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Preliminary communication

Studies on 3,6-anhydro-osazones of higher monosaccharides: characterization and anomeric configuration

MOHAMMED A. E. SALLAM

Department of Chemistry, Faculty of Science, Alexandria University, Alexandria (Egypt)

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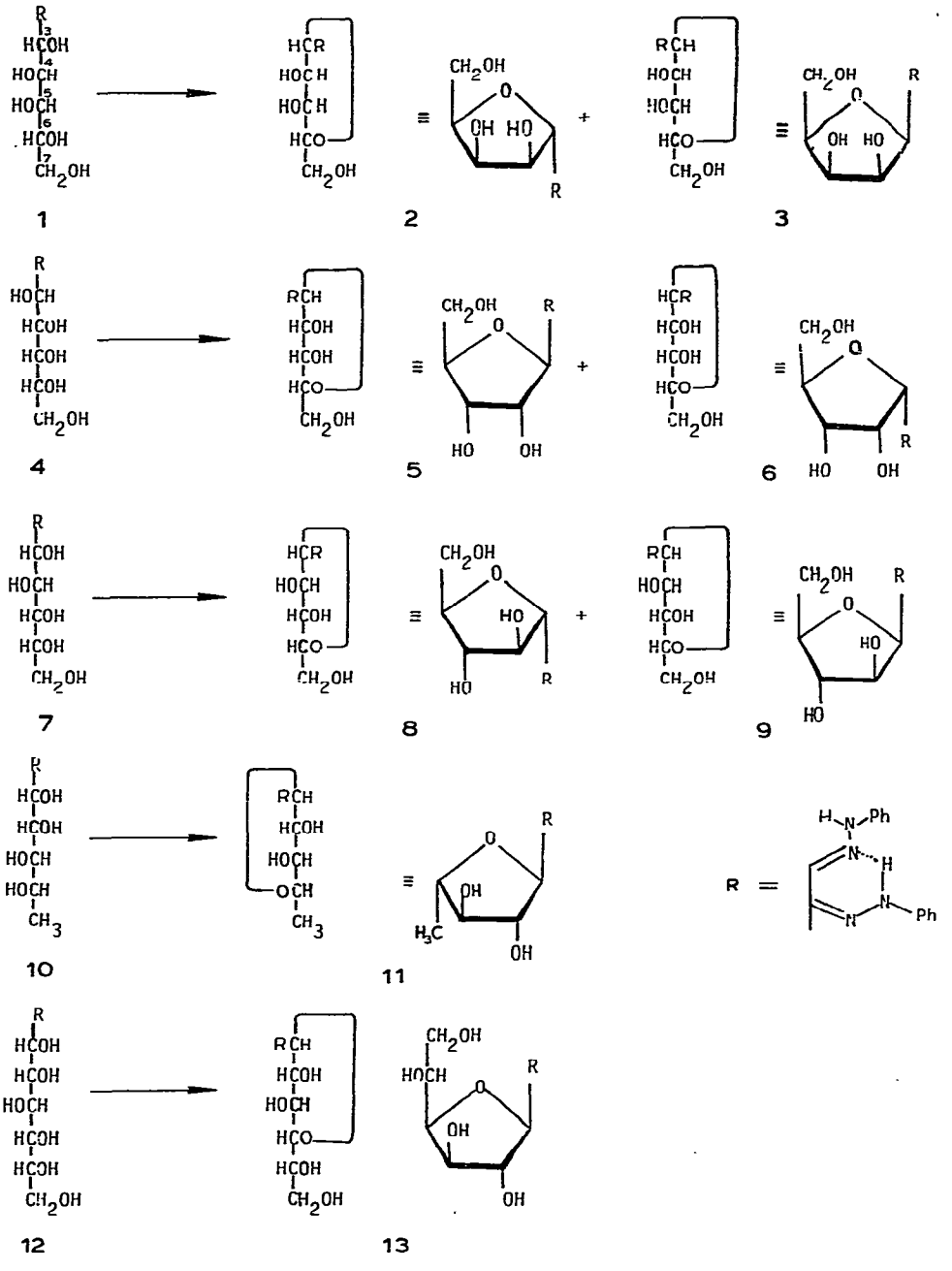
Monosaccharide 3,6-anhydro-osazones[1–3] are *C*-aldofuranosyl compounds used as precursors for the synthesis of *C*-nucleoside analogs[4] that are needed for biochemical investigations and antibiotic or antiviral research[5]. They are readily prepared by dehydrative cyclization of monosaccharide osazones in refluxing, methanolic sulfuric acid solution. However, they have not been used extensively for the synthesis of *C*-nucleoside analogs, because of uncertainty as to their anomeric configuration[6].

In the present communication, a series of 3,6-anhydro-osazones from higher monosaccharides was investigated by thin-layer chromatography (t.l.c.), and their anomeric configuration was ascertained by circular dichroism (c.d.), and high-resolution, n.m.r. spectroscopy. Monitoring of the reaction by t.l.c. indicated the formation of two isomeric, 3,6-anhydro-osazone derivatives from higher monosaccharide osazones having *trans*-3,4-hydroxyl groups. The preponderant anomer was formed with inversion at C-3 of the starting osazone (C-1 of the aldosyl group formed), and the minor, without inversion. Two such anomers were detected[7] from the reaction of D-*arabino*-hexulose phenylosazone, but the proportion of the minor anomer is usually higher from higher monosaccharide osazones than from hexulose phenylosazones. Saccharide phenylosazones having *cis*-3,4-hydroxyl groups produce a single anomer, without inversion of the configuration of C-3 of the starting osazone. This finding permits rational development of a synthesis of *C*-nucleoside analogs from these compounds.

The formation of two isomeric 3,6-anhydro-osazones from higher monosaccharides having *trans*-3,4-hydroxyl groups, and only one isomer from those having *cis*-3,4-hydroxyl groups, supports the mechanism suggested by El Khadem[6] for anhydro-osazone formation. The preponderance of the sterically favored 3,6-anhydro-osazone isomer having the *cis*-3,4 arrangement is in accord with an empirical rule[8] for anhydro-osazone formation. The C-3 atom tends to have the same configuration as C-4, irrespective of the configuration of C-3 in the starting osazone. The reason for the increase in the proportion of the sterically disfavored isomer (having *trans*-3,4-hydroxyl groups) from the dehydration of higher monosaccharide phenylosazones than from the corresponding hexulose derivatives is at present unclear.

D-*galacto*-Heptulose phenylosazone (**1**) produces two isomeric 3,6-anhydro-osazones, **2** and **3** (see Scheme 1), in the ratio of 3:2. Anomer **2** has m.p. 234°; R_F 0.44 (solvent *A*, 3:1 benzene–ethanol), 0.48 (solvent *B*, 2:1:1 benzene–chloroform–ethanol).



Scheme 1

Its c.d. spectrum showed a positive Cotton-effect at 390–420 nm of opposite sign to that of the Cotton effect of the precursor D-*galacto*-heptulose phenylosazone, indicating that the α-D-*lyxo* configuration is formed, by inversion of C-3 in the Fischer projection formula **1**. The second isomer, **3**, has m.p. 246°; R_F 0.37 (solvent *A*), 0.45 (solvent *B*). Its c.d. spectrum showed a negative Cotton-effect at 340–390 nm, identical in sign to that of the Cotton effect of the precursor osazone **1**, supporting the β-D-*lyxo* configuration.

D-*altro*-Heptulose phenylosazone (**4**) affords two 3,6-anhydro osazone derivatives, **5** and **6**, in the ratio of 5:1. Compound **5** has m.p. 160–162°; R_F 0.64 (solvent *A*), 0.74 (solvent *B*). Its c.d. spectrum showed a negative Cotton-effect at 338–440 nm, opposite in sign to that of the precursor, D-*altro*-heptulose phenylosazone (**4**), which is in accord with the β-D-*ribo* configuration. The second isomer, **6**, has m.p. 245°; R_F 0.67 (solvent *A*). 0.76 (solvent *B*). Its c.d. spectrum showed a positive Cotton-effect, at 338–378 nm, having the same sign of Cotton effect as the precursor phenylosazone **4**, indicating the α-D-*ribo* configuration.

D-*gluco*-Heptulose phenylosazone (**7**) produces two isomers, **8** and **9**, in the ratio of 3:2. Anomer **8** has m.p. 168–170°; R_F 0.56(solvent *A*), 0.56 (solvent *B*). Its 360-MHz, high-resolution, n.m.r. spectrum showed the anomeric proton at δ 4.32 ($J_{1',2'}$ 1.0 Hz), indicating[9] the trans arrangement for H-1 and H-2 of the glycosyl group. This α-D-configuration is supported by the high, positive, optical rotation, $[\alpha]_D^{22}$ +110° (*c* 0.25, acetone), which is in agreement with the α-D-*arabino* configuration. The second anomer, **9**, has m.p. 187–188°; R_F 0.36 (solvent *A*), 0.33 (solvent *B*). Its high-resolution, n.m.r. spectrum (360 MHz) showed the anomeric proton at δ 4.01 ($J_{1',2'}$ 9.43 Hz), consistent with the cis arrangement for H-1 and H-2. This β-D configuration is supported by the negative rotation, $[\alpha]_D^{22}$ −27.8° (*c* 1.0, acetone), which is in accord with the β-D-*arabino* configuration of the glycosyl group.

However, 7-deoxy-L-*manno*-heptulose phenylosazone (**10**) produces a single isomer (**11**), having the opposite configuration at C-3. It has m.p. 212–215°, $[\alpha]_D^{22}$ −108.2° (*c* 1.0 acetone); R_F 0.67 (solvent *A*), 0.61 (solvent *B*). Its n.m.r. spectrum at 90 MHz showed the anomeric proton (C-3 proton in the osazone) at δ 4.58, having $J_{1',2'}$ 6.76 Hz. The C-4 proton appeared at δ 4.0, shifted to lower field than H-3, which appeared at δ 3.88. The methyl protons appeared at δ 1.32. The β-L configuration of the aldosyl group was assigned from the deshielding of the C-4 proton and the shielding of the methyl protons[10,11], which was supported by the high, negative rotation.

D-*glycero*-D-*gulo*-Octulose phenylosazone (**12**) also afforded a single anomer (**13**), having a configuration the opposite of that of C-3 of the precursor osazone. It has m.p. 192°; R_F 0.55 (solvent *A*), 0.31 (solvent *B*). The configuration of C-3 was determined[8,12] from its c.d. spectrum. It was, therefore, the β-D-glucosyl derivative.

All of these compounds showed in their high-resolution, mass spectra the exact molecular ions in agreement with the calculated values.

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