SYNTHESIS OF 5-CYLOPROPYLURIDINE AND 5-CYCLOPROPYL-6-AZAURIDINE*

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Reaction of 5-cyclopropyluracil and 5-cyclopropyl-6-azauracil trimethylsilyl derivatives with 1-O-acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranose in 1,2-dichloroethane under catalysis of stannic chloride afforded the protected nucleosides *III* and *IV* from which the blocking groups were removed with the formation of 5-cyclopropyluridine (*I*) and its 6-azaanalogue *II*. The ^{1}N-NMR spectra of compounds *I* and *II* are almost identical with those of 5-substituted uridines and their 6-aza counterparts.

In connection with investigations on the relationship between chemical structure and biological activity numerous 5-alkyluridines[1-3] and 5-alkyl-2'-deoxyuridines[4] have been prepared. From compounds of this type, 5-ethyl-2'-deoxyuridine[5,6] proved of special interest because of the virostatic activity free of the undesirable mutagenic effects. The structurally related 5-vinyluridine[7] and 5-vinyl-2'-deoxyuridine[7] have been recently reported. In the present paper*, we wish to describe syntheses of 5-cyclopropyluridine (*I*) and 5-cyclopropyl-6-azauridine (*II*), *i.e.* 6-cyclopropyl-2-β-D-ribofuranosyl-*as*-triazine-3,5(2*H*,4*H*)-dione; these pyrimidine nucleosides substituted in the aglycon moiety by the cyclopropyl group are of interest as potential antimetabolites.

In the synthesis of the nucleoside *I*, the starting 5-cyclopropyluracil was subjected to reaction with hexamethyldisilazane to afford 5-cyclopropyl-2,4-bis(trimethylsilyloxy)pyrimidine. Reaction of this silylated base with 1-O-acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranose in 1,2-dichloroethane under catalysis of stannic chloride yielded 1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-5-cyclopropyluracil (*III*) which was converted to the free nucleoside *I* by the action of methanolic ammonia. The trimethylsilyl derivative of 5-cyclopropyl-6-azauracil was analogously transformed into

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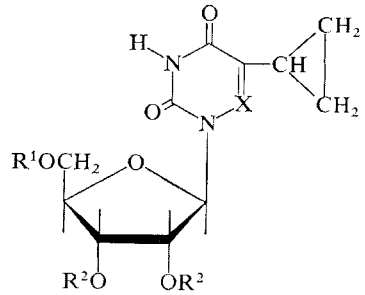
2-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-6-cyclopropyl-*as*-triazine-3,5(2*H*,4*H*)-dione (*IV*). The protecting groups of compound *IV* were removed with the formation of the free 6-azanucleoside *II*. For purposes of characterisation, the nucleosides *I* and *II* were subjected to reaction with 2,2-dimethoxypropane to afford the corresponding 2',3'-O-isopropylidene derivatives *V* and *VI*.



I; $R^1 = R^2 = H$, X = CH
II; $R^1 = R^2 = H$, X = N
III; $R^1 = R^2 = Bz$, X = CH
IV; $R^1 = R^2 = Bz$, X = N
V; $R^1 = H$, $2R^2 = C(CH_3)_2$, X = CH
VI; $R^1 = H$, $2R^2 = C(CH_3)_2$, X = N

Compound *I* was assigned the β-configuration on the basis of the known steric course of the Vorbrüggen nucleoside synthesis[9,10] as well as on the basis of the ^{1}H-NMR spectrum of the isopropylidene derivative *V*. The relatively low value ($J_{1',2'} = 2{\cdot}0$ Hz) of the coupling constant of the $H_{1'}$ anomeric proton permits assignment of the β-configuration on the basis of known relationships[11,12]. According to the Imbach rule[13,14], the β-configuration of compound *V* is favoured by the difference of chemical shifts due to methyl groups ($\Delta\delta = 0{\cdot}20$ p.p.m.). In the ^{1}H-NMR spectrum of the free nucleoside *I*, the concentration of $H_{2'}$, $H_{3'}$, and $H_{4'}$ proton signals in a narrow region (3·88–4·02 p.p.m.) is characteristic of ribonucleosides with *anti* conformation[15]. The chemical shift of the H_6 proton in compound *I* (7·64 p.p.m.) is very similar to chemical shift values of the H_6 proton reported[3] for 5-isopropyluridine and 5-tert-butyluridine (7·7 p.p.m.). The shielding effect of the cyclopropane ring[16] does not thus manifest itself in the case of compound *I*.

The β-configuration of compound *II* and its derivatives was established on the basis of spectral evidence analogously to compound *I*. The nucleoside 6-azaanalogue *II* and its isopropylidene derivative *VI* exhibit low values[12] of the coupling constant of the $H_{1'}$ proton ($J_{1',2'} = 3{\cdot}0$ Hz and 1·2 Hz, resp.). The chemical shift difference of methyl groups in compound *VI* equal to 0·18 p.p.m. is capable of being used as criterion of β-configuration[13,14]. When compared with pyrimidine nucleosides with *anti* conformation of the aglycon moiety, the $H_{2'}$ and $H_{3'}$ proton signals in the ^{1}H-NMR spectrum of compound *II* are shifted downfield while a small shift in the opposite direction may be observed in the case of the $H_{4'}$ proton. Similar shifts

of $H_{2'}$, $H_{3'}$, and $H_{4'}$ protons occur in the ^{1}H-NMR spectrum of 6-azauridine. In the case of 6-azauridine, this shift is according to Robins and coworkers[15] due to anisotropy of the lone electron pair of sp^2 orbital of the nitrogen atom at position 6. The relatively high coupling constant values of $H_{4'}$, $H_{5'a}$, and $H_{5'b}$ protons in compound *II* ($J_{4',5'a} = 4{\cdot}1$ Hz and $J_{4',5'b} = 5{\cdot}8$ Hz) are comparable with the corresponding values of 6-azauridine[15] ($J_{4',5'a} = 3{\cdot}6$ Hz and $J_{4',5'b} = 5{\cdot}5$ Hz) and suggest for compound *II* in dimethyl sulfoxide a predominant population of rotamers with *gauche-trans* or *trans-gauche* conformation on the exocyclic bond $C_{4'}$—$C_{5'}$. The similarity of ^{1}H-NMR spectra of sugar moieties of compound *II* and 6-azauridine allows to assume the *anti* conformation of the aglycon in compound *II* similar to 6-azauridine where this conformation was established[17] by measurement of the $^5J_{5,1'}$ coupling constant.

The UV spectra of compound *I* and *II* exhibit bathochromic shift of the absorption band in the 270 nm region corresponding to the shift observed with 5-cyclopropyluracil[19] and 5-cyclopropyl-6-azauracil[18]. The CD spectra of compounds *I* and *II* correspond by band position of Cotton effects and their sign to those of 5-substituted uridines and their 6-aza derivatives[20–22] (for a survey of reporsts on the CD spectra of nucleosides see ref.[23]). Resemblance of CD spectra supports conclusion based on ^{1}H-NMR spectra about the *anti* conformation of aglycons in compounds *I* and *II*. The CD spectrum of compound *II* lacks the band of the $n-\pi^*$ transition occurring in CD spectra of 6-azauridine and its 5-methyl derivative[22]. When the B_{2u} band of compound *II* is compared with the corresponding band of 5-methyl-6-azauridine, a shift to longer wavelengths can be observed which is probably due

TABLE I

CD Spectra of Some Pyrimidine and *as*-Triazine Nucleosides

Compound	pH	Spectral bands, nm ($\Delta\varepsilon$)					
		B_{2u}		B_{1u}		E_{1u}	
I	7·0[a]	274·5	(+1·31)	241	(−1·00)		
VII[b]	7·0[a]	274	(+1·63)	244	(−2·55)		
II	7·0[a]	271·5	(−2·19)	241·5	(−1·76)	212	(+4·74)
II	9·0[c]	266·5	(−2·16)			227·5	(+0·87)
VIII[d,e]	7·0[a]	260	(−1·16)	244 sh	(−0·85)	208	(+1·59)
VIII[d,f]	9·0	260	(−3·06)			211	(+0·95)

[a] Measured in water, [b] 5-Isopropyluridine; data from ref.[3], [c] Measured in a borate buffer solution. [d] 5-Methyl-6-azauridine. [e] Band of the $n-\pi^*$ transition at 304 nm ($\Delta\varepsilon$ +0·035). [f] Data from ref.[22], band of the $n-\pi^*$ transition at 296 nm ($\Delta\varepsilon$ +0·47).

to the conjugation effect of the cyclopropane ring; contrary to expectations, the B_{2u} band of the uracil derivative *I* does not exhibit a similar shift.

Fragmentations in mass spectra of compounds *I* and *II* are almost identical (including the peak intensity) with those of pyrimidine nucleosides[24,25].

EXPERIMENTAL

Melting points were taken on a heated microscope stage (Kofler microblock). Analytical samples were dried at 25°C/0·05 Torr for 8 h. The ^{1}H-NMR spectra were measured on the Varian HA 100 apparatus in hexadeuteriodimethyl sulfoxide (tetramethylsilane as internal standard). Spin coupling constants were determined by the double resonance technique. Chemical shifts δ in p.p.m. The UV spectra were recorded on the Specord UV VIS apparatus (Carl Zeiss, Jena). The CD spectra were taken on a Model II Roussel-Jouan Dichrograph spectropolarimeter. The $[\alpha]_D$ values were determined on the Perkin Elmer MC 141 polarimeter. The mass spectra were measured on a MS 902 spectrometer with double fosusing. Thin-layer chromatography was performed on ready-for-use Silufol UV_{254} (Kavalier Glassworks, Votice, Czechoslovakia) silica gel sheets in the solvent systems S_1, ethyl acetate–acetone–methanol–water (14 : 1 : 0·5 : 0·5); S_2, ethyl acetate–benzene (2 : 1); S_3, 1-butanol–water (6 : 1); and S_4, benzene–ethyl acetate (4 : 1). Electrophoresis (2 h) was performed on the Whatman No 1 paper at 35 V/cm in 0·1M triethylammonium borate buffer solution (pH 6·55). Spots were detected under the Chromatolite lamp.

5-Cyclopropyl-2,4-bis(trimethylsilyloxy)pyrimidine

A stirred suspension of 5-cyclopropyluracil[19] (1·0 g; 6·6 mmol), hexamethyldisilazane (8 ml), and trimethylchlorosilane (1 ml) was refluxed until the base dissolved (15 h) and the solution evaporated at 40°C/15 Torr. The residue was fractionated under diminished pressure to afford 1·5 g (77%) of the silylated base, b.p. 105–110°C/4 Torr.

6-Cyclopropyl-3,5-bis(trimethylsilyloxy)-*as*-triazine

5-Cyclopropyl-6-azauracil[18] (0·9 g; 5·9 mmol) was silylated as above (5 h). Fractional distillation yielded 1·4 g (80%) of the silylated base, b.p. 110–114°C/4 Torr.

1-(2,3,5-Tri-O-benzoyl-β-D-ribofuranosyl)-5-cyclopropyluracil (*III*)

Stannic chloride (1 ml) in 1,2-dichloroethane (15 ml; freshly distilled over phosphorus pentoxide) was added with cooling (0°C) to a mixture of 1-O-acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranose (3·2 g; 6·35 mmol), 5-cyclopropyl-2,4-bis(trimethylsilyloxy)pyrimidine (1·5 g; 5·1 mmol), and fresh 1,2-dichloroethane (100 ml). The mixture was kept at room temperature for 2 days and washed with an equal volume of saturated aqueous sodium hydrogen carbonate. The organic layer was separated and passed through a thin layer of Hyflo Super Cel. The solid on the filter was washed with a small volume of 1,2-dichloroethane. The filtrate and washings were combined, dried over anhydrous magnesium sulfate, and evaporated under diminished pressure. The residue was dissolved in the solvent mixture (30 ml) benzene–ethyl acetate (7 : 1) to deposit after several hours 0·72 g of compound *III*. The mother liquors were chromatographed on a column (2·5 cm × 35 cm) of silica gel in the solvent system benzene–ethyl acetate (1 : 1). The chromatographically homogeneous fractions were combined and evaporated. The residue was dissolved in a small volume

of benzene to deposit after 12 h at 5°C an additional crop of crystalline compound *III* which was collected with suction and washed with ether. Overall yield, 1·64 g (53%, referred to the silylated base) of compound *III*, m.p. 191—192°C. Crystallisation from benzene–ethyl acetate (1 : 1) afforded the analytical sample, m.p. 193—194°C; $[\alpha]_D^{20}$ −84·99° (*c* 0·5, benzene). R_F in S_4: 0·26. For $C_{33}H_{28}N_2O_9$ (596·6) calculated: 66·43% C, 4·73% H, 4·71% N; found: 66·86% C, 4·96% H, 4·56% N.

2-(2,3,5-Tri-O-benzoyl-β-D-ribofuranosyl)-6-cyclopropyl-*as*-triazine-3,5(2*H*,4*H*)-dione (*IV*)

Stannic chloride (2 ml) in 1,2-dichloroethane (10 ml; freshly distilled over phosphorus pentoxide) was added with cooling (0°C) to a mixture of 2,3,5-tri-O-benzoyl-β-D-ribofuranose (4·0 g; 7·9 mmol), 6-cyclopropyl-3,5-bis(trimethylsilyloxy)-*as*-triazine (1·4 g; 4·7 mmol), and fresh 1,2-dichloroethane (100 ml). The mixture was kept at room temperature for 15 h, treated with additional stannic chloride (1 ml), kept for 12 h more, and processed analogously to compound *III* to afford 0·73 g of compound *IV*. Another crop was obtained by chromatography of mother liquors on a column (2·5 cm × 30 cm) of silica gel in the solvent system benzene–ethyl acetate (7 : 1), evaporation of fractions, and crystallisation of the residue from ethanol–acetone. Overall yield, 0·85 g (30%, referred to the silylated base) of compound *IV*, m.p. 197—198°C. Crystallisation from acetone–ethanol afforded the analytical sample, m.p. 198—199°C; $[\alpha]_D^{20}$ −67·26° (*c* 0·5, benzene). R_F in S_4: 0·44. For $C_{32}H_{27}N_3O_9$ (597·6) calculated: 64·31% C, 4·55% H, 7·03% N; found: 64·38% C, 4·76% H, 7·24% N.

5-Cyclopropyluridine (*I*)

Compound *III* (0·35 g; 0·6 mmol) was kept in 15% methanolic ammonia (70 ml) for 3 days at room temperature. The mixture was evaporated under diminished pressure, the residue triturated with ether (15 ml), and the solid collected with suction. Yield, 160 mg of the nucleoside *I*, m.p. 199°C. Crystallisation from ethanol (2 ml) and methanol (0·5 ml) afforded 90 mg of compound *I*, m.p. 199—200°C. R_F: 0·59 (in S_3) and 0·32 (in S_1). Electrophoretical mobility: 8 cm (uridine, 9·0 cm). UV spectrum, in water: λ_{max} 272 nm (log ε 3·89); in 0·1M-NaOH: λ_{max} 272 nm (log ε 3·78). ^{1}H-NMR spectrum: δ 0·63 (m, 4 H, CH_2 of the cyclopropane ring), 1·62 (m, 1 H, CH of the cyclopropane ring), 3·65 (m, 2 H, $H_{5'a}$, $H_{5'b}$), 3·88 (m, 1 H, $H_{4'}$), 4·02 (m, 2 H, $H_{2'}$, $H_{3'}$), 5·80 (d, 1 H, $H_{1'}$, $J_{1',2'}$ = 4 Hz), 7·64 (s, 1 H, H_6), 11·17 (broad s, 1 H, NH). Mass spectrum: *m/e* 284 (M), 195 (M − 89), 181 (base + 30), 152 (protonated base, base peak), 133. For $C_{12}H_{16}N_2O_6$ (284·2) calculated: 50·70% C, 5·68% H, 9·85% N; found: 50·74% C, 5·70% H, 9·55% N.

2′,3′-O-Isopropylidene-5-cyclopropyluridine (*V*)

A mixture of compound *I* (50 mg), acetone (2 ml), and 2,2-dimethoxypropane (1 ml) was treated with dioxane (0·1 ml) saturated at 0°C with hydrogen chloride. The whole was kept at room temperature for 2 h, neutralised with a few drops of triethylamine, and evaporated under diminished pressure. The residue was chromatographed on a column (1 cm × 20 cm) of silica gel in the solvent system ethyl acetate–benzene (2 : 1). Combined fractions were evaporated and the residue was dissolved in a small amount of methanol to deposit crystals which were collected on a porous plate. Recrystallisation from methanol yielded compound *V*, m.p. 186°C. R_F: 0·74 (in S_1) and 0·25 (in S_2). ^{1}H-NMR spectrum: δ 0·64 (m, 4 H, 2 CH_2 of the cyclopropane ring), 1·31 (s, 3 H, CH_3), 1·51 (s, 3 H, CH_3), 1·60 (m, 1 H, CH of the cyclopropane ring), 3·61 (m, 2 H, $H_{5'a}$ and $H_{5'b}$), 4·08 (m, 1 H, $H_{4'}$, $J_{4',5'}$ = 4·0 Hz), 4·77 (m, 1 H, $H_{3'}$), 4·86 (m, 1 H, $H_{2'}$, $J_{2',3'}$ = 6·2 Hz), 5·86 (d, 1 H, $H_{1'}$, $J_{1',2'}$ = 2·0 Hz), 7·48 (s, 1 H, H_6), 11·27 (broad s, 1 H, NH). Mass spectrum:

m/e 324 (M), 309 (M − 15), 181 (base + 30), 173 (S), 152 (protonated base, base peak), 59 (C_3H_7O). For $C_{15}H_{20}N_2O_6$ (324·3) calculated: 55·55% C, 6·22% H, 8·64% N; found: 56·05% C, 6·37% H, 8·84% N.

5-Cyclopropyl-6-azauridine (6-Cyclopropyl-2-β-D-ribofuranosyl-*as*-triazine-3,5(2*H*,4*H*)-dione) (*II*)

Compound *IV* (850 mg; 1·4 mmol) was kept in 15% methanolic ammonia (100 ml) for 3 days at room temperature. The mixture was evaporated under diminished pressure and the residue chromatographed on a column (2·5 cm × 25 cm) of silica gel in the solvent system S_1. Fractions of R_F 0·40 (as determined by thin-layer chromatography in S_1) were combined and evaporated. The residue was coevaporated with five portions of benzene (bath temperature 55°C) and the final residue dissolved in a mixture of benzene (2 ml) and ethanol (0·5 ml). The solution was evaporated under diminished pressure to the consistence of a sirup which deposited crystals in the course of several days. Yield of compound *II* (dried over potassium hydroxide pellets in a desiccator), 240 mg (59%); m.p. 173—174°C. Recrystallisation from a small volume of ethanol yielded 155 mg of the analytically pure compound *II*, m.p. 174—175°C. R_F: 0·40 (in S_1) and 0·62 (in S_3). Electrophoretical mobility: 9·0 cm (uridine, 9·0 cm). UV spectrum, in water: λ_{max} 276 nm (log ε 3·79), in 0·1M-NaOH: λ_{max} 262 nm (log ε 3·75). ^{1}H-NMR spectrum: δ 0·92 (m, 4 H, 2 CH_2 of the cyclopropane ring), 2·15 (m, 1 H, CH of the cyclopropane ring), 3·38 (m, 1 H, $H_{5'a}$), 3·57 (m, 1 H, $H_{5'b}$, $J_{5'b,5'a}$ = 12·0 Hz), 3·80 (m, 1 H, $H_{4'}$, $J_{4',5'a}$ = 4·1 Hz, $J_{4',5'b}$ = 5·8 Hz), 4·06 (m, 1 H, $H_{3'}$, $J_{3',4'}$ = 5·0 Hz), 4·17 (m, 1 H, $H_{2'}$, $J_{2',3'}$ = 4·8 Hz), 5·91 (d, 1 H, $H_{1'}$, $J_{1',2'}$ = 3·0 Hz), 12·06 (broad s, 1 H, NH). Mass spectrum: *m/e* 285 (M), 196 (M − 89), 182 (base + 30), 153 (protonated base, base peak), 133 (S). For $C_{11}H_{15}N_3O_6$ (285·2) calculated: 46·31% C, 5·30% H, 14·73% N; found: 46·15% C, 5·33% H, 14·53% N.

6-Cyclopropyl-2-(2,3-O-isopropylidene-β-D-ribofuranosyl)-*as*-triazine-3,5(2*H*,4*H*)-dione (*VI*)

Procedure described in the case of compound *V* was used to convert the nucleoside *II* into the isopropylidene derivative *VI*, m.p. 157°C (ethanol). Thin-layer chromatography, R_F: 0·47 (in S_2) and 0·84 (in S_1). ^{1}H-NMR spectrum: δ 0·93 (m, 4 H, CH_2 of the cyclopropane ring), 1·30, (s, 3 H, CH_3), 1·48 (s, 3 H, CH_3), 2·15 (m, 1 H, CH of the cyclopropane ring), 3·39 (m, 2 H, $H_{5'a}$, $H_{5'b}$), 4·03 (m, 1 H, $H_{4'}$, $J_{4',5'}$ = 6·7 Hz), 4·69 (m, 1 H, $H_{3'}$, $J_{3',4'}$ = 2·7 Hz), 4·93 (m, 1 H, $H_{2'}$, $J_{2',3'}$ = 5·9 Hz), 6·08 (d, 1 H, $H_{1'}$, $J_{1',2'}$ = 1·2 Hz), 12·13 (broad s, 1 H, NH). Mass spectrum: *m/e* 325 (M), 310 (M − 15), 182 (base + 30), 173, 153 (protonated base, base peak), 59 (C_3H_7O); high resolution: M − 15, $C_{13}H_{16}N_3O_6$; calculated: 310·1039; found: 310·1039. For $C_{14}H_{19}N_3O_6$ (325·3) calculated: 51·68% C, 5·89% H, 12·92% N; found: 51·43% C, 5·59% H, 12·44% N.

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