Quinoxalines Derived from D-Galactose and *o*-Phenylenediamine in Acidic Media

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Quinoxalines derived from D-galactose with *o*-phenylenediamine (OPD) in acidic media under reflux were studied by using GLC and NMR measurements. Four quinoxaline derivatives were obtained from the reaction mixture, and were identical with those derived from D-glucose. The yields of 2-(D-*lyxo*-tetrahydroxybutyl)quinoxaline (GA-III), and the stereoisomeric derivative of GA-III, *i.e.*, 2-(D-*arabino*-tetrahydroxybutyl)quinoxaline (ATBQ), were 13.2 and 5.3%, respectively. The ratio of GA-III to ATBQ derived from D-galactose was reciprocally coincident with that from D-glucose. Some proposals are made on the relationship between the isomerization of these sugars and the formation of quinoxaline derivatives.

2-(D-*Arabino*-tetrahydroxybutyl)quinoxaline (ATBQ) is known as a condensation product of D-glucose or D-fructose with *o*-phenylenediamine (OPD), and a structure has been proposed by Horton and Miller,¹⁾ and other investigators.^{2,3)}

In the course of studies on quinoxaline formation from D-glucose in acidic media, we isolated 2-(1',2',3',4'-tetrahydroxybutyl)-quinoxaline (GA-III) which is a stereoisomer of ATBQ, and three other quinoxalines. Since ATBQ and GA-III were found to be stereoisomers of each other,⁴⁾ we were interested in studying the fine structures of GA-III and ATBQ.

Most of the quinoxaline derivatives formed in alkaline media including Na₂SO₃ are dihydro-forms at the C-1' of the side chain of the quinoxaline ring, such as 2-hydroxy-methyl-3-(2',3'-dihydroxypropyl)quinoxaline, 2-(2',3',4'-trihydroxybutyl)quinoxaline, and 2-(2',3'-dihydroxypropyl)quinoxaline.^{5,6)} This fact also suggests that some isomerization or enolization must occur before or after condensation. In this paper, we describe the configurational difference of GA-III and ATBQ.

We prepared GA-III, ATBQ and their acetates as reported previously.⁴⁾ When D-

galactose was used for the substrate of quinoxaline formation instead of D-glucose, quinoxaline derivatives identical with those from D-glucose were obtained, as shown in Fig. 1. The proportion of each quinoxaline derivatives formed was estimated to be GA-I 33.3%, G-1 4.4%, ATBQ 5.3% and GA-III 13.2%, using standard calibration curves. The total yield of quinoxalines from D-galactose was 56%. Excluding GA-I, GA-III was found to be the predominant derivative, and the ratio of GA-III to ATBQ was about 2.5. Considering that the ratio of ATBQ (18%) to GA-III (6.5%) from D-glucose was 2.7~2.8,⁴⁾ the configuration of the side chain of GA-III and ATBQ does not seem to change readily from that of the original hydroxyl groups of D-glucose under these acidic reaction conditions. To confirm this, the above two derivatives were studied by ¹H-NMR and ¹³C-NMR spectroscopies, as shown in Figs. 2, 3, and Table I. There were several differences in these two specimens. The δ_H value of GA-III at H-2' appeared in a lower field (5.87) than that of ATBQ (5.81). The $J_{1',2'}$ value of GA-III was 5.0 Hz and that of ATBQ, 3.4 Hz, whereas the $J_{2',3'}$ values of GA-III and ATBQ were 7.2 and

FIG. 1. Gas-liquid Chromatogram of TMS-Ethers of Quinoxaline Derivatives Obtained from D-Galactose in an Acidic Medium.

An aliquot of a 3 hr reaction mixture was evaporated to dryness. To the residue was added 0.1 ml of pyridine containing an internal standard, followed by trimethylsilylation, and the products were subjected to GLC, using a glass column (0.2×150 cm) packed with 4% SE-52 on Gaschrom Q (80~100 mesh). The column temperature was raised from 140°C to 220°C at a rate of 2°C/min. GA-I, 2-(2',3'-dihydroxypropyl)-3-methylquinoxaline; G-I, 2-(2',3',4'-trihydroxybutyl) quinoxaline; ATBQ, 2-(D-arabino-tetrahydroxybutyl) quinoxaline; GA-III, 2-(D-lyxo-tetrahydroxybutyl) quinoxaline; I.S., internal standard (β -phenyl-D-glucoside).

8.8 Hz, respectively. The δ_c values of 63.2 and 72.2 for GA-III, and 64.2 and 72.0 for ATBQ were assigned to C-4' and C-3', respectively, from our previous experience of very similar structures at side chains⁷⁾ of the quinoxaline ring.⁸⁾ The δ_c values of 74.5 for GA-III and 73.1 for ATBQ were attributed to C-1' after selective decoupling at the H-1' proton. These results suggest that the configuration of the hydroxyl residue at C-1' and C-2' should be erythro for GA-III and threo for ATBQ, and that the projected angle between the C-H bonds on C-1' and C-2' is approximately 130° for GA-III and 50° for ATBQ in the favored rotamer state.^{1,9)} Similarly, the $J_{2',3'}$ values of GA-III and ATBQ indicate projected angles of approximately 150° and 180°, respectively, between the C-H bonds on C-2' and C-3' in the favored rotamer state.

The value of specific rotation of ATBQ was -110° , whereas that of GA-III was almost the opposite ($+130^\circ$). These results also suggest

FIG. 2. 100 MHz ^1H -NMR Spectra of Acetylated GA-III (A) and ATBQ (B) in CDCl_3 .

FIG. 3. Proton Noise-decoupled 25.2 MHz ^{13}C FT-NMR of GA-III (A) and ATBQ (B) in $\text{DMSO}-d_6$.

A, 2-(D-lyxo-tetrahydroxybutyl) quinoxaline; B, 2-(D-arabino-tetrahydroxybutyl) quinoxaline.

that the hydroxyl residues of GA-III and ATBQ may have opposite configurations, at least at the C-2' position, which corresponds to the C-4 position of the original sugar.

On the basis of these results, we propose these zig-zag structures of the side chains of GA-III and ATBQ.¹⁾

TABLE I. ¹H-NMR SPECTRAL DATA ON GA-III AND ATBQ DERIVED FROM D-GALACTOSE AND D-GLUCOSE

The spectra were determined in CDCl₃ with tetramethylsilane as an internal standard at 100 MHz. The chemical shifts are given as δ -values in ppm. Singlet, s; doublet, d; double doublet, dd; quartet, q; multiplet, m.

Protons	Chemical shift		Integral protons		Multiplicity		Coupling constant	
	GA-III	ATBQ	GA-III	ATBQ	GA-III	ATBQ	GA-III	ATBQ
H-3	8.900	8.852	1	1	s	s		
H-5,8	8.079	8.086	2	2	m	m		
H-6,7	7.775	7.839	2	2	m	m		
H-1'	6.331	6.320	1	1	d	d	$J_{1',2'}=5.0$	$J_{1',2'}=3.4$
H-2'	5.872	5.808	1	1	q	q	$J_{2',3'}=7.2$	$J_{2',3'}=8.8$
H-3'	5.244	5.393	1	1	m	m		
Ha-4'	4.391	4.370	1	1	dd	dd	$J_{3',4a'}=3.4$	$J_{3',4a'}=3.2$
Hb-4'	4.162	4.167	1	1	dd	dd	$J_{3',4b'}=5.4$	$J_{3',4b'}=5.0$
1'-OAc	2.236	2.241	3	3	s	s	$J_{4a',4b'}=12.5$	$J_{4a',4b'}=12.5$
2'-OAc	2.070	2.103	3	3	s	s		
3'-OAc	2.043	2.059	3	3	s	s		
4'-OAc	2.004	1.934	3	3	s	s

GA-III

ATBQ

It is interesting that both of these stereoisomeric derivatives are easily obtained from either D-glucose or D-galactose. In the alkaline solution, D-glucose, D-mannose and D-fructose form the same 1,2-dicarbonyl compounds, followed by the formation of the same quinoxaline derivatives by condensation with OPD. Therefore, we cannot determine the degree of isomerization for each. Since D-galactose is the C₄ epimer of D-glucose, the quinoxalines formed are considered to differ only in the configuration of the hydroxyl group at the C-2' position of the side chain in the quinoxaline ring. If it is assumed that OPD does not have any specific effect on the isomerization of sugars in solution, we may estimate the ratio or rate of isomerization of the epimers in an acidic solution from the quinoxalines formed. The approximate ratios of epimerization of D-glucose to D-galactose, or D-galactose to D-glucose, were almost equal and estimated to be in the range of 35% to 40% of the original sugars. Furthermore, the transformation between GA-III and ATBQ probably

did not occur under the reaction conditions used, because no significant changes in the amounts of GA-III and ATBQ were observed by gas-liquid chromatography with time. In alkaline media, enediol or dicarbonyl compounds of sugars¹⁰⁾ are formed first by cleavage of the C-C linkages, followed by the formation of various quinoxaline derivatives by condensation with OPD, as reported previously.^{11,12)} In acidic media, however, such a decomposition of sugar does not seem to occur, and the C₄ epimer of the original sugar may be formed as a result of 3,4-enediol formation.

EXPERIMENTAL

All evaporations were carried out below 40°C. Melting points were measured with a Kofler hot stage apparatus and are uncorrected. The value of specific rotation was analyzed with a Union Giken PM-60 High Sensitivity Polarimeter. 100 MHz ¹H-NMR spectra of acetylated quinoxalines in CDCl₃ and 25.2 MHz ¹³C-NMR spectra of quinoxalines in DMSO-*d*₆ were analyzed with a Varian XL-100. GLC was carried out with a Yanagimoto GCG-550F on a column (0.2 × 150 cm) of 4% SE-52, as described previously.^{4,7)} Elementary analysis was made with a Yanagimoto MT-1 CHN-corder.

2-(D-Arabetetrahydroxybutyl)quinoxaline (ATBQ). This compound was prepared from D-glucose as reported

previously⁴⁾: mp 190~191°C; $[\alpha]_D^{25} - 110^\circ$ (c 0.4, MeOH); UV $\lambda_{\max}^{\text{MeOH}}$ nm (ϵ): 237 (30,700), 317 (8240); IR $\nu_{\max}^{\text{KBr}}$ cm⁻¹: 3260 (br), 2910, 1520, 1370 (s), 1250, 1090, 1045 (s), 975, 870 (s), 775 and 755.

2-(D-Lyxo-tetrahydroxybutyl)quinoxaline (GA-III).

This compound was prepared from D-galactose by the procedure described previously.^{4,7)} Equimolar amounts of D-galactose and OPD were suspended in a mixture of methanol, acetic acid and deionized water (8:1:2, v/v), with bubbling of nitrogen gas and refluxed at 80°C under deoxygenated conditions for 3 hr in a three-necked flask. After evaporation of the reaction mixture, the residue was extracted with acetone. The acetone-insoluble materials were dissolved in ethanol, and this solution was subjected to silica gel column chromatography using *n*-hexane-ether-ethanol (2:2:1) as an effluent solvent. The main fractions containing the desired quinoxaline, GA-III, were pooled and evaporated to dryness, and the residue was dissolved in hot ethanol. After cooling of the solution, colorless fine needles were obtained: mp 173°C; $[\alpha]_D^{25} + 130^\circ$ (c 0.4, MeOH); UV $\lambda_{\max}^{\text{MeOH}}$ nm (ϵ): 237 (27,700), 317 (7280); IR $\nu_{\max}^{\text{KBr}}$ cm⁻¹: 3320, 3280, 3185, 2910, 2860, 1520, 1485, 1310 (s), 1290 (s), 1205 (s), 1135, 1090, 1025 (s), 975, 805, 755 (s) and 645. Found: C, 57.59; H, 5.64; N, 11.19. Calcd. for C₁₂H₁₄N₂O₄: C, 58.72; H, 5.73; N, 11.62%.

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