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LETTERS TO THE EDITOR

To the 85th Anniversary of birthday of late Yu.G. Gololobov

Synthesis of 4-Hydroxybenzamides and Their Salts

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Hydroxybenzamides are important and well known nitrogen-containing compounds. Their derivatives attract considerable interest owing to the wide range of their biological activity [1–7].

Certain derivatives of 4-hydroxybenzamide exhibit cerebroprotective activity; however, the low solubility in water limits their bioavailability. In view of the above, in this work we prepared the water-soluble salt forms of 4-hydroxybenzamides and studied their cerebroprotective activity *in vivo*.

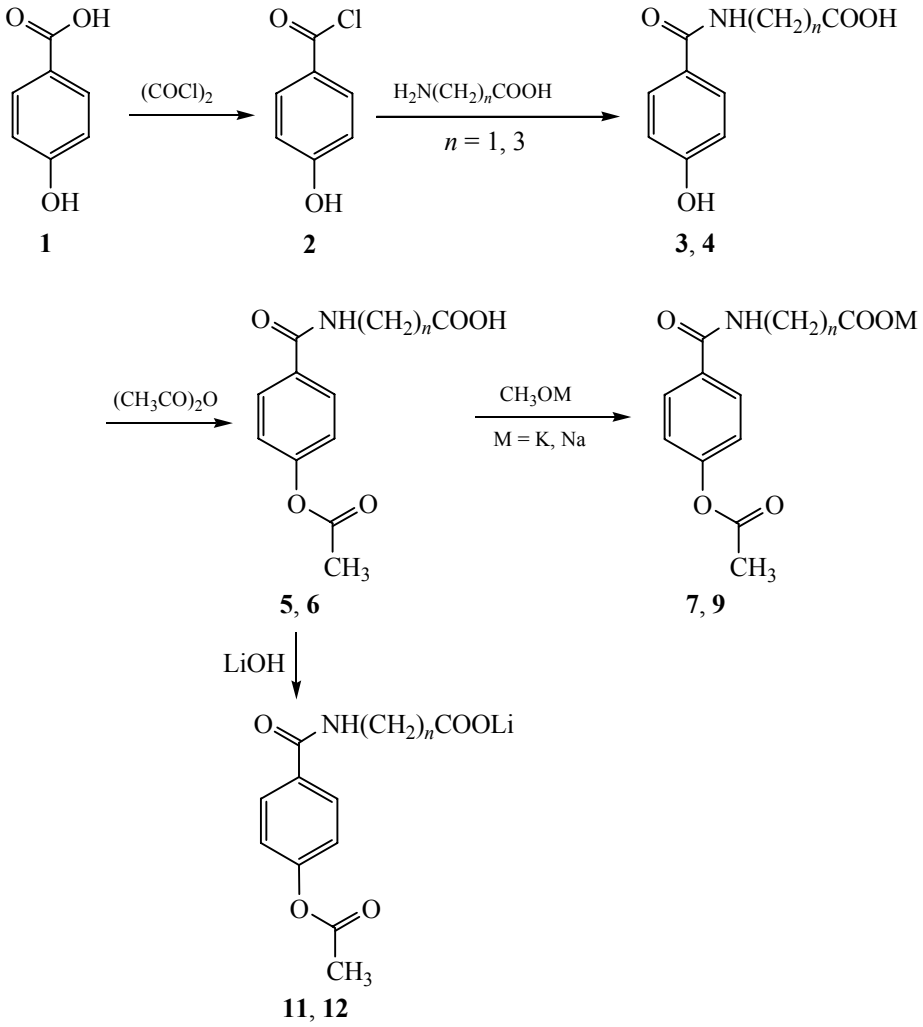
First, we prepared 4-hydroxybenzoyl chloride **2** from 4-hydroxybenzoic acid **1**. Carboxylic acid chlorides are generally prepared via the reaction of thionyl chloride with the corresponding carboxylic acid. A serious drawback of this method is the requirement of high purity of thionyl chloride: it should always be additionally purified prior to use. Furthermore, the reaction should be carried out upon slight boiling at 30°C; overheating or cooling would reduce the product yield and purity. In the case of hydroxybenzoic acid, the excess of thionyl chloride is usually distilled off to afford the crude hydroxybenzoyl chloride that is introduced in further reactions without purification [8] to avoid the product decomposition. Isolation of pure hydroxybenzoyl chloride requires multiple purification stages, since the product as-prepared via the thionyl chloride method contains 1–2% of organosulfur compounds formed via the side reaction of thionyl chloride with phenolic hydroxy group of hydroxybenzoic acid [9]. Such product contamination is a serious problem as far as preparation of biologically active compounds and drugs is concerned [7]; moreover, it significantly reduces the yield of the target product in the case of multi-stage synthesis. The mentioned drawbacks could be overcome by using oxalyl chloride [10] instead of thionyl chloride. The latter method has afforded hydroxybenzoyl chloride in high yields (up to 91%) and free of the sulfur-containing admixtures.

The target 4-hydroxybenzamides, 4-hydroxyhippuric acid **3** and 4-[(4-hydroxybenzoyl)amino]butanoic acid **4**, were prepared via the Schotten–Baumann reaction of compound **2** with glycine or γ-aminobutyric acid, respectively, in aqueous alkali solution [7]. Compound **3**: yield 85%, white crystals, mp 220–223°C; compound **4**: yield 73%, white crystals, mp 170–173°C.

Acetylation [11] of 4-hydroxybenzamides **3** and **4** gave derivatives **5** (yield 78%) and **6** (yield 76%), respectively; the latter products were further converted into the water-soluble potassium, sodium, and lithium salts **7**–**12**. The potassium and sodium salts were prepared via the interaction of potassium (or sodium) methylate with 4-hydroxybenzamides at room temperature. The lithium salts were synthesized via the interaction with anhydrous lithium hydroxide in benzene [12, 13].

The high solubility of compounds **7**–**12** allowed determination of their cerebroprotective (anti-ischemic) activity *in vivo*. The cerebrovascular insufficiency was simulated via a single-step irreversible bilateral occlusion of common carotid arteries under the chloral hydrate anesthesia (intraperitoneal introduction,

Scheme 1.



n = 1, M = K (**7**); *n* = 3, M = K (**8**); *n* = 1, M = Na (**9**); *n* = 3, M = Na (**10**); *n* = 1 (**11**), 3 (**12**).

40 mg/kg). Introduction of compounds **7**, **8**, **9**, and **12** resulted in a significant cerebroprotective effect. The LD_{50} value (reflecting the acute toxicity) was above 2000 mg/kg for compounds **7**, **8**, **9**, and **12** (2543 mg/kg for compound **7**), allowing for classifying the prepared salts of 4-hydroxybenzamides as low-toxic compounds (Scheme 1). The best results were obtained in the case of potassium *N*-(4-acetoxybenzoyl)glycinate [14]; that compound is recommended for further pharmacological studies.

In summary, in this work we prepared and studied new water-soluble salts of 4-hydroxybenzoic acid amides with amino acids, combining the low toxicity with significant anti-ischemic activity. Those compounds are interesting in view of possible application as efficient cerebroprotective drugs.

Preparation of compounds 3–5 has been described elsewhere [15].

4-[(4-Acetoxybenzoyl)amino]butanoic acid (6). 0.2 mol of acetic anhydride and 0.2 mL of conc. sulfuric acid were sequentially added to 0.1 mol of compound **4**; the reaction mixture was spontaneously heated up to 75°C, and the solution became transparent. The reaction mixture was stirred at that temperature during 20 min, and then cooled down to ambient, poured in cold water, and left standing for 2 h. The formed crystals were filtered off, washed with water, and dried. Yield 76%, white crystals, mp 195–197°C. ^{1}H NMR spectrum (DMSO-d_6, 500 MHz), δ, ppm: 8.35 s (1H, NH), 7.18–7.79 m (4H, Ph), 2.28 s [3H, $C(O)CH_3$], 1.59–3.16 m ($6H,C_3H_6$). Mass spectrum (ESI-MS), *m*/*z*: 265 $[M]^+$. Found, %: C

58.78; H 4.69; N 5.27. $C_{13}H_{15}NO_5$. Calculated, %: C 58.86; H 5.70; N 5.28.

^{1}H NMR spectrum was recorded using a Bruker DRX500 spectrometer with HMDS as internal reference. Mass spectrum (ESI-TOF) was recorded using a Hewlett Packard GC 5890 Series II/MSD 5972 spectrometer. The metal content was measured using a Shimadzu AA-670 spectrophotometer (Li 670.8 nm, K 766.5 nm, and Na 589.0 nm).

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