Antimicrobial Activity of Triethylammonium Chloride–*N*-Substituted *N'*-Cyano-*O*-(triphenylstannyl)-isourea Complexes

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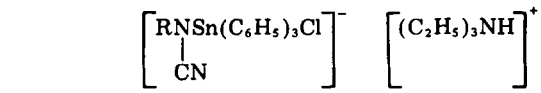
Abstract □ The triethylammonium chloride complexes of *N*-substituted *N'*-cyano-*O*-(triphenylstannyl)isoureas were generally found to be better antifungal and antibacterial agents than the uncomplexed compounds.

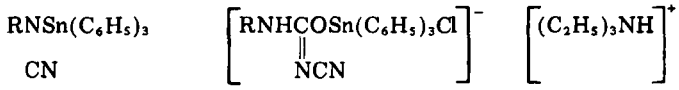
Keyphrases □ *N*-Substituted *N'*-cyano-*O*-(triphenylstannyl)isoureas—complexes with triethylammonium chloride, antibacterial and antifungal activities □ Antimicrobial agents—*N*-substituted *N'*-cyano-*O*-(triphenylstannyl)isourea-triethylammonium chloride complexes, bacterial and fungal screens

Many biocidal applications have been found or suggested for organotin compounds (1, 2). Their use in agriculture as fungicides and pesticides (3–5) is of special interest because they degrade to nontoxic inorganic compounds and, therefore, appear to pose little threat to the environment (6–10). Recently, some diorganotin dihalide and di-pseudohalide complexes were shown to exhibit antitumor activity (11, 12).

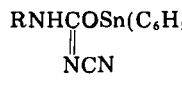
It was previously found that triethylammonium (organocyanoamino)chlorotriphenylstannates (I), which are the triethylammonium chloride complexes of *N*-substituted *N*-(triphenylstannyl)cyanamides (II), exhibit higher antifungal activity than the II compounds (13). It was of interest to determine if the triethylammonium chloride complexes (III) (14) of some previously tested *N*-substituted *N'*-cyano-*O*-(triphenylstannyl)isourea compounds (IV) (15) would likewise exhibit higher antifungal activity than the IV compounds. It was also of interest to compare the antibacterial activity of the III and IV compounds.



[I]



[II] [III]



[IV]

EXPERIMENTAL SECTION

The series III compounds were individually dissolved in tetrahydrofuran. The preparation of sterile solutions of the compounds, the fungi employed, the antimicrobial testing procedures, and the determination of growth inhibition were reported previously (15). The preparation of the series III compounds was described previously (14).

Table I—Antifungal Activity of Triethylammonium Chloride–*N*-Substituted *N'*-Cyano-*O*-(triphenylstannyl)isourea Complexes (III) and *N*-Substituted *N'*-Cyano-*O*-(triphenylstannyl)isoureas (IV)

		Aspergillus niger (*ATCC 12845*)			*Chaetomium globosum* (*ATCC 6205*)			*Cladosporium carpophilum* (*ATCC 12117*)			*Fusarium monoliforme* (*ATCC 10052*)			*Myrothecium verrucaria* (*ATCC 9095*)			*Penicillium notatum* (*ATCC 9179*)			*Rhizopus stolonifer* (*ATCC 10404*)			*Saccharomyces cerevisiae* (*ATCC 9896*)			*Trichoderma viride* (*ATCC 8678*)			*Trichophyton mentagrophytes* (*ATCC 9129*)		
Compound	R	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
IIIa	C_2H_5	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	−	−	+	+	+	−	−	−	+	+	+
IIIb	CH_2=CHC-H_2	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	−	−	+	+	+	−	−	−	+	+	+
IIIc	cyclo-C_6H_{11}	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	−	−	+	+	+	−	−	−	+	+	+
IIId	C_6H_5	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	−	−	+	+	+	−	−	−	+	+	+
IIIe	*p*-F C_6H_4	+	+	+	−	+	+	−	+	+	+	+	+	+	+	+	+	+	+	−	−	−	+	+	+	−	−	−	+	+	+
IVa	C_6H_5	−	+	+	−	+	+	−	+	+	−	+	+	+	+	+	−	+	+	−	+	+	−	−	2+	−	−	+	+	+	2+
IVb	cyclo-C_6H_{11}	−	+	2+	−	+	+	+	+	+	−	+	+	−	+	+	−	+	+	−	+	+	−	−	+	−	−	+	+	+	2+

[a] Concentrations of compounds employed in micrograms per milliliter; key: (−) no inhibition of growth; (+) partial inhibition of growth; (2+) complete inhibition of growth.

Table II—Antibacterial Activity of Triethylammonium Chloride–*N*-Substituted *N'*-Cyano-*O*-(triphenylstannyl)isourea Complexes (III) and *N*-Phenyl-*N'*-cyano-*O*-(triphenylstannyl)isourea (IVa)

		Escherichia coli[a]			*Micrococcus agilis*[a]			*Bacillus subtilis*[a]			*Staphylococcus aureus*[a]		
Compound	R	1[b]	10	100	1	10	100	1	10	100	1	10	100
IIIa	C_2H_5	−	−	−	2+	2+	2+	2+	2+	2+	−	−	+
IIIb	CH_2=$CHCH_2$	−	−	−	2+	2+	2+	2+	2+	2+	−	−	−
IIIc	cyclo-C_6H_{11}	−	−	−	2+	2+	2+	2+	2+	2+	+	2+	2+
IIId	C_6H_5	−	−	−	2+	2+	2+	+	2+	2+	−	2+	2+
IIIe	*p*-F C_6H_4	−	−	−	2+	2+	2+	2+	2+	2+	2+	2+	2+
IVa	C_6H_5	−	−	−	2+	2+	2+	+	2+	2+	−	+	2+

[a] Obtained from the culture collection of the Department of Biological Sciences, St. John's University. [b] Concentration of compounds employed, in micrograms per milliliter; key: (−) no inhibition of growth; (+) partial inhibition of growth; (2+) complete inhibition of growth.

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RESULTS AND DISCUSSION

The data in Table I show that each of the series III compounds behaved essentially identically toward each of the 10 test fungi. All of the series III compounds were inactive towards *Rhizopus stolonifer* and *Trichoderma viride* at all concentrations. In this regard they were inferior to the previously tested series IV compounds, which partially inhibited *R. stolonifer* at 10 μg/mL and *T. viride* at 100 μg/mL (15). With the exception of IIIe, the series III compounds partially inhibited the growth of the other eight test fungi at a concentration of 1 μg/mL. Employment of higher concentrations did not improve the antifungal activity. Compound IIIe differed from the other series III compounds only in that it was inactive towards *Chaetomium globosum* and *Cladosporium carpophilum* at 1 μg/mL. In comparison with the series III compounds, IVa was inactive towards *Aspergillus niger*, *Ch. globosum*, *Cl. carpophilum*, *Fusarium monoliforme*, *Penicillium notatum*, and *Saccharomyces cerevisiae* at 1 μg/mL. Compound IVb was also inferior to the series III compounds in that it was inactive towards *A. niger*, *Ch. globosum*, *F. monoliforme*, *Myrothecium verrucaria*, *P. notatum*, and *S. cerevisiae* at 1 μg/mL. Furthermore, the series IV compounds were inactive towards *S. cerevisiae* even at 10 μg/mL. Thus, the series III compounds generally exhibited higher antifungal activity than the series IV compounds.

The data in Table II show that all of the series III compounds were inactive towards the Gram-negative bacterium *Escherichia coli* at all concentrations. In this regard they resembled the previously tested IVa (15). All of the series III compounds behaved identically towards the two Gram-positive bacteria *Micrococcus agilis* and *Bacillus subtilis*, totally inhibiting the growth of these bacteria at a concentration of 1 μg/mL. In this regard they were somewhat better than IVa, which only partially inhibited *B. subtilis* at 1 μg/mL. The most effective series III compound against *Staphylococcus aureus* was IIIe, which totally inhibited the growth of this bacterium at 1 μg/mL. In contrast, IVa was inactive towards *St. aureus* at 1 μg/mL. Thus, the series III compounds generally exhibited higher antibacterial activity than IVa.

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Acylation of Hemoglobin by Aspirin-Like Diacyl Esters

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Received April 5, 1983 from the *Department of Chemistry, Northwestern University, Evanston, IL 60201.* Accepted for publication May 19, 1983.

Abstract □ Aspirin-like diacyl esters of different steric disposition have been prepared and compared with acetylsalicylate in their abilities to modify hemoglobin.

Keyphrases □ Diacyl esters—aspirin derivatives, acylation of hemoglobin □ Hemoglobin—acylation by aspirin-like diacyl esters, sickle cell anemia

In a previous paper (1), it has been shown that aspirin can acylate hemoglobin and thereby provide a novel approach to the alteration of sickle hemoglobin. Acetylsalicylate is the prototype of a general class of monoacyl esters of salicylic acid. Consequently, a variety of such esters have been synthesized (2) and examined for their effectiveness in modifying hemoglobin S and in inhibiting the aggregation process leading to sickling.

Among variants in aspirin-like derivatives are the diacyl esters of dihydroxybenzoic acids. These seem attractive because they would present two active acyl groups to the protein when it forms a reaction complex with a reagent molecule. We have prepared, therefore, a series of such diacyl ester compounds of different steric structure and compared their abilities to modify hemoglobin.

EXPERIMENTAL SECTION

A variety of hydroxybenzoic acids were purchased from commercial sources[1]. Their mono- and diacyl esters were synthesized by methods described in the literature (3-7). The derivatives prepared are listed in Table I.

[1] Aldrich Chemical Co., for example.

Of the compounds obtained, only 3,5-diacetoxybenzoic acetic anhydride (XI) has not been reported in the literature. It appeared as a by-product in the mother liquor (chloroform–petroleum ether) from the preparation of the diacetoxybenzoic anhydride (X). The fine white precipitate which appeared in the mother liquor after standing for several hours was removed by filtration, washed with petroleum ether, and dried without heat, mp 71–72°C. This product, insoluble in aqueous $NaHCO_3$ at room temperature, bubbled on heating. It did not give a positive $FeCl_3$ test for free phenol. ^{1}H-NMR and

Table I—Modification of Hemoglobin by Aspirin-like Mono- and Diacyl Esters

Compound	Concentration, mM	Modification of Oxyhemoglobin A[a], %
I	10	22.5
II	10	23.1
	20	34.2
III	10	26.3
	20	36.8
IV	10	27.7
	20	37.3
V	5	32.3
	10	49.3
VI	5	19.1
	10	37.4
VII	10	78.7
VIII	5	36.3
	10	53.0
IX	5	23.8
	10	46.7
X	5	26.3
XI	5	45.0
	10	79.2

[a] Hemoglobin concentration = 1 mM.