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SYNTHESIS OF (±)-JULANDINE AND (±)-CRYPTOPLEURINE

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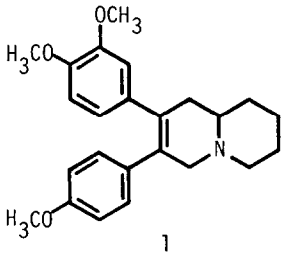
Summary: An efficient synthesis of (±)-julandine and (±)-cryptopleurine has been achieved starting from the isoxazolidine formed via nitrone cycloaddition reaction.

Cryptopleurine (2), forming a rare group of alkaloids with the phenanthro[9,10-b]quinolizidine skeleton together with cryptopleuridine,[1] has been shown to possess unique and interesting biological properties[2] including vesicant and anticancer[2b] activities. For this reason and to study structure–activity relationship, this alkaloid and its biogenetic congener, julandine (1), have recently received the intense attention, and three independent syntheses[3–5] of cryptopleurine (2) based on biogenetic considerations have been reported.[6] We now describe a new, efficient synthesis of (±)-julandine and (±)-cryptopleurine.

Our synthesis of the alkaloids 1 and 2 began with the preparation of the isoxazoridine 5 as a key intermediate which was attained by the 1,3-diporlar cycloaddition reaction of 2,3,4,5-tetrahydropyridine 1-oxide (3) with 3,4-dimethoxystyrene (4). The reaction performed in boiling toluene proceeded regioselectively to give the oily product in 93% yield (NMR ($CDCl_3$) δ 3.84 and 3.87 (s, 3H each), 4.94 (br m, 1H, OC<u>H</u>Ar); MS m/e 263 (M^+, base)). Reductive N–O bond fission of 5 with zinc in aqueous acetic acid (r.t., 2.5 h) gave the amino alcohol 6 in 90% yield (mp 148–149 °C; IR ($CHCl_3$) 3630–3150 cm^{-1}; NMR ($CDCl_3$) δ 3.85 and 3.87 (s, 3H each), 4.96 (br t, J = 6 Hz, ArC<u>H</u>OH), 6.81 (s, 2H), 6.92 (s, 1H)). Treatment of the amino alcohol 6 with p-methoxyphenylacetyl chloride in dichloromethane in the presence of K_2CO_3 (0 °C, 4 h) yielded a chromatographycally separable mixture of the amido alcohol 7 (mp 134–135 °C; IR ($CHCl_3$) 3325, 1605 cm^{-1}; NMR ($CDCl_3$) δ 3.77, 3.84, and 3.87 (s, 3H each)) and the amido ester 8 (IR ($CHCl_3$) 1725, 1605 cm^{-1}), the latter of which, the minor product, was subsequently hydrolyzed (aqueous MeOH, K_2CO_3, reflux, 1 h) to produce 7 (total yield of 7: 64%). The amido alcohol 7 was then converted to the keto amide 9 (IR ($CHCl_3$) 1660, 1600 cm^{-1}; NMR ($CDCl_3$) δ 3.76 (s, 3H, OCH_3), 3.92 (s, 6H, 2 x OCH_3)) by Collins oxidation (CH_2Cl_2, r.t., 2 h) in 82% yield. Aldol condensation of the keto amide 9 was accomplished by treatment of sodium ethoxide in ethanol (reflux, 2 h), affording the lactam 10 (mp 142.5–143 °C (lit.[3] 141–142 °C)) in 67% yield which was then converted to (±)-julandine (1) (mp 139–140 °C) with $LiAlH_4$ (THF–Et_2O, reflux, 1 h) in 63% yield. Synthetic (±)-julandine exhibited the identical spectra (IR, NMR) with those of a natural sample and was proved to be directly identical in all respects with an authentic synthetic specimen. On the other hand, upon irradiation of lactam 10 (high pressure Hg lamp, dioxane, I_2, r.t., 20 h), two fluorescent photocyclization products, 11 (mp 194–196 °C (lit.[3] 194–195 °C)) and 12 (mp 155–156 °C; NMR ($CDCl_3$) δ 3.85, 3.95, and 4.03 (s, 3H each), 7.30 and 7.79 (AB q, J = 9 Hz, 2H), 7.22 (dd,

J = 9 and 3 Hz, 1H), 9.17 (d, J = 3 Hz, 1H), 9.32 (d, J = 9 Hz, 1H)) were obtained in 49 and 14% yields, respectively. The former product with the adequate methoxyl substitution mode on the ring A was finally led to (±)-cryptopleurine (2) (mp 201–202 °C (lit.[4] 199–200 °C)) by reduction with $LiAlH_4$ in THF in 95% yield. The synthetic substance was found to be identical with natural (-)-cryptopleurine by comparison of TLC and NMR ($CDCl_3$) and IR ($CHCl_3$) spectra.



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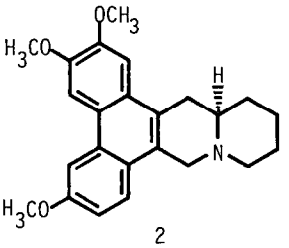

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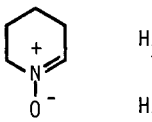

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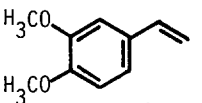

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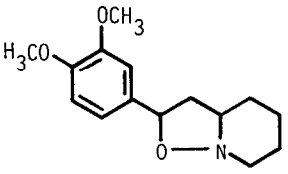

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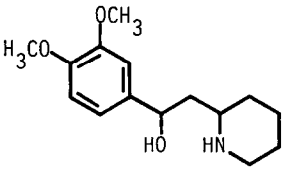

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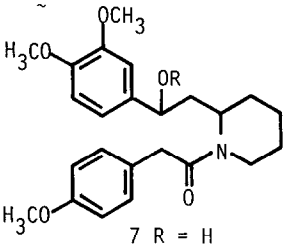
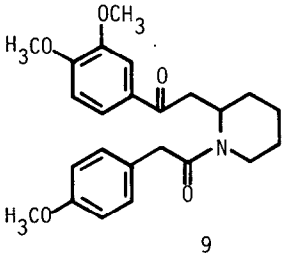


7 R = H
8 R = $COCH_2C_6H_4$-p-OCH_3



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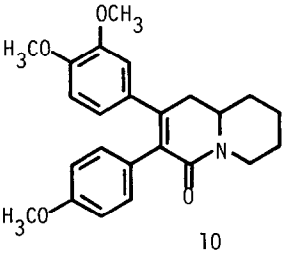

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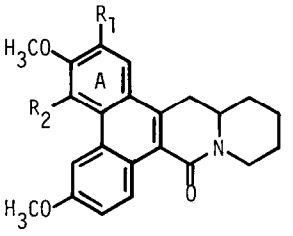

11 R_1 = OCH_3; R_2 = H
12 R_1 = H; R_2 = OCH_3

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