Carbohydrate Research, 36 (1974) 191–195

Note

A new reaction of sugar orthoesters: rearrangement into anhydrides

ALEXEY F. BOCHKOV, IVAN V. OBRUCHNIKOV, VLADIMIR N. CHERNETSKY, AND NIKOLAY K. KOCHETKOV

N. D. Zelinsky Institute of Organic Chemistry, Academy of Sciences of U.S.S.R., Moscow (U.S.S.R.)

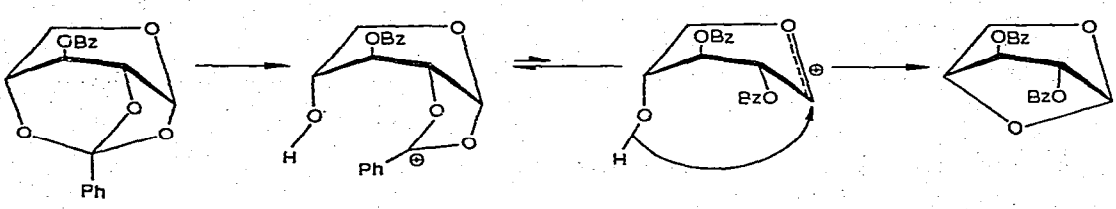
(Received January 7th, 1974; accepted for publication, January 16th, 1974)

Derivatives of α-D-xylopyranose 1,2,4-orthoesters (*e.g.*, **1**) isomerize[1] into 1,5-anhydro-β-D-xylofuranose derivatives (*e.g.*, **2**) under the conditions of the orthoester method of glycosylation[2,3]. We now report on the similar behaviour of 3-*O*-acetyl-β-L-arabinofuranose 1,2,5-orthobenzoate (**3**).

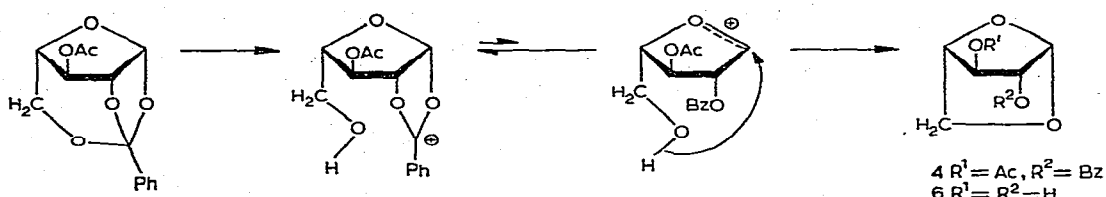
Treatment of **3** with mercury(II) bromide in nitromethane gave a mixture of compounds, the major components of which were the monomeric anhydride **4** (40%) and the dimeric anhydride **5** (14%); the structures of **4** and **5** were proved as follows.

Saponification of **4** and **5** gave the anhydrides **6** and **7**, respectively, treatment of which with acetic anhydride and pyridine gave the diacetate **8** and the tetra-acetate **9**. Hydrolysis of **6** and **7**, under conditions appropriate for cleavage of furanosidic linkages, gave arabinose as the only reducing sugar. The p.m.r. spectra of **4**, **5**, **8**, and **9** confirmed the number of ester groups in each compound; the signal of one of the acetyl groups in the spectrum of **5** (but not of **9**) had an unusual chemical shift (δ 1.25), probably due to the influence of one of the aromatic rings. The $J_{1,2}$ value (2.5 Hz) for **4** is characteristic of a bridgehead proton coupled to a vicinal *exo*-proton in this type of bicyclic system[4] (*cf.* the p.m.r. spectrum[1] of **2**). Successive methylation, hydrolysis, reduction, and acetylation of anhydride **6** gave 2,3-di-*O*-methyl-L-arabinitol triacetate (**10**), identified by g.l.c., as the only product. Similarly, from anhydride **7**, an equimolar mixture of **10** and 3,5-di-*O*-methyl-L-arabinitol triacetate, identified by g.l.c. and g.l.c.–m.s. (*cf.* ref. 5), was obtained. Periodate oxidation of **6** followed by reduction with sodium borohydride and acetylation gave the diacetate **11**, which was identified by comparison with the optical antipode (**12**) prepared by similar treatment of 1,6-anhydro-β-D-glucopyranose. A similar reaction sequence converted anhydride **7** into a mixture of arabinitol penta-acetate and glycerol triacetate.

The low values of the specific rotations of the dianhydride **7**, and its esters **5** and **9**, indicate structures containing two arabinofuranose residues with opposite, anomeric configurations. Molecular models show that, for **7**, only one such structure is sterically possible, namely, α-L-arabinofuranose β-L-arabinofuranose 1,5′:2,1′-dianhydride.

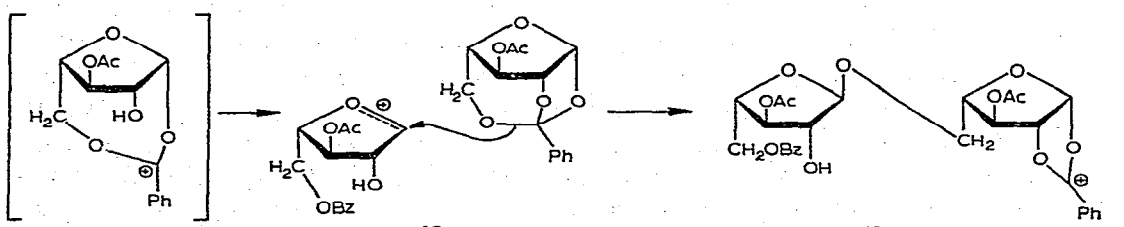


1 13 14 2

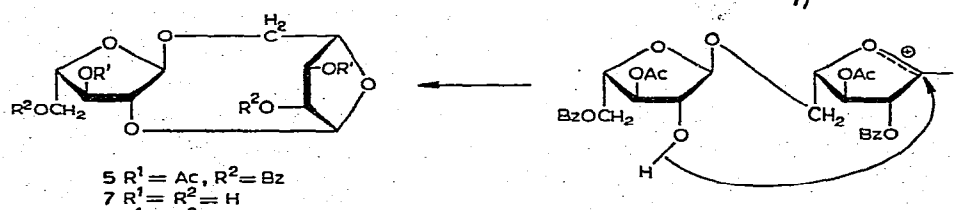


3 15 16

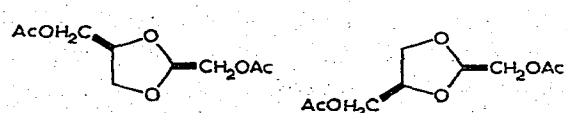
4 R^1 = Ac, R^2 = Bz
6 R^1 = R^2 = H
8 R^1 = R^2 = Ac



17 18 19



5 R^1 = Ac, R^2 = Bz
7 R^1 = R^2 = H
9 R^1 = R^2 = Ac



11 12

The formation of anhydrides **2**, **4**, and **5** can be rationalized as follows. Each reaction is believed to be initiated by protonation of one of the oxygen atoms of the orthoester tricyclic system. The resulting acyloxonium ions, each containing a free hydroxyl group, are in equilibrium with their considerably more-reactive isomers, namely, glycosyl cations. If sterically possible, these ions are stabilized by cyclization to give anhydrides. When such a reaction course is precluded, polymerisation occurs to give polysaccharide derivatives. Thus, for the α-D-xylopyranose 1,2,4-orthoesters **1**, protonation of O-4 leads to an equilibrium mixture of ions **13** and **14**, in which, initially, the conformation of the orthoester (see ref. 6) should be retained. Such a conformation of ion **14** is characterised by the short distance between HO-4 and the glycosidic centre, which facilitates cyclization to the anhydride **2**. For the arabinose derivative **3**, protonation of O-5 also leads to an equilibrium of cations **15** and **16**, of which **16** can cyclize to give anhydride **4**. Alternative protonation of O-2 gives the comparatively unstable (*cf.* ref. 7), seven-membered acyloxonium ion **17**, which isomerises into the glycosyl cation **18**. Molecular models indicate that the latter cation has no sterically permitted way of intramolecular stabilization and therefore reacts intermolecularly with another orthoester molecule by nucleophilic attack at C-1 from the less hindered α-side. The resulting dimeric acyloxonium ion **19** is also unable to react intramolecularly, but its isomer **20** can cyclize by attack of HO-2′ on the β-side (but not the α-side) of the glycosidic centre to give the dianhydride **5**.

Therefore, polymerization of orthoesters can occur only when intramolecular cyclization is suppressed or if polymerization is promoted by some special factor. The polymerization of xylose orthoesters could be effected by initiation of the reaction by acylium ions, which protected O-4 by ester formation and made intramolecular cyclization impossible [8]. Polymerization of the orthoester **3** to give a regular polysaccharide proceeded only in the presence of an active alcohol initiator[11], glycosylation of which could compete with intramolecular reactions. The macrocyclic, trimeric orthoester of D-glucose[9], which, structurally, is closely related to the orthoesters **1** and **3**, has no sterically permitted way of cyclization and its polymerization proceeds easily without the need for an alcohol initiator[10].

EXPERIMENTAL

Gas–liquid chromatography (g.l.c.) was performed with LChM-8MD and Pye-105 instruments, with nitrogen as the carrier gas, a flame-ionization detector, and the following columns: *A*, 3% PNPGS; *B*, 3% SE-30; *C*, 3% ECNSS-M. G.l.c.–m.s was performed with a Varian MAT-Gnom. spectrometer, and p.m.r. spectra were recorded with a Varian DA-60-IL spectrometer. Solvents and adsorbents were prepared as previously described[2,3].

Isomerisation of 3-O-acetyl-β-L-arabinofuranose 1,2,5-orthobenzoate (**3**). — Orthoester[12] **3** (1 g, 3.57 mmoles) and mercury(II) bromide (12 mg, 33 μmoles) were dried at $\sim 10^{-5}$ mmHg (see ref. 8) in a tube, nitromethane (3 ml, dried and redistilled at 10^{-5} mmHg over CaH_2) was distilled into the mixture at 10^{-5} mmHg, and the

tube was then sealed and heated at 115° for 10 days. T.l.c. (silica gel, chloroform–butanone, 98:2) then revealed compounds with R_F 0.66, 0.53, 0.36, 0.30, 0.25, 0,17, 0.14, and 0.09 in decreasing amounts. Column chromatography on silica gel gave compounds with R_F 0.66 (**4**, 0.4 g, 40%) and 0.53 (**5**, 0.14 g, 14%).

Crystallisation of **4** from ether–pentane gave 3-*O*-acetyl-1,5-anhydro-2-*O*-benzoyl-β-L-arabinofuranose (0.36 g, 36%), which was homogeneous by g.l.c. (column *A*) and t.l.c., and had m.p. 74–75°, $[\alpha]_D$ +222.5° (*c* 1, chloroform). P.m.r. data (CCl_4): δ 2.08 (*s*, AcO), 4.77 (*dd*, $J_{2,1}$ 2.5, $J_{2,3}$ 1.5 Hz, H-2), 5.76 (*d*, $J_{1,2}$ 2.5 Hz, H-1), and multiplets for 5 H with centres at ~7.5 and ~8.0 (BzO) (Found: C, 60.99; H, 5.12. $C_{14}H_{14}O_6$ calc.: C, 60.43; H, 5.05%).

Crystallisation of **5** from benzene–pentane gave homogeneous 3-*O*-acetyl-5-*O*-benzoyl-α-L-arabinofuranose 3-*O*-acetyl-2-*O*-benzoyl-β-L-arabinofuranose 1,5′:2,1′-dianhydride (0.12 g, 12%), m.p. 152–155°, $[\alpha]_D$ +24° (*c* 1, acetone). P.m.r. data ($CDCl_3$): δ 1.25 (*s*, AcO), 2.02 (*s*, AcO), multiplets for 10 H with centres at ~7.5 and ~8.0. (2 BzO) [Found: C, 60.58; H, 5.38; mol. wt. (ebulliometry), 520. $C_{28}H_{28}O_{12}$ calc.: C, 60.43; H, 5.05; mol. wt., 556].

Saponification (sodium methoxide) of **5** gave syrupy, homogeneous (t.l.c.) **7**, $[\alpha]_D$ +2° (*c* 2, methanol). The syrupy tetra-acetate (**9**) of **7** had $[\alpha]_D$ +12° (*c* 2, chloroform). P.m.r. data ($CDCl_3$): poorly resolved *s* at δ 2.12, 2.15, 2.17, and 2.21 (4 AcO).

1,5-Anhydro-β-L-arabinofuranose (**6**). — Anhydride **4** (0.13 g), deacetylated with methanolic sodium methoxide in the usual way, gave, after crystallisation from chloroform–pentane, **6** (50 mg, 80%), m.p. 69–72°, $[\alpha]_D$ +25° (*c* 1, methanol) (Found: C, 45.30; H, 6.48. $C_5H_8O_4$ calc.: C, 45.54; H, 6.06%).

The syrupy 2,3-diacetate **8** had $[\alpha]_D$ +76° (*c* 1, chloroform). P.m.r. data (CCl_4): δ 2.02 (*s*, 2 AcO) and 5.55 (*d*, $J_{1,2}$ 2.0 Hz, H-1).

Acid hydrolyses. — Anhydrides **6** and **8** (0.5 mg of each) were hydrolysed with 12.5mM oxalic acid at 100° for 3 h. Only arabinose was found in each hydrolysate (p.c., butanone–boric acid–acetic acid, 9:1:1).

Methylation analyses. — Anhydride **6** (60 mg) was methylated[13], giving the homogeneous (g.l.c., column *A*) methyl ether, which was hydrolysed with 0.5M H_2SO_4 (0.3 ml) at 100° for 3 h. The product was reduced with sodium borohydride and esterified with acetic anhydride in pyridine. The product was identified by comparison with authentic material as 1,4,5-tri-*O*-acetyl-2,3-di-*O*-methyl-L-arabinitol by g.l.c. [columns *A*, (145°) and *C* (100°)].

When anhydride **7** (20 mg) was treated as described above, 2,3-di-*O*-methyl- and 3,5-di-*O*-methyl-L-arabinitol triacetates, in the ratio 1:1, were identified by g.l.c. On g.l.c.–m.s., the mass spectrum of 1,2,4-tri-*O*-acetyl-3,5-di-*O*-methyl-L-arabinitol contained peaks, *inter alia*, with *m/e* 43, 45, 87, 99, 101, 129, 161, and 189, and that of 1,4,5-tri-*O*-acetyl-2,3-di-*O*-methyl-L-arabinitol contains peaks, *inter alia*, with *m/e* 43, 87, 99, 101, 117, 129, and 189.

Periodate oxidation. — Anhydride **6** (5 mg) was treated with 0.2M sodium metaperiodate (0.4 ml) at room temperature for 24 h. Excess of reagent was destroyed

with ethylene glycol, and the reaction product was reduced with sodium borohydride and esterified with acetic anhydride in pyridine. The product was identical [g.l.c., columns *A* (2°/min from 90°) and *B* (70°)] with that obtained when 1,6-anhydro-β-D-glucopyranose was treated by essentially the same procedure.

Similar oxidation of anhydride **7**, followed by reduction with sodium borohydride, hydrolysis with 12.5mM oxalic acid, a second reduction with sodium borohydride, and acetylation gave arabinitol penta-acetate and glycerol triacetate, which were identified (g.l.c., column *A*, 2°/min, from 110°) by comparison with authentic compounds.

ACKNOWLEDGMENTS

The authors thank Dr. S. S. Taitz and Dr. L. M. Rappoport for the ebulliometric determination.

REFERENCES

1 A. F. Bochkov, I. V. Obruchnikov, and N. K. Kochetkov, *Zh. Obshch. Khim.*, 42 (1972) 2766.
2 N. K. Kochetkov, A. J. Khorlin, and A. F. Bochkov, *Tetrahedron*, 23 (1967) 693.
3 N. K. Kochetkov, A. F. Bochkov, T. A. Socolovskaja, and V. I. Snyatkova, *Carbohyd. Res.*, 16 (1971) 17.
4 J. S. Brimacombe, F. Hunedy, A. K. Al-Radhi, *Carbohyd. Res.*, 11 (1969) 331.
5 H. Björndal, B. Lindberg, and S. Svensson, *Carbohyd. Res.*, 5 (1967) 433.
6 L. G. Vorontsova, A. F. Bochkov, I. V. Obruchnikov, V. I. Andrianov, and B. L. Tarnopolsky, *Carbohyd. Res.*, 23 (1972) 326.
7 H. Paulsen, *Advan. Carbohyd. Chem. Biochem.*, 26 (1971) 127.
8 A. F. Bochkov, I. V. Obruchnikov, and N. K. Kochetkov, *Zh. Obshch. Khim.*, 44 (1974) 1197.
9 N. K. Kochetkov and A. F. Bochkov, *Tetrahedron Lett.*, (1967) 4669.
10 N. K. Kochetkov and A. F. Bochkov, *Carbohyd. Res.*, 9 (1969) 61.
11 N. K. Kochetkov, A. F. Bochkov, and Y. G. Jazlovetsky, *Carbohyd. Res.*, 9 (1967) 49.
12 N. K. Kochetkov, A. J. Khorlin, A. F. Bochkov, and Y. G. Jazlovetsky, *Izv. Akad. Nauk. SSSR, Ser. Khim.*, (1966) 2030.
13 S. Hakamori, *J. Biochem.*, 55 (1964) 205.