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Transformations of (*R*)-4-Menthen-3-one and Its Derivatives with the Participation of Hydride-, Nitrogen- and Sulphur-Containing Reagents

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Abstract

Reactivity data of (*R*)-4-menthen-3-one and routes of its transformations with the participation of hydride, sulphur and nitrogen-containing reactants were generalized and systematized. An opportunity to prepare a range of new potentially pharmacologically active sulphides, sulphoxides, acetamides and an oxime of the menthane series based on (*R*)-4-menthen-3-one and its derivatives was demonstrated using the Ritter reaction, nucleophilic and electrophilic thiating, nitrosation, oximation. Resulting from the carried out systematic research of reactions of (*R*)-4-menthen-3-one and its derivatives with aluminium- and boron-containing hydride reagents, it was detected that *i*-Bu_2AlH was the most stereospecific hydride reducing agent for (*R*)-4-menthen-3-one to (1*R*,3*R*)-*n*-menth-4-en-3-ol. It was found that the $BH_3 \cdot THF$ complex was a stereospecific hydride agent for the oxo-group of (*R*)-4-menthen-3-one and regiospecific but a low-stereoselective hydroborating reagent for its multiple bond and that of (1*R*,3*R*)-*n*-menth-4-en-3-ol.

Key words: (*R*)-4-menthen-3-one, hydride, sulphur- and nitrogen-containing reagents, transformations

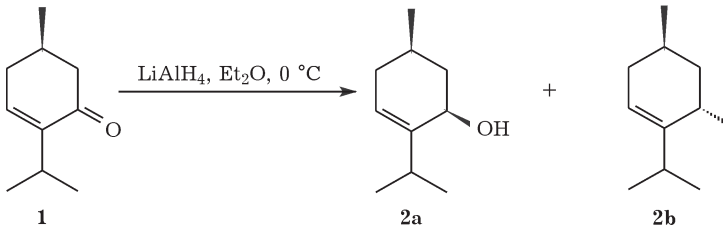
INTRODUCTION

The presence of a conjugated enone system in (*R*)-4-menthen-3-one **1** available from *l*-menthol opens up great prospects for its use in organic synthesis. Additionally, there is an asymmetric centre that is not affected during reactions in enone **1**, which is important when preparing biologically active substances including low molecular mass bioregulators. A significantly lower reactivity of menthenone **1** compared to other cyclic unsaturated α,β-unsaturated ketones in 1,2- and 1,4-addition of organometallic reagents and inertness in the Michael reaction was reported earlier [1, 2].

The present article generalizes results on the reactivity of (*R*)-4-menthen-3-one and its transformation routes in the reactions of hydride reduction, hydroboration-oxidation, thiating, the Ritter reaction, oximation and the behaviour of the resulting oxime in the Beckman rearrangement, nitrosation reactions.

(*R*)-4-MENTHEN-3-ONE IN THE REACTIONS WITH ALUMINIUM- AND BORON-CONTAINING HYDRIDES

Earlier, it was demonstrated [3] that reduction of optically pure (*R*)-4-menthen-3-one **1** with $LiAlH_4$ in Et_2O at 0 °C proceeded with the formation of a mixture (93 : 7) (1*R*,3*R*)-(**2a**)-



Scheme 1.

and (1*R*,3*S*)-(**2b**) of diastereomeric *n*-menth-3-en-3-ols (Scheme 1).

With a view to obtaining optically pure enol **2a**, a series of experiments was carried out, where aluminum- ($LiAlH_4$, *i*-Bu_2AlH) and boron-($NaBH_4$) containing hydride reagents, solvents (Et_2O, THF, CH_2Cl_2, EtOH) and reaction temperature (−78, 0, 25 °C) were varied [4]. Experimental results are given in Table 1.

It was found that replacing Et_2O with THF (exp. No. 3) for $LiAlH_4$ at 0 °C almost did not change stereoselectivity in a reduction reaction. At the same time, an increase in temperature to 25 °C decreased the content of stereoisomer **2a** (exp. Nos. 4 and 5) up to 75−87 %. The reaction proceeded stereospecifically at −78 °C, regardless of the ether solvent used (exp. Nos. 1 and 2).

For $NaBH_4$, the reaction proceeded stereospecifically at −78 °C both in THF and EtOH (exp. 12 and 13). An increase in temperature led to a dramatic decrease in stereoselectivity (exp. Nos. 14−17), especially when carrying out the reaction in THF.

i-Bu_2AlH turned out to be the most selective reductant: in all options, except for exp. No. 10 (Et_2O, 25 °C), it led to the formation of the sole diastereomer, *i. e.* **2a**.

It was noted that the formation of a saturated alcohol for all the performed options of hydride reduction of (*R*)-4-menthen-3-one **1** was not observed (by data of capillary GLC and by

TABLE 1

Yield and the ratio of stereoisomeric (1*R*,3*R*)-(**2a**)- and (1*R*,3*S*)-(**2b**)-*n*-menth-4-en-3-ols *vs.* the nature of the hydride reducing agent and temperature

Exp. No.	Amount of cycloenone **1**, g	Reductant	Solvent	Temperature, °C	Yield, g (%)	Content, %, by GLC	
						2a	**2b**
1	0.30	$LiAlH_4$	THF	−78	0.26 (86)	100	0
2	0.30	$LiAlH_4$	Et_2O	−78	0.25 (83)	100	0
3	0.30	$LiAlH_4$	THF	0	0.22 (73)	92	8
4	0.30	$LiAlH_4$	Et_2O	25	0.24 (79)	87	13
5	0.30	$LiAlH_4$	THF	25	0.23 (76)	75	25
6	0.50	$LiAlH_4$	Et_2O	−78	0.43 (85)	100	0
7	0.50	$LiAlH_4$	CH_2Cl_2	−78	0.45 (89)	100	0
8	0.50	*i*-Bu_2AlH	Et_2O	0	0.41 (81)	100	0
9	0.50	*i*-Bu_2AlH	CH_2Cl_2	0	0.44 (87)	100	0
10	0.50	*i*-Bu_2AlH	Et_2O	25	0.40 (79)	86	14
11	0.50	*i*-Bu_2AlH	CH_2Cl_2	25	0.46 (91)	100	0
12	0.30	*i*-Bu_2AlH	THF	−78	0.26 (86)	100	0
13	0.30	*i*-Bu_2AlH	EtOH	−78	0.25 (83)	100	0
14	0.30	$NaBH_4$	THF	0	0.24 (79)	79	21
15	0.30	$NaBH_4$	EtOH	0	0.26 (86)	91	9
16	0.30	$NaBH_4$	THF	25	0.27 (89)	75	25
17	0.30	$NaBH_4$	EtOH	25	0.27 (89)	80	20

the absence of a doublet signal in the area of 50 ppm in the ^{13}C NMR spectrum).

As a result, it was detected that *i*-Bu_2AlH was the most stereospecific hydride reducing agent for (*R*)-4-menthen-3-one **1** to enol [5].

(*R*)-4-MENTHEN-3-ONE AND (1*R*,3*R*)-*n*-MENTH-4-EN-3-OL IN HYDROBORATION-OXIDATION REACTIONS

A mixture (3 : 2 by GLC and NMR data) of epimeric (1*R*,2*R*,3*S*,5*R*)-(**3a**)- and (1*R*,2*R*,3*R*,5*R*)-(**3b**)-5-methyl-2-(1-methylethyl)cyclohexane-1,3-diols was obtained during the treatment of cycloenone **1** by another known hydride and hydroborating reagent that is $BH_3 \cdot THF$ complex obtained *in situ* from $BF_3 \cdot OEt_2$ and $NaBH_4$ in THF followed by oxidation with alkaline hydrogen peroxide. A similar mixture of **3a** and **3b** epimers is formed during hydroboration-oxidation of (1*R*,3*R*)-*n*-menth-4-en-3-ol **2a**. This indicates that the $BH_3 \cdot THF$ complex is a stereospecific hydride reagent of the oxo function in (*R*)-4-menthen-3-one **1** and a regiospecific and low-selective hydroborating agent of a multiple bond in it and its hydride reduction product **2a** (Scheme 2).

Stereoisomers identification of **3a** and **3b** epimers after chromatographic separation was carried out by ^1H and ^{13}C NMR spectroscopy. Spectral analysis of **3a** and **3b** was performed by comparison with spectral parameters of various menthol isomers and close structural analogs that are isopropylcyclohexanols and menthone.

It was found that NMR spectra contained signals of only one diastereomer pair that is *meso*-(**3a**) and *dl*-(**3b**).Chemical shift values in carbon spectra and spin-spin coupling constants of methine protons at hydroxyl groups (^3J = 10.6 Hz of the triplet and 4.2 Hz of the doublet component) indicate the equautorial orientation of all the four substituents of symmetrical *meso*-isomer **3a**. Differences in chemical shift values in carbon spectra and spin-spin coupling constants of methine protons at oxy functions (H_a – 4.25 dt, ^3J = 4.1 and 9.9 Hz; H_s – 4.12 dt, ^3J = 4.9 and 3.1 Hz), as well as more upfield signal of a carbon atom C-2 51.70 ppm indicate the axial orientation of one of the hydroxyl groups of *dl*-isomer **3b**. Spectral parameters of Me- and *i*-Pr substituents are close in *l*-menthol and correspond to their equatorial orientation in both stereoisomeric **3a** and **3b** diols.

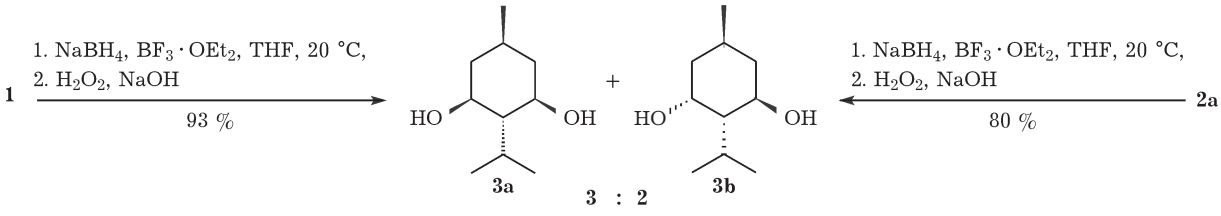
Thus, it was found that the $BH_3 \cdot THF$ complex was a stereospecific hydride reducing agent of the oxo group of (*R*)-4-menthen-3-one **1** and regiospecific but a poorly stereoselective hydroborating reagent of its multiple bond and (1*R*,3*R*)-*n*-menth-4-en-3-ol **2a**.

THIATING OF (*R*)-4-MENTHEN-3-ONE AND ITS DERIVATIVES

It is known that the introduction into the terpene molecule of a sulphur-containing fragment increased the range of the exhibited biological activity of the compound, which was earlier demonstrated on an example of (−)-carvone, (*R*)-pulegone, (−)-carveol, (+)-*cis*-verbenol [6]. Therefore, with a view to obtaining thioterpenoids based on (*R*)-4-menthen-3-one **1**, a series of experiments was performed on both electrophilic (under conditions of $ZnCl_2$ or $BF_3 \cdot OEt_2$ catalysis) and nucleophilic (in the presence of K_2CO_3 or AcONa) addition of thiols (PhSH, *n*-$C_{12}H_{25}SH$, $HS(CH_2)_2SH$) to enone **1** in solvents of various nature at a temperature of 20 or 55 °C [7].

As a result, a decreased reactivity of the investigated enone **1** in the reaction of catalyzed thiating with the participation of thiols (PhSH or *n*-$C_{12}H_{25}SH$) was detected in comparison with (−)-carvone [8], which is probably due to steric effects of the *i*-Pr group.

It is noteworthy that inertness of enone **1** in electrophilic addition reactions of $HS(CH_2)_2SH$

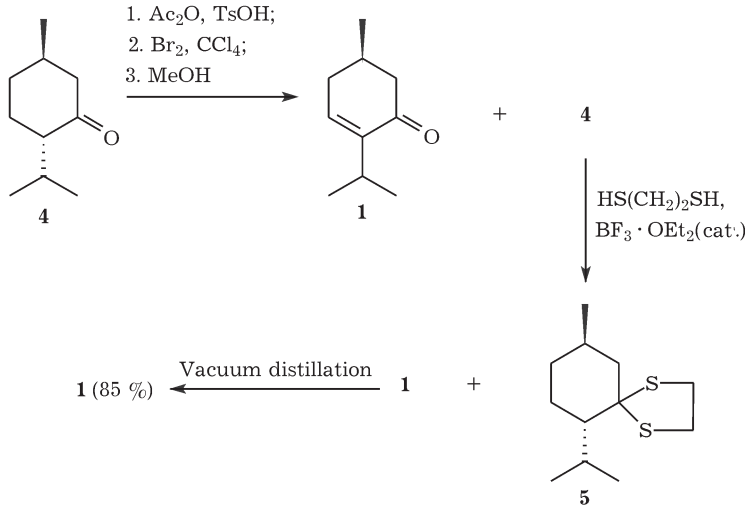


Scheme 2.

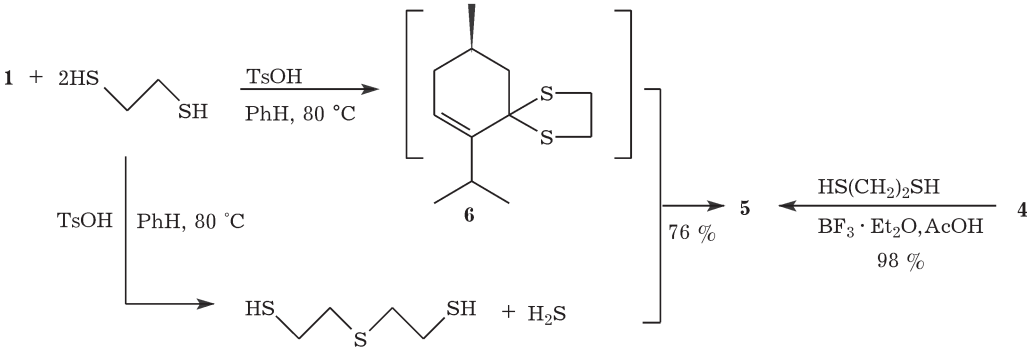
under conditions of $ZnCl_2$ or $BF_3 \cdot OEt_2$ catalysis provided the basis for the developed method for purifying (*R*)-4-menth-3-one **1** from impurities of (-)-menthone **4** [9]: it is known that (*R*)-4-menth-3-one **1** obtained from (-)-menthone **4** is often contaminated (to 10 mass %) by the latter. Moreover, usual methods for purifying, including chromatography, do not provide the required purity of enone **1**.Therefore, based on the assumption that *R*-4-menth-3-one **1** showed inertness in the addition reaction of thiols, a method for purifying the latter based on the ability of cation **4** to quantitatively form dithiolane **5** [10] in the presence of catalytic amounts of $BF_3 \cdot OEt_2$ was proposed, unlike α,β-unsaturated cyclic ketone **1** (Scheme 3).

At the same time, we managed to obtain unsaturated dithiolane **5** during the action of $HS(CH_2)_2SH$ on menthenone **1** under more rigid conditions (TsOH, 80 °C, 24 h), while PhSH was inert under these conditions. Apparently, initially formed allyl dithiolane **6** is further reduced to its unsaturated analog **5** under the action of H_2S that is allocated during thermal decomposition of $HS(CH_2)_2SH$, which is confirmed by the presence of$HS(CH_2)_2S(CH_2)_2SH$ and elemental sulphur in the reaction mass. The mass spectrum of the reaction mixture contains has the following molecular ions: 153.0 $[M-H]^-$, 171.0 ($[M-H]^- + H_2O$), 120.0 $([M-H]-SH)^+$. Signals at 34.78 *и* 26.62 ppm in the ^{13}C NMR spectrum indicate the formation of $HS(CH_2)_2S(CH_2)_2SH$. Stereochemistry of sulphur-containing product **5** is confirmed by NMR spectroscopic data and counter synthesis from (−)-menthone **4** (Scheme 4).

It was found [9] when studying thiating of epoxyketone **7** available from **1**, according to



Scheme 3.



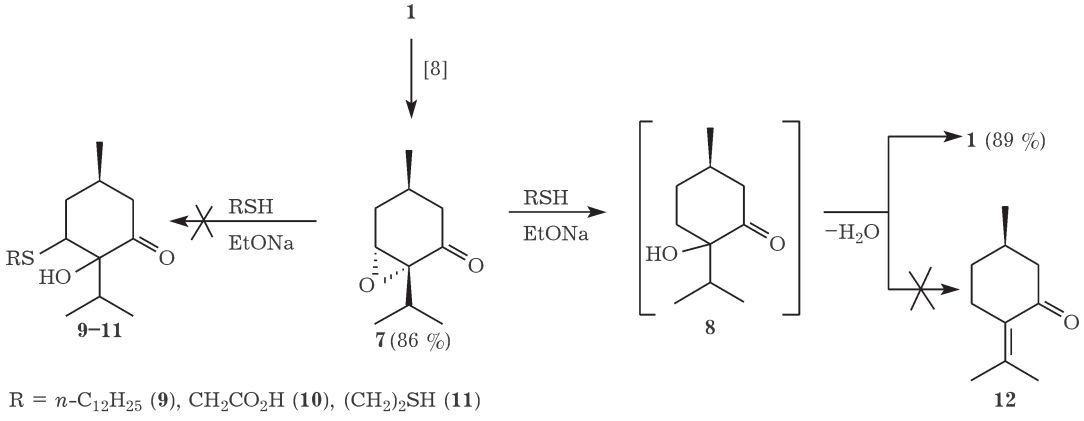
Scheme 4.

[11], n-$C_{12}H_{25}SH$ (or $HS(CH_2)_2SH$ or $HSCH_2CO_2H$), that it occurred analogously to transformations of carvon-1,2-oxide [12]: regeneration of initial (*R*)-4-menthene-3-one **1** probably *via* the dehydration stage of intermediate ketol **1**, and not the formation of hydrosulphides **9–11**. In turn, the preparation of enone **1**, and not (*R*)-pulegone **12** is confirmed by GLC method and spectral data: the presence in the ^1H NMR spectrum of a signal of an olephinic proton of HC=C–C=O in the region of 5.6 ppm and by the opposite phases of the signals of carbon atoms in the multiple bond of α,β-unsaturated ketone **1** in the ^{13}C NMR spectrum in the JMOD mode (Scheme 5).

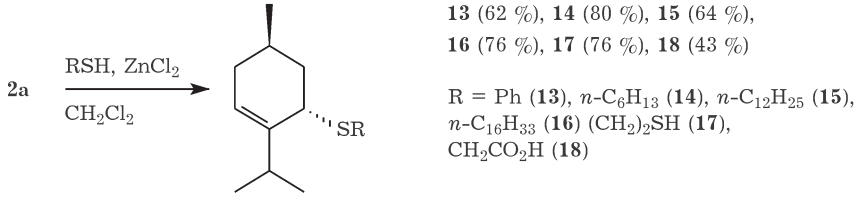
Thiating of (1*R*,3*R*)-*n*-menth-4-ene-3-ol **2a**, unlike (*R*)-4-menthene-3-one **1**, proceeds smoothly already at room temperature under catalytic conditions using $ZnCl_2$ with substitution of the hydroxyl group by a sulphide functional group [13]. The formation of sulphides **13–18** is accompanied (according to PMR and capillary GLC) by a total conversion of the configuration of an oxygen-containing asymmetric centre [6], as noted earlier for *cis*-verbenol [14] (Scheme 6).

Stereochemistry of the reaction products that are terpene sulphides **13–18** was found by PMR data. Thus, the values of spin-spin coupling constants in the spectrum of alcohol **2a** at C-1 carbon atom (^3J = 8.4 and 5.3 Hz) speak of the equatorial orientation of the hydroxyl functional group, and, on the contrary, small values for proton spin-spin coupling constants (^3J = 5.4 and 6.3 Hz) at C-6 (in sulphides **13–18**) and C-1 carbon atoms (in sulphides **13**, **17**, **18**) indicate the axial orientation of sulphur-containing substituents. Therefore, thiating of *n*-menth-4-ene-3-ol **2a** is accompanied by a total conversion of the configuration of a hydroxyl-containing asymmetric centre.

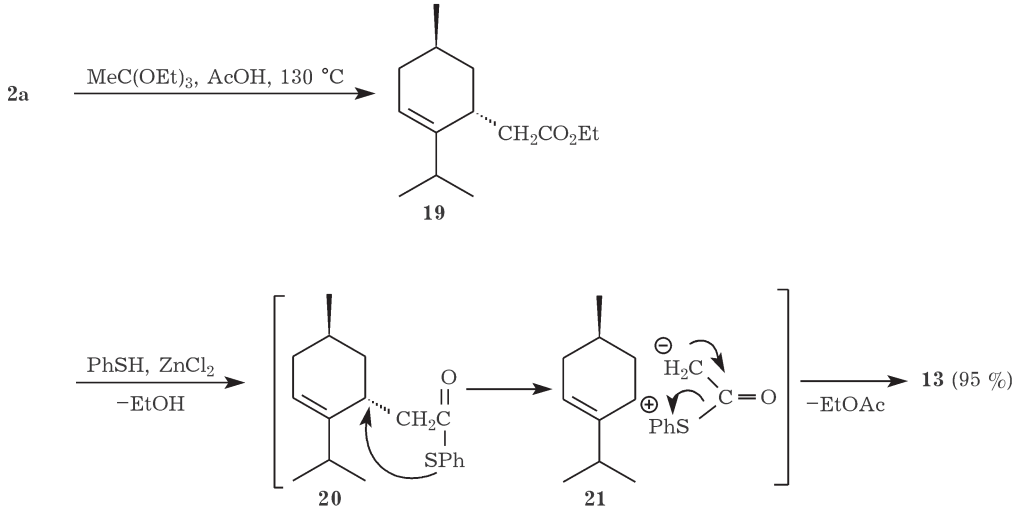
The interaction of acetate **19** that is the product of full configuration conversion of a hydroxyl-containing centre during the orthoester Claisen rearrangement (1*R*,3*R*)-*n*-menth-4-ene-3-one **2a** [13] occurs with PhSH during $ZnCl_2$ catalysis without the rotation of the configuration of an asymmetric centre at C-1 carbon atom with the formation of sulphide **13** obtained earlier from *n*-menth-4-ene-3-ol **2a** [9]. The reaction proceeds by the S_Ni mechanism according to the following presumptive scheme: acetate **19**



Scheme 5.



Scheme 6.



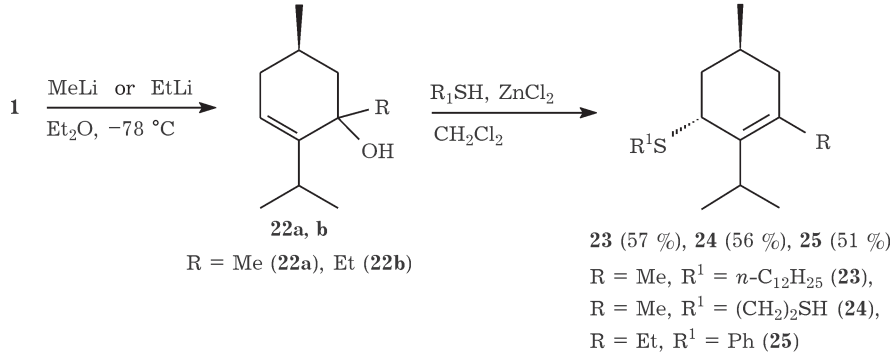
Scheme 7.

is initially transformed into intermediate compound **20** that further dissociates with the formation of a contact ion pair **21**.Components of such a pair are found very close to each other; therefore, a nucleophilic (PhS^-) attack forcedly happens from the same side, where a leaving group ($^-CH_2CO_2Et$) was found before this. Moreover, decomposition of a contact ion pair proceeds so fast that PhS^- frontally attacks a carbonium ion before it manages to pass into the flat condition. As a result, sulphide **13** is formed (Scheme 7).

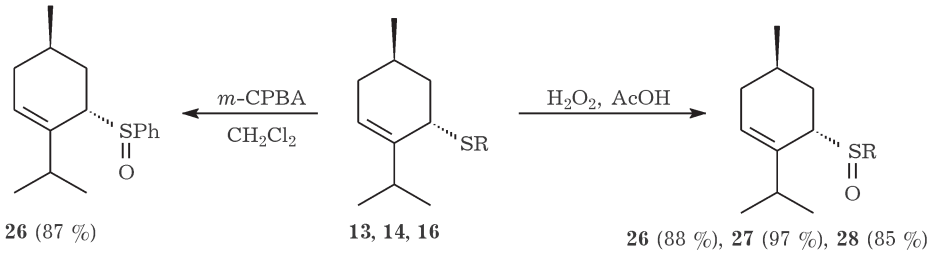
Thiating of tertiary alkyl alcohols **22a,b** that are adducts of 1,2-litium-organic compounds to enone **1** [15, 16] in the presence of catalytic amounts of $ZnCl_2$ also occurs with substitution of the hydroxyl group [9].Moreover, unlike (1*R*,3*R*)-*n*-menth-3-ol **2a**, the reaction is accompanied by an alkyl rearrangement with the formation of secondary terpene sulphides **23**–**25**, in PMR spectra of which a signal of the olefinic proton disappears with the preservation of other signals of the initial enols **22a,b**. Small values for proton spin-spin coupling constants (^3J = 1.4 and 4.3 Hz) at C-1 carbon atom in terpene sulphides **23**–**25** testifies the axial orientation of thioalkyl fragments (Scheme 8).

Sulphides **13**, **14**, **16** yield menthene sulphoxides **26**–**28** during oxidation with 30 % H_2O_2 in AcOH and MCPB in CH_2Cl_2 (Scheme 9).

Thus, the reactivity of available (*R*)-4-menthenone **1** and its derivatives in electrophilic and nucleophilic thiating was studied and their opportunities in the synthesis of potentially biologically active sulphides and sulphoxides of the menthene series were demonstrated.



Scheme 8.



26 (87 %) **13, 14, 16** **26** (88 %), **27** (97 %), **28** (85 %)

R = Ph (**13, 26**), n-C_6H_{13} (**14, 27**), n-$C_{16}H_{33}$ (**16, 28**)

Scheme 9.

REACTIONS OF (*R*)-4-MENTHEN-3-ONE AND ITS DERIVATIVES WITH NITROGEN-CONTAINING REAGENTS

Nitrogen-containing derivatives of the menthene series have various types of biological activity: antiviral, antitumour, cytostatic, analgesic, *etc*. Therefore, with a view to enhancing an opportunity to use enone **1** in the direction towards biologically active compounds, transformations of enone **1** and its derivatives in reactions with the participation of nitrogen-containing reagents were studied.

It is known that an uncatalyzed reaction of diazomethane with α,β-unsaturated ketones usually proceeds as 1,3-dipolar cycloaddition and leads to the formation of pyrazolines, pyrolysis of which is used to prepare olefins and cyclopropanes. Additionally, pyrazolines are semiproducts in the synthesis of some drugs.

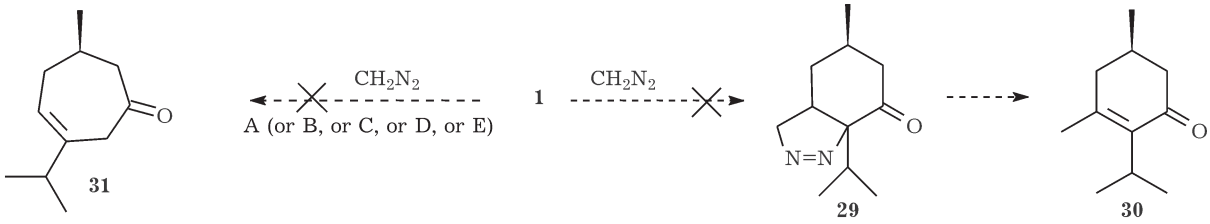
In this regard, the interaction of (*R*)-4-menthene-3-one **1** with diazomethane was studied [1]. However, only the initial substrate was isolated when carrying out the reaction in Et_2O and CH_2Cl_2 and the formation of polyethylene that is the product of carbene polymerization was observed.

If homologation of the initial compound usually happens during catalysis of the interaction of diazomethane with enones, then the attempts to carry out this process with the participation of menthenone **1** did not lead to the formation of the desired products **29**–**31** (Scheme 10).

Another approach to pyrazolines provides for the interaction of α,β-unsaturated carbonyl compounds with hydrazine. Herewith, the primary attack happens on the carbonyl group with the formation of hydrazones followed by their cyclization. However, menthenone **1** showed inertness and in this case when using both commercial 30 % and 100 % hydrazine hydrate *in situ* generated from its salt (Scheme 11).

Apparently, inertness of (*R*)-4-menthene-3-one **1** in pyrazoline formation reactions is a consequence of both polarization disturbance of a multiple bond in the enone system and steric hindrances in the cyclohexene ring that the α-Pr^i group introduces.

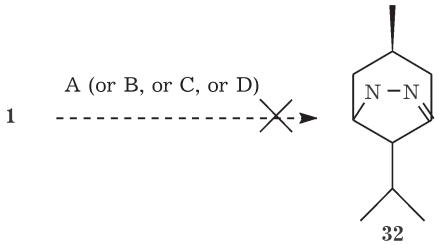
It is known that the oxime function is easily transformed in various functional groups, such as carbonyl, amino-, cyano- and nitro-. Therefore, by using the interaction of enone **1** with hydroxylamine hydrochloride in the presence



31 **29** **30**

A [$AlCl_3$]; B[$BF_3 \cdot OEt_2$]; C[LiCl, MeOH]; D[$Pd(acac)_2$]; E[$Cu(OAc)_2$]

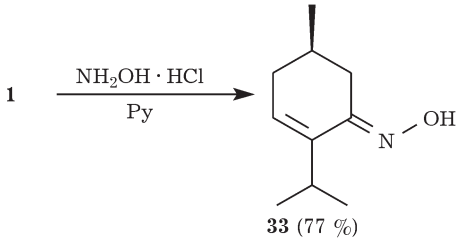
Scheme 10.



A[$N_2H_4 \cdot HBr$, EtOH, HCl]; B[N_2H_4 (30 %), EtOH, HCl]; C[$N_2H_4 \cdot HBr$, NaOH (10 %), 15 °C]; D[$N_2H_4 \cdot HBr$, KOH, EtOH, 78 °C]

Scheme 11.

of pyridine optically pure menthenone **33** was obtained [17]. Comparison of a melting point (57–58 °C) with UV spectrum (EtOH, λ_{max}= 232 nm, lg ε = 3.55) of the synthesized oxime **33** with parameters of *sin*-oxime obtained earlier by Ewschinazi H. E. *et al.* [18] (m.p. of 66–67 °C, λ_{max} = 242 nm, lg ε = 4.1) demonstrated their substantial difference. Additionally, if shifting of signals was observed in the ^{1}H NMR spectrum for *sin*-oxime recorded in $CDCl_3$ in the presence of benzene, this phenomenon was not observed for product **33**. Based on these differences, as well as the fact that *syn*-oximes usually have higher melting points, the *anti*-configuration was assigned to the resulting compound **33**:

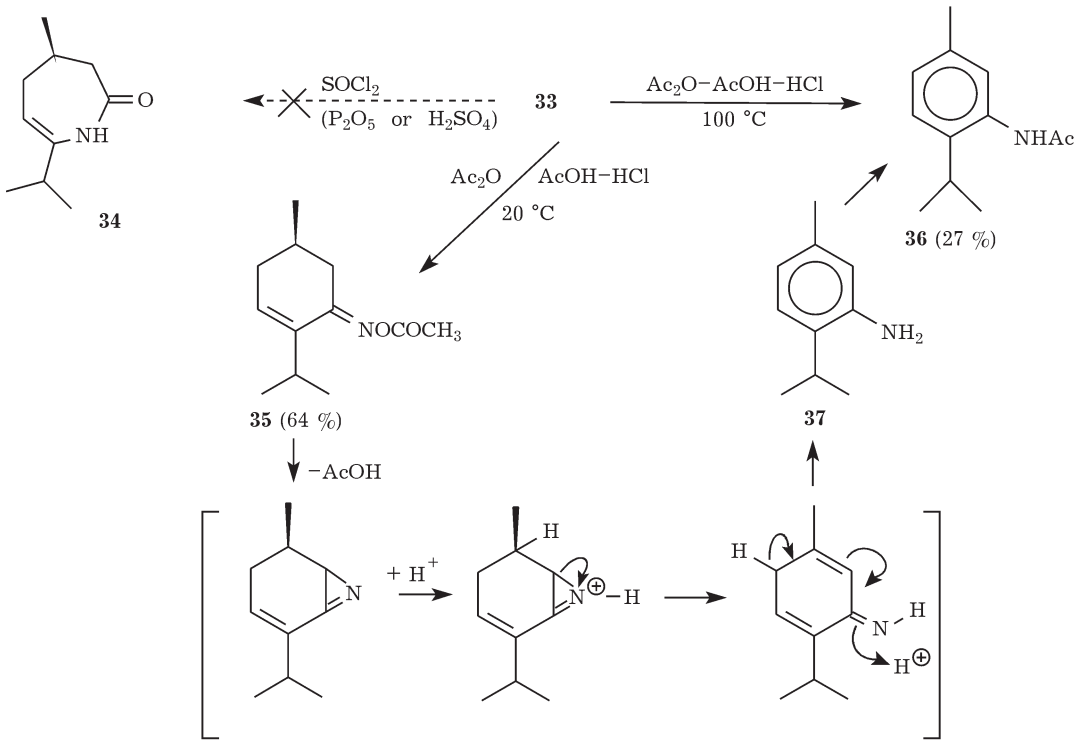


It is known that with rare exceptions, *anti*-oximes under conditions of the Beckman rearrangement either do not enter into the reaction or resinify. Oxime **33** could be transformed to tetrahydroazepine **34** with successful carrying out this process.

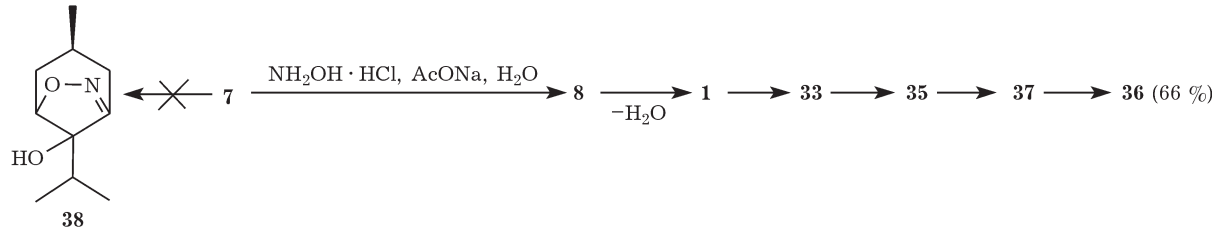
However, the oxime does not undergo the rearrangement, and when treated with thionyl chloride and mainly, tarring occurs under the action of phosphoric anhydride and concentrated sulphuric acid. The use of Beckmann mixture (Ac_2O–AcOH–HCl) as a reagent at 20 and 100 °C led to O-acyl derivative of oxime **35** and acetamide **36**, respectively, that is the product of its further aromatization [17]. This can be explained by the initial formation of compound **35** that is sequentially transformed to amine **37** by means of Semmler–Wolf and its further acylation up to compound **36** (Scheme 12).

Additionally, the interaction of epoxyketone **7** with $NH_2OH \cdot HCl$ in the presence of AcONa is also accompanied by the formation of aromatic acetamide **36** [19], and not assumed 1,2-dioxopyrazol derivative **38**, like for (*S*)-pulegone [20]. Apparently, the observed result is also driven by steric effects of the *i*-Pr group and a lower reactivity of the *endo*-cyclic double bond in enone **1**. The formation of compound **35** can be represented by the following probable scheme: resulting ketoalcohol **8** is transformed into oxime **33** *via* consecutive dehydration stages to enone **1** and the interaction with $NH_2OH \cdot HCl$ and further into its O-acyl derivative **35**. The latter is transferred into amine **37** by means of Semmler–Wolf and further into the desired acetamide **36** (Scheme 13).

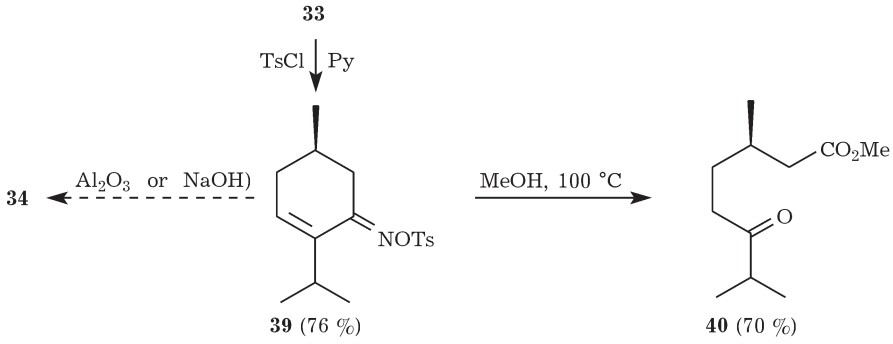
It is known that most ofarylsulphonates of oximes are extremely reactive compounds and undergo the Beckman rearrangement already during synthesis. However, stable O-tosyl oxime derivative **39** was isolated resulting from the reaction of oxime **33** with *para*-toluene sulphochloride. Compound **39** shows inertness towards some traditional reagents, for example, to aluminium oxide and NaOH (in a mixture of THF–H_2O). At the same time, during its heating in an ampoule at 100 °C, a complex mixture was formed in MeOH, from which (*S*)-3,7-dimethyl-6-oxooctanic acid methyl ether **40** was isolated in a yield of 70 %. The latter compound is a synthon in the synthesis of the sex pheromone of meal worm (*Tenebrio molitor* L.), iden-



Scheme 12.



Scheme 13.



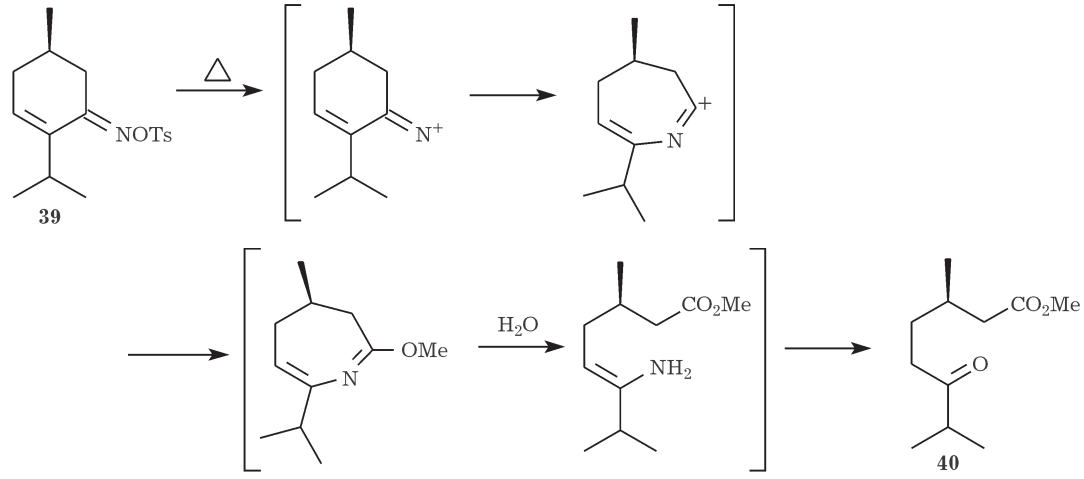
Scheme 14.

tical to previously obtained from menthone **4** using the key stage of the Baeyer–Villiger reaction [21] (Scheme 14).

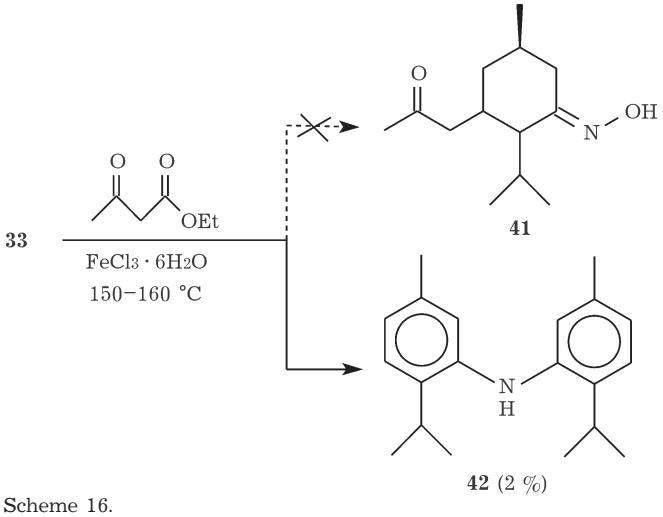
The proposed reaction mechanism is generally consistent with already known transformations of tosylates of oximes.It is noteworthy that the Beckman rearrangement of the corresponding tosylate proceeds with denitration, leading to ketoester **40** (Scheme 15).

It is known from research works carried out under A. Tkachev [22] that conjugated oximes can participate in the Michael reaction with the formation of bicyclic derivatives.In this regard, the behaviour of oxime **33** obtained from menthenone **1** and having a unique enone system of oxime **33** was studied in the Michael reaction with acetoacetic ester in the presence of catalytic amounts of ferric chloride.However, instead of the desired adduct **41** that is a nitrogen-containing compound with a broader range of chemical potentials in comparison with oxime **33**, the resulting product represented a complex stable complex with the iron (III) ion, as evidenced by the form of signals of hydrogen and carbon atoms in ^{1}H and ^{13}C NMR spectra. Unfortunately, we managed to isolate in a pure state only a minor component that, according to spectral data, represented di-3-(*para*-cymene) amine **42** (Scheme 16).

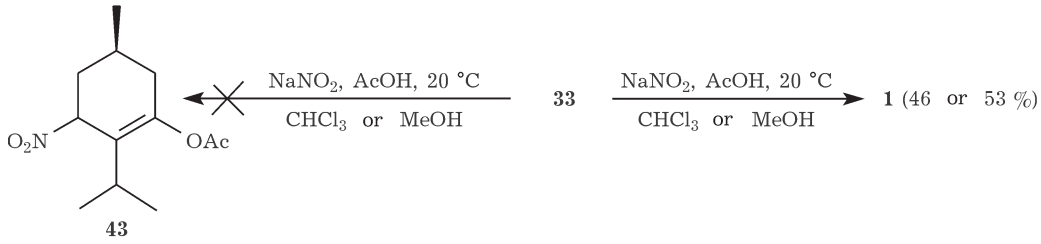
There are data that oximes of a series of cyclic α,β-unsaturated ketones turn into unsaturated nitroacetates that are precursors of heterocyclic compounds [23]. At the same time, ni-



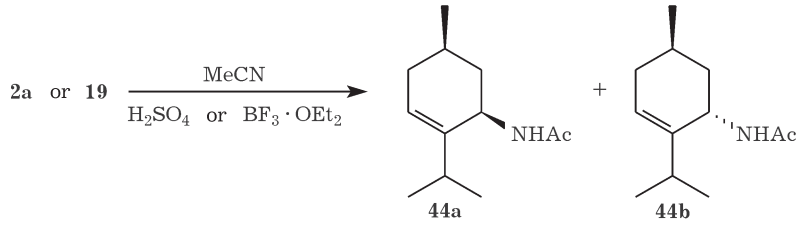
Scheme 15.



Scheme 16.



Scheme 17.



Scheme 18.

trosation of (*R*)-4-menthene-3-one *anti*-oxime **33** with the $NaNO_2$–AcOH system in MeOH or $CHCl_3$, likewise (–)-carvone oxime [24], does not lead to the expected unsaturated nitroacetate **43**: regeneration of initial (*R*)-4-menthene-3-one **1** is observed [19] (Scheme 17).

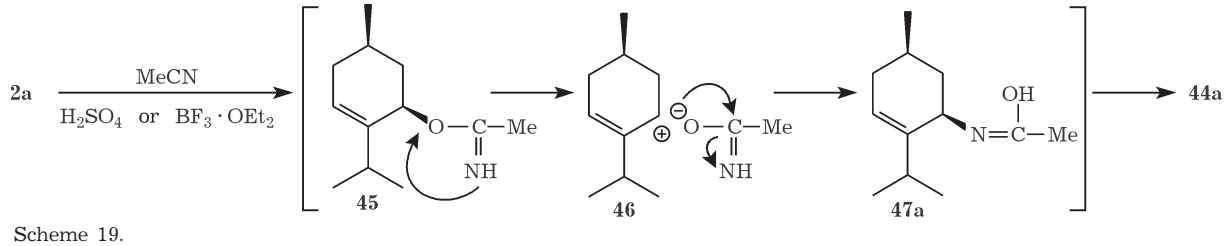
A convenient and common method for the synthesis of pharmacologically active acetamides is the Ritter reaction with the participation of derivatives of terpenes. A mixture of acetamides **44a** and **44b** in the ratios of (55 : 45) and (69 : 31), respectively, is formed, according to capillary GLC and PMR data, withthe involvement of (1*R*,3*R*)-*n*-menth-4-ene-3-one **2a** into this reaction and use of H_2SO_4 and $BF_3 \cdot OEt_2$ as catalysts. At the same time, compound **19** turns into a mixture (57 : 43) of the same isomers with the prevalence of **44b** during H_2SO_4 catalysis. Apparently, this is related to simultaneous implementing S_N1 and S_Ni substitution mechanisms (Scheme 18).

Thus, according to the S_N1 mechanism, the formation of a mixture of acetamides **44a,b** in equal ratio occurs.The enrichment of the latter with stereoisomer **44a** for (1*R*,3*R*)-*n*-menth-3-ol **2a** or **44b** for acetate **19** is probably driven by proceeding of the reaction according to the S_Ni mechanism.

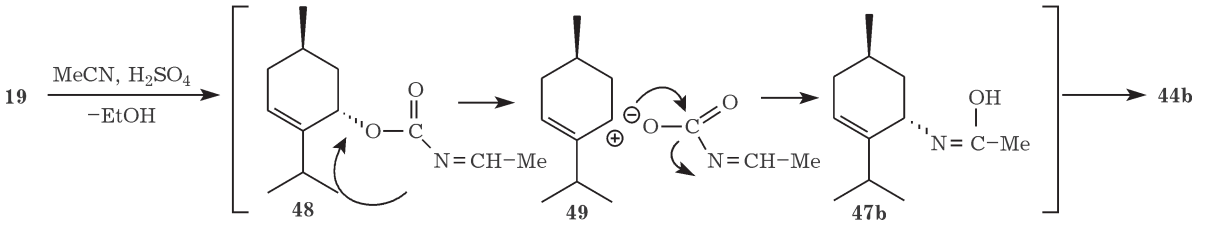
It shows that adduct **45** initially formed from alcohol **2a** further dissociates with the formation of a contact ion pair **46** that is decomposed *via* the stage of unstable compound (**47a**) into **44a** (Scheme 19).

The formation of acetamide **44b** from acetate **19** *via* the stages of substitution **48** product of the ethoxy group in **19** happens in a similar way by the S_Ni mechanism for the –N=CHMe fragment of a contact ion pair **49** and compound **47b** formed during elimination of an ethyl acetate molecule (Scheme 20).

As a result, it was demonstrated that the Ritter reaction with the participation of (1*R*,3*R*)-



Scheme 19.



Scheme 20.

n-menthene-3-ol **2a** or the product **19** of its orthoester Claisen rearrangement under conditions of H_2SO_4 or $BF_3 \cdot OEt_2$ catalysis proceeded simultaneously according to both S_N1 and S_Ni mechanism with the formation of an enriched mixture of acetamides **44a, b**. Moreover, the use of a Lewis acid ($BF_3 \cdot OEt_2$) as a catalyst in comparison with a protonic acid (H_2SO_4) leads to the prevalence of the S_Ni mechanism when preparing diastereomeric acetamides **44a, b**.

CONCLUSION

Thus, the present paper systematizes the data for studies of reactions of (*R*)-4-menthene-3-one and its derivatives with aluminium- and boron-containing hydride reagents depending on the temperature and the nature of the solvent, a range of new optically active sulphides, sulphoxides, acetamides and oxime of methane series based on the above compounds using the Ritter reaction, nucleophilic and electrophilic thiating, nitrosation, oximation was obtained.

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