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

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Abstract □ Five ethyl *N*-aryl-*S*-(triphenylstannyl)isothiocarbamates were synthesized by the reaction of 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-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 □ Isothiocarbamates, various—synthesized, evaluated for antibacterial and antifungal activity □ Antibacterial activity—various isothiocarbamates evaluated □ Antifungal activity—various isothiocarbamates evaluated □ Organotin compounds—various *N*-aryl-*S*-(triphenylstannyl)isothiocarbamates synthesized, evaluated for antibacterial and antifungal activity □ 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 (I*a*, R = C_6H_5) was compared to that of its oxygen analog (II*a*, R = C_6H_5), and some differences were noted. Compound I*a* also was investigated for antibacterial activity and was

Table I—Ethyl *N*-Aryl-*S*-(triphenylstannyl)isothiocarbamates [a]

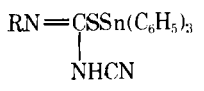
Compound	R	Yield, %[b]	Melting Point[c]	Formula	Analysis, %	Calc.	Found
III*a*	C_6H_5	84	113–114°	$C_{27}H_{25}NOSSn$	C	61.16	60.92
					H	4.75	4.80
					N	2.64	2.92
					S	6.05	6.24
					Sn	22.38	22.22
III*b*	*p*-FC_6H_4	91	79–82°	$C_{27}H_{24}FNOSSn$	C	59.15	59.17
					H	4.41	4.27
					F	3.47	3.64
					N	2.55	2.73
					S	5.85	5.80
					Sn	21.65	21.26
III*c*	*p*-$O_2NC_6H_4$	71	95–98°	$C_{27}H_{24}N_2O_3SSn$	C	56.37	56.52
					H	4.21	4.23
					N	4.87	5.07
					S	5.57	5.43
					Sn	20.63	20.92
III*d*	*p*-NCC_6H_4	97	82–85°	$C_{28}H_{24}N_2OSSn$	C	60.57	60.72
					H	4.36	4.57
					N	5.04	5.35
					S	5.77	6.06
					Sn	21.38	21.02
III*e*	2-Naphthyl	51	65–68°	$C_{31}H_{27}NOSSn$	C	64.16	64.18
					H	4.69	4.75
					N	2.41	2.70
					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 (III*a*), 92 hr (III*b*), 17 hr (III*c*), 18 hr (III*d*), and 96 hr (III*e*). [b] Based on material melting within 5° of the analytical sample. [c] Refers to the analytical sample; recrystallization solvents were *n*-pentane (III*b*–III*d*), ether (III*a*), and ether–*n*-pentane (III*e*).

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

Compound	C=N[b]	C_6H_5 Ring Vibration (2–4)	SnS (5)	Sn $(C_6H_5)_3$ (4, 6–10) ν_{as}	ν_s
III*a*	1623 s	453 s	320 s[c]	274 s	231[d]
III*b*	1621 s	442 s	359 s[e]	272 s	224 s[f]
III*c*	1621 s	452 s[g]	329 m[h]	269 s	224 s[i]
III*d*	1629 s	452 s[j]	314 m	266 s	242 s
III*e*	1613 s	452 s[k]	345 s	275 s	232 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}. [g] Bands were present at 444 s and 439 s cm^{-1}. [h] A band was present at 373 m cm^{-1}. [i] A band was present at 202 m cm^{-1}. [j] A band was present at 448 cm^{-1}. [k] A band was present at 445 s cm^{-1}. [l] Bands were present at 249 s and 260 s cm^{-1}.



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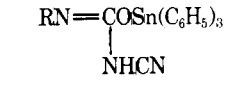
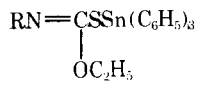
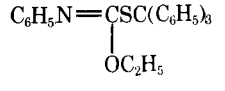


II



III



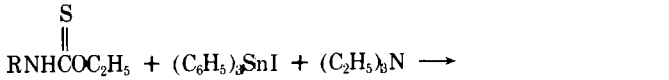
IV

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 III*a* (R = C_6H_5).

RESULTS AND DISCUSSION

Synthesis—Compounds III*a*–III*e* (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.



Scheme I

Biological Results—The data in Table III show that each organotin compound, except III*e*, behaved identically toward the test fungi. Compound III*e* differed from the other organotin compounds in that it did not completely inhibit the growth of *Cladosporium carpophilum* at 100 μg/ml. The organotin compounds showed the greatest activity toward *Trichophyton mentagrophytes*, completely inhibiting the growth of this fungus at 10 μg/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 μg/ml.

A comparison of the present data with those obtained previously for *N*-substituted *N'*-cyano-*S*-(triphenylstannyl)isothioureas (Series I) showed that III*a*–III*e* generally possess greater antifungal activity. For example, while most of the Series I compounds were completely inactive toward *C. carpophilum* and *Saccharomyces cerevisiae*, III*a*–III*d* completely inhibited the former at 100 μg/ml and partially inhibited the latter at 10 μg/ml. Furthermore, while many Series I compounds were inactive at 10 μg/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 μg/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 μg/ml. A comparison of the present data with those obtained previously for I*a* showed that III*a*–III*e* were considerably less active toward *B. subtilis* than I*a*.

EXPERIMENTAL[1]

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)

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

Compound	*Aspergillus niger* (ATCC 12845)		*Chaetomium globosum* (ATCC 6205)		*Cladosporium carpophilum* (ATCC 12117)		*Fusarium moniliforme* (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)	
	1[a]	10	100	1	10	100	1	10	100	1	10	100	1	10	100	1	10	100	1	10	100
III*a*	+	+	+	+	+	+	2+	2+	2+	+	+	+	+	+	+	+	+	+	+	+	+
III*b*	+	+	+	+	+	+	2+	2+	2+	+	+	+	+	+	+	+	+	+	+	+	+
III*c*	+	+	+	+	+	+	2+	2+	2+	+	+	+	+	+	+	+	+	+	+	+	+
III*d*	+	+	+	+	+	+	2+	2+	2+	+	+	+	+	+	+	+	+	+	+	+	+
III*e*	+	+	−	+	−	−	+	−	−	+	+	−	+	+	−	−	−	−	+	+	+
IV	−	−	−	+	−	−	2+	−	−	−	−	−	−	−	−	−	−	−	−	−	−

[a] 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.

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

Compound	*Bacillus subtillis*[a]			*Escherichia coli*			*Micrococcus agilis*			*Staphylococcus aureus*		
	1[b]	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+
IIId	−	+	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).

REFERENCES

(1) E. J. Kupchik, M. A. Pisano, A. V. Raghunath, R. A. Cardona, N. Formaini, and C. Alleguez, *J. Pharm. Sci.*, **64**, 1259 (1975).

(2) C. J. Cattenach and E. F. Mooney, *Spectrochim. Acta A*, **24**, 407 (1968).

(3) L. Verdonck and G. P. van der Kelen, *J. Organomet. Chem.*, **40**, 135 (1972).

(4) R. C. Poller, *Spectrochim. Acta*, **22**, 935 (1966).

(5) H. Schumann, I. Schumann-Ruidisch, and M. Schmidt, in "Organotin Compounds," vol. 2, A. K. Sawyer, Ed., Dekker, New York, N.Y., chap. 6.

(6) J. R. May, W. R. McWhinnie, and R. C. Poller, *Spectrochim. Acta A*, **27**, 969 (1971).

(7) T. N. Srivastava and S. K. Tandon, *ibid.*, **27**, 593 (1971).

(8) T. N. Srivastava, *J. Organomet. Chem.*, **16**, P53 (1969).

(9) I. Wharf, J. Z. Lobos, and M. Onyszchuk, *Can. J. Chem.*, **48**, 2787 (1970).

(10) N. S. Dance, W. R. McWhinnie, and R. C. Poller, *J. Chem. Soc. Dalton Trans.*, **1976**, 2349.

(11) E. E. Reid, "Organic Chemistry of Bivalent Sulfur," vol. 4, Chemical Publishing Co., New York, N.Y., 1962, p. 274.

(12) I. Heilbron, "Dictionary of Organic Compounds," 4th ed., vol. 5, Oxford, London, England, 1965, p. 3126.

(13) E. E. Reid, "Organic Chemistry of Bivalent Sulfur," vol. 4, Chemical Publishing Co., New York, N.Y., 1962, p. 272.

(14) E. J. Kupchik, M. A. Pisano, D. K. Parikh, and M. A. D'Amico, *J. Pharm. Sci.*, **63**, 261 (1974).

Antifungal Properties of Halofumarate Esters

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Abstract □ 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 iodofumarate (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 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 □ Antifungal activity—various halofumarate alkyl esters evaluated □ Structure–activity relationships—various halofumarate alkyl esters evaluated for antifungal activity

Interest in developing agents for activity against infections due to opportunistic fungi in debilitated and immunosuppressed 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, Aspergillus, Mucor,* and *Cryptococcus* (4).

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,