SYNTHESIS AND THREE-DIMENSIONAL STRUCTURES OF GEOMETRICAL ISOMERS OF SOME 4-SUBSTITUTED 1,2,5-TRIMETHYL-4-ACETOXY- AND 1,2,5-TRIMETHYL-4-BENZOXYPIPERIDINES

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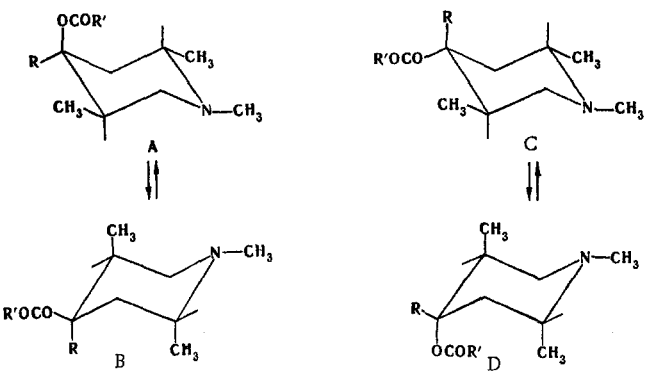
UDC 547.823:541.63:543.422:538.113

Stereoisomers of the corresponding 4-substituted 1,2,5-trimethyl-4-acetoxy- and 1,2,5-trimethyl-4-benzoxypiperidines were obtained by acylation of the geometrical isomers of 1,2,5-trimethyl-4-piperidol and its 4-ethynyl, 4-ethyl, and 4-phenyl-substituted derivatives. The preferred conformations of the investigated esters were elucidated by means of the PMR and IR spectra.

Continuing our investigation of the interrelationship between the structures and reactivities of stereoisomers of substituted 1,2,5-trimethyl-4-piperidols (I-IV), we found it necessary to ascertain the preferred conformations of their acetoxy and benzoxy derivatives. With this end in mind, we undertook the synthesis of the geometrical isomers of some substituted 1,2,5-trimethyl-4-acetoxy- and 1,2,5-trimethyl-4-benzoxypiperidines (Vβ, γ-XII β, γ) and elucidated their preferred conformations in solutions.



γ-Isomers β-Isomers

Vβ,γ R=H, R'=CH_3; VIβ,γ R=HC≡C, R'=CH_3; VIIβ,γ R=C_2H_5, R'=CH_3; VIIIβ,γ R=C_6H_5, R'=CH_3; IXβ,γ R=H, R'=C_6H_5; Xβ,γ R=HC≡C, R'=C_6H_5; XIγ R=C_2H_5, R'=C_6H_5; XIIγ R=C_6H_5, R'=C_6H_5.

The previously described [1-4] geometrical isomers of 1,2,5-trimethyl-4-piperidol (Iβ,γ) and its 4-ethynyl (IIβ,γ), 4-ethyl (IIIβ,γ), and 4-phenyl (IVβ, γ) derivatives* were used as the starting materials for the synthesis of esters Vβ,γ-XIIβ, γ.

*In [1] the geometrical isomers of Iβ,γ were designated as the α and β isomers, respectively, while IVβ was designated as the α isomer in [4].

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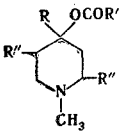
TABLE 1. Geometrical Isomers of 4-Substituted 1,2,5-Trimethyl-4-acyloxypiperidines and Their Analogs



Compound	R	R′	R″	mp, °C	Empirical formula	Found, %		Calc., %		Yield, %
						C	H	C	H	
Vγ	H	CH_3	CH_3	245—247	$C_{10}H_{19}NO_2 \cdot HCl$	54,1	9,0	54,2	9,1	65
Vβ				168—169		53,9	9,1			90
VIγ	C≡CH	CH_3	CH_3	209,5—210	$C_{12}H_{19}NO_2 \cdot HCl$	58,4	8,2	58,6	8,2	48
VIIγ	C_2H_5	CH_3	CH_3	171—172	$C_{12}H_{23}NO_2 \cdot HCl$	57,7	9,3	57,7	9,7	67
VIIβ				175—176,5		57,8	9,3			52
VIIIβ	C_6H_5	CH_3	CH_3	153,5—154,5	$C_{16}H_{23}NO_2 \cdot HCl$	64,6	8,1	64,5	8,1	46
IXγ	H	C_6H_5	CH_3	149—150	$C_{15}H_{21}NO_2 \cdot HCl$*	—	—	—	—	61
XIγ	C_2H_5	C_6H_5	CH_3	191—192	$C_{17}H_{25}NO_2 \cdot HCl$	65,3	8,5	65,4	8,4	64
XVIII	C≡CH	C_6H_5	H	176—177	$C_{15}H_{17}NO_2 \cdot HCl$†	—	—	—	—	79
XIX	C_2H_5	C_6H_5	H	156—157	$C_{15}H_{21}NO_2 \cdot HCl$‡	—	—	—	—	80

*Found: Cl 12.3; N 4.8%. Calculated: Cl 12.5; N 5.0%.
†Found: Cl 12.7; N 5.0%. Calculated: Cl 12.7; N 5.0%.
‡Found: Cl 12.6; N 5.0%. Calculated: Cl 12.5; N 4.9%.

In conformity with the configuration of the starting 4-piperidols (Iβ, γ-IVβ, γ) [5, 6], the investigated compounds (V-XII) are divided into two configurative series (the β and γ isomers) as a function of the three-dimensional orientation of the substituents in the 4 and 5 positions of the piperidine ring. The acyloxy group in geometrical isomers Vγ-XIIγ is in the cis position with respect to the adjacent methyl group but in the trans position relative to the same substituent in isomers Vβ-Xβ [5, 6].

The previously undescribed stereoisomeric acetates (Vβ, γ, VIγ, VIIβ, γ, and VIIIβ) and benzoates (IXγ and XIγ) were obtained as the hydrochlorides by acetylation of piperidol bases I-IV with acetic anhydride or a mixture of acetic anhydride and acetyl chloride and, respectively, by benzoylation with benzoyl chloride. The use of a mixture of anhydride and acetyl chloride for the acetylation makes it possible to lower the reaction temperature from 120-130° to 60-70°, shorten the reaction time, and obtain purer esters. Using a similar route, we obtained the previously described VIβ [2], VIIIγ [4], IXβ [1], Xβ, γ [2, 7], and XIIγ [8] that were also necessary for our investigation. In this case, it was qualitatively noted that acetates Vγ-VIIIγ and benzoates IXγ-XIIγ are formed more rapidly and more readily than their stereoisomers (Vβ-Xβ); this attests to the more facile esterification of the axially oriented hydroxyl group of the starting 4-piperidols (Iγ-IVγ) as compared with the equatorial hydroxyl group of Iβ-IVβ.

We were unable to accomplish the benzoylation of IIIβ and IVβ, since raising the reaction temperature and increasing the reaction time lead to the formation of products of the substitution of the hydroxyl group by chlorine or products of their dehydrochlorination. Benzoylation of 1-methyl-4-piperidol (XIII) [9], 1-methyl-4-ethynyl-4-piperidol (XIV) [10], and 1-methyl-4-ethyl- (XV) [10] and 1-methyl-4-phenyl-4-piperidols (XVI) [11] gave 4-substituted 1-methyl-4-benzoxypiperidines XVII-XX, which we used as model compounds. Benzoates XVII and XX were previously described in [9, 12], respectively. The properties and yields of the new acyloxypiperidines are presented in Table 1.

The configurations of Vβ, γ-XIIβ, γ are unambiguously predetermined by the three-dimensional structures of the starting piperidols (Iβ, γ-IVβ, γ), which were established in [5, 6], since the acylation of the hydroxyl group proceeds without involvement of the asymmetrical center and inversion of the three-dimensional configuration in the 4 position of the piperidine ring. At the same time, the preferred conformations of the investigated esters in solutions may differ substantially from the conformations of the starting piperidols (Iβ, γ-IVβ, γ) because of the difference in the conformational energy ($-\Delta G°$) of the OH and OCOR' groups [13] and the associated possibility of a shift in the conformational equilibria (A ⇌ B and C ⇌ D) to favor conformers B and C. This sort of shift of the conformational equilibria as a result of partial or complete conversion of the ring of conformer A seemed most likely for esters of piperidol Iγ (acetate Vγ and benzoate IXγ), which we also studied in greatest detail by means of the PMR and IR spectra.

TABLE 2. Chemical Shifts and Width of the Signal of the 4-H Proton in the PMR Spectra of Stereoisomers of 4-Substituted 4-Acycloxypiperidines

Compound	Chemical shift, ppm	Signal width with respect to the outside peaks, Hz	Solvent
Vγ	5,0	8,0	$CDCl_3$
	5,0	8,0	CD_3OD
Vβ	4,2	26,0	CCl_4
	4,4	25,5	$CDCl_3$
IXγ	5,05	20,0	$CDCl_3$
	5,05	20,5	C_6H_6
IXβ	5,01	19,5	CD_3OD
	4,6	25,5	$CDCl_3$
XVII	4,95	25,0	$CDCl_3$

TABLE 3. Vibrational Frequencies of the C–O Bonds of Acetoxy and Benzoxy Groups in the IR Spectra of Acetates V-XII and Benzoates XVII-XX

Compound	ν_{C-O}, cm^{-1}	Orientation of the acyloxy group	Molecular conformation*
Vβ	1250	*e*	2*e*4*a*5*e*
Vγ	1243, 1253	*a*	2*e*4*e*5*e*
VIβ	1240	*e*	2*e*4*a*5*e*
VIγ	1232, 1243, 1253	*a*	2*e*4*e*5*e*
VIIβ	1258	*e*	2*e*4*a*5*e*
VIIγ	1236, 1257	*a*	2*e*4*e*5*e*
VIIIβ	1240†	*e*	2*e*4*a*5*e*
VIIIγ	1225, 1235†	*a*	2*e*4*e*5*e*
IXβ	1280‡	*e*	2*e*4*a*5*e*
IXγ	1280‡	*e*	2*a*4*a*5*a*
Xβ	1280	*e*	2*e*4*a*5*e*
Xγ	1265, 1275	*a*	2*e*4*e*5*e*
XIγ	1255, 1285	*a*	2*e*4*e*5*e*
XIIγ	1240, 1285	*a*	2*e*4*e*5*e*
XVII	1280	*e*	4*a*
XVIII	1290	*e*	4*a*
XIX	1280, 1290	*a*	4*e*
XX	1280, 1295	*a*	4*e*

*The orientations of the CH_3 groups in the 2 and 5 positions and of substituent R in the 4 position of the piperidine ring are indicated.
† Spectrum of the hydrochloride in KBr pellets.
‡ Spectrum of a thin layer of the base.

In the PMR spectra of Vβ, γ and IXβ, γ, the signal of the 4-H proton, which is deshielded by the adjacent acyloxy group, is markedly shifted to weak field (4.2-5 ppm) (Table 2) and can therefore to a first approximation be regarded as the X part of the ABCX system. The 4-H signal at 4.2 ppm in the PMR spectrum of acetate Vβ is a sextet with a width (with respect to the outside peaks) of 26 Hz (Table 2); this attests to its axial orientation. It is precisely in this case that the sum of the constants of the vicinal spin–spin coupling of the 4-H proton with the adjacent 3-H and 5-H protons ($\Sigma J = 2J_{aa} + J_{ae}$) should be 25-30 Hz (assuming $J_{aa} \simeq$ 10-12 Hz and $J_{ae} \approx$ 3-5 Hz) [14, 15]. In contrast to this expectation, the 4-H signal in the spectrum of isomeric acetate Vγ appears as a weakly resolved multiplet with a width of 8 Hz. From this, it was concluded that this proton is equatorially oriented (since $\Sigma J = 2J_{ae} + J_{ee} \approx 8$ Hz in this case) and that Vβ and Vγ are epimers with respect to $C_{(4)}$ of the piperidine ring. The signal of the 4-H proton in the spectrum of Vγ is shifted to weak field as compared with the signal of this proton in the spectrum of Vβ; this is also characteristic for an equatorial proton [14]. Thus it follows from the PMR spectra that the molecules of acetates Vβ, γ in solutions do not undergo the A → B and C → D conversions and consequently have the same preferred conformation as in the starting secondary alcohols (Iβ, γ). The A → B conversion is also unlikely for acetates VIγ-VIIIγ, for which the A conformer is additionally stabilized by the equatorial orientation of substituent R. In geometrical isomers of acetates VIβ-VIIIβ, the existence of the C → D conversion and of preferred conformation D might have been expected only for VIIIβ.

As it turned out, A → B conversions are also absent for VIγ-VIIIγ, and C → D conversion is absent for their geometrical isomers (VIβ-VIIIβ), which is confirmed by the IR spectra (Table 3). Acetates Vβ-VIIIβ have a unique symmetrical absorption band in the region of the stretching vibrations of the C–O bond

(1200-1260 cm^{-1}); according to [16-18], this is evidence for an equatorial orientation of the acetoxy group of these compounds and their existence primarily as C conformers. At the same time, the spectra of the epimeric acetates (Vγ-VIIIγ) are characterized by the presence of two or three close-in-frequency absorption bands in the same region of the spectrum (Table 3).

This sort of character of the spectrum, which is associated with the axial orientation of the acetoxy group [16-18] of these compounds and the existence of primarily A conformers in solutions, is explained by the fact that in rotamers of the A type, rotation of the axial acetoxy group is restrained owing to its steric interaction with the axial 2-H and 6-H protons, which leads to the existence of several rotamers simultaneously.

In the PMR spectrum of benzoate IXβ, as in the spectrum of acetate Vβ, the signal of the 4-H proton appears as a sextet with a width of 25.5 Hz at δ 4.6 ppm (Table 2); this indicates that it is axially oriented [14, 15]. The signal of this proton is shifted to weak field by 0.2 ppm as compared with the signal of the 4-H proton of acetate Vβ, apparently because of the greater deshielding effect of the benzoxy group as compared with the acetoxy group. At the same time, it is shifted to strong field by 0.35 ppm as compared with the signal of the 4-H proton in the PMR spectrum of benzoate XVII; this may be explained by the shielding effect of the methyl groups in benzoate IXβ.

The signal of the 4-H proton in the PMR spectrum of benzoate IXγ is shifted to weak field as compared with the 4-H signal of isomer IXβ, but its width, which reflects the sum of the vicinal spin–spin coupling constants (ΣJ), is 19.5-20.5 Hz (Table 2) in all of the investigated solvents rather than 8 Hz as in the corresponding acetate (Vγ). This sort of width of the multiplet of the 4-H signal in the spectrum of IXγ can occur only for an axial orientation of this proton [14, 15]; this attests to conversion of the ring and to the existence in solutions of benzoate IXγ of the conformation equilibrium A $\rightleftharpoons$ B, which is shifted markedly to favor conformer B. The shift of the signal of the 4-H proton in IXγ to weak field as compared with the 4-H signal of its isomer (IXβ) is apparently associated with the anisotropy of the magnetic susceptibility of the axial 2-CH_3 group of the B conformer of IXγ. The shift of the A $\rightleftharpoons$ B conformational equilibrium in solutions of benzoate IXγ to favor conformer B because of conversion of the ring seems somewhat unexpected, since, in this case, two CH_3 groups prove to be simultaneously in the axial position. In connection with the fact that this sort of orientation may prove to be energically unfavorable, one cannot exclude the possibility of the existence of benzoate IXγ in a different conformation, for example, in the form of a distorted chair. As far as benzoates XIγ, XIIγ, XIX, and XX are concerned, the existence in solutions of them of preferred conformers B because of ring conversion A $\rightleftharpoons$ B is unlikely, since the advantageousness of conformers A additionally increases owing to the equatorial orientation of the bulky C_2H_5 and C_6H_5 groups. This is confirmed by their IR spectra. The literature does not contain any data on the possibility of the use of differences in the character of the absorption bands of the stretching vibrations of the C–O bond of the benzoxy group in the 1200-1300 cm^{-1} region for establishing its three-dimensional orientation in molecules of stereoisomeric benzoates of the IXβ, γ, Xβ,γ, XIγ, and XIIγ type. Nevertheless, we observed a definite analogy in the difference in the IR spectra of stereoisomers of acetates Vβ, γ-VIIIβ, γ and benzoates IXβ, γ and Xβ, γ. A complex multiplet absorption band at 1240-1290 cm^{-1} is observed in the spectra of benzoates Xγ-XIIγ and their analogs (XIX and XX); in analogy with [16-18], this is apparently a consequence of the axial orientation of the benzoxy group of these compounds. In contrast to the latter, the IR spectra of benzoates IXβ, Xβ, XVII, and XVIII contain a single symmetrical absorption band of the C–O bond, which, in analogy with [16-18], corresponds to an equatorial orientation of the benzoxy group.

One can expect a substantial contribution of conformers B and D to conformational equilibria A $\rightleftharpoons$ B and C $\rightleftharpoons$ D for the benzoates Xβ, γ and XVIII obtained from 4-ethynyl-4-piperidols IIβ,γ and XIV, since the conformational energy of the ethynyl group is low (0.18 kcal/mole [19]). The PMR spectra of these compounds do not provide an answer to this question, since analysis of the signals from the ring protons is difficult. Two bands are observed at 1240-1270 cm^{-1} in the IR spectrum of benzoate Xγ; this most likely is evidence for an axial orientation of the benzoxy group and for the existence of preferred conformer A in solutions of Xγ. However, these data cannot yet be considered as definitive proof of the conformation of benzoates Xβ, γ, XIγ, XIIγ and their analogs (XVIII-XX), and the problem of the preferred conformation of these compounds requires additional investigation.

EXPERIMENTAL*

The IR spectra of 0.03 M solutions of the bases in CCl_4 were recorded with a UR-20 spectrometer. The IR spectra of the hydrochlorides were obtained from mineral oil suspensions and KBr pellets. The

*L. B. Vinberg and A. I. Lutsyka participated in the experimental work.

PMR spectra were measured with a CHART S-60-IL spectrometer with an operating frequency of 60 MHz with tetramethylsilane as the internal standard.

Hydrochlorides of the Stereoisomers of 4-Substituted 1,2,5-Trimethyl-4-acetoxypiperidines (Vβ, γ-VIIIβ, γ) (Table 1). A mixture of 0.028 mole of acetyl chloride and 0.028 mole of acetic anhydride was added to a solution of 0.014 mole of the stereoisomeric piperidols (Iβ, γ-IVβ, γ) in 30 ml of dry benzene, and the mixture was refluxed moderately for 1-4 h. The end of the reaction was monitored by means of thin-layer chromatography. The precipitated acetate hydrochloride crystals were removed by filtration, washed with dry ether, and recrystallized from acetone–alcohol.

Hydrochlorides of 4-Substituted 1,2,5-Trimethyl-4-benzoxypiperidines (IXβ, γ-XIIβ, γ) and Their Analogs (XVII-XX) (Table 1). A 0.06-mole sample of benzoyl chloride was added to a solution of 0.023 mole of piperidols Iβ, γ-IVβ, γ and XIII-XVI in 40 ml of dry benzene, and the mixture was refluxed moderately for 2-2.5 h. The end of the reaction was monitored by means of thin-layer chromatography. The benzene was removed by distillation, and the crystalline precipitated benzoate hydrochlorides were recrystallized from acetone–ethanol.

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