Organic Syntheses

A Publication
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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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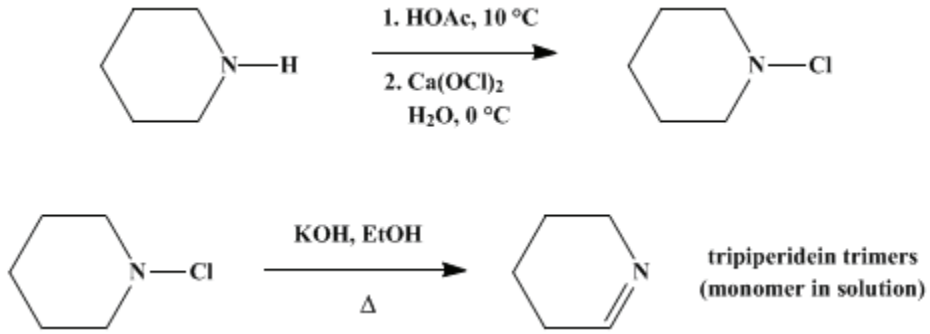
2,3,4,5-TETRAHYDROPYRIDINE TRIMER

[Pyridine, 2,3,4,5-tetrahydro-, trimer]



Submitted by George P. Claxton, Lloyd Allen, and J. Martin Grisar[1].
Checked by Henry F. Russell, Richard J. Sundberg, and Carl R. Johnson.

1. Procedure

A. N-*Chloropiperidine*. A 500-ml., three-necked flask fitted with a mechanical stirrer, a dropping funnel, and a thermometer is charged with 170 g. (2.00 moles) of piperidine (Note 1). The flask is cooled in an acetone–ice bath, the piperidine is stirred, and 120 g. (2.00 moles) of glacial acetic acid is added dropwise at such a rate that the temperature does not exceed 10° (Note 2).

A 3-l., three-necked flask fitted with a mechanical stirrer, a dropping funnel, and a thermometer is charged with an aqueous solution of 2.2 moles of calcium hypochlorite (Note 3), and the piperidine acetate prepared above is placed in the dropping funnel. The hypochlorite solution is stirred and cooled to 0° to −5° with a methanol–ice bath, and the piperidine acetate is added dropwise over a period of 1.25 hours while the temperature is maintained below 0°. After an additional 15 minutes of stirring, equal portions of the mixture are placed in two 2-l. separatory funnels and extracted three times with a total of about 1300 ml. of diethyl ether. The ether extract is placed in a 2-l. flask dried overnight over anhydrous sodium sulfate in a cold room at 4° and filtered. The bulk of the ether is removed with a water bath maintained below 60° (Note 4).

B. 2,3,4,5-*Tetrahydropyridine trimer*. A 3-l., three-necked, round-bottomed flask equipped with a sealed mechanical stirrer, a dropping funnel, and a reflux condenser fitted with a calcium chloride drying tube is charged with 264 g. (4.71 moles) of potassium hydroxide and 1250 ml. of absolute ethanol. This mixture is stirred with a Teflon paddle (Note 5) and heated to reflux, effecting solution. The *N*-chloropiperidine solution prepared in Part A is filtered through glass wool directly into the dropping funnel and added dropwise to the well-stirred, boiling reaction mixture over a period of *ca.* 2.5 hours (Note 6). The resulting mixture is stirred for an additional 2 hours without heating and allowed to stand at least 24 hours at room temperature, during which time tetrahydropyridine trimerizes. Precipitated potassium chloride is removed by filtration, washed with two 150-ml. portions of absolute ethanol, and set aside for later use. The washes are combined with the filtrate, ethanol is distilled off an a steam bath under reduced pressure, and the distillate saved for further processing (Note 7). The residue remaining after distillation and the recovered potassium chloride are then combined in 750 ml. of water, and the resulting solution is extracted four times with a total of 500 ml. of ether. After standing over anhydrous magnesium sulfate for 4 hours, the extract is filtered and concentrated on a rotary evaporator with gentle warming. The resulting oily residue is dissolved in 75 ml. of acetone, and the solution is cooled to −20° overnight. If no seed crystals are available, the walls of the flask are scratched with a glass rod, inducing crystallization. The precipitate is collected by vacuum filtration and washed twice with 20-ml. portions of cold (−20°) acetone, giving 64–80 g. (39–48%) of tetrahydropyridine trimer, m.p. 58–61° (Note 8).

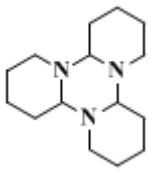
2. Notes

1. Freshly distilled piperidine was used.
2. Ice was added to the mixture as required to dissolve any precipitated material and keep the viscous solution clear.
3. MC and B Manufacturing Chemists HTH grade 70% calcium hypochlorite was used. The solution required for the procedure was prepared by placing 680 g. of 70% calcium hypochlorite and 3 l. of water in a 5-l. flask and stirring overnight. The mixture was allowed to settle for several hours, and the supernatant was vacuum-filtered through Celite and glass wool, giving enough hypochlorite solution for a single run. By centrifugation of the suspension remaining after decanting, enough hypochlorite solution for another run could be obtained. The molarity of the solution was determined by iodometric titration: 1 g. of potassium iodide was dissolved in 25 ml. of water, and 15 ml. of 10% sulfuric acid and 1 ml. of the hypochlorite solution were added. The red solution was titrated with 0.10 *N* sodium thiosulfate. When the color changed to faint yellow, 1 ml. of starch solution was added, and the titration was continued to the colorless end point. The concentration was then determined according to the following formula: ¼[(ml. $Na_2S_2O_3$ reagent)(normality $Na_2S_2O_3$)] = molarity of $Ca(OCl)_2$
4. *Caution! To avoid a rapid, spontaneous decomposition that results in complete loss of N-chloropiperidine, the ether should not all be boiled off, nor should the temperature exceed 60°. The crude product should be used immediately in Part B.*
5. Use of a wire stirrer caused darkening of the ethanolic potassium hydroxide solution.
6. Isotripiperidein (m.p. 97–98°) is obtained if insufficient potassium hydroxide is used or if stirring is not sufficiently vigorous[2] (see Discussion).
7. It is recommended that this solvent be reused in later runs.[2,3] The submitters found that substantial amounts of product can be recovered from this distillate after a few days of standing. Thus, it appears that some tetrahydropyridine distils as monomer with the ethanol and trimerizes in the distillate. The checkers found that when the reaction was worked up after 24 hours of standing, the majority of the product was in the ethanol distillate. Therefore, they allowed the distillate to stand for several days, concentrated it by rotary evaporation, and crystallized the residue from acetone. The resulting tetrahydropyridine trimer was combined with the otherwise obtained.
8. Two trimers are known: α- (m.p. 60–62°) and β- (m.p. 70–73°) tripiperidein.[2] The β-form, usually obtained as a crude, white solid (m.p. 40–68°), may be converted to the more stable α-isomer by recrystallizing from acetone containing 2% water.[2] α-Tripiperidein is best stored in a close container over potassium hydroxide and may be kept for over a year in this manner.

3. Discussion

There is one standard procedure for preparing 2,3,4,5-tetrahydropyridine.[2,3] No acceptable alternative method is available except that *N*-chlorosuccinimide may be substituted for calcium hypochlorite.[4] Similar reaction sequences have been used to prepare substituted 2,3,4,5-tetrahydropyridines,[4,5] pyrroline,[6] and substituted pyrrolines.[7]

2,3,4,5-Tetrahydropyridine is useful for condensation with pyrroles and indoles,[8,9,10] β-ketoacids,[11,12,13,14] β-ketoesters,[15] and for a novel and very general reaction with magnesium chelates formed by reaction of methyl ketones with magnesium methyl carbonate.[16,17] The highly reactive monomer trimerizes on standing to tripiperidein, which exists in two interconvertible crystalline forms designated as α and β:



In the absence of base, the trimer can rearrange to iso-tripiperidein, a product of self-condensation.[11,18] In the presence of base, however, α-tripiperidein is stable for over a year. In solution, tripiperidein readily detrimerizes to the monomer, which is in equilibrium with δ-aminovaleraldehyde

(5-aminopentanal).[9]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 8, 26

References and Notes

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

ethanolic potassium hydroxide

2,3,4,5-Tetrahydropyridine trimer

Pyridine, 2,3,4,5-tetrahydro-, trimer

tetrahydropyridine trimer

Isotripiperidein

tripiperidein

α-Tripiperidein

2,3,4,5-tetrahydropyridines

iso-tripiperidein

ethanol (64-17-5)

sulfuric acid (7664-93-9)

acetic acid (64-19-7)

ether,
diethyl ether (60-29-7)

sodium sulfate (7757-82-6)

potassium iodide (7681-11-0)

sodium thiosulfate (7772-98-7)

acetone (67-64-1)

potassium hydroxide (1310-58-3)

piperidine (110-89-4)

N-chlorosuccinimide (128-09-6)

potassium chloride (7447-40-7)

hypochlorite (14380-61-1)

magnesium sulfate (7487-88-9)

calcium hypochlorite (7778-54-3)

piperidine acetate

magnesium methyl carbonate

PYRROLINE

N-Chloropiperidine (2156-71-0)

δ-aminovaleraldehyde,
5-aminopentanal

TETRAHYDROPYRIDINE,
2,3,4,5-TETRAHYDROPYRIDINE