Tetrahedron Vol. 41, No. 13, pp. 2737 to 2743, 1985
Printed in Great Britain.

0040-4020/85 $3.00 + .00
Pergamon Press Ltd.

4,6-THIOANHYDRO-HEXOPYRANOSIDES. SYNTHESIS AND CHEMICAL BEHAVIOUR OF METHYL 2-O-p-TOLUENESULFONYL-4,6-THIOANHYDRO-α-D-GULOPYRANOSIDE

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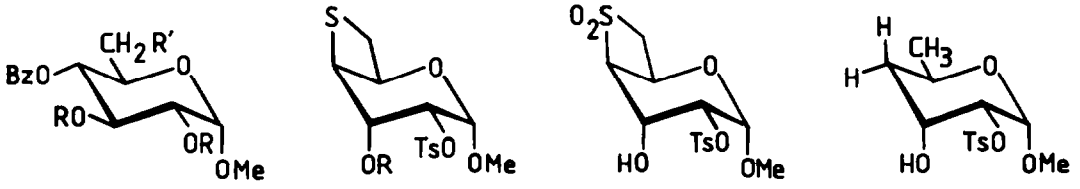
(*Received in UK* 11 *February* 1985)

Summary - Methyl 4-O-benzoyl-6-bromo-6-deoxy-α-D-glucopyranoside (1, Figure 1) was converted, via the corresponding ditosylate 2, into methyl 2,3-di-O-p-toluenesulfonyl-4-O-benzoyl-6-S-acetyl-6-thio-α-D-glucopyranoside (3) by a selective nucleophilic displacement of 6-bromo-group with thioacetate. Unexpectedly, on treating the compound 3 with an excess of sodium methoxide in benzene-methanol (1:1) at room temperature, methyl 2-O-p-toluenesulfonyl-4,6-thioanhydro-α-D-gulopyranoside (4) was obtained in a yield of 84%. In order to determine the structure of the relatively unstable oily product 4, some stable crystalline derivatives (5, 6 and 7) were prepared. Detailed analysis of the ^{1}H-NMR-spectra (200 MHz) of 6 and 7 gave the conclusive evidence for the structure of 4. A self-imposing mechanism of the clean and smooth transformation of 3 to 4 is proposed,involving: a) formation of 9 (Figure 2) as a crucial intermediate and b) a highly regioselective epoxide opening in 9 (at C-4) by an intramolecular nucleophilic attack of the mercaptide anion from C-6.

Thio-sugars have been intensively studied for many years[1,2], not only for chemical reasons but also due to the fact that some of their derivatives represent suitable intermediates for syntheses of various important carbohydrate and non-carbohydrate compounds, while several other thio-sugars themselves show significant biological activity.

Our recent interest in this field has been connected with chemical transformations of D-glucose in order to obtain thio-analogues of 3,6-anhydro-[3] and/or 4,6-anhydro-hexopyranoses representing suitable intermediates in preparations of the corresponding dideoxy-sugars.

In this paper we are reporting the first results of our study relating to a synthesis of a suitably functionalized derivative of 6-thio-D-glucose, as well as to its chemical transformation occuring upon a basic treatment. For this purpose we selected as a starting compound readily available methyl 4-O-benzoyl--6-bromo-6-deoxy-α-D-glucopyranoside[4] (the compound 1, Figure 1) which was converted into the corresponding ditosylate 2 by a standard synthetic procedure. In the subsequent step we obtained 6-S-acethyl-6-thio-derivative 3, in a very satisfactory yield, by a selective nucleophilic displacement of 6-bromo-group of 2 by a thioacetate anion, leaving both tosylate groups at C-2 and C-3 unchanged. Inded, the compound 3 represents a real starting point of our present study, Namely, in a surprisingly clean and smooth one-pot multistep reaction, the compound 3 was converted into 4,6-thio-anhydro-derivative 4 (in 84% yield) on treatment with an excess of sodium methoxide in benzene-methanol (1:1) at room temperature.



1 R = H; R' = Br
2 R = Ts; R' = Br
3 R = Ts; R' = SAc

4 R = H
5 R = Ts

6

7

Figure 1.

We are suggesting a mechanism depicted in Figure 2 to explain this interesting multistep chemical transformation.

Methanolysis of 6-S-acetyl- and 4-O-benzoyl-groups in the starting compound 3 should proceed in an expected way, thus affording the intermediate 8 (represented only as a less stable reactive conformer 8a). The further logical step involves formation of the corresponding allo-epoxide 9 (Fig. 2) which should exist in a conformation equilibrium. The last step of this transformation must then include highly regioselective intramolecular nucleophilic attack of the mercaptide anion from C-6 at the C-4 position of the epoxide ring of 9 (this is valid for both conformations, 9a and 9b).

In order to explain the exlusive formation of 4 one has to take into account Baldwin's rules[5]. Namely, an intramolecular nucleophilic opening of three-membered rings (thus including epoxides), with simultaneous formation of new cyclic structures, proceeds according to rules which are midway in respect to those for tetrahedral and trigonal systems. Since 3-to 7-Exo-Tet and 3-to 7-Exo-Trig modes

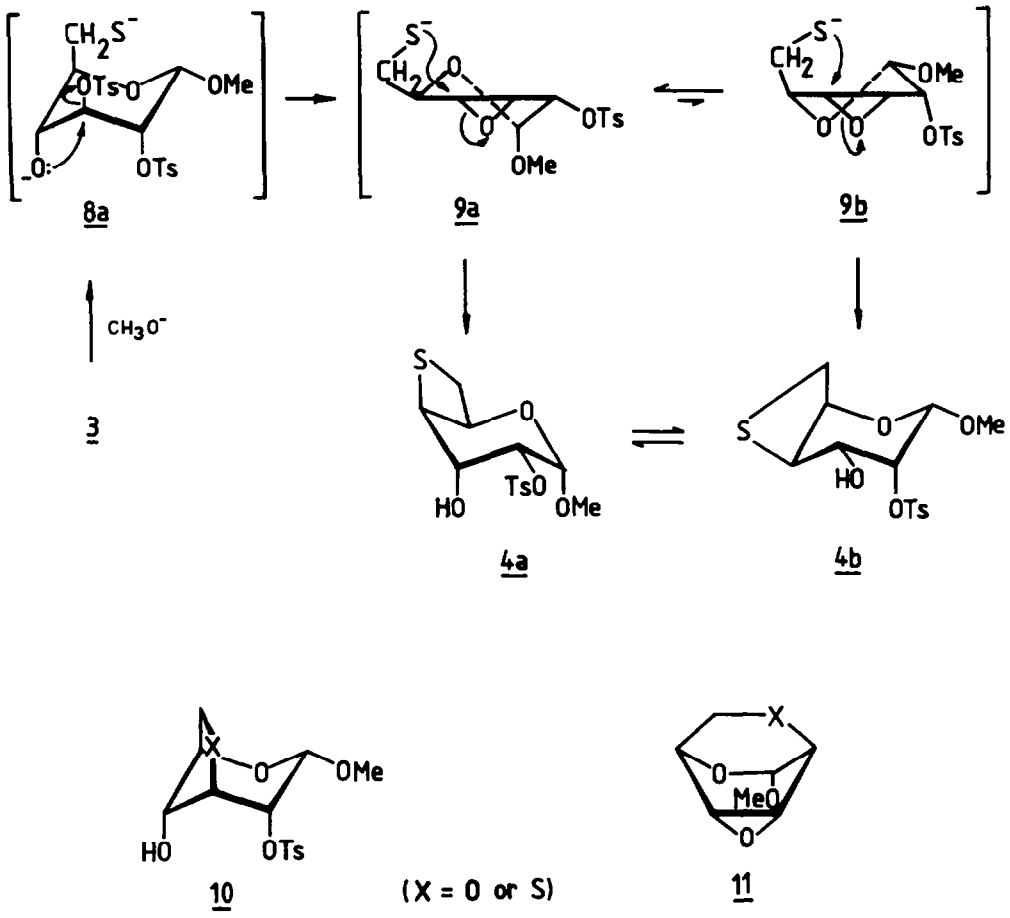


Figure 2.

of ring closure are all favoured processes, while 5-to 6-Endo-Tet and 3-to 5-Endo--Trig are disfavoured ones[5], in our epoxide system (9) 4-Exo-Tet-Trig* mode of ring closure is the only preffered process (i.e. the other theoretically alternative process, 5-Endo-Tet-Trig, is disfavoured). It is worth mentioning that similar observations were already made in carbohydrate chemistry[6,7]. However, our finding deserves an additional comment. Namely, it is clear that formation of 10 (Figure 2) opposes Baldwin's rules, but formation of 11 (Figure 2) should be in accord with these rules. Indeed, there is a 6-O-analogue of our epoxide system 9, described in the literature[8], where an alkaline treatment leads exclusively to the compound 11 (X=O, Figure 2). Obviously, this example belongs to 6-Exo-Tet case which is a favourable one. Since the outcomes of our work and the mentioned work[8] are different, one might rise the following question: if there are several favourable ring-forming processes within a single molecule, how to predict the most favourable one? In our case (X=S) obviously 4-Exo-Tet-Trig is preffered over 6-Exo-Tet

*Tet-Trig suffix designates a case between tetrahedral and trigonal systems.

process, but the other case[8] is just opposite. Although Baldwin himself noticed that his rules can be applied only if X is a first row element[5] and found that sulfur can undergo the normally disfavoured 5-Endo-Trig process[9], e.g., our case (corresponding to Baldwin's rules) should stimulate further studies with an aim of: a) generalizing the behaviour of the other but first row elements (like S, e.g.) in ring-forming processes, and b) predicting the most favourable ring-forming process among several in principle favourable ring closing reaction within a single molecule. Finally, we believe that the observed differences in formations of 4 and 11 can be explained by a simple fact that thio-oxetane system is considerably more stable that the oxetane one due to a less strained C-S-C bonds in respect to C-O-C ones (i.e., an angle close to 90° is much more favourable for S than for O). Clearly, this fact reflects correspondingly to the energies of the transition states leading to thio-oxetane and oxetane systems.

In order to determine the structure of the compound 4 (isolated in a form of colourless oil) we had to derivatize it due to its instability (it decomposes slowly on standing giving a variety of products). Therefore, the compound 4 was first converted to the stable crystalline ditosylate 5 which was characterized by IR-, ^{1}H-NMR- and M-spectra as well as by a satisfactory elemental mycroanalysis.

In addition, the product 4 was oxidized by monoperphthalic acid to the corresponding sulfone 6 in a good yield. ^{1}H-NMR-spectrum of the sulfone shows two overlaped signals for H-1 and H-2 at 4.909 ppm. Upon irradiation of these signals the multiplet at 4.194 ppm (H-3) was simplified. The signal for H-3 was changed as well after deuteration of the sample, proving that the hydroxyl group is bound to C-3, what is in accordance with the proposed 4,6-thioanhydro- structure of 4.

Finally, thio-oxetane 4 was catalytically desulfurized in the presence of Raney-nickel, whereupon dideoxy-derivative 7 was obtained as the only reaction product. In the ^{1}H-NMR-spectrum of 7 the signal for H-2 apears as a triplet at 4.440 ppm, which upon irradiation of the anomeric proton (4.696 ppm) changes to a doublet. That means, there is only one proton at the vicinal C-3 carbon atom bearing the hydroxyl group. This fact proves unambiguously the structure of 4,6-dideoxy--derivative 7 which can only be formed from the corresponding 4,6-thioanhydro-precursor 4.

EXPERIMENTAL

General methods. - Melting points were determined using a Büchi SMP-20 apparatus and are not corrected. Optical rotations were meansured on a Polamat A (Karl Zeiss - Jena) polarimeter in chloroform solutions. IR-spectra were recorded on a Perkin Elmer 457 spectrphotometer and band positions (ν_{max}) are given in cm^{-1}. ^{1}H-NMR-spectra were recorded on a Varian FT-80A or Bruker WP-200 SY spectro-

meters using $CDCl_3$ solutions and tetramethylsilane as an internal standard. Chemical shifts (δ) are given in ppm values. Mass spectra were taken on a VG-7035 mass spectrometer (at 70 eV).

Methyl 2,3-di-O-p-toluenesulfonyl-4-O-benzoyl-6-bromo-6-deoxy-α-D-glucopyranoside (2). - Methyl 4-O-benzoyl-6-bromo-6-deoxy-α-D-glucopyranoside (1)[4] (1.00 g; 2.80 mmole) and p-toluenesulfonylchloride (1.60 g; 8.40 mmole) were dissolved in dry pyridine (15 ml) and the resulting solution was left at room temperature for 10 days. The reaction mixture was then poured into cold diluted HCl (35 ml; H_2O/ /conc. HCl 7:3), and the obtained suspension was extracted with $CHCl_3$ (3 x 20 ml). The combined extract was washed with water (to pH 6-7), dried (Na_2SO_4) and evaporated. The crude oily product 2 (2.09 g) was crystallized from methanol affording colourless crystals of the compound 2 (1.75 g; 94.59%), mp 100-106°. An analytical sample obtained after recrystallization from methanol had mp 110-113° and $|\alpha|_D$ +7.42 (c 2.06). IR(KBr): 1720(C=O,Bz), 1600(C=C arom., Bz,Ts), 1375-1360(ν_{as}S=O, Ts), 1260(C-O-C, Bz), 1190-1180(ν_{sim}S=O, Ts). ^{1}H-NMR(80 MHz): 2.26, 2.45 (2s, each 3H, $2CH_3$ from Ts), 3.40(s, 3H, OCH_3), 3.30-3.55 (m, 2H, H-6), 3.90-4.20(m, 1H, H-5), 4.32(dd, 1H, H-2, $J_{2,3}$ 8Hz, $J_{2,1}$ 4Hz), 4.97 (d, 1H, H-1, $J_{1,2}$ 4Hz), 5.15-5.45(m, 2H, H-3 and H-4), 6.95-8.00(several signals, 13H, 2Ts and Bz). Mass spectrum (m/e): 638(M^+-OCH_3). Anal. Calc. for $C_{28}H_{29}BrO_{10}S_2$: C, 50.23; H, 4.37; Br, 11.93; S, 9.57. Found: C, 50.59; H, 4.40; Br, 11.50; S, 9.47.

Methyl 2,3-di-O-p-toluenesulfonyl-4-O-benzoyl-6-S-acetyl-6-thio-α-D-glucopyranoside (3). - A suspension of the compound 2 (0.34 g; 0.50 mmole) and potassium thioacetate (0.17 g; 1.49 mmole) in ethyl methyl ketone (12.5 ml) was refluxed with stirring, in an atmosphere of nitrogen, for 0.5 hour. The undissolved reagent was filtered off and washed with chloroform (3 x 10 ml). The combined filtrate was dried (Na_2SO_4) and evaporated. The obtained crude oily product (0.40 g) was chromatographed on a column of silica gel (20 g; benzene-ethylacetate 19:1). The chromatographically purified compound 3 was obtained as yellow oil (0.32 g), which on crystallization from ether-hexane afforded colourless crystals, mp 78-82° (0.23 g; 68.13%). An analytical sample of 3, obtained after recrystallization from ethanol, had mp 102-105° and $|\alpha|_D$ +10.93 (c 1.09). IR(KBr): 1690 (C=O, SAc). ^{1}H-NMR(80 MHz): 2.20(s, 3H, SAc), 2.22, 2.42(2s, each 3H, 2 CH_3 from Ts), 2.82(dd, 1H, H-6, $J_{6,6'}$ 14Hz, $J_{6,5}$ 8Hz), 3.17(dd, 1H, H-6', $J_{6',6}$ 14Hz, $J_{6',5}$ 4Hz), 3.35(s, 3H, OCH_3), 3.7--4.10(m, 1H, H-5), 4.30(dd, 1H, H-2, $J_{2,3}$ 8Hz, $J_{2,1}$ 4Hz), 4.92(d, 1H, H-1, $J_{1,2}$ 4Hz), 5.10-5.35(m, 2H, H-3 and H-4), 6.95-7,95 (several signals, 13H, 2Ts and Bz). Mass spectrum (m/e): 633(M^+-OCH_3). Anal. Calc. for $C_{30}H_{32}O_{11}S_3$: C, 54.22; H, 4.82; S, 14.46. Found: C, 54.41; H, 5.03; S, 14.20.

Methyl 2-O-p-toluenesulfonyl-4,6-thioanhydro-α-D-gulopyranoside (4). - The compound 3 (0.71 g; 1.07 mmole) was dissolved in dry benzene (14 ml) and to thus obtained solution was added 1M sodium methoxide in methanol (14 ml). The resulting solution was stirred at room temperature for 3 hours. The reaction mixture was then poured into 5%aqueous acetic acid (30 ml) and shaked vigorously. After separation of the benzene layer, the water phase was re-extracted with benzene (3 x 15 ml). The combined benzene solution was washed with saturated aq. sodium bicarbonate, dried (Na_2SO_4), and evaporated. The crude compound 4 (0.47 g), was chromatographically purified on a column of silica gel (120 g; benzene-acetone 19:1), whereupon the pure compound 4 was obtained as a colourless oil (0.31 g; 83.79%). IR(film): 3490 (OH), 1600(C=C arom. from Ts), 1370(ν_{as}S=O, Ts), 1195-1180(ν_{sim}S=O, Ts). ^{1}H-NMR(80 MHz): 2.47(s, 3H, CH_3 from Ts), 2.75(d, 1H, J 10.7 Hz), 3.45(s, 3H, OCH_3), 3.35-3.60

(m,3H), 4.10(d, 1H, J 5.3 Hz), 4.70(t, 1H), 4.97(d, 1H, J 3.2 Hz), 5.17(t, 1H), 7.25-7.90(q, 4H from Ts). Mass spectrum (m/e): 346(M^+), 315(M^+-OCH_3), 300(M^+-CH_2S). Due to instability of the compound 4 a correct microanalysis could not be obtained.

Methyl 2,3-di-O-p-toluenesulfonyl-4,6-thioanhydro-α-D-gulopyranoside (5). - The compound 4 (0.28 g; 0.81 mmole) and p-toluenesulfonylchloride (0.58 g; 3.03 mmole) were dissolved in dry pyridine (5 ml) and the resulting solution was left at room temperature for 5 days. The reaction mixture was then poured into cold diluted HCl (10 ml; H_2O/conc. HCl 7:3), and the obtained suspension was extracted with $CHCl_3$ (3 x 10 ml). The combined extract was washed with water (to pH 6-7), dried (Na_2SO_4) and evaporated. The obtained crude product was chromatographically purified on a column of silica gel (25 g; benzene-acetone 19:1). The purified compound 5 was obtained as a colourless oil (0.28 g) which after crystallization from methanol afforded colourless crystals (0.21 g; 52%), mp 122-123° and $[\alpha]_D$ +102.88 (c 1.08). IR(KBr): 1600(C=C arom., Ts), 1380-1370(ν_{as}S=O, Ts), 1190-1180(ν_{sim}S=O, Ts). ^{1}H-NMR (200 MHz): 2.448(s, 6H, $2CH_3$ from Ts), 3.027(dd, 1H, H-6_{endo}, $J_{5,6}$ 6,5 Hz, $J_{6,6'}$ 10.0 Hz). 3.342(dd, 1H, H-$6'_{exo}$, $J_{6',5}$ 4.5 Hz, $J_{6',6}$ 10.0 Hz), 3.361(s, 3H, OCH_3), 3.809(t, 1H, H-4, $J_{3,4} = J_{4,5}$ = 6.4 Hz), 4.754-4.773(several signals, 2H, H-1 and H-3), 4.841(m, 1H, H-5), 5.099(t, 1H, H-2, $J_{2,1} = J_{2,3}$ = 3.3 Hz), 7.150-7.750 (several signals, 8H, from 2Ts). Mass spectrum (m/e): 368(M^+-MeOH). Anal. Calc. for $C_{21}H_{24}O_8S_3$: C, 50.40; H, 4.80; S, 19.20. Found: C, 50.35; H, 4.89; S, 19.37.

Oxidation of the compound 4 with monoperphthalic acid. - A solution of the compound 4 (0.1473 g; 0.43 mmole) in ether (4 ml) and 0.16 M monoperphthalic acid in ether (6 ml) was kept at room temperature for 5 hours. The resulting reaction mixture was then diluted with choloform (30 ml), washed with 5% $NaHCO_3$ (3 x 15 ml) and finally with water (3 x 15 ml). After drying the extract (with Na_2SO_4) and removal of the solvent, the crude product 6 remained as a colourless oil (0.1505 g) solidifying on standing. Upon recrystallization from mixture of acetone-ether, the pure sulfone 6 was obtained in a form of colourless needles (0.1289 g; 80.10%), mp 144-145° and $[\alpha]_D$ +102.9 (c 0.65). IR(KBr): 3460(OH), 1370(ν_{as}S=O from Ts), 1330 (ν_{as}S=O, sulfone), 1190 (ν_{sim}S=O from Ts), 1150(ν_{sim}S=O, sulfone). ^{1}H-NMR(200 MHz): 2.467(s, 3H, CH_3 from Ts), 3.455(d, 1H, OH, $J_{OH,3}$ 9.9 Hz), 3.489(s, 3H, OCH_3), 4.001(d, 1H, H-6_{endo}, $J_{6,6'}$14Hz),4.194(m, 1H, H-3), 4.306(octet, 1H, H-$6'_{exo}$, $J_{6',6}$ 14 Hz, $J_{6',5}$ 5.6 Hz, $J_{6',4}$ 1.6 Hz), 4.586(t, 1H, H-5, $J_{5,4}$ 5.6 Hz, $J_{5,6'}$5.6 Hz), 4.653(m, 1H, H-4), 4.909-4.930 (m, 2H, H-1 and H-2), 7.375-7.875(q, 4H from Ts). Mass spectrum (m/e): 347(M^+-OCH_3). Anal. Calc. for $C_{14}H_{18}O_8S_2$: C, 44.44; H, 4.76; S, 16.93. Found: C, 44.03; H, 4.82; S, 16.62.

Methyl 2-O-p-toluenesulfonyl-4,6-dideoxy-α-D-ribo-hexopyranoside (7). - The compound 4 (0.3093 g; 0.89 mmole) was dissolved in abs. ethanol (18 ml) and ethylacetate (1 ml) and to thus obtained solution was added an ethanol suspension of a commercial Raney-nickel catalyst (2 ml; "Fluka"). The hydrogenation was carried out at atmospheric pressure of H_2 and at room temperature for 6 hours. The catalyst was filtered off and washed thoroughly with CH_2Cl_2. After removal of solvent, the residue was extracted several times with warm CH_2Cl_2. Evaporation of CH_2Cl_2 left the crude product (7) in a form of colourless oil (0.2184 g). Upon crystallization from hexane, the pure compound 7 was obtained (0.2011 g; 71.19%), mp 82-84° and $[\alpha]_D$ +57.63 (c 0.62). IR(KBr): 3415(OH), 1600(C=C arom. from Ts), 1350(ν_{as}S=O, Ts), 1190-1170(ν_{sim}S=O, Ts). ^{1}H-NMR(200 MHz): 1.183(d, 3H, H-6, $J_{6,5}$

6.2 Hz), 1.440-1.684(m, 1H, H-4ax), 1.855-2.000(m, 1H, H-4eq), 2.452(s, 3H, CH_3 from Ts), 3.358(s, 3H, OCH_3), 3.501(d, 1H, OH, $J_{OH,3}$ 9.0 Hz), 3.879-4.024 (broad signal, 1H, H-3), 4.049-4.220(m, 1H, H-5), 4.440 (t, 1H, H-2, $J_{2,1} = J_{2,3} = 3.5$ Hz), 4.696(d, 1H, H-1, $J_{1,2}$ 3.5 Hz), 7.342-7.855(q, 4H, from Ts). Mass spectrum (m/e): 285(M^+-OCH_3). Anal. Calc. for $C_{14}H_{20}O_6S$: C, 53.16; H, 6.33; S, 10.13. Found: C, 53.25; H, 6.29; S, 9.93.

Acknowledgement: The authors are grateful to Dr Z. Dinya and Dr A. Somogyi from Kossuth Lajos University in Debrecen (Hungary) for measuring the mass spectra.

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