SYNTHESIS AND SOME STRUCTURAL CHARACTERISTICS OF CAFFEINE AND ISOCAFFEINE HOMOLOGS

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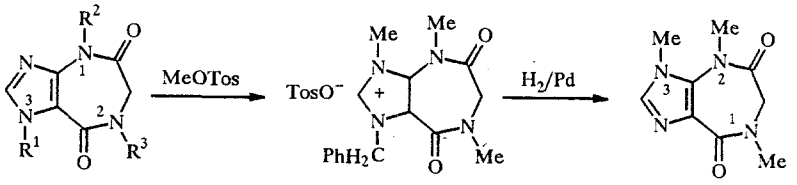
As a result of methylation and subsequent catalytic debenzylation, 1-benzylimidazo[4,5-e][1,4]diazepine was converted to the corresponding imidazo[5,4-e][1,4]diazepine. Thermodynamic parameters of inversion in isomeric imidazo[4,5-e]- and imidazo[5,4-e][1,4]diazepines were determined by dynamic ^1H NMR. The total energy of the compounds being compared was calculated by molecular-mechanics methods.

Imidazo[4,5-e][1,4]diazepines I, cyclic homologs of natural xanthines, have been described previously [1-3]. We synthesized a new heterocyclic system, imidazo[5,4-e][1,4]diazepine II, an isomer of compound Ia.



I III II

I a $R^1=R^2=R^3=Me$, b $R^1=CH_2Ph$, $R^2=R^3=Me$

Substance II was obtained from diazepine Ib by N-methylation followed by debenzylation of the obtained salt III over palladium.

Methyl p-toluenesulfonate was chosen as the methylating agent because when methyl iodide was used to convert compound Ia to the required compound III, debenzylation occurred and the methiodide of compounds Ia and II was formed [4].

Dynamic ^1H NMR was used to study the relation of the thermodynamic inversion parameters of the seven-membered ring in isomers Ia and II to their structure (Table 1).

In the spectrum of compound Ia at room temperature, protons of the CH_2 group gave a singlet at 3.98 ppm (Fig. 1a). With decreasing temperature, the peak from these protons broadened, and at 238 K it split into two components (Fig. 1b), which indicates retardation of inversion of the seven-membered ring. At 173 K, methylene protons gave a quartet corresponding to the AB spin system (Fig. 1c). The peak from the B proton partially overlapped the peak of $N_{(3)}$—CH_3 protons (integrated intensity 4H).

TABLE 1. Positions of Peaks in PMR Spectrum of Compounds Ia (in CD_2Cl_2) and II (in $CDCl_3$) at 293 K

Compound	Chemical shift, δ, ppm						Barrier to inversion of seven-membered ring, ΔG, kJ/mole
	N^1—CH_3	N^2—CH_3	N^3—CH_3	=CH	CH_2		
					A	B	
Ia	3,39	3,14	3,90	7,66	3,98*		47,9±0,2
II	3.17	3.35	3.74	7.43	4.13	3.74**	63.2±0.2

*At T = 173 K the chemical shifts of the methylene protons were δ_A = 4.17 ppm and δ_B = 3.90 ppm, and $^2J_{AB}$ = −14.9 Hz.

**$^2J_{AB}$ = −13.3 Hz.

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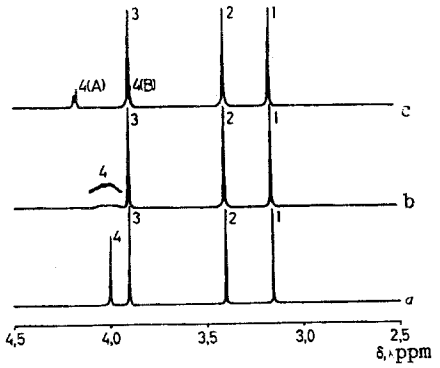

Fig. 1

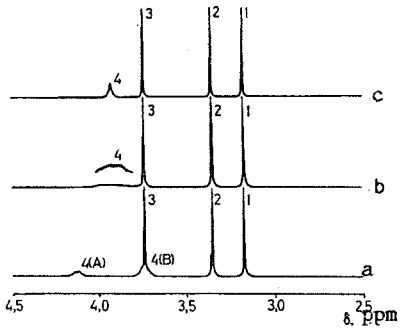

Fig. 2

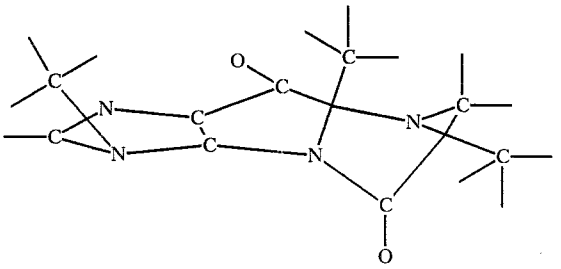

Fig. 3

Fig. 1. Fragment of PMR spectrum of 0.01 mole of compound Ia per liter of CD_2Cl_2: a) 293 K; b) 238 K; c) 173 K. Assignment: 1) $N_{(2)}$—CH_3; 2) $N_{(1)}$—CH_3; 3) $N_{(3)}$—CH_3; 4) CH_2.

Fig. 2. Fragment of PMR spectrum of 0.01 mole of compound II per liter of $CDCl_3$: a) 293 K; b) 313 K; c) 323 K. Assignment: 1) $N_{(1)}$—CH_3; 2) $N_{(2)}$—CH_3; 3) $N_{(3)}$—CH_3; 4) CH_2.

Fig. 3. Model of preferred conformation of compound II.

In the case of compound II at room temperature, the protons of the CH_2 group are magnetically unequivalent, and the spectrum contained two coalesced spin doublets corresponding to an AB-type system (Fig. 2a).

The peak of one of the CH_2 protons was below the peak of the $N_{(3)}$—CH_3 protons (integrated intensity 4H). During heating, these peaks broadened, and at 313 K they coalesced into one peak (Fig. 2b). With further heating, the peak from the CH_2 group narrowed and at 323 K it had a chemical shift of 3.92 ppm (Fig. 2c). Hence, we can conclude that even at room temperature in the case of compound II the inversion process of the seven-membered ring was hindered.

The barriers to inversion of the seven-membered rings were calculated according to Eyring's equation. As is evident from Table 1, the barrier to inversion of compound II is 1.5 times as great as that of compound Ia.

The total energy of the studied compounds was calculated by methods of molecular mechanics, and their preferred conformations were modeled. For compound II, we observed steric proximity of the methyl groups $N_{(2)}$—CH_3 and $N_{(3)}$—CH_3, which led to their mutual collision (Fig. 3). As a result, the strain of the seven-membered ring increased, and its inversion was hindered. In the case of compound Ia, such steric interaction was absent. This was confirmed by the calculated values of the total energy for compounds Ia and II, 106 kJ/mole and 181 kJ/mole, respectively.

Thus, comparison of the conformations of cyclic caffeine homolog Ia and the cyclic isocaffeine homolog (isomeric to it) that we synthesized enables determination of steric hindrances in the molecule of the latter, which probably explains the significant difference of the barriers to inversion of the seven-membered ring in the investigated compounds.

EXPERIMENTAL

The course of the reaction and the purity of the substances were monitored by thin-layer chromatography on Silufol UV-254 plates. The ^1H NMR spectra were obtained with a Bruker AM-250 (250 MHz) spectrometer in a Fourier-transform mode. The pulse width was 4 μsec, the response time was 3.047 sec, the number of storages was 8, and the delay between pulses was 3 sec. The internal standard was TMS, and the rounding error δ was 0.002 ppm. The temperature in the spectrometer

sensor was established and maintained with precision 0.5°C. Stabilization was carried out with deuterium nuclei of the solvent ($CDCl_3$ and Cd_2Cl_2).

The data of elemental analysis for C, H, N, and S correspond to the calculated results.

1,4,7-Trimethyl-4,5,7,8-tetrahydro-6H-imidazo[4,5-e][1,4]diazepine-5,8-dione (Ia). This compound was synthesized according to [5].

1-Benzyl-3,4,7-trimethyl-5,6,7,8-tetrahydro-6H-imidazoline[4,5-e][1,4]diazepine-5,8-dione p-Toluenesulfonate (III, $C_{23}H_{26}N_4O_5S$). A mixture of 2.84 g (10 mmoles) of compound Ib and 5 g of methyl p-toluenesulfonate was kept at 130°C for 4 h. Then 100 ml of ether was added to the cooled mixture, and the whole was left for 24 h. The precipitate was filtered and washed on the filter with ether and hexane. The mp was 204-205°C. PMR spectrum ($CDCl_3$): 9.76 (1H, singlet, 2-H); 7.03-7.54 (9H, multiplet, Ph); 5.50 (2H, quartet, CH_2—Ph, J = 7.1); 4.50, 3.50 (2H, quartet, 6-H, J = 15.0); 3.93 (3H, singlet, 3-CH_3); 3.19 (3H, singlet, 4-CH_3); 2.99 (3H, singlet, 7-CH_3); 2.27 ppm (3H, singlet, CH_3—Ph). The yield was 4.5 g (96%).

1,5,8-Trimethyl-4,5,7,8-tetrahydro-6H-imidazo[5,4-e]diazepine-4,7-dione (II, $C_9H_{13}N_4O_2$). We dissolved 2.35 g (5 mmoles) of compound III in 50 ml of methanol. About 50 mg of freshly prepared palladium black was added and hydrogenated with H_2 at atmospheric pressure and 20°C until disappearance of the starting compound (monitoring by thin-layer chromatography). After completion of the reaction, the catalyst was filtered and washed on the filter with methanol. The filtrates were combined, and 0.28 g (5 mmoles) of KOH was added. After dissolution of the KOH, the methanol was evaporated to dryness on a rotor-type evaporator. The dry residue was thoroughly extracted with hot acetone. The acetone was evaporated. The obtained product was recrystallized from an acetone—hexane mixture. The mp was 236-238°C. The yield was 0.64 g (62%).

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