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Synthesis of a Benzo[b]-1,5-naphthyridine Derivative as a Potential Constrained NK_1 Receptor Antagonist

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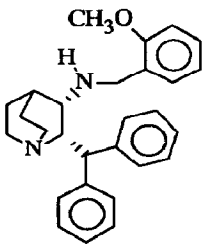
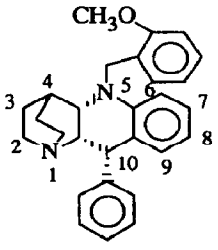
Abstract: : A short synthesis of a cyclic constrained analogue **1** of the potent Substance P antagonist (±) CP-96345 is described. The key feature is the formation of the benzo[b]-1,5-naphthyridine system at the very last step of the synthesis throught an intramolecular arylation of an amine promoted by a strong base. If the tricyclic system was synthesized first, 2-methoxy benzylation of both the nitrogen atoms occurred.

In the last years a great interest has been given to NK_1 receptor antagonists for their potential usefulness in many pathological situations. CP-96345[1] was the first described potent non-peptidic antagonist. Since benzo[b]-1,5-naphthyridine derivatives, as constrained analogues of CP-96345, could be potent NK-1 receptor antagonists and represent powerful tools for the development of a pharmacophoric model, we planned to synthesize 2H-1,4-ethano-3,4,4a,5,10,10a-hexahydro-5-(2-methoxyphenyl) methyl-10-phenyl-benzo[b]-1,5-naphthyridine (compound **1**).



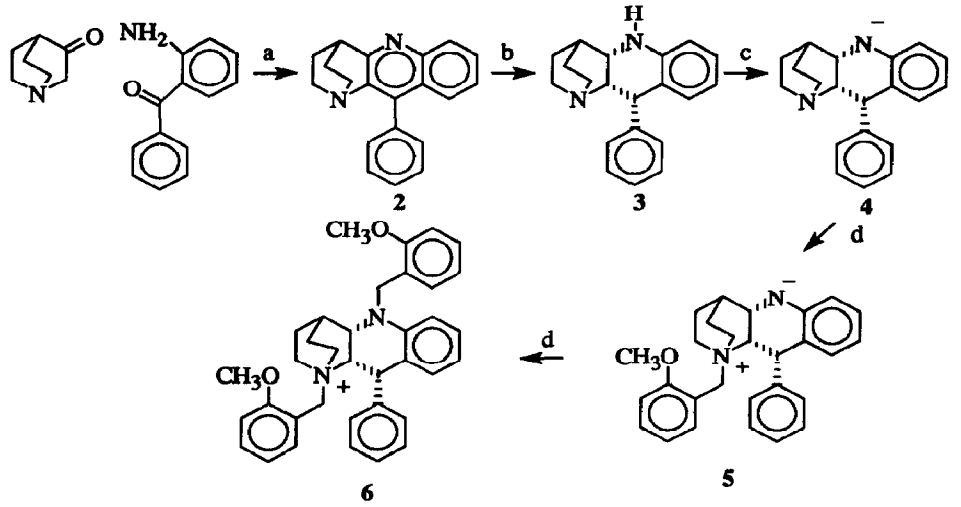
CP-96345



1

Friedländer synthesis[2] with quinuclidin-3-one and 2-amino-benzoquinone gave the 10-phenyl-benzo[b]-1,5-naphthyridine **2** which was reduced with sodium/propanol to the corresponding hexahydro derivative **3** in a yield of 67%. Although three stereogenic carbon atoms were in the molecule, only one diasteroisomer was detected[3]. ^1H nmr in C_6D_6 showed for both $J_{4a,10a}$ and $J_{10,10a}$ a value of 9.6 Hz. The rigid structure of the ring-system prevents rotation around the C_{4a}-C_{10a} bond and the dihedral angle calculated from $J_{4a,10a}$ was in accordance only with a *cis* configuration. The relative position of H_{10} and H_{10a} was more ambiguous since angles calculated from $J_{10,10a}$ were in accordance with both *cis* and *trans* configurations. The NOESY

spectrum revealed a strong cross-peak between the latter protons which, when compared with the cross-peak for a methylenic pair, gave an estimated distance between H_{10} and H_{10a} of about 2.2 Å, in accordance with the *cis* configuration. In conclusion the structure of compound 3 was (4aRS, 10RS, 10aRS)-1,4-ethano-3,4,4a,5,10,10a-hexahydro-10-phenyl-benzo[b]-1,5-naphthyridine.



a) OH^- b) Na, n-PrOH c) LDA d) 2-MeO-C_6H_4- CH_2-Cl

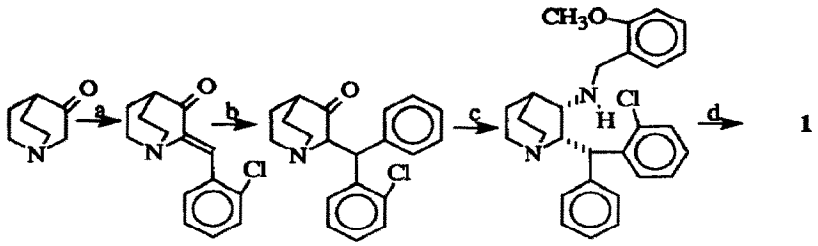
Compound 3 was treated at low temperature with one equivalent of butyl lithium (BuLi) or lithium diisopropylamide (LDA) followed by 2-methoxybenzylbromide. The major product, obtained in 37% yield, had ^1H and ^{13}C nmr and ms data in accordance with the proposed structure of compound 6[4], but almost 40% of the starting amine 3 was recovered. When two equivalents of BuLi were used, amine 3 was no longer detected but no significant improvement in the yield of the product 6 was achieved. Anyway, under the conditions used, the desired compound 1 was never found.

Since benzylation of the nitrogen of the quinuclidine moiety in compound 3 does not occur under neutral conditions, even at room temperature, the initial formation of the anion 4, due to the action of a strong base such as LDA, must play an important role in the ensuing reaction. Probably the anion 4 easily added a 2-methoxybenzyl group on the nitrogen in position 1 owing to the formation of the highly stabilized zwitterionic species 5, which then could add another 2-methoxybenzyl group on nitrogen in position 5.

Since the desired product 1 could not be obtained by this procedure, another synthetic approach, based on the synthesis of CP-96345[5], was followed.

Thus 3-quinuclidinone was condensed with 2-chlorobenzaldehyde and subsequently with phenyl magnesium bromide in the presence of CuBr to give compound 7 (yield 45%) as a mixture of two

diasteroisomers in a ratio of roughly 70 : 30. The major isomer was purified, and reacted with 2-methoxybenzylamine and sodium borohydride to give the parent (2,3 -*cis*) quinuclidine **8** (yield 37%) [5].



a) 2-Cl-C_6H_4-CHO, OH^- b) Ph-MgBr, CuBr c) 2-MeO-C_6H_4- CH_2NH_2, $NaBH_4$ d)BuLi

Final cyclization was done with a stoichiometric amount of BuLi in THF, for 2 hours at -60°C, in a yield of 83%. Probably the reaction occurred through the initial formation of an aryne intermediate[6], which could intramolecularly react with the amine to give the final product (4aRS, 10RS, 10aRS) 2H-1,4-ethano-3,4,4a,5,10,10a-hexahydro-5-(2-methoxyphenyl) methyl-10-phenyl-benzo[b]-1,5-naphthyridine **1**[7].

As in the case of compound **2**, the relative configuration between H in positions 10 and 10a was assessed by a NOESY experiment in $CDCl_3$. The cross-peak relating these protons was not dependable because of a strong interference with J-coupling effects. Another cross-peak, however, between H_{4a} and H_{10}, together with a value for $J_{4a,10a}$ =10.3 Hz and for $J_{10,10a}$ = 8.4 Hz, demonstrated the *cis* configuration for these hydrogens.

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References and notes

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2. Coffen, D.L.; Wong F. *J. Org. Chem.* **1974**, 39, 1765-1767.
3. ^1H nmr (200 MHz, $CDCl_3$) ; δ 7.2-7.5 (m, 5H, ArH), 7.07 (t, 1H, J=7.9 Hz, ArH.), 6.68 (m, 2H, ArH), 6.50 (d, 1H, J=7.9 Hz, ArH), 3.95 (d, 1H, J=9.2 Hz; H_{10a}), 3.7 (vb s, 1H, NH), 3.23-3.48 (m, 3H), 2.97 (m, 1H), 2.71 (m, 2H), 2.17 (m, 1H), 1.83 (m,1H), 1.67 (m, 2H), 1.39 (m, 1H); ^{13}C nmr (50 MHz; CDCl3) 21.47, 27.63, 43.12, 52.02 (CH), 30.24, 46.77, 55.96, 66.48 (CH_2), 116.11, 121.09, 128.81, 128.89, 129.49, 130.73 (2C), 131.12 (2C) (CH Ar), 143.40, 148.60 (C^s Ar); ms: m/z 290 (M^+)

4. ^{1}H nmr (200 MHz, $CDCl_3$) ; δ 7.92 (d, 1H J = 7.4, ArH), 6.8-7.4 (m, 13H, ArH), 6.76 (d, 1H, J = 8.2, ArH), 6.60 (t, 1H, J = 7.8, ArH), 6.46 (d, 1H, J = 7.8, ArH), 5.68 (d, 1H, J = 9.8, H_{10a}) 4.77 + 5.38 (2d, J = 9.8, $PhCH_2$-N^+), 4.97 (s, 1H, H_{10}), 4.15 + 4.45 (2d, J = 14.8, $PhCH_2$-N), 3.79 (m, 1H, H_{4a}), 3.67 (s, 3H, OCH_3), 4.01 (s, 3H, OCH_3), 2.7 + 2.95 (m, 4H, $2CH_2N^+$), 2.45 (m, 1H, H_4), 1.5-2.2 (m, 4H); ^{13}C nmr (50MHz; $CDCl_3$) 57.19, 57.39 (CH_3) 21.53, 24.11, 46.17, 52.55, 58.68, 59.14 (CH_2), 26.07, 43.44, 57.53, 74.36 (CH), 112.24, 112.94, 114.99, 120.84, 122.45, 123.45, 128.96, 130.07 (2C), 130.61, 130.69 (2C), 131.76, 131.90, 134.28, 138.28 (CH Ar), 117.71, 125.68 (2C), 139.95, 147.89, 159.10, 160.44 (C^s Ar); ms: m/z 531 (M^+)

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7. ^{1}H nmr (200 MHz, $CDCl_3$); δ 7.2-7.4 (m, 6H, ArH), 7.04 (m, 1H, ArH), 6.8-7.0 (m, 2H, ArH), 6.6-6.8 (m, 2H, ArH), 4.48 (dd, 2H, J = 16.9, CH_2Ar), 4.22 (d, 1H, J = 8.4, H_{10}), 3.91 (s, 3H, CH_3O), 3.71 (dd, 1H, J = 8.4, 10.3, H_{10a}), 3.40 (d, 1H, J = 10.3, H_{4a}), 3.17 (m, 1H), 2.75-3.0 (m, 2H), 2.63 (m, 1H), 2.26 (m, 1H), 1.3-1.9 (m, 4H).; ^{13}C nmr (50 MHz, $CDCl_3$) 57.28 (CH_3),21.76, 27.67, 43.99, 48.04, 51.77 (CH_2), 27.32, 48.51, 60.46, 66.33 (CH), 111.90, 115.18, 120.14, 122.37, 128.60, 129.25, 129.54, 129.59, 130.36, 130.58 (2C), 130.75 (2C) (CH Ar), 128.11, 134.57, 144.42, 148.55, 158.87 (C^s Ar); ms : m/z 410 (M^+)

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