sitions are localized mainly in the chromone fragment of the molecule. In the case of the hydroxy derivatives, the absorption bands of flavone undergo a relatively small bathochromic shift, but because of their closeness the individual components either overlap or, conversely, are resolved. This explains the substantial differences in the form of the spectra of the hydroxyflavones.

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REDUCTIVE AMINATION OF *l*-MENTHOL BY ALIPHATIC NITRILES

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UDC 547.233:07.088.8

The reductive amination of *l*-menthol with aliphatic nitriles has been studied. A probable scheme of the mechanism of the reaction has been put forward and the stereochemical composition of its products has been determined. It has been established with the aid of the ^{13}C NMR method that the reaction forms a mixture of isomeric optically-active N-alkylmenthyl-, -neomenthyl-, -isomenthyl-, and -neoisomenthylamines in a ratio of 54:24:17:5. The absolute configurations of the amines obtained have been determined.

The synthesis of nitrogen-containing compounds in the p-menthane series is of considerable interest, since these substances possess a broad spectrum of biological action [1, 2]. Continuing investigations [3-6] on the synthesis of amino derivatives of monoterpenes and their synthetic analogs, we have studied the reductive amination of *l*-menthol (I) with aliphatic nitriles, namely acetonitrile, acrylonitrile, and butyronitrile in a catalytic apparatus of the flow-through type under a pressure of hydrogen in the presence of heterogeneous catalyst.

In spite of the fact that menthol has been known for a long time [7], its chemical transformations have been little studied. This is due to the low reactivity of the hydroxy group in the menthol molecule resulting from the steric effect of the neighboring alkyl groups. Our

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Translated from Khimiya Prirodnykh Soedinenii, No. 3, pp. 312-317, May-June, 1981. Original article submitted December 30, 1980.

0009-3130/81/1703-0238$07.50

investigations have enabled us to establish that menthol takes part comparatively readily in the catalytic hydroamination reaction with the formation of the corresponding N-alkyl-2-isopropyl-5-methylcyclohexylamines.

As is known [8], the hydroamination reaction is a complex multistage process including a series of successive stages of the hydrogenation of various chemical bonds and condensation, and therefore the choice of catalyst for all these stages is of great importance. We have used a copper–alumina catalyst modified with lithium hydroxide (15% Cu/Al_2O_3 + 6% LiOH) [9]. This is a typical metal-support heterogeneous bifunctional catalyst in which the reduced copper possesses a hydrogenating and dehydrogenating action and the support a dehydrating and deaminating action. The influence of the modification of the catalyst by lithium hydroxide consists, in the first place, in the neutralization of the acidic centers of the support, which are probably catalytically active together with the metallic centers in the hydroamination reaction. The use of this catalyst permits the hydroamination reaction of methanol to be performed with aliphatic nitriles with a high degree of selectivity in which there are practically no products of the possible side reactions of the deamination and disproportionation of the amines on the acidic centers of the support.

The reaction was performed at temperatures of 250-270°C, a space velocity of 0.3 h^{-1}, and a pressure of hydrogen of 10-15 atm. The main reaction product was a mixture of isomeric optically active N-alkyl-2-isopropyl-5-methylcyclohexylamines (VII-X) containing N-alkyl derivatives of menthylamine (VII), of neomenthylamine (VIII), of isomenthylamine (IX), and of neoisomenthylamine (X) in a ratio of 54:24:17:5. In addition, the catalysate was found to contain a mixture of isomeric menthols (I, IV-VI) and a mixture of menthone (II) and isomenthone (III) in a ratio of 3:1. The compositions and yields of the reaction products are given in Table 1.

On the basis of literature information [10] and also of our own results, we consider that the limiting stage of the reaction is the dehydrogenation of the menthol to menthone, this dehydrogenation being in equilibrium with the processes of the hydrogenation of the latter with the formation of a mixture of menthol and neomenthol. Obviously, simultaneously with the formation of menthone its isomerization to isomenthone takes place, and the latter, adding a molecule of hydrogen, gives a mixture of isomenthol (V) and neoisomenthol (VI). The reaction of the ketones (II) and (III) with the primary amine formed in the reduction of the nitrile leads (through a stage of the formation of the corresponding N-menthylidenealkylamines (XI and XII) to a mixture of the isomeric secondary amines (VII-X). The absence of the Schiff's bases (XI) and (XII) from the catalysate is probably due to the readiness with which these compounds are reduced to the amines [11, 12]. Thus, we consider that the reaction scheme of the reductive amination of menthol by aliphatic nitriles has the following form:

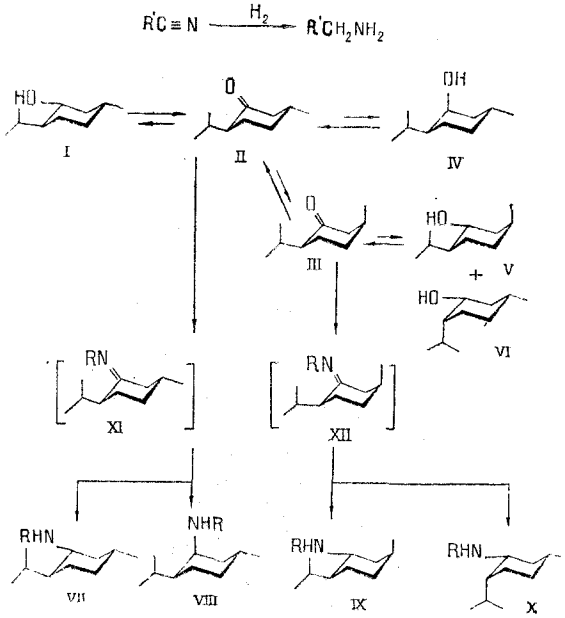

TABLE 1. Yields and Compositions of the Products of the Reductive Amination of 1-Menthol with Aliphatic Nitriles (pressure of hydrogen 15 atm, temperature 250-270°C, space velocity 0.3 h^{-1}, catalyst 15% copper/Al_2O_3 + 6% lithium hydroxide)

R	Composition of the reaction				Composition of the mixture of isomeric N-alkyl-2-isopropyl-5-methylcyclohexylamines, %			
	total yield of amines, %	mixture* of alcohols	menthone	isomenthone	menthylamines	neomenthylamines	isomenthylamines	neoisomenthylamines
$-C_2H_5$	74.0	16 0	7.0	3.0	56	20	19	5
$-C_3H_7$	71.0	18.0	8.0	3.0	50	30	15	5
$-C_4H_9$	66.0	18.0	12.0	4.0	55	22	18	5

*The menthol—neomenthol—isomenthol—neoisomenthol ratio determined by the GLC method was 70:15:10:5.

It must be mentioned that the main components of the mixture of amines (VI-X) are the products (VII and VIII) of the reductive amination of menthone (II) (about 80%), which is sterically more favorable than isomenthole (III) and predominates in the equilibrium (II) ⇄ (III). Of the amines (VII-X), on the basis of general conformational ideas, the most stable is the N-menthylamine (VII) with the triequatorial arrangement in the cyclohexane ring, its proportion in the mixture of amines being about 60%. The least stable is the neoisomenthylamine (X) (amount in the mixture 5%). The predominant formation of the N-alkylmenthylamine is probably explained by both energetic and steric factors. Compounds with the equatorial arrangement of the substituents are more stable because of the smaller steric stresses than compounds with the axial arrangement of the substituents. This is confirmed by thermodynamic calculations [13]. The steric influence of the isopropyl groups adjacent to the reaction center of the Schiff's base (XI) consists in the fact that the hydrogenation of a >C=N bond in the axial direction is sterically more favorable [14], because of which N-alkylamenthylamines with the equatorial arrangement of the amino groups are formed.

From the mixture of secondary amines (VII-X) by preparative GLC we succeeded in isolating the individual (containing ≥90% of the main isomer) N-alkylmenthylamine (VII) and N-alkylneomenthylamine (VIII), the properties of which are given in Table 2.

The structures of the N-alkyl-2-isopropyl-5-methylcyclohexylamine synthesized were shown by the methods of IR, mass, and ^{13}C NMR spectroscopy, and also by spectropolarimetry.

The IR spectra of the amines of the p-menthane series obtained each have a characteristic absorption band in the 3300-3350 cm^{-1} region due to the stretching vibrations of the secondary amino group. Bands at 2960, 2925, 2875, 2850, 1460, 1370, 1386, 1260, 1240, 1170, 1120, and 1015 cm^{-1} are due to the vibrations of the bonds of the structural fragments of the p-menthane hydrocarbon skeleton.

The mass spectra of all the amines obtained contained peaks corresponding to the molecular ions M^+. The subsequent fragmentation of the molecules under the action of electron impact took place with the cleavage of the C_5-C_{10} and C_2—C_7 bonds. This led to a series of ions characteristic for the mass spectra of compounds of the p-menthane series (M − 15) and (M − 43) [15].

A criterion of the determination of the structures and configurations of the N-alkyl-2-isopropyl-5-methylcyclohexylamines from their ^{13}C NMR spectra was a comparison of the experimental and calculated chemical shifts of the ^{13}C nuclei of the isomeric menthylamines. The isomeric menthols were used as model compounds, the chemical shifts of ^{13}C nuclei of these having been determined previously [16]. The good agreement of the chemical shifts of the carbon atoms of the ring (with the exception of the position of attachment of the polar substituent and of the carbon atoms connected with it) and the alcohols and amines in view of the close conformational energies of —OH and —NHR groups permit a conclusion to be drawn concerning a conformational composition of the individual isomers identical with those of the alcohols. All the isomeric menthylamines (VII-X) were conformationally homogeneous.

The optical rotatory dispersion curves of the N-alkylmenthylamines consist of smooth negative curves and those of the neomenthylamines smooth positive curves.

On the basis of their spatial structures and optical activities, the absolute configurations of the secondary amines synthesized were determined as: (—)-(1R:2S:5R) for the N-alkyl-

TABLE 2. Properties of the N-Alkyl-2-isopropyl-5-methylcyclohexylamines Obtained

Configuration of R	bp, °C (mm Hg)	d_4^{20}	n_D^{20}	MR_D found	MR_D calc.	$[\alpha]_D^{20}$, deg	Found, % C	Found, % H	Found, % N	Formula	Calculated, % C	Calculated, % H	Calculated, % N
Ie, 2e, 5e													
$-C_2H_5$	117–118 (15)	0,7846	1,4565	63,52	63,64	−50,9	78,65	13,71	7,87	$C_{12}H_{25}N$	78,61	13,74	7,64
$-C_3H_7$	127–129 (15)	0,7398	1,4580	72,79	72,87	−46,8	79,20	13,82	7,12	$C_{13}H_{27}N$	79,11	13,79	7,10
$-C_4H_9$	133–139 (15)	0,7039	1,4587	82,06	82,11	−44,9	79,61	15,85	6,93	$C_{14}H_{29}N$	79,54	13,82	6,62
Ia, 2e, 5e													
$-C_2H_5$	115–117 (15)	0,7855	1,4572	63,59	63,64	−24,9	78,53	13,71	7,92	$C_{12}H_{25}N$	78,61	13,74	7,64
$-C_3H_7$	126–127 (15)	0,7411	1,4590	72,80	72,87	+19,2	79,06	13,90	7,31	$C_{13}H_{27}N$	79,11	13,79	7,10
$-C_4H_9$	135–137 (15)	0,7053	1,4595	82,01	82,11	+17,4	79,64	13,75	6,44	$C_{14}H_{29}N$	79,54	13,82	6,62

TABLE 3. Chemical Shifts of ^{13}C Nuclei of the Isomeric N-Alkyl-2-isopropyl-5-methylcyclohexylamines

R	Configuration	^{13}C chemical shifts* C_1	C_2	C_3	C_4	C_5	C_6	C_7	C_8	C_9	C_{10}	C_{11}	C_{12}	C_{13}	C_{14}
$-C_2H_5$	1e, 2e, 5e	57,9	48,7	24,2	35,5	32,5	42,9	25,8	16,0	21,5	22,7	41,0	16,2	—	—
	iso 1e, 2e, 5a	53,9	46,9	21,3	30,9	27,2	37,2	26,3	19,5	21,6	21,1	41,7	16,1	—	—
	neo 1a, 2e, 5e	53,9	49,0	25,3	36,0	25,7	38,6	29,2	20,8	21,6	22,7	42,0	16,1	—	—
	neoiso 1e, 2a, 5e	59,7	45,0	25,7	31,6	30,9	36,9	26,7	22,1	22,2	22,9	42,3	15,8	—	—
$-C_3H_7$	1e, 2e, 5e	58,1	48,8	24,3	35,5	32,5	43,0	25,9	16,0	21,5	22,7	48,9	24,3	12,0	—
	iso 1e, 2e, 5a	54,0	47,0	21,3	31,0	27,2	37,3	26,3	19,5	21,5	21,1	49,5	24,2	12,0	—
	neo 1a, 2e, 5e	54,1	48,9	25,2	35,9	25,7	38,8	29,2	20,8	21,5	22,7	49,8	24,1	12,0	—
	neoiso 1e, 2a, 5e	59,7	45,2	25,7	31,6	30,8	36,8	26,7	22,1	22,2	22,8	50,2	24,1	12,0	—
$-C_4H_9$	1e, 2e, 5e	58,2	48,9	24,3	35,6	32,5	43,0	25,9	16,0	21,5	22,8	46,6	33,6	20,8	14,2
	iso 1e, 2e, 5a	54,1	47,0	21,3	31,0	27,3	37,3	26,4	19,5	21,6	21,1	47,3	33,5	20,8	14,2
	neo 1a, 2e, 5e	54,2	49,0	25,3	36,0	25,8	38,9	29,2	20,8	21,5	22,8	47,5	33,4	20,8	14,2

*The chemical shifts of the ^{13}C nuclei of N-butylneoisomenthylamine could not be assigned.

menthylamines, (+)-(1S:2S:5R) for the neomenthylamines, (+)-(1R:2S:5S) for the isomenthylamines, and (+)-(1R:2R:5R) for the neoisomenthylamines.

EXPERIMENTAL

The reductive amination of *l*-menthol having mp 42-43°C, bp 212°C (760 mm), d_4^{20} 0.890, $[\alpha]_D^{20}$ −50.1° (ethanol), (1R:2R:5R) by aliphatic nitriles was carried out in the following way: a solution of the menthol in the corresponding nitrile (in a ratio of 1.0 M:1.2 M) was passed in a continuous apparatus of the flow-through type in the range of temperatures of from 250-270°C under a hydrogen pressure of 10-15 atm and with a space velocity of 0.3 h^{-1} through a layer of catalyst consisting of 15% of copper and 6% of lithium hydroxide deposited on industrial γ-alumina.

The resulting reaction mixture was separated by preparative GLC in a chromatograph at a temperature of the column thermostat of 120-130°C in a column (3 m × 12-4 mm) filled with Chromaton N-AW-DMCS (0.2-0.25 mm), washed with a 5% soution of KOH in ethanol and impregnated with 20% of Apiezon L.

All the compounds isolated by preparative GLC were subjected to vacuum distillation before the investigations. The purity of the substances obtained was checked by the GLC method on a LKhM-7A chromatograph with programming of the temperature from 90 to 200°C on a column (2 m × 5 mm) filled with Chromosorb W (60-80 mesh) and crystalline KOH (9:1) impregnated with Apiezon K (12%). The IR spectra of the compounds under investigation 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 present in the form of liquid films between KBr plates.

The mass spectra were taken on a Varian MAT-311 instrument with a cathode emission current of 1000 mA and an energy of the ionizing electrons of 10 eV. The temperature of evaporation of the samples was 150-200°C, and the temperature of the ion source 200°C.

The ^{13}C NMR spectra were taken on a WH-90 spectrometer with a resonance frequency for ^{13}C of 22.62 MHz under conditions of complete decoupling from protons. For interpretation, spectra were taken with off-resonance decoupling. The concentration of the solutions was 1:4 by volume in deuteroacetone. The deuterated solvent was used to stabilize the magnetic field. The chemical shifts of the ^{13}C nuclei were determined relative to an internal standard — tetramethylsilane. All the spectra were taken under conditions of integrative detection using a memory volume of 8 K for the real part of the spectrum. The width of the spectrum was 2400 Hz. The measuring pulse of the ^{13}C was 8 μsec (approx 60°).

The optical rotatory dispersion curves were recorded on a Jasco J-20 spectropolarimeter in ethanolic solution at a concentration of 0.1 M in the frequency range of 250-600 nm.

SUMMARY

The reductive amination of *l*-menthol with aliphatic nitriles has been studied. The stereochemical composition of the reaction products has been determined and a probable scheme for its origin has been suggested. It has been established with the aid of the ^{13}C NMR method that the reaction forms a mixture of isomeric optically active N-alkyl derivatives of menthylamine, neomenthylamine, isomenthylamine, and neoisomenthylamine in a ratio of 54:24:17:5. The absolute configurations of the amines obtained have been determined.

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