Pergamon

Tetrahedron Letters 40 (1999) 3905–3908

TETRAHEDRON LETTERS

An Expedient Synthesis of 9-Keto-2-methyl-5-(dimethoxyphenyl)morphans†

Joannes T.M. Linders*[,a,‡], Judith L. Flippen-Anderson[b], Clifford F. George[b] and Kenner C. Rice[a]

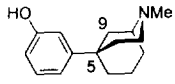
[a]Laboratory of Medicinal Chemistry, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Maryland 20892-0815, United States of America.
[b]Laboratory for the Structure of Matter, Naval Research Laboratory, Code 6030, Washington D.C. 20375, United States of America.

Received 9 February 1999; accepted 15 March 1999

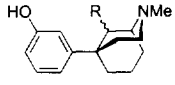
Abstract: An expedient synthesis of ortho-methoxy substituted 9-keto-5-phenylmorphans has been developed, featuring a Thorpe-Zieger cyclization to construct the substituted 2-phenylcyclohexanone intermediate. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: Thorpe-Ziegler reaction; alkylation; phenylmorphans

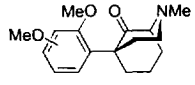
5-(3-Hydroxyphenyl)-2-methylmorphan **1** was discovered during the fifties by May and Murphy[1] as an analgesic with a potency comparable to morphine. Intensive studies in the early seventies uncovered an unusual pattern of agonist and antagonist activity and addictive properties. The (+)-enantiomer (1S,5R) proved to be a potent agonist (4-5x morphine), which substituted for morphine in morphine-dependent monkeys, and showed addictive properties comparable to morphine.[2] However, its optical antipode, being equipotent to morphine in analgesic potency, also showed antagonist activity, and precipitated withdrawal in morphine-dependent monkeys. Later, it was shown that both enantiomers of **1** bind potently to the μ-receptor.[3]



1



2a R = α-OH
2b R = β-OH
2c R = α-Me
2d R = β-Me



3a 2,3-diMeO
3b 2,5-diMeO

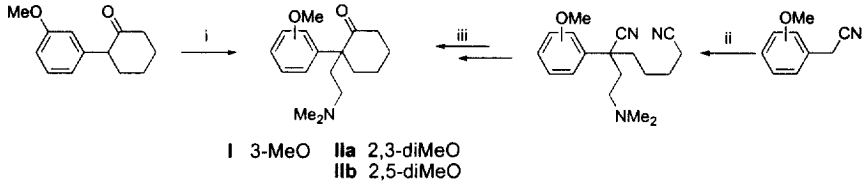
Substituted phenylmorphans have been shown to exhibit interesting properties, in particular the 9-hydroxy and 9-methyl derivatives **2a-d**.[4,5,6] The 9α-hydroxy derivative **2a** is a strong antinociceptive agent while its epimer **2b** is inactive.[4] The (+)-enantiomer of **2c** is devoid of analgesic activity, but shows nalorphine-like antagonist activity.[5] Very recently, Carroll and coworkers showed that the 9β-methyl epimer **2d** is a potent, pure antagonist at μ, κ, and δ opioid receptors.[6]

† *Dedicated to Dr. Leendert Maat on the occasion of his 65th birthday.*
‡ Present address: Department of Medicinal Chemistry, Janssen Research Foundation, B-2340 Beerse, Belgium.

0040-4039/99/$ - see front matter © 1999 Elsevier Science Ltd. All rights reserved.
PII: S0040-4039(99)00566-3

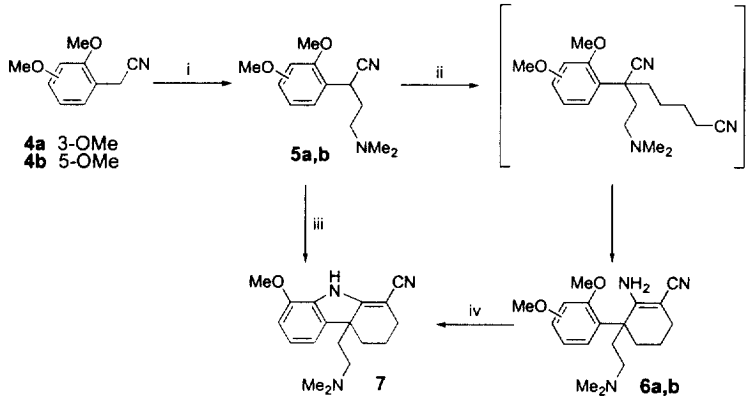
In the ongoing efforts of our lab to delineate the SAR of phenylmorphans[7] and oxide-bridged phenylmorphans,[8] we were interested in the synthesis of ortho-methoxy substituted 9-ketophenylmorphans **3**.

The original synthesis of **1** by May and Murphy featured a low-yielding benzylic alkylation of 2-(3-methoxyphenyl)cyclohexanone with dimethylaminoethyl chloride to give **I** (Scheme 1).[1] Even after careful optimization, the substituted phenylcyclohexanone **I** was obtained in only 40% yield, the remainder being the O-alkylated product.[9] Even more serious problems were expected for the synthesis of our target molecules, because the ortho-methoxy substituent increases both the steric hindrance and the stabilization of the benzylic anion, probably leading to an even lower yield of the desired C-alkylation (**IIa,b**). Furthermore, the required ortho-methoxy substituted 2-phenylcyclohexanones can be prepared only by a multistep synthesis.[10,11]



Scheme 1. (i) $ClCH_2CH_2NMe_2$.HCl/NaH, DMF (ref. 1, 9); (ii) double alkylation; (iii) Thorpe-Ziegler reaction, hydrolysis.

We therefore explored a different approach,[12] based on the construction of the cyclohexanone ring by means of a Thorpe-Ziegler cyclization of an appropriately substituted benzyl cyanide.[13] (Scheme 1) It was shown before that this cyclization also works with an additional substituent in the benzylic position.[14] Furthermore, early introduction of the basic N,N-dimethylaminoethyl sidechain would simplify work-up and purification.



Scheme 2. (i) $NaNH_2/ClCH_2CH_2NMe_2$: **5a**.oxalate 71%, **5b**.oxalate 41%; (ii) 3 eq. $NaNH_2$, $Br(CH_2)_4CN$: **6a** 65%, **6b**.oxalate 58%; (iii) 4 eq. $NaNH_2$, $Br(CH_2)_4CN$: **7**.oxalate 25%; (iv) 1 eq $NaNH_2$.

Treatment of the benzyl cyanide **4a,b**[15,16] with 1 eq. of sodium amide (Scheme 2), followed by alkylation with dimethylaminoethyl chloride gave the amine **5a,b**[17] in 71% isolated yield, along with 25% of starting material, which could be recovered by acid-base extraction. The critical step was the alkylation with bromovaleronitrile. Formation of the sodium salt of **5a,b** with sodium amide (3eq) in THF, followed by addition of the bromide gave the dicyanide which under the reaction conditions directly cyclized to the cyano enamine **6a,b**, easily recognized by its strong IR absorption at 2190 cm^{-1}.[18] Surprisingly, when **5a** was treated with a larger excess of base, a different product was formed, which according to NMR and MS analysis contained only one methoxy group. Single crystal X-ray[19] showed this compound to be carbazole **7**[20] (Fig. 1), presumably formed by a nucleophilic displacement of the aromatic methoxy group by the deprotonated enamine.[21] Indeed, treatment of **6a** with $NaNH_2$ (1 eq.) also gave **7**.

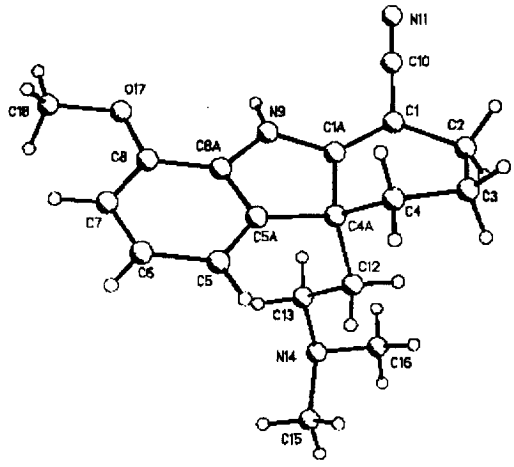
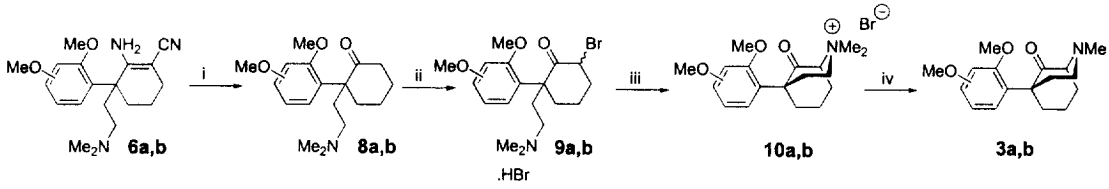


Figure 1. X-ray of compound 7 (free base)

Acid hydrolysis of the enamine and cyanide functions in **6a,b**, followed by decarboxylation gave the desired substituted phenylcyclohexanones **8a,b** (Scheme 3). Bromination gave the α-bromo ketones **9a,b**, conveniently isolated as the HBr salt, as described for the meta-methoxy derivative.[1] However, in contrast to the original synthesis of **1**, neutralization failed to give the cyclized product **10a,b**. Only when the free base of **9a,b** was heated in xylene for 2-4 h, the quaternary compound **10a,b** was obtained, together with small amounts of the tertiary amine **3a,b**.[22] Thermal decomposition of the quaternary salt **10a,b** gave the tertiary amine **3a,b** in good yield, which was crystallized as the HCl salt (Scheme 3).



Scheme 3. (i) $H_2O/HCl/H_3PO_4$: **8a**.HBr 82%, **8b**.HBr 75%; (ii) $Br_2/CHCl_3$: **9a** 82%, **9b** 80%; (iii) a. NH_4OH, b. Δ, p-xylene; (iv) Δ, 1-nonanol: **3a**.HCl 51% (from **8a**), **3b**.HCl 44% (from **8b**).

In summary, we have shown that 9-keto-5-(dimethoxyphenyl)morphans **3a,b** can be synthesized efficiently using a Thorpe Ziegler reaction to construct the cyclohexanone ring. The reaction sequence does not involve chromatographic separations and is amenable to large-scale synthesis of **3a,b.**

Acknowledgements: J.T.M.L. gratefully acknowledges financial support from the Fogarty foundation. J.L.F.-A. and C.F.G. acknowledge support from the Office of Naval Research and the National Institute on Drug Abuse. The authors wish to thank Noel Whittaker, Wesley White, and Herman Yeh (LAC, NIDDK, NIH) for mass spectral and NMR analysis.

References and notes

1 May, E.L.; Murphy, J.G. *J. Org. Chem.* **1955**, *20*, 1197-1201.
2 May, E.L.; Takeda, M. *J. Med. Chem.* **1970**, *13*, 805-807.
3 Froimowitz, M.; Pick, C.G.; Pasternak, G.W. *J. Med. Chem.* **1992**, *35*, 1521-1525.
4 Awaya, H.; May, E.L.; Jacobson, A.E.; Aceto, M.D. *J. Pharm. Sci.* **1984**, *73*, 1867-1868.
5 Awaya, H.; May, E.L.; Aceto, M.D.; Merz, H.; Rogers, M.E.; Harris, L.S. *J. Med. Chem.* **1984**, *27*, 536-539.
6 Thomas, J.B.; Zheng, X.; Mascarella, S.W.; Rothman, R.B.; Dersch, C.M.; Partilla, J.S.; Flippen-Anderson, J.L.; George, C.F.; Cantrell, B.E.; Zimmerman, D.M.; Carroll, F.I. *J. Med. Chem.* **1998**, *41*, 4143-4149.
7 Bertha, C.M.; Flippen-Anderson, J.L.; Rothman, R.B.; Porreca, F.; Davis, P.; Xu, H.; Becketts, K.; Cha X.-Y., Rice, K.C. *J. Med. Chem.* **1995**, *38*, 1523-1537.
8 Burke Jr, T.R.; Jacobson, A.E.; Rice, K.C.; Weissman, B.A.; Cheng, H.; Silverton, J.V. *J. Med. Chem.* **1986**, *29*, 748-751.
9 Rogers, M.E. May, E.L. *J. Med. Chem.* **1974**, *17*, 1328-1330.
10 Nachtsheim, C.M., Frahm, A.W. *Arch. Pharm.* **1989**, *322*, 187-197.
11 Wildman, W.C., Wildman, R.B. *J. Org. Chem.* **1952**, *17*, 581-594.
12 Bonjoch, J.; Casamitjana, N.; Bosch, J. *Tetrahedron* **1988**, *44*, 1735-1741.
13 Schaefer, J.P.; Bloomfield, J.J. *Org. React.* **1967**, *15*, 3-203.
14 a) Horning, E.C.; Horning, M.G.; Platt, E.J. *J. Am. Chem. Soc.* **1948**, *70*, 2072-2075. b) Horning, E.C.; Horning, M.G.; Platt, E.J. *J. Am. Chem. Soc.* **1950**, *72*, 2731-2732.
15 Itoh, K.; Oka, Y. *Chem. Pharm. Bull.* **1980**, *28*, 2862-2867.
16 Harley-Mason, J.; Jackson, A.H. *J. Chem. Soc.* **1954**, 1165-1171.
17 All new compounds were characterized by NMR, MS and elemental analysis. All yields refer to isolated crystalline compounds and are unoptimized.
18 Baldwin, S. *J. Org. Chem.* **1961**, *58*, 3288-3295.
19 Compound **7** crystallized in the tetragonal space group $P\bar{4}2_1c$ with a = b = 13.134(2) Å, c = 19.624 Å, and $\alpha = \beta = \gamma = 90°$. 2535 reflections were collected on a Siemens automated 4-circle diffractometer. The structure was solved by direct methods and refined on F^2 values to a final R-factor of 0.072 for 1272 independent reflections. Coordinates and tables of bond lengths and angles have been deposited at the Cambridge Crystallographic Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.
20 IUPAC name of **7**: 4a-(2-N,N-dimethylamino)ethyl-8-methoxy-2,3,4,4a-tetrahydro-9*H*-carbazole-1-carbonitrile.
21 Nucleophilic displacement of aromatic methoxy groups by lithium amides has been reported before: Ten Hoeve, W; Kruse, C.G.; Luteyn, J.M.; Thiecke, J.R.G.; Wynberg, H. *J. Org. Chem.* **1993**, *58*, 5101-5106.
22 The striking difference in reactivity/stability between **9a,b** and its meta-methoxy derivative from the synthesis of **1** must be due to steric hindrance to assume the phenyl equatorial conformation which is needed for the cyclization to occur.