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# Condensation Products of 1-Aryl-4-carboxy-2- pyrrolidinones with *o*-Diaminoarenes, *o*-Aminophenol, and Their Structural Studies

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ABSTRACT: *A series of 2-substituted benzimidazoles, benzoxazoles were synthesized by the condensation reactions of 1-aryl-4-carboxy-2-pyrrolidinones and aromatic ortho-diamines or ortho-aminophenol. Alkylation of benzimidazoles with iodoalkanes led to 1-aryl-4-(1-alkyl-1H-benzimidazol-2-yl)-2-pyrrolidinones or 1,3-dialkylbenzimidazolium iodides. N-Substituted γ-amino acids were prepared by the hydrolysis of 1-aryl-4-(1H-benzimidazol-2-yl)-2-pyrrolidinones in sodium hydroxide solution, followed by treatment with acetic acid. The structure of the synthesized products was investigated using IR and $^{1}H$, $^{13}C$ NMR spectra, MM2 molecular mechanics, and AM1 semiempirical quantum mechanical methods.* © 2006 Wiley Periodicals, Inc. Heteroatom Chem 17:47–56, 2006; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20171

## *INTRODUCTION*

The condensation of *o*-diaminobenzenes with carboxylic acids or their derivatives is the most important method for synthesis of a wide range of benzimidazoles. The range of reaction conditions used is quite wide—from merely heating the diamines with carboxylic acid to heating in the presence of acids such as hydrochloric acid [1–3], PPA [4–7], and others. Careful choice of reaction conditions is essential if good yields are to be obtained in all instances [8,9]. The heating of reagents together in the presence of hydrochloric acid, usually around 4 M, are the most widely used conditions (Philips method) [10]. Fused heterocycles such as benzimidazoles, benzoxazoles are very useful intermediates for the development of pharmaceutical compounds.

The synthesis of 2-substituted benzimidazoles and benzoxazoles with 1-aryl-2-pyrrolidinone fragment and the features of the structural details of the obtained products are presented in this paper.

## *RESULTS AND DISCUSSION*

Most of 2-substituted benzimidazoles **2** were obtained by heating a mixture of 1-aryl-4-carboxy-2-pyrrolidinones and 1,2-diaminobenzene at 170°C for 2 h and then at 230°C for 30 min. The mentioned derivatives were also prepared by the Philips method, but in worse yields. Compound **2e** was obtained by the Philips method in 17% yield while heating without solvent gave 79% yield.

It should be noted that only those of 4-carboxy-2-pyrrolidinones possessing halogen in aromatic ring

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reacted under conditions of the Philips method. Otherwise, reaction practically failed. In the case of the reaction catalyzed by the hydrochloric acid, the formation of benzimidazole ring and the yields depend probably on the polarization of the carbonyl bond in carboxyl group [11].

1-Aryl-4-(1,3-benzoxazol-2-yl)-2-pyrrolidinones **5a,d,f** were obtained from the corresponding pyrrolidinones **1a,d,f** by heating with *o*-aminophenol at 170°C for 2 h and then at 230°C for 30 min.

1-Substituted 2-pyrrolidinones are acid resistant, but in basic medium they cleave forming corresponding *N*-arylamino-3-carboxybutanoic salts. N-aryl substituted γ-amino acids **6** were synthesized by heating suitable bisubstituted 2-pyrrolidinones **2** in sodium hydroxide solution, followed by acidification of these solutions with acetic acid to pH 6.

Alkylation of benzimidazoles **2a,d,e,h** in the presence of potassium hydroxide and sodium carbonate with excess of ethyl or methyl iodide without solvent at room temperature led to 1-aryl-4-(1-methyl-1*H*-benzimidazol-2-yl)-2- pyrrolidinones **7** and 1-aryl-4-(1-ethyl-1*H*-benzimidazol-2-yl)-2-pyrrolidinones **8** in quantitative yields. Hardly soluble in organic solvents 1,3-dialkylbenzimidazolium iodides **9** were obtained using DMF as a solvent.

The structure of the study compounds was investigated using IR and $^{1}H$, $^{13}C$ NMR spectra. The assignment of the resonances in the NMR spectra was based on the chemical shift theory and signal intensity arguments, multiplicities, and comparison with structurally related compounds [12,13]. $^{1}H$, $^{13}C$ NMR spectroscopic data were unambiguous in most cases, and their reliability was checked by $^{13}C$ NMR DEPT, $^{1}H/^{13}C$ 2D (HETCOR) NMR experiments. The data of the $^{1}H$ and $^{13}C$ NMR chemical shifts are listed in Tables 1–5. The carbon atoms in tables are marked according to the numbering given in Scheme 1.

The more exhaustive information about the structural features of the study compounds was obtained using NMR data together with the computer molecular modeling results.

The investigated compounds possess pyrrolidinone ring [14,15], which atoms feel sensitively the influence of its 1,4-substituents. The structural changes as in the benzene fragment as in the benzimidazole ring moieties affect the pyrrolidinone fragment specifically. The nonsubstituted pyrrolidinone has a nearly planar structure (RMS deviation from plane according to the Mopac AM1 data are 0.000 Å, MM2 – 0.114 Å). The studies of **2**-series of the

**TABLE 1** $^{13}C$ NMR Chemical Shifts ($\delta$, in ppm) of Compounds **2a–e**

| | **2a** | **2b** | **2c** | **2d** | **2e** |
|---|---|---|---|---|---|
| C-1 | 139.20 | 137.51 | 132.39 | 140.53 | 138.47 |
| C-2 | 119.43 | 135.40 | 121.26 | 117.50 | 121.22 |
| C-3 | 128.61 | 130.59 | 113.79 | 133.10 | 131.39 |
| C-4 | 123.98 | 126.56 or 126.48 | 155.83 | 123.64 | 115.81 |
| C-5 | 128.61 | 127.37 | 113.79 | 130.30 | 131.39 |
| C-6 | 119.43 | 126.56 or 126.48 | 121.26 | 118.96 | 121.22 |
| C-2′ | 171.89 | 171.40 | 171.34 | 172.39 | 172.13 |
| C-3′ | 37.48 | 36.03 | 37.24 | 37.50 | 37.42 |
| C-4′ | 30.62 | 31.97 | 30.65 | 30.48 | 30.43 |
| C-5′ | 52.07 | 53.98 | 52.40 | 51.98 | 51.91 |
| C-8 | 154.91 | 155.06 | 154.93 | 154.76 | 154.78 |
| C-10 | 118.43 or 110.98 | 118.51 or 110.97 | 118.34 or 111.19 | 118.42 or 110.99 | 118.41 or 110.95 |
| C-11 | 121.90 or 121.09 | 121.48 or 121.10 | 121.26 | 122.02 or 121.14 | 121.91 121.07 |
| C-12 | 121.90 or 121.09 | 121.48 or 121.10 | 121.26 | 122.02 or 121.14 | 121.91 or 121.07 |
| C-13 | 118.43 or 110.98 | 118.51 or 110.97 | 118.34 or 111.19 | 118.42 or 110.99 | 118.41 or 110.95 |
| C-14 | 142.76 or 134.50 | 142.83 or 134.48 | 142.79 or 134.34 | 142.80 or 134.73 | 142.71 or 134.00 |
| C-15 | 142.76 or 134.50 | 142.83 or 134.48 | 142.79 or 134.34 | 142.80 or 134.73 | 142.71 or 134.00 |
| Others | | 2-Me 17.49 | 4-OMe 55.15 | | |

**TABLE 2** $^{13}$C NMR Chemical Shifts ($\delta$, in ppm) of Compounds **2g, 2h, 2k, 3d, 3e, 4f**

| | **2g** | **2h** | **2k** | **3d** | **3e** | **4f** |
|---|---|---|---|---|---|---|
| C-1 | 139.84 | 134.94 | 142.84 | 140.20 | 138.50 | 138.12 |
| C-2 | 115.62, 115.56 | 135.12 | 118.51 | 117.94 | 121.38 | 120.86 |
| C-3 | 129.93 | 131.17 | 133.11 | 133.11 | 131.54 | 128.50 |
| C-4 | 120.25, 120.19 | 136.74 | 121.84 | 124.52 | 115.90 | 127.74 |
| C-5 | 126.19 | 127.08 | 128.79 | 131.22 | 131.54 | 128.50 |
| C-6 | 122.69 | 126.47 | 111.03 | 119.68 | 121.38 | 120.86 |
| C-2′ | 172.64 | 171.56 | 172.01 | 171.19 | 172.11 | 172.18 |
| C-3′ | 37.48 | 36.10 | 35.69 | 36.78 | 37.38 | 37.02 |
| C-4′ | 30.50 | 32.01 | 32.19 | 29.78 | 30.36 | 30.02 |
| C-5′ | 51.96 | 54.14 | 53.52 | 51.11 | 51.90 | 52.05 |
| C-8 | 154.73 | 155.23 | 154.56 | 155.19 | 156.51 | 154.41 |
| C-10 | 118.39 or 110.92 | Not obs. | 116.06 or 115.79 | 114.22 | 114.51 | 115.42 or 114.37 |
| C-11 | 121.39 | 121.48 | 121.93 or 121.16 | 130.49 | 130.49 | 132.50 |
| C-12 | 121.39 | 121.48 | 121.93 or 121.16 | 123.91 | 124.28 | 123.55 |
| C-13 | 118.39 or 110.92 | Not obs. | 116.06 or 115.79 | 117.90 | 117.90 | 115.42 or 114.34 |
| C-14 | 142.44 or 134.64 | Not obs. | 137.65 or 134.51 | 134.29 | 134.58 | 134.84 |
| C-15 | 142.44 or 134.64 | Not obs. | 137.65 or 134.51 | 140.19 | 141.38 | 138.38 |
| Others | 130.15<br>129.65<br>129.14<br>128.64<br>($CF_3$) | 2-Me 17.47<br>4-Me 20.57 | | | | |

**TABLE 3** $^{13}$C NMR Chemical Shifts ($\delta$, in ppm) of Compounds **5a, 7d, 9d**

| | | | **9d** | |
|---|---|---|---|---|
| | **5a** | **7d** | *Low Intensity Form* | *High Intensity Form* |
| C-1 | 139.04 | 140.53 | 140.11 | 139.84 |
| C-2 | 119.54 | 117.54 | 117.83 | 118.30 |
| C-3 | 128.69 | 133.10 | 133.14 | 133.10 |
| C-4 | 124.20 | 123.60 | 124.04 | 124.41 |
| C-5 | 128.69 | 130.26 | 130.47 | 130.40 |
| C-6 | 119.54 | 118.89 | 119.18 | 119.67 |
| C-2′ | 171.38 | 172.42 | 171.18 | 170.93 |
| C-3′ | 36.29 | 37.04 | 36.21 | 34.94 |
| C-4′ | 30.30 | 29.50 | 27.60 | 25.89 |
| C-5′ | 50.87 | 51.51 | 50.62 | 49.42 |
| C-8 | 150.48 | 154.85 | 153.73 | 151.68 |
| C-10 | 110.77 | 109.85 | 112.23 or 114.91 | 112.96 |
| C-11 | 125.12 or 124.49 | 121.36 or 121.86 | 124.95 or 125.25 | 126.38 |
| C-12 | 125.12 or 124.49 | 121.36 or 121.86 | 124.95 or 125.25 | 126.38 |
| C-13 | 119.54 | 118.61 | 112.23 or 114.91 | 112.96 |
| C-14 | 150.48 | 136.20 | Not obs. | 131.72 |
| C-15 | 140.46 | 141.66 | Not obs. | 131.72 |
| Others | | 28.37<br>7-NMe | 31.15<br>7,9-NMe | 32.55<br>7,9-NMe |

**TABLE 4** $^{13}C$ NMR Chemical Shifts ($\delta$, in ppm) of Compounds **6a, 6c, 6d, 6e, 6f, 6i** and Extended Hückel Partial Charges* for C-3′ and C-4′ Atoms (**First Line in Cells is Obtained by MM2, While Second Line is Obtained by AM1)

| | **6a** | **6c** | **6d** | **6e** | **6f** | **6i** |
|---|---|---|---|---|---|---|
| C-1 | 148.32 | 142.57 | 149.88 | 147.63 | 147.27 | 142.97 |
| C-2 | 112.05 | 113.19 | 111.14 | 114.01 | 113.40 | 112.98 |
| C-3 | 128.92 | 114.69 | 133.76 | 131.42 | 128.59 | 116.44 |
| C-4 | 115.83 | 150.82 | 115.17 | 106.40 | 119.02 | 145.61 |
| C-5 | 128.92 | 114.69 | 130.39 | 131.42 | 128.59 | 116.44 |
| C-6 | 112.05 | 113.19 | 110.76 | 114.01 | 113.40 | 112.98 |
| C-2′ | 173.17 | 173.39 | 173.09 | 173.13 | 173.10 | 173.34 |
| C-3′ | 35.52 | 35.65 | 35.38 | 35.36 | 35.37 | 35.60 |
| * | −0.108/ | −0.108/ | −0.113/ | −0.102/ | −0.102/ | −0.109/ |
| C-3′ | −0.526 | −0.526 | −0.538 | −0.538 | −0.529 | −0.533 |
| C-4′ | 35.85 | 36.07 | 35.78 | 35.84 | 35.78 | 36.12 |
| * | 0.005/ | 0.003/ | 0.014/ | 0.015/ | 0.015/ | 0.003/ |
| C-4′ | 0.078 | 0.077 | 0.082 | 0.082 | 0.076 | 0.071 |
| C-5′ | 46.76 | 47.66 | 46.46 | 46.67 | 46.73 | 47.20 |
| C-8 | 154.56 | 156.25 | 155.78 | 155.84 | 155.82 | Not obs. |
| C-10 | Not obs. | Not obs. | | Not obs. | Not obs. | Not obs. |
| C-11 | Not obs. | Not obs. | | Not obs. | Not obs. | Not obs. |
| C-12 | 121.18 | 121.37 or 121.21 | 121.25 | 121.23 | 121.22 | 121.76 or 121.16 |
| C-13 | 121.18 | 121.37 or 121.21 | 121.25 | 121.23 | 121.22 | 121.76 or 121.16 |
| C-14 | Not obs. | Not obs. | Not obs. | Not obs. | Not obs. | Not obs. |
| C-15 | Not obs. | Not obs. | Not obs. | Not obs. | Not obs. | Not obs. |
| Others: | | 55.34 $OCH_3$ | | | | 4-OPh C-1″ – 158.89 C-2″, C-6″ – 116.44 C-3″, C-5″ – 129.75 C-4″ – 121.01 |

molecular models of the synthesized products have suggested that there are some changes in the geometry of the pyrrolidinone ring (Table 6). Changes in the geometry affect the values of the chemical shift in $^{13}C$ NMR and $^{1}H$ NMR spectra. The suitable values of the chemical shift differences of the pyrrolidinone atoms arising due to variant substitution in benzene ring are also summarized in Table 6. It has been noticed that C-3′, C-4′, and C-5′ atoms of pyrrolidinone ring are affected more significantly by o-substituents in benzene ring (**2b, 2h**, and **2k**). The influence on C-3′ atom and both of its hydrogens had a shielding effect, on C-4′ atom and the hydrogen attached to it—deshielding effect, but C-5′ atoms were deshielded though both of its hydrogens were shielded. Molecular modeling data were in accordance with this interpretation. It was impossible to evaluate the electronic effects of 1N-substitution on the pyrrolidinone ring of the study compounds by molecular modeling data. It may be considered that the shielding or deshielding direction could be jumbled due to the arising of the extended π-system between benzene ring and N(1′)-CO fragment. The molecular-modeling experiments of all study compounds have shown the formation of partially double bond between N(1′)–C(2)O fragment.

The molecules of the synthesized compounds include the benzimidazole fragment. The exploration of the structural features by $^{13}C$ NMR spectra of such type of compounds excites some problems [16]. Owing to the versatility of the heterocyclic part, two tautomer forms of the benzimidazole fragment are presumed [12,13]. The characteristics of the solution and of the rest of the molecule determine the rate of transitions between the tautomer forms. Obviously, dimethylsulfoxide affects specific solvation of the compounds examined [16]. Although six signals of benzimidazole fragment of benzene moiety in $^{13}C$ NMR spectra of compounds **2a, 2b, 2d, 2e, 2g, 2k** are broadened, they are well resolved. The suitable signals in compound **2c** are poorly resolved and broadened. All signals in compound **2h** with the exception of signal at 121.48 ppm are only within the noise level.

NMR spectra of compounds **3d, 3e, 4f**, and **7d** showed that the introduction of the substituent (Cl or $CH_3$) at C-11 or N-1 position of benzimidazole fragment stabilized its form [17–19]. The carbon

**TABLE 5** IR and $^1$H NMR Spectroscopic Data of the Study Compounds

| | *IR, v ($cm^{-1}$)* | *$^1$H NMR ($\delta$, in ppm), J (Hz)* |
|---|---|---|
| **2a** | 1694 (C═O), 2779, 2911, 3059, 3185, 3372 (NH) + (ArH) | 2.91–3.12 (m, 2H, $CH_2CO$), 3.95–4.07 (m, 1H, CH), 4.18–4.33 (m, 2H, $CH_2N$), 7.08–7.73 (m, 9H, ArH), 12.45 (br. s, 1H, NH) |
| **2b** | 1669 (C═O), 2921, 3048, 3101, 3170, 3419 (NH) + (ArH) | 2.15 (s, 3H, *o*-$CH_3$), 2.91–3.09 (m, 2H, $CH_2CO$), 4.01–4.20 (m, 3H, CH + $CH_2N$), 7.10–7.68 (m, 8H, ArH), 12.42 (br. s, 1H, NH) |
| **2c** | 1694 (C═O), 2835 ($OCH_3$), 2909, 3054, 3180, 3378 (NH) + Ar(H) | 2.94–3.04 (m, 2H, $CH_2CO$), 3.75 (s, 3H, $OCH_3$), 3.91–4.08 (m, 1H, CH), 4.15–4.27 (m, 2H, $CH_2N$), 6.90–7.65 (m, 8H, ArH), 12.43 (br. s, 1H, NH) |
| **2d** | 1694 (CO), 2683, 2844, 3058 (NH) + (ArH) | 2.92–3.14 (m, 2H, $CH_2CO$), 3.92–4.08 (m, 1H, CH), 4.18–4.36 (m, 2H, $CH_2N$), 7.08–7.93 (m, 8H, ArH), 12.44 (br. s, 1H, NH) |
| **2e** | 1713 (C═O), 2637, 2767, 2852, 2909, 2962, 3057, 3180 (NH) + (ArH) | 2.96–3.08 (m, 2H, $CH_2CO$), 3.93–4.08 (m, 1H, CH), 4.15–4.32 (m, 2H, $CH_2N$), 7.06–7.73 (m, 8H, ArH), 12.44 (br. s, 1H, NH) |
| **2f** | | 3.04–3.12 (m, 2H, $CH_2CO$), 3.90–4.53 (m, 3H, CH + $CH_2N$), 7.16–7.83 (m, 8H, ArH), 12.91 (br. s, 1H, NH) |
| **2g** | 1693 (C═O), 2704, 2751, 2790, 2852, 2913, 2956, 3066 (NH) + (ArH) | 2.95–3.16 (m, 2H, $CH_2CO$), 4.96–4.11 (m, 1H, CH), 4.22–4.46 (m, 2H, $CH_2N$), 7.10–8.24 (m, 8H, ArH), 12.46 (br. s, 1H, NH) |
| **2h** | 1674 (C═O), 2920, 2965, 3049, 3099 (NH) + (ArH) | 2.12 (s, 3H, *p*−$CH_3$), 2.29 (s, 3H, *o*-$CH_3$), 2.94–2.97 (m, 2H, $CH_2CO$), 4.03–4.11 (m, 3H, $CH_2N$ + CH), 7.09–7.57 (m, 7H, ArH), 12.47 (br. s, 1H, NH) |
| **2i** | 1683 (C═O), 2785, 3053, 3180 (NH) + (ArH) | 2.93–3.25 (d, 2H, $CH_2CO$), 3.83–4.37 (m, 3H, $CH_2N$ + CH), 6.90–7.82 (m, 13H, ArH), 12.44 (br. s, 1H, NH) |
| **2k** | 1707 (C═O), 2614, 2730, 2809, 2908, 2967, 3027, 3085, 3139, 3397 (NH) + (ArH) | 2.95–3.01 (m, 2H, $CH_2CO$), 4.00–4.27 (m, 3H, $CH_2N$ + CH), 7.16–7.75 (m, 8H, ArH), 12.48 (br. s, 1H, NH) |
| **3d** | 1710 (C═O), 2579, 2608, 2676, 2775, 2857, 2900, 3107, 3406 (NH) + (ArH) | 3.17–3.21 (m, 2H, $CH_2CO$), 4.30–4.55 (m, 3H, $CH_2N$ + CH), 7.24–7.88 (m, 7H, ArH), 12.60 (br. s, 1H, NH) |
| **3e** | 1708 (C═O), 2599, 2733, 2889, 3059, 3369 (NH) + (ArH) | 2.99–3.06 (m, 2H, $CH_2CO$), 4.03–4.21 (m, 1H, CH), 4.21–4.30 (m, 2H, $CH_2N$), 7.19–7.70 (m, 7H, ArH), 12.69 (br. s, 1H, NH) |
| **4f** | 1711 (C═O), 2631, 2825, 2883, 3028, 3066, 3397 (NH) + (ArH) | 2.41 (s, 3H, 11-$CH_3$), 2.95–3.11 (m, 2H, $CH_2CO$), 3.94–4.05 (m, 1H, CH), 4.19–4.32 (m, 2H, $CH_2N$), 6.97–7.76 (m, 7H, ArH), 12.39 (br. s, 1H, NH) |
| **5a** | 1697 (C═O) | 3.03–3.11 (m, 2H, $CH_2CO$), 4.23–4.36 (m, 3H, CH + $CH_2N$), 7.16–7.73 (m, 7H, ArH) |
| **5d** | 1701 (C═O) | 3.00–3.20 (m, 2H, $CH_2CO$), 4.00–4.58 (m, 3H, CH + $CH_2N$), 7.13–7.98 (m, 7H, ArH) |
| **5f** | 1692 (C═O) | 3.00–3.20 (m, 2H, $CH_2CO$), 4.00–4.4 (m, 3H, CH + $CH_2N$), 7.2–8.0 (m, 7H, ArH) |
| **6a** | 1603 (C═O), 2842, 2925, 3054, 3286, (NH) + (NH) + (OH) + (ArH) | 2.80–2.97 (m, 2H, $CH_2CO$), 3.27–3.52 (m, 2H, $CH_2N$), 3.61–3.70 (m, 1H, CH), 5.83 (br. s, 1H, NH), 6.54–7.53 (m, 9H, ArH), 12.30 (br. S, 1H, NH of benzimidazole) |
| **6c** | 1576 (C═O), 2632, 2933, 3057, 3257 (NH) + (NH) + (OH) + (ArH) | 2.79–2.96 (m, 2H, $CH_2CO$), 3.23–3.47 (m, 2H, $CH_2N$), 3.62–3.68 (m, 1H, CH), 3.65 (s, 3H, $OCH_3$), 6.59–7.53 (m, 9H, ArH + NH), 12,21 (br. s, 1H, NH of benzimidazole) |
| **6d** | 1600 (C═O), 2855, 2920, 3068, 3283, (NH) + (NH) + (OH) + (ArH) | 2.79–2.96 (m, 2H, $CH_2CO$), 3.30–3.68 (m, 3H, CH + $CH_2N$), 6.20 (br. t, 1H, NH), 6.54–7.53 (m, 8H, ArH), 12.28 (br. s, 1H, NH of benzimidazole) |

*Continued*

**TABLE 5** Continued

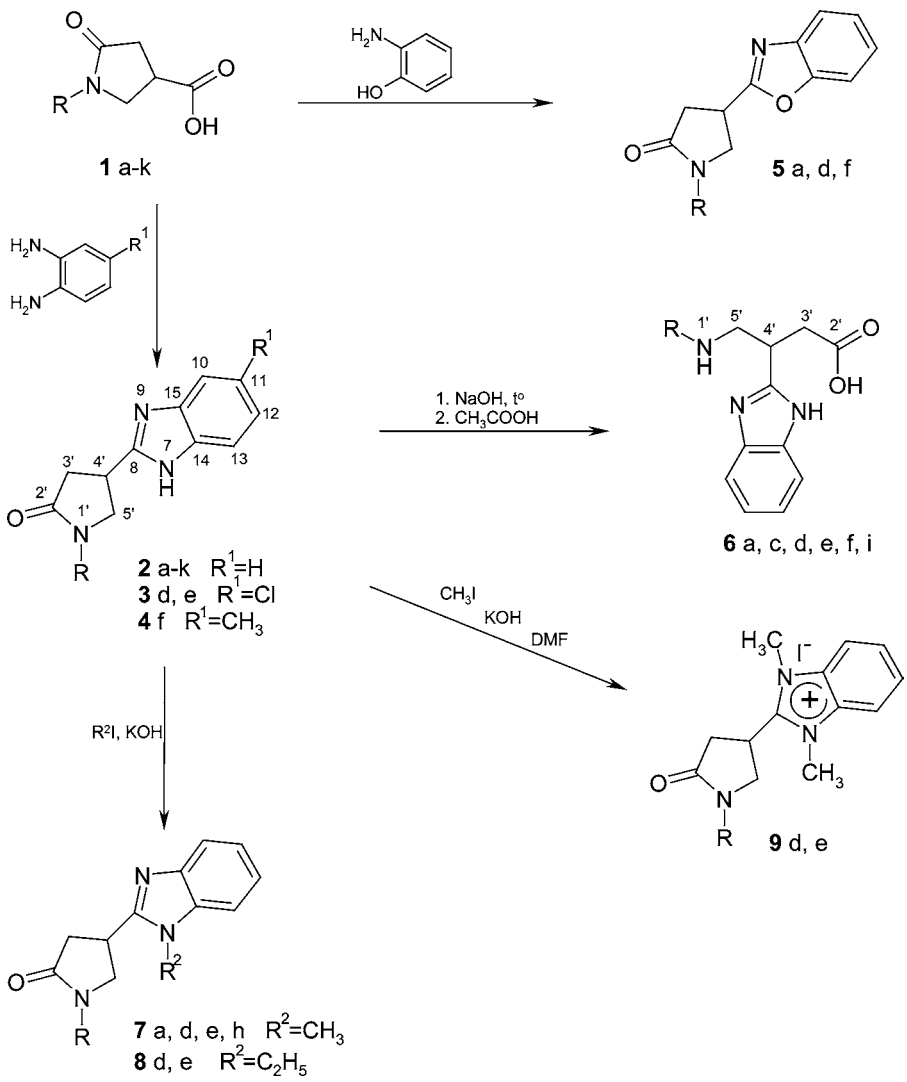
| | *IR, v ($cm^{-1}$)* | *$^1$H NMR ($\delta$, in ppm), J (Hz)* |
|---|---|---|
| **6e** | 1593 (C=O), 2734, 2844, 2916, 3069, 3283, (NH) + (NH) + (OH) + (ArH) | 2.78–2.96 (m, 2H, $CH_2CO$), 3.28–3.50 (m, 2H, $CH_2N$), 3.58–3.67 (m, 1H, CH), 6.09 (br. s, 1H, NH), 6.60–7.53 (m, 8H, ArH), 12.15 (br. s, 1H, NH of benzimidazole) |
| **6f** | 1598 (C=O), 2743, 2844, 2920, 3073, 3165, 3283, (NH) + (NH) + (OH) + (ArH) | 2.78–2.97 (m, 2H, $CH_2CO$), 3.27–3.51 (m, 2H, $CH_2N$), 3.58–3.67 (m, 1H, CH), 6.07 (br. s, 1H, NH), 6.64–7.54 (m, 8H, ArH), 12.45 (br. s, 1H, NH of benzimidazole) |
| **6i** | 1590 (C=O), 2744, 2843, 2923, 3072, 3284, 3407 (NH) + (NH) + (OH) + (ArH) | 2.79–2.96 (m, 2H, $CH_2CO$), 3.28–3.67 (m, 3H, CH + $CH_2N$), 5.80 (br. s, 1H, NH), 6.67–7.53 (m, 8H, ArH), 12.55 (br. s, 1H, NH of benzimidazole) |
| **7a** | 1702 (C=O) | 2.98–3.06 (m, 2H, $CH_2CO$), 3.82 (s, 3H, $CH_3$), 4.00–4.39 (m, 3H, $CH_2N$ + CH), 7.13–7.80 (m, 9H, ArH) |
| **7d** | 1697 (C=O) | 2.95–3.20 (m, 2H, $CH_2CO$), 3.82 (s, 3H, $NCH_3$), 4.08–4.40 (m, 3H, $CH_2N$ + CH), 7.11–7.90 (m, 8H, ArH) |
| **7e** | 1696 (C=O) | 2.99–3.07 (m, 2H, $CH_2CO$), 3.82 (s, 3H, $CH_3$), 4.03–4.45 (m, 3H, $CH_2N$ + CH), 7.10–7.80 (m, 8H, ArH) |
| **7h** | 1694 (C=O) | 2.13 (s, 3H, *p*-$CH_3$), 2.27 (s, 3H, *o*-$CH_3$), 2.91–3.05 (m, 2H, $CH_2CO$), 3.80 (s, 3H, $NCH_3$), 4.05–4.36 (m, 3H, $CH_2N$ + CH), 7.07–7.75 (m, 8H, ArH) |
| **8d** | 1710 (C=O) | 1.36 (t, 3H, $J = 7.5$ Hz, N–$CH_2\underline{CH_3}$), 2.99–3.07 (m, 2H, $CH_2CO$), 4.03–4.50 (m, 5H, N–$\underline{CH_2}CH_3$ + $CH_2N$ + CH), 7.06–8.06 (m, 8H, ArH) |
| **8e** | 1709 (C=O) | 1.41 (t, 3H, $J = 7.5$ Hz, N–$CH_2\underline{CH_3}$), 3.01–3.20 (m, 2H, $CH_2CO$), 4.08–4.60 (m, 5H, N–$\underline{CH_2}CH_3$ + $CH_2N$ + CH), 7.11–7.87 (8H, m, ArH) |
| **9d** | 1702 (C=O) | 3.12–3.36 (m, 2H, $CH_2CO$), 4.05 (s of low intensity form, 3H, $NCH_3$), 4.15 (s of high intensity form, 3H, $NCH_3$), 4.34–4.60 (m, 2H, $CH_2N$), 4.75–4.92 (m, 1H, CH), 7.20–8.14 (m, 8H, ArH) |
| **9e** | 1704 (C=O) | |

resonances of benzimidazole of benzene moiety became sharp. The molecular modeling data of these compounds showed that, as expected, the benzimidazole fragment system is essentially planar. It was determined that the substituents of Cl and Br and $CH_3$ are quite coplanar with respect to benzimidazole plane.

The NMR spectra of compound **5a** were assigned by comparison with the model compounds [12,13]. The disappearance of proton signal of the NH group in $^1$H NMR spectrum confirmed existence of the above-mentioned **5a** compound. The study compounds **9d,e** were synthesized as a salt derivatives. The formation of such salts is widely described in the literature [20–23]. The structure of compound **9d** in our case was analyzed in more detail. Molecular modeling studies demonstrated the most negative of the nitrogen atoms in the parent (**2d)** molecule of **9d**. This investigation revealed that the benzimidazole protonated at N-3 (Extended Hückel partial charge is −0.523 a.u.) to form the cationic species. Taking into account the possibility of formation of the tautomeric forms in the protonated compounds, two forms of compounds were suggested. NMR spectra of compound **9d** gave two sets of resonances with the intensity rate 1:9.

A series of compounds **6** with the cleaved pyrrolidinone ring were synthesized. The comparison of study compounds **6a, 6c, 6d, 6e** with their parent cyclization products permits to examine the structure of these compounds as well as that of **6f** and **6i** by the NMR spectroscopy. Carboxylic groups produce $^{13}$C NMR resonances at 173 ppm that are typical to the saturated, open chain products. The difference of the chemical shifts of the pairs of C-3′ and C-4′ carbons in **6**-series compounds is quite close—nearly 0.4 ppm—meanwhile that of the suitable cyclic pair carbons is 7.0 ppm.

The tendencies of the changes of extended Hückel partial charges calculated for the atoms C-3′ and C-4′ of the open chain molecules of **6**-series (Table 4) are in the satisfactory agreement with the variation of the suitable NMR chemical shifts. The proton resonance of N(1′)H group recorded at ∼6.0 ppm in $^1$H NMR spectra confirmed the existence of open chain compounds. These signals have a low intensity and are broad. In the case of compound **6d**, a broad triplet indicated the interaction




**SCHEME 1** Synthesis of benzimidazole and benzoxazole derivatives. **R** = (a) $C_6H_5$; (b) 2-$CH_3$-$C_6H_4$; (c) 4-$CH_3O$-$C_6H_4$; (d) 3-Cl-$C_6H_4$; (e) 4-Br-$C_6H_4$; (f) 4-Cl-$C_6H_4$; (g) 3-$CF_3$-$C_6H_4$; (h) 2,4-$(CH_3)_2$-$C_6H_3$; (i) 4-$C_6H_5$-O-$C_6H_4$; (j) 2-Br-$C_6H_4$.

between 1-NH and 5′-$CH_2$ fragment due to slow exchange. The proton of NH of benzimidazole moiety is observed as particularly broadened singlet at ~12.3 ppm. Only one or two resonances of C-11 and C-12 atoms at 121 ppm are visible in the $^{13}C$ NMR spectra. Other carbon atoms of the benzimidazole fragment are more sensitive to the charge distribution changes and are not observed in all open chain compounds.

## *EXPERIMENTAL*

The $^1H$ and $^{13}C$ NMR spectra were recorded on a AC 250-P Bruker 250 MHz and Varian Unity Inova 300 MHz spectrometer operating in Fourier transform mode with TMS as an internal standard. The IR spectra were measured in a Perkin-Elmer FT-IR system Spectrum GX ( KBr tablets). Silica gel plates (Silufol UV-254) were used for analytical TLC. All melting points were taken in one tail-end open capillary tubes. The physical properties, analytical data, and yields are presented in Table 7.

### *Method A: General Procedure for the Preparation of 1-Phenylsubstituted 4-(1H-benzimidazol-2-yl)-2-pyrrolidinones (**2a–n**)*

A mixture of 2-pyrrolidinone **1a–k** (0.1 mol) and 1,2-diaminobenzene (14.04 g, 0.13 mol) was heated at 170°C for 2 h and then at 230°C for 30 min. The reaction mixture was cooled to the room temperature and 150 mL of 5% solution of sodium carbonate was

**TABLE 6** The Length of the Bond between Benzene and Pyrrolidinone Ring, N(1′) Atom's RMS Deviation from the Benzene Ring Plane (ND), RMS Deviation from the Plane of the Pyrrolidinone Ring (PD). The Differences of the Chemical Shifts Arising due to Variant Substituents in Benzene Ring in Compounds **2a–e, 2g, 2h, 2k**

| | *Length of C(1)—N (1′) (Å) | *ND (Å) | *PD (Å) | **$\Delta\delta$ (ppm) | | | |
|---|---|---|---|---|---|---|---|
| | | | | C-2′ | C-3′/$CH_2$ | C-4′/CH | C-5′/$CH_2$ |
| **2a** | 1.433/ | 0.004/ | 0.153/ | – | – | – | – |
| | 1.406 | 0.006 | 0.045 | | | | |
| **2b** | 1.455/ | 0.022/ | 0.136/ | −0.49 | −1.45/ | 1.35/ | 1.91/ |
| | 1.416 | 0.003 | 0.072 | | −0.04, −0.06 | 0.09 | −0.13, −0.19 |
| **2c** | 1.433/ | 0.010/ | 0.122/ | −0.55 | −0.24/ | 0.03/ | 0.33/ |
| | 1.407 | 0.003 | 0.046 | | −0.02, 0.08 | −0.01 | −0.02, –0.05 |
| **2d** | 1.434 | 0.003/ | 0.146/ | 0.50 | 0.02/ | −0.14/ | −0.09/ |
| | 1.404 | 0.006 | 0.044 | | 0.00, 0.02 | 0.10 | −0.01, −0.01 |
| **2e** | 1.435 | 0.003/ | 0.144/ | 0.24 | −0.06/ | −0.19/ | −0.16/ |
| | 1.403 | 0.008 | 0.041 | | −0.02, 0.00 | −0.02 | −0.01, 0.00 |
| **2g** | 1.403 | 0.014/ | 0.142/ | 0.72 | 0.00/ | −0.12/ | −0.11/ |
| | 1.403 | 0.004 | 0.039 | | 0.04, 0.10 | 0.02 | 0.08, 0.05 |
| **2h** | 1.451 | 0.026/ | 0.128/ | 0.33 | −1.38/ | 1.39/ | 2.07/ |
| | 1.415 | 0.006 | 0.065 | | −0.04, −0.06 | 0.08 | −0.14, −0.20 |
| **2k** | 1.440 | 0.014/ | 0.163/ | 0.12 | −1.78/ | 1.57/ | 1.45/ |
| | 1.411 | 0.002 | 0.061 | | −0.05, −0.02 | 0.10 | −0.12, −0.18 |

*First line in cells is obtained by MM2, second line is obtained by AM1.
**First line in cells—of the carbon atoms of pyrrolidinone ring, second—of each hydrogen.

**TABLE 7** Characterization of the Study Compounds and Elemental Analysis Data

| | Yield (%) | mp (°C) | Molecular Formula (Molecular Weight) | Found (Calcd) | | |
|---|---|---|---|---|---|---|
| | | | | C | H | N |
| **2aA** | 76 | 215–216 | $C_{17}H_{15}N_3O$ (27733) | 7342 (7363) | 564 (545) | 1529 (1515) |
| **2bA** | 73 | 220–221 | $C_{18}H_{17}N_3O$ (29136) | 7444 (7421) | 601 (588) | 1425 (1442) |
| **2cA** | 63 | 224–225 | $C_{18}H_{17}N_3O_2$ (30736) | 7024 (7034) | 563 (558) | 1376 (1367) |
| **2dA** | 80 | 226–227 | $C_{17}H_{14}ClN_3O$ (31177) | 6534 (6549) | 466 (453) | 1365 (1348) |
| **2eA** | 79 | 220–221 | $C_{17}H_{14}BrN_3O$ (35622) | 5744 (5732) | 409 (396) | 1158 (1180) |
| **2eB** | 17 | | | | | |
| **2fA** | 70 | 212–213 | $C_{17}H_{14}ClN_3O$ (31177) | 6530 (6549) | 441 (453) | 1356 (1348) |
| **2fB** | 15 | | | | | |
| **2gA** | 65 | 221–222 | $C_{18}H_{14}F_3N_3O$ (34533) | 6255 (6261) | 415 (409) | 1216 (1217) |
| **2hA** | 62 | 179–180 | $C_{19}H_{19}N_3O$ (30538) | 7492 (7473) | 617 (627) | 1371 (1376) |
| **2iA** | 70 | 212–213 | $C_{23}H_{19}N_3O_2$ (36943) | 7461 (7478) | 501 (518) | 1151 (1137) |
| **2kA** | 80 | 291–292 | $C_{17}H_{14}BrN_3O$ (35622) | 5748 (5732) | 400 (396) | 1199 (1180) |
| **3d** | 15 | 167–168 | $C_{17}H_{13}Cl_2N_3O$ (34622) | 5907 (5898) | 377 (378) | 1206 (1214) |
| **3e** | 18 | 142–143 | $C_{17}H_{13}BrClN_3O$ (39067) | 5233 (5227) | 342 (335) | 1062 (1076) |
| **4f** | 16 | 179–180 | $C_{18}H_{16}ClN_3O$ (32580) | 6630 (6636) | 499 (495) | 1287 (1290) |
| **5a** | 60 | 148–149 | $C_{17}H_{14}N_2O_2$ (27831) | 7347 (7337) | 501 (507) | 1020 (1007) |
| **5d** | 50 | 136–137 | $C_{17}H_{13}ClN_2O_2$ (31276) | 6505 (6529) | 433 (419) | 902 (896) |
| **5f** | 53 | 174–175 | $C_{17}H_{13}ClN_2O_2$ (31276) | 6520 (6529) | 430 (419) | 905 (896) |
| **6a** | 87 | >170 dec | $C_{17}H_{17}N_3O_2$ (29534) | 6930 (6914) | 601 (580) | 1402 (1423) |
| **6c** | 86 | >149 dec | $C_{18}H_{19}N_3O_3$ (32537) | 6633 (6645) | 573 (589) | 1301 (1291) |
| **6d** | 93 | >180 dec | $C_{17}H_{16}ClN_3O_2$ (32979) | 6175 (6192) | 474 (489) | 1291 (1274) |
| **6e** | 91 | >179 dec | $C_{17}H_{16}BrN_3O_2$ (37424) | 5437 (5456) | 442 (431) | 1105 (1123) |
| **6f** | 95 | >192 dec | $C_{17}H_{16}ClN_3O_2$ (32979) | 6175 (6192) | 474 (489) | 1291 (1274) |
| **6i** | 87 | >198 dec | $C_{23}H_{21}N_3O_2$ (38744) | 7155 (7130) | 531 (546) | 1057 (1085) |
| **7a** | 88 | 162–163 | $C_{18}H_{17}N_3O$ (29136) | 7407 (7421) | 594 (588) | 1455 (1442) |
| **7d** | 93 | 166–167 | $C_{18}H_{16}ClN_3O$ (32580) | 6618 (6636) | 504 (495) | 1277 (1290) |
| **7e** | 94 | 194–195 | $C_{18}H_{16}BrN_3O$ (37025) | 5855 (5839) | 426 (436) | 1150 (1135) |
| **7h** | 83 | 138–139 | $C_{20}H_{21}N_3O$ (31941) | 7502 (7521) | 680 (663) | 1300 (1316) |
| **8d** | 91 | 132–133 | $C_{19}H_{18}ClN_3O$ (33983) | 6710 (6716) | 520 (534) | 1254 (1237) |
| **8e** | 90 | 167–168 | $C_{19}H_{18}BrN_3O$ (38428) | 5957 (5939) | 491 (472) | 1074 (1093) |
| **9d** | 40 | 273–274 | $C_{19}H_{21}ClIN_3O$ (46976) | 4860 (4858) | 457 (451) | 885 (895) |
| **9e** | 48 | 248–249 | $C_{19}H_{21}BrIN_3O$ (51421) | 4445 (4438) | 415 (412) | 808 (817) |

added and refluxed for 10 min and left to cool. The residue was filtered, washed with water, and crystallized from appropriate solvent.

*Method B: General Procedure for the Preparation of 1-Phenylsubstituted 4-(1H-benzimidazol-2-yl)-2-pyrrolidinones (***2e, f, 3d, e, 4f***) (Philips Method)*

2-Pyrrolidinone **1d,e,f** (0.05 mol) and 1,2-diaminobenzene in 150 mL of 10% hydrochloric acid were heated at reflux for 24 h. The reaction mixture was cooled, the residue was filtered, and washed with water. Produced crystals were poured over with 75 mL of 5% solution of sodium carbonate; the mixture was heated at reflux for 10 min and left to cool. The residue was filtered and washed with water, dried, and crystallized from the appropriate solvent.

*General Procedure for the Preparation of 1-Phenylsubstituted 4-(1H-benzoxozol-2-yl)-2-pyrrolidinones (***5a,d,f***)*

Mixture of 2-pyrrolidinone **1a,d,f** (0.1 mol) and 2-aminophenole (14.17 g, 0.13 mol) was heated at 170°C for 2 h and then at 230°C for 30 min. The reaction mixture was cooled to room temperature, and 150 mL of 5% solution of sodium carbonate was added and heated at reflux for 10 min and left to cool. The residue was filtered, washed with water, and crystallized from appropriate solvent.

*General Procedure for the Preparation of 3-(1H-Benzimidazol-2-yl)-4[(substituted phenyl)-amino]butanoic Acids (***6a,c,d,e,f,h***)*

N-substituted γ-amino acids were prepared by the hydrolysis of 1-aryl-4-(1*H*-benzimidazol-2-yl)-2-pyrrolidinones in 20% sodium hydroxide solution at reflux temperature for 4 h, followed by treatment with acetic acid (pH ~ 6).

*General Procedure for the Synthesis of 1-Aryl-4-(1-methyl-1H-benzimidazol-2-yl)-2-pyrrolidinones (***7a,d,e,h***) and 1-Aryl-4-(1-ethyl-1H-benzimidazol-2-yl)-2-pyrrolidinones (***8d,e***)*

A mixture of 1-arylsubstituted 4-(1*H*-benzimidazol-2-yl)-2-pyrrolidinones **2a,d,e,h** (0.01 mol), KOH powder (0.05 mol), potassium carbonate (0.025 mol), and 30 mL of methyl iodide or ethyl iodide was stirred for 3–4 h at room temperature, 50 mL of acetone were added, mixture was filtered, and filtrate was concentrated in vacuo. The residue was poured out with water (50 mL), stirred for a few minutes, and crystals were filtered and washed with water. The product was crystallized from the appropriate solvent.

*Synthesis of 2-(1-Aryl-5-oxopyrrolidin-3-yl)-1,3-dimethyl-1H-3,1-benzimidazol-3-ium Iodides (***9d,e***)*

Benzimidazole **2d,e** (0.02 mol) was dissolved in dimethylformamide (30 mL). Potassium hydroxide powder (4.48 g, 0.08 mol) was added to a stirred mixture. After 5 min, methyl iodide (9.7 ml, 0.16 mol) was dropwise added during 15 min. The mixture was stirred for 30 min and left for 12 h at room temperature. The solvent was evaporated under reduced pressure; residue was poured out with water (100 mL). The precipitate was filtered, washed with water, and heated at reflux in 50 mL acetone for 10 min. After cooling, the residue was filtered and crystallized from the appropriate solvent.

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