A Model for Firefly Luciferin Biosynthesis

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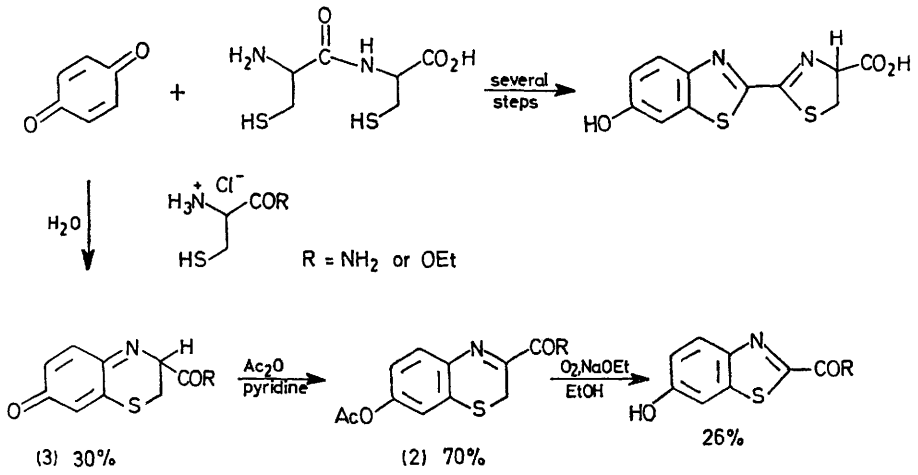
Summary The suggestion that firefly luciferin arises from *p*-benzoquinone and cysteine in nature offers a synthesis of the benzothiazole nucleus which may be related to a possible biosynthesis.

IN many bioluminescent systems there are small molecule substrates called luciferins, whose enzyme-catalysed oxidation results in light emission.[1] These molecules have unique structures, and their biosynthesis is interesting.

Conventional methods of determining the biosynthetic pathways[2] are difficult to apply to organisms with luciferins of known structure, and we have attempted to stimulate hypothesis by devising possible biomimetic syntheses. Having achieved a synthesis of analogues of Cypridina and Coelenterate luciferins,[3] we turned to the very different structure of firefly luciferin(**1**).

The thiazoline ring must be derived from cysteine, but the benzothiazole ring system has no exact precedent in nature.[4] However, noting that *p*-benzoquinone occurs frequently in certain members of the Coleoptera[5] [to which all firefly genera belong], a reasonably convincing biosynthesis can be suggested. Condensation of cysteinyl cysteine with *p*-benzoquinone and excision of the extra methylene group would provide the luciferin structure directly (Scheme).

We preferred to avoid the problems presented by the second cysteine group (particularly with respect to oxidation) and synthesised a more easily handled benzothiazine (**2**). This was prepared (as the ethyl ester) by heating equal weights of *p*-benzoquinone and cysteine ethyl ester hydrochloride (450 mg) in 200 ml boiling water. The ester (**3**, R = OEt) was obtained as a yellow solid (30% yield based on cysteine ethyl ester) on cooling. Since hydroquinone can be isolated from such reactions, the most likely route is *via* addition of the sulphydryl group followed by oxidation by excess quinone and cyclisation. Acetylation in the usual way (70% yield) isomerised the quinonoid material to the benzothiazine. Oxidation was best carried out on the amide (R = NH_2, 40 mg) in dry ethanol (20 ml) to which sodium (300 mg) had been added. Passing of oxygen through this solution for 8 h at room temperature gave a 26% yield of the benzothiazole. Although the primary condensation product[6] (**3**) can be isomerised and oxidised directly, isomerisation prior to oxidation gave the best yields. Several mechanisms for the ring contraction are possible, but the most probable is that involving the rearrangement of an intermediate peroxide. All new compounds gave satisfactory analyses and easily interpreted spectral data.



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