Pestic. Sci. 1994, **40**, 141–146

Synthesis and Acaricidal Activity of 3-Aryl-5-arylmethyl-1,3,4-oxa(thia)diazol-2(3*H*)-ones

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(Revised manuscript received 8 September 1993; accepted 5 November 1993)

Abstract: A series of new 1,3,4-oxa(thia)diazol-2(3*H*)-ones were synthesized and tested as acaricides. High activities against eggs of *Tetranychus urticae* (Koch) were found for derivatives bearing an *ortho*-halo-substituted phenyl group in position 3, and a benzyl group *para*-substituted by a branched C_3–C_6 alkoxy group in position 5 of the hetero-ring. The best compounds attained the miticidal potency of clofentezine.

1 INTRODUCTION

Clofentezine is an highly selective acaricide for the control of phytophagous mites on top fruit.[1,2] It has found favourable acceptance in integrated pest-management programmes because of its strong ovicidal activity against Tetranychidae and its safeness to non-target organisms. The structural feature of the product is a central 1,2,4,5-tetrazine ring substituted in positions 3 and 6 by two 2-chlorophenyl groups.

Disubstituted pyrimidines,[3] pyridazines,[3] 1,2,4-triazoles,[3,4] 1,2,4-oxa(thia)diazoles,[3,5,6] 1,3,4-oxa(thia)-diazol-2(3*H*)-ones[7] and 2,4-dihydro-3*H*-1,2,4-triazol-3-ones[7] have also been reported to possess acaricidal activity. The patent literature would suggest that, for such compounds, and for clofentezine and related tetrazines,[2] one *ortho*-substituted phenyl group is necessary to impart good ovicidal effect. However, the achievement of optimal activity in each class depends on the other substituent bonded to the heterocyclic nucleus.

Miticidal oxa(thia)diazolones and dihydrotriazolones previously disclosed were limited to diaryl and aryl-pyridyl derivatives.[7] In order to investigate further these chemical classes, we synthesized and tested new disubstituted compounds bearing only one aryl group on the central hetero-ring. Remarkable ovicidal activities against *Tetranychus urticae* (Koch) were found for a series of 5-(4-alkoxybenzyl)-3-(2-halophenyl)-1,3,4-oxa(thia)-diazol-2(3*H*)-ones.[8]

2 EXPERIMENTAL

2.1 General

Chemical structures, physicochemical properties, and ovicidal activities against *T. urticae* of the compounds synthesized are reported in Tables 1–8. Compounds containing an asymmetric carbon atom were obtained as racemic mixtures. Purification of the final products was usually performed by column chromatography on silica gel 60 (0·040–0·063 mm, Merck), eluting with hexane + ethyl acetate solutions. High-performance liquid chromatography analyses were carried out with a Waters 501 pump combined with a Waters 484 detector, using Lichrospher 10 RP 18 (Merck) as the stationary phase and acetonitrile + water + isopropanol (50 + 20 + 30 by volume) as the mobile phase. Melting points were determined using a Buchi SMP-20 apparatus and are uncorrected. Refractive indices were determined using a Galileo RG 701 refractometer. Elemental analyses, [^{1}H]NMR spectra and mass spectra were consistent with the proposed structures.

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Pestic. Sci. 0031-613X/94/$09.00

2.2 Synthesis

Target compounds were prepared according to established procedures, outlined in Fig. 1. Oxadiazolones **2–54** (Tables 1–5) and thiadiazolones **59–71** (Table 8) were obtained by cyclization with trichloromethyl chloroformate of hydrazides or thiohydrazides **1a–c** (Route A). Oxadiazolethiones **55** and **56** (Table 6) were prepared from the corresponding oxadiazolones by treatment with Lawesson's reagent (Route B). Dihydrotriazolones **57** and **58** (Table 7) were synthesized by opening the corresponding oxadiazolones with methylamine and cyclizing the intermediate acylsemicarbazides with potassium hydroxide.[9]

Hydrazides **1a**, **1b**, and **1c** were obtained respectively by: condensation of an acyl chloride with an arylhydrazine; treatment of the corresponding hydrazides with Lawesson's reagent; condensation of a 4-alkoxybenzaldehyde with 2-chlorobenzoic hydrazide followed by lithium aluminum hydride reduction of the resulting hydrazones.[10]

2.2.1 *Route A: synthesis of oxa(thia)diazolones*

A solution of hydrazide or thiohydrazide **1a–1c** (0·02 mol) in toluene (80 ml) was added dropwise to a stirred solution of trichloromethyl chloroformate (TMCF, 0·025 mol) in toluene (20 ml). The mixture was heated at 100°C for 3 h under nitrogen. After cooling to room temperature, water (250 ml) was added and the mixture extracted with diethyl ether (3 × 80 ml). The organic layer was washed with brine (50 ml), dried with sodium sulfate, filtered and concentrated under reduced pressure. The reaction product was purified by

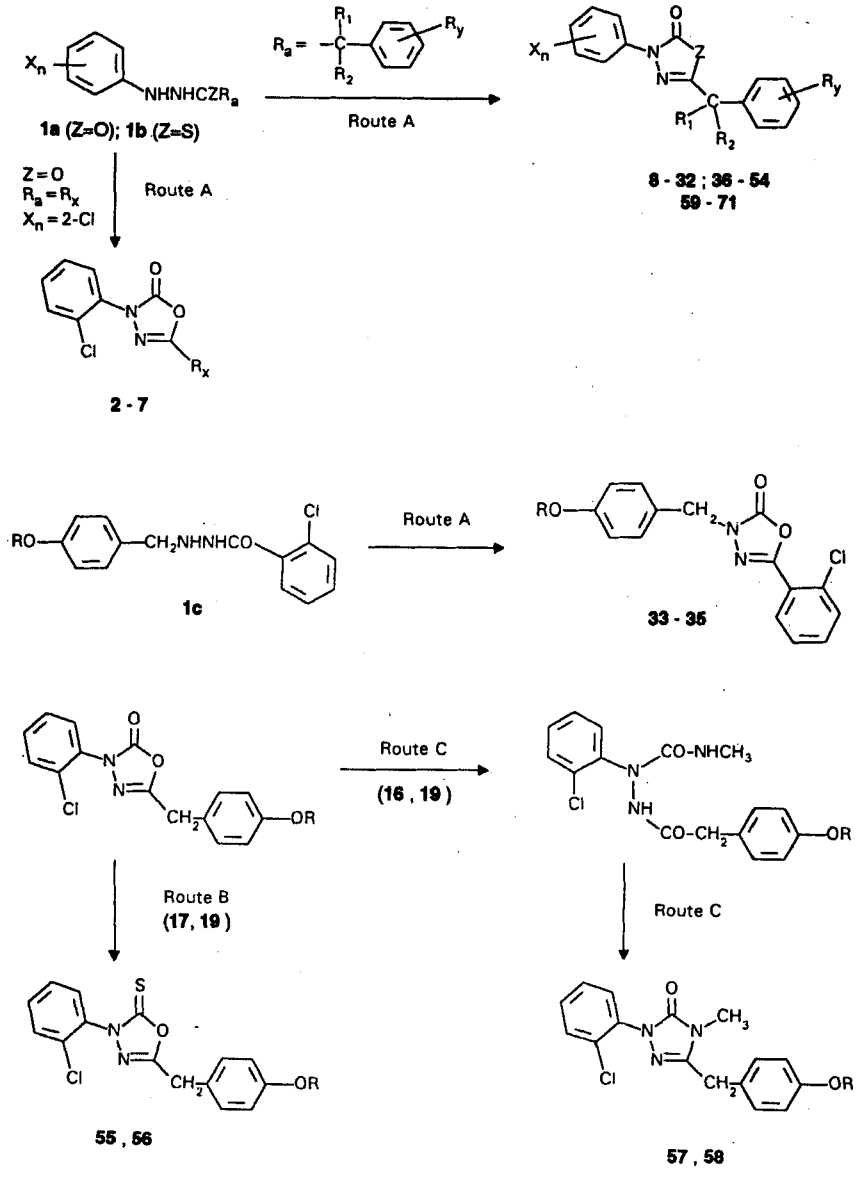


Fig. 1. Synthetic routes to the compounds studied.

column chromatography, eluting with hexane + ethyl acetate (85 + 15 by volume). Yields ranged from 60 to 85 %.

2.2.2 *Route B: synthesis of oxadiazolethiones*

A solution of oxadiazolone **17** or **19** (0·005 mol) and Lawesson's reagent (0·006 mol) in xylene (60 ml), was heated under reflux with stirring for 6 h. After cooling to room temperature, the mixture was diluted with water (150 ml) and extracted with diethyl ether (3 × 60 ml). The organic layer was dried with sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography, eluting with hexane + ethyl acetate (85 + 15 by volume). Compounds **55** and **56** were obtained in 85 % yields.

2.2.3 *Route C: synthesis of dihydrotriazolones*

A mixture of compound **16** or **19** (0·005 mol), dioxane (20 ml) and methylamine (150 g litre^{-1} aqueous solution, 20 ml) was refluxed for 3 h with stirring. Crushed potassium hydroxide (0·0075 mol) was added and the heating continued for 8 h. After cooling to room temperature, the reaction mixture was diluted with saturated aqueous ammonium chloride (100 ml), and extracted with ethyl acetate (3 × 50 ml). The organic layer was dried with sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography, eluting with hexane + ethyl acetate (1 + 1 by volume). Compounds **57** and **58** were obtained, respectively, in 70 % and 74 % isolated yields.

2.3 Bioassay

2.3.1 *Ovicidal activity against* T. urticae

Leaf discs, 2·5 cm diameter, were cut from bean leaves with egg deposit (80–100) laid during the previous 24 h. Two discs for each dose rate were dipped into water + acetone solutions (9 + 1 by volume) containing the compound under test and 'Tween 20' (0·5 g litre^{-1}). Discs treated with water + acetone were used as controls. Treated discs were placed on moistened cotton in open Petri dishes and kept at 25°C and 60 % relative humidity. The number of unhatched eggs was recorded seven days after treatment and the mortality was calculated using Abbott's correction for any spontaneous failure to emerge observed in the control. The activity ratings reported in Tables 1–8 represent the following ranges of LC_{85} values (mg litre^{-1}):

1 >200; **2** ⩽200, >60; **3** ⩽60, >20; **4** ⩽20, >6; **5** ⩽6, >2; **6** ⩽2, >0·6; **7** ⩽0·6.

3 RESULTS AND DISCUSSION

Clofentezine and the previously reported[7] diaryl oxadiazolones **2** and **3** were selected as reference compounds for the present study (Table 1). We initially prepared a number of analogous 5-substituted 3-(2-chlorophenyl)-1,3,4-oxadiazol-2(3*H*)-ones.

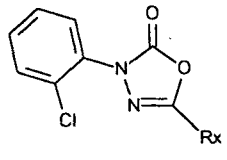
Compounds bearing *n*-heptyl, cyclohexyl, 4-isopropyloxyphenyl, and 2-(4-isopropyloxyphenyl)ethyl groups in the 5-position (**4**–**7**, Table 1), were inactive at the highest dose tested (200 mg litre^{-1}).

In the series of arylmethyl derivatives (Table 2), good ovicidal activities were achieved when the benzyl ring was *para*-substituted by a suitable alkoxy group. Indeed, the ovicidal effect of 4-alkoxybenzyl compounds **13**–**26** was strongly dependent on both the number of carbon atoms and the type of alkyl chain. The methoxy (**13**) and ethoxy (**14**) derivatives were, respectively, inactive and poorly active. On the other hand, compounds having an α or β branched C_3–C_6 alkoxy group were found to be more effective acaricides than reference oxadiazolones **2** and **3**. Best compounds (rating 6) were the *sec*-butyloxy (**19**), 3-pentyloxy (**21**) and cyclopentyloxy (**22**) derivatives. In general, linear chains gave derivatives with lower activities (*cf.* **15** with **16**, **17** with **18** and **19**). The efficacy was also progressively reduced for branched alkoxy groups containing more than six carbon atoms (**25**, **26**).

Moderate or poor activities were shown by the 4-butyl (**11**, **12**), 4-phenoxy (**27**), 4-benzyloxy (**28**), 3-Cl-4-alkoxy (**30**) and 4-alkylthio (**32**) compounds. Shifting the alkoxy group from the *para* (**16**) to the *ortho* (**31**) or *meta* (**29**) position resulted in complete loss of activity.

Reversing the positions of the 2-chlorophenyl and

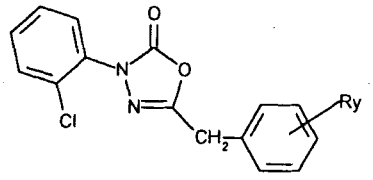
TABLE 1
Structure and Acaricidal Activity of Non-benzylic 3-(2-chlorophenyl)-1,3,4-oxadiazol-2(3*H*)-ones



Compound	R_x	*m.p.* (°C) *or* n_D^{20a}	*Activity rating*[b]
Clofentezine			7
2	2-Chlorophenyl	111–12	4
3	2,6-Dichlorophenyl	89–91	4
4	*n*-Heptyl	1·5216	1
5	Cyclohexyl	1·5534	1
6	4-Isopropyloxyphenyl	111–12	1
7	2-(4-Isopropyloxyphenyl)ethyl	1·5669	1

[a] ±0·0001.
[b] See Section 2.3.1.

TABLE 2
Structure and Acaricidal Activity of 5-arylmethyl-3-(2-chlorophenyl)-1,3,4-oxadiazol-2(3*H*)-ones



Compound	R_y	*m.p.* (°C) *or* n_D^{20a}	*Activity rating*[b]
8	H	75–6	1
9	2-Cl	1·5979	1
10	4-Cl	106–8	1
11	4-Isobutyl	1·5670	2
12	4-*tert*-Butyl	67–8	2
13	4-Methoxy	66–7	1
14	4-Ethoxy	78–9	2
15	4-*n*-Propyloxy	68–9	4
16	4-Isopropyloxy	55–6	5
17	4-*n*-Butyloxy	64–5	4
18	4-Isobutyloxy	47–9	5
19	4-*sec*-Butyloxy	1·5725	6
20	4-Isopentyloxy	1·5638	4
21	4-(3-Pentyloxy)	1·5642	6
22	4-Cyclopentyloxy	61–2	6
23	4-(2-Ethyl)butyloxy	1·5602	5
24	4-Cyclohexyloxy	1·5784	4
25	4-Cyclohexylmethoxy	82–3	4
26	4-(2-Ethyl)hexyloxy	1·5513	3
27	4-Phenoxy	86–7	3
28	4-Benzyloxy	97–9	2
29	3-Isopropyloxy	1·5703	1
30	3-Cl-4-isopropyloxy	1·5817	1
31	2-Isopropyloxy	1·5720	1
32	4-Isopropylthio	1·5976	2

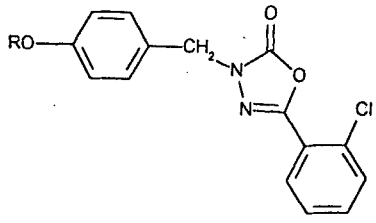
[a] ±0·0001.
[b] See Section 2.3.1.

4-alkoxybenzyl groups on the oxadiazolone nucleus gave less active derivatives, as shown by comparison of compounds **33–35**(Table 3) with their positional isomers **14, 16** and **19**.

The dependence of the acaricidal effect on the substituents present on the 3-aryl group was assessed with the 4-isopropyloxybenzyl and 4-*sec*-butyloxybenzyl compounds **36–48** (Table 4). The only substitutions which maintained the activities of the 2-Cl derivatives **16** and **19** were the 2-Cl-4-F (**39**) and the 2-Br (**46**). *Meta*- (**40**) and *para*- (**37**) chloro isomers were completely inactive.

The influence on the miticidal activity of substituting the benzylic position with lower alkyl groups was studied with compounds **49–54** (Table 5). The introduction of one methyl group strongly increased the ovicidal effect of the isopropyloxy derivative **49** (*cf.* **16**) which attained the potency range of clofentezine (rating 7).

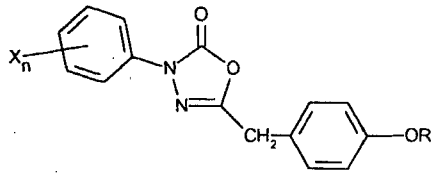
TABLE 3
Structure and Acaricidal Activity of 3-(4-alkoxyphenyl)methyl-5-(2-chlorophenyl)-1,3,4-oxadiazol-2(3*H*)-ones



Compound	*R*	*m.p.* (°C) *or* n_D^{20a}	*Activity rating*[b]
33	Ethyl	70–1	1
34	Isopropyl	54–5	4
35	*sec*-Butyl	1·5805	4

[a] ±0·0001.
[b] See Section 2.3.1.

TABLE 4
Structure and Acaricidal Activity of 5-(4-alkoxyphenyl)methyl-3-aryl-1,3,4-oxadiazol-2(3*H*)-ones



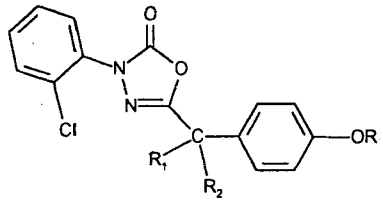
Compound	X_n	*R*	*m.p.* (°C) *or* n_D^{20a}	*Activity rating*[b]
36	H	Isopropyl	82–3	1
37	4-Cl	Isopropyl	81–2	1
38	2,4-Cl_2	Isopropyl	66–7	1
39	2-Cl-4-F	Isopropyl	53–4	5
40	3-Cl	*sec*-Butyl	1·5738	1
41	2,3-Cl_2	*sec*-Butyl	1·5746	1
42	2,6-Cl_2	Isopropyl	96–8	2
43	2-F	Isopropyl	54–6	3
44	2-CF_3	Isopropyl	84–5	1
45	2-Methyl	*sec*-Butyl	1·5594	5
46	2-Br	*sec*-Butyl	1·5763	6
47	2,6-F_2	*sec*-Butyl	47–8	4
48	2-Methoxy	*sec*-Butyl	66–7	4

[a] ±0·0001.
[b] See Section 2.3.1.

The isobutyloxy derivative **53** was equivalent to **18**, whereas the cyclopentyloxy compound **54** was less active than **22**.

The introduction of one ethyl, one isopropyl or two methyl groups (**50–52**) brought about a drastic fall in activity.

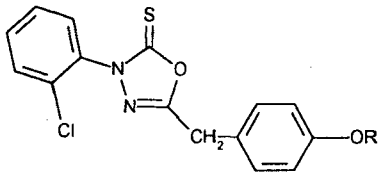
TABLE 5
Structure and Acaricidal Activity of 5-[1-(4-alkoxyphenyl)-alkyl]-3-(2-chlorophenyl)-1,3,4-oxadiazol-2(3*H*)-ones



Compound	R_1	R_2	*R*	*m.p.* (°C) *or* n_D^{20}[a]	*Activity rating*[b]
49	CH_3	H	Isopropyl	1·5694	7
50	Ethyl	H	Isopropyl	66–8	1
51	Isopropyl	H	Isopropyl	78–9	1
52	CH_3	CH_3	Isopropyl	54–5	2
53	CH_3	H	Isobutyl	1·5573	5
54	CH_3	H	Cyclopentyl	1·5703	5

[a] ±0·0001.
[b] See Section 2.3.1.

TABLE 6
Structure and Acaricidal Activity of 5-(4-alkoxyphenyl)methyl-3-(2-chlorophenyl)-1,3,4-oxadiazole-2(3*H*)-thiones



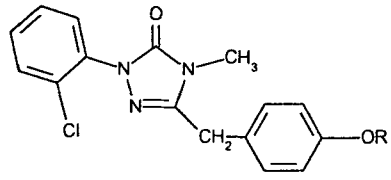
Compound	*R*	*m.p.* (°C)	*Activity rating*[b]
55	*n*-Butyl	67–9	1
56	*sec*-Butyl	59–60	4

[a] See Section 2.3.1.

As a further step in our structure–activity optimization work we modified the central heterocyclic ring. Substitution of the *exo*cyclic oxygen atom of compounds **17** and **19** by sulfur led to the considerably less effective oxadiazolethiones **55** and **56** (Table 6). A strongly reduced activity was also observed when the ring oxygen atom was replaced by a methylamino group (dihydrotriazolones **57** and **58**, Table 7).

Compounds with similar or increased ovicidal potencies were obtained when the ring oxygen atom was replaced by sulfur, as shown by the series of thiadiazolones **59–71** (Table 8). The 2-Cl-4-F (**60**), the 2-Br (**63**) and the α-methylbenzyl (**61, 65, 67**) derivatives were found to be as active as the corresponding oxadiazolones (*cf.* **39, 46, 49, 53, 54**). The α-unsubstituted 2-chlorophenyl-4-

TABLE 7
Structure and Acaricidal Activity of 5-(4-alkoxyphenyl)methyl-2-(2-chlorophenyl)-4-methyl-2,4-dihydro-3*H*-1,2,4-triazol-3-ones



Compound	*R*	n_D^{20}[a]	*Activity rating*[b]
57	Isopropyl	1·5834	2
58	*sec*-Butyl	1·5779	2

[a] ±0·0001.
[b] See Section 2.3.1.

alkoxybenzyl thiadiazolones were, in general, more effective than the oxa-compounds. A clear increase in miticidal activity (rating 7) was observed for the isobutyloxy (**64**) and the isopropyloxy (**59**) compounds (*cf.* **18, 16**).

High-performance liquid chromatography measurements[11] showed that thiadiazolones are more hydrophobic than the corresponding oxadiazolones. An increase of lipophilic character, which in part parallels the bioactivity, is also observed through the series of oxadiazolones **13–23**. Therefore, our results appear to suggest that both molecular shape and lipophilicity are factors which determine the ovicidal efficacy of the compounds studied.

In general, derivatives active against eggs showed activity also against larvae of *T. urticae*. However, both oxadiazolones and thiadiazolones turned out to be far more effective as ovicides than as larvicides. At the highest dose tested (200 mg litre^{-1}), all compounds were inactive or weakly active against adult females of the mite.

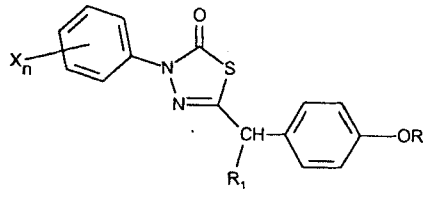
An important biological property of clofentezine is the activity against winter eggs of *Panonychus ulmi* (Koch).[1,2] In a preliminary field trial, late winter application of compound **66** on apple trees (250 mg a.i. litre^{-1}), gave very good control of *P.ulmi* population until the end of June.

ACKNOWLEDGEMENTS

This work was partly conducted within the contract 'Programma Nazionale di Ricerca per la Chimica' entrusted to Istituto Guido Donegani S.p.A. by the Italian Ministry of University and Scientific and Technological Research.

TABLE 8

Structure and Acaricidal Activity of 5-[1-(4-alkoxyphenyl)alkyl]-3-aryl-1,3,4-thiadiazol-2(3*H*)-ones



Compound	X_n	R_1	*R*	*m.p.* (°C) *or* n_D^{20}[a]	*Activity rating*[b]
59	2-Cl	H	Isopropyl	1·6009	7
60	2-Cl-4-F	H	Isopropyl	1·5853	5
61	2-Cl	CH_3	Isopropyl	1·5927	7
62	2-Cl	H	*sec*-Butyl	1·5894	6
63	2-Br	H	*sec*-Butyl	1·5973	6
64	2-Cl	H	Isobutyl	1·5900	7
65	2-Cl	CH_3	Isobutyl	1·5795	5
66	2-Cl	H	Cyclopentyl	1·6080	7
67	2-Cl	CH_3	Cyclopentyl	1·5902	5
68	2-Cl	H	3-Pentyl	1·5855	6
69	2-Cl	H	2-Ethylbutyl	1·5810	6
70	2-Cl	H	Cyclohexyl	1·6025	5
71	2-Cl	H	Cyclohexylmethyl	85–6	4

[a] ±0·0001.

[b] See Section 2.3.1.

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