

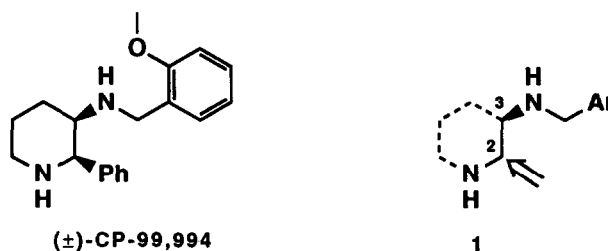
## SYNTHESIS OF (±)-CP-99,994: A HIGHLY POTENT SUBSTANCE P ANTAGONIST

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**Abstract:** The synthesis of racemic CP-99,994, a highly potent substance P antagonist is reported. The synthesis outlined here is suitable for developing structure activity relationships for this important class of compounds.

Substance P (SP),<sup>1</sup> an eleven amino acid peptide identified by von Euler and Gaddum in 1931<sup>2</sup> and characterized by Leeman in 1970,<sup>3</sup> has been implicated in the pathogenesis of diverse diseases such as arthritis, asthma, inflammatory bowel disease and schizophrenia.<sup>4</sup> The pharmacology of SP and its precise role in various disorders is complicated by the presence of multiple receptor subtypes and by the lack of potent and selective antagonists. All the SP receptor antagonists described until recently have been made by modification of SP itself. Their use in *in vivo* animal models and as drugs is severely limited because of rapid degradation by proteases and poor oral absorption.

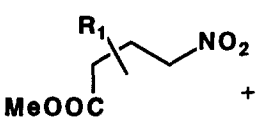
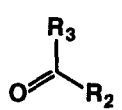
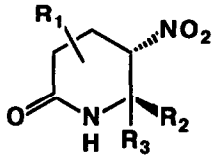
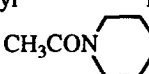

We have been engaged in developing non-peptidic SP antagonists;<sup>5,6</sup> the activity of several prototypes synthesized in our laboratory prompted us to consider CP-99,994 as a target.<sup>7</sup> We report here the synthesis of racemic CP-99,994 *via* a method which is suitable for exploring structure activity relationships (structure 1).



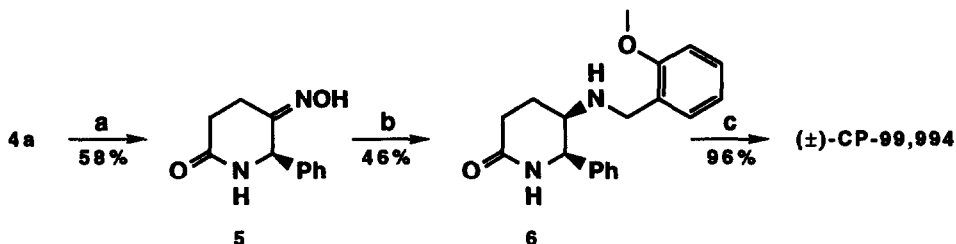
The choice of synthetic route called for two considerations: (1) the piperidine must be constructed in a manner which permits investigation of the effects of a variety of substituents at C-2 and other ring positions of 1 on SP receptor binding, and (2) the synthetic protocol should be reliable and require few chromatographic steps. This analysis prompted us to explore the condensation of  $\gamma$ -nitrobutyrate with aldehydes and ketones in the presence of ammonium acetate.<sup>8</sup> In the case of (±)-CP-99,994 the functionalized piperidine ring was efficiently assembled by the Knoevenagel reaction of benzaldehyde with methyl 4-nitrobutanoate in the presence of ammonium acetate, followed by intramolecular cyclization to yield the thermodynamically stable **4a** in 98% yield.

This reaction is general and facile: heteroaromatic, alicyclic and acyclic aldehydes (examples **3b-f**, Table 1) undergo this condensation reaction to afford **4b-f** in good yield. Surprisingly, even ketones undergo this condensation to produce **4g** and **4h** albeit in low yield. The reaction was also successful when substituted methyl 4-nitrobutanoates (**2i** and **2j**) were employed in the reaction. Thus, the use of methyl 2-methyl-, and methyl 4-methyl-, 4-nitro butanoate afforded 1:1 mixtures **4i** and **4j** respectively. In all cases investigated, after the completion of the reaction analytically pure products **4** crystallized out on cooling (0°C). The *trans* stereochemistry between the C-3 nitro and the C-2 substituent in adducts **4** (**a-f**, **i**, **j**) was assigned from <sup>1</sup>H-NMR ( $J_{2,3} = 8\text{Hz}$ ).<sup>7</sup>

**Table 1:** Condensation of methyl  $\gamma$ -nitrobutyrates with aldehydes and ketones

		+		$\longrightarrow$		
	<b>2</b>		<b>3</b>		<b>4</b>	
	R <sub>1</sub>		R <sub>2</sub>		R <sub>3</sub>	Yield
a	H		Ph		H	98%
b	H		cyclohexyl		H	82%
c	H		<i>tert</i> -butyl		H	67%
d	H		2-furyl		H	72%
e	H		2-thiophenyl	H		93%
f	H		3-pyridyl		H	67%
g	H					17%
h	H					24%
i	2-CH <sub>3</sub>		Ph		H	87%
j	4-CH <sub>3</sub>		Ph		H	90%

We anticipated the creation of a *cis*- relationship between the C-2 and C-3 amino substituents of CP-99,994 *via* protonation of the nitronate anion of **4a**.<sup>9</sup> However, various conditions (LDA, -78°C, AcOH or 20% KOH-H<sub>2</sub>SO<sub>4</sub>, -5°C) afforded nearly equal mixture of *cis* and *trans* isomers. Fortuitously, the two step process involving a Nef reaction<sup>10</sup> and reduction of the oxime of the formed ketone was a very convenient and reliable method for the generation of *cis* C-2 and C-3 stereochemistry.



**Reagents :** a) 1. *tert*-BuOK-O<sub>3</sub>, -78°C; Me<sub>2</sub>S; 2. NH<sub>2</sub>OH·HCl; b) 1. Raney Ni, H<sub>2</sub>; 2. 2-OMe-benzaldehyde, NaBH<sub>3</sub>CN, 4Å sieves; 3. SiO<sub>2</sub>-gel column; c) 1. BMS, THF, reflux; 2. HCl-Et<sub>2</sub>O

**Scheme 1**

Typically the nitro group of the condensation product 4a was oxidatively processed with ozone in the presence potassium *tert*-butoxide at -78°C.<sup>11</sup> The crude reaction mixture, after quenching with dimethyl sulfide was treated with excess hydroxylamine (5.0 equiv) to afford the oxime 5 in 58% isolated yield. The use of potassium *tert*-butoxide instead of sodium ethoxide is essential for success of this reaction which otherwise goes only to partial completion. Reduction of 5 with neutral Raney Ni in ethanol proceeded smoothly to provide a mixture of amines (*cis/trans* : 3/1) in quantitative yield. The major isomer was assigned the *cis* stereochemistry from the coupling constant in the <sup>1</sup>H-NMR (*J*<sub>2,3</sub> = 4Hz). Reductive amination of this mixture with *o*-methoxy benzaldehyde and sodium cyanoborohydride in methanol in the presence of 4Å sieves followed by flash chromatography (3% methanol in methylene chloride) afforded 6 in 46% yield. The reduction of 6 with borane dimethylsulfide (THF, reflux, 15hr) afforded the expected diamine which was isolated as a white solid dihydrochloride salt (96%) and crystallized from methanol-ethanol to afford white crystalline (±)-CP-99,994 (83%, overall yield 26% from 4a; scheme 1);<sup>12</sup> its structure was confirmed by X-ray analysis.<sup>7,13</sup> Similarly following the chemistry described in the scheme 1, 4b-4j were converted to the compounds represented by the structure 1. Data describing the activity of these compounds will be reported in due course.

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- 12 Satisfactory spectral data were obtained for all new compounds:  
**Compound 5.**  $^1\text{H-NMR}$  (DMSO- $d_6$ , 300MHz,  $\delta$ ) : 2H, m, 2.04-2.22 ppm; 1H, m, 2.4-2.42 ppm; 1H, dt, 2.71 ppm ( $J = 8, 16$  Hz); 1H,d, 5.02 ppm ( $J = 4$ Hz); 5H, m, 7.28-7.41 ppm; 1H, d, 8.35 ppm ( $J = 4$ Hz); 1H, s, 10.99 ppm.  
**Compound 6.**  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ , 300MHz,  $\delta$ ) : 1H, m, 1.81-1.96 ppm; 1H, m, 2.0-2.18 ppm; 1H, dt, 2.4 ppm ( $J = 4.5, 16$  Hz); 1H, ddd, 2.75 ppm ( $J = 6.5, 10.5, 16$  Hz); 3H, s, 3.48 ppm; 1H, dd, 3.54 ppm ( $J = 13.8$  Hz); 1H, dd, 3.76 ppm ( $J = 13.8$  Hz); 1H, d, 4.72 ppm ( $J = 4$  Hz); 1H, bs, 5.72 ppm; 1H, d, 6.71 ppm ( $J = 8$  Hz); 1H, t, 6.8 ppm ( $J = 7.7$  Hz); 1H, dd, 7.04 ppm ( $J = 1.8, 7.2$  Hz); 1H, dt, 7.17 ppm ( $J = 1.6, 8.2$  Hz); 5H, m, 7.2-7.44 ppm. HRMS : Calculated for  $\text{C}_{19}\text{H}_{22}\text{N}_2\text{O}_2$ -310.1682 Found 310.1649.  
**(+)-CP-99,994.**  $^1\text{H-NMR}$  (free base,  $\text{CDCl}_3$ , 300MHz,  $\delta$ ) : 1H, bd, 1.33-1.45 ( $J = 12.5$  Hz); 1H, dt, 1.53-1.7 ppm ( $J = 3.5, 13.4$  Hz), 1H, dt, 1.84-2.01 ppm ( $J = 4.0, 13.0$  Hz); 1H, bd, 2.09-2.19 ppm ( $J = 13.7$  Hz); 2H, m, 2.72-2.86 ppm; 1H, bd, 3.22-3.3 ppm ( $J = 12.2$  Hz); 1H, d, 3.4 ppm ( $J = 14$  Hz); 3H, s, 3.44 ppm; 1H, d, 3.67 ppm ( $J = 11.4$  Hz); 1H, d, 3.87 ppm ( $J = 2.3$  Hz); 1H, d, 6.66 ppm ( $J = 8.2$  Hz); 1H, bt, 6.79 ppm ( $J = 7.4$  Hz); 1H, dd, 6.97 ppm ( $J = 1.7, 7.4$  Hz); 6H, m, 7.1-7.36 ppm.  $^{13}\text{C-NMR}$  (free base,  $\text{CDCl}_3$ ,  $\delta$ ) : 20.4, 28.2, 46.7, 47.8, 54.7, 54.8, 64.0, 109.8, 120.0, 126.3, 126.5, 127.8, 128.2, 128.3, 129.6, 142.5 and 157.6. HRMS : Calculated for  $\text{C}_{19}\text{H}_{24}\text{N}_2\text{O}$ -296.1889 Found -296.1904.
- 13 CP-99,994 was tested in vitro binding affinity for the SP receptor in Human IM-9 cell using [ $^{125}\text{I}$ ]-BH-SP of substance P. It had an  $K_i$  of  $0.48 \pm 0.2$  nM. For details see McLean, S.; Ganong, A.; Seymour, P. A.; Snider, R. M.; Desai, M. C.; Rosen, T.; Bryce, D. K.; Longo, K. P.; Reynolds, L. D.; Robinson, G.; Schmidt, A. W.; Heym, J.: Pharmacology of CP-99,994; a nonpeptide antagonist of the tachykinin NK1 receptor- paper communicated to *J. Pharmacol. Exp. Ther.* (1992).

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