THE IR ABSORPTION SPECTRA AND SPATIAL STRUCTURE OF THE STEREOISOMERIC 1, 2, 5-TRIMETHYL-4-HYDROXYPIPERIDYL-4-CARBINOLS

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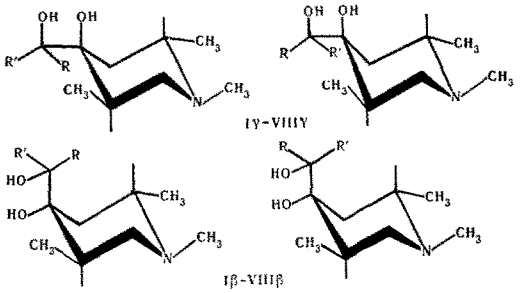
The spatial structure of the geometric isomers of some 1, 2, 5-trimethyl-4-hydroxypiperidyl-4-carbinols is investigated with the aid of IR spectroscopy, and their spatial configurations and conformations are explained by analysis of the intramolecular hydrogen bonding.

The object of this work was to examine the spatial configurations and conformations of the stereoisomeric 1, 2, 5-trimethyl-4-hydroxypiperidyl-4-carbinols (Iβ, γ–VIIIβ, γ) which we had previously prepared [1]. These differed in the spatial orientation of the substituents on C-4 of the piperidine ring, and also, in several cases, in the spatial configuration at the asymmetric carbinol center in the side chain. The spatial structure of Iβ, γ–VIIIβ, γ was determined by the configurations and conformations of the starting α-ketols and α-hydroxyesters, which have been determined by IR spectroscopy [2, 3].



Iγ–VIIIγ

Iβ–VIIIβ

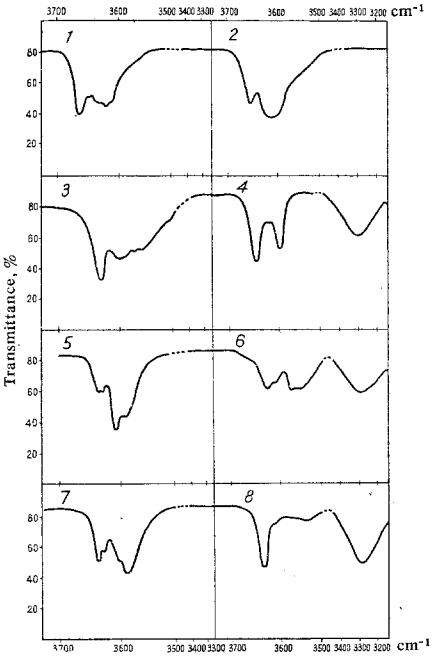
I R = R′ = H; II R = CH_3, R′ = H; III R = C_6H_5, R′ = H; IV R = CH_3, R′ = C_6H_5; V R = C_6H_5, R′ = CH_3; VI R = C_2H_5, R′ = C_6H_5; VII R = C_6H_5, R′ = C_2H_5; VIII R = R′ = C_6H_5

The most probable spatial disposition of the substituents at the asymmetric center in the side chain in the diastereoisomeric glycols IIβ, γ–VIIβ, γ was established previously [1] by the rule of asymmetric induction [4] on the basis of the stereospecificity of the mode of synthesis of these compounds.

It was necessary to confirm the validity of the conclusions concerning stereochemistry which were arrived at in [1], and to examine the conformational properties of the molecules in question in connection with the spatial orientation and mutual positions of the three functional groups.

Much information on the configuration of the asymmetric carbinol centers in the glycols IIβ, γ–VIIβ, γ is obtained by examination of the IR spectra of their solutions in the valency vibrational region of the hydroxyl group. It is known [5–7] that the diastereoisomeric (erythro- and threo-) α-glycols, and related compounds with vicinal functional groups, for example β-amino alcohols [6], differ considerably in their IR spectra in this region, the threo-isomers usually being characterized by more stable hydrogen bonding. On the other hand, the spatial orientation and mutual disposition of the functional groups in the molecules of the glycols Iβ, γ–VIIIβ, γ must have a substantial effect on the nature of the intramolecular hydrogen bonds in these compounds. We therefore measured the IR spectra of solutions of the glycols Iγ–VIIIγ and Iβ–VIIIβ in the 3100–3700 cm^{-1} region, in concentrations from 10^{-3} to $5 \cdot 10^{-3}$ molar to exclude the possibility of intermolecular association (measurement of the relationship between the observed bands and concentration showed that, in the range of concentrations from 10^{-2} to 10^{-4} M, no change occurred in the relative intensities of the bands due to 'bound' and 'free' hydroxyl groups). The results of these measurements are given in the Table.

From the general principles of conformational analysis, and investigations of the conformation of the starting α-ketoalcohols and α-hydroxyesters [2, 3], the glycols Iγ–VIIγ must be related to conformationally similar



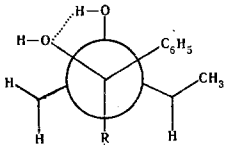
IR Absorption spectra of stereoisomeric 1, 2, 5-trimethyl-4-hydroxypiperidyl-4-carbinols. 1) 1, 2, 5-Trimethyl-4-hydroxypiperidyl-4-carbinol (Iγ); 2) 1, 2, 5-Trimethyl-4-hydroxypiperidyl-4-carbinol (Iβ); 3) 1, 2, 5-Trimethyl-4-diphenylcarbinol (VIIIγ); 4) 1, 2, 5-Trimethyl-4-hydroxypiperidyl-4-diphenylcarbinol (VIIIβ); 5) threo-1, 2, 5-Trimethyl-4-hydroxypiperidyl-4-ethylphenylcarbinol (VIγ); 6) threo-1, 2, 5-Trimethyl-4-hydroxypiperidyl-4-ethylphenylcarbinol (VIIβ); 7) erythro-1, 2, 5-Trimethyl-4-hydroxypiperidyl-4-ethylphenylcarbinol (VIIγ); 8) erythro-1, 2-5-Trimethyl-4-hydroxypiperidyl-4-ethylphenylcarbinol (VIβ).

compounds.

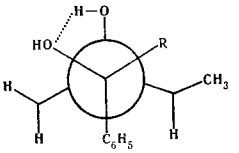
Comparison of molecular models shows that, in compounds of this type, the formation of intramolecular hydrogen bonds is possible by the interaction of the vicinal hydroxyl groups, and also of one of the hydroxyl groups with the neighboring phenyl group, as in the OH... π interaction investigated in [7, 8] in the case of β-vinyl and β-arylethanols.

The spectra of the glycols Iγ–VIIIγ (see figure) show valency vibrational bands due to the free hydroxyl groups at 3605–3650 cm^{-1}, and wide, sometimes weakly split, bands due to the bound hydroxyl groups at 3560–3595 cm^{-1}. The regular reduction in the frequency of the valency vibrational bands in the glycols Iγ (3647 cm^{-1}), IIγ, IIIγ (3630–3635 cm^{-1}), and IVγ–VIIIγ (3605–3620 cm^{-1}) allows these bands to be assigned to the vibrations of the primary, secondary, and tertiary hydroxyl groups, respectively, on the carbinol carbon atom in the side chain (a similar regularity in the change in frequency of the vibrational bands due to free hydroxyl groups has been observed [9] in the primary, secondary, and tertiary cyclohexanediols). Consequently, in the formation of intramolecular OH... OH hydrogen bonds in these compounds, the proton donors must be predominantly the axial hydroxyl groups at C-4 of the piperidine ring.

In order to determine the erythro- and threo-configurations in the diastereoisomeric pairs of glycols IVγ, Vγ and VIγ, VIIβ, the absorptions in the valency vibrational region of the bound hydroxyl groups were examined. The configurations at the asymmetric carbinol centers were determined by the mutual positions of the hydroxyl groups, and the substituents with the greatest effective volume [1].



γ-erythro-isomers



γ-threo-isomers

The spectroscopic method for the identification of the erythro and threo-configurations in a series of diastereoisomeric α-glycols and β-amino alcohols has previously been based on a comparison of the shift in frequency of the bound hydroxyl bands (Δ_νOH-threo > Δ_νOH-erythro) [5, 6], or the ratio between the molar extinction coefficients of the bound and free hydroxyl bands ($\varepsilon_{bound}/\varepsilon_{free}$)threo- > ($\varepsilon_{bound}/\varepsilon_{free}$) erythro- [7]. Neither of these methods is of universal applicability, and their use becomes very difficult in complex systems which are capable of various modes of intramolecular interaction. Our compounds may be said to belong to such systems. Their spectra typically show a complex curve in the OH vibrational region, with the bands due to the free and bound hydroxyl groups intersecting to a greater or lesser extent, thus rendering extremely unreliable any measurement of the above-mentioned parameters.

It is also well known that the nature of the intramolecular hydrogen bonds is usually reflected fairly clearly in the values of the integral intensities of the bands due to the bound hydroxyl groups [10]. When significant intersection of the curves for the free and bound hydroxyl groups occurs, the only parameter which can be measured reliably is the total integral intensity. It may therefore be suggested with a considerable degree of confidence that an increase in the relative intensity of the band due to the bound hydroxyl groups must be accompanied by an increase in the total integral intensity.

Inspection of molecular models of the glycols IVγ–VIIγ shows that the formation of both possible types of intramolecular hydrogen bonds (OH... OH and OH... Ph) is more preferred in the threo-isomers, other things being equal. Consequently, in each pair of erythro- and threo-isomers, it is to be expected that there will be significant differences in the values of the total integrated intensities of the valency vibration bands of the OH group. Our measurements (see table) fully confirm this assumption. Isomers IVγ and VIγ, which were assigned the threo-configuration according to Cram's rule [1], actually show large values for the total integral intensities in comparison with the corresponding erythro-isomers Vγ and VIIγ, and their analogs IIγ and IIIγ.

Amongst compounds Iγ–VIIIγ, the spectrum of the glycol VIIIγ is especially noteworthy in that it shows an anomalous broad band due to the hydroxyl group, with maxima at 3565 and 3520 cm^{-1}. The absorption at 3520 cm^{-1} may be assigned to vibration of the OH... N bond, by analogy with the related similar band (3539 cm^{-1}) in the spectra of 3-piperidols [11] in the "chair" conformation. The formation of bonds of this type in the glycol VIIIγ could occur as

a result of substantial deformation of the valency angle at C-4, bringing the ring into a more planar "chair" conformation [9], and favoring the approach of the nitrogen atom and the hydroxyl group in the side chain. Such a deformation, of course, would become particularly apparent in the glycol VIIIγ, in the series Iγ–VIIIγ, since it possesses a bulky diphenylcarbinol substituent on the C-4 of the piperidine ring.

Frequencies and Integral Intensities of the Valency Vibrations of the Hydroxyl Groups in the IR Spectra of the Stereoisomeric 1, 2, 5-Trimethyl-4-hydroxypiperidyl-4-carbinols

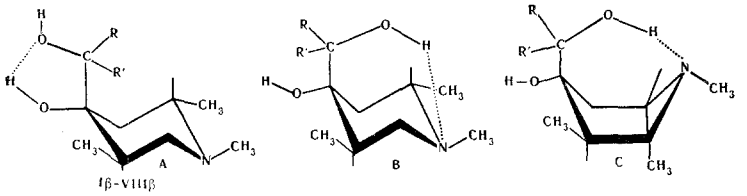
Compound	R	R′	Diastero-isomer	Vibration frequency, cm^{-1}				Integral intensities, $10^4 l \cdot mole^{-1} \cdot cm^{-2}$	
				νOH-free	νOH-bound			A_1*	A_2**
Iγ	H	H	—	3647	3580—3592	—	—	0.89	—
IIγ	CH_3	H	Erythro	3635	3568—3580	—	—	0.90	—
IIIγ	C_6H_5	H	Erythro	3630	3570—3602	—	—	0.65	—
IVγ	CH_3	C_6H_5	Threo	3612	3567—3582	—	—	1.09	—
Vγ	C_6H_5	CH_3	Erythro	3617	3566—3579	—	—	0.86	—
VIγ	C_2H_5	C_6H_5	Threo	3615	3565—3582	—	—	1.02	—
VIIγ	C_6H_5	C_2H_5	Erythro	3620	3568—3580	—	—	0.95	—
VIIIγ	C_6H_5	C_6H_5	—	3605	3565 broad	3520 broad	—	1.20	—
Iβ	H	H	—	3647	3585—3602	—	—	0.85	—
IIβ	CH_3	H	Threo	3634	3581	—	3350	0.53	0.69
IIIβ	C_6H_5	H	Threo	3623	3582	—	3320	0.79	0.21
IVβ	CH_3	C_6H_5	Erythro	3631	3580 weak	3535	3300	0.52	0.99
Vβ	C_6H_5	CH_3	Threo	3612	3550—3565	—	3280	0.71	0.85
VIβ	C_2H_5	C_6H_5	Erythro	3630	—	3520	3290	0.42	1.33
VIIβ	C_6H_5	C_2H_5	Threo	3615	3550—3566	—	3280	0.65	0.93
VIIIβ	C_6H_5	C_6H_5	—	3638	3587	—	3300	0.74	0.97

*A_1 is the total integral intensity of the free and bound hydroxyl groups in the 3500-3650 cm^{-1} region.

**A_2 is the integral intensity of the bands at 3300 cm^{-1}.

In the spectra of the glycols Iβ–VIIIβ (see figure), as also in their epimers Iγ–VIIIγ, a regular reduction in the free hydroxyl vibration frequency is observed on passing from Iβ (3647 cm^{-1}) to IIβ, IIIβ (3634–3623 cm^{-1}) and Vβ, VIIβ (3612–3615 cm^{-1}). In the ditertiary glycols IVβ, VIβ, and VIIIβ, these frequencies have significantly higher values (3630, 3631, and 3638 cm^{-1}) than in Vβ, VIIβ, and IVγ–VIIIγ.

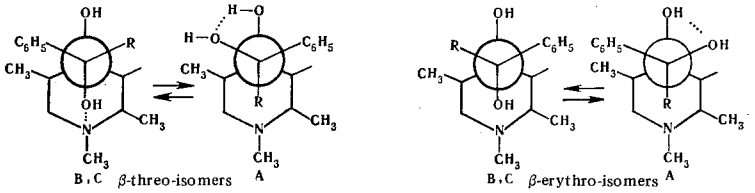
At the same time, the spectra of glycols IIβ–VIIIβ differ considerably from those of their epimers IIγ–VIIIγ. This difference is related to the appearance in the spectra of IIβ–VIIIβ of strong absorption bands between 3280 and 3350 cm^{-1}, except in the case of Iβ, where this band is absent. From inspection of molecular models and consideration of the conformations of the starting ketols of the β-configuration [2], it may be concluded that compounds IIβ-VIIIβ are capable of existing in solution as mixtures of the conformers A, B, and C as a result of rotameric conversions, caused by rotation of the carbinol grouping in the side chain around the C-4 to C-7 bond.



The spectra of IIβ–VIIIβ should in principle, therefore, show the three types of absorption bands due to the bound hydroxyl groups participating in the OH... OH and OH... Ph bonds, the OH... N bond in the "chair" conformation of the rotamer B, and the OH... N bond in the "boat" conformation of rotamer C. These compounds do, in fact, show these three types of absorption due to the bound hydroxyl group (see figure). The bands at 3550–3600 cm^{-1} are very similar in shape and position to the absorption bands of the bound hydroxyl groups in the spectra of glycols Iγ–VIIIγ, and may, therefore, be assigned to the same type of vibrations (OH... OH and OH... Ph). The bands between 3520 and 3535 cm^{-1} are assigned to the OH—N vibrations in the "chair" conformation [11] of the rotamers B. The strong band at 3280–3350 cm^{-1} must apparently be assigned to the vibration of the hydroxyl group participating in the OH... N hydrogen bond in the "boat" conformation of the rotamers C. It will be seen from the Table that glycols IIβ–VIIIβ exist as equilibrium mixtures of the conformers A, B, and C, whilst the less sterically hindered compound Iβ exists exclusively as the rotamer A. It follows from measurements of the integral intensities of the bands at 3280–3350 cm^{-1} that as the effective volume of the substituent on the carbinol atom in the side chain increases in the series IIIβ, IVβ,

Vβ, VIβ, VIIβ, VIIIβ, so does the relative proportion of the conformer C. At the same time, compounds IIβ–VIIIβ may be divided into two types, according to the nature of their spectra. The spectra of compounds of the first type (IIβ, IIIβ, Vβ, VIIβ) show relatively strong bands at 3550–3580 cm^{-1}, but no bands at 3500–3540 cm^{-1}. The spectra of compounds of the second type (IVβ and VIβ) are characterized by a substantial reduction in intensity, or absence, of absorption at 3550–3590 cm^{-1}, and the appearance of bands at 3520–3535 cm^{-1}. Since the latter bands have been assigned above, it may be concluded that the relative proportion of the rotameric form B in the "chair" conformation in compounds of the first type is increased relatively to compounds of the second type. The total integral intensity of the bands due to the free and bound hydroxyl groups in the "chair" conformation (3500–3650 cm^{-1}) in compounds of the first type ($0.5-0.8 \cdot 10^4 \cdot l \cdot mole^{-1} \cdot cm^{-2}$) is increased relatively to that of compounds of the second type ($0.4-0.5 \cdot 10^4 \cdot l \cdot mole^{-1} \cdot cm^{-2}$). At the same time as the change in the integral intensity of the OH... N band at 3280–3350 cm^{-1} occurs (characterizing the contribution of conformation C), an inverse relationship is observed in the two types of compound under consideration ($0.2-0.9 \cdot 10^4 \cdot l \cdot mole^{-1} \cdot cm^{-2}$). These results show that both the rotameric conversion A ⇌ B, and also the conformational equilibrium A ⇌ C and B ⇌ C, depend to a large extent, not only on the effective volume, but also on the spatial disposition (erythro- and threo-configurations) of the substituents on the carbinol atom in the side chain.

It follows from inspection of molecular models that in the threo-isomers, as a result of the substantial repulsion of the bulky phenyl group and the methyl group at C-5, the rotamers B and C are less favored, and for this reason, in these compounds intramolecular hydrogen bonds of the OH... OH and OH... Ph type are formed preferentially, leading to the formation of rotamer A. At the same time, in the erythro-isomers, by the same reasoning the formation of OH... N bonds is preferred, giving rotamers B and C.



Thus, the glycols IIβ, IIIβ, Vβ, and VIIβ, which give spectra of the first type, are of course assigned the threo-, and compounds IVβ and VIβ, with spectra of the second type, the erythro-configurations. This is in agreement with the configurations of these compounds as derived from steric directivity of their synthesis, [1] and from the rule of asymmetric induction [4].

Comparison of the spectra of the stereoisomeric glycols Iγ–VIIIγ and their epimers Iβ–VIIIβ indicates that, in the rotameric conversion A ⇌ B ⇌ C, in none of the glycols Iβ–VIIIβ does conversion of the piperidine ring occur.

EXPERIMENTAL

The spectra of the compounds were measured on a double beam UR-10 spectrometer with KBr optics (400–700 cm^{-1}), and LiF (2000–4000 cm^{-1}), in CCl_4 solution at concentrations of 10^{-3} to $5 \cdot 10^{-3}$ M, and in absorbing layers of thickness 0.5–2 cm.

The integral intensities of the valency vibration absorption bands of the free and bound hydroxyl groups were measured at 23°. The scanning speed did not exceed 32 cm^{-1}/min. The spectral slit width in the 3200–3350 cm^{-1} region was 3.9 cm^{-1}, in the 3470–3490 cm^{-1} region 4.5 cm^{-1}, and in the 3605–3615 region 5.7 cm^{-1}. The linearity of the rotameric scale of the instrument was checked by the method described in [12]. The integral optical densities were calculated by the numerical integration of the observed dispersion function $D_\nu = \ln(I_0/I)_\nu = f(\nu)$, corresponding to the experimental shape of the band, cut off at the base line.

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