STEREOSPECIFICITY OF THE ADDITION OF HYDROGEN CYANIDE TO THE CARBONYL GROUP OF SUBSTITUTED 4-PIPERIDONES. SYNTHESIS AND THREE-DIMENSIONAL STRUCTURES OF SUBSTITUTED 4-HYDROXY-4-CYANOPIPERIDINES

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Mixtures of stereoisomers of the corresponding 4-hydroxy-4-cyanopiperidines were synthesized by the reaction of substituted 4-piperidones with hydrogen cyanide by an exchange reaction with acetone cyanohydrin. The ratios of the stereoisomers in the resulting mixtures of stereoisomeric 4-piperidone cyanohydrins were determined by means of the ^{13}C NMR spectra, and the three-dimensional structures were established by direct determination of the orientation of the cyano group in their molecules. A dependence of the quantitative ratios of the stereoisomeric cyanohydrins of the substituted 4-piperidones on the reaction temperature was demonstrated.

The investigation of the stereospecificity of the addition of hydrogen cyanide to the carbonyl group of substituted 4-piperidones by determination of the compositions and three-dimensional structures of the resulting stereoisomeric 4-hydroxy-4-cyanopiperidines is an important stage in the search for methods for the synthesis of physiologically active compounds of the piperidine series. A number of studies [1-4], in which contradictory data on the compositions and three-dimensional structures of the stereoisomers formed, have been devoted to this problem. The stereochemistry of the cyanohydrin synthesis has been studied in greater detail in a number of six-membered ketones of the cyclohexane series [5-8]. However, in all of these studies the determination of the quantitative ratios and three-dimensional structures of the geometrical isomers of cyanohydrins was carried out on the basis of data obtained by an indirect method – by conversion of the resulting stereoisomeric cyanohydrins to the corresponding derivatives (ketols and hydroxy ethers) and determination of their three-dimensional structures by means of the IR and UV spectra.

To ascertain the stereospecificity of the addition of hydrogen cyanide to the carbonyl group of substituted 4-piperidones we used the possibility of establishing the three-dimensional structures and quantitative ratios of the resulting stereoisomers of cyanohydrins of the piperidine series by means of the direct determination of the orientation of the cyano group by ^{13}C NMR spectroscopy.

TABLE 1. 4-Hydroxy-4-cyanopiperidines IX-XIV*

Compound	Empirical formula	mp, °C (from ethyl acetate)	IR spectrum, ν, cm^{-1}	Yield, %
α,β-IX	$C_{13}H_{16}N_2O$	134...135	2225 (C≡N), 3020 (OH), 3290 (NH)	75
α,β-X	$C_{14}H_{18}N_2O$	139...141	2230 (C≡N), 3020 (OH), 3285 (NH)	78
α,β-XI	$C_{13}H_{16}N_2O$	115...116	2225 (C≡N), 3150 (OH)	81
α,β-XII	$C_{14}H_{18}N_2O$	94...98	2225 (C≡N), 3040 (OH)	84
α,β-XIII	$C_{14}H_{18}N_2O$	141...143	2225 (C≡N), 3070 (OH)	82
α,β-XIV	$C_{15}H_{20}N_2O$	123...124	2220 (C≡N), 3080 (OH)	85

*The mixture of cyanohydrins α,β-VIII has mp 145-146°C according to the data in [2].

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TABLE 2. ^{13}C NMR Spectra of 4-Hydroxy-4-cyanopiperidines VIII-XIV*

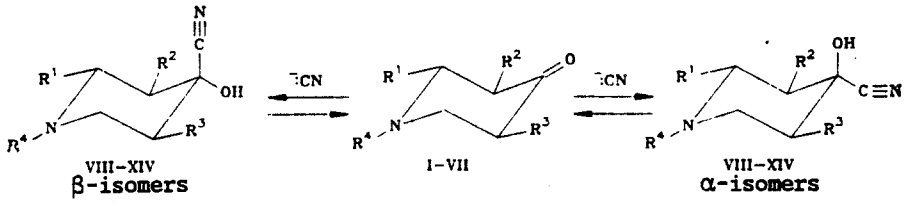
Compound	Stereoisomer	Orientation of the C=N group	δ, ppm (half widths of the unresolved multiplet signals, Hz)									
			$C_{(2)}$	$C_{(3)}$	$C_{(4)}$	$C_{(5)}$	$C_{(6)}$	C≡N	N—CH_3	2-R**	3-CH_3	5-CH_3
VIII	α	*e*	51,0	37,7	67,1	40,3	56,0	121,5 (7)	45,2	18,4 (7)	—	12,1 (8)
	β	*a*	55,1	38,3	71,5	41,0	59,6	119,5 (21)	44,2	18,6 (7)	—	11,9 (7)
IX	α	*e*	62,6	***	70,5	***	***	123,3 (7)	—	142,8 (11)	13,4 (8)	—
	β	*a*	66,6	44,4	74,4	***	***	121,4 (24)	—	142,2 (11)	12,4 (6)	—
X	α	*e*	59,9	44,5	72,3	***	***	120,7 (6)	—	142,0	***	12,8
	β	*a*	64,6	46,1	76,7	40,7	49,8	117,9 (20)	—	141,3	11,2	12,3
XI	α	*e*	63,3	44,4	64,6	35,9	49,8	121,9 (7)	43,1	141,8	—	—
	β	*a*	66,6	45,8	68,3	37,1	52,9	121,1 (24)	42,6	141,3	—	—
XII	α	*e*	69,8	44,5	68,6	37,3	49,6	121,6 (8)	43,6	140,4	13,0 (7)	—
	β	*a*	73,1	46,0	72,6	37,7	52,8	119,7 (24)	43,3	140,1 (11)	12,1 (7)	—
XIII	α	*e*	68,9	45,9	69,6	38,5	56,6	122,1 (8)	43,1	141,9	—	13,2
	β	*a*	72,0	46,9	74,1	40,0	60,0	120,2 (22)	42,6	141,2 (10)	—	12,9 (7)
XIV	α	*e*	70,1	45,3	***	***	57,0	120,6 (5)	43,8	141,0	***	13,4
	β	*a*	73,4	46,6	77,5	40,3	60,3	117,9 (18)	43,3	140,4 (11)	12,2	12,9 (7)

*In d_6-DMSO for VIII-X and XIII; in $CDCl_3$ for XI, XII, and XIV.

**VIII R = CH_3; IX-XIV R = C_{quat} C_6H_5.

***Signal not identified.

As the starting 4-piperidones we used the industrially accessible piperidone I, which is a mixture of 2a5e-cis and 2e5e-trans isomers [9], as well as a number of substituted 2-phenyl-4-piperidones (II-VII), which are stereohomogeneous compounds with an equatorial orientation of all of the ring substituents [10]. The conversion of 4-piperidones I-VII to the corresponding substituted 4-hydroxy-4-cyanopiperidines VIII-XIV (Table 1) was carried out by a known method [11]. The compositions and three-dimensional structures of the stereoisomers formed were established on the basis of the ^{13}C NMR spectra (Table 2) with complete broad-band suppression of the protons, as well as on the basis of the monoresonance spectra (without decoupling of the protons).



Compound	R^2	R^3	R^4	Compound	R^2	R^3	R^4	Compound	R^2	R^3	R^4
I	H	CH_3	CH_3	VI	H	CH_3	CH_3	XI	H	H	CH_3
II	CH_3	H	H	VII	CH_3	CH_3	CH_3	XII	CH_3	H	CH_3
III	CH_3	CH_3	H	VIII	H	CH_3	CH_3	XIII	H	CH_3	CH_3
IV	H	H	CH_3	IX	CH_3	H	H	XIV	CH_3	CH_3	CH_3
V	CH_3	H	CH_3	X	CH_3	CH_3	H				

* I, VIII $R^1=CH_3$; III—VII, IX—XIV $R^1=C_6H_5$.

The spatial orientation of the cyano group relative to the ring can be determined unambiguously by means of NMR spectroscopy from the magnitude of the vicinal constant of spin-spin coupling (SSC) between the nucleus of the carbon atom of the CN group and the 3-H and 5-H protons of the piperidine ring, since it is known that $^3J_{CH}$ is characterized by a Karplus dependence on the dihedral angle [12, 13] (Table 2). Since the direct determination of the J_{CH} long-range spin–spin coupling constants (SSCC) from the spectra without proton decoupling is, as a rule, impossible [14], we used the method proposed in [15]. The orientations of the substituents attached to the quaternary carbon atoms were determined taking into account the fact that the width of the multiplet of the X nucleus in ABS, ABCX, etc., spin systems (here A, B, and C are the protons and X is the carbon nucleus) is close to the sum of all of the small constants of SSC of the X nucleus with the B, A, and C nuclei [16].

The width of the signal of the nucleus of the carbon atom of the cyano group in the spectra of the β isomers of cyanohydrins VIII-XIV is 18-24 Hz; this is in agreement with the presence in this fragment of two axial-axial vicinal constants of CH and thus provides unambiguous evidence for an axial orientation of the CN group in these isomers. The width of the analogous signal in the spectra of the α isomers of VIII-XIV is equal to 5-8 Hz, which is possible only in the case of an equatorial orientation of the cyano group.

The signals of the ^{13}C nuclei of the cyano group in the spectra of the β isomers are located at stronger field (117.9-121.4 ppm) as compared with the corresponding signals in the spectra of the α isomers (120.6-123.3 ppm); it should be noted that the difference in the chemical shifts (CS) of these signals in the spectra of the α and β isomers increases with an increase in the number of methyl substituents attached to the $C_{(3)}$ and $C_{(5)}$ atoms of the piperidine ring (XI-XIV).

The orientation of the substituents attached to the $C_{(2)}$, $C_{(3)}$, and $C_{(5)}$ atoms was established on the basis of the CS of the carbon nuclei of these groups in the spectra with complete proton decoupling, as well as from the half widths of the individual components of the quartets of the methyl groups and the singlet of the quaternary carbon atom of the phenyl group in the ^{13}C monoresonance spectra [15].

The determination of the quantitative ratios of the α and β isomers in mixtures of the stereoisomers of cyanohydrins VIII-XIV was carried out from the integral intensities of the analogous signals in the ^{13}C NMR spectra [17].

The ratios of the stereoisomers as a function of the temperature conditions under which the reaction was carried out were obtained (Table 3).

On the basis of an analysis of the ^{13}C NMR spectroscopic data for the mixtures of cyanohydrins formed we established that the addition of hydrogen cyanide to the carbonyl group of substituted 4-piperidones I-VII generally proceeds stereospecifically and leads to the formation of mixtures of two stereoisomers of the corresponding substituted cyanohydrins VIII-XIV

TABLE 3. Ratios of the Stereoisomers in Substituted Cyanohydrins VIII-XIV

T_r,* °C	α:β ratio						
	VIII	IX	X	XI	XII	XIII	XIV
83...95	0,8:1	0,5:1	0,3:1	0,8:1	0,4:1	0,5:1	0,2:1
20...22	0,6:1	—	—	—	0,1:1	—	0:1
0...3	0,2:1	—	—	—	0:1	—	0:1

*This is the reaction temperature.

with preponderance of the β stereoisomers in them. The latter are obtained by axial incorporation of the cyano group during nucleophilic attack by the cyanide ion at the carbonyl group of the 4-piperidones. The stereospecificity of the reaction depends on the structure of the starting piperidones. When axial methyl substituents attached to the $C_{(2)}$ and $C_{(6)}$ atoms of the piperidine ring are absent, an increase in the number of such substituents in the α position in the carbonyl group leads to stereoselectivity of the reaction, which is expressed in an increase in the percentages of the mixtures of the β stereoisomers of the cyanohydrins with an axial orientation of the cyano group of XI-XIV. However, the orientations of the substituents in the piperidine ring of cyanohydrins IX-XIV remain the same (equatorial), as in the starting piperidones II-VII. We simultaneously observed that the mixture of the cis and trans isomers of 1,2,5-trimethyl-4-piperidone (I), which is 25% enriched in the cis form, according to the method in [18], with an axial 2-CH_3 group on reaction with acetone cyanohydrin at 20-22°C also forms a mixture of two stereoisomers of cyanohydrin α,β-VIII in a ratio of 0.8:1. The α,β-VIII stereoisomers differ with respect to the orientation of the cyano group and have the same equatorial orientation of the methyl substituents attached to the $C_{(2)}$ and $C_{(5)}$ atoms. This fact can be explained as follows: piperidone I is a conformationally labile compound and undergoes isomerization during the addition of hydrogen cyanide to the more stable trans isomer via a known scheme [9]. In this connection, in all cases of the synthesis of cyanohydrins from a mixture of the cis and trans isomers of piperidone I we obtained only mixtures of the α and β isomers of cyanohydrin VIII with a trans orientation of the methyl groups, which differ only with respect to the orientation of the substituents attached to the $C_{(4)}$ atom of the piperidine ring and not with respect to the orientation of the methyl substituents attached to the $C_{(2)}$ and $C_{(5)}$ atoms, as Tosunyan and coworkers indicate without adducing any evidence [1].

We also studied the effect of the reaction temperature on the stereospecificity of the addition of hydrogen cyanide to the carbonyl group of substituted 4-piperidones I, V, and VII. Stereohomogeneous cyanohydrins β-XII and β-XIV with an axial cyano group are formed when the syntheses from piperidones V and VII at 0-3°C; this indicates the strict stereospecificity of the reaction under these conditions. In the case of piperidone I under these conditions the reaction is also stereospecific, but leads to the formation of a mixture of cyanohydrin isomers α,β-VIII with preponderance of the β isomer. When the temperature is increased, the amount of the α isomers, which have an equatorial cyano group, increases in the stereoisomeric mixtures of cyanohydrins (Table 3).

Thus the data obtained provide evidence for a dependence of the stereospecificity of the reversible addition of hydrogen cyanide to the carbonyl group of substituted 4-piperidones on both kinetic factors, which affect the rate of formation of the stereoisomers of the corresponding cyanohydrins and promote axial incorporation of the cyano group, and on thermodynamic factors, which promote the formation of the more stable stereoisomer with an equatorial cyano group. With an increase in the temperature one observes partial dissociation of the initially formed cyanohydrin stereoisomer with an axial cyano group, and the percentage of the α isomer with an equatorial oriented cyano group increases in the mixture of stereoisomeric cyanohydrins.

EXPERIMENTAL

The ^{13}C NMR spectra with complete proton decoupling and the ^{13}C monoresonance spectra of cyanohydrins VIII-XIV were recorded with a Bruker WP-80 spectrometer at an operating frequency for the ^{13}C nuclei of 20.15 MHz with $CDCl_3$ and d_6-DMSO as the solvents. In assigning the signals in the ^{13}C NMR spectra, in addition to the chemical shifts, we took into account the multiplicities of the signals in the spectra obtained with incomplete proton decoupling, as well as the widths of the signals in the spectra without proton decoupling. The IR spectra of suspensions of the substances in mineral oil were recorded with a Specord IR-75 spectrometer.

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