Stereochemical study of 7-aryl-1,7,8,8a-tetrahydro-3(2*H*)indolizinones by ^1H and ^{13}C NMR

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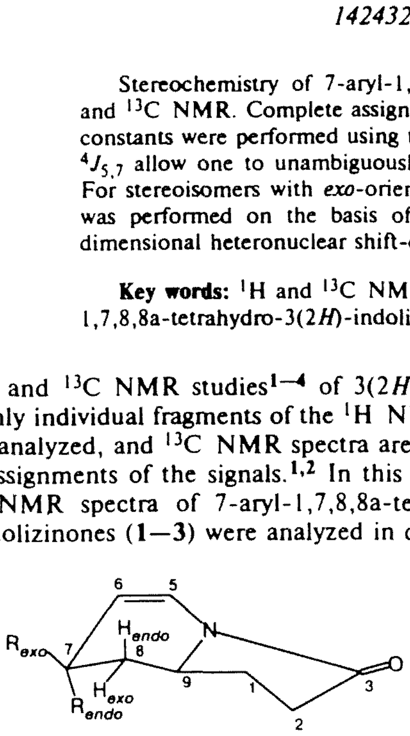
Stereochemistry of 7-aryl-1,7,8,8a-tetrahydro-3(2*H*)-indolizinones was studied by ^1H and ^{13}C NMR. Complete assignment of ^1H NMR signals and analysis of $^1H-^1H$ coupling constants were performed using the iterative PANIC program. Values of $^3J_{6,7}$, $^3J_{7,8endo}$, and $^4J_{5,7}$ allow one to unambiguously identify the corresponding *exo*- and *endo*-stereoisomers. For stereoisomers with *exo*-orientation of H(7), complete assignment of ^{13}C NMR signals was performed on the basis of analysis of the $^{13}C-^1H$ coupling constants using two-dimensional heteronuclear shift-correlating spectroscopy.

Key words: ^1H and ^{13}C NMR, $^1H-^1H$ and $^{13}C-^1H$ NMR coupling constants, 7-aryl-1,7,8,8a-tetrahydro-3(2*H*)-indolizinones.

In ^1H and ^{13}C NMR studies[1-4] of 3(2*H*)-indolizinones, only individual fragments of the ^1H NMR spectra[3,4] are analyzed, and ^{13}C NMR spectra are recorded without assignments of the signals.[1,2] In this work, ^1H and ^{13}C NMR spectra of 7-aryl-1,7,8,8a-tetrahydro-3(2*H*)-indolizinones (**1—3**) were analyzed in detail.



1: R_{exo} = H; R_{endo} = Ph

2: R_{exo} = Ph; R_{endo} = H

3: R_{exo} = H; R_{endo} = 4-$O_2NC_6H_4$

The ^1H NMR parameters of compounds **1—3** are presented in Table 1, and the values of ^{13}C NMR chemical shifts (CS) and $^{13}C-^1H$ coupling constants are presented in Table 2. Assignment of signals in the ^1H NMR spectra is difficult due to close values of chemical shifts, except weak-field H(5) and H(6) signals. Selective double resonance was used for analysis of the ^1H NMR spectra of compounds **1—3**. The exact values of CS and coupling constants were obtained by calculations of the corresponding four- and five-spin systems using the iterative PANIC program. The fragment of the experimental spectrum of compound **1** (1.5—2.6 ppm) and calculated subspectra for analysis of the signals of $H(1)_{endo}$, $H(1)_{exo}$, $H(2)_{endo}$, and $H(2)_{exo}$ as well as $H(8)_{endo}$ and $H(8)_{exo}$ protons are presented in Fig. 1.

Stereochemistry of compounds **1—3** can be studied on the basis of detailed analysis of geminal, vicinal, and allylic coupling constants ($^4J_{5,7}$) in the ^1H NMR spectra taking into account the known correlation of these coupling constants and geometry of individual molecular fragments.[5-7] Geminal coupling constants of protons at C(1), C(2), and C(8) are negative[7] and lie in the normal range of values (see Table 1). It is known that geminal coupling constants are almost independent of sizes of the cycle but are sensitive to the character of substituents at the carbon atom.[5] An increase in the absolute value of $^2J_{H(2)_{endo},H(2)_{exo}}$ compared to the other $^2J_{H-H}$ values (see Table 1) is related to the hyperconjugation effect with the adjacent carbonyl group. This effect corresponds to the negative contribution to the constant.[5] Vicinal coupling constants with the known dependence of the bihedral angle of the corresponding fragment are the most stereochemically informative.[6] In our case, the differences in the $^3J_{6,7}$ and $^3J_{7,8_{endo}}$ values in compounds **1** and **2** (see Table 1) make it possible to unambiguously assign *exo*- and *endo*-stereoisomers. These stereoisomers can also be identified by transoid allylic coupling constants $^4J_{5,7}$, whose values and signs both depend on the geometry of the fragment.[7] In our case, $^4J_{5,7}$ should be negative for the *endo*-orientation of H(7).[7] We also observed $^4J_{6,8_{exo}}$ corresponding to the zigzag configuration. This allows one to assume that this coupling constant fragment is close to planar one, because the σ-mechanism of interaction transfer predominates for these coupling constants, and their values decrease sharply when the bond system deflects from the plane.[7]

The ^{13}C NMR signals of compounds **1** and **3** were assigned taking into account the effect of hybridization of C atoms on their CS, signal intensities, on the basis of

Translated from *Izvestiya Akademii Nauk. Seriya Khimicheskaya*, No. 3, pp. 591—593, March, 1996.

Table 1. Values of CS (δ, ppm) and $^1H-^1H$ coupling constants (Hz) of compounds **1—3***

Atom	**1**		**2**		**3**	
	δH	*J*	δH	*J*	δH	*J*
H(1)$_{endo}$	1.63	$^2J_{1_{exo}} = -12.13$ $^3J_{2_{endo}} = 12.27$ $^3J_{2_{exo}} = 8.90$ $^3J_{8a} = 9.51$	1.59	$^2J_{1_{exo}} = -13.80$ $^3J_{2_{endo}} = 13.81$ $^3J_{2_{exo}} = 10.53$ $^3J_{8a} = 9.44$	1.69	$^2J_{1_{exo}} = -12.35$ $^3J_{2endo} = 12.21$ $^3J_{2_{exo}} = 9.04$ $^3J_{8a} = 9.72$
H(1)$_{exo}$	2.13	$^3J_{2_{endo}} = 9.22$ $^3J_{2_{exo}} = 0.51$ $^3J_{8a} = 6.24$	—**	$^3J_{2_{endo}} = 9.16$ $^3J_{2_{exo}}$ —** $^3J_{8a} = 6.35$	2.17	$^3J_{2endo} = 9.24$ $^3J_{2_{exo}} = 0.41$ $^3J_{8a} = 6.36$
H(2)$_{endo}$	2.45	$^2J_{2_{exo}} = -16.70$	2.49	$^3J_{2_{exo}} = -15.21$	2.47	$^3J_{2_{exo}} = -16.84$
H(2)$_{exo}$	2.40		2.44		2.42	
H(5)	7.11	$^3J_{5,6} = 8.05$ $^4J_{5,7} = 0.61$	6.94	$^3J_{5,6} = 8.15$ $^4J_{5,7} = -2.35$	7.17	$^3J_{5,6} = 8.25$ $^4J_{5,7} = 0.81$
H(6)	5.20	$^3J_{6,7} = 5.67$ $^4J_{8_{exo}} = 1.33$	5.10	$^3J_{6,7} = 1.50$ $^4J_{8_{exo}} = 1.50$	5.00	$^3J_{6,7} = 5.17$ $^4J_{8_{exo}} = 1.22$
H(7)	3.64	$^3J_{8_{endo}} = 5.92$ $^3J_{8_{exo}} = 1.40$	3.66	$^3J_{8_{endo}} = 11.54$ $^3J_{8_{exo}} = 5.42$	3.75	$^3J_{8endo} = 6.17$ $^3J_{8_{exo}} = 1.52$
H(8)$_{endo}$	1.86	$^2J_{8exo} = -13.04$ $^3J_{8a} = 11.94$	—**	$^2J_{8_{exo}}$ —** $^3J_{8a} = 11.80$	1.95	$^2J_{8_{exo}} = -13.21$ $^3J_{8a} = 12.11$
H(8)$_{exo}$	2.08	$^3J_{8a} = 2.90$	—**	$^3J_{8a} = 2.86$	2.98	$^3J_{8a} = 2.98$
H(8a)	5.08		3.94		3.50	

* No signals of protons of phenyl substituents are presented.

** Overlapping of the signals of H(1)$_{exo}$, H(8)$_{endo}$, and H(8)$_{exo}$ in the range of 2.19 to 2.38 ppm.

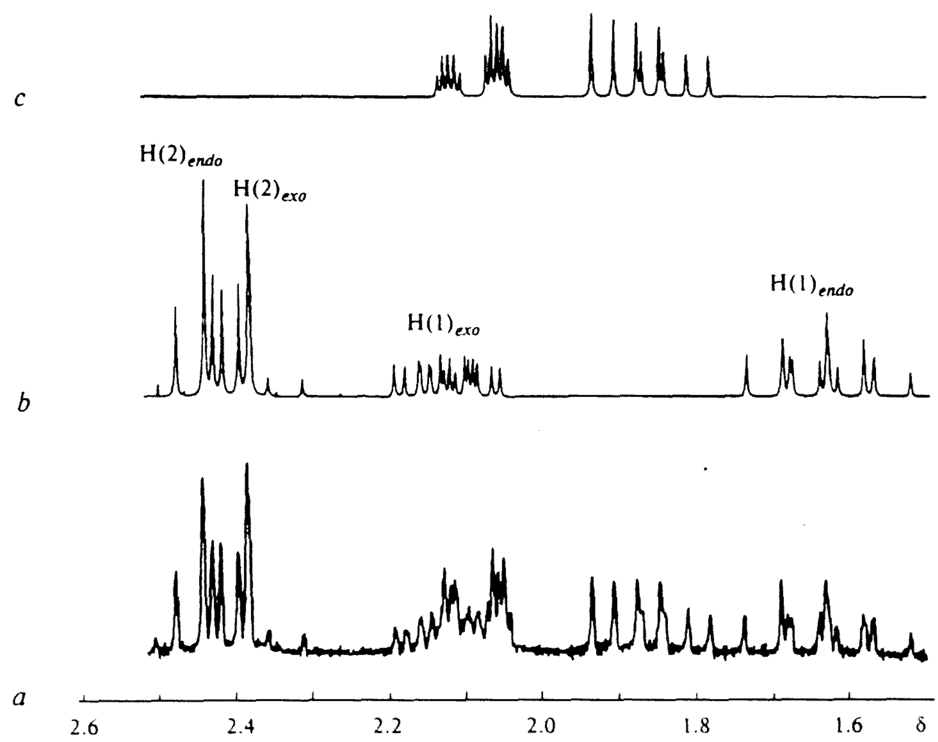


Fig. 1. Experimental (*a*) and calculated (*b*, *c*) ^{1}H NMR subspectra of the aliphatic region of compound **1**.

analysis of coupling constants $^1J_{C-H}$,[8,9] and using two-dimensional heteronuclear NMR spectroscopy XHCORR[10] for the $^1H-^{13}C$ correlation. The close CS values of H(5) and aromatic protons in the ^{1}H NMR spectra of compounds **1** and **3** result in overlapping of the corresponding cross-peaks in the 2D-XHCORR spec-

Table 2. Values of ^{13}C NMR CS (δ, ppm) and $^1J_{CH}$ coupling constants (Hz) of compounds **1** and **3**

Atom	**1**		**3**	
	δC	$^1J_{CH}$	δC	$^1J_{CH}$
C-1	26.27	133.70	26.22	132.61
C-2	30.99	134.24	30.83	133.15
C-3	172.34	—	171.51	—
C-5	122.56	178.75	123.64	179.11
C-6	109.34	163.85	107.39	165.30
C-7	38.17	129.34	38.06	131.15
C-8	50.75	141.69	50.23	142.05
C-1′(Ph)	144.66	—	146.91	—
C-2′(Ph)	128.25	158.04	129.08	129.08
C-3′(Ph)	128.40	159.49	123.64	123.64
C-4′(Ph)	126.54	160.58	152.13	—

tra; therefore, these signals were assigned on the basis of the ^{13}C—^{1}H coupling values. An increase in the $^1J_{C-H}$ value of C(5) due to the effect of the directly bound nitrogen atom[9] compared to $^1J_{C-H}$ coupling constants of aromatic hydrocarbons allows one to discriminate between C(5) and C(4′). The signals of phenyl rings were assigned by the additive scheme.[11] In the ^{13}C NMR spectrum of compound **3**, the signals of C(5) and C(3′) overlap, but appear in the proton-coupled spectrum due to a considerable difference between $^1J_{C-H}$ of these hydrocarbons (see Table 2).

Thus, $^3J_{6,7}$, $^3J_{7,8_{endo}}$, and $^4J_{5,7}$ values make it possible to unambiguously identify *exo-* and *endo*-isomers of 7-phenyl-1,7,8,8a-tetrahydro-3(2*H*)-indolizinones.

Experimental

Compounds **1—3** were prepared by intramolecular Diels—Alder reaction of the corresponding α,β-unsaturated *N*-pentenoylaldimines by the known procedure.[4] The nitrophenyl derivative was isolated as one stereoisomer **3**.

^{1}H and ^{13}C NMR spectra of compounds **1—4** (concentrations of 50 to 100 mg mL^{-1} in CDCl$_3$) were recorded on a Bruker AC-200 instrument (200.13 MHz and 50.33 MHz, respectively) at ~20 °C in 5-mm tubes with SiMe$_3$ as an internal standard. ^{1}H NMR spectra were analyzed using the iterative PANIC program (version 850501) on an ASPECT-3000 computer; the mean-square deviations were <0.05. ^{13}C NMR spectra were recorded using standard POWGATE and GATEDEC subprograms at 64 K and a spectral width of 12000 Hz. ^{13}C—^{1}H coupling constants were measured after increasing the number of points to 128 K with a final digital resolution of 0.18 Hz. Two-dimensional spectra were recorded using the standard XHCORR subprogram (1 K × 128 points, digital resolution of 10.94 Hz in *f1* and 11.77 Hz in *f2*, delay between pulses of 2 s) with optimization for 140 and 160 Hz.

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Received April 4, 1995;
in revised form June 14, 1995