ACTA CHEMICA SCANDINAVICA 13 (1959) 1305–1308

Fungus Pigments

XI.* 2-Amino-3-hydroxymethylphenol from Cinnabarin

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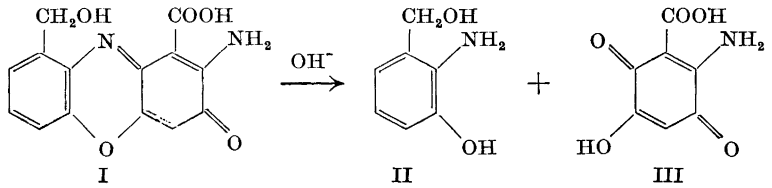
Alkaline hydrolysis of cinnabarin has yielded 2-amino-3-hydroxymethylphenol, whose structure was established by synthesis. This definitely proved the presence of a hydroxymethyl group in cinnabarin.

In earlier papers of this series [1–3] evidence has been advanced supporting structure I for cinnabarin. The same structure was independently proposed by Cavill *et al.* [4,5].

Direct proof for the presence of the hydroxymethyl group was, however, lacking. That cinnabarin has a side chain in position 9 was shown by the formation of benzoxalone-4-carboxylic acid upon oxidation [1], but its nature was only indirectly deduced [2,6].

As has already been described,[2,3] cinnabarin treated with alkali yields cinnaquinone, which is most probably 3-amino-6-hydroxybenzoquinone-2-carboxylic acid (III). Cinnaquinone originates evidently from the quinonoid part of the phenoxazinone ring system. Assuming that its formation is due to a simple hydrolytic cleavage of the central ring, 2-amino-3-hydroxymethylphenol (II), should be formed from the benzenoid ring.



I II III

The mother liquor remaining after the sodium salt of cinnaquinone had been removed [2], upon saturation with carbon dioxide and extraction with ether did indeed give a compound with the properties to be expected of II.

Part X, *Acta Chem. Scand.* **12** (1958) 1762.

It had the composition $C_7H_9NO_2$ and was readily soluble in water but difficultly soluble in hydrocarbons. Acetylation gave a tri-acetate. The U.V.-spectrum had a maximum at 290 mμ (log ε 3.78) and an inflexion at $\sim$ 230 mμ. It showed great similarity to the spectrum of *o*-aminophenol [7]. In alkaline solution a bathochromic shift of the maximum to 302 mμ (log ε 3.63) occurred. In acidic solution the maximum was shifted to 275 mμ (log ε 3.36). The spectrum was then practically identical with that of *m*-cresol [8].

The spectrum of the acetate was somewhat anomalous. One would have expected it to be similar to the spectrum of *o*-aminophenol diacetate, which has a maximum at 236 mμ (log ε 4.06) with a very weak inflexion at 280 mμ. (Le Rosen and Smith [9] report 238 mμ (log ε 3.93) for this maximum). Instead, it had a weak maximum at 260 mμ (log ε 2.74) and only end absorption down to 220 mμ.

The maximum of *o*-aminophenol diacetate is certainly due to the acetanilide group, as shown by the very similar absorption of acetanilide, with maxima at 242 mμ (log ε 4.16) and 280 mμ (log ε 2.70) [10]. Apparently the acetoxymethyl group in 2-amino-3-hydroxymethylphenol triacetate sterically hinders the conjugation between the aromatic ring and the acetamide group and the absorption is probably essentially that of the benzene ring. Alkyl groups in the *ortho*-position interfere sterically with this conjugation as has been noted earlier [10,11].

The fact that the compound obtained from cinnabarin was indeed 2-amino-3-hydroxymethylphenol (II) was finally proven through its synthesis by the lithium aluminium hydride reduction of methyl 3-hydroxyanthranilate. This was prepared according to Angyal *et al.*[12], with minor modifications, as indicated in the experimental part.

The reduction of methyl 3-hydroxyanthranilate did not proceed very well. The reduction was first carried out in boiling ether using a large excess of lithium aluminium hydride. Although this method gave some of the desired compound, considerable hydrogenolysis to 2-amino-*m*-cresol occurred. This supports the results of Conover and Tarbell [13], who report considerable hydrogenolysis in the reduction of methyl anthranilate, particularily if the reaction time is extended to several hours. In order to minimise the hydrogenolysis, attempts were made to carry out the reduction by reverse addition of the theoretical amount of lithium aluminium hydride. A heavy precipitate was formed at once, however, and even after boiling the mixture for several hours, considerable unreacted lithium aluminium hydride remained in the solution. Only a very minute amount of 2-amino-3-hydroxymethylphenol could be isolated using this particular method. The use of methyl 3-acetoxy anthranilate was similarly unsatisfactory.

The best procedure was finally found to be by slowly adding methyl 3-hydroxy anthranilate at room temperature to a moderate excess of lithium aluminium hydride, and allowing the mixture to stand for some hours at room temperature. In this way, a yield of approximately 50 % 2-amino-3-hydroxymethylphenol was obtained. Its m.p. was slightly lower than that found for the substance obtained from cinnabarin but no m.p. depression was observed in a mixture test. Its rather high carbon content indicated the presence of some 2-amino-*m*-cresol. It was best characterised as its triacetate,

which was readily obtained in a pure state. There was no m.p. depression when this was mixed with the corresponding derivative obtained from cinnabarin, and their I.R.-spectra were identical.

EXPERIMENTAL

3-Methoxy-2-nitrobenzoic acid was prepared according to Nyc and Mitchell [14]. For the separation of 3-methoxy-2-nitrobenzoic acid from the other isomers, the reaction mixture was completely dissolved in the minimum quantity of hot ethyl alcohol. Upon cooling, large glass-like crystals first appeared. When small clusters of white needles began to separate on the surface of the big ones, the crystals were filtered off and recrystallised once from ethyl alcohol. In this way a very consistent yield of 1.15 g of 3-methoxy-2-nitrobenzoic acid (m. p. 260—265°; lit.[14] 260—263°) was obtained from 10 g *m*-methoxybenzoic acid. When attempts were made to carry out the reaction on a larger scale, difficulties were encountered in regulating the reaction temperature.

3-Hydroxy-2-nitrobenzoic acid was prepared according to Angyal *et al.*[12] The pyridine hydrochloride melt was dissolved in water and the solution thoroughly extracted with ethyl acetate. After drying this was evaporated under vacuum to a small volume. Light petroleum was then added. 3-Hydroxy-2-nitrobenzoic acid crystallised as yellow crystals, m. p. 178—180° (Hegedüs [15] gives m. p. 176—178° for a crude product). Yield 1.6 g from 2 g 3-methoxy-2-nitrobenzoic acid.

Methyl 3-hydroxy-2-nitrobenzoate was prepared from the foregoing by esterification with methyl alcohol and sulphuric acid. Recrystallised from water, it formed colourless needles, of m. p. 114—115° (lit.[16] 115°).

Methyl 3-hydroxy anthranilate. Methyl 3-hydroxy-2-nitrobenzoate (2 g) dissolved in alcohol was hydrogenated with a palladium-on-charcoal catalyst at room temperature and ordinary pressure. In four hours 680 ml of hydrogen were taken up. The solution was evaporated to dryness under vacuum. The residue was recrystallised from an ethyl-acetate-light petroleum mixture, giving almost colourless crystals (0.8 g), m. p. 97—98° (lit.[17] 94°).

The mother liquor contained more of the same substance, but this was contaminated with considerable red-coloured material, from which it was difficult to free the crystals.

Methyl 3-acetoxy-2-nitrobenzoate. Methyl 3-hydroxy-2-nitrobenzoate was acetylated with acetic anhydride and a drop of pyridine. After standing over night the mixture was poured into water. Methyl 3-acetoxy-2-nitrobenzoate separated as an oil which solidified on scratching the container. Recrystallisation from light petroleum gave colourless crystals m. p. 54—54.5°. (Found: C 50.58; H 3.89. $C_{10}H_9NO_6$ requires C 50.21; H 3.79).

Methyl 3-acetoxyanthranilate. Methyl 3-acetoxy-2-nitrobenzoate (2.25 g) dissolved in ethyl alcohol was hydrogenated with a palladium-on-charcoal catalyst at room temperature and ordinary pressure. The hydrogen consumption amounted to 600 ml (Theor. 635 ml). The solution was evaporated under vacuum and turned to a dark red colour. Benzene was added to the residue and a red precipitate was filtered off. Light petroleum was carefully added to the benzene solution precipitating dark impurities. The almost colourless solution was evaporated to dryness under vacuum. Sublimation (90—100°/0.02 mm) and further crystallisation from ligroin gave colourless crystals (0.66 g), m. p. 94—95°. (Found: C 57.05; H 5.36. $C_{10}H_{11}NO_4$ requires C 57.41; H 5.30). It gave a large m. p. depression when mixed with methyl 3-hydroxyanthranilate, m. p. 97—98°.

2-Amino-3-hydroxymethylphenol (II). a) Methyl-3-hydroxyanthranilate (500 mg) dissolved in ether was added dropwise to a stirred suspension of lithium aluminium hydride (500 mg) in ether. The mixture was allowed to stand 2 h. Water was then added carefully to destroy the excess of lithium aluminium hydride. A little sodium hydroxide was added to facilitate the dissolving of the precipitate. The aqueous layer was separated and saturated with carbon dioxide. It was then extracted thoroughly with ether until a sample of the extract left no crystalline residue. The precipitate which formed during the introduction of carbon dioxide did not interfere with the extraction. It was found advisable to introduce more carbon dioxide from time to time during the extraction because the pH showed a tendency to rise.

The ether extract was evaporated under vacuum and the residue dissolved in a small amount of water, filtered and evaporated under vacuum. The red oily residue was treated with benzene whereupon it crystallised. The crystals were filtered off and addition of light petroleum to the mother liquor gave more of the same crystals. Altogether 190 mg were obtained. Recrystallisation from ethyl acetate-benzene and subsequent sublimation (120—130°/0.01 mm) yielded colourless needles, m. p. 124—125°. (Found: C 61.37; H 6.49; N 10.33. $C_7H_9NO_2$ requires C 60.42; H 6.52; N 10.07). Main I.R.-maxima (KBr-disc): 3 510, 3 430, 3 330, 3 100, 2 880, 1 630, 1 583, 1 500, 1 472, 1 373, 1 305, 1 280, 1 265, 1 168, 1 080, 1 000, 980, 938, 925, 865, 773 and 721 cm^{-1}.

The acetate of 2-amino-3-hydroxymethylphenol was prepared by acetylation with acetic anhydride and a drop of pyridine. After standing over night the mixture was evaporated under vacuum and the crystalline residue recrystallised from benzene-light petroleum, m. p. 117°. (Found: C 58.64; H 5.66; N 5.69. $C_{13}H_{15}NO_5$ requires C 58.86; H 5.70; N 5.28.) Main I.R.-maxima (KBr-disc): 3 280, 3 040, 2 800, 1 778, 1 748, 1 656, 1 590, 1 517, 1 469, 1 451, 1 432, 1 371, 1 265, 1 218, 1 192, 1 088, 1 062, 1 018, 965, 860, 783, 753 and 733 cm^{-1}.

b) Cinnabarin (400 mg) was treated with 2 N sodium hydroxide as previously described [3]. After filtering off the sodium salt of cinnaquinone, the alkaline solution remaining was saturated with carbon dioxide, and thoroughly extracted with ether. The residue from the ether extract was dissolved in a small amount of water, filtered and evaporated under vacuum. The crystalline residue was sublimed at 100—110°/0.01 mm. The sublimate (40 mg) was recrystallised from ethyl acetate-benzene and found to have a m. p. of 125—126°. (Found: C 60.70; H 6.35; N 9.91. $C_7H_9NO_2$ requires C 60.42; H 6.52; N 10.07.) No m. p. depression was observed when the sublimate was mixed with material prepared according to a).

The acetate was prepared as described above and had m. p. 117°. It gave no m. p. depression when mixed with the corresponding derivative described under a), and their I.R.-spectra were identical.

The analyses have been carried out by Dr. A. Bernhardt, Mülheim, Germany. The I.R.-spectra have been taken by Mr. J. Miettinen of this department.

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Received May 4, 1959.