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Anticonvulsants Related to U-54494 Prepared From *cis*-1,2- and *cis*-2,3-Diaminotetralin

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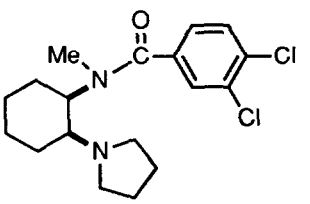
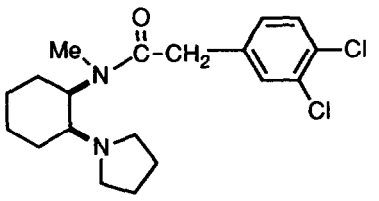
cis-Diaminotetralins ***4*** *and* ***10*** *were converted in 4 steps to benzologs of the novel anticonvulsant U-54494. Attempted alkylation of* ***4*** *and* ***10*** *with 1,4-dibromobutane provided mixtures of the bis-pyrrolidino compounds and starting free bases together with the desired mono-pyrrolidino compounds* ***5*** *and* ***11****. Treatment of these mixtures with ethyl chloroformate followed by chromatographic separation gave the carbamates* ***7*** *and* ***12****. Reduction of these carbamates with* $LiAlH_4$ *provided the N-methylamino compounds* ***8*** *and* ***14****. Finally, benzamide formation gave rise to the analogs of U-54494, compounds* ***9*** *and* ***15****.*

Racemic U-54494 (**1**), first reported by Szmuszkovicz and VonVoigtlander,[1] is a novel anticonvulsant currently in phase I clinical trials.[2] The structurally related phenylacetamide **2** (1R, 2S) is a potent and selective *sigma* agonist.[3] Our interest in extending the virtually unexplored SAR in this *cis*-1,2-amino amide series led us to consider the synthesis of the benzo-fused analogs **9** and **15** from *cis*-1,2- and 2,3-diaminotetralin, respectively.



U-54494 (**1**)
(racemic)



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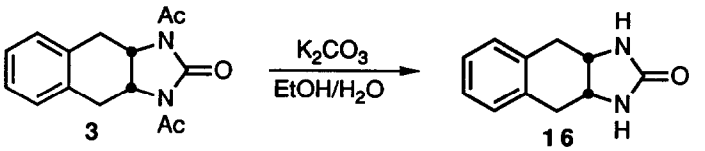
Results and Discussion

Both of the requisite cis diaminotetralins have been reported previously. Hara *et al.* synthesized *cis*-1,2-diaminotetralin•2HCl (**10**) in 5 steps from 1,2-dihydronaphthalene via the corresponding bis-azide.[4] Although the bis HCl salt **4b** and free base **4c** have been prepared previously by reduction of *cis*-2,3-diazidotetralin, we prepared *cis*-2,3-diaminotetralin derivative **4a** by hydrolysis of **3**[5] with barium hydroxide at 140°C. Under milder conditions (K_2CO_3, EtOH/H_2O, Δ) only the acetate groups were hydrolyzed and the urea **16** was obtained exclusively (eq 1).



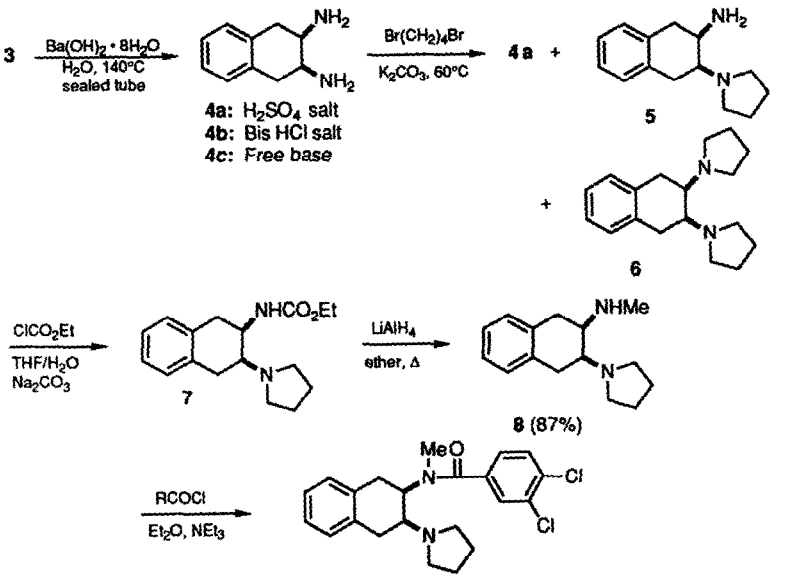
3 **16** (1)

The conversion of these *cis*-diaminotetralin derivatives to the target amides **9** and **15** is outlined in Schemes I and II. The synthetic strategies for each case are identical. The starting diamines were alkylated with dibromobutane to give the monopyrrolidino compounds **5** and **11**. Treatment of **5** and **11** with ethyl chloroformate produced the ethyl carbamates **7** and **13** which were reduced with lithium aluminum hydride to give diamines **8** and **14**. Amide formation with 3,4-dichlorobenzoyl chloride produced **9** and **15**.

Although most of the steps in this synthetic strategy were straightforward, a complication arose in the alkylation of the starting diamines **4** and **10**. Under standard conditions it was not possible to avoid the formation of the bis-pyrrolidino compounds **6** and **12**. This problem was especially severe in the case of the 2,3-isomer where a ca. 1:1:2 mixture of **4c**, **5**, **6** was obtained (Scheme I). In the 1,2-diaminotetralin series alkylation occurred predominantly at the less hindered 2-amino position to give **11** without any indication of alkylation at the 1-amino position; however, mass spectral analysis indicated a slight contamination from the bis-pyrrolidino compound **12** and the free base of **10**. The regiochemistry of the major product was established most conclusively by analysis of the ^1H NMR spectrum of its subsequent carbamate and amide derivatives. The spectra of these derivatives were most consistent with the structures **13** and **15** shown in Scheme II.[5a]

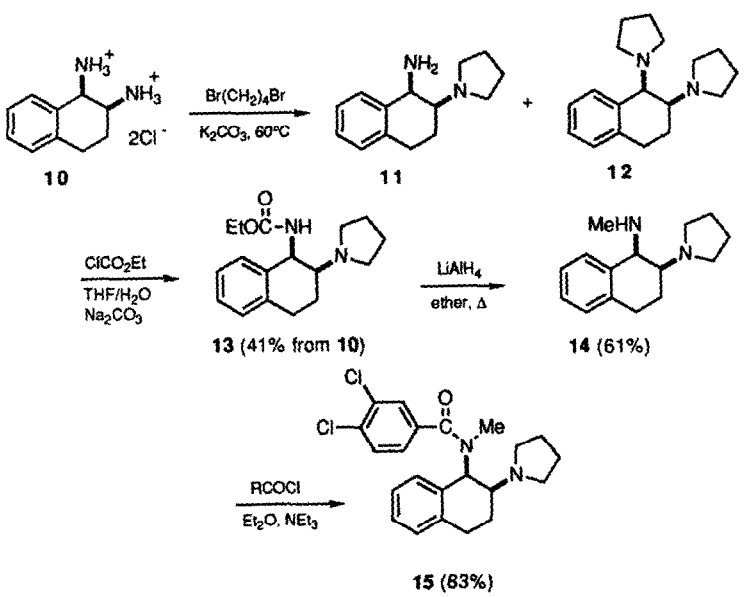
Bis-alkylation is a common phenomenon with acyclic diamines and strategies to overcome this problem have typically relied on the use of a vast excess of the diamine component.[6] Since the

Scheme I



9 (83%): R=3,4-dichlorophenyl

Scheme II



15 (83%)

use of excess diamine was not practical in our case, we resorted to using a 1:1 ratio of reagents. Due to the mixtures encountered in this alkylation step and the difficulties associated with separation and purification of these diamines, we did not attempt any purification at this stage. Instead, the mixture was treated with ethyl chloroformate and the desired carbamate product was isolated by chromatography.

In summary, the first congeners of the anticonvulsant U-54494 have been synthesized from *cis*-1,2-and 2,3-diaminotetralin. These analogs of U-54494 are less effective antagonists of maximal electroshock seizures in mice than U-54494. As in the prototype, no indication of analgesic activity was detected in the opioid binding assay even though these compounds are structurally related to the opioid 1,2-diamine class of analgesics.

Experimental Section

General Procedures. ^{1}H NMR spectra were obtained on a GN 300 (300 MHz) or a 200 MHz Magnachem instrument, and were recorded in $CDCl_3$ unless otherwise noted. Proton chemical shifts are given in ppm relative to Me_4Si (=0 ppm, ^{1}H). ^{1}H NMR coupling constants (J)are given in Hertz. IR spectra were recorded on a Perkin-Elmer infrared spectrometer. Melting points were measured using a Thomas-Hoover unimelt apparatus and are uncorrected. Mass spectra were obtained on MAT CH-5-DF (FAB), and Finnigan 8230 B (EI) mass spectrometers. Radial chromatography was performed on a Chromatotron Model 7924 using Merck silica gel 60 PF as the stationary phase.

Elemental analyses were performed by M-H-W Laboratories, Phoenix, Arizona.

Tetrahydrofuran (Fisher, certified) was purified by refluxing over sodium under nitrogen followed by distillation. Following extractive isolations, ether extracts were dried with $MgSO_4$ and methylene chloride extracts were dried with $NaSO_4$. In both cases the dried organic solutions were filtered and concentrated to afford the crude products.

Compound **3**[5] and 1,2-diaminotetrahydronaphthalene·2HCl (**10**)[4] were prepared according to literature procedures

***cis*-Diamine 4.** According to the procedure previously reported by Kohn[7] for the hydrolysis of *d*-biotin, compound **3** (1 00 g, 3.67 mmol) was treated with $Ba(OH)_2 \cdot 8H_2O$ (19.4 g, 61 1 mmol) in 10 mL of water to afford 762 mg (80%) of **4** as a white solid: mp 295°C (dec); ^{1}H NMR (200 MHz) (D_2O) δ 2 90 (dd, J = 8, 18, 2H), 3.20 (dd, J = 5, 18, 2H), 3 96 (app t, J = 6), 7 13 (m, 4H); IR (KBr) 3620 (NH), 3420 (NH), 1610, 1525, 1100, 750 cm^{-1}, High Resolution MS (FAB) Calcd for $C_{10}H_{15}N_2$: 163.1235. Found 163.1220; Anal. Calcd for $C_{10}H_{16}N_2O_4S$: C, 46.14; H, 6.20; N, 10 76; S, 12 32 Found: C, 46.32; H, 6 27, N,10 58; S, 12.21.

Urea 16. A solution of **3** (26 mg, 0 095 mmol) and K_2CO_3 (152 mg, 1.10 mmol) in 66% ethanol/H_2O was heated at reflux for 6 h.[8] The solvent was removed by rotary evaporation, and the residue was partitioned between CH_2Cl_2 (30 mL) and H_2O (20 mL). The layers were separated,

and the aqueous layer was back extracted with CH_2Cl_2 (3 x 10 mL). The combined organic phases gave 12 mg (67%) of urea **16** as a white solid: mp 200°C; ^{1}H NMR (200 MHz) δ 2.73 (d, J = 15, 2H), 2.87 (d, J = 12, 2H), 4.22 (s), 5.20 (s, 2 x NH), 7.17 (m, 4H); IR (film) 3220 (br, NH), 1680, 1650 cm^{-1}; MS (EI) at m/z 188 (M^+); Anal. Calcd for $C_{12}H_{12}N_2O$: C, 70.19; H, 6.43; N, 14.88. Found: C, 69.92; H, 6.29; N, 14.61.

Carbamate 7. A slurry of **4** (350 mg, 1.35 mmol), 1,4-dibromobutane (291 mg, 1.35 mmol), and K_2CO_3 (560 mg, 4.05 mmol) in acetonitrile (30 mL) was heated at reflux for 2 days. After cooling, the solvent was removed by rotary evaporation. The residue was partitioned between CH_2Cl_2 (80 mL) and sat. aq. Na_2CO_3 (40 mL). The layers were separated, and the aqueous layer was washed with CH_2Cl_2 (2 x 40 mL). The combined organic layers gave rise to 274 mg of crude product as a brown oil. Mass spectral analysis indicated the presence of **4c**, **5** and **6**; however, no separation of components was attempted at this point: MS (EI) m/e 270 (M^+ for **6**), 216 (M^+ for **5**), 162 (M^+ for **4c**). The mixture of diamines **4c**, **5**, and **6** (270 mg) was dissolved in 20 mL of 5% THF/H_2O and treated with K_2CO_3 (86 mg, 0.63 mmol) and ethyl chloroformate (68 mg, 0.63 mmol). The reaction mixture was stirred for 1 h after which the THF was removed by rotary evaporation. The aqueous residue was extracted with ether (3 x 50 mL). The combined ether extracts produced 295 mg of a yellow oil. Purification of this oil by radial chromatography (95:4:1, $CHCl_3$/MeOH/NH_4OH) gave 200 mg of **6** (0.55 mmol, 41% based on **4a**) and 70 mg (0.24 mmol, 18% yield based on **4a**) of the desired oily carbamate **7**. For analytical purposes the bis hydrochloride of **6** was prepared.

For the bis hydrochloride of **6**: mp 260°C (dec); ^{1}H NMR (200 MHz) δ 1.98 (m, 8H), 3.15-3.50 (m, 12H), 4.23 (t, J = 7, 2H), 7.16 (m, 4H); MS (EI) m/z at 270(M^+ for free base); Anal. Calcd for $C_{18}H_{28}N_2Cl_2 \cdot 1/4H_2O$: C, 62.15; H, 8.26; N, 8.05; Cl, 20.38. Found: C, 62.26; H, 8.28; N, 8.14; Cl, 20.27.

For **7**: ^{1}H NMR (200 MHz) δ 1.24 (m, 3H, CH_3), 1.81 (s, 4H), 2.55-3.23 (m, 9H), 4.11 (m, 2H, OCH_2), 4.31 (m, 1H), 5.03 (m, 1H), 7.10 (s, 4H); MS (EI) at m/z 288 (M^+).

Carbamate 13. A slurry of **10** (400 mg, 1.70 mmol), 1,4-dibromobutane (368 mg, 1.70 mmol), and K_2CO_3 (705 mg, 5.10 mmol) in 30 mL of acetonitrile was refluxed for 3 days. The crude diamine product was isolated as described above to give 319 mg (87% based on **11**) of a yellow oil. Mass spectral analysis indicated the presence of **10**, **11** and **12**; however, no separation of components was attempted at this point: MS (CI, isob) 271 (M^++1 for **12**), 217 (M^++1 for **11**), 163 (M^++1 for the free base of **10**). The mixture of diamines **10**, **11**, and **12** was treated with ethyl chloroformate and the product was isolated as described above for the synthesis of carbamate **7**. The crude product was purified by its extraction into 4N HCl followed by neutralization with Na_2CO_3 and re-extraction into methylene chloride. Starting from **10**, the oily carbamate **13** was obtained in 41% overall yield: .^{1}H NMR (200 MHz) (mixture of 2 conformers) δ 1.20 (m, 3H), 1.65 (m, 4H), 1.82 (m, 2H), 2.11-2.90 (m, 7H), 4.13 (m, 2H), 5.05 and 5.28 (two m, total of 1H), 5.65 and 7.50 (two m, total of 1H, NH); HRMS (EI) Calcd for $C_{17}H_{24}N_2O_2$: 288.1838. Found: 288.1844.

Diamine 8. A slurry of $LiAlH_4$ (43 mg, 1.13 mmol) in 15 mL of THF was heated at reflux for 5 min. To this stirred solution was added carbamate **7** (193 mg. 0.67 mmol) as a solution in THF (10 mL). The reaction mixture was stirred for 18 h at room temperature and for 2 h at reflux. To the cooled (0°C) mixture was added sequentially, H_2O (43 μl), 15 % NaOH (43 μl), and H_2O (129 μl). This heterogeneous mixture was stirred at room temperature for 30 min, and then filtered through celite. The celite was washed with ether (3 x 30 mL), and the combined filtrates were concentrated to provide 139 mg (90%) of **8** as a colorless oil: ^{1}H NMR (200 MHz) δ 1.81 (m, 4H), 2.33-3.10 (m, 10 H), 2 45 (s, 3H, NCH_3), 7.08 (s, 4H), HRMS (EI) Calcd for $C_{15}H_{22}N_2$: 230.1783. Found: 230.1771.

Diamine 14. Prepared as described above for compound **8** using carbamate **13**. Diamine **14** was obtained in a 61% yield as a colorless oil. ^{1}H NMR (200 MHz) supported the proposed structure, but showed the presence of a small amount of **8**. The product was used directly in the next step without further purification.

Amide 9. A solution of diamine **8** (138 mg, 0.60 mmol) and triethylamine (67 mg, 0.66 mmol) in ether (35 mL) was treated with solid 3,4-dichlorobenzoyl chloride (125 mg, 0.60 mmol), and stirred for 18 h. The reaction mixture was partitioned between aq. sat. Na_2CO_3 and ether. The layers were separated and the aqueous layer was back-extracted with ether (3x). The combined ether layers gave rise to 251 mg of a yellow oil. The crude product was purified by radial chromatography (95:4:1, $CHCl_3$/MeOH/NH_4OH) to give 200 mg (83%) of **9** as a yellow oil, which was converted to the hydrochloride: mp (MeOH/ether) 220°C (dec); ^{1}H NMR (D_2O) (200 MHz) δ 2.09 (m, 4H), 2.76 (s, 3H, NCH_3), 3.22 (m, 4H), 3.51 (m, 2H), 3.85 (m, 2H), 4.19 (m, 1H), 5.44 (m, 1H), 7.26 (s, 4H), 7.40 (m, 1H), 7.65 (m, 2H); HRMS (FAB) Calcd for $C_{22}H_{24}Cl_2N_2O$: 403.1344. Found: 403.1325; Anal. Calcd for $C_{22}H_{24}Cl_2N_2O \cdot HCl \cdot 0.5\ H_2O$: C, 58.82,; H, 5.79; N, 6.23. Found: C, 59.88; H, 5.57; N, 5.77.

Amide 15. Prepared as described for amide **9** using diamine **14**. The crude product was purified by radial chromatography (99:1, ether/MeOH) to give **15** as a yellow oil (49%). For analytical purposes the HCl salt was prepared: mp 200°C(dec); ^{1}H NMR (300 MHz) δ 2.08 (m, 2H), 2.35 (m, 3H), 2.67 (m, 1H), 2.97 (m, 2H), 2.99 (s, 3H, NCH_3), 3.20 (m, 2H), 3.33 (m, 1H), 3.93 (m, 1H), 4.29 (m, 1H), 6.70 (d, J = 3, 1H), 7.19 (d, J = 7, 1H), 7.28 (m, 3H), 7.54, d, J = 8, 1H), 8.04 (d, J = 2, 1H), 8.23 (dd, J = 2,8, 1H); IR (KBr) 3450 (NH), 1630 (CO) cm^{-1}; HRMS Calcd for $C_{22}H_{25}Cl_2N_2O$: 403.1344. Found: 403.1327; Anal. Calcd for $C_{22}H_{24}Cl_2N_2O \cdot HCl$: C, 60.08; H, 5.73; Cl, 24.18, N, 6.37. Found: C, 59.89; H, 5.80; Cl, 23.69; N, 6.22.

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