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Biological Activity of Halogen-Containing Derivatives of *N*-Substituted Quinone Imines

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Abstract: The different halogen-containing derivatives of *N*-substituted quinone imines have been synthesized by the halogenation and hydrohalogenation of the corresponding quinone imines. *N*,*N*'-(Cyclohexa-2-en-1,4-diylidene)-diarylsulfonamides are good insecticides. They cause 89–97% of the insects to die. Compared with quinone imine, compounds having 4-oxocyclohexa-2,5-en-1-ylidene structure show higher fungicidal activity. *N*-(3,5-Dichloro-4-oxocyclohexa-2,5-dien-1-ylidene)-4-methylbenzene-1-sulfonamide and 4-chloro-*N*-[2,3,5,5,6,6-hexachloro-4-oxocyclohexa-2-en-1-ylidene]benzene-1-sulfonamide inhibit the growth and development of *Phytophthora infestans* by 82 and 81%, respectively. *N*-[2,3,5,5,6,6-Hexachloro-4-oxocyclohexa-2-en-1-ylidene]-4-methylbenzene-1-sulfonamide has a high herbicidal activity. The compounds with the largest number of chlorine atoms have the highest insecticidal, fungicidal, and herbicidal activity.

Keywords: quinone; quinone imine; 4-oxocyclohexa-2,5-dien-1-ylidene; halogen derivatives; hydrohalogenation; halogenation; herbicide; insecticide; fungicide.

1. Introduction

Quinone imines and their derivatives containing the structure of 4-iminocyclohexa-2,5-diene-1,4-one are representatives of a large family of quinoid compounds. They exist in natural products [1, 2], endogenous biochemical substances [3,4], drugs [5, 6], and environmental objects [7, 8].

Natural quinones perform many functions in biological systems. Their most important role is in the electron transfer in metabolic processes such as photosynthesis and respiration in humans [9].

When using drugs, natural products, and environmental chemicals, the formation of quinone compounds is essential to human life. Quinones can cause a variety of harmful effects and can also have beneficial physiological effects [4].

On the one hand, quinone imines are highly active metabolites, which can cause dangerous effects [10–13]. They are responsible for cytotoxicity [12, 14, 15], immunotoxicity [12, 16], and carcinogenesis [12, 14, 16].

On the other hand, they can be antimalarial drugs [6], cytoprotective agents [17], can exhibit anti-inflammatory [17] and antioxidant [2, 3, 5] activity, causing changes in the redox state [17]. Some quinone methides and quinone imines have anticancer activity [18,19], and quinone imine sulfonamides exhibit antibacterial activity [20].

Halogen-containing quinoid compounds show hepatotoxicity [10, 21], carcinogenicity [22], and can be used as anticancer drugs [23]. They are widely used as pesticides [8, 24, 25].

Various halogen-containing derivatives of quinone imines have been previously synthesized [26–29], but their biological activity has not been investigated. The purpose of this work is to study the biological activity of quinone imine derivatives containing halogen atoms.

2. Materials and Methods

2.1. General experimental details.

The ^{1}H NMR spectra were obtained on a Varian VXR-300 spectrometer, 300 MHz. TMS was an internal standard. $CDCl_3$ was used as a solvent. The purity of the halogen derivatives of quinone imines was determined by TLC using Silufol UV-254 plates. Acetone was a solvent. A mixture of benzene and hexane, 10:1, was used as eluent. The spots on the plate were developed under UV light. All melting points were uncorrected.

N-(4-Oxocyclohexa-2,5-dien-1-ylidene)arylsulfonamides 1–4, *N*-[4-oxocyclohex-2-en-1-ylidene]arylsulfonamides 5, 6, *N*-[4-oxo-3,4-dihydronaphthalen-1(2*H*)-ylidene]-arylsulfonamides 12, 13, and *N*,*N*'-(cyclohex-2-en-1,4-diylidene)-diarylsulfonamides 17–19, 33, 34 were synthesized by halogenation of the corresponding quinone imines by procedure [26, 27].

N-[4-Oxonaphthalen-1(4*H*)-ylidene]arylsulfonamides 7–11, 29–31, *N*,*N*'-(cyclohexa-2,5-diene-1,4-diylidene)diarylsulfonamides 14–16, 32, and *N*-(4-oxocyclohexa-2,5-dien-1-ylidene)arylsulfonamides 20–28 were synthesized by hydrohalogenation of the quinone imines by procedure [28].

The characteristics of all compounds synthesized in this work correspond to literary data [29].

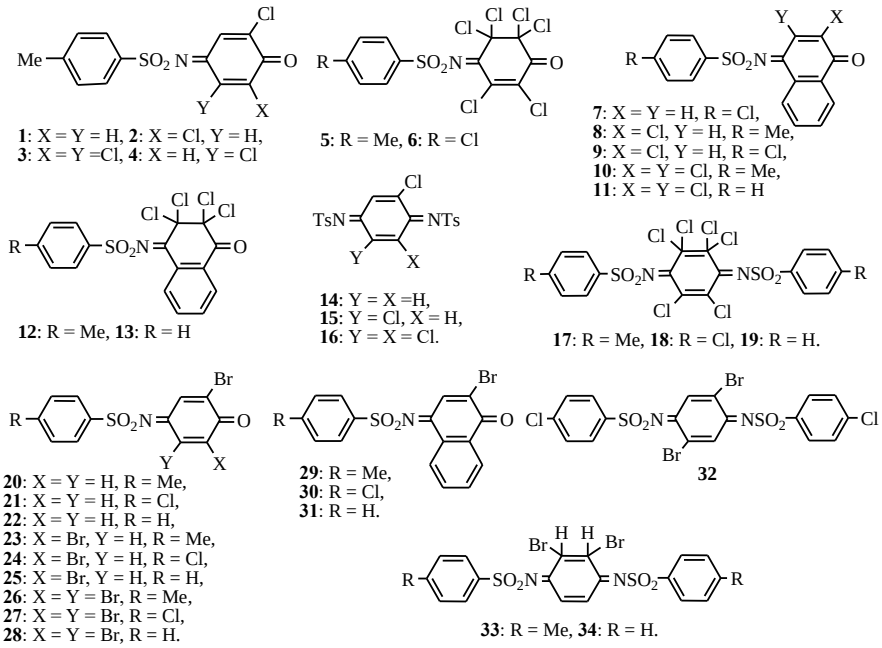
2.2. Biological studies.

The study of the biological activities of halogen derivatives of quinone imines was carried out in the laboratory of protective-stimulating products of the Kyiv environmental protection company “Creoma”, Ukraine.

3. Results and Discussion

The compounds 1–34 (scheme 1) were studied for insecticidal activity against *Musca domestica* (house flies), *Sitophilus oryzae* (rice weevils), *Tetranychus urticae* (spider mites), and *Aphis fabae Scopoli* (black beet aphids). The concentration of the compound in the test solution was 0.5%. In the tests for the anti-nematode activity against galls forming on cucumber roots, the concentration of the compound applied to the soil was 80 mg/kg.

House flies *(Musca domestica)* are ubiquitous flies usually found on decaying garbage, feces, and human food. They are very harmful because they carry microorganisms, including pathogens [30]. Rice weevil (*Sitophilus oryzae*) is the main pest of grains stored in the subtropics and tropics [31]. The spider mite (*Tetranychus urticae*) is one of the most widespread omnivorous herbivores, feeding on more than 1,000 plants, causing economic losses to both ornamental and agricultural plants [32]. The black beet aphids (*Aphis fabae Scopoli*) are one of the more significant menaces to forests and agriculture [33].



Scheme 1. The halogen derivatives of quinone imines.

The results of the tests for insecticidal and anti-nematode activities of compounds 1–34 are shown in Table 1.

Table 1. The test results of anti-nematode and insecticidal activities of compounds 1–34**.**

Compound number	The death index of insects and mites, %				The reduction of gall formation on cucumber roots, %
	House flies	Rice weevils	Spider mites	Black beet aphids	
1	53	38	0	4	18
2	3	24	44	0	9
3	14	5	36	0	3
4	0	68	14	6	0
5	14	11	61	8	0
6	2	14	42	7	0
7	0	15	5	16	0
8	0	56	0	10	0
9	11	22	62	0	37
10	0	65	16	0	0
11	8	43	51	0	0
12	0	14	0	0	0
13	16	24	66	0	20
14	5	13	0	7	0
15	0	24	10	10	0
16	3	38	26	12	0
17	0	91	72	3	0
18	2	97	69	3	31
19	4	46	0	0	0
20	0	3	0	4	47
21	0	5	0	0	66
22	0	0	0	0	25
23	0	0	0	0	46
24	5	5	15	0	39
25	5	8	0	0	46
26	5	5	0	0	0
27	5	8	0	0	0
28	16	3	0	0	0
29	89	76	0	0	50
30	0	3	0	0	0
31	0	0	0	0	0
32	0	0	12	11	0
33	0	6	1	8	0
34	0	14	11	0	0

Compounds 17 and 18 showed good results. The death index was 91% and 97% at the action on rice weevils and 72% and 69% for spider mites. It should be noted that compound 18 has the maximum number of chlorine atoms in composition.

Table 2. The results of the test for the fungicidal activity of compounds 1–34.

Compound number	Inhibition of the growth and development,%							
	Colonies of bacteria and fungi, concentration of 0.003%					Green plant diseases		
						Concentration of 0.1%		Concentration of 0.05%
	Xanthomonas malvacearum	*Fusarium moniliforme*	*Penicillium cyclopium*	*Venturia Inaegualis*	*Aspergillius niger*	*Phytophthora infestans*	*Botrytis cinerea*	*Oidium erysiphoides*
1	14	18	17	22	0	0	0	0
2	21	31	0	16	13	82	62	0
3	21	31	0	27	36	0	29	0
4	6	27	0	29	17	40	0	0
5	14	25	0	27	13	0	0	herbicide effect
6	0	0	0	0	20	81	53	41
7	13	8	0	21	0	0	0	30
8	0	29	0	0	27	0	54	0
9	20	18	0	5	29	0	63	0
10	14	22	27	0	0	37	58	66
11	29	13	0	26	0	71	23	56
12	20	70	37	41	41	0	0	60
13	29	51	23	42	39	22	4	61
14	0	0	0	0	20	0	0	78
15	0	0	0	0	0	60	0	45
16	28	27	0	27	13	0	0	0
17	14	2	11	5	11	0	0	19
18	0	34	0	16	7	69	0	53
19	43	20	27	11	0	0	0	0
20	14	33	0	31	17	0	42	0
21	14	7	0	36	29	0	0	0
22	0	26	0	27	0	0	0	0
23	14	45	12	50	23	0	24	0
24	28	28	18	40	0	59	14	0
25	21	16	18	31	23	0	62	0
26	28	9	12	27	23	13	20	0
27	14	33	0	40	5	0	0	0
28	0	33	31	50	0	0	0	0
29	21	40	0	45	0	21	0	0
30	7	14	0	40	5	0	52	0
31	21	33	12	18	0	0	25	0
32	37	11	0	13	0	0	0	0
33	50	79	68	62	69	0	0	0
34	42	73	56	75	70	0	0	0

Among the bromine-containing derivatives, compound 29 was the most active. It caused 89% of the houseflies and 76% of rice weevil to die. Other compounds showed a relatively low insecticidal activity.

Under the action of compound 21, the maximum reduction of gall formation on cucumber roots was 66%. Compared with other compounds, the bromine-containing *N*-(4-oxocyclohexa-2,5-dien-1-ylidene)-arylsulfonamides 20–25 had a higher anti-nematode activity. But the activity of the remaining compounds against galls forming on cucumber roots was either very low or equal zero.

To study the bactericidal activity of the compounds 1–34, we investigated their action on eight objects: *Fusarium moniliforme, Penicillium cyclopium, Aspergillus niger, Venturia Inaequalis, Xanthomonas malvacearum, Botrytis cinerea, Oidium erysiphoides, Phytophthora infestans. Xanthomonas malvacearum* causes blackarm. *Penicillium cyclopium* affects cereal products and grains. *Venturia inaequalis* causes the apple scab disease. *Fusarium moniliforme* indices corn stalk and ear rot. *Aspergillus niger* causes aspergillosis in human and animals.
The responses of four types of fungi, *Penicillium cyclopium, Venturia Inaequalis, Aspergillus niger*, and *Fusarium moniliforme* were tested on a solid medium. The effects of the tested

compounds on *Botrytis cinerea*, *Oidium erysiphoides*, and *Phytophthora infestans* were studied on green plants. The test results of the activity of the compounds 1–34 are shown in Table 2.

Compounds 12, 13, 23, 28, 33, and 34 showed relatively high fungicidal activity against fungi when tested on a solid medium. Compounds 2 and 6 showed significant fungicidal activity against *Phytophthora infestans*, inhibiting the development of the disease by 82 and 81%, respectively. Inhibition of the growth and development of diseases of the green plant diseases was 50–70% when using compounds 8–15, 18, 24, 25, 30.

Thus, the compounds having a 4-oxocyclohex-2-en-1-ylidene structure and compounds having a quinone imine ring had fungicidal activity. Although 4-oxocyclohex-2-en-1-ylidene structures are more active than quinoid compounds (see Table 2).

The herbicidal activity of compounds 1-34 was also tested. The studies were carried out on wheat, sorghum, oats, buckwheat, and radish. The concentration of the tested compound was equal to 5 kg per hectare. The tests were performed in two ways. The first method was to spray the soil before sowing. Moreover, the second was to spray the vegetative half of the plants. Of all the compounds studied, only aryl sulfonamide 5 showed a high herbicidal effect.

4. Conclusions

N,*N*'-(Cyclohex-2-ene-1,4-diylidene)-diarylsulfonamides are good insecticides. They cause 89–97% of the insects to die. The compounds are having a 4-oxocyclohex-2-en-1-ylidene structure show higher fungicidal activity than quinone imines. *N*-(3,5-Dichloro-4-oxocyclohexa-2,5-dien-1-ylidene)-4-methylbenzene-1-sulfonamide and 4-chloro-*N*-[2,3,5,5,6,6-hexachloro-4-oxocyclohex-2-en-1-ylidene]benzene-1-sulfonamide inhibit the growth and development of *Phytophthora infestans* by 82 and 81%, respectively. *N*-[2,3,5,5,6,6-Hexachloro-4-oxocyclohex-2-en-1-ylidene]-4-methylbenzene-1-sulfonamide has a high herbicidal activity. The compounds with the largest number of chlorine atoms have the highest insecticidal, fungicidal, and herbicidal activity.

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Conflicts of Interest

The authors declare no conflict of interest.

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