(S)-1,3-DIMETHYL-3-HYDROXY-5-METHOXYOXINDOLE: BY-PRODUCT IN THE SYNYHESIS OF PHYSOSTIGMINE

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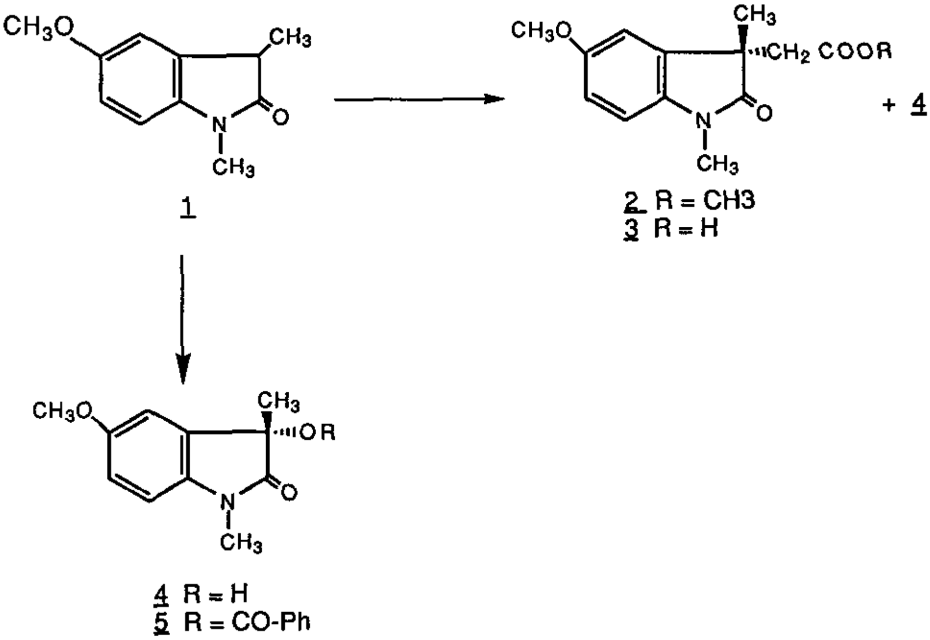
Abstract- (S)-1,3-Dimethyl-3-hydroxy-5-methoxyoxindole (**4**) was obtained as a by-product in the asymmetric alkylation of oxindole (**1**) with methyl chloroacetate in the presence of N-[(4-trifluoromethyl)benzyl]cinchonium bromide. Its structure was established by spectral data. Optically active (**4**) of (S)-configuration was obtained from oxindole (**1**) on air oxidation in the presence of the chiral catalyst N-[(4-trifluoromethyl)benzyl]cinchonium bromide.

INTRODUCTION

Asymmetric alkylation of oxindole (**1**) with chloroacetonitrile in the presence of the chiral catalyst N-[(4-trifluoromethyl)benzyl]cinchonium bromide (CPTC) afforded a useful intermediate for preparing natural physostigmine.[1] This reaction, when executed with methyl chloroacetate and catalyzed by CPTC in the presence of sodium hydroxide, afforded as a neutral compound the ester (**2**), and as the material soluble in NaOH the acid (**3**)in a total yield of 85%. However, the optical purity of these materials was low (66% ee for **2** and 31.4% ee for **3**). It was found that a polar (tlc) by-product was obtained in this reaction, which was separated by chromatography, and shown on the basis of spectral data and its ms of 207 (M^+) to be the oxindole (**4**) with a OH-group at C-3. The compound was optically active, and showed when compared with optically pure material an ee% of the (S)-enantiomer of 14 %. Optically pure **4** was obtained from **1** when treated in benzene and NaOH in the presence of CPTC. The material obtained after workup and chromatography on silica gel afforded **4** of mp 130-131 °C and $[\alpha]_D$ -14.1 ° (c 1.5, EtOH), and after repeated crystallization from ether optically pure **4** (14%) as slightly yellow crystals of mp 116-117 °C and $[\alpha]_D$ -104 ° (c 1.5, EtOH). ^{1}H-Nmr analysis of this material in using chiral europium-shift reagents showed this material to be at least 95% optically pure. The assignment of the (S)-configuration was made by converting **4** into the benzoate (**5**), and measuring **4** and **5** by the cd exitation chirality method.[2] The stereoselective hydroxylation of **1** in the presence of the chiral catalyst CPTC is noteworth since it maybe applicable to an enantioselective hydroxylation of prochiral enolizable oxindoles.



EXPERIMENTAL

Melting points were determined on ZED-2 electroheating melting point apparatus. ^{1}H-Nmr spectra were measured on an XL-200 (200 MHz) spectrometer and chemical shifts are reported in δ with tetramethylsilane as the internal reference. Mass spectra were taken on a Finnigan 4021 instrument. Elemental analysis were done by the Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences.

Methyl 1,3-dimethyl-5-methoxyoxindolyl-3-acetate (2) and **1,3-dimethyl-5-methoxyoxindolyl-3-acetic acid (3)**. To a 25 ml flask immersed in an ice water bath was added under N_2, benzene (30 ml), oxindole (**1**) (239 mg, 1.25 mmol), CPTC (87.5 mg, 0.19 mmol) and 50% NaOH (5 ml). A solution containing 272 mg (2.5 mmol) of methyl chloroacetate in benzene (2.5 ml) was added dropwise within 1.5 h. The reaction mixture was stirred for 4 h, then the ice bath was removed. Stirring was continued for another 5 h at room temperature, then 12.5 ml of ice water was added. The mixture was extracted with 1.5% HCl (12.5 mlx3), washed with brine, dried over Na_2SO_4. After evaporation of solvent, the residue was chromatographied (silica gel, CH_2Cl_2/EtOAc = 14:1) to give product (**2**) as a gum 50 mg (16.9%): $[\alpha]_D$ -13.2 ° (c 0.4, EtOH), ee = 66.3%.[3] Ms and ^{1}H-nmr are identical with those of racemic material.[4] The tlc of the ether extract (silica gel, CH_2Cl_2/MeOH = 9 : 1) showed the presence of a polar impurity of ms 207 (M^+) which was found to be identical with compound (**4**) described below.

The aqueous layer obtained from extraction of reaction mixture with ether was acidified with 10% HCl, then extracted by $CHCl_3$ (25 mlx3). The organic layer was washed with brine, and dried over Na_2SO_4. Evaporation of solvent gave compound (3) as a powder (212 mg, 68.1%): $[\alpha]_D$ -15.3 ° (c 1, EtOH), ee = 31.4%;[3] EIms (m/z): 249 (M^+); ^{1}H-Nmr ($CDCl_3$): δ 1.43 (s, 3H, C3-CH_3), 2.84 (m, 2H, -CH_2-), 3.17 (s, 3H, N-CH_3), 6.67-6.90 (m, 3H, Ar-H), 10.35 (br , 1H, -COOH).

1,3-Dimethyl-3-hydroxy-5-methoxyoxindole (4). To a 25 ml flask was added benzene (12 ml), oxindole (**1**) (95.5 mg, 0.5 mmol) and CPTC (34.9 mg, 0.075 mmol), then 2 ml of 50% NaOH solution were added. The mixture after standing for 12 h was extracted with ether (10 mlx3). The combined extracts were washed with brine, and dried over $MgSO_4$. After evaporation of solvent and chromatography (silica gel, petroleum ether : EtOH = 3 : 1), oxindole (**4**) was obtained as crystals (62 mg, 50%): mp 130-131 °C; $[\alpha]_D$ -14.1 ° (c 1.5, EtOH), ee = 13%; EIms (m/z): 207 (M^+, 100%), 190 (M^+-OH, 35.43%); ^{1}H-Nmr ($CDCl_3$): δ 1.60 (s, 3H, C3-CH_3), 3.18 (s, 3H, N-CH_3), 3.80 (s, 3H, O-CH_3), 6.67-7.06 (m, 3H, Ar-H). Anal.Calcd for $C_{11}H_{13}NO_3$: C 63.71, H, 6.28, N 6.76; Found: C 63.64, H 6.17, N 6.58.

Purification and CD-spectrum of 3(S)-1,3-dimethyl-3-hydroxy-5-methoxyoxindole (4). Compound (**4**) (955 mg) was dissolved in ether (80 ml) and refluxed until complete dissolution. The solution was cooled to room temperature and left standing in the refrigerator overnight. Recrystallization (2 X) gave pure (**4**) (65 mg, 13.6%): mp 116-117 °C; $[\alpha]_D$ -104 ° (c 1.5, EtOH), $[\alpha]_D$ -85.3 ° (c 0.4, $CHCl_3$); cd spectrum in MeOH: Δε 220 nm, +24.8; Δε 260 nm, -9; ^{1}H-nmr by using Eu(hfc)$_3$ showed ee >= 95%.

Determination of the optical purity of 4. 200 MHz ^{1}H-Nmr ($CDCl_3$): addition of Eu(hfc)$_3$ showed δ 1.60 (s, 3H, C3-CH_3) as two single peaks, with an ee > 95% for the pure material and an ee = 13% for the original material. The $[\alpha]_D$ values measured for these compounds agree with nmr analysis.

The absolute configuration of optically pure hydroxyoxindole (4), 3(S)-3-Benzoyloxy-1,3-dimethyl-5-methoxyoxindole (5). 50 mg (0.242 mmol) of optically pure **4** and 36 mg (0.255 mmol) of benzoyl chloride were added with CCl_4 (10 drops) and dry pyridine (10 drops). The mixture was allowed to stand at room temperature for 12 h. The reaction mixture was dissolved in ether, washed with 10% NaOH,10% HCl, brine, and then dried over $MgSO_4$. Evaporation of solvent gave compound (**5**) as a crystal (68 mg, 90%): mp 75-77 °C; $[\alpha]_D$ -39.3 ° (c 0.15, $CHCl_3$); EIms (m/z): 311 (M^+); ^{1}H-nmr ($CDCl_3$): δ 1.50 (s, 3H, C3-CH_3), 3.55 (s, 3H, N-CH_3), 3.70 (s, 3H, O-CH_3), 6.67-7.20 (m, 8H, Ar-H); cd spectrum in MeOH: Δε 220 nm, +24.8; Δε 260 nm, -11.3.

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