SYNTHESIS OF 6'-METHYLATED RETICULINES AND TETRAHYDROPAPAVEROLINES

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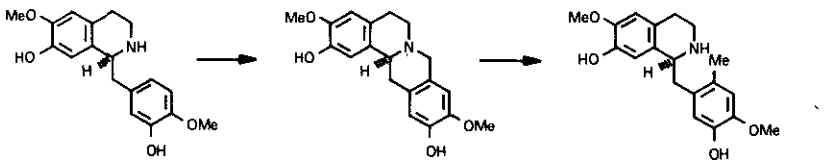
Abstract —— Racemic 6'-methylreticuline and the racemate and both enantiomers of 6'-methyl-N-norreticuline and 6'-methyltetrahydropapaveroline were synthesized from the appropriate isomers of coreximine diacetate (1). Reduction of crystalline chloromethylcarbamate 2 with LAH gave (±)-6'-methylreticuline (5) directly. Hydrogenation of (±)-2 and the optical isomers followed by hydrazinolysis provided the corresponding 6'-methyl-N-norreticulines (6, 6a, 6b) which were converted to the racemate and enantiomers of 6'-methyltetrahydropapaveroline (8, 8a, 8b) by O-demethylation with 48% hydrobromic acid.

The interaction of 1-benzyl-substituted tetrahydroisoquinolines (TIQ) and tetrahydropapaverolines (THP) with dopaminergic and adrenergic receptors appears to require specific molecular conformations.[1,2]

Restricting the rotation of the benzyl substituent of TIQ and THP by incorporation into rigid polycyclic systems has, as far as explored, not afforded compounds which would interact specifically with ß-adrenergic receptor sites.[3] Hindering the rotation of the 1-benzyl group around the C_1-C_9-axis, another possibility to retain conformers in restricted form, can be achieved by introducing substituents in either of the two aromatic moieties of 1-benzyl-TIQ. The improved selectivity for ß-adrenergic receptors of 5-methyltrimetoquinol[4] may well be the result of the formation of a preferred conformation. Evidence that increased specificity for adrenergic receptors also can be obtained by substituting the aromatic moiety of the benzyl substituent was recently found with 6'-bromo-N-norreticulines[3,5] which showed more ß-adrenergic specificity than the parent compounds. To further explore the effects of steric hinderance in 1-benzyl-substituted TIQ, we have prepared 6'-methyl-substituted analogs, in which the bromine atom is replaced by a methyl group. TIQ alkaloids, substituted in the aromatic part of the 1-benzyl substituent with a hydroxymethyl[6] or a formyl group[7] are known, but their methyl congeners have not been reported.

We now describe a facile synthesis of (±)-6'-methylreticuline (5), the racemate and the enantiomers of the nor-analogs 6, 6a, 6b and the corresponding 6'-methyltetrahydropapaverolines (8, 8a, 8b). As illustrated below, 6b was obtained from S-(-)-N-norreticuline, via S-(-)-coreximine.

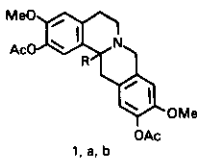


S-(−)-N-Norreticuline S-(−)-Coreximine S-(+)-6'-Methyl-N-norreticuline

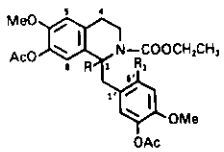
An opening of the berbine bridge in coreximine diacetate (1) with a chloroformate, previously explored in principle by Hanaoka et al.[7], and by us in connection with another project,[8] afforded the crystalline chloride 2, further converted into the methyl-substituted derivative 3 by catalytic hydrogenation over Pd/C-catalyst. Conversion of the diacetate 3 into the required TIQ was accomplished as follows: Reduction of 3 with LAH in THF directly afforded (±)-6'-methylreticuline (5), and treatment of 3 with refluxing 80% hydrazine[9] for 5 days gave a mixture of (±)-6'-methyl-N-norreticuline (6) and its 4'-O-demethyl-congener 7, readily separated by column chromatography over silica gel. The structure of the slower moving triol 7 was secured by electron impact mass spectroscopy, which showed the expected fragmentation. O-Demethylation of 6 or 7 with refluxing 48% HBr afforded identical samples of (±)-6'-methyl-THP (8) as the hydrobromide salt.
Repetition of these reaction sequences with R-(+)-coreximine diacetate (1a), prepared from R-(+)-coreximine[10], and its S-(-)-enantiomer 1b, prepared from S-(-)-coreximine[10] afforded 6a and 6b, respectively. O-Demethylation of 6a and 6b afforded 8a and 8b, respectively.
It is interesting to note that 6a, corresponding in absolute configuration to R-(+)-N-norreticuline showed a negative specific rotation of $[\alpha]_D^{20}$ -10.4° (c 1.4, $CHCl_3$), which may indicate a substantially different solution conformation of R-(-)-6a relative to R-(+)-N-norreticuline. The results of the biological screening of 8, 8a and 8b will be reported elsewhere.

EXPERIMENTAL

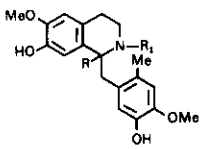
Melting points were taken on a Fisher-Johns apparatus and are uncorrected. Elemental analyses were performed by the Section on Microanalytical Services and Instrumentation of this laboratory. Optical rotations were measured by using a Perkin-Elmer Model 241 polarimeter with solvents and concentrations specified. The IR spectra were determined by using a Beckman 4230 instrument. ^1H NMR spectra were obtained on Varian HR-220 and JEOL FX-100 spectrometers with Me_4Si as the internal reference. Intermediate range pH strips (pH 0-6 and 5-10) from Aldrich Chemical Company, Inc. Milwaukee, WI. were used for pH determinations. Chemical ionization mass spectra (CI-MS) were determined by using a Finnigan 1015D spectrometer with a Model 6000 data collection system. Electron ionization mass



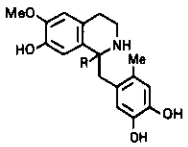
1, a, b



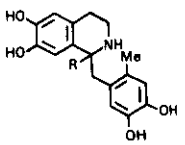
2, a, b, R_1 = CH_2Cl
3, a, b, R_1 = Me



4, R_1 = $COOCH_2CH_3$
5, R_1 = Me
6, a, b, R_1 = H



7, a, b,



8, a, b,

Rac . R = H
a R-, R = —H
b . S-, R = ■ H

spectra (EI-MS) were obtained with a Hitachi-Perkin-Elmer RMU-6E spectrometer (70 ev). Silica gel GF thin layer chromatography plates for analytical and preparative purposes were purchased from Analtech, Inc., Newark, DE.

(±)-3',7-Diacetoxy-6'-methyl-4',6-dimethoxy-1,2,3,4-tetrahydro-2-ethoxycarbonyl-1-benzyl-isoquinoline (3):

A mixture of 2[8] (7.6 g, 14.6 mmol) and Pd-C(10%) catalyst (2.5 g) in glacial acetic acid (110 ml) was hydrogenated at 50 psi at room temperature for 21 h. The catalyst was filtered, washed with glacial acetic acid (3 x 10 ml) and the filtrate was diluted with a large excess of water (800 ml) and extracted with a mixture of $CHCl_3$-isopropanol (3:1, 5 x 200 ml). The combined organic layer was concentrated to 50 ml and then washed with water (3 x 20 ml). The organic layer was dried ($MgSO_4$) and the solvent was removed in vacuo to leave an oily residue, which was digested with ether (50 ml) to afford 3 as white crystals (6.1 g, 89%): mp 142°C; IR ($CHCl_3$): 1760 (O-acetate), 1690 (carbamate) and 1620 (aromatic) cm^{-1}; ^1H NMR ($CDCl_3$, for the mixture of rotamers): δ 1.01 and 1.06 (2t, 3H, $CH_2\underline{CH_3}$), 2.03 (s, 3H, Ar.Me) 2.20 and 2.22 (2s, each 3H, 2 OAc), 2.51-3.49 (m, 6H, 3 CH_2), 3.66 and 3.70 (2s, each 3H, 2 OMe), 4.00 (m, 1H, Ar.CH.N) and 6.44-6.76 (m, 4H, 4 Ar.H); EI-MS m/e 485 (M^+); CI-MS (NH_3) m/e 486 (M^++1); Anal. Calcd. for $C_{26}H_{31}NO_8$: C, 64.31; H, 6.43; N, 2.88. Found: C, 64.23; H, 6.52; N, 2.85%.

(±)-6'-Methyl-N-ethoxycarbonyl-N-norreticuline (4), (±)-6'-Methyl-N-norreticuline (6) and (±)-6-Methyl-N-nor-4'-demethyl-N-norreticuline (7):

A solution of 3 (3.1 g, 6.39 mmol) in 80% hydrazine (110 ml) was heated to solution and then heated for 5 days (oil bath temperature 120°C), under an argon atmosphere. The reaction mixture was cooled and concentrated under vacuum to leave a residue, which was treated with 2% aqueous HCl solution (60 ml) and washed with ether (3 x 20 ml) (neutral fraction, 300 mg). The aqueous acidic layer was basified with concentrated aqueous ammonia (pH 9) and extracted with a mixture of $CHCl_3$-isopropanol (3:1, 3 x 50 ml). The combined organic layer was dried ($MgSO_4$) and the solvent was evaporated to leave a residue (1.02 g, basic fraction).

The neutral fraction was purified by crystallization from a mixture of CH_2Cl_2-ether to afford 4 (230 mg, 9%) as a white solid: mp 183°C; IR ($CHCl_3$): 3560 (OH), 1685 (carbamate) and 1600 (aromatic) cm^{-1}; ^1H NMR ($CDCl_3$, for the mixture of rotamers): δ 1.02 and 1.22 (2t, 3H, $CH_2\underline{CH_3}$), 2.16 (s, 3H, ArMe), 2.48-3.56 (m, 6H, 3 CH_2), 5.24 (m, 1H, Ar.CH.N), 6.40 (s, 1H, Ar.H), 6.48 (s, 1H, Ar.H) and 6.52 (S, 2H, 2 Ar.H); CIMS (NH_3) m/e 402 (M^++1); Anal. Calcd. for $C_{22}H_{27}NO_6$: C, 65.81; H, 6.77; N, 3.48. Found: C, 65.63; H, 6.90; N, 3.46%.

The basic fraction was purified by column chromatography over silica gel eluting with a mixture of $CHCl_3$-MeOH (9:1) to afford a fraction which was crystallized from a mixture of CH_2Cl_2-ether to afford pure 6 (400 mg, 19%): mp 107°C; IR ($CHCl_3$): 3560 (OH) and 1600 (aromatic) cm^{-1}; ^1H NMR ($CDCl_3$ + CD_3OD (3:1)): δ 2.30 (s, 3H, Ar.Me), 2.50-3.40 (m, 6H, 3 CH_2), 3.86 (s, 6H, 2 OMe), 4.03 (m, 1H, Ar.CH.N), 6.57 (s, 1H, Ar.H), 6.67 (s, 1H, Ar.H) and 6.74 (s, 2H, Ar.H); CIMS (NH_3) m/e 330 (M^++1); Anal. Calcd. for $C_{19}H_{23}NO_4 \cdot 1/2\ H_2O$: C, 67.43; H, 7.14; N, 4.13. Found:

C, 67.18; H, 7.40; N, 4.51%

Further elution of the column with a mixture of $CHCl_3$-MeOH (8:2) afforded a residue, which on crystallization from acetone gave pure 7 (225 mg, 11%): mp 165°C; IR(KBr): 3440(OH) and 1610 (aromatic) cm^{-1}; ^1H NMR (CD_3OD): δ 2.13 (s, 3H, Ar.Me), 2.53-3.04 (m, 6H, 3 CH_2), 3.76 (s, 3H OMe), 3.96 (m, 1H, Ar.CH.N), 6.52 (s, 1H, Ar.H), 6.56 (s, 2H, 2 Ar.H) and 6.60 (s, 1H, Ar.H); CI-MS (NH_3) m/e 316 (M^++1); Anal. Calcd. for $C_{18}H_{21}N\,O_4.1/2\,H_2O$: C, 66.64; H, 6.83; N, 4.31. Found: C 66.87; H, 6.52; N, 4.45%.

(±)-6'-Methyl-N-ethoxycarbonyl-N-norreticuline (4):

A mixture of 3 (760 mg, 1.56 mmol) and MeOH (5 ml) was heated to solution, treated with 2% aqueous NaOH solution (10 ml), H_2O (5 ml), $CHCl_3$ (10 ml), and stirred at room temperature for 1 h. The organic solvents were evaporated in vacuo and the remaining basic aqueous layer was washed with $CHCl_3$ (3 x 10 ml), rendered acidic with dilute HCl solution (pH 5) and then extracted with $CHCl_3$ (3 x 10 ml). The combined organic layer was washed with water (2 x 10 ml), dried (Na_2SO_4) and concentrated in vacuo to leave an oily residue, which was crystallized with ether to afford 4 as a colorless solid (568 mg, 91%); identical in all respects with the material obtained as described above.

(±)-6'-Methylreticuline (5):

A solution of 3 (300 mg, 0.61 mmol) in dry THF (10 ml) was added dropwise to a refluxing mixture of LAH (200 mg) in dry THF (20 ml) and the resulting suspension was refluxed for 6 h. The reaction mixture was cooled and concentrated aqueous NH_3 solution (1.25 ml) was added cautiously to yield a grey precipitate. The reaction mixture was stirred at room temperature for 30 min, filtered, and the solid was washed with THF (4 x 5 ml). The solid was dissolved in 10% aqueous NaOH solution, acidified with concentrated HCl (pH 1) and then rendered alkaline with concentrated aqueous NH_3 (pH 9). The reaction mixture was treated with $CHCl_3$ (20 ml), shaken well and the resulting emulsion was filtered through celite (2 g). The celite and solid were extracted with a warm mixture of $CHCl_3$-isopropanol (3:1) (5 x 15 ml). The organic layer was separated, washed with water (2 x 10 ml), dried (Na_2SO_4), evaporated to afford a crude residue (250 mg), which was purified by preparative TLC over silica gel in CH_2Cl_2-MeOH (8.5:1.5) to afford a solid residue which was crystallized from a mixture of CH_2Cl_2-petroleum ether to afford a pure 5 (150 mg, 72%) as a white solid: mp 163°C; IR ($CHCl_3$): 3550 (OH) and 1600 (aromatic) cm^{-1}; ^1H NMR ($CDCl_3$): 2.04 (s, 3H, Ar.Me), 2.44 (s, 3H, N.Me), 2.60-3.44 (m, 6H, 3 CH_2), 3.64 (m, 1H, Ar.CH.N), 3.84 (s, 6H, 2 OMe), 6.16 (s, 1H, Ar.H), 6.52 (s, 1H, Ar.H), 6.60 (s, 1H, Ar.H) and 6.72 (s, 1H, Ar.H); CI-MS (NH_3) m/e 344 (M^++1); Anal. Calcd. for $C_{20}H_{25}NO_4.1/2H_2O$: C, 68.15; H, 7.43; N, 3.97. Found: C, 68.53; H, 7.18; N, 4.09%.

(±)-6'-Methyltetrahydropapaveroline.hydrobromide (8.HBr) From 6:

A solution of 6 (100 mg, 30 mmol) in aqueous HBr (48%, reagent grade, 5 ml) was refluxed for 2.5 h under an argon atmosphere. The reaction mixture was cooled and concentrated under high vacuum to leave a residue, which on crystallization from a mixture of EtOH-ether afforded pure 8.HBr (82 mg, 71%): mp 251°C (d); IR (KBr): 3360 (OH) and 1610 (aromatic) cm^{-1}; ^1H NMR (CD_3OD): δ 2.08 (s, 3H, Ar.Me), 2.48-3.68 (m, 6H, 3 CH_2), 4.44 (m, 1H, Ar.CH.N), 6.37 (s, 1H, Ar.H), 6.57 (s, 1H, Ar.H)

and 6.60 (s, 2H, 2 Ar.H); CI-MS (CH_4) m/e 302 (M^++1); Anal. Calcd. for $C_{17}H_{20}NO_4Br$: C, 53.42; H, 5.27; N, 3.66; Br, 20.90. Found: C, 52.87; H, 4.93; N, 3.52; Br, 20.52%.

From 7: Treatment of 7 (20 mg, 0.06 mmol) with 48% aqueous HBr as described above, gave a residue after concentrating the reaction mixture under high vacuum, which was crystallized from EtOH-ether to afford pure 8.HBr (16 mg, 84%); mp 251°C (d); identical in all respects with the authentic sample, prepared earlier.

R-(+)-Coreximinediacetate (1a):

A solution of R-(+)-coreximine[10] (2.6 g, 7.95 mmol) in pyridine (76 ml) and acetic anhydride (22 ml) was stirred at room temperature for 21 h. The reaction mixture was concentrated under reduced pressure to leave an oily residue, which was taken up in toluene (5 ml) and concentrated under reduced pressure (this process was repeated 3 times to remove the traces of pyridine and acetic anhydride) to afford a solid residue. This residue was treated with water (50 ml) and the mixture was extracted with $CHCl_3$ (3 x 20 ml). The combined organic extracts were dried (Na_2SO_4) and the solvent was evaporated to leave a residue, which was crystallized from a mixture of CH_2Cl_2-ether to afford 1a (2.9 g, 90%): mp 197°C; $[a]_D^{20}$ +211.3° (c 0.52, $CHCl_3$): superimposable with 1; ^1H NMR ($CDCl_3$): δ 2.30 (s, 3H, OAc), 2.32 (s, 3H, OAc), 2.51-3.70 (m, 8H, 4 CH_2), 3.76 (s, 3H, OMe), 3.80 (s, 3H, OMe), 3.95 (m, 1H, Ar.CH.N), 6.64 (s, 1H, Ar.H), 6.68 (s, 1H, Ar.H), 6.76 (s, 1H, Ar.H) and 6.88 (s, 1H, Ar.H); EI-MS m/e 411 (M^+); Anal. Calcd. for $C_{23}H_{25}NO_6$: C, 67.13; H, 6.12; N, 3.40. Found: C, 66.92; H, 6.31; N, 3.41%.

R-(+)-6'-Chloromethyl-3',7-diacetoxy-4',6-dimethoxy-1-benzyl-1,2,3,4-tetrahydro-2-ethoxycarbonyl-isoquinoline (2a):

A mixture of 1a (2.4 g, 5.83 mmol) in $CHCl_3$ (EtOH free, 25 ml) and ethyl chloroformate (95 ml) was refluxed for 44 h (oil bath temperature 110°C) until TLC showed the absence of 1a. The reaction mixture was concentrated under reduced pressure to leave a residue, which was treated with 2% aqueous HCl solution (50 ml) and extracted with ether (3 x 20 ml). The combined ether extracts were washed with water (2 x 10 ml), dried (Na_2SO_4) and concentrated in vacuo to afford an oily residue (3.0 g): CI-MS (NH_3) m/e 520 (M^++1).

R-(+)-6'-Methyl-3',7-diacetoxy-4',6-dimethoxy-1-benzyl-1,2,3,4,-tetrahydro-2-ethoxycarbonyl-isoquinoline (3a):

A mixture of 2a (3.0 g, 5.78 mmol) in glacial acetic acid (65 ml) and Pd/C (10%, 900 mg) was hydrogenated at 50 psi at room temperature until the starting material completely disappeared by TLC. (67 h). The reaction mixture was worked up as described above for the preparation of 1 to afford a crude oily residue (2.9 g), which was purified by filtration through silica gel on elution with a mixture of CH_2Cl_2-MeOH (9.93:0.08) to afford a colorless oily residue 3a (2.5 g) (mixture of rotamers): CI-MS (NH_3) m/e 486 (M^++1).

R-(-)-6'-Methyl-N-norreticuline (6a):

A solution of 3a (2.5 g, 5.15 mmol) in 80% hydrazine (40 ml) was heated (oil bath temperature 120°C) for 5 days under an argon atmosphere. The reaction mixture was worked up as described earlier for the preparation of 6, to afford the basic fraction as solid residue (900 mg), which was chromatographed over silica gel and eluted with a mixture of $CHCl_3$-MeOH (9:1) to afford a nearly

pure solid (500 mg). Crystallization from a mixture of CH_2Cl_2-ether yielded pure 6a (379 mg, 24%): mp 178°C; $[\alpha]_D^{20}$ -10.4° (c 1.4, $CHCl_3$); IR ($CHCl_3$): superimposable with 6; ^1H NMR ($CDCl_3$): δ 2.28 (s, 3H, Ar.Me), 2.64-3.34 (m, 6H, 3 CH_2), 3.82 (s, 6H, 2 OMe), 4.00 (m, 1H, Ar.CH.N), 6.56 (s, 1H, Ar.H) 6.64 (s, 1H, Ar.H), 6.72 (s, 1H, Ar.H) and 6.76 (s, 1H, Ar.H); CIMS (NH_3) m/e 330 (M^++1); Anal. Calcd. for $C_{19}H_{23}NO_4.H_2O$: C, 65.68; H, 7.25; N, 4.03. Found: C, 65.38; H, 7.34; N, 4.22%.

R-(-)-6'-Methyltetrahydropapaveroline hydrobromide (8a.HBr):

A solution of 6a (100 mg, 0.30 mmol) in aqueous HBr (48%, reagent grade, 6 ml) was refluxed (oil bath temperature 110°C) under an argon atmosphere for 4 h. The reaction mixture was worked up as described above for the preparation of 8, to afford a solid residue (111 mg, 97%), which was crystallized from a mixture of EtOH-CH_2Cl_2 to afford pure 8a.HBr (109 mg, 94%): mp 195°C; $[\alpha]_D^{20}$ -31.0° (c 0.53, MeOH); IR (KBr): superimposable with 8; ^1H NMR (CD_3OD): δ 2.08 (s, 3H, Ar.Me), 2.56-3.80 (m, 6H, 3 CH_2), 4.44 (m, 1H, Ar.CH.N), 6.37 (s, 1H, Ar.H), 6.57 (s, 1H, Ar.H) and 6.60 (s, 2H, 2 x Ar.H); CIMS (NH_3): m/e 302 (M^++1); Anal. Calcd. for $C_{17}H_{20}NO_4Br.3H_2O$: C, 46.90; H, 5.78; N, 3.21; Br, 18.35. Found: C, 46.57; H, 5.62; N, 3.05; Br, 18.20%.

S-(-)-Coreximine diacetate (1b):

Treatment of S-(-)-coreximine[10] (4.3 g, 13.1 mmol) with pyridine (120 ml) and acetic anhydride (35 ml) and workup as described above for 1a, afforded a solid residue, which was crystallized from a mixture of CH_2Cl_2-ether to afford pure yellowish 1b (4.3 g, 80%): mp 198°C; $[\alpha]_D^{20}$ -211.2° (c 0.5, $CHCl_3$), IR ($CHCl_3$): superimposable with that of 1a; ^1H NMR ($CDCl_3$): δ 2.30 (s, 6H, 2 OAc), 2.46-4.04 (m, 9H, 4 CH_2 and Ar.CH.N), 3.78 (s, 6H, 2 OMe), 6.40 (s, 1H, Ar.H), 6.68 (s, 1H, Ar.H), 6.78 (s, 1H, Ar.H) and 6.88 (s, 1H, Ar.H); CI-MS (CH_4) m/e 412 (M^++1); Anal. Calcd. for $C_{23}H_{25}NO_6$: C, 67.13; H, 6.12; N, 3.40. Found: C, 66.93; H, 6.02; N, 3.25%.

S-(-)-6'-Chloromethyl-3',7-diacetoxy-4',6-dimethoxy-1-benzyl-1,2,3,4,-tetrahydro-2-ethoxycarbonyl-isoquinoline (2b):

A solution of 1b (4.2g, 10.21 mmol) in $CHCl_3$ (50 ml, EtOH free) and ethyl chloroformate (220 ml) was treated as for 1a above to afford an oily residue of 2b (5.78 g): (mixture of two rotamers); CI-MS (CH_4) m/e 520 (M^++1).

S-(-)-3',7-Diacetoxy-6'-methyl-4',6-dimethoxy-1-benzyl-1,2,3,4-tetrahydro-2-ethoxycarbonyl-isoquinoline (3b):

A mixture of 2b (5.7 g, 10.98 mmol) in glacial acetic acid (175 ml) and Pd/C (10%, 2.5 g) was hydrogenated at 50 psi overnight and worked up as described earlier in case of 3, to afford an oily residue 3b (4.67 g) (mixture of rotamers): CI-MS (NH_3) m/e 468 (M^++1).

S-(+)-6'-Methyl-N-norreticuline (6b):

Treatment of 3b (4.0 g, 8.56 mmol) with 80% hydrazine (66 ml) for 5 days as in the preparation of 6, gave a crude residue which was purified by column chromatography over silica gel exactly as described above for 6a. The residue was crystallized from a mixture of CH_2Cl_2-ether to afford 6b (600 mg, 21%): mp 179°C; $[\alpha]_D^{20}$ +10.2° (c 1.45, $CHCl_3$); IR($CHCl_3$): superimposable with that of 6; ^1H NMR ($CDCl_3$): δ 2.28 (s, 3H, Ar.Me), 2.56-3.32 (m, 6H, 3 CH_2), 3.84 (s, 6H, 2 OMe), 4.00 (m, 1H, Ar.CH.N), 6.56(s, 1H, Ar.H), 6.66 (s, 1H, Ar.H) and 6.76 (s, 2H, 2 Ar.H); CI-MS (NH_3) m/e 330

(M^++1); Anal. Calcd. for $C_{19}H_{23}NO_4.H_2O$: C, 65.68; H, 7.25; N, 4.03. Found: C, 66.01; H, 6.87; N, 4.08%.

S-(+)-6'-Methyltetrahydropapaveroline hydrobromide (8b.HBr):

A solution of 6b (100 mg, 0.30 mmol) in 48% aqueous HBr (5 ml) was treated as described earlier for 8.HBr, to afford 8b.HBr (80 mg, 70%): mp 194°C; $[\alpha]_D^{20}$ +30.4° (c, 0.53, MeOH); IR (KBr): superimposable with that of 8; ^{1}H NMR (CD_3OD): δ 2.08 (s, 3H, Ar.Me), 2.52-3.60 (m, 6H, 3 CH_2), 4.48 (m, 1H, Ar.CH.N), 6.38 (s, 1H, Ar.H), 6.58 (s, 1H, Ar.H) and 6.62 (s, 2H, 2 Ar.H); CI-MS (NH_3): m/e 302 (M^++1); Anal. Calcd. for $C_{17}H_{20}NO_4Br.2H_2O$: C, 48.93; H, 5.55; N, 3.35; Br. 19.14. Found: C, 48.57; H, 5.81; N, 3.20; Br, 19.04%.

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