5'-HALOGENO-2',3'-SULPHITES IN THE SYNTHESIS OF 2',5'-DIDEOXY-5-FLUOROURIDINE AND RELATED ANALOGUES*

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On heating with imidazole in dimethylformamide, a mixture of (+)- and (−)-epimers of 5'-chloro-2',3'-O-sulphinyl derivative *Ia*, *IIa* (*Ib*, *IIb*) affords a single 2,2'-anhydro derivative *IIIa* (*IIIb*). On heating with HCl in dimethylformamide, the cyclonucleoside *IIIa* (*IIIb*) affords the 2',5'-dichloro derivative *IVa* (*IVb*) and/or with HBr the 2'-bromo-5'-chloro derivative *Va* (*Vb*). Partial reduction with tributyltin hydride proceeds more selectively at the 2'-bromo-5'-chloro derivative *Va* (*Vb*) than at the 2',5'-dichloro derivative *IVa* (*IVb*), to afford the 5'-chloro-2'-deoxy derivative *VIa* (*VIb*). On prolongation of reduction period, the 2',5'-dideoxy nucleoside *VIIa* (*VIIb*) is formed from *IVa* (*IVb*). A partial dehalogenation of the 5-fluoro atom occurs on reduction of *IVb* and *VIIIb*. The 5'-chloro cyclonucleoside *IIIa* (*IIIb*), by cleavage with 1 equiv. of NaOH and reduction, affords the 5'-deoxyarabino derivative *IXa* (*IXb*). 2',3'-O-Isopropylidene-5-fluorouridine (*X*) is described. The activity of the 5-fluoro derivatives towards the inhibition of RNA and DNA synthesis in cultured L1210 leukemia cells is compared. 2'-Deoxy-5-fluorouridine, as the only one, exhibits the inhibitory effect *vs* DNA synthesis. 5-Fluorouridine demonstrates far highest activity *vs* RNA synthesis. 2',5'-Dideoxy-5-fluorouridine and 1-[(*RS*)tetrahydrofuran-2-yl]-5-fluorouracil are inactive.

Since the first communication dealing with the remarkable biological activity[1,2] of 5-fluoro derivatives of uracil and its nucleosides, these compounds attract attention until the most recent time (*cf.* ref.[3] and papers therein quoted). Two of the fluoro derivatives, namely, 5-fluorouracil[1,5] and Ftorafur[4] (1-[(*RS*)tetrahydrofuran-2-yl]-5-fluorouracil), were introduced into clinics. 5-Fluorouracil[5-7] and 2'-deoxy-5-fluorouridine[8,9] were proved to inhibit thymidylate synthetase[2,3,10], and 2'-deoxy-5-fluorouridine 5'-phosphate[2,10] to be the active form of these inhibitors. A similar mechanism of action was proposed for 5-fluorouridine[3] and also for Ftorafur. Clinical evaluation[11,12] indicates that Ftorafur is less toxic and more effective than 5-fluorouracil. Ftorafur is a repository and transportable form[13,14] of 5-fluorouracil; the pseudoglycosidic C—N bond is enzymatically cleaved[11] by non-specific liver microsome oxidases with a slow release of 5-fluorouracil. There is no significant difference in biological activity between the *R* and *S* isomers of Ftorafur[14]. Although

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5-fluorouridine[15,6,7] is easy available, less attention was devoted to the study of its biological activity[3].

It was interesting to prepare some other derivatives of 5-fluorouridine, particularly those which are unable to form the 5′-monophosphate, as the 5′-deoxy derivative of 5-fluorouridine[16] and the 5′-deoxy derivative of 2′-deoxy-5-fluorouridine, and to compare their biological activity with a series of the fluoro analogues, *i.e.*, 5-fluorouracil, 5-fluorouridine, Ftorafur, 2′-deoxy-5-fluorouridine, 2′,3′-isopropylidene-5-fluorouridine.

In analogy with recent papers on reactivity of cyclic carbonates[17–20], 2′,3′-cyclic sulphite as another alkali-labile protecting group is demonstrated in preparation of further nucleoside analogues.

Both isomers[16] *Ia* and *IIa* of 5′-chloro-5′-deoxy-2′,3′-O-sulphinyluridine, epimeric at sulphur atom, afford a single 2,2′-anhydro nucleoside *IIIa* when heated with imidazole in dimethylformamide. The mixture of epimeric sulphites *Ia*, *IIa* was therefore used for the preparation of the anhydro derivative *IIIa*. The formation of epimeric sulphites was described previously[16] (by modification of the reaction of Kikugawa and Ichino[21]). The uracil analogue *IIIa* was obtained in a high yield on heating of the epimeric mixture *Ia*, *IIa* with imidazole in dimethylformamide for 2 h. Analogously, the epimeric sulphites of the 5-fluoro analogue *Ib*, *IIb* afforded quantitative yield of the anhydro derivative *IIIb* within 15 min.

In analogy with the reaction[17,19,20] of 2,2′-anhydronucleosides, the 2,2′-anhydro--5′-chloro nucleoside *IIIa* was converted to the 2′,5′-dichloro derivative *IVa* (85·5%) on heating with hydrogen chloride in dimethylformamide at 100°C. Similarly, the 2′-bromo-5′-chloro derivative *Va* (86%) was obtained on heating of the cyclonucleoside *IIIa* with hydrogen bromide in dimethylformamide (100°C). By the same procedure, the 5-fluoro analogue *IIIb* afforded, on heating with hydrogen chloride, the 2′,5′-dichloro derivative *IVb* (80%) and on heating with hydrogen bromide, the 2′-bromo-5′-chloro derivative *Vb* (78%).

The dihalogeno derivatives *IVa*, *Va* (*IVb*, *Vb* resp.) were used for the preparation of deoxynucleosides by reductive dehalogenation with tributyltin hydride[19,22,23] under the initiation of 2,2′-azobis(2-methylpropionitrile). During the reduction, a different reactivity of primary and secondary halogen was observed. The result is in accordance with the reactivity of alkyl halides which decreases in the order tertiary, secondary, primary[22,24]. During the reduction of the dihalogeno derivatives *IVa*, *Va* (*IVb*, *Vb*, resp.), the secondary 2′-halogen was found to be reduced preferably. After 1·5 h, the 5′-chloro-2′-deoxy derivative *VIa* was obtained as the predominant compound (47%) along with the 2′,5′-dideoxy derivative *VIIa* (16·5%) and the starting compound *IVa* (9%). Similarly, with the 5-fluoro analogue *IVb* the secondary chloride was preferentially reduced to afford the 5′-chloro-2′-deoxy derivative *VIb* (53%) along with the starting compound *IVb* (11·5%).

The reduction rate of alkyl halides was also found[22,25] to be decreasing in the order iodine, bromine, chlorine, fluorine. Corresponding to that, the selectivity of reduction of 2',5'-dihalogeno derivatives was pronounced when the substituent at the position 2' was the bromo atom. The uridine derivative *Va* yielded the 5'-chloro--2'-deoxy derivative *VIa* (71%) and the fluoro analogue *Vb* afforded the 5'-chloro--2'-deoxy nucleoside *VIb* (67%).

Upon prolongation of the reduction time by an order of magnitude (12 h), the primary halogen of the 2',5'-dichloro derivative *IVa* was also reduced yielding the 2',5'-dideoxy derivative *VIIa* (64%) along with a small amount of the 5'-monochloro derivative *VIa* (7%). The yields of tributyltin hydride reduction were found to vary to ±10% of the figures given.

It is also described that the aliphatic alkyl fluorides are not reduced by alkyltin hydrides[22] while the vinylic fluorine can be reductively cleaved off by an addition-elimination mechanism[26]. During the prolonged reductive dehalogenation of the primary halogen at the 5-fluoro analogue *IVb*, a partial reduction of the 5-fluoro atom of the pyrimidine moiety was observed. On separation, the dideoxy derivative *VIIb* (54%) and the 5'-monochloro derivative *VIb* (6%) were obtained along with the dideoxy derivative of the uracil series *VIIa* (6%). The partial reductive dehalogenation of the 5-fluoro atom was observed recently at the preparation of 5'-deoxy--5-fluorouridine[16].

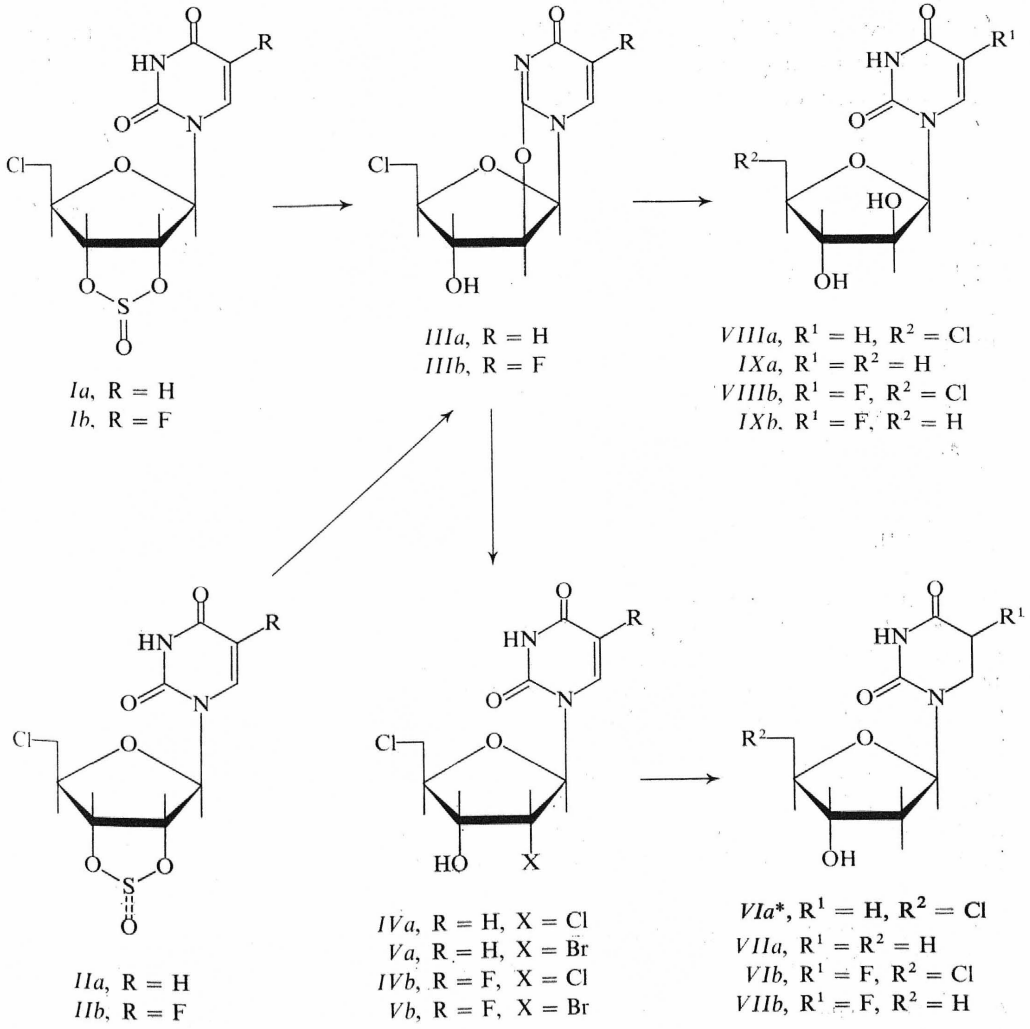
On reaction with o e equivalent of sodium hydroxide, the 5'-chloro-2,2'-anhydro derivative *IIIa* (*IIIb*, resp.) was converted to the 5'-chloroarabinosyl derivative *VIIIa* (76%) (90% of *VIIIb*, resp.). By subsequent reduction of the 5'-chloro derivative *VIIIa* with tributyltin hydride, the 5'-deoxyarabinosyl derivative *IXa* (69%) was

TABLE I
Inhibition of Nucleic Acid Synthesis

Compound	ED_{50}, μM	
	DNA	RNA
5-Fluorouracil	>1 000	55
5-Fluorouridine[33]	>1 000	0·33
2'-Deoxy-5-fluorouridine[34]	200	58
5'-Deoxy-5-fluorouridine[16]	>1 000	615
2',5'-Dideoxy-5-fluorouridine	>1 000	>1 000
1-((*RS*)tetrahydrofuran-2-yl)-5-fluorouracil	>1 000	>1 000
2',3'-O-Isopropylidene-5-fluorouridine	>1 000	725

formed. In the case of the 5-fluoro analogue *VIIIb*, the 5′-deoxy derivative *IXb* (41%) was obtained. Simultaneously, a small amount of the uracil analogue *IXa* (5%) was formed.

In a comparative study done at Stanford Research Institute the fluoro analogues were tested in cultured lymphoid leukemia L1210 cells for inhibition of nucleic acid synthesis by recently reported procedures[27,28]. The test results for inhibition of RNA and DNA synthesis are expressed as the dose (ED_{50}) in micromoles causing a 50% inhibition of the nucleic acid synthesis. 1% Dimethyl sulfoxide was used to dissolve all compounds tested[28].



* In the formula *VI* (*VII*) the 5,6 double bound is missing.

In the comparative test it was supposed that the molecular structure of the compounds studied remains unchanged under the experimental conditions. In accordance with the proposal, Ftorafur bearing no hydroxyl groups did not show any activity. Of the compounds tested, 2'-deoxy-5-fluorouridine, as the only one, exhibited the inhibition of DNA synthesis. By far the highest activity towards RNA synthesis was observed with 5-fluorouridine. As expected, 2',3'-isopropylidene-5-fluorouridine (*X*) was found to be substantially less active than the unsubstituted 5-fluorouridine. 5'-Deoxy-5-fluorouridine which cannot form the 5'-phosphate ester exhibited an activity comparable (somewhat surprisingly) with the isopropylidene derivative *X*.

The test results indicate that either the primary hydroxyl group in the 5' position (at 2',3'-isopropylidene-5-fluorouridine) or the two vicinal hydroxyl groups in the 2' and 3' positions (at 5'-deoxy-5-fluorouridine) are sufficient to retain a part of the inhibitory effect of 5-fluorouridine. Contrary to that, the only hydroxyl group in the 3' position at the 2',5'-dideoxy derivative *VIIb* is not sufficient for the activity of the preparate.

The test is in agreement with the suggestion that Ftorafur initially has to be cleaved to 5-fluorouracil to exhibit a biological activity[29]. The test also indicates that the highly specific and considerable activity of 5-fluorouridine *vs* RNA synthesis has to follow another mechanism than the mere long transformation to 2'-deoxy-5-fluorouridine 5'-phosphate and the inhibition of thymidylate synthetase. The recent studies[30–32] on the ribosyl derivative of 5-fluorouracil suggest additional sites of action for 5-fluorouridine. The above test results strongly support this suggestion and the importance of high activity of 5-fluorouridine.

EXPERIMENTAL

Melting points were taken on a heated microscope stage (Kofler block). Ultraviolet spectra were recorded on a CF-4 apparatus (Optica, Milano). Infrared spectra were taken on a UR-20 apparatus (Carl Zeiss, Jena). Optical rotations were measured on an automatic Perkin–Elmer 141 MC polarimeter. Column chromatography was performed on the Pitra silica gel (particle size, 30–60 μ; 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 following systems: S_1 ethyl acetate, S_2 ethyl acetate–acetone–ethanol–water (20 : 2 : 2 : 1), S_3 ethyl acetate–acetone–ethanol–water (16 : 3 : 2 : 2), S_4 toluene–ethyl acetate (1 : 2). R_F value in S_1: *IVa* 0·56, *Va* 0·66, *VIa* 0·28, *VIb* 0·38, *VIIb* 0·28, *VIIIb* 0·36, *IXb* 0·24; S_2: *VIIa* 0·46, *VIIIa* 0·66, *IXa* 0·59; S_3: *IIIa* 0·34, *IIIb* 0·51; S_4: *IVb* 0·56, *Vb* 0·59, *X* 0·39.

(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-*a*]pyrimidin-6-one (*IIIa*)

A solution of epimeric 5'-chloro-5'-deoxy-2',3'-O-sulphinyluridines (*Ia*, *IIa*), prepared[16] from 488 mg (2 mmol) of uridine, and imidazole (140 mg) in dimethylformamide (10 ml) was heated at 150°C for 2 h. Dimethylformamide was evaporated *in vacuo*. Crystallization of the residue

from ethanol gave 331 mg (68%) of compound *IIIa*, m.p. 199·5—201·5°C. On chromatography of mother liquors on a silica gel column (30 g) in the system ethyl acetate–acetone–ethanol–water (16 : 3 : 3 : 3), an additional crop (44 mg, 9%) of the same compound *IIIa* was obtained. $[\alpha]_D^{25}$ −12·8° (*c* 0·45; water). UV spectrum (water): λ_{max} 225 and 249 nm (log ε = 4·01 and 3·98). λ_{min} 213 and 235 nm (log ε 3·88 and 3·92). IR spectrum (KBr): 3200 cm^{-1} (OH), 1663 cm^{-1} (C=O), 1620, 1537 and 1484 cm^{-1} (ring). For $C_9H_9ClN_2O_4$ (244·6) calculated: 44·18% C, 3·71% H, 11·45% N, 14·49% Cl; found: 44·35% C, 3·87% H, 11·72% N, 14·49% Cl.

(2*R*)-(2α,3β,3aβ,9aβ)-2,3,3a,9a-Tetrahydro-7-fluoro-3-hydroxy-2-chloromethyl-6*H*-furo-[2′,3′ : 4,5]oxazolo[3,2-*a*]pyrimidin-6-one (*IIIb*)

A solution of epimeric 5′-chloro-5′-deoxy-2′,3′-O-sulphinyl-5-fluorouridines (*Ib*,*IIb*), prepared[16] from 524 mg (2 mmol) of 5-fluorouridine, and imidazole (140 mg) in dimethylformamide (10 ml) was heated at 150°C for 15 min. Dimethylformamide was then evaporated *in vacuo*. Crystallization of the residue from ethanol furnished 402 mg (76·5%) of *IIIb*, m.p. 194—195°C. Chromatography of mother liquors on a column of silica gel (30 g) in the solvent system ethyl acetate–acetone–ethanol–water (36 : 6 : 4 : 3) afforded an additional amount (67 mg, 13%) of *IIIb* with an identical melting point. $[\alpha]_D^{25}$ −24·7° (*c* 0·49; water). UV spectrum (water): λ_{max} 225 and 253 nm (log ε = 3·89 and 3·99), λ_{min} 217 and 235 nm (log ε = 3·85 and 3·81). IR spectrum (KBr): sh 3410 and 3334 cm^{-1} (OH), 1678 cm^{-1} (C=O), 1634 cm^{-1} (C=C). For $C_9H_8ClFN_2O_4$ (262·6) calculated: 41·16% C, 3·07% H, 10·67% N, 13·50% Cl, 7·23% F; found: 41·23% C, 3·12% H, 10·71% N, 13·79% Cl, 7·33% F.

2′,5′-Dichloro-2′,5′-dideoxyuridine (*IVa*)

A solution of compound *IIIa* (489 mg, 2 mmol) in 7 ml of 10% hydrogen chloride in dimethylformamide was heated at 100°C for 15 min. Dimethylformamide was evaporated *in vacuo* and the residue was coevaporated with a mixture of methanol and toluene. Chromatography of the residue on a silica gel column (75 g) in ethyl acetate yielded 600 mg of a UV absorbing fraction. On crystallization from 2-propanol, 420 mg (75%) of compound *IVa* were obtained, m.p. 163 to 164°C. Crystallization of mother liquors afforded additional 60 mg (10·5%) of *IVa* of the same melting point. $[\alpha]_D^{25}$ +10·8° (*c* 0·50; water). UV spectrum (water): λ_{max} 259 nm (log ε = 4·09), λ_{min} 236 nm (log ε = 3·93). IR spectrum (KBr): 3395 cm^{-1} (OH), 3211 cm^{-1} (NH), 1719 and 1680 cm^{-1} (C=O), 1627 cm^{-1} (C=C). For $C_9H_{10}Cl_2N_2O_4$ (281·1) calculated: 38·45% C, 3·59% H, 9·97% N, 25·23% Cl; found: 38·60% C, 3·79% H, 10·24% N, 25·32% Cl.

2′,5′-Dichloro-2′,5′-dideoxy-5-fluorouridine (*IVb*)

A solution of compound *IIIb* (525 mg, 2 mmol) in 7 ml of 10% hydrogen chloride in dimethylformamide was heated at 100°C for 30 min. After evaporation of dimethylformamide *in vacuo* the residue was coevaporated with a mixture of methanol and toluene and then chromatographed on a silica gel column (75 g) in benzene–ethyl acetate (2 : 3). The residue of the UV absorbing fraction was crystallized from 2-propanol affording 373 mg (62%) of compound *IVb*, m.p. 154—156°C. The mother liquors yielded additional 105 mg (17·5%) of the same compound *IVb*. $[\alpha]_D^{25}$ +12·1° (*c* 0·45; water). UV spectrum (water): λ_{max} 207 and 267 nm (log ε = 4·12 and 4·07), λ_{min} 234 nm (log ε = 3·47). IR spectrum (KBr): 3484 cm^{-1} (OH), 3194 cm^{-1} (NH), 3087 cm^{-1} ($C_{(6)}$—H), 1722 and 1698 cm^{-1} (C=O), 1087 cm^{-1} (C—F), 715 cm^{-1} (C—Cl). For $C_9H_9Cl_2$. FN_2O_4 (299·1) calculated: 36·14% C, 3·03% H, 9·37% N, 23·71% Cl, 6·35% F; found: 36·43% C, 3·30% H, 9·09% N, 23·32% Cl, 6·53% F.

2′-Bromo-5′-chloro-2′,5′-dideoxyuridine (*Va*)

A solution of 2,2′-anhydro derivative *IIIa* (734 mg, 3 mmol) in 9 ml of 1M hydrogen bromide in dimethylformamide was heated at 100°C for 10 min. After evaporation of the solvent *in vacuo* the residue was chromatographed on a silica gel column (100 g) in benzene–ethyl acetate (2 : 5). Crystallization of the residue of the UV absorbing fraction from 2-propanol afforded 750 mg (77%) of compound *Va*, m.p. 181–185°C. An additional amount of the same compound *Va* (90 mg, 9%) was recovered from mother liquors. $[\alpha]_D^{25}$ +8·7° (*c* 0·52; water). UV spectrum (water): λ_{max} 257 nm (log ε = 4·14), λ_{min} 229 nm (log ε = 3·48). IR spectrum (KBr): 3394, 3218 cm^{-1} (OH, NH), 1717 and 1680 cm^{-1} (C=O), 1626 cm^{-1} (C=C). For $C_9H_{10}BrClN_2O_4$ (325·6) calculated: 33·20% C, 3·10% H, 8·61% N, 24·55% Br, 10·89% Cl; found: 32·98% C, 3·29% H, 8·54% N, 24·27% Br, 10·77% Cl.

2′-Bromo-5′-chloro-2′,5′-dideoxy-5-fluorouridine (*Vb*)

A solution of the 2,2′-anhydro derivative *IIIb* (263 mg, 1 mmol) in 3 ml of 1M hydrogen bromide in dimethylformamide was heated at 100°C for 15 min. Dimethylformamide was evaporated *in vacuo* and the residue was chromatographed on a column of silica gel (30 g) in benzene–ethyl acetate (2 : 5). On crystallization of the residue of the UV absorbing fraction from 2-propanol, 175 mg (51%) of compound *Vb* were obtained, m.p. 152–157°C. The mother liquors afforded additional 93 mg (27%) of the same compound *Vb*. $[\alpha]_D^{25}$ +10·9° (*c* 0·42; water). IR spectrum (KBr): 3479 cm^{-1} (OH), 3195 cm^{-1} (NH), 3080 cm^{-1} ($C_{(6)}$—H), 1721 and 1695 cm^{-1} (C=O), 1666 cm^{-1} (C=C). For $C_9H_9BrClFN_2O_4$ (343·55) calculated: 31·46% C, 2·64% H, 8·16% N, 23·26% Br, 10·32% Cl, 5·53% F; found: 31·33% C, 2·87% H, 8·20% N, 22·97% Br, 10·09% Cl, 5·54% F.

1-(5-Chloro-2,5-dideoxy-β-D-*erythro*-pentofuranosyl)pyrimidin-2,4(1*H*,3*H*)-dione (*VIa*)

A) To a refluxing solution of compound *Va* (163 mg, 0·5 mmol) in the mixture of benzene (4·5 ml) and methanol (1·5 ml), 1M solution of tributyltin hydride in benzene (1 ml) was added. After a 10 min heating the mixture was evaporated *in vacuo*. The residue was treated with light petroleum (3 × 5 ml) and chromatographed on a silica gel column (20 g) in ethyl acetate. Crystallization of the residue of the UV absorbing fraction from 2-propanol furnished 78 mg (63%) of compound *VIa*, m.p. 152–153°C. Additional 10 mg (8%) of the same compound were recovered from mother liquors. $[\alpha]_D^{25}$ +15·8° (*c* 0·71; water). UV spectrum (water): λ_{max} 261 nm (log ε = 4·05), λ_{min} 231 nm (log ε = 3·38). IR spectrum (KBr): 3395 and 3198 cm^{-1} (OH, NH), 1725 and 1672 cm^{-1} (C=O), sh 1631 cm^{-1} (C=C). For $C_9H_{11}ClN_2O_4$ (246·7) calculated: 43·82% C, 4·50% H, 11·36% N, 14·37% Cl; found: 43·95% C, 4·56% H, 11·44% N, 14·40% Cl.

B) To a solution of compound *IVa* (281 mg, 1 mmol) in the mixture of benzene (9 ml) and methanol (3 ml) at reflux temperature, 1M solution of tributyltin hydride in benzene (2 ml) and 2,2′-azobis(2-methylpropionitrile) (10 mg) were added. The mixture was refluxed for additional 1·5 h and then evaporated *in vacuo*. The residue was washed with light petroleum (3 × 5 ml) and chromatographed on a silica gel column (30 g) in ethyl acetate. The first UV absorbing fraction was crystallized from 2-propanol what afforded 26 mg (9%) of the starting compound *IVa*. Crystallization of the second (main) fraction from the same solvent afforded 87 mg (35%) of the 2′-deoxy derivative *VIa*, identical with the product prepared by procedure *A*. Mother liquors furnished additional 30 mg (12%) of the same compound *VIa*. The third fraction afforded 35 mg (16·5%) of the 2′,5′-dideoxy derivative *VIIa* after crystallization from ethanol.

1-(5-Chloro-2,5-dideoxy-β-D-*erythro*-pentofuranosyl)-5-fluoropyrimidin-2,4(1*H*,3*H*)-dione (*VIb*)

A) To a refluxing solution of compound *Vb* (150 mg, 0·5 mmol) in the mixture of benzene (4 ml) and methanol (1 ml), 1M solution of tributyltin hydride in benzene (1 ml) and 2,2′-azobis(2-methylpropionitrile) (10 mg) were added. After 15 min of heating, the mixture was evaporated *in vacuo* and the residue was treated with light petroleum. The deposited precipitate was pulverized in light petroleum, the solid was collected by filtration on a sinter glass and washed with the same solvent (4 × 2 ml). Crystallization from 2-propanol afforded 64 mg (48%) of compound *VIb*, m.p. 175–178°C. On chromatography of mother liquors on a silica gel column (15 g) in benzene–ethyl acetate (2 : 3), additional crop of compound *VIb* (25 mg, 19%) was obtained. $[\alpha]_D^{25}$ +13·8° (*c* 0·40; water). UV spectrum (water): λ_{max} 269 nm (log ε = 4·01), λ_{min} 234 nm (log ε = 3·33). IR spectrum (KBr): 3414, 3185 cm^{-1} (OH, NH), 1724 and 1680 cm^{-1} (C=O). For $C_9H_{10}ClFN_2O_4$ (264·65) calculated: 40·84% C, 3·81% H, 10·59% N, 13·40% Cl, 7·18% F; found: 40·90% C, 4·03% H, 10·33% N, 13·32% Cl, 7·34% F.

B) To a solution of compound *IVb* (299 mg, 1 mmol) in the mixture of benzene (6 ml) and methanol (1 ml) at reflux temperature, 1M solution of tributyltin hydride in benzene (6 ml) and 2,2′-azobis(2-methylpropionitrile) (10 mg) were added. The solution was refluxed for additional 1 h and then evaporated *in vacuo*. The residue was treated with light petroleum (15 ml) and extracted with water (2 × 15 ml). The aqueous solution was evaporated *in vacuo* and the residue was chromatographed on a column of silica gel (30 g) in benzene–ethyl acetate (2 : 3) affording 35 mg (11·5%) of the starting material *IVb* at first. The next fraction afforded 141 mg (53%) of 5′-chloro-2′-deoxy derivative *VIb* (identical with the product prepared according to the procedure *A*) on crystallization from 2-propanol.

1-(2,5-Dideoxy-β-D-*erythro*-pentofuranosyl)pyrimidin-2,4(1*H*,3*H*)-dione (*VIIa*)

A solution of compound *IVa* (281 mg, 1 mmol) in the mixture of benzene (6 ml) and methanol (3 ml) was refluxed for 12 h. During this period of time, a 1M solution of tributyltin hydride in benzene (12 ml) and 2,2′-azobis(2-methylpropionitrile) (40 mg) were added. The mixture was evaporated *in vacuo* and the residue was treated with light petroleum (30 ml). The mixture was extracted with water (2 × 30 ml). The aqueous solution was washed with light petroleum (20 ml) and evaporated *in vacuo*. The residue was chromatographed on a silica gel column (80 g) in ethyl acetate. The residue of the main fraction afforded on crystallization from ethanol 114 mg (54%) of the dideoxy derivative *VIIa*, m.p. 158–159°C. Additional 28 mg (10%) of the same compound (identical with an authentic specimen[20]) were recovered from mother liquors. For $C_9H_{12}N_2O_4$ (212·2) calculated: 50·94% C, 5·70% H, 13·20% N; found: 51·05% C, 5·79% H, 13·01% N. Crystallization of the residue of the first fraction from 2-propanol yielded 18 mg (7%) of monochloro derivative *VIa*.

1-(2,5-Dideoxy-β-D-*erythro*-pentofuranosyl)-5-fluoropyrimidin-2,4(1*H*,3*H*)-dione (*VIIb*)

The title compound *VIIb* was prepared from the 2′,5′-dichloro derivative *IVb* (299 mg, 1 mmol) using the same procedure as in the case of the uridine derivative *VIIa*. Yield, 125 mg (54%), m.p. 174–177°C. $[\alpha]_D^{25}$ +36·3° (*c* 0·37; water). UV spectrum (water): λ_{max} 270 nm (log ε = 3·98), λ_{min} 235 nm (log ε = 3·27). IR spectrum (KBr): 3455 cm^{-1} (OH), 3163 cm^{-1} (NH), 1699 and 1677 cm^{-1} (C=O), sh 1645 cm^{-1} (C=C). For $C_9H_{11}FN_2O_4$ (230·2) calculated: 46·95% C, 4·82% H, 12·17% N, 8·25% F; found: 47·14% C, 4·63% H, 12·18% N, 8·44% F. Along with the title compound *VIIb*, the monochloro derivative *VIb* (15 mg, 6%) and the uracil derivative *VIIa* (10 mg, 6%) were obtained.

1-(5-Chloro-5-deoxy-β-D-arabinofuranosyl)uracil (*VIIIa*)

A solution of 5'-chloro anhydronucleoside *IIIa* (734 mg, 3 mmol) in 0·1M sodium hydroxide (31·5 ml) was stirred at room temperature for 1·5 h and then neutralized with Dowex 50(H^+). The resin was filtered off and washed with water. The combined filtrates were evaporated *in vacuo*. Crystallization of the residue from 2-propanol yielded 500 mg (63·5%) of compound *VIIIa*, m.p. 189—191°C. In addition, 100 mg (13%) of the same compound were obtained from mother liquors. $[\alpha]_D^{25}$ +110·3° (*c* 0·42; methanol). UV spectrum (water): λ_{max} 207 and 262 nm (log ε = = 3·97 and 4·05), λ_{min} 231 nm (log ε = 3·34). IR spectrum (KBr): 3390 cm^{-1} (OH), 3180 cm^{-1} (NH), 1695 and 1663 cm^{-1} (C=O). For $C_9H_{11}ClN_2O_5$ (262·6) calculated: 41·16% C, 4·22% H, 10·66% N, 13·50% Cl; found: 41·11% C, 4·37% H, 10·86% N, 13·58% Cl.

1-(5-Chloro-5-deoxy-β-D-arabinofuranosyl)-5-fluorouracil (*VIIIb*)

Compound *VIIIb* was prepared from anhydronucleoside *IIIb* (786 mg, 3 mmol) in the yield of 756 mg (90%), m.p. 211—214°C, by the same procedure as used in the preparation of compound *VIIIa*. $[\alpha]_D^{25}$ +116·1° (*c* 0·50; methanol). UV spectrum (water): λ_{max} 207 and 269 nm (log ε = 3·97 and 3·95), λ_{min} 234 nm (log ε = 3·23). IR spectrum (KBr): 3448, 3380 and 3167 cm^{-1} (OH, NH), sh 1705 and 1683 cm^{-1} (C=O). For $C_9H_{10}ClFN_2O_5$ (280·6) calculated: 38·52% C, 3·59% H, 9·98% N, 12·63% Cl, 6·77% F; found: 38·80% C, 3·78% H, 9·99% N, 12·44% Cl, 7·00% F.

1-(5-Deoxy-β-D-arabinofuranosyl)uracil (*IXa*)

To a solution of the 5'-chloro derivative *VIIIa* (263 mg; 1 mmol) in methanol (6 ml) at reflux temperature, 1M solution of tributyltin hydride in benzene (5 × 3 ml) and 2,2'-azobis(2-methylpropionitrile) (5 × 10 mg) were added stepwise during 20 h. The reaction mixture was then evaporated *in vacuo* and the residue was treated with light petroleum (10 ml) and extracted with water (25 ml). The aqueous solution was repeatedly washed with light petroleum (2 × 10 ml) and evaporated *in vacuo*. The residue was chromatographed on a silica gel column (40 g) in the solvent system ethyl acetate–acetone–ethanol–water (20 : 2 : 1 : 1). Crystallization of the residue of the UV absorbing fraction from 2-propanol afforded 120 mg (52·5%) of the 5'-deoxy derivative *IXa*, m.p. 164—165·5°C. Additional 38 mg (16·5%) of compound *IXa* were obtained from mother liquors. $[\alpha]_D^{25}$ +106·15° (*c* 0·46; water). UV spectrum (water): λ_{max} 210 and 264 nm (log ε = 3·92 and 4·00), λ_{min} 232 nm (log ε = 3·28). IR spectrum (KBr): 3471, 3378 and 3182 cm^{-1} (OH: NH). 1700 and 1675 cm^{-1} (C=O), 1624 cm^{-1} (C=C). For $C_9H_{12}N_2O_5$ (228·2) calculated: 47·36% C, 5·30% H, 12·28% N; found: 47·32% C, 5·28% H, 12·51% N.

1-(5-Deoxy-β-D-arabinofuranosyl)-5-fluorouracil (*IXb*)

The compound *IXb* was prepared from 5'-chloro derivative *VIIIb* (281 mg, 1 mmol) by the same procedure as in the case of the uracil derivative *IXa*. The reaction time was 16 h. Chromatography on a silica gel column (80 g) in ethyl acetate afforded the required 5-fluorouracil derivative *IXb*. Subsequently, the solvent system ethyl acetate–acetone–ethanol–water (20 : 2 : 1 : 1) eluted the uracil derivative *IXa*. The residue of the first (ethyl acetate) fraction afforded 101 mg (41%) of compound *IXb*, m.p. 188—191°C after crystallization from 2-propanol. $[\alpha]_D^{25}$ +102·7° (*c* 0·28; water). UV spectrum (water): λ_{max} 209 and 271 nm (log ε = 3·92 and 3·94), λ_{min} 236 nm (log ε = 3·18). IR spectrum (KBr): 3462, 3409 cm^{-1} (OH, NH), 1706 and 1681 cm^{-1} (C=O), sh 1660 cm^{-1} (C=C). For $C_9H_{11}FN_2O_5$ (246·2) calculated: 43·90% C, 4·50% H, 11·38% N,

7·72% F; found: 43·96% C, 4·42% H, 11·14% N, 7·80% F. The residue of the second fraction was crystallized from 2-propanol to afford 12 mg (5%) of a compound which was identical with 5′-deoxyarabinosyluracil *IXa*.

2′,3′-O-Isopropylidene-5-fluorouridine (*X*)

The mixture of 5-fluorouridine (262 mg, 1 mmol), acetone (8 ml), ethyl orthoformate (1 ml), and 1M-HCl in dimethylformamide (0·1 ml) was stirred at room temperature for 16 h. Then, sodium hydrogen carbonate (50 mg) was added and the mixture was stirred for additional 10 min. The insoluble material was filtered off and washed with acetone (2 × 2 ml). The combined filtrates were evaporated *in vacuo* and the residue was crystallized from ethanol affording 224 mg (74%) of isopropylidene derivative *X*, m.p. 197–198°C. $[\alpha]_D^{25}$ −19·0° (*c* 0·24; methanol). UV spectrum (water): λ_{max} 209 and 270 nm (log ε 3·91 and 3·93), λ_{min} 235 nm (log ε 3·15). IR spectrum (KBr): 3254 cm^{-1} (OH, NH), 1709 and 1684 cm^{-1} (C=O), 1663 cm^{-1} (C=C), 1383 and 1376 cm^{-1} ($(CH_3)_2C$=). For $C_{12}H_{15}FN_2O_6$ (302·3) calculated: 47·68% C, 5·00% H, 9·27% N, 6·29% F; found: 47·66% C, 5·09% H, 9·31% N, 6·01% F.

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