(2.0 g, 0.050 mol), water (400 ml), and 95% alcohol (700 ml) was stirred for 18 hr. After several separation steps, the only alkali-soluble material that could be identified was unchanged benzenesulfonamide (0.8 g). Other products included a trace of solid (40 mg) whose melting point (123–125°) and infrared absorption spectrum agreed with those of diphenyl sulfone; a trace of oil whose R_f value suggested its identity as unchanged 1,3-dibromopropene; 3.7 g (19%) of *N*,*N*-di(3-bromallyl)benzenesulfonamide with R_f (benzene) 0.58 and with $n^{25}D$ 1.5801; and 3.1 g (15%) of *N*,*N*-di(3-bromallyl)benzenesulfonamide with R_f (benzene) 0.28 and with $n^{22}D$ 1.5704. The absorption curves for the last two materials were essentially the same, both showing ir (neat) 3075, 1613, 1350, 1170 cm^{-1}; nmr (CCl_4) δ 3.82 (q, 4, J = 4 Hz, $2CH_2N$), 6.15 (m, 4, olefinic H's), and 7.60 ppm (m, 5, aromatic H's). A roughly 1:1 mixture of the last two materials was analyzed.

Anal. Calcd for $C_{12}H_{13}Br_2NO_2S$: C, 36.46; H, 3.29; Br, 40.51. Found: C, 36.42; H, 3.33; Br, 40.70.

1,3-Dibromopropene with the Silver Derivative of Benzenesulfonamide.—The silver salt was prepared[9,10] by adding silver nitrate (0.25 g, 1.5 mmol) in 2 ml of water to a stirred solution of benzenesulfonamide (0.2 g, 1.5 mmol) and sodium hydroxide (0.6 g) in 2 ml of water. The resulting brown-yellow silver derivative of benzenesulfonamide was collected, washed with 95% alcohol and ether, and dried in a desiccator. The derivative weighed 0.33 g and showed mp 220–230° dec.

A heterogeneous mixture of 1,3-dibromopropene (0.2 g, 1 mmol), the silver derivative (0.32 g, 1.2 mmol), and ether (45 ml) was stirred at room temperature for 16 hr. Processing the reaction mixture afforded no sign of *N*-(3-bromallyl)benzenesulfonamide. According to thin layer chromatographic evidence, the viscous oily product contained *N*,*N*-di(3-bromallyl)benzenesulfonamide. This was substantiated by recovery of the same material from column chromatography (neutral alumina) and comparing its nmr curve with the corresponding material obtained from the sodio derivative. The neat crude oil before separation showed an ir peak at 3200 cm^{-1}, an indication that a propargyl group might be present.

(9) A. Hantzsch and E. Voegelen, *Chem. Ber.*, **34**, 3142 (1901).
(10) J. Casella, unpublished work at Boston University.

Registry No.—2 (Ar = Ph), 32111-09-4; **2** (Ar = $C_6H_4CH_3$-*p*), 5577-13-9; **3** (Ar = Ph), 32111-11-8; **4** (Ar = Ph, R = CH_2CH=$CHBr$), 32111-12-9; **4** (Ar = Ph, R = $CH_2C_6H_4NO_2$-*p*), 32207-42-4; **4** (Ar = Ph, R = CH_2COC_6HPh-*p*), 32111-13-0; **4** Ar = Ph, R = CH_2COOEt), 32120-94-8; **4** (Ar = $C_6H_4CH_3$-*p*, R = CH_2Ph), 32120-95-9; **4** (Ar = $C_6H_4CH_3$-*p*, R = $CH_2C_6H_4Br$-*p*), 32120-96-0; **4** (Ar = $C_6H_4CH_3$-*p*, R = CH_2CH=$CHPh$), 32120-97-1; **4** (Ar = $C_6H_4CH_3$-*p*, R = Bu), 32120-98-2; **4** (Ar = $C_6H_4CH_3$-*p*, R = CH_2CH_2Ph), 32120-99-3; **5** (Ar = Ph, R = CH_2CH=$CHBr$), 32121-00-9; **5** (Ar = $C_6H_4CH_3$-*p*, R = $CH_2C_6H_4Br$-*p*), 10504-96-8; **5** (Ar = $C_6H_4CH_3$-*p*, R = CH_2Ph), 1576-37-0; **5** (Ar = Ph, R = $CH_2C_6H_4NO_2$-*p*), 32121-03-2; **5** (Ar = $C_6H_4CH_3$-*p*, R = C_2CH=$CHPh$), 32121-04-3; **5** (Ar = $C_6H_4CH_3$-*p*, R = CH_2CH_2Ph), 5450-75-9; *cis*-1,3-dibromopropene, 32121-06-5; *trans*-1,3-dibromopropene, 32121-07-6; 1,2,3-tribromopropane, 96-21-9; *N*,*N*-di(3-bromoallyl)benzenesulfonamide, 32111-14-1.

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Nucleosides. LXXI. 3′-Amino-3′-deoxyhexopyranosyl Nucleosides. VI. Reactions of Some Mesyloxy Nucleosides[1]

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The reactions of variously mesylated 1-(3-acetamido-3-deoxy-β-D-glucopyranosyl)uracils were studied in order to examine the behavior of their neighboring groups. Alkaline treatment of the 2′,4′,6′-trimesylate (**5**) afforded the 4′,6′-dimesylate of the 2,2′-anhydromanno nucleoside **6** which by further alkaline treatment gave 1-(3-acetamido-2,6-anhydro-3-deoxy-4-*O*-mesyl-β-D-mannosyl)uracil (**7**) and 1-(3-acetamido-2,6-anhydro-3-deoxy-β-D-talosyl)uracil (**8**). The nmr spectra of **7** and **8** were consistent with the bicyclo[2.2.2]octane system for their carbohydrate moieties. Treatment of 1-(3-acetamido-3-deoxy-2,4-di-*O*-mesyl-6-*O*-trityl-β-D-glucosyl)-uracil (**12**) with alkoxide gave the 2,2′-anhydro derivative **13** which was detritylated and then hydrolyzed in alkali to the 4′-mesylate of 3′-acetamidomannosyluracil (**16**). When nucleoside **12** is detritylated first and then treated with alkali, 1-(3-acetamido-3-deoxy-β-D-talopyranosyl)uracil (**19**) was formed which was converted to its crystalline triacetate **20** and hydrogenated to the 5,6-dihydro derivative **21**. The unexpected chemical shift for the 2′-acetoxy signal in the nmr spectrum of **21** relative to **20** was observed and assigned unequivocally by the syntheses and spectral comparison with the analogous 4′,6′-di-*O*-deuterioacetylated derivatives **25** and **26**. Attempts to prepare a 2,6′-anhydro nucleoside **31** from 1-(3-acetamido-2-*O*-acetyl-3-deoxy-β-D-glucopyranosyl)uracil (**29**) *via* its 4′,6′-dimesylate **30** was not successful. The 6′-mesylate **32** of **29** was displaced by nucleophiles (iodide or benzoate) to afford compounds **33**. Treatment of the 6′-iodo analog **33b** with silver fluoride in pyridine afforded 1-(3-acetamido-2-*O*-acetyl-3,6-dideoxy-β-D-*xylo*-hex-5-enopyranosyl)uracil (**34**).

Previous reports[2] from this laboratory dealt with the syntheses of 3′-deoxy-3′-aminohexopyranosyl nucleosides from uridine as part of a program designed toward the synthesis of analogs of certain nucleoside antibiotics[2e] containing amino sugar moieties. It was found[2d] that treatment of 1-(3-acetamido-3-deoxy-2-*O*-mesyl-4,6-*O*-benzylidene-β-D-glucosyl)uracil (**1**) with sodium methoxide gave the crystalline 2,2′-anhydromannosyl nucleoside **2** in high yield as the sole product rather than the oxazoline derivative **3**

(1) This investigation was supported in part by funds from the National Cancer Institute, National Institutes of Health, U. S. Public Health Service (Grant No. CA 08748).

(2) (a) K. A. Watanabe and J. J. Fox, *Chem. Pharm. Bull.*, **12**, 975 (1964); (b) *J. Org. Chem.*, **31**, 211 (1966); (c) K. A. Watanabe, J. Beranek, H. A. Friedman, and J. J. Fox, *ibid.*, **30**, 2735 (1965); (d) ref 2b; (e) J. J. Fox, K. A. Watanabe, and A. Bloch, *Progr. Nucleic Acid Res. Mol. Biol.*, **5**, 251 (1966).

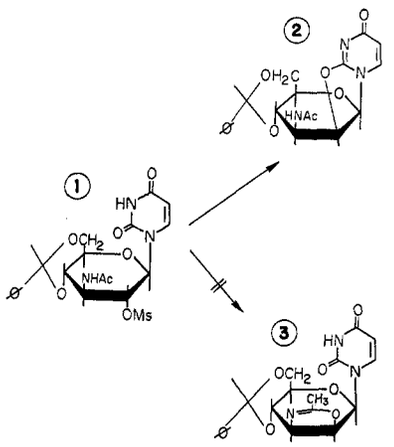

Figure 1.

(Figure 1). Thus, in spite of the known facility for oxazoline formation with other acetamido sugars vicinally substituted with sulfonyloxy groups, it is clear that (with uracil as the aglycon) the 2-carbonyl participated preferentially to the 3′-acetamido group in an intramolecular displacement reaction. The potential biological importance[2e] of amino sugar nucleoside derivatives warranted a study of the chemistry of variously mesylated 3′-acetamido-3′-deoxyhexosyluracils in order to examine the behavior of their neighboring groups (Figure 2).

Crystalline 1-(3-acetamido-3-deoxy-tri-*O*-mesyl-β-D-glucopyranosyl)uracil (**5**) was prepared by exhaustive mesylation of 3′-acetamidoglucosyluracil (**4**). This derivative (**5**) contains three leaving groups and several potential intramolecular nucleophiles. The behavior of this compound toward sodium ethoxide as well as that of mono- and di-O-mesylated nucleosides derived from **4** was investigated.

When treated with 1 equiv of sodium methoxide in anhydrous methanol, compound **5** was rapidly converted to 2,2′-anhydro-1-(3-acetamido-4,6-di-*O*-mesyl-β-D-mannosyl)uracil (**6**) with uv spectral characteristics (λ_{max}^{MeOH} 247 and 277 mμ) similar to those of *2*. Compound **6** was treated further with 2 equiv of anhydrous sodium ethoxide. After prolonged refluxing, approximately 1.2 equiv of alkoxide was consumed and five products were detected on tlc. After addition of water to the reaction mixture, only two products were detected by tlc. From this hydrolysate two crystalline products were isolated.

The structure of one of these crystalline products was established as **8** on the basis of the following data: the elemental analyses were consistent with **8**; nmr analyses showed the absence of mesyloxy substituents and the presence of only three replaceable protons suggestive of an anhydro-type structure. The uv spectrum was also similar to that for uracil nucleosides[3] and differed from those for anhydro nucleoside structures[4] involving a bridge between the aglycon and sugar moiety. The presence of a doublet at low field (NH, τ 2.31, J = 7.2 Hz) which disappears after addition of CD_3COOD showed that the 3′-acetamido group was not involved in a bridged structure. The configuration at C-2′ was readily established by the small H-1′–H-2′ coupling (anomeric signal, τ 4.02, $J_{1',2'} \cong 0$) diagnostic for the gauche relationship. Treatment of **8** with acetic anhydride in pyridine gave a crystalline mono-*O*-acetate (**9**) whose nmr spectrum showed a doublet for one proton at τ 4.80 ($J \cong 10.0$ Hz). This large coupling rules out C-2′ as the position of attachment of the acetoxy group since H-2′ is cis to both H-1′ and H-3′. Finally, since only *one* proton was shifted downfield upon O-acetylation of **8** to **9**, position 6 can be excluded as the site of acetylation. Therefore, the acetoxy group is linked to C-4′, and, consequently, the anhydro linkage in the sugar moiety must exist between the 2′ and 6′ positions. The large H-3′–H-4′ coupling of ~10.0 cps is indicative of a cis relationship for these protons in a dioxabicyclo[2.2.2]octane[5] system.

The structure of the second crystalline product was established as 1-(3-acetamido-2,6-anhydro-3-deoxy-4-*O*-mesyl-β-D-mannosyl)uracil (**7**) on the following evidence: the uv spectrum of **7** resembled uridine. The nmr spectrum showed that it contained one acetyl and one mesyl group and only two replaceable protons (τ 1.05 and −1.66) attributable to the acetamido and N-3 protons, respectively. The anomeric singlet at τ 4.15 and a narrow downfield singlet at τ 5.09 (integrated for one proton) suggested that the mesyloxy function was attached to C-4′ and that the anhydro bridge was formed between the 2′ and 6′ positions. In such a dioxabicyclo[2.2.2]octane system, H-3′ and H-4′ or H-4′ and H-5′ are no longer in trans-diaxial arrangement so that the H-4′ signal would become a singlet. However, the nmr data alone are not sufficient to establish the structure definitively since, if the chemical shifts of H-2′ and H-3′ were very close, both the H-1′ and H-4′ signals may become singlets even though the couplings between H-1′ and H-2′ or between H-3′ and H-4′ are large.[6]

When compound **7** was treated with sodium iodide in acetone followed by catalytic hydrogenation, starting material was recovered unchanged, whereas even under milder conditions the trimesylate **5** afforded the 6-deoxy derivative **10**. It is thus clear that the mesyloxy substituent in **7** is not on C-6′ and, since **7** was derived from intermediate **6**, the mesyloxy substituent is linked to C-4′. Compound **7** was also recovered unchanged after treatment with acetic anhydride in pyridine, which ruled out the possibility of free hydroxyl functions in this compound. These data establish the structure of **7**.

The overall conversion of the 2′,2-anhydro nucleoside **6** to the 2′,6′-anhydro derivatives **7** and **8** is readily explained by the alcoholysis or hydrolysis at C-2 of **6** to generate an intermediate 2′-hydroxy anion, which displaces the 6′-mesyloxy function by attack on the primary carbon atom to form a 2′,6′-anhydro linkage. Such an intramolecular displacement is eminently feasible if the intermediate structure containing the 2′-hydroxy anion adopts a boat (*B2*) conformation which would place the C-2′ substituent very close to C-6′. The conversion of **7** to **8** probably occurs by participation of the 3′-acetamido group *via* an oxazo-

(3) J. J. Fox and D. Shugar, *Biochim. Biophys. Acta*, **6** 369 (1952).

(4) J. F. Codington, I. L. Doerr, and J. J. Fox, *J. Org. Chem.*, **30**, 476 (1965).

(5) J. S. Webb, R. W. Broschard, D. B. Cosulich, J. H. Mowat, and J. E. Lancaster, *J. Amer. Chem. Soc.*, **84**, 3183 (1962); K. Tori, Y. Takano, and K. Kitahonoki, *Chem. Ber.*, **97**, 2798 (1964); K. Somekawa, T. Matsuo, and S. Kumamotoi *Bull. Chem. Soc. Jap.*, **42**, 3499 (1969).

(6) J. Musher and E. J. Corey, *Tetrahedron*, **18**, 791 (1962).

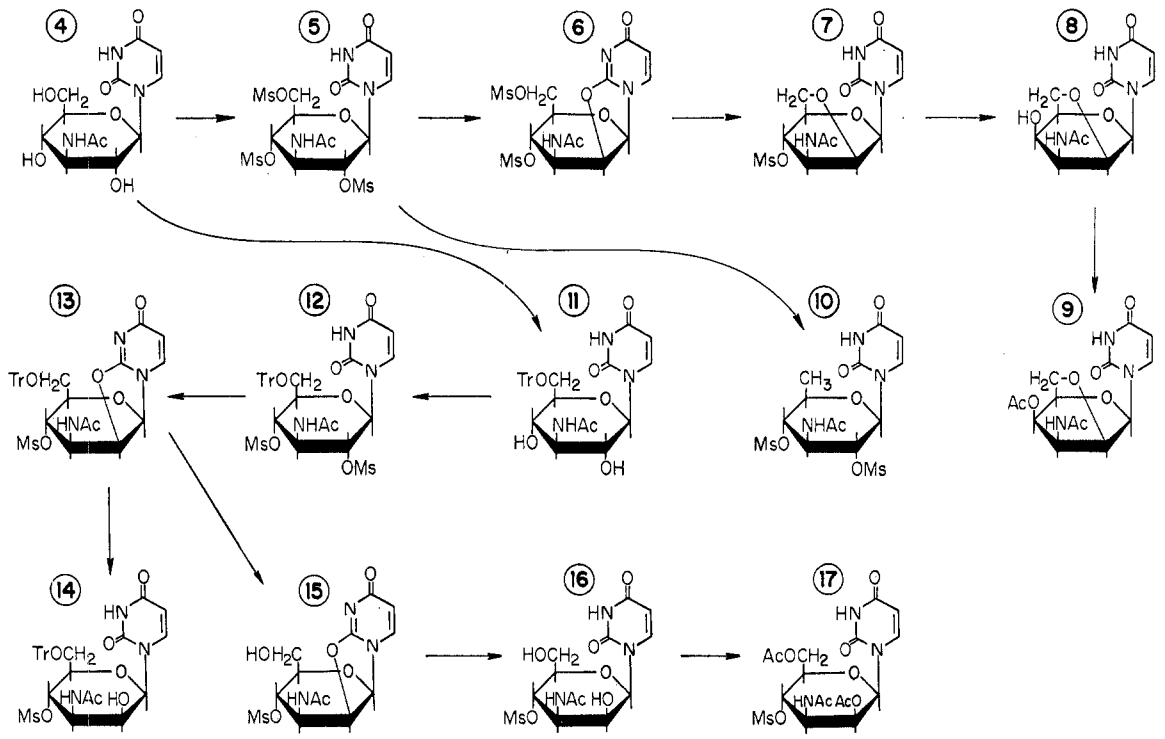

Figure 2.

line intermediate. The formation of **7** and **8** from **6** is somewhat akin to the conversion of 2′,3′-epoxylyxofuranosyluracils by sodium benzylate to 2′,5′-anhydro nucleosides previously reported from this laboratory.[7] The formation of a (2.2.2)bicyclic system is of interest. Only few examples of bicyclic [2.2.2] carbohydrates have been reported.[8-11]

It is noted that a 3′,6′-cyclic linkage with a nitrogen bridge was not detected among the products formed by reaction of **6** with sodium methoxide even though the formation of such a pyrrolidine derivative could be expected from an internal displacement of the C-6′ mesyloxy group by attack of acetamide nitrogen.[12] An examination of molecular models shows that a *B1* or *1C* conformation would be required for the pyrrolidine linkage to form. However, such conformations would not bring the acetamido nitrogen as close to C-6′ as does the *2B* conformation for the 2′-oxygen atom. The preferential formation of a 2′,6′-anhydro bridge may be due, therefore, mainly to the closer proximity of the 2′-hydroxy anion to C-6′.

Compound **8** was a very minor component formed in the overall reaction of **6** with sodium methoxide. When the reaction time was prolonged, the proportion of **8** was increased. This phenomenon is readily explained by intermediate **7** which slowly undergoes solvolysis[13] to the talo nucleoside **8** *via* an oxazoline derivative formed by anchimeric assistance of the 3′-acetamido group. When compound **5** was refluxed with 3 equiv of *aqueous* sodium hydroxide for 20 hr, compound **8** was isolated as the major product (*ca.* 30%) together with a small amount of **7**.

It was of interest to study the behavior of a di-*O*-mesyl derivative in which there is no leaving group at the 6′ position. For this purpose the 6′-*O*-trityl derivative **11** was prepared from **4**. After mesylation, the di-*O*-mesylate **12** was treated with 1 equiv of sodium methoxide in methanol. Crystalline 2,2′-anhydro nucleoside **13** was obtained which upon hydrolysis gave the mono-*O*-mesyl-*manno* nucleoside **14**. It is noted that, as in the reaction of **1** → **2** or **5** → **6**, the reaction of **12** with alkoxide also produced a 2,2′-anhydro linkage (compound **13**), showing again the preference of the 2-carbonyl over other potential intramolecular nucleophiles in the initial displacement. Detritylation of **14** gave 1-(3-acetamido-3-deoxy-4-*O*-mesyl-β-D-mannopyranosyl)uracil (**16**). The di-*O*-acetate **17** was prepared from **16** as a reference compound for nmr studies. Compound **16** was obtained alternatively from **13** by detritylation to **15** followed by hydrolysis. The nmr data of these compounds are listed in Table I.

Attempts to displace the 4-mesyloxy group of **13** in boiling methanolic sodium methoxide by anchimeric assistance of the 3′-acetamido function were unsuccessful and starting material was recovered unchanged. However, it was found (Figure 3) that after detritylation of **12** to **18**, displacement of both mesyloxy functions in alkali occurred with the formation of a nucleoside (**19**). This compound was purified and acetylated to its crystalline tetraacetate and characterized as the talo nucleoside (**20**). The conversion of **18** to **20** may have involved anchimeric assistance of the 6′-hydroxy anion, rather than the 3′-acetamido group, in displacement of the 4′-mesyloxy substituent.

(7) I. L. Doerr, J. F. Codington, and J. J. Fox, *J. Org. Chem.*, **30**, 467 (1965).

(8) L. N. Owen and P. A. Robins, *J. Chem. Soc.*, 326 (1949).

(9) D. A. Rosenfeld, N. K. Richtmyer, and C. S. Hudson, *J. Amer. Chem. Soc.*, **70**, 2201 (1948).

(10) N. A. Hughes, *J. Chem. Soc. C*, 2263 (1969).

(11) A. Zabacova and J. Jary, *Collect. Czech. Chem. Commun.*, **29**, 2042 (1964).

(12) H. H. Baer and T. Neilson, *Can. J. Chem.*, **43**, 840 (1965), suggested the possible formation of a 3,6-pyrrolidine structure by reaction of methyl 3-acetamido-2,3-dideoxy-4,6-di-*O*-mesyl-β-D-glucoside with sodium acetate in refluxing methanol; however, their data did not permit definitive structural assignment.

(13) B. R. Baker and R. E. Schaub, *J. Amer. Chem. Soc.*, **77**, 5900 (1955).

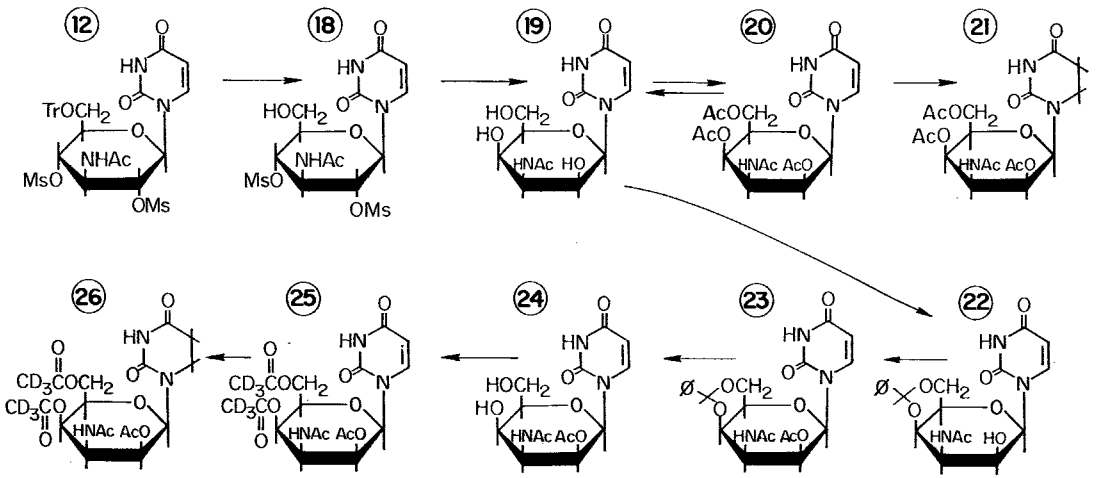

Figure 3.

TABLE I.—NUCLEAR MAGNETIC RESONANCE PARAMETERS FOR 1-(3-ACETAMIDO-3-DEOXY-β-D-HEXOSYL)URACILS[a]

	Chemical shifts, τ											Coupling constants, Hz			
Compd	H-1′	H-2′	H-3′	H-4′	H-5′	H-6′,6″	H-5	H-6	3′-NH	NAc	OAc	OMs	$J_{1',2'}$	$J_{2',3'}$	$J_{3',4'}$	$J_{4',5'}$
4	4.56	———	6.2–6.5; 4(H)	———		6.58	4.27	2.38	2.09	8.11			9.0			
5	3.91		5.32			5.60	4.28	2.48	1.91	8.12		6.92, 6.85, 6.77	8.0			
7	4.15	5.85	5.61	5.09			4.36	2.10	1.05	8.04		6.70	~0			
8	4.02	———	5.4–6.3; 5(H)	———			4.22	2.04	2.31	8.05			~0		~0	
9	3.94	5.82	5.35	4.80	6.19	5.82	4.32	2.03	1.94	8.09	7.92		~0	1.5	10.0	2.0
10	4.00					8.76	4.25	2.39	1.67	8.10		6.90, 6.77	8.0			
11	4.54						4.28	2.46		8.13			8.0			
12	3.97						4.14	3.38	1.86	8.12		7.15, 6.89	~9.0			
14	4.12			5.37			4.22	2.40	2.00	8.12		7.08	~0		9.0	
17	3.81	4.83	5.25	5.17	5.7	5.7	4.33	2.52	1.80	8.15	7.95, 7.90	6.73	~0	~2.0	~9.0	
18	4.04	5.30		~5.3		~6.4	4.29	2.47	1.93	8.14		6.94, 6.80	8.5			
19	4.35		5.91	6.1		6.6	4.42	2.31	2.07	8.07			~0			
20	4.01	4.92	5.28	4.92	5.57	5.92	4.38	2.56		8.17	8.00, 7.97, 7.88		~1.0	3.5	3.5	4.0
21	4.33	4.95	5.37	4.95		5.93				8.18	8.01, 7.88 (2)		~1.5	3.5	3.5	4.0
22[b]	3.78	5.42	5.02				4.30	1.92	1.15	7.91			~1.0	4.0		
23	3.99	4.94	5.31				4.32	2.47	2.21	8.15	7.96		~1.0	3.5	3.5	
23[b]	3.57	4.02	4.67	——5.5–5.7——			4.18	2.09	1.07	8.23	8.01		~1.0	3.0	3.0	
24[b]	3.63	3.97	~4.9			5.62	4.38	2.10	~1.4	8.18	7.94		~1.0	3.5		
25	4.01	4.92	5.28	4.92	5.57	5.92	4.18	2.56	2.27	8.17	7.97		~1.5	3.5	3.5	4.0
26	4.33	4.95	5.28	4.95		5.93			2.32	8.18	7.88		~1.0	3.5	3.5	4.0
30	3.95	4.83	———	5.1–5.7; 4 (H)	———		4.26	2.40	1.97	8.17	8.08	6.83, 6.77	8.5	10.0		
32	4.17	5.01	———	5.3–6.7; 4 (H)	———		4.32	2.48	2.17	8.18	8.12	6.83	8.5	10.0		
33a	4.18	4.95	——5.7–6.4; 3 (H)——			5.47	4.30	2.47	~2.3	8.17	8.10		8.5	9.5		
33b	4.17	5.08	———	5.5–6.7; 4 (H)	———		4.25	2.58	2.15	8.20	8.12		8.5	9.5		
34	4.24	4.75	——5.6–6.4——			5.23	4.25	2.23	2.03	8.16	8.08		8.5	9.5		

[a] In DMSO unless specified othersie. [b] In pyridine.

Assignment of the talo configuration to **20** is based on the following data: this nucleoside differs in melting point, optical rotation, and ir spectrum from the known tetraacetylated derivatives of the corresponding gluco,[2a,b] manno,[14] and galacto[14] isomers. The nmr spectrum of **20** showed a very narrow doublet for the anomeric proton signal at τ 4.01 ($J_{1',2'} \cong 1.0$ Hz). The narrow signal at τ 4.92 integrated for two protons (H-2′, H-4′), indicating that the couplings between the sugar ring protons are very small. The sextet for the H-3′ signal at τ 5.28 collapsed by deuterioacetic acid treatment to a narrow triplet ($J_{2',3'} \cong 3.5$ cps). These data (Table I) are in good agreement with the talo configuration in which all the sugar ring protons are in a gauche relationship with their neighbors.

The nmr data for **20** do not rule out any one of the two chair conformations (*C1* or *1C*). However, an examination of a Courtauld molecular model of **20** showed that it was impossible to build a *1C* conformation for this compound due to steric hindrance by the three bulky axial substituents which this conformation requires. On the other hand, the *C1* conformational model showed no serious interactions between the bulky functional groups. The nmr data as well as the examination of Courtauld molecular models also rule out any boat conformation because in each of these one of the dihedral angles defined by H-1′–H-2′, H-2′–H-3′, or H-3′–H-4′ must approach 0° and should exhibit a large coupling. Such a large coupling is not shown by the nmr spectrum of **20**. The data described thus far would warrant the assignment of the talo configuration in the *C1* conformation (in DMSO) to **20**.

Previous nmr studies[14] of a host of pyrimidine nucleosides from this laboratory have shown that removal of the anisotropy of the 5,6 double bond by hydrogenation produced an effect on the chemical shift of the C-2′-acetoxy resonance. A generalization was developed from these studies which stated that, in the case of pyranosyl–pyrimidine nucleosides, when the C-2′-acetoxy group and the pyrimidine are in a cis relationship, the C-2′-acetoxy resonance will be shifted upfield by 0.21–0.23 ppm when the 5,6 double bond is hydrogenated. When a trans-diequatorial relationship obtains, a small but significant downfield shift of the C-2′-acetoxy signal occurs upon removal of the unsaturation. This approach was applied to the talo nucleoside **20**.

The nmr spectrum of **20** exhibited four acetyl signals in DMSO-d_6 at τ 8.17, 8.00, 7.97, and 7.88. The 5,6-dihydro derivative **21**, obtained by hydrogenation of **20** over Adams catalyst, exhibited acetyl signals at τ 8.18, 8.01, and 7.88 (the latter signal integrating for six protons). A diamagnetic shift expected for one of the acetoxy resonances in **21** on the basis of earlier studies[14] with nucleosides was not observed. Indeed, these compounds (**20** and **21**) comprise the first example in the pyrimidine nucleoside area of the failure to conform to the generalization on upfield 2′-acetoxy resonance shifts for nucleosides bearing a cis relationship between the aglycon and the 2′-acetoxy group.

It should be noted that the generalizations proposed[14] for pyrimidine nucleosides assumed *a priori* a chair conformation for the carbohydrate and a *substantial* population in the anti conformation (that is, the 5,6 double bond sits over the sugar ring). The failure of the pair **20** and **21** to obey these generalizations may be due to either of the following. (a) The population of conformers in the anti form may deviate substantially from the norm in which the plane of the uracil moiety lies perpendicular to the plane of the sugar ring and the 5,6 double bond "sits over" the sugar ring. Due to the nonbonded interactions inherent in the talo configuration, deformation of the chair and/or twisting the aglycone about the C-1′–N bond to a form more nearly adopted in, say, the 2,2′-anhydro derivative (~90° deflection) can be expected so that the C-2′-acetoxy substituent lies outside the cone of anisotropy produced by the 5,6 double bond. (b) The acetoxy resonance at τ 7.88 of **20** shifted diamagnetically to τ 8.01 in **21** while the two other acetoxy resonances at τ 8.00 and 7.97 gave paramagnetic shifts. In order to examine the latter possibility (b) it is necessary to assign the acetoxy resonances in **20** and **21** with certainty by a synthesis of 1-(4,6-di-*O*-deuterioacetyl-3-acetamido-di-*O*-acetyl-β-D-talopyranosyl)-uracil (**25**, see Figure 3). The acetyl signals for **25** appeared at τ 8.18 and 7.97 and (aside from the absence of C-4′ and C-6′ acetoxy resonances) the rest of the nmr spectrum was identical with that exhibited by the undeuterioacetylated isomer **20**. Hydrogenation of **25** over platinum catalyst proceeded very slowly and after 3 days only ~50% reduction occurred. The acetyl signals of this mixture (**25** and **26**) appeared at τ 8.18, 7.97, and 7.88, integrating approximately in a ratio of 2:1:1 protons respectively. Therefore, the acetyl signal at τ 8.18 is assigned to the *N*-acetyl group because the 2′ substituent should be most affected by the aglycon which is in cis relationship to it. Consequently, the 2′-acetoxy signal is at τ 7.97 in **20** and it is this signal which had moved *downfield* in **21** on removal of anisotropy by reduction of the 5,6 double bond. Thus possibility b is ruled out.

The possibility remains that a substantial population of conformers in **20** and **21** deviate from the anti conformation so that the C-2′ acetoxy group is outside of the positive region of the anisotropic cone produced by the 5,6 double bond. Frič, *et al.*,[15] have shown in ORD studies with pyrimidine nucleosides that the orientation of the 2′ position "exerts a strong influence on the magnitude of the amplitude of the Cotton effect but not in its sign." Emerson, *et al.*,[16] have shown that the effect of inversion of the 2′-hydroxyl group (ribosyl → arabinosyl) is to hold the pyrimidine ring in a more rigid conformation, thereby *increasing* the magnitude of the Cotton effect. The ORD data for the gluco (**27**), manno (**28**), and talo (**20**) nucleosides are given in Figure 4. Thus, while the molar amplitude of the Cotton effect of the manno nucleoside relative to the gluco isomer is increased, the talo isomer is considerably *lower*, contrary to what might be expected from the previous studies.[15,16] However, Emerson[16] has also shown that, as the uracil moiety in nucleosides departs from the anti conformation, the Cotton effect is reduced in amplitude. The ORD

(14) R. J. Cushley, K. A. Watanabe, and J. J. Fox, *J. Amer. Chem. Soc.*, **89**, 394 (1967).

(15) I. Frič, J. Šmejkal, and J. Farkaš, *Tetrahedron Lett.*, 75 (1966).

(16) T. R. Emerson, R. J. Swan, and T. L. V. Ulbricht, *Biochemistry*, **6**, 843 (1967).

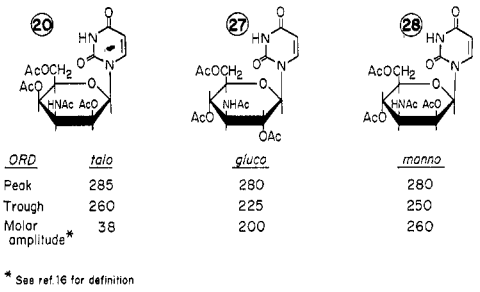

Figure 4.

data in Figure 4 are at least consistent with the hypothesis that the "failure" of **20** and **21** to obey the C-2 -acetoxy shift generalization of Cushley, *et al.*,[14] may be a result of altered conformer populations away from *anti* in these derivatives; hence ORD studies should accompany nmr studies in cases inconsistent with the acetoxy shift rules.[14]

It is noted that the formation of 2,6′- or 2,4′-anhydro nucleosides was not observed when the 2′,4′,6′-tri-*O*-mesylate (**5**, Figure 2) was treated with alkoxide and, instead, the 2,2′-anhydro derivative **6** was formed preferentially as the first step. The 2,2′-anhydro nucleoside **2** previously reported[2d] and those reported herein probably exist in the *C1* conformation. Recently, 2,3′-anhydro-1-(β-D-glycopyranosyl)pyrimidines were synthesized.[17,18] These latter structures probably adopt a *2B* (boat) conformation, though the *1C* conformation is possible but less likely. The hitherto unknown 2,4′-anhydro nucleoside structure would require a *B1* conformation whereas the 2,6′-anhydro isomer (also unknown) could probably take a *1C* or twist conformation.

Attempts to prepare (Figure 5) a 2,6′-anhydro nucleoside (*e.g.*, **31**, R′ = mesyl or H) from the 4′,6′-dimesylate **30** or the 6′-mesylate **32** were not successful. These latter compounds were synthesized readily by exhaustive or by selective mesylation of the known[2d] 1-(3-acetamido-2-*O*-acetyl-3-deoxy-β-D-glucopyranosyl) uracil (**29**). Treatment of the dimesylate **30** with lithium aluminum hydride in tetrahydrofuran (conditions by which the 2,4-dimesylate of methyl 3-benzamido-3,6-dideoxy-α-L-glucoside was converted into the 3,4-epiminogalactoside derivative)[18] caused complete loss of selective absorption in the ultraviolet, indicating that the 5,6 double bond of the aglycon was reduced. Therefore, this reaction was not studied further. Heating of **30** and **32** with potassium *tert*-butoxide in DMF gave intractable mixtures, although under identical conditions 1-(2-deoxy-3,4-di-*O*-mesyl-β-D-*erythro*-pentopyranosyl)uracil afforded a 2,3′-anhydro nucleoside.[17] Reaction of **32** with sodium benzoate in DMF did not afford a 2,6′-anhydro derivative but rather the crystalline 6′-benzoate **33a** in 80% yield. Similarly, treatment of **32** with sodium iodide in DMF afforded the 6′-iodo derivative **33b**. It may be postulated that in the course of reaction of **32** to **33** a 2,6′-anhydro derivative may have been an intermediate, but evidence for such a mechanism is lacking. Indeed, treatment of the 6′-iodo nucleoside **33b** with silver acetate in methanol (conditions which

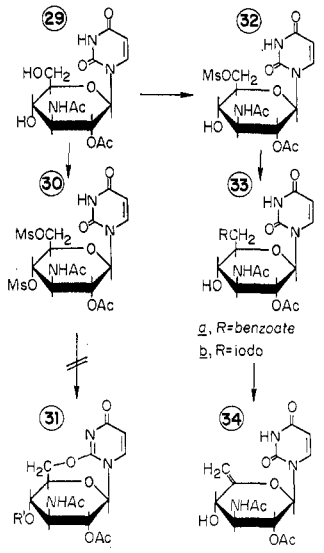

Figure 5.

convert a 5′-iodouridine into a 2,5′-anhydrouridine)[19] gave several products of which the major component was characterized as the 5′,6′-unsaturated derivative **34**. Crystalline **34** was synthesized in good yield from **33b** using silver fluoride in pyridine[20] as the reagent.

Experimental Section

Melting points were determined on a Thomas–Hoover apparatus and are not corrected. Elementary analyses were performed by Galbraith Laboratories, Knoxville, Tenn., and by Spang Microanalytical Laboratory, Ann Arbor, Mich. The nmr spectra were determined on a Varian A-60 spectrometer using tetramethylsilane as internal reference. Thin layer chromatography (tlc) was performed on silica gel GF_{254} (Merck) using the following solvent systems: solvent A, acetone–chloroform–water (5:1:1); B, *n*-butyl alcohol–water (84:16); C, chloroform–methanol (9:1). The uv spectra were determined on a Cary Model 15 spectrophotometer.

1-(3-Acetamido-3-deoxy-2,4,6-tri-*O*-mesyl-β-D-glucosyl)uracil (5).—Compound **4**[2a] (9.45 g, 0.03 mol) was dissolved in pyridine (190 ml) and cooled in an ice bath. Mesyl chloride (9.2 ml, 0.12 mol) was added to the stirred solution. The mixture was kept overnight at room temperature and evaporated to dryness. A small amount of pyridine was removed azeotropically with ethanol (100 ml) and the gummy residue was triturated twice with ethanol (50 ml). The ethanol-insoluble material was dissolved in hot water (30 ml) and diluted with hot ethanol (400 ml). The crystals which deposited after cooling the mixture were filtered and washed with 95% ethanol (20 ml). Amber-colored product (**5**, 8.5 g) was obtained in 57% yield: mp 165–168°; $[\alpha]_D$ +40° (*c* 0.75, H_2O); uv λ_{max}^{MeOH} 255 mμ (ε 10,900), λ_{min}^{MeOH} 226 mμ (ε 3000).

Anal. Calcd for $C_{15}H_{23}O_{18}N_3S_3$: C, 32.78; H, 4.22; N, 7.65; S, 17.50. Found: C, 32.76; H, 4.63; N, 7.59; S, 17.45.

Reaction of Compound 5 with Sodium Ethoxide, to 7 and 8.—A mixture of **5** (8.25 g, 0.015 mol) in ethanol (450 ml) and 0.48 *N* sodium ethoxide (33.5 ml) was refluxed for 30 min. A neutral, clear solution was obtained (uv λ_{max}^{EtOH} 248 and 227 mμ, λ_{min}^{EtOH} 233 mμ). A second mole of sodium ethoxide (0.48 *N*, 31 ml) was added and after 30 min under reflux temperature the reaction was neutral. Finally, sodium ethoxide (0.48 *N*, 12 ml) was added to the mixture and refluxing was continued for 1 hr. Sodium mesylate (3.4 g) precipitated on cooling and was removed by filtration. The filtrate contained five compounds as determined by tlc in solvent A. The filtrate was condensed to ~300 ml, then diluted with water (200 ml) and 1 *N* sodium hydroxide (15 ml). The mixture was warmed to 45–50° for 30

(17) G. Etzold, R. Hintsche, and P. Langen, *Tetrahedron Lett.*, 4827 (1967).

(18) A. D. Barford and A. C. Richardson, *Carbohyd. Res.*, **4**, 408 (1967).

(19) D. M. Brown, A. R. Todd, and S. Varadarajan, *J. Chem. Soc.*, 868 (1957).

(20) L. Hough and B. A. Otter, *Chem. Commun.*, 173 (1966); J. P. H. Verheyden and J. G. Moffatt, *J. Amer. Chem. Soc.*, **88**, 5684 (1966).

min. Tlc examination showed that the solution contained two compounds. The mixture was neutralized to pH ~6.0–6.4 with 1 *N* acetic acid (20 ml). After evaporation of the solvent, the residue was dissolved in water (25 ml) and allowed to stand overnight at room temperature, after which colorless crystals (platelets) separated. After recrystallization from ethanol–water, 0.22 g of **8**, mp 260–261°, $[\alpha]_D$ −10° (*c* 0.11, pyridine), was obtained.

Anal. Calcd for $C_{12}H_{15}O_6N_3$: C, 48.48; H, 5.09; N, 14.14. Found: C, 48.48; H, 5.10; N, 14.08.

The filtrate of crude **8** (T.O.D.[21] = 91,000) was applied on a column of Dowex 50 (H^+) (500 g) and the column was washed with water (5.6 l.). The uv-absorbing fractions (T.O.D. = 45,400) were collected and concentrated to dryness. The residue (1.55 g) was dissolved in a small amount of water and precipitated by adding six volumes of ethanol. After two recrystallizations by the same procedure, colorless microcrystals of **7** were obtained, 350 mg, mp 175–176°.

Anal. Calcd for $C_{13}H_{17}O_8N_3S \cdot 0.5C_2H_5OH$: C, 42.20; H, 5.06; N, 10.54; S, 8.05. Found: C, 42.58; H, 5.16; N, 10.64; S, 8.13. (The sample contained ethanol as determined by nmr.)

1-(3-Acetamido-2,6-anhydro-3-deoxy-β-D-talopyranosyl)uracil (8).—Compound **5** (2.7 g, 0.0052 mol) was dissolved in a mixture of methanol (54 ml), water (27 ml), and 1 *N* sodium hydroxide (15.6 ml) and the mixture was refluxed for 48 hr. The mixture was evaporated to dryness and the residue was further dried azeotropically by distillation with ethanol. The residue was extracted with boiling ethanol (three 30-ml portions). Sodium mesylate (1.3 g) was obtained as ethanol-insoluble crystals. The ethanol extracts were combined and evaporated to dryness and the residue was crystallized from a small amount of water. Compound **8** separated as colorless crystals, 419 mg (29%), mp 260–261°. The nmr and ir spectra were identical with those of **8** obtained previously.

1-(3-Acetamido-4-*O*-acetyl-2,6-anhydro-3-deoxy-β-D-talosyl)uracil (9).—Acetic anhydride (2.4 ml) was added to a suspension of **8** (0.11 g) in dry pyridine (1.8 ml). The mixture was stirred overnight, after which it was treated with ethanol (2.5 ml). After evaporation of the mixture, the residue was triturated with ether (10 ml). A colorless powder, mp 163–165°, was obtained which was crystallized from ethanol–chloroform (0.1 g, mp 165–167°): $[\alpha]_D$ +15° (*c* 0.78, ethanol); uv λ_{max}^{MeOH} 261 mμ (ε 9200), λ_{min}^{MeOH} 228 mμ (ε 1400).

Anal. Calcd for $C_{14}H_{17}N_3O_7 \cdot H_2O$: C, 48.28; H, 5.17; N, 12.07. Found: C, 48.54; H, 4.91; N, 11.95.

1-(3-Acetamido-3,6-dideoxy-2,4-di-*O*-mesyl-β-D-glucosyl)uracil (10).—A mixture of **5** (0.55 g) and sodium iodide (1.5 g) in acetone (4.5 ml) in a sealed tube was heated on a steam bath for 25 min. After cooling, the precipitated sodium mesylate was filtered and washed with acetone (5 ml). The combined filtrate and washings were evaporated to dryness to a syrup which was then dissolved in 50% aqueous ethanol (20 ml) and hydrogenated at room temperature in the presence of 5% Pd/C catalyst (0.5 g). After consumption of 1 mol of hydrogen (3 hr), the catalyst was removed by filtration and the filtrate was evaporated to dryness. The residue was dissolved in a mixture of ethanol and water and treated batchwise with Dowex 50 (H^+) and Dowex 1 (acetate) to remove sodium and iodide ions. After removal of the resins, the filtrate was evaporated to dryness and the residue was crystallized (0.3 g, mp 176–179° eff) from acetone–ether. Recrystallization of the precipitate from methanol–water gave an analytical sample: mp 188.5–191°; $[\alpha]_D$ +22° (*c* 0.7, H_2O); paper electrophoretic migration, +3.4 cm (borate buffer pH 9.2, 900 V, 3.5 hr).

Anal. Calcd for $C_{14}H_{21}O_{10}N_3S_2 \cdot H_2O$: C, 36.83; H, 4.86; N, 9.21; S, 14.05. Found: C, 36.86; H, 4.82; N, 9.28; S, 14.08.

The presence of one molecule of water of crystallization was shown by nmr spectroscopy.

1-(3-Acetamido-3-deoxy-6-*O*-trityl-β-D-glucopyranosyl)uracil (11).—A mixture of **4** (15.7 g) and trityl chloride (15.4 g) in pyridine (300 ml) was heated at 80° for 6 hr and allowed to remain at room temperature overnight. Another charge of trityl chloride (10.1 g) was added and the mixture was heated to 80° for 5 hr. The cooled mixture was poured into a stirred, ice–water mixture (2.5 l.). The precipitate was collected and triturated with a mixture of ethanol (60 ml) and ether (400 ml) in order to remove tritanol. The insoluble solid (mp 159–162°) was dissolved in acetone (1:1) and diluted with petroleum ether (bp 30–60°) (2 l.). After standing overnight, crystallization of **11** occurred (17.0 g): mp 165–168°; $[\alpha]_D$ +15° (*c* 0.74, MeOH); uv λ_{max}^{MeOH} 252 mμ (ε 11,000); λ_{min}^{MeOH} 239 mμ (ε, 7200). An analytical sample was prepared by recrystallization from ethanol, mp 165–168°.

Anal. Calcd for $C_{31}H_{31}N_3O_7 \cdot {}^2/_3C_2H_5OH$: C, 66.01; H, 5.99; N, 7.14. Found: C, 65.90; H, 5.87; N, 7.40.

1-(3-Acetamido-3-deoxy-2,4-di-*O*-mesyl-6-*O*-trityl-β-D-glucosyl)uracil (12).—Mesyl chloride (4.28 ml) was added to a stirred, ice-cold solution of **11** (9.46 g, 0.017 mol) in pyridine (95 ml). The reaction mixture was kept overnight at room temperature and then poured into an ice–water mixture (1.2 l.) with stirring. The amber-colored precipitate was filtered and washed with a small amount of water. The solid (10.1 g, mp 198–201°) was dissolved in pyridine and treated with charcoal. The hot filtrate was treated with a few drops of water and cooled. Colorless crystals of **12** (7.5 g) precipitated: mp 201–202°; $[\alpha]_D$ +61° (*c* 0.7, pyridine); uv λ_{max}^{MeOH} 257 mμ (ε 10,200), λ_{min}^{MeOH} 240 mμ (ε 7200).

Anal. Calcd for $C_{33}H_{35}O_{11}N_3S_2$: C, 55.52; H, 4.94; N, 5.89; S, 8.98. Found: C, 55.11; H, 5.16; N, 5.75; S, 8.85.

2,2′-Anhydro-1-(3-acetamido-3-deoxy-4-*O*-mesyl-6-*O*-trityl-β-D-mannosyl)uracil (13).—A mixture of **12** (14.3 g, 0.02 mol), methanol (1.2 l.), and 0.47 *N* sodium ethoxide (40 ml) was refluxed gently for 30 min and concentrated to ~70 ml. After dilution of the alcoholic solution with ethyl acetate (120 ml), the precipitate (sodium mesylate, 1.99 g) was removed by filtration. The filtrate was concentrated to a syrup, dissolved in ethanol, and poured into ice–water (700 ml). After filtration, the precipitate (12.9 g) was dissolved in chloroform (50 ml). Tlc (solvent B) showed one major spot accompanied by two small spots. The mixture was applied to an alumina column (500 g, neutral AG 7 grade). The column was washed with a mixture of chloroform and methanol (3:1). Eluted fractions were monitored by tlc and those containing the major spot were combined and evaporated to dryness. The residue was dissolved in chloroform (20 ml) and the solution was diluted with *n*-heptane. A white powder (7.8 g) precipitated, mp 161–164°. This product (**13**) exhibited a shoulder at ~250 mμ in its uv spectrum.

Anal. Calcd for $C_{32}H_{31}O_8N_3S$: C, 62.22; H, 5.06; N, 6.80; S, 5.19. Found: C, 61.93; H, 5.22; N, 6.54; S, 5.02.

1-(3-Acetamido-3-deoxy-4-*O*-mesyl-6-*O*-trityl-β-D-mannosyl)uracil (14).—Compound **13** (5.60 g) was stirred in a mixture of ethanol (400 ml), water (100 ml), and 1 *N* sodium hydroxide (8 ml) for 15 min at room temperature. During this period the uv spectrum of the mixture changed to a uridinelike absorption. The reaction mixture was neutralized with 1 *N* acetic acid (20 ml) to ~pH 6. After evaporation of the solvent, the residue was triturated with water (three 20-ml portions). The almost colorless solid (mp 159–162°) was dissolved in methanol and diluted with water from which product **14** precipitated: 4.3 g; mp 165–168°; uv λ_{max}^{MeOH} 258 mμ, λ_{min}^{MeOH} 242 mμ.

Anal. Calcd for $C_{32}H_{33}O_9N_3S$: C, 60.46; H, 5.23; N, 6.61; S, 5.04. Found: C, 59.98; H, 5.46; N, 6.33; S, 4.93.

2,2′-Anhydro-1-(3-acetamido-3-deoxy-4-*O*-mesyl-β-D-mannopyranosyl)uracil (15).—The trityl derivative (**13**, 2.15 g, 0.0035 mol) was dissolved in a mixture of ethanol (38 ml) and water (49 ml). The mixture was gently refluxed for 3.5 hr and evaporated to dryness. The residue was triturated with water (10 ml) and filtered from trityl alcohol (0.81 g). The filtrate was evaporated to dryness and the colorless residual solid was recrystallized from water to afford needles: mp 194–196°; $[\alpha]_D$ −17° (*c* 0.66, MeOH); uv λ_{max}^{MeOH} 248 and 227 mμ (ε 10,600 and 10,000), λ_{min}^{MeOH} 236 mμ (ε 9700). (For analyses, a small sample was recrystallized from methanol.)

Anal. Calcd for $C_{13}H_{17}O_8N_3S \cdot CH_3OH$: C, 41.26; H, 5.40; N, 10.31; S, 7.86. Found: C, 40.87; H, 5.52; N, 10.17; S, 7.95.

The aqueous mother liquor of recrystallization was adsorbed on a column of Dowex 50 (H^+) (6 ml) and washed with water (1500 ml). The eluate was concentrated to ~3 ml and the solution was kept at 4° for 3 days. Colorless needles (80 mg) separated, mp 190–191°. The ir spectrum of this crystalline material was identical with that of compound **16** prepared from **15**. (See below.)

1-(3-Acetamido-3-deoxy-4-*O*-mesyl-β-D-mannopyranosyl)uracil (16) from 15.—Compound **15** (440 mg) was dissolved in a mixture of dioxane (15 ml), water (15 ml), and 0.1 *N* sodium hydroxide (10 ml). The solution was kept at room temperature for 1 hr, after which it was neutralized with Dowex 50 (H^+) (3 ml). The resin was filtered and washed with water (200 ml). The combined

(21) Total optical density.

filtrate and washings were evaporated to ~1.5 ml and diluted with ethanol (1.5 ml). The mixture was kept at 4° overnight. Colorless needles (298 mg) separated: mp 193–195°; $[\alpha]_D$ +26° (*c* 0.73, H_2O); uv $\lambda_{max}^{H_2O}$ 260 mμ (ε 10,600), $\lambda_{min}^{H_2O}$ 228 mμ (ε, 2000).

Anal. Calcd for $C_{13}H_{19}O_9N_3S \cdot H_2O$: C, 37.95; H, 5.15; N, 10.21; S, 7.79. Found: C, 37.26; H, 5.30; N, 9.96; S, 7.72.

1-(3-Acetamido-2,6-di-*O*-acetyl-3-deoxy-4-*O*-mesyl-β-D-mannosyl)uracil (17).—Compound **16** (250 mg) was acetylated with acetic anhydride (2.5 ml) in pyridine (2 ml) overnight at room temperature. The clear solution was evaporated to dryness and traces of pyridine and acetic anhydride were removed by azeotropic distillation with ethanol. The residual colorless solid was crystallized from methanol–ethanol to yield compound **17**, 220 mg, mp 195°, $[\alpha]_D$ +34° (*c* 78, MeOH).

Anal. Calcd for $C_{17}H_{23}N_3O_{11}S$: C, 42.76; H, 4.86; N, 8.80; S, 6.71. Found: C, 42.75; H, 4.98; N, 9.06; S, 7.05.

1-(3-Acetamido-3-deoxy-2,4-di-*O*-mesyl-β-D-glucopyranosyl)uracil (18).—Compound **12** (7.13 g, 0.01 mol) was dissolved in warm acetic acid (80 ml). The solution was diluted with water (20 ml) and the mixture was heated on a steam bath for 45 min. After evaporation of the solvent, the residue was partitioned between water (80 ml) and ether (80 ml). The aqueous layer was separated and washed with ether (80 ml), and evaporated to dryness. The residue was crystallized from ethanol. Recrystallization from ethanol yielded pale yellow crystals, 3.21 g (70%), mp 160–161°, $[\alpha]_D$ +39° (*c* 0.82 pyridine).

Anal. Calcd for $C_{14}H_{21}O_{11}N_3S_2$: C, 35.67; H, 4.49; N, 8.91; S, 13.60. Found: C, 35.28; H, 4.61; N, 8.67; S, 13.42.

1-(3-Acetamido-2,4,6-tri-*O*-acetyl-3-deoxy-β-D-talosyl)uracil (20).—Compound **18** (471 mg, 0.001 mol) was dissolved in a mixture of water (8 ml) and 1 *N* sodium hydroxide (1 ml). The mixture was refluxed for 10 min, at which time the reaction mixture became neutral. Another charge of 1 *N* sodium hydroxide (1 ml) was added and the mixture was refluxed for 30 min. The neutral mixture was evaporated to dryness. The residue was dried further by azeotropic distillation with toluene and acetylated with acetic anhydride (2 ml) and pyridine (2 ml) overnight. After evaporation of the solvent, the residue was mixed with chloroform (2 ml) and chromatographed over silica gel G column (10 g, 2.2 × 5 cm) using 10% methanol in chloroform. Compound **20** (187 mg) was obtained as colorless crystals after recrystallization from methanol, mp 186–189°, $[\alpha]_D$ +41° (*c* 0.96, pyridine).

Anal. Calcd for $C_{18}H_{23}O_{10}N_3$: C, 48.98; H, 5.22; N, 9.52. Found: C, 48.96; H, 5.14; N, 9.49.

1-(3-Acetamido-2,4,6-tri-*O*-acetyl-3-deoxy-β-D-talosyl)-5,6-dihydrouracil (21).—A mixture of compound **20** (200 mg) and platinum oxide (100 mg) in methanol (50 ml) and acetic acid (1 ml) was reduced for 20 hr at room temperature. The catalyst was filtered and the filtrate was concentrated *in vacuo* to a residue which was crystallized from methanol, 172 mg, mp 153–154°, $[\alpha]_D$ 0 (*c* 1.0, MeOH).

Anal. Calcd for $C_{18}H_{25}O_{10}N_3$: C, 48.76; H, 5.64; N, 9.48. Found: C, 48.52; H, 5.81; N, 9.23.

1-(3-Acetamido-3-deoxy-β-D-talopyranosyl)uracil (19).—To the suspension of compound **20** (2.1 g) in methanol (55 ml) was added 1 *N* sodium methoxide (1 ml). A clear solution was obtained immediately. After 3 hr, the mixture was evaporated to dryness and the residue was dissolved in 20 ml of water and treated batchwise with Dowex 50 (H^+) (2 ml). The resin was filtered and washed with a small amount of water. The combined filtrate and washings were evaporated to a syrup which was homogeneous as determined by tlc (solvent B) and nmr spectroscopy, but which did not crystallize. The yield of this syrup (**19**) was quantitative (1.5 g).

1-(3-Acetamido-4,6-*O*-benzylidene-3-deoxy-β-D-talosyl)uracil (22).—Compound **19** (1.13 g) was mixed with ~1.5 g of zinc chloride (freshly fused and pulverized) and freshly distilled benzaldehyde (20 ml). The mixture was shaken for 16 hr and then poured into an ice–water mixture (200 ml). Ether (200 ml) was added to the suspension and the mixture was stirred vigorously for 20 min. The insoluble solid was removed by filtration and washed with ether. Purification from hot methanol gave a colorless powder (850 mg) which did not crystallize but which was homogeneous to tlc. The mother liquor contained a considerable amount of compound **19**, indicating that appreciable debenzylidenation had occurred. The nmr spectrum of the colorless powder was consistent with compound **22**.

1-(3-Acetamido-2-*O*-acetyl-4,6-di-*O*-benzylidene-3-deoxy-β-D-talosyl)uracil (23).—Compound **22** (850 mg) was acetylated with acetic anhydride (1 ml) in pyridine (5 ml) for 2 hr at room temperature. The solvent was removed by evaporation and traces of pyridine and acetic anhydride were removed by codistillation with toluene. The residue was dissolved in a small amount of methanol and the mixture was left overnight at room temperature. A small amount of insoluble material was removed and the filtrate was evaporated to dryness. The residue was triturated with a small amount of water and ether. A colorless powder (500 mg) was obtained which was homogeneous on tlc. The nmr spectrum of this product (see Table I) was consistent with compound **23**.

1-(3-Acetamido-2-*O*-acetyl-3-deoxy-4,6-di-*O*-deuterioacetyl-β-D-talosyl)uracil (25).—Compound **23** (500 mg) was dissolved in 80% acetic acid. After the solution was diluted with 5 ml of water, the mixture was heated on a steam bath for 45 min and then cooled to room temperature. The mixture was shaken in a hydrogen atmosphere in the presence of 5% palladium-on-charcoal catalyst (100 mg) for 30 min. After filtration from catalyst, the filtrate was evaporated to dryness. Traces of acetic acid were removed by azeotropic distillation with toluene. The residue (compound **24**) was dissolved in pyridine (3 ml) and treated with deuterioacetic anhydride (0.5 ml) at room temperature for 1 hr. The solvent was removed by distillation *in vacuo* and the residue was dissolved in a small amount of 10% methanol in chloroform and applied on a column of silica gel G (10 g, 6 × 2 cm). The column was eluted with 10% methanol in chloroform. Appropriate fractions were collected, concentrated to dryness, and crystallized from methanol. The yield of compound **25**, after two recrystallizations from methanol, was 184 mg, mp 186–189°, $[\alpha]_D$ +40° (*c* 0.7, pyridine).

Anal. Calcd for $C_{18}H_{17}D_6O_{10}N_3$: C, 48.32; H, and D, 6.49; N, 9.40. Found: C, 48.49; H and D, 6.27; N, 9.56.

1-(3-Acetamido-2-*O*-acetyl-3-deoxy-4,6-di-*O*-mesyl-β-D-glucosyl)uracil (30).—Compound **29**[2d] (2.5 g, 0.007 mol) was dissolved in pyridine (50 ml). Mesyl chloride (1.1 ml) was added dropwise to the stirred, ice-cold solution. The mixture was kept at 4° for 30 min, after which it remained at room temperature overnight. The solvent was evaporated to dryness and the residue was triturated with 35 ml of ice–water. Crystals separated (2.6 g, 76%) which were filtered and recrystallized from methanol to yield 2.04 g of **30**, mp 199–202° dec, $[\alpha]_D$ +24° (*c* 0.9, pyridine).

Anal. Calcd for $C_{16}H_{23}O_{12}N_3S_2$: C, 37.42; H, 4.51; N, 8.13; S, 12.49. Found: C, 37.34; H, 4.42; N, 8.07; S, 12.48.

1-(3-Acetamido-2-*O*-acetyl-3-deoxy-6-*O*-mesyl-β-D-glucosyl)uracil (32).—To a stirred, cold solution of compound **29** (2.5 g) in pyridine (100 ml) was added mesyl chloride (0.5 ml). After 30 min, ice was added and the mixture was stirred for 5 min. After evaporation of the mixture to dryness, the residue was triturated with ethanol. Product (compound **32**) crystallized, 2.33 g, mp 229–230° dec, $[\alpha]_D$ +16° (*c* 1.2, pyridine).

Anal. Calcd for $C_{15}H_{21}O_{10}N_3S$: C, 41.37; H, 4.86; N, 9.65. Found: C, 41.28; H, 4.87; N, 9.55.

1-(3-Acetamido-2-*O*-acetyl-6-*O*-benzoyl-3-deoxy-β-D-glucosyl)uracil (33a).—A mixture of compound **32** (225 mg) and dry sodium benzoate (144 mg) in DMF (10 ml) was refluxed for 30 min. After cooling, insoluble precipitate was filtered and the filtrate was evaporated to dryness. The residue was extracted with acetone and the acetone extracts were applied to two silica gel PF_{254} plates (20 × 20 cm, 2 mm thick). The plates were developed in a mixture of chloroform and methanol (4:1). The major band was scraped off and extracted with acetone. The acetone extracts were evaporated and the residue was dissolved in ethyl acetate. After removal of a small amount of insoluble material by filtration, the filtrate was concentrated *in vacuo* and the residue was crystallized from ethyl acetate–benzene. Colorless crystals, 207 mg (80%), were obtained which sintered at 143–145° but had no definite melting point, $[\alpha]_D$ +55° (*c* 0.8, pyridine).

Anal. Calcd for $C_{21}H_{23}O_9N_3$: C, 54.66; H, 5.02; N, 9.11. Found: C, 54.21; H, 5.08; N, 9.03.

1-(3-Acetamido-2-*O*-acetyl-3,6-dideoxy-6-iodo-β-D-glucosyl)uracil (33b).—A mixture of compound **32** (1.0 g) and sodium iodide (0.5 g) in DMF (40 ml) was refluxed for 30 min and then evaporated to dryness. The residue was chromatographed over a silica gel G (50 g) column using a chloroform–methanol (10:1) solvent system as the eluent. Appropriate fractions were collected and concentrated to dryness. The residue was crystal-

lized from a small amount of acetone, 530 mg (46%), mp 191–193°, $[\alpha]_D$ +7.2° (*c* 1.3, pyridine).

Anal. Calcd for $C_{14}H_{18}O_7N_3I$: C, 35.99; H, 3.88; N, 8.99. Found: C, 35.93; H, 3.87; N, 8.92.

(1-(3-Acetamido-2-*O*-acetyl-3,6-dideoxy-β-D-*xylo*-hex-5-eno-pyranosyl)uracil (34).—A mixture of compound **33b** (708 mg) and silver fluoride (1.83 g) in pyridine (20 ml) was shaken for 3 hr and filtered. The filtrate was evaporated to dryness and the residue was dissolved in methanol (100 ml). A small amount of insoluble material was removed by filtration. Hydrogen sulfide was bubbled into the methanol solution to precipitate silver ion. The dark mixture was filtered through a Celite bed and the filtrate was concentrated to dryness. The residue was dissolved in a small amount of methanol and applied to two silica gel PF_{254} plates (20 × 20 cm, 2 mm). The plates were developed with chloroform–methanol (4:1). The main band was removed and extracted with acetone–methanol (4:1) and concentrated to dryness. The residue was crystallized from acetone, 297 mg, mp 145–146°, $[\alpha]_D$ −63° (*c* 1.2, pyridine).

Anal. Calcd for $C_{14}H_{17}O_7N_3$: C, 49.56; H, 5.05; N, 12.38. Found: C, 49.40; H, 5.07; N, 12.32.

Registry No.—**4**, 4338-36-7; **5**, 32254-26-5; **7**, 32254-27-6; **8**, 32254-28-7; **9**, 32254-29-8; **10**, 32254-30-1; **11**, 32254-31-2; **12**, 32254-32-3; **13**, 32254-33-4; **14**, 32254-34-5; **15**, 32254-35-6; **16**, 32254-36-7; **17**, 32367-45-6; **18**, 32254-37-8; **19**, 32254-38-9; **20**, 32254-39-0; **21**, 32304-21-5; **22**, 32254-40-3; **23**, 32254-41-4; **24**, 32254-42-5; **25**, 32254-43-6; **26**, 32254-44-7; **30**, 32304-22-6; **32**, 32254-45-8; **33a**, 32254-46-9; **33b**, 32254-47-0; **34**, 32254-48-1.

Nucleosides. LXXIII. Ribosyl Analogs of Chloramphenicol[1]

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The synthesis of *p*-(5-dichloroacetamido-5-deoxy-β-D-ribofuranosyl)nitrobenzene (**20b**) and *p*-(β-D-ribofuranosyl)nitrobenzene 5-phosphate (**12**) from β-D-ribofuranosylbenzene (**6**) are described. Precursor **6** was obtained by condensation of diphenylcadmium with tri-*O*-benzoyl-D-ribofuranosyl chloride (**2**) and the β configuration of **6** was established by periodate and nmr studies. Acetylation and nitration of **6** afforded a mixture of the *o*- and *p*-nitro isomers **10a** and **10b** which was resolved after deacetylation to *o*- and *p*-(β-D-ribofuranosyl)-nitrobenzene (**11a** and **11b**). The para isomer **11b** was acetonated, phosphorylated, and deisopropylidenated to give the 5-phosphate **12**. Acetonation of **6** followed by mesylation, azidation, and reduction afforded the amine **16**. Dichloroacetylation of **16** followed by deisopropylidenation gave (5-dichloroacetamido-5-deoxy-β-D-ribofuranosyl)benzene (**18**) which was converted in two steps to the *o*- and *p*-nitro derivatives **20a** and **20b**.

It was reported[2] that the antibiotic chloramphenicol (a protein synthesis inhibitor) adopts a "curled" conformation (Figure 1) in solution and, as such, resembles the nucleotide, uridine 5′-phosphate. It has been suggested further that the mode of action of this antibiotic may be related to this conformation.[2,3] If this hypothesis is valid, one might expect that *p*-(5-dichloroacetamido-5-deoxy-β-D-ribosyl)nitrobenzene(**20b**) or *p*-(β-D-ribofuranosyl)nitrobenzene 5-phosphate (**12**) may also be inhibitors of protein synthesis. This paper deals with the synthesis of **12** and **20** as part of our program directed toward the preparation of nucleoside analogs of potential biochemical significance.

The glucopyranosylbenzene derivative (**1**, Figure 2) has been prepared by Hurd and Bonner[4] by condensation of poly-*O*-acetyl-α-D-glucosyl chloride with phenylmagnesium bromide. Zhdanov, *et al.*,[5] have prepared ribopyranosylbenzene analogously by using the corresponding ribopyranosyl chloride. The β configuration was assumed for **1**[6] solely by analogy of optical rotation data with a related derivative of the xylo series. With diphenylcadmium as the condensing agent, Hurd and Holysz[7] also obtained compound **1**, albeit in lower yield. Mertes, *et al.*,[8] reacted bis(2,6-dibenzyloxypyridyl-3)cadmium with tri-*O*-benzoyl-D-ribofuranosyl chloride (**2**) and obtained the corresponding 3-ribosylpyridine derivative. Attempts in our laboratory to apply the condensation of phenylmagnesium bromide with **2** in order to prepare **6** were unsuccessful. However, the use of diphenylcadmium with **2** in refluxing benzene solution afforded the "nucleoside" **3** in 20% yield. The major product of this reaction (**2** → **3**) was the sugar ketal **4** which, after saponification with methoxide, afforded the crystalline ketal **5**. Proof of the structure of **5** as 1,2-*O*-diphenylmethylidene-α-D-ribofuranose was obtained by elemental analyses, by nmr measurements, and by acid hydrolysis to benzophenone and ribose. Ketals analogous to **5** had been reported[7] from similar type reactions. Debenzoylation of **3** with sodium methoxide in methanol yielded the unblocked nucleoside **6**.

The β configuration for **3** and **6** was established as follows. Periodate oxidation of **6** afforded the dialdehyde **7**, which was reduced with sodium borohydride to the trialcohol **8**. Deacetylation of **1** followed by a similar oxidation and reduction afforded a trialcohol which was identical (melting point, mixture melting point, optical rotation) with compound **8** obtained from **3**. The nmr spectrum of **1** in pyridine-d_5 and of its deacetylated derivative in DMSO-d_6 all show large splittings for H-1–H-2 ($J \cong 10$ Hz) which establishes definitively the β configuration for **1** and, thereby, the β configuration for **3** and **6**.

Nitration of the tri-*O*-acetate **9** of **6** was accomplished

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(2) O. Jardetzky, *J. Biol. Chem.*, **238**, 2498 (1963).

(3) N. S. Beard, S. A. Armentrout, and A. S. Weisberger, *Pharmacol. Rev.*, **21**, 213 (1969).

(4) C. D. Hurd and W. A. Bonner, *J. Amer. Chem. Soc.*, **67**, 1972 (1945).

(5) Yu. A. Zhdanov, G. A. Dorol'chenko, and L. A. Kubasskaya, *Dokl. Akad. Nauk SSSR*, **128**, 1185 (1959); *Chem. Abstr.*, **54**, 8644 (1960).

(6) W. A. Bonner and C. D. Hurd, *J. Amer. Chem. Soc.*, **73**, 4290 (1951).

(7) C. D. Hurd and R. P. Holysz, *ibid.*, **72**, 2005 (1950).

(8) M. P. Mertes, J. Zielinski, and C. Pillar, *J. Med. Chem.*, **10**, 320 (1967).