Anal. Calcd for $C_{16}H_{12}O_4N_4$: C, 47.62; H, 4.80; N, 22.22. Found: C, 47.59; H, 4.59; N, 22.05.

9-(2′,3′,4′,6′-Tetra-*O*-acetyl-β-D-glucopyranosyl)purine.—A finely pulverized mixture of 1.4 g of purine and 3.2 g of 1,2,3,4,6-penta-*O*-acetyl-β-D-glucopyranose[18] was fused in a similar manner to that described above. Recrystallization of the crude product from methanol and ethyl acetate gave 360 mg (8.4 % yield) of the titled compound as colorless needles: mp 199.5–200°; λ_{max}^{EtOH} 261.5 mμ.

Anal. Calcd for $C_{19}H_{22}O_9N_4$: C, 50.60; H, 4.92; N, 12.44. Found: C, 50.51; H, 4.91; N, 12.32.

9-β-D-Glucopyranosylpurine (9).—9-(2′,3′,4′,6′-Tetra-*O*-acetyl-β-D-glucopyranosylpurine (277 mg) was treated with 40 ml of methanolic ammonia as described above. The methanolic solution was evaporated to dryness, and recrystallization from ethanol and water gave 171 mg (98.5% yield) of 9 as colorless platelets: mp 205–205.5°; $[\alpha]^{11.5}D$ −1.5° (*c* 0.8, water); $\lambda_{max}^{H_2O}$ 261.5 mμ (ε 7810); $\lambda_{max}^{1\ N\ HCl}$ 262.5 mμ (ε 11,280); $\lambda_{max}^{pH\ 9.18}$ 262.5 mμ (ε 11,300).

Anal. Calcd for $C_{11}H_{14}O_5N_4$: C, 45.30; H, 5.19; N, 19.24. Found: C, 45.71; H, 5.21; N, 19.13.

Registry No.—1, 15981-63-2; 2, 15981-64-3; 3, 550-33-4; 4, 2149-71-5; 5, 15981-67-6; 6, 15981-68-7; 7, 15981-71-2; 8, 15981-69-8; 9, 15981-70-1; 9-(2′,3′,5′-tri-*O*-acetyl-β-D-xylofuranosyl)purine, 15981-47-2; 7-(2′,3′,5′-tri-*O*-acetyl-β-D-xylofuranosyl)purine, 15981-44-9; 9-(2′,3′,4′-tri-*O*-acetyl-β-D-ribopyranosyl)-purine, 15981-45-0; 9-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyl)purine, 15981-46-1.

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The Proton Magnetic Resonance Spectra of Pentofuranose Derivatives

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The proton magnetic resonance spectra of a number of derivatives of D-arabinose, D-lyxose, D-ribose, and D-xylose in their furanose forms have been measured. The pmr parameters have been shown to be of diagnostic value in structural studies and form the basis for speculations regarding the conformations of these substances in solution. A novel example of "virtual long-range coupling," involving a hydroxyl hydrogen, is discussed.

The large difference between spin–spin coupling constants for vicinal hydrogens in a saturated six-membered ring, dependent on whether these hydrogens are axial–axial (J = *ca.* 6–11 Hz), axial–equatorial, or equatorial–equatorial (J = *ca.* 1–5.4 Hz),[2] has led to the solution of a large number of structural and stereochemical problems involving such ring systems.[3] Parallel success for five-membered ring compounds has not been so marked. This is in part due to the paucity of data on compounds containing these rings as well as the much greater complexity of the problem of conformation resulting from the large number of "extreme" conformations which are possible for five-membered rings[4] and the resultant uncertainty in the projected bond angles for vicinal hydrogens. Nevertheless, a number of problems have been solved and information is accumulating on the pmr parameters of variously substituted five-membered ring systems.[3b,5]

As part of a broad study of derivatives of sugars in the furanose form,[6] we have examined the pmr spectra of a number of acylated pentofuranoses with the aim of providing data for structural and stereochemical problems and with the view of relating the observed coupling constants to possible conformations.

For most of the compounds studied, the difference in chemical shift of H-1 and H-2 and of H-3 and H-4 is large compared with the couplings $J_{1,2}$ and $J_{3,4}$, respectively. For a number of the compounds, the difference in chemical shift between H-4 and H-5,H-5′ is sufficiently large to result in the C-5 methylene protons having no observable first-order effects upon the signals due to H-3. In such cases, the hydrogens attached to the ring could be considered independently of H-5,-H-5′ and they may be classified as an AKLX system.[7] For others, H-4, H-5, and H-5′ form a strongly coupled system (*i.e.*, the difference in chemical shift of these three protons is less than, or of the same order as, the spin–spin coupling between them) which results in a broadening of the signals due to H-3; in such cases, H-3 may be said to experience virtual long-range coupling with H-5,H-5′.[8] In order to obtain spectra amenable to first-order analysis, acyloxy groups on C-2 and C-3 were chosen such that the difference in chemical shift of H-2 and H-3 was several times the value of the coupling constant, $J_{2,3}$. This procedure introduced the problem of comparing coupling constants for CH–CH fragments bearing different sub-

(1) Associate in the Visiting Program of the National Institutes of Health, 1962–1964.

(2) R. U. Lemieux, R. K. Kullnig, H. J. Bernstein, and W. G. Schneider, *J. Amer. Chem. Soc.*, **80**, 6098 (1958).

(3) For example, see (a) J. B. Stothers in "Technique of Organic Chemistry," Vol. XI, K. W. Bentley, Ed., Interscience Publishers, Inc., New York, N. Y., 1963, p 175; (b) L. D. Hall, *Advan. Carbohyd. Chem.*, **19**, 51 (1964); (c) J. W. Emsley, J. Feeney, and L. H. Sutcliffe, "High Resolution Nuclear Magnetic Resonance Spectroscopy," Vol. 2, Pergamon Press Ltd., Oxford, 1966.

(4) (a) K. S. Pitzer and W. E. Donath, *J. Amer. Chem. Soc.*, **81**, 3213 (1957); (b) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience Publishers, Inc., New York, N. Y., 1965, Chapter 4.

(5) (a) R. U. Lemieux, *Can. J. Chem.*, **39**, 116 (1961); (b) D. Gagnaire and P. Vottero, *Bull. Soc. Chim. Fr.*, 2779 (1963); (c) R. J. Abraham and K. A. McLauchlan, *Mol. Phys.*, **5**, 195, 513 (1962); (d) G. Casini and L. Goodman, *J. Amer. Chem. Soc.*, **86**, 1427 (1964); (e) L. Goodman, *ibid.*, **86**, 4167 (1964); (f) R. J. Abraham, L. D. Hall, L. Hough, and K. S. McLauchlan, *J. Chem. Soc.*, 3699 (1962); (g) L. D. Hall, *Chem. Ind.* (London), 950 (1963); (h) R. U. Lemieux and R. Nagarajan, *Can. J. Chem.*, **42**, 1270 (1964); (i) B. Capon and D. Thacker, *Proc. Chem. Soc.* (London), 369 (1964).

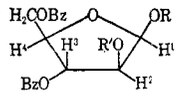
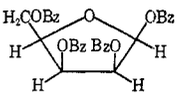
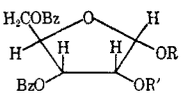
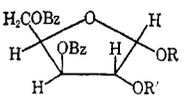
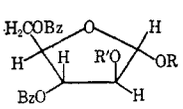
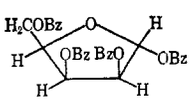
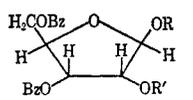
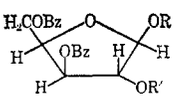
(6) A. K. Bhattacharya, R. K. Ness, and H. G. Fletcher, Jr., *J. Org. Chem.*, **28**, 428 (1963), and references cited therein.

(7) J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High Resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N. Y., 1959, p 98.

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

TABLE I

CHEMICAL SHIFTS OF SOME PENTOFURANOSE DERIVATIVES[a,b]

Compd	No.	R	R′	Ref	Chemical shift, δ					
					H-1	H-2	H-3	H-4	H-5,H-5′	Others
	1	Bz	Bz	*c*	6.93	5.97	6.23		4.77	
	2	Bz	Ac	*c*	6.77	5.73	6.00		4.70	2.05 (Ac)
	3	Bz	Ms	*c*	6.77	5.58	6.00		4.72	3.05 (Ms)
	4	Bz	H	*c*	6.62	4.75	5.72		4.65	
	5			*d*	6.90	5.80	6.28	4.97	4.78	
	6	Bz	Bz	*e*	6.98	5.77	5.97	4.95	4.75	
	7	Bz	Ac	*e*	6.83	5.58	5.85	4.88	4.72	2.02 (Ac)
	8	Bz	Ms	*e*	6.85	5.47	5.82	4.87	4.68	3.03 (Ms)
	9	Bz	H	*e*	6.70	~4.70	5.62		~4.70	3.07 (OH)
	10	Bz	Bz	*f*	6.98	5.98	6.27	5.12	4.65	
	11	Ac	Bz	*g*	6.74	5.83	6.15	5.02	4.60	2.04 (Ac)
	12	Bz	Ms	*h*	6.83	5.63	6.05	5.03	4.57	3.07 (Ms)
	13	Bz	H	*h*	6.67	4.78	5.78	5.00	4.53	3.65 (OH)
	14	Bz	Bz	*c*	6.80	5.88	5.73		4.85	
	15	Me	Bz	*c*	5.25	5.48	5.62		4.67	
	16			*d*	6.82	6.02	6.25	5.08	4.75	
	17	Bz	Bz	*i*	6.72	6.05	6.05		5.00–5.42	
	18	Bz	Ac	*j*	6.55	5.80	5.93		4.93–4.35	2.12 (Ac)
	19	Ac	Bz	*i*	6.47	5.82	5.97		4.95–4.35	1.98 (Ac)
	20	Ac	Ac	*k*	6.30	5.58	5.82		4.63	1.97, 2.10 (Ac)
	21	Bz	Ms	*l*	6.60	5.55	5.83		4.67	3.07 (Ms)
	22	Bz	H	*j*	6.47		5.63			
	23	Bz	Bz	*f*	6.72	5.87	6.01	5.13	4.73	
	24	Ac	Bz	*h*	6.45	5.70	5.93	5.03	4.68	2.10 (Ac)

[a] Ac = H_3CCO, Bz = C_6H_5CO, Me = H_3C, Ms = H_3CSO_2. [b] Chemical shifts are expressed in parts per million (ppm) from tetramethylsilane as an internal standard. Spectra were measured in deuteriochloroform solution except that of **15** where acetonitrile was used. [c] R. K. Ness and H. G. Fletcher, Jr., *J. Amer. Chem. Soc.*, **80**, 2007 (1958). [d] See ref 6. [e] R. K. Ness and H. G. Fletcher, Jr., *J. Amer. Chem. Soc.*, **78**, 4710 (1956). [f] H. G. Fletcher, Jr., *ibid.*, **75**, 2624 (1953). [g] J. J. Fox, N. Jung, J. Davoll, and G. B. Brown, *ibid.*, **78**, 2117 (1956). [h] See Experimental Section. [i] R. K. Ness, H. W. Diehl, and H. G. Fletcher, Jr., *ibid.*, **76**, 763 (1954). [j] R. K. Ness and H. G. Fletcher, Jr., *J. Org. Chem.*, **22**, 1465 (1957). [k] R. K. Ness and H. G. Fletcher, Jr., *J. Amer. Chem. Soc.*, **76**, 1663 (1954). [l] Obtained as a syrup by mesylation of **22**.

stituents, but our results indicate that, in general, hydroxyl, acetoxy, benzoyloxy, and mesyloxy groups produce comparable effects, in agreement with the view that substituent effects are, to a large extent, mirrored by the electronegativity of the atom directly bonded to the CH–CH fragment.[9]

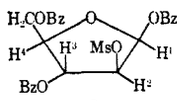
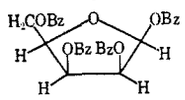
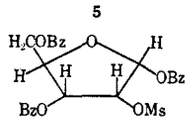
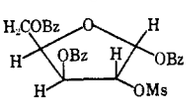
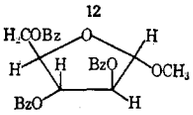
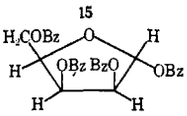
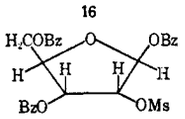
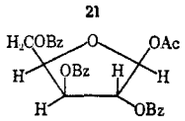
The first-order chemical shifts for a variety of closely related pentofuranose derivatives are given in Table I. For those cases in which H-4 and H-5,5′ are clearly separated, the shift of H-5,H-5′ is reported as a single value, although spectra measured at 100 MHz have shown that in fact the chemical shift difference between H-5 and H-5′ is often not zero. When H-4, H-5, and H-5′ form a strongly coupled system, if the multiplet is narrow, the midpoint is reported; otherwise the range of absorption is given. Some first-order coupling constants are given in Table II, the compounds chosen being those for which the chemical-shift difference between H-2 and H-3 is larger than $J_{2,3}$. Other cases are discussed below under the individual sugars.

β-Arabinofuranose Series (1–4).—The spectra of the compounds for which $\delta_{2,3}$ was smaller than the value for **3** showed splittings in the signals due to H-2 and H-3 somewhat smaller than those reported for **3** in Table II. For **2**, the doublet due to H-1 was split by 4.3 Hz and the doublet of doublets due to H-3 has spacings of 7.2 and 4.6 Hz. At 100 MHz, these spacings became 4.6, 7.0, and 5.0 Hz, respectively. Such changes demonstrate the errors introduced by first-order treatment. For the present purposes, however, the magnitude of these errors is such that the application of the parameters to structural and conformational questions will not be invalidated. Hydrogens 4, 5, and 5′ in this group of compounds form a strongly coupled system and consequently the signals due to H-3 are considerably broader than those due to H-2. This broadening may be used to good advantage in assigning the doublet of doublets to the hydrogens concerned. That this broadening is due at least partly to virtual coupling was demonstrated by comparing

(9) For a review of earlier work, see C. N. Banwell and N. Sheppard, *Discussions Faraday Soc.*, **34**, 115 (1962); (a) K. L. Williamson, *J. Amer. Chem. Soc.*, **85**, 516 (1963); (b) P. Laszlo and P. von R. Schleyer, *ibid.*, **86**, 1171 (1964); (c) R. J. Abraham and K. G. R. Pachler, *Mol. Phys.*, **7**, 165 (1963–1964); (d) A. D. Cohen and T. Schaefer, *ibid.*, **10**, 209 (1966).

TABLE II

FIRST-ORDER COUPLING CONSTANTS OF SOME PENTOFURANOSE DERIVATIVES[a,b]

	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$
 3	4.5	7.2	5.1
 5	4.6	5.5	4.3
 8	4.3	6.5	2.3
 12	4.4	6.4	6.8
 15	<0.5	1.6	4.9
 16	1.5	5.2	5.4
 21	<0.5	4.6	7.0
 24	<0.5	1.8	5.2

[a] Bz = C_6H_5CO, Ms = H_3CSO_2, Ac = H_3CCO. [b] Values were obtained from spectra measured in deuteriochloroform solution except for **15** where acetonitrile was used.

the spectra of **2** measured at 60 and 100 MHz. The signals due to H-3 were considerably sharper in the latter case as a result of the greater chemical-shift difference (in hertz) between H-4 and H-5, H-5′.

β-Lyxofuranose (5).—In the spectrum of β-D-lyxofuranose tetrabenzoate (**5**) both H-2 and H-3 appear as a triplet, the center peaks of which are broad. The center peak of the higher field triplet revealed itself as two peaks under high resolution but the broad center peak of the lower field triplet could not be resolved. The assignment of the lower field multiplet to H-3 was supported by the broadening of these signals, in part at least as a result of strong coupling between H-4, H-5, and H-5′. As in the case of **2** above, this broadening (at 60 MHz) was reduced in the spectrum measured at 100 MHz; for this spectrum, the peaks of the lower field triplet were almost the same height as those due to H-2 and the signals due to H-4 were now readily distinguished from those due to H-5,H-5′. Final verification of the assignment was achieved by a spin-decoupling experiment at 60 MHz. The triplet at 5.80 ppm collapsed to a doublet on irradiating downfield using a frequency of 66 Hz.

α-Ribofuranose Series (6–9).—In this series, H-1 appears as a well defined doublet, H-2 and H-3 as two generally well separated doublets, of doublets, and H-4 as a multiplet clearly separated from the signals due to H-5,H-5′. The reasonably large chemical-shift difference between H-4 and H-5,H-5′ results in the signals due to H-3 appearing as sharp peaks of about the same height as those due to H-2. Compound **8** provides a test case for the validity of the first-order treatment used to provide the coupling constants listed in Table II. At 100 MHz, the spacings which correspond to $J_{1,2}$, $J_{2,3}$, and $J_{3,4}$ in Table II are 4.4, 6.45, and 2.4 Hz, respectively.

The spectrum of **9**, the subject of an earlier study,[5g] reveals an interesting substitution effect. We find the coupling instants $J_{1,2}$, $J_{2,3}$, and $J_{3,4}$ to be 4.3, 6.6, and 1.6 Hz, respectively. The value for $J_{3,4}$ is significantly smaller than the corresponding value for **8**. That this is not a general phenomenon associated with the effect of a hydroxyl group (compared with an acyloxy group) attached to C-2, is shown by the corresponding coupling constants of compound **4** which are almost identical with the values for compound **3**.

α-Xylofuranose Series (10–13).—The typical pattern for these compounds is a well-defined doublet for H-1, a doublet of doublets for H-2, and H-3 appearing as a triplet as a result of the small difference between $J_{2,3}$ and $J_{3,4}$. The multiplet due to H-4 is clearly shifted from the signals due to H-5,H-5′. Isolation of compound **13** by chromatography of the hydrolysis products from 2,3,5-tri-*O*-benzoyl-D-xylofuranosyl bromide (see Experimental Section) was readily monitored by the pmr spectra of the eluted materials. The spectrum of the pure tribenzoate provided unequivocal proof of its structure: a doublet, spacing 4.5 Hz, at 6.67 ppm and a triplet, outside spacing 12.7 Hz, at 5.78 ppm can only be accommodated by the structure proposed. The hydroxyl hydrogen appeared as a well-defined doublet, spacing 6.0 Hz at 3.65 ppm.

α-Arabinofuranose Series (14–15).—The signals for H-1 in the spectra for these compounds appeared as a somewhat broadened single peak. A doublet (not clearly resolved in all cases) arose from H-2. The very small difference in chemical shift of H-4 and H-5,H-5′ resulted, in many cases, in H-3 giving rise to a very broad peak. Studies[10] on some related compounds have shown that H-1 is coupled to H-3; no doubt such long-range coupling can contribute to the lack of resolution of the H-3 signal in the spectra of some of these benzoates. The chemical-shift difference of H-4 and H-5,H-5′ was found to be solvent dependent and, in the spectrum of **15** in acetone or acetonitrile, H-3 appeared as a doublet in which each limb showed signs of further splitting (H-4, H-5, and H-5′ appeared as a number of peaks spread over 25 Hz).

β-Ribofuranose Series (17–22).—Compound **20** provided an example of a substitution effect. In the spectrum of this compound, H-1 appears as a doublet with a spacing of 1.0 Hz; $J_{2,3}$ = 4.9 Hz and $J_{3,4}$ = 5.6 Hz. This last coupling is considerably less than the value for **21** and results in the two central lines of the H-3 doublet of doublets appearing as an unresolved peak. In the spectrum of **22**, H-1 appeared as a single peak and H-3 as a doublet of doublets; spacings were 4.7 and 7.1 Hz, respectively.

(10) J. D. Stevens, results to be published.

β-Xylofuranose Series (23–24).—In the spectra of these compounds, H-1 appears as a single peak, H-2 appears as a doublet with small spacing, and H-3 appears as a doublet of doublets, the smaller spacing of which was not resolved for **23**. The signal for H-4 appears as a multiplet well shifted from H-5,H-5′.

General Features of the Spectra.—Examination of Tables I and II shows that the pmr spectrum of an acylated aldose in the furanose form may generally provide a basis for the assignment of the relative configuration of the four asymmetric carbon atoms involved in the five-membered ring. The most striking feature is the clear-cut difference between the cases in which the groups on C-1 and C-2 are *cis* and *trans*. These values are so characteristic that an assignment of relative configurations at these centers can be made when only one member of an anomeric pair is available. Other groups of workers[5e,i] have previously noted the diagnostic value of $J_{1,2}$ in aldofuranosides; while the great utility of this generalization should not be minimized, various β-ribo nucleosides (*trans* at C-1–C-2) show $J_{1,2}$ values which fail to distinguish them from their anomers.[11–14] We will return to this topic presently.

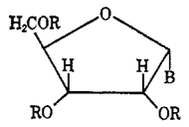
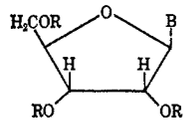
Considering the other couplings around the ring, there are several pairs of compounds which cannot be differentiated using the coupling constants alone, *e.g.*, **14** and **23**. As discussed below, chemical-shift differences may be used to define the relative configurations. An interesting feature of the couplings reported in Table II is the magnitude of the coupling between several of the vicinal *trans* hydrogens. Whereas the coupling constant for vicinal *cis* hydrogens is in the range of 4.3 to 6.8 Hz, the values for vicinal *trans* hydrogens vary from a very small value (<0.5 Hz) to 7.2 Hz. These ranges agree very well with those predicted from the application of the Karplus curve to neighboring *cis* and *trans* hydrogens in a five-membered ring.[15] The considerable overlap between these two ranges of coupling constants obviously precludes the assignment of *cis* or *trans* relationship for neighboring hydrogens in a five-membered ring when the coupling constant between those hydrogens is greater than about 4 Hz. On the other hand, it would appear that a coupling constant less than about 4 Hz may be ascribed to neighboring *trans* hydrogens.

From the chemical shifts listed in Table I we see that, for an anomeric pair of compounds, H-1 is at lower field when the substituents at C-1 and C-2 are *cis* than when they are *trans*. That is, when the substituent at C-2 is on the same side of the ring as H-1, the anomeric proton is shielded compared with H-1 in the epimeric compound. For pairs of compounds isomeric at C-4, when the C-4 substituent is on the same side of the ring as H-3, this hydrogen is shielded compared with the other isomer but, otherwise, no simple, consistent shielding effect of substituent groups upon H-2 and H-3 is evident. With the exception of the α-ribofuranose series, when H-4 is *cis* to the oxygen function at C-3, the signals for H-4 are merged in with those due to H-5,H-5′. This relative chemical shift of H-4 and H-5,H-5′ may be of diagnostic value. For example, the chemical-shift difference between H-4 and H-5,H-5′ in the β-xylofuranose derivative **23** clearly differentiates it from the α-arabinofuranose compound **14**. The exceptional case of α-ribofuranose appears to offer a simple means for the assignment of anomeric configuration in the ribofuranose series, at least for those cases in which the C-2, C-3, and C-5 hydroxyl groups are esterified. Thus, whereas the signals for H-4 are clearly separated from those due to H-5,H-5′ in the spectra of **6**, **7**, and **8**, in the spectra of the corresponding β derivatives H-4 is not clearly defined.

As mentioned earlier, various anomeric ribo nucleosides give $J_{1,2}$ values which do not permit the assignment of anomeric configuration. Some examples of these, the anomeric triacetates and tribenzoates of the ribazoles (5,6-dimethyl-1-D-ribofuranosylbenzimidazoles) are shown in Table III. Whereas $J_{1,2}$ is the same for all four structures, it will be noted that H-1 in the β isomers resonates at higher field than in the α isomers and thus assignment of anomeric configuration is possible. The same phenomenon has been observed with other ribazole derivatives[14] as well as with other nucleosides.[12b] The signal for H-4 appears as a clearly defined multiplet in the spectra of the α-ribazole esters whereas the signals for H-4, H-5, and H-5′ appear essentially as a single peak in the spectra of the β-ribazole esters. The generality of these observations for anomeric ribo nucleosides has yet to be determined.

TABLE III

CHEMICAL SHIFTS OF RIBAZOLE ESTERS[a,b]

	R	Ref	Chemical shift H-1	$J_{1,2}$, Hz	H-4	H-5,H-5′
	Ac[e]	*c*	6.47	5.0	4.62	4.35
	Bz	*d*	6.70	5.0	4.95	4.74
	Ac[f]	*c*	6.08	5.0	4.42	
	Bz	*d*	6.11	5.0	4.95	

[a] Ac = H_3CCO, Bz = C_6H_5CO, B = 5,6-dimethylbenzimidazole-1-yl. [b] Chemical shifts are expressed in parts per million (ppm) from tetramethylsilane as an internal standard. Spectra were measured in deuteriochloroform. [c] See Experimental Section. [d] See ref 13. [e] Registry no.: 16162-41-7. [f] Registry no.: 16162-45-1.

Finally, it may be noted that, with the exception of the α-arabinofuranose derivatives, H-2 in those compounds listed in Table I which have an acyloxy group at C-2 resonates at higher field than does H-3.

Application to Some Acylated Pentofuranosyl Halides.—An examination of the pmr spectra of some acylated pentofuranosyl halides has shown that these spectra are closely comparable to the spectra of the corresponding fully acylated pentofuranoses. For example, the H-1 signal in the *trans* halides, 2,3,5-tri-*O*-benzoyl-α-D-arabinofuranosyl bromide[16] and chloride,[6] appears as a singlet while the H-1 signal from the

(11) C. D. Jardetzky, *J. Amer. Chem. Soc.*, **84**, 62 (1962).

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

(13) J. D. Stevens, R. K. Ness, and H. G. Fletcher, Jr., *J. Org. Chem.*, **33**, 1805 (1968).

(14) M. Haga, R. K. Ness, and H. G. Fletcher, Jr., *ibid.*, **33**, 1810 (1968).

(15) R. U. Lemieux and D. R. Lineback, *Ann. Rev. Biochem.*, **32**, 155 (1963).

(16) See Table I, ref *c*.

corresponding *cis* (β) anomers is a doublet of 4.5 Hz. This similarity of the spectra of fully acylated aldoses and the derived acylated glycosyl halides has been noted earlier in the pyranose series.[17] This simple means of ascertaining the anomeric configuration of pentofuranosyl halides has proved of great utility in this laboratory[13,14,18] and, in the course of the present study, was used to reexamine 3,5-di-*O*-benzoyl-D-ribofuranosyl bromide[19] and chloride.[20] These highly reactive halides may be prepared through brief action of hydrogen chloride or bromide on 1,3,5-tri-*O*-benzoyl-α-D-ribofuranose (**9**) in dichloromethane or dichloromethane–carbon tetrachloride solution but, as discussed in an earlier publication from this laboratory,[21] their optical rotations do not permit the assignment of anomeric configurations. Turning now to pmr spectroscopy, we have found that the anomeric hydrogen of the chloride gives rise to a single peak at 6.12 ppm and the other low field signal is a doublet of doublets; spacings were 4.5 and 7.0 Hz, at 5.77 ppm. The spectrum was similar to that of **22** and clearly denotes a β anomer. On the other hand, the spectrum of the bromide was very similar to that of **9** with a doublet (4.2 Hz) at 6.85 ppm, characteristic of an α anomer. When 1,3,5-tri-*O*-benzoyl-α-D-ribofuranose (**9**) is treated with hydrogen halides, it is probable that the β glycosyl halides are formed initially. The β-chloride crystallizes out directly while the more reactive β-bromide anomerizes in solution and then crystallizes out as the α anomer.

Virtual Long-Range Coupling Involving a Hydroxyl Group.—In the course of the present research, the spectrum of 1,3,5-tri-*O*-benzoyl-α-D-ribofuranose (**9**) in acetone was recorded. In contrast to the readily interpreted chloroform solution spectrum of this compound, the spectrum in acetone solution included a four-peak multiplet for H-1 and a multipeak pattern for H-3. In chloroform, these hydrogens appeared as a clear-cut doublet and doublet of doublets, respectively.[5g] The apparent anomaly was clarified by examining the spectrum of the tribenzoate (**9**) in mixtures of acetone and chloroform. In pure chloroform, the hydroxyl hydrogen appeared as a doublet at 3.07 ppm. Using mixtures of acetone and chloroform, this doublet appeared at lower fields as the acetone concentration increased. Thus for 10, 20, and 40% acetone in chloroform (v/v), the hydroxyl doublet appeared at 3.75, 4.13, and 4.52 ppm, respectively. The H-1 and H-3 multiplets were well defined in these spectra. For 60% acetone in chloroform, the hydroxyl hydrogen had merged into the complex multiplet between 4.5 and 5.0 ppm, originating from hydrogens 2, 4, 5, and 5′. The signal for H-1 no longer appeared as a well-defined doublet but there was now much "filling in" between the outer peaks, which remained at a separation of 4.3 Hz, and H-3 appeared as a complex multiplet of six peaks. We conclude that the "extra" peaks observed in the patterns for H-1 and H-3 of **9** in acetone solution is the result of the small chemical shift between H-2 and the hydroxyl hydrogen. Thus these two hydrogens now form a strongly coupled system which theory predicts[8] will cause H-1 and H-3 to appear as multiplets consisting of many more peaks than is observed in the first-order type spectrum produced by **9** in chloroform solution.

It is useful to note that the virtual long-range coupling effect does not result in any significant change in the spacing of the strong outer peaks of the multiplet concerned. This point is illustrated nicely by the present example, the separation of the strong outer peaks of the multiplets for H-1 and H-3 being the same for the spectra using acetone and chloroform as solvents.

The acetone solution spectrum also provides an example of the appearance of combination lines (referred to as "wings" by Musher and Corey[8]) as a result of the strong coupling between H-2 and the hydroxyl hydrogen. Two low intensity peaks (somewhat broadened) were clearly visible on the high field side of the H-3 multiplet (at 9.7 and 11.9 Hz from the center of this multiplet). The corresponding peaks on the low field side were present, though not clearly defined. All of the features observed in the acetone solution spectrum were reproduced by computation using the FREQINT III program.[22] A series of computations, using a range of values for the chemical shift between H-2 and the hydroxyl hydrogen, showed that the combination lines associated with H-3 increased in intensity and moved toward the center of the multiplet as this chemical shift was decreased. The observed positions of the combination lines are accounted for by a difference in chemical shifts of between 2 and 0 Hz. These conclusions were strongly supported by the spectrum of the *O*-deuterated compound (**9**, R = Bz, R′ = D) in acetone solution in which H-1 and H-3 appeared as a doublet and a doublet of doublets, respectively, identical with the signals observed for the chloroform solution.

Conformations of Pentofuranose Derivatives.—The application of pmr spectroscopy to the determination of conformations of organic molecules is now firmly established. The various factors which may affect the coupling constant between vicinal protons with a projected bond angle have been noted[23] and it appears that one of the most important of these factors is the electronegativity of the substituents attached to the CH–CH moiety in question.[9] In the compounds under study, each carbon atom in the five-membered ring bears an oxygen atom and C-1 is attached to two oxygen atoms. Obviously, if we are going to attempt to correlate the coupling constants $J_{1,2}$, $J_{2,3}$, and $J_{3,4}$ with projected bond angles, it will be necessary to make a correction to the observed $J_{1,2}$ value in order to put this coupling constant on the same basis as those between vicinal hydrogens attached to carbon atoms bearing only one oxygen atom. The form that this correction should take is as yet unknown. It has been shown[24] that for 3-*O*-methyl-6,6-di-*C*-deuterio-β-D-glucopyranose tetraacetate $J_{1,2}$ = 8.2 Hz and $J_{4,5}$ = 9.7 Hz. In this case the projected bond angles approximate 180° and the "correction" which would have to be made to the coupling for H-1 and H-2 is 1.5 Hz.

(17) (a) D. Horton and W. N. Turner, *J. Org. Chem.*, **30**, 3387 (1965); (b) B. Coxon, *Tetrahedron*, **22**, 2281 (1966).

(18) C. P. J. Glaudemans and H. G. Fletcher, Jr., *J. Org. Chem.*, **29**, 3286 (1964); *J. Amer. Chem. Soc.*, **87**, 4636 (1965).

(19) See Table I, ref *k*.

(20) See Table I, ref *e*.

(21) See Table I, ref *j*.

(22) We thank Dr. A. A. Bothner-By of the Mellon Institute for providing us with a copy of this program.

(23) M. Karplus, *J. Amer. Chem. Soc.*, **85**, 2870 (1963).

(24) R. U. Lemieux, J. D. Stevens, and R. R. Fraser, *Can. J. Chem.*, **40**, 1955 (1962).

Application of this correction to the observed value of $J_{1,2}$ in β-D-galactopyranose pentaacetate (8.4 Hz[25]) gives a value that is very close to that observed ($J_{1,2}$ = 10.0 Hz) in 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl cyanide, a product of the condensation of 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl bromide with mercuric cyanide.[26] Although it is reasonable to expect that the value of the correction factor will not be independent of the projected bond angles formed, we note that the slopes of the lines produced by plotting electronegativity of substituents against coupling constants for the hexachlorobicyclo[2.2.1]heptene series[9a] are roughly the same for the projected angles of 0 and 120°. For these angles, the changes in vicinal coupling constants for acetoxy *vs.* cyano substituents are 1.7 and 2.6, respectively. The corresponding change for a projected angle of about 180° has been shown above to be 1.6 Hz. Hence, as a first approximation, we may simply add a fixed amount to the values found for $J_{1,2}$ in the spectra of aldose derivatives, regardless of the magnitudes of the couplings involved. In this paper +1.5 Hz is used as the correction factor for values of $J_{1,2}$. In relating observed coupling constants with dihedral angles, the Karplus relationship[27] has been found to be generally applicable to carbohydrate structures.[28]

There are two extreme modes of deformation of the cyclopentane ring from planarity. In one of these, the C_s or envelope conformation, one ring atom is moved out of the plane of the other four atoms and in the other, the C_2 or twist conformation, two adjacent atoms are moved out of the plane of the other three atoms, one above this plane and the other below.[4a] For the pentofuranose compounds, each of these forms will give rise to ten possible maximally puckered conformations. Corresponding to each of the eight sets of coupling constants presented in Table II, the twenty modes of deformation of the furanose ring were examined using the dihedral angles calculated for the C_s and C_2 forms by Abraham and McLauchlan.[29] For this purpose, 1.5 Hz was added to the observed values of $J_{1,2}$. For the three cases in which H-1 appeared as a single peak, $J_{1,2}$ was assumed to be in the range −0.5 to +0.5 Hz (the coupling constant involved is obviously of small magnitude and to date no evidence has been presented to show the sign of this coupling), giving "corrected" values of 1.0 to 2.0 Hz. By using the range of calculated dihedral angles corresponding to different amounts of buckling in the two modes,[29] it was possible to examine each of the twenty conformations of a particular compound and select a degree of buckling that produced angles consistent with one or more of the coupling constants found. This procedure allowed the elimination of a considerable number of conformations for each compound. Of the remaining possibilities, a number could be neglected by a consideration of the main nonbonded interactions. The most important of these involve (1) eclipsed neighboring groups in C_s conformations and (2) opposing 1,3 "axial" groups in both C_s and C_2 conformations. In discussing the various possibilities, we will use the convenient symbolism employed by Bishop and Cooper[30] in which the carbon atom or atoms which are out of the plane are indicated by a superscript or subscript depending on whether the movement of the atom is in the same direction as the substituent at C-4 or in the opposite direction, respectively, and the symbols E and T are used for the envelope and twist conformations.

A phenomenon which is of some importance in sugar derivatives is the so-called "anomeric effect."[31] This evidently results from the interaction of the dipoles operating in the two C-1–O bonds which tend to become oriented in opposite directions. The importance of this effect in connection with the conformations assumed by various sugar derivatives containing the pyranose ring has been demonstrated a number of times.[17,25] A comparison of the coupling constants reported in Table II for pairs of compounds which are related by the disposition of the substituents around the ring shows that the anomeric effect is of some importance in these furanose compounds. Thus, if the anomeric effect were of no significance here, the coupling $J_{2,3}$ should be roughly the same for β-arabinofuranose and for β-xylofuranose and the corrected value of $J_{1,2}$ in the β-arabinofuranose case should approximate the value of $J_{3,4}$ in the β-xylofuranose case and *vice versa*. Although this argument does not take into account the different spatial requirements of the acyloxy and acyloxymethyl groups, the disparity in the coupling constants being compared is so great that we are forced to conclude that the anomeric effect is of some importance in at least one of this pair of compounds. On the other hand, for another pair (α-ribofuranose and α-lyxofuranose) the coupling constants are more or less complementary. For the compounds which have elements of symmetry (treating all four-ring substituents as if they were identical), *i.e.*, β-lyxofuranose, α-xylofuranose, α-arabinofuranose, and β-ribofuranose, if the anomeric effect were of no significance, we would expect the deformation of the rings in these compounds to be such that the projected angles H-1 to H-2 and H-3 to H-4 would be more or less the same, either as a result of an equilibrium between two conformations such as E^2 and E^3 for β-lyxofuranose or inherently from one particular conformation such as T_3^2 in this case. As a result of this, the corrected values for $J_{1,2}$ should be the same as the observed value of $J_{3,4}$ in these four types of structures. Once again, this is clearly not the case for β-lyxofuranose, α-arabinofuranose, and β-ribofuranose, although for α-xylofuranose the two values are reasonably close.

Table IV lists the conformations which give the best agreement with observed coupling constants. For comparison, the conformations proposed by Bishop and Cooper[30] for the methyl *aldo*-pentofuranosides on the basis of nonbonded interactions are included. In a number of cases, more than one conformation accounts reasonably well for the observed coupling con-

(25) R. U. Lemieux and J. D. Stevens, *Can. J. Chem.*, **43**, 2059 (1965).
(26) B. Coxon and H. G. Fletcher, Jr., *Chem. Ind.* (London), 662 (1964).
(27) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959).
(28) In "Advances in Organic Chemistry," Vol. 2, R. A. Raphael, E. C. Taylor, and H. Wynberg, Ed., Interscience Publishers, Inc., New York, N. Y., 1960, p 311, H. Conroy has presented a plot of dihedral angles *vs.* coupling constants which appears to provide reasonable angles for the coupling constants found for sugar derivatives.[15] We have used a curve giving the following value (coupling constant in Hz): 0° (8.0), 30° (6.0), 60° (1.8), 90° (0.0), 120° (3.9), 150° (8.3), and 180° (10.2).
(29) R. J. Abraham and K. A. McLauchlan, *Mol. Phys.*, **5**, 513 (1962).
(30) C. T. Bishop and F. P. Cooper, *Can. J. Chem.*, **41**, 2743 (1963).
(31) J. T. Edward, *Chem. Ind.* (London), 1102 (1955); see R. U. Lemieux in "Molecular Rearrangements," Part 2, P. de Mayo, Ed., Interscience Publishers, Inc., New York, N. Y., 1964, p 735, for a detailed discussion.

TABLE IV
CONFORMATION OF ALDOPENTOFURANOSE DERIVATIVES

Series	Esters (present work)	Methyl *aldo*-pentofuranosides[a]
β-Arabinofuranose	T_2^1 (E_2)	E_2
β-Lyxofuranose	T_3^2 T_2^3	T_2^3
α-Xylofuranose	T_1^0 (T_3^2)	T_3^2
α-Ribofuranose	T_1^2 (E^2)	E^2
α-Arabinofuranose	T_1^0	T_3^2 T_2^3
α-Lyxofuranose	T_3^4 (E_3)	T_2^3 (E_3)
β-Xylofuranose	T_2^3 (E^3)	T_3^2 (E_3)
β-Ribofuranose	T_2^3	E^3

[a] See ref 30.

stants. In such cases, the alternative, not quite so favorable conformation, is included in parentheses.

For α-xylofuranose, the T_3^2 conformation is reasonably satisfactory but it requires a value for $J_{2,3}$ considerably greater than that observed; the T_1^0 conformation provides a good correlation of projected angles with observed coupling constants. In the case of α-ribofuranose, the T_1^2 conformation is somewhat better than the E^2 form as regards angle correlation and it provides a better arrangement for the ring oxygen and the anomeric oxygen (for the anomeric effect). As for α-xylofuranose, the T_1^0 conformation provides a satisfactory correlation of projected angles with coupling constants for α-arabinofuranose. This conformation is particularly favorable for the anomeric effect. The T_3^2 (or E_3) conformation proposed for the β-xylofuranose series as a result of studies of the methyl *aldo*-pentofuranosides[30] is not in agreement with the coupling observed with the β-xylofuranose esters (Table II). However, no one conformation provides a satisfactory explanation for the observed coupling constants in this case.

Finally, we wish to emphasize the fact that the present, decidedly imperfect state of our knowledge in this area requires that we regard these conformational assignments as having a highly speculative nature.

Experimental Section

Spectra were measured using an approximately 0.5 *M* concentration on a "hybrid" Varian HA60-A60 spectrometer. Melting points correspond to corrected values. Mallinckrodt silicic acid (100 mesh) was used for chromatography; chloroform for chromatography was rendered alcohol-free by passage through a column of silicic acid immediately prior to use.

Crude 1-*O*-Acetyl-2,3,5-tri-*O*-benzoyl-β-D-xylofuranose (24).—A solution of β-D-xylofuranose tetrabenzoate[32] (200 mg) in a solution of hydrogen bromide in glacial acetic acid (1 ml, 45%, w/v) was kept at room temperature for 1 hr and then concentrated *in vacuo*. Glacial acetic acid (3 ml) was added to the syrupy residue and the solution was concentrated *in vacuo*. Glacial acetic acid containing 2% of acetic anhydride (15 ml) and anhydrous silver acetate (800 mg) were added to the residue and the mixture was stirred at room temperature for 2 hr. The solid was removed by filtration, the solution was concentrated *in vacuo* and the residue, after dissolving in chloroform, was washed with aqueous sodium bicarbonate. After concentration, the chloroform solution was passed through a column of silicic acid to give crude, syrupy **24**, $[\alpha]^{20}D$ +43.7° (*c* 2.86, chloroform). The presence of a small amount of **11** was indicated by a peak at 2.04 ppm.

1,3,5-Tri-*O*-benzoyl-2-*O*-methylsulfonyl-α-D-xylofuranose (12).—β-D-Xylofuranose tetrabenzoate (5 g) was dissolved in dichloromethane (50 ml) and hydrogen bromide was bubbled into the solution for 15 min. The solution was stored at room temperature and then concentrated *in vacuo* and the residue, dissolved in acetone (20 ml), was treated with water (2 ml). The solution was stored at +5° for 70 min and then concentrated *in vacuo* until the acetone had been removed. Dichloromethane was added and the solution was washed with aqueous sodium bicarbonate solution, dried, and concentrated *in vacuo*. After being dissolved in chloroform, the product was chromatographed on silicic acid, using chloroform for elution to give a fraction (2.64 g) with an nmr spectrum (strong doublet of 4.5 Hz at 6.7 ppm) which showed it to be 1,3,5-tri-*O*-benzoyl-α-D-xylofuranose (**13**). Elution with acetone–chloroform (1:4, v/v) gave a second fraction (1.62 g) which showed a weak doublet at 6.7 ppm and a much stronger multiplet at 5.7 ppm; this fraction was mainly 2,3,5-tri-*O*-benzoyl-D-xylofuranose.

A portion (603 mg) of the first fraction was dissolved in dichloromethane (*ca.* 1.5 ml) and the solution added portion wise to an ice-cold and stirred mixture of dry pyridine (6 ml) and methanesulfonyl chloride (0.5 ml). The reaction mixture was left at room temperature for 1.5 hr and the excess of methanesulfonyl chloride was then decomposed through the addition of a little water. After dilution with dichloromethane, the solution was washed with dilute sulfuric acid and aqueous sodium bicarbonate solution; on concentration, it gave a yellow syrup (534 mg) which proved to be unstable in ethanol, its solution in this solvent darkening on standing. The crude product was chromatographed on silicic acid using chloroform for elution and a fraction obtained which crystallized from ethanol–ethyl acetate–pentane to yield 300 mg (43%): mp 106–108°; $[\alpha]^{20}D$ +135° (*c* 1.12, chloroform).

Anal. Calcd for $C_{27}H_{24}O_{10}S$ (540.52): C, 59.99; H, 4.48. Found: C, 60.12; H, 4.48.

1-(2,3,5-Tri-*O*-acetyl-α-D-ribofuranosyl)-5,6-dimethylbenzimidazole (α-Ribazole Triacetate).—A sample (204 mg) of α-ribazole[13] was acetylated with pyridine–acetic anhydride at room temperature overnight and the product was worked up in conventional fashion to yield a syrup which was chromatographed on silicic acid using chloroform for elution. The syrupy product (230 mg) was freed of solvent by heating *in vacuo*, $[\alpha]^{20}D$ +50.7° (*c* 2.06, chloroform).

1-(2,3,5-Tri-*O*-acetyl-β-D-ribofuranosyl)-5,6-dimethylbenzimidazole (β-Ribazole Triacetate).—β-Ribazole[13] (260 mg) was acetylated as described above and the product was chromatographed to give a syrup (336 mg), $[\alpha]^{20}D$ −41.4° (*c* 2.20, chloroform). Some of this was dissolved in a warm ethanolic solution of picric acid; on cooling the solution deposited a crystalline **picrate** which was recrystallized from ethanol–ethyl acetate: mp 173–175°; $[\alpha]^{20}D$ −13.2° (*c*, 2.21, chloroform).

Anal. Calcd for $C_{26}H_{27}N_5O_{14}$ (633.55): C, 49.29; H, 4.30; N, 11.06. Found: C, 49.01; H, 4.07; N, 11.09.

Registry No.—**12**, 16162-42-8; **13**, 16162-43-9; **21**, 16162-44-0; **24**, 16162-35-9.

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(32) See Table I, ref *f*.