

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

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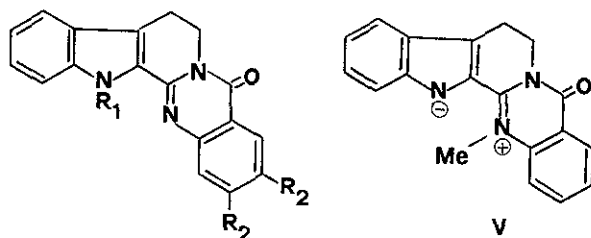
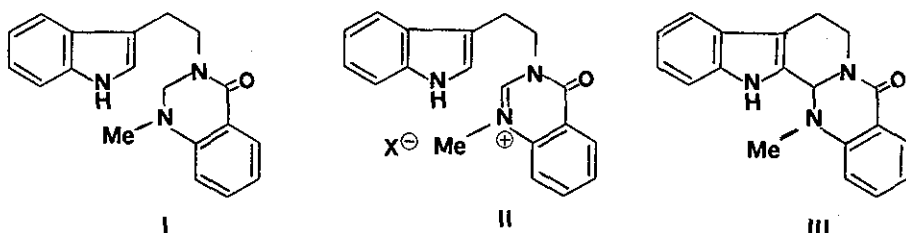
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Treatment of the tetracyclic lactam (I) with $\text{Hg}(\text{OAc})_2$ gives (+)-evodiamine (III) which is in turn regiospecifically oxidized to rutaecarpine (IVa) by MnO_2 or to dehydroevodiamine (V) by other oxidants.

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 $[\pi_4s + \pi_2s]$ 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-methylantrhanilic 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)-quinazolinone (I)⁸ in 84% overall yield. Oxidation of (I) with $\text{Hg}(\text{OAc})_2$ (2 equiv) in $\text{AcOH-H}_2\text{O}$ (9:1) at r.t. for 24 hr afforded (+)-evodiamine (III), m.p. 268° (acetone) [lit.⁹ $267-70^\circ$ 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.



IVa $\text{R}_1, \text{R}_2 = \text{H}$
 IVb $\text{R}_1 = \text{H}, \text{R}_2 = \text{OMe}$
 IVc $\text{R}_1 = \text{H}, \text{R}_2 = \text{OCH}_2\text{O}$
 IVd $\text{R}_1 = \text{Me}, \text{R}_2 = \text{H}$

Despite its stability toward further oxidation by $\text{Hg}(\text{OAc})_2$,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 $257-8^\circ$).¹³ Furthermore we have found that (III) can be converted into (V) by a variety of oxidants. In particular, $\text{Ti}(\text{OAc})_3$ (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-6¹⁷ 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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- 10 A longer reaction times (r.t., 48 hr) or further treatment of (III) with a fivefold excess of oxidant yielded only a trace amount of (V) and overoxidation product(s) (tlc).
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- 13 The conversion evodiamine - rutaecarpine was previously effected by thermolysis ¹⁴⁻¹⁶. In our hands the yields were erratic and low. Thermolysis of evodiamine in sealed ampoule at 210° or in refluxing DMF gave first dehydroevodiamine (<5%) which then rearranged to a (1:1) mixture of rutaecarpine and the [1,7]-methyl shift product 13-methylrutaecarpine (IVd) in about 80% yield.
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- 18 Dehydroevodiamine was also obtained by POCl₃-promoted condensation of 2,3,4,9-tetrahydro-1H-pyrido [3,4-b] indol-1-one with N-methylantranilic acid methyl ester in 68% yield(I.J. Pachter and G.Suld, J. Org. Chem., 1960, 25, 1680).

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