

Prostanoids and Related Compounds. VI.¹⁾ Synthesis of Isoindolinone Derivatives Possessing Inhibitory Activity for Thromboxane A₂ Analog (U-46619)-Induced Vasoconstriction

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We have synthesized 3-(*o*, *m* or *p*-substituted benzylidene)isoindolinone and 3-(2-*o*, *m* or *p*-substituted phenylethylidene)isoindolinone, which possess inhibitory activity for thromboxane A₂ analog (U-46619)-induced vasoconstriction.

Keywords isoindolinone derivative; thromboxane A₂ analog (U-46619); prostacyclin

Thromboxane A₂ (TXA₂) was discovered by Hamberg *et al.*²⁾ as a highly unstable and biologically active compound produced from prostaglandin (PG) endoperoxide, which is a potent stimulator of platelet aggregation and mediates vascular and pulmonary smooth muscle contraction.³⁾ TXA₂ plays an important role in the maintenance of vascular homeostasis together with prostacyclin (PGI₂), which has the opposite pharmacological properties.

However, oversynthesis of TXA₂ has been considered to be implicated in circulatory disorders and asthmatic conditions. Therefore, TXA₂ receptor antagonists and PGI₂ derivatives should be clinically useful as therapeutic agents for thrombosis, asthma, ischemia, and myocardial infarction.^{4–7)}

Recently, we have found that some isoindolinone derivatives⁸⁾ inhibit TXA₂ analog (U-46619)⁹⁾-induced vasoconstriction. In this paper, we wish to report the synthesis of these isoindolinone derivatives.

Sekiya and Terao¹⁰⁾ have reported the synthesis of 3-benzylideneisoindolinone, which inhibited U-46619-induced vasoconstriction in a screening test.¹¹⁾ We assumed that the activity of 3-benzylideneisoindolinone is based on the structural similarity between 3-benzylideneisoindolinone and PGI₂. So, in order to obtain thromboxane receptor antagonists, we designed 3-benzylideneisoindolinone derivatives (1) and 3-(2-phenylethylidene)isoindolinone derivatives (2) by making the following structural modifications of PGI₂ (Chart 1): (1) modification of the 2-oxabicyclo-[3.3.0]octane ring by replacement of the isoindolinone ring; (2) modification of the α side chain of PGI₂ by replacement of the aryl-substituted exocyclic olefin; (3) modification of the 1-COOH group by replacement of the OH group, or of the 1-COOCH₃ group by replacement of OCH₃.

In these isoindolinone derivatives (1 and 2), it is considered that the exo-olefin of 3-benzylideneisoindolinone derivatives (1) or 3-(2-phenylethylidene)isoindolinone derivatives (2) is equivalent to the 5,6-double bond of PGI₂ (Chart 1). Therefore, we have introduced a *p*-hydroxy group or *p*-methoxy group in the benzene ring of 3-benzylideneisoindolinone (1) and an *m*-hydroxy group or *m*-methoxy group in 3-(2-phenylethylidene)isoindolinone (2). Furthermore, to identify the molecular structure responsible for the biological activities of isoindolinone derivatives, we have synthesized 3-benzylideneisoindolinone, 3-(*o*, *m* or *p*-substituted benzylidene)isoindolinone derivatives (1a—c, 6a—6c), 3-(2-phenylethylidene)isoindolinone and 3-(2-*o*, *m* or

p-substituted phenylethylidene)isoindolinone derivatives (2a—c, 10a—c).

3-Benzylideneisoindolinone and 3-(2-phenylethylidene)isoindolinone were prepared according to the literature procedure.¹⁰⁾

Compounds 1a—c and 6a—c were synthesized according to the reaction sequence shown in Chart 2. Compounds 1a, 1b and 1c were synthesized from (*o* or *m*)-methoxybenzaldehyde (3a and 3b) except 1c, which was synthesized from *p*-methoxybenzyl chloride 5c. Each aldehyde 3 was treated with 37% formalin in methanol to give the alcohol 4 according to the literature procedure¹²⁾ (4a: 75% yield, 4b: 87%). Each alcohol 4 was treated with SOCl₂ in dry benzene at 50 °C for 2 h to afford the chloride 5 (5a: 67% yield, 5b: 70%). Subsequently, phthalimide (1 eq) was reacted with the Grignard reagent (2 eq) prepared from 5 with Mg in dry tetrahydrofuran (THF) to afford the corresponding alcohol, which was used without further purification. Each crude alcohol was treated with 15% aqueous HCl for 30 min at room temperature to afford 6 (6a: 16% yield, 6b: 12%, 6c: 18%). The structures of compounds 6a, 6b and 6c were confirmed by analyses of their proton nuclear magnetic resonance (¹H-NMR) and infrared (IR) spectra as described in the experimental section. The ¹H-NMR spectra of 6a, 6b and 6c showed a singlet at 3.81—3.94 ppm due to the methoxy group, a characteristic singlet at 6.53—6.64 ppm due to the olefinic proton and a broad singlet at 8.28—8.42 ppm due to the amido proton. The IR spectra of 6 showed carbonyl absorption. Compounds 6 were treated with AlCl₃ in chlorobenzene under Ar at 95 °C for 2 h to afford 1 (1a: 9% yield, 1b: 8%, 1c: 13%). The structures of compounds 1a, 1b and 1c were confirmed by analyses of their ¹H-NMR and IR spectra as described in the experimental section. The ¹H-NMR spectra of 1a, 1b and 1c showed a

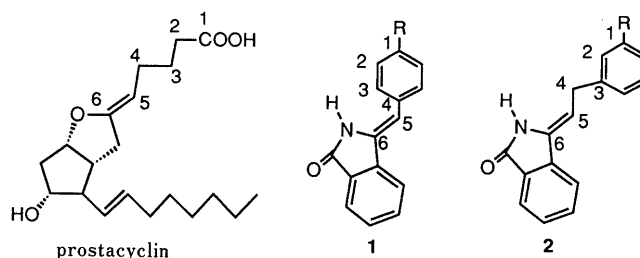


Chart 1

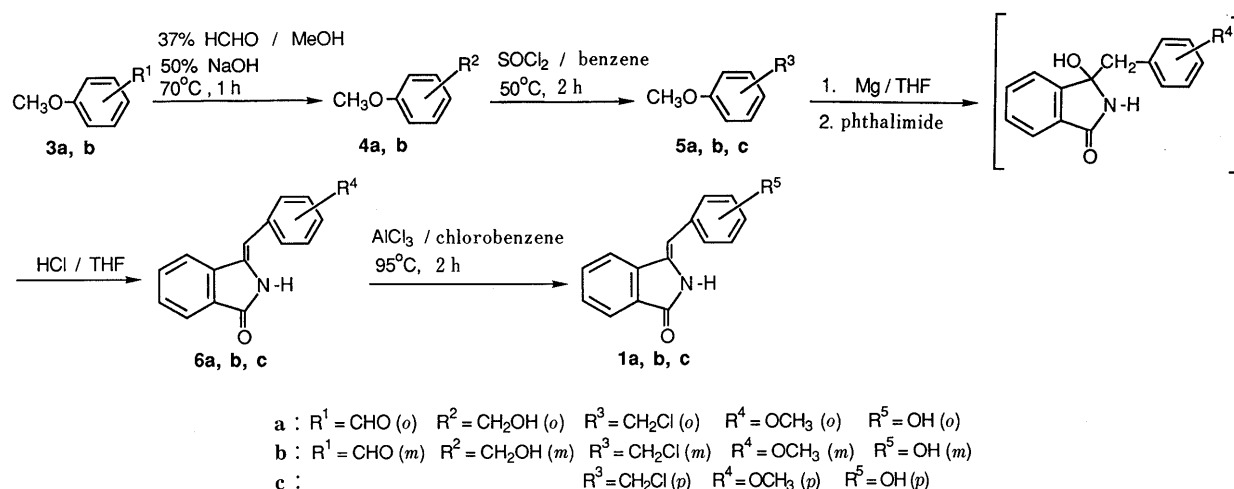


Chart 2

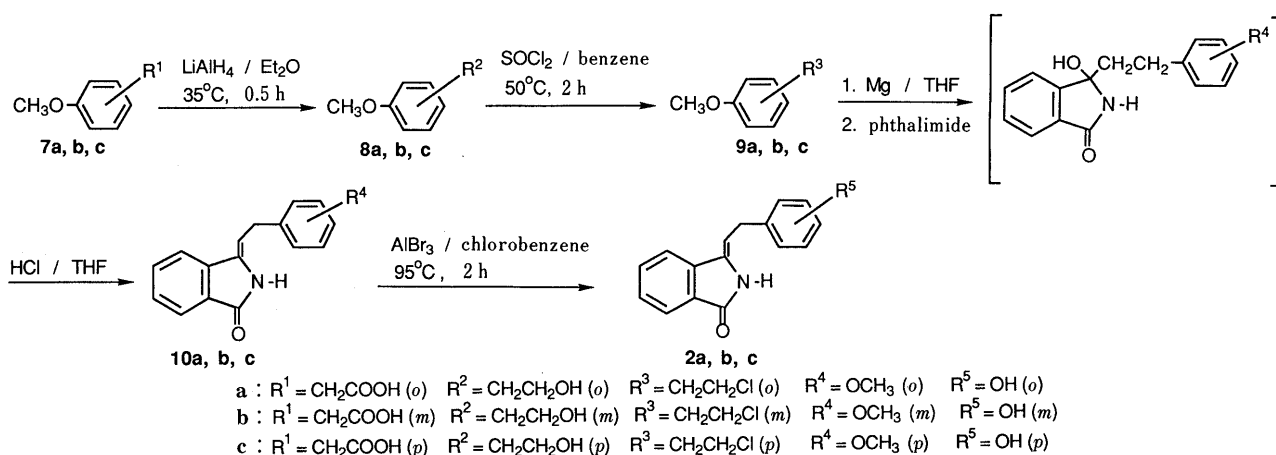


Chart 3

characteristic singlet at 6.62–6.65 ppm due to the olefinic proton and the IR spectra showed carbonyl and hydroxyl absorptions.

Compounds **2a–c** and **10a–c** were synthesized according to the reaction sequences in Chart 3. Compounds **2a**, **2b** and **2c** were synthesized from (*o*, *m* or *p*)-methoxyphenylacetic acid, **7a**, **7b** and **7c**. Treatment of **7** with lithium aluminum hydride in dry ether afforded the corresponding alcohol **8** (**8a**: 87% yield, **8b**: 97%, **8c**: 85%). Each alcohol **8** was treated with SOCl₂ in dry benzene at 50 °C for 2 h to afford the chloride **9** (**9a**: 75% yield, **9b**: 81%, **9c**: 74%). Subsequently, phthalimide (1 eq) was reacted with the Grignard reagent (2 eq) prepared from **9** with Mg in THF to afford the corresponding alcohol, which, without further purification, was treated with 15% HCl aqueous for 30 min at room temperature to afford **10** (**10a**: 43% yield, **10b**: 51%, **10c**: 14%). The structures of compounds **10a**, **10b** and **10c** were confirmed by analyses of their ¹H-NMR and IR spectra as described in the experimental section. The ¹H-NMR spectra of **10a**, **10b** and **10c** showed a characteristic doublet at 3.60–3.75 ppm due to methylene protons with a coupling constant of 7.7–8.4 Hz, a singlet at 3.79–3.90 due to methoxy protons, a triplet at 5.78–5.81 ppm due to the olefinic proton with a coupling constant of 7.7–8.4 Hz and a broad singlet at 8.12–9.32 ppm due

to the amido proton. The IR spectra of **10** showed carbonyl absorption. Compounds **10** were treated with AlBr₃ in chlorobenzene under Ar at 95 °C for 2 h to afford **2** (**2a**: 31% yield, **2b**: 29%, **2c**: 32%). The structures of compounds **2a**, **2b** and **2c** were confirmed by analyses of the ¹H-NMR and IR spectra as described in the experimental section. The ¹H-NMR spectra of **2a**, **2b** and **2c** showed a characteristic doublet at 3.72–3.73 ppm due to methylene protons with a coupling constant of 8.0–8.3 Hz and a triplet at 5.86–5.87 ppm due to the olefinic proton with a coupling constant of 8.0–8.3 Hz. The IR spectra of **2** showed carbonyl and hydroxyl absorptions.

The inhibitory activity for U-46619-induced vasoconstriction of pig coronary artery was measured for **1a**, **1b**, **1c**, **2a**, **2b**, **2c**, **6a**, **6b**, **6c**, **10a**, **10b**, **10c**, 3-benzylidene-isindolinone and 3-(2-phenylethylidene)isindolinone. Of the 3-benzylideneisindolinone derivatives (3-benzylideneisindolinone, **6a**, **6b**, **6c**, **1a**, **1b**, **1c**), compounds **6a**, **6b** and **1b** exhibited similar activity to 3-benzylideneisindolinone, whereas **6c**, **1a** and **1c** showed only weak activity. Of the 3-(2-phenylethylidene)isindolinone derivatives [**10a**, **10b**, **10c**, **2a**, **2b**, **2c**, 3-(2-phenylethylidene)isindolinone], the activities of **10a** and **10b** were greatly enhanced. Compounds **10c** and **2b** exhibited similar activity to 3-(2-phenylethylidene)isindolinone, but **2a** and **2b** showed only weak ac-

tivity. Of all the compounds, **10a** and **10b** showed the most potent activity.

These results indicate that 3-(2-phenylethylidene)isoindolinone derivatives have higher activities than 3-benzylideneisoindolinone derivatives.

Experimental

Melting points were determined on a micro-melting point apparatus (Yanagimoto) and are uncorrected. IR spectra were taken on JASCO A-202 and JASCO IR-810 infrared spectrophotometers and are given in cm^{-1} . $^1\text{H-NMR}$ spectra were recorded on a JEOL JNM-FX90q (90 MHz) spectrophotometer in CDCl_3 . Chemical shifts are given in δ (ppm) downfield from tetramethylsilane, and the abbreviations of signal patterns are as follows: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad. Thin layer chromatography (TLC) was performed on silica gel (Kieselgel 60F₂₅₄ on aluminum sheets, Merck). All compounds were located by spraying the TLC plate with sulfuric acid and heating it on a hot plate. Preparative TLC was performed on a preparative layer chromatography plate (Kieselgel 60F₂₅₄ 2 mm and 0.5 mm, Merck). Column chromatography was performed on silica gel (Kieselgel 60, 70–230 mesh, Merck).

Preparation of (*o* or *m*)-Methoxybenzyl Alcohol (4a, b) A solution of NaOH (3.5 g, 44.2 mmol) in H_2O (3.5 ml) was added in portions to a stirred solution of (*o* or *m*)-methoxybenzaldehyde (**3**) (4.0 g, 29.4 mmol), 37% formalin (3.1 g, 38.2 mmol) and methanol (40 ml) at 65 °C. The mixture was stirred at 70 °C for 1 h. After the mixture had cooled, H_2O was added, and the whole was extracted with CHCl_3 twice. The CHCl_3 extract was dried over MgSO_4 and concentrated *in vacuo* to give **4** as a colorless oil, which was used without further purification. The yields of *o*-methoxybenzyl alcohol **4a** and *m*-methoxybenzyl alcohol **4b** were 77 and 85%, respectively.

Preparation of (*o* or *m*)-Methoxybenzyl Chloride (5a, b) Thionyl chloride (2.2 g, 18.8 mmol) was added in portions to a stirred solution of (*o* or *m*)-methoxybenzyl alcohol (**4**) (2.0 g, 18.8 mmol) in dry benzene (10 ml) at 0 °C. The mixture was stirred for 2 h at 50 °C, then concentrated *in vacuo*. The resulting residual oily material was distilled *in vacuo* to give **5** as a colorless oil. The yields of *o*-methoxybenzyl chloride **5a** and *m*-methoxybenzyl chloride **5b** were 67 and 70%, respectively.

Preparation of 3-[(*o*, *m* or *p*)-Methoxybenzylidene]isoindolinone (6a–c) A solution of (*o*, *m* or *p*)-methoxybenzyl magnesium chloride was prepared by the usual method from **5** (1.5 g, 9.7 mmol) and Mg (0.26 g, 10.7 mg atom) in dry THF (5 ml). The solution was stirred at 50 °C for 1 h, then allowed to cool. Phthalimide (0.7 g, 4.8 mmol) in dry THF (20 ml) was gradually added to this Grignard reagent, then the mixture was stirred for 8 h at room temperature and cooled. Aqueous HCl (15%, 20 ml) was added to the reaction mixture at 0 °C and the whole was stirred for 30 min at room temperature. The reaction mixture was extracted with AcOEt twice. The organic solution was washed with brine, dried over MgSO_4 and concentrated *in vacuo*. The residue was subjected to column chromatography on SiO_2 using a 1:1 mixture of *n*-hexane–AcOEt as the eluent to give **6**. The yields of **6a**, **6b** and **6c** were 16, 12 and 18%, respectively.

3-(*o*-Methoxybenzylidene)isoindolinone (6a): White powder from EtOH. mp 174–175 °C. IR (KBr): 1747 (C=O). *Anal.* Calcd for $\text{C}_{16}\text{H}_{13}\text{NO}_2$: C, 76.48; H, 5.21; N, 5.57. Found: C, 76.18; H, 5.25; N, 5.59. $^1\text{H-NMR}$: 3.94 (3H, s), 6.64 (1H, s), 6.94–7.89 (8H, m), 8.30 (1H, brs).

3-(*m*-Methoxybenzylidene)isoindolinone (6b): White powder from EtOH. mp 164–166 °C. IR (KBr): 1740 (C=O). *Anal.* Calcd for $\text{C}_{16}\text{H}_{13}\text{NO}_2$: C, 76.48; H, 5.21; N, 5.57. Found: C, 76.22; H, 4.94; N, 5.46. $^1\text{H-NMR}$: 3.81 (3H, s), 6.54 (1H, s), 6.86–7.90 (8H, m), 8.42 (1H, brs).

3-(*p*-Methoxybenzylidene)isoindolinone (6c): White powder from EtOH. mp 194–196 °C. IR (KBr): 1754 (C=O). *Anal.* Calcd for $\text{C}_{16}\text{H}_{13}\text{NO}_2$: C, 76.48; H, 5.21; N, 5.57. Found: C, 76.47; H, 5.18; N, 5.51. $^1\text{H-NMR}$: 3.86 (3H, s), 6.53 (1H, s), 6.96–7.90 (8H, m), 8.28 (1H, brs).

Preparation of 3-[(*o*, *m* or *p*)-Hydroxybenzylidene]isoindolinone (1a–c) Aluminum chloride (366 mg, 2.8 mmol) was added to a solution of **6** (300 mg, 1.2 mmol) in chlorobenzene (10 ml) under Ar, then the mixture was stirred at 10 °C for 15 min, and at 95 °C for 2 h. After the mixture had cooled, 2% HCl aqueous (50 ml) was added. The whole was extracted with AcOEt twice, and the extract was washed with 5% aqueous NaOH and brine, dried over MgSO_4 and concentrated *in vacuo*. The resulting residue was purified by PTLC with *n*-hexane–AcOEt (1:2) to afford **1**. The yields of **1a**, **1b** and **1c** were 9, 8 and 13%, respectively.

3-(*o*-Hydroxybenzylidene)isoindolinone (1a): White powder from EtOAc. Decomposition 300 °C. IR (KBr): 1682 (C=O), 3242 (OH). *Anal.* Calcd for $\text{C}_{16}\text{H}_{13}\text{NO}_2$: C, 76.48; H, 5.21; N, 5.57. Found: C, 76.47; H, 5.18; N, 5.51. $^1\text{H-NMR}$: 6.65 (1H, s), 6.79–7.99 (8H, m).

3-(*m*-Hydroxybenzylidene)isoindolinone (1b): White powder from EtOAc. mp 234–237 °C. IR (KBr): 1695 (C=O), 3417 (OH). *Anal.* Calcd for $\text{C}_{16}\text{H}_{13}\text{NO}_2$: C, 76.48; H, 5.21; N, 5.57. Found: C, 76.47; H, 5.18; N, 5.51. $^1\text{H-NMR}$: 6.62 (1H, s), 6.87–7.98 (8H, m).

3-(*p*-Hydroxybenzylidene)isoindolinone (1c): White powder from EtOAc. mp 245–248 °C. IR (KBr): 1678 (C=O), 3331 (OH). *Anal.* Calcd for $\text{C}_{16}\text{H}_{13}\text{NO}_2$: C, 76.48; H, 5.21; N, 5.57. Found: C, 76.47; H, 5.18; N, 5.51. $^1\text{H-NMR}$: 6.65 (1H, s), 6.80–7.94 (8H, m).

Preparation of (*o*, *m* or *p*)-Methoxyphenylethyl Alcohol (8a–c) A solution of (*o*, *m* or *p*)-methoxyphenylacetic acid (**7**) (8.0 g, 48 mmol) in dry ether (40 ml) was added in portions to a stirred solution of lithium aluminum hydride (2.3 g, 60 mmol) in dry ether (40 ml) at 0 °C. The mixture was refluxed for 30 min. It was cooled, then 10% NaHCO_3 aqueous (20 ml) was added at 0 °C, followed by 20% NaOH aqueous (10 ml). The precipitates were removed by suction and washed with a small quantity of ether. The combined filtrate was extracted with ether (30 ml $\times$ 2), then the extract and washings were dried over MgSO_4 and concentrated *in vacuo* to give **8** as a colorless oil, which was used without further purification. The yields of *o*-methoxyphenylethyl alcohol **8a**, *m*-methoxyphenylethyl alcohol **8b** and *p*-methoxyphenylethyl alcohol **8c** were 87, 87 and 85% respectively.

Preparation of (*o*, *m* or *p*)-Methoxyphenylethyl Chloride (9a–c) Thionyl chloride (6.5 g, 54.2 mmol) was added in portions to a stirred solution of (*o*, *m* or *p*)-methoxyphenylethyl alcohol (**8**) (6.4 g, 41.7 mmol) in dry benzene (10 ml) at 0 °C. The mixture was stirred for 2 h at 50 °C, then cooled, and concentrated *in vacuo*. The residual oily material was distilled *in vacuo* to give **9** as a colorless oil. The yields of *o*-methoxyphenylethyl chloride **9a**, *m*-methoxyphenylethyl chloride **9b** and *p*-methoxyphenylethyl chloride **9c** were 75, 81 and 75%, respectively.

Preparation of 3-[2-(*o*, *m* or *p*)-Methoxyphenylethylidene]isoindolinone (10a–c) A solution of (*o*, *m* or *p*)-methoxyphenylethyl magnesium chloride was prepared by the usual method from **9** (3.0 g, 17.6 mmol) and Mg (0.46 g, 19.3 mg atoms) in dry THF (10 ml). The Grignard reagent was stirred at 50 °C for 1 h and cooled. To this solution, a solution of phthalimide (1.3 g, 8.8 mmol) in dry THF (20 ml) was gradually added, then the mixture was stirred for 8 h at room temperature. Subsequently, 15% HCl aqueous (20 ml) was added at 0 °C. The reaction mixture was stirred for 30 min at room temperature, and extracted with AcOEt (30 ml $\times$ 2). The extract was washed with brine, dried over MgSO_4 and concentrated *in vacuo*. The residue was subjected to column chromatography on SiO_2 using a 1:1 mixture of *n*-hexane–AcOEt as the eluent to give **10**. The yields of **10a**, **10b** and **10c** were 43, 51 and 43%, respectively.

3-(2-*o*-Methoxyphenylethylidene)isoindolinone (10a): White powder from EtOH. mp 204–206 °C. IR (KBr): 1700 (C=O). *Anal.* Calcd for $\text{C}_{17}\text{H}_{15}\text{NO}_2$: C, 76.96; H, 5.70; N, 5.28. Found: C, 76.18; H, 5.25; N, 5.59. $^1\text{H-NMR}$: 3.60 (2H, d, $J=8.4$ Hz), 3.90 (3H, s), 5.78 (1H, t, $J=8.4$ Hz), 6.89–7.85 (8H, m), 8.12 (1H, brs).

3-(2-*m*-Methoxyphenylethylidene)isoindolinone (10b): Pale yellow needles recrystallized from EtOH. mp 162–167 °C. IR (KBr): 1702 (C=O). *Anal.* Calcd for $\text{C}_{17}\text{H}_{15}\text{NO}_2$: C, 76.96; H, 5.70; N, 5.28. Found: C, 76.22; H, 5.61; N, 5.13. $^1\text{H-NMR}$: 3.75 (2H, d, $J=7.7$ Hz), 3.79 (3H, s), 5.81 (1H, t, $J=7.7$ Hz), 6.77–7.66 (8H, m), 9.32 (1H, brs).

3-(2-*p*-Methoxyphenylethylidene)isoindolinone (10c): Pale yellow needles recrystallized from EtOH. mp 165–168 °C. IR (KBr): 1706 (C=O). *Anal.* Calcd for $\text{C}_{17}\text{H}_{15}\text{NO}_2$: C, 76.96; H, 5.70; N, 5.28. Found: C, 76.18; H, 5.25; N, 5.59. $^1\text{H-NMR}$: 3.67 (2H, d, $J=7.9$ Hz), 3.80 (3H, s), 5.79 (1H, t, $J=7.9$ Hz), 6.85–7.89 (8H, m), 8.59 (1H, brs).

Preparation of 3-[2-(*o*, *m* or *p*)-Hydroxyphenylethylidene]isoindolinone (2a–c) Aluminum bromide (694 mg, 2.6 mmol) was added to a solution of **10** (300 mg, 1.1 mmol) in chlorobenzene (10 ml) under Ar, then the mixture was stirred at 10 °C for 15 min and at 95 °C for 2 h. It was cooled, then 2% HCl aqueous (50 ml) was added. The reaction mixture was extracted with AcOEt (40 ml $\times$ 2), and the extract was washed with 5% aqueous NaOH (20 ml), dried over MgSO_4 and concentrated *in vacuo*. The resulting residue was purified by PTLC with *n*-hexane–AcOEt (1:2) to afford **2**. The yields of **2a**, **2b** and **2c** were 31, 29 and 32%, respectively.

3-(2-*o*-Hydroxyphenylethylidene)isoindolinone (2a): White powder recrystallized from EtOAc. mp 157–160 °C. IR (KBr): 1690 (C=O), 3239 (OH). *Anal.* Calcd for $\text{C}_{16}\text{H}_{13}\text{NO}_2$: C, 76.48; H, 5.21; N, 5.57. Found: C, 76.47; H, 5.18; N, 5.51. $^1\text{H-NMR}$: 3.72 (2H, d, $J=8.3$ Hz), 5.87 (1H, t, $J=8.3$ Hz), 6.70–7.71 (8H, m).

3-(2-*m*-Hydroxyphenylethylidene)isoindolinone (**2b**): White powder recrystallized from EtOAc. mp 176—178 °C. IR (KBr): 1680 (C=O), 3300 (OH). *Anal.* Calcd for C₁₆H₁₃NO₂: C, 76.48; H, 5.21; N, 5.57. Found: C, 76.47; H, 5.18; N, 5.51. ¹H-NMR: 3.73 (2H, d, *J*=8.1 Hz), 5.86 (1H, t, *J*=8.1 Hz), 6.59—7.81 (8H, m).

3-(2-*p*-Hydroxyphenylethylidene)isoindolinone (**2c**): White powder recrystallized from EtOAc. mp 184—185 °C. IR (KBr): 1674 (C=O), 3203 (OH). *Anal.* Calcd for C₁₆H₁₃NO₂: C, 76.48; H, 5.21; N, 5.57. Found: C, 76.47; H, 5.18; N, 5.51. ¹H-NMR: 3.72 (2H, d, *J*=8.0 Hz), 5.86 (1H, t, *J*=8.0 Hz), 6.59—7.82 (8H, m).

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References and Notes

- 1) Part V: K. Miyajima, M. Takemoto, K. Achiwa, *Chem. Pharm. Bull.*, **39**, 3175 (1991).
- 2) M. Hamberg, J. Svensson, B. Samuelsson, *Proc. Natl. Acad. Sci. U.S.A.*, **72**, 2994 (1975).
- 3) a) S. S. Bhagwat, P. R. Hamann, W. C. Still, *J. Am. Chem. Soc.*, **107**, 6372 (1985); b) S. S. Bhagwat, P. R. Hamann, W. C. Still, S. Bunting, F. A. Fitzpatrick, *Nature* (London), **315**, 511 (1985).
- 4) S. Moncada, R. J. Gryglewski, S. Bunting, J. R. Vane, *Prostaglandins*, **12**, 715 (1976).
- 5) S. Moncada, S. Bunting, K. Mullane, P. Thorogood, J. R. Vane, *Prostaglandins*, **13**, 611 (1977).
- 6) S. Moncada, E. A. Higgs, J. R. Vane, *Lancet*, **1977**, i, 18.
- 7) F. P. Nijkamp, S. Moncada, H. L. White, J. R. Vane, *Eur. J. Pharmacol.*, **44**, 179 (1979).
- 8) Y. Kato, H. Ebiiike, K. Achiwa, N. Ashizawa, T. Kurihara, F. Kobayashi, *Chem. Pharm. Bull.*, **38**, 2060 (1990).
- 9) (15*S*)-15-Hydroxy-11,9-(epoxymethano)prosta-5(*Z*),13(*E*)-dienoic acid. a) G. Diminno, V. Bertele, L. Bionchi, B. Barbieri, C. Cerletti, E. Dejana, G. D. Gaetano, M. J. Silver, *Thromb. Haemostasis.*, **45**, 103 (1981); b) G. L. Bundy, *Tetrahedron Lett.*, **1957**, 1975.
- 10) M. Sekiya, Y. Terao, *Yakugaku Zasshi*, **88**, 1085 (1968).
- 11) Unpublished data.
- 12) Z. Horii, J. Tauji, T. Inoi, *Yakugaku Zasshi*, **77**, 252 (1957).