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Preliminary communication

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

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Monosaccharide 3,6-anhydro-osazones[1–4] are *C*-aldofuranosyl precursors for the synthesis of *C*-nucleoside analogs. They are readily obtained by dehydrative cyclization of monosaccharide osazones in refluxing, methanolic sulfuric acid solution. The anomeric configuration of the products constitutes a problem for the development of using these compounds for the synthesis of *C*-nucleosides. An empirical rule[5] for the assignment of the anomeric configuration was suggested on the basis of the circular-dichroism properties of these compounds. In a previous communication[4], a series of 3,6-anhydro-osazones of higher monosaccharides was investigated, and the anomeric configuration was determined by use of circular dichroism and n.m.r. spectroscopy. Recently[6], some exceptions to the empirical rule[5], based on circular dichroism alone, were found on checking the anomeric configuration by n.m.r. spectroscopy, and it was concluded that the circular-dichroism assignment should be supported by n.m.r.-spectral results.

In this communication, a series of 3,6-anhydro-osazone derivatives of D- and L-hexoses (see Scheme 1) was investigated by thin-layer chromatography (t.l.c.), and the anomeric configuration was ascertained by high-resolution, n.m.r. spectroscopy. Monitoring of the reaction with t.l.c. indicated the formation of two isomeric 3,6-anhydro-osazone derivatives from phenylosazones of hexoses 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). The minor isomer was obtained without inversion. Identical results were obtained for higher-monosaccharide analogs. However, the minor isomer was usually obtained in smaller proportion than from the phenylosazones of higher monosaccharides.

The n.m.r. assignment for the anomeric configuration of the hexose analogs is in agreement with the c.d. results previously[5] obtained. The preponderant isomer

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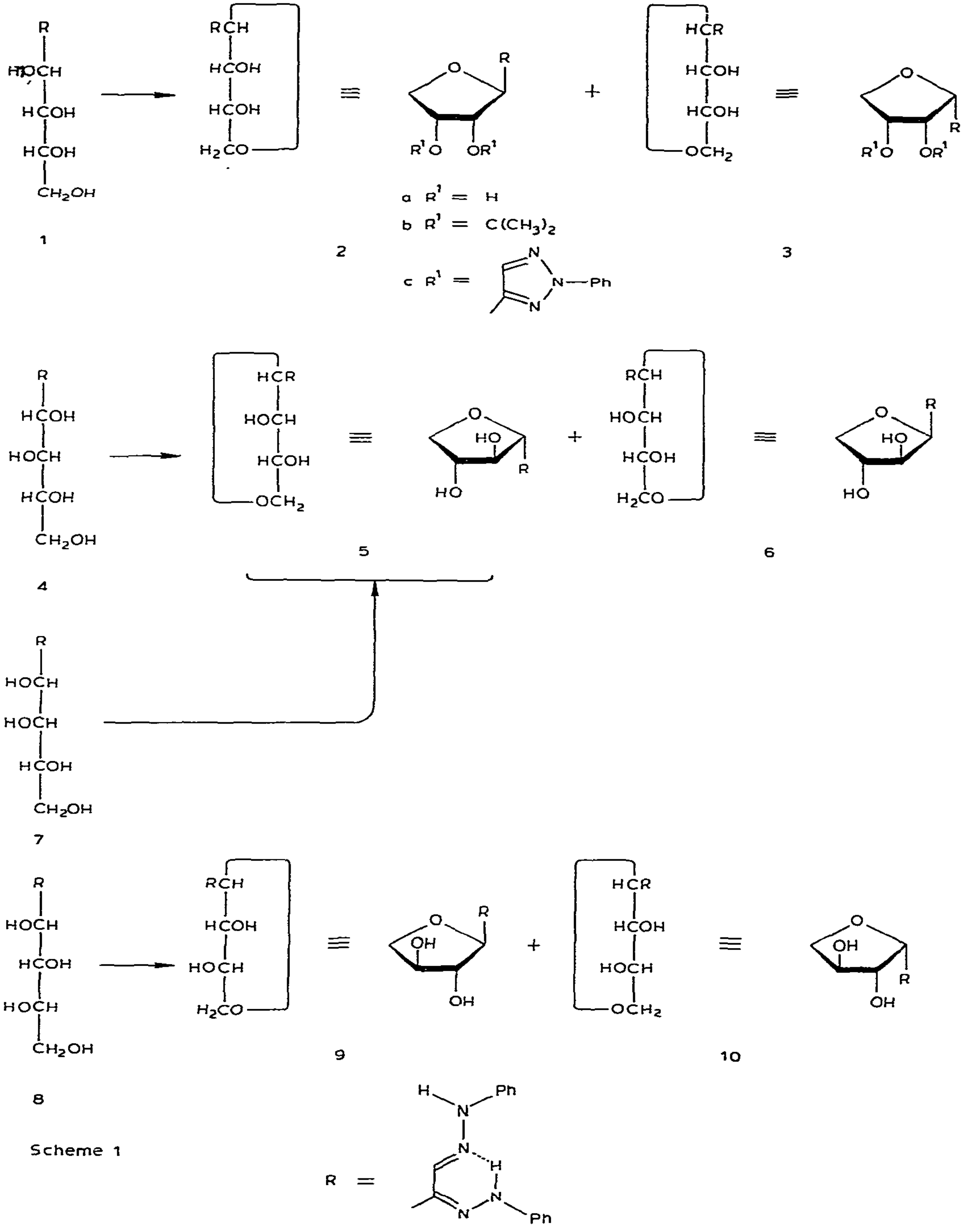

Scheme 1

obtained has the two hydrazone groups *trans* to the 4-hydroxyl group, as indicated previously by the c.d. empirical rule[5]. These n.m.r.-spectral results support the mechanism suggested by El Khadem[7] for 3,6-anhydro-osazone formation, which proved to be generally valid for the D- as well as the L-hexose phenylosazones.

D-*arabino*-Hexulose phenylosazone (D-glucose phenylosazone; **1**) affords two isomeric 3,6-anhydro-osazones (**2** and **3**), in the ratio of 3:1. Anomer **2a** has m.p. 179°; R_F 0.60. Its high-resolution, n.m.r. spectrum showed the anomeric proton at δ 4.17 as a doublet ($J_{1',2'}$ 6.3 Hz), and, on conversion into the 2′,3′-isopropylidene acetal **2b**, the anomeric proton appeared at δ 4.32 ($J_{1',2'}$ 3.61 Hz), in accord[8] with the β-D-*erythro* configuration (which is obtained by inversion at C-3 in the Fischer projection formula **1**). On refluxing with copper sulfate, the minor isomer **3a**, R_F 0.67, gave the 3,6-anhydro-triazole derivative **3c**; its n.m.r. spectrum showed the anomeric proton at δ 4.66 ($J_{1',2'}$ 6.3 Hz), in accord[8] with the α-D-*erythro* configuration.

D-*xylo*-Hexulose phenylosazone (D-gulose phenylosazone; **4**) affords two isomers, **5** and **6**. The preponderant isomer, **5**, has m.p. 224°; R_F 0.45. Its high-resolution, n.m.r. spectrum (acetone-d_6) showed the anomeric proton as a doublet at δ 4.389 ($J_{1',2'}$ 4.06 Hz), in accord with the α-D-*threo* configuration, obtained by inversion at C-3 in the Fischer projection formula **4**. The minor isomer **6** was detected by t.l.c. (R_F 0.50) as a trace in the mother liquor of **6**.

However, D-*lyxo*-hexulose phenylosazone (D-galactose phenylosazone; **7**) gives a single isomer, identical to **5**, and having the same R_F value (0.45), and m.p. and mixed m.p. (224–225°). Its n.m.r. spectrum (Me_2SO-d_6) showed the anomeric proton at δ 5.08 ($J_{1',2'}$ 4.2 Hz), supporting the α-D-*threo* configuration suggested for **5**, which is also obtained without inversion at C-3 of the Fischer projection formula **7**. The production of **5** as the preponderant isomer from **4**, and as the sole isomer from **7**, is direct evidence for the hypothesis given for 3,6-anhydro-osazone formation.

L-*xylo*-Hexulose phenylosazone (L-sorbose phenylosazone; **8**) affords two 3,6-anhydro-osazone derivatives (**9** and **10**) in the ratio of 4:1. The preponderant isomer (**9**) has m.p. 220°; R_F 0.60. Its n.m.r. spectrum showed the anomeric proton as a doublet at δ 4.38 ($J_{1',2'}$ 4.18 Hz), in agreement with the α-L-*threo* configuration formed with inversion at C-3 in the Fischer projection formula **8**. The minor isomer (**10**) has R_F 0.53; its n.m.r. spectrum showed the anomeric proton as a doublet at δ 4.03 ($J_{1',2'}$ 8.39 Hz), indicating[8] the β-L-*threo* configuration.

These compounds showed correct elemental analyses. T.l.c. was conducted with 3:1 benzene–ethanol, and the n.m.r. spectra were recorded with an NTC (360 MHz) instrument.

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