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Fungus Pigments

XIV.* On the Oxidation of Phenoxazin-3-ones

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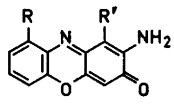
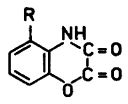
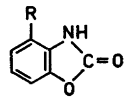
2,3-Dihydro-2,3-dioxo-4*H*-1,4-benzoxazine-5-carboxylic acid (III) is formed upon oxidation of tramesanguin and cinnabarin with hydrogen peroxide. It can be further oxidised to 2-oxobenzoxazoline-4-carboxylic acid (IV). It is proposed that 4*H*-1,4-benzoxazine-2,3-dione-derivatives are intermediates during the oxidation of other 2-amino-phenoxazin-3-ones as well.

That 2-aminophenoxazin-3-ones upon oxidation give derivatives of benzoxazolinone was first observed by Johnson and coworkers.[1] Several other similar reactions have been reported later.[2–4] Hydrogen peroxide,[1] chromic acid,[2] and potassium permanganate [4] have been used as oxidants.

In view of these observations we were rather suprised to find that oxidation of tramesanguin (I) with hydrogen peroxide gave the expected 2-oxobenzoxazoline-4-carboxylic acid (IV) only as a minor product. Oxidation with chromic acid on the other hand gave only (IV). The major product in the hydrogen peroxide-oxidation was a crystalline compound of m.p. 298—300°, which could be separated from the 2-oxobenzoxazoline-4-carboxylic acid due to its lower solubility in ethyl acetate.







I R = COOH; R' = CHO III R = COOH IV R = COOH
II R = R' = COOH V R = H VI R = H
VII R = R' = H

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The compound has an I.R.-absorption at 1795, 1735, and 1680 cm^{-1} in the carbonyl region. Its U.V. maximum at 318 mμ is at a slightly longer wavelength than that of (IV) (302 mμ).[4] In both cases a bathochromic shift is observed upon addition of alkali. However, with the new compound this is accompanied by a reduction of the intensity; whereas the opposite is true of (IV). The analysis indicated a composition $C_9H_5O_5N$. On the basis of this evidence 2,3-dihydro-2,3-dioxo-4*H*-1,4-benzoxazine-5-carboxylic acid (III) is apparently a reasonable structure.

This structure proposal could also be confirmed through a synthesis of (III) by condensation of 3-hydroxyanthranilic acid with oxalyl chloride. This synthesis is analogous to the synthesis of 4*H*-1,4-benzoxazine-2,3-dione (V) by Puxeddu and Sanna.[6]

Oxidation of cinnabarinic acid (II) with hydrogen peroxide similarly gave (III), although the yield was poorer in this case.

As (III) still contains the complete skeleton of the central ring in the phenoxazin-3-one system of (I) and (II), it seems probable that its formation is the first step in the oxidation of these phenoxazin-3-ones. This view finds support in the fact that (III) could be further oxidised to (IV) by, for instance, potassium permanganate. Analogously, (V) could also be oxidised to benzoxazolinone (VI).

It does not appear unreasonable to assume that all oxidations of phenoxazin-3-ones to benzoxazolinones proceed through the corresponding 4*H*-1,4-benzoxazine-2,3-dione-derivatives. An attempt to sustain this hypothesis by the oxidation of 2-aminophenoxazin-3-one was to no avail. No (V) could be found among the oxidation products, only (IV) in poor yield, in agreement with the observation of Bullock and Johnson.[6] Apparently (V) is oxidised further, faster than it is formed.

EXPERIMENTAL

The melting points were determined on a Kofler-microscope. The U.V.- and I.R.-spectra were measured on Beckman DK-2 and IR 5 instruments, respectively. The analyses were carried out by Dr. A. Bernhardt, Mülheim, Germany.

2,3-Dihydro-2,3 dioxo-4H-1,4-benzoxazine-5-carboxylic acid (III). The starting material, 3-hydroxyanthranilic acid was prepared from 2-nitro-3-hydroxybenzoic acid [7] following the method of Shu-wei *et al.*[8] for the preparation of 2-amino-3-hydroxy-4-methoxybenzoic acid.

3-Hydroxyanthranilic acid (200 mg) was refluxed with a mixture of equal parts of oxalyl chloride and benzene (56 ml) until the evolution of hydrogen chloride ceased. The mixture was filtered and evaporated to a small volume under vacuum. Water was added and the aqueous solution was extracted with ether. The residue, after removal of the ether, was sublimated under vacuum and the sublimate crystallised from ethyl acetate giving 2,3-dihydro-2,3-dioxo-4*H*-1,4-benzoxazine-5-carboxylic acid as slightly yellow crystals, m.p. 302–304°. (Found: C 52.13; H 2.88; N 6.80. $C_9H_5O_5N$ requires: C 52.18; H 2.43; N 6.76). U.V.-spectrum (EtOH): λ_{max} 318 mμ (log ε 3.79), λ_{min} 285 mμ (log ε 3.54). I.R.-maxima (KBr): 3250m, 1795s, 1735s, 1680s, 1620m, 1495m, 1465m, 1410s, 1365m, 1310m, 1280s, 1275s, 1220m, 1180s, 1145m, 1080w, 1000w, 885m, 820m, 801m, 785m, 765s, 710m, 645w cm^{-1}.

Oxidation of tramesanguin (I). Tramesanguin (240 mg) was suspended in 2 N sodium hydrogen carbonate solution (10 ml) and 30 % hydrogen peroxide (1.5 ml) was added. The mixture was allowed to stand until all of the tramesanguin had disappeared. The slightly yellow solution was acidified and extracted with ether. The ether was removed

and the residue was treated with ethyl acetate. The crystalline precipitate of 2,3-dihydro-2,3-dioxo-4*H*-1,4-benzoxazine-5-carboxylic acid was filtered off (40 mg). It was further purified by recrystallisation from dioxane/ethyl acetate, m.p. 298–300°. Its U.V.- and I.R.-spectra were superimposable upon those of the synthetic material described above.

Oxidation of cinnabarinic acid (II). This was done in the same way as described above for the oxidation of tramesanguin. The yield of oxidation product from 100 mg of cinnabarinic acid was only 5 mg.

Oxidation of 2,3-dihydro-2,3-dioxo-4H-1,4-benzoxazine-5-carboxylic acid (III). 2,3-Dihydro-2,3-dioxo-4*H*-1,4-benzoxazine-5-carboxylic acid (20 mg) was dissolved in sodium carbonate solution and potassium permanganate was added until the violet colour persisted for some time. The solution was acidified with sulphuric acid and the manganese dioxide dissolved by addition of sodium hydrogen sulphite. Ether extraction gave 2-oxobenzoxazoline-4-carboxylic acid, indentical with an authentic specimen.[4]

4H-1,4-Benzoxazine-2,3-dione (V) was prepared according to Puxeddu and Sanna.[6] It was best purified by recrystallisation from acetone/benzene, m.p. 260–263° (Ref. 6, m.p. 258–259°). (Found: C 58.79; H 3.18; N 8.56. $C_8H_5O_3N$ requires: C 58.90; H 3.09; N 8.59). U.V.-spectrum (EtOH): λ_{max} 303 mμ (log ε 3.86) (Ref. 9, λ_{max} 303 mμ (log ε 3.76)). I.R.-maxima: 1770s, 1700s, 1600m, 1495s, 1430w, 1380s, 1280w, 1260w, 1220m, 1160s, 1155s, 1115m, 950w, 915w, 870w, 840w, 785w, 770s, 710m, 640m cm^{-1}.

Oxidation of 4H-1,4-benzoxazine-2,3-dione (V). 4*H*-1,4-benzoxazine-2,3-dione (140 mg) was oxidised with potassium permanganate as described above for the oxidation of 2,3-dihydro-2,3-dioxo-4*H*-1,4-benzoxazine-5-carboxylic acid. The oxidation product was identified as benzoxazinone (VI) by its m.p. 142–143°, its U.V.-spectrum with λ_{max}^{EtOH} 273 mμ (log ε 3.80), 279 mμ (infl.) (log ε 3.72), λ_{min}^{EtOH} 244 mμ (log ε 3.06) and its I.R.-spectrum,[10] which were identical with those of an authentic sample prepared according to Bywater *et al.*[11]

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