SYNTHESIS AND SPATIAL STRUCTURE OF THE GEOMETRICAL ISOMERS OF 4-SUBSTITUTED 1-tert-BUTYL-3-METHYL-PIPERIDIN-4-OLS AND 4-ACYLOXY-1-tert-BUTYL-3-METHYLPIPERIDINES

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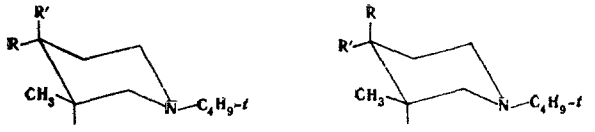
In order to study the interrelationship between the structure, reactivity, and spectroscopic characteristics of the stereoisomeric piperidines, starting from 1-tert-butyl-3-methylpiperidin-4-one the synthesis has been performed of the geometric isomers of some 4-substituted 1-tert-butyl-3-methylpiperidin-4-ols and 4-acyloxy-1-tert-butyl-3-methylpiperidines. The spatial structures of the compounds obtained have been determined by IR and PMR spectroscopy.

In the investigation of the interrelationship of the structure, reactivity, and spectroscopic characteristics of stereoisomers of 4-substituted piperidin-4-ols and 4-acyloxypiperidines, we were faced with the necessity of obtaining compounds of this class containing a tert-butyl substituent at the nitrogen atom of the piperidine ring, fixing the axial orientation of the p-orbital of the electrons of the nitrogen atom. The present paper describes the synthesis of a number of compounds of this type – geometric isomers of 4-substituted 1-tert-butyl-3-methylpiperidin-4-ols (IIβ,γ – Vβ,γ) and of 4-acyloxy-1-tert-butyl-3-methylpiperidines (VIβ,γ – Xβ,γ) differing in the spatial orientation of the substituent R.



IIγ—Xγ IIβ—Xβ

R = H, HC≡C, C_2H_5, C_6H_5; R' = OH, $OCOCH_3$, $OCOC_6H_5$.

As the starting material for the preparation of the compounds under investigation we used 1-tert-butyl-3-methylpiperidin-4-one (I) [1]. In agreement with information given by Mistryukov et al. [2], the reduction of the hydrochloride of the piperidinone with aluminum isopropoxide in isopropanol gave a 96% yield of a mixture of stereoisomers of 1-tert-butyl-3-methylpiperidin-4-ol (IIβ,γ, R = H, R' = OH) containing, according to TLC, 61% of the isomer (IIγ) and 38% of its epimer (IIβ). The individual secondary alcohols (IIβ,γ) were obtained by the preparative chromatography of their stereoisomeric mixture on columns of alumina. For the synthesis of analogs of the alcohols (IIβ,γ) containing a tertiary hydroxy group we used the ethynylation of the piperidinone (I) with sodium acetylide in liquid ammonia, leading with a yield of 92% to a mixture of stereoisomers of 1-tert-butyl-4-ethynyl-3-methylpiperidin-4-ol (IIIβ,γ; R = HC≡C, R' = OH). The chromatographic separation of this mixture showed that it contains 72% of the geometric isomer of the acetylenic alcohol (IIIβ) and 24% of its epimer (IIIγ). By exhaustive catalytic hydrogenation in the presence of Raney nickel catalyst, the acetylenic alcohols (IIIβ,γ) were converted into the geometric isomers of 1-tert-butyl-4-ethyl-3-methylpiperidin-4-ol (IVβ,γ); R = C_2H_5, R' = OH). A geometric isomer of 1-tert-butyl-3-methyl-4-phenylpiperidin-4-ol (Vγ; R = C_6H_5; R' = OH) was synthesized by the reaction of the piperidinone (I) with phenyllithium [3].

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TABLE 1. Geometric Isomers of 4-Substituted 1-tert-Butyl-3-methylpiperidin-4-ols and 4-Acyloxy-1-tert-butyl-3-methylpiperidines

Compound	R	R'	mp, °C	R_f	Empirical formula	Found, %				Calculated, %				Yield, %
						C	H	Cl	N	C	H	Cl	N	
IIβ	OH	H	58—59 a	0,1	$C_{10}H_{21}NO$	70,4	12,2		7,8	70,2	12,3		8,2	96
IIγ	H	OH	86—87 a	0,3		—	—		8,4					
IIIβ	OH	C≡CH	73—74,5 a	0,1	$C_{12}H_{21}NO$	73,8	10,6		7,3	73,9	10,7		7,2	92
IIIγ	C≡CH	OH	92,5—93 b	0,6		73,9	10,4		7,1					
IVβ	OH	C_2H_5	c	0,2	$C_{12}H_{25}NO$	72,6	12,3		7,1	72,4	12,6		7,0	99
IVγ	C_2H_5	OH	— b	0,4		72,4	12,3		6,8					88
VIβ	OCOCH$_3$	H	258—259	0,9	$C_{12}H_{23}NO_2 \cdot HCl$	57,3	9,7	14,2	5,5	57,8	9,6		5,6	92
VIγ	H	OCOCH$_3$	228—229	0,6		57,6	9,9	14,2	6,1			14,2		87
VIIβ	OCOCH$_3$	C≡CH	233—233,5 d	0,8	$C_{14}H_{23}NO_2 \cdot HCl$	61,4	8,5	13,1	—	61,5	8,7	13,0	—	84
VIIγ	C≡CH	OCOCH$_3$	231—231,5 d	0,8		61,3	8,5	13,3	—					78
VIIIβ	OCOCH$_3$	C_2H_5	182—183	0,9	$C_{14}H_{27}NO_2 \cdot HCl$	60,6	9,9	12,6	—	60,7	10,1	12,8	—	92
VIIIγ	C_2H_5	OCOCH$_3$	203—204	0,7		60,2	9,7	12,6	—					81
IXγ	C_6H_5	OCOCH$_3$	108—109 b	0,9	$C_{18}H_{27}NO_2$	74,8	9,3	—	4,9	74,7	9,3	—	4,8	80
Xβ	OCOC$_6$H$_5$	H	237—237,5	0,9	$C_{17}H_{25}NO_2 \cdot HCl$	65,2	8,5	11,5	4,8	65,5	8,4	11,4	4,5	96
Xγ	H	OCOC$_6$H$_5$	247—248	0,7		65,4	8,5	11,5	5,0					72

[a] After sublimation in vacuum. [b] From hexane. [c] bp 88–89°C (5 mm). [d] mp of a mixture of compounds (VIIβ) and (VIIγ) 216–218°C.

The acetylation of the piperidinols (IIβ,γ-IVβ,γ) and (Vγ) with a mixture of acetic anhydride and acetyl chloride gave the hydrochlorides of the corresponding stereoisomeric acetates (VIβ,γ-VIIIβ,γ) and (IXγ). The reaction of the stereoisomeric piperidinols (IIβ,γ) with benzoyl chloride gave the stereoisomeric 4-benzoyloxy-1-tert-butyl-3-methylpiperidines (Xβ,γ). The properties and yields of the compounds synthesized are given in Table 1.

Judging from the results of TLC, the esterification of the stereoisomers of the alcohols (IIγ-IVγ) takes place more rapidly and easily than that of compounds (IIβ-IVβ), which, according to Mistryukov and Kucherov [4] shows the axial orientation of the hydroxy group in the alcohols (IIγ-Vγ) and its equatorial position in the isomers (IIβ-IVβ). This conclusion concerning the spatial orientation of the hydroxy groups of the piperidinols (IIβ,γ-IVβ,γ), in agreement with literature information [5-7], is also confirmed by the lower adsorption capacity and greater R_f values of compounds (IIγ-IVγ) as compared with their isomers (IIβ-IVβ) (Table 1), and also by the chromatographic mobility of compounds (IIβ,γ) on GLC [2].

To establish the configurations of the stereoisomeric alcohols (IIIβ,γ) and (IVβ,γ) and to confirm Mistryukov's conclusions [2, 3] on the spatial structure of compounds (IIβ,γ) and (Vγ), we made use of the IR spectra of the acetoxy and benzoyloxy derivatives obtained from them (VIβ,γ-Xβ,γ). In the spectra of the geometric isomers of the acetates (VIβ-VIIIβ) and the benzoate (Xβ) in the region of the stretching vibrations of the C−O bond of the acyloxy group at 1220-1280 cm^{-1} there is a singlet symmetrical absorption band [8-12], which is the spectral characteristic of the equatorial orientation of the acetoxy group of these compounds (Table 2). At the same time, the spectra of the acetates (VIγ-IXγ) and the benzoate (Xγ) are characterized by the presence in the same region of two or three absorption bands of similar frequency (Table 2), which confirms the axial arrangement of their acetoxy and benzoyloxy groups. The characteristics of the IR spectra of the derivatives (VIβ,γ-Xβ,γ) show the equatorial orientation of the hydroxy groups in the alcohols (IIβ-IVβ) corresponding to them and, consequently, their axial orientation in compounds (IIγ-Vγ).

We confirmed the spatial configurations of the piperidinols (IIβ,γ) and their acetoxy and benzoyloxy derivatives (VIβ,γ) and (Xβ,γ) established in this way by means of their PMR spectra, in which it was possible to identify the resonance signal of the 4-H proton deshielded by the neighboring hydroxyl or acyloxy group [13]. This signal, which is located in the 2.8-3.2-ppm-region (Table 3) can be considered to a first approximation as the X part of an ABCX spin system. A measurement of the width of this signal enabled the sum of its spin−spin coupling constants (SSCCs) with the vicinal protons in positions 3 and 5 (J_{34} and J_{45}) to be determined and by means of them, the axial or equatorial orientation of the 4-H proton [14-17].

TABLE 2. Frequencies of the Stretching Vibrations of the C–O Bonds of the Acetoxy and Benzoyloxy Groups in the IR Spectra of the Acetates (VIβ,γ-Xβ,γ) and the Benzoates (Xβ,γ)

Compound	Stretching vibrations, ν_{C-O}, cm^{-1}	Orientation of acyloxy group	Conformation of the molecule[a]
VIβ	1235	*e*	1*e*3*e*4*a*
VIγ	1225, 1240	*a*	1*e*3*e*4*e*
VIIβ	1250	*e*	1*e*3*e*4*a*
VIIγ	1225, 1245	*a*	1*e*3*e*4*e*
VIIIβ	1250	*e*	1*e*3*e*4*a*
VIIIγ	1220, 1255	*a*	1*e*3*e*4*e*
IXγ	1230, 1260, 1270	*a*	1*e*3*e*4*e*
Xβ	1280	*e*	1*e*3*e*4*a*
Xγ	1250, 1260, 1275	*a*	1*e*3*e*4*e*

[a]The orientation of the substituent on the nitrogen atom, of the 3-CH_3 group and of the 4-R substituent is shown.

TABLE 3. Chemical Shifts and Widths of the Signals of the 4-H Proton in the PMR Spectra of the Stereoisomers of 1-tert-Butyl-3-methylpiperidin-4-ols (IIβ,γ) and the Hydrochlorides of the 4-Acyloxy-1-tert-butyl-3-methylpiperidines (VIβ,γ; Xβ,γ)

Compound	Chemical shift δ, ppm	Width of signal (for extreme peaks), Hz	Solvent
IIβ	2,8	34	CCl_4
IIγ	3,2	14	CCl_4
VIβ	4,6	28	CD_3OD
VIγ	4,9	10	CD_3OD
Xβ	4,9	29	CD_3OD
Xγ	5,1	10	CD_3OD

In the case of axial orientation, the 4-H proton undergoes diaxial and axial–equatorial coupling with the 3-H and 5-H protons. Such a combination of splittings leads to a proton signal with a width of 28-34 Hz, reflecting the sum of the SSCCs of the vicinal protons $\Sigma J = J_{3a4a} + J_{4a5a} + J_{4a5e}$ [14-17]. In the case of the equatorial orientation of the 4-H proton, because of the smaller equatorial–axial and diequatorial couplings the sum of the SSCCs $\Sigma J = J_{3a4e} + J_{4e5a} + J_{4e5e}$ proves to be considerably smaller and, corresponding to it, the width of the signal of the 4-H proton should be of the order of 9-14 Hz [14-17].

In the PMR spectrum of the isomer (IIβ), the signals of the 4-H proton at 2.8 ppm form a multiplet with a width (between the extreme peaks) of 34 Hz, which shows the axial orientation of the 4-H proton and the equatorial orientation of the 3-CH_3 group [14-17]. In the spectrum of the geometric isomer (IIγ), the signal of the 4-H proton also appears in the form of a feebly resolved multiplet with a width of 14 Hz, which confirms its equatorial orientation [14-17], and is shifted downfield as compared with the signal of the 4-H proton in the isomer (IIβ), which is likewise characteristic for an equatorial proton [16].

In the spectra of the acetates (VIβ,γ) and of the benzoates (Xβ,γ), just as in their 1-methyl analogs [12], the signal of the 4-H proton deshielded by the neighboring acyloxy group is strongly shifted in the downfield direction (4.6-5.1 ppm) (Table 3). In the case of the acetate (VIβ) and the benzoate (Xβ), just as for the piperidinol (IIβ), the signal of the 4-H proton consists of a multiplet with a width of 28-29 Hz, which shows its axial position. In the spectra of the geometric isomers of the acetate (VIγ) and the benzoate (Xγ), the signal of the 4-H proton consists of a multiplet with a width of 10 Hz, which corresponds to the equatorial orientation of this proton. In the PMR spectra of compounds (VIγ and Xγ), just as in their 1-methyl analogs [12], the 4-H signal is shifted downfield as compared with the signal of this proton in either of compounds (VIβ, Xβ), which is also characteristic for an equatorial proton [16].

It follows from the features of the PMR spectra that the geometric isomers of the piperidinol (IIβ) and its acyloxy derivatives (VIβ, Xβ) have equatorially oriented 3-CH_3 and OH (or OCOR) groups and, consequently, the trans configuration relative to these substituents. In their turn, the isomeric alcohol (IIγ) and its acyloxy derivatives (VIγ, Xγ) are their epimers and have the cis configuration relative to the equatorial 3-CH_3 group and the axial hydroxy (or acyloxy) group.

The PMR spectra of the alcohols (IIIβ,γ, IVβ,γ) and of their acetates (VIIβ,γ, VIIIβ,γ) are not susceptible to first-order analysis, but the similar natures of the IR spectra of the acetates (VIβ-VIIIβ)

and (VIγ-VIIIγ) convincingly confirm the trans configuration of the alcohols (IIIβ, IVβ) and their derivatives (VIIβ, VIIIβ), on the one hand, and the cis configuration of their isomers (IIIγ, IVγ) and their acyloxy derivatives (VIIγ, VIIIγ) on the other hand.

EXPERIMENTAL

The IR spectra of the hydrochlorides were recorded on a UR-20 instrument in paraffin oil. The PMR spectra of solutions in CCl_4 and deuteromethanol with concentrations of about 20% were measured on a CHARTS-60-IL instrument at a working frequency of 60 MHz using TMS as internal standard. Thin-layer chromatography was performed on plates with nonfixed alumina of activity grade II using ether as solvent and iodine vapor as the chromogenic agent.

Geometric Isomers of 1-tert-Butyl-3-methylpiperidin-4-ol (IIβ,γ). A mixture of 2.8 g (13 mmoles) of the hydrochloride of 1-tert-butyl-3-methylpiperidin-4-ol (I), 6 g of aluminum isopropoxide, and 38 ml of isopropanol was boiled for 3 h 30 min, after which the reaction mixture was hydrolyzed with 25 ml of 50% aqueous caustic potash. The organic layer was extracted with ether and the extract was dried with $MgSO_4$. Elimination of the solvent yielded 2.25 g (96%) of a mixture of the stereoisomeric piperidinols (IIβ,γ), which were subjected to preparative separation on a chromatographic column (diameter 28 mm, 250 g of Al_2O_3 of activity grade II) using ether as the eluent. The first 16 portions of eluate (about 900 ml) yielded 1.37 g (61%) of the isomer (IIγ), and the subsequent portions (about 700 ml) 0.85 g (38%) of its epimer (IIβ).

Geometric Isomers of 1-tert-Butyl-4-ethynyl-3-methylpiperidin-4-ol (IIIβ,γ). At −50°C with the continuous passage of acetylene, a solution of 5 g of the piperidinone (I) in 20 ml of dry ether was added over 20 min to a suspension of sodium acetylide in liquid ammonia (from 1.15 g of sodium and 250 ml of liquid ammonia). The reaction mixture was stirred with the simultaneous passage of acetylene for another 6 h, after which it was left to stand for 15 h, during which time the temperature gradually rose to 18°C. The reaction mixture was hydrolyzed with 20 ml of water, and it was then saturated with potassium carbonate and extracted with 200 ml of ether. The combined ethereal extracts were neutralized with dry carbon dioxide (to slight turbidity). After the elimination of the solvent, 5.3 g (92%) of a mixture of the stereoisomers (IIIβ,γ) was obtained, and this was separated on a chromatographic column (diameter 60 mm, 530 g of Al_2O_3 of activity grade II) using chloroform as the eluent. The first 20 portions of eluate (about 400 ml) gave 1.3 g (24%) of (IIIγ), and the subsequent portions (about 900 ml) gave 3.8 g (72%) of its isomer (IIIβ).

1-tert-Butyl-4-ethyl-3-methylpiperidin-4-ols (IVβ,γ). A solution of 1.5 g of the piperidinol (IIIγ) in 150 ml of anhydrous ethanol was hydrogenated in the presence of a Raney nickel catalyst. Hydrogenation ceased after the absorption of 350 ml of hydrogen. The solvent was distilled off, giving 1.35 g (88%) of the ethylpiperidinol (IVγ). By a similar procedure, the acetylenic alcohol (IIIβ) yielded compound (IVβ).

Hydrochlorides of the Stereoisomers of 4-Substituted 4-Acetoxy-1-tert-butyl-3-methylpiperidines (VIβ,γ-IXβ,γ). To 0.02 mole of geometric isomer of one of the piperidinols (IIβ,γ-Vβ,γ) was added a mixture of 0.2 mole of acetyl chloride and 0.2 mole of acetic anhydride, after which the mixture was boiled moderately at 100-110°C for 1-2 h. The completeness of the reaction was checked by means of thin-layer chromatography. The hydrochlorides were precipitated and washed with dry ether, and they were then recrystallized from anhydrous ethanol.

Hydrochlorides of the Stereoisomeric 4-Benzoyloxy-1-tert-butyl-3-methylpiperidines (Xβ,γ). A mixture of 0.01 mole of the piperidinol (IIγ) and 0.04 mole of benzoyl chloride was boiled for about 1 h at 110-150°C. The completion of the reaction was checked by means of thin-layer chromatography. The hydrochloride of the benzoate (Xγ) that deposited was washed with dry ether and was recrystallized to constant melting point from anhydrous ethanol. The benzoate (Xβ) was obtained similarly from the piperidinol (IIβ).

LITERATURE CITED

1. É. A. Mistryukov, N. I. Aronova, and V. F. Kucherov, Izv. Akad. Nauk SSSR, Otd. Khim. Nauk, 932 (1961).
2. É. A. Mistryukov, G. T. Katvalyan, and G. N. Smirnova, Izv. Akad. Nauk SSSR, Ser. Khim., 1131 (1970).
3. É. A. Mistryukov and N. I. Aronova, Izv. Akad. Nauk SSSR, Otd. Khim. Nauk, 877 (1962).
4. É. A. Mistryukov and V. F. Kucherov, Izv. Akad. Nauk SSSR, Otd. Khim. Nauk, 627 (1961).
5. D. H. R. Barton, Experientia, 6, 316 (1950).

6. D. H. R. Barton, J. Chem. Soc., 1027 (1953).
7. B. V. Unkovskii, I. A. Mokhir, and E. M. Urinovich, Zh. Obshch. Khim., 33, 1808 (1963).
8. N. B. Chapman and R. E. Parker, J. Chem. Soc., 3634 (1960).
9. R. E. Lyle and G. G. Lyle, J. Org. Chem., 24, 1679 (1959).
10. O. V. Agashkin, G. S. Litvinenko, D. V. Sokolov, and S. S. Chasnikova, Zh. Obshch. Khim., 31, 862 (1961).
11. B. V. Unkovskii, Yu. F. Malina, I. P. Boiko, T. D. Sokolova, and M. G. Zaitseva, Zh. Organ. Khim., 3, 757 (1967).
12. T. D. Sokolova, Yu. V. Kolosov, Yu. F. Malina, S. V. Bogatkov, and B. V. Unkovskii, Khim. Geterotsikl. Soedin., 50 (1973).
13. I. N. Shoolery and M. T. Rogers, J. Amer. Chem. Soc., 80, 5121 (1958).
14. E. Garbish and D. Patterson, J. Amer. Chem. Soc., 85, 3228 (1963).
15. D. H. Williams and N. S. Bhacca, J. Amer. Chem. Soc., 86, 2742 (1964).
16. N. Bhacca and D. Williams, Applications of NMR Spectroscopy in Organic Chemistry, Holden–Day (1964).
17. B. I. Ionin and B. A. Ershov, NMR Spectroscopy in Organic Chemistry [in Russian], Khimiya, Leningrad (1967), p. 221.