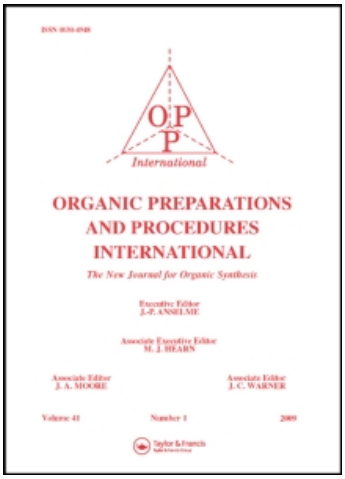


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# A SUPERIOR SYNTHESIS OF CHOLINERGIC ANABASEINE

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and H. Ringsdorf, *Angew. Chem. Int. Ed. Engl.*, **19**, 938 (1980).

6. H. Koch, Ph. D. Dissertation, Universitat Mainz, Germany (1983); B. Tieke, *Adv. Pol. Sci.*, **71**, 79 (1985).

7. L. Brandsma, "*Preparative Acetylenic Chemistry,*" CH 8, Elsevier (1988); H.G. Viehe, Ed., "*Chemistry of Acetylenes,*" pp. 665-688, Marcel Dekker (1969).

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## A SUPERIOR SYNTHESIS OF CHOLINERGIC ANABASEINE

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(12/27/94)

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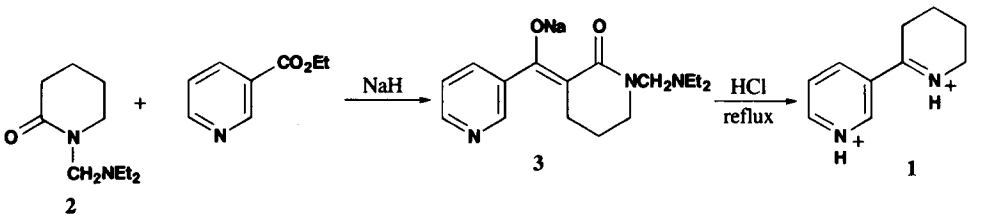
Anabaseine, (3,4,5,6-tetrahydro-2,3'-bipyridine, **1**), a naturally occurring neurotoxin produced by hoplonemertine sea worms[1] competes with the natural neurotransmitter acetylcholine when binding to nicotinic receptor sites. Such compounds are of considerable current interest because it is believed[2] that loss of cholinergic pathways in cell to cell communication contributes to the early loss of memory (Alzheimer's disease). Now underway in many laboratories is a major emphasis on developing novel cholinergic derivatives. Anabaseine is the precursor of 3-benzylidene[3-5] and 3-cinnamylidene[6] derivatives that have novel binding properties to $\alpha_4\beta_2$ and $\alpha_7$ binding sites in the human brain. Such derivatives command the intense current interest of pharmacologists. We now report a shortened and improved preparation of **1** especially designed for large commercial production because it avoids the use of costly low temperatures and expensive reagents as found in some other preparations.

Three different routes to **1** have been reported. One involves the addition of 3-pyridyl lithium to cyclopentanone followed by a Schmidt reaction with hydrazoic acid.[7] A second employs a rearrangement of 1-nicotinoyl-2-piperidone induced thermally by CaO[8] and a third is based on a mixed Claisen condensation.[9,10] A Claisen route also serves to provide 5'-fluoroanabaseine,[10] N-methyl anabaseine[11] and the tobacco alkaloid myosmine,[12] the 1-pyrroline counterpart of **1**.




Our approach also uses the mixed Claisen condensation of nicotinic ester and the enolate ion of protected 2-piperidone[9] in the form of a base stable but acid labile aminomethyl N-protecting group. We prepared the novel aminal of the piperidone **2** (80%) and then generated the amide enolate ion with NaH in toluene. The resultant sodium salt of the 3-nicotinoyl-2-piperidone intermediate **3** was hydrolyzed directly in hot acid to the ß-keto carboxylic acid which underwent decarboxylation to **1**. Our extensive studies on the ring-chain equilibrium properties of **1**[13,14] provided insight that allows the original work-up[9] and those of others[10] to be shortened considerably. We simply isolated the dihydrochloride salt from the acidic hydrolysis mixture and bypass the isolation of the unstable cyclic free base. The overall yield of this convenient synthesis is 57% starting with 2-piperidone.



## EXPERIMENTAL SECTION

All starting materials were purchased from Alrich Chemical Co. Mps were taken on a Thomas-Hoover apparatus and are uncorrected. The Proton NMR spectra were recorded on a Varian Gemini 300 MHz spectrometer using TMS as an internal standard. The preparation of **3** gives rise to material with a variable *keto-enol* ratio and hence a variable NMR spectrum.

**1-(Diethylaminomethyl)-2-piperidone (2).**- A mixture of 2-piperidone (10 g, 0.10 mole), aqueous formaldehyde (37% by wt) (9.8 mL, 0.12 mole), and diethylamine (12.5 mL, 0.12 mole) was heated at reflux with stirring [the reaction initially is exothermic upon addition of diethylamine]. After 8 hrs, the reaction was concentrated under reduced pressure and 20 mL of brine was added. The aqueous phase was extracted 5 times with 50 mL portions of ether. The combined etheral extracts were dried over sodium sulfate and concentrated to yield 16.7 g of a slightly brown liquid. The product was purified by vacuum distillation with 14.7 g (80% yield) of the colorless product distilling at 113°/3.1 mm. $^1$H NMR ($CDCl_3$): δ 4.05, (N-$CH_2$-N, s, 2H), 3.22 ($CH_2$, bm, 2H), 2.5 ($CH_2$-N, q, 4H), 2.25 ($CH_2$, bm, 2H), 1.7 ($CH_2$-$CH_2$, bm, 4H), 0.95 ppm ($CH_3$, t, 6H). HRMS (EI) Calcd for $C_{10}H_{20}N_2O$: 184.1576. Found: 184.1572.

**Sodium Salt of the Aminal of 3-Nicotinoyl-2-piperidone (3).**- To a solution of **2** (9.90 g, 0.0540 mole), ethyl nicotinate (7.4 mL, 0.054 mole) and toluene (50 mL) slowly was added a 60% dispersion in mineral oil of sodium hydride (4.3 g, 0.11 mole). [Hydrogen gas was evolved.] The suspension was heated at reflux while stirring. After 4 hrs another equivalent (2.1 g, 0.054 mole) of sodium hydride was added. After another 4 hrs of stirring at reflux the reaction was filtered by suction. [The collected solid is excess NaH and was destroyed by the cautious addition of ethanol.] The filtrate was cooled to

0° and the product slowly precipitated (the solution might need some agitation to get product to precipitate; it has a tendency to supersaturate). The product was collected and dried to give 16.2 g of a slightly yellow solid (97% yield). [The solid is hygroscopic and slowly turns to a sticky orange material. The $^1$H NMR consisted of a mixture of *enol* and *keto* tautomers.]

$^1$H NMR (DMSO-$d_6$): δ 9.2 (H2', keto, s), 8.75 (H2' + H6', enol, m), 8.6 (H6' keto, d), 8.3 (H4' keto, d), 7.85 (H4' enol, d), 7.4 (H5' keto, dd), 7.3 (H5' enol, dd), 4.4 (CH, keto, t), 4.25 (N-$CH_2$-N, enol, s), 4.15 (N-$CH_2$-N, keto, d), 3.45 (m), 2.6 ($CH_2$, m), 2.5 ($CH_2$, m), 2.2 ($CH_2$, m), 2.05 ($CH_2$, m), 1.8 ($CH_2$, m) and 1.05 (m, $CH_3$).

**Anabaseine Dihydrochloride (1).**- Sodium salt **3** (900 mg, 2.89 mmoles) was heated at reflux for 12 hrs in a 5:1 mixture of conc. HCl and acetone (the acetone aids in the precipitation of NaCl). The reaction was cooled and the NaCl was filtered off. The filtrate was diluted with 70 mL of isopropyl alcohol and allowed to stand at 0°. The dihydrochloride salt crystallized slowly to yield 500 mg (74%) of white needle-like crystals, mp 175-179° (dec.), lit[14] mp 175-180° (dec.).

$^1$H NMR (DMSO-$d_6$): δ 9.15 ppm (H2', s, 1H), 8.95 (H6', d, 1H), 8.60 (H4', d, 1H), 8.1 (N-H, b, 2H), 7.85 (H5', dd, 1H), 3.2 ($CH_2$, m, 2H), 2.8 ($CH_2$, m, 2H), 1.62 ppm ($CH_2$, m, 4H).

*Anal.* Calcd for $C_{10}H_{14}Cl_2N_2 \cdot H_2O$: C, 47.81; H, 6.42; N, 11.15. Found: C, 47.70; H, 6.42; N, 11.07

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## REFERENCES

1. W. R. Kem, "*Handbook of Natural Toxins: Marine Toxins and Venoms*;" A.T. Tu, Ed. Marcel Dekker, Vol. 4: New York, N. Y. 1988.

2. "*Cholinergic Basis for Alzheimer's Therapy*", R. Becker and E. Giacobini, Eds., Birkhausen, Boston, 1991.

3. J. A. Zoltewicz, K. Prokai-Tatrai, L. B. Bloom and W. R. Kem, *Heterocycles*, **35**, 171 (1993).

4. E. M. Meyer, C. M. de Fiebre, B. E. Hunter, C. E. Simpkins, N. Frauworth and N. E. C. de Fiebre, *Drug Dev. Res.*, **31**, 127 (1994).

5. E. J. Martin, K. S. Panickar, M. A. King, M. Deyrup, B. E. Hunter, G. Wang and E. M. Meyer, *ibid.*, **31**, 135 (1994).

6. C. M. de Fiebre, E.M. Meyer, J. C. Henry, S. I. Muraskin, W. R. Kem and R. L. Papke, *Mol. Pharmacol.*, **47**, 164 (1995).

7. G. F. Alberici, J. Andrieux, G. Adam and M. M. Plat, *Tetrahedron Lett.*, **24**, 1937 (1983).

8. B. P. Mundy and B. R. Larsen, *Synth. Commun.*, **2**, 31 (1972).

9. E. Späth and L. Mamoli, *Ber.*, **69**, 1082 (1936).

10. E. Leete, *J. Org. Chem.*, **44**, 165 (1979).

11. K. H. Büchel and F. Korte, *Chem. Ber.*, **95**, 2438 (1962).

12. M. W. Hu, W. E. Bondinell and D. Hoffmann, *J. Labelled Compd. Radiopharm.*, **10**, 79 (1974).

13. J. A. Zoltewicz, L. B. Bloom and W. R. Kem, *J. Org. Chem.*, **54**, 4462 (1989).

14. J. A. Zoltewicz, L. B. Bloom and W. R. Kem, *Bioorg. Chem.*, **18**, 395 (1990).

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## A PRACTICAL SYNTHESIS OF 4-(3',4'-DIHYDROXYLPHENYL)-1,2,3,4-TETRAHYDROISOQUINOLINE

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4-Aryl substituted 1,2,3,4-tetrahydroisoquinoline have been found to have dopamine agonist activity,[1] those with a 3,4-dihydroxylphenyl group at C-4 and unsubstituted on nitrogen being the most active. 4-Arylisoquinolines have been prepared by palladium-catalyzed coupling of aryl halides with diethyl (4-isoquinolyl) borane.[3] Miller and Svoboda[4] also described the coupling 4-bromoisoquinoline with either phenylboronic acid or 3,4-dimethoxylphenylboronic acid to give the 4-arylisoquinolines; however, this method suffers in that the starting materials are not readily available, thus making it impractical for large-scale synthesis. Schwan *et al.*[5] reported to use hydrobromic acid or polyphosphric acid (PPA) to prepare the 4-phenyltetrahydroisoquinoline albeit in very low yield; only cleavage products were obtained when the aromatic ring bears strong electron-withdrawing groups. Jacob and Nicoles[1, 2] used anhydrous aluminum chloride to effect the cyclization of the N-benzyl-1-(3,4-dimethoxyphenyl)-2-aminoethanol, but this method has two disadvantages. First, the yield was not very high and second, aluminum chloride is very sensitive to moisture. We now report a very efficient and economical synthesis of the most active tetrahydroisoquinoline is 4-(3',4'-dihydroxylphenyl)-1,2,3,4-tetrahydroisoquinoline (**6**)[2] on multigram scale for further biological evaluation.

In our scheme, we used sodium cyanide and ammonium chloride instead of trimethylsilyl cyanide.[2] It was reported the benzylamine and aromatic aldehyde or ketone were obtained as the major products when 48% HBr or PPA were used to cyclize N-substitutedbenzyl-1-substitutedphenyl-2- aminoethanol.[5] This indicates strong acids led not only to the dehydration of the alcohol but also to the protonation of the secondary amine. The protonated nitrogen become more electron-withdrawing