A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at http://www.nap.edu/catalog.php?record_id=12654). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

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These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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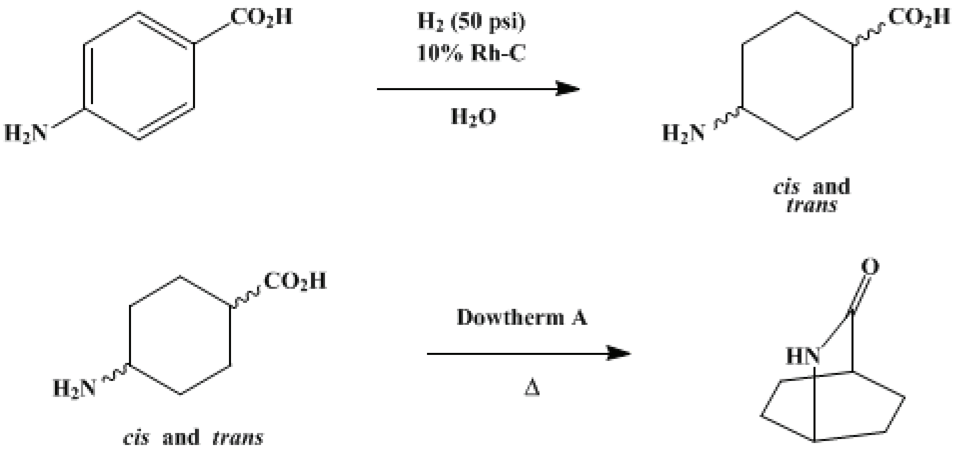
3-ISOQUINUCLIDONE

[2-Azabicyclo[2.2.2]octan-3-one]



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Checked by Peter Campbell and Ronald Breslow.

1. Procedure

A. *cis- and trans-4-Aminocyclohexanecarboxylic acid*. A mixture of 27.4 g. (0.20 mole) of *p*-aminobenzoic acid (Note 1), 200 ml. of water, and 2 g. of 10% rhodium-0.1% palladium on carbon catalyst (Note 2) is placed in a pressure bottle and hydrogenated at 50 p.s.i. When 0.6 mole of hydrogen has been absorbed (Note 3), the mixture is filtered and concentrated under reduced pressure until crystals start to form (Note 4). The mixture is diluted with 200 ml. of dimethylformamide and cooled to 5°, filtered, washed with dimethylformamide, then methanol, and dried, giving 19.4–20.3 g. (68–71%) of *cis*- and *trans*-4-aminocyclohexanecarboxylic acid, m.p. 292–296° (Note 5).

B. *3-Isoquinuclidone*. A mixture of 4.53 g. of *cis*- and *trans*-4-aminocyclohexanecarboxylic acid and 30 ml. of Dowtherm A (Note 6) is heated as rapidly as possible to reflux temperature. Heating is continued for 20 minutes during which time the water formed is allowed to distill away; at the end of this time, solution has taken place. The solution is allowed to cool to room temperature and is diluted with 100 ml. of isooctane. The solution is extracted three times with 50-ml. portions of water. The combined water extracts are treated with charcoal, filtered, and concentrated to dryness under reduced pressure. The residue is crystallized from cyclohexane giving 3.20–3.33 g. (81–84%) of 3-isoquinuclidone, m.p. 197–198° (Note 5).

2. Notes

1. Purchased from B. L. Lemke and Co., Inc., 199 Main Street, Lodi, New Jersey. The checkers used material from Eastman Organic Chemicals Department.
2. A mixture of 5.26 g. of rhodium chloride trihydrate, 0.34 g. of palladium chloride, 18 g. of carbon (Darco G-60), and 200 ml. of water is rapidly stirred and heated to 80°. Lithium hydroxide hydrate (2.7 g.) dissolved in 10 ml. of water is added all at once and the heating stopped. The mixture is stirred overnight, filtered, and washed with 100 ml. of 0.5 v/v% aqueous acetic acid. The product is dried under reduced pressure at 65°, giving 20.6–21 g. of the catalyst. One gram of this catalyst consumes 0.0022–0.0028 mole of hydrogen in aqueous suspension.[2]
3. The checkers found that the reduction requires 4–5 days, whereas the submitter reported the reaction requires 24 hours. Fresh catalyst is added whenever the rate of hydrogen uptake significantly decreases. When fresh catalyst is added to the reaction vessel, it is important that it first be wet with solvent and that the hydrogen be well evacuated. Opening the mixture to the atmosphere without careful evacuation

will produce a hydrogen-oxygen mixture which may explode on contact with fresh catalyst.
4. It is necessary to concentrate the solution to one-fifth volume before crystals form.
5. The submitters report the preparation scaled up by fifty-fold with similar yields and purities.
6. Purchased from Dow Chemical Co., Midland, Michigan.

3. Discussion

Ferber and Brückner[3] reduced *p*-aminobenzoic acid using Adams catalyst (PtO_2) at atmospheric pressure, and Schneider and Dillman[4] reduced *p*-aminobenzoic acid using 10% ruthenium on carbon at 140 atm. and 70°. 3-Isoquinuclidone has been prepared, by the previously mentioned investigators,[3,4] by heating the dry 4-aminocyclohexane carboxylic acid at elevated temperatures.

The described method of preparation of 3-isoquinuclidone has the following advantages: The isolation of the *cis* form of 4-aminocyclohexane carboxylic acid is not required in order to obtain a good yield; the amount of 3-isoquinuclidone that can be prepared at a time is limited only by the size of available equipment; the yield is excellent and the workup is easy and straightforward.

3-Isoquinuclidone has been found to be an excellent substitute for camphor for molecular weight determinations.[2]

References and Notes

1. Research Laboratories, Parke, Davis & Company, Ann Arbor, Michigan.
2. W. M. Pearlman, *Tetrahedron Lett.*, **1663** (1967).
3. E. Ferber and H. Brückner, *Ber.*, **76**, 1019 (1943).
4. W. Schneider and R. Dillmann, *Ber.*, **96**, 2377 (1963).

Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

3-ISOQUINUCLIDONE

10% rhodium-0.1% palladium on carbon

acetic acid (64-19-7)

methanol (67-56-1)

hydrogen (1333-74-0)

cyclohexane (110-82-7)

carbon (7782-42-5)

palladium chloride (7647-10-1)

hydrogen-oxygen (7732-18-5)

camphor (21368-68-3)

dimethylformamide (68-12-2)

ruthenium on carbon (7440-18-8)

2-Azabicyclo[2.2.2]octan-3-one (3306-69-2)

4-aminocyclohexane carboxylic acid,
cis- and trans-4-Aminocyclohexanecarboxylic acid (1776-53-0)

isooctane (592-27-8)

rhodium chloride trihydrate (20765-98-4)

Lithium hydroxide hydrate (1310-66-3)

p-aminobenzoic acid (150-13-0)