Cyclisation of a Dehydropeptide Derivative: a Model for Cypridina Luciferin Biosynthesis

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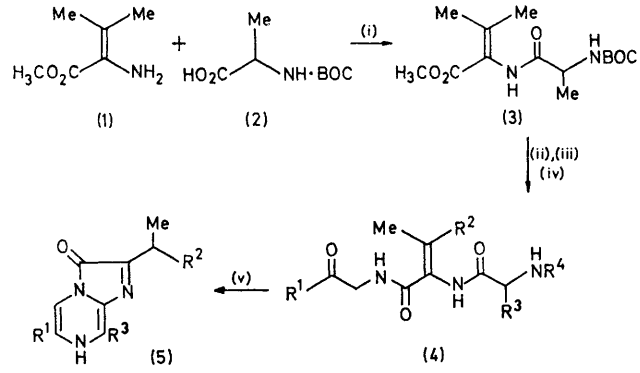
Summary The structure of Cypridina luciferin suggests a biosynthesis from three amino-acids; cyclisation of a modified tripeptide proceeds in excellent yield, providing a useful route to this interesting class of compound.

THE structure[1] (**5**; R^1 = 3-indolyl, R^2 = Et, R^3 = $(CH_2)_3$-$NHC(NH_2):NH$ of the luciferin from the small ostracod crustacean *Cypridina hilgendorfii* could reasonably be assumed to arise from tryptophan, isoleucine, and arginine. At some stage decarboxylation and dehydrogenation must occur. Formation of the tripeptide tryptophanylisoleucylarginine is a likely first step. We suggest that oxidation (3 double-bond equivalents) at this stage predisposes the oxidised peptide to cyclisation. Attention has already been drawn to the possible significance of dehydroamino-acids in this connection.[2] With this in mind, the peptide (**4**; R^1 = 3-indolyl, R^2 = Et, and R^3 = $(CH_2)_3NHC(NH_2):NH$ is a suitable precursor.

To test the synthetic value of this suggestion we synthesised (**4**; R^1 = Ph, R^2 = R^3 = Me) as follows. Dehydro-

valine methyl ester (1), prepared by reduction of methyl 3-methyl-2-nitrobut-2-enoate,[3] was coupled with *dl*-t-butoxycarbonyl-alanine using isobutyl chloroformate in tetrahydrofuran with triethylamine as catalyst. The protected dehydrodipeptide (yield 60%) (3; BOC = t-butoxycarbonyl) m.p. 104—105° was hydrolysed in 1N-NaOH solution and the resulting acid was coupled with ω-aminoacetophenone using ethyl chloroformate. The modified tripeptide (4; R^4 = BOC), m.p. 168—169°, λ_{max} 240 nm (ε 22,200), when dissolved in trifluoroacetic acid, evolved CO_2 giving the hydrotrifluoroacetate of (4; R^4 = H) in 42% yield from (3). Treatment of this salt in dimethylformamide with K_2CO_3 at 135° under N_2 for 3 h gave the compound (5; R^1 = Ph, R^2 = R^3 = Me) apparently in quantitative yield (t.l.c.). This imidazolopyrazine is unstable as the free base, and work-up required the addition of concentrated hydrochloric acid to the reaction mixture, followed by filtration through alumina deactivated by HCl using CH_2Cl_2–isopropyl alcohol–HCl as eluent. Recrystallisation from isopropyl alcohol gave pure material in a yield of 58% based on protected tripeptide. The cyclisation product (5, as hydrochloride) has m.p. 160—175°, λ_{max} (H_2O) 245 (ε 19,300), 285 (9000), 350 (4500), and 414 (7600) nm, and is, as expected, strongly chemiluminescent. Details of this luminescence will be reported later.

Attempted cyclisations of small peptides and their derivatives usually proceed either by diketopiperazine[4] formation by cleavage of a peptide link or by dimerisation particularly in the case of tripeptides.[5] Preliminary attempts[6] to cyclise the analogue of (4; R^4 = H) lacking the double bond suggest that cleavage is a major reaction in this case. The synthetic route outlined should prove general, since other starting materials are readily available, and we are investigating this. All new compounds gave satisfactory analyses and i.r. and n.m.r. spectra.



REAGENTS: (*i*) Et_3N, Bu^t O·CO·Cl, THF; (*ii*) NaOH; (*iii*) Et_3N, EtO·CO·Cl; (*iv*) $PhCO·CH_2·NH_2$ *in* THF; (*v*) $CF_3·CO_2H$; (*vi*) K_2CO_3 *in* DMF.

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[1] Previous syntheses of this luciferin fully establish the structure (a) Y. Kishi, T. Goto, S. Inoue, S. Sugiura, and M. Kishimoto, *Tetrahedron Letters*, **1966**, 3544; Y. Kishi, S. Sugiura, S. Inoue, and T. Goto, *J. Pharm. Soc.* (*Japan*), 1969, **89**, 1657; (b) T. P. Karpetsky and E. H. White, *J. Amer. Chem. Soc.*, 1971, **93**, 233.

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