[Chem. Pharm. Bull.]
32(2) 578-584 (1984)

**Inhibitors of Cyclic Adenosine 3',5'-Monophosphate Phosphodiesterase in
Phyllostachys nigra MUNRO var. *henonis* STAPF. and *Phragmites*
communis TRIN., and Inhibition by Related Compounds¹⁾**

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(Received June 11, 1983)

Cyclic adenosine 3',5'-monophosphate (AMP) phosphodiesterase inhibitors present in the culms of *Phyllostachys nigra* MUNRO var. *henonis* STAPF. and the rhizomes of *Phragmites communis* TRIN. (Gramineae) were identified as 2,5-dimethoxy-*p*-benzoquinone, *p*-hydroxybenzaldehyde, syringaldehyde, coniferylaldehyde, vanillic acid, ferulic acid and *p*-coumaric acid. The structure-activity relationship was investigated with 12 derivatives of *p*-benzoquinone, 22 derivatives of benzaldehyde, 10 derivatives of benzyl alcohol, 24 derivatives of benzoic acid and 32 derivatives of C₆-C₃ related compounds.

Keywords—*Phyllostachys nigra* var. *henonis*; *Phragmites communis*; 2,5-dimethoxy-*p*-benzoquinone; *p*-hydroxybenzaldehyde; syringaldehyde; coniferylaldehyde; vanillic acid; ferulic acid; *p*-coumaric acid; cyclic AMP phosphodiesterase inhibitor

We have demonstrated that measurement of cyclic adenosine 3',5'-monophosphate (AMP) phosphodiesterase inhibition can be used as a screening method to detect biologically active compounds present in medicinal plants used in traditional medicines. Inhibitors present in the roots of *Anemarrhena asphodeloides*²⁾ and in the fruits of *Forsythia suspensa*³⁾ were identified as norlignans and lignans, respectively. Several polymethoxy flavonoids were isolated as inhibitors from the peels of *Citrus reticulata* and from the rhizomes of *Iris florentina*.⁴⁾ Saponins and alkaloids were isolated as inhibitors from the roots of *Polygala tenuifolia*⁵⁾ and from the wood of *Picrasma quassioides*,¹⁾ respectively. This paper deals with the identification of cyclic AMP phosphodiesterase inhibitors present in the culms of *Phyllostachys nigra* MUNRO var. *henonis* STAPF, used as an antipyretic, expectorant and antiemetic agent in Chinese medicine, and in the roots of *Phragmites communis* TRIN., which has been used as an antipyretic and diuretic agent in Chinese medicine. The structure-activity relationship in one hundred analogous compounds was investigated, and the results are discussed.

Results and Discussion

The aqueous extracts obtained from the dried culms of *Phyllostachys nigra* MUNRO var. *henonis* STAPF. (Gramineae) and the dried rhizomes of *Phragmites communis* TRIN. (Gramineae) were divided into chloroform-soluble and -insoluble fractions. The chloroform-soluble fractions from both species were found to be more active than the chloroform-insoluble fractions.

In order to identify the cyclic AMP phosphodiesterase inhibitors, both the plants materials were extracted with hot methanol and the extracts were fractionated as described in the experimental section. The fractions that showed relatively high inhibitory effect were

TABLE I. Inhibitory Activity^{a)} of *p*-Benzoquinones and Phenol Derivatives on Cyclic AMP Phosphodiesterase

Compound No.	R ₁	R ₂	R ₃	R ₄	R ₅	R ₆	IC 50 ^{b)} ($\times 10^{-5}$ M)	Source
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1	H	H	H	H			9.3	Commercial ^{c)}
2	Me	H	CHMe ₂	H			19.0	Takeda Ph.
3	Me	H	H	OMe			3.3	Tokyo Univ.
4	OMe	H	OMe	H			12.5	P.n.
5	OMe	H	H	OMe			14.6	Takeda Ph.
6	OH	Me	H	OMe			20.0	Takeda Ph.
7	Cl	Cl	Cl	Cl			4.6	Takeda Ph.
8	Cl	OMe	Cl	OMe			5.7	Takeda Ph.
9	ONa	ONa	-CO-CO-				12.7	Takeda Ph.

10	Me	H					500	Takeda Ph.
11	Me	Me					13.8	Takeda Ph.
12	OMe	OMe					1.0	Takeda Ph.

13	H	H	H	H			13.7	Commercial ^{e)}
14	OH	H	H	H			32.5	Commercial ^{c)}
15	OMe	H	H	H			210	Commercial ^{c)}
16	H	OH	H	H			17.5	Commercial ^{c)}
17	H	OMe	H	H			12.9	Commercial ^{c)}
18	H	H	OH	H			18.0	P.n. & P.c.
19	H	H	OMe	H			48.5	Commercial ^{c)}
20	H	H	OAc	H			32.9	Synthesis
21	OH	OH	H	H			> 500	Commercial ^{c)}
22	OH	OMe	H	H			9.3	Commercial ^{c)}
23	OMe	OMe	H	H			> 500	Commercial ^{c)}
24	OH	H	OH	H			> 500	Commercial ^{c)}
25	OMe	H	OMe	H			105	Commercial ^{c)}
26	OH	H	H	OH			> 500	Commercial ^{c)}
27	OMe	H	H	OMe			130	Commercial ^{c)}
28	H	OH	OH	H			85.5	Commercial ^{c)}
29	H	OMe	OH	H			5.4	Commercial ^{c)}
30	H	OH	OMe	H			50.0	Commercial ^{c)}
31	H	OMe	OMe	H			7.9	Commercial ^{c)}
32	H	OMe	H	OMe			48.8	Commercial ^{c)}
33	H	OMe	OH	OMe			8.3	P.n.
34	H	OMe	OMe	OMe			34.9	Synthesis ^{c)}

35	H	H	H	H			227	Commercial ^{c)}
36	OH	H	H	H			65.0	Commercial ^{c)}
37	OMe	H	H	H			108	Commercial ^{d)}
38	H	OH	H	H			210	Commercial ^{d)}

TABLE I (continued)

Compound No.	R ₁	R ₂	R ₃	R ₄	R ₅	R ₆	IC 50 ^{b)} ($\times 10^{-5}$ M)	Source
39	H	OMe	H	H			66.7	Synthesis
40	H	H	OH	H			10.2	Commercial ^{c)}
41	H	H	OMe	H			51.4	Commercial ^{c)}
42	H	OH	OH	H			> 500	Synthesis
43	H	OMe	OH	H			32.5	Commercial ^{c)}
44	H	OMe	OMe	H			42.9	Commercial ^{c)}

45	H	H	H	H	H	H	410	Commercial ^{c)}
46	OH	H	H	H	H	H	152	Commercial ^{c)}
47	OH	H	H	H	H	Me	240	Commercial ^{c)}
48	OMe	H	H	H	H	H	460	Commercial ^{c)}
49	OMe	H	H	H	H	Me	> 500	Commercial ^{c)}
50	H	OH	H	H	H	H	> 500	Commercial ^{c)}
51	H	OH	H	H	H	Me	87.5	Commercial ^{c)}
52	H	OMe	H	H	H	H	> 500	Commercial ^{d)}
53	H	H	OH	H	H	H	149	Commercial ^{c)}
54	H	H	OH	H	H	Me	68.4	Synthesis
55	H	H	OMe	H	H	H	19.7	Commercial ^{c)}
56	OH	OH	H	H	H	H	> 500	Commercial ^{c)}
57	OH	H	OH	H	H	H	82	Commercial ^{c)}
58	OH	H	H	OH	H	H	81	Commercial ^{c)}
59	OH	H	H	H	OH	H	86	Commercial ^{c)}
60	H	OH	H	OH	H	H	81	Commercial ^{c)}
61	H	OH	OH	H	H	H	> 500	Commercial ^{c)}
62	H	OH	OMe	H	H	H	> 500	Commercial ^{c)}
63	H	OMe	OH	H	H	H	41.7	P.c.
64	H	OMe	OH	H	H	Me	56.6	Synthesis
65	H	OMe	OMe	H	H	H	> 500	Commercial ^{c)}
66	OH	OH	OH	H	H	H	27.1	Commercial ^{c)}
67	OH	H	OH	H	OH	H	82.4	Commercial ^{c)}
68	H	OMe	OH	OMe	H	H	202	Commercial ^{c)}

69	H	H	H				55.3	Commercial ^{c)}
70	OMe	H	H				26.9	Synthesis
71	H	OMe	H				11.3	Synthesis
72	H	H	OMe				21.0	Synthesis
73	H	OMe	OH				19.4	P.n.

74	H	H	H				> 500	Commercial ^{c)}
75	OMe	H	H				28.0	Synthesis
76	H	OMe	H				10.4	Synthesis
77	H	H	OMe				33.8	Synthesis

78	H	H	H	H	H		92.6	Commercial ^{c)}
79	OH	H	H	H	H		26.5	Commercial ^{c)}

TABLE I (continued)

Compound No.	R ₁	R ₂	R ₃	R ₄	R ₅	R ₆	IC 50 ^{b)} ($\times 10^{-5}$ M)	Source
80	OH	H	H	H	Me		136	Synthesis
81	OMe	H	H	H	H		427	Commercial ^{c)}
82	(<i>cis</i> -)OMe	H	H	H	H		> 500	Commercial ^{c)}
83	H	OH	H	H	H		86.6	Commercial ^{c)}
84	H	OH	H	H	Me		208	Synthesis
85	H	OMe	H	H	H		146	Commercial ^{c)}
86	H	H	OH	H	H		11.6	P.c.
87	H	H	OH	H	Me		34.3	Synthesis
88	H	H	OMe	H	H		> 500	Commercial ^{c)}
89	H	OH	OH	H	H		106	Commercial ^{c)}
90	H	OH	OMe	H	H		73.7	Commercial ^{c)}
91	H	OMe	OH	H	H		60.3	P.c.
92	H	OMe	OMe	H	H		> 500	Commercial ^{d)}
93	H	OMe	OMe	H	Me		58.6	Synthesis
94	H	OMe	OH	OMe	H		20.3	B.p.
95	H	OMe	OMe	OMe	H		> 500	Synthesis

96	OH	H	H	H	H		> 500	Commercial ^{e)}
97	H	OH	H	H	H		> 500	Commercial ^{e)}
98	H	H	OH	H	H		> 500	Commercial ^{e)}
99	H	OH	OH	H	H		> 500	Commercial ^{e)}
100	OH	H	H	OH	H		19.2	Commercial ^{e)}

a) Samples were tested for cyclic AMP phosphodiesterase activity in duplicate by the method described in a previous paper.²⁾ All samples were added as DMSO solution (in the final assay medium DMSO concentration did not exceed 2%).

b) IC 50 value is the concentration of a compound required to give 50% inhibition of cyclic AMP phosphodiesterase activity. IC 50 of the reference inhibitor, papaverine, was 3.0 ($\times 10^{-5}$ M).

P.n.: *Phyllostachys nigra* MUNRO var. *henonis* STAPF.

P.c.: *Phragmites communis* TRIN.

B.p.: *Betula platyphylla* var. *japonica*.

c) Tokyo Kasei Kogyo Co., Ltd.

d) Aldrich Chemical Company, Inc.

e) Wako Pure Chemical Industries, Ltd.

further fractionated by column chromatography on silica gel and preparative thin layer chromatography (TLC), and each fraction was tested for cyclic AMP phosphodiesterase inhibition.

As inhibitors of cyclic AMP phosphodiesterase, 2,5-dimethoxy-*p*-benzoquinone, *p*-hydroxybenzaldehyde, syringaldehyde and coniferylaldehyde were isolated from the dried culms of *Phyllostachys nigra* MUNRO var. *henonis* STAPF, and *p*-hydroxybenzaldehyde, vanilic acid, ferulic acid and *p*-coumaric acid were separated from the dried rhizomes of *Phragmites communis* TRIN. This is the first report of isolation of these inhibitors from these plants, and the first report on 2,5-dimethoxy-*p*-benzoquinone, syringaldehyde and coniferylaldehyde from gramineae plants.

In order to investigate the structure-activity relationship, a number of related compounds were tested for cyclic AMP phosphodiesterase inhibitory activity. The results are summarized in Table I.

Among 12 *p*-benzoquinone congeners (1–12), almost all the compounds showed a

strong inhibitory effect. Among 22 benzaldehyde (**13**—**34**), 10 benzyl alcohol (**35**—**44**) and 24 benzoic acid (**45**—**68**) congeners, the change of an aldehyde group to an alcohol or carboxyl group generally caused the activity to fall. Among benzaldehydes, the compounds with a methoxyl group at only one *meta* position, **17**, **22**, **29**, **31**, were more active than the other compounds. Among benzaldehydes and benzyl alcohols, the compounds with a methoxy group in the *para* position, **19**, **31**, **34**, **41**, **44**, were less active than the corresponding *para* hydroxyl compounds, **18**, **29**, **33**, **40**, **43**.

Among 27 C₆—C₃ related compounds (**69**—**95**), the change of a —CH=CH—CHO group to —CH=CH—COOH caused a decrease of activity, but the change of a —CH=CH—CHO group to —CH=CH—CH₂OH had no effect. Among the compounds with a —CH=CH—CHO or —CH=CH—CH₂OH group, the introduction of a methoxyl group *meta* to these groups increased the inhibitory effect. However, an introduction of a methoxyl group at the *para* position of cinnamic acid derivatives decreased the activity.

Experimental

All melting points were determined with a micro-melting point apparatus and are uncorrected. The infrared (IR) spectra were recorded with a Hitachi 295 spectrometer. The proton nuclear magnetic resonance (¹H-NMR) and carbon 13 nuclear magnetic resonance (¹³C-NMR) spectra were recorded with JEOL JNM-4H-100 and Hitachi R-900 spectrometers, respectively, and chemical shifts are given on the δ (ppm) scale with tetramethylsilane as an internal standard (s, singlet; d, doublet; dd, double doublet; br s, broad singlet; q, quartet). The mass spectra (MS) were measured with a JEOL JMS-01SG-2 mass spectrometer.

Column chromatography was carried out on Wako gel C-200 (Wako Pure Chemical Ind., Ltd.). Thin layer chromatography (TLC) was performed on pre-coated silica gel K 6 plates (0.25 mm, Whatman), and the developing solvent was CHCl₃—MeOH (10:1). The spots on the plates were detected with an ultraviolet (UV) lamp or by spraying 10% H₂SO₄ followed by heating.

Sample of Medicinal Plants—Dried *Bambusae Caulis* in Taenis (Japanese name Chikujyo) and the dried rhizomes of *Phragmites communis* TRIN. (Japanese name Rokon) were purchased from Uchida Pharmacy for Oriental Medicine (Tokyo).

Assay Method for Cyclic AMP Phosphodiesterase—Samples were tested for cyclic AMP phosphodiesterase activity in duplicate by the method described in a previous paper.²⁾ All the inhibitors were added as solution in dimethylsulfoxide (DMSO). The presence of DMSO in the assay medium at up to 2% concentration is known to have no effect on the enzyme activity. The IC₅₀ value is the concentration of a compound required for 50% inhibition of cyclic AMP phosphodiesterase activity.

Enzymes and Chemicals—Beef heart phosphodiesterase was purchased from Boehringer. Snake venom nucleotidase and cyclic AMP were obtained from Sigma, and [³H]-cyclic AMP from the Radiochemical Centre. Papaverine, a reference inhibitor, was purchased from Tokyo Kasei Kogyo Co., Ltd. (Tokyo). Of the compounds listed in Table I, **2** and **5**—**12** were kindly presented by M. Goto of the Central Research Division of Takeda Chemical Industries, Ltd., Kyoto. Compounds **3** and **94** were prepared in our laboratory. The commercial compounds were purchased from Tokyo Kasei Kogyo Co., Ltd., Aldrich Chemical Company, Inc. and Wako Pure Chemical Industries, Ltd. (see Table I).

Separation of Benzoquinone and Formylphenols from *Phyllostachys nigra* MUNRO var. *henonis* STAPF.—Extraction and Separation: Dried commercial *Bambusae Caulis* in Taenis (30 g) was continuously extracted with water (400 ml) at 90—100 °C and the aqueous extract (1.40 g) was divided into CHCl₃-soluble (0.07 g) and -insoluble (1.07 g) fractions. These fractions were tested for inhibitory effect on cyclic AMP phosphodiesterase.

In a large-scale extraction, fresh *Bambusae Caulis* in Taenis (16.3 kg), which was prepared from *Phyllostachys nigra* MUNRO var. *henonis* STAPF by removing the outer green skin, was extracted successively with MeOH at 70 °C for 48 h. The MeOH extract was concentrated, then dissolved in water and divided into CHCl₃-soluble (54.2 g) and insoluble fractions. Both of the fractions were evaporated to dryness and the residue were subjected to the cyclic AMP phosphodiesterase inhibition test. The CHCl₃-soluble fraction was more active than the insoluble fraction. The CHCl₃ soluble fraction was chromatographed on silica gel with hexane, benzene, CHCl₃ and MeOH as eluents: each eluate was tested for inhibitory effect on cyclic AMP phosphodiesterase.

2,5-Dimethoxy-*p*-benzoquinone (4**)**: The fractions eluted with benzene were concentrated and recrystallized from MeOH to give yellow needles of **4** (0.49 g, yield, 0.03%), mp 225 °C (dec.) (lit.,⁶⁾ mp ca. 250 °C), which was identified by direct comparison (TLC, IR, ¹H-NMR and mixed mp) with an authentic sample.

***p*-Hydroxybenzaldehyde (**18**)**: The fractions eluted with CHCl₃ were concentrated and recrystallized from benzene to give colorless needles of **18** (0.73 g, yield, 0.004%), mp 115—117 °C (lit.,⁷⁾ mp 116 °C), which was identified

by direct comparison (TLC, IR, MS, $^1\text{H-NMR}$ and mixed mp) with an authentic sample.

4-Hydroxy-3,5-dimethoxybenzaldehyde (Syringaldehyde, 33): The fractions eluted with $\text{CHCl}_3\text{-MeOH}$ (20:1) were concentrated and recrystallized from CHCl_3 to give pale yellow needles of **33** (0.30 g, yield, 0.0018%), mp 112—113°C (lit.,⁸) mp 113°C, which was identified by direct comparison (TLC, IR, $^1\text{H-NMR}$ and mixed mp) with an authentic sample.

4-Hydroxy-3-methoxycinnamaldehyde (coniferylaldehyde, 73): The fractions eluted with $\text{CHCl}_3\text{-MeOH}$ (10:1) were concentrated to give a oily compound, $^1\text{H-NMR}$ (CDCl_3) δ : 3.92 (3H, s), 6.15 (1H, br s), 6.57 (1H, dd, $J=8$, 16 Hz), 6.93 (1H, d, $J=8$ Hz), 7.02 (1H, d, $J=8$ Hz), 7.06 (1H, d, $J=16$ Hz), 9.63 (1H, d, $J=8$ Hz). MS m/z : 178 (M^+ , 100), 163 ($\text{M}^+ - \text{CH}_3$, 11), 147 (30), 135 (28), 107 (20), 77 (18), 51 (12). $^{13}\text{C-NMR}$ (CDCl_3) δ : 193.70 (d), 153.21 (d), 149.12 (s), 147.12 (s), 126.70 (s), 126.47 (d), 124.16 (d), 115.07 (d), 109.60 (d), 56.05 (q). This compound was derivatized to the 2,4-dinitrophenylhydrazone, mp 267—268°C (dec.) (lit.,⁹) mp 265—266°C, which was identified from the spectral data.

Separation of Formyl- and Carboxylphenols from *Phragmites communis* TRIN.—Extraction and Separation: Dried rhizomes (10 g) were continuously extracted with water at 90—100°C for 6 h and the water extract (1.42 g) was divided into CHCl_3 -soluble (0.04 g) and -insoluble (1.35 g) fractions. In a large-scale extraction, dried rhizomes (5 kg) were extracted continuously with MeOH at 70°C for 48 h. The MeOH extract (41.8 g) was taken up in H_2O and extracted with ether, ethyl acetate and *n*-butanol. The ether extract was divided into 5% NaOH soluble and insoluble fractions. These extracts were concentrated and tested for inhibitory effect on cyclic AMP phosphodiesterase. The NaOH soluble fraction was more active than other fractions, so this fraction was further fractionated by means of neutralized silica gel chromatography and preparative TLC, monitored for inhibitory activity against phosphodiesterase. The fractions containing compounds of $R_f=0.34$, 0.36, 0.40 and 0.58 were found to be active and were separated by preparative TLC.

***p*-Coumaric Acid (86):** The active compound showing $R_f=0.34$ was recrystallized from acetone- H_2O to give colorless needles of **86**, mp 222°C (lit.,¹⁰) mp 210—213°C, which was identified by direct comparison (TLC and mixed mp) with an authentic sample.

Vanilic Acid (63): The active compound showing $R_f=0.36$ was recrystallized from 50% EtOH to give colorless needles of **63**, mp 211—212°C (lit.,¹¹) mp 210°C, which was identified by direct comparison (TLC and mixed mp) with an authentic sample.

Ferulic Acid (91): The active compound showing $R_f=0.40$ was recrystallized from H_2O to give colorless needles of **91**, mp 174°C (lit.,¹²) mp 174°C, which was identified by direct comparison (TLC and mixed mp) with an authentic sample.

***p*-Hydroxybenzaldehyde (18):** The active compound showing $R_f=0.58$ was recrystallized from EtOH-hexane to give colorless needles of **18**, mp 115—116°C (lit.,⁷) mp 116°C, which was identified by direct comparison (TLC and mixed mp) with an authentic sample.

Acetylation of Phenolic Hydroxyl Group—A solution of **18** (250 mg) in a mixture of Ac_2O and pyridine was allowed to stand at room temperature overnight, then poured into ice-water. The product was then purified in the usual manner and recrystallized from acetone to give colorless needles of **20** (20 mg), mp 158—160°C, which was identified from the spectral data, MS m/z (%): 164 (M^+ , 33), 121 (100), and $^1\text{H-NMR}$ (CDCl_3) δ : 2.32 (3H, s), 7.23 (2H, d, $J=9$ Hz), 7.91 (2H, d, $J=9$ Hz), 10.05 (1H, s).

Methylation of Phenolic Hydroxyl Group—(1) An ether solution of **33** was treated with diazomethane etherate and the mixture was allowed to stand at room temperature overnight. The solvent was evaporated off to give the methylether (**34**), which was identified from the spectral data, MS m/z (%): 196 (M^+ , 100) and $^1\text{H-NMR}$ (CDCl_3) δ : 3.94 (9H, s), 7.14 (2H, s), 9.90 (1H, s).

(2) An ether solution of **94** was methylated with diazomethane by the same method as described above. The product was dissolved in EtOH, then NaOH aqueous solution was added. The mixture was refluxed for 1 h, then concentrated, and the residue was poured into water, acidified with HCl and extracted with ether. The ether extract was dried over Na_2SO_4 then evaporated to dryness to give the methylether (**95**), which was identified from the spectral data, MS m/z (%): 238 (M^+ , 100) and $^1\text{H-NMR}$ (CDCl_3) δ : 3.91 (9H, s), 6.38 (1H, d, $J=16$ Hz), 7.00 (2H, s), 7.58 (1H, d, $J=16$ Hz).

Reduction of Phenolic Aldehydes—Each phenolic aldehyde, **17** and **28**, was reduced with LiAlH_4 in dry ether to give the corresponding benzyl alcohol (**39** and **42**), which was identified from the spectral data (MS and $^1\text{H-NMR}$).

Esterification of Phenolic Acids—Each phenolic acid, **53**, **63**, **79**, **83**, **86** and **92**, was esterified with CH_2N_2 in ether or MeOH-conc. H_2SO_4 to give the corresponding acid methylester (**54**, **64**, **80**, **84**, **87** and **93**), which was purified with silica gel column chromatography and identified from the spectral data (MS and $^1\text{H-NMR}$).

Acknowledgement The authors wish to thank Dr. M. Goto of the Central Research Division, Takeda Chemical Industries, Ltd. for providing authentic benzoquinones. Thanks are also due to Dr. K. Kawai of Hoshi College of Pharmacy for the authentic sample of 2,5-dimethoxy-*p*-benzoquinone. We thank Miss. Y. Sakamoto for $^1\text{H-NMR}$ spectral measurement, and Mr. M. Takayama for mass spectral measurement.

References and Notes

- 1) A part of this study was presented at the 101st and 102nd Annual Meetings of the Pharmaceutical Society of Japan, Kumamoto and Osaka, April 1981 and April 1982. This paper forms part VI of "Inhibitors of Cyclic AMP Phosphodiesterase in Medicinal Plants." Part V: Y. I. Sung, K. Koike, T. Nikaido, T. Ohmoto, and U. Sankawa, *Chem. Pharm. Bull.*, "accepted."
- 2) T. Nikaido, T. Ohmoto, H. Noguchi, T. Kinoshita, H. Saitoh, and U. Sankawa, *Planta Medica*, **43**, 18 (1981).
- 3) T. Nikaido, T. Ohmoto, T. Kinoshita, U. Sankawa, S. Nishibe, and S. Hisada, *Chem. Pharm. Bull.*, **29**, 3586 (1981).
- 4) T. Nikaido, T. Ohmoto, U. Sankawa, T. Hamanaka, and K. Totsuka, *Planta Medica*, **46**, 162 (1982).
- 5) T. Nikaido, T. Ohmoto, H. Saitoh, U. Sankawa, S. Sakuma, and J. Shoji, *Chem. Pharm. Bull.*, **30**, 2020 (1982).
- 6) J. D. Bu'Lock, *J. Chem. Soc.*, **1955**, 575.
- 7) L. F. Fieser and M. Fieser, "Organic Chemistry," 3rd ed., Reinhold, New York, 1956, p. 681.
- 8) I. A. Pearl, *J. Am. Chem. Soc.*, **70**, 1746 (1948).
- 9) R. A. Black, A. A. Rosen, and S. L. Adams, *J. Am. Chem. Soc.*, **75**, 5344 (1953).
- 10) O. H. Wheeler and C. B. Covarrubias, *J. Org. Chem.*, **28**, 2015 (1963).
- 11) I. A. Pearl, *Org. Syn.*, **30**, 101 (1950).
- 12) I. A. Pearl and D. L. Beyer, *J. Org. Chem.*, **16**, 221 (1951).