Tetrahedron Letters, Vol. 33, No. 16, pp. 2103-2106, 1992
Printed in Great Britain

0040-4039/92 $5.00 + .00
Pergamon Press Ltd

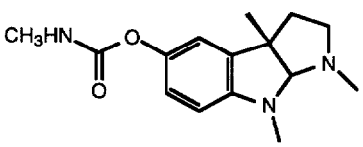
SYNTHESIS AND CARBAMOYLATION OF 1,2,3,4,5,6-HEXAHYDRO-1,3-DIMETHYL-2,6-METHANO-1,3-BENZODIAZOCIN-8-OL: BRIDGED ANALOGUES OF PHYSOSTIGMINE

David M. Fink * and Richard C. Allen

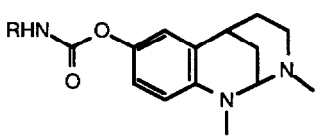
Hoechst-Roussel Pharmaceuticals Inc. P.O. Box 2500 Somerville, N.J. 08876

Abstract: The synthesis and carbamoylation of 2,6-methano-1,3-benzodiazocin-8-ol is described. A one pot silyl-aryl ether to carbamate transformation was developed. The compounds are analogues of the cholinesterase inhibitor physostigmine.

Physostigmine (**1**), the principal alkaloid of the Calabar bean, is a potent cholinesterase inhibitor which is currently in clinical trials for the treatment of Alzheimer's Disease (AD).[1] In our exploration of analogues of physostigmine as agents for the treatment of AD,[2] we were prompted to prepare the geometric isomers **2**, in which the angular methyl group of physostigmine has become a bridging carbon in the new compounds. It has been previously noted that these two types of ring systems share common structural elements.[3] Further examination of the three dimensional shape of these compounds revealed a striking similarity which led to the preparation of the 2,6-methano-1,3-benzodiazocin-8-ol carbamates **2a,b,c** described below.



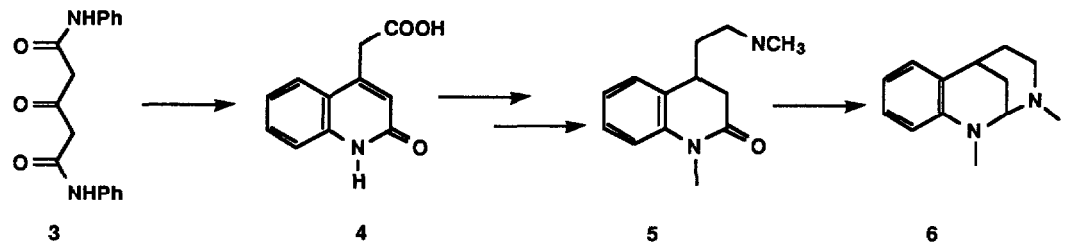
PHYSOSTIGMINE 1



2a R=cyclohexyl
2b R=methyl
2c R=1-methylbenzyl

In the early 1960's Kametani and Mitsuhashi reported the preparation of a variety of 2,6-methanobenzodiazocines as analogues of benzomorphan analgesics, including the parent (unsubstituted) 1,3-isomer in which we were interested.[4,5] The key steps in this synthesis (Scheme 1) were an acid catalyzed aromatic substitution reaction (**3** → **4**) and a reductive cyclization (**5** → **6**). The overall yield for the reported 8 step process was 2-3%. In light of the low yield encountered in the initial cyclization (31%), and the low overall yield in Kametani's route to the 2,6-methano-1,3-benzodiazocines, we pursued an alternate strategy. Our route to this ring system is shown in Scheme 2. The key steps in the synthesis of the nucleus are: 1. an intramolecular Michael addition (**10**→**11**) to prepare the dihydroquinolinone **11**, and 2. a reductive cyclization (**15**→**16**) as in Kametani's synthesis. In addition, a new one-pot procedure for the transformation of an aryl-silyl ether into a carbamate was developed.

Scheme 1

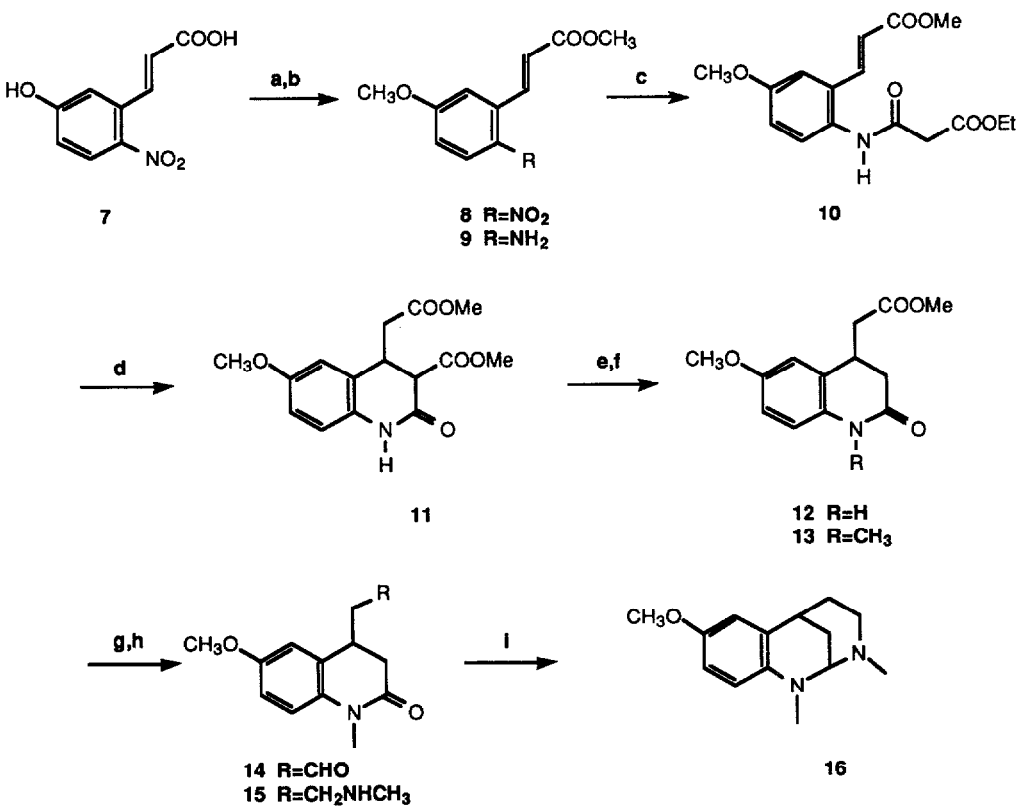


The substrate for the Michael addition **10** was readily prepared starting from 2-nitro-5-hydroxycinnamic acid.[6] Methylation of both the acid and phenol moieties ($(CH_3O)_2SO_2$, K_2CO_3, acetone, reflux), followed by chemical reduction of the nitro group with aqueous titanium trichloride provided the amine-ester **9**.. Subsequent acylation of **9** with ethyl malonyl chloride in the presence of 4-polyvinyl pyridine then afforded the precursor for the Michael addition **10**. Cyclization of **10** with excess sodium methoxide in methanol provided the desired dihydroquinolinone **11**. In addition to effecting the cyclization, treatment with sodium methoxide also accomplished the transesterification of the ethyl ester to a methyl ester, allowing for a more facile removal of the ester in the subsequent step. Decarbalkoxylation of the diester **11** under Krapcho conditions[7] followed by methylation of the quinolinone with sodium hydride and methyl iodide gave the amide ester **13** in 30-40% overall yield after column chromatography.[8]

Transformation of the ester **13** into the methylamine **15** was accomplished in two steps. Selective reduction of the ester to the aldehyde **14** by reaction with DiBAl and morpholine[9] followed immediately by reductive amination (CH_3NH_2•HCl, $NaBH_3CN$)[10] provided **15**, the substrate for the following cyclization, in 55% yield. Reductive cyclization of the amine **15** to the bridged tricycle **16** was readily accomplished in 64% yield by treatment with sodium metal in refluxing n-butanol. Demethylation of the ether proceeded smoothly in the presence of excess BBr_3 to afford the desired phenol **17**. Due to the air sensitive nature of this phenol, special care to exclude oxygen during the demethylation and subsequent work-up was necessary. The compound was purified by formation and recrystallization of the fumarate salt.

Due to the difficulty encountered in handling **17** as the free base, we explored the possibility of protecting the crude phenol as a silyl ether, and then transforming this compound into the desired carbamates (Scheme 3). In the event, demethylation as described above, followed by silylation of the crude phenol ($(i\text{-}Pr)_3SiOTf$, lutidine) gave the silyl ether **18** in 66% yield. Initial attempts at the one-pot conversion of **18** into the cyclohexyl carbamate **2a** failed. For example, treatment of **18**

Scheme 2



7

8 R=NO_2
9 R=NH_2

10

11

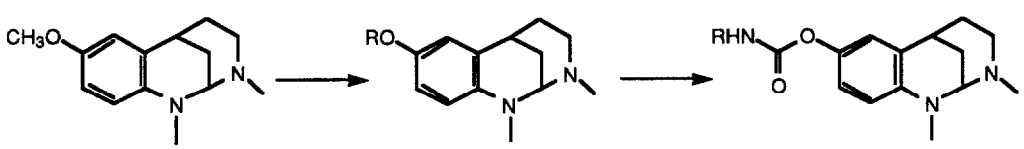
12 R=H
13 R=CH_3

14 R=CHO
15 R=CH_2NHCH_3

16

a) $(MeO)_2SO_2$, K_2CO_3, acetone, reflux; b) aq. $TiCl_3$,NH_4OAc,THF; c) ethyl malonyl chloride, 4-polyvinyl-pyridine, CH_2Cl_2, rt; d)1.3 eq. NaOMe,MeOH reflux; e)NaCl, aq. DMSO,150-160°C; f) NaH, MeI, DMSO, rt; g) RED-Al, morpholine, toluene, -25°C; h) 5 eq. $MeNH_2$ HCl, $NaBH_3CN$, MeOH; i) 20 eq. Na, n-BuOH, reflux

Scheme 3



16

17 R=H
18 R=$(i\text{-}Pr)_3Si$

2a R=cyclohexyl
2b R=methyl
2c R=1-methylbenzyl

with tetra-n-butylammonium fluoride followed by cyclohexyl isocyanate provided only trace amounts of the expected product. Presumably, under these conditions, the equilibrium between

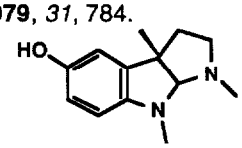
the phenoxide formed upon desilylation of the ether and the carbamoyl anion favors the phenoxide. In the hope of changing this equilibrium, a number of variables, including solvent, counterion and temperature were investigated. We found that addition of excess lithium chloride to the reaction mixture prior to the introduction of the isocyanate gave the desired product **2a** in 64% yield.[11] In the same fashion, carbamates **2b** and **2c** were prepared in 43% and 54% yield, respectively. One of the compounds, **2b**, was found to be a potent cholinesterase inhibitor (IC_{50} = 0.06 uM).[12]

The synthesis of the 8-methoxy-2,6-methano-1,3-benzodiazocine **16** was efficiently accomplished in 8 steps and 10-14% yield. Methodology for the one pot transformation of silyl aryl ethers into carbamates was developed and should prove useful in for the preparation of carbamates from other unstable phenols.

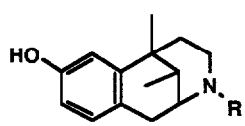
Acknowledgements: The authors wish to thank Francis P. Huger and Gina Bores for the cholinesterase inhibition data and Dana Hallberg, Anastasia Linville and Marc Agnew for spectral data.

REFERENCES

1. *Script* **1991** *No. 1643*, 22.
2. Hamer, R.R.I.; Huger, F.P.; Bores, G.M.; Aschoff, S.M.; Errico, C.L.; Glamkowski, E.J.; Helsley, G.C. and Gorman, A.J. Manuscript submitted for publication.
3. It has been noted that the phenolic oxygens and tertiary amines of eseroline (i) and the benzomorphans (ii) overlap. Galli, A.; Renzi, G.; Bartolini, A.; Malmberg-Aiello, P. *J. Pharm. Pharmacol.* **1979**, *31*, 784.



I



II

4. Kametani, T.; Kigasawa, K.; Hiiragi, M.; Wakisaka, K. *Heterocycles*, **1974**, *2*, 349.
5. Kametani, T.; Kigasawa, K.; Hiiragi, M.*Chem. Pharm. Bull.* **1965**, *13*, 1220.
6. U.S. Patent 4,424,150
7. Krapcho, A.P.; Lovey, A.J. *Tetraheron Lett.* **1973**, 957.
8. The first six reactions were routinlely run on a 0.15 mol scale with no purification until the final step. All new compounds exhibited satisfactory spectral data (NMR, IR and MS).
9. Kanazawa, R.; Tokoroyama, T. *Synthesis*, **1976**, 526.
10. Borch, R.F.; Bernstein, M.D.; Durst, H.D. *J. Amer. Chem. Soc.* **1971**, *93*, 2897.
11. Ten equivalents of lithium chloride were routinely added, however the amount of reagent was not optimized.
12. Compounds were assayed according to the prodecure described in: Ellman, G.L.; Courtney, K.D.; Andres, Jr., V.; and Featherstone, R.M. *Biochem. Pharmacol.* **1961**, *7*, 88.

(Received in USA 10 January 1992)