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STEREOSPECIFIC REDUCTION OF D-FRUCTOSE OXIME[1]

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Abstract—Catalytic reduction of D-fructose oxime yielded 2-amino-2-deoxy-D-mannitol which was isolated as the crystalline peracetylated derivative. This was converted to 2-acetamido-2-deoxy-D-mannitol. The mono- and di-O-isopropylidene derivatives of this material were prepared. Oxidation of the latter, followed by hydrolysis yielded small amounts of a product having the same R_f as 2-acetamido-2-deoxy-D-mannose.

REDUCTION of hexose oximes yields the corresponding hexitolamine. The latter can then be oxidized to the hexosamine.[2-6] The steric configuration of the resulting amino group is strongly influenced by the conditions employed for the reduction. Thus, calalytic hydrogenation over platinum in acid medium directs the new group to the *cis* position with respect to its immediate neighbor, while sodium and alcohol leads to the *trans* configuration. This stereospecificity was found in the present study on the reduction of fructose oxime.

D-Fructose was converted to the oxime and the latter was hydrogenated in the presence of platinum catalyst. Subsequent acetylation of the product gave a crystalline 2-acetamido-1,3,4,5,6-penta-O-acetyl-2-deoxy-D-mannitol which was isolated in 45% yield. Deacetylation with barium methoxide gave 2-acetamido-2-deoxy-D-mannitol.

By the method of preparation, the above product might be either 2-acetamido-2-deoxy-D-glucitol or 2-acetamido-2-deoxy-D-mannitol. The latter structure was assigned to our product since neither the physical constants of this material nor the fully acetylated material conform with those of 2-acetamido-2-deoxy-D-glucitol.[7]

In order to prove the structure unequivocally, 2-acetamido-2-deoxy-D-mannitol was prepared from 2-amino-2-deoxy-D-mannose by N-acetylation followed by reduction with sodium borohydride. The product had a melting point, specific rotation and IR spectrum identical with that of the 2-acetamido-2-deoxy-D-mannitol prepared from fructose oxime.

When the 2-acetamido-2-deoxy-D-mannitol was treated with copper sulfate in acetone, a crystalline mono-O-isopropylidene derivative was isolated in good yield.

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On the other hand, when hydrochloric acid was used as the catalyst, 2-acetamido-2-deoxy-3,4,5,6-di-O-isopropylidene-D-mannitol was obtained. This was isolated as the crystalline diacetyl derivative upon treatment with acetic anhydride in pyridine. The structure of the di-O-isopropylidene derivative was not studied. However, it is tentatively proposed to be the 3,4,5,6 isomer on the basis of steric considerations and because treatment with an oxidizing agent oxidizes carbon-1.

Catalytic oxidation of the di-O-isopropylidene derivative of 2-acetamido-2-deoxy-D-mannitol with platinum[8] followed by removal of the isopropylidene groups yielded a sugar having the same R_f as 2-deoxy-2-acetamido-D-mannose.[9]

EXPERIMENTAL

2-Acetamido-1,3,4,5,6-penta-O-acetyl-2-deoxy-D-mannitol. To a solution of 52·5 g hydroxylamine hydrochloride in 350 ml methanol at 0°, 448 ml 1·67N alcoholic sodium ethoxide were added. The precipitate which formed was removed by filtration and 90 g D-fructose added to the supernatant. The mixture was stirred 3 hr when the fructose completely dissolved. After 12 hr, the solvent was evaporated under red. press. and the oxime dissolved in 350 ml glacial acetic acid. The solution was hydrogenated (PtO_2 at 3 atm for 12 hr) one mole H_2 being absorbed. The catalyst was filtered off and the solution evaporated *in vacuo* at room temp. The residue was dissolved in 500 ml pyridine and 350 ml acetic anhydride, and kept at 0° for 2 days. The precipitate which formed was collected by filtration, washed thoroughly with water and recrystallized from methanol, m.p. 187–8°, $[\alpha]_D^{20}$ - 13·6° (*c*, 2 chloroform). The yield was 33% on the basis of fructose and 45% when calculated for fructose oxime. (Found: C, 49·70; H, 6·10; N, 3·19. Calc. for $C_{16}H_{27}O_{11}N$: C, 49·8; H, 6·23 N, 3·23%).

2-Acetamido-2-deoxy-D-mannitol. To a solution of 10 g 2-acetamido-1,3,4,5,6-penta-O-acetyl-2-deoxy-D-mannitol in 350 ml methanol, 4·5 ml 0·9N methanolic barium methoxide were added and the mixture kept at 0° for 3 days. The crystalline product was recrystallized from ethanol, m.p., 138°, $[\alpha]_D^{20}$ −7·7 (*c*, 2 water), yield 93%. (Found: C, 43·00; H, 7·62; N, 6·28. Calc. for $C_8H_{17}O_6N$: C, 42·99; H, 7·67; N, 6·23%).

2-Acetamido-2-deoxy-D-mannitol from 2-amino-2-deoxy-D-mannose.[10] To a solution of 500 mg 2-amino-2-deoxy-D-mannose hydrochloride in 12 ml water and 1·2 ml methanol, 14 ml Dowex-1 (carbonate form) were added and the mixture cooled to 0–5°. Acetic anhydride (0·3 ml) was added dropwise with continuous stirring, 0·1 ml being added at 10 min intervals. After keeping the mixture at 5° overnight, it was filtered and washed with water. The combined filtrate and wash were passed through a Dowex 50 (H-form) column (approximately 5 ml vol). The eluate was concentrated *in vacuo*, and the residue dissolved in ethanol and ether. The product could not be crystallized and was therefore carried directly to the next step.

To a solution of 600 mg of the above product in 12 ml water at 0°, 6 ml 10% $NaBH_4$ aq were added dropwise over a period of 15 min. Acetic acid was then added to a pH of 5, and the solution passed over a column of Dowex 50 (acid form) and washed with water. The combined eluate and wash were evaporated to dryness, *in vacuo*. Boric acid was removed by repeated addition of methanol and evaporation to dryness. The residue was recrystallized from ethanol and ether, m.p. 138–9, $[\alpha]_D^{20}$ −7·7 (*c*, 2 water). (Found: C, 43·04; H, 7·73; N, 6·20. Calc. for $C_8H_{17}O_6N$: C, 42·99; H, 7·67; N, 6·23%).

2-Acetamido-2-deoxymono-O-isopropylidene-D-mannitol. 2-Acetamido-2-deoxy-D-mannitol prepared from D-fructose oxime and 15 g anhydrous $CuSO_6$ were suspended in 500 ml acetone and stirred 3 days. The precipitate was filtered off, the solution evaporated *in vacuo*, and the residue dissolved in ethanol. Addition of pet. ether yielded a crystalline precipitate which recrystallized twice, m.p. 165°, yield, 70%, $[\alpha]_D^{20}$ +4·8 (*c*, 2 water). (Found: C, 50·19; H, 8·02; N, 5·44. Calc. for $C_{11}H_{21}O_6N$: C, 50·3; H, 7·99; N, 5·33%).

2-Acetamido-1-O-acetyl-2-deoxy-3,4,5,6-di-O-isopropylidene-D-mannitol. A suspension of 10 g 2-acetamido-2-deoxy-D-mannitol in 200 ml acetone was acidified with 4 ml conc. HCl and stirred

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[10] The authors acknowledge the able assistance of Harvey Steiner in carrying out this reaction.

3 hr. The solution was then neutralized with $PbCO_3$, the precipitate filtered off, and after addition of 1 g Ag_2CO_3 evaporated to dryness. The residue was dissolved in ethanol, filtered and again evaporated. The remaining sirup was dissolved in a mixture of 50 ml pyridine and 35 ml acetic anhydride and kept at room temp for 1 day. The reaction mixture was poured on ice water, and extracted several times with chloroform. The combined chloroform extracts were washed with water $NaHCO_3$ aq and $CuSO_4$ aq, then dried with Na_2SO_4 and evaporated to dryness. The residue was dissolved in ethanol and precipitated with pet. ether, yield 20%, m.p. 176°, $[\alpha]_D^{20}$ +6·2° (*c*, 2 chloroform). (Found: C, 55·27; H, 7·34; N, 4·30. Calc. for $C_{16}H_{27}O_7N$: C, 55·70; H, 7·82; N, 4·07%)

The di-O-isopropylidene derivative was oxidized with Pt according to the procedure of Heyns and Paulsen.[8] The oxidation product was dissolved in acetic acid and kept at 100° for 15 min. Neutralization of the acid followed by paper chromatography showed the presence of a major spot having the same R_f as 2-acetamido-2-deoxy-D-mannose.