ACTA CHEMICA SCANDINAVICA 18 (1964) 2309–2312

Synthesis of 2,3-Dihydroxy-5,6-dimethyl-1,4-benzoquinone and its Monomethyl Ether

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2,3-Dihydroxy-5,6-dimethyl-1,4-benzoquinone and 2-hydroxy-3-methoxy-5,6-dimethyl-1,4-benzoquinone have been prepared by alkaline demethylation of aurantiogliocladin (the corresponding dimethoxyquinone). The paper further describes an unambiguous synthesis of 2,3-dihydroxy-5,6-dimethyl-1,4-benzoquinone from 2-hydroxy-5,6-dimethyl-1,4-benzoquinone.

Two new benzoquinonoid pigments have been isolated from cultures of the mould *Gliocladium roseum* (see Ref.[7]). An investigation of their molecular constitution gave clear evidence that one of the pigments is 2,3-dihydroxy-5,6-dimethyl-1,4-benzoquinone; the other one was shown to be the corresponding monomethyl ether. These quinones, neither of which has been described previously, have now been synthesized and the synthetic materials were found to be identical with the natural pigments.

Many methoxyquinones give intense colours, characteristic of the corresponding hydroxyquinones, in strongly alkaline solutions; alkaline hydrolysis of, for instance, 2,5-dimethoxy-1,4-benzoquinone has for a long time been known to yield methanol and 2,5-dihydroxy-1,4-benzoquinone.[1] A recent investigation on the relation between the stability of methoxyl groups and structure [2] showed that also fairly alkali stable quinone derivatives, such as 2,6-dimethoxy-1,4-benzoquinone, gave a quantitative amount of methanol by treatment with 0.5 M sodium hydroxide at 100° for 4 h (in the absence of air). Aurantiogliocladin (2,3-dimethoxy-5,6-dimethyl-1,4-benzoquinone) would thus be expected to yield the corresponding dihydroxy compound on alkaline demethylation, with intermediate formation of the monomethoxy derivative. This was confirmed by preliminary experiments, which showed that the reaction could be controlled by variations of the experimental conditions, so as to give either of the two possible demethylation products of aurantiogliocladin.

2-Hydroxy-3-methoxy-5,6-dimethyl-1,4-benzoquinone was formed in an almost quantitative yield by treatment of aurantiogliocladin with 1 M sodium

hydroxide at 25° for 5 min. 2,3-Dihydroxy-5,6-dimethyl-1,4-benzoquinone was obtained on prolonged treatment, and by increasing the temperature or the pH of the solution. The yield of the latter compound was, however, limited by the occurrence of secondary reactions (ring fission of the dihydroxyquinone [3] and formation of polymeric products [1]). Treatment of aurantiogliocladin or of 2-hydroxy-3-methoxy-5,6-dimethyl-1,4-benzoquinone with 2 M sodium hydroxide at 25° for 1 h in the absence of air was found to give a satisfactory yield (40—50 %) of 2,3-dihydroxy-5,6-dimethyl-1,4-benzoquinone.

The dihydroxy-*o*-xyloquinone was, further, synthesized from 2-hydroxy-5,6-dimethyl-1,4-benzoquinone. Thiele-Winter acetylation [4] of the latter compound gave tetraacetoxy-*o*-xylene, reaction occurring at the only vacant quinonoid position. This substance, on hydrolysis, gave tetrahydroxy-*o*-xylene which, on oxidation with air at pH 6, gave 2,3-dihydroxy-5,6-dimethyl-1,4-benzoquinone.

Attempts to prepare the hydroxymethoxy-*o*-xyloquinone by the introduction of a hydroxyl group (according to Thiele-Winter) into the only available quinonoid position of 2-methoxy-5,6-dimethyl-1,4-benzoquinone were unsuccessful.

EXPERIMENTAL

Alkaline demethylation of aurantiogliocladin. Definite quantities of aurantiogliocladin (final concentration 0.01 M) were dissolved in aqueous sodium hydroxide (10^{-6}—10 M) at 25°. The demethylation process was followed by chromatographic analysis [5] of samples of the reaction solution, withdrawn at fixed intervals (from 5 min to 24 h). These preliminary experiments, the results of which are summarized in Table 1, showed that aurantiogliocladin was stable below pH 10. At pH 12—14 it was demethylated at a moderate rate, making it possible to isolate the intermediate monohydroxyquinone. In 10 M sodium hydroxide hydrolysis of the methoxyl groups took place rapidly; the solution showed an intense bluish purple colour after some seconds (anion of the monohydroxyquinone) which changed to faint red within half a minute (doubly charged anion of the dihydroxyquinone). On rapid addition of conc. hydrochloric acid the colour became more intense (pH 6—12; singly charged anion of the dihydroxyquinone) and finally changed to yellow

Table 1. Alkaline hydrolysis of the methoxyl groups of aurantiogliocladin as a function of time and pH. The figures in the table give percentages of the unchanged starting material (I), the mono- (II), and the didemethylation product (III).

Time		Hydroxyl ion concentration (M)						
		0.001	0.01	0.1	1	2	5	10
5 min	I	100	100	80	0	0	0	0
	II	0	0	20	95	90	50	0
	III	0	0	0	0	5	30	65
1 h	I	100	70	25	0	0	0	0
	II	0	30	70	50	0	0	0
	III	0	0	5	40	65	50	30
24 h	I	95	10	0	0	0	0	0
	II	5	65	0	0	0	0	0
	III	0	20	40	50	10	10	0

(the undissociated dihydroxyquinone). On prolonged treatment with strong alkali the dihydroxy compound decomposed completely.

Increasing the temperature of the reaction mixtures seemed not to be advantageous. At 100° aurantiogliocladin was readily demethylated also in neutral solutions; the demethylation products formed were, however, destroyed completely within some minutes.

2-Hydroxy-3-methoxy-5,6-dimethyl-1,4-benzoquinone. Aurantiogliocladin (1 g) was dissolved in water (200 ml) and an equal volume of 2 M sodium hydroxide was added. The solution, which gradually changed colour from yellow to intense bluish-purple, was kept at 25° for 5 min, when it was neutralized by the addition of conc. hydrochloric acid and extracted twice with petroleum ether (40–60°). Evaporation of the petroleum ether yielded 0.06 g of unchanged aurantiogliocladin. The purple aqueous solution was then acidified (pH 2) with conc. hydrochloric acid and extracted three times with 150 ml of ether. The combined ethereal extracts were evaporated and the residue was sublimed at 100° in a vacuum (1 mm Hg), yielding 0.82 g of crude 2-hydroxy-3-methoxy-5,6-dimethyl-1,4-benzoquinone. After two recrystallizations from petroleum ether the material gave a constant m.p. of 70°. (Found: C 59.50; H 5.61; OCH_3 17.31. Calc. C 59.34; H 5.53; OCH_3 17.04.)

This substance gave the same reactions as the methoxyhydroxyquinone (compound A) isolated from *G. roseum*.[7] The synthetic and the natural material, further, proved to be identical in mixed melting-point determinations and in chromatographic tests. Both materials showed identical ultra-violet and infra-red absorption spectra.

2,3-Dihydroxy-5,6-dimethyl-1,4-benzoquinone. A stream of nitrogen was being passed through a 2 M aqueous solution of sodium hydroxide (200 ml) and after 10 min aurantiogliocladin (0.5 g) was added. It dissolved quickly, giving an intense purple colour which slowly faded to red. After 1 h (at 25°) the solution was acidified (pH 2) with conc. hydrochloric acid and extracted three times with an equal volume of ether. Removal of the ether in a vacuum gave a brown, syrupy, residue which was chromatographed on Whatman No. 3 MM paper, using butanol-propanol-2 M ammonium hydroxide (1:6:3 by vol.) as the solvent.[5] The bluish purple zone corresponding to the dihydroxyquinone (R_F 45–55; the only benzoquinonoid product that could be detected on the chromatogram) was cut out of the air-dried paper, moistened with dilute hydrochloric acid, and extracted with ether. The ethereal eluat was extracted with bicarbonate solution. The purple extract on acidification became yellow, and the quinone was reextracted with petroleum ether (40–60°). Evaporation of most of the solvent yielded 2,3-dihydroxy-5,6-dimethyl-1,4-benzoquinone (0.19 g) with a constant m.p. of 182° (decomp.) after one recrystallization from petroleum ether. (Found: C 57.08; H 4.89; OCH_3 nil. Calc.: C 57.14; H 4.80; OCH_3 nil.)

The dihydroxy-*o*-xyloquinone (90 mg) was prepared in a similar way from 2-hydroxy-3-methoxy-5,6-dimethyl-1,4-benzoquinone (170 mg).

The synthetic material had the same chemical and physical properties as the dihydroxyquinone isolated from *G. roseum*;[7] the identity with the natural product was, further, established by mixed melting-point determinations.

Thiele-Winter reactions. *o*-Xyloquinone was converted into 2-hydroxy-5,6-dimethyl-1,4-benzoquinone by means of the Thiele-Winter reaction, hydrolysis of the resulting triacetate, and oxidation with ferric chloride of the polyphenol so formed.[6] It was obtained as yellow needles, m.p. 116°. (Found: C 62.88; H 5.36. Calc.: C 63.15; H 5.30.)

2-Hydroxy-5,6-dimethyl-1,4-benzoquinone (3.5 g) was dissolved in a mixture of acetic anhydride (35 ml) and conc. sulphuric acid (1.5 ml). After 5 days the solution was poured into ice and water; the oil obtained solidified on standing overnight. Tetraacetoxy-*o*-xylene crystallized from methanol in clusters of colourless plates, m.p. 97°. (Found: C 57.04; H 5.45. Calc. for $C_{16}H_{16}O_8$: C 56.80; H 5.36.)

The tetraacetate (1.5 g) was refluxed for 30 min with methanol (15 ml) and conc. sulphuric acid (0.5 ml) in an atmosphere of nitrogen. Water was added and the methanol removed by distillation in a vacuum. The tetrahydroxy-*o*-xylene was extracted with ether and the ether removed, giving a brownish semi-solid residue. This was dissolved in water (50 ml) and the solution was aerated for a few minutes, when it rapidly became

intense purple. The colour changed to yellowish brown on addition of conc. hydrochloric acid (2 ml) and 2,3-dihydroxy-5,6-dimethyl-1,4-benzoquinone was extracted with ether from the acid solution. After three recrystallizations from petroleum ether (40—60°) it was obtained as microscopic bunches of orange needles, m.p. 182° (decomp.). (Found: C 57.48; H 4.88. Calc.: C 57.14; H 4.80.)

2-Methoxy-5,6-dimethyl-1,4-benzoquinone was obtained by reaction of the corresponding hydroxy compound with ethereal diazomethane.[6] It crystallized from petroleum ether in bright yellow needles, m.p. 110° (unchanged on sublimation). This compound does not appear to undergo the usual Thiele-Winter reaction. The quinone (0.2 g) was added to 2 ml of a mixture of acetic anhydride (20 ml) and conc. sulphuric acid (1 ml). The orange solution was poured into ice-water after 2 weeks. Since no precipitate was formed on standing overnight at 4°, the solution was extracted with ether. The lemon-yellow needles (0.08 g) separating on removal of most of the solvent were sublimed in a vacuum (1 mm Hg) at 100°, and proved to be identical with the starting material in mixed melting-point determinations (m.p. 110°) and in chromatographic comparisons.[5]

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Received September 5, 1964.