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Heterocyclic Compounds. VII. The Synthesis of Cinnabarin (1)

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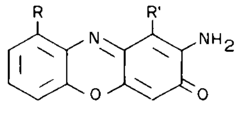
Cinnabarin (I) (2-5), cinnabarinic acid (II) (6), and tramesanguin (III) (7) are three related pigments found in the fungus *Coriolus sanguineus* Fr. (8) that possess phenoxazone structures (9-13). The diacid II has been synthesized in a separate study by the oxidative coupling of 2-amino-3-hydroxybenzoic acid (VII) (14). A similar technique involving both 2-amino-3-hydroxybenzyl alcohol (VIII) and the corresponding benzoic acid VII can simultaneously afford four different phenoxazones (I, II, IV, and V) (15, 16). Separation of the individual components would yield a dual preparation of both cinnabarin and cinnabarinic acid.

This reaction was tested by oxidation of an equimolar ethanolic solution of both compounds VII and VIII with *p*-benzoquinone in the presence of air. The crude product was first washed with sodium bicarbonate solution to remove cinnabarinic acid, then chromatographed on alumina to yield the dialcohol, followed by a trace of isocinnabarin.



I, R = CH_2OH; R' = COOH

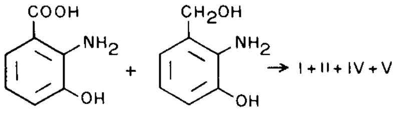
II, R = COOH; R' = COOH

III, R = COOH; R' = CHO

IV, R = CH_2OH; R' = CH_2OH

V, R = COOH; R' = CH_2OH

VI, R = CH_2OAc; R' = COOH



VII VIII

The residual dark-brown band was rechromatographed over magnesium oxide to produce cinnabarin, which was confirmed by conversion into the known *O*-acetylcinnabarin (VI) (5). A statistical combination of VII and VIII should give equal amounts of the four phenoxazones; however, the actual quantities obtained were skewed in favor of dialcohol. This result might be explanable on the basis of steric factors, internal chelation, or by the relative stability of different radical intermediates.

EXPERIMENTAL

Cinnabarin (I).

To a stirred solution of 2-amino-3-hydroxybenzyl alcohol (0.122 g., 0.876 millimoles) in deoxygenated methanol (200 ml.) was added a solution of 3-hydroxyanthranilic acid (0.134 g., 0.875 millimoles) in deoxygenated methanol (200 ml.), followed dropwise by a solution of *p*-benzoquinone (0.325 g., 3.01 millimoles) in deoxygenated methanol (50 ml.). After 24 hours the solvent was removed, and the remaining material extracted with 5% sodium bicarbonate solution to give cinnabarinic acid (0.007 g.). The insoluble dark residue was dissolved in *N,N*-dimethylformamide and evaporated onto magnesium oxide, which was added to the top of a previously prepared column of aluminum oxide. Elution with methanol or 0.5% acetic acid in acetone gave 2-amino-1,9-bis-(hydroxymethyl)phenoxazone-3 (0.137 g.), identical with an authentic sample. An intermediate band, obtained with 5% acetic acid-acetone, yielded a second red solid, whose spectral properties were in accord for isocinnabarin. The fractions obtained by use of 10-25% acetic acid-acetone were combined, evaporated to dryness, and rechromatographed on magnesium oxide. The crude cinnabarin fraction, eluted with 5% acetic acid-acetone, was taken to dryness, redissolved in ethanol, boiled to coagulate colloidal material, filtered through a Celite pad, and evaporated to afford cinnabarin (0.059 g.), identical with authentic material on the basis of spectral and thin-layer chromatographic comparisons. Acetylation with acetic anhydride in the presence of perchloric acid formed *O*-acetylcinnabarin, identical with authentic material by mixed melting point, spectral and thin-layer chromatographic comparisons.

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(17) The melting points are uncorrected. The IR spectra were determined as pressed potassium bromide disks with a Perkin-Elmer Model 421 spectrophotometer, and UV spectra were obtained in methanol on a Cary Model 14 spectrophotometer. Microanalyses were furnished by the Microanalytical Laboratory, Department of Chemistry, Stanford University. Thin-layer chromatography utilized Silica Gel G as the support and methanol for development.

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