3′-Deoxynucleosides. IV. Pyrimidine 3′-Deoxynucleosides

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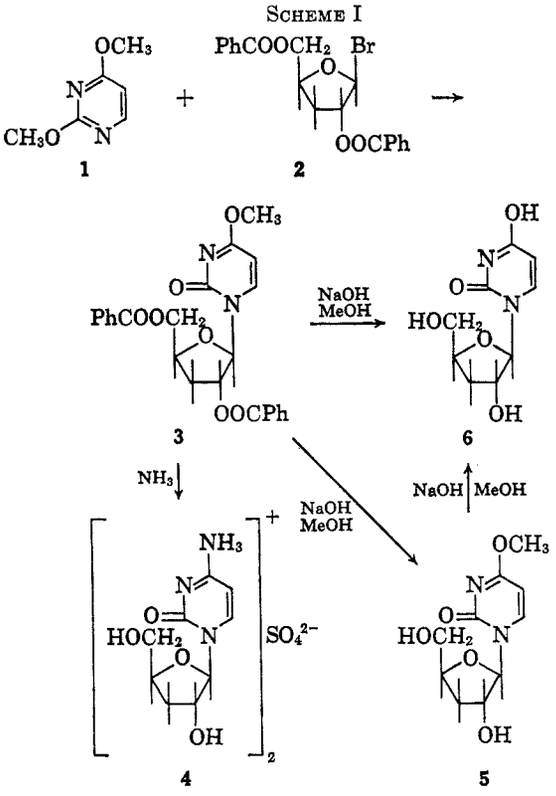
The 1-(3-deoxy-D-ribofuranosyl) derivatives of uracil, cytosine, thymine, and 5-methylcytosine have been synthesized *via* Hilbert–Johnson reactions of 2,5-di-O-acyl-3-deoxy-D-ribofuranosyl bromide with the appropriate 2,4-dialkoxypyrimidine followed by methanolysis or ammonolysis. Both the α and β anomers were produced although the *trans* rule predicts that only *trans* (β) coupling products would be formed. The optical rotations of the α and β anomeric pairs were found to be the reverse of those predicted by Hudson's rules of isorotation. Assignments of the anomeric configuration of the products and intermediates were made, in part, on the basis of nmr as well as optical rotatory dispersion. Some properties characteristic of the α and β anomers are tabulated.

Previous publications[1] have described the synthesis of several purine 3′-deoxynucleosides *via* coupling reactions between 2,5-di-O-benzoyl-3-deoxy-D-ribofuranosyl bromide (2,5-di-O-benzoyl-3-deoxy-D-*erythro*-pentofuranosyl bromide) and the appropriate chloromercuripurine. The interesting biological and biochemical properties of these products prompted the synthesis of the pyrimidine 3′-deoxynucleosides which are described in this paper.

Examination of the literature[2] led to the conclusion that, for the synthesis of pyrimidine 3′-deoxynucleosides, the mercuri procedure would be the method of choice. However, attempts to react 3-deoxy-D-ribofuranosyl bromide as either its 2,5-di-O-acetyl or 2,5-di-O-benzoyl derivative with dithyminylmercury or N-acetylcytosinemercury by the usual procedures either failed completely or gave only very small yields of the desired products. The exact reason for the failure of the mercuri procedure in reactions of 3-deoxy-D-ribofuranosyl halides with these pyrimidinemercury derivatives, in view of several successful syntheses[1] using this halo sugar with chloromercuripurines, has not been determined.[3]

Because of our inability to synthesize useful amounts of the pyrimidine 3′-deoxynucleosides by the mercuri procedure, their synthesis by the Hilbert–Johnson[4] method was undertaken. In the first of these syntheses (shown in Scheme I), 2 equiv of 2,4-dimethoxypyrimidine (**1**)[4] in methylene chloride was stirred with 2,5-di-O-benzoyl-3-deoxy-D-ribofuranosyl bromide (**2**)[1b] for several days. The course of the reaction was very easily followed by tlc. After 3 days, the reaction was judged to be complete and 1-(2,5-di-O-benzoyl-3-deoxy-β-D-ribofuranosyl)-4-methoxy-2(1H)-pyrimidinone (**3**) was separated by chromatography on alumina as an oil which could not be crystallized. Treatment of the pyrimidinone **3** with ammonia in alcohol at 100° gave 3′-deoxycytidine which was isolated as the crystalline sulfate **4**. Partial hydrolysis of the intermediate **3** with aqueous sodium hydroxide in methanol at 60° for 1 hr yielded crystalline 1-(3-deoxy-β-D-ribofuranosyl)-4-methoxy-2(1H)-pyrimidinone (**5**) from which the benzoyl blocking groups of the sugar moiety had been removed. If the hydrolysis of **3** was allowed to proceed for 7 hr, completely unblocked 3′-deoxyuridine (**6**) was obtained. In a similar manner the intermediate hydrolysis product **5** was also converted to 3′-deoxyuridine (**6**).

SCHEME I



Because the coupling product **3** in this sequence of reactions was an oil, it was decided to use a 3-deoxyribose derivative that would give intermediates more amenable to crystallization. To this end, methyl 3-deoxy-β-D-ribofuranoside (**7**)[1b] (see Scheme II) was converted to the 2,5-di-O-*p*-nitrobenzoyl derivative **8** which when treated with hydrogen bromide in acetic acid gave 2,5-di-O-*p*-nitrobenzoyl-3-deoxy-β-D-ribofuranosyl bromide (**9**) as a stable, crystalline product in good yield. The β configuration of the anomeric carbon of the bromo sugar **9** as well as the methyl glycoside **8** was assigned on the basis of the low coupling constants shown by the C-1 protons in their nmr spectra. When this new halo sugar **9** reacted with 2,4-dimethoxypyrimidine (**1**) in methylene chloride, crystalline 1-(2,5-di-O-*p*-nitrobenzoyl-3-deoxy-β-D-ribofuranosyl)-4-methoxy-2(1H)-pyrimidinone (**11**) (Scheme III)

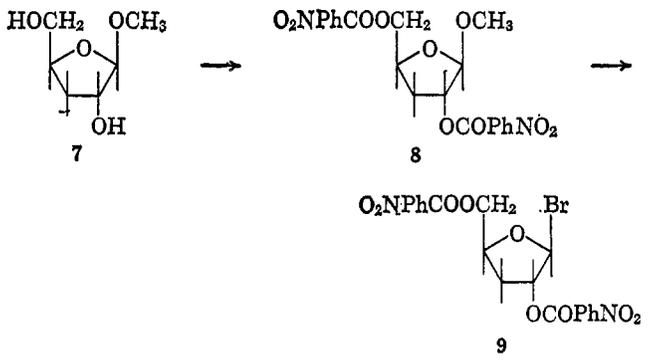
(1) (a) E. Walton, R. F. Nutt, S. R. Jenkins, and F. W. Holly, *J. Am. Chem. Soc.*, **86**, 2952 (1964); (b) E. Walton, F. W. Holly, G. E. Boxer, R. F. Nutt, and S. R. Jenkins, *J. Med. Chem.*, **8**, 659 (1965); (c) S. R. Jenkins, F. W. Holly, and E. Walton, *J. Org. Chem.*, **30**, 2851 (1965).

(2) See, *e.g.*, J. J. Fox and I. Wempen, *Advan. Carbohydrate Chem.*, **14**, 283 (1959).

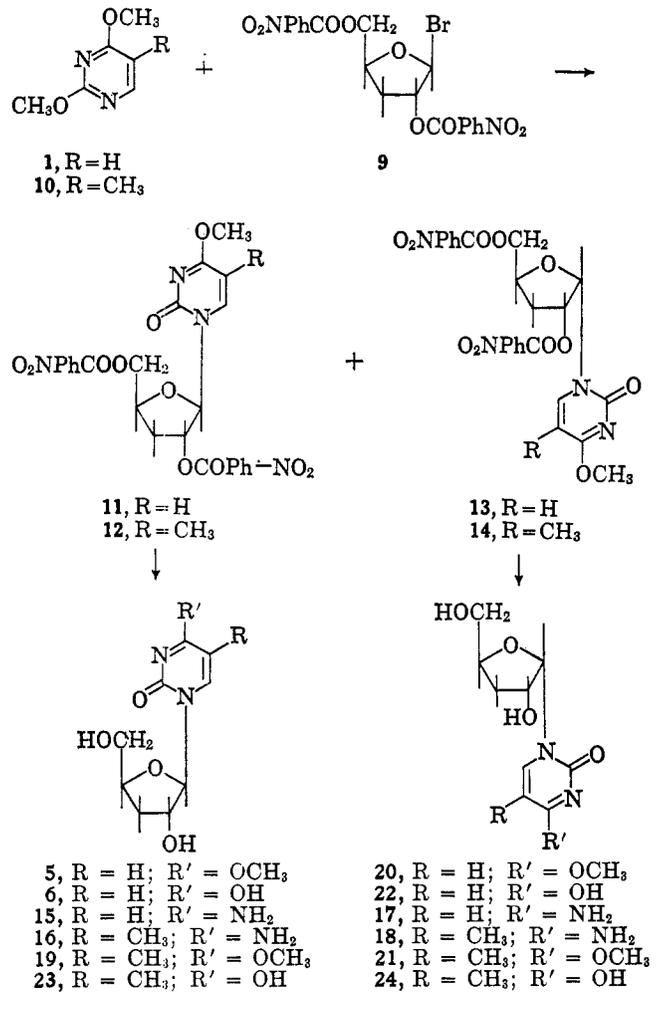
(3) W. W. Zorbach and G. J. Durr, Jr. [*J. Org. Chem.*, **27**, 1474 (1962)] have reported the failure of 2,6-dideoxy-3,4-di-O-*p*-nitrobenzoyl-β-D-*ribo*-hexopyranosyl chloride to give the desired nucleoside in reactions with mercury derivatives of thymine.

(4) G. E. Hilbert and T. B. Johnson, *J. Am. Chem. Soc.*, **52**, 2001, 4489 (1930).

SCHEME II



SCHEME III



was obtained after fractional crystallization and chromatography on alumina.

From the chromatography, a second crystalline product was obtained which from its properties (R_f, ultraviolet and infrared absorption spectra, melting point, and analysis) was a 1-substituted pyrimidinone, isomeric with **11**. It was concluded that this second product was the α anomer, 1-(2,5-di-O-*p*-nitrobenzoyl-3-deoxy-α-D-ribofuranosyl)-4-methoxy-2(1H)-pyrimidinone (**13**). The formation, in substantial yields, of the α anomer from a halo sugar bearing a 2-acyloxy function capable of neighboring group participation was at the time unexpected and constitutes another exception to the *trans* rule.[5] Similar results from Hilbert–Johnson reactions have already been reported in the synthesis of 1-D-ribopyranosylthymine[6] as well as 1-D-ribofuranosylthymine.[7] More recent publications report[8] the isolation of both the α and β anomers of nucleosides from fusion reactions involving polyacyl sugar halides and trimethylsilyloxy derivatives of pyrimidines. The optical rotations (see Table I) of the anomeric products **11** and **13** failed, as did those of the pyrimidine nucleosides reported earlier,[2,6-8,9a] to conform to Hudson's isorotation rules.[9b]

Treatment of the β intermediate **11** with alcoholic ammonia at 100° gave 3′-deoxycytidine (**15**) which in this case was isolated as the crystalline free base, whereas previously it had been isolated as the sulfate **4**. The anomeric form, 1-(3-deoxy-α-D-ribofuranosyl)-cytosine (**17**), was obtained when the α intermediate **13** was heated with alcoholic ammonia. Stepwise deblocking of both intermediate coupling products **11** and **13**, first with sodium methoxide in methanol to remove the *p*-nitrobenzoyl groups and finally with methanolic hydrogen chloride to cleave the 4-methoxyl group gave both 3′-deoxyuridine (**6**) and its α isomer (**22**) as well as the α and β forms of 1-(3-deoxy-D-ribofuranosyl)-4-methoxy-2(1H)-pyrimidinone (**20** and **5**).

In a similar manner 2,4-dimethoxy-5-methylpyrimidine (**10**)[4] in reaction with 2,5-di-O-*p*-nitrobenzoyl-3-deoxy-β-D-ribofuranosyl bromide gave both the α and β anomers of 1-(2,5-di-O-*p*-nitrobenzoyl-3-deoxy-D-ribofuranosyl)-4-methoxy-5-methyl-2(1H)-pyrimidinone (**14** and **12**) which were converted by ammonolysis into the α and β anomers of 1-(3-deoxy-D-ribofuranosyl)-5-methylcytosine (**18** and **16**). Stepwise removal of the *p*-nitrobenzoyl groups and cleavage of the 4-methoxy substituent from both **14** and **12** produced the α and β forms of 1-(3-deoxy-D-ribofuranosyl)-thymine (**24** and **23**) as well as the intermediate pyrimidinones **21** and **19**.

The experience gained in the synthesis of these new pyrimidine 3′-deoxynucleosides in which both the α and β forms were obtained in practical yield makes it appear likely that the Hilbert–Johnson reaction may be a generally useful method for obtaining both the α and β anomers of pyrimidine nucleosides.[10]

Configurational Assignments.—That all of the 3′-deoxynucleosides reported in this paper are 1-substituted pyrimidines is clearly indicated by the similarity of their ultraviolet absorption spectra at various

(5) B. R. Baker, Ciba Foundation Symposium, Chemistry and Biology of Purines, Little, Brown and Co., Boston, Mass., 1957, p 120.

(6) T. Naito and T. Kawakami, *Chem. Pharm. Bull.* (Tokyo), **10**, 627 (1962).

(7) J. Farkaš, L. Kaplan, and J. J. Fox, *J. Org. Chem.*, **29**, 1469 (1964).

(8) (a) T. Nishimura, B. Shimizu, and I. Iwai, *Chem. Pharm. Bull.* (Tokyo), **12**, 1471 (1964); (b) T. Nishimura and B. Shimizu, *ibid.*, **13**, 803 (1965).

(9) (a) M. Hofer, R. Duschinsky, J. J. Fox, and N. Yung, *J. Am. Chem. Soc.*, **81**, 4112 (1959); (b) C. S. Hudson, *ibid.*, **31**, 66 (1909).

(10) It should be noted that there was evidence that the α anomer of 1-(2,5-di-O-benzoyl-3-deoxy-D-ribofuranosyl)-4-methoxy-2(1H)-pyrimidinone (**3**) was also produced in the reaction of the halo sugar **2** with 2,4-dimethoxypyrimidine (**1**). Tlc of the crude reaction product showed a zone with an R_f in keeping with that to be expected for the α anomer of **3**. However, a comparison of the relative zone sizes indicated that the ratio of α anomer to β anomer produced in these reactions was higher when the *p*-nitrobenzoyl-blocked sugar was used than in the case where the blocking groups were benzoyl. Apparently, the α–β anomer ratio is a function of the nature of the participating 2-acyloxy group. This observation concurs with the proposal of M. Prystaš and F. Šorm [*Collection Czech. Chem. Commun.*, **29**, 2956 (1964)] that the protecting groups of the sugar component as well as the electronegativity of the substituent in the 5-position of the pyrimidine affect the ratio of anomers produced in the Hilbert–Johnson reaction. The possibility of selecting conditions to control the ratio of anomers produced may enhance the preparative value of this method for synthesizing pyrimidine nucleosides.

TABLE I

PHYSICAL CONSTANTS OF 1-(2,5-DI-O-*p*-NITROBENZOYL-3-DEOXY-D-RIBOFURANOSYL)-4-METHOXY-2-(1H)-PYRIMIDINONES

Compd (configuration)	$[\alpha]_D$, deg (*c*, $CHCl_3$)	λ_{max}^{Nujol}, μ (ester)	Nmr ($H_{1'}$) τ^{CDCl_3}	Nmr ($H_{1'}$) $J_{1',2'}$, cps	Tlc R_f[a]
11 (β)	−9.2 (1.09)	5.78, 5.83	3.95	1.3	0.41
13 (α)	−237 (1.02)	5.77	3.54	3.8	0.32
12 (β)	−27 (0.67)	5.81, 5.86	3.79	1.3	0.64
14 (α)	−222 (0.23)	5.79	3.41	3.8	0.37

[a] On alumina in chloroform.

TABLE II

PYRIMIDINE 3′-DEOXYNUCLEOSIDES

Compd (configuration)	$[\alpha]_D$, deg	*c*, H_2O	$[\alpha]_{578}$, deg	$\lambda_{max}^{H_2O}$, mμ ($\epsilon \times 10^{-3}$) pH 1	pH 7	pH 13	ORD λ, mμ	ORD [ϕ], deg	*a*	Nmr ($H_{1'}$) τ^{H_2O}	Nmr ($H_{1'}$) $J_{1',2'}$, cps
6 (β)	+25	1.02	+28	263 (10.6)	264 (10.6)	263 (7.6)	282	+9,920	+290	4.21	1.8
				212 (9.1)	212 (9.3)		249	−19,050			
22 (α)	−134	0.134	−142	263 (10.1)	264 (10.5)	263 (7.9)	279	−15,350	−478	3.92	3.9
				205 (8.9)	205 (9.4)	213 (11.2)	244	+32,400			
15 (β)	+54	0.71	+58	282 (13.1)	272 (8.9)	273 (8.9)	291	+10,500			
				216 (7.5)	232 (6.7)	232 (6.8)			+244	4.19	1.3
					215 (7.5)		247	+13,950			
17 (α)	−130	0.73	−141	282 (13.4)	273 (9.4)	273 (9.0)	290	−12,900			
				214 (10.0)	225[a] (8.3)	225[a] (8.2)			−338	3.93	3.5
							249	+20,900			
23 (β)	+1.4	0.44	+2.3	269 (9.5)	269 (9.6)	268 (7.0)	290	+4,600			
									+190	4.19	1.8
							251	−14,400			
24 (α)	−112	0.17	−118	269 (9.9)	269 (10.0)	268 (7.6)	285	−11,100			
									−343	3.93	3.9
							247	+23,200			
16 (β)	+30	0.59	+32	288 (12.5)	278 (8.6)	278 (8.6)[b]	297	−6,530			
				214 (11.0)	225[a] (8.8)	225[a] (8.8)[b]			+180	4.18	1.5
					212 (12.7)	213 (12.7)[b]	252	−12,200			
18 (α)	−141	0.175	−149	289 (12.5)	278 (8.9)	278 (8.7)[b]	296	−10,050			
				210[a] (11.8)	225[a] (8.7)	225[a] (9.3)[b]			−231	3.93	3.5
					212 (12.8)		252	+12,950			

[a] Inflection. [b] pH 11.

pH values to the ultraviolet absorption spectra of authentic 1-substituted pyrimidines.[11] The ultraviolet spectral data for the pyrimidine 3′-deoxynucleosides are recorded in Table II.

In their characterization of the abnormal 5-methyluridine of Roberts and Visser[12] as the α anomer of 1-D-ribofuranosylthymine, Farkaš, Kaplan, and Fox[7] made use of oxidative cleavage of the α-*cis*-glycol of the ribofuranosyl group with metaperiodate to indicate, from the uptake of oxidant, the size of the ring and, from the rotation of the oxidation product, the α configuration of the C-1 position of the carbohydrate moiety. As additional proof of the α configuration these workers noted the resistance of the abnormal α anomer to enzymic glycosyl cleavage with nucleoside phosphorylases under conditions which rapidly brought about splitting of the corresponding β isomer of 1-D-ribofuranosylthymine. However, as the 3′-deoxynucleosides have no α-*cis*-glycol functionality, they are not amenable to oxidative cleavage with metaperiodate. The resistance of 3′-deoxynucleosides[13] to glycosyl splitting by appropriate nucleoside phosphorylases, no matter what the anomeric configuration, precludes the use of enzymes in designating the anomeric configuration of these products. As the chemical and biochemical methods used by Fox and his co-workers could not be used with the 3-deoxynucleosides, other methods were used to assign the anomeric configuration of the isomeric pairs of products reported in this paper.

Several years ago 3′-deoxyuridine was obtained[14] from a synthesis starting with uridine by a route which would not be expected to have altered the β configuration of the anomeric carbon. The very good agreement of the melting point as well as the ultraviolet absorption spectral data of **6** with these properties reported[14] for the 3′-deoxyuridine obtained from uridine support the designation of **6**, obtained by the Hilbert–Johnson method, as 1-(3-deoxy-β-D-ribofuranosyl)uracil.[15] As the isomeric product **22** obtained in the same reaction along with **6** is also a 1-(3-deoxy-D-ribofuranosyl)uracil, it must be the α anomer, 1-(3-deoxy-α-D-ribofuranosyl)uracil (**22**). It should be noted (Table II) that the rotations of the α anomer **22**, $[\alpha]_D$ −134°, and the β isomer **6**, $[\alpha]_D$ +25°, are not in agreement with Hudson's isorotation rules.[9b] These

(11) A complete review of the ultraviolet absorption characteristics of variously substituted pyrimidines is given by Fox and Wempen.[2]

(12) M. Roberts and D. W. Visser, *J. Am. Chem. Soc.*, **74**, 668 (1952).

(13) Private communication from Dr. Morris Zimmerman of these laboratories.

(14) D. M. Brown, D. B. Parihar, A. Todd, and S. Varadarajan, *J. Chem. Soc.*, 3028 (1958).

(15) Unfortunately, no optical rotation of 3′-deoxyuridine was reported by the earlier workers.[14]

rotations do, however, parallel the rotations reported[16] for the anomers of several similarly constituted pyrimidine nucleosides whose rotational relationship was also the reverse of that predicted by Hudson's rules of isorotation. Similarly, for the other pyrimidine 3′-deoxynucleoside anomeric pairs, the more dextrorotatory anomer was assigned[17] the β configuration, whereas the more levorotatory was assigned the α-D configuration as indicated in Table II.

We have also measured the optical rotatory dispersion curves of the pyrimidine 3′-deoxynucleosides. The results, in Table II, which indicate that the α and β anomers show negative and positive Cotton effects, respectively, parallel the results obtained[18] earlier for other 1-pyrimidine D-nucleosides. These new ORD data are significant in that they record the first such measurements on anomeric pairs of nucleosides having a 2-hydroxy group in the sugar moiety. Previously, such data on nucleoside α anomers[18] were restricted to 2′-deoxy compounds.[19]

Although these anomeric configurational assignments obtained by means of optical rotational data seem valid, independent and confirmatory assignments based on nmr data were made. The usefulness of nmr spectra through application of the Karplus curve as an aid in determining the anomeric configuration of pyranoid compounds is firmly established. With furanoid compounds, however, where the exact conformation of the ring is usually neither known nor predictable,[20] the method is somewhat limited.[21] If, *e.g.*, the coupling constant for the $C_{1'}$–$C_{2'}$ protons ($J_{1',2'}$) is low (<2 cps) a definitive *trans* assignment for those protons can be made. On this basis, compounds **6**, **15**, **23**, and **16** having $J_{1',2'}$ values of only 1.8, 1.3, 1.8, and 1.5 cps (see Table II) can be safely assigned the β (*trans*) configuration, and the corresponding anomers **22**, **17**, **24**, and **18** are, then, the α (*cis*) configuration by elimination. Examination of Table I shows that **11** and **12**, the precursors of the β anomers, also show low coupling constants in their nmr spectra for the $C_{1'}$–$C_{2'}$ protons and the designation of **11** and **12** as β anomers and **13** and **14** as α anomers was made on this basis. It is interesting to note that the $C_{1'}$ proton resonances (Table I) of the blocked α intermediates, **13** and **14**, are found at somewhat lower field (about 0.5 and 0.4 ppm) than the corresponding resonances for the β anomers **11** and **12**. Similarly, for the final products, the $C_{1'}$ proton resonances of the α anomers, as shown in Table II, are at lower field (0.25–0.29 ppm) than the corresponding β anomers. This chemical shift may be characteristic of furanoid α-D (*cis*) anomers.[22]

Listed in Table I are other physical properties of the blocked pyrimidine 3′-deoxynucleoside intermediates which are characteristic of their anomeric configuration. For example, the solid state infrared absorption spectra of the acylated pyrimidinones **11** and **12** with the β-D configuration show a split ester carbonyl band, whereas the spectra of **13** and **14** having the α-D configuration show a single, sharp ester carbonyl absorption band. Tlc studies of **11**, **12**, **13**, and **14** on alumina where chloroform was used as the eluent showed that in each anomeric pair the β (*trans*) form was more mobile and gave higher R_f values than the α (*cis*) form.[23] As in the case of the final products listed in Table II, the β anomers of all of the intermediates were more dextrorotatory than the corresponding α anomers.

(16) See, *e.g.*, the rotations reported for the anomers of 1-(2-deoxy-D-ribofuranosyl)-5-fluorouracil, 1-(2-deoxy-D-ribofuranosyl)-5-fluorocytidine, 1-(2-deoxy-D-ribofuranosyl)cytidine, and 1-(2-deoxy-D-ribofuranosyl)thymine by (a) Hoffer, *et al.*,[9a] for the 1-(2-deoxy-D-ribofuranosyl)thymines by (b) R. U. Lemieux and M. Hoffer, *Can. J. Chem.*, **39**, 110 (1961); for the anomers of 1-D-ribofuranosylthymine and 1-D-ribofuranosyl-5-methylcytidine by (c) Farkaš, Kaplan, and Fox;[7] for the 1-D-ribopyranosyl- and 1-D-xylopyranosylthymines by (d) Naito and Kawakami;[6] for the anomers of 1-(2-deoxy-D-ribofuranosyl)-5-hydroxymethyluracil by (e) R. Brossmer and E. Röhm, *Angew. Chem., Intern. Ed. Engl.*, **3**, 66 (1964); for the 1-D-ribofuranosyluracils by (f) Nishimura, Shimizu, and Iwai;[8a] and for the anomeric 1-D-lyxofuranosyl- and 1-D-arabinofuranosyluracils and the corresponding derivatives of thymine by (g) Nishimura and Shimizu.[8b]

(17) In 1959 (see ref 9a) it was recognized that the optical rotations of 1-pyrimidine 2′-deoxy-D-nucleosides did not conform to Hudson's rules, and Fox and Wempen (ref 2, p 340) cautioned that assignment of configuration to derivatives of 2-deoxyribose on the basis of rotational data only is certainly unwarranted. Later Farkaš, Kaplan, and Fox[7] extended this warning to pyrimidine nucleosides in general. On the basis of the rotations reported for the compounds described in ref 16a–e, T. R. Emerson and T. L. V. Ulbricht [*Chem. Ind.* (London), 2129 (1964)] proposed that for all pyrimidine N¹-D-nucleosides Hudson's rules are reversed, whereas for purine N⁹-nucleosides, Hudson's rules are obeyed. However, more recent work has shown that this is not always the case. For example, M. Prystaš and F. Šorm [*Collection Czech. Chem. Commun.*, **29**, 121 (1964)] report, for the anomeric 5-iodo-2′-deoxyuridines, rotations of +21.8° (α) and +7.4° (β). Here, the rotations conform to Hudson's rules in that the α anomer is more dextrorotatory than the β anomer. Similarly for purine nucleosides, L. Vargha and J. Kuszmann [*Ann.*, **684**, 231 (1965)] have reported the rotations of α- and β-9-(2,3-epoxy-D-ribofuranosyl)adenine as $[\alpha]_D$ −91° and $[\alpha]_D$ 0°, clearly contrary to Hudson's rules. It appears that assignment of the anomeric configuration of the anomers of either purine or pyrimidine nucleosides solely on the basis of Hudson's optical rotational rules as modified by Emerson and Ulbricht is also somewhat hazardous especially in those instances involving unusual structural changes in the sugar or aglucone. We were, however, able to make the anomeric configurational assignments of the pyrimidine 3′-deoxynucleosides from their optical rotational properties with reasonable confidence because (1) the pyrimidine portions of these new compounds are the same as those in the nucleosides described in ref 17, all of which show optical rotations which are the reverse of those predicted by Hudson's rules; and (2) the 3′-deoxyribofuranosyl moiety of these compounds is compatible with reversed optical rotations as demonstrated by 3′-deoxyuridine which has been related configurationally to uridine.

(18) (a) Lemieux and Hoffer;[16b] (b) J. T. Tang and T. Samejina, *J. Am. Chem. Soc.*, **85**, 4039 (1963); (c) T. L. V. Ulbricht, J. P. Jennings, P. M. Scopes, and W. Klyne, *Tetrahedron Letters*, **13**, 695 (1964). It should not be inferred, however, that anomeric configurational assignments can be made on the basis of ORD measurements alone. While it is true that the ORD measurements reported both here and in ref 18a–c all show negative Cotton effects for α anomers and positive Cotton effects for β anomers of 1-pyrimidine D-nucleosides, this is not always the case. (d) T. L. V. Ulbricht, T. R. Emerson, and B. J. Swan [*Biochem. Biophys. Res. Commun.*, **19**, 643 (1965)] have recently reported that the α anomers of certain pyrimidine nucleosides show positive Cotton effects, whereas the β anomers show negative Cotton effects. The hope that optical rotational properties could be used, unsupported by other data, for anomeric configurational assignments in either the pyrimidine or purine nucleosides has not as yet been substantiated.

(19) ORD data for several 1-D-pentofuranosylpyrimidines were presented by I. Iwai, B. Shimizu, and T. Nishimura at the 150th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept 12–17, 1965; Abstracts, p 10D.

(20) Progress is being made toward an understanding of the conformation of furanose rings in nucleosides and nucleotides. See, *e.g.*, (a) C. D. Jardetzky, *J. Am. Chem. Soc.*, **84**, 62 (1962); (b) M. Sundaralingam, *ibid.*, **87**, 599 (1965).

(21) For recent reviews on this subject, see (a) R. U. Lemieux and D. R. Lineback, *Ann. Rev. Biochem.*, **32**, 155 (1963); (b) R. J. Ferrier and N. R. Williams, *Chem. Ind.* (London), 1696 (1964); see also B. Capon and D. Thacker, *Proc. Chem. Soc.*, 369 (1964).

(22) Nishimura, Shimizu, and Iwai[8a] and Nishimura and Shimizu[8b] have tabulated nmr spectral data for the α and β anomers of the 1-D-ribo-, D-lyxo-, and D-arabinofuranosylpyrimidines which show that the $C_{1'}$ proton resonances of the $H_{1'}$–$H_{2'}$ *cis* anomers are found at lower field than those of the $H_{1'}$–$H_{2'}$ *trans* anomers.

(23) Nishimura and Shimizu[8b] have listed R_f data for the anomers of unblocked 1-D-arabinofuranosyl- and 1-D-lyxofuranosyluracil and -thymine. Here the β (*cis*) anomers showed greater mobility than the α (*trans*) products.

Experimental Section[24]

1-(2,5-Di-O-benzoyl-3-deoxy-β-D-ribofuranosyl)-4-methoxy-2(1H)-pyrimidinone (3).—A solution of 4.2 g (30 mmoles) of 2,4-dimethoxypyrimidine (**1**)[4] in 200 ml of methylene chloride was treated with 2,5-di-O-benzoyl-3-deoxy-D-ribofuranosyl bromide [from 5 g (14 mmoles) of methyl 2,5-di-O-benzoyl-3-deoxy-β-D-ribofuranoside][18a,b] in 40 ml of methylene chloride and stirred at 25° for 3 days. A small amount of solid which had separated from solution was filtered and the filtrate was concentrated to dryness. Additional solid separated in the residue and it was removed by filtration after adding 10 ml of benzene and 5 ml of petroleum ether (bp 30–60°). The dried by-product (2-hydroxy-4-methoxypyrimidine, 300 mg) melted at 198–202°: $\lambda_{max}^{pH\ 7}$, mμ (ε × 10⁻³), 268 (4.9), $\lambda_{max}^{pH\ 1}$ 271 (4.7), $\lambda_{max}^{pH\ 13}$ 278 (5.8), 218 (9.4).

Anal. Calcd for $C_5H_6N_2O_2$: C, 47.62; H, 4.80; N, 22.22. Found: C, 47.67; H, 4.77; N, 22.22.

The filtrate was concentrated and the residual oil (9.9 g) was dissolved in 500 ml of ether and washed with two 100-ml portions of cold 5% hydrochloric acid to remove the excess 2,4-dimethoxypyrimidine. The dried ether solution was concentrated and the residual oil was chromatographed on alumina in chloroform. Fractions were pooled on the basis of tlc on alumina in chloroform and 1.52 g (25%) of chromatographically pure 1-(2,5-di-O-benzoyl-3-deoxy-β-D-ribofuranosyl)-4-methoxy-2(1H)-pyrimidinone (**3**,) R_f 0.40, was obtained. Another 700 mg (11%) of slightly less pure product was obtained by combining several other fractions. This material was used directly in the reactions described below without further characterization.

3′-Deoxycytidine Sulfate (4).—A mixture of 580 mg (1.29 mmoles) of 1-(2,5-di-O-benzoyl-3-deoxy-β-D-ribofuranosyl)-4-methoxy-2(1H)-pyrimidinone (**3**), 3 ml of methanol, and 2.5 ml of concentrated ammonium hydroxide was heated in a sealed tube at 100° for 16 hr. The solvents were removed and the residue was dissolved in 50 ml of water and washed with three 25-ml portions of chloroform to remove benzamide. The water layer was concentrated and the residual oil was dissolved in 25 ml of water. The water solution was treated with 2 g of moist IR45 (OH^-) resin for 8 min. The mixture was filtered and the resin was washed with water. The filtrate and washings were concentrated and the residue was dissolved in 5 ml of ethanol and 2.5 ml of water and adjusted to pH 3 with 5 *N* sulfuric acid. The solvents were removed and several small portions of ethanol were distilled from the residue to remove last traces of water. The dried salt crystallized from ethanol. Recrystallization from 3.5 ml of ethanol gave 97 mg (30%) of 3′-deoxycytidine sulfate (**4**), mp 201–202°. Tlc on cellulose in water showed only one zone (R_f 0.78): [α]D +48°, $[\alpha]_{578}$ +51° (*c* 0.72, water).

Anal. Calcd for $C_{18}H_{28}N_6O_{12}S$: C, 39.13; H, 5.11; N, 15.21. Found: C, 38.88; H, 5.02; N, 15.09.

3′-Deoxyuridine (6).—A solution of 750 mg (1.66 mmoles) of 1-(2,5-di-O-benzoyl-3-deoxy-β-D-ribofuranosyl)-4-methoxy-2(1H)-pyrimidinone (**3**) in 15 ml of methanol and 5 ml of 1.0 *N* sodium hydroxide was heated at 65° for 8 hr. The course of the reaction was followed by periodic examination of the ultraviolet absorption spectrum. The solution was concentrated to dryness and the residue was dissolved in 30 ml of water. The water solution was treated with 6 g of moist Dowex 50 (H^+) resin and, after 5 min the mixture was filtered and washed well with water. The filtrate and washings were extracted with three portions of ether to remove benzoic acid and were concentrated to dryness. The residue was recrystallized from 4 ml of methanol and two crops of product, 147 mg (mp 176–178.5°) and 43 mg (mp 175–178°), were obtained. Recrystallization of the combined crops from 3 ml of methanol gave 160 mg (42%) of 3′-deoxyuridine (**6**), mp 178–179° (lit.[11] mp 178°). Tlc on cellulose in water showed only one zone (R_f 0.88).

Anal. Calcd for $C_9H_{12}N_2O_5$: C, 47.37; H, 5.30; N, 12.28. Found: C, 47.51; H, 5.45; N, 12.02.

1-(3-Deoxy-β-D-ribofuranosyl)-4-methoxy-2(1H)-pyrimidinone (5).—A solution of 0.80 g (1.78 mmoles) of 1-(2,5-di-O-benzoyl-3-deoxy-β-D-ribofuranosyl)-4-methoxy-2(1H)-pyrimidinone (**3**) in 18 ml of methanol and 2.13 ml of 2.5 *N* sodium hydroxide was heated at 60° for 1.5 hr. The solution was cooled to 25° and concentrated to a residue of oil and crystals. The residue in 35 ml of water was stirred with 7 g of Dowex 50 (H^+) resin for 5 min. The pH of the solution dropped from 13 to 3 and at the same time benzoic acid precipitated. The mixture was filtered and the solids were washed with water. The filtrate and washings were washed with three 30-ml portions of ether and concentrated to a residual solid which when recrystallized from 7.5 ml of methanol gave 130 mg of crude product, mp 170–187°. A second crop (70 mg, mp 180–189°) was obtained from the filtrate. Two recrystallizations of 133 mg of the combined crops from methanol gave 67 mg (23%) of 1-(3-deoxy-β-D-ribofuranosyl)-4-methoxy-2(1H)-pyrimidinone (**5**), mp 191–193°, [α]D +82°, $[\alpha]_{578}$ +88° (*c* 0.5, MeOH). Tlc on cellulose in water showed one zone (R_f 0.91): $\lambda_{max}^{pH\ 7}$, mμ (ε × 10⁻³), 273 (6.7), 208 (18.0); $\lambda_{max}^{pH\ 13}$ 274 (6.6); $\lambda_{max}^{pH\ 1}$ 275 (6.6).

Anal. Calcd for $C_{10}H_{14}N_2O_5$: C, 49.58; H, 5.83; N, 11.57. Found: C, 49.66; H, 5.96; N, 11.37.

3′-Deoxyuridine (6). From 5.—A solution of 22.7 mg (0.094 mmole) of 1-(3-deoxy-β-D-ribofuranosyl)-4-methoxy-2(1H)-pyrimidinone (**5**) in 0.9 ml of methanol and 0.1 ml of 1 *N* sodium hydroxide was heated at 60–70° for 7 hr. During this time the ultraviolet absorption maximum shifted from 273 to 264 mμ. The reaction solution was concentrated to dryness and the residue was dissolved in 1 ml of water. The water solution was treated with a small amount of Dowex 50 (H^+) resin and after about 5 min, the pH of the solution had dropped from 11 to 6.4. The resin was removed by filtration and washed with water. The filtrate and washings were concentrated to dryness and three small portions of methanol were concentrated from the residue to remove last traces of water. Two recrystallizations of the residue from methanol gave 11.5 mg (54%) of 3′-deoxyuridine, mp 175.5–177.5°. The infrared absorption spectrum of this product was identical with that of 3′-deoxyuridine produced in the one-step hydrolysis of **3**.

Methyl 2,5-Di-O-*p*-nitrobenzoyl-3-deoxy-β-D-ribofuranoside (8).—A solution of 2.0 g (13.5 mmoles) of methyl 3-deoxy-β-D-ribofuranoside[18a,b] in 50 ml of dry pyridine at 0° was stirred and treated with 7.5 g (40.5 mmoles) of *p*-nitrobenzoyl chloride. The mixture was stirred at 25° for 20 hr, concentrated to 20 ml, and diluted with 100 ml of chloroform. The chloroform solution was washed with three 50-ml portions of saturated sodium bicarbonate and 50 ml of water, dried, and concentrated to 7 g of residual oil. The oil was crystallized from 10 ml of benzene by adding petroleum ether, and 4.6 g of product, mp 106–109°, was obtained. Recrystallization of 4.2 g from a small amount of benzene by adding petroleum ether gave 4.1 g (75%) of methyl 2,5-di-O-*p*-nitrobenzoyl-3-deoxy-β-D-ribofuranoside (**8**): mp 108–110°; [α]D −33.1°, $[\alpha]_{578}$ −34.5° (*c* 1.0, $CHCl_3$); λ_{max}^{MeOH} 258 mμ (ε 27,000); τ^{CDCl_3} 4.9 (C-1 proton, $J_{1',2'}$ = 0 cps).

Anal. Calcd for $C_{20}H_{18}N_2O_{10}$: C, 53.81; H, 4.06; N, 6.28. Found: C, 53.83; H, 3.91; N, 6.29.

2,5-Di-O-*p*-nitrobenzoyl-3-deoxy-β-D-ribofuranosyl Bromide (9).—A warm solution of 3.8 g (8.51 mmoles) of methyl 2,5-di-O-*p*-nitrobenzoyl-3-deoxy-β-D-ribofuranoside (**8**) in 16 ml of acetic acid was cooled to 10° and treated with 1 ml of acetyl bromide. Sixteen milliliters of a cold 33% (w/w) hydrogen bromide in acetic acid solution was added and the mixture was kept at 10° for 20 min during which time a solid precipitated. Tlc on alumina in benzene–chloroform (1:1) showed zones (developed with iodine vapor) at R_f 0.18 (halo sugar), 0.56 (by-product), and 0.66 (starting material). Disappearance of the spot at R_f 0.66 after about 10 min indicated that the reaction was complete. The reaction mixture was concentrated to dryness and three 20-ml portions of dry toluene were removed at reduced pressure to remove last traces of hydrogen bromide and acetic acid. The crystalline residue (mp 118–124°) was recrystallized from 20 ml of methylene chloride and 40 ml of ether which gave 3.4 g (81%) of 2,5-di-O-*p*-nitrobenzoyl-3-deoxy-β-D-ribofuranosyl bromide (**9**): mp 128–131°; [α]D −50°, $[\alpha]_{578}$ −52° (*c* 1.18, CH_2Cl_2); $\lambda_{max}^{CH_2Cl_2}$ 261 mμ (ε 28,900); τ^{CDCl_3} 3.39 (C-1 proton, $J_{1',2'}$ = 0.8 cps).

Anal. Calcd for $BrC_{19}H_{15}N_2O_9$: C, 46.08; H, 3.05; Br, 16.14; N, 5.66. Found: C, 46.04; H, 2.79; Br, 16.44; N, 5.88.

1-(2,5-Di-O-*p*-nitrobenzoyl-3-deoxy-β-D-ribofuranosyl)-4-methoxy-2(1H)-pyrimidinone (11) and 1-(2,5-Di-O-*p*-nitrobenzoyl-3-deoxy-α-D-ribofuranosyl)-4-methoxy-2(1H)-pyrimidinone (13).

(24) All melting points were determined on a micro hot stage and are corrected. Methanol and methylene chloride were dried over Molecular Sieves Type 4A. Solvent concentrations were carried out at reduced pressure in a rotary evaporator. Tlc was carried out on plates dried at ambient temperature and pressure. The zones for the 3′-deoxynucleosides were located by ultraviolet absorption and dilute potassium permanganate spray, whereas those for the blocked intermediates were located with iodine vapor. Column chromatographic separations were performed on short columns with a height:diameter ratio of about 1:1. The nmr spectra were determined using a Varian Associates 4300B spectrometer (60 Mc).

—A solution of 1.51 g (10.8 mmoles) of 2,4-dimethoxypyrimidine (**1**)[4] in 60 ml of dry methylene chloride was treated with a solution of 2.5 g (5.05 mmoles) of 2,5-di-O-*p*-nitrobenzoyl-3-deoxy-β-D-ribofuranosyl bromide (**9**) in 20 ml of dry methylene chloride and stirred at 25° for 5 days. Tlc on alumina in chloroform indicated very little change in composition after 3 days. The reaction solution was washed with two 25-ml portions of 5% hydrochloric acid and with 25 ml of 10% potassium bicarbonate and 10 ml of saturated sodium chloride. The methylene chloride was concentrated and the residual glass was chromatographed on 60 g of alumina in chloroform. Fractions were pooled on the basis of their behavior on tlc. One portion (760 mg) gave from methanol 500 mg of solid, mp 175–190°, which when recrystallized from ethyl acetate–petroleum ether gave 290 mg (11%) of 1-(2,5-di-O-*p*-nitrobenzoyl-3-deoxy-β-D-ribofuranosyl)-4-methoxy-2(1H)-pyrimidinone (**11**): mp 193–194°; λ_{max}^{MeOH} 262 mμ (ε 30,000).

Anal. Calcd for $C_{24}H_{20}N_4O_{11}$: C, 53.34; H, 3.73; N, 10.37. Found: C, 53.47; H, 4.02; N, 10.00.

From the filtrates and another column fraction, an additional 350 mg (total yield 24%) of **11**, mp 191–193°, was obtained after several recrystallizations. A second major column fraction (1 g) gave, after being recrystallized from benzene, 640 mg (24%) of 1-(2,5-di-O-*p*-nitrobenzoyl-3-deoxy-α-D-ribofuranosyl)-4-methoxy-2(1H)-pyrimidinone (**13**): mp 184–186°; λ_{max}^{MeOH} 261 mμ (ε 28,400).

Anal. Found: C, 53.30; H, 3.97; N, 10.31.

3′-Deoxyuridine (6). Alkaline Hydrolysis of 11.—A solution of 580 mg (1.07 mmoles) of 1-(2,5-di-O-*p*-nitrobenzoyl-3-deoxy-β-D-ribofuranosyl)-4-methoxy-2(1H)-pyrimidinone (**11**) in 8 ml of methanol and 3.57 ml of 1 *N* aqueous sodium hydroxide was heated at 75° for 5 hr. The solution was concentrated and the residue was dissolved in 20 ml of water. Treatment of the water solution with 4.5 g of moist Dowex 50 (H^+) resin for 5 min caused *p*-nitrobenzoic acid to precipitate. The mixture was filtered and the solids were washed with water. The filtrate and washings were washed twice with ether and concentrated. Small amounts of methanol were distilled from the residue to remove last traces of water. The residue (217 mg), when crystallized from 3 ml of methanol, gave 150 mg (62%) of 3′-deoxyuridine, mp 176–178°.

1-(3-Deoxy-β-D-ribofuranosyl)-4-methoxy-2(1H)-pyrimidinone (5). Methanolysis of 11.—A suspension of 520 mg (0.963 mmole) of 1-(2,5-di-O-*p*-nitrobenzoyl-β-D-ribofuranosyl)-4-methoxy-2(1H)-pyrimidinone (**11**) in 12 ml of dry methanol was treated with a solution prepared from 38 mg (1.65 mg-atoms) of sodium and 3 ml of dry methanol. The mixture was refluxed for 1 hr and concentrated to dryness. About 20 ml of water was added to the residue and the insoluble methyl *p*-nitrobenzoate was removed and washed well with water. The filtrate and washings were treated with 4 g of wet Dowex 50W-X4 (H^+) resin for 10 min. The resin was removed and washed with water, and the filtrate and washings were extracted with three 30-ml portions of ether. The water layer was filtered and concentrated to dryness and the residue (190 mg) when crystallized from 2 ml of methanol gave 175 mg (75%) of 1-(3-deoxy-β-D-ribofuranosyl)-4-methoxy-2(1H)-pyrimidinone (**5**), mp 187–191°.

1-(3-Deoxy-α-D-ribofuranosyl)-4-methoxy-2(1H)-pyrimidinone (20).—By the method described above for the synthesis of **5**, 760 mg (1.4 mmoles) of 1-(2,5-di-O-*p*-nitrobenzoyl-3-deoxy-α-D-ribofuranosyl)-4-methoxy-2(1H)-pyrimidinone (**13**) was converted to 156 mg (46%) of 1-(3-deoxy-α-D-ribofuranosyl)-4-methoxy-2(1H)-pyrimidinone (**20**), mp 209–211°. Tlc on cellulose in water showed a single spot (R_f 0.91): $[\alpha]_D$ −182°, $[\alpha]_{578}$ −194° (*c* 0.26, water); $\lambda_{max,\,mμ}^{H_2O}$ (ε × 10^{-3}), 275, 204 (6.9, 17.9), $\lambda_{max}^{pH\ 1}$ 276, 210 (6.8, 11.5), $\lambda_{max}^{pH\ 13}$ 275 (7.0).

Anal. Calcd for $C_{10}H_{14}N_2O_5$: C, 49.58; H, 5.83; N, 11.57. Found: C, 49.55; H, 5.80; N, 11.87.

3′-Deoxyuridine (6). Acidic Cleavage of 5.—A suspension of 25 mg (0.103 mmole) of 1-(3-deoxy-β-D-ribofuranosyl)-4-methoxy-2(1H)-pyrimidinone (**5**) in 1 ml of dry methanol was treated with 0.12 ml of a 27% (w/w) solution of hydrogen chloride in dry methanol and the mixture was stirred for 72 hr. Complete solution was obtained during the first few minutes of stirring. The course of the reaction was followed by periodically checking the ultraviolet absorption spectrum of a small sample of the reaction solution under both acidic and basic conditions. After 72 hr no further change in the ultraviolet absorption spectrum was noted and the reaction solution was concentrated to dryness. Two portions of benzene were distilled from the residue in order to remove the last traces of hydrogen chloride. Crystallization of the residue from a small amount of methanol gave 15.1 mg (64%) of 3′-deoxyuridine, mp 176–178°.

1-(3-Deoxy-α-D-ribofuranosyl)uracil (22).—In the manner described above for the synthesis of **6** from **5**, 130 mg (0.54 mmole) of 1-(3-deoxy-α-D-ribofuranosyl)-4-methoxy-2-(1H)-pyrimidinone (**20**) was converted to 56.2 mg (65%) of 1-(3-deoxy-α-D-ribofuranosyl)uracil (**22**), mp 125.5–126.5°. Tlc on cellulose in water shows one zone (R_f 0.88).

Anal. Calcd for $C_9H_{12}N_2O_5$: C, 47.37; H, 5.30; N, 12.28. Found: C, 47.57; H, 5.22; N, 11.99.

3′-Deoxycytidine (15).—A mixture of 300 mg (0.56 mmole) of 1-(2,5-di-O-*p*-nitrobenzoyl-β-D-ribofuranosyl)-4-methoxy-2(1H)-pyrimidinone (**11**) in 3.6 ml of methanol, previously saturated with ammonia at 0°, was heated at 100° in a sealed tube for 20 hr. The clear solution was concentrated to dryness, and 20 ml of water was added to the residue. The insoluble *p*-nitrobenzamide was removed and washed well with water. The filtrate and washings were extracted with three portions of chloroform and concentrated to dryness. Recrystallization of the residual solid from methanol–ether gave 99 mg (80%) of 3′-deoxycytidine (**15**), mp 224–230°. Tlc on cellulose in water shows one zone (R_f 0.75).

Anal. Calcd for $C_9H_{13}N_3O_4$: C, 47.57; H, 5.77; N, 18.49. Found: C, 47.49; H, 5.80; N, 18.53.

1-(3-Deoxy-α-D-ribofuranosyl)cytosine (17).—By the method described above for the preparation of **15**, 300 mg (0.56 mmole) of 1-(2,5-di-O-*p*-nitrobenzoyl-3-deoxy-α-D-ribofuranosyl)-4-methoxy-2(1H)-pyrimidinone (**13**) gave 103 mg (82%) of 1-(3-deoxy-α-D-ribofuranosyl)cytosine (**17**), mp 225–229°.

Anal. Found: C, 47.39; H, 6.02; N, 18.31.

1-(2,5-Di-O-*p*-nitrobenzoyl-3-deoxy-β-D-ribofuranosyl)-4-methoxy-5-methyl-2(1H)-pyrimidinone (12) and 1-(2,5-Di-O-*p*-nitrobenzoyl-3-deoxy-α-D-ribofuranosyl)-4-methoxy-5-methyl-2(1H)-pyrimidinone (14).—A solution of 4.47 g (28.8 mmoles) of 2,4-dimethoxy-5-methylpyrimidine (**10**)[7] in 240 ml of dry methylene chloride was stirred and treated with 6.67 g (13.5 mmoles) of 2,5-di-O-*p*-nitrobenzoyl-3-deoxy-β-D-ribofuranosyl bromide (**9**). The course of the reaction was followed by tlc on alumina in chloroform. After 72 hr the reaction mixture was concentrated to a residual solid. Leaching the residue with ether removed 3.6 g of starting pyrimidine **10** contaminated with a small amount of the β anomer of the desired product. The ether-insoluble solid (7.0 g) was dissolved in chloroform and chromatographed on 70 g of alumina. After removal of a small amount of unreacted pyrimidine, a fraction containing 980 mg of almost pure β-anomer was obtained. Recrystallization of this material from benzene–petroleum ether gave 510 mg of product, mp 163–167°. A second recrystallization from ethyl acetate–petroleum ether gave 420 mg of purified 1-(2,5-di-O-*p*-nitrobenzoyl-3-deoxy-β-D-ribofuranosyl)-4-methoxy-5-methyl-2(1H)-pyrimidinone (**12**): mp 163–167°; λ_{max}^{MeOH} 261 mμ (ε 28,200).

Anal. Calcd for $C_{25}H_{22}N_4O_{11}$: C, 54.15; H, 4.00; N, 10.11. Found: C, 54.16; H, 4.38; N, 10.20.

Further elution of the column with chloroform gave two additional fractions (1.89 g) of predominantly α anomer but containing some of the β anomer. The next column fraction yielded 520 mg of almost pure α anomer. Recrystallization of this material from methanol gave 500 mg of product, mp 217–218°. A second recrystallization from chloroform–methanol gave 440 mg of 1-(2,5-di-O-*p*-nitrobenzoyl-3-deoxy-α-D-ribofuranosyl)-4-methoxy-5-methyl-2(1H)-pyrimidinone (**14**): mp 218–219°; λ_{max}^{MeOH} 260 mμ (ε 26,200).

Anal. Found: C, 54.09; H, 4.08; N, 9.90.

Several recrystallizations of the α-rich fractions gave an additional 710 mg of the α anomer, mp 218–220°. All remaining fractions and the mother liquors from the crystallizations were combined and rechromatographed on a short alumina column. Crystallization of selected fractions gave additional amounts of the pure α and β anomers. A total of 1.3 g (18%) of α- and 2.07 g (28%) of β-1-(2,5-di-O-*p*-nitrobenzoyl-3-deoxy-D-ribofuranosyl)-4-methoxy-5-methyl-2(1H)-pyrimidinone was obtained.

1-(3-Deoxy-β-D-ribofuranosyl)-4-methoxy-5-methyl-2(1H)-pyrimidinone (19).—A solution of 1.54 g (2.78 mmoles) of 1-(2,5-di-O-*p*-nitrobenzoyl-3-deoxy-β-D-ribofuranosyl)-4-methoxy-5-methyl-2(1H)-pyrimidinone (**12**) in 34 ml of dry methanol was treated with a solution prepared from 100 mg (4.35 mmoles) of sodium and 3 ml of dry methanol and the mixture was refluxed for 1 hr. The reaction mixture was worked up in essentially the same manner as that used for 1-(3-deoxy-β-D-ribofuranosyl)-4-methoxy-2(1H)-pyrimidinone (**5**) from **11**. Two recrystallizations of the crude product (640 mg, mp 193–196°) from methanol

gave 258 mg of 1-(3-deoxy-β-D-ribofuranosyl)-4-methoxy-5-methyl-2(1H)-pyrimidinone (**19**), mp 196–198°. Tlc on cellulose in water showed one zone at R_f 0.88: $[\alpha]_D$ +25°, $[\alpha]_{578}$ +27° (*c* 0.77, water); $\lambda_{max}^{H_2O}$, mμ (ε × 10^{-3}), 280 (6.6), 203 (18.6), 215 (infl) (12.0).

Anal. Calcd for $C_{11}H_{16}N_2O_5$: C, 51.56; H, 6.29; N, 10.93. Found: C, 51.26; H, 6.33; N, 10.96.

By reworking the filtrates from the recrystallizations another 186 mg of product, mp 196–198°, was obtained. The total yield was 444 mg (62%).

1-(3-Deoxy-α-D-ribofuranosyl)-4-methoxy-5-methyl-2(1H)-pyrimidinone (21).—By the method described above for the synthesis of **19**, 960 mg (1.73 mmoles) of 2,5-di-O-*p*-nitrobenzoyl-3-deoxy-α-D-ribofuranosyl)-4-methoxy-5-methyl-2(1H)-pyrimidinone (**14**) gave a total of 292 mg (66%) of 1-(3-deoxy-α-D-ribofuranosyl)-4-methoxy-5-methyl-2(1H)-pyrimidinone (**21**), mp 185–187°. Tlc on cellulose in water showed one zone at R_f 0.9: $[\alpha]_D$ −157°, $[\alpha]_{578}$ −166° (*c* 0.22, water), $\lambda_{max}^{H_2O}$, mμ (ε × 10^{-3}), 281 (6.6), 204 (18.9).

Anal. Found: C, 51.42; H, 6.07; N, 11.04.

1-(3-Deoxy-β-D-ribofuranosyl)thymine (23).—A suspension of 395 mg (1.54 mmoles) of 1-(3-deoxy-β-D-ribofuranosyl)-4-methoxy-5-methyl-2(1H)-pyrimidinone (**19**) in 15 ml of methanol was treated with 1.5 ml of 30.6% (w/w) hydrogen chloride in methanol and the solution was kept at 25°. After 6 days no further change in the ultraviolet absorption spectrum could be observed. The solution was concentrated to dryness and one portion of methanol and three successive portions of benzene were distilled from the residue. The residue when crystallized from 1 ml of methanol and 3 ml of ether gave 300 mg (81%) of 1-(3-deoxy-β-D-ribofuranosyl)thymine (**23**) which melted at 96–100°, resolidified, and remelted at 155–157°. For analysis, a sample was twice recrystallized from methanol–ether and dried to constant weight at 56°.

Anal. Calcd for $C_{10}H_{14}N_2O_5$: C, 49.58; H, 5.83; N, 11.57. Found: C, 49.49; H, 5.84; N, 11.22.

1-(3-Deoxy-α-D-ribofuranosyl)thymine (24).—In the manner described above for the synthesis of **23**, 279 mg (1.09 mmoles) of 1-(3-deoxy-α-D-ribofuranosyl)-4-methoxy-5-methyl-2(1H)-pyrimidinone (**21**) gave 200 mg (76%) of 1-(3-deoxy-α-D-ribofuranosyl)-5-methyluracil (**24**), mp 188–191°. Tlc on cellulose in water showed one zone at R_f 0.86.

Anal. Found: C, 49.72; H, 6.07; N, 11.69.

1-(3-Deoxy-β-D-ribofuranosyl)-5-methylcytosine (16).—A mixture of 400 mg (0.72 mmole) of 1-(2,5-di-O-*p*-nitrobenzoyl-3-deoxy-β-D-ribofuranosyl)-4-methoxy-5-methyl-2(1H)-pyrimidinone (**12**) and 5 ml of methanol, saturated with ammonia at 0°, was heated at 100° in a sealed tube for 16 hr. The reaction mixture was worked up as in the synthesis of **15**. Crystallization of the crude product three times from methanol–ether gave a total of 90 mg (52%) of 1-(3-deoxy-β-D-ribofuranosyl)-5-methylcytosine (**16**), mp 223–226°. Tlc on cellulose in water showed one zone at R_f 0.76.

Anal. Calcd for $C_{10}H_{15}N_3O_4$: C, 49.78; H, 6.27; N, 17.42. Found: C, 49.56; H, 6.06; N, 17.76.

1-(3-Deoxy-α-D-ribofuranosyl)-5-methylcytosine (18).—As described above for the preparation of **16**, 300 mg (0.55 mmole) of 1-(2,5-di-O-*p*-nitrobenzoyl-3-deoxy-α-D-ribofuranosyl)-4-methoxy-5-methyl-2(1H)-pyrimidinone (**14**) gave 81 mg (50%) of 1-(3-deoxy-α-D-ribofuranosyl)-5-methylcytosine (**18**), mp 191–192° with a transition at 173°. Tlc on cellulose in water showed a single zone at R_f 0.78.

Anal. Found: C, 49.49; H, 6.23; N, 17.31.

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2-Amino-2-deoxy-D-xylose and 2-Amino-2-deoxy-D-ribose and Their 1-Thioglycofuranosides[1]

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Glycol cleavage of 2-acetamido-2-deoxy-3,4-*O*-isopropylidene-D-glucose diethyl dithioacetal (I) with subsequent aldehyde reduction and acid hydrolysis resulted in a new synthesis of 2-amino-2-deoxy-D-xylose hydrochloride (IV). Improved preparative directions are cited for ethyl 2-acetamido-2-deoxy-1-thio-α-D-xylofuranoside (VII), which on methylsulfonylation and inversion on C-3 by sodium acetate, with subsequent acid hydrolysis, led to a new synthesis of 2-amino-2-deoxy-D-ribose hydrochloride (X). Two crystalline derivatives of a 1-thiofuranoside of X are described which, together with VII, will be used in nucleoside syntheses.

Syntheses of all of the 2-amino-2-deoxypentoses were first reported from this laboratory[2-7] except for the D-*arabino* isomer which was reported by Kuhn and Baschang.[8] Having need of relatively large quantities of 2-amino-2-deoxy-D-xylose[2] and 2-amino-2-deoxy-D-ribose,[5] we have devised new syntheses for these substances. For the former, 2-acetamido-2-deoxy-D-glucose diethyl dithioacetal[9] was converted into its 3,4-di-*O*-isopropylidene cyclic acetal[10] (I) (see Scheme I) and this was oxidized with lead tetraacetate to a syrupy mixture whose main component was undoubtedly the aldehyde II produced by cleavage between C-5 and C-6. Restricted glycol cleavage of a dithioacetal presents difficulties owing to the oxidizability of the sulfur atoms herein present in their most reduced state.[11] II was characterized as its crystalline thiosemicarbazone IIa. Reduction of syrupy, impure II with sodium borohydride produced largely 3,4-di-*O*-isopropylidene-D-xylose diethyl dithioacetal (III) which was charac-

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