GEOMETRICAL ISOMERISM OF 2'-PIPERIDINOMETHYL-5-ARYLIDENECREATININES

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The aminomethylation of 5-arylidenecreatinines with paraformaldehyde and piperidine in benzene leads to 2'-piperidinomethyl-5-arylidenecreatinines, in which the geometrical isomerism in relation to the C(2) = N(2') and C(5) = C bonds was observed.

The 5-arylidenepseudothiohydantoins are aminomethylated at the exocyclic nitrogen atom by secondary amines in hydroxyl-containing mediums [1], and give the products of the bisaminomethylation at the exo- and endocyclic nitrogen atoms in benzene [2]. The piperidinomethyl derivatives of the aza analogs of these compounds - the 5-arylidenecreatinines (Ia-e) - could not be obtained in hydroxyl-containing mediums. The procedure for the isolation of the Mannich bases, analogous to that utilized in the case of the thia analogs [1], led to viscous oils not undergoing separation into the individual substances. The 2'-piperidinomethyl-5-arylidenecreatinines (IIa-e) (Table 1) were obtained by performing the reaction in abs. benzene with paraformaldehyde as the methylene component.

The site of the aminomethylation was established by the comparison of the PMR spectra of the Mannich bases (IIa-e) with the spectra of their thia analogs [1] and the corresponding imidazolo[3,2-a]triazines [3], the products of the aminomethylation of the compounds (Ia-e) by primary amines: the absorption of the methylene protons at 4.16 ppm (Table 1) corresponds unconditionally to the N(2')-substitution, whereas the resonances of the N(3)CH2 protons should occur at a lower field.
The compounds (IIa-e) are very labile. They decompose to the initial 5-arylidenecreatinines (Ia-e) on chromatography on Silufol and on attempts to recrystallize them from ethanol or aprotic solvents and to reprecipitate them at the temperature of 20°C from benzene with hexane.

In the PMR spectra of the compounds (IIa-e) (Table 1), as well as the spectra of the 5-arylidenecreatinines (Ia-e) [4], the aromatic protons absorb with the characteristic splitting into two AA'MM'X multiplets [compounds (IIa, c)] or two AA'XX' doublets [compounds (IIb, d,e)]. According to the data of the work [4], such a type of aromatic absorption indicates the imino structure of these compounds in DMSO-D_6. The singlet of the methylene protons of the aminomethyl group at 4.16 ppm lies at a higher field than could possibly be expected for the sterically more favorable 2'-E-isomer of the imino form [3, 5]. On the other hand, the position of the signal of these protons is almost the same as that in the 2'-Z-isomers of the thia analogs of the compounds (IIa-e) [5].

The occurrence of the compounds (IIa-e) in the form of the sterically hindered 2'-Z-isomers may be explained on the assumption that they are obtained as a result of the deamino-demethylation of the resulting intermediate 2,3-bispiperidinomethyl derivatives of 5-arylidenecreatinines having the 2'-Z-configuration, and that the barrier to the 2'-Z → 2'-E isomerization is adequately high. The following facts are fully in agreement with such an explanation. The PMR spectrum of the solution of the equimolar mixture of the compounds (Ie) and (IIe) in DMSO-D_6, taken 3 days after preparation, contains the new signal at 4.30 ppm, which has approximately the same intensity as the signal at 4.16 ppm, which we assign to the absorption of the methylene protons of the 2'-E-isomer obtained as a result of the transfer of the aminomethyl group from the 2'-Z-isomer to 5-p-bromobenzylidenecreatinine (Ie). The 2'-Z-isomer of the compound (IIe), dissolved in CDCl_3 at the temperature of 20°C, transforms spontaneously into the less soluble 2'-E-isomer which precipitates from the solution after several minutes. In the PMR spectrum of the solution of this isomer in CDCl_3, the signal of the methylene protons lies at 4.32 ppm. Such a position for the signal of the N(2')CH_2 is typical of the E-configuration of the methylene group in relation to the C(2)=N(2') bond [3].

A feature of the PMR spectra of the Mannich bases (IIa-e) is the splitting of the resonances of the N(1)CH_3 and C(5)=CH protons (Table 1) which could be connected with the already noted solvolytic instability of these compounds, which decompose to the initial 5-arylidenecreatinines (Ia-e) by the action of the residual water of the solvent. However, such an interpretation of the PMR spectra of the compounds (IIa-e) is in agreement neither with the reproducibility of the relative intensity of the components of the "doublets" nor with the absence of the signal of the piperidinocarbinol methylene protons, which should be formed as a result of the hydrolytic deaminomethylation of these compounds, from the spectra. Such an interpretation also does not allow an explanation of the spectral picture arising after the addition of 1-2 drops of D_2O or H_2O to the solution of the compound (II) in DMSO-D_6. Thus, besides the signal of the methylene protons at 4.16 ppm in the PMR spectrum of compound (IIe), there appears the signal at 3.92 ppm; the ratio of the intensities is ~1:2, i.e., the same as for the components of the "doublets" before the addition of water. The signal of the methine proton at 6.10 ppm is displaced to low field to 6.20 ppm, and the signal at 6.16 ppm remains in place. The signal of the methyl protons at 3.14 ppm is displaced to 3.08 ppm, almost combining with the unchanged signal at 3.10 ppm; the relative intensity of the components of the "doublets" is unchanged. The signals of the methine (6.10 ppm) and methyl (3.10 ppm) protons undergo only a weak paramagnetic or diamagnetic shift correspondingly by 0.02 ppm in the PMR spectrum of 5-p-bromobenzylidenecreatinine (Ie) after the addition of D_2O.

In all probability, the explanation is that the Mannich bases (IIa-e) exist in the form of the mixture of the cis,trans-isomers in relation to the C(5)=C bond. Such isomers were isolated for the structurally close 2-oxo- and 2-thio-5-arylidene-4-thiazolidinones [6]. The signal of the methine proton at 6.16 ppm for the main 5'-Z-isomer of compound (IIe) lies at a lower field by comparison with the signal at 6.10 ppm for the minor 5'-E-isomer due to the deshielding influence of the carbonyl group [6]. On the addition of a small amount of D_2O or H_2O to the solution in DMSO-D_6, the signals of the methine and methylene protons of the 5'-E-isomer of this compound are shifted owing to solvation effects. At the same time, the signals of the analogous protons of the 5'-Z-isomer are insensitive to hydration. On the other hand, the signal of the methyl protons of the 5'-Z-isomer at 3.14 ppm are more sensitive to the added water than the analogous signal of the 5'-E-isomer at 3.10 ppm. The singlet character of the signals of the C(5)=CH (6.10 ppm) and CH_3 (3.10 ppm) protons in the compound (Ie) is explained by the fact that it only occurs in the form of the 5'-E-isomer according to the method of isolation [7].