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Note

Condensation of *o*-phenylenediamine with dehydro-L-ascorbic acid derivatives and analogs

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Dehydro-L-ascorbic acid (**2**, R = CHOH-CH_2OH) reacts readily with an excess of *o*-phenylenediamine[1–3] to give[3] the quinoxaline **5** (R = CHOH-CH_2OH). In contrast, the reaction of **2** with one mole of *o*-phenylenediamine has been reported to give an unstable product[4,5] attributed[5] as the quinoxalinone **3** (R = CHOH-CH_2OH). We have investigated this reaction polarographically and have proposed a probable mechanism[6]. We have also condensed *o*-phenylenediamine with derivatives and analogs of **2**, and report here† on the condensation pathway.

When the oxidation of L-ascorbic acid analogs (**1a–c**) was followed by the addition of an excess of *o*-phenylenediamine, the corresponding quinoxalines (**5a–c**) were obtained‡ in 62, 31, and 40% yields, respectively, for **5a**, **5b**, and **5c**; **1b** gave the quinoxaline lactone **4b** in 23% yield. Hydrolysis of **5a** in aqueous hydrochloric acid gave the lactone **4a** almost quantitatively. Quinoxaline **5a** was also obtained from **4a** and an excess of *o*-phenylenediamine. Interconversion between **4a** and **5a** was thus readily achieved. These results are consistent with that of the condensation of dehydro-L-ascorbic acid with an excess of *o*-phenylenediamine, as reported earlier[3].

In the condensation of **2** with an excess of *o*-phenylenediamine, the intermediacy of **3** was confirmed by phenylhydrazine trapping according to the procedure of El Ashry *et al.*[5]. Treatment of **2a** stepwise with equimolar amounts of *o*-phenylenediamine and phenylhydrazine gave quinoxalinone **7** in 80% yield, accompanied by trace of quinoxalines **8** and **4a**, indicating that the major pathway is formation of quinoxalinone **3**, while a minor one is formation of lactone **4** in the condensation step of **2** with an equimolar amount of *o*-phenylenediamine.

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†The reaction of aryl analogs of **2** (R = aryl) with *o*-phenylenediamine have been reported[3,7].
‡The yield is based on the amount of **1** used.

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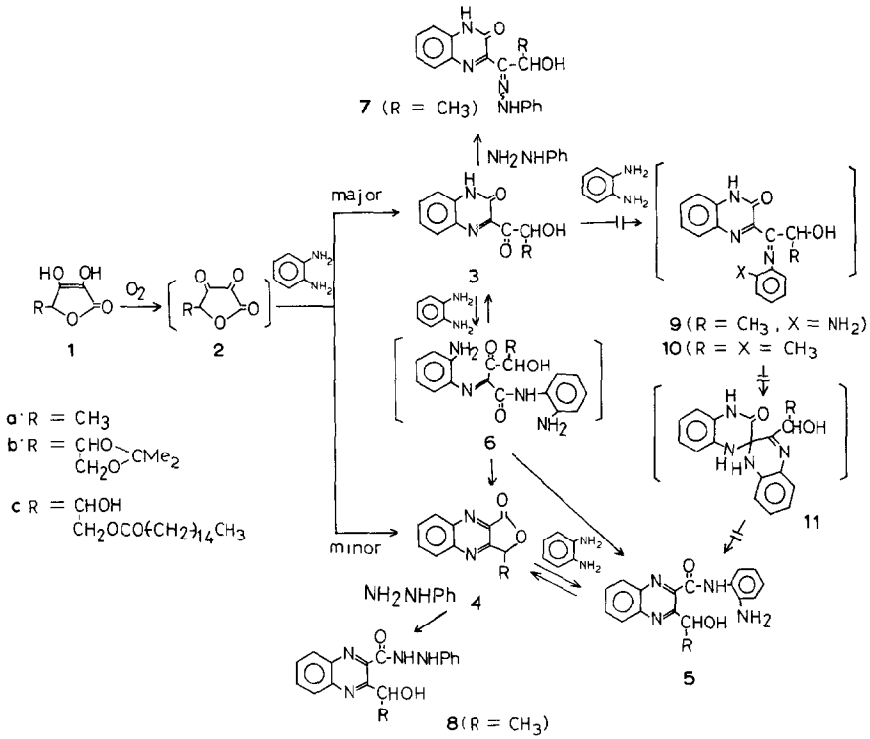
The reaction of **2a** with one and then a second mole of *o*-phenylenediamine gave **5a** and **4a** in 28 and 38% yields, respectively; the quinoxalinone **9** was not formed. The stepwise reaction of **2a** with equimolar amounts of *o*-phenylenediamine and *o*-toluidine gave a complicated mixture containing lactone **4a** (26%), but such adducts as **10** could not be isolated.

Based on these results, it is improbable that **3a** condenses with *o*-phenylenediamine to give adduct **9**, with further transformation into a spiro compound (**11**) *via* intramolecular cyclization and subsequent collapse[6,8] to **5**. The reaction pathway from **3** to **5** may involve fission of the amide bond of **3** by *o*-phenylenediamine to give an adduct **6**, which is rapidly transformed into **4** and/or **5**, as shown in the scheme. This reaction suggests that *o*-phenylenediamine behaves both as reactant and catalyst for the formation of **4** and/or **5**,



EXPERIMENTAL

General methods. — Melting points are uncorrected. 3,4-Dihydroxy-5-methylfuran-2-on[9] (**1a**) and 5,6-*O*-isopropylidene-L-ascorbic acid[10] (**1b**) were prepared according to the literature. All other reagents were commercially available. I.r. spectra were recorded with a Jasco A-3 spectrometer as thin films (Nujol). Mass spectrometry, ^{1}H-n.m.r. spectroscopy (solvent, Me_2SO-d_6; internal

standard, Me_4Si), and elemental analyses were carried out in the Department of Applied Fine Chemistry, Faculty of Engineering, Osaka University.

Reaction of analogs (**2a–c**) *of dehydro*-L-*ascorbic acid with an excess of o-phenylenediamine.* — A methanolic solution of **1** (30–40 mg/mL) was oxidized[11] by O_2/charcoal for 1–2 h, and then the solvent was evaporated *in vacuo*. The remaining residue was dissolved in small amounts of ethanol and 2 molar equivs. of *o*-phenylenediamine was added all at once to the solution. After 1 day, the precipitated solids were filtered off and recrystallized from ethanol. In the case of **1b**, lactone **4b** was isolated during the filtration procedure.

2-(2-Aminophenylcarbamoyl)-3-(1-hydroxyethyl)quinoxaline (**5a**). — This compound had m.p. 135–137° (dec.); ν_{CO} 1670 cm^{-1}; *m/z* 308 (M^+); ^{1}H-n.m.r.: δ 1.6 (d, 3 H, *J* 6 Hz, CH_3), 5.1 (m, 2 H, NH_2), 5.4 (m, 1 H, CH), 5.6 (d, 1 H, *J* 6 Hz, OH), 6.6–8.2 (m, 8 H, Ar), and 10.0 (br s, 1 H, CO-NH).

Anal. Calc. for $C_{17}H_{16}N_4O_2$: C, 66.22; H, 5.23; N, 18.17. Found: C, 66.37; H, 5.21; N, 18.03.

2-(2-Aminophenylcarbamoyl)-3-(2,3-O-isopropylidene-L-threo-*glycerol-1-yl)-quinoxaline* (**5b**). — M.p. 130–132° (dec); ν_{CO} 1680 cm^{-1}; *m/z* 394 (M^+); ^{1}H-n.m.r.: δ 1.5 (s, 6 H, 2 CH_3), 3.6–4.2 (2 m, 2 H, CH_2), 4.7 (m, 1 H, O-CH), 5.0 (br s, 2 H, NH_2), 5.5 (m, 1 H, CH), 5.9 (t, 1 H, *J* 8 Hz, OH), 6.4–8.2 (m, 8 H, Ar), and 10.1 (br s, 1 H, CO-NH).

Anal. Calc. for $C_{21}H_{22}N_4O_4$: C, 63.94; H, 5.62; N, 14.21. Found: C, 63.58; H, 5.70; N, 14.05.

3-(2,3-O-Isopropylidene-L-threo-*glycerol-1-yl)quinoxaline-2-carboxylic acid γ-lactone* (**4b**). — M.p. 230–235° (dec); ν_{CO} 1760 cm^{-1}; *m/z* 286 (M^+); ^{1}H-n.m.r.: δ 1.2 (2 s, 6 H, 2 CH_3), 4.4 (d, 2 H, *J* 8 Hz, CH_2), 4.8 (d t, 1 H, *J* 8, 4 Hz, CH), 6.0 (d, 1 H, *J* 4 Hz, CH-OCO), and 8.0–8.5 (m, 4 H, Ar).

Anal. Calc. for $C_{15}H_{14}N_2O_4$: C, 62.93; H, 4.93; N, 9.79. Found: C, 62.83; H, 4.84; N, 9.81.

2-(2-Aminophenylcarbamoyl)-3-(3-O-hexadecanoyl-L-threo-*glycerol-1-yl)-quinoxaline* (**5c**). — M.p. 115–117° (dec, from ethanol–acetone); ν_{CO} 1740 and 1660 cm^{-1}; *m/z* 592 (M^+); ^{1}H-n.m.r.: δ 0.8–1.0, 1.1–1.6, 2.1 (3 m, 31 H, hexadecanoyl), 4.0–4.4 (m, 3 H, CH_2 + CH), 4.8–5.2 (m, 3 H, 2 OH + CH), 5.5 (br s, 2 H, NH_2), 6.5–8.3 (m, 8 H, Ar), and 10.1 (br s, 1 H, CO-NH).

Anal. Calc. for $C_{34}H_{48}N_4O_5$: C, 68.89; H, 8.16; N, 9.45. Found: C, 68.91; H, 8.26; N, 9.14.

Interconversion between **4a** *and* **5a**. — Compound **5a** (700 mg, 2.3 mmol) was stirred in 0.8M HCl (15 mL) for 1 day at room temperature. Precipitated solids were filtered (fraction *A*). The filtrate was saturated with sodium chloride and extracted with ethyl acetate. Insoluble material (fraction *B*) was separated from the organic layer. Fractions *A* and *B* were collected, and small amounts of acetone–methanol were added. Unreacted **5a** was recovered from the insoluble portion by treatment with alkali (conversion 62%). Compound **4a** was obtained by the evaporation of the soluble portion (316 mg, 100% based on reacted **5a**). Compound

4a was also obtained from the reaction of **2a** with an excess of *o*-phenylenediamine in aqueous hydrochloric acid for 2 days at 50–60°, according to Dahn and Moll[3].

3-(1-Hydroxyethyl)quinoxaline-2-carboxylic acid γ-lactone (**4a**). — M.p. 165–167° (dec); ν_{CO} 1780 cm^{-1}; *m/z* 200 (M^+); ^{1}H-n.m.r.: δ 1.8 (d, 3 H, *J* 8 Hz, CH_3), 5.9 (q, 1 H, *J* 8 Hz, CH), and 8.0–8.5 (m, 4 H, Ar).

Anal. Calc. for $C_{11}H_8N_2O_2$: C, 65.99; H, 4.03; N, 13.99. Found: C, 65.80; H, 3.90; N, 13.96.

Conversion of **4a** *into* **5a**. — Compound **4a** (100 mg, 0.5 mmol) in 70% aqueous methanol (15 mL) was boiled under reflux with *o*-phenylenediamine (180 mg, 1.6 mmol) for 4 h. The mixture contained **4a** and **5a** (1:1.8) from l.c. analysis (Lichrosorb RP-8).

Phenylhydrazine trapping experiments. — A solution of **2a** in 2 mL of ethanol was mixed with *o*-phenylenediamine (162 mg, 1.5 mmol) and phenylhydrazine according to El Ashry *et al.*[5]. The resultant quinoxalinone derivative (**7**, 367 mg, 80%) was found to be a mixture of two isomers (*syn* and *anti* about the imino bond of the side chain) by ^{1}H-n.m.r. spectroscopy. The ratio of *syn* to *anti* isomer was estimated to be 0.42. The formation of the quinoxaline **8**, together with **4a** in the mixture, was also confirmed by t.l.c. (silica gel) comparison with authentic samples prepared in another way.

3-(2-Hydroxy-1-phenylhydrazonoethyl)-2(1H)-quinoxalinone (**7**). — M.p. 200–205° (dec, from ethanol); ν_{CO} 1650 cm^{-1}; *m/z* 308 (M^+); ^{1}H-n.m.r.: δ 1.4 (d, 2.1 H, *J* 6 Hz, CH_3), 4.7–5.2 (m, 1.4 H, CH + OH); for the *anti* isomer δ 1.5 (d, 0.9 H, *J* 6 Hz, CH_3), 5.2–5.5 (m, 0.3 H, CH), 6.1 (d, 0.3 H, *J* 5 Hz, OH); for the *syn* isomer, δ 6.8–8.0 (m, 9 H, Ar), and 10.4–13.0 (2 br s + m, 2 H, N-NH + CO-NH). Geometrical isomeric assignment was not made for aryl group signals.

Anal. Calc. for $C_{17}H_{16}N_4O_2$: C, 66.22; H, 5.23; N, 18.17. Found: C, 66.04; H, 5.26; N, 17.96.

Alternative synthesis of quinoxaline derivative **8**. — Compound **4a** (1 mmol) in methanol (15 mL) was boiled under reflux with phenylhydrazine (0.3 mL) for 16 h according to Dahn and Moll[3]. The precipitate was collected and recrystallized from ethanol; yield 75%.

3-(1-Hydroxyethyl)quinoxaline-2-carboxylic acid phenylhydrazide (**8**). — M.p. 168–170°; ν_{CO} 1650 cm^{-1}; *m/z* 308 (M^+); ^{1}H-n.m.r.: δ 1.6 (d, 3 H, *J* 6 Hz, CH_3), 5.5 (s, 1 H, OH), 5.3–5.6 (m, 1 H, CH), and 6.7–8.4 (m, 9 H, Ar).

Anal. Calc. for $C_{17}H_{16}N_4O_2$: C, 66.22; H, 5.23; N, 18.17. Found: C, 66.05; H, 5.23; N, 18.12.

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