2',3'-O-CARBONYL DERIVATIVES OF 6-AZAURIDINE IN THE SYNTHESIS OF ITS 5'-SUBSTITUTED AND 5'-DEOXY DERIVATIVES

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Received December 20th, 1986

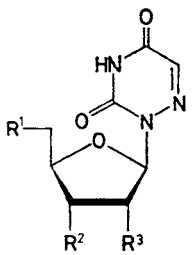
Preparation of 2',3'-O-carbonyl derivatives of 5'-deoxy-6-azauridine and 6-azauridine using 1,1'-carbonyldiimidazole has been elaborated. 5'-Chloro and 5'-bromo derivatives were prepared by treatment of the 5'-O-mesyl derivative with quaternary ammonium halides, 5'-chloro derivatives also by direct halogenation with thionyl chloride in hexamethylphosphortriamide or with tetrachloromethane, triphenyl phosphine, and dimethylformamide. Derivatives of 5'-bromo-6-azauridine were reduced with tributyltin hydride to 5'-deoxy-6-azauridine compounds. 6-Azauridine 2',3'-carbonate (*IVa*) and its 5'-derivatives *IVc* and *IVe* on treatment with imidazole in dimethylformamide afforded 2,2'-anhydronucleosides *IIIa*–*IIIc*. The 2,2'-anhydro-5'-deoxy compound *IIIc* underwent alkaline hydrolysis to 5'-deoxy-1-β-D-arabino-pentofuranosyl-6-azauracil (*VIa*). Treatment of 2,2'-anhydro-5'-deoxy-5'-chloro derivative *IIIb* with hydrogen chloride led to 2',5'-dichloro derivative *If*.

Investigating the formation of nucleoside carbonates we have found[1–4] that 1,1'-carbonyldiimidazole[5] forms in high yields cyclic 2',3'-carbonates on reaction with nucleosides having *ribo*-arrangement on the sugar residue and no (unprotected) hydroxy group on the carbon atom 5'. This method, with some modifications, was used in syntheses of monosaccharides[6] and amino sugars[7] for protection of both the secondary hydroxyl groups by a group relatively stable in acidic media (*cf.* ref.[8]). In this way we prepared nucleoside carbonates *IVa*–*IVe*.

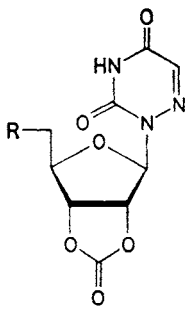
Methanesulfonyl carbonate *IVb* was obtained in 89% yield by mesylation of 6-azauridine carbonate *IVa* (ref.[3]). Compound *IVb* was also obtained from *Ib* by treatment with 1,1'-carbonyldiimidazole in dimethylformamide in 60% yield. The deblocking of the carbonate *IVb* was effected in 87% yield by treatment with 0·1 mol . l^{-1} methanolic sodium methoxide at room temperature[3,4].

Since the reaction of alkali metal bromides with mesylates in acetone (analogous to the method[4,9] used for preparation of 5'-iodo nucleosides) was not suitable for preparative work, we used dimethylformamide as solvent with a five-fold excess of tetrabutylammonium bromide at 130°C. In this way we prepared *Vb*, *Id*, and *IVd* from *Va*, *Ib*, and *IVb* in the yields 48%, 58%, and 76%, respectively. Smaller excess of tetrabutylammonium bromide resulted in incomplete or slower conversion of the

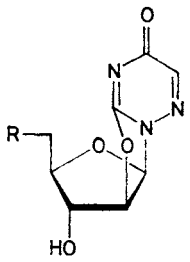
methanesulfonyl derivative. We utilized our experience for the preparation of 5'--chloro-5'-deoxy-2',3'-O-carbonyl-6-azauridine (*IVc*) from *IVb* by reaction with benzyltrimethylammonium chloride in dimethylformamide in 48% yield.



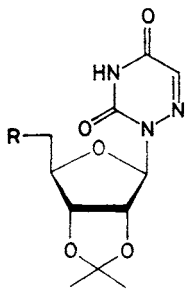
I a, $R^1 = R^2 = R^3 = OH$
I b, $R^1 = OMs$; $R^2 = R^3 = OH$
I c, $R^1 = Cl$; $R^2 = R^3 = OH$
I d, $R^1 = Br$; $R^2 = R^3 = OH$
I e, $R^1 = H$; $R^2 = R^3 = OH$
I f, $R^1 = R^3 = Cl$; $R^2 = OH$
I g, $R^1 = Cl$; $R^2 = R^3 = OOCCH_3$



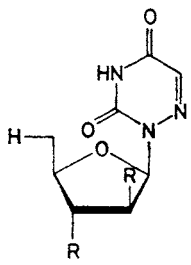
IV a, R = OH
IV b, R = OMs
IV c, R = Cl
IV d, R = Br
IV e, R = H



III a, R = OH
III b, R = Cl
III c, R = H



V a, R = OMs
V b, R = Br
V c, R = H



VI a, R = OH
VI b, R = $OOCCH_3$

Ms = Methanesulfonyl

The bromo carbonate *IVd* and chloro carbonate *IVc* were also prepared by treatment of the corresponding halogeno derivatives *Id* and *Ic* with 1,1'-carbonyldiimidazole at room temperature in the respective yields of 40% and 38%, the lower yields being obviously due to the losses during the prolonged chromatography on silica gel.

5'-Bromo-5'-deoxy derivatives were reduced in acceptable yields with tributyltin hydride under initiation with 2,2'-azobis(2-methylpropionitrile)[10]. Thus, the 5'-bromo-5'-deoxy carbonate *IVd* was reduced to the deoxy carbonate *IVe*; the yield was somewhat lower (36%) than in the uridine series[4] where generally the reduction (under the same conditions) is easier (yield 81% after 2 h). The azauridine derivative was reduced with difficulty (yield 36% after 6 h). Apparently, the long heating caused partial decomposition of the carbonate: This is supported by the fact that the free bromo derivative *Id* was reduced in the same time but in higher yield (60%). In the analogous reaction of *Vb* the deoxy derivative *Vc* was obtained in an 81% yield (after 1·5 h).

A similar reduction of 5'-chloro derivatives of 6-azauridine has not been observed. The time required for reduction of the bromo derivative *IVd* was at least three times longer than for the analogous uracil derivative[4]. Similarly, for 3',5'-di-O-acetyl-2'-chloro-2'-deoxy-6-azauridine the reduction time was twice as long as for the analogous uracil derivative and seven times longer than for the 6-azauracil 2'-bromo derivative[3]. Thus, the reduction is generally easier for uracil than for 6-azauracil, for bromo than for chloro, and for 2'-halogeno than for 5'-halogeno, derivatives. The time required for reduction of the 5'-chloro derivative *Ic* should be several tens of hours which is incompatible with the stability of the compounds. These conclusions agree with the literature data[11,12] as well as with our observation that reduction with tributyltin hydride is not suitable for the 5'-chloro derivatives *Ic*, *IVc* or *If*, *Ig*.

The deoxy carbonate *IVe* was also prepared (in 80% yield) by reaction of deoxynucleoside *Ie* with 1,1'-carbonyldiimidazole in dimethylformamide. When the reaction was performed at 150°C, already after 2 hours it gave another product, presumably bis(2,2'-anhydro-β-D-arabinosyl-6-azauracil) 3',3''-carbonate.

Alternatively, deoxy derivative *Ie* was obtained by acid-catalyzed removal of the isopropylidene group in *Vc*. Similar procedure was used in the preparation of 5'-bromo-5'-deoxy-6-azauridine (*Id*) from the bromo derivative *Vb*. Also reduction of *Id* with tributyltin hydride in the presence of 2,2'-azobis(2-methylpropionitrile)[10] or cleavage of the carbonate *IVe* in boiling water[4] gave *Ie*.

The carbonate *IVe* served as an intermediate in the synthesis of anhydro derivative *IIIc*. The structure of *IVe* was verified by its conversion into the deoxy derivative *Ie*, prepared from *Id* or *Vc*. The anhydro compound *IIIc* was obtained by heating *IVe* with imidazole in dimethylformamide at 150°C (*cf.* ref.[3]). The same reaction was applied to the conversion of *IVc* and *IVa* to *IIIb* and *IIIa*, respectively (yields 80% and 59%). Instead of imidazole, sodium hydrogen carbonate was used[13] as a base in the preparation of an analogous anhydronucleoside in the uridine series[4].

The removal of the protecting group in boiling water is markedly slower in the 6-azauridine than in the uridine series. Whereas the carbonate derived from uridine or 5'-deoxyuridine was cleaved with boiling water during 4·5 h and 6 h, respectively[4],

the reaction time for the corresponding 6-aza analogues *IVa* and *IVe* was 10 h and 18 h, respectively. Because of the long heating required, we looked for milder deblocking methods applicable to *IVa*. The compound was cleaved in aqueous pyridine (33%) during 45 min at reflux or during 4 days at room temperature. Analogous deblocking for uridine[14] takes 15 min. Methanolic sodium methoxide[15] cleaved *IVa* in several minutes. In all four cases, the 6-azauridine *Ia* was isolated in almost quantitative yield. Other published cleavage reagents include concentrated aqueous ammonia for purine nucleosides[8], 0·5M-NaOH in 50% aqueous dioxane for 2',3'-O--carbonyl-5'-O-trityluridine[14] or 0·1 mol l^{-1} aqueous buffer, pH 8·0, for an inosine derivative[8].

The deblocking of cyclic 2',3'-carbonates with methanolic sodium methoxide, mentioned above as the best method, was also used in further cases. Thus, the methanesulfonyl carbonate *IVb* was converted in 87% yield to the sulfonyl derivative *Ib* identical with a sample prepared according to the literature[9], and chlorocarbonate *IVc* was transformed to *Ic*, again in a high yield (91%).

For the preparation of a series of chloro nucleosides analogous to the above-described bromo derivatives we investigated two methods of direct chlorination of 6-azauridine. The first (ref.[16]) consisted in reaction of the nucleoside with tetrachloromethane, triphenylphosphine, and dimethylformamide. Application to the 6-azauridine (*Ia*) gave the chloro derivative *Ic* in 37% yield, the reaction being slower than with uridine. In accord with the literature[16], we have found that the bromination is more difficult than chlorination. Bromination of *Ia* according to this method gave the bromo compound *Id* in very low yield. The second method was based on halogenation of nucleosides with thionyl halides in hexamethylphosphortriamide[17], which has been studied by us in more detail[18–22]. Reaction of nucleoside *Ia* with thionyl chloride afforded 5'-chloronucleoside *Ic* along with two isomeric 5'-chloro-5'-deoxy-2',3'-O-sulfinyl-6-azauridines[19]. The composition of the reaction mixture and the ratio of the isolated products strongly depended on the reaction conditions and the work-up procedure. When the whole reaction was carried out at room temperature and hexamethylphosphortriamide was distilled off only after decomposition of thionyl chloride and neutralization of the acids with sodium hydrogen carbonate solution, compound *Ic* was isolated as the principal product. This was acetylated with an acidic acetylation mixture[23,24] to the 2',3'-di-O-acetyl derivative *Ig*.

The chlorination reagent – a mixture of thionyl chloride and hexamethylphosphortriamide – was also used in the preparation of the chloro carbonate *IVc* by chlorination of *IVa*. This reaction again illustrates the suitability of the carbonate protecting group, used already in sugar chemistry[25].

On treatment with imidazole in dimethylformamide, the chlorocarbonate *IVc* afforded the anhydro derivative *IIIb* which was opened with hydrogen chloride in dimethylformamide to give 2',5'-dichloronucleoside *If*.

The above-mentioned preparation of nucleosides of *arabino*-configuration *via* cyclic carbonate has been utilized in the preparation of *VIa*. Similarly to *IIIa* (ref.[26]), the anhydro derivative *IIIc* was cleaved with 0·1M-NaOH to 5'-deoxy-*arabino* derivative *VIa*. As with its uracil analogue[4], *VIa* was acetylated[23,24] to the di-O-acetyl derivative *VIb* because the free deoxy derivative *VIa* was not obtained in the crystalline state. The chromatographic behaviour on TLC of compounds presented and some close derivatives is surveyed in Table I.

TABLE I
Thin-layer chromatography on Silufol

Compound	S_1[a]	S_2[a]	S_3[a]
Ia	0·10	0·40	0·00
Ib	0·28	0·60	0·02
Ic	0·58	0·82	0·08
2'-Chloro-2'-deoxy-6-azauridine[3]	0·45	0·63	0·06
Id	0·61	0·82	0·11
2'-Bromo-2'-deoxy-6-azauridine[3]	0·53	0·75	0·08
Ie	0·43	0·62	0·05
2'-Deoxy-6-azauridine[3]	0·13	0·41	0·01
If	0·88	>0·9	0·42
Ig	0·94	>0·9	0·48
3',5'-Di-O-acetyl-2'-chloro-2'-deoxy-6-azauridine[3]	0·94	>0·9	0·49
IIIa	0·04	0·25	0·00
IIIb	0·32	0·50	0·03
IIIc	0·20	0·36	0·02
IVa	0·55	0·76	0·05
IVb	0·75	0·83	0·12
IVc	0·94	>0·9	0·39
IVd	0·94	>0·9	0·44
IVe	0·88	>0·9	0·32
2',3'-O-Carbonyl-5'-O-trityl-6-azauridine[3]	0·93	>0·9	0·56
2',3'-O-Isopropylidene-6-azauridine[27]	0·63	0·86	0·12
Va (ref.[11])	0·83	>0·9	0·30
Vb	0·96	>0·9	0·69
Vc	0·93	>0·9	0·58
VIa	0·30	0·50	0·03
VIb	0·92	>0·9	0·41

[a] S_1 Ethyl acetate, S_2 ethyl acetate–methanol 10 : 1, S_3 ethyl acetate–benzene 1 : 1.

EXPERIMENTAL

Melting points were determined on a Boetius micro melting point apparatus (G.D.R.), optical rotations on a Perkin–Elmer 141 MC polarimeter. Infrared spectra were taken on a UR-20 (Zeiss, Jena) spectrophotometer, wavenumbers are given in cm^{-1}. ^1H NMR spectra were measured on a Tesla BS-467 (60 MHz) instrument in hexadeuteriodimethyl sulfoxide with deuteriochloroform (hexamethyldisiloxane as internal standard, unless stated otherwise). Chemical shifts are given on δ-scale (in ppm), coupling constants, J, and band widths, W, in Hz. All parameters were obtained by first-order analysis. Mass spectra were measured on an AEI-901 spectrometer, unless stated otherwise. Preparative chromatography was carried out on columns of silica gel according to Pitra (60—120 μm, Service Laboratories of this Institute), thin-layer chromatography (TLC) was performed on silica gel G according to Stahl (Woelm) and on ready-to-use SILUFOL TLC plates. Spots were detected by UV (254 nm) absorption and/or by spraying with sulfuric acid followed by heating. Solutions were dried over anhydrous sodium sulfate and taken down on a rotatory evaporator at bath temperature 40—50°C and pressure 2—2·5 kPa. Analytical samples were dried over phosphorus pentoxide at about 25 Pa.

Hydrolysis of 6-Azauridine 2′,3′-O-Carbonate (*IVa*)

A solution of azauridine 2′,3′-O-carbonate[3] (*IVa*, 1/2 crystal ethyl acetate; 31·5 mg; 0·1 mmol) in water (5 ml) was refluxed for 10 h. After evaporation, the residue was crystallized from 2-propanol–methanol (3 : 2) affording 21 mg (85%) of *Ia*, identical with an authentic sample.

The title compound was prepared in 86% yield also by standing of *IVa* (0·1 mmol) in water (4 ml) and pyridine (2 ml) at room temperature for 4 days or in 89% yield by heating the solution to 100°C for 45 min. Also treatment of *IVa* (45 mg) with 0·1 mol l^{-1} methanolic sodium methoxide (5 ml) at room temperature for 20 min, followed by neutralization with Dowex 50 W (H^+-form, prewashed with methanol) gave *Ia*; yield 82%.

5′-O-Methanesulfonyl-6-azauridine (*Ib*)

A mixture of 5′-O-methanesulfonyl-2′,3′-O-carbonyl-6-azauridine (*IVb*; 400 mg; 1·1 mmol), methanol (4 ml) and 1 mol l^{-1} methanolic sodium methoxide (0·4 ml) was stirred at room temperature for 30 min. After neutralization with Dowex 50 W (H^+-form, prewashed with methanol), the mixture was filtered, the solvent evaporated and the residue crystallized from methanol, affording 32 mg (87%) of *Ib*, m.p. 182—184°C (reported[9] m.p. 181—182°C), $[\alpha]_D^{25}$ −65·6° (*c* 0·5; dimethylformamide). UV spectrum (methanol): λ_{max} 265 nm (log ε 3·78), λ_{min} 230 nm (log ε 3·45). IR spectrum (KBr): 3 417; 3 390 sh; 3 290 (NH), 1 722; 1 689; 1 665 (C=O), 1 599 (C=N), 1 350 (SO_2 asymmetric), 1 186 (SO_2 symmetric). ^1H NMR spectrum: 12·26 broad, 1 H (NH), 7·51 d, 1 H (H-5, J(5, NH) = 2·0), 5·94 d, 1 H (H-1′, J(1′, 2′) = 2·0), 3·95 to 4·50 m, 7 H (H-2′ + H-3′ + H-4′ + 2 H-5′ + 2 OH), 3·06 s, 3 H (methanesulfonyl). The compound was identical with an authentic sample[9].

5′-Deoxy-5′-chloro-6-azauridine (*Ic*)

A) Thionyl chloride (0·5 ml; 0·83 g; 6·95 mmol) was mixed with hexamethylphosphortriamide (5 ml) and, after standing for 5 min, 6-azauridine (*Ia*; 0·49 g; 2 mmol) was added. The mixture was stirred at room temperature for 2 h, diluted with water (50 ml), cooled with ice and adjusted to pH 6 by addition of solid sodium hydrogen carbonate with stirring. After filtration and evaporation, the residue was extracted with benzene–ethyl acetate–methanol (1 : 1 : 1) mixture (50 ml) and with ethyl acetate–methanol (1 : 1; 2 × 50 ml). The combined extracts were evaporated at 90°C/10 Pa and chromatographed on a silica gel column (125 g) in ethyl acetate. Fraction,

containing *Ic*, was taken down and the obtained oil (348 mg) was crystallized from ethyl acetate, affording 312 mg (59%) of *Ic*, m.p. 143–146°C, $[\alpha]_D^{25}$ −114° (*c* 0·5; methanol). UV spectrum (methanol): λ_{max} 264 nm (log ε 3·84), λ_{min} 227 nm (log ε 3·51). IR spectrum (Nujol): 3 469; 3 393; 3 188 (OH and NH), 1 708; 1 693; 1 675 (C=O), 1 589 (C=N). ^{1}H NMR spectrum: 6·03 d, 1 H (H-1′, *J*(1′, 2′) = 3·0), 4·32 dd, 1 H (H-2′, *J*(2′, 1′) = 3·0; *J*(2′, 3′) = 4·5), 3·90–4·30 m, 4 H (H-3′ + H-4′ + 2 OH), 3·77 dd, 1 H (H-5′, *J*(5′, 4′) = 4·0; *J*(5′, 5″) = 11·0), 3·58 dd, 1 H (H-5″, *J*(5″, 4′) = 6·0; *J*(5″, 5′) = 11·0), 7·46 s, 1 H (H-5), 12·20 broad, 1 H (NH). Mass spectrum contains a fragment B + 30 and fragment of the unsubstituted base. Oxidation with IO_4^- in a phosphate buffer at pH 6·8: consumption 1·01 equivalent in 8 min, then no further consumption. For $C_8H_{10}ClN_3O_5$ (263·6) calculated: 36·45% C, 3·82% H, 13·45% Cl, 15·94% N; found: 36·57% C, 3·91% H, 13·52% Cl, 15·69% N.

B) A mixture of *Ia* (245 mg; 1 mmol), triphenylphosphine (800 mg; 3 mmol), tetrachloromethane (0·5 ml; 5 mmol), and dimethylformamide (5 ml) was stirred at room temperature for 24 h and diluted with methanol (50 ml). The solvent was evaporated and the residue chromatographed on a column of silica gel (100 g; ethyl acetate–benzene 2 : 1). The partially resolved mixture was rechromatographed on a silica gel column (50 g) in ethyl acetate–benzene (2 : 3). The product-containing fractions were evaporated and crystallized from ethyl acetate to give 90 mg (37%) of *Ib*, identical with the compound prepared under *A*. The other chromatographic fractions were not investigated.

C) A mixture of 5′-deoxy-5′-chloro-2′,3′-O-carbonyl-6-azauridine (*IVc*; 40 mg; 0·14 mmol), methanol (4 ml), and 1 mol l^{-1} methanolic sodium methoxide (0·4 ml) was stirred at room temperature for 30 min, neutralized with Dowex 50 W (H^+-form, prewashed with methanol) and filtered. Evaporation of the solvent and crystallization from ethyl acetate afforded 33 mg (91%) of *Ic*, identical with the product obtained under *A*.

5′-Bromo-5′-deoxy-6-azauridine (*Id*)

A) Hydrochloric acid (17%, 2 ml) was added to a solution of bromo derivative *Vb* (1·3 g; 3·73 mmol) in formic acid (98%, 30 ml). After standing for 10 days, the solution was evaporated and the residue chromatographed on silica gel (150 g; ethyl acetate). The main fraction (659 mg; 57%) was crystallized from ethyl acetate–ether–methanol to give 283 mg of *Id*, m.p. 141–143°C, $[\alpha]_D^{25}$ −90·9° (*c* 0·4; methanol). IR spectrum (Nujol): 3 385; 3 340; 3 165 (OH and NH bonded), 1 720; 1 693; 1 675 (C=O), 1 590 (C=N). UV spectrum (methanol): λ_{max} 263 nm (log ε 3·75), λ_{min} 229 nm (log ε 3·46). ^{1}H NMR spectrum (deuterium exchange performed with perdeuterioacetic acid): 7·44 s, 1 H (H-5), 12·20 broad, 1 H (HN), 6·03 d, 1 H (H-1′, *J*(1′, 2′) = 3·0), 4·35 q, 1 H (H-2′, *J*(2′, 1′) = 3·0; *J*(2′, 3′) = 5·0,) 3·95–4·20 m, 2 H (H-3′, H-4′), 3·64 dd, 1 H (H-5′, *J*(5′, 4′) = 4·0; *J*(5′, 5″) = 11·0), 3·45 dd, 1 H (H-5″, *J*(5″, 4′) = 6·0; *J*(5′, 5″) = 11·0), 4·0 broad, 2 H (2 OH). For $C_8H_{10}BrN_3O_5$ (308·1) calculated: 31·19% C, 3·27% H, 25·94% Br, 13·64% N; found: 31·47% C, 3·46% H, 25·42% Br, 13·87% N.

B) A mixture of compound *Ib* (ref.[9]; 162 mg; 0·5 mmol), tetrabutylammonium bromide (831 mg; 2·5 mmol), and dimethylformamide (5 ml) was kept at 130°C for 2 h. After evaporation, the residue was chromatographed on silica gel (130 g; ethyl acetate–benzene 2 : 1). The main fraction (130 mg; 84%) was crystallized from ethyl acetate to give 118 mg (76%) of the same product as obtained by procedure *A*.

5′-Deoxy-6-azauridine (*Ie*)

A) Hydrochloric acid (17%, 2 ml) was added to a solution of *Vc* (269 mg; 1 mmol) in formic acid (98%; 10 ml). The mixture was set aside for 14 days at room temperature, evaporated and the

residue was chromatographed on silica gel (100 g) in ethyl acetate–benzene (2 : 1). The main fraction afforded 162 mg (71%) of *Ie* which was crystallized from ethyl acetate–methanol–ether to give 110 mg (48%) of the product, m.p. 148·5–150·5°C. Upon recrystallization from ethanol the m.p. rose to 177–178·5°C, $[\alpha]_D^{25}$ −146° (*c* 0·2; methanol). IR spectrum (KBr): 1 717; 1 689 (C=O), 1 590 (C=N), 3 413 and 3 370 (OH and NH). UV spectrum (methanol): λ_{max} 266 nm (log ε 3·81), λ_{min} 227 nm (log ε 3·51). ^{1}H NMR spectrum (deuterium exchange by perdeuterioacetic acid): 5·91 d, 1 H (H-1′, *J*(1′, 2′) = 3·0), 4·25 dd, 1 H (H-2′, *J*(2′, 1′) = 3·0), *J*(2′, 3′) = = 6·0), 3·85 t, 1 H (H-3′, *J*(3′, 2′) = *J*(3′, 4′) = 6·0), 3·85 pentet, 1 H (H-4′, *J*(H-4′, CH_3) = 7·0), 1·23 d, 3 H (CH_3 (3 H-5′)), 4·90 broad, 1 H (OH), 5·15 broad, 1 H (OH), 12·18 broad, 1 H (NH), 7·50 s, 1 H (H-5). For $C_8H_{11}N_3O_5$ (229·2) calculated: 41·92% C, 4·84% H, 18·33% N; found: 42·03% C, 4·87% H, 18·01% N.

B) Tributyltin hydride in benzene (2 ml, *c* 1 mol l^{-1}) was added to a mixture of *Id* (70 mg; 0·23 mmol) and ethanol (1 ml). 2,2′-Azobis(2-methylpropionitrile) (5 mg) was added to the boiling mixture and was then refluxed for 6 h. Every 2 h another portion (5 mg) of 2,2′-azobis-(2-methylpropionitrile) was added. After evaporation, the residue was chromatographed on silica gel (30 ml, ethyl acetate–benzene 2 : 1), affording 47 mg of the product which was crystallized from ethyl acetate–methanol; yield 31 mg (60%) of *Ie*, identical with the product obtained by procedure *A*.

C) An aqueous solution (6 ml) of *IVe* (51 mg; 0·2 mmol) was refluxed for 18 h. After evaporation, the residue was dissolved in methanol and filtered with charcoal, the solvent was evaporated and the residue (46 mg; 94%) crystallized from ethanol, affording 32 mg (70%) of *Ie*, m.p. 177 to 178·5°C, identical with the product prepared ad *A*.

2′,5′-Dichloro-2′,5′-dideoxy-6-azauridine (*If*)

A mixture of *IIIb* (123 mg; 0·5 mmol), dimethylformamide (1·5 ml), and 35% solution of hydrogen chloride in dimethylformamide (0·9 ml) was heated to 100°C for 3 h. Dimethylformamide was evaporated at 50°C/10 Pa and the residue was chromatographed on a column of silica gel (100 g) in ethyl acetate–benzene (7 : 3). The residue after evaporation of the main fraction was dissolved in an acetone–benzene mixture, the solvents were evaporated and the product *If* (115 mg; 82%) was obtained as a foam; $[\alpha]_D^{25}$ −111° (*c* 0·8; methanol). UV spectrum (methanol): λ_{max} 261 nm (log ε 3·83), λ_{min} 223 nm (log ε 3·49). IR spectrum (chloroform): 3 375 (NH, free), 3 584 br (OH), 1 726; 1 705 (C=O), 1 619 (C=N). ^{1}H NMR spectrum: 6·30 d, 1 H (H-1′, *J*(1′, 2′) = 4·0), 4·71 t, 1 H (H-2′, *J*(2′, 1′) = 4·0; *J*(2′, 3′) = 5·0), 4·44 t, 1 H (H-3′, *J*(3′, 2′) = *J*(3′, 4′) = 5·0), 4·18 broad q, 1 H (H-4′), 3·80 dd, 1 H (H-5′, *J*(5′, 4′) = 4·0), *J*(5′, 5″) = 11·5), 3·63 dd, 1 H (H-5″, *J*(5″, 4′) = 5·0), 7·45 s, 1 H (H-5), 12·32 broad, 1 H (NH). For $C_8H_9Cl_2N_3O_4$ (282·1) calculated: 34·06% C, 3·22% H, 25·14% Cl, 14·90% N; found: 33·91% C, 3·59% H, 24·57% Cl, 14·74% N.

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

A mixture of *Ic* (146 mg; 0·57 mmol), glacial acetic acid (5 ml), acetyl chloride (0·196 ml), and acetic anhydride (2·5 ml) was stirred at room temperature for 24 h. After evaporation, the residue was chromatographed on silica gel in ethyl acetate–benzene (1 : 1); yield 120 mg (61%) of oily *Ig*; $[\alpha]_D^{25}$ −72·8° (*c* 0·6; methanol). IR spectrum (chloroform): 3 377 (NH), 1 740–1 750 (C=O acetate), 1 728 and 1 705 (C=O, azauracil), 1 593 (C=N). UV spectrum (methanol): λ_{max} 260 nm (log ε 4·08), λ_{min} 223 nm (log ε 3·76). For $C_{12}H_{14}ClN_3O_7$ (347·7) calculated: 41·45% C, 4·06% H, 10·20% Cl, 12·08% N; found: 41·25% C, 4·28% H, 9·98% Cl, 11·87% N.

(2*R*)-(2α,3β,3aβ,9aβ)-2,3,3a,9a-Tetrahydro-3-hydroxy-2-hydroxymethyl-6*H*-furo[2′,3′:4,5]oxazolo[3,2-*b*][1,2,4]triazin-6-one (*IIIa*)

A mixture of carbonate *IVa* (63 mg; 0·2 mmol), imidazole (15 mg; 0·22 mmol), and dimethylformamide (1 ml) was heated to 150°C for 4 h. After evaporation, the residue was chromatographed on a column of silica gel (15 g, ethyl acetate–methanol 20 : 1), affording 42 mg (92%) of material which on crystallization from ethanol (1 ml) gave 27 mg (59%) of *IIIa*, identical with an authentic sample[26].

(2*R*)-(2α,3β,3aβ,9aβ)-2,3,3a,9a-Tetrahydro-3-hydroxy-2-chloromethyl-6*H*-furo[2′,3′:4,5]-oxazolo[3,2-*b*][1,2,4]triazin-6-one (*IIIb*)

A) A solution of *IVc* (170 mg; 0·59 mmol) and imidazole (45 mg; 0·65 mmol) in dimethylformamide (4 ml) was heated to 150°C for 12 h. Traces of the starting *IVc* were still present even after this time. Dimethylformamide was evaporated *in vacuo* at 45°C and the residue was chromatographed on silica gel (100 g; ethyl acetate). The principal fraction afforded *IIIb*, which was crystallized from methanol; yield 65 mg (45%); m.p. 135–138°C. The mother liquors gave another portion (50 mg; 35%) of the product; $[\alpha]_D^{25}$ −26·6° (*c* 0·5, water). UV spectrum (methanol): λ_{max} 256 nm (log ε 3·71), λ_{min} 239 nm (log ε 3·60); UV spectrum (water): λ_{max} 223 nm (log ε 3·85), 254 nm (log ε 3·84), λ_{min} 213 nm (log ε 3·78), 238 nm (log ε 3·73). IR spectrum (dimethyl sulfoxide): strong bands 1 698, 1 682, 1 604, 1 558, 1 540, 1 457. ^{1}H NMR spectrum (tetramethylsilane as internal standard): 8·05 s, 1 H (H-5), 6·37 d, 1 H (H-1′, J(1′, 2′) = 5·8), 5·43 dd, 1 H (H-2′, J(2′, 1′) = 5·8; J(2′, 3′) = 1·0), 4·55 broad d, 1 H (H-3′, J(3′, 2′) = 1·0; J(3′, 4′) = 3·0), 4·41 sextet, 1 H (H-4′, J(4′, 3′) = 3·0; J(4′, 5′) = J(4′, 5″) = 6·0), 3·54 d, 2 H (2 H-5′, J(5′, 5″) = = 6·0). For $C_8H_8ClN_3O_4$ (245·6) calculated: 39·12% C, 3·28% H, 14·43% Cl, 17·11% N; found: 39·37% C, 3·58% H, 14·03% Cl, 16·62% N.

(2*R*)-(2α,3β,3aβ,9aβ)-2,3,3a,9a-Tetrahydro-3-hydroxy-2-methyl-6*H*-furo[2′,3′:4.5]oxazolo[3,2-*b*][1,2,4]triazin-6-one (*IIIc*)

A mixture of *IVe* (160 mg; 0·63 mmol), imidazole (43 mg; 0·64 mmol), and dimethylformamide (2·5 ml) was heated to 150°C for 2·5 h. After evaporation, the residue was chromatographed on a column of silica gel (50 g) in ethyl acetate. The main fraction afforded 134 mg of the product which was crystallized from methanol–ethyl acetate–ether; yield 105 mg (78%) of *IIIc*, m.p. 190 to 191°C, $[\alpha]_D^{25}$ −52·8° (*c* 0·5; water). UV spectrum (water): λ_{max} 224 nm (log ε 3·80), 254 nm (log ε 3·79), λ_{min} 238 nm (log ε 3·67). IR spectrum (KBr): 3 305 (OH), 1 696, 1 660, 1 607, 1 538, 1 467, 1 452. ^{1}H NMR spectrum: 7·58 s, 1 H (H-5), 6·27 d, 1 H (H-1′, J(1′, 2′) = 5·5), 5·33 dd, 1 H (H-2′, J(2′, 1′) = 5·5; J(2′, 3′) = 1·0), 4·10—4·35 m, 2 H (H-3′ + H-4′), 1·13 d, 3 H (CH_3, J(CH_3, H-4′) = 7·0), 3·40 broad, 1 H (OH). For $C_8H_9N_3O_4$ (211·2) calculated: 45·50% C, 4·30% H, 19·90% N; found: 45·66% C, 4·49% H, 20·13% N.

5′-O-Methanesulfonyl-6-azauridine 2′,3′-O-Carbonate (*IVb*)

A) 6-Azauridine 2′,3′-O-carbonate (*IVa*, with 1/2 mol of crystal ethyl acetate[3], 1·0 g; 3·1 mmol) was coevaporated with pyridine (3 × 50 ml) and then dissolved in pyridine (50 ml). Methanesulfonyl chloride (1·48 ml) was added in small portions to the ice-cooled solution which was then stirred at 0°C for 1 h. After standing at +5°C for 20 h, the mixture was evaporated and the residue was chromatographed on a column of silica gel (150 g; benzene–acetone 8 : 2). The main fraction afforded 987 mg (89%) of *IVb*, m.p. 179–181°C, $[\alpha]_D^{25}$ −35·8° (*c* 0·5; acetone). IR spectrum (Nujol): 1 818 (C=O, carbonate), 1 722 and 1 685 br (C=O, azauracil), 1 589 (C=N), 1 363 (SO_2 asymmetric), 1 167 (SO_2 symmetric), 3 175 (NH). UV spectrum (water): λ_{max} 258 nm (log ε

3·71), λ_{min} 222 nm (log ε 3·47). ^{1}H NMR spectrum (TESLA, 80 MHz): 12·41 broad, 1 H (NH), 7·50 s, 1 H (H-5'), 6·26 broad s, 1 H (H-1'), 5·64 dd, 1 H (H-2', J(2', 1') = 1·0; J(2', 3') = 6·0), 5·34 dd, 1 H (H-3', J(3', 2') = 6·0; J(3', 4') = 3·0), 4·50–4·76 m, 1 H (H-4'), 4·36 m, 2 H (2 H-5'), 3·07 s, 3 H (methanesulfonyl). For $C_{10}H_{11}N_3O_9S$ (349·3) calculated: 34·39% C, 3·17% H, 12·03% N, 9·18% S; found: 34·62% C, 3·44% H, 12·09% N, 9·25% S.

B) A solution of 5'-O-methanesulfonyl-6-azauridine[9] (*Ib*, 1 g; 3·1 mmol) and 1,1'-carbonyldiimidazole (1 g; 200%) in dimethylformamide (25 ml) was set aside at room temperature for 4 h. After evaporation, the residue was chromatographed on a column of silica gel (150 g; benzene–acetone 8 : 2). The main fraction gave 650 mg (60%) of *IVb*, identical with the product of procedure *A*.

2',3'-O-Carbonyl-5'-chloro-5'-deoxy-6-azauridine (*IVc*)

A) Hexamethylphosphortriamide (2 ml) and thionyl chloride (0·2 ml; 2·78 mmol) were mixed and set aside for 5 min at room temperature. Compound *IVa* (162 mg; 0·5 mmol) was added and the mixture was allowed to stand at room temperature for 4 h. After evaporation at 90°C/10 Pa, the residue was chromatographed on a column of silica gel (100 g; benzene–ethyl acetate 1 : 1). The main fraction was evaporated (120 mg) and the product crystallized from ethyl acetate–methanol to give 44 mg (33%) of *IVc*, m.p. 180–190°C (decomp.); $[\alpha]_D^{25}$ −99·7° (*c* 0·5; acetone). UV spectrum (methanol): λ_{max} 259 nm (log ε 3·83), λ_{min} 223 nm (log ε 3·40). IR spectrum (KBr): 1 813 (C=O, carbonate), 1 728, 1 711, 1 692 (C=O, azauracil). ^{1}H NMR spectrum (deuteriochloroform, tetramethylsilane as internal stadard): 7·43 s, 1 H (H-5), 12·37 broad, 1 H (NH), 6·32 broad s, 1 H (H-1'), 5·62 dd, 1 H (H-2', J(2', 1') = 1·5; J(2', 3') = 7·3), 5·33 dd, 1 H (H-3', J(3', 2') = 7·3; J(3', 4') = 2·8), 4·52 td, 1 H (H-4', J(4', 3') = 2·8; J(4', 5') = = 7·5), 3·68 d, 2 H (2 H-5', J(5', 5'') = 7·5). For $C_9H_8ClN_3O_6$ (289·6) calculated: 37·32% C, 2·78% H, 12·24% Cl, 14·51% N; found: 37·54% C, 3·12% H, 12·33% Cl, 14·47% N.

B) A mixture of carbonate *IVb* (100 mg; 0·29 mmol), benzyltrimethylammonium chloride (265 mg; 1·4 mmol), and dimethylformamide (3 ml) was heated to 130°C for 30 min. After evaporation at 90°C/10 Pa, the residue was chromatographed on a silica gel column (50 g) in benzene–ethyl acetate (1 : 1). The main fraction afforded 60 mg of crude product which was crystallized from ethyl acetate–methanol to give 40 mg (48%) of *IVc*, identical with the product obtained by procedure *A*.

C) A mixture of *Ic* (450 mg; 1·71 mmol), 1,1'-carbonyldiimidazole (648 mg; 4 mmol), and dimethylformamide (6 ml) was stirred at room temperture for 90 min. After removal of the solvent at 45°C/10 Pa, the residue was chromatographed on a silica gel column (120 g) in benzene–acetone (9 : 1). The main fraction gave 230 mg of crude product which on crystallization from ethyl acetate–methanol afforded 190 mg (38%) of *IVc*, identical with the compound obtained ad *A*.

5'-Bromo-5'-deoxy-6-azauridine 2',3'-Carbonate (*IVd*)

A) A solution of *IVb* (1·63 g; 4·67 mmol) and tetrabutylammonium bromide (7·7 g; 23·3 mmol) in dimethylformamide (70 ml) was heated to 130°C for 30 min. The solvent was evaporated, the residue dissolved in ethyl acetate and washed with water (3 × 75 ml). The organic solution was dried, the solvent evaporated and the residue chromatographed on a column of silica gel (100 g) in benzene–acetone (9 : 1). The crude product, obtained from the main fraction (906 mg; 58%), was crystallized from acetone–benzene to give 548 mg (35%) of *IVd*, m.p. 217–219·5°C; $[\alpha]_D^{25}$ −100·8° (*c* 0·2; acetone). IR spectrum (KBr): 3 190; 3 170; 3 125 (NH), 1 810 (C=O carbonate), 1 725; 1 708; 1 693 (C=O azauracil). UV spectrum (methanol): λ_{max} 258 nm (log ε 3·76), λ_{min} 222 nm (log ε 3·44). ^{1}H NMR spectrum: 6·33 broad s, 1 H (H-1', J(1', 2') = 1·0), 5·63

broad d, 1 H (H-2', $J(2', 1') = 1{\cdot}0$; $J(2', 3') = 7{\cdot}0$), 5·32 dd, 1 H (H-3', $J(3', 2') = 7{\cdot}0$; $J(3', 4') = 2{\cdot}5$), 4·57 td, 1 H (H-4', $J(4', 3') = 2{\cdot}5$; $J(4', 5') = J(4', 5'') = 7{\cdot}0$), 3·53 td, 2 H (2 H-5', $J(5', 4') = 7{\cdot}0$; $J(5', 5'') = 12{\cdot}0$), 7·45 s, 1 H (H-5), 12·45 broad, 1 H (NH). For $C_9H_8BrN_3O_6$ (334·1) calculated: 32·36% C, 2·41% H, 23·92% Br; 12·58% N; found: 32·53% C, 2·55% H, 23·55% Br, 12·41% N.

B) A solution of *Id* (308 mg; 1 mmol) and 1,1'-carbonyldiimidazole (324 mg; 2 mmol) in dimethylformamide (4 ml) was set aside for 30 min at room temperature. After evaporation, the residue was chromatographed on a silica gel column (50 g) in benzene–acetone (9 : 1). The main fraction (217 mg; 65%) on crystallization gave 133 mg (40%) of *IVd*, identical with the compound prepared according to procedure *A*.

5'-Deoxy-6-azauridine 2',3'-Carbonate (*IVe*)

A) A mixture of *IVd* (250 mg; 0·75 mmol), ethanol (3 ml), and tributyltin hydride in benzene (1 mol l^{-1}; 3 ml) was refluxed for 2 h. 2,2'-Azobis(2-methylpropionitrile) was added in 5 mg portions at the onset of the refluxing and then after 1 h. The solvents were evaporated and the residue was chromatographed on a column of silica gel (80 g) in benzene–acetone (9 : 1). The material, obtained by evaporation of the main fraction, was triturated with benzene and filtered affording 68·3 g (36%) of *IVe*, identical with the product obtained ad *B*. Minor fractions afforded 28 mg (15%) of *Ie*.

B) A solution of *Ie* (53 mg; 0·23 mmol) and 1,1'-carbonyldiimidazole (75 mg; 0·46 mmol) in dimethylformamide (2 ml) was set aside at room temperature for 15 min. After evaporation, the residue was chromatographed on a silica gel column (20 g) in benzene–acetone (9 : 1). The obtained product was triturated with benzene, affording 48 mg (81%) of *IVe* which melted at 180°C with decomposition (the last portions of the solid melted at 210°C). The m.p. did not improve on recrystallization from acetone–ethyl acetate. $[\alpha]_D^{25}$ —100·5° (*c* 0·2; acetone). IR spectrum (KBr): 3 193; 3 165 sh; 3 120; 3 081 (NH), 1 854; 1 813 (C=O carbonate), 1 726 sh; 1 708 sh; 1 693 (C=O azauracil), 1 594 (C=N). UV spectrum (methanol): λ_{max} 261 nm (log ε 3·72), λ_{min} 222 nm (log ε 3·35). ^{1}H NMR spectrum: 7·51 s, 1 H (H-5), 12·35 broad, 1 H (NH), 6·20 broad s, 1 H (H-1'), 5·63 dd, 1 H (H-2', $J(2', 1') = 1{\cdot}5$; $J(2', 3') = 7{\cdot}5$), 5·08 dd, 1 H (H-3', $J(3', 2') = 7{\cdot}5$; $J(3', 4') = 3{\cdot}0$), 4·43 qd, 1 H (H-4', $J(4', 3') = 3{\cdot}0$; J(H-4', CH_3) = 6·5), 1·35 d, 3 H (CH_3, H-4') = 6·5). For $C_9H_9N_3O_6$ (255·2) calculated: 42·36% C, 3·55% H, 16·47% N; found: 42·11% C, 3·71% H, 16·07% N.

5'-Bromo-5'-deoxy-2',3'-O-isopropylidene-6-azauridine (*Vb*)

A solution of 5'-O-methanesulfonyl-2',3'-O-isopropylidene-6-azauridine[9] (*Va*, 726 mg; 2 mmol) and tetrabutylammonium bromide (3·2 g; 10 mmol) in dimethylformamide (30 ml) was heated to 130°C for 30 min. The solvent was evaporated at 50°C and the residue dissolved in ethyl acetate (100 ml). After washing with water (5 × 30 ml), the organic layer was dried over magnesium sulfate, filtered and taken down. Crystallization of the residue (560 mg) from ethanol afforded 336 mg (48%) of *Vb*, m.p. 140—142°C, $[\alpha]_D^{25}$ —119° (*c* 0·5; ethyl acetate). IR spectrum (chloroform): 3 376 (free NH), 3 200 (bonded NH), 1 726; 1 701 (C=O), 1 590 (C=N). UV spectrum (ethanol): λ_{max} 264 nm (log ε 3·73), λ_{min} 244 nm (log ε 3·26). ^{1}H NMR spectrum (tetramethylsilane as internal standard): 6·27 broad s, 1 H (H-1', $J(1', 2') = 1{\cdot}0$), 5·05 dd, 1 H (H-2', $J(2', 1') = 1{\cdot}0$; $J(2', 3') = 6{\cdot}0$), 4·84 dd, 1 H (H-3', $J(3', 2') = 6{\cdot}0$; $J(3', 4') = 2{\cdot}6$), 4·38 sextet, 1 H (H-4', $J(4', 3') = 2{\cdot}6$; $J(4', 5') = J(4' 5'') = 7{\cdot}2$), 3·43 d, 2 H (2 H-5', $J(5', 4') = J(5'', 4') = 7{\cdot}5$), 7·37 s, 1 H (H-5), 12·20 broad, 1 H (NH), 1·37 and 1·56 2 × s, 3 H (CH_3). For $C_{11}H_{14}$·

.BrN_3O_5 (348·2) calculated: 37·95% C, 4·05% H, 22·95% Br, 12·07% N; found: 37·96% C, 4·05% H, 23·43% Br, 11·98% N.

5′-Deoxy-2′,3′-O-isopropylidene-6-azauridine (*Vc*)

A mixture of the bromo derivative *Vb* (560 mg; 1·6 mmol) and tributyltin hydride (346 mg; 6·4 mmol) in benzene (10 ml) was refluxed for 1·5 h, 2,2′-azobis(2-methylpropionitrile) (20 mg) being added to the hot solution before it started to boil. After evaporation, the residue was applied on a silica gel column (250 g). Elution with ethyl acetate–benzene (1 : 1) afforded 350 mg (81%) of *Vc* as a foam; $[\alpha]_D^{25}$ −96° (*c* 0·5; methanol). IR spectrum (chloroform): 3 377 (NH), 1 723; 1 703; 1 695 (C=O), 1 588 (C=N), 1 384; 1 376 (geminal dimethyl, δ CH_3). UV spectrum (methanol): λ_{max} 263 nm (log ε 3·74), λ_{min} 227 nm (log ε 3·44). For $C_{11}H_{15}N_3O_5$ (269·3) calculated: 49·07% C, 5·62% H, 15·61% N; found: 48·81% C, 5·87% H, 14·98% N.

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

A solution of *IIIc* (70 mg; 0·33 mmol) in 0·1M-NaOH (4 ml) was set aside at room temperature for 1·5 h, neutralized with Dowex 50 W (H^+-form) and filtered. Evaporation afforded 70 mg of an oily *VIa* which was dissolved in a mixture of acetic acid (2·4 ml), acetyl chloride (0·1 ml), and acetic anhydride (1·3 ml) and allowed to stand at room temperature for 12 h. After evaporation, the residue was dried *in vacuo* (10 Pa) and crystallized from ethanol, giving 35 mg (34%) of *VIb*, m.p. 144–147°C; $[\alpha]_D^{25}$ −78° (*c* 0·8, methanol). UV spectrum (methanol): λ_{max} 263 nm (log ε 3·81), λ_{min} 226 nm (log ε 3·53). IR spectrum (chloroform): 3 377 (NH, free), 3 200 (NH, bonded), 1 745 (C=O, acetate), 1 722; 1 700 (C=O, azauracil), 1 591 (C=N).For $C_{12}H_{15}N_3O_7$ (313·3) calculated: 46·01% C, 4·83% H, 13·41% N; found: 45·57% C, 5·04% H, 12·94% N.

The authors are indebted to Dr M. Masojídková for measurement and interpretation of the ^{1}H NMR *spectra, to Mr P. Formánek and Mrs K. Matoušková for measurement of the* UV *and* IR *spectra and to Dr P. Fiedler for interpretation of the latter. Their thanks are also due to Mrs Z. Ledvinová for optical rotation measurements, to the staff of the Analytical Laboratory of this Institute (Dr J. Horáček, Head) for performing the analyses, to Dr A. Trka for measurement and interpretation of mass spectra and to Dr J. Krupička for polarographic measurement. They also thank Dr L. Hein, Dr H. Hřebabacký, and Dr J. Brokeš for valuable information and stimulating advice. The excellent technical assistance of Mrs J. Hlaváčková is gratefully acknowledged.*

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Translated by M. Tichý.