NUCLEOPHILIC SUBSTITUTION AT C^2 OF HEXOPYRANOSES

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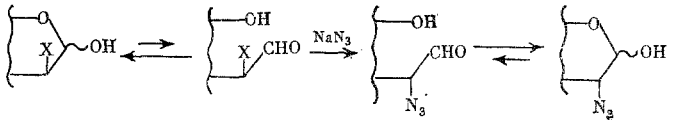
Three methods are known for the synthesis of 2-azido-2-desoxy-D-galactose derivatives: the traditional method, which is based on the nucleophilic opening of epoxides [1]; the azido-nitrate method [2]; and the halo-azide method [3]. At the same time, only the method given in [1], which is characterized by being multistep, is applicable for the analogous D-glucose derivatives. In order to create a convenient method for the synthesis of 2-2-azido-2-desoxy-D-glucose from 2-substituted D-mannopyranose derivatives we studied the nucleophilic substitution at C^2 in 2-O-mesyl-D-mannopyranose (I) and 2-bromo-2-desoxy-D-mannopyranose (II).

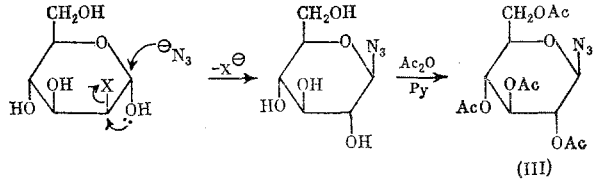
The fact that this seemingly most natural approach was not realized up to now is associated with the unusually difficult nucleophilic substitution at C^2 of hexopyranoses [4, 5]: the transition state in the S_N2 reaction is destabilized by the dipole–dipole interaction of the negatively charged nucleophile with the hemiacetal fragment of the sugar. Even substitution by a neutral nucleophile, like hydrazine, is strongly hindered [4]. Consequently, it can be said that substitution at the C^2 of hexopyranoses is uniquely forbidden.

Easy nucleophilic substitution should be observed for the acyclic forms of compounds (I) and (II), which represent α-sulfonyloxy or α-halo aldehydes. We started with the premise that compounds (I) and (II) in polar DMF will exist as an equilibrium mixture of the cyclic and acyclic forms, in which connection the latter will enter into the reaction with NaN_3 (Scheme 1), even though it is present in small amount, because it is much more reactive.



(1)

Actually, whereas the mixture of 2-O-mesyl-α,β-methyl-D-mannopyranosides remains unchanged on prolonged reaction with NaN_3 at 150°C, the derivatives with a free hemiacetal group, (I) and (II), quickly reacted at a lower temperature. Thus, mesylate (I) reacted completely with 2 equiv. of NaN_3 in 6 h at 70° to give, after acetylation (Ac_2O in pyridine), a single product that absorbed at 2100 cm^{-1} ($-N_3$), whose yield was 87%. However, the obtained compound proved to be not 2-azido-2-desoxy-D-glucoside acetate, but instead 2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl azide (III), which followed from the PMR spectral data and by comparing with an authentic specimen. This result can be explained by progress of the reaction by the following scheme:



(III)

(2)

X = OMs (I), Br (II).

Nucleophilic attack by group X of the hydroxyl at C^1 should proceed easily (for the α-anomer), since both groups are axial [6] in the preferred pyranose $^4C_1$ conformation. It should be mentioned that the formation of the epoxide was not observed in the absence of the nucleophile and only the starting mesylate (I) was isolated.

To check the theoretical possibility of nucleophilic substitution at C^2 taking place via the acyclic form (Scheme 1), we ran the analogous reaction with the D-galactose derivative, with 2-O-mesyl-D-galactopyranose (IV), where the leaving group in the $^4C_1$ conformation is equatorial, which excludes the possibility of forming the intermediate three-membered ring [6]. Mesylate (IV) did not react with NaN_3 under the above indicated condi-

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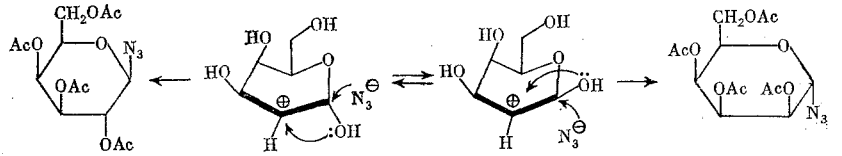
tions, but at 150° in the presence of dibenzo-18-crown-6 it underwent complete conversion in 30 min. Two products were isolated after acetylation and chromatographic separation of the mixture: 2,3,4,6-tetra-O-acetyl-α-D-galactopyranosyl azide (V) and 2,3,4,6-tetra-O-acetyl-α-D-talopyranosyl azide (VI) in respective yields of 27 and 49%. Like in the reaction of mesylate (I), the product of the direct replacement of the mesyloxy group by the azido group was also absent in this case.



(V) (VIIα) (VIIβ) (VI) (3)

Compounds (V) and (VI) were identified via the PMR spectra and by comparing with authentic specimens. The fact that the formation of products, both with inversion and with a retention of the configuration at C^2, is observed when mesylate (IV) reacts with NaN_3 can be explained by progress of the reaction by the S_N1 mechanism with the formation of the cations, (VIIα) and (VIIβ).

As a result, the 2-O-mesyl derivatives of D-mannose and D-galactose react with a nucleophile only in their cyclic form.

Mesylate (I) was synthesized by the mesylation of 1,3,4,6-tetra-O-acetyl-β-D-mannopyranose (VIII) in the presence of sym-collidine and subsequent O-deacylation in aqueous acetone in the presence of a cationite. Reproduction of the method given in [7] for the synthesis of the starting tetraacetate (VIII) led to a constantly low yield (6-9%, instead of the 29% indicated in [7]). Consequently, another variation was proposed, which leads to (VIII) in a stable yield of 30%, and specifically by the hydrolysis of D-mannose ethyl orthoacetate with a 1 M HCl solution in acetone (cf. [8]); hydrolysis of the orthoester with 90% AcOH solution (cf. [9]) lowers the yield of (VIII) substantially.

EXPERIMENTAL

The melting points were determined on a Boetius apparatus. The optical rotations were measured on a Perkin–Elmer 141 instrument at 20-25°. The PMR spectra were obtained on a Varian XL-100 instrument (100 MHz) using TMS as the internal standard. The TLC was run on Kieselgel 60 F-254 plates (Merck), and the compounds were detected by heating at 200-220°. The column chromatography was run on silica gel L, 40-100 μm (Chemapol, Czechoslovakia). The IR spectra were recorded on a UR-20 instrument as Nujol mulls. The solvents were evaporated in vacuo at 30-40°.

1,3,4,6-Tetra-O-acetyl-β-D-mannopyranose (VIII). To 100 ml of Ac_2O was added 3 drops of 57% $HClO_4$ solution and at 40-45°, with stirring, was added 26.4 g of D-mannose. After 1 h were added 5.5 g of red P and then at 15°, in drops, 15 ml of bromine, after which 9.2 ml of water was added slowly. After 2 h the mixture was poured on ice, extracted with 3 × 150 ml of $CHCl_3$, and the extract was washed in succession with water, $NaHCO_3$ solution, and water, dried over $CaCl_2$, filtered, and evaporated. The obtained acetobromomannose was converted as such to the ethyl orthoacetate in the following manner. To a solution of the bromide in 20 ml of MeCN were added 15 ml of abs. EtOH and 30 ml of sym-collidine, and the mixture was kept for 10 h at 45°. The mixture was diluted with 350 ml of $CHCl_3$, washed in succession with water, 2 × 250 ml of 0.5 M HCl solution, and water, and dried over $CaCl_2$. The obtained after evaporation orthoester was dissolved in 400 ml of acetone and 40 ml of 1 M HCl solution was added. After 30 min the acetone was evaporated, the residue was extracted with 600 ml of $CHCl_3$, and the extract was washed with water and dried over $CaCl_2$. To the residue after evaporation was added 500 ml of ether, thus causing the crystallization of (VIII); yield 30%, mp 164, $[\alpha]_D$ −22° (C 1, $CHCl_3$); cf. [7].

2-O-Mesyl-D-mannopyranose (I). To 16.4 g of (VIII) and 20 ml of sym-collidine in 60 ml of CH_2Cl_2 at 20° was added 10 ml of mesyl chloride. After 5 h the mixture was diluted with 500 ml of $CHCl_3$, washed in succession with water, 0.5 M HCl solution, and $NaHCO_3$ solution, dried over $CaCl_2$, filtered, and evaporated. The residue was recrystallized from a $CHCl_3$–ether mixture to give 92% of 1,3,4,6-tetra-O-acetyl-2-O-mesyl-β-D-mannopyranose, mp 117°, $[\alpha]_D$ −33° (C 1, $CHCl_3$). The obtained mesylate (13.7 g) was refluxed for 5 h in a mixture of 150 ml of dioxane and 60 ml of water in the presence of cationite IR-120 (H^+). The mixture was evaporated to dryness and the refluxing was repeated another 2 times. The cationite was filtered, the filtrate was evaporated, and the residue was dissolved in MeOH and let stand in the refrigerator overnight. We obtained 70% of crystalline (I), mp 130°, $[\alpha]_D$ +2° (C 1, water); cf. [10].

Reaction of Mesylate (I) with NaN_3. A mixture of 6 g of (I) and 3 g of NaN_3 in 100 ml of DMF was stirred for 6 h at 70°. To the warm solution were added 10 ml of pyridine and 10 ml of Ac_2O, and after 1 h another 10 ml of each, and the mixture was let stand overnight at 20°. The mixture was diluted with 1 liter of $CHCl_3$, washed in succession with 1 M HCl solution, $NaHCO_3$ solution, and water, and dried over $CaCl_2$. The solution was decolorized with active carbon, filtered through a bed of silica gel, evaporated, and the residue was recrystallized from ether. The yield of 2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl azide (III) was 87%, mp 129°, $[\alpha]_D$ −33° (C 1, $CHCl_3$); IR spectrum: 2100 cm^{-1}; cf. [11].

The acetolysis of (III) in an Ac_2O + $HClO_4$ mixture leads to 1,2,3,4,6-penta-O-acetyl-α-D-glucopyranose, mp 114.5°, $[\alpha]_D$ + 101° (C 1, $CHCl_3$).

Reaction of Mesylate (IV) with NaN_3. As described for the D-mannose derivative, we obtained the syrupy 2-O-mesyl-D-galactopyranose (IV) from 1,3,4,6-tetra-O-acetyl-α-D-galactopyranose [9]. A mixture of 6 g of (IV), 3 g of NaN_3, and 0.1 g of dibenzo-18-crown-6 was refluxed for 20 min in 50 ml of DMF, cooled, and treated with 15 ml of Ac_2O and 15 ml of pyridine. After 3 h the mixture was diluted with 1 liter of $CHCl_3$, washed in the usual manner, and chromatographed on silica gel in the system: 1:3 ethyl acetate–toluene. Sequential elution gave 2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl azide (V) in 27% yield, mp 96°, $[\alpha]_D$ −16° (C 1, $CHCl_3$), IR spectrum: 2100 cm^{-1} (cf. [12]), and 2,3,4,6-tetra-O-acetyl-α-D-talopyranosyl azide (VI) in 49% yield, mp 55-56° (ether–hexane), $[\alpha]_D$ + 145° (C 1, $CHCl_3$), IR spectrum: 2100 cm^{-1}, PMR spectrum (δ, ppm, $CDCl_3$); 1.98 s (3H, OAc), 2.06 s (3H, OAc), 2.12 s (6H, 2 OAc), 5.49 d (1H, H^1, $J_{1,2}$ = 2.0 Hz), 5.00 m (1 H, H^2, $J_{2,3}$ = 3.6 Hz, $J_{2,4}$ = 1.0 Hz), 5.22 d.d. (1H, H^3, $J_{3,4}$ = 3.6 Hz), 5.35 m (1H, H^4), 4.44 m (1H, H^5), 4.25 m (2H, $H^{6,6'}$). The acetolysis of (V) in an Ac_2O + $HClO_4$ mixture leads to 1,2,3,4,6-penta-O-acetyl-α-D-galactopyranose, mp 95.5°, $[\alpha]_D$ +107° ($CHCl_3$). Compound (VI) under the same conditions gives 1,2,3,4,6-penta-O-acetyl-α-D-talopyranose, mp 107°, $[\alpha]_D$ +70° ($CHCl_3$).

CONCLUSIONS

The 2-O-mesyl derivatives of hexopyranoses react with NaN_3 to give the 1-azido derivatives, in which connection the reaction of the D-mannose derivative proceeds with complete inversion of the configuration at C^2, while the reaction of the D-galactose derivative proceeds with a partial retention of the configuration at C^2.

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