, 5'-OCH_3), 3.68 (q, 2 x 2H, 4'- and 5'-H), 4.03 (s, 3H, 4-OCH_3), 5.37 (s, 2H, 1'-H), 5.94 (d, 1H, 5-H), 7.65 (d, 1H, 6-H); high resolution ms: m/z 214.0952 (M^+ for $C_9H_{14}N_2O_4$: Calcd. 214.095).

General Procedure for the Synthesis of 1-(Alkoxymethyl)uracils **4a-c**.

A mixture of **3a-c** (1 mmole) in 2*M* sodium hydroxide (2.50 ml) was stirred at room temperature for 26 hours, neutralized with excess Dowex 50 (H^+), and evaporated to dryness. The residue was extracted with diethyl ether. The solvent was removed under reduced pressure to give **4a-c**.

5-Ethyl-1-(2-hydroxyethoxymethyl)uracil (**4a**).

This compound was recrystallized from ethanol as colorless needles in a 20% yield; ^1H nmr (DMSO-d_6): δ 1.04 (t, 3H, 5-CH_3), 2.21 (q, 2H, 5-CH_2), 3.49 (s, 2 x 2H, 4'- and 5'-H), 4.65 (s, 1H, 5'-OH, deuterium oxide-exchangeable), 5.08 (s, 2H, 1'-H), 7.51 (s, 1H, 6-H), 11.29 (s, 1H, NH, deuterium oxide-exchangeable); ms: m/z 214 (M^+).

5-Ethyl-1-(2-methoxyethoxymethyl)uracil (**4b**).

This compound was recrystallized from ethanol as colorless needles in a 52% yield; ^1H nmr (DMSO-d_6): δ 1.04 (t, 3H, 5-CH_3), 2.21 (q, 2H, 5-CH_2), 3.23 (s, 3H, 5'-OCH_3), 3.51 (m, 2 x 2H, 4'- and 5'-H), 5.07 (s, 2H, 1'-H), 7.51 (s, 1H, 6-H), 11.30 (s, 1H, NH, deuterium oxide-exchangeable); ms: m/z 228 (M^+).

1-(2-Methoxyethoxymethyl)uracil (**4c**).

This compound was recrystallized from diethyl ether as colorless, fine needles in a 12% yield; ^1H nmr (DMSO-d_6): δ 2.50 (s, 3H, 5'-OCH_3), 3.51 (q, 2 x 2H, 4'- and 5'-H), 5.08 (s, 2H, 1'-H), 5.61 (d, 1H, 5-H), 7.69 (d, 1H, 6H), 11.32 (s, 1H, NH, deuterium oxide-exchangeable); ms: m/z 200 (M^+).

General Procedure for the Synthesis of 1-(Alkoxymethyl)-cytosines **5a-c**.

A mixture of **3** (7.5 mmoles) and methanolic ammonia (15 ml) was heated in a bomb at 100° for 24 hours. After the reaction mixture was evaporated to dryness under reduced pressure, the residue was washed with hot benzene (10 ml x 3), and diethyl ether (10 ml x 3) to give **5**.

5-Ethyl-1-(2-hydroxyethoxymethyl)cytosine (**5a**).

This compound was recrystallized from methanol as colorless needles in a 59% yield; ^1H nmr (DMSO-d_6): δ 1.10 (t, 3H, 5-CH_3), 2.31 (q, 2H, 5-CH_2), 3.54 (s, 2 x 2H, 4'- and 5'-H), 4.70 (s, 1H, 5'-OH), 5.17 (s, 2H, 1'-H), 7.14 (s, 2H, NH_2), 7.51 (s, 1H, 6-H); ms: m/z 213 (M^+).

5-Ethyl-1-(2-methoxyethoxymethyl)cytosine (**5b**).

This compound was recrystallized from ethanol as colorless plates in a 5% yield; ^1H nmr (DMSO-d_6): δ 1.10 (t, 3H, 5-CH_3), 2.34 (q, 2H, 5-CH_2), 3.27 (s, 3H, 5'-OCH_3), 3.58 (s, 2 x 2H, 4'-and 5'-H), 5.14 (s, 2H, 1'-H), 7.14 (s, 2H, NH_2), 7.48 (s, 1H, 6-H); ms: m/z 227 (M^+).

1-(2-Methoxyethoxymethyl)cytosine (**5c**).

This compound was recrystallized from ethanol as colorless needles in a 26% yield; ^1H nmr (DMSO-d_6): δ 3.34 (s, 3H, 5'-OCH_3), 3.58 (s, 2 x 2H, 4'- and 5'-H), 5.14 (s, 2H, 1'-H), 5.85 (s, 1H, 5-H), 7.22 (s, 2H, NH_2), 7.75 (d, 1H, 6-H); ms: m/z 199 (M^+).

Preparation of 1-(1-Ethoxyethyl)-5-ethyluracil (**8**).

To a solution of 5-ethyl-2,4-bis(trimethylsilyloxy)pyrimidine [13] (**6**, 1.92 g, 6.74 mmoles) and 1,1-diethoxyethane (**7**, 0.792 g, 8.41 mmoles) in 1,2-dichloroethane (96.4 ml), anhydrous tin(IV) chloride (1.75 g) was added and the solution was allowed to stand for 2 days at room temperature. After the addition of chloroform (50 ml), the mixture was poured into ice-water and filtered. The organic layer was washed with 5% sodium hydrogencarbonate and with water.

The solvent was evaporated to dryness under reduced pressure. The residue was recrystallized from ethyl acetate as colorless, fine needles in a 77% yield; ^1H nmr (DMSO-d_6): δ 1.04 (t, 3H, 5-CH_3), 1.10 (t, 3H, 1'-CH_3), 1.39 (d, 3H, 2'-H), 2.25 (q, 2H, 5-CH_2), 3.39 (q, 2H, 1'-CH_2), 5.74 (q, 1H, 1'-H), 7.40 (s, 1H, 6-H), 11.25 (br s, 1H, NH, deuterium oxide-exchangeable).

Preparation of 5-Ethyl-1-(tetrahydro-2*H*-pyran-2-yl)uracil (**10**).

To a solution of **6** (5.12 g, 18 mmoles) in acetonitrile (95.6 ml), anhydrous tin(IV) chloride (1.44 ml) was added. Then, a solution of 2-methoxytetrahydropyran (**9**, 2.78 g, 23.9 mmoles) in 1,2-dichloroethane (47.8 ml) was added, and the solution was stirred for 2 hours at room temperature. After the addition of 1,2-dichloroethane (480 ml), the mixture was poured into ice-water. The organic layer was washed with 5% sodium hydrogencarbonate and with water. The solvent was evaporated to dryness under reduced pressure, and the residue was recrystallized from ethyl acetate as colorless needles in a 57% yield; ^1H nmr (DMSO-d_6): δ 1.03 (t, 3H, 5-CH_3), 1.47 (m, 1H, 5'-H), 1.63 (m, 1H, 5'-H), 1.70 (m, 1H, 4'-H), 1.76 (m, 2H, 3'-H), 1.89 (m, 1H, 4'-H), 2.23 (q, 2H, 5-CH_2), 3.58 (m, 1H, 6'-H), 4.00 (q, 1H, 6'-H), 5.47 (dd, 1H, 2'-H, J = 10.6, 2.2 Hz), 7.47 (s, 1H, 6-H), 11.30 (s, 1H, NH, deuterium oxide-exchangeable).

Preparation of 5-Ethyl-1-(tetrahydrofuran-2-yl)uracil (**12**).

To a solution of 2-methoxytetrahydrofuran (**11**, 3.73 g, 36.5 mmoles) in 1,2-dichloroethane (21.93 ml), a solution of **6** (2.08 g, 7.3 mmoles) in acetonitrile (43.86 ml) was combined. Then, anhydrous tin(IV) chloride (0.83 ml) was added and the mixture was stirred for 50 hours at room temperature. After the addition of 1,2-dichloroethane (220 ml), the mixture was poured into ice-water. The organic layer was washed with 5% sodium hydrogencarbonate and with water. The solvent was evaporated to dryness under reduced pressure. The residue was purified by silica gel column chromatography using methanol in dichloromethane (0-7%), and was recrystallized from ethyl acetate as colorless needles, in a 72% yield; ^1H nmr (DMSO-d_6): δ 1.03 (t, 3H, 5-CH_3), 1.91-2.02 (m, 3H, 3'- and 4'-H), 2.21 (m, 1H, 3'-H), 2.24 (q, 2H, 5-CH_2), 3.81 (q, 1H, 5'-H), 4.16 (q, 1H, 5'-H), 5.94 (dd, 1H, 2'-H, J = 6.3, 3.2 Hz), 7.32 (s, 1H, 6-H), 11.24 (t, 1H, NH, deuterium oxide-exchangeable).

Preparation of 2,2'-Anhydro-1-β-D-arabinofuranosyl-5-ethyluracil (**14**).

5-Ethyluridine (**13**, 136.1 mg, 0.5 mmole) [1a,13] was dissolved in *N,N*-dimethylformamide (0.5 ml) with diphenyl carbonate (123.2 mg) and sodium bicarbonate (17.5 mg). The mixture was heated at 150° for 10 minutes and then was allowed to cool to room temperature. The resulting solution was poured into diethyl ether (25 ml) with vigorous stirring. Water (25 ml) was added to the heterogeneous mixture. The aqueous solution was washed with diethyl ether (25 ml x 2) and was evaporated to dryness. The residue was purified by preparative tlc (dichloromethane:methanol = 17:3). The compound (Rf = 0.20) was recrystallized from ethyl acetate as colorless prisms, 77.3 mg (61%); ^{1}H nmr (DMSO-d_6): δ 1.04 (t, 3H, 5-CH_3), 2.24 (q, 2H, 5-CH_2), 3.16 (q, 1H, 5'-H), 3.26 (q, 1H, 5'-H), 4.06 (m, 1H, 4'-H), 4.37 (s, 1H, 3'-H), 5.01 (br s, 1H, 5'-OH, deuterium oxide-exchangeable), 5.18 (d, 1H, 2'-H), 6.04 (br s, 1H, 3'-OH, deuterium oxide-exchangeable), 6.29 (d, 1H, 1'-H, J = 5.6 Hz), 7.67 (s, 1H, 6-H).

Preparation of 5-Ethyl-3'-*O*-acetyl-2'-bromo-2'-deoxyuridine (**15**).

To a solution of **14** (0.8 g, 3.1 mmoles) in *N,N*-dimethylformamide (1.43 ml) and ethyl acetate (12.87 ml), acetyl bromide (0.92 ml) was added, and the solution was refluxed for 5 hours at 120°. After the mixture was evaporated to dryness at 40° under reduced pressure, the residue was extracted with ethyl acetate (30 ml). The solvent was washed with water (16 ml x 2) and was evaporated under reduced pressure to a colorless powder in a 92% yield. The resulting product was of sufficient purity for direct use in subsequent reactions.

For characterization, this material was purified by silica gel column chromatography using methanol in dichloromethane (0-5%), and was recrystallized from ethyl acetate as colorless crystals; ^{1}H nmr (DMSO-d_6): δ 1.05 (t, 3H, 5-CH_3), 2.14 (s, 3H, 3'-CH_3COO), 2.22 (q, 2H, 5-CH_2), 3.59 (m, 2H, 5'-H), 4.16 (d, 1H, 4'- H), 4.82 (q, 1H, 2'-H), 5.30 (q, 1H, 3'-H), 5.41 (br s, 1H, 5'-OH, deuterium oxide-exchangeable), 6.16 (d, 1H, 1'-H, J = 7.6 Hz), 7.70 (s, 1H, 6-H), 11.46 (s, 1H, NH, deuterium oxide-exchangeable).

Preparation of 5-Ethyl-2'-β-D-deoxyuridine (**16**).

To a solution of **15** (0.9 g, 2.3 mmoles) and sodium acetate (0.84 g) in 75% methanol (45 ml), 1% Pd-C (3 g) was added, and the mixture was stirred until the calculated amount of hydrogen absorption had occurred at constant pressure. After the catalyst was filtered off, the solvent was evaporated. The residue was diluted with water, extracted with chloroform (x 2), and evaporated. The residue was dissolved in 20% methanolic ammonia (12 ml) and was stored overnight at 5°. Subsequently, the mixture was evaporated under reduced pressure and was purified by preparative tlc (dichloromethane:methanol = 17:3). The compound (Rf = 0.3) was recrystallized from ethanol-ethyl acetate as colorless, fine needles, 0.3 g (49%), mp 151-153° (lit [15a] 152-153°); uv (water): λmax 267 nm.

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