Antimicrobial Activity of *N*-Substituted *N*-(Triphenylstannyl)cyanamides and Triethylammonium (Organocyanoamino)chlorotriphenylstannates

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Abstract □ *N*-Substituted *N*-(triphenylstannyl)cyanamides were studied and found to be better antifungal agents than the previously tested *N*-substituted *N'*-cyano-*S*-(triphenylstannyl)isothioureas and *N*-substituted *N'*-cyano-*O*-(triphenylstannyl)isoureas. They were similar in activity to the previously tested ethyl *N*-aryl-*S*-(triphenylstannyl)-isothiocarbamates. The antifungal activity of triethylammonium (organocyanoamino)chlorotriphenylstannates, which are the triethylammonium chloride complexes of *N*-substituted *N*-(triphenylstannyl)-cyanamides, was similar to or better than that of the *N*-substituted *N*-(triphenylstannyl)cyanamides. Triethylammonium (acetylcyanoamino)chlorotriphenylstannate and triethylammonium dichlorotriphenylstannate were highly inhibitory toward Gram-positive bacteria.

Keyphrases □ *N*-(Triphenylstannyl)cyanamides, *N*-substituted—evaluated for antifungal activity □ Triethylammonium (organocyanoamino)chlorotriphenylstannates—evaluated for antifungal and antibacterial activity □ Antifungal activity—*N*-substituted *N*-(triphenylstannyl)cyanamides and triethylammonium (organocyanoamino)-chlorotriphenylstannates evaluated □ Antibacterial activity—triethylammonium (acetylcyanoamino)chlorotriphenylstannate and triethylammonium dichlorotriphenylstannate evaluated □ Organotin compounds—*N*-substituted *N*-(triphenylstannyl)cyanamides and triethylammonium (organocyanoamino)triphenylstannates evaluated for antibacterial activity, triethylammonium (acetylcyanoamino)triphenylstannate and triethylammonium dichlorostannate evaluated for antibacterial activity □ Structure–activity relationships—cyanamides evaluated for antifungal activity, chlorotriphenylstannates evaluated for antifungal and antibacterial activity

Many biocidal applications have been found or suggested for organotin compounds (1). The biological effects of organotin compounds were stressed in a recent symposium (2). Their use in agriculture as fungicides and pesticides is of special interest because they degrade to nontoxic inorganic compounds and, therefore, appear to pose little threat to the environment (3–7). Recently, ethyl *N*-aryl-*S*-(triphenylstannyl)isothiocarbamates (Series I) (8), which contain a tin–sulfur bond, were found to be generally better antifungal agents than another class of compounds having a tin–sulfur bond, namely, *N*-substituted *N'*-cyano-(triphenylstannyl)isothioureas (Series II) (9). The former compounds were also generally better antifungal agents than some previously studied compounds having a tin–oxygen bond, namely, *N*-substituted *N'*-cyano-*O*-(triphenylstannyl)isoureas (Series III) (10).

The purpose of the present study was to evaluate the antimicrobial activity of some recently reported compounds (11, 12) having a tin–nitrogen bond, namely, *N*-substituted *N*-(triphenylstannyl)cyanamides (Series IV) and triethylammonium (organocyanoamino)chlorotriphenylstannates (Series V). The latter compounds are anionic organotin complexes. The anionic organotin complex, triethylammonium dichlorotriphenylstannate (VI) (12), which is structurally simpler than V, also was evaluated.

RESULTS AND DISCUSSION

The data in Table I show that each of the Series IV compounds behaved essentially identically toward *Cladosporium carpophilum* (ATCC 12117), *Fusarium monoliforme* (ATCC 10052), *Myrothecium verrucaria* (ATCC 9095), *Penicillium notatum* (ATCC 9179), *Rhizopus stolonifer* (ATCC 10404), *Saccharomyces cerevisiae* (ATCC 9896), and *Trichoderma viride* (ATCC 8678). In the case of *C. carpophilum*, *F. monoliforme*, *M. verrucaria*, *P. notatum*, and *R. stolonifer*, each compound partially inhibited fungal growth at all three concentrations, with the exception of IV*a*, IV*c*, IV*e*, IV*f*, and IV*i*. Compounds IV*a*, IV*c*, and IV*f* were inactive toward *C. carpophilum* at 1 μg/ml, IV*i* was inactive toward both *P. notatum* and *R. stolonifer* at 1 μg/ml, and IV*e* was inactive toward *S. cerevisiae* at 10 μg/ml.

Each Series IV compound partially inhibited *Aspergillus niger* (ATCC 12845) at both 1 and 10 μg/ml. Each compound also completely inhibited growth at 100 μg/ml, with the exception of IV*e*–IV*g* and IV*i*, which only partially inhibited growth. The Series IV compounds exhibited partial inhibition of growth of *Chaetomium globosum* (ATCC 6205) at all concentrations, with the exception of IV*a*, IV*e*, and IV*i*, which completely inhibited growth at 100 μg/ml. The Series IV compounds showed the greatest activity toward *Trichophyton mentagrophytes* (ATCC 9129), with seven compounds completely inhibiting growth at 100 μg/ml.

In general, the Series IV compounds were much better antifungal agents than the previously tested Series II compounds and, with the exception of *T. mentagrophytes* toward which the antifungal activity was the same, were better fungal inhibitors than the Series III compounds. The Series IV compounds were more effective against *A. niger* but less effective against *C. globosum*, *T. mentagrophytes*, and *C. carpophilum* than the Series I compounds; the Series IV and Series I compounds exhibited essentially identical activity toward the other six fungi.

The antifungal activity of the Series V compounds (Table II), which are the triethylammonium chloride complexes of the Series IV compounds, was similar to or better than that of the Series IV compounds. The Series V compounds were more active than the Series IV compounds toward *C. globosum*, *P. notatum*, *S. cerevisiae*, and *T. viride*. For ex-

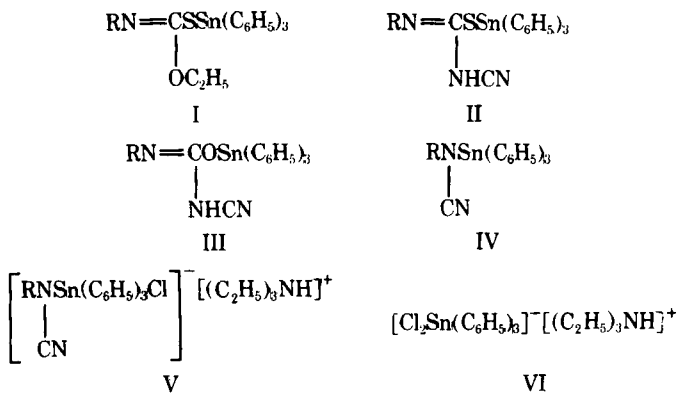

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Table I—Antifungal Activity of *N*-Substituted *N*-(Triphenylstannyl)cyanamides

Compound	R	*A. niger*			*C. globosum*			*C. carpophilum*			*F. moniliforme*			*M. verrucaria*			*P. notatum*			*R. stolonifer*			*S. cerevisiae*			*T. viride*			*T. mentagrophytes*		
		1[a]	10	100	1	10	100	1	10	100	1	10	100	1	10	100	1	10	100	1	10	100	1	10	100	1	10	100	1	10	100
IV*a*	$CH_3C(=O)$	+	+	2+	+	+	2+	—	+	+	+	+	+	+	+	+	+	+	+	+	+	+	—	+	+	—	+	+	+	+	2+
IV*b*	$C_2H_5C(=O)$	+	+	2+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	—	+	+	—	+	+	+	+	2+
IV*c*	$C_6H_5C(=O)$	+	+	2+	+	+	+	—	+	+	+	+	+	+	+	+	+	+	+	+	+	+	—	+	+	—	+	+	+	+	2+
IV*d*	$C_6H_5CH_2C(=O)$	+	+	2+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	—	+	+	—	+	+	+	+	2+
IV*e*	$p\text{-}O_2NC_6H_4C(=O)$	+	+	+	+	+	2+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	—	—	+	—	+	+	+	+	2+
IV*f*	$CF_3C(=O)$	+	+	+	+	+	+	—	+	+	+	+	+	+	+	+	+	+	+	+	+	+	—	+	+	—	+	+	+	2+	2+
IV*g*	$CH_3OC(=O)$	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	—	+	+	—	+	+	+	+	+
IV*h*	$C_2H_5OC(=O)$	+	+	2+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	—	+	+	—	+	+	+	+	+
IV*i*	$C_6H_5SO_2$	+	+	+	+	+	2+	+	+	+	+	+	+	+	+	+	—	+	+	—	+	+	—	+	+	—	+	+	+	+	2+

[a] Indicates concentrations of compounds employed in micrograms per milliliter; – indicates no inhibition of growth, + indicates partial inhibition, and 2+ indicates complete inhibition.

Table II—Antifungal Activity of Triethylammonium (Organocyanoamino)chlorotriphenylstannates and Triethylammonium Dichlorotriphenylstannate

Compound	R	*A. niger*			*C. globosum*			*C. carpophilum*			*E. moniliforme*			*M. verrucaria*			*P. notatum*			*R. stolonifer*			*S. cerevisiae*			*T. viride*			*T. mentagrophytes*		
		1[a]	10	100	1	10	100	1	10	100	1	10	100	1	10	100	1	10	100	1	10	100	1	10	100	1	10	100	1	10	100
V*a*	$CH_3C(=O)$	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	2+
V*b*	$C_2H_5C(=O)$	+	+	2+	+	+	2+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	—	+	+	+	+	+	+	+	2+
V*c*	$C_6H_5C(=O)$	+	+	+	+	+	2+	+	+	+	—	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
V*d*	$CH_3OC(=O)$	+	+	2+	+	+	2+	+	+	+	+	+	+	+	+	+	+	+	2+	+	+	+	—	+	+	+	+	+	+	+	+
V*e*	$C_2H_5OC(=O)$	+	+	2+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	2+	+	+	+	+	+	+	+	+	+	+	+	2+
V*f*	$C_6H_5CH_2OC(=O)$	+	+	+	+	2+	2+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	—	+	2+	+	+	+	+	+	2+
V*g*	$C_6H_5SO_2$	+	+	2+	+	+	2+	+	+	+	+	+	2+	+	+	+	+	+	+	+	+	+	+	+	2+	+	+	+	+	2+	2+
VI	—	+	+	+	+	+	2+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	—	+	+	+	+	+	+	+	+

[a] Indicates concentrations of compounds employed in micrograms per milliliter; – indicates no inhibition of growth, + indicates partial inhibition, and 2+ indicates complete inhibition.

Table III—Antibacterial Activity of Triethylammonium (Acetylcyanoamino)chlorotriphenylstannate and Triethylammonium Dichlorotriphenylstannate

Compound	*B. subtilis*[a]			*E. coli*			*S. aureus*		
	1[b]	10	100	1	10	100	1	10	100
Va	2+	2+	2+	—	—	+	2+	2+	2+
VI	2+	2+	2+	—	—	+	+	2+	2+

[a] Bacteria were obtained from the culture collection of the Department of Biological Sciences, St. John's University. [b] Indicates concentration of compounds employed in micrograms per milliliter; — indicates no inhibition of growth, + indicates partial inhibition of growth, and 2+ indicates complete inhibition of growth.

ample, only three of the Series IV compounds completely inhibited *C. globosum* at 100 μg/ml, whereas five of the Series V compounds exhibited this activity. Furthermore, none of the Series IV compounds inhibited *P. notatum* at 100 μg/ml, whereas two of the Series V compounds exhibited this activity. Furthermore, none of the Series IV compounds showed activity against *S. cerevisiae* and *T. viride* at 1 μg/ml, whereas four of the Series V compounds were partially active against *S. cerevisiae* and all of the Series V compounds were partially active against *T. viride* at this concentration. In addition, two of the Series V compounds completely inhibited *S. cerevisiae* at 100 μg/ml. The simple anionic complex, VI, exhibited equal or less activity than the Series V compounds.

The data in Table III show that Va and VI behaved in an almost identical manner toward specific test bacteria. Both compounds completely inhibited *Bacillus subtilus* at the lowest level (1 μg/ml) of organotin compound. Both compounds were equal to the previously tested *N*-phenyl-*N'*-cyano-*S*-(triphenylstannyl)isothioureas (II, R = C_6H_5) in this regard (9). On the other hand, the previously tested Series I compounds (8) were completely inactive at this concentration, while the previously tested *N*-phenyl-*N'*-cyano-*O*-(triphenylstannyl)isourea (III, R = C_6H_5) (10) only partially inhibited growth at this concentration. Compound Va behaved identically to the Series I compounds and to II (R = C_6H_5) in that it completely inhibited the growth of *Staphylococcus aureus* at 1 μg/ml. Compound III (R = C_6H_5) was inactive at this concentration (10). Compounds Va and VI were no more active than some previously studied compounds toward *Escherichia coli* (8–10).

EXPERIMENTAL

The Series IV compounds were individually dissolved in tetrahydrofuran. The Series V compounds and VI were individually dissolved in acetone. The preparation of sterile solutions of the compounds, the fungi employed, the antimicrobial testing procedures, and the determination of growth inhibition were reported previously (10).

Compounds Va and VI also were investigated for antibacterial activity according to the procedure reported earlier (10).

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Determination of Isophenindamine in Phenindamine Tartrate Using an Argentated High-Performance Liquid Chromatographic Mobile Phase

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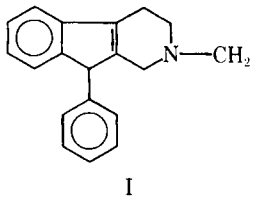
Abstract □ A high-performance liquid chromatographic procedure was developed for the determination of isophenindamine in phenindamine tartrate bulk powder. The method employs a reversed-phase column and a mobile phase containing methanol, 0.001 *M* HNO_3, and silver nitrate.

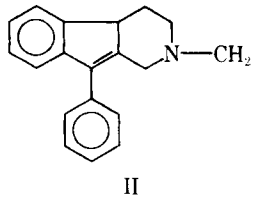
Keyphrases □ Isophenindamine—analysis, high-performance liquid chromatography, argentated mobile phase, phenindamine tartrate bulk powder □ High-performance liquid chromatography—isophenindamine, analysis in phenindamine tartrate bulk powder □ Phenindamine tartrate—analysis of isophenindamine in bulk powder, high-performance liquid chromatography, argentated mobile phase □ Antihistaminics—phenindamine tartrate, analysis of bulk powder for isophenindamine, high-performance liquid chromatography, argentated mobile phase

The role of histamine in anaphylactic shock and allergic conditions stimulated research for specific histamine antagonists. A series of antihistaminics including phenindamine (I) was synthesized (1). Distinct differences were observed between I and isophenindamine (II) when administered intravenously.

Because of the possible formation of II during the manufacture of phenindamine tartrate, a method for the determination of II was desired. A UV spectrophotometric procedure based on the fact that the wavelength of maximum absorbance for each compound is slightly different



I



II

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