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Note

A pyrido[1,2*a*]quinoxaline derivative: reaction product of D-*threo*-2,5-hexodiulose with *o*-phenylenediamine

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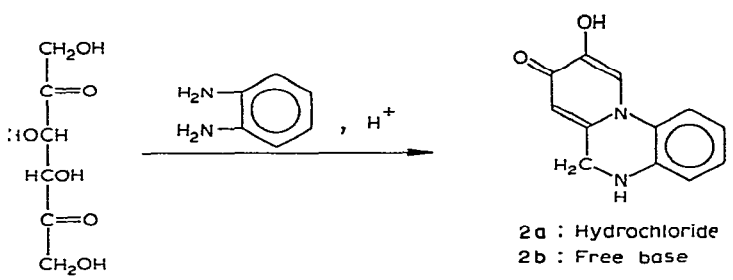
This work arose from attempts to synthesize nitrogen heterocycles from 2,5-dicarbonyl saccharide derivatives (D-*threo*-2,5-hexodiulose[1–3] and D-*threo*-2,5-hexodiulosonate[4,5]) with the aim of studying the chemistry and biological activity of such heterocycles.

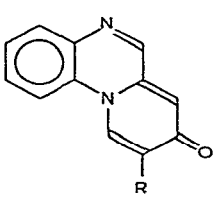
In a previous paper[6–8], it was shown that these saccharides are useful intermediates for synthesis of pyridazine derivatives. This note describes a reaction product of D-*threo*-2,5-hexodiulose (**1**) with *o*-phenylenediamine.

It has long been known[9–11] that reducing sugars react with this *o*-diamine to give mainly quinoxalines, together with imidazoles. However, the reaction of **1** with *o*-phenylenediamine dihydrochloride resulted in the formation of a tricyclic nitrogen heterocycle, 5,6-dihydro-9-hydroxy-8-oxopyrido[1,2*a*]quinoxaline hydrochloride (**2a**).

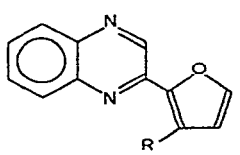


1

2a : Hydrochloride
2b : Free base



7a : R = H
7b : R = OH



8a : R = H
8b : R = OH

Such a heterocyclic system is relatively uncommon, except for the compounds that have been termed glucazidone (**7a**) and oxyglucazidone[12] (**7b**), formed by dehydration of the polyhydroxyl chain of 2-(D-*arabino*-tetrahydroxybutyl)quinoxaline. However, these products (**7a** and **7b**) were later shown to be 2-(2-furyl)quinoxaline derivatives (**8a** and **8b**, respectively)[13] and not pyrido[1,2a]quinoxalines.

Condensation of **1** with the *o*-diamine dihydrochloride was conducted in water at room temperature. After two days, **2a** was obtained in 30–35% yield. The free base **2b** was obtained by neutralization with potassium carbonate, followed by recrystallization from ethanol.

The structure of **2b** followed from spectroscopic evidence, as shown in Table I, and was confirmed by its chemical behavior and by synthesis. The u.v. spectrum of **2b**

TABLE I

MICROANALYTICAL AND SPECTRAL DATA

Elemental analysis		*U.v.* λ_{max}^{MeOH}	*I.r.* ν_{max}^{KBr}	*N.m.r.*[b]	*Mass spectrum*
Calc. (%)[a]	*Found* (%)	*nm* (*log* ε)	(cm^{-1})	*δ, p.p.m., assignment*	m/e
C: 59.75	59.99	223 (4.46)	3060	4.90, s, –NH–C*H*$_2$–	214 (M^+)
H: 5.39	3.93	253 (4.11)	1640	6.38, s, =C*H*–CO–	
N: 11.61	11.23	276 (4.13)	1600	7.20–8.32, m, –C*H*=C*H*–C*H*=C*H*–	
		313 (3.40)	1455	8.67, s, –CO–C(OH)=C*H*–	
			1320	5.60[c], s, N*H*	
			1200	3.42[c], s, O*H*	
			1070		
			1055		
			750		

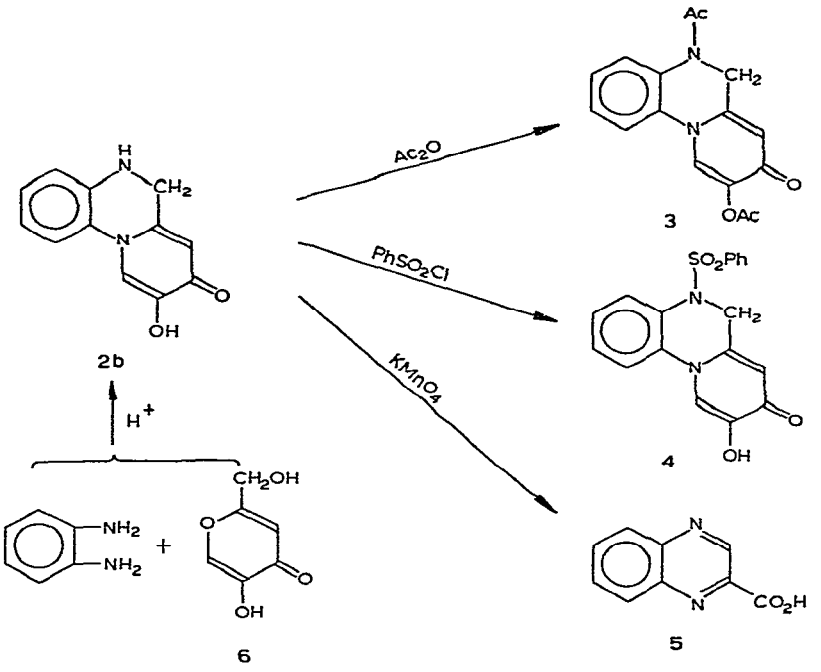
[a]Empirical formula: $C_{12}H_{10}N_2O_2 \cdot 1.5H_2O$. [b]Spectrum at 60 MHz in Me_2SO-d_6. [c]Exchanges upon addition of D_2O.

is closely similar to spectra of authentic 1-methyl-2-(hydroxymethyl)-5-hydroxy-4-pyridone[14] [λ_{max}^{MeOH} nm (log ε): 281(4.09)] and authentic 1,2,3,4-tetrahydroquinoxaline[15] [λ_{max}^{MeOH} nm (log ε): 219(4.45), 254(3.63), and 310(3.54)]. The i.r. spectrum of **2b** shows carbonyl vibration at 1640 cm^{-1} attributable to the C=O group of a γ-pyridone[16].

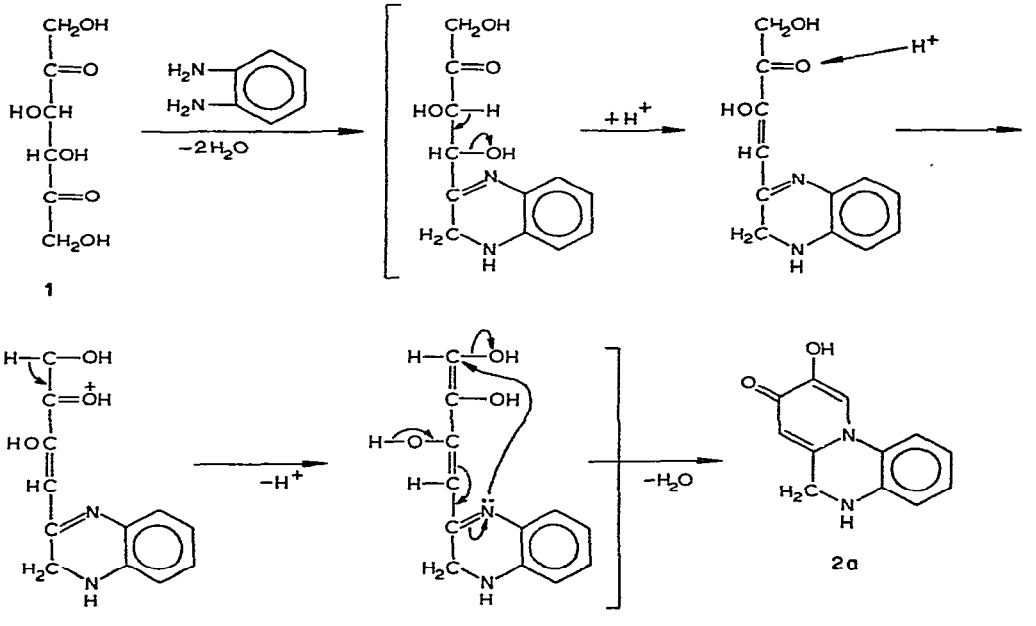
Acetylation of **2b** with acetic anhydride and pyridine afforded the corresponding diacetate (**3**). Treatment of **2b** with benzenesulfonyl chloride gave the corresponding monobenzenesulfate (**4**). Oxidation of **2a** with permanganate afforded quinoxaline-2-carboxylic acid (**5**), identical with an authentic sample[17]. Furthermore, compound **2b** was synthesized by condensation of kojic acid (**6**) with *o*-phenylenediamine dihydrochloride in water.

All of these data are thus consistent with the structure assigned to **2b**. The starting material (**i**) used in this experiment was obtained by the action of *Acetobacter* on D-glucitol[18].

The formation of the γ-pyridone ring attached to the quinoxaline ring may be



best explained in terms of a β-hydroxy–carbonyl elimination, 1,2-enolization[19], and cyclization of the sugar moiety, as deduced from the formation[20,21] of kojic acid (**6**) from **1**.



EXPERIMENTAL

General methods. — Melting points are uncorrected. I.r., u.v., n.m.r., and mass spectra were recorded with Hitachi EPI-G2, Hitachi 124, Hitachi 20-B, and Nihondenshi O1-SG spectrometers, respectively. All evaporations were performed under diminished pressure below 50°. T.l.c. was effected on Kieselgel G with methanol and detection was with 2% ferric sulfate reagent.

Reaction of D-threo-*2,5-hexodiulose* (**1**) *with* o-*phenylenediamine dihydrochloride.* — A solution of D-*threo*-2,5-hexodiulose (1.78 g) in water (20 ml) was treated with *o*-phenylenediamine dihydrochloride (1.81 g), and the mixture was kept for 2 days at room temperature under nitrogen. After filtration, the mixture was evaporated to dryness and the residue extracted with hot methanol (300 ml). The extract was evaporated almost to dryness to give a dark-brown, crystalline mass. Recrystallization from methanol gave 5,6-dihydro-9-hydroxy-8-oxopyrido[1,2a]quinoxaline hydrochloride (**2a**) as canary-yellow needles (0.75 g, 30%), m.p. >300°; $\lambda_{max}^{H_2O}$ 228 (log ε 4.48), 253(4.35), 293(3.91), and 350 nm(3.86); ν_{max}^{KBr} 3330 (OH or NH) and 1640 cm^{-1} (C=O); n.m.r. (Me_2SO-d_6+D_2O): δ 5.08 (s, 2H, $-CH_2-$), 6.70 (s, 1H, $-CH_2-C=CH-CO-$), 7.40–8.30 (m, 4H, aryl), 9.02 [s, 1H, =N–C*H*=C(OH)–]; t.l.c.: R_F 0.70 (yellow spot without spray reagent).

Anal. Calc. for $C_{12}H_{10}N_2O_2 \cdot HCl$: C, 57.48; H, 4.39; Cl, 14.17; N, 11.18. Found: C, 57.08; H, 4.44; Cl, 14.44; N, 11.24.

5,6-Dihydro-9-hydroxy-8-oxopyrido[*1,2*a]*quinoxaline* (**2b**). — Compound **2a** (700 mg) in water (100 ml) was neutralized with potassium carbonate. An orange-red solid precipitated rapidly. After 16 h of refrigeration, the product was collected, washed with water, and recrystallized from methanol–water to give **2b** (400 mg, 66.9%) as orange-red, fine needles, m.p. >300°.

5-Acetyl-5,6-dihydro-9-acetoxy-8-oxopyrido[*1,2*a]*quinoxaline* (**3**). — Compound **2b** (100 mg) was acetylated with acetic anhydride (0.8 ml) and pyridine (2 ml) for 16 h at room temperature. Pouring the mixture onto ice–water gave a yellow, crystalline solid that was washed with water and recrystallized from methanol–water to give **3** (108 mg, 77.6%) as white, fine needles, m.p. 169.5° (decomp.); λ_{max}^{MeOH} 219 (log ε 4.50), 252(4.23), and 348 nm (3.93); ν_{max}^{KBr} 1765 and 1735 cm^{-1} (C=O); n.m.r. (Me_2SO-d_6) δ 5.62 (s, 2H, $-CH_2-$), 6.97 (s, 1H, $-CH_2-C=CH-CO-$), 7.40–8.20 (m, 4H, aryl), 8.79 [s, 1H, =N–C*H*=C(OH)–], 2.10 (s, 3H, $-OCOCH_3$), 2.39 (s, 3H, $=NCOCH_3$).

Anal. Calc. for $C_{16}H_{14}N_2O_2$, C, 64.40; H, 4.70; N, 9.39. Found, C, 64.40; H, 4.70; N, 8.90.

5-Benzenesulfonyl-5,6-dihydro-9-hydroxy-8-oxopyrido[*1,2*a]*quinoxaline* (**4**). — A solution of **2b** (100 mg) in dry pyridine (4 ml) was treated with benzenesulfonyl chloride (80 mg), and kept for 18 h at room temperature. Evaporation yielded a brown syrup that crystallized spontaneously. Recrystallization from ethanol gave canary-yellow, fine needles of **4** (130 mg, 78.6%), m.p. 193° (decomp.); ν_{max}^{KBr} 1618 (C=O), 1320, and 1150 cm^{-1} (SO_2).

Anal. Calc. for $C_{18}H_{14}N_2O_4S$: C, 61.10; H, 3.96; N, 7.80; S, 9.04. Found: C, 61.10; H, 3.96; N, 7.41; S, 8.71.

Oxidation of **2a**. — Potassium permanganate (5 g) in water (100 ml) was added dropwise at room temperature to a stirred solution of **2a** (1 g) in water (50 ml). Manganese dioxide was removed and the yellow solution, after acidification, was extracted with chloroform. The residue left after evaporation of the chloroform was crystallized from ethanol to yield colorless needles (0.1 g), m.p. 210°, identical (mixed m.p. and i.r. and u.v. spectra) with authentic quinoxaline-2-carboxylic acid (**5**).

Reaction of kojic acid (**6**) *with o-phenylenediamine dihydrochloride.* — A solution of **6** (1.42 g) in water (40 ml) was treated with *o*-phenylenediamine dihydrochloride (1.81 g), and the mixture was heated for 5 h at 95°. The mixture containing some unchanged **6** and *o*-phenylenediamine dihydrochloride (t.l.c., R_F 0.55 and 0.75, respectively), was evaporated to dryness and the residue extracted with hot methanol (300 ml). The extract was evaporated almost to dryness to give a mass of crude crystals. Recrystallization from methanol (three times) gave canary-yellow, fine needles (0.5 g, 20%), identical (elemental analysis and i.r. and u.v. spectra) with **2a** obtained from the reaction of **1** with *o*-phenylenediamine dihydrochloride.

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