Preparative Synthesis of 4-Hydroxy(Alkylolox, Arylolox)-3-methoxy(ethoxy)phenylmethylene(4-carboxyphenyl)amines

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Received December 17, 2004

Abstract—By reactions of vanillin, vanillal, and their esters with 4-aminobenzoic acid in methanol formerly unknown E-isomers of azomethines (Schiff’s bases) were prepared.

DOI: 10.1134/S1070428002120084

Azomethines (Schiff’s bases) are widely used as biologically active compounds, liquid crystals, dyes, luminophors, and polymer stabilizers [1–4]. Based on azomethines efficient drugs were developed exhibiting antidepressant, anticonvulsant, antimicrobial, soporific, psychotropic, nematocidal, antiphlogistic, antitumor, etc. action [5, 6]. Owing to the presence of a polarized C=N heterobond the azomethines are valuable initial products for the synthesis of heterocyclic compounds [7] and β-arylamino ketones, efficient agents of topical anesthesia [8, 9].

In this study we developed a preparative synthesis of previously unknown derivatives of available natural aldehydophenols (vanillin and vanillal) and of their esters I. The condensation of vanillin and esters I with 4-aminobenzoic acid (II) in anhydrous methanol while heating at reflux gave rise to 4-hydroxy(alkylolox, arylolox)-3-methoxy(ethoxy)phenylmethylene(4-carboxyphenyl)amines IIIa–IIIy and IVa–IVk. The reaction was complete within 1.5–2 h, occurred under mild conditions with no catalyst that ensured the retention of the labile ester group. As a result of the process initial compounds I and II were converted in preparative yields 90–95% into the corresponding azomethines with a reactive carboxy group IIIa–IIIy and IVa–IVk. It is presumable that the synthesized compounds IIIa–IIIy and IVa–IVk would prove to be promising for investigating their biological, phototropic, and photochromic activity, spectral characteristics, for preparation therefrom valuable products and optical materials [6], and for further application as accessible synthons in a condensation with CH-acids in order to obtain β-arylamino ketones [8, 9].

The structure of prepared azomethines IIIa–IIIy and IVa–IVk was confirmed by elemental analysis, IR, UV, 1H NMR spectra, and by titrimetric evaluation of the molecular weight. According to the 1H NMR spectra the azomethines obtained were individual E-isomers of 98±1% purity. In the 1H NMR spectra of these compounds the
characteristic signals of the proton HC=N appeared as a singlet at 8.5 ppm. The chemical shift of the proton in the Z-isomer is located usually by 0.5 ppm downfield due to its occurrence in the deshielding field of the benzene ring from the amino acid part of the molecule [10].

In order to confirm the spatial arrangement of compounds obtained IIIa–IIIb and IVa–IVk we carried out quantum-chemical calculations of the heat of formation \((H_f)\) for \(E\)- and \(Z\)-isomers of compounds IIIb, IIIp, IVb, and IVg in the framework of the semiempirical approximation MNDO-PM3 [11] applying GAMESS [12] software. We performed a total optimization of all bond lengths, bond and dihedral angles in the compounds under investigation. The calculations gave the following values of \(H_f\) kcal mol\(^{-1}\), for \(E\)-isomers: \(-136.6\) (IIIb), \(-100.8\) (IIIp), \(-141.5\) (IVb), \(-105.6\) (IVg); for \(Z\)-isomers: \(-136.1\) (IIIb), \(-100.3\) (IIIp), \(-141.1\) (IVb), \(-104.8\) (IVg).

The quantum-chemical calculations revealed that the \(E\)-configuration is more energetically favorable by 0.4–0.7 kcal mol\(^{-1}\) than the \(Z\)-configuration. The data of the quantum-chemical calculations are well consistent with the X-ray diffraction analysis studies of related compounds [13–15].

**EXPERIMENTAL**

IR spectra were recorded on a Fourier spectrometer Nicolet Protege-460 from samples pelletized with KBr. UV spectra were measured on a spectrophotometer Specord UV Vis from \(1 \times 10^{-4}\) M solutions in methanol.

\(^1\)H NMR spectra were registered on a spectrometer Tesla BS-587A (100 MHz) from 5% solutions in \((CD_3)\)SO, chemical shifts were measured from an internal reference OMTS. The molecular weights were determined by alkalimetric titration of carboxy groups with 0.1 N solution of NaOH in the presence of phenolphthalein as indicator. Vanillin esters I were prepared by procedure [16].

**4-Hydroxy(alkyloxy, aryloxy)-3-methoxy-(ethoxy)phenylmethylene(4-carboxyphenyl)-amines IIIa–IIIy and IVa–IVk (Schiff’s bases). General procedure.** In 50–100 ml of anhydrous methanol was dissolved 0.01 mol of vanillin, vanillal, or their ester I, and 0.01 mol of 4-aminobenzoic acid (II) (for compounds IIIy and IVk 0.02 mol) was added, the solution obtained was heated at reflux for 1.5–2 h and left standing for 20–30 h at 20–23°C. The separated precipitate of azomethines IIIa–IIIy and IVa–IVk was filtered on a glass frit, washed with a little of methanol, and dried in a vacuum. The obtained compounds IIIa–IIIy and IVa–IVk were sufficiently pure and did not require recrystallization.

The used methanol was repeatedly applied after distillation through a Vigreux column.

**4-Hydroxy-3-methoxyphenylmethylenе(4-carboxyphenyl)amine (IIIa).** Yield 94%, mp 208–209°C (from methanol). IR spectrum, \(\nu\), cm\(^{-1}\): 1850–3650 (OH), 3071, 3009 (CH\(_\text{Ar}\); and =CH), 2960, 2924, 2852 (CH\(_{\text{alk}}\)), 1681, 1660 (C=O), 1630 (C=N), 1584, 1513, 1454, 1430, 1367 (Ar), 1315, 1284, 1218, 1167, 1121, 1026, 973 (CO), 855, 816, 776, 740, 697, 659, 635, 613 (CH\(_\text{Ar}\)).

UV spectrum, \(\lambda_{\text{max}}(\epsilon): 206(16000), 234(10000), 295(11000), 335(14000)\). \(^1\)H NMR spectrum, \(\delta\), ppm: 3.96 s (3H, CH\(_3\)), 6.50 br.s (1H, OH), 6.55–7.95 m (7H, C\(_6\)H\(_5\) and C\(_6\)H\(_4\)), 8.50 s (1H, HC=N), 9.82 s (1H, CO\(_2\)H). Found, %: C 66.57; H 5.02; N 4.89. \(M^+\) 265.6. \(C_{15}H_{13}NO_4\). Calculated, %: C 66.41; H 4.83; N 5.16. \(M^+\) 271.3.

**Acetoxy-3-methoxyphenylmethylenе(4-carboxyphenyl)amine (IIIb).** Yield 90%, mp 212–213°C (from methanol). IR spectrum, \(\nu\), cm\(^{-1}\): 2000–3620 (OH), 3080, 3010 (CH\(_\text{Ar}\); and =CH), 2975, 2940, 2920, 2890, 2880, 2840, 2800 (CH\(_{\text{alk}}\)), 1759, 1681 (C=O), 1629 (C=N), 1600, 1581, 1510, 1464, 1449, 1430, 1369 (Ar), 1315, 1287, 1270, 1219, 1194, 1160, 1114, 1031, 1014, 976, 949 (CO), 873, 860, 834, 774, 756, 699, 673, 640, 609 (CH\(_\text{Ar}\)).

UV spectrum, \(\lambda_{\text{max}}(\epsilon): 205(23000), 220(18000), 280(22200), 295(22200), 315(13000)\). \(^1\)H NMR spectrum, \(\delta\), ppm: 2.28 s (3H, CH\(_3\)COO), 3.88 s (3H, CH\(_3\)O), 6.40–8.10 m (7H, C\(_6\)H\(_5\) and C\(_6\)H\(_4\)), 8.53 s (1H, HC=N), 9.94 s (1H, CO\(_2\)H). Found, %: C 65.46; H 5.04; N 4.20. \(M^+\) 298.1. \(C_{17}H_{12}NO_4\). Calculated, %: C 65.17; H 4.83; N 4.47. \(M^+\) 313.3.

**4-Propionyloxy-3-methoxyphenylmethylenе(4-carboxyphenyl)amine (IIIc).** Yield 92%, mp 184–185°C (from methanol). IR spectrum, \(\nu\), cm\(^{-1}\): 2000–3650 (OH), 3075, 3055, 3010 (CH\(_\text{Ar}\); and =CH), 2965, 2939, 2924, 2875, 2851, 2880 (CH\(_{\text{alk}}\)), 1757, 1683 (C=O), 1630 (C=N), 1599, 1585, 1504, 1464, 1417, 1367 (Ar), 1315, 1287, 1275, 1216, 1204, 1167, 1138, 1125, 1076, 1033, 1010, 971 (C–O), 891, 865, 823, 804, 774, 748, 698, 661, 612 (CH\(_\text{Ar}\)).

UV spectrum, \(\lambda_{\text{max}}(\epsilon): 206(24000), 220(19000), 280(22000), 295(22000), 315(14000)\). \(^1\)H NMR spectrum, \(\delta\), ppm: 1.27 t (3H, CH\(_2\)CH\(_3\)), 2.54 q (2H, CH\(_2\)), 3.88 s (3H, CH\(_3\)O), 6.40–8.12 m (7H, C\(_6\)H\(_5\) and C\(_6\)H\(_4\)), 8.52 s (1H, HC=N), 9.93 s (1H, CO\(_2\)H). Found, %: C 66.32; H 5.41; N 4.07. \(M^+\) 309.6. \(C_{18}H_{14}NO_5\). Calculated, %: C 66.05; H 5.23; N 4.28. \(M^+\) 327.3.

**4-Butyroxy-3-methoxyphenylmethylenе(4-carboxyphenyl)amine (IIIb).** Yield 92%, mp 139–140°C (from methanol). IR spectrum, \(\nu\), cm\(^{-1}\): 2100–3650 (OH), 3080, 3069, 3008 (CH\(_\text{Ar}\); and =CH), 2965, 2935, 2877, 2850,