NUCLEIC ACID COMPONENTS AND THEIR ANALOGUES. CXLIX.*
SYNTHESIS OF PYRIMIDINE NUCLEOSIDES DERIVED FROM 1-DEOXY-D-PSICOSE

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Reaction of glycosyl bromides *XVIII* and *XIX* with silyl derivatives of uracil, thymine or N^4-acetylcytosine afforded the protected nucleosides *IV*—*IX*. Reduction of the bromomethyl group in nucleosides *IV*—*VI* with tri-n-butyltin hydride led to the protected nucleosides *X*—*XII* derived from 1-deoxy-D-psicose. Alkaline methanolysis of compounds *X*—*XII* led to the free nucleosides *I*—*III*.

In connection with investigations on the relation between chemical structure and biological activity of nucleosidic antibiotics, we have been interested in the preparation of psicofuranin[1] analogues containing the pyrimidine nucleus as aglycone.

Reports on syntheses of nucleosides derived from ketosugars are not numerous and relate mainly to the purine nucleosides. Thus in 1959, Baker and coworkers[2] reported the synthesis of 9-(α-D-fructofuranosyl)- and 9-(β-D-fructopyranosyl)adenine. Soon thereafter appeared reports on syntheses of psicofuranin[3,4] and its 1-deoxy derivative[5]. The synthesis of 9-(β-L-sorbopyranosyl)adenine[6] has been published recently. All these syntheses use the mercuri process. In the pyrimidine series, the anomeric 1-(L-sorbopyranosyl)thymines have been described[7]. As starting compounds in syntheses of these pyrimidine nucleosides, the corresponding L-sorbosylureas have been used. The synthesis of psicofuranin and some analogues of the pyrimidine as well as purine series has been patented by Schroeder[8] and is based on the reaction of 3-O-methanesulfonyl-D-fructose with alkali metal salts of the corresponding bases.

In the present paper, we wish to report the synthesis of 1-(1-deoxy-β-D-psicofuranosyl)uracil (*I*), 1-(1-deoxy-β-D-psicofuranosyl)thymine (*II*) and 1-(1-deoxy-β-D-psicofuranosyl)cytosine (*III*). In the synthesis of compounds *I*—*III*, methyl 3,4,6-tri-O-*p*-toluyl-1-bromo-1-deoxy-β-D-psicofuranoside (*XVI*) has been used as the starting compound. As reported earlier[5], compound *XVI* was converted to 3,4,6-tri-O-*p*-toluyl-1-bromo-1-deoxy-D-psicofuranosyl bromide (*XVIII*). Reaction of the bromide *XVIII* with 2,4-bis(trimethylsilyloxy)pyrimidine in acetonitrile in the presence of mercuric acetate ("silylation process[9]") led to the required 1-(3,4,6-tri-O-*p*-toluyl-

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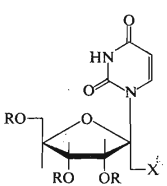
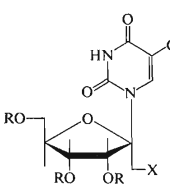
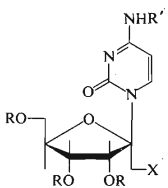
1-bromo-1-deoxy-β-D-psicofuranosyl)uracil (*IV*) in 17% yield. Reaction of the bromide *XVIII* with silylated thymine (2,4-bis(trimethylsilyloxy)-5-methylpyrimidine) or silylated N^4-acetylcytosine (2-trimethylsilyloxy-4-(N-trimethylsilylacetamido)pyrimidine) afforded 1-(3,4,6-tri-O-*p*-toluyl-1-bromo-1-deoxy-β-D-psicofuranosyl)thymine (*V*) and 1-(3,4,6-tri-O-*p*-toluyl-1-bromo-1-deoxy-β-D-psicofuranosyl)-4-acetamido-1,2-dihydro-2-pyrimidinone (*VI*), resp. Also 3,4,6-tri-O-*p*-toluyl-1-chloro-1-deoxy-D-psicofuranosyl bromide (*XIX*) reacts with the above silylated bases to afford the protected nucleosides *VII*–*IX*. Since the nucleosidation yields are relatively low (15–20%), we have tried to prepare some of the protected nucleosides with the use of the mercuri process. Thus, treatment of monomercurithymine with the bromide *XVIII* in acetonitrile afforded the nucleoside *V* in 9% yield and reaction of the mercuric salt of N^4-acetylcytosine with the same bromide *XVIII* led to a 3% yield of the nucleoside *VI*. It may be seen that in our case the silylation process gives better yields than the mercuri process. The low nucleosidation yields with ketosugars are probably due to elimination of hydrogen halide. The formation[7] of 1,3,4,5-tetra-O-acetyl-2-deoxy-L-sorbo-2,3-pyranosene was demonstrated in reaction of 1,3,4,5-tetra-O-acetyl-α-L-sorbopyranosyl chloride with the mercuric salt of thymine.



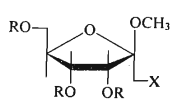
I; R = X = H
IV; R = *p*-$CH_3C_6H_4CO$, X = Br
VII; R = *p*-$CH_3C_6H_4CO$, X = Cl
X; R = *p*-$CH_3C_6H_4CO$, X = H
XIII; R = CH_3CO, X = H



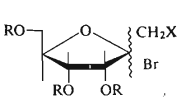
II; R = X = H
V; R = *p*-$CH_3C_6H_4CO$, X = Br
VIII; R = *p*-$CH_3C_6H_4CO$, X = Cl
XI; R = *p*-$CH_3C_6H_4CO$, X = H
XIV; R = CH_3CO, X = H



III; R = R′ = X = H
VI; R = *p*-$CH_3C_6H_4CO$ X = Br, R′ = CH_3CO
IX; R = *p*-$CH_3C_6H_4CO$ X = Cl, R′ = CH_3CO
XII; R = *p*-$CH_3C_6H_4CO$ X = H, R′ = CH_3CO
XV; R = R′ = CH_3CO, X = H



XVI; R = *p*-$CH_3C_6H_4CO$, X = Br
XVII; R = *p*-$CH_3C_6H_4CO$, X = Cl



XVIII; R = *p*-$CH_3C_6H_4CO$, X = Br
XIX; R = *p*-$CH_3C_6H_4CO$, X = Cl

The steric course of the nucleosidation of halogenoses *XVIII* and *XIX* is quite uniform no anomers being chromatographically detected in mother liquors after crystallisation of protected nucleosides *IV*–*IX*. In view of this uniformity and on the basis of Baker's rule[10] the nucleosides *IV*–*IX* may be ascribed the β-configuration at the anomeric centre.

Reduction of the bromomethyl group in compounds *IV*–*VI* to the methyl group was effected similar to an earlier paper[5] with the use of tri-n-butyltin hydride[11] in the presence of 2,2'-azobis(isobutyronitrile) in refluxing benzene. An analogous reduction of the chloromethyl group in compound *VIII* with the same reducing agent failed even with the use of a prolonged reaction period. Treatment of protected nucleosides *X*–*XII* with methanolic barium methoxide afforded the free nucleosides *I*–*III* which were characterised in the form of crystalline peracetyl derivatives *XIII*–*XV* since the elemental analyses of the parent compounds *I*–*III* were not satisfactory even after purification with the use of silica gel or Dowex 1 (formate) ion exchange resin.

The CD Cotton effect of compounds *I*–*III* and their peracetyl derivatives *XIII* to *XV* (Table I) shows at 264–272 nm ($\mathbf{B}_{2u}$ transition[12]) the same sign as that of pyrimidine β-D-ribosides[13,14]. This observation makes possible to ascribe to compounds *I*–*III* and *XIII*–*XV* the β-configuration in accordance with the conclusion obtained with the protected nucleosides *IV*–*IX* on the basis of Baker's rule. Other CD spectral bands cannot be reliably correlated since in the case of ketonucleosides some bands are not developed. Thus, *e.g.*, the CD spectrum of compound *I* lacks the $\mathbf{B}_{1u}$ band and one of the $\mathbf{E}_{1u}$ bands which are present in the CD spectrum of uridine.

The nucleosides *I*–*III* do not inhibit the growth of *Escherichia coli* in concentrations as high as 100 μg/ml.

EXPERIMENTAL

Melting points were taken on a heated microscope stage (Kofler block) and are not corrected. Analytical samples were dried at 25°C/0·05 Torr for 12 hours. Paper chromatography (Table II) was performed on paper Whatman 1 in the solvent system S_1, 1-butanol–ethanol–water (40 : 11 : 19), and S_2, 2-propanol–30% aqueous ammonia–water (4 : 1 : 2). Electrophoresis was carried out on paper Whatman No 1 at 40 Volt/cm for 2 hours in the buffer solutions E_1, 0·05M triethylamine borate (pH 7·5), and E_2, 0·05M sodium hydrogen citrate. Ultraviolet spectra were taken on an Optica Milano CF-4 apparatus. CD spectra were measured on a Roussel-Jouan Dichrograph II Model CD-185 spectropolarimeter.

Starting Material

Acetonitrile was distilled over calcium hydride prior to use. The "silylated" bases, namely, 2,4-bis(trimethylsilyloxy)pyrimidine, 2,4-bis(trimethylsiloxy)-5-methylpyrimidine, and 2-trimethylsilyloxy-4-(N-trimethylsilylacetamido)pyrimidine were prepared according to Wittenburg[15] with the use of trimethylchlorosilane as catalyst. The procedure was as follows. A mixture of 0·1 mol of the base (uracil, thymine or N^4-acetylcytosine), hexamethylsilazane (25 ml), and trimethylchlorosilane (2·5 ml) was refluxed until the starting base dissolved (1–5 hours). The unreacted silylation mixture was removed by distillation at 100°C/15 Torr and the residue fractionated at 140–150°C (bath temperature)/0·1 Torr (with uracil and thymine derivatives). In the case of the cytosine derivative, the crystalline destillation residue was directly used in the subsequent reaction. Methyl 3,4,6-tri-O-*p*-toluyl-1-bromo- and methyl 3,4,6-tri-O-*p*-toluyl-1-chloro-1-deoxy-β-D-psicofuranosides (*XVI* and *XVII*) were prepared according to a reported procedure[16].

Protected Nucleosides *IV*—*IX* (Silylation Process, Method A)

A solution of the methyl glycoside *XVI* or *XVII* (15 mmol) in methylene chloride (45 ml) was treated under ice-cooling with a 30% solution of hydrogen bromide in acetic acid (45 ml). The mixture was allowed to stand for 30 minutes in ice and for 10 minutes at room temperature, diluted with additional methylene chloride (75 ml), and poured onto ice. The organic layer was separated, washed successively with three 20 ml portions of ice-cold water and three 25 ml portions of a precooled (0°C) saturated aqueous solution of sodium hydrogen carbonate, dried at 0°C over anhydrous sodium sulfate for 1 hour, and evaporated under diminished pressure.

TABLE I

Ultraviolet and CD Spectra (λ, in nm) of Free Nucleosides *I*—*III* (water) and Their Peracetyl Derivatives *XIII*—*XV* (96% ethanol)

Compound	λ_{max} (log ε)	$10^{-3} . [\Theta] (\lambda)$	
I	263 (3·97), 208 (3·87)	+5·18 (266), + 3·28 (212)	
II	270 (3·96), 208 (3·86)	+4·08 (272), — 0·28 (239),	+5·29 (218)
III	272 (3·91)	+4·81 (272), — 1·25 (235),	+1·16 (219)
XIII	261 (4·07), 210 (4·01)	+5·18 (264), +10·19 (212)	
XIV	266 (3·88), 214 (3·71)	+5·16 (272), +14·35 (217)	
XV	262 (4·03)	—	

TABLE II

Paper Chromatography (R_F values) and Electrophoresis (mobility in cm)

Compound	S_1	S_2	E_1	E_2
I	0·50	0·61	6·5	— 1·1
Uracil	0·42	0·55	—3·0	— 1·5
Uridine	0·36	0·49	6·8	— 0·9
II	0·60	0·71	6·7	— 1·2
Thymine	0·57	0·65	—2·6	— 1·4
5-Methyluridine	0·43	0·59	7·8	— 0·9
III	0·42	0·71	3·2	—16·6
Cytosine	0·33	0·63	—4·2	—24·6
Cytidine	0·22	0·57	6·1	—14·9

TABLE III

Physical and Chemical Properties of Nucleosides *I*–*XV*

Compound	Yield, % $[\alpha]_D^{25}$	M.p., °C (solvent)	Formula (m.w.)	Calculated/Found % C	% H	% N	% X
I	65[a]	sirup	$C_{10}H_{14}N_2O_6$	46·51	5·46	10·85	
	6·4[e]		(258·2)	45·45	5·92	10·32	
II	72[a]	sirup	$C_{11}H_{16}N_2O_6$	48·53	5·92	10·29	
	−12·0[e]		(272·3)	47·67	6·90	9·56	
III	56[a]	sirup	$C_{10}H_{15}N_3O_5$	46·69	5·88	16·33	
	6·3[e]		(257·25)	46·92	5·74	15·68	
IV	17[b]	184–185	$C_{34}H_{31}BrN_2O_9$	59·06	4·52	4·05	11·56
	32·0[d]	(ethanol)	(691·6)	59·36	4·53	3·93	11·79
V	20[b]	199–200	$C_{35}H_{33}BrN_2O_9$	59·58	4·71	3·98	11·33
	10·7[d]	(methanol)	(705·6)	59·44	4·45	4·03	11·88
VI	16[b]	172–174	$C_{36}H_{34}BrN_3O_9$	59·02	4·68	5·74	10·91
	−9·9[d]	(ethanol)	(732·6)	59·18	4·72	6·09	11·12
VII	14[b]	185–186	$C_{34}H_{31}ClN_2O_9$	63·11	4·83	4·33	5·48
	23·3[d]	(ethanol)	(647·1)	63·22	4·88	4·72	5·73
VIII	20[b]	194–195	$C_{35}H_{33}ClN_2O_9$	63·59	5·03	4·28	5·36
	11·7[d]	(methanol)	(661·1)	63·30	5·12	4·34	5·13
IX	19[b]	197–198	$C_{36}H_{34}ClN_3O_9$	62·83	4·98	6·11	5·15
	−12·3[d]	(ethanol)	(688·15)	63·15	5·17	6·37	5·32
X	90[c]	sirup	$C_{34}H_{32}N_2O_9$	66·66	5·27	4·57	
	13·6[d]		(612·65)	67·01	5·46	4·20	
XI	80[c]	sirup	$C_{35}H_{34}N_2O_9$	67·08	5·47	4·47	
	−3·3[d]		(626·6)	66·89	5·41	4·32	
XII	79[c]	sirup	$C_{36}H_{35}N_3O_9$	66·15	5·40	6·43	
	−29·6[d]		(653·7)	65·88	5·47	6·51	
XIII	11·9[d]	186·5–187[f]	$C_{16}H_{20}N_2O_9$	50·01	5·24	7·29	
			(384·4)	50·19	5·52	7·09	
XIV	−21·8[d]	163–164[g]	$C_{17}H_{22}N_2O_9$	51·25	5·57	7·03	
			(398·4)	51·45	5·76	7·04	
XV	−32·5[d]	172–173·5[f]	$C_{18}H_{23}N_3O_9$	50·82	5·46	9·99	
			(425·4)	50·54	5·56	9·72	

[a] Yields of alkaline methanolysis; [b] yields obtained by method A and related to the methyl glycoside *XVI* and *XVII*, resp.; [c] yields of the tri-n-butyltin hydride reduction; [d] in ethyl acetate, $c = 0{\cdot}5$; [e] in water; [f] di-n-propyl ether–methanol (10 : 1); [g] di-n-propyl ether.

The residual sirup was dissolved in acetonitrile (25 ml) and the solution treated with the silylated base (30 mmol) and mercuric acetate (4·80 g; 15 mmol). The resulting mixture was stirred 12 hours at room temperature and 5 minutes at 50°C. The acetonitrile was removed under diminished pressure at 30°C and the residue was dissolved in chloroform (50 ml). The insoluble portion was filtered off and washed with two 10 ml portions of chloroform. The filtrates were combined, washed successively with three 25 ml portions of 10% aqueous potassium iodide and two 25 ml portions of water, dried over sodium sulfate, and evaporated under diminished pressure. The residue was chromatographed on a column of silica gel in the solvent mixture benzene–ethyl acetate, the ratio of solvents being 2 : 1 (with compound *IV*), 5 : 2 (*V*), 1 : 3 (*VI*), 5 : 2 (*VII*), 3 : 1 (*VIII*), and 1 : 2 (*IX*). For physical and chemical data see Table III.

Compounds *V* and *VI* (Mercuri Process, Method B)

A solution of the bromide *XVIII* (prepared from 1·22 g *i.e.* 2 mmol of the methyl glycoside *XVI*) in acetonitrile (30 ml) was treated with monomercurithymine (0·325 g; 1 mmol) and molecular sieves Potassit 1 (2 g). The mixture was kept at room temperature for 12 hours and then refluxed for 1 hour. The insoluble portion was filtered off and the filtrate processed similarly to method A. Column chromatography on silica gel and the subsequent crystallisation afforded 0·065 g (9·1%, based on monomercurithymine) of compound *V*, m.p. 198°C (ethanol), undepressed on admixture with the specimen obtained by method A. An analogous reaction of the mercuric salt of N^4-acetylcytosine (0·35 g; 1 mmol) and the bromide *XVIII* (obtained from 1·22 g *i.e.* 2 mmol of the methyl glycoside *XVI*) followed by chromatography on silica gel and crystallisation afforded 0·021 g of compound *VI* (2·9%, based on the mercuric salt), m.p. 173—174°C (ethanol), undepressed on admixture with the specimen obtained by procedure A.

Protected Nucleosides *X*—*XII*

A solution of compounds *IV*—*VI* (3 mmol) in benzene (75 ml) was treated with tri-n-butyltin hydride (1·40 g; 6 mmol) and 2,2′-azobis(isobutyronitrile) (70 mg), the whole refluxed for 20 minutes, and evaporated under diminished pressure. The residue was chromatographed on a column of silica gel in the solvent system benzene–ethyl acetate, the volume ratio of these solvents being 2 : 1 (with compounds *X* and *XI*) and 1 : 3 (with compound *XII*). For physical and chemical properties of compounds *X*—*XII* see Table III.

Free Nucleosides *I*—*III*

The protected nucleoside *X*—*XII* (2 mmol) was added at 0°C to 0·2M methanolic barium methoxide (45 ml) and the mixture was kept at 0°C under occasional stirring for 12 hours. The resulting mixture was then saturated with carbon dioxide under ice-cooling, treated with several drops of 30% aqueous ammonia, and kept at room temperature for 15 minutes. The precipitate of barium carbonate was then filtered off and washed with two 5 ml portions of water. In the course of several hours, the filtrate deposited methyl *p*-toluylate which was collected with suction and washed with a small volume of water. The filtrates were combined, evaporated under diminished pressure, and the residue chromatographed on a column of silica gel in the solvent ethyl acetate–acetone–ethanol–water, the volume ratio of these solvents being 4 : 1 : 1 : 1 (with compounds *I* and *II*) or 4 : 1 : 2 : 2 (with compound *III*). For physical and chemical properties of compounds *I*—*III* see Table III.

Acetylated Nucleosides *XIII*—*XV*

A mixture of the nucleoside *I*—*III* (50 mg), acetic anhydride (1 ml), and pyridine (2 ml) was kept at room temperature for 12 hours, diluted with methanol (2 ml), kept at room temperature for additional 2 hours, and evaporated under diminished pressure to dryness. The residue was coevaporated with toluene and then crystallised from a mixture di-n-propyl ether–methanol (10 : 1). For physical and chemical properties of compounds *XIII*—*XV* see Table III.

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