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BRIEF COMMUNICATIONS

Synthesis of 2,2,6,6-Tetramethylpiperidine Derivatives

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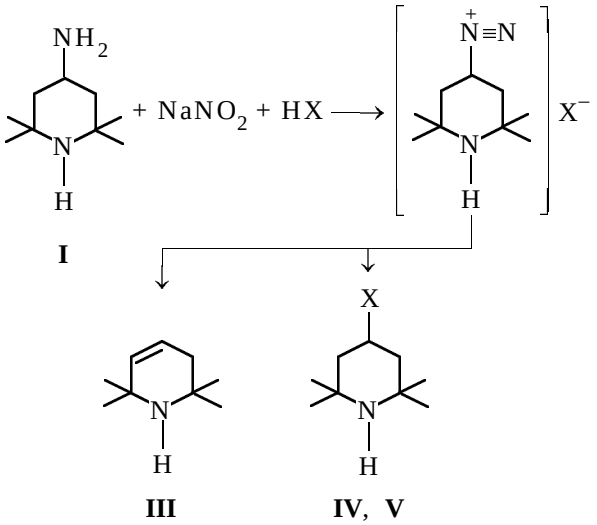
Abstract—Diazotization of 4-amino-2,2,6,6-tetramethylpiperidine in acetic or sulfuric acid affords 2,2,6,6-tetramethyl-1,2,3,6-tetrahydropyridine in high yield. Under the same conditions, the corresponding nitroxyl radical transforms into 4-hydroxy-2,2,6,6-tetramethylpiperidine-1-oxyl.

Recently, there has been much interest in synthesis of 2,2,6,6-tetramethylpiperidine derivatives, which are widely used for stabilization of polymers and monomers against light and heat [1, 2]. In this work, we studied the synthesis of nitroxyl radicals and sterically hindered amines by diazotization of 4-amino-2,2,6,6-tetramethylpiperidine **I** and 4-amino-2,2,6,6-tetramethylpiperidine-1-oxyl **II**. Compound **I** is commercially available and is used for production of polymer photostabilizers.

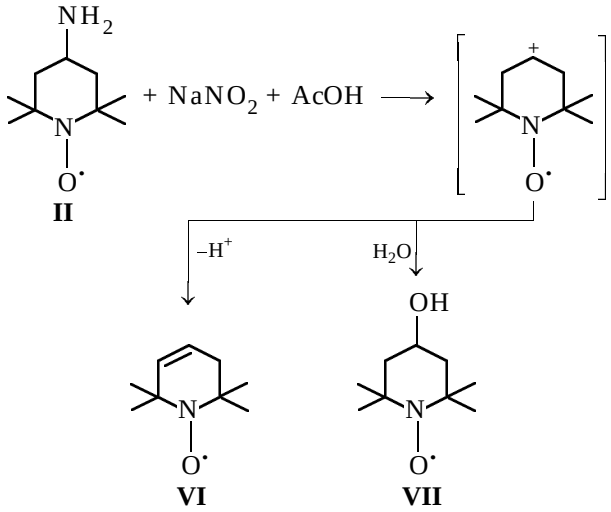
Diazotization of **I** in the presence of HCl or HBr gave 1,2,5,6-tetrahydro-2,2,6,6-tetramethylpyridine **III** in 80% yield. Under these conditions, 4-chloro-2,2,6,6-tetramethylpiperidine **IV** or 4-bromo-2,2,6,6-tetramethylpiperidine **V** is formed in 10–15% yield, along with **III**.



where X = Cl (**IV**), Br (**V**).

The best result was obtained when diazotization was performed in the presence of acetic or sulfuric acid (yield of **III** 90%). This is due to the fact that the acetate and sulfate ions are less nucleophilic than the chloride and bromide ions. Thus, the proposed reaction can be used for preparing **III**. Oxidation of **III**–**V** with hydrogen peroxide in the presence of Na_2WO_4 yields the corresponding nitroxyl radicals [3].

Of particular interest is diazotization of 4-amino-2,2,6,6-tetramethylpiperidine-1-oxyl **II**:



This reaction cannot be performed in the presence of mineral acids, as the radical center decays under these conditions [4]. However, the reaction can be performed in the presence of 30% acetic acid, which leaves the radical center intact. The nitroxyl group strongly affects the reaction course. The yield of **VI** is as low as 10% (cf. **III**), and the major product (80% yield) is 4-hydroxy-2,2,6,6-tetramethylpiperi-

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dine-2-oxyl **VII** (cf. **IV** and **V**). Probably, the reaction pathway depends on the basicity of the initial substances. With **I**, elimination of N_2 and HX is the prevailing process.

When diazotization of **I** is performed in glacial acetic acid, the only reaction product is 4-acetylamino-2,2,6,6-tetramethylpiperidine **VIII**. Compound **II** is also acylated with glacial acetic acid at room temperature; the yield of 4-acetylamino-2,2,6,6-tetramethylpiperidine-1-oxyl **IX** is 95%. According to [5], 2,2,6,6-tetramethylpiperidine derivatives are only acylated with acetic anhydride.

EXPERIMENTAL

2,2,6,6-Tetramethyl-1,2,5,6-tetrahydropyridine III and 4-chloro-2,2,6,6-tetramethylpiperidine IV. To a solution of 7.8 g (0.05 mol) of amine **I** in 10 ml of water, 9 ml of HCl (ρ = 1.19 g ml^{-1}) was added. Then, a solution of 5.2 g (0.075 mol) of $NaNO_2$ in 10 ml of water was added dropwise with stirring. In the course of the reaction, the pH was maintained within 3–5 by adding aqueous HCl (1 : 1). After the reaction was complete, the mixture was alkalized first with K_2CO_3 and then with KOH to pH 10–12, after which it was extracted with benzene (3 × 10 ml). The benzene extracts were combined, the solvent was evaporated, and the residue was distilled under atmospheric pressure. Yield of **III** 5.5 g (80%), bp 143–145°C (cf. bp 145–146°C [3]). The residue was recrystallized from methanol. Yield of colorless crystalline compound **IV** 0.9 g (10%), mp 37–38°C; the compound was identified using a mixing test with an authentic sample [6].

When the reaction was performed in HBr, the yield of **III** was 80%, and that of 4-bromo derivative **V**, 10%; mp 43–45°C (from methanol; cf. mp 44–45°C [6]).

2,2,6,6-Tetramethyl-1,2,5,6-tetrahydropyridine-1-oxyl VI and 4-hydroxy-2,2,6,6-tetramethylpiperidine-1-oxyl VII. To a solution of 8.5 g (0.05 mol) of **II** in 40 ml of distilled water, 20 ml of glacial acetic acid was added, the mixture was cooled to 5°C, and a solution of 6.4 g (0.075 mol) of $NaNO_2$ in 20 ml of water was gradually added. The resulting mixture was stirred for 2 h, alkalized with a KOH solution to pH 10–11, and extracted with benzene (3 × 50 ml). The benzene extracts were combined, the solvent was removed, and the residue was treated with hexane (50 ml). Compound **VI** passed into hexane, and compound **VII** remained in the residue. After removal of the solvent, 0.9 g (12%) of **VI** was obtained; mp 34–35°C (cf. mp 33°C [3]). The insoluble product **VII** was purified by column chromatography (l = 50 cm, r = 1.5 cm, sorbent Al_2O_3, Brockmann grade II, eluent CH_2Cl_2). Yield of **VII** 6.8 g (80%). The mixing test with an authentic sample gives no depression of the melting point [3].

4-Acetylamino-2,2,6,6-tetramethylpiperidine-1-oxyl IX. To 30 ml of glacial acetic acid, we added with stirring 2.6 g (0.015 mol) of radical **II**. The stirring was continued for 1 h, after which the mixture was alkalized with a KOH solution to pH 10–11 and extracted with methylene chloride (3 × 30 ml). The organic extracts were combined and dried over Na_2SO_4; the solvent was removed. The remaining red-orange crystalline compound **IX** (3.3 g, 95%) was recrystallized from water; mp 145–146°C. The compound was identified by a mixing test with an authentic sample and by comparison of the IR spectra [3].

CONCLUSIONS

(1) Diazotization of 4-amino-2,2,6,6-tetramethylpiperidine in HCl, HBr, H_2SO_4, and dilute AcOH affords 2,2,6,6-tetramethyl-1,2,5,6-tetrahydropyridine in 80–90% yield.

(2) Diazotization of 4-amino-2,2,6,6-tetramethylpiperidine-1-oxyl in 30% AcOH gives 4-hydroxy-2,2,6,6-tetramethylpiperidine-1-oxyl in 80% yield.

(3) In glacial AcOH, 4-amino-2,2,6,6-tetramethylpiperidine and the corresponding radical are converted virtually completely to the corresponding *N*-acetyl derivatives.

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