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SYNTHESIS AND BIOLOGICAL ACTIVITY OF SOME NITROGEN-CONTAINING ANALOGS OF EMODIN

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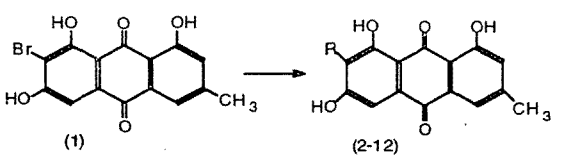
Investigations of the synthesis of nitrogen-containing derivatives of hydroxyanthraquinones with the aim of isolating new biologically active substances are extremely promising, since among them compounds with a high biological activity, including antitumoral activity, have been found [1-3].

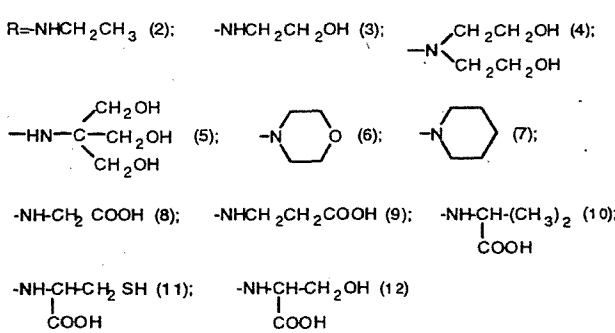
We have made a planned synthesis of nitrogen-containing derivatives of 1,6,8-trihydroxy-3-methylanthraquinone (emodin) from 7-bromo-1,6,8-trihydroxy-3-methylanthraquinone (**1**) with aliphatic (ethylamine, ethanolamine, diethanolamine, trihydroxymethylaminomethane) and heterocyclic (morpholine, piperidine) amines, and also amino acids (glycine, β-alanine, *L*-valine, *L*-serine, *L*-cysteine). Compound (**1**) was obtained by the procedure described in [4].

The amination of halogenoanthraquinones was carried out both in the absence and in the presence of catalysts such as Lewis acids, which activate the substrate through interaction with the carbonyl groups [5]. When reactions of (**1**) with amines were performed in the presence of the catalyst $AlCl_3$ at room temperature in an excess of amines, 4-10 h from the beginning of the reaction the formation of a dominating reaction product and from two to four other products was observed, i.e., nucleophilic exchange of the OH groups also took place.

Amino acids dissolve far more readily in water than in the usual organic solvents, while compound (**1**) is insoluble in water. When the reaction of (**1**) with amino acids was carried out under various conditions with various mixtures of solvents (ethanol–water (3:1); dioxane–water (3:1); 1 N NaOH; dioxane–1 N NaOH), and various HBr acceptors (K_2CO_3, triethylamine, pyridine), either no reaction took place or the yield of reaction products was low (10-15%) even on prolonged (up to 70 h) heating at a temperature of 70-96°C.



(1) (2-12)



R=-NHCH$_2$CH$_3$ (2); -NHCH$_2$CH$_2$OH (3); -N(CH$_2$CH$_2$OH)$_2$ (4); -NH-C(CH$_2$OH)$_3$ (5); -N(CH$_2$)$_5$O (6); -N(CH$_2$)$_5$ (7); -NH-CH$_2$COOH (8); -NHCH$_2$CH$_2$COOH (9); -NH-CH(CH$_3$)$_2$-COOH (10); -NH-CH(COOH)-CH$_2$SH (11); -NH-CH(COOH)-CH$_2$OH (12)

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In the reactions of (**1**) with amino acids, a high efficacy of phase-transfer catalysts was found, and, by analogy with the work of Pushkino et al. [6-8], the use of the crown ether dicyclohexyl-18-crown-6 permitted a considerable rise in the rate of the reactions and an increase in the yield of products to 64-79%. The highest yield of products (**8-12**) was observed in the solvent mixture dioxane-1 N NaOH on heating to 80-90°C. The use of tetrabutylammonium chloride, 18-crown-6, and dibenzo-18-crown-6 as catalysts proved less effective.

Thus, the IR spectra of (**2-7**) retained the absorption bands of C=O groups (1675-1620 cm^{-1}) but lacked the absorption bands of a C−Br bond, and in the high-frequency regions of the spectra of (**2**, **3**, and **5**) absorption bands of the stretching vibrations of an N−H bond (3275-3235 cm^{-1}) were observed. The PMR spectra of (**2-7**) and a comparison of them, with the spectrum of (**1**) showed that, together with the chemical shifts of the substituents at the nitrogen atom. [sic]. Compounds (**2-12**) were purified chromatographically on columns of silica gel, (**8-12**) being eluted with benzene−ethanol in ratios of from 10:1 to 1:1. The structures of (**2-12**) were shown by the results of elementary analysis and by IR and PMR spectroscopy. In the high-frequency regions of the IR spectra of the emodin derivatives (**8-12**) there were absorption bands of the stretching vibrations of NH groups (3190-3170 cm^{-1}). A continuous series of bands characteristic for amino acid derivatives was found in the 2800-2300 cm^{-1} region and there were absorption bands of the carbonyl groups of the anthraquinone fragments in the 1675-1615 cm^{-1} region and of the COOH groups of the amino acids at 1715-1705 cm^{-1}, the absorption band of a C−Br bond being absent.

We have studied the antitumoral activity of the compounds obtained on rats with Pliss's transplantable lymphosarcoma (PTS), Walker's carcinosarcoma (WCS), and sarcoma 45 (S-45) and on mice with sarcoma 180 (S-180) and sarcoma 37 (S-37). The results of the tests show that the compounds synthesized considerably inhibited the growth of PTS, S-45, and S-37 in comparison with the initial emodin and (**1**).

In a study of the compounds obtained as agents for protecting potatoes from viral diseases, compounds (**5**) and (**7**) proved to be the most active, the antiviral activity of (**5**) amounting to about 67%. In addition, (**5**) also possessed a phytostimulating action: as a result of its use the yield of potato tubers increased by 30%.

The compounds synthesized have been investigated for fungicidal activity on potato tubers infected with fusarial dry rot. The keepability of the tubers in the variants treated with certain preparations was 14% higher than in the control and the waste due to the rot 9-9.95% lower.

Thus, from natural emodin we have synthesized a number of nitrogen-containing derivatives of hydroxyanthraquinones among which substances have been revealed that possess antitumoral, antiviral, and fungicidal activities.

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