The effect of the nature of the substituent at the nitrogen atom on transformations of 3-bromo-2,2,6,6-tetramethyl-4-piperidinone and its 1-hydroxy and 1-oxyl derivatives under conditions of the Favorsky rearrangement

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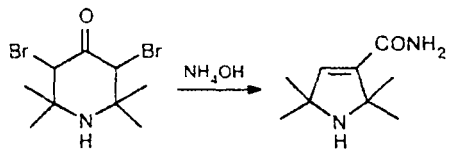
3-Bromo-2,2,6,6-tetramethyl-4-oxopiperidine-1-oxyl reacts with NH_4OH to give 3-carbamoyl-2,2,5,5-tetramethylpyrrolidine-1-oxyl, a product of the Favorsky rearrangement. 3-Bromo-2,2,6,6-tetramethyl-4-piperidinone is transformed under these conditions into a bicyclic amino ketone, while its 1-hydroxy derivative affords acyclic nitrosoenone.

Key words: the Favorsky rearrangement, α-bromoketones of the tetramethylpiperidine series, 2,6-dimethyl-6-nitrosohept-2-en-4-one, 1-aza-2,2,6,6-tetramethyl-4-oxobicyclo[3.1.0.]hexane.

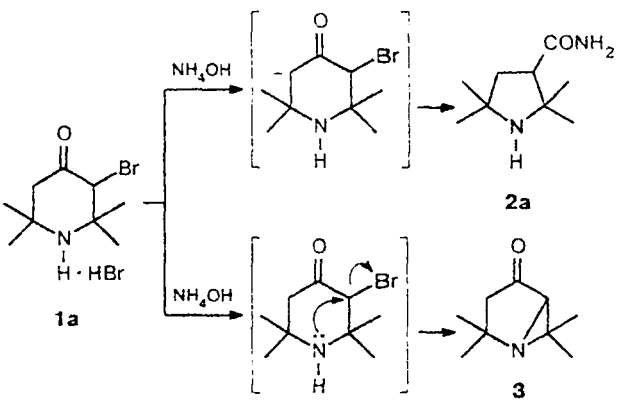
As a rule, α-haloketones treated with bases undergo the Favorsky rearrangement.[1,2] In the 2,2,6,6-tetramethyl-4-piperidinone (TMP) series, the Favorsky rearrangement has been studied for 3,5-dibromoderivatives. The reaction of 3,5-dibromo-TMP with NH_4OH results in 2,2,5,5-tetramethyl-3-pyrroline-3-carboxamide, while with amines it gives substituted amides.[3,4]



Analogously, the 1-oxyl derivative of this α,α′-dibromoketone reacts with amines to give 3-carbamoyl-2,2,5,5-tetramethyl-3-pyrroline-1-oxyls, and the reaction with EtONa in EtOH leads to the corresponding ester.[5] The reaction of 3,5-dibromo-TMP with NH_4OH is a key stage in the synthesis of the spin labels, pyrroline- and pyrrolidinenitroxyls. Usually, the transformation of tetramethylpyrrolines into tetramethylpyrrolidines is performed by hydrogenation.[3,6] However, it seems more expedient to obtain the latter from monobromoderivatives of TMP *via* the Favorsky rearrangement. Indeed, it was shown earlier[7] that 3-bromo-TMP (**1a**) is transformed under the action of MeONa in MeOH into methyl 2,2,5,5-tetramethylpyrrolidine-3-carboxylate. No examples of the Favorsky rearrangement of 1-hydroxy-TMP have been reported so far.

Reactions of monobromoketones (**1a—c**) with NH_4OH are studied in the present work with the aim of synthesizing 2,2,5,5-tetramethylpyrrolidine-3-carboxamides (**2a—c**). It turned out that compounds **1a—c** react with NH_4OH in completely different ways. Amine **1a** is transformed into a bicyclic aminoketone **3**, which was identified by comparison with a compound described earlier, while amide **2a** is formed only as a minor product (yield 9—13%) (Scheme 1).

Scheme 1



Under these conditions, hydroxylamine **1b** undergoes ring-opening to give nitrosoenone **4** (Scheme 2).

Only nitroxyl **1c** is converted completely into amide **2c**, a rearrangement product (Scheme 3).

A comparison of literature data with the data obtained in the present work suggests that the direction of the reactions of dibromo-TMP, dibromo-TMP-1-oxyl, and monobromoketones **1a—c** with bases is determined

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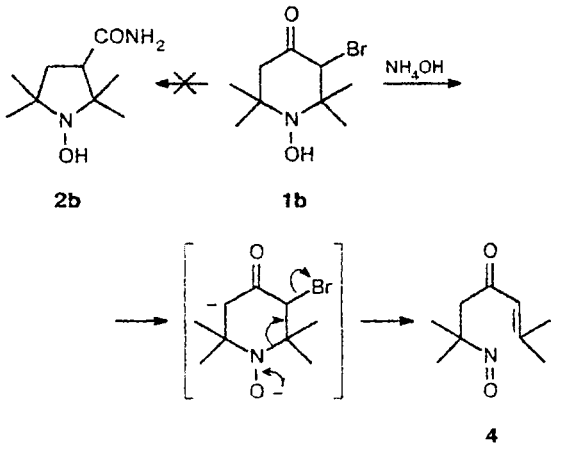
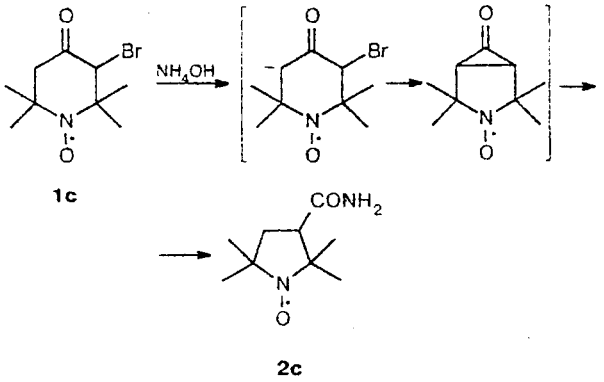
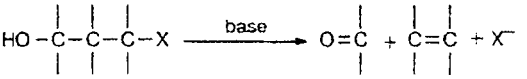
Scheme 2



Scheme 3



by two factors: the strength of the base attacking the C(5) atom and the nucleophilicity of the N atom. In the case of nitroxyl **1c**, the nucleophilicity of the N atom is small, and that is why the Favorsky rearrangement into amide **2c** takes place. The result of the reaction of amine **1a** with NH_4OH is formally determined by the competition between the intramolecular attack of a carbanion at the C(5) atom and that of nitrogen towards the C(3) atom. Apparently, in this case, the rate of formation of the carbanion is small, and therefore intramolecular nucleophilic replacement of the N atom by the Br atom occurs to form aziridine **3**. In principle, cyclization of β-haloamines is a standard method for the synthesis of aziridines.[8] However, in this case, the formation of bicyclic aziridine is surprising because of the considerable steric hindrances in the series of TMP. Earlier, compound **3** was obtained by another method, namely, by the action of bases on 1-chloro- or 1-acyloxy-TMP.[9] The formation of minor amounts of amide **2a** along with **3** attests that the rate of intramolecular substitution in **1a** is comparable with the rate of the formation of the carbanion at the C(5) atom. It is evident that when a stronger base enters into the reaction, the rate of formation of the carbanion increases and can be higher than the rate of intramolecular nucleophilic substitution. It is this situation that takes place under the action of MeONa, when amine **1a** is rearranged into methyl 2,2,5,5-tetramethylpyrrolidinecarboxylate. A question arises: why does 3,5-dibromo-TMP give a product of the Favorsky rearrangement when treated with NH_4OH instead of a product of intramolecular cyclization as monobromoketone **1a** does? Probably, the introduction of the second Br atom increases the rate of formation of the carbanion and, at the same time, somewhat decreases the nucleophilicity of the heterocyclic N atom. The ratio of these rates favors the Favorsky rearrangement. In the case of hydroxylamine **1b**, ionization of the N—OH bond seems to occurs first, which initiates fragmentation. Homomorphous γ-haloalcohols react analogously, undergoing fragmentation when treated with bases:[10]



One would assume that any 4-substituted 1-hydroxy-3-bromotetramethylpiperidines would undergo fragmentation in the presence of bases. However, 3-bromo-1,4-dihydroxy-2,2,6,6-tetramethylpiperidine does not undergo fragmentation under these conditions. It gives a product of ring-contraction, *viz.*, 1,3-dihydroxy-2-isopropenyl-5,5-dimethylpyrrolidine.[11]

Experimental

The IR spectra were recorded on a Specord instrument in CCl_4 and the ^1H NMR spectra were recorded on a Bruker WP-80-SY instrument with $CDCl_3$ in HMDS as the external standard. The synthesis of bromoketones **1a—c** was described earlier.[7]

Reaction of 3-bromo-2,2,6,6-tetramethyl-4-piperidine (1a) with NH_4OH. A freshly prepared solution of **1a** hydrobromide obtained from triacetoneamine hydrochloride (19.15 g, 0.1 mol) in 100 mL of $CHCl_3$ was added dropwise with stirring and cooling with ice water to 150 mL of conc. NH_4OH. The reaction mixture was stirred at ~20 °C for 4 h and left for 1 day. The organic layer was separated and dried with Na_2SO_4. $CHCl_3$ was removed and the residue was distilled *in vacuo*. The product (9.33 g, 61%) was obtained with b.p. 83—86 °C (11 Torr), n_D^{20} 1.4640. ^1H NMR, δ: 1.14 (s, 3 H, Me); 1.23 (s, 6 H, 2 Me); 1.38 (s, 3 H, Me); 2.07 (d, 2 H, CH_2); 2.28 (s, 1 H, CH). The product was identified as the known[9] 1-aza-2,2,6,6-tetramethylbicyclo[3.1.0.]hexan-4-one **3** on the basis of its refraction index and ^1H NMR spectrum. The aqueous layer was saturated with KOH and the precipitate that formed was filtered off and dried in air. Amide **2a** (2.19 g, 13%) was obtained as colorless crystals, m.p. 126—128 °C after purification by sublimation *in vacuo* (*cf.* Ref. 3: m.p. 130 °C). These crystals in a mixture with authentic 2,2,5,5-tetramethylpyrrolidine-3-carboxamide did not depress the melting point.

Reaction of 3-bromo-1-hydroxy-2,2,6,6-tetramethyl-4-piperidine (1b) with NH_4OH. **1b** (0.87 g, 3.5 mmol) was added

with vigorous stirring to 15 mL of conc. NH_4OH cooled to −10 °C. The solution turned deep blue, and blue crystals of monomer **4** gradually precipitated. After being kept at ~20 °C for 1 day, the solution and the precipitate became colorless. The precipitate was filtered off and dried in air. Dimer **4** (0.42 g, 71%) was obtained (m.p. 89—90 °C). It was steam-distilled, and the blue oil obtained was transformed in 2 days into colorless crystals of dimer. It was dried in air, m.p. 91.5—92 °C (92 °C for the described dimer of 2,6-dimethyl-6-nitrosohept-2-en-4-one).[12] The IR spectrum of the monomer, ν/cm^{-1}: 1690 (C=O), 1637 (C=C), 1560 (N=O) coincides with that published.[12] The ^1H NMR spectrum of the monomer, δ: 1.24 (s, 6 H, 2 Me); 1.86 (d, 3 H, =C—Me, ^4J = 1.3 Hz); 2.08 (d, 3 H, =C—Me, ^4J = 1.3 Hz); 3.04 (s, 2 H, CH_2); 6.01 (m, 1 H, CH=C, ^4J = 1.3 Hz).

Reaction of 3-bromo-2,2,6,6-tetramethyl-4-oxopiperidine-1-oxyl (1c) with NH_4OH. **1c** (9.96 g, 40 mmol) was added with stirring and ice-cooling to 200 mL of conc. NH_4OH. The reaction mixture was stirred at ~20 °C for 4 h and left for 1 day. Then the solution was saturated with solid KOH, and the precipitate that formed was filtered off and dried in air to yield 5.36 g of **2c**. The filtrate was extracted with $CHCl_3$ and the extract was dried with Na_2SO_4, concentrated, and washed with ether. An additional amount of amide **2c** (0.98 g) was obtained from the extract. The overall yield of 2,2,5,5-tetramethyl-3-carbamoylpyrrolidine-1-oxyl **2c** was 6.34 g (86%), m.p. 172—173 °C (from EtOAc). When this material was mixed with authentic **2c** (*cf.* Ref. 6: m.p. 174 °C) it did not depress the melting point.

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