BENZYLIDENE DERIVATIVES OF 2-SUBSTITUTED 4.5; 1',2'-GLYCO-Δ^2-OXAZOLINES

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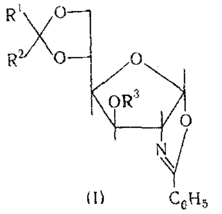
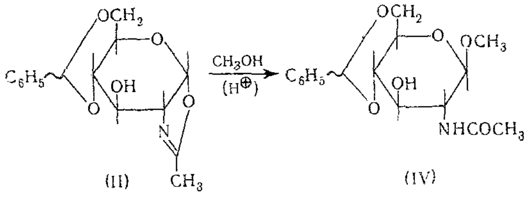
The oxazoline grouping in 4,5:1',2'-glyco-Δ^2-oxazolines, while being a glycosylating function [1, 2], can also be employed for the selective substitution of amino sugars in C_1 and C_2 [3, 4]. In this connection the combination of oxazoline protection with other protecting groups used in mono- and amino sugars chemistry assumes considerable importance. In particular great interest attaches to 2-substituted 4,5;1',2'-glyco-Δ^2-oxazolines containing one free hydroxyl group. The sole example of this type of derivative described previously is 2-phenyl-4,5-(5,6-O-isopropylidene-2-desoxy-D-glucofurano)-Δ^2-oxazoline (Ia), obtained by the acetonylation of N-benzoyl-D-glucosamine in the presence of dry hydrogen chloride [5]. Analogous derivatives of the pyranose form of aminosugars are unknown.

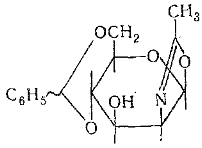
We have studied the condensation of benzaldehyde with N-benzoyl-D-glucosamine, and also with 2-methyl-4,5-(2-desoxy-D-glucopyrano)- and 2-methyl-4,5-(2-desoxy-D-mannopyrano)-Δ^2-oxazoline in order to prepare compounds of the type mentioned. The benzylidene derivative of 4,5;1',2'-glucopyrano-Δ^2-oxazoline failed to form directly from N-benzoyl-D-glucosamine. After the action of benzaldehyde in the presence of dry hydrogen chloride on this monosaccharide the only benzylidene derivative detected in the reaction mixture proved to be 2-phenyl-4,5-(5,6-O-benzylidene-2-desoxy-D-glucofurano)-Δ^2-oxazoline (Ic). The furanose form of compound (Ic) and also its 3-O-acetate (Id) was demonstrated by mass spectrometry* and further by comparison of the NMR spectra of acetate (Id) and 2-phenyl-4,5-(3-O-acetyl-5,6-O-isopropylidene-2-desoxy-D-glucofurano)-Δ^2-oxazoline (Ib).



(I)



(II) (IV)



(III)

(Ia) $R^1 = R^2 = CH_3$, $R^3 = H$;
(Ib) $R^1 = R^2 = CH_3$, $R^3 = COCH_3$;
(Ic) $R^1 = R^3 = H$, $R^2 = C_6H_5$;
(Id) $R^1 = H$, $R^2 = C_6H_5$, $R^3 = COCH_3$

The signals of the protons at H_3 (5.46 and 5.55 ppm respectively) in the NMR spectra of compounds (Ib) and (Id) showed an equal sum for the spin-spin interaction constants ($J_{3,4} + J_{3,2} \sim 3.5$ Hz) from which it follows that the structures of the fragments of the molecules (Ib) and (Id) including $C_2-C_3-C_4$ of the carbohydrate ring are identical. The presence, in the NMR spectra of oxazoline (Ic) and its acetate (Id), of two

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*For a detailed discussion of the mass spectra of compounds (Ia-d), (II) and (III) see [6].

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signals approximately equal in intensity in the region 5.6-6.0 ppm, which corresponded to the protons R_1 of the benzylidene group, indicates that compounds (Ic) and (Id) are mixtures of diastereoisomers differing in configuration at C_2 of the dioxolane ring.

The 4, 6-O-benzylidene derivatives of 4, 5; 1', 2'-glycopyrano-Δ^2-oxazolines were obtained on condensing glucopyrano-Δ^2-oxazolines with benzaldehyde in the presence of zinc chloride under absolutely dry conditions. 2-Methyl-4, 5-(4, 6-O-benzylidene-2-desoxy-D-glucopyrano)-Δ^2-oxazoline (II) was synthesized by this means from 2-methyl-4, 5-(2-desoxy-D-glucopyrano)-Δ^2-oxazoline. Similarly 2-methyl-4, 5-(4, 6-O-benzylidene-2-desoxy-D-mannopyrano)-Δ^2-oxazoline (III) was obtained from 2-methyl-4,5-(2-desoxy-D-mannopyrano)-Δ^2-oxazoline. The structures of benzylidene derivatives (II) and (III) were confirmed by their mass spectra [6]. Further the structure of compound (II) was proved by conversion into 4,6-O-benzylidene-2-acetamido-2-desoxy-β-methyl-D-glucopyranoside (IV) identical with that described previously [7].

Compounds (II) and (III) differ in stability. Benzylidene derivative (III) having the manno configuration is a stable compound while oxazoline (II), with the gluco configuration, decomposes noticeably even on storage for several hours. It should be noted in this connection that we did not obtain 2-phenyl-4, 5-(4, 6-O-benzylidene-2-desoxy-D-glucopyrano)-Δ^2-oxazoline from 2-phenyl-4, 5-(2-desoxy-D-glucopyrano)-Δ^2-oxazoline under the conditions described above, probably because of its high lability. These results correlate well with data [8] on the glycosylating activity of certain sugar oxazoline derivatives. Thus methanolysis of 2-methyl-4, 5-(3, 4, 6-tri-O-acetyl-2-desoxy-D-mannopyrano)-Δ^2-oxazoline is over in 72 h and of 2-methyl-4, 5-(3, 4, 6-tri-O-acetyl-2-desoxy-D-galactopyrano)-Δ^2-oxazoline in 2 h while in the case of 2-phenyl-4, 5-(3, 4, 6-tri-O-acetyl-2-desoxy-D-glucopyrano)-Δ^2-oxazoline methanolysis is totally complete after 10 min.

EXPERIMENTAL

Thin-layer chromatography (silica gel KSK, 150-200 mesh, gypsum) was used with solvent systems (A) absolute ether, and (B) chloroform : methanol (95 : 5). Spots were visualized with concentrated H_2SO_4 at 150°. Preparative chromatography was carried out on aluminum oxide (activity IV). Solvents were evaporated off in vacuum at a temperature not greater than 45°C.

2-Phenyl-4, 5-(5, 6-O-benzylidene-2-desoxy-D-glucofurano)-Δ^2-oxazoline (Ic). To 100 ml freshly distilled benzaldehyde saturated with anhydrous HCl to a weight increase of 4.8 g, was added 8.50 g N-benzoyl-D-glucosamine and the mixture shaken until complete solution (4-5 h) at room temperature. A solution of 25 ml $N(C_2H_5)_3$ in 500 ml absolute ether was added with stirring and cooling, the precipitate of triethylamine hydrochloride which separated was filtered off, the filtrate evaporated, and the benzaldehyde removed at 1-2 mm and 50°. The residue was treated several times with petroleum ether to remove traces of benzaldehyde and dried. The solid (5.80 g) was recrystallized from benzene (or methanol) (Ic) (3.98 g : 38%) was obtained having mp 201-202°; $[\alpha]^{25}_D$ + 64° (c 1.0; $CHCl_3$); the substance was chromatographically homogeneous, R_f 0.3 (system A). Found %: C 68.20; H 5.49. $C_{20}H_{19}NO_5$. Calculated %: C 68.00; H 5.38. IR spectrum (here and subsequently in Nujol): 1635 cm^{-1} (C=N).*

2-Phenyl-4, 5-(3-O-acetyl-5, 6-O-benzylidene-2-desoxy-D-glucofurano)-Δ^2-oxazoline (Id). (Ic) (0.35 g) was acetylated with 0.8 ml Ac_2O in 2 ml pyridine. (Id) (0.285 g: 72%) was obtained of mp 88-89° (from n-hexane, −10°); $[\alpha]^{20}_D$ +34° (c 2.8; $CHCl_3$): the substance was chromatographically homogeneous, R_f 0.5 (system A). Found %: C 66.72; H 5.58; N 3.60. $C_{22}H_{21}NO_6$. Calculated %: C 66.83; H 5.35; N 3.54. IR spectrum: 1744 (OAc), 1643 cm^{-1} (C=N).

2-Methyl-4, 5-(4, 6-O-benzylidene-2-desoxy-D-glucopyrano)-Δ^2-oxazoline (II). A mixture of 1.02 g 2-methyl-4, 5-(2-desoxy-D-glucopyrano)-Δ^2-oxazoline [4], 50 ml freshly distilled benzaldehyde and 0.4 g freshly fused $ZnCl_2$ was stirred for 5-6 h in vacuum over P_2O_5. The reaction mass was poured into a mixture of saturated $KHCO_3$ solution and crushed ice, extracted with $CHCl_3$ (5 × 50 ml), dried over $MgSO_4$, evaporated, and the excess benzaldehyde distilled off at 50° (1 mm). The syrup obtained was dissolved in $CHCl_3$, treated once again with saturated $KHCO_3$ solution, dried, and evaporated. The residue was treated with petroleum ether and then chromatographed on alumina, eluting with a gradient of $CHCl_3 - CHCl_3$ + methanol (9 : 1). A colorless syrup was obtained, the yield of (II) being 0.73 g (51%),

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*Absorption bands at 1510-1570 cm^{-1} corresponding to the deformation vibration of the N−H bond of secondary amides were completely absent from the spectra of compounds (Ic), (Id), (II), and (III).

$[\alpha]_D^{20}$ +3.1° (c 4.0, $CHCl_3$) R_f 0.4 (system B). Found %: C 61.31; H 6.20. $C_{15}H_{17}NO_5$. Calculated %: C 61.85; H 5.88. IR spectrum: 1670 cm^{-1} (C=N).

2-Methyl-4,5-(4,6-O-benzylidene-2-desoxy-D-mannopyrano)-Δ^2-oxazoline (III). (III) was obtained from 2-methyl-4,5-(2-desoxy-D-mannopyrano)-Δ^2-oxazoline [4] in a manner similar to (II). On drying at 50° (1 mm) the product crystallized completely. After recrystallization from a mixture of methanol-ether-petroleum ether the yield was 62%, mp 172.5-174.5°, $[\alpha]_D^{17}$ −22.6° (c 0.71; $CHCl_3$); R_f 0.37 (system B). Found %: C 61.80; H 5.81; N 4.57. $C_{15}H_{17}NO_5$. Calculated %: C 61.85; H 5.88; N 4.88. IR spectrum: 1680 cm^{-1} (C=N).

4,6-Benzylidene-2-desoxy-2-acetamido-β-methyl-D-glucopyranoside (IV). (II) (100 mg) was dissolved in 10 ml 0.01 N H_2SO_4 in absolute methanol and stirred for 2 h. The solution was neutralized with $BaCO_3$, the precipitate filtered off, the filtrate evaporated down, and the residue recrystallized from methanol. (IV) was obtained having mp 296-298°, $[\alpha]_D^{20}$ −96° (C 0.1; CH_3OH). Literature data [7]: mp 298-300°, $[\alpha]_D^{24}$ −95° (c 0.33; CH_3OH).

CONCLUSIONS

A convenient method of obtaining partially substituted 2-desoxy-2-amino sugars with a free hydroxyl group at C_3 has been developed using the synthesis of benzylidene derivatives of 2-methyl-(or phenyl)-4,5; 1'2'-glyco-Δ^2-oxazolines as examples.

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