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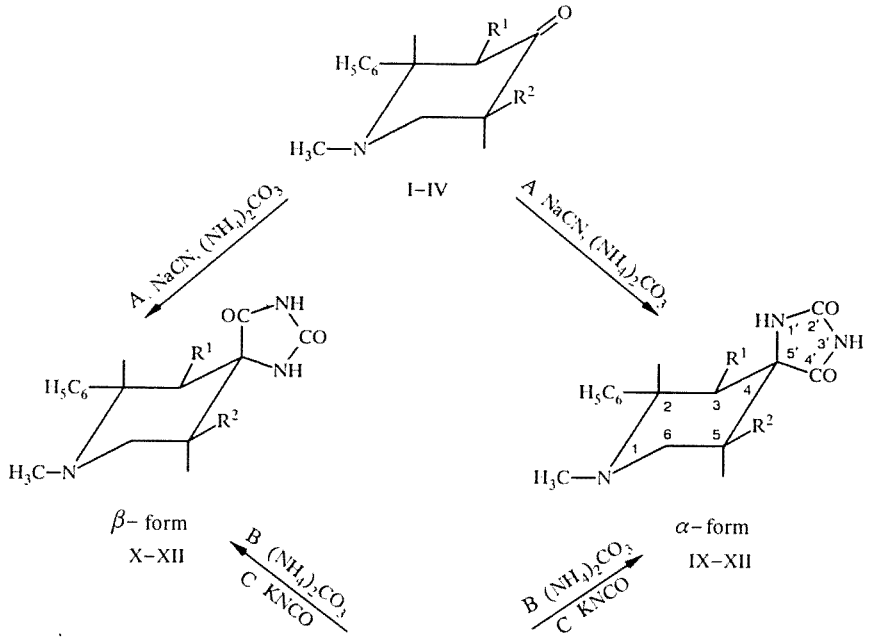
SYNTHESIS AND SPATIAL STRUCTURE OF METHYL SUBSTITUTED 2-PHENYLPIPERIDINE-4-SPIRO-5′-IMIDAZOLIDINE-2′,4′-DIONES

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

Piperidine-4-spiro-5′-imidazolidine-2′,4′-diones have been synthesized from the appropriate methyl substituted 2-phenyl-4-hydroxypiperidines and 4-cyano-4-aminopiperidines by the Bucherer–Bergs and Strecker methods. The stereochemical composition and spatial structure of the compounds synthesized have been established from ^1H and ^{13}C NMR data.

We have synthesized the piperidine-4-spiro-5′-imidazolidine-2′,4′-diones (IX)-(XII) from the methyl substituted 4-hydroxy-2-phenylpiperidines (I)-(IV) and from the 4-amino-4-cyanopiperidine derivatives (IX)-(XII) with the aim of searching for new biologically and physiologically active substances. The spirohydantoins (IX)-(XII) were obtained by the reaction of the 4-hydroxypiperidines (I)-(IV) with sodium cyanide and ammonium carbonate in 50% ethanol by the Bucherer–Bergs method [1, 2] or from the corresponding α-aminonitriles (V)-(VIII) under the conditions of the Bucherer–Bergs reaction (3, 4]. The piperidinespirohydantoins (X)-(XII) were also obtained from the α-aminonitriles (VI)-(VIII) by the Strecker method [5], by the reaction of α-aminonitrile hydrochlorides with potassium cyanate in acetic acid. The properties and yields of the piperidinespirohydantoins (IX)-(XII) are given in Table 1. The stereochemical composition and spatial structure of the spirohydantoins (IX)-(XII) were established from a combination of the ^1H and ^{13}C NMR spectral data given in Tables 2 and 3 respectively.



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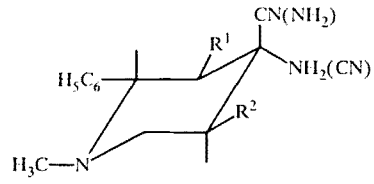

V–VIII

I, V, IX $R^1 = R^2 = H$; II, VI, X $R^1 = CH_3$, $R^2 = H$; III, VII, XI $R^1 = H$, $R^2 = CH_3$; IV, VIII, XII $R^1 = R^2 = CH_3$

The mutual orientation of the heterocycles in the substituted piperidinespiroimidazolidine-2′,4′-diones was established by comparing the ^{13}C and ^1H NMR spectra of the α and β forms. In the single resonance ^{13}C spectrum the size of the $^3J_{CH}$ coupling constant of the $C_{(4')}$ atom with the axial protons at $C_{(3)}$ and $C_{(5)}$ was greater for the β forms (Table 3) [6].

In the PMR spectra of the β forms of the spirohydantoins (Table 2) the axial protons of the $C_{(2)}$ and $C_{(6)}$ atoms fall in the region of the deshielding affect of the carbonyl group ($C_{(4')}$=O) and are displayed at lower field than the analogous protons of the α forms.

Quantitative ratios of the stereoisomers in mixtures were determined from the integrated intensities of signals of identical carbon nuclei in the ^{13}C NMR spectra [6, 7].

We established that the reaction of the 4-hydroxypiperdines (I)-(IV) with sodium cyanate and ammonium carbonate and the reaction of α-aminonitriles (V)-(VIII) with ammonium carbonate lead to the same spirohydantoints (IX)-(XII). The spirohydantoin (IX) is formed only as the α isomer while the spirohydantoins (X)-(XII) are a mixture of α and β stereoisomers with a predominance of the α form [(X), (XI) α 90%; (XII) α 55%]. It was possible to isolate the pure isomers of these compounds by recrystallization of the stereo-isomeric mixtures of spirohydantoins (X) and (XI). The Bucherer–Bergs reaction therefore leads to a mixture of α and β forms of spirohydantoins in which the α isomer predominates.

The reaction of α-aminonitriles (VI)-(VIII) with potassium cyanate by Strecker's method [5] occurs with a high stereoselectivity and leads to the preparation of pure β stereoisomers of the spirohydantoins (X)-(XII).

EXPERIMENTAL

The ^1H NMR spectra of the compounds being investigated were recorded on a WM 250 (Bruker) spectrometer for 2-3% solutions in DMSO-d_6, internal standard was HMDS. The ^{13}C NMR spectra were recorded for 20-40% solutions in DMSO-d_6 onBruker WP 80DS and BrukerWM 400 spectrometers at frequencies of 20.15 and 100.6 MHz respectively. Chemi-

TABLE 1. Substituted 1-Methyl-2-phenylpiperidine-4-spiro-5′-imidazolidine-2′,4′-diones (IX)-(XII)

Compound	Empirical formula	mp, °C	Method (from 80% alcohol)	Yield of stereo-isomeric mixture % (content of pre-dominant isomer, %)
IX α	$C_{14}H_{17}N_3O_2$	253-256	A	72 (100α)
			B	86 (100α)
X α	$C_{15}H_{19}N_3O_2$	278-280	A	69 (90α)
			B	77 (90α)
X β	$C_{15}H_{19}N_3O_2$	304-305	C	32 (100β)
XI α	$C_{15}H_{19}N_3O_2$	268-270	A	65 (90α)
			B	77 (90α)
XI β	$C_{15}H_{19}N_3O_2$	252-253	C	32 (100β)
XII α,β	$C_{16}H_{21}N_3O_2$	268-272	A	85 (55α)
			B	77 (55α)
XII β	$C_{16}H_{21}N_3O_2$	247-249	B	28 (100β)

TABLE 2. Parameters of ^1H NMR Spectra of the Substituted Piperidine-4-spiro-5′-imidazolidine-2′,4′-diones (IX)-(XII)

Compound	Proton chemical shifts, δ, ppm											Coupling constants, J, Hz	
	N-CH_3	2a-H	C_6H_5	3a-H	3e-H (3-CH_3)	5a-H	5e-H (5-CH_3)	6a-H	6e-H	1′-H	3′-H	$^3J_{2,3a}$	$^3J_{5a,6a}$
IX α	1,90	3,16	7,28	1,79	1,56	1,97	1,50	2,41	2,87	8,68	10,7	11,6	12,5
X α	1,85	2,83	7,27	1,95	(0,31)	2,08	1,63	2,44	2,85	8,28	10,7	10,7	13,2
X β	1,85	3,21	7,27	1,77	(0,42)	2,00	1,91	2,83	2,76	7,68	10,4	10,5	13,7
XI α	1,88	3,13	7,27	1,83	1,56	2,11	(0,68)	2,11	2,72	8,46	10,7	12,0	11,1
XI β	1,90	3,51	7,27	1,72	1,80	1,99	(0,81)	2,57	2,74	7,78	10,5	10,7	12,0
XII α	1,83	2,80	7,22	1,96	(0,33)	2,16	(0,73)	2,20	2,70	8,10	10,5	10,5	*
XII β	1,85	3,25	7,27	1,82	(0,44)	2,10	(0,85)	2,65	2,73	7,57	10,4	10,3	11,5

*Signal not identified.

TABLE 3. Parameters of ^{13}C NMR Spectra of the Substituted Piperidine-4-spiro-5′-imidazolidine-2′,4′-diones (IX)-(XII)

Compound	Chemical shifts of ^{13}C nuclei, δ, ppm (halfwidth of unresolved multiplet signal, Hz)										
	Piperidine ring carbon atoms					Substituent carbon atoms				Imidazolidine ring carbon atoms	
	$C_{(2)}$	$C_{(3)}$	$C_{(4)}$	$C_{(5)}$	$C_{(6)}$	N–CH_3	C_2–Ph	C_3–CH_3	C_5–CH_3	C'_2	C'_4
IXα	67,8	46,1	65,1	36,9	54,6	46,9	147,2	–	–	160,1 (2,5)**	181,2 (7,0)**
Xα	73,8	47,9	68,9	37,8	54,9	44,7	145,9	16,0	–	161,1 (2,3)**	181,9 (7,0)**
Xβ	74,5	47,1	67,0	38,0	55,0	44,7	146,4	15,5	–	160,7	181,1 (16,0)
XIα	67,9	47,3	69,0	39,2	61,9	46,9	147,1	–	16,0	161,0 (2,7)**	181,2 (8,0)**
XIβ	68,4	47,3	67,2	41,4	62,1	46,9	147,2	–	16,1	160,5 (3,2)**	180,7 (17,4)
XIIβ	74,4	47,5	71,3	41,3	61,7	47,4	146,3	15,5	16,3	161,1 (2,9)**	179,4 (15)

*Allowing for C_6H_5.

**Coupling constant $^3J_{CH}$.

cal shifts of ^{13}C nuclei were measured completely decoupled from protons relative to DMSO-d_6 (δ 39.6 ppm) as internal standard. When assigning signals in the ^{13}C NMR spectra the multiplicity of signals in spectra without complete decoupling from protons and the breadth of signals in the spectra with no decoupling from protons were taken into consideration in addition to values of chemical shifts.

The methyl substituted 4-hydroxy-2-phenylpiperidines (I)-(IV) were synthesized as described in [8] and compounds (V)-(VIII) as described in [9]. The main characteristics of the substances synthesized are given in Table 1.

Data of elemental analysis for C, H, and N corresponded with calculated values.

1-Methyl-2-phenylpiperidine-4-spiro-5′-imidazolidine-2′,4′-dione (IXα). **A**. A mixture of 4-hydroxy-1-methyl-2-phenylpiperidine (I) (1 g: 5.3 mmole), sodium cyanide (0.39 g: 8 mmole), and ammonium acetate (1.52 g: 16 mmole) in 50% ethyl alcohol (15 ml) was heated for 8 h at 55-60°C and for 1 h on a boiling water bath. The solvent was distilled off in vacuum. The solid residue was washed with cold water. with ether, and recrystallized form 80% ethyl alcohol. 1-Methyl-2-phenylpiperidine-4-spiro-5′-imidazolidine-2′,4′-dione (IXα) (0.94 g) was obtained.

B. A solution of 4-amino-4-cyanopiperidine (V) (2.1 g: 0.01 mole) and ammonium acetate (2.88 g: 0.03 mole) in 50% ethyl alcohol (20 ml) was heated for 8 h at 55-60°C and for 1 h on a boiling water bath. Processing of the reaction mixture was carried out as for method A. 1-Methyl-2-phenylpiperidine-4-spiro-5′-imidazolidine 2′,4′-dione (IXα) (2.06 g) was obtained.

1,3-Dimethyl-2-phenylpiperidine-4-spiro-5′-imidazolidine-2′,4′-dione (Xβ). The spirohydantoin (X) was synthesized by methods A and B as described above and by method C.

C. A solution of the aminonitrile hydrochloride (VI) (5 g: 18.8 mmole) and potassium cyanate (1.53 g: 19 mmole) in acetic acid (14.5 ml) and water (2 ml) was heated on a boiling water bath. After 1 h concentrated HCl (8 ml) was added and the heating continued for 20 min. The reaction mixture was cooled, filtered, the residue evaporated to half volume, made alkaline with 10% NaOH solution, and cooled. The precipitated crystals were filtered off and recrystallized form 80% ethyl alcohol. The spirohydantoin (Xβ) (1.63 g) was obtained.

The spirohydantoins (XI) and (XII) were synthesized by similar methods.

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