b) A suspension of the hydrobromide of (II) in ethyl acetate was saturated with dry HCl until the precipitate dissolved completely, and it was heated for 3 h at 50°C. The composition of the mixture after neutralization by saturated K_2CO_3 was: 8% cis-(II) and 92% trans-(II) (GLC data).

Hydrobromide of the e-Epimer of trans-N-tert-Butyl-4,5-dimethyl-3-piperidone (e-XII). A solution of 0.1 g of the hydrobromide of (II) in 25 ml of liquid NH_3 was given an addition of 1.5 ml of absolute ethanol and an excess of Li. The usual treatment gave a 3:97 mixture of the epimeric alcohols, which, were converted into the hydrobromides and crystallized from an MeOH−ethyl acetate mixture. The hydrobromide of pure (GLC) e-(XII) with mp 262-263°C was obtained. Found: C, 49.40; H, 9.12; H, 5.38; Br, 31.36%. Calculated for $C_{11}H_{24}NOBr$: C, 49.62; H, 9.02; N, 5.20; Br, 30.01%. IR spectrum (base, CCl_4, 0.005 M): 3610 cm^{-1} (free OH).

CONCLUSIONS

In 3-ketopiperidines an e-methyl at C^4 specifically shields the axial region of the carbonyl only with respect to reduction by aluminum isopropoxide and, to a lesser degree, to reduction over platinum.

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CONVENIENT MEANS OF CONVERTING NITROXYL
# RADICALS INTO O-METHYLHYDROXYLAMINES

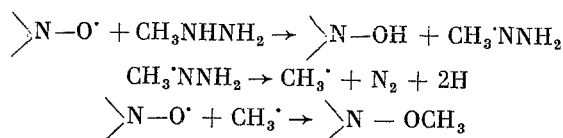G. I. Shchukin, I. A. Grigor'ev,
and L. B. Volodarskii

Sterically hindered O-methylhydroxylamines (O-MHA) are convenient diamagnetic analogs of nitroxyl radicals particularly in the study of the influence of the nitroxyl group on the chemical and spectral properties of other functional groups available in structurally similar paramagnetic and diamagnetic compounds. In comparison with the usually used hydroxylamines they possess the advantage that for them the possibility of ready regeneration of the initial nitroxyl radicals (NR) is absent. However, until the present there has been no convenient and universal means of synthesizing O-MHA. Sterically hindered O-MHA are formed on alkylating the corresponding hydroxylamines with methyl iodide in the presence of strong bases [1], however in many cases the synthesis of the initial hydroxylamines has specific difficulties as a result of their instability and ready oxidation to NR [2]. Another method is the alkylation of the hydroxylamine anion with methyl iodide or dimethyl sulfate, the anion is generated directly from NR by reduction of the latter with organometallic compounds or with metallic sodium [3]. The O-MHA are formed from NR on interaction with methylmagnesium iodide [4] but for this there must be no functional groups in the molecule which react with Grignard reagent [5]. The formation of O-MHA is also known by the interaction of NR with acetyl benzoyl peroxide [6] and methyltrichlorotitanium [7]. The NR of piperidine form O-phenylhydroxylamines in addition to hydroxylamines on interaction with phenylhydrazine [8]. It might have been expected that the interaction of NR with methylhydrazine also led to O-MHA. In addition it seemed of interest to consider this reaction for NR of 3-imidazoline-3-oxide since on interaction of the latter with hydrazine deoxygenation of the nitrone group occurs [9].

It was discovered by us that on interacting NR derivatives of 3-imidazoline-3-oxides (Ia-e) with methylhydrazine the formation of 1-methoxy-3-imidazoline-3-oxides (IIIa-e) occurred in addition to reduction of the radical center to hydroxylamines (IIa-e). In this reaction no products of deoxygenation of the nitrone group were formed.

(I a—e)　　(II a—e)　　(III a—e)

R = Me (a), Et (b), Ph (c), CONH$_2$ (d), CH=NOH (e)
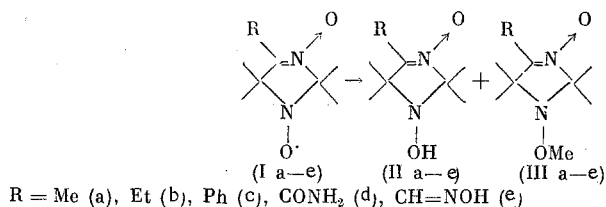
The ratio of products of reduction and of O-methylation was 7:3. By analogy with the reactions between NR of piperidine and phenylhydrazine [2] the following scheme may be proposed for the reaction between NR and methylhydrazine

$$>N-O^{\cdot} + CH_3NHNH_2 \rightarrow >N-OH + CH_3^{\cdot}NNH_2$$

$$CH_3^{\cdot}NNH_2 \rightarrow CH_3^{\cdot} + N_2 + 2H$$

$$>N-O^{\cdot} + CH_3^{\cdot} \rightarrow >N-OCH_3$$

The NR of 3-imidazoline-3-oxide reacted with methylhydrazine during 20-30 min but the similar reaction of radical (IVa) under analogous conditions and even using a large excess of methylhydrazine occurred very slowly in air and failed to lead to disappearance of the initial NR (checked by TLC on Silufol). This reaction proceeded to completion only in an inert atmosphere (Ar) on keeping the reaction mixture for 20 h. Other NR of 3-imidazoline (IVb, c) interacted with methylhydrazine under analogous conditions. The ratio of obtained products of reduction (Va-c) and of O-methylation (VIa-c) was also 7:3.

(IV a—c)　　(V a—c)　　(VI a—c)

R = Me (a), Ph (b), CH=NOMe (c).
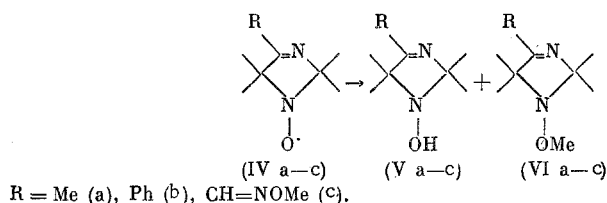
Since the reaction rate is determined by the first stage of oxidation of methylhydrazine by NR (decomposition of the resulting hydrazyl radical and recombination of the methyl radical with NR occurs rapidly), the difference in behavior of the NR of 3-imidazoline-3-oxide (I) and 3-imidazoline (IV) in the given reaction is evidently linked with the difference in oxidizing properties of these radicals and the stability of the corresponding hydroxylamines towards oxidation by oxygen of the air. It was shown in [10] that the NR of 3-imidazoline-3-oxide were stronger oxidizing agents than NR of 3-imidazoline but the corresponding hydroxylamines regenerated the initial NR appreciably more slowly in the presence of oxygen of the air. Evidently the rapid and complete course of reaction for (I) and the need to use an inert atmosphere for radicals (IV) are explained by these reasons.

The NR of 4-imidazolidinones are close in oxidative properties to NR of 3-imidazoline-3-oxide [10] as a result of which they must readily react with methylhydrazine. In reality 3-methoxy-4-oxo-2,2,5,5-tetramethylimidazolidine-1-oxide (VII) was converted in air in 30% yield to 1,3-dimethoxy-4-oxo-2,2,5,5-tetramethylimidazolidine (VIII).

Products (II), (III), and (V), (VI) were formed in the ratio indicated above after disappearance of the initial NR (check by TLC on silufol and by disappearance of color from the reaction mixture). If the reaction mixture remained in the air for several hours then the yield of the O-methylation product was increased, for example for radical (Ic) to 84%. This may explain the regeneration of the initial NR as a result of interaction of the resulting hydroxylamine (IIc) with dissolved oxygen from the air and subsequent reaction of NR with methylhydrazine.

The O-methylation reaction with methylhydrazine failed to occur with NR containing 4-dihalomethyl groups. Interaction of methylhydrazine with the radical center occurred more rapidly than the nucleophilic

TABLE 1. Products of Reaction of Nitroxyl Radicals (Ia–g), (IVa–c), and (VII) with Methylhydrazine

Compound	Yield, %	mp, °C (solvent), bp, °C (mm Hg)	Found / Calculated C	H	N	Empirical formula	UV spectrum λ_{max} (log ε)	PMR spectrum 2,2,5,5-CH₃	1-OCH₃	signals of other protons
(IIIa)	31 [a]	84–85 (3)	57,8 / 58,1	9,4 / 9,7	14,6 / 15,4	$C_9H_{18}N_2O_2$	232(3,98)	1,32[b] s (6H), 1,45 s (6H)	3,66	1,88 s (3H, 4-CH₃)
(IIIb)	30 [a]	62–63 (3)	59,8 / 60,0	10,2 / 10,0	13,7 / 14,0	$C_{10}H_{20}N_2O_2$	236(4,00)	1,30[b] s (6H), 1,44 s (6H)	3,64	1,14 t (3H), $J=7$Hz, CH₃CH₂, 2,30 q (2H), $J=7$Hz, CH₃CH₂
(IIId)	30 [a]	129–130 (hexane–benzene)	50,5 / 50,2	7,9 / 7,9	19,6 / 19,5	$C_9H_{17}N_3O_3$	262(4,01)	1,54[b] s (12H)	3,69	
(IIIe)	23 [a]	168–169 (ethyl acetate)	50,7 / 50,2	7,4 / 7,9	19,1 / 19,5	$C_9H_{17}N_3O_3$	203(3,85) 242(3,85) 295(4,16)	1,50[b] s (12H)	3,69	8,09 s (1H, CH=)
(IIIf)	42	129–131 (hexane)	31,3 / 31,4	4,7 / 4,7	7,7 / 8,1	$C_9H_{16}Br_2N_2O_2$ [d]	202(3,78) 268(3,94)	1,52[e] s (6H), 1,61 s (6H)	3,67	6,56 s (1H, CHBr₂)
(IIIg)	45	87–89 (hexane)	42,5 / 42,4	6,4 / 6,3	11,0 / 11,0	$C_9H_{16}Cl_2N_2O_2$ [f]	203(3,60) 256(4,03)	1,54[e] s (6H), 1,62 s (6H)	3,67	6,93 s (1H, CHCl₂)
(VIa)	20 [g]	41 (3)	63,3 / 63,5	10,3 / 10,6	16,2 / 16,5	$C_9H_{18}N_2O$	—	1,17[b] s (6H), 1,24 s (6H)	3,56	1,82 s (3H, 4-CH₃)
(VIb)	29 [g]	Oil	72,5 / 72,4	8,5 / 8,6	12,3 / 12,1	$C_{14}H_{20}N_2O$	205(4,23) 239(4,00)	1,34[b] s (6H), 1,41 s (6H)	3,59	7,12–7,34 s (3H) and 7,54–7,81 m (2H, C₆H₅)
(VIc)	30 [g]	65–66 (3)	56,6 / 56,3	9,4 / 8,9	19,3 / 19,7	$C_{10}H_{19}N_3O_2$	236(4,16)	1,22[b] s (6H), 1,37 s (6H)	3,59	3,92 s (3H, =NOCH₃), 7,56 s (1H, CH=)
(VIII)	33 [a]	77–78 (15)	53,2 / 53,5	9,1 / 8,9	13,4 / 13,9	$C_9H_{18}N_2O_3$	—	1,22[b] s (6H), 1,36 s (6H)	3,60	3,78 s (3H, 3-OCH₃)

a) Reaction time 20–30 min.
b) In CCl₄.
c) In CD₃OD.
d) Found Br 46.4%, calculated Br 46.5%.
e) In CDCl₃.
f) Found Cl 27.4%, calculated Cl 27.8%.
g) Reaction time 20 h.

substitution reaction at the dihalomethyl group. The (I) methoxy derivatives (IIIf) and (IIIg) were obtained in 30% yield from 4-dibromomethyl- (If, R = CHBr$_2$) and 4-dichloromethyl-2,2,5,5-tetramethyl-3-imidazoline-3-oxide-1-oxyls (Ig, R = CHCl$_2$). Compounds (IIIf) and (IIIg) were also formed on interaction of (IIIa) with N-bromo- and N-chlorosuccinimides in CCl$_4$.

EXPERIMENTAL

IR spectra were taken on a UR-20 spectrometer, UV spectra on a Specord UV-Vis instrument in alcohol, and PMR spectra on a Varian A-56-60 spectrometer for 5-7% solutions, internal standard was HMS. The synthesis of NR (Ia-g), (IIIa-c) and (VII) has been described in [11]. IR spectra of 1-methoxy derivatives were close to the IR spectra of the corresponding NR with the exception of bands at 2815-2830 cm^{-1} (w) and 1060-1070 cm^{-1} (s) characteristic for NOCH$_3$ groups. Yields, melting or boiling points, data of elemental analysis, and spectra of the synthesized compounds are given in Table 1.

General Procedure for Obtaining O-Methylhydroxylamines. Methylhydrazine sulfate (3 mmole) was added to a solution of NR (3 mmole) in methanol (15 ml) followed by the addition of triethylamine (25 mmole). After decolorization of the reaction mixture the methanol was evaporated, water (10 ml) was added to the residue, and the mixture was extracted with CHCl$_3$. The extract was dried over MgSO$_4$, filtered, CHCl$_3$ evaporated, and the residue chromatographed on a column of silica gel with CHCl$_3$ as eluent. Reactions for NR (IIIa-c) were carried out in an argon atmosphere.

1-Methoxy-2,2,5,5-tetramethyl-4-phenyl-3-imidazoline-3-oxide (IIIc) was obtained in 28% yield, mp 72-74°C (cf. [12]).

The spectral characteristics of 1-methoxy-2,2,4,5,5-pentamethyl-3-imidazoline-3-oxide (IIIa), 1-methoxy-2,2,5,5-tetramethyl-4-ethyl-3-imidazoline-3-oxide (IIIb), 4-carbamoyl-1-methoxy-2,2,5,5-tetramethyl-3-imidazoline-3-oxide (IIId), 1-methoxy-4-hydroxyiminomethyl-2,2,5,5-tetramethyl-3-imidazoline-3-oxide (IIIe), 4-dibromomethyl-1-methoxy-2,2,5,5-tetramethyl-3-imidazoline-3-oxide (IIIf), 4-dichloromethyl-1-methoxy-2,2,5,5-tetramethyl-3-imidazoline-3-oxide (IIIg), 1-methoxy-2,2,4,5,5-pentamethyl-3-imidazoline (VIa), 1-methoxy-2,2,5,5-tetramethyl-4-phenyl-3-imidazoline (VIb), 1-methoxy-4-methoxyiminomethyl-2,2,5,5-tetramethyl-3-imidazoline (VIc), 1,3-dimethoxy-4-keto-2,2,5,5-tetramethylimidazolidine (VIII) are given in Table 1.

4-Dibromomethyl- (IIIf) and 4-Dichloromethyl-1-methoxy-2,2,5,5-tetramethyl-3-imidazoline-3-oxides (IIIg) were obtained by halogenation of compound (IIIa) with N-bromosuccinimide (NBS) and N-chlorosuccinimide (NCS) respectively according to [13].

CONCLUSIONS

On interacting nitroxyl radicals with methylhydrazine sterically hindered O-methylhydroxylamines were formed in addition to hydroxylamines. The reaction rate depended on the oxidative properties of the nitroxyl radicals.

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DERIVATIVES OF 3-THIOCYANOPHENOTHIAZINE

## COMMUNICATION 2: DIRECTION OF THE THIOCYANATION

REACTION IN 2-CHLOROPHENOTHIAZINE

A. A. Shtyrlina, D. Kh. Yarmukhametova, K. M. Enikeev, I. É. Ismaev and I. A. Nuretdinov

UDC 542.91:547.869

Phenothiazine and its derivatives have varied biological activities [1, 2] in which the introduction into the aromatic ring of substituents with various electronic properties has a notable influence. This influence can be observed in the instance of 10-aminoacylphenothiazines containing substituents in the aromatic ring [3].

The introduction of the thiocyano group into the aromatic ring of phenothiazine by treating it with potassium thiocyanate and bromine in an acetic acid medium has been reported [4]. The reaction proceeds under mild conditions and, depending on the proportions of the reagents, leads to the formation of the mono and dithiocyano derivatives
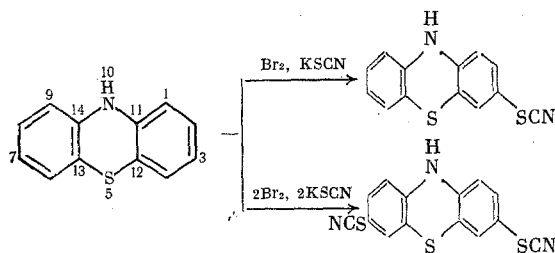
For monothiocyanation of phenothiazines already having a substituent in the ring it is necessary to establish the structures of the compounds obtained inasmuch as the substituent may go in either of the aromatic rings. In this paper we use the conventional numbering of the atoms of phenothiazine [4].

The present communication involves the study of the thiocyanation of 2-chlorphenothiazine under the conditions described by Bodea and Terdic [5]. This reaction can proceed in two directions
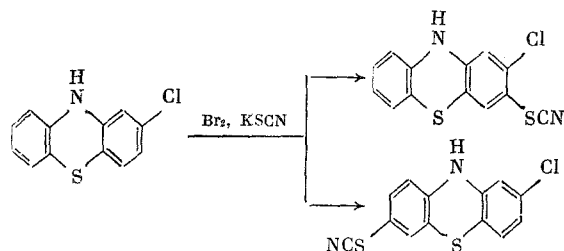
Differentiation of the products substituted in positions 3 and 7 is not possible by chemical methods. We established structures of the monothiocyano derivatives of 2-chlorphenothiazine by ^{1}H NMR methods and by ^{13}C NMR (see Table). The phenothiazine derivatives which we studied show multispin interactions of ^{1}H nuclei. Analysis of the ^{1}H NMR spectra of these compounds is shown in a separate paper. ^{13}C NMR spectroscopy permits a sufficiently rigorous determination of the directions of the reactions. For comparison and accurate interpretation of the spectral parameters of these compounds we made supplementary studies of the ^{13}C NMR spectra of phenothiazine (I), 2-chlorphenothiazine (II) and 3-thiocyanophenothiazine (III).