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SYNTHESIS AND BIOLOGICAL ACTIVITY OF BROMINATED PHENOLS WITH LACTAMOMETHYL MOIETIES — NATURAL COMPOUNDS ANALOGUES

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Abstract

This paper describes the synthesis of the brominated polyphenols with lactams fragments, which are analogues of natural marine compounds, and their biological activity research. Eight target substances were obtained with good yields via bromination of pyrrolidone and caprolactam derivatives of catechol, resorcinol, pyrogallol, phloroglucinol and propyl gallate by bromine in acetic acid or dioxane dibromide. The structures of all the obtained compounds were proved using IR spectroscopy and ^{1}H- and ^{13}C-NMR spectrometry, and, for several compounds, by mass-spectroscopy. The composition of the target substances was confirmed using elemental analysis. For the first time it was shown that dioxane dibromide can form polybrominated aromatic derivatives, while the reaction proceeds also in *ortho*-position to hydroxyl groups. Results of antimicrobial activity research against various pathogenic organisms (both Gram-negative and Gram-positive, together with fungus) revealed that, among all compounds, only 1-(3,5-dibromo-2,4-dihydroxybenzyl)pyrrolidin-2-one displayed antibacterial activity against *Staphylococcus epidermidis* INA 01254 with minimum inhibitory concentration equals to 16 μg/ml

Keywords

Polyphenols, brominated compounds, natural compounds analogues, antibacterial activity

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Introduction. It is known that natural bromophenols, mainly isolated from marine animals and plants, possess a variety of biological activities: antibacterial [1, 2], antiradical [3, 4], anticancer [5–7, antifungal [8, 9], and etc. Among them,

the number of amide- and lactam-containing compounds have been revealed [8, 9]. The ecological function of these substances is considered to be a chemical defense and as deterrents for other marine organisms [11]. However, despite the large number of useful properties, its isolation has some difficulties, because of the limited number of bromophenols in marine algae. That is why it was considered to find natural compounds analogues, which obtaining is much easier.

Continuing our research of chemistry of lactam-containing phenol derivatives [12, 13], it was decided to study the halogenation of some of the previously obtained compounds and, in particular, bromination. One of the closest natural analogue of these substances is 1-[2,5-dibromo-3,4-dihydroxy-6-(2,3,6-tribromo-4,5-dihydroxybenzyl)benzyl]pyrrolidin-2-one isolated from marine red alga *Symphyocladia latiuscula* [8]. Generally, brominated catechol derivatives are the most common in nature; however, phloroglucinol and resorcinol ones may also be found [14, 15]. We decided to extend the number of the studied compounds by using pyrogallol and ester of gallic acid with either pyrrolidone or caprolactam substituents. Brominated pyrogallol compounds possess hypoglycemic activity by inhibiting aldose reductase [16]; gallic acid esters themselves are used as antioxidants, while their brominated derivatives exhibit radical-scavenging activity [17]. Thus, natural-like compounds based on them are of great interest. It should be noted, that the main approach to the synthesis of brominated lactamomethyl compounds is an N-alkylation of the lactam ring with appropriate organic halide [18]. The bromination of lactam-containing phenols has not been considered previously. There are many ways to obtain brominated phenols by carrying the reaction with bromine in various solvents [19, 20] or by oxidative bromination [21, 22]. We, however, decided to study not only the excessive bromination, but also a selective one, leading to the partially brominated compounds. We chose dioxane dibromide as a soft acting brominating reagent, which is suitable for highly reactive systems, for example coumarins [23]. It has such benefits as easy isolation of target substances and stereoselective substitution in *para*-position to hydroxyl group [24, 25]. Moreover, it is necessary to mention that this reagent is more eco-friendly than metal-containing ones, such as vanadium-containing [26] or molybdenum-containing [27].

Material and methods. The initial substances were obtained according to the previously described methodology [12, 13]. Common reagents and solvents: dioxane, bromine, chloroform, hexane, acetic acid, ethyl acetate, sodium sulfite, sodium bicarbonate — were purchased from commercial suppliers (Acros and Sigma-Aldrich). TLC analyses were performed on Macherey-Nagel ALUGRAM Xtra SIL G UV254 plates. The melting points were determined using a Stuart

SMP30 instrument. The IR spectra were recorded using an Agilent Carry 600 spectrometer equipped with an attenuated total reflectance (ATR) device. The ^{1}H and ^{13}C NMR spectra were recorded at ambient temperature using a Bruker Avance II 300 spectrometer (^{1}H, 300 MHz; ^{13}C, 75 MHz) in $CDCl_3$ or DMSO-d_6; Me_4Si was used as the internal reference. Mass-spectra of the synthesized compounds were registered on MS-30 Kratos (EI, 70 eV). Elemental analysis was performed using a Vario MicroCube apparatus.

Procedure for the bromination in acetic acid. To a slurry of lactam-containing phenol (0.01 mmol) in acetic acid (20 ml) was added dropwise a solution of bromine (4.8 g, 1.6 ml, 0.03 mmol) in acetic acid (10 ml) at room temperature. The substance dissolved and the solution yellowed. After the addition, the solution was continually stirred at room temperature for 2 h. The reaction was checked by TLC analysis. Subsequently, the mixture was poured into water (50 ml) and ethyl acetate (20 ml). Resulting mixture was neutralized with sodium bicarbonate and sodium sulfite were carefully added until all the remaining bromine reacted. The water layer was twice extracted with ethyl acetate; the combined organic layer was dried over calcined magnesium sulfate, and the volatiles were removed in vacuum. The residue was allowed to crystallize under hexane.

1-(2,3,4-tribromo-5,6-dihydroxybenzyl)pyrrolidin-2-one **7a**

Yield 3.00 g (67.6 %), m.p. 193–195 °C.

^{1}H NMR ($CDCl_3$ with 10 % DMSO-d_6, δ, ppm, $^{3}J_{HH}$, Hz): 1.69 (p, 2H, 4-C<u>H</u>$_2$ in lactam, $^{3}J_{HH}$ = 7.3); 2.03 (t, 2H, 3-C<u>H</u>$_2$ in lactam, $^{3}J_{HH}$ = 8.1); 3.29 (t, 2H, 5-C<u>H</u>$_2$ in lactam, $^{3}J_{HH}$ = 7.0); 4.29 (s, 2H, Ar-C<u>H</u>$_2$-N).

^{13}C NMR ($CDCl_3$ with 10 % DMSO-d_6, δ, ppm): 17.2 (4-CH_2 in lactam); 29.5 (3-CH_2 in lactam); 43.8 (N<u>C</u>H$_2$Ar); 48.5 (5-CH_2 in lactam); 112.3; 114.9; 116.6; 118.9; 144.1; 145.2 (six atoms of Ar ring); 176.8 (C=O).

FT-IR, ν, cm^{-1}: 1634 (C=O).

Calc., %: C 29.76, H 2.27, N 3.16. Found, %: C 29.91, H 2.31, N 3.06.

$C_{11}H_{10}Br_3NO_3$

1-(2,3-dibromo-4,5,6-trihydroxybenzyl)pyrrolidin-2-one **8a**

Yield 1.32 g (34.6 %), m.p. 157–159 °C. TLC: R_f = 0.51 (EtOAc).

^{1}H NMR (DMSO-d_6, δ, ppm, $^{3}J_{HH}$, Hz): 1.89 (m, 2H, 4-C<u>H</u>$_2$ in lactam); 2.27 (t, 2H, 3-C<u>H</u>$_2$ in lactam, $^{3}J_{HH}$ = 7.7); 3.35 (t, 2H, 5-C<u>H</u>$_2$ in lactam, $^{3}J_{HH}$ = 6.7); 4.49 (s, 2H, Ar-C<u>H</u>$_2$-N).

^{13}C NMR (DMSO-d_6, δ, ppm): 18.1 (4-CH_2 in lactam); 30.5 (3-CH_2 in lactam); 43.7 (N<u>C</u>H_2Ar); 48.1 (5-CH_2 in lactam); 104.7; 109.3; 116.1; 135.0; 145.4; 145.9 (six atoms of Ar ring); 176.4 (C=O).
FT-IR, ν, cm^{-1}: 1638 (C=O).
Calc., %: C 34.67, H 2.91, N 3.68. Found, %: C 34.87, H 2.94, N 3.55. $C_{11}H_{11}Br_2NO_4$

1-(3,5-dibromo-2,4-dihydroxybenzyl)pyrrolidin-2-one **9a**
Yield 1.39 g (38.0 %), m.p. 167–169 °C. TLC: R_f = 0.64 (EtOAc).
^{1}H NMR (DMSO-d_6, δ, ppm, $^3J_{HH}$, Hz): 1.91 (p, 2H, 4-C<u>H</u>$_2$ in lactam, $^3J_{HH}$ = 8.0); 2.30 (t, 2H, 3-C<u>H</u>$_2$ in lactam, $^3J_{HH}$ = 8.0); 3.35 (t, 2H, 5-C<u>H</u>$_2$ in lactam, $^3J_{HH}$ = 7.3); 4.27 (s, 2H, Ar-C<u>H</u>$_2$-N); 7.32 (s, 1H, Ar-<u>H</u>); 9.67 (s, 1H, -O<u>H</u>); 10.11 (s, 1H, -O<u>H</u>).
^{13}C NMR (DMSO-d_6, δ, ppm): 17.9 (4-CH_2 in lactam); 30.6 (3-CH_2 in lactam); 42.1 (N<u>C</u>H_2Ar); 47.7 (5-CH_2 in lactam); 101.0; 103.0; 118.2; 132.3; 151.7; 153.4 (six atoms of Ar ring); 176.52 (C=O).
FT-IR, ν, cm^{-1}: 1626 (C=O).
Calc., %: C 36.19, H 3.04, N 3.84. Found, %: C 36.51, H 3.15, N 3.74. $C_{11}H_{11}Br_2NO_3$

General procedure for the preparation of bromine-substituted phenol derivatives 9b–14b. To a slurry of **1–6** (0.01 mmol) in dioxane (50 ml) was added dropwise a solution of bromine (0.01 mmol) in dioxane (20 ml) at room temperature. The substance dissolved and the solution yellowed. After the addition, the solution was continually stirred at room temperature for 2 h. The reaction was checked by TLC analysis. Subsequently, the solvent was evaporated *in vacuo*. Water (20 ml) and chloroform (20 ml) were added to the resulting orange oil, and after that sodium bicarbonate and sodium sulfite were carefully poured into the mixture until the reaction medium was neutralized and all the remaining bromine reacted. The organic layer was dried over calcined magnesium sulfate, and the volatiles were removed in vacuum. The residue was allowed to crystallize under hexane.

1-(3,5-dibromo-2,4-dihydroxybenzyl)pyrrolidin-2-one **9b**
Yield 2.83 g (77.4 %). All spectral data are the same as for **9a**

1-(5-bromo-2,3,4-trihydroxybenzyl)pyrrolidin-2-one **10b**
Yield 1.96 g (65.0 %), m.p. 170 °C.

^{1}H NMR (DMSO-d_6, δ, ppm, $^3J_{HH}$, Hz): 1.91 (p, 2H, 4-C<u>H</u>$_2$ in lactam, $^3J_{HH}$ = 7.3); 2.28 (t, 2H, 3-C<u>H</u>$_2$ in lactam, $^3J_{HH}$ = 8.0); 3.32 (t, 2H, 5-C<u>H</u>$_2$ in lactam, $^3J_{HH}$ = 7.0); 4.21 (s, 2H, Ar-C<u>H</u>$_2$-N); 6.74 (s, 1H, Ar-<u>H</u>); 8.83 (bs, 1H, –O<u>H</u>); 9.06 (bs, 1H, -O<u>H</u>); 9.19 (bs, 1H, -O<u>H</u>).

^{13}C NMR (DMSO-d_6, δ, ppm): 17.8 (4-CH_2 in lactam); 30.7 (3-CH_2 in lactam); 41.5 (N<u>C</u>H$_2$Ar); 47.4 (5-CH_2 in lactam); 100.3; 117.0; 122.6; 135.6; 143.7; 144.5 (six atoms of Ar ring); 175.7 (C=O).

FT-IR, ν, cm^{-1}: 1629 (C=O).

Calc., %: C 43.73, H 4.00, N 4.64. Found, %: C 43.91, H 4.13, N 4.41.

$C_{11}H_{12}BrNO_4$

1,3-bis[(2-oxopyrrolidine-1-yl)methyl]-5-bromo-2,4,6-trihydroxybenzene **11b**

Yield 2.68 g (67.1 %), m.p. 161–163 °C.

^{1}H NMR (CDCl$_3$ with 10% DMSO-d_6, δ, ppm, $^3J_{HH}$, Hz): 1.90 (p, 4H, 4-C<u>H</u>$_2$ in lactam, $^3J_{HH}$ = 7.3); 2.26 (t, 4H, 3-C<u>H</u>$_2$ in lactam, $^3J_{HH}$ = 8.1); 3.49 (t, 4H, 5-C<u>H</u>$_2$ in lactam, $^3J_{HH}$ = 7.0); 4.26 (s, 4H, Ar-C<u>H</u>$_2$-N); 7.82 (bs, 3H, -O<u>H</u>).

^{13}C NMR (CDCl$_3$ with 10 % DMSO-d_6, δ, ppm): 17.9 (4-CH_2 in lactam); 30.3 (3-CH_2 in lactam); 37.4 (N<u>C</u>H$_2$Ar); 48.9 (5-CH_2 in lactam); 91.5; 105.1; 153.3; 155.3 (six atoms of Ar ring); 177.3 (C=O).

FT-IR, ν, cm^{-1}: 1598 (C=O).

Calc., %: C 48.13, H 4.80, N 7.02. Found, %: C 48.30, H 4.84, N 6.99.

$C_{16}H_{19}BrN_2O_5$

propyl 2-bromo-3,4,5-trihydroxy-6-[(2-oxopyrrolidin-1-yl)methyl]benzoate **12b**

Yield 1.62 g (41.7 %), m.p. 167–170 °C.

^{1}H NMR (CDCl$_3$, δ, ppm, $^3J_{HH}$, Hz): 1.02 (t, 3H, -C<u>H</u>$_3$; $^3J_{HH}$ = 7.3); 1.80 (sext, 2H, -C<u>H</u>$_2$CH$_3$, $^3J_{HH}$ = 7.3); 2.04 (p, 2H, 4-C<u>H</u>$_2$ in lactam, $^3J_{HH}$ = 7.3); 2.46 (t, 2H, 3-C<u>H</u>$_2$ in lactam, $^3J_{HH}$ = 8.1); 3.54 (t, 2H, 5-C<u>H</u>$_2$ in lactam, $^3J_{HH}$ = 7.3); 4.29 (t, 2H, -OC<u>H</u>$_2$CH$_2$, $^3J_{HH}$ = 6.7); 4.32 (s, 2H, Ar-C<u>H</u>$_2$-N, partially overlapping with the previous peak).

^{13}C NMR (CDCl$_3$, δ, ppm): 10.6 (<u>C</u>H$_3$ group in ester); 17.9 (4-CH_2 in lactam); 21.9 (<u>C</u>H$_2$ group in ester); 30.5 (3-CH_2 in lactam); 40.8 (N<u>C</u>H$_2$Ar); 48.9 (5-CH_2 in lactam); 67.8 (O<u>C</u>H$_2$ group in ester); 97.4; 113.6; 127.3; 135.1; 141.8; 143.5 (six atoms of Ar ring); 167.94; 178.20 (two C=O groups).

FT-IR, ν, cm^{-1}: 1715 (C=O in carboxylic group); 1638 (C=O in lactam group).

Calc., %: C 46.41, H 4.67, N 3.61. Found, %: C 46.50, H 4.78, N 3.38.
$C_{15}H_{18}BrNO_6$

1-(2,3-dibromo-4,5,6-trihydroxybenzyl)azepan-2-one **13b**
Yield 0,06 g (13,7 %), m.p. 128–131 °C. TLC: R_f = 0.7 (EtOAc).
^{1}H NMR (DMSO-d_6, δ, ppm, $^3J_{HH}$, Hz): 1.45–1.60 (m, 6H, 4,5,6-C$\underline{H}_2$ in lactam);
2.51 (2H, 3-C$\underline{H}_2$ in lactam, overlapping with DMSO peak);
3.50 (m, 2H, 7-C$\underline{H}_2$ in lactam); 4.60 (s, 2H, Ar-C$\underline{H}_2$-N).
^{13}C NMR (DMSO-d_6, δ, ppm): 23.1 (4-CH_2 in lactam);
27.7 (5-CH_2 in lactam); 29.3 (6-CH_2 in lactam); 36.3 (3-CH_2 in lactam);
47.9 (N$\underline{C}H_2$Ar); 48.8 (7-CH_2 in lactam); 104.6; 116.2; 116.8; 134.6; 145.1;
146.1 (six atoms of Ar ring); 177.7 (C=O).
FT-IR, ν, cm^{-1}: 1578 (C=O).
Calc., %: C 38.17, H 3.70, N 3.42. Found, %: C 38.33, H 3.81,
N 3.21. $C_{13}H_{15}Br_2NO_4$

1-(5-bromo-2,3,4-trihydroxybenzyl)azepan-2-one **14b**
Yield 2.65 g (80.3 %), m.p. 195–198 °C. TLC: R_f = 0.59 (EtOAc).
^{1}H NMR ($CDCl_3$, δ, ppm, $^3J_{HH}$, Hz): 1.35–1.49 (m, 6H, 4,5,6-C$\underline{H}_2$ in lactam);
2.31 (m, 2H, 3-C$\underline{H}_2$ in lactam); 3.21 (m, 2H, 7-C$\underline{H}_2$ in lactam);
4.10 (s, 2H, Ar-C$\underline{H}_2$-N); 6.57 (s, 1H, Ar-H).
^{13}C NMR ($CDCl_3$, δ, ppm): 22.9 (4-CH_2 in lactam); 27.4 (5-CH_2 in lactam);
29.5 (6-CH_2 in lactam); 36.3 (3-CH_2 in lactam); 48.6 (N$\underline{C}H_2$Ar);
49.9 (7-CH_2 in lactam); 98.9; 116.0; 123.0; 134.4; 143.1;
143.6 (six atoms of Ar ring); 178.0 (C=O).
FT-IR, ν, cm^{-1}: 1588 (C=O).
Calc., %: C 47.29, H 4.88, N 4.24. Found, %: C 47.44, H 4.97, N 4.11.
$C_{13}H_{16}BrNO_4$

Determination of antimicrobial activity. The following microorganisms were used as test strains for determination of antimicrobial activity: *Escherichia coli* ATCC 25922, *Staphylococcus aureus* FDA 209P (MSSA), *S. aureus* INA 00761 (MRSA), *Staphylococcus epidermidis* INA 01254, *Mycobacterium smegmatis* mc^2 155, *Saccharomyces cerevisiae* INA 01129.

The minimum inhibitory concentration (MIC) was determined by the method of two-fold serial dilutions in the concentration range from 64 to 1 μg/ml according to [28]. The test substances were dissolved in DMSO, then water was

added; as a result, the DMSO concentration was 20 %. The solution was sterilized by membrane filtration. Bacteria were grown on a nutrient medium of the following composition (%): glucose-1, peptone-0.5, tryptone-0.3, NaCl-0.5, tap water, pH 7.2–7.4. The seeding density was 10^7 cells/ml. Cultivation was carried out at 37 °C for 20 h.

Results and discussion. The general synthesis scheme is depicted on the Fig. 1.

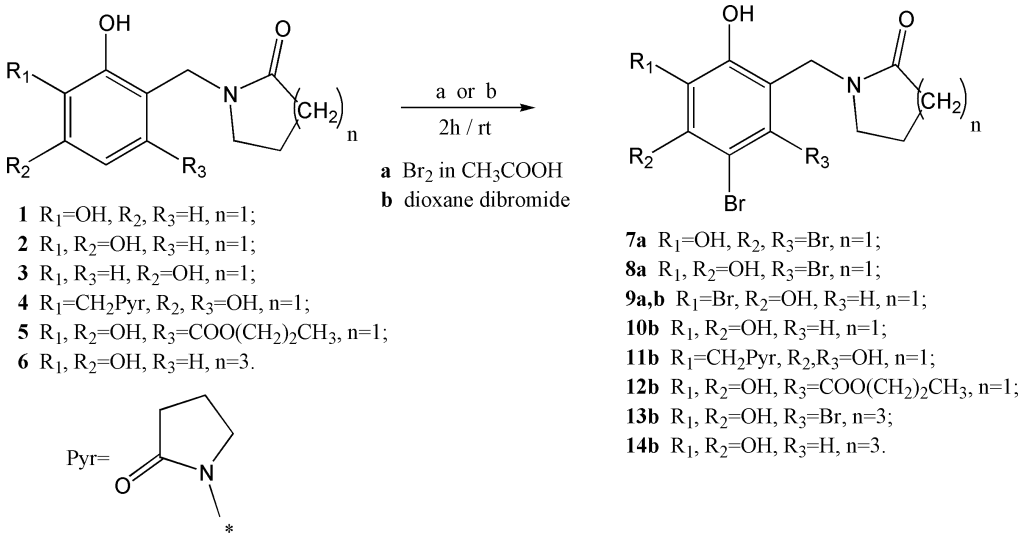

Fig. 1. Synthetic route for the preparation of **7a**–**14b**

Firstly, an excessive bromination [29] of lactam-containing phenols was provided in order to obtain synthetic analogues of natural compounds. Perbrominated derivatives **7a** and **8a** were obtained from catechol **1** and pyrogallol **2**, respectively. Resorcinol **3** produced di-substituted product **9a**. Heating of **3**, as well as **9a**, with excess of bromine in acetic acid at 70°C [30] led to destruction of the target compound; only 1,1'-methylenebis(pyrrolid-2-one) was isolated with a high yield. Thus, our attempts to obtain perbrominated resorcinol derivative were unsuccessful. The structures of the synthesized compounds were proved using IR spectroscopy and ^{1}H- and ^{13}C-NMR spectrometry. In the most cases, protons of phenolic hydroxyl groups are not observed due to rapid intermolecular exchange. Noteworthy, that ^{13}C-NMR spectra of products contain no significant changes in chemical shifts' values comparing to those of starting compounds. For instance, for the compound **9a** the greatest deviation in values of chemical shifts is for aromatic carbon connected to lactamomethyl substituent, reaching 4.69 ppm.

Although highly-brominated phenols are more common in nature, mono-substituted compounds are also known [4, 14, 31, 32]. We studied the reaction of several lactam-containing phenols with dioxane dibromide in order to synthesize the derivatives of catechol, resorcinol, phloroglucinol, pyrogallol and gallic acid. Firstly, the reaction of **3** with dioxane dibromide was carried out. The ratio of starting material and dioxane dibromide was mol per mol, but, unexpectedly, instead of a mono-brominated product, a bis-product **9** was obtained. The reaction was detected by TLC, showing that not all the substrate entered into reaction. So, it was decided to add the second equivalent of dioxane dibromide. Therefore, only a spot of the resulting compound remained on the plate, and it was identified, using NMR and MS, as the same bis-product as **9a**. This method of bromination gave significantly better yield than bromine in acetic acid. The MS-spectrum of **9b** (Fig. 2) is typical for di-bromo compounds with three peaks of molecular ion, corresponding to different isotopes of bromine, with the intensities ratio 1:2:1.

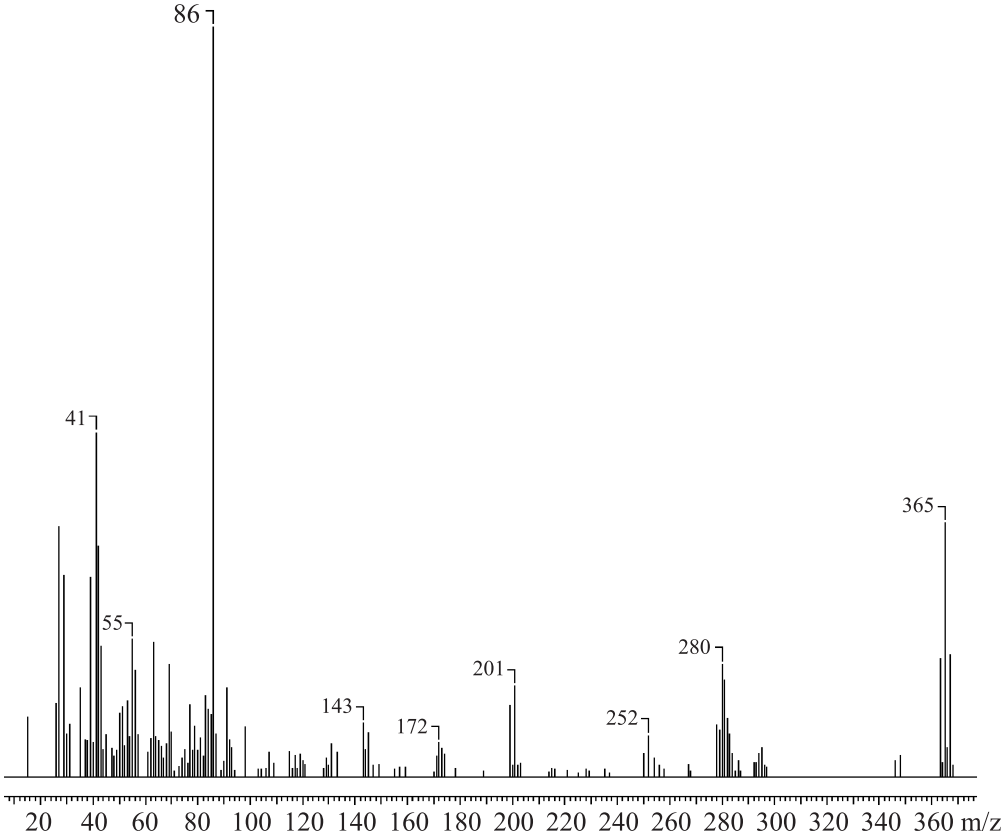

Fig. 2. Mass-spectrum of the **9b**

Obtaining of **10b**–**12b** was similar. Nevertheless, the synthesis of **13b** was quite different. The mixture discolored too quickly, that is why an excess of the brominating reagent was added and reaction time was increased. Surprisingly, the product **13b** was identified as bis-product, and the reaction was complicated by partially resinification, which caused the decreasing of yield. However, unlike resorcinol derivative **7**, careful addition of dioxane dibromide with immediate isolation of product allowed to obtain a mono-substituted product **14b**. It can be explained by the fact that in this case the reaction proceeds stepwise, compared to **9**, where the bromine stands in two positions at once. In our previous research [33], we revealed that caprolactam fragment possesses less electron-donating properties comparing to pyrrolidone one, which may cause such effect. This makes the isolation of mono-substituted product **14b** possible in contrast to derivatives of phenols with pyrrolidone moiety. However, further investigations are needed to explain why pyrrolidone-containing pyrogallol derivative **2** did not form correspondent bis-product even with the excess of dioxane dibromide.

Brominated phenols reveal antimicrobial activity against different kinds of pathogenic organisms [1, 2, 8–10]. Usually, they are represented by catechol derivatives, but some resorcinol ones are also effective [15]. According to these data, we decided to study antimicrobial activity by previously described method [28, 34] for two of the novel compounds: perbrominated catechol derivative **7a** and di-substituted resorcinol one **9**. To search for antimicrobial activity, we selected as test strains a Gram-negative bacterium (*E. coli*), Gram-positive bacteria (including *M. smegmatis*), and a fungus (baking yeast *Sac. cerevisiae*). In the studied concentration range, only compound **9** showed antimicrobial activity against *S. epidermidis*:

	MIC, μg/ml
Escherichia coli ATCC 25922	> 64
Staphylococcus aureus FDA 209P (MSSA)	> 64
Staphylococcus aureus INA 00761 (MRSA)	> 64
Staphylococcus epidermidis INA 01254	16
Mycobacterium smegmatis mc^2 155	> 64
Saccharomyces cerevisiae RIA 259	> 64

Conclusion. In this study, eight novel derivatives of brominated polyphenols were synthesized with fine yields. All products were characterized by FT-IR, MS, NMR (^{1}H, ^{13}C) and elemental analysis. For the first time it was shown that dioxane dibromide can form polybrominated aromatic derivatives in case of lactam-containing polyphenols with the reaction proceeding also

in *ortho*-position to hydroxyl groups. Antimicrobial activity against various pathogenic species was estimated for the two synthesized compounds, revealing that 1-(3,5-dibromo-2,4-dihydroxybenzyl)pyrrolidin-2-one **9** inhibit the growth of *Staphylococcus epidermidis* INA 01254 with MIC = 16 μg/ml.

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