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SYNTHESIS OF THE BENZENOID ANALOGUE OF THE CHINESE NOOTROPIC AGENT HUPERZINE A

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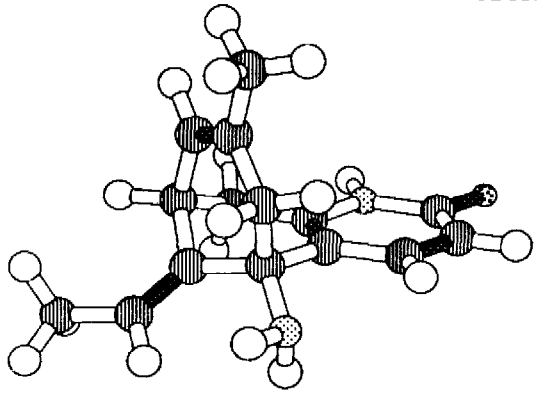
SUMMARY: *A short synthesis of the benzene isostere of huperzine A, an anticholinesterase of potential use in the treatment of Alzheimer's disease, is described starting from β-tetralone.*

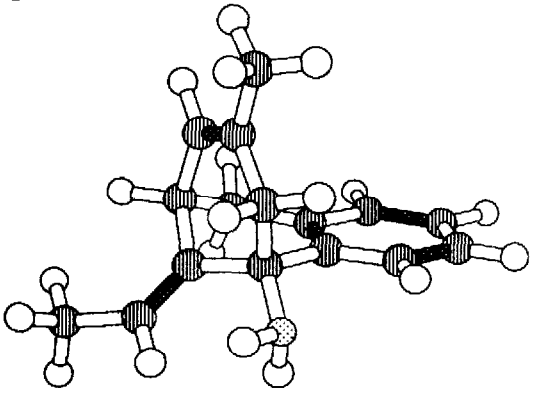
Huperzine A and B are two new Lycopodium alkaloids isolated from *Huperzia serrata* (Thunb.) Trev. = *Lycopodium serratum* Thunb., a Chinese folk medicine.[1] In studies performed both in China and the United States, these compounds have been found to improve memory and learning in animals. Huperzine A is now being investigated clinically for use in myasthenia gravis, Alzheimer's disease, and senile memory loss. In studies carried out at the Zhejiang Taizhan Hospital involving 100 aged individuals suffering from various forms of memory impairment, huperzine A was in fact shown to improve memory 1-4 h after injection.[2] As a consequence of these findings we have undertaken studies aimed at the development of synthetic routes to huperzine A and selected analogues of it.[3] It is our hope that we may be able to improve upon Nature's original contribution of a "nootropic" agent in order to procure an orally active, centrally acting, well tolerated acetylcholinesterase inhibitor for use in the treatment of senile dementia.[5]

In this article we describe a short synthesis of an analogue (**2**) of huperzine A containing a benzene ring in place of the pyridone ring structure. This particular analogue was prepared in order to ascertain the relevance of the pyridone ring to the acetylcholinesterase inhibitory activity of huperzine A. MacroModel generated structures of huperzine A and its analogue **2** are displayed below (Figure 1, also see Scheme 1).

FIGURE 1



Huperzine A (1)



Huperzine Analogue (2)

The synthesis was begun using commercially available β-tetralone (Scheme 1). This compound was α-carbomethoxylated[6], and the resulting β-keto ester **3** then reacted with methacrolein in the presence of 1,1,3,3-tetramethylguanidine (TMG) as catalyst to afford **4**. TMG was found to be the most effective catalyst for carrying out this tandem Michael addition/aldol condensation reaction.[7] The stereoisomeric mixture of products **4** was then converted to its mesylate and a solvolytic elimination reaction brought about using sodium acetate in acetic acid.[8] The olefin **5** was isolated in 42% yield along with unreacted trans, diequatorial mesylate **6**. The Wittig reaction of **5** with ethylidenetriphenylphosphorane was carried out next to afford the olefin mixture **7** (*E*/*Z* = 10:90).[9] This olefin mixture was readily isomerized with thiophenol in the presence of AIBN to provide olefin mixture **8** (*E*/*Z* = 80:20).[10] The carbomethoxy group of **8** was hydrolyzed by a solution of 20% NaOH in THF and MeOH to provide the acid **9**. Under these reaction conditions, only the ester of *E*-olefin stereochemistry underwent saponification, while the ester of *Z*-olefin stereochemistry was recovered and could be recycled through the olefin isomerization step. Lastly, the carboxyl group of **9** was transformed to an amino group through a sequence of steps involving acid chloride formation, Curtius rearrangement, and carbamate hydrolysis.[11,12]

This short sequence of chemical operations provides an efficient route to racemic **2**, a close structural analogue of huperzine A. The discovery that TMG is able to efficiently catalyze the direct conversion of **3** to **4** provides the main simplifying feature of the synthetic scheme. The synthetic strategy detailed herein is being applied to the preparation of huperzine A.[3b] While the anticholinesterase activity of **2** and related analogues will be reported fully elsewhere, preliminary studies indicate that **2** is approximately 1000 fold less potent than natural huperzine A.[13]

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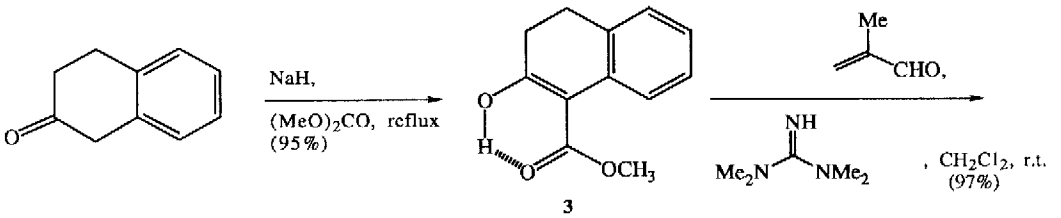
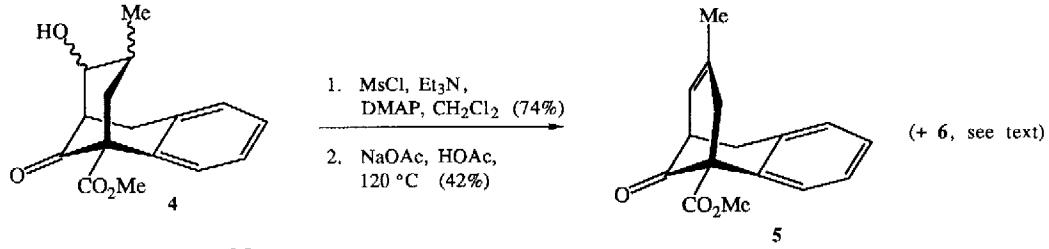
REFERENCES

1. J.-S. Liu, Y.-L. Zhu, C.-M. Yu, Y.-Z. Zhou, Y.-Y. Han, F.-W. Wu, and B.-F. Qi, *Can. J. Chem.*, **64**, 837 (1986).
2. X.-C. Tang, Y.-F. Han, X.-P. Chen, and X.-D. Zhu, *Acta Pharm. Sin.*, **7**, 507 (1986); S.-L. Zhang, *New Drugs and Clinical Remedies*, **5**, 260 (1986).
3. (a) Acetylcholine is believed to adopt a completely extended {180°, 180°} conformation both at the nicotinic cholinergic receptor and during hydrolysis by acetylcholinesterase.[4] A graphical overlay of this extended conformation of acetylcholine with the conformationally constrained structure provided by huperzine A shows a good coincidence of the heteroatom groups. The extra lipophilic domains contained within huperzine A may be essential to penetration of the blood-brain barrier. (b) The total synthesis of huperzine A has been completed and will be published elsewhere.

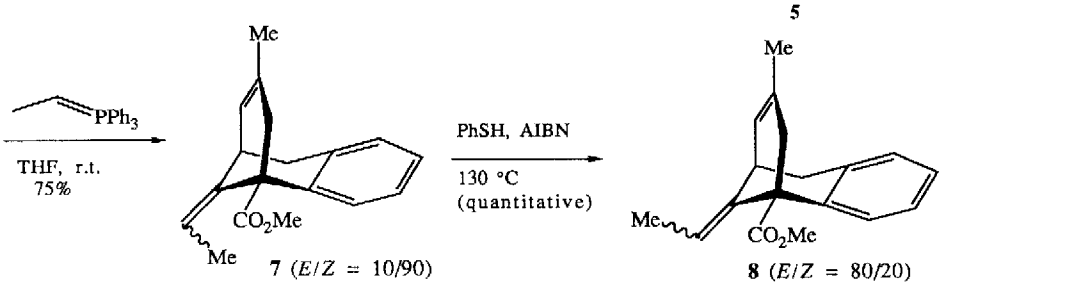
SYNTHESIS OF A BENZENE ISOSTERE OF HUPERZINE A



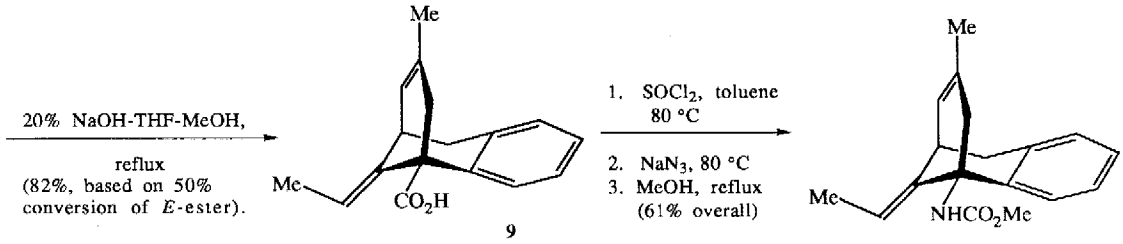
3



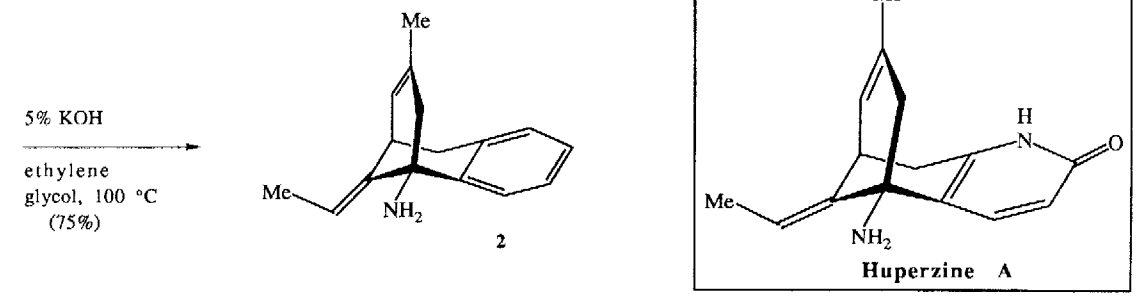
4 5



7 (*E*/*Z* = 10/90) 8 (*E*/*Z* = 80/20)



9 10



2

4. D. L. Beveridge and R. J. Radna, *J. Am. Chem. Soc.*, **93**, 3759 (1971); C. Chothia and P. Pauling, *Proc. Nat. Acad. Sci.*, **65**, 477 (1970); M. Martin-Smith, G. A. Snail, and J. B. Stenlake, *J. Pharm. Pharmac.*, **19**, 561 (1967).

5. No direct comparison of the efficacy of huperzine A vis-à-vis THA, a substance currently being studied clinically in the treatment of Alzheimer's disease, is available. For a report on THA, see: W. K. Summers, L. V. Majovski, G. M. Marsh, K. Tachiki, and A. Kling, *New Eng. J. Med.*, **315**, 1241 (1986).

6. E. W. Colvin, J. Martin, and B. Shroot, *Chem. and Ind.*, 2130 (1966).

7. TMG is known to catalyze the Michael addition of nitroalkanes to various Michael acceptors: G. P. Pollini, A. Barco, and G. DeGiuli, *Synthesis*, 44 (1972).

8. E. W. Colvin, J. Martin, W. Parker, R. A. Raphael, B. Shroot, and M. Doyle, *J. Chem. Soc., Perkin Trans. I*, 860 (1972).

9. C. Sreekmar, K. P. Darst, and W. C. Still, *J. Org. Chem.*, **45**, 4260 (1980).

10. U. T. Bhalerao and H. Rapoport, *J. Am. Chem. Soc.*, **93**, 4835 (1971).

11. M. Sunagawa, J. Katsube, and H. Yamamoto, *Tetrahedron Lett.*, 1281 (1978).

12. Spectral data for compounds **5**, **9**, and **2** follow:

5: R_f = 0.29 (20% ethyl acetate in hexanes); IR 2920, 2841, 1738, 1578, 1491, 1435, 1352, 1265, 1238, 1163, 1142, 1084, 1034, 999, 970, 954, 912, 831, 756, 725, 654 cm^{-1}; ^1H NMR δ 7.22-7.26 (m, 2 H), 7.12-7.15 (m, 1 H), 6.90-6.93 (m, 1 H), 5.35-5.36 (m, 1 H), 3.75 (s, 3 H), 3.38-3.45 (m, 2 H), 3.14 (m, 1 H), 3.14 (d, 1 H, *J* = 14.7 Hz), 2.62 (d, 1 H, *J* = 17.4 Hz), 1.59 (s, 3 H); ^{13}C NMR δ 208.2, 171.7, 139.3, 133.8, 132.7, 128.6, 127.5, 126.8, 123.2, 61.5, 52.3, 47.6, 46.2, 37.8, 22.1; mass spectrum (m/z) 256 (M^+), 224, 197, 169, 153; exact mass calcd for $C_{16}H_{16}O_3$: 256.1099; found 256.1100.

9: R_f = 0.26 (40% ethyl acetate in hexanes); IR 2700-3600 (br), 2961, 2924, 2855, 1703, 1450, 1277, 1246, 721, 655; ^1H NMR δ 7.13-7.18 (m, 2 H), 7.04-7.07 (m, 2 H), 5.35 (br s, 1 H), 5.31 (q, 1 H, *J* = 6.7 Hz), 3.61 (br s, 1 H), 2.99-3.14 (m, 2 H), 2.83 (dd, 1 H, *J* = 16.2, 1.3 Hz), 2.27 (d, 1 H, *J* = 17.0 Hz), 1.72 (d, 3 H, *J* = 6.5 Hz), 1.53 (s, 3 H); mass spectrum (m/z) 254 (M^+), 209, 181, 84, 49; exact mass calcd for $C_{17}H_{18}O_2$: 254.1307; found 254.1307.

2: R_f = 0.25 (40% ethyl acetate in hexanes); IR 3381, 2962, 2919, 2860, 1485, 1448, 1439, 1429, 1378, 1043, 834, 765, 719 cm^{-1}; ^1H NMR δ 7.77 (dd, 1 H, *J* = 7.8, 1.2 Hz), 7.11-7.28 (m, 2 H), 7.02 (d, 1 H, *J* = 7.6 Hz), 5.52 (q, 1 H, *J* = 6.7 Hz), 5.40-5.42 (m, 1 H), 3.66 (t, 1 H, *J* = 4.7 Hz), 3.04 (dd, 1 H, *J* = 16.3, 5.1 Hz), 2.83 (dd, 1 H, *J* = 16.2, 1.4 Hz), 2.26 (br s, 2 H), 1.84 (br s, $-NH_2$), 1.73 (d, 3 H, *J* = 6.8 Hz), 1.52 (s, 3 H); mass spectrum (m/z) 225 (M^+), 210, 170, 130; exact mass calcd for $C_{16}H_{19}N$: 225.1517; found 225.1517.

13. The anticholinesterase studies were carried out by Dr. Israel Hanin of Loyola University Stritch School of Medicine on a subcontract from NIA Grant No. 1R01AG07591.

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