3H) — H-6', H-4', H-3'; 6.0 (d, 2.5 Hz, 1H) — H-8; 5.81 (d, 2.5 Hz, 1H) — H-6; 5.2 (q, J_{trans} = 13.0 Hz, J_{cis} = 3.5 Hz, 1H) — H-2; 2.7 (m, J_{gem} = 17.5 Hz, J_{cis} = 3.5 Hz, J_{trans} = 13.0 Hz, 2H) — H-3-trans, H-3-cis.

Mass spectrum (m/z): 288, 179, 152, 136, 135.

SUMMARY

Six flavanones have been isolated from Siberian tansy for the first time: isosakuranetin, naringenin, homoeriodictyol, 2',5,5',7-tetrahydroxyflavanone, 2',5,5',7-tetrahydroxy-6-methoxyflavanone, and 4',5,7-trihydroxy-6-methoxyflavanone. The last two are new compounds.

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SYNTHESIS AND STRUCTURE OF AMINO ESTERS OF MENTHOL

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UDC 547.492.2+333.3

The conditions for the acylation of (—)-menthol with monochloroacetyl chloride have been studied. Amino esters of (—)-menthol have been obtained by the nucleophilic replacement of the chlorine in (—)-menthol monochloroacetate by residues of secondary amines. Their properties and their mass, IR, and ^{13}C NMR spectra are described.

Analysis of literature information has shown that of amines of the terpene series particular interest is presented by derivatives of menthol, many of which are biologically active substances with diuretic, antimicrobial, antiviral, and ganglion-blocking properties [1-3].

In the present paper we describe the synthesis and spatial structures of new amino esters of menthol.

The amino esters of menthol were obtained from menthol monochloroacetate and secondary amines in accordance with the following scheme (see next page).

The acylation of (—)-menthol (I) was effected with monochloroacetyl chloride, which is more reactive than the acid and reacts with the alcohol faster.

The reaction gave a 78-80% yield of (—)-menthol monochloroacetate (II) (MMCA). It must be mentioned that the yield of menthol monochloroacetate depends strongly on the solvent used and the temperature conditions. As solvents we used CCl_4, tetrahydrofuran, and benzene.

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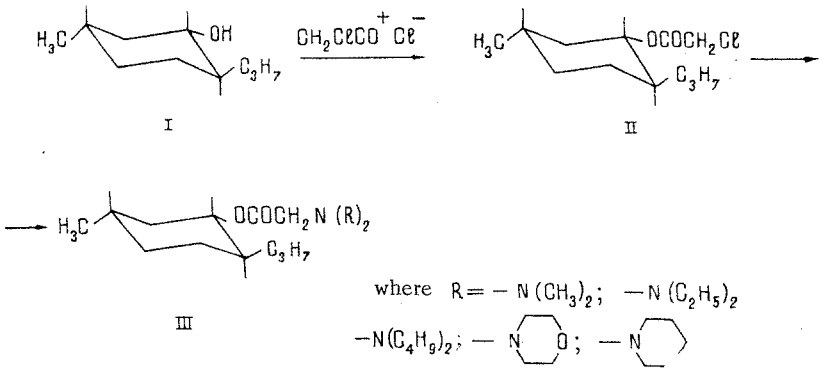


I II III

The best results were obtained in the case of benzene, which is apparently connected with its solvating capacity. Since benzene does not solvate CH_2ClCO^+ and Cl^- ions, the attack of CH_2ClCO^+ on the O atom of menthol is facilitated.

The reaction was carried out in the temperature interval of 50-60°C; a rise in the temperature lead to a fall in the yield of menthol monochloroacetate because of pronounced resin formation.

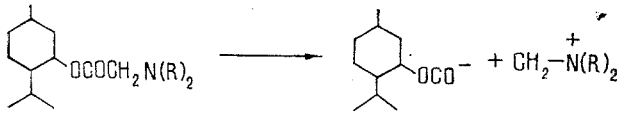
According to ^{13}C NMR results, the menthol monochloroacetate obtained was conformationally homogeneous and the substituents were presented in the triequatorial position. The formation of menthol monochloroacetate (II) in which the original configuration of the alcohol (I) is retained shows that the reaction takes place completely at the oxygen atom and the bonds of the asymmetric carbon atom are not affected.

Thanks to the considerable mobility of the chlorine in the α position to the carbonyl group in menthol monochloroacetate, the replacement of chlorine by an amino group took place readily and with high yield. At the same time, the exchange reaction took place more readily with amines of higher basicity. In the series dimethyl-, diethyl-, and dibutylamines the basicity rises with an increase in the size of the radicals. However, the small yield of the products of the reaction of menthol monochloroacetate with dibutylamine shows the existence of an influence of steric factors. This is also confirmed by the fact that the better accessibility of the nitrogen atom in piperidine also leads to a higher reactivity of this amine than of diethylamine although the induction effects of the radicals of these amines are the same. Morpholine reacts similarly to piperidine.

The characteristics of (−)-p-menth-3-yl dimethylaminoacetate (IV); (−)-p-menth-3-yl diethylaminoacetate (V), (−)-p-menth-3-yl dibutylaminoacetate (VI), (−)-p-menth-3-yl morpholinoacetate (VII), and (−)-p-menth-3-yl piperidinoacetate (VIII) are given in Table 1.

The structures of the compounds synthesized were confirmed by the results of elementary analysis and by mass, IR, and ^{13}C NMR spectra.

The mass spectra of the amino esters of menthol are characterized by an appreciable peak of the molecular ion, the intensity of which amounts to 10% of the maximum. The fragmentation of these compounds is due almost exclusively to the nitrogen atom, which is the site of the charge. The main ion in the spectrum is obtained by the cleavage of the —CO—CH_2— bond of the molecule



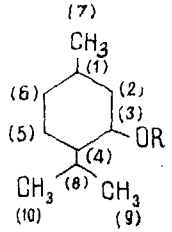
This ion is characteristic, and its position in the spectrum serves as a proof of the presence of a particular amine grouping in the molecule.

The chemical shifts of the signals of the ^{13}C nuclei in the ^{13}C NMR spectrum are given in Table 2. The assignment of the chemical shifts was made on the basis of a comparison of the results obtained and the previously known chemical shifts of menthol [4] and of a number of amino derivatives [5, 6]. It can be seen from Table 2 that the chemical shifts of the carbon nuclei of the cyclohexane ring (with the exception of $C_{2,3,4}$ and of the methyl groups 7, 9, and 10) differ little from the chemical shifts of the corresponding carbon atoms in

TABLE 1. Characteristics of the Compounds Synthesized

Compound	bp (nm Hg)	n_D^{20}	d_4^{20}	MR_D		Found, %			Empirical formula	Calculated, %			$[\alpha]_D^{20}$
				found	calculated	C	H	N		C	H	N	
IV	110—110.5 (6)	1,4712	0.856	70,42	70,24	69,51	11.02	5.68	$C_{14}H_{27}O_2$	69.72	11.20	5,80	—74.8 (c 1.03; alc.)
V	105—106 (4)	1.4724	0.844	79,26	79.48	71,56	11.40	5.00	$C_{16}H_{31}O_2$	71,38	11,53	5,20	—66,1 (c 1,05; alc.)
VI	132—133 (3)	1,4700	0.910	97,74	97,95	73,46	11,84	4,13	$C_{20}H_{39}O_2$	73 85	12.00	4,30	—56.0 (c 1,18; alc.)
VII	143—144 (4)	1,4742	0,999	78,72	78,92	67,53	10,12	4,70	$C_{16}H_{29}O_3$	67,85	10,24	4,95	—50.3 (c 1,08; alc.)
VIII	145—146 (2)	1,4742	0,969	81 61	81.89	72,29	10,98	4,82	$C_{17}H_{31}O_2$	72,59	11.05	4.98	—54,2 (c 1,03; alc.)

TABLE 2. ^{13}C NMR Chemical Shifts (δ, ppm) of the Menthane Derivatives



Compound	R	Carbon atom															
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
I	H	31,8	45,2	71,5	50,2	23,3	34,7	22,3	20.8	16,1	21,2	—	—	—	—	—	—
II	—$^{11}CO^{12}CH_2Cl$	31,5	41,1	76,5	47,1	23,6	34,2	22,0	26,4	16,4	20,7	166,9	40 7	—	—	—	—
IV	—$^{11}CO^{12}CH_2N^{13}(CH_3)_2$	31,5	41,0	74,5	47,0	23,5	34,3	22,0	26,4	16,3	20,8	170,0	60,6	45,1	—		—
V	—$^{11}CO^{12}CH_2N^{13}(C^{14}H_5)_2$	31,5	41,1	74,2	47,1	23,5	34,4	22,1	26,4	16,3	20 8	170,6	54,0	47,8	12,3	—	—
VI	—$^{11}CO^{12}CH_2N^{13-16}(C_4H_9)_2$	31,5	41,2	73,9	47,2	23,6	34,5	22,1	26,4	16,4	20,8	170,9	55,2	54,3	30,0	20,6	14,1
VII	—$^{11}CO^{12}CH_2N^{13}$$^{14}O$	31,4	41,0	74,5	47,0	23,5	34,3	22,0	26,4	16,4	20,7	169,5	59,8	53,3	66,7	—	—
VIII	—$^{11}CO^{12}CH_2N^{13}$^{15}	31,5	41,1	74,2	47,1	23,6	34,4	22,0	26,4	16,4	20,7	170,0	60,5	54,2	25,9	24,0	—

menthol. According to the ^{13}C NMR results, all the compounds synthesized were pure both conformationally and with respect to their content of other possible stereoisomers, each consisting of a single isomer with the triequatorial position of the substituents.

The IR spectrum of the initial menthol is characterized by an absorption band at 3275 cm^{-1} (OH group). In the spectrum of a dilute solution (C = 0.001 M in CCl_4) the absorption band of the free hydroxy group appears at 3634 cm^{-1} with pronounced asymmetry on the low-frequency side, which can be ascribed to axial-equatorial isomerism. In the 3634 cm^{-1} region we observe an enveloping contour which consists of two unresolved absorption bands corresponding to the absorption of hydroxy groups in the equatorial and the axial positions. In accordance with this, we can assign the doublet of bands at 1047 and 1027 cm^{-1} to the stretching vibration of the C–O bond. The acyl and isopropyl substituents appear in the spectrum in accordance with literature information [7]. In the spectra of the compounds synthesized, the absorption bands of a hydroxy group are absent, which shows substitution at the hydroxy group. The spectra of all the compounds show absorption bands in the 1728-1750 cm^{-1} region due to the vibrations of the C=O bonds and at 1175-1210 cm^{-1}, due to the vibrations of C–O bonds. These bnads show the ester nature of the compounds synthesized. The C–O-ring bond vibration appears at 1012-1020 cm^{-1}. The active methylene group is characterized by stretching vibrations of the C–H bonds at 1420 cm^{-1}.

EXPERIMENTAL

The purity of the compounds obtained was established by the GLC method on a LKhM-7A chromatograph with programming of the temperature from 90 to 200°C in a 2 m × 0.5 mm column filled with Chromosorb W (60-80 mesh) and crystalline KOH (9%) impregnated with Apiezon K (12%).

IR spectra were recorded on a UR-20 spectrometer in the range of frequencies of 400-3800 cm^{-1} using slit program 4 with a rate of scanning of 60 cm^{-1}/min. The compounds were used in the form of liquid films between KBr plates and as solutions in CCl_4 in concentrations of 0.1 and 0.001 M.

Mass spectra were taken on a Varian MAT-311 instrument at a cathode emission current of 1000 mA and an energy of the ionizing electrons of 10 eV. The temperature of the ion source was 200°C.

^{13}C NMR spectra were recorded on an H-90 spectrometer with a resonance frequency for ^{13}C of 22.63 MHz under conditions of proton decoupling. The concentration of the solutions was 1:4 by volume in $CHCl_3$ + $CDCl_3$. The deuterated solvent was used for stabilization. The chemical shifts of the ^{13}C nuclei were determined relative to an internal standard — tetramethylsilane (TMS). The width of the spectrum was 1600 Hz. The measurement pulse for ^{13}C was 8 μsec (approximately 60°).

(–)-Menthol Monochloroacetate (II). With cooling, 16.9 g (0.13 mole) of monochloroacetyl chloride was added to a mixture of 15.4 g (0.1 mole) of (–)-menthol, 7.9 g (0.1 mole) of pyridine, and 0.03 g of hydroquinone in 150 ml of dry benzene, after which the reaction mixture was heated at 40-50°C for 5 h. The resulting precipitate of pyridine hydrochloride was decomposed with water, the benzene layer was separated off, and the aqueous layer was extracted with benzene. Fractionation in vacuum yielded the desired product, $C_{12}H_{21}O_2Cl$. Yield 92%, mp 144.5-145°C (15 mm Hg), mp 38-39°C, $[\alpha]_D^{20}$ 69.4° (c 1.13; ethanol).

The (–)-menthol amino esters (IV)-(VIII) were synthesized by a procedure described previously [8].

SUMMARY

New amino derivatives of (–)-menthol have been synthesized, and their structures and properties have been studied by physicochemical methods.

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CEMBRANE ALCOHOLS — A NEW TYPE OF HORMONAL PLANT GROWTH INHIBITOR

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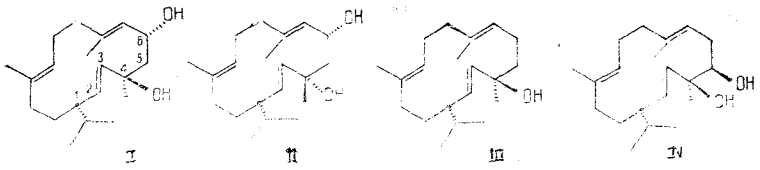
UDC 547.594.4.03

Three new cembrane alcohols have been synthesized and have been tested for growth-inhibiting activity together with a number of known compounds. By the selection and testing of cembrane derivatives a structural fragment has been found which, as is assumed, is responsible for the appearance of the growth-inhibiting activity of cembrane alcohols.

Springer et al. [1] have established that the diols (I) and (II) isolated in 1962 by Roberts and Rowland [2] from tobacco leaves are hormonal plant growth inhibitors. In view of this, the question arises of whether this biological activity is a property only of the diols (I) and (II) or is also characteristic of other cembrane compounds having common structural features. In order to investigate this, we have carried out -rials in a standard test on sections of wheat coleoptiles [3] a number of cembrane alcohols described previously and some obtained for the first time. The results are given in Table 1.



I II III IV

To establish the role of the secondary hydroxy groups in the manifestation of the biological activity of the diol (I), we tested a substance not containing this group — isocembrol (III) — and an isomer of the diol (I) — the diol (IV). It was found that the presence or absence of a secondary hydroxy group at C_6 or C_5 did not appreciably affect the growth-inhibiting activity of cembrane compounds having a hydroxy group at C_4. These substances were not inferior to diol (I) in activity.

When the tertiary hydroxy group was eliminated from the molecule of the diol (IV) (the alcohol (V)), activity appeared only at a high concentration of the solution. A similar fall in biological activity was observed for the 2,3-epoxy derivative of isocembrol (VI).

Thus, for the manifestation of hormonal growth-inhibiting activity the presence of fragment A ($R=CH_3$) in the molecule of a cembrane compound is apparently necessary.

It is interesting to note that when one of the trisubstituted double bonds of isocembrol was epoxidized (the epoxy alcohol (VII)), the activity rose, probably through the increase in the polarity of the molecule. (See scheme on following page.)

The epimerization of isocembrol at C_4 (4-epiisocembrol (VIII)) led to decrease in activity, as for the diol (II) isolated from tobacco leaves. On the other hand, replacement

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