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SYNTHESIS OF BIOLOGICALLY ACTIVE BROMINE DERIVATIVES OF QUERCETIN

A. D. Nagimova, G. E. Zhusupova, and M. S. Erzhanova

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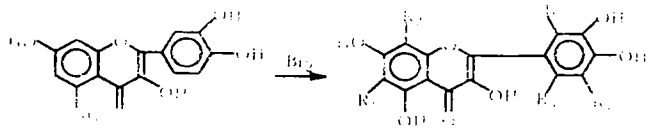
The synthesis of a series of bromine derivatives of quercetin differing by the number of bromine atoms introduced is described. It has been shown that in the dynamics of the bromination process the deciding factors affecting the qualitative and quantitative compositions of the reaction products are the temperature regime and the ratio of the reactants. Thus, the use of equimolar amounts of the reactants in dioxane in the temperature interval from 20 to 25°C gives a monobromo derivative, while all other conditions give mixtures of bromo derivatives. The antiviral and antitumoral activities of the mono- and dibromo derivatives of quercetin have been studied.

Natural flavonoids are distinguished by the breadth of their therapeutic action and their low toxicity. They exert an influence on the enzyme and immune systems of the organism [1, 2] and on metabolic processes [3], and exhibit antiarrhythmic [4], antimicrobial [5-7], antiviral [8, 9], antioxidant [10-12], and antitumoral and radioprotective [13] properties. With the aim of expanding the arsenal of drugs with a physiological action we have carried out a directed synthesis of bromine derivatives of a natural hydroxyflavone – quercetin, 3,5,7,3′,4′-pentahydroxyflavone (**1**).

The bromination of aromatic compounds has been studied and provides a logical theoretical basis for analyzing the reaction mechanism and the structures of the compounds obtained [14, 15]. The positive mesomeric effect between the unshared pairs of electrons of the oxygen atoms of the phenolic hydroxyls and the π-electrons of the double bonds of the benzene rings of quercetin (p,π-conjugation) leads to elevated reactivity of its 2′-, 5′-, 6-, 6′-, and 8-positions.

We studied bromination in organic solvents. To find the optimum conditions for obtaining mono- and dibromo derivatives of quercetin, we varied the molar ratio of quercetin and bromine from 1:1 to 1:4, the reaction temperature from 20 to 85°C, and the reaction time from 1 to 72 h. 6-Monobromoquercetin (**2**) was obtained in 2 h at 20-25°C by the action of an equimolar amount of bromine in dioxane, while 6,8-dibromoquercetin (**3**) was obtained in acetic acid at 35-40°C in 1 h. Compound (**2**) can be used both as the final product and as an intermediate for the introduction of new prognosticated groups. It must be mentioned that in the dynamics of the bromination of quercetin a decisive role is played by the temperature regime; in particular, elevated temperatures lead to an intensification of electrophilic substitution with the formation of a mixture of bromine derivatives:



The synthesized compounds (**3**)-(**5**) were separated by preparative paper chromatography in the butane-1-ol–acetic acid–water (40:12.5:29) system. This lengthy and laborious process proved to be successful, while separation on a column

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with various sorbents did not give the desired results. The compounds synthesized were identified on the basis of physicochemical constants. The positions of introduction of the bromine atoms in compounds (**2**)-(**4**) were determined by comparing their PMR spectra with the spectrum of the initial quercetin [16, 17] from the disappearance of the signals of the corresponding protons.

Some of the compounds synthesized were investigated for antiviral and antitumoral activities in order to establish regularities in the structure-activity series with a quantitative change in the number of monotypical reaction groups introduced. According to the results obtained in the Scientific Research Institute of the Potato and Vegetable Industry (Almaty) compounds, (**2**) and (**3**) possess an antiviral action in a wide range of concentrations (from 0.0005 to 0.5%).

An increase in the number of electron-accepting bromine atoms apparently affects the main chain of conjugation and, consequently, the degrees of hydrophilicity and mobility of the hydrogen atoms of the phenolic hydroxyls of the initial compound.

EXPERIMENTAL

Melting points were determined on a Kofler block, PMR spectra were taken in DMSO on a Varian-100 instrument with TMS as internal standard, and IR spectra on a UR-10 instrument in KBr tablets. R_f values were determined in the following systems: 1) butane-1-ol-acetic acid–water (40:12.5:29), and 2) benzene–acetic acid–water (125:72:3) on FN-11 paper. The preparative chromatographic separation of the synthesized compounds was achieved on FN-11 paper previously washed in 20% aqueous formic acid.

6-Bromoquercetin (2). A solution of 0.2 ml (0.0039 mole) of bromine in 10 ml of dioxane was slowly added dropwise to a solution of 1.0 g (0.0033 mole) of quercetin (**1**) in 80 ml of dioxane. The reaction was continued at 20-22°C for 2 h. The resulting precipitate was washed with water and dried. This gave 1.085 g (86.1%) of compound (**2**) with mp 270-272°C (from 60% aqueous ethanol). Found %: C 47.89, 47.75; H 2.94, 2.63; Br 21.85, 21.02; $C_{15}H_9O_7Br$. Calculated %: C 47.24; H 2.36; Br 20.99; M 381. IR spectrum (KBr, ν, cm^{-1}): 610 (C-Br); 1600, 1490, 1470 (Ar); 1680 (C=O); 3300 (Ar–OH). PMR (100 MHz, DMSO, ppm): 6.47 (s, H-8), 6.77 (d, H-5′), 7.59 (d, H-2′), 7.77 (d, H-6′); R_f 0.78 (syst. 1).

6,8-Dibromoquercetin (3). At 35-40°C, 0.4 ml (0.0078 mole) of bromine was slowly added dropwise to a solution of 1.0 g (0.0033 mole) of (**1**) in 100 ml of glacial acetic acid. After an hour's vigorous stirring, a yellow-green precipitate deposited. The reaction mixture was concentrated, and the precipitate was washed with water and dried. This gave 1.2 g (78.95%) of compound (**3**) with mp 254-256°C (from 60% aqueous ethanol) Found %: C 39.3, 38.9; H 1.8, 1.53; Br 33.50, 33.92; $C_{15}H_8O_7Br_2$. Calculated %: C 39.13; H 1.74; Br 34.78, M 460. IR spectrum (KBr, ν, cm^{-1}); 690 (C-Br), 1560, 1530, 1470 (Ar), 1640 (C=O), 3480 (Ar-OH). PMR (100 MHz, DMSO, ppm) 6.71(d, H-5′), 7.56(d, H-2′), 7.64(d, H-6′). R_f 0.79 (syst. 1), 0.39 (syst. 2).

2′,5′,6,8-Tetrabromoquercetin (4) and 2′,5′,6,6′,8-Pentabromoquercetin (5). At 75-80°C, 0.8 ml (0.0154 mole) of bromine in 40 ml of dioxane was slowly added dropwise to a solution of 1.0 g (0.0033 mole) of (**1**) in 100 ml of dioxane. After eight hours' vigorous stirring, the reaction mixture was evaporated to dryness. The residue was dissolved in water and the solution was brought to a boil and filtered. On cooling, it deposited a precipitate of (**4**), mp 248-250°C (from water). Found %: C 28.07; H 1.24; Br 51.01; $C_{15}H_6O_7Br_4$. Calculated %: C 29.1; H 0.96; Br 51.7; M 618. PMR (100 MHz, DMSO, ppm): 8.09 (s, H-6′), R_f 0.87 (syst. 1), 0.83 (syst. 2). The residual reaction mixture was separated by preparative paper chromatography on FN-11 paper in system 1. Compounds (**2**)-(**5**) were isolated. For substance (**5**), mp 135-137°C. Found %: C 24.1; H 0.82; Br 56.9; $C_{15}H_5O_7Br_5$. Calculated %: C 28.52; H 0.72; Br 57.39; M 697. There were no signals of protons in the PMR spectrum. R_f 0.90 (syst. 1), 0.86 (syst. 2).

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