Conversion of the Nitro Group to the Hydroxyamino Group with Preservation of Configuration at the α-Carbon: Use of Low-Temperature Tin(II) Chloride Reduction

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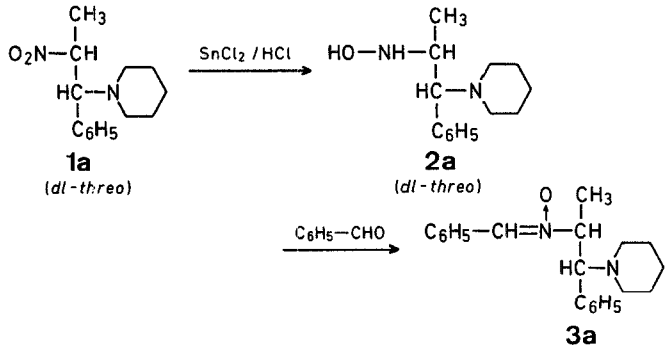
In a study of the stereochemistry of the addition of amines to (2-nitropropenyl)-benzene, it was found that the reduction of nitro groups of the addition products to amino groups could be performed without epimerization at the α-carbon by treatment with an excess of tin(II) chloride in hydrochloric acid[1]. We have since discovered that if reaction temperatures are held below 10 °C when this procedure is employed, the process can easily be halted at the hydroxylamine stage, as illustrated by conversion of *dl-threo*-1-phenyl-1-piperidino-2-nitropropane **(1a)** to *dl-threo*-1-phenyl-1-piperidino-2-hydroxyaminopropane **(2a)** in 90% yield.



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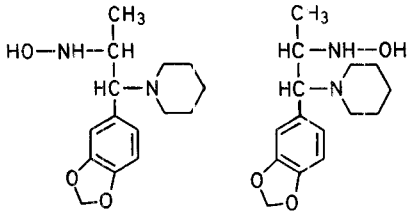
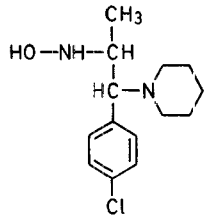
This method of preparation of hydroxylamine derivatives from nitro compounds has also been applied very successfully to preparation of four congeners of compound **2a**, *dl-threo*-1-(3,4-methylenedioxyphenyl)-1-piperidino-2-hydroxyaminopropane **(2b)**, *dl-erythro*-1-(3,4-methylenedioxyphenyl)-1-piperidino-2-hydroxyaminopropane **(2c)**, *dl-threo*-1-(4-chlorophenyl)-1-piperidino-2-hydroxyaminopropane **(2d)**, and *dl-threo*-1-phenyl-1-(1,2,3,4-tetrahydroisoquinolino)-2-hydroxyaminopropane **(2e)** and may represent a broadly applicable procedure.

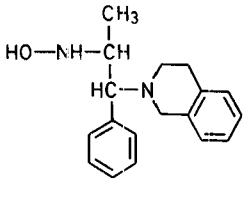


2b

2c
(*dl*-*erythro*)



2d



2e

Although a 4 to 1 molar proportion of the reducing agent was used, the relatively low reaction temperature largely halted reduction at the hydroxylamine stage. Hoffmann and Meyer[2], who first prepared an *N*-alkylhydroxylamine by tin(II) chloride reduction of a nitroalkane, allowed the reaction temperature to rise and obtained the hydroxylamine only because the amount of tin(II) chloride used was limited to one mol per mol of nitro compound. The early work did not include examination of the stereochemistry of this reduction method.

The reduction product **2a** and the other congeners **2b–e** showed the properties expected of hydroxylamines. They all reduced Tollen's reagent and **2a** was further characterized through formation of a nitrone **3a** by reaction with benzaldehyde.

Reduction of the nitro compound **1a** by the established zinc dust/aqueous ammonium chloride procedure[3] gave a broadly-melting product (m.p. ~97–105 °C) which did not yield a single substance upon recrystallization. The material gave a Tollen's test, and is presumed to represent a mixture of the *dl-erythro*- and *dl-threo*-hydroxylamines.

***dl-threo*-1-Phenyl-1-piperidino-2-nitropropane[1] (1a):**
This compound is prepared by a new procedure which allows conversion of initially-formed but unisolated *erythro*-isomer to the more stable *threo*-configuration. 1-Phenyl-2-nitro-1-propene[4] (130 g, 0.8 mol) and piperidine (130 ml, 111.5 g, 1.6 mol) are dissolved and heated under reflux for 2 h in a 4:1 (v/v) mixture of petroleum ether (b.p. 65–110 °C) and absolute ethanol (400 ml). When the mixture is cooled, white crystals separate; yield: 107.8 g (53%); m.p. 84–89 °C. Recrystallization from the same solvent mixture raises the m.p. to 97–99 °C; recovery: 71 g.

***dl-threo*-1-Phenyl-1-piperidino-2-hydroxyaminopropane (2a):**
Compound **1a** (20 g, 0.00853 mol) dissolved in concentrated hydrochloric acid (70 ml) is added dropwise to a stirred solution of tin(II) chloride dihydrate (64.7 g, 0.341 mol) in concentrated hydrochloric acid (65 ml). The tin(II) chloride solution is cooled in an ice bath throughout the addition, the rate of which is controlled so as to keep the reaction temperature from rising above 10 °C. Stirring is continued for 1 h after the addition is complete, then the mixture is made basic by careful addition of aqueous sodium hydroxide. Repeated extractions of the basic mixture with ether (4 × 400 ml) yield an ether extract which is dried with magnesium sulfate and evaporated to remove the ether; yield of fine white needles: 17.0 g (90%); m.p. 130–132 °C. Recrystallization from ethyl acetate raises the m.p. to 138–139 °C. The product reduces Tollen's reagent.

$C_{14}H_{22}N_2O$	calc.	C 71.75	H 9.46	N 11.96
(234.3)	found	71.32	9.36	11.69

Compounds **2b–e** (Table) were prepared similarly.

Conversion of *dl-threo*-1-Phenyl-1-piperidino-2-hydroxyaminopropane (2a) to Nitrone 3a:
A solution of freshly distilled benzaldehyde (1.0 g, 9.4 mmol) in 95% ethanol (10 ml) is added to a solution of **2a** (2.0 g, 9.4 mmol) in 95% ethanol (10 ml). After a reaction period of a few minutes the mixture is cooled and a small amount of water added. A white solid separates; yield 2.75 g (93%); m.p. 154–157 °C. Recrystallization from a water/ethanol mixture gives white crystals, m.p. 157–161 °C, of *N*-*(1-methyl-2-phenyl-2-piperidinoethyl)-benzaldoxime* **(3)**. Following a further crystallization from petroleum ether (b.p. 65–110 °C), the m.p. is 157–159 °C.

$C_{21}H_{26}N_2O$	calc.	C 78.22	H 8.13	N 8.69
(322.4)	found	78.37	8.01	8.76

I.R. (nujol): ν = 2900, 1590, 1460, 1380, 1160, 1140, 1190, 1080, 1030, 980, 920, 890, 860 cm^{-1}.

Table. Compounds **2b–e** prepared

Product	Yield [%]	m.p. [°C]	Molecular formula[a]	
2b	85	164–165°	$C_{15}H_{22}N_2O_3$	(278.4)
2c	65	167–169°[b]	$C_{15}H_{22}N_2O_3$	(278.4)
2d	75	154–156°	$C_{14}H_{21}ClN_2O$	(268.8)
2e	95	160–162°	$C_{18}H_{22}N_2O$	(282.4)

[a] Satisfactory microanalyses obtained: C ±0.30, H ±0.29, N ±0.30. Microanalyses were performed by Geller Laboratories, West Englewood, New Jersey and Drs. G. Weiler and F. B. Strauss, Oxford, England.

[b] Mixture m.p. with *threo*-isomer: 140–155 °C.

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