STEREOCHEMISTRY OF THE HYDROCYANATION OF HYDROXYPIPERIDIN-4-ONES

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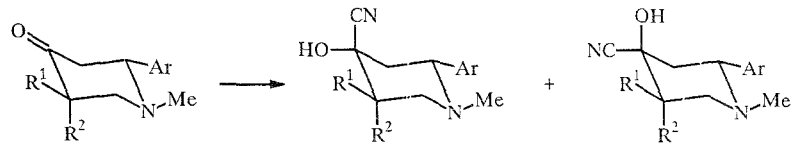
Preparative methods have been developed for the preparation of stereoisomers of 3,4-dihydroxy-1,3-dimethyl-6-(4-chlorophenyl)-4-cyanopiperidin-4-ones. Products with the cyano group equatorial predominate in the equilibrium mixtures of the cyanohydrins synthesized.

The hydrocyanation of piperidin-4-ones has been the center of attention of a number of groups for a long time [1-5]. However the stereochemistry of the products obtained could not be determined because of the difficulty of identifying the stereoisomers. Only recently has it been possible to confirm via ^{13}C NMR spectroscopy the axial configuration of the cyano group in the cyanhydrins obtained as the predominant products in the papers cited [5]. It was suggested in the same paper, on the basis of the effect of temperature on the steric control of hydrocyanation of piperidin-4-ones, that the stereoisomer with the equatorial cyano group was the more thermodynamically stable.

In a continuation of investigations of 3,4-dihydroxypiperidinones possessing biological activity [6-8], the products and stereochemistry of the hydrocyanation of 3-hydroxypiperidin-4-ones have been studied with the objective of synthesizing cyclic analogs of γ-aminobutyric acid.

The piperidinones I and II react with hydrogen cyanide in mixtures of ether or carbon tetrachloride with hexane to give the cyanohydrins III and V. In contrast, the isomers IV and VI were formed when the reaction was carried out with acetone cyanohydrin and an approximately equimolar amount of triethylamine. The reactions occur with high stereoselectivity over a few minutes and compounds III-VI crystallize from the reaction mixtures in an almost pure form.

To determine the stability and equilibrium composition of the hydrocyanation products, the reaction of piperidinones I and II with hydrogen cyanide in deuteromethanol in the presence of trimethylamine was studied. Under these conditions equilibrium mixtures of the cyanohydrins III and IV (40:60) or V and VI (20:80) were formed from piperidinone I (after 40 min) and piperidinone II (after 60 min), respectively. It should be noted that the ratios immediately after mixing the reagents were 80:20 for III and IV and 55:45 for V and VI.



I, II III, V IV, VI

Ar = *p*-Cl-C_6H_4; I, III, IV R^1 = OH, R^2 = Me; II, V, VI R^1 = Me, R^2 = OH

Cyanohydrins III-VI also isomerized in deuteromethanol in the absence of trimethylamine, but the reaction was considerably slower.

Identification of the pure cyanohydrins III-VI was based on IR, ^{13}C and ^1H NMR spectroscopy (Tables 1 and 2). In the ^1H NMR spectra of cyanohydrins III-VI the signals of the 5-H and 6-H protons were observed as three quartets and those of the 2-H protons as two doublets or an unresolved AB system with constants which showed that the piperidine ring had the chair conformation [6, 9].

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TABLE 1. Physicochemical Properties of the Cyanohydrins III-VI

Compound	m.p., °C	^{1}H NMR spectrum*: chemical shift, δ, ppm							coupling constant, J, Hz			IR spectrum, ν_{OH}, cm^{-1}	Yield, %
		1-CH_3	3-CH_3	$^aH_6$	$^aH_5$	$^eH_5$	$^aH_2$	$^eH_2$	$^aH_6$ $^aH_5$	$^aH_6$ $^eH_5$	$^aH_5$ $^eH_5$		
III	203...204	1,99	1,49	3,21	1,85	2,06	2,48	2,88	11,5	3,5	13,5	3610, 3600	76
IV	170...173	2,06	1,79	3,22	2,01	2,22	2,58	2,63	11,5	3,5	14,5	3600, 3550	93
V	136...137	2,05	1,47	3,22	1,94	2,22	2,68	2,91	12,0	3,0	14,0	3550, 3470	80
VI	125...123	2,02	1,42	3,22	2,42	1,95	2,68	2,68	12,0	3,0	14,0	3600, 3470	85

*The spectrum of compound III was recorded in CD_3OD, those of IV-VI in $CDCl_3$.

TABLE 2. ^{13}C NMR Spectra of Cyanohydrins III-VI

Compound	Chemical shift, δ, ppm							
	$C_{(2)}$, t	$C_{(3)}$, s	$C_{(4)}$, s	$C_{(5)}$, t	$C_{(6)}$, d	N—CH_3, q	3-CH_3, q	C ≡ N*
III	66,02	72,99	77,10	45,33	68,04	43,68	20,52	121,99 dd
IV	62,65	72,08	74,17	44,45	64,23	44,11	24,20	121,69 br.s
V	65,21	73,87	71,85	43,34	67,94	43,34	21,84	122,36 dd
VI	62,61	73,87	71,48	42,14	63,96	43,75	21,91	122,23 br.s

*Multiplicities arise from the vicinal CN—H interactions.

Comparison of the IR spectra of cyanohydrins V and VI showed that the band at 3470 cm^{-1} belonged to the axial 3-OH group hydrogen bonded to the ring nitrogen atom, while the bands at 3600 and 3550 cm^{-1} corresponded to the free axial 4-OH group of cyanohydrin VI and equatorial 4-OH group of cyanohydrin V, hydrogen bonded intramolecularly to the 3-OH group.

In the IR spectrum of cyanohydrin III two free OH bands were observed at 3600 cm^{-1} while bands of free and bound OH groups were observed at 3600 and 3550 cm^{-1} in the spectrum of IV. Products obtained from 3-hydroxypiperidin-4-ones by reduction and reaction with organometallic compounds have similar spectral characteristics [7, 8].

Configurations of the $C_{(4)}$ substituents in cyanohydrins III and IV were determined by ^{13}C NMR spectroscopy. The carbon signals of these compounds appeared in the expected regions (Table 2). The form of the nitrile carbon signal is determined by three-bond coupling to atom 5-H since atoms $C_{(3)}$ and $C_{(4)}$ are quaternary. A relation between $^{13}C-^1H$ coupling constants and dihedral angles is known, analogous to that for hydrogen atoms expressed via the Karplus equation [10]. Compounds III and IV have the same chair conformation and differ only in the orientation of the substituent at $C_{(4)}$. It is clear that the $^3J_{CN^a,{}^aH_5}$ coupling constant in the ^{13}C NMR spectrum should be larger for the cyanohydrin with the axial nitrile group than for that with the equatorial nitrile group.

The signal of the nitrile carbon in compound III is a doublet of doublets with couplings of 3.5 and 10 Hz. Calculations of the spectral parameters using the PANIC program showed that these values correspond within experimental limits to the $^3J_{CN^a,{}^eH_5}$ and $^3J_{CN^a,{}^aH_5}$ coupling constants respectively. The nitrile carbon signal for compound IV is broad singlet with a halfwidth of 3.7 Hz. The $^3J_{CN,H}$ coupling constants correspond to literature data for similar compounds [11, 12] and indicate the axial orientation of the nitrile group in cyanohydrin III and the equatorial orientation of the nitrile group in compound IV.

EXPERIMENTAL

^{1}H NMR spectra of cyanohydrin solutions in $CDCl_3$ and CD_3OD were recorded on Bruker WM-360 and Bruker AC-200 spectrometers at 360 and 200 MHz respectively. ^{13}C NMR spectra of compounds III-VI in DMSO-D_6 and CD_3OD were

recorded on Bruker AC-200 and Bruker WM-360 spectrometers with working frequencies of 51 and 90 MHz for ^{13}C nuclei respectively. In addition to spectra with and without proton coupling, a narrow spectral region containing the signals of the nitrile carbons of compounds III and IV was recorded with a resolution of 0.3 Hz. IR spectra of dilute solutions of compounds III-VI (10^{-3} mole/liter) in CCl_4 and $CHCl_3$ were recorded on a Specord IR-75 spectrometer.

Monitoring of experiments and of product purity was carried out by TLC using Kieselgel strips.

C, H and N elemental analysis results for compounds III-VI agreed with calculated values. Physical constants and yields for the compounds synthesized are given in Table 1 and ^{13}C NMR spectra are given in Table 2.

Determination of the equilibrium composition of the hydrocyanation products was carried out at 25-27°C in CD_3OD with initial piperidinone or cyanohydrin concentrations of 0.41 mole/liter and hydrogen cyanide and triethylamine concentrations of 1.8 and 1.5 mole/liter respectively. The quantitative ratios of the stereoisomers were determined from the integrated intensities of the 3-CH_3 signals in the ^1H NMR spectra.

3*e*,4*e*-Dihydroxy-1,3*a*-dimethyl-2*e*-(4-chlorophenyl)-4*a*-cyanopiperidine (III, $C_{14}H_{17}N_2O_2Cl$). Piperidinone I (1 g, 0.0041 mole) was dissolved in ether (3 ml) and hexane (7 ml) and hydrogen cyanide (2 ml) were added. The product which precipitated over a few minutes was recrystallized from an ethyl acetate hexane mixture to give chromatographically pure diol III (0.8 g, 76%).

3*a*,4*e*-Dihydroxy-1,3*e*-dimethyl-2*e*-(4-chlorophenyl)-4*a*-cyanopiperidine (V, $C_{14}H_{17}N_2O_2Cl$) was obtained analogously to III in 80% yield from piperidinone II in a mixture of carbon tetrachloride and hexane.

3*e*,4*a*-Dihydroxy-1,3*e*-dimethyl-2*e*-(4-chlorophenyl)-4*e*-cyanopiperidine (IV, $C_{14}H_{17}N_2O_2Cl$). Piperidinone I (5 g, 0.02 mole) was dissolved in a mixture of acetone cyanohydrin (3 ml) and triethylamine (3.2 ml). A mixture of ether and hexane was added to the reaction mixture a few minutes after crystallization began and the precipitate was filtered off 10-15 min later to give the chromatographically pure cyanohydrin IV (4.9 g, 93%).

3*a*,4*a*-Dihydroxy-1,3*e*-dimethyl-2*e*-(4-chlorophenyl)-4*e*-cyanopiperidine (VI, $C_{14}H_{17}N_2O_2Cl$) was obtained analogously to IV in 85% yield from piperidinone II.

REFERENCES

1. I. I. Nazarov and A. A. Akhrem, *Zh. Obshch. Khim.*, **25**, 1345 (1955).
2. I. I. Nazarov and B. V. Unkovskii, *Zh. Obshch. Khim.*, **26**, 318 (1956).
3. B. V. Unkovskii, G. S. Gusakova, and I. A. Mokhir, *Zh. Obshch. Khim.*, **30**, 3986 (1960).
4. B. V. Unkovskii, N. P. Mulaev, Yu. V. Malina, and O. D. Saralidze, *Khim. Geterotsikl. Soedin.*, No. 4, 654 (1968).
5. B. V. Unkovskii, M. Yu. D'yakov, T. D. Sokolova, and B. V. Rozhnov, *Khim. Geterotsikl. Soedin.*, No. 10, 1359 (1990).
6. A. M. Zvonok, V. A. Mashenkov, A. P. Lugovskii, and L. S. Stanishevskii, *Zh. Prikl. Spektrosk.*, **42**, 643 (1985).
7. L. S. Stanishevskii, I. G. Tishchenko, A. Ya. Guzikov, A. M. Zvonok, and L. A. Khil'manovich, *Zh. Org. Khim.*, **11**, 643 (1975).
8. A. M. Zvonok, A. P. Lugovskii, V. A. Mashenkov, and L. S. Stanishevskii, *Zh. Org. Khim.*, **18**, 2108 (1986).
9. V. F. Bystrov, *Usp. Khim.*, **41**, 512 (1981).
10. D. E. Hansen, *Progr. Nucl. Magn. Spectroscopy*, **14**, 175 (1981).
11. S. W. Werhly, A. D. Marchand, and S. Werhly. *Interpretation of Carbon-13 NMR Spectra*, Wiley, Chichester (1988), pp. 79, 126.
12. A. S. Aliev and A. A. Fomichev, *Khim. Geterotsikl. Soedin.*, No. 4, 512 (1989).