

OXIDATIVE DEGRADATION OF 1,4-BENZOQUINONE AMINO AND HYDROXY DERIVATIVES INTO MALEIC AND FUMARIC ACIDS

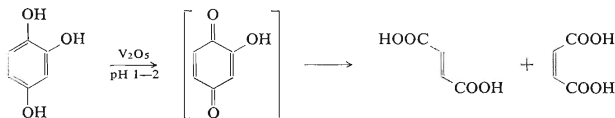
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When treated with an acidic solution of sodium perchlorate in the presence of a catalytical amount of ammonium metavanadate, the hydroxy and amino derivatives of 1,4-benzoquinone undergo an oxidative degradation to maleic and fumaric acids, the ratio of which depends on the substituents. The following products were obtained: a mixture of maleic acid and fumaric acid from 1,2,4-trihydroxybenzene or 1-amino-2,3,4-trihydroxybenzene; a mixture of methylmaleic acid and methylfumaric acid from 1-methyl-2,4,5-trihydroxybenzene; phthalic acid from 2-amino-1,4-naphthoquinone; and phenylmaleic acid from 2-amino-1,4-dihydroxy-5-phenylbenzene.

In connection with the synthesis of showdomycin¹ it appeared advisable to work out a procedure for a relatively mild degradation of benzene derivatives to substituted maleic acids. Consequently, it was of interest to study oxidation of polyhydric phenols. Since the oxidation of these phenols in neutral and alkaline media is known to afford complex mixtures of products^{2,3}, we paid attention to oxidations in acidic solutions. In contrast to 1,4-dihydroxybenzene, the oxidation of 1,2,4-trihydroxybenzene with sodium perchlorate in the presence of a catalytic amount of ammonium metavanadate in acidic media does not end in the stage of a quinone⁴ but is followed by an oxidative degradation of the intermediary 2-hydroxy-1,4-benzoquinone under the formation of a mixture of maleic acid and fumaric acid (Scheme 1).



An analogous oxidation of 1-methyl-2,4,5-trihydroxybenzene affords a mixture of methylmaleic acid and methylfumaric acid. 1-Amino-2,3,4-trihydroxybenzene is by a similar procedure oxidized to a mixture of maleic acid and fumaric acid *via* 2,3-dihydroxy-1,4-benzoquinone as intermediate. The amino derivatives of 1,4-benzoquinone undergo an analogous oxidative degradation as do the hydroxy deri-

vatives. Thus, 2-amino-1,4-dihydroxy-5-phenylbenzene (not isolated; obtained by reduction of 2-azido-5-phenyl-1,4-benzoquinone⁵) affords phenylmaleic acid which was characterised by conversion into 4-phenyl-1,2,3,6-tetrahydropyridazine-3,6-dione. 2-Amino-1,4-naphthoquinone appears as a suitable model for the study of intermediates of the oxidative degradation. In addition to the expected phthalic acid, 2,2-dichloro-1,3-indanedione was isolated. The latter derivative is very probably formed by chlorination of 1,3-indanedione since the mass spectrum exhibits inter alia peaks at the mass 146 and 180 attributable to molecular ions of 1,3-indanedione and 2-chloro-1,3-indanedione. None of these diones, however, can be regarded as an intermediate in the oxidative degradation of 2-amino-1,4-naphthoquinone because the formation of phthalic acid by oxidation of this aminoquinone is much faster.

A fission of the bond between the carboxyl and the enolic hydroxyl is assumed to represent the primary step in the oxidative degradation because the corresponding alkoxy derivatives of 1,4-benzoquinone are relatively stable under the oxidation conditions. The formation of 1,3-indanedione from 2-amino-1,4-naphthoquinone may be regarded as an additional though indirect proof of this assumption.

The isomerisation at the double bond and the formation of *trans*-isomers occurs in the course of the oxidative degradation because maleic acid was shown to be stable under the reaction conditions and not to isomerize into fumaric acid. The ratio of *cis*- and *trans*-isomers in the reaction mixture depends on substituents. Thus, in the oxidation of 1,2,4-trihydroxybenzene, the ratio of maleic acid to fumaric acid is 55 : 45; in the oxidation of 1-methyl-2,4,5-trihydroxybenzene, methylmaleic and methylfumaric acids are obtained in the ratio of 75 : 25. On the other hand, only phenylmaleic acid was obtained by oxidation of 2-amino-1,4-dihydroxy-5-phenylbenzene; the reaction mixture did not contain any *trans*-isomer, as shown by electrophoresis.

EXPERIMENTAL

Melting points were taken on a heated microscope stage (Kofler block). Paper electrophoresis was performed at pH 2.65 in the buffer solution 1 : 1 2M-CH₃COOH - 0.2M-CH₃COONH₄ (detection with a solution of KMnO₄; the mobility values of the *trans*-isomers are half as great as those of the *cis*-isomers. Gas chromatography of esters was effected on an EPN (1,2,3,4-tetrakis(2-cyanoethoxy)butane) column. Identity of maleic acid, fumaric acid, methylmaleic acid, and methylfumaric acid with authentic specimens was established by electrophoresis and also by gas chromatography of the corresponding dimethyl esters.

Degradation of 1,2,4-trihydroxybenzene. A boiling aqueous 1M-NaClO₄ (55 ml) containing 55 mg of ammonium metavanadate and adjusted to pH 1-2 by the addition of hydrochloric acid, was treated dropwise with a solution of 1,2,4-trihydroxybenzene (2.6 g; 20 mmol) in water (20 ml) at such a rate to allow the transient red color of hydroxyquinone to disappear. The resulting light yellowish brown solution was cooled and extracted continuously with ether for 7 h. Evaporation of the extract afforded a mixture of maleic acid and fumaric acid (yield, 1.62 g;

70%). A sample of this mixture (58 mg; 0.5 mmol) was diluted with dimethylformamide (5 ml) and treated under stirring first with silver oxide (460 mg; 2.0 mmol) and then, after 30 min, with methyl iodide (1.0 ml) under cooling. The reaction mixture was stirred for additional 20 h, filtered, and the material on the filter washed with ether. The filtrate and washings were combined, diluted with water (25 ml), and extracted with two 10 ml portions of ether. The ethereal extract was dried and evaporated to afford a mixture of dimethyl maleate and dimethyl fumarate in the ratio of 55 : 45, as shown by gas chromatography at 140°C.

Degradation of 1-methyl-2,4,5-trihydroxybenzene was performed analogously to that of 1,2,4-trihydroxybenzene. Extraction with ether afforded a mixture of methylmaleic and methylfumaric acid in 53.5% yield. This mixture was methylated and the methyl esters gas-chromatographed at 160°C; the ratio of dimethyl methylmaleate to dimethyl methylfumarate was 75 : 25.

*Degradation of 1-amino-2,3,4-trihydroxybenzene*⁶. The ethereal extracts afforded a mixture of maleic and fumaric acid in 49% yield. Conversion to dimethyl esters and gas chromatography showed the ratio 38 : 62 of dimethyl maleate to dimethyl fumarate.

Degradation of 2-amino-1,4-naphthoquinone. A boiling 1M solution of sodium perchlorate in 70% CH₃COOH containing 27 mg of ammonium metavanadate was treated dropwise under stirring with a solution of 2-amino-1,4-naphthoquinone⁷ (1.75 g; 10 mmol) in glacial acetic acid (20 ml) at such a rate to allow each time the transient red color to disappear. The acetic acid was then removed by distillation and the residue diluted with water (30 ml) to obtain 315 mg of a precipitate which was identified by mass spectroscopy as 2,2-dichloro-1,3-indanedione, m.p. 122–124°C (ethanol); reported⁸, m.p. 125–127°C. The mother liquor was adjusted with hydrochloric acid to pH 2 and continuously extracted with ether for 6 hours. The extract was concentrated to deposit 1.25 g (70%) of phthalic acid, m.p. 190–192°C; distillation at ordinary pressure afforded phthalic anhydride, m.p. 130°C.

Degradation of 2-amino-1,4-dihydroxy-5-phenylbenzene. Powdered zinc was added portionwise (4.0 g total) under stirring to a suspension of 2-azido-5-phenyl-1,4-benzoquinone⁵ (2.26 g; 10 mmol) in glacial acetic acid (25 ml). The reaction mixture was kept at room temperature for 30 min, treated dropwise with concentrated hydrochloric acid (4.0 ml), and filtered to remove the remaining zinc. The filtrate was adjusted with hydrochloric acid to pH 1–2 and oxidized analogously to 2-amino-1,4-naphthoquinone. The acetic acid was then evaporated, the residue diluted with water (70 ml), heated to the boiling point, and the resulting solution filtered while hot. The filtrate was continuously extracted with ether for 6 hours, the ethereal extract concentrated, the concentrate treated with saturated aqueous sodium hydrogen carbonate, and filtered with active charcoal. The filtrate was acidified with hydrochloric acid and extracted continuously for 6 h with ether. The extract was evaporated to afford 990 mg (50.5%) of phenylmaleic acid, m.p. 122°C (water); reported⁹, m.p. 125–127°C.

4-Phenyl-1,2,3,6-tetrahydropyridazine-3,6-dione. A mixture of the above phenylmaleic acid (192 mg; 1 mmol), hydrazine dihydrochloride (115 mg; 1.1 mmol), and 3.0 ml of water was heated at 100°C for 5 h, cooled down, the cyclic hydrazide (56 mg) collected with suction, and recrystallised from ethanol to afford leaflets which melt at 272–273°C and simultaneously transform into needles, m.p. 283–284°C; reported¹⁰, m.p. 272–273°C. For C₁₀H₈N₂O₂ (188.2) calculated: 63.82% C, 4.22% H, 14.89% N; found: 63.95% C, 4.27% H, 14.81% N.

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