PREPARATION OF 2-PYRIMIDINONE NUCLEOSIDES FROM URACIL NUCLEOSIDES*

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Received November 10th, 1976

Reaction of benzoylated nucleosides of uracil (*I*) and its 5-substituted derivatives *VI* with phosphorus pentasulfide afforded the perbenzoylated nucleosides of 4-thiouracil *II* and *VII* that are converted on treatment with methyl iodide to nucleosides of 4-methylthio-2-pyrimidinone *III* and *VIII*. Their hydrazinolysis yielded 4-hydrazino-2-pyrimidinones *IV* and *IX*. These compounds are converted on treatment with silver oxide or manganese dioxide to perbenzoylated nucleosides of 2-pyrimidinone *V* and its 5-substituted derivatives *X* from which the free nucleosides were prepared by methanolysis. This route was used to prepare β- (*Vi*) and α-ribofuranoside (*Vm*), β-D-arabinofuranoside (*Vj*), β-D-xylofuranoside (*Vk*), β-D-ribopyranoside (*Vl*) and 2'-deoxy--β-D-ribofuranoside (*Vn*) of 2-pyrimidinone and β-D-ribo or 2'-deoxyribonucleosides of 5-fluoro--2-pyrimidinone (*Xe,f*) and of 5-methyl-2-pyrimidinone (*Xb*). By an analogous sequence of reactions, 2',3',5'-tri-O-acetyluridine (*Ih*) afforded the 2',3',5'-tri-O-acetyl derivative *Vh* and the free 1-(β-D-ribofuranosyl)-4-hydrazino-5-methyl-2-pyrimidinone (*IXb*) gave 1-(β-D-ribofuranosyl)--5-methyl-2-pyrimidinone (*Xb*). The decomposition of 1-methyl-4-hydrazino-2-pyrimidinone (*IVa*) was examined with the use of various metal oxide and metal catalysts. Under the conditions stated, 1-methyl-4-(1-methylhydrazino)- and 1-methyl-4-(2-phenylhydrazino)-2-pyrimidinone (*XI* and *XII*) were not split to the 2-pyrimidinone derivative *Va*.

In view of the marked biological activity of nucleosides derived from 2-pyrimidinone, the preparation and properties of these compounds have been repeatedly examined in this Laboratory[1-5]. The preparative methods consist in nucleosidation of chloromercuri 2-pyrimidinone[3] with halogenoses, reaction of trimethylsilyloxypyrimidine with halogenoses[5] or peracyl sugars in the presence of stannic chloride[6], and reaction of 2-pyrimidinone sodium salt with 2-O-*p*-toluenesulfonyl sugars.[7] In some cases, particularly with less accessible sugars or some substituted 2-pyrimidinones, these methods are not suitable from the preparative point of view. Attention was therefore focussed on a potential conversion of nucleosides of the uracil series to nucleosides of 2-pyrimidinone, namely, on removal of the oxo group from position 4

* Part CXC in the series Nucleic Acid Components and their Analogues; Part CLXXXIX: This Journal *42*, 1890 (1977).

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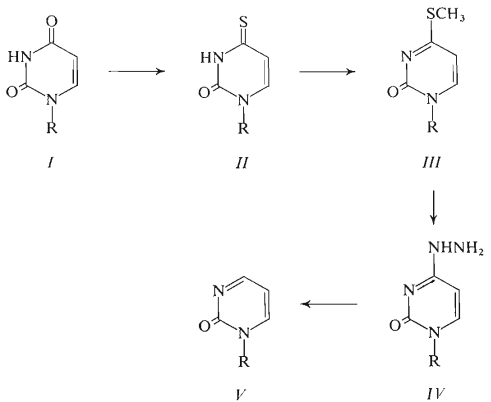
of the uracil moiety. An earlier report on such a conversion by reduction with sodium amalgam[8] did not prove justified[4,9]. Of a greater reliability appears the method consisting in desulfurisation of 4-thiouracil derivatives by means of deactivated Raney nickel as developed in this Laboratory[4] but the danger of the undesirable reduction at position 5,6 of the 2-pyrimidinone ring system still exists. As we have recently reported[10], the cleavage of N^1-alkyl derivatives of 4-hydrazino-2-pyrimidinone (*IV*) with silver oxide readily affords the corresponding N^1-alkyl derivatives of 2-pyrimidinone *V*. Since the starting compounds *IV* are easily accessible from uracil derivatives *I via* the 4-thio derivatives *II* and the 4-methylmercapto derivatives *III* and the reaction takes place with free bases as well as in the presence of various substituents at position N^1, it was desirable to attempt a similar conversion in the series of nucleoside derivatives.



I *II* *III* *IV* *V*

In formulae *I*– *V*:

a, R = CH_3
b, R = 2,3,5-tri-O-benzoyl-β-D-ribofuranosyl
c, R = 2,3,5-tri-O-benzoyl-β-D-arabinofuranosyl
d, R = 2,3,5-tri-O-benzoyl-β-D-xylofuranosyl
e, R = 2,3,5-tri-O-benzoyl-α-D-ribofuranosyl
f, R = 2,3,4-tri-O-benzoyl-β-D-ribopyranosyl
g, R = 3,5-di-O-benzoyl-2-deoxy-β-D-ribofuranosyl
h, R = 2,3,5-tri-O-acetyl-β-D-ribofuranosyl

In formula *V*:

i, R = β-D-ribofuranosyl
j, R = β-D-arabinofuranosyl
k, R = β-D-xylofuranosyl
l, R = β-D-ribopyranosyl
m, R = α-D-ribofuranosyl
n, R = 2-deoxy-β-D-ribofuranosyl

In the first stage, the effect of catalysts and solvents on the cleavage of hydrazino derivatives *IV* was examined. Silver oxide[10] sometimes interferes in isolation and purification of products by the formation of complexes with heterocyclic derivatives. The cleavage was examined with the use of N^1-methyl-(*IVa*) and 1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-4-hydrazino-2-pyrimidinone (*IVb*) as model compounds. The results are shown in Table I. It may be seen that the cleavage of the N^1-methyl derivative *IVa* to compound *Va* can be accomplished in the presence of several oxides or metals (particularly the platinum metals) as catalysts. The reaction proceeds both in water and alcohols or dioxane but always the presence of an at least small amount of water is required. In some instances, *e.g.*, with silver oxide in methanol, the reaction of compound *IVa* is accompanied by the formation of the uracil derivative *Ia* as a by-product (compound *Va* does not change under analogous conditions).

TABLE I

Effect of Catalysts and Solvents on the Cleavage of 4-Hydrazino Derivatives *IVa* (→ *Va* and *Ia*) and *IVb* (→ *Vb*)

Catalyst	Solvents	*Va*, %	*Ia*, %	*Vb*, %
Ag_2O	water (25°C)	60	+[a]	0
	methanol (reflux)	30	70	—
	80% methanol (reflux)	—	—	80
	95% dioxane (reflux)	90	0	80
MnO_2	dioxane (25°C)	57	0	10
	methanol (reflux)	+[a]	—	—
	water (25°C)	+[a]	—	—
MoO_3	dioxane (25°C)	80	20	50
OsO_4	80% dioxane (25°C)	30	70	60[b]
Cr_2O_3, Fe_2O_3, Co_2O_3	80% dioxane (reflux)	0	—	0
	methanol (reflux)	0	—	0
	water (reflux)	0	—	0
Cu	80% dioxane (25°C)	25	0	—
	dioxane (25°C)	0	—	—
	methanol (reflux)	5	70	0
	water (reflux)	5	70	0
Pt, Ru, Pd, Pd/C[c]	dioxane (reflux)	100	0	0
	water (reflux)	80	0	—
	methanol (reflux)	60	0	0
Ag	80% dioxane (reflux)	100	—	0

[a] Small amount; [b] strongly contaminated product; [c] 10% palladium on active charcoal.

In this connection, the corresponding 4-(1-methylhydrazino) and 4-(2-phenylhydrazino) derivatives *X* and *XI* were prepared by reaction of 1-methyl-4-methylthio-2-pyrimidinone (*IIIa*) with methyl- and phenylhydrazine, resp. Under conditions shown in Table I, compounds *X* and *XI* were resistant to the action of catalysts that bring about the cleavage of the 4-hydrazino derivative *IVa*. The conversion *IV* → *V* is thus limited to compounds of the type *IV* with an unsubstituted hydrazino group.

The choice of solvents is restricted with nucleoside derivatives protected in the sugar moiety by acyl groups that increase the stability of the nucleoside bond. In the case of compound *IVb*, silver oxide or manganese dioxide in aqueous ethanol or in aqueous dioxane (Table I) proved to be more suitable catalysts than the platinum metals. The reaction is slow at room temperature and much faster at the reflux temperature of the reaction mixture.

The starting compounds *IV* and *IX* were prepared by a sequence of reactions starting from the nucleoside derivatives of uracil *I* and *VI* that were converted to perbenzoyl derivatives by reaction with benzoyl cyanide in acetonitrile[11]. On treatment with phosphorus pentasulfide in dioxane[12], the 4-thio derivatives *II* and *VII* were obtained and converted in a high yield to the methylmercapto derivatives *III* and *VIII* by the action of methyl iodide in the presence of an equimolar amount of methanolic sodium methoxide. When refluxed in dioxane with an equimolar amount of hydrazine hydrate, compounds *III* and *VIII* are transformed to the 4-hydrazino derivatives *IV* and *IX* free of any by-products. The crystallising ability of the latter compounds is low; with some exceptions amorphous products were obtained after chromatography on silica gel. An analogous procedure was used in another

TABLE II
2-Pyrimidinone Nucleosides *V* and *X*

Compound	Yield %	R_F		E^b	λ_{max}, nm		
		S_3	S_4[a]		pH 1	pH 7	pH 13
Vi	85	0·23	0·63	0·94	312	304	315
Vj	76	0·23	0·64	0·95	312	304	315
Vk	70	0·23	0·60	0·94	312	304	315
Vl	80	0·22	0·61	0·10	310	305	316
Vm	70	0·24	0·60	0·94	310	305	315
Vn	62	0·35	0·68	0	310	306	313
Xb	61	—	0·67	1·0	322	315	
Xe	55	0·21	0·65	0·92	318	318	325
Xf	70	0·27	0·75	0	318	318	325

[a] Uridine, R_F 0·50; [b] electrophoretical mobility referred to uridine; 5-fluorouridine, E = 1·55.

connection by Fox and coworkers[13]. The present technique made possible to develop a general method for the preparation of compounds of the type *IV* and *IX*; in spite of the three-step synthesis, the final yield is high and the product is obtained in pure state[14,15].

The catalytic cleavage of the hydrazino derivatives *IV* and *IX* under the above conditions was smooth. The course of the reaction can be checked by chromatography. After removal of the catalyst, the mixture is purified by chromatography on silica gel or neutral alumina, and derivatives *V* and *X* are isolated by crystallisation.

The ultraviolet spectra of compounds *V* and *X* exhibit a characteristic maximum in the 300 nm region (Table II), *cf.*[3,4]. This maximum also occurs in spectra of benzoyl derivatives *Vb* to *Vg* and *Xa,c,d* (at 280—290 nm) as sharply separated from the main band of aromatic absorption. Typical of the 2-pyrimidinone system is the fluorescence of compounds *V* and *X* which may be observed not only with the free nucleosides but also in the case of the benzoyl derivatives. The ^{1}H-NMR spectra of benzoylated nucleosides *V* and *X* exhibit all the expected signals of sugar protons. The character of these spectra (Table III) confirms the anomeric purity and excludes any changes at the anomeric centre in the course of the reaction sequence. Characteristic signal of the 2-pyrimidinone derivatives is the H_4 multiplet with compounds *V* and *X*, and the doublet of doublets of the H_5 proton with compounds *V* (*cf.*[5]). On the other hand, the H_6 signal of the

TABLE III

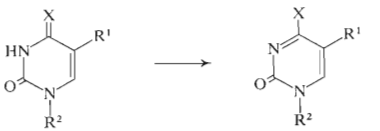
^{1}H-NMR Spectra (deuteriochloroform)

Compound[a]	H_4[b] H_5[c]	H_6	$H_{1'}$	$H_{2'}$ $H_{3'}$	$H_{4'}$ 2 $H_{5'}$
			($J_{1'2'}$)	($J_{2'3'}$)	($J_{4'5'}$)
Vb	8·58 m 6·22 dd	8·05	6·39 d (3·0)	5·86 m	4·80 m
Vc	8·46 m 6·35 dd	8·02 dd	6·90 d (5·0)	5·10—5·80 d	4·20—4·50 m
Vd	8·68 m 6·41 dd	8·05 dd	6·20 (1·0)	5·80 m	4·90—5·10 m 4·45—4·90 m
Ve	8·53 m 6·3 dd	7·96 dd	6·78 d (9·5)	5·48 dd 6·31 t (3·0)	5·58 m 4·15—4·45 m (6·0)
Vh[d]	8·62 t 6·39 dd	8·02 dd	6·07 d (3·0)	5·20—5·60 m	4·10—4·60 m
Xa	8·45 —[c]	—	6·49 d (4·5)	5·79 dd 5·93 t (6·0)	4·79 m 4·94 dd (2·0)

[a] Arom. protons: m (9 H) 7·20—7·70 ppm and m (6 H + H_6) 7·70—8·20 ppm; [b] $J_{4,5}$ = 4·0; [c] $J_{5,6}$ = 7·0; [d] $COCH_3$ s(6 H) 2·13 ppm and s (3 H) 2·09 ppm; [e] $C_{(5)}$—CH_3 s (3 H) 1·82 ppm.

heterocyclic nucleus coalesces with the multiplet of aromatic protons in the 7·8—8·0 ppm region and may be thus assigned only approximately. In the case of the 5-methyl derivative *Xa*, a singlet of the methyl group may be observed at 1·82 ppm in accordance with the structure.

The above method of preparation of nucleosides *V* and *X* is mild enough as confirmed by conversion of 2',3',5'-tri-O-acetyluridine (*Ih*) into the triacetyl derivative *Vh* which was accomplished by the present reaction sequence. Both the thiation of compound *Ih* and the hydrazinolysis of the 4-methylthio derivative *IIIh* are much slower than the analogous reactions of the 2',3',5'-tri-O-benzoyl derivatives *Ib* and *IIIb*. The resulting triacetyl derivative *Vh* is identical with the specimen prepared by another route[5]. The cleavage of hydrazino derivatives *IV* and *IX* may also be applied to the free nucleoside derivative. Thus, methanolysis of compound *IXa* yielded 1-(β-D-ribofuranosyl)-4-hydrazino-5-methyl-2-pyrimidinone (*IXb*), the reaction of which with silver oxide afforded 1-(β-D-ribofuranosyl)-5-methyl-2-pyrimidinone (*Xb*) identical with the specimen prepared by another route[4]. In view of the easier work-up of the reaction mixture and purification of product, the use of benzoyl derivatives is undoubtedly more advantageous.



VI, X = O
VII, X = S

VIII, X = SCH_3
IX, X = $NHNH_2$
X, X = H

In formulae *VI*–*X*:

a, $R^1 = CH_3$, R^2 = 2,3,5-tri-O-benzoyl-β-D-ribofuranosyl
b, $R^1 = CH_3$, R^2 = β-D-ribofuranosyl
c, R^1 = F, R^2 = 2,3,5-tri-O-benzoyl-β-D-ribofuranosyl
d, R^1 = F, R^2 = 3,5-di-O-benzoyl-2-deoxy-β-D-ribofuranosyl
e, R^1 = F, R^2 = β-D-ribofuranosyl
f, R^1 = F, R^2 = 2-deoxy-β-D-ribofuranosyl

The conversion of uracil nucleosides *I* and *VI* to nucleosides of 2-pyrimidinone derivatives *V* and *X* made possible the preparation of numerous protected compounds with modified sugar moiety (*Vb*–*Vh*) and the preparation of ribo- and 2-deoxyribonucleosides of 5-substituted 2-pyrimidinones (*Xa,c,d*). The properties of thus obtained products do not differ from those of materials obtained by other routes[3–5]. The free nucleosides were prepared from benzoyl derivatives by methanolysis and were characterised by chromatography and UV spectra (Table II).

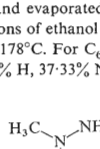
Accessibility of the starting uracil nucleosides *I* and *VI* allows to prepare by the present route the otherwise hardly available nucleoside derivatives of 2-pyrimidinone series including the highly labile nucleosides of 5-fluoro-2-pyrimidinone *Xe,f* which are of biological interest[14-16].

EXPERIMENTAL

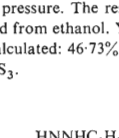
Melting points were taken on a heated microscope (Kofler block) and were not corrected. Solutions were taken down on a rotatory evaporator at 40°C/15 Torr and substances were dried over phosphorus pentoxide at 0·1 Torr. Thin-layer chromatography was performed on ready-for-use Silufol UV_{254} (Kavalier Glassworks, Votice, Czechoslovakia) silica gel sheets in the solvent systems S_1, benzene–ethyl acetate (75 : 25); S_2, chloroform–ethanol (95 : 5); and S_3, chloroform–ethanol (80 : 20). Electrophoresis was carried out on paper Whatman No 3 MM (20 V/cm, 90 min) in 0·1M triethylammonium borate (pH 7·5). Paper chromatography was effected in the solvent system S_4, 2-propanol–conc. aqueous ammonia–water (7 : 1 : 2), on paper Whatman No 1. Preparative separations were performed on 40 × 15 × 0·3 cm layers of indicator-containing silica gel or on columns packed with 100 or 200 g of the Pitra macroporous silica gel, particle size 30—60 μm (both adsorbents are produced by Service Laboratories of this Institute). In the column chromatography, 30 ml fractions were taken. The UV spectra were measured in methanol (the free nucleosides in water) on a Specord apparatus. The ^{1}H-NMR spectra were recorded in deuteriochloroform (hexamethyldisiloxane as internal standard) on a Varian 100 apparatus (chemical shifts in ppm of the δ scale, coupling constants in Hz). The optical rotation was measured (*c* 0·5) in dimethylformamide.

1-Methyl-4-(1-methylhydrazino)-2-pyrimidinone (*XI*)

A mixture of compound[10] *IIIa* (3·12 g; 20 mmol), methylhydrazine (3 ml), and water (100 ml) was refluxed for 5 h and evaporated under diminished pressure. The residue was coevaporated with three 50 ml portions of ethanol and then crystallised from ethanol. Yield, 2 g (65%) of compound *XI*, m.p. 176—178°C. For $C_6H_{10}N_4O$ (154·2) calculated: 46·73% C, 6·54% H, 36·34% N; found: 47·48% C, 6·68% H, 37·33% N. R_F value: 0·20 in S_3.



XI



XII

1-Methyl-4-(2-phenylhydrazino)-2-pyrimidinone (*XII*)

A mixture of compound[10] *IIIa* (1·56 g; 10 mmol), phenylhydrazine (1 g; 10 mmol), and water (100 ml) was refluxed for 48 h, evaporated under diminished pressure, and the residue chromatographed on a column of silica gel (100 g) in the solvent system S_3. The product-containing frac-

tions were pooled, evaporated under diminished pressure, and the residue crystallised from ethanol. Yield, 0·75 g (38%) of compound *XII*, m.p. 207–210°C. For $C_{11}H_{12}N_4O$ (216·2) calculated: 61·09% C, 5·59% H, 25·91% N; found: 59·65% C, 5·67% H, 24·66% N. R_F value: 0·31 in S_3.

1-Methyl-2-pyrimidinone (*Va*)

The reaction was performed with 280 mg (2 mmol) of compound *IVa* and 2 mmol of the catalyst (*cf.*[10]) under conditions given in Table I and checked by chromatography in the solvent system S_3. When the reaction was complete, the mixture was filtered through Celit, washed with the appropriate solvent, and the filtrates were evaporated under diminished pressure. The product was isolated on a layer of silica gel in the solvent system S_3. The product-containing band was eluted with methanol, the eluate evaporated under diminished pressure, and the residue crystallised from ethyl acetate and light petroleum. For the yield see Table I. Compound *Va* was identical (R_F, m.p., UV spectrum) with the specimen prepared earlier[10].

Effect of the Catalyst and Solvents on the Cleavage of Compound *IVb*

The reaction was performed with 5·7 mg (0·01 mmol) of compound *IVb* and 0·01 mmol of the appropriate catalyst in 5 ml of the solvent (see Table I) and checked by chromatography in the solvent system S_2 with the use of compound *Va* as the standard. For the results see Table I.

Nucleoside Benzoates *Ib,f,g* and *VIc,d*

2′,3′,5′-Tri-O-benzoyluridine (*Ib*) and 3′,5′-di-O-benzoyl-2′-deoxyuridine (*Ig*) were prepared according to ref.[11] 1-(2,3,4-Tri-O-benzoyl-β-D-ribopyranosyl)uracil (*If*) was obtained by a reported procedure[21]. 2′,3′,5′-Tri-O-benzoyl-5-fluorouridine (*VIc*) and 3′,5′-di-O-benzoyl-2′-deoxy-5-fluorouridine (*VId*) were prepared according to ref.[17].

1-(2,3,5-Tri-O-benzoyl-β-D-arabinofuranosyl)uracil (*Ic*)

Triethylamine (2 ml) was added to a mixture of 1-(β-D-arabinofuranosyl)uracil[18] (4·0 g; 16·4 mmol), benzoyl cyanide (7·3 g; 56 mmol), and acetonitrile (100 ml) and the whole stirred at room temperature for 2 h. Ethanol (5 ml) was then added, the mixture evaporated under diminished pressure, and the residue crystallised from ethyl acetate. Yield, 7·5 g (82%) of compound *Ic*, m.p. 203°C (reported[19], m.p. 202–203°C); $[\alpha]_D^{25} + 36{\cdot}4°$. ^{1}H-NMR spectrum: 4·57 (br q, 1 H) $H_{4'}$; 4·85 (d, 2 H, $J_{5',4'} = J_{5'',4'} = 5{\cdot}0$) 2 $H_{5'}$; 5·53 (d, 1 H, $J_{5,6} = 8{\cdot}0$, $J_{5,NH} \sim 1$) H_5; 5·71 (dd, 1 H, $J_{3',2'} = 2{\cdot}0$, $J_{3',4'} = 4{\cdot}0$) $H_{3'}$; 5·86 (dd, 1 H, $J_{2',1'} = 4{\cdot}0$, $J_{2',3'} = 2{\cdot}0$) $H_{2'}$; 6·50 (d, 1 H, $J_{1',2'} = 4{\cdot}0$) $H_{1'}$; 7·66 (d, 1 H) H_6; 11·05 (br, 1 H) NH; arom. protons 7·25–7·70 (m, 9 H) + + 7·80–8·15 (m, 6 H).

1-(2,3,5-Tri-O-benzoyl-β-D-xylofuranosyl)uracil (*Id*)

Triethylamine (1 ml) was added to a mixture of 1-(β-D-xylofuranosyl)uracil[20] (6·1 g; 25 mmol), benzoyl cyanide (10·5 g; 80 mmol), and acetonitrile (100 ml) and the whole was stirred at room temperature for 30 min. Ethanol (5 ml) was then added and the mixture evaporated under diminished pressure. The residue was crystallised from ethanol to afford 9·2 g (66%) of compound *Id*, m.p. 118–120°C (reported[20,21], m.p. 116–118°C); $[\alpha]^{25} + 58{\cdot}1°$. ^{1}H-NMR spectrum: 4·70–4·95 (m, 3 H) $H_{4'}$ + 2 $H_{5'}$; 5·67 (t, 1 H) $H_{2'}$; 5·72 (d, 1 H, $J_{5,6} = 8{\cdot}0$, $J_{5,NH} < 1$) H_5;

5·86 (dd, 1 H, $J_{3',2'} = 1·5$, $J_{3',4'} = 3·5$) $H_{3'}$; 6·25 (d, 1 H, $J_{1',2'} = 2·4$) $H_{1'}$; 7·75 (d, 1 H) H_6; 8·70 (br, 1 H) NH; arom. protons 7·25—7·65 (m, 9 H) + 7·90—8·15 (m, 6 H).

1-(2,3,5-Tri-O-benzoyl-α-D-ribofuranosyl)uracil (*Ie*)

Triethylamine (1 ml) was added to a mixture of α-uridine[22] (3·8 g; 15·6 mmol), benzoyl cyanide (9 g; 62 mmol), and acetonitrile (20 ml), the whole stirred at room temperature for 3 h, and evaporated under diminished pressure. The residue was coevaporated with three 20 ml portions of benzene and then chromatographed on a column of silica gel (150 g) in chloroform. The product-containing fractions were pooled, evaporated under diminished pressure, and the residue was crystallised from ethanol. Yield, 7·5 g (86%) of compound *Ie*, m.p. 202°C (reported[23], m.p. 203—205°C); $[\alpha]_D^{25}$ +80·7°; R_F value 0·35 in S_2.

2',3',5'-Tri-O-acetyluridine (*Ih*)

A suspension of uridine (5 g) in acetic anhydride (100 ml) was treated with boron trifluoride etherate (2·5 ml), the mixture stirred at room temperature under exclusion of atmospheric moisture until homogeneous and evaporated at 40°C/0·1 Torr. The residue was coevaporated with two 50 ml portions of toluene at 40°C/0·1 Torr and with three 50 ml portions of ethanol at 40°C/15 Torr. The final residue was dissolved in chloroform (200 ml), the solution washed with water (50 ml) and saturated aqueous sodium hydrogen carbonate until neutral, dried over anhydrous magnesium sulfate, filtered, and the filtrate evaporated under diminished pressure. The residue was crystallised from ethanol to afford 5·1 g (70%) of compound *Ih*, identical with an authentic specimen.

4-Thiouracil Derivatives *II* and *VII*

A mixture of compound *I* or *VI* (10 mmol each), phosphorus pentasulfide (6 g), and dioxane (200 ml) is refluxed under exclusion of atmospheric moisture and the reaction is checked by chromatography in the solvent system S_1. When the reaction is complete, the mixture is filtered through Celit while hot, the material on the filter washed with dioxane, and the filtrates are evaporated under diminished pressure. The residue is dissolved in chloroform or dichloromethane, the solution washed with 50 ml portions of saturated aqueous sodium hydrogen carbonate until neutral, dried over anhydrous magnesium sulfate, filtered, and the filtrate evaporated under diminished pressure. The residue was repeatedly coevaporated with ethanol and then crystallised from ethanol. For the yields (60—90%), properties, and analyses of thus-prepared compounds *II* and *VII* see Table IV.

4-Methylmercapto-2-pyrimidinone Derivatives *III* and *VIII*

To a mixture of compound *II* or *VII* (8 mmol), water (20—40 ml), and methyl iodide (3 ml), a solution of sodium hydroxide (8 mmol) in methanol (30 ml) is added and the whole is stirred at room temperature until the reaction is complete (for 1—2 h), as indicated by chromatography of samples in the solvent system S_1. When crystals of the product deposit, the mixture is diluted with water (200 ml), filtered, the material on the filter washed with water, and crystallised from ethanol. When crystals are not deposited after the addition of water, the mixture is extracted with two 100 ml portions of chloroform, the extracts are combined, washed with two 100 ml portions

of water, dried over anhydrous magnesium sulfate, filtered, and the filtrate is evaporated under diminished pressure. The residue is crystallised from ethanol. For the yields, properties, and analyses of thus-prepared compounds *III* and *VIII* see Table V.

4-Hydrazino-2-pyrimidinone Derivatives *IV* and *IX*

A mixture of compound *III* or *VIII* (7 mmol), dioxane (100 ml), and 80% hydrazine hydrate (0·5 ml) is refluxed until the reaction is complete, as determined by chromatography of samples in the solvent system S_2. The mixture is cooled down and evaporated under diminished pressure. The residue is repeatedly coevaporated with ethanol and then chromatographed on a layer of loose silica gel in the solvent system S_2. The product-containing band is eluted with methanol and the eluate is evaporated under diminished pressure. Yield, 70–95% of the chromatographically homogeneous amorphous product *IV* or *IX*. For yields, properties, and analyses of thus-prepared compounds see Table VI.

TABLE IV

Perbenzoyl Derivatives of 4-Thiouracil Nucleosides *II* and *VII*

Compound yield, %	M.p., °C	$[\alpha]_D^{25}$ [a] R_F in S_1	Formula (mol.weight)	Calculated/Found			
				% C	% H	%N	%S
IIc (68)	112	+124·4° 0·80	$C_{30}H_{24}N_2O_8S$ (572·6)	62·93 61·90	4·23 4·27	4·89 5·62	5·60 6·28
IId (82)	129	+108·8° 0·78	$C_{30}H_{24}N_2O_8S$ (572·6)	62·93 63·66	4·23 4·37	4·89 5·39	5·60 5·78
IIe (82)	118–120	− 84·4° 0·75	$C_{30}H_{24}N_2O_8S$ (572·6)	62·93 63·63	4·23 4·30	4·89 4·98	5·60 5·72
IIf (82)	123	− 14·1° 0·80	$C_{30}H_{24}N_2O_8S$ (572·6)	62·93 63·10	4·23 4·01	4·89 4·75	5·60 5·30
IIg (71)	212	+ 38·5 0·58	$C_{23}H_{20}N_2O_6S$ (452·5)	61·05 60·96	4·46 4·21	6·19 6·07	7·09 7·31
VIIa (87)	192	−112° 0·78	$C_{31}H_{26}N_2O_8S$ (586·6)	63·47 62·77	4·47 5·04	4·78 4·52	5·47 6·35
VIIc (85)	162	− 89·4° 0·79	$C_{30}H_{23}FN_2O_8S$ [b] (590·6)	61·00 61·04	3·92 4·04	4·74 5·06	5·43 6·03
VIId (65)	211	+ 68·2 0·77	$C_{23}H_{19}FN_2O_6S$ [c] (470·5)	58·71 57·69	4·07 4·14	5·96 5·29	6·82 6·71

[a] Dimethylformamide as solvent, *c* 0·5; [b] calculated: 3·22% F, found: 3·14% F; [c] calculated: 4·04% F, found: 4·10% F.

Perbenzoyl Derivatives of 2-Pyrimidinone Nucleosides *V* and *X*

A. A mixture of compound *IV* or *IX* (1 mmol), silver oxide (350 mg), and ethanol (50 ml) is refluxed until the reaction is complete (for 2–3 h, as indicated by chromatography in the solvent system S_2), filtered through Celit, the material on the filter washed with ethanol, and the filtrates are evaporated under diminished pressure. The residue is dissolved in chloroform (100 ml), the solution washed with two 100 ml portions of 10% aqueous potassium iodide, 10% aqueous sodium thiosulfate (50 ml), and water (100 ml), dried over anhydrous magnesium sulfate, filtered and the filtrate evaporated under diminished pressure. The residue is chromatographed on a layer of loose silica gel in solvent systems S_1 or S_2; the product-containing band is eluted with methanol, the eluate evaporated, and the residue crystallised from ethanol. In an alternative, the crude product is dissolved in benzene and chromatographed on a column of neutral alumina (50 g) in benzene. The elution is performed with the use of an ethyl acetate gradient in benzene, the eluate is evaporated, and the residue crystallised from ethanol. Yield, 50–60%.

TABLE V

Perbenzoyl Derivatives of 4-Methylthio-2-pyrimidinone Nucleosides *III* and *VIII*

Compound yield, %	M.p., °C	$[\alpha]_D^{25}$ [a] R_F in S_1	Formula (mol.weight)	Calculated/Found			
				% C	% H	% N	% S
IIIb	212–214	+129·3°	$C_{31}H_{26}N_2O_8S$	63·47	4·47	4·78	5·47
(79)		0·63	(586·6)	63·50	4·70	5·51	5·31
IIIc	145	+131·7°	$C_{31}H_{26}N_2O_8S$	63·47	4·47	4·78	5·47
(88)		0·63	(586·6)	63·47	4·53	5·34	5·91
IIId	89	+134·0°	$C_{31}H_{26}N_2O_8S$	63·47	4·47	4·78	5·47
(90)		0·59	(586·6)	62·01	4·42	4·99	5·76
IIIe	139	− 78·7°	$C_{31}H_{26}N_2O_8S$	63·47	4·47	4·78	5·47
(89)		0·52	(586·6)	64·84	4·53	5·52	5·85
IIIf	192	− 8·06°	$C_{31}H_{26}N_2O_8S$	63·47	4·47	4·78	5·47
(86)		0·57	(586·6)	63·21	4·64	5·08	5·84
IIIg	169	+ 24·8°	$C_{24}H_{22}N_2O_6S$	61·79	4·75	6·01	6·87
(79)		0·38	(466·5)	62·09	4·95	6·39	7·30
VIIIa	83–85	− 37·9°	$C_{32}H_{28}N_2O_8S$	63·98	4·70	4·66	5·34
(94)		0·50	(600·7)	63·37	4·66	5·00	5·37
VIIIc	187	− 17·7°	$C_{31}H_{25}FN_2O_8S$ [b]	61·58	4·17	4·63	5·30
(88)		0·51	(604·6)	61·41	4·20	5·11	5·61
VIIId	174	+ 46·00	$C_{24}H_{21}FN_2O_6S$ [c]	59·49	4·37	5·78	6·62
(82)		0·37	(484·5)	61·56	4·90	5·49	7·23

[a] Dimethylformamide as solvent, *c* 0·5; [b] calculated: 3·14% F, found: 3·31% F; [c] calculated: 3·92% F, found 4·96% F.

B. A mixture of compound *IV* or *IX* (1 mmol), silver oxide (350 mg), dioxane (50 ml), and water (5 ml) is processed according to paragraph *A*. The crude product is chromatographed on a layer of loose silica gel and then crystallised from ethanol.

C. A mixture of compound *IV* or *IX* (1 mmol), manganese dioxide (130 mg), and ethanol (50 ml) is refluxed and processed according to paragraph B. Yields, properties, and analyses of thus-prepared compounds *V* and *X* are shown in Table VII and the ^{1}H-NMR spectra in Table III.

1-(D-Glycosyl)-2-pyrimidinones (*Vi* to *Vn*, *Xb*,*e*, *f*)

A solution of compound *V* or *X* (1 mmol) in methanol (50 ml) is adjusted to pH 9 (moistened pH-paper) by the addition of 0·1M methanolic sodium methylate and then kept at room temperature overnight. The mixture is neutralised with dry Dowex 50 X 8 (H^+) ion exchange resin, filtered, and the resin washed with methanol. The filtrate and washings are combined and evaporated under diminished pressure. The residue is dissolved in water (20 ml), the aqueous solution washed with two 20 ml portions of ether, evaporated, and the residue coevaporated with three

TABLE VI

Perbenzoyl Derivatives of 4-Hydrazino-2-pyrimidinone Nucleosides *IV* and *IX*

Compound yield, %	M.p., °C $[\alpha]_D^{25}$ [a]	R_F in S_1 R_F in S_2	Formula (mol.weight)	Calculated/Found % C	% H	% N
IVb	[d]	0·09	$C_{30}H_{26}N_4O_8$	63·15	4·59	9·82
(88)	+43·15°	0·29	(570·5)	62·80	4·01	10·21
IVc	[d]	0·09	$C_{30}H_{26}N_4O_8$	63·15	4·59	9·82
(87)	+45·25°	0·27	(570·5)	61·60	4·41	10·44
IVd	[d]	0·09	$C_{30}H_{26}N_4O_8$	63·15	4·59	9·82
(91)	+41·38°	0·27	(570·5)	62·53	3·37	10·12
IVe	[d]	0·09	$C_{30}H_{26}N_4O_8$	63·15	4·59	9·82
(75)	−63·52°	0·29	(570·5)	61·99	4·11	9·99
IVg	[d]	0·12	$C_{23}H_{22}N_4O_6$	61·32	4·93	12·45
(84)	−17·2°	0·30	(450·5)	59·94	5·46	11·48
IXa	137[e]	0·10	$C_{31}H_{28}N_4O_8$	63·69	4·83	9·58
(74)	−47·69°	0·25	(584·6)	57·56	5·00	11·06
IXc	138–140[f]	0·01	$C_{30}H_{25}FN_4O_8$ [b]	61·22	4·28	9·52
(85)	−69·9°	0·23	(588·5)	58·17	4·49	10·38
IXd	87[e]	0·05	$C_{23}H_{21}FN_4O_6$ [c]	58·97	4·52	11·96
(94)	−14·7	0·32	(468·4)	57·64	4·41	11·77

[a] Dimethylformamide as solvent, *c* 0·5; [b] calculated: 3·23% F, found: 3·01% F; [c] calculated: 4·06% F; found: 3·87% F; [d] amorphous foam; [e] ethyl acetate–light petroleum; [f] ethanol.

20 ml portions of ethanol under diminished pressure. The final residue is chromatographed on a layer of loose silica gel in the solvent system S_3, the product-containing band eluted with methanol, the eluate evaporated, and the residue dried under diminished pressure. For yields and properties of thus-prepared nucleosides see Table II.

1-(2,3,5-Tri-O-acetyl-β-D-ribofuranosyl)-4-hydrazino-2-pyrimidinone (*IVh*)

A mixture of 2′,3′,5′-tri-O-acetyluridine (*Ih*; 3·7 g; 10 mmol), phosphorus pentasulfide (6 g), and dioxane (300 ml) is refluxed for 10 h, filtered while hot, the material on the filter washed with dioxane, and the combined filtrates evaporated under diminished pressure. The residue is dissolved in chloroform (100 ml), the solution washed with 50 ml portions of saturated aqueous sodium hydrogen carbonate and two 100 ml portions of water, dried over anhydrous magnesium sulfate, filtered, and the filtrate evaporated under diminished pressure. The residual foamy 2′,3′,5′-tri-O-acetyl-4-thiouridine (*IIh*; 90%) in dioxane (100 ml) and water (20 ml) is successively

TABLE VII

Perbenzoyl Derivatives of 2-Pyrimidinone Nucleosides *V* and *X*

Compound yield, %	M.p., °C	$[\alpha]_D^{25}$ [a]	R_F (S_2)	Formula (mol.weight)	Calculated/Found		
					% C	% H	% N
Vb (37—60)	154	+ 14·44°	0·40	$C_{30}H_{24}N_2O_8$ (540·5)	66·66 66·33	4·48 4·65	5·18 5·57
Vc (83)	129	+ 68·6°	0·40	$C_{30}H_{24}N_2O_8$ (540·5)	66·66 63·40	4·48 4·84	5·18 5·48
Vd (83)	91—92	— 12·0°	0·42	$C_{30}H_{24}N_2O_8$ (540·5)	66·66 65·70	4·48 4·63	5·18 5·52
Ve (63)	224	— 36·92°	0·35	$C_{30}H_{24}N_2O_8$ (540·5)	66·66 66·13	4·48 4·44	5·18 5·15
Vf (63)	81	−135·0°	0·36	$C_{30}H_{24}N_2O_8$ (540·5)	66·66 65·65	4·48 4·66	5·18 5·88
Vg (51)	—	+ 36·6°	0·39	$C_{23}H_{20}N_2O_6$ (420·4)	65·70 67·13	4·79 4·73	6·66 5·05
Xa (50)	203	+ 18·23°	0·37[b]	$C_{31}H_{26}N_2O_8$ (554·6)	67·13 67·65	4·73 4·81	5·05 5·40
Xc (86)	91—93	+19·3°	0·48	$C_{30}H_{23}FN_2O_8$ (558·5)	64·51 62·58	4·15 4·09	5·02[c] 4·89
Xd (80)	140	— 27·90	0·52	$C_{23}H_{19}FN_2O_6$ (438·4)	63·01 62·61	4·37 4·16	6·39[d] 6·17

[a] Dimethylformamide as solvent, *c* 0·5; [b] R_F 0·18 in S_1; [c] calculated: 3·40% F, found: 3·37% F; [d] calculated: 4·33% F, found: 4·48% F.

treated with methyl iodide (3 ml) and sodium hydroxide (9 mmol) in methanol (20 ml). The whole is stirred at room temperature until the reaction is complete (as indicated by chromatography of samples in the solvent system S_2) and evaporated under diminished pressure. The residue is chromatographed on a column of silica gel (200 g) in the solvent system S_2. Fractions containing the compound *IIIh* are pooled, evaporated, and the residue is dried to afford 2·2 g (61%) of compound *IIIh* as an amorphous foam, R_F value 0·25 in S_2. A mixture of this product (5·5 mmol), dioxane (50 ml), and 80% hydrazine hydrate (0·5 ml) is refluxed until the reaction is complete (as indicated by chromatography of samples in the solvent system S_3), evaporated under diminished pressure, and the residue chromatographed on two layers of loose silica gel in 9 : 1 chloroform–ethanol. The product-containing band is eluted with methanol, the eluate evaporated under diminished pressure, and the residue crystallised from ethyl acetate–light petroleum. Yield, 1·25 g (60%) of compound *IVh*, m.p. 117°C. For $C_{15}H_{20}N_4O_8$ (384·3) calculated: 46·88% C, 5·23% H, 14·58% N; found: 47·36% C, 5·20% H, 13·91% N. R_F values: 0·35 in S_2 and 0·16 in S_3.

1-(2,3,5-Tri-O-acetyl-β-D-ribofuranosyl)-2-pyrimidinone (*Vh*)

A mixture of compound *IVh* (2 mmol) and silver oxide (0·7 g) was processed analogously to the preparation of benzoyl derivatives *V* and *X*, procedure *B*. Yield, 0·5 g (70%) of compound *Vh* which was crystallised from ethyl acetate–light petroleum; $[\alpha]_D^{20}$ +26·7°. For $C_{15}H_{18}N_2O_8$ (354·3) calculated: 50·85% C, 5·12% H, 7·90% N; found: 49·48% C, 5·18% H, 7·03% N.

1-(β-D-Ribofuranosyl)-5-methyl-2-pyrimidinone (*Xb*)

A solution of compound *IXa* (584·6 mg; 1 mmol) in methanol (20 ml) was adjusted to pH 9 (moistened pH-paper) by the addition of 0·1M methanolic sodium methoxide, the whole kept at room temperature overnight, neutralised with dry Dowex 50 X 8 (H^+) ion exchange resin, filtered, the resin washed with methanol, and the combined filtrates evaporated under diminished pressure. The residue was dissolved in water (10 ml), the aqueous solution extracted with two 10 ml portions of ether, and the aqueous phase evaporated. The residual compound *Xa* was coevaporated with two 10 ml portions of ethanol. A mixture of compound *Xa* (136 mg, 0·5 mmol), ethanol (25 ml), and silver oxide (150 mg) was refluxed until the reaction was complete (as indicated by chromatography of samples in the solvent system S_3), filtered through Celit, the material on the filter washed with ethanol, and the combined filtrates were evaporated under diminished pressure. The residue was purified by chromatography on a layer of loose silica gel in the solvent system S_3. The product was eluted with methanol, the eluate evaluated under diminished pressure, and the residue crystallised from ethanol. Yield, 75 mg (61%) of compound *Xb*, m.p. 178°C. For $C_{10}H_{14}N_2O_5$ (242·2) calculated: 49·58% C, 5·83% H, 11·56% N; found: 49·19% C, 6·10% H, 11·36% N.

The authors wish to thank Professor V. Herout, Director of this Institute, for making possible the scientific visit of one of them (D. C.). Thanks are also due to Mrs B. Kopecká for excellent technical assistance, Dr M. Masojídková for measurement and interpretation of ^{1}H-NMR *spectra, and Mrs Z. Ledvinová for measurement of optical rotations.*

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Translated by J. Pliml.