A NEW APPROACH TO QUINAZOLINOCARBOLINE ALKALOIDS: SYNTHESIS OF (±)-EVODIAMINE, RUTAECARPINE AND DEHYDROEVODIAMINE

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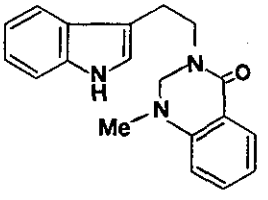
Treatment of the tetracyclic lactam (I) with $Hg(OAc)_2$ gives (±)-evodiamine (III) which is in turn regiospecifically oxidized to rutaecarpine (IVa) by MnO_2 or to dehydroevodiamine (V) by other oxidants.

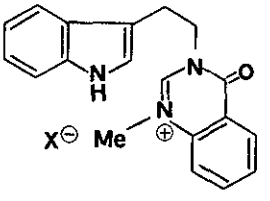
Recently the synthesis of quinazolinocarboline alkaloids has received considerable attention by Kametani *et al.* which obtained evodiamine (III), rutaecarpine (IVa) and euxylophoricines A and C (IVb,c) through a fascinating regiospecific $[\pi^4{}_s+\pi^2{}_s]$ cycloaddition of a keteneimine (generated *in situ* by SO_2 extrusion from the sulfinamide anhydride of anthranilic acid) with 4,9-dihydro-3H-pyrido[3,4-b]indole.[1-5]

As part of our continuing study of the structure elucidation and characterization of quinazolinocarboline alkaloids,[6] we wish to report herein a novel synthesis of (III) and also its regiospecific oxidation either to rutaecarpine (IVa) or to dehydroevodiamine (V).

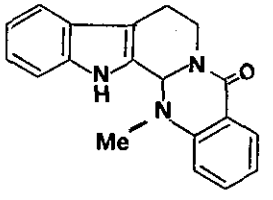
Condensation of tryptamine with N-methylanthranilic acid (CBr_4, PPh_3, refluxing toluene, 5 hr)[7] followed by intramolecular amidomethylation (36% CH_2O, HCl, refluxing MeOH, 3 hr) gave rise to 2,3-dihydro-1-methyl-3(1H-indol-3-yl)ethyl-4(1H)-quinazolone (I)[8] in 84% overall yield. Oxidation of (I) with $Hg(OAc)_2$ (2 equiv) in AcOH-H_2O (9:1) at r.t. for 24 hr afforded (±)-evodiamine (III), m.p. 268°(acetone) [lit.[9] 267-70° for (±)-evodiamine] in 92% isolated yield. The formation of (III) takes place via intramolecular acid-catalyzed interaction of the electrophilic carbon of the intermediate 3,4-dihydro-4-oxoquinazolinium salt (II) with the nucleophilic position 2 of the indole moiety.



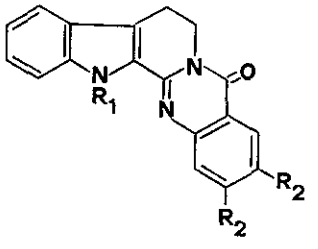
I



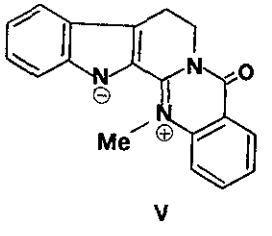
II



III



IVa $R_1, R_2 = H$
IVb $R_1 = H$, $R_2 = OMe$
IVc $R_1 = H$, $R_2 = OCH_2O$
IVd $R_1 = Me$, $R_2 = H$



V

Despite its stability toward further oxidation by $Hg(OAc)_2$,[10] (III) is smoothly oxidized by excess active MnO_2(Merck)[11] in CH_2Cl_2 (r.t., 3 hr) to 85% rutaecarpine (IVa), m.p. 257° (benzene)(lit.[12] 257-8°).[13] Furthermore we have found that (III) can be converted into (V) by a variety of oxidants. In particular, $Tl(OAc)_3$(3 equiv, CH_2Cl_2, r.t., 16 hr) and DDQ(2 equiv, CCl_4, r.t., 25 hr) gave (V) in 85 and 67% yield respectively, and the yield (65% in our hands) by alkaline $KMnO_4$ oxidation in acetone at 0° [14-16]were markedly improved (91%) by using dicyclohexyl-18-crown-6[17] in CH_2Cl_2 (r.t., 30 min).[18]

Thus we have developed a mild, high-yield non-thermal approach to (±)-evodiamine, rutaecarpine, dehydroevodiamine and the accumulated evidences suggest that it will be of general applicability in synthesis of various substituted quinazolinocarboline alkaloids.

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