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SYNTHESIS OF CONFORMATIONALLY RESTRICTED SUBSTANCE P ANTAGONISTS

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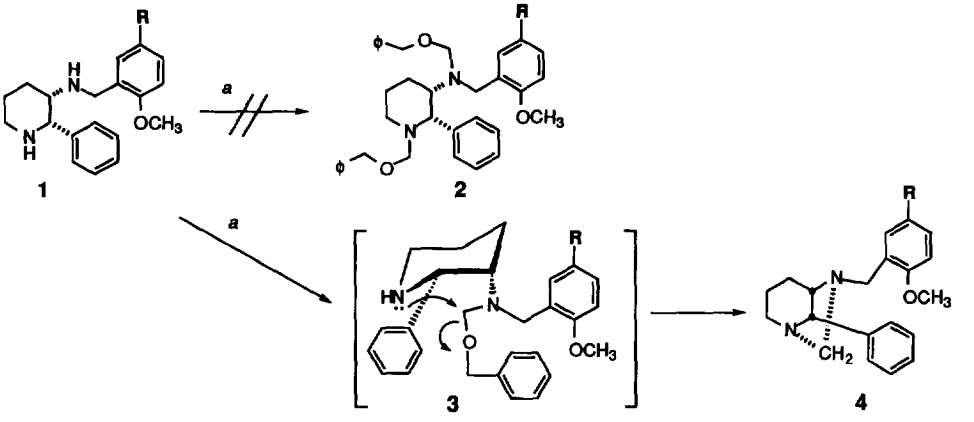
Abstract: Reaction of CP-99,994 (**1**) with benzyl chloromethyl ether under basic conditions produced the novel 1,6-diazabicyclo[3.2.1]octane system in good yield; analogs containing this nucleus display high binding affinity for substance P receptors. The ethylene homologue of **1a**, diamine **7**, shows enhanced inhibitory activity and may more closely approximate the binding conformation of **1a** at the NK_1 receptor.

Substance P (SP) is an undecapeptide with potential relevance in inflammatory processes, e.g., asthma, arthritis.[1] The recent disclosure of a variety of potent and selective non-peptide SP antagonists has intensified research efforts to develop more efficacious compounds and has broadened our understanding of the role of SP in a variety of diseases.[2]

During the course of our investigation of SP-selective antagonists, it became necessary to protect the secondary amines of our template molecule, CP-99,994 (**1a**, R=H), during modifications to the benzylic side chain. The first protecting group we considered was the benzyloxymethyl moiety.[3] Using two equivalents of sodium hydride in anhydrous THF, the dianion of **1a**[4] was generated and treated with two equivalents of benzyl chloromethyl ether (BCE) at room temperature, as illustrated in Scheme 1.



Reagents: (a) 2 equiv. $ClCH_2OCH_2C_6H_5$, 2 equiv. NaH, THF

Scheme 1

Following workup, the isolated crude solid was recrystallized. There was no evidence of the benzyl ether protons expected for **2a** by ^{1}H-NMR but, instead, an increase in the integration within the 3.5-4.0 ppm (δ) region corresponding to the presence of two additional protons. An X-Ray analysis of a single crystal showed conclusively the formation of the new bicyclic structure **4a** in which the nitrogen atoms had been linked by a methylene spacer.[5]

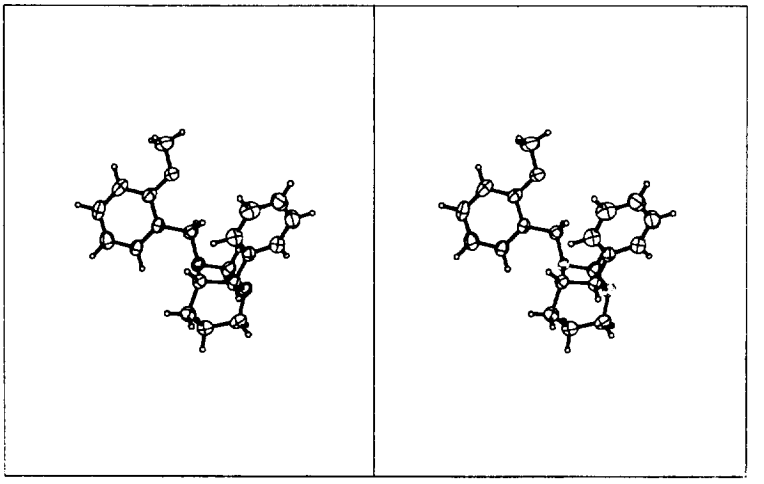
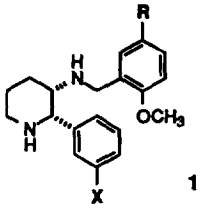


Figure 1. Stereoscopic view of the X-ray crystal structure of compound **4a**

As to the mechanism of this reaction, we propose that the initial alkylation of the exocyclic amine produces intermediate **3**. The resulting aminal then undergoes nucleophilic attack by the piperidine nitrogen; this appears to be the rate limiting step in the cyclization to **4a**, as evidence of its formation by TLC and HPLC requires several hours to develop. Subsequent loss of benzyl alcohol provides the novel 1,6-diazabicyclo[3.2.1]octane **4a**. Interestingly, reaction of **1a** with 37% aqueous formaldehyde solution in refluxing methanol gave product **4a**, although in a slightly lower yield.

We repeated this process with other analogs of **1a** as the starting diamine, as shown in Table 1.[6,7] In general, compounds **4a-e** display NK_1 binding comparable to the corresponding non-bridged compounds **1a-e**, with the exception of **4b,c** which exhibit approximately five-fold weaker potencies.

A possible concern with respect to the observed activity of **4a** was the potential instability of the geminal diamine portion of this molecule and related analogs; *i.e.*, is compound **4a** converted to **1a** after a period of time in the test medium? When **4a** was suspended in the buffer solution used in our binding assay, no evidence of instability was observed over a period of five days at room temperature.



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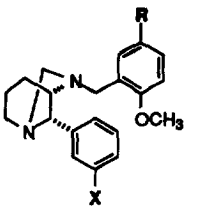

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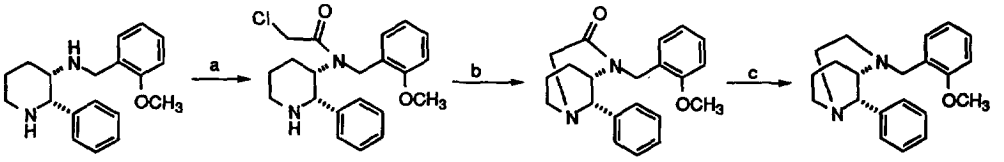
No.	R	X	IC_{50} (nM)[6]	No.	IC_{50} (nM)[6]
1a	H	H	0.53± 0.01 (35)	4a	0.61 ± 0.058 (3)
1b		H	1.2 ± 0.35 (3)	4b	6.1 ± 3.0 (3)
1c	Cl	F	0.61 ± 0.17 (3)	4c	3.8 ± 0.26 (3)
1d	F	Cl	3.3 ± 0.94 (3)	4d	1.2 ± 0.39 (3)
1e	NSO_2Me | CH_3	H	0.21 ± 0.036 (4)	4e	0.27 ± 0.04 (3)

Table 1

As a means of further evaluating the effects on SP antagonism resulting from conformational constraint of **1a**, we next prepared the ethylene homologue **7a** as shown in scheme 2; this compound would be expected to demonstrate greater chemical and metabolic stability than diamine **4a**. Treatment of **1a** with chloroacetyl chloride and TEA in THF gave, after flash chromatography, amide **5** which was cyclized to lactam **6** by stirring with 1.1 equivalents of potassium tert-butoxide in THF at 25 °C for 12 hours. Treatment of a THF solution of **6** with 1.1 equivalents of borane•THF complex at reflux for one hour gave, after workup and silica gel chromatography, the pure 1,4-diazabicyclo[3.3.1]nonane **7a**.



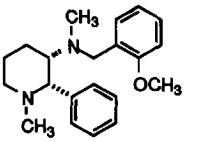
1a **5** **6** **7a**

Reagents: (a) $ClCH_2COCl$, TEA, THF; (b) t-BuOK, THF; (c) BH_3•THF, THF

Scheme 2

Compound **7a** is a potent SP inhibitor with an IC_{50} of 0.36±0.12 nM (n=3), which is in close agreement with the value determined for compound **1a**, suggesting that, like **4a** this modification produces a molecule whose conformation more closely approximates that of diamine **1a** when bound to the receptor. By

comparison, the bis-N-methylated analog **8** shows a 40-fold lower affinity (IC_{50} = 14.0 nM, n=3) than **1a**. We are preparing other structurally constrained analogs of **7a** to determine whether this is a general phenomenon.



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In summary, the use of benzyl chloromethyl ether provides an alternative method to the use of formaldehyde in the prepartion of novel, conformationally restricted, substance P antagonists. Further investigations of the SAR of structurally rigid SP receptor antagonists are ongoing; the results of one of these studies has recently appeared[8] and others will be reported in future communications.

Acknowledgment. We are grateful for the X-ray determination of compound **4a** performed by Dr. Jon Bordner and Ms. Deb DeCosta and for the many helpful recommendations offered by Dr. John Lowe.

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1. Payan, D.G. *Ann. Rev. Med.*, **1989**, *40*, 341.

2. (a) Snider, R.M.; Constantine, J.W.; Lowe, J.A., III; Longo, K.P.; Lebel, W.S.: Woody, H.A.; Drozda, S.E.; Desai, M.C.; Vinick, F.J.; Spencer, R.W.; Hess, H.-J. *Science*, **1991**, *251*, 435. (b) Swain, C.J.; Seward, E.M.; Sabin, V.; Owen, S.; Baker, R.; Cascieri, M.A.; Sadowski, S.; Strader, C.; Ball, R.G. *Bioorg. Med. Chem Lett.*, **1993**, *3(8)*, 1703. (c) Lowe, J.A., III *Ann. Rep. Med. Chem.*, **1993**, *28*, 99.

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4. Desai, M.C.; Lefkowitz, S.L.; Thadeio, P.F.; Longo, K.P.; Snider, R.M. *J. Med. Chem.*, **1992**, *35*, 4911.

5. A representative crystal, grown from methanol/methylene chloride, was surveyed. The absolute configuration was fixed because C4 and C5 were known to have the S-configuration. Coordinates, anisotropic temperature factors, distances and angles are available from the authors.

6. Inhibition of ^{125}I-Bolton-Hunter substance P was determined using human IM-9 cells, as described in McLean, S.; Ganong, A.; Seymour, P.A.; Snider, R.M.; Desai, M.C.; Rosen, T.; Bryce, D.K.; Longo, K.P.; Reynolds, L.S.; Robinson, G.; Schmidt, A.W.; Siok, C.; Heym, J. *J. Pharmacol. Exp. Ther.*, **1993**, *267(1)*, 472. IC50 ± s.e.m. (nM) are presented for (n) determinations.

7. Satisfactory spectral data were obtained for all new compounds.

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