植物成長調節剤としてのイソクロマン-3-オン類の系統的な合成と構造活性相関について

誌名	日本農薬学会誌
ISSN	03851559
著者名	渡辺,克二 谷口,栄二
発行元	日本農薬学会
巻/号	19巻3号
巻号補足	
掲載ページ	p. 209-219
発行年月	1994年8月

J. Pesticide Sci. **19**, 209–219 (1994)

Original Article

Systematic Syntheses and Structure-Activity Relationships of Substituted and Nonsubstituted Isochroman-3-ones as Plant Growth Regulators

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(Received February 18, 1994; Accepted April 27, 1994)

In order to obtain lead compounds for new plant growth regulators, systematic syntheses of isochroman-3-ones and their plant growth regulating activity were investigated. 1-Substituted isochroman-3-ones were synthesized by the reduction and cyclization of 2-acylphenylacetic acids which were obtained by dichromate oxidation of 3-substituted indenes. 1-Substituted-6,7-dimethoxyisochroman-3-ones were synthesized in a similar manner from the corresponding 2-acylphenylacetic acids which were obtained by the Freidel-Crafts acylation of 3,4-dimethoxyphenylacetic acid with acyl halides. The isochroman-3-ones without substituent on the 1-position were obtained by regio selective chloromethylation or hydroxymethylation of phenylacetic acids. The isochroman-3-ones without substituent on the lactone ring had no activity on hypocotyl and radicule elongations of lettuce seedlings at 10 ppm. The 1-phenyl, benzyl and stryl substituted compounds promoted the radicule elongation while inhibited the hypocotyl elongation of lettuce seedlings at 10 ppm. We concluded that the inhibition might be attributed to auxin transport inhibition and the elongation might be attributed to antiauxin activity.

INTRODUCTION

We have searched for lead compounds among a series of naturally occurring benzopyranes, because they have various biological activities. For example, sclerotinin and sclerin (2-dihydrobenzopyran-1,3-dione), produced by *Sclerotinia* sp. promote remarkably seed germination and shoot elongation of rice, caster bean, mung bean and other plants.[1,2] Hydrangenol (2-dihydrobenzopyran-1-one) isolated from the flowers of *Hydrangea hortensia* has synergistic effect on elongation by gibberellin.[3] Flavonoids (1-benzopyran-4-one) widely distributed in plant kingdom have been suggested to be naturally occurring auxin transport inhibitors.[4]

Until now, isochroman-3-ones (2-dihydrobenzopyran-3-one) have been synthesized as the key intermediates for syntheses of isoquinolin alkaloids.[5-7] However, there have been no reports on investigation of their systematic syntheses and biological activities. In this paper, systematic syntheses of various isochroman-3-ones and their biological activities were described.

MATERIALS AND METHODS

1. *Syntheses of Compounds*

There are three synthetic routes for isochroman-3-ones; reduction and cyclization of 2-acylphenylacetic acids, specific introduction of hydroxymethyl into the 6 position of phenylacetic acid, and Vaeyer-Villiger reaction of 2-indanones.

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1.1 Syntheses of 1-substituted isochroman-3-ones

Key intermediates for the syntheses of 1-substituted isochroman-3-ones were 2-acylphenylacetic acids, which can be easily converted to 1-substituted isochroman-3-ones by a reduction and cyclization. Various kinds of the 2-acylphenylacetic acids were obtained by using two synthetic methods.

One method was oxidative cleavage of 3-substituted indenes (method **c**) obtained by the following two methods (Fig. 1): the alkylation of indene with benzyl chloride using the phase transfer catalysis, TEBAC, to give 3-benzyl indenes (method **a**)[8] (34 to 52% yields); the alkylation of indene with alkyl halides using $NaNH_2$ to give 3-phenethyl and lauryl substituted indenes (method **b**) (50 and 48%).

The other method was Friedel-Crafts acylation of phenylacetic acids (method **g**), by which 1-substituted 6,7-dimethoxyisochroman-3-ones and 6,8-dimethoxyisochroman-3-one (**I-13** to **I-23**) were synthesized (Fig. 1). 3,4-Dimethoxyphenylacetic acid esters and acylhalides reacted smoothly in the presence of $AlCl_3$ to give 2-acyl-4,5-dimethoxyphenylacetic acid esters (method **g**) (15 to 57% yields).[9] 2-Acetyl-3,5-dimethoxyphenylacetic acid ester was obtained according to Bycroft & Roberts.[10] These esters were hydrolyzed to the corresponding acids in aq. NaOH solution (method **h**).

The resulting 2-acyl phenylacetic acids were easily converted to the isochroman-3-ones by the reduction and cyclization with $NaBH_4$ and dil. HCl (method **d**). 1-Strylisochroman-3-one (**I-11**) was obtained in a similar manner from 2-cinnamoylphenylacetic acid. 1-Phenacylideneisochroman-3-one (**I-12**) was obtained by the dehydration of 2-(1′,3′-dioxo-3′-phenylpropyl)phenylacetic acid[11] by Ac_2O (method **f**).

Synthesized 1-substituted isochroman-3-ones were listed in Table 1. Synthesized 1-substituted 6,7-dimethoxy, and 6,8-dimethoxyisochroman-3-ones were listed in Table 2. All melting points were uncorrected. The IR spectra were measured on a Shimadzu IR-420 spectrophotometer and the ^1H NMR were measured on a JEOL JNX-FX 100 spectrometer, using tetramethylsilane as an internal standard. Mass spectra were obtained on a ESCO EMD-05A mass spectrometer. Chemical shifts and couplings of protons on the 1 and 4 positions in ^1H NMR spectra, and absorption bands of C=O stretching vibration of lactones

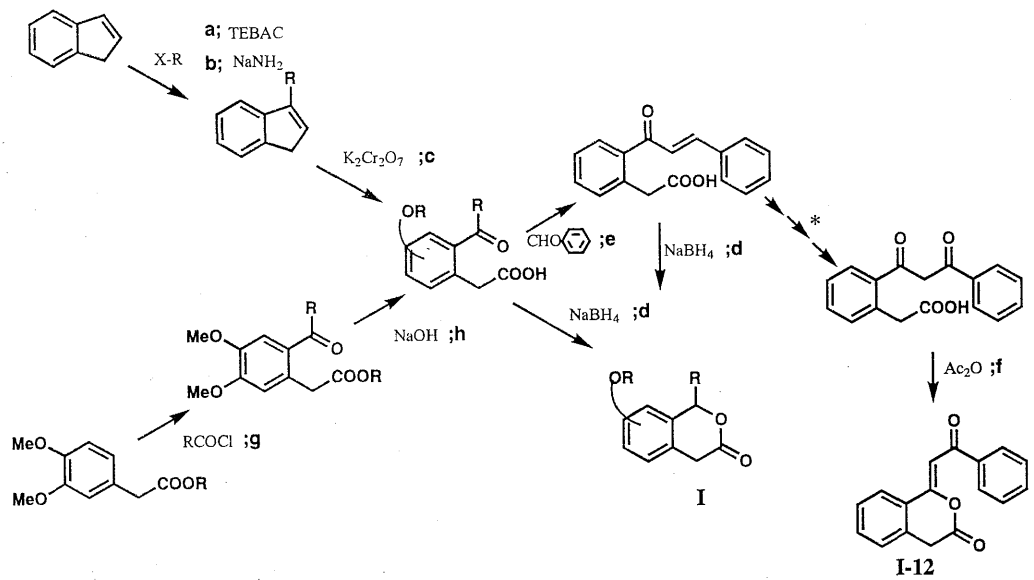

Fig. 1 Synthetic routes of 1-substituted isochroman-3-ones.

* shown in previous paper.[11]

Table 1 Synthesized 1-substituted isochroman-3-ones.

Compd. No.	R	3-Substituted indene		Isochroman-3-one	
		Yield[a] (%)	mp (°C/)[c] bp (°C/mmHg)	Yield[b] (%)	mp (°C/)[c] bp (°C/mmHg)
I-1	*m,p*-diClBz	36	177–179/0.55	5.6	126/Pe.E
I-2	*p*-OMeBz	39	76–78/E	10.3	89–91/E
I-3	*m,p*-OCH_2O-Bz	52	Chromat.	1.9	94–96/E
I-4	*p*-Cl-Bz	47	158–162/0.3	23.4	109–111/AcOEt+E
I-5	Bz	52	132–138/0.6	9.6	91–93/E
I-6	5-indanyl	34	141–151/0.9	8.8	97–100/E
I-7	*o*-Cl-Bz	40	137–138/0.5	17.5	108–109/E+H
I-8	*o,p*-diClBz	34	96–99/Pe.E	23.5	175–176/CH+E
I-9	Phenethyl	50	156–160/2.0	42.0	59–61/E
I-10	Lauryl	48	155–160/0.8	20.8	46–47/Bz
I-11	Stryl	75[d]	107–109/E	54.0	92–94/E
I-12	Phenacylidene			38.0[e]	130–132/Bz

[a] Yield from indene (method **a** and **b**).
[b] Yield from 3-substituted indene (method **c** and **d**).
[c] Figures show pressure of vacuum distillation. The acronyms stand for the solvents for recrystallization. E stands for ether, H: hexane, CH: chloroform, Pe.E: petroleum-ether, Bz: benzene. Chromat. means that the compound was purified by silica-gel column chromatography.
[d] Yield from 2-acetylphenylacetic acid (method **e**).
[e] Yield from 2-(1′,3′-dioxopropyl)phenylacetic acid (method **f**).

Table 2 Synthesized 1-substituted 6,7-dimethoxy, and 6,8-dimethoxyisochroman-3-ones.

Compd. No.	R	2-Acylphenylacetic acid methyl ester		Isochroman-3-one	
		Yield[a] (%)	mp (°C/)[c]	Yield[b] (%)	mp (°C/)[c]
I-13	*p*-Cl-Ph	15	116–119/E+H	67	152–154/Pe.E
I-14	*m,p*-DiOMePh	35	140–144/DCE+E	14	115–116/CH+E
I-15	α-Naphtyl	46	98–100/E	52	154–156/Me
I-16	β-Naphtyl	40	149–151/CH+E	30	83–84/Et
I-17	Phenethyl	15	Chromat./E	33	84–85/E
I-18	Phenylpropyl	18	Chromat.	17	Chromat.
I-19	Bz	48	96–98/E	10	104–106/Et
I-20	*p*-Cl-Bz	45	123–125/E	13	168–171/CH+E
I-21	α-Naphtmethyl	34	111–113/CH+E	12	148–150/Et
I-22	*iso*Pro	57	65–66/E+H	39	82–85/E+Pe.E
I-23	Me	62[d]	62/Pe.E	63	61–62/E+H
	6,8-diOMe	(ref. 64[12])			

[a] Yield from methyl 3,4-dimethoxyphenylacetate (method **g**).
[b] Yield from 2-acylphenylacetic acid methyl ester (method **h** and **d**).
[c] The acronyms stand for the solvents for recrystallization. E stands for ether, H: hexane, CH: chloroform, Pe.E: petroleum ether, Me: methanol, Et: ethanol, DCE: dichloroethane. Chromat. means that the compound was purified by silica-gel column chromatography.
[d] Yield from methyl 3,5-dimethoxyphenylacetate (method **g′**).

Table 3 ^{1}H NMR, IR and elemental analysis data of synthesized 1-substituted isochroman-3-ones.

Compd. No.	^{1}H NMR $\delta_{TMS}^{CDCl_3}$ ppm[a]		IR ν_{max}^{KBr} cm^{-1}	Elemental analysis			
				Found. (%)		Calcd. (%)	
	1	4	C=O	H	C	H	C
I-1	5.58 (t, 1H)	3.62, 3.26 (d, 1H)	1740	4.06	62.47	3.94	62.56
I-2	5.60 (t, 1H)	3.43, 2.83 (d, 1H)	1742	6.06	76.08	6.01	76.10
I-3	5.57 (t, 1H)	3.50, 3.06 (d, 1H)	1735	5.00	72.39	5.00	72.33
I-4	5.60 (t, 1H)	3.00, 3.50 (d, 1H)	1735[b]	4.82	70.31	4.80	70.46
I-5	5.64 (t, 1H)	3.44, 2.86 (d, 1H)	1740[b]	6.00	80.38	5.92	80.65
I-6	5.60 (t, 1H)	3.48, 3.12 (d, 1H)	1740	6.54	80.99	6.52	81.99
I-7	5.63 (dd, 1H)	3.65 (s, 2H)	1745	4.99	70.16	4.80	70.46
I-8	5.60 (dd, 1H)	3.68 (s, 2H)	1745	3.84	61.99	3.94	62.56
I-9	5.30 (t, 1H)	3.75 (s, 2H)	1738	6.37	81.05	6.39	80.92
I-10	5.30 (t, 1H)	3.70 (s, 2H)	1740[b]	10.12	79.59	10.19	79.70
I-11	5.94 (d, 1H)	3.68 (s, 2H)	1740	5.64	81.43	5.64	81.58
I-12	—	3.90 (s, 2H)	1780	4.65	77.03	4.65	77.25
I-13	6.30 (s, 1H)	3.60 (s, 2H)	1755	4.70	63.45	4.74	64.05
I-14	6.28 (s, 1H)	3.60 (s, 2H)	1730	5.88	65.95	5.85	66.27
I-15	6.40 (s, 1H)	3.70 (s, 2H)	1750	5.45	74.82	5.42	75.43
I-16	6.47 (s, 1H)	3.62 (d, 2H)	1740	5.39	74.94	5.42	75.43
I-17	5.25 (t, 1H)	3.65 (s, 2H)	1730	6.50	72.62	6.45	73.05
I-18	5.25 (t, 1H)	3.64 (s, 2H)	1738	6.80	72.69	6.79	73.59
I-19	5.56 (t, 1H)	3.38, 2.80 (d, 1H)	1737	6.16	72.13	6.08	72.42
I-20	5.60 (t, 1H)	3.48, 3.06 (d, 1H)	1740	5.25	64.52	5.15	64.97
I-21	5.67 (dd, 1H)	3.68, 3.32 (d, 1H)	1740	5.82	75.29	5.79	75.79
I-22	5.05 (d, 1H)	3.62 (s, 2H)	1730	7.28	66.93	7.23	67.18
I-23	5.75 (q, 1H)	3.64 (s, 2H)	1738	6.37	64.68	6.34	64.85

[a] Chemical shifts and couplings of protons on 1 and 4 positions. The acronyms in parentheses shows coupling of the protons. s stands for singlet signal, d: doublet, dd: double doublet, t: triplet, q: quartet.

[b] $\nu_{max}^{CHCl_3}$.

in IR spectra were summarized in Table 3.

1-Strylisochroman-3-one (method **d**). $NaBH_4$ (0.9 g) was added to a mixture containing 2-cinnamoylphenylacetic acid (4.5 g), which had been synthesized by the method (method **e**) as reported previously,[11] in EtOH (10 ml) with cooling. The mixture was allowed to stand overnight. After evaporation of the solvent, the residue was acidified with 10% HCl solution. After stirring for 4 hr, the product was extracted with dichloromethane. The extract was washed with aq. Na_2CO_3 solution and dried. Evaporation of the solvent gave an oily residue which was chromatographed on a silica-gel column. Elution with Et_2O and hexane afforded 1-strylisochroman-3-one (**I-11**), which was recrystallized from Et_2O. Yield 2.28 g (54%) mp 92–94°C. Found: C, 81.43; H, 5.64, Calcd. for $C_{17}H_{14}O_2$: C, 81.58; H, 5.64%. NMR $\delta_{TMS}^{CDCl_3}$ ppm: 3.68 (2H, s, Ph-CH$_2$–CO), 5.94 (H, d, J=5 Hz, O–CH-Ph), 6.30 (H, dd, J=5 Hz, 16 Hz, HC–CH=CH), 6.52 (H, d, J=16 Hz, CH=CH-Ph), 7.04–7.40 (9H, m). IR ν_{max}^{KBr} cm^{-1}: 1740 (C=O), 1210 (C–O–C).

1-Phenacylideneisochroman-3-one (method **f**). 2-(1′,3′-Dioxo-3′-phenylpropyl)phenylacetic acid (0.27 g)[11] in Ac_2O (1 ml) was refluxed for 30 min. Evaporation of the solvent and recrystallization of the residue from benzene gave 1-phenacylideneisochroman-3-one (**I-12**). Yield 0.1 g (38%). Found: C, 77.03; H, 4.65, Calcd. for $C_{17}H_{12}O_3$: C, 77.25; H, 4.65%. NMR $\delta_{TMS}^{CDCl_3}$: 3.90 (2H, s, Ph-CH$_2$–C=O), 6.65 (H, s,

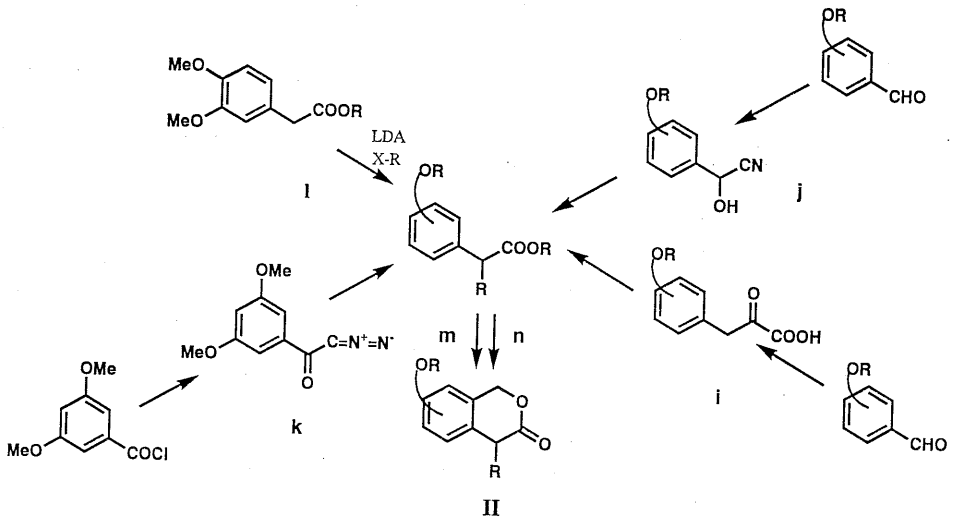

Fig. 2 Synthetic routes of isochroman-3-ones without 1-substituent.

Table 4 Synthesized isochroman-3-ones without 1-substituent.

Compd. No.	R_4	R_5	R_6	R_7	R_8	Methyl phenylacetate		Isochroman-3-one	
						Yield[a] (%)	mp (°C/)[c] bp (°C/mmHg)	Yield[b] (%)	mp (°C/)[c]
II-1			OMe			30	92–97/4.0	14	74–76/E
II-2			OMe	OMe				75	107–108/CH+E
II-3		OMe	OMe			16	Chromat.	16	56–58/E+H
II-4			OMe	OMe	OMe	27	Chromat.	31	86–88/E
II-5			$-OCH_2O-$			30	123–126/2.0	75	131–132/Et
II-6			OH	OMe		35	123–124/Bz+CH	31	178–180/AcOH
II-7			OMe	OH		45[d]	140–141/Bz+CH	11	174–176/A+H
II-8		OH	OMe			38	Chromat.		114–116/E
II-9		OZ[e]	OMe					46	163–165/AcOEt
II-10			OH	OH				33	185–187/AcOEt
II-11				OMe	OH	35	123–124/CH	71	177–179/A
II-12	Me		OMe	OMe		68[f]	Chromat.	64	120–122/E+H
II-13	*iso*Pro		OMe	OMe		30[f]	Chromat.	58	137–139/CH+E
II-14	Lauryl		OMe	OMe		38[f]	Chromat.	38	57–59/Me
II-15	AcOEt		$-OCH_2O-$					22	Chromat.
III								38[g]	79–81/E

[a] Yield from benzaldehyde (method **i** and **j**).

[b] Yield from methyl phenylacetate (method **m** and **n**).

[c] Figures show pressure of vacuum distillation. The acronyms in parentheses stand for the solvents for recrystallization. E stands for ether, H: hexane, CH: chloroform, Bz: benzene, A: acetone, Et: ethanol. Chromat. means that the compound was purified by silica-gel column chromatography.

[d] Yield of chloromethylation of protected compound.

[e] Z stands for methanesulfonyl.

[f] Yield of alkylation (method **l**).

[g] Yield from 2-indanone (method **o**).

C=CH–C=O), 7.09–9.00 (m, 9H). IR ν_{max}^{KBr} cm^{-1}: 1780 (C–C=O), 1660 (C=O), 1600 (C=C), 1150 (C–O–C). MS: *m/z* 264 (M^+; relative intensity 9.5%), 118 (PhCOCH; 37.5), 105 (PhCO; 100), 90 (50), 89 (30.7), 77 (Ph; 87.4).

1.2 Syntheses of isochroman-3-ones without substituent at 1-position

Isochroman-3-ones (**II-1** to **II-15**) without substituent at 1 position were synthesized by regio selective chloromethylation (method **m**) or hydroxymethylation (method **n**) of the phenylacetic acids or Vaeyer-Villiger reaction of 2-indanone (method **o**). Various kinds of phenylacetic acids were synthesized by the following four methods (Fig. 2). From benzaldehydes, 3-methoxy, 2,3-dimethoxy, 3,4,5-trimethoxy, 3,4-methylenedioxy phenylacetic acids were obtained *via* azalactones (method **i**),[13] and 3-hydroxy-4-methoxy, 4-hydroxy-3-methoxy, 2-hydroxy-3-methoxy phenylacetic acids obtained *via* mandelonitrile (method **j**).[14] From benzoyl chloride, 3,5-dimethoxy phenylacetic acid was obtained by Wolff-rearrangement of the diazo-ketone (method **k**).[10] Alkylation on α-position of phenylacetic acid was done using LDA and alkyl halide (method **l**).[15]

8-Hydroxy-7-methoxyisochroman-3-one (**II-11**) was obtained by regio selective hydroxymethylation of 3-hydroxy-4-methoxyphenylacetic acid as Nagata *et al.* reported.[7] 6,7-Dihydroxyisochroman-3-one (**II-10**) was obtained by the demethylation of 6,7-dimethoxyisochroman-3-one by BBr_3. 4-Carboethoxy-6, 7-methylenedioxyisochroman-3-one (**II-15**) was obtained by carboethoxylation of 6,7-methylenedioxyisochroman-3-one with diethylcarbonate. Isochroman-3-one (**III**) was obtained by oxidation of 2-indanone as reported by Swan.[5] Synthesized isochroman-3-ones

Table 5 ^{1}H NMR, IR and elemental analysis data of synthesized isochroman-3-one without 1-substituent.

Compd. No.	^{1}H NMR $\delta_{TMS}^{CDCl_3}$ ppm[a]		IR ν_{max}^{KBr} cm^{-1}[b]		Elemental analysis			
					Found. (%)		Calcd. (%)	
	1	4	C=O	O–H	H	C	H	C
II-1	5.23 (s, 2H)	3.64 (s, 2H)	1740		5.70	66.97	5.66	67.46
II-2	5.24 (s, 2H)	3.60 (s, 2H)	1740		5.79	63.12	5.81	63.09
II-3	5.22 (s, 2H)	3.72 (s, 2H)	1740		5.92	63.09	5.80	63.45
II-4	5.30 (s, 2H)	3.60 (s, 2H)	1745		6.06	60.12	5.92	60.49
II-5	5.16 (s, 2H)	3.57 (s, 2H)	1742		4.17	62.57	4.20	62.50
II-6	5.20 (s, 2H)	3.54 (s, 2H)	1727	3350	5.32	61.27	5.19	61.85
II-7	5.20 (s, 2H)	3.60 (s, 2H)	1728	3380	5.06	61.40	5.19	61.85
II-8	5.27 (s, 2H)	3.72 (s, 2H)	1710	3400	5.19	61.38	5.19	61.85
II-9	5.24 (s, 2H)	3.82 (s, 2H)	1730		4.49	48.43	4.44	48.53
II-10	5.13 (s, 2H)	3.52 (s, 2H)	1720	3250 3430	4.49	59.08	4.47	60.00
II-11	5.40 (s, 2H)	3.60 (s, 2H)	1730	3380	5.14	61.74	5.19	61.85
II-12	5.32 (s, 2H)	3.54 (q, 1H)	1738		6.28	64.71	6.35	64.85
II-13	5.08 (d, 1H) 5.50 (d, 1H)	3.26 (d, 1H)	1740		7.25	67.01	7.25	67.18
II-14	5.12 (d, 1H)	3.53 (t, 1H)	1730		9.82	73.45	9.64	73.37
II-15	5.07 (d, 1H) 5.53 (d, 1H)	4.54 (s, 1H)	1730[c] 1750		4.49	58.23	4.58	59.09
III	5.26 (s, 2H)	3.67 (s, 2H)	1740		5.42	72.74	5.44	72.96

[a] Chemical shift and couplings of protons on 1 and 4 positions. The acronyms in parentheses shows coupling of the protons. s stands for singlet signal, d: doublet, dd: double doublet, t: triplet, q: quartet.

[b] Absorption bands of C=O vibration of lactone and phenolic O–H.

[c] $\nu_{max}^{CHCl_3}$.

without 1-substituent were listed in Table 4. The chemical shifts and couplings of protons on the 1 and 4 positions in ^{1}H NMR spectra, and absorption bands of the C=O and the O–H in IR spectra were summarized in Table 5. The followings are examples of the synthetic procedures.

6,7-Dimethoxyisochroman-3-one (method **m**).[6] A mixture of methyl 3,4-dimethoxyphenylacetate (3.92 g), glacial AcOH (10 ml), conc. HCl (3.3 ml), and 40% formalin (3.3 ml) was stirred at 100°C for 4.5 hr and then poured into water. The reaction mixture was extracted with chloroform and the extract was washed with saturated aq. $NaHCO_3$ and water, and then dried. Evaporation of the solvent, and recrystallization of the residue from EtOH gave 6,7-dimethoxyisochroman-3-one (**II-2**). Yield 2.91 g (75%) mp 107–108°C. (ref. 110–112°C[6]) Found: C, 63.12; H, 5.79, Calcd. for $C_{11}H_{12}O_4$: C, 63.09; H, 5.81%. NMR $\delta_{TMS}^{CDCl_3}$ ppm: 3.60 (2H, s, Ph-$\underline{CH_2}$–C=O), 5.24 (2H, s, Ph-$\underline{CH_2}$–O), 6.10 (6H, s, $\underline{OCH_3}$), 6.35 (2H, s). IR ν_{max}^{KBr} cm^{-1}: 1740 (O–C=O).

7-Methoxy-8-hydroxyisochroman-3-one (method **n**).[7] A mixture of 3-hydroxy-4-methoxyphenylacetic acid[14] (4.3 g) and benzeneboronic acid (5.4 g) in benzene (213 ml) was stirred under reflux for 20 hr with azeotropic removal of water, during which a 1–2 g portion of paraformaldehyde was added at intervals of 2 or 3 hr, and benzene boronic acid (0.5 g) was added after 9 hr. After evaporation of the solvent, water was added to the residue. The mixture was stirred at 100°C for 1.5 hr. The solid formed was filtered off and the mixture was extracted with dichloromethane. The extract was washed with water and dried. Evaporation of the solvent and recrystallization of the residue from acetone-Et_2O gave 7-methoxy-8-hydroxyisochroman-3-one (**II-11**). Yield 3.2 g (71%) mp 177–179°C. (ref. 183–185°C[7]) Found: C, 61.74; H, 5.14, Calcd. for $C_{11}H_{10}O_4$: C, 61.85; H, 5.19%. NMR $\delta_{TMS}^{CDCl_3}$ ppm: 3.60 (2H, s, Ph-$\underline{CH_2}$–C=O), 3.80 (3H, s, $O\underline{CH_3}$), 5.40 (2H, s, Ph-$\underline{CH_2}$–O), 6.70 (H, s, $O\underline{H}$), 6.90 (2H, d, J=8.0 Hz). IR ν_{max}^{KBr} cm^{-1}: 3380 (O–H), 1730 (O–C=O).

Isochroman-3-one (method **o**).[5] Powdered potassium persulfate (8.57 g) was gradually added to a stirred solution of sulfuric acid (12.2 ml), in water (4.1 ml), followed by the addition of absolute EtOH (17 ml) at 15°C. A solution of indan-2-one (2.1 g) in absolute EtOH (17 ml) was added to the mixture at −2 to 3°C during 1 hr. The mixture was stirred for another 30 min at 3°C and 1.5 hr until 18°C. After addition of water to the mixture, the product was extracted with chloroform. The extract was washed with aq. $NaHCO_3$ solution and water, and then dried. Evaporation of the solvent and recrystallization of the residue from petroleum-ether gave isochroman-3-one (**III**). Yield 0.78 g (33%) mp 79–81°C. (ref. 82–83°C[5]) Found: C, 72.74; H, 5.24, Calcd. for $C_9H_8O_2$: C, 72.94; H, 5.44.

2. Biological Activity

2.1 Plant growth regulating activity

The test compounds were dissolved in 1 ml acetone and poured onto a filter paper placed on the bottom of a Petri dish (ϕ=9 cm). After complete evaporation of the solvent, 10 ml of water was added. Seeds (20 seeds for lettuce; 12 seeds for rice) were sowed in it and cultured in an environment-controlled growth room (12 hr photoperiod; relative humidity 60±5%; temperature 25±1°C). The growth regulatory activity of the compounds was evaluated after 5 days by inspecting the rate of elongation or reduction of the radicles and hypocotyles or coleoptiles. The effect on growth was indicated by the percentages of the averaged lengths of treated plants to those of untreated controls.

2.2 Antiauxin activity (Lamina joint test[16])

Ten lamina joint sections excised from the second leaves of etiolated rice seedlings (*Oryza sativa* cv. Reihou), cultivated at 30°C in darkness for 7 days, were used. After having been floated on distilled water for 1 day at 30°C in darkness, they were transferred into the test solution. After 24 hr, the magnitudes of the inclination angles between laminae and sheaths were measured. Antiauxin activity was expressed by the inhibiting activity of the inclination caused by 50 ppm IAA.

RESULTS AND DISCUSSION

1. Syntheses

In the syntheses of 1-substituted isochroman-3-ones, oxidation of 3-substituted

indenes by dichromate (method **c**) was difficult to control as suggested by Halford & Weissmann[12] (Table 1). Especially, yields were quite low for 3-benzylindenes. In these cases the crude products were used in the following reaction without further purification (Table 1).

All of non-substituted isochroman-3-ones synthesized were shown in Table 4. 3,4-Dimethoxy and 3,4-methylenedioxyphenylacetic acids were chloromethylated (method **m**) selectively on the 6 position to give desired lactones (**II-2**, **5**),[6] in which electrophile attacked only at the 6 position of phenylacetic acid as the results of activation by alkoxy substituents. From the other methoxy phenylacetic acids, the desired lactones (**II-1**, **3**, **4**) were obtained in poor yields (14 to 31%), in which chloromethylation at undesired positions seemed to proceed. From 3-hydroxy-4-methoxyphenylacetic acid, 6-hydroxy-7-methoxyisochroman-3-one (**II-6**) were obtained by the reaction. With the other hydroxyphenylacetic acids, it was impossible to isolate the desired lactones from by-products. In this case, the protection of hydroxy group with an electron-withdrawing group was effective to afford the desired lactones, 6-methoxy-7-hydroxyisochroman-3-one (**II-7**) and 5-hydroxyisochroman-3-one (**II-8**) were obtained using phenacyl group[17] and methanesulfonyl group as the protecting group respectively. Bulky alkyl substituents on α-position of the phenylacetic acid seemed to disturb the hydroxymethylation, provably due to steric hindrance, then lowered the yield (**II-12**, **13**, **14**).

2. *Biological Activities*

Biological activities of isochroman-3-ones (**II-1** to **II-11**) without substituent at the 1 position were shown in Table 6. 6-MeO (**II-1**), 6,7-methylenedioxy (**II-5**), and 7-MeO, 8-OH (**II-11**) derivatives inhibited hypocotyl elongation of lettuce seedlings at 100 ppm, while all

Table 6 Plant growth regulating activities[a] of the isochroman-3-ones without 1-substituent in lettuce seedling and rice seedling tests.

Compd. No.	Lettuce				Rice			
	Radicle		Hypocotyl		Radicle		Coleoptile	
	100	10	100	10	100	10	100	10 (ppm)
II-1	−	±	−−−	±	±	±	±	±
II-2	±	±	±	±	±	±	−	±
II-3	±	±	−	±	+	+	±	±
II-4	±	±	−	±	±	±	±	±
II-5	±	±	−−−	±	±	++	±	±
II-6	±	±	±	±	±	±	±	±
II-7	±	±	±	±	±	±	±	±
II-8	++	±	−	±	nd	nd	nd	nd
II-9	+	±	−	±	nd	nd	nd	nd
II-10	+	±	±	±	+	±	±	±
II-11	++++	±	−−	±	++++	+++	±	+
II-12	++	+	−−−	−	nd	nd	nd	nd
II-13	−−	+	−−−	−	nd	nd	nd	nd
II-14	++	+	−	−	±	nd	±	nd
II-15	±	±	−−−	±	−	±	±	±
III	×	±	×	±	nd	±	nd	±
Control	22.8 mm		4.6 mm		157.2 mm		22.4 mm	

[a] ++++: over 80% stimulation, +++: 60–79% stimulation, ++: 40–59% stimulation, +: 20–39% stimulation, ±: 0–19% stimulation and 0–19% inhibition, −: 20–39% inhibition, −−: 40–59% inhibition, −−−: 60–79% inhibition, ×: germination inhibition.

nd means not determined.

Table 7 Plant growth regulating activities[a] of the 1-substituted isochroman-3-ones in lettuce seedling test.

Compd. No.	Hypocotyl			Radicle		
	100	10	1	100	10	1
I-1	−−−	−−−	−−	++	+++	+
I-2	−−−	−−−	−−	±	++++	++
I-3	−−−	−−	±	±	+++	+
I-4	−−−	−−	nd	++	+++	nd
I-5	−−−	−	nd	+	++	nd
I-6	−−−	±	±	±	+	±
I-7	−−	±	±	+++	+++	+
I-8	±	±	±	+	+	±
I-9	−−−	±	±	+	+	±
I-10	±	±	nd	+	+	nd
I-11	−−	−	±	++++	++++	++
I-12	nd	±	+	nd	+	++
I-13	−−	−−−	nd	±	+++	nd
I-15	−−−	−	+	±	++	++
I-16	−−−	−	±	+++	+++	++
I-17	−−	±	±	±	+	±
I-18	−−	±	±	+	++	±
I-19	−	−	−	+++	+++	±
I-20	±	±	−	+++	+++	±
I-21	±	±	±	±	±	±
I-22	−−−	−	nd	±	±	nd
I-23	−−−	−−	nd	−−−	±	nd
BA[b]	nd	−−	−	nd	±	±
NPA[b]	−−	−−	−	−−−	−	−
Isox[b]	−−	−−	−−	−−	−	−
pCIBA[b]	−	±	±	±	++++	+++
IAA	×	+	±	×	+	±
GA_3	++++	++++	++++	+	+	+
ABA	×	×	−−	×	×	−−−

[a] ++++: over 80% stimulation, +++: 60–79% stimulation, ++: 40–59% stimulation, +: 20–39% stimulation, ±: 0–19% stimulation and 0–19% inhibition, −: 20–39% inhibition, −−: 40–59% inhibition, −−−: 60–79% inhibition.

[b] Data in the previous paper[19] were used. **BA** stands for 3-phenacylideneisobenzofuran-1(3*H*)-one, **NPA**: *N*-naphtylphthalamic acid, **Isox**: 2-(3′-phenylisoxazol-5′-yl)phenylacetic acid[11], **pCIBA**: *p*-chlorophenoxyisobutylic acid.

nd means not determined.

of them had no activity at 10 ppm. 4-Substituted isochroman-3-ones (**II-12**, **13**, **14**), except for the 4-carboethoxy derivative (**II-15**), inhibited the hypocotyl elongation at 10 ppm. Most of the isochroman-3-ones without substituent at 1 position had no significant growth regulating activity on rice seedlings, and only 7-MeO, 8-OH derivative (**II-11**) promoted the radicule elongation at 10 to 100 ppm.

As shown in Table 6, the lettuce seedlings test was highly sensitive than the rice seedlings test for screening non-substituted and substituted isochroman-3-ones. In substituted isochroman-3-ones (Table 7), Bz substituted isochroman-3-ones (**I-1** to **I-8**) showed higher inhibiting activity than the other substituted isochroman-3-ones (**I-9** to **I-12**) in hypocotyl elongation. Indanyl (**I-6**), *o*-ClBz (**I-7**) and *o*,*p*-diClBz (**8**) derivatives had weak activities at 100 ppm, but *m*, *p*-diClBz (**I-1**), and *p*-OMeBz (**I-2**) derivatives had higher activities at 1 ppm than 3-phenacylideneisobenzofuran-

Table 8 Competitive effect of some substituted isochroman-3-ones on IAA (50 ppm)-induced lamina inclination of rice seedlings.

Compd.	Inclination (°)			
	50 ppm		5 ppm	
	+IAA	−IAA	+IAA	−IAA
I-5	58.8 (62.5%)		84.9 (93.3%)	
I-11	51.6 (56.7%)	47.9	72.2 (80.2%)	45.5
I-12	56.8 (62.4%)		87.2 (96.9%)	
I-18	52.5 (57.7%)		88.6 (97.4%)	
Isox	65.2 (71.6%)		86.0 (94.5%)	
pCIBA	50.8 (55.8%)	37.3	74.0 (81.3%)	44.3
Control	91.0 (100%)	51.3		

Figures in parentheses show % inclination rates to control (50 ppm IAA).

1(3*H*)-one (**BA**) and *N*-naphthylphthalamic acid (**NPA**), the well known auxin transport inhibitors, and comparable to 2-(3′-phenylisoxazol-5′-yl)phenylacetic acid (**Isox**), an auxin transport inhibitor.[11] Among 1-substituted 6,7-dimethoxyisochroman-3-ones (**I-13** to **I-22**), Ph derivatives (**I-13**, **15**, **16**) strongly inhibited the hypocotyl elongation, but Bz derivatives (**I-19** to **21**) did not inhibit.

Most of isochroman-3-ones with the inhibiting activity of hypocotyl elongation also promoted radicule elongation. However, 1-styryl (**I-11**), *o*-ClBz (**I-7**) isochroman-3-ones, *β*-Napht (**I-16**), Bz (**I-19**), and *p*-ClBz (**I-20**) 6,7-dimethoxyisochroman-3-ones promoted radicule elongation but did not highly inhibit hypocotyl elongation. **I-5**, **I-11**, **I-12** and **I-18** were potent competitive inhibitors for auxin comparable to **pCIBA**, potent antiauxin, while **Isox**, a potent auxin transport inhibitor[11] was less active as an antiauxin (Table 8). As only **pCIBA** promoted the radicule elongation among plant hormones (Table 7), the promotion of radicule elongation by isochroman-3-ones might be attributed to their antiauxin activity.

We suppose that the inhibiting activities of the hypocotyl elongation by the isochroman-3-ones might be attributed to auxin transport inhibition from the following reasons; i) the inhibiting activity of the hypocotyl elongation were only induced by auxin transport inhibitors (**BA**, **NPA**, **Isox**) (Table 7), ii) the degrees of both inhibiting activities had been found to be correlated.[18,19] Isochroman-3-ones might interact with the same active site with the known auxin transport inhibitors because the structural requirements of isochroman-3-ones for the inhibiting activity of hypocotyl elongation were similar to those of the benzoic acid lactones of auxin transport inhibitors.[20] However detailed structural requirements for the activities were little different between the both groups. **BA**, one of the most active auxin transport inhibitors of benzoic acid group,[21] inhibited the elongation of radicule, whereas 1-phenacylideneisochroman-3-one (**I-12**) which had the same structural moiety with **BA**, had no inhibitory activities. Our former study[11] showed that 2-phenyl-5*H*-pyrazolo[5, 1-*a*]isoquinolin-5-one, which had the fused ring structure of **I-12**, had the higher auxin transport inhibiting activity comparable to the benzoic acid group. The comparison of the structure activity relationship of the phenylacetic acid group with those of benzoic acid group will be discussed in the next paper (Watanabe & Taniguchi, under contribution).

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要　　約

植物成長調節剤としてのイソクロマン-3-オン類の系統的な合成と構造活性相関について

渡辺克二，谷口栄二

新規な骨格を有する生理活性物質の検索を目的として，合成例が少ないイソクロマン-3-オンの合成と植物生理活性を検討した．1-置換イソクロマン-3-オンは2-アシルフェニル酢酸の還元・環化により，1位に置換基を有しないイソクロマン-3-オンはフェニル酢酸の6位の選択的なクロロメチル化もしくはヒドロキシメチル化により合成した．ラクトン環状に置換基を有する化合物が高い生理活性を有していた．1-ベンジル，1-フェニル化合物で活性が高く，これらはレタスの幼根の徒長と幼茎の伸長抑制を誘導した．幼根の徒長は抗オーキシン作用により，幼茎の伸長抑制はオーキシンの移動阻害によるものと推察された．