STEREOCHEMISTRY OF THE REACTIONS OF CYANOHYDRINS OF SUBSTITUTED 4-PIPERIDONES WITH AMMONIA AND AMINES. SYNTHESIS AND STRUCTURE OF SUBSTITUTED 4-AMINO-, 4-METHYLAMINO-, AND 4-DIMETHYLAMINO-4-CYANOPIPERIDINES

B. V. Unkovskii, M. Yu. D'yakov, T. D. Sokolova, V. B. Rozhnov, and G. V. Cherkaev

The action of ammonia, methylamine, or dimethylamine on substituted 4-hydroxy-4-cyanopiperidines in a modified Strecker synthesis gave mixtures of stereoisomers of the corresponding 4-amino-, 4-methylamino- and 4-dimethylamino-4-cyanopiperidine. ^1H and ^{13}C NMR spectroscopy was used to determine the structure of these products. Unusual stereocontrol was found for the reaction of methylamine and dimethylamine with cyanohydroxypiperidine with substituents at $C_{(2)}$ and $C_{(5)}$ in the ring.

In our preceding communication [1], we described the synthesis of substituted 4-cyano-4-hydroxypiperidines Iα,β-IVα,β and established their structure. The stereochemistry of the addition of hydrogen cyanide to the carbonyl group of the starting ketones was elucidated.

In a continuation of that study, we investigated the direction of the reaction of cyanohydrins Iα,β-IVα,β with ammonia and amines, leading to the corresponding substituted 4-amino-, 4-methylamino-, and 4-dimethylamino-4-cyanopiperidines V-XIV. Such compounds are intermediates in the synthesis of various biologically active compounds [2-5]. Syntheses have been reported for some piperidine α-aminonitriles [3,5,6] and their carbocyclic analogs [7-9], but the structure of these compounds was not established in the work of Vartanyan [3, 5] and Mousseron [9].

^1H and ^{13}C NMR spectroscopy was used to establish the structure of aminonitriles V-XIV and elucidate the stereochemical control in a modified Strecker synthesis with cyanohydrins of substituted 4-piperidones. Using our previous data [1], starting cyanohydrins Iα,β-IVα,β are mixtures of stereoisomers having equatorial orientation of all the methyl and phenyl substituents in the piperidine ring and different orientation of the cyano and hydroxyl groups.

Aminonitriles V-XIV were synthesized by the saturation of methanolic solutions of cyanohydrins Iα,β-IVα,β by gaseous ammonia or amines at 0-5°C. The reaction is complete after 120-168 h [10]. This method gave quantitative yields of stereoisomer mixtures of previously described [5, 11] substituted 4-amino- and 4-methylamino-4-cyanopiperidines VIIIα,β, XIIα,β, and XIVβ as well as previously unreported aminonitriles Vα,β-VIIα,β, IXα,β, Xα,β, XIβ, and XIIIβ. On the other hand, the reaction of cyanohydrin IIα,β with dimethylamine leads to a single stereoisomer, dimethylaminonitrile XIIIβ in 10% yield, while the corresponding dimethylaminonitriles could not be obtained at all by this method from cyanohydrins Iα,β and IIα,β.

In contrast to phenyl-substituted cyanohydrins Iα,β-IIIα,β, 4-cyano-4-hydroxy-1,2,5-trimethylpiperidine IVα,β reacts readily with dimethylamine to give a single stereoisomer of dimethylaminonitrile, XIVβ [10]. The properties and yields of previously unreported aminonitriles are given in Table 1.

M. V. Lomonosov Moscow State Institute of Fine Chemical Technology, 117571 Moscow; Institute of Chemical Sciences of the Kazakh Academy of Sciences, 480100 Alma-Ata. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 12, pp. 1621-1627, December, 1992. Original article submitted October 30, 1990.

0009-3122/92/2812-1389$12.50

TABLE 1. 4-Amino-, 4-Methylamino- and 4-Dimethylamino-4-cyanopiperidines

Compound	Chemical formula	mp, °C (from hexane)	n_D^{20}	Yield, %
V α,β	$C_{14}H_{19}N_3$	—	1,5051	98
VI β	$C_{14}H_{19}N_3$	96...98	—	92
VII β	$C_{15}H_{21}N_3$	74...76	—	97
IX β	$C_{15}H_{21}N_3$	99...100	—	95
X α,β	$C_{15}H_{21}N_3$	—	1,5121	97
XI β	$C_{16}H_{23}N_3$	81...83	—	80
XIII β	$C_{16}H_{23}N_3$	*	1,5162	10

*Compound isolated by chromatography on a column packed with grade-II-activity alumina.

In light of the difficulty of separating and assigning the signals of the carbon atoms of the minor α-stereoisomers, the spectral parameters of only the β-isomers of aminonitriles V-XIV are given in Tables 2 and 3, while only the parameters for the signals of the ^{13}C atoms of the cyano groups are given for isomers Vα-Xα and XIIα; the identification of these cyano group signals is not difficult.

The quantitative ratio of the stereoisomers of V-XIV in the reaction mixture was established relative to the intensities of identical carbon nuclei in the ^{13}C NMR spectra with complete proton decoupling [12].

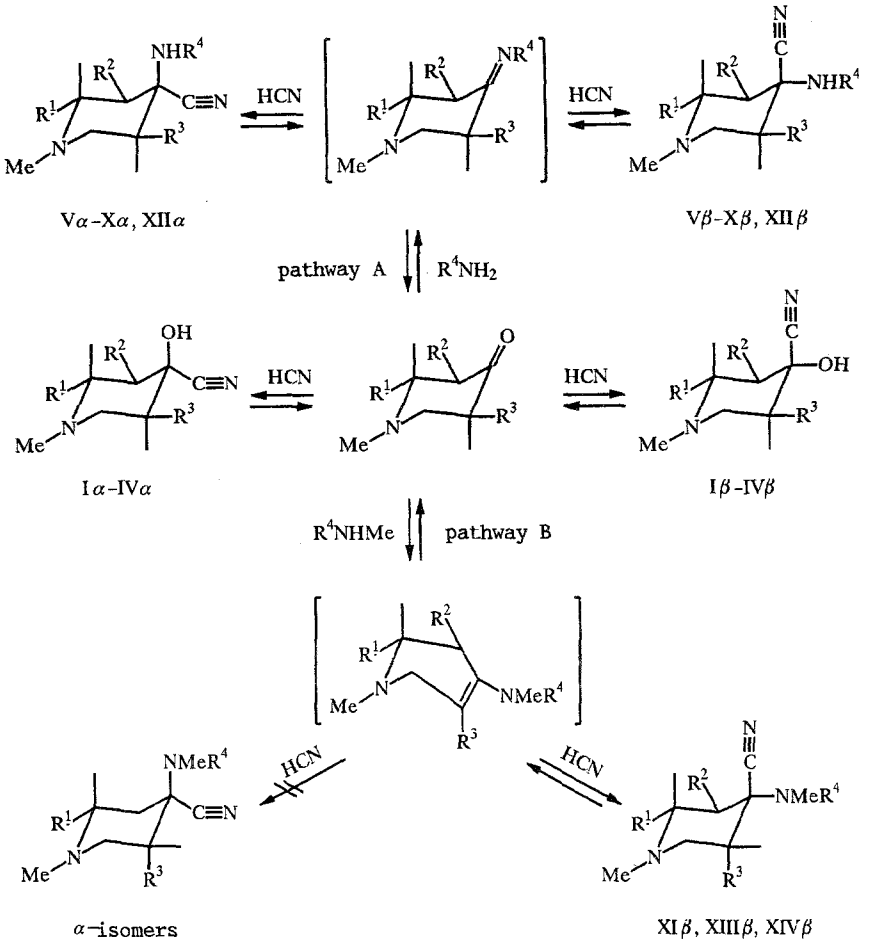
The orientation of the cyano group in the stereoisomers of aminonitriles V-XIV was determined using the width of the unresolved ^{13}C NMR signals for the cyano groups in the monoresonance spectra. The width at half-height of the ^{13}C NMR signal of the cyano group of the β-stereoisomers of aminonitriles V-XIV is 20-24 Hz in the monoresonance spectra, while the width of the cyano group signal of the α-isomers of V-X and XII is only 7-8 Hz (see Table 2). These findings indicate that the cyano group in the α-isomers are equatorial, while this group in the β-isomers is axial [13].

The orientation of the substituents at $C_{(2)}$, $C_{(3)}$, and $C_{(5)}$ of the piperidine ring was determined using the ^1H NMR data for the coupling constants of the vicinal protons, 2-, 3-, 5- and 6-H, in the piperidine ring.

Analysis of the ^{13}C and ^1H NMR data of the aminonitriles synthesized showed that the reaction of the mixtures of cyanohydrin stereoisomers Iα,β-IVα,β with ammonia leads to mixtures of the α- and β-stereoisomers of aminonitriles Vα,β-VIIIα,β, in which the fraction of the β-isomer with axial orientation of the cyano group and equatorial amino group is 80-90%. These reactions proceed through the formation of the corresponding 4-iminopiperidines (Scheme) [6, 7, 11, 14]. Thus, the ratio the α- and β-isomers of the aminonitrile reaction products hardly depends on the ratio of these isomers in the starting cyanohydrins. Our data indicate that the attack of the C=N bond of the imino group by the cyanide anion leads to the predominant formation of stereoisomers Vβ-VIIIβ with an axial cyano group. In this case, the orientation of the substituents in the piperidine ring is completely retained.

The reaction of cyanohydrins Iα,β, IIα,β, and IVα,β with methylamine proceeds analogously to give a mixture of stereoisomers of methylaminonitriles IXα,β, Xα,β, and XIIα,β, in which the β-stereoisomers with an axial cyano group and equatorial orientation of the substituents at $C_{(2)}$ and $C_{(3)}$ or $C_{(5)}$ in the ring also predominant (80-90%). We have found that the reaction of cyanohydrin mixture IIIα,β with methylamine leads to the stereocontrolled formation of only one aminonitrile isomer, namely, XIβ. The axial orientation of the cyano group in this compound was established using ^{13}C NMR spectroscopy. The positions of the substituents at $C_{(2)}$ and $C_{(3)}$ was established using PMR spectroscopy, which the coupling constant of the vicinal 2-H and 3-H is 10.5 Hz, indicating the *trans*-diaxial orientation of these protons. Thus, the methyl group at $C_{(3)}$ and the phenyl group at $C_{(2)}$ are equatorial. We found an unusual steric course for this reaction since, as indicated by ^1H PMR spectroscopy, a change occurs in the configuration of the piperidine ring during the reaction such that the methyl group at $C_{(5)}$ becomes axial. This conclusion follows from the coupling constants of the $C_{(6)}H_2$ methylene group with 5-H (2.5 and 3.0 hz). Such ^3J values correspond to equatorial orientation of 5-H. Thus, the methyl group at $C_{(5)}$ in XIβ has axial orientation. The axial orientation of the methyl substituent at $C_{(5)}$ in the piperidine ring in dimethylaminonitriles XIIIβ and XIVβ.

The starting configuration of the piperidine ring and axial orientation of the methyl group at $C_{(5)}$ in these cases is probably a consequence of the conversion of the corresponding cyanohydrins into aminonitriles XIβ, XIIIβ, and XIVβ through pathway B (see Scheme) and the corresponding enamines, namely, substituted 4-methylamino- or 4-dimethylamino-1,2,5,6-tetrahydropyridines [6, 14]. Thus, our data indicate that the formation of aminonitriles XIβ, XIIIβ,



I(α,β) R^1 = Ph, R^2 = Me, R^3 = H; II(α,β) R^1 = Ph, R^2 = H, R^3 = Me; III(α,β) R^1 = Ph, R^2 = R^3 = Me; IV(α,β) R^1 = R^3 = Me, R^2 = H; V(α,β) R^1 = Ph, R^2 = Me, R^3 = R^4 = H; VI(α,β) R^1 = Ph, R^2 = R^4 = H, R^3 = Me; VII(α,β) R^1 = Ph, R^2 = R^3 = Me, R^4 = H; VIII(α,β) R^1 = R^3 = Me, R^2 = R^4 = H; IX(α,β) R^1 = Ph, R^2 = R^4 = Me, R^3 = H; X(α,β) R^1 = Ph, R^2 = H, R^3 = R^4 = Me; XI(β) R^1 = Ph, R^2 = R^3 = Me, R^4 = H; XII(α,β) R^1 = R^3 = R^4 = Me, R^2 = H; XIII(β) R^1 = Ph, R^2 = H, R^3 = R^4 = Me; XIV(β) R^1=R^3=R^4 = = Me, R^2 = H

and XIVβ through pathway B and the corresponding enamines is probably a consequence of the structure of the starting cyanohydrins and amines. In these cases, the addition of hydrogen cyanide to the enamine double bond proceeds stereoselectively through *trans* addition to give single stereoisomers of XIβ, XIIIβ, and XIVβ with an axial cyano group and is accompanied by change in the orientation of the equatorial methyl group at $C_{(5)}$ in the ring and its shift to axial orientation.

Cyanohydrins Iα,β and IIIα,β do not react with dimethylamine. This failure may be attributed to the steric hindrance produced by the substituents at $C_{(2)}$ and $C_{(5)}$ in the ring.

EXPERIMENTAL

The ^{1}H NMR spectra of the compounds studied were taken on a Bruker WM-250 spectrometer at 250 MHz for 2% solutions in $CDCl_3$. The chemical shifts of the protons were measured relative to HMDS as the internal standard. The ^{13}C NMR spectra with complete hydrogen decoupling and the monoresonance spectra were taken on a Bruker WP-80 DC spectrometer at 20.15 MHz using $CDCl_3$ as the solvent.

Cyanohydrins Iα,β-IVα,β were synthesized as described in our previous work [1], while V-XIV were synthesized as described by Urinovich [11]. The major indices of the products are given in Table 1. The elemental analysis data corresponded to the calculated values.

TABLE 2. ^{13}C NMR Spectral Parameters for Substituted 4-Amino-, 4-Methylamino-, and 4-Dimethylamino-4-cyanopiperidines

Compound	δ, ppm												β/α stereoisomer ratio
	$C_{(2)}$	$C_{(3)}$	$C_{(4)}$	$C_{(5)}$	$C_{(6)}$	N—CH_3	$C_{(2)}$—R^{1}*	$C_{(3)}$—CH_3	$C_{(5)}$—CH_3	C ≡ N** (β-isomer)	C ≡ N** (α-isomer)	N—R^{4}***	
V	72,4	45,6	54,6	36,7	52,3	43,1	140,1	11,8	—	121,0 (24)	123,0 (8)	—	90/10
VI	66,4	46,5	54,9	40,0	59,9	42,5	141,6	—	12,7	121,1 (22)	123,2 (7)	—	80/20
VII	72,7	46,2	59,9	39,6	59,7	42,9	140,8	12,1	13,0	119,6 (20)	123,1 (7)	—	90/10
VIII	55,2	45,6	54,9	39,9	60,1	41,3	19,1	—	12,5	121,1 (24)	123,0 (7)	—	90/10
IX	72,0	43,7	60,2	32,4	51,5	42,3	140,7	11,7	—	118,9 (24)	120,8 (7)	29,7	80/20
X	66,2	42,6	61,4	38,6	60,1	42,8	141,8	—	12,7	118,9 (23)	120,6 (7)	29,7	90/10
XI	73,1	38,8	64,2	32,8	58,5	43,8	141,4	11,3	12,0	120,0 (20)	—	29,0	100/0
XII	54,9	41,7	61,3	38,3	61,2	41,3	19,3	—	12,4	118,2 (24)	120,6 (7)	29,5	90/10
XIII	66,8	37,9	64,9	34,2	59,0	40,3	142,6	—	11,5	118,0 (22)	—	38,7	100/0
XIV	55,5	36,8	64,7	34,1	59,3	41,9	19,6	—	11,4	117,8 (20)	—	38,4	100/0

*The signal for the α-carbon atom of the phenyl group is given in the spectra for V-VII, IX-XI,and XIII.

**The halfwidth of the unresolved multiplet is given in parenthesis, Hz.

***In the spectra of IX-XI, $R^4 = CH_3$; the signals for the carbon atoms of the dimethylamino group are given for XIII and XIV

TABLE 3. ^{1}H NMR Spectral Parameters for Substituted 4-Amino-, 4-Methylamino-, and 4-Dimethylamino-4-cyanopiperidines

Compound	δ, ppm										J, Hz		
	2-H_a	2-C_6H_5 (2-CH_3)	3-H_a	3-H_e (3-CH_3)	5-H_a (5-CH_3)	5-H_e (5-CH_3)	6-H_a	6-H_e	N—CH_3	4-NH (N—CH_3)	$^3J_{2a3a}$	$^3J_{6a5a}$ ($^3J_{6e5a}$)	$^3J_{6a5e}$ ($^3J_{6e5e}$)
VI	2,92	7,28	1,87	1,99	2,10	(1,14)	2,34	3,22	2,03	1,66	12,0	12,0 (3,0)	—
VII	2,82	7,28	1,86	(0,78)	2,09	(1,16)	2,33	2,88	1,95	1,66	10,5	12,0 (3,5)	—
VIII	2,34	(1,11)	1,51	1,95	1,78	(1,05)	2,09	2,72	2,26	1,58	12,0	12,0 (4,0)	—
IX	2,82	7,28	1,88	(0,72)	1,80	2,26	2,49	3,02	1,95	1,67 (2,52)	10,3	13,1 (4,0)	2,9
XI	2,80	7,30	2,04	(0,72)	(1,27)	2,26	2,74	2,90	1,92	1,66 (2,48)	10,5	—	3,0 (2,5)
XII	2,20	(1,12)	1,32	2,11	1,90	(1,03)	2,20	2,74	2,29	1,63 (2,51)	12,5	12,5 (3,5)	—
XIII	3,12	7,29	1,80	1,90...2,40*	(1,24)	1,90...2,40*	2,69	2,89	1,98	(2,26)	12,0	—	2,5 (2,5)
XIV	2,02...2,25*	(1,12)	1,50	1,84	(1,09)	2,02...2,25*	2,57	2,73	2,24	(2,29)	12,5	—	2,5 (2,5)

4-Amino-1,3-dimethyl-2-phenyl-4-cyanopiperidine (Vα,β). A solution of 4.61 g (0.02 mole) 4-hydroxy-1,3-dimethyl-2-phenyl-4-cyanopiperidine Iα,β in 15 ml methanol was saturated with gaseous ammonia for 1 h with external cooling to 0-5°C. The reaction mixture was left with a calcium chloride tube at room temperature for five days and the solvent was removed in vacuum at ≤20°C. The oily residue was dissolved in ether and dried over anhydrous magnesium sulfate. Ether was distilled off to give 4.5 g of a mixture of stereoisomeric aminonitriles Vα,β.

Products VI-XIV was obtained analogously by saturating cyanohydrins Iα,β-IVα,β with ammonia, methylamine, or dimethylamine.

REFERENCES

1. B. V. Unkovskii, M. Yu. D'yakov, T. D. Sokolova, and V. B. Rozhnov, Khim. Geterotsikl. Soedin., No. 10, 1358 (1990).
2. E. S. Nikitskaya, G. S. Arutyunyan, M. D. Mashkovskii, and L. N. Yakhontov, Khim.-Farm. Zh., **8**, No. 2, 16 (1974).
3. S. A. Vartanyan, A. O. Tosunyan, M. R. Bagdasaryan, and V. N. Madakyan, Arm. Khim. Zh., **27**, 417 (1974).
4. B. Hermans, P. Daele, C. Westeringh, C. Eycken, I. Boey, and P. A. Janssen, J. Med. Chem., **9**, 49 (1966).
5. S. A. Vartanyan, A. O. Tosunyan, and V. N. Madakyan, Arm. Khim. Zh., 25, 163 (1972).
6. E. S. Nikitskaya, L. M. Alekseeva, Yu. N. Sheinker, and L. N. Yakhontov, Khim. Geterotsikl. Soedin., No. 12, 1672 (1971).
7. H. S. Tager, J. Am. Chem. Soc., **94**, 968 (1972).
8. I. T. Edward and C. Iitraugsri, Canad. J. Chem., **53**, 3339 (1975).
9. M. Mousseron, I.-M. Kamenka, and M. R. Darvich, Bull. Soc. Chim. France, No. 1, 208 (1970).
10. B. V. Unkovskii, Yu. S. Matyukhin, Yu. F. Malina, and E. M. Urinovich, Khim. Geterotsikl. Soedin., No. 9, 1224 (1973).
11. E. M. Urinovich, Conformational Studies on Stereoisomeric 4-Ethynyl- and 4-Cyano-4-piperidols and Some of Their Derivatives [in Russian], Chemical Sciences Candidate's Dissertation, Moscow (1967).
12. N. M. Sergeev, NMR Spectroscopy [in Russian], Moscow Univ., Moscow (1981), p. 279.
13. V. B. Rozhnov, O. V. Agashkin, T. D. Sokolova, B. V. Unkovskii, and Yu. F. Malina, Zh. Org. Khim., **25**, 1097 (1985).
14. Yu. M. Shafran, V. A. Bakulev, and V. S. Mokrushin, Usp. Khim., **58**, 250 (1989).