IMPROVEMENTS IN THE TOTAL SYNTHESIS OF PHYSOSTIGMINE: REDUCTIVE CYCLIZATION OF OXINDOLES TO TRICYCLIC INDOLENINEPYRROLIDINES WITH LITHIUM ALUMINUM HYDRIDE IN TETRAHYDROFURAN

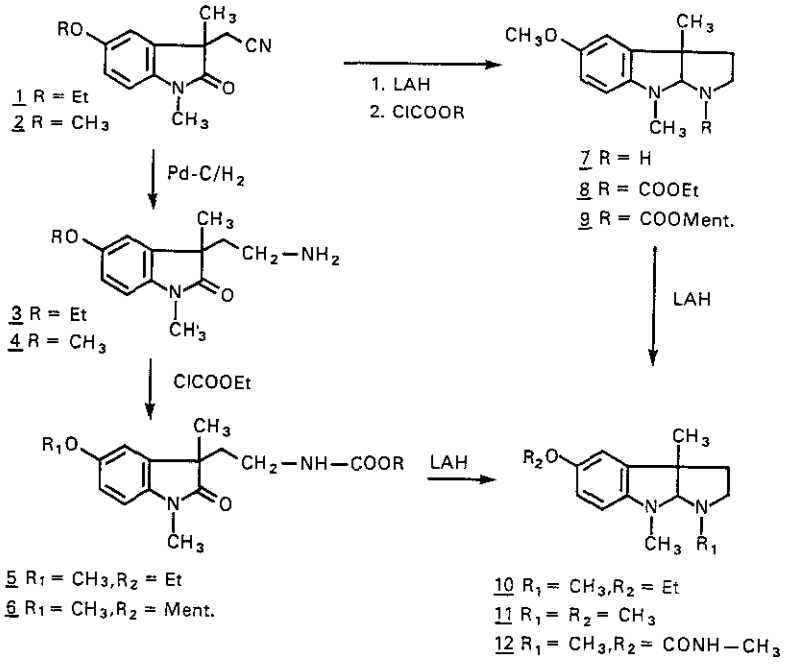
Qian-Sheng Yu and Arnold Brossi*

Medicinal Chemistry Section, Laboratory of Analytical Chemistry, NIDDK, National Institutes of Health, Bethesda, Maryland 20892 U.S.A.

Abstract - Reductive cyclization of oxindole 2 and carbamate 5 with LAH in THF afforded the indolenineпyrrolidines 7 and 11 in high yield. The former compound is an important intermediate in our synthesis of (-)- and (+)-physostigmine (optical isomers of 12). Menthylcarbamates 6 and 9 prepared from 4 and 7 with menthyl chloroformate could not be separated respectively on TCL by standard techniques.

Total synthesis of (-)-physostigmine ((-)-12)[1] by the Julian route[2] is accomplished from cyanide 1 by catalytic reduction to amine 3, followed by reductive cyclization of an optically active N-methyl analog of 3 (-NH-CH_3 instead of -NH_2) to (-)-O-ethyleseroline ((-)-10) with sodium in alcohol, and routine conversion of ether into methyl carbamate. The NIH-variant of this route, accomplished with O-methyl ether analogs, uses the sodium in alcohol cyclization step to afford nor-compound 7 from amine 4, resolved into optical isomers by a urea-separation-alcoholysis method.[3] Details of the latter route for preparing unnatural (+)-physostigmine ((+)-12) in quantity were recently reported.[4] Reductive cyclization of 4 with sodium in alcohol requires large amounts of sodium, almost twice the amount of sodium to that of substrate, making this procedure which requires large amounts of solvents cumbersome and labor intensive. We now report that conversion of carbamate 5 obtained from amine 4 with ethyl chloroformate into 11, and direct conversion of nitrile 2 into tricyclic intermediate 7, could be accomplished by reduction with LAH in THF. Similar reduction of oxindoles into homo-analogs of deoxyeseroline was reported by Hino.[5] Compound 11 (82%) and 7 (80%) were obtained as fumarates identical in

every respect with comparision samples prepared earlier.[3,4] Similarly carbamate 8 afforded 11 under these reaction conditions. Although menthyl carbamates of prochiral amines have been separated into diastereomers by HPLC[6], carbamates 6 and 9, obtained from 4 and 7 respectively with commercially available (-)-menthyl chloroformate[7], did not separate on TLC which in our experience is a good test to assess a possible practical separation by chromatographic methods.[3,4] Synthesis of 11 from 5 is greatly simplified by this procedure, but it will require an optical resolution of this acid sensitive material to obtain intermediates useful for a synthesis of optically active physostigmines. Direct conversion of nitrile 2 into O-methylnoreseroline (7), however, simplifies the NIH-route for preparation of these alkaloids considerably.



EXPERIMENTAL

Melting points were determined on a Fisher-Johns point apparatus. ^{1}H-Nmr spectra were taken on a varian XL-300 (300 MHz) spectrometer, and chemical shifts are reported in with tetramethylsilane as the internal reference. Mass spectra were taken on a Finnigan 1015 D instrument (C). Elemental analyses were performed by Atlantic Microlab Inc. (Atlanta, Georgia).

(±)-1,3-Dimethyl-3-β-(N-ethoxycarbonyl)-aminoethyloxindole (5). The hydrochloride of compound 4 (270 mg, 1 mmol) and K_2CO_3 (414 mg, 3 mmol) were added to CH_2Cl_2 (10 ml) and H_2O (5 ml), and then ClCOOEt (217 mg, 2 mmol) was added. The reaction mixture was stirred under N_2 atmosphere at rt for 1 h. The organic layer was separated and washed by brine, and dried with $MgSO_4$. Evaporation of solvent gave the oily product 5 (307 mg, 100%): ms (CI), m/z 307 (M^++1); ^{1}H-nmr ($CDCl_3$): 6.75 (m,3H, Aromatic H), 4.62 (br. 1H, N-H), 4.00 (q, 2H, -OC<u>H</u>$_2$-CH_3, J=7), 3.80 (s, 3H, -O-CH_3), 3.18 (s, 3H, N-CH_3), 2.92 (m,2H,-C<u>H</u>$_2$-NH-), 1.94-2.17 (m, 2H,-C<u>H</u>$_2$-CH_2NH-), 1.38 (s, 3H,-CH_3), 1.18 (t, 3H, -O-CH_2-C<u>H</u>$_3$, J=7). Anal. Calc. for $C_{16}H_{22}N_2O_4$: C,62.72; H, 7.24; N,9.15. *Found C, 62.50; H, 7.31; N, 9.05.*

Menthyl Carbamate (6). Similarly obtained from 4 and menthyl chloroformate: gum; $[\alpha]_D^{22}$ -55.3° (C=1.5, EtOH); ms(CI), m/z 417 (M^++1); TLC, one spot, Rf 0.4 (silica gel, CH_2Cl_2:MeOH=15:1).

(±)-O-Methyl-N(1)-noreseroline (7). Nitrile 2 (50 mg, 0.22 mmol) was dissolved in THF (5 ml) and $LiAlH_4$ (33 mg, 0.44 mmol) was added too. The reaction mixture was first stirred under N_2 atmosphere (1 h) and then heated to reflux. After refluxing for 5 min, the solvent was evaporated and the residue dissolved in HCl (2 ml, 2N). The acidic aqueous solution was washed by Et_2O (20 ml), then basified with Na_2CO_3, and then extracted with Et_2O (20 ml x 3). The ether extract was dried with $MgSO_4$ and concentrated to about 2 ml, a saturated EtOH solution of fumaric acid (30 mg) was added. Crystallization of the salt from ethanol gave the fumarate of 7 (60 mg, 80%): mp 197-198°C; ms(CI), m/z 219 (M^++1); ^{1}H-nmr (D_2O): 6.87-6.95 (m, 2H, C4-H and C6-H), 6.69 (m, 1H, C7-H), 5.09 (s, 1H, C9-H), 3.79 (s, 3H, O-CH_3), 3.20-3.60 (m, 2H, C2-H_2), 3.09 (s, 3H, N8-CH_3) 2.85 (br. 3H, N1-CH_3), 2.39 (m, 2H, C3-H_2), 1.49 (S, 3H, C10-CH_3). Anal. Calc. for $C_{13}H_{18}N_2O.C_4H_4O_4$: C,61.06; H, 6.63; N.8.38. Found: C.60.96; H, 6.67; N.8.37. This salt was identical by TLC and mp with a reference sample.

Ethyl Carbamate (8). Obtained from 7 with ethyl chloroformate as given for preparation of 3: gum; ms (EI), m/z 290 (M^+). Anal. Calc. for $C_{16}H_{22}N_2O_3 \cdot 1/4\ H_2O$: C,65.17; H,7.61; N, 9.50, Found: C, 65.03; H,7.50; N,9.43.

Menthyl Carbamate (9). Similarly obtained from 7 with menthyl chloroformate: gum; $[\alpha]_D^{22}$ -52.9° (C=0.4, EtOH); ms (CI), m/z 401 (M^++1); TLC, one spot, Rf 0.7 (silica gel, Hexanes: Et_2O = 1: 1).

(±)-O-Methyleseroline (11).

A. From Carbamate 5. Compound 5 (307 mg, 1mmol) was dissolved in THF (15 ml), and $LiAlH_4$ (76 mg, 2 mmol) was then added. The reaction mixture was stirred under N_2 atmosphere at reflux for 0.5 h. After evaporation of solvent, the residue was dissolved in HCl (2N, 3 ml), washed with Et_2O (20 ml), basified by Na_2CO_3, and then extracted with Et_2O (20 ml x 4). The ether extract was dried with $MgSO_4$, concentrated to about 2 ml, and added with a saturated alcoholic solution of fumaric acid (140 mg). Crystallization of the salt from EtOH gave crystalline fumarate of 11 (286 mg, 82%): mp 156-157°C; MS (CI), m/z 233 (M^++1); ^{1}H-nmr (D_2O): 6.87-6.98 (m,2H,C4-H and C6-H), 6.59-6.64 (m,1H,C7-H), 5.12 (s, 1H, C9-H), 3.80 (s,3H, O-CH_3), 3.41-3.47 (m, 2H, C2-H_2), 3.00 (s, 3H, N8-CH_3), 2.39 (m, 2H, C3-H_2), 1.49 (3, 3H, C10-CH_3). Anal. Calc. for $C_{14}H_{20}N_2O.C_4H_4O_4$:C, 59.11; H, 6.45; N, 6.89. Found: C, 59.15; H, 6.44; N, 6.86. This salt was identical by TCL and mp with a reference sample.

B. From Carbamate 8. Reduction of 8 with LAH in THF was carried out at rt for 1 h, and worked up as mentioned above and afforded the fumarate of 11 (80%) which was identical with a standard sample.

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