Synthesis and Antimicrobial Activity of Ethyl *N*-Aryl-*S*-(triphenylstannyl)isothiocarbamates

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Abstract \square Five ethyl N-aryl-S-(triphenyltin iodide with the appropriate ethyl N-arylthiocarbamate in the presence of triethylamine. The IR spectrum of each compound was obtained over the $4000-200\text{-cm}^{-1}$ range, and some bands were assigned. These new compounds were found to be generally better antifungal agents than the previously tested N-substituted N'-cyano-S-(triphenylstannyl)isothioureas. The new compounds were also investigated for antibacterial activity and were especially inhibitory toward Gram-positive species. Except for their lower activity toward Bacillus subtilis, their antibacterial activity was identical

to the previously tested N-phenyl-N'-cyano-S-(triphenylstannyl)isothiourea.

Keyphrases \square Isothiocarbamates, various—synthesized, evaluated for antibacterial and antifungal activity \square Antibacterial activity—various isothiocarbamates evaluated \square Antifungal activity—various isothiocarbamates evaluated \square Organotin compounds—various N-aryl-S-(triphenylstannyl)isothiocarbamates synthesized, evaluated for antibacterial and antifungal activity \square Structure—activity relationships—various isothiocarbamates evaluated for antibacterial and antifungal activity

Recently, the antifungal activity of five N-substituted N'-cyano-S-(triphenylstannyl)isothioureas (Series I) was described (1). The antifungal activity of one compound (Ia,

 $R = C_6H_5$) was compared to that of its oxygen analog (IIa, $R = C_6H_5$), and some differences were noted. Compound Ia also was investigated for antibacterial activity and was

Table I-Ethyl N-Aryl-S-(triphenylstannyl)isothiocarbamates a

Compound		Y ield, % b			Analysis, %			
	R		Melting Point ^c	Formula		Calc.	Found	
IIIa	C_6H_5	84	113-114°	$C_{27}H_{25}NOSSn$	С	61.16	60.92	
					H N S Sn	4.75	4.80	
					N	2.64	2.92	
					S	6.05	6.24	
***	na 11				Sn	22.38	22.22	
IIIb	$p ext{-}\mathrm{FC}_6\mathrm{H}_4$	91	79–82°	$C_{27}H_{24}FNOSSn$	С	59.15	59.17	
					H F N S Sn C	4.41	4.27	
					F	3.47	3.64	
					N	2.55	2.73	
					S	5.85	5.80	
***	0.370.44				Sn	21.65	21.26	
IIIc	$p ext{-} ext{O}_2 ext{NC}_6 ext{H}_4$	71	95–98°	$C_{27}H_{24}N_2O_3SSn$	Ç	56.37	56.52	
					Ĥ	4.21	4.23	
					N S Sn	4.87	5.07	
					S	5.57	5.43	
*** 1	2100 11				Sn	20.63	20.92	
IIId	$p ext{-} ext{NCC}_6 ext{H}_4$	97	82–85°	$C_{28}H_{24}N_2OSSn$	C	60.57	60.72	
					H N S Sn	4.36	4.57	
					N	5.04	5.35	
					S	5.77	6.06	
***					Sn	21.38	21.02	
ΠIe	2-Naphthyl	51	65–68°	$C_{31}H_{27}NOSSn$	C	64.16	64.18	
					H	4.69	4.75	
					H N S	2.41	2.70	
					\mathbf{s}	5.53	5.61	
					Sn	20.45	20.30	

^a Triphenyltin iodide, ethyl N-arylthiocarbamate, and triethylamine (1:1:2 mole ratio) were allowed to react in ether at the reflux temperature for 40 hr (IIIa), 92 hr (IIIb), 17 hr (IIIc), 18 hr (IIId), and 96 hr (IIIe). ^b Based on material melting within 5° of the analytical sample. ^c Refers to the analytical sample; recrystallization solvents were n-pentane (IIIb-IIId), ether (IIIa), and ether-n-pentane (IIIe).

Table II—IR Spectra of Ethyl N-Aryl-S-(triphenylstannyl)isothiocarbamates a

		C_6H_5		Sn $(C_6H_5)_3$ (4, 6–10)		
Compound	$C=N^b$	Ring Vibration (2-4)	SnS (5)	$\nu_{\rm as}$	ν _в	
IIIa	1623 s	453 s	$320~\mathrm{s}^c$	274 s	231^{d}	
IIIb	1621 s	442 s	359 s^{e}	272 s	224 s^f	
IIIc	1621 s	452 s^g	$329~\mathrm{m}^{h}$	269 s	224 s^i	
IIId	1629 s	$452~\mathrm{s}^{j}$	314 m	266 s	$242 \mathrm{s}$	
IIIe	1613 s	$452 s^k$	345 s	275 s	$232~\mathrm{m}^{l}$	

a Values are expressed in centimeters ¹; s = strong, m = medium, and w = weak. The data for 4000–400 cm⁻¹ were obtained using potassium bromide pellets. The data for 400–200 cm⁻¹ were obtained using mineral oil. b This assignment is uncertain because of the presence of aromatic C=C bands in this region. c A band was present at 372 m cm⁻¹. d A band was present at 204 w cm⁻¹. e A band was present at 386 m cm⁻¹. f A band was present at 204 w cm⁻¹. B Bands were present at 444 s and 439 s cm⁻¹. h A band was present at 373 m cm⁻¹. A band was present at 202 m cm⁻¹. A band was present at 448 cm⁻¹. A band was present at 445 s cm⁻¹. Bands were present at 249 s and 260 s cm⁻¹.

especially inhibitory toward Gram-positive species; furthermore, its antibacterial activity was considerably greater than that of its oxygen analog.

The purpose of the present study was to evaluate the antimicrobial activity of another class of compounds having a tin-sulfur bond, namely, ethyl N-aryl-S-(triphenylstannyl)isothiocarbamates (Series III), and ethyl N-phenyl-S-tritylisothiocarbamate (IV), which is the carbon analog of IIIa ($R = C_6H_5$).

RESULTS AND DISCUSSION

Synthesis—Compounds IIIa—IIIe (Table I) are new compounds and were prepared by the reaction of triphenyltin iodide with the appropriate ethyl N-arylthiocarbamate in the presence of triethylamine (Scheme I). The compounds were identified by elemental analysis (Table I) and IR spectra (Table II). Compound IV was synthesized by allowing ethyl N-phenylisothiocarbamate to react with trityl chloride in the presence of triethylamine.

Biological Results—The data in Table III show that each organotin compound, except IIIe, behaved identically toward the test fungi. Compound IIIe differed from the other organotin compounds in that it did not completely inhibit the growth of Cladosporium carpophilum at $100~\mu\text{g/ml}$. The organotin compounds showed the greatest activity toward Trichophyton mentagrophytes, completely inhibiting the growth of this fungus at $10~\mu\text{g/ml}$. Compound IV exhibited considerably less antifungal activity than the organotin compounds, being completely inactive toward three fungi; it was most active against C. carpophilum, completely inhibiting the growth of this fungus at $100~\mu\text{g/ml}$.

A comparison of the present data with those obtained previously for N-substituted N'-cyano-S-(triphenylstannyl)isothioureas (Series I) showed that IIIa-IIIe generally possess greater antifungal activity. For example, while most of the Series I compounds were completely inactive toward C. carpophilum and Saccharomyces cerevisiae, IIIa-IIId completely inhibited the former at $100 \, \mu g/ml$ and partially inhibited the latter at $10 \, \mu g/ml$. Furthermore, while many Series I compounds were inactive at $10 \, \mu g/ml$, none of the Series III compounds failed to inhibit, at least partially, fungal growth at this concentration.

The data in Table IV show that each organotin compound behaved in an identical manner toward specific test bacteria. Both Micrococcus agilis and Staphylococcus aureus were inhibited completely at the lowest level (1 μ g/ml) of organotin compound. Compound IV was considerably less active than the organotin compounds, being completely inactive against Bacillus subtilis and Escherichia coli; it did, however, completely inhibit M. agilis at 100 μ g/ml. A comparison of the present data with those obtained previously for Ia showed that IIIa-IIIe were considerably less active toward B. subtilis than Ia.

EXPERIMENTAL¹

Ethyl N-(p-Nitrophenyl)-S-(triphenylstannyl)isothiocarbamate (III c)—A mixture of triphenyltin iodide (9.54 g, 0.02 mole), ethyl N-(p-nitrophenyl)thiocarbamate (11) (4.53 g, 0.02 mole), triethylamine (4.05 g, 0.04 mole), and ether (250 ml) was refluxed for 17 hr. The solvent was evaporated below 35°, and the mixture was stirred with benzene (200 ml)

 $\begin{array}{c} \mathbf{S} \\ \parallel \\ \mathrm{RNHCOC_2H_5} + (C_6H_5)_3\mathrm{SnI} + (C_2H_5)_3\mathrm{N} \longrightarrow \\ & \left[(C_2H_5)_3\mathrm{NH} \right]^+ \mathrm{I}^- + \mathrm{III}a\mathrm{-III}e \\ & Scheme\ I \end{array}$

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Table III—Antifungal Activity of Ethyl N-Aryl-S-(triphenylstannyl)isothiocarbamates and Ethyl N-Phenyl-S-tritylisothiocarbamate

¹ Melting points were determined with a Mel-Temp capillary melting-point apparatus and are uncorrected. IR data were obtained with a Beckman IR 8 spectrophotometer. The far IR data were obtained with a Perkin-Elmer model FIS-3 IR spectrophotometer and with a Perkin-Elmer model 21 double-beam IR spectrophotometer fitted with a cesium bromide prism and purged with nitrogen. Elemental analyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, N.Y.

Table IV—Antibacterial Activity of Ethyl N-Aryl-S-(triphenylstannyl)isothiocarbamates and Ethyl N-Phenyl-S-tritylisothiocarbamate

Compound	, Bacillus subtillisª		Escherichia coli		Micrococcus agilis		Staphylococcus aureus					
	16	10	100	1	10	100	1	10	100	1	10	100
IIIa	_	+	+	_	_	+	2+	2+	2+	2+	2+	2+
IIIb	_	+	2+	-	_	+	2+	2+	2+	2+	2+	2+
IIIc	_	+	2+	_	_	+	2+	2+	2+	2+	2+	2+
ΠId	_	+	2+	_	_	+	2+	2+	2+	2+	2+	2+
IIIe	_	+	2+	_	_	+	2+	2+	2+	2+	2+	2+
IV		_	_	_	_		_	+	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.

and filtered to give 2.98 g (65%) of triethylammonium iodide, mp 173–175° [lit. (12) mp 181°].

The benzene was evaporated from the filtrate below 35°, and the mixture was stirred with n-heptane and filtered to give 10.88 g (95%) of IIIc, mp 96–106°. Recrystallization from n-pentane gave 8.11 g (71%) of IIIc, mp 95–98°. Further recrystallization from n-pentane did not change the melting point.

The other compounds in Table I were prepared in a similar manner. Ethyl N-Phenyl-S-tritylisothiocarbamate (IV)—A mixture of trityl chloride (5.58 g, 0.02 mole), ethyl N-phenylthiocarbamate (13) (3.63 g, 0.02 mole), triethylamine (4.05 g, 0.04 mole), and acetonitrile (200 ml) was stirred at 25° for 47 hr. The solvent was evaporated, the residue was stirred with benzene (200 ml), and the mixture was filtered to give 2.69 g (98%) of triethylammonium chloride, mp 255° [lit. (12) mp 253–254°].

The benzene was evaporated from the filtrate, the residue was stirred with n-heptane (100 ml), and the mixture was cooled and filtered to give 7.82 g (92%) of IV, mp 126–135°. Recrystallization from n-pentane gave 4.82 g (57%) of IV, mp 133–137°; IR: 1626 s (C=N) cm⁻¹.

Anal. — Calc. for $C_{28}H_{25}NOS$: C, 79.40; H, 5.95; N, 3.31; S, 7.57. Found: C, 79.47; H, 6.05; N, 3.48; S, 7.44.

Biological Methods—The compounds were individually dissolved in tetrahydrofuran except for IIId, which was solubilized in benzene. The preparation of sterile solutions of the compounds, the fungi employed, the antimicrobial testing procedures, and the determination of growth inhibition were reported previously (14).

The compounds also were investigated for antibacterial activity according to the procedure reported earlier (14).

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Antifungal Properties of Halofumarate Esters

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Abstract \square Alkyl esters (C_1-C_4) of the four halofumaric acids were tested for antifungal activity against Candida albicans, Aspergillus niger, Mucor mucedo, and Trichophyton mentagrophytes at pH 5.6 and 7.0 in the absence and presence of 10% beef serum in Sabouraud dextrose agar. The most toxic compound to each organism was: C. albicans, ethyl odofumarate (0.054 mmole/liter); A. niger, methyl bromofumarate (0.090 mmole/liter); M. mucedo, methyl fluorofumarate (0.037 mmole/liter); and T. mentagrophytes, ethyl iodofumarate (0.020 mmole/liter). The

Interest in developing agents for activity against infec-

tions due to opportunistic fungi in debilitated and im-

munosuppressed patients led to a search for potentially

useful classes of compounds (1-3). The fungi that are the

most frequent invaders include species of Candida, As-

order of overall activity of the six most toxic compounds was: ethyl iodofumarate > ethyl chlorofumarate > methyl iodofumarate = methyl bromofumarate > methyl chlorofumarate > ethyl bromofumarate.

Keyphrases □ Halofumarate alkyl esters, various—antifungal activity evaluated \square Antifungal activity—various halofumarate alkyl esters evaluated \square Structure–activity relationships—various halofumarate alkyl esters evaluated for antifungal activity

DISCUSSION

A previous study of the fungitoxicity of 2-bromo-3-fluorosuccinate esters and related compounds indicated that a systematic examination of the halofumarate esters would be worthwhile (5). Fluorofumaric (6), chlorofumaric (7), bromofumaric (8), and iodofumaric (9) acids were esterified by heating under reflux with methanol, ethanol, 1-propanol,

pergillus, Mucor, and Cryptococcus (4).