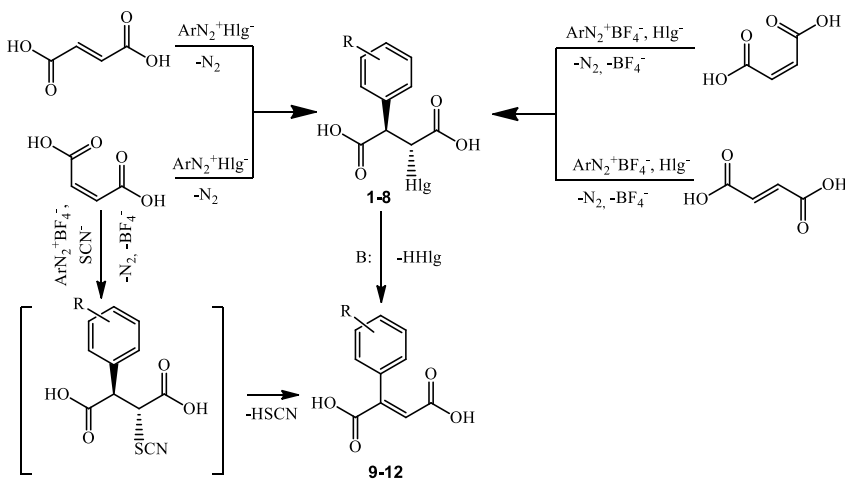


SYNTHESIS OF BIOACTIVE DERIVATIVES OF UNSATURATED DICARBOXYLIC ACIDS

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3-Aryl-2-chloro(bromo)butanedioic acids **1-8** were synthesized by interaction of aryldiazonium halides and tetrafluoroborates with maleic and fumaric acids under conditions of Meerwein and anionarylation reactions. Compounds **1-8** were dehydrohalogenated to 2-aryl-2-butenedioic acids **9-12** under the action of strong bases and also formed in the conditions of the thiocyanatoarylation reaction.



1-12: Hlg = Cl (**1-4**), Br (**5-8**); R = H (**1, 5, 9**), 4-CH₃ (**2, 6, 10**), 4-CH₃O (**3, 7, 11**), 4-Br (**4, 8, 12**)

It was established that the yields of halogenarylated products of maleic and fumaric acids are 10-15% higher under the anionarylation

conditions in comparison with the Meerwein reaction. The yields of acids **1-8** are higher (~10%) under the conditions of fumaric acid anionarylation, which, in our opinion, is due to the mechanism of *trans*-addition of aryl radical and halogen-ion to the carbon-carbon double bond, which is easier to implement in case of fumaric acid [1].

A feature of the reactivity of maleic and fumaric acids under the conditions of Meerwein and halogenarylation reactions is the dominant route of identical structure anionarylated derivatives formation. Despite the spatial configuration of the initial unsaturated acids, the same products are formed during the reaction, indicating the *trans*-attachment of the aryl radical and the halogen atom to the carbon-carbon multiple bond. In the case of maleic acid, the transformation of the substrate structure occurs at the stage of arylalkyl radical - an intermediate of Meerwein and anionarylation reactions [2].

The main products of reactions of aryldiazonium tetrafluoroborates with maleic and fumaric acids in the presence of SCN-anions are arylation products - 2-aryl-2-butenedioic acids **9-12**. Probably, the intermediate compound is an unstable thiocyanatoarylation product, the stabilization of which occurs as a result of the elimination of Hydrogen thiocyanate.

Thus, the anionarylation reactions of unsaturated dicarboxylic acids make it possible to modify these compounds by introducing aromatic fragments with preserving of both carboxyl groups, which opens up a wide range of possibilities for obtaining of new derivatives with practically useful properties.

We studied the antimicrobial properties of 2-chloro(bromo)-3-arylbutanedioic acids **1-8** and 2-aryl-2-butenedioic acids **9-12** against 5 museum strains of microorganisms: *S. aureus* ATCC 6538, *E. coli* ATCC 25922, *C. albicans* ATCC 885-653, *B. cereus* ATCC 6633, *P. aeruginosa* ATCC 9027 (Table 1).

It was shown that the most sensitive to the action of the synthesized substances were *S. aureus* and *C. albicans* bacteria, the growth of which was delayed in the concentration range of 62.5-250 µg/ml. Compounds **1-12** are relatively low in activity against gram-negative rods, pseudomonads and spore-forming gram-positive rods.

Table 1

Antibacterial and antifungal activity of compounds 1-12

№	Microorganisms strains									
	<i>S. aureus</i>		<i>E. coli</i>		<i>C. albicans</i>		<i>B. cereus</i>		<i>P. aeruginosa</i>	
	Minimum inhibitory (MIC) and bactericidal (MBC) concentrations, µg/ml									
	MI C	MB C	MI C	MB C	MI C	MB C	MI C	MB C	MI C	MB C
1	62.5	125	500	n/a	62.5	125	250	500	250	500
2	62.5	125	500	n/a	62.5	125	250	500	250	500
3	62.5	125	250	500	62.5	125	250	500	250	500
4	125	250	250	500	125	250	250	500	125	250
5	62.5	125	500	n/a	62.5	125	250	500	250	500
6	62.5	125	250	500	62.5	125	250	500	500	n/a
7	62.5	125	500	n/a	250	500	500	n/a	500	n/a
8	62.5	125	250	500	250	500	250	500	500	n/a
9	125	250	500	n/a	250	500	250	500	500	n/a
10	250	500	n/a	n/a	500	n/a	n/a	n/a	n/a	n/a
11	250	500	n/a	n/a	500	n/a	250	500	n/a	n/a
12	125	250	500	n/a	125	250	500	n/a	250	500

The antibacterial and antifungal properties of the synthesized maleic acid derivatives are expressed at a fairly low level, so in order to enhance them it is advisable to modify the structure of acids **1-12** by introducing specific pharmacophore groups into the aromatic fragments or converting them into water-soluble salts.

References

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