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A NOVEL SYNTHESIS OF OCHOTENSINE-TYPE ISOQUINOLINES BY THERMOLYSIS

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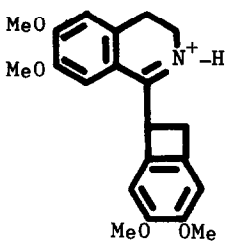
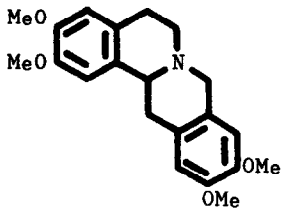
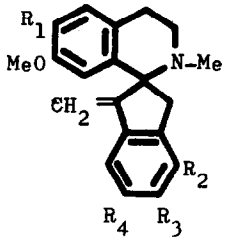
Recently we described the preparation of (±)-xylopinine (2) from the benzocyclobutenyl precursor 1 by thermal rearrangement.[1] As an extension of this method, we now wish to report a novel synthesis of the spirobenzylisoquinoline 3 which is structurally related to the alkaloid ochotensine (4) and the previously described diphenol 5.[2]



1



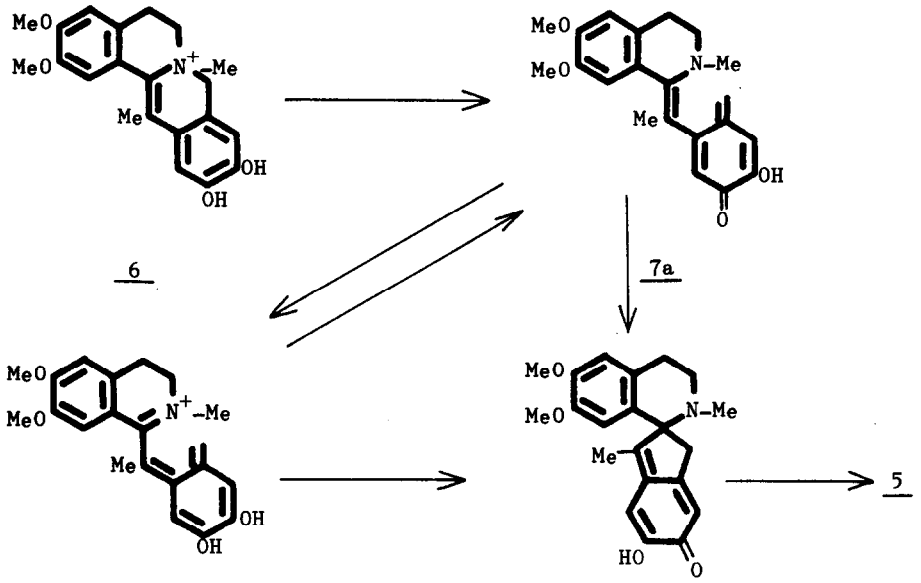
2
(Xylopinine)



3 : $R_1=R_3=R_4=OMe$, $R_2=H$
4 : $R_1=OH$, $R_2+R_3=OCH_2O$, $R_4=H$
5 : $R_1=OMe$, $R_2=H$, $R_3=R_4=OH$

The rationale for the synthesis of 3 was the expectation that the substituted benzocyclobutenylisoquinolinium salt 13 would thermally rearrange via the o-quinodimethane 14 since it possesses the same electronic environment as the intermediate 7 which was postulated by Shamma and Jones[2] in their in vitro biogenetic conversion of the protoberberine methide 6 via 8 to yield the diphenol 5. Based on this premise, the benzocyclobutenylcarboxamide 12 was obtained by standard methods.[3] However, it was surprising that 12 on Bischler-Napieralski reaction did not yield the corresponding 3,4-dihydroisoquinolinium salt 13 but instead afforded the desired spirobenzylisoquinoline 3. It is

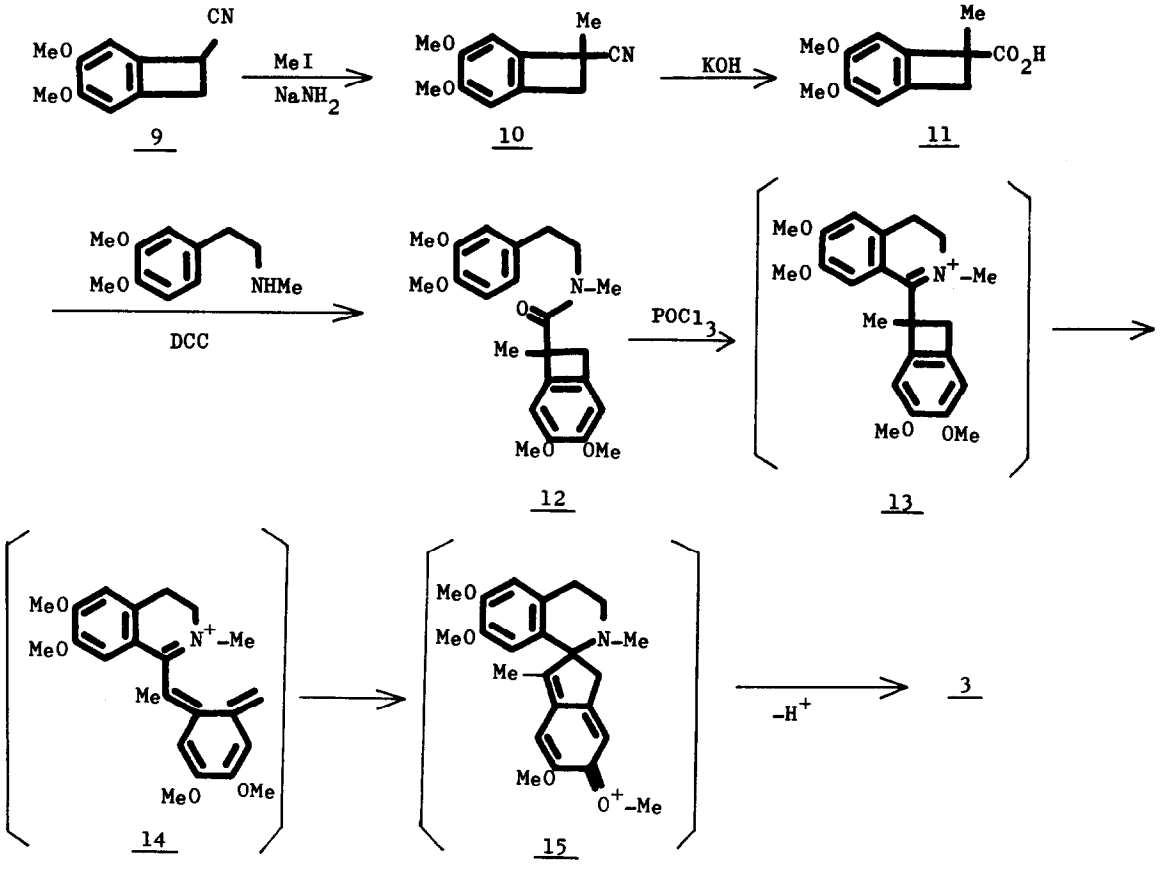
probable that 13 was initially formed and ther. thermally rearranged via 14 and 15 to yield 3. This finding thus provides a more direct route to the ochotensine-type alkaloids than the stepwise procedures heretofore reported.[4]



Treatment of the known cyanobenzocyclobutene 9[5] with methyl iodide in the presence of sodium amide[6] in refluxing benzene afforded the methyl-substituted derivative 10 [45.0 % yield; mp 72.5 - 73.0°; $\nu_{max}^{CHCl_3}$ 2220 cm^{-1}; m/e 203 for $C_{12}H_{13}O_2N$: δ (in $CDCl_3$) 1.73 (3H, singlet, ≥C-Me), 3.41 (2H, a pair of doublets, internal chemical shift with 21 Hz, and J = 14 Hz), 3.84 (6H, singlet, 2 x OMe), 6.68 and 6.75 ppm (2H, each singlet, aromatic protons)]. Hydrolysis of 10 was readily accomplished by the procedure of Cava[7] to provide the corresponding acid 11 [82.4 % yield; mp 91.5 - 92°; $\nu_{max}^{CHCl_3}$ 1705 cm^{-1}; m/e 222 for $C_{12}H_{14}O_4$; δ (in $CDCl_3$) 1.68 (3H, singlet, ≥C-Me), 3.21 (2H, a pair of doublets, internal chemical shift with 29 Hz and J = 14 Hz), 3.84 (6H, singlet, 2 x OMe), 6.71 and 6.75 (2H, each singlet, aromatic protons), and 8.08 ppm (1H, broad singlet, disappeared with D_2O, COOH]. Condensation of 11 with an equimolar amount of N-methylhomoveratrylamine in the presence of dicyclohexylcarbodiimide[8] gave the amide 12 [51.6 % yield; an oil, $\nu_{max}^{CHCl_3}$ 1620 cm^{-1}; m/e 399 for $C_{23}H_{29}NO_5$; δ (in $CDCl_3$) 1.64 (3H, singlet, ≥C-Me), 2.91 (3H, singlet, NMe), 2.60 - 3.70 (6H, multiplet, 3 x CH_2), 3.80 (9H, singlet, 3 x OMe) and 3.83 (3H, singlet, OMe), 6.62 (1H,

singlet, aromatic proton), 6.72 (3H, singlet, aromatic protons), and 6.95 ppm (1H, singlet, aromatic proton)].

Bischler-Napieralski reaction of the amide 12 with two equivalents of phosphorus oxychloride in refluxing benzene for 22 hr afforded the spirobenzylisoquinoline 3 [14.0 % yield[9]; mp 46 - 49°, $\nu_{max}^{CHCl_3}$ 850 cm^{-1} (endo methylene group); m/e 381 for $C_{23}H_{27}NO$; δ (in $CDCl_3$) 2.15 (3H, singlet, NMe), 2.75 - 3.40 (6H, multiplet, 3 x CH_2), 3.62, 3.82, 3.88, and 3.92 (12H, each singlet, 4 x OMe), 4.87 and 5.55 (2H, each singlet, two vinylic protons), and 6.28, 6.53, 6.75 and 7.03 ppm (4H, each singlet, four aromatic protons).



The above transformations demonstrate a facile and convenient entry into the synthesis of the ochotensine class of alkaloids. Studies are now in progress to prepare naturally occurring spirobenzylisoquinolines by this novel method.

References

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9. Optimumization of the reaction conditions is at present under investigation since 35 % of the amide 12 was also recovered.