Synthesis of some bis- and mono-2-hydroxybenzoic acid derivatives and the determination of their acidity constants

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Several bis- and mono-2-hydroxybenzoic acid derivatives were synthesized by the reaction of methyl 2-hydroxybenzoate with some alcohols (diols, polyols and amino alcohols) and their acidity constants were determined in 60% aqueous ethanol by the potentiometric titration method. It has been shown that the biochemical behaviour of these compounds is greatly dependent on their acidity. It appears that the ester derivatives are weaker acids than the amide derivatives and, therefore, can be potential byproducts involved in the processes of metal ions transport in plants, whereas the introduction of -OH and -CH₃ groups has a very small effect on the biochemical properties.

Keywords: 2-hydroxybenzoic acid derivatives, synthesis, acidity constants.

INTRODUCTION

It is known that a large number of 2-hydroxybenzoic acid derivatives exhibit a certain biological activity and that compounds among them having phenolic -OH groups represent the ligands involved in the process of metal ions transport in plants. In previous papers we have described the synthesis of some selected bis-2-hydroxybenzamide and ester derivatives, as well as the stability of their complexes with various metal ions.

Now we report the results related to the transesterification of methyl 2-hydroxybenzoate with selected alcohols (propan-1,2-diol, glycerol and 2,2-bis(hydroxymethyl)propan-1,3-diol) and aminoalcohols (2-aminoethan-1-ol, 1-aminopropan-2-ol and 2-amino-2-(hydroxymethyl)propan-1,3-diol). The following mono- and bis-2-hydroxybenzoate ester and amide derivatives were obtained: propane-1,2-diyl bis(2-hydroxybenzoate) (1), 2-hydroxypropyl 2-hydroxybenzoate (2), 2-hydroxypropane-1,3-diy l bis(2-hydroxybenzoate) (3), 2,2-bis(hydroxymethyl)propane-1,3-diyl bis(2-hydroxybenzoate) (4), 2-(2-hydroxybenzamido)ethyl 2-hydroxybenzoate (7), N-(2-hydroxybenzamido)ethanethiol 2-hydroxybenzoate (8), etc.

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ethyl)-2-hydroxybenzamide (8), 2-(2-hydroxybenzamido)-1-methylethyl 2-hydroxybenzoate (9), N-(2-hydroxypropyl)-2-hydroxybenzamide (10) and N-[tris(hydroxymethyl) methyl]-2-hydroxybenzamide (11) (Fig. 1).

The reactions were carried out at 150 °C in the presence of sodium as catalyst. Under these reaction conditions, when the transesterification was carried out in a mole ratio of 2:1 of methyl 2-hydroxybenzoate and the corresponding alcohol (propan-1,2-diol, glycerol, 2-aminoethan-1-ol, 1-aminopropan-2-ol and 2-amino-2-(hydroxymethyl)propan-1,3-diol) the bis-2-hydroxybenzoic acid derivatives 1, 3, 7 and 9 were obtained in the yields 80, 26, 12 and 15 %, respectively and the mono-2-hydroxybenzoic acid derivatives 8, 10 and 11 in the yields 32, 40 and 21 %, respectively.

In contrast, the reaction of methyl 2-hydroxybenzoate with a three-fold molar excess of propan-1,2-diol or 2,2-bis(hydroxymethyl)propan-1,3-diol resulted in the corresponding mono-derivative 2 (42 % yield) or bis-derivative 4 (18 % yield).

In view of the fact that the biochemical behaviour of these compounds is greatly dependent on their acidity, we determined their acidity constants.

The acidity constants of the synthesized derivatives of 2-hydroxybenzoic acid 1–4 and 7–11, monoprotic or diprotic weak acids, were determined by potentiometric titration.3,7

EXPERIMENTAL

All the chemicals used were of analytical reagent grade. Methyl 2-hydroxybenzoate was purified by distillation (b.p. 219–222 °C).
IR spectra were recorded on a Perkin-Elmer 457 spectrophotometer. 1H- and 13C-NMR spectra were taken on a Bruker AC 200 MHz instrument; the chemical shifts (δ) are given in ppm values and coupling constants (J) in Hz. Mass spectra were obtained on a Finnigan MAT 8230 BENDIC (m/z values and ion abundances are given). Melting points were determined on a Büchi SMP-20 apparatus and were not corrected.

The protonation equilibria were investigated by potentiometric titration of a mixture of the given 2-hydroxybenzoic acid derivative and hydrochloric acid with a solution of LiOH at 25 ± 0.1 °C under nitrogen atmosphere, in 60% (m/m) aqueous ethanol solution of constant ionic strength (0.5 mol dm⁻³ LiCl). Changes in the H₂O⁺ concentration were followed with a pH201 Radiometer glass electrode and a silver-silver chloride reference electrode prepared after Brown.⁸

Quantitative evaluation of the data was carried out using Eq. (1), giving the relationship between the experimental emf values (E) and the equilibrium H₂O⁺ concentration, [H₂O⁺]:

\[ E = E^0 + (RT/F) \log [H_3O^+] + \beta_{H} \cdot [H_3O^+] + \beta_{OH} \cdot K_w/[H_3O^+] \]

where E is constant which includes the standard potential of the glass electrode, βH and βOH are fitting parameters in acidic and alkaline media for correction of experimental errors of the glass electrode, K_w is the autoionization constant of water (10⁻¹⁴).⁹

The emf was measured with a Radiometer digital pH meter, PHM 64.

**General procedure for the synthesis of compounds 1–4 and 7–11**

A mixture consisting of methyl 2-hydroxybenzoate (20 mmol), the corresponding alcohol (10 mmol), propan-1,2-diol, glycerc, 2-aminoethanol-1-ol, 1-aminopropan-2-ol, or 2-amino-2-hydroxymethyl) propan-1,3-diol and sodium (1 mmol) was heated on an oil bath at 150 °C under atmospheric pressure, with the continuous removal of methanol for 2 h. Afterwards, di-stilled water (100 ml) and hydrochloric acid (1:1, to pH 6–7) were added to the residue.

**Propane-1,2-diyI bis-(2-hydroxybenzoate) (1)**

According to the general procedure, compound 1 precipitated upon addition of water and hydrochloric acid (1:1, to pH 6–7) to the reaction mixture. The precipitated solid was washed with water, dried and recrystallized from 95% ethanol to give 1 in 80% yield, m.p. 76–76.5 °C. IR spectrum (KBr, νmax): 3450 (O-H), 3190 (C-H, am), 2980, 2880 (C-H, aliph.), 1670 (C=O, ester), 1615, 1590 (C=C, am), 1490, 1470 (C=C, C=O), 1405, 1350 (C-H, aliph.), 1230, 1260, 1265, 1215, 1190, 1095 (C-O-C, ester), 980 (C-H, 870 (C-H, 6)). 1H-NMR spectrum (CDCl₃): 1.52 (d, 3H, CH₃, JCH₃ = 6.5), 5.41 (dd, 1H, Ha from CH₂, JCH₂ = 11.9, JH₂CH₂ = 6.4), 4.58 (dd, 1H, Hb from CH₂, JBCH₂ = 3.7), 5.59 (m, 1H, CH₆), 6.89 (m, 2H, H-5, am.), 6.99 (d, 2H, H-3, am.), 7.14 (m, 2H, H-4, am.), 7.84 (m, 2H, H-6, am.), 10.63, 10.72 (2x, 2H, 2-OH, phenol). 13C-NMR spectrum (CDCl₃): 16.49 (CH₃), 66.49 (CH₂), 69.21 (CH), 111.91 and 112.21 (C-1, am.), 117.59 (C-3, am.), 119.19 and 119.29 (C-5, am.), 129.83 and 129.86 (C-6, am.), 13.599 and 13.589 (C=O, am.), 161.75 and 161.68 (C=2, am.), 169.66 and 169.45 (C=O, ester). Mass spectrum: 316 (M⁺, 20), 180 (18), 179 (100), 121 (94), 122 (22), 121 (94), 120 (50), 93 (28), 92 (28), 65 (12). For C₁₇H₁₇O₉ (316.3) calculated: 64.55 % C, 5.10 % H; found: 64.75 % C, 5.24 % H.

**2-Hydroxypropyl 2-hydroxybenzoate (2)**

To prepare compound 2, a mixture of methyl 2-hydroxybenzoate (10 mmol), propan-1,2-diol (30 mmol) and sodium (7 mmol) was treated according to the general procedure as described above. The precipitated solid of a crude compound 2 was recrystallized from water to give pure compound 2 in a yield of 42%, m.p. 78.5 – 79 °C. IR spectrum (KBr, νmax): 3380, 3300 (O-H), 1600 (C=O, ester), 1520 (C=C, am), 1495 (C=C, C=O, aliph.), 1350, 1300 (C-H, aliph.), 1260, 1235, 1160, 1095 (C-O-C, ester), 980 (O-H, 805, 780 (C-H, 6). 1H-NMR spectrum (CDCl₃): 1.31 (d, 3H, CH₃, JCH₃ = 6.2), 2.30 (bs, 1H, CH₂-OH), 4.14 – 4.39 (m, 3H, CH₂ and CH, JCH₂CH₂ = 6.8, JCH₂CH₂CH₂ = 3.5, JH₂CH₂ = 11.0), 6.88 (m, 1H, H-5, am.), JH₂ =
1. $J_{AB} = 7.1, J_{BC} = 8.1, 6.98 (dd, 1H, H-3, arom.), J_{AC} = 8.5, 7.47 (m, 1H, H-4, arom.), J_{AD} = 1.8, 7.86 (dd, 1H, H-6, arom.). 10.71 (s, 1H, OH, phenol). $^{13}$C-NMR spectrum (CDCl$_3$): 19.26 (CH$_3$), 65.91 (CHOH), 70.06 (CH$_6$), 112.09 (C-1, arom.), 117.62 (C-3, arom.), 119.19 (C-5, arom.), 129.79 (C-6, arom.), 135.91 (C-4, arom.), 161.62 (C-2, arom.), 170.00 (C=O, ester). Mass spectrum: 197 (M$^+$+1, 100), 179 (10), 121 (5). For C$_9$H$_{12}$O$_4$ (196.2) calculated: 61.22% C, 6.12% H; found: 61.17% C, 6.08% H.

2-Hydroxypropane-1,3-diyld bis(2-hydroxybenzoate) (3)

According to the general procedure, crude compound 3 was extracted from the reaction mixture with ethyl acetate. The extract was dried over anhydrous sodium sulfate and evaporated. Pure compound 3 was obtained after chromatography on a short column of silica gel (benzene - ethyl acetate 9:1 and 7:3) and recrystallization from a mixture of dichloromethane - hexane in a yield of 26%, m.p. 86.5 - 87°C. IR spectrum (KBr, $\nu_{max}$): 3350-3380 and 3250-3100 (OH), 1675 (C=O, ester), 1615, 190, 1490 (C=C, arom.), 1460, 1420 (C-H, aliph.), 1300, 1260, 1140, 1000 (C-O-C, ester), 760 (C-H). $^{13}$C-NMR spectrum (DMSO-d$_6$): 4.24 (m, 1H, HOC=CH), 4.41 (m, 2H, C=H), 5.71 (bs, 1H, CH=O), 6.94 (t, 2H, H-5, $J_{AB} = 7.8, J_{BC} = 8.0, J_{BD} = 0.8), 6.98 (dd, 2H, H-3, $J_{AD} = 8.2, 7.2$ (m, 2H, H-4, $J_{BC} = 1.7, J_{BD} = 1.7), 7.86 (dd, 2H, H-6, 10.46 (bs, 2H, 2OH, phenol). $^{13}$C-NMR spectrum (DMSO-d$_6$): 66.00 (CHOH), 66.64 (CO$_2$CH$_2$), 112.59 (C-1), 117.39 (C-3), 119.39 (C-5), 130.28 (C-6), 135.78 (C-4), 160.15 (C=2), 166.85 (C=O). Mass spectrum: 333 (M$^+$+1, 100), 315 (28), 19 (7.6). For C$_9$H$_{12}$O$_4$ (323.2) calculated: 61.45% C, 4.85% H; found: 61.78% C, 4.95% H.

2,2-Bis(hydroxymethyl)propane-1,3-diyld bis(2-hydroxybenzoate) (4)

To prepare compound 4, a mixture of methyl 2-hydroxybenzoate (10 mmol), 2,2-bis(hydroxymethyl)propane-1,3-diol (30 mmol) and sodium (7 mmol) was treated according to the general procedure. The crude compound 4 was extracted from the reaction mixture with ethyl acetate. The extract was dried over anhydrous sodium sulfate and evaporated. Pure compound 4 was obtained after column chromatography (benzene - ethyl acetate 9:1 and 2:1) and recrystallization from acetone-hexane in a yield of 18%, m.p. 86.5 - 87°C. IR spectrum (KBr, $\nu_{max}$): 3350-3380 and 3250-3100 (OH), 2960, 2860 (C-H, aliph.), 1675 (C=O, ester), 1615 (C=C, arom.), 1475, 1465 (C-H, aliph.), 1300, 1260, 1140, 1060 (C-O-C, ester), 760 (C-H). $^{13}$C-NMR spectrum (CD$_2$CO-d$_6$): 3.88 (d, 4H, 2CHOH, $J_{CH} = 6.2$), 4.33 (t, 2H, 2OH, 4.57 (t, 4H, 2CH$_2$OO), 6.93 (m, 4H, H-5, H-3, H-4, arom.), 7.52 (m, 2H, H-4, arom., J$_{BC} = 1.8, J_{AB} = 7.2, J_{AC} = 8.6), 7.91 (dd, 2H, H-6, arom., J$_{BC} = 7.9), 10.69 (bs, 2H, 2OH, phenol). $^{13}$C-NMR spectrum (CD$_2$CO-d$_6$): 45.60 (C=CH$_2$) (CH$_2$OH)$_2$, 61.65 (CH-OH), 65.13 (CH$_2$OCO$_2$), 113.27 (C-1, arom.), 118.14 (C-3, arom.), 120.06 (C-5, arom.), 130.82 (C-6, arom.), 136.65 (C-4, arom.), 162.29 (C-2, arom.), 170.64 (C=O, ester). Mass spectrum: 377 (M$^+$+1, 100), 257 (9), 241 (10). For C$_9$H$_{12}$O$_4$ (376.4) calculated: 60.63% C, 5.36% H; found: 61.00% C, 5.21% H.

2-(2-Hydroxybenzamido)ethyl 2-hydroxybenzoate (7)

According to the general procedure, crude compound 7 was extracted from the reaction mixture with ethyl acetate. Purified compound 7 was obtained under analogous experimental conditions as described for compound 3, in a yield of 12%, m.p. 98°C. IR spectrum (KBr, $\nu_{max}$): 3410 (OH, NH), 3180, 3080 (C=H, arom.), 2980 (C-H, aliph.), 1690 (C=O, ester), 1650 (C=O, amide), 1620, 1600, 1580 (C=C, arom.), 1500 (C=N-H), 1470 (C=H, arom.), 1300, 1250, 1210, 1100, 1050 (C-O-C, C=O, C=O, C=O, C=O), 750 (C-H). $^{13}$C-NMR spectrum (CD$_2$CO-d$_6$): 3.89 (m, 2H, 2CHOH, $J_{CH} = 5.5, J_{CH} = 5.8), 4.59 (t, 2H, 2CHOH), 6.83 (m, 1H, H-5, from C$_9$H$_{12}$OHCONH), 7.52 (O, 1H, H-3, from C$_9$H$_{12}$OHCONH), 7.40 (m, 1H, H-4, from C$_9$H$_{12}$OHCONH, J$_{BC} = 1.5, J_{BD} = 8.3), 7.52 (m, 1H, H-4 from C$_9$H$_{12}$OHCOO, J$_{BC} = 1.5), 7.76 (dd, 1H, H-6 from C$_9$H$_{12}$OHCONH), 7.90 (dd, 1H, H-6 from C$_9$H$_{12}$OHCOO, J$_{BC} = 8.0, 8.39 (bs, 1H, NH), 10.65 (s, 1H, OH from C$_9$H$_{12}$OHCOO), 12.39 (s, 1H, OH from C$_9$H$_{12}$OHCOO). $^{13}$C-NMR spectrum (CD$_2$CO-d$_6$): 39.23 (CH$_3$NH), 64.80 (CH$_2$COO), 113.19 (C-1 from C$_9$H$_{12}$OHCONH), 118.11 (C-3 from C$_9$H$_{12}$OHCOO), 118.63 (C-3 from C$_9$H$_{12}$OHCONH), 119.27 (C-5 from C$_9$H$_{12}$OHCONH), 120.05 (C-5 from
N-(2-hydroxyethyl)-2-hydroxybenzamide (8)

Compound 8 was prepared under the same experimental conditions as described for compounds 3 and 7. Compound 8 was recrystallized from chloroform (yield 38 %, m.p. 117 °C). IR spectrum (KBr, νmax cm⁻¹): 3410, 3320 (→OH, →NH), 3100 (→C–H, amine), 2950, 2800 (→C–H, aliph.), 1650 (→C=O, amide), 1620, 1590, 1520 (C=C, arom.), 1500 (→C=N–H, δ), 1480–1460 (→C–H, δ), 1380, 1240, 1070 (→C–O–N–), 980 (→O–H, →OH), 760 (→C–H, δ). 1H-NMR spectrum (CDCl₃): 3.53 (m, 2H, CH₂NCO). 3.12 (t, 2H, CH₂OH), 1.98–1.90 (m, 3H, H₃), 1.84 (m, 1H, H₅), J₆,₅ = 8.8, J₅,₄ = 9.4, J₄,₃ = 9.0, J₃,₂ = 9.8, 6.88 (dd, 1H, H₃, J₃,₄ = 8.3, J₂,₃ = 7.8, 7.39 (m, 1H, H₄), J₄,₅ = 1.6, 5.80–5.76 (m, 2H, H₂N, H₂O), 12.75 (s, 1H, OH, phenol). 13C-NMR spectrum (CDCl₃): 42.92 (CH₂N), 61.13 (CH₂OH), 115.49 (C–1), 118.54 (C–3), 119.16 (C–5), 127.57 (C–6), 134.60 (C–4), 162.41 (C–2), 171.18 (C=O). Mass spectrum: 182 (M⁺+1, 100). For C₁₁H₁₄NO₂ (181.2) calculated: 95.67 % C, 6.08 % H, 7.73 % N; found: 95.61 % C, 6.29 % H, 7.53 % N.

2-(2-Hydroxybenzamido)-1-methylethyl 2-hydroxybenzoate (9)

Crude compound 9 was extracted from the reaction mixture with ethyl acetate. The extract was dried over anhydrous sodium sulfate and evaporated. Pure compound 9 was obtained as an oil in a yield of 15 % after chromatography on short column of silica gel (benzene → ethyl acetate 9:1 and 7:3). IR spectrum (film, νmax cm⁻¹): 3490–3150 (→OH, →NH, →C–H, arom.,) 1670 (→C=O, ester), 1645 (→C=O, amide), 1600, 1590, 1540 (C=C, arom.), 1560, 1200, 1200, 1150, 1090 (C=C, ester), 740 (→C–H, δ). 1H-NMR spectrum (CDCl₃): 1.47 (d, 3H, CH₃, J₃,₂CH₂ = 6.4), 3.63–3.89 (m, 2H, CH₂), 5.41 (m, 2H, CH₂), 6.70–7.90 (m, 8H, arom. and H, NH), 10.68, 12.20 (2s, 2H, 2OH, phenol). 13C-NMR spectrum (CDCl₃): 17.81 (CH₃), 43.42 (CH₂), 71.24 (CH), 112.08 and 114.17 (C–1, arom.), 117.66 and 118.51 (C–3, arom.), 118.78 and 119.27 (C–5, arom.), 125.38 and 129.82 (C–6, arom.), 134.36 and 136.07 (C–4, arom.), 161.39 and 161.73 (C=O, arom.), 170.17 (C=O).

N-(2-hydroxypropyl)-2-hydroxybenzamide (10)

Pure compound 10 was obtained as an oil in a yield of 40 % under analogous experimental conditions as described for compound 9. IR spectrum (film, νmax cm⁻¹): 3490–3250 (→OH, →NH), 2900 (→C–H, aliph.), 1635 (→C=O, amide), 1600, 1550, 1495 (C=C, arom.), 1450, 1370, 1340 (→C–H, aliph.), 1310, 1250, 1150 (C=C–O–N–), 760 (→C–H, δ), 1.19 (d, 3H, CH₃, J₃,₂CH₂ = 6.4), 3.24, 3.56 (2m, CH₂), J₃,₂CH₂ = 13.8, J₃,₂CH₂ = 7.7, J₃,₂CH₂ = 3.0, J₃,₂CH₂ = 5.3, J₃,₂CH₂ = 6.1), 1.95 (m, 1H, CH), 3.99 (m, 1H, CH), 6.78 (m, 1H, H₅), J₅,₆ = 1.0, J₆,₆ = 7.1, J₆,₇ = 8.1, 6.91 (dd, J₃,₂ = 1H, H₃, arom., J₃,₂ = 8.5), 7.32 (m, 1H, H₄, arom., J₃,₂ = 1.8), 7.38–7.55 (m, 2H, H₆, arom., J₄,₅ = 12.17 (bs, 1H, OH, phenol). 13C-NMR spectrum (CDCl₃): 20.74 (CH₂), 46.64 (CH₂), 66.91 (CH), 114.31 (C–1, arom.), 118.08 (C–3, arom.), 118.88 (C–5, arom.), 126.16 (C–6, arom.), 134.15 (C–4, arom.), 160.61 (C–2, arom.), 170.34 (C=O, amide).

N-[tris(hydroxyethyl)methyl]-2-hydroxybenzamide (11)

Compound 11 was obtained under analogous experimental conditions as described for compound 8 (yield 21 %, m.p. 122–123 °C). IR spectrum (KBr, νmax cm⁻¹): 3490–3050 (→OH, →NH), 2940 (→C–H, aliph.), 1645 (→C=Oamide), 1605, 1550 (C=C, arom.), 1460, 1355, 1320 (C=O, δ), 1250, 1160, 1120, 1060, 1020 (→C–O–N, δ), 760 (→C–H, δ). 1H-NMR spectrum (DMSO-d₆): 3.65 (bs, 6H, 3CH₂OH), 4.93 (bs, 3H, 3OH), 6.90 (m, 2H, H₃, H₅), arom., 7.35 (m, 1H, H₄, arom., J₄,₅ = 8.4, J₅,₆ = 1.5), 7.88 (dd, H₆, H₇, arom., J₆,₇ = 7.8, 8.49 (s, 1H, H, CONH), 11.52 (bs, 1H, OH, phenol). 13C-NMR spectrum (DMSO-d₆): 60.37 (→C–N→(CH₂OH)₂), 62.51 (CH₂OH), 116.99 (C–3, arom.), 118.35 (C–4, arom.), 119.13 (C–5, arom.), 150.00 (C–6, arom.), 133.15 (C–4, arom.), 157.39
(C-2, arom), 166.83 (OHCONH). Mass spectrum: 242 (M+1; 100). For C₁₆H₁₇NO₃ (241.2) calculated: 54.77% C, 6.27% H, 5.81% N; found: 54.65% C, 6.54% H, 5.97% N.

RESULTS AND DISCUSSION

Protonation constants were determined from 3–5 independent titrations. The calculations concerning the calibration of the electrode system (E₀, slope, β1 and β2) were performed using the computer program PSEQUAD.¹⁰

The obtained values of acidity constants of the new compounds 1–4 and 7–11 are presented in Table 1.

| TABLE I. Protonation constants in 60% (m/m) ethanol at 25±0.1 °C and I₀ = 0.5 mol dm⁻³ (LiCl) |
|-----------------------------------------------|------------------|------------------|
| Compound | pKₐ¹ | pKₐ²⁰ |
| 1 | 9.26±0.04 | 9.44±0.09 |
| 2 | 9.59±0.02 | - |
| 3 | 9.27±0.02 | 9.30±0.01 |
| 4 | 9.30±0.03 | 9.66±0.07 |
| 5⁰ | 9.45±0.07⁰ | 9.85±0.05⁰ |
| 6⁰ | 9.64±0.01⁰ | 10.03±0.05⁰ |
| 7 | 8.63±0.02 | 9.37±0.06 |
| 8 | 8.53±0.08 | - |
| 9 | 8.72±0.08 | 9.31±0.24 |
| 10 | 8.96±0.02 | - |
| 11 | 8.00±0.01 | - |

¹Average deviations are shown. ²Ref. 3.

Compounds 1–4 are the ortho-substituted ester derivatives and compounds 7–11 are ortho-substituted amide derivatives of phenol. All the compounds are acids, stron-
ger than phenol ($pK_a = 10.73$)$^7$, which can be explained by the negative inductive effect ($-I$) of the carbonyl group, as well as by a negative resonance effect ($-R$) of the ester/amide substituent. If the acidity constants of methyl 2-hydroxybenzoate$^6$ ($pK_a = 9.83$)$^7$ and of compounds 1–4 are compared with the acidity constants of $N$-methyl-2-hydroxybenzamide ($pK_a = 8.75$)$^7$ and compounds 7–11, it is evident that the ester derivatives (methyl 2-hydroxybenzoate and compounds 1–4) are weaker acids than $N$-methyl-2-hydroxybenzamide and the new amides 7–11.

In addition to the $-I$ and $-R$ effects mentioned above, the acid strength of the investigated compounds is also essentially influenced by the intramolecular hydrogen bonds. In the molecules of methyl 2-hydroxybenzoate and of compounds 1–4 favourable intramolecular hydrogen bonds are involved, whereas in the dissociated forms destabilizing repulsive dipole–dipole interactions are in operation (Scheme 1).

However, in $N$-methyl-2-hydroxybenzamide and compounds 7–11, two potential intramolecular hydrogen bonds exist, so that both forms are present in a dynamic equilibrium (Scheme 2). The form in which the hydrogen bond is between the amino group and the phenolic group (b in Scheme 2) allows an easier detachment of proton from the $-OH$ group, i.e., the acidity of this group is enhanced. On the other hand, the dissociated forms are stabilized by the same intramolecular hydrogen bonds. Hence, $N$-methyl-2-hydroxybenzamide and compounds 7–11 are stronger acids than methyl 2-hydroxybenzoate and compounds 1–4.

![Scheme 2](image)

A further analysis of the $pK_a$ values of esters 1–4 shows that compound 1 is a stronger acid than compound 5 (Ref. 3) because it contains a methyl group. This methyl group, by its $+I$ effect, contributes to the strength of the intramolecular hydrogen bond.
between the carbonyl oxygen atom and the phenolic hydrogen, the consequence being an increased acidity of the phenolic group (Scheme 3).

![Scheme 3](image)

If compared with compound 6, compounds 3 and 4 contain additional OH and CH2OH groups, respectively, which also contribute to the acidity of the phenolic OH group. Hence, compounds 3 and 4 are stronger acids than compound 6. In an analogous way the acid properties of the N-substituted 2-hydroxybenzamides (compounds 7–11) can also be explained. The strongest acid is compound 11 because it contains three hydroxymethyl groups, whereas the weakest acid is compound 9, in which the methyl group, by its +I effect, increases the electronic density on the nitrogen atom of the amide group (Scheme 4). This weakens the intramolecular hydrogen bond between the phenolic oxygen and the amide hydrogen, the consequence being a hindered detachment of the proton from the phenolic group.

![Scheme 4](image)

It follows from the above that the ester derivatives of 2-hydroxybenzoic acid are weaker acids than the amide derivatives, so that their complexing properties are more pronounced. Hence, they can participate in the transport of metal ions in biological systems to a greater extent. On the other hand, the presence of the –OH and –CH3 groups in compounds 1, 3 and 4 increases only slightly the acidity of the phenolic groups compared with compound 6, and hence the complexing capabilities are insignificantly decreased, so that a small difference in the biochemical activity of the given compounds could be expected.

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ИЗВОД
СИНТЕЗА НЕКИХ БИС- И МОНО-ДЕРВИТА 2-ХИДРОКСИБЕНЗОЕВЕ КИСЕЛИНЕ И ОДРЕЖИВАЊЕ ЊИХОВИХ КИСЕЛINSКИХ КОНСТАНТИ

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Синтетизован су бис- и моно-деривати 2-хидроксибензойне киселине реакцијом метил-2-хидроксибензога и алкохола (диола, полкога и амино алкохола) и одређене су њихове киселинске константе у 60 %-ном этанолу, потенциометријском митрацијом. Показало се да оматерија у електролиту могу да усвојују у већој мери у пропорцији алкилата биолошки амиди дерибати.


REFERENCES
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