SYNTHESIS OF (±)-PHYSOVENINE AND (±)-7-BROMOPHYSOVENINE FROM INTERMEDIATES OF THE SYNTHESIS OF PHYSOSTIGMINES

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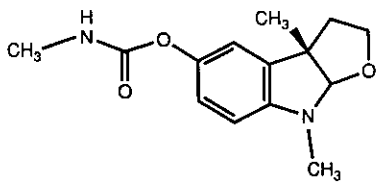
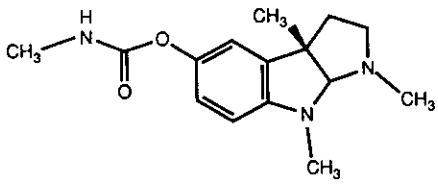
Abstract - Facile synthesis of (±)-physovenine (1) was accomplished from oxindole 3, an intermediate in Julian's total synthesis of physostigmines (2A and 2B). C-Alkylation of 3 with methyl bromoacetate afforded ester 4 which was reduced with LAH in THF at 0°C to directly afford tetrahydrofuroindole 6. Ether cleavage of 6 with BBr_3 in dichloromethane afforded phenol 7, and (±)-physovenine (1) on treatment of 7 with methyl isocyanate in ether. Bromination of 1 with bromosuccinimide in methanol afforded (±)-7-bromophysovenine (8).

Physovenine (1A), a minor alkaloid of the Calabar beans,[1a-c] inhibited acetylcholinesterase (AChE) from erythrocytes in a manner similar to natural (-)-physostigmine (2A).[2] Structure and configuration of 1A shown in its formula were elaborated on the basis of spectral data[1a] and proven to be correct by synthesis of 1A[3] and its optical antipode 1B[2] from intermediates of the synthesis of (-)- and (+)-physostigmine. Several other syntheses of 1 have appeared since then which were reviewed.[1c] Improved methodology to accomplish formation of the tricyclic system present in 2 from oxindoles,[4] suggested that ester 4, readily available from 3 (of the Julian synthesis of 2[5]) by C-alkylation with methyl bromoacetate, might provide a useful intermediate in a simpler synthesis of 1. This proved to be the case, and the results are reported here. Reduction of 4 with LAH in refluxing ether afforded alcohol 5, but gave tetrahydrofuroindole 6 when carried out with LAH in THF at 0°C. The oily ether 6 showed the expected spectral properties, and converted with BBr_3 in dichloromethane smoothly into crystalline phenol 7*, already described elsewhere.[6] Reaction of phenol 7 in dry ether with methyl isocyanate and a speck of sodium, as described in the physostigmine synthesis,[7] afforded 1 of mp 143-144°C and identical on the basis of spectral data with material prepared

*We assigned phenol 7 the name physovenol; analogous to eserol. The IUPAC name for 7 is 3,3a,8,8a-tetrahydro-3a,8-dimethyl-2H-furo[2,3-b]indol-5-ol. Compound 6 is therefore named physovenol methyl ether.



1A



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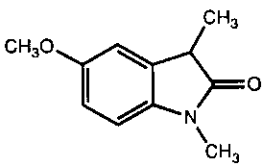

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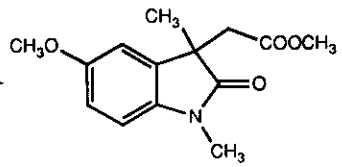

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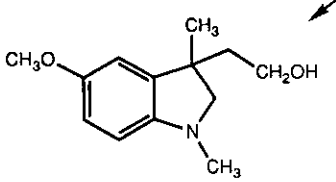

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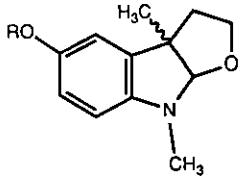
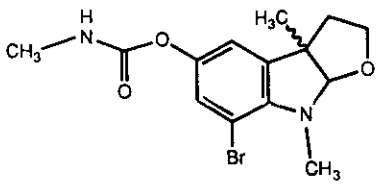


6 R = CH_3
7 R = H
1 R = $CONHCH_3$

1 NBS / HBr



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elsewhere by a different route.[6] Bromination of 1 with bromosuccinimide, afforded as described in the physostigmine series,[8] (±)-7-bromophysovenine (8). That bromination had occurred at C(7) is evident from its ^{1}H-nmr spectrum showing absence of the H-C(7) and the down field shift of the H-C(6). We are presently exploring several avenues to achieve an optical resolution of 1 and intermediates of its synthesis, and will report on the anti-AChE effects of these compounds in due course.

EXPERIMENTAL

Melting points were determined on Fisher Johns or Heating Stage Microscope "RCH" Kofler apparatus. ^{1}H-Nmr spectra were measured on a EM306L(60MHz) or Varian XL-300 (300MHz) spectrometer and chemical shifts are reported in δ with tetramethylsilane as the internal reference. Mass spectra were taken on a Finnigan 4021 or 1015D instrument. Ir spectra were measured on a Perkin-Elmer 683 instrument. Elemental analysis were done by the Shanghai Institute of Organic Chemistry, Academia Sinica.

1,3-Dimethyl-5-methoxyoxindolyl-3-acetic acid methyl ester (4)

1,3-Dimethyl-5-methoxyoxindole[1] (3, 6 g, 31.4 mmol) was dissolved in 45 ml MeOH, sodium (1.86 g) added and the reaction mixture refluxed for 0.5 h. Methyl bromoacetate (12.8 g, 84 mmol, 7.95 ml) was added dropwise, and the reaction was maintained at reflux for 1 h. The solvent was evaporated and the residue was partitioned between ethyl acetate and water. The organic layer was washed first with 2% aqueous hydrochloric acid, followed by brine. After drying ($MgSO_4$) and concentration, 4 was obtained as tan crystals from ethyl acetate/petroleum ether (6.3 g, 76%); mp 83-84°C, ^{1}H-nmr ($CDCl_3$), δ 1.36 (s, 3H, C3-C$\underline{H}_3$), 2.82 (d, 1H, -C$\underline{H}_2$-αorβ, J=16.5 Hz), 2.99 (d, 1H, -C$\underline{H}_2$-αorβ, J=16.5 Hz), 3.23 (s, 3H, N-C$\underline{H}_3$), 3.47 (s, 3H, $CO_2C\underline{H}_3$), 3.75 (s, 3H, -OC$\underline{H}_3$), 6.78-6.82 (m, 3H, 3 x Ar-$\underline{H}$); ms(CI), m/z 264 (M^++1). Anal. Calcd for $C_{14}H_{17}NO_4$: C, 63.86; H, 6.51; N, 5.31. Found: C, 63.77; H, 6.47; N, 5.34.

1,3-Dimethyl-5-methoxyindolinyl-3-ethanol (5)

Compound 4 (263 mg, 1 mmol) was dissolved in anhydrous ether (15 ml) and $LiAlH_4$ (150 mg) was added in portions. After refluxing for 3 h, the solvent was evaporated and the residue was dissolved in 2N HCl (10 ml). The acid solution was washed with ether (10 ml), then made basic with 10% Na_2CO_3, and extracted with ether (20 ml x 3). The extract was dried with $MgSO_4$ and then evaporation of the solvent gave a residue which was chromatographed on silical gel (petroleum ether/ethyl acetate, 100:40) to give 5 as an oil (190 mg, 86%); ir 3350 cm^{-1} (-OH); ^{1}H-nmr ($CDCl_3$), 1.20 (s, 3H, -C$\underline{H}_3$), 2.55 (s, 3H, N-C$\underline{H}_3$), 3.67 (s, 3H, OC$\underline{H}_3$), 6.40-6.60 (m, 3H, Ar-$\underline{H}$), no C9-H observed; ms(EI), m/z 221 (M^+ -CH_3), 176 (M^+ -CH_2CH_2OH). Anal. Calcd for $C_{13}H_{19}NO_2 \cdot 1/8H_2O$: C, 69.84; H, 8.56; N, 6.26. Found: C, 69.47; H, 8.72; N, 5.94.

(+)-Physovenol methyl ether (6)

Compound 4 (810 mg, 3.08 mmol) was dissolved in THF (80 ml) and $LiAlH_4$ (480 mg) was added in portions. After stirring for 1 h at 0°C, saturated brine was added dropwise until no more H_2 evolution was evident. The THF solution was filtered to remove the solid and then the solvent was evaporated. The residue which resulted was dissolved in ethyl acetate, washed with brine and then dried over $MgSO_4$. Evaporation of solvent gave residue which was chromatographed on silica gel column (petroleum ether/ethyl acetate, 100:4) to give 6 as oil (580 mg, 86%); ir - no carbonyl group; ^{1}H-nmr (CCl_4), δ 1.37 (s, 3H, CH_3), 2.10-2.80 (m, 2H, CH_2), 2.76 (s, 3H, N-CH_3), 3.60 (s, 3H, OCH_3), 3.00-4.00 (m, 2H, C3-2H), 4.83 (s, 1H, C9-H), 5.90-6.20 (m, 1H, C7-H), 6.20-6.60 (m, 2H, C6 and C4-H), ms(EI), m/z 219 (M^+). Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.20; H, 7.81; N, 6.39. Found: C, 71.26; H, 8.21; N, 6.57.

(±)-Physovenol (7)

Compound 6 (105 mg, 0.48 mmol) was dissolved in CH_2Cl_2 (5 ml) and then BBr_3 (0.4 ml) in CH_2Cl_2 (2 ml) was added dropwise while stirring under N_2 at room temperature. After 3 h, solvents were removed and the residue was dissolved in H_2O (5 ml) and made alkaline with an aqueous solution of $NaHCO_3$. After extraction with ether (10 ml x 3), the organic layer was washed with brine (10 ml) and dried over $MgSO_4$. Evaporation of solvent gave and oil which was treated with benzene to give 7 as a powder (40 mg, 41%); mp 119.5-121°C; ^{1}H-nmr (acetone-d_6), δ 1.37 (s, 3H, C10-CH_3), 2.03 (s, 3H, N8-CH_3), 2.05 (m, 2H, C3-2H), 3.30-3.37 (m, 1H, C2-H$_{\alpha \text{ or } \beta}$), 3.81-3.87 (m, 1H, C2-H$_{\alpha \text{ or } \beta}$), 4.91 (s, 1H, C9-H), 6.21 (d, 1H, C7-H, J=8.2 Hz), 6.41 (dd, 1H, C6-H, J=7.9 Hz, J=1.9 Hz), 6.63 (d, 1H, C4-H, J=1.8 Hz): ms(CI), m/z 205 (M^+), 188 (M^+ -OH), 174, 160. Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.91; H, 7.25; N, 6.73.

(±)-Physovenine (1)

(±)-Physovenol (7, 1.2 g, 6.0 mmol) was dissolved in 95 ml of freshly opened THF, and a small piece of Na was added. After stirring for 5 min, methyl isocyanate (6.27 ml) was added and the reaction was stirred for 10 h with a drying tube attached. The piece of Na was removed and the solvent was evaporated. The residue was chromatographed on silica gel (CH_2Cl_2/MeOH, 100:1). Physovenine (1) crystallizes from CH_2Cl_2/diisopropyl ether (908 mg, 64%); mp 143.5-144.5°C (lit.[6] 142-145°C); ^{1}H-nmr ($CDCl_3$), δ 1.48 (s, 3H, C10-CH_3), 2.00-2.18 (m, 2H, C3-CH_2), 2.88 (d, 3H, CH_3-NH, J=4.79 Hz), 2.92 (s, 3H, N8-CH_3), 3.46-3.53 (m, 1H, C2-CH$_{\alpha \text{ or } \beta}$), 3.95-4.00 (m, 1H, C2-CH$_{\alpha \text{ or } \beta}$), 4.99 (br s, 1H, NH), 5.40 (s, 1H, C9-CH), 6.43 (d, 1H, C7-H, J=9.0 Hz), 6.86-6.89 (m, 2H, C4 and C6-H); ms(CI), m/z 263 (M^++1), 206.

(±)-7-Bromophysovenine (8)

Physovenine (1, 100 mg, 0.38 mmol) was dissolved in 2.5 ml of anhydrous MeOH. A drop of 48% HBr and N-bromosuccinimide (70 mg, 0.39 mmol) were added and the reaction mixture was maintained at room temperature for 2 h. After removal of solvent, 8 was crystallized from MeOH/diisopropyl ether (65 mg, 50%); mp 151-152°C; ^{1}H-nmr ($CDCl_3$), δ 1.46 (s, 3H, C10-CH_3), 2.00-2.14 (m, 2H, C3-CH_2), 2.87-2.92 (d, 3H, CH_3-NH, J=4.7 Hz), 3.27 (s, 3H, N8-CH_3), 3.52-3.59 (m, 1H, C2-$H_{\alpha or \beta}$), 3.95-4.00 (m, 1H, C2-$H_{\alpha or \beta}$), 4.91 (br s, 1H, NH), 5.84 (br s, 1H, C9-H), 6.82 (s, 1H, C4-H), 7.04 (s, 1H, C6-H); ms(CI), m/z 341, 343 (M^++1, M^++3), 284, 286. Anal. Calcd for $C_{14}H_{17}N_2O_3Br$: C, 49.28; H, 4.98; N, 8.21; Br, 23.42. Found: C, 49.33; H, 5.06; N, 8.13; Br, 23.50.

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