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STEREOCHEMISTRY OF HYDROCYANATION OF 3-HYDROXY-4-ALKYLIMINOPIPERIDINES

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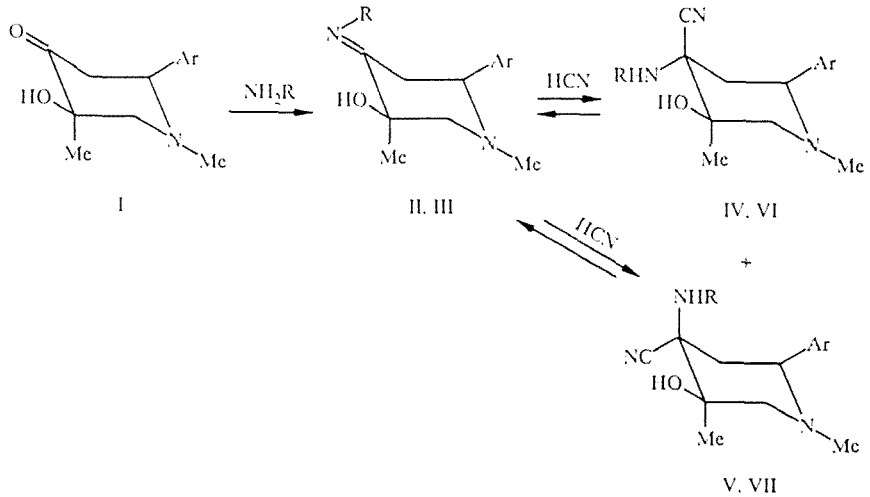
We have studied the stereochemistry of hydrocyanation of 3-hydroxy-4-alkyliminopiperidines. We have developed preparative synthesis methods for stereoisomeric 4-alkylamino-3e-hydroxyl-1,3a-dimethyl-6e-(4-chlorophenyl)piperidines.

Hydrocyanation of cyclic ketones and their corresponding azomethines, of interest for studying the stereochemistry of nucleophilic addition at a double bond [1-3], is also an important method for obtaining starting compounds for synthesis of biologically active compounds, in particular conformationally rigid analogs of γ-aminobutyric acid [4].

In our preceding papers, we studied addition of hydrocyanic acid to 3-hydroxypiperidin-4-ones [5, 6]. We showed that the reaction occurs stereoselectively, and, under conditions of kinetic or thermodynamic control, products are formed with different orientations of the cyano group. In this paper, we have investigated the stereochemistry and hydrocyanation products of azomethines II and III, obtained from piperidine I and primary amines.

We have established that upon reaction of compounds II, III with hydrocyanic acid in diethyl ether or benzene, mixtures of aminonitriles IV and V or VI and VII respectively are formed. The reaction occurs in both cases with high stereoselectivity; and upon crystallization the aminonitriles IV, VI are isolated in practically pure state in 85-90% yield. When carrying out the indicated reactions in acetonitrile over the course of several days, the aminonitriles V, VII are crystallized from the reaction mixtures in 70-75% yields.



I II, III IV, VI

V, VII

I–VII Ar = 4-ClC_6H_4; II, IV, V R = CH_2Ph; III, VI, VII R = Me

Identification of the compounds obtained was done on the basis of IR, ^1H NMR, and ^{13}CNMR spectroscopy data. Thus the IR spectra of azomethines II, III are characterized by the presence of bands for the stretching vibrations of the C=N bond in the region 1670-1675 cm^{-1} and the hydroxyl group, connected by an intramolecular hydrogen bond with the unshared electron pair of the nitrogen atom of the azomethine group, at 3390-3400 cm^{-1}. In the IR spectra of the aminonitriles V,

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TABLE 1. ^{1}H NMR Spectra of Aminonitriles IV-VII in $CDCl_3$

Compound	Chemical shifts, ppm							Spin–spin coupling constant (J), Hz		
	3-CH_3	N—CH_3	6-H_b	5-H_b	5-H_e	2-H_a	2-H_e	$J_{6\text{-}Ha\ 5\text{-}Ha}$	$J_{6\text{-}Hb\ 5\text{-}He}$	$J_{5\text{-}Hb\ 5\text{-}He}$
IV	1,60	2,04	3,30	1,73	2,16	2,87	2,65	12,0	3,5	14,0
V	1,84	1,98	3,24	1,86	2,10	2,91	2,55	11,5	3,5	14,5
VI	1,53	2,03	3,24	1,59	2,08	2,84	2,61	12,0	3,0	14,0
VII	1,83	1,97	3,24	1,85	2,07	2,82	2,53	11,5	3,0	14,5

VII, the stretching vibrations of the OH group are observed at 3600-3610 cm^{-1}, which corresponds to the stretching vibrations of the free hydroxyl group [7]. In the spectra of the aminonitriles IV, VI, there are two bands for the stretching vibrations of the OH group: one not connected by an intramolecular hydrogen bond at 3600-3620 cm^{-1}, and one connected by a weak intramolecular hydrogen bond with the nitrile group at 3570-3580 cm^{-1}, and one connected by a weak intramolecular hydrogen bond with the nitrile group at 3570-3580 cm^{-1}. The stretching vibrations of the NH group of the aminonitriles are observed in the region 3300-3360 cm^{-1}.

In the ^{1}H NMR spectra of compounds IV-VII (see Table 1), the signals from the protons at $C_{(5)}$ and $C_{(6)}$ are observed in the form of three quadruplets, while the signals from the protons at $C_{(2)}$ are observed in the form of two doublets with spin–spin coupling constant indicating a chair-like conformation of the piperidine ring [8].

The orientation of the substituents at $C_{(4)}$ of aminonitriles IV-VII was confirmed on the basis of ^{13}C NMR spectroscopy data using the technique suggested earlier in [5]. We found that the signal from the carbon atom of the nitrile group of the aminonitriles IV, VI in the spectra (without proton decoupling to suppress interaction with the protons of the amino group) is a doublet of doublets with observed splitting 3.0 and 10.5 Hz. The calculation of the spectral parameters (using the PANIC program included in the standard software for the instrument) showed that these quantities are $J_{CN_a\ 5\text{-}Ha}$ and $J_{CN_a\ 5\text{-}He}$ respectively. The signal from the carbon atom of the nitrile group of compounds V, VII is a broadened singlet with halfwidth 4 Hz. The presented values correspond to literature data for related systems [5, 6, 9] and suggest an axial orientation for the CN group for the aminonitriles IV, VI and an equatorial orientation of the CN group for the aminonitriles V, VII.

With the goal of determining the factors affecting the stereochemistry and equilibrium composition of the hydrocyanation products, we studied the interaction of the azomethines II, III with hydrocyanic acid in different solvents. We established that immediately after mixing the reagents in deuterochloroform, deuteromethanol, or dimethylsulfoxide-D_6, the products with an axial nitrile group IV, VI are present as 90, 65, and 45% respectively. The equilibrium mixtures formed upon holding the aminonitriles in the same solvents in the presence or in the absence of trimethylamine and hydrocyanic acid are characterized by a practically equal ratio of stereoisomers, independent of the nature of the solvent and the presence of trimethylamine, which however significantly accelerates the isomerization process.

EXPERIMENTAL

The ^{1}H NMR spectra in $CDCl_2$ and the ^{13}C NMR spectra in DMSO-D_6 of the aminonitriles IV-VII were obtained on the AS-200 spectrometer with operating frequencies of 200 and 51 MHz for the ^{1}H and ^{13}C nuclei respectively. With the goal of increasing the digital resolution for compounds IV-VII narrow spectral intervals containing the signal from the hydrogen atom of the nitrile group are recorded; the digital resolution in this case was 0.3 Hz. The IR spectra of dilute solutions of compounds II-VII (10^{-3} moles/liter) in CCl_4 were recorded on the Specord IR-75 spectrometer. The process and purity of the products were monitored using TLC on silica gel.

The elemental analysis data for the synthesized compounds for C, H, N correspond to the calculated values.

Determination of the ratio of stereoisomers of aminonitriles under quasikinetic conditions and the equilibrium composition of the hydrocyanation products was done at a temperature of 23-25°C in CD_3OD, $CDCl_3$, and DMSO-D_6 for initial concentrations of azomethines or aminonitriles 0.15 moles/liter, and initial concentrations of hydrocyanic acid and trimethylamine 0.8 and 0.7 moles/liter respectively. The quantitative ratio of the stereoisomers was established from the integrated intensity of the signals from the 3-CH_3 group of the ^{1}H NMR spectra.

4-Benzylimino-3e-hydroxy-1e,3a-dimethyl-6e-(4-chlorophenyl)piperidine (II, $C_{20}H_{23}N_2OCl$). 3 ml benzylamine was added to a solution of 5.5 g (0.022 moles) piperidine I in 100 ml benzene and the mixture was allowed to stand over anhydrous sodium sulfate for 15 h at a temperature of 18-20°C. Then the solution was decanted from the residue, the benzene was driven off at reduced pressure, and the residue was crystallized from heptane. Obtained: 6.9 g (93%) azomethine II. mp 98-100°C. IR spectrum: 3390, 1670 cm^{-1}.

3e-Hydroxy-1e,3a-dimethyl-4-methylimino-6e-(4-chlorophenyl)piperidine (III, $C_{14}H_{19}N_2OCl$) was obtained similarly by treating compound I with a saturated solution of methylamine in benzene. Yield, 80%. mp 94-95°C. IR spectrum: 3400, 1675 cm^{-1}.

3e-Hydroxy-1e,3a-dimethyl(4e-methylamino)-6e-(4-chlorophenyl-4a-cyanopiperidine (VI, $C_{15}H_{20}N_3OCl$). Piperidine I (5 g, 0.02 moles) was dissolved in 50 ml benzene saturated with methylamine and held over sodium sulfate at 18-20°C for 15 h. Then 3 ml hydrocyanic acid was added to the reaction mixture. The solution was decanted from the residue and the solvent was driven off at reduced pressure. After recrystallization of the residue from heptane, 4.8 g chromatographically pure compound VI was obtained. Yield, 90%. mp 103-104°C. IR spectrum: 3600, 3570, 3360 cm^{-1}.

4e-Benzylamino-3e-hydroxy-1e,3a-dimethyl-6e-(4-chlorophenyl)-4a-cyanopiperidine (IV, $C_{21}H_{24}N_3OCl$) was synthesized similarly from compound I and benzylamine. Yield, 85%. mp 137-138°C. IR spectrum: 3620, 3580, 3330 cm^{-1}.

Compounds IV, VI can be also synthesized by reaction of the corresponding azomethines with hydrocyanic acid in anhydrous diethyl ether.

4e-Benzylamino-3e-hydroxy-1e-3a-dimethyl-6e-(4-chlorophenyl)-4e-cyanopiperidine(V, $C_{21}H_{24}N_3OCl$). Hydrocyanic acid (3 ml) along with triethylamine (dropwise) were added to a solution of 3.5 g (0.011 moles) azomethine II in 12 ml acetonitrile and allowed to stand at 18-20°C for several days. The precipitated product was removed and after crystallization from diethyl ether, 2.9 g aminonitrile V was obtained. Yield, 75%. mp 151-152°C. IR spectrum: 3610, 3350 cm^{-1}.

3e-Hydroxy-1e,3a-dimethyl-4a-methylamino-6e-(4-chlorophenyl)-4e-cyanopiperidine (VII, $C_{15}H_{20}N_3OCl$) was synthesized similarly, starting from azomethine III. Yield, 70%. mp 113-114°C. IR spectrum: 3600, 3360 cm^{-1}.

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