

OPIANIC ACID IN THE SYNTHESIS OF BENZIMIDAZOLE DERIVATIVES

G. S. Borodkin,¹ L. Yu. Ukhin,^{1*} L. V. Belousova,¹
 E. N. Shepelenko,² and A. V. Alekseenko¹

*Heating an equimolar mixture of opianic acid and *o*-phenylenediamine in MeOH or EtOH produced 2-(2-carboxy-3,4-dimethoxyphenyl)benzimidazole, which was readily dehydrated in refluxing acetic or propionic anhydride to 11*H*-1,2-dimethoxyisoindolo[2,3-*a*]benzimidazol-11-one. Analogous reactions were carried out with 4,5-dichloro-*o*-phenylenediamine.*

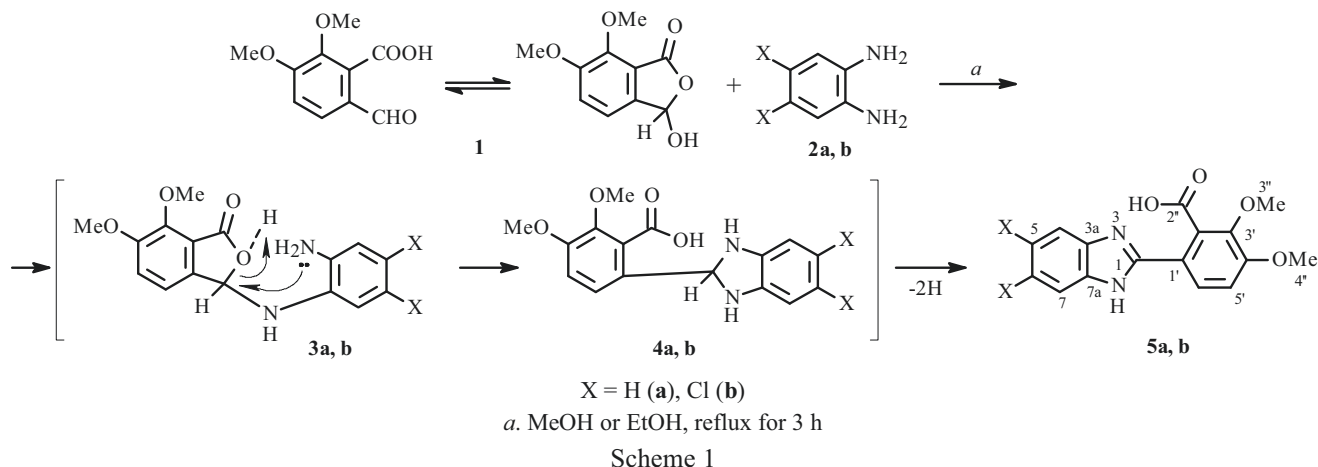
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Benzimidazole derivatives are lead compounds in medicinal chemistry [1]. Incorporation of natural biologically active compounds into the synthesis of benzimidazole derivatives causes interesting variations in their properties.

Prolonged refluxing of an equimolar mixture of tautomeric *o*-formylbenzoic acid and *o*-phenylenediamine in EtOH or MeOH was reported to form 2-(2-carboxyphenyl)benzimidazole [2, 3].

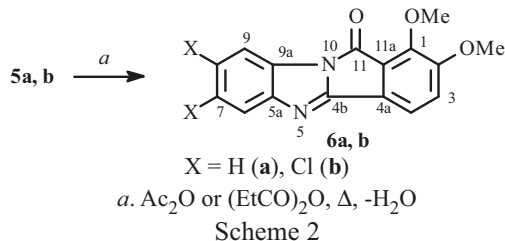
Natural opianic acid (*o*-formyl-2,6-dimethoxybenzoic acid) is also tautomeric and, as a rule, undergoes reactions characteristic of *o*-formylbenzoic acid. One example of this was published [4]. As it turned out, its reaction with *o*-phenylenediamine was no exception. Prolonged refluxing of an equimolar mixture of the reagents in MeOH or EtOH formed 2-(2-carboxy-3,4-dimethoxyphenyl)benzimidazole (**5a**). Scheme 1 illustrates a possible reaction mechanism. We hypothesized that the reaction began with formation of aminophthalide **3a**, like for anilines [5]. Then, **3a** recycled into benzimidazoline **4a**, which was oxidized by atmospheric O₂ into **5a**.

Compound **5a** was also included in a series of benzimidazole derivatives [6] that were prepared with catalysis by Cu-containing plant oxidases, i.e., laccases [7] (according to Chemical Abstracts Service, this is the only reference to this product). However, spectral and physical characteristics of this compound were not given in the paper.



1) Research Institute of Physical and Organic Chemistry, Southern Federal University, 194/2 Prosp. Stachki, Rostov-on-Don, 344090, Russian Federation, fax: (863) 243 47 00, e-mail: may@ipoc.sfedu.ru; 2) Southern Scientific Center, Russian Academy of Sciences, 41 Chekhov St., Rostov-on-Don, 344006, Russian Federation; e-mail: dubon@ipoc.sfedu.ru. Translated from *Khimiya Prirodnikh Soedinenii*, No. 1, January–February, 2017, pp. 99–101. Original article submitted April 28, 2016.

An analogous previously undescribed compound **5b** was obtained from the reaction of opianic acid with 4,5-dichloro-1,2-phenylenediamine. In contrast with **5a**, where a precipitate separated after refluxing for 2.5 h, the precipitate in this reaction appeared in the first few minutes. However, the IR spectrum showed that it consisted mainly of phthalide **3b**, which converted with subsequent prolonged refluxing into benzimidazole derivative **5b**. This confirmed the proposed mechanism. In this instance, the reaction should be conducted in EtOH because refluxing in MeOH did not convert phthalide **3b** into **5b**. Compounds **5a** and **5b** were readily dehydrated by refluxing acetic or propionic anhydrides into the previously also unknown 11*H*-1,2-dimethoxyisoindolo[2,3-*a*]benzimidazol-11-one **6a** and 11*a*-1,2-dimethoxyisoindolo[2,3-*a*]-7,8-dichlorobenzimidazol-11-one **6b**, respectively (Scheme 2).



The proposed structures were confirmed by complete assignment of resonances in their NMR spectra, for which two-dimensional COSY pulse sequences were used for PMR spectra; HSQC and HMBC, for ¹³C NMR spectra; and HMBC, for ¹⁵N NMR spectra. The agreement of the chemical shifts (CS) for C(4)H/C(7)H and C(5)H/C(6)H in **5a** and C(4)H/C(7)H in **5b** could be explained by migration of the amine proton between the N atoms (N-1 and N-3) as a result of fast intermolecular exchange with H₂O in the solvent (DMSO-*d*₆). This would make the benzimidazole moieties in **5a** and **5b** symmetric.

Compounds **5a** and **5b**, which combined a benzimidazole moiety and a 2-carboxy-3,4-dimethoxyphenyl group, were interesting as potential biologically active compounds, like dimethoxyisoindolonobenzimidazole derivatives **6a** and **6b**. Our results from testing using the PASS Internet program supported this. According to the tests, **5a** and **5b** could act as inhibitors of various enzyme-catalyzed biochemical redox processes; **6a** and **6b** would highly probably manifest sedative properties.

EXPERIMENTAL

IR spectra were recorded on a Varian Excalibur 3100 FTIR instrument. PMR, ¹³C NMR, and ¹⁵N NMR spectra were recorded on an Avance-600 spectrometer (Bruker). Mass spectra were obtained on a Shimadzu GCMS-QP 2010 SE GC-MS with direct sample introduction into the ion source (EI, 70 eV). Elemental analyses of all compounds agreed with those calculated.

2-(2-Carboxy-3,4-dimethoxyphenyl)benzimidazole (5a). A mixture of opianic acid (0.93 g, 5 mmol), *o*-phenylenediamine (0.54 g, 5 mmol), MeOH (15 mL), and AcOH (2 drops) was refluxed for 3.5 h. A precipitate began to form after 2.5 h. The mixture was cooled. The precipitate was filtered off, rinsed with MeOH, and dried to afford a colorless compound. Yield 0.27 g (18%). The filtrate was refluxed another 2 h and left for 1 d. More compound (0.2 g) with the same IR spectrum was isolated for a total yield of 0.47 g (31%). The compound was insoluble in refluxing MeCN, MeNO₂, and *i*-PrOH; soluble with heating in DMF and propylenecarbonate; mp 240–242°C (propylenecarbonate). IR spectrum (ν, cm⁻¹): 3100 br. (OH, NH), 1692 (C=O), 1629, 1595, 1570 (Ar), 1279 (C-O-CH₃). ¹H NMR spectrum (600 MHz, DMSO-*d*₆, δ, ppm, J/Hz): 3.80 (3H, s, CH₃-4''), 3.92 (3H, s, 3''-OCH₃), 7.19 (2H, m, H-5, 6), 7.28 (1H, d, J_{6,5'} = 8.5, H-6'), 7.55 (2H, m, H-4, 7), 7.68 (1H, d, J_{5',6'} = 8.5, H-5'). ¹³C NMR spectrum (150 MHz, DMSO-*d*₆, δ, ppm): 56.03 (s, C-3''), 60.97 (s, C-4''), 113.01 (s, C-6'), 114.93 (s, C-4), 114.97 (s, C-7), 119.63 (s, C-2'), 121.84 (s, C-5), 121.84 (s, C-6), 124.30 (s, C-5'), 130.49 (s, C-1'), 139.20 (s, C-3a), 139.20 (s, C-7a), 145.39 (s, C-4'), 149.85 (s, C-2), 153.53 (s, C-3'), 167.47 (s, C-2'). Mass spectrum (EI, 70 eV), *m/z* (*I*_{rel}, %): 298 (M⁺, 40), 280 (82), 265 (20), 254 (100), 252 (55).

2-(2-Carboxy-3,4-dimethoxyphenyl)-5,6-dichlorobenzimidazole (5b). Opianic acid (0.11 g, 0.5 mmol) in EtOH (5 mL) was heated until dissolved, treated with 4,5-dichloro-*o*-phenylenediamine (0.1 g, 0.55 mmol) and AcOH (2 drops), and refluxed for 3 h. A small amount of crystalline precipitate consisting mainly of phthalide **3b** according to the IR spectrum* formed almost immediately. The mixture was cooled in ice. The precipitate was filtered off, rinsed with cold EtOH and petroleum ether, and dried to afford a slightly cream-colored compound, mp 251–253°C, yield 0.062 g (28%). IR spectrum

*IR spectrum (ν, cm⁻¹): 3470 (NH), 3373 (NH₂, as), 3308 (NH₂, s), 1736 (C=O), 1034 (C-O-C, as), 855 (C-O-C, s).

(ν , cm^{-1}): 3200 br. (OH, NH), 1692 (C=O), 1625, 1593, 1574 (Ar). ^1H NMR spectrum (600 MHz, DMSO- d_6 , δ , ppm, J/Hz): 3.80 (3H, s, CH_3 -4''), 3.93 (3H, s, 3''-OMe), 7.30 (1H, d, $J = 8.6$, H-6'), 7.67 (1H, d, $J = 8.6$, H-5'), 7.77 (2H, s, H-4, 7), 12.98 (2H, s, OH, NH). ^{13}C NMR spectrum (150 MHz, DMSO- d_6 , δ , ppm): 55.79 (s, C-3''), 60.45 (s, C-4''), 113.15 (s, C-6'), 115.61 (s, C-4), 115.61 (s, C-7), 119.00 (s, C-2'), 123.92 (s, C-5), 123.92 (s, C-6), 124.20 (s, C-5'), 130.16 (s, C-1'), 138.42 (s, C-3a), 138.42 (s, C-7a), 145.53 (s, C-4'), 152.18 (s, C-2), 153.64 (s, C-3'), 166.24 (s, C-2''). Mass spectrum (EI, 70 eV), m/z (I_{rel} , %): 366 (M^+ , 47), 368 (36), 348 (34), 322 (45), 321 (87), 276 (100).

11H-1,2-Dimethoxyisoindolo[2,1-a]benzimidazol-11-one (6a). Compound **5a** (0.3 g, 1 mmol) was refluxed in Ac_2O (1.5 mL) until dissolved (~5 min), cooled, treated with *i*-PrOH (3 mL), washed with petroleum ether, and dried to afford yellow crystals, mp 150–152°C (*i*-PrOH), yield 0.23 g (82%). IR spectrum (ν , cm^{-1}): 1755 (C=O), 1628, 1562, 1494 (Ar), 1269, 1245 (C-O- CH_3). ^1H NMR spectrum (600 MHz, CDCl_3 , δ , ppm, J/Hz): 3.92 (3H, s, 2-OMe), 4.16 (3H, s, CH_3O -1), 7.03 (1H, d, $J = 8.0$, H-3), 7.25 (1H, t, $J = 7.7$, H-7), 7.28 (1H, t, $J = 7.7$, H-8), 7.49 (1H, d, $J = 8.0$, H-4), 7.64 (1H, d, $J = 7.7$, H-4), 7.75 (1H, d, $J = 7.7$, H-9). ^{13}C NMR spectrum (150 MHz, CDCl_3 , δ , ppm): 56.47 (s, C-2'), 62.45 (s, C-1'), 112.45 (s, C-9), 116.74 (s, C-3), 117.91 (s, C-4), 120.76 (s, C-6), 124.34 (s, C-4a), 123.92 (s, C-6), 124.81 (s, C-7), 125.21 (s, C-11a), 125.70 (s, C-8), 129.94 (s, C-9a), 149.23 (s, C-5a), 149.88 (s, C-1), 155.90 (s, C-4b), 156.07 (s, C-2), 159.01 (s, C-11). ^{15}N NMR spectrum (60 MHz, CDCl_3 , δ , ppm): 185.90 (s, N-10), 243.50 (s, N-5). Mass spectrum (EI, 70 eV), m/z (I_{rel} , %): 280 (M^+ , 100), 265 (27), 237 (40), 235 (15), 207 (12).

11H-1,2-Dimethoxyisoindolo[2,1-a]-7,8-dichlorobenzimidazol-11-one (6b). Compound **5b** (30 mg, 0.08 mmol) was refluxed in Ac_2O (2 mL) until dissolved (~2–3 min), and cooled. The whole mixture crystallized and was treated with *i*-PrOH (3 mL) and cooled in ice. The precipitate was filtered off, washed with *i*-PrOH and petroleum ether, and dried to afford yellow crystals, mp 233–235°C (*i*-PrOH), yield 24 mg (80%). IR spectrum (ν , cm^{-1}): 1741 (CO), 1626, 1556, 1493 (arom), 1255 (C-O- CH_3). ^1H NMR spectrum (600 MHz, CDCl_3 , δ , ppm, J/Hz): 3.97 (3H, s, CH_3O -2), 4.18 (3H, s, CH_3O -1), 7.10 (1H, d, $J = 8.1$, H-3), 7.54 (1H, d, $J = 8.1$, H-4), 7.74 (1H, s, H-6), 7.89 (1H, s, H-9). ^{13}C NMR spectrum (150 MHz, CDCl_3 , δ , ppm): 56.62 (s, C-2'), 62.56 (s, C-1'), 113.87 (s, C-9), 117.08 (s, C-3), 118.51 (s, C-4), 121.99 (s, C-6), 123.70 (s, C-4a), 124.77 (s, C-11a), 128.88 (s, C-7), 128.99 (s, C-9a), 129.77 (s, C-8), 148.59 (s, C-5a), 150.32 (s, C-1), 156.60 (s, C-2), 157.41 (s, C-4b), 158.52 (s, C-11). ^{15}N NMR spectrum (60 MHz, CDCl_3 , δ , ppm): 182.80 (s, N-10), 239.50 (s, N-5). Mass spectrum (EI, 70 eV), m/z (I_{rel} , %): 348 (M^+ , 100), 350 (63), 333 (14), 321 (15), 319 (24).

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