PROGRESS TOWARDS A PRACTICAL TOTAL SYNTHESIS OF CALABAR ALKALOIDS: TOTAL SYNTHESIS OF (-)-ESERMETHOLE AND (-)-PHYSOVENOL METHYL ETHER FROM (3S)-1,3-DIMETHYL-3-CARBOXYMETHYL-5-METHOXYOXINDOLE

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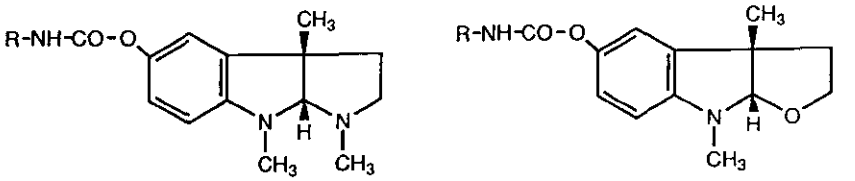
Abstract- Chemical resolution of the oxindoleacetic acid (**7**) with brucine in water yielded the acid (**7a**) of (3S)-absolute configuration. Acid (**7a**), in using conventional methods, was converted into nitrile (**8a**), lactone (**9a**) and amides (**10a**), and (**11a**) respectively. Amide (**10a**), on reduction with LAH in refluxing THF, directly yielded (-)-esermethole (**12a**), and amide (**11a**) similarly gave (-)-N^1-benzylnoresermethole (**13a**). Reduction of ester (**6a**) with LAH in refluxing THF yielded (-)-physovenol methyl ether (**14a**).

INTRODUCTION- Renewed interest in the Calabar alkaloids (-)-physostigmine (**1a**) and (-)-physovenine (**2a**) which are short acting anti-cholinesterase agents,[1-3] is manifested with several total chiral synthesis of these alkaloids,[4-7] including the elegant 12-step synthesis of (-)-physostigmine from 5-benzyloxyindole by Marino.[8] This upsurge of interest in Calabar alkaloids may have been prompted by (-)-heptylphysostigmine (**3a**) which was reported to be much longer acting, and of possible medical use in the treatment of Alzheimer's disease.[9-11]

The chiral syntheses of Calabar alkaloids so far reported, although compelling in design and execution, are lengthy, and the overall yields of optically active products are lower than those obtained in the classical synthesis of Julian and Pikl,[12,13] or the NIH-modification.[14-16] The latter two routes are somewhat handicapped by the tedious chemical resolution of intermediates - the Julian-Pikl synthesis, also used to prepare unnatural (+)-physostigmine and (+)-physovenine

Figure 1: Calabar Alkaloids and Carbamate Analogues

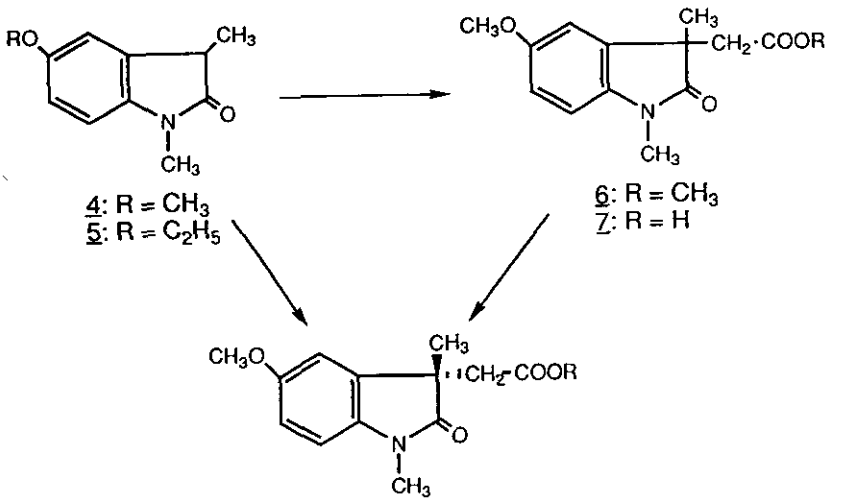


1a: R = CH_3
3a: R = C_7H_{15}

2a

(enantiomers of **1a**, **2a**), [17] gave optically pure material only after 8 crystallizations of salts obtained from eserethole (ethyl ether analog of **12a**) and L-(+)-tartaric acid, and the NIH-synthesis required a careful chromatographic separation of urea precursors for making **14a**, the N^1-nor analog of **12.a** The recently reported and so far most practical synthesis of (-)-esermethole (**12a**) from oxindole (**4**)

Figure 2: Synthesis of the Chiral (3S)-Acetic Acid 7a



4: R = CH_3
5: R = C_2H_5

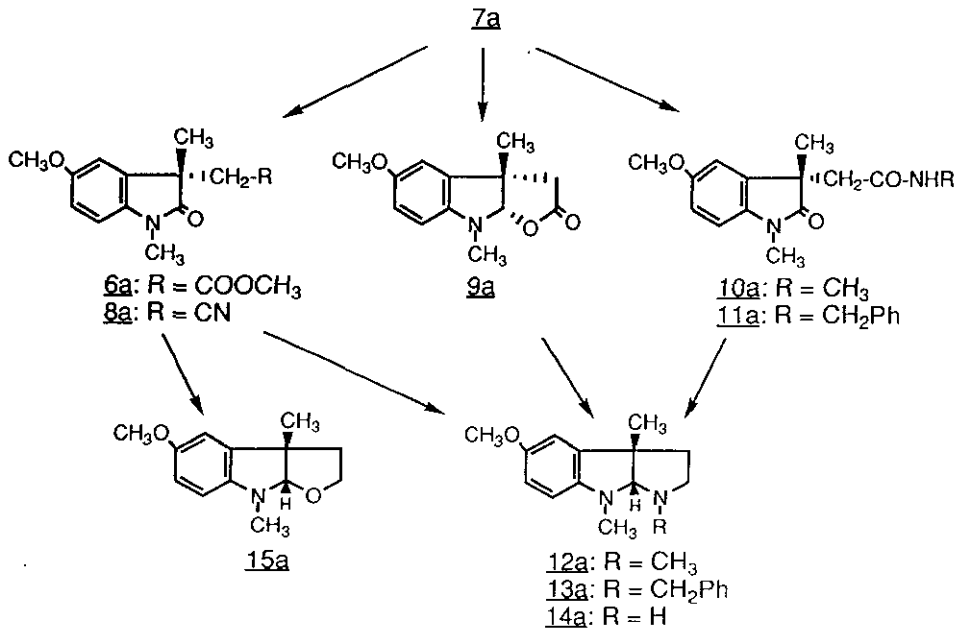
6: R = CH_3
7: R = H

6a: R = CH_3
7a: R = H

by an asymmetric alkylation with chloroacetonitrile in the presence of chiral catalysts gave the nitrile (**8a**) in 83% yield. Compound (**8a**) had only 73% e.e. of the S-enantiomer, and it required further purification.[3] The anticholinesterase activity of Calabar alkaloids and their carbamate analogs is enantiospecific,[18] and requires properly configurated intermediates to perfect their synthesis. This has been accomplished here with the optically active acid (**7a**). This acid is readily available from oxindole (**4**), or (**5**), on C-alkylation with methyl bromoacetate to give ester (**6**) from **4**.[19] Alkaline hydrolysis of **6** yielded racemic acid (**7**) [20] which was resolved with brucine in water. The acid (**7a**) was obtained from the brucine salt in 35% yield. The (3S)-configuration of **7a** is secured with its conversion into **12a**, **13a**, **14a** and **15a** (Figure 3) which were used earlier to prepare the natural Calabar alkaloids.[1-3]

CHEMISTRY- Acid (**7a**) gave in straight forward chemical reactions the (+)-rotating nitrile (**8a**),[3] and the lactone (**9a**) which was earlier prepared in racemic form[1] and recently obtained from acid (**7**) by a selective reduction of its sodium salt with $LiBHEt_3$ at 0 °C.[20] Another entry into the optically active Calabar alkaloids was achieved with the amides (**10a**) and (**11a**) obtained from **7a** on reaction with methyl isocyanate and benzyl isocyanate, respectively, in the presence of triethylamine. They afforded with LAH in refluxing THF directly (-)-esermethole **12a** and (-)-N[1]-benzylnoresermethole

Figure 3 : Synthesis of Optically Active Intermediates



(**13a**), respectively.[21] Reduction of ester (**6a**) obtained from **7a** with LAH in THF gave (-)-physovenol methyl ether(**15a**) in high yield.[22]

The asymmeric alkylation of **4** with methyl bromoacetate in the presence of chiral catalysts afforded the ester (**6a**) which had 63% e.e. of the (S)-enantiomer when compared by rotation with the optically pure material prepared from **7a**. Details will be reported separately.

COMMENTS- The overall yield of (-)-esermethole (**12a**) from **4** via **7**, **7a** and **10a**, and applicable to other oxindole ethers, such as **5**, is somewhat lower than that obtained in the asymmetric alkylation of **4** with chloroacetonitrile.[3] The route from **7a**, however, has the advantage that it uses a simple chemical resolution step with water as the solvent, which allows full recovery of the resolving agent. It gives at the same time an easy access to the unnatural (+)-enantiomer of **7a** which is ideally suited to further develop the unnatural (+)-series of the Calabar alkaloids.[22] In addition, the use of amides to perfect the formation of the indolopyrrolidine tricyclus allows great versatility with regard to the N^1-substituent in the N^1-substituted nor-alkaloids.

EXPERIMENTAL

Melting points were determined on ZMD-2 electroheating melting point apparatus. Optical rotations ($[\alpha]_D$) were mesured on Perkin-Elmer-241MC automatic polarimeter. ^{1}H-Nmr spectra were mesured on a EM306L (60 MHz) spectrometer and chemical shifts were 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 Science.

1,3-Dimethyl-5-methoxyoxindole-3-acetic acid (**7**). Methyl ester (**6**) (8 g, 30.3 mmol) was dissolved in methanol (200 ml) containing sodium hydroxide (10 g, 0.25 mmol), and the reaction mixture was stirred at room temperature for 2 h. The solvent was evaporated, the residue was rendered acidic with 3N HCl, then extracted with ethyl acetate, the EtOAc extract was dried ($MgSO_4$) and evaporated, to give colorless crystals of **7** (7.1 g, 28.5 mmol, 94%): mp 120-121 °C. (EtOAc) ^{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), 3.75 (s, 3H, O-CH_3), 6.77-6.90 (m, 3H, Ar-H), 10.35 (br, 1H, -COOH); Elms (m/z): 249 (M^+).

(-)-(3S)-1,3-Dimethyl-5-methoxyoxindole-3-acetic acid (**7a**). Acid (**7**) (7.1 g, 28.5 mmol) and brucine hydrate (13.3 g, 32.3 mmol) were dissolved in water (150 ml) under cautious warming. The clear solution was left standing for 12 h at room temperature and the brucine salt filtered, and crystallized three times from water, to afford optically pure brucine salt of **7a** (6.5 g): mp 115 °C (H_2O); $[\alpha]_D$ -33.2 ° (c 1.0, EtOH); Anal. Calcd for $C_{36}H_{42}N_3O_8 \cdot 4H_2O$: C 60.34, H 6.98, N 5.87; Found: C 60.59, H 6.81, N 5.87.

The brucine salt obtained above was dissolved in water (200 ml) under warming, 5N sodium hydroxide solution (30 ml) was added and the brucine which precipitated removed by filtration. The

brucine can be crystallized from acetone-water to afford material which is optically pure and can be reused. The filtrate was acidified with 2N HCl and acid (**7a**) was extracted with ethyl acetate, to afford after washing the extract with brine, drying ($MgSO_4$) and concentration the optically pure acid (**7a**) as colorless crystals (2.5 g, 35%): mp 124-125 °C(isopropyl ether); $[\alpha]_D$ -48.7 ° (c 0.96, $CHCl_3$); Anal. Calcd for $C_{13}H_{15}NO_4$: C 62.65, H 6.02, N 5.62; Found: C 62.25, H 5.89, N 5.55. The material is on tlc identical with racemic (**7**) (silica gel, CH_2Cl_2 with 1% MeOH).

(-)-(3S)-1,3-Dimethyl-5-methoxyoxindole-3-acetic acid methyl ester (**6a**). 266 mg (1.07 mmol) of compound (**7a**), 22.15 mg (1.61 mmol) of anhydrous K_2CO_3 were added to 15 ml of acetone, then 2 g (14.1 mmol) of CH_3I was added. The reaction mixture was stirred overnight at room temperature under N_2. After evaporation of solvent, the residue was partitioned between Et_2O and H_2O. The organic layer was washed by brine, dried over Na_2SO_4. Evaporation of solvent gave **6a** as an oil 230 mg (82.3%): $[\alpha]_D$ -19.9 ° (c 0.94, EtOH).

(-)-Physovenol methyl ether (**15a**). 230 mg (0.87mmol) of **6a** was dissolved in 6 ml of THF, and 48 mg (1.26 mmol) of LAH was added in portion. The mixture was stirred under N_2 for 1 h. The solvent was evaporated and residue was partitioned between 1.5% HCl and Et_2O. The organic layer was washed with brine, dried over Na_2SO_4 and evaporation to give **15a** as an oil 182 mg (95%): $[\alpha]_D$ -81.2 ° (c 0.6, EtOH) [lit., [22] -80.3 ° (c 0.6, EtOH)]; ms and ^{1}H-nmr were identical with those reported for the racemic compound.[19]

(-)-3a,8-Dimethyl-5-methoxy-3,3a,8,8a-tetrahydrofuro[2,3-*b*]indol-2-one (**9a**). Compound (**9a**) was made from **7a** as described in the racemic series:[20] mp 95-97 °C; $[\alpha]_D$ -48.7 ° (c 1.6, EtOH); ms and ^{1}H-nmr are identical with those of racemic compound.[20]

(-)-(3S)-1,3-Dimethyl-5-methoxyoxindole-3-acetonitrile (**8a**). 249 mg (1 mmol) of compound (**7a**) was dissolved in dry pyridine (5 ml) and cooled to 0 °C, and added dropwise with methanesulfonyl chloride (114.5 mg, 1 mmol). After 1 h dry ammonia gas was passed through the solution for 5 min, and excess ammonia was removed in the vacuum for 5 min. The solution was cooled to 0 °C and added with methanesulfonyl chloride (114.5 mg, 1 mmol) and stirred for 24 h at room temperature. The reaction mixture was then poured into 2N HCl under cooling and the pH adjusted to 7.0. Extraction with ethyl acetate, washing with brine, drying ($MgSO_4$) and removal of solvent afforded nitrile (**8a**) as a yellowish oil (219 mg, 95%): $[\alpha]_D$ +57.5 ° (c 0.5, $CHCl_3$); ^{1}H-nmr ($CDCl_3$): δ 1.52 (s, 3H, C3-CH_3), 2.71 (m, 2H, CH_2-CN), 3.24 (s, 3H, O-CH_3), 6.78-6.82 (m, 3H, Ar-H); Elms (m/z): 230 (M^+), 215 (M^+-CH_3), 190 (M^+-CH_2CN).

(3aS-cis)-N^1-Noresermethole (**14a**). Nitrile (**8a**) (784 mg, 3.4 mmol) was dissolved in THF (60 ml) and added with LAH (600 mg, 15.8 mmol). After stirring for 1 h at room temperature, the reaction mixture was refluxed for 10 min, the solvent was evaporated and the residue was dissolved in 2N HCl. The aqueous solution was washed with ether, then rendered alkaline with $NaHCO_3$, extracted

with ether, dried ($MgSO_4$), and concentrated in vacuum to 10 ml. The ether concentrate was added with a saturated alcoholic solution of fumaric acid (500 mg) to afford on standing the fumarate salt of (**14a**) (980 mg, 89%): mp 199-200 °C(EtOH/Et_2O); $[\alpha]_D$ -73 ° (c 0.7, MeOH); ^{1}H-nmr is identical with that reported in the lit.[21].

(-)-(3S)-1,3-Dimethyl-5-methoxy-3-acetic acid methylamide (10a). In a sealed tube was added compound (**7a**) (230 mg, 0.92 mmol), methyl isocyanate (114 mg, 2 mmol) and triethylamine (5 mg, 0.05 mmol) in dry toluene (2 ml). The sealed tube was heated in an oil bath and the reaction mixture was stirred with magnetic stirrer for 2.5 h, while the temperature of the oil bath was kept at about 70 °C. Then the tube was opened, the mixture was stirred for another 1 h and the temperature was kept at 90 °C at same time. After evaporation of solvent the residue was dissolved in $CHCl_3$ (2.5 ml), washed with 1N NaOH (0.5 ml) and brine and dried over $MgSO_4$. Evaporation of $CHCl_3$ gave crude product which was recrystallized from hexane to give the methylamide (**10a**) as crystals (169 mg, 70%): mp 148-149 °C; $[\alpha]_D$ -29.6 ° (c 0.5, $CHCl_3$); Elms (m/z): 262 (M^+); ^{1}H-nmr ($CDCl_3$): δ 1.35 (s, 3H, CH_3), 2.60-2.80 (m, 2H,-CH_2-CO-), 2.85 (s, 3H, $NHCH_3$), 3.17 (s, 3H, N-CH_3), 3.76 (s, 3H, -O-CH_3), 6.70-6.90 (m, 3H, Ar-H). Anal. Calcd for $C_{14}H_{18}N_2O_3$: C 38.13, H 6.91, N 10.68; Found: C 38.10, H 7.10, N 10.51.

(-)-(3S)-1,3-Dimethyl-5-methoxyoxindole-3-acetic acid benzylamide (11a). The benzylamide (**11a**) was prepared as described for the preparation of **10a**, using benzyl isocyanate instead of methyl isocyanate. Compound (**11a**) was obtained as crystals (80.2%): mp 104-105 °C (isopropyl ether); $[\alpha]_D$ -48.9 ° (c 1.0, $CHCl_3$); Elms (m/z): 338 (M^+); ^{1}H-nmr ($CDCl_3$): δ 1.20 (s, 3H, -CH_3), 4.20-4.50 (m, 2H, Ph-CH_2), 6.50-7.50 (m, 8H, Ar-H). Anal. Calcd for $C_{20}H_{22}N_3O_3$: C 70.98, H 6.55, N 8.28; Found: C 70.9, H 6.70, N 8.14.

(-)-O-Methyleseroline (12a). A. Compound (**12a**) was made from lactone (**9a**) as described in lit.[20]. B. LAH (72 mg, 1.89 mmol) was added to THF (2 ml) and heated in an oil bath to reflux with stirring under N_2. The methylamide (**10a**) (160 mg, 0.61 mmol) in THF (1 ml) was added dropwise into the above reflux mixture during 0.5 h. After stirring for 1 h at reflux the reaction mixture was cooled to room temperature, then saturated brine was added dropwise until no more H_2 evolution was evident. The residue (its TLC showed 2 spots) was chromatoggraphed on silica gel (CH_2Cl_2/MeOH, 100:1) to give the less polar major product as a gum, which was added to a saturated alcoholic solution of fumaric acid (79 mg, 0.68 mmol)) and left overnight in refrigerator to give the fumarate salt of **12a** (127 mg, 60%): mp 135-136 °C; $[\alpha]_D$ -98 ° (c 1, MeOH): ms and ^{1}H-nmr are identical with (+)-O-methyleseroline fumarate.[15]

(-)-N^1-Benzyl-O-methylnoreseroline (13a). Compound (**13a**) was similarly prepared from **11a** as described for the preparation of **12a**. Chromatography gave the less polar major product (**13a**) as an oil (65%): $[\alpha]_D$ -50.1 ° (c 1, $CHCl_3$): ms and ^{1}H-nmr are identical with a standard sample.[19]

ACKNOWLEDGEMENT

We would like to thank Dr. Xiao-shu He for excellent technical assistance, and to Drs. Harold Stern and Danilo Massari of ExPharma, Padova, Italy, for financial support.

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Received, 9th November, 1992