

PREPARATION OF 3-DEOXY SACCHARIDES

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A method of the preparation of 3-deoxyaldoses has been elaborated. Under the effect of $\text{Ca}(\text{OH})_2$ on 3-deoxy-aldos-2-ulose a mixture of epimeric lactones of 3-deoxyaldonic acids is formed in which the epimer with 2,4-*threo* arrangement predominates, which is in agreement with Maltby's rule. Reduction of corresponding lactones gave 3-deoxy-D-*ribo*-hexose, 3-deoxy-D-*arabino*-hexose, 3-deoxy-D-*xylo*-hexose, 3-deoxy-D-*lyxo*-hexose, 3-deoxy-D-*erythro*-pentose, and 3-deoxy-D-*threo*-pentose.

Of the 3-deoxysaccharides only 3-deoxy-D-*erythro*-pentose¹ has been isolated from natural material. In contrast to this, their synthetic preparation is rather well elaborated. The opening of a suitable anhydro ring^{1,2} is so far one of the most often used methods of their preparation. In addition to the rather difficult preparation of starting anhydro derivatives the disadvantage of this method consists in the formation of a second deoxy derivative (most often 2-deoxy derivative). Further methods of preparation¹ (as for example the preparation of vinyl ethers, preparation from sugar xanthates, extension of the chain from 2-deoxysaccharides), have a rather limited use, due to difficulty in obtaining starting substances.

In this paper we concentrated on the working out of a general preparation of 3-deoxysaccharides. It is known^{3,4} that in alkaline medium 3-deoxy-D-*erythro*-hexos-2-ulose affords a mixture of 3-deoxy-D-*ribo*-hexonic acid and 3-deoxy-D-*arabino*-hexonic acid; similarly 3-deoxy-D-*threo*-hexos-2-ulose⁵ gives a mixture of 3-deoxy-D-*xylo* and 3-deoxy-D-*lyxo*-hexonic acids. We found that other 3-deoxyaldos-2-uloses also give in alkaline medium a mixture of epimeric lactones, the reduction of which then gives corresponding 3-deoxysaccharides. In this paper we describe the preparation of all theoretically possible 3-deoxy derivatives of aldopentoses and aldohexoses.

The most important step in the preparation of 3-deoxyaldoses is the synthesis of starting 3-deoxyaldos-2-uloses. El Khadem and coworkers⁶ found that under the effect of benzoylhydrazine on aqueous solutions of monosaccharides in the presence of aromatic amines bis benzoylhydrazones of 3-deoxyaldos-2-uloses are obtained from which free 3-deoxyaldos-2-uloses can be prepared easily. The course of the

reaction is not unambiguous and it is dependent on the reaction conditions. For example, during the preparation of 3-deoxy-D-*erythro*-hexos-2-ulose bis(benzoylhydrazone) we found by thin-layer chromatography that at least 7 substances are present in the reaction mixture. Even small deviations from the prescribed reaction conditions may result in a more difficult isolation of the expected product, 3-deoxyaldos-2-ulose bis(benzoylhydrazone), from the reaction mixture, and thus also lower yield. Moreover, even when respecting the reaction conditions described by El Khadem^{6,7} accurately, we were unable to prepare 3-deoxy-D-*erythro*-hexos-2-ulose bis(benzoylhydrazone) in yields claimed by the mentioned author (35%), but achieved substantially lower yields. A change in the reaction conditions (larger amount of acetic acid and ethanol) enabled us to prepare 3-deoxy-D-*erythro*-hexos-2-ulose bis(benzoylhydrazone) in 39% yield. Similarly for other bis(benzoylhydrazones) of 3-deoxyaldos-2-uloses the modification of the reaction conditions given in ref.^{6,7} increased the yields of the corresponding bis(benzoylhydrazones).

Under the effect of $\text{Ca}(\text{OH})_2$ on 3-deoxyaldos-2-uloses 3-deoxyaldonic acids or their lactones are formed. The mechanism of this reaction was proposed by Isbell⁸. In the first reaction step deoxydicarbonyl intermediate is formed by β -elimination which further undergoes benzilic rearrangement under formation of 3-deoxyaldonic acids. Maltby's rule⁹ may be applied to the course of this reaction; it was derived for Fischer-Kiliani cyanohydrin synthesis (if pH of the reaction mixture is higher than 7) and it says that from the two possible epimers that with the 2,4-*threo* arrangement is formed in higher yield. In our case too lactones of 3-deoxy-D-*arabino*-hexonic, 3-deoxy-D-*xylo*-hexonic and 3-deoxy-D-*threo*-pentonic acids (*i.e.* lactones with 2,4-*threo* arrangement) are formed in larger amounts than the corresponding epimeric lactones of 3-deoxy-D-*ribo*-hexonic, 3-deoxy-D-*lyxo*-hexonic and 3-deoxy-D-*erythro*-pentonic acids, *i.e.* those with 2,4-*erythro* arrangement). This selectivity may be explained by the fact that in the so-called zig-zag conformation, when $\text{C}_{(2)} \rightarrow \text{C}_{(4)}$ are in one plane in consequence of the 1 \rightarrow 3 interaction of the hydroxyl groups, both groups in 2,4-*erythro* isomers come into a disadvantageous position in comparison with the positions of these hydroxyl groups in 2,4-*threo* isomers (Fig. 1).

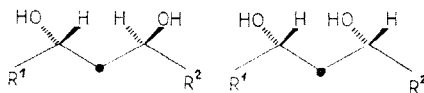


FIG. 1

Zig-Zag Conformation of 2,4-*threo*- and 2,4-*erythro*-Isomers of 3-Deoxy-D-aldonic Acids
 R^1 for pentoses $-\text{CH}_2-\text{OH}$, for hexoses $-\text{CH}(\text{OH})-\text{CH}_2\text{OH}$; R^2 $-\text{COOH}$.

The arrangement of hydroxyl groups on carbon atoms $C_{(2)}$, $C_{(4)}$ also affects the chromatographic mobility of lactones of 3-deoxyaldonic acids. The epimers with 2,4-*erythro* arrangement possess a greater mobility than epimers with the 2,4-*threo* arrangement (Table I). This fact can be utilized for quantitative evaluation of mixtures of epimeric lactones.

TABLE I
 R_F Values of γ -Lactones of 3-Deoxy-D-aldonic Acids on Paper

Configuration	<i>arabino</i>	<i>ribo</i>	<i>xylo</i>	<i>lyxo</i>	<i>threo</i>	<i>erythro</i>
R_F in B	0.58	0.62	0.55	0.64	0.66	0.70
R_F in C	0.34	0.43	0.26	0.37	0.52	0.60

EXPERIMENTAL

The melting points were determined on a Kofler block. Optical rotation was determined on an automatic polarimeter of Perkin-Elmer, model 141. The IR spectra were measured on a Perkin-Elmer, model 457 spectrophotometer. Thin-layer chromatography on silica gel G was carried out in system A, chloroform-methanol (6 : 1), partition chromatography on paper Whatman No 1 and preparative chromatography on Whatman cellulose powder was carried out in systems B, acetone-butanol-water (7 : 2 : 1), and C, water saturated 2-butanone. Detection of lactones on paper was carried out with hydroxylamine and ferric chloride¹⁰, detection of 3-deoxyaldoses with potassium periodate and benzidine¹¹. Preparation of 3-deoxyaldos-2-uloses was carried out according to literature⁶.

3-Deoxyhexos-2-ulose bis(benzoylhydrazone)

D-erythro isomer: To a solution of 2 g of D-glucose in 72 ml of ethanol and 8 ml of water acetic acid (1.6 ml) and *p*-toluidine (0.8 g) were added and the mixture refluxed for 30 minutes. Benzoylhydrazine (2.6 g) was then added and refluxing continued for 7 hours. After cooling the solution was concentrated to 25–30 ml. After 16 hours standing the separated crystals were filtered off, washed with ethanol, ether and dried. Yield, 1.1 g, m.p., 188–190°C. From the mother liquor another 0.33 g of pure hydrazone were obtained. Concentration of the mother liquor to approx. 15 ml gave further 0.5 g of crystals containing in addition to the required product (in system A: R_F 0.76) substances of R_F 0.49 and 0.30. Column chromatography (3 × 55 cm) on silica gel L 100–160 mesh in system A of mother liquors gave 0.3 g of pure product of m.p. 189–191 °C. Total yield 1.73 g (39.5%). Crystallization from ethanol gave an analytically pure sample, m.p. 192–193°C $[\alpha]_D^{22} + 19.8^\circ$ (*c* 0.5, pyridine), in agreement with literature⁶. *D-threo isomer*: A mixture of 1.8 g of D-galactose, 43 ml of ethanol, 5 ml of water, 2 ml of acetic acid and 1 g of *p*-toluidine was refluxed for 30 minutes, then added with 4.08 g of benzoyl-hydrazine and further refluxed for 6 hours. Yield, 1.6 g (40%), m.p. 199–203°C, $[\alpha]_D^{22} - 49^\circ$ (*c* 1, pyridine). Crystallization from

ethanol gave a substance of m.p. 204–206°C $[\alpha]_D^{22} - 52.1^\circ$ (*c* 1, pyridine), in accordance with literature⁶.

3-Deoxypentos-2-ulose bis(benzoylhydrazone)

D-glycero isomer: A mixture of 2 g of *D*-xylose, 32 ml of ethanol, 8 ml of water, 0.8 ml of acetic acid, and 0.8 g of *p*-toluidine was refluxed for 30 minutes, 2.6 g of benzoylhydrazine was added to it and the refluxing continued for another 3 hours. After cooling the first crop of crystals was obtained (0.94 g) which was filtered off, washed with ethanol and ether. From the mother liquor another 0.16 g of product were obtained. Total yield 1.1 g (46%), m.p. 228–230°C, $[\alpha]_D^{22} - 16.1^\circ$ (*c* 1, pyridine) Crystallization from ethanol gave a pure sample, m.p. 228–230°C, $[\alpha]_D^{22} - 18.2^\circ$ (*c* 1, pyridine), in agreement with the literature⁶.

γ -Lactones of 3-Deoxyaldonic Acids

A solution of 3 g of 3-deoxyaldos-2-ulose in 2000 ml of a saturated Ca(OH)₂ solution was allowed to stand at room temperature for 18 hours. It was then neutralized with solid carbon dioxide, heated to 100°C and filtered. The filtrate was concentrated to 120–150 ml and filtered through a column of Amberlite IR-120 (H⁺). The eluate was concentrated and the residue containing a mixture of epimeric γ -lactones of 3 deoxyaldonic acids was chromatographed on a Whatman cellulose column with water saturated 2-butanone. The course of separation was observed by paper chromatography. Fractions containing pure lactones were combined and concentrated, and crystallized from ethanol.

D-ribo and *D*-arabino isomers: Starting with 3 g of 3-deoxy-*D*-erythro-hexos-2-ulose 2.2 g of a syrup were obtained which was chromatographed to give 0.5 g (16.6%) of γ -lactone of 3-deoxy-*D*-ribo-hexonic acid, m.p. 108–109°C and $[\alpha]_D^{22} + 26.2^\circ$ (*c* 1, H₂O), in accordance with the literature¹², and 0.97 g (32.3%) of γ -lactone of 3-deoxy-*D*-arabino-hexonic acid, m.p. 90–92°C, $[\alpha]_D^{22} + 5.8^\circ$ (*c* 1, H₂O). Literature¹² gives m.p. 92–93°C, $[\alpha]_D^{22} + 6.4^\circ$ (*c* 0.8, H₂O). A fraction containing a mixture of both lactones (0.43 g) was also obtained from which another 0.15g of *D*-ribo γ -lactone crystallized out, so that the total yield was 0.65 g (21.6%).

TABLE II

Physical Constants of 3-Deoxy-*D*-aldoses

3-Deoxy- <i>D</i> -aldose	Yield, %	M.p. °C	$[\alpha]_D^{22a}$	Literature		
				m.p., °C.	$[\alpha]_D$	ref.
<i>ribo</i> -Hexose	62	103–105	+ 30°	105–106	+ 32°	12
<i>arabino</i> -Hexose	56	133–141	+ 50.3°	141–142	+ 53.1°	17
<i>xylo</i> -Hexose	60	sirup	+ 5.1°	sirup	+ 6.94°	18
<i>lyxo</i> -Hexose	52	sirup	– 6.9°	sirup	– 10.4°	18
<i>erythro</i> -Pentose	52	sirup	– 6.3°	sirup	– 8.2°	19
<i>threo</i> -Pentose	46	sirup	– 3.1°	sirup	–	16

^a In water, *c* 1, equilibrium.

D-xylo and *D*-lyxo isomers: Using 3 g of 3-deoxy-*D*-threo-hexos-2-ulose 2.1 g of a syrup were obtained. After chromatographic separation 0.62 g (20.6%) of a sirupy γ -lactone of 3-deoxy-*D*-lyxo-hexonic acid, $[\alpha]_D^{22} - 41.2^\circ$ (*c* 1, H₂O), and 1.1 g (36.6%) of γ -lactone of 3-deoxy-*D*-xylo-hexonic acid, m.p. 143–145°C, $[\alpha]_D^{22} - 46.1^\circ$ (*c* 1, H₂O), were obtained. For the latter lit.¹³ gives m.p. 142–143°C, $[\alpha]_D^{22} - 47.8^\circ$ (*c* 1, H₂O).

D-threo and *D*-erythro isomers: Using 3 g of 3-deoxy-*D*-glycero-pentos-2-ulose 1.85 g of syrup were obtained. After chromatographic separation 0.42 g (14%) of a sirupy γ -lactone of *D*-erythro-pentonic acid, $[\alpha]_D^{22} + 22.1^\circ$ (*c* 1, H₂O), and 0.68 g (22.7%) of a sirupy γ -lactone of 3-deoxy-*D*-threo-pentonic acid, $[\alpha]_D^{22} + 28.0^\circ$ (*c* 1, H₂O) were obtained. IR spectra (nujol) of both lactones: $\nu(\text{C}=\text{O})$ 1765 cm⁻¹. Both lactones were converted to brucine derivatives. The brucine salt of 3-deoxy-*D*-threo-pentonic acid had m.p. 134–136°C, $[\alpha]_D^{22} - 33.1^\circ$ (*c* 1, H₂O). Lit.¹⁴ gives m.p. 133–135°C, $[\alpha]_D^{22} - 32^\circ$ (*c* 2-28, H₂O). Brucine salt of 3-deoxy-*D*-erythro-pentonic acid had m.p. 197–198°C, $[\alpha]_D^{22} - 21.4^\circ$ (*c* 1, H₂O). Lit.¹⁴ gives m.p. 195–198°C, $[\alpha]_D^{22} - 23.4^\circ$ (*c* 1, H₂O).

3-Deoxyaldoses

3-Deoxyaldoses were prepared by reduction of corresponding lactones with 2.5% sodium amalgam¹⁵. To a solution of 0.5 g of the lactone in 10–15 ml of dilute H₂SO₄ (pH 3–3.5) at 5°C Amberlite OR-120 (H⁺) (15 ml) was added, followed by gradual addition (under stirring at 5°C) of 10 g of 2.5% NaHg. The reaction mixture was then stirred for one hour, decanted from mercury, filtered from Amberlite, which was washed with water. The filtrates were neutralized with BaCO₃, filtered, concentrated to a sirup and chromatographed on a Whatman cellulose column, using the system B as eluent. The results are presented in Table II. 3-Deoxy-*D*-threo-pentose was converted to its 1-benzyl-1-phenylhydrazone. Our product had m.p. 85–86°C, $[\alpha]_D^{22} 15.4^\circ$ (*c* 1, pyridine). Lit.¹⁶ gives m.p. 86–86.5°C, $[\alpha]_D^{22} + 16.2^\circ$ (*c* 1, pyridine).

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