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Synthesis and Biological Activity of Certain Derivatives of Anesthesine (Benzocaine)

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Abstract—Certain derivatives of ethyl *p*-aminobenzoate were synthesized with the purpose of creating biologically active oligomeric condensation products.

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Currently revealing substances possessing bactericidal activity toward the microorganism strains playing a role in human pathology is of great importance. The demand for new antimicrobial and antitumor agents is also growing.

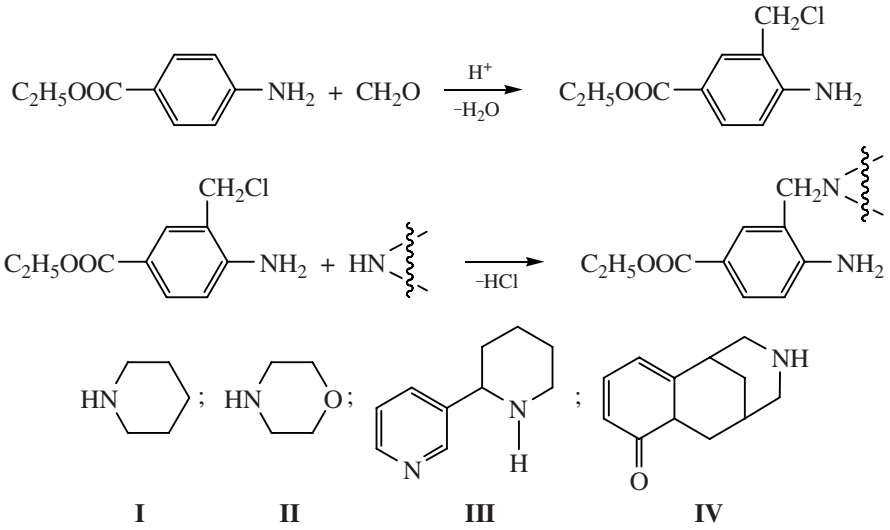
Continuing search for biologically active compounds among *p*-aminobenzoic acid derivatives, we reacted ethyl 4-aminobenzoate and a 40% solution of formaldehyde in boiling water at pH 1–2 under atmospheric pressure and then modified the preparated novolak with secondary amines (piperidine, morpholine, anabasine, and cytisine):

To find out whether the prepared compounds are feasible for treating germ diseases, we tested ethyl 4-amino-3-(cytisinomethyl)benzoate (**IV**) for antimicrobial and cytotoxic activity (Tables 1 and 2).

The cytotoxicity of ethyl 4-amino-3-(cytisinomethyl)benzoate was estimated in the test of survival rate of *Artemia salina* (Leach) sea crayfish maggots by the Brine shrimp cytotoxicity method [1–5].

The antimicrobial activity of ethyl 4-amino-3-(cytisinomethyl)benzoate was tested using test strains recommended by the State Pharmacopoeia: *Staphylococcus aureus* ATSS 6538, *Bacillus subtilis* ATSS 6633, *Escherichia coli* ATSS 25922, *Pseudomonas aeruginosa* ATSS 9027, and *Candida albicans* yeast fungus ATSS 885-653.

It was established that compound **IV** shows an expressed antifungal activity *Candida albicans* yeast fungus and an expressed cytotoxic activity toward *Artemia salina* sea crayfish maggots.



I **II** **III** **IV**

Table 1. Cytotoxicity testing results[a]

Compound	Maggots death rate after 24 h			LD_{50}, μg ml^{-1}	95% confidence interval	Activity
	100 μg ml^{-1}	10 μg ml^{-1}	1 μg ml^{-1}			
Ethyl 4-amino-3-(cytisinomethyl) benzoate	89.91	46.62	26.64	6.895	2.894–14.601	Possesses

[a] Growth inhibition zone is absent. The growth inhibition zone diameters (GIZD) smaller than 10 mm and continuous growth in a cup were assessed as absence of antibacterial activity, GIZD 10–15 mm, as weak activity, GIZD 15–20 mm, as moderate activity, and GIZD > 20 mm, as expressed activity.

Table 2. Antimicrobial activity testing results

Сщьзщгтв	*Staphylococcus aureus*	*Bacillus subtilis*	*Escherichia coli*	*Pseudomonas aeruginosa*	*Candida albicans*
Ethyl 4-amino-3-(cytisinomethyl) benzoate	16±0.1	17±0.1	18±0.2	16±0.2	21±0.2
Lincomycin hydrochloride	24±0.1	22±0.1	21±0.2	–	
Nystatine				22±0.1	

EXPERIMENTAL

Ethyl [4-amino-3-(piperidinomethyl)]benzoate (I). Concentrated hydrochloric acid, 0.5 ml, 40% formaldehyde, and 2.12 g of piperidine were added to 4.1 g of aqueous anesthesine. The mixture was heated on a boiling water bath for 3 h, and water was then distilled off at the same temperature in water-jet-pump vacuum. The product was purified and recrystallized from alcohol. Yield 73 %, mp 132–133°C.

Ethyl 4-amino-3-(morpholinomethyl)benzoate (II) was prepared in a similar way. Yield 54%, mp 157–158ºC.

Ethyl 4-amino-3-(anabasinomethyl)benzoate (III) was prepared in a similar way. Yield 51%, mp 137–138ºC.

Ethyl 4-amino-3-(cytisinomethyl)benzoate (IV) was prepared in a similar way. Yield 45%, mp 168–169ºC.

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