Acta Chemica Scandinavica B 28 (1974) 853—856

Conversion of Penta-*O*-acetyl-1,2-*O*-isopropylidene-*aldehydo*-D-glucose into Tri-*O*-acetyl-2,3-dideoxy-*aldehydo*-D-*erythro*-hex-2-enose

KLAUS BOCK AND CHRISTIAN PEDERSEN

Department of Organic Chemistry, Technical University of Denmark, DK-2800 Lyngby, Denmark

Acetolysis of 3,5,6-tri-*O*-acetyl-1,2-*O*-isopropylidene-α-D-glucofuranose gave 1-*R*-1,3,4,5,6-penta-*O*-acetyl-1,2-*O*-isopropylidene-*aldehydo*-D-glucose (*2*) and a small amount of the 1-*S*-isomer (*3*). Treatment of (*2*) with hydrogen bromide in acetic acid yielded mainly *trans*-4,5,6-tri-*O*-acetyl-2,3-dideoxy-*aldehydo*-D-*erythro*-hex-2-enose (*4*). Besides, a small amount of 2,3,5,6-tetra-*O*-acetyl-D-glucofuranose was formed. The mechanism of the formation of (*4*) is discussed.

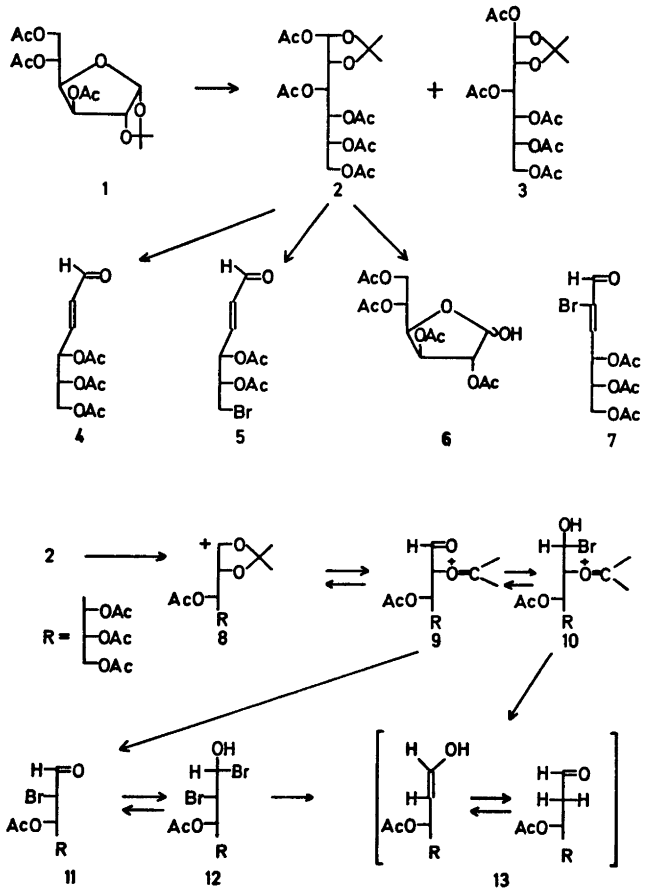

Table 1. Proton NMR spectra in deuteriochloroform. Chemical shifts are in ppm and observed 1st order coupling constants in Hz.

Compound	H1	H2	H3	H4	H5	H6	H6′	J_{12}	J_{23}	J_{24}	J_{34}	J_{45}	J_{56}	$J_{56'}$	$J_{66'}$
2	6.25	4.35	5.38	5.46	5.14	4.15	4.24	2.2	4.9		2.9	8.5	3.0	4.0	12.5
3	6.36	4.18	5.62	5.28	5.04	4.2–4.3		3.8	7.2		1.7	9.0	3.1	3.1	
4	9.60	6.30	6.75	5.80	5.30	4.32	4.22	7.2	15.4	1.5	4.9	4.9	4.4	6.0	12.2
5	9.58	6.30	6.72	5.81	5.28	3.4–3.6		7.2	15.4	1.4	5.0	5.0	4.6	6.0	
7	9.26		7.04	6.05	5.45	4.20	4.30				7.8	4.8	4.6	5.8	12.0

Both Brigl and Zerrweck [1] and Schlubach *et al.*[2] have shown that acetolysis of tri-*O*-acetyl-1,2-*O*-isopropylidene-α-D-glucofuranose (*1*) gives a crystalline product in good yield, and several structures were proposed for this product. In a recent paper Magnani and Mikuriya [3] have shown by NMR spectroscopy that the product is an *aldehydo*-D-glucose derivative, (*2*) or (*3*).

We have also studied the acetolysis of (*1*) and obtained the same product as that described by the above mentioned authors. In addition, we isolated a minor amount of an isomeric material. Proton NMR spectra of the two products (Table 1) show that they both contain an isopropylidene group and five *O*-acetyl groups in agreement with structures (*2*) and (*3*), as found by Magnani and Mikuriya [3] for the major product. The low field position of H4 in both products rule out the furanose structure proposed by Schlubach *et al.*[2] The main product (*2*) has $J_{12}=2.2$ Hz whereas J_{12} of the minor product (*3*) is 3.8 Hz. This indicates a *trans* orientation of H1 and H2 in (*2*) and a *cis* orientation in (*3*). On this basis the configuration of C1 in (*2*) is assumed to be *R* and that of (*3*) is *S*. ^{13}C NMR data (Table 2) further confirm the structures.

In connection with other work (*2*) was treated with hydrogen bromide in acetic acid for 24 h. This gave an unstable mixture which was hydrolysed with water and silver carbonate. From the product thus obtained was isolated 45 % of the unsaturated aldehyde (*4*). Besides, small amounts of the 6-bromo-aldehyde (*5*) and of tetra-*O*-acetyl-D-glucofuranose (*6*) were obtained. The structure of (*4*) was proved through ^{1}H and ^{13}C NMR spectra (Tables 1 and 2) and

Table 2. ^{13}C NMR spectra in deuteriochloroform. Chemical shifts are in ppm relative to internal tetramethylsilane.

Compound	C1	C2	C3	C4	C5	C6	O–C–O	C–$(CH_3)_2$		H_3C–C=O
1	104.6	88.7	74.2	76.3	67.1	62.9	112.1	26.5	25.9	20.3
2	95.8	80.7	68.5[a]	68.2[a]	68.0[a]	61.4	113.0	26.5	26.3	20.6 20.1
3	93.3	77.5	68.5[a]	68.1[a]	67.6[a]	61.2	111.9	27.8	25.7	20.3
4	191.6	132.9	147.6	70.5[a]	70.1[a]	61.0				
5	191.6	133.6	147.8	72.0[a]	71.2[a]	28.9				
7	184.6	130.4	144.7	70.8[a]	70.3[a]	61.4				

[a] Assignment may be reversed.

by comparison with an authentic sample prepared according to Fraser-Reid and Radatus.[4]

The first step in the reaction of (*2*) with hydrogen bromide in acetic acid is probably a protonation followed by loss of acetic acid to give (*8*) which could rearrange to (*9*). The latter type of ion has been described by Barton *et al.*[5] Since (*9*) contains a good leaving group it could react with bromide ions to give (*11*) which, in the presence of HBr, would be in equilibrium with (*12*). NMR spectra directly on the reaction mixture show no aldehydic protons, indicating that (*12*) is favoured; this also applies to the equilibrium between (*9*) and (*10*) (see below). Reaction of the latter with bromide ions could result in elimination of bromine and formation of (*13*). Alternatively, (*9*) would be in equilibrium with (*10*) which, by a similar reaction with bromide ions, could give (*13*), bromine, and acetone. It is also possible that (*10*) could yield (*11*) by migration of bromine from C1 to C2 with simultaneous displacement of acetone. Bromoacetone was found in the reaction product, and it is probably formed in a secondary reaction between the bromine eliminated from (*10*) or (*12*) and acetone.

The 2-deoxy-aldehyde (*13*) is probably the final product from the reaction of (*2*) with hydrogen bromide in acetic acid. It loses acetic acid to some extent when the reaction mixture is worked up, and the elimination is completed by the subsequent treatment with water and silver carbonate.

When (*2*) was allowed to react with hydrogen bromide in acetic acid for only 1 h the 2-bromo-aldehyde (*7*) could be isolated together with a rather large amount of (*6*). The latter is probably formed by hydrolysis of the ions (*9*) or (*10*) during work up, followed by acyl-migration and ring-closure. After 24 h reaction (*7*) could not be found. Since it must arise from (*11*) by elimination of acetic acid during work up the latter would appear to be present in the initial stage of the reaction, as proposed above, but disappears later as it is converted into (*13*) *via* (*12*).

When pure (*7*) was treated with HBr in acetic acid for 24 h in the presence of acetone it gave (*4*) after work up. In the absence of acetone the main product was unreacted (*7*) and only small amounts of (*4*) were formed. The first step must be addition of HBr to (*7*) followed by elimination of bromine which then reacts with acetone.

The conclusion is that (*13*) is formed from (*9*) or (*10*) *via* the 2-bromo-compound (*11*), or to some extent, directly from (*10*) by elimination of bromine and acetone.

Pure (*7*) was prepared in good yield by reaction of (*4*) with bromine followed by elimination of HBr by treatment with silver carbonate and water.

EXPERIMENTAL

Melting points are uncorrected. Proton NMR spectra were obtained on Varian A-60 and HA-100 instruments, ^{13}C spectra on a Bruker WH-90 instrument. Thin layer chromatography (TLC) was performed on silica gel PF_{254} (Merck); for preparative work 1 mm layers on 20 × 40 cm plates were used. Spots were visualized with UV light or by charring with a hot wire.

*Acetolysis of tri-*O*-acetyl-1,2-*O*-isopropylidene-α-*D*-glucofuranose.* A mixture of (*1*) (40.0 g) and powdered, anhydrous $ZnCl_2$ (11.0 g) was dissolved in acetic anhydride (80 ml) by stirring at 0 °C. The solution was kept at +5° for 24 h. Ice and water was then added and the mixture was stirred until the oily precipitate had crystallized. The product was then filtered off, washed with water and dried. The crude material (40 g) was shown by NMR spectroscopy to be a mixture of (*2*) and (*3*) in a *ca.* 12:1 ratio. Two recrystallizations from ethanol gave 29.0 g (56 %) of 1-*R*-1,3,4,5,6-penta-*O*-acetyl-1,2-*O*-isopropylidene-*aldehydo*-D-glucose (*2*), m.p. 136–138 °C. Further recrystallizations from ethanol and from ether-pentane did not change the m.p., $[\alpha]_D^{22}$ +58.3° (*c* 3.0, $CHCl_3$). (Reported[1] m.p. 141 °C, $[\alpha]_D$ +60.5°).

In two experiments fractional crystallization of the material in the mother liquor gave a small amount of the 1-*S*-isomer (*3*), m.p. 139–140 °C, $[\alpha]_D^{20}$ −19.0° (*c* 1.4, $CHCl_3$). (Found: C 50.94; H 6.22. Calc. for $C_{19}H_{28}O_{12}$; C 50.88; H 6.29). Attempts to repeat the isolation of (*3*) from the mother liquors of other preparations of (*2*) were unsuccessful.

Preparation of (*2*) from (*1*) by treatment with acetic anhydride and sulfuric acid, as described by Schlubach *et al.*,[2] gave lower yields than those obtained when zinc chloride was used.

Reaction of (*2*) with hydrogen bromide in acetic acid

For 24 h. The isopropylidene-derivative (*2*) (820 mg) was dissolved in 8 ml of glacial acetic acid containing 30 % HBr and the solution was kept at room temp. for 24 h. It was then diluted with dichloromethane and washed with water and aqueous sodium hydrogencarbonate, dried ($MgSO_4$) and evaporated. The residue in acetone

(6 ml) was stirred over night with water (0.5 ml) and silver carbonate (1.0 g). Filtration through activated carbon and evaporation gave a crude product which was separated into 3 fractions by preparative TLC using ether-pentane (3:1) as eluent. The fastest moving fraction gave 35 mg (6.5 %) of the 6-bromo-compound (*5*) as a *cis-trans* mixture in a 2/5 ratio. The product was a syrup and the two isomers could not be separated, λ_{max} 217 nm (ethanol). Proton and ^{13}C NMR data are given for the *trans* isomer in Tables 1 and 2.

The next fraction gave 220 mg (45 %) of 4,5,6-tri-*O*-acetyl-2,3-dideoxy-*aldehydo*-D-*erythro-trans*-hex-2-enose (*4*) as a syrup, $[\alpha]_D^{20}$ +25.3° (*c* 4.3, $CHCl_3$), λ_{max} 217 nm (ethanol) (reported [4] $[\alpha]_D$ +12.0°, λ_{max} 217 nm). A 2,4-dinitrophenylhydrazone had m.p. 111–112 °C (reported [4] m.p. 108–109 °C). Proton and ^{13}C NMR data were identical with those of an authentic sample prepared according to Ref. 4.

The slowest moving fraction gave 53 mg (9 %) of tetra-*O*-acetyl-D-glucofuranose (*6*) which was acetylated to give the pentaacetate as a 1:2 mixture of the α- and β-anomers. Proton NMR spectra were identical with those of previously described compounds.[6]

Isolation of bromoacetone. A solution of (*2*) (5.0 g) in HBr–HOAc (8 ml) was kept for 24 h at room temp. Dichloromethane (75 ml) was then added and the solution was washed twice with water and once with aqueous $NaHCO_3$ and dried ($MgSO_4$). The dichloromethane was distilled off through a Vigreux column and the residue was distilled at 50 mmHg pressure. A fraction of 1.0 g was collected, b.p. 40 °C. This lachrymatory product consisted of a mixture of bromoacetone and acetic acid. A proton NMR spectrum gave signals at δ 2.4 and 4.0 and a ^{13}C spectrum at 27.1, 35.7, and 199.5 ppm. Both spectra were identical with those of an authentic sample.

B. For 1 h. A solution of (*2*) (1.0 g) in HBr-HOAc (10 ml) was kept for 1 h at room temp. and then worked up. The product was treated with water and silver carbonate as described above. The crude product (737 mg) was purified by preparative TLC (ether-pentane 3:1). The main fraction (332 mg) was a mixture of (*4*) and the 2-bromo-compound (*7*) as seen from an NMR spectrum. The ratio between (*4*) and (*7*) varied from 1:2 to 1:5 in different experiments. It was not possible to separate the two compounds and (*7*) was therefore only identified by comparing proton NMR spectra of the mixture with those of pure (*7*) and (*4*).

Another fraction gave 170 mg (22 %) of (*6*), characterized through its NMR spectrum.

4,5,6-Tri-O-*acetyl-2-bromo-2,3-dideoxy*-aldehydo-D-erythro-*hex-2-enose* (*7*). To a solution of (*4*) (350 mg) in tetrachloromethane (5 ml) was added a solution of bromine (0.08 ml) in tetrachloromethane (1.4 ml) and the solution was kept for 10 min at room temp. Silver carbonate (2.0 g) and acetonitrile (15 ml) were then added and the mixture was stirred for 1 h. The silver salts were filtered off, the solvent was removed and the residue was dissolved in dichloromethane and washed with aqueous $NaHCO_3$, dried and evaporated. Preparative TLC (ether-pentane 3:1) gave 195 mg (43 %) of (*7*) as a syrup, $[\alpha]_D^{20}$ +24.5° (*c* 0.84, $CHCl_3$), λ_{max} 235 nm (ethanol). The compound was unstable and a satisfactory analysis could therefore not be obtained. NMR spectral data (Tables 1 and 2) were in agreement with the structure. A mass spectrum showed no molecular peak, but two peaks at *m/e* 290 and 292, resulting from loss of acetic acid and showing that bromine was present.

Conversion of (*7*) *to* (*4*). A mixture of (*7*) (260 mg), HBr in acetic acid (3 ml), and acetone (0.2 ml) was kept for 24 h at room temp. It was then worked up and treated with silver carbonate and water as described above. The product was separated into two fractions by preparative TLC. The fast moving fraction gave 20 mg (8 %) of the 6-bromo-aldehyde (*5*). The slow moving fraction gave 107 mg (49 %) of (*4*). Both products were characterized through their NMR spectra.

Microanalyses were performed by Novo Microanalytical Laboratory.

REFERENCES

1. Brigl, P. and Zerrweck, W. *Ber. Deut. Chem. Ges. 66* (1933) 936.
2. Schlubach, H. H., Rauchenberger, W. and Schultze, A. *Ber. Deut. Chem. Ges. 66* (1933) 1248.
3. Magnani, A. and Mikuriya, J. *Carbohyd. Res. 28* (1973) 158.
4. Fraser-Reid, B. and Radatus, B. *J. Amer. Chem. Soc. 92* (1970) 5288.
5. Barton, D. H. R., Magnus, P. D., Smith, G., Streckert, G. and Zurr, D. *J. Chem. Soc. Perkin Trans. 1* (1972) 542.
6. Bock, K. and Pedersen, C. *Acta Chem. Scand. 26* (1972) 2360.

Received March 6, 1974.