SYNTHESIS OF 2'-DEOXYTHYMIDINE, 2'-DEOXY-5-FLUOROURIDINE, AND 2'-DEOXY-6-AZAURIDINE FROM RIBONUCLEOSIDES*

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Received February 27th, 1974

5-Methyluridine (*Ia*), 5-fluorouridine (*Ib*), and 6-azauridine (*Ic*) react with diphenyl carbonate to afford substituted $O^{2,2'}$-anhydronucleosides *II* which yield 3',5'-di-O-benzoyl-$O^{2,2'}$-anhydronucleosides *III* on treatment with benzoyl cyanide. By reaction with hydrogen chloride in dimethylformamide, compounds *III* are converted to the 2'-chloro-2'-deoxy-3',5'-di-O-benzoyl derivatives *IV* which yield the 3',5'-di-O-benzoyl-2'-deoxy nucleosides *V* by dehalogenation with tri-n-butyltin hydride. The whole process was completed by alkali-catalysed methanolysis of compounds *V* with the formation of the free 2'-deoxynucleosides *VI*, namely, 2'-deoxythymidine (*VIa*), 5-fluoro-2'-deoxyuridine (*VIb*), and 2'-deoxy-6-azauridine (*VIc*). Compound *VIa* and 2'-deoxyuridine (*VId*) were also prepared by a direct dehalogenation of 2'-chloro-2'-deoxyribonucleosides *VII* which had been obtained from the anhydronucleosides *IIa* and *IId* by reaction with hydrogen chloride in dimethylformamide.

Recently, there has been developed in this Laboratory a new modification of the conversion of pyrimidine ribonucleosides to the corresponding 2'-deoxyribonucleosides consisting in transformation of 3',5'-di-O-benzoyl-$O^{2,2'}$-anhydronucleosides to 3',5'-di-O-benzoyl-2'-chloro-2'-deoxyuridine derivatives by a stereospecific opening of the anhydro bond on treatment with hydrogen chloride; dehalogenation of the latter derivatives with tri-n-butyltin hydride affords the corresponding 2'-deoxyribonucleosides or their 3',5'-dibenzoates. This method has been successfully used in the synthesis of 2'-deoxyuridine and its L-enantiomer[1,2], 6-methyl-2'-deoxyuridine[3,4], and related compounds[5]; attention has been especially devoted to the application in the series of nucleosides with modified sugar residues. In this direction, simple syntheses have been effected of 2'-deoxy-α-ribonucleosides[6], 2'-deoxy-α-lyxofuranosides[7], and 3'-deoxy-β-D-psicofuranoside[8] derived from uracil and cytosine, from readily accessible starting materials.

* Part CLXVIII in the series Nucleic Acid Components and Their Analogues; Part CLXVII: This Journal *39*, 3100 (1974).

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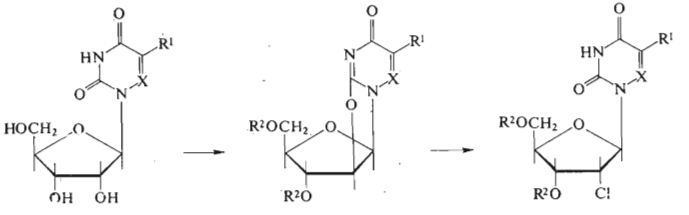
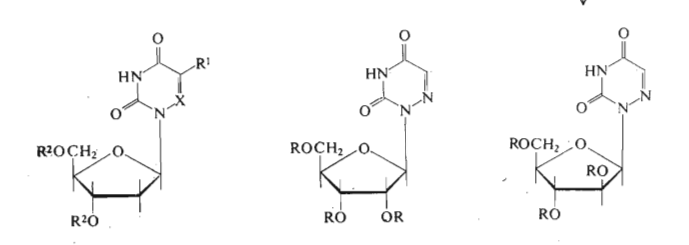
The key intermediate of this transformation is the $O^{2,2'}$-anhydronucleoside; it was the accessibility of these intermediates from sugar 2'-amino-1,2-oxazolines and derivatives of acetylenic acids[1-8] or related compounds[9] which made possible the realisation of the whole project. In special cases, it may be advantageous to prepare the $O^{2,2'}$-anhydrouridine derivative from ribonucleosides, *i.e.*, an uridine derivative modified on the heterocyclic moiety. Such a procedure might be preferable in cases when the corresponding 2'-deoxyuridine derivative is interesting from a biochemical or other standpoint but is accessible only with difficulty by a direct deoxyribosylation of a heterocyclic base or by the chemical modification of 2'-deoxyuridine. In contrast to deoxyribosylation, the synthesis of ribonucleosides by reaction of a benzoylated halogenose with a mercury salt of the heterocyclic base or by the Hilbert-Johnson reaction[10] is in most cases less complicated. The aim of the present work is to demonstrate the applicability of the above mentioned transformation



I *II*, $R^2 = H$; *III*, $R^2 = C_6H_5CO$ *IV*, $R^2 = C_6H_5CO$; *VII*, $R^2 = H$

In formulae *I*—*VII*; *a*, $R^1 = CH_3$, X = CH; *b*, $R^1 = F$, X = CH; *c*, $R^1 = H$, X = N; *d*, $R^1 = X = H$



VIII R = C_6H_5CO *IX* R = C_6H_5CO *V*, $R^2 = C_6H_5CO$; *VI*, $R^2 = H$

SCHEME 1

of uridine derivatives to 2'-deoxyuridine derivatives in the case of nucleosides modified on the heterocyclic moiety. As typical syntheses there are shown preparations of 2'-deoxythymidine (*VIa*), 5-fluoro-2'-deoxyuridine (*VIb*), and 2'-deoxy-6-azauridine (*VIc*) from the ribonucleosides *I*.

The general route is shown on Scheme 1. The modified β-D-ribonucleoside *I* is converted to the $O^{2,2'}$-anhydronucleoside *II* by reaction with diphenyl carbonate in the presence of sodium hydrogen carbonate. The procedure of Moffatt[11] using the phosphoric acid hexamethyltriamide as solvent is fully satisfactory. In most cases, a quantitative yield of the anhydronucleoside *II* is obtained. The crude *II* is directly benzoylated to the 3',5'-di-O-benzoate *III* by reaction with benzoyl cyanide[12] in an aprotic solvent, preferably dimethylformamide or acetonitrile. By the action of anhydrous hydrogen chloride in dimethylformamide, compound *III* is converted to the 2'-chloro-2'-deoxynucleoside *IV*. The configuration of the C—Cl bond is *ribo* in all cases as indicated by NMR spectra and in accordance with the earlier observed[2] stereospecificity of the anhydro bond opening in compounds of the type *III*. Reaction of the chloro derivative *IV* with tri-n-butyltin hydride[2] affords the 3',5'-di-O-benzoyl-2'-deoxyuridine *V* in a quantitative yield. In the last step, the protecting benzoyl groups of compound *V* are removed by an alkali-catalysed methanolysis with the formation of the free 2'-deoxyuridine derivative *VI*.

The principle of the whole reaction sequence, *i.e.*, conversion of the $O^{2,2'}$-anhydronucleoside *via* the 2'-deoxy-2'-chloro derivative to the 2'-deoxynucleoside may also be realised without the use of protecting groups. This alternative is demonstrated by the sequence *II* → *VII* → *VI* with the uracil and thymine derivative (Scheme 1); since, however, all these three types of products are soluble in water, a time-consuming deionisation of the reaction mixture is required in order to isolate compound *VII*. On the other hand, the isolation of all intermediates in the series of benzoyl derivatives is easy; since the benzoylation with benzoyl cyanide is a rapid and quantitative process, it is more advantageous to perform the whole transformation with benzoylated intermediates.

In spite of the ready accessibility of 2'-deoxythymidine, there may be some interest in its preparation by the above procedure since the corresponding starting ribonucleoside, namely, 5-methyluridine (*Ia*) is obtained by the Hilbert-Johnson reaction in an unusually high yield. The original synthesis[13] of compound *Ia* was somewhat modified in the present work. The first synthetic steps in the thymine series, compounds *Ia*—*IIIa*, have been reported earlier[2]; when compared with the earlier[2] applied 2'-deoxy-2'-iodo derivative, the present 2'-deoxy-2'-chloro derivative *IVa* is more advantageous. 3',5'-Di-O-benzoyl-2'-deoxythymidine (*Va*) and 2'-deoxythymidine (*VIa*) obtained as the final products, are identical with authentic specimens on paper chromatography, UV spectra, and NMR spectra.

2'-Deoxy-5-fluorouridine (*VIb*) attracts attention because of the bacteriostatic and virostatic effects[14]. Its synthesis by deoxyribosylation[15] is not satisfactory.

On the other hand, 5-fluorouridine (*Ib*) is readily accessible either by ribosylation of 5-fluorouracil mercuric salt[16] or, more recently, by fluorination of uridine[17]. The direct preparation of 5-fluoro-2'-deoxyuridine[17] (*VIb*) by fluorination of 2'-deoxyuridine is less advantageous since the starting compound is rather labile and expensive; it was therefore desirable to examine another route. In this respect, the synthetic transformation of 5-fluorouridine (*Ib*) to compound *VIb* proved satisfactory. The organotin reagent reduces selectively the C—Cl bond in the presence

TABLE I

Chromatography (R_F values in solvent systems S_1 to S_5) and Electrophoretical Mobilities (in buffer solutions E_1 and E_2)

Compound	S_1	S_2	S_3	S_4	S_5	E_1[a]	E_2[b]
Ia	0·52	0·32	—	0·50	—	0	1·00
Ib	0·54	0·40	—	0·60	—	0·46	1·64
Ic	0·45	0·40	—	—	—	0·52	2·00
Id	0·45	0·26	—	0·40	—	0	1·00
IIa	0·60	0·35	—	0·18	—	−0·05	−0·10
IIb	0·47	0·43	—	0·15	—	0	1·04
IIc	0·56	0·32	—	—	—	0·10	0
IId	0·56	0·29	—	0·05	—	−0·08	−0·13
IIIa	—	—	0·46	0·20	—	—	—
IIIb	—	—	0·47	0·15	—	—	—
IIIc	—	—	0·40	0·10	—	—	—
IIId	—	—	0·40	0·10	—	—	—
IVa	—	—	0·78	—	0·50	—	—
IVb	—	—	0·70	—	0·52	—	—
IVc	—	—	0·76	—	0·50	—	—
IVd	—	—	0·70	—	0·45	—	—
Va	—	—	0·48	—	0·30	—	—
Vb	—	—	0·50	—	0·35	—	—
Vc	—	—	0·40	—	0·36	—	—
Vd	—	—	0·42	—	0·30	—	—
VIa	0·58	0·42	—	0·48	—	0	0
VIb	0·56	0·45	—	0·43	—	0·46	1·04
VIc	0·57	0·40	—	0·52	—	0·52	1·25
VId	0·57	0·40	—	0·56	—	0	0
VIIa	0·60	0·60	—	0·87	—	0	0
VIId	0·57	0·62	—	0·80	—	0	0
VIII	—	—	0·80	—	—	—	—
IX	—	—	0·70	—	—	—	—

[a] Referred to uridine 3'-phosphate; [b] referred to uridine.

of the C—F bond, since no 2'-deoxyuridine is formed. Under conditions of a radical reaction with tri-n-butyltin hydride, such a stability of the C—F bond is not surprising. Similar to the thymine series, the identity of the final product *VIb* was confirmed by comparison with an authentic material[17] while the structure of all intermediates is in accord with elemental analysis and NMR spectra.

Finally, the preparation of 2'-deoxy-6-azauridine (*VIc*) from 6-azauridine (*Ic*) has been examined. In spite of the biochemical interest[18] in 6-azauracil and particularly 6-azauridine (*Ic*), 2'-deoxy-6-azauridine has not been investigated in detail since the preliminary experiments did not indicate any activity and because of its difficult accessibility. 2'-Deoxy-6-azauridine has been obtained in a moderate yield by a direct deoxyribosylation of a partially protected 6-azauracil[19]. On the other hand, 6-azauridine (*Ic*) represents a readily accessible starting material. The principal difficulty in the 6-azauracil series consists in the preparation of $O^{2,2'}$-anhydro-6-azauridine (*IIc*). The reaction gives a lower yield than in the above cases obviously because of the high lability and the acidic character of compound *IIc* (*cf.*[20]). The formation of $O^{2,2'}$--anhydronucleosides by reaction of ribonucleosides with diphenyl carbonate has been shown[21] to involve the stage of 2',3'-cyclic carbonates which are opened by an attack of the pyrimidine ring 2-oxo group with the formation of the $O^{2,2'}$-anhydro bond. This S_N2 reaction is of course negatively affected by an increased acidity of the heterocyclic system. After benzoylation of the crude reaction mixture, there were isolated the 2',3',5'-tri-O-benzoates of 6-azauridine (*VIII*) and of 1-(β-D-arabinofuranosyl)-6-azauracil (*IX*) in addition to the principal product *IIIc*. The further processing of compound *IIIc* was analogous to other types. The final 2'-deoxy--6-azauridine (*VIc*) was isolated in a pure state and its structure was confirmed on the basis of chromatographical, electrophoretical and spectroscopical behaviour as well as by NMR spectra of compound *VIc* and the corresponding intermediates.

The above syntheses of 2'-deoxyuridine derivatives modified on the heterocyclic moiety from the corresponding ribonucleosides involve starting compounds, intermediates, and final products of different chemical characters; consequently, the general nature and applicability of the novel transformation to various types of uracil nucleosides is demonstrated. In view of the simplicity, high yields in all steps, and stereospecificity, the present method might be more advantageous than the direct deoxyribosylation.

EXPERIMENTAL

Unless stated otherwise, solutions were taken down on a rotatory evaporator at 35°C/15 Torr and analytical samples were dried over phosphorus pentoxide at 0.1 Torr. Melting points were taken on a heated microscope stage (Kofler block) and are not corrected.

Methods. Paper chromatography was performed by the descending technique on paper Whatman No 3 MM in the solvent systems S_1, 2-propanol–conc. aqueous ammonia–water (7 : 1 : 2), and S_2, 1-butanol–acetic acid–water (5 : 2 : 5). Thin-layer chromatography on ready-for-use

Silufol UV_{235} silica gel foils (Kavalier Glassworks, Votice, Czechoslovakia) was carried out in the solvent systems S_3, chloroform–ethanol (97 : 3), S_4, chloroform–ethanol (8 : 2), and S_5, benzene–ethyl acetate (7 : 3). Paper electrophoresis was performed by the technique of Markham and Smith[22] on paper Whatman No 3 MM at 20 V/cm (1 h) in the buffer solutions E_1, 0·1M triethylammonium hydrogen carbonate (pH 7·5), and E_2, 0·1M triethylammonium borate (pH 7·5). For the R_F values and electrophoretical mobilities see Table I. The NMR spectra were taken on a Varian 100 apparatus in deuteriochloroform or hexadeuteriodimethyl sulfoxide with the use of hexamethyldisiloxane as internal standard. The δ values of chemical shifts are given in p.p.m.; the coupling constants are expressed in Hz.

5-Methyluridine[13] (*Ia*)

A suspension of 2,3,5-tri-O-benzoyl-1-O-acetyl-D-ribofuranose (100 g; 0·2 mol) in ether (1 000 ml) was saturated at 0°C with gaseous hydrogen chloride, the solution kept at room temperature for 4 days under exclusion of atmospheric moisture (calcium chloride tube), and evaporated under diminished pressure. After coevaporation with four 50 ml portions of toluene, the residue was dissolved in acetonitrile (500 ml); dried over phosphorus pentoxide), the solution treated with 2,4-dimethoxy-5-methylpyrimidine[23], the whole refluxed (calcium chloride tube) for 7 h, and evaporated under diminished pressure. The residue was dissolved in chloroform (200 ml), the solution saturated at 0°C with gaseous hydrogen chloride, kept at room temperature overnight, and evaporated under diminished pressure. In order to remove hydrogen chloride, the residue was coevaporated with three 50 ml portions of toluene. The final residue was dissolved in hot ethanol (500 ml) and the solution cooled externally with ice to deposit the tribenzoate of compound *Ia*, which was collected with suction, washed with ethanol, and dried under diminished pressure. The mother liquor was evaporated and the residue crystallised (active charcoal) from ethanol to afford an additional crop of the chromatographically homogeneous product (R_F 0·40 in S_3). Overall yield, 66 g (58%) of 2′,3′,5′-tri-O-benzoyl-5-methyluridine.

The above tribenzoate was kept at room temperature in 0·1M methanolic sodium methoxide overnight and neutralised with dry Dowex 50 (H^+) cation exchange resin. The resin was filtered off and washed with methanol (200 ml). The combined filtrate and washings were evaporated under diminished pressure, the residue treated with water (100 ml), the aqueous phase washed with three 50 ml portions of ethanol, and finally evaporated under diminished pressure. The residue was crystallised from ethanol to afford 26 g (50%, referred to the halogenose) of 5-methyluridine, m.p. 185°C, homogeneous on chromatography (solvent systems S_1 and S_2) and electrophoresis (buffer solution E_2) and identical with an authentic specimen[13].

2′-Chloro-2′-deoxy-3′,5′-di-O-benzoyl-5-methyluridine (*IVa*)

A mixture of 5-methyluridine (*Ia*; 10·0 g; 38·7 mmol), diphenyl carbonate (11·5 g), sodium hydrogen carbonate (250 mg), and phosphoric acid hexamethyltriamide (40 ml) was heated at 150°C 20 min under occasional stirring and under exclusion of atmospheric moisture (calcium chloride tube). The mixture was then cooled down, diluted with water (500 ml), and washed with three 100 ml portions of chloroform. The aqueous phase was evaporated under diminished pressure, the residue coevaporated with three 50 ml portions of ethanol, and finally dried *in vacuo*. To the suspension of this residue in dimethylformamide (50 ml) there was added benzoyl cyanide (16·5 g; 126 mmol) and then with stirring drops of triethylamine (total, 2 ml) until the exothermic reaction set in. After stirring for 15 min, there was added ether (500 ml), the product collected with suction, washed with ether, and dried. Yield, 15 g (86·5%) of 3′,5′-di-O-benzoyl-5-methyl-$O^{2,2'}$-

-anhydrouridine (*IIIa*), m.p. > 250°C, chromatographically homogeneous (S_3) and identical with an authentic specimen[2].

A solution of compound *IIIa* (11·2 g; 25 mmol) in 2M hydrogen chloride in dimethylformamide (100 ml) was heated at 100°C under exclusion of atmospheric moisture (calcium chloride tube) until compound *IIIa* disappeared (90 min), as shown by thin layer chromatography in S_3. The mixture was then poured into water (1000 ml), the precipitate of compound *IVa* collected with suction, washed with water until neutral, and dissolved in chloroform (200 ml). The solution was dried over anhydrous magnesium sulfate, filtered, the filtrate evaporated, and the residue crystallised from ethanol (100 ml) to afford 5·5 g (45·5%) of compound *IVa*, m.p. 185—186°C, chromatographically homogeneous in S_3. Optical rotation: $[\alpha]^{25}$ −45·2° (*c* 0·5; dimethylformamide). From the mother liquor, there may be obtained additional 35% of the amorphous but chromatographically homogeneous compound *IVa*. For $C_{24}H_{21}ClN_2O_7$ (484·9) calculated: 59·44% C, 4·36% H, 7·31% Cl, 5·77% N; found: 59·20% C, 4·59% H, 7·16% Cl, 6·07% N.

3',5'-Di-O-benzoyl-2'-deoxythymidine (*Va*)

A stirred mixture of compound *IVa* (4·8 g; 10 mmol), tri-n-butyltin hydride (9·6 g), and benzene (70 ml) was refluxed until the reaction was complete (40 min), as shown by thin-layer chromatography in the solvent system S_5. The mixture was cooled down, diluted with light petroleum (200 ml), the product collected with suction, washed with light petroleum, and crystallised from ethanol to afford 4·27 g (95%) of the chromatographically homogeneous (solvent systems S_3 and S_5) compound *Va*, m.p. 194—195°C, undepressed on admixture with an authentic specimen[12].

2'-Chloro-2'-deoxy-5-methyluridine (*VIIa*)

5-Methyluridine (*Ia*; 2·0 g; 7·8 mmol) was converted into $O^{2,2'}$-anhydro-5-methyluridine (*IIa*) as described above in the case of compound *IVa*. The residue of compound *IIa* was dried over phosphorus pentoxide at 0·1 Torr and then heated in 6M hydrogen chloride in dimethylformamide (30 ml) for 3 h at 100°C. The solution was cooled down, diluted with acetone (400 ml), and adjusted dropwise with triethylamine to pH 7·5 (moistened pH paper). The triethylamine hydrochloride was filtered off and washed with acetone (100 ml). The combined filtrate and washings were evaporated under diminished pressure, the residue triturated with acetone (100 ml), the solid filtered off, and washed with acetone (50 ml). The filtrate and washings were evaporated again, the residue dissolved in water (50 ml), an the aqueous solution applied to a column (150 ml) of Amberlite IR 4 B (in the acetate cycle; 100—200 mesh) ion exchange resin. The column was eluted with water, the UV-absorbing fraction evaporated, and the residue applied in water to a column (100 ml) of Dowex 50 X 8 (H^+) ion exchange resin. The column was eluted with water, the UV-absorbing fraction evaporated under diminished pressure, the residue coevaporated with three 50 ml portions of ethanol, and finally crystallised from ethanol (cyclohexane was added until the solution was turbid). Yield, 1·5 g (70%) of the chromatographically homogeneous (solvent systems S_2 and S_4) compound *VIIa*, m.p. 190—192°C, $[\alpha]_D^{25}$ −10·4° (*c* 1, dimethylformamide). For $C_{10}H_{13}ClN_2O_5$ (276·7) calculated: 43·40% C, 4·73% H, 12·81% Cl, 10·12% N; found: 43·38% C, 4·71%, 12·67% Cl, 10·22% N. NMR spectrum (hexadeuteriodimethyl sulfoxide): 1·94 (s, 3 H) 5-CH_3; 3·71 (m, 2 H) 2 $H_{5'}$; 4·02 (m, 1 H); 4·27 (m, 1 H); 4·93 (t, 1 H) $H_{2'}$; 6·10 (d, 1 H, $J_{1',2'} = 6·0$) $H_{1'}$; 7·80 (br s, 1 H) H_6.

2'-Chloro-2'-deoxyuridine (*VIId*)

A mixture of $O^{2,2'}$-anhydrouridine (*Id*; 10·0 g; 44·3 mmol; *cf.*[11]) and 6M hydrogen chloride in dimethylformamide (130 ml) was heated at 100°C for 2 h, cooled down, diluted with acetone

(1 000 ml), and adjusted to pH 7·5 (moistened pH paper) with triethylamine. The suspension was filtered, the solid washed with acetone (100 ml), the filtrate and washings evaporated, the residue triturated with acetone (100 ml), the mixture filtered, and the solid washed with acetone (50 ml). The filtrate and washings were evaporated under diminished pressure, the residue deionised analogously to compound *VIIa*, and crystallised from ethanol. Yield, 9·40 g (81%) of the compound *VIId*, m.p. 201–202°C, $[\alpha]_D^{25}$ +15·8° (*c* 1, dimethylformamide). For $C_9H_{11}ClN_2O_5$ (262·7) calculated: 41·14% C, 4·22% H, 13·49% Cl, 10·66% N; found: 41·17% C, 4·36% H, 13·37% Cl, 10·09% N. NMR spectrum (hexadeuteriodimethyl sulfoxide): 3·63 (m, 2 H) 2 $H_{5'}$; 3·95 (m, 1 H); 4·19 (m, 1 H); 4·40 (t, 1 H) $H_{2'}$; 5·57 (d, 1 H) H_5; 6·02 (d, 1 H, $J_{1',2'} = 6·0$) $H_{1'}$; 7·91 (d, 1 H; $J_{5,6} = 7·8$) H_6.

2'-Deoxythymidine (*VIa*)

A. A solution of compound *Va* (2·25 g; 5 mmol) in 0·1M methanolic sodium methoxide was kept at room temperature overnight, neutralised with dry Dowex 50 (H^+) ion exchange resin, the resin filtered off, and washed with methanol. The filtrate and washings were evaporated under diminished pressure, the residue dissolved in water (50 ml), the aqueous phase washed with two 25 ml portions of ether, and evaporated under diminished pressure. The residue was coevaporated with ethanol and then crystallised from ethanol to afford 0·97 g (80%) of compound *VIa*, m.p. 186°C, undepressed on admixture with an authentic specimen and identical on chromatography in solvent systems S_1, S_2, and S_4 as well as on electrophoresis in buffer solution E_2.

B. A mixture of compound *VIIa* (1·38 g; 6 mmol), tri-n-butyltin hydride (2·0 g), dioxane (40 ml), and azobisisobutyronitrile (0·1 g) was refluxed until the starting material disappeared, as shown by thin-layer chromatography in S_4 (2 h). The mixture was then evaporated under diminished pressure, the residue diluted with water (200 ml), the solution washed with three 50 ml portions of ether, and the aqueous phase evaporated under diminished pressure. The residue was coevaporated with two 25 ml portions of ethanol and finally crystallised from ethanol. Yield, 0·85 g (70%) of the chromatographically homogeneous (S_1, S_2, and S_4) compound *VIa*, m.p. 186°C.

2'-Deoxyuridine (*VId*)

A mixture of compound *VIId* (5·0 g; 19 mmol), tri-n-butyltin hydride (10 g), dioxane (80 ml), and azobisisobutyronitrile (0·2 g) was refluxed for 4 h (complete reaction, as shown by thin-layer chromatography in S_4), evaporated under diminished pressure, the residue diluted with water (200 ml), and washed with three 50 ml portions of ether. The aqueous phase was evaporated under diminished pressure, the residue coevaporated with three 25 ml portions of ethanol and finally crystallised from ethanol. Yield, 4·1 g (95%) of compound *VId*, m.p. 163°C, homogeneous on chromatography (S_1, S_3, and S_4) as well as electrophoresis (D_2) and identical with an authentic specimen.

3',5'-Di-O-benzoyl-$O^{2,2'}$-anhydro-6-azauridine (*IIIb*)

A mixture of 6-azauridine (*Ib*; 5·0 g; 20·4 mmol), diphenyl carbonate (6 g), sodium hydrogen carbonate (1·5 g), and phosphoric acid hexamethyltriamide was heated with stirring at 150°C for 45 min under exclusion of atmospheric moisture (calcium chloride tube), poured into water (200 ml), washed with chloroform (three 50 ml portions), and the aqueous phase evaporated under diminished pressure. The residue was coevaporated with three 50 ml portions of ethanol and one 50 ml portion of toluene, and dried under diminished pressure. To the dry residue there

was added acetonitrile (100 ml), benzoyl cyanide (9·5 g; 72·5 mmol) and finally drops of triethylamine (total, 10 ml) until the exothermic reaction set in. After 1 h at room temperature, the mixture was evaporated under diminished pressure and the residue applied in chloroform (50 ml) to a column of 30—50 mesh silica gel (300 g) packed in chloroform. The product *IIIb* (R_F 0·44 in S_3) was eluted with chloroform, the eluate evaporated under diminished pressure, and the residue crystallised from ethanol. Yield, 2·8 g (31·5%) of compound *IIIb*, m.p. 194 to 195°C, $[\alpha]_D^{25}$ −45·3° (*c* 1; dimethylformamide). For $C_{22}H_{17}N_3O_7$ (435·4) calculated: 60·68% C, 3·93% H, 9·65% N; found: 60·57% C, 4·15% H, 10·00% N. NMR spectrum ($CDCl_3$): 4·33 (q, 1 H; $J_{5'',4'} = 5·5$, $J_{gem} = 12·0$) $H_{5''}$; 4·51 (q, 1 H; $J_{5',4'} = 5·5$, $J_{gem} = 12·0$) $H_{5'}$; 4·81 (m, 1 H; $J_{4',3'} = 2·5$, $J_{4',5'} = J_{4',5''} = 5·5$) $H_{4'}$; 5·73 (d, 1 H; $J_{3',4'} = 2·5$, $J_{3',2'} = 0·5$) $H_{3'}$; 5·78 (d, 1 H; $J_{2',3'} = 0·5$, $J_{2',1'} = 5·5$) $H_{2'}$; 6·44 (d, 1 H; $J_{1',2'} = 5·5$) $H_{1'}$; 7·20—8·10 (m, 11 H) arom. + H_5.

Furthermore, there was isolated from the reaction mixture 2·8 g (25%) of 2',3',5'-tri-O-benzoyl-6-azauridine (*VIII*), m.p. 194—195°C (undepressed on admixture with an authentic specimen), $[\alpha]_D^{25}$ −55·8° (*c* 1; dimethylformamide); the identity with an authentic specimen[24] was demonstrated by thin-layer chromatography in S_3. There was also obtained after crystallisation from ethanol 3·0 g (26·5%) of 1-(2,3,5-tri-O-benzoyl-β-D-arabinofuranosyl)-6-azauracil (*IX*), m.p. 240—242°C, $[\alpha]_D^{25}$ −68·5° (*c* 1; dimethylformamide); R_F 0·70 in S_3. For $C_{29}H_{23}N_3O_8$ (557·5) calculated: 62·47% C, 4·15% H, 7·54% N; found: 62·61% C, 4·26% H, 7·59% N.

3',5'-Di-O-benzoyl-2'-chloro-2'-deoxy-6-azauridine (*IVb*)

A solution of compound *IIIb* (1·9 g; 4·36 mmol) in 3M hydrogen chloride in dimethylformamide (25 ml) was heated at 100°C for 90 min under exclusion of atmospheric moisture (calcium chloride tube), poured into water (200 ml), the precipitate collected with suction, washed with water, and dissolved in chloroform (100 ml). The solution was dried over anhydrous magnesium sulfate, filtered, and the filtrate evaporated. The residue was chromatographed on two 40 × 16 × 0·3 cm layers of the fluorescent-indicator-containing silica gel in the solvent system S_3. Bands of the product (R_F 0·76 in S_1) were eluted with methanol, the eluate evaporated, and the residue dried under diminished pressure to afford 1·15 g (56%) of the chromatographically (S_3) homogeneous compound *IVb*, amorphous foam, $[\alpha]_D^{25}$ −39·0° (*c* 0·5, dimethylformamide). For $C_{22}H_{18}ClN_3O_7$ (471·9) calculated: 55·99% C, 3·84% H, 7·51% Cl, 8·90% N; found: 55·87% C, 3·94% H, 7·52% Cl, 9·14% N. NMR spectrum ($CDCl_3$): 4·44—4·94 (compl. m, 3 H) $H_{4'}$ + 2 $H_{5'}$; 5·05 (dd, 1 H; $J_{2',1'} = 4·5$, $J_{2',3'} = 5·1$) $H_{2'}$; 5·77 (m, 1 H) $H_{3'}$; 6·54 (d, 1 H; $J_{1',2'} = 4·5$) $H_{1'}$; 7·27 (s, 1 H) H_5; 7·25—9·20 (10 H) aromatic protons.

3',5'-Di-O-benzoyl-2'-deoxy-6-azauridine (*Vb*)

A mixture of compound *IVb* (0·84 g; 1·77 mmol), tri-n-butyltin hydride (1·6 g), benzene (16 ml), and azobisisobutyronitrile was refluxed for 6 h (as shown by thin-layer chromatography in S_4, the reaction was not complete in spite of the long reflux) and evaporated under diminished pressure. The residue was chromatographed on one layer (see above) of silica gel in the solvent system S_5. Bands of compound *IVb* (R_F 0·50 in S_5) and the product *Vb* (R_F 0·36 in S_5) were eluted with methanol and the eluates evaporated. The residue of compound *Vb* was crystallised from ethanol to afford 480 mg (62·5%) of compound *Vb*, m.p. 175—176°C. For $C_{22}H_{19}N_3O_7$ (437·4) calculated: 60·40% C, 4·38% H, 9·60% N; found: 59·76% C, 4·46% H, 9·59% N. NMR spectrum ($CDCl_3$): 2·42 (s, 1 H; $J_{2',1'} = 6·5$, $J_{2',3'} = 3·9$, $J_{gem} = 14·0$) $H_{2''}$; 2·92 (m, 1 H, $J_{2'',1'} = 6·5$) $H_{2''}$; 4·35—4·80 (compl. m, 3 H) $H_{4'}$ + 2 $H_{5'}$; 5·73 (m, 1 H; $J_{3',2'} = 3·9$) $H_{3'}$; 7·25—8·10 (compl. m, 11 H) aromatic protons + H_5. The starting compound *IVb* was recovered in 175 mg (21%) yield.

2′-Deoxy-6-azauridine (*VIb*)

A solution of compound *Vb* (0·2 g; 0·46 mmol) in 0·1M methanolic sodium methoxide (20 ml) was kept at room temperature for 2 days, neutralised with dry Dowex 50 X 8 (H^+) cation exchange resin, filtered, and the resin on the filter washed with methanol (50 ml). The filtrate and washings were evaporated under diminished pressure, the residue diluted with water (50 ml), washed with three 25 ml portions of ether, and the aqueous phase evaporated. The residue was coevaporated with two 25 ml portions of ethanol and finally crystallised from ethanol and ether (until turbid) to afford 68 mg (63%) of compound *VIb* homogeneous on chromatography (S_1 and S_2) and electrophoresis (E_1 and E_2). For $C_8H_{11}N_3O_5$ (229·2) calculated: 41·91% C, 4·84% H, 18·33% N; found: 42·32% C, 4·92% H, 18·75% N.

3′,5′-Di-O-benzoyl-5-fluoro-O$^{2,2'}$-anhydrouridine (*IIIc*)

A mixture of 5-fluorouridine[16] (*Ic*; 1·4 g; 5·35 mmol), diphenyl carbonate (1·52 g), sodium hydrogen carbonate (0·04 g), and phosphoric acid hexamethyltriamide was heated under exclusion of atmospheric moisture (calcium chloride tube) at 150°C for 40 min (as shown by thin-layer chromatography in S_4, the reaction was complete), cooled down, diluted with water (100 ml), and washed with three 25 ml portions of ether and one 25 ml portion of ether. The aqueous phase was evaporated and the residue dried by coevaporation with three 25 ml portions of ethanol and finally *in vacuo*. To this chromatographically pure residue of compound *IIc* there was added acetonitrile (70 ml), benzoyl cyanide (3·43 g; 26·2 mmol) and finally, drop by drop, triethylamine (1·7 ml). The mixture was stirred for 15 min, diluted with ether (200 ml), the solid collected with suction, washed with ether, and dried *in vacuo*. Yield, 1·7 g (71%) of the chromatographically homogeneous compound *IIIc*, m.p. >250°C. For $C_{23}H_{17}FN_2O_7$ (452·4) calculated: 61·05% C, 3·78% H, 4·20% F, 6·19% N; found: 61·50% C, 3·84% H, 4·35% F, 6·82% N.

3′,5′-Di-O-benzoyl-2′-chloro-2′-deoxy-5-fluorouridine (*IVc*)

A solution of compound *IIIc* (1·6 g; 3·5 mmol) in 1M hydrogen chloride in dimethylformamide (38 ml) was heated at 100°C for 1 h under exclusion of atmospheric moisture (calcium chloride tube) and poured with stirring into water (400 ml). The solid was collected with suction, washed with water, dissolved in chloroform (100 ml), the solution dried over anhydrous magnesium sulfate, filtered, the filtrate evaporated under diminished pressure, and the residue crystallised from ethanol to afford 1·4 g (80%) of compound *IVc*, m.p. 223—224°C. For $C_{23}H_{18}ClFN_2O_7$ (488·9) calculated: 56·50% C, 3·50% H, 7·25% Cl, 3·88% F, 5·73% N; found: 55·47% C, 3·95% H, 7·04% Cl, 3·84% F, 5·80% N. NMR spectrum ($CDCl_3$): 4·56 (m, 3 H) $H_{4'} + 2\,H_{5'}$; 5·10 (t, 1 H; $J_{1',2'} = J_{2',3'} = 6{\cdot}0$) $H_{2'}$; 5·67 (m, 1 H) $H_{3'}$; 6·14 (dd, 1 H; $J_{1',2'} = 6{\cdot}0$) $H_{1'}$; 7·30—8·10 m, 1 H) aromatic protons and H_6; 11·95 (br s) NH.

3′,5′-Di-O-benzoyl-5-fluoro-2′-deoxyuridine (*Vb*)

A mixture of compound *IVc* (1·7 g; 3·5 mmol), tri-n-butyltin hydride (4·5 g), benzene (30 ml), and azobisisobutyronitrile (14 mg) was refluxed with stirring for 50 min (according to thin-layer chromatography in the solvent system S_5, the reaction was quantitative) and then evaporated under diminished pressure. The residue was triturated with light petroleum (100 ml), the solid collected with suction, washed with light petroleum, and crystallised from ethanol. Yield, 1·0 g (63%) of the chromatographically homogeneous (S_3 and S_5) compound *Vc*, m.p. > 250 °C. For $C_{23}H_{19}FN_2O_7$ (454·4) calculated: 60·79% C, 4·21% H, 4·18% F, 6·16% N; found: 61·25% C, 4·57% H, 4·22% F, 6·54% N.

5-Fluoro-2'-deoxyuridine (*VIc*)

A solution of compound *Vc* (0·7 g; 1·55 mmol) in 0·1M methanolic sodium methoxide was processed analogously to compound *VIb*. Crystallisation from ethanol–ether afforded 93 mg (26%) of compound *VIc*, chromatographically (solvent systems S_1, S_2 and S_4) as well as electrophoretically (buffer solutions E_1 and E_2) homogeneous and identical with an authentic specimen[17].

One of the authors (D.C.) thanks Professor Dr V. Herout, Director of this Institute, for making possible his scientific stay. Thanks are also due to Dr M. Masojídková for measurement and interpretation of NMR spectra, and Dr M. Prystaš of this Institute for valuable discussions. The excellent technical assistance of Mrs B. Kopecká is gratefully acknowledged.

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Translated by J. Pliml.