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TOTAL SYNTHESIS OF PHENOLIC BALFOURODENDRON ALKALOIDS[1]

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Summary. The total synthesis of (±)-ribaline is reported; in combination with earlier findings, this represents a formal total synthesis of (±)-ribalinidine.

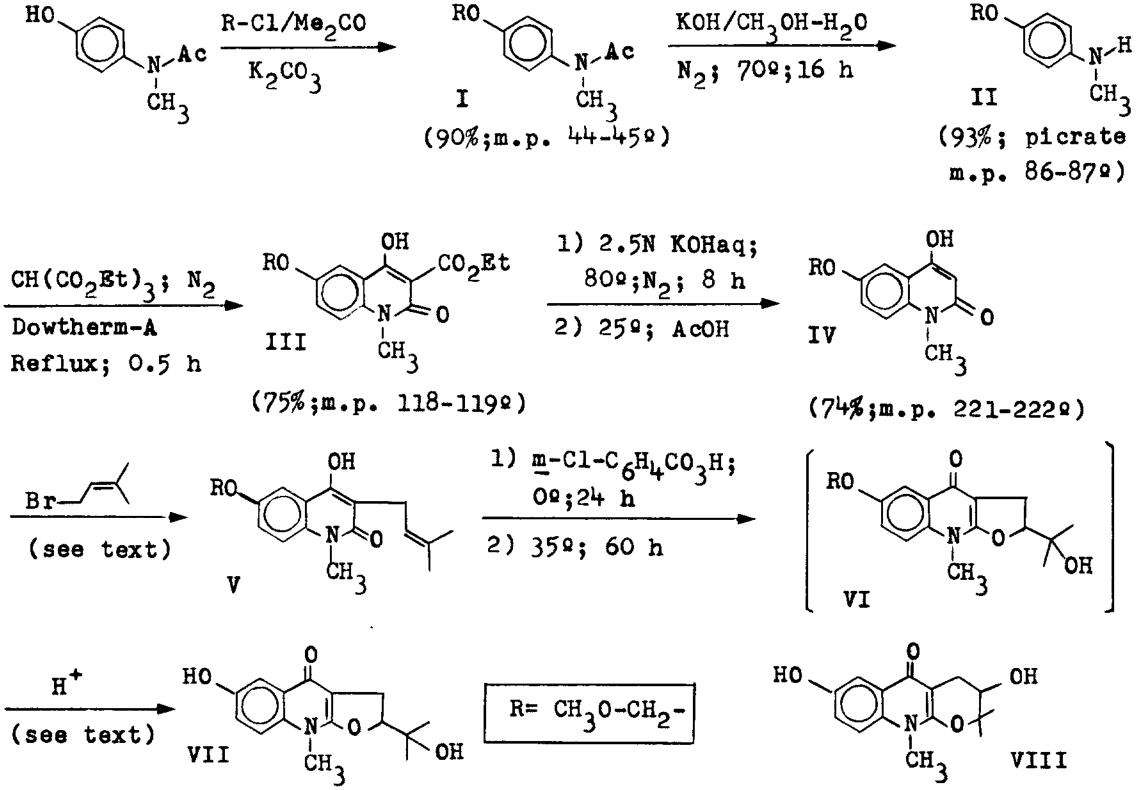
Numerous dihydrofuro or dihydropyrano quinolinic alkaloids have been isolated from Rutaceae[2] (e.g. Lunasia and Balfourodendron species) and several routes have been reported with regard to synthesis of some of the compounds.[3] We report here the first synthesis of examples bearing a phenolic function.

Since the reaction of diethyl malonate[3] and II failed to give the 4-hydroxy-2-quinolone IV, we have successfully employed tricarbethoxymethane for this cyclization, followed by hydrolysis and decarboxylation (see Scheme).

Another key feature of the route was the regioselective prenylation of IV at C_3 which led to V; the conditions and operational details for this step are critical. The reaction was carried out at 35º under N_2 with stirring (48 h): prenyl bromide(1.1 mmol) in toluene(1 ml) was added to IV(1 mmol) which had been dissolved in 1 N NaOH aq(1 ml) and mixed with C_6H_6(1.25 ml). After 12 h, 2 N NaOH aq(0.25 ml) and prenyl bromide(0.55 mmol) in toluene were again added, followed by two further additions at 12 h intervals of these reagents; the amounts were decreased each time to one half that of the preceding. After evaporation of the organic solvent, the residue was extracted with 1 N NaOH aq; acidification of the extract with AcOH caused the precipitation of the crude product (NMR: 56% yield of V and 24% of unreacted IV) which gave pure V (m.p. 140-141º; 45% yield) after crystallization from C_6H_6 and then from EtOAc.[4]

The cyclization of V via its epoxide to give crude VI(extracted at 0º with 1 M H_3PO_4aq; showed mainly one spot on TLC; 95% yield) was done similarly to analogous examples.[5] To remove the phenolic protective group, the crude VI

(0.1 mmol) was heated at 100º for 30 min in AcOH(0.3 ml) and 0.2 M H_2SO_4aq(0.3 ml). Addition of NaOAc(0.15 mmol) and picric acid(0.1 mmol) in AcOH(0.2 ml) gave a 77% yield of (±)-ribaline(VII) as picrate salt, m.p. 221-223º dec.(from alcohol). The latter was identical to an authentic sample[6] via comparison of mixed m.p. and IR spectra. This also represents a total synthesis of (±)-ribalinidine(VIII), a phenolic dihydropyrano-4-quinolone alkaloid, for earlier[6] we had described the isomerization of (±)-ribaline(VII) to (±)-VIII.



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