tion distilling at 60–61.5° was collected. Longer or shorter reaction times and higher or lower temperatures failed to produce a yield in excess of 18%. Vapor phase chromatographic analysis of the products from various experiments indicated a purity of 70–90%. Redistillation of the 60–61.5° fraction afforded little additional purity. This material was used in the reaction with benzylamine. The purest sample was employed in spectral studies; IR (neat): 2150 (—C≡CH) cm.$^{-1}$; NMR (CCl_4): 1.65 (d, 3, C—CH_3), 2.43 (d, 1, —C≡CH), and 4.50 (quartet of doublets, 1, Cl—CH).

N-3-(1-Butynyl)-benzylamine Hydrochloride—Similar to a procedure described by Hennion and Nelson (7), a mixture of the above chloro compound (2.5 g.), benzylamine (13.1 g.), and water (3.2 ml.) was stirred at room temperature for 60 hr. At the end of this time, an equal volume of water (15 ml.) was added and two phases formed. The upper layer (organic phase) was separated, and the bottom layer (aqueous phase) was diluted again with an equal volume of water. Again two phases formed and the upper layer was combined with the first. Ether (25 ml.) was added, this solution was washed with water (2 × 5 ml.) and dried over potassium hydroxide, and the ether was removed *in vacuo*. The residue was distilled through a Vigreaux column, and the fraction distilling at 168–172°/17 mm. Hg was collected; IR (neat): 3400 (>NH) and 2150 (—C≡CH) cm.$^{-1}$; NMR (CCl_4): 1.31 (d, 3, C—CH_3), 2.16 (d, 1, —C≡CH), 3.38 (quartet of doublets, 1, N—CH), 3.88 (d, 2, $ArCH_2$), and 7.22 (s, 5, ArH). This fraction was dissolved in 50 ml. of anhydrous ether, and hydrogen chloride gas was passed through the solution, giving 1.2 g. of a white solid (22% yield based on pure 3-chloro-1-butyne). Several crystallizations from benzene afforded an analytically pure sample, m.p. 210.5–211.5°.

Anal.—Calc. for $C_{11}H_{11}ClN$: C, 67.52; H, 7.16; N, 7.16. Found: C, 67.37; H, 6.97; N, 7.00.

REFERENCES

(1) L. R. Swett, W. B. Martin, J. D. Taylor, G. M. Everett, A. A. Wykes, and Y. C. Gladish, *Ann. N.Y. Acad. Sci.*, **107**, 891(1963).

(2) G. M. Everett and R. G. Wiegand, *Proc. Int. Pharmacol. Meet., 1st*, **8**, 85(1962).

(3) G. M. Everett, R. G. Wiegand, and F. U. Rinaldi, *Ann. N.Y. Acad. Sci.*, **107**, 1068(1963).

(4) W. Lovenberg, R. J. Levine, and A. S. Sjoerdsma, *J. Pharmacol. Exp. Ther.*, **135**, 7(1962).

(5) G. F. Hennion and J. J. Sheehan, *J. Amer. Chem. Soc.*, **71**, 1964(1949).

(6) G. F. Hennion, J. J. Sheehan, and D. E. Maloney, *ibid.*, **72**, 3542(1950).

(7) G. F. Hennion and K. W. Nelson, *ibid.*, **79**, 2142(1957).

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Synthesis and Antifungal Activity of Polyhalophenyl Esters of Pyridyl- and 4-Quinolylcarbamic Acids IV

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Abstract □ Polyhalophenyl esters of 2-, 3-, and 4-pyridyl- and 2-phenyl-4-quinolylcarbamic acids were synthesized. All prepared compounds inhibited the growth of *Candida albicans* at 50-mcg./ml. concentration.

Keyphrases □ Pyridylcarbamic acid, polyhalophenyl esters—synthesis, antifungal activity □ 2-Phenyl-4-quinolylcarbamic acid, polyhalophenyl esters—synthesis, antifungal activity □ Carbamic acid esters—synthesis, antifungal activity □ Antifungal agents, potential—polyhalophenyl esters of pyridyl- and 2-phenyl-4-quinolylcarbamic acids

In a continuation of the studies on the chemistry and antifungal activity of substituted carbamic acid esters (1–3), polyhalophenyl esters of 2-, 3-, and 4-pyridyl- and 2-phenyl-4-quinolylcarbamic acids were synthesized by interaction of the appropriate azide and polyhalophenol (Scheme I).

$$RCOCl \rightarrow RCON_3 \rightarrow RNHCO_2Ar$$

R = 2-, 3-, or 4-pyridyl or 2-phenyl-4-quinolyl
Ar = 2,4,6-tribromophenyl, 2,4,6-trichlorophenyl, 2,4,6-triiodophenyl, or pentachlorophenyl

Scheme I

EXPERIMENTAL[1]

Picolinyl azide was prepared according to Meyer and Mally (4). Nicotinyl azide was prepared by the method of Curtius and Mohr (5). Isonicotinyl azide was synthesized according to Yoshikowa (6). 2-Phenyl-4-quinolylcarboxazide was obtained by the method of John *et al.* (7).

2-Pyridylcarbamic Acid Pentachlorophenyl Ester—2-Pyridyl azide, 0.74 g. (5 mmoles), and 1.33 g. (5 mmoles) of pentachlorophenol in 30 ml. of dry toluene were gently refluxed for 30 min. After evaporation of the solvent under reduced pressure, the residue was recrystallized from 80% ethanol to give 1.16 g. (60%), m.p. 135°; *m/e* 384, 386, 388, and 390; ν_{max}: 2900, 1710, 1620, 1540, 1470, 1440, 1410, 1360, 1320, 1250, 1150, 995, 980, 880, 778, and 715 cm.$^{-1}$.

3-Pyridylcarbamic Acid 2,4,6-Triiodophenyl Ester—This compound was prepared in a similar manner to its pentachlorophenyl analog; *m/e* 592; ν_{max}: 3300, 1750, 1580, 1550, 1480, 1420, 1200, 1060, 1020, 850, 810, 780, 740, and 703 cm.$^{-1}$.

4-Pyridylcarbamic Acid 2,4,6-Triiodophenyl Ester—This compound was prepared in a similar manner to its pentachlorophenyl analog; *m/e* 592; NMR (dimethyl sulfoxide): τ 7.9–8.1 (d, 2H,

[1] Melting points were taken on a Kofler hot-stage microscope and are uncorrected. The IR spectra were determined with a Leitz model III spectrograph. NMR spectra were obtained on a Varian A60A instrument. Mass spectra were determined with a Varian Mat 111 instrument.

Table I—Polyhalophenyl Esters of Pyridyl- and 4-Quinolylcarbamic Acids

R	Ar	Melting Point	Yield, %	Formula[a]	RNHCO$_2$Ar Calc.	RNHCO$_2$Ar Found
2-Pyridyl	2,4,6-Trichlorophenyl	142°	25	$C_{12}H_7Cl_3N_2O_2$	C 45.35	45.30
					H 2.20	2.22
2-Pyridyl	2,4,6-Tribromophenyl	115°	20	$C_{12}H_7Br_3N_2O_2$	C 31.92	32.04
					H 1.55	1.60
2-Pyridyl	2,4,6-Triiodophenyl	140°	25	$C_{12}H_7I_3N_2O_2$	C 24.30	24.29
					H 1.18	1.11
2-Pyridyl	Pentachlorophenyl	135°	60	$C_{12}H_7Cl_5N_2O_2$	C 37.25	37.30
					H 1.29	1.28
3-Pyridyl	2,4,6-Trichlorophenyl	225°	25	$C_{12}H_7Cl_3N_2O_2$	C 45.35	45.33
					H 2.20	2.19
3-Pyridyl	2,4,6-Tribromophenyl	145°	30	$C_{12}H_7Br_3N_2O_2$	C 31.92	31.88
					H 1.55	1.62
3-Pyridyl	2,4,6-Triiodophenyl	165°	45	$C_{12}H_7I_3N_2O_2$	C 24.30	24.32
					H 1.18	1.20
3-Pyridyl	Pentachlorophenyl	90°	30	$C_{12}H_5Cl_5N_2O_2$	C 37.25	37.25
					H 1.29	1.31
4-Pyridyl	2,4,6-Trichlorophenyl	146°	60	$C_{12}H_7Cl_3N_2O_2$	C 45.35	45.38
					H 2.20	2.27
4-Pyridyl	2,4,6-Tribromophenyl	160°	20	$C_{12}H_7Br_3N_2O_2$	C 31.92	31.99
					H 1.55	1.48
4-Pyridyl	2,4,6-Triiodophenyl	145°	50	$C_{12}H_7I_3N_2O_2$	C 24.30	24.33
					H 1.18	2.01
4-Pyridyl	Pentachlorophenyl	130°	35	$C_{12}H_5Cl_5N_2O_2$	C 37.25	37.37
					H 1.29	1.21
2-Phenyl-4-quinolyl	2,4,6-Trichlorophenyl	167°	80	$C_{22}H_{13}Cl_3N_2O_2$	C 59.52	60.01
					H 2.93	3.03
2-Phenyl-4-quinolyl	2,4,6-Tribromophenyl	175°	65	$C_{22}H_{13}Br_3N_2O_2$	C 45.75	45.60
					H 2.25	2.26
2-Phenyl-4-quinolyl	2,4,6-Triiodophenyl	180°	45	$C_{22}H_{13}I_3N_2O_2$	C 36.76	36.70
					H 1.81	1.86
2-Phenyl-4-quinolyl	Pentachlorophenyl	135°	60	$C_{22}H_{11}Cl_5N_2O_2$	C 51.51	51.40
					H 2.14	2.22

[a] IR, NMR, and mass spectra of all compounds were as expected.

α-hydrogens), 7.69 (s, 2H, aromatic H), 7.35 (s, 1H, NH), and 6.65–6.85 (d, 2H, β-hydrogens).

2-Phenyl-4-quinolylcarbamic Acid 2,4,6-Tribromophenyl Ester—This compound was prepared in a similar manner to the pyridyl analog; ν_{max}: 3330, 3050, 1755, 1615, 1560, 1538, 1445, 1380, 1280, 1200, 995, 860, 810, 775, 765, 745, and 690 cm.$^{-1}$.

All other compounds were prepared similarly. The physical data of prepared compounds are listed in Table I.

All prepared compounds were tested against *Candida albicans*[1] *in vitro* using BBL Sabouraud dextrose agar medium. Concentrations of 10 and 50 mcg./ml. of each compound were used. Compounds were dissolved in acetone, diluted with hot culture medium to the desired concentration, and autoclaved at 120° for 1 hr.

Pentachlorophenyl esters of 2-pyridyl- and 2-phenyl-4-quinolylcarbamic acids inhibited the growth at 10 mcg./ml. concentrations against the blank. Slight growth inhibition was observed with other compounds at the same concentrations.

After 5 days at 28°, the growth was entirely inhibited with 50-mcg./ml. concentrations of all compounds prepared.

[1] This microorganism was obtained from the Department of Parasitology, Public Health Institute, Tehran, Iran.

REFERENCES

(1) N. Sharghi, I. Lalezari, G. Niloufari, and F. Ghabgharan, *J. Med. Chem.*, **13**, 1248(1970).

(2) I. Lalezari and H. Golgolab, *ibid.*, **14**, 1017(1971).

(3) I. Lalezari, H. Golgolab, and M. Emami, *ibid.*, **14**, 1123 (1971).

(4) H. Meyer and J. Mally, *Monatsh. Chem.*, **33**, 397(1912).

(5) T. Curtius and E. Mohr, *Chem. Ber.*, **31**, 2493(1898).

(6) T. Yoshikowa, *Yakugaku Zasshi*, **78**, 479(1958); through *Chem. Abstr.*, **52**, 17265(1958).

(7) H. John, V. Grossmann, and V. Fischl, *Chem. Ber.*, **59**, 1448(1926).

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