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THE SYNTHESIS OF A 4-PHENYLISOQUINOLINE FROM A 3-PHENYLISOQUINOLINE BY UTILIZATION OF A NITROGEN ANALOG OF THE PINACOL REARRANGEMENT

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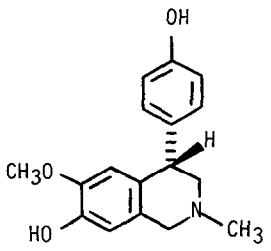
Abstract. The nitrogen analog of the pinacol rearrangement has been utilized for the preparation of a 4-phenylisoquinoline **9** from the intermediate amino alcohol **8**.

Recent interest in the development of synthetic approaches to 4-phenylisoquinolines has been stimulated both by the isolation of the Amaryllidaceae alkaloid (-)-cherylline (**1**)[1] from several species of Crinum and the desire for certain 4-phenyl-1,2,3,4-tetrahydroisoquinoline analogs of the mixed acting sympathomimetic amine ephedrine.[2] Several of these congeners are dopamine agonists that have displayed interesting CNS antidepressant activity.[2,3] 3-Phenylisoquinolines of the general type represented by structures **4** and **5** have become readily available through the condensation of homophthalic anhydrides and Schiff bases.[4] We have recently become interested in the possibility that an appropriately substituted 3-phenylisoquinoline could be transformed into a 4-phenylisoquinolines by the utilization of a phenyl migration during a nitrogen analog of the well-known pinacol rearrangement.[5,6] As reported in the present communication, this strategy has found some limited success in the partial conversion of the intermediate amino alcohol **8** to the desired 4-Phenylisoquinoline **9** (Scheme I).



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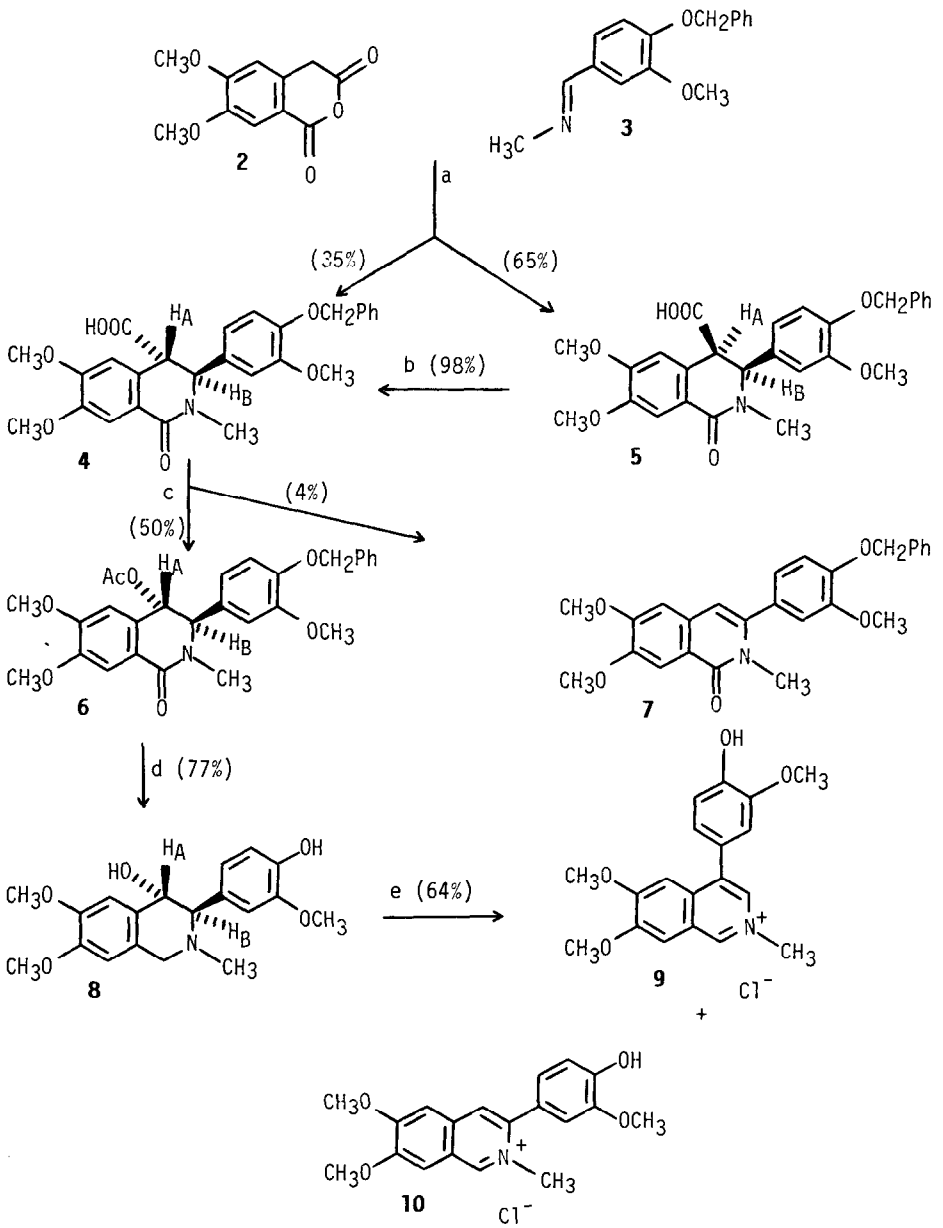
The condensation of **2** with **3** provided **5**[7] as the major product. Also obtained was a minor trans diastereomer **4**.[8] The thermodynamically less stable isomer **5** could be converted to **4** in refluxing acetic acid.[4] Oxidative decarboxylation of **4** with lead tetraacetate and

Scheme I

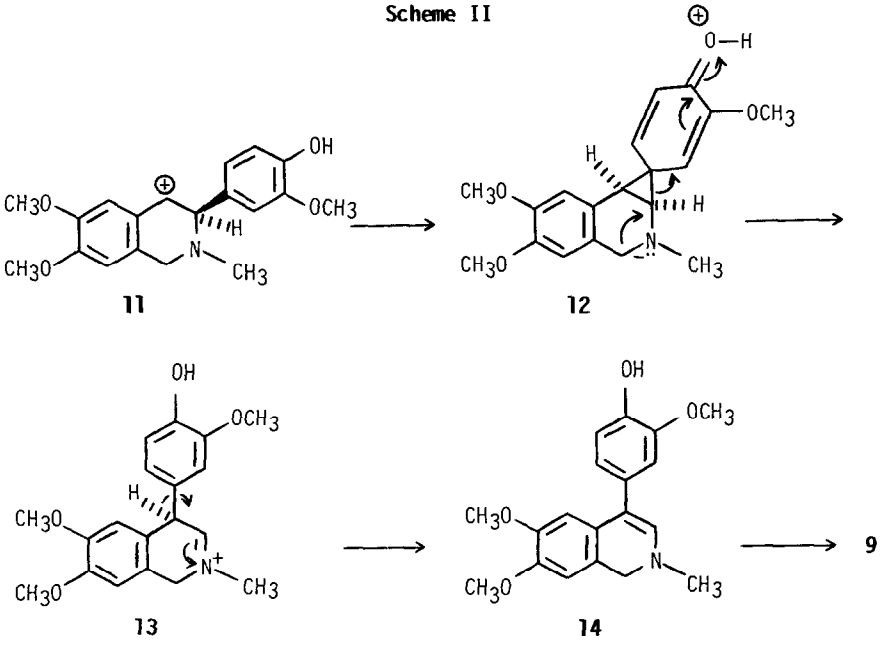


[a] $CHCl_3$, 23 °C (0.5 h). [b] AcOH, reflux (16 h). [c] $Pb(OAc)_4$, $Cu(OAc)_2$, pyridine, benzene, 80 °C (3 h). [d] (1) $LiAlH_4$, THF, reflux (27 h); (2) H_2, Pd/C, AcOH, 23 °C (1 h). [e] (1) Pd/C, AcOH, reflux (24 h); (2) Aq. NaCl.

cupric acetate gave the acetate **6**[9] accompanied by small amounts of the olefin **7**.[10] Reaction of **6** with lithium aluminum hydride followed by catalytic hydrogenolysis of the benzyl ether, afforded the desired amino alcohol **8**.[11] Treatment of compound **8** with palladium on charcoal in refluxing acetic acid, followed by filtration of the catalyst and evaporation of the solvent, gave an oily residue which was converted to solid material in the presence of 15% aq NaCl. NMR analysis of this mixture was consistent with a 2:1 mixture of the positional isomers **10** and **9**, respectively. Ion pair tlc using silica gel and 5% NaBr in methanol clearly indicated the presence of two products having R_f = 0.53 (**9**)[12] and R_f = 0.70 (**10**).[13,14] The N-methyl signal of the 3-phenyl isomer **10** (δ 4.14) appears upfield relative to that of the 4-phenyl isomer **9** (δ 4.39) due to the shielding effect of the adjacent phenyl substituent in **10**.

Both products **9** and **10** probably arise from a common intermediate carbonium ion **11** (Scheme II), which can undergo either deprotonation and dehydrogenation to form **10** or phenyl group migration (**11**⟶**12**⟶**13**) followed by deprotonation and dehydrogenation to yield **9**. The proposed intermediates **13** and **14** were not detected in the reaction mixture. It is noteworthy that the isopropyl ether derivative of the phenol **8** gives only the corresponding isopropyl derivative of **10** when subjected to the reaction conditions. Although β-amino alcohols have previously been reported to undergo the "semipinacolic rearrangement", the reaction involves the conversion of a primary amine to a diazonium ion, followed by cleavage and migration of the group attached to the adjacent carbinol carbon.[15]

Scheme II



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7. M.p. 210-212 °C; NMR ($CDCl_3$ + pyridine-d_5) δ10.50 (br s, 1 H, exchangeable with D_2O), 8.58-6.70 (m, 10 H), 5.08 (d, 1 H, J_{AB} = 6 Hz), 4.94 (s, 2 H), 4.70 (d, 1 H, J_{AB} = 6 Hz), 3.89 (s, 3 H), 3.79 (s, 3 H), 3.51 (s, 3 H), 3.08 (s, 3 H).

8. M.p. 98-100 °C; NMR ($CDCl_3$) δ 7.98 (br s, 1 H, exchangeable with D_2O), 7.62-6.44 (m, 10 H), 5.03 (s, 3 H), 3.85 (s, 3 H), 3.79 (s, 3 H), 3.76 (s, 1 H), 3.72 (s, 3 H), 3.06 (s, 3 H).

9. NMR ($CDCl_3$) δ 7.71 (s, 1 H), 7.34 (s, 5 H), 6.80-6.43 (m, 4 H), 5.80 (d, 1 H, J = 2 Hz), 5.06 (s, 2 H), 4.72 (d, 1 H, J = 2 Hz), 3.96 (s, 3 H), 3.84 (s, 3 H), 3.76 (s, 3 H), 3.11 (s, 3 H), 2.08 (s, 3 H).

10. NMR ($CDCl_3$) δ 7.80 (s, 1 H), 7.42-7.34 (m, 6 H), 6.90 (s, 2 H), 6.82 (s, 1 H), 6.36 (s, 1 H), 5.21 (s, 2 H), 4.01 (s, 3 H), 3.96 (s, 3 H), 3.91 (s, 3 H), 3.42 (s, 3 H).

11. Monohydrate, mp 79-82 °C; NMR ($CDCl_3$) δ 6.96 (s, 1 H), 6.83-6.67 (m, 3 H), 6.49 (s, 1 H), 4.67 (d, 1 H, J_{AB} = 7 Hz), 3.82 (s, 3 H), 3.81 (s, 3 H), 3.74 (s, 3 H), 3.69 (d, 1 H, J = 15 Hz), 3.48 (d, 1 H, J = 15 Hz), 3.22 (d, 1 H, J = 7 Hz), 2.13 (s, 3 H). Anal. Calcd for $C_{19}H_{23}NO_5$ H_2O: C, 62,78; H, 6.94; N, 3.85. Found: C, 62.41; H, 6.85; N, 3.54.

12. NMR (DMSO-d_6) δ 9.42 (s, 1 H), 8.47 (s, 1 H), 7.83 (s, 1 H), 7.43 (s, 1 H), 7.19 (s, 1 H), 7.05 (s, 2 H), 4.39 (s, 3 H), 4.01 (s, 3 H), 3.93 (s, 3 H), 3.83 (s, 3 H).

13. NMR (DMSO-d_6) δ 9.59 (s, 1 H), 8.16 (s, 1 H), 7.75 (s, 1 H), 7.69 (s, 1 H), 7.21 (s, 1 H), 7.02 (d, 1 H, J = 10 Hz), 6.99 (d, 1 H, J = 10 Hz), 4.14 (s, 3 H), 4.04 (s, 3 H), 4.01 (s, 3 H), 3.81 (s, 3 H). Coupling of the two ortho aromatic protons of the phenyl group of **10** (J = 10 Hz) was not evident in **9** because of coincidental overlap.

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