

# 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<sup>-1</sup> 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 (Ia,

R = C<sub>6</sub>H<sub>5</sub>) was compared to that of its oxygen analog (IIa, R = C<sub>6</sub>H<sub>5</sub>), and some differences were noted. Compound Ia also was investigated for antibacterial activity and was

**Table I—Ethyl *N*-Aryl-*S*-(triphenylstannyl)isothiocarbamates<sup>a</sup>**

Compound	R	Yield, % <sup>b</sup>	Melting Point <sup>c</sup>	Formula	Analysis, %		
					Calc.	Found	
IIIa	C <sub>6</sub> H <sub>5</sub>	84	113–114°	C <sub>27</sub> H <sub>25</sub> 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
IIIb	<i>p</i> -FC <sub>6</sub> H <sub>4</sub>	91	79–82°	C <sub>27</sub> H <sub>24</sub> FNOSn	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
IIIc	<i>p</i> -O <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	71	95–98°	C <sub>27</sub> H <sub>24</sub> N <sub>2</sub> O <sub>3</sub> SSn	Sn	21.65	21.26
					C	56.37	56.52
					H	4.21	4.23
					N	4.87	5.07
					S	5.57	5.43
IIId	<i>p</i> -NCC <sub>6</sub> H <sub>4</sub>	97	82–85°	C <sub>28</sub> H <sub>24</sub> N <sub>2</sub> OSSn	Sn	20.63	20.92
					C	60.57	60.72
					H	4.36	4.57
					N	5.04	5.35
					S	5.77	6.06
IIIe	2-Naphthyl	51	65–68°	C <sub>31</sub> H <sub>27</sub> NOSSn	Sn	21.38	21.02
					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

<sup>a</sup> 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). <sup>b</sup> Based on material melting within 5° of the analytical sample. <sup>c</sup> 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<sup>a</sup>**

Compound	C=N <sup>b</sup>	C <sub>6</sub> H <sub>5</sub> Ring Vibration (2–4)	SnS (5)	Sn (C <sub>6</sub> H <sub>5</sub> ) <sub>3</sub> (4, 6–10)	
				ν <sub>as</sub>	ν <sub>s</sub>
IIIa	1623 s	453 s	320 s <sup>c</sup>	274 s	231 <sup>d</sup>
IIIb	1621 s	442 s	359 s <sup>e</sup>	272 s	224 s <sup>f</sup>
IIIc	1621 s	452 s <sup>g</sup>	329 m <sup>h</sup>	269 s	224 s <sup>i</sup>
IIId	1629 s	452 s <sup>j</sup>	314 m	266 s	242 s
IIIe	1613 s	452 s <sup>k</sup>	345 s	275 s	232 m <sup>l</sup>

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



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

Compound	<i>Bacillus subtilis</i> <sup>a</sup>			<i>Escherichia coli</i>			<i>Micrococcus agilis</i>			<i>Staphylococcus aureus</i>		
	1 <sup>b</sup>	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+	—	—	+

<sup>a</sup> Bacteria were obtained from the culture collection of the Department of Biological Sciences, St. John's University. <sup>b</sup> 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<sup>-1</sup>.

*Anal.*—Calc. for C<sub>28</sub>H<sub>25</sub>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 IIIc, 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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Received May 31, 1977, from Boyce Thompson Institute for Plant Research, Yonkers, NY 10701.

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**Abstract** □ Alkyl esters (C<sub>1</sub>–C<sub>4</sub>) 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,