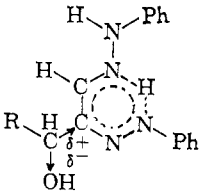
are stabilized neither in the **1** nor in the **1′** form, but they are present in a quasiaromatic structure between the resonance limit forms **1** and **1′**, as represented by the following structure:



This structure is supported by X-ray data.[6a,12] The electron density projection shows that the six-membered chelate ring is approximately planar and also essentially coplanar with the two benzene rings. Furthermore, their bond angles lie in the neighborhood of 120°. This is what should be expected in an aromatic system.

The quasiaromatic nature of the chelate structure was also substantiated by polarographic analysis.[4] The stabilization energy of the chelated sugar phenylosazones was found to be about 10 kcal./mole higher, than for the nonchelated sugar methylphenylosazones. This value is much higher than the usual chelation energy.

Besides, the proposed structure may explain the sharp difference between the C-1 and C-2 phenylhydrazone groups in almost all their reactions, such as methylation,[15] osotriazole formation,[16] etc., as well as the privileged position[17–19] of the C-3 hydroxyl in the sugar osazones. This is due to the electron-attractive effect of the quasiaromatic chelate system.

(15) S. Akiya and S. Tejima, *J. Pharm. Soc. Japan*, **72**, 894, 1574 (1952).
(16) F. Weygand, H. Griesebach, K.-D. Kirchner, and M. Haselhorst, *Chem. Ber.*, **88**, 487 (1955).
(17) L. L. Engel, *J. Am. Chem. Soc.*, **57**, 2419 (1935).
(18) A. El Khadem, E. Schreier, G. Stöhr, and E. Hardegger, *Helv. Chim. Acta*, **35**, 993 (1952).
(19) L. Mester and A. Major, *J. Am. Chem. Soc.*, **79**, 3232 (1957).

Experimental

N.m.r. Spectra. The n.m.r. spectra of the compounds reported in this communication were determined at 60 Mc. with tetramethylsilane as an internal reference on an A-60 Varian Associates spectrometer, Palo Alto, Calif.

High-resolution n.m.r. spectrum at HR 100 Mc. of tetra-O-acetyl-D-galactose phenylosazone and decoupling with the double resonance method was determined by Dr. A. Melera, Service Center of the Varian A. G., Zurich, Switzerland.

All the compounds used had melting points reported in the literature.[20–27]

Deuteration. Deuteration of the nonchelated imino group was effected by shaking the deuteriochloroform solution of the acetylated osazones with deuterium oxide at room temperature for a few minutes. The deuteration of the imino group involved in the chelation was achieved by shaking the deuteriochloroform solution with deuterium oxide in a fused glass tube and by heating in a water bath for 10 to 30 min.

Acknowledgment. We would like to express our appreciation to Professor M.-M. Janot (Paris) for his suggestion, and to Mrs. M. Mester and Mrs. L. Allais for their assistance.

(20) O. Diels, E. Cluss, H. J. Stephan, and R. König, *Ber.*, **71**, 1189 (1938).
(21) E. Fischer, *ibid.*, **17**, 579 (1884).
(22) M. L. Wolfrom, M. Konigsberg, and S. Soltzberg, *J. Am. Chem. Soc.*, **58**, 490 (1936).
(23) E. Fischer and J. Tafel, *Ber.*, **20**, 1088 (1887).
(24) A. Hofmann, *Ann.*, **366**, 316 (1909).
(25) H. von Pechmann, *Ber.*, **30**, 2460 (1897).
(26) E. E. Percival and E. V. Percival, *J. Chem. Soc.*, 1320 (1937).
(27) E. Votoček and R. Vondraček, *Ber.*, **37**, 3848 (1904).

Conformations of the Furanose Ring in Nucleic Acids and Other Carbohydrate Derivatives in the Solid State[1]

M. Sundaralingam

Contribution from the Department of Biological Structure, University of Washington, Seattle, Washington 98105. *Received July 6, 1964*

Conformations of the furanose ring in nucleic acids and other carbohydrate derivatives arrived at from X-ray and neutron diffraction data are presented. The puckering in the furanose ring, involving the C-2′ or C-3′ atom, results in four conformeric possibilities: C-2′-endo, C-3′-exo, C-3′-endo, and C-2′-exo; their differences and similarities are discussed. The puckering when described as a twist of the C-2′–C-3′ bond relative to the plane defined by C-1′, O-1′, and C-4′ falls into the following classes: C-2′-endo–C-3′-exo, C-3′-endo–C-2′-exo, C-3′-endo–C-2′-endo, and C-2′-exo–C-3′-exo. The reactions of some cis and trans 1,2-glycols in "mobile" and "rigid" furanose systems are correlated with the projected valency angles formed by the hydroxyl groups. The influence of puckering on furanoside molecular parameters is discussed. The molecular parameters presented will be of considerable help in constructing accurate models of nucleic acids. Presence of an "equatorial" hydroxyl group on the out-of-plane carbon atom leads to rehybridization of the carbon atom orbitals, as seen by the shortening of the C–OH bond length and the widening of the C–C–OH bond angle, with a resulting change in the C–H bond character. It is noted that the interaction of the C-5′ protons with the ring protons is different for the three favored orientations of the C-5′–O-5′ bond.

(1) This work was supported by U. S. Public Health Service Grant AM 3288 of the National Institutes of Health.

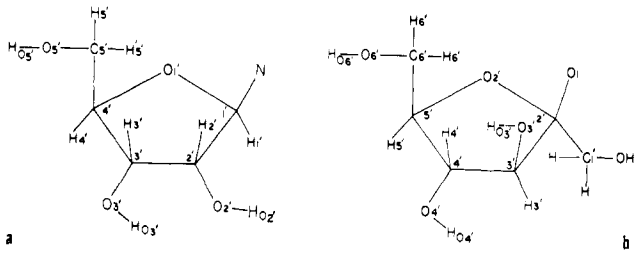


Figure 1. Chemical configurations and numbering in (a) ribofuranosyl and (b) fructofuranosyl moieties.

The tetrahydrofuran ring occurs in a variety of important biological molecules, in particular the nucleic acids and other carbohydrate derivatives. While the majority of carbohydrates in nature exists in the pyranose form, a number of biologically important molecules, notably the nucleic acids, contain carbohydrate moieties in the furanose form. Indeed, D-ribose and 2-deoxy-D-*erythro*-pentose (the sugars in nucleic acids) and D-fructose apparently occur in nature only as the furanose derivatives. Information on the conformations of the furanoside moiety would be of considerable importance in nucleic acid model building, and knowledge regarding the shapes of the furanosides would contribute toward a better understanding of their chemical reactions and physical properties.

The puckering in the furanose ring is mainly due to the torsional forces about the single bonds, arising from the nonbonded interactions of the substituent atoms, which are in opposition to the forces striving to retain tetrahedral bond angles. Apparently the energy gained in staggering the substituent atoms is greater than that lost in increasing the angle strain. Spencer[2] has pointed out that in the ribose and its deoxy derivative there is a preferred puckering involving either the C-2′ or C-3′ atom. Since precise structural knowledge of the furanosides is meager, a detailed understanding of their geometry has remained obscure. However, with the advent of high-speed electronic computers, it has become possible to refine structures as far as the experimental data warrant. Recently, we have carried out a precise analysis of the crystal structure of cytidylic acid b.[3] This communication stems from the observations made of the many interesting conformational features exhibited by the furanoside portion in the following, more accurately investigated compounds: (i) cytidylic acid (CMP),[3] (ii) 5-fluoro-2′-deoxy-β-uridine (FUDR),[4] (iii) adenylic acid (AMP),[5] (iv) calcium thymidylate (TMP),[6] (v) deoxyadenosine (DA),[7] and (vi) sucrose.[8] All of these structures were elucidated by X-ray diffraction methods except sucrose, which was studied by neutron diffraction techniques.[9]

(2) M. Spencer, *Acta Cryst.*, **12**, 59 (1959).
(3) (a) M. Sundaralingam and L. H. Jensen, to be published; (b) M. Sundaralingam and L. H. Jensen, Abstracts, American Crystallographic Association, Bozeman, Mont., July 1964, p. 50.
(4) R. D. Harris and W. M. Macintyre, *Biophys. J.*, 203 (1964).
(5) J. Kraut and L. H. Jensen, *Acta Cryst.*, **16**, 79 (1963).
(6) K. N. Trueblood, P. Horn, and V. Luzzati, *ibid.*, **14**, 965 (1961).
(7) D. G. Watson, D. J. Sutor, and P. Tollin, private communication (1963).
(8) (a) G. M. Brown and H. A. Levy, *Science*, **141**, 921 (1963); (b) private communication (1963).
(9) Earlier X-ray investigation of sucrose itself (C. A. Beevers, T. R. R. McDonald, J. H. Robertson, and F. Stern, *Acta Cryst.*, **5**, 689 (1952)) is of insufficient accuracy to be utilized in the present report.

Here we shall describe the primary (major) and secondary (minor) puckering of the furanose ring, their consequences on the projected valency angles,[10] and their possible influence on the dimensions of the furanoside residue. Also, the cuprammonium reaction and the periodate and lead tetraacetate cleavage of 1,2-glycols will be discussed.

In Table I are shown the root-mean-square (r.m.s.) deviations of the in-plane atoms for all possible combinations of four-atom planes. It is to be noted that in the fructofuranosyl moiety of sucrose the atoms O-2′, C-2′, C-3′, C-4′, and C-5′ occupy the same relative positions as O-1′, C-1′, C-2′, C-3′, and C-4′, respectively, of the ribofuranoside (see also Figure 1). The four atoms that best fit a plane have the lowest r.m.s. deviation, indicated in the table in boldface. It is seen, therefore, in the furanoside portion of CMP, FUDR, and sucrose that atom C-2′ is involved in the primary (major) puckering, while in AMP, TMP, and DA, atom C-3′ is involved. Furthermore, when C-3′ is associated with the major puckering, the next best four-atom plane is that for which C-2′ is out-of-plane, and *vice versa*, except in TMP where the next best four-atom plane is formed with C-4′ out-of-plane. In this respect the puckering in AMP and TMP are different. The out-of-plane atom (C-2′ or C-3′) in CMP, FUDR, AMP, and TMP is on the same side ("*endo*")[11-13] as C-5′. Interestingly, in DA, C-3′ is displaced on the opposite side ("*exo*"). Analogous displacement of C-2′ on the opposite side has not been encountered in the hitherto investigated nucleic acid components. However, this feature is exhibited by the fructofuranosyl moiety of sucrose, where C-3′, occupying the same relative position as C-2′ in the ribofuranoside, is displaced on the opposite side (*exo*) of C-6′ and O-1. The latter atoms occupy the same relative positions as C-5′ and N, respectively, in the ribofuranoside.

Table I.[a] R.m.s. Deviations of the Atoms Comprising the Plane for the Five Possible Four-Atom Planes

Atom excluded in calcn. of plane	R.m.s., Å. CMP	FUDR	Sucrose	AMP	TMP	DA
O-1′	0.195	0.203	0.175	0.196	0.156	0.171
C-1′	0.138	0.153	0.132	0.212	0.163	0.162
C-2′	**0.026**	**0.031**	**0.036**	*0.106*	0.110	*0.089*
C-3′	*0.088*	*0.089*	*0.065*	**0.022**	**0.017**	**0.010**
C-4′	0.173	0.180	0.148	0.143	*0.084*	0.126
Average e.s.d. in positional coordinate (Å.)	0.0047	0.007	0.0015	0.008	0.014	0.010

[a] In all tables the ribose numbering has been used for the fructofuranose ring.

The displacements of the furanoside atoms from the best four-atom plane are shown in Table II where the deviations of the in-plane atoms are shown in italic.[14]

(10) R. E. Reeves, *Advan. Carbohydrate Chem.*, **6**, 108 (1951).
(11) C. D. Jardetzky, *J. Am. Chem. Soc.*, **82**, 229 (1960).
(12) C. D. Jardetzky, *ibid.*, **83**, 2919 (1961).
(13) C. D. Jardetzky, *ibid.*, **84**, 62 (1962).
(14) See also R. U. Lemieux and R. Nagarajan, *Can. J. Chem.*, 42, 1270 (1964).

Table II. Deviations (Å.) of the Atoms from the Best Four-Atom, Least-Squares Plane of the Furanose Ring[a]

Atom	Ribose in CMP	2-Deoxy-D-erythro-pentose in FUDR	Fructose in sucrose	Ribose in AMP	2-Deoxy-D-*erythro*-pentose in TMP	2-Deoxy-D-*erythro*-pentose in DA
C-1′	*−0.020*	*−0.024*	*0.028*	*−0.026*	*0.021*	*0.013*
C-2′	−0.609	−0.629	0.542	*0.016*	*−0.012*	*−0.007*
C-3′	*0.018*	*0.022*	*−0.025*	−0.664	−0.527	0.552
C-4′	*−0.030*	*−0.036*	*0.042*	*−0.016*	*0.013*	*0.008*
O-1′	*0.032*	*0.038*	*−0.045*	*0.027*	*−0.021*	*−0.013*
N	−0.860	−0.864	−1.265	−1.293	−1.099	−1.182
O-2′	−0.434	...	0.250	1.402	...	...
O-3′	1.380	1.369	0.741	−0.524	−0.130	1.970
C-5′	−1.246	−1.297	−1.048	−0.690	−0.723	−1.345
O-5′	−2.485	−1.248	−2.342	−2.143	−2.130	−1.642

[a] The deviations of the atoms included in the calculation of the least-squares planes are shown in italic.

In the ribofuranose of CMP, the primary puckering is due to the displacement of C-2′ by about 0.6 Å. from the least-squares plane of the remaining ring atoms. That these latter atoms display a secondary (minor) puckering[3] is quite convincing from considerations of the estimated standard deviations achieved in this work, about 0.005 Å. in the positional coordinates. Incidentally, the estimated standard deviations of the positional coordinates achieved for CMP are the best reported to date for a nucleoside or nucleotide. The secondary puckering in the 2-deoxy-D-*erythro*-pentose ring of FUDR and the fructofuranose ring of sucrose

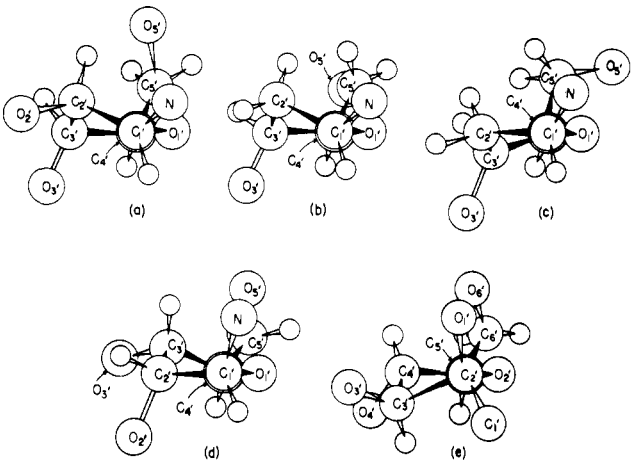


Figure 2. The furanose ring as viewed along C-1′→C-4′, and in the best four-atom plane (the latter atoms are assumed to be coplanar), of (a) CMP, (b) FUDR, (c) DA, (d) AMP, and (e) sucrose.

is also evident. Considering the estimated standard deviations reported for AMP and TMP, the secondary puckering in these compounds is not conclusive, while in DA, C-3′-*exo*, atoms C-1′, C-2′, C-4′, and O-1′ define a perfect plane, within experimental error. Contrary to earlier beliefs,[11] it is clear from the above considerations that the ribose conformation is independent of whether the base is a pyrimidine or purine system in nucleosides and nucleotides.

The furanosides as viewed along the direction C-1′... C-4′, and in the best four-atom plane of the furanose rings, are shown in Figure 2. In these drawings the four atoms constituting the least-squares plane are assumed to be coplanar. It is seen that the *cis*-hydroxyl groups in the ribofuranosides of CMP,

Table III. The C-5′...N Distances (Å.)

		Average
CMP (C-2′-*endo*)	4.215	4.25
FUDR (C-2′-*endo*)	4.147	
AMP (C-3′-*endo*)	4.274	
TMP (C-3′-*endo*)	4.347	
DA (C-3′-*exo*)	3.819	3.88
Sucrose (C-2′-*exo*)	3.951	

(Figure 2a) and AMP (Figure 2d) are *cis* with respect to the least-squares plane formed by the five-ring atoms, but *trans* with respect to the four-atom, least-squares plane (Table II). On the other hand, in the fructofuranosyl portion of sucrose (Figure 2e) the *trans*-hydroxyl groups are *trans* and *cis* with respect to the five- and four-atom least-squares planes, respectively. The major difference between CMP (Figure 2a) and FUDR (Figure 2b) is in the orientation of the C-5′-

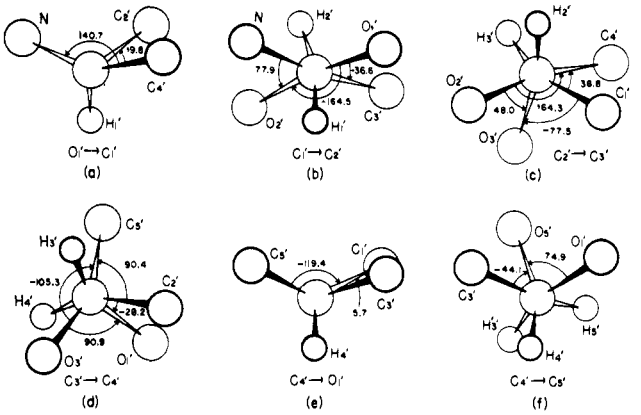


Figure 3. Projected valency angles of the ribofuranosyl moiety in CMP (C-2′-*endo*).

O-5′ bond. In CMP (C-2′-*endo*) and AMP (C-3′-*endo*) the displacements of the ring and substituent atoms are approximately related by a mirror plane perpendicular to the C-1′...C-4′ direction.[15] In Figures 2a, 2b, and 2c, the orientations of the bonds C-1′–N and C-4′–C-5′ (quasi-equatorial and quasi-axial, respectively) are quite similar while these are interchanged in Figures 2d and 2e. The latter feature is also exhibited by TMP. The C-2′- and C-3′-*exo* puckering results in a C-5′...N distance of about 0.4

(15) M. Sundaralingam and L. H. Jensen, Abstracts, American Crystallographic Association, Bozeman, Mont., July 1964, p. 51.

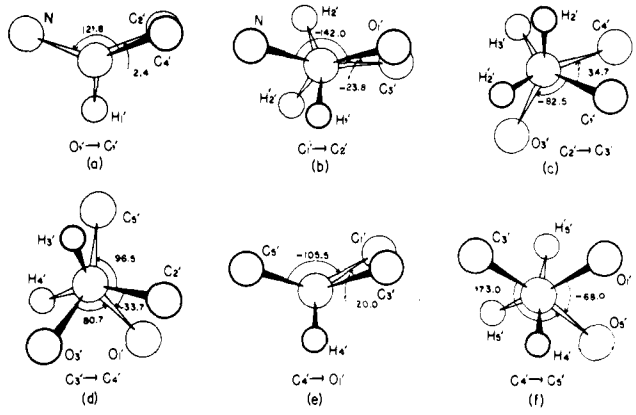


Figure 4. Projected valency angles of the 2-deoxy-D-erythro-pentosyl moiety in DA (C-3′-*exo*).

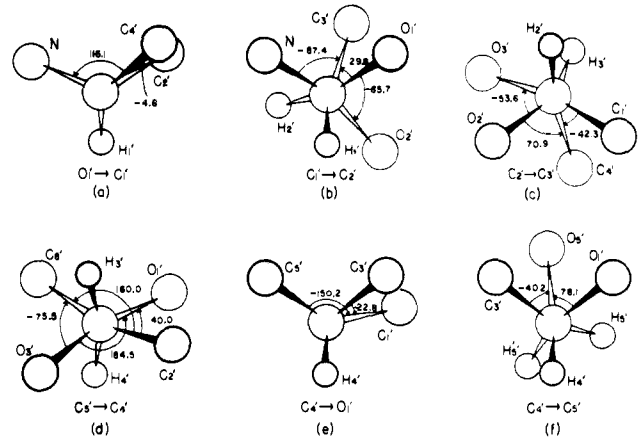


Figure 5. Projected valency angles of the ribofuranosyl moiety in AMP (C-3′-*endo*).

Å. less than that for the C-2′- and C-3′-*endo* cases (Table III). Therefore, conformational interconversions, *endo* to *exo*, *e.g.*, will considerably affect the size, shape, and possibly the properties of nucleic acids, as has also been pointed out by Jardetzky.[11] In contrast to AMP, the C-3′-*exo* pucker in DA is accompanied by a change in orientation of the C-5′–O-5′ bond, thereby reducing the distance between the glycosyl N and one of the protons on C-5′. Also in DA the distances of the C-5′ protons to H-2′ and H-3′ are shorter than in AMP, while the distance to H-4′ is longer. Further, in DA, the dihedral angles between the C-5′ protons and H-4′ (H-5′–C-5′–C-4′–H-4′ and H′-5′–C-5′–C-4′–H-4′, respectively) are about 70 and 170° (Figure 4f), while in AMP these angles are about 90 and 20° (Figure 5f). It is noteworthy that the C-5′–O-5′ orientation in FUDR is different from those of AMP and DA. Consequently the interaction between the C-5′ protons and the ring protons would be different here. The H-1′–H-2′ (H-1′–C-1′–C-2′–H-2′) dihedral angles for CMP (C-2′-*endo*), DA (C-3′-*exo*), and AMP (C-3′-*endo*) are in agreement with Jardetzky's values,[11] but in sucrose (C-2′-*exo*), the C-1′–O-3′ (C-1′–C-2′–C-3′–O-3′) dihedral angle is 84.7° in contrast to the H-1′–H-2′ dihedral angle of 105° for the C-2′-*exo* case.[11]

When the out-of-plane atom, C-2′ or C-3′, in the ribofuranoside is on the same side (*endo*) as C-5′, then the oxygen atom attached to the displaced carbon atom falls nearly into the best four-atom plane (equatorial) (Tables II and IV). But if the puckering is such that the displaced atom is on the opposite side (*exo*) of C-5′, as in DA, then the oxygen is directed away (axial) from the plane. Likewise in sucrose H-3′, occupying the same relative position as O-2′ in the ribofuranoside, is directed away (axial) from the best four-atom, least-squares plane.

The puckering in the furanose ring can also be visualized as a twist of the C-2′–C-3′ bond with respect to the plane defined by the remaining ring atoms,[16] Table V. The two cases C-2′-*endo* (CMP and FUDR) and C-3′-*exo* (DA), with respect to the best four-atom plane, can be described as C-2′-*endo*–C-3′-*exo*, with respect to the plane defined by C-1′, O-1′, and C-4′. Similarly, C-3′-*endo* (AMP) and C-2′-*exo* (sucrose) can be designated as C-2′-*exo*–C-3′-*endo*. However, in TMP, though the primary puckering is C-3′-*endo* as in AMP, the puckering with respect to the three-atom plane is C-3′-*endo*–C-2′-*endo*, where both C-3′ and C-2′ are located on the same side of the plane as C-5′ and N. If the puckering in TMP is real, then one may anticipate the occurrence of a C-2′-*exo*–C-3′-*exo* system where both C-2′ and C-3′ are located on the opposite side.

Conformation Angles of the Furanose Ring Bonds. The puckering in the furanose ring can be described in terms of a twist angle[8] (or projected valency angle)[10] about each single bond. The twist angle $\phi_{C\text{-}2'\text{-}C\text{-}3'}$, for example, of the bond C-2′–C-3′ is defined as the angle made by the projection of the bond C-3′–C-4′ relative to the projection of the bond C-2′–C-1′, when viewed in the direction of the bond C-2′–C-3′; and the angle is called positive when measured counterclockwise from the near carbon atom C-2′ to the far carbon atom C-3′. These angles, for the furanosides under consideration, are listed in Table VI. There is good agreement in the riboside of CMP and the 2-deoxy-D-*erythro*-pentoside of FUDR, where C-2′ is out on the same side of C-5′. In sucrose the comparable atom (C-3′) is displaced in the opposite fashion, thus resulting not only in different signs for the angles but also differences in their magnitudes. Interestingly, in AMP (C-3′-*endo*) the angles have the same sign as in sucrose (C-2′-*exo*) though the magnitudes differ.

Table IV. The Orientations of the Substituents[a]

Out-of-plane atom	N	H-1′	H-2′	O-2′	H-3′	O-3′	H-4′	C-5′
CMP C-2′-*endo*	e	a	a	e	e	a	e	a
FUDR C-2′-*endo*	e	a	a	e	e	a	e	a
DA C-3′-*exo*	e	a	a	e	e	a	e	a
AMP C-3′-*endo*	a	e	e	a	a	e	a	e
TMP C-3′-*endo*	a	e	e	a	a	e	a	e
Sucrose C-2′-*exo*	a	e	e	a	a	e	a	e

[a] a and e designate "axial" and "equatorial," respectively. It should be noted that these orientations are an oversimplification of what may be termed as quasi-axial, quasi-equatorial, and bisectional.[12]

(16) In cyclopentane the form in which two atoms are displaced from the plane of the remaining atoms is referred to as the "half-chair form," and the case in which one atom is displaced from the plane of the other four atoms is referred to as the "envelope form."[17]

(17) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p. 248, and references therein.

Table V. Deviations (Å.) of the Atoms from the Plane Defined by C-1′, C-4′, and O-1′

Out-of-plane atom	C-2′-*endo*–C-3′-*exo*			C-2′-*exo*–C-3′-*endo*		C-2′-*endo*–C-3′-*endo* TMP
	CMP	FUDR	DA	AMP	Sucrose	
C-2′	0.494	0.494	0.060	−0.120	−0.373	0.098
C-3′	−0.146	−0.170	−0.504	0.573	0.207	0.602
C-5′	1.236	1.281	1.353	0.722	1.049	0.698
N	0.889	1.183	1.187	1.279	1.300	1.103

Table VI. The Conformation Angles of the Furanose Ring Bonds

Compd.	$\phi_{O\text{-}1'\text{-}C\text{-}1'}$	$\phi_{O\text{-}1'\text{-}C\text{-}2'}$	$\phi_{C\text{-}2'\text{-}C\text{-}3'}$	$\phi_{C\text{-}3'\text{-}C\text{-}4'}$	$\phi_{C\text{-}4'\text{-}O\text{-}1'}$
CMP (C-2′-*endo*)	−19.8	36.6	−38.8	28.2	−5.7
FUDR (C-2′-*endo*)	−19.5	37.1	−40.3	30.1	−6.8
Sucrose (C-2′-*exo*)	14.6	−31.1	35.0	−27.3	8.2
AMP (C-3′-*endo*)	4.8	−29.8	42.3	−40.0	22.8
TMP (C-3′-*endo*)	−3.9	−17.5	31.1	−34.7	25.0
DA (C-3′-*exo*)	−2.4	23.8	−34.7	33.7	−20.0

Although in TMP the primary puckering is similar to that in AMP, the conformation angles in the two compounds differ considerably in their magnitudes but the signs are similar, except for the reversal in the sign of $\phi_{O\text{-}1'\text{-}C\text{-}1'}$. This is explained as due to the differences in the secondary puckering. It is noteworthy that the opposite mode of pucker involving the C-3′ atom in DA makes its conformation angles opposite to that in AMP but similar in sign to those of CMP and FUDR (C-2′-*endo*). It is seen, therefore, that there is a similarity in the C-2′-*endo* and C-3′-*exo* conformations on one hand and the C-2′-*exo* and C-3′-*endo* forms on the other. The differences in the magnitudes of the twist angle within each of these sets arise from differences in the twist of the bond C-2′–C-3′ with respect to the remaining three atom planes to which reference has been made. It is seen, therefore, that changes in the twist of the C-2′–C-3′ bond with respect to the C-1′, O-1′, and C-4′ plane can result in the following interconversions.

$$\text{C-2′-}endo \rightleftharpoons \text{C-3′-}exo;\ \text{C-3′-}endo \rightleftharpoons \text{C-2′-}exo.$$

The observed differences in the puckering of the furanose rings in these compounds are probably due to the different H-bonding schemes adopted by the furanoside moieties in the crystal lattice, and some of the differences may be ascribed to the type of substituent in the furanose ring. It may be mentioned here that the furanose ring assumes different conformations even in solution[11–13] and possesses considerable conformational purity.[18]

The bond opposite the out-of-plane atom, being farthest removed, has the smallest value for the conformation angle. The next smallest angle is opposite the atom that is excluded in the calculation of the next best four-atom plane. Thus in CMP, FUDR, AMP, and sucrose the smallest and next smallest conformation angles involve O-1′–C-1′ and C-4′–O-1′ bonds, and in TMP the bonds involved are O-1′–C-1′ and C-1′–C-2′. In fact, the magnitudes of the conformation angles of the ring bonds opposite the atoms excluded in the calculation of the four-atom least-squares planes increase with increase in the r.m.s. deviations of the in-plane atoms (Tables I and VI). The maximum value attained for the conformation angle of the furanose ring bond is about ±40°, which is to be compared with the uniform values of about ±55° in the pyranose ring of sucrose[8] in the chair conformation, where the staggering is practically complete.

The compounds CMP, DA, AMP, and sucrose demonstrate the four possible kinds of primary puckering of the furanose ring involving the C-2′ and C-3′ atoms. The conformations about their ring bonds and the exocyclic C-4′–C-5′ bonds are illustrated in Figures 3, 4, 5, and 6, respectively. The drawings present the

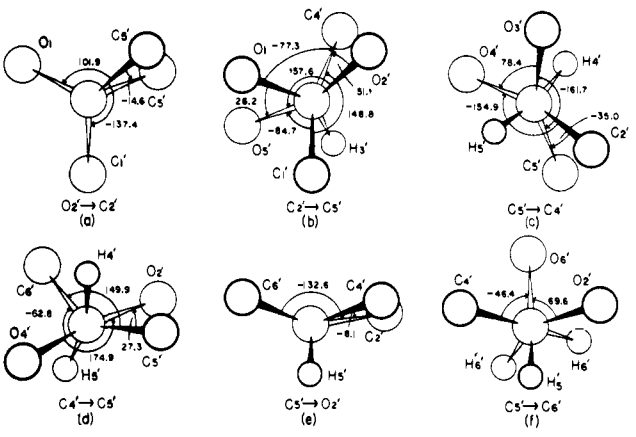


Figure 6. Projected valency angles of the fructofuranosyl moiety in sucrose (C-2′-*exo*).

view along the bonds shown by the arrow, and the H atoms are indicated in plausible positions. The values of the conformation angles involving the non-H atoms are also inserted in the figures. It is seen that the conformations are either partially eclipsed or incompletely staggered. Some projected valency angles for TMP and FUDR are shown in Table VII. The two substituents on each of the four ring-carbon atoms are of geometrically different types, and can be designated as "axial" and "equatorial," respectively, depending on whether the bonds to the substituents are approximately perpendicular or parallel to the furanose ring plane. The orientations of the substituents for the six compounds under consideration are shown in Table IV, where the abbreviations a and e represent "axial" and "equatorial" orientations. It is to be noted that in the first row of this table, O-2′ of ribose

(18) R. U. Lemieux, *Can. J. Chem.*, **39**, 116 (1961).

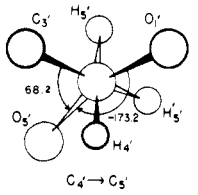


Figure 7. Projected valency angles about the C-4′–C-5′ bond in FUDR.

should be replaced by H′-2′ for the deoxyribose, and similarly the appropriate substitution should be made for sucrose. The resemblances in the orientations of the substituents in CMP and FUDR (C-2′-*endo*) to DA (C-3′-*exo*) on one hand, and AMP and TMP (C-3′-*endo*) to sucrose (C-2′-*exo*) on the other, is noteworthy.

Table VII. Some Projected Valency Angles in FUDR and TMP

Angle	Angle, deg. FUDR	TMP
C-4′–O-1′–C-1′–N	140.5	128.4
N–C-1′–C-2′–C-3′	−153.9	−111.8
C-1′–C-2′–C-3′–O-3′	−78.4	−154.3
C-2′–C-3′–C-4′–C-5′	89.6	155.1
O-3′–C-3′–C-4′–O-1′	85.7	158.2
O-3′–C-3′–C-4′–C-5′	−154.6	−81.4
C-5′–C-4′–O-1′–C-1′	−116.9	−151.4
C-3′–C-4′–C-5′–O-5′	68.2	−57.4
O-1′–C-4′–C-5′–O-5′	−173.2	62.8

Orientation of the C-5′–O-5′ Bond. It would be expected that the bond C-5′–O-5′ has three energetically favored staggered conformations around the C-4′–C-5′ linkage. All three forms have been isolated, and these are shown for CMP (Figure 2a), FUDR (Figure 2b), and DA (Figure 2c). The values of the projected angles for the different cases are indicated in Figures 3f, 7, and 4f, respectively. The orientation of the C-5′–O-5′ bond in CMP, AMP, TMP, and sucrose is remarkably constant and appears to be a more frequent conformation. It is clear, therefore, that the changes in the orientation of the substituents accompanying different modes of ring pucker and the three conformational alternatives for the C-5′–O-5′ bond have to be considered in polynucleotide model building. It appears that the torsion angle ϕ_{CN}[19] prefers the "*anti*" range irrespective of the orientation of the C-5′–O-5′ bond.

Reactions of cis and trans 1,2-Glycols. In view of the puckering observed in the furanosides it may be concluded that hydroxyls with projected angles of 0° ("true" *cis*) and 120° ("true" *trans*) cannot exist. In the ribofuranosyl residue of CMP (C-2′-*endo*) and AMP (C-3′-*endo*) the *cis* hydroxyls make projected angles of 48.0 and 53.6°, respectively, while in the fructofuranosyl moiety of sucrose (C-2′-*exo*) the *trans* hydroxyls make a projected angle of 78.4°.[20] Hence the projected angles in the *cis* and these *trans* derivatives are not very different.

In Table VIII are listed the probable values of the projected angles of the hydroxyl groups in the four types of furanoside rings, for hydroxyls in the 2′- and 3′-positions (in ribose numbering), exhibiting the four different conformations. It is noteworthy that the *cis* hydroxyls in the ribo- and mannofuranoside rings subtend a dihedral angle of about 50° for the four conformations. This small angle explains the extremely rapid cleavage of these cyclic glycols by periodate and lead tetraacetate, which form a cyclic intermediate prior to scission of the glycolic linkage.[21] The projected angles of the *trans* hydroxyls in fructo- and galactofuranosyl moieties fall into two groups with about 75 and 160° angles. The slow oxidation of the *trans* forms (for example, α-D-arabinofuranoside and ethyl β-D-galactofuranoside) are attributed to a projected angle of 120°.[22,23] From analogy with the fructofuranosyl moiety the dihedral angles in these compounds may be predicted to be acute angles, about 75°, with the α-D-arabinofuranoside either in the C-2′-*exo* or C-3′-*endo* conformation and ethyl β-D-

Table VIII. Projected Valency Angles and Orientation of C-2′–O-2′ and C-3′–O-3′ Bonds for the Different Conformations of the *cis* and *trans* 1,2-Glycols,[a] Involving Puckering of the C-2′ or C-3′ Atom

Projected valency angle, deg.		Orientation of C-2′–O-2′	Orientation of C-3′–O-3′
a. Ribofuranoside (*cis* hydroxyls)			
C-2′-*endo*	48.0 (CMP)	Equatorial	Axial
C-3′-*exo*	50	Equatorial	Axial
C-2′-*exo*	50	Axial	Equatorial
C-3′-*endo*	53.6 (AMP)	Axial	Equatorial
b. Fructofuranoside (or arabinofuranoside) (*trans* hydroxyls)			
C-2′-*endo*	160	Axial	Axial
C-3′-*exo*	160	Axial	Axial
C-2′-*exo*	78.4 (sucrose)	Equatorial	Equatorial
C-3′-*endo*	75[b]	Equatorial	Equatorial
c. Mannofuranoside (*cis* hydroxyls)			
C-2′-*endo*	50	Axial	Equatorial
C-3′-*exo*	50	Axial	Equatorial
C-2′-*exo*	50	Equatorial	Axial
C-3′-*endo*	50	Equatorial	Axial
d. Galactofuranoside (*trans* hydroxyls)			
C-2′-*endo*	75	Equatorial	Equatorial
C-3′-*exo*	75	Equatorial	Equatorial
C-2′-*exo*	160	Axial	Axial
C-3′-*endo*	160	Axial	Axial

[a] With hydroxyls on the C-2′ and C-3′ carbon atoms in the riboside numbering. [b] See ref. 20.

(19) J. Donohue and K. N. Trueblood, *J. Mol. Biol.*, **2**, 363 (1960).

(20) By modern standards the crystal structure of sucrose sodium bromide dihydrate (SSBD), solved in projections (C. A. Beevers and W. Cochran, *Proc. Roy. Soc.* (London), **A190**, 257 (1947)), cannot be considered a precise determination; nonetheless, some features of the geometry of the fructofuranosyl residue in this structure are worthy of mention. The conformation of the furanose ring here is C-3′-*endo* (C-3′-*endo*–C-2′-*endo* in terms of the twist of the bond C-2′–C-3′ relative to the plane defined by C-1′, O-1′ and C-4′, and therefore, similar to TMP; see text) in contrast to the C-2′-*exo* conformation in sucrose. The dihedral angle formed by the *trans*-hydroxyl groups is about 70° and is in agreement with the estimated value for a C-3′-*endo* conformation cited in Table VIIIb of text.

(21) J. Honeyman and C. J. G. Shaw, *J. Chem. Soc.*, 2454 (1959).

(22) E. L. Jackson and C. S. Hudson, *J. Am. Chem. Soc.*, **59**, 994 (1937).

(23) M. S. Newman "Steric Effects in Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1956, pp. 383, 384.

galactofuranoside in the C-2′-*endo* or C-3′-*exo* conformation. If these compounds completely resist oxidation they will possess conformations with projected angles of about 160°[14] (Table VIII). Due to the "flexibility" of the furanose ring *trans* 1,2-glycols with dihedral angles of 160° may undergo conformational transformation to give dihedral angles of 75° "in response to the forces of complex formation."

Even with these angles (75°) the bridging of the *trans* hydroxyl groups by the oxidizing agents appears to be less favorable than in the *cis* case. At any rate, it seems reasonable now, from considerations of the projected angle, that the cyclic intermediate is also the precursor in the oxidation of these *trans* 1,2-glycols, and therefore, the oxidation mechanism of Cordner and Pausaker[24] need not be invoked here.

The geometrical requirements for the formation of cuprammonium complex, assuming the copper atom bridges the oxygens of the hydroxyls, seem more stringent than the periodate and lead tetraacetate oxidation, since only the *cis* forms the cuprammonium complexes. Presumably this has to do with the smaller size of the copper atom in contrast to the lead and iodine atoms.

Now it can be explained quite convincingly that the resistivity to oxidation of the bridged bicyclic anhydrosugars, *e.g.*, 1,6-anhydro-β-D-glucofuranose,[25] 1,6-anhydro-α-D-galactofuranose,[25] 2,7-anhydro-β-D-*altro*-heptulofuranose,[26] 2,7-anhydro-α-L-*galacto*-heptulofuranose,[27] and 2,6-anhydro-β-D-fructofuranose[28] is due to conformational rigidity imposed on the furanose ring which assumes conformations where the hydroxyls make projected angles of about 160°, which does not permit the formation of the cyclic intermediates by the complexing and oxidizing agents.

That the bridged bicyclic system is not essential for the hydroxyl groups to display a projected angle of about 160° was recently documented by Lemieux and Nagarajan who discovered a "rigid" furanoside ring in 1′-2-anhydro-1-(α-D-fructofuranosyl)-β-D-fructofuranose. The α-D-fructofuranosyl moiety in this spiro cyclic system was highly resistant to periodate oxidation and this was attributed to a dihedral angle of about 150° between the hydroxyl groups. It may be noted, therefore, that even in the *trans* 1,2-glycols of the furanosides projected angles close to 180° can be attained as in the *trans* 1,2-glycols of six-membered rings.[29]

Consequences of Puckering on Bond Lengths and Angles. Some interesting features of the bond lengths and angles in the furanosides as a consequence of puckering are the following.

(1) The average value of the 18 C–C bonds in the furanose ring of the six compounds is 1.523 ± 0.004 Å., and the average C-4′–C-5′ bond length is 1.516 Å. These values are considerably shorter than the C–C diamond bond of 1.54 Å. and, furthermore, the C-4′–C-5′ bond seems to be shorter than the "normal" C–C single bond value of 1.533 Å.[30]

(2) The ring C-1′–O-1′ bond adjacent to the glycosidic linkage, average about 1.427 Å., is shorter than the ring C-4′–O-1′ bond, average about 1.450 Å. This feature is probably a consequence of the presence of electronegative atoms, O-1′ and N, with nonbonded electrons adjacent to C-1′.

(3) The exocyclic C–O bond involving the out-of-plane carbon atom averages about 1.404 Å., excepting DA, while that involving the in-plane carbon atom averages about 1.434 Å. The latter value is in agreement with the normal C–O distance of 1.429 ± 0.004[31] and 1.427 ± 0.007 Å.[32]

(4) The internal C–C–C angles involving the out-of-plane carbon average about 100.9°, which is about 1.6° less than the average value of 102.5° involving the in-plane atom. These angles are considerably less than the tetrahedral bond angle.

(5) The average internal C–C–O bond angle of 105.8°, while it is significantly greater than the internal C–C–C angle, is still significantly less than the tetrahedral value.

(6) The internal C–O–C angle averages about 109.3° and is the only internal angle close to the tetrahedral bond angle.

(7) The exocyclic C–C–O bond angle involving the out-of-plane carbon averages 115.3°, except DA, and is 6° greater than that involving the in-plane carbon, 109.3°.

(8) The average O-1′–C-1′–N and O-1′–C-4′–C-5′ bond angles of 107.6 and 109.2°, respectively, are significantly less than the average C-2′–C-1′–N and C-3′–C-4′–C-5′ bond angles of 112.9 and 116.6°, respectively.[33]

There appears to be a striking correlation between the ring pucker, the exocyclic C–O bond length, and the exocyclic C–C–O bond angles. Curiously, when the external C–C–O angles open up to a value of about 115°, the C–O distance contracts by about 0.03 Å. from the normal value, suggesting that the hybrid orbital of the C atom is between sp^3 and sp^2. When the external C–C–O angles are close to the tetrahedral bond angle, the C–O distance assumes the normal value irrespective of whether the carbon atom involved is in-plane or out-of-plane. This fact is exemplified by DA, where the opposite mode of puckering gives the C–C–O external angle values close to 109.5° and the C-3′–O-3′ bond length is 1.422 Å.

In the fructofuranosyl moiety of sucrose, the C–O distance of 1.401 Å. and the average C–C–O external angle of 115.7° involving the out-of-plane atom (C-3′) are analogous to those found in CMP, FUDR, and AMP. On the other hand, the C–O distance of 1.419 Å. and the average C–C–O external angle of 112.0° involving the in-plane atom (C-4′) lie between the values found for the out-of-plane and in-plane atoms, excepting DA. It may be noted that both C-3′ and C-4′

(24) J. P. Cordner and K. H. Pausaker, *J. Chem. Soc.*, **102** (1953).
(25) (a) R. J. Dimler, H. A. Davis, and G. E. Hilbert, *J. Am. Chem. Soc.*, **68**, 1377 (1946); (b) B. H. Alexander, R. J. Dimler, and C. L. Mehltretter, *ibid.*, **73**, 4658 (1951).
(26) N. K. Richtmyer and J. W. Pratt, *ibid.*, **78**, 4717 (1956).
(27) L. C. Stewart, E. Zissis, and N. K. Richtmyer, *J. Org. Chem.*, **28**, 1842 (1963).
(28) H. R. Goldschmid and A. S. Perlin, *Can. J. Chem.*, **38**, 2178 (1960).
(29) R. E. Reeves, *J. Am. Chem. Soc.*, **72**, 1499 (1950).
(30) L. S. Bartell, *ibid.*, **81**, 3497 (1959).
(31) V. Bussetti, M. Mammi, and G. Carazzola, *Z. Krist.*, **119**, 310 (1963).
(32) P. Venkateswarlu and W. Gordy, *J. Chem. Phys.*, **23**, 1200 (1955).
(33) It may be noted that the exocyclic C–C bond length, C–C–C bond angle, and the ring C–O bond lengths in the pyranose system (W. G. Ferrier, *Acta Cryst.*, **16**, 1023 (1963); H. McD. McGeachin and C. A. Beevers, *ibid.*, **10**, 227 (1957)) are similar to those found here.

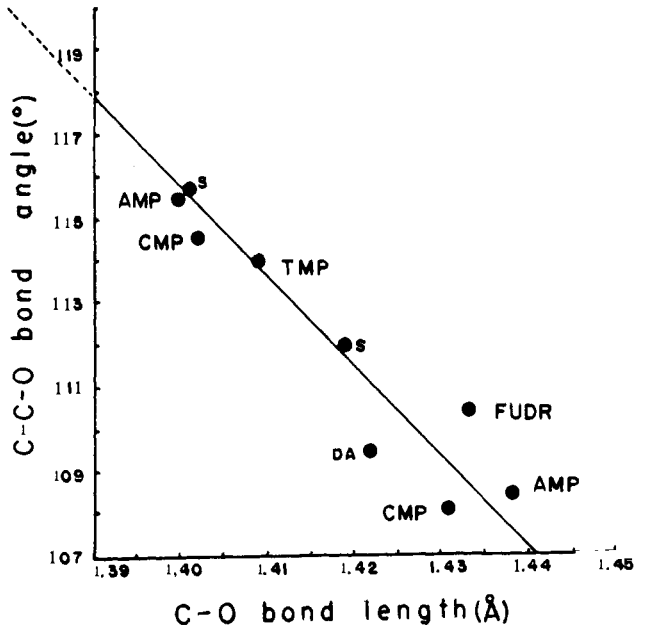


Figure 8. Graph of C–O bond lengths *vs.* C–C–O external bond angle. S is the abbreviation for sucrose.

in the fructofuranosyl moiety are displaced quite appreciably and by about the same amount from the plane of the other three atoms (Table V), in contrast to the other examples cited, where the displacement of one of the atoms is more pronounced than the other.

The dependence of the C–O bond length on the C–C–O external bond angle may be represented by the straight-line graph as illustrated in Figure 8. All the points in the graph were given equal weight. The slope of the line indicates that for every degree increase in the C–C–O external bond angle the C–O distance shortens by about 0.0047 Å. Theoretically, therefore, for external angles of 120 and 129.5° the extrapolated C–O bond lengths will be 1.380 and 1.347 Å., respectively. The latter is the case when the carbon atom attached to the oxygen atom lies in the plane of the adjacent carbon atoms in the ring. These values may be compared with the values for the C–O distances in carbonyl and carboxylate groups. Interestingly, the C–O bond shortens only when it is in the equatorial orientation, while the axial C–O bond (in DA) possesses a normal value. The rehybridization of the carbon atom apparently results in a gain in the sp^2 character of the C–O bond (equatorial) and a gain in the p-character of the C–H bond (axial). These ideas may find possible application in assigning conformations to furanosides from p.m.r. studies.

Acknowledgment. The author gratefully thanks Professor L. H. Jensen and Dr. D. G. Watson of this department and Dr. W. S. Chilton of the Department of Chemistry for their interest and helpful criticism of the manuscript, and Drs. G. M. Brown, H. A. Levy, D. G. Watson, D. J. Sutor, and P. Tollin for access to data in advance of publication.

Studies of Nucleosides and Nucleotides. XXIV.[1] Purine Cyclonucleosides. I. 8,2′-Cyclonucleoside Derived from 2-Chloro-8-mercapto-9-β-D-xylofuranosyladenine[2]

Morio Ikehara and Hiroshi Tada

Contribution from the Faculty of Pharmaceutical Sciences, School of Medicine, Hokkaido University, Sapporo, Japan. *Received March 2, 1964*

The synthesis of 2-chloro-8-mercapto-9-(2′-O-acetyl-3′-O-tosyl-5′-O-methoxycarbonyl-β-D-xylosyl)adenine (IV) was achieved by Davoll's method. Compound IV gave 8,2′-anhydro-2-chloro-8-mercapto-β-D-arabinofuranosyladenine (V) on treatment with sodium methoxide in methanol. The structure of V was elucidated by chemical and physical methods. Desulfurization of V with Raney nickel followed by hydrogenation over palladized charcoal gave 2′-deoxyadenosine, identical with naturally occurring nucleoside. Hydrolysis of V in acidic and alkaline media was investigated.

Among the various reactions of nucleosides, increasing interest is being shown in the synthesis of cyclonucleosides[3] (anhydronucleosides) because of their utility in the elucidation of anomeric configurations[4] and in serving as precursors for chemical alteration of the sugar moiety.[5] Previous studies in this area have been restricted mainly to pyrimidine nucleosides.[6]

(1) Part XXIII of this series: M. Ikehara, F. Ishikawa, and H. Uno, *Chem. Pharm. Bull.* (Tokyo), **12**, 267 (1964).

(2) The preliminary account of this work has been reported: M. Ikehara and H. Tada, *J. Am. Chem. Soc.*, **85**, 2344 (1963).

(3) J. J. Fox and I. Wempen, *Advan. Carbohydrate Chem.*, **14**, 283 (1959).

(4) V. M. Clark, A. R. Todd, and J. Zussman, *J. Chem. Soc.*, 2959 (1951); W. Anderson, D. H. Hayes, A. M. Michelson, and A. R. Todd, *ibid.*, 1882 (1954); B. R. Baker and J. P. Joseph, *J. Am. Chem. Soc.*, **77**, 15 (1955); R. W. Chambers, J. G. Moffatt, and H. G. Khorana, *ibid.*, **79**, 3747 (1957).

(5) D. M. Brown, A. R. Todd, and S. Varadarajan, *J. Chem. Soc.*, 2388 (1950); A. M. Michelson and A. R. Todd, *ibid.*, 816 (1955); J. J. Fox and N. C. Miller, *J. Org. Chem.*, **28**, 936 (1963), and previous papers by J. J. Fox and collaborators; J. H. Horwitz, J. Chua, J. A. Urbansky, and M. Noel, *ibid.*, **28**, 942 (1963).

(6) During the course of this investigation, a study by Holmes and Robins[7] dealing with the synthesis of a 3,5′-cyclonucleoside from a cyclonucleoside salt[8] of a purine nucleoside appeared.

(7) R. E. Holmes and R. K. Robins, *J. Org. Chem.*, **28**, 3483 (1963).

(8) See V. M. Clark, *et al.*, ref. 4.