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Note

Some quinoxaline derivatives from dehydro-D-*arabino*-ascorbic acid

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In a program in our laboratory devoted to the synthesis of heterocyclic compounds in the carbohydrate series, different heterocycles have been prepared, including imidazoles[1], pyrazoles[2,3], triazoles[4], and isoxazolines[4]. In the present Note, we describe the ring transformation of D-*arabino*-ascorbic acid into quinoxaline derivatives through its reaction with *o*-phenylenediamine.

The reaction of dehydro-L-ascorbic acid with *o*-phenylenediamine gives a variety of products that depend upon the reaction conditions and the ratio of the reactants[5–11]. The condensation of dehydro-L-ascorbic acid with one mol. equiv. of *o*-phenylenediamine, gave the monoquinoxaline derivatives[5–7]. On the other hand, the reaction of two mol of *o*-phenylenediamine with one mol of dehydro-L-ascorbic acid was a subject for argument, as different structures[5,10,11] were proposed for the reaction product. The structure proposed by Dahn and Moll[10], for a quinoxaline 3-hydroxyalkyl 2-carboxylic acid anilide obtained, depended on its infrared spectrum.

We have now extended this reaction to the 5-epimer of dehydro-L-ascorbic acid, namely, D-*erythro*-2,3-hexodiulosono-1,4-lactone. Thus, oxidation of D-*arabino*-ascorbic acid with an equimolar amount of *p*-benzoquinone in aqueous solution at room temperature, followed by reaction with two equivalents of *o*-phenylenediamine, gave a yellow, crystalline product (**4**), namely, 3-(D-*erythro*-glycerol-1-yl)quinoxaline-2-carboxylic acid *o*-aminoanilide, instead of the bis-quinoxaline derivative proposed by Erlbach and Ohle[5]. The infrared spectrum of **4** showed a band in the carbonyl frequency region at 1680 cm^{-1}.

Periodate oxidation of **4** consumed two mol of the oxidant, affording 3-formylquinoxaline-2-carboxylic acid *o*-aminoanilide (**5**), favoring the acyclic structure of its precursor. The reaction of *o*-phenylenediamine with dehydro-D-*arabino*-ascorbic acid, *via* the acyclic 2,3-hexodiulosonic acid (**3**), was supported by the fact that dehydroascorbic acid exists[12] in solution as an equilibrium mixture of the 1,4-lactone and the acyclic acid.

Acid hydrolysis of 3-(D-*erythro*-glycerol-1-yl)quinoxaline-2-carboxylic acid *o*-aminoanilide (**4**) afforded the monoquinoxaline **6**, namely, 3-(D-*erythro*-glycerol-1-yl)quinoxaline- 2-carboxylic γ-lactone. Its infrared spectrum showed the lactone band at 1760 cm^{-1}, and the hydroxyl absorption at 3450 cm^{-1}, with disappearance

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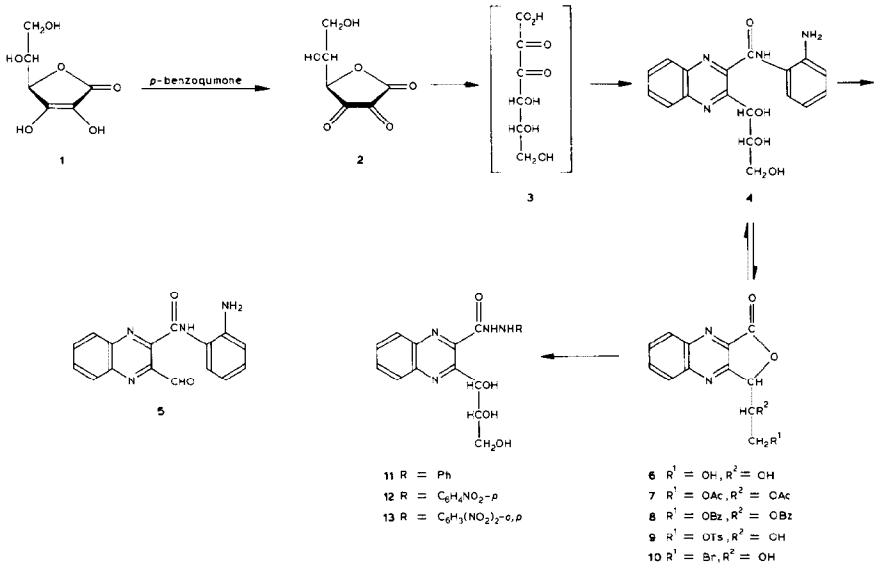

of the amide band of its precursor. This mono-quinoxaline **6** readily reverts to compound **4** upon treatment with *o*-phenylenediamine, whereby the lactone ring is opened. Acetylation of **6** with boiling acetic anhydride, or with acetic anhydride–pyridine, gave 3-(D-*erythro*-2,3-di-*O*-acetylglycerol-1-yl)quinoxaline-2-carboxylic γ-lactone (**7**). Similarly, benzoylation of **6** with benzoyl chloride in pyridine afforded the dibenzoate (**8**). Selective *p*-toluenesulfonylation of **6** gave the mono-*p*-toluenesulfonate (**9**). In addition, treatment of compound **6** with HBr–HOAc gave the bromodeoxy derivative (**10**).

Treatment of compound **6** with phenyl-, (*p*-nitrophenyl)-, or (2,4-dinitrophenyl)-hydrazine in methanol afforded the corresponding quinoxaline-2-carboxylic acid hydrazides (**11–13**).

EXPERIMENTAL

General methods. — Melting points were determined with a Tottoli (Büchi) apparatus and are uncorrected. I.r. spectra were recorded with a 580 B Perkin–Elmer spectrometer, and n.m.r. spectra (for solutions in chloroform-*d*), with tetramethylsilane as the standard, with a Varian EM 390 instrument. Chemical shifts are given on the δ scale. Microanalyses were performed in the Chemistry Department, Faculty of Science, Cairo University, Cairo, Egypt.

*3-(*D-erythro-*Glycerol-1-yl)quinoxaline-2-carboxylic acid* o-*aminoanilide* (**4**). — A mixture of D-*arabino*-ascorbic acid (17.6 g, 0.1 mol) and *p*-benzoquinone (10.8 g, 0.1 mol) in 1:1 methanol–water (200 mL) was stirred for 2 h at room temperature, treated with a solution of *o*-phenylenediamine (21.8 g, 0.2 mol) in methanol

(100 mL), heated for 2 h at 40°, and allowed to cool. The solid that separated out was filtered off, successively washed with water, ethanol, and ether, and dried (yield 23.6 g). It was recrystallized from ethanol, giving yellow needles, m.p. 218–219° (lit.[5] m.p. 210–212°); ν_{max}^{KBr} 3450 and 1680 cm^{-1} (OCN); λ_{max}^{EtOH} 240 and 282 nm (log ε 3.77 and 3.13); λ_{min}^{EtOH} 224 and 270 nm (log ε 3.58 and 3.09).

Anal. Calc. for $C_{18}H_{18}N_4O_4$: C, 61.0; H, 5.1; N, 15.8. Found: C, 60.6; H, 5.1; N, 16.0.

*3-(*D-erythro-*Glycerol-1-yl)quinoxaline-2-carboxylic γ-lactone* (**6**). — A suspension of compound **4** (1 g) in water (20 mL) was treated with 0.1M hydrochloric acid (50 mL) and stirred for 24 h at room temperature. The solid was filtered off, washed successively with water and ethanol, and dried (yield 0.5 g). It was recrystallized from ethanol, to give colorless needles, m.p. 184–186° (lit.[5] m.p. 184–186°).

*3-(*D-erythro-*2,3-Di-*O*-acetylglycerol-1-yl)quinoxaline-2-carboxylic γ-lactone* (**7**). — A suspension of compound **6** (0.1 g) in acetic anhydride (10 mL) was refluxed for 30 min. The mixture was poured onto crushed ice, and the product was filtered off, successively washed with water and ethanol, and dried (yield 0.1 g). It was recrystallized from ethanol: colorless needles, m.p. 178–179° (lit.[5] m.p. 185–186°); ν_{max}^{KBr} 1750 cm^{-1} (ester + lactone C=O); λ_{max}^{EtOH} 246 and 318 nm (log ε 4.56 and 3.92); λ_{min}^{EtOH} 226 and 284 nm (log ε 4.22 and 3.82); ^{1}H-n.m.r. data: δ 1.95 and 2.05 (2 s, 6 H, 2 $OCOCH_3$), 4.5 (m, 2 H, H-3), 5.7 (m, 1 H, H-2), 5.95 (d, 1 H, $J_{1,2}$ 6 Hz, H-1), and 7.4–8.4 (m, 4 H, quinoxaline).

3-Formylquinoxaline-2-carboxylic o-*aminoanilide* (**5**). — A suspension of compound **4** (1 g) in water (50 mL) was treated with a solution of sodium metaperiodate (2 g) in water (50 mL), and shaken for 24 h at room temperature. The solid was filtered off, washed with water, and dried. It was recrystallized from ethanol; brown needles, m.p. 212–214°; ν_{max}^{KBr} 1700 (COH) and 1660 cm^{-1} (OCN); λ_{max}^{EtOH} 240 and 307 nm (log ε 3.95 and 3.37); λ_{min}^{EtOH} 224 and 270 nm (log ε 3.80 and 3.35).

Anal. Calc. for $C_{16}H_{12}N_4O_2$: C, 65.8; H, 4.1. Found: C, 65.3; H, 4.0.

*3-(*D-erythro-*2,3-Di-*O*-benzoylglycerol-1-yl)quinoxaline-2-carboxylic γ-lactone* (**8**). — A solution of compound **6** (0.1 g) in dry pyridine (10 mL) was treated with benzoyl chloride (0.1 mL), and the mixture was kept overnight at room temperature. The mixture was poured onto crushed ice, and the product was filtered off, successively washed with water and ethanol, and dried. It was recrystallized from ethanol; colorless needles, m.p. 172–174°; ν_{max}^{KBr} 1760 cm^{-1} (ester + lactone C=O).

Anal. Calc. for $C_{26}H_{18}N_2O_6$: C, 68.7; H, 4.0; N, 6.2. Found: C, 68.5; H, 4.2; N, 6.3.

Reaction of compound **6** *with* o-*phenylenediamine.* — A solution of compound **6** (1 g) in methanol (20 mL) was treated with a solution of *o*-phenylenediamine (1 g) in methanol (20 mL), and stirred for 2 h at 40°. The solid was filtered off, washed with methanol, and dried. It was recrystallized from ethanol; yellow needles, m.p. 218–219°, alone, or admixed with compound **4**.

p-*Toluenesulfonate* (**9**). — A solution of compound **6** (0.1 g) in dry pyridine

TABLE I

MICROANALYTICAL AND INFRARED-SPECTRAL DATA FOR COMPOUNDS **11–13**

Compound	*R*	*M.p (degrees)*	*Molecular formula*	*Analysis*				*ν (cm⁻¹) OCN*
					C	*H*	*N*	
11	C_6H_5	165–167	$C_{18}H_{18}N_4O_4$	Calc.	61.0	5.1		1660
				Found	61.3	5.3		
12	$C_6H_4NO_2$-*p*	190–192	$C_{18}H_{17}N_5O_6$	Calc.	54.1	4.3	17.5	1660
				Found	53.8	4.7	17.1	
13	$C_6H_3(NO_2)_2$-*o,p*	195–197	$C_{18}H_{16}N_6O_8$	Calc.	48.7	3.6	18.9	1660
				Found	48.9	3.8	19.3	

(10 mL) was treated with *p*-toluenesulfonyl chloride (0.1 g). The mixture was kept overnight at room temperature, and then poured onto crushed ice. The product was filtered off, successively washed with water and ethanol, and dried. It was recrystallized from ethanol; colorless needles, m.p. 148–150°; ν_{max}^{KBr} 3450 (OH) and 1730 cm^{-1} (lactone C=O).

Anal. Calc. for $C_{19}H_{16}N_2O_6S$: C, 57.0; H, 4.0; N, 7.0. Found: C, 57.2; H, 4.1; N, 6.8.

*3-(*D-erythro-*3-Bromo-3-deoxyglycerol-1-yl)quinoxaline-2-carboxylic γ-lactone* (**10**). — A suspension of compound **6** (0.1 g) in HBr–HOAc (30 mL) was stirred for 24 h at room temperature. Water (40 mL) was added, and the solid that separated out was filtered off, washed successively with water and ethanol, and dried. It was recrystallized from ethanol, to give colorless needles, m.p. 170–172°; ν_{max}^{KBr} 3450 (OH) and 1740 cm^{-1} (lactone C=O).

Anal. Calc. for $C_{12}H_9BrN_2O_3$: C, 46.6; H, 2.9. Found: C, 46.8; H, 3.0.

*3-(*D-erythro-*Glycerol-1-yl)quinoxaline-2-carboxylic acid hydrazides* (**11–13**). — A solution of compound **6** (1 g) in ethanol was treated with phenyl-, (*p*-nitrophenyl)-, or (2,4-dinitrophenyl)-hydrazine (1 g). The mixture was heated under reflux for 6 h, concentrated to a small volume, and kept at room temperature. The solid that separated out was filtered off, successively washed with water and ethanol, and dried. Each product was recrystallized from ethanol, giving pale-yellow needles (see Table I).

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