16. Q. M. Saucier, B. Festy, and G. B. Le Pecq, Biochimie, 53, 973-980 (1971).
17. H. C. Scarborough, B. C. Lawes, J. L. Minielli, and J. L. Compton, J. Org. Chem., 27, 957-961 (1962).
18. World Health Org. Spec. Program for Research and Training in Tropical Diseases, 1, (1976).

SYNTHESIS AND BIOLOGICAL ACTIVITY OF CERTAIN PHENYLAZOSELENAZOLES

Z. I. Popova, A. A. Tsurkan, and P. N. Steblyuk

UDC 615.28:547.789.81].012.1

We have previously obtained azo products [2-4] that exhibit antibacterial and antifungal activity by the azo coupling of aromatic amines and sulfanilamide preparations with 2-arylidenhydrazino-4-phenylselenazoles [2]. As a continuation of our studies we synthesized compounds I-XXX (see Table 1). The diazo components used to obtain those compounds were aniline, p-phenetidine, sulfanilic acid, sodium p-aminosalicylate, benzocaine, novocaine, and the following sulfanilamides: Streptocid, Sulfacyl, Urosulfan, sulfaguanidine, Norsulfasol, Etasol, and Sulfadimezine.

The antimicrobial activity of the synthesized compounds was tested on five strains of bacteria and fungi: *Staphylococcus aureus, E. coli, B. pyocyaneus, B. anthracoides,* and *Candida albicans*. The test results are presented in Table 1.

The products formed by azo coupling with amines were found to be more active against staphylococci (compound X) than against the other microorganisms. Compounds XI and XIV were more active against *Candida albicans*. The most active compound of this group was the coupling product of 2-(4-methoxybenzylidene) hydrazino-4-phenylselenazole and diazotized sulfanilic acid (compound VI) which suppressed *B. anthracoides* growth at a dilution of 1:16,000 and *Candida albicans* at 1:64,000. Azocoupling with benzocaine and novocaine resulted, as expected, in compounds IX-XIV which did not exhibit any significant antimicrobial activity. The test results for 2-arylidenhydrazino-4-phenyl-5-p-R-sulfamoylphenylazoselenazole demonstrated activity against both staphylococci and *Candida albicans*.

The coupling product of diazotized urosulfan (compound XVIII) exhibited the greatest activity against *B. anthracoides*.

Thus, the results of the study demonstrated that the tested compounds characteristically exhibit antibacterial and antifungal activity.

EXPERIMENTAL — CHEMICAL

2-(4-Methoxybenzylydenhydrazino)-4-phenyl-5-p-phenylazoselenazole (II). A 1-ml (0.01 mole) portion of freshly distilled aniline was dissolved while stirring in 10 ml of HCl (1:3). The solution was placed in an ice bath. After the solution was cooled to 0°C a solution of 0.69 g (0.01 mole) of sodium nitrite in 4 ml of water was added dropwise to the mixture. A 4.4-g (0.01 mole) portion of 2-(4-methoxybenzylydenhydrazino)-4- phenylselenazole was dissolved upon heating in 40 ml of ethanol. After cooling, diazotized aniline was added to the resultant solution as the temperature was maintained at 0-5°C. This resulted in the formation of thick crimson-red colored paste. Yield 1.5 g (78%). Red plates, mp 204-206°C (from ethanol). Found, %: N 15.29; Se 15.55. $C_{23}H_{19}N_5OSe$. Calculated, %: N 15.21; Se 15.59. Compounds I, III-XXX were obtained in a similar fashion.

EXPERIMENTAL — BIOLOGICAL

The bacteriostatic and mycostatic activity of the synthesized compounds was examined by the generally accepted method [1] of series dilutions in a liquid nutrient. An aminopeptide, preliminarily diluted with water at a pH of 7.2, was used as the nutrient medium. The testing of a compound's activity against the indicated test microbes consisted of broad spectrum activity tests, beginning with a dilution of 1:2000 (500 μg/ml), on five strains of the fol-

I. P. Pavlov Ryazan' Medical Institute. Zaporozh'e Medical Institute. Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 21, No. 1, pp. 49-52, January, 1987. Original article submitted December 18, 1985.

0091-150X/87/2101-0045$12.50

TABLE 1. 2-Arylidenhydrazino-4-phenyl-5-p-R-phenylazoselenazoles

Compound	Ar	R	Yield, %	mp, °C	Found N, %	Empirical formula	Calculated N, %	Minimum microorganism growth suppression concentration at a 1:1000 dilution				
								Staphylococcus aureus 209P	Escherichia coli 675	Pseudomonas aeruginosa 165	B. anthracoides 1312	Candida albicans
I	2-OHC_6H_4CH	H	90	185—7	15,75	$C_{23}H_{17}N_5OSe$	15,69	1:2	1:2	1:2	1:2	—
II	4-$OCH_3C_6H_4CH$	H	78	204—6	15,29	$C_{24}H_{19}N_5OSe$	15,21	1:2	1:1	—	—	—
III	3-OCH_3-4-OHC_6H_3CH	H	91	203—5	14,74	$C_{24}H_{19}N_5O_2Se$	14,70	1:4	1:4	1:4	1:4	1:4
IV	3,4-$(OCH_3)_2C_6H_3CH$	H	88	197—9	14,33	$C_{25}H_{21}N_5O_2Se$	14,28	1:4	—	1:4	—	1:4
V	4-$OCH_3C_6H_4CH$	—OC_6H_5	84	192—4	13,94	$C_{31}H_{23}N_5O_2Se$	13,89	1:2	1:4	1:4	1:2	1:4
VI	4-$OCH_3C_6H_4CH$	—SO_3H	74	196—7	13,02	$C_{24}H_{19}N_5O_4SSe$	12,96	1:8	1:4	1:8	1:16	1:64
VII	2-OHC_6H_4CH	—COOH + 3-OH	91	215—7	13,91	$C_{23}H_{17}N_5O_4Se$	13,83	1:4	1:4	1:2	—	1:4
VIII	3-OCH_3-4-OHC_6H_3CH	—COOH + 3-OH	82	167—9	13,10	$C_{24}H_{19}N_5O_4Se$	13,05	—	—	—	1:1	1:1
IX	3-OCH_3-4-OHC_6H_3CH	—$COOC_2H_5$	89	237—9	12,82	$C_{26}H_{23}N_5O_4Se$	12,79	1:1	1:4	1:2	1:2	—
X	3,4-$(OCH_3)_2C_6H_3CH$	—$COOC_2H_5$	86	202—4	12,51	$C_{27}H_{25}N_5O_4Se$	12,46	1:8	1:2	1:4	1:4	1:4
XI	C_6H_5CH	—$COO(CH_2)_2N(C_2H_5)_2$	76	216—8	14,71	$C_{29}H_{30}N_6O_2Se$	14,65	1:4	1:4	1:4	1:4	1:8
XII	2-OHC_6H_4CH	—$COO(HC_2)_2N(C_2H_5)_2$	81	224—6	14,32	$C_{30}H_{30}N_6O_2Se$	14,26	—	1:2	1:4	1:4	1:4
XIII	4-$OCH_3C_6H_4CH$	—$COO(CH_2)_2N(C_2H_5)_2$	72	190—3	14,03	$C_{30}H_{32}N_6O_2Se$	13,93	1:4	1:4	1:4	1:4	1:2
XIV	3-OCH_3-4-OHC_6H_3CH	—$COO(CH_2)_2N(C_2H_5)_2$	79	215—7	13,62	$C_{30}H_{32}N_6O_4Se$	13,56	1:4	1:4	1:4	1:4	1:8
XV	4-$OCH_3C_6H_4CH$	NH_2SO_2—	79	235—7	15,63	$C_{23}H_{20}N_6O_4SSe$	15,58	—	—	1:2	1:1	1:4
XVI	$(CH_3)_2C$	$CH_3CONHSO_2$—	96	215—8	16,72	$C_{20}H_{20}N_6O_4SSe$	16,69	1:2	1:4	1:4	1:4	1:4
XVII	2-OHC_6H_4CH	$CH_3CONHSO_2$—	91	270—2	14,92	$C_{34}H_{30}N_6O_4SSe$	14,81	1:2	1:4	1:8	1:4	1:8
XVIII	2-OHC_6H_4CH	$NH_2CONHSO_2$—	95	278—9	17,32	$C_{23}H_{19}N_7O_4SSe$	17,25	1:2	1:4	1:4	1:32	1:2
XIX	4-$OCH_3C_6H_4CH$	$NH_2CONHSO_2$—	73	193—5	16,92	$C_{24}H_{21}N_7O_4SSe$	16,83	1:4	1:4	1:2	1:2	—
XX	3,4-$(OCH_3)_2C_6H_3CH$	$NH_2CONHSO_2$—	78	197—9	16,09	$C_{25}H_{23}N_7O_4SSe$	16,01	1:4	1:4	1:4	—	1:4
XXI	2-OHC_6H_4CH	$NH_2C(=NH)NHSO_2$—	92	203—5	19,78	$C_{23}H_{20}N_8O_4SSe$	19,74	1:4	1:4	1:4	1:4	1:8
XXII	3-OCH_3-4-OHC_6H_3CH	$NH_2C(=NH)NHSO_2$—	91	194—6	18,83	$C_{24}H_{22}N_8O_4SSe$	18,75	1:4	1:4	1:4	1:4	1:8
XXIII	3,4-$(OCH_3)_2C_6H_3CH$	$NH_2C(=NH)NHSO_2$—	90	193—5	18,40	$C_{25}H_{24}N_8O_4SSe$	18,31	1:2	1:4	1:4	1:1	1:4
XXIV	2-OHC_6H_4CH	(thiazolyl-2)$NHSO_2$-dia	89	184—6	16,18	$C_{21}H_{17}N_7O_4SSe$	16,11	1:2	1:4	1:2	—	1:2
XXV	2-OHC_6H_4CH	(5-ethylthiazolyl-2)$NHSO_2$-	91	255—7	17,61	$C_{25}H_{23}N_7O_4S_2Se$	17,56	1:4	—	1:2	1:4	1:8
XXVI	4-$OCH_3C_6H_4CH$	(5-ethylthiazolyl-2)$NHSO_2$-	75	175—7	17,23	$C_{27}H_{25}N_7O_4S_2Se$	17,19	1:8	1:4	1:4	1:4	1:2
XXVII	3-OCH_3-4-OHC_6H_3CH	(5-ethylthiadiazolyl-1-2)$NHSO_2$-	85	260—2	16,83	$C_{27}H_{24}N_8O_4S_2Se$	16,78	1:4	—	1:4	1:4	1:4
XXVIII	C_6H_5CH	(5-ethylthiadiazolyl-1-2)$NHSO_2$-	90	180—3	18,16	$C_{25}H_{22}N_8O_4SSe$	18,20	1:4	1:4	1:4	1:2	1:2
XXIX	2-OHC_6H_4CH	(3,4-dimethylpyrimidyl-1-2)$NHSO_2$-	95	176—8	17,80	$C_{28}H_{24}N_8O_4SSe$	17,73	1:2	1:1	1:1	1:1	1:4
XXX	3-OCH_3-4-OHC_6H_3CH	(3,4-dimethylpyrimidyl-1-2)$NHSO_2$-	88	174—6	16,98	$C_{30}H_{28}N_8O_4SSe$	16,92	1:4	1:4	1:4	1:4	1:8

lowing microorganisms: *Staphylococcus aureus*, *E. coli*, *B. anthracoides*, and *Candida albicans*. The microbial load for the bacteria was 2.5×10^5 cells of an aminopeptide 18-h culture per 1 ml of medium. The experiment was conducted in the following manner: Five mg of substance were dissolved in 1 ml of dimethylformamide (water-insoluble substances), i.e., the resultant concentration was 1:200. A 4.5-ml portion of distilled water was added to that 0.5 ml of solution to make it a 1:2000 dilution (500 μg/ml). Then, 2 ml of aminopeptide were added to 2 ml of the resultant solution to bring the concentration to 1:4000 (250 μg/ml). A 1-ml portion of amino peptide was then added to 1 ml of the last solution which brought the concentration to 1:8000 (125 μg/ml), etc., in order to obtain the following concentrations, respectively: 1:16,000 (62.5 μg/ml), 1:32,000 (31.25 μg/ml), and 1:64,000 (15.6 μg/ml).

A liquid Sabouraud medium (pH 6.0-6.8) was used to cultivate the fungi. It was prepared in the following manner: A 20-g portion of glucose and 10 g of peptone were dissolved in 1 liter of distilled water. The mixture was then sterilized at 110°C for 15 min.

A 3-ml portion of Sabouraud's medium was poured under sterile conditions into each of a total of 10-12 test tubes of which the last was the control. A 5-mg portion of the test substance was dissolved in 1 ml of dimethylformamide to which 9 ml of distilled water were added. The initial dilution (1:2000) contained the test preparation at a concentration of 500 μg/ml. Three ml of the solution from the first test tube were transferred to a second test tube, from which a 3 ml portion was again transferred to a third test tube, etc. Three ml of solution of the penultimate test were poured out. No preparation was inserted into the last test tube or into the control. The concentration of the preparation was halved in each successive test tube so that the following series of dilutions was obtained: 1:2000 (500 μg/ml), 1:4000 (250 μg/ml), 1:8000 (125 μg/ml), 1:16,000 (62.5 μg/ml), etc. The microbial load for the fungi was 500,000 reproductive bodies per 1 ml. After the cultivation, the test tube rack was vigorously agitated and placed into an incubator and maintained there at 27°C for 14 days. The microorganisms' sensitivity to the preparation was measured by the preparation's minimum dose at which no fungal growth was observed.

LITERATURE CITED

1. Methods of Experimental Chemotherapy [in Russian], G. N. Pershin (ed.), 2nd edn., Moscow (1971), pp. 318-319.
2. A. A. Tsurkan and Z. I. Popova, Nauchn. Tr. Ryazan. Med. Inst., 50, 64-68 (1974).
3. A. A. Tsurkan, Z. I. Popova, and N. I. Titova, 3rd All-Russian Congress of Pharmacists: Materials [in Russian], Sverdlovsk (1975), pp. 264-265.
4. A. A. Tsurkan, Z. I. Popova, and D. A. Kulikova, Khim.-farm. Zh., No. 11, 54-57 (1979).