1023. *Reactions at Position 1 of Carbohydrates. Part II.*[1] *The Variation of Optical Rotation of Some Aryl Glucosides with Temperature.*

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The temperature coefficients of optical rotation (sodium D-line) of some aryl D-glucopyranosides and their tetra-*O*-acetyl derivatives have been measured. With the exceptions of *o*-nitrophenyl α- and β-D-glucopyranoside and tetra-*O*-acetyl-β-D-glucopyranoside all the compounds examined showed only slight dependence of optical rotation on temperature. Possible causes of the large temperature-dependence for the three above-named glucosides are discussed.

An exception to Hudson's second isorotation rule [2] was noted by Montgomery *et al.*[3] who found that the $2B_{Ac}$ value calculated from the observed optical rotations of the *o*-nitrophenyl tetra-*O*-acetyl-D-glucopyranosides was high owing to the anomalous positive rotation of the β-anomer. [Values for the *m*- and *p*-nitrophenyl glucoside acetates were unexceptional.] The result was confirmed by Pigman [4] who showed in addition that the acetylated 2,4- and 2,6-dinitrophenyl β-D-glucopyranosides had anomalous positive rotations. He found that these high rotations decrease rapidly on elevation of temperature and at 150° they approach the values expected from application of Hudson's rules. The effect also occurs in the D-galactoside series since Snyder and Link [5] showed that *o*-nitrophenyl tetra-*O*-acetyl-β-D-galactopyranoside also has an anomalous positive rotation and a high variation of optical rotation with temperature. Further they

Table 1.

2,3,4,6-Tetra-*O*-acetyl derivatives of aryl β-D-glucosides.

Aglycone	M. p.	$[\alpha]_D$ in $CHCl_3$ (*c*)	Literature values: M. p.	Literature values: $[\alpha]_D$ in $CHCl_3$	Ref.
Group A					
o-Nitrophenyl	159—161°	+43·2° (1·98)	160·5—161·5°	+43·0°	*A*
o-Chlorophenyl	149—151	−50·2 (1·02)	149—150	−51·6	*B*
o-Bromophenyl *	149—151	−53·7 (1·0)	—	—	
o-Iodophenyl	159—161	−57·4 (1·0)	154—155	−48·2	*C*
1-Naphthyl	177—178	−76·4 (0·5)	178—179	−72	*D*
Group B					
o-Acetylphenyl	150—152	−49·9 (0·97)	151—152·5	—	*E*
			148—150	−43	*F*
o-Methoxycarbonylphenyl	158—159	−31·1 (1·0)	160·5	−29·3	*G*
2,6-*Dibromophenyl* †	132—134	−8·0 (1·0)	—	—	—
Group C					
Phenyl	125—126	−22·5 (1·0)	124—125	−22·0	*D*
2-Naphthyl	134—135	−20·2 (3·0)	135—136	−19	*D*
p-Bromophenyl	132—133	−18·5 (2·9)	133	−17·8	*H*
m-Chlorophenyl ‡	112—114	−21·8 (1·1)	131·5—133·5	−22·8	*B*
			112·5	−25·3	*I*

* Found: C, 48·1; H, 4·65; Br, 15·8; Ac, 34·0. $C_{20}H_{23}BrO_{10}$ requires C, 47·7; H, 4·6; Br, 15·9; Ac, 34·2%. † Found: C, 41·0; H, 3·9; Br, 27·6. $C_{20}H_{22}Br_2O_{10}$ requires C, 41·3; H, 3·8; Br, 27·5%. ‡ Recryst. from methanol.

Refs.: (*A*) Latham, May, and Mosettig, *J. Org. Chem.*, 1950, **15**, 884. (*B*) Nath and Rydon, *Biochem. J.*, 1954, **57**, 1. (*C*) Jermyn, *Austral. J. Chem.*, 1955, **8**, 403. (*D*) Helferich and Schmitz-Hillebrecht, *Ber.*, 1933, **66**, 378. (*E*) Jerzmanowska and Markiewicz, *Roczniki Chem.*, 1956, **30**, 59. (*F*) Helferich, Scheiber, Streeck, and Vorsatz, *Annalen*, 1935, **518**, 211. (*G*) Helferich and Lutzmann, *Annalen*, 1939, **537**, 11. (*H*) Hurd and Bonner, *J. Amer. Chem. Soc.*, 1945, **67**, 1764. (*I*) Bonner, Kubitshek, and Drisko, *J. Amer. Chem. Soc.*, 1952, **74**, 5082.

[1] Part I, Overend, Peacocke, and Smith, *J.*, 1961, 3487.
[2] Hudson, *J. Amer. Chem. Soc.*, 1909, **31**, 66.
[3] Montgomery, Richtmyer, and Hudson, *J. Amer. Chem. Soc.*, 1942, **64**, 690.
[4] Pigman, *J. Res. Nat. Bur. Stand.*, 1944, **33**, 129.
[5] Snyder and Link, *J. Amer. Chem. Soc.*, 1953, **75**, 1758.

demonstrated that *o*-nitrophenyl β-D-gluco-, β-D-galacto-, and α-L-arabino-pyranoside have temperature coefficients of optical rotation of the same order of magnitude as their fully acetylated derivatives, but in each case the optical rotation increased rather than decreased with increase of temperature.

Pigman considered that steric interaction between the *o*-nitro-group and the substituents attached to the asymmetric centres of the pyranoid ring was probably responsible for such anomalous effects. At room temperature these interactions would prevent the molecule from assuming some of the conformations which it could take up in the absence of the *o*-nitro-substituent in the aglycone, and if each conformation makes a contribution to the optical rotation an anomalous value would be expected. At higher temperatures thermal energy would counteract the steric interactions and the optical rotation would change to a value more in accord with expectation. In the present work this problem has been examined further and the temperature coefficients of optical rotation of a number of *ortho*-substituted aryl D-glucopyranosides have been measured.

TABLE 2.

Aryl D-glucopyranosides.

Aglycone	M. p.	$[\alpha]_D$ (*c* in H_2O)	Literature values M. p.	Literature values $[\alpha]_D$ (H_2O)	Ref.	Periodate uptake [n] (mol.)
α-Anomers						
p-Nitrophenyl	213—215°	+222° (0·42)	216°	+215°	3	1·90
o-Nitrophenyl	184—186	+228 (0·46)	186—188	+206	3	1·89
β-Anomers						
Phenyl	172—173	−73·7 (0·92)	175—176 171—172	−71·9 —	*J* *B*	1·88
2-Naphthyl (+H_2O) [m]	188—190	—	188	−26·7 (95% Me_2CO)	*K*	1·87
,, (anhyd.) [a]	191—192	−77·3 (0·73 in 96% EtOH)	183	−88	*C*	
p-*Bromophenyl*						
(+H_2O) [b]	179—181	—	—	—	—	
(anhyd.) [c]	179—181	−69·9 (1·0)	—	—	—	1·86
m-*Chlorophenyl*						
(+2H_2O) [d]	179—181	—	—	—	—	1·94
(anhyd.) [e]	179—181	−85 (0·5)	179—180	−36·3	*B*	
o-Nitrophenyl.....	169—171	−116 (0·64)	168—170 152	−140·4 −106	*B* 3	1·80
o-Aminophenyl [f]	174—176	−70·3 (0·93)	183·5—184·5	−71·2	*A*	—
o-Chlorophenyl	170—171	−80·7 (0·63)	170—171	−90·6	*B*	1·76
o-*Bromophenyl* [g]	149—150	−65 (0·9)	—	—	—	1·87
o-Iodophenyl [h]	162—163	−58·5 (1·1)	156	−48·5	*C*	1·83
1-*Naphthyl* [i]	174—175	−94·3 (0·68)	—	—	—	1·84
o-Acetylphenyl [j]	152—153	−66 (0·98)	152—154	−66·5	*F*	1·81
o-Methoxycarbonyl-phenyl [k]	106—108	−67·7 (0·89)	107	−64·4	*G*	1·84
2,6-*Dibromophenyl* [l] ...	176—178	±0 (0·5) −2·0 (96% EtOH)	—	—	—	1·79

[a] Obtained by heating the monohydrate *in vacuo* over phosphoric oxide at 120°. [b] Found: C, 41·4; H, 4·8; H_2O, 3·95. $C_{12}H_{15}BrO_6$,0·75H_2O requires C, 41·3; H, 4·8; H_2O, 3·9%. [c] Obtained by heating the hydrate at 110° *in vacuo* over phosphoric oxide (Found: C, 43·1; H, 4·5; Br, 24·1. $C_{12}H_{15}BrO_6$ requires C, 43·0; H, 4·5; Br, 23·8%). [d] Found: C, 44·3; H, 6·1; H_2O, 11·0. $C_{12}H_{15}ClO_6$,2H_2O requires C, 44·1; H, 5·9; H_2O, 11·0%. [e] Obtained by heating the dihydrate at 110° *in vacuo* over phosphoric oxide (Found: C, 49·7; H, 5·1; Cl, 12·0. Calc. for $C_{12}H_{15}ClO_6$: C, 49·6; H, 5·2; Cl, 12·2%). [f] Recryst. from ethyl acetate–ethanol. The literature constants refer to a hydrate of composition $C_{12}H_{17}NO_6$,0·75H_2O. [g] Found: C, 43·2; H, 4·5; Br, 23·2%. [h] Recryst. from ethanol. [i] Found: C, 62·8; H, 5·95. $C_{16}H_{18}O_6$ requires C, 62·7; H, 5·9%. Recryst. from ethyl–acetate ethanol. [j] Recryst. from ethyl acetate–ethanol. [k] Recryst. from ethanol. [l] Recryst. from ethanol–water (Found: C, 34·9; H, 3·4; Br, 38·3. $C_{12}H_{14}Br_2O_6$ requires C, 34·8; H, 3·4; Br, 38·6%). [m] Recrystallised from ethanol–water. [n] Formaldehyde was not produced in any of the oxidations.

Refs.: *A*—*G*, see Table 1. (*J*) Fischer and von Mechel, *Ber.*, 1916, **49**, 2813. (*K*) Robertson and Waters, *J.*, 1930, 2729.

The compounds examined are listed in Tables 1 and 2. They were prepared according to the methods outlined in the Experimental section. That the aryl D-glucosides listed in Table 2 had the pyranoside structure was proved by periodate oxidation (see Table 2).

The optical rotations were measured over a range of about 50° and for all the compounds studied the specific rotations were plotted against temperature, yielding good straight lines. The rates of variation of specific rotation per degree Centigrade were calculated from the slopes of these lines. These rates were corrected for the rates of change of optical rotation arising from concentration changes on expansion of the solvent by means of the known temperature-variation of the densities of the solvents. These corrected values are shown in Table 3.

TABLE 3.

Temperature-dependence of optical rotation.

Aglycone	$d[\alpha]_D/dT$ for acetylated D-glucopyranoside in $(CHCl_2)_2$	$d[\alpha]_D/dT$ for D-glucopyranoside in water	Aglycone	$d[\alpha]_D/dT$ for acetylated D-glucopyranoside in $(CHCl_2)_2$	$d[\alpha]_D/dT$ for D-glucopyranoside in water
α-Anomer			*β-Anomer*		
o-Nitrophenyl...	+0·021°(0·50)	−0·67° (0·45)	*m*-Chlorophenyl	+0·033°(1·99)	+0·14° (0·50)
p-Nitrophenyl...	+0·044 (0·49)	−0·17 (0·40)	*p*-Bromophenyl	+0·033 (2·00)	+0·08 (1·00)
β-Anomer			2,6-Dibromophenyl	−0·003 (2·00)	0·00 (0·50)
Phenyl	+0·023 (1·50)	+0·065 (0·92)	*o*-t-Butylphenyl	+0·042 (1·50)	+0·085 * (1·03)
o-Nitrophenyl...	−0·37 (2·02)	+0·72 (0·63)	*o*-Methoxycarbonylphenyl...	+0·061 (0·99)	+0·15 (0·89)
o-Aminophenyl	+0·052 (1·51)	+0·10 (0·945)	*o*-Acetylphenyl	+0·007 (1·49)	+0·11 (0·98)
o-Chlorophenyl	+0·034 (1·50)	+0·13 (0·63)	1-Naphthyl ...	+0·025 (1·00)	+0·12 (0·68)
o-Bromophenyl	+0·020 (1·49)	+0·11 (0·90)	2-Naphthyl ...	+0·023 (2·01)	+0·046 † (0·725)
o-Iodophenyl ...	+0·041 (1·50)	+0·093 (1·11)			

* Solvent: 50% (v/v) aqueous ethanol. † Solvent: 96% (w/w) aqueous ethanol.
The values in parentheses are concentrations.

With the exceptions of *o*-nitrophenyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucoside and 2,6-dibromophenyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucoside, all the acetylated aryl β-D-glucopyranosides examined showed a change in optical rotation to a less negative value on heating from room temperature to 70°. The changes are all approximately similar in magnitude to that of phenyl tetra-*O*-acetyl-β-D-glucopyranoside in which the aglycone is unsubstituted. The specific rotations of 2,6-dibromophenyl β-D-glucopyranoside and its tetra-acetate both showed negligible change on elevation of temperature. The result obtained for *o*-nitrophenyl tetra-*O*-acetyl-β-D-glucopyranoside was similar to that reported by Pigman [4] who used nitrobenzene as solvent. Variation in the nature or site of substitution of the halogen atom in monohalogenophenyl β-D-glucopyranoside or the tetra-*O*-acetate had no significant effect on the temperature coefficient of optical rotation. Although 1-naphthyl tetra-*O*-acetyl-β-D-glucopyranoside has a high (negative) specific rotation (−72·5°) at room temperature, when the glycoside was heated the change in rotation proceeded at a rate similar to that for the corresponding unsubstituted phenyl glycoside. Both *o*- and *p*-nitrophenyl tetra-*O*-acetyl-α-D-glucopyranoside showed normal rates of variation of optical rotation with temperature.

The optical rotations of all the aryl β-D-glucopyranosides studied, except 2,6-dibromophenyl β-D-glucopyranoside, became less negative with increasing temperature. Apart from *o*-nitrophenyl β-D-glucopyranoside the rates of variation of specific rotation of these compounds were all of the same magnitude. (As with the corresponding acetylated compounds the largest rate was found for *o*-methoxycarbonylphenyl β-D-glucoside.) *o*-Nitrophenyl β-D-glucopyranoside gave a large temperature variation of specific rotation which was in good agreement with that given by Snyder and Link.[5] (Our value of 0·72° per degree Centigrade can be compared with a value of 0·75° obtained when Snyder and Link's results are corrected for density changes.)

Pigman and Isbell [6] have pointed out that when a group which is *meta*-directing in aromatic electrophilic substitution is substituted in the aglycone of phenyl β-D-glucopyranoside the molecular rotation of the *para*-isomer is appreciably greater than that of the *ortho*-form (see Table 4). At higher temperatures we find that the nitro-group follows the pattern shown by other *meta*-directing groups at room temperature. Also, at the higher temperatures the values of the molecular rotations of *o*- and *p*-nitrophenyl β-D-glucoside tend towards those found for other *meta*-directing groups at room temperature. Therefore, like its acetylated derivative *o*-nitrophenyl β-D-glucopyranoside has an unusually high rotation at room temperature.

TABLE 4.

Molecular rotations of some substituted phenyl β-D-glucopyranosides.[6]

Subst.	CO_2H	CO_2Me	$CH_2{\cdot}CN$	Ac	CHO	NO_2 at 20°	NO_2 at 70°
ortho-Posn. ...	−18,400°	−20,200°	−19,700°	−19,800°	−18,000°	−34,900°	−24,100°
para-Posn. ...	−24,400°	−24,500°	−21,000°	−28,100°	−26,900°	−32,200°	−29,800° *

* Calc. by extrapolation of the results cited in ref. 5.

From these results it appears that the anomaly under discussion cannot arise entirely from steric interaction resulting from the presence of a large substituent in the *ortho*-position of the aglycone (cf. Pigman [4] and Snyder and Link [5]). If this were the true explanation replacement of the nitro-substituent by a t-butyl, acetyl, methoxycarbonyl, or iodo-group would not be expected greatly to alter the anomaly. In fact it destroys the effect. A large group located *ortho* to a nitro-group causes it to be twisted out of the plane of the benzene ring.[7] An asymmetric group (*e.g.*, glucosyl) would induce further asymmetry into the molecule as the nitro-group would be more likely to be twisted one way than the other. This could be a possible cause of the anomalous optical rotation of the *o*-nitrophenyl glycosides. In this case, on increase of temperature steric interactions would be reduced and the optical rotatory behaviour would become normal. It is difficult, however, to reconcile this explanation with the results obtained with some of the other *ortho*-substituted glycosides. It is difficult to escape the conclusion that the reason for the odd behaviour of the *o*-nitrophenyl glycosides resides in some property of the nitro-group, other than shape or size. It may be that the powerful N–O dipole results in an interaction between the nitro-group and the sugar moiety. This interaction would be repulsive if it were between the nitro-group and the C–O dipole of an acetate group, but attractive if between a nitro-group and a hydroxyl group. It will be recalled that *o*-nitrophenyl glucopyranoside and its tetra-acetate differ in the sign of the temperature coefficients of optical rotation. In the present state of knowledge, however, this explanation must remain speculative.

EXPERIMENTAL

Aryl Tetra-O-acetyl-β-D-glucopyranosides.—The majority of the compound are listed in Table 1. The glycosides in group A were obtained by heating together (under reflux for 4—6 hr.) tetra-*O*-acetyl-α-D-glucopyranosyl bromide, an excess of potassium carbonate, and a slight excess of the appropriate phenol in anhydrous acetone. The products were precipitated by addition of water and cooling to 0°, and recrystallised from ethanol or ethanol–acetone. The compounds in group B were prepared by cooling and triturating a mixture of tetra-*O*-acetyl-α-D-glucopyranosyl bromide (0·025 mol.), the appropriate phenol (0·03 mol.), silver oxide (0·022 mol.), and quinoline (0·08 mol.). After storage in a desiccator for 30 min. with stirring every 10 min. the mixture was extracted with glacial acetic acid (40 ml.). In each case the product was precipitated by pouring the extract into water (400 ml.) at 0° and was recrystallised from ethanol. The tetra-acetates in group C were synthesised by heating penta-*O*-acetyl-β-D-glucopyranose (0·075 mol.), the phenol (0·32 mol.), and toluene-*p*-sulphonic acid

[6] Pigman and Isbell, *J. Res. Nat. Bur. Stand.*, 1941, **27**, 9.

[7] See M. Wepster in "Progress in Stereochemistry," ed. by Klyne and de la Mare, Butterworths Scientific Publ., London, 1958, Vol. II, pp. 99—156.

(1 g.) at 110°/15 mm. for 1·5 hr. Benzene (200 ml.) was added and the solution was washed successively with water, several times with 10% sodium hydroxide, and water. The benzene layer was dried (Na_2SO_4) and evaporated at 15 mm. to give a residue which recrystallised from ethanol. *o*-t-Butylphenyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucoside, m. p. 189—191°, $[\alpha]_D^{23}$ −34·7° (*c* 0·98 in $CHCl_3$) {Nath and Rydon [8] give m. p. 191°, $[\alpha]_D^{22}$ −34·8° (in $CHCl_3$)}, was prepared similarly except that heating was prolonged to 2 hr. and the excess of *o*-t-butylphenol was removed by distillation *in vacuo* as it is not very soluble in alkali. *o*-Aminophenyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucoside (78%), m. p. 131—133°, $[\alpha]_D^{21}$ −34·1° (*c* 1·1 in MeOH), −26·9° (*c* 1·0 in $CHCl_3$) {Latham *et al.*[9] give m. p. 132—133°, $[\alpha]_D^{20}$ −33·9° (in MeOH)}, was prepared by the reduction of *o*-nitrophenyl tetra-*O*-acetyl-β-D-glucopyranoside (3 g.) in 1,4-dioxan (100 ml.) at room temperature and atmospheric pressure with hydrogen and Raney nickel. The product was isolated in standard manner and recrystallised from ethanol.

Aryl Tetra-O-*acetyl*-α-D-*glucopyranosides*.—*o*- and *p*-Nitrophenyl 2,3,4,6-tetra-*O*-acetyl-α-D-glucoside {m. p. 101—103°, $[\alpha]_D^{20}$ +178° (*c* 0·49 in $CHCl_3$), and m. p. 109—110°, $[\alpha]_D^{24}$ +170·4° (*c* 0·21 in $CHCl_3$) respectively} were prepared by heating penta-*O*-acetyl-α-D-glucopyranose (0·075 mol.) and the nitrophenol (0·35 mol.) with zinc chloride (7 g.) in a mixture (22 ml.) of acetic anhydride (5 vol.) and acetic acid (95 vol.) at 125° for 1 hr. under a vacuum. Benzene (200 ml.) was added and the solution was washed successively with water, 5% sodium hydroxide solution (several times), and water. Evaporation of the dried (Na_2SO_4) benzene layer afforded a syrup which was triturated and recrystallised from ethanol. An attempt to prepare *o*-chlorophenyl 2,3,4,6-tetra-*O*-acetyl-α-D-glucoside by this route (except that the reaction was not carried out under reduced pressure) yielded the β-isomer. If the time of heating was increased to 1·5 or 4 hr., only oily products could be isolated. Likewise, when *o*-bromophenol was used with this method, only the β-form of *o*-bromophenyl 2,3,4,6-tetra-*O*-acetyl-D-glucoside was obtained.

Aryl D-*Glucopyranosides*.—The aryl tetra-*O*-acetyl-D-glucopyranosides were deacetylated in methanol by the Zemplén–Pacsu procedure. The compounds listed in Table 2 were obtained. Except where indicated the products were recrystallised from water. *o*-t-Butylphenyl β-D-glucoside was obtained only in syrupy form, $[\alpha]_D^{20}$ −58·5° (*c* 1·0 in 50% EtOH–H_2O).

Periodate Oxidations.—The glycosides were oxidised with 0·015M-sodium metaperiodate and the uptake of oxidant was measured according to Aspinall and Ferrier's procedure.[10] The results are shown in Table 2. The glycosides were then oxidised with the reagent according to O'Dea and Gibbons's method [11] to determine whether formaldehyde was produced in the reaction.

Solvent.—Technical *sym*-tetrachloroethane was distilled over sodium hydrogen carbonate, and the fraction, b. p. 145—148°, was collected and stored over sodium hydrogen carbonate.

Procedure.—The optical rotations were measured with a Hilger polarimeter with a sodium lamp as light source. Lagged 2 dm. jacketed polarimeter tubes were used, through which water from a thermostat (control to ±0·2°) was circulated. The initial temperature of the solution (20·0° or 25·0°) was increased by steps of 5° to a final value of 70°. To measure the temperature of the solution a thermometer was inserted through the centre-filling aperture of the polarimeter tube. When equilibrium was reached for each temperature, the thermometer was removed and the rotation of the solution recorded. The rotation of every solution studied always returned to within ±0·01° of its initial value, when the solution was cooled to room temperature, showing that the process is completely reversible.

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[8] Nath and Rydon, *Biochem. J.*, 1954, **57**, 1.
[9] Latham, May, and Mosettig, *J. Org. Chem.*, 1950, **15**, 884.
[10] Aspinall and Ferrier, *Chem. and Ind.*, 1957, 1216.
[11] O'Dea and Gibbons, *Biochem. J.*, 1953, **55**, 580.