

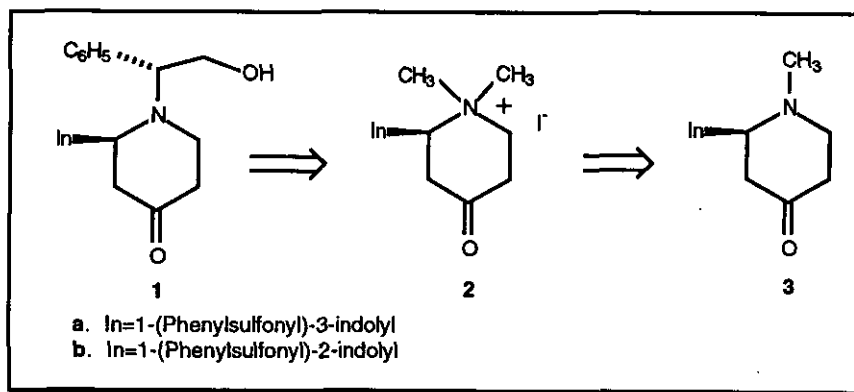
SYNTHESIS OF CHIRAL 2-ARYL-4-PIPERIDONES

Mario Rubiralta,* Anna Diez, Cristina Vila, Josep Castells, and Isabel López

Laboratory of Organic Chemistry, Faculty of Pharmacy,
University of Barcelona, 08028 Barcelona, Spain

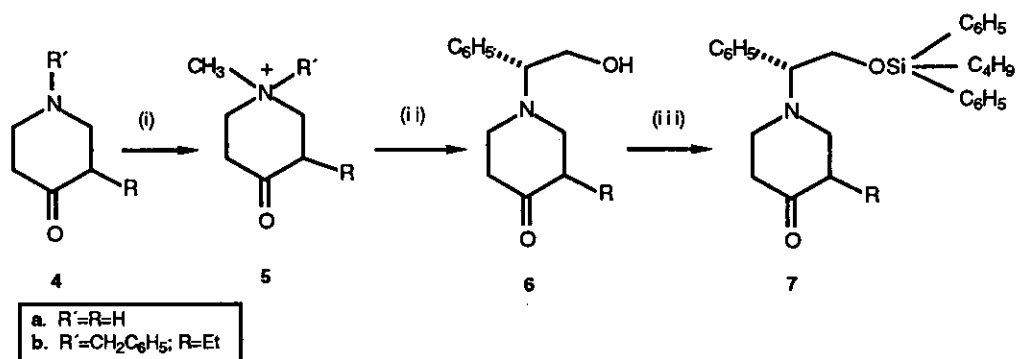
Abstract--The synthesis of chiral 2-(2-indolyl)- and 2-(3-indolyl)-4-piperidones by reaction of *N,N*-dimethyl-4-oxo-2-[1-(phenylsulfonyl)-indolyl]piperidinium iodide and (*R*)-(-)-phenylglycinol is reported.

Some years ago we developed an improved synthesis of 2-aryl-4-piperidones which has been applied to the synthesis of a large number of compounds related to natural products and pharmacologically active compounds.^{1,2} However, until now there is no suitable way described to prepare chiral 2-aryl-4-piperidones, even if very recently, the synthesis of chiral 4-piperidones by the use of a rarely employed reaction between *N,N*-dimethyl-4-oxopiperidinium iodide and (*S*)-(-)- α -methylbenzylamine has been reported.³ In this paper we describe the application of this methodology using (*R*)-(-)-phenylglycinol and 2-arylpiperidinium salts (**2**) to obtain chiral 2-[1-(phenylsulfonyl)-2-indolyl]- and 2-[1-(phenylsulfonyl)-3-indolyl]-4-piperidones (**1a**) and (**1b**) (Scheme 1).



Scheme 1

We first treated piperidinium salts (**5**) with (*R*)-(-)-phenylglycinol and K_2CO_3 in ethanol obtaining the chiral piperidones (**6**) in reasonable yields.^{4,5} Then, the hydroxy group was protected as a silyl ether (**7**).⁶ It is worth mentioning that the quaternization reaction of **4b**⁷ into **5b** only yielded the hydrate form of **5b**.^{8,9} This fact was corroborated by the spectroscopic data. Thus, in the ir spectrum of **5b**.H₂O no absorption at 1705 cm^{-1} but an intense OH band were observed, and the ¹³C nmr spectrum presented a typical chemical shift value of $\delta\ 95.5$ for C-4. After heating **5b**.H₂O at 80°C under a 5 mmHg vacuum for 2 hours the dehydrated compound (**5b**) was obtained, which clearly showed the absorption at 1710 cm^{-1} in the ir spectrum and the signal at $\delta\ 208.5$ in the ¹³C nmr characteristic of the carbonyl function. Reaction of piperidinium salt (**5b**) with (*R*)-(-)-phenylglycinol in the standard conditions yielded a 1:1 diastereomeric mixture of chiral 4-piperidones (**6b**)¹⁰ in 40% yield, which was separated by flash chromatography and the isomers were identified by spectroscopic data. In particular, signals at $\delta\ 60.8$ and 69.3 were observed for the hydroxyethyl chain in the ¹³C nmr spectra of both compounds and significant differences were only observed for C-2 and

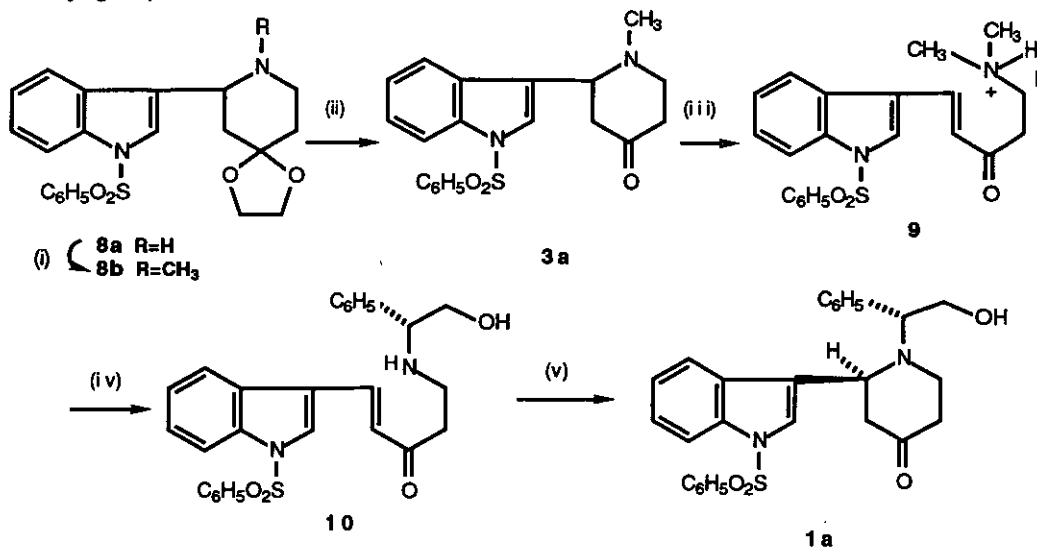


Reagents and Conditions: (i) CH_3I (5 eq.), acetone, room temperature (a: 98%, b: 79%). (ii) 1. (*R*)-(-)-phenylglycinol (1 eq.), K_2CO_3 (2 eq.), $\text{C}_2\text{H}_5\text{OH}-\text{H}_2\text{O}$, Δ ; 2. slow addition of **5a** in CH_2Cl_2 ; 3. Δ , 3-5 h (a: 56%, b: 40%). (iii) TBDPSCI (1.2 eq., imidazole (2 eq.), CH_2Cl_2 , Δ , 12 h (~95%).

Scheme 2

C-6 (56.0 and 47.8 for isomer ($\alpha R,3S$), and δ 51.3 and 52.4 for isomer ($\alpha R,3R$), respectively) indicating that the ethyl substituent adopts an equatorial orientation in the preferred ring conformation of each isomer.

In a further step, we prepared 2-indolyl-4-piperidone (**3a**) by methylation of piperidine (**8a**)¹ and hydrolysis of the resulting acetal (**8b**). Quaternization of piperidone (**3a**) with an excess of methyl iodide in acetone led to enone (**9**)¹¹ as the result of the piperidone ring fragmentation.^{12,13} Formation of **9** was evidenced by the presence of two doublets ($J=16$ Hz) at δ 6.8 and 7.7 in the ¹H nmr spectrum corresponding to the *trans* olefin protons and by the ¹³C nmr chemical shift at δ 199.5 for the carbonyl group. Formation of **9** as a hydroiodide was showed by subsequent liberation to the free amine (**9**) with an aqueous potassium carbonate solution. The most significant modification observed in the ¹H nmr spectra was the shielding ($\Delta\delta$ 0.55) of the singlet corresponding to the *N*-methyl groups.



Reagents and Conditions: (i) CH₃I (1.5 eq.), acetone, room temperature, 5 h (91% yield). (ii) 4N HCl, CH₃OH, Δ , 10 h (96% yield). (iii) CH₃I (4 eq.), acetone, room temperature (65% yield). (iv) 1. (*R*)-(-) phenylglycinol (1 eq.), C₂H₅OH-H₂O, K₂CO₃; 2. **9** in CH₂Cl₂, slow addition, Δ , 5 h. v) EtOH, room temperature, overnight.

Scheme 3

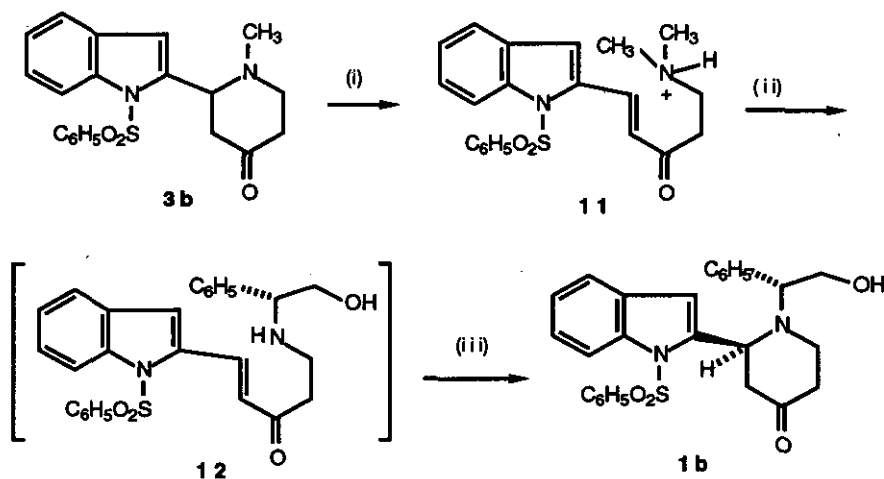
The following treatment of **9** with (*R*)-(-)-phenylglycinol provided enone (**10**),¹⁴ which furnished piperidone (**1a**)¹⁵ by cyclization in ethanol. Compound (**1a**) showed to be a single diastereomer, in which the 2-aryl substituent is in an axial disposition (δ 4.55, doublet of doublets, $J=7$ and 5 Hz). It is worth noting that transformation of 4-ketopiperidinium salts such as **5** into **6** usually involves a three step mechanism: (i) opening of the piperidine ring by a Hofmann β -elimination promoted by the base; (ii) Michael addition of the chiral amine; and (iii) displacement of dimethylamine.^{9,16,17} A similar mechanism could be expected in the transformation of **3a** into **1a**, but instead, enone (**10**) is isolated, which indicates that a substitution of the ammonium salt takes place before the Michael addition.

Finally, piperidone (**3b**), obtained from its corresponding acetal by hydrolysis,¹⁸ was also quaternized with an excess of methyl iodide (Scheme 4). In a similar manner than in the previous case, enone (**11**)¹⁹ was isolated, which was identified by its spectroscopic data. Reaction of **11** with (*R*)-(-)-phenylglycinol furnished enaminone (**12**), which was directly cyclized yielding satisfactorily the desired piperidone (**1b**).^{20,22}

The formation of a single epimer in the case of 2-indolyl-4-piperidones (**1**) can be accounted for by considering an equilibrium between the open enones (**10** and **12**) and the cyclized structures, which leads to the exclusive formation of the thermodynamically most stable isomer.

ACKNOWLEDGEMENTS

This work has been supported by the DGICYT (Spain) through Grant PB-88/0316. We also thank the "Departament d'Ensenyament", Generalitat de Catalunya, for the fellowships given to C. V. and I. L..



Reagents and Conditions: (i) CH_3I (4 eq.), acetone, room temperature (60%) (ii) 1. (*R*)-(-)-phenylglycinol, $\text{C}_2\text{H}_5\text{OH}-\text{H}_2\text{O}$, K_2CO_3 , Δ ; 2. **11** in CH_2Cl_2 is slowly added, Δ , 5 h (iii) $\text{C}_2\text{H}_5\text{OH}$, room temperature, overnight.

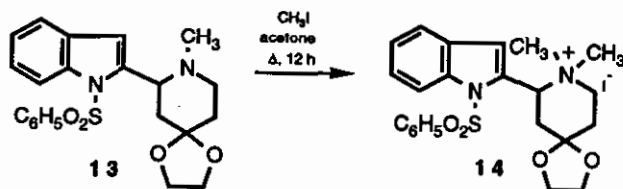
Scheme 4

REFERENCES

1. M. Rubiralta, A. Diez, C. Vila, Y. Troin, and M. Feliz, *J. Org. Chem.*, **1991**, *56*, 6292.
2. For a review on the synthesis and synthetic applications of 2-aryl-4-piperidones, see: M. Rubiralta, E. Giralt, and A. Diez, "Piperidine. Structure, Preparation, Reactivity, and Synthetic Applications of Piperidine and Its Derivatives", Elsevier, Amsterdam, 1991, pp. 313-434.
3. M. E. Kuehne, P. A. Matson, and W. G. Bornmann, *J. Org. Chem.*, **1991**, *56*, 513.
4. All new compounds were identified by their spectral data, optical rotation, and elemental analysis.
5. **6a**: $[\alpha]_D -19.3^\circ$ ($c=1$, $\text{C}_2\text{H}_5\text{OH}$); ir (CHCl_3) 3456 (OH), 1716 (CO); ^1H nmr 2.50-2.60 (m, 2H, COCH_2), 2.68 (m, 2H, 2-Ha), 2.89 (m, 2H, 2-He), 3.70-4.10 (m, 3H, NCH

- CH₂), 7.10-7.50 (m, 5H, ArH); ¹³C nmr 41.5 (C-3), 48.5 (NCH₂), 60.9 (HOCH₂), 69.5 (NCH), 128.4, 128.6, 135.0, 208.4 (CO).
6. **7a**: [α]_D -6° (c=1, C₂H₅OH); ir (CHCl₃) 1712 (CO); ¹H nmr 1.10 (s, 9H, CH₃), 2.43 (t, J=6 Hz, 4H, COCH₂), 2.82 (t, J=6 Hz, 4H, NCH₂), 3.70 (t, J=6 Hz, 2H, NCH), 3.95 and 4.12 (2 dd, J=11, 6 Hz, 1H each, SiOCH₂), 7.10-7.80 (m, 15H); ¹³C nmr 26.4 (SiCH₃), 41.2 (SiOCH₃), 41.5 (C-3), 50.7 (C-2), 66.0 (SiOCH₂), 70.1 (NCH), 121.7, 127.2, 127.5, 127.8, 129.6, 129.7, 133.4, 134.9, 135.7, 140.2, 210.3 (CO).
7. J. Bonjoch, A. Linares, M. Guardiola, and J. Bosch, *Heterocycles*, **1987**, *26*, 2165.
8. (a) R. E. Lyle, R. E. Adel, G. G. Lyle, *J. Org. Chem.*, **1959**, *24*, 342. (b) J. Bosch, M. Rubiralta, *An. Quím.*, **1983**, *79C*, 27.
9. M. M. A. Hassan and A. F. Casy, *Tetrahedron*, **1970**, *26*, 4517.
10. **6b** ($\alpha R, 3S$): ir (CHCl₃) 3430 (OH), 1712 (CO); ¹H nmr 0.87 (t, J=7 Hz, 3H, CH₃), 1.25 (m, 1H, CHCH₃), 1.80 (m, 1H, CHCH₃), 3.72 (t, J=5 Hz, 1H, NCH), 3.85 (dd, J=10, 5 Hz, 1H, CHOH), 4.03 (dd, J=10, 5 Hz, 1H, CHOH), 7.1-7.5 (m, 5 H, ArH); ¹³C nmr 11.4 (CH₃), 20.4 (CH₂), 40.8 (C-5), 47.8 (C-6), 51.6 (C-3), 56.0 (C-2), 60.8 (CH₂OH), 69.3 (NCH), 127.5, 128.2, 129.0, 134.8, 209.8 (CO).
11. **9**.hydroiodide: ir (KBr) 1645 (C=O); ¹H nmr 2.85 (s, 6H, +NCH₃), 3.40-3.50 (m, 4H, CH₂CH₂), 6.85 (d, J=16 Hz, 1H, =CHCO), 7.65 (d, J=16 Hz, 1H, =CHIn), 7.00-8.00 (m, 10H); ¹³C nmr 35.3 (COCH₂), 43.5 (NCH₃), 52.8 (NCH₂), 113.7, 121.0, 124.5, 124.9, 125.8, 127.0, 129.6, 130.1, 134.5, 136.2, 199.5 (CO). **9**: ¹H nmr 2.30 (s, 6H, NCH₃), 2.70 and 2.85 (2 t, J=7 Hz, 2H each, CH₂CH₂), 6.89 (d, J=16 Hz, 1H, =CHCO), 7.72 (d, J=16 Hz, 1H, =CHIn), 7.20-8.05 (m, 10H); ¹³C nmr 39.0 (COCH₂), 45.3 (NCH₃), 54.2 (NCH₂), 113.8, 120.8, 124.3, 125.7, 126.3, 126.7, 128.8, 129.6, 133.7, 134.5, 199.2 (CO).
12. For a similar formation of enones from quaternary salts of 4-piperidones, see: (a) J.-Y. Laronze, J. Sapi, and J. Lévy, *Synthesis*, **1988**, 619. (b) V. Baliah, R. Jeyaraman, and L. Chandrasekaran, *Chem. Rev.*, **1983**, *83*, 379. (c) P. Slosse and C. Hootelé, *Tetrahedron*, **1981**, *37*, 4287.

13. For an acid catalyzed similar ring opening of a 2-phenyl-4-piperidone, see: R. Paugam and L. Wartski, *Tetrahedron Lett.*, **1991**, *32*, 491.
14. **10**: $[\alpha]_D -21^\circ$ ($c=1$, C_2H_5OH); ir ($CHCl_3$) 3550 (OH), 1670 (CO), 1604 (C=C); 1H nmr 3.50-4.00 (m, 4H, CH_2CH_2), 3.60-3.80 (m, 2H, $HOCH_2$), 3.85 (dd, $J=10$, 4 Hz, 1H, NCHPh), 6.80 (d, $J=16$ Hz, 1H, =CHCO), 7.70 (d, $J=16$ Hz, 1H, =CHIn), 7.10-8.00 (m, 15H); ^{13}C nmr 40.0 (COCH₂), 42.0 (NCH₂), 64.7 ($HOCH_2$), 65.9 (NCHPh), 113.8 (In-C7), 120.7 (In-C4), 124.7 (In-C5), 125.7 (In-C6), 125.9 (=CH), 126.9 and 127.3 (C_6H_5 -ortho), 128.2 (C_6H_5 -ipso), 129.2 and 129.6 (C_6H_5 -meta), 134.3 and 134.4 (C_6H_5 -para), 198.7 (C=O).
15. **1a**: $[\alpha]_D -3.0^\circ$ ($c=1$, C_2H_5OH); ir ($CHCl_3$) 3500 (OH), 1715 (C=O); 1H nmr 2.33 (td, $J=11.5$, 3 Hz, 1H, 5-Ha), 2.90 (dd, $J=13$, 10 Hz, 1H, 3-Ha), 3.00-3.14 (m, 1H), 3.30-3.41 (m, 1H), 3.35-3.60 (m, 2H), 6.98 (br s, 1H, In-2H), 7.10-8.20 (m, 14H); ^{13}C nmr 41.3 (C-5), 44.6 (C-3), 47.8 (C-6), 57.3 (C-2), 61.1 (CH_2OH), 63.2 (NCHPh), 114.4, 120.6, 123.8, 125.0, 125.7, 126.9, 128.5, 129.2, 129.5, 134.2, 207.2 (CO).
16. M. E. Kuehne and R. S. Muth, *J. Org. Chem.*, **1991**, *56*, 2701.
17. M. Yu. Dyakov, T. D. Sokolova, A. V. Peretokin, A. S. Moskovkin, and B. V. Unkovskii, *Chem. Heterocycl. Comp.*, **1991**, *26*, 183.
18. (a) M. Rubiralta, A. Diez, C. Vila, *Tetrahedron*, **1990**, *46*, 4443. (b) M. Rubiralta, J. Luque, M. Orozco, A. Diez, I. López, unpublished results.
19. **11**: mp 184-186°C (acetone); 1H nmr (200 MHz, $CDCl_3$ - CD_3OD) 2.98 (s, 6H, NCH₃), 3.44 (br t, $J=7$ Hz, 2H, COCH₂), 3.88 (br t, $J=7$ Hz, 2H, NCH₂), 6.85 (d, $J=16$ Hz, 1H, =CH), 7.20 (s, 1H, In-3H), 7.20-7.60 (m, 7H), 7.72 (d, $J=7.5$ Hz, 1H, In-7H), 8.20 (d, $J=7.5$ Hz, 1H, In-4H), 8.42 (d, $J=16$ Hz, 1H, =CH); ^{13}C nmr (CD_3OD) 34.2 (COCH₂), 42.2 (NCH₃), 52.1 (NCH₂), 113.7, 114.5, 121.5, 124.2, 125.8, 125.6, 126.3, 128.9, 132.9, 133.9, 196.1 (CO).
20. The acetal **13**,¹⁸ precursor of 2-indolyl-4-piperidone (**3b**), was transformed into piperidinium salt (**14**),²¹ in good yield, without formation of opened product.



21. **14**: ^1H nmr 1.55 (d, $J=14$ Hz, 1H, 3-He), 2.05 (d, $J=14$ Hz, 1H, 5-He), 2.40 (td, $J=14, 4$ Hz, 1H, 5-Ha), 3.13 (t, $J=13$ Hz, 1H, 3-Ha), 3.31 (s, 3H, axial NCH_3), 3.42 (s, 3H, equatorial NCH_3), 3.65 (t, $J=14$ Hz, 1H, 6-Ha), 3.9-4.2 (m, 4H, OCH_2), 4.60 (d, $J=14$ Hz, 1H, 6-He), 5.80 (d, $J=13$ Hz, 1H, 2-Ha), 7.20-7.75 (m, 9H), 8.30 (d, $J=7$ Hz, 1H); ^{13}C nmr 30.1 (C-5), 37.1 (C-3), 43.4 (axial NCH_3), 54.2 (equatorial NCH_3), 63.5 (C-6), 64.9 and 65.4 (OCH_2), 65.6 (C-2), 103.9 (C-4), 116.1, 121.0, 122.8, 125.4, 125.8, 127.6, 128.8, 129.5, 135.1, 136.8, 138.2.
22. **1b**: Ir (CHCl_3) 3691 (OH), 1714 (CO); ^1H nmr 1.72 (br d, $J=13$ Hz, 1H, 3Ha), 1.80-2.00 (m, 1H), 2.30-3.00 (m, 4H), 3.80-4.05 (m, 3H, PhCHCH_2), 6.80 (s, 1H, In-3H), 7.00-8.20 (m, 9H); ^{13}C nmr 34.4 (C-5), 42.1 and 42.5 (C-3 and C-6), 54.1 (C-2), 58.9 (CH_2OH), 64.2 (NCHPh), 115.2, 120.9, 123.8, 124.7, 126.3, 126.7, 128.0, 129.1, 129.3, 133.9, 206.7 (CO); ms (m/z , %) 475 (1), 443 (70), 412 (100), 367 (99), 271 (54), 196 (12), 143 (51), 106 (60).

Received, 24th December, 1991