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EXTENSION OF THE SAR IN THE 1,2-DIAMINOCYCLOHEXANE PHENYLACETAMIDE TEMPLATE

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Abstract - Rigid analogs of 3,4-dichloro-*N*-methyl-*N*-[(1-methyl-2-piperidinyl)phenylmethyl]-benzeneacetamide (**3**), were prepared and allowed to extend the SAR of the U-50,488 template.

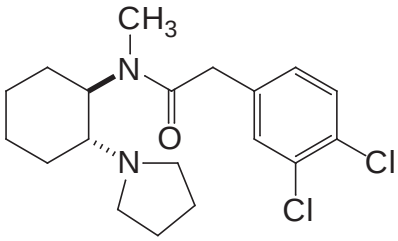
INTRODUCTION

The disclosure[1a,b] of the selective κ opiate agonist U-50,488 (**1**) has been followed by the preparation of many additional agonists based on the 1,2-diaminocyclohexane phenylacetamide template.[2a,b] The involvement of the κ receptor, which began simplistically with the analgesic activity, has grown to include several other areas of importance in biology.[2a,b]

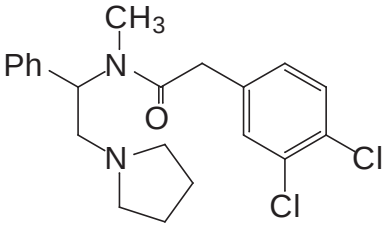
The northwest region of U-50,488 has been subjected to some scrutiny which has been summarized and elaborated upon.[3] One of the active compounds in this group is ICI199441 (**2**),[4] in which a phenyl substituent was introduced in the northwest region of an open chain analog. Compound (**2**) was further elaborated by the DuPont Merck group to produce an active compound (**3**).[5] This compound represents a considerable conformational and structural modification by introducing an *N*-methyl group on the basic nitrogen of piperidine and incorporating the terminal methylene group of the chain into the piperidine ring.

We recently have become interested in the benzoquinolizidine template in connection with anti-amnesic and anti-acetylcholinesterase activities[6a,b] and, thus, had occasion to extend the SAR study of compound (**3**). We rigidified the template by incorporating the 1,2-diamine into the benzoquinolizidine structure and producing two analogs in the phenylacetamide series related to U-50,488 (compounds (**8a**) and (**8b**)) and two analogs in the benzamide series related to the μ agonist U-47,700[1] (compound (**7a**) and (**7b**)).

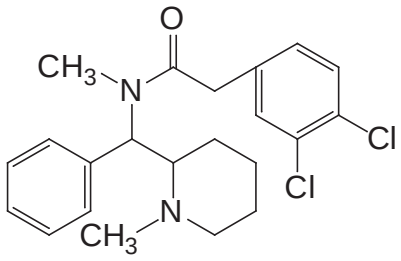
Dedicated to Professor Albert I. Meyers on the occasion of his 70th birthday.



1, U-50,488



2, ICI199441

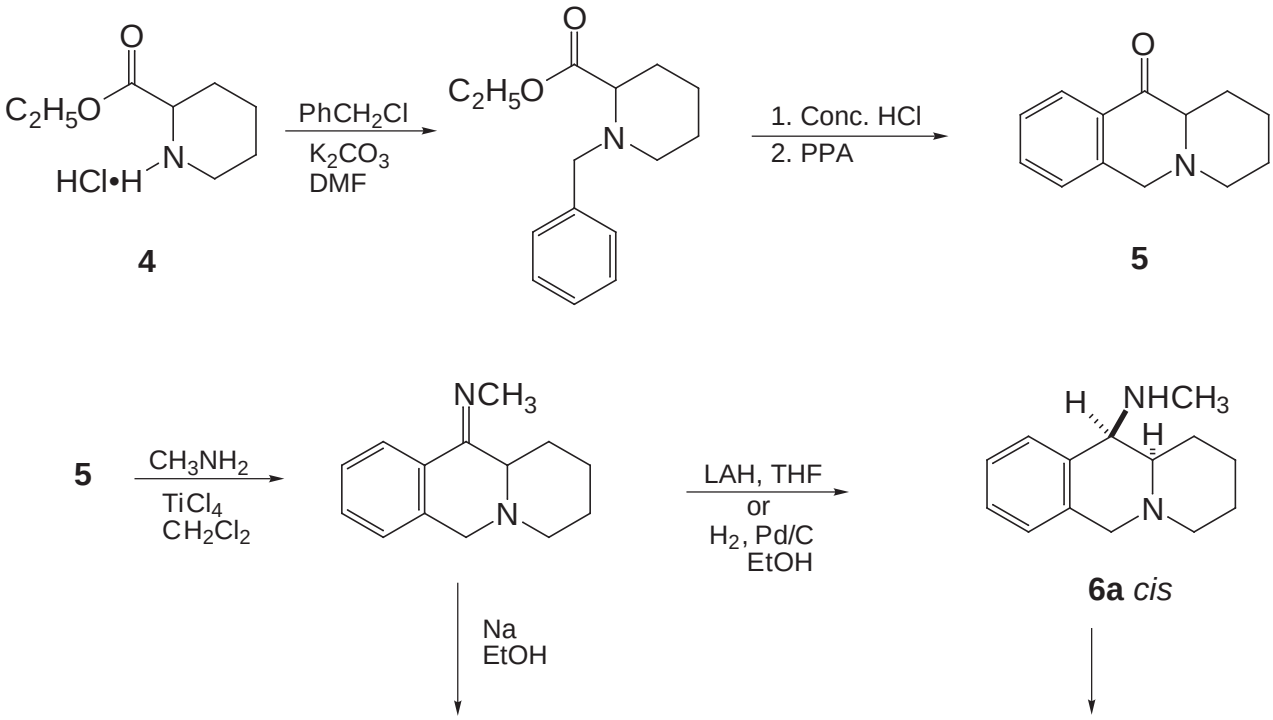


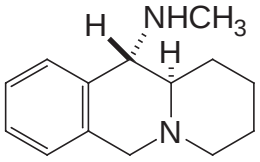
3, DuPont Merck

CHEMISTRY

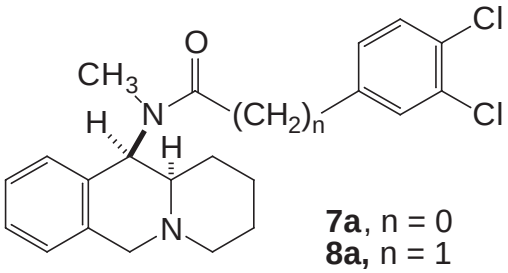
The starting *cis*- and *trans*-methylaminobenzoquinolizidines ((**6a**) and (**6b**)) were available from our previous work.[6] They were prepared from the amino ketone (**5**) which, in turn, was prepared according to the literature[7] from ethyl pipecolinate hydrochloride (**4**) as shown in the Scheme. The final products (**7a,b**) and (**8a,b**) were prepared by acylation of (**6a**) and (**6b**).

Scheme

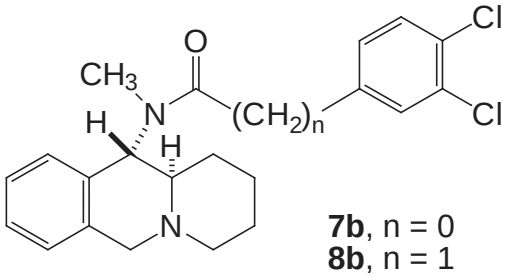




6b *trans*



7a, n = 0
8a, n = 1



7b, n = 0
8b, n = 1

BIOLOGICAL STUDIES AND CONCLUSION

Compounds (**7a,b**) and (**8a,b**) were inactive in μ, δ and κ binding assays.[8]

The lack of opioid activities of the above compounds may be ascribed to undesired conformational rigidity forced upon the environment of the basic nitrogen by incorporating it into the benzoquinolizidine.

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were recorded on a Varian spectrometer at 300 MHz for proton and 75 MHz for carbon in $CDCl_3$ solution. Peak positions are indicated in ppm downfield from internal TMS in δ units. MS spectra were obtained on a MAT CH-5-DF (FAB), and Finnigan 8230 B (EI) mass spectrometers. Flash column chromatography was done on silica gel (E. M. Merck silica gel 60, 230-400 mesh) in the stated solvents. Melting points were obtained on a Thomas-Hoover apparatus and are uncorrected. Product purities were routinely checked by TLC. THF was tested for peroxides (aqueous KI) prior to use and used without further purification or drying. All reactions were performed under a nitrogen atmosphere in oven- or flame-dried glassware unless otherwise noted.

3,4-Dichloro-*N*-methyl-*N*-[*cis*-1,3,4,6,11,11a-hexahydro-2*H*-benzo[*b*]quinolizin-11-yl]benzamide (7a).

3,4-Dichlorobenzoyl chloride (282 mg, 1.35 mmol) and Et_3N (188 μL, 1.35 mmol) were added to the solution of **6a** (265 mg, 1.23 mmol) in CH_2Cl_2 (10 mL). The mixture was stirred at rt for 10 h and then diluted with CH_2Cl_2 (100 mL). The mixture was washed with sat. Na_2CO_3 (10 mL) and brine (10 mL), dried (Na_2SO_4) and concentrated to give a red solid (457 mg). The crude solid was recrystallized from EtOAc/hexanes to give **7a** as a yellow solid (311 mg, 44% yield): mp 119-121°C; ^{1}H NMR (300 MHz) δ 7.0-7.6 (m, 7 H, aromatic), 5.85 (d, J = 4.58, 1 H, CH-N-C=O), 3.82 (d, J = 15.4, 1 H, 1/2 Ar-CH_2-N), 3.20 (d, J = 15.4, 1 H, 1/2 Ar-CH_2N), 3.03 (d,

J = 10.92, 1 H, 1/2 CH_2N), 2.64 (s, 3 H, NCH_3), 2.46 (m, 1 H, CH-N), 1.2-2.0 (m, 7 H, 3 x CH_2 + 1/2 CH_2N); ^{13}C NMR (75 MHz) δ 169.72, 136.74, 136.21, 133.47, 132.81, 132.24, 130.46, 128.82, 128.68, 127.51, 126.98, 125.98, 125.78, 61.84, 58.43, 56.80, 52.24, 35.18, 27.71, 25.64, 24.15; MS (FAB), m/z 389 (76, M + H), 185 (100), 173 (34); HRMS (FAB) m/z calcd for ($C_{12}H_{22}N_2OCl_2$ + H) 389.1187, found 389.1137; Anal. Calcd for $C_{21}H_{22}N_2OCl_2$: C, 64.79; H, 5.70; N, 7.20, Cl, 18.21. Found: C, 64.49; H, 5.63; Cl, 18.19; N, 6.89.

3,4-Dichloro-*N*-methyl-*N*-[*trans*-1,3,4,6,11,11a-hexahydro-2*H*-benzo[*b*]quinolizin-11-yl]benzamide (7b).

The solution of 3,4-dichlorobenzoyl chloride (196 mg, 0.94 mmol) in CH_2Cl_2 (5 mL) was added to the solution of **6a** and **6b** (182 mg, 0.85 mmol, **6a:6b** = 2:3) and Et_3N (130 µL, 0.94 mmol) in CH_2Cl_2 (10 mL). The mixture was stirred at rt for 10 h and then diluted with CH_2Cl_2 (100 mL). The mixture was washed with sat. Na_2CO_3 (10 mL), brine (10 mL), dried (Na_2SO_4) and concentrated to give a red oil (328 mg). The crude mixture was separated on radial chromatography eluting with hexanes/EtOAc (3/1) to give **7 a** and **7 b** as yellow oils.

7b: Crystallization from hexanes/EtOAc gave a yellow solid: mp 140-143°C (89 mg; 45% yield); ^1H NMR (300 MHz) δ 7.1-7.70 (m, 7 H, aromatic), 4.74 (d, J = 9.2, 1 H, Ar-CH-N), 3.86 (d, J = 15.7, 1 H, 1/2 CH_2N), 3.46 (d, J = 15.7, 1 H, 1/2 CH_2N), 3.00 (m, 1 H, 1/2 CH_2N), 2.81 (s, 3 H, NCH_3), 2.40 (dt, J = 3.0, 10.9, 1 H, CHN), 2.15 (dt, J = 11.9, 2.7, 1 H, 1/2 CH_2N), 0.87-2.0 (m, 6 H, 3 x CH_2); ^{13}C NMR (75 MHz) δ 171.03, 136.01, 135.04, 134.05, 133.07, 131.95, 130.67, 129.08, 127.66, 127.14, 126.43, 126.01, 125.03, 63.79, 60.19, 57.90, 56.13, 29.72, 29.51, 26.66, 25.04; MS (FAB), m/z 389 (79, M + H), 185 (100), 173 (21); HRMS (FAB) m/z calcd for ($C_{21}H_{22}N_2OCl_2$ + H) 389.1187, found 389.1168; Anal. Calcd for $C_{21}H_{22}N_2OCl_2 \cdot 0.4H_2O$: C, 63.61; H, 5.80; N, 7.06; Cl, 17.88. Found C, 63.74; H, 5.68; N, 6.91; Cl, 17.67.

7 a: Identical by ^1H NMR to the sample obtained above from pure **6 a**.

3,4-Dichloro-*N*-methyl-*N*-[*cis*- and *trans*-1,3,4,6,11,11a-hexahydro-2*H*-benzo[*b*]quinolizin-11-yl]benzeneacetamide (8a and 8b).

A solution of 3,4-dichlorophenylacetic acid (314 mg, 1.53 mmol) and CDI (248 mg, 1.53 mmol) in CH_2Cl_2 (20 mL) was stirred at rt for 5 h. A solution of a mixture of **6a** and **6b** (298 mg, 1.39 mmol, **6a:6b** = 2:3) in CH_2Cl_2 (20 mL) was added to the reaction mixture over 5 min. The mixture was stirred at rt for 24 h, and then poured into an aqueous Na_2CO_3 solution (2 N, 50 mL), and extracted with CH_2Cl_2 (2 x 30 mL). The combined extracts were dried and concentrated. The residue was separated on radial chromatography eluting with hexanes/EtOAc (3/1) to give **8b** (291 mg; 52% yield) and **8a** (175 mg; 31% yield) as yellow oils.

8a: ^1H NMR (300 MHz) δ 7.0-7.6 (m, 7 H, aromatic), 5.85 (d, J = 4.5, 1 H, CH-N-C=O), 3.85 (d, J = 15.2, 1 H, 1/2 (CH_2N), 3.70 (s, 2 H, $ArCH_2C$=O), 3.24 (d, J = 15.2, 1 H, 1/2 CH_2N), 3.06 (bd, J = 11.8, 1 H, 1/2 CH_2N), 2.79 (s, 3 H, NCH_3), 2.42 (ddd, J = 11.0, 4.5, 3.5, 1 H, CH-N), 1.96 (td, J = 11.9, 2.7, 1 H, 1/2 CH_2N), 1.0-1.9 (m, 6 H, 3 x CH_2); ^{13}C NMR (75 MHz) δ 170.76, 136.05, 135.40, 132.70, 132.49, 131.05, 130.38, 130.38, 128.85, 128.65, 127.39, 126.83, 125.74,

62.06, 58.53, 56.86, 52.16, 40.12, 33.21, 27.91, 25.68, 24.13; MS (FAB), m/z 403 (63, M + H), 185 (100); HRMS (FAB) m/e calcd for ($C_{22}H_{24}N_2OCl_2$ + H) 403.1344, found 403.1344.

8b: ^{1}H NMR (300 MHz), δ 6.7-7.5 (m, 7 H, aromatic), 4.90 (d, J = 15.9, CHN), 3.85-4.00 (d, J ~ 15.90, 1 H, 1/2 CH_2N), 3.80 (s, 2 H, $ArCH_2C$=O), 3.4-3.6 (d, J ~ 15.9, 1 H, 1/2 CH_2N), 3.10 (m, 1 H, 1/2 CH_2N), 2.65 (s, 3 H, NCH_3), 2.5-0.9 (m, 8 H, 1/2 CH_2N, CHN, 3 x CH_2).

The oil (**8b**) was converted to a maleic acid salt which was recrystallized from MeOH/EtOAc to give an off-white solid: mp 170-172°C; MS (FAB), m/z 403 (100, M + H), 186 (51); Anal. Calcd for $C_{22}H_{24}N_2OCl_2$•$C_4H_4O_4$: C, 60.12; H, 5.43; N, 5.39; Cl, 13.65. Found: C, 60.01; H, 5.47; N, 5.29; Cl, 13.45.

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