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Syntheses and Biological Activities of Some Dithiolanylidenemalonate Derivatives and Related Compounds

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The dithiolane ring and malonate moiety of isoprothiolane fungicide were modified to get 4-acyloxy and hydrazide or urea derivatives. Some urea derivatives showed considerable fungicidal activities. Herbicidal activity was also found in a few compounds.

INTRODUCTION

Several dithiolane derivatives are known as agrochemicals and natural products with a variety of agrochemically interesting activities (Maekawa, 1985; Taninaka, 1985). They include fungicide, (isoprothiolane: diisopropyl 1,3-dithiolan-2-ylidenemalonate, **Ia),** insecticide (phosfolan: 2-(diethoxyphosphinylimino)-1,3-dithiolane), acaricide -fungicide (quinomethionate: 6-methyl-1,3-dithiolo〔4,5-〕quinoxaline-2-one), acetylcholine antagonist (nereistoxin: 4-dimethylamino-1,2-dithiolane), and plant growth retardant (asparagusic acid: 1,2-dithiolane-4-carboxylic acid). Many ketene dithioacetals including isoprothiolane have been synthesized and evaluated for pesticides (Taninaka, 1978; Taninaka ***et al., 1976).*** Intending to increase the plant systemic activity in dithiolane fungicides, we tried to modify the structure of isoprothiolane. Since there is a tendency that alcohols, acids, amides, hydrazides and ureas appear to move rather readily in symplast or apoplast (Wakabayashi, 1985), structure modifications were mainly performed 1) on the dithiolane ring to introduce a hydroxyl group followed by acylation to protect it and 2) on the malonate ester group to transform into amide, hydrazide or urea derivatives.

MATERIALS AND METHODS

Chemicals

All melting points were uncorrected. 1H NMR spectra were determined on a JEOL JNM-FX 100 spectrometer using tetramethylsilane as an internal standard and all samples were prepared in $CDCl_3$ unless otherwise noted.

Diisopropyl 1,3-dithiolan-2-ylidenemalonate (isoprothiolane; ***Ia)***

This is a gift from Nippon Noyaku, Ltd. Osaka. Colorless crystals, m.p. 50.5°C. NMRδ_H: 1.29 (12H, d, J=6Hz, $2CH(CH_3)_2$), 3.37 (4H, s, $S(CH_2)_2S$), 5.12 (2H, m, $2CHMe_2$). NMRδ_H (DMSO-d,): 1.23 (12H, d, J=6Hz), 3.44 (4H, s), 4.96 (2H, m). δ_C ($CDCl_3$): 21.8 ($4CH_3$), 37.8 ($S(CH_2)_2S$), 68.6 (2CH), 111.8 (C=), 164.9 (2C=O), 172.5 (=C).

Diethyl 1,3-dithiolanylidenemalonate (1b)

Refluxing an isoprothiolane ethanolic solution in the presence of sodium ethoxide for 5 hr gave **1b** in 61% yield. It was purified by silica-gel chromatography eluted with a hexane-ethyl acetate mixture (5:1). M.p. 97-99°C. NMR δ_H: 1.32 (6H, t, J=7Hz, $2CH_2CH_3$), 3.36 (4H, s, $S(CH_2)_2S$), 4.34 (4H, q, J= 7Hz, CH_2CH_3).

Dimethyl homolog (1c) was similarly obtained from isoprothiolane by reacting with sodium methoxide. M.p. 69-69.5°C. NMR δ_H: 3.39 (4H, s, SCH_2CH_2S), 3.79 (6H, s, $2OCH_3$).

Diisopropyl 4-hydroxy-1,3-dithiolanylidenemalonate (2)

To a mixture of dimethyl sulfoxide (DMSO; 50 ml) and pulverized KOH (6g) were dropwise added diisopropyl malonate (9.4g) and CS_2 (3.8g) with stirring at 15-20°C. After stirring for lhr, chloroacetaldehyde (9.8g) was added to the mixture. Stirred at 50-70°C for 2hr, the reaction mixture was extracted with ether. The ether extract was washed with brine, dried over Na_2SO_4, concentrated, and chromatographed on a silica gel column by eluting with a hexane-ethyl acetate mixture (3:1). The product (3.6g) was recrystallized from diisopropyl ether. M.p. 73-73.5°C. NMR δ_H: 1.28 (12H, dd, $2CH(CH_3)_2$), 2.96 (1H, d, J= 10Hz, HO), 3.52 (2H, d, J=3.6Hz, CH_2S), 5.08 (2H, m, $2CHMe_2$), 5.80 (1H, m, OCHCH,).

Diisopropyl 4-acetoxy-1,3-dithiolanylidenemalonate (3)

The 4-hydroxy derivative 2 of isoprothiolane was acetylated with acetic anhydride in pyridine. The product in 84% yield was purified with silica-gel column chromatography. M.p. 77-79°C. NMR δ_H: 1.28 (12H, dd, $2CH(CH_3)_2$), 2.05 (3H, s, CH_3CO,), 3.54 (2H, d, J=3.5Hz, CH_2S), 5.06 (2H, m, $2CHMe_2$), 6.46 (1H, t, $SCHCH2$).

Diisopropyl 4-benzoyloxy-1,3-dithiolunylidenemalonate (4)

Benzoyl chloride reacted with 2 in pyridine. The product was chromatographed on a silica-gel column and recrystallized from hexane. M.p. 93.5-94.5°C. Yield 31%. NMR δH: 1.28 (12H, dd, $2CH(CH_3)_2$), 3.68 (2H, d, J=3.5Hz, $CHCH_2S$), 5.08 (2H, m, $2CHMe_2$), 6.72 (1H, t, J=3.5Hz, OCHCH,), 7.3-8.1 (5H, m, C_6H_5).

Diisopropyl 4-(N-benzyloxycarbonyl-L-alanyloxy)-1.3-dithiolanylidenemalonate (5)

To a dichloromethane solution containing 2 (1.73g), Z-L-alanine (1.4g), and 4-dimethylaminopyridine (O.lg) was added dicyclohexylcarbodiimide (DCC; 1.3g). After overnight stirring of the mixture, the reaction was stopped by adding 4 drops of acetic acid. Precipitate was filtered off and the filtrate was extracted with ether. The extract was washed subsequently with 5% HCl, 5% Na_2CO_3, and brine, dried over Na_2SO_4, and concentrated. The residue was chromatographed on a silica-gel column eluted with a hexane-ethyl acetate mixture (6:1) to afford white crystals (0.5g), which was recrystallized from diisopropyl ether. M.p. 116-118°C. NMR δ_H: 1.2-1.4 (15H, m, $2CH(CH_3)_2$ and $NCHCH_3$), 3.56 (2H, b, CH_2S), 4.28 (1H, m, $NHCHMe$), 4.96-5.24 (5H, m, $2CHMe_2$, benzyl-CH, and NH), 6.48 (1H, b, OCHCH,), 7.28 (5H, s, C_6H_5).

Diisopropyl 4-(dimethoxyphosphinothioyloxy)-1,3-dithiolanylidenemalonate (6)

To a mixture of 2 (0.5g) and triethylamine (0.2 ml) in dichloromethane cooled in an

ice-bath was added dropwise dimethyl phosphorochloridothionate (0.2 ml). During stirring for one day at room temperature triethylamine (0.2 ml) and dimethyl phosphorochloridothionate (0.4 ml) were added. The reaction mixture was washed with 5% HCl and water and dried over Na_2SO_4. The concentrated residue was chromatographed on a silica-gel column eluted with a hexane-ethyl acetate mixture (6:1) to give a yellowish oil (0.07 g). NMR δ_H: 1.28 (12H, dd, $2CH(CH_3)_2$), 3.6 (2H, b, $CHCH_2S$), 3.7 (6H, dd, J= 14Hz, $P(OCH_3)_2$), 5.06 (2H, m, $2CHMe_2$), 6.32 (1H, m, $OCHCH_2$).

Diisopropyl 4-chloro-1,3-dithiolanylidenemalonate (7)

Compound 2 was chlorinated by reaction with thionyl chloride in usual manner. NMR δ_H: 1.30 (12H, dd, $2CH(CH_3)_2$), 3.68 (2H, m, $CHCH_2S$), 5.04 (2H, m, $2CHMe_2$), 5.86 (1H, t, $ClCHCH_2$).

***Dehydrochlorination of** 4-chloro-1,3-dithiolanylidenemalonate 7*

The mixture of 7 (1.2 mmole), potassium iodide (1.3 mmole) and potassium phthalimide (1.5 mmole) or imidazole (1.5 mmole) in DMF was heated at 150°C till 7 disappeared on monitoring TLC. The reaction mixture was extracted with ether, worked up and chromatographed to give pale orange crystals of diisopropyl 1,3-dithiolenylidenemalonate 8 in a 90% yield. NMR δ_H 1.32 (6H, d, $CH(CH_3)_2$, 5.11 (2H, m, $CHMe_2$), 7.03 (2H, s, HC=CH). Anal. Found: C, 49. 93; H, 5.56. Calcd. for $C_{12}H_{16}O_4S_2$: C, 50.00; H, 5.56%.

Reaction of 1,3- dithiolunylidenemalonates with hydrazine

To the ethanolic solution of isoprothiolane (2.9 g) was added dropwise hydrazine hydrate (0.7 ml) with stirring. After stirring overnight precipitate was collected by filtration and recrystallized from ethanol to give 2.05 g of **9a**. M.p. 179-181°C. Anal. Found: C, 36.58; H, 5.83; N, 18.78. Calcd. for $C_9H_{14}N_2O_3S_2.N_2H_4$: C, 36.73; H, 6.12; N, 19. 05%. NMR δ_H(DMSO-d_6): 1.20 (6H, d, $CH(CH_3)_2$), 3.04 (4H, b, $S(CH_2)_2S$), 3.2-5.2 (7H, b, $NHNH_2$ & NH_2NH_2), 4.8 (1H, m, $CHMe_2$).

Reacting with hydrazine the ethyl homolog of isoprothiolane (1b) gave a similar product **9b**. M.p. 176-178°C. Anal. Found: C, 34.86; H, 5.40; N, 19.52. Calcd. for $C_8H_{16}N_4O_3S_2$: C, 34.39: H, 5.42; N, 20.06%.

***Isopropyl hydrogen** 1,3-dithiolan-2-ylidenemalonate (10a)*

An aqueous ethanolic solution containing isoprothiolane (20 g) and NaOH (2.8 g) was stirred and refluxed for several hours. After removal of ethanol under reduced pressure, precipitate produced by addition of water was filtered off. Acidification of the filtrate with 5% HCl gave crystals. These were dissolved in ethyl acetate and chromatographed on a silica gel column by eluting with hexane-ethyl acetate mixtures (4:1-1:2) to give 7.9 g of colorless crystals, which were recrystallized from diisopropyl ether. M.p. 104-105.5°C. NMR δ_H: 1.42 (6H, d, J= 8Hz, $CH(CH_3)_2$, 3.43(4H, s, SCH_2CH_2S), 5.22 (1H, m, $CHMe_2$), 12.96-13.42 (1H, b, COOH). Anal. Found: C, 43,41; H, 4.87. Calcd. for $C_9H_{12}O_4S_2$: C, 43.53; H, 4.88%.

The ethyl (**10b**) and methyl (**10c**) homologs were similarly obtained from the corresponding diethyl and dimethyl esters, respectively. **10b**, m.p. 139-142°C. NMR δ_H: 0.73 (3H, t, J = 7Hz, CH_2CH_3), 3.46 (4H,s, SCH_2CH_2S), 4,44 (2H, q, CH_2Me), 12.90-

13.26 (1H, b, COOH). Anal. Found: C, 40.99; H, 4.20. Calcd. for $C_8H_{10}O_4S_2$: 41.01; H, 4.31% **10c**, m.p. 131–132°C. NMR δ_H: 3.04 (4H, s, SCH_2CH_2S), 3.97 (3H, s, OCH,), 12.84-13.20 (1H, b, COOH). Anal. Found: C, 38.27; H, 3.67. Calcd. for $C_7H_8O_4S_2$: C, 38.18; H, 3.67%.

2-Isopropoxycarbonyl-2-(1,3-dithiolan-2-ylidene)acetohydrazide ***11a)***

A mixture of **10a** ***(2.5 g),*** N-hydroxysuccinimide (1.3 g) and DCC (2.3 g) in dichloromethane was stirred for 3 hr, then hydrazine hydrate (0.6 ml) was added to the mixture. After further stirring for 12 hr, 3 drops of acetic acid were added to stop the reaction and precipitation was removed by filtration. The filtrate was washed with 5% Na_2CO_3 and brine, dried over Na_2SO_4 and concentrated. To the residue a small amount of dimethylformamide (DMF) was added and insoluble materials were filtered off. Crystals produced by addition of water to the filtrate were collected and recrystallized from ethanol to afford 0.6 g of pale yellowish crystals. M.p. 151–153°C. NMR δ_H: 1.37 (6H, d, J = 6Hz, $CH(CH_3)_2$, 3.32 (4H, s, SCH_2CH_2S), 3.79-4.16 (2H, b, NH_2), 4.15 (1H, m, $CHMe_2$), 8.90-9.17 (1H, b, NH). Anal. Found: C, 41.30; H, 5.45; N, 10.63. Calcd. for $C_9H_{14}N_2O_3S_2$: C, 41.20; H, 5.39; N, 10.68%.

2-Isopropoxycarbonyl-2-(1,3-dithiolan-2-ylidene)acetophenylhydrazide ***(11b)***

By employing phenylhydrazine 11b was similarly obtained. M.p. 186–187.5°C. NMR δ_H: 1.42 (6H, d, J= 6 Hz, $CH(CH_3)_2$), 2.27 (4H, s, SCH_2CH_2S), 4.23 (1H, m, $CHMe_2$), 6.28 (1H, d, J= 5Hz, NH), 6.68-7.29 (6H, m, NH and C_6H_5). Anal. Found: C, 53.14; H, 5.39; N, 8.29. Calcd. for $C_{15}H_{18}O_3S_2N_2$: C, 53.22; H, 5.37; N, 8.29%.

4-(1,3-Dithiolan-2-ylidene)pyrazolidine-3,5-dione ***(12a)***

To an ethanol solution of sodium ethoxide prepared from 55 mg of metallic sodium was added the monoester hydrazide 11a (640 mg) with stirring in an ice-bath. After stirring for 12 hr, the residue obtained by removal of ethanol under reduced pressure was dissolved in water and filtered. Acidifying the filtrate with 5% HCl afforded precipitates which were recrystallized from water to give 170 mg of yellow crystals. M. p. 243-280°C (decomp.). NMR δ_H (DMSO-d,): 3.56 (4H, s, $SCH_2CH_2$2S), 9.66-9.90 (2H, b, NHNH). Anal. Found: C, 35.64; H, 2.98; N, 13.79. Calcd. for $C_6H_6O_2S_2B_2$: C, 35.63; H, 3.00; N, 13.85%.

1-Phenyl-4-(1,3-dithiolan-2-ylidene)pyrazolidine-3,5-dione ***(12b)***

The above mentioned procedure was applied to 11b. The product was recrystallized from methanol to give yellow crystals, m.p. 246–247°C. Yield 60%. NMR δ (DMSO-d_6): 3.66 (4H, s, SCH_2CH_2), 6.92-7.70 (5H, m, C_6H_5), 10.40-11.00 (1H, b, NH). Anal. Found: C, 51.93; H, 3.77; N, 10.06. Calcd. for $C_{12}H_{10}O_2S_2N_2$: C, 51.77; H, 3.62; N, 10.07%.

1-Methyl-2-phenyl-4-(1,3-dithiolan-2-ylidene)pyrazolidine-3.5-dione ***(13a) and*** *3-methoxy-1-phenyl-4-(1,3-dithiolan-2-ylidene)pyrazoline-5-one* ***(14a)***

To a DMF suspension of NaH (50%, 80 mg) was added 12b (0.5 g) with stirring. After stirring for 1 hr, methyl iodide (98%, 0.12 ml) was added to the mixture chilled in an ice-bath. Addition of water to the reaction mixture stirred for 12 hr gave precipitation. The products were submitted to silica-gel column chromatography.

Eluates with hexane-ethyl acetate mixtures (3:1-1:2) afforded 0.49 g of the N-methyl product (13a) and 0.05 g of the O-methyl isomer (14a). The former was further purified by recrystallization from ethanol.

13a: Yellow crystals, m.p. 197-198°C. NMR δ: 3.14 (3H, s, NCH_3), 3.56 (4H, s, SCH, CH_2S), 7.05-7.53 (5H, m, C_6H_5). Anal. Found: C, 53.39; H, 4.19; N, 9.58. Calcd. for $C_{13}H_{12}O_2N_2S_2$: C, 53.40; H, 4.15; N, 9.58%.

14a: Yellowish orange crystals, m.p. 170-170.5°C. NMR δ_H: 3.52 (4H, s, SCH_2CH_2S), 4.03 (3H, s, OCH,), 6.94-7.42 and 7.81-10.02 (5H, m, C_6H_5). Anal. Found: C, 53.58; H, 4.18; N, 9.63. Calcd. for $C_{13}H_{12}O_2N_2S_2$: C, 53.40; H, 4.15; N, 9.58%.

1-Benzyl-2-phenyl-4-(1,3-dithiolan-2-ylidene)pyrazolidine-3,5-dione (13b) ***and*** *3-benzyloxy-1-phenyl-4-(1,3-dithiolan-2-ylidene)pyrazoline-5-one (14b)*

Benzylation of **12b** with benzyl bromide similarly occurred on the nitrogen atom and the enolic oxygen atom to give 13b and 14b.

13b: Yellow crystals, yield 89%, m.p. 143-144°C. NMR δ_H: 3.52 (4H, s, SCH_2CH_2S), 4.72 (2H, s, NCH,), 6.83-7.47 (10H, m, $2C_6H_4$). Anal. Found: C, 61.89; H, 4.38; N, 7.57. Calcd. for $C_{19}H_{16}O_2N_2S_2$: C, 61.93; H, 4.39; N, 7.60%.

14b: Yellowish orange crystals, yield 4.5%, m.p. 183-184°C. NMR δ_H: 3.53 (4H, s, SCH_2CH_2S), 5.41 (2H, s, OCH,), 6.95-7.65 and 7.85-8.10 (10H, m, $2C_6H_5$). Anal. Found: C, 51.57; H, 4.45; N, 7.50. Calcd. for $C_{19}H_{16}O_2N_2S_2$: C, 61.93; H, 4.39; N, 7.60%.

1-Benzoyl-2-phenyl-4-(1,3-dithiolan-2-ylidene)pyrazolidine-3,5-dione (13c)

Under similar conditions for 13a synthesis, 12b reacted with benzoyl chloride to give only N-benzoyl product. The product (yield 26%) was purified by recrystallization from a DMF-ethanol mixture, yellow crystals, m.p. 251-261°C (sublimation). NMR δ_H: 3.69 (4H, s, SCH_2CH_2S), 7.07-7.93 (10H, m, $2C_6H_5$). Anal. Found: C, 59.77; H, 3.83; N, 7.44. Calcd. for $C_{19}H_{14}O_3N_2S_2$: C, 59.66; H, 3.70; N, 7.33%.

3-Isopropoxy-1-phenyl-4-(1,3-dithiolan-2-ylidene)pyrazoline-5-one (14c)

Isopropyl bromide reacted with 12b under the similar conditions for the syntheses of 13a and **14a**, except heating at 50°C for the last 3 hr. The product was chromatographed on a sillicagel column eluted with a hexane-ethyl acetate mixture and recrystallized from a diisopropyl ether-hexane (1:1) mixture to give yellow crystals, m.p. 151-153°C, yield 28%. NMR δ_H: 1.45 (6H, d, J= 6Hz, $CH(CH_3)_2$), 3.51 (4h, s, SCH_2CH_2S), 5.13 (1H, m, $OCHMe_2$), 6.92-8.01 (5H, m, C_6H_5). Anal. Found: C, 56.19; H, 5.04; N, 8.83. Calcd. for $C_{15}H_{16}O_2N_2S_2$: C, 56.22; H, 5.04; N, 8.74%.

1,2-Diphenyl-4-(1,3-dithiolan-2-ylidene)pyrazolidine-3,5-dione ***(13d)***

To DMSO containing pulverized KOH (0.25 g) were dropwise added 1,2-diphenylpyrazolidine-3,5-dione (15a; 0.5 g) and CS_2 (0.16 g) with stirring at 15-20°C. After stirring for 1 hr, the mixture was added with 1,2-dibromoethane (0.2 ml) and heated at 50-70°C. Water was added to the reaction mixture after 2.5 hr to cause precipitation. The precipitate was recrystallized from ethanol to afford yellow crystals (0.22 g), m.p. 208-211°C. NMR δ_H: 3.58 (4H, s, SCH_2CH_2S), 6.97-7.45 (10H, m, $2C_6H_5$). Anal. Found: C, 60.52; H, 4.01; N, 7.88. Calcd. for $C_{18}H_{14}O_2N_2S_2$: C, 60.99; H, 3.99; 7.90%.

1,2-Diphenylpyrazolidine-3,5-dione (15a)

To a mixture of 1,2-diphenylhydrazine (3.7 g) and NaH (60%, 0.96 g) in chlorobenzene (15 ml) was dropwise added diethyl malonate (3.3 ml) with stirring in an ice-bath. After refluxed for 9 hr, while produced ethanol was removed by evaporation, the mixture was added with dichloromethane and water. The separated aqueous phase was washed with dichloromethane and acidified with 5% HCl. The precipitate was recrystallized from ethanol to get pale yellow crystals (0.72 g), m.p. 178-179°C. NMR δ_H: 3.56 (2H, s, CH_2), 7.00-7.41 (10H, m, $2C_6H_5$). Anal. Found: C, 70.91; H, 4.91; N, 10.86. Calcd. for $C_{15}H_{12}O_2N_2$: C, 71.41; H, 4.80; N, 11.11%.

4,4-Dimethyl-1,2-diphenylpyrazolidine-3,5-dione (15b)

To dry DMF containing NaH (62.5%, 0.08 g) was added **15a** (0.5 g) with stirring in an ice-bath. After stirred for 2 hr at room temperature, the mixture was chilled with ice, added with methyl iodide (98%, 0.13 ml), and stirred further for 6 hr. The mixture was diluted with water and extracted with ethyl acetate. The extract was worked up and chromatographed. Colorless crystals (0.14 g) were obtained by recrystallization from hexane, m.p. 129-133°C. NMR δ_H: 1.51 (6H, s, $2CH_2$), 7.16-7.36 (10H, m, $2C_6H_5$). Anal. Found: C, 72.15; H, 5.31; N, 10.52. Calcd. for $C_{17}H_{16}O_2N_2$: C, 72.83; H, 5.76; N, 9.99%.

1,2-Diphenyl-4,4-(3-dipicolyl)-pyrazolidine-3,5-dione (15c)

3-Picolyl chloride reacted with **15a** under similar conditions as for synthesis of 15b. The product was purified by column and thin-layer chromatographies and then recrystallized from acetone to give light yellow crystals, m.p. 194-196°C, with 7% yield. NMR δ_H: 2.35 (4H,s,$2CH_2$), 6.29-6.55 (4H, m), 6.92-7.27 (8H, m), 7.59-7.76 (2H, m), 8.38-8.62 (4H, m). Anal. Found: C, 74.62; H, 5.10; N, 12.87. Calcd. for $C_{27}H_{22}O_2N_4$:C, 74.63; H, 5.11; N, 12.90%.

4-Geranyl-1,2-diphenylpyrazolidine-3,5-dione (15d)

The reaction of 15a with geranyl chloride was conducted as described for 15b. The product was extracted with ether, chromatographed on a silica-gel column, and recrystallized from hexane to give light yellow crystals, m.p. 107-108.5°C, with 10% yield. NMR δ_H: 1.56 (3H, s, CH_3), 1.85 (6H,s,$2CH_3$), 1.93 (4H, b, CH_2CH_2), 2.73-2.96 (2H, m, CH,), 3.34-3.51 (1H, t, CH), 4.90-5.29 (2H, m, 2C=CH), 7.00-7.40 (10H, m, $2C_6H_5$). Anal. Found: C, 76.92; H, 7.20; N, 7.11. Calcd. for $C_{25}H_{28}O_2N_2$: C, 77.27; H, 7.28; N, 7.21%.

4-Bis(methylthio)methylene-1,2-diphenylpyrazolidene-3,5-dione (16)

Product by the reaction of 15a with carbon disulfide and methyl iodide under conditions described for the synthesis of 13d was chromatographed and recrystallized from diisopropyl ether to give yellowish orange crystals, m.p. 142-143.5°C, with 51% yield. NMR δ_H: 2.77 (6H, s, $2SCH_3$), 6.97-7.54 (10H, m, $2C_6H_5$). Anal. Found: C, 60.70; H, 4.55; N, 7.82. Calcd. for $C_{18}H_{16}O_2N_2S_2$: C, 60.64; H, 4.53; N, 7.86%.

***N*-[2-(1,3-Dithiolan-2-ylidene)-2-(isopropoxycarbonyl)acetyl]-*N'*-phenylurea (17b)**

The mixture of isopropyl hydrogen 1,3-dithiolan-2-ylidene-malonate (**10a**, 0.2g)

and thionyl chloride (2 ml) was stirred at room temperature for 12 hr then at 70-80°C for 2 hr. After removal of excess thionyl chloride under reduced pressure and then by azeotrope with toluene, to the residue dissolved in dichloromethane was added phenylurea with stirring in an ice-bath. After stirred for 12 hr at room temperature, the mixture was washed with water, 5% Na_2SO_4, and brine and dried over Na_2SO_4. The product was purified by thin-layer chromatography and then recrystallization from ethanol to get colorless crystals (56 mg), m.p. 147-149°C. NMRδ_H: 1.44 (6H, d, J = 7 Hz, $CH(CH_3)_2$, 3.38 (4H, s, SCH_2CH_2S), 5.18 (1H, m, $CHMe_2$), 6.86-7.66 (5H, m, C_6H_5), 10.30-10.58 (2H, b, 2NH). Anal. Found: C, 52.40; H, 4.93; N, 7.67. Calcd. for $C_{16}H_{18}O_4N_2S_2$: C, 52.43; H, 4.96; N, 7.65%.

N-〔*2-(1,3-Dithiolan-2-ylidene)-2-(ethoxycarbonyl)acetyl*〕-*N'-phenylurea* (**17c**)

According to the procedure for **17b**, this was prepared form **10b**. Colorless crystals, m.p. 159-160°C. Yield, 57%. NMRδ_H: 1.44 (3H, t, J = Hz, CH_2CH_3), 3.40 (4H, s, SCH_2CH_2 S), 4.35 (2H, q, J= 7Hz, CH_2Me), 6.87-7.60 (5H, m, C_6H_5), 10.15-10.69 (2H, b, 2NH). Anal. Found: C, 51.18; H, 4.59; N, 7.99. Calcd. for $C_{15}H_{16}O_4N_2S_2$: C, 51.11; H, 4.59; N, 7.95%.

N-〔*2-(1,3-Dithiolan-2-ylidene)-2-(methoxycarbonyl)acetyl*〕-*N'-phenylurea* (**17d**)

According to the procedure for **17b**, this was prepared from **10c**. Colorless crystals, m.p. 165-166°C. Yield, 32%. NMRδ_H: 3.40 (4H, s, SCH_2CH_2S), 3.93 (3H, s, OCH_3), 6.90 -7.67 (5H, m, C_6H_5), 10.04-10.32 (1H, b, NH), 10.40-10.70 (1H, b, NH). Anal. Found: C, 49.81; H, 4.21; N, 8.30. Calcd. for $C_{14}H_{14}O_4N_2S_2$: C, 49.68; H, 4.18; N, 8.28%.

1-Phenyl-5-(1,3-dithiolan-2-ylidene)perhydropyrimidine-2,4,6-trione (**18b**)

To a dry ethanol solution of sodium ethoxide prepared from 0.25 g of metallic sodium was added isoprothiolane (3 g). To the mixture refluxed for 2 hr was added dropwise a hot ethanol solution of phenylurea (1.5 g). The reaction mixture was refluxed for 8 hr, cooled, and poured into water. Formed precipitate was recrystallized from a DMF-ethanol mixture to give 0.86 g of crystals, m.p. 241-267°C (subl.). NMR δ_H: (DMSO-d_6): 13.48 (4H, SCH_2CH_2S), 7.06-7.56 (5H, m, C_6H_5), 11.21-11.47 (1H, s, NH). Anal. Found: C, 50.89; H, 3.31; N, 9.14. Calcd. for $C_{13}H_{10}O_3N_2S_2$: C, 50.96; H, 3.30; N, 9.15%.

*1-**Methyl**-3-phenyl-5-(1,3-**dithiolan**-2-ylidene)perhydropyrimidine-2,4,6-trione* (**19a**)

To a suspension of NaH (60%, 0.05 g) in dry DMF was added 0.3 g of **18b** and the mixture was stirred at room temperature. After 1 hr methyl iodide (98%, 0.08 ml) was added to the mixture. Stirring was continued for 12 hr and the reaction mixture was poured into water. Formed precipitate was collected and recrystallized from ethanol to afford light yellow crystals (0.21 g), m.p. 229-238-C (subl.). NMRδ_H: 3.42 (4H, s, SCH_2 CH_2S), 3.46 (3H, s, NCH_3), 7.08-7.58 (5H, m, C_6H_5). Anal. Found: C, 52.53; H, 3.81; N, 8.73. Calcd. for $C_{14}H_{12}O_3N_2S_2$: C, 52.48; H, 3.78; N, 8.75%.

1-Isobutyl-3-phenyl-5-(1,3-dithiolan-2-ylidene)perhydropyrimidine-2,4,6-trione (19b)

This was prepared from **18b** and isobutyl bromide according to the procedure for **19a**. The product was recrystallized from ethyl acetate to give light yellow crystals, yield 19%, m.p. 229–238°C (subl.). NMR δ_H: 0.95 (6H, $CH(CH_3)_2$), 2.15 (1H, m, $CHMe_2$), 3.45 (4H, s, SCH_2CH_2S), 3.81 (2H, d, J= 7Hz, NCH_2CH), 7.10-7.59 (5H, m, C_6H_5). Anal. Found: C, 56.15; H, 4.98; N, 7.70. Calcd. for $C_{17}H_{18}O_3N_2S_2$: C, 56.32; H, 5.01; N, 7.73%.

Bioassays

All bioassays were carried out at the Biological Research Center of Nihon Noyaku Co. First screening for fungicides was performed according to the routine procedures at 200 ppm against *Alternaria mali, Botrytis cinerea, Cercospora* ***kikuchii, Cochliobolus miyabeanus,*** *Erysiphe* ***graminis,*** *Fusarium oxysporum f. sp. cucumerinum,* ***Phytophthora infestans, Pseudomonas*** *lachrymans, Pseudoperonospora* ***cubensis,*** *Puccinia* ***coronata,*** *Pyricularia* ***oryzae, Rhizoctoniu solani,*** and ***Xanthomonas oryzae.*** Since four of these 13 phytopathogens showed certain sensitivity to the tested chemicals, the assay procedures are briefly described only for them. *Alternaria mali* was inoculated on apple leaves on the same day with treatment by spraying of a test chemical. The fungicidal activity was compared with that of polyoxins. ***Phytophthora infestans*** was inoculated on tomato plants in a pot one day after spraying of a test chemical. Pseudoperonospora cubensis was inoculated on cucumber plants in a pot one day after treatment with a test chemical by spraying. *Pyricularia oryzae* was inoculated on rice plants in a pot one day before treating with a test chemical by spraying.

Herbicidal activities for paddy field were assayed by pouring test chemicals to water of 3 cm depth at the dose of ***50*** g/a and surveyed the weed density two weeks after treatment. Rice plants, *Oryza* ***sativa,*** were treated 6 days after transplanting. *Scirpus* ***juncoides*** was at the emergence or first leaf stage. ***Echinochloa*** *crusgalli* and *Cyperus* ***serotinus*** were at the first leaf stage. *Sagittaria pygmaea* was at the second leaf stage.

For insecticidal activities *Spodoptera litura* larvae were fed with artificial feed containing a test chemical at 500 ppm. *Nilaparvata lugens* larvae of resistance strain to organophosphate and carbamate insecticides were put on rice seedlings which had been treated with a test chemical by dipping in a 200 ppm suspension and dried.

RESULTS AND DISCUSSIONS

Syntheses

Modification of the dithiolane ring of isoprothiolane (1a) was performed by synthesizing the 4-hydroxy derivative (2) from diisopropyl malonate, carbon disulfide, and chloroacetaldehyde (Taninaka, 1978). It was derived into some acyl (3, 4, 5) and phosphoryl esters (6)(Fig. 1). The hydroxy derivative was converted into the 4-chloro derivative (7). Any attempts to introduce a nitrogen containing heterocycle such as imidazole and phthalimide to the dithiolane ring by using 7 were unsuccessful and only a dehydrochlorinated dithiolene 8 was obtained in a high yield.

The diethyl (1b) and dimethyl (1c) homologs of isoprothiolane were readily prepared by transesterification. Preparation of hydrazide derivatives was tried from several

routes. The direct reaction of hydrazine with dithiolanylidenemalonate diesters (la, b) gave monoester hydrazides **(9a,** b). These crystals contained equimolar hydrazine of crystallization. The monoester hydrazides (11) were smoothly synthesized via reactive esters produced from N-hydroxysuccinimide and partially hydrolized isoprothiolane **(10a)** (Fig. 2). Their cyclization into pyrazolidine-3,5-dione (12) was not satisfactory by refluxing in ethanol, but was well performed in the presence of sodium ethoxide at room temperature (El-Rayyers and Al-Awadi, 1985). The direct synthesis of the

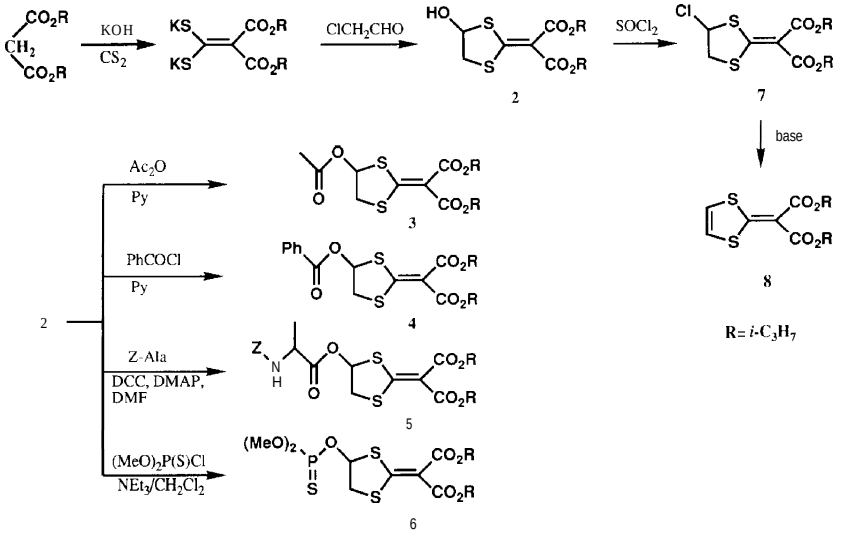


Fig. 1.

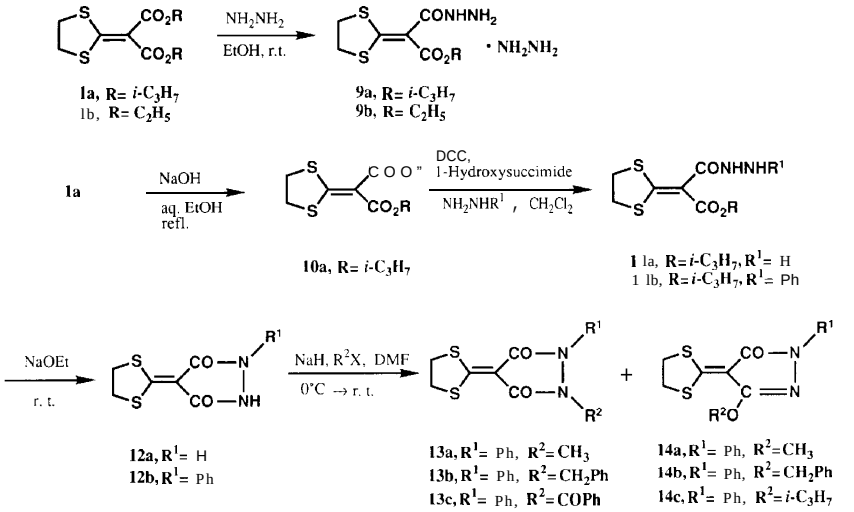


Fig. 2.

dithiolanylidenepyrazolidinedione from the corresponding malonyl dichloride and hydrazine was rather unsatisfactory. Alkylation of the pyrazolidinediones (12) occurred on both the nitrogen and enolic oxygen atoms, whereas acylation occurred exclusively on the nitrogen atom. *N,* N, '-Diphenyldithiolanylidenepyrazolidinedione **(13d)** was conveniently synthesized via malonyl *N,N'*-diphenylhydrazide **(15a)** (Vennerstom and Holmes, 1987). The dithiolanylidene moiety was constructed by the reaction of the malonyl hydrazide with carbon disulfide in the presence of potassium hydroxide followed by reaction with ethylene dibromide (Fig. 3). According to this manner 4-bis(methylthio)methylene-1,2-diphenylpyrazolidene-3,5-dione (16) was synthesized by using methyl iodide. The alkylation of the active methylene carbon of the malonyl hydrazide gave some 4-alkylated pyrazolidenediones (**15b,** c, d).

Some ureides were also synthesized from dithiolanylidnemalonates (1). Monoester ureides (17) were obtained from the malonate half esters (10) by chlorination of the carboxyl group followed by acylation of ureas (Fig. 4). The cyclic ureides (**18**), i.e. barbiturate derivatives, were synthesized by the reaction of 1 with ureas in the presence of sodium ethoxide. Further introduction of an alkyl group on the nitrogen atom was similarly performed as done for the hydrazine derivatives.

Biological activities

Agrochemical routine screening was performed in Nihon Noyaku Co. for fungicides, herbicides, and insecticides. Only positive results, except for isoprothiolane homologs whose fungicidal activity has been well documented (Taninaka, 1978), are listed in Table 1. Some urea derivatives (**17b,c,d, 18b, 19a**) showed considerable fungicidal fungicidal against *Pyricularia oryzae* or *Pseudopernospora cubensis.* The *N*-phenyl cyclic ureide (**18b**) was more active to the former than the latter. Introduction of a methyl group to the N_3 position (**19a**), however, lost the activity to the *Pyricularia* and significantly increased the activity toward the *Psudoperonospora.* That of isobutyl

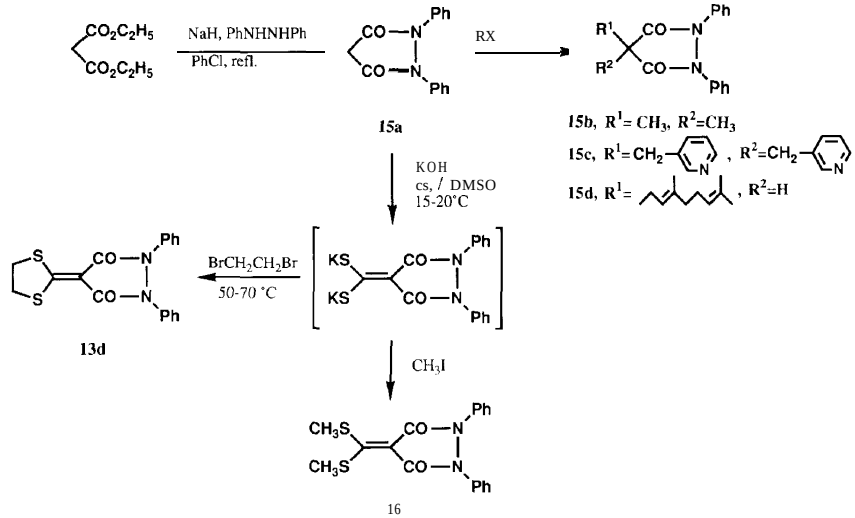


Fig. 3.

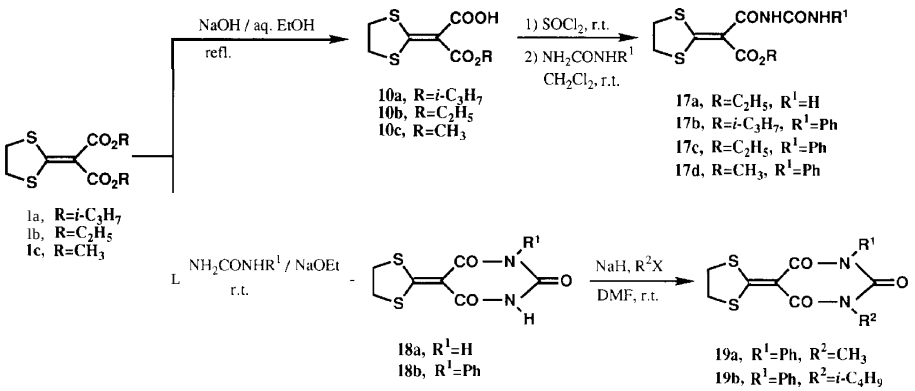


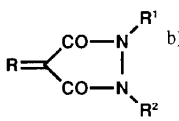
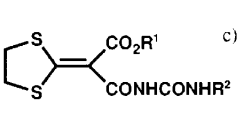
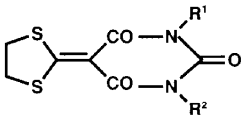
Fig. 4.

Table 1. Fungicidal Activities of Test Chemicals

Compound No.	R	R^1	R^2	Alm	Phi	Psc	Pyo	Rhs
Cyclic hydrazides [a]								
12b		Ph	H		C	-	-	
13d		Ph	H					C
15a	H_2	Ph	Ph			-	C	-
15b	Me_2	Ph	Ph		C			
Monoester ureides [b]								
17a		Et	H	B	-			
17b		*i*-Pr	Ph			A		-
17c		Et	Ph			A		-
17d		Me	Ph			A		
Cyclic ureides [c]								
18b		H	Ph			C	A	-
19a		Me	Ph		C	A		- -
19b		i-Bu	Ph			c		

Alm = *Alternaria mali*, Phi = *Phytophthora infestans*, Psc = *Pseudoperunospora cubensis*, Pyo = *Pyricularia orizae*, Rhs = *Rhizoctonia solani*

A : 95-100 % suppression, B: 85-94 %, C :60-84 %, - : less than 59 %.

a) 
b) 
c) 

group (**19b**) only lost the anti-rice blast activity. In monoester ureides only the isopropyl ester (17b) showed activity against the *Psudoperonospora,* whereas the ethyl and methyl esters were not active to it but to the *Pyricularia*. Some cyclic phenylhydrazides showed weak activity toward some plant diseases.

Some ureides, particularly monoester phenylureides, showed herbicidal activities. The most active one **17c** suppressed 60 to 95 % of the growth of *Echinochloa crusgalli, Scirpus juncoides, Cyperus* ***serotinus,*** and *Sagittaria pygmaea* at the dose of 500 g/lOa. For the last two species it showed 70 to 90 % suppression at 160 g/10a dose. Phytotoxicity to rice plants was not observed at 500 g/lOa.

Weak insecticidal activities against *Nilaparvata lugens* larvae and *Spodoptera litura* larvae were found in some ester N-phenylureides and cyclic ureides.

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