CONVENIENT METHOD FOR SYNTHESIS OF 2-METHYL-GLYCO[2,1-d]-2-OXAZOLINES

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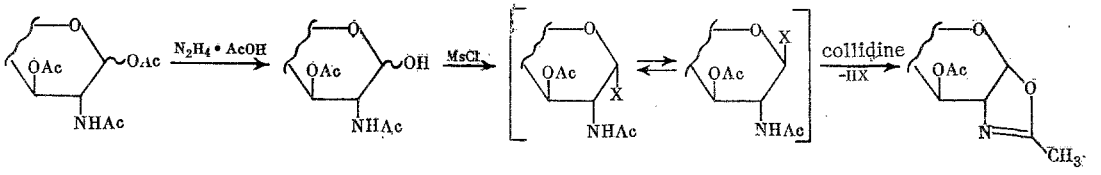
The oxazoline derivatives of carbohydrates are widely used as glycosylating agents in the stereospecific synthesis of 1,2-trans-glycosaminides [1, 2]. Of the two approaches to the synthesis of glyco-oxazolines the first consists in the cyclization of glycosaminyl chlorides by treatment with either halide ions and bases [3] or silver salts and bases [4]. A disadvantage of this method is the need of synthesizing the glycosyl chlorides, which are obtained under strongly acid conditions (HCl in acetyl chloride), which in the case of oligosaccharides can lead to a partial destruction [5], and in the case of acid-labile oligosaccharides, also to a complete destruction of the glycoside linkages. The other method includes the reaction of the 1,2-trans-acetates of aminosugars with Lewis acids, usually with $FeCl_3$ [6], and its range of application is limited to several available 1,2-trans-acetates of monosaccharides and of one disaccharide [7].

A new general method is proposed in the present paper for the synthesis of the oxazoline derivatives of carbohydrates, which excludes cleavage of the glycoside linkages (when applied to oligosaccharides), and apparently also assures retention of practically all of the protective groupings. The method consists in converting the peracetates of aminosugars (either pure or as a mixture of the anomers) by treatment with $H_4N_2 \cdot AcOH$ in DMF [8] to the partial acetates with a free hemiacetal hydroxyl, which without purification are treated with mesyl chloride in the presence of sym-collidine.



X=OMs or Cl

The hemiacetal hydroxyl was freed by heating at 20-50°C for 1-2 h. In the case of the oligosaccharides the reaction mixture was then diluted with $CHCl_3$ and washed with water; the yield of the product was practically quantitative. In the case of the monosaccharides the deacetylation product is readily soluble in the aqueous phase and consequently the DMF was distilled off first, after which the mixture was diluted with $CHCl_3$ and washed with saturated NaCl solution; here the yield is 85-95%. The obtained compounds with a free hemiacetal hydroxyl were treated with 1-1.2 equiv. of MsCl and 2-2.5 equiv. of sym-collidine in CH_2Cl_2 under anhydrous conditions at 0-20° for 24-48 h. The yields of the oxazoline derivatives of the monosaccharides in the last step are 75-80%, and over 90% for the oxazolines of the oligosaccharides.

In this manner were obtained the oxazoline derivatives of N-acetyl-D-glucosamine (Ia), N-acetyl-D-galactosamine (Ib), N-acetyllactosamine (IIa) and its (1 → 3) isomer (IIb), and also the determinant trisaccharide group of blood Le^a (III). (see Scheme on following page).

The IR spectra of the obtained (I)-(III) have a band at 1670 cm^{-1} (C=N) and lack the absorption band of the amide group.

EXPERIMENTAL

The optical rotations were measured on a Perkin–Elmer 141 polarimeter in $CHCl_3$ solution (C 1). The TLC was run on Silufol UV-254 plates (Chemapol, Czechoslovakia). The IR spectra were taken on a UR-20 instrument. The solvents were removed in vacuo at 35-40°.

2-Methyl-(3,4,6-tri-O-acetyl-1,2-didesoxy-α-D-glucopyrano)[2,1-d]-2-oxazoline (Ia). N-Acetyl-D-glucosamine (1 mmole) was acetylated with an Ac_2O–pyridine mixture in the usual manner, the reagents were

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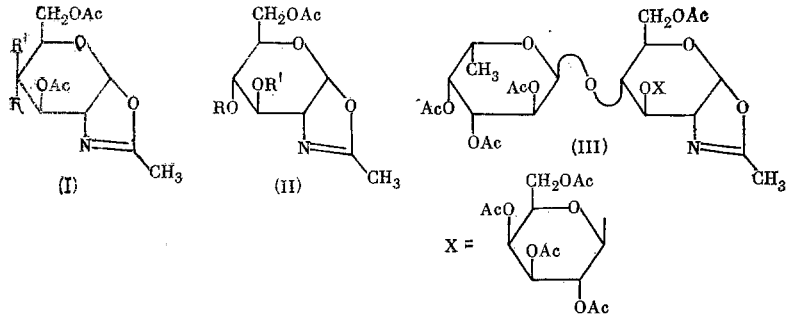

(Ia) R = OAc, R′ = H (IIa) R = X, R′ = Ac
(Ib) R = H, R′ = OAc (IIb) R = Ac, R′ = X

distilled off, the residue was dissolved in 20 ml of DMF, after which 1.1 mmoles of $H_4N_2 \cdot AcOH$ was added and the mixture was stirred until solution was complete and then for another 1-2 h (checked by TLC), the DMF was evaporated, and the residue was dissolved in 100 ml of $CHCl_3$, washed with saturated NaCl solution, and dried over $MgSO_4$. The solution was evaporated, the residue was dissolved in 20 ml of CH_2Cl_2, and 1.2 mmoles of MsCl and 2.5 mmoles of sym-collidine were added. After 24 h the solution was diluted with 100 ml of CH_2Cl_2, washed with $NaHCO_3$ solution, then with satd. NaCl solution containing 5% of AcOH, again with $NaHCO_3$ solution, dried over $MgSO_4$, and evaporated to dryness. We obtained (Ia) as a colorless syrup in 75% yield, $[\alpha]_D^{20}$ + 11° (cf. [3, 4]).

2-Methyl-[4,6-di-O-acetyl-3-O-(2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl)-1,2-didesoxy-α-D-glucopyrano][2,1-d]-2-oxazoline (IIb). As described above, 0.5 mmole of 2-acetamido-3-O-(β-D-galactopyranosyl)-2-desoxy-D-glucose [9] was acetylated and then treated with 0.6 mmole of $H_4N_2 \cdot AcOH$. The solution was diluted with 50 ml of $CHCl_3$, washed with water, evaporated, and the residue was distilled off with toluene. The residue was dissolved in 10 ml of CH_2Cl_2 and then 0.6 mmole of MsCl and 1.25 mmoles of sym-collidine were added to the solution. After 48 h the mixture was diluted with 50 ml of $CHCl_3$, washed in succession with $NaHCO_3$ solution, 5% AcOH solution, and $NaHCO_3$ solution, dried over $MgSO_4$, and evaporated to dryness. We obtained (IIb) as an amorphous product in 87% yield, $[\alpha]_D^{20}$ + 6° (cf. [7]).

In a similar manner were obtained: 2-methyl-(3,4,6-tri-O-acetyl-1,2-didesoxy-α-D-galactopyrano)-[2,1-d]-2-oxazoline (Ib) in 80% yield from N-acetyl-D-galactosamine, $[\alpha]_D^{20}$ + 80° (cf. [10]); 2-methyl-[3, 6-di-O-acetyl-4-O-(2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl)-1,2-didesoxy-α-D-glucopyrano][2,1-d]-2-oxazoline (IIa) in 83% yield from N-acetyllactosamine $[\alpha]_D^{20}$ + 35° (cf. [11]); 2-methyl-[6-O-acetyl-3-O-(2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl)-4-O-(2,3,4-tri-O-acetyl-α-L-fucopyranosyl)-1,2-didesoxy-α-D-glucopyrano][2,1-d]-2-oxazoline (III) as a syrup, in 82% yield, $[\alpha]_D^{20}$ − 31°, from 2-acetamido-2-desoxy-3-O-(β-D-galactopyranosyl)-4-O-(α-L-fucopyranosyl)-D-glucose [12].

CONCLUSIONS

A convenient method was proposed for the synthesis of oxazoline derivatives of mono- and oligosaccharides in high yields and under mild conditions, which exclude the destruction of the glycoside linkage in the oligosaccharides.

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