

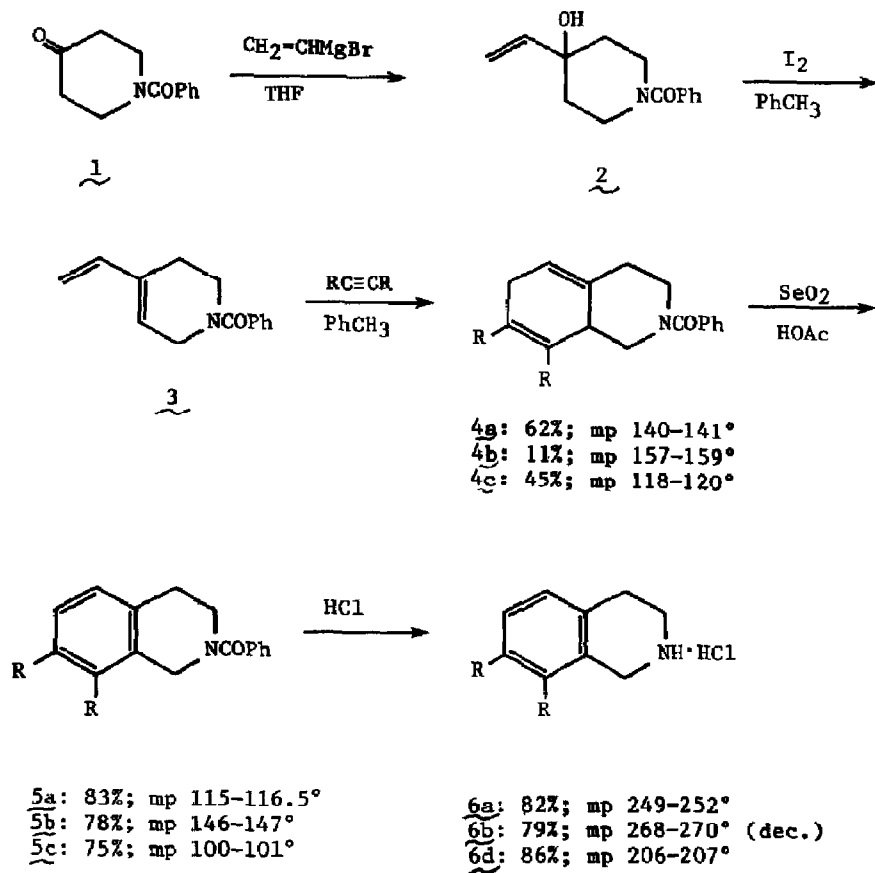
A DIELS-ALDER ROUTE TO 7,8-DISUBSTITUTED-1,2,3,4-TETRAHYDROISOQUINOLINES

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**Summary:** A novel synthesis of some difficultly accessible tetrahydroisoquinolines has been developed, utilizing a Diels-Alder reaction sequence.

Recent studies<sup>1</sup> have demonstrated that certain 1,2,3,4-tetrahydroisoquinolines are potent inhibitors of phenylethanolamine N-methyltransferase, the enzyme that catalyzes the final step of epinephrine biosynthesis.<sup>2</sup> Optimal inhibitory activity has been displayed by those compounds bearing electron withdrawing substituents at the 7 and 8 positions of the tetrahydroisoquinoline ring. However, the synthesis of such compounds is generally tedious and inefficient, since it involves the Pomeranz-Fritsch reaction,<sup>3</sup> which works poorly on electron deficient systems. We thus sought an alternate sequence, and report here a novel Diels-Alder route to 7,8-disubstituted tetrahydroisoquinolines, which are only difficultly accessible by conventional procedures.<sup>4</sup>

The key intermediate in this sequence is diene **3**, which was prepared in two steps from commercially available N-benzoyl-4-piperidone (**1**). Thus, treatment of **1** with vinylmagnesium bromide (1.5 eq, THF, 0°, 2 h) followed by silica gel chromatography (CH<sub>2</sub>Cl<sub>2</sub>-EtOAc, 6:4) afforded a 75% yield of the vinyl carbinol **2**:<sup>5</sup> IR (neat) 2.91 (O-H), 6.15 (amide); NMR (CDCl<sub>3</sub>) δ 7.40 (s, 5, aromatic), 6.2-4.9 (m, 3, vinyl), 3.4 (m, 4), 1.6 (m, 4). Dehydration of **2** was effected by treatment with 5 mole percent of iodine<sup>6</sup> in refluxing toluene (4 h),<sup>7</sup> giving a 65% yield of **3** after chromatography on silica gel (CH<sub>2</sub>Cl<sub>2</sub>-EtOAc, 9:1): IR (neat) 6.13 (amide); NMR (CDCl<sub>3</sub>) δ 7.30 (s, 5, aromatic), 6.55-4.9 (m, 4, vinyl), 4.2 (m, 2), 3.6 (m, 2), 2.3 (m, 2). The dehydration could also be carried out with SOCl<sub>2</sub> (1.3 eq, 24 h) or SOBr<sub>2</sub> (1.2 eq, 1.25 h) in pyridine (0-5°), the yields of **3** being ca. 40% under these conditions.<sup>8</sup>

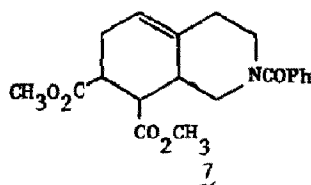


$\underline{\text{a}}$ : R = CF<sub>3</sub>  
 $\underline{\text{b}}$ : R = C<sub>6</sub>H<sub>5</sub>  
 $\underline{\text{c}}$ : R = CO<sub>2</sub>CH<sub>3</sub>  
 $\underline{\text{d}}$ : R = CO<sub>2</sub>H

Diels-Alder reaction of diene 3 with perfluoro-2-butyne (1.7 eq, toluene, 110-110°, 23 h, trace hydroquinone)<sup>9</sup> afforded a 62% yield of the crystalline adduct 4a: mp 140-141°; IR (nujol mull) 6.16 (amide); NMR (CDCl<sub>3</sub>) δ 7.38 (s, 5, aromatic), 5.5 (m, 1, vinyl), 3.3-2.1 (m, 9). Aromatization was effected by treatment with SeO<sub>2</sub> (1.15 eq, HOAc, reflux, 15-30 min),<sup>10</sup> affording 5a in 83% yield: mp 115-116.5°; IR (nujol mull) 6.13 (amide); NMR (CDCl<sub>3</sub>) δ 7.60, 7.30 (AB q, 2, J = 7 Hz, C<sub>5</sub> H and C<sub>6</sub> H), 7.30 (s, 5, aromatic), 4.90 (br s, 2, C<sub>1</sub> H), 3.80 (br t, 2, J = 6 Hz, C<sub>3</sub> H), 3.04 (br t, 2, J = 6 Hz, C<sub>4</sub> H). Hydrolysis of the benzoyl group (12 N HCl, reflux, 3 h) then produced the tetrahydroisoquinoline 6a in 82% yield: mp 249-252°;<sup>11</sup> IR (nujol mull) 3.6-4.1 (amine salt), 6.32 (aromatic); NMR (CDCl<sub>3</sub>-DMSO-d<sub>6</sub>) δ 7.7 (br s, 2, aromatic), 4.2 (br s, 2, C<sub>1</sub> H), 3.1 (m, 4, C<sub>3</sub> H and C<sub>4</sub> H).

In a similar manner, diene 3 was reacted with dibenzoylacetylene<sup>12</sup> and dimethyl acetylenedicarboxylate to afford ultimately 6b and 6d,<sup>13</sup> as indicated in the scheme. Reaction with the unsymmetrical dienophile ethyl propiolate in refluxing xylene gave a 71% yield of a 1:1 mixture of the two possible regioisomeric Diels-Alder adducts.

While useful for the synthesis of some difficultly accessible 7,8-disubstituted tetrahydroisoquinolines, this Diels-Alder route seems to be limited to the use of active acetylenic dienophiles. Thus, Me<sub>3</sub>SiC≡CSiMe<sub>3</sub> and PhC≡CPh failed to react with 3 even in refluxing decalin. Maleic anhydride did add to 3, but the diester (7: mp 119-120°; 45% from 3) derived from this product (HCl, CH<sub>3</sub>OH) was not oxidized to 5c under the established conditions.

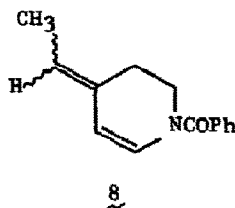


The use of functionalized derivatives of 3 to expand the scope of this sequence is under investigation.

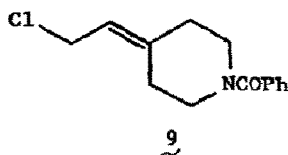
Acknowledgement: We express our appreciation to David Staiger and Gary Zuber for some of the NMR and IR spectra, to Denise Hauck for GC-MS work, and to Edith Reich, Gail Johnson, and Suzanne Jancsik for the combustion analyses.

## References and Notes

1. W.E. Bondinell, F.W. Chapin, G.R. Girard, C. Kaiser, A.J. Krog, A.M. Pavloff, M.S. Schwartz, J.S. Silvestri, P. Vaidya, and R.G. Pendleton, *J. Med. Chem.*, **23**, 0000 (1980).
2. J. Axelrod, *J. Biol. Chem.*, **237**, 1657 (1962).
3. W.J. Gensler, *Org. React.*, **6**, 191 (1951).
4. For the synthesis of octahydroisoquinoline derivatives by a Diels-Alder route, see: (a) F.P. Nauck and J.E. Sundeen, U. S. Patent 3,898,236; August 5, 1975; (b) J.R.L. Smith, R.O.C. Norman, M.E. Rose, A.C.W. Curran, and J.W. Lewis, *J. Chem. Soc., Perkin Trans. I*, 2868 (1979).
5. Satisfactory IR and NMR spectra were obtained for all compounds. All crystalline materials gave acceptable combustion analyses.
6. P.A. Robins and J. Walker, *J. Chem. Soc.*, 3249 (1956).
7. The use of more iodine and longer reaction times led to the isomerization of 3 to 8.



8. The  $\text{SOCl}_2$  reaction proceeded through 9, which could be isolated and characterized. The analogous intermediate was not detected in the  $\text{SOBr}_2$  case.



9. This reaction was run in a pressure vessel, due to the volatility of perfluoro-2-butyne.
10. This oxidation was also performed with 10% Pd-C (cumene, reflux, 2 h), giving a 31% yield of 5a.
11. The melting point of an authentic sample of 6a is 250-252° (W.E. Bondinell, Smith Kline & French Laboratories, personal communication.)
12. R.E. Lutz and W.R. Smithey, *J. Org. Chem.*, **16**, 51 (1951).
13. The amide deblocking of 5c was accompanied by ester hydrolysis, producing 6d.

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