926. *The Preparation and Properties of Aryl 2-Deoxy-α-D-glucopyranosides.*

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A number of aryl 2-deoxy-α-D-glucopyranosides have been prepared and their properties investigated. These compounds are less stable towards acidic hydrolysis than the corresponding alkyl derivatives.

A LARGE variety of aryl β-D-glucopyranosides has been prepared through the Koenigs–Knorr [1-3] and the Helferich and Schmitz-Hillebrecht [4] reactions and their properties have been investigated. The corresponding α-anomers, however, are not generally available.[3,5] The Helferich and Schmitz-Hillebrecht reaction, which consists of heating the acetylated sugars with a phenol in presence of an acidic catalyst (toluene-*p*-sulphonic acid or zinc chloride), usually gives an αβ-mixture from which the α-anomer often cannot be isolated.[5] We have found with 1 : 3 : 4 : 6-tetra-*O*-acetyl-2-deoxy-α-D-glucose that this reaction proceeds very readily and provides a variety of aryl 2-deoxy-α-D-glucopyranoside triacetates which can be easily deacetylated by the Zemplén method.[6] The products thus obtained include phenyl 2-deoxy-α-D-glucopyranoside first prepared by Helferich and Iloff [7] by the same method, and other substituted phenyl derivatives used in the following investigations, and listed in Table 4.

The alkaline hydrolysis of phenyl glycosides is facilitated by the anchimeric assistance [8] of a *trans*-hydroxyl group at position 2 and by electron-attracting substituents in the phenyl group. Consequently *p*-nitrophenyl α-D-glucopyranoside is hydrolysed by hot alkaline solutions while the corresponding phenyl derivative shows extreme resistance.[9,10] Treatment of phenyl and *p*-nitrophenyl 2-deoxy-α-D-glucopyranoside with 0·1N-sodium hydroxide at 100° produced a similar result. In the absence of a

[1] Koenigs and Knorr, *Ber.*, 1901, **34**, 957.
[2] Fischer and Mechel, *Ber.*, 1916, **49**, 2813.
[3] Helferich and K.-H. Jung, *Annalen*, 1954, **589**, 77.
[4] Helferich and Schmitz-Hillebrecht, *Ber.*, 1933, **66**, 378.
[5] Bonner, Kubitshek, and Drisko, *J. Amer. Chem. Soc.*, 1952, **74**, 5082.
[6] Zemplén and Pacsu, *Ber.*, 1929, **62**, 1613.
[7] Helferich and Iloff, *Z. physiol. Chem.*, 1933, **221**, 252.
[8] Ballou, *Adv. Carbohydrate Chem.*, 1954, **9**, 59.
[9] Nath and Rydon, *Biochem. J.*, 1954, **57**, 1.
[10] Montgomery, Richtmyer, and Hudson, *J. Amer. Chem. Soc.*, 1943, **65**, 3.

2-hydroxyl group the nitrophenyl glycoside was hydrolysed rapidly, and the corresponding unsubstituted derivative remained unchanged.

The rate of acidic hydrolysis of glycosides is affected by the modification of the carbohydrate moiety as well as by the aglycone group. It has been shown that phenyl glucopyranosides are hydrolysed faster than the corresponding methyl glucopyranosides [11] and, further, the normal glycosides are more stable towards acidic hydrolysis than are the corresponding 2-deoxy-glycosides.[12,13] The rate of hydrolysis of the 2-deoxy-α-D-glucopyranosides with N-hydrogen chloride at 20° (Table 1) reflects the additive effect of these two factors, which results in the rapid acidic hydrolysis of phenyl 2-deoxy-α-D-glucopyranoside.

TABLE 1. *Acidic hydrolysis of 2-deoxy-α-D-glucosides.*

Glycoside	10^4k (sec.$^{-1}$)
Methyl 2-deoxy-α-D-glucopyranoside	2·2
Methyl 2-deoxy-α-D-glucopyranuronoside amide	1·1
p-Aminophenyl 2-deoxy-α-D-glucopyranoside	84·3
Phenyl 2-deoxy-α-D-glucopyranoside	181·6

Detailed investigation of the rate of acidic hydrolysis of other available aryl 2-deoxy-α-D-glucosides was made difficult by their insolubility in cold aqueous acid and their extremely rapid hydrolysis at elevated temperatures. However it was possible to determine the time required for the optical rotation of these compounds to reach a constant value on hydrolysis with 0·001N-hydrochloric acid at 100°. The results (Table 2) indicate the effect of the substituents.

TABLE 2. *Acidic hydrolysis of aryl 2-deoxy-α-D-glucopyranosides.*

Aryl group	(Me)	*p*-$NO_2{\cdot}C_6H_4$	*p*-C_6H_4Cl	1-$C_{10}H_7$	*p*-C_6H_4Me	Ph
Time (min.)	(165)	35	15	11	10	6

The above results are in general agreement with those obtained by Nath and Rydon,[9] indicating that, in contrast with the alkaline hydrolysis, the acidic hydrolysis of the phenyl glucosides is facilitated by electron-repelling substituents in the benzene ring.

TABLE 3. *Optical rotation of normal and 2-deoxy-α-D-glucopyranosides.*

	2-Deoxyglucoside			Normal glucoside			Diff.	
Aglycone	$[\alpha]_D$	$[M']_D$	Solv.	$[\alpha]_D$	$[M]_D$	Solv.	$[M]_D - [M']_D$	Ref
Me	135°	24,000°	H_2O	158·9°	30,800°	H_2O	6800	[a]
Et	120	23,200	,,	152	31,800	,,	8600	13, [b]
Ph	161	38,600	MeOH	180·8	46,300	,,	7700	2
p-C_6H_4Me	166	42,200	,,	178	48,100	,,	5900	[c]
p-$NH_2{\cdot}C_6H_4$	181	46,200	,,	194·1	52,600	MeOH	6400	[d]
p-$NO_2{\cdot}C_6H_4$	210	59,800	,,	215	64,700	H_2O	4900	[e]
			Acetyl derivatives					
Ph	142	52,000	$CHCl_3$	168·7	64,400	$CHCl_3$	12,400	[c]
p-C_6H_4Me	136·6	51,900	MeOH *	162	64,200	,,	12,300	[c]
p-C_6H_4Cl	150	60,100	$CHCl_3$	165·5	69,000	,,	8900	5
p-$NO_2{\cdot}C_6H_4$	179	73,600	,,	200	85,400	,,	11,800	[e]

* Not strictly comparable owing to solvent differences.

[a] Hughes, Overend, and Stacey, *J.*, 1949, 2846; Rüber, *Ber.*, 1924, **57**, 1797. [b] Ferguson, *J. Amer. Chem. Soc.*, 1932, **54**, 4086. [c] Nisizawa, *Bull. Chem. Soc. Japan*, 1941, **16**, 155. [d] Goebel, Babers, and Avery, *J. Exp. Med.*, 1932, **55**, 761. [e] Montgomery, Richtmyer, and Hudson, *J. Amer. Chem. Soc.*, 1942, **64**, 690.

In Table 3 the molecular optical rotations of the 2-deoxy-α-D-glucopyranosides are compared with those of the corresponding α-D-glucopyranosides. The difference between each pair is between 4900 and 8600 for the free glycosides and 8900 and 12,400 for the acetylated derivatives. According to the theories of optical rotation [14] these should represent

[11] Heidt and Purves, *J. Amer. Chem. Soc.*, 1944, **66**, 1385.
[12] Overend, Shafizadeh, and Stacey, *J.*, 1950, 671.
[13] Butler, Laland, Overend, and Stacey, *J.*, 1950, 1433.
[14] Whiffen, *Chem. and Ind.*, 1956, 964.

the contribution of the asymmetry at position 2 of the normal glucosides to the total molecular rotation.

Experimental

1 : 3 : 4 : 6-*Tetra*-O-*acetyl*-2-*deoxy*-α-D-*glucose*.—2-Deoxy-D-glucose (7 g.) was added to a mixture of dry pyridine (40 c.c.) and freshly distilled acetic anhydride (25 c.c.) and kept at 0°. After 3 days, when the sugar had completely dissolved, the solution was poured into water and extracted with chloroform. The extract was washed with 1% sulphuric acid, dilute sodium hydrogen carbonate, and finally water. After drying ($MgSO_4$), the solvent was removed by evaporation and the residue evaporated again with absolute alcohol. The syrupy **1 : 3 : 4 : 6**-tetra-*O*-acetyl-2-deoxy-α-D-glucose crystallised on trituration with ethanol and was repeatedly recrystallised from the same solvent. In some experiments extraction was eliminated by seeding the aqueous solution and filtering the crystals which separated on storage. The product (8·4 g.) had m. p. 108—109°, $[\alpha]_D^{19}$ +105° (*c* 0·8 in MeOH) (Overend, Stacey, and Stanek [15] give m. p. 91° and $[\alpha]_D^{20}$ +12·3°; Helferich and Iloff [7] give m. p. 109—110°, $[\alpha]_D^{21}$ +109°) (Found: C, 50·8; H, 5·9. Calc. for $C_{14}H_{20}O_9$: C, 50·6; H, 6·1%).

Phenyl 2-*Deoxy*-α-D-*glucopyranoside Triacetate*.—**1 : 3 : 4 : 6**-Tetra-*O*-acetyl-2-deoxy-α-D-glucose (2·2 g.) and phenol (2 g.) were heated with powdered anhydrous zinc chloride (0·4 g.), with vigorous stirring, at 70° for 35 min. At intervals the acetic acid generated was removed under diminished pressure. The mixture was extracted with benzene (100 c.c.), and the extract filtered, repeatedly washed with 5% sodium hydroxide solution and water, dried ($MgSO_4$), and evaporated to a syrup which crystallised on trituration with ethanol. Recrystallisation from ethanol afforded phenyl 2-deoxy-α-D-glucopyranoside triacetate as large cubes (0·9 g.), m. p. 90°, $[\alpha]_D^{18}$ +141° (*c* 1·12 in MeOH), +142° (*c* 3·58 in $CHCl_3$) (Helferich and Iloff [7] give m. p. 87—88°, $[\alpha]_D^{21}$ +146°) (Found: C, 59·1; H, 6·0. Calc. for $C_{18}H_{22}O_8$: C, 59·0; H, 6·0%).

Phenyl 2-*Deoxy*-α-D-*glucopyranoside*.—Phenyl 2-deoxy-α-D-glucopyranoside triacetate (0·4 g.) was dissolved in dry methanol (25 c.c.), sodium (0·06 g.) was added, and the whole left for 18 hr. at room temperature, then treated with carbon dioxide and evaporated to dryness. The residue was extracted with methanol, and the extract evaporated to a syrup which readily crystallised. Recrystallisation from ethanol afforded phenyl 2-deoxy-α-D-glucopyranoside as needles (0·21 g.), m. p. 163·5°, $[\alpha]_D^{20}$ +161° (*c* 0·52 in MeOH) {Helferich and Iloff [7] give m. p. 162—163°, $[\alpha]_D$ +159° (in H_2O)} (Found: C, 60·2; H, 6·7. Calc. for $C_{12}H_{16}O_5$: C, 60·0; H, 6·7%).

TABLE 4. *Aryl* 2-*deoxy*-α-D-*glucopyranosides*.

No.	2-Deoxy-α-D-glucopyranoside	Yield (%)	Shape	No.	2-Deoxy-α-D-glucopyranoside	Yield (%)	Shape
	Triacetates				*Free glycosides*		
1	*p*-Tolyl	44	Powder	8	*p*-Tolyl	82	Plates
2	*p*-Chlorophenyl	54	Needles	9	*p*-Chlorophenyl	94	Needles
3	*o*-Chlorophenyl	23	Plates	10	*o*-Chlorophenyl	73	Powder
4	*p*-Hydroxyphenyl	9·5	Needles	11	*p*-Nitrophenyl	93	Needles
5	*m*-Hydroxyphenyl	27	Plates	12	α-Naphthyl	89	Needles
6	*p*-Nitrophenyl	37	Needles				
7	α-Naphthyl	31	Conglomerates				

				Found (%)				Required (%)		
No.	M. p.	$[\alpha]_D$ (in MeOH)	Temp.	C	H	N	Formula	C	H	N
1	209—205°	+136·6°	15°	60·0	6·3	—	$C_{19}H_{24}O_8$	60·0	6·3	—
2	133	143	16	53·9	5·2	—	$C_{18}H_{21}O_8Cl$	54·0	5·2	—
3	84—85	109	16	54·1	5·2	—	$C_{18}H_{21}O_8Cl$	54·0	5·2	—
4	154	159	18	56·7	6·0	—	$C_{18}H_{22}O_9$	56·5	5·8	—
5	109—110	126·5	17	56·5	5·4	—	$C_{18}H_{22}O_9$	56·5	5·8	—
6	140—141	170	18	51·7	5·2	3·5%	$C_{18}H_{21}O_{10}N$	52·6	5·1	3·4%
7	85	140	19	63·6	5·7	—	$C_{22}H_{24}O_8$	63·5	5·8	—
8	170	166	19	61·6	6·8	—	$C_{13}H_{18}O_5$	61·5	7·1	—
9	204—205	158	16	52·6	5·3	—	$C_{12}H_{15}O_5Cl$	52·6	5·5	—
10	151—153	123	16	52·0	5·4	—	$C_{12}C_{15}O_5Cl$	52·6	5·5	—
11	173—174	210	19	50·5	5·0	4·7	$C_{13}H_{15}O_7N$	50·5	5·3	4·9
12	157	53·6	19	65·3	6·1	—	$C_{16}H_{18}O_5$	65·1	6·2	—

[15] Overend, Stacey, and Staněk, *J.*, 1949, 2841.

Substituted Phenyl 2-Deoxy-α-D-glucopyranosides.—The compounds listed in Table 4 were prepared essentially by the process described for phenyl 2-deoxy-α-D-glucopyranoside triacetate and its deacetylated product.

p-*Aminophenyl 2-Deoxy-α-D-glucopyranoside.*—*p*-Nitrophenyl 2-deoxy-α-D-glucopyranoside (0·5 g.) in methanol (30 c.c.) was shaken with Raney nickel in an atmosphere of hydrogen. After 2 hr. the reaction was complete. The solution was then filtered and evaporated. Recrystallisation of the residue from methanol–ethyl acetate afforded p-*aminophenyl 2-deoxy-α-D-glucopyranoside* as long plates (0·36 g.), m. p. 179°, $[\alpha]_D$ +181° (*c* 0·54 in MeOH) (Found: C, 55·9; H, 6·8; N, 5·6. $C_{12}H_{17}O_5N$ requires C, 56·5; H, 6·7; N, 5·5%).

Alkaline Hydrolysis of p-*Nitrophenyl 2-Deoxy-α-D-glucopyranoside.*—*p*-Nitrophenyl 2-deoxy-α-D-glucopyranoside (16 mg.) was dissolved in 0·1N-sodium hydroxide (20 c.c.) and kept at 100° under efficient reflux to ensure a constant concentration. At short intervals samples (1 c.c.) were withdrawn, diluted with cold water (9 c.c.), and cooled at 0°. The colour intensity of these light yellowish-green solutions was measured with a Spekker electrophotometer with Ilford filter No. 601. The extent of the hydrolysis was determined by comparing the results with the absorption curve of sodium *p*-nitrophenoxide, previously obtained by measuring a set of standard solution as described by Dyfverman and Lindberg.[16] The results are as follows:

Time (min.)	0	5	10	20	41	60	85	100
Hydrolysis (%)	—	14·4	34·4	54·9	75·1	86·7	98·4	100

Under identical conditions phenyl 2-deoxy-α-D-glucopyranoside remained unaffected and showed a constant optical rotation.

Acid Hydrolysis.—(a) *At room temperature.* Methyl 2-deoxy-α-D-glucopyranuronoside amide, methyl 2-deoxy-α-D-glucopyranoside, phenyl 2-deoxy-α-D-glucopyranoside, and *p*-aminophenyl 2-deoxy-α-D-glucopyranoside were dissolved in N-hydrochloric acid, and their rates of hydrolysis were followed polarimetrically at room temperature (19° ± 1°). The results obtained are summarised in the annexed Tables.

Methyl 2-deoxy-α-D-"glucuronamide" (*c* 0·96)

Time (hr.)	0	6½	18½	51	66	91	120	163	195	384
$[\alpha]_D^{18-20}$	114·5	106	98	77	68·8	58·4	54·2	47·7	43·7	39·5
Hydrolysis (%)	0	11·3	22	50	60·9	74·8	80·4	90	94·4	100

Methyl 2-deoxy-α-D-glucopyranoside (*c* 0·77)

Time (hr.)	0	6	19	27	43	51	66	79	98	268
$[\alpha]_D^{18-20}$	134	118	95	84·4	6·3	61·1	53·2	48	46·8	41·5
Hydrolysis (%)	0	17·4	42·2	53·6	73·1	78·8	87·3	92·9	94·2	100

p-*Aminophenyl 2-deoxy-α-D-glucopyranoside* (*c* 0·27)

Time (min.)	0	30	50	98	145	180	205	380
$[\alpha]_D^{18}$	180	92·6	88·8	59·2	44·5	37	33·3	29·6
Hydrolysis (%)	0	58	60	80	88·3	90	97	100

Phenyl 2-deoxy-α-D-glucopyranoside (*c* 0·27)

Time (min.)	0	6	19	34	45	59	101	136
$[\alpha]_D^{18}$	161	126	85	59	52	44·5	33·4	29·6
Hydrolysis (%)	0	26·5	57·6	77	83	88	96	100

(b) *At* 100°. The glycosides (70 mg.) were dissolved in hot 0·002N-hydrochloric acid (25 c.c.) and kept at 100° under very efficient reflux to ensure a constant volume. At short intervals aliquot parts (2 c.c.) were withdrawn and rapidly cooled at 0°. When hydrolysis was advanced enough to allow the measurement of the optical rotation, without unchanged material crystallising, the rate of hydrolysis was followed polarimetrically to the final constant rotation. The results obtained are given in Table 2.

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[16] Dyfverman and Lindberg, *Acta Chem. Scand.*, 1950, **4**, 878.