C-Glycosyl Nucleosides. I. Studies on the Synthesis of Pseudouridine and Related Compounds

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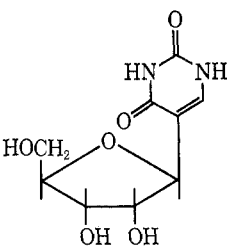
Condensation of 2,4-di-*tert*-butoxypyrimidin-5-yllithium with 2,4:3,5-di-*O*-benzylidene-*aldehydo*-D-ribose gives, in good yield, the allo and altro isomers of 5-(2,4:3,5-di-*O*-benzylidene-D-pentahydroxypentyl)-2,4-di-*tert*-butoxypyrimidine (**5a** and **6a**) that can be separated chromatographically. Cyclization of both isomers in dilute hydrochloric acid gives almost exclusively the α- and β-furanose forms of pseudouridine. Milder acidic treatment of **5a** and **6a** using 80% acetic acid at room temperature gives the allo and altro isomers of 5-(2,4:3,5-di-*O*-benzylidene-D-pentahydroxypentyl)uracil (**7b**, **8b**) while at 100° both the *tert*-butyl and benzylidene groups are removed giving the corresponding 5-(pentahydroxypentyl)uracils (**9a**, **10a**). Acidic cyclization of the latter compounds occurs under mild conditions, the altro isomer giving almost exclusively natural β-pseudouridine (**1**) while the allo isomer initially gives predominantly α-pseudouridine (**2**) which rapidly equilibrates to **1**. Oxidation of either **5a** or **6a** gives a common ketone which can be reduced almost stereospecifically to the allo alcohol **5a** with metal hydrides. Since such a reduction can be done using sodium borotritiide, the overall process provides a unique route for the synthesis of pseudouridines labeled selectively at $C_{1'}$ of the sugar. Acetylation of the pentitols (**9a** and **10a**) gives the corresponding pentaacetates which, upon reaction with ammonia, are converted into the 1'-acetamido-1'-deoxy compound **17**.

The presence of 5-(β-D-ribofuranosyl)uracil (**1**) as the principal minor component in transfer RNA has led to considerable interest in this *C*-glycosyl nucleoside.[3] Syntheses of both the naturally occurring β isomer **1** and of its α-furanosyl isomer **2** were achieved by Shapiro and Chambers[4] *via* condensation of 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl chloride with 2,4-dimethoxypyrimidin-5-yllithium, but the yields were only 2 and 1%.



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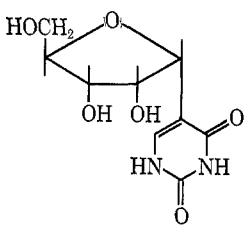


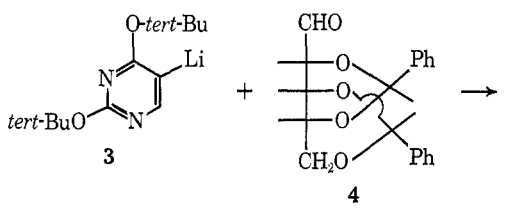
2

A substantial improvement in this synthesis was achieved by Brown, *et al.*,[5] who condensed 2,4-di-*tert*-butoxypyrimidin-5-yllithium (**3**) with 2,4:3,5-di-*O*-benzylidene-*aldehydo*-D-ribose (**4**) giving a mixture of epimeric alcohols (**5a** and **6a**) that were not isolated as such but rather directly treated with methanol containing 10% concentrated hydrochloric acid at 60° for 2 min. This treatment effected removal of the *tert*-butyl and benzylidene protecting groups and led to simultaneous formation of the 1,4-anhydro sugars giving **1** and **2** in yields of 18 and 8%. Only traces of the pyranose isomers were formed. Subsequently, Asbun and Binkely have condensed 2,4-dibenzyloxypyrimidin-5-yllithium with several protected aldehydo sugars[6a] and aldonolactones[6b] as an approach to the synthesis of sugar analogs of pseudouridine.

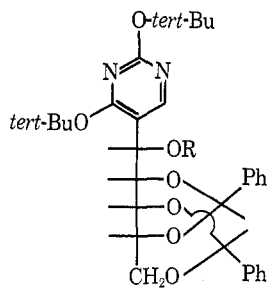
(1) Syntex Postdoctoral Fellow, 1966–1968.
(2) Syntex Postdoctoral Fellow, 1964–1965.
(3) For a review on the chemistry and biochemisry of pseudouridine, see (a) R. W. Chambers, *Progr. Nucl. Acid Res. Mol. Biol.*, **5**, 349 (1966); (b) E. Goldwasser and R. L. Heinrickson, *ibid.*, **5**, 399 (1966).
(4) R. Shapiro and R. W. Chambers, *J. Amer. Chem. Soc.*, **83**, 3920 (1961).
(5) (a) D. M. Brown, M. G. Burdon, and R. P. Slatcher, *Chem. Commun.*, 77 (1965); (b) D. M. Brown, M. G. Burdon, and R. P. Slatcher, *J. Chem. Soc.*, 1051 (1968).
(6) (a) W. A. Asbun and S. B. Binkley, *J. Org. Chem.*, **31**, 3315 (1966); (b) W. A. Asbun and S. B. Binkley, *ibid.*, **33**, 140 (1968).

With the objective of clarifying the mild and selective formation of anhydro sugar rings during the synthesis of **1** and **2** by the method of Brown, *et al.*,[5] we have reinvestigated these reactions in some depth and present our findings in this paper. In addition, we were motivated by the possibility of using certain intermediate products for the preparation of tritium-labeled pseudouridines which might be of interest for biochemical studies.

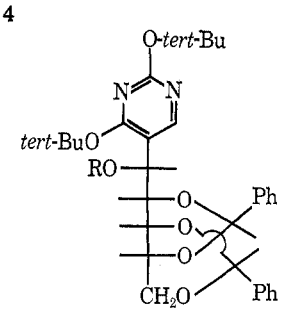
In our hands the condensation of **3** and **4** in tetrahydrofuran proceeded very rapidly at a low temperature and gave two major products of very similar polarity together with some 2,4-di-*tert*-butoxypyrimidine and unidentified carbohydrate products. A partial separation of the isomeric products (**5a** and **6a**) in a combined yield of 69% could be obtained by chromatography on a column of silicic acid. Complete resolution was achieved by preparative tlc of the overlapping fractions giving the less polar isomer 5-(2,4:3,5-di-*O*-benzylidene-D-*allo*-pentahydroxypentyl)-2,4-di-*tert*-butoxypyrimidine (**5**) in 25% yield and the corresponding altro isomer **6** in 37% yield.



3 **4**



5a, R = H
b, R = *p*-iodobenzoyl



6a, R = H
b, R = *p*-iodobenzoyl

The assignments of configurations to **5a** and **6a** is based predominantly upon optical rotatory dispersion (ORD) spectra which are shown in Figure 1. It has

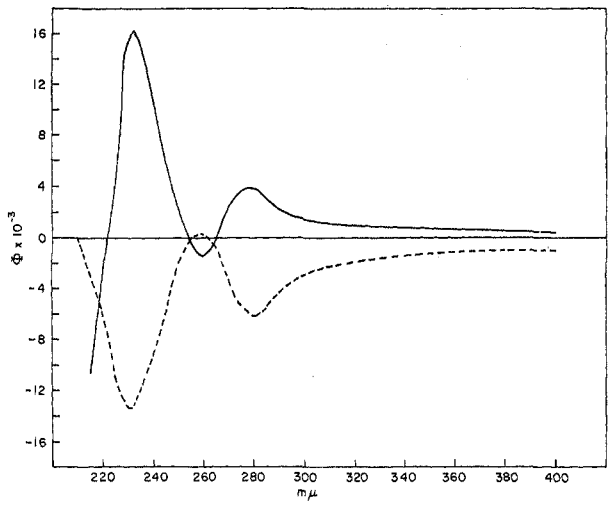
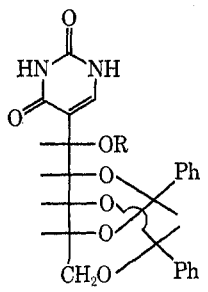


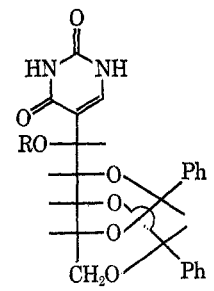
Figure 1.—ORD spectra (MeOH) of compounds **5a** (—) and **6a** (---).

long been recognized that the sign of the $[\alpha]_D$ of aromatic and heterocyclic polyols is governed by the configuration of the asymmetric center adjacent to the unsaturated ring. Thus, polyol derivatives of benzimidazoles,[7] pyrazoles,[8] triazines,[9] and other simple aromatics[10] are shown to have positive rotations when the $C_{1'}$ hydroxyl is on the right-hand side of a normal Fischer projection and negative rotations when on the left. More recently, these rules have been extended to show that various heterocyclic polyols with *S* chirality at $C_{1'}$ (OH on the right in the Fischer projection) give positive Cotton effects while those with *R* chirality give negative Cotton effects.[11] Since the longer wavelength Cotton effect (centered about the λ_{max}) of the less polar compound is positive, we have assigned this compound the allo configuration **5a** while the more polar isomer is considered to be the altro isomer **6a**. It will be seen that many compounds derived from **5** also show positive Cotton effects while those originating from **6** retain negative Cotton effects, thereby strengthening these assignments.

We have attempted to use the method of Horeau[12] to independently determine the configurations of **5a** and **6a** but, unfortunately, both compounds lead to residual acid with very small negative rotations. We have also attempted to prepare derivatives suitable for X-ray crystallographic analysis but have as yet been unsuccessful. Thus, reactions of **5a** and **6a** with *p*-iodobenzoyl chloride gave the appropriate 1′-*O*-*p*-iodobenzoates (**5b** and **6b**) only as amorphous solids. Brief treatment of **5b** and **6b** with 80% acetic acid selectively removed the *tert*-butoxy groups from the pyrimidine rings giving the free uracil derivatives **7a** and **8a** in crystalline form. Unfortunately, both compounds could be obtained only as tiny crystals that were not sufficiently large for X-ray analysis.



7a, R = *p*-iodobenzoyl
b, R = H



8a, R = *p*-iodobenzoyl
b, R = H

It has been previously shown that brief treatment of a mixture of **5a** and **6a** with hot methanolic hydrochloric acid leads to a mixture of β- and α-pseudouridine (**1** and **2**).[5] The same is true for the pure isomers, separate treatment of **5a** and **6a** with concentrated hydrochloric acid–methanol (1:9) under reflux for 1 min giving the β- and α-furanose isomers **1** and **2** in ratios of 1.1:1 and 2.6:1, respectively, as judged by borate electrophoresis at pH 9.6.[13] No appreciable pyranose isomers were formed. Examination of aliquots following shorter treatments with acid showed that almost complete formation of **1** and **2** had occurred during the first 30 sec and that the degree of stereospecificity was greater during the early phases of the reaction. Thus, treatment of **6a** led initially to almost exclusively β-pseudouridine (**1**) which then partially isomerized to its α anomer before **6a** had disappeared. Similar treatment of **5a** led initially to a preponderance of the α isomer **2**, but the rate of anomeric isomerization was rapid and gave an α:β mixture of 6:4 by the time cyclization was complete. In preparative reactions, treatment of **6a** with ethanolic hydrochloric acid under reflux for 40 sec gave a mixture of 76% β-pseudouridine (**1**), 12% α-pseudouridine (**2**), and 12% monobenzylidene compounds. Only traces of pyranosides were formed. From this mixture pure **1** could be obtained in 56% yield by direct crystallization. Similar treatment of **5a** gave a 6:4 mixture of **2** and **1** which was separated by borate ion exchange chromatography giving crystalline **2** and **1** in yields of 40 and 27%. Since removal of the hydrochloric acid on a larger scale can prove troublesome, the latter reaction was also done using sulfuric acid in aqueous methanol followed by precipitation of barium sulfate. Acidic cyclization of **6a** could also be conducted in methanol–hydrochloric acid (9:1) at room temperature for 24 hr and, once again, pure **1** was obtained in 50% yield by direct crystallization. Similar treatment of **5a** gave a mixture of **1** and **2** that required ion exchange separation.

In order to determine the sequence of steps in the acidic conversion of **5a** and **6a** to **1** and **2**, milder treatments were studied. Thus, it could be shown that the first point of attack is the *tert*-butyl ethers on the uracil rings. Treatment of **5a** with 80% acetic acid at room temperature for 2.5 hr gave essentially a single product that was isolated in crystalline form in 80% yield and shown to be 5-(2,4:3,5-di-*O*-benzylidene-D-*allo*-pentahydroxypentyl)uracil (**7b**) by analytical and spectroscopic methods. Similar treatment of **6a** gave the crystalline D-altro isomer **8b** in a yield of 74%.

(7) N. K. Richtmyer and C. S. Hudson, *J. Amer. Chem. Soc.*, **64**, 1612 (1942).

(8) (a) H. El Khadem, *J. Org. Chem.*, **28**, 2478 (1963); (b) J. A. Mills, *Aust. J. Chem.*, **17**, 277 (1964).

(9) M. Bobek, J. Farkaš, and F. Šorm, *Collect. Czech. Chem. Commun.*, **32**, 3572 (1967).

(10) H. El Khadem and Z. M. El-Shafei, *Tetrahedron Lett.*, 1887 (1963).

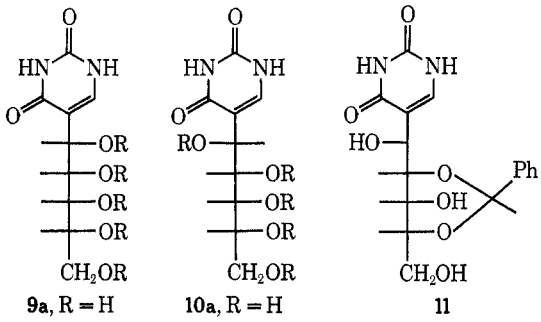
(11) W. S. Chilton and R. C. Krahn, *J. Amer. Chem. Soc.*, **89**, 4129 (1967); (b) W. S. Chilton and R. C. Krahn, *ibid.*, **90**, 1318 (1968); (c) G. G. Lyle and M. J. Piazza, *J. Org. Chem.*, **33**, 2478 (1968).

(12) A. Horeau and H. B. Kagan, *Tetrahedron*, **20**, 2431 (1964).

(13) Under these conditions there is a clear separation between the four furanose and pyranose isomers of 5-ribosyluracil.

As with the parent compounds, the ORD spectra of **7b** and **8b** gave opposite Cotton effects centered about 240 mμ with **8b** being negative in sign. The spectra of both compounds also show small troughs in the 285–290-mμ region which presumably originate from a spectral transition of the benzylidene groups that are common to both molecules.

More vigorous hydrolysis of **5a** and **6a** using 60–80% acetic acid at 100° led to the removal of both the *tert*-butyl and benzylidene groups and gave the crystalline, isomeric 5-(pentahydroxypentyl)uracils (**9a** and **10a**) with the D-allo and D-altro configurations, respectively, in yields of 61 and 72%. Once again these products showed Cotton effects of opposite sign and directly related to those of **5a** and **6a**. Some minor cyclization to pseudouridines accompanied this treatment and, to simplify the work-up, the reactions were usually terminated before the benzylidene group was completely removed. In one case, the mother liquors from a preparation of **10a** were purified by preparative tlc giving a 17% yield of the monobenzylidene derivative **11**. Since this compound did not reduce periodate, it was shown to have the 2,4-*O*-benzylidene structure rather than being its 3,5-substituted isomer. A chromatographically similar compound was also formed during preparation of **9** but has not been isolated.



Cyclization of the pentitols **9a** and **10a** can also be readily achieved by mild acidic treatment and here the stereochemistry of the process can be more clearly defined. Thus a suspension of **10a** in 1 *N* hydrochloric acid was stirred at room temperature and gave a clear solution after roughly 3 hr. After 6–8 hr, extensive formation of almost exclusively β-pseudouridine (**1**) had occurred and even after 24 hr the mixture contained only the β isomer **1** and roughly 5% of **2**. In a preparative reaction, pure **1** was isolated from such a reaction in 75% yield by direct crystallization, and this could undoubtedly be improved by chromatography of the mother liquors. On the other hand, **9a** was more readily soluble in 1 *N* hydrochloric acid and had completely cyclized within 3 hr giving predominantly α-pseudouridine (**2**) and only about 10% of the β isomer. Prolonged acidic treatment led to increased isomerization, the ratio of 2:1 being roughly 4:1 after 5 hr and 1:1 after 30 hr. No pyranose isomers were present by borate electrophoresis. The equilibration of the various pseudouridine isomers has been studied in 1 *N* hydrochloric acid at 100° by Cohn[14] in his classical paper on the structure of the natural product and has been mechanistically rationalized by Chambers, *et al.*[15] The much more facile anomerization of **2** relative to **1** does not, however, appear to have been previously noted. The cyclization reaction has been suggested to proceed *via* an SN1 process involving a common, allylically stabilized carbonium ion derived from $C_{1'}$ of **9a** or **10a**. Since **10a** leads almost exclusively to **1** while **9a** gives initially a preponderance of **2**, a common, *free* carbonium ion is probably not involved. An inspection of molecular models shows that the conversions of **9a** to **2** and of **10a** to **1** both involve an inversion of configuration at $C_{1'}$ of the pentitol moiety. Thus, the cyclization reaction may well involve an SN2 type of displacement of the protonated $C_{1'}$-hydroxyl group by the $C_{4'}$ hydroxyl. The alternative intermediacy of a solvent-stabilized $C_{1'}$-carbonium ion that is attacked by $C_{4'}$ OH with net inversion of configuration cannot be excluded. A direct SN2 displacement reaction has also been postulated[16] for the acid-catalyzed cyclization of simple pentitols, but, in this case, it is the primary hydroxyl group that is protonated thus leading to retention of configuration. It is interesting to note that acid-catalyzed cyclization of the 6-aza analogs of **9a** and **10a**, prepared in an ingenious way by Bobek, *et al.*,[17] leads to the 2′,5′- rather than the desired 1′,4′-anhydro compounds. This has been explained[17] by a decreased ability of the 6-azauracil moiety, relative to that of uracil, to stabilize a 1′-carbonium ion. In the present work we are confident that the anhydro bridge formed is the desired 1′,4′ structure. This is based upon the identical physical properties of **1** to the natural product and, in particular, on the nmr spectra of **1** and **2** in pentadeuteriopyridine. In these spectra the $C_{1'}$ protons appear as quartets at 5.43 and 5.62 ppm showing small allylic coupling to C_6 H of the uracil ring.[18] Acetylation of **1** and **2** gave the triacetates in which the 2′, 3′, and 5′ protons were typically deshielded by up to 1 ppm while C_1' H remained essentially unchanged. This clearly shows that there is not an hydroxyl group at $C_{1'}$ as would be the case in the 2′,5′-anhydro compounds such as **12**.

In the course of their work on the synthesis of 5-substituted uracils, Asbun and Binkley[6a] have also obtained, by a different route, a compound referred to as 5-α-D-ribitol uracil and considered to be **9a** from its ORD spectrum. The reported melting point is close to that of both **9a** and **10a**, and the reported positive Cotton effect suggests that this assignment is correct. This assignment is based, however, upon an ORD spectrum of **1** that appears to bear no similarity at all to that obtained by us (see Experimental Section). This compound was obtained following treatment with 0.2 *N* sulfuric acid for 16 hr and has led to the suggestion that cyclization does not occur readily even under more vigorous conditions. In a subsequent paper, these authors[6b] have also prepared **1** in an overall yield of 10% by a process that involves the intermediate formation of **9a** or **10a** which was not isolated but which did cyclize with 0.2 *N* sulfuric acid. In our

(14) W. E. Cohn, *J. Biol. Chem.*, **235**, 1488 (1960).

(15) R. W. Chambers, V. Kurkov, and R. Shapiro, *Biochemistry*, **2**, 1192 (1963).

(16) B. G. Hudson and R. Barker, *J. Org. Chem.*, **32**, 3650 (1967).

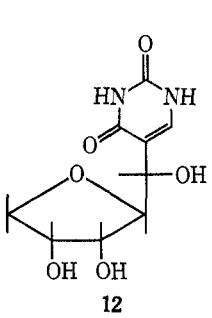
(17) M. Bobek, J. Farkaš, and F. Šorm, *Collect. Czech. Chem. Commun.*, **34**, 1673 (1969).

(18) A similar allylic coupling of the anomeric proton in naturally occurring **1** has recently been observed in D_2O by F. E. Hruska, A. A. Grey, and I. P. C. Smith, *J. Amer. Chem. Soc.*, **92**, 4088 (1970).

hands 0.2 *N* sulfuric acid at 23° proved to be inefficient for the cyclization of both **9a** and **10a**, only about 10% conversion to **1** and **2** being achieved in 16 hr. The use of 1 *N* hydrochloric acid as above does, however, clarify the stereochemistry of the cyclization process.

Oxidation of both **5a** and **6a** using dimethyl sulfoxide activated by either acetic anhydride[19] or dicyclohexylcarbodiimide[20] gave crystalline 5-(2,4:3,5-di-*O*-benzylidene-1-keto-D-*ribo*-tetrahydroxypentyl)-2,4-di-*tert*-butoxypyrimidine (**13**) in high yield. This oxidation can also be achieved using manganese dioxide in acetonitrile.[21] Reduction of this ketone with either sodium borohydride or lithium aluminum hydride was essentially stereospecific giving **5a** and **6a** in ratios of 94:6 and 96:4, respectively. Since **5a** can be readily converted into both **1** and **2**, the reduction of **13** with sodium borotritiide would appear to provide a facile route for the synthesis of **1** or **2** bearing a specific tritium label at $C_{1'}$ of the sugar. Such an isotopic synthesis has not been carried out but might prove useful for biochemical studies on pseudouridines.

Selective removal of the *tert*-butyl groups from **13** could be achieved by treatment with 80% acetic acid at room temperature giving **14** in almost quantitative yield. More vigorous treatment of **13** with 50% acetic acid at 100° leads to extensive decomposition and the reaction has not been examined further.



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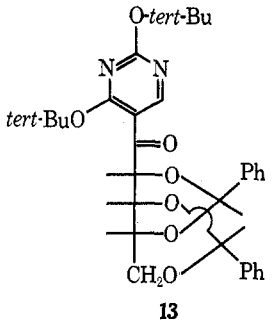
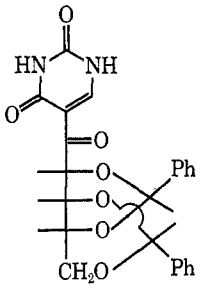
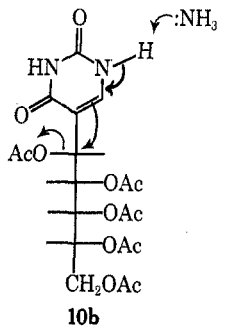


13

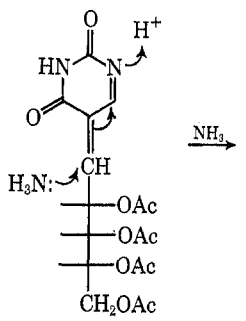


14

Acetylation of **9a** and **10a** gave the corresponding pentacetates **9b** and **10b** in high yields. Deacetylation of these derivatives with methanolic ammonia or ammonium hydroxide did not, however, regenerate the original pentitols. Thus, treatment of either **9b** or **10b** led to very similar paper chromatographic patterns containing a major spot which showed some tendency to partially separate into a second minor component. By preparative tlc on microcrystalline cellulose, the major product from **10b** was obtained in crystalline form in 57% yield. By paper chromatography in several solvents this compound behaved very similarly to **2**, but borate electrophoresis (pH 9.2) showed it to be slower moving than either **1** or **2**. This compound had the typical ultraviolet spectrum of a pseudouridine derivative and rapidly consumed 2.90 mol of periodate[22] with release of 1.00 mol of formaldehyde.[23] The nmr spectrum of this compound did not show resolution of the sugar protons but contained a 3-proton singlet at 1.91 ppm typical of an *N*-acetyl derivative. Based upon the elemental analysis of this compound, we consider it to be the acetamidotetraol (**17**). This structure could arise by rapid base-catalyzed elimination of acetate from $C_{1'}$ of **10b** giving the olefin **15** which then undergoes conjugate addition of ammonia giving **16** followed by O → N acetyl migration.



10b



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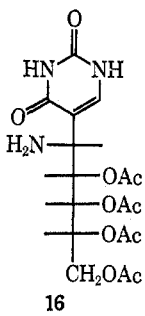

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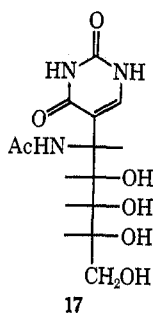

17

Since **17** shows a negative Cotton effect in its ORD spectrum, we tentatively assign it the D-altro configuration. This sequence of events is very similar to that known to occur during reaction of penta-*O*-acetyl-1-deoxy-1-nitrohexitols,[24] or the nitro olefins derived from them,[25] with ammonia giving 2-acetamido-1,2-dideoxy-1-nitrohexitols. A related participation of the uracil ring has also been shown to occur during the conversion of 5-acetoxymethyluracil to 5-methoxymethyluracil with sodium methoxide.[26] By the pathway **10b** → **17**, both **9b** and **10b** would be expected to give the same ultimate mixture of acetamido epimers dictated by the steric restraints on **15**. While a shortage of **9b** has prevented its preparative conversion to pure **17**, the chromatographic and electrophoretic patterns of the crude reaction mixtures are so similar as to make this seem likely.

The synthetic routes described in this paper would appear to make pure samples of both isotopically labeled and unlabeled **1** and **2** quite readily available.

(19) J. D. Albright and L. Goldman, *J. Amer. Chem. Soc.*, **89**, 2416 (1967).
(20) K. E. Pfitzner and J. G. Moffatt, *ibid.*, **87**, 5661 (1965).
(21) R. M. Evans, *Quart. Rev. Chem. Soc.*, **13**, 61 (1959).
(22) J. S. Dixon and D. Lipkin, *Anal. Chem.*, **26**, 1092 (1954).
(23) R. M. Burton, *Methods Enzymol.*, **3**, 246 (1957).
(24) C. Satoh and A. Kiyomoto, *Carbohyd. Res.*, **7**, 138 (1968).
(25) (a) A. N. O'Neill, *Can. J. Chem.*, **37**, 1747 (1959); (b) M. B. Perry and J. Furdova, *ibid.*, **46**, 2859 (1968).
(26) D. V. Santi and A. L. Pogolotti, *Tetrahedron Lett.*, 6159 (1968).

Experimental Section

Thin layer chromatography (tlc) was performed using 0.25-mm layers of Merck silica gel GF and preparative tlc on 20 × 100 cm glass plates coated with a 1.3-mm layer of Merck silica gel HF. Nuclear magnetic resonance spectra were obtained using a Varian HA-100 spectrometer and are reported as parts per million downfield from an internal standard of tetramethylsilane. The assignments of sugar protons were generally confirmed by spin decoupling. We are particularly grateful to Dr. M. L. Maddox and Mrs. J. Nelson for their cooperation in nmr studies. Optical rotatory dispersion (ORD) spectra were obtained using a Jasco ORD/UV-5 instrument. Elemental analyses were obtained by Dr. A. Bernhardt, Mühlheim, Germany, and other instrumental analyses were by the staff of the Analytical Laboratory of Syntex Research.

5-Bromo-2,4-di-*tert*-butoxypyrimidine.—This compound was prepared from 5-bromo-2,4-dichloropyrimidine essentially according to Brown, *et al.*,[5b] and purified by sublimation in 83% yield: λ_{max}^{MeOH} 225 mμ (ε 10,700), 276 (5900); nmr ($CDCl_3$) 1.59 and 1.63 ppm (s, 9, *tert*-BuO), 8.24 (s, 1, C_6 H).

2,4:3,5-Di-*O*-benzylidene-*aldehydo*-D-ribose (4) and Its Methyl Hemiacetal.—The hydrated aldehydo sugar was prepared essentially according to Zinner[27] and was dried *in vacuo* at 100° for 3 hr prior to use: ν_{max} (KBr) 1740 cm^{-1}. Crystallization from methanol gave a methyl hemiacetal with mp 153–155°; $[\alpha]^{23}D$ −30.1° (*c* 1.0, $CHCl_3$); nmr ($CDCl_3$) 3.49 (s, 3, OMe), 4.0 (m, 4, $C_{3'}$ H, $C_{4'}$ H, and $C_{5'}$ H_2), 4.41 (m, 1, $C_{2'}$ H), 4.8 (m, 1, $C_{1'}$ H sharpening with D_2O), 5.69 (s, 1, $ArCHO_2$), 5.81 (s, 1, $ArCHO_2$), 7.4 ppm (m, 10, arom).

Anal. Calcd for $C_{20}H_{22}O_6$: C, 67.03; H, 6.19; O, 26.79. Found: C, 67.06; H, 6.03; O, 26.99.

Upon heating *in vacuo* at 185° for 2 min, the hemiacetal was converted to the free aldehyde which distilled to the cooler parts of the flask and was identified by an intense carbonyl band at 1740 cm^{-1}.

5-(2,4:3,5-Di-*O*-benzylidene-D-*allo*-pentahydroxypentyl)-2,4-di-*tert*-butoxypyrimidine (5a) and Its D-Altro Isomer (6a).—A solution of 5-bromo-2,4-di-*tert*-butoxypyrimidine (10.7 g, 35 mmol) in anhydrous tetrahydrofuran (100 ml) was cooled to −70° in an atmosphere of argon. To this stirred solution was added, *via* a rubber septum, a solution of butyllithium (24.5 ml of 1.5 *M*, 36.7 mmol), and the resulting yellow solution was stirred for 25 min. A solution of freshly dried (100° at 1 mm for 3 hr) **4** (11.4 g, 35 mmol) in tetrahydrofuran (150 ml) was added dropwise over 30 min, and the mixture was then allowed to warm to room temperature overnight. After removal of roughly half the solvent *in vacuo*, the residue was partitioned between ether and water and the aqueous phase was extracted several times with ether. The combined ether extracts were dried ($MgSO_4$) and evaporated leaving a syrup (20 g) that was chromatographed on a column containing 1 kg of silicic acid using chloroform. This clearly separated a little 2,4-di-*tert*-butoxypyrimidine [bp 60° (0.1 mm); mp 47–50°; nmr 1.47 (s, 18, *tert*-BuO), 6.06 (d, 1, $J_{5,6}$ = 5.5 Hz, C_5 H), 7.93 ppm (d, 1, $J_{5,6}$ = 5.5 Hz, C_6H)[28] from **5a** and **6a** which were partially separated. The overlapping fractions were further purified by tlc using three passes with carbon tetrachloride–acetone (87:13). The less polar compound **5a** (4.80 g, 25%) was obtained in crystalline form and had mp 170–171° from ether–hexane; λ_{max}^{MeOH} 266 mμ (ε 5800); $[\alpha]^{23}D$ +17.5° (*c* 0.1, MeOH); ORD, see Figure 1; nmr ($CDCl_3$) 1.48 and 1.56 (s, 9, *tert*-BuO), 3.25 (d, 1, $J_{H,OH}$ = 5 Hz, $C_{1'}$ OH), 3.7–4.4 (m, 5, $C_{2'}$, $C_{3'}$, $C_{4'}$, and $C_{5'}$ H's), 5.10 (q, 1, $J_{1',2'}$ = 2.4 Hz, $J_{H,OH}$ = 5 Hz, $C_{2'}$ H), 5.58 and 5.77 (s, 1, $ArCHO_2$), 7.4 (m, 10, arom), 8.35 ppm (s, 1, C_6 H).

Anal. Calcd for $C_{31}H_{38}N_2O_7$: C, 67.62; H, 6.96; N, 5.09. Found: C, 67.79; H, 7.13; N, 4.99.

The more polar altro isomer **6a** was obtained as a chromatographically homogeneous, but noncrystalline foam (7.04 g, 37%): λ_{max}^{MeOH} 266 mμ (ε 5700); $[\alpha]^{23}D$ −66.7° (*c* 0.27, MeOH); ORD, see Figure 1; nmr ($CDCl_3$) 1.53 and 1.57 (s, 9, *tert*-BuO), 3.0 (m, 1, $C_{1'}$ OH), 3.9–4.5 (m, 5, $C_{2'}$, $C_{3'}$, $C_{4'}$, and $C_{5'}$ H's), 5.13 (br d, 1, $J_{1',2'}$ = 2 Hz, $C_{1'}$ H), 5.69 and 5.76 (s, 1, $ArCHO_2$), 7.4 (m, 10, arom), 8.30 ppm (s, 1, C_6 H).

Anal. Calcd for $C_{31}H_{38}N_2O_7$: C, 67.62; H, 6.96; N, 5.09. Found: C, 67.71; H, 7.12; N, 4.91.

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5-(1-*p*-Iodobenzoyl-2,4:3,5-di-*O*-benzylidene-D-*allo*-pentahydroxypentyl)uracil (7a).—A solution of **5a** (400 mg, 0.72 mmol) and *p*-iodobenzoyl chloride (450 mg, 1.7 mmol) in pyridine (2 ml) was kept for 3 hr at 23°. It was then diluted with ether and extracted several times with aqueous sodium bicarbonate. The dried ether solution was purified by preparative tlc using carbon tetrachloride–acetone (19:1) to give **5b** (411 mg) as a homogeneous, noncrystalline foam. This material (390 mg) was treated at room temperature for 7 min with 80% acetic acid giving a partially crystalline precipitate that was collected and washed with 80% acetic acid and then water. Crystallization from chloroform–ethanol gave **7a** as tiny needles with mp 222–224°; λ_{max}^{MeOH} 258 mμ (ε 22,300); nmr (DMSO-d_6) 3.8–4.7 (m, 5, $C_{2'}$, $C_{3'}$, $C_{4'}$, and $C_{5'}$ H's), 5.68 and 5.95 (s, 1, $ArCHO_2$), 6.28 (d, 1, $J_{1',2'}$ = 4.5 Hz, $C_{1'}$ H), 7.2–7.5 (m, 10, arom), 7.60 (s, 1, C_6 H), 7.60 and 7.88 (d, 2, *J* = 8 Hz, *p*-iodobenzoyl), 11.3 ppm (br s, 1, NH).

Anal. Calcd for $C_{30}H_{25}N_2O_8I$: C, 53.90; H, 3.77; N, 4.19; I, 18.99. Found: C, 53.74; H, 4.24; N, 4.16; I, 18.99.

5-(1-*p*-Iodobenzoyl-2,4:3,5-di-*O*-benzylidene-D-*altro*-pentahydroxypentyl)uracil (8a).—The altro compound **6a** (400 mg) was treated with *p*-iodobenzoyl chloride as above giving 396 mg of the noncrystalline ester **6b** which was treated with 80% acetic acid for 15 min at 23°. In this case, precipitation did not occur and the product was isolated by dilution with chloroform and washing with aqueous sodium bicarbonate. After evaporation of the organic phase and crystallization from methylene chloride–ethanol, **8a** (205 mg) was obtained as tiny crystals with mp 239–240° (mixture melting point with **7a** 207–218°); λ_{max}^{MeOH} 258 mμ (ε 24,500); nmr (DMSO-d_6) 3.8–4.6 (m, 5, $C_{2'}$, $C_{3'}$, $C_{4'}$, and $C_{5'}$ H's), 5.63 and 5.94 (s, 1, $ArCHO_2$), 6.24 (d, 1, $J_{1',2'}$ = 5 Hz, $C_{1'}$ H), 7.2–7.5 (m, 10, arom), 7.51 (s, 1, C_6 H), 7.80 and 7.99 (d, 2, *J* = 8 Hz, *p*-iodobenzoyl), 10.92 and 11.23 (br s, 1, NH).

Anal. Calcd for $C_{30}H_{25}N_2O_8I$: C, 53.90; H, 3.77; N, 4.19; I, 18.99. Found: C, 53.93; H, 3.98; N, 4.29; I, 19.00.

5-(2,4:3,5-Di-*O*-benzylidene-D-*allo*-pentahydroxypentyl)uracil (7b).—A solution of **5a** (250 mg) in 80% acetic acid (4 ml) was kept at 23° for 2.5 hr while following the hydrolysis by tlc using chloroform–methanol (9:1). The mixture was then diluted with ethyl acetate and washed with saturated aqueous potassium carbonate. Evaporation of the organic phase and purification of the residue by preparative tlc using carbon tetrachloride–acetone (1:1) followed by crystallization from methanol gave 159 mg (80%) of **7b** as fine needles of mp 247–248° as a methanol solvate: λ_{max}^{MeOH} 265 mμ (ε 8000); $[\alpha]^{23}D$ +3.2° (*c* 0.1, MeOH); ORD (MeOH) positive Cotton effect with a peak at 257 mμ (Φ +15,900°), a trough at 234 mμ (Φ +2300°), and a peak at 223 mμ (Φ +7100°); nmr (DMSO-d_6) 3.17 (s, 3, MeOH), 3.9 (m, 3, OCH), 4.2 (m, 2, OCH), 4.78 (br d, 1, $J_{H,OH}$ = 5 Hz, $C_{1'}$ H), 5.53 (d, 1, $J_{H,OH}$ = 5 Hz, $C_{1'}$ OH), 5.62 and 5.75 (s, 1, $ArCHO_2$), 7.2–7.5 (m, 11, arom and C_6 H), 11.0 ppm (br s, 2, N_1 H and N_3 H).

Anal. Calcd for $C_{23}H_{22}N_2O_7$·MeOH: C, 61.27; H, 5.57; N, 5.97. Found: C, 61.15; H, 5.34; N, 6.00.

5-(2,4:3,5-Di-*O*-benzylidene-D-*altro*-pentahydroxypentyl)uracil (8b).—A solution of **6a** (250 mg) in 80% acetic acid (4 ml) was kept at 23° for 2.5 hr and worked up exactly as above. Crystallization from methanol–ether gave **8b** (148 mg, 74%) as short needles of mp 253–254° with gas evolution; λ_{max}^{MeOH} 262 mμ (ε 7700); $[\alpha]^{23}D$ −100.8° (*c* 0.1, MeOH); ORD (MeOH) negative Cotton effect with a trough at 260 mμ (Φ −14,800°), crossover at 242 mμ, and a peak at 234 mμ (Φ +4700°); nmr (pyridine-d_5) 3.95–4.6 (m, 4, $C_{3'}$, $C_{4'}$, and $C_{5'}$, H's), 4.68 (d, 1, $J_{1',2'}$ = 3 Hz, $C_{2'}$ H), 5.77 (d, 1, $J_{1',2'}$ = 3 Hz, $C_{1'}$ H), 5.81 and 5.98 (s, 1, $ArCHO_2$), 7.3–7.8 (m, 10, arom), 8.0 (s, 1, C_6 H).

Anal. Calcd for $C_{23}H_{22}N_2O_7$·MeOH: C, 61.27; H, 5.57; N, 5.96. Found: C, 61.03; H, 5.20; N, 6.02.

After drying *in vacuo* at 100°, the free compound was obtained.

Anal. Calcd for $C_{23}H_{22}N_2O_7$: C, 63.01; H, 5.06; N, 6.39. Found: C, 63.54; H, 5.16; N, 6.48.

5-(D-*allo*-Pentahydroxypentyl)uracil (9a).—A solution of **5a** (1.0 g) in 80% acetic acid (20 ml) was heated at 100° for 8 min and evaporated to dryness. Trituration of the residue with ethanol gave 252 mg (53%) of pure **9a**. Retreatment of the evaporated mother liquors with 60% acetic acid at 100° for 5 min gave a further 105 mg of product and recrystallization from 90% ethanol gave a total of 292 mg (61%) of **9a** with mp 191–192° (mixture melting point with **10a** 184–186°); $\lambda_{max}^{H_2O}$ 264 mμ (ε 7500); $[\alpha]^{23}D$ +55.8° (*c* 0.2, H_2O); ORD (MeOH) positive Cotton effect with a peak at 260 mμ (Φ +4000°), a trough at 233 mμ

(Φ +300°), and a peak at 219 mμ (Φ +1700°); nmr (DMSO-d_6) 3.2–5.1 (m, 11, all sugar CH and OH including 4.65 ppm, d, 1, $J_{1',2'}$ = 4.5 Hz, $C_{1'}$ H), 7.26 ppm (s, 1, C_6 H).

Anal. Calcd for $C_9H_{14}N_2O_7$: C, 41.30; H, 5.35; N, 10.69. Found: C, 41.29; H, 5.51; N, 10.91.

5-(D-*allo*-Pentaacetoxypentyl)uracil (9b).—A mixture of **9a** (300 mg), pyridine (5 ml), and acetic anhydride (1.0 ml) was stirred overnight at 23°. After evaporation of the solvent the residue was dissolved in chloroform, washed with bicarbonate and with water, dried, and evaporated. Preparative tlc using chloroform–methanol (9:1) gave a single band that was eluted giving 458 mg (85%) of the pentaacetate (**9b**) as a foam that could not be crystallized: λ_{max}^{MeOH} 262 mμ (ϵ 7900); $[\alpha]^{23}D$ +73° (*c* 0.2, MeOH); ORD (MeOH) positive Cotton effect with a peak at 264 mμ (Φ +7100°), crossover at 244 mμ, and a trough at 230 mμ (Φ −4100°); nmr ($CDCl_3$) 2.02, 2.05, and 2.10 (9 H) (s, 3, OAc), 4.1–4.6 (m, 2, $C_{5'}$ H_2), 5.35 (m, 2, $C_{3'}$ H and $C_{4'}$ H), 5.70 (t, 1, $J_{1',2'} = J_{2',3'}$ = 5.5 Hz, $C_{2'}$ H), 5.99 (d, 1, $J_{1',2'}$ = 5.5 Hz, $C_{1'}$ H), 7.58 ppm (s, 1, C_6 H).

Anal. Calcd for $C_{19}H_{24}N_2O_{12}$: C, 48.31; H, 5.12; N, 5.93. Found: C, 48.64; H, 5.24; N, 6.29.

5-(D-*altro*-Pentahydroxypentyl)uracil (10a).—A solution of **6a** (0.75 g) in 60% acetic acid (20 ml) was heated at 100° for 6 min and evaporated to dryness. Trituration of the residue with methanol gave 243 mg of almost pure **10a**. The mother liquors which contained some monobenzylidene derivative **11** were evaporated to dryness and retreated as above with acetic acid for 5 min giving a further 69 mg (total yield 87%) of almost pure **10a**. Recrystallization from aqueous ethanol gave 255 mg (72%) of **10a** with mp 197–199°; $\lambda_{max}^{H_2O}$ 263 mμ (ϵ 7400); $[\alpha]^{22}D$ −96.0° (*c* 0.1, MeOH); ORD (H_2O) negative Cotton effect with a trough at 252 mμ (Φ −10,600°) and a peak at 232 mμ (Φ −1700°); nmr (DMSO-d_6) 3.4–3.7 (m, 5, $C_{2'}$, $C_{3'}$, $C_{4'}$, and $C_{5'}$ H's), 4.3 (m, 1, OH), 4.6 (m, 3, OH), 4.78 (s, 1, $C_{1'}$ H), 7.20 (s, 1, C_6 H), 10.5–11.0 ppm (m, 2, N_1 H and N_3 H).

Anal. Calcd for $C_9H_{14}N_2O_7$: C, 41.30; H, 5.35; N, 10.69. Found: C, 41.46; H, 5.50; N, 10.63.

5-(2,4-*O*-Benzylidene-D-*altro*-pentahydroxypentyl)uracil (11).—During preparation of **10a** a less polar by-product was usually detected by tlc. In one experiment on hydrolysis of **6a** (650 mg) as above this product was isolated by preparative tlc on microcrystalline cellulose using 1-butanol–acetic acid–water (5:2:3). Crystallization from ethyl acetate–methanol gave 70 mg (17%) of **11** with mp 218–219°; λ_{max}^{MeOH} 262 mμ (ϵ 7700); $[\alpha]^{23}D$ −144° (*c* 0.1, MeOH); ORD (MeOH) negative Cotton effect with a trough at 255 mμ (Φ −16,900°), a peak at 235 mμ (Φ −11,500°), and a trough at 220 mμ (Φ −27,200°); nmr ($CDCl_3$) 3.6 (br s, 5, $C_{2'}$, $C_{3'}$, $C_{4'}$, and $C_{5'}$ H's), 4.95 (d, 1, $J_{1',6}$ = 1 Hz, $C_{1'}$ H), 5.53 (s, 1, $ArCHO_2$), 7.40 (br s, 6, Ar and C_6 H). The compound did not reduce periodate.

Anal. Calcd for $C_{16}H_{18}N_2O_7$: C, 54.85; H, 5.18; N, 8.00. Found: C, 54.70; H, 5.71; N, 8.18.

5-(D-*altro*-Pentaacetoxypentyl)uracil (10b).—A suspension of **10a** (310 mg) in pyridine (3 ml) and acetic anhydride (3 ml) was stirred at 23° for 45 hr. After addition of water, the mixture was extracted into chloroform, washed with bicarbonate, and evaporated leaving a crystalline residue that was recrystallized from methylene chloride–ether giving 471 mg (84%) of **10b** with mp 181–182°. An analytical sample had mp 183–184°; λ_{max}^{MeOH} 262 mμ (ϵ 7500); $[\alpha]^{23}D$ −38.7° (*c* 0.1, MeOH); ORD (MeOH) negative Cotton effect with a trough at 265 mμ (Φ −14,500°), crossover at 250 mμ, and a peak at 233 mμ (Φ +15,600°); nmr ($CDCl_3$) 2.01, 2.04, 2.06, and 2.11 (6 H) (s, 3, OAc), 4.25 (m, 2, $C_{5'}$ H_2), 5.3 (m, 2, $C_{3'}$ H and $C_{4'}$ H), 5.55 (q, 1, $J_{1',2'}$ = 2.5 Hz, $J_{2',3'}$ = 8 Hz, $C_{2'}$ H), 5.99 (d, 1, $J_{1',2'}$ = 2.5 Hz, $C_{1'}$ H), 7.37 (br d, 1, J_{6,N_1H} = 4 Hz, C_6 H), 9.93 (br s, 1, N_3 H), 10.25 ppm (br d, J_{6,N_1H} = 4 Hz, N_1 H).

Anal. Calcd for $C_{19}H_{24}N_2O_{12}$: C, 48.31; H, 5.12; N, 5.93. Found: C, 48.31; H, 5.25; N, 5.98.

5-β-D-Ribofuranosyluracil (1) and 5-α-D-Ribofuranosyluracil (2). A. From 6a in Hot Acid.—A solution of **6a** (250 mg) in ethanol (4.5 ml) was heated under reflux on a boiling water bath. Concentrated hydrochloric acid (0.5 ml) was added and after 40 sec the mixture was chilled in ice and evaporated to dryness under high vacuum. The residue was repeatedly coevaporated with ethanol until the odor of hydrochloric acid was absent and was then partitioned between water and ether. Following evaporation of the aqueous phase the residue was crystallized from ethanol giving 62 mg (56%) of **1** that was pure by borate electrophoresis and had mp 222–223° (reported mp 222–224°,[5b] 223–224°[4]); $\lambda_{max}^{H_2O}$ 262 mμ (ϵ 7900); $\lambda_{max}^{pH\ 12}$ 287 mμ (ϵ 7800); A_{280}/A_{260} (pH 12) = 2.10; ORD (H_2O) negative Cotton effect with a trough at 284 mμ (Φ −700°), crossover at 274 mμ, and a peak at 253 mμ (Φ +2300°); nmr (pyridine-d_5) 4.13 (q, 1, J_{gem} = 12 Hz, $J_{4',5'a}$ = 3 Hz, $C_{5'a}$ H), 4.32 (q, 1, J_{gem} = 12 Hz, $J_{4',5'b}$ = 3 Hz, $C_{5'b}$ H), 4.61 (m, 1, $C_{4'}$ H), 4.85 (t, 1, $J_{2',3'} = J_{3',4'}$ = 4.5 $C_{3'}$ H), 4.98 (t, 1, $J_{1',2'} = J_{2',3'}$ = 4.5 Hz, $C_{2'}$ H), 5.43 (q, 1, $J_{1',2'}$ = 4.5 Hz, $J_{1',6}$ = 1 Hz, $C_{1'}$ H), 8.16 ppm (d, 1, $J_{1',6}$ = 1 Hz, C_6 H). Acetylation with acetic anhydride and pyridine quantitatively gave the 2′,3′,5′-tri-*O*-acetate that was isolated by preparative tlc using chloroform–2-propanol (9:1): nmr (pyridine-d_5) 1.99, 2.03, and 2.08 (s, 3-OAc), 4.95–5.15 (m, 3, $C_{4'}$ H and $C_{5'}$ H_2), 5.26 (d, 1, $J_{1',2'}$ = 4.5 Hz, $C_{1'}$ H with slight allylic coupling), 5.86 (t, 1, $J_{2',3'} = J_{3',4'}$ = 6 Hz, $C_{3'}$ H), 6.13 (q, 1, $J_{1',2'}$ = 4.5 Hz, $J_{2',3'}$ = 6 Hz, $C_{2'}$ H), 7.90 ppm (s, 1, C_6 H).

B. From 6a at Room Temperature.—A solution of **6a** (250 mg) in methanol (2.25 ml) and concentrated hydrochloric acid (0.25 ml) was kept at 23° for 24 hr during which time some pure **1** crystallized from solution. The mixture was evaporated to dryness and worked up as in A giving 62 mg (56%) of pure **1** with mp 222–223°.

C. From 5a.—A solution of **5a** (550 mg, 1 mmol) in methanol–hydrochloric acid (10 ml, 9:1) was treated as in A above. The aqueous solution following ether extraction was made 0.1 *M* in ammonium hydroxide and 0.05 *M* in boric acid and applied to a 3.5 × 35 cm column of Dowex-1 (HCO_3^-) resin. After a water wash the column was eluted with a linear gradient starting with 4 l. of 0.02 *M* boric acid, pH 9.3 in the mixing vessel, and 4 l. of 0.1 *M* ammonium bicarbonate in the reservoir. Following two very small peaks, two major, well-separated peaks emerged. The first peak (3500 OD units at 263 mμ) was evaporated to dryness, repeatedly coevaporated with methanol, and then passed through a 1 × 15 cm column of Dowex 50 (H^+) resin. The eluate was evaporated to dryness and coevaporated three times with methanol. The final residue was crystallized from ethanol giving 98 mg (40%) of electrophoretically pure α-pseudouridine (**2**) with mp 218–219° (reported[5b] mp 207–210°); $\lambda_{max}^{H_2O}$ 263 mμ (ϵ 7500); $\lambda_{max}^{pH\ 12}$ 288 mμ (ϵ 5600); A_{280}/A_{260} (pH 12) = 1.51; ORD (H_2O) positive Cotton effect with a peak at 283 mμ (Φ +3200°), crossover at 275 mμ, a trough at 255 mμ (Φ −13,100°), crossover at 234 mμ, and a peak at 230 mμ (Φ +1200°); nmr (pyridine-d_5) 4.16 (q, 1, J_{gem} = 12 Hz, $J_{4',5'a}$ = 4.5 Hz, $C_{5'a}$ H), 4.37 (q, 1, J_{gem} = 12 Hz, $J_{4',5'b}$ = 3 Hz, $C_{5'b}$ H), 4.67 (m, 1, $C_{4'}$ H), 5.0 (m, 2, $C_{2'}$ H and $C_{3'}$ H), 5.62 (q, 1, $J_{1',2'}$ = 3 Hz, $J_{1',6}$ = 1.5 Hz, $C_{1'}$ H), 7.98 ppm (d, 1, $J_{1',6}$ = 1.5 Hz, C_6 H). Acetylation (acetic anhydride, pyridine) gave the 2′,3′,5′-tri-*O*-acetate that was isolated by preparative tlc using chloroform–2-propanol (9:1) with mp 175–177°; nmr (pyridine-d_5) 1.99 (s, 9, 2′-, 3′-, and 5′-OAc), 4.4–4.8 (m, 3, $C_{4'}$ H and $C_{5'}$ H_2), 5.75 (q, 1, $J_{1',2'}$ = 3 Hz, $J_{1',6}$ = 1.5 Hz, $C_{1'}$ H), 5.92 (q, 1, $J_{2',3'}$ = 5 Hz, $J_{3',4'}$ = 4 Hz, $C_{3'}$ H), 6.25 (q, 1, $J_{1',2'}$ = 3 Hz, $J_{2',3'}$ = 5 Hz, $C_{2'}$ H), 7.99 (d, 1, $J_{1',6}$ = 1.5 Hz, C_6 H).

The second major peak (2500 OD units at 263 mμ) was worked up in an identical way giving 67 mg (27%) of β-pseudouridine (**1**) with mp 222–223° from ethanol.

D. From 5a and 6a with Sulfuric Acid.—A roughly equal mixture of **5a** and **6a** (0.8 mmol) was dissolved in methanol–4 *N* sulfuric acid (3:1) and heated at 100° for 6 min. It was then diluted with water, extracted with ether, and brought to pH 8 with barium hydroxide. After centrifugation the supernatant liquid was separated by ion exchange chromatography as in C giving traces (total of 1.6%) of pyranosyl pseudouridines followed by **1** and **2** which were isolated crystalline as above in yields of 29 and 22%.

E. From 10a.—A suspension of **10a** (50 mg) in 1 *N* hydrochloric acid was stirred at room temperature for 22 hr, a clear solution resulting after 3 hr. The solution was carefully evaporated to dryness and coevaporated several times with ethanol giving a white residue that was crystallized from ethanol giving 35 mg (75%) of pure **1** identical with that above.

5-(2,4:3,5-Di-*O*-benzylidene-1-keto-D-*ribo*-tetrahydroxypentyl)-2,4-di-*tert*-butoxypyrimidine (13). A.—A solution of **5a** (300 mg) in DMSO (2 ml) and acetic anhydride (1.3 ml) was kept at 23° for 24 hr. After addition of chloroform, the solution was extracted several times with aqueous sodium bicarbonate, dried ($MgSO_4$), and evaporated. Preparative tlc using carbon tetrachloride–acetone (9:1) gave 274 mg (92%) of crystalline **13** with mp 250–252° from ethanol;[29] λ_{max}^{MeOH} 252 mμ (ϵ 10,900), 283

(29) In some experiments a lower melting form (mp 154–156°) was obtained. Recrystallization of this compound with seeding by the higher melting form gave mp 252–254°.

(11,000); $[\alpha]^{23}D$ −44.2° (*c* 0.2, MeOH); ORD (MeOH) multiple Cotton effect with a peak at 335 mμ (Φ +8300°), crossover at 307 mμ, a trough at 290 mμ (Φ −7500°), crossover at 277 mμ, a shoulder at 265 mμ (Φ +5100°), and a peak at 238 mμ (Φ +30,500°); nmr ($CDCl_3$) 1.60 and 1.62 (s, 9, *tert*-BuO), 3.9–4.5 (m, 4, $C_{3'}$, $C_{4'}$, and $C_{5'}$ H's), 5.45 (d, 1, $J_{2',3'}$ = 8 Hz, $C_{2'}$ H), 5.67 and 5.82 (s, 1, $ArCHO_2$), 7.3–7.6 (m, 10, arom), 8.40 ppm (s, 1, C_6H).

Anal. Calcd for $C_{31}H_{36}N_2O_7$: C, 67.86; H, 6.61; N, 5.11. Found: C, 67.73; H, 6.76; N, 4.92.

The same compound was obtained by oxidation of **6a** in a similar way.

B.—A crude mixture of **5a** and **6a** (500 mg) in acetonitrile (30 ml) was stirred for 1 hr at room temperature with activated manganese dioxide (9 g). After filtration through Celite, the filtrates were evaporated to dryness leaving a chromatographically homogeneous, crystalline residue. Recrystallization from ethanol gave 219 mg (45%) of **13** identical with that above.

Metal Hydride Reduction of 13. A. Using Sodium Borohydride.—Sodium borohydride (7 mg) was slowly added to a slurry of **13** (45 mg) in methanol (2 ml). After 10 min the solvent was evaporated and the residue was partitioned between benzene and water. Evaporation of the benzene left a crystalline residue of almost pure **5a**. Quantitative tlc using carbon tetrachloride–acetone (85:15) showed the product to contain 94% **5a** and 6% **6a** with quantitative recovery.

B. Using $LiAlH_4$.—Lithium aluminum hydride (5 mg) was added to a solution of **13** (45 mg) in tetrahydrofuran (2 ml) and after 30 min the mixture was worked up as above giving crystalline, almost pure **5a** that was shown by tlc to be 96% **5a** and 4% **6a**.

5-(2,4:3,5-Di-*O*-benzylidene-1-keto-D-*ribo*-tetrahydroxypentyl)uracil (14).—A suspension of finely divided **13** (400 mg) in 80% acetic acid (5 ml) was stirred at 25° for 1.5 hr. During this time **13** dissolved and was replaced by fine needles of **14** (283 mg) which were removed by filtration. Addition of water to the filtrate gave a further 17 mg (total yield), 300 mg (94%) of **14** which was recrystallized from ethanol with mp 269–271° dec; λ_{max}^{MeOH} 290 mμ (ε 7400), 227 (sh, 5700); $[\alpha]^{23}D$ −91.4° (*c* 0.1, MeOH); ORD (MeOH) negative Cotton effect with a trough at 296 mμ (Φ −9000°), crossover at 278 mμ, and a peak at 262 mμ (Φ +4800°); nmr (pyridine-d_5) 4.0–4.6 (m, 3, $C_{4'}$ H and $C_{5'}$ H_2), 4.68 (t, 1, $J_{2',3'}$ = $J_{3',4'}$ = 9 Hz, $C_{3'}$ H), 5.92 and 6.23 (s, 1, $ArCHO_2$), 6.48 (d, 1, $J_{2',3'}$ = 9 Hz, $C_{2'}$ H), 7.2–7.8 (m, 10, arom), 8.21 ppm (s, 1, C_6H).

Anal. Calcd for $C_{23}H_{20}N_2O_7$: C, 63.30; H, 4.62; N, 6.42. Found: C, 63.15; H, 4.45; N, 6.04.

5-(D-*altro*-1-Acetamido-2,3,4,5-tetrahydroxypentyl)uracil (17).—A solution of **10b** (350 mg, 0.71 mmol) in methanol (5 ml) and concentrated ammonium hydroxide (5 ml) was kept at 23° for 5 hr and then evaporated to dryness *in vacuo*. Preparative tlc on three Avicel plates using 1-butanol–acetic acid–water (5:2:3) gave a major band moving just slower than α-pseudouridine. Elution with water and evaporation gave a syrup (4250 OD units at 260 mμ, 81%) that was dissolved in hot 90% methanol to remove some insoluble material, evaporated, and crystallized from 90% ethanol giving 122 mg (57%) of **17** with mp 223–224°; λ_{max}^{MeOH} 262 mμ (ε 7400); $[\alpha]^{23}D$ +52.4°; ORD (H_2O) negative Cotton effect with a trough at 258 mμ (Φ −11,600°), crossover at 242 mμ, and a peak at 230 mμ (Φ +6100°); nmr (DMSO-d_6–D_2O) 1.91 (s, 3, $C_{1'}$ NAc), 3.2–3.7 (m, 5, $C_{2'}$, $C_{3'}$, $C_{4'}$, and $C_{5'}$ H's), 5.15 (br, s, 1, $C_{1'}$ H), 7.29 ppm (s, 1, C_6 H). The compound consumed 3.0 equiv of periodate[22] with release of 1.0 equiv of formaldehyde.[23]

Anal. Calcd for $C_{11}H_{17}N_3O_7$: C, 43.56; H, 5.65; N, 13.86; O, 36.93. Found: C, 43.68; H, 5.84; N, 13.34; O, 36.91.

Registry No.—**1**, 1445-07-4; **1** 2′,3′,5′-tri-*O*-acetate, 24800-34-8; **2**, 1017-66-0; **2** 2′,3′,5′-tri-*O*-acetate, 28455-49-4; **4** methyl hemiacetal, 28399-55-5; **5a**, 28455-50-7; **6a**, 28399-56-6; **7a**, 28399-57-7; **7b**, 28399-58-8; **8a**, 28455-51-8; **8b**, 28399-59-9; **9a**, 28399-60-2; **9b**, 28399-61-3; **10a**, 13039-98-0; **10b**, 28399-63-5; **11**, 28399-64-6; **13**, 28399-65-7; **14**, 28399-66-8; **17**, 28399-67-9.

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Reactions of Diaryl Disulfides with Active, Nonnucleophilic Alkylating Agents[1]

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Reaction of diphenyl disulfide with triethyloxonium fluoroborate or diethoxycarbonium fluoroborate gave diethylphenylsulfonium fluoroborate and *S*-ethylsulfonium salts of ethyl *p*-thiophenoxyphenyl sulfide (**5**) and of a product assigned the structure of ethyl *p*-(*p*-thiophenoxyphenyl)thiophenoxyphenyl sulfide (**6**). Recovered diphenyl disulfide, thianthrene (**3**), and the *S*-ethylsulfonium salt of ethyl *o*-thiophenoxyphenyl sulfide (**4**) were also obtained in smaller amounts. The products obtained from alkylation of mixtures of diphenyl disulfide with diphenyl disulfide-d_{10} or anisole showed that formation of all products proceeded through intermolecular steps. Formation of all products of these reactions, as well as the reaction of di-β-naphthyl disulfide with trimethyloxonium fluoroborate to give dibenzothianthrene (**8**), could be explained as proceeding by S-alkylation of the disulfides, followed by nucleophilic attack upon the unalkylated sulfur atom by another disulfide molecule or by anisole.

The structural similarities between *sym*-diphenylhydrazines and diphenyl disulfides have prompted several research groups to react diphenyl disulfide with strong protonic acids[2,3] or with boron trifluoride,[2] in attempts to obtain rearrangements similar to the benzidine rearrangements of diphenylhydrazines.[4] These attempts have been unsuccessful, resulting either in no reaction[2] or in formation of ill-characterized polymers.[3] It has been suggested[3] that the polymeric materials may arise by oxidation and sulfonation of a 4,4′-dimercaptobiphenyl resulting from rearrangements of the benzidine type, but no concrete support for this proposal has been offered.

There are indeed excellent reasons why reactions analogous to the benzidine rearrangement are unlikely to occur during the reactions of diphenyl disulfides with proton acids. Benzidine rearrangements of most *sym*-diphenylhydrazines have been found to proceed from the diprotonated forms.[4] The very low basicity of disulfides, as compared to hydrazines, requires that much stronger acids must be used even for monopro-

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