SYNTHETIC STUDIES TOWARDS A *trans*-3, 4-DIAMINE DERIVATIVE OF PIPERIDINE MIMICKING BUSPIRONE[a]

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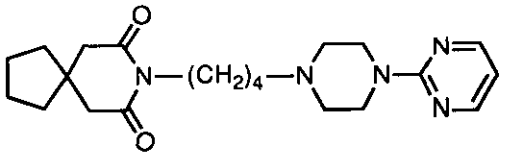
Abstract - Based on modeling experiment of buspirone we synthesized the sterically restricted analog, namely the piperidine 3,4-*trans*-amino amide (**3**). Preliminary biological evaluation is reported.

The disclosure that buspirone (**1**), an anxiolytic drug, has high selective affinity for $5HT_{1A}$ receptors[1a,b] led us to investigate the structural correlation between buspirone and the piperidine analog of 1,2-amino amide U-48,753 (**2**).[2]



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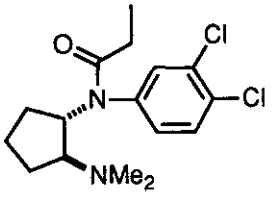

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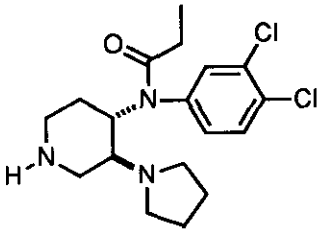

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[a]Dedicated to Dr. Arnold Brossi on the occasion of his 70th birthday.
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Indeed, a Dreiding model of **3** showed striking superimposition with that of **1**. The eastern portion of **3** showed a overlap with the 1-pyrimidinylpiperazine portion (eastern portion) of **1**. On the other hand, the flexible western portion of **1** can reasonably mimic the western part of **3**. This can be seen in Figure 1.

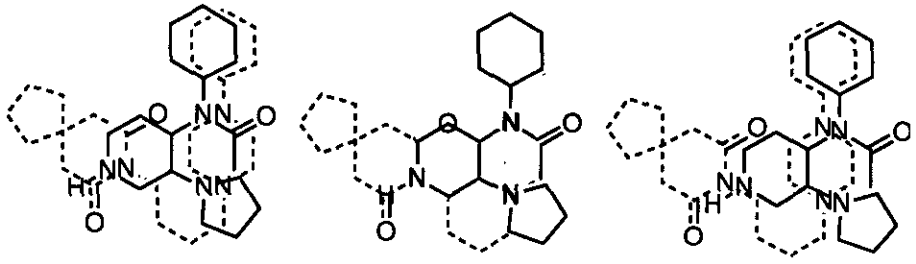
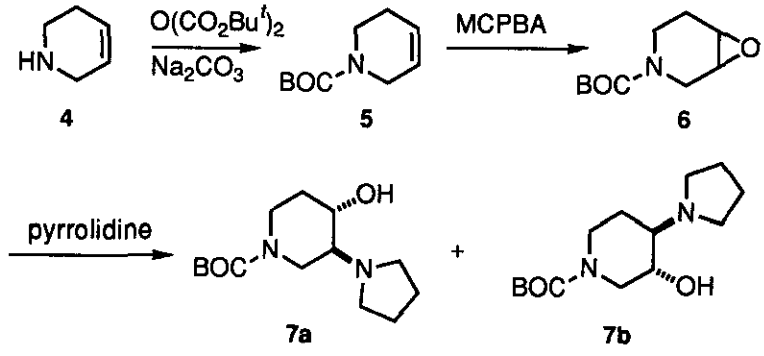


Figure 1. The two dimensional representations of **1** (dashed lines) and **3** (solid lines) illustrates the favorable disposition of the three nitrogen atoms in these molecules for overlap in their three dimensional conformation.

Encouraged by the above observation we initiated a synthetic approach toward **3**. Commercially (Aldrich) available 1,2,3,6-tetrahydropyridine[3] (**4**) was the most convenient starting material for this project. Protection of the amine functionality in **4** was readily accomplished using the BOC group[4] (*cf.*[5]). Epoxidation of the protected tetrahydropyridine (**5**), followed by reaction with pyrrolidine led to the corresponding amino alcohols (**7a**) and (**7b**) as a mixture of regioisomers. Since the next reaction proceeds via regiospecific ring opening of the common aziridinium ion intermediate (**8**),[6] no attempt was made to separate these isomers.

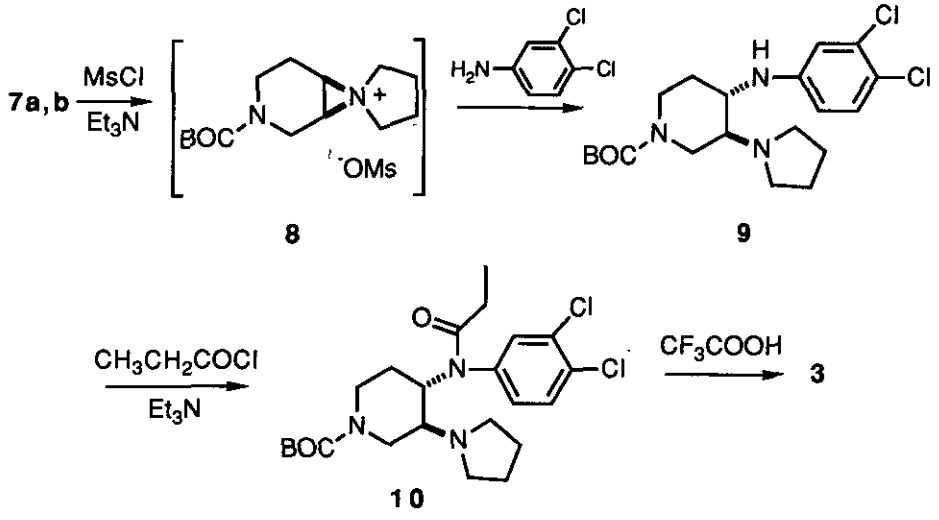
Scheme 1



4 **5** **6** **7a** **7b**

The above isomeric mixture of amino alcohols was reacted with methanesulfonyl chloride in presence of triethylamine as base to obtain the mesylates, and the mesylate mixture without isolation was treated with 3,4-dichloroaniline following the procedure described earlier[2] to afford **9**.[7] The diamine (**9**) was easily converted to the amide (**10**) according to standard methods. Finally, the protecting group was removed by treatment of **10** with trifluoroacetic acid to give the desired compound (**3**).

Scheme 2



At first, every step of the above sequence **7**→**3** was not clean and low in yield. The situation changed dramatically after we distilled the hydroxyamine mixture (**7a** and **7b**). The above four steps were carried out without significant separation of the intermediates, and the overall yield was improved to 39% starting from **7**.

In conclusion, a piperidine 3,4-*trans*-amino amide compound was prepared, and subjected to preliminary biological evaluation.[8]

Finally, modeling by computer supports the original hypothesis that buspirone and **3** can place their nitrogens in similar orientations. However, it also demonstrates that the required buspirone conformations are not necessarily the most energetically favorable ones, and that the aryl rings in the two molecules cannot readily assume similar positions relative to the nitrogens.

EXPERIMENTAL

General. All of the dry solvents and reagents were prepared from reagent grade materials by conventional methods. Product purities were routinely checked by tlc. THF was dried over benzophenone ketyl. Other commercial reagents and solvents were used without further purification.

200 MHz ^{1}H nmr spectra were recorded on a Magnachem instrument, 300 MHz ^{1}H nmr were obtained on a GN 300 spectrometer in $CDCl_3$ solution. Peak positions are indicated in ppm downfield from internal TMS in δ units. Mass spectra were obtained on a MAT CH-5-DF (FAB), and Finnigan 8230 B (EI) mass spectrometers.

Molecular modeling of buspirone and **3** was performed using the Mosaic modeling system, which is derived from MacroModel.[9] Conformational searching was performed on the unprotonated structures using MULTIC submode[10] coupled with energy minimization using BatchMin.[9,11] Minimizations were performed in vacuo, with a distance-dependent dielectric $\varepsilon_{ij} = r_{ij}$, using the MM2* forcefield.[11] Differences in energy of a few kcal/mole are not significant for the present (qualitative) purposes.

1-*tert*-Butoxycarbonyl-3,4-dehydropiperidine (5)[4]

A mixture of 1, 2, 3, 6-tetrahydropyridine (**4**) (4.59 g, 55.2 mmol) in 4 ml of 10% aqueous Na_2CO_3 was cooled to 0 °C and di-*tert*-butyl dicarbonate (12 g, 55.2 mmol) was added in portions to the stirred solution. Some CO_2 evolution was apparent while the solution turned yellow. The stirring was maintained at 0 °C for 1 h , and at room temperature overnight. The reaction mixture was partitioned between brine (30 ml) and ether (60 ml). The ether layer was dried ($MgSO_4$) and concentrated in vacuo to furnish **5** (10 g, 99%) as a yellow oil. This was further purified by passing through a short plug of silica gel eluting with CH_2Cl_2 to obtain a colorless oil: ^{1}H Nmr (300 MHz) δ 1.45 (s, 9 H), 2.11 (br s, 2 H), 3.46 (td, J = 5.6, 1.3 Hz, 2 H), 3.86 (m, 2 H), 5.65 (m, 1 H), 5.80 (m, 1 H); ms (EI) [M$^+$] 183; HRms Calcd for $C_{10}H_{17}NO_2$: 183.1259. Found: 183.1224.

1-*tert*-Butoxycarbonyl-3,4-epoxypiperidine (6)

1-*tert*-Butoxycarbonyl-3, 4-dehydropiperidine (**5**) (4.6 g, 25 mmol) was dissolved in 50 ml CH_2Cl_2 and cooled to 0 °C. A solution of *m*-chloroperbenzoic acid (60%) (10 g, 35 mmol) in 100 ml CH_2Cl_2 was added dropwise over 30 min. The ice-bath was removed and the resulting colorless reaction mixture was stirred for 4 h. It was then washed three times with 5% aqueous K_2CO_3, and once with

brine. The organic layer was dried over Na_2SO_4, filtered, and evaporated to give **6** (4.4 g, 89%) as a colorless oil: ^1H Nmr (200 MHz) δ 1.49 (s, 9 H), 2.00 (m, 2 H), 3..01-3.90 (m, 6 H); ms (EI) m/z at 199 [M+]; HRms (EI) Calcd for $C_{10}H_{17}NO_3$: 199.1208. Found: 199.1205.

1-*tert*-Butoxycarbonyl-*trans*-4-pyrrolidinyl-3-hydroxypiperidine (7a) and 1-*tert*-Butoxycarbonyl-*trans*-3-pyrrolidinyl-4-hydroxypiperidine (7b)

A mixture of 1-*tert*-butoxycarbonyl-3,4-epoxypiperidine (**6**) (5.23 g, 25 mmol), pyrrolidine (5 ml, 60 mmol) and H_2O (2 ml) was heated at 80 °C for 20 h with stirring. The reaction mixture was cooled, diluted with Et_2O (50 ml), and washed with saturated Na_2CO_3, followed by H_2O. The ether solution was dried (Na_2SO_4) and concentrated. The residue was distilled under vacuum to give **7** as a brown oil (3.13 g, 46%, 112-190 °C/0.1 torr): ^1H Nmr (200 MHz) δ 1.46 (s, 9 H), 1.76 (m, 4 H), 2.03 (m, 1 H), 2.47-2.83 (m, 7 H), 3.20-3.65 (m, 2 H), 4.00-4.37 (m, 2 H); ms (EI) m/z 270 (41, M^+), 252 (2), 214 (75), 197 (24), 170 (90), 97 (100), 57 (45); HRms (EI) Calcd for $C_{14}H_{26}N_2O_3$: 270.1943; Found: 270.1944.

Synthesis of 9 from mixture of 7 via a common aziridinium (8)

Methanesulfonyl chloride (3.67 mmol, 284 ul) was added dropwise to a mixture of alcohols (**7a** and **7b**) (902 mg, 3.34 mmol) and triethylamine (3.67 mmol, 511 ul) in CH_2Cl_2 (10 ml) during 5 min at 0 °C. The reaction mixture was stirred at 0 °C for 2 h, and then the solvent was removed by rotary evaporation. The mixture was transferred to a bomb together with 3,4-dichloroaniline (5.01 mmol, 806 mg). The bomb was heated at 90 °C for 20 h. The crude product was dissolved in ether (200 ml) and washed with saturated Na_2CO_3 (2 x 30 ml) and brine (2 x 30 ml). The ether solution was dried (K_2CO_3) and evaporated to produce an oil (2.17 g). The oil was used in the next step directly. In another experiment, repeated chromatography of the above oil using $CHCl_3$:MeOH:29%NH_4OH (95:4:1) as eluent afforded **9** as a colorless oil: ^1H Nmr (300 MHz) δ 1.47 (s, 9 H), 1.78 (m, 4 H), 2.26 (dq, J = 13.5, 3.4 Hz, 1 H), 2.73 (m, 6 H), 2.98 (m, 2 H), 3.25 (m, 1 H), 3.95 (br d, J = 13.7 Hz, 1 H), 4.20 (br s, 1 H), 4.87 (br s, 1 H), 6.52 (dd, J = 8.7, 2.7 Hz, 1 H), 6.71 (d, J = 2.7 Hz, 1 H), 7.18 (d, J = 8.8 Hz, 1 H); ms (EI) m/z at 413 (M^+); HRms (FAB) Calcd for ($C_{20}H_{29}N_3O_2Cl_2$ + H): 414.1715. Found: 414.1721.

1-*tert*-Butoxycarbonyl-*trans*-4-*N*-(3,4-dichlorophenyl)propanamido-3-pyrrolidinylpiperidine (10)

A solution of propionyl chloride (1.3 ml, 15 mmol) in ether (10 ml) was added dropwise to an ice-cold solution of **9** (2.17 g, crude) and triethylamine (2.1 ml, 15 mmol) in ether (40 ml) during 10 min. The solution was stirred for 24 h at room temperature. The reaction mixture was extracted with aqueous HCl (10%, 2 x 20 ml). The acidic solution was basified by the addition of solid sodium hydroxide and extracted with ether (3 x 50 ml). Combined ether extracts were washed with brine (2 x 30 ml). Drying (K_2CO_3) and evaporation of the solvent afforded **10** as a brown oil (905 mg). The product was subjected to the next step directly, but it was purified by chromatography (silica gel, $CHCl_3$/MeOH/29%NH_4OH = 95/4/1) in a separate experiment for the purpose of characterization: ^{1}H Nmr (300 MHz) δ 1.01 (t, J = 7.4 Hz, 3 H), 1.51 (s, 9 H), 1.65-1.95 (m, 7 H), 2.23 (m, 1 H), 2.50-2.85 (m, 7 H), 4.05 (m, 1 H), 4.20 (m, 1 H), 4.96 (td, J = 11.7, 3.8 Hz, 1 H), 6.90 (m, 1 H), 7.45 (d, J = 8.4 Hz, 1 H), 7.69 (m, 1 H); ms (EI) m/z 469 (3, M+), 396 (3), 369 (90), 252 (48), 57 (100); HRms (FAB) Calcd for ($C_{23}H_{33}N_3O_3Cl_2$ + H): 470.1977. Found: 470.1986.

***trans*-4-*N*-(3,4-Dichlorophenyl)propanamido-3-pyrrolidinylpiperidine (3)**

Compound (**10**) (535 mg, crude) was dissolved in trifluoroacetic acid (4 ml) and the solution was stirred at room temperature for 3 h. Ice (50 g) was added to the mixture followed by the addition of solid NaOH. The mixture was then extracted with ether (3 x 60 ml), dried over $MgSO_4$ and concentrated in vacuo to give a red oil (514 mg). The crude product was purified by column chromatography (silica gel, $CHCl_3$/MeOH/29%NH_4OH = 90/9/1) to give **3** as a yellow oil (281 mg, 39% yield from **7**): ^{1}H Nmr (300 MHz) δ 7.72 (br s, 1 H), 7.47 (d, J = 7.9 Hz, 1 H), 7.21 (br s, 1 H), 6.95 (br s, 1 H), 4.93 (td, J = 11.6, 3.9 Hz, 1 H, CHNC=O), 3.17 (ddd, J = 11.5, 3.3, 1.0 Hz, 1 H), 3.00 (br d, J = 11.1 Hz, 1 H), 2.50-2.85 (m, 6 H), 2.31 (td, J = 10.8, 3.7 Hz, 1 H), 1.70-2.00 (m, 7 H), 1.42 (br s, 1 H), 1.03 (t, J = 7.4 Hz, 3 H, CH_3); ^{13}C nmr (75 MHz) δ 172.88, 138.09, 132.75, 132.26, 129.90, 57.18, 54.54, 46.48, 45.71, 42.83, 31.60, 28.31, 23.91, 9.57; ms (EI) m/z 369 (12, M+), 209 (24), 152 (15); HRms (EI) Calcd for $C_{18}H_{25}N_3OCl_2$: 369.1375; Found: 369.1376. The hydrochloride salt was prepared by treatment with excess etheral HCl and recrystalized from methanol-ether: mp 192 °C (decomp.); HRms (FAB) Calcd for [$C_{18}H_{25}N_3OCl_2$ + H]: 370.1453; Found: 370.1448.

Molecular Modeling

Conformational searching of **3** yielded 613 minima, only 40 of which fell within 5.0 kcal/mol of the global minimum conformation shown in Figure 2. Unsurprisingly, all 40 structures were in chair conformations with equatorial substituents, and thus placed the three nitrogens in the same relative positions; they are distinguished primarily by whether the phenyl ring is above or below the plane of the piperidine ring, and also by different orientations and conformations of the pyrrolidine ring. Conformational searching of buspirone yielded 529 minima, all within 6.7 kcal/mole of the global minimum (414 within 5.0 kcal/mol). These conformations were systematically overlaid on the global minimum conformation of **3** so as to minimize the RMS separation of the corresponding nitrogens of the two molecules as shown in Figure 2. Seven buspirone conformations with energies *ca.* 3.6 kcal/mole above the global minimum could be overlaid on **3** with an RMS deviation of less than 0.3 Å; the best match is shown in Figure 2. Additional conformations *ca.* 1.5 kcal/mol above the global minimum could be overlaid less well, with an RMS deviation of *ca.* 0.7 Å. The 17 lowest energy conformations all were greater than 1.1 Å RMS. For comparison, the worst possible fit of any buspirone conformation to **3** is 2.2 Å RMS.

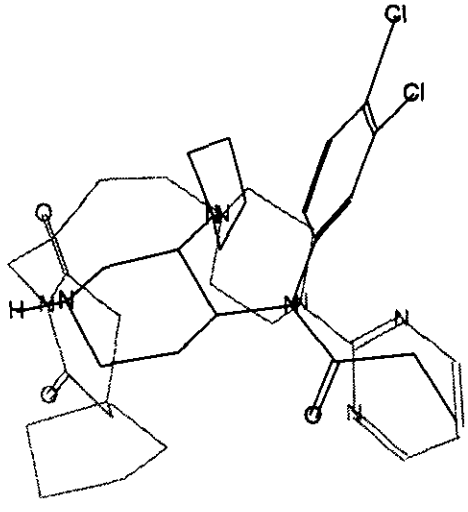


Figure 2. Closest overlay of minimized conformations of compound (**1**) (in gray) with low energy conformation of compound (**3**) (in black).

ACKNOWLEDGMENT

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6. For earlier observation of such common intermediate formation, see: a) Reference 4; b) Reference 5.
7. We observed the regioselectivity of this ring opening before in the case of the Cbz (instead of Boc) protected intermediate (**8**) with methylamine.[5]
8. In relation to the hypothetical antidepressant activity of compound (**3**): 1) *in vitro* results indicated that compound (**3**) has weak affinity for the cloned neuronal serotonin transporter (less than 1/10 fluoxetine) and 2) *in vivo* was inactive in the behavioral despair paradigm at doses up to 10 mg/kg. With respect to buspirone like receptor activity, compound (**3**) was found to be inactive (K_i > μM) in the 5-HT_{1A} binding assay.
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11. BatchMin V3.5a. Note that the MM2* force field supplied with BatchMin differs significantly from the authentic MM2 treatment (N. L. Allinger, *J. Am. Chem. Soc.*, **1977**, *99*, 8127).

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