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CYPRIDINA BIOLUMINESCENCE VI

A NEW ROUTE FOR THE SYNTHESIS OF CYPRIDINA LUCIFERIN AND ITS ANALOGS

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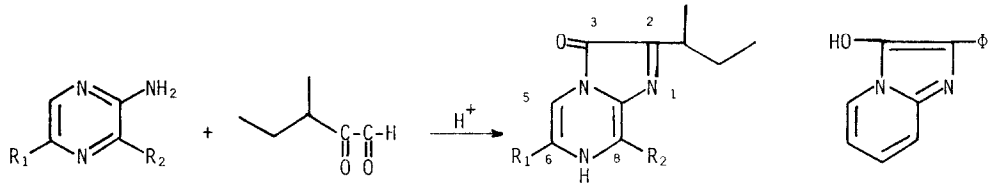
A total synthesis of Cypridina luciferin (I), a bioluminescent substance obtained from Cypridina hilgendorfii (1), was achieved in 1966 (2) by reductive condensation of an appropriate 2-aminopyrazine derivative and α-keto acid, but the yield was too low to use this route for preparative purposes. Two routes for the synthesis of 3,7-dihydroimidazo[1,2-a]-pyrazin-3-one ring system have since been developed. The one (3) consists of the condensation of a 2-bromopyrazine derivative and an α-amino acid ester followed by cyclization by an acid catalyst, and the other (4) the condensation of a 2-aminopyrazine derivative, an aldehyde and sodium cyanide followed by cyclization in the presence of an alkoxide. These methods, however, are difficult to be applied to the synthesis of the luciferin itself, since some of the reaction conditions in these routes are not applicable for the substances containing indole and/or guanidine moieties.

We found that α-keto aldehydes could be condensed with 2-aminopyrazines in dilute hydrochloric acid to give in good yields the dihydroimidazopyrazinone derivatives. For example, condensation of 2-aminopyrazine with methylglyoxal and with phenylglyoxal gave 2-methyl- and 2-phenyl-3,7-dihydroimidazo[1,2-a]pyrazin-3-one (5) in yield of 73% and 76%, respectively. 5-(Indol-3-yl)-2-aminopyrazine, on condensation with methylglyoxal, also afforded the 2-methyl-6-indolyl derivative (yield 70%)(5). The mildest conditions used and the excellent yields open the possibility that this route be applicable to the synthesis of the luciferin itself.

A solution of etioluciferin (II) dihydrobromide and crude (racemic) α-keto-β-methyl-valeraldehyde (6) in aqueous methanol containing a small amount of hydrobromic acid was refluxed for 1.5 hr, and then evaporated to a half volume. The remaining solution was diluted with acetone and the precipitates were collected and washed with acetone to give crude (racemic) luciferin (I) dihydrobromide (yield 70%), which was chromatographed twice on alumina (solvent: n-butanol) and then recrystallized thrice from methanol-acetone to



(II) (I) (III)

R_1 = 3-indolyl; R_2 = $-CH_2CH_2CH_2NHC(=NH)NH_2$

give almost colorless fine needles, m.p. 252-253° (yield ca. 30%). UV, IR and NMR spectra of the synthetic luciferin were indistinguishable with those of natural luciferin. Bioluminescence activity of this synthetic (racemic) luciferin was essentially the same as that of the natural (optically active) luciferin.

This synthetic method was also applied to 2-aminopyridines. Thus, for example, condensation of 2-aminopyridine with phenylglyoxal gave in good yield 2-phenylimidazo[1,2-a]-pyridin-3-ol (III) (5). This compound could also be synthesized by the cyanide method. Schmid and Gründig (7) had claimed that condensation of 2-aminopyridine with ω-bromo-ω-nitroacetophenone afforded the imidazopyridinol (III), m.p. 81.5-82°, but our reinvestigation disclosed that the product was actually 2-benzoylaminopyridine, m.p. 82-84°, mass M^+ 198.

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