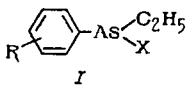
RELATIONSHIP BETWEEN THE STRUCTURE AND ANTIMICROBIAL ACTION IN THE SERIES OF CHLORO AND DIALKYLAMINO DERIVATIVES OF ETHYLARYLARSINES

É. A. Rudzit, F. D. Yambushev,
A. D. Koveshnikov, I. V. Berezovskaya,
N. Kh. Tenisheva, D. A. Kulikova,
and G. N. Neshchadim

UDC 615.281:546.19].015.11

The study of the possibilities of increasing the selectivity of the antimicrobial action of arsenic-containing preparations is of definite interest. Compounds of this kind have not yet found use as antibacterial or antifungal agents. There is only a single report on the antimycotic properties of certain organic arsenic derivatives, in particular, thioesters of acids of trivalent arsenic of the type of R_2AsSR, containing halogen atoms or dialkylamine groups as substituents [1].

The purpose of this investigation was to synthesize and test the bacteriostatic, mycostatic, and toxic action for white mice of asymmetrically substituted ethylarsines of the type



I

R = o-, m-, p-$CH_3C_6H_4$; o-, m-, p-CH_3O, X = Cl (Cl (Ia — f), N $(CH_3)_2$ (Ig, h), N $(C_2H_5)_2$ (Ii, j)

Secondarily substituted ethylarylchloroarsines I (X = Cl) were synthesized by the method described earlier [2, 3] of interaction of aryl dichloroarsines $RAsCl_2$ with tetraethyllead (Table 1).

The method, rather simple and economical, provides for a yield of the final products of up to 90-95%.

Ethylarylaminoarsines were synthesized by the reaction of aminolysis of asymmetrically substituted ethylarylchloroarsines I (X = Cl) in the liquid phase (see Table 1):

$$I\,(X = Cl) + 2NH\,(R')_2 \rightarrow I\,(X = NR'_2).$$

All the compounds studied possess substantial antibacterial and antifungal activity (Table 2).

Despite the great similarity in chemical structure, the substances differ substantially in degree of expression of antimicrobial properties. The discrepancy of the values of the minimum mycostatic concentrations with respect to all three strains of fungi reaches 10-fold. The minimum bacteriostatic concentrations for *Staphylococcus* differ 50-fold, for *E. coli* up to 30-fold. The maximum tolerable doses for mice vary from 3 to 100 mg/kg.

If we judge the selectivity of the antimicrobial action of the preparations according

Scientific-Research Institute for Biological Testing of Chemical Compounds, Kupavna, Moscow Region. Kazan' Pedagogical Institute. Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 10, No. 9, pp. 19-22, September, 1976. Original article submitted January 9, 1976.

TABLE 1. Chloro and Dialkylamino Derivatives of Ethylarylarsines (I)

Compound	R	Yield, %	Boiling point, deg/mm	d_4^{20}	n_D^{20}	MR_D found	MR_D calculated	As, found (%)	Gross formula	As, calculated (%)
Ia	H	94	108/10	1,3503	1,5875	53,88	52,06	34,23	$C_8H_{10}AsCl$	34,64
Ib	o-CH_3	92	125/5	1,3467	1,5880	57,59	57,68	32,23	$C_9H_{12}AsCl$	32,53
Ic	m-CH_3	87	106/3	1,336	1,5838	57,75	57,68	32,45	$C_9H_{12}AsCl$	32,53
Id	p-CH_3	92	105/3	1,323	1,5840	57,75	57,68	32,27	$C_9H_{12}AsCl$	32,53
Ie	o-CH_{30}	87	130/5	1,3980	1,5840	59,08	59,32	30,07	$C_9H_{12}AsClO$	30,42
If	p-CH_{30}	90	150/5	1,3782	1,5847	59,93	59,32	29,95	$C_9H_{12}AsClO$	30,42
Ig	H	55	133/18	1,1907	1,5604	61,11	61,37	33,09	$C_{10}H_{16}AsN$	33,33
Ih	o-CH_{30}	28	146/10	1,3009	1,5700	66,66	67,63	29,05	$C_{11}H_{18}AsNO$	29,41
Ii	o-CH_3	60	143/10	1,1346	1,5460	75,53	75,22	28,56	$C_{13}H_{22}AsN$	28,08
Ij	p-CH_3	60	148/15	1,1212	1,5420	74,94	75,22	27,91	$C_{13}H_{22}AsN$	28,08

TABLE 2. Antimicrobial Activity and Toxicity of Derivatives of Alkylarylarsines (I)

Compound	Minimum mycostatic or bacteriostatic concentrations (in μg/ml)					Maximum tolerable doses for mice (in mg/kg)
	Aspergillus niger	Candida albicans	Trichophiton gypseum	Staphulococcus aureus	E. coli	
Ia	1,9	1,9	0,9	0,39	0,39	10
Ib	1,9	0,9	0,24	0,39	0,39	10
Ic	3,9	0,24	0,24	0,39	0,39	3
Id	3,9	1,9	0,48	12,5	25,0	30
Ie	7,8	3,9	1,9	3,1	6,2	10
If	15,6	3,9	1,9	0,78	3,1	100
Ig	1,9	1,9	1,9	0,39	0,39	10
Ih	7,8	3,9	1,9	0,39	0,78	10
Ii	1,9	1,9	0,9	1,5	1,5	10
Ij	7,8	7,8	0,9	3,1	3,1	30

to the ratio of their toxicity and activity with respect to microbes, we can note 10-fold fluctuations of this index for *Aspergillus niger* and *Trichlophiton gypseum*, threefold for the pathogen of candidosis and *Staphylococcus*, and sixfold for *E. coli*.

The antibacterial and antifungal properties do not show a parallel change when the substituents are varied. Thus, the introduction of a methyl group into the o or m position of the phenyl ring of ethylphenylchloroarsine (Ia) is accompanied by a change in the antifungal activity but does not influence the degree of expression of the antibacterial action (Ib, c). Analogous substitution in the p position has no significant effect on the antifungal properties but sharply reduces the antibacterial effect (Id). The toxicity of the preparations for white mice is not correlated with the toxicity for microbes. The compound If is distinguished by the greatest selectivity of the antibacterial and anticandidosis action; the preparation Id especially selectively acts upon *Trichophiton gypseum* and *Candida albicans*. It is interesting that they are both p-substituted ethylphenylchloroarsines, and in the first case the substituent is a methoxy group, in the second a methyl.

Ethylphenyldimethylaminoarsine (Ig) does not differ in biological activity from ethylphenylchloroarsine (Ia). The introduction of a methoxy group into the o position of the phenyl ring of the preparation Ig is not accompanied by any significant change in its biological properties. The compound Ii, differing from Ig by the presence of a methyl group in the o position of the phenyl radical and by the presence of a diethylamine group, is analogous to the initial compound in antimycotic activity, but has a substantially weaker effect on bacteria. The substance Ij, which is a p isomer of preparation Ii, is inferior to the latter in antimicrobial properties, but superior in tolerance for mice.

Thus, our investigation gives evidence of the promise of further attempts to increase the selectivity of the antimicrobial action of organoarsenic compounds (in particular, derivatives of alkylarylarsines) and the search for new antibacterial and antifungal agents in this series.

EXPERIMENTAL

Ethyl-p-tolylchloroarsine (Id). A 50-g portion of p-tolylchloroarsine was heated on an oil bath to 110° with continuous passage of CO_2. Then 22.7 g tetraethyllead was added dropwise to the heated p-tolyldichloroarsine cautiously with constant mixing. The beginning of the reaction was indicated by a turbidification of the reaction mass and the formation of a white precipitate. The effectiveness of this reaction depends on the purity of the reagents, the rate of addition of tetraethyllead, and the temperature optimum. When freshly redistilled components were used and the internal temperature of the medium was maintained in the range 95-100°, the induction period was sharply reduced. Under the indicated conditions, the interaction of the reacting substances begins from the moment of contact of the first drops of tetraethyllead with aryldichloroarsines, which is accompanied by a sharp jump in the internal temperature of the medium and the formation of lead chloride, which precipitates in the form of a white powdered precipitate. The reaction is conducted until the detection of liberation of ethyl chloride through the calcium chloride tube. Then the product is redistilled under vacuum at 105° (3 mm); yield 44.7 g (92%) Id. The compounds Ia-c, e, f were synthesized analogously.

N,N-Dimethylaminoethylphenylarsine (Ig). An ether solution of 30 g ethylphenylchloroarsine was cooled to −18°. Then dimethylamine was added with mixing. The occurrence of the reaction is characterized by a white crystalline precipitate, which is formed during the interaction of the reacting components. Then mixing of the reaction mixture was continued at room temperature; after 50 min the crystals were separated and the solvent removed. Vacuum redistillation yielded 17 g (55%) of compound Ig.

The product Ih was synthesized by an analogous method.

N,N-Diethylaminoethyl-p-tolylarsine (Ij). A 10-g portion of ethyl-p-tolylchloroarsine in 100 ml absolute diethyl ether was cooled to −15°. Then 6.2 g of diethylamine was added dropwise with constant mixing. A characteristic feature permitting the judgment of the beginning of the reaction is a turbidification of the reaction mixture and the formation of a white precipitate. After the end of the addition of the entire calculated amount of diethylamine, mixing of the reaction mass was continued, removing the cooling bath, for 40 min. Then the precipitate was separated and washed three times with ether. After removal of the solvent, vacuum redistillation was conducted, with a yield of 7 g (60%) of the product Ij.

The antimicrobial action of the investigated chemical compounds was tested on a liquid nutrient medium by the method of serial dilutions [4]. The samples were cultured on Saburo's medium, the bacteria on Hottinger's broth. The activity of the compounds was evaluated according to the minimum concentration (in micrograms per ml) necessary for retarding the growth of a test culture of the microorganism.

The toxicity was studied on noninbred white mice, weighing 18-24 g, with subcutaneous injection of the substances in vegetable oil. The maximum tolerable dose was determined in milligrams per kg on the basis of 14-day observation.

LITERATURE CITED

1. I. D. Neklesova, N. V. Egorova, and M. A. Kudrina, Dokl. Akad. Nauk SSSR, 166, 1121 (1966).
2. G. Kh. Kamai and Yu. F. Gatilov, Zh. Obshch. Khim., 31, 1844 (1961).
3. F. D. Yambushev, Yu. F. Gatilov, N. Kh. Tenisheva, et al., Zh. Obshch. Khim., 44, 2205 (1974).
4. G. N. Pershin (editor), Methods of Experimental Chemotherapy [in Russian], Moscow (1959).