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

The northwest region of U-50,488 has been subjected to some scrutiny which has been summarized and elaborated upon.\textsuperscript{3} One of the active compounds in this group is ICI199441 (2),\textsuperscript{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).\textsuperscript{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\textsuperscript{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 $\mu$ agonist U-47,700\textsuperscript{1} (compound (7a) and (7b)).

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

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

Scheme
BIOLOGICAL STUDIES AND CONCLUSION
Compounds (7a,b) and (8a,b) were inactive in µ, δ and κ binding assays. 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
1H and 13C NMR spectra were recorded on a Varian spectrometer at 300 MHz for proton and 75 MHz for carbon in CDCl₃ 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-2H-benzo[b]quinolizin-11-yl]benzamide (7a).
3,4-Dichlorobenzoyl chloride (282 mg, 1.35 mmol) and Et₃N (188 µL, 1.35 mmol) were added to the solution of 6a (265 mg, 1.23 mmol) in CH₂Cl₂ (10 mL). The mixture was stirred at rt for 10 h and then diluted with CH₂Cl₂ (100 mL). The mixture was washed with sat. Na₂CO₃ (10 mL) and brine (10 mL), dried (Na₂SO₄) 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; 1H 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-CH₂-N), 3.20 (d, J = 15.4, 1 H, 1/2 Ar-CH₂-N), 3.03 (d,
J = 10.92, 1 H, 1/2 CH₂N), 2.64 (s, 3 H, NCH₃), 2.46 (m, 1 H, CH-N), 1.2-2.0 (m, 7 H, 3 x CH₂ + 1/2 CH₂N); ¹³C 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 (C₁₂H₂₂N₂OCl₂ + H) 389.1187, found 389.1137; Anal. Calcd for C₂₁H₂₂N₂OCl₂: 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-2H-benzo[b]quinolinizin-11-yl]benzamide (7b).
The solution of 3,4-dichlorobenzoyl chloride (196 mg, 0.94 mmol) in CH₂Cl₂ (5 mL) was added to the solution of 6a and 6b (182 mg, 0.85 mmol, 6a:6b = 2:3) and Et₃N (130 µL, 0.94 mmol) in CH₂Cl₂ (10 mL). The mixture was stirred at rt for 10 h and then diluted with CH₂Cl₂ (100 mL). The mixture was washed with sat. Na₂CO₃ (10 mL), brine (10 mL), dried (Na₂SO₄) 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 7a and 7b 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 CH₂N), 3.46 (d, J = 15.7, 1 H, 1/2 CH₂N), 3.00 (m, 1 H, 1/2 CH₂N), 2.81 (s, 3 H, NCH₃), 2.40 (dt, J = 10.9, 1 H, CHN), 2.15 (dt, J = 11.9, 2.7, 1 H, 1/2 CH₂N), 0.87-2.0 (m, 6 H, 3 x CH₂); ¹³C 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, 29.90, 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 (C₂₁H₂₂N₂OCl₂ + H) 389.1187, found 389.1168; Anal. Calcd for C₂₁H₂₂N₂OCl₂·0.4H₂O: 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.

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

3,4-Dichloro-N-methyl-N-[cis- and trans-1,3,4,6,11,11a-hexahydro-2H-benzo[b]quinolinizin-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 CH₂Cl₂ (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 CH₂Cl₂ (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 Na₂CO₃ solution (2 N, 50 mL), and extracted with CH₂Cl₂ (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 CH₂N), 3.70 (s, 2 H, ArCH₂C=O), 3.24 (d, J = 15.2, 1 H, 1/2 CH₂N), 3.06 (bd, J = 11.8, 1 H, 1/2 CH₂N), 2.79 (s, 3 H, NCH₃), 2.42 (dddd, J = 11.0, 4.5, 3.5, 1 H, CH-N), 1.96 (td, J = 11.9, 2.7, 1 H, 1/2 CH₂N), 1.0-1.9 (m, 6 H, 3 x CH₂); ¹³C 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$_{2}$OCl$_{2}$ + 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$_2$N), 3.80 (s, 2 H, ArCH$_2$C=O), 3.4-3.6 (d, J ~ 15.9, 1 H, 1/2 CH$_2$N), 3.10 (m, 1 H, 1/2 CH$_2$N), 2.65 (s, 3 H, NCH$_3$), 2.5-0.9 (m, 8 H, 1/2 CH$_2$N, 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$_{2}$OCl$_{2}$•C$_4$H$_4$O$_4$: 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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REFERENCES


