

Table III—Antibacterial Activity of Some Xanthenes and Benzophenones against *Escherichia coli* (K12) and *Streptococcus faecalis* (8043)

Number	Compound	—ID ₅₀ , moles/l.—	
		<i>E. coli</i>	<i>S. faecalis</i>
I ^a		>10 ⁻³	1 × 10 ⁻³ ^b
XV ^c		>10 ⁻³	9 × 10 ⁻⁴
XVII ^c		>10 ⁻³	8 × 10 ⁻⁴
XIX		>10 ⁻³	1 × 10 ⁻³
XX ^c		— ^d	— ^d
XXI ^e		3 × 10 ⁻⁴	3 × 10 ⁻⁴ /
XXV		>10 ⁻³	>10 ⁻³
XXVII ^e		1 × 10 ⁻³	9 × 10 ⁻⁴
XXXI ^c	1,8-Dihydroxyxanthone (6)	>>10 ⁻³	>>10 ⁻³
XXXII	2,2',3,3'-Tetrahydroxybenzo-phenone (5, 6)	6 × 10 ⁻³ ^b	1 × 10 ⁻³ ^b

^a Suspension. ^b One hundred percent inhibition at 10⁻³ M. ^c Compound precipitated when test solution was added to medium. ^d No effect at 10⁻³ M; at 10⁻² M, a 36% growth enhancement was observed. ^e No effect at 10⁻³ M; at 10⁻² M, an 81% growth enhancement was observed. / One hundred percent inhibition at 10⁻⁴ M.

XXXII) showed borderline activity (ID₅₀ values of about 10⁻⁴ M) against one or the other of these organisms.

REFERENCES

- (1) R. A. Finnegan, K. E. Merkel, and N. Back, *J. Pharm. Sci.*, **61**, 1599(1972).
- (2) R. A. Finnegan and P. L. Bachman, *ibid.*, **54**, 633(1965).
- (3) R. A. Finnegan and J. K. Patel, *J. Chem. Soc., Perkin I*, 1896 (1972).
- (4) R. A. Finnegan, J. K. Patel, and P. L. Bachman, *Tetra-*

hedron Lett., **1966**, 6087.

(5) R. A. Finnegan and K. E. Merkel, *J. Org. Chem.*, **37**, 2986 (1972).

(6) K. E. Merkel, Ph. D. thesis, State University of New York at Buffalo, Buffalo, N. Y., 1970.

(7) J. K. Patel, M. S. thesis, State University of New York at Buffalo, Buffalo, N. Y., 1967.

(8) A. Bloch, M. H. Fleysber, R. Thedford, R. J. Maue, and R. H. Hall, *J. Med. Chem.*, **9**, 886(1966).

(9) D. A. Shuman, A. Bloch, R. K. Robins, and M. J. Robins, *ibid.*, **12**, 653(1969).

(10) R. A. Finnegan, R. A. Stephani, G. Ganguli, S. N. Ganguly, and A. K. Bhattacharya, *J. Pharm. Sci.*, **57**, 1039(1968).

(11) R. A. Finnegan and D. Knutson, *Tetrahedron Lett.*, **1968**, 3429.

(12) R. A. Finnegan and D. Knutson, *Chem. Commun.*, **1966**, 172.

ACKNOWLEDGMENTS AND ADDRESSES

Received April 14, 1972, from the Department of Medicinal Chemistry, State University of New York at Buffalo, Buffalo, NY 14214

Accepted for publication October 5, 1972.

Most of the data in Tables I and II were presented to the Medicinal Chemistry Section, APhA Academy of Pharmaceutical Sciences, Las Vegas meeting, April 1967 (Abstracts of Papers, p. 77).

Supported by Grant GM 11412 from the National Institutes of Health, U. S. Public Health Service, Bethesda, MD 20014

This manuscript was written while R. A. Finnegan was a Guest Professor at the Institut für Pharmazeutische Arzneimittellehre, der Universität München. He thanks the Directors of the Institute and their colleagues for their hospitality during this period.

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Synthesis and Antifungal Activity of Polyhalophenyl Esters of *p*-Sulfamoylcarbanilic Acid

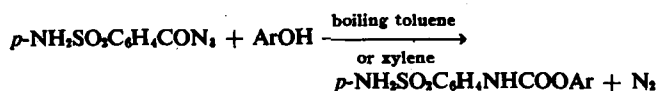
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Abstract □ Several polyhalophenyl esters of *p*-sulfamoylcarbanilic acid were prepared and tested for antifungal activity against *Candida albicans*, *Penicillium notatum*, and *Aspergillus niger*. Pentachloro-, tribromo-, and triiodophenyl esters were found to be the most active.

Keyphrases □ *p*-Sulfamoylcarbanilic acid, polyhalophenyl esters—synthesized and screened as potential antifungal agents □ Antifungal agents, potential—synthesis and screening of polyhalophenyl esters of *p*-sulfamoylcarbanilic acid

Recently, it was reported that polyhalophenyl esters of *p*-substituted carbamic acids as well as polyhalophenyl esters of pyridyl- and quinolyl-4-carbamic acids (1, 2) showed significant antifungal activities.

In the present work, a series of polyhalophenyl esters of *p*-sulfamoylcarbanilic acid was prepared by interaction of *p*-sulfamoylbenzoyl azide and the appropriate phenol in boiling toluene or xylene (Scheme I).



Scheme I

The physical data of all new compounds are reported in Table I. The antifungal activity of all compounds was determined¹ *in vitro* against *Candida albicans* 1959-2, *Penicillium notatum* 154-3, and *Aspergillus niger* A-23. Concentrations of 5, 10, and 25 mcg./ml. of each compound were used.

Compounds II-IV were dissolved in acetone, Compounds I and V were dissolved in 60% ethanol, and Compounds VI-XI were dissolved in 96% ethanol, all at concentrations of 5 mg./10 ml. These solutions were diluted with hot culture medium to the desired concen-

¹ Using BBL Sabouraud dextrose agar medium. The microorganisms were obtained from the Department of Parasitology, Public Health Institute, Iran.

Table I—Physical Constants of Substituted Polyhalophenyl Esters of *p*-Sulfamoylcarbanilic Acid

Compound Number	R	Yield, %	Melting Point	Formula	Analysis, %		
					Calc.	Found	
I	Ethyl	70	235 ^a	C ₉ H ₁₂ N ₂ O ₄ S	C	44.26	44.10
II	Phenyl	25	160 ^b	C ₁₃ H ₁₂ N ₂ O ₄ S	H	4.91	5.11
					C	53.42	53.10
III	<i>p</i> -Tolyl	40	215 ^b	C ₁₄ H ₁₄ N ₂ O ₄ S	H	4.10	3.90
					C	55.08	55.15
IV	<i>p</i> -Nitrophenyl	20	235–236 ^b	C ₁₃ H ₁₁ N ₃ O ₆ S	H	4.59	4.62
					C	48.29	48.26
V	<i>p</i> -Chlorophenyl	50	225 ^a	C ₁₃ H ₁₁ Cl ₂ N ₂ O ₄ S	H	3.40	3.48
					C	47.77	47.80
VI	2,4-Dichlorophenyl	70	240 ^a	C ₁₃ H ₁₀ Cl ₂ N ₂ O ₄ S	H	3.36	3.32
					C	43.21	43.10
VII	2,4,5-Trichlorophenyl	40	212 ^a	C ₁₃ H ₉ Cl ₃ N ₂ O ₄ S	H	2.77	2.80
					C	39.44	39.15
VIII	2,4,6-Trichlorophenyl	30	215 ^a	C ₁₃ H ₉ Cl ₃ N ₂ O ₄ S	H	2.27	2.30
					C	39.44	39.42
IX	2,4,6-Tribromophenyl	60	230 ^a	C ₁₃ H ₉ Br ₃ N ₂ O ₄ S	H	2.27	2.24
					C	29.48	29.51
X	2,4,6-Triiodophenyl	70	220 ^a	C ₁₃ H ₉ I ₃ N ₂ O ₄ S	H	1.70	1.65
					C	23.28	23.32
XI	Pentachlorophenyl	70	195 ^a	C ₁₃ H ₇ Cl ₅ N ₂ O ₄ S	H	1.34	1.32
					C	33.58	33.58
					H	1.93	1.89

^a Recrystallized from ethanol plus water. ^b Recrystallized from acetone.

Table II—Antifungal Activity of Some Polyhalophenyl Esters of *p*-Sulfamoylcarbanilic Acid^a

Compound	<i>Penicillium notatum</i>			<i>Candida albicans</i>			<i>Aspergillus niger</i>		
	5 mcg./ml.	10 mcg./ml.	25 mcg./ml.	5 mcg./ml.	10 mcg./ml.	25 mcg./ml.	5 mcg./ml.	10 mcg./ml.	25 mcg./ml.
IX	—	—	+	—	—	+	—	+	2+
X	—	+	2+	+	2+	2+	+	2+	2+
XI	+	2+	2+	2+	2+	2+	—	2+	2+

^a — equals no inhibition, 2+ equals complete inhibition.

trations and autoclaved at 120° for 2 hr. Five replicates of each concentration were prepared. The antifungal activities of pentachloro-, tribromo-, and triiodophenyl esters are reported in Table II. The antifungal activities of all other compounds were insignificant. The pentachlorophenyl ester was the most active of this series.

EXPERIMENTAL³

p-Sulfamoylbenzoylhydrazide was prepared according to Shimizu *et al.* (3).

Preparation of *p*-Sulfamoylbenzoyl Azide—To an ice-cold solution of 2.15 g. (10 mmoles) of *p*-sulfamoylbenzoylhydrazide in 50% acetic acid (25 ml.), a 5% aqueous solution of 0.69 g. (10 mmoles) of sodium nitrite was added with stirring. The resulting precipitate was filtered, washed with cold water, and dried to give 1.92 g. (85%) of *p*-sulfamoylbenzoyl azide, m.p. 100° dec.

Preparation of *p*-Sulfamoylcarbanilic Acid Ethyl Ester—A solution of *p*-sulfamoylbenzoyl azide, 2.26 g. (10 mmoles), in 15 ml. of ethanol was refluxed for 4 hr. The reaction mixture was diluted with water, the resulting precipitate was filtered, and the solid was recrystallized from aqueous ethanol to give 1.70 g. (70%) of the title

compound, m.p. 235°; NMR (CF₃CO₂H): τ 9.2 (t, 3H, CH₃), 6.1 (q, 2H, CH₂), 2.7 (q, 4H, ArH), and 2.3 (s, 2H, NH₂).

Preparation of *p*-Sulfamoylcarbanilic Acid Pentachlorophenyl Ester—A solution of 0.452 g. (2 mmoles) of *p*-sulfamoylbenzoyl azide and 0.355 g. (2 mmoles) of pentachlorophenol in 20 ml. of dry toluene was gently refluxed for 4 hr. After evaporation of the solvent under reduced pressure, the residue was recrystallized from 96% ethanol to give 0.650 g. (70%) of the title compound, m.p. 195°; IR (KBr) ν_{max}: 3400, 3320 (C—H and N—H), 1700 (C=O), 1595, 1540 (carbamate)(C—H), 1415, 1390, 1210, 1060 (C—H), 1300, and 1152 (SO₂NH₂) cm.⁻¹.

All other carbanilic acid derivatives were prepared similarly (Table I).

REFERENCES

- (1) I. Lalezari and H. Golgolab, *J. Med. Chem.*, **14**, 1017(1971).
- (2) I. Lalezari, H. Golgolab, and M. Emami, *ibid.*, **14**, 1123(1971).
- (3) M. Shimizu, T. Naito, G. Ohta, K. Suzuki, A. Kasaharo, K. Murai, and K. Asano, *J. Pharm. Soc. Jap.*, **72**, 1939(1952).
- (4) F. Bergmann, *J. Amer. Chem. Soc.*, **68**, 765(1946).

ACKNOWLEDGMENTS AND ADDRESSES

Received August 1, 1972, from the Departments of Biochemistry, Parasitology, and Chemistry, University of Tehran, Tehran, Iran.

Accepted for publication September 27, 1972.

The authors are grateful to Dr. C. Mofidi for his encouragement.

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³ Melting points were taken on a Kofler hot-stage microscope and are uncorrected. The IR spectra were determined with a Leitz model III spectrophotometer. NMR spectra were obtained on a Varian A 60A instrument.