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Peroxide-induced Rearrangement of Carbohydrate Acetals

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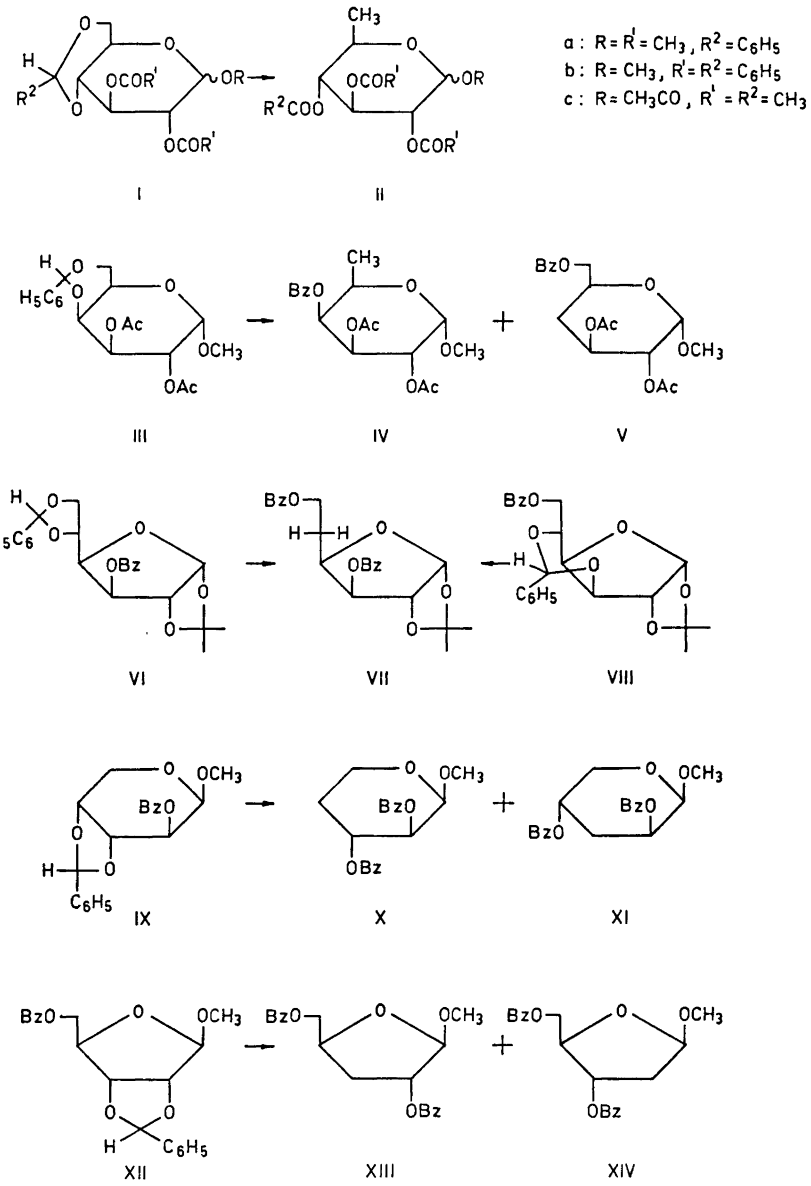
When acetylated methyl 4,6-*O*-benzylidene-α-D-glucopyranoside is treated with di-*tert*-butyl peroxide a rearrangement takes place to a methyl 6-deoxy-α-D-glucopyranoside. A similar treatment of methyl 4,6-*O*-benzylidene-α-D-galactopyranoside yields a mixture of 6-deoxy-galactoside and 4-deoxy-D-*xylo*-hexopyranoside. 3-*O*-Benzoyl-5,6-*O*-benzylidene-1,2-*O*-isopropylidene-α-D-glucofuranose and 6-*O*-benzoyl-3,5-*O*-benzylidene-1,2-*O*-isopropylidene-α-D-glucofuranose both give a 5-deoxy-D-*xylo*-hexofuranose as the main product. Methyl 5-*O*-benzoyl-2,3-*O*-benzylidene-β-D-ribofuranoside forms a mixture of 2- and 3-deoxy-D-*erythro*-pentofuranosides when heated with peroxide.

It has been reported that cyclic acetals, when heated with di-*tert*-butyl peroxide, will undergo a radical–induced rearrangement to give carboxylic esters. Thus Huyser and Garcia [1] found that 2-phenyl-1,3-dioxolane could be rearranged into ethyl benzoate. This type of rearrangement has also been achieved by an acetone sensitized photochemical reaction.[2–4] If such reactions could be applied to cyclic acetals derived from carbohydrates they would provide a convenient route for the preparation of deoxy-sugars since many carbohydrate acetals are readily available.

The photochemically induced rearrangement has actually been attempted in the sugar series by Matsuura *et al.*[5] who subjected methyl 2,3-*O*-benzylidene-β-D-ribofuranoside to photolysis. They, however, did not isolate any deoxyribose derivatives, but found that methyl 2- or 3-*O*-benzoyl-β-D-ribofuranoside had been formed. We have found that cyclic acetals of carbohydrates will undergo peroxide induced rearrangement to give deoxy-sugars in moderate yields.

Thus, when methyl 2,3-di-*O*-acetyl-4,6-*O*-benzylidene-α-D-glucopyranoside (Ia) was heated with di-*tert*-butyl peroxide at 140°C for 7 h methyl 2,3-di-*O*-acetyl-4-*O*-benzoyl-6-deoxy-α-D-glucopyranoside (IIa) was obtained in 41 % yield. The isomeric 4-deoxy-D-*xylo*-pyranoside (V) was not found. The corresponding dibenzoate (Ib) under similar conditions gave methyl tri-*O*-benzoyl-α-D-quinonopyranoside (IIb) in 27 % yield.



In these experiments di-*tert*-butyl peroxide was used in excess, thus serving as a solvent. The yields were rather low due to radical or thermally induced decomposition of the products. Since the benzoate (Ib) was rather insoluble in di-*tert*-butyl peroxide it was attempted to dilute the reaction mixture with

chlorobenzene, which has a boiling point (132°C) at which the peroxide decomposes to radicals at a reasonable rate.[6] This did, however, not improve the yield of (IIb). Attempts to rearrange unacylated compounds, such as methyl 4,6-*O*-benzylidene-α-D-glucopyranoside, were not successful because of the low solubility of such compounds in di-*tert*-butyl peroxide and in chlorobenzene.

In analogy with the results described above treatment of 4,6-*O*-ethylidene-tri-*O*-acetyl-β-D-glucopyranose (Ic) with di-*tert*-butyl peroxide gave tetra-*O*-acetyl-6-deoxy-β-D-glucopyranose (IIc).

Whereas the glucose derivatives (I) gave only 6-deoxy-compounds treatment of methyl di-*O*-acetyl-4,6-*O*-benzylidene-α-D-galactopyranoside (III) with di-*tert*-butyl peroxide yielded a mixture of methyl 2,3-di-*O*-acetyl-4-*O*-benzoyl-6-deoxy-α-D-galactopyranoside (IV) and methyl 2,3-di-*O*-acetyl-6-*O*-benzoyl-4-deoxy-α-D-*xylo*-hexopyranoside (V) with the latter predominating.

The two benzylidene derivatives (VI) and (VIII), both derived from 1,2-*O*-isopropylidene-α-D-glucofuranose, were found to react more readily with peroxide than the pyranose derivatives described above. Thus (VI) and (VIII) had disappeared completely after treatment with peroxide for 3 – 6 h at 120°C whereas most of the pyranose derivatives required *ca.* 20 h. Both (VI) and (VIII) gave 3,6-di-*O*-benzoyl-5-deoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranose (VII) as the main product, and only traces of the isomeric 6-deoxy-D-glucofuranose and 3-deoxy-D-*ribo*-hexofuranose derivatives, which could arise from (VI) and (VIII), respectively, were found.

Methyl-2-*O*-benzoyl-3,4-*O*-benzylidene-β-D-arabinopyranoside (IX) required 20 h heating with di-*tert*-butyl peroxide for complete conversion and gave a mixture of the 4- and the 3-deoxy-pentosides (X) and (XI). These could not be separated; but chromatography of the debenzoylated product gave methyl 4-deoxy-β-D-*threo*-pentopyranoside and methyl 3-deoxy-β-D-*threo*-pentopyranoside, identical with those described by Hanessian *et al.*[7,8]

The reaction of methyl 5-*O*-benzoyl-2,3-*O*-benzylidene-β-D-ribofuranoside (XII) with di-*tert*-butyl peroxide was completed within 3 h at 120°C and gave a 55 % yield of a product which consisted mainly of methyl 2,5-di-*O*-benzoyl-3-deoxy-β-D-*erythro*-pentofuranoside (XIII) mixed with a small amount of the 2-deoxy-ribose derivative (XIV). The two compounds could not be separated; but chromatography of the debenzoylated product gave 8 % methyl 2-deoxy-β-D-*erythro*-pentofuranoside, identified as its di-*p*-nitrobenzoate,[9] and 33 % methyl 3-deoxy-β-D-*erythro*-pentofuranoside. The latter was converted into the pure dibenzoate (XIII).[10]

The rearrangements described above probably follow the pathway suggested for 2-substituted 1,3-dioxolanes.[1] The initial step is an abstraction of the acetalic hydrogen atom followed by rearrangement of the cyclic radical thus formed. Recombination with a hydrogen atom finally yields the deoxy-sugar.

Attempts to carry out the rearrangement with dibenzoyl peroxide, in boiling benzene or chlorobenzene, were unsuccessful; only unreacted starting material was found. We also tried to carry out a photochemically induced rearrangement[2–4] by irradiation of the benzylidene derivative (Ia), or the ethylidene derivative (Ic), in acetone solution with a medium pressure mercury lamp. However, no reaction took place in the course of 24 h.

EXPERIMENTAL

Thin layer chromatography (TLC) was performed on silica gel PF_{254} (Merck); for preparative work 1 mm layers were used on 20 × 40 cm plates. NMR spectra were obtained on Varian A-60 or HA-100 instruments.

Di-tert-*butyl peroxide* was a commercial product. It was kept for 24 h over potassium hydroxide and distilled *in vacuo* before use.

Methyl-2,3-di-O-*acetyl-4*-O-*benzoyl-6-deoxy*-α-D-*glucopyranoside* (*IIa*). A mixture of methyl 2,3-di-*O*-acetyl-4,6-*O*-benzylidene-α-D-glucopyranoside [11] (450 mg) and di-*tert*-butyl peroxide (1.0 ml) was stirred magnetically while heated to 140°C in an oil bath for 7 h. Evaporation *in vacuo* gave a residue which was purified by preparative TLC, using ether – pentane (1:2) as eluent, to give 185 mg (41 %) of (IIa) as a colourless syrup, $[\alpha]_D^{23} = +59.4°$ (*c* 6, $CHCl_3$). (Found: C 59.16; H 6.12. Calc. for $C_{18}H_{22}O_8$: C 59.00; H 6.05). An NMR spectrum (Table 1) was in agreement with the proposed structure.

Methyl tri-O-*benzoyl-6-deoxy*-α-D-*glucopyranoside* (*IIb*). Methyl 2,3-di-*O*-benzoyl-4,6-*O*-benzylidene-α-D-glucopyranoside (Ib) [11] (327 mg) and di-*tert*-butyl peroxide (1.0 ml) were heated to 160°C for 20 h. Evaporation *in vacuo* gave a dark syrup which was separated into two components by preparative TLC (ether – pentane 1:2). The fast moving compound was the 6-deoxy-compound (IIb) 88 mg (27 %), which was recrystallized from methanol, m.p. 142 – 143°C, $[\alpha]_D^{23} = +52.0°$ (*c* 2.3, $CHCl_3$) (reported [12] m.p. 146 – 147°C, $[\alpha]_D = +57°$). NMR spectral data are given in Table 1.

In a separate experiment (Ib) (336 mg) was dissolved in chlorobenzene (8 ml); *ca.* 4 ml was then distilled off and peroxide (1.0 ml) was added. The solution was heated at a bath temperature of 135°C and monitored by TLC (ether – pentane 1:2). After 7 h starting material was still present; more peroxide (0.5 ml) was added and the heating was continued over night (23 h total). Work up as described above gave 110 mg (32 %) of (IIb), m.p. 140 – 141°C.

Tetra-O-*acetyl-6-deoxy-β*-D-*glucopyranose* (*IIc*). Tri-*O*-acetyl-4,6-*O*-ethylidene-β-D-glucopyranose (Ic) [13] (403 mg) was heated to 125°C for 20 h with peroxide (2.0 ml). The solvent was evaporated and the residue was purified by preparative TLC (benzene – ethyl acetate 4:1). The main fraction gave 93 mg (23 %) of (IIc) which was recrystallized from ether – pentane, m.p. 144 – 145°C, $[\alpha]_D = +20.0°$ (*c* 2.2, $CHCl_3$) [reported [14] m.p. 145°C, $[\alpha]_D^{24} = +22°$ (*c* 4, $CHCl_3$)].

In a separate experiment 2.16 g of (Ic) was heated with peroxide (6.0 ml) to 125°C for 24 h. Evaporation of the peroxide gave a syrup which contained a trace of the starting material (Ic) as seen from an NMR spectrum. The product was dissolved in ether and treated with activated carbon, the ether was evaporated and the residue was crystallized from methanol to give 225 mg (10 %) of (IIc), m.p. 134 – 138°C. The material in the mother liquor was purified by preparative TLC, using two elutions with ethyl acetate-pentane (1:4), to give an additional 526 mg (24 %) of (IIc), m.p. 128 – 135°C.

Rearrangement of methyl di-O-*acetyl-4,6*-O-*benzylidene*-α-D-*galactopyranoside (III)*. A mixture of (III) [15] (362 mg) and peroxide (1.0 ml) was heated to 120°C for 8 h. The product was separated into two fractions by preparative TLC (ether – pentane 1:1). The fast moving fraction gave 58 mg (16 %) of methyl 2,3-di-*O*-acetyl-4-*O*-benzoyl-6-deoxy-α-D-galactopyranoside (IV), crystallized from methanol, m.p. 76 – 77°C, $[\alpha]_D = +187°$ (*c* 3, $CHCl_3$); (Found: C 59.17; H 5.96. Calc. for $C_{18}H_{22}O_8$: C 59.00; H 6.05).

The slow moving fraction gave 91 mg (25 %) of methyl 2,3-di-*O*-acetyl-6-*O*-benzoyl-4-deoxy-α-D-*xylo*-hexopyranoside (V) as a syrup, $[\alpha]_D^{21} = +111°$ (*c* 4.6, $CHCl_3$). (Found: C 59.43; H 6.44). NMR spectral data of (IV) and (V) are given in Table 1.

Rearrangement of 3 -O-*benzoyl-5,6*-O-*benzylidene-1,2*-O-*isopropylidene*-α-D-*glucofuranose* (*VI*). The peroxide (2.0 ml) and (VI) [16] (418 mg) was heated to 120°C for 3 h. Preparative TLC with ether – pentane (1:4) as eluent gave two fractions. The fast moving fraction gave 32 mg (8 %) of a compound which, as seen from an NMR spectrum, was 3,5-di-*O*-benzoyl-6-deoxy-1,2-*O*-isopropylidene-α-D-glucofuranose. It was not investigated further.

The next fraction gave 3,6-di-*O*-benzoyl-5-deoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranose (VII) as a syrup, 189 mg (45 %), $[\alpha]_D^{23} = -27.0°$ (*c* 7.8, $CHCl_3$). (Found: C 66.85; H 5.98; Calc. for $C_{23}H_{24}O_7$; C 66.99; H 5.87). Its NMR spectrum (Table 1) was identical with that of a compound prepared by benzoylation of 5-deoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranose.[17]

Table 1. NMR spectra of deoxy-sugars in deuteriochloroform. Chemical shifts (δ-values) and coupling constants (Hz).

Compound	H 1	H 2	H 3	H 4	H 5	H 6	$-OCH_3$	$-OAc$
αIIa	~4.9	~4.95	5.08	5.66	4.03	1.25	3.44	1.68
	$J_{12}=4$	$J_{23}=9.5$	$J_{34}=9.5$	$J_{45}=9.8$	$J_{56}=6.5$			2.08
αIIb	5.18	5.28	6.14	5.36	4.2	1.35	3.47	
	$J_{12}=3.8$	$J_{23}=9.5$	$J_{34}=9.5$	$J_{45}=9.5$	$J_{56}=6.3$			
βIIc	5.74	4.87	5.26	5.12	3.75	1.25		2.04, 2.08
	$J_{12}=8$	$J_{23}=9$	$J_{34}=9.5$	$J_{45}=9.5$	$J_{56}=6.5$			2.15
IV	5.1	5.3	5.58	5.6	4.3	1.28	3.48	1.98
	$J_{12}=3.4$	$J_{23}=10$	$J_{34}=3$	$J_{45}=0.6$	$J_{56}=6.6$			2.1
V	4.94	4.80	5.31	4a=1.67	4.2	4.3–4.45	3.68	1.97
	$J_{12}=3.8$	$J_{23}=10$	$J_{34e}=5.5$	4e=2.24	$J_{4e5}=2.5$	$J_{56}\simeq 3$		2.0
			$J_{34a}=11.5$	$J_{4a4e}=12$	$J_{4a5}=12$	$J_{56}'\simeq 4$		
VII	5.98	4.68	5.45	~4.6	H5=H5′=2.2	4.3–4.6	$H_3C-C-CH_3$	
	$J_{12}=3.7$	$J_{23}=0$	$J_{34}=2.8$	$J_{45}=J_{45}'=6.6$	$J_{56}=6.6$	$J_{66}'=13.6$	1.55, 1.34	
X	5.1	5.28	5.73	4a=2.4	5a=3.95		3.43	
	$J_{12}=3.5$	$J_{23}=10.0$	$J_{34a}=10.6$	4e=2.63	5e=3.75	$J_{4e4a}=12.3$		
			$J_{34e}=5.4$	$J_{4e5e}=2.2$	$J_{4e5a}=2.8$	$J_{5a5e}=12.3$		
XI	5.05	5.5	2.3–2.6	~5.6	5a=4.0			
	$J_{12}=3.6$	$J_{23}=5.8$	$J_{35e}=1.6$	$J_{45a}=1.7$	5e=3.8			
		$J_{23}'=10.8$	$J_{45e}=1.6$	$J_{5a5e}=12.8$				
XIII	5.08	5.43	3=2.05*b*, 3′=1.83*b*	~4.75	H5=4.5			
	$J_{12}=0$	$J_{23}'=1.4b$	$J_{34}=8.5b$	$J_{45}=4.1$	H5′=4.6			
	$J_{23}=4.6^b$	$J_{33}'=14.5b$	$J_{3'4}=7.0b$	$J_{45}'=6.2$	$J_{55}'=11.8$			
[a]	5.27	H2=2.63	5.69	4.8–4.4			3.4	
	$J_{12}=2.4$	H2′=2.44	$J_{22}'=14$	$J_{2'3}=5.0$	$J_{34}=2.4$			
	$J_{12}'=5.0$		$J_{23}=7.0$					

[a] Methyl 2-deoxy-3,5-di-*O*-*p*-nitrobenzoyl-β-D-*erythro*-pentofuranoside. [b] in benzene solution.

Rearrangement of 6-O-benzoyl-3,5-O-benzylidene-1,2-O-isopropylidene-α-D-glucofuranose (VIII). A mixture of (VIII)[18] (502 mg) and peroxide (2.0 ml) was heated at 125°C for 6 h. The product was separated into 3 fractions by preparative TLC using 2 elutions with ethyl acetate-pentane (1:4). The fast moving zone gave the 5-deoxy-compound (VII) (152 mg, 32 %), identical with the product described above as seen from an NMR spectrum. The next fraction contained unchanged (VIII) (47 mg, 9 %). The slow moving fraction yielded 47 mg (9 %) of a product which was not investigated closely. An NMR spectrum indicated that it was 5,6-di-*O*-benzoyl-3-deoxy-1,2-*O*-isopropylidene-α-D-*ribo*-hexofuranose.

Rearrangement of methyl 2-O-benzoyl-3,4-O-benzylidene-β-D-arabinopyranoside (IX). A mixture of (IX)[19] (293 mg) and peroxide (1.0 ml) was heated to 125°C for 20 h. Preparative TLC (ether – pentane 1:2) gave 104 mg (36 %) of a product which was a mixture of two deoxy-compounds as seen from NMR spectra. They could not be separated completely. The NMR spectra (Table 1) were measured on almost pure products, obtained after several chromatographic separations.

In a separate experiment (IX) (1.0 g) and peroxide (6.0 ml) were kept at 120°C for 20 h. The peroxide was then evaporated and the residue was debenzoylated with sodium methoxide in methanol. After neutralisation with Amberlite IR-120 and evaporation a brown syrup was obtained. This was separated into 2 fractions by preparative TLC (chloroform – methanol 9:1). The fast moving fraction (109 mg) was rechromatographed to give 54 mg (19 %) of methyl 4-deoxy-β-D-*threo*-pentopyranoside as a syrup, $[\alpha]_D^{23} = -157°$ (*c* 2, MeOH) (reported [7] $[\alpha]_D = -151°$).

The slow moving fraction gave 135 mg which was also rechromatographed. This gave 90 mg (22 %) of methyl 3-deoxy-β-D-*erythro*-pentopyranoside as a syrup, $[\alpha]_D^{23} = -176°$ (*c* 4, MeOH) (reported [7] $[\alpha]_D = -176°$). NMR spectra of the two products in D_2O confirmed their structures. Their mass spectra were identical with those reported by Hanessian.[7,8]

Rearrangement of methyl 5-O-benzoyl-2,3-O-benzylidene-β-D-ribofuranoside (XII). (XII)[20] (234 mg) was heated with peroxide (1 ml) at 120°C for 4 h. The product was purified by preparative TLC (ether – pentane 1:2) to give 135 mg (56 %) of a product which was shown from NMR spectra to consist mainly of methyl 2,5-di-*O*-benzoyl-3-deoxy-β-D-*erythro*-pentofuranoside (XIII) and a small amount of the 2-deoxy-compound (XIV). These two could not be separated.

In a separate experiment 1.5 g of (XII) was heated with peroxide (5.0 ml) to 120°C for 4 h. The product was debenzoylated as described above and the debenzoylated material was chromatographed on a column of silica gel (75 g) using chloroform-methanol (9:1) as eluent.

The first fraction (54 mg, 8 %) gave an NMR spectrum in D_2O which showed that it was methyl 2-deoxy-β-D-*erythro*-pentofuranoside. It was treated with *p*-nitrobenzoyl chloride (250 mg) in pyridine (5 ml) and worked up in the usual way to give 157 mg (8 %) of methyl 2-deoxy-3,5-di-*O*-*p*-nitrobenzoyl-β-D-*erythro*-pentofuranoside. The product was purified by preparative TLC (ether – pentane 1:2) and crystallized from benzene-pentane, m.p. 142 – 143°C, $[\alpha]_D^{23} = -5.9°$ (*c* 5, $CHCl_3$) (reported [9] m.p. 143 – 144°C, $[\alpha]_D = -5.4$).

The next fraction (52 mg, 8 %) was a mixture of 2- and 3-deoxy-compounds. The third fraction (204 mg, 33 %) was shown by NMR spectra in D_2O to be methyl 3-deoxy-β-D-*erythro*-pentofuranoside. Benzoylation with benzoyl chloride (0.5 ml) in pyridine (5 ml) gave 408 mg (27 %) of (XIII) which was recrystallized from ether – pentane, m.p. 80 – 81°C, $[\alpha]_D = -33°$ (*c* 2.2, $CHCl_3$) [reported [10] m.p. 80 – 81, $[\alpha]_D = -32°$ (*c* 1.7, $CHCl_3$)]

Microanalyses were performed by Dr. A. Bernhardt.

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