PREPARATION OF 2'-DEOXYRIBONUCLEOSIDES AND THEIR 5-HALOGENO DERIVATIVES*

Josef BROKEŠ, Hubert HŘEBABECKÝ and Jiří BERÁNEK

Institute of Organic Chemistry and Biochemistry, Czechoslovak Academy of Sciences, 166 10 Prague 6

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Two routes are described for the synthesis of 2'-deoxyribonucleosides from ribonucleosides. The reaction of uridine (*Ia*) with acetyl bromide affords the acetylated 2'-bromo derivative *IIIe* (73%) and triacetyluridine (*Ib*; 7%). The tributyltin hydride reduction of the reaction mixture yields diacetyl-2'-deoxyuridine (*IIIc*; 71%) along with triacetyluridine (*Ib*; 8%). On reaction of 5-fluorouridine (*Ic*) with acetyl bromide, the triacetyl-5-fluorouridine (*Id*; 39%) and the diacetyl-2'-bromo derivative *IIIg* are obtained. The tributyltin hydride reduction of *IIIg* affords diacetyl-2'-deoxy-5-fluorouridine (*IIIh*; 47·5%, referred to *Ic*). The reaction of cyclouridine (*IIa*) with acetyl chloride and the subsequent tributyltin hydride reduction followed by methanolysis furnishes 2'-deoxyuridine (*IIId*; 88·5%, referred to *IIa*). Diphenyl carbonate (*IV*) is prepared by reaction of phosgene with phenol in pyridine. On reaction with N-bromosuccinimide, diacetyl-2'-deoxyuridine (*IIIc*) (2'-deoxyuridine *IIId*, resp.) affords di-O-acetyl-5-bromo-2'-deoxyuridine (*IIIj*; 78%) (5-bromo-2'-deoxyuridine *IIIk*; 43%, resp.).

The reductive dehalogenation of 2'-halogeno-2'-deoxyribonuclecsides was found to be a suitable route leading to 2'-deoxyribonucleosides[1]. The method developed in early studies[2,3] was simplified later on in the step of preparation of 2'-halogeno nucleosides by the nucleophilic cleavage of 2,2'-anhydronucleosides with hydrogen halides[4,5]. The improvement was based on an earlier reaction with the 2,3'-anhydro derivatives[6]; the cleavage of the 2,3'-anhydro bond with acyl halides was also reported in the same paper[6]. The cleavage of 2,2'-anhydronucleosides proceeds by the action of a hydrogen halide in protic[3–5] as well as in aprotic[7,8] solvent, or by heating of the hydrochlorides of anhydronucleosides which was noticed several times[5–7] and experimentally performed with the hydrochloride of cyclouridine[9]. The cleavage of 2,2'-anhydronucleosides with acyl halides was described recently[10,11]; with the tritylanhydronucleosides, the reaction affords the diacyl-2'-halogeno derivatives[9] under simultaneous detritylation, cleavage of the anhydro bond, and acylation. A cleavage of unsubstituted pyrimidine nucleosides by acyl bromides under the formation of the acylated 2'-halogeno-2'-deoxyribonucleosides was also developed recently[10,11]. The introduction of the selective reductive dehalogenation with alkyltin hydrides was another important improvement in the preparation of 2'-deoxynucleosides. The first report on the reaction of organotin hydrides[12–14] with olefins and on their use as selective reducting agents led to the wide application of the method in organic chemistry[15–17]. Following the first application in the field of nucleosides[18], the method has been commonly used in the preparation of deoxynucleosides[19–25,8,9] in our Laboratories.

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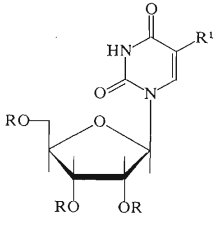
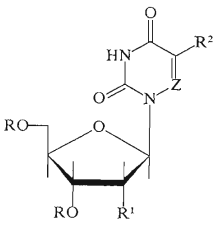
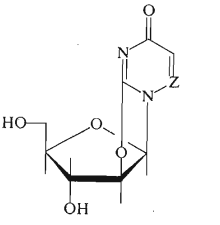
From the above mentioned results it can be concluded that there are two equivalent approaches giving 2'-deoxyribonucleosides in high yields starting from ribonucleosides. In the first case, uridine (*Ia*) was converted to cyclouridine *IIa* by the reaction[26] with diphenyl carbonate (*IV*) in hexamethylphosphoric triamide[27]. The reagent, diphenyl carbonate (*IV*) was prepared by reaction of phosgene with phenol in pyridine[28], in analogy with the preparation of substituted diphenyl carbonates[29]. On reaction with acetyl chloride, cyclouridine (*IIa*) was transformed[10] to the acetylated 2'-chlorouridine (*IIIa*) which was then reduced with tributyltin hydride in benzene under initiation of 2,2'-azobis(2-methylpropionitrile) to afford the diacetyl derivative of 2'-deoxyuridine *IIIc*. On deacetylation with methanolic ammonia, 2'-deoxyuridine (*IIId*) was obtained in 88·5% yield (referred to the starting cyclouridine *IIa*). In the other method, uridine (*Ia*) was treated with acetyl bromide in refluxing acetonitrile to afford a mixture[10] of the acetylated 2'-bromo derivative *IIIe* and triacetyluridine (*Ib*).



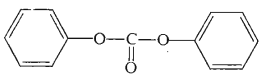
Ia, R = R¹ = H
Ib, R = Ac, R¹ = H
Ic, R = H, R¹ = F
Id, R = Ac, R¹ = F



IIIa, R = Ac, R¹ = Cl, R² = H, Z = CH
IIIb, R = R² = H, R¹ = Cl, Z = CH
IIIc, R = Ac, R¹ = R² = H, Z = CH
IIId, R = R¹ = R² = H, Z = CH
IIIe, R = Ac, R¹ = Br, R² = H, Z = CH
IIIf, R = R² = H, R¹ = Br, Z = CH
IIIg, R = Ac, R¹ = Br, R² = F, Z = CH
IIIh, R = Ac, R¹ = H, R² = F, Z = CH
IIIi, R = R¹ = H, R² = F, Z = CH
IIIj, R = Ac, R¹ = H, R² = Br, Z = CH
IIIk, R = R¹ = H, R² = Br, Z = CH
IIIl, R = R² = H, R¹ = Cl, Z = N



IIa, Z = CH
IIb, Z = N



IV

The mixture was reduced with tributyltin hydride and then chromatographed on silica gel to yield diacetyl-2'-deoxyuridine (*IIIc*; 71%) and triacetyluridine (*Ib*; 8%).

The chromatography of the products of the reaction of uridine (*Ia*) with acetyl bromide afforded a crystalline diacetyl-2'-bromo derivative *IIIe* (73·2%), in addition to triacetyluridine (*Ib*; 6·8%). The compound *IIIe* is not stable even in the crystalline form. On standing at room temperature, the crystalline compound deacetylated to a mixture of lower acetylated derivatives which was not analyzed in details. The spontaneous deacetylation is similar to some extent to that observed at 2,3,4,5-tetra--O-acetyl-1-bromo-1-deoxy-D-psicose[30]. While the spontaneous deacetylation of *IIIe* proceeded at laboratory temperature, the acidic deacetylation of *IIIe* in a 50% formic acid required a 4 h reflux to be completed. In contrast to the 2'-bromo derivative *IIIe*, the 2'-chloro derivative *IIIa* is a stable compound and no deacetylation was observed on several months storage.

The reaction with acetyl bromide[41] was also utilized to transform 5-fluorouridine (*Ic*) to 2'-deoxy-5'-fluorouridine (*IIIi*). A mixture of the acetyl derivatives of 5-fluorouridine *Id* and 2'-bromo-5-fluorouridine *IIIg* was obtained. Chromatography on silica gel afforded 39% of *Id* along with the 2'-bromo derivative *IIIg* which was then reduced with tributyltin hydride. The subsequent chromatography on silica gel afforded diacetyl-2'-deoxy-5-fluorouridine (*IIIh*) (47·5%; referred to the starting 5-fluorouridine *Ic*).

In connection with the halogenation of uridine 5'-diphosphate, the reaction of N-bromosuccinimide with the diacetyl derivative of 2'-deoxyuridine (*IIIc*) and with the unsubstituted nucleoside *IIId* was studied. The reaction of *IIIc* in acetonitrile and the subsequent chromatography on silica gel afforded the crystalline diacetyl derivative of 5-bromo-2'-deoxyuridine (*IIIj*) in 78% yield; 5-bromo-2'-deoxyuridine (*IIIk*) was obtained from the unsubstituted nucleoside *IIId* in 43% yield. At the attempted preparation of 5-bromouridine 5'-diphosphate by reaction of uridine 5'-diphosphate with N-bromosuccinimide (in analogy with the preparation of 5-bromouridine 5'-monophosphate[31]), a cleavage of the diphosphate bond occurred; the monophosphate of 5-bromouridine in the form of barium salt (56%) along with the mere 9% of 5'-diphosphate of 5-bromouridine were isolated from the reaction mixture. Later on, the method was utilized in the preparation of 5-bromo-2'-deoxyuridine 5'-monophosphate[32]. 5-Bromo-2'-deoxyuridine has been prepared earlier by reaction of bromine with 2'-deoxyuridine and its acetyl derivative in water[33–35] or in acetic anhydride[36]. The reaction with halogenosuccinimide for preparation of the 5-halogeno derivatives of 2'-deoxyuridine[37–40] was used only recently.

An attempt was made to prepare the hydrochloride of cyclouridine (*IIa* .HCl) in a crystalline form what was achieved on crystallization from methanol. Analogously, it was attempted to prepare the crystalline hydrochloride of cyclo-6-azauridine (*IIb* . HCl). On crystallization of the amorphous *IIb* . HCl (prepared[41] from 5'-trityl--cycloazauridine) from methanol, the crystalline cycloazauridine *IIb*, as a free nucleo-

side, was obtained under the release of hydrogen chloride. The facile solvolysis of *IIb* . HCl in protic medium differs from the behaviour of cyclouridine hydrochloride (*IIa* . HCl) and is in accordance with the lower basicity of 6-azauracil nucleosides in comparison with the nucleosides of uracil series[42].

In addition to that, on standing of the methanolic solution of *IIb* . HCl, a nucleophilic cleavage of the anhydro bond occurred even at room temperature under the formation of the 2'-chloro derivative *IIIl*. In contrast to a difficult formation[41,43,44] of the 2,2'-anhydro bond in 6-aza series, the nucleophilic cleavage of the anhydro bond in 6-aza series proceeds considerably easier (in comparison with the uridine series), analogously to the cleavage of anhydronucleosides with ammonia[41] and amines[44].

Comparative experiments of the cleavage of the anhydro bond with methanolic hydrogen chloride (in both uracil and 6-azauracil series) were performed at the laboratory and at the elevated temperature. At room temperature, the cleavage of the anhydro bond in 6-aza series was terminated within several hours under a quantitative formation of the 2'-chloro derivative *IIIl*. Contrary to that, the anhydro derivative *IIa* of the uracil series afforded the 2'-chloro derivative *IIIb* (21%) and arabinofuranosyluracil (18%; caused by the presence of traces of moisture) on standing for two months. At 50°C, the cleavage of the anhydro bond in 6-aza series under the formation of *IIIl* was accomplished within 1 h while in the uracil series, the starting compound *IIa* (30%) and 2'-chlorouridine (*IIIb*; 42%) were isolated from the reaction mixture after an 8 h reflux.

EXPERIMENTAL

Melting points were measured on a heated microscope stage (Kofler block). Ultraviolet spectra were recorded on a CF-4 apparatus (Optica, Milano) and the infrared spectra on a UR-20 apparatus (Carl Zeiss, Jena). Optical rotations were measured on an automatic Perkin–Elmer 141 MC polarimeter. Analytical samples were dried at 0·4 Torr. Column chromatography was carried out on silica gel according to Pitra (particle size, 30–60 μm; produced by Service Laboratories of this Institute). Thin-layer chromatography was carried out on ready-for-use fluorescent silica gel Silufol plates UV 254 (Kavalier, Czechoslovakia) in the solvent systems: S_1 ethyl acetate–benzene (3 : 1) and S_2 ethyl acetate–methanol (9 : 1). R_F values in S_1 (S_2): *Ib* 0·29 (0·85), *Ic* 0·04 (0·57), *Id* 0·64 (0·94). *IIIa* 0·56 (0·91), *IIIc* 0·20 (0·76), *IIId* 0 (0·26), *IIIe* 0·56 (0·91), *IIIf* 0 (0·31), *IIIh* 0·54 (0·92), *IIIi* 0·05 (0·57), *IIIj* 0·66 (0·94), *IIIk* 0·10 (0·63).

Diphenyl Carbonate (*IV*)

In a hood, to a solution of phenol (188 g; 2 mol) in benzene (500 ml) and pyridine (316·4 g, 4 mol) a solution of phosgene (150 g, 1·5 mol) in toluene (700 ml) was slowly added with stirring and external cooling with ice-water. After additional stirring without cooling for 2 h, the mixture was decomposed with water (100 ml). The organic layer was separated and successively washed with dilute hydrochloric acid (1 : 2), saturated sodium hydrogen carbonate, and water, dried

over magnesium sulphate, and filtered. The filtrate was evaporated *in vacuo* and the residue was crystallized from cyclohexane (360 ml) yielding 169 g (78·8%) of diphenyl carbonate (*IV*), chromatographically homogeneous, m.p. 77—79°C. Additional 14·2 g of the same compound *IV* (m.p. 76—78°C) were obtained from mother liquors. Over-all yield, 88·5%.

3',5'-Di-O-acetyl-2'-deoxyuridine (*IIIc*)

To a refluxing suspension of uridine (*Ia*; 2·01 g; 8·2 mmol) in acetonitrile (150 ml), acetyl bromide (5 ml) was added and the reflux was continued for 40 min. The solution was evaporated *in vacuo*, the residue was dissolved in chloroform (200 ml). The chloroform solution was extracted with water (3 × 20 ml) and evaporated *in vacuo*. The residue was coevaporated with the mixture of ethanol and benzene 1 : 1 (3 × 50 ml). To the thus obtained mixture of 2',3',5'-tri-O-acetyluridine (*Ib*) and 1-(3,5-di-O-acetyl-2-bromo-2-deoxy-β-D-ribofuranosyl)uracil (*IIIe*), 0·5M solution of tributyltin hydride in benzene (50 ml) and (under reflux) 2,2'-azobis(2-methylpropionitrile) (50 mg) were added. The solution was refluxed for 30 min and evaporated under reduced pressure. The syrupy residue was triturated with light petroleum (100 ml) and the whole was left to stand overnight. The precipitated product was chromatographed on a silica gel column (350 g) in the system ethyl acetate–benzene (3 : 1). The more mobile fraction afforded 0·25 g (8%) of *Ib*, homogeneous on TLC. The next fraction yielded 1·82 g (71%) of the diacetyl deoxy derivative *IIIc* in the form of a solid foam.

3',5'-Di-O-acetyl-2'-bromo-2'-deoxyuridine (*IIIe*)

A mixture of *Ib* and *IIIe* obtained by the preceding procedure from 2·01 g (8·2 mmol) of uridine (*Ia*) was chromatographed on a silica gel column (530 g) in ethyl acetate–benzene 1 : 1 (3 500 ml; fractions 1—174). Fractions 89—128 afforded 2·48 g (77%) of the chromatographically homogeneous *IIIe* which was crystallized from ethanol (15 ml) to yield 2·06 g (62·5%) of *IIIe*, m.p. 113—115°C. The mother liquors afforded additional 270 mg (10·7%) of *IIIe*. $[\alpha]_D^{25} + 8{\cdot}8°$ (*c* 0·49, ethyl acetate). UV spectrum (ethanol): λ_{max} 257 nm (log ε 3·94), λ_{min} 228 nm (log ε 3·39). IR spectrum (chloroform): 3 392 cm^{-1} (NH), 1 754 cm^{-1} (C=O acetate), sh 1 720, 1 703 and sh 1 695 cm^{-1} (C=O uracil), 1 637 cm^{-1} (C=C). For $C_{13}H_{15}BrN_2O_7$ (391·2) calculated: 39·91% C, 3·87% H, 20·43% Br, 7·16% N; found: 39·95% C, 3·91% H, 20·47% Br, 7·12% N. Fractions 129—140 contained a mixture of *Ib* and *IIIe* (70 mg) while fractions 141—174 contained chromatographically homogeneous *Ib* (200 mg, 6·8%).

2'-Deoxyuridine (*IIId*)

A mixture of cyclouridine (*IIa*; 2·26 g; 10 mmol) and acetonitrile (250 ml) was heated to reflux, then acetyl chloride (20 ml) was added and the mixture was refluxed for 7 h; the starting compound completely dissolved after 5 h. The solution was evaporated *in vacuo*. The residue was dissolved in ethyl acetate (300 ml), the solution was washed with water (2 × 50 ml) and evaporated *in vacuo*. The residue was coevaporated with benzene (2 × 100 ml) and methanol (100 ml). A 0·5M solution of tributyltin hydride in benzene (60 ml; 30 mmol) and 2,2'-azobis(2-methylpropionitrile) (50 mg) were added to the residue (3·46 g) and the solution was refluxed for 30 min. The solution was diluted with ethyl acetate (50 ml) and poured on a column of silica gel (190 g). The column was washed with ethyl acetate–benzene 1 : 1 (500 ml) and then eluted with ethyl acetate–benzene 3 : 1 (1 200 ml). The UV absorbing fraction was evaporated *in vacuo*. A 10% methanolic ammonia (100 ml) was added to the residue and the whole was kept at room temperature overnight. The solution was evaporated *in vacuo* and the residue crystallized from methanol.

Yield, 1·55 g of 2′-deoxyuridine (*IIId*), identical with an authentic specimen. Mother liquors afforded additional 0·47 g of 2′-deoxyurdine. Total yield of *IIId*, 2·01 g (88·5%).

3′,5′-Di-O-acetyl-2′-deoxy-5-fluorouridine (*IIIh*)

To a refluxing mixture of 5-fluorouridine (*Ic*; 526 mg; 2 mmol) and acetonitrile (20 ml), acetyl bromide (0·6 ml) was added dropwise and the whole was refluxed for 10 min. The solution was evaporated *in vacuo* and the residue was dissolved in ethyl acetate (300 ml); the solution was washed with water (3 × 20 ml), evaporated *in vacuo*, and the residue was coevaporated with methanol. The final residue (834 mg) was chromatographed on a silica gel column (180 g) in ethyl acetate–benzene 1 : 1. On evaporation *in vacuo*, the more mobile fractions afforded 512 mg of the chromatographically homogeneous, syrupy residue of 1-(3,5-di-O-acetyl-2-bromo-2-deoxy-D-ribofuranosyl)-5-fluorouracil (*IIIg*) while the slower fractions afforded 303 mg (39%) of the chromatographically homogeneous residue of 2′,3′,5′-tri-O-acetyl-5-fluorouridine (*Id*), identical with an authentic specimen[45]. A 1M solution of tributyltin hydride in benzene (6 ml) and 2,2′-azobis-(2-methylpropionitrile) (20 mg) were added to the residue of *IIIg* and the whole was heated to reflux (2 min). The solution was cooled and light petroleum (100 ml) was added under stirring. The deposited precipitate was filtered off and triturated with light petroleum (50 ml), then filtered off again, and dried (366 mg). Crystallization from ethanol (4 ml) afforded 314 mg (47·5%) of *IIIh*, m.p. 149–150°C; reported[46], m.p. 151·5–152°C. $[\alpha]_D^{25}$ +24·6° (*c* 0·48; ethyl acetate). UV spectrum (methanol): λ_{max} 269 nm (log ε 3·97), λ_{min} 236 nm (log ε 3·41). For $C_{13}H_{15}FN_2O_7$ calculated: 47·28% C, 4·58% H, 8·48% N, 5·75% F; found: 47·71% C, 4·52% H, 8·47% N, 5·94% F.

2′-Deoxy-5-fluorouridine (*IIIi*)

A solution of the diacetyl derivative *IIIh* (153 mg; 0·5 mmol) in 17% methanolic ammonia (20 ml) was kept at room temperature for 12 h. The solution was evaporated *in vacuo* and the chromatographically homogeneous residue (125 mg) was crystallized from ethanol. Deposited crystals were filtered off and washed with ethyl acetate. Yield, 89 mg (72%) of *IIIi*; m.p. 149–150°C, identical with an authentic specimen (reported: ref.[47], m.p. 150–151°C; ref.[48], m.p. 153°C). The mother liquors contained *IIIi* as the single UV absorbing compound.

3′,5-Di-O-acetyl-5-bromo-2′-deoxyuridine (*IIIj*)

A solution of 3′,5′-di-O-acetyl-2′-deoxyuridine (*IIIc*; 1 g; 3·2 mmol) and N-bromosuccinimide (1·42 g; 8 mmol) in acetonitrile (30 ml) was kept at room temperature for 12 h and evaporated *in vacuo*. The residue was chromatographed on a silica gel column (135 g) in ethyl acetate–benzene 1 : 1. The UV absorbing fraction was evaporated under reduced pressure and the residue (1·34 g) was crystallized from ethanol (4 ml) to afford 0·73 g (58%) of *IIIj*, m.p. 150–153°C; on recrystallization, m.p. 153–154°C (reported: ref.[49], 138–140°C; ref.[36], 153–155°C). The mother liquors (0·45 g) afforded additional 0·25 g (20%) of the same compound. Total yield, 78%. $[\alpha]_D^{20}$ −20·0° (*c* 0·5; ethyl acetate). UV spectrum (ethanol): λ_{max} 278 nm (log ε 3·92), λ_{min} 241 nm (log ε 3·19). IR spectrum (chloroform): 3386 cm^{-1} (NH), 1747 cm^{-1} (C=O acetate), sh 1721, 1709 and sh 1695 cm^{-1} (C=O bromouracil), 1627 cm^{-1} (C=C). For $C_{13}H_{15}BrN_2O_7$ (391·2) calculated: 39·91% C, 3·87% H, 20·43% Br, 7·16% N; found: 40·09% C, 4·02% H, 20·29% Br, 7·00% N.

5-Bromo-2'-deoxyuridine (*IIIk*)

A mixture of 2'-deoxyuridine (*IIId*; 228 mg; 1 mmol), N-bromosuccinimide (445 mg; 2·5 mmol), and acetonitrile (15 ml) was stirred at room temperature until it dissolved (*c.* 3 h) and then kept at 3°C for 12 h. The solution was evaporated *in vacuo* and the residue was chromatographed on a silica gel column (30 g) in ethyl acetate. The UV absorbing fractions were combined and evaporated *in vacuo*. Crystallization of the residue (205 mg) from ethanol (2 ml) afforded 104 mg of *IIIk* melting at 181–183°C, in accordance with lit.[33,34]; also reported, 185–187°C (ref.[50]), 187–189°C (ref.[35]), and 192–193°C (ref.[36]). The mother liquors (87 mg) afforded additional 28 mg of the same compound. Total yield, 43% of *IIIk*. $[\alpha]_D^{20}$ +18·5° (*c* 0·3; methanol). Reported[50], $[\alpha]_D^{25}$ +25·5° (*c* 0·094; water). UV spectrum (ethanol): λ_{max} 278 nm (log ε 3·92) λ_{min} 242 nm (log ε 3·17); reported[50], λ_{max} 281 nm (log ε 3·94). IR spectrum (nujol): 3413 and sh 3350 cm^{-1} (OH, NH), 1712 and 1681 cm^{-1} (C=O), 1621 cm^{-1} (C=C). For $C_9H_{11}BrN_2O_5$ (307·1) calculated: 35·20% C, 3·61% H, 26·02% Br, 9·32% N; found: 35·41% C, 3·72% H, 25·63% Br, 9·35% N.

Cleavage of (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-*a*]pyrimidin-6-one (*IIa*) by Methanolic Hydrogen Chloride

A) To a solution of cyclouridine (*IIa*; 100 mg) in methanol (5 ml), an 8M ethereal hydrogen chloride (1 ml) was added. After refluxing for 8 h the mixture contained unreacted cyclouridine (*IIa*) and 2'-chlorouridine (*IIIb*). The solution was evaporated *in vacuo*, the residue was repeatedly coevaporated with benzene and chromatographed on a silica gel column in ethyl acetate. Yield, 49 mg (42%) of *IIIb* (identical with an authentic specimen[9]); besides, 30 mg (30%) of crystalline starting product *IIa* were recovered. *B*) On standing at room temperature for 2 months, the reaction mixture (the same one as in *A*) contained, beside the small amount of the starting compound *IIa*, *IIIb* and arabinofuranosyluracil. Chromatography on a silica gel column (15 g) afforded 25 mg (21·6%) of *IIIb* along with 20 mg (18·5%) of arabinofuranosyluracil, identical with an authentic specimen[41].

Cleavage of (5a*R*)-(5aα,7β,8α,8aα)-5a,7,8,8a-Tetrahydro-8-hydroxy-7-(hydroxymethyl)-2*H*-furo[2',3':4,5]oxazolo [3,2-*b*] [1, 2, 4]triazin-2-one (*IIb*) by Methanolic Hydrogen Chloride

A) A solution of cycloazauridine hydrochloride[41] (*IIb*.HCl; 100 mg) in a 1·5M methanolic hydrogen chloride (5 ml) afforded, after heating at 50°C for 1 h, the chromatographically homogeneous 2'-chloro-6-azauridine (*IIIl*) (identical with an authentic specimen[9]) in a quantitative yield. *B*) The reaction mixture prepared in the same manner as in *A* afforded *IIIl* in a quantitative yield on standing at room temperature for 4 h. *C*) The methanolic solution of *IIb*.HCl is unstable even at room temperature and undergoes a slow cleavage to form *IIIl*.

(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-*a*]pyrimidin-6-one Hydrochloride (*IIa*.HCl)

To a suspension of cyclouridine (*IIa*; 500 mg) in methanol (3 ml), an 8M ethereal hydrogen chloride (3 ml) was added dropwise under stirring. The compound *IIa* dissolved during the addition and the hydrochloride *IIa*.HCl was gradually deposited. Dry ether (20 ml) was added dropwise after 15 min and the stirring was continued for 30 min. The precipitate was repeatedly decanted with ether and dried over potassium hydroxide in a vacuum desiccator. Yield, 498 mg (86·2%) of the chromatographically homogeneous *IIa*.HCl. The compound was recrystallized from a small amount of methanol. The crystals which are easily soluble in methanol were collected with suction and washed with cold methanol; 280 mg of *IIa*.HCl were obtained, m.p. 147–149°C.

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

From *IIa*.HCl (2·625 g; 10 mmol), the crystalline *IIIb* (chromatographically homogeneous and identical with an authentic specimen[9]) was obtained[9]. Yield, 2·342 g (89·2%).

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