# Synthesis and Antibacterial and Antifungal Activities of 5-Nitro-2-furfurylidene Polyhalophenoxyacethydrazides VIII

F. AFGHAHI ˣ, S. YAZDANY, and I. LALEZARI

**Abstract** □ Fifteen 5-nitro-2-furfurylidene phenoxyacethydrazides were synthesized, and the antibacterial and antifungal activities of the compounds prepared were determined against different microorganisms. The *o*-methoxy derivative was found to be the most active compound.

**Keyphrases** □ 5-Nitro-2-furfurylidene polyhalophenoxyacethydrazides—synthesis, antibacterial and antifungal activities □ Antibacterial and antifungal activities—5-nitro-2-furfurylidene polyhalophenoxyacethydrazides □ Antifungal and antibacterial activities—5-nitro-2-furfurylidene polyhalophenoxyacethydrazides

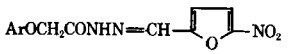
Recently, it was shown that 5-nitro-2-furfurylidene arylthioacethydrazides and 5-nitro-2-furfurylidene arylsulfonylacethydrazides (1) as well as 5-nitro-2-furfurylidene *p*-sulfonyl- and *p*-sulfamoylbenzhydrazides (2) displayed antibacterial activity. Several polyhalophenyl esters of substituted carbamic and carbanilic acids also were found to inhibit the growth of some fungi (3–6). On the basis of these observations, it was of interest to investigate the antibacterial and antifungal activities of compounds having both polyhalophenyl and 5-nitro-2-furfurylidene groups in their molecules.

A series of 5-nitro-2-furfurylidene polyhalophenoxyacethydrazides was prepared by interaction of 5-nitro-2-furfural and appropriate phenoxyacethydrazides. Several other 5-nitro-2-furfurylidene phenoxyacethydrazides were also synthesized for comparison of biological activity. *o*-Methoxy-5-nitro-2-furfurylidene phenoxyacethydrazide (Compound 5) was found to be the most active compound of this series. All compounds prepared are listed in Table I.

## DISCUSSION

All compounds prepared were tested against *Bacillus subtilis* (NCTC 3610), *Klebsiella pneumoniae* (ATCC 10031), *Sarcina lutea* (ATCC 9341), *Staphylococcus aureus* (ATCC 6538), and *Bacillus cereus* (NCIB 9373). Nitrofurazone was used as a control. The compounds were dissolved in dimethylformamide at 0.5% concentration. Standard paper disks of 6-mm diameter were im-

**Table I**—5-Nitro-2-furfurylidene Polyhalophenoxyacethydrazide



| Compound | Ar | Melting Point | Yield, % | Formula | Analysis, % Calc. | Found |
|---|---|---|---|---|---|---|
| 1 | $C_6H_5$ | 155° | 83 | $C_{13}H_{11}N_3O_5$ | C 53.97 | 54.06 |
| | | | | | H 3.80 | 3.70 |
| 2 | *o*-$CH_3C_6H_4$ | 163–164° | 72 | $C_{14}H_{13}N_3O_5$ | C 55.44 | 55.31 |
| | | | | | H 4.29 | 4.33 |
| 3 | *m*-$CH_3C_6H_4$ | 183–185° | 78 | $C_{14}H_{13}N_3O_5$ | C 55.44 | 55.51 |
| | | | | | H 4.29 | 4.28 |
| 4 | *p*-$CH_3C_6H_4$ | 178° | 80 | $C_{14}H_{13}N_3O_5$ | C 55.44 | 55.41 |
| | | | | | H 4.29 | 4.22 |
| 5 | *o*-$CH_3OC_6H_4$ | 176–179° | 66 | $C_{14}H_{13}N_3O_6$ | C 52.66 | 52.69 |
| | | | | | H 4.07 | 3.96 |
| 6 | *m*-$ClC_6H_4$ | 198° | 89 | $C_{13}H_{10}ClN_3O_5$ | C 48.22 | 48.20 |
| | | | | | H 3.09 | 3.11 |
| 7 | *p*-$ClC_6H_4$ | 195–198° | 82 | $C_{13}H_{10}ClN_3O_5$ | C 48.22 | 48.20 |
| | | | | | H 3.09 | 3.02 |
| 8 | *p*-$BrC_6H_4$ | 190–191° | 85 | $C_{13}H_{10}BrN_3O_5$ | C 42.39 | 42.42 |
| | | | | | H 2.71 | 2.76 |
| 9 | 2,4-$Cl_2C_6H_3$ | 220–222° | 91 | $C_{13}H_9Cl_2N_3O_5$ | C 43.57 | 43.50 |
| | | | | | H 2.51 | 2.55 |
| 10 | 2,4,5-$Cl_3C_6H_2$ | 210° | 71 | $C_{13}H_8Cl_3N_3O_5$ | C 39.74 | 39.69 |
| | | | | | H 2.03 | 2.08 |
| 11 | 2,4,6-$Cl_3C_6H_2$ | 195° | 80 | $C_{13}H_8Cl_3N_3O_5$ | C 39.74 | 39.70 |
| | | | | | H 2.03 | 2.00 |
| 12 | $C_6Cl_5$ | 255–260° | 74 | $C_{13}H_6Cl_5N_3O_5$ | C 33.80 | 33.72 |
| | | | | | H 1.32 | 1.39 |
| 13 | *m*-$NO_2C_6H_4$ | 200° | 69 | $C_{13}H_{10}N_4O_7$ | C 46.70 | 46.66 |
| | | | | | H 2.99 | 3.05 |
| 14 | *p*-$NO_2C_6H_4$ | 254° | 71 | $C_{13}H_{10}N_4O_7$ | C 46.70 | 46.71 |
| | | | | | H 2.99 | 2.90 |
| 15 | Thymyl | 160–162° | 76 | $C_{17}H_{19}N_3O_5$ | C 59.13 | 59.19 |
| | | | | | H 5.50 | 5.43 |

**Table II**—Antibacterial Activity

| Compound | Zone of Inhibition, Average Size, mm | | | | |
|---|---|---|---|---|---|
| | *B. subtilis* | *K. pneumoniae* | *S. lutea* | *Staph. aureus* | *B. cereus* |
| 1 | 11 | — | — | 14[a] | 15 |
| 2 | 11 | — | — | 15[a] | 16 |
| 3 | 18 | — | — | 18[a] | 21 |
| 4 | 14 | 15 | — | 19[a] | 18 |
| 5 | 21 | 14 | 14 | 19 | 20 |
| 6 | 12 | — | — | 12 | 20 |
| 7 | 8 | — | — | 12[a] | 20 |
| 8 | 13 | 13 | — | 15 | 20 |
| 9 | — | — | — | 15[a] | 20 |
| 10 | — | — | — | — | 20 |
| 11 | — | — | — | 12[a] | 20 |
| 12 | 13 | 8 | 15 | 15 | 15 |
| 13 | 12 | 12 | 8 | 15 | 18 |
| 14 | — | — | — | — | — |
| 15 | 12 | 12 | 16 | 12[a] | 16 |
| Nitrofurazone | 23 | 20 | 17 | 20 | 21 |

[a] Inhibition zones were hazy.

mersed in solution and placed on an inoculated assay medium surface[1]. Disks containing pure dimethylformamide were used as controls and did not show antibacterial activity. There were four replicates for each compound. The antibacterial activity of the compounds prepared is reported in Table II.

All compounds prepared were also tested against *Candida albicans*[2] (1959-2), *Penicillium notatum*[2] (154-3), and *Aspergillus niger*[2] (A-23). Concentrations of 10, 25, and 50 μg/ml were used. The compounds were dissolved in dimethylformamide at concentrations of 5 mg/ml, and these solutions were diluted with hot sterile culture medium[3] to the desired concentrations. Griseofulvin was used as a control. A culture medium containing pure dimethylformamide was used and did not show antifungal activity. The antifungal activity of all tested compounds and griseofulvin was insignificant at concentrations of 10 and 25 μg/ml. The antifungal activity of the compounds at the 50-μg/ml concentration is reported in Table III.

## EXPERIMENTAL[4]

**Substituted Ethyl Phenoxyacetates**—These compounds were prepared by interaction of the appropriate sodium phenolate and ethyl chloroacetate or ethyl bromoacetate in boiling ethanol as described by Haskelberg (7).

**Pentachlorophenoxyacethydrazide**—To a solution of 3 g (0.01 mole) of ethyl pentachlorophenoxyacetate (7) in 35 ml of ethanol, 2 ml (0.03 mole) of 80% hydrazine hydrate was added and the solution was allowed to stand for 8 hr at room temperature. After cooling, the crystalline mass was filtered and recrystallized from 95% ethanol to give 2.64 g (78%) of hydrazide as white crystals, mp 210–215°; molecular weight by mass spectrometry, *m/e* 337–339; IR: $\nu_{max}$ 3300, 1663, 1541, 1422, 1385, 1344, 1292, 808, and 707 $cm^{-1}$.

*Anal.*—Calc. for $C_7H_5Cl_5N_2O_2$: C, 28.36; H, 1.48. Found: C, 28.29; H, 1.53.

**5-Nitro-2-furfurylidene Pentachlorophenoxyacethydrazide (Compound 12)**—Pentachlorophenoxyacethydrazide (0.338 g, 1 mmole) was dissolved in 10 ml of alcohol and treated with a solution of 0.141 g (1 mmole) of 5-nitro-2-furaldehyde in 5 ml of alcohol. The reaction mixture was warmed gently on a water bath for 15 min. After cooling, the precipitate was filtered and recrystallized from dimethylformamide–water (7:3) to give 0.341 g (74%) of the desired compound, mp 255–260°; molecular weight by mass spectrometry *m/e* 461–462; IR: $\nu_{max}$ 3100, 1690, 1541, 1472, 1396, 1351, 1250, 1051, 955, 916, 783, and 710 $cm^{-1}$; $UV_{max}$ 375 nm.

All other 5-nitro-2-furfurylidene derivatives were prepared similarly (Table I).

**Table III**—Antifungal Activity[a] of 5-Nitro-2-furfurylidene Polyhalophenoxyacethydrazides

| Compound | *C. albicans* | *P. notatum* | *A. niger* |
|---|---|---|---|
| 1 | + | + | + |
| 2 | + | + | + |
| 3 | − | + | − |
| 4 | + | + | − |
| 5 | + | + | − |
| 6 | + | + | + |
| 7 | − | + | − |
| 8 | − | − | − |
| 9 | − | + | − |
| 10 | − | + | + |
| 11 | − | + | − |
| 12 | + | + | + |
| 13 | − | + | − |
| 14 | − | + | − |
| 15 | + | + | − |
| Griseofulvin | + | + | + |

[a] + = complete inhibition, and − = no inhibition.

## REFERENCES


(1) I. Lalezari, P. Lowlavar, and N. Mazhari, *J. Med. Chem.*, **15**, 115(1972).

(2) I. Lalezari, V. Gharavi, and N. Mazhari, *J. Pharm. Sci.*, **63**, 1485(1974).

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

(4) I. Lalezari, H. Golgolab, A. Shafiee, and M. Wossoughi, *J. Pharm. Sci.*, **62**, 332(1973).

(5) A. Shafiee, I. Lalezari, S. Yazdany, and A. Pournorouz, *ibid.*, **62**, 839(1973).

(6) I. Lalezari, G. Mohtat, F. Afghahi, and M. Alilou, *ibid.*, **62**, 1733(1973).

(7) L. Haskelberg, *J. Org. Chem.*, **12**, 426(1943).


## ACKNOWLEDGMENTS AND ADDRESSES


Received June 25, 1974, from the *Department of Chemistry and Industrial Pharmacy, University of Tehran, Tehran, Iran.*

Accepted for publication October 8, 1974.

The authors are indebted to Dr. A. Vaziri of Isfehan University for scientific advice.



[x] To whom inquiries should be directed.


[1] BBL antibiotic assay medium 1.

[2] Microorganisms were obtained from the Department of Parasitology, Public Health Institute, Tehran, Iran.

[3] Difco Sabouraud dextrose agar medium.

[4] Melting points were taken on a Kofler hot-stage microscope and are uncorrected. IR spectra were recorded on a Leitz model III spectrograph. UV spectra were obtained on a Varian Techtron 635 instrument. NMR spectra were taken on a Varian A60A instrument. Mass spectra were recorded on a Varian Mat 111 spectrograph. All compounds were subjected to IR, NMR, and mass spectrometry and the results were as expected.