Relationship between Structure and Phytogrowth-Inhibitory Activity of 2,5-Dihydroxy-1,4-dithiane-Related Compounds

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Ten derivatives (II—VI and VIII—XII) from 2,5-dihydroxy-1,4-dithiane (I) and 2,5-dihydroxy-2,5-dimethyl-1,4-dithiane (VII) showed inhibitory activity against the growth of root of *Brassica rapa* L. The inhibitory activity of all ten derivatives was higher than that of the original compounds I and VII. In particular, VIII—XII inhibited the germination of this plant at the concentration of 1.0×10^{-3} M. Among the derivatives VIII—XII, IX exhibited the strongest inhibition. Compound III had the most potent inhibitory activity among the derivatives II—VI. The results indicate that acylation of hydroxyl group with propionic acid enhances the activity. The inhibitory effect of VIII—XII was much stronger than that of II—VI. The findings suggest that methyl groups at 2,5 dispositions play an important role in the inhibitory activity of 2,5-dihydroxy-1,4-dithiane-related compounds. In both derivatives II—VI and VIII—XII, the inhibitory effect of the substituent was in the order of propionyl > acetyl > butyryl > valeryl >isobutyryl. All radicles of this plant treated with the compounds I—XII showed negative geotropism.

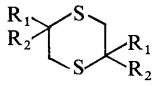
Keywords 2,5-dihydroxy-2,5-dimethyl-1,4-dithiane; 2,5-dihydroxy-1,4-dithiane; *Brassica rapa* L.; phytogrowth-inhibitory activity; radicle; negative geotropism; 2,5-dihydroxy-1,4-dithiane-related compound; structure–activity relationship

It has recently been reported that 2,5-dihydroxy-1,4-dithiane (I), 2,5-diacetoxy-1,4-dithiane (II), 2,5-dihydroxy-2,5-dimethyl-1,4-dithiane (VII) and 2,5-diacetoxy-2,5-dimethyl-1,4-dithiane (VIII) showed phytogrowth-inhibitory activities.[1] All radicles of plants treated with the four compounds were also found to exhibit negative geotropism, with VIII showing the most potent phytogrowth-inhibitory activity. No work has been done, however, on the phytogrowth-inhibitory activity of the other 2,5-dihydroxy-1,4-dithiane derivatives.

We therefore prepared the acyl-derivatives of I and VII and examined their phytogrowth-inhibitory activities to obtain more strongly active substances.

In this work, ten acyl-derivatives (II—VI and VIII—XII, Table I) of I and VII were derived and their inhibitory activities on the root of *Brassica rapa* were investigated. The structure–activity relationship is also discussed.

TABLE I. Chemical Structures of Ten Derivatives (I—XII) of I and VII



Compound	R_1	R_2
2,5-Dihydroxy-1,4-dithiane (I)	OH	H
2,5-Diacetoxy-1,4-dithiane (II)	$OCOCH_3$	H
2,5-Dipropionyloxy-1,4-dithiane (III)	$OCOCH_2CH_3$	H
2,5-Dibutyryloxy-1,4-dithiane (IV)	$OCOCH_2CH_2CH_3$	H
2,5-Diisobutyryloxy-1,4-dithiane (V)	$OCOCH(CH_3)_2$	H
2,5-Divaleryloxy-1,4-dithiane (VI)	$OCOCH_2CH_2CH_2CH_3$	H
2,5-Dihydroxy-2,5-dimethyl-1,4-dithiane (VII)	OH	CH_3
2,5-Diacetoxy-2,5-dimethyl-1,4-dithiane (VIII)	$OCOCH_3$	CH_3
2,5-Dimethyl-2,5-dipropionyloxy-1,4-dithiane (IX)	$OCOCH_2CH_3$	CH_3
2,5-Dibutyryloxy-2,5-dimethyl-1,4-dithiane (X)	$OCOCH_2CH_2CH_3$	CH_3
2,5-Diisobutyryloxy-2,5-dimethyl-1,4-dithiane (XI)	$OCOCH(CH_3)_2$	CH_3
2,5-Dimethyl-2,5-divaleryloxy-1,4-dithiane (XII)	$OCOCH_2CH_2CH_2CH_3$	CH_3

Materials and Methods

Chemicals 2,5-Dihydroxy-1,4-dithiane (I), 2,5-dihydroxy-2,5-dimethyl-1,4-dithiane (VII) and both derivatives (II—VI and VIII—XII) were used for the phytogrowth-inhibitory activity test. Sodium 2,4-dichlorophenoxyacetate (Tokyo Kasei Industry Co., Ltd.) was employed as a standard. Compound I [(racemate), Aldrich Chemical Co., Ltd.]: mp 130 °C (dec.). 2,5-Diacetoxy-1,4-dithiane (II)[1]: mp 178 °C (dec.). MS *m/z*: 236.0157 (M^+, Calcd for $C_8H_{12}O_4S_2$: 236.0176). 2,5-Dipropionyloxy-1,4-dithiane (III): a solution of I (1.0 g) in a mixture of propionic anhydride (5 ml) and pyridine (5 ml) was allowed to stand at room temperature overnight. After the reaction mixture had been treated in the usual way, the product was recrystallized from EtOH to give colorless needles, mp 137.6—140.8 °C (dec.). Yield: 66.0%. MS *m/z*: 264.0491 (M^+, Calcd for $C_{10}H_{16}O_4S_2$: 264.0489). 2,5-Dibutyryloxy-1,4-dithiane

TABLE II. ^{1}H-NMR Data for 2,5-Dihydroxy-1,4-dithiane Derivatives (I—XII)

Compound	Chemical shift (ppm) (Coupling constant Hz)
I[a]	2.80 (2H, dd, J=13.9, 5.8), 3.71 (2H, dd, J=13.9, 1.5), 4.93 (2H, dd, J=5.8, 1.5)
II[a]	2.18 (6H, s), 2.81 (2H, dd, J=4.7, 14.6), 3.69 (2H, dd, J=14.6, 1.8), 5.83 (2H, dd, J=4.7, 1.8)
III	1.06 (6H, t, J=7.6), 2.40 (4H, q, J=7.6), 2.87 (2H, dd, J=14.5, 4.9), 3.51 (2H, dd, J=14.5, 1.9), 5.85 (2H, dd, J=4.9, 1.9)
IV	0.91 (6H, t, J=7.4), 1.59 (4H, qt, J=7.4, 7.0), 2.36 (4H, t, J=7.0), 2.87 (2H, dd, J=14.5, 4.7), 3.50 (2H, dd, J=14.5, 1.6), 5.84 (2H, d, J=1.6)
V	1.12 (6H, d, J=6.9), 1.13 (6H, d, J=6.9), 2.61 (2H, qq, J=6.9, 6.9), 2.87 (2H, dd, J=14.4, 5.0), 3.51 (2H, dd, J=14.4, 1.8), 5.81 (2H, dd, J=5.0, 1.8)
VI	0.87 (6H, t, J=7.1), 1.31 (4H, m), 1.53 (4H, m), 2.37 (4H, t, J=7.1), 2.86 (2H, dd, J=14.6, 4.4), 3.48 (2H, dd, J=14.6, 1.9), 5.83 (2H, dd, J=4.4, 1.9)
VII[a]	1.48 (6H, s), 2.60 (2H, d, J=13.8), 3.39 (2H, d, J=13.8), 5.80 (2H, s)
VIII[a]	2.18 (6H, s), 2.35 (6H, s), 3.85 (4H, s)
IX	1.06 (6H, t, J=7.4), 2.18 (6H, s), 2.62 (4H, q, J=7.4), 3.85 (4H, s)
X	0.87 (6H, t, J=7.3), 1.57 (4H, qt, J=7.3, 7.2), 2.18 (6H, s), 2.58 (4H, t, J=7.2), 3.85 (4H, s)
XI	1.11 (12H, d, J=6.9), 2.18 (6H, s), 2.79 (2H, qq, J=6.9, 6.9), 3.84 (4H, s)
XII	0.85 (6H, t, J=7.2), 1.26 (4H, m), 1.54 (4H, m), 2.18 (6H, s), 2.60 (4H, t, J=7.3), 3.85 (4H, s)

Solvent: dimethylsulfoxide-d_6 except for XII ($CDCl_3$). *a*) Ref. 1.

(IV), 2,5-diisobutyryloxy-1,4-dithiane (V) and 2,5-divaleryloxy-1,4-dithiane (VI) were derived from I following the same method as for III. 2,5-Dibutyryloxy-1,4-dithiane (IV): colorless needles, mp 82.3 °C (dec.). Yield: 61.1%. MS *m/z*: 292.0795 (M^+, Calcd for $C_{12}H_{20}O_4S_2$: 292.0801). 2,5-Diisobutyryloxy-1,4-dithiane (V): colorless needles, mp 95.1 °C (dec.). Yield: 50.0%. MS *m/z*: 292.0799 (M^+, Calcd for $C_{12}H_{20}O_4S_2$: 292.0801). 2,5-Divaleryloxy-1,4-dithiane (VI): off-white crystalline powder, mp 70.6—72.2 °C (dec.). Yield: 85.6%. MS *m/z*: 320.1121 (M^+, Calcd for $C_{14}H_{24}O_4S_2$: 320.1114). Compound VII (Aldrich Chemical Co., Ltd.): mp 64—65 °C (dec.). 2,5-Diacetoxy-2,5-dimethyl-1,4-dithiane (VIII)[1]: yellow oil. 2,5-Dimethyl-2,5-dipropionyloxy-1,4-dithiane (IX): a solution of VII (1.0 g) in a mixture of propionic anhydride (2.5 ml) and pyridine (2.5 ml) was heated at 50—60 °C for 60 min and allowed to stand at room temperature overnight. After the reaction mixture had been treated in the usual way, the product obtained was a yellow oil. Yield: 43.9%. 2,5-Dibutyryloxy-2,5-dimethyl-1,4-dithiane (X), 2,5-diisobutyryloxy-2,5-dimethyl-1,4-dithiane (XI) and 2,5-dimethyl-2,5-divaleryloxy-1,4-dithiane (XII) were derived from VII by the same method as for IX. As mentioned above, parent peaks (M^+) could be found in high resolution electron impact (EI) mass spectrometry of acyl derivatives II—VI. On the other hand, only peaks corresponding to 1/2 M^+ were confirmed in the high resolution EI mass spectrometry of acyl derivatives VIII—XII. Thus, the high resolution fast atom bombardment (FAB) mass spectrometry of acyl derivatives VIII—XII was further examined, and no parent peaks (M^+) were found in the high resolution FAB mass spectrometry of these compounds either. The reason for this is not yet clear. Compound X: yellow oil. Yield: 6.26%. Compound XI: pale brown oil. Yield: 38.7%. Compound XII: yellow oil. Yield: 77.0%. The nuclear magnetic resonance (^{1}H-NMR) data of ten acyl-compounds (II—VI and VIII—XII) are listed in Table II.

Growth-Inhibitory Activity Test of 2,5-Dihydroxy-1,4-dithiane Derivatives (I—XII) on the Root of *Brassica rapa* L. The inhibitory activity test on the root length of this plant was carried out by the method used previously.[1] The root weight of the treated group and the control group, after being dried at room temperature, was measured and averaged. The inhibitory effect was expressed as the ratio of root weight to that of the control (1.00).

Results

Growth-Inhibitory Effect of 2,5-Dihydroxy-1,4-dithiane (I) Derivatives (II—VI) on the Root of *Brassica rapa* L. The inhibitory activities of I and its derivatives (II—VI) on *Brassica rapa* were investigated by measuring root length and weight. The results are summarized in Tables III and IV. Compound I and its derivatives (II—VI) showed inhibitory activity on both the length and weight of root of this plant. At the concentration less than 2.0×10^{-4} M, the inhibitory activity of the derivatives (II—VI) was much higher than that of the original compound I, with III exhibiting the strongest inhibitory activity. The inhibitory effect of V was weak. Unlike I, these derivatives inhibited the growth of the plant root even at the low concentration of 3.0×10^{-5} M. The inhibitory effect of the substituents was in the order of propionyl > acetyl > butyryl > valeryl > isobutyryl. All radicles of this plant treated with I and their derivatives showed negative geotropism at every concentration. The data on inhibitory activities of I and II were almost equal to those given in the previous paper.[1]

Growth-Inhibitory Effect of 2,5-Dihydroxy-2,5-dimethyl-1,4-dithiane (VII) Derivatives (VIII—XII) on the Root of *Brassica rapa* L. The inhibitory effect of VII and its derivatives (VIII—XII) on *Brassica rapa* was examined by measuring the root length and weight. As shown in Tables V and VI, five derivatives, like VII, inhibited the growth of the root of this plant. Compound VII and its derivatives (VIII—XII) completely inhibited plant germination at the concentration of 1.0×10^{-3} M. Among the tested compounds, IX, like III among the derivatives (II—VI), had the most potent inhibitory activity. Like V in the derivatives (II—VI), the inhibitory effect of XI was weak. On the other hand, all derivatives inhibited plant growth even at the low concentration of 3.0×10^{-5} M. The inhibitory activity of the substituents, like derivatives (II—VI), was in the order of propionyl > acetyl > butyryl > valeryl > isobutyryl. All radicles of this plant treated with VII and their derivatives showed negative geotropism at every concentration. The

TABLE III. Growth-Inhibitory Activities of Derivatives (II—VI) of I on the Length of Root of *Brassica rapa* L.

Concentration (M)	Growth (ratio)[a]						
	I	II	III	IV	V	VI	2,4-D[b]
1.0×10^{-3}	0.06	0.05	0.15	0.29	0.34	0.23	0.01
2.0×10^{-4}	1.02	0.14	0.10	0.20	0.43	0.30	0.02
1.0×10^{-4}	1.36	0.32	0.19	0.34	0.46	0.39	0.05
3.0×10^{-5}	1.40	1.01	0.83	0.73	0.89	0.75	0.08

a) Growth in control experiments after 7 d was taken as 1.00. Quantity of light: 9000 lux. Experimental size: 20 seeds/group, 2 groups. *b*) Sodium 2,4-dichlorophenoxyacetate.

TABLE IV. Weight of the Root of *Brassica rapa* L. Treated with I Derivatives (II—VI)

Concentration (M)	Growth (ratio)[a]						
	I	II	III	IV	V	VI	2,4-D[b]
1.0×10^{-3}	0.12	0.11	0.27	0.25	0.28	0.30	0.003
2.0×10^{-4}	0.73	0.12	0.17	0.18	0.37	0.33	0.018
1.0×10^{-4}	1.01	1.12	0.34	0.29	0.39	0.39	0.019
3.0×10^{-5}	1.06	1.11	0.77	0.82	0.92	0.72	N.T.[c]

a) Growth in control experiments after 7 d was taken as 1.00. Quantity of light: 9000 lux. Experimental size: 20 seeds/group, 2 groups. *b*) Sodium 2,4-dichlorophenoxyacetate. *c*) N.T.: not tested.

TABLE V. Growth-Inhibitory Activities of Derivatives (VIII—XII) of VII on the Length of the Root of *Brassica rapa* L.

Concentration (M)	Growth (ratio)[a]						
	VII	VIII	IX	X	XI	XII	2,4-D[b]
1.0×10^{-3}	—[c]	—[c]	—[c]	—[c]	—[c]	—[c]	0.01
2.0×10^{-4}	0.52	0.11	0.09	0.23	0.33	0.23	0.02
1.0×10^{-4}	0.87	0.28	0.14	0.60	0.89	0.37	0.05
3.0×10^{-5}	0.91	0.85	0.70	0.81	0.96	0.78	0.08

a) Growth in control experiments after 7 d was taken as 1.00. Quantity of light: 9000 lux. Experimental size: 20 seeds/group, 2 groups. *b*) Sodium 2,4-dichlorophenoxyacetate. *c*) —: no germination.

TABLE VI. Weight of the Root of *Brassica rapa* L. Treated with VII Derivatives (VIII—XII)

Concentration (M)	Growth (ratio)[a]						
	VII	VIII	IX	X	XI	XII	2,4-D[b]
1.0×10^{-3}	—[c]	—[c]	—[c]	—[c]	—[c]	—[c]	0.003
2.0×10^{-4}	0.35	0.34	0.12	0.32	0.52	0.35	0.018
1.0×10^{-4}	0.92	0.17	0.28	0.73	0.91	1.06	0.019
3.0×10^{-5}	0.78	0.71	0.79	1.40	1.01	1.35	N.T.[d]

a) Growth in control experiments after 7 d was taken as 1.00. Quantity of light: 9000 lux. Experimental size: 20 seeds/group, 2 groups. *b*) Sodium 2,4-dichlorophenoxyacetate. *c*) —: no germination. *d*) N.T.: not tested.

inhibitory effects of VII and VIII were as strong as those given previously.[1]

Discussion

Ten derivatives (II—VI and VIII—XII, Tables I and II) exhibited a growth-inhibitory effect on the roots of *Brassica rapa* L. like the original compounds I and VII (Tables III—VI).[1] The findings indicate that the phytogrowth-inhibitory action might be a common biological activity of 2,5-dihydroxy-1,4-dithiane-related compounds; the inhibitory activity of all acyl derivatives (II—VI and VIII—XII) was much higher than those of the original compounds I and VII.[1] In particular, the introduction of propyl group to hydroxyl groups of I and VII enhanced the activity, indicating that propyl groups attached to hydroxyl groups of C-2 and -5 of 1,4-dithiane skeleton play an important role in the phytogrowth-inhibitory activity of 2,5-dihydroxy-1,4-dithiane related compounds. As regards the inhibitory effects of propyl and other acyl groups, it has been confirmed by molecular mechanical calculation that distance between these acyl groups is closely related to the inhibitory activity.[2] The inhibitory effects of VII-XII at every concentration were also stronger than those of I—VI. The results demonstrate the importance of methyl groups attached to C-2,5 of 2,5-dihydroxy-1,4-dithiane-related compounds on the phytogrowth-inhibitory activity. However, it is not clear whether the difference of activities between the two derivatives is due to (1) the differences of steric effect of methyl groups or (2) the differences of their physicochemical characteristics caused by introduction of methyl group. As a preliminary step to clarifying the inhibitory effect of methyl groups in these derivatives, we are investigating the stable conformation in an ideal molecular model by molecular mechanical calculation.[2]

Like I and VII,[1] negative geotropism was found in all radicles of this plant treated with the ten acyl derivatives. The results suggest that negative geotropism might be a common feature of phytogrowth-inhibitory activity of 2,5-dihydroxy-1,4-dithiane-related compounds. Radicles of bean treated with morphactin have already been reported to show negative geotropism.[3] It has also been found by Yamaguchi and Street[4] that radicles derived from soybean after prolonged storage exhibited negative geotropism.

In addition to 2,5-dihydroxy-1,4-dithiane derivatives, 1,3-dithianum[5] and 1,4-dithianum derivatives[5-9] were earlier reported to have phytogrowth-inhibitory activity. However, only 2,5-dihydroxy-1,4-dithiane-related compounds have shown negative geotropism.

Further studies on the synthesis of various derivatives of I and VII and their phytogrowth-inhibitory activities are in progress, together with their mechanisms.

References and Notes

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