A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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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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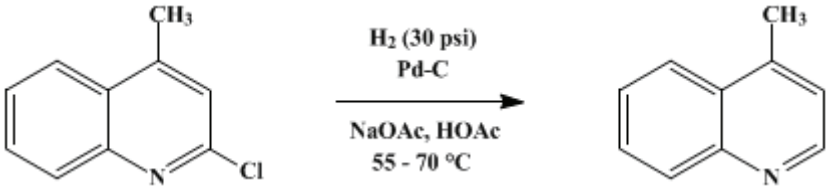
LEPIDINE



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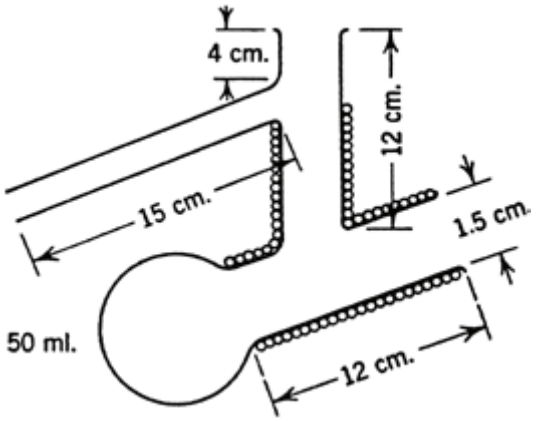
1. Procedure

In a 500-ml. Erlenmeyer flask are placed 20 g. (0.11 mole) of pure 2-chlorolepidine[1] (Note 1), 9.3. g. (0.11 mole) of powdered anhydrous sodium acetate, and 200 ml. of glacial acetic acid. The mixture is heated to about 70° and shaken until solution is complete. The solution is transferred to a pressure bottle of an apparatus for catalytic reduction,[2] equipped with a heating element and a variable resistance. The flask is rinsed with two 10-ml. portions of hot glacial acetic acid. Then 3 g. of palladium on carbon is added (Note 2), the bottle is attached to the shaking machine, and the variable resistance is adjusted until the temperature of the liquid is between 55° and 70° (Note 3). The bottle is swept out with hydrogen, an initial pressure of about 1.8–2.2 atm. (26–33 lb.) is applied, and the shaking is started. Hydrogen absorption is rapid during the first 15 minutes and then gradually slackens; the theoretical amount is absorbed in 1.5–2 hours. To ensure complete reduction, shaking is continued an additional 30 minutes. The warm acid solution is separated from the catalyst by filtration through a 1- to 2-mm. layer of Norit on a Büchner funnel. The bottle and funnel are washed with three 30-ml. portions of glacial acetic acid. The acetic acid is removed from the combined filtrates by heating to 70° under reduced pressure (water pump, 25 mm.). The residue is dissolved in 50 ml. of water and transferred to a 500-ml. separatory funnel, an additional 25 ml. of water being used for washing. The water solution is made basic to litmus with 30% sodium hydroxide (about 40–100 ml.) and extracted with one 100-ml. portion of ether and then with two 50-ml. portions. The ether extracts are combined and dried overnight with about 30 g. of solid potassium hydroxide. The ether is removed by distillation from a 250-ml. flask, and the residue is transferred to a modified 50-ml. distilling flask (Note 4), three 5-ml. portions of anhydrous ether being used to ensure complete transference. After the ether is removed, the residue distils at 126–127°/14–15 mm. The product is colorless, water clear, and weighs 13–14 g. (81–87%) (Note 5) and (Note 6).

2. Notes

1. Pure 2-chlorolepidine, m.p. 58–59°, should be used.
2. The catalyst is previously prepared in an apparatus for catalytic hydrogenation,[2] in which are placed 0.5 g. of palladous chloride, 3.0 g. of Norit, and 20 ml. of distilled water. The bottle is swept out with hydrogen and then shaken with hydrogen for 2–3 hours at 2–3 atm. (40 lb.) pressure. The palladium on carbon is collected on a Büchner funnel, washed with five 50-ml. portions of distilled water, then with five 50-ml. portions of 95% ethanol, and finally twice with ether. Upon drying, about 3 g. of the catalyst is obtained. It is stored in a vacuum desiccator over solid sodium hydroxide. If the reduction of the chlorolepidine does not proceed normally, the used catalyst should be removed by suction filtration and a fresh 3-g. portion of catalyst added. Failure of the reduction step is usually due to an inactive catalyst or to impurities in the acetic acid or chlorolepidine. The palladium catalysts, prepared as described elsewhere in this volume, are also satisfactory for the reduction of 2-chlorolepidine.
3. The reduction does not proceed smoothly at room temperature with the palladium catalyst. Raney nickel may be used as a catalyst with ethanol containing potassium hydroxide at room temperature, but about 15 hours is required for reduction.
4. The submitters used a special flask having the shape and dimensions shown in Fig. 17. The two necks were wrapped with asbestos cord. The checkers used an ordinary Claisen flask (50 ml.).

Fig. 17.



5. By distillation of the crude product from four runs, a yield of 92% was obtained.
6. The submitters have followed the same procedure in preparing the compounds listed below from the corresponding 2-chloro derivatives. The ether extractions and distillation steps were omitted when solid products were obtained.

Compound	*Product* % *Crude*	% *Purified*	*B.P. or M.P.*
6-Methyllepidine	100	87	B.p. 137°/12 mm.
8-Methyllepidine	94	90	M.p. 54–55°
5,8-Dimethyllepidine	96	86	B.p. 154–56°/13 mm.
6,8-Dimethyllepidine	100	91	M.p. 55–56°
6-Methoxylepidine monohydrate	100	80	M.p. 50–52°
5,8-Dimethoxylepidine	98	90	M.p. 94–95°
2-Methyl-6-methoxyquinoline *	96	..	M.p. 62–65°

* From 2-methyl-4-chloro-6-methoxyquinoline.

3. Discussion

The process described above is essentially that of Ainley and King,[3] who prepared 6-methoxylepidine. Lepidine has also been prepared by the reduction of 2-chlorolepidine with hydrogen and Raney nickel,[4] with tin[5,6,7,8] or zinc[7] and hydrochloric acid, and with concentrated hydriodic acid and red phosphorus;[9] by the reduction of 2-iodolepidine with iron and dilute sulfuric acid;[10] by the zinc dust distillation of 2-hydroxy-4-methylquinoline under reduced pressure[11] or of 2-hydroxy-3-cyano-4-methylquinoline;[12] by the reduction of 2-hydroxy-4-methylquinoline with concentrated hydriodic acid and red phosphorus;[13] by the distillation of 1,2,3,4-tetrahydroquinoline-4-carboxylic acid with zinc dust in a stream of hydrogen;[14] by decarboxylation of 4-methylquinoline-2-carboxylic acid;[15] by leading vapors of aniline and crotonaldehyde over a contact catalyst at above 500°;[16] by heating aniline and vinyl methyl ketone with sulfuric acid and nitrobenzene;[17] by heating aniline and β-hydroxyethyl methyl ketone in the presence of concentrated sulfuric acid and nitrobenzene[18] or aniline hydrochloride and ethanol;[19] by heating aniline and β-chloroethyl methyl ketone in the presence of concentrated hydrochloric acid and nitrobenzene or arsenic acid[20,21] or in the presence of aniline hydrochloride, ethanol, and nitrobenzene;[22] by heating a mixture of acetone, formaldehyde, and aniline hydrochloride;[23,24] by passing vapors of acetylene and aniline over aluminum oxide at 360–420°;[25] and by passing vapors of aniline and acetaldehyde or paraldehyde over aluminum oxide in a copper tube at 480°.[26] Campbell and Schaffner[27] have described the preparation of lepidine in 70–73% yields by the reaction of aniline hydrochloride with methyl vinyl ketone, 1,3,3,-trimethoxybutane, or 1-methoxybutanone-3 in ethanol in the presence of ferric and zinc chloride.

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

red phosphorus

ferric and zinc chloride

ethanol (64-17-5)

acetaldehyde (75-07-0)

sulfuric acid (7664-93-9)

acetylene (74-86-2)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

ether (60-29-7)

sodium acetate (127-09-3)

aniline (62-53-3)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

formaldehyde (50-00-0)

iron (7439-89-6)

aniline hydrochloride (142-04-1)

tin (7440-31-5)

arsenic acid (1327-52-2)

Raney nickel (7440-02-0)

acetone (67-64-1)

carbon,
Norit (7782-42-5)

potassium hydroxide (1310-58-3)

zinc (7440-66-6)

palladium (7440-05-3)

Nitrobenzene (98-95-3)

hydriodic acid (10034-85-2)

palladous chloride (7647-10-1)

aluminum oxide (1344-28-1)

Lepidine (491-35-0)

2-Chlorolepidine,
chlorolepidine (634-47-9)

2-hydroxy-4-methylquinoline (607-66-9)

β-hydroxyethyl methyl ketone (590-90-9)

2-methyl-4-chloro-6-methoxyquinoline (50593-73-2)

6-Methyllepidine (826-77-7)

8-Methyllepidine (13362-80-6)

5,8-Dimethyllepidine

6,8-Dimethyllepidine

6-Methoxylepidine monohydrate

5,8-Dimethoxylepidine

2-Methyl-6-methoxyquinoline (1078-28-0)

6-methoxylepidine (41037-26-7)

2-iodolepidine

2-hydroxy-3-cyano-4-methylquinoline

1,2,3,4-tetrahydroquinoline-4-carboxylic acid

4-methylquinoline-2-carboxylic acid

crotonaldehyde (123-73-9)

vinyl methyl ketone,
methyl vinyl ketone (78-94-4)

β-chloroethyl methyl ketone (6322-49-2)

1,3,3,-trimethoxybutane (6607-66-5)

1-methoxybutanone-3 (6975-85-5)

paraldehyde (123-53-7)