Pergamon

Tetrahedron 56 (2000) 4071–4077

TETRAHEDRON

Dipole-Stabilized Carbanions in Series of Cyclic Aldonitrones. Part 2: Reactions of the Metalated Aldonitrones—Derivatives of 3-Imidazoline 3-Oxide and 2*H*-Imidazole 1-Oxide with Aldehydes and Ketones☆

Maxim A. Voinov,* Igor A. Grigor'ev and Leonid B. Volodarsky

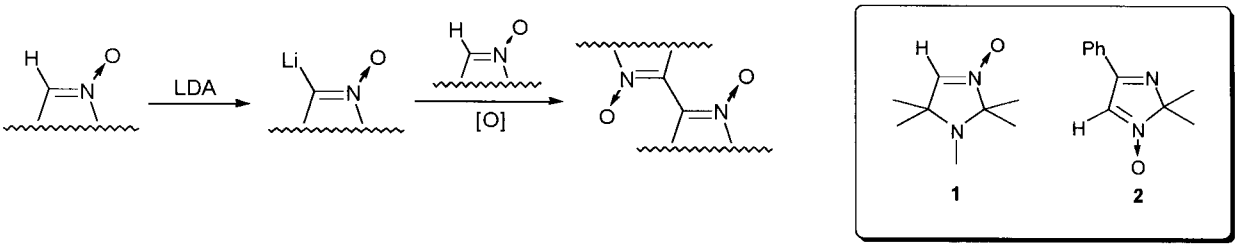
Novosibirsk Institute of Organic Chemistry, Ave. akad. Lavrent'eva 9, 630090 Novosibirsk, Russia

Received 8 February 2000; revised 24 March 2000; accepted 13 April 2000

Abstract—Metalated aldonitrones of 3-imidazoline 3-oxide and 2*H*-imidazole 1-oxide series react with a wide variety of aldehydes and ketones leading to the unknown α-hydroxymethyl nitrones. Reaction of 2,2-dimethyl-4-phenyl-2*H*-imidazole 1-oxide with allylacetone spontaneously lead to tricyclic 3,3,8-trimethyl-1-phenyl-5a,6,7,8-tetrahydro-3*H*,5*H*-4-oxa-2,3a-diaza-cyclopenta[*c*]pentalen-8-ol. The hydroxy group of (1,2,2,5,5-pentamethyl-2,5-dihydro-1H-imidazol-3-oxide-4-yl)phenylmethanol is substituted with piperidine to give, after further transformations, (1,2,2,5,5-pentamethyl-2,5-dihydro-1*H*-imidazol-4-yl)phenylmethanone.

Although cyclic aldonitrone chemistry has been known for a few decades, there is an area of reactivity of these compounds that has not been explored yet. In particular, the reactions of metalated aldonitrones with electrophilic reagents have not been studied before, though the prerequisites for such an investigation to succeed have been reported. Namely, the nitrone α-hydrogen was found to possess sufficient acidity for carbanion generation due to the -*I*-effect of *N*-oxide group.[1,2]

In view of increasing interest of investigators to nitrones as compounds with a wide spectrum of biological activity,[3] as well as to their synthetic application,[4] the synthesis of the nitrones, diversely substituted at α-carbon of nitrone group, is of interest. However, there is no general procedure to introduce substituents to the α-position of the nitrone group. In particular, an extended set of α-amino oximes,[5] α-hydroxylamino oximes,[6] α-hydroxylimino ketones[7a–c] and 1,2-dioximes[7d] is needed for the widely explored α-substituted derivatives of 3-imidazoline 3-oxides, 2*H*-imidazole 1-oxides and 1,3-dioxides[8] to be synthesized. The procedure based on the reaction of aldonitrones with



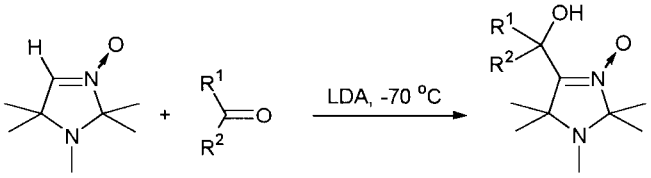
Scheme 1.

☆ Part I: see Ref. 10.

Keywords: nitrones; metalation; dipole-stabilized organolithiums; 3-imidazoline 3-oxide; 2*H*-imidazole 1-oxide; 1,3-dipolar cycloaddition; α-hydroxymethyl nitrones.

* Corresponding author. Fax: +7-3832-344752; e-mail: maxx@nioch.nsc.ru

0040–4020/00/$ - see front matter
PII: S0040-4020(00)00321-5



1 3a-n

Entry	No.	R^1	R^2	Yield, %	Entry	No.	R^1	R^2	Yield, %
1	**3a**	H	Ph	70	8	**3h**	CH_3	Ph	70
2	**3b**	H	CH_3	55	9	**3i**	CH_3	2-Thienyl	50
3	**3c**		$-(CH_2)_5-$	47	10	**3j**	CH_3	2-Pyridyl	65
4	**3d**		$-(CH_2)_4-$	40	11	**3k**	H	2-Pyrryl	55
5	**3e**		$-(CH_2)_{11}-$	46	12	**3l**	Ph	Ph	75
6	**3f**	CH_3	$CH_2=CH-$	65	13	**3m**	CH_3	Ferrocenyl	60
7	**3g**	CH_3	$CH_2=CH-CH_2-CH_2-$	62	14	**3n**	$-CH_2-C(CH_3)_2-N(\cdot O)-C(CH_3)_2-CH_2-$		65

Scheme 2.

nucleophilic reagents has a limited scope.[9] The solution to this problem is the reversal of the aldonitrone group's conventional reactivity by means of its metalation, thereby obtaining dipole-stabilized organolithiums reactive with respect to different electrophiles.

We have recently reported that aldonitrones **1** and **2** are metalated in an LDA ethereal solution[10] yielding the dimeric products as a result of the process depicted in Scheme 1. As follows from this scheme, the non-metalated aldonitrone molecule acts as an electrophilic reagent in this reaction. This indicated that metalated aldonitrones could react with other electrophiles under appropriate conditions.

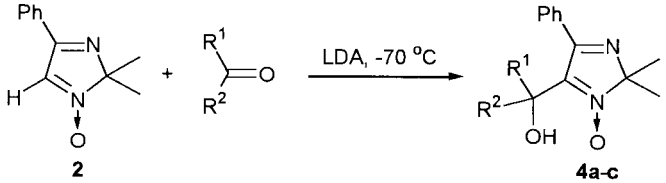
In this paper we describe the study of the reactions of metalated aldonitrones **1** and **2** with aldehydes and ketones.

Results and Discussion

The reactions of **1** and **2** with carbonyl compounds were carried out using a similar procedure to aldonitrone metalation described earlier.[10] The difference was that the ethereal solution containing the mixture of aldonitrone and carbonyl compound (1:1.3–1:1.5 ratio) was added to the LDA ethereal solution. This order of reactant mixing allowed us to suppress the dimeric product formation completely.

Thus, the reaction of 1,2,2,5,5-pentamethyl-3-imidazoline 3-oxide **1** with benzaldehyde in the ethereal solution of LDA lead in a good yield to (1,2,2,5,5-pentamethyl-2,5-dihydro-1*H*-imidazol-3-oxide-4-yl)phenylmethanol **3a** (Scheme 2, R^1=H, R^2=Ph). The nitrone group was intact in **3a** (ν_{max} 1612 cm^{-1} for C=N, a typical value for an alkylnitrone[11]).

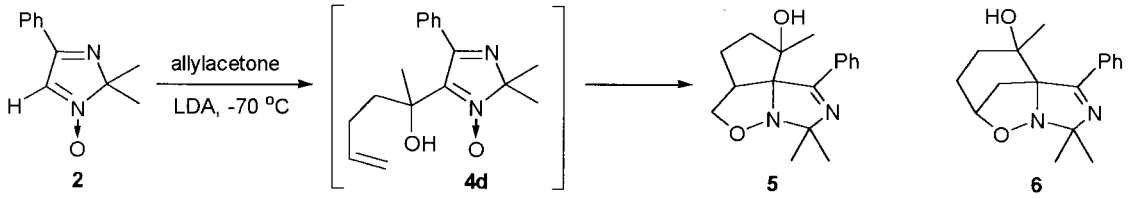
A wide variety of aliphatic, aromatic and heteroaromatic aldehydes and ketones were introduced into the reaction with aldonitrone **1** (see Scheme 2). Carbonyl compounds, containing double bonds both isolated and conjugated with the carbonyl group, could be introduced into the reaction as well (Scheme 2, Entry 6,7). It is interesting to note that no products of Michael addition were detected in the latter case. The dipole-stabilized organolithiums formed reacted with the carbonyl group solely. The compound containing



2 4a-c

Entry	No.	R^1	R^2	Yield, %	Entry	No.	R^1	R^2	Yield, %
1	**4a**	H	Ph	66	3	**4c**	H	$(CH_3)_2C=CH-(CH_2)_2-C(CH_3)=CH-$	67
2	**4b**	H	CH_3	58	4	**5**	CH_3	$CH_2=CH-CH_2-CH_2-$	72

Scheme 3.



Scheme 4.

the nitroxide moiety was introduced into the reaction also (Entry 14).

In the case of 2,2-dimethyl-4-phenyl-2*H*-imidazole 1-oxide **2** no less than 1.5-fold excess of electrophilic reagent was needed to suppress the dimerization completely. The reaction of **2** with benzaldehyde in the ethereal solution of LDA successfully afforded (2,2-dimethyl-5-phenyl-2*H*-imidazol-3-oxide-4-yl)phenylmethanol **4a** (Scheme 3, R^1=H, R^2=Ph) which retained the nitrone group (ν_{max} 1568 cm^{-1}, characteristic of conjugated C=N in 5-alkyl 2H-imidazole 1-oxides[11]).

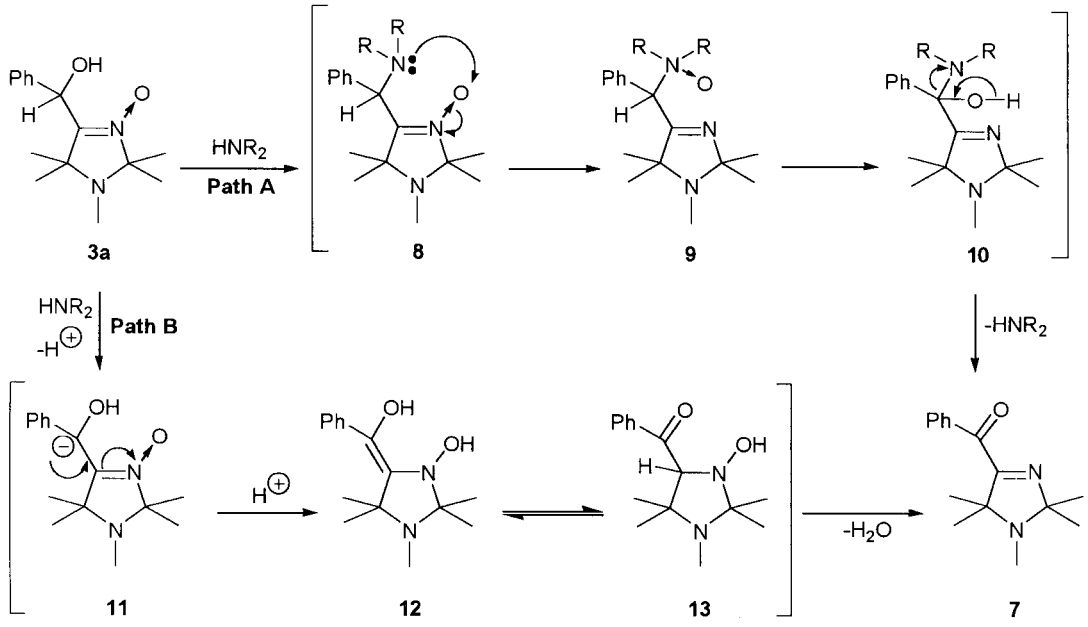
Similarly, aliphatic carbonyl compounds were introduced into the reaction with aldonitrone **2** (see Scheme 3). Neither 3-imidazoline **1** nor 2*H*-imidazole **2** react with (1*R*)-(+)-camphor, apparently due to steric reasons. According to the NMR spectra data, the derivative **4c** represents a 1:2 mixture of ***Z*** and ***E*** isomers corresponding to the isomer ratio in the starting citral (according to GLC data).

Interestingly, the reaction of **2** with allylacetone gave instead of hydroxymethyl derivative **4d**, the compound which had the same formula, but different spectral characteristics. As deduced from UV, IR and ^{13}C NMR spectra, the structure of this compound lacked the nitrone group. Analytical and spectral data allowed us to assign the compound structure of 3,3,8-trimethyl-1-phenyl-5a,6,7,8-tetrahydro-3*H*,5*H*-4-oxa-2,3a-diaza-cyclopenta[*c*]pentalen-8-ol **5**.[12] Its formation can be easily rationalized by intramolecular 1,3-dipolar cycloaddition of the terminal double bond to the nitrone group in the intermediate hydroxymethyl derivative **4d** (Scheme 4). The alternative isomer **6** was rejected based on the CH_2 group signals positions in the ^1H and ^{13}C NMR spectra. The atoms of this group resonate in the much lower field in comparison with the CH group ones.

Although **5** has three asymmetric centres it was found from the ^{13}C NMR spectrum to be formed as only one diastereomer. To the best of our knowledge, the data on 1,3-dipolar cycloadditions of inactivated double bonds, both in inter- and intramolecular mode, to the nitrone group of 2*H*-imidazole *N*-oxides have not been reported earlier.[13] The questions concerning the spatial configuration of the tricyclic compound **5** and stereoelectronic factors which generate only one diastereomer lie outside the scope of the present publication and will be discussed elsewhere.

Our attempts to synthesize an analogous tricyclic compound starting from the 3-imidazoline derivative **3g** failed.

The ^{13}C NMR spectra of the synthesized compounds showed the nitrone group carbon atom signals shifted downfield about 5–10 ppm compared with the position of



Scheme 5.

the corresponding signals in α-alkylnitrones (~136 ppm for 2*H*-imidazole 1-oxides[6a] and ~142 ppm for 3-imidazoline 3-oxides[14]) (see Experimental). These arise apparently due to N→O···H–O hydrogen bonding.[15] The broad bands in the IR-spectra in the region 3200–4000 cm^{-1} do not change their position upon dilution, evidence of the intramolecular character of hydrogen bonding. In the ^{13}C NMR spectra of **3j** the nitrone group carbon atom showed the signal at 145.21 ppm, that is more high field compared with other hydroxymethyl derivatives (~150 ppm). This is apparently due to OH-group hydrogen bonding to the more basic pyridine nitrogen.

Taking into account the similarity of the nitrone's and ketone's electron structure[16] it is reasonable to assume that β-hydroxy ketones (acyloins) and the β-hydroxy nitrones synthesized here would have similar reactivity. In particular, the acyloin hydroxy group is known to be substituted with primary and secondary amines.[17] However, the prolonged refluxing of the mixture of nitrone **3a** and piperidine in benzene led to formation of the unexpected (1,2,2,5,5-pentamethyl-2,5-dihydro-1*H*-imidazol-4-yl)-phenylmethanone **7**. Similar transformations of the 4-alkylamino-3-imidazoline 3-oxides have been observed earlier.[18] The possible paths of hydroxymethyl nitrone **3a** transformation to 3-imidazoline derivative **7** are depicted in Scheme 5.

Long refluxing of the mixture of nitrone **3a** with not less basic but less nucleophilic triethylamine instead of piperidine do not lead to **7** formation, so one could suppose that the **path B** is improbable and the **path A** is the only realizable in this transformation. Apparently, this transformation is related to the aldehyde formation in the Meisenheimer rearrangement.[19]

In summary, aldonitrones in the sequence of lithiation and electrophilic substitution with aldehydes and ketones provide a synthesis of α-hydroxymethyl substituted nitrones derivatives.

Experimental

Melting points (uncorrected) were measured using a Kofler plate. IR spectra were obtained on Specord-IR and Bruker Vector 22 spectrometers. UV spectra were recorded on a Specord UV–VIS spectrometer in ethanol. ^1H and ^{13}C NMR spectra were recorded on Bruker AC-200 (200.132 and 50.323 MHz, for ^1H and ^{13}C, respectively) and Bruker AM-400 (400.136 and 100.614 MHz, for ^1H and ^{13}C, respectively) at 300 K. $CDCl_3$ (δ_H=7.24, δ_C=76.69) was used as a solvent both for ^1H and ^{13}C NMR. EPR spectrum was recorded on Bruker ESP 300 spectrometer. 3-Imidazoline 3-oxide **1** was prepared according to a literature procedure,[14] 2*H*-imidazole 1-oxide **2**—according to procedure.[6a] Elemental analyses of the compounds synthesized were performed in the Microanalysis Laboratory of the Novosibirsk Institute of Organic Chemistry.

Reaction with carbonyl compounds (general procedure)

The LDA ethereal solution (25 ml, 9.5×10^{-3} mol) was placed under argon in the three-necked flat-bottomed flask fitted with magnetic stirrer, dropping funnel and thermometer, and cooled to −70°C. Then, the combined solution of **1** or **2** (1.9×10^{-3} mol) with carbonyl compound (2.5×10^{-3}–2.8×10^{-3} mol in 10 ml of ether was added dropwise over 15 min upon stirring. The reaction mixture was stirred for 10 min at −70°C, allowed to warm-up to room temperature and decomposed with 10 ml of H_2O. The ethereal layer was separated and the aqueous phase was extracted with $CHCl_3$ (3×10 ml). The combined organic layers were dried ($MgSO_4$), then the solvent was evaporated in a rotary evaporator. Residue was separated on preparative thin-layer chromatographic plate (silica gel for nitrones **3a**–**i**,**k**–**n**; $CHCl_3$ or $CHCl_3$+0.5% CH_3OH as eluent, **4b** – $CHCl_3$–hexane 10:1 as eluent), Al_2O_3 for nitrones **3j**, **4a**–**c**; ethyl acetate–CCl_4 1:1 as eluent for **3j**, hexane-ethyl acetate 7:1 as eluent for **4a**; hexane-ethyl acetate 10:3 as eluent for **4c**).

(1,2,2,5,5-Pentamethyl-2,5-dihydro-1*H*-imidazol-3-oxide-4-yl)phenylmethanol (3a). Colourless crystals, mp 120–122°C (from hexane–EtOAc, 10:1); IR (KBr, cm^{-1}): 2820 (NCH_3), 3200 (OH); IR ($CHCl_3$, cm^{-1}): 1612 (C=N), 3200 (OH); UV (EtOH, λ_{max}) 241 nm (ϵ=15000); ^1H NMR δ (ppm): 0.93, 1.23, 1.41, 1.43 (each s, 3H, CH_3), 2.25 (s, 3H, NCH_3), 5.33 (s, 1H, CH), 7.21–7.33 (m, 3H, Ph), 7.42–7.50 (m, 2H, Ph); ^{13}C NMR δ (ppm): 23.06, 23.40, 23.94, 24.12 (CH_3), 26.45 (NCH_3), 63.45 (C_5), 70.03 (C–OH), 89.47 (C_2), 126.71 (*o*-Ph), 128.12 (*p*-Ph), 128.49 (*m*-Ph), 140.69 (*i*-Ph), 148.59 (C=N). Anal. Calcd for $C_{15}H_{22}N_2O_2$: C, 68.70; H, 8.40; N, 10.69. Found: C, 68.88; H, 8.54; N, 10.64.

(1,2,2,5,5-Pentamethyl-2,5-dihydro-1*H*-imidazol-3-oxide-4-yl)methylmethanol (3b). Colourless crystals, mp 76–78°C (from hexane–EtOAc, 20:1); IR (KBr, cm^{-1}): 1600 (C=N); UV (EtOH, λ_{max}) 234 nm (ϵ=8200); ^1H NMR δ (ppm): 1.19, 1.27 (each s, 3H, CH_3), 1.41 (s, 6H, $2CH_3$), 1.50 (d, 3H, CH_3, J_{H-H}=7 Hz), 2.31 (s, 3H, NCH_3), 4.4 (dq, 1H, CH, $^3J_{HH}$=7 Hz, $^3J_{H-OH}$=10 Hz), 6.33 (d, 1H, OH, J_{H-OH}=10 Hz); ^{13}C NMR δ (ppm): 20.12, 22.75, 22.88, 24.17 (CH_3), 24.51 (CH_3COH), 26.76 (NCH_3), 63.01 (C_5), 63.44 (C–OH), 89.37 (C_2), 149.47 (C=N). Anal. Calcd for $C_{10}H_{20}N_2O_2$: C, 60.00; H, 10.00; N, 14.00. Found: C, 60.03; H, 10.15; N, 13.84.

1-(1,2,2,5,5-Pentamethyl-2,5-dihydro-1*H*-imidazol-3-oxide-4-yl)cyclohexanol (3c). Colourless crystals, mp 95–96°C (from hexane); IR (KBr, cm^{-1}): 1575 (C=N), 2800 (NCH_3); IR (CCl_4, cm^{-1}): 1587 (C=N), 2820 (NCH_3), 3225 (OH); UV (EtOH, λ_{max}) 236 nm (ϵ=2800); ^1H NMR δ (ppm): 1.32, 1.38 (each s, 6H, $2CH_3$), 2.28 (s, 3H, NCH_3), 1.45–2.16 (m, 10H, $5CH_2$), 7.49 (s, 1H, OH); ^{13}C NMR δ (ppm): 20.47, 25.37, 32.99 (CH_2), 23.85, 24.12 (CH_3), 26.14 (NCH_3), 64.41 (C_5), 72.12 (C–OH), 88.82 (C_2), 152.12 (C=N). Anal. Calcd for $C_{14}H_{26}N_2O_2$: C, 66.14; H, 10.23; N, 11.02. Found: C, 66.29; H, 10.35; N, 11.16.

1-(1,2,2,5,5-Pentamethyl-2,5-dihydro-1*H*-imidazol-3-oxide-4-yl)cyclopentanol (3d). Colourless crystals, mp 134–136°C (from hexane); IR (KBr, cm^{-1}): 1580 (C=N); IR ($CHCl_3$, cm^{-1}): 3375 (OH); UV (EtOH, λ_{max}) 237 nm (ϵ=10200); ^1H NMR δ (ppm): 1.32, 1.42 (each s, 6H,

2CH_3), 1.62–2.25 (m, 8H, 4CH_2), 2.32 (s, 3H, NCH_3), 7.04 (broad s, 1H, OH); ^{13}C NMR δ (ppm): 23.87, 23.97 (CH_3), 26.30 (NCH_3), 22.68, 36.80 (CH_2), 64.11 (C_5), 79.65 (C–OH), 88.89 (C_2), 151.22 (C=N). Anal. Calcd for $C_{13}H_{24}N_2O_2$: C, 65.00; H, 10.00; N, 11.66. Found: C, 65.05; H, 10.04; N, 11.72.

1-(1,2,2,5,5-Pentamethyl-2,5-dihydro-1*H*-imidazol-3-oxide-4-yl)cyclododecanol (3e). Colourless crystals, mp 131–133°C (from hexane); IR (KBr, cm^{-1}): 1562 (C=N), 2820 (NCH_3); IR ($CHCl_3$, cm^{-1}): 3250 (OH); UV (EtOH, λ_{max}) 239 nm (ϵ=8400); ^{1}H NMR δ (ppm): 1.34 (broad s, 18H, 9CH_2), 1.37, 1.41 (each s, 6H, 2CH_3), 1.85 (m, 2H, CH_2), 2.13 (m, 2H, CH_2), 2.29 (s, 3H, NCH_3), 7.71 (s, 1H, OH); ^{13}C NMR δ (ppm): 19.82, 22.26, 22.53, 25.92, 26.37, 30.54 (CH_2), 23.98, 24.67 (CH_3), 26.19 (NCH_3), 64.80 (C_5), 75.92 (C–OH), 88.55 (C_2), 152.33 (C=N). Anal. Calcd for $C_{20}H_{38}N_2O_2$: C, 71.01; H, 11.24; N, 8.28. Found: C, 71.23; H, 11.37; N, 7.91.

2-(1,2,2,5,5-Pentamethyl-2,5-dihydro-1*H*-imidazol-3-oxide-4-yl)-but-3-en-2-ol (3f). Colourless crystals, mp 86–88°C (from pentane); IR (KBr, cm^{-1}): 1583 (C=N), 2820 (NCH_3); IR (CCl_4, cm^{-1}): 3380 (OH); UV (EtOH, λ_{max}) 239 nm (ϵ=9600); ^{1}H NMR δ (ppm): 1.30, 1.33, 1.41, 1.42 (each s, 3H, CH_3), 1.57 (s, 3H, C*H*$_3$COH), 2.30 (s, 3H, NCH_3), ***ABX:*** 5.22 (***X***, dd, 1H, =CH_2, $^1J_{HH}$=1 Hz, $^3J_{HH}$=10 Hz), 5.44 (***B***, dd, 1H, =CH_2, $^1J_{HH}$=1 Hz, $^3J_{HH}$=17 Hz), 6.04 (***A***, dd, 1H, =CH, $^3J_{HH}$=10 Hz, $^3J_{HH}$=17 Hz), 7.94 (s, 1H, OH); ^{13}C NMR δ (ppm): 23.72, 23.95, 24.13 (CH_3), 26.28 (NCH_3), 64.50 (C_5), 72.99 (C–OH), 89.02 (C_2), 114.08 (=CH_2), 138.53 (=CH), 150.08 (C=N). Anal. Calcd for $C_{12}H_{22}N_2O_2$: C, 63.72; H, 9.73; N, 12.39. Found: C, 63.61; H, 9.69; N, 12.33.

2-(1,2,2,5,5-Pentamethyl-2,5-dihydro-1*H*-imidazol-3-oxide-4-yl)-hex-5-en-2-ol (3g). Colourless crystals, mp 82–84°C (from hexane); IR (KBr, cm^{-1}): 1587 (C=N), 2820 (NCH_3); IR ($CHCl_3$, cm^{-1}): 3375 (OH); UV (EtOH, λ_{max}) 235 nm (ϵ=10600); ^{1}H NMR δ (ppm): 1.32, 1.36 (each s, 3H, CH_3), 1.41 (s, 6H, 2CH_3), 1.46 (s, 3H, C*H*$_3$COH), 2.31 (s, 3H, NCH_3), 1.56–1.78 (m, 1H, CH_2), 1.95–2.28 (m, 3H, CH_2), ***ABX:*** 4.91 (***X***, dd, 1H, =CH_2, $^1J_{HH}$=1.5 Hz, $^3J_{HH}$=10 Hz), 4.99 (***B***, dd, 1H, =CH_2, $^1J_{HH}$=1.5 Hz, $^3J_{HH}$=17 Hz), 5.81 (***A***, m, 1H, =C*H*–CH_2–, $^3J_{HH}$=10 Hz (*cis*), $^3J_{HH}$=17 Hz (*trans*), $^3J_{HH}$=6.5 Hz), 7.42 (broad s, 1H, OH); ^{13}C NMR δ (ppm): 23.22, 23.57, 23.70, 24.61 (CH_3), 24.76 (*C*H$_3$COH), 26.22 (NCH_3), 27.39, 38.77 (CH_2), 64.60 (C_5), 73.29 (C–OH), 89.15 (C_2), 114.49 (=CH_2), 138.42 (=CH), 151.40 (C=N). Anal. Calcd for $C_{14}H_{26}N_2O_2$: C, 66.14; H, 10.24; N, 11.02. Found: C, 66.41; H, 10.20; N, 10.99.

1-(1,2,2,5,5-Pentamethyl-2,5-dihydro-1*H*-imidazol-3-oxide-4-yl)-1-phenylethanol (3h). Colourless crystals, mp 118–120°C (from hexane–EtOAc, 10:1); IR (CCl_4, cm^{-1}): 1569 (C=N), 3375 (OH); UV (EtOH, λ_{max}) 239 nm (ϵ=8200); ^{1}H NMR δ (ppm): 0.94, 1.28, 1.38, 1.41 (each s, 3H, CH_3), 1.82 (s, 3H, C*H*$_3$COH), 2.25 (NCH_3), 7.21–7.36 (m, 3H, Ph), 7.48–7.57 (m, 2H, Ph), 8.16 (s, 1H, OH); ^{13}C NMR δ (ppm): 23.08, 23.57, 24.26, 24.36 (CH_3), 25.20 (*C*H$_3$COH), 26.05 (NCH_3), 64.67 (C_5), 74.14 (C–OH), 88.79 (C_2), 125.90 (*o*-Ph), 127.56 (*p*-Ph), 127.66 (*m*-Ph), 143.53 (*i*-Ph), 151.30 (C=N). Anal. Calcd for C $C_{16}H_{24}N_2O_2$: C, 69.56; H, 8.69; N, 10.14. Found: C, 69.73; H, 8.75; N, 10.10.

1-(1,2,2,5,5-Pentamethyl-2,5-dihydro-1*H*-imidazol-3-oxide-4-yl)-1-thiophen-2-yl-ethanol (3i). Pale yellow crystals, mp 78–80°C (from hexane–EtOAc, 20:1); IR (KBr, cm^{-1}): 1581 (C=N), 2820 (NCH_3); IR ($CHCl_3$, cm^{-1}): 3387 (OH); UV (EtOH, λ_{max}) 236 nm (ϵ=14340); ^{1}H NMR δ (ppm): 0.95, 1.35, 1.43, 1.45 (each s, 3H, CH_3), 1.92 (s, 3H, C*H*$_3$COH), 2.28 (s, 3H, NCH_3), 6.92, 7.05, 7.24 (each m, 1H, CH, Thienyl), 8.73 (s, 1H, OH); ^{13}C NMR δ (ppm): 23.44, 23.74, 24.01, 24.15 (CH_3), 26.20 (*C*H$_3$COH), 26.40 (NCH_3), 64.75 (C_5), 72.65 (C–OH), 89.14 (C_2), 124.24 (C5-Thienyl), 125.29 (C4-Thienyl), 126.18 (C3-Thienyl), 148.30 (*i*-Thienyl), 150.52 (C=N). Anal. Calcd for $C_{14}H_{22}N_2O_2S$: C, 59.57; H, 7.80; N, 9.93; S, 11.35. Found: C, 59.77; H, 8.16; N, 10.12; S, 11.10.

1-(1,2,2,5,5-Pentamethyl-2,5-dihydro-1*H*-imidazol-3-oxide-4-yl)-1-pyridin-2-yl-ethanol (3j). Colourless crystals, mp 81–83°C (from hexane); IR (KBr, cm^{-1}): 1575 (C=N), 2820 (NCH_3); IR ($CHCl_3$, cm^{-1}): 1588 (C=N), 3350 (OH); UV (EtOH, λ_{max}) 238 nm (ϵ=8250); ^{1}H NMR δ (ppm): 1.27, 1.38 (each s, 3H, CH_3), 1.36 (s, 6H, 2CH_3), 1.88 (s, 3H, C*H*$_3$COH), 2.29 (s, 3H, NCH_3), 7.15, 7.66, 7.93, 8.42 (each m, 1H, CH, Pyridyl); 7.57 (s, 1H, OH); ^{13}C NMR δ (ppm): 23.61, 23.83, 24.07, 24.12 (CH_3), 24.89 (*C*H$_3$COH), 26.36 (NCH_3), 65.11 (C_5), 75.16 (C–OH), 88.95 (C_2), 121.03 (C5-Pyridyl), 122.44 (C3-Pyridyl), 136.55 (C4-Pyridyl), 147.39 (C6-Pyridyl), 145.21 (C=N), 151.37 (*i*-Pyridyl). Anal. Calcd for $C_{15}H_{23}N_3O_2$: C, 64.98; H, 8.30; N, 15.16. Found: C, 65.03; H, 8.40; N, 14.93.

(1,2,2,5,5-Pentamethyl-2,5-dihydro-1*H*-imidazol-3-oxide-4-yl)-(1H-pyrrol-2-yl)methanol (3k). Colourless crystals, mp 92–94°C (from hexane–EtOAc, 6:1); IR (KBr, cm^{-1}): 1550 (C=N); IR ($CHCl_3$, cm^{-1}): 3350 (OH); UV (EtOH, λ_{max}) 228 nm (ϵ=11200), 264 nm (ϵ=5600); ^{1}H NMR δ (ppm): 1.03, 1.35, 1.41, 1.47 (each s, 3H, CH_3), 2.30 (s, 3H, NCH_3), 5.08 (d, 1H, CH, $^3J_{HH}$=10.5 Hz), 5.94 (d, 1H, OH, $^3J_{HH}$=10.5 Hz), 6.07, 6.13, 6.75 (each m, 1H, CH, Pyrryl), 10.18 (broad s, 1H, NH); ^{13}C NMR δ (ppm): 23.16, 23.61, 24.02 (CH_3), 26.73 (NCH_3), 62.69 (C–OH), 63.20 (C_5), 89.40 (C_2), 107.70 (C4-Pyrryl), 107.75 (C3-Pyrryl), 119.09 (C5-Pyrryl), 130.99 (*i*-Pyrryl), 150.10 (C=N). Anal. Calcd for $C_{13}H_{21}N_3O_2$: C, 62.15; H, 8.37; N, 16.73. Found: C, 62.44; H, 8.41; N, 16.71.

(1,2,2,5,5-Pentamethyl-2,5-dihydro-1*H*-imidazol-3-oxide-4-yl)diphenylmethanol (3l).Colourless crystals, mp 166-168°C (from hexane–EtOAc, 1:3); IR (KBr, cm^{-1}): 1575 (C=N); IR ($CHCl_3$, cm^{-1}): 3370 (OH); UV (EtOH, λ_{max}) 241 nm (ϵ=6600); ^{1}H NMR δ (ppm): 0.93, 1.49 (each s, 6H, 2CH_3), 2.29 (s, 3H, NCH_3), 7.20–7.45 (m, 10H, Ph); 8.29 (s, 1H, OH); ^{13}C NMR δ (ppm): 23.95 (CH_3), 26.35 (NCH_3), 65.20 (C_5), 78.94 (C–OH), 88.57 (C_2), 127.69 (*o*-Ph), 127.82 (*p*-Ph), 128.17 (*m*-Ph), 142.81 (*i*-Ph), 150.55 (C=N). Anal. Calcd for $C_{21}H_{26}N_2O_2$: C, 74.55; H, 7.69; N, 8.28. Found: C, 74.67; H, 7.66; N, 8.30.

1-Ferrocenyl-1-(1,2,2,5,5-pentamethyl-2,5-dihydro-1*H*-imidazol-3-oxide-4-yl)ethanol (3m). Orange crystals, mp.

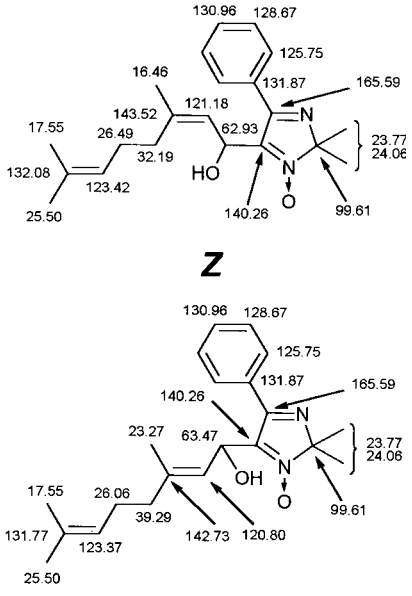
159–162°C (from hexane–EtOAc, 10:1); IR (KBr, cm^{-1}): 1570 (C═N); IR ($CHCl_3$, cm^{-1}): 3175 (OH); UV (EtOH, λ_{max}) 236 nm (ϵ=12800), 268 nm (ϵ=3200), 419 nm (ϵ=160); ^{1}H NMR δ (ppm): 0.78, 1.18, 1.36, 1.38 (each, s, 3H, CH_3), 1.83 (s, 3H, CH_3COH), 2.20 (s, 3H, NCH_3), 4.13 (m, 2H, 2CH), 4.19, 4.47 (each m, 1H, CH), 4.24 (s, 5H, 5CH), 7.95 (s, 1H, OH); ^{13}C NMR δ (ppm): 23.66, 23.93, 24.83 (CH_3), 26.19 (NCH_3), 66.92, 67.78, 67.80, 68.33 (CH, Ferrocenyl), 68.91 (C′H, Ferrocenyl), 64.68 (C_5), 71.52 (C–OH), 88.82 (C_2), 93.20 (*i*-Ferrocenyl), 151.29 (C═N). Anal. Calcd for $C_{20}H_{28}N_2O_2Fe$: C, 62.50; H, 7.29; N, 7.29. Found: C, 62.58; H, 7.20; N, 7.24.

2,2,6,6-Tetramethyl-4-(1,2,2,5,5-pentamethyl-2,5-dihydro-1*H*-imidazol-3-oxide-4-yl)piperidine-4-ol-1-yloxy (3n). Pale red solid, mp 202–203°C (from hexane–EtOAc, 1:10); IR (KBr, cm^{-1}): 1575 (C═N); IR ($CHCl_3$, cm^{-1}): 3390 (OH); UV (EtOH, λ_{max}) 238 nm (ϵ=7800); EPR ($CHCl_3$): a_N=15.7 G; Anal. Calcd for $C_{17}H_{32}N_3O_3$: C, 62.58; H, 9.82; N, 12.88. Found: C, 62.71; H, 10.03; N, 12.72.

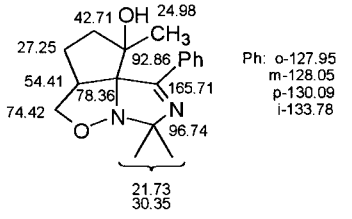
(2,2-Dimethyl-4-phenyl-2*H*-imidazol-1-oxide-5-yl)phenylmethanol (4a). Colourless crystals, mp 125–127°C (from hexane–EtOAc, 4:1); IR (KBr, cm^{-1}): 1570 (C═N); IR ($CHCl_3$, cm^{-1}): 3375 (OH); UV (EtOH, λ_{max}) 234 nm (ϵ=10200), 281 nm (ϵ=8400); ^{1}H NMR δ (ppm): 1.64, 1.67 (each, s, 3H, CH_3), 5.83 (d, 1H, OH, $^3J_{HH}$=10.5 Hz), 5.92 (d, 1H, CH, $^3J_{HH}$=10.5 Hz), 7.33 (s, 5H, Ph), 7.35-7.65 (m, 5H, Ph); ^{1}C NMR δ (ppm): 24.01 (CH_3), 69.26 (CH), 100.00 (C_2), 126.32 (*o*-Ph), 127.72 (4-*o*-Ph), 128.55 (*p*-Ph), 128.79 (*m*-Ph), 128.97 (4-*m*-Ph), 131.13 (4-*p*-Ph), 131.53 (4-*i*-Ph), 139.90 (*i*-Ph), 139.40 (C═N(O), 165.05 (C═N). Anal. Calcd for $C_{18}H_{18}N_2O_2$: C, 73.47; H, 6.12; N, 9.52. Found: C, 73.42; H, 6.35; N, 9.38.

1-(2,2-Dimethyl-4-phenyl-2*H*-imidazol-1-oxide-5-yl)ethanol (4b). Colourless crystals, mp 122–123°C (from hexane–EtOAc, 10:1); IR (KBr, cm^{-1}): 1562 (C═N); IR ($CHCl_3$, cm^{-1}): 3400 (OH); UV (EtOH, λ_{max}) 233 nm (ϵ=9200), 282 nm (ϵ=8400); ^{1}H NMR δ (ppm): 1.59 (s, 6H, $2CH_3$), 1.57 (d, 3H, CH_3, $^3J_{HH}$=7 Hz), 4.96 (dq, 1H, CH, $^3J_{HH}$=7 Hz, $^3J_{HH}$=10 Hz), 5.15 (d, 1H, OH, $^3J_{HH}$=10 Hz), 7.40–7.76 (m, 5H, Ph); ^{13}C NMR δ (ppm): 19.84 (*C*H_3–C–OH), 23.89, 24.01 (CH_3), 63.21 (CH), 99.60 (C_2), 127.59 (*o*-Ph), 128.87 (*m*-Ph), 131.12 (*p*-Ph), 132.10 (*i*-Ph), 141.09 (C═N(O), 165.02 (C═N). Anal. Calcd for $C_{13}H_{16}N_2O_2$: C, 67.24; H, 6.89; N, 12.07. Found: C, 67.27; H, 6.93; N, 11.91.

1-(2,2-Dimethyl-4-phenyl-2*H*-imidazol-1-oxide-5-yl)-3,7-dimethyl-octa-2,6-dien-1-ol (4c). Obtained as mixture of ***E*** and ***Z*** isomers. Pale yellow oil; IR (KBr, cm^{-1}): 1565 (C═N); IR ($CHCl_3$, cm^{-1}): 3400 (OH), 3600 (OH); UV (EtOH, λ_{max}) 235 nm (ϵ=15800), 276 nm (ϵ=11400); ^{1}H NMR δ (ppm):[20] ***Z***: 1.62 (broad s, 3H, C═CH_3), 1.70 (d, 3H, C═ (CH_3)), 1.60 (s, 6H, CH_3), 1.94–2.07 (m, 4H, $2CH_2$), 4.79–5.18 (broad m, 2H, CH, OH), 7.35–7.73 (m, 5H, Ph); ***E:*** 1.52 (broad s, 3H, C═CH_3), 1.61 (d, 6H, C═$(CH_3)_2$), 1.60 (s, 6H, CH_3), 1.94–2.07 (m, 4H, $2CH_2$), 4.79–5.18 (broad m, 2H, CH, OH), 7.35–7.73 (m, 5H, Ph); Anal. Calcd for $C_{21}H_{28}N_2O_2$: C, 74.12; H, 8.23; N, 8.23. Found: C, 74.32; H, 8.45; N, 8.39.



3,3,8-Trimethyl-1-phenyl-5a,6,7,8-tetrahydro-3*H*,5*H*-4-oxa-2,3a-diaza-cyclopenta[c]pentalen-8-ol (5). The combined organic extract from the reaction of ***2*** with allylacetone was allowed to stand for three days over a desiccant ($MgSO_4$). Then the solvent was evaporated and the residue was separated on Al_2O_3 with hexane–EtOAc 7:1 as eluent. Pale yellow oil; IR ($CHCl_3$, cm^{-1}): 1606 (C═N), 3275 (OH); UV (EtOH, λ_{max}) 244 nm (ϵ=1078); ^{1}H NMR δ (ppm): 0.94, 1.35, 1.50 (each s, 3H, CH_3), 1.73–2.06 (m, 4H, $2CH_2$), 3.56 (m, 1H, CH), 3.72 (dd, 1H, CH_2, $^2J_{HH}$=8.5 Hz, $^3J_{HH}$=3 Hz), 3.75 (dd, 1H, CH_2, $^2J_{HH}$=8.5 Hz, $^3J_{HH}$=6 Hz), 4.70 (s, 1H, OH), 7.27–7.40 (m, 3H, Ph), 7.75–7.82 (m, 2H, Ph); Anal. Calcd for $C_{17}H_{22}N_2O_2$: C, 71.33; H, 7.69; N, 9.79. Found: C, 71.36; H, 7.70; N, 9.79.



(1,2,2,5,5-Pentamethyl-2,5-dihydro-1*H*-imidazol-4-yl)-phenylmethanone (7). The mixture of hydroxymethyl derivative ***3a*** (0.001 mol) and piperidine (0.0025 mol) was refluxed about 100 h in 5 ml of dry benzene with azeotropic removal of the water formed. The course of reaction was monitored by TLC (Silufol®, $CHCl_3$). The reaction mixture was washed with water (2×5 ml), water phase was extracted with $CHCl_3$ (2×5 ml), the combined organic extract was dried with $MgSO_4$, evaporated under reduced pressure,

and the residue was separated on silica gel with $CHCl_3$ as eluent. Colourless oil; IR ($CHCl_3$, cm^{-1}): 1590 (C═N), 1665 (C═O), 2800 (NCH_3); UV (EtOH, λ_{max}) 257 nm (ϵ=9667), 355 nm (ϵ=174); ^1H NMR δ (ppm): 1.34, 1.42 (each s, 6H, $2CH_3$), 2.33 (s, 3H, NCH_3), 7.35–7.59 (m, 3H, Ph), 7.98–8.05 (m, 2H, Ph); ^{13}C NMR δ (ppm): 23.46, 25.78 (CH_3), 26.66 (NCH_3), 70.21 (C_5), 89.66 (C_2), 128.13 (*m*-Ph), 129.89 (*o*-Ph), 133.36 (*p*-Ph), 135.93 (*i*-Ph), 171.49 (C═N), 191.55 (C═O). Anal. Calcd for $C_{15}H_{20}N_2O$: C, 73.77; H, 8.20; N, 11.47. Found: C, 74.01; H, 8.34; N, 11.51.

Acknowledgements

The authors would like to thank the *Russian Foundation for Basic Research* (grant No. 97-03-32864a) for financial support, Prof Dr Vladimir Reznikov for fruitful and stimulating discussion and Dr Dmitrii Mazhukin for critically reading the manuscript.

References

1. Brown, R. F. C.; Clark, V. M.; Todd, Sir A. *J. Chem. Soc.* **1965**, 2337–2340.

2. Boocock, D. G.; Darcey, B. R.; Ullman, E. F. *J. Am. Chem. Soc.* **1968**, *90*, 5945–5946.

3. (a) Kliegel, W. *Pharmazie*, **1978**, *33* (6), 331–335. (b) Johnson, C. R.; Taylor, J. D.; Honn, K. V.; Cheng, S. US Patent US4,758,669. Appl. 859,694,05. *Chem. Abstr.* **1988**, *109* (17), 149366a. (c) Anana, R. D.; Ng, H.; Hawlett, S. E.; Knaus, E. E. *Arch. Pharm. Pharm. Med. Chem.*, **1997**, *330* (3), 53–58. (d) Ellwood, C. W.; Tikhonov, A. Ya. *PCT Int. Appl.* WO9803,479. *Chem. Abstr.* **1998**, *128* (13), 153919t. (e) Tikhonov, A. Ya.; Mazhukin, D. G.; Grigor'eva, L. N.; Khlestkin, V. K.; Voinova, N. N.; Syropyatov, B. Ya.; Shrinkina, S. S.; Volodarsky, L. B. *Arch. Pharm. Pharm. Med. Chem.*, **1999**, *332* (9), 305–308.

4. Torssell, K. B. G. *Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis*, VCH Publishers, 1988.

5. Martin, V. V.; Volodarskii, L. B. *Khim. Geterotsikl. Soedin.*, **1979**, *1*, 103–109. *Chem. Abstr.* **1979**, *90*, 186860s.

6. (a) Kirilyuk, I. A.; Grigor'ev, I. A.; Volodarskii, L. B. *Izv. Akad. Nauk. SSSR. Ser. Khim.*, **1991**, *9*, 2122–2127. *Chem. Abstr.* **1991**, *115*, 279911j; (b) Volodarsky, L. B.; Tikhonov, A. Ya. *Synthesis* **1986**, 704–715.

7. (a) Putsykin, Yu. G.; Volodarskii, L. B. *Izv. Sib. Otd. Akad. Nauk. SSSR. Ser. Khim.*, **1969**, *9* (4), 86–93. *Chem. Abstr.* **1970**, *72*, 54514a. (b) Volodarskii, L. B.; Lysak, A. N.; Koptyug, V. A. *Khim. Geterotsikl. Soedin.*, **1968**, *2*, 334–338. *Chem. Abstr.* **1968**, *69*, 96577s. (c) Kirilyuk, I. A.; Grigor'ev, I. A.; Petrenko, O. P.; Volodarskii, L. B. *Izv. Akad. Nauk. SSSR. Ser. Khim.*, **1993**, *12*, 2096–2100. (d) Samsonov, V. A.; Volodarskii, L. B. *Khim. Geterotsikl. Soedin.*, **1980**, *6*, 808–813. *Chem. Abstr.* **1980**, *93*, 186242d.

8. Volodarsky, L. B.; Grigor'ev, I. A. Synthesis of Heterocyclic Nitroxides. In *Imidazoline Nitroxides*, Volodarsky, L. B., Ed.; CRC Press: Boca Raton, 1988; 1, pp 5–28 Chap. 2.

9. Döpp, D., Döpp, H., Nitrones. In: *Methoden der Organischen Chemie* (Houben-Weyl); Klamann, D., Hagemann, H., Eds.; Georg Thieme Verlag: Stuttgart: New York, 1990; Bd. E14b, Teil 2, S. 1372–1544.

10. Voinov, M. A.; Grigor'ev, I. A.; Volodarsky, L. B. *Heterocycl. Comm.* **1998**, *4* (3), 261–270.

11. Mitasov, M. M.; Grigor'ev, I. A.; Shchukin, G. I.; Korobeinicheva, I. K.; Volodarskii, L. B. *Izv. Sib. Otd. Akad. Nauk. SSSR. Ser. Khim.*, **1978**, *2* (1), 112–116. *Chem. Abstr.* **1978**, *88*(26), 200214b.

12. The assignment of ^{13}C NMR signals were made with the use of data for compounds with related tricyclic carbon skeleton: Weyerstahl, P.; Marschall, H.; Seelmann, I.; Jakupovic, J. *Eur. J. Org. Chem.*, **1998**, 1205–1212.

13. Clark, B. A. J.; Evans, T. J.; Simmonds, R. G. *J. Chem. Soc. Perkin Trans. I.* **1975**, *18*, 1803–1806.

14. Grigor'ev, I. A.; Martin, V. V.; Shchukin, G. I.; Mamatyuk, V. I.; Volodarskii, L. B. *Khim. Geterotsikl. Soedin.*, **1985**, *2*, 247–251. *Chem. Abstr.* **1985**, *103* (1), 5831b.

15. Grigor'ev, I. A.; Mamatyuk, V. I.; Shchukin, G. I.; Martin, V. V.; Volodarskii, L.B. *Khim. Geterotsikl. Soedin.*, **1986**, *8*, 1065–1072. *Chem. Abstr.* **1987**, *106* (21), 175673f.

16. Hamer, J.; Macaluso, A. *Chem. Rev.* **1964**, *64*, 473–495.

17. Klemmensen, P.; Schroll, G.; Lawesson, S.-O. *Ark. Kemi* **1968**, *28*, 405–411.

18. Grigor'ev, I. A.; Volodarskii, L.B. *Zh. Org. Khim.*, **1975**, *11* (6), 1328–1332. *Chem. Abstr.* **1975**, *83* (25), 206157d.

19. Castagnoli Jr, N.; Cymerman, J. C.; Melikian, A. P.; Roy, S. K. *Tetrahedron* **1970**, *26*, 4319–4327.

20. The following monograph has been used upon the NMR spectra interpreting: Wehrli, F. W.; Hishida, T. The Use of Carbon ^{13}C Nuclear Magnetic Resonance Spectroscopy in Natural Products Chemistry. In *Progress in the chemistry of organic natural products*; Springer-Verlag: 1979; 36, pp 24–33.