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Unusual Structure and Reactions of 1-Phenlpyrazol-5-one Annulated with 1-Methylpiperidine. A Rare Case of Auto-Alkylation

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Abstract—The interaction of 1-alkyl-3-alkoxycarbonylpyperidin-4-ones with phenylhydrazine has led to 5-alkyl-2-phenyl-3,3a,4,5,6,7-hexahydro-2*H*-pyrazolo-[4,3-*c*]pyridin-3-ones. The prepared compounds are unstable and undergo a series of uncommon transformations; their mechanisms have been suggested basing on the structural analysis of the product mixtures.

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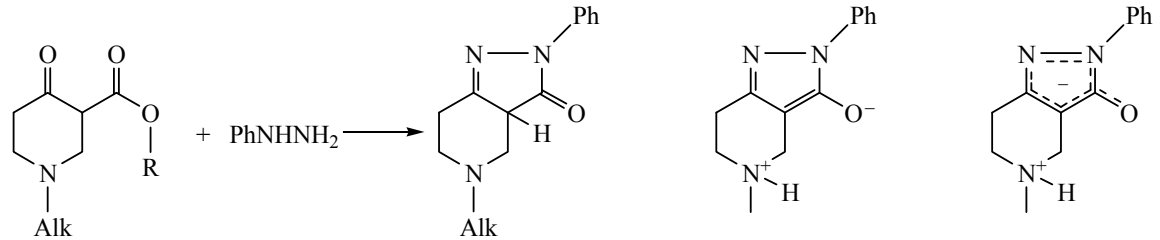
The stability of 2-aryl-3,3a,4,5,6,7-hexahydro-2*H*-pyrazolo[4,3-*c*]pyridin-3-one derivatives significantly depends on the nature of the substituent at N^5 atom. The 5-acyl, 5-aryl, or 5-pyridinylmethyl derivatives are usually stable substances existing in one of tautomeric forms, common for non-annulated pyrazol-5-ones as well (CH-, OH-, or NH-tautomer) [1–5]. Such compounds have been suggested as bioactive compounds and drugs [3–5]. The attempts to prepare 5-alkyl (Alk = Me, Et, or Pr) derivatives **II** under standard conditions of pyrasol-5-ones synthesis have failed. In particular, refluxing of keto esters **I** with phenylhydrazine in an alcohol or in benzene leads to a complex mixture of 5–7 different products [6] instead of anticipated **II**.

In order to extend the investigation of this unexpected behavior, this work aimed to determine the structure of the compounds isolated from the above-describe reaction mixtures and to explain the instability of 5-alkyl-2-aryl-3,3a,4,5,6,7-hexahydro-2*H*-pyrazolo[4,3-*c*]-pyridin-3-ones.

5-Alkyl-2-phenyl-3,3a,4,5,6,7-hexahydro-2*H*-pyrazolo[4,3-*c*]pyridin-3-ones **IIa–IIc** could prepared from the respective phenylhydrazine and 1-alkyl-3-alkoxycarbonylpiperydin-4-ones **Ia–Ic** only at room temperature or below. They could not be recrystallized, thus, the crystal structure elucidation by X-ray diffraction was impossible. Likely, their structure could be represented by zwitterions **III** or **IV**, which was unusual for pyrazol-5-ones. Additionally, three hydrochlorides of 5-methylpyrazolone **IIa** were obtained, differing in the acid to base ratio (2**IIa**·HCl, 2**IIa**·3HCl, and **IIa**·2HCl) [7], the attempts to isolate the base from them failed as well.

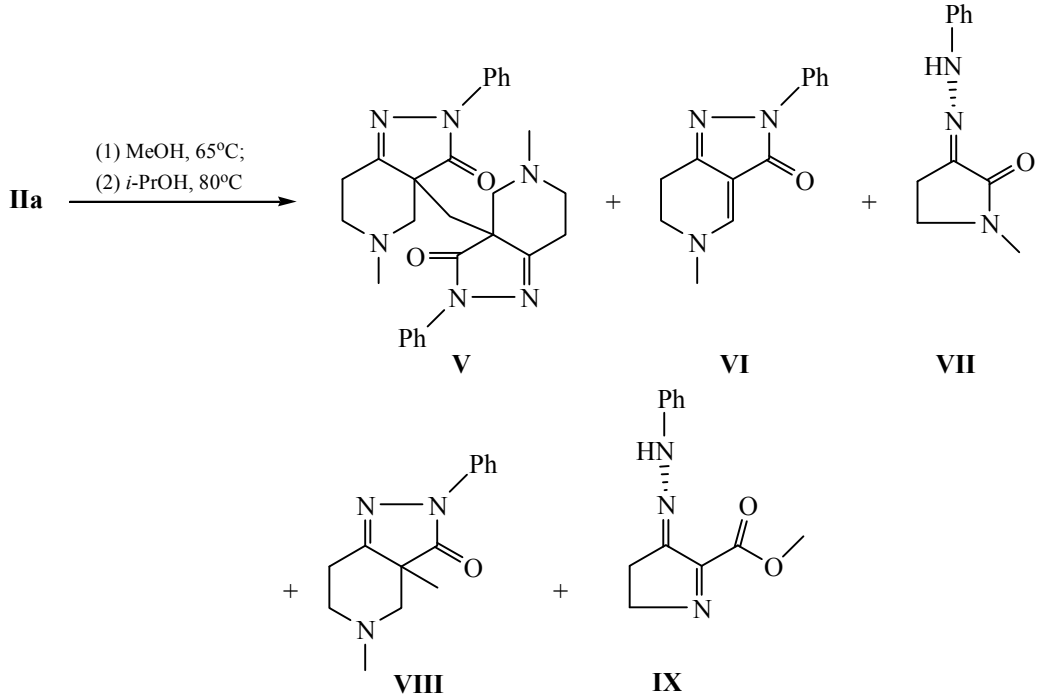
Thus, a preliminary conclusion at that stage was as follows. In the solutions, 5-alkylpyrazolones **IIa–IIc**



Ia–Ic **IIa–IIc** **III** **IV**

Alk = Me (**a**), Et (**b**), Pr (**c**); R = Me or Et.

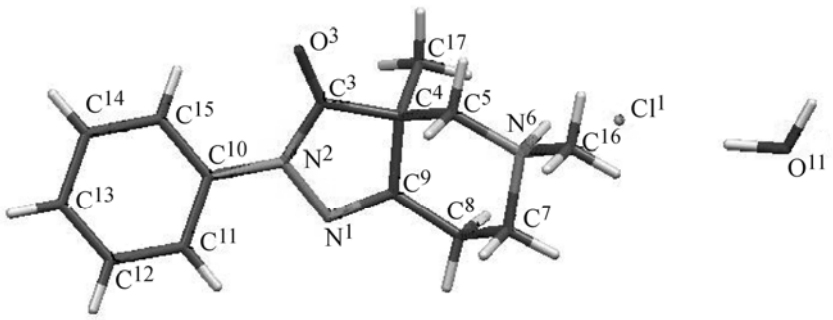
were completely converted into a complex mixture of compounds; the transformation was especially fast in the halogenated solvents. Similar processes occurred in the course of attempts to recrystallize them from alcohols or other solvents, to prepare them in boiling solvents (alcohols or benzene), to isolate **IIa** from its hydrochlorides. By means of TLC of the mixtures, 5 to 7 products were detected. First, from the products of transformations of 5-methyl derivative **IIa**, three compounds were isolated and identified: bis(5-methyl-2-phenyl-3,3a,4,5,6,7-hexahydro-2*H*-pyrazolo[4,3-*c*]-pyridin-3-one-3a-yl)methane (**V**), 5-methyl-2-phenyl-2,3,6,7-tetrahydro-5*H*-pyrazolo[4,3-*c*]pyridin-3-one (**VI**), and 1-methyl-3-(*E*-phenylhydrazono)pyrrolidin-2-one (**VII**) [8, 9]. Depending on the preparation conditions, the purification method, and the solvent nature, the composition of mixture of 5-alkyl-pyrazolones **IIa–IIc** decomposition products varied significantly. For example, upon dissolution in DMSO, **IIa** was almost quantitatively converted to **IV**. The major products of the reaction of phenylhydrazine with keto esters **Ia** or **Ib** in the boiling solvent (alcohol or benzene) were **V, VI**, and **VII**. When **IIa** prepared at 15–20°C was refluxed in methanol during 4 h, the yellow oily substance was obtained, besides product **V**. According to ^{1}H, ^{13}C and ^{15}N NMR data, that yellow matter contained approximately equal amounts of 2-phenyl-3a,5-dimethyl-3,3a,4,5,6,7-hexahydro-2*H*-pyrazolo[4,3-*c*]pyridin-3-one (**VIII**) and 2-metoxy-carbonyl-3-phenylhydrazonopyrroline (**IX**).



In contrast to the IR spectra of **V** ($\nu_{C=O}$ 1698 cm^{-1}), its dihydrochloride ($\nu_{C=O}$ 1708 cm^{-1}), **VI** ($\nu_{C=O}$ 1663 cm^{-1}), and **VII** ($\nu_{C=O}$ 1678 cm^{-1}) [8, 9], in the spectra of **IIa** and its dihydrochloride there were no distinct bands in the region of C=O stretching; the bands in the range of NH group vibrations (above 3000 cm^{-1}) were absent as well. Instead, an intensive broadened band in the range of 2100–2600 cm^{-1} was observed, assigned to ν_{CN^+H}. Noteworthily, the same band was found in the spectrum of dichloride **V**.

In the ^{1}H NMR spectra of **IIa** registered in D_2O and CD_3OD, only phenyl and methyl signals were clearly detected; apparently that was a result of proton exchange processes. The signals of methylene groups were observed as wide singlets, sometimes poorly resolved into triplets. The mobile proton signal was not detected in the spectra.

Basing on the collected spectral data, we concluded that in crystals and in the solutions (D_2O and CD_3OD) **IIa** could not exist in one of the usual pyrazolone forms (as CH-, OH- or NH-tautomer), but it was a zwitterionic tautomer **III** or **IV**. The latter form was likely more stable, as one of cations of 2**IIa**·HCl revealed that structure [7]. We suppose that it was the presence of the quaternary ammonium group in **IIa** that caused its specific properties.



General view of hydrochloride hydrate **VIII**·HCl·H_2O molecule in crystal. Selected bond lengths and angles: N^1–N^2 1.417(2), N^1–C^9 1.284(2), C^3–C^4 1.521(3), C^4–C^9 1.500(3), C^8–C^9 1.487(3) Å; $N^1N^2C^3$ 112.4(1)°, $N^2N^1C^9$ 106.8(1)°, $N^1C^9C^4$ 114.2(1)°, $C^3C^4C^9$ 100.1(1)°, $C^5N^6C^7$ 112.2(1)°; $N^1N^2C^{10}C^{11}$ 16.5(3)°.

Compounds **V–VII** were isolated in the individual forms, and their structures were confirmed with the IR spectroscopy and 1D and 2D NMR experiments (COSY, ^{1}H–^{13}C/^{1}H–^{15}N HSQC, and HMBC). Using 2D DOSY and 1D DPFG NOE, we measured the self-diffusion coefficients and NOE. Moreover, the structures were confirmed by X-ray diffraction [8, 9]. Unfortunately, we failed to separate compounds **VIII** and **IX**, and in that case NMR studies were carried out with their mixture. However, the signals of **VIII** and **IX** in ^{1}H NMR spectra ($CDCl_3$) could be discriminated taking advantage of the DOSY method, due to noticeably different self-diffusion coefficients, 1.32×10^{-9} m^2/s (**VIII**) and 1.06×10^{-9} m^2/s (**IX**). Then, their structures were elucidated via a variety of homo- and heteronuclear correlation NMR methods. The good agreement of the experimental ^{13}C/^{15}N chemical shifts with those computed by the DFT GIAO method additionally confirmed the conclusions on the structures.

According to the NOE data and comparison of the calculated and measured ^{13}C/^{15}N chemical shifts, only the *E*-isomer of **VII** existed in DMSO-d_6, whereas in $CDCl_3$ it appeared as mixture of *E*- and *Z*-isomers (~1 : 1). Strong Overhauser effect between NH and H^4 protons confirmed that **IX** existed in the form of *E*-isomer in $CDCl_3$.

The 3a-methyl derivative **VIII** formed stable hydrochloride that was isolated in the form of monohydrate. In this work, its structure was for the first time determined by X-ray diffraction; it was found that **VIII**·HCl·H_2O formed monoclinic crystals (space group $P2_1/c$). The geometry of the molecule is shown in the figure.

To summarize, we suggest that the reason for a variety of the above-discussed transformations of **IIa–IIc** is the zwitterionic structure of its molecule **IV** containing the protonated nitrogen. Possibly, the zwitterion is in tautomeric equilibrium with the classic tautomeric forms of pyrazolones, as demonstrated by smooth oxidation to dehydropiperidine **VI**. The formation of 3a-methylpyrazolone **VIII** can be explained by a rare case of auto-alkylation with **IIa** ammonium group at the 3a-C atom of another **IIa** molecule with simultaneous piperidine ring contraction to give phenylhydrazone **IX**. The pathways to diheterylmethane **VI** and phenylhydrazone **VII** are still unclear. Formation of **VI** upon heating of **IIa** in ethanol, propanol-2, or benzene, and when using keto ester **Ib** as a precursor excluded the previously suggested participation of formaldehyde in this process [6]. (It was previously stated that formaldehyde could be formed via oxidation of methanol that was in turn evolved from methyl keto ester **Ia**).

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