TRANSFORMATION OF 3-DEOXYSACCHARIDES IN ALKALINE MEDIUM

Š. KUČÁR

Chemical Institute,
Slovak Academy of Sciences, 809 33 Bratislava

Received October 29th, 1975

Treatment of 3-deoxyaldoses with a saturated $Ca(OH)_2$ solution gives 3-deoxyhexuloses in a high yield of about 65%. In this manner 3-deoxy-D-*erythro*-hexulose and 3-deoxy-D-*threo*-hexulose were prepared. It was found, that the arrangement at $C_{(3)}$ in the saccharide molecule has a decisive effect on the course of conversions. For chromatographic detection of the products a new detection reagent was used with which deoxyhexuloses may be distinguished from other deoxyaldoses, and 6-deoxyaldoses from 2-, 3- and 4-deoxyaldoses.

In alkaline medium saccharides undergo three types of reaction: enolization, β-elimination and fragmentation. Great attention has been devoted[1-3] to the explanation of these reactions. For enolization which was described for the first time by de Bruyn and van Ekenstein[4] it is supposed that an 1,2-enediol is always an intermediate from which both epimeric aldoses and 2-ketose are formed. In the case of unsubstituted aldoses 1,2-endiol can be rearranged to 2,3-enediol, which leads either to the formation of a 3-ketose or to a change in configuration of the OH group at $C_{(3)}$. In the second type of reaction – β-elimination – a splitting off of the hydroxy group in the position β to the carbonyl group of the saccharide takes place, in consequence of which 3-deoxyaldosuloses are formed *via* the intermediate 2,3-enediol. During the fragmentation the saccharide molecule is cleaved under formation of a mixture of substances among which lactic acid predominates. Which type of reaction will be predominant depends both on the reaction conditions and mainly on the substituent at $C_{(3)}$. In unsubstituted saccharides, *i.e.* when the carbon atom $C_{(3)}$ carries a hydroxyl group, enolization mainly takes place, while β-elimination takes place to a small extent only[5]. In a case when the hydroxyl group at $C_{(3)}$ is benzylated the dominant type of reaction is β-elimination[6]. Hence, it can be supposed that when 3-deoxyaldoses are used, *i.e.* on substitution of a hydrogen atom for the OH group on $C_{(3)}$, β-elimination is suppressed completely, and during enolization the rearrangement of the 1,2-enediol to 2,3-enediol cannot take place, so that the resulting

Part I in the series Transformation of Deoxy Saccharides.

compounds in this reaction should be a mixture of two epimeric aldoses and of the corresponding 2-ketose. The subject of this paper is the proof of this assumption.

For the observation of the reaction course all four possible 3-deoxyhexoses were employed, *i.e.* 3-deoxy-D-*ribo*-, 3-deoxy-D-*arabino*-, 3-deoxy-D-*xylo*- and 3-deoxy-D-*lyxo*-hexose. The conversions were carried out with saturated $Ca(OH)_2$ solution, 1M-LiOH solution at room temperature, and pyridine under reflux. The most effective transformation reagent was found to be $Ca(OH)_2$ which causes an approximately 65% formation of 3-deoxy-D-*erythro*-hexulose after 48 hours reaction, or 3-deoxy-D-*threo*-hexulose after 72 hours. A further prolongation of the reaction time does not increase the amount of the ketose formed, but the amount of degradation products was increased. Lithium hydroxide causes a slightly more rapid conversion, but the amount of the degradation products is much greater than when $Ca(OH)_2$ was used. When the reaction time was prolonged to 7 days a 100% decomposition of 3-deoxyaldose to degradation products took place. From 3-deoxy-D-*ribo*-hexose or 3-deoxy-D-*xylo*-hexose their epimeric aldoses are formed in amounts smaller than in the case of the conversion of 3-deoxy-D-*arabino*-hexose or 3-deoxy-D-*lyxo*-hexose. It is true that during the conversion of 3-deoxyaldoses in pyridine no epimeric aldose was formed and no degradation product either, but the amount of 3-deoxyketose was small.

For the separation of the transformation products paper chromatography was found most suitable for analytical purposes, while for quantitative separations microcrystalline cellulose was more convenient. A combination of urea and diphenylamine was used for the detection of products after quantitative separation, representing a specific detection reagent for deoxyhexuloses, giving a yellow coloration, while ketoses gave a dark-grey colour. This reagent can also be used for the differentiation of 6-deoxyaldoses (brown coloration) from 2-deoxy-, 3-deoxy- and 4-deoxyaldoses, which give red spots.

From the results obtained it is evident that a substitution of the hydroxy group on $C_{(3)}$ by a hydrogen atom has an effect on the behaviour of 3-deoxyaldoses in alkaline medium. The reaction takes place *via* the 1,2-enediol exclusively, while affording 3-deoxyhexulose preferentially. In this manner both possible 3-deoxyhexuloses were prepared: 3-deoxy-D-*erythro*-hexulose and 3-deoxy-D-*threo*-hexulose. Up till today a single preparation of 3-deoxy-D-*erythro*-hexulose from 3-deoxyfructosazine is known in literature[7]. The preparation of 3-deoxy-D-*threo*-hexulose has not yet been described in literature. The structure of 3-deoxy-D-*threo*-hexulose was proved by elemental analysis, preparation of its 4-nitrophenylosazone which was identical with that of 3-deoxy-D-*xylo*-hexose, and reduction with sodium borohydride, giving a mixture of two sugar alcohols, 3-deoxy-D-*xylo*-hexitol and 3-deoxy-D-*lyxo*hexitol.

It may be stated that in the reactions of 3-deoxyaldoses, which are carried out in alkaline medium the possibility of the formation of 3-deoxyhexuloses should be taken into account.

EXPERIMENTAL

The melting points were carried out on a Kofler block. Optical rotation was measured on an automatic polarimeter Perkin-Elmer, model 141. Paper chromatography was carried out on Whatman No 1 paper, preparative chromatography on microcrystalline cellulose[12] (column 4·5 . 60 cm) with water-saturated 2-butanone as eluent. The detection of deoxysaccharides was carried out with urea[8] and diphenylamine[9], while sugar alcohols were detected with potassium periodate and benzidine reagent[10]. 3-Deoxyaldoses were prepared according to ref.[11]. Quantitative evaluation of paper chromatograms was carried out with an ERI-10 densitometer (Zeiss, Jena).

3-Deoxy-D-*erythro*-hexulose

A) 3-Deoxy-D-*arabino*-hexose (500 mg) in 50 ml of saturated $Ca(OH)_2$ solution were allowed to stand at room temperature for 48 hours. The mixture was neutralized with Amberlite IR-120 (H^+), the exchanger was removed by filtration and the filtrate evaporated to a syrupy consistency. According to paper chromatography the reaction mixture contained about 65% of 3-deoxy-D-*erythro*-hexulose, 25% of 3-deoxy-D-*arabino*-hexose, and 3% of 3-deoxy-D-*ribo*-hexose. Separation on cellulose gave 287·5 mg (57·5%) of 3-deoxy-D-*erythro*-hexulose of m.p. 110–113°C, $[\alpha]_D^{21}$ −70·1° (3 min) → −42·5° (40 min) (*c* 1; H_2O). After crystallization from ethanol the m.p. was 113–115°C. Literature[7] gives m.p. 112–114°C, $[\alpha]_D^{24}$ −69° (4 min) → 43·5° (40 min) (*c* 1; H_2O). Further, 120 mg of 3-deoxy-D-*arabino*-hexose, 30 mg of a fraction containing 3-deoxy-D-*arabino*-hexose and 3-deoxy-D-*erythro*-hexulose, and 10 mg of 3-deoxy-D-*arabino*-hexose and 10 mg of 3-deoxy-D-*ribo*-hexose.

B) 3-Deoxy-D-*ribo*-hexose (500 mg) in 50 ml of a saturated $Ca(OH)_2$ solution was allowed to stand at room temperatures for 48 hours. Working up as under A) gave 270 mg (54%) of 3-deoxy-D-*erythro*-hexulose, 130 mg of 3-deoxy-D-*ribo*-hexose, and 50 mg of a mixture of 3-deoxy-D-*erythro*-hexulose and 3-deoxy-D-*ribo*-hexose. 3-Deoxy-D-*arabino*-hexose was formed in trace amounts only.

3-Deoxy-D-*threo*-hexulose

A) 3-Deoxy-D-*xylo*-hexose (300 mg) in 30 ml of a saturated $Ca(OH)_2$ solution was allowed to stand at room temperature for 72 hours. The mixture was neutralized with Amberlite IR-120 (H^+), the ion exchanger was removed by filtration and the filtrate concentrated to give a syrup. According to paper chromatography the reaction mixture contained about 65% of 3-deoxy-D-*threo*-hexulose, 25% of 3-deoxy-D-*xylo*-hexose, and 5% of 3-deoxy-D-*lyxo*-hexose. Preparative separation on cellulose afforded 175 mg (55%) of syrupy 3-deoxy-D-*threo*-hexulose of $[\alpha]_D^{22}$ +12·6° (*c* 1·55; H_2O), 25 mg of a fraction containing 3-deoxy-D-hexose and 13 mg of 3-deoxy-D-*lyxo*-hexose.

B) 3-Deoxy-D-*lyxo*-hexose (200 mg) in 20 ml of a saturated $Ca(OH)_2$ solution was allowed to stand at room temperature for 72 hours. Working up as under *A*) gave 122 mg (61%) of syrupy 3-deoxy-D-*threo*-hexulose of $[\alpha]_D^{22}$ +12·1° (*c* 1·14; H_2O), 42·5 mg of 3-deoxy-D-*lyxo*-hexose, and 11·3 mg of 3-deoxy-D-*xylo*-hexose. The relative chromatographic mobility of 3-deoxy-D-*xylo*-hexose is taken as 1, that of 3-deoxy-D-*threo*-hexulose was 1·27, and of 3-deoxy-D-*lyxo*-hexose 1·75. For 3-deoxy-D-*threo*-hexulose $C_6H_{12}O_5$ (164·2) calculated: 43·90% C, 7·37% H; found: 43·78% C, 7·24% H.

Preparation of *p*-Nitrophenylosazone of 3-Deoxy-D-*threo*-hexulose

Acetic acid (0·35 ml) was added to a mixture of 65 mg of 3-deoxy-D-*threo*-hexulose and 200 mg of *p*-nitrophenylhydrazine in 2·5 ml of water and the mixture was heated at 100°C for 75 minutes. After 24 hours' standing the separated product was filtered off and washed with water, 2M-CH_3COOH and a mixture of ethanol and ether (2 : 3). The residue was crystallized from ethanol. Yield 53·5 mg (31%) of the red *p*-nitrophenylosazone of 3-deoxy-D-*threo*-hexulose, m.p. 241 to 243°C and $[\alpha]_D^{21}$ +48° (*c* 0·52, C_6H_5N). Mixture melting point with the substance prepared from 3-deoxy-D-*xylo*-hexose in an analogous manner was undepressed. For $C_{18}H_{20}N_6O_7$ (432·4) calculated: 50·00% C, 4·66% H, 19·44% N; found: 50·08% C, 4·75% H, 19·60% N.

Reduction of 3-Deoxy-D-*threo*-hexulose with $NaBH_4$

Sodium borohydride (2 mg) in 0·5 ml of water was added to a solution of 10 mg of 3-deoxy-D-*threo*-hexulose in 0·5 ml of water and the mixture was allowed to stand at room temperature for 2 hours. A drop of CH_3COOH was added and the solution was concentrated. According to paper chromatography a mixture of two substances was formed which were identical with the reference samples of 3-deoxy-D-*xylo*-hexitol and 3-deoxy-D-*lyxo*-hexitol prepared on reduction with $NaBH_4$ of 3-deoxy-D-*xylo*-hexose or 3-deoxy-D-*lyxo*-hexose. Relative chromatographic mobilities: 3-deoxy-D-*xylo*-hexitol 1·67, 3-deoxy-D-*lyxo*-hexitol 1·95, glucose 1.

Detection of 3-Deoxy-D-hexuloses

The chromatographic paper is first sprayed with a 4% aqueousoalcoholic solution of urea (acidified with 2M-HCl) and then allowed to dry at room temperature. It was then sprayed with the diphenylamine reagent and the paper was heated at 100°C for 3 minutes.

REFERENCES

1. Sowden J. C.: Advan. Carbohyd. Chem. *12*, 35 (1957).
2. Speck J. C.: Advan. Carbohyd. Chem. *13*, 63 (1958).
3. Anet E. F. L. J.: Advan. Carbohyd. Chem. *19*, 181 (1964).
4. de Bruyn C. A. L., Alberda van Ekenstein W.: Rec. Trav. Chim. Pays-Bas *14*, 156, 203 (1958).
5. Kenner J., Richards G. N.: J. Chem. Soc. *1957*, 3019.
6. Machell G., Richards G. N.: J. Chem. Soc. *1960*, 1938.
7. Kohn R., Haas H. J., Seeliger A.: Chem. Ber. *94*, 2534 (1961).
8. Dedender R.: C. R. Acad. Sci., Ser. A *230*, 997 (1950).
9. Hais I., Macek K.: *Handbuch der Papierchromatographie*, Bd I., p. 741. Fischer-Verlag, Jena 1958.
10. Cifonnelli J. A., Smith F.: Anal. Chem. *26*, 1132 (1954).
11. Kučár Š., Zámocký J., Bauer Š.: This Journal *40*, 457 (1975).
12. Kuniak Ľ., Alinče B.: Czech. 132508, Chem. Abstr. *73*, 67850 (1970).

Translated by Ž. Procházka.