# Indium as a Reducing Agent: Selective Reduction of the Heterocyclic Rings in Quinolines, Isoquinolines and Quinoxalines

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**Abstract:** The heterocyclic ring in quinolines, isoquinolines and quinoxalines is selectively reduced using indium metal in aqueous ethanol.

The selective reduction of the heterocyclic ring in benzo-fused heterocyclic compounds such as quinolines and isoquinolines is an important transformation since the resulting tetrahydro derivatives serve as useful synthetic intermediates.[1] A number of methods have been used for this transformation including catalytic hydrogenation or transfer hydrogenation, lithium in liquid ammonia, diborane, sodium borohydride in the presence of nickel(II) chloride, lithium triethylborohydride, or sodium cyanoborohydride.[2] We now report a new method for the selective reduction of quinolines, isoquinolines and quinoxalines using indium metal in aqueous ethanol.

Indium metal has found a few uses in organic chemistry of late, most notably in the generation of synthetically useful allylindium species.[3,4] However, the first ionisation potential of indium (5.8 eV),[3] which is lower than zinc (9.4 eV) or tin (7.3 eV) and close to that of alkali metals such as sodium (5.1 eV), suggests that the metal ought to participate readily in single electron transfer processes, and therefore be a potent reducing agent. As part of a wider study of the reducing properties of indium metal,[5] we found that it provides an extremely simple method for the reduction of benzo-fused heterocycles such as quinolines to the corresponding 1,2,3,4-tetrahydro derivatives.

The reduction of a series of quinolines was carried out by simply heating the substrate with indium powder in aqueous ethanol containing ammonium chloride,[6] and gave, after chromatography, the corresponding 1,2,3,4-tetrahydroquinolines in modest to good yield (Table 1). A number of functional groups are tolerated, including alkyl, aryl, alkoxy, and amide, although the yield from 6-chloroquinoline was poor. 2-Chloroquinoline, in which the halide is much more activated, was completely reduced to 1,2,3,4-tetrahydroquinoline in 79% yield. Nitro groups are also reduced; 6-nitroquinoline was cleanly reduced to 6-aminoquinoline (82%) with no further reduction of the heterocyclic ring being observed.[7]

The reduction of isoquinolines and quinoxalines was also briefly investigated, and again the heterocyclic ring was cleanly reduced in good yield (Table 2).

In summary, the use of indium metal provides a simple method for the selective reduction of heterocyclic rings which proceeds readily in aqueous solvent.

**Acknowledgments**

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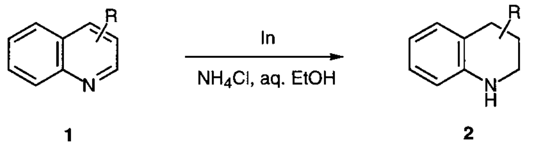
**Table 1.** Reduction of quinolines to 1,2,3,4-tetrahydroquinolines



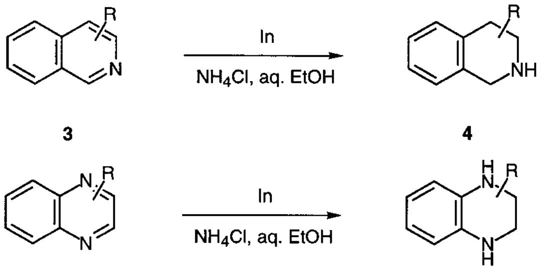
1 2

| *1/2* | *R* | *Yield / %* |
|---|---|---|
| **a** | H | 52 |
| **b** | 2-Me | 46 |
| **c** | 3-Me | 76 |
| **d** | 4-Me | 73 |
| **e** | 2,4-$Me_2$ | 30[a] |
| **f** | 2-Ph | 40 |
| **g** | 6-MeO | 42 |
| **h** | 6-AcNH | 60 |
| **i** | 6-Cl | 25 |
| **j** | 3,4-$C_6H_4$ | 72[b] |

[a] Product is exclusively *cis*

[b] Product is 1,2-dihydrophenanthrine

**Table 2.** Reduction of isoquinolines and quinoxalines to 1,2,3,4-tetrahydro derivatives



3 4 5 6

| *Compounds* | *R* | *Yield / %* |
|---|---|---|
| **3a/4a** | H | 78 |
| **3b/4b** | 3-Me | 71 |
| **5a/6a** | 2-Me | 92 |
| **5b/6b** | 2,3-$Me_2$ | 90[a] |

[a] Product is formed as 2:1 mixture of *cis*:*trans* isomers

## References and Notes

(1) Katritzky, A. R.; Rachwal, S.; Rachwal, B. *Tetrahedron* **1996**, *52*, 15031-15070

(2) For a compilation of references, see: reference 1, and Srikrishna, A.: Reddy, J. R.; Viswajanani, R. *Tetrahedron* **1996**, *52*, 1631-1636.

(3) For a review, see: Cintas, P. *Synlett* **1995**, 1087-1096.

(4) For more recent uses of allylindium reagents, see: Loh, T. P.; Cao, G. Q.; Pei, J. *Tetrahedron Lett*. **1998**, *39*, 1453-1456; Yi, X. H.; Meng, Y.; Li, C. J. *Chem. Commun.* **1998**, 449-450; Paquette, L. A.; Isaac, M. B. *Heterocycles* **1998**, *47*, 107-110.

(5) Others have reported the use of indium hydride reagents for reduction reactions in organic synthesis: for examples, see Miyai, T.; Inone, K.; Yasuda, M.; Shibata, I.; Baba, A. *Tetrahedron Lett*. **1998**, *39*, 1929-1932; Yamada, M.; Horie, T.; Kawai, M.; Yamamura, H.; Araki, S. *Tetrahedron* **1997**, *53*, 15685-15690; Yamada, M.; Taneka, K.; Butsugan, Y.; Kawai, M.; Yamamura, H.; Araki, S. *Main Group Metal Chem*. **1997**, *20*, 241-246; Yamada, M.; Tanaka, K.; Araki, S.; Butsugan, Y. *Tetrahedron Lett*. **1995**, *36*, 3169-3172.

(6) To a solution of the substrate (1.9 mmol) in ethanol (10 ml) was added saturated ammonium chloride solution (3 ml) and indium powder (2.0 g). The mixture was stirred and heated under reflux. When the reaction appeared complete by TLC (typically 1 - 5 days), the cooled reaction mixture was diluted with water (50 ml) and filtered through Celite . The aqueous filtrate was adjusted to pH ~ 9 with 4 M NaOH and extracted with dichloromethane (3 x 15 ml). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash chromatography to yield the 1,2,3,4-tetrahydro compound, the identity of which was confirmed by comparison of spectroscopic data with literature values.

(7) There is a reported example of an apparent nitro group reduction in the presence of indium metal during an attempted addition of the allylindium reagent to 4-nitrobenzaldehyde (Chan, T. H.; Isaac, M. B. *Pure Appl. Chem.* **1996**, *68*, 919-924). We have found that the reduction of nitro groups with indium metal is a general reaction (C. J. Moody and M. R. Pitts, *Synlett* **1998**, 1028).