CHEMISTRY

MOLECULAR GEOMETRY AND ELECTRON STRUCTURE OF 8-ARYL-3,5-DI[(*E*)-1-ARYLIDEN]-1,2,3,5,6,7-HEXAHYDROCYCLOPENTANO[*b,e*]PYRIDINES

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ABSTRACT

Series were synthesized: 8-aryl-3,5-di[(*E*)-1-aryliden]-1,2,3,5,6,7-hexahydrocyclopentano[*b,e*] pyridines. Owing to the unique chemical structure of distyrylpyridines there is an opportunity to determine their preferable geometry in solutions from the simple analysis of their ^{1}H-NMR spectra. The spectral data confirms the preferably planar conformation for the compounds with side five-membered aromatic rings. In the case of six-membered aromatic cycles the steric hindrances appears, which induces definite violation in planarity of such molecules, but only slight distortion of conjugation between their fragments. In the cases, when additional steric hindrance exists (*ortho*-substituents in the side rings), the planarity of styryl fragments, and especially – the conjugation of pyridine moiety with the cycle at C-8 decreases substantially.
The intramolecular charge transfer from the side aromatic to the central pyridine moiety takes place at excitation of the studied distyrylpyridine molecules. In the excited S_1 state many of them must become more planar as well.

Introduction. Three main directions can be classified among synthetic ways of getting dicyclopentanopyridines:

1. Condensation of aldehydes and ketones with ammonium and amines;
2. High-temperature reactions of cyclopentanone and its derivatives with amines;
3. The use of 1.5-diketons to develop a dicyclopentanopyridine system.

The first studies of the reaction of aldehydes and ketones with ammonium were done by Hanch. In 1920 A.Ye Chychybabin was the first to use cyclic ketones in this synthesis. It has been found out that condensation can go on in different ways and it depends on both the aldehyde nature and the reaction conditions. V. Balian, R. Jeyaraman, studying the condensation of cyclic ketones, namely cyclohexanone and cycloheptanone with aromatic aldehydes in the presence of ammonium acetate, found out that azabicycloketones were formed in this reaction [1-3].

So, when condensation conditions are identical, cyclohexanone gives azabicycloketones, and cyclopentanone – 8-aryliden-1,2,3,5,6,7-dicyclopentano[*b,e*]pyridines. The authors assume that the reason of such behavior of cyclopentanone is possibly in its conformational differences from cyclohexanone. Cyclopentanone mostly exists in “half-chair shape” conformation, and negatively-charged carbanione centers, which play a major role in the formation of azabicycloketones, are difficult to spatially attack with positive centers of iminodycarbonine ion, which is formed of aromatic aldehydes and ammonia [4-6].

Thus, it is assumed that in this reaction the development of benzylidencyclopentanone, formed of cyclopentanone and benzaldehyde, occurs first; it takes part in this trimolecular condensation with further creation of 8-aryl-diaryliden-1,2,3,5,6,7- dicyclopentano[*b,e*]pyridines. This mechanism describes the interaction of reactants quite objectively, it has some inaccuracy though [7]. Modeling a molecular structure shows a close spatial contact between C_8-hydrogen and hydrogen atom of benzylidene grouping. The purpose of the research is to work out synthesis methodology of 8-aryl-3,5-di[(*E*)-1-aryliden]-1,2,3,5,6,7- hexahydrocyclopentano[*b,e*]pyridines and to identify the conformation of synthesized compounds in solutions by comparing chemical sal shifts in ^{1}H-NMR spectra.

Results and Discussion. Stereo-chemical modeling confirms that hexahydrocyclopentano[*b,e*]pyridines may exist in the form of three geometric isomers: *EE*-, *EZ*- and *ZZ*-, which differ by configuration from substituents near double C=C-links of styryl groupings [8-9].

Among them *EZ*- and *ZZ*-isomers are compounds with complicated steric effect and changed conjugation of π-system, where styryl residues leave the area of a molecule to a great extent. Steric obstacles are fewer in number in conformations of *EE*-isomer [10-11]. Thus the formation of mostly *EE*-isomers is expected to occur in the conditions of carrying out the synthesis of 8-aril-3,5-di[(*E*)-1-aryliden]-1,2,3,5,6,7- hexahydrocyclopentano[*b,e*]pyridines.

^{1}H-NMR and ^{13}C-NMR spectra prove that synthesized dicyclopentanopyridines are symmetric compounds, in which signals of atom-substituents in 2 and 6, 3 and 5 positions of central core coincide (symmetry group C_{2v}). Due to this coincidence proton signals of aryliden groups have twice as higher intensity as similar protons of aryl residue in position 8. Proton signals of methyl groups look like complex multiplets which are in strong, about 3 m.p., fields. Methyliden protons are descreened considerably, which is why their signals are shifted to "aromatic" area of spectrum, up to 7.5.m.p. These data, along with fluorescence spectra and statistics of quantum-chemical calculations, are the main proof in favor of *EE*-configuration of synthesized compounds. In the studied reaction of three-component condensation we could get hexahydrocyclopentano[*b,e*]pyridines, which had *EZ*-configuration (compounds 1.1-1.2), only in some cases.

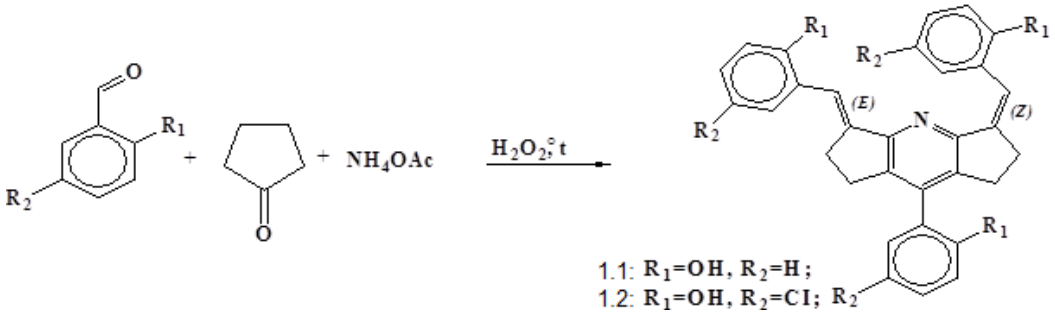

Fig. 1. Hexahydrocyclopentano[b,e]pyridines with EZ-configuration (compounds 1.1-1.2)

EZ-configuration of compounds 1.1-1.2 is confirmed with data of spectra ^{1}H-NMR (Fig. 2.), where signals of atom-substituents in positions 2 and 6, 3 and 5 of central core are not equivalent, contrary to 8-aryl-3,5-di[(*E*)-1-aryliden]-1,2,3,5,6,7- hexahydrocyclopentano[*b,e*]pyridines with *EE*-configuration (Fig. 1.) [12-15].

Each proton gives its signal in NMR spectrum of *EZ*-isomer 1.1. Proton signals of methyl groups look like multiplets which are at 1.4-3.0 m.p. As it was expected, proton signals of every aromatic core look like duplets with constant spin-spin interaction (KCCB) of 8 Hz and 2 Hz, and duplet of duplets with the same constant values. Proton signals of one of the cores were considerably shifted to weak fields comparing with the other two. Most likely they belong to protons of aromatic residue in position 8. Signals of methyliden protons were shifted to weak fields, up to 8.6 m.p. Proton signals of hydroxygroups were separated as to their position in spectrum. Two of them are at level 12.3 and 12.4 m.p., and another one – at 4.6 m.p. Strong-field position of the latter shows its significant screening/covering with cyclic flows of aromatic residue, which is most likely possible for proton of hydroxygroup residue in position 8. A significant shift of signals of the first two protons to weak fields, up to 12.6 m.p., is possible when they form intra-molecular hydrogenous bond. Such assumption is confirmed with color reaction (intensive brown coloring) of compounds 1.1-1.2, treated with alcohol solution of ferric chloride (III). Computer-aided modeling of *ZZ*-isomer geometry states that such compound as *EE*-isomer must have degenerate (simplified) spectrum ^{1}H-NMR [16]. Due to

compound symmetry and fast exchange of conformations for styryl residues, signals of symmetrically positioned protons in *EE*-isomer must coincide as well.

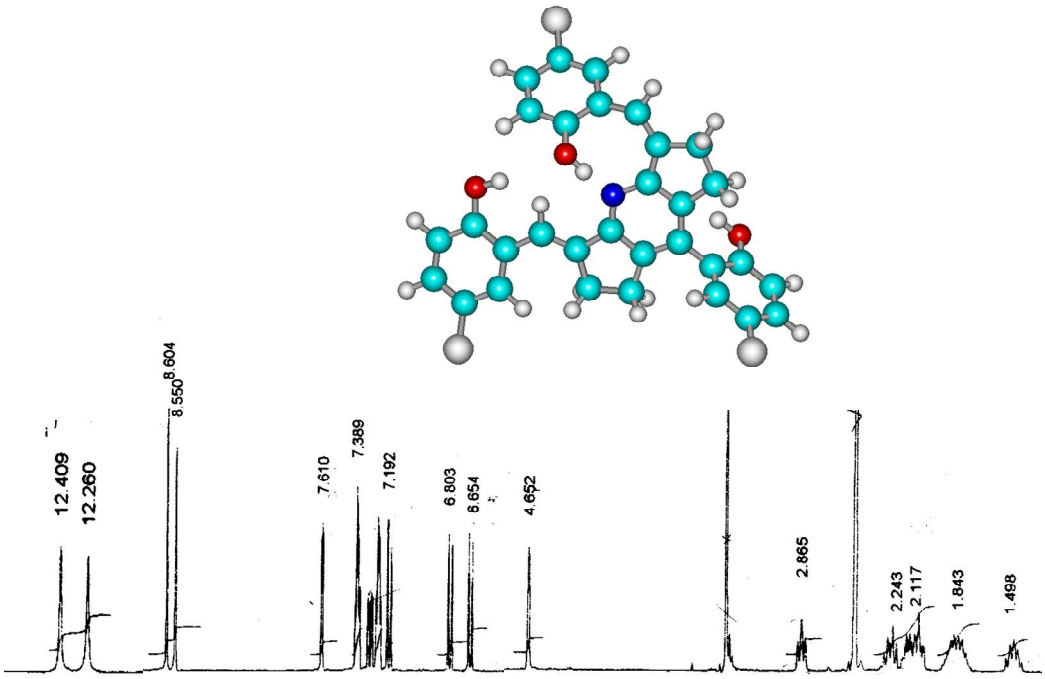

Fig. 2. Molecule geometry (optimized within PM3 method) and spectrum ^{1}H-NMR 4-chloro-2-3.5-di[(E)-1-(5-chloro-2-hydroxy phenyl)methyliden]-1,2,3,5,6,7-1,2,3,5,6,7-hexahydrocyclopentano[b,e]pyridine

Along with 8-aryl-3,5-di[(*E*)-1-aryliden]-1,2,3,5,6,7- hexahydrocyclopentano[*b,e*]pyridines, the products, which were not mentioned in this reaction of three-component condensation of aldehydes, cyclopentanone and ammonium acetate (ammonium), were singled out and characterized, namely diarylidencyclopentanones 1.3-1.6 (Fig. 3.). These compounds were registered in reaction mixture using TLC method in all cases, but they could be received only when the reaction was stopped at early stages, heating period was short and the product mixture was further separated by means of column chromatography [17-20].

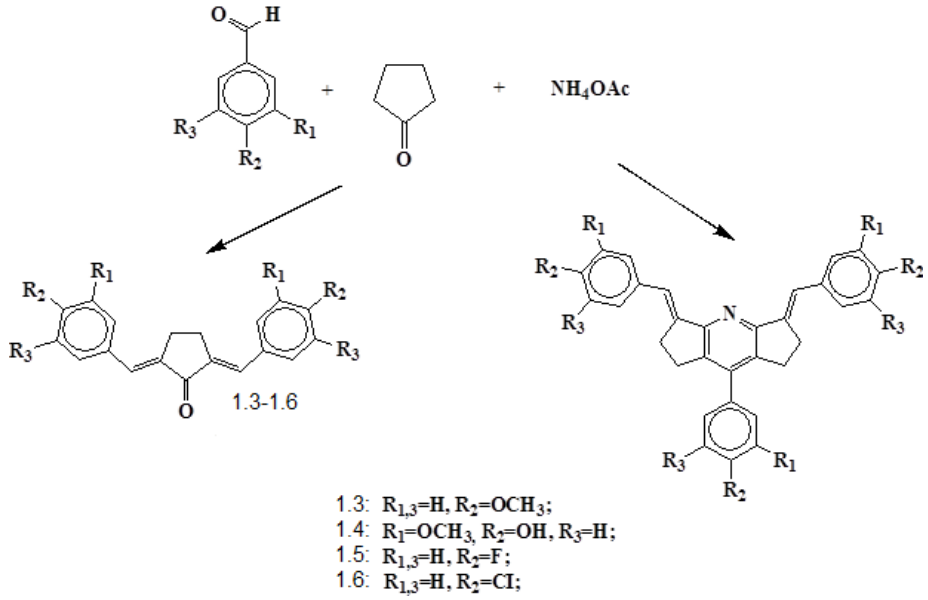

Fig. 3. Diarylidencyclopentanones 1.3-1.6

In case of the interaction between 9-antracencarbaldehyde and 2-hydroxy-1-naphtalenaldehyde, only diarylidencyclopentanones were formed, which probably can be explained by spatial obstacles during condensation of these aldehydes.

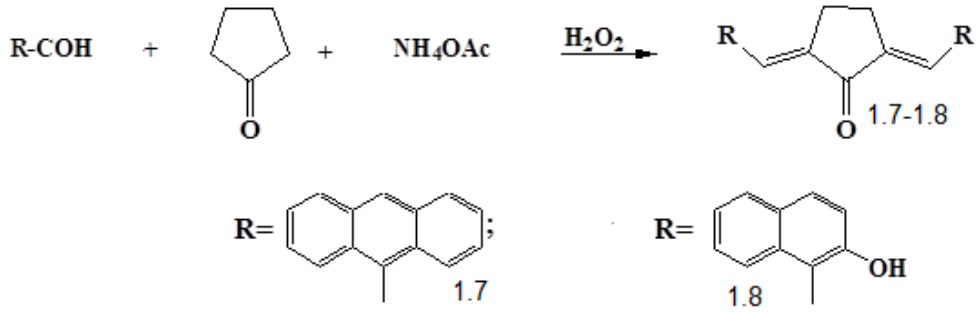

Fig. 4. Diarylidencyclopentanones 1.7-1.8

So, in the condensation reaction of aldehydes, cyclopentanone and ammonium acetate or ammonium, besides *EE*- and *EZ*-isomers of 8-aryl-3,5-di[(*E*)-1-aryliden]-1,2,3,5,6,7-hexahydrocyclopentano[*b,e*]pyridines, diarylidencyclopentanones were also formed.

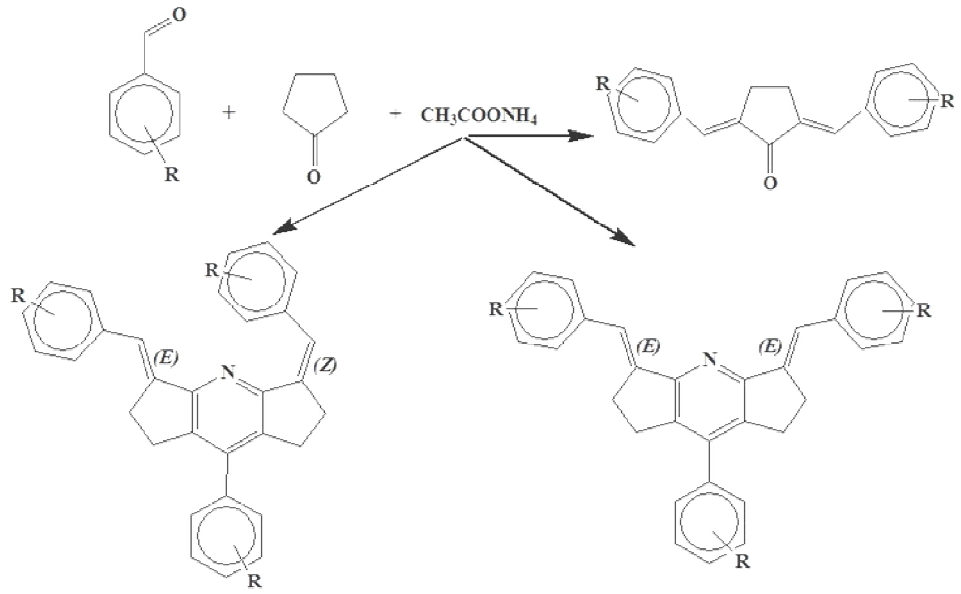

Fig. 5. EE- and EZ-isomers of 8-aryl-3,5-di[(E)-1-aryliden]-1,2,3,5,6,7-hexahydrocyclopentano[b,e]pyridines, diarylidencyclopentanones

All the received 8-aryl-3,5-di[(*E*)-1-aryliden]-1,2,3,5,6,7-hexahydrocyclopentano[*b,e*]pyridines as well as diarylidencyclopentanones were received in a chromatographically clean form and characterized by physical-chemical analysis methods. Masses of molecular ions of all substances correspond to calculated values based on mass-spectrometry data. Molecules of 8-aryl-3,5-di[(*E*)-1-aryliden]-1,2,3,5,6,7-hexahydrocyclopentano[*b,e*]pyridines must differ significantly in the geometry of conjugated molecule part both in a regular state and in a very labile state.

They can be classified into two groups according to this parameter:

a) Derivatives, where indirect substituent R is pentatomic heterocycle, are mostly in planar conformation;

b) In cases when side substituents R are hexamerous aromatic cycles, molecule loses planar nature because of steric obstacles. In this situation cycle at C-8 shifts away from the area of a central pyridine ring the most, at angle ~50°.

In case of *ortho*-substituted compound, all side benzene cycles come out of the pyridine moiety area at a big angle due to steric obstacles. This conformation state of molecules is confirmed

with ^{1}H-NMR spectra. It is known that proton escape from the area of conjugated system of multiple bonds leads to the shift of its signal in the spectrum into a strong field [21]. Comparing the signal position of *ortho*-protons of side substituents for compounds 8-aryl-3,5-di[(*E*)-1-aryliden]-1,2,3,5,6,7-hexahydrocyclopentano[*b,e*]pyridines in a much stronger field than proton of residue in position 8 of dicyclopentanopyridine (Table 1). At the same time, the opposite is seen for all other compounds 1.3-1.5: regardless of the solvent used, signals of *ortho*-protons of the residue at C-8 are in much stronger fields. This situation is typical for the solutions both in low-polar chloroform and in high-polar DMSO. In our opinion, this fact is a direct proof that in the solutions only molecules of the derivatives with pentamerous cycles are mainly in planar conformation and other compounds 1.3-1.5 are in non-planar one. At least one aromatic residue in their molecules has a considerable deviation from the area of pyridine moiety. Further specification of molecule conformation state of pyridines 1.3-1.5 can be done based on the chemical shifts of proton signals of methyl groups. Depending on their spatial position, aromatic residues can screen uncover these protons [22-25].

Thus, symmetry of the molecules of dicyclopentanopyridines causes the situation when proton signals of two aryliden residues in their ^{1}H-NMR spectra coincide in pairs. Because of this, they differ in intensity from proton signals of aryl residue. Due to such unique peculiarity in the structure, the feasibility to identify conformation of these compounds in solutions by means of comparing chemical signal shifts in their ^{1}H-NMR spectra was found. Spectroscopic findings state that compounds with pentamerous heteroaromatic substituents have the highest planar conformation. If substituents are hexamerous aromatic cycles, they move from the molecule area to the angle at which conjugation among individual molecule parts maintains. Provided additional steric difficulties occur (*ortho*-constituent in side rings), planar state of styryl fragments and in particular conjugation of pyridine moiety with a cycle in position 8 decreases considerably.

Table 1. Data of ^{1}H-NMR spectroscopy for derivative compounds from dicyclopentano[*b,e*]pyridine, used to restore their conformation in solutions

	Compound	Solvent	$\delta_{стирил}$*	$\delta(C_8)$*	$\delta_{стирил} - \delta(C_8)$	2- та 6- CH_2- groups, δ(H)	1- та 7- CH_2- groups, δ(H)
1.3	8-(4- methoxyphenyl)-3,5- di [(E)-1-(4-methoxyphenyl) methylidene]-1,2,3,5,6,7-hexahydrodicyclopenta[b,e]pyridine $C_{34}H_{31}NO_3$	$CDCl_3$	7.54	7.32	0.22	3.10-3.18	2.92-3.00
1.4	4-3,5-di[(E)-1-(4- hydroxy-3- methoxyphenyl) methylidene]-1,2,3,5,6,7-hexahydrodicyclopenta[b,e]pyridine-8-il-2-methoxyphenyl $C_{34}H_{31}NO_6$	$CDCl_3$ DMSO	7.05 7.18	6.90 7.04	0.15 0.14	3.09-3.17	2.95-3.03
1.5	3,5-di[(E)-1-(4-fluorophenyl)methylidene]-8-(4-fluorophenyl)- 1,2,3,5,6,7-hexahydrodicyclopenta[b,e]pyridine $C_{31}H_{22}F_3N$	$CDCl_3$	7.47	7.24	0.23	3.13-3.21	2.96-3.04

* Chemical shifts (p.p.m.) for *ortho*-protons of the styryl moieties or of the cycle at C-8 of pyridine moiety

Experimental. Materials. General methodology of synthesis of 8-aryl-3,5-di[(*E*)-1-aryliden]-1,2,3,5,6,7- hexahydrocyclopentano[*b,e*]pyridines.

Two methods with the use of improved methodology were used to carry out synthesis of dicyclopentanopyridines, the initial variant of which was described by V. Balian, R. Jeyaraman [1].

The solution of benzaldehyde (10 mmol), cyclopentanone (5 mmol) and ammonium acetate (50 mmol) and 30 %-hydrogen pyroxide (5 mmol) was exposed in ethanol (25 ml) for 1 hour at temperature 70-80°C. Then reaction mixture was cooled, and as a result sediment was formed after 12 hours of exposure at room temperature. It was filtered and washed with acetone. Cleaning of the compounds was done with column chromatography on silica gel, using the mixture of chloroform-methanol (98:2, v/v) as eluent. Recrystallization was done from acetone.

Instruments. ^{1}H-NMR spectra were measured on spectrometer Varian Mercury (400 MHz). Thin-layer chromatography (TLC) was done on Silufol UV - 254 plates in chloroform-methanol system, 9:1.

Quantum-chemical calculations of 8-aril-3,5-di[(*E*)-1-aryliden]-1,2,3,5,6,7-hexahydrocyclopentano [*b,e*] pyridines geometry were made with semi-empirical methods AM1 and PM3, using MOPAC 6.0 program.

Reagents and solvents. The solvents, used for synthesis, were classified as “clean”. The control over the reaction and purity of synthesized compounds was exercised by thin-layer chromatography (TLC) on silica gel-60, F-254, 5x20 cm (Selecto Scientific, USA) in chloroform-methanol mixture (98:2, 9:1, 85:15, v/v) using УФ-detector with irradiation equal to 254 and 356 nm.

Conclusions. Series were synthesized: 8-aryl-3,5-di[(*E*)-1-aryliden]-1,2,3,5,6,7-hexahydrocyclopentano[*b,e*]pyridines. The possibility to identify the conformation of synthesized compounds in solutions by means of comparing chemical signal shifts in spectra ^{1}H-NMR was found.

It has been established that the compounds with pentatomic heteroaromatic substituents have the highest planar conformation. If the substituents are hexamerous aromatic cycles, they leave the molecule area and move to the angel where conjugation among individual molecule parts maintains

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