Vanillin Esters of Aliphatic Acids in the Synthesis of 4,7-Phenanthroline Derivatives

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Abstract—Condensation of vanillin esters of aliphatic acids with 6-aminoquinoline and cyclic c-diketones (1,3-cyclohexanedione and dimedone) afforded new 2-methoxy-4-(11-oxo-7,8,9,10,11,12-hexahydrobenzo[b][4,7]-phenanthrolin-12-yl)phenyl esters of carboxylic acids.

Vanillin, 4-hydroxy-3-methoxybenzaldehyde, is a well-known naturally occurring substance used in manufacturing confectionery, perfumery, and cosmetics. Inasmuch as vanillin molecule contains a highly reactive carbonyl group, this compound is of interest as an efficient reagent for organic synthesis. We are developing new synthetic approaches to building up fused nitrogen-containing heterocycles of aza- and diazaphenanthenone series (benzop-[a]phenanthridines, benzo[7]quinolones, and 4,7-phenanthenolines [1–4]) that bring a wide range of aromatic aldehydes into condensation with 2-naphthyl-6-aminoquinoline, and CH-acids. As a source of methoxyphenyl substituent and of methine fragment for the structure of aza-heterocycles vanillin plays an exclusive role in the synthesis of biologically active compounds: analogs of bactericides, cardioprotectors, enzyme inhibitors, analgetics, and alkaloids [5–8].

The arising heterocycles possess low reactivity due to their complicated structure and sparing solubility in organic solvents. Therefore their further modification is difficult. It is presumably that an introduction into the heterocycle molecule of an alkylphenoxy carbonyl group with the chain in the alkyl from C1 to C12 would change the relation between hydrophilic and lipophilic characteristics of the compound and would extend its biological opportunities. We carried out the esterification of the hydroxy group in the vanillin with acyl chlorides of aliphatic acids aiming at involving vanillin esters in reaction with aromatic amines and CH-acids in order to prepare previously unknown alkylcarbonyl derivatives of aza- and diazaphenanthenone.

Here we report on results of the study of vanillin aliphatic acids esters Ia–k behavior in the condensation with 6-aminoquinoline (II) and cyclic β-diketones, 1,3-cyclohexanedione (III) and 5,5-dimethyl-1,3-cyclohexane-dione (dimedone) (IV). The condensation was performed with esters of carboxylic acids (C1−C12) both with linear and branched chain, and also with esters of monochloro-acetic and 3-(4-methylphenoxy)propionic acids (see scheme).

Esters Ia−k were obtained in preparative yield (75–85%) from acyl chlorides and vanillin by heating at reflux in dchioromethane in the presence of pyridine. The condensation of esters Ia−k with 6-aminoquinoline (II) and 1,3-cyclohexanedione (III) or dimedone (IV) was carried out by heating at reflux in 1-butanol equilibrium amounts of reagents without catalyst. The reaction afforded in 60–92% yield individual 2-methoxy-4-(11-oxo-7,8,9,10,11,12-hexahydrobenzo[b][4,7]-phenanthrolin-12-yl)phenyl carboxylates (Va−k) and their dimethyl derivatives Vla−k. The formation of products of benzo[b]fusion indicates that in the three-component reagents mixture first diketone III or IV reacts with aldehyde Ia−k (a) or with amine II (b) affording respectively enol (A) or enamine (B). The reaction of intermediates (A) or (B) with the third component (II or I) results in formation of the same enaminketoster (C) that on dehydration is converted into compounds Va−k or Vla−k. The theoretically presumable alternative (c) of a reaction going through isolation of azomethine that is observed at the use as CH-acids of cyclic monocarbonyl compounds [1, 3] does not occur in the reaction we study between vanillin carboxylates I, 6-aminoquinoline (II), and diketones III and IV, for this reaction pathway should have provided derivatives of benzo[b][4,7]phenanthrolone (D).

The synthesized alkylphenoxy carbonyl derivatives of benzo[b][4,7]phenanthroline Va−k and Vla−k are colorless or light-yellow substances; their characteristics are
compiled in Table 1. As seen from Table 1, the structure of alkyl group R, the presence of a halogen atom or of a methylphenoxy substituent in the vanillin ester molecule, and also the introduction of methyl groups into the β-diketone molecule do not significantly affect the yield of the target products. The maximum yield was obtained with compounds Vf and VIIf with alkyl group chain C₅. A considerably reduced yield of 4,7-phenanthrolines VI and VIIh, i (R = C₃H₇, C₁₀H₂₃) is due apparently to losses at isolation caused by better solubility in alcohol. It is worth noting that at longer alkyl substituent and at introduction of methyl groups into the molecule of the phenanthroline ester its solubility in water grows. This fact increases the opportunities of the compounds for biological testing [9, 10] and finding substances with a wide range of physiological activity.

The structure of compounds Va–k and VIa–k was established on the force of IR, NMR, and mass spectra. In the IR spectra of phenanthrolines Va–k and VIa–k are present the characteristic bands of the stretching and bending vibrations of NH group at 3310–3300 and 1655–1650 cm⁻¹ respectively. The stretching vibrations of the keto group conjugated with the enamine moiety appear at 1615–1610 cm⁻¹. The carbonyl of the ester group gives rise to a strong absorption band in the region 1640–1630 cm⁻¹. The shift of this band to low frequency region is obviously due to involvement of the ester group into intermolecular hydrogen bonds.