SYNTHESIS AND BIOLOGICAL ACTIVITY OF BIS-DERIVATIVES SPIRO-2-OXINDOLE

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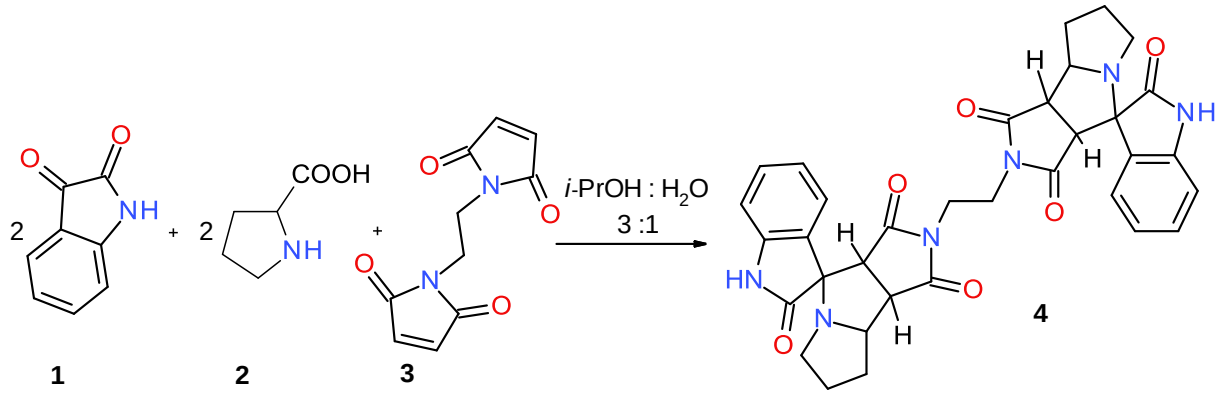
Introduction. One of the most important tasks of modern synthetic organic chemistry is the synthesis of new biologically active substances (BASs) in order to create new drugs based on them that have high therapeutic influence and minimal side effects. In the arsenal of modern medicine drugs are dominated. The active substances of them are molecules of heterocyclic structure. One of the directions for the synthesis of such substances is the creation of new bis-spirooxindoles. On the one hand, the nucleus of these BASs underlies many natural alkaloids that exhibit a wide range of biological activity. On the other hand, the synthesis of compounds containing two identical pharmacophoric fragments covalently combined in one molecule is a perspective direction in the creation of dual drugs.

Aim. To get ethylene-N,N'-bis(spiroindole-3,3'-pyrrolo[3,4-c]pyrrolizidine-2a', 7a'-dihydro-2,2',7'(1H,1'H,5'H)-trion) to investigate the reaction of the three-component interaction between isatin, proline and N,N'-ethylene-bis-maleinimide to study the antimicrobial and antioxidant biological activity of the synthesized compound.

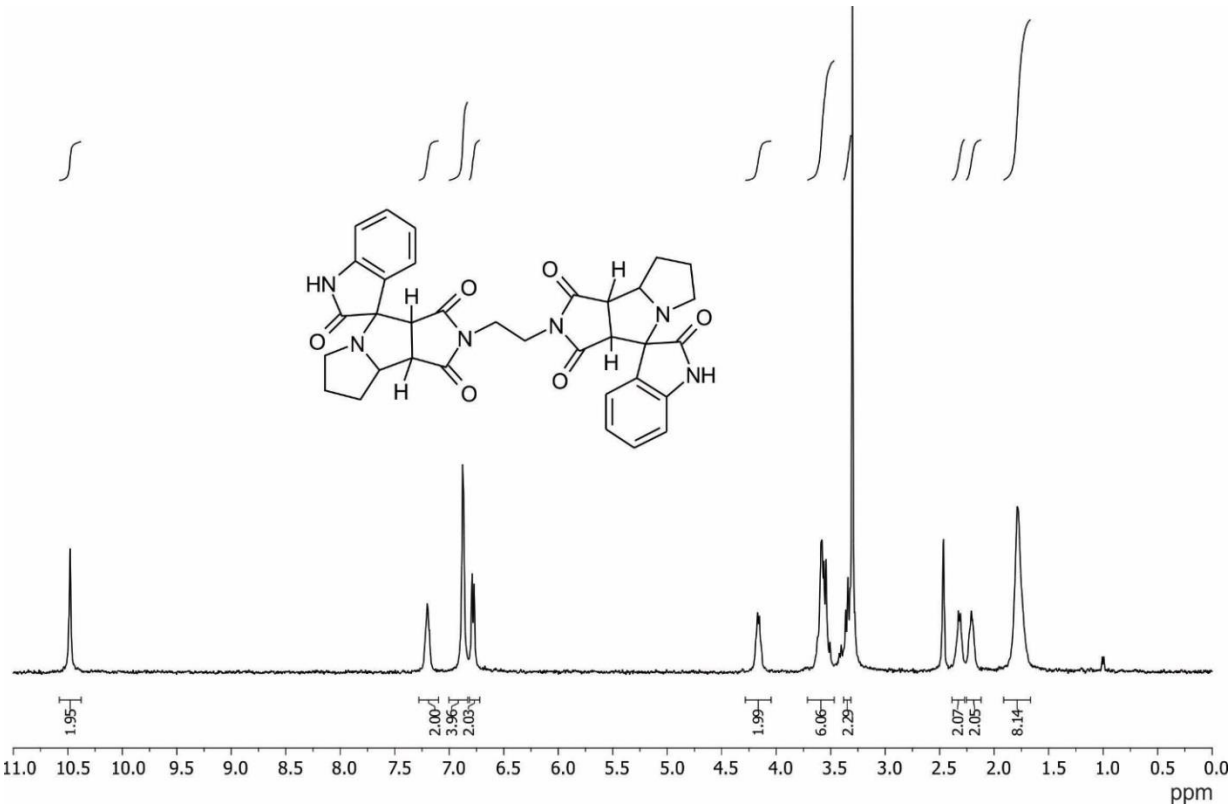
Materials and methods. Methods of synthetic organic chemistry, NMR-^{1}H spectroscopy, modern biological methods of research, the analysis of the obtained results and their generalization.

Results and discussion. A new symmetric derivative of ethylene-N,N'-bis (spiroindole-3,3'-pyrrolo[3,4-c]pyrrolizidine-2a',7a'-dihydro-2,2',7'(1H,1'H,5'H)-trion) 4 was synthesized by three-component domino-condensation of twice the excess of isatin 1 and proline 2 with N,N'-ethylene-bis-maleinimide 3 in isopropanol : water: 3 : 1 ratio, according to the scheme



During the reaction, a rapid evolution of CO_2 (decarboxylation step) was observed. Subsequently, the bright red color of the solution changed to bright green; in 10 minutes the solution turned blue and then Indian blue. It is likely to assume that such a change of bright colors occurred at the stage of azomethinilide formation. In general, the reaction lasted 4 hours. After discoloration of the reaction mixture, a precipitate dropped out from the boiling solution, which was filtered off, dried and recrystallized from the mixture *i*-PrOH-H_2O (1:1) to obtain an amorphous white product.

On the ^{1}H NMR spectrum of the compound obtained, the signals of the protons of the ABCD-system of the 2-oxindole moiety are present in the aromatic proton region 6.78… 7.2 ppm in the form of two doublets and a multiplet, the signals of ethylene link protons within the limits of 3.49… 3.65 ppm in the form of multiplets. In the low-lying region of the spectrum about 10.5 ppm. there is an NH signal of protons of the 2-oxindole nucleus in the form of an extended singlet. The signals of protons of the pyrrolo[3,4-c]pyrrolizidine system are observed within 1.78… 4.16 ppm. in the form of doublets and multiplets.



^{1}H NMR spectrum of ethylene-N,N'-bis(spiroindole-3,3'-pyrrolo[3,4-c]pyrrolizidine-2a',7a'-dihydro-2,2',7'(1H,1'H,5'H) -trion)

The nucleus of spiroindole-3,3'-pyrrole forms the basis of many natural alkaloids with pronounced biological activity, including antimicrobial and antioxidant. So it was decided to investigate the target compound we received for these activities. Antimicrobial activity was studied in vitro by diffusion in agar. The level of antimicrobial activity of the substance was recorded by the diameter of the growth retardation zone of microorganisms (Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa, Bacillus subtilis, Proteus vulgaris, Candida albicans) around the hole with the introduced drug in comparison with the control. All microorganisms were sensitive to test compound 4. Growth retardation zones were larger than the Synthomycine and Metronidazole comparisons. Investigation of the antioxidant properties of the synthesized compound 4 was performed in vitro using a model of spontaneous lipid peroxidation (LPO) in the liver homogenate. The decrease of the content of TBK reactants (products of reaction with thiobarbituric acid) in the samples indicated the manifestation of the antioxidant activity of the test substance. Test substance 4 reduced the content of TBK reactants to the level of intact indicators. At the same time, there was a concentration dependence on the manifestation of antioxidant activity, that is, an increase in the concentration of the test substance in the sample led to a more significant decrease of the content of TBK reactants in the homogenate of the liver.

Conclusions. Ethylene-N,N'-bis(spiroindole-3,3'-pyrrolo[3,4-c]pyrrolizidine-2a',7a'-dihydro-2,2',7'(1H,1'H,5'H)-trion) was synthesized. The course of the 1,3-dipolar cycloaddition reaction was investigated. The structure and individuality of the synthesized compounds using modern physical-instrumental methods of analysis were proved. Antimicrobial and antioxidant activity of the synthesized compound was studied. The potential of ethylene-N,N'-bis(spiroindole-3,3'-pyrrolo[3,4-c] pyrrolizidine-2a',7a'-dihydro-2,2',7'(1H,1'H,5'H)-trion) to further study the pharmacological properties was shown.