Acaricidal Activity of Thioketal Adducts of Pyruvoyl Chloride Phenylhydrazones and Related Compounds

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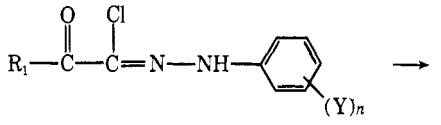
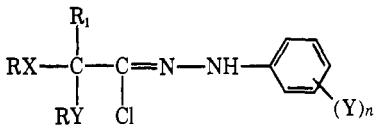
Substituted pyruvoyl chloride phenylhydrazones (I) react with alkanethiols and alkanedithiols to give thioketal adducts (II, X and Y = S) that are highly active as miticides. The thioketal adducts are more active than the related ketals (II, X and Y = O). High miticidal activity is found for a wide variety of ring substituted thioketal phenylhydrazones, although the position of the substituent groups in isomeric compounds can significantly alter miticidal activity. Replacement of the acid chloride function by other groups reduces or eliminates miticidal activity. Compounds that show good miticidal activity also have good mite repellent activity.

A recent report from our laboratories (Kaugars and Gemrich, 1969) described a series of benzoyl chloride phenylhydrazones that is highly active as miticides. One of these compounds, benzoyl chloride (2,4,6-trichlorophenyl)hydrazone, has been extensively field tested and has been assigned the trademark Banomite. Concurrent with our investigation of the benzoyl chloride phenylhydrazones we have synthesized other types of acid chloride phenylhydrazones, several of which have shown miticidal activity. In this communication we describe the conversion of pyruvoyl chloride phenylhydrazones (I, $R_1 = CH_3$) and related compounds of structure I to the ketal (X and Y = O), hemithio-



I

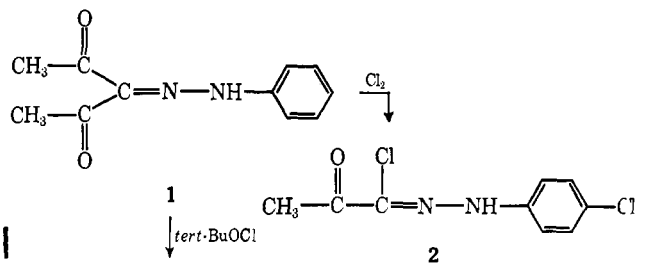


II

ketal (X = S, Y = O) and thioketal (X and Y = S) adducts of structure II. The excellent miticidal and mite repellent activities of the thioketal adducts are also described.

MATERIALS AND METHODS

Chemical Methods. Reaction of 2,4-pentanedione with benzenediazonium chloride gave 2,3,4-pentanetrione-3-phenylhydrazone (**1**) (Beyer and Claisen, 1888) and this



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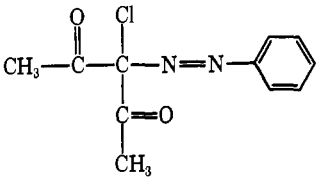

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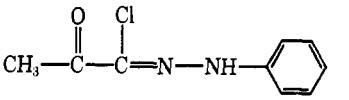

4

reacted with chlorine to give pyruvoyl chloride 1-[(*p*-chlorophenyl)hydrazone] (**2**) (Moon, 1972). Chlorination of **1** with *tert*-butyl hypochlorite gave, after methanolysis of the initially formed 3-chloro-3-phenylazo-2,4-pentanedione (**3**), pyruvoyl chloride 1-(phenylhydrazone) (**4**) (Moon, 1972). The other intermediates of structure I were prepared by the same reaction sequence from the appropriate β-diketone and substituted benzenediazonium chloride; alternate syntheses for some of these compounds have been described (Dieckmann and Platz, 1905; Bülow and Neber, 1913; Favrel, 1927; Huisgen and Koch, 1955; Parkes and Tinsley, 1934).

Condensation of pyruvoyl chloride 1-[(2,4-dichlorophenyl)hydrazone] (**6**) with ethylene glycol and 2-mercaptoethanol in the presence of *p*-toluenesulfonic acid under standard ketalization conditions (Fieser and Fieser, 1967; Draber *et al.*, 1970) gave the adducts **15** and **16**, respectively. The thioketal adducts were readily prepared by standard reaction of the intermediate ketone with an alkanethiol or alkanedithiol at 0–25°C in chloroform in presence of boron trifluoride etherate (Fieser and Fieser, 1967). The ethanedithiol adducts were obtained in crystalline form when the reaction solutions were diluted with ether and cooled to −60°C; initial purification of the other thioketal adducts was accomplished by chromatography on silica gel.

Reaction of 2-methyl-1,3-dithiolane-2-carbonyl chloride (2,4-dichlorophenyl)hydrazone (**11**) with one equivalent of hydrogen peroxide in acetic acid gave the monosulfoxide **21**. Compound **11** reacted with potassium cyanide, dimethylamine, and thiophenol to give **39**, **40**, and **41**, respectively. Controlled reaction of 2,3,4-pentanetrione 3-[(2,4-dichlorophenyl)hydrazone] with ethanedithiol afforded **42**.

Biological Methods. Lima bean plants in the primary leaf stage were infested with adults and nymphs of the two-spotted spider mite (*Tetranychus urticae*) 24 hr prior to treatment. The plants were sprayed to "wet" with an

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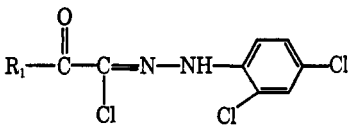
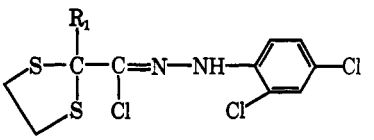
Table I. Chemical Data and Miticidal Activities of Ketone and Dithioketal Acid Chloride (2,4-Dichlorophenyl)hydrazones





R_1	Compound number	Miticidal activity LC_{50}, ppm	Miticidal activity Repellency, ppm	Compound number	mp, °C	Calcd, %	Found, %	Miticidal activity LC_{50}, ppm	Miticidal activity Repellency, ppm
H	5[a]	>100[f]	>100	10	87–90	C, 36.65 H, 2.77 Cl, 32.46 N, 8.55 S, 19.57	36.90 3.03 32.44 8.35 19.33	45	50
CH_3	6[b]	>100[f]	25	11	108–110	C, 38.66 H, 3.25 Cl, 31.13 N, 8.20 S, 18.77	38.38 3.41 31.54 8.20 19.12	8	12
C_2H_5	7[c]	>100[f]	>100	12	47–48	C, 40.52 H, 3.68 Cl, 29.91 N, 7.88	40.83 3.57 29.80 7.77	21	12
n-C_5H_{11}	8[d]	>100[f]	>100	13	*g*	C, 45.28 H, 4.81 Cl, 26.74 N, 7.04 S, 16.12	45.86 4.74 25.87 6.75 17.00	55	50
	9[e]	>100[f]	>100	14	107–109	C, 48.10 H, 3.21 Cl, 26.09 N, 6.87 S, 15.73	47.63 3.42 26.62 6.88 15.62	37	100

[a] Draber *et al.* (1970). [b] Bülow and Neber (1913). [c] Mp 108–110°C. [d] Mp 76°C. [e] Parkes and Tinsley (1934). [f] In initial tests these compounds showed good miticidal activity at 500 ppm but little activity at 100 ppm. [g] This compound, a liquid, was purified by chromatography on silica gel.

emulsified formulation of the acid chloride phenylhydrazone (50 mg of chemical dissolved in 20 ml of tetrahydrofuran and diluted to 500 ml with a 0.0132% v/v water solution of Tween 20 emulsifier; lower concentrations were obtained by dilution with additional Tween 20 water solution). The plants were examined 4 to 6 hr posttreatment and again after 24 hr to determine "repellency" (a phenomenon by which the mites spin down from the leaf surface). The number of mites spinning down and the distance traveled in spinning appeared to be directly related to the activity of the compound. The mites generally did not drop off, but from time to time returned to the leaf surface. As the toxic effects of the chemical became apparent, the mites no longer spun down. Four days after treatment percentage mortality readings were made for mixed populations of adults and nymphs. LC_{50} values were obtained by interpolating the value from an eye-fitted log-probit plot of the concentration *vs.* percentage mortality.

The acaricide standard dicofol routinely produced LC_{50} values in the range of 30–50 ppm in this test but gave no evidence of repellency.

RESULTS AND DISCUSSION

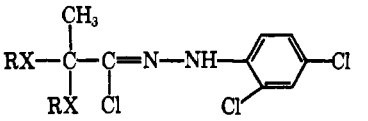
Most of the ketone intermediates (I) used in this study showed miticidal activity; this has been described by Büchel *et al.* (1969) and Draber *et al.* (1970) for compounds **3** and **5**. The ketones showed significant activity only at or above 100 ppm, whereas the thioketal adducts were active at much lower rates. This can be seen in Table I, where the effect of the ketone substituent R_1 on the activity of a series of ketone- and thioketal-(2,4-dichlorophenyl)hydrazones is considered. While all thioketal adducts showed good miticidal and mite repellent activities, the most active chemical was 2-methyl-1,3-dithiolane-2-carbonyl chloride (2,4-dichlorophenyl)hydrazone (**11**), where R_1 is CH_3.

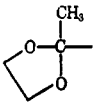
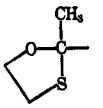
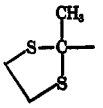
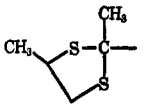
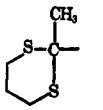
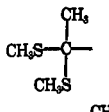
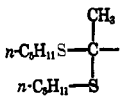
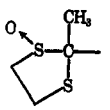
A series of ketal and thioketal adducts of pyruvoyl chloride 1-[(2,4-dichlorophenyl)hydrazone] (**6**) was prepared (Table II). The thioketal **11** was more active than the hemithioketal **16** and much more active than the ketal **15**. Similar activities were found for the cyclic thioketals **11**, **17**, and **18** and the methanethiol adduct **19**, while the pentanethiol adduct **20** had reduced activity. Oxidation of **11** to the monosulfoxide **21** reduced the miticidal activity.

The activity of derivatives of 2-methyl-1,3-dithiolane-2-carbonyl chloride phenylhydrazone differing only in their substitution in the phenyl ring is shown in Table III. Monosubstitution in the phenyl ring generally gave chemicals with improved activity (**23**–**31**) over the parent compound (**22**). Further substitution also gave highly active chemicals, the activity for the isomeric dichlorophenylhydrazones **11**, **32**, **33**, and **34** being markedly dependent on the position of the chlorine substituents. Introduction of a nitro group (compound **36**) reduced miticidal activity, as was previously found for the benzoyl chloride phenylhydrazones (Kaugars and Gemrich, 1969).

We have found that replacement of the acid chloride function in **11** by other groups reduces or eliminates miticidal activity. Of the compounds shown in Table IV only the acid bromide phenylhydrazone **38** was active at 500 ppm (100% mite control). Provided, however, that the acid chloride function is retained, considerable structural variation can be

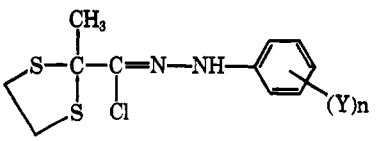
Table II. Chemical Data and Miticidal Activities of Ketal and Thioketal Adducts of Pyruvoyl Chloride 1-(2,4-Dichlorophenyl)hydrazone



Compound number	RX—C(CH3)— RX	mp, °C	Analysis		Miticidal activity	
			Calcd, %	Found, %	LC_{50}, ppm	Repellency, ppm
15		85–87	C, 42.67 H, 3.59 Cl, 34.36 N, 9.05	42.66 3.43 34.21 8.70	>124	>100
16		70–73	C, 40.57 H, 3.40 Cl, 32.66 N, 8.60 S, 9.85	40.33 3.34 32.80 8.58 10.05	17	12
11		108–110	C, 38.66 H, 3.25 Cl, 31.13 N, 8.20 S, 18.77	38.38 3.41 31.54 8.20 19.12	8	12
17		77–78	C, 40.40 H, 3.96 N, 7.85	40.83 3.94 7.89	6	6
18		97–98	C, 40.51 H, 3.68 Cl, 29.90 N, 7.88 S, 18.03	40.70 3.56 29.99 7.94 17.65	10	12
19		37–39	C, 38.43 H, 3.81 Cl, 30.94 N, 8.15 S, 18.66	38.56 3.95 31.27 8.20 18.66	14	12
20		*b*	C, 50.05 H, 6.40 Cl, 23.33	50.90 6.13 23.88	>46	>50
21		61–63	C, 36.93 H, 3.10 Cl, 29.74 N, 7.83 S, 17.93	37.12 3.18 29.94 7.94 18.01	>100[a]	>100

[a] Compound 21 showed good miticidal activity at 500 ppm, but little activity at 100 ppm. [b] This compound, a liquid, was purified by chromatography on silica gel.

Table III. Chemical Data and Miticidal Activities of 2-Methyl-1,3-dithiolane-2-carbonyl Chloride Phenylhydrazones



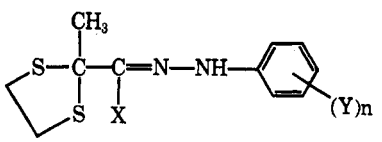
Compound number	$(Y)_n$	mp, °C	Analysis		Miticidal activity	
			Calcd, %	Found, %	LC_{50}, ppm	Repellency, ppm
22	Unsubstituted	63–65	C, 48.42 H, 4.80 N, 10.27	48.35 4.76 10.03	92	>100
23	2-CH_3	95–98	C, 50.24 H, 5.27 N, 9.77	50.16 5.69 9.41	39	50
24	2-F	64–65	C, 45.43 H, 4.16 N, 9.68	45.52 4.19 9.76	27	25

(Continued)

Table III (*Continued*)

Compound number	$(Y)_n$	mp, °C	Analysis		Miticidal activity	
			Calcd, %	Found, %	LC, ppm	Repellency
25	2-CF_3	105–106	C, 42.29 H, 3.55 N, 8.22	42.29 3.57 8.30	22	12
26	3-CF_3	120–122	C, 42.29 H, 3.55 N, 8.22	42.40 3.51 8.09	12	6
27	4-F	84–85	C, 45.43 H, 4.16 N, 9.63	45.67 4.19 9.77	44	50
28	4-Cl	97–99	C, 42.99 H, 3.94 N, 9.12	43.06 4.06 8.81	16	25
29	4-Br	101–102	C, 37.56 H, 3.44 N, 7.97	37.82 3.49 7.98	13	12
30	4-CH_3	105–106	C, 50.24 H, 5.27 N, 9.77	50.42 5.07 9.84	38	50
31	4-OCH_3	90–91	C, 47.59 H, 4.99 N, 9.25	47.86 5.03 9.34	68	100
32	2,3-Cl_2	160–161	C, 38.66 H, 3.25 N, 8.20	38.68 3.39 7.95	>75	>100
33	2,5-Cl_2	199–200	C, 38.66 H, 3.25 N, 8.20	38.64 3.06 8.28	63	100
34	3,4-Cl_2	102–103	C, 38.66 H, 3.25 N, 8.20	38.91 3.37 8.26	24	50
35	2-Cl, 5-CF_3	147–148	C, 38.40 H, 2.96 N, 7.47	38.63 3.00 7.30	11	12
36	2-Cl, 4-NO_2	138–139	C, 37.50 H, 3.15 N, 11.93	37.14 3.07 11.95	>74	>100
37	2,4,6-Cl_3	90–92	C, 35.12 H, 2.68 N, 7.45	35.42 2.99 7.51	17	25

Table IV. Chemical Data for Thioketal Phenylhydrazones



Compound number	X	$(Y)_n$	mp, °C	Analysis	
				Calcd, %	Found, %
38	Br	4-Br	88–90	C, 33.35 H, 3.05 N, 7.07	33.28 3.12 6.87
39	CN	2,4-Cl_2	153–155	C, 43.37 H, 3.34 N, 12.65	43.44 3.04 12.33
40	$N(CH_3)_2$	2,4-Cl_2	78–80	C, 44.57 H, 4.89 N, 20.24	44.62 5.05 20.37
41	SC_6H_5	2,4-Cl_2	113–116	C, 49.17 H, 3.88 N, 6.75	49.61 4.13 6.66
42	$COCH_3$	2,4-Cl_2	194–195	C, 44.70 H, 4.04 N, 8.02	44.90 4.33 8.15

made in the thioketal adducts (structure II) without loss of the excellent miticidal and mite repellent activity.

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LITERATURE CITED

Beyer, C., Claisen, L., *Chem. Ber.* **21,** 1697 (1888).
Büchel, K. H., Draber, W., Hammann, I., Unterstenhöfer, G., Netherlands Patent 68-13353 (1969).
Bülow, C., Neber, P., *Chem. Ber.* **46,** 2370 (1913).
Dieckmann, W., Platz, L., *Chem. Ber.* **38,** 2986 (1905).
Draber, W., Büchel, K. H., Hammann, I., Unterstenhöfer, G., South African Patent 69-3968 (1970).
Favrel, G., *Bull. Soc. Chim. Fr.* **41,** 1494 (1927).
Fieser, L. F., Fieser, M., "Reagents for Organic Synthesis," Wiley, New York, N.Y., 1967, pp 356–376.
Huisgen, R., Koch, H.-J., *Justus Liebigs Ann. Chem.* **591,** 200 (1955).
Kaugars, G., Gemrich, E. G., 158th National Meeting, *American Chemical Society*, New York, N.Y., September 1969.
Moon, M. W., *J. Org. Chem.* **37,** 386 (1972).
Parkes, G. D., Tinsley, S. G., *J. Chem. Soc.* 1861 (1934).

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