2',3'-O-CARBONYL DERIVATIVES OF URIDINE AND 6-AZAURIDINE. SYNTHESIS OF 2'-DEOXYURIDINE, 2'-DEOXY-6-AZAURIDINE AND 2'-DEOXY-6-AZACYTIDINE*

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Received November 27th, 1975

A preparation was developed of nucleoside 2',3'-carbonates by reaction of 5'-substituted ribonucleosides with 1,1'-carbonyldiimidazole under mild conditions. The 2',3'-O-carbonyl derivatives *IIb* and *IIc*, resp., were prepared in 89% yields from 5'-trityl-6-azauridine (*Ib*) and 5'-trityluridine (*Id*) by reaction with 2 equivalents of 1,1'-carbonyldiimidazole in dimethylformamide (pyridine). Conversion of the trityl carbonyl derivatives *IIb* (*IIc*) to the trityl anhydro derivative *IIIa* (*IIIb*), the subsequent detritylation to *IVa* (*IVb*), ring-opening to the 2'-chloro derivative *Va* (*Ve*), and the tributyltin hydride reduction of the acetyl derivative *Vb* (*Vf*) to the corresponding 2-(2--deoxy-β-D-*erythro*-pentofuranosyl)-1,2,4-triazine-3,5(2*H*,4*H*)-dione (*VIa*) and 1-(2-deoxy-β-D--*erythro*-pentofuranosyl)pyrimidine-2,4(1*H*,3*H*)-dione (*IVd*) was examined in the 6-azauracil and uracil series. The 2'-deoxy derivative *VIb* was transformed into 2'-deoxy-6-azacytidine [2-(2-deoxy-β-D-*erythro*-pentofuranosyl)-5-amino-1,2,4-triazin-3(2*H*)-one] (*VIIIa*). Compound *Vb* was similarly converted to compound *VII*. Diacetyl-2'-bromo-6-azauridine (*Vc*) was prepared in 34% yield by reaction of 6-azauridine with acetyl bromide in acetonitrile.

In the field of nucleosides, continued attention (beginning with the work of Todd[1]) has been paid to anhydronucleosides[2] as highly reactive and biologically interesting substances. A simple method for the preparation of 2,2'-anhydronucleosides was developed by Fox and Wempen[3,4] by reaction of uridine with 1,1'-thiocarbonyldiimidazole. The corresponding 2',3'-thiocarbonate (assumed by Fox as the virtual intermediate) was prepared almost simultaneously by Ruyle and coworkers[5] and transformed to the 2,2'-anhydronucleoside. By reaction of purine nucleosides with diphenyl carbonate, the corresponding 2',3'-O-carbonyl derivatives were prepared by Hampton and Nichol[6]. In the uridine series, this reaction gave a 2,2'-anhydronucleoside; the 2',3'-carbonate was assumed as the intermediate. Carbonates of pyri-

* Part X in the series Analogues of Nucleosides; Part VI: Nucl. Acids Res. Spec. Publ. No *1*, s9 (1975); Part VII: Nucl. Acids Res. Spec. Publ. No *1*, s57 (1975); Part VIII: Nucl. Acids Res. Spec. Publ. No *1*, s61 (1975); Part IX: Nucl. Acid. Res. Spec. Publ. No *1*, s65 (1975).

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midine nucleosides have been for the first time prepared by Letsinger and Ogilvie[7] from the free nucleoside by reaction with *p*-nitrophenyl chloroformate; the uridine 2′,3′-carbonate was converted to the anhydronucleoside by Ogilvie and Iwacha[8]. In addition to these methods, the cyclic 2′,3′-carbonates of nucleosides were also obtained by nucleosidation of sugar cyclic carbonates[9–12]. The above methods were used in the preparation of cyclic carbonates of nucleosidic derivatives of uracil[5,7,8,11,13,14,18], hypoxanthine[6,15,16], guanosine[15,17], 6-azauracil[13,14,18], thymine[19], cytosine[14], adenine[9,12] as well as of nucleosides with a nonclassic sugar moiety[9–12].

In contrast to the chemistry of nucleosides, the application of the carbonate protecting group has been widely examined in the field of sugars[20]. The carbonates of saccharides were prepared by the action of phosgene in pyridine[20,22], esters of chloroformic acid[20], hexachloroacetone[21], and 1,1′-carbonyldiimidazole[12,21] or by transesterification of diaryl carbonates[20,22].

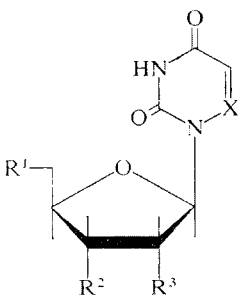
In this Laboratory, the reaction with 1,1′-thiocarbonyldiimidazole has been utilized in the preparation of 2,2′-anhydro derivatives of the 6-azauracil series[23,24] and the reaction of diphenyl carbonate with cytidine has also been examined. In contrast to uridine and purine nucleosides, the reaction with cytidine affords directly arabinofuranosylcytosine in one reaction step[25,26]; the 2′,3′-cyclic carbonate and the 2,2′-anhydro derivative are assumed as intermediates.

The reaction of nucleosides with 1,1′-carbonyldiimidazole has not been so far reported in the literature despite the advantageous preparation and application of this reagent[27,28] in comparison with 1,1′-thiocarbonyldiimidazole. Consequently, attention has been now paid to the 2′,3′-O-carbonyl group as the alkali-labile protecting group of the *cis*-diol system, suitable for syntheses in the field of nucleosides and nucleotides. In the present paper, we wish to report the preparation of cyclic 2′,3′-carbonates by reaction of 1,1′-carbonyldiimidazole with pyrimidine nucleosides of the *ribo* series bearing a protected reactive hydroxylic function at position 5′ or lacking this function. In connection with the earlier observations on the different reactivity[23,24,29] in the uridine and the 6-azauridine series, it appeared advisable to perform the first fundamental steps simultaneously in the two series.

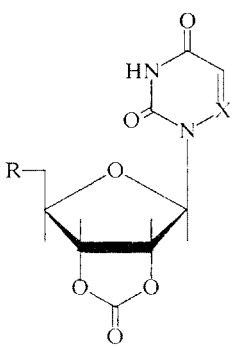
The starting 5′-trityl derivative[30] *Ib* (*Id*) was converted under very mild conditions to the corresponding 2′,3′-O-carbonyl derivative *IIb* (*IIc*) in 89% yield by reaction with 1,1′-carbonyldiimidazole[27,28] in dimethylformamide or pyridine. 5′-O-Trityluridine[31] (*Id*) was prepared analogously to the tritylazauridine *Ib* (ref.[30]). In the present work, 1,1′-carbonyldiimidazole was used either in the form of a solid[28] or in the form of a solution prepared *in situ* analogously to that of 1,1′-thiocarbonyldiimidazole[32]. The 2′,3′-O-carbonyl derivatives were prepared with the use of 2·0–2·5 equivalents of 1,1′-carbonyldiimidazole. The excess of the reagent resulted in a more rapid quantitative conversion of the starting substance. The reaction cannot be

accelerated by heating; the heating results in the formation of the anhydro derivative *III* in accordance with observations on reactions of 2′,3′-thiocarbonates[32]. Imidazole (produced from 1,1′-carbonyldiimidazole in the course of the preparation of 2′,3′-carbonates) acts as the base necessary for the formation of anhydronucleosides, again in accord with the earlier analogous observations[2,32]. This reaction course was confirmed by reaction of 5′-O-trityl-6-azauridine (*Ib*) with 1,1′-carbonyldiimidazole in dimethylformamide at 140°C and by reaction of the trityl carbonate *IIb* with imidazole under otherwise identical reaction conditions; both reactions afforded the same anhydronucleoside *IIIa*. The reaction with 1,1′-carbonyldiimidazole has also been utilized in the preparation of other cyclic carbonates[14,33].

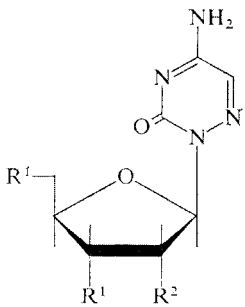
The trityl carbonate *IIc* was also prepared (yield, 64%) with the use of phosgene in pyridine. In the preparation of nucleoside 2′,3′-carbonates, the application of phos-



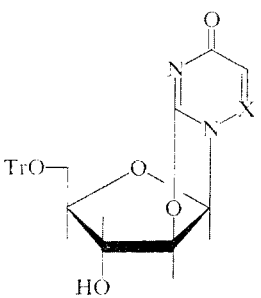
	R^1	R^2	R^3	X
Ia,	HO	HO	HO	N
Ib,	TrO	HO	HO	N
Ic,	HO	HO	HO	CH
Id,	TrO	HO	HO	CH
Ia,	HO	HO	Cl	N
Vb,	AcO	AcO	Cl	N
Vc,	AcO	AcO	Br	N
Vd,	HO	HO	Br	N
Ve,	HO	HO	Cl	CH
Vf,	AcO	AcO	Cl	CH
VIa,	HO	HO	H	N
VIb,	AcO	AcO	H	N
VIc,	AcO	AcO	H	CH
VId,	HO	HO	H	CH



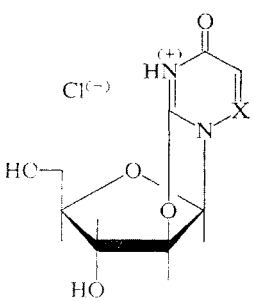
	R	X
IIa,	HO	N
IIb,	TrO	N
IIc,	TrO	CH



	R^1	R^2
VII,	AcO	Cl
VIIIa,	HO	H
VIIIb,	AcO	H



	X
IIIa,	N
IIIb,	CH



	X
IVa,	N
IVb,	CH

Ac = acetyl, Tr = triphenylmethyl

gene has not been so far reported. Nevertheless, the reaction with 1,1'-carbonyldiimidazole was found to be more advantageous, particularly with respect to the yield and work-up of the reaction mixture. Detritylation of the trityl carbonate *IIb* with ethereal hydrogen chloride[34] afforded the carbonyl derivative *IIa* in 90% yield; the reaction is not accompanied by cleavage of the carbonate. Conversion of the trityl carbonyl derivative *IIb* (*IIc*) to the trityl anhydro derivative *IIIa* (*IIIb*) was performed with imidazole in dimethylformamide at 140°C in a high yield (84% of *IIIa* and 77% of *IIIb*), analogously to reactions of uridine thiocarbonyl derivative[5]. Detritylation of the anhydro derivative *IIIa* (*IIIb*) with ethereal hydrogen chloride[24,34] afforded the hydrochloride of the anhydro compound *IVa* (*IVb*) in an almost quantitative yield. When heated in dimethylformamide, the hydrochlorides *IVa* and *IVb* afford the corresponding 2'-chloro derivatives *Va* and *Ve*. A similar cleavage of the hydrochlorides of 2,3'-anhydro derivatives[35] and of 2,2'-anhydronucleosides[34,36] has been reported earlier. When heated in dimethylformamide, anhydrouridine hydrochloride gave the 2'-chloro derivative *Ve* in 88% yield, analogously to the literature[37]. A similar conversion of the hydrochloride of the 6-azauracil derivative *IVa* was accomplished in a high yield by heating in dimethylformamide with excess hydrogen chloride. When subjected to a simultaneous detritylation and opening of the anhydro ring by the action of excess hydrogen chloride in dimethylformamide, the trityl anhydro derivatives *IIIa* and *IIIb* afforded the corresponding 2'-chloro derivatives in a high yield (92% of *Va* and 85% of *Ve*). By the action of acetyl chloride in refluxing acetonitrile (6 h), the trityl anhydro derivative *IIIa* furnished (a simultaneous detritylation, opening of the anhydro ring, and acetylation) the diacetyl 2'-chloro derivative *Vb* in 76% yield. An analogous reaction was described in the case of the 2,3'-anhydro derivatives[35] and 2,2'-anhydronucleosides[38]. With the use of dimethylformamide instead of acetonitrile, the disappearence of the starting anhydro derivative from the reaction mixture is faster (45 min) but the yield of the required 2'-chloro derivative is considerably lower, in accordance with literature[38]. The 2'-chloro derivative *Va* (*Ve*) was converted by acidic acetylation[30] to the corresponding diacetyl derivative *Vb* (*Vf*) in an almost quantitative yield.

The diacetyl 2'-bromo derivative *Vc* was prepared in 34% yield directly from 6-azauridine (*Ia*) by the action of acetyl bromide in refluxing acetonitrile as reported in the case of uridine[38]. As the competitive by-product of this reaction, 2',3',5'-tri-O-acetyl-6-azauridine (50%) is obtained. The use of dimethylformamide instead of acetonitrile results in a lowered yield of the halo derivative (similarly to the preceding case). Replacement of acetyl bromide by acetyl chloride results in the formation of 2',3',5'-tri-O-acetyl-6-azauridine as the main reaction product while only trace amounts of the corresponding 2'-chloro derivative *Vb* are obtained.

The structural analogy of 2'-halo derivatives *Vb*, *Vc*, and *Vf* was demonstrated by physical methods as well as by conversion into the deoxy derivatives *VIb* and *VIc* on treatment with tributyltin hydride[36,39–46] in the presence of 2,2'-azobis(2-me-

thylpropionitrile). The time of the reduction in refluxing benzene was 7 h in the case of 6-azauridine 2'-chloro derivative *Vb* (61%), 1 h in the case of the analogous 2'-bromo derivative *Vc* (64%), and 4 h with the uridine 2'-chloro derivative *Vf*. 2'-Deoxyuridine [1-(2-deoxy-β-D-*erythro*-pentofuranosyl)pyrimidine-2,4(1*H*, 3*H*)-dione] (*VId*) was obtained in 78% yield without isolation of the intermediary chloro diacetyl derivative *Vf* and deoxy diacetyl derivative *VIc*. An analogous procedure has been earlier used[36] in the preparation of 3',5'-di-O-benzoyl-2'-deoxy-6-azauridine from 2,2'-anhydro-1-(3,5-di-O-benzoyl-β-D-arabinofuranosyl)-6-azauracil *via* the 2'-chloro derivative obtained on treatment with hydrogen chloride in dimethylformamide. The deoxy derivative *VIb* was deacetylated in 87% yield with methanolic hydrogen chloride at room temperature with the formation of 2'-deoxy-6-azauridine[47] [2-(2-deoxy-β-D-*erythro*-pentofuranosyl)-1,2,4-triazine-3,5(2*H*, 4*H*)-dione] (*VIa*), identical with an authentic specimen[47]. Methanolic hydrogen chloride was also used to deacetylate the 2'-bromo diacetyl derivative *Vc* with the formation of 2'-bromo-2'-deoxy-6-azauridine (*Vd*) in 66% yield. By reaction with thionyl chloride and dimethylformamide in chloroform[48] and the subsequent treatment with ammonia, the 2'-chloro derivative *Vb* was converted *via* the not isolated 2-(3,5-di-O-acetyl-2-deoxy-2-chloro-β-D-*ribo*-pentofuranosyl)-5-chloro-1,2,4-triazin-3(2*H*)-one into the 3',5'-di-O-acetyl-2'-deoxy-2'-chloro-6-azacytidine (*VII*) in 43% yield. The diacetyl 2'-deoxy derivative *VIb* was analogously[48] transformed into the diacetyl derivative *VIIIb* of the 6-azacytosine series (in 80% yield). Deacetylation with methanolic ammonia at room temperature yielded 78% of 2'-deoxy-6-azacytidine [2-(2-deoxy-β-D-*erythro*-pentofuranosyl)-5-amino-1,2,4-triazin-3(2*H*)-one] (*VIIIa*) of a lower melting point value than stated by literature[49] but otherwise identical with the authentic specimen[49].

The derivatives of 1-(2-deoxy-β-D-*erythro*-pentofuranosyl)-6-azauracil and derivatives of 1-(3-deoxy-β-D-*threo*-pentofuranosyl)-6-azauracil[44-46] as well as the derivatives of 1-(2-deoxy-2-halo-β-D-*ribo*-pentofuranosyl)-6-azauracil and derivatives of 1-(3-deoxy-3-halo-β-D-*arabino*-pentofuranosyl)-6-azauracil[44-46] were observed to exhibit similar R_F values on thin-layer chromatography, as shown in the Experimental.

EXPERIMENTAL

Melting points were taken on a heated microscope stage Boetius. The UV spectra were recorded on a CF-4 Optica Milano apparatus. The IR spectra were taken on a UR-20 Carl Zeiss, Jena, apparatus. The ^{1}H-NMR spectra were measured on a Tesla 80 MHz (Czechoslovakia) apparatus with hexamethyldisiloxane as internal standard; chemical shifts (δ values) are expressed in p.p.m. and the coupling constants in Hz, unless stated otherwise. The optical rotations were measured on a Perkin-Elmer 141 MC polarimeter. Analytical samples were dried at 0·5 Torr. Column chromatography was performed on the Pitra silica gel (particle size, 30–60 μm; produced by Service Laboratories of this Institute). Solutions were taken down under diminished pressure

on a rotatory evaporator at 20—40°C/0·5—20 Torr. Dried solvents were stored over molecular sieves.

2′,3′-O-Carbonyl-5′-O-trityl-6-azauridine (*IIb*)

A) 1,1′-Carbonyldiimidazole (6·5 g; 40 mmol) was added to a solution of 5-O-trityl-6-azauridine[30] (*Ib*; 10 g; 20·5 mmol) in dimethylformamide (100 ml). The whole mixture was kept at room temperature for 30 min and evaporated. The oily residue was dissolved in ethyl acetate (150 ml), the solution washed with five 60 ml portions of water, dried over anhydrous magnesium sulfate, and evaporated. The residue was dissolved in acetone (250 ml) and the solution poured with stirring into a mixture (1 000 ml) of ice and water. After 30 min, the precipitate was collected with suction and dried. Yield, 8·01 g (76%) of compound *IIb*, $[\alpha]_D^{25}$ −37·2° (*c* 0·48, chloroform). UV spectrum (methanol): λ_{min} 245 nm (log ε 3·67), λ_{max} 261 nm (log ε 3·73). IR spectrum (chloroform): 3374 and 3188 cm^{-1} (NH), 1818 and 1840 sh cm^{-1} (C=O carbonate), 1726 and 1702 cm^{-1} (C=O 6-azauracil). For $C_{28}H_{23}N_3O_7$ (513·5) calculated: 65·49% C, 4·51% H, 8·18% N; found: 65·42% C, 4·75% H, 8·17% N.

B) 1,1′-Carbonyldiimidazole (400 mg; 2·5 mmol) was added to a solution of the tritylazauridine *Ib* (488 mg; 1 mmol) in pyridine (10 ml). After 60 min at room temperature, the mixture was processed analogously to paragraph *A*. Yield, 455 mg (89%) of the carbonate *IIb*, identical with the specimen prepared by procedure *A*.

2,2′-Anhydro-1-(5-O-trityl-β-D-arabinofuranosyl)-6-azauracil (*IIIa*)

Imidazole (1 g; 14·69 mmol) was added to a solution of the cyclic carbonate *IIb* (7·2 g; 14·02 mmol) in dimethylformamide (100 ml), the mixture heated at 140°C for 1 h, evaporated, and the residue crystallised from ethanol. Yield, 6·1 g (84·4%) of the cyclonucleoside *IIIa*, m.p. 114 to 117°C, identical with an authentic specimen[23].

2′,3′-O-Carbonyl-6-azauridine (*IIa*)

Ethereal hydrogen chloride (22 ml of a 16% solution) was added with stirring to a mixture of compound *IIb* (1·5 g; 2·92 mmol) and ether (30 ml). The stirring was continued at room temperature for 1 h. The mixture was then kept in an ice-box overnight, filtered, the insoluble portion washed with ether (100 ml), and recrystallised from a mixture of ethyl acetate and methanol. Yield, 400 mg (43·5%) of compound *IIa*, m.p. 151—153°C, containing 0·5 molecule of ethyl acetate. Additional 440 mg (47·8%) of the same substance were obtained from mother liquors. Optical rotation: $[\alpha]_D^{25}$ −81·3° (*c* 0·52, methanol). UV spectrum (methanol): λ_{min} 221 nm (log ε 3·48), λ_{max} 259 nm (log ε 3·74). IR spectrum (nujol): 3518 cm^{-1} (OH), 1820 cm^{-1} (C=O carbonate). 1745 sh cm^{-1} (C=O ethyl acetate), 1729 and 1705 cm^{-1} (C=O 6-azauracil), 1596 cm^{-1} (C=N). ^{1}H-NMR spectrum (deuteriochloroform with hexadeuteriodimethyl sulfoxide; the exchange was performed with the use of perdeuterioacetic acid): 12·25 (broad, 1 H, NH, exchangeable proton), 7·34 (s, 1 H, $H_{5'}$), 6·24 (broad s, 1 H, $H_{1'}$, $J_{1',2'}$ = 1·0), 5·55 (dd, 1 H, $H_{2'}$, $J_{2',3'}$ = = 7·0), 5·23 (dd, 1 H, $H_{3'}$, $J_{3',4'}$ = 3·0), 4·28 (m, 1 H, $H_{4'}$), 3·50 (broad d, 2 H, 2 $H_{5'}$), 4·15 (broad s, 1 H, OH, exchangeable proton), ethyl acetate: 4·0 (q, 2 H, CH_2), 1·15 (t, 3 H, CH_3), 1·92 (s, 3 H, $OCOCH_3$). For $C_9H_9N_3O_7 \cdot 0{\cdot}5\ C_4H_8O_2$ (315·2) calculated: 41·91% C, 4·16% H, 13·33% N; found: 41·82% C, 4·27% H, 13·34% N.

2′-Deoxy-2′-chloro-6-azauridine (*Va*)

A) The trityl anhydro derivative *IIIa* (1 g; 1·95 mmol) was detritylated as reported[24]. The resulting hydrochloride *IVa* was dissolved in dimethylformamide (15 ml) and the solution treated with 40% hydrogen chloride in dimethylformamide (2 ml). The whole was heated at 100°C for 45 min and the dimethylformamide evaporated. After coevaporation with two 10 ml portions of ethanol, the residue was chromatographed on silica gel (130 g) in ethyl acetate to afford 398 mg of a substance which was recrystallised from ethyl acetate. Yield, 266 mg (52%) of the chloro derivative *Va*, m.p. 140·5–143°C, and additional 133 mg (25·9%) of the same product from mother liquors. Optical rotation: $[\alpha]_D^{25}$ −122° (*c* 0·49, methanol). UV spectrum (methanol): λ_{min} 223 nm (log ε 3·42), λ_{max} 262 nm (log ε 3·71). IR spectrum (nujol): 3546 and 3432 cm^{-1} (OH), 3383 sh, 3200, 3171 sh, and 3121 cm^{-1} (OH and NH), 1730, 1700, and 1689 cm^{-1} (C=O), 1582 cm^{-1} (C=N). ^{1}H-NMR spectrum (deuteriochloroform with hexadeuteriodimethyl sulfoxide; the exchange was performed with the use of perdeuterioacetic acid): 7·41 (s, 1 H, H_5), 6·14 (d, 1 H, $H_{1'}$, $J_{1',2'} = 4·5$), 4·61 (t, 1 H, $H_{2'}$, $J_{2',3'} = 5·0$), 4·33 (t, 1 H, $H_{3'}$), 3·91 (q, 1 H, $H_{4'}$, $J_{3',4'} = J_{4',5'} = J_{4',5''} = 4·0$), 3·51 (m, 2 H, 2 $H_{5'}$), exchangeable protons 12·17 (broad s, 1 H, NH) and 4·50 (s, 2 H, 2 OH). For $C_8H_{10}ClN_3O_5$ (263·6) calculated: 36·45% C, 3·82% H, 15·94% N, 13·45% Cl; found: 36·58% C, 3·79% H, 16·11% N, 13·33% Cl.

B) Hydrogen chloride in dimethylformamide (1 ml of 40% solution) was added to a solution of the trityl anhydro compound *IIIa* (240 mg; 0·47 mmol) in dimethylformamide (4 ml), the whole heated at 100°C for 30 min, and evaporated. The residue was chromatographed on a column of silica gel (50 g) in ethyl acetate to afford 120 mg of a substance which was recrystallised from ethyl acetate. Yield, 94 mg (75·9%) of the chloro derivative *Va*, identical with the specimen from paragraph *A*. Mother liquors yielded additional 20 mg (16·1%) of the same substance.

3′,5′-Di-O-acetyl-2′-deoxy-2′-chloro-6-azauridine (*Vb*)

A) The chloro derivative *Va* (298 mg; 1·13 mmol) was dissolved with stirring in a mixture of acetic acid (10 ml), acetyl chloride (0·4 ml), and acetic anhydride (5 ml). The solution was kept at room temperature for 16 h, evaporated, and the residue coevaporated with three 10 ml portions of ethanol. The final residue was dissolved in boiling ethanol and the solution cooled down to deposit a gel which was dried and powdered. Yield, 388 mg (98·7%) of compound *Vb* in the form of a solid, $[\alpha]_D^{25}$ −75·5° (*c* 0·51, ethanol). UV spectrum (methanol): λ_{max} 259 nm (log ε 3·72), λ_{min} 223 nm (log ε 3·45). IR spectrum (chloroform): 3376 cm^{-1} (NH), 1743 cm^{-1} (C=O acetate), 1726 and 1704 cm^{-1} (C=O 6-azauracil), 1592 cm^{-1} (C=N). ^{1}H-NMR spectrum (deuteriochloroform, tetramethylsilane as internal standard): 7·51 (s, 1 H, H_5), 6·39 (d, 1 H, $H_{1'}$, $J_{1',2'} = 4·5$), 4·88 (t, 1 H, $H_{2'}$, $J_{2',3'} = 5·0$), 5·35 (t, broad 1 H, $H_{3'}$, $J_{3',4'} = 4·0$), 3·98 to 4·55 (m, 3 H, $H_{4'}$ + 2 $H_{5'}$), 2·16 (s, 3 H, $OCOCH_3$), 2·06 (s, 3 H, $OCOCH_3$), 9·96 (s broad, 1 H, NH). For $C_{12}H_{14}ClN_3O_7$ (347·7) calculated: 41·45% C, 4·06% H, 12·08% N, 10·20% Cl; found: 41·47% C, 4·29% H, 11·92% N, 9·95% Cl.

B) A solution of compound *IIIa* (240 mg; 0·47 mmol) in acetonitrile (15 ml) and acetyl chloride (0·5 ml) was refluxed for 6 h, evaporated, and the residue chromatographed on a column of silica gel (120 g) in 1 : 1 ethyl acetate–benzene to afford 123 mg (76%) of compound *Vb*, identical with the specimen prepared according to paragraph *A*.

3′,5′-Di-O-acetyl-2′-bromo-2′-deoxy-6-azauridine (*Vc*)

Ten 0·5 ml portions of acetyl bromide were added in 30 s intervals with stirring into a refluxing mixture of 6-azauridine (*Ia*; 1 g; 4·08 mmol) and acetonitrile (50 ml). The reflux was continued

for 20 min, the mixture evaporated, and the residue coevaporated with two 25 ml portions of 2-propanol. The final residue was dissolved in ethyl acetate (15 ml), the solution washed with three 10 ml portions of water, dried over anhydrous magnesium sulfate, filtered, and the filtrate evaporated. The residue was chromatographed on a column of silica gel (300 g) in 1 : 1 ethyl acetate–benzene to afford 760 mg (50·2%) of 2',3',5'-tri-O-acetyl-6-azauridine (identical with an authentic specimen[50]) and 550 mg (34·4%) of compound *Vc* which was deposited from 2-propanol as a gel and dried, $[\alpha]_D^{25}$ −65·2° (*c* 0·51, ethanol). UV spectrum (methanol): λ_{min} 223 nm (log ε 3·44), λ_{max} 259 nm (log ε 3·75). IR spectrum (chloroform): 3375 cm^{-1} (NH), 1743 cm^{-1} (C=O acetate), 1725 and 1704 cm^{-1} (C=O 6-azauracil), 1593 cm^{-1} (C=N). ^{1}H-NMR spectrum (deuteriochloroform): 7·51 (s, broad, 1 H, H_5), 6·52 (d, 1 H, $H_{1'}$, $J_{1',2'}$ = 5·3), 4·86 (t, 1 H, $H_{2'}$, $J_{2',3'}$ = 5·3), 5·30 (broad t, 1 H, $H_{3'}$, $J_{3',4'}$ = 4·5), 3·95–4·50 (m, 3 H, $H_{4'}$ + 2 $H_{5'}$), 2·09 (s, 3 H, $OCOCH_3$), 2·19 (s, 3 H, $OCOCH_3$). For $C_{12}H_{14}BrN_3O_7$ (392·2) calculated: 36·75% C, 3·60% H, 10·71% N, 20·38% Br; found: 36·80% C, 3·67% H, 10·64% N, 20·04% Br.

2'-Bromo-2'-deoxy-6-azauridine (*Vd*)

A solution of compound *Vc* (392 mg; 1 mmol) in 0·25M methanolic hydrogen chloride (10 ml) was kept at room temperature for 40 h and evaporated. The residue (300 mg) was crystallised from ethyl acetate to afford 85 mg (27·6%) of compound *Vd*, m.p. 132–134°C; the mother liquors yielded additional 118 mg (38·3%) of the same substance, $[\alpha]_D^{25}$ −104·5° (*c* 0·72, methanol). UV spectrum (methanol): λ_{min} 225 nm (log ε 3·49), λ_{max} 261 nm (log ε 3·80). IR spectrum (nujol): 3530, 3442 cm^{-1} (OH), 3212 cm^{-1} (NH), 1729, 1696, and 1688 sh cm^{-1} (C=O), 1582 cm^{-1} (C=N). ^{1}H-NMR spectrum (hexadeuteriodimethyl sulfoxide with deuteriochloroform; the exchange was performed with the use of perdeuterioacetic acid): 12·28 (broad s, 1 H, NH), 7·54 (s, 1 H, H_5), 6·31 (d, 1 H, $H_{1'}$, $J_{1',2'}$ = 5·0), 4·72 (t, 1 H, $H_{2'}$, $J_{2',3'}$ = 5·0), 4·25 (t, 1 H, $H_{3'}$, $J_{3',4'}$ = 5·0), 3·94 (q, 1 H, $H_{4'}$), 3·52 (2 × dd, 2 H, $H_{5'}$ + $H_{5''}$, $J_{5',4'}$ = 4·0, $J_{5'',4'}$ = 5·0, $J_{5',5''}$ = 11·6), 3·80 (broad, 2 H, OH). For $C_8H_{10}BrN_3O_5$ (308·1) calculated: 31·19% C, 3·27% H, 13·64% N, 25·94% Br; found: 31·68% C, 3·31% H, 13·64% N, 25·82% Br.

2-(3,5-Di-O-acetyl-2-deoxy-β-D-*erythro*-pentofuranosyl)-1,2,4-triazine-3,5(2*H*,4*H*)-dione (*VIb*)

A) Tributyltin hydride (16 ml of a 0·5M solution in benzene) was added to a solution of compound *Vb* (776 mg; 2·23 mmol) in benzene (10 ml). The mixture was heated to the boiling point and then 2,2'-azobis(2-methylpropionitrile) (20 mg) was added. The whole was refluxed for 7 h-two additional 5 mg portions of the above nitrile were introduced during the heating. The mixture was evaporated and the residue chromatographed on a column of silica gel (150 g) in 1 : 1 ethyl acetate–benzene to afford 430 mg (61·5%) of compound *VIb* as a sirup, $[\alpha]_D^{25}$ −20·5° (*c* 0·50, ethyl acetate). UV spectrum (methanol): λ_{max} 263 nm (log ε 3·70), λ_{min} 228 nm (log ε 3·39). IR spectrum (chloroform): 3375 cm^{-1} (NH), 1734 br, 1702 cm^{-1} (C=O), 1590 cm^{-1} (C=N) ^{1}H-NMR spectrum (deuteriochloroform, tetramethylsilane as internal standard): 9·58 (broad s, 1 H, NH), 7·49 (s, 1 H, H_5), 6·58 (broad t, 1 H, $H_{1'}$, $J_{1',2'}$ = 6·0, $J_{1',2''}$ = 5·0), 2·81 (pentet, 1 H, $H_{2'}$, $J_{2',3'}$ = 6·0, $J_{gem2',2''}$ = 13·0), 2·20–2·55 (m, 1 H, $H_{2''}$), 5·33 (m, 1 H, $H_{3'}$), 4·0–4·40 (m, 3 H, $H_{4'}$ + $H_{5'}$ + $H_{5''}$), 2·09 (s, 3 H, $OCOCH_3$), 2·05 (s, 3 H, $OCOCH_3$). For $C_{12}H_{15}N_3O_7$ (313·3) calculated: 46·01% C, 4·83% H, 13·41% N; found: 45·99% C, 5·19% H, 13·07% N.

B) Compound *Vc* (100 mg; 0·25 mmol) was reduced analogously to paragraph *A*. The reaction was accomplished in 1 h, when the reaction mixture contained only trace amount of the starting *Vc*. Column chromatography on silica gel (40 g) in 1 : 1 ethyl acetate–benzene yielded 50 mg (63·8%) of the sirupous compound *VIb*, identical with the specimen prepared by procedure *A*.

2-(2-Deoxy-β-D-*erythro*-pentofuranosyl)-1,2,4-triazine-3,5(2*H*,4*H*)-dione (*VIa*)

Methanolic hydrogen chloride (0·1 ml of a 5N solution) was added to a solution of compound *VIb* (320 mg; 0·73 mmol) in methanol (10 ml), the whole kept at room temperature for 5 days, and evaporated. Crystallisation of the residue from a mixture of ethyl acetate and methanol yielded 100 mg (60%) of 2′-deoxy-6-azauridine (*VIa*), m.p. 135·5—138°C, undepressed on admixture with an authentic sample[47]. Work-up of mother liquors afforded additional 45 mg (27%) of the same substance, $[\alpha]_D^{25}$ −122·4° (*c* 0·55, methanol). UV spectrum (methanol): λ_{min} 228 nm (log ε 3·40), λ_{max} 265 nm (log ε 3·71). Reported[47]: m.p. 140°C; $[\alpha]_D^{24}$ −117° (*c* 2·7, pyridine), λ_{max} (ethanol) 267 nm (log ε 3·69). IR spectrum (nujol): 1726, 1716, 1690 cm^{-1} (C=O), 3493, 3413, 3182, 3116 cm^{-1} (OH and NH), 1590 cm^{-1} (C=N). ^{1}H-NMR spectrum (hexadeuteriodimethyl sulfoxide with deuteriochloroform): 12·10 (broad, 1 H, NH), 7·47 (s, 1 H, H_5), 6·35 (q, 1 H, $H_{1'}$, $J_{1',2'} = 6·0$, $J_{1',2''} = 7·0$), 2·47 (pentet, 1 H, $H_{2'}$, $J_{2',3'} = 6·0$, $J_{gem\,2',2''} = 13·0$), 2·10 (dq, 1 H, $H_{2''}$, $J_{2'',3'} = 5·0$, $J_{2'',1'} = 7·0$), 4·30 (q, 1 H, $H_{3'}$), 3·76 (q, 1 H, $H_{4'}$), 3·45 (2 × q, 2 H, 2 $H_{5'}$, $J_{4',5'} = 5·0$, $J_{5'',4'} = 6·0$, $J_{gem\,5',5''} = 11·0$).

3′,5′-Di-O-acetyl-2′-deoxy-2′-chloro-6-azacytidine (*VII*)

Thionyl chloride (0·38 ml; 5·2 mmol) and dimethylformamide (0·05 ml) were added to a suspension of compound *Vb* (174 mg; 0·5 mmol) in chloroform (3·5 ml) and the whole mixture was refluxed for 8 h (two 30 μl portions of dimethyformamide were added in 3 h intervals during this reflux). The mixture was evaporated and the residue dissolved in chloroform (4 ml). Methanolic ammonia (2·5 ml of a 17% solution) was added with stirring and ice-cooling to the chloroform solution, the stirring continued for 5 min, the mixture filtered through Celite, and the filtrate evaporated. The residue was chromatographed on a column of silica gel (35 g) in 10 : 1 ethyl acetate–methanol to afford a sirup (122 mg). Crystallisation from ethyl acetate yielded 75 mg (43·3%) of compound *VII*, m.p. 176—178·5°C, $[\alpha]_D^{25}$ −82·3° (*c* 0·51, methanol). UV spectrum (methanol): λ_{max} 264 nm (log ε 3·92), λ_{min} 228 nm (log ε 3·42). IR spectrum (chloroform): 1746 cm^{-1} (C=O acetate), 1658 cm^{-1} (NH_2 + C=O of 6-azacytosine), 1606 cm^{-1} (C=N). For $C_{12}H_{15}ClN_4O_6$ (346·7) calculated: 41·57% C, 4·36% H, 16·16% N, 10·23% Cl; found: 41·54% C, 4·50% H, 16·32% N, 10·49% Cl.

2-(3,5-Di-O-acetyl-2-deoxy-β-D-*erythro*-pentofuranosyl)-5-amino-1,2,4-triazin-3(2*H*)-one (*VIIIb*)

Thionyl chloride (1 ml) and dimethylformamide (0·16 ml) were added to a solution of compound *VIb* (400 mg; 1·28 mmol) in chloroform (10 ml), the whole refluxed for 4 h, treated with additional dimethylformamide (0·07 ml), and the reflux continued for 3 h. The solution was evaporated and the residue dissolved in chloroform (10 ml). Methanolic ammonia (6·5 ml of a 17% solution) was added with stirring and external ice-cooling to the chloroform solution, the mixture stirred for 5 min, filtered through Celite, and the filtrate evaporated. The residue was chromatographed on a column of silica gel (250 g) in 10 : 1 ethyl acetate–methanol to afford 320 mg (80%) of compound *VIIIb* as a foam, $[\alpha]_D^{25}$ −93° (*c* 0·56, methanol). UV spectrum (methanol): λ_{max} 272 nm (log ε 3·76), λ_{min} 237 nm (log ε 3·41). IR spectrum (chloroform): 3150 cm^{-1} (NH_2 bound), 1740 cm^{-1} (C=O acetate), 1661 cm^{-1} (C=O of 6-azacytosine), 1631 cm^{-1} (NH_2 of 6-azacytosine), 1600 cm^{-1} (6-azacytosine ring). For $C_{12}H_{16}N_4O_6$ (312·3) calculated: 46·15% C, 5·16% H, 17·94% N; found: 46·65% C, 5·63% H, 17·43% N.

2-(2-Deoxy-β-D-*erythro*-pentofuranosyl)-5-amino-1,2,4-triazin-3(2*H*)-one (*VIIIa*)

A solution of the diacetyl derivative *VIIIb* (312 mg; 1 mmol) in 15% methanolic ammonia (5 ml) was kept at room temperature for 3 days, evaporated, and the residue crystallised from a mixture of methanol and ethyl acetate. Yield, 180 mg (78%) of 2'-deoxy-6-azacytidine (*VIIIa*), m.p. 238–242°C, identical with an authentic specimen[49]. UV spectrum (ethanol): λ_{max} 266 nm (log ε 3·83), λ_{min} 230 nm (log ε 3·41). Reported[49]: m.p. 249–250°C; λ_{max} (ethanol) 266 nm (log ε 3·88). IR spectrum (nujol): 3390, 3345, 3290, 3230, and 3211 cm^{-1} (OH and NH bound), 1676 and 1618 cm^{-1} (C=O and NH_2), 1581 cm^{-1} (C=N). ^{1}H-NMR spectrum (hexadeuteriodimethyl sulfoxide with deuteriochloroform; the exchange was performed with the use of perdeuterioacetic acid): 6·47 (t, 1 H, $H_{1'}$, $J_{1',2'} = J_{1',2''} = 6·5$), 2·06 (dq, 1 H, $H_{2'}$, $J_{2',1'} = 6·5$, $J_{2',3'} = 4·0$, $J_{gem\,2',2''} = 13·0$), 2·46 (pentet, 1 H, $H_{2''}$, $J_{2'',1'} = J_{2'',3'} = 6·5$, $J_{gem\,2'',2'} = 13·0$), 4·31 (dt, 1 H, $H_{3'}$, $J_{3',2'} = 4·0$, $J_{3',2''} = 6·5$, $J_{3',4'} = 4·0$), 3·79 (broad q, 1 H, $H_{4'}$), 3·46 (m, 2 H, $H_{5'} + H_{5''}$, $J_{5',4'} = 6·0$, $J_{5'',4'} = 4·5$), 7·50 (s, 1 H, H_5), 7·77 (broad, 2 H, NH_2), 3·30 (broad, HO and HOD from dimethyl sulfoxide).

5-O-Trityluridine (*Id*)

A solution of uridine (*Ic*; 20 g; 82 mmol) and trityl chloride (dried at 0·1 Torr for 2 h; 25·2 g; 90 mmol) in pyridine (200 ml) was kept at room temperature for 10 days and evaporated. The residue was dissolved in acetone (80 ml) and the solution added dropwise with stirring into a mixture (1 000 ml) of ice and water (1 : 1). The aqueous supernatant was decanted, the precipitate covered with ice-cold water (200 ml), and kept overnight. The solid was collected with suction, washed with water, dried by coevaporation with five 150 ml portions of ethanol, and finally crystallised from ethanol (200 ml). Yield, 28·3 g (71%) of compound *Id*, m.p. 198–200°C, identical with an authentic specimen[31].

2',3'-O-Carbonyl-5'-O-trityluridine (*IIc*)

A) A solution of phosgene (7 g; 71 mmol) in toluene (40 ml) was added dropwise with stirring and cooling with ice into a solution of imidazole (20·4 g; 0·3 mol) in dichloromethane (200 ml). The mixture was stirred at room temperature for 2 h, the precipitate of imidazole hydrochloride was collected with suction, and the filtrate was evaporated (the operations were performed under exclusion of atmospheric moisture). The residual 1,1'-carbonyldiimidazole was treated at room temperature with a solution of compound *Id* (10·2 g; 21 mmol) in dimethylformamide (15 ml) and toluene (100 ml), the whole kept at room temperature for 60 min, and evaporated. The residue was dissolved in ethyl acetate (700 ml), the solution washed with four 50 ml portions of water, dried over anhydrous magnesium sulfate, filtered, and the filtrate evaporated. The residue was dissolved in acetone (25 ml) and the solution added dropwise with stirring into a mixture (600 ml) of ice and water. The whole was stirred for 1 h, the precipitate collected with suction, and dried by repeated coevaporation with ethanol. Yield, 9·58 g (89%) of compound *IIc*, m.p. 133–137°C (after recrystallisation from ethanol); reported[7], m.p. 134·5 to 135·5°C.

B) A solution of phosgene (356 mg; 3·6 mmol) in toluene (2 ml) was added dropwise with stirring into an ice-cooled solution of compound *Id* (1·1 g; 2·26 mmol) in pyridine (7 ml) and toluene (40 ml). The mixture was stirred without cooling for 1 h, evaporated under diminished pressure, and the residue repeatedly coevaporated with ethyl acetate–ethanol (1 : 1). The final residue was chromatographed on a column of silica gel (300 g) in ethyl acetate–benzene (4 : 1).

The *IIc*-containing fractions were evaporated and the residue (820 mg) recrystallised from ethanol. Yield, 739 mg (63·8%) of compound *IIc*, identical with the specimen prepared in paragraph *A*.

2,2′-Anhydro-1-(5-O-trityl-β-D-arabinofuranosyl)uracil (*IIIb*)

A solution of the carbonyl derivative *IIc* (4·85 g; 9·46 mmol) and imidazole (1·5 g; 22 mmol) in dimethylformamide (10 ml) was heated at 150°C (bath temperature) for 45 min, cooled down, and diluted with ether (500 ml). The precipitate was collected with suction, washed with ether, and crystallised from ethanol (130 ml). Yield, 3·43 mg (77·4%) of compound *IIIb*, m.p. 217 to 220°C (reported, m.p.[51] 215—218°C and m.p.[3] 217—219°C). Work-up of mother liquors yielded an additional crop (540 mg; 12·2%) of compound *IIIb*.

2,2′-Anhydro-1-(β-D-arabinofuranosyl)uracil Hydrochloride (*IVb*)

Ethereal hydrogen chloride (130 ml of a 10% solution) was added to a stirred suspension of compound *IIIb* (6·4 g; 13·6 mmol) in ether (130 ml). The whole was stirred at room temperature for 1 h and then kept at 0°C overnight. The solid was collected with suction, washed with ether, and dried under diminished pressure. Yield, 3·54 g (99%) of the crude hydrochloride *IVb*, m.p. 135°C (decomp.); reported[34], m.p. 167° (decomp.). For $C_9H_{10}N_2O_5.HCl$ (262·7) calculated: 41·15% C, 4·21% H, 10·66% N; 13·50% Cl; found: 41·39% C, 4·42% H, 11·04% N, 13·59% Cl. Without any further purification, the product was used in the preparation of 2′-chloro-2′-deoxyuridine (*Ve*).

2′-Chloro-2′-deoxyuridine (*Ve*)

A) A solution of the crude hydrochloride *IVb* (525 mg; 2 mmol) in dimethylformamide (8 ml) was heated at 95°C (bath temperature) for 1 h, evaporated, and the residual sirup repeatedly coevaporated with benzene. Crystallisation from ethanol yielded 461 mg (87·8%) of the chloro derivative *Ve*, m.p. 200—205°C; reported, m.p.[51] 202—206°C and m.p.[36] 201—202°C.

B) Hydrogen chloride in dimethylformamide (0·5 ml of a 40% solution) was added to a solution of compound *IIIb* (249 mg; 0·53 mmol) in dimethylformamide (4 ml), the mixture heated at 95°C (bath temperature) for 2 h, and evaporated under diminished pressure. The residue was repeatedly coevaporated with benzene and finally chromatographed on a column of silica gel (200 g) in the solvent system ethyl acetate–acetone–ethanol–water (4 : 1 : 1 : 1). The *Ve*-containing fractions were evaporated and the residue crystallised from ethanol. Yield, 119 mg (85·5%) of the chloro derivative *Ve*, identical with the substance prepared in paragraph *A*.

2′-Deoxyuridine (*VId*)

A mixture of the chloro derivative *Ve* (394 mg; 1·5 mmol), glacial acetic acid (12 ml), acetyl chloride (0·5 ml), and acetic anhydride (6·5 ml) was stirred at room temperature overnight and evaporated. The residue was repeatedly coevaporated with toluene and ethanol. The chromatographically homogeneous diacetyl derivative *Vf* was obtained in the form of a foam. A solution of tributyltin hydride (6 mmol) in benzene (6 ml) was added to the crude *Vf* (520 mg), the mixture heated to the boiling point, and treated with 2,2′-azobis(2-methylpropionitrile) (20 mg). The mixture was refluxed for 4 h, evaporated, and the residue chromatographed on a column of silica gel (130 g) in ethyl acetate. The *VIc*-containing fractions were evaporated and the residue deacetylated as follows. Methanol (2 ml) and methanolic ammonia (2 ml of a 19% solution) were added to the crude acetyl derivative *VIc* (440 mg), the mixture kept at room temperature

overnight, evaporated, and the residue coevaporated with three 10 ml portions of ethanol. Crystallisation from ethanol yielded 267 mg (78%, referred to the starting material *Ve*) of 2′-deoxyuridine *VId*, m.p. 163°C, identical with an authentic specimen[36].

R_F Values of Some Derivatives

The chromatography was performed in a 9 × 18 × 21 cm glass chamber containing 50 ml of the solvent S_1 (ethyl acetate) on the bottom, without saturation with vapours, at room temperature (18–22°C), on ready-for-use Silufol^R UV 254 (Kavalier Glassworks, Votice, Czechoslovakia) silica gel plates (the front was always allowed to travel a 10 cm path). The following R_F values (in parentheses) were observed: *VIa* (0·13), 3′-deoxy-*threo*-pentofuranosyl-6-azauracil (0·09), *VIb* (0·75), 2′,5′-di-O-acetyl-3′-deoxy-*threo*-pentofuranosyl-6-azauracil (0·82), 5′-O-acetyl-2′-deoxy-*erythro*-pentofuranosyl-6-azauracil (0·47), 5′-O-acetyl-3′-deoxy-*threo*-pentofuranosyl-6-azauracil (0·43), *Va* (0·45), 3′-deoxy-3′-chloro-*arabino*-6-azauracil (0·56), *Vb* (0·94), 2′,5′-di-

TABLE I

Thin-Layer Chromatography on Silica Gel (for conditions see the Experimental)

Solvent systems: S_1, ethyl acetate; S_2, ethyl acetate–methanol (10 : 1); and S_3, ethyl acetate–methanol (1 : 1).

Derivative	S_1	S_2	S_3	6-Azaanalogue	S_1	S_2	S_3
Ic	0·03	0·22	0·76	*Ia*	0·10	0·40	0·82
Id	0·57	0·80	0·87	*Ib*	0·81	[a]	[a]
IIc	0·68	[a]	[a]	*IIb*	0·93	[a]	[a]
[b]	0·29	0·60	0·84	*IIa*	0·55	0·76	[a]
[c]	0	0·02	0·50	[g]	0·04	0·25	0·80
IIIb	0·02	0·18	0·79	*IIIa*	0·43	0·88	[a]
Ve	0·23	0·49	0·84	*Va*	0·45	0·63	[a]
Vf	0·78	0·90	[a]	*Vb*	0·94	[a]	[a]
VId	0·04	0·25	0·78	*VIa*	0·13	0·41	[a]
VIc	0·48	0·75	[a]	*VIb*	0·75	0·81	[a]
—	—	—	—	[h]	0·47	0·65	[a]
[d]	0·77	0·85	0·89	*Vc*	0·92	[a]	[a]
—	—	—	—	*Vd*	0·59	0·75	[a]
[e]	0·61	0·87	[a]	[i]	0·81	[a]	[a]
—	—	—	—	*VII*	0·09	0·49	0·82
—	—	—	—	*VIIIa*	0	0·02	0·32
—	—	—	—	*VIIIb*	0·03	0·21	0·67
[f]	0	0·02	0·41	[j]	0	0·02	0·38

[a] R_F value > 0·90; [b] uridine 2′,3′-carbonate[33]; [c] 2,2′-anhydrouridine[6]; [d] 3′,5′-di-O-acetyl-2′-bromo-2′-deoxyuridine[38]; [e] 2′,3′,5′-tri-O-acetyluridine[52]; [f]; cytidine; [g] 2,2′-anhydro-6-azauridine[24]; [h] 5′-O-acetyl-2′-deoxy-6-azauridine; [i] 2′,3′,5′-tri-O-acetyl-6-azauridine[30]; [j] 6-azacytidine[48].

-O-acetyl-3′-deoxy-3′-chloro-*arabino*-6-azauracil (0·93), *Vc* (0·92), 2′,5′-di-O-acetyl-3′-deoxy-3′--bromo-*arabino*-6-azauracil (0·94), *Vd* (0·53), 3′-bromo-3′-deoxy-*arabino*-6-azauracil (0·59). For other R_F values see Table I.

The authors wish to thank Mrs J. Hlaváčková for excellent technical assistance, Dr H. Hřebabecký and Dr J. Brokeš for valuable discussions, Dr M. Masojídková for measurement and interpretation of ^{1}H-NMR *spectra, Dr P. Fiedler for interpretation of* IR *spectra, Mr P. Formánek for measurement of* UV *and* IR *spectra, The Analytical Department (Head, Dr J. Horáček) of this Institute for elemental analyses, Dr J. Pliml and Dr M. Prystaš for authentic samples of deoxynucleosides, and Mrs Z. Ledvinová for measurement of optical rotations.*

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Translated by J. Pliml.