

TOTAL SYNTHESIS OF RACEMIC PHYSOSTIGMINE, PHYSOVENINE AND ITS SULFUR ANALOGUE BY THE OXINDOLE-5-O-TETRAHYDROPYRANYL ETHER ROUTE ¹⁾

Qian-sheng Yu* and Bao-yuan Lu

Shanghai Institute of Organic Chemistry, Academia Sinica, 354 Fenglin Lu, Shanghai 200032, China

and Xue-Feng Pei ²⁾

Department of Chemistry, Georgetown University, Washington DC 20057, USA

Abstract- 1,3-Dimethyl-5-tetrahydropyranyloxyoxindole (**4**) was synthesized from 4-methylaminophenol sulfate (metol) (**1**). Phase transfer catalyzed C3-alkylation of compound (**4**) produced alcohol (**5**), nitrile (**8**), and thioalcohol (**13**) after treatment of bromide (**12**) with thiourea. Compound (**5**) and (**13**) were converted into racemic physovenine (**7**) and thiaphysovenine (**15**) by reaction with LAH, *in situ* deprotection, and reaction of phenols with methyl isocyanate. Conversion of nitrile (**8**) into racemic physostigmine (**11**) which included a reductive *N*-methylation of **9** was similarly accomplished.

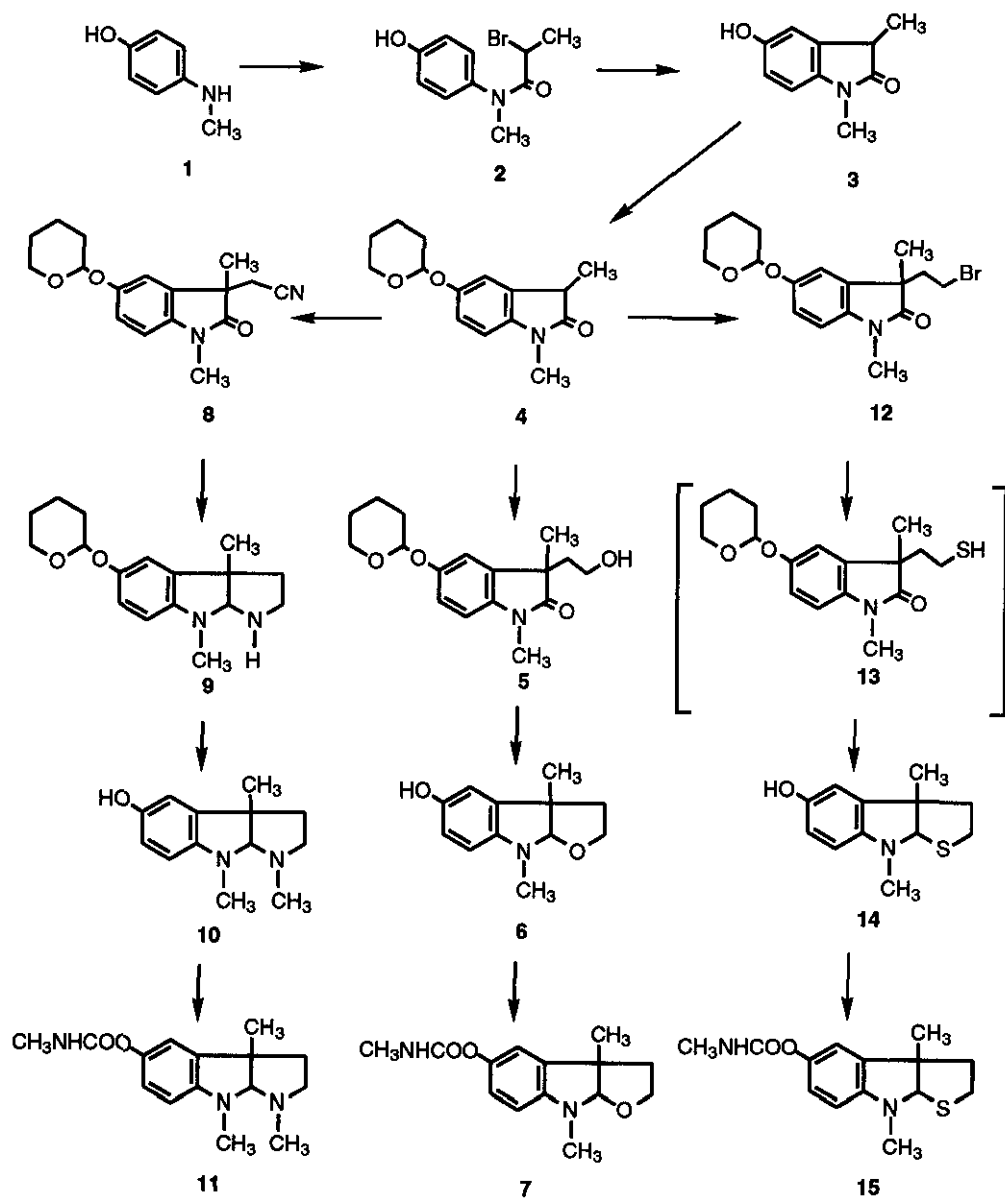
Physostigmine, a major alkaloid from *Calabar* beans,¹ is being evaluated in Alzheimer's diseases and its total synthesis, therefore, receives attention. Several new synthesis of natural (-)-physostigmine have recently been reported. ²⁻⁹ Improvements in its synthesis from oxindoles prepared by the Julian route ^{10,11} were also made. They included a chromatographic separation of urea diastereomers, ¹²⁻¹⁴ a C3 alkylation catalyzed by chiral transfer reagents,¹⁵ a resolution of an oxindole-3-acetic acid with brucine, ¹⁶ and a resolution of carbinolamine with di-*p*-toluyl tartaric acid.¹⁷ The 1, 3-dimethyl-5-alkoxy(methoxy or ethoxy)oxindole used in these syntheses was prepared from phenacetin in 5 steps, requiring removal of the alkyl-protecting group at a later stage by a Lewis acid, such as boron tribromide. We now present the 1, 3-dimethyl-5-tetrahydropyranyloxyoxindole (**4**) synthesized from 4-methylaminophenol sulfate (metol) in three

¹⁾ This paper is dedicated to Dr. Arnold Brossi, at the occasion of his 70th birthday.

²⁾ Xue-Feng Pei is a Visiting Fellow in Laboratory of Neuroscience, NIA, NIH, Bethesda, MD 20892, USA

steps as novel entity. The C3 alkylation is executed in basic milieu which leaves the protecting group intact.

Synthesis of Julian's oxindole (**3**) from metol (**1**), the preparation of the tetrahydropyranyl ether (**4**), and its conversion into alcohol (**5**), nitrile (**8**), and bromide (**12**) in alkylation reactions catalyzed by tetrabutylammonium iodide (TBAI) were achieved in high yields. Compound (**12**) was transformed



into thioalcohol (**13**) on reacting it with thiourea. Reaction of **5** and **13** with lithium aluminum hydride (LAH) followed by treatment with 2N HCl, directly gave (\pm)-physovenol (**6**), and (\pm)-thiaphysovenol (**14**). Cyclization of nitrile (**8**) with LAH gave **9**, and reductive N-methylation followed by treatment with 2N HCl gave (\pm)-eseroline (**10**). (\pm)-Physovenine (**7**), (\pm)-physostigmine (**11**), and (\pm)-thiaphysovenine (**15**) were obtained from phenols (**6**, **10**, and **14**), on reaction with methyl isocyanate, respectively.

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EXPERIMENTAL

Melting points were determined on ZMD-2 electroheating point apparatus. $^1\text{H-Nmr}$ spectra were measured on a JEOL-90Q spectrometer and chemical shifts were reported in δ with tetramethylsilane as the internal reference. Mass spectra were taken on a Finnigan 4021 instrument. Elemental analyses were done at the Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences.

4-Hydroxy-N-methyl-N-(α -bromopropionyl)aniline (2): The sulfate of 4-methylaminophenol (**1**) (100.0 g, 0.29 mol) was dissolved in 1000 ml of H_2O with heating. After adding 300 ml of saturated aqueous solution of NaHCO_3 , the base was precipitated and extracted with ether (700, 500, 200 ml). The combined ether layers were washed with brine, dried over Na_2SO_4 , to give after evaporation of ether free base (**1**) as crystals (70.0 g, 98 %). The free base (**1**) (29.0 g, 0.235 mol) was dissolved in 200 ml of THF, and 2-bromopropionyl bromide (21 g, 0.1 mol) was added dropwise under cooling in an ice bath. After the addition the reaction mixture was refluxed for 1.5 h. Evaporation of solvent gave a residue which was crystallized from acetone to give **2** as colorless crystals (24.5 g, 0.095 mmol, 95 %, based on 2-bromopropionyl bromide): mp 129-130 $^\circ\text{C}$; Clms (m/z): 258 (M^+); $^1\text{H-nmr}$ (CDCl_3): 1.70 (3H, d, CH_3 , $J=18\text{ Hz}$), 3.25 (3H, s, N-CH_3), 4.48 (1H, q, $-\text{CH}$, $J=18\text{ Hz}$), 6.80-7.00 (4H, m, Ar-H); ir (cm^{-1}): 1628 (m, N-CO-), 560, 620 (w, C-Br), 1450, 1500, 1600 (Ar, core). Anal. Calcd for $\text{C}_{10}\text{H}_{12}\text{NO}_2\text{Br}$: C 46.52, H 4.68, N 5.43. Found: C 46.49, H 4.49, N 5.43.

1, 3-Dimethyl-5-hydroxyoxindole (3): A mixture of **2** (47.8 g, 0.185 mol) and AlCl_3 (61.7 g, 0.46 mol) was heated in an oil bath at around 60 $^\circ\text{C}$ with manual stirring with a steel bar. After a short time, the reaction became vigorous accompanied with the formation of HCl. After solidification, another 61.7 g (0.46 mol) of AlCl_3 was added and the temperature of the oil bath raised to 180-185 $^\circ\text{C}$. The solid mixture of reactants was stirred with a steel bar until it became a dark liquid, and then kept at this temperature for 1 h. The hot homogeneous melt was poured into an enamel tray, and pulverized whilst cooling in a mortar and decomposed by addition of 0.5 kg of crushed ice to give **3** as reddish crystals (31.7 g, 97 %). After recrystallization from ethanol, colorless crystals were obtained: mp 219 $^\circ\text{C}$ (lit.¹⁰: mp 219 $^\circ\text{C}$).

1,3-Dimethyl-5-tetrahydropyranyloxyoxindole (4): 1, 3-Dimethyl-5-hydroxyoxindole (**3**) (4.2 g, 24 mmol) was dissolved in 150 ml of THF. After addition of *p*-toluenesulfonic acid monohydrate (0.5 g, 2.4 mmol), 3, 4-dihydro-2H-pyran (5.0 g, 60 mmol) was added dropwise under stirring at 30-40 °C, and the reaction mixture kept for 10 h at this temperature. The reaction was quenched by adding saturated aqueous solution of NaHCO₃ and the solvent removed in vacuo. The residue was extracted by ether, washed with brine, and dried over MgSO₄. Evaporation of the ether gave sticky material, which was crystallized from ether-petroleum ether to give **4** as white crystals (5.61 g, 90.5%); mp 92-94 °C; Elms (m/z): 262 (M⁺); ¹H-nmr (CCl₄): 1.60 (3H, d, -CH₃, J = 18 Hz), 1.80-2.40 (6H, m, -CH₂CH₂CH₂-), 2.90-3.10 (2H, m, -CH₂-O-), 3.50 (3H, s, N-CH₃), 4.20 (1H, q, -CH, J = 18 Hz), 4.60-4.90 (1H, m, -CHOAr), 7.10-7.70 (3H, m, Ar-H); ir (cm⁻¹): 1680-1700 (s, -CO-NR), 1600, 1500, 1450 (m, Ar. core), 1285-1240, 1045-1020 (m, Ar-O-R), 1080, 810 (pyranyl). Anal. Calcd for C₁₅H₁₉NO₃: C 68.94, H 7.33, N 5.36. Found: C 68.72, H 7.43, N 5.24.

1,3-Dimethyl-3-(2'-hydroxyethyl)-5-tetrahydropyranyloxyoxindole (5), 1,3-Dimethyl-3-cyanomethyl-5-tetrahydropyranyloxyoxindole (8) and 1,3-Dimethyl-3-(2'-bromoethyl)-5-tetrahydropyranyloxyoxindole (12)

General procedure: Compound (**4**) (261 mg, 1 mmol) was dissolved in dry THF (10 ml), the container was deoxygenated and kept under N₂. On stirring with a magnetic bar, tetrabutylammonium iodide (TBAI) (40 mg) and KOH (200 mg) were added. After stirring for 10 min, epoxyethane (132 mg, 3 mmol), or chloroacetonitrile (136 mg, 1.5 mmol,) or 1,2-dibromoethane (282 mg, 1.5 mmol) were added dropwise at room temperature. The reaction whilst stirring at room temperature was monitored by tlc, and stopped when the reaction was completed. After filtering through a Celite pad and evaporation of THF, the residue was extracted with ether, washed with brine, dried over MgSO₄, and concentrated in vacuo to give the desired products.

Compound (**5**): The reaction was accomplished after 5 h. Evaporation of solvent gave the product as a yellow oil and it crystallized on standing in a refrigerator overnight. Recrystallization from ether gave **5**, as colorless crystals (259 mg, 85 %); mp 119-120.5 °C; Elms (m/z): 305 (M⁺); ¹H-nmr (CDCl₃): 1.25 (3H, s, -CH₃), 1.30 (2H, m, -[CH₂]-CH₂OH), 1.29-2.00 (6H, m, -CH₂CH₂CH₂-), 2.70 (2H, m, -CH₂O), 3.10 (2H, m, -CH₂OH), 3.25 (3H, s, N-CH₃), 5.32 (1H, m, -CHOAr), 6.70-7.30 (3H, m, Ar-H); ir (cm⁻¹): 3200-3600 (m, b, -OH), 1680-1700 (-CO-NR); Anal. Calcd for C₁₇H₂₃NO₄: C 66.86, H 7.59, N 4.58. Found: C 66.62, H 7.63, N 4.32.

Compound (**8**): The reaction time was about 1-2 h. Evaporation of solvent gave the product quantitatively as a yellow oil which on standing gave colorless crystals: mp 114 °C; Elms (m/z): 301 (M⁺+1); ¹H-nmr (CDCl₃): 1.52 (3H, s, CH₃), 1.60-2.0 (6H, m, -CH₂CH₂CH₂), 2.50 (2H, m, -CH₂CN), 2.80 (2H, m, OCH₂O), 3.20 (3H, s, NCH₃), 5.30 (1H, m, Ar-H). Anal. Calcd for C₁₇H₂₀NO₃: C 67.98, H 6.71, N 9.33. Found: C 67.90, H 6.84, N 9.27.

Compound (**12**): The reaction time was about 24 h, Evaporation of solvent gave the product quantitatively as a yellow oil which on standing gave colorless crystals: mp 120-121.5 °C; Elms (m/z): 368 (M⁺); ¹H-nmr (CDCl₃): 1.23 (3H, s, CH₃), 1.35 (2H, m, -[CH₂]-CH₂Br), 1.30-2.10 (6H, m, -CH₂CH₂CH₂), 2.60 (2H, m, -CH₂-Br), 3.50 (3H, s, NCH₃), 5.35 (1H, m, -CHOAr), 6.80-7.10 (3H, m,

Ar-H); ir (cm^{-1}): 1700 ($-\text{CO}-\text{NR}_2$), 1600, 1500, 1450 (Ar, core), 560-590 (C-BrO). Anal. Calcd for $\text{C}_{17}\text{H}_{22}\text{NO}_3\text{Br}$: C 55.44, H 6.02, N 3.80, Br 21.70. Found: C 55.38, H 6.13, N 3.72, Br 21.70.

(\pm)-*Physovenol* (**6**): Alcohol (**5**) (85.4 mg, 0.28 mmol) was dissolved in dry THF (6 ml), LAH (31 mg, 0.82 mmol) was added slowly while the solution was cooled in an ice bath. The reaction mixture was stirred at room temperature under N_2 for 1 h, and the residue after the evaporation of solvent was rendered acidic with 2N HCl, stirred at room temperature for 0.5 h, and extracted with ether (3X5 ml). The extracts were washed with brine, dried over MgSO_4 and evaporated to give an oil which on treatment with benzene gave **6** as crystals (49 mg, 85.3 %): mp 120-122 °C (lit.¹⁸: mp 119.5-121 °C). Spectra were identical with those of the (-)-enantiomer.¹⁸

(\pm)-*Physovenine* (**7**): Physovenol (**6**) (49 mg, 0.24 mmol) was dissolved in 4.9 ml anhydrous ether under N_2 , and added with about 1 mg (0.04 mmol) of sodium. After stirring for 5 min, methyl isocyanate (0.05 ml, 0.09 mmol) was dropped in slowly. The reaction mixture was stirred overnight at room temperature. Evaporation of solvent gave a residue which was chromatographed to give **7** as white crystals (55.5 mg, 86.6 %): mp 143-144 °C (lit.¹⁸: mp 143.5-144.5 °C); Spectra were identical with those of the (-)-enantiomer.¹⁸

(\pm)-*O-Tetrahydropyranyl-N¹-noreseroline* (**9**): Nitrile (**8**) (300 mg, 1 mmol) was dissolved in THF (20 ml) and LAH (150 mg, 4 mmol) was added under stirring at 0 °C. The reaction mixture was stirred at room temperature under N_2 for 1 h. Evaporation of solvent gave a residue which was treated with a saturated aqueous solution of Na_2SO_4 , then extracted with ether (3X20 ml). The extracts were washed with brine (20 ml), dried over MgSO_4 . Evaporation of solvent gave **9** as a gum (290 mg, quantitatively): Elms (m/z): 289 ($M^+ + 1$), ^1H -nmr (CDCl_3): 1.40-2.13 (6H, m, $-\text{CH}_2\text{CH}_2\text{CH}_2$), 1.50 (3H, s, C3a- CH_3), 2.00-2.60 (4H, m, C2- H_2 , C3- H_2), 2.85 (3H, s, N8- CH_3), 2.90-3.15 (2H, m, CH_2O), 5.11 (1H, s, C9-H), 5.35 (1H, m, CHOAr), 6.30-6.87 (3H, m, Ar-H); ir (film): 3200-3400 (s, NH), 1600 (w), 1500 (s).

(\pm)-*Eseroline* (**10**): Compound (**9**) (288 mg, 1 mmol) was dissolved in CH_3OH (6.6 ml) and 37 % of CH_2O (0.6 ml) was added. After stirring for 3 h at room temperature under N_2 , the reaction mixture was cooled to 0 °C and NaBH_4 (165 mg, 4.46 mmol) was added in small portion, and stirring continued for another 0.5 h at room temperature. Evaporation of solvent gave a residue which was dissolved by 2N HCl (10 ml), stirred for 30 min, then washed with petroleum ether to remove organic impurities. The aqueous solution was basified by slow addition of solid NaHCO_3 and extracted with ether (3X10 ml). The extracts were dried over MgSO_4 and evaporated in vacuo to give residue as a gum which was crystallized from ether-petroleum ether to give **10** as crystals (226 mg, 85 %): mp 137-138 °C (lit.¹³: mp 139 °C); Spectra were identical with those of the (+)-enantiomer.¹³

(\pm)-*Physostigmine* (**11**): Compound (**10**) (50 mg, 0.2 mmol) was dissolved in 5 ml of dry ether under N_2 , and about 1 mg (0.04 mmol) of sodium was added. The reaction mixture was stirred for 5 min at room temperature, then methyl isocyanate (0.012 ml, 0.2 mmol) was added dropwise. The reaction mixture was stirred at room temperature for 2 h. After the removal of sodium the solvent was evaporated to give **11** as a gum (50 mg, 90.6 %). Spectra were identical with those of (-)-physostigmine. Above product (50 mg) was dissolved in ether and equivalent ethanolic solution of

salicylic acid was added. Crystallization gave salicylate of **11** as crystals (71 mg, 95 %): mp 161-162 °C (lit.¹⁹; mp 161-162 °C).

(±)-*Thiaeseroline* (**14**): Bromide (**12**) (358 mg, 1 mmol) and thiourea (76.12 mg, 1 mmol) were mixed in absolute ethanol (5 ml), and heated in an oil bath for 8 h, then cooled to room temperature, and filtered. The solid was washed with ether, then dissolved in 10 % NaOH (3 ml). The aqueous solution was refluxed for 2 h, and after cooling neutralized with dilute H₂SO₄ and extracted with ether. The extracts were washed with brine, dried over MgSO₄ and concentrated to give the crude thioalcohol (**13**) as an orange reddish glue (236 mg, 73.5 %). The above compound (300 mg, 0.93 mmol) was dissolved in dry THF (20 ml), and LAH (150 mg, 3.9 mmol) was added at 0 °C. The reaction mixture was stirred at room temperature under N₂ for 1 h, then concentrated in vacuo to remove THF. The residue was rendered acidic by addition of 2N HCl, stirred for 0.5 h, and extracted with ether. The extracts were washed with brine, dried over MgSO₄ and concentrated in vacuo to give a red solid which was crystallized from acetone to give **14** as colorless crystals (188 mg, 85 %): mp 100-103 °C. Spectra were identical with those of (-)-enantiomer.²⁰

(±)-*Thiaphysovenine* (**15**): Compound (**14**) (231 mg, 1 mmol) was dissolved in dry ether (20 ml) under N₂. About 1 mg (0.04 mmol) of fresh sodium was added and stirring continued at room temperature for 5 min. Then methyl isocyanate (0.06 ml, 1 mmol) was added dropwise and stirring continued for about 20 h. After removal of Na, evaporation of solvent gave a residue which was dissolved in ethyl acetate (20 ml), washed with 0.1 N NaOH (10 ml), then brine (10 ml), and dried over MgSO₄. Evaporation of solvent gave a crude product as an oil which was recrystallized from ether/acetone to give **15** as colorless crystals (211.5 mg, 80 %): mp 150-152 °C. Spectra were identical with those of (-)-enantiomer.²⁰

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