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STUDIES OF SYNTHESIS AND CONFORMATION IN THE D-RIBOPYRANOSE SERIES

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Abstract—Reactions of tribenzoyl α- and β-D-ribopyranosyl bromides with mercuric cyanide yielded 2,3,4-tri-O-benzoyl-β-D-ribopyranosyl cyanide. Its structure and configuration were proved by reduction with LAH to 6-amino-1,5-anhydro-6-deoxy-L-allitol, deamination of which gave 1,5-anhydro-L-allitol. The latter was identified by comparison with its D-enantiomer prepared from D-allose. The ring conformations of twelve 2,3,4-tribenzoyl-D-ribopyranose derivatives, and of two related acetyl compounds have been determined by PMR spectroscopy at 60 or 100 Mc/s. The operation, or non-operation of the anomeric effect appears to be the principal factor determining which particular chair conformation (Cl or 1C) predominates. The chemical shift and coupling constant differences in these derivatives and in their conformations are discussed. The anomeric proton in tribenzoyl β-D-ribopyranosyl iodide is unusually deshielded.

REACTIONS of *cis*-α-acetoxy glycopyranosyl halides with silver and mercuric cyanides have been found to yield at least one or both of two types of nitrogen containing product. Thus when 2,3,4,6-tetra-O-acetyl-α-D-galactopyranosyl[1-3] and 2,3,4-tri-O-acetyl-α-D-xylopyranosyl[4] bromides were treated with mercuric cyanide in nitromethane, high yields of the corresponding β-D-glycopyranosyl 1-cyanides were obtained.

The structure and anomeric configuration of the β-D-galactopyranosyl cyanide tetra-acetate were proved conclusively by chemical,[2] and PMR spectroscopic[3] methods. In contrast, reaction of the closely related 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide with mercuric cyanide under the same conditions afforded only a low yield (12%) of the β-1-cyanide, but significantly, an equal quantity of isomeric 3,4,6-tri-O-acetyl-1,2-O-(1-cyanoethylidene)-α-D-glucopyranose was isolated,[5] a product which could be obtained in appreciably greater yield by reaction of the bromide with silver cyanide in xylene, or with mercuric cyanide in hydrogen cyanide. The proton coupling constants in the pyranose ring of this bicyclic molecule were interpreted in favour of a twist boat conformation.[6]

Since the factors governing the formation and yields of these cyano derivatives are not yet clear, and because of their importance in relation to Koenigs-Knorr syntheses utilizing mercuric cyanide as catalyst, it was of interest to study the reaction of this cyanide with a *trans*-2-acyloxy-1-halide. Such halides are readily available in

[1] N. Constantzas and J. Kocourek, *Chem. Listy* **52**, 1629 (1958); *Coll. Czech. Chem. Comm.* **24**, 1099 (1959); J. Kocourek, *Chem. Ber.* **94**, 3346 (1961); B. Helferich and K. L. Bettin, *Ibid.* **94**, 1159 (1961).

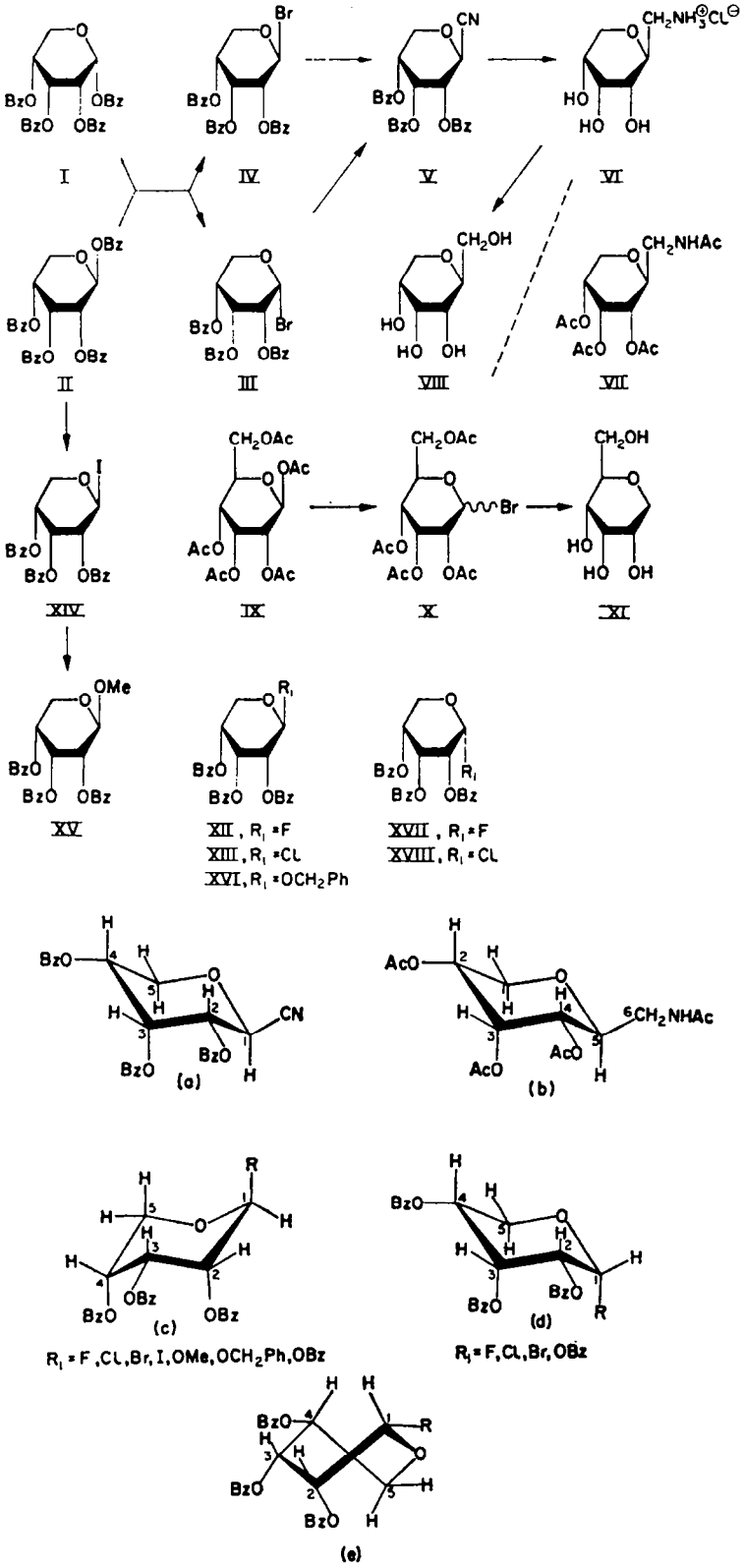
[2] B. Coxon and H. G. Fletcher, Jr., *J. Amer. Chem. Soc.* **86**, 922 (1964).

[3] B. Coxon and H. G. Fletcher, Jr., *Chem. & Ind.* 662 (1964).

[4] B. Helferich and W. Ost, *Chem. Ber.* **95**, 2612 (1962).

[5] B. Coxon and H. G. Fletcher, Jr., *J. Amer. Chem. Soc.* **85**, 2637 (1963).

[6] B. Coxon and L. D. Hall, *Tetrahedron* **20**, 1685 (1964). See however, R. U. Lemieux and A. R. Morgan, *Canad. J. Chem.* **43**, 2199 (1965).


I
II
III
IV
V
VI
VII
VIII
IX
X
XI
XII, R1 = F
XIII, R1 = Cl
XIV
XV
XVI, R1 = OCH2Ph
XVII, R1 = F
XVIII, R1 = Cl
(a)
(b)
(c)
(d)
(e)
R1 = F, Cl, Br, I, OMe, OCH2Ph, OBz
R1 = F, Cl, Br, OBz

the D-ribopyranose series as the thermodynamically preferred β-anomers, and since the benzoate esters are particularly stable, and convenient to handle, 2,3,4-tri-O-benzoyl-β-D-ribopyranosyl bromide (IV)[7] was chosen, therefore, as a suitable substrate. The ring conformations of the 2,3,4-tri-O-benzoyl-D-ribopyranosyl halides are of some importance to the discussion of their nucleophilic substitution and elimination reactions. An investigation of these conformations and of those of some related compounds has been made therefore, by the method of PMR spectroscopy, with particular reference to the factors influencing conformational preference.

EXPERIMENTAL

Paper chromatography was carried out by the descending method in either butan-1-ol–pyridine–water, 10:3:3 v/v (solvent A), or in EtOAc–AcOH–water, 9:2:2: v/v (solvent B). TLC was performed on either 20 cm glass plates, or microscope slides, coated in each case with Kieselgel G (E. Merck A.G., Darmstadt). The separated compounds were detected with dilute H_2SO_4 in the usual manner. M.ps were determined on a Kofler micro-heating stage and IR spectra on Unicam S.P. 100 and 200 spectrometers. Selected absorption maxima (cm^{-1}, in nujol unless stated otherwise) are listed as either strong (s), medium (m), or weak (w) intensity, with probable assignments.

The PMR spectra were taken from solutions of 160–300 mg of compound in 0·35–0·5 ml of solvent, except that occasionally poor solubility necessitated the use of saturated solutions. Field-swept spectra were measured on a Varian A-60 spectrometer at 60 Mc/s using tetramethylsilane (TMS) as internal reference, and 2% v/v benzene in CCl_4 as a calibration standard.[8] Spectra at 100 Mc/s were obtained from Varian HA-100 instruments internally locked on TMS in the frequency-sweep mode of operation, except that spectrum integrals were measured in the field sweep mode. The sweep calibration was checked with a Venner 333-6 frequency counter, and frequency swept double resonance experiments were carried out by the addition of a Muirhead-Wigan Decade oscillator. The line positions used to derive coupling constants were measured at a sweep width of 250 c/s.

With the aid of the Varian C-1024 time averaging computer the partial 100 Mc/s spectrum of I was obtained by subtraction of the spectrum of its pure β-anomer (II)[7] from that of the mixture of I and II prepared by benzoylation of D-ribose.[7] The spectrum of the anomeric mixture was divided into two sections, which were then subjected to separate subtraction processes. One section consisted of the mixed signals of H_2, H_3 and H_4 in the 2 anomers, and the other, of those from H_{5e} and H_{5a}. The two sections were allotted 1,024 computer channels each, and sweep widths of 250 and 100 c/s respectively. 1–5 spectral scans of the mixture were accumulated in the memory core of the computer, and a normal spectrum was also recorded. A similar spectrum of the β-anomer was then recorded, a suitable resonance was chosen, and by adjustment of the spectrometer sweep offset and gain controls, the position and amplitude of this resonance were matched with those of the corresponding resonance in the spectrum of the mixture. The computer was then switched to "subtract" and the same number of spectral scans (1–5) of the β-anomer were accumulated. Due to variable computer readout time, the time-averaged subtraction spectra were calibrated by comparison of the spacing of two widely separated lines with that in a normally recorded spectrum.

ABX analyses were carried out by the methods of Bernstein *et al.*[9] Line positions recalculated from the theoretical transition energies usually agreed with the experimental positions within 0·2 c/s.

2,3,4-*tri*-O-*benzoyl*-β-D-*ribopyranosyl cyanide* (V)

(a) *From* 2,3,4-*tri*-O-*benzoyl*-β-D-*ribopyranosyl bromide* (IV).[7] A suspension of the β-bromide (4·05 g), and dry $Hg(CN)_2$(2g, 1 mole equiv) in CH_3NO_2 (40 ml, dried over $CaSO_4$) was stirred at room temp for 5 min, when a cupric acetate–benzidine test indicated that HCN was being evolved. After further stirring for 0·5 hr the mixture was almost homogeneous, but during the succeeding 20 hr a colourless powder precipitated. The suspension was then poured into a mixture of 1N KBr solution

[7] R. Jeanloz, H. G. Fletcher, Jr. and C. S. Hudson, *J. Amer. Chem. Soc.* **70**, 4052 (1948); H. G. Fletcher, Jr., and R. K. Ness, *Ibid.* **77**, 5337 (1955).

[8] Technical bulletin from Varian A. G., Zürich, Switzerland.

[9] [a] H. J. Bernstein, J. A. Pople and W. G. Schneider, *Canad. J. Chem.* **35**, 65 (1957);
[b] *High Resolution Nuclear Magnetic Resonance* p. 132. McGraw-Hill, New York (1959).

(200 ml), ice-water (200 ml), and MeOH (50 ml). A pale yellow syrup separated, and was extracted with CH_2Cl_2 (2 × 100 ml) whence the combined extracts were washed with 1N KBr (150 ml), water and dried ($MgSO_4$). Concentration yielded a pale yellow syrup which crystallized on evaporation with EtOH. Crystallization from hot EtOH containing a little CH_2Cl_2 gave colourless rosettes 2·58 g (71%), m.p. 156–166° (with preliminary softening). TLC in 20:1 v/v benzene–ether indicated the presence of a trace of a slower moving impurity which was not removed by recrystallization from MeOH containing a little $CHCl_3$. The impure material (1·8 g) was therefore dissolved in benzene (10 ml), and was chromatographed on a squat column of silicic acid (20 g, 100 mesh). Elution with benzene (700 ml) yielded 1·55 g of material which on recrystallization from acetone–hexane gave pure V as colourless rods, 1·41 g, m.p. 170–171°, unchanged by a further recrystallization from EtOAc–hexane. $[\alpha]_D^{26}$ −76·4° (c, 1·15 in $CHCl_3$). (Found: C, 68·9; H, 4·5; N, 2·9; C_6H_5CO, 66·9. $C_{27}H_{21}NO_7$ requires: C, 68·8; H, 4·5; N, 3·0; C_6H_5CO, 66·9%.) IR data, ν_{max} 1730 s (C=O), 1604 m, 1590 m, and 1495 m (C_6H_6). No absorption was observed in the 2000–2300 cm^{-1} region.[10] Another preparation in which ten times the quantities of reactants and half the volume of solvent were used, gave in two crops a total yield of 85% of crude cyanide. This material was suitable for use in subsequent preparations without further purification.

(b) *From* 2,3,4-*tri*-O-*benzoyl*-α-D-*ribopyranosyl bromide* (III).[11] The α-bromide was treated with $Hg(CN)_2$ in CH_3NO_2 as for the β-bromide. HCN was detected in the vapour above the suspension after the latter had been stirred at room temp for 23 hr. The mixture was then diluted with CH_2Cl_2, washed with 1N KBr solution and water, dried ($MgSO_4$), and concentrated to a syrup, which on crystallization from di-ethyl ether–di-isopropyl ether yielded 20% of product m.p. 162–165°. Recrystallization from CH_2Cl_2–di-isopropyl ether, and then from EtOH–di-isopropyl ether afforded 2,3,4-tri-O-benzoyl-β-D-ribopyranosyl cyanide as colourless rods, m.p. 170°, undepressed on admixture with that prepared from the β-bromide, and showing $[\alpha]_D^{26}$ −74·9° (c, 0·64 in $CHCl_3$). The IR spectra of the two products were identical. NMR spectroscopy indicated that the mother liquors of preparation (b) consisted of mainly 2,3,4-tri-O-benzoyl-β-D-ribopyranosyl cyanide, however, crystallization of a second crop (32%) from ethanolic solution yielded only rather impure material, m.p. 150–160°.

*6-Amino-1,5-anhydro-6-deoxy-*L*-allitol hydrochloride* (VI). A solution of 2,3,4-tri-O-benzoyl-β-D-ribopyranosyl cyanide (10 g) in dry tetrahydrofurane (100 ml) was added dropwise at a rapid rate to a stirred suspension of LAH (4·45 g) in tetrahydrofurane (50 ml). After 0·75 hr, the stirred mixture was boiled under reflux for a further 0·25 hr, and excess of hydride was then destroyed by the cautious addition of EtOH, followed by water, and concentrated NH_4OH (60 ml, *d*, 0·88). Filter-cel which had previously been washed with water and 5N NH_4OH was stirred into the mixture, which was then filtered through a thin layer of Filter-cel, and the filtered solids washed with 5N NH_4OH (500 ml). The filtrate was concentrated to a vol. of ca. 60 ml, and was passed through a column (2·5 × 30 cm) of Amberlite IR-120(H) resin which was then eluted with water (1 l), followed by 0·5N NH_4OH. The eluate (2 l) was collected after it had become alkaline and was then evaporated to a syrup interspersed with white particles. This was dried by several distillations with absolute EtOH, and was then extracted with boiling EtOH (6 × 150 ml). The filtered extracts were concentrated to a pale yellow syrup (2·38 g) which crystallized partially during drying at 60°, but which could not be induced to crystallize satisfactorily from a solvent. The amino derivative was, therefore, characterized as its hydrochloride. A solution of the syrup in 1N HCl (18 ml) was thrice evaporated with absolute EtOH (50 ml), and the resulting syrup dried over KOH at 35–40°. Crystallization from aqueous acetone yielded colourless needles, 2·73 g (65%), m.p. 63–66°. After 3 recrystallizations from aqueous acetone, the air dried 6-amino-1,5-anhydro-6-deoxy-L-allitol hydrochloride (2·17 g) had m.p. 67–69°, decreased to 60–62° on drying under vacuum for 2 days at 35°. This latter material showed $[\alpha]_D^{25}$ −23° (c, 1·5 in water), and elemental analysis indicated that it was still slightly hydrated. The analytical sample was, therefore, redried at 75°. (Found: C, 36·0; H, 7·0; N, 6·8; Cl, 17·8. $C_6H_{14}ClNO_4$ requires: C, 36·1; H, 7·1; N, 7·0; Cl, 17·8%.) IR data: ν_{max} 3475–3325 s (OH), 3150 s (broad band), 1633 m, and 1510 m (NH_3^+), 2775 m–2460 w (diffuse absorption of amine salt). The product showed a single spot on paper chromatograms (solvent A) when detected with ninhydrin, and with $NaIO_4$–$AgNO_3$ sprays.

*6-Acetamido-2,3,4-tri-*O*-acetyl-1,5-anhydro-6-deoxy-*L*-allitol* (VII). Conventional acetylation of

[10] *cf.* L. J. Bellamy, *The Infra-red Spectra of Complex Molecules* p. 225. Methuen, London (1956).
[11] R. K. Ness, H. G. Fletcher, Jr., and C. S. Hudson, *J. Amer. Chem. Soc.* 73, 959 (1951).

VI in Ac_2O–pyridine at room temp yielded 6-acetamido-2,3,4-tri-O-acetyl-1,5-anhydro-6-deoxy-L-allitol as an almost colourless syrup, $[\alpha]_D^{27}$ −18·4° (*c*, 1·25 in $CHCl_3$), which was homogeneous according to TLC in EtOAc, acetone, and in 1:1 v/v mixtures thereof. (Found: C, 50·8; H, 6·45; N, 4·3. $C_{14}H_{21}NO_8$ requires: C, 50·8; H, 6·4; N, 4·2%.) IR data (in $CHCl_3$): ν_{max} 3440 m and 1532 s (NH), 1746 s (OAc), 1671 s (NAc).

Deamination of 6-amino-1,5-anhydro-6-deoxy -L-*allitol hydrochloride* (VI). To a solution of the amine hydrochloride (1·07 g) in ice-cold 10% v/v AcOHaq (30 ml) was added $NaNO_2$ (1 g). The mixture was kept at 0° for 2 hr, then at room temp for 3 hr, and was then deionized by stirring with a mixture of Amberlite IR-120(H) and IR-45(OH) resins. After filtration, the solution was concentrated to a syrup which was freed of AcOH by distilling off toluene. The syrup (0·73 g) crystallized partially during drying over $CaCl_2$–NaOH at 40°, and was found to reduce hot Fehling solution. Paper chromatography of the syrup in solvent B ($NaIO_4$–$AgNO_3$ sprays) indicated the presence of two major components with $R_{GLUCOSE}$(R_G) 1·9 and 2·8, and two minor components R_G 3·5 and 3·8. The component with R_G 2·8 also gave yellow–brown colourations with *p*-anisidine hydrochloride, and orcinol–hydrochloric acid sprays. A mixture of the syrup (0·7 g), 2,5-dichlorophenylhydrazine (0·7 g) and MeOH (20 ml) was then boiled to near dryness on the steam-bath. The addition of MeOH (20 ml) to the semi-crystalline residue, and the boiling process were repeated thrice (total heating time 0·75 hr), and the pale brown solid was then extracted with ether (5 × 50 ml). The almost colourless powder which remained dissolved completely in water (20 ml), and was deionized as described above. The solution was filtered through a thin layer of charcoal on Filter-cel which was then washed with EtOHaq. Paper chromatography of the filtrate revealed that the three faster moving components of the syrupy mixture had been removed, and concentration then yielded a colourless solid, 0·46 g (54%). Recrystallization from EtOH afforded clusters of plates, m.p. 147–150° which after two further recrystallizations from EtOH were pure 1,5-*anhydro*-L-*allitol* (VIII), m.p. 151–152°, $[\alpha]_D^{27}$ −33·4° (*c*, 1·26 in water). (Found: C, 44·2; H, 7·3. $C_6H_{12}O_5$ requires: C, 43·9; H, 7·4%.) R_G 1·9 in solvent B. Its IR spectrum was identical with that of 1,5-anhydro-D-allitol whose preparation is described below.

The combined dextrorotatory ethereal extracts were evaporated to a brown syrup which was dissolved in benzene, reprecipitated by the addition of pet. ether (b.p. 60–80°) and then washed five times with pet. ether. Crystallization of the syrup from MeOHaq yielded fine yellow needles of a light sensitive 2,5-dichlorophenylhydrazone, 0·254 g, m.p. 53–57°. Recrystallization from MeOHaq gave material which was unstable even when stored in darkness, and hence was not investigated further.

1,2,3,4,6-*Penta*-O-*acetyl*-β-D-*allopyranose* (IX)

β-D-Allopyranose (1·01 g) was acetylated[13] in a mixture of Ac_2O (15 ml) and dry pyridine (15 ml) at room temp for 23 hr. Isolation of the product in the usual manner yielded 1,2,3,4,6-penta-O-acetyl-β-D-allopyranose as a clear syrup, 2·2 g (quantitative). The structure and anomeric purity of the penta-acetate were indicated by its PMR spectrum measured in $CDCl_3$. No attempt was made therefore to crystallize the product, which was used directly in the next preparation.

2,3,4,6-*Tetra*-O-*acetyl*-D-*allopyranosyl bromide* (X)

The syrupy 1,2,3,4,6-penta-O-acetyl-β-D-allopyranose (2·2 g) was stirred with a mixture of a 45% w/v solution of HBr in AcOH (5 ml) and Ac_2O (1 ml) for 2 hr. The solution was then diluted with CH_2Cl_2 (100 ml), washed twice with ice-water, and once with ice-cold $NaHCO_3$aq, and dried ($MgSO_4$) overnight at 5°. Evaporation of the solution then afforded the crude bromo derivative as a pale brown syrup which was dried over $CaCl_2$ for 2 hr at 30–35°, 2·16 g (93%).

Reduction of 2,3,4,6-*tetra*-O-*acetyl*-D-*allopyranosyl bromide* (X) *with LAH*

A solution of the bromide (2·16 g) in dry ether (100 ml) was added dropwise over 0·25 hr to a stirred suspension of LAH (2·37 g) in ether (50 ml). The mixture was boiled under reflux with stirring for 0·75 hr, then diluted cautiously with EtOH until reaction ceased. Water, concentrated NH_4OH (50 ml, *d*, 0·88) and Filter-cel were added to the mixture which was then filtered through a layer of

[13] *cf.* R. U. Lemieux and C. Brice, *Canad. J. Chem.* **34**, 1006 (1956).

Filter-cel, and the filtered solids washed with 5N NH_4OH (300 ml) followed by water. The filtrate was concentrated to ca. 100 ml, and deionized by passage through columns of Amberlite IR-120(H) (2 × 30 cm), and IR-45(OH) 2 × 10 cm). Concentration to dryness followed by crystallization from boiling EtOH yielded crude 1,5-anhydro-D-allitol as colourless clusters of plates, 0·49 g (57%), m.p. 148–150°. Paper chromatography in solvent B indicated the presence of an impurity (R_G 1·33) which reacted strongly with $NaIO_4$–$AgNO_3$ sprays, and which was not removed from the material by 3 recrystallizations from EtOH. The products were therefore separated by chromatography on three sheets of Whatman No. 3MM filter paper. Extraction of the faster moving zone with hot MeOH followed by deionization and concentration of the extract yielded clusters of needles, which on recrystallization from EtOH afforded hexagonal plates, 0·26 g, m.p. 150–151°. A further recrystallization from EtOH gave pure XI, m.p. 151–152°, $[\alpha]_D^{27}$ +34·0° (*c*, 1·54 in water). (Found: C, 44·0; H, 7·4. Calc. for $C_6H_{12}O_5$: C, 43·9; H, 7·4%.) In solvent B the anhydride had R_G 1·9. IR data, ν_{max} 3450–3340 s (OH). Theander reported[13] m.p. 147–148° and $[\alpha]_D^{22}$ +26° (in water).

Isolation in a similar manner of the slower moving component on the paper chromatogram yielded square prisms of allitol, 0·025 g, m.p. 149–150°, not depressed by admixture with an authentic specimen of allitol, and showing R_G 1·33 in solvent B as did also the authentic specimen.

2,3,4-*Tri*-O-*benzoyl*-β-D-*ribopyranosyl iodide* (XIV)

The method by which Ness *et al.*[14] prepared 2,3,4,6-tetra-O-benzoyl-α-D-glucopyranosyl iodide was applied to 1,2,3,4-tetra-O-benzoyl-β-D-ribopyranose, except that the reaction time was extended to 24 hr. Crystallization of the product from ether–pet. ether (b.p. 40–60°) at +5° yielded only colourless rectangular prisms (61%), m.p. 110–113° (dec). Three recrystallizations from dry ether–CH_2Cl_2–pet. ether gave unstable, light-sensitive 2,3,4-tri-O-benzoyl-β-D-ribopyranosyl iodide, m.p. 117–118° (dec), $[\alpha]_D^{26}$ −254° (*c*, 1·87 in abs $CHCl_3$). (Found: C, 55·4; H, 3·6; I, 21·0; $C_{26}H_{21}IO_7$ requires: C, 54·6; H, 3·7; I, 22·2%.) IR absorption, ν_{max} 1715 s (C=O), 1600 m, 1585 w, and 1495 w (C_6H_5). TLC of the iodide on silica gel resulted in its almost complete conversion to a product with the same mobility as 2,3,4-tri-O-benzoyl-D-ribopyranose. At room temp the iodo derivative gradually became brown, but could be stored satisfactorily for several weeks at +5° over $CaCl_2$–KOH.

Reaction of 2,3,4-*tri*-O-*benzoyl*-β-D-*ribopyranosyl iodide* (XIV) *with methanol*

A mixture of the iodide (0·74 g) and dry MeOH (5 ml) was boiled under reflux for 2 min. On cooling of the solution colourless prisms separated, 0·37 g (58%), m.p. 106–109°. Recrystallization from MeOH gave XV, m.p. 108·5–110°, undepressed when mixed with authentic material.

PMR spectra of the following known compounds were also measured. Compounds XII[15]; XIII;[11] XV;[16] XVI;[17] XVII[15] and XVIII.[11]

RESULTS AND DISCUSSION

2,3,4-tri-O-benzoyl-β-D-ribopyranosyl bromide (IV) was obtained by the method of Fletcher and Ness[7] from the mixture of α-(I) and β-(II) D-ribopyranose tetrabenzoates which results from direct benzoylation of D-ribose. Reaction of the *trans*-bromide (IV) with one mole of mercuric cyanide in dry nitromethane gave a crystalline product in good yield. IR, elemental, and benzoyl analyses suggested that this product was tri-benzoylribosyl cyanide or isocyanide. Its PMR spectra in pyridine-d_5 (Fig. 1) and in $CDCl_3$ were somewhat different in type to those of other D-ribopyranose derivatives, and it was not immediately clear what the spacing of 7·4 c/s in the signal of the anomeric proton (in pyridine-d_5) implied in terms of anomeric configuration and molecular conformation. The structure and configuration were therefore proved chemically using the procedure adopted for other glycosyl cyanide derivatives.[2,5]

[13] O. Theander, *Acta Chem. Scand.* **12**, 1887 (1958).
[14] R. K. Ness, H. G. Fletcher, Jr. and C. S. Hudson, *J. Amer. Chem. Soc.* **72**, 2200 (1950).
[15] C. Pedersen and H. G. Fletcher, Jr., *J. Amer. Chem. Soc.* **82**, 941 (1960).
[16] R. Jeanloz, H. G. Fletcher, Jr. and C. S. Hudson, *J. Amer. Chem. Soc.* **70**, 4055 (1948).
[17] H. G. Fletcher, Jr. and R. K. Ness, *J. Amer. Chem. Soc.* **76**, 760 (1954).

Reduction of the cyano product with LAH yielded a primary amine which was conveniently isolated as its hydrochloride. Acetylation of the amine hydrochloride in acetic anhydride–pyridine afforded a syrupy product whose PMR spectrum (Fig. 2) integral indicated that it contained only four acetyl methyl groups. The amine therefore has a cyclic structure. Deamination of the amine hydrochloride with nitrous acid in aqueous acetic acid gave a complex mixture which contained a reducing sugar. On removal

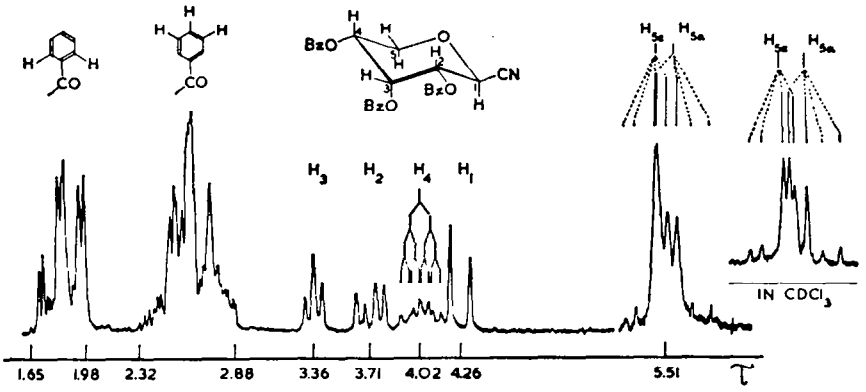


FIG. 1. PMR spectrum of 2,3,4-tri-O-benzoyl-β-D-ribopyranosyl cyanide (V) in pyridine-d_5 at 60 Mc/s.

of the latter product as its unstable 2,5-dichlorophenyl hydrazone, a crystalline material remained which proved to be 1,5-anhydro-L-allitol (VIII). This was identified by comparison with its D-enantiomer (XI) which was synthesized from D-allose by conversion of 1,2,3,4,6-penta-O-acetyl-β-D-allopyranose (IX) to the 1-bromo derivative (X) followed by reduction of the latter with lithium aluminium hydride, a method previously used for the synthesis of several other 1,5-anhydro hexitols.[18] The conclusion of Theander[13] that 1,5-anhydro-D-allitol (XI) is one of the products of reduction of 1,5-anhydro-2,3-dioxo-D-glucitol is confirmed by the stereospecific synthesis of XI reported here. The amine hydrochloride precursor of the L-anhydride (VIII) may therefore be described as 6-amino-1,5-anhydro-6-deoxy-L-allitol hydrochloride (VI; 1-amino-2,6-anhydro-1-deoxy-D-allitol hydrochloride); its tetra-acetyl derivative as 6-acetamido-2,3,4-tri-O-acetyl-1,5-anhydro-6-deoxy-L-allitol (VII), and hence the product from the reaction of the β-D-ribopyranosyl bromide with mercuric cyanide is 2,3,4-tri-O-benzoyl-β-D-ribopyranosyl cyanide (V). By analogy with the formation of 1-deoxy-D-*galacto*heptulose as a by-product in nitrous acid deaminations of 1-amino-2,6-anhydro-1-deoxy-D-*glycero*-L-*manno*heptitol,[9] the reducing sugar formed from the amine hydrochloride (VI) is most probably 1-deoxy-D-allulose. The β-cyanide (V) could also be isolated (in lower yield) by condensation of 2,3,4-tri-O-benzoyl-α-D-ribopyranosyl bromide (III) with mercuric cyanide, a reaction which parallels those of the *cis*-α-acetoxy halides described earlier.[1–5]

An interesting feature of all reactions of glycopyranosyl bromides with mercuric and silver cyanides investigated thus far, has been the liberation of hydrogen cyanide.

[18] R. K. Ness, H. G. Fletcher, Jr. and C. S. Hudson, *J. Amer. Chem. Soc.* **72**, 4547 (1950); R. K. Ness and H. G. Fletcher, Jr. *Ibid.* **75**, 2619 (1953); E. Zissis and N. K. Richtmyer, *Ibid.* **77**, 5154 (1955).

In the case of the reaction of 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide (XIX) with mercuric cyanide it was demonstrated[5] that the hydrogen moiety probably arises from the sugar derivative and not from the reaction solvent. Reinvestigation of the reaction of this bromide with *silver* cyanide in boiling xylene has afforded evidence for the formation of a minor quantity of 2,3,4,6-tetra-O-acetyl-2-hydroxy-D-glucal (XX). In addition to the major product, 3,4,6-tri-O-acetyl-1,2-O-(1-cyanoethylidene)-α-D-glucopyranose, described previously,[5] TLC of the total product revealed a minor

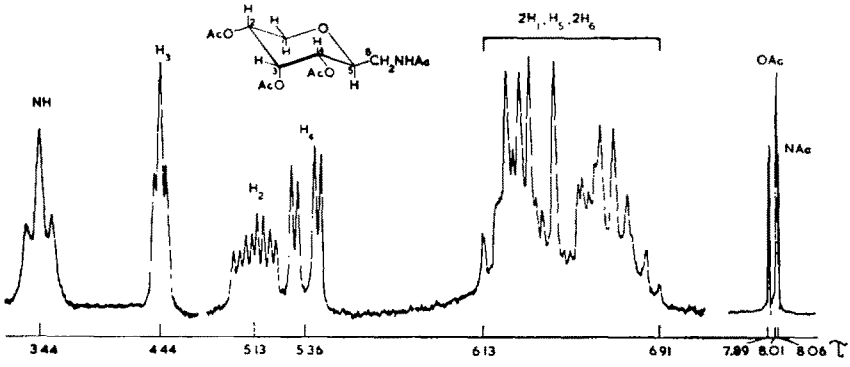
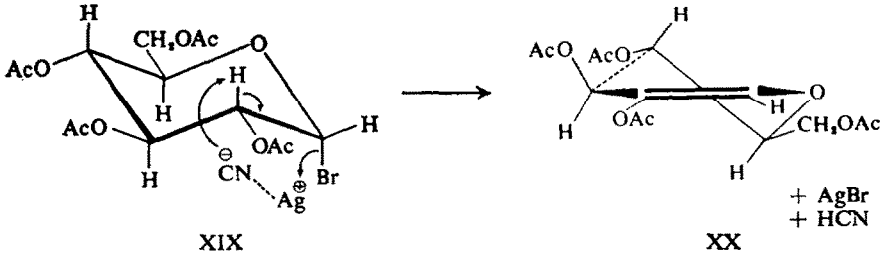


FIG. 2. PMR spectrum of 6-acetamido-2,3,4-tri-O-acetyl-1,5-anhydro-6-deoxy-L-allitol (VII) in $CDCl_3$ at 100 Mc/s.

component with the same mobility as the D-glucal derivative (XX). A PMR spectrum of the total product in deuterochloroform contained in low intensity the characteristic singlet at τ 3·36, doublet ($J_{3,4} = 4{\cdot}4$ c/s) at τ 4·43, and singlet at τ 5·66 corresponding to H_1, H_3 and $2H_6$ respectively in the D-glucal derivative.[19] The small value of $J_{3,4}$ seems to indicate partial flattening of the half-chair conformation (XX). Comparison of the spectrum integrals of the H_1 doublet of the 1,2-O-(cyanoethylidene) derivative and the H_1 singlet of XX indicated that these two components were present in proportions of approximately 7:1 respectively. On the basis of the 53% yield of the cyanoethylidene compound reported previously,[5] the yield of XX must therefore be at least 7%. As might be expected, elimination of hydrogen bromide appears to be responsible for the production of hydrogen cyanide in these reactions. The mechanism of dehydrobromination of XIX catalysed by organic bases has been classified recently as E2 tending towards E1.[19]



XIX XX

[19] cf. R. U. Lemieux and D. R. Lineback, *Canad. J. Chem.* **43**, 94 (1965).

Direct elimination of hydrogen bromide from 2,3,4-tri-O-benzoyl-β-D-ribopyranosyl bromide (IV) would however require a major contribution from the El mechanism since the *cis*-stereochemistry of hydrogen on C_2 and bromine on C_1 is not favourable to E2. Alternatively, anomerization of the β-bromide (IV) to the α-bromide (III) would give H_2 and bromine a *trans*-diaxial orientation (*vide infra*). It is very likely, however, that the presence of heavy metal ions would promote the formation of a carbonium ion.

2,3,4-Tri-O-benzoyl-β-D-ribopyranosyl iodide (XIV) was required for studies of chemical shift and conformation, and was synthesized therefore by reaction of the tetrabenzoate (II) with hydrogen iodide in acetic acid. Its structure and anomeric configuration followed directly from its reaction with methanol which gave the β-methyl pyranoside (XV), and from its high negative specific rotation.[20]

The PMR data obtained by measurement of the 2,3,4-tri-O-benzoyl-D-ribopyranosyl derivatives and related compounds at 60 or 100 Mc/s are shown in Tables 1 and 2. Most of the chemical shifts (Table 1) and coupling constants (Table 2) were derived by 1st order analysis except that for the D-ribopyranosyl derivatives, the multiplets resulting from H_{5e} and H_{5a} were also analysed by the ABX method, by consideration of H_{5e}, H_{5a}, and H_4 as a separate spectral sub-system. This procedure appeared to be justified since in nearly all of the compounds studied the signal of H_3 appeared as a narrow triplet (occasionally modified by small long range couplings) at appreciably lower field than the multiplets due to H_2 and H_4. The proton group composed of H_{5e}, H_{5a}, H_3 and H_4 may therefore be classified as an ABMX sub-system which may be analysed by an extension of the ABX method.[21] It is easily shown that if $J_{AM} = J_{BM} = 0$, then the sixteen transition energies of the A and B nuclei in the ABMX system[21] reduce to the eight energies of AB in ABX. In the D-ribopyranosyl derivatives, the values of $J_{3,5e}$ and $J_{3,5a}$ were either small or zero, and hence this condition is assumed to hold. The numerical values of $\tau_{5a} - \tau_{5e}$ recorded in Table 1 correspond to δ_{AB} derived from the ABX analyses, but their attached signs resulted from the multiplet assignments. The values of the coupling constants $J_{4,5e}$ and $J_{4,5a}$ calculated from the ABX analyses are compared in Table 2 with those from the 1st order analyses as an illustration of the differences which can arise between these methods. The spectral parameters which influence these differences are discussed below. The values of $J_{5e,5a}$ (J_{AB}) derived by the two methods are, of course, identical.

In pyridine-d_5, the 2,3,4-tri-O-benzoyl-β-D-ribopyranosyl cyanide (V) displayed a well resolved spectrum (Fig. 1), with the H_1 doublet appearing at higher field than the quartet, triplet, and quintet due respectively to H_2, H_3, and H_4. If it is assumed that the spacing of 7·4 c/s in the H_1 doublet is too large to represent the coupling of vicinal protons in *gauche* arrangement, then this provides further physical evidence (in addition to an appreciable negative specific rotation) for the β-anomeric configuration of V. However, *gauche* couplings which are at least as large as 5·3 c/s are possible in carbohydrate derivatives[22] (see also Table 2). Taken together, the coupling constants $J_{1,2} = 7{\cdot}4$, $J_{2,3} = J_{3,4} = 3{\cdot}2$, $J_{4,5e} = 2{\cdot}25$, and $J_{4,5a} = 8{\cdot}95$ c/s suggest that the β-cyanide (V) exists to a major extent in the C1 conformation (A), since the values of 7·4 and 8·95 c/s correspond most closely to couplings of vicinal diaxial protons, whereas

[20] A. K. Bhattacharya, R. K. Ness and H. G. Fletcher, Jr., *J. Org. Chem.* **28**, 428 (1963).
[21] B. D. N. Rao and P. Venkateswarlu, *Proc. Indian Acad. Sci.* **52A**, 109 (1960).
[22] B. Coxon, *Tetrahedron* **21**, 3481 (1965).

TABLE 1. 1ST ORDER CHEMICAL SHIFTS (τ VALUES) OF 2,3,4-TRI-O-BENZOYL-D-RIBOPYRANOSYL DERIVATIVES AND RELATED COMPOUNDS IN $CDCl_3$

Compound	R_1	H_1	H_2	H_3	H_4	H_{5e} and H_{5a}	$\tau_{5a} - \tau_{5e}$[c]	R_1	$R_2 = R_3 = R_4 = OBz$
I[a,d]	α-OBz	3·40 d[e]	4·34 t	3·80 t	4·48 sx (at least)	5·78 o	−0·375	1·72	— 3·05 m
II[a]	β-OBz	3·37 d	4·26 t	3·96 t	≈4·28[f]	5·70 o	−0·139	1·90	— 2·91 m
V[b]	β-CN	4·96 d	4·34 q	3·90 t	≈4·44[f]	5·78 o	0·159	—	1·60–2·89 m
		4·26 d[g]	3·71 q[g]	3·36 t[g]	4·02 qi[g]	5·51 sp[g]	0·110[g]	—	1·65–1·98 m, 2·32–2·88 m[g]
IX[b,h]	β-OAc	3·95 d	4·98 q	4·25 t	≈4·95[f]	5·74 m ($H_5 + 2H_6$)	—	$R_1 = R_2 = R_3 = R_4 = R_6 = OAc$ 7·81 (R_3), 7·87, 7·92, 7·97 (×2)(R_1, R_2, R_4, R_6)	
XII[b]	β-F	4·12 q	4·10–4·41[f]			5·69 sp	—	—	1·89–2·97 m
		≈4·2[f]	4·17–4·45[f]		≈4·35[f]	5·75 o	0·149	—	1·98–2·93 m
XIII[b]	β-Cl	3·66 d	4·30 q	3·97 t	≈4·3[f]	5·62 o	0·272	—	1·85–2·94 m
IV[b]	β-Br	3·25 d	4·16 q	3·82 t	≈4·19[f]	5·57 o	0·174	—	1·80–2·88 m
XIV[a]	β-I	2·94 d[f]	4·23 q[f]	3·88 t	≈4·25[f]	5·82 o	0·128	—	1·97–2·93 m
XV[a]	β-OMe	5·04 d	4·49 q	4·21 t	≈4·44[f]	5·91 o	−0·119	6·60	1·96–2·89 m
XVI[b]	β-OCH_2Ph	4·80 d	4·41[f]	4·14 t	≈4·4[f]	5·83 sp	−0·163	5·29 q (CH_2), 2·69 m (Ph)	1·93–2·97 m
XVII[a]	α-F	4·19 q[f]	4·72 sx[f]	3·84 m	4·56 qi (at least)[f]	5·81 o + t	−0·349	—	1·84–2·85 m
XVIII[a]	α-Cl	3·67 q	4·54 q	3·84 m	4·58 sx (at least)[f]	5·80 o + t	−0·428	—	1·75–2·86 m
III[b]	α-Br	3·27 d	4·53 q	3·75 m	4·48 sx (at least)[f]	5·73 o + t	−0·356	—	1·62–2·91 m
	R_5	H_5	H_4	H_3	H_2	H_{1e} and H_{1a}	$\tau_{1a} - \tau_{1e}$	R_5	$R_4 = R_3 = R_2 = OAc$
VII[a,i]	β-CH_2NHAc	6·13–6·91[f]	5·36 q	4·44 t	5·13 o	6·13–6·91[f]	—	6·13–6·91[f] (CH_2) 3·44 t[f] (NH) 8·06 (NAc)	8·01 (×2) (R_2 and R_4) 7·89 (R_3)

[a] Measured at 100 Mc/s.
[b] Measured at 60 Mc/s.
[c] δ_{AB} derived by ABX analyses of the H_{5e} and H_{5a} multiplets. The positive signs given for the β-halides are not definitely proven.
[d] Measured from the mixture of I and II.
[e] Signal multiplicities are symbolized by d(doublet), t(triplet), q(quartet), qi(quintet), sx(sextet), sp(septet), o(octet) and m(complex multiplet).
[f] Unresolved.
[g] Measured in pyridine-d_5 solution.
[h] 1,2,3,4,6-Penta-O-acetyl-β-D-allopyranose.
[i] 6-Acetamido-2,3,4-tri-O-acetyl-1,5-anhydro-6-deoxy-L-allitol. The shifts are arranged under those of the corresponding protons in the D-ribopyranosyl derivatives.
[j] Broad multiplet.

TABLE 2. 1ST ORDER PROTON COUPLING CONSTANTS (c/s) OF 2,3,4-TRI-O-BENZOYL-D-RIBOPYRANOSYL DERIVATIVES AND RELATED COMPOUNDS IN $CDCl_3$

Compound	R_1	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5e}$[c]	$J_{4,5a}$[c]	$J_{5e,5a}$	$J_{1,3}$	$J_{3,5e}$	Predominant Chair Conformation
I[a]	α-OBz	3·7	3·4	3·2	4·6 (4·51)	9·3 (9·39)	10·9	—	—	Cl
II[a]	β-OBz	3·5	3·6	3·6	3·9 (4·12)	2·5 (2·27)	12·95	—	—	1C
V[b]	β-CN	6·7	3·2	3·2	4·3 (3·58)	6·6 (7·34)	12·4	—	—	Cl
		7·4[d]	3·2[d]	3·2[d]	4·05 (2·25)[d]	7·15 (8·95)[d]	12·3[d]	—	—	Cl
IX[b,e]	β-OAc	8·6	2·9	2·9	—	—	—	—	—	Cl
XII[a,f]	β-F	1·5	—	—	1·35 (1·25)	1·9 (1·96)	13·5	—	—	1C
XIII[b]	β-Cl	1·7	3·9	3·9	1·7 (1·64)	1·9 (1·93)	14·0	—	—	1C
IV[b]	β-Br	1·2	3·9	3·9	1·4 (1·34)	1·5 (1·53)	13·8	—	—	1C
XIV[a]	β-I	≈1·0	4·0	4·0	1·5 (1·44)	1·6 (1·63)	13·4	—	—	1C
XV[a]	β-OMe	2·5	3·8	3·8	2·8 (2·93)	2·1 (1·96)	13·0	—	—	1C
XVI[b,g]	β-OCH_2Ph	2·4	3·8	3·8	2·95 (3·10)	2·5 (2·35)	13·25	—	—	1C
XVII[a,h]	α-F	3·3	3·3	2·9	5·3 (5·20)	10·75 (10·87)	10·9	—	0·7	Cl
XVIII[a]	α-Cl	4·4	3·3	3·3	5·1 (5·05)	10·7 (10·75)	10·9	0·4	1·0	Cl
III[a]	α-Br	4·4	≈3·0	3·1	5·6 (5·26)	10·65 (10·96)	10·8	—	0·9	Cl
	R_5	$J_{4,5}$	$J_{3,4}$	$J_{2,3}$	$J_{1e,2}$	$J_{1a,2}$	$J_{1e,1a}$			
VII[a,i]	β-CH_2NHAc	10·1	2·8	2·6	5·6	10·5	—			Cl

[a] Measured at 100 Mc/s.
[b] Measured at 60 Mc/s.
[c] Coupling constants listed in parentheses after the 1st Order values were obtained by ABX analyses of the signals due to H_{5e} and H_{5a}.
[d] Measured in pyridine-d_5 solution.
[e] 1,2,3,4,6-Penta-O-acetyl-β-D-allopyranose.
[f] $J_{H_1,F_1} = 49·2$ c/s.
[g] J_{AB} (benzylic protons) = 12·2 c/s at +55° and +42°, and 12·0 c/s at −10° and −50°.
[h] $J_{H_1,F_1} = 53·7$ c/s; $J_{H_2,F_1} = 25·1$ c/s.
[i] 6-Acetamido-2,3,4-tri-O-acetyl-1,5-anhydro-6-deoxy-L-allitol, $J_{6,NH} = 5·6$ c/s, the other coupling constants are arranged so as to correspond with those in the columns above.

the smaller couplings are characteristic of protons with the *gauche* orientation[23]. However, the value of $J_{1,2}$ is not as large as might be expected for the Cl conformation in view of the fact that 2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl cyanide which appears to exist exclusively in this conformation, showed $J_{1,2} = 10.0$c/s.[3] Furthermore, some of the couplings of (V) measured from deuterochloroform solutions (Table 2) were significantly different to those described above. The smaller values $J_{1,2} = 6{\cdot}7$ and $J_{4,5a} = 7{\cdot}34$ c/s suggest that in the less polar deuterochloroform some redistribution of a conformational equilibrium of V takes place in the direction of the alternative 1C chair conformation in which the cyano group is axial. As the temperature of the deuterochloroform solution was reduced through −10°, −40°, −50°, to −64°, all of the multiplets in the spectrum became extremely broad in comparison with the resonance of TMS. At −64°, in the H_1 region of the spectrum, there appeared a broad singlet, and at higher field, a broad doublet, spacing approximately 10 c/s. These signals may correspond to H_1 in the 1C and C1 (A) chair conformations respectively.

From the 100 Mc spectrum (Fig. 2) of 6-acetamido-2,3,4-tri-O-acetyl-1,5-anhydro-6-deoxy-L-allitol (VII), 1st order analysis of the octet at τ 5·13 due to H_2 (X) yielded $J_{1e,2} = 5{\cdot}6$ and $J_{1a,2} = 10{\cdot}5$ c/s. These coupling constants could not be determined by ABX analysis of the H_{1e} and H_{1a} multiplets, since even at 100 Mc/s these were overlapped by the signals of H_5 and $2H_6$. 1st order treatment of the X multiplet is given therefore with the reservation that it is valid only if $\nu_{1e} - \nu_{1a}(\delta_{AB})$ is suitably large.[24] Together with those above, the other values $J_{2,3} = 2{\cdot}6$, $J_{3,4} = 2{\cdot}8$ and $J_{4,5} = 10{\cdot}1$ c/s obtained, indicate that the tetra-acetate (VII) is likely to be almost entirely in the Cl conformation (B), since the diaxial couplings $J_{1a,2}$ and $J_{4,5}$ are quite large. The τ values of the acetyl methyl groups (Table 1) are consistent with the presence of only one axial acetoxy group in the preferred conformation.[25] The PMR spectrum of VII therefore provides further proof of the β anomeric configuration of the cyanide (V) precursor.

At 60 Mc/s the multiplets due to H_1 in 2,3,4-tri-O-benzoyl-β-D-ribopyranosyl fluoride (XII), chloride (XIII), and bromide (IV) were easily recognizable at low field. For the fluoride (XII) H_1 appeared as a wide quartet which straddled the complex multiplet due to H_2, H_3, and H_4 because of the 49·2 c/s coupling with fluorine. Since the chemical shifts of H_2, H_3, and H_4 are rather similar, it was not immediately certain that the smaller spacing in the H_1 quartet approximated to a true value of $J_{1,2}$ since this spacing could in principle be modified by virtual coupling.[26] However, redetermination of the spectrum of XII at 100 Mc/s produced little change in this spacing, or in those in the $2H_5$ multiplet. At 100 Mc/s the upfield half of the H_1 quartet was obscured by the signals of H_2, H_3, and H_4. The approximate chemical shift of H_4 was established by means of a frequency-swept double resonance experiment. Irradiation at a point 1·4 ppm downfield from the $2H_5$ octet caused the latter to collapse to an AB quartet. In the 60 Mc spectra of the β-chloride (XIII) and β-bromide (IV), H_1

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

[24] N. S. Bhacca and D. H. Williams, *Applications of NMR Spectroscopy in Organic Chemistry. Illustrations from the steroid field* p. 46, 148. Holden-Day, San Francisco (1964).

[25] L. D. Hall, *Adv. Carbohydrate Chem.* **19**, 51 (1964).

[26] J. I. Musher and E. J. Corey, *Tetrahedron* **18**, 791 (1962).

occurred as a doublet of small splitting, H_3 as a sharp triplet, and $2H_5$ as an octet. The signals of H_2 and H_4 overlapped. The resonance due to H_1 in 2,3,4-tri-O-benzoyl-β-D-ribopyranosyl iodide (XIV) was not immediately assignable, however, since a resolved doublet was not visible at low field. Integration of the 60 Mc and 100 Mc spectra suggested that the H_1 signal lay in the region of the aromatic protons. That H_1 is indeed represented by the unresolved doublet (broadened singlet) which appeared at the high field edge of the aromatic proton resonances (Fig. 3a) was confirmed by frequency sweep double resonance experiments at 100 Mc/s. When H_2 and H_4 (the complex multiplet at τ 4·24) were irradiated (Fig. 3b), the unresolved doublet at τ 2·94

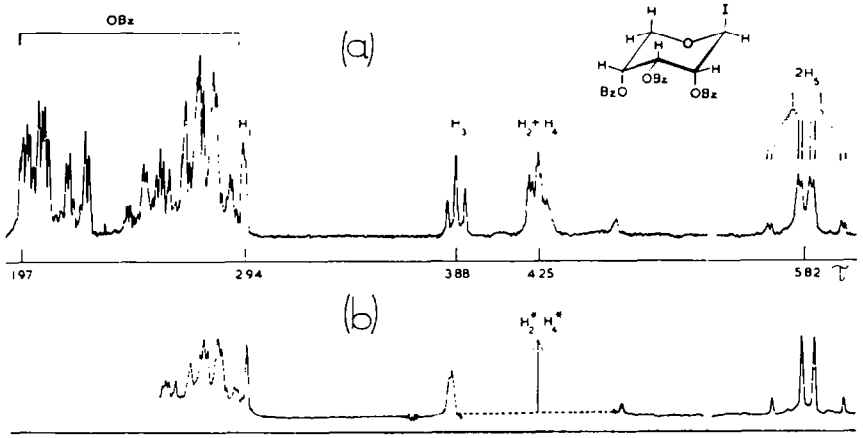


FIG. 3. PMR spectra of 2,3,4-tri-O-benzoyl-β-D-ribopyranosyl iodide (XIV) in $CDCl_3$ at 100 Mc/s,
(a) single resonance spectrum,
(b) frequency-swept double resonance; irradiation of H_2 and H_4.

became a sharp singlet. Observed also, was the collapse of the H_3 triplet to a broad singlet, and of the $2H_5$ octet to an AB quartet, thus providing confirmation of the assignments of these protons. Conversely, irradiation at the unresolved doublet produced sharpening of the H_2 multiplet, and irradiation at the position of the $2H_5$ octet caused simplification of the H_4 multiplet.

H_1 in the β-iodide (XIV) is therefore unusually strongly deshielded for a proton on a saturated pyranose ring. A slightly better separation of its signal from those of the aromatic protons was achieved in carbon tetrachloride solution.

In the four β-halides, the ranges of values of the vicinal proton coupling constants were determined to be $J_{1,2} = 1·0–1·7$, $J_{2,3} = 3.9–4.0$ $J_{3,4} = 3·9–4·0$, $J_{4,5e} = 1·25–1·64$, and $J_{4,5a} = 1·53–1·96$ c/s. On the basis that these values represent couplings of pairs of protons in the *gauche* orientation,[23] all four β-halides therefore, exist predominantly in the 1C chair conformation (C). Since the values of $J_{1,2}$ are quite small, and in fact, typical of protons in di-equatorial orientation,[22] the contribution of the alternative C1 chair conformation in which H_1 and H_2 are diaxial, must also be small. It has recently been reported that tri-O-acetyl-β-D-ribopyranosyl bromide exists in the 1C conformation.[27]

[27] D. Horton and W. N. Turner, *Chem. Communications* No. 6, 113 (1965); *J. Org. Chem.* **30**, 3387 (1965).

The spectra of the methyl and benzyl β-D-ribopyranoside tribenzoates (XV and XVI respectively) were similar to those of the β-halides except that the doublet due to H_1 appeared at higher field than H_2, H_3 and H_4. The 60 Mc spectrum of the benzyl glycoside is shown in Fig. 4. The non-equivalence of the benzylic methylene protons increased as the temperature of the deuterochloroform solution was reduced and is due presumably to the neighbouring asymmetry in the molecule.[28] AB analysis[9] of the methylene quartet obtained at temperatures of 42°, −10°, and −50° gave values

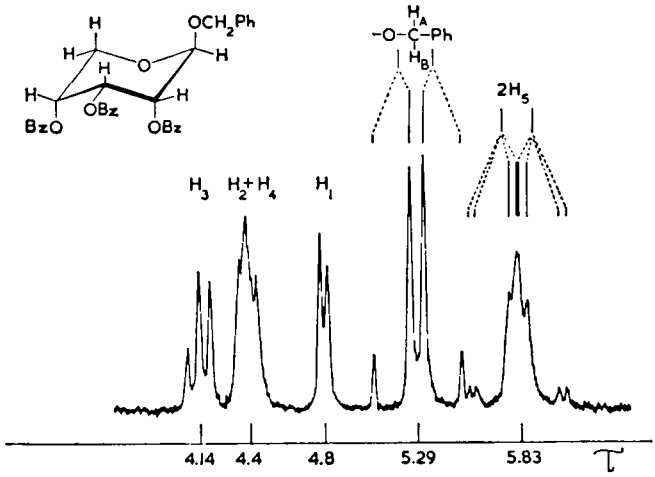


FIG. 4. Partial PMR spectrum of benzyl 2,3,4-tri-O-benzoyl-β-D-ribopyranoside (XVI) in $CDCl_3$ at 60 Mc/s.

of δ_{AB} equal to 10·9, 12·7 and 13·5 c/s respectively. It has been suggested for other asymmetric benzyl ethers that the proximity of the asymmetric centre to the benzyl group results in a preferred conformation of the phenyl ring with respect to the methylene protons, and that the principal contribution to the non-equivalence originates in the magnetic anisotropy of the phenyl group.[29]

The coupling constants listed in Table 2 imply that the glycosides (XV and XVI) also exist mainly in the 1C conformation (C). However, the fact that the values of $J_{1,2}$, $J_{4,5e}$, and $J_{4,5a}$ in the glycosides are somewhat greater than those in the β-halides probably indicates that the glycosides are conformationally less homogeneous than the halides, since an increased contribution from the C1 form would cause these couplings to be larger. It is assumed that the change in electronegativity caused by replacing halogen with oxygen would not increase the values of these three couplings appreciably. Studies of the variation of coupling constants with substituent electronegativity suggest that couplings of protons near to an oxygen substituent are often smaller than those near to halogen (except perhaps, for fluorine).[30]

[28] L. M. Jackman, *Applications of NMR spectroscopy in Organic Chemistry* p. 101. Pergamon Press, London (1959).

[29] G. M. Whitesides, D. Holtz and J. D. Roberts, *J. Amer. Chem. Soc.* **86**, 2628 (1964).

[30] R. E. Glick and A. A. Bothner-By, *J. Chem. Phys.* **25**, 362 (1956); K. L. Williamson, *J. Amer. Chem. Soc.* **85**, 516 (1963); R. J. Abraham and K. G. R. Pachler, *Mol. Phys.* **7**, 165 (1963); K. L. Williamson, C. A. Lanford and C. R. Nicholson, *J. Amer. Chem. Soc.* **86**, 762 (1964).

The spectrum (Fig. 5a) of β-D-ribopyranose tetrabenzoate (II) yielded values of $J_{1,2}$ (3·5 c/s) and of the larger $J_{4,5}$ coupling (4·12 c/s) which were greater than those in the glycosides, suggesting a further increased contribution from the C1 conformation, although the 1C form appeared still to predominate. If it is assumed that these are the only conformations present, that the coupling of 4·12 c/s results from time-averaging of $J_{4e,5e}$ and $J_{4a,5a}$, and also (somewhat arbitrarily) that $J_{1e,2e} = J_{4e,5e} = 1{\cdot}5$ c/s for a pure 1C conformation, and $J_{1a,2a} = 7{\cdot}0$ and $J_{4a,5a} = 10{\cdot}0$ c/s for a pure C1 form, then calculations suggest that the relative proportions of these conformations are approximately 2:1 respectively.

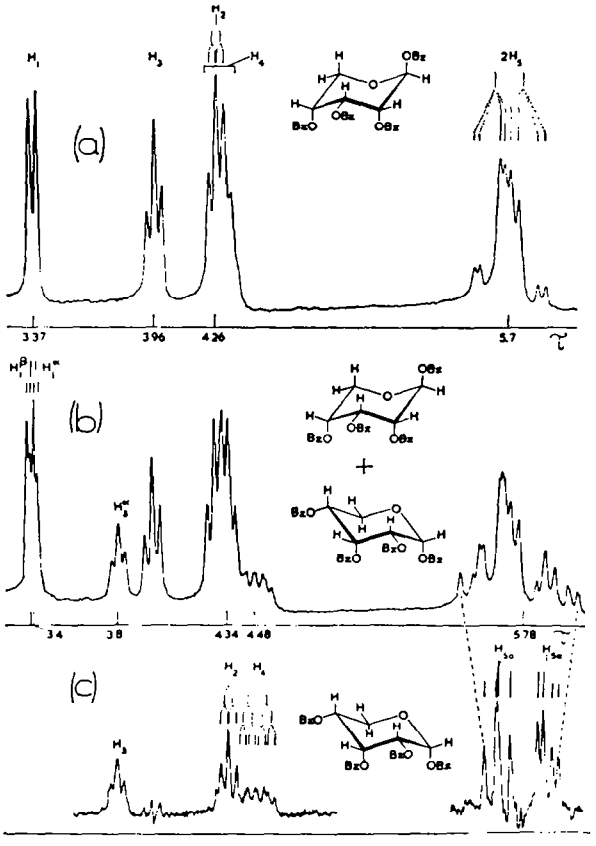


FIG. 5. Partial PMR spectra of 1,2,3,4-tetra-O-benzoyl-D-ribopyranoses in $CDCl_3$ at 100 Mc/s,

(a) pure β-anomer (II),
(b) mixture of α- and β-anomers (I and II)
(c) α-anomer (I), obtained by electronic subtraction of (a) from (b).

For α-D-ribopyranose tetrabenzoate (I), which is not known in pure form,[20] a useful PMR spectrum (Fig. 5c) was obtained at 100 Mc/s by electronic subtraction of the spectrum (Fig. 5a) of β-D-ribopyranose tetrabenzoate from that (Fig. 5b) of the *mixture* of α and β-anomers using the Varian C-1024 time-averaging computer. The appearance of a large vicinal coupling constant (9·39 c/s) in the quartet at lower field in the H_5 region of the spectrum necessitated the assignment of this multiplet to axial

H_5, coupled probably with axial H_4. The remaining vicinal couplings $J_{1,2} = 3{\cdot}7$, $J_{2,3} = 3{\cdot}4$, $J_{3,4} = 3{\cdot}2$ and $J_{4,5e} = 4{\cdot}51$ c/s are characteristic of protons in the *gauche* arrangement and when taken with the value of $J_{4,5a}$ are consistent with the existence of the majority of α-D-ribopyranose tetrabenzoate (I) in the C1 chair conformation (D) in which the approximate proton dihedral angles are $\phi_{1,2} = \phi_{2,3} = \phi_{3,4} = \phi_{4,5e} = 60°$, and $\phi_{4,5a} = 180°$. However, if it is assumed that the vicinal coupling constants in these compounds could also vary appreciably with substituent electronegativity,[30] its orientation[31,22] and with other factors,[32] then the skew conformation (E) must also be considered as a possibility. The ambiguity in interpretation of the vicinal coupling constants arises because the approximate proton dihedral angles for the skew (E) are $\phi_{1,2} = \phi_{4,5e} = 71°$, $\phi_{2,3} = \phi_{3,4} = 33°$ and $\phi_{4,5a} = 169°$, values which are not completely inconsistent with the couplings mentioned above. A similar situation prevailed in tri-benzoyl-α-D-ribopyranosyl fluoride (XVII), chloride (XVIII), and bromide (III), the spectra of which were quite similar to that of the α-tetrabenzoate (I), and again required the assignment of H_{5a} at lower field than H_{5e}.

The vicinal proton–proton coupling constants of these halides (Table 2) were also consistent with either the C1 chair conformation (D) or less likely, the flexible form (E). In the spectrum of the α-fluoride (XVII), H_{5e} appeared as an unresolved octet. On irradiation of H_{5e}, the H_3 multiplet sharpened up giving a triplet, thus suggesting long range coupling of H_3 with H_{5e}. The extra splitting (0·7 c/s) is obviously not due to virtual coupling[26] since the pairs of protons H_3 and H_4, and H_4 and H_{5a} are, by virtue of their large chemical shift, only weakly coupled. The multiplet assignments of the other ring protons were confirmed by comparison of 60 and 100 Mc spectra, and by further homonuclear double irradiation experiments at 100 Mc/s. Fluorine magnetic resonance data of the anomeric tribenzoyl D-ribopyranosyl fluorides (XII and XVII) have been reported.[33] Similarly, the α-chloride (XVIII) and α-bromide (III) also displayed true long range couplings of H_{5e} with H_3, the signals of H_{5e} appearing as well resolved octets. Additionally, the 100 Mc spectrum (Fig. 6a) of the chloride showed a small extra splitting (0·4 c/s) in the H_1 doublet, and H_3 as a complex multiplet at τ 3·84. Irradiation of H_3 (Fig. 6b) resulted in the disappearance of the small splitting from the H_1 multiplet, collapse of the H_{5e} octet to a quartet, and also simplification of the overlapping H_2 and H_4 multiplets to the expected pattern. Since H_2 and H_3 are only weakly coupled, the 0·4 c/s splitting in the H_1 quartet may therefore be assigned as a true long range coupling of H_1 with H_3. Further confirmation of the assignments was provided by simultaneous irradiation of H_2 and H_4 (Fig. 6c), when the H_1 and H_3 multiplets collapsed each to a broadened singlet, and appropriate, although incomplete, collapse of the H_{5a} triplet and H_{5e} octet occurred. The observation of the long range couplings over four bonds in the three α-halides is most consistent with their existence in the C1 conformation (D) in which the proton pairs H_1 and H_3, and H_3 and $H_{5(e)}$ have the di-equatorial orientation in which this type of coupling occurs most frequently.[22,34,35] The coupling of H_{3e} to H_{5e} in α-D-ribopyranose

[31] D. H. Williams and N. S. Bhacca, *J. Amer. Chem. Soc.* **86**, 2742 (1964); H. Booth, *Tetrahedron Letters* 411 (1965).

[32] M. Karplus, *J. Chem. Phys.* **30**, 11 (1959); *J. Amer. Chem. Soc.* **85**, 2870 (1963).

[33] L. D. Hall and J. F. Manville, *Chem. & Ind.* 991 (1965).

[34] L. D. Hall and L. Hough, *Proc. Chem. Soc.* 382 (1962); S. Sternhell, *Rev. Pure and Appl. Chem.* **14**, 15 (1964).

[35] B. Coxon, *Carbohydrate Research* **1**, 357 (1966).

tetra-acetate has been reported.[36] Such coupling, if present in α-D-ribopyranose tetra-benzoate (I) might not have been resolved by the methods used to obtain its spectrum. However, in the spectrum (Fig. 5b) of the anomeric mixture, the triplet due to H_3^{α} *is* somewhat broader than that of H_3^{β}. The appearance of the signal of H_{5a} at lower field than that of H_{5e} in the α-tetrabenzoate and α-halides may in the C1 conformation (D) be attributed to substantial deshielding of H_{5a} by the axially opposed substituents at C_1 and C_3.[27,36,37] However, it could also be argued that H_{5a} in the skew

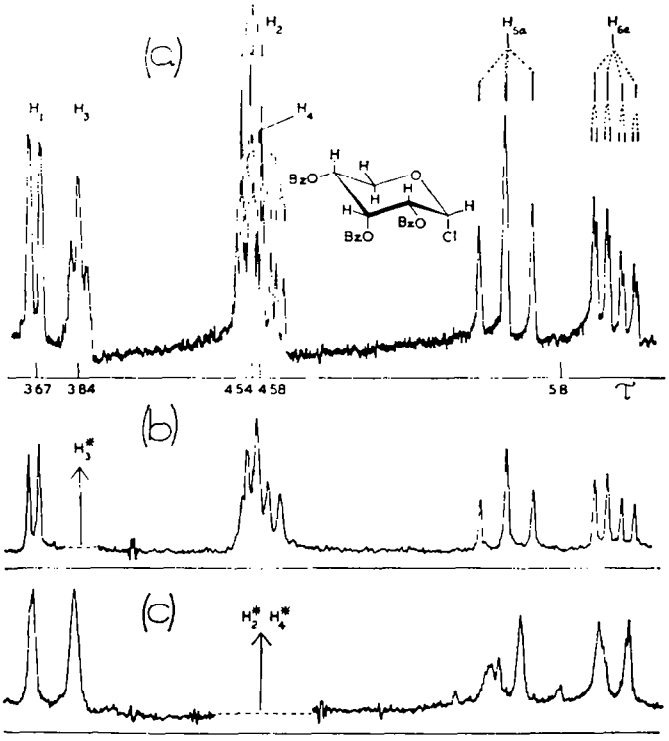


FIG. 6. Partial PMR spectra of 2,3,4-tri-O-benzoyl-α-D-ribopyranosyl chloride (XVIII) in $CDCl_3$ at 100 Mc/s,
(a) single resonance spectrum,
(b) irradiation of H_3,
(c) irradiation of H_2 and H_4.

form (E) might be deshielded because of its proximity to the axial and quasi-axial oxygen atoms at C_2, and C_3 respectively. Although the skew form (E) has only one truly axial substituent, because of the anomeric effect,[38] this conformation is unlikely for those compounds in which the equatorial substituent R_1 contains an electron-rich atom bonded to C_1. In fact, the particular chair conformation adopted by each of the tribenzoyl D-ribopyranosyl derivatives appears to be determined by the manner in

[36] R. U. Lemieux and J. D. Stevens, *Canad. J. Chem.* **43**, 2059 (1965).
[37] Ref. 24, p. 75.
[38a] J. T. Edward, *Chem & Ind.* 1102 (1955);
[b] R. U. Lemieux, *Molecular Rearrangements* (Edited by P. de Mayo) Part 2; p. 735. Interscience, New York (1963).

which the anomeric effect operates for the substituent at C_1. Thus all of the halides, glycosides, and 1-benzoates studied exist predominantly in that conformation (either C or D) in which the substituent at C_1 is axially oriented. The β-cyanide (V) occupies a key position in this respect, since it demonstrates that modification of the electric nature of the 1-substituent, *without change of its configuration*, can produce a major change in the conformational equilibrium. The series of compounds formed by tri-acetyl-β-D-ribopyranosyl bromide, β-D-ribopyranose tetra-acetate, and 6-acetamido-2,3,4-tri-O-acetyl-1,5-anhydro-6-deoxy-L-allitol (VII) offer a further convincing demonstration of the influence of the 1-substituent in determining the preferred conformations of D-ribopyranose derivatives. As mentioned previously the β-bromide was found to exist almost entirely in the 1C conformation,[27] the β-tetra-acetate apparently exists as a mixture of approximately equal proportions of 1C and C1 forms,[36] and the 1,5-anhydro-L-allitol derivative (VII) assumes exclusively the C1 conformation (B) in which the acetamidomethylene group is equatorial.

The question of the relative magnitudes of anomeric effects for various substituents at C_1 (and C_5) is one of considerable interest. It is reasonable to suppose that these magnitudes will be governed mainly by the effective charge density at the substituent atom attached directly to C_1 because of the proximity of this atom to the atomic dipole of the ring oxygen. The results of the present study support the view that the anomeric effect is important for all four halogen atoms, as might be expected from the fact that the dipole moments of carbon-halogen bonds are moderately large and similar.[39] It may be re-emphasized that correlation with substituent electronegativity is not useful in this respect. (For example, iodine and carbon have almost identical electronegativities.) The greater observed conformational homogeneity of the β-D-ribopyranosyl halides as compared with the β-1-esters and β-glycosides therefore agrees with the expectation[40] that the anomeric effect of halogen atoms should be large. It has been estimated recently that the anomeric effect of a 1-chloro substituent on a glucopyranose ring in acetonitrile is about 2 kcal/mole,[41] whereas that of the acetoxy group (in 1:1 Ac_2O:AcOH) was found to be 1·5 kcal/mole.[38b] In cyclohexane derivatives at least, the A-values of halogen, methoxyl, acetoxy, and cyano substituents are all rather small and similar,[42a] and hence this parameter is expected to be of lesser importance in determining the conformational equilibria of the β-D-ribopyranose derivatives. It is noteworthy that the A-value of the acetoxy group in pentopyranose tetra-acetates was found[43] to be only 0·36 kcal/mole, that is, less than the range of A-values quoted[42a,44] for acetoxy groups in cyclohexane derivatives. It would be expected however,[42b] that the A-value of the acetamidomethylene group would be appreciably greater, thus favouring the C1 chair (B). On the basis of electron density at the first substituent atom, it might also be expected that 1 or 5 substituents such as $—CH_2NHAc$, $—CH_2OAc$, and $—CH(SO_2Et)_2$ would display a small *reverse* anomeric effect[45] (that is, a preference for the equatorial orientation additional to that due to

[39] J. W. Smith, *Electric dipole moments* p. 92. Butterworths, London (1955).

[40] E. L. Eliel, N. L. Allinger, S. J. Angyal and G. A. Morrison, *Conformational Analysis* p. 377. Interscience, New York (1965).

[41] R. U. Lemieux and J. Hayami, *Canad. J. Chem.* **43**, 2162 (1965).

[42] Ref. 40 *a* p. 44; *b* p. 45

[43] Ref. 38 *b* p. 737.

[44] R. U. Lemieux and J. W. Lown, *Canad. J. Chem.* **42**, 893 (1964).

[45] R. U. Lemieux and A. R. Morgan, *Canad. J. Chem.* **43**, 2205 (1965).

steric effects) because of the induction of a small positive charge at the carbon atom by the electrophilic substituent(s). Similar considerations suggest that the anomeric effect of acyloxy groups should be slightly less than that of an alkoxy substituent since mesomeric electron withdrawal would in the ester be expected to reduce the C_1—O_1 dipole to some extent. Unfortunately, much of the relevant data in the literature have been recorded for different solvents, or have been calculated using A-values derived from cyclohexane derivatives.[46] In the absence of suitable interaction free energy data for the benzoyloxy substituent, the provision of a more quantitative analysis of the conformational equilibria of the tri-benzoyl-ribopyranose derivatives is difficult. However, it appears that the free energy difference between the chair conformations is small enough for the preferred conformation to be determined by the operation, or non-operation of the anomeric effect.

From Table 2 it may be seen that certain coupling constants are (unexpectedly) characteristic of each chair conformation. Thus although the protons in the pairs H_2—H_3, and H_3—H_4 have the same type of *gauche* (axial-equatorial) orientation in the C1 and 1C conformations, the values of $J_{2,3}$ and $J_{3,4}$ (2·8–3·4, and 2·6–3·3 c/s respectively) in the C1 chair are characteristically smaller than those (3·6–4·0 c/s) in the compounds which exist predominantly in the 1C conformation. As expected, the values in the conformationally less homogeneous β-1-benzoate lie at the lower end of the range for the 1C conformation. It does not appear possible to rationalize these differences by means of the *trans*-coplanar electronegativity effect.[31] Since the proton pairs H_2—H_3, and H_3—H_4 in the 1C conformation (C) possess more electronegative atoms in *trans*-coplanar orientation than they do in the C1 conformation (A, B, or D), it might be expected that the values of $J_{2,3}$ and $J_{3,4}$ in the 1C conformation would be smaller than those in the C1, whereas, in fact, the opposite was observed. Application of the Karplus relationship[32] to these couplings however, suggests that the proton dihedral angles $\phi_{2,3}$ and $\phi_{3,4}$ are smaller in the 1C conformation than in the C1. Such deformation (flattening) of the 1C chair could result from increased separation of the axially opposed acyloxy substituents at C_2 and C_4, which would also cause some enlargement of $\phi_{1,2}$ and $\phi_{4,5e}$. In agreement with this, the conformationally homogeneous β-halides displayed values of $J_{1,2}$ and $J_{4,5e}$ which were smaller than those of $J_{4,5a}$. A similar 1:3 diaxial steric repulsion might be expected in the α-derivatives existing in the C1 conformation (D). However, the presence of the ring oxygen may be expected to cause some local flattening of the pyranose ring;[22] the values of $J_{1,2}$ in the C1 chair (D) do tend to be larger than those of $J_{2,3}$ and $J_{3,4}$.

In attempting to rationalize the greater thermodynamic stability of the β-halides, it is not possible to compare the 1:3 diaxial interactions in conformations (C) and (D) directly, since the α-halides (D) contain an extra *gauche* interaction. Moreover, the presence of four substituents on the same side of the pyranose ring may be a destabilizing factor of some magnitude.

It has been frequently (but not always) observed that vicinal J_{ee} is smaller than vicinal J_{ea} in conformationally homogeneous pyranose rings. Further examples of this effect were found in the present investigation (Table 2). Some possible reasons for it have recently been reviewed.[22]

In the D-ribopyranose derivatives there appears also to be a conformational

[46] cf. C. B. Anderson and D. T. Sepp, *Chem & Ind.* 2054 (1964).

dependence of the geminal coupling $J_{5e,5a}$. Thus the numerical values of $J_{5e,5a}$ (10·8–10·9 c/s) for the α-halides and α-benzoate in the C1 chair (D) are appreciably smaller than those (13·4–14·0 c/s) of the β-halides in the 1C conformation (C). The conformationally less homogeneous β-cyanide, β-benzoate and β-glycosides displayed values intermediate between the two extremes, but closer in each case to those in the predominant conformation. If it is assumed that these geminal couplings have negative sign then the results agree with the predictions of a recently described molecular orbital theory of geminal coupling;[47] namely, that methylene protons in vicinal *gauche* and *trans* orientation to an electronegative substituent should show a geminal coupling constant more negative than that of protons both in *gauche* relationship with the substituent. These steric situations are exemplified by the benzoyloxy substituent at C_4 in the 1C and C1 conformations (C and D) respectively.

The differences in the values of $J_{4,5e}$ and $J_{4,5a}$ derived from 1st order and from ABX analyses are of some interest. If the 1st order spacings in the AB octet corresponding to J_{AX} and J_{BX} are denoted by S_{AX} and S_{BX} respectively, then from the equations of Bernstein *et al.*[9] we have

(1)

$$S_{AX} = J_{AX} - \tfrac{1}{2}(J_{AX} - J_{BX}) + \tfrac{1}{2}[\delta_{AB} + \tfrac{1}{2}(J_{AX} - J_{BX})]\left\{1 + \frac{J_{AB}^2}{[\delta_{AB} + \tfrac{1}{2}(J_{AX} - J_{BX})]^2}\right\}^{1/2} - \tfrac{1}{2}[\delta_{AB} - \tfrac{1}{2}(J_{AX} - J_{BX})]\left\{1 + \frac{J_{AB}^2}{[\delta_{AB} - \tfrac{1}{2}(J_{AX} - J_{BX})]^2}\right\}^{1/2}$$

and

(2)

$$S_{BX} = J_{BX} + \tfrac{1}{2}(J_{AX} - J_{BX}) - \tfrac{1}{2}[\delta_{AB} + \tfrac{1}{2}(J_{AX} - J_{BX})]\left\{1 + \frac{J_{AB}^2}{[\delta_{AB} + \tfrac{1}{2}(J_{AX} - J_{BX})]^2}\right\}^{1/2} + \tfrac{1}{2}[\delta_{AB} - \tfrac{1}{2}(J_{AX} - J_{BX})]\left\{1 + \frac{J_{AB}^2}{[\delta_{AB} - \tfrac{1}{2}(J_{AX} - J_{BX})]^2}\right\}^{1/2}$$

from which it is evident that S_{AX} and S_{BX} tend towards J_{AX} and J_{BX} respectively either for values of δ_{AB} (in c/s) which are large compared with J_{AB} and $J_{AX} - J_{BX}$, or for small values of $J_{AX} - J_{BX}$. These conclusions are borne out by the data in Tables 1 and 2. In the β-halides, β-glycosides, and β-1-benzoate the difference between J_{AX} and J_{BX} is small and hence the 1st order spacings are reasonably good approximations to the true coupling constants. In the α-halides and α-1-benzoate, although $J_{AX} - J_{BX}$ is large, the chemical shift δ_{AB} is now also large, and again $S_{AX} \approx J_{AX}$, and $S_{BX} \approx J_{BX}$. The agreement is not as good in the case of the α-bromide since δ_{AB} is smaller due to determination of the spectrum at 60 Mc/s rather than at 100 Mc/s. For the β-cyanide, δ_{AB} is small (especially in pyridine), and $J_{AX} - J_{BX}$ is large. In this case, 1st order analysis gives very poor values of the coupling constants (Table 2).

Addition of equations (1) and (2) gives

$$J_{AX} - S_{AX} = -(J_{BX} - S_{BX})$$

from which it is apparent that if S_{AX} is a minimum value of J_{AX}, then S_{BX} is necessarily a *maximum* value of J_{BX}, and *vice-versa*. This effect is also reflected in the data in Table 2.

[47] J. A. Pople and A. A. Bothner-By, *J. Chem. Phys.* **42**, 1339 (1965).

In the $\alpha\beta$ anomeric pairs of 1-benzoates, fluorides, chlorides, and bromides which were studied, the chemical shifts of H_1 in each pair of anomers are very similar. This is due presumably to the fact that the α and β anomers exist predominantly in different chair conformations, both of which contain the anomeric proton in equatorial orientation, and hence not subject to any marked differences in shielding. If it should transpire that the shielding influences of axial benzoyloxy substituents on neighbouring equatorial hydrogens are comparable with those of acetoxy groups,[36] then the similarity would be a consequence of balancing of the effect on equatorial H_1 of the axial 2-benzoyloxy group in the 1C conformation (C), with that of the axial 3-benzoyloxy substituent in the C1 form (D).

The chemical shifts (τ values) of H_1 in the β-halides decreased progressively from fluoride to chloride to bromide to iodide. A similar trend was evident in the three α-halides examined (Table 2). It has been proposed[48] that the chemical shifts of protons and carbon-13 nuclei in several groups of aliphatic and aromatic halides are best considered on the basis of three effects; namely, inductive, intramolecular Van der Waals dispersion, and magnetic anisotropy.[49] For methyl halides it was suggested[48] that the Van der Waals deshielding effect could outweigh the positive shielding due to anisotropy. However, the results from the D-ribopyranosyl halides parallel those obtained[50] for the methine protons in cyclohexyl and isopropyl halides where Van der Waals deshielding evidently dominates the screening contributions from both the anisotropy, and the inductive effect. Since the Van der Waals deshielding may be taken to be inversely proportional to the sixth power of the internuclear distance,[51] whereas the anisotropic shielding is approximately dependent on the inverse cube of the distance (and an an angular term),[52] the Van der Waals deshielding might be expected to become relatively more important for smaller internuclear distances, and particularly so for the larger halogen atoms which are expected to produce a large dispersion effect.[48,51] In several polyhalogenocyclohexanes, the axial carbon–halogen (X) bonds appear to be bent away from the main axis of the ring by 7–8°.[53] Such deformation undoubtedly causes some reduction of the exocyclic H—C—X bond angle,[54] and hence also of the H—X internuclear distance. Since the D-ribopyranosyl halides exist almost entirely in the conformations in which the halogen is axial, diminution of the H_1—X internuclear distance by 1:3 diaxial repulsions may be more pronounced in these than in the cyclohexyl monohalides which exist predominantly in the equatorial conformation. The deshielding effect in passing from fluoride to iodide does appear to be greater in the ribopyranosyl halides than in the cyclohexyl and isopropyl series. It is interesting in this respect that the H—C—X bond angle in methyl halides decreases from fluoride to iodide.[53b]

As mentioned above, H_{5a} in the α-D-ribopyranosyl halides and α-1-benzoate resonates at lower field than H_{5e}. However, the changes in this deshielding for different halogens at C_1 do not appear to be especially significant. For the β-halides in the 1C

[48] T. Schaefer, W. F. Reynolds and T. Yonemoto, *Canad. J. Chem.* **41**, 2969 (1963).
[49] A. A. Bothner-By and J. A. Pople, *Ann. Rev. Phys. Chem.* **16**, 43 (1965).
[50] Ref. 9 *b*, p. 279; Ref. 28, p. 54.
[51] R. J. Abraham and J. S. E. Holker, *J. Chem. Soc.* 806 (1963); Ref. 24, p. 189.
[53] H. M. McConnell, *J. Chem. Phys.* **27**, 226 (1957).
[53a] *Interatomic distances*. Special publication No. 18. The Chemical Society, London (1958); [b] Supplement (1965).
[54] Ref. 40, p. 46, 126, 451, 456.

conformation (C) the assignments given for the H_{5e} and H_{5a} multiplets are not entirely unambiguous since these protons displayed quite similar chemical shifts, and also similar couplings to H_4. These assignments (Tables 1 and 2) place H_{5e} at lower field than H_{5a} and give $J_{4e,5e}$ smaller values than $J_{4e,5a}$. However, if deshielding of H_{5a} by the *syn*-axial halogen at C_1 and the *trans*-axial benzoyloxy group at C_4, together with shielding of H_{5e} by the latter group were especially marked,[55] then the assignments of H_{5e} and H_{5a} might have to be reversed. Such reversal would not affect the main conformational deductions, but is likely at least for the β-glycosides and β-1-benzoate wherein an appreciable contribution from the C1 conformation causes the larger $J_{4,5}$ coupling to be interpreted as the result of time-averaging of $J_{4e,5e}$ and $J_{4a,5a}$ in the 1C and C1 conformations respectively. The assignments of the β-glycosides and β-1-benzoate are therefore given on this basis.

In the 1C conformation (C) the resonance of axial H_3 at lower field than equatorial H_2 and H_4 is due probably to deshielding of H_3 by *syn*-axial R_1 and *trans*-axial benzoyloxy substituents at C_2 and C_4,[55a] augmented perhaps by shielding of H_2 and H_4 by the axial groups at C_4 and C_2 respectively.[55b] The chemical shifts of H_{3a} and H_{5a} in the β-halides decrease somewhat from fluoride to bromide, but increase again in the iodide, and hence no definite influence of the size of the axial 1-halogen may be inferred.

In conclusion, it may be mentioned that the β-halides exist in the ideal conformation (C) for anchimeric participation of the 2-benzoyloxy group in reactions which involve displacement of the halogen. This is in agreement with the observation[20] that although the β-halides are thermodynamically more stable than are the α-halides, they are also considerably more reactive in nucleophilic substitution reactions.

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[55a] Ref. 24, p. 185; [b] cf. Ref. 36.