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Short Research Article

Mechanism of the Bischler–Napieralski exocyclic and endocyclic dehydration products in the radiosynthesis of (*R*)-(-)-(6a-^{14}C)apomorphine†

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Abstract: This paper will outline the mechanism of the Bischler–Napieralski cyclodehydration for the radiosynthesis of (*R*)-(-)-[6a-^{14}C]apomorphine **1**. The carbon-14 radiosynthesis of (*R*)-(-)-[6a-^{14}C]apomorphine was first reported by Kitson and Knagg in May 2006. The Bischler–Napieralski cyclodehydration of 3,4-dimethoxy-2-nitrophenyl-*N*-phenethyl[carboxyl-^{14}C]acetamide **5** was initiated using a mixture of P_2O_5/$POCl_3$ in refluxing toluene. This generated the endocyclic dehydration product 1-(3,4-dimethoxy-2-nitrobenzyl)dihydro[1-^{14}C]isoquinoline **4**. The Bischler–Napieralski endocyclic dehydration by-product was identified from ^{1}H NMR and MS to be 3-(6,7-dimethoxyanthranil)-dihydro[1-^{14}C]isoquinoline **7**. The action of $POCl_3$ in acetonitrile on 3,4-dimethoxy-2-nitrophenyl-*N*-phenethyl[carboxyl-^{14}C]acetamide **5** gave exclusively the exocyclic dehydration product 1-(3,4-dimethoxy-2-nitrobenzal)-1,2,3,4-tetrahydro[1-^{14}C]isoquinoline **8**. Copyright © 2007 John Wiley & Sons, Ltd.

Keywords: apomorphine; cyclodehydration; Bischler–Napieralski; exocyclic; endocyclic

Introduction

(6a*R*)-(-)-Apomorphine [(6a*R*)-(-)-(5,6,7-tetrahydro-6-methyl-4*H*-dibenzo-[de,g]-quinoline-10,11-diol)][1,2] can be prepared from the acid catalysed rearrangement of (5*R*,6*S*,9*R*,13*S*,14*R*)-(-)-morphine.[3] This results in retention of one of its chiral centres (14*R*) to leave a single ***R*** stereogenic centre at the 6a carbon atom (Scheme 1).

Structure and function of (6a*R*)-(-)-apomorphine

(6a*R*)-(-)-Apomorphine is a potent non-selective D_1/D_2 agonist at the dopamine receptor and is used to treat Parkinson's disease (**D**$_2$ receptor).[4] Another application is in the treatment of erectile dysfunction (**D**$_1$ receptor).[5] (6a*R*)-(-)-Apomorphine has the following structural features:

- (*R*) Chiral centre at carbon 6a.
- Contains an *ortho*-phenol motif (ring D).
- Tetracyclic 'aporphine' carbon skeleton (rings A, B, C and D).
- Tetrahydroisoquinoline nucleus (rings A and B).
- 'Near planar' structure.
- *Pharmacophore*: Dopamine can adopt many conformations due to single bond rotation in the alkylamine side chain. Apomorphine contains a rigid dopamine pharmacophore within its framework to prevent rotation thereby facilitating biological activity (Scheme 2).[6,7]

Results and discussion

The retrosynthesis for the incorporation of a single carbon-14 label at the (*R*) stereogenic centre to give (*R*)-(-)-[6a-^{14}C]apomorphine **1** is shown in Scheme 3. The disconnection of the *ortho* aryl carbon–carbon bond in (*R*)-(-)-[6a-^{14}C]apomorphine dimethyl ether **2** gives the 1-(3,4-dimethoxy-2-nitrobenzyl)-2-methyl-1,2,3,4-tetrahydro[1-^{14}C]isoquinoline **3**. This key intermediate was synthesized from the active starting material 3,4-dimethoxy-2-nitrophenyl-*N*-phenethyl[carboxyl-

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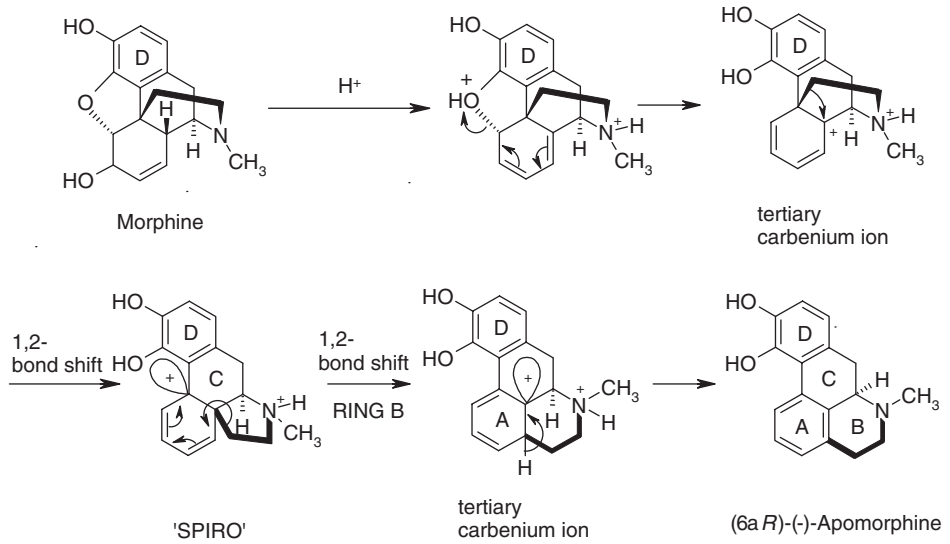
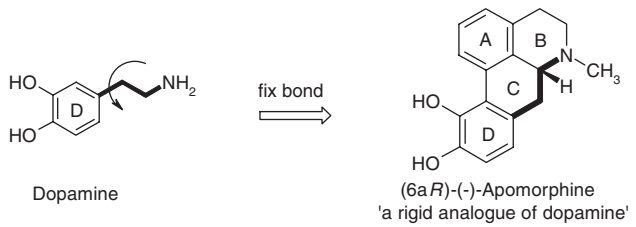


Scheme 1



Scheme 2

^{14}C]acetamide **5** via the application of the Bischler–Napieralski cyclodehydration to give 1-(3,4-dimethoxy-2-nitrobenzyl)dihydro[1-^{14}C]isoquinoline **4**. *N*-Methylation followed by reduction of the endocyclic double bond in **4** gave **3**. A final Pschorr reductive ring closure followed by chiral separation gave **2** and *O*-demethylation to (*R*)-(-)-[6a-^{14}C]apomorphine **1**.

Bischler–Napieralski endocyclic dehydration product

A successful Bischler–Napieralski cyclodehydration was accomplished by activating the amide function between rings A and D in the substrate 3,4-dimethoxy-2-nitrophenyl-*N*-phenethyl[carboxyl-^{14}C]acetamide **5** using P_2O_5/$POCl_3$ in toluene (Scheme 4).[8,9] This generated ring B in the endocyclic dehydration product 1-(3,4-dimethoxy-2-nitrobenzyl)dihydro[1-^{14}C]isoquinoline **4**. A powerful dehydrating mixture incorporating P_2O_5/$POCl_3$ generates the imine phosphate/pyrophosphate which further eliminates to give the nitrilium salt.[10] This is then set up for a 'suggested' 6-*endo-dig* cyclization from ring A to trap the nitrilium salt to form ring B in the endocyclic product **4**.

This was confirmed by ^{1}H NMR (d_6-DMSO, 200 MHz) δ 7.55 (d, 1H, $J = 6.8$ Hz), 7.39–7.10 (m, 5H), 4.05 (s, 2H), 3.87 (s, 3H), 3.85 (s, 3H), 3.48 (t, 2H, $J = 7.3$ Hz), 2.59 (t, 2H, $J = 7.8$ Hz) and positive ion electrospray [LC-MS-ES] with a *pseudo* molecular ion $[MH]^+$ bundle at m/z 327/329 confirming the structure as a single carbon-14 label. No triplet was observed for the isoquinoline nitrogen in **4** therefore indicating that the structure is the imine tautomer.

Bischler–Napieralski endocyclic dehydration by-product

During the reaction with P_2O_5/$POCl_3$ in toluene another product was isolated (Scheme 5) and characterised by MS and ^{1}H NMR. Positive ion [LC-MS-ES] gave a *pseudo* molecular ion $[MH]^+$ bundle at m/z 309/311 and ^{1}H NMR (d_6-DMSO, 200 MHz) δ 7.74 (d, 1H, $J =$ 6.9 Hz), 7.66 (d, 1H, $J = 9.4$ Hz), 7.57 (t, 1H, $J = 6.9$ Hz), 7.50 (t, 1H, J=6.4 Hz), 7.42 (d, 1H, $J = 8.3$ Hz), 7.23 (d, 1H, $J = 9.4$ Hz), 4.04 (s, 3H), 3.94 (s, 3H), 3.94 (t, 2H, $J = 7.0$ Hz), 2.81 (t, 2H, $J = 7.0$ Hz). The above data are consistent with structure **7** having a substituted anthranil ring from the cyclodehydration of the nitrophenyl moiety with the reactive methylene group[11] in **5** to give the intermediate 6,7-dimethoxy-*N*-phenethylanthranil-3-[carboxy-^{14}C]amide **6**. The amide moiety was further dehydrated to initiate the intramolecular cyclization via the phenethylamino group to give 3-(6,7-dimethoxyanthranil)-dihydro[1-^{14}C]isoquinoline **7**.

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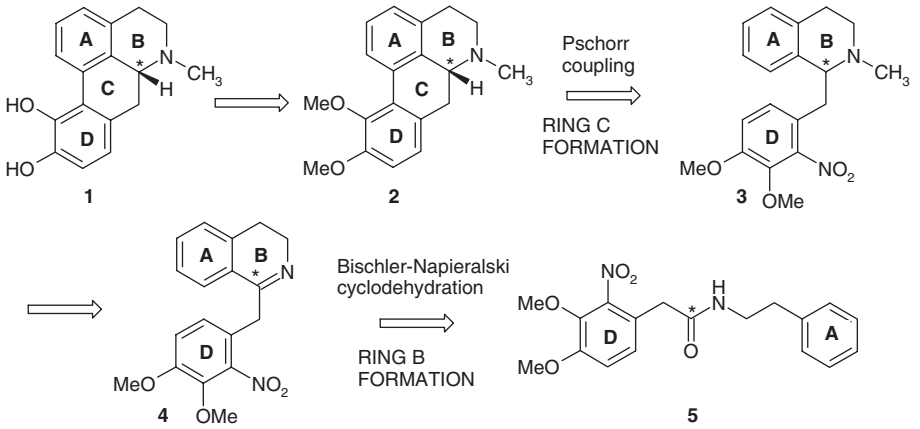
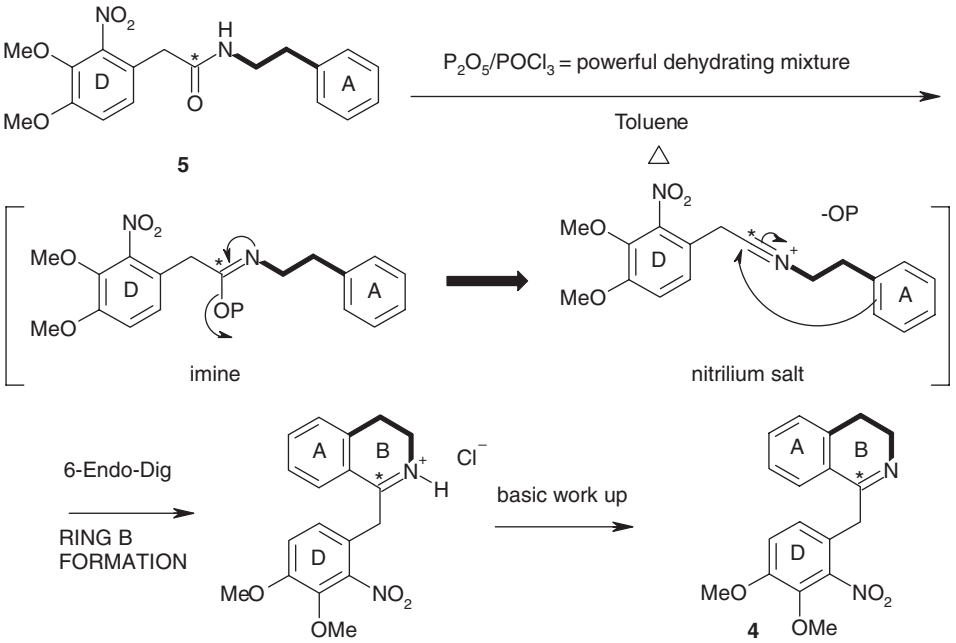


Scheme 3



Scheme 4

Bischler–Napieralski exocyclic dehydration product

When the cyclodehydration of **5** was carried out with $POCl_3$ in refluxing acetonitrile (Scheme 6) it gave exclusively the exocyclic product, 1-(3,4-dimethoxy-2-nitrobenzal)-1,2,3,4-tetrahydro[1-^{14}C]isoquinoline **8**.[12] This product was identified by ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 7.75 (d, 1H, $J = 9.4$ Hz), 7.40–7.20 (m, 5H), 7.10 (d, 1H, $J = 9.4$ Hz), 6.75 (bt, 1H, NH), 4.20 (s, 3H), 4.00 (s, 3H), 3.80 (q, 2H, $J = 7.3$ Hz), 3.00 (t, 2H, $J = 7.3$ Hz) and LRMS analysis by positive-ion EI produced the expected ion bundle [M^+] at m/z 326/328 as expected for a single carbon-14 label.

Using the dehydrating agent $POCl_3$ without P_2O_5 on 3,4-dimethoxy-2-nitrophenyl-*N*-phenethyl[carboxyl-^{14}C]acetamide **5** generated the imine chloride intermediate. This intermediate can be trapped by ring A to form ring B via a 'suggested' 6-endo trig cyclization. The formation of ring B produced a common 'tetrahedral' intermediate which can lead to either the endocyclic or exocyclic dehydration product. The aromatic nitro group may provide neighbouring group participation (NGP) to initiate an E2 elimination of HCl to form a double bond (stilbene) which is conjugated throughout the exocyclic dehydration product, 1-(3,4-dimethoxy-2-nitrobenzal)-1,2,3,4-tetrahydro[1-^{14}C]isoquinoline **8**.

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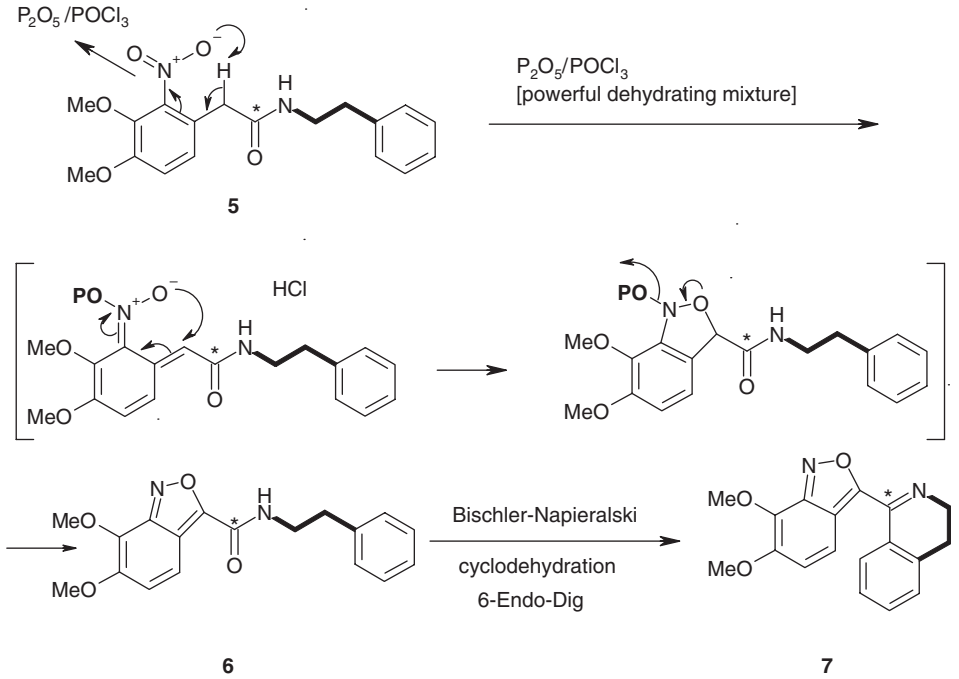
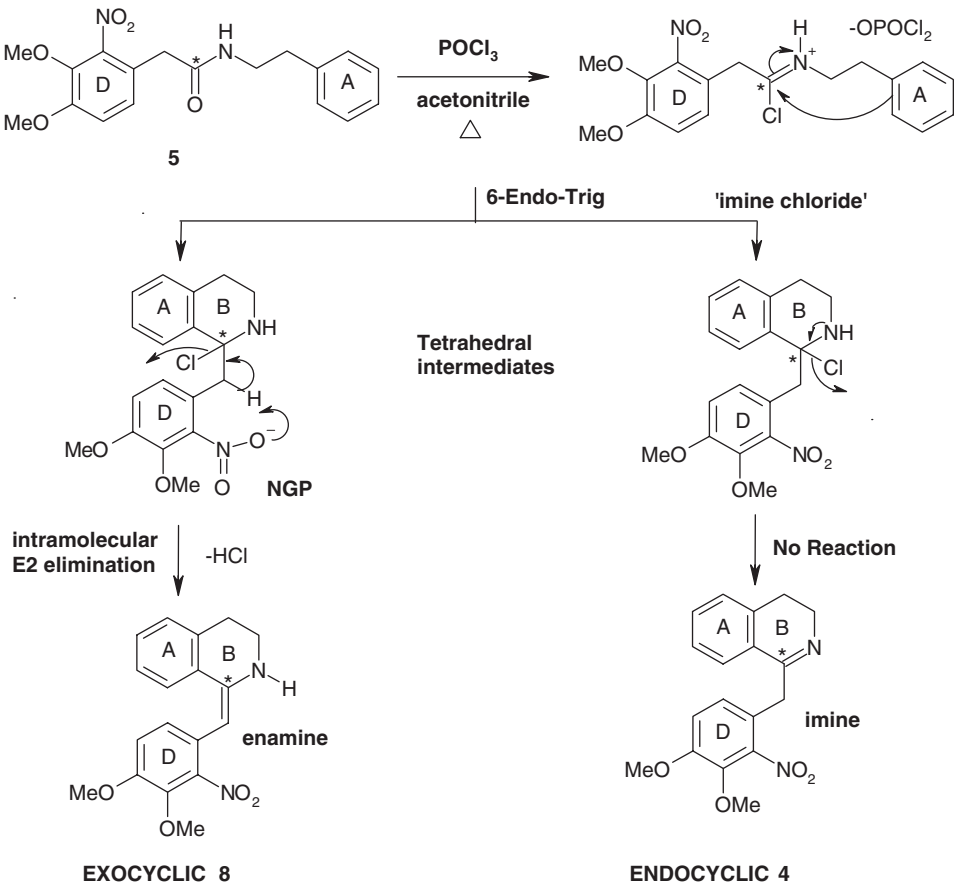


Scheme 5



Scheme 6

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The enamine proton (*NH*) in the tetrahydroisoquinoline **8** gave a triplet in the ^{1}H NMR and did not exchange with D_2O indicating **8** was non-basic. This product did not undergo *N*-methylation with methyl iodide. Consequently, there was no evidence by ^{1}H NMR and MS of elimination of HCl for the formation of the dihydroisoquinoline nucleus in the endocyclic dehydration product 1-(3,4-dimethoxy-2-nitrobenzyl)dihydro[1-^{14}C]isoquinoline **4**.

Conclusion

These mechanisms demonstrate that the Bischler–Napieralski cyclodehydration using $P_2O_5/POCl_3$ does not give a single product. The cyclodehydration is influenced by the presence of the nitro group on the phenyl moiety in 3,4-dimethoxy-2-nitrophenyl-*N*-phenethyl[carboxyl-^{14}C]acetamide **5**. This cyclodehydration step is important in the synthesis of the aporphine alkaloids. When the substituted aromatic ring in which ring closure is to occur is not strongly activated as in **5**, an endocyclic dehydration by-product was isolated. This was identified from MS and ^{1}H NMR to be 3-(6,7-dimethoxyanthranil)-dihydro[1-^{14}C]isoquinoline **7**.

REFERENCES

1. Kitson SL, Knagg E. *J Label Compd Radiopharm* 2006; **49**: 517–531.
2. Roth HJ, Eger K, Troschute R. *Pharmaceutical Chemistry*, vol. 12. Ellis Horwood: Chichester, 1991; 633–635.
3. Neumeyer JL, Neustadt BR, Oh KH, Weinhardt KK, Boyce CB. *J Med Chem* 1973; **16**: 1223–1228.
4. Thomas F, Muir A, Stirton J, Macphee G, Hudson S. *Pharm J* 2001; **267**: 600–612.
5. Segraves RT. *J Urol* 1991; **145**: 1174–1175.
6. Borrelli B. *Neurosci Biobehav Rev* 2000; **24**: 125–132.
7. Lal S. *Prog Neuropsychopharmacol Biol Psychiatry* 1988; **12**: 117–164.
8. EI-Sayrafi S, Rayyan S. *Molecules* 2001; **6**: 279–286.
9. Fodor G, Gal G, Phillips BA. *Angew Chem Int Ed Engl* 1972; **11**: 919–920.
10. Fodor G, Nagubandi S. *Tetrahedron* 1980; **36**: 1279–1300.
11. Wunsch KH, Boulton AJ. *Adv Heterocycl Chem* 1967; **8**: 277–379.
12. Weisbach JA, Burns C, Macko E, Douglas B. *J Med Chem* 1963; **6**: 91–97.

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