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Rapid Communication

Design and Stereoselective Synthesis of Conformationally Constrained Analogues of Zimeldine

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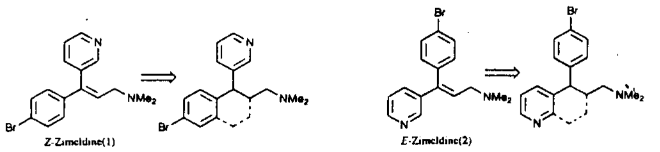
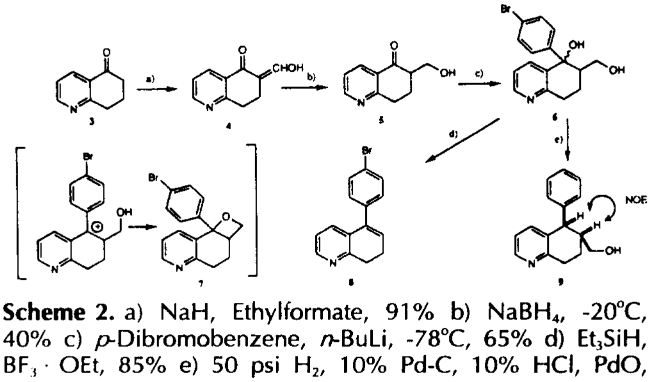
Most of the commonly used antidepressant drug (*e. g.* imipramine and amitriptyline) have cardiovascular side effects (orthostatic hypotension, tachycardia, arrhythmia) due to the action of these drugs at cholinergic and adrenergic sites (Ankier, 1986). The goal of this research program is to design and sythesize very selective inhibitors for the uptake of either, but not both, norepinephrine (NE) or serotonin (5HT). Examining the relation between the conformation of these molecules and their selectivity for inhibition of the uptake of NE or 5HT could provide an understanding of the molecular mechanisms involved. Such information could lead to even safer antidepressant drugs with diminished cardiovascular side effects. Furthermore, drugs that are selective for inhibition of the uptake of 5HT (*e.g.* fluoxetine) show promise as aspects for obesity control (Grunewald *et al.*, 1986a). In order to find new drugs with enhanced selectivity for the uptake of 5HT which could be useful as antidepressants requires an understanding of the structural features of these drugs that results in their selectivity for the 5HT uptake carrier. As part of a search for the explanation of the dramatic pharmacological difference between (*Z*)-Zimeldine (**1**, a selective inhibitor of the reuptake of serotonin) and (*E*)-Zimeldine (**2**, a selective inhibitor of norepinephrine) in presynaptic nerve endings (Hoberg *et al.*, 1981), we sought a convenient synthesis of conformationally defined analogues of **1** and **2** in the quinoline and naphthalene skeleton. We wondered if subtle changes in low energy conformations of the members of each of these pairs might be, at least in part, responsible for the neurotransmitter selectivity (Grunewald *et al.*, 1986b). Therefore, a detailed molecular mechanics study of the conformational space available to *E*- and *Z*-zimeldine was performed and their constrained analogues were designed. In this paper, we describe the synthesis of constrained *E*-zimeldine analogs in highly stereoselective manner.

For the synthesis of tetrahydro Zimeldine analogues, 6-hydroxymethyl quinolone (**5**) was chosen as a key intermediate. The quinolinone (**3**) was formylated with ethyl formate in the pesence of sodium hydride, and the β-keto aldehyde (**4**) could be cleanly isolated in high yield. The selective reduction of formyl group was achieved by carrying out the reaction with sodium borohydride in cooled (-20°C) methanol affording the hydroxymethyl quinolone (**5**) which easily led to the carbinol (**6**) through 1,2-addition reaction with 4-bromolithium. When the carbinol (**5**) was treated with triethylsilane in the presence of boron trifluoride, (Smonou *et al.*, 1988) unexpected dihydroquinoline (**8**) was obtained via the possible oxetane intermediate (**7**). Next, we investigated the medium hydrogen pressure hydrogenolysis reaction. Surprisingly, upon treatment of the carbinol (**6**) with 10%Pd-C in 10%hydrochloric acid under 50 psi hydrogen pressure, (Mitsui *et al.*, 1966) the *cis* debrominated tetrahydroquinoline (**9**) was only obtained as a sole product. The configuration of the alcohol (**9**) was determined by proton nmr coupling constant of benzyl proton (4.43 ppm, *J*=2.5 Hz) as well as NOE experiment of two methine protons.



Scheme 1



Scheme 2. a) NaH, Ethylformate, 91% b) NaBH$_4$, -20°C, 40% c) *p*-Dibromobenzene, *n*-BuLi, -78°C, 65% d) Et$_3$SiH, BF$_3$ · OEt, 85% e) 50 psi H$_2$, 10% Pd-C, 10% HCl, PdO, 65%.

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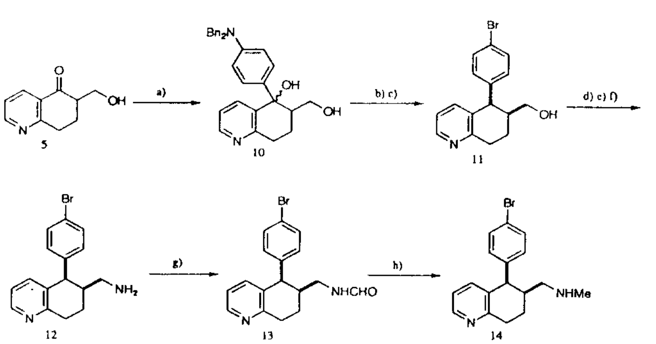
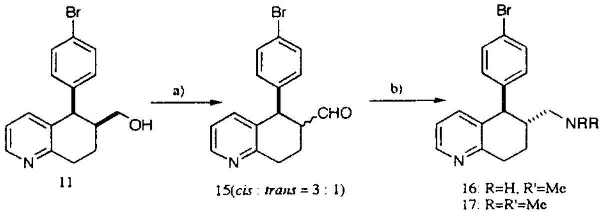


Scheme 3. a) 4-Bromo-*N*,*N*-Dibenzylaniline, *n*-BuLi, THF, -78°C, 66% b) 50 psi H_2, 10% Pd-C, PdO, 10% HCl, 75% c) $NaNO_2$, CuBr, 48% HBr, 53% d) *p*-TsCl, pyr, 86% e) NaN_3, DMF, 83% f) $LiAlH_4$, THF, 80% g) ethylformate, sealed tube, 90°C, 71% h) AlH_3, THF, 86%



Scheme 4. a) DMSO, Oxalyl chloride, 55% b) Me_2NH HCl, $NaBH_3CN$, 33% or $MeNH_2$, $NaBH_3CN$, 57%

Based on the above reaction result we modified one of the bromine of 1,4-dibromobenzene to dibenzylamine group which could be converted to halogen atom by Sandmeyer reaction (Harrington *et al.*, 1984).

Hydroxymethylquinolone (**5**) was treated with 4-bromodibenzylaniline containing of *n*-buthyllithium to provide the carbinol (**10**). Hydrogenolysis of **10** performed in the forementioned condition and consecutive treatment of sodium nitrite with copper bromide in 48%hydrobromic acid afforded the desired cis tetrahydroquinoline (**11**) as expected. The stereochemistry of **11** was also unambigously confirmed by NOE experiment of benzyl proton and homobenzyl methine as well as the coupling constant of benzyl proton in its proton nmr spectrum (4.32 ppm, *J*=4.9 Hz). Conversion of alcohol (**11**) to amine (**12**) was achieved by general method. Tosylation of alcohol (**11**) with *p*-toluenesulfonyl chloride followed by replacing azide and subsequent reduction with lithium aluminum hydride produced the amine (**12**) which was formylated with ethylformate in sealed tube at 90°C. Reduction of formylamine (**13**) with alane resulted in the *cis* methylamine (**14**), *cis-E*-Zimeldine analogue.

The aldehyde (**15**) was obtained by Swern oxidation of the alcohol (**11**) as a mixture (*cis*: *trans*=3 : 1). Without isolation of two isomers Borch reductive amination with methylamine or dimethylamine performed to give the corresponding *trans* amines (**16, 17**), *trans-E*-Zimeldine analogues, as a single isomer, respectively (Borch *et al.*, 1971).

Now we could accomplish the stereoselective synthesis of *cis* and *trans* 5,6-disubstitued quinoline derivatives. The evaluation of prepared conformationally constrained Zimeldine analogues as possible inhibitors of neurotransmitters is in progress.

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Spectral data of **11**; mp 135-137 C; 1H NMR ($CDCl_3$) d 8.37-8.36 (m, 1H), 7.31, 6.85 (AB-q, each 2H, *J*= 8.4 Hz), 7.30-7.22 (m, 1H), 7.09-6.98 (m, 1H), 4.32 (d, 1H, *J*=4.9 Hz), 3.42-3.18 (m, 2H), 3.11-3.01 (m, 1H), 2.41-1.53 (m, 4H); 13C NMR ($CDCl_3$) 157.0,

147.8, 140.6, 138.6, 131.9, 131.0, 121.6, 120.6, 64.4, 44.8, 40.6, 31.7, 19.9; MS (EI) m/e 317, 319 (M^+, 1 : 1), 220 (33), 180 (100), 179 (30), 152 (29), 130 (76), 77 (36). *Anal.* Calcd for $C_{16}H_{16}BrNO$: C, 60.39; H,5.07; N, 4.40. Found: C, 60.72; H, 5.23; N, 4.32.