1-HYDROXY- AND 1-NITROSO-2, 5-DIMETHYLPIPERID-4-ONES AND THEIR DERIVATIVES

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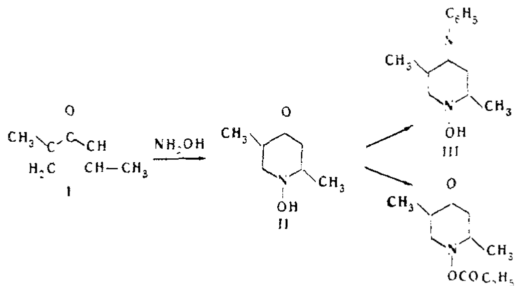
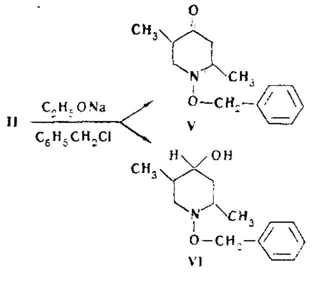
Derivatives of 1-hydroxy-2,5-dimethylpiperid-4-one substituted at the hydroxy and the carbonyl groups have now been prepared and the IR spectra of some of them have been studied. 1-Nitroso-2, 5-dimethylpiperid-4-one has been prepared from 2,5-dimethylpiperid-4-one and subjected to various reactions at the nitroso- and the carbonyl groups. The IR spectra of the N-nitroso-compounds prepared are discussed.

N-Hydroxy- and N-nitroso-substituted γ-piperidones and γ-piperidols are of interest as starting compounds for the synthesis of physiologically active substances and are convenient materials for studying the stereochemistry of the piperidone system.

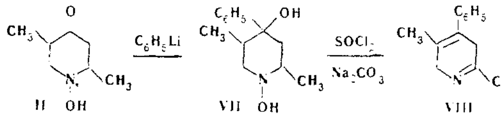
1-Hydroxy-2, 5-dimethylpiperid-4-one (II) [2] was prepared by condensation of propenyl isopropenyl ketone (I) with hydroxylamine, as described by the authors in a previous paper [1]. Continuing research on the synthesis of this type of compound, we turned to the synthesis of various derivatives of the piperidone (II). Condensation of this ketone with aniline afforded 1-hydroxy-2, 5-dimethylpiperid-4-ylideneaniline (III) and the reaction of the piperidone II with propionyl chloride afforded 1-propionoxy-2, 5-dimethylpiperid-4-one (**IV**).



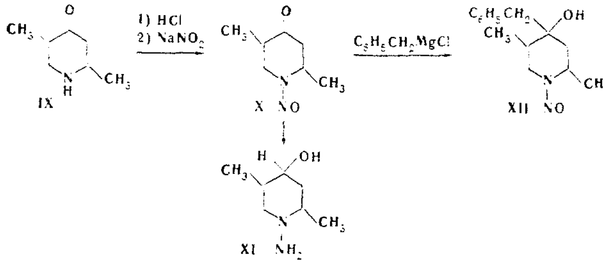
By successive treatment of the piperidone II with sodium ethoxide and benzyl chloride in ethanol we had previously obtained 1-benzyloxy-2, 5-dimethylpiperid-4-one (V) [2]. Further study of the products of this reaction showed that in these conditions partial reduction of the carbonyl group of the piperidone V occurs. A small quantity of 1-benzyloxy-2,5-dimethylpiperid-4-ol (VI) is formed.



The reaction of **II** with phenyllithium afforded a mixture of 1-hydroxy-2, 5-dimethyl-4-phenylpiperid-4-ols (VII). From this product, three isomeric compounds with mps 142–144° C, 160.2–162.5° C, and 196–198° C were isolated. From the elementary analysis of the high melting isomer, it can be shown that it crystallizes with one molecule of methanol. Treatment of the mixture of isomeric piperidols VII with thionyl chloride followed by sodium carbonate gave a bisdehydrated product—2, 5-dimethyl-4-phenyltetradehydropiperidine (VIII).

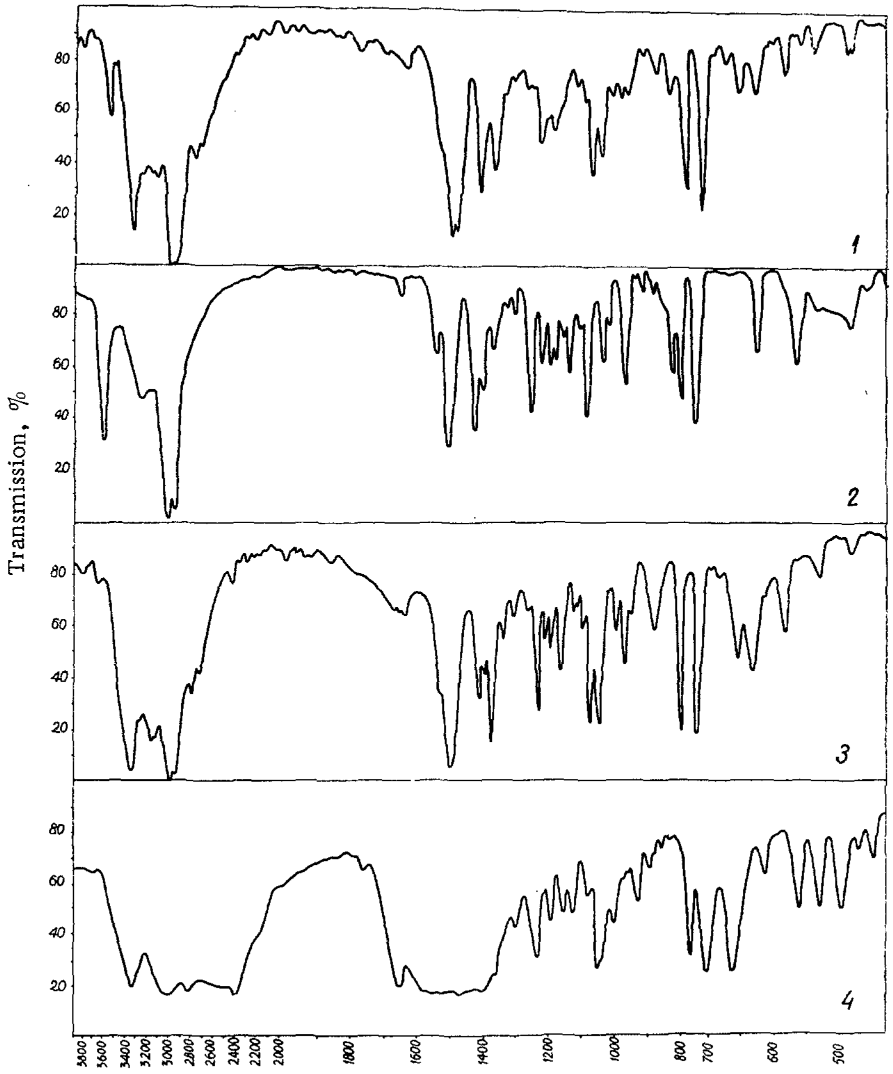


Nitrosation of 2, 5-dimethylpiperid-4-one (IX) [3] afforded 1-nitroso-2, 5-dimethylpiperid-4-one (**X**), isolated in the form of pale-green needles, mp 57–58° C. The nitroso group is attached to the nitrogen atom because in these conditions 1, 2, 5-trimethylpiperid-4-one [3] is not nitrosated. Reduction of the piperidone **X** with stannous chloride in HCl gave 1-amino-2, 5-dimethylpiperid-4-ol (**XI**) and the piperidone IX. However, reduction of the piperidone **X** with zinc in acetic acid, tin in hydrochloric acid, and titanium trichloride in acetic acid apparently leads to reductive deamination and affords only 2, 5-dimethylpiperid-4-one (IX). Compound **X**, like the N-alkyl-γ-piperidols, reacts with organomagnesium compounds. Its reaction with benzylmagnesium chloride afforded 1-nitroso-2, 5-dimethyl-4-benzylpiperid-4-ol (XII) with a 36% yield.



The IR spectra of some of the products were studied in the solid state.

The IR spectra of the mixture of isomeric 1-hydroxy-2, 5-dimethyl-4-phenylpiperid-4-ols VII, mp 115–140° C (figure, curve 1) shows a narrow band in the region of hydroxyl group stretching vibrations at 3522 cm^{-1} which apparently corresponds to intramolecular hydrogen bonding (3600–3500 cm^{-1}) of the type OH···O or OH···N. Hence, it may be concluded that there is a certain proportion of molecules



IR Spectra: 1) starting mixture of isomeric 1-hydroxy-2, 5-dimethyl-4-phenylpiperid-4-ols VII, mp 115–140° C; 2) γ-isomer, mp 142–144° C; 3) β-isomer, mp 160.2–162.5° C; 4) α-isomer, mp 196–198° C.

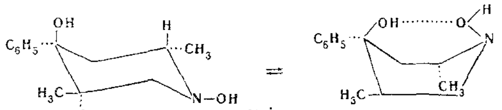
with a boat-shaped conformation in the isomeric mixture of piperidols VII. A single intense narrow band at 3300 cm^{-1} corresponds to intermolecular hydrogen bonds of the type OH···O or OH···N.

In IR spectrum of the piperidol VII, mp 142–144° C (figure, curve 2) shows an intense narrow band at 3520 cm^{-1} corresponding to an OH group with an intramolecular hydrogen bond to the group > N—OH. Its intensity suggests that the majority of the molecules possess a boat-shaped conformation. The band at 3180 cm^{-1} corresponds to a stretching vibration of a bound OH group of the polymer type. This conclusion is in harmony with data on the IR spectra of 1-hydroxy-2,5-dimethylpiperid-4-one (II) and 1-hydroxy-2,5-dimethylpiperidine, published previously [2]. In the IR spectra of these compounds, bands at 3220 and 3230 cm^{-1}, respectively correspond to stretching vibrations of the group $\rangle$N—OH band only by an intermolecular hydrogen bond of the polymer type. The absence of an intense narrow band in the 3600–3500 cm^{-1} region in the spectra of piperidone II suggests that its basic structure is the chair conformation.

In the spectrum of piperidol VII, mp 160.2–162.5° C (figure, curve 3), a highly intense band at 3315 cm^{-1} of the dimer type overlaps with a polymeric band at 3110 cm^{-1}.

An intense broad bond at 3240 cm^{-1} in the IR spectra of piperidol VII, mp 196–198° C (figure, curve 4), may be assigned to a polymeric form.

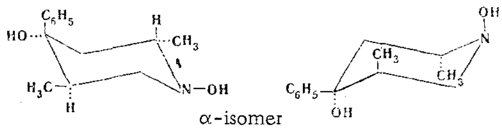
The IR spectroscopic data and chromatographic analysis may serve as a basis for preliminary conclusions concerning the structure of isomeric 1-hydroxy-2,5-dimethyl-4-phenylpiperid-4-ols (VII). By analogy with the isomeric 1,2,5-trimethyl-4-phenylpiperid-4-ols [5], we shall introduce the following nomenclature for the piperidols VII: the isomer with mp 196–198° C—(α); with mp 160.2–162.5° C—(β); with mp 142–144° C—(γ). These piperidols are found, approximately, in the following proportions α : β : γ (1 : 0.65 : 1). Apparently, as is also the case with the isomeric 1,2,5-trimethyl-4-phenyl-piperid-4-ols, the isomers formed in the predominant proportion belong to the category of piperidone derivatives with a trans-equatorial arrangement of the methyl groups at C_2 and C_5. The conditions necessary for the formation of strong intramolecular bonds of the —OH— $\rangle$N—OH type are realized in piperidols with axial OH groups at C_4. IR spectroscopic data show that the piperidol VII, mp 142–144° C, i.e., the γ-isomer, is in this category. Blockage arising from the intramolecular hydrogen bond of the hydroxyl groups at C_4 and at the nitrogen explains the relatively high R_f value of this isomer. Consequently, it may be assumed that the isomer has the following structure:



γ-isomer

1e-hydroxy-2e, 5e-dimethyl-4e-phenylpiperid-4a-ol. The principal conformation of this compound in the solid state is the boat-form.

The α-isomer, for which an intermolecular polymeric form is characteristic and which has a relatively low R_f value because of the existence of free hydroxyl groups (in the chromatographic process), possibly possesses the structure of 1e-hydroxy-2e,5e-dimethyl-4a-phenylpiperid-4e-ol or a conversion form of it.



α-isomer

Naturally, the methyl groups at C_2 and C_5 occupy the cis-position in the β-isomer. A consideration of steric factors affecting the reaction of phenyllithium with 1-hydroxy-2,5-dimethylpiperid-4-one suggests that both the phenyl radical at C_4 and the methyl group at C_5 are in the trans position. However, further experimental data are required before conclusions are reached concerning the conformation of the β-isomer of the piperidol VII.

EXPERIMENTAL

1-Hydroxy-2,5-dimethylpiperid-4-ylideneaniline (III). A mixture of 14.3 g (0.1 mole) of the piperidone II, 10.2 g (0.11 mole) of aniline, and 10 drops of glacial acetic acid in 50 ml of dry toluene was boiled for 10 hr. After 1.5 ml of water had separated, the toluene was distilled off and the residue was vacuum-distilled. Yield 59.6% of III, a resinous substance with a light green color, bp 143–145° C (1 mm). Found, %: N 12.81, 12.71, calculated for $C_{13}H_{18}N_2O$, %: N 12.84.

1-Propionoxy-2,5-dimethylpiperid-4-one (IV). A solution of 10 g (0.07 mole) of the piperidone II in 22 ml of dry pyridine and 25 ml of dry benzene was stirred in a three-necked flask fitted with a reflux condenser, stirrer, and dropping funnel. 13 g (0.14 mole) of propionyl chloride was added to this mixture over 20 min at room temperature. The mixture was stirred for 6 hr at 20° C and for 20 min at the boiling point of benzene. The reaction mixture was cooled, poured into 300 ml water, treated with caustic soda, and extracted with ether. After drying with sodium sulphate, the ether and benzene were driven off and the residue was vacuum-distilled. After recrystallization from ethanol the fraction with bp 100–101° C (2 mm) yielded 3.8 g (27%) of IV as rhombic crystals, mp 43° C. Found, %: N 6.76, 7.00. Calculated for $C_{10}H_{17}NO_3$, %: N 7.03.

1-Benzyloxy-2,5-dimethylpiperid-4-one (V) and 1-benxyloxy-2,5-dimethylpiperid-4-ol (VI). A solution of 20 g (0.14 mole) of the piperidol II in 150 ml of absolute ethanol was added to the sodium ethoxide, prepared from 3.68 g (0.16 g-at) of sodium in 200 ml of absolute ethanol. The mixture was stirred for 15 min at room temperature and 21 g (0.17 mole) of benzyl chloride was added. Stirring at room temperature was continued for 6 hr. The ethanol was distilled off and the residue was extracted with ether. The ether extracts were washed with 15% caustic soda solution, dried, and vacuum-distilled. This yielded 10 g of a fraction with bp 139–145° C (3 mm) which partially crystallized on cooling. Yield 0.2 g of VI as long green needles, mp 121.5–122.5° C (from ethanol). IR spectrum 3230 cm^{-1} (—OH). Found, %: N 5.96, 6.10. Calculated for $C_{14}H_{21}NO_2$, %: N 5.95. The liquid fraction remaining after the removal of the piperidol VI was vacuum-distilled. This gave 8 g (24.5%) 1-benzyloxy-2,5-dimethylpiperid-4-one (V) as a green liquid, bp 139–141° C (3 mm); n_D^{20} 1.5278. Found, %: N 6.25, 6.06; MR_D 67.27. Calculated for $C_{14}H_{19}NO_2$, %: N 6.01; MR_D 67.37. The hydrochloride of the piperidone V, precipitated from ethanol with acetone, melted at 247–249° C. Found, %: N 5.58, 5.53. Calculated $C_{14}H_{19}NO_2 \cdot HCl$, %: N 5.23.

1-Hydroxy-2,5-dimethyl-4-phenylpiperid-4-ol (VII). The experiment was performed in a stream of nitrogen. 14.3 g (0.1 mole) of the piperidone II in 300 ml of absolute ether was added over 1 hr 30 min to the phenyllithium prepared from 2.8 g (0.4 g-at) of lithium and 47.1 g (0.3 mole) of bromobenzene in 200 ml of absolute ether. During the addition the vessel was cooled in an ice-salt mixture. The mixture was stirred with cooling for 1 hr and then left at room temp for 40 hr, after which it was boiled with stirring for a further 2 hr. 150 ml of water and 30 ml 18% and 50 ml of conc HCl were added successively and slowly to the cooled reaction mixture. The aqueous layer was saturated with sodium carbonate and 7 g of potassium hydroxide was added to it. The organic bases then separated out were extracted with ether and dried. The ether was distilled off leaving 19.5 g of a thick pale pink liquid, which crystallized completely. This residue was vacuum-distilled. The fraction with bp 172–175° C (2 mm), (11 g), consisted of a mixture of isomeric piperidols VII. Yield 50%. After distillation it formed a green glass-like mass which on trituration was transformed into a white powder, mp 41–80° C. After recrystallization from ethyl acetate, mp 115–140° C. Found, %: N 6.55, 6.49. Calculated for $C_{13}H_{19}NO_2$, %: N 6.33. Chromatography on plates with alumina (activity II) using the methanol—ethyl acetate (1 : 9) system revealed two spots: R_f 0.65 and 0.10. Preparative separation of 2 g of this mixture was performed in a column (l = 75 cm, d = 1.7 cm) with the same solvent system. The isomer with mp 196–198° C was eluted with methanol. The following products were obtained successively: 0.54 g of an isomer with mp 142–144° C, R_f 0.66; 0.35 g of an isomer with mp 160.2–162.5° C, R_f 0.64; 0.1 g of an intermediate fraction, mp 156–161° C, R_f 0.55 and 0.10; 0.57 g of an isomer with mp 196–198° C, R_f 0.1.

2,5-Dimethyl-4-phenyltetradehydropiperine (VIII). 39 ml (0.54 mole) of thionyl chloride was added with stirring at 0° C over 40 min to a solution of 20 g (0.09 mole) of a mixture of the isomeric piperidols VII (mp 41–80° C) in 1 l of absolute ether. The mixture was stirred for 1 hr with cooling, 1 hr at room temp, and 1 hr 30 min at the boiling point of ether, and was then left standing at room temp for 10 hr. The ether and excess thionyl chloride were distilled off. The residual mass was dissolved in 200 ml of water, ether was added, and the aqueous layer was saturated with sodium carbonate. The ether extracts were dried and vacuum-distilled twice. This yielded 6 g (36%) of VIII, bp 99–100° C (1 mm); n_D^{20} 1.5700. Found, %: N 6.72, 6.72; MR_D 59.36. Calculated for $C_{13}H_{15}N$, %: N 7.57; MR_D 58.64. **IR spectrum:** 1670 cm^{-1} ($\rangle C{=}N{-}$); 1600 cm^{-1} (planar vibrations of the benzene ring); stretching vibrations of a C=C bond conjugated with the benzene ring apparently occur as an inflection at 1580 cm^{-1} on the low-frequency wing of the band at 1600 cm^{-1}. The band at 1448 cm^{-1} relates to deformation vibrations of the active methylene groups. There is also a band in the stretching vibration region at 3300 cm^{-1}, which indicates the presence of an impurity containing an OH group in the product VIII.

Picrate: mp 171–172° C (from ethanol). Found, %: N 13.70; 13.65. Calculated for $C_{13}H_{15}N \cdot C_6H_3N_3O_7$, %: N 13.53. **Methiodide:** mp 197–199° C (from ethanol). Found, %: N 4.19, 4.20. Calculated for $C_{13}H_{15}N \cdot CH_3I$, %: N 4.28.

1-Nitroso-2,5-dimethylpiperid-4-one (X). 25.4 g (0.2 mole) of the piperidone IX (bp 87–90° C (12 mm), n_D^{20} 1.4670) was dissolved in a mixture of 100 ml of water and 51 ml of conc HCl in a three-necked flask fitted with a reflux condenser, stirrer, and dropping funnel. The flask was cooled with ice-water, and a saturated aqueous solution of 42 g (0.61 mole) sodium nitrite was added with stirring over 20 min. Cooling was discontinued and the solution was stirred a further 15 min, followed by the addition of 70 g of NaCl to the reaction mixture and stirring for a further 10 min. This gave 15 g of crystals, and a further 4 g of crystals was obtained by extraction with ether from the residual aqueous solution. Total yield of X, 19 g (61%), long needles with a green tint, mp 57–58° C (from ether), bp 109–110° C (0.5 mm). Found, %: C 53.84, 53.58; H 9.11, 8.16; N 17.63, 17.55. Calculated for $C_7H_{12}N_2O_2$, %: C 53.83, H 7.75; N 17.94. IR spectrum: 1715 cm^{-1} ($\rangle C{=}O$); 1420, 1221 cm^{-1} ($\rangle N{-}N{=}O$). Oxime of the piperidone X, mp 152–154° C (from ethanol). Found, %: N 24.35, 24.23. Calculated for $C_7H_{13}N_3O_2$, %: N 24.55. IR spectrum: 3260 cm^{-1} (OH); 1662 cm^{-1} ($\rangle C{=}N{-}$); 1370 cm^{-1} ($\rangle N{-}N{=}O$).

Reduction of 1-nitroso-2,5-dimethylpiperid-4-one (X). a) With stannous chloride in hydrochloric acid. A small crystal of sodium iodide was added to 20 g (0.13 mole) piperidone X and 50 g (0.26 mole) $SnCl_2$, dissolved in 200 ml ethanol, and then 45 ml of conc HCl was added over 15 min. The mixture was stirred for 1 hr, a further 20 ml of conc HCl was added, and stirring was continued for 2 hr at 55–60° C and 1 hr at 75–80° C. Ethanol was distilled off in a partial vacuum. 200 ml of water saturated with caustic potash was added to the residue and it was extracted with ether, and the extract was dried. The ether was evaporated off and the residue vacuum-distilled. Fraction 1) bp 67–69° C (3 mm), 2.7 g, n_D^{20} 1.4678. Fraction 2) bp 123–124° C (3 mm), 3 g. The first fraction proved to be 2,5-dimethylpiperid-4-one (IX). The second fraction yielded 2.8 g (15.4%) of 1-amino-2,5-dimethylpiperid-4-ol (XI), mp 130–132° C (from acetone), Found, %: C 58.88; H 10.58; N 19.79, 19.69. Calculated for $C_7H_{16}N_2O$, %: C 58.28; H 11.29; N 19.43.

The IR spectrum of XI showed a narrow band at 3380 cm^{-1} characterizing the stretching vibrations of an NH primary amino group and a band at 1640 cm^{-1} due to NH_2 deformation vibrations. The OH group stretching vibrations apparently occur in the 3150–2750 cm^{-1} region and are masked by other bands. **Picrate:** mp 189–189.5° C (from ethanol). Found, %: N 18.11, 18.84, Calculated for $C_7H_{16}N_2O \cdot C_6H_3N_3O_7$, %: N 18.76.

b) With zinc in acetic acid. 34 g (0.52 g-at) zinc dust was added to a solution of 20 g (0.13 mole) of the piperidone X in a mixture of 200 ml of water, 100 ml of ethanol and 15 ml of glacial acetic acid and then 62 ml glacial acetic acid was added at 0° C over 30 min with energetic stirring. Stirring was continued with cooling for 45 min and then at 65° C for 20 min. The ethanol and excess acetic acid were distilled off in a partial vacuum. The residue was dried with caustic potash and extracted with ether. Distillation yielded 4 g of 2,5-dimethylpiperid-4-one (IX), bp 53–54° C (2 mm); n_D^{20} 1.4665. **Picrate:** mp 135–137° C.

(c) With titanium trichloride in hydrochloric acid. 333 ml of a 15% solution of $TiCl_3$ and 38.5 ml of conc HCl were added to a solution of 15.6 g (0.1 mole) of the piperidone X in 100 ml of ethanol at 0° C. The mixture was stirred for 1 hr at room temp. and for 1 hr at 60° C. Sodium carbonate was added to neutrality, and caustic potash until saturation. The mixture was extracted with ether. On distillation, 8 g of IX was obtained, bp 70–71° C (4 mm); n_D^{20} 1.4680. **Picrate:** mp 135–136° C (from ethanol).

(d) With tin in hydrochloric acid. 23.7 g (0.2 g-at) of granulated tin was added to a solution of 23 g (0.15 mole) of the piperidone X in 20 ml of 18% HCl. Then 65 ml of conc HCl was added over 30 min at a temp. of the reaction mixture of 55–60° C. The mixture was then heated at 80° C for 30 min. Following the usual procedure, 3 g of IX was obtained, bp 85–87° C (10 mm); n_D^{20} 1.4682. **Picrate:** mp 136–137° C (from ethanol).

The picrates obtained in experiments b), c), and d), when mixed with the picrate of the known 2,5-dimethylpiperid-4-one [3], gave undepressed mps.

1-Nitroso-2,5-dimethyl-4-benzylpiperid-4-ol (XII). A saturated ethereal solution of 15.6 g (0.1 mole) of X was added dropwise to the benzylmagnesium chloride prepared from 4.8 g (0.2 g-at) of magnesium and 31.6 g (0.25 mole) of benzyl chloride in 150 ml of absolute ether at –10° C. The mixture was stirred with cooling for 4 hr and at room temp. for 10 hr, and was boiled for 30 min. 150 ml water and 80 ml of 18% HCl were added successively with cooling. The ether layer was separated off, combined with the ether extracts of the aqueous solution, and dried. Yield 9 g (36%) of XII as pale pink crystals, mp 163–165° C (from ethanol). Found, %: C 68.01, 67.57; H 8.05, 8.10; N 10.66, 10.41. Calculated for $C_{14}H_{20}N_2O_2$, %: C 67.74; H 8.12; N 11.29. IR spectrum: 3430 cm^{-1} (—OH); 1383, 1230 cm^{-1} ($\rangle N{-}N{=}O$).

The IR spectra were recorded on a UR-10 spectrophotometer in the ranges of Li F, NaCl, and KBr prisms from 3800 to 400 cm^{-1} in mineral oil.

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