Preparation and Fungicidal Activity of 5-Substituted Hydantoins and Their 2-Thio Analogs

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5-(Arylmethylene)hydantoins (4–19) and 5-(arylmethylene)-2-thiohydantoins (20–37) have been synthesized by condensation of aromatic aldehydes with hydantoin (1) or 2-thiohydantoin (2) in the presence of ethanolamine. A number of 5-alkyl- and 5-(arylmethyl)hydantoins (40–48) and their 2-thio analogs (50–55) were synthesized from amino acids. All of these compounds were tested for pesticidal activity.

INTRODUCTION

The biological activity of hydantoin and 2-thiohydantoin derivatives has been known for a long time. The hydantoin nucleus containing an active urea moiety is responsible for a variety of biological activities such as antiarrhythmic (Havera and Strycker, 1976; Somma et al., 1981; Vidrio et al., 1980), antihypertensive (Blaha and Weichet, 1974; Warner-Lambert Co., 1984), antiviral (Bharucha et al., 1974), antineoplastic (Peng et al., 1975), anticonvulsant (Cortes et al., 1985), and antimycobacterial activities (Zaidi et al., 1980). Hydantoins also exhibit platelet aggregation (Barraclough et al., 1989) and aldose reductase (Sarges et al., 1988; Rizzi et al., 1989) inhibition.

Hydantoins are also utilized as pesticides. Some hydantoin derivatives possess a herbicidal activity. It was found that, e.g., the 3-(dihalogenomethoxycarbonyloxyphenyl)-5-isopropylidenehydantoin compounds (Hirai et al., 1988), 5-(aminomethylene)hydantoins (Prisbylla, 1989), and phosphorylaminophenylhydantoins (Theodoridis, 1990) have herbicidal activity. Hydantocidin, a new herbicidal natural product (Sugai et al., 1990), is a unique type of herbicide.

Compounds with a hydantoin skeleton exhibited bactericidal as well as fungicidal activities. The most important hydantoin fungicide, iprodione [3-(3,5-dichlorophenyl)-*N*-isopropyl-2,4-dioxoimidazolidine-1-carboxamide] (Sauli, 1972), is primarily a contact fungicide, inhibiting simultaneously the germination of spores and the growth of fungus mycelium. Hydantoin fungicides are environmentally safe because they degrade in the soil to biologically inactive compounds (Burgaud et al., 1975). A number of publications have been made about the fungicidal and bactericidal activity of hydantoins and their 2-thio analogs (Tottori et al., 1974; Hubele, 1975; Delegan et al., 1978; Lebed and Lebedeva, 1980; Moore, 1986; Kujundzic et al., 1988). Other authors (Matolcsy et al., 1969) have tested 5-(benzylidene)- and 5-(furfurylidene)-2-thiohydantoin for antifungal activity on *Alternaria tennuis* and *Botrytis alli*. 5-(4-Chlorobenzylidene)hydantoin and four (chlorosulfonylbenzylidene)hydantoins were highly active against vine downy mildew and wheat rust (Cremlyn et al., 1988). Several 5-substituted hydantoins and 2-thiohydantoins showed fungicidal and bactericidal activity (Ghoneim et al., 1987).

Now we report the synthesis and fungicidal activity of 5-(arylmethylene)hydantoins and 5-alkyl- and 5-(arylmethyl)hydantoins and their 2-thio analogs.

EXPERIMENTAL PROCEDURES

General Methods. All melting points were measured on a Koffler hot-stage apparatus and are uncorrected. TLC was performed on a Kieselgel 60 F_{254} (Merck) layer using benzene–methanol 8:2 (v/v) and chloroform–methanol 9:1 (v/v) eluents. ^{1}H NMR spectra were recorded on a Bruker WP 200 SY instrument at 200 MHz using TMS as an internal standard in DMSO-d_6. Chemical shifts are given in ppm (δ). Mass spectra were scanned on a VG 7035 (GC–MS-DS) instrument in EI mode at 70 eV.

Hydantoin (1), which was necessary for our studies, was synthesized from glycine and urea without isolation of hydantoic acid (Hosztafi et al., 1985); 2-thiohydantoin was prepared from glycine and ammonium thiocyanate via 1-acetyl-2-thiohydantoin (Thielemann, 1978).

Hydantoin (1). A mixture of 7.5 g (100 mmol) of glycine, 14.0 g (230 mmol) of urea, and 12 mL of water was stirred and refluxed for 12 h. Then the reaction mixture was cooled in an ice–water bath, and 9 mL of sulfuric acid was dropped in. Heating was continued for an additional 1 h. The mixture was allowed to stand at 0–5 °C in the refrigerator for 1 h. The crystalline product was collected by filtration. The mother liquor was evaporated to dryness and the residue crystallized from water or acetic acid. The total yield was 7.1 g (70%): $C_3H_4N_2O_2$ M_w 100.08; mp 220–22 °C; ^{1}H NMR (DMSO-d_6) δ 3.85 (s, CH_2, 2 H), 7.72 (s, N1H, 1 H), 10.62 (s, N3H, 1 H); MS (EI, 70 eV) 100 (M^+, 100).

1-Acetyl-2-thiohydantoin was obtained from glycine and ammonium thiocyanate in acetic anhydride in the presence of acetic acid according to the literature (Thielemann, 1978). The yield was 68%: $C_5H_6N_2O_2S$ M_w 158.18; mp 176 °C; ^{1}H NMR (DMSO-d_6) δ 2.68 (s, $NCOCH_3$, 3 H), 4.42 (s, CH_2, 2 H), 12.60 (s, N3H, 1 H); MS (EI, 70 eV) 158 (M^+, 95), 116 (100).

2-Thiohydantoin (2). 1-Acetyl-2-thiohydantoin (1.58 g, 10 mmol) was mixed with 16 mL of 10% (m/m) hydrochloric acid and heated under refluxing conditions for 1 h. Afterward, the reaction mixture was treated with active carbon and filtered hot. It was purified by repeated crystallization from water. The yield of 2-thiohydantoin was 1.0 g (86%): $C_3H_4N_2OS$ M_w 116.14; mp 230–32 °C; ^{1}H NMR (DMSO-d_6) 4.08 (s, CH_2, 2 H), 9.95 (s, N1H, 1 H), 11.64 (s, N3H, 1 H); MS (EI, 70 eV) 116 (M^+, 100).

5-(Arylmethylene)hydantoins (4–19): General Procedure. Hydantoin (1; 1.0 g, 10 mmol) was dissolved in 10 mL of water at 70 °C. After the hydantoin had dissolved, the pH of the mixture was adjusted with saturated sodium hydrogen carbonate solution to 7. Then 0.9 mL of ethanolamine was added, and the temperature was increased to 90 °C. A solution of 10 mmol of aromatic aldehyde and 10 mL of ethanol was added dropwise and stirred for 4 h. Ethanol was removed by evaporation in vacuo, the solution was cooled, and the precipitate was filtered off. The characterization data of the products are recorded in Table I.

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Table I. Physical Data of Compounds Prepared

compd	substituents	yield, %	mp, °C	formula
4	$R_1 = R_2 = R_3 = R_4 = H$	89	220–222[a]	$C_{10}H_8N_2O_2$
5	$R_3 = OCH_3$, $R_1 = R_2 = R_4 = H$	85	242–244[a]	$C_{11}H_{10}N_2O_3$
6	$R_1 = OCH_3$, $R_2 = R_3 = R_4 = H$	83	177–178[a]	$C_{11}H_{10}N_2O_3$
7	$R_2 = R_3 = OCH_3$, $R_1 = R_4 = H$	77	283–284[a]	$C_{12}H_{12}N_2O_4$
8	$R_2 = R_3 = R_4 = OCH_3$, $R_1 = H$	87	266–267[c]	$C_{13}H_{14}N_2O_3$
9	$R_2R_3 = OCH_2O$, $R_1 = R_4 = H$	64	253–254[a]	$C_{11}H_8N_2O_4$
10	$R_1 = CH_3$, $R_2 = R_3 = R_4 = H$	65	244–245[a]	$C_{11}H_{10}N_2O_2$
11	$R_3 = OH$, $R_1 = R_2 = R_4 = H$	58	312–313[a]	$C_{10}H_8N_2O_3$
12	$R_1 = OH$, $R_2 = R_3 = R_4 = H$	92	293–295[d]	$C_{10}H_8N_2O_3$
13	$R_2 = OCH_3$, $R_3 = OH$, $R_1 = R_4 = H$	64	271–272[a]	$C_{11}H_{10}N_2O_4$
14	$R_2 = OH$, $R_3 = OCH_3$, $R_1 = R_4 = H$	65	304–305[a]	$C_{11}H_{10}N_2O_4$
15	$R_1 = OH$, $R_2 = OCH_3$, $R_3 = R_4 = H$	44	228–229[a]	$C_{11}H_{10}N_2O_4$
16	$R_3 = Cl$, $R_1 = R_2 = R_4 = H$	46	303–305[a]	$C_{10}H_7ClNO_2$
17	$R_1 = R_3 = Cl$, $R_2 = R_4 = H$	83	317–318[a]	$C_{10}H_6Cl_2NO_2$
18	$R_3 = NO_2$, $R_1 = R_2 = R_4 = H$	75	312–314[b]	$C_{10}H_7N_3O_4$
19	indol-3-ylmethylene	89	342–344[e]	$C_{12}H_9N_3O_2$
20	$R_1 = R_2 = R_3 = R_4 = H$	87	268–269[b]	$C_{10}H_8N_2OS$
21	$R_3 = OCH_3$, $R_1 = R_2 = R_4 = H$	89	264–265[b]	$C_{11}H_{10}N_2O_2S$
22	$R_1 = OCH_3$, $R_2 = R_3 = R_4 = H$	82	234–236[b]	$C_{11}H_{10}N_2O_2S$
23	$R_3 = OCH_3$, $R_1 = R_3 = R_4 = H$	76	239–241[b]	$C_{11}H_{10}N_2O_2S$
24	$R_2 = R_3 = OCH_3$, $R_1 = R_4 = H$	83	238–239[b]	$C_{12}H_{12}N_2O_3S$
25	$R_2 = R_3 = R_4 = OCH_3$, $R_1 = H$	74	243–245[b]	$C_{13}H_{14}N_2O_4S$
26	$R_3 = N(CH_3)_2$, $R_1 = R_2 = R_4 = H$	82	254–256[b]	$C_{12}H_{13}N_3OS$
27	$R_1 = OH$, $R_2 = R_3 = R_4 = H$	78	272–274[b]	$C_{10}H_8N_2O_2S$
28	$R_3 = OH$, $R_1 = R_2 = R_4 = H$	85	303–304[b]	$C_{10}H_8N_2OS$
29	$R_2 = OCH_3$, $R_3 = OH$, $R_1 = R_4 = H$	96	239–240[b]	$C_{11}H_{10}N_2O_3S$
30	$R_2 = OH$, $R_3 = OCH_3$, $R_1 = R_4 = H$	88	287–289[b]	$C_{11}H_{10}N_2O_3S$
31	$R_3 = Cl$, $R_1 = R_2 = R_4 = H$	92	281–282[b]	$C_{10}H_7ClN_2OS$
32	$R_2 = R_3 = Cl$, $R_1 = R_4 = H$	85	260–262[a]	$C_{10}H_6Cl_2N_2OS$
33	$R_1 = R_3 = Cl$, $R_2 = R_4 = H$	80	271–273[a]	$C_{10}H_6Cl_2N_2OS$
34	$R_3 = NO_2$, $R_1 = R_2 = R_4 = H$	90	294–296[b]	$C_{10}H_7N_3O_3S$
35	indol-3-ylmethylene	84	325–327[a]	$C_{12}H_9N_3OS$
36	thiophene-2-ylmethylene	96	252–253[a]	$C_8H_6N_2OS_2$
37	furan-2-ylmethylene	82	259–261[a]	$C_8H_8N_2O_2S$
40	$(CH_3)_2CHCH_2$–	51	213–214[b]	$C_7H_{12}N_2O_2$
41	$CH_3CH_2CH(CH_3)$–	41	207–208[b]	$C_7H_{12}N_2O_2$
42	$C_6H_5CH_2$–	92	187–189[b]	$C_{10}H_{10}N_2O_2$
43	p-$MeOC_6H_4CH_2$–	93	179–181[b]	$C_{11}H_{12}N_2O_3$
44	$(CH_3)_2C(SH)$–	77	247–248[b]	$C_8H_{10}N_2O_2S$
45	C_6H_5–	87	177–178[b]	$C_9H_8N_2O_2$
46	p-$OHC_6H_4CH_2$–	83	258–259[b]	$C_{10}H_{10}N_2O_3$
47	$(CH_3)_2CH$–	84	144–146[b]	$C_6H_{10}N_2O_2$
48	o-$CH_3C_6H_4CH_2$–	77	214–215[b]	$C_{11}H_{12}N_2O_2$
50	$C_6H_5CH_2$–	95	181–182[b]	$C_{10}H_{10}N_2OS$
51	$CH_3SCH_2CH_2$–	94	147–148[b]	$C_6H_{10}N_2OS_2$
52	$(CH_3)_2CH$–	85	135–136[b]	$C_6H_{10}N_2OS$
53	$(CH_3)_2CHCH_2$–	92	175–176[b]	$C_7H_{12}N_2OS$
54	C_6H_5–	91	227–228[b]	$C_9H_8N_2OS$
55	$CH_3CH_2CH(CH_3)$–	66	115–117[b]	$C_7H_{12}N_2OS$

[a] Acetic acid. [b] Ethanol. [c] Ethanol–chloroform 1:1 (v/v). [d] Methanol–water 1:1 (v/v). [e] Benzyl alcohol.

5-(Arylmethylene)-2-thiohydantoins (20–27): General Procedure. A mixture of 1.16 g (10 mmol) of 2-thiohydantoin (2), 10 mmol of aromatic aldehyde, 0.9 mL of ethanolamine, and 40 mL of ethanol was stirred at 80 °C. The reaction was monitored by TLC. Complete reaction was usually detected after ca. 30 min. The solution was concentrated under reduced pressure and cooled, and the product was filtered off. The characterization data of these compounds are recorded in Table I.

5-(4-Nitrobenzylidene)hydantoin (18) was prepared according to the procedure given for compounds 4–19, but two byproducts, *erythro-* and *threo*-4-nitro-α-(hydroxybenzyl)hydantoin (18a and 18b) also formed. The mixture was chromatographed on Kieselgel and eluted with chloroform–methanol 9:1 (v/v). The data of 18 are given in Table I. Howie et al. (1990) reported an efficient method for the preparation of 18, but we could not compare it with our method because the yields were absent.

5-Substituted Hydantoins from Amino Acids (40–42, 44–47). A mixture of 20 mmol of amino acid, 2.0 g of potassium cyanate (25 mmol), and 60 mL of water was stirred for 2 h at 100 °C. The solution was cooled, and the pH was adjusted with acetic acid to 4. The precipitate was collected and washed with cold water. Hydantoic acid was refluxed in 60 mL of 20% hydrochloric acid (m/m) for 2 h. The mixture was cooled, and the crystalline product was filtered off. The data of products are recorded in Table I.

5-Substituted 2-Thiohydantoins (50–55). A mixture of 20 mmol of amino acid, 1.8 g of ammonium thiocyanate (23 mmol), 20 mL of acetic anhydride, and 3 mL of acetic acid was stirred for 1 h at 100 °C. The solution was poured into water, and the precipitate was filtered off. The crude 1-acetyl-2-thiohydantoin was suspended in 30 mL of 10% hydrochloric acid (m/m) and refluxed for 1 h. The solution was cooled and allowed to stand at 4 °C overnight. The precipitated crystalline material was filtered off and washed with water (see Table I).

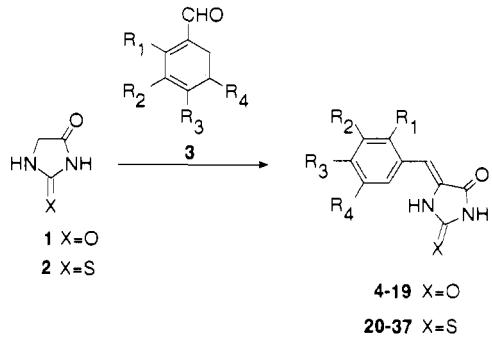
5-(2-Methylbenzyl)hydantoin (48) was synthesized from **10** by reduction with 47% hydroiodic acid in the presence of red phosphorus.

5-(4-Methoxybenzyl)hydantoin (43) was prepared from **5** by catalytic hydrogenation in 1 N sodium hydroxide solution in the presence of Raney Ni catalyst (Hosztafi et al., 1985).

RESULTS AND DISCUSSION

Synthesis. The synthesis of 5-(arylmethylene)hydantoins and 5-(arylmethylene)-2-thiohydantoins is demonstrated in Scheme I. The reaction of hydantoin (1) or 2-thiohydantoin (2) and aromatic aldehydes (3) results in

Scheme I

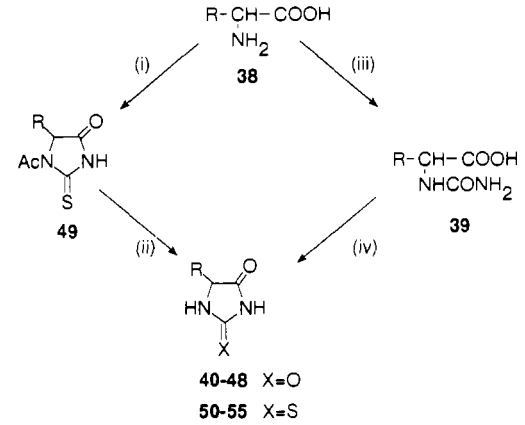


the corresponding 5-arylmethylene derivatives (**4–19** and **20–37**) as was first shown by Wheeler and Hoffmann (1911). They carried out the reaction in glacial acetic acid and acetic anhydride in the presence of fused sodium acetate. Boyd and Robson (1935) observed that the condensation of hydantoin and aromatic aldehydes occurred in pyridine in the presence of piperidine or diethylamine. Acetic acid (Billek, 1961; Kleemann et al., 1981), propionic acid (Kleemann et al., 1981), water (Hosztafi et al., 1985; Mirviss, 1986), and ethanol–water mixture (Imai et al., 1986) have also been used as condensation media. Sodium acetate (Billek, 1961), ethanolamine (Britton and Smith, 1958; Hosztafi et al., 1985), urea (Imaki and Takuma, 1986), ammonium bicarbonate (Mirviss, 1986), and amino acids or their salts (Tanaka and Nakayasu, 1986) have been used as condensation agents. 2-Thiohydantoin (**2**) and aromatic aldehydes were condensed in acetic acid in the presence of fused sodium acetate (Alberti and Vercellone, 1958) or in acetic acid in the presence of piperidine (Thielemann, 1971). It is evident that the ethanolamine method resulted in higher yields and purer material upon comparison with methods using other condensing agents. Mineral acids were used to precipitate the product in those procedures which applied ethanolamine as condensing agent. We found that it was unnecessary. We first carried out the condensation of 2-thiohydantoin with aromatic aldehydes in the presence of ethanolamine in ethanol. We found that in the first step of the reaction arylidene imines (Schiff bases) were formed. We isolated the Schiff base in some cases. The reaction of these bases with hydantoin or 2-thiohydantoin was rapid. The reaction did not take place in the absence of ethanolamine. The Schiff bases were the reactive species in this reaction, which played an important role in the arylidene transfer.

The synthesis of 5-substituted hydantoins and their 2-thio analogs is depicted in Scheme II. Hydantoic acids (**39**) were prepared from amino acids (**38**) under treatment with potassium cyanate in water (Dakin, 1910). These carbamoyl compounds were converted to hydantoins (**40–48**) under refluxing with 20% hydrochloric acid (m/m). 1-Acetyl-2-thiohydantoins were prepared from amino acids (**38**) with ammonium thiocyanate in the presence of acetic acid and acetic anhydride. These compounds were hydrolyzed to the corresponding 2-thiohydantoins (**50–55**) under refluxing with 10% hydrochloric acid (m/m).

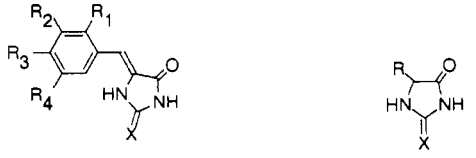
Due to the low solubilities of hydantoins in most nonpolar solvents, all ^{1}H NMR spectra have been recorded in DMSO-d_6. The derivatives were characterized by their chemical shifts and multiplicities. Chemical shifts of the olefin proton deviated slightly under the influence of hydantoin ring elements. For example, olefin protons of 5-(arylmethylene)hydantoins and 5-(arylmethylene)-2-thiohydantoins appeared as singlets at 6.38 (**7**, **13**), 6.78 (**19**), and 6.86 (**35**), respectively. The most interesting differences are found in the NH signals. The ^{1}H NMR

Scheme II [a]



[a] Reagents: (i) NH_4SCN; (ii) 10% HCl (m/m), reflux; (iii) KOCN; (iv) 20% HCl (m/m), reflux.

Table II. Fungicidal and Bactericidal Activity of 5-Substituted Hydantoins and Their 2-Thio Analogs[a]



compd	*E. graminis* f. sp. *tritici*, 1000 ppm	*P. leucotricha*, 1000 ppm	*U. appendiculatus*, 1000 ppm	*B. cinerea*, 1000 ppm	*E. carotovora*, 1000 ppm
8	0[b]	0	0	0	4
9	3	4	0	0	0
13	0	0	0	0	4
19	3	3	0	0	0
20	0	0	4	0	0
24	4	4	4	2	0
28	0	0	4	0	0
29	0	0	4	0	0
33	0	0	0	3	0
35	0	0	4	1	0
36	0	0	4	1	0
ziram	0	0	3	1	0

[a] **4**, **7**, **17**, **21**, **33**, **35**, **40**, **43**, **50**, and **52** were tested against the above parasites, but they were inactive. [b] 0 = 0–25%; 1 = 25.1–50%; 2 = 50.1–75%; 3 = 75.1–95%; 4 = 95.1–100% disease control related to water-sprayed plants.

spectra of the 5-(arylmethylene)hydantoins showed that N1 and N3 protons appeared at approximately 9.9 and 11.5, respectively. For example, the N1 proton of **5** resonated at 9.98 and the N3 proton at 10.63. The 4-nitro compound **18** gave the N1H signal at 10.92 and the N3H signal at 11.46. These singlets appeared between 11.80 (**35**, **37**)–12.50 (**32**) and 11.95 (**35**)–12.56 (**34**) in the case of 5-(arylmethylene)-2-thiohydantoins. The C5 proton peaks of the 5-substituted hydantoins and 2-thiohydantoins appeared between 3.93 (**47**) and 5.40 (**54**). The N1 and N3 protons of the 5-substituted hydantoins appeared in the region 7.84 (**46**)–8.40 (**45**) and 10.36 (**46**)–10.80 (**45**). In the case of the 2-thio analogs these peaks appeared between 9.00 (**51**)–10.48 (**54**) and 11.40 (**50**)–11.85 (**54**). Consequently, the chemical shifts of the N1 and N3 protons of hydantoins were assigned lower than those of the 2-thio analogs. The identification of these protons simplified after addition of D_2O. The N1H and N3H signals disappeared. The molecular ion peaks (M^+) of the hydantoins and 2-thiohydantoins were identified easily, because these peaks generally had higher relative intensities than the other fragments. The mass spectra of these derivatives have shown that cleavage of the hydantoin

and 2-thiohydantoin takes place by α-fission at the C4 carbonyl group.

Fungicidal Activity. The synthesized compounds were screened for pesticidal activity (Table II). Only the fungicidal effect was significant. The potential fungicide activity against agricultural diseases was tested in vivo on the following host–parasite relationships: tomato late blight (*Phytophthora infestans*) on tomato plants; wheat powdery mildew (*Erysiphe graminis f.* sp. *tritici*) on wheat seedlings; apple powdery mildew (*Podosphaera leucotricha*) on apple seedlings; *Sclerotinia* rots (*Sclerotinia sclerotiorum*) on sunflower plants; bean rust (*Uromyces appendiculatus*) on French bean plants; gray mold (*Botrytis cinerea*) on horse bean plants. The bactericidal activity was tested against bacterial rot of potatoes (*Erwinia carotovora* ssp. *carotovora*) on potato slices. From the screening results it is evident that only compounds **8** and **13** have significant bactericidal activity. The fungicidal effects are remarkable. Compound **24** showed the broadest range of activity, with control against powdery mildews, rust, and gray mold. Compounds **9** and **19** showed only powdery mildew activity. Some compounds showed activity only against rust: **20**, **28**, **29**, **35**, and **36**. All of these compounds are more fungicidal/bactericidal against plant pathogens than ziram. The 5-alkyl- and (arylmethyl)hydantoins and -thiohydantoins did not show considerable biological activity. The compounds that showed fungicidal/bactericidal activity are 5-(arylmethylene)hydantoins and 2-thiohydantoins. On the basis of these results it can be concluded that the arylidene carbon–carbon double bond has a basic role in fungicidal activity. The introduction of OCH_3 and OH groups at positions 3 and 4 of the aromatic ring is advantageous.

Supplementary Material Available: Table of ^1H NMR and MS data for the compounds prepared (3 pages). Ordering information is given on any current masthead page.

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