SOME STEREOCHEMICAL FEATURES OF THE FORMATION OF SPIROIMIDAZOLIDINE-2,4-DIONE AND SPIROIMIDAZOLIDINE-2,4-DITHIONE FROM 1,2,5-TRIMETHYL-4-PIPERIDONE

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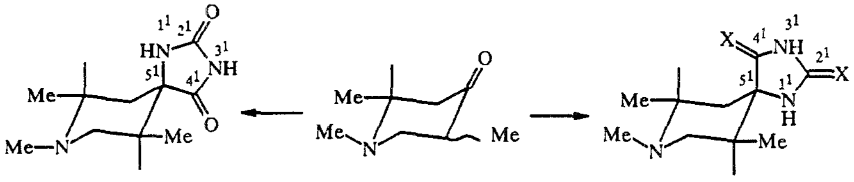
1,2,5-Trimethyl-4-piperidone was used as the starting reagent in the synthesis of stereoisomeric 1,2,5-trimethylpiperidine-4-spiro-5'-imidazolidine-2',4'-dione and its sulfur analog. The structures of these products were elucidated using ^1H and ^{13}C NMR spectroscopy.

In a continuation of a study of the stereochemistry of reactions involving the carbonyl group of substituted 4-piperidones [1, 2], we investigated the isomer composition of 1,2,5-trimethylpiperidine-4-spiro-5'-imidazolidine-2',4'-dione (II) and its thioanalog, 1,2,5-trimethylpiperidine-4-spiro-5'-imidazolidine-2',4'-dithione (III) obtained using reported procedures [3] from the corresponding available 1,2,5-trimethyl-4-piperidone (I), which is a mixture of *trans* and *cis* stereoisomers [4].



II
α-isomer

I

II, III
β-isomer

II, III X=O, X=S

The preparation of II has been described but, on the basis of the IR spectral [5] and mass spectral data [6], different workers came to opposite conclusions concerning the structure of the stereoisomers of spiroidantoin II. ^{13}C and ^1H NMR spectroscopy was used to establish the configurations of II and III.

The approximate ratio of the stereoisomers formed in the case of spiroidantoin II was determined using the intensities of the analogous signals in the ^{13}C NMR spectra with complete proton decoupling [7]. The parameters of the ^{13}C and ^1H NMR spectra of spiroidantoins II and III are given in Tables 1 and 2, respectively.

Identification of the signals for $C'_{(4)}$ and $C'_{(2)}$ in the imidazolidine ring in the ^{13}C NMR spectra of the compounds studied is straightforward since they are downfield relative to the signals of the carbon atoms of the piperidine ring. On the other hand, the signal of the carbonyl carbon atom of the imidazolidine ring $C'_{(4)}$ is located downfield relative to $C'_{(2)}$, which is a ureidic carbon [3, 8]. The orientation of $C'_{(4)}$ in the stereoisomers was determined, as in the case of piperidine cyanohydrins and α-aminonitriles [1, 2], using the circumstance that, upon axial orientation of this atom (in the β isomers), it is in a transoid position relative to the axial protons at $C_{(3)}$ and $C_{(5)}$ of the piperidine ring and, thus, should have a lower $^3J(^{13}C, {}^1H)$ coupling constant in the ^{13}C NMR monoresonance spectrum than in the case of an equatorial orientation of $C'_{(4)}$

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TABLE 1. ^{13}C NMR Spectral Parameters for 1,2,5-Trimethylpiperidine-4-spiro-5′-imidazolidine-2′,4′-dione (II) and 1,2,5-Trimethylpiperidine-4-spiro-5′-imidazolidine-2′,4′-dithione (III)

Compound	Isomer	^{13}C NMR chemical shifts, δ, ppm (half-width of unresolved multiplet, Hz)									
		$C_{(2)}$	$C_{(3)}$	$C_{(4)}$	$C_{(5)}$	$C_{(6)}$	$N—CH_3$	$C_{(2)}—CH_3$	$C_{(5)}—CH_3$	$C'_{(2)}$	$C'_{(4)}$
II	α	52,0	36,1	64,2	33,8	57,4	41,0	18,5	10,3	155,2	176,1 (8,0)
	β	52,3	36,3	64,2	34,0	57,6	41,2	18,7	10,8	155,3	175,4 (16,0)
III	β	50,1	40,1	75,6	36,5	55,1	41,4	18,5	10,4	178,9	207,4 (16,0)

TABLE 2. ^1H NMR Spectral Parameters for 1,2,5-Trimethylpiperidine-4-spiro-5′-imidazolidine-2′,4′-dione (II) and 1,2,5-Trimethylpiperidine-4-spiro-5′-imidazolidine-2′,4′-dithione (III)

Compound	Isomer	Proton chemical shifts, δ, ppm											Coupling constant, Hz	
		$N—CH_3$	2a-H	$C_{(2)}—CH_3$	3a-H	$C_{(3)}—CH_3$	5a-H	$C_{(5)}—CH_3$	6a-H	6e—H	$N'_{(1)}—H$	$N'_{(3)}—H$	$^3J_{2a3a}$	$^3J_{5a6a}$
II	α	2,14	2,14	0,94	1,56	1,42	1,96	0,63	1,98	2,51	8,06	10,6	11,0	11,5
	β	2,16	2,55	0,98	1,44	1,71	1,80	0,76	2,46	2,55	7,55	*		
III	β	2,19	3,18	0,92	1,55	1,75	2,04	0,67	3,0	2,45	9,1	10,3	13,5	11,8

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*Signal not identified.

(in the α-isomers) since it is found in a gauche position to the protons at $C_{(3)}$ and $C_{(5)}$. The values of the $^3J(^{13}C_{(4)}, ^1H)$ coupling constant was determined relative to the width of the unresolved multiplet for this carbon atom (Table 1).

The PMR spectral data also support the orientation of the imidazolidine ring of the α- and β-stereoisomers. The signals of the axial protons at $C_{(2)}$ and $C_{(6)}$ of the piperidine ring in the β-isomer are shifted downfield in comparison to the α-isomers due to the deshielding effect of the axially-oriented carbonyl group.

The methyl substituents at $C_{(2)}$ and $C_{(5)}$ in the piperidine ring in the α- and β-stereoisomers of II and III occupy an equatorial position as indicated by the ^3J(H,H) coupling constant at $C_{(2)}$, $C_{(3)}$, $C_{(5)}$, and $C_{(6)}$ (Table 2).

Combined analysis of the data of the ^1H and ^{13}C NMR spectra indicated that spiroidantoin II is a mixture of α- and β-stereoisomers differing in the position of the spiro-rings with 70% of the α-isomer, while the pure β-stereoisomer was isolated from the reaction mixture in about 20% yield in the case of III.

EXPERIMENTAL

The ^1H NMR spectra were taken on a Bruker WM-250 spectrometer for 2-3% solutions in DMSO-d_6 with HMDS (δ 0.055) as the internal standard. The ^{13}C NMR spectra were taken for 20-40% solutions in DMSO-d_6 on Bruker WP-80 DS and Bruker WM-400 spectrometers at 20.15 and 100.6 MHz, respectively. The chemical shifts of the ^{13}C nuclei were measured in spectra with complete proton decoupling relative to DMSO-d_6 (δ 39.6 ppm) as the internal standard. In assigning the signals in the ^{13}C NMR spectra, the multiplicity of the signals in the spectra with partial proton decoupling was taken in to account along with the chemical shift values.

The elemental analysis data for C, H, and N corresponded to the calculated values.

1,2,5-Trimethylpiperidine-4-spiro-5′-imidazolidine-2′,4′-dione (II) was synthesized according to Urinovich [5].

1,2,5-Trimethylpiperidine-4-spiro-5′-imidazolidine-2′,4′-dithione (III, $C_{10}H_{17}N_3S_2$). A mixture of 3.68 g (0.026 mole) 1,2,5-trimethyl-4-piperidone (I), 2 g (0.043 mole) sodium cyanide, 2.1 g (0.04 mole) ammonium hydrochloride, and

3.3 g (0.043 mole) carbon disulfide in 35 ml ethanol was heated for 24 h at 50-55°C. The hot solution was filtered. The mother liquor was evaporated to half volume and cooled. The crystalline precipitate was filtered off to give 1.1 g (18%) 1,2,5-trimethylpiperidine-4-spiro-5′-imidazolidine-2′,4′-dithione (III), mp 283-284°C (dec., from ethanol). The ^{13}C and ^{1}H NMR spectra of III are given in Tables 1 and 2, respectively.

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