5-Dimethylamino-1,3-dithiane類の合成と殺虫活性

誌名	日本農薬学会誌
ISSN	03851559
巻/号	163
掲載ページ	p. 397-404
発行年月	1991年8月

J. Pesticide Sci. **16**, 397–404 (1991)

Original Article

Synthesis and Insecticidal Activity of 5-Dimethylamino-1,3-dithianes*

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(Received May 16, 1990)

A series of 2-cyano-5-dimethylamino-1,3-dithianes was synthesized and their insecticidal and miticidal activities were examined. Most of the compounds prepared in this study exhibited potent activities against rice stem borers, two-spotted spider mites, small brown plant hoppers, common cutworms and twenty-eight-spotted ladybirds. Substitution of electron-withdrawing groups (chloro, bromo, nitro or trifluoromethyl) on the benzene ring in aryl derivatives or alkyl group having a carbon six to ten on the nitrogen atom of carbamoyl in carbamoyl derivatives such as 2-(4-bromophenyl)-2-cyano-5-dimethylamino-1,3-dithiane (**2a-4**) and 2-cyano-5-dimethylamino-2-(*N-n*-nonylcarbamoyl)-1,3-dithiane (**2b-13**), respectively, enhanced the activities.

INTRODUCTION

In the previous studies of synthesis and insecticidal activity on nereistoxin-related compounds, 5-dialkylamino-1,3-dithiane derivatives were prepared by taking advantage of the reactivity and availability of bensultap (**1**),[1] and the insecticidal activity of 1,3-dithianes were examined.[2] While studying effects of substituents in 1,3-dithianes on the insecticidal potency, we found that the dialkylamino, especially dimethylamino, group at the 5-position of 1,3-dithiane was essential for the insecticidal activity. Both insecticidal and miticidal activities of monomethylamino derivatives were weak in comparison with those of dimethylamino derivatives. The relationships between the alkylamino groups at the 2-position in 1,3-dithianes and their insecticidal activity showed fair agreement with those seen in the 1,2-dithiolane series.[3]

It is found that 5-dimethylamino-1,3-dithianes bearing electron-withdrawing group(s) such as cyano, carbamoyl, ethoxy carbonyl or acetyl at the 2-position are superior in insecticidal activity to 2-alkyl substituted derivatives.

This paper describes the synthesis and the reactivity of 2-cyano-5-dimethylamino-1,3-dithianes having substituted aryl or carbamoyl at the 2-position. Their structure-activity relationships are also discussed.

MATERIALS AND METHODS

1. Synthesis of 1,3-Dithiane Derivatives

IR spectra were taken on a Shimadzu A-102 spectrometer. ^{1}H NMR spectra were recorded on a Hitachi 60B (60 MHz) or a Varian EM-390 (90 MHz) spectrometer.

1.1 General procedure

2-Aryl-2-cyano-5-dimethylamino-1,3-dithianes (**2a**) (in Table 1) and 2-carbamoyl-2-cyano-5-dimethylamino-1,3-dithianes (**2b**) (in Table 2) were prepared by a method similar to the reported one,[4,5] as shown in Fig. 1.

* Studies on Nereistoxin and its Related Compounds (Part II). For Part I, see Ref. 2).

Table 1 Biological activity of 2-cyano-5-dimethylamino-2-substituted aryl-1,3-dithianes.

Compd. No. **2a**	Ar	Mortality RSB 50 μg/g	SBP 50 ppm	TSM 500 ppm	TL LC_{50} ppm
1	C_6H_5	100	15	10	200
2	4-FC_6H_4	100	15	100	130
3	4-ClC_6H_4	100	75	100	120
4	4-BrC_6H_4	100	100	100	25
5	4-$NO_2C_6H_4$	100	95	60	18
6	4-$NH_2C_6H_4$	100	45	100	25
7	4-$MeOC_6H_4$	100	20	100	35
8	4-MeC_6H_4	100	85	100	25
9	3-FC_6H_4	100	85	100	18
10	3-ClC_6H_4	100	85	80	10
11	3-BrC_6H_4	100	70	100	15
12	3-$NO_2C_6H_4$	100	70	100	15
13	3-$CF_3C_6H_4$	100	95	100	18
14	3-MeC_6H_4	100	30	80	120
15	2-FC_6H_4	100	55	100	15
16	2-ClC_6H_4	100	95	100	15
17	2-BrC_6H_4	100	85	100	10
18	2-$NO_2C_6H_4$	100	85	70	19
19	2-$MeOC_6H_4$	100	20	100	30
20	2-MeC_6H_4	100	20	60	100
21	3,4-$Cl_2C_6H_3$	100	40	50	12
22	2,6-$Cl_2C_6H_3$	100	99	80	15
23	3,5-$Cl_2C_6H_3$	100	55	100	133
24	2,5-$F_2C_6H_3$	100	30	100	30
25	2,5-$Me_2C_6H_3$	100	15	100	25
	NTX	100	80	50	

RSB: Rice stem borers, SBP: Small brown plant hoppers, CC: Common cutworms, TSM: Two-spotted spider mites, TL: Twenty-eight-spotted ladybirds, NTX: nereistoxin, 4-dimethylamino-1, 2-dithiolane.

Compound **1** [*S,S'*-2-dimethylaminotrimethylene di(benzenethiosulfonate)] was allowed to react with aryl acetonitriles and cyano acetamides, which had been either obtained commercially or synthesized by general methods,[6] in the presence of a base, *i.e.*, triethylamine or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), to give 2-aryl- and 2-carbamoyl-1,3-dithianes, respectively.

1,3-Dithiane derivatives were synthesized by the following methods:

1.2 2-(4-Bromophenyl)-2-cyano-5-dimethylamino-1,3-dithiane (**2a-4**)

p-Bromophenyl acetonitrile (2.00 g, 0.01 mol) and **1** (4.3 g, 0.01 mol) were dissolved in chloroform (20 ml) and DBU (3.0 g, 0.02 mol) was added with vigorously stirring at room temperature. The mixture was stirred at 40°C for 4 hr. The reaction mixture was then washed with water, dried over anhydrous magnesium sulfate ($MgSO_4$) and concentrated to dryness. The residue was purified by silica gel column chromatography (eluent, $CHCl_3$) to give **2a-4** (2.25 g, 73.8%) as a light-yellow crystal melting at 112–113°C [oxalate, mp 207–208°C (dec.)]. ^{1}H NMR $\delta_{TMS}^{CDCl_3}$ ppm: 2.32 (6H, s, NMe_2), 3.05–3.60 (5H, m, CH_2-CH-CH_2), 7.51–8.22 (4H, m, Ar-H). Anal. Found: C, 45.39; H, 4.21; N, 8.01, Calcd. for $C_{13}H_{15}BrN_2S_2$: C, 45.48; H, 4.40; N, 8.16. By a similar procedure 2-aryl derivatives (**2a**) were prepared. The physical and analytical data on these compounds are shown in Table 3.

1.3 2-Cyano-2-(N,N-dimethylcarbamoyl)-5-dimethylamino-1,3-dithiane (**2b-18**)

To a vigorously stirred mixture of *N,N*-dimethyl cyanoacetamide (1.12 g, 0.01 mol)

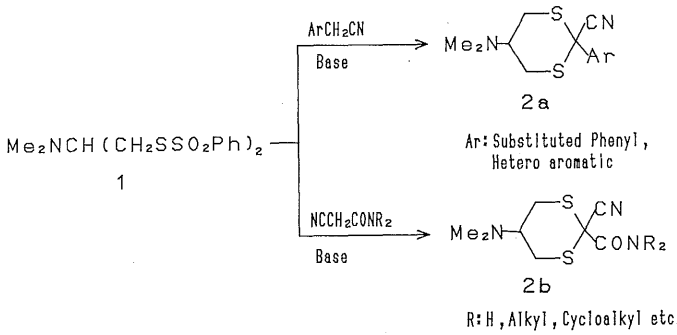

Fig. 1 Synthesis of 2-cyano-5-dimethylamino-1,3-dithianes.

Table 2 Biological activity of 2-cyano-5-dimethylamino-2-substituted carbamoyl-1,3-dithianes.

Compd. No. **2b**		Mortality %				TL LC_{50} ppm
		RSB 50 μg/g	SBP 50 ppm	CC 500 ppm	TSM 500 ppm	
1	NH_2	100	35	100	100	30
2	NHMe	100	50	90	100	25
3	NHEt	100	20	80	90	6
4	NHPr	100	20	60	100	11
5	NHPr-*i*	100	20	40	100	40
6	NHBu	100	20	80	100	40
7	NHBu-*s*	100	25	80	100	33
8	NHBu-*t*	100	45	80	100	20
9	NHC_5H_{11}	100	29	50	50	10
10	NHC_6H_{13}	100	65	70	100	10
11	NHC_7H_{15}	100	80	80	90	23
12	NHC_8H_{17}	100	80	80	100	23
13	NHC_9H_{19}	100	100	90	100	23
14	$NHC_{10}H_{21}$	100	85	50	90	20
15	$NHC_{14}H_{29}$	100	25	70	70	33
16	NHC_3H_5 (cyc.)	100	25	50	40	8
17	NHC_6H_{11} (cyc.)	100	40	50	80	25
18	NMe_2	100	20	80	70	11
19	NEt_2	100	24	80	80	15
20	NPr-i_2	100	26	60	100	16
21	$(CH_2)_4N$-	100	25	20	100	10
22	$MeN(CH_2CH_2)_2N$	100	35	20	100	20
	NTX	100	80	90	50	

RSB: Rice stem borers, SBP: Small brown plant hoppers, CC: Common cutworms, TSM: Two-spotted spider mites, TL: Twenty-eight-spotted ladybirds, NTX: nereistoxin, 4-dimethylamino-1,2-dithiolane.

and **1** (4.3 g, 0.01 mol) in chloroform (20 ml), triethylamine (2.1 g, 0.02 mol) was added and stirred at 40°C for 4 hr. The reaction mixture was washed with water, dried over $MgSO_4$ and concentrated to dryness. The mixture was chromatographed on silicagel column and eluted with chloroform to give **2b-18** as a light-yellow crystal melting at 80–81°C [oxalate, mp 177–178°C (dec.)]. The yield was 72.4%. ^{1}H NMR $\delta_{TMS}^{CDCl_3}$ ppm: 2.33 (6H, s, NMe_2), 3.03 (6H, bs, $CONMe_2$), 2.71–3.40 (5H, m, CH_2-CH-CH_2). Anal. Found: C, 46.46; H, 6.49; N, 16.15, Calcd. for $C_{10}H_{17}N_3OS_2$: C, 46.30; H, 6.61; N, 16.20. By a similar procedure 2-carbamoyl derivatives (**2b**) were prepared. The physical and analytical data on these compounds are shown in Table 4.

2. Oxidation and Reduction of 1,3-Dithianes

2.1 General procedure

The reaction of compound **2a-3** with oxidizing or reducing agent are shown in Fig. 2.

Compound **2a-3** was oxidized with one equivalent of *m*-chloroperbenzoic acid (*m*CPBA) or sodium metaperiodate to give *S*-monooxide (**3**). Oxidation of **2a-3** with three equivalents of *m*CPBA or four equivalents of cerium ammonium nitrate (CAN)[7,8] gave 4-dimethylamino-1,2-dithiolane 1-oxide (**4**, NTXO).[9] Compound **2a-3** was reduced with sodium borohydride to yield 2-dimethylamino-1,3-dimercaptopropane (**5**, NTXH)

2.2 2-(4-Chlorophenyl)-2-cyano-5-dimethylamino-1,3-dithiane 1-oxide (**3**)

Compound **2a-3** (3.0 g, 0.01 mol) was dissolved in methanol (120 ml) and a solution of sodium metaperiodate (2.2 g/35 ml H_2O) was

Table 3 Physical and analytical data on 2-cyano-5-dimethylamino-2-substituted aryl-1,3-dithiane.

Compd. No. **2a**	Yield (%)	mp (°C)	Formula	C (%)		H (%)		N (%)	
				Calcd.	Found	Calcd.	Found	Calcd.	Found
1	79.8	87–88	$C_{13}H_{16}N_2S_2$	59.05	58.86	6.10	6.03	10.59	10.34
2	82.3	68–69	$C_{13}H_{15}FN_2S_2$	55.29	55.03	5.35	5.02	9.92	9.73
3	87.0	110–111	$C_{13}H_{15}ClN_2S_2$	52.25	52.31	5.06	5.03	9.37	9.43
4	73.8	207–208[a)]	$C_{15}H_{17}BrN_2O_4S_2$	41.58	41.68	3.95	3.92	6.46	6.39
5	69.5	198–199[a)]	$C_{15}H_{17}N_3O_4S_2$	45.10	44.81	4.29	4.11	10.52	10.18
6	61.3	141–142[a)]	$C_{15}H_{19}N_3O_4S_2$	48.76	48.43	5.18	5.01	11.37	11.64
7	78.0	194–195[a)]	$C_{16}H_{20}N_2O_5S_2$	49.98	49.67	5.24	5.24	7.29	7.29
8	77.0	95–96	$C_{14}H_{18}N_2S_2$	60.39	60.28	6.52	6.49	10.06	9.87
9	82.0	69–70	$C_{13}H_{15}FN_2S_2$	55.29	55.04	5.35	5.11	9.92	9.65
10	81.0	94–95	$C_{13}H_{15}ClN_2S_2$	52.25	52.18	5.06	5.08	9.37	9.41
11	66.9	195–196[a)]	$C_{15}H_{17}BrN_2O_4S_2$	41.58	41.35	3.95	3.81	6.46	6.25
12	71.0	195–196[a)]	$C_{15}H_{17}N_3O_6S_2$	45.10	44.88	4.29	4.11	10.52	10.25
13	65.0	155–156[a)]	$C_{16}H_{17}F_3N_2O_4S_2$	45.49	45.76	4.06	4.14	6.63	6.41
14	63.0	176–177[a)]	$C_{10}H_{20}N_2O_4S_2$	52.15	51.96	5.47	5.31	7.60	7.24
15	78.0	101–102	$C_{13}H_{15}FN_2S_2$	55.29	55.67	5.35	5.24	9.92	9.59
16	75.0	90–91	$C_{13}H_{15}ClN_2S_2$	52.25	52.10	5.06	5.05	9.37	9.71
17	76.0	112–113	$C_{13}H_{15}BrN_2S_2$	45.48	45.39	4.40	4.21	8.16	8.06
18	63.0	131–132	$C_{13}H_{15}N_3O_2S_2$	50.47	50.42	4.89	4.78	13.58	13.45
19	51.2	219–220[a)]	$C_{16}H_{20}N_2O_5S_2$	49.88	50.11	5.24	5.24	7.29	7.18
20	76.0	235–236[a)]	$C_{16}H_{20}N_2O_4S_2$	52.15	52.22	5.47	5.48	7.60	7.53
21	71.0	206–207[a)]	$C_{15}H_{16}Cl_2N_2O_4S_2$	42.56	42.63	3.81	3.87	6.62	6.46
22	64.9	190–191	$C_{15}H_{16}Cl_2N_2O_4S_2$	42.56	42.41	3.81	3.66	6.62	6.59
23	69.0	225–226[a)]	$C_{15}H_{16}Cl_2N_2O_4S_2$	42.56	42.35	3.81	3.67	6.62	6.39
24	65.0	232–233[a)]	$C_{15}H_{16}F_2N_2O_2S_2$	46.15	46.13	4.13	4.16	7.18	7.09
25	74.0	144–145	$C_{15}H_{20}N_2S_2$	61.60	61.88	6.89	6.83	9.58	9.58

a) Melting points of oxalate salts. All melting points are uncorrected.

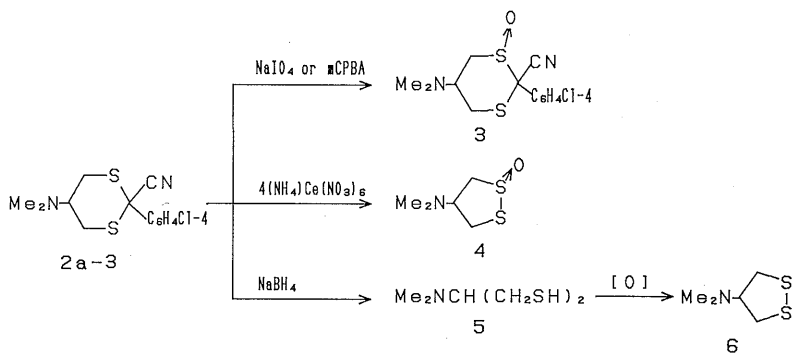

Fig. 2 Oxidation or reduction of compound **2a-3**.

added with vigorous stirring at 25°C. The mixture was stirred at 25°C for 30 min. The reaction mixture was poured into a separate funnel together with chloroform (300 ml), washed with aq. $NaHCO_3$, dried over $MgSO_4$ and concentrated to dryness. The residue was added to oxalic acid (1.0 g) in acetonitrile (100 ml) and kept at room temperature overnight. The precipitate was collected and recrystallized from 95% EtOH to yield **3** (2.0 g, 51.4%) as a colorless crystal melting at 142–144°C (dec.). ^1H NMR $\delta_{TMS}^{D_2O}$ ppm:

Table 4 Physical and analytical data on 2-cyano-5-dimethylamino-2-substituted carbamoyl-1,3-dithianes.

Compd. No. **2b**	Yield (%)	mp (°C)	Formula	C (%)		H (%)		N (%)	
				Calcd.	Found	Calcd.	Found	Calcd.	Found
1	76.0	168–169	$C_8H_{13}N_3OS_2$	41.54	41.39	5.66	5.59	18.16	18.19
2	69.0	90–91	$C_9H_{15}FN_3OS_2$	44.06	43.74	6.16	6.14	17.13	17.08
3	71.0	101–102	$C_{10}H_{17}N_3OS_2$	46.30	46.26	6.61	6.67	16.20	16.09
4	67.4	74–75	$C_{11}H_{19}N_3OS_2$	48.32	48.48	7.09	6.80	15.37	15.47
5	66.8	154–155[a)]	$C_{13}H_{21}N_3O_5S_2$	42.96	42.86	5.82	5.82	11.56	11.13
6	64.9	143–144[a)]	$C_{14}H_{23}N_3O_5S_2$	44.55	44.10	6.14	6.02	11.13	10.86
7	69.3	139–140[a)]	$C_{14}H_{23}N_3O_5S_2$	44.55	44.50	6.14	6.10	11.13	10.84
8	65.6	164–165[a)]	$C_{14}H_{23}N_3O_5S_2$	44.55	44.31	6.14	6.20	11.13	10.87
9	83.5	195–196[a)]	$C_{15}H_{25}N_3O_5S_2$	46.02	46.58	6.44	6.40	10.73	10.89
10	77.5	95–96[a)]	$C_{15}H_{27}N_3O_5S_2$	47.39	46.92	6.71	6.64	10.36	10.15
11	70.9	89–90[a)]	$C_{17}H_{29}N_3O_5S_2$	48.67	49.02	6.97	6.62	10.02	9.77
12	68.4	111–112[a)]	$C_{18}H_{31}N_3O_5S_2$	49.86	49.33	7.21	7.23	9.69	9.49
13	71.2	91–92[a)]	$C_{19}H_{33}N_3O_5S_2$	50.98	51.00	7.43	7.14	9.39	9.27
14	64.0	47–48	$C_{18}H_{33}N_3OS_2$	58.18	58.43	8.95	8.75	11.31	11.39
15	47.8	58–59	$C_{22}H_{41}N_3OS_2$	61.78	61.83	9.66	9.56	9.82	9.62
16	48.0	137–138	$C_{11}H_{17}N_3OS_2$	48.68	48.54	6.31	6.28	15.48	15.75
17	67.0	132–133	$C_{14}H_{23}N_3OS_2$	53.64	53.92	7.39	7.36	13.40	12.86
19	73.1	66–67	$C_{12}H_{21}N_3OS_2$	50.14	50.26	7.36	7.25	14.62	14.61
20	73.0	93–94	$C_{14}H_{25}N_3OS_2$	53.30	53.45	7.99	7.90	13.32	13.28
21	70.4	197–198[a)]	$C_{14}H_{21}N_3O_5S_2$	44.79	44.65	5.64	5.69	11.19	11.74
22	72.4	165–166[a)]	$C_{15}H_{24}N_4O_5S_2$	44.32	44.16	5.95	5.58	13.78	13.79

[a)] Melting points of oxalate salts. All melting points are uncorrected.

3.12 (6H, s, NMe_2), 3.51–4.33 (5H, m, CH_2-CH-CH_2) IR ν_{max}^{KBr} cm^{-1}: 1080 (S=O). Anal. Found: C, 44.18; H, 4.09; N, 6.75, Calcd. for $C_{15}H_{17}N_7O_5S_2$: C, 44.50; H, 4.23; N, 6.92.

2.3 4-Dimethylamino-1,2-dithiolane 1-oxide (NTXO, **4**)

Cerium ammonium nitrate (3.0 g, 0.04 mol) was added within 5 min to a solution of **2a-3** (3.0 g, 0.01 mol) in water-acetonitrile (1 : 4, 50 ml). The mixture was stirred at 10°C for 2.5 hr. Then water (50 ml) was added and the mixture was extracted with dichloromethane (50 ml, four times). The combined organic phase was washed with water (50 ml, four times), dried over $MgSO_4$ and concentrated *in vacuo* to give a pale-yellow oil. The oil was added oxalic acid (1.0 g) in acetonitrile (100 ml) and kept at room temperature overnight. Then the precipitate was collected and recrystallized from 95% EtOH to give **4** (1.1 g, 43.1%) as a colorless crystal melting at 156°C (dec.). ^{1}H NMR $\delta_{TMS}^{D_2O}$ ppm: 3.12 (6H, s, NMe_2), 3.15–4.32 (5H, m, CH_2-CH-CH_2). IR ν_{max}^{KBr} cm^{-1}: 1078 cm^{-1} (S=O).

2.4 2-Dimethylamino-1, 3-dimercaptopropane (NTXH, **5**)

Compound **2a-3** (3.0 g, 0.01 mol) was dissolved in methanol (20 ml) and sodium borohydride (3.0 g, 0.04 mol) was added with vigorous stirring at 5°C. The mixture was stirred at 5°C for 4 hr, washed with aq. $NaHCO_3$, dried over $MgSO_4$ and concentrated to dryness. The oil was added to an acetonitrile solution (100 ml) of oxalic acid (1.0 g) and kept at room temperature overnight. Then the precipitate was collected and recrystallized from 95% EtOH to yield **5** (1.5 g, 62.2%) as a colorless crystal melting at 119–120°C (dec.). ^{1}H NMR $\delta_{TMS}^{D_2O}$ ppm: 2.97 (6H, s, NMe_2), 3.11 (4H, d, J=5.5 Hz, CH_2), 3.44 (1H, qn, CH). IR ν_{max}^{KBr} cm^{-1}: 2475 cm^{-1} (SH).

3. Pests and Test Methods

3.1 Test against common cutworms (Spodoptera litura FABRICIUS)

Test compounds were sprayed at 500 ppm

on soybean seedlings in a pot (9 cm in diameter). After 2 hr two leaves were shone off and separately placed in an ice-cream cup (6 cm in diameter, 4 cm deep). Into the cup, 3rd-instar larvae were released. The cups were kept at 25°C for 48 hr and dead larvae were counted. Ten larvae were used for each dose and the experiments were duplicated.

3.2 Test against small brown planthoppers (Laodelphax srtiatellus FALLÉN)

Each compound was dissolved in a small amount of DMF and diluted with water to prepare a test solution of 50 ppm. Eight rice plant seedlings (7 days after germination) were dipped into the test solution for 10 sec. The seedlings were then placed at the bottom of a test tube containing 1 ml of water. Ten 3rd-instar larvae were released into the tube and after 6 days dead insects were counted. The test tube was maintained at 28°C under a 16 hr light–8 hr dark cycle.

3.3 Test against rice stem borers (Chilo suppressalis WALKER), two-spotted spider mites (Tetranychus urticae KOCH) and twenty-eight-spotted ladybirds (Henosepilachna vigintioctapunctata FABRICIUS)

Biological activity against rice stem borers, twenty-eight-spotted ladybirds and two-spotted spider mites was determined according to the methods reported in the preceding paper.[2)]

RESULTS AND DISCUSSION

In order to study requirements of substituents at the 2-position of 1,3-dithiane, 2-cyano-5-dimethylamino-1,3-dithianes having substituted aryl or carbamoyl at the 2-position were synthesized and their biological activity against rice stem borers (RSB), two-spotted spider mites (TSM), small brown planthoppers (SBP), twenty-eight-spotted ladybirds (TL) and common cutworms (CC) was examined.

As shown in Table 1, 2-substituted aryl-1,3-dithianes (**2a**) had potent activity against RSB and TSM, except for **2a-1**. 4-Bromo (**2a-4**), 4-nitro (**2a-5**), 3-trifluoromethyl (**2a-13**), 2-chloro (**2a-16**) and 2,6-dichloro (**2a-22**) phenyl derivatives were highly insecticidal against SBP.

The insecticidal activity of 2-aryl compounds (**2a**) against TL was affected by the substituent on the benzene ring and the position of the substituent. Against TL, 3- or 2-halogenated derivatives (**2a-9**–**2a-11**, **2a-15**–**2a-17**) were highly active, while 4-halogenated derivatives (**2a-2**–**2a-4**) were relatively inactive insecticidally. Dichlorophenyl (**2a-21**–**2a-23**), difluorophenyl (**2a-24**) and dimethylphenyl (**2a-25**) derivatives were also insecticidally inactive compared with monosubstituted phenyl compounds except 2,6-dichlorophenyl derivative (**2a-22**). When the halogen atom was replaced by methoxy, methyl or amino group, their activity against SBP decreased, while nitro derivatives **2a-5**, **2a-12** and **2a-18** remained insecticidally as potent as halogen derivatives.

Against SBP and TL, the compounds having electron-withdrawing group(s) such as chloro, bromo, nitro or trifluoromethyl on the benzene ring had stronger insecticidal activity than unsubstituted compound (**2a-1**). **2a-4**, **2a-13** and **2a-16** had highest activity against RSB, SBP, TL and TSM.

To examine the effect of replacement of the aryl group by a carbamoyl group, compounds (**2b**) were prepared and examined for their insecticidal and miticidal activities (Table 2).

A series of 2-carbamoyl derivatives (**2b**) had potent insecticidal activity against RSB, TSM and TL. Against CC, **2b** had strong activity comparable to that of NTX (4-dimethylamino-1,2-dithiolane) except for cyclic amino derivatives (**2b-21** and **2b-22**). The activity of **2b** against SBP depended on the substituent on the nitrogen atom and the length of the carbon chain. Compounds **2b-10**–**2b-14**, in the carbamoyl groups of which carbon was six to ten, were highly active, but other compounds were relatively inactive. The potency of **2b** against SBP decreased in the following order: **2b-13** (C9: carbon chain length 9)> **2b-14** (C10)>**2b-11** (C7)=**2b-12** (C8)>**2b-10** (C6).

Against TL, all synthesized **2b** compounds (**2b-1**–**2b-22**) were potent, **2b-3** and **2b-16** in particular.

Based on the structure-activity relationships, requirements of substituents on 1,3-dithianes are summarized as follows:

1) A dialkylamino group, especially dimethylamino, at the 5-position is essential to enhance insecticidal activity.

2) The presence of electron-withdrawing groups at the 2-position increases insecticidal activity.
3) Both electron-withdrawing groups (*i.e.*, chloro, bromo, nitro or trifluoromethyl) on the benzene ring in aryl compounds and alkyl group having carbon six to ten at the nitrogen atom of carbamoyl in carbamoyl compounds enhance insecticidal activity.

In an attempt to confirm whether 1,3-dithiane derivatives are prodrugs, oxidation reduction of 1,3-dithianes were examined. 5-Dimethylamino-1,3-dithianes having electron-withdrawing group(s) at the 2-position easily turned 4-dimethylamino-1,2-dithiolane 1-oxide (**4**, NTXO) or 2-dimethylamino-1,3-dimercaptopropane (**5**, NTXH) by chemical oxidation or reduction, respectively. When **2a-3** was oxidized with one equivalent of *m*-chloroperbenzoic acid (*m*CPBA) or sodium metaperiodate, *S*-monooxide (**3**) was obtained. Oxidation of **2b-3** with three equivalents of *m*CPBA or four equivalents of cerium ammonium nitrate gave NTXO, and reduction of **2a-3** with sodium borohydride gave NTXH. The compounds (**3**–**5**) showed potent insecticidal activity.

Studies have shown that the mode of action of NTX and some of its derivatives is the blocking of cholinergic receptors in the insect central nervous system.[10-14] It is known that cartap (*S,S'*-[2-(dimethylamino)trimethylene] bis(thiocarbamate)) and bensultap [**1**, *S,S'*-2-dimethylaminotrimethylene di(benzenethiosulfonate)] have insecticidal activity comparable to that of NTX. Metabolic studies have indicated that these derivatives are metabolized into NTX and/or NTXO,[15-17] which are considered to be the true active substance. Because of the structural similarity between nereistoxin derivatives and 5-dimethylamino-1,3-dithianes (*i.e.*, both have a dimethylamino group located at the third position from the sulfur atom) and the similarity in observed symptoms in insects, fish and warm-blooded animals, it was speculated that the mode of action must be similar.

From the chemical reactivity of 2-cyano-5-dimethylamino-1,3-dithianes bearing substituted carbamoyl or phenyl at the 2-position and their symptomatic similarity with cartap and bensultap, it is suggested that NTX and/or NTXO may be derived from 5-dimethylamino-1,3-dithianes in a living body, probably by a Pummerer-type reaction. In fact, on a single oral administration of **2a-3** to mice, major metabolites in the urine were NTX and NTXO.[18] Further studies on the metabolites of 1,3-dithianes are now in progress.

The above results led us to conclude that 1,3-dithianes which are converted to 1,2-dithiolanes like NTX or NTXO must be a prodrug of bioactive 1,2-dithiolanes and a new type of insecticides.

ACKNOWLEDGMENTS

The authors wish to thank Drs. Yasuo Sato and Yoshiyuki Kono for their assistance in the biological test.

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要　　約

5-Dimethylamino-1,3-dithiane類の合成と殺虫活性*

光寺弘幸，小西和雄

5位にジメチルアミノ基を，2位に電子吸引性基を導入した1,3-dithiane誘導体が強い殺虫・殺ダニ活性を有することを前報で報告した．本報では，5位にジメチルアミノ基を，2位の一方にシアノ基を，もう一方に置換ベンゼンまたは置換カルバモイルを有する1,3-dithiane誘導体を合成し，その構造と生物活性の関係を検討した．その結果，いずれの化合物も優れた殺虫活性を示した．なかでも，2位の一方にハロゲン置換ベンゼンまたは，窒素原子が炭素数6から10のアルキルで置換されたカルバモイル基を有する誘導体が強い殺虫・殺ダニ活性を示した．とくに，2-cyano-5-dimethylamino-2-(*N*-*n*-nonylcarbamoyl)-1,3-dithianeは，ニカメイガ，ヒメトビウンカ，ハスモンヨトウ，ニジュウヤホシテントウムシ，ナミハダニに卓効を示した．2-Cyano-5-dimethylamino-1,3-dithiane類の酸化，還元反応でネライストキシンモノオキシド（4-dimethylamino-1,2-dithiolane 1-oxide），およびジヒドロネライストキシン（2-dimethylamino-1,3-dimercaptopropane）が得られ，また合成した1,3-dithiane誘導体の殺虫活性発現の仕方，殺虫スペクトルがネライストキシン関連化合物（カルタップ，ベンスルタップ等）と酷似していた．これらのことより，著者らが合成した1,3-dithiane誘導体もカルタップ，ベンスルタップ等と同様に生体内においてネライストキシンに変換され殺虫・殺ダニ活性を示すプロドラッグと考えられ，2位の電子吸引性基は生体内への浸透を促し，代謝によってネライストキシンに変換されやすくするために有用であると考えられる．

* ネライストキシンおよびその関連化合物の研究（第2報）