A ONE-STEP SYNTHESIS OF EVODIAMINE AND RUTECARPINE

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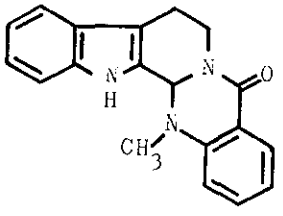
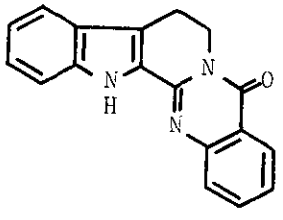
Evodiamine (1) and rutecarpine (2) were synthesised by condensation of 3,4-dihydro-β-carboline (5) with the keteneimines (6 and 12) derived from N-methylanthranilic acid (7) and anthranilic acid (10), respectively.

Evodiamine (1) and rutecarpine (2), the indoloquinazoline alkaloids found in Evodia rutaecarpa,[1,2] have been synthesised by many

Chart 1



(1)

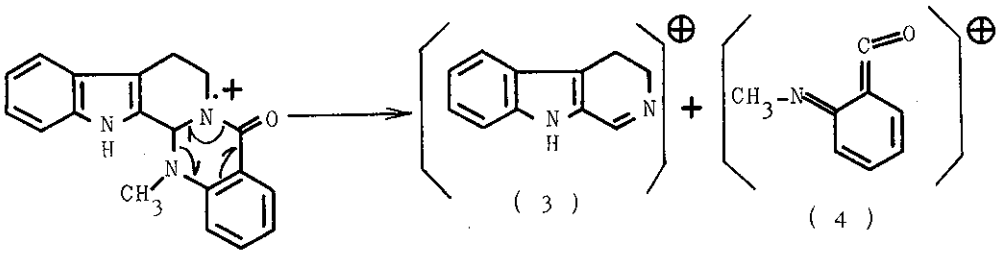


(2)

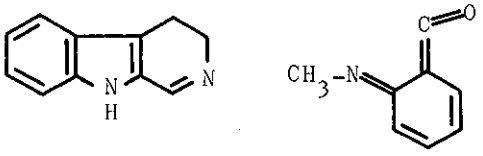
methods.[3-7] Alternatively, we investigated their synthesis via the cycloaddition reaction developed in our laboratory[8] and now wish to report our successful results.

The mass spectral cleavage of evodiamine (1) involves a retro Diels-Alder type fragmentation of D ring, to form two characteristic ions, the 3,4-dihydro-β-carboline ion (3) and keteneimine ion (4). Since the Woodward-Hoffmann rule[9] suggests the [4 + 2]cycloaddition to be a reversible reaction, we utilized the synthons (5 and 6), corresponding to the fragment ions (3 and 4), for a new synthetic procedure for evodiamine (1).

Chart 2



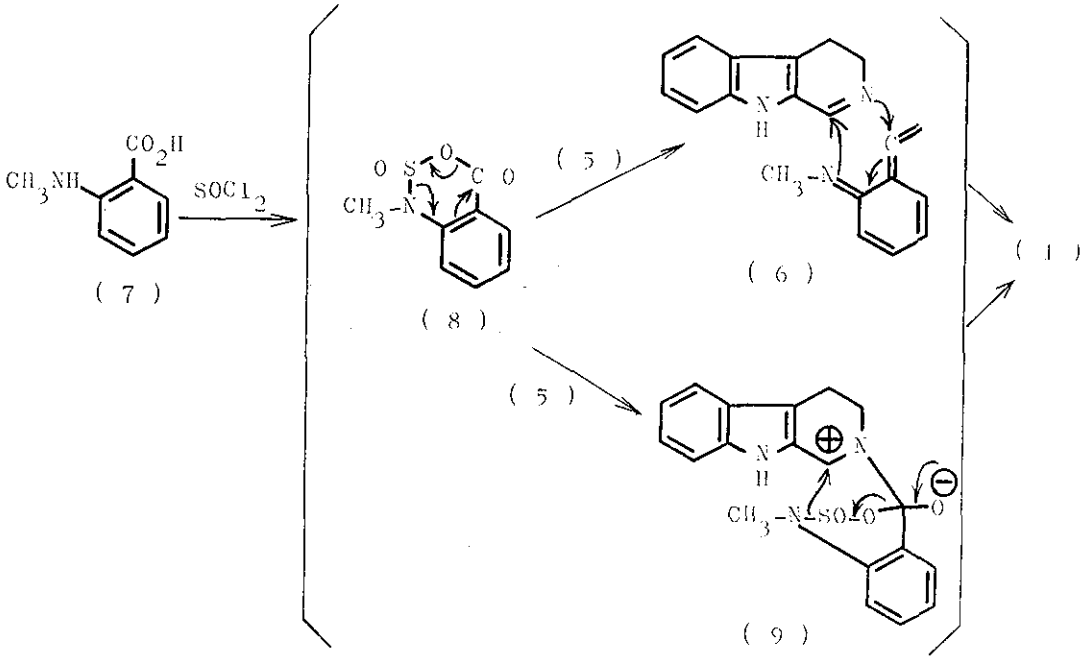
(3) (4)



(5) (6)

Heating N-methylanthranilic acid (7) with thionyl chloride in dry benzene gave an unstable sulfinamide anhydride (8), which upon treatment with 3,4-dihydro-β-carboline (5) in dry benzene at room temperature evolved sulfur dioxide to afford regioselectively evodiamine (1), m.p. 268 - 270° (lit.,[10] m.p. 270 - 272°), m/e 303 (M^+), in 65 % yield. The i.r. [ν max ($CHCl_3$) 3475 and 1640 cm^{-1}], u.v. [ν max (MeOH) 292, 283, 273, and 268 nm] and n.m.r. [δ ($CDCl_3$) 2.53 (3H, s, NCH_3) and 5.90 (1H, s, CH)] spectra of (1) were superimposable with those of the natural product.

Chart 3

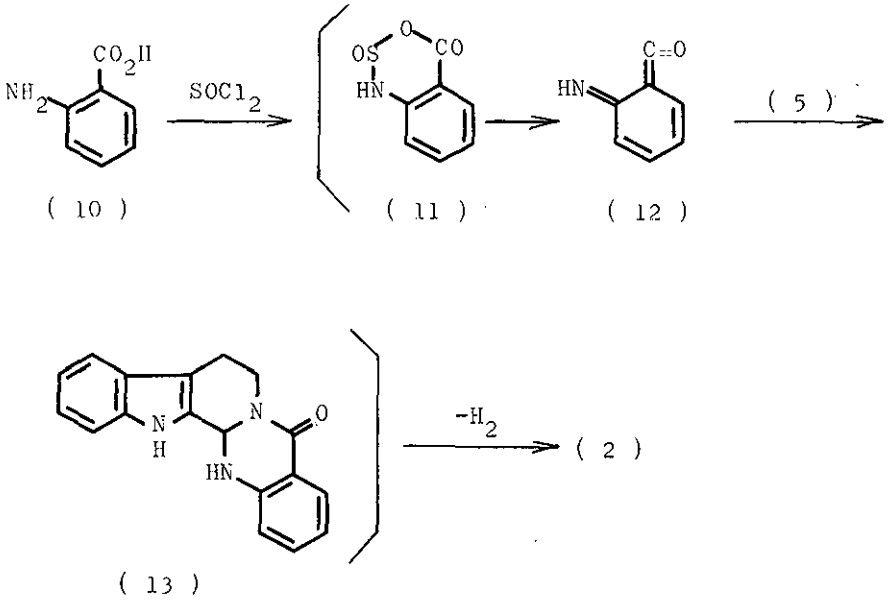


In this reaction, the sulfinamide anhydride (8) was presumably converted into the keteneimine (6) followed by regioselective reaction with 3,4-dihydro-β-carboline (5) by a concerted ($_{\pi}4 + _{\pi}2$)-cycloaddition pattern to form evodiamine (1). However a stepwise mechanism via the intermediate (9) can not be ruled out.

Since the above route is based on mass spectral fragmentation, we propose that this type of synthesis is called "Synthesis Based on Mass Spectral Cleavage (Retro Mass Spectral Synthesis)".

In a similar manner, rutecarpine (2) was also obtained in one step. Thus, treatment of the sulfinamide anhydride (11),[11] derived

Chart 4



(10) (11) (12) (13) (2)

from anthranilic acid (10) and thionyl chloride, with 5 in dry benzene at room temperature gave in 85 % yield rutecarpine (2), m.p. 259° (lit.,[3] m.p. 258°), m/e 287 (M^+), by a spontaneous dehydrogenation of the initial product (13). Our product was identical with natural rutecarpine in i.r. [ν max (KBr) 3325 and 1655 cm^{-1}], u.v. [ν max (MeOH) 361, 344, 330, 288, and 276 nm] and n.m.r. [δ ($CDCl_3$) 3.23 (2H, t, J 7 Hz, $ArCH_2$) and 4.60 (2H, t, J 7 Hz, NCH_2)].

Thus, we have accomplished a one-step synthesis of evodiamine and rutecarpine by Synthesis Based on Mass Spectral Cleavage (Retro mass spectral synthesis).

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