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EXPERIMENTAL DETAILS

Exceptionally Potent Antispermatogenic Compounds from 8-Halogenation of (4a*RS*,5*SR*,9b*RS*)Hexahydroindeno[1,2-c]pyridines

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Synthesis of (4a*RS*,5*SR*,9b*RS*)-2-Ethyl-2,3,4,4a,5,9b-hexahydro-8-iodo-7-methyl-5-(4-carbomethoxyphenyl)-1H-indeno[1,2-c]pyridine Hydrochloride (2b) and **its (*l*)-enantiomer ((*l*)-2b).** *Method A.* To a stirred solution of **1b**, (4a*RS*,5*SR*,9b*RS*)-2-ethyl-2,3,4,4a,5,9b-hexahydro-7-methyl-5-(4-carbomethoxyphenyl)-1H-indeno[1,2-c]pyridine (341 mg, 0.88 mmol) in glacial acetic acid (2 mL) was added 62% $HClO_4$ (1 mL) followed by HgO (205 mg, 0.95 mmol). The mixture was briefly sonicated in order to effect a homogeneous solution. A solution of iodine (235 mg, 0.925 mmol) in glacial acetic acid (17 mL) was added dropwise over 15 min and the resulting mixture was stirred at room temperature overnight. The orange-red mixture was poured into water (100 mL), cooled to 5°C, basified to pH 12 with 30% NaOH, and extracted with ether (3 x 75 mL). The clear, colorless ether extracts were combined, washed successively with water (20 mL) and brine (30 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo to afford the crude free base of **2b** (448 mg). The free base was transformed into the HCl salt using 3% methanolic hydrogen chloride and recrystallized from EtOAc-MeOH to give 400 mg (89%) of **2b**. m.p. = >190°C (dec.). See below for analytical data. The active enantiomer, **(*l*)-2b**, was synthesized in a similar fashion starting from **(*l*)-1b**. $[\alpha]_D$ = -5.6 (c = 1.18, $CHCl_3$).

Method B. Acid **2a** (181 mg, 0.39 mmol) was dissolved in 7.0 mL of methanol and then filtered into a 50 mL flask equipped with drying tube and addition funnel. The solution was cooled in an acetone/dry ice bath and $SOCl_2$ (722 mg, 6.07 mmol) was added dropwise. The solution was allowed to warm to room temperature and stirred overnight. Solvent was evaporated and the residue was neutralized with NaOH (10%), extracted with CH_2Cl_2 and vacuum dried, leaving 164 mg of yellowish oil. Flash column chromatography on silica ($CHCl_3$:MeOH, 50:1) provided 108 mg free base as yellowish solid. The free base was acidified with ethereal HCl to give **2b**: ^{1}H NMR (250 MHz, $CHCl_3$) δ 1.18 (3H, t, J=7.2 Hz), 1.67 (1H, bd), 2.08 (2H, m), 2.32 (3H, s), 2.38 (1H, bs), 2.50-2.55 (3H, m), 2.86 (1H, m), 3.02 (1H, m), 3.45 (1H, m), 3.92 (3H, s), 4.17 (1H, d, J=10.0), 6.78 (1H, s), 7.24 (2H, d, J=8.2 Hz), 7.72 (1H, s), 8.00 (2H, d, J=8.2). HRMS: Calcd. For $C_{23}H_{26}NO_2I$ (corresponding to the free base): m/z 475.1008. Found: m/z 475.1004. Anal. Calcd for $C_{23}H_{27}ClINO_2$: C, 54.00; H, 5.32; N, 2.74; Total halogen as Cl, 13.68. Found: C, 53.82; H, 5.29; N, 2.70; Total halogen as Cl, 13.92.

Synthesis of (4a*RS*,5*SR*,9b*RS*)-2-Ethyl-2,3,4,4a,5,9b-hexahydro-8-iodo-7-methyl-5-(4-carboxyphenyl)-1H-indeno[1,2-c]pyridine Hydrochloride (2a). *Method C.* Methyl ester **2b** prepared by Method A above (200 mg, 0.47 mmol) was refluxed for 4 hr in 40 mL of 9% HCl solution. Solvent was evaporated under reduced pressure and the residue was taken up in CH_2Cl_2. The CH_2Cl_2 extract was washed with brine, dried over $MgSO_4$, filtered and concentrated. Flash column chromatography on silica ($CHCl_3$:MeOH, 10:1) followed by recrystallization from CH_2Cl_2/MeOH (8:2) gave the acid **2a**, ^{1}H NMR (250 MHz, $CDCl_3/CD_3OH$) δ 1.38 (3H, t, J=7.2 Hz), 2.0-2.1 (1H, m), 2.33 (3H, s), 2.66 (2H, m), 3.19 (3H, m), 3.40 (1H, m), 3.60 (2H, m), 4.36 (1H, d, J=9.3 Hz), 6.89 (1H, s), 7.26 (2H, d, J=8.2 Hz), 7.89 (1H, s), 7.97

(2H, d, J=8.3 Hz). HRMS Calcd for $C_{22}H_{24}NO_2I$ (corresponding to the free base): m/z 461.0852. Found: m/z 461.0857. Anal. Calcd for $C_{22}H_{25}ClINO_2$: C, 53.11; H, 5.07; N, 2.82; Total halogen as Cl, 14.08. Found: C, 53.30; H, 5.08; N, 2.72; Total halogen as Cl, 14.17.

Method D. To a solution of **1a,** (4a*RS*,5*SR*,9b*RS*)-2-Ethyl-2,3,4,4a,5,9b-hexahydro-7-methyl-5-(4-carboxyphenyl)-1H-indeno[1,2-c]pyridine hydrochloride (250 mg, 0.673 mmol) in 2mL of acetic acid was added 6 mL of a 1:1 mixture of acetic acid and perchloric acid. HgO (1.35 mmol) was added and the reaction mixture was stirred at room temperature until the HgO dissolved. A solution of I_2 (427 mg, 1.68 mmol) in 4 mL of acetic acid and 6 mL of CH_2Cl_2 was added dropwise to the reaction mixture by addition funnel. The reaction mixture was stirred overnight at room temperature and then filtered through celite. The red solid was washed with water and CH_2Cl_2. The combined biphasic filtrate was separated by separatory funnel. The organic phase was washed with saturated sodium bisulfite solution, dried over sodium sulfate (anhydrous), filtered and concentrated to give 234 mg of free base as yellowish brown solid which was converted to the hydrochloride **2a** in the usual way.

Synthesis of (4a*RS*,5*SR*,9b*RS*)-2-ethyl-8-bromo-7-methyl-2,3,4,4a,5,9b-hexahydro-5-(4-carboxyphenyl)-1H-indeno[1,2-c]pyridine hydrochloride (3a). (4aRS,5SR,9bRS)-2-Ethyl-8-iodo-7-methyl-2,3,4,4a,5,9b-hexahydro-5-(4-carboxylphenyl)-1H-indeno[1,2-c]pyridine hydrochloride (200 mg, 0.402 mmol) was dissolved in 20 mL THF and 0.4 mL hexamethylphosphoramide. To this solution was added 50 mg sodium hydride (60% in mineral oil). The mixture was refluxed for 1 h and then cooled to -78°C. *Tert*-Butyllithium solution (0.73 mL, 1.1 M in pentane, 0.804 mmol) was added slowly. After the addition the mixture was stirred at -78°C for 20 min. 1,2-Dibromoethane (1 mL) was added. The mixture was stirred at -78°C for another 30 min and then warmed to room temperature. 5% hydrochloric acid was added to the solution until the solution became acidic. The mixture was extracted with methylene chloride. The methylene chloride solution was washed with brine and dried over $MgSO_4$. The crude product was purified with flash column chromatography(silica, CH_2Cl_2:MeOH, 10:1) to afford the title compound **3a**: 30 mg, 17% yield. m.p., 169.6-170.3 °C. ^{1}H NMR (250 MHz, D_2O-$CDCl_3$), δ 1.25 (3H, t, J = 7.0 Hz), 1.72 (1H, bd), 1.90-2.15 (1H, m), 2.19 (3H, s), 2.36 (1H, m), 2.5-2.65 (1H, m), 2.7-3.0 (3H, m), 3.2-3.4 (4H, m), 3.4-3.6 (1H, m), 4.13 (1H, d, J = 10.5 Hz), 6.71 (1H, s), 7.11 (2H, d, J = 8.0 Hz), 7.43 (1H, s), 7.89 (2H, d, J = 8.0 Hz). MS: 413 (M). HRMS: Calcd for $C_{22}H_{24}NO_2Br$ (corresponding to the free base): m/z 413.0990. Found: m/z 413.0994. Anal. ($C_{22}H_{25}O_2BrClN\bullet1.8H_2O$): Calculated C 54.68, H 5.22, N 2.90; Found C 54.77, H 5.52, N 2.57.

Synthesis of (4a*RS*,5*SR*,9b*RS*)-2-ethyl-8-chloro-7-methyl-2,3,4,4a,5,9b-hexahydro-5-(4-carboxyphenyl)-1H-indeno[1,2-c]pyridine hydrochloride (4a). (4aRS,5SR,9bRS)-2-Ethyl-8-iodo-7-methyl-2,3,4,4a,5,9b-hexahydro-5-(4-carboxylphenyl)-1H-indeno[1,2-c]pyridine hydrochloride (250 mg, 0.5 mmol) was dissolved in 25 mL THF and 0.5 mL HMPA. To this solution was added 60 mg sodium hydride (60% in mineral oil). The mixture was refluxed for 1 h and then cooled to -78°C. *Tert*-Butyllithium solution (0.91 mL, 1.1 M in pentane, 1.04 mmol) was added slowly. After the addition the mixture was stirred at -78°C for 20 min. A solution of hexachloroethane (2.46 g, 10.4 mmol) in 2 mL THF was added. The mixture was stirred at -78° C for another 30 min and then warmed to room temperature. 5% Hydrochloric acid was added to the solution until the solution became acidic. The mixture was extracted with methylene chloride. The methylene chloride solution was washed with brine and dried over $MgSO_4$. The crude product was purified with flash column chromatography (silica, CH_2Cl_2:MeOH, 10:1) to afford the title compound **4a**, 60 mg, 30% yield. ^{1}H NMR (250 MHz, D_2O-$CDCl_3$) δ 1.35 (3H, t, J = 7.2 Hz), 1.75-1.95 (1H, m), 2.30 (3H, s), 2.45-2.75 (2H, m), 2.80-3.15 (2H, m), 3.20-3.50

(4H, m), 3.50-3.70 (1H, m), 4.25 (1H, d, J = 10 Hz), 6.80 (1H, s), 7.25 (2H, d, J = 7.5 Hz), 7.32 (1H, s), 8.0 (2H, d, J = 7.5 Hz). MS: 370 (M). HRMS Calcd for $C_{22}H_{24}NO_2Cl$ (corresponding to the free base): m/z 369.1495. Found: m/z 369.1494. Anal. ($C_{22}H_{25}O_2Cl_2N$): Calculated C 65.50, H 6.20, N 3.45; Found C 65.65, H 6.73, N 3.59.