gas had ceased. After filtration, the solution was concentrated *in vacuo* and the residue was crystallized from methanol: 0.2 g (91%), mp 198° dec, $[\alpha]^{20}D$ +35° (*c* 0.85 in 50% v/v aqueous dioxan, no mutarotation on standing overnight).

Anal. Calcd for $C_{25}H_{19}NO_7$ (325.33): C, 55.38; H, 5.87; N, 4.31. Found: C, 55.39; H, 5.90; N, 4.55.

The 3-*O*-benzoyl derivative was stored overnight with acetic anhydride in pyridine. Pyridine, etc., was removed by codistillation with toluene and the residue was shown to be essentially homogeneous by thin layer chromatography. The nmr spectrum of the product indicated that it was predominantly the α anomer: τ 3.7 (H_1, $J_{1,2}$ = 3.5 cps), 7.77, 7.88, 8.05, 8.15 (Ac).

Mass Spectra.—In an initial attempt to distinguish further between IV and V and to prove that V was a furanose[18] derivative, their mass spectra were obtained.

As expected, V showed a peak (although weak) at *m/e* 306 corresponding to M − ($CH_2OAcCHOAc$–). Such a peak was completely absent from IV and thus provided corroboration that V is indeed in the furanose form. Also, the mass spectra of V and of the anomeric mixture obtained by treatment of XI with mercuric benzoate were closely similar, thus substantiating the conclusion that this reaction had given an anomeric mixture of 1-*O*-benzoates and confirming that V was a 1-*O*-benzoate.

It has been previously observed[19] that the fragmentation pattern of acetylated aminosugars differs markedly from the fragmentation of acetylated sugars. In the compounds we have examined the presence of a benzoyl group further complicated the situation. With both IV and V, a peak at *m/e* 346 was obtained corresponding to M − C_6H_5CO. However with V a strong peak at *m/e* 304 was obtained corresponding to loss of C_6H_5CO (105) and CH_2=C=O (42) from the parent molecule. The corresponding peak in IV was negligibly small. Until more examples have been studied the reason for this difference must remain a matter of conjecture.

Acknowledgments.—We wish to express our thanks to Dr. Henry M. Fales of the National Heart Institute for mass spectra. We are indebted to the staff of the Section on Microanalytical Services and Instrumentation of this institute for elementary analyses.

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N-Acyl Derivatives of 2-Acylamino-2-deoxyhexoses. Nuclear Magnetic Resonance Spectra and Conformations

THOMAS D. INCH,[1] JACK R. PLIMMER,[2] AND HEWITT G. FLETCHER, JR.

National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, Public Health Service, U. S. Department of Health, Education, and Welfare, Bethesda, Maryland 20014

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The nmr spectra of some 1,3,4,6-tetra-*O*-acetyl-2-(*N*-acylacylamino)-2-deoxyhexoses and of some 2-acetamido-1,3,4,6-tetra-*O*-acetyl-2-deoxyhexoses of the D-glucose, D-galactose, and D-mannose series have been studied. In contrast to the spectra of the second class of compounds, those of the first class are readily analyzed. The coupling constants for representatives of the D-glucose and D-galactose series clearly show these compounds to exist in the normal chair conformation. In *N*-acylacylamino derivatives of the D-glucose series, the signal from the axial proton at C_1 occurs at lower field than the signal for the equatorial C_1 proton, a reversal of the normal situation which has not hitherto been observed at C_1. The conformational implications of the nmr spectra are discussed.

Since the pioneering experiments of Lemieux, *et al.*,[3] in 1958, nuclear magnetic resonance has become a widely used and nearly essential tool for the elucidation of structural and configurational problems in the carbohydrate field.[4] In only a few cases,[5,6] however, has it been possible to obtain the parameters thought necessary to describe unequivocally the precise conformation of a pyranose ring. Although nmr spectroscopy has provided an elegant means for the determination of the configuration of some of the more recently described aminosugars,[7] complete first-order analyses of the nmr spectra of the 2-amino-2-deoxyhexopyranoses (or, more usually, of 2-acetamido-1,3,4,6-tetra-*O*-acetyl-2-deoxyhexopyranoses) have not been reported. It is immediately apparent from the spectrum of 2-acetamido-1,3,4,6-tetra-*O*-acetyl-2-deoxy-β-D-glucopyranose (**5**, Figure 1) that the region of the spectrum from 4.95 to 5.44 ppm (H_3 and H_4) and the region from 3.7 to 4.5 ppm (H_2, H_5, H_6, and $H_{6'}$) cannot readily be analyzed although, of course, the coupling constant $J_{1,2}$ provides an indication of anomeric configuration.[8] Inch and Fletcher[8,9] have recently described 2-(*N*-acylacylamino)-2-deoxyhexopyranose derivatives which may readily be prepared through the *N*-acylation of substances such as **5** or its α anomer **6**. The nmr spectra of these derivatives proved to be much more informative. The present paper describes an analysis of the spectra of 2-(*N*-acylacylamino)-2-deoxyhexose derivatives of the D-glucose, D-galactose, and D-mannose series.

Experimental Section

Nmr Spectra.—Spectra were measured in deuteriochloroform using a Varian A-60 spectrometer at 60 Mc/sec, and the results quoted refer to these spectra unless otherwise stated. Chemical shifts are reported in parts per million from the internal tetramethylsilane standard. No true coupling constants have been calculated and the results, given in cycles per second (*e.g.*, $J_{1,2}$ = 4 cps), refer to measured line spacings. Spin–spin decoupling experiments[10] were performed using a Varian HA-100 internal proton stabilized spectrometer at 100 Mc/sec.

In order to identify (and eliminate) the NH signal from the 2-acetamido-1,3,4,6-tetra-*O*-acetyl-2-deoxyhexopyranoses, the deuteriochloroform solutions of these substances were overlayered with D_2O and left at room temperature (with occasional shaking)

(1) Fellow in the Visiting Program of the National Institutes of Health, 1964–1965.

(2) Visiting Scientist in the Visiting Program of the National Institutes of Health, 1964–1966.

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

(4) L. D. Hall, *Advan. Carbohydrate Chem.*, **19**, 51 (1964).

(5) L. D. Hall, L. Hough, K. A. McLauchlan, and K. Pachler, *Chem. Ind.* (London), 1465 (1962).

(6) R. J. Abraham, L. D. Hall, L. Hough, and K. A. McLauchlan, *J. Chem. Soc.*, 3699 (1962).

(7) *E.g.*, P. W. K. Woo, H. W. Dion, L. Durham, and H. S. Mosher, *Tetrahedron Letters*, 735 (1962).

(8) T. D. Inch and H. G. Fletcher, Jr., *J. Org. Chem.*, **31**, 1815 (1966).

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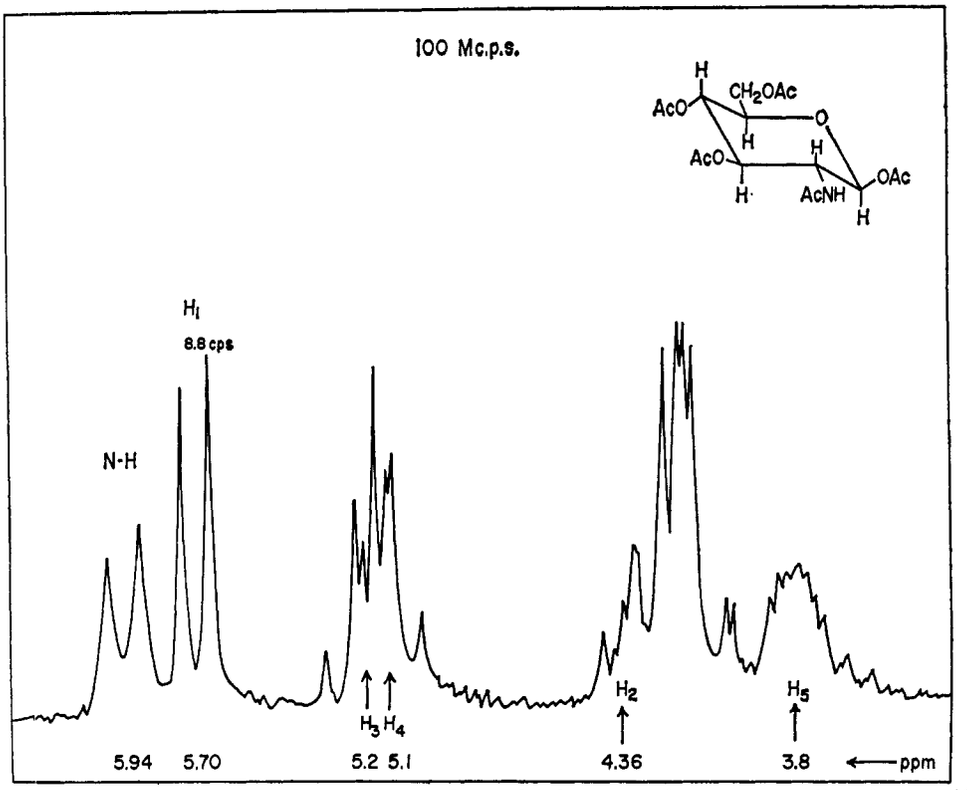

Figure 1.—Nmr spectrum of 2-acetamido-1,3,4,6-tetra-*O*-acetyl-2-deoxy-β-D-glucopyranose (5) in deuteriochloroform.

for 24 hr. Under these conditions, replacement of NH by ND was essentially complete, the spectrum showing no doublet for NH and the multiplet for H_2 collapsing to the expected quartet.

1,3,4,6-Tetra-*O*-acetyl-2-(*N*-acetylbenzamido)-2-deoxy-α-D-galactopyranose (8).—A solution of 2-acetamido-1,3,4,6-tetra-*O*-acetyl-2-deoxy-α-D-galactopyranose[11] (0.28 g) and benzoyl chloride (0.2 ml) in dry pyridine (5 ml) was stored overnight at room temperature and then was poured into ice–water. The product was extracted with dichloromethane, the combined extracts being washed successively with dilute hydrochloric acid, aqueous sodium bicarbonate, and water. Moisture was removed with magnesium sulfate, the solution was concentrated, and the residue was chromatographed on silica gel[12] using benzene–ether (1:1). The product (8) crystallized on removal of the solvent and was recrystallized from ether: 0.20 g (56%), mp 108–109° (cor), $[\alpha]^{20}D$ +29° (*c* 0.8, chloroform).

Anal. Calcd for $C_{23}H_{27}NO_{11}$ (493.47): C, 55.98; H, 5.52; N, 2.84. Found: C, 55.83; H, 5.62; N, 2.92.

1,3,4,6-Tetra-*O*-acetyl-2-(*N*-acetylbenzamido)-2-deoxy-α-D-mannopyranose (12).—2-Acetamido-2-deoxy-D-mannose (1 g) was added to a solution of zinc chloride (1.2 g) in acetic anhydride (18 ml) and the mixture stirred at 81° (bath temperature) for 9 min. It was then poured into ice–water and neutralized with sodium bicarbonate. The product was extracted with dichloromethane and the combined extracts were washed several times with water. Moisture was removed with magnesium sulfate and the solution was concentrated *in vacuo* to a syrup from which toluene was distilled *in vacuo* until residual acetic anhydride was removed (0.96 g). The nmr spectrum of the syrup showed a signal at 5.83 ppm which was assumed to arise from H_1 of **10**; a signal at 5.76 ppm was assigned to H_1 of **9**. The relative amplitudes of the two signals suggested that the ratio of **9**:**10** was 2:3. Thin layer chromatography in a variety of solvent systems failed to separate the two anomers. A portion (0.3 g) of this syrup was dissolved in a mixture of pyridine (3 ml) and benzoyl chloride (0.4 ml) and the solution was left overnight at room temperature. It was then poured into ice–water and the crude product was extracted with dichloromethane. After successive washings with 3 *N* hydrochloric acid, water, aqueous sodium bicarbonate, and water, the combined extracts were dried with magnesium sulfate and concentrated *in vacuo* to a syrup which was chromatographed on silica gel[12] using ether containing 1% of methanol. Elution afforded **12** (95 mg, 13%); after several later fractions containing both **11** and **12**, pure **11** was eluted (95 mg, 13%). Compound **12** was rechromatographed in the same fashion but efforts to obtain it in crystalline form were without success: $[\alpha]^{20}D$ −18.3° (*c* 0.83, chloroform).

Anal. Calcd for $C_{23}H_{27}NO_{11}$ (493.47): C, 55.98; H, 5.52; N, 2.84. Found: C, 55.92; H, 5.32; N, 2.79.

In view of the elementary composition of this substance and of its specific rotation as compared with that of **11**, it is designated as the α anomer **12**.

1,3,4,6-Tetra-*O*-acetyl-2-(*N*-acetylbenzamido)-2-deoxy-β-D-mannopyranose (11).—2-Acetamido-1,3,4,6-tetra-*O*-acetyl-2-deoxy-β-D-mannopyranose[13] (0.168 g) was dissolved in a mixture of pyridine (1.5 ml) and benzoyl chloride (0.2 ml) and the solution was kept at room temperature overnight. It was then poured into ice–water and the product was extracted with dichloromethane. The combined extracts were washed successively with 3 *N* hydrochloric acid, water, saturated aqueous sodium bicarbonate, and water, dried with magnesium sulfate, and concentrated *in vacuo*. The product was crystallized[14] and recrystallized from ether–cyclohexane: 0.105 g (49%), mp 120.4–121.4° (cor), $[\alpha]^{20}D$ −79.6° (*c* 0.854, chloroform).

Anal. Calcd for $C_{23}H_{27}NO_{11}$ (493.47): C, 55.98; H, 5.52; N, 2.84. Found: C, 56.12; H, 5.33; N, 2.81.

Discussion

The first compound examined was 1,3,4,6-tetra-*O*-acetyl-2-(*N*-acetylacetamido)-2-deoxy-β-D-glucopyranose (1) and, by way of an example, the nmr spectrum (Figure 2) and proton assignments (Table I), will be discussed in some detail.

The usual initial assumption was made[3] that the low-field doublet at 6.60 ppm, with a spacing of 8.3 cps, corresponded to H_1. Irradiation of H_1 caused a collapse of the H_2 quartet centered at 3.90 ppm to a doublet still superimposed on what was later shown to be H_5. Since it was impossible to irradiate H_2 without also

(11) M. Stacey, *J. Chem. Soc.*, 272 (1944).
(12) E. Merck, A.-G., Darmstadt, Germany, 0.05–0.20 mm.
(13) A. N. O'Neill, *Can. J. Chem.*, **37**, 1747 (1959).
(14) Seed crystals of **11** were initially obtained after chromatography of the crude product on silica gel using ether containing 1% of methanol.

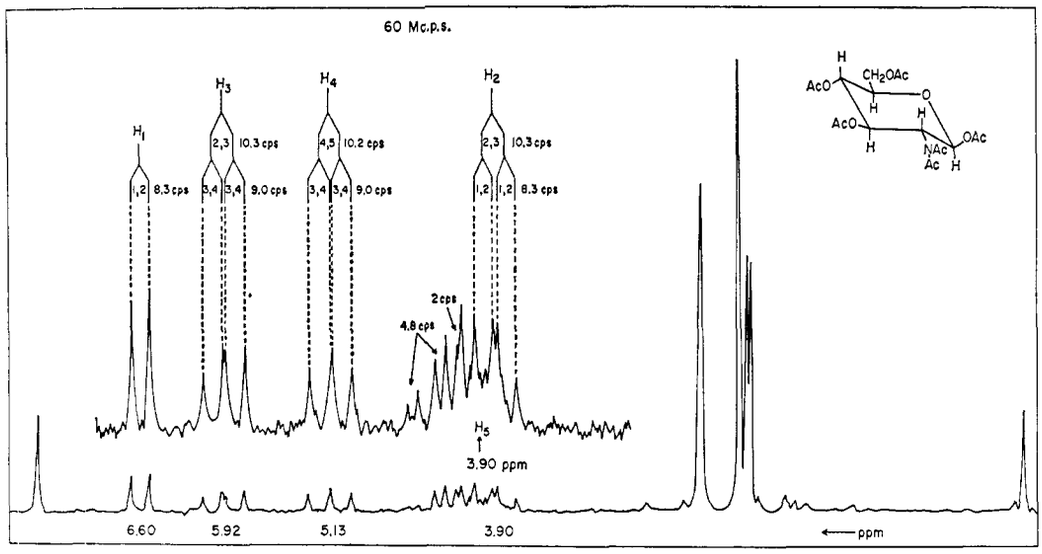

Figure 2.—Nmr spectrum of 1,3,4,6-tetra-*O*-acetyl-2-(*N*-acetylacetamido)-2-deoxy-β-D-glucopyranose (1) in deuteriochloroform.

TABLE I

ASSIGNMENTS IN THE NMR SPECTRA OF 2-AMINO-2-DEOXY-D-GLUCOPYRANOSE DERIVATIVES[a]

	Chemical shifts[b]					Coupling constants[c]					
Compd[d]	H_1	H_2	H_3	H_4	H_5	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$	$J_{5,6'}$
1	6.60	3.90	5.92	5.13	3.9	8.3	10.3	9.0	10.2	(4.7)	2.0
2	6.25	4.66	6.11	5.10	4.1	3.5	10.3	9.0	9.0	...	...
3	(6.55)	(4.23)	(5.91)	5.07	(3.9)	(8.5)	(10.0)	9.0	(10.0)	(4.5)	(1.9)
4	6.40	(5.12)	6.02	(5.10)	4.2	3.5	11.0	9.0	(9.0)	...	...
5	5.77	4.44	(~5.2)	(~5.1)	~3.9	8.8	...	...	...	...	...
6	6.20	(4.46)	(~5.2)	(~5.2)	4.0	3.5	...	...	...	...	...

[a] For details regarding these measurements see Experimental Section. The figures in parentheses were obtained using a Varian HA-100 spectrometer. [b] Chemical shifts in parts per million. [c] Coupling constants in cycles per second. [d] 1, 1,3,4,6-Tetra-*O*-acetyl-2-(*N*-acetylacetamido)-2-deoxy-β-D-glucopyranose; 2, 1,3,4,6-tetra-*O*-acetyl-2-(*N*-acetylacetamido)-2-deoxy-α-D-glucopyranose; 3, 1,3,4,6-tetra-*O*-acetyl-2-(*N*-acetylbenzamido)-2-deoxy-β-D-glucopyranose; 4, 1,3,4,6-tetra-*O*-acetyl-2-(*N*-acetylbenzamido)-2-deoxy-α-D-glucopyranose; 5, 2-acetamido-1,3,4,6-tetra-*O*-acetyl-2-deoxy-β-D-glucopyranose; 6, 2-acetamido-1,3,4,6-tetra-*O*-acetyl-2-deoxy-α-D-glucopyranose.

irradiating H_5, nothing was to be gained by irradiating H_2 in order to detect H_3. However, when the quartet at 5.92 ppm was irradiated, the H_2 quartet collapsed to a doublet as did also the quartet at 5.13 ppm. Thus H_3 was placed at 5.92 ppm and H_4 at 5.13 ppm. Irradiation of H_4 caused the signal from H_3 to collapse to the expected doublet and also caused a change in the spectrum around 3.90 ppm although the quartet previously assigned to H_2 was unaffected; thus H_5 was placed at 3.90 ppm. Recently Lemieux and Stevens,[15] in a thorough investigation of 1,2,3,4,6-penta-*O*-acetyl-β-D-glucopyranose, have shown that $J_{5,6}$ and $J_{5,6'}$ = 4.7 and 1.9 cps. By analogy, we have attributed signals at 4.53, 4.32, and 4.18 ppm, with spacings of 4.7, 4.7, and 2.0 cps, to H_6 and $H_{6'}$.

The spectra of compounds 2–6 were similarly examined with the results shown in Table I. No coupling constants could be determined for **5** and **6** but spin–spin decoupling experiments permitted approximate allocations of chemical shifts. The implications of these findings will now be considered.

Since chemical shift differences between adjacent protons are much larger than the corresponding coupling constants, virtual long-range coupling effects[16] should not be important. Further, the axial arrangement of H_2, H_3, H_4, and H_5 (and of H_1 in the β anomers) of glucose derivatives in the normal chair conformation makes long-range coupling effects unlikely since it has been suggested[17] that long-range coupling occurs only between equatorial protons. Thus, it is reasonable to assume that the measured line spacings of **1–4** as shown in Table I will closely approximate the true coupling constants. Various workers have attempted to substitute such constants into the Karplus equation[18] (or one of its subsequent modifications[6,19,20]) in order to determine precise molecular conformations. Since it has been shown that allowance must be made for substituent effects[21] and also that a separate parameter is required for the C_1–C_2 portion,[4] particularly where there is an axial C_2 substituent, the calculation of accurate projected valency angles will not be attempted. However, it can be assumed that the coupling constant between hydrogens on adjacent carbon atoms will be two or three times greater (8–12 cps) when their bond angle is *ca.* 180° (antiperiplanar) than when the angle is *ca.* 60° (*gauche*). In the latter case the coupling constant is *ca.* 3–3.5 cps although this may not necessarily be so for $J_{1,2}$. In both normal and alternate

(15) R. U. Lemieux and J. D. Stevens, *Can. J. Chem.*, **43**, 2059 (1965).
(16) J. I. Musher and E. J. Corey, *Tetrahedron*, **18**, 791 (1962).
(17) L. D. Hall and L. Hough, *Proc. Chem. Soc.*, 382 (1962).
(18) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959).
(19) F. A. L. Anet, *Can. J. Chem.*, **39**, 789 (1961); R. U. Lemieux, J. D. Stevens, and R. R. Fraser, *ibid.*, **40**, 1955 (1962).
(20) R. W. Lenz and J. P. Heeschen, *J. Polymer Sci.*, **51**, 247 (1961).
(21) P. Lazlo and P. von R. Schleyer, *J. Am. Chem. Soc.*, **85**, 2709 (1963); K. L. Williamson, *ibid.*, **85**, 516 (1963).

TABLE II

ASSIGNMENTS IN THE NMR SPECTRA OF 2-AMINO-2-DEOXY-D-GALACTOPYRANOSE AND -D-MANNOPYRANOSE DERIVATIVES[a]

	Chemical shifts[b]					Coupling constants[c]			
Compd[d]	H_1	H_2	H_3	H_4	H_5	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$
7	6.25	4.66	5.25	5.41	4.2	3.5	13	3.5	~3.5
8	6.41	5.33	5.88	5.62	~4.2	3.1	12.4	3.2	3.2
9	5.9	4.82	(5.1 →	5.2)	3.85	1.6	...	...	...
10	6.01	...	...	...	4.2	1.6	...	...	...
11	6.08	5.54	5.54	5.91	3.87	1.8	4.0	10.0	9.0
12	6.61	5.20	5.51	5.25	4.2	5.5	4.4	5.8	6.0

[a] For details regarding these measurement see Experimental Section. [b] Chemical shifts in parts per million. [c] Coupling constants in cycles per second. [d] **7**, 2-acetamido-1,3,4,6-tetra-*O*-acetyl-2-deoxy-α-D-galactopyranose; **8**, 1,3,4,6-tetra-*O*-acetyl-2-(*N*-acetylbenzamido)-2-deoxy-α-D-galactopyranose; **9**, 2-acetamido-1,3,4,6-tetra-*O*-acetyl-2-deoxy-β-D-mannopyranose; **10**, 2-acetamido-1,3,4,6-tetra-*O*-acetyl-2-deoxy-α-D-mannopyranose; **11**, 1,3,4,6-tetra-*O*-acetyl-2-(*N*-acetylbenzamido)-2-deoxy-β-D-mannopyranose; **12**, 1,3,4-6-tetra-*O*-acetyl-2-(*N*-acetylbenzamido)-2-deoxy-α-D-mannopyranose.

chair conformations[22] the theoretical projected valency angles between protons on adjacent carbons are either 60 or 120°. On this basis, inspection of Table I leaves no doubt that compounds **1**–**4** exist in the normal chair conformation. For the β anomers all the C–H dihedral angles are antiperiplanar and only in the α anomers is the expected *gauche* relationship encountered. While other data are lacking, the $J_{1,2}$ coupling constants for **5** and **6** provide no reason for supposing that these substances exist in any conformation other than the normal one.

Lemieux and Stevens[15] have recently demonstrated the utility of chemical shift data in elucidating conformations. For example, these authors have shown that, in the normal chair conformation, replacement of an axial proton at C_1 or C_3 by an acetoxy group causes an axial H_5 to be deshielded by *ca.* 0.25 ppm. All their results were related to 1,2,3,4,6-penta-*O*-acetyl-β-D-glucopyranose which was used as a reference standard and had H_5 at 3.9 ppm. It was suggested that such chemical shifts could be used to distinguish between α and β anomers. In Table I it will be seen that compounds **1**, **3**, and **5** have H_5 at 3.9 ppm, whereas **2**, **4**, and **6** have H_5 at 4.1, 4.2, and 4.0 ppm, respectively, and it is, therefore, apparent that Lemieux and Stevens' suggestion for determining anomeric configurations applies equally well to these aminosugar derivatives.

Since H_4 is remote from C_1 and C_2 its chemical shift would not be expected to be greatly influenced by changes in anomeric configuration or by changes in the nitrogen-attached substituents at C_2; this appears to be true. *N*-acylation of the 2-acylamino function causes the most significant changes in chemical shift at H_1 and H_3. Both *N*-benzoylation and *N*-acetylation of **5** caused H_1 to be markedly deshielded (by 0.78 and 0.83 ppm, respectively). While *N*-acylation of **6** produced only a small deshielding of H_1 (by 0.2 and 0.05 ppm), H_3 is substantially deshielded in **1** and **4** (by 0.7–0.8 ppm). It will be noticed that the H_3 proton in the α anomers (**2** and **4**) is at lower field than the H_3 proton in the β anomers (**1** and **3**); the additional deshielding probably arises from the axial acetoxy group. The deshielding influence of an equatorial diacylamino group appears to be much greater where the adjacent proton is axial than when the adjacent proton is equatorial. Thus the net effect of an equatorial diacylamino group at C_2 is to cause the H_1 axial proton (in the β anomer) to be shifted to a lower field than the H_1 equatorial proton (in the α anomer). This phenomenon may be used to distinguish between anomers but contrasts markedly from the normal situation where an axial H_1 proton appears at higher field than an equatorial H_1 proton. In discussing protons other than H_1, Lemieux and Stevens[15] have pointed out that the earlier generalization[3] that equatorial protons appear at lower field than axial protons is subject to modification if certain deshielding influences are present.

It is evident that the deshielding effect caused by a diacylamino group is associated with the carbonyl group and not with the aromatic ring since the effects caused by *N*-acylation and *N*-benzoylation of the acetamido group are of the same magnitude. Jackman[23] has discussed possible reasons why the presence of a neighboring carbonyl group causes a large downfield shift. One possibility is that the anisotropy of the carbonyl group may cause low-field shifts if the proton is in the plane of the carbonyl group rather than perpendicular to it. Again, it is possible that the diamagnetic circulations associated with the proton would tend to be inhibited by the presence of a strong electric field. Finally, the possibility of a deshielding effect resulting from withdrawal of the proton away from the bonding electrons cannot be neglected.

The introduction of a second *N*-acyl group also produces changes in the chemical shift of H_2 but more examples need to be studied before this phenomenon can be rationalized.

It is apparent that the changes in chemical shift produced by *N*-acylation of the acylamino group are dependent upon and indicative of molecular conformation although the possibility of conformational change accompanying such a substitution cannot be ignored. This information, used in conjunction with the coupling constants, seemed to afford an excellent approach to the problem of the conformation of aminosugar derivatives. To test the validity of this approach, the investigation was extended to appropriate derivatives of the D-galactopyranose series. Nmr spectra were obtained from 2-acetamido-1,3,4,6-tetra-*O*-acetyl-2-deoxy-α-D-galactopyranose (**7**) and from its *N*-benzoyl derivative (**8**); the data derived therefrom are given in Table II and it will be seen that the spectrum of **7**, alone among the 2-acetamido-1,3,4,6-tetra-*O*-acetyl-

(22) The terms "normal" and "alternate" will be used here to describe the two possible chair conformations; *cf.* E. L. Eliel, N. L. Allinger, S. J. Angyal, and F. A. Morrison, "Conformational Analysis," Interscience Publishers, Inc., New York, N. Y., 1965, p 364. These correspond to the C1 and 1C forms suggested by R. E. Reeves [*Advan. Carbohydrate Chem.*, **6**, 107 (1951)].

(23) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press Inc., New York, N. Y., 1959, p 122.

2-deoxyhexopyranoses examined, was amenable to complete analysis. From the coupling constants it is evident that both **7** and **8** exist in the normal chair form and that no major conformational change is brought about by the introduction of the second acyl group. The small changes in coupling constants which do occur (Table II) may truly represent minor changes in ring shape or they may result from substituent effects; in any event, they do not affect the validity of the procedure. It is seen that H_5 is at 4.2 ppm as expected when the C_1 acetoxy group is also axial and that H_4 is slightly deshielded by substitution. As in the D-glucopyranose series, H_3 is markedly deshielded by the diacylamino group (0.63 ppm) and H_1 only slightly deshielded (0.16 ppm). Thus the data from these D-galactopyranose derivatives is consonant with those found in the D-glucopyranose series.

The conformations of α- and β-D-mannopyranose derivatives have been the subject of much discussion since their nmr spectra show abnormally small $H_{1,2}$ coupling constants. Lenz and Heeschen[20] have suggested that β-D-mannose has a half-chair conformation. Lemieux and Stevens[15] have postulated a normal chair conformation (or, at least, one closely similar thereto) for both of the anomeric D-mannopyranose pentaacetates but did not comment on the small $J_{1,2}$ values. In addition, Hall and co-workers[5] have shown that D-lyxopyranose derivatives exist in the alternate chair form. It was, therefore, of interest to examine the two anomeric 2-acetamido-1,3,4,6-tetra-*O*-acetyl-2-deoxy-D-mannopyranoses and their *N*-benzoyl derivatives to ascertain whether these substances would yield additional information bearing on their conformation. Data from the nmr spectra of the four substances (**9**–**12**) are given in Table II and it may be noted that, as in the D-glucopyranose series discussed earlier, the spectra of the *N*-acylacylamino derivatives (**11** and **12**) were readily amenable to analysis while those of the *N*-acylamino derivatives (**9** and **10**) afforded less information.

In the case of **11**, the $J_{3,4}$ and $J_{4,5}$ values are consonant with the *trans*-diaxial relationships of the normal conformation while $J_{2,3}$ suggests a slight contraction from a 60° dihedral angle. The $J_{1,2}$ value, small as is characteristic of the D-mannopyranose series,[24] might be interpreted as suggesting an increase in the dihedral angle over that indicated in the D-glucose and D-galactose series. If reliance is put on the $J_{1,2}$ and $J_{2,3}$ values, it becomes evident that the coupling constants of **11** are consistent with those to be expected from a flexible ring close to the $S_{1,5}E$ conformation depicted by Isbell and Tipson.[25] However, *N*-benzoylation of **9** (to form **11**) causes H_4 to be deshielded by *ca.* 0.7 ppm; the $S_{1,5}E$ conformation appears to offer no explanation for this but the normal conformation, with H_4 and the *N*-acetylbenzamido group in an axial-axial arrangement would be expected to show such a shift. In view, then, of the uncertainties involved in interpreting $J_{1,2}$ values of aldopyranoses, the balance of evidence here indicates that **11** most probably exists in a form close to the normal one.

The observed coupling constants of **12** stand in marked contrast to those of **11** and, indeed, to all other structures discussed here. They could be construed as indicating that **12** exists as an approximately 1:1 equilibrium mixture of the normal and alternate chair conformations. However, two arguments appear to oppose such an interpretation. First, it is likely that the alternate chair conformation will be energetically less favorable than the normal chair form owing to the strong diaxial interaction between the C_4- and C_6-acetoxy groups which would be involved. Hence, any chair equilibrium would be expected to favor the normal form. Second, it would be expected that, in the normal chair form, the H_4 chemical shift would be close to 5.9 ppm while, in the alternate chair form, the equatorial H_4 would certainly not be higher than 5.2 ppm and so the predicted average chemical shift would be much nearer to 5.5 ppm than observed (5.25 ppm). On balance, then, the existing evidence appears to favor a flexible form for **12** over an equilibrium mixture of chair forms.

Unfortunately **10** was not obtained in pure form; from the limited nmr data available there is no basis for suggesting that this substance exists in other than the normal chair form. It is, of course, possible that conversion of **10** to **12** may involve a conformational change.

The generalization[3] that the methyl protons of axial acetoxy groups appear at lower field than the methyl protons of equatorial acetoxy groups has been much used as an aid to configurational assignment. The acetoxy chemical shifts for compounds **1**–**9** and **11**–**12** are shown in Table III. At present these figures do little more than emphasize previous warnings that such a generalization, although applicable to esters of the simple sugars, must be treated with utmost caution when substituent groups other than acetoxy are present. If, however, it becomes possible to allocate each acetoxy signal to a specific group (*e.g.*, through deuteration studies) then it is likely that the chemical shifts of these groups will provide valuable conformational information.

TABLE III

CHEMICAL SHIFTS OF ACETOXY GROUPS

Compd	Chemical shift, ppm[a]
1	2.02, 2.03, 2.10 (d) 2.33 (d) (NAc_2)
2	1.96, 2.03, 2.10, 2.13 2.33 (d) (NAc_2)
3	1.96, 2.03 (d), 2.10 (d)
4	1.78, 1.83, 1.88, 2.03, 2.11
5	1.95, 2.07 (d), 2.10, 2.13
6	1.95, 2.06 (d), 2.09, 2.20
7	1.95, 2.03 (d), 2.19 (d)
8	1.71, 1.81, 1.87, 2.03, 2.17
9	2.03, 2.08, 2.12
11	1.88, 1.97 (d), 2.05, 2.08
12	1.87, 1.97, 2.03 (d), 2.1

[a] d = doublet.

(24) Numerous structures of unquestioned conformation give apparently abnormal coupling constants when electronegative groups are present. D. H. Williams and N. S. Bhacca [*J. Am. Chem. Soc.*, **86**, 2742 (1964)] noted that the J_{ea} value obtained with an axial acetoxy compound was abnormally low (2.5–3.2 cps). If the N-acylacylamino group in **11** is regarded as an analogous substituent, the very low value of $J_{1,2}$ = 1.8 may be regarded as normal. However, Williams and Bhacca also found that J_{ae} is abnormally high when an acetoxy group is equatorial. Pursuing this analogy with the compounds under discussion here, one would predict relatively large $J_{1,2}$ values for **2** and **4**. As seen in Table I, the value observed was 3.5 cps in both cases.

(25) H. S. Isbell and R. S. Tipson, *J. Res. Natl. Bur. Std.*, **A64**, 171 (1960).

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C-2 Oxyanion Participation in the Base-Catalyzed Cleavage of *p*-Nitrophenyl β-D-Galactopyranoside and *p*-Nitrophenyl α-D-Mannopyranoside[1]

ROBERT C. GASMAN[1] AND DONALD C. JOHNSON[2]

The Institute of Paper Chemistry, Appleton, Wisconsin 54911

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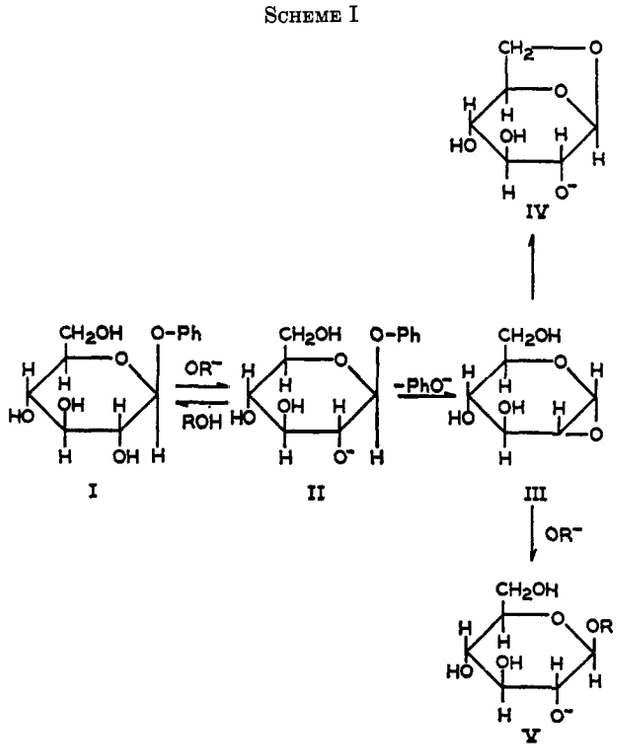
p-Nitrophenyl 2-*O*-methyl-β-D-galactopyranoside and *p*-nitrophenyl 2-*O*-methyl-α-D-mannopyranoside were synthesized and their cleavage reactions were compared with those of *p*-nitrophenyl β-D-galactopyranoside and *p*-nitrophenyl α-D-mannopyranoside. The cleavage rates (35–55°) and products formed from these glycosides (all capable of a *trans*-diaxial orientation at C-1 and C-2) in methanolic and aqueous base solution were studied. Reaction of the glycosides in methanolic sodium methoxide resulted in over-all retention of configuration, whereas the 2-*O*-methylglycosides gave substantial amounts of *p*-nitroanisole and its reduction products (formed by secondary reaction with 2-*O*-methyl sugar). Kinetic studies included the effect of base concentration, the hydrogen isotope effect, ionic strength effects, and the effect of hydrogen peroxide. Blocking of the C-2 oxygen by a methyl group caused an enormous decrease in the rate of cleavage and a change in reaction pathway in both cases. The *p*-nitrophenyl glycosides react by neighboring-group participation of the C-2 oxyanion, whereas the 2-*O*-methylglycoside reactions proceed, at least in methanolic sodium methoxide, by bimolecular nucleophilic aromatic substitution.

Previous studies of the reaction of *para*-substituted phenyl D-glucosides[3] in basic solution (Scheme I) have shown that the β anomer reacts by a process which involves neighboring C-2 oxyanion participation.[4] A stereochemical requirement for operation of this process, axial disposition of the C-2 anion and the C-1 phenoxyl, may be fulfilled in the β-D-glucoside structure but not in the α. The structures of phenyl β-D-galactosides and phenyl α-D-mannosides also meet this stereochemical requirement. However, the information available concerning the β-galactosides is too limited to show whether or not the neighboring C-2 oxyanion process is important for their reactions as well.[4] No investigations specifically concerned with the role of the C-2 oxyanion in the reaction of phenyl α-D-mannosides have been reported.

SCHEME I



Previous investigators,[4,5] in considering reactions of *para*-substituted phenyl β-D-glucosides, have noted what appeared to be a trend toward an ionic mechanism as the electron-withdrawing character of the substituent increased. The basis for this observation was the downward trend in yield of 1,6-anhydro-β-D-glucopyranose toward 50% (*i.e.*, suggesting the anomeric carbon could be attacked equally well from either side of the ring as the electron-withdrawing character of the *para* substituent increased).

The primary purpose of this study, therefore, was to ascertain whether or not the neighboring-group process found to be important in the phenyl β-D-glucoside reactions extended to the reaction of other phenyl glycosides. A subordinate objective, however, was to determine whether or not incursion of an ionic mechanism was significant when the strong electron-withdrawing *p*-nitrophenyl group was the aglycon. To accomplish these purposes the rates and products formed in the reactions of the *p*-nitrophenyl glycosides and *p*-nitrophenyl 2-*O*-methylglycosides of β-galactose and α-mannose in methanolic and aqueous base solution were studied.

Results

Product Analysis.—Initial compositions of reaction mixture solutions, time, temperature of reaction, and

(1) A portion of a thesis submitted by R. C. Gasman in partial fulfillment of the requirements of The Institute of Paper Chemistry for the degree of Doctor of Philosophy from Lawrence University, Appleton, Wis., Jan 1966.

(2) To whom inquiries should be addressed.

(3) All glycosides referred to herein are glycopyranosides.

(4) C. E. Ballou, *Advan. Carbohydrate Chem.*, **9**, 59 (1954).

(5) C. M. McCloskey and G. H. Coleman, *J. Org. Chem.*, **10**, 184 (1945).