HINDERED INTERNAL ROTATION ABOUT THE C—N PARTIALLY DOUBLE BOND IN N-ACYL DERIVATIVES OF 1,2,3,4-TETRAHYDROQUINOLINE

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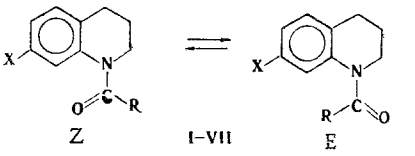
The inhibited internal rotation about the C—N partially double bond in N-acyl-1,2,3,4-tetrahydroquinolines was investigated by NMR spectroscopy. It is demonstrated that these compounds exist in the form of Z and E conformers, and their ratios are determined under the conditions of stereochemical rigidity. The activation parameters of internal rotation about the C—N bond, specifically the barrier to rotation, as a function of the form of the acyl grouping were calculated.

Nuclear magnetic resonance spectroscopy has been used with great success in recent years for the study of processes involving hindered internal rotation about partial double bonds [1].

Hindered internal rotation in N-acyl-1,2,3,4-tetrahydroquinolines has been studied by a number of researchers [2-4]; it was established that these compounds exist in the form of two conformers, viz., Z (endo) and E (exo), which exist in equilibrium.

The present research is devoted to a study of the effect of the nature of R in the acyl grouping and of the substituent in the benzene part of N-acyl-tetrahydroquinolines I-VII on the activation parameters for internal rotation about the C—N bond (specifically, the barrier to rotation) and to shed some light on the problem of the ratios of the existing conformers under the conditions of stereochemical rigidity.



I X=R=H; II X=NO_2, R=H; III X=H, R=CH_3; IV X=NO_2, R=CH_3; V X=NO_2, R=CH_2Cl; VI X=NO_2, R=C_2H_5; VII X=NO_2, R=CF_3

N-Formyltetrahydroquinoline (I) was obtained by reduction of quinoline with formic acid in triethylamine [5], while N-acetyl derivative III was obtained by acylation of tetrahydroquinoline with acetic anhydride [6]. 7-Nitro-N-acyltetrahydroquinolines II, IV, and VII were previously described by some of us [7] and were obtained by refluxing 7-nitrotetrahydroquinoline with the appropriate acylating agents. 7-Nitro-N-propionyltetrahydroquinoline (VI) was similarly synthesized.

The NMR spectra of I-VII were studied; a detailed calculation of the activation parameters by analysis of the complete form of the line (ACFL) was made for I-V.

No difficulties were encountered in the assignment of the signals of the methylene protons of the heterocyclic fragment. The weak-field signal was assigned to the protons in the 2 position, since the deshielding effect of the adjacent nitrogen atom affects the shielding of these protons. The character of the splitting and the magnitudes of the chemical shifts make it possible to assign these signals to the region of methylene protons (Table 1). Signals corresponding to an AMX system with the following spin—spin coupling constant (SSCC) are observed in the aromatic proton region for II and IV-VII: $^3J_{56} \approx 8.5$ Hz, $^4J_{68} \approx 2.0$ Hz, and $^5J_{58} \approx 0$ Hz. Splitting (≈1 Hz) due to coupling through four bonds with the protons in

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TABLE 1. ^{1}H Chemical Shifts (δ, ppm) of N-Acyltetrahydroquinolines at 28°C

Compound	Solvent	2-H	3-H	4-H	5-H	6-H	7-H	8-H	COR
I[a]	DMSO	3,62	1,80	2,72	6,90—7,10			8,19[b]	8,29 (27%) 8,78 (73%)
II[a]	DMSO	3,68	1,90	2,74	7,35	7,78	—	8,15 (67%) 9,11 (33%)	8,32 (33%) 8,90 (67%)
III	$CDCl_3$	3,88	2,06	2,84	6,90—7,50			8,41	2,32
IV	$CDCl_3$	3,88	2,06	2,92	7,29	7,91	—	8,41	2,30
V	$CDCl_3$	3,88	2,10	2,92	7,34	7,98	—	8,52	4,08
VI	$CDCl_3$	3,80	2,02	2,86	7,28	7,90	—	8,48	2,56 (CH_2); 1,20 (CH_3)
VII	$CDCl_3$	3,90	2,14	3,00	7,26	8,02	—	8,62	

[a]Two signals of the acyl substituent and two signals of the 8-H proton are observed for I and II; their percentages are indicated in parentheses. [b]A second signal of the 8-H proton lies in the atomatic proton region.

the 4 position is observed for the 5-H proton (Table 1). The assignment of the signals of the aromatic protons in I and III cannot be made unambiguously without additional experiments because of the pronounced coupled character of this spin system.

Two signals of a formyl proton and two signals of an 8-H proton are observed for I and II at room temperature; this constitutes evidence for the existence of two conformers under these conditions. Only one signal is observed for the remaining compounds at 28°C. On the basis of the singlet form of the signal of the acyl group it has been incorrectly concluded [8, 9] that the N-acyltetrahydroquinolines exist in the form of one E conformer. A study of the dipole moments of these compounds [2] and an investigation of the low-temperature PMR spectra [3, 4] provided evidence for the presence of two conformers in equilibrium. The signal of the acyl substituent is consequently the average signal of two interconverted conformers.

The ^{13}C NMR spectra at various temperatures were obtained for I. Two groups of signals with an intensity ratio of 4:1 corresponding to the E and Z conformers of this compound are observed in the spectrum of a solution in dimethyl sulfoxide (DMSO) at 28°C (Fig. 1a). The use of the method of incomplete suppression of spin—spin coupling made it possible to assign the signals of the quaternary carbon atoms; the signals of the carbon atoms of the heterocyclic fragment were also assigned rather simply. The values obtained (Table 2) are in agreement with the analogous literature data [10].

A study of the PMR spectra of III-V at low temperatures also confirms the existence of two conformers in equilibrium. Broadening of the signals of the protons of the acyl substituents and of the protons attached to C_8 is observed in the spectra when the temperature is lowered. At temperatures below 215°K internal rotation is slowed down so much that signals of both the Z and E conformers are observed in the spectra (Table 3). Internal rotation in N-acyltetrahydroquinolines is more "hindered" in the case of formyl derivatives, for which spectra corresponding to two rotational isomers are observed even at room temperature. Integration of the signals under conditions of stereochemical rigidity, i.e., when both forms show up in the NMR spectra, makes it possible to determine ratios of the Z and E conformers that are in agreement with the literature data [4] (Table 4).

The activation parameters were found by treatment of the temperature dependence of the rate constants in accordance with the Arrhenius equation and transition state theory. To calculate the barrier to internal rotation we use the transformed Eyring equation

$$\Delta G^* = 4.576 \cdot 10^{-3} T [10.319 - \log(K/T)],$$

where K is the rate constant (in reciprocal seconds) at temperature T (in degrees Kelvin). The calculated activation parameters are presented in Table 5.

The following principles are observed in the analysis of the data in Table 5.

1. The barrier to internal rotation (ΔG*) for the N-formyl derivatives is 6-8 kcal/mole higher than for the N-acetyl derivatives. This is probably explained by deviation of

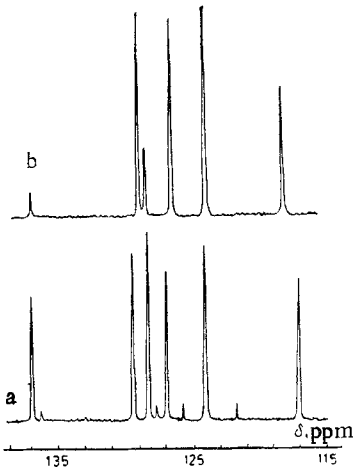

Fig. 1

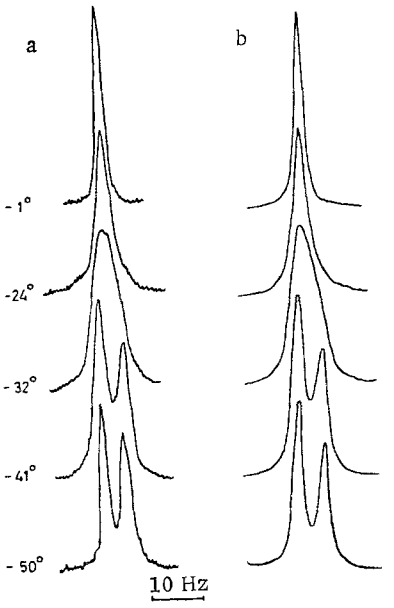

Fig. 2

Fig. 1. ^{13}C NMR spectra of the aromatic carbon atoms of N-formyltetrahydroquinoline in DMSO at 28 (a) and 150°C (b).

Fig. 2. Form of the line of the PMR signal of the protons of the methyl group in N-acetyltetrahydroquinoline observed experimentally (a) and calculated by the method of analysis of the complete form of the line (ACFL) (b).

TABLE 2. ^{13}C Chemical Shifts (δ, ppm) for N-Formyltetrahydroquinolines at 28°C

C_2	C_3	C_4	C_5	C_6	C_7	C_8	C_9	C_{10}	CO
39,9	21,9	26,8	129,6	124,1	127,1	117,1	137,3	128,5	161,3

the acetyl group from the plane of the aromatic ring as a consequence of steric interaction of the bulkier methyl group with the 8-H proton; the conjugation of the unshared pair of the nitrogen atom with the π electrons of the carbonyl group decreases in this case, and this leads to freer rotation about the C–N bond. We have already arrived at a similar conclusion in an analysis of the electronic absorption spectra of the compounds under consideration [11].

2. The positive activation entropies (ΔS*) for II-V indicate possible complication of the internal rotation by processes involving intermolecular interactions.

3. The introduction of a nitro group in the aromatic ring does not have a substantial effect on the activation parameters for inhibited internal rotation.

The determination of the activation parameters of internal rotation by means of PMR spectroscopy is possible in those cases in which the signals of the acyl substituents and the 8-H protons do not fall in the regions of the other signals and cannot be analyzed by the ACFL method. This case is not always realized, and the use of ^{13}C NMR spectroscopy is therefore most informative in the study of internal rotation in N-acyltetrahydroquinolines.

EXPERIMENTAL

7-Nitro-N-propionyl-1,2,3,4-tetrahydroquinoline (VI). A 4.8-g (0.027 mole) sample of 7-nitrotetrahydroquinoline was refluxed with excess propionyl chloride for 1 h, after which the mixture was poured into water, and the precipitate was separated and recrystallized from ethanol to give 5.9 g (95%) of pink crystals with mp 127°C. UV spectrum (ethanol), λ_{max} (log ε) 330 (3.11) and 250 nm (4.08). Found C 61.6; 61.4; H 6.1; 6.0%. $C_{12}H_{14}N_2O_3$ Calculated: C 61.5; H 6.0%.

TABLE 3. Chemical Shifts of the 8-H Protons and the Protons of the Acyl Substituents for III-V at Low Temperatures (solutions in $CDCl_3$)

Compound	Temp., °K	δ, ppm	
		8-H	COR
III	223	a	2,16 (80%) 2,27 (20%)
IV	215	8,79 (57%) 7,86 (43%)	2,45 (57%) 2,36 (43%)
V	228	8,71 (64%) 7,99 (36%)	4,33 (64%) 4,24 (36%)

[a]The signal of the 8-H proton is not separate from the multiplet.

TABLE 4. Conformational Energies (ΔG^0) and Ratios of the Conformers for I-V

Compound	Solvent	Temp., °K	Z, %	E, %	$K=\frac{[E]}{[Z]}$	ΔG^0, kcal/mole
I	DMSO	301	27	73	2,73	−0,6
II	DMSO	301	33	67	2,02	−0,42
III	Mesitylene	301	14	86	6,2	−1,08
	$CDCl_3$	223	20	80	3,95	−0,6
IV	$CDCl_3$	215	57	43	0,76	0,11
V	$CDCl_3$	228	64	36	0,56	0,26

TABLE 5. Free Energies of Activation (ΔG^*), Activation Energies (ΔE^*), and Activation Entropies (ΔS^*) for Inhibited Internal Rotation in N-Acyltetrahydroquinolines

Compound	Solvent	Rigidity temp.,[a] °K	ΔG^*, kcal/mole	ΔS^*, cal-mole^{-1}-deg	ΔE^*, kcal/mole
I	DMSO	308	18,1∓0,1	−4∓1	17,6∓1
I[b]	DMSO	308	18,0∓0,5	−1∓3	18,0∓1
II	DMSO	314	18,7∓0,2	17∓4	24,6∓0,9
	Mesitylene	314	18,0∓0,6	26∓8	26,0∓1,5
III	$CDCl_3$	236	12,1∓0,2	23∓8	20,0∓2,0
IV	$CDCl_3$	223	12,0∓0,3	12∓5	16,1∓1,0
V	$CDCl_3$	226	10,4∓0,1	36∓5	21,9∓1,0

[a]This is the temperature at which $K = 1\ sec^{-1}$. [b]The data were obtained from the ^{13}C NMR spectra, in the remaining cases the data were obtained from the PMR spectra.

The NMR spectra were recorded with a Varian XL-100 spectrometer with an operating frequency for protons of 100 MHz. Conditions involving stabilization with respect to the signal of an internal standard [dimethyl sulfoxide (DMSO) and tetramethylsilane (TMS)] were used in the PMR experiments. The ^{13}C NMR spectra were recorded under conditions of complete suppression of spin—spin coupling of the carbon and proton nuclei with the aid of a pulse method with Fourier transformation. The chemical shifts are presented in parts per million relative to TMS with an accuracy up to 0.01 ppm.

The temperature was measured by means of temperature standards (methanol for low temperatures and ethylene glycol for high temperatures) in accordance with calibration of the temperature dependence of the difference in the chemical shifts in the standards [12].

The rate constants for internal rotation were found by the ACFL method [13] with the aid of the program for the Varian 620/F computer composed in Basic algorithmic language. The resulting temperature dependence of the K constants made it possible to calculate the activation parameters for internal rotation. The temperature-dependent form of the line of the

signal of the protons of the methyl group in N-acetyltetrahydroquinoline was observed experimentally (Fig. 2a) and calculated by the ACFL method (Fig. 2b).

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SYNTHESIS AND REACTIONS OF PYRROLO[2,3-c]AZEPINE DERIVATIVES*

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The construction of the pyrrolo[2,3-c]azepine system by the reaction of 2-oxo-3-hydroxy-4-cyano-2H,1,5,6,7-tetrahydroazepine with glycine ester and subsequent cyclization of the resulting N-substituted amino nitrile in an alcohol solution of sodium ethoxide was studied. The pyrrolo[2,3-c]azepine system was converted to the three-ring pyrimido[4',5':4,5]pyrrolo[2,3-c]azepine system, the alkylation of which gave N,N-dialkyl and N,N,N-trialkyl derivatives. Cyclization of 3-benzyl-4,6-dioxo-5-(N,N-dimethyl)aminoethyl-6H,3,4,7,8,9,10-hexahydropyrimido-[4',5':4,5]pyrrolo[2,3-c]azepine hydrochloride under the influence of phosphorus oxychloride gave the four-ring pyrazino[3,2,1-b,c]azepino[3,4-b]pyrrolo[3,2-d]-pyrimidine system. The structures of the compounds obtained were confirmed by their IR, UV, and PMR spectra.

In developing our research on the preparation of condensed heterocyclic compounds on the basis of lactams, in the present research we studied methods for the construction of the pyrrolo[2,3-c]azepine system and the transition from the latter to various multiring compounds using 2-oxo-3-hydroxy-4-cyano-2H-1,5,6,7-tetrahydroazepine (I) [2] as the starting compound.

The presence in I of enolized keto and CN groups created the prerequisites for the construction of a pyrrole ring with the participation of these groups as in the synthesis of furo[2,3-b]pyridines [3]. With this end in mind we investigated the reaction of hydroxy nitrile I with glycine ester. A study of this reaction showed that a substituted amino nitrile (II) is formed most smoothly when hydroxy nitrile I is heated with excess glycine ester hydrochloride in glacial acetic acid in the presence of sodium acetate. Pyrrolo[2,3-c]azepine (III) was obtained in good yield by cyclization of amino nitrile II by heating in an alcohol solution of sodium ethoxide.

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