

PRACTICAL SYNTHESIS OF UNNATURAL

(+) -PHYSOSTIGMINE AND CARBAMATE ANALOGUES

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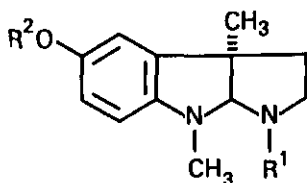
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Abstract - Details of a synthesis of unnatural (+)-physostigmine (5) prepared from urea 1 via (+)- eseroline (4) are given. Preparation of (+)-octylcarbamate 6, (+)-benzylcarbamate 7, (+)-phenylcarbamate 8 and (+)-N-methylphysostigmine (9) from (+)-eseroline (4) is also described.

(+)-Physostigmine (5), the unnatural antipode of the alkaloid (-)-physostigmine from Calabar beans¹ inhibits acetylcholinesterase in vitro more than 100 times less than the natural alkaloid², but blocks the open channel of the nicotinic acetylcholine receptor similarly.³ Several analogs of (-)-physostigmine with different carbamate side chains showed even higher inhibitory potency of cholinesterases and are presently being further evaluated⁴. These findings mark Calabar alkaloids as very interesting biochemical tools and an efficient chemical synthesis of compounds of the unnatural (+)-series was therefore, highly desirable. This seemed particularly warranted since the original synthesis of 5 was only accomplished by a tedious separation of optical isomers at an intermediate stage, affording optically pure 5 in low yield only.⁵ Urea 1, obtained as the faster moving diastereomer after reaction of (±)-N1-O-methylnoreseroline with S-(-)-1-phenylethyl-isocyanate (silica gel, CH₂Cl₂/MeOH)⁶, and converted into 2 in refluxing butanol in the presence of sodium butoxide, represents a key intermediate in our synthesis of (+)-physostigmine (5) and carbamate analogues. Although preparation of (+)-eseroline (4) from 1 was reported⁷, the present procedure using pentanol instead of butanol and isolating intermediates as fumarate salts, constitutes a much superior method to prepare these compounds and is, therefore, presented in detail. Decomposition of urea 1 in refluxing pentanol in the presence of sodium pentoxide prepared in situ, afforded the fumarate salt of 2 in high yield. Reductive N-methylation of the fumarate salt of 2 with

formaldehyde and sodium borohydride afforded the fumarate of 3 in 62% yield. O-Demethylation of 3 with boron tribromide afforded 4 (85%). (+)-Eseroline (4) prepared from its fumarate salt in the usual way ($\text{NaHCO}_3/\text{Et}_2\text{O}$) afforded by reaction with methylisocyanate 5 isolated as the salicylate (74%). The free base of 5 prepared from its salicylate was in every respect identical to natural (-)-physostigmine except for its opposite optical behavior.⁸ Reaction of 4 with octylisocyanate, benzylisocyanate and phenylisocyanate afforded carbamates 6, 7 and 8 respectively and (+)-N-methylphysostigmine (9) was obtained from 4 by reaction with dimethylcarbamoyl chloride by the procedure given for preparing its (-)-enantiomer.⁹



	<u>R¹</u>	<u>R²</u>
1,	$\begin{array}{c} \text{CH}_3 \\ \downarrow \\ \text{CONHCHPh} \end{array}$	CH ₃
2,	H	CH ₃
3,	CH ₃	CH ₃
4,	CH ₃	H
5,	CH ₃	CONHCH ₃
6,	CH ₃	CONH(CH ₂) ₇ CH ₃
7,	CH ₃	CONHCH ₂ C ₆ H ₅
8,	CH ₃	CONHPh
9,	CH ₃	CON(CH ₃) ₂

EXPERIMENTAL

Melting points were determined on a Fisher-Johns melting point apparatus, and optical rotations were measured on a Perkin-Elmer 241 MC polarimeter. ¹H-nmr spectra were measured on a Varian XL-300 (300 MHz) spectrometer, and chemical shifts are reported in δ with tetramethylsilane as the internal reference. Mass spectra were taken on a Finnigan 1015 D instrument (C). Flash column chromatography was done with grade 60, 60 Å silica gel (Merck) (from Aldrich Chemical Company, Inc.)

(+)-N(1)-O-Methylnoreseroline (2): Sodium (8 g) was dissolved in pentanol (350 ml), and after its disappearance urea 1 (7.86 g, 21.5 mmol) added, and the reaction mixture refluxed for 2 h in nitrogen atmosphere. After evaporation of the solvent in vacuo the residue was dissolved in H₂O (150 ml) and extracted with Et₂O (2 x 200 and 2 x 100 ml). The ether extracts were combined, washed with brine (50 ml), dried (Na₂SO₄) and concentrated. A saturated ethanolic solution of fumaric acid (3.0 g) was added to give the fumarate salt of 2 (6.78 g, 93.4%): mp 199-200°C; $[\alpha]_D^{25} +73.0^\circ$ (c=0.5, MeOH); ¹H-nmr(D₂O), 1.47(s, 3H, C10-CH₃), 2.18-2.47(m, 2H, C3-H₂), 2.99(s, 3H, N8-CH₃), 2.92-3.48(m, 2H, C2-H₂), 3.79(s, 3H, O-CH₃), 5.11(s, 1H, C9-H), 6.60-6.64(m, 1H, C7-H), 6.87-6.97(m, 2H, C4-H and C6-H); ms(CI), m/z 219 (M⁺+1). Anal. Calc. for C₁₃H₁₈N₂O₄: C,61.06; H,6.63; N,8.38. Found: C,61.01; H,6.64; N,8.32.

(+)-O-Methyleseroline (3): The fumarate salt of 2 (6.48 g, 19.38 mmol) was dissolved in MeOH (100 ml) and Et₃N (6.48 ml) and CH₂O (9.72 ml) added. The reaction mixture was stirred for 3h at room temperature in nitrogen atmosphere, then cooled to 0°C and NaBH₄ (2.92 g) slowly added and the mixture stirred for 0.5h at room temperature. After evaporation of the solvent, HCl solution (2 M) was added to dissolve solid borane complexes. The acidic aqueous solution was washed once with Et₂O (30 ml), made basic with saturated Na₂CO₃ solution, then extracted with ether (2 x 100, 2 x 50). The ether solutions were combined, washed with brine (50 ml) and dried over Na₂SO₄. After evaporation of the solvent, the concentrated residue was added to a saturated alcoholic solution of fumaric acid (2.70 g), and left overnight in the refrigerator to give the fumarate salt of 3 (5.13 g, 62.10%): mp 137-138°C; $[\alpha]_D^{25} +98.7^\circ$ (c=0.8, MeOH); ¹H-nmr(D₂O), 1.49(s, 3H, C10-CH₃), 2.39 (m, 2H, C3-H₂), 2.85(s, 3H, N1-CH₃), 3.09(s, 3H, N8-CH₃), 3.20-3.60(m, 2H, C2-CH₂), 3.79(s, 3H, O-CH₃), 5.09(s, 1H, C9-H), 6.67(m, 1H, C7-H), 6.87-6.95(m, 2H, C4-H and C6-H); ms(CI), m/z 232(M⁺+1). Anal. Calc. for C₁₄H₂₀N₂O₄: C,59.11; H,6.45; N,6.89. Found: C,59.40; H,6.62; N,6.89.

(+)-Eseroline (4): The fumarate salt of 3 (4.58 g, 11.29 mmol) was dissolved in H₂O (20 ml), basified by NaHCO₃ solution, extracted with Et₂O(2x100/and 2x50 ml). After washing with brine (20 ml), the extract was dried by Na₂SO₄ to give, after evaporation of the ether 3. Base 3 was dissolved in CH₂Cl₂ (50 ml) and BBr₃ (99.99%, 5ml) dissolved in CH₂Cl₂(50 ml) was added dropwise to the above solution with stirring. Stirring was continued for 2 h at room temperature in nitrogen atmosphere. After evaporation of solvent, the residue was dissolved in MeOH (20 ml) and stirred for 10 min. Evaporation of the MeOH gave a residue which was dissolved in H₂O (20 ml), basified with a saturated aqueous solution of NaHCO₃, extracted by

Et₂O (2x200+50 ml), washed by brine (50 ml) and dried over Na₂SO₄. Evaporation of Et₂O gave a brown oily base 2 which crystallized after staying overnight in the refrigerator. Washing the crystals with cold Et₂O gave crystalline 4 (2.23 g, 85.02%): mp 125-126°C; [α]_D + 112° (c=0.45, MeOH). Anal. Calc. for C₁₃H₁₈N₂O: C, 71.52; H, 8.31; N, 12.84. Found: C, 71.44; H, 8.36; N, 12.70. Fumarate Salt: Crystalline base 4 (100 mg) was dissolved in Et₂O (5 ml), then added to a saturated alcohol solution of fumaric acid (63.8 mg) to afford the fumarate of 4 (150 mg, 98.0%): mp 200-202°C; [α]_D + 103.0° (c=0.3, MeOH); ¹H-nmr(D₂O), 1.48(s, 3H, C10-CH₃), 2.17-2.47(m, 2H, C3-H₂), 2.80(s, 3H, N1-CH₃), 3.07(s, 3H, N8-CH₃), 3.24-3.52(m, 2H, C2-H₂), 5.05(s, 1H, C9-H), 6.63(m, 1H, C7-H), 6.77-6.80(m, 2H, C4-H and C6-H); ms(CI), m/z 219(M⁺+1). Anal. Calc. for C₁₃H₁₈N₂O · C₄H₄O₄: C, 61.06; H, 6.63; N, 8.38. Found: C, 60.98; H, 6.67; N, 8.37.

(+)-Physostigmine (5): (+)-Eseroline (4) (500 mg, 2.30 mmol) was dissolved in anhydrous Et₂O (50 ml) and a small piece of sodium (about 5 mg) added. The resulting solution was stirred for 1.5 min. at room temperature in nitrogen atmosphere. Methylisocyanate (156 mg, 2.74 mmol) was added dropwise and stirring continued for 5 min. The solvent was moved in vacuo and the residue dissolved in Et₂O (50 ml), washed by brine (20 ml) and dried over Na₂SO₄. The residue obtained after evaporation of ether was added to an ether solution (10 ml) of salicylic acid (378 mg) to give a white precipitate which was crystallized from EtOH to give crystalline salicylate of 5 (720 mg, 74.35%): mp 183-184°C; [α]_D + 75.0° (c=0.5, EtOH). (+) Physostigmine (5) prepared from the salicylate salt in the usual way and crystallized from ether: mp 84-85°C; [α]_D + 75.0° (c=0.5, CHCl₃); ir, ¹H-nmr, ms: identical with those of (-) physostigmine.

(+)-Octylcarbamoyl eseroline (6): (+)-Eseroline (4) (150 mg, 0.687 mmol) was dissolved in anhydrous Et₂O (15 ml) and a small piece of sodium (4) (about 5 mg) added. After stirring for 1.5 min. at room temperature in nitrogen atmosphere, octylisocyanate (128 mg, 0.826 mmol) was added dropwise. After the addition was complete, the solvent was evaporated immediately. The residue was flash chromatographed on a silica gel column (CH₂Cl₂/MeOH, 100:1-100:2) to give 6 as an oil (160 mg, 62.0%): [α]_D + 53.2° (c=1.2, CHCl₃); ¹H-nmr(CDCl₃), 0.88(t, 3H, J=7, terminal CH₃), 1.28-1.60(m, 12H, -(CH₂)_n-), 1.42(s, 3H, C10-CH₃), 1.94(m, 2H, C3-H₂), 2.53(s, 3H, N1-CH₃), 2.60-2.73(m, 2H, C2-H₂), 2.91(s, 3H, N8-CH₃), 3.25(m, 2H, N-CH₂-), 4.11(s, 1H, C9-H), 6.32(d, 1H, J=8, C7-H), 6.75-6.81(m, 2H, C6-H and C4-H); ms(CI), m/z 374 (M⁺+1). Anal. Calc. for C₂₂H₃₅N₃O₂: C, 70.78; H, 9.45; N, 11.26. Found: C, 70.74; H, 9.50; N, 11.21.

(+)-Benzylcarbamoyleseroline (7): Similarly prepared from (+)-eseroline (4) with benzylisocyanate (EtOAc, 41.4%): mp 84-85°C; $[\alpha]_D +56.9^\circ$ (c=0.5, CHCl₃); ¹H-nmr (CDCl₃), 1.42(s, 3H, C10-CH₃), 1.91-1.96(m, 2H, C3-H₂), 2.54(s, 3H, N1-CH₃), 2.60-2.75(m, 2H, C2-H₂), 2.91(s, 3H, N8-CH₃), 4.10(s, 1H, C9-H), 4.40(d, 2H, J=4, Ph-CH₂-), 6.34(d, 1H, J=8, C7-H), 6.78-6.84(m, 2H, C4-H and C5-H), 7.30-7.35(m, 5H, Aromatic H); ms(Cl), m/z 352 (M⁺+1). Anal. Calc. for C₂₁H₂₅N₃O₂: C, 71.76; H, 7.17; N, 11.96: Found. C, 71.89; H, 7.20; N, 11.91.

(+)-Phenylcarbamoyleseroline (8): Similarly prepared from (+)-eseroline (4) with phenylisocyanate (EtOAc, 64.7%): mp 140-142°C; $[\alpha]_D + 69.8^\circ$ (c=0.5, CHCl₃), ¹H-nmr (CDCl₃), 1.44(s, 3H, C10-CH₃), 1.95 (m, 2H, N8-CH₃), 2.55 (s, 3H, N1-CH₃), 2.70 (m, 2H, C2-H₂), 2.93(s, 3H, N8-CH₃), 4.13 (s, 1H, C9-H), 6.36 (d, 1H, J=7, C7-H), 6.85 (m, 2H, C4-H and C6-H), 7.06-7.45 (m, 5H, Aromatic H); ms (Cl), m/z 338 (M⁺+1). Anal. Calc. for C₂₀H₂₃N₃O₂: C, 71.19; H, 6.87; N, 12.46; Found: C, 71.12; H, 6.92; N, 12.43.

(+)-N-Methylphysostigmine (9): Prepared from (+)-eseroline by reaction with dimethylcarbamoyl chloride in the presence of pyridine as described for the (-)-enantiomer⁹ (62.9%): The gum-like material was crystallized from ether-hexane (62.9%: mp 73-75°C; $[\alpha]_D +76.1^\circ$ (c=0.5, CHCl₃); ¹H-nmr (CDCl₃), 1.43(s, 3H, C10-H), 1.92-1.97(m, 2H, C3-H₂), 2.54(s, 3H, N1-CH₃), 2.59-2.76(m, 2H, C2-H), 2.91(s, 3H, N8-CH₃), 2.99(s, 3H, N-CH₃), 3.07(s, 3H, N-CH₃'), 4.12(s, 1H, C9-H), 6.34(d, 1H, J=8, C7-H), 6.75-6.80(m, 2H, C4-H and C6-H); ms(Cl), m/z 290 (M⁺+1). Anal. Calc. for C₁₆H₂₃N₃O₂: C, 66.41; H, 8.01; N, 14.51. Found: C, 66.51; H, 8.05; N, 14.51.

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Received, 4th November, 1987