A Facile One-Step Synthesis of Benz[4,5]canthin-6-one (1)

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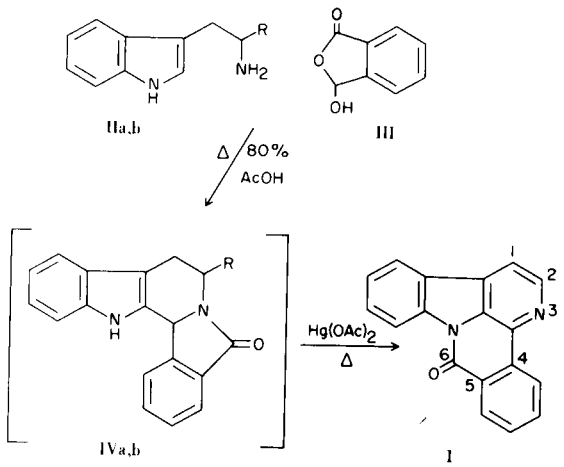
Sir:

Some naturally occuring alkaloids possessing the canthine ring system (2a-g) have recently shown interesting antibacterial activity in our laboratories. This finding led us to devise a facile one-step synthesis potentially applicable to the preparation of large quantities of compounds related to this class. Thus benz[4,5]canthin-6-one (9*H*-benz[*h*]indolo[3,2,1-*d*,*e*][1,5]naphthyridin-9-one) (I) which is the benz- analog of the alkaloid canthin-6-one (2a-c), was synthesized in high yields from commercially available compounds. Several workers have reported syntheses of canthin-6-one (3) and its derivatives (2e,2g,3,4). However, most of these methods with the exception of the procedure of Bartlett and Taylor (4), give poor yields. Synthesis of I has been reported by Marion and Manske (5) and Berti *et al.* (6) by quite different methods, also in very poor yields. Our procedure involves Pictet-Spengler cyclization, followed by mercuric acetate dehydrogenation leading to aromatization, decarboxylation and lactamization. It is unusual for mercuric acetate to dehydrogenate tetrahydro-β-carbolines to fully aromatic systems. However, this reagent has been extensively used in the preparation of dihydro-β-carbolinium compounds (7).



a, R = COOH
b, R = H

Equimolar quantities (10 mmoles) of (±)-tryptophan (IIa) (2.04 g.) and phthalaldehydic acid (III) (1.5 g.) were stirred together in 80% aqueous acetic acid (100 ml.) for 24 hours on a steam bath. Mercuric acetate (12 mmoles, 3.83 g.) in 25 ml. of the same solvent was added dropwise over a period of one half hour with continued heating and stirring and the reaction was allowed to proceed for an additional 6 hours. Saturation with hydrogen sulfide, followed by aeration at 80° and filtration of mercury metal and sulfides of mercury through diatomaceous earth, provided a dark brown filtrate which deposited yellow needles on cooling. The crystals were filtered and dried to yield 1.58 g. of I as the mono acetate salt, m.p. 218-221°. The mother liquor was chromatographed over neutral alumina (100 g.) to yield an additional 0.42 g. of I isolated as the acetate salt (total yield 60%). Recrystallizations from benzene yielded I as yellow needles, m.p. 223-224° (lit. (6), m.p. 226-227°). Elemental and spectral analyses supported the structural assignment. In particular, the uv spectrum closely resembled that of canthin-6-one (2a).

That compound IVa (6,8) is an intermediate was shown after preparing this compound independently from IIa and III by the procedure of Wawzonek and Nelson (8) using dilute sulfuric acid. Compound IVa when treated with mercuric acetate in aqueous acetic acid on a steam bath gave I in good yield along with metallic mercury. Similarly, compound IVb derived from tryptamine (IIb) and III (8) gave I in good yield. The mechanism and the scope of this synthetic procedure is currently being investigated in our laboratories. The facile nature of this synthesis coupled with general interest in the pharmacological properties of β-carboline derivatives prompt us to report this communication.

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