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6-DEOXY-5-THIO-L-TALOPYRANOSE

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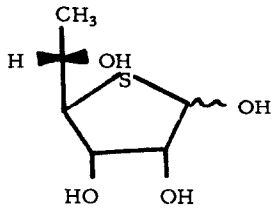
Thiofuranose sugars containing sulfur in the ring have been prepared by introduction of sulfur groups through displacement of sulfonyloxy functions at C_4.[2,3,4,5] In a seemingly analogous fashion, Owen and Ragg[6] have reported the synthesis of 6-deoxy-4-thio-L-talofuranose (I) by treatment of the readily available methyl 2,3-O-isopropylidene-4-O-tosyl-α-L-rhamnopyranoside (III) with potassium thiolbenzoate in N,N-dimethylformamide, followed by subsequent hydrolysis of the resulting thiolbenzoate.

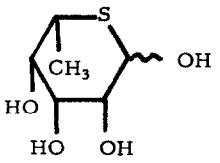
However, we have recently discovered[7] that compound II and related sulfonate esters in the D series undergo novel rearrangements when treated under displacement conditions with azide, acetate, or hydroxide ions. The structural consequence of these rearrangements has been the introduction of the nucleophile into the five position with contraction of the pyranoside to a furanoside ring. The similarity of some of these reaction conditions with those reported by Owen and Ragg had lead us to re-investigate the reaction of compound II with thiolbenzoate ion.

The purpose of this communication is to show that the resulting thiosugar of Owen and Ragg is 6-deoxy-5-thio-L-talopyranose (VIII), the first crystalline 6-deoxy-5-thio-hexose to be reported, and to describe a more efficient synthetic sequence to this thiosugar.

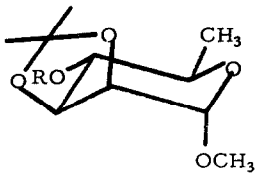
The starting material of Owen and Ragg (compound II) was subjected to their reported reaction conditions and the resulting thiolbenzoate (VI) was shown to be identical with their reaction product by comparison of physical properties, m.p. 103-104°, $[\alpha]_D^{28°}$ + 3.8° (c, 0.69 in $CHCl_3$); reported (VIIa) m.p. 104-105°, $[\alpha]_D^{25°}$ - 2.8° (c, 3.5 in $CHCl_3$). The yields were also comparable, being 11% in the case of Owen and Ragg (16.1 g. of starting material) and 3.2% in our case (0.5 g. of starting material).



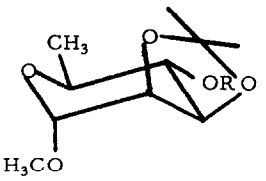
I, L-talo



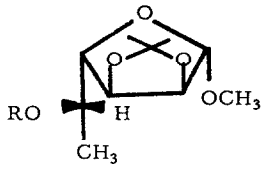
VIII, L-talo



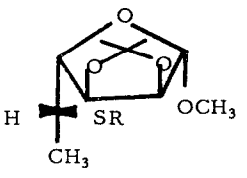
D-manno (rhamno)
II, R = Tos



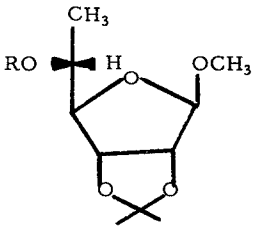
L-manno (rhamno)
III, R = Tos



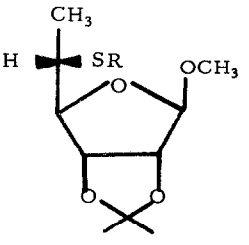
β-L-allo
IV, R = Bros



α -D-talo
VI, R = C_6H_5CO



β-D-allo
V, R = Tos



α -L-talo
VIIa, R = C_6H_5CO
VIIb, R = H

The structure was proven by independent synthesis in a similar manner to the earlier structural determinations[7] of rearranged products. The known methyl 2,3-O-isopropylidene-5-O-brosyl-6-deoxy-β-L-allofuranoside[7] (IV, 100 mg.) when allowed to react with potassium thiolbenzoate in N,N-dimethylformamide at 105° for one hour afforded a quantitative yield of crude product melting at 95-98°. Two recrystallizations followed by preparative thin layer chromatography and a final recrystallization from 95% ethanol gave 40% of the analytically pure product (VI), m.p. 103.5-104°, $[\alpha]_D^{28}$ + 4° (c, 0.68 in $CHCl_3$). The mixture melting point with the product from II was undepressed and the infrared spectra of the two in chloroform were superimposable. The proton magnetic resonance spectra, in $CDCl_3$, was consistent with the proposed structure and showed a doublet at 1.43 δ (J = 6.5 cps) for the 6-C-CH_3 group, a doublet at 1.53 δ for the isopropylidene group hydrogens, a singlet at 3.37 δ for the 1-C-OCH_3 group, an octet at 3.99 δ ($J_{5,6}$ = 6.5 cps, $J_{4,5}$ = 8.5 cps) for the 5-C-H, a doublet of doublets at 4.32 δ ($J_{4,5}$ = 8.5 cps, $J_{3,4}$ = 1.5 cps) for the 4-C-H, a doublet of doublets at 4.76 δ ($J_{3,4}$ = 1.5 cps, $J_{2,3}$ = 6 cps) for the 3-C-H, a doublet at 4.63 δ ($J_{2,3}$ = 6 cps, $J_{1,2}$ = 0 cps) for the 2-C-H, a singlet at 5.02 δ ($J_{1,2}$ = 0 cps) for the anomeric 1-C-H, and a multiplet (5 H's, ratio 3:2) at 7.73 δ for the aromatic hydrogens of the 5-thiolbenzoate group.

After the structural determination, using IV available in our laboratory in small quantities from our previous investigation,[7] it became apparent that the corresponding sulfonate (V), readily accessible from L-rhamnose, would provide the key intermediate in the practical synthetic approach to the thiosugar (VIII). This proved to be the case.

L-rhamnose was converted to V according to the literature procedure.[8] This intermediate (2.5 g. scale) when subjected to mild displacement conditions with potassium thiolbenzoate gave a 75% yield of the analytically pure 5-thiolbenzoate (VIIa) after dilution of the reaction with water and repeated recrystallizations, m.p. 104-105°, $[\alpha]_D^{27}$ - 3.4 (c, 1.0 in CH_3OH) $\nu_{max}^{CHCl_3}$ 1660 cm^{-1} (SBz). In contrast, the other intermediate (III) (16.1 g. scale), when subjected to the more difficult conditions of the rearrangement reaction gave only 11% of VIIa. Saponification of the thiolbenzoate group with sodium

methoxide in dry de-gassed methanol under nitrogen afforded an oil which after chromatography over silica gel had $[\alpha]_D^{27}$ - 17.5° (c, 0.8 in $CHCl_3$); reported[6] $[\alpha]_D^{25}$ - 15° (c, 1.4 in $CHCl_3$). The yield was 64%. Thin layer chromatography in three solvent systems indicated that the thiol (VIIb) was homogeneous, ν_{max}^{neat} 2550 cm^{-1} (SH). This 5-mercapto compound (VIIb) was hydrolyzed with 0.2 N sulfuric acid at 60° under a nitrogen stream. The reaction was complete after 9 hrs., after which time the free sugar was purified by chromatography over silica gel to yield 70% of the 6-deoxy-5-thio-L-talo-pyranose (VIII), m.p. 110-113°, $[\alpha]_D^{27}$ -127° (c, 0.4 in CH_3OH); reported[6] m.p. 111-114°, $[\alpha]_D^{26}$ - 130 (c, 1 in CH_3OH). The infrared spectrum of VIII showed no SH absorption, and is consistent with the proposed pyranose structure. Acetylation of the free sugar resulted in the corresponding crystalline tetra-O-acetate (83% yield), m.p. 130-131° (reported[6] m.p. 131-132°), $\nu_{max}^{CHCl_3}$ 1750 cm^{-1} (O-acetate) with no S-acetate absorption in the infrared spectrum.

In summary, it has been shown that the new thiosugar VIII resulted from rearrangement rather than normal displacement of the tosylate III; furthermore, a practical synthetic procedure for the production of VIII has been described.

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