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Study of the Reaction of Hydroxybenzoyl Chlorides and Their Derivatives with Imidazole

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Abstract—The reaction of hydroxybenzoyl chlorides with imidazole was studied on an example of the Schotten–Baumann reaction of salicyloyl and acetylsalicyloyl chlorides with imidazole, which, according to soe published data, can take two different ways. It was shown that the Schotten–Baumann reaction with imidazole involves imidazole ring opening (Bamberger cleavage) to form 1,2-bis(salicyloylamino)ethylene and 1,2-bis(acetylsalicyloylamino)ethylene rather than *N*-salicyloylimidazole and *N*-acetylsalicyloylimidazole. *N*-Hydroxybenzoylimidazoles were synthesized by the reaction of hydroxybenzoyl chlorides (and derivatives) with a double excess of imidazole in an aprotic solvent (chloroform, benzene, or diethyl ether) at room temperature. The highest yields (about 80%) of *N*-hydroxybenzoylimidazoles were obtained in chloroform. Some of the newly synthesized compounds were tested for psychotropic (open field and passive avoidance response tests) and analgesic activities (vocalization threshold test). The best results were obtained with *N*-(2-hydroxybenzoyl)imidazole, which showed an evident analgesic activity, and, therewith, the motor score and oriented exploratory activity parameters were higher than in the control group.

Keywords: hydroxybenzamides, *N*-hydroxybenzoylimidazoles, Schotten–Baumann reaction, Bamberger imidazole cleavage, biological activity

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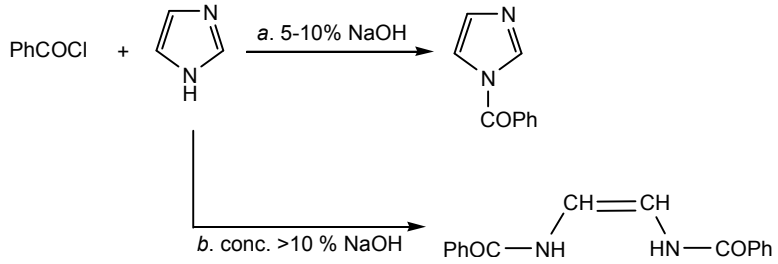
Amides of hydroxybenzoic acids exhibit diverse pharmacological activity: antipyretic, sedative, anticonvulsant, choleretic, neuroleptic, etc. We previously showed that the modification of hydroxybenzoic acids with physicologically active amino acid residues produces unexpected changes in the biological activity of such derivatives *N*-Hydroxybenzoyl derivatives of γ-aminobutyric acid (GABA) and glycine showed anti-depressive (anxiolytic), antiamnestic, psychostimulant, and cerebroprotective effects [1]. The role of such molecular fragments can also be played by heterocyclic structures. For example, *N*-acyl-imidazoles are not only acylating agents and structural components of biomolecules, but also compounds with a broad-spectrum biological activity [2–4].

The aim of the present work was to synthesize *N*-hydroxybenzoyl derivatives of imidazole using hydroxybenzoyl chlorides as acylating agents. To this end, we studied the reactions of salicyloyl chloride and acetylsalicyloyl chlorides with imidazole in different conditions. As known, *N*-acylimidazoles are unstable in an alkaline medium. However, there is controversial information in the literature on the reaction of benzoyl chloride with imidazole. According to some sources, this reaction forms *N*-benzoylimidazole [2], while according to other, more numerous sources, the reaction under the same conditions but a higher concentration of alkali involves imidazole ring opening to form 1,2-bis(benzoylamino)ethylene (Bamberger cleavage; Scheme 1) [5–7]. The ring opening product has a *cis*-configuration and is stabilized by intermolecular hydrogen bonds [6].

The relative contribution of one or the other reaction route, nucleophilic substitution (Scheme 1, route *b*) or cleavage (Scheme 1, route *b*), depends on different factors, specifically, the concentration and strength of the attacking nucleophile (base), the nature of the solvent, the reaction temperature, and the structure of the substrate. For example, if the concentration of the base is low, the product ratio will depend on the structure of the cation. However, it was found that Bamberger cleavage occurs with both in unsubstituted and substituted imidazoles, as well as benzimidazoles and adenines, and is insensitive to the nature of the *N*-acylating agent [7].

Scheme 1.



The mechanism of the cleavage reaction was studied on an example of the modification of a protein containing a histidine fragment using diethyl pyrocarbonate as an acylating agent at pH ≈6 (Scheme 2) [7].

We suggested that the observation of different routes of the *N*-acylation reaction (Scheme 1), reported in the literature, is explained by that the transition state of the cleavage reaction has a stronger charge distribution (Scheme 2), taking into account the effect of the solvent. In this connection, to prepare the target compounds, we studied the reactions of salicyloyl chloride and acetyl salicyloyl chloride with imidazole in different solvents. Presumably, under the Schotten–Baumann reaction conditions, these reactions follow the mechanism shown in Scheme 3.

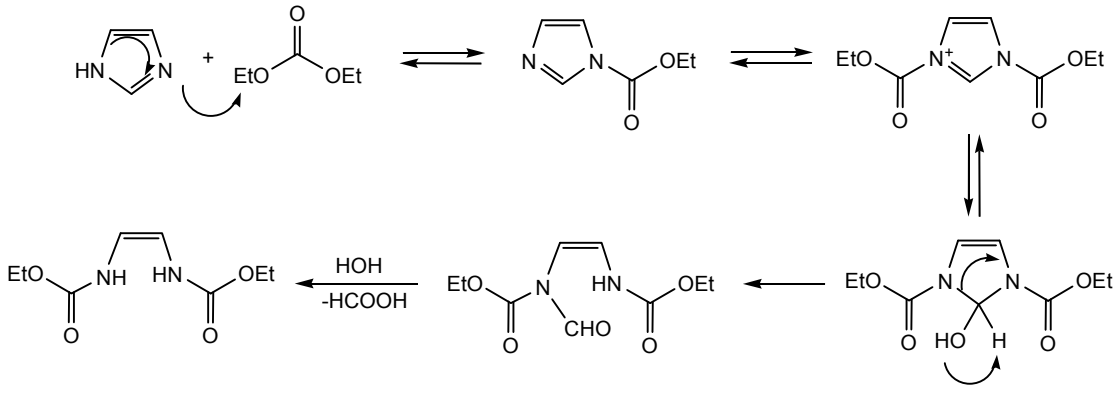
The positive change on the ammonium nitrogen atoms in transition state **A** has a strong *–I* effect of the electron-deficient CH^+ carbon, and further on the ring opens under the action of the OH^- base to form compound **2a** or **2b**. Thus, we found that the use of the Schotten–Baumann reaction reactions (6 N NaOH) for preparing *N*-salicyloylimidazole and *N*-acetyl-salicyloyl-imidazole, too, leads to the Bamberger cleavage of the imidazole ring (Scheme 3) to give the final reaction products in yields higher than 70% (see table).

To preserve the ring and obtain *N*-hydroxybenzoyl imidazole derivatives, the acid chlorides were reacted with a double excess of imidazole in apolar aprotic solvents (chloroform, diethyl ether, benzene) at room temperature (Scheme 4). The excess imidazole played the role of an electron acceptor. Attempted replacement of imidazole in this role by pyridine and trimethylamine resulted in a radical decrease in the yields of the substitution products.

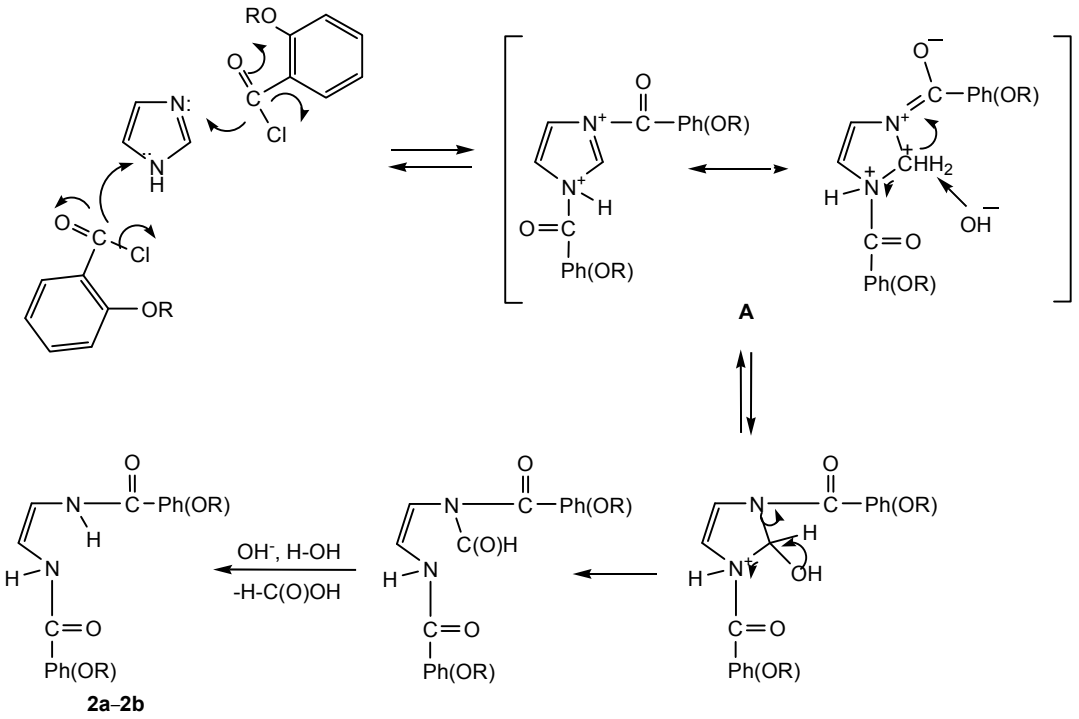
Aprotic nucleophilic solvents are polar to a greater or smaller extent (see table), and the higher the dielectric constant of the solvent, the more the solvent favors charge separation in the starting molecules or transition states, and, consequently, drives the nucleophilic reaction.

Considering the reaction in terms of acid–base interactions, solvents with a higher donor number, which strongly solvate the electron-deficient reagent, slightly decelerate the substitution reaction, thereby decreasing the yield of the target products. In this connection, the most optimal solvent for the synthesis of *N*-hydroxybenzoyl imidazole derivatives is chloroform (see table), which has the lowest donor

Scheme 2.



Scheme 3.



RO: 2-hydroxy (**2a**); 2-acetyloxy (**2b**).

number and highest dielectric constant among the solvents studied (benzene, chloroform, diethyl ether) [8].

We tested the newly synthesized imidazole derivatives for biological activity, and some of them showed psychotropic and analgesic activity.

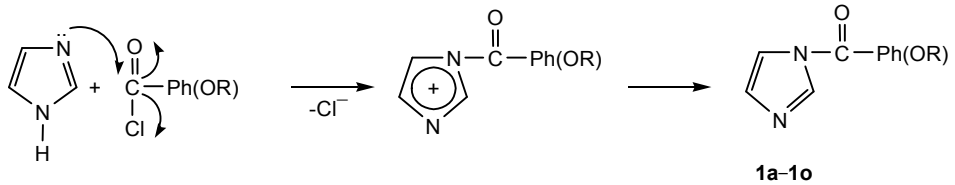
The study of behavioral disorders in animals (cognitive and mnestic) was performed using standard psychotropic tests, specifically an open field and a passive avoidance response test. The analgesic activity was assessed using the vocalization threshold test with preventive injection of the test compounds and diclofenac as a reference drug. Compound **1a** showed an evident analgesic activity, statistically reliably higher than the respective values for the control group and comparing with those for diclofenac; therewith, the motor score and oriented exploratory activity parameters were reliably higher than in the control group. Similar trends with insignificant variability were observed in the other groups, but the differences between the groups did not reach statistical significance.

Effect of the solvent on the yield of substitution and cleavage products

Solvent	μ	Dielectric constant	Donor number	Yield, %	
				substitution	cleavage[a]
Benzene	0	2.28	3.5	58 (**1a**) 61 (**1i**)	–
Chloroform	1.87	4.70	1.0	85 (**1a**) 87 (**1i**)	–
Diethyl ether	1.25	4.34	19.2	80 (**1a**) 79 (**1i**)	–
Water	–	84.0	18.0	–	87 (**2a**) 74 (**2b**)

[a] Under the Schotten–Baumann reaction conditions (6 N aqueous NaOH).

Scheme 4.



1a–1o

RO: 2-OH (**1a**), 3-OH (**1b**), 4-OH (**1c**), 2,3,4-OH (**1d**), 2-OMe (**1e**), 3-OMe (**1f**), 4-OMe (**1g**), 2,3,4-OMe (**1h**), 2-OAc (**1i**), 3-OAc (**1j**), 4-OAc (**1k**), 2,3,4-OAc (**1l**), 2,4-OH (**1m**), 2,4-OAc (**1n**), 2,4-OMe (**1o**).

EXPERIMENTAL

The ^{1}H NMR spectra (DMSO-d_6) were recorded on a Bruker AM300 spectrometer (300 MHz), internal reference HMDS. The mass spectra were recorded on a Finnigan Trace DCQ GCMS system using an SGE BPX-5 column (30 m × 0.32 mm), ionizing energy 70 eV. The melting points were determined on a Stuart SMP-30 melting point apparatus at a heating rate of 10 deg/min. Elemental analysis was performed on a Perkin Elmer Series II 2400 analyzer. Thin-layer chromatography was performed on Silufol UV-254 plates, eluent hexane–ethyl acetate, 1 : 3.

Acid chlorides were synthesized by the reactions of corresponding acids with oxalyl chloride [9–10].

Synthesis of hydroxybenzoylimidazoles. A solution of 50 mmol of acid chloride in 10 mL of chloroform was slowly added dropwise to a solution of 100 mmol of imidazole in 70 mL of anhydrous chloroform. Imidazole hydrochloride precipitated immediately. The mixture was stirred for 30 min at room temperature. The precipitate was separated, and the organic layer was washed with cold water (3 × 10 mL), dried over sodium sulfate, and dried in air. The residue was washed with cold water and dried in air.

***N*-(2-Hydroxybenzoyl)imidazole (1a).** Yield 11.73 g (85%), viscous oil. R_f 0.62, n_D^{20} 1.637. ^{1}H NMR spectrum, δ, ppm: 8.49 s (1H, OH), 7.97 s (1H, CH, imidazole), 7.75 d (1H, CH, imidazole), 7.55 d (1H, CH, imidazole), 7.37 d (1H$_{arom}$), 7.06–7.01 m (2H$_{arom}$), 6.96 d (2H$_{arom}$). Mass spectrum (ESI), *m/z*: 188 $[M]^+$. Found, %: C 63.83; H 4.32; N 14.87. $C_{10}H_8O_2N_2$. Calculated, %: C 63.82; H 4.28; N 14.89.

***N*-(3-Hydroxybenzoyl)imidazole (1b).** Yield 11.31 g (82%), viscous oil. R_f 0.57, n_D^{20} 1.618. ^{1}H NMR spectrum, δ, ppm: 8.33 s (1H, OH), 8.02 s (1H, CH, imidazole), 7.81 d (1H, CH, imidazole), 7.36–7.31 m (4H, 2CH$_{arom}$, 2CH, imidazole), 7.11–7.02 m (1H$_{arom}$). Mass spectrum (ESI), *m/z*: 188 $[M]^+$. Found, %: C 63.84; H 4.30; N 14.87. $C_{10}H_8O_2N_2$. Calculated, %: C 63.82; H 4.28; N 14.89.

***N*-(4-Hydroxybenzoyl)imidazole (1c).** Yield 11.04 g (80%), viscous oil. R_f 0.54, n_D^{20} 1.645. ^{1}H NMR spectrum, δ, ppm: 8.33 s (1H, OH), 8.02 s (1H, CH, imidazole), 7.77 d (1H, CH, imidazole), 7.57 d (2H$_{arom}$), 7.38 d (1H, CH, imidazole), 6.87 s (2H$_{arom}$). Mass spectrum (ESI), *m/z*: 188 $[M]^+$. Found, %: C 63.82; H 4.30; N 14.87. $C_{10}H_8O_2N_2$. Calculated, %: C 63.82; H 4.28; N 14.89.

***N*-(3,4,5-Trihydroxybenzoyl)imidazole (1d).** Yield 10.20 g (60%), yellow crystals. R_f 0.84, mp 70–72°C. ^{1}H NMR spectrum, δ, ppm: 8.03–7.98 m (3H, 2OH, CH, imidazole), 7.89 s (1H, OH), 7.76 d (1H, CH, imidazole), 7.36 d (1H, CH, imidazole), 6.72 d (2H$_{arom}$). Mass spectrum (ESI), *m/z*: 220 $[M]^+$. Found, %: C 54.56; H 3.68; N 12.82. $C_{10}H_8O_4N_2$. Calculated, %: C 54.55; H 3.66; N 12.72.

***N*-(2-Methoxybenzoyl)imidazole (2e).** Yield 13.37 g (88%), viscous oil. R_f 0.25, n_D^{20} 1.583. ^{1}H NMR spectrum, δ, ppm: 7.93 s (1H, CH, imidazole), 7.76 d (1H, CH, imidazole), 7.69 d (1H$_{arom}$), 7.49 t (1H$_{arom}$), 7.37 d (1H, CH, imidazole), 7.12–7.08 m (2H$_{arom}$), 3.81 s (3H, CH$_3$). Mass spectrum (ESI), *m/z*: 202 $[M]^+$. Found, %: C 65.38; H 4.00; N 13.83. $C_{11}H_{10}O_2N_2$. Calculated, %: C 65.34; H 4.98; N 13.85.

***N*-(3-Methoxybenzoyl)imidazole (1f).** Yield 13.06 g (86%), viscous oil. R_f 0.23, n_D^{20} 1.577. ^{1}H NMR spectrum, δ, ppm: 8.03 s (1H, OH), 7.78 s (1H, CH, imidazole), 7.37–7.32 m (4H, 2CH$_{arom}$, 2CH, imidazole) 7.12 d (1H$_{arom}$), 3.81 s (3H, CH$_3$). Mass spectrum (ESI), *m/z*: 202 $[M]^+$. Found, %: C 65.35; H 4.99; N 13.81. $C_{11}H_{10}O_2N_2$. Calculated, %: C 65.34; H 4.98; N 13.85.

***N*-(4-Methoxybenzoyl)imidazole (1g).** Yield 14.43 g (85%), yellow crystals. R_f 0.20, mp 96–98°C. ^{1}H NMR spectrum, δ, ppm: 8.05 s (1H, CH, imidazole), 7.72 d (1H, CH, imidazole), 7.55 d (2H$_{arom}$), 7.34 d (1H, CH,

imidazole), 7.05 d ($2H_{arom}$), 3.77 s (3H, CH_3). Mass spectrum (ESI), *m/z*: 202 $[M]^+$. Found, %: C 65.33; H 4.99; N 13.87. $C_{11}H_{10}O_2N_2$. Calculated, %: C 65.34; H 4.98; N 13.85.

***N*-(3,4,5-Trimethoxybenzoyl)imidazole (1h).** Yield 18.33 g (77%), yellow crystals. R_f 0.18, mp 54–56°C. ^{1}H NMR spectrum, δ, ppm: 8.01 s (1H, CH, imidazole), 7.76 d (1H, CH, imidazole), 7.36 d (1H, CH, imidazole), 7.12–7.09 m ($2H_{arom}$), 3.81 s (9H, $3CH_3$). Mass spectrum (ESI), *m/z*: 262 $[M]^+$. Found, %: C 59.56; H 5.40; N 10.69. $C_{13}H_{14}O_4N_2$. Calculated, %: C 59.54; H 5.38; N 10.68.

***N*-(2-Acetoxybenzoyl)imidazole (1i).** Yield 15.66 g (87%), viscous oil. R_f 0.31, n_D^{20} 1.596. ^{1}H NMR spectrum, δ, ppm: 7.99 s (1H, CH, imidazole), 7.76–7.72 m (2H, CH, imidazole, CH_{arom}), 7.49 t ($1H_{arom}$), 7.35 m ($2H_{arom}$, CH, imidazole), 7.21 d ($1H_{arom}$), 2.25 (3H, CH_3). Mass spectrum (ESI), *m/z*: 230 $[M]^+$. Found, %: C 62.61; H 4.40; N 12.11. $C_{12}H_{10}O_3N_2$. Calculated, %: C 62.60; H 4.38; N 12.17.

***N*-(3-Acetoxybenzoyl)imidazole (1j).** Yield 14.58 g (81%), viscous oil. R_f 0.28, n_D^{20} 1.588. ^{1}H NMR spectrum, δ, ppm: 8.07 s (1H, CH, imidazole), 7.78 d (1H, CH, imidazole), 7.68–7.57 m ($2H_{arom}$), 7.42–7.28 m (4H, $2CH_{arom}$, 2CH, imidazole), 2.35 s (3H, CH_3). Mass spectrum (ESI), *m/z*: 230 $[M]^+$. Found, %: C 62.65; H 4.33; N 12.19. $C_{12}H_{10}O_3N_2$. Calculated, %: C 62.60; H 4.38; N 12.17.

***N*-(4-Acetoxybenzoyl)imidazole (1k).** Yield 14.76 g (82%), viscous oil. R_f 0.25, n_D^{20} 1.599. ^{1}H NMR spectrum, δ, ppm: 8.03 s (1H, CH, imidazole), 7.84–7.66 d ($2H_{arom}$), 7.36 d (1H, CH, imidazole), 7.25–7.21 d ($2H_{arom}$), 2.21 s (3H, CH_3). Mass spectrum (ESI), *m/z*: 230 $[M]^+$. Found, %: C 62.62; H 4.35; N 12.12. $C_{12}H_{10}O_3N_2$. Calculated, %: C 62.60; H 4.38; N 12.17.

***N*-(3,4,5-Triacetoxybenzoyl)imidazole (1l).** Yield 18.34 g (62%), yellow crystals. R_f 0.49, mp 63–64°C. ^{1}H NMR spectrum, δ, ppm: 8.23 s (1H, CH, imidazole), 7.76 d (1H, CH, imidazole), 7.55 d ($2H_{arom}$), 7.36 d (1H, CH, imidazole), 2.25 s (6H, $2CH_3$), 2.19 s (3H, CH_3). Mass spectrum (ESI), *m/z*: 346 $[M]^+$. Found, %: C 55.50; H 4.10; N 8.01. $C_{16}H_{14}O_7N_2$. Calculated, %: C 55.49; H 4.07; N 8.07.

***N*-(2,4-Dihydroxybenzoyl)imidazole (1m).** Yield 9.69 g (63%), yellow crystals. R_f 0.72, mp 64–66°C. ^{1}H NMR spectrum, δ, ppm: 8.52 s (1H, OH), 8.33 s (1H, OH), 7.97 s (1H, CH, imidazole), 7.77 d (1H, CH, imidazole), 7.39–7.36 m (2H, CH_{arom}, CH, imidazole), 6.52–6.47 m ($2H_{arom}$). Mass spectrum (ESI), *m/z*: 204 $[M]^+$. Found, %: C 58.91; H 3.91; N 13.75. $C_{10}H_8O_3N_2$. Calculated, %: C 58.82; H 3.95; N 13.72.

***N*-(2,4-Diacetoxybenzoyl)imidazole (1m).** Yield 16.18 g (68%), yellow crystals. R_f 0.38, mp 51–53°C. ^{1}H NMR spectrum, δ, ppm: 8.01 s (1H, CH, imidazole), 7.78–7.75 d (2H, CH_{arom}, CH, imidazole), 7.35 d (1H, CH, imidazole), 7.19 d ($1H_{arom}$), 7.09 s ($1H_{arom}$), 2.26 s (3H, CH_3), 2.16 s (3H, CH_3). Mass spectrum (ESI), *m/z*: 288 $[M]^+$. Found, %: C 58.29; H 4.22; N 27.74. $C_{14}H_{12}O_5N_2$. Calculated, %: C 58.33; H 4.20; N 27.75.

***N*-(2,4-Dimethoxybenzoyl)imidazole (1n).** Yield 13.16 g (71%), yellow crystals. R_f 0.20, mp 46–48°C. ^{1}H NMR spectrum, δ, ppm: 7.98 s (1H, CH, imidazole), 7.77 d (1H, CH, imidazole), 7.36 d ($1H_{arom}$), 6.72 d ($2H_{arom}$), 3.82 s (3H, CH_3), 3.78 s (3H, CH_3). Mass spectrum (ESI), *m/z*: 232 $[M]^+$. Found, %: C 62.07; H 5.21; N 12.08. $C_{12}H_{12}O_3N_2$. Calculated, %: C 62.06; H 5.21; N 12.06.

1,2-Bis[(2-hydroxybenzoyl)amino]ethylene **2a** and 1,2-bis[(2-acetyloxybenzoyl)amino]ethylene **2b** were prepared by the procedure in [11].

1,2-Bis[(2-hydroxybenzoyl)amino]ethylene (**2a**). Yield 4.72 g (87%), white crystals. R_f 0.74, mp 151–152°C. ^{1}H NMR spectrum, δ, ppm: 9.48–9.42 m (2H, 2OH), 8.15–8.09 m (2H, 2NH), 7.79–7.55 m ($2H_{arom}$), 7.06–6.98 m ($2H_{arom}$), 6.98–6.81 m ($2H_{arom}$), 3.61–3.58 m (2H, 2CH). Mass spectrum (ESI), *m/z*: 298 $[M]^+$. Found, %: C 64.45; H 4.71; N 9.35. $C_{16}H_{14}O_4N_2$. Calculated, %: C 64.42; H 4.73; N 9.39.

1,2-Bis[(2-acetyloxybenzoyl)amino]ethylene (**2b**). Yield 3.94 g (74%), white crystals. R_f 0.43, mp 156–157°C. ^{1}H NMR spectrum, δ, ppm: 8.03–7.79 m ($2H_{arom}$), 7.75–7.68 m (2H, 2NH), 7.54–6.48 m ($2H_{arom}$), 7.44 m ($2H_{arom}$), 7.48–3.19 m ($2H_{arom}$), 6.59–6.57 m (4H, 2CH), 2.23–2.17 (6H, $2CH_3$). Mass spectrum (ESI), *m/z*: 382 $[M]^+$. Found, %: C 62.80; H 4.75; N 7.32. $C_{16}H_{14}O_4N_2$. Calculated, %: C 62.82; H 4.74; N 7.33.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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