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SYNTHESIS OF (-)- AND (+)-ESERMETHOLE VIA CHEMICAL RESOLUTION OF 1,3-DIMETHYL-3-(2-AMINOETHYL)-5-METHOXYOXINDOLE

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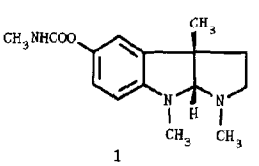
Abstract. A new synthesis of (-)- and (+)-esermethole (**2** and **7** respectively), penultimate intermediates to (-)- and (+)-physostigmine, is described. Phase-transfer catalyzed dimethylation of 3-cyanomethyl-5-methoxyoxindole (**3**) and successive hydrogenation of the cyano group gave 1,3-dimethyl-3-(2-aminoethyl)-5-methoxyoxindole (**5**), which was efficiently resolved with optically active tartaric acids. Subsequent conversion to a carbamate and reductive cyclization performed by a standard method afforded both the enantiomers of esermethole. The enantiomeric excesses, determined by chiral HPLC analysis, were greater than 99.5%. In particular, analytical HPLC resolution of **5**, previously reported as unfeasible, was achieved.

(-)-Physostigmine (**1**) has been used as a clinically important anticholinesterase agent and more recently the therapeutic properties for Alzheimer's disease shown by some analogues of this alkaloid have stimulated a renewed interest in its pharmacology and chemistry[1,2].



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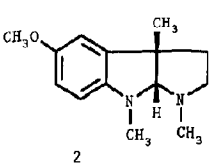

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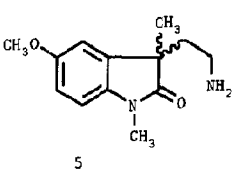

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Over the last 60 years a number of syntheses of (-)-physostigmine has been reported[3-10]. Some of these involve resolutions of diastereomeric salts as the crucial stereoselective step[3-5] or employ this methodology to improve the enantiomeric excess of enantiomerically enriched intermediates, previously prepared through asymmetric synthesis[9]. However, the described resolution processes are quite laborious and, sometimes, difficult to reproduce. In fact, due to the low degree of stereoselectivity exhibited by the resolving agents in the selected operative conditions, more than one crystallization is required or two different resolving agents must be used in sequence. In contrast, we describe herein a new synthesis of (-)-esermethole (**2**) and its enantiomer (**7**), penultimate intermediates to (-)- and (+)-physostigmine respectively, based on a very efficient resolution of their racemic precursor 1,3-dimethyl-3-(2-aminoethyl)-5-methoxyoxindole (**5**) *via* salt formation with optically active tartaric acid and selective crystallization (see Scheme).

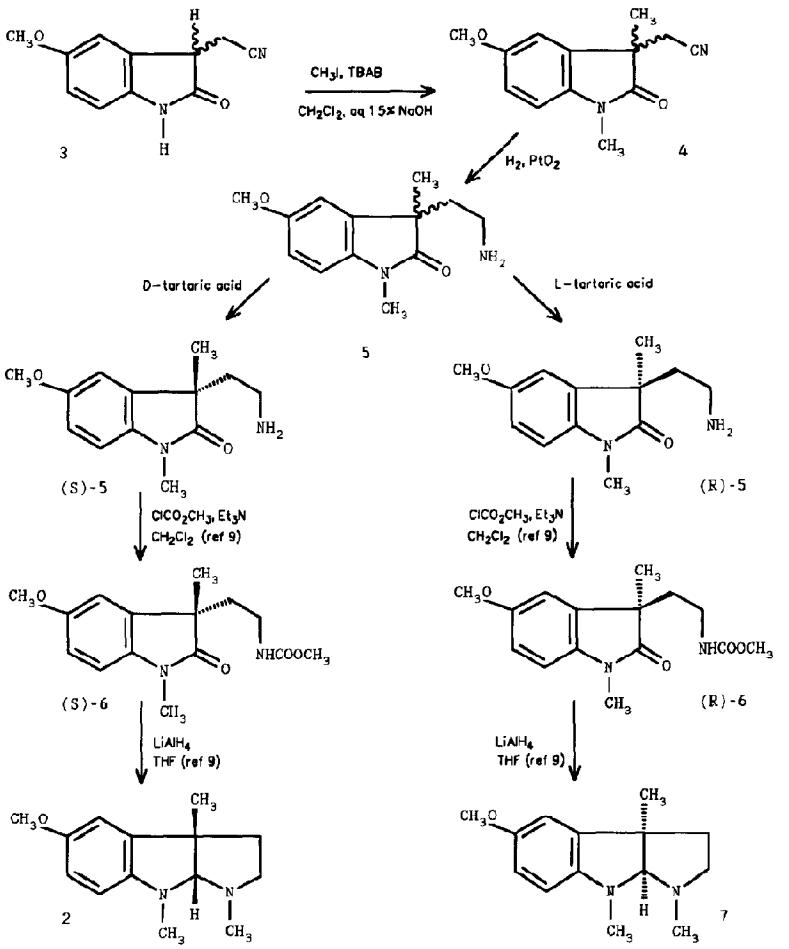
Racemic 3-cyanomethyl-5-methoxyoxindole (**3**), prepared from p-anisidine by a standard method[11], was methylated at the 1 and 3 positions by treatment with CH_3I in CH_2Cl_2 and aqueous 15% NaOH in the presence of tetrabutylammonium bromide as a phase-transfer catalyst. The dialkylation was quantitative and 1,3-dimethyl-3-cyanomethyl-5-methoxyoxindole (**4**) was isolated, after working up, in 79% yield. Intermediate **4** was therefore catalytically reduced (H_2, PtO_2, H^+, MeOH) to the corresponding primary amine **5**. Again the reaction proceeded quantitatively and **5** was isolated as the hydrochloride by crystallization from ethanol in 84% yield. Successive treatment of the amine hydrochloride with 0.6 equiv of D-tartaric acid and KOH in water gave a white precipitate, which was recrystallized from water. The free base was recovered in optically active form from the recrystallized product by CH_2Cl_2-1M NaOH extraction. Its enantiomeric excess was determined to be 99.6% by HPLC on a chiral stationary phase[12] and the S configuration was assigned on the basis of a subsequent two step conversion to (-)-esermethole (**2**) by the literature method[9]. Chiral HPLC analysis of the amine recovered from the precipitate before the recrystallization showed a 94% e.e..

X-ray analysis established that the white solid, whence enantiomerically pure (S)-**5** had been recovered, was the hydrogen tartrate dihydrate of the latter.

Using an approach analogous to that described above, resolution of **5** by L-tartaric acid afforded (R)-**5** in analogous chemical and optical yields (e.e.>99.5%).

The conversion to carbamates (S)- and (R)-**6** and the subsequent respective

Scheme



cyclization to **2** and **7** did not affect the optical purity achieved in the resolutive step. Indeed the enantiomeric excesses of (S)-**6**, **2**, (R)-**6** and **7**, determined by chiral HPLC analysis according to standard methods[13], were unchanged in comparison with those of (S)- and (R)-**5**.

Moreover, it is to be emphasised that selective crystallizations could be successfully performed in the presence of optically active tartaric acid

and KOH using crude **5** hydrochloride, which resulted from hydrogenation after removal of the catalyst and the solvent.

In summary, this paper describes an efficient and simple approach to the preparation of (-)- and (+)-esermethole in high enantiomeric excesses. In fact the treatment of their penultimate synthetic precursor **5** with D and L-tartaric acid, followed by only one recrystallization, allowed us to obtain (S)- and (R)-**5** respectively, both with enantiomeric excesses greater than 99.5%.

Experimental Section

Melting points are uncorrected. Optical rotations were measured in a 1-dm cell of 1 ml capacity using a Perkin-Elmer 241 polarimeter. ^{1}H NMR spectra were recorded on a Bruker AC 200 instrument. HPLC analyses were performed on Chiralcel columns (250x4.6 mm I.D.) from Daicel using a Waters 510 pump and a Pye Unicam PU 4025 UV detector (analytical wavelength 254 nm). Chromatographic data were collected and processed on a Waters 740 Data Module.

1,3-Dimethyl-3-cyanomethyl-5-methoxyoxindole (4). A mixture of 3-cyanomethyl-5-methoxyoxindole **3** (30 g, 148.4 mmol), tetrabutylammonium bromide (5 g, 15.5 mmol) and CH_3I (19.4 ml, 311 mmol) in CH_2Cl_2 (300 ml) and aq NaOH (15%, 300 ml) was stirred at 30°C for 2 h. The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (2x200 ml). Evaporation of the combined organic extracts gave an oily residue (40 g), which was dissolved in ethyl acetate (250 ml) and washed with 3 N HCl (3x70 ml) and aq NaCl (30%, 3x80 ml). The organic phase was dried with Na_2SO_4 and concentrated in vacuo yielding a tick brownish oil (33.3 g) which became solid upon standing. This material was triturated with hexane and filtered to give **4** (28 g, 79%) as a slightly brownish amorphous solid: mp 84-86°C (Lit.[14] m.p. 75-76°C); ^{1}H NMR ($CDCl_3$) δ 1.5 (s, 3 H), 2.55 (d, 1 H), 2.85 (d, 1 H), 3.2 (s, 3 H), 3.8 (s, 3 H), 6.8-6.9 (m, 2 H), 7.1 (d, 1 H).

1,3-Dimethyl-3-(2-aminoethyl)-5-methoxyoxindole (5). 1,3-Dimethyl-3-cyanomethyl-5-methoxyoxindole **4** (12 g, 52.1 mmol) was taken up in MeOH (100 ml) and concd HCl (17.4 ml) and PtO_2 (1.2 g) was added. The mixture was shaken in hydrogen at room temperature and atmospheric pressure until the uptake of hydrogen had ceased. This occurred after 15 h. The catalyst was filtered and rinsed with MeOH (30 ml). The combined filtrate was concentrated in vacuo and the solid residue crystallized from ethanol yielding **5** hydrochloride (11.8 g, 84%) as a white solid: mp 212-215°C; ^{1}H NMR of the free base ($CDCl_3$) δ 1.25 (br s, 2 H), 1.35 (s, 3 H), 1.8-2.5

(m, 4 H), 3.2 (s, 3 H), 3.8 (s, 3 H), 6.7–6.85 (m, 3 H). Anal. Calcd. for $C_{13}H_{19}ClN_2O_2$: C, 57.67; H, 7.07; Cl, 13.09; N, 10.35. Found: C, 57.49; H, 7.05; Cl, 12.98; N, 10.32.

(3S)-1,3-Dimethyl-3-(2-aminoethyl)-5-methoxyoxindole [(S)-5]. A stirred mixture of the hydrochloride of racemic 1,3-dimethyl-3-(2-aminoethyl)-5-methoxyoxindole **5** (58.32 g, 215.4 mmol), D-tartaric acid (19.4 g, 129.3 mmol) and KOH (7.25 g, 129.3 mmol) in water (376 ml) was heated on a steam bath. The resulting solution was cooled to 8°C and the formed white precipitate was collected by filtration. The free amine recovered from a sample of this precipitate by treatment with 1N NaOH–CH_2Cl_2 exhibited a 94% e.e. (determined by HPLC on the chiral stationary phase Chiralcel OD (Daicel), using hexane–ethanol–water–triethylamine 88/12/0.42/0.08, flow-rate 0.2 ml/min)[12]. Recrystallization from water (210 ml) gave 35 g of white solid, from which (S)-**5** (15.4 g, 30.5% of the starting racemic **5**) was recovered by 1N NaOH–CH_2Cl_2 extraction as a pale yellow oil: $[\alpha]_D^{20}$ -26.4 (c 1, EtOH); 99.6% e.e., determined by chiral HPLC analysis[12]. ^{1}H NMR spectrum was identical with that of racemic **5**. X-ray analysis indicated that the recrystallized product was the hydrogen tartrate dihydrate of (S)-**5**.

(3S)-1,3-Dimethyl-3-[2-[(methoxycarbonyl)amino]-ethyl]-5-methoxyoxindole [(S)-6]. (3S)-1,3-Dimethyl-3-(2-aminoethyl)-5-methoxyoxindole (S)-**5** was converted into (S)-**6** as described[9]: 99.6% e.e. (determined by HPLC on the chiral stationary phase Chiralcel OD (Daicel), using hexane–isopropanol 90/10, flow-rate 1 ml/min)[13]; ^{1}H NMR (DMSO) δ 1.25 (s, 3 H), 1.85–1.95 (m, 2 H), 2.50–2.67 (m, 2 H), 3.11 (s, 3 H), 3.45 (s, 3 H), 3.75 (s, 3 H), 6.82–7.03 (m, 4 H). The product was obtained as an oil and used in the next step without purification.

(–)-Esermethole (2). (3S)-1,3-Dimethyl-3-[2-[(methoxycarbonyl)amino]-ethyl]-5-methoxyoxindole (S)-**6** was converted into **2** as described[9]: m.p. 53–54°C (Lit.[9] 52.5–54°C); b.p. 155°C (0.08 mbar); $[\alpha]_D^{20}$ -137.4 (c 0.35, benzene) [Lit.[9] $[\alpha]_D$ -136.7 (c 0.35, benzene)]; 99.6% e.e. (determined by HPLC on the chiral stationary phase Chiralcel OJ (Daicel), using hexane–isopropanol 95/5, flow-rate 0.6 ml/min)[13]; ^{1}H NMR ($CDCl_3$) δ 1.4 (s, 3 H), 1.95 (m, 2 H), 2.55 (s, 3 H), 2.6–2.8 (m, 2 H), 2.9 (s, 3 H), 3.75 (s, 3 H), 4.05 (s, 1 H), 6.4 (dd, 1 H), 6.65 (m, 2 H).

(3R)-1,3-Dimethyl-3-(2-aminoethyl)-5-methoxyoxindole [(R)-5]. (R)-**5** was obtained from racemic 1,3-dimethyl-3-(2-aminoethyl)-5-methoxyoxindole **5** as described for the preparation of (S)-**5**, using L-tartaric acid as resolving agent: $[\alpha]_D^{20}$ +26.4 (c 1, EtOH); 99.7% e.e. (determined by chiral HPLC analysis)[12]. ^{1}H NMR was identical with that of (S)-**5**.

(3R)-1,3-Dimethyl-3-[2-[(methoxycarbonyl)amino]-ethyl]-5-methoxyoxindole

[(R)-6]. (3R)-1,3-Dimethyl-3-(2-aminoethyl)-5-methoxyoxindole (R)-**5** was converted into (R)-**6** as described[9]: 99.7% e.e. (determined by chiral HPLC analysis)[13]. ^{1}H NMR was identical with that of (S)-**6**.

(+)-Esermethole (7). (3R)-1,3-Dimethyl-3-[2-[(methoxycarbonyl)amino]-ethyl]-5-methoxyoxindole (R)-**6** was converted into **7** as described[9]: $[\alpha]_D^{20}$ +137.6 (c 0.35, benzene); 99.7% e.e. (determined by chiral HPLC analysis)[13]. ^{1}H NMR, m.p. and b.p. were identical with those of **7**.

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