SYNTHESIS OF 3'-AZIDO-2',3'-DIDEOXY-6-METHYLURIDINE, 2',3'-DIDEOXY-6-METHYLURIDINE AND 2',3'-DIDEOXY--2',3'-DIDEHYDRO-6-METHYLURIDINE

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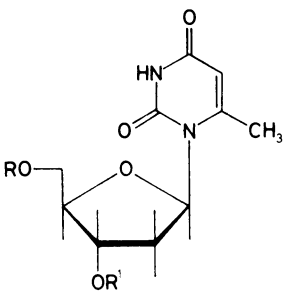
Received November 29, 1989
Accepted December 18, 1989

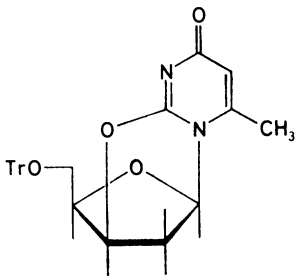
3'-Azido-2',3'-dideoxy-6-methyluridine (*VIb*) was prepared, together with its N^3-isomer *VIIb*, by opening the 2,3'-bond in anhydronucleoside *III* with lithium azide in dimethylformamide and subsequent detritylation. The anhydro derivative *III* was synthesized from 2'-deoxy-6-methyluridine (*I*) by tritylation, mesylation and closure of the 2,3'-anhydro bond with 1,8-diazabicyclo-[5.4.0]undec-7-ene. Dideoxy derivative *XV* was prepared by Barton deoxygenation of phenoxythiocarbonyl derivative *IX* followed by desilylation with tetrabutylammonium fluoride. Reduction of bis(phenoxythiocarbonyl) derivative *XV* with tributyltin hydride afforded 2',3'-dideoxy--2',3'-didehydro derivative *XVI*. The compound *XV* was obtained from arabinosyl derivative *XIII* which arises, along with 5,6-dihydro derivative *XIV*, by reaction of anhydronucleoside *XII* with lithium hydroxide in aqueous methanol. Desilylation of compound *XVI* with tetrabutylammonium fluoride resulted in quantitative removal of 6-methyluracil.

As found by Mitsuya and coworkers[1], 3'-azido-2',3'-dideoxythymidine (AZT, previously synthesized by Horwitz[2]) significantly inhibits the replication of HIV. The drug is clinically utilized for treatment of AIDS patients. Since this compound causes severe side-effects with some patients and generally acts suppressively to bone marrow[3], many other nucleoside analogs with anti-HIV activity have been synthesized and their structure – antiviral activity relationships have been investigated[4]. Nucleosides with an azido group in *erythro*-3'-position exhibit the highest antiviral activity. Although the uracil derivative (AZU) is less effective than AZT, its in vitro therapeutic index is more advantageous[5]. Introduction of a methyl group into position 5 of the pyrimidine base increases the activity. Also 5-ethyl derivatives are highly active[6], the activity, however, decreases with higher alkyl groups.

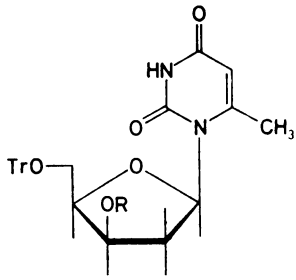
Nucleosides of 6-methyluracil differ from the corresponding thymine derivatives primarily by their molecular conformation. It was of interest to ascertain whether compounds, corresponding structurally to AZT and other anti-retrovirus nucleosides, retain the biological effect also in the series of isomeric 6-methyluracil derivatives. As the starting material for preparation of 3'-azido derivative *VIb* and dideoxy



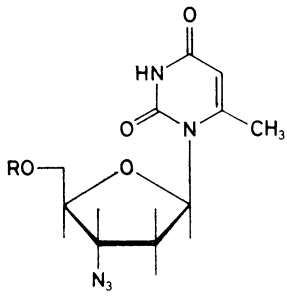
I, R = R^1 = H
II, R = Tr ; R^1 = Ms
VIII, R = TBDPS ; R^1 = H
IX, R = TBDPS ; R^1 = $CSOC_6H_5$



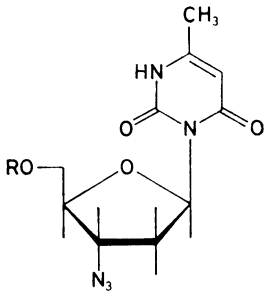
III



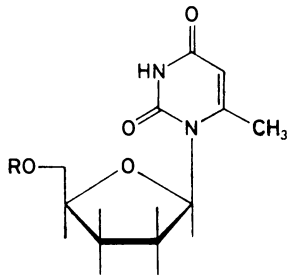
IV, R = H
V, R = Ms



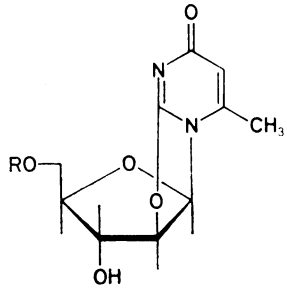
VI a, R = Tr
VI b, R = H



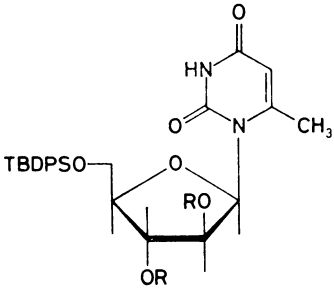
VII a, R = Tr
VII b, R = H



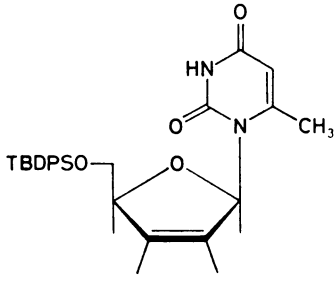
X a, R = TBDPS
X b, R = H



XI, R = H
XII, R = TBDPS



XIII, R = H
XV, R = $CSOC_6H_5$



XVI

Ms = methanesulfonyl ; **TBDPS** = tert-butyldiphenylsilyl ; **Tr** = trityl

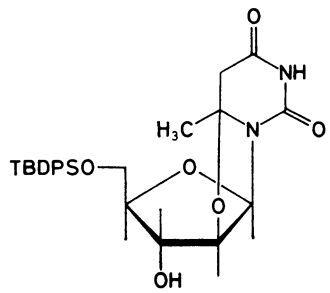
derivative *Xb* we used 2′-deoxy-6-methyluridine[7,8] (*I*). Tritylation and subsequent mesylation without isolation of the intermediates afforded 3′-O-mesyl-5′-O-trityl derivative *II* which was converted into the anhydro derivative *III* by treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in acetonitrile. The opening of 2,3′-bond with sodium azide in dimethylformamide at 150°C resulting in a relatively high yield of 3-azido-2,3-dideoxy-β-D-ribofuranosyl derivative is described in the literature (see e.g. ref.[9]). However, heating the anhydro derivative *III* with lithium azide in dimethylformamide to 150°C (bath) for 3 h afforded the azido derivative *VIa* in a yield of only 15%; the principal reaction product (71%) was the azido derivative *VIIa* in which the sugar moiety is bonded to the N-3 atom of the base. A similar N-1 → → N-3 migration was described for 2,2′-anhydronucleosides[10] or for the reaction of 3′,5′-di-O-benzoyl-6-methoxycarbonyl-2,2′-anhydrouridine with hydrogen chloride in dimethylformamide[11]. This mechanism assumes an attack by nucleophilic ion in position C-1′ and preservation of the 2,3′-bond for a time long enough to allow the reaction at the activated C-1′ center with the 6-substituted uracil derivatives, of the sugar moiety. Such a reaction takes place preferentially in position N-3 of the heterocyclic base. The distinct formation of the isomeric 2,3′-anhydronucleoside derived from 3-(2-deoxy-β-D-lyxofuranosyl)-6-methyluracil was not proven, probably because it reacts rapidly with the azide to give compound *VIIa*. Interestingly, contrary to the 6-methoxycarbonyluracil derivative[11], in this case neither the glycosidic bond is activated by protonation nor the active sugar intermediate can be stabilized by formation of the 1′,2′-benzooxonium ion or α-halogenose. However, the anomeric homogeneity of the obtained compound *VIIa* proves not only retention of the 2,3′-bond during the migration but also sufficient reactivity of the active center in position 1′ of the reaction intermediate. Similarly, the reaction of 2,3′-anhydro-1--(2′-deoxy-5-O-triphenylmethyl-β-D-ribofuranosyl)thymine with lithium azide leads to a mixture of 1-(3-azido-2,3-dideoxy-5-O-triphenylmethyl-β-D-ribofuranosyl)-thymine and its 3-isomer in the ratio 9 : 1 (cf. ref.[12]). Therefore, the azido derivative *VIa* was also prepared from the mesyl derivative *V* by reaction with lithium azide in dimethylformamide. The required mesylate *V* was prepared by treatment of the 2,3′-anhydro derivative *III* with a solution of lithium hydroxide in 90% aqueous methanol and subsequent mesylation of the formed 2′-deoxy *threo*-derivative *IV*. Heating of both trityl derivatives *VIa* and *VIIa* in 80% acetic acid afforded the free nucleosides *VIb* and *VIIb*.

The infrared spectrum of the trityl derivative *VIa* exhibits an NH-band at 3 392 cm^{-1} which corresponds to the frequency of an NH-group in position 3 of the uracil ring, whereas the NH-band of the trityl derivative *VIIa* appears at 3 416 cm^{-1}. This frequency corresponds to an NH-group in position 1 of the uracil moiety (cf. ref.[13]). Another proof of the structure *VIIb* is provided by the ultraviolet spectra. Whereas for compound *VIb* the shape of the UV spectrum *VIIb* exhibits a marked bathochromic shift (from 264 nm in water to 288 nm at pH 12) and an increased

band intensity (from ε 9 320 to 11 610) which is characteristic of N-3 substituted uracil derivatives (see ref.[13] and references therein). The ^{1}H NMR spectra of azido derivatives *VIb* and *VIIb* are very similar (including coupling constants), differing only in the position of the H-1′ proton signal (5·99 ppm for *VIb* and 6·48 ppm for *VIIb*). This indicates the same configuration, and a very similar conformation, of both the sugar moieties, the difference in the H-1′ signals being in accord with the different substitution of the base.

Synthesis of the 2′,3′-dideoxy derivative *Xb* started from 2′-deoxy-6-methyluridine (*I*) which was first converted into the 5′-O-tert-butyldiphenylsilyl derivative *VIII* and then into the 3′-O-phenylthiocarbonyl compound *IX*. Barton deoxygenation[14] of *IX*, followed by desilylation of the intermediate *Xa* with tetrabutylammonium fluoride, afforded the free nucleoside *Xb* whose UV and ^{1}H NMR spectra agreed with its structure.

As starting compound for preparation of the didehydro derivative *XVI* we used the easily accessible anhydro derivative *XI* (refs[7,8]). However, alkaline hydrolysis of its 5′-O-tert-butyldiphenylsilyl derivative *XII* afforded the desired arabinosyl derivative *XIII* in only 20% yield. The principal reaction product was the didehydro derivative *XIV* arising in intermolecular addition of the 2′-OH group to the 5,6-double



XIV

bond. Its structure was suggested on the basis of the ^{1}H NMR spectrum. It exhibited two doublets at 2·60 ppm and 2·96 ppm, corresponding to an AB system of two H-5 protons with geminal coupling constant amounting to 15 Hz. The configuration at the C-6 carbon atom was not studied. However, the character of the ^{1}H NMR spectrum indicates the presence of only one of the two possible diastereoisomers. The already known 1-(β-D-arabinofuranosyl)-6-methyluracil also has this structure as is evident from its ^{1}H NMR spectrum[7]. A similar course of the 2,2′-anhydro bond cleavage was observed with ethyl 2,2′-anhydro-1-(β-D-arabinofuranosyl)-orotate[10]. In alkaline solutions of compound *XIV* there is an equilibrium between the compounds *XIII* and *XIV* with the latter predominating. Upon addition of

aqueous ammonia to a methanolic solution of *XIV*, a 1 : 5 equilibrium between *XIII* and *XIV* is established. Treatment of the arabinosyl derivative *XIII* with phenoxythiocarbonyl chloride in acetonitrile in the presence of 4-dimethylaminopyridine afforded the 2',3'-di-O-(phenoxythiocarbonyl) derivative *XV*. Its reaction with tributyltin hydride in toluene, catalyzed by 2,2'-azo-bis(2-propionitrile) gave the desired 2',3'-dideoxydidehydro drivative *XVI*. A similar reaction has been described[15] for 2',3'-O-bis(dithiocarbonates) of nucleosides. However, an attempted desilylation of compound *XVI* under usual conditions led to destruction of the nucleoside and we isolated 6-methyluracil as the only product.

Neither of the compounds *VIb*, *VIIb* and *Xb* exhibited any significant in vitro activity against HIV-1.

EXPERIMENTAL

Melting points were determined on a Koffer block and are uncorrected. UV spectra were obtained with a Pye Unicam PU 8800 instrument, IR spectra with a UR-20 (Carl Zeiss, Jena) spectrometer (wavenumbers are given in cm^{-1}). ^1H NMR spectra were measured in hexadeuterodimethyl sulfoxide on a Tesla BS-497 (100 MHz) spectrometer with tetramethylsilane as internal standard. Chemical shifts are given in ppm (δ-scale) and coupling constants (J) in Hz. Column chromatography was performed on silica gel according to Pitra (particle size 30–60 μm; Service Laboratories of this Institute). Thin-layer chromatography (TLC) was carried out on Silufol UV 254 sheets (Kavalier, Votice) in the following systems: S1 ethyl acetate; S2 ethyl acetate–toluene (1 : 1); S3 ethyl acetate–acetone–ethanol–water (36 : 6 : 5 : 3). Unless stated o herwise, solvents were evaporated at 40°C/2 kPa and compounds dried over phosphorus pentoxide at 13 Pa. The anti-HIV activity was determined in MT-4 cells infected with the HTLV-III_B strain of HIV-1, using a cytopathogenicity assay described previously[16]. The cytopathogenicity assay was based on cell viability measured by the trypan blue exclusive procedure.

1-(2-Deoxy-3-O-methanesulfonyl-5-O-triphenylmethyl-β-D-*erythro*-pentofuranosyl)-6-methyluracil (*II*)

A solution of 2'-deoxynucleoside[8] *I* (9·69 g, 40 mmol) and triphenylmethyl chloride (13 g, 50 mmol) in pyridine (120 ml) was heated to 100°C for 1 h under stirring, cooled to 0°C and methanesulfonyl chloride (6 ml, 77 mmol) was added under stirring. After standing at +4°C overnight and at room temperature for 3 h, the mixture was cooled to 0°C and water (5 ml) was added. The mixture was concentrated to a half of the original volume and the residue added dropwise to stirred ice-cold water (1·5 l). The precipitate was collected on filter, washed with water (1 l), air-dried and dissolved in chloroform (100 ml). The solution was dried over anhydrous sodium sulfate and applied onto a column of silica gel (100 g). Elution with ethyl acetate–toluene (4 : 1) afforded a UV-absorbing fraction. This was taken down and the residue crystallized from 2-propanol to give 8·93 g (39%) of derivative *II*, m.p. 132–134°C; R_F 0·67 (S1). For $C_{30}H_{30}N_2O_7S$ (562·6) calculated: 64·04% C, 5·37% H, 4·98% N, 5·70% S; found: 63·88% C, 5·40% H, 4·94% N, 5·68% S. ^1H NMR spectrum: 2·29 s, 3 H (CH_3); 2·10–2·60 m, 2·82–3·20 m, 2 H (2 × H-2'); 3·21–3·36 m, 2 H (2 × H-5'); 3·96–4·18 m, 1 H (H-4'); 5·18–5·43 m, 1 H (H-3'); 6·11 dd, 1 H (H-1', J(1', 2a') = 4·0; J(1', 2b') = 8·5); 7·11–7·47 m, 15 H (H-arom.); 11·19 s, 1 H (H-3).

2,3'-Anhydro-1-(2-deoxy-5-O-triphenylmethyl-β-D-*threo*-pentofuranosyl)-6-methyluracil (*III*)

A solution of mesyl derivative *II* (5·63 g, 10 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (2 ml, 13·4 mmol) in acetonitrile (80 ml) was set aside at room temperature overnight. The reaction mixture was then added dropwise under stirring into ice-cold water (1·4 l), the precipitate was filtered, washed with water (1 l) and dried on the air and then in a desiccator over potassium hydroxide. Crystallization from toluene afforded 4·2 g (90%) of anhydro derivative *III*, m.p. 135–138°C; R_F 0·53 (S3). For $C_{29}H_{26}N_2O_4$ (466·5) calculated: 74·66% C, 5·62% H, 6·00% N; found: 74·50% C, 5·61% H, 6·01% N.

1-(2-Deoxy-5-O-triphenylmethyl-β-D-*threo*-pentofuranosyl)-6-methyluracil (*IV*)

A mixture of anhydro derivative *III* (3·72 g, 8 mmol) and 2% lithium hydroxide solution in 90% aqueous methanol (50 ml) was stirred at room temperature for 24 h. The obtained solution was neutralized with solid carbon dioxide and the solvent was evaporated. The residue was dissolved in chloroform (100 ml), the solution washed with water (3 × 20 ml), dried over anhydrous sodium sulfate and the solvent evaporated to give 3·81 g of a residue. A part (500 mg) was chromatographed on a column of silica gel (50 g) in ethyl acetate, affording 360 mg (71%) of derivative *IV* as a solid foam; R_F 0·59 (S1). For $C_{29}H_{28}N_2O_5$ (484·5) calculated: 71·88% C, 5·82% H, 5·78% N; found: 72·11% C, 6·08% H, 5·84% N. ^{1}H NMR spectrum: 2·00–2·30 m, 2·50–2·90 m, 2 H (2 × H-2'); 2·34 s, 3 H (CH_3); 3·22–3·50 m, 2 H (2 × H-5'); 3·81–4·03 m, 1 H (H-4'); 4·05–4·33 m, 1 H (H-3'); 5·12 d, 1 H (OH, J(OH, 3') = 7·8); 5·59 d, 1 H (H-5, J = 0·5); 6·04 dd, 1 H (H-1', J(1', 2a') = 6·0; J(1', 2b') = 9·0); 7·11–7·41 m, 15 H (H-arom.); 11·37 s, 1 H (H-3). The remaining part of the material from the above chromatography (3·31 g) was used without further purification in the next reaction step.

1-(2-Deoxy-3-O-methanesulfonyl-5-O-triphenylmethyl-β-D-*threo*-
-pentofuranosyl)-6-methyluracil (*V*)

Methanesulfonyl chloride (1 ml, 12·9 mmol) was added at 0°C to a stirred solution of crude derivative *IV* (3·31 g, 6·8 mmol) in pyridine (15 ml). After standing at 0°C for 1 h and at room temperature for 4 h, the reaction mixture was added dropwise to ice-cold water (400 ml). The precipitate was collected, washed with water (300 ml) and dried, first on air and then over potassium hydroxide. The material (3 g) was crystallized from toluene to give 2·26 g of mesylate *V*, m.p. 148–149°C; R_F 0·68 (S1). Chromatography of the mother liquors on a column of silica gel (50 g) in ethyl acetate–toluene (4 : 1) afforded further product (200 mg). Total yield 55% (based on *III*). For $C_{30}H_{30}N_2O_7S$ (562·6) calculated: 64·04% C, 5·37% H, 4·98% N, 5·70% S; found: 64·20% C, 5·54% H, 4·98% N, 5·54% S. ^{1}H NMR spectrum: 2·29 s, 3 H (CH_3); 2·30 to 3·00 m, 2 H (2 × H-2'); 3·01 s, 3 H (CH_3SO_2); 3·11–3·52 m, 2 H (2 × H-5'); 4·07–4·33 m, 1 H (H-4'); 5·19–5·39 m, 1 H (H-3'); 5·56 s, 1 H (H-5); 6·26 t, 1 H (H-1', J(1', 2a') = J(1', 2b') = 7·5); 7·10–7·60 m, 15 H (H-arom.); 11·30 bs, 1 H (H-3).

1-(3-Azido-2,3-dideoxy-5-O-triphenylmethyl-β-D-*erythro*-
-pentofuranosyl)-6-methyluracil (*VIa*)

A solution of mesylate *V* (2·26 g, 4 mmol) and lithium azide (0·78 g, 16 mmol) in dimethylformamide (30 ml) was concentrated in vacuo to half of the original volume and then heated to 100°C for 20 min under argon. After cooling, the solution was added dropwise into ice-cold water (250 ml). The precipitate was filtered, washed with water (200 ml) and dried on air and then in a desiccator over potassium hydroxide. Yield 1·79 g of *VIa*. A part (0·75 g) was chromato-

graphed on a column of silica gel (40 g) in ethyl acetate–toluene (3 : 2). The UV-absorbing eluate was concentrated, the residue dissolved in toluene (10 ml) and added dropwise under stirring to light petroleum (150 ml). The precipitate was filtered, washed with light petroleum and air-dried to give 0·72 g (84%) of compound *VIa*, m.p. 155–157°C; R_F 0·42 (S2). For $C_{29}H_{27}N_5O_4$ (509·6) calculated: 68·35% C, 5·34% H, 13·74% N; found: 68·25% C, 5·25% H, 13·53% N. IR spectrum (chloroform): 3 392 (NH free); 3 186 (NH bonded); 3 060 (CH); 2 104 (N_3); 1 728, 1 706 (C=O); 1 625 (C=C); 1 600, 1 495 (phenyl); 1 107, 1 091, 1 079 (C–O). (KBr): 3 200 (NH); 2 104 (N_3); 1 728, 1 704 (C=O); 1 629 (C=C); 1 089 (C–O). ^{1}H NMR spectrum: 2·29 s, 3 H (CH_3); 23·0–3·00 m, 2 H (2 × H-2′); 2·90–3·14 m, 2 H (2 × H-5′); 3·74–3·94 m, 1 H (H-4′); 4·44 q, 1 H (H-3′, J(3′, 2a′) = J(3′, 2b′) = J(3′, 4′) = 8·0); 5·54 s, 1 H (H-5); 6·04 dd, 1 H (H-1′, J(1′, 2a′) = 3·7; J(1′, 2b′) = 6·2); 7·11–7·61 m, 15 H (H-arom.); 11·17 bs, 1 H (H-3).

1-(3-Azido-2,3-dideoxy-β-D-*erythro*-pentofuranosyl)-6-methyluracil (*VIb*)

A solution of trityl derivative *VIa* (1·02 g, 2 mmol) in 80% acetic acid (10 ml) was heated to 106°C for 30 min. After cooling, butanol (10 ml) was added, the solvent evaporated, the residue co-evaporated with toluene (3 × 10 ml) and chromatographed on a column of silica gel (35 g) in ethyl acetate. The UV-absorbing fraction was concentrated and the residue mixed with several drops of water. The solid material was crystallized from ethyl acetate to give monohydrate of azidonucleoside *VIb* (380 mg, 67%), m.p. 78–80°C; R_F 0·30 (S1). For $C_{10}H_{13}N_5O_4.H_2O$ (285·3) calculated: 42·11% C, 5·30% H, 24·55% N; found: 42·15% C, 5·19% H, 24·53% N. UV spectrum (water): λ_{max} 260 nm (ε 11 990), λ_{min} 229 nm (ε 3 190); pH 12: λ_{max} 260 and 211 nm (ε 8 520 and 13 910), λ_{min} 242 nm (ε 5 900). IR spectrum (KBr): 3 502, 3 250, 3 056 (OH and NH); 2 107 (N_3); 1 727, 1 704, 1 685 (C=O); 1 628 (C=C); 1 089, 1 073, 1 055 (C–O). ^{1}H NMR spectrum: 2·27 s, 3 H (CH_3); 1·97–2·35 m, 1 H (H-2a′); 2·86 m, 1 H (H-2b′, J(2a′, 2b′) = 13·5; J(2b′, 1′) = 4·5; J(2b′, 3′) = 9·0); 3·51–3·81 m, 3 H (2 × H-5′, H-4′); 4·37 m, 1 H (H-3′, J(3′, 2a′) = J(3′, 4′) = 7; J(3′, 2b′) = 9·0); 4·91 t, 1 H (5′-OH, J(OH, 5′) = 5·4); 5·52 d, 1 H (H-5, J = 1·0); 5·99 dd, 1 H (H-1′, J(1′, 2a′) = 9·0; J(1′, 2b′) = 4·5); 11·10 s, 1 H (H-3).

3-(3-Azido-2,3-dideoxy-5-O-triphenylmethyl-β-D-*erythro*-pentofuranosyl)-6-methyluracil (*VIIa*)

A solution of anhydro derivative *III* (933 mg, 2 mmol) and lithium azide (0·4 g, 8 mmol) in dimethylformamide (6 ml) was heated to 150°C (bath) for 3 h under argon. After cooling and addition of water (40 ml), the reaction mixture was extracted with chloroform (30 ml), the organic layer washed with water (3 × 10 ml), dried over anhydrous sodium sulfate and the solvent evaporated in vacuo. The residue was chromatographed on a column of silica gel (15 g) in toluene–ethyl acetate (1 : 1). The first fraction (R_F 0·42 in S2) was evaporated, the residue dissolved in acetone (4 ml) and the solution added dropwise into ice-cold water (50 ml). The precipitate was filtered, washed with water (40 ml) and dried on air and then in vacuo over potassium hydroxide. Yield 720 mg (71%) of azido derivative *VIIa*. For $C_{29}H_{27}N_5O_4$ (509·6) calculated: 68·36% C, 5·34% H, 13·74% N; found: 68·14% C, 5·44% H, 13·72% N. IR spectrum (chloroform): 3 416, 3 228, 3 191, 3 121 (NH); 3 061 (C–H); 2 140 (N_3); 1 726, 1 667 (C=O); 1 602, 1 496 (phenyl); 1 092, 1 080 (C–O). ^{1}H NMR spectrum: 2·02 s, 3 H (CH_3); 2·08–2·45 m, 2·55 to 2·85 m, 2 H (2 × H-2′); 3·16–3·37 m, 2 H (2 × H-5′); 3·85 m, 1 H (H-4′, J(4′, 5b′) = J(4′, 5a′) = = 5·5; J(4′, 3′) = 7·6); 4·38 q, 1 H (H-3′, J(3′, 2a′) = J(3′, 2b′) = J(3′, 4′) = 7·6); 5·43 d, 1 H (H-5, J = 0·7); 6·55 dd, 1 H (H-1′, J(1′, 2a′) = 9·0; J(1′, 2b′) = 3·8); 7·11–7·61 m, 15 H (H-arom.); 11·05 s, 1 H (H-3). The second fraction (R_F 0·42 in S2) was taken down, the residue was dissolved in toluene (2 ml) and added dropwise into stirred light petroleum (30 ml). The

crystalline precipitate was filtered and washed with light petroleum, affording 152 mg (15% of azido derivative *VIa* identical (m.p., IR and ^{1}H NMR spectra) with the substance prepared from mesyl derivative *V*.

3-(3-Azido-2,3-dideoxy-β-D-*erythro*-pentofuranosyl)-6-methyluracil (*VIIb*)

A solution of trityl derivative *VIIa* (501 mg, 1 mmol) in 80% acetic acid (5 ml) was heated to 106°C for 30 min. After cooling, butanol (5 ml) was added and the solvents were evaporated. The residue was coevaporated with toluene (3 × 5 ml) and crystallized from water to afford 200 mg (75%) of azido derivative *VIIb*, m.p. 116–118°C; R_F 0·39 (S1). For $C_{10}H_{13}N_5O_4$ (267·2) calculated: 44·94% C, 4·90% H, 26·21% N; found: 45·16% C, 4·80% H, 25·92% N. UV spectrum (water): λ_{max} 264 nm (ε 9 320), λ_{min} 232 nm (ε 2 300); pH 12: λ_{max} 288 and 217 nm (ε 11 610 and 8 180), λ_{min} 246 nm (ε 900). IR spectrum (KBr): 3 350, 3 266, 3 180, 3 119 (OH, NH); 2 108 (N_3); 1 727, 1 671 (C=O); 1 671 (C=C); 1 124, 1 104, 1 069 (C–O). ^{1}H NMR spectrum: 2·01 s, 3 H (CH_3); 2·15 m, 1 H (H-2a', J(2a', 1') = 8·7; J(2a', 2b') = 13·5; J(2a', 3') = 6·6); 2·80 m, 1 H (H-2b', J(2b', 1') = 4·8; J(2b', 3') = 8·7); 3·31–3·81 m, 3 H (2 × H-5', H-4'); 4·41 m, 1 H (H-3', J(3', 4') = 6·6); 4·77 bs, 1 H (OH); 5·47 d, 1 H (H-5, J = 1·0); 6·48 dd, 1 H (H-1'); 11·24 s, 1 H (H-3).

1-(5-O-Tert-butyldiphenylsilyl-2-deoxy-β-D-*erythro*-pentofuranosyl)-6-methyluracil (*VIII*)

Tert-butyldiphenylsilyl chloride (5·5 ml, 20 mmol) was added to a solution of 2'-deoxynucleoside[8] *I* (4·84 g, 20 mmol) and imidazole (2·72 g, 40 mmol in dimethylformamide (50 ml). After standing at room temperature for 20 h, the solvent was evaporated, the residue dissolved in chloroform (200 ml), the solution washed with water (3 × 80 ml) and dried over anhydrous sodium sulfate. The solvent was evaporated in vacuo and the residue chromatographed on a column of silica gel (800 g) in ethyl acetate. Yield 8·76 g (91%) of silyl derivative *VIII* as a solid foam; R_F 0·57 (S1). For $C_{26}H_{32}N_2O_5Si$ (480·6) calculated: 64·97% C, 6·71% H, 5·83% N; found: 64·88% C, 6·75% H, 5·78% N. ^{1}H NMR spectrum: 0·99 s, 9 H ($(CH_3)_3C$); 2·28 s, 3 H (CH_3); 1·89–2·27 m, 2·50 to 2·83 m, 2 H (2 × H-2'); 3·81 m, 3 H (H-4', 2 × H-5'); 4·31 m, 1 H (H-3'); 5·16 d, 1 H (OH, J(OH, 3') = 5·5); 5·51 s, 1 H (H-5); 6·07 dd, 1 H (H-1', J(1', 2a') = 5·3, J(1', 2b') = 8·8); 7·34–7·50 m, 7·54–7·70 m, 10 H (H-arom.); 11·07 s, 1 H (H-3).

1-(5-O-Tert-butyldiphenylsilyl-2-deoxy-3-O-phenoxythiocarbonyl-β-D-*erythro*-pentofuranosyl)-6-methyluracil (*IX*)

4-Dimethylaminopyridine (975 mg, 8 mmol) and phenoxythiocarbonyl chloride (0·9 ml, 6·5 mmol) were added to a solution of silyl derivative *VIII* (1·93 g, 4 mmol) in acetonitrile (15 ml). The mixture was stirred at room temperature for 24 h, the insoluble portion was filtered, washed with acetonitrile and the combined filtrates were concentrated. After evaporation of the solvent, the residue was chromatographed on a column of silica gel (100 g) in ethyl acetate–toluene (1 : 1) to give 1·47 g (60%) of compound *IX* as a solid foam; R_F 0·54 (S2). For $C_{33}H_{36}N_2SSi$ (616·8) calculated: 64·26% C, 5·88% H, 4·54% N, 5·20% S; found: 64·16% C, 6·10% H, 4·74% N, 4·95% S.

5'-O-Tert-butyldiphenylsilyl-2',3'-dideoxy-6-methyluridine (*Xa*)

To a stirred solution of thiocarbonyl derivative *IX* (1·34 g, 2 mmol) in toluene (20 ml) was added at 90°C 1M tributyltin hydride in toluene (4 ml), followed by 2,2'-azobis(2-methylpropionitrile) (50 mg). After 30 min, the solution was cooled and the solvent evaporated. Chromatography

of the residue on a column of silica gel (120 g) in ethyl acetate–toluene (1 : 1) afforded 770 mg (83%) of dideoxy derivative *Xa* as a solid foam; R_F 0·36 (S2). For $C_{26}H_{32}N_2O_4Si$ (464·6) calculated: 67·21% C, 6·94% H, 6·03% N; found: 67·31% C, 7·01% H, 5·89% N. ^{1}H NMR spectrum: 0·99 s, 9 H ($(CH_3)_3C$); 1·68–2·28 m, 4 H (2 × H-3′, 2 × H-2′); 2·29 s, 3 H (CH_3); 3·78 d, 2 H (2 × H-5′, J(5a′, 4′) = J(5b′, 4′) = 4·5); 3·87–4·17 m, 1 H (H-4′); 5·51 s, 1 H (H-5); 6·00 t, 1 H (H-1′, J(1′, 2a′) = J(1′, 2b′) = 6·0); 7·35–7·51 m, 7·55–7·71 m, 10 H (H-arom.); 11·10 s, 1 H (H-3).

2′,3′-Dideoxy-6-methyluridine (*Xb*)

A solution of silyl derivative *Xa* (750 mg, 1·6 mmol) in dioxane (7 ml) was mixed with 1M tetrabutylammonium fluoride in tetrahydrofuran (1·6 ml). After standing at room temperature for 4 h, the reaction mixture was taken down and the residue chromatographed on a column of silica gel (50 g); elution first with ethyl acetate and then with ethyl acetate–acetone–ethanol–water (36 : 6 : 5 : 3). Yield 210 mg (58%) of compound *Xb* as a syrup; R_F 0·37 (S3). For $C_{10}H_{14}N_2O_4$ (226·2) calculated: 53·08% C, 6·23% H, 12·38% N; found: 52·90% C, 6·44% H, 12·17% N. UV spectrum (water): λ_{max} 261 nm (ε 10 350), λ_{min} 229 nm (ε 2 490); pH 12: λ_{max} 262 and 210 nm (ε 7 460 and 11 630), λ_{min} 241 nm (ε 4 630). ^{1}H NMR spectrum: 1·76–2·15 m, 4 H (2 × H-3′, 2 × H-2′); 2·29 s, 3 H (CH_3); 3·15–3·55 m, 2 H (2 × H-5′); 3·91 m, 1 H (H-4′); 4·66 t, 1 H (OH, J(OH, 5′) = 5·5); 5·49 s, 1 H (H-5); 5·96 dd, 1 H (H-1′, J(1′, 2a′) = 5·8; J(1′, 2b′) = 7·3); 11·03 s, 1 H (H-5).

2,2′-Anhydro-1-(5-O-tert-butyldiphenylsilyl-β-D-arabinofuranosyl)-6-methyluracil (*XII*)

Tert-butyldiphenylsilyl chloride (5·5 ml, 20 mmol) was added to a solution of anhydro derivative[7,8] *XI* (4·82 g, 20 mmol) and imidazole (2·72 g, 40 mmol) in dimethylformamide (70 ml). The solution was set aside at room temperature overnight, the solvent evaporated in vacuo and the residue dissolved in ethyl acetate (200 ml). The solution was washed with water (3 × 30 ml), dried over anhydrous sodium sulfate and the solvent was evaporated in vacuo, yielding 9·22 g of crude product. A part (0·5 g) of this material was chromatographed on a column of silica gel (50 g) in ethyl acetate–acetone–ethanol–water (20 : 3 : 1 : 1) to give 330 mg (63%) of anhydro derivative *XII* as a solid foam; R_F 0·70 (S3). For $C_{26}H_{30}N_2O_5Si$ (478·6) calculated: 65·23% C, 6·32% H, 5·85% N; found: 65·25% C, 6·39% H, 5·96% N. IR spectrum (chloroform): 3 280 (OH); 1 666 (C=O); 1 562 (C=N); 1 115 (Si-phenyl). ^{1}H NMR spectrum: 0·92 s, 9 H ($(CH_3)_3C$); 2·29 s, 3 H (CH_3); 3·39–3·74 m, 2 H (2 × H-5′); 4·09–4·68 m, 1 H (H-4′); 4·41–4·51 m, 1 H (H-3′); 5·23 dd, 1 H (H-2′, J(2′, 1′) = 6·0; J(2′, 3′) = 1·5); 5·76 d, 1 H (H-5, J = 1·0); 6·01 d, 1 H (OH, J(OH, 3′) = 4·7); 6·49 d, 1 H (H-1′, J(1′, 2′) = 6·0); 7·32–7·72 m, 10 H (H-arom.).

Reaction of Anhydro Derivative *XII* in Lithium Hydroxide Solution

A solution of crude anhydro derivative *XII* (8·72 g; prepared from 18·9 mmol of anhydro derivative *XI*) in a solution of lithium hydroxide monohydrate (2 g, 47·7 mmol) in methanol containing 10% water (100 ml) was allowed to stand at room temperature overnight. After neutralization with solid carbon dioxide, the solvent was evaporated and the residue chromatographed on a column of silica gel (500 g) in ethyl acetate. Crystallization of the first fraction from toluene–light petroleum (9 : 1) afforded 4·71 g (50% based on compound *XI*) of 2′,6-anhydro-1-(5-O-tert-butyldiphenylsilyl-β-D-arabinofuranosyl)-5,6-dihydro-6-hydroxy-6-methyluracil (*XIV*), m.p. 149 to 150°C; R_F 0·26 (S2), 0·70 (S1). For $C_{26}H_{32}N_2O_6Si$ (496·6) calculated: 62·88% C, 6·50% H, 5·64% N; found: 62·75% C, 6·36% H, 5·57% N. IR spectrum (chloroform): 3 402 (NH); 1 731

(C=O); 1 115 (Si–phenyl). ^{1}H NMR spectrum: 1·00 s, 9 H ($(CH_3)_3C$); 1·37 s, 3 H (CH_3); 2·60 d, 1 H (H-5a, J(5a, 5b) = 15·0); 2·96 d, 1 H (H-5b); 3·63–3·98 m, 3 H (H-4′, 2 × H-5′); 4·03–4·25 m, 1 H (H-3′); 4·58 d, 1 H (H-2′, J(2′, 1′) = 4·2); 5·63 d, 1 H (OH, J(OH, 3′) = = 5·0); 5·86 d, 1 H (H-1′, J(1′, 2′) = 4·2); 7·34–7·52 m, 7·56–7·76 m, 10 H (H-arom.); 10·55 s, 1 H (H-3). Further fraction afforded 1·40 g of 1-(5-O-tert-butyldiphenylsilyl-β-D-arabinofuranosyl)-6-methyluracil (*XIII*) as a solid foam; R_F 0·54 (S1). For $C_{26}H_{32}N_2O_6Si$ (496·6) calculated: 62·88% C, 6·50% H, 5·64% N; found: 62·56% C, 6·56% H, 5·36% N. IR spectrum (chloroform): 3 410 (NH); 3 200 (OH); 1 703 (C=O); 1 616 (C=C); 1 373 (CH_3); 1 139, 1 057 (C–O, Si–O–C); 1 115 (Si–phenyl). ^{1}H NMR spectrum: 0·99 s, 9 H ($(CH_3)_3C$); 2·33 s, 3 H (CH_3); 3·48–4·28 m, 5 H (2 × H-5′, H-4′, H-3′, H-2′); 5·41 d, 2 H (OH, H-5); 6·15 d, 1 H (OH, J = 6·5); 7·38–7·52 m, 7·60–7·74 m, 10 H (H-arom.); 11·14 s, 1 H (H-3).

Reaction of Dihydro Derivative *XIV* in Alkaline Medium

Concentrated aqueous ammonia (1 ml) was added to a solution of dihydro derivative *XIV* (2·48 g, 5 mmol) in methanol (20 ml). After standing overnight at room temperature, the reaction mixture was concentrated in vacuo and the residue chromatographed on a column of silica gel (150 g) in ethyl acetate. Yield 2·01 g (81%) of the starting dihydro derivative *XIV* and 410 mg (16·5%) of arabinosyl derivative *XIII*, identical with the product obtained above.

1-(5-O-Tert-butyldiphenylsilyl-2,3-O-diphenoxythiocarbonyl-
-β-D-arabinofuranosyl)-6-methyluracil (*XV*)

Phenoxythiocarbonyl chloride (1·5 ml, 10·8 mmol), followed by 4-dimethylaminopyridine (1·51 g, 12·4 mmol), was added to a stirred solution of arabinosyl derivative *XIII* (1·49 g, 3 mmol) in acetonitrile (20 ml). After stirring for 20 h at room temperature, the undissolved portion was filtered, washed with a small amount of acetonitrile and the combined filtrates were taken down. The residue was chromatographed on a column of silica gel (200 g) in toluene–ethyl acetate (3 : 1). The UV-absorbing fraction was evaporated, the crystalline residue was triturated with light petroleum and collected on filter, affording 1·47 g (67%) of phenoxythiocarbonyl derivative *XV*, m.p. 156–158°C; R_F 0·73 (S2). For $C_{38}H_{40}N_2O_7S_2Si$ (728·9) calculated: 62·61% C, 5·53% H, 3·84% N, 8·80% S; found: 62·90% C, 5·41% H, 4·07% N, 8·54% S.

1-(5-O-Tert-butyldiphenylsilyl-2,3-didehydro-2,3-dideoxy-
-β-D-pentofuranosyl)-6-methyluracil (*XVI*)

A solution of 1M tributyltin hydride (2 ml), followed by 2,2′-azobis(2-propionitrile) (20 mg), was added to a stirred solution of diphenylthiocarbonyl derivative *XV* (769 mg, 1 mmol) in toluene (10 ml) at 100°C. After 15 min, the mixture was cooled and applied onto a column of silica gel (80 g). The UV-absorbing fraction obtained by elution with ethyl acetate–toluene (3 : 1), was evaporated and the product was crystallized from cyclohexane to give 370 mg (80%) of didehydro derivative *XVI*, m.p. 124–127°C; R_F 0·37 (S2). For $C_{26}H_{30}N_2O_4Si$ (462·6) calculated: 67·50% C, 6·54% H, 6·06% N; found: 67·75% C, 6·66% H, 6·18% N. IR spectrum (chloroform): 3 399 (NH); 1 716 (C=O); 1 624 (C=C base); 1 115 (Si–phenyl). ^{1}H NMR spectrum: 0·99 s, 9 H ($(CH_3)_3C$); 2·29 s, 3 H (CH_3); 3·64–3·91 m, 2 H (2 × H-5′); 4·75 to 5·98 m, 1 H (H-4′); 5·50 s, 1 H (H-5); 5·96–6·22 m, 2 H (H-2′, H-3′); 6·65 bs, 1 H (H-1′); 7·32 to 7·52 m, 7·53–7·71 m, 10 H (H-arom.); 11·05 s, 1 H (H-3).

Desilylation of 5′-O-Tert-butyldiphenylsilyl-2′,3′-didehydro-
-2′,3′-dideoxy Derivative *XVI*

To a solution of silyl derivative *XVI* (92 mg, 0·2 mmol) in tetrahydrofuran (0·4 ml) was added 1M solution of tetrabutylammonium fluoride (0·2 mmol) in tetrahydrofuran. The reaction was monitored by TLC in the systems S2 and S3. Spots were detected by UV light and flame-heating. After 15 min no starting silyl derivative *XVI* was present in the reaction mixture which was then applied onto a column of silica gel (20 g) and eluted with the system S3 in the course of 15 min. The fraction of R_F 0·52 was crystallized from methanol to afford 16 mg (64%) of product whose IR spectrum was identical with that of 6-methyluracil. The chromatography gave further 8 mg of a mixture of 6-methyluracil and a compound which was easily detected on TLC by flame heating. In the same easy manner were detected 2′,3′-didehydro-2′,3′-dideoxynucleosides. Attempted rechromatography afforded only 6-methyluracil.

The authors are indebted to Mrs F. Pospíšilová for the excellent technical assistance, Dr P. Fiedler for interpretation of the IR *spectra, Mrs J. Jelínková for* ^{1}H NMR *spectral measurements and the staff of the Analytical Laboratory (Dr V. Pechanec, Head) of this Institute for elemental analyses.*

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Translated by M. Tichý.