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ESTABLISHMENT OF THE CONFIGUATIONS OF HEXAHYDRO-4-(4-ETHOXYCARBONYL-BUTYL)-3α-HYDROXY-2-OXO-1H-THIENO[3,4-d]IMIDAZOLES FROM PMR SPECTRAL DATA

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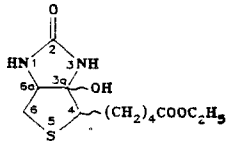
UDC 547.535'785.5:543.422.25

The configurations of isomeric hexahydro-4-(4-ethoxy-carbonylbutyl)-3α-hydroxy-2-oxo-1H-thieno[3,4-d]imidazoles were determined by PMR spectroscopy by means of angular and temperature dependences of the vicinal spin—spin coupling constants (SSCC).

It is known that α,γ- and α,β-ureido(thioureido) aldehydes or ketones can have ring or open forms and can exist in solutions in the form of tautomeric mixtures [1]. We have established that hexahydro-4-(4-ethoxycarbonylbutyl)-3α-hydroxy-2-oxo-1H-thieno[3,4-d]imidazoles I and II have ring structures, according to data from the IR spectra (the presence in the spectra of characteristic absorption for a hydroxy group) and the mass spectra (the absence of fragmentation that is characteristic for oxo compounds [2]). The peak of a molecular ion (m/z 288), from which a molecule of water (m/z 270) and the side aliphatic chain are ejected with the formation of an ion with mass 141, the peak of which is the maximum peak in the spectrum, is observed in the mass spectrum of I. The presence of peaks of ions with m/z 228 and 245 is due to fragmentation of the urea grouping. It was found by PMR spectroscopy that this compound is a mixture of two isomers that differ with respect to the orientation of the hydroxy group attached to the $C_{(3a)}$ atom with respect to the aliphatic chain attached to the $C_{(4)}$ atom. One of these isomers (I) was isolated in pure form and had mp 136-138°C (Found, %: C 50.0, H 6.6, N 9.5. Calculated: C 50.0, H 7.0, N 9.7). Isomer II could not be isolated in pure form, and this compound was therefore studied in the mixture with isomer I.



I cis(R and OH trans), II trans (R and OH cis).

*Deceased.

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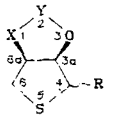
TABLE 1. Parameters of the PMR Spectra* of Solutions of I and II in Deuteropyridine (18°C)

Compound	δ, ppm					J, Hz				
	6a-H	6-H′	6-H″	4-H	N—H	6aH, 6H′	6aH, 6H″	6H′, 6H″	4H, 4′H′	4H, 4′H″
I	4,43	3,30	2,76	3,45	8,61 7,80	6,5	5,4	12,0	4,5	10,1
II	4,46	3,21		3,68	8,44 7,65	5,4	1,0	12,5	4,2	10,1

*The chemical shifts were determined as the centers of the multiplets, and the SSCC (J) were determined as the distances between the lines in the spectra.

The parameters of the PMR spectra of solutions of these compounds in deuteropyridine are presented in Table 1. In assigning the signals to certain protons we used recording of the spectra with spectrometers with different operating frequencies (200 and 360 MHz), the ratios of the integral intensities of the signals, literature analogies, and experiments involving double homonuclear resonance. The configurations of these compounds were determined by means of the angular dependence of the vicinal spin—spin coupling constants (SSCC) [3] and their temperature dependences [4]. The experimentally found temperature dependences of the constants are shown in Fig. 1.

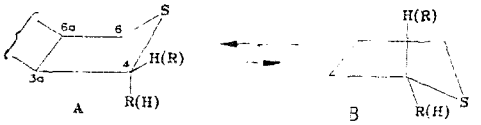
We have previously determined the configurations and have studied the conformational states of a number of similar two-ring compounds III-X [5-10].



III-X

III X=N=, Y=C—C_6H_5, R=H; IV X=NH, Y=C=O, R=H; V X=N—$COOCH_3$, Y==C=O, R=H; VI X=N=, Y=C—C_6H_5, R=$COOCH_3$, trans; VII X=N=, Y=C—C_6H_5, R=$(CH_2)_4COOCH_3$, cis, VIII X=N=, Y=C—C_6H_5, R—$(CH_2)_4COOCH_3$ trans; IX X=NH, Y=C=O, R=$(CH_2)_4COOH$, cis, X X=NH, Y=C=O, R=$(CH_2)_4COOH$, trans

As in the case of biotin [11], a preferred envelope conformation (C_S) of the tetrahydrothiophene ring, the flap of which is turned toward the second ring (A), was found for all of these compounds:



The sum of the vicinal SSCC along the $C_{(6a)}$—$C_{(6)}$ bond ($\Sigma J_{6a,6}$) in the spectra of these compounds is small: It is 4.2-6.7 Hz for III-V, VII, and IX, as compared with 6.6-8.3 Hz (R trans) for VI, VII, and X. The certain increase in the sum of the constants for compounds with a trans configuration of the substituent attached to the $C_{(4)}$ atom (VI, VII, and X) is associated with an increase in the contribution of conformer B, in which the substituent is pseudoequatorially oriented. However, conformation A with a pseudoaxial orientation of the substituent attached to the $C_{(4)}$ atom also remains the preferred conformation for these compounds.

The sum of the vicinal SSCC along the $C_{(6a)}$—$C_{(6)}$ bond for II is 6.4 Hz (Table 1), i.e., it lies in the range of the values of this sum for previously investigated compounds. Of the two constants for this bond, one increases appreciably with an increase in the temperature ($\Delta J_{6aH,6H'}$ = 0.71 Hz when ΔT = 92°C, Fig. 1, line 1), while the other is virtually independent of the temperature ($\Delta J_{6aH,6H''}$ = 0.08 Hz when ΔT = 92°C, Fig. 1, line 3). This behavior of the vicinal constants with a change in the temperature makes it possible to assign $J_{6aH,6H'}$ to the trans constant and $J_{6aH,6H''}$ to the cis constant [4]. The magnitudes of the constants and their temperature dependences correspond to the conformational equilibrium A ⇄ B with preferred conformation A.

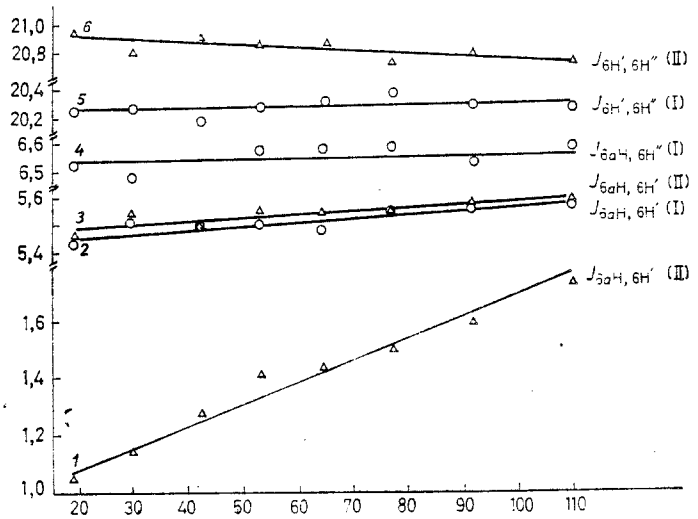


Fig. 1. Temperature dependences of I and II.

For I the sum of the vicinal SSCC along the $C_{(6a)}$—$C_{(6)}$ bond substantially exceeds the analogous sum of the constants for II and for all of the previously investigated compounds: $\Sigma J_{6a,6}$ = 11.9 Hz (Table 1). Both of the vicinal SSCC ($J_{6aH,6H'}$, $J_{6aH,6H''}$) remain virtually unchanged with a change in the temperature (Fig. 1, lines 2 and 4). The increase in the sum of the vicinal constants and the absence of their temperature dependences constitute evidence that for I, in contrast to all of the previously investigated similar two-ring compounds and to II, the populations of the conformations are virtually the same in the conformational equilibrium A ⇄ B, i.e., a significant shift of the conformational equilibrium toward conformation B occurred.

As noted above, a small shift toward conformation B is characteristic for two-ring compounds with a trans configuration of the substituent attached to the $C_{(4)}$ atom and is explaine by the pseudoaxial orientation of this substituent in conformation A. For such an isomer in the case of the compounds under consideration the steric hindrance experienced by the substituent attached to the $C_{(4)}$ atom in conformation A should become greater as a result of replacement of the hydrogen atom attached to the $C_{(3)}$ atom by a hydroxy group cis-oriented relative to it. An increase in the contribution of conformation B should be expected precisely for this isomer. Compound I (a large sum of the vicinal constants, no temperature dependences is therefore the trans isomer, and II is the cis isomer. The calculated torsion angles $\psi_{6a,6}$ and populations of conformation A (P_A) for different values of coefficient J^0 in the Karplus equation are presented in Table 2. Two variants of the assignment of the vicinal constants to cis and trans constants were examined for I, since the absence of temperature dependences does not enable one to make an unambiguous assignment. Since two electronegative substituents (—N— and —O—) are attached to the $C_{(3a)}$ atom, the generally used lower boundary of J^0 (8 Hz) is decreased: J^0 values were limited by the value of $\psi_{6a,6}$ obtained in the calculation: When $\psi_{6a,6}$ = 40°, some bond angles in the tetrahydrothiophene ring are close to 90° [12], i.e., the puckering of this five-membered ring approaches an anomalously large value. The trans-vicinal constants were used in calculating population P_A. It was assumed that the dihedral angles in the CH_2—CH fragment are joined at "equal" 120° values [12]. From Table 2 one can see that the variant of assignment with the large cis-vicinal constant (6.5 Hz) is more suitable for I, since for close populations of conformations A and B (P_A ~ 0.5) the observed constants correspond to a two-ring system with a smaller degree of puckering of the tetrahydrothiophene ring. Equilibrium A ⇄ B when P_A > 0.85 satisfactorily describes the experimental data for II.

EXPERIMENTAL

The PMR spectra of I and II were obtained with Bruker WH-360 and WP-200 spectrometers (360 and 200 MHz). The pulse duration was 1.5 μsec, and the lag between pulses was 1 sec. The solvent was deuteropyridine (C_5D_5N), and the internal standard was tetramethylsilane (TMS). The temperature dependences of the SSCC were obtained with a WP-200 spectrometer. At each point the temperature was determined from the temperature dependence of the chemical shifts of the signals of ethylene glycol. The mass spectrum was obtained with a Jeol JMS-01-

TABLE 2. Torsion Angles $\psi_{6a,6}$ and Populations of Conformation A (P_A) for Different Values of Coefficient J^0

Indexes of $J^{cis}_{6a,6H'}$ Hz	Compound I													Compound II						
	5,4							6,5						5,4						
J^0, Hz	6,8	7,2	7,6	8,0	8,5	9,0	10,0	7,2	7,5	8,0	8,5	9,0	9,5	9,8	6,8	7,2	7,6	8,0	8,5	9,0	10,0
$\psi_{6a,6}$°	27	30	33	35	37	39	43	18	21	26	29	32	34	36	27	30	33	35	37	39	43
P_A	0	0,11	0,20	0,27	0,34	0,40	0,53	0	0,12	0,27	0,36	0,43	0,48	0,51	0,85	0,86	0,88	0,89	0,91	0,92	0,96

Sg-2 spectrometer with direct introduction of the samples into the ion source at 140-160°C. The temperature of the ionization chamber was 130°C, the ionizing voltages were 75 and 15 V, and the emission current was 250 μA.

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CALCULATION OF THE PHYSICOCHEMICAL PROPERTIES OF THIENOPYRIDINES BY THE PARISER–PARR–POPLE (PPP) METHOD

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The dipole moments, diamagnetic susceptibilities, chemical shifts of the ^{1}H, ^{13}C, and ^{14}N nuclei, and the energies of the lowest singlet–singlet transitions of aza-substituted thiophenes and benzo[b]thiophenes were calculated within the framework of the bonded variant of perturbation theory by the Pariser–Parr–Pople (PPP) method. A scale of aromatic character of the investigated class of compounds is given on the basis of the current distributions found.

Thienopyridines, like other structures similar to them, are of substantial theoretical interest, since π-surplus (the thiophene ring) and π-deficient (the pyridine ring) fragments are united in one molecule [1]. In addition, they are also of interest for pharmacology because of the high physiological activity of some derivatives of this series [2]. A method for taking into account the d orbitals of the sulfur atom in describing the electronic structures and physicochemical characteristics of sulfur-containing heterocycles was previously developed [3] within the π-electron approximation of the MO LCAO SCF method on the basis of the Longuet–Higgins model. In the present paper it is used to calculate the dipole moments, energies of the lowest singlet–singlet transitions, diamagnetic susceptibilities, and chemical shifts of the ^{1}H, ^{13}C, and ^{14}N nuclei of a number of thienopyridines.

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