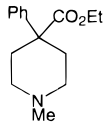
A Diastereospecific Synthesis of 2-Methyl-5β-phenyl-5α-carbethoxy-2-azabicyclo[2.2.1]heptane: A Ring-Constrained Analogue of Meperidine

Stephen M. Husbands, Richard H. Kline, Andrew C. Allen,† and Amy Hauck Newman*

Psychobiology Section, National Institute on Drug Abuse-Intramural Research Program, National Institutes of Health, 5500 Nathan Shock Drive, Baltimore, Maryland 21224

Received September 29, 1997

Meperidine (**1**) is an atypical μ-opioid agonist that displays psychostimulant effects[1] that suggest it might also share some pharmacological characteristics with cocaine. Indeed it has recently been shown that, under certain conditions, meperidine will fully substitute for cocaine in squirrel monkeys, in a drug discrimination model of drug abuse.[2] One hypothesis that has been proposed is that this effect may be due to meperidine interacting at a high affinity binding domain on the dopamine transporter (DAT).[2,3] The psychostimulant effects of cocaine are also believed to result from its blockade of dopamine uptake. However, in contrast to meperidine, cocaine appears to bind to both high and low affinity sites.[4] Although the meperidine structure has been studied in relation to its μ-opioid activity,[5] no work has been carried out to identify the conformation adopted on binding to the DAT.



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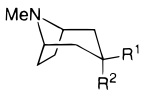
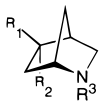


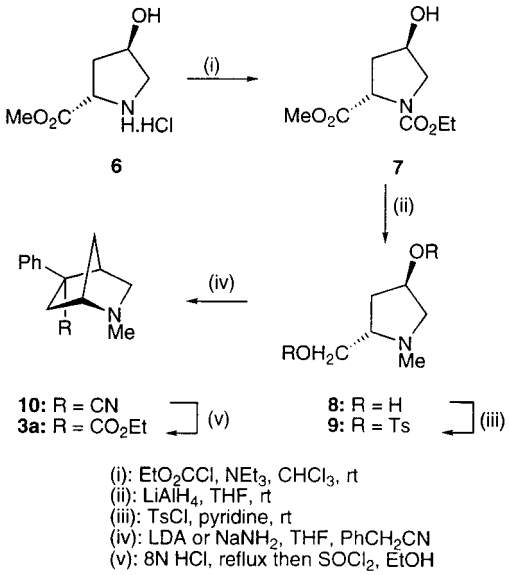
2a: R^1=Ph, R^2=CO_2Et
2b: R^1=CO_2Et, R_2=Ph



3a: R^1=Ph, R^2=CO_2Et, R^3=Me
3b: R^1=CO_2Et, R^2=Ph, R^3=Me
4a: R^1=Ph, R^2=CO_2Et, R^3=Ts
4b: R^1=CO_2Et, R^2=Ph, R^3=Ts
5a: R^1=Ph, R^2=CO_2Et, R^3=H
5b: R^1=CO_2Et, R^2=Ph, R^3=H

Meperidine is a 4-phenylpiperidine that has significant structural flexibility and can exist in both chair and boat conformations. To gain a better understanding of the conformation adopted on binding to the DAT, we were interested in studying ring constrained analogues in which the important pharmacophores are held rigidly with respect to one another. Analogues of the chair conformation of meperidine have been prepared and include the tropanes (**2a**, **2b**).[6] In contrast, no compounds are commercially available that mimic the boat conformation of meperidine. Analogues **3a** and **3b** have been prepared previously, to study binding to the μ-opioid receptor and appeared ideal for our own studies.[5] However, we were unable to repeat the original synthesis, satisfactorily. Specifically, the detosylation of the **4a**, **4b** mixture to **5a**, **5b** could not be performed using the originally reported procedure nor a number of alternative reagents and conditions. This original synthesis also required the separation of the two diastereomers by column chromatography and recrystallization, whereas we now report the diastereospecific synthesis of one of the desired diastereomers using a procedure that is readily reproducible.

Scheme 1



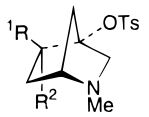
(i): EtO_2CCl, NEt_3, $CHCl_3$, rt
(ii): $LiAlH_4$, THF, rt
(iii): TsCl, pyridine, rt
(iv): LDA or $NaNH_2$, THF, $PhCH_2CN$
(v): 8N HCl, reflux then $SOCl_2$, EtOH

trans-L-Hydroxyproline methyl ester (**6**) is readily made from commercially available *trans*-L-hydroxyproline[7] which could be converted into **3a** in five steps (Scheme 1). Formation of the ethyl carbamate (**7**) was achieved by treating **6** with ethyl chloroformate and triethylamine in $CHCl_3$. This was followed by reduction with lithium aluminum hydride (2 equiv) to give the NMe, diol **8**. Tosylation using 2.4 equivalents of TsCl in pyridine (4 °C) gave **9** in 18% yield (over the three steps). Alkylation with phenylacetonitrile anion was attempted with three different bases. It was found that best results were obtained with LDA or $NaNH_2$ in THF, a multicomponent mixture being formed with NaH in DMSO. Thus treatment of **9** with phenylacetonitrile (1.2 equiv) and LDA (2.7 equiv) in THF yielded **10** (48%). Utilization of $NaNH_2$ in THF led to a 37% yield of **10**. Interestingly, these successful alkylations resulted in only one diastereoisomer being formed.[8] This is in contrast to alkylation utilizing the bulkier *N*-tosyl analogue of **9**, where both isomers are formed (**4a**, **4b**).[7] This is an unusual finding, in that the smaller group resulted in greater stereoselectivity and may be explained by consideration of the likely transition states **11a** and **11b** (Figure 1). Clearly the phenyl group has a much greater steric bulk than the nitrile, and thus transition state **11a** should be favored over **11b**, leading to formation of the *exo*-phenyl product. However, in the case of the NTs intermediate, edge to face interactions between the two phenyl groups can be envisioned, thus stabilizing the more hindered transition state.

* Corresponding author. Ph 410-550-1455. FAX 410-550-1648. email: anewman@irp.nida.nih.gov
† Current address: Smith Kline Beecham, Research and Development, King of Prussia, PA 19406.

(1) Himmelsbach, C. K. *J. Pharmacol. Exp. Ther.* **1942**, *75*, 64.
(2) Izenwasser, S.; Newman, A. H.; Cox, B. M.; Katz, J. L. *Eur. J. Pharmacol.* **1996**, *297*, 9.
(3) Katz, J. L.; Newman, A. H.; Izenwasser, S. *Pharmacol. Biochem. Behav.* **1997**, *57*, 1.
(4) Madras, B. K.; Fahey, M. A.; Bergman, J.; Canfield, D. R.; Spealman, R. D. *J. Pharmacol. Exp. Ther.* **1989**, *251*, 131.
(5) Portoghese, P. S.; Mikhail, A. A.; Kupferberg, H. J. *J. Med. Chem.* **1968**, *11*, 219.
(6) Daum, S. J.; Martini, C. M.; Kullnig, R. K.; Clarke, R. L. *J. Med. Chem.* **1975**, *18*, 196.
(7) Remuzon, P. *Tetrahedron* **1996**, *52*, 13803.
(8) The configuration at C-5 was determined by NOE experiments. Irradiation of the H-6 *exo*, but not the H-6 *endo*, proton caused an enhancement of the signal for the phenyl ring.
(9) See the Supporting Information. Newman, A. H.; Kline, R. H.; Allen, A. C.; Izenwasser, S.; George, C.; Katz, J. L. *J. Med. Chem.* **1995**, *38*, 3933.

S0022-3263(97)01791-X
Published on Web 01/14/1998



11a: R^1 = Ph, R^2 = CN
11b: R^2 = Ph, R^1 = CN

Figure 1. Transition states of intermediate nitrile.

This leads to the observed 6:4 ratio of *exo*:*endo*-phenyl isomers.[5] In the present work, where the smaller NMe group is utilized, no phenyl−phenyl interactions are possible, leading to specific formation of the *exo*-phenyl product via the least hindered transition state. Hydrolysis of **10** in 8 N HCl, followed by esterification, gave the desired conformationally restricted analogue of meperidine (**3a**).[8]

Thus, we have demonstrated a diastereospecific synthesis of the bridged meperidine analogue **3a**. The synthesis of the opposite diastereomer using tosyl-like, phenyl-containing groups and the pharmacological characterization of these compounds are in progress.

Supporting Information Available: Experimental procedures[9] and spectral data are available for compounds **3a** and **6**−**10** (4 pages).

JO971791Z